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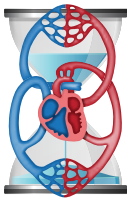
# 2017 APS Summer Conferences



Cardiovascular Aging: New Frontiers and Old Friends

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Westminster, CO


Physiological Bioenergetics: Mitochondria from Bench to Bedside

August 27-30, 2017
San Diego, CA

## Special Program and Abstract Issue

# A Confusion of Journals: What is PubMed Now?

**Kent Anderson**
***CEO, RedLink and RedLink Network***

What is PubMed? Is it a search engine? A credentialing system? A filter? Is it a publisher? An enabler of open access (OA) publishing? A technology provider? A competitor? Depending on the situation, you can answer each of the above in the affirmative, despite the contradictions many of the combinations may cause.

Twenty years ago, PubMed was a credentialing system, an online port of the MEDLINE index. This shift of medium quickly made it a search engine, but one built on a manual and highly curated index. If your journal was in MEDLINE/PubMed, it had gone through an exhaustive evaluation and had earned a badge of legitimacy. You were searching a credentialing system. You were getting filtered results based on MEDLINE inclusion criteria, which were well-accepted.

Starting with *E-Biomed* and stretching to PubMed Central, the credentialing system pegged in many users' minds morphed into a publisher [a primary publisher in the case of at least two journals (1), and, for a time, three (2)], a competitor (3–7), and a technology provider (8). Its management also has advanced the cause of OA publishing, in both legitimate and controversial ways (9). Part of the extension of PubMed's original purpose has come through brand extension via PubMed Central, which has been used to muddy the waters about what is PubMed and what is not. PubMed inclusion has been used, for example, as an incentive for journals to include themselves in PubMed Central, eroding the idea that PubMed is a neutral arbiter of quality (10).

Now, a new twist is emerging, and that seems to be that PubMed may be consciously or unwittingly acting as a facilitator of predatory or unscrupulous publishing.

In a paper published in *Neuroscience* (11), the authors analyzing the neurology and neuroscience journals included in PubMed found that:

- Twenty-five predatory neurology journals were indexed in PubMed, accounting for 24.7% of all predatory neurology journals.
- Fourteen predatory neuroscience journals were indexed in PubMed, accounting for 16.1% of all predatory neuroscience journals.
- Only one of the 188 predatory neuroscience or neurology journals appeared in the DOAJ index.
- Only 54.6% of the journals deemed predatory in neuroscience actually contained articles.

The authors note how PubMed Central provides a backdoor into PubMed and the National Library of Medicine (NLM) for these predatory publishers:

> "Noteworthy, predatory journals are retrievable in the catalog of the National Library

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# Mentoring Forum

## Changing Careers: Are You Ready and What Steps Do You Take?

**Megan M. Mitzelfelt**
*Development Manager, American Physiological Society*


Megan M. Mitzelfelt

Leaving research was, in my opinion, the best step I have taken for my career and life and has been for many of my friends and colleagues as well. A career change might be the right choice for you, too. But how do you know? And what steps do you take? In the following article, I summarize five signs that indicate you may be ready for a career change and provide concrete steps you should take to explore options and position yourself for a new career should you so choose to pursue one. Next, I tell the story of my leaving academic research to pursue a fundraising career and provide an overview of the fundraising profession. Finally, I address the elephant in the room: regret. Changing careers is not necessarily a sign of failure and, as in my case, might be the best choice you could make.

### Signs You May Be Ready For A Career Change

The following are signs you may be ready for a career change.

#### *1) Unhappy or Dissatisfied*

If you find yourself dreading going to lab each day and you've felt this way for a long time – say throughout graduate school, your postdoctoral fellowship, and maybe even your first faculty position – it is likely time for a change.

Even though I loved coming up with new project ideas that I believed would help humanity, I found I was immensely unhappy slogging through day-to-day activities and experiments in the lab – both in graduate school and in my postdoc. This negatively impacted my research productivity and my home life.

#### *2) No Longer Engaged or Interested*

If you find you are no longer excited about research and are just going through the motions each day in the lab, it may be time to reevaluate your chosen career path. It may be as simple as finding a more engaging project or lab environment, or it may be that research is not right for you.

I had classmates in graduate school who, although they finished their PhD, were just never fully interested and invested in research and certainly did not want to be continuously seeking grant support for their own salaries. Many ended up choosing to pursue jobs in science-related sales/marketing or consulting and are again excited about their work.

#### *3) Overworked and Stressed Out*

If you feel overworked and stressed to the point that it negatively affects your life outside of work, it is likely time for a career change. No career is ever worth endangering your health and happiness.

For example, I had a friend who was so stressed out during his postdoctoral fellowship that he developed gastritis and ended up in the hospital due to stress-induced atrial fibrillation – in his 30s! After this incident, he decided to pursue a non-research career and has been happier and healthier ever since.

#### *4) See No Growth Opportunity*

If the job market is tight and you have not had or do not think you will have success moving "up the ladder," it might be time for a change.

Knowing that after 5 years in my postdoctoral fellowship, there was an 85% chance that I would still not have obtained a tenure-track academic research position and that, even if I did, the chance of my being awarded an R01 was strikingly low, I decided to start exploring other career options and gaining experience in teaching and science writing, just in case.

#### *5) Want a Different Lifestyle*

If you want to a different lifestyle than your current career can provide (e.g., more time with your family, higher earning potential, to work from home, to more directly help others, etc.), then it may be time to change

careers. Matching your lifestyle preference to your career is the best way to achieve satisfaction.

When deciding whether I wanted to pursue another postdoc, I determined that I wanted to instead have a more long-term position that provided set working hours each week. This was very important to me as a new mom.

## Steps to Changing Careers

It might be that only one of the signs above apply to you and you are not certain whether a career change is in the cards. Or it may be that all apply and you are certain that you need to make a change. Either way, the five steps below will ensure that you have options.

Life is ever-changing, and you never know what may happen. For example, you may suddenly have to move because of your spouse's relocation or a sick relative. Or you may lose your current position due to lack of funding. Either way, you need to be prepared for anything.

So, how do you prepare yourself for a career change?

### *1) Become an Extrovert*

Networking is the key to success. Although many people find it difficult to be an extrovert, it is in the best interest of your career to get out there, talk to others, and make yourself known. But how do you get started?

**Present Your Work.** Attend as many scientific meetings as you can and submit an abstract for an oral presentation every time (if possible). Your oral presentations will make you known to others in your field and ultimately make it easier to develop personal relationships with those who can and will help you achieve your career goals. You never know who knows who and what relationships will be the most fruitful.

I orally presented my work numerous times at the APS annual meeting and at smaller regional meetings in Florida. These small meetings were particularly helpful to me because they fostered relationships that helped me obtain a postdoctoral fellowship.

APS has several smaller meetings each year. You should check them out because you never know who you will meet and what opportunities may be presented. APS often gives out travel awards to attend these meetings, particularly if you are a speaker.

**Explore and Join Professional Associations.** If you are interested in a particular field (e.g., science or medical writing, marketing, teaching, etc.) explore the professional associations that serve these fields and find out if you can join. Nonmembers also are often able to attend events, especially at local chapters, so get involved, learn about the field, and develop your network.

For example, I joined the American Medical Writers Association and National Science Teachers Association when I was a postdoc.

**Attend Social and Networking Events.** Go to any and every social or networking event that has even a smidge of relevance to your current field or one in which you have interest. These might include events held by your institution, local professional networking groups, or professional associations in which you are a member or are interested.

As a postdoc, I became interested in the medical writing field, so I attended some of the American Medical Writers Association local chapter events and presentations. These meetings gave me the confidence to pursue freelance science writing opportunities. Ultimately, I wrote articles for a vitamin magazine and coordinated the publication of a reference text on sex differences in physiology.

**Serve on Committees.** Explore and apply for volunteer opportunities, especially committee service, at associations in which you are a member. You would never believe the connections that you make through committee service.

My service on the APS Trainee Advisory Committee is likely to be the primary reason I am now working at APS and in fundraising. During my, albeit short, service, I was introduced to APS Executive Director Martin Frank and the rest is history.

### *2) Be Adventurous*

Nobody will ever give you a job just because you want it. They need to know that you have the skills and expertise required to be successful; and the ultimate way to demonstrate this is through experience. So, be adventurous, particularly as a graduate student and a postdoctoral fellow.

**Volunteer.** Volunteer to train undergraduates and/or new technicians in the laboratory to gain supervisory experience. Volunteer for your institutional postdoctoral association to demonstrate leadership and teamwork skills. Volunteer for a local nonprofit about which you are passionate. One place to find such opportunities is volunteermatch.org. The skills you learn and knowledge/experience you gain can be a great boon to your future career change.

During graduate school, I helped to start a nonprofit that raised funds to support research grants on the mechanisms and treatment of triple negative breast cancer. I gained experience in marketing and fundraising, both of which helped me to move into a fundraising career.

**Search and Apply for Jobs.** Always be searching for new job opportunities, even if you like your current position. You never know what may become available. You might even be able to find a contract job that provides you with valuable experience.

As a postdoc, I became interested in medical/science writing since I had always been quite a good writer. I applied for part-time writing opportunities and was given the chance to write an article for LifeExtension, a vitamin magazine you will likely find in a vitamin store. Although I did not really enjoy writing such articles, the experience gave me demonstrable writing and marketing skills that I could include on my resume.

**Take an Internship or Course.** If available at your institution, intern with an administrative office in which you have interest (e.g., technology transfer, communications and public relations, development, research administration, etc.). You might also take in-person or online courses to gain knowledge and skills in a particular area of interest.

For example, my husband interned for the Emory Office of Technology Transfer during his postdoctoral fellowship. His internship was instrumental in obtaining his first position in technology transfer.

If you are worried that these activities will take time away from your research efforts as a graduate student and postdoc, no need to worry. OMB and NIH have clarified that graduate students and postdocs supported by federal research grants are both trainees and employees, and are expected to engage in career development activities. If you'd like to read more about this policy, please see *nexus.od.nih.gov/all/2014/10/10/defining-the-dual-role-of-graduate-students-and-postdocs-supported-by-research-grants/*.

There is also the NIH Broadening Experiences in Scientific Training (BEST) program. I highly recommend that you check it out at *www.nihbest.org*.

### *3) Create a Plan*

After you have had a chance to build your network and gain some experience in an area that interests you, it is time to make a plan. But how do you do this?

There is a fantastic resource available to science trainees known as myIDP or individual development plan (*myidp.sciencecareers.org*). The individual development plan helps you in the following ways.

**Determine your skills, interests, and values.** These assessments allow you to reflect on what you are good at doing and what you enjoy doing the most. The ultimate goal is to align those two categories along with what you value in life and work to predict which careers will be a best fit for you.

**Identify a career.** myIDP will predict, based on assessment of your skills, interests, and values, which of 20 different science-related careers will fit you best. Careers include research, teaching, biotech, pharma, marketing, writing, etc.

**Make a strategic plan.** The IDP program also helps you create a strategic plan for the coming year to achieve your career goals and, if desired, will provide reminders to keep you engaged.

### *4) Be Flexible*

Life does not always work out the way you had planned. That's what makes it interesting. So be flexible with your career and life plans.

I had no plan to become a development (aka fundraising) professional. Even after my postdoctoral fellowship, I still desired an academic teaching position with a little bit of research included. My husband had no plan to become a technology transfer professional. But we were flexible, took chances, and in the end followed what made us happy and feel fulfilled. You should, too.

## My Story: From Postdoc to Fundraiser

In fall 2013, the day before Thanksgiving and 2 and half years into my postdoctoral fellowship at Emory University, I found out that my husband had been offered and accepted his dream job in technology transfer at the University of Maryland and that I was pregnant.

Needless to say, life throws curveballs.

Not wishing to separate my growing family for long, I ended my fellowship after 3 years and moved to Maryland without a clue as to what my next career step would be. I interviewed for a community college teaching position and a postdoctoral fellowship at the NIH, but neither felt right. To stay in academic research, I would have needed to start all over again, and I already knew the struggle that lay ahead had I chosen to pursue a tenure-track academic research professorship. As a new mother, I was looking for something that was stable, had normal work hours, and would still contribute to science.

As luck would have it, a position in fundraising opened up at APS.

I was on the APS Trainee Advisory Committee, and, while attending EB 2014, I happened to speak with APS Executive Director Martin Frank and mentioned that I was moving to Maryland without a clue as to what was next. He informed me that a position at APS for a development officer would soon be opening up and suggested I apply. My first reaction was: "What is development?" So I explored a little further, discovered it was a position in fundraising, in which I had a little experience, and I applied. Although, due to my relative inexperience, I wasn't chosen for the development officer position, APS opened up a support position in development, and I got the job.

I absolutely love fundraising because every day I work to better society and the world. Even more, because I work for APS, I can remain connected to and support the physiology research and teaching community that I have so come to love and appreciate.

### *What Do Fundraisers Do?*

Fundraisers seek charitable gifts and grants from individuals, corporations, private foundations, and the federal government to support the work of a nonprofit organization. There are many different fundraising activities, including seeking annual gifts, major gifts, planned gifts, corporate sponsorships, foundation grants, and federal grants; managing fundraising teams or campaigns; managing the donor database and performing prospect research; and much more. There exist positions specific to each of these activities, particularly in large nonprofits that depend on donated funds for the majority of their revenue. More general positions, in which you perform all activities, exist in smaller nonprofits and those like APS that have a new fundraising program and/or depend to a lesser extent on donations and grants.

### *Fundraising is a Profession*

Fundraising is a full-fledged profession with academic degrees and research, professional associations, and certifications. The Association of Fundraising Professionals (AFP) supports the fundraising profession just as APS supports the physiology research and teaching profession. Should you have any interest in learning more about the fundraising profession, please visit *www.afpnet.org*. Opportunities within the field have been and continue to grow as the number of nonprofits and individuals with accumulated wealth have grown substantially over the past few decades.

I chose recently to complete the AFP Diploma in Fundraising Management in which I learned fundraising best practices and used academic research to inform and improve our fundraising practice at APS. I am working toward the Certified Fund Raising Executive (CFRE) credential, a preferred qualification for many fundraising jobs.

### *Researchers are Fundraisers*

The best part is that you already have experience in fundraising. A huge part of your job as an academic research scientist has been to seek and acquire federal and/or private grant support for your training and research program. Grant writing skills are highly in-demand. Many nonprofits, including academic institutions, hire grant writers to acquire foundation and federal grant support. Also, it is a sub-field of fundraising that has its own certification through the American Grant Writers Association.

Because of my background as a physiology researcher, I brought experience with science-related grant writing and knowledge of the most likely federal and corporate funders (i.e., NIH, NSF, and pharma and biotech companies) to my current position. I also brought knowledge about the key issues within the physiology research and teaching enterprise. My experience and knowledge has been immensely helpful with identifying funding opportunities, tailoring funding requests, and being successful in acquiring support. Yet, I have also had to learn a tremendous amount, and APS has generously invested in my professional training.

## On Regretting the Road Not Taken

People often ask me if I miss research. The answer is not really. I do not regret "the road not taken" – academic research – and I would say that most all of my friends and colleagues who have left research do not regret it either.

Regret is a risk that you should consider. I have encountered regret mostly in those who left academic research out of necessity and not choice. They often feel as if they are a failure. If you love research, it is what you should be doing and put all of your effort into making sure you succeed. However, if you think you could be just, if not more, happy in another career, then I am certain it is worth the risk of regret to explore and possibly pursue a new one. It is absolutely not a failure.

For anyone who is considering such a change, I'd be happy to discuss your ideas, answer questions, and address your reservations about changing careers anytime. Contact me at *mmitzelfelt@the-aps.org* or (301) 634-7991. ●

## Megan Metzelfelt Biography

Megan Mitzelfelt is Development Manager at the American Physiological Society. She obtained her PhD in Medical Science with a concentration in Physiology and Pharmacology from the University of Florida in 2011. Megan completed a postdoctoral fellowship at Emory University under the mentorship of Distinguished Professor and Past APS President Douglas C. Eaton in 2014. More details about Megan's professional career may be found at *www.linkedin.com/in/mmitzelfelt*.

*Continued from page 305:*

## A Confusion of Journals: What is PubMed Now?

> of Medicine (NLM), are labeled by a unique NLM identification number, and are referenced as 'Not currently indexed for MEDLINE. Only citations for author manuscripts are included.'"

This is the kind of fine print that will escape the attention of most users and that itself is unclear as to reliability, process, or value. Are we to think that something that appears in PubMed and the NLM but not in MEDLINE has some lesser status? The confusion is multi-layered for users.

This study was published in April, but went largely unnoticed until the authors published on August 19, 2017 a letter based on the same research in the *Lancet* (12). In this letter, the authors state their recommendations thusly:

> "Furthermore, although the National Library of Medicine refers to these journals under the descriptor 'Not currently indexed for MEDLINE,' citations for author manuscripts are labelled as 'included.' Thus, highly regarded databases like PubMed and PubMed Central should raise the bar for journal acceptance, and join the Directory of Open Access Journals, Scopus, and MEDLINE in imposing stringent criteria for inclusion of journals and publishers."

As one blogger notes about the study and the letter in the *Lancet* (13):

> "The PubMed database managers have irresponsibly allowed it to become a repository of citations to predatory journal articles. Among other things, the next time you see a questionable journal proudly announcing that it is indexed in Pubmed, chances are that the journal is predatory. Contrary to the popular notion that only genuine and distinguished journals which take peer-reviewing seriously and follow all the norms of scientific publishing are indexed in PubMed, many predatory journals too are included in PubMed. The same holds true for PubMed Central too."

PubMed's brand has long been muddled in ways that pass lower-quality works through the system under cover of prestige. This has real consequences. A recent article in *BusinessWeek* outlines how the "predatory" publisher OMICS (14) is being used by pharmaceutical companies to quickly get citations for studies major journals won't accept and run meetings to push their products.

Despite being caught red-handed publishing "fake science" in Canada (15), OMICS doesn't seem fazed. In response, it is running today's standard playbook built on bluster and bombast, including calling accusations against it "fake news" and its founder claiming implausibly, "We've never made a mistake." Currently the subject of a U.S. Federal Trade Commission prosecution, OMICS:

> ". . . first got into trouble with the U.S. government in 2011. The National Institutes of Health, a division of the U.S. Department of Health and Human Services, banned OMICS journals from indexing in PubMed Central, one of the world's primary databases for medical research, given "serious concerns" about its practices. In 2013, HHS accused OMICS of trademark infringement and using the names of employees at the NIH and PubMed Central 'in an erroneous and/or misleading manner.'"

While OMICS is ostensibly banned from PubMed Central, it doesn't take long to come across the *OMICS Journal of Radiology* in PubMed and PubMed Central (16). This again shows what a confusion of journals PubMed has become. One URL you get on the first page of a simple Google search for OMICS in PubMed (17) is *https://www.ncbi.nlm.nih.gov/labs/journals/omics-j-radiol/*, with the curious "labs" element in it. At the top of the resulting page, it reads, "A PubMed Lab

experiment" (18). Clicking on this tagline takes you to a blog entry from September 7, 2016 (19), which talks about this new experiment apparently aimed at letting users follow certain journals. It seems like an experiment that never took off, yet a Google search finds the page, an OMICS journal with a full accoutrement of PubMed elements is discoverable, and PubMed citations are easily retrieved (20).

PubMed's brand has long been muddled in ways that pass lower-quality works through the system under cover of prestige. This has real consequences.

You may also have caught that the reporters from *BusinessWeek* were also confused by what PubMed Central is, describing it as "one of the world's primary databases for medical research." PubMed describes itself as "a free full-text archive of biomedical and life sciences journal literature." Yet, you can find articles about quantum chromodynamics (QCD) from the *European Physics Journal C, Particles and Fields*, in PubMed Central (21). There are hundreds of entries for astrophysics, many of which seem irrelevant to biomedicine and life sciences. Several U.S. funding agencies also use PMC as their repository (22), including the Department of Homeland Security and the Department of Veteran Affairs. It seems "biomedical and life sciences" are quite broadly defined by PMC.

Maybe PubMed is confusing even to itself?

In addition to the dubious role of certification databases when it comes to questionable journals, the role of scientists in the predatory publishing phenomenon is the subject of a recent article in *Nature* by David Moher, Larissa Shamseer, Kelly Cobey, and their colleagues (23). In their review of nearly 2,000 biomedical articles from more than 200 journals thought to be predatory, more than half of the corresponding authors hailed from high- and upper-middle-income countries using World Bank criteria. This flies in the face of the common assumption that predatory publishers are exploiting desperate authors in low-income countries. More worrying is that, of the 17% of the sampled articles that reported a funding source, the NIH was the most frequently named funder. The U.S. itself produced more articles in this sample than any other country save India. The authors note: "Our experience with these journals is that they provide both poor vetting and poor access. Their websites and archiving systems are unstable. Although some articles appear in PubMed (often after a delay), the titles are not indexed by Medline and are difficult to find."

What's the thread through PubMed over the years since it was ported from MEDLINE? The unifying theme I see is a hunger to adapt. At times, this has been a boon – the port of MEDLINE to PubMed was a smart move, and some interface changes have been commendable. At other times, these adaptations have revealed a clear lack of purpose and mission, such as the controversial involvement with *eLife*, the competition with publisher brands and traffic, and now the loose standards that have allowed unscrupulous publishers to enter PubMed via PMC.

Adaptation is required to remain relevant, but there have to be limits, or the adaptation may cause the entity to simply dissipate into the environment via entropy. PubMed seems to be giving into entropy. It needs to realize this moment calls for something else – clarity, standards, and credentialing that means something. Their opportunity is not to follow, but to lead. ●

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# Committee Reports

## APS Council Holds Summer Meeting in Bethesda

The APS Council held its annual summer meeting in Bethesda, MD, July 18–20, 2017, at the Bethesda Marriott Pooks Hill. Each summer, the Council invites the APS Committee Chairs to the summer meeting to present their annual committee reports to Council. The committee reports begin on page 315.

The Council also received the Strategic Plan developed in conjunction with Minding Your Business. The Strategic Plan was published in the September 2017 issue of *The Physiologist*. To implement all aspects of the Strategic Plan, the Council created seven task forces to review and evaluate various aspects of the Society's activities and programs.

Council approved a 1-year renewal of the Undergraduate Research Excellence Fellowship.

Council approved the request for travel funds for the Chapter Advisory Committee Chair for 2018.

Council approved the 2016 Audit Report presented by the Finance Committee.

Council approved the request from the Membership and FAPS Committee to approve the slate of 19 new Fellows of the APS. Council also approved the request to add a multi-year payment of membership dues without subsequent year increases.

Council approved the request to eliminate retroactive payment on multi-year memberships. Council also approved the request not to increase the dues for FY 2018 for affiliate, undergraduate, and graduate members.

Council approved the request to change the name of the "Novel Disease Model Award" to the "Transitional Research Award."

In addition to presenting their reports, the chairs discussed the highlights of their committees' activities and programs during the past year, and updated Council on the committee's goals and plans for the coming year. The chairs did not submit requests for new committee programs to Council this year.

The Society's Executive Director, Martin Frank, also informed the Council that it was his intention to retire from APS as of June 30, 2018. Dennis Brown and the Council expressed their appreciation for his nearly 33 years of service to the Society. The Council also made plans to issue an RFP to identify an executive search firm to assist the Society in the recruitment and selection of the next APS executive director.

Each year during the Summer Council meeting, APS hosts an employee appreciation reception. The reception provides an opportunity for members of Council and the committee chairs to meet with the

Committee chairs. Front row (*left* to *right*): Sean Stocker, Meredith Hay, Curt Sigmund, Andrew Roberts, Caroline Rickards, Eric Lazartigues. Back row (*left* to *right*): Barbara Goodman, Erica Dale, Robert Brock, Robert Hester, Layla Al-Nakkash, David Pollock, Jeffrey Osborn, Mari Hopper, Laura McCabe

Council. Front row (seated) (*left* to *right*): Sean Stocker, Curt Sigmund, Jane Reckelhoff, Dennis Brown, Jeff Sands, Meredith Hay. Back row (*left* to *right*): Merry Lindsey, Lisa Leon, Robert Hester, Irene Solomon, Charles Lang, Willis Samson, Jeffrey Osborn, Ronald Lynch, Harold Schultz, David Gutterman

Staff. *Left* to *right:* Dennis Brown, Kevin Kaneschige, Esther Samuel, Dell Pillers-Cline, Bonnie Bright, Alice Ra'anan, Veronica Purvis, Eric Pesanelli, Jami Jones, Martin Frank, Robert Price

APS staff. During the reception, APS President Dennis Brown thanked the staff saying, "APS has the best staff, and it is a pleasure for me to present the staff with their service awards this year. APS is presenting 10 awards, which is a testament to the Society and its leadership. The staff helps APS run smoothly and ensures that the ideas that Council and the Chairs have become a reality."

The highlight of the reception every year is the recognition of those staff members who have worked for APS for 5 years or more (anniversary is based on 5-year intervals). Each employee celebrating an anniversary receives a certificate of appreciation and a gift certificate. This year, APS President Dennis Brown presented 25-year certificates to Eric Pesanelli (Art Editorial Manager) and Alice Ra'anan (Director of Government Relations); a 20-year certificate to Dell Pillars-Cline (Accounting Manager); a 15-year certificate to Gil Ebner (Peer Review Manager); 10-year certificates to Esther Samuels (Administrative Assistant / Awards Coordinator), Bonnie Bright (Journal Coordinator), Jami Jones (Peer Review), and Daniel Pisconte (Peer Review); and 5-year certificates to Kevin Kaneshige (Director of IT) and Veronica Purvis (Director of Marketing and Communications). ●

## Animal Care and Experimentation Committee

Jeff Henegar, Chair

The Animal Care and Experimentation (ACE) Committee met in Bethesda on October 18–19, 2016, and at Experimental Biology in Chicago on April 22, 2017.

**EB 2018 Public Affairs Symposium.** The ACE Committee is organizing a symposium on "Avoiding Common Pitfalls in Preclinical Animal Research Design" that will be presented at EB 2018. The symposium will discuss study design factors such as selecting the appropriate animal model, satisfying FDA requirements for preclinical data, and biological variables to consider when writing an NIH grant.

**SABV.** During the fall 2016 meeting, two NIH speakers briefed the ACE Committee about NIH's new policies regarding the inclusion of sex as a biological variable (SABV). The committee developed follow-up questions that APS President Dennis Brown sent Janine Clayton, Director of NIH's Office of Research on Women's Health.

**Reducing regulatory burden.** The committee has begun identifying actions IACUCs can take to reduce regulatory burden. Examples include using the Veterinary Verification and Consultation process to simplify approval for minor protocol changes and designated member review of protocols. It was also suggested that IACUCs encourage researchers to write their protocols to permit some flexibility with respect to aspects, such as the estimated numbers of animals needed and timing of medication, and that IACUCs only assign USDA pain categories to species regulated under the Animal Welfare Act, unless a funding agency requires this. Science policy analyst Linda Yang has been working with the committee to post information on these topics to the APS website at *http://www.the-aps.org/mm/SciencePolicy/AnimalResearch/Regulatory-Burden/Reducing-Burden-Specifics*.

**Clarifying OLAW policies.** On July 11, 2016, I wrote to Office of Laboratory Animal Welfare (OLAW) Director Pat Brown to request clarification about eligibility criteria for non-scientist IACUC members and when institutions should count rodents in breeding colonies. In her reply, Brown stated that the criterion for a non-scientist member is an individual who is naive to the scientific process. She also said that it does not matter when rodents in breeding colonies are counted as long as all animals bred for research are counted, whether or not they are used in experiments.

**Mandatory dog and cat adoption bills.** Anti-research groups are pushing legislation in several states that would require research institutions to take specific steps to arrange for the adoption of dogs and cats at the conclusion of research studies. The APS submitted testimony opposing a mandatory adoption bill in the state of Maryland on the grounds that the state should not attempt to micro-manage post-research adoption procedures. That bill failed, but similar legislation has been adopted in other states.

**Public records requests.** Anti-research groups have escalated their use of public records requests to obtain information about animal research for their campaigns. One group has been using the federal Freedom of Information Act to obtain institutional self-reports of non-compliance from NIH's OLAW. Another has been using state open records laws to get information about the disposition of dogs and cats at the conclusion of research studies. A third group obtains research protocols to critique the study design.

**Animal transportation.** During its fall meeting, the committee met with Robert Dysko, DVM, Director of the University of Michigan's Unit for Laboratory Animal Medicine. Dysko explained that various companies that transport research animals face many logistical and regulatory challenges and are now under increasing pressure from animal rights groups. For these reasons, it is important for research institutions to provide whatever support they can, and, for this reason, the University of Michigan adopted a position statement in support of research animal transportation. In 2014, the APS adopted a position statement titled "Air Transport of Animals Advances Human and Animal Welfare" (*http://www.the-aps.org/mm/SciencePolicy/About/Policy-Statements/Animal-Air-Transport.html*).

**Chapter Advocacy Outreach Program.** This program was developed to help physiologists become more effective advocates by providing speakers at APS Chapter meetings. It is a joint project of the APS Science Policy and Animal Care and Experimentation Committees. The Office of Science Policy provides information to the Chapter Advisory Committee each year concerning the program and providing a list of sample topics. Chapter representatives are invited to request a speaker, with the APS covering that person's travel expenses. The Office of Science Policy received three requests in 2013; two in 2014; one in 2015; and three in 2016. To date, no requests have been received in 2017.

**@SciPolAPS.** This is the Twitter feed the APS Office of Science Policy uses to disseminate information about science policy issues, including animals in research. The staff typically puts out about six tweets per day, and about 90% of these tweets typically get some kind of response, i.e., a retweet or a comment. As of June, 2017, @SciPolAPS had nearly 2,500 followers, and some of these individuals are well known in the fields of science policy and science communications. Nearly 18% of those who follow @SciPolAPS have at least 1,000 followers of their own, whereas 5.8% have at least 5,000 followers. In addition, five of those who subscribe to the feed have over 1 million followers.

**States United for Biomedical Research.** The APS provides support to state-based efforts to defend research through States United for Biomedical Research, a consortium of research advocacy groups.

*Council accepted the report of the Animal Care and Experimentation Committee.* ●

# Awards Committee

Sean D. Stocker, Chair

## Career Enhancement Awards

The RCEA ($20,000) and TCEA ($10,000) are offered once per year (spring) and reviewed by the Awards Committee (June). Regular APS members (>2 years) are eligible to apply for either award. In 2016, the evaluation criteria were reassessed for both awards, and new metrics were developed. Unfortunately, the committee did not have access to these documents and began working on newly revised criteria this past spring (2017). These documents are still in revision due to a recent Awards Committee meeting for the RCEAs and TCEAs. Finally, an NIH scoring scale was adopted for all applications.

**2016 RCEAs (total number of applications: 8)**
- Pooneh Bagher (Texas A&M)
- Sarah Lindsey (Tulane)
- Lucienne Morcillo (Federal University of Rio de Janeiro)
- Srinivas Sriramula (LSU Health Science Center)
- Steven Swoap (Williams College)

**2017 RCEAs (total number of applications: 16)**
- Eunhee Chung (University of Texas at San Antonio)
- Paige Geiger (University of Kansas Medical Center)
- Jaume Padilla (University of Missouri)
- William Schrage (University of Wisconsin-Madison)
- Alexander Staruschenko (University of Wisconsin-Milwaukee)

**2016 TCEAs (total number of applications: 8)**
- Lisa Harrison-Bernard (LSU)
- Fernanda Marondes (Piracicaba Dental School, University of Campinas)
- Susan Marsh (Washington State University)
- Leslie Sprunger (Washington State University)

**2017 TCEAs (total number of applications: 4)**
- Josef Brandauer (Gettysburg College)

## Young Investigator Awards

APS supports four awards for young investigators (postdoctoral fellows, residents, early career stage professionals):
- Arthur Guyton Award for Excellence in Integrative Physiology
- Lazaro J. Mandel Young Investigator Award
- Shih Chun Wang Young Investigator Award
- Dean Franklin Young Investigator Award

The submission deadline is shortly after the Experimental Biology abstract deadline. Applications are reviewed and discussed in December/January. Awards are presented at the EB meeting. The number of applications has remained relatively stable over the past 3 years.

**Table 1.** ***Number of applications***

| Award | 2015 | 2016 |
|---|---|---|
| Arthur Guyton Award | 7 | 9 |
| Lazaro J. Mandel Award | 7 | 2 |
| Shih Chun Wang Award | 8 | 5 |
| Dean Franklin Award | 13 | 8 |
| Total | 35 | 24 |

## 2017 Awardees (Presented at 2017 Experimental Biology Meeting)

**Arthur Guyton Award for Excellence in Integrative Physiology**
- Justin L. Grobe (University of Iowa)

**Lazaro J. Mandel Young Investigator Award**
- Prabhleen Singh (University of California - San Diego)

**Shih Chun Wang Young Investigator Award**
- Jin O-Uchi (Cardiovascular Research Center, Brown University)

**Dean Franklin Young Investigator Award**
- Aaron Polichnowski (East Tennessee State University)

## Award Committee Activities

**Archiving Documents and Standard Operating Procedure.** A library has now been created on APS Connect for the Awards Committee. The intent of the folder is to provide a database for award descriptions,

award evaluation criteria, contact information, and a Standard Operating Procedure (SOP) document.

**Development of an Awards Committee SOP.** The Awards Committee has begun drafting an SOP to define committee member roles and conflict of interest policy. The document should assist the new committee chair and members regarding roles and responsibilities on the committee.

**Outcome and Impact of the Awards Program.** The Awards Committee has indicated that the RCEAs, TCEAs, and other awards need to be assessed on a regular basis. The committee will develop assessment surveys to distribute to awardees on an annual basis.

*Council accepted the report of the Awards Committee.* ●

# Career Opportunities in Physiology Committee

Thomas A. Pressley, Chair

The Career Opportunities in Physiology Committee (COPC) serves as a resource for current information regarding career options in physiology, professional development at diverse levels, and fostering career interest in physiology.

## Career Development at Experimental Biology

In 2017, committee members Clintoria Richards-Williams and Josef Brandauer chaired the session titled, "The Many Facets of a 'Teaching Career." The purpose of the symposium was to identify likely positions and succeed in "successful teaching." Experts from a variety of institutions with diverse teaching loads spoke for about 25 minutes each, and then participated in a short panel discussion. The workshop drew a good-sized group of about 150 attendees. Recording of these talks, as well as additional materials, are being prepared for posting on the APS website.

For 2018, committee members Josef Brandauer and Bryan Becker will co-chair the COPC Symposium, "Hallmarks of and Ground Rules for Productive Collaborations in Science."

## Career Presentations at APS Conferences

Since 2006, the committee has worked with the organizers of APS conferences to include career development sessions and/or activities at those meetings. These have included both informal sessions at the APS table/booth and formal sessions with a room assignment. The committee receives support from the APS for a workshop at one APS conference per year. APS member Jennifer Sasser chaired a career development session at the "Inflammation, Immunity and Cardiovascular Disease" conference held in Westminster, CO, August 24-27, 2016. APS member Magdalena Alonso-Galicia chaired a session at the "Integrative Biology of Exercise VII" conference held in Phoenix, AZ, November 2-4, 2016.

## Undergraduate Summer Research Fellowship Program

The APS Undergraduate Summer Research Fellowship (UGSRF) Program was established in 2000 with the goal "to excite and encourage undergraduate students worldwide to pursue a career as a basic research scientist." It has developed into a flagship APS program that influences hundreds of undergraduates. It supports up to 24 full-time undergraduate students annually to work in the laboratories of established investigators. Faculty sponsors/advisors must be active members of the APS in good standing. These fellowships provide a $4,000 summer stipend to the student (10 weeks of support), a $300 grant to the faculty sponsor/advisor, and a $1,300 travel award/reimbursement for the students to attend and present their data (if appropriate) at EB. Financial support for the program is provided by the APS and the host laboratories. In addition to their laboratory work, the UGSRFs complete interactive online assignments that explore how to structure a research project/series of experiments and that explore/discuss physiology-related careers.

In the application cycle for 2017, 92 eligible applicants were reviewed by the Committee, and the names of 24 suggested awardees were forwarded to Council for approval. Over the 18-year history of the program, the program has received well over 1,000 applications, with an average funding rate of 33%. Evidence that the program is indeed encouraging interest in research is provided by the continued involvement of UGSRF students in APS activities. Nearly all 2016 UGSRF students attended EB. Eight were awarded 2017 Barbara A. Horwitz/John M. Horowitz Outstanding Undergraduate Abstract Awards, and five went on to win 2017 David S. Bruce Excellence in Undergraduate Research Awards.

## APS Undergraduate Research Excellence Fellowship Program

The APS Undergraduate Research Excellence Fellowship (UGREF) Program was launched in 2013 with the goal "to encourage undergraduate students worldwide who are already involved in research to continue on that track toward a career as a basic research scientist." Students with previous research experience are encouraged to apply. The UGREF Program annually supports up to six full-time second- to fourth-year undergraduate students who have >9 months of research experience to continue working in the laboratories of established investigators. Both students and faculty sponsors/advisors must be active members of the APS in good standing. These fellowships provide a $4,000 summer stipend to the student, a $300 grant to the faculty sponsor/advisor, and a $1,300 travel award/reimbursement for the students to attend and present their data at EB. As with the UGSRFs, funding for the UGREF program is provided by the APS and the host laboratories, and awardees are selected by the committee with subsequent approval by Council.

The UGREFs complete interactive online assignments exploring how to structure a research project/series of experiments and exploring/discussing physiology-related careers. The UGREF activities are built on UGSRF activities, developing UGREFs' writing and presentation skills. UGREFs are also required to submit an abstract to EB.

In the application cycle for 2017, 30 applicants were reviewed by the committee, and the names of six suggested awardees were forwarded to Council for approval. Over the 5-year history of the program, the program has received well over 100 applications, with an average funding rate of 20%. Although a relatively new APS initiative, the UGREF program is achieving its goal of encouraging continued interest in research for experienced undergraduates while maintaining a rigorous review process. Janine DeBlasi, a 2016 UGREF awardee, received both a 2017 Barbara A. Horwitz/John M. Horowitz Outstanding Undergraduate Abstract Award and a 2017 David S. Bruce Excellence in Undergraduate Research Award. She continues a tradition of outstanding presentations by UGREF awardees at EB.

## Undergraduate Orientation Session at EB

Since 2008, all undergraduates who submit a first-author abstract to APS are invited to a special Saturday session. It is a joint project of COPC and the Education and Trainee Advisory Committees. The session includes "how-to" presentations on making the most of the EB meeting, making a poster presentation, and introducing oneself. It has served as the formal recognition session for the UGSRFs. Again this year, for the third time, it also served as the formal recognition session for the UGREFs, and STRIDE and IOSP Fellows. It serves as an informal recognition for the Barbara A. Horwitz/John M. Horowitz Outstanding Abstract awardees, as well as for the video contest award winners.

The EB 2017 orientation session was organized by committee members Josef Brandauer and Rasna Sabharwal, and attracted well over 100 undergraduate students. As in the past, undergraduate students who submitted a first-author physiology poster were invited, and announcements were posted in e-mails to the trainee and All-APS listservs. Members of the APS Executive Cabinet welcomed the undergraduate students and presented certificates to the UGSRF, UGREF, STRIDE, and IOSP Fellows. All three committees were well-represented, with multiple members attending to talk with the students during and after the session and assist in distributing materials.

## APS Careers Poster

COPC sends a physiology careers poster to each U.S. and Canadian undergraduate biology/life sciences department to encourage students to visit the APS website and attract students to physiology graduate

work. The most recent poster has been distributed annually since 2012.

Since 2016, the poster has been sent as a hard copy to every life science department in the U.S. and Canada. A follow-up e-mail includes a digital file of the poster, and a second follow-up e-mail includes links for the undergraduate summer research fellowship programs. A digital copy of the poster is also available on the APS website.

## APS Career Cards

Based on feedback from teachers, the committee replaced a career brochure previously distributed by the APS with trading cards describing the work of diverse physiologists (career stage, research area, gender, racial/ethnic group, etc.) that are made available online and to teachers on request. COPC coordinates with the Education Committee so that career cards can be distributed as part of PhUn Week activities. During each calendar year, a different group of scientists are featured in a new set of cards. These career cards provide an opportunity for greater interaction with students. If students go to the website on the card, they can answer a question about the physiologist on the card, unlocking an additional biography card that they can print out. Overall, the cards offer a way to be more interactive with the students who receive them.

Feedback has been very positive from both physiologists and teachers about the trading cards. Sets have been distributed during PhUn Week activities, as well as at the APS booth during the National Association of Biology Teachers Conference, Association of Middle Level Educators Conference, and the EB 2017 Teacher-Student Workshop. These distributions are usually followed by a spike in web traffic on the APS Careers website, suggesting that links on the cards were used. As we accumulate a larger number of cards, the committee plans to work with the Education Committee to develop teaching resources that go along with the trading cards, providing a more effective learning tool for teachers and students.

In 2017, cards depicting Jane Reckelhoff, Dennis Brown, and three younger APS researchers were developed. COPC members Caroline Appleyard, Eileen Chang, and Bryan Becker developed a new Physio-Fact trading card, highlighting the gastrointestinal system.

## Developing Physiology Interest at the Elementary Level

The COPC works closely with the Education Office to develop materials appropriate for young students. An expansion of the current Phizzy Bear activity booklet provides age-appropriate activities that align with new K-12 science education standards. The new activity book is a resource for Physiology Understanding (PhUn) Week outreach to early elementary students. With the help of the Puerto Rico Physiological Society (an APS chapter), the activity was also translated into Spanish. It is expected that the artwork can be used for future early elementary projects, such as interactive web pages or digital interactive stories or activity books.

## Career Outreach Resources

The APS Careers website was developed by the COPC and launched in March 2003. It provides extensive resources for two major purposes: 1) to assist students and new and experienced physiologists in the development of their careers and 2) to help the general public gain a better understanding of the work that physiologists do. The site includes resources for elementary, middle/high school, undergraduate, graduate/professional, postdoctoral fellows, new investigators, established investigators, and the general public. Within each section, the user finds resource categories customized to their needs. The specific resources (such as biographies, hands-on experiments, career resources, etc.) are written at the appropriate educational level. It also serves as a dissemination site for the online versions of EB career-related sessions developed by the COPC and Women in Physiology and Trainee Advisory Committees. It also includes hyperlinks for career development resources associated with each skill listed in the APS-ACDP List of Professional Skills.

In 2011-2012, the career website was reconfigured to better fit both the new website content management system and to provide easier access to the growing set of professional development resources APS has developed for trainees. Features include a "Career Development and Mentoring Forum" that provides one-click access to APS resources (webinars, EB symposia, Mentoring Forum articles, etc.). All resources on the site are catalogued in the Life Sciences Teaching Resource Community digital library and pushed to the website as a folder of resources, allowing new materials to easily be added to individual pages. Along similar lines, the

committee has developed APS Career Presentations that consist of downloadable PowerPoint files for use at the middle and high school levels, as well as lower and upper undergraduate levels.

In 2015, committee members Erika Boesen and Norma Ojeda reviewed the content of the website and career presentations, respectively, and they raised concerns that the material is becoming out-of-date. As a result, the committee has conducted multiple discussions that review the purpose, objectives, and overall concepts for these resources as preparation for redesign and implementation of the overall APS website. We are currently waiting for feedback from the recent strategic planning session as we continue to refine these ideas.

## APS Local and Regional Science Fair Awards

This program encourages APS members to make an APS physiology award at their local or regional science fair at the elementary, middle, or high school level. The program provides opportunities for students from elementary through high school to learn what physiology is and to become "associated with the field" through recognition of their work. The program also builds connections between APS members and their local schools. Finally, it encourages local fairs to promote physiology-based projects to their students, since there are potential awards to be won. Student winners receive an APS t-shirt and a certificate for the best physiology project. The teachers of the winning students receive the APS book, *Women Life Scientists: Past, Present, and Future,* and an APS resource packet. Up to 100 awards are available each year on a first-come, first-served basis. Advertisements are posted in *The Physiologist* and the All-APS News Update e-mail for members, and sent to all past participants. The judge (or judges) must be an APS member in good standing who is willing to present the award on behalf of the APS to the student with the best physiology project (one winning student per science fair). Standard conflict-of-interest policies apply. After the science fair, the judge reports the winner's name and school via an online report form. Winners' names and pictures are posted on the APS Local and Regional Science Fair website.

During the 2016-2017 academic year, 17 requests for a science fair award packet were received from APS members. The COPC has worked to increase the number of APS members participating in the APS Local and Regional Science Fair Awards program. To this end, the COPC took advantage of dissemination mechanisms already in place during PhUn Week 2016 (webpage, electronic communications, participants, etc.). Importantly, these mechanisms allowed the APS Local and Regional Science Fair Awards program to benefit from the established connections between PhUn Week participants and local schools.

## Physiology Video Contest for Undergraduate and Graduate Students

In 2011, the COPC launched the APS video contest, *APS Presents...Phantastic Physiology Voyage: "Function Follows Form,"* designed to engage undergraduate and graduate students by creating engaging accurate, informative, and entertaining physiology videos for the general public. These videos must creatively demonstrate and/or explore a specific physiological function in 5 minutes or less (including credits). The video can be staged as a short play, commercial, news broadcast, talk show, music video, or documentary. The contest rules are based on a review of video contests sponsored by other professional associations and foundations. They include standards for copyright, use of humans or animals, and use of university facilities.

A selection committee consisting of members of the COPC and past APS Summer Research Teachers (invited) evaluates the videos and identifies a first-place video based on specific criteria for approval by Council. The YouTube links to the finalists' videos are promoted through the APS website and APS Facebook sites. The YouTube viewing statistics are used to name the Viewer's Choice Award-winning video (i.e., the video with the most "hits" on YouTube during the period leading up to EB). The contest makes two awards: a $750 first prize is given to the best video as selected by the committee, and $250 is given for the Viewer's Choice Award. The best video, selected by the committee, is shown and announced at the Undergraduate Orientation Session at EB. All of the videos meeting eligibility requirements are shown at the Undergraduate Poster Session at EB, and the winner of the Viewer's Choice Award is announced at this session.

The Committee received seven submissions for review in the 2017 cycle. The applicants included

both undergraduate and graduate students. The committee selected and forwarded to Council for approval "Goodpasture Syndrome and Kidneys" by Melissa Traver, Samantha Lyons, and Andrianna Walsh of Centenary College of Louisiana. The video takes advantage of a rapid-drawing technique. "Sleeping: What is Going on in Your Body?" by Mohamed Bonna of Mansoura University received the Viewer's Choice award, which was selected by the general viewing public. Multiple entries from the same schools suggest that undergraduate professors are encouraging students to create videos as part of their classes.

One of the advantages of the video contest is that the videos continue to promote physiology long after the contest has ended. Each video remains on YouTube (unless the video creator deletes it), and it can be accessed with links from other sites. For example, each video is catalogued in the Life Science Teaching Resource Community with an embedded YouTube link. An awardee from 2013, "Hillbilly Hypoglycemia," by Michael Ridlehoover, Alexis Wren, and Zachary Minter of Augusta University, has accumulated 4,322 views and inspired the development of a lesson plan by faculty members at Georgia Regents University that uses the video as its basis.

## Excellence in Professional Student (MD or DO) Research Travel Award

The APS Excellence in Professional Student (MD or DO) Research Travel Award program launched in 2013 with the goal "to encourage MD or DO students to attend, present their research, and participate fully in the Experimental Biology (EB) meeting." The award supports up to 10 MD or DO students who are first authors on abstracts to attend EB, present their research, and attend an orientation session. Faculty sponsors/advisors must be active members of the APS in good standing. Applicants are reviewed by the committee, and suggested awardees are submitted to Council for approval.

In the application cycle for 2017, 20 applicants were reviewed by the committee, and the names of 10 suggested awardees were forwarded to Council for approval. These students were matched with a mentor for EB, similar to what is done for the Minority Travel Fellows program. Fellows and mentors corresponded via e-mail and then met each other at an orientation session on Sunday morning. This session was organized by COPC members Rasna Sabharwal, Daniel Craighead, and Kellie Anne Hyndman. Assigned mentors and additional clinician scientists were also present and participated in one-on-one "speed mentoring" of the students during the session.

With a total of 43 awards provided by the program since its inception, it seems clear that the program's goals of encouraging MD or DO students to attend, present their research, and participate fully in the EB meeting are being met.

*Council accepted the report of the Career Opportunities in Physiology Committee.* ●

# Chapter Advisory Committee


Mari Hopper, Chair

The Chapter Advisory Committee (CAC) would first like to thank Michael (Mike) Sturek for his service as CAC chair from 2014 to 2016. Sturek turned the chair position over to Mari Hopper on January 1, 2017. Since the first of the year, CAC has embarked on a number of activities including the following.

*1)* Upon election, newly elected CAC chair worked with APS staff to update the CAC chapter roster and establish communication with all chapters.

*2)* In March of 2017, CAC met online, and established goals for the coming year.

- Establish frequent communication with and between chapters to identify their challenges and recognize best practices.

- Market chapter achievement. Employ marketing strategies to promote chapter achievements at the local and national level and utilize contributions to *The Physiologist* and APS website to expand chapter awareness among APS members. Establish a presence at EB meetings.

- Grow the chapter program. Leverage chapter expertise and enthusiasm to grow the program to 20 active chapters by the year 2020. Although chapters are expected to establish themselves as independent nonprofit organizations, individuals with a vision to establish a chapter should know that the CAC, other established chapters, and the APS are there to assist.

*3)* CAC chair gathered data via Annual Chapter Reports. Reports indicated that over the past year, 10 chapters held annual meetings at the state level. In all, over 1,000 participants (both APS members and non-members) gave over 500 talks and many awards, including at the high school and undergraduate levels. State meetings heavily involved trainees and provided mechanisms to not only present research but present opportunities for trainees and early career faculty to plan and lead meetings. Most states also included opportunities to "educate the educator," career development, and interactive sessions for high school and undergraduate students.

*4)* Meetings at EB provided a face-to-face opportunity for CAC to address an agenda that included ideas to strengthen chapters, promote new chapter development, improve procedures for data reporting and grant submission, and to establish a presence at EB 2018. A sub-committee of CAC members wrote and submitted a proposal for EB in 2018.

*5)* CAC grant applications were reviewed by APS members, and, pending APS Council approval, three chapters will receive funds to support outreach and education in 2017–2018.

Over the past year, 10 states held annual meetings. State meetings provide an excellent opportunity to learn from APS-sponsored keynote and advocacy speakers, as well as the vast variety of research and educational presentations. State meetings engage individuals, high school through senior faculty, many of whom do not have the opportunity to attend national meetings. State chapters are proud of the role they play in engaging trainees in planning and implementation of chapter activities, and thus preparing trainees for future leadership roles within the APS.

Currently, CAC is assisting California to establish a chapter and providing new chapter information to APS members in three additional states. If APS members are interested in learning more about how chapters promote the APS mission at the "grass roots" level, they are encouraged to contact the CAC chair, or, better yet, to attend a chapter meeting.

*Council accepted the report of the Chapter Advisory Committee.* ●

# Committee on Committees


Lisa Leon, Chair

The Committee on Committees (CoC) is comprised of one representative who is appointed by each of the 12 APS Section Steering Committees plus two councilors who serve as the chairperson and incoming chairperson. The responsibility of the CoC is to nominate individuals to serve on APS committees as well as outside bodies where APS is represented. The CoC members are responsible for identifying motivated and qualified members of their section who can served on an APS committee. The responsibility of the CoC is to weigh the expertise and diversity of the applicant pool to identify the strongest representative for each committee and to minimize the number of section representatives on each committee, when possible.

## Summary of Experimental Biology Deliberations 2017

The CoC meeting deliberations started with a summary of the types of diversity considerations that each APS section representative should consider as they review the applications. Bill Yates summarized diversity as being inclusive of geographic location (no two representatives from the same state or same institution), ethnicity, sex, and APS section. Yates emphasized that it is especially important to only have one representative from each state on the lobbying committees (e.g., ACE).

The CoC meeting was attended by a representative from each of the APS sections who provided a number of recommendations to improve the CoC process. The initial discussion focused on the need for subcommittees to decrease the workload for each CoC member who has to read through all of the applications (180 this year). It was suggested that subcommittees of two to three APS section representatives could be formed to review a subset of the CoC applications and bring those recommendations to the CoC meeting for discussion to ensure thorough review and streamline the process. Unfortunately, it became apparent that the committee chairpersons were often recommending individuals who were not eligible to serve on that committee. The section representatives suggested that the subcommittees could be responsible for recognizing this issue earlier in the process to streamline the procedure.

A second recommendation was to have a list of how many people are needed for each committee. The current procedure relies on a member list for each committee that shows the year that the individual is expected to rotate off. A list of the number and type of members needed for that year would be more appropriate and easier to decipher. It was emphasized that this could be used by the subcommittee to ensure an adequate number of applicants are identified. Table 1 provides a list of the positions that needed to be filled by the CoC during their deliberations at the Experimental Biology meeting. This is the type of list that the incoming chairperson will provide to the committee in 2018 based on their recommendation to help streamline the process. An additional column identifying which sections are currently represented on each committee will be provided to ensure adequate representation and limited or no section duplication.

**Table 1.** ***List of vacant positions and current section affiliations***

| Committee | No. of Vacant Positions | Current Section Affiliations on Committee |
|---|---|---|
| Animal Care and Experimentation | 4 members | WEH; Endo/Metab (3); GI; CV; Resp; CEPS |
| Awards | 5 members, 1 trainee | CNS (2); WEH; Renal; Teaching (2) GI |
| Career Opportunities in Physiology | 3 members (1 clinical position) | Cell; EEP (2); NCAR (2); Resp; CV; Renal; WEH (2) |
| Communications | 4 members, 1 trainee | Teaching; EEP; Endo/Metab (2); WEH; CV |
| Conference | 2 members | Renal (2); GI; CAMPS; CNS; EEP |
| Daggs | 2 members | CV; EEP; GI |
| Distinguished Physiologists | 5 members | Cell; GI; Endo/Metab; CAMPS; WEH; Resp |

| | | |
|---|---|---|
| Education | 5 members, 1 trainee | Teaching (2); Renal (2); CV (2); WEH; CNS; GI; Resp |
| Finance | 1 Chairperson, 1 young faculty member, 1 member (elected to Council) | CNS; Endo/Metab; Resp; GI |
| International | 4 members | NCAR (2); Resp; CNS (2); WEH (2); EEP; 1 unknown |
| Membership | 0 members | CV |
| Perkins | 1 Chairperson, 2 members | CV |
| Physiologist in Industry (Chairperson only) | 5 members | CV; CNS; Renal (2); GI; Teaching; 1 unknown |
| Porter Physiology Development | 3 members | GI (2); CV; Endo/Metab; NCAR; CNS (2); WEH; 1 unknown |
| Publications | 2 members | WEH; Teaching; CNS; Resp; Renal |
| Science Policy | 4 members | GI; CNS; Resp; Cell; CV; WEH; Comp; Endo/Metab; Renal |
| Women in Physiology | 1 Chairperson, 2 members, 2 trainees | CEPS (2); EEP; NCAR; Resp (2); WEH (2); EEP; CNS; Renal |

Additional recommendations from the section representatives is for the CoC chairperson to provide a separate list to the section representatives of the following: *1)* applicants who applied to multiple committees; *2)* trainee applicants only; *3)* chairperson applicants only. In addition, it would be helpful for applicants to indicate which committee they would prefer to serve on if submitting multiple applications. The CoC had to deduce this based on the section representative's knowledge of the applicant, which was not always thorough or sufficient. They also felt that earlier distribution of the membership spreadsheet for each of the committees would provide more adequate lead time to complete the process given the large workload.

Overall, the CoC representatives are enthusiastic about serving on the committee and are able to identify highly qualified and motivated section members to fill the vacancies, but the large workload and short time compromises their ability to review the applications as thoroughly as may be needed.

*Council accepted the report of the Committee on Committees.* ●

# Communications Committee

Barbara Goodman, Chair

## Membership

In 2017, the committee welcomed four new members (Grant Kolar, Megan Rhoads, Nicholas Stylopoulos, and Audrey Vasauskas) in addition to continuing members (Barb Goodman, Shawn Bender, Anne Crecelius, Kim Henige, Emily Johnson, Pascale Lane, Ben Miller, and Council Liaison Bill Yates). Three members (Melissa Bates, Jessica Faulkner, and Jorge Serrador) rotated off.

We received 17 committee applications to replace 5 members rotating off at the end of 2017. We are pleased to welcome the following new members to the committee for January 2018:

- Doug Curran-Everett
- Jeffery Tessem
- Amanda Leblanc
- Sandy Martin
- Yasina Somani
- Merry Lindsey (New Council Representative)

The committee is supported by APS marketing and communications staff (Stacy Brooks, Coleen Kitaguchi, Erica Roth, and Veronica Purvis).

## Ongoing Activities

The Communications Committee continues to serve in an advisory role to the Communications Office staff. In

addition, the ongoing tasks for the Communications Committee members include:

- EB 2017 Communications Symposium
- I Spy Physiology blog
- PhysiologyInfo (PIO) website
- AAS mass media fellowship
- Special projects and science communication educational activities

The committee meets three times annually, most recently at EB 2017 in Chicago. Topics discussed included the following.

### *EB 2017 Communications Symposium Wrap-Up*

This year's Communications Committee symposium, "Creative Science Communications through Improv," was facilitated by Chicago's Second City Comedy Troupe. We had a very good turnout, with approximately 43 of 50 spots filled. Attendees fully participated and gave positive feedback about the improv exercises. Several said it was a good reminder to be kind, listen, and reserve judgement. Committee members in attendance agreed that Second City Works did a great job facilitating participation. Second City sent two follow-up handouts, which the Communications Office shared with attendees. The handouts reinforced the ideas of working together to communicate effectively and the "listening to understand" concept they introduced during the session.

The session was organized by Session Chair Barb Goodman, Session Co-chair Anne Crecelius, and APS staffer Stacy Brooks.

The committee also discussed plans for the 2018 symposium and decided that they wanted to focus on social media. The session, tentatively titled "Social Media for the Professional Scientist," is still being organized. However, topics likely to be covered include established and emerging platforms popular with researchers, the use of analytics to measure social impact, and best practices of popular scientists on social media.

### *I Spy Physiology Blog*

Although the APS Communications Office handles day-to-day planning and management of the I Spy Physiology blog, the Communications Committee members and past-committee members continue to play a major role in the blog as ongoing blog contributors. So far in 2017, they have contributed 10 (of 24 total) posts on a variety of physiological topics. Committee member Audrey Vasauskas is serving as our new volunteer blog editor.

Posts that highlight APS members (either as writers or subjects) remain popular. The committee has plans to continue reaching out to and featuring members in the future by working on:

- Profiles of black physiologists during Black History Month in February, which could include profiles from the Porter 50th anniversary book.
- Profiles of Hispanic physiologists during Hispanic History Month (August 15 to September 15), which could include profiles from the Porter 50th anniversary book.
- An "Ask the Expert" series in which a specialist helps guide the reader through understanding a selected journal article.
- A "My Science Story" series, similar to the profiles written for Women's History Month profiles.
- Soliciting more male and underrepresented minority contributors (all of whom have not been as well represented among contributors to the blog).

Since launching in February 2015, we have published 123 posts, garnering nearly 33,000 views from nearly 22,000 unique visitors!

### *PhysiologyInfo.org (PIO) Website*

At the committee's meeting in December, the group voted to conduct a section-by-section audit of the PIO site. Committee members Anne Crecelius, Kim Henige, and Grant Kolar were the first to review sections (cardiovascular, exercise, and immune sections, respectively) and reported on their findings at EB.

They all noted, to the agreement of all members, that the sections were too long and had inconsistent formatting. A larger discussion followed about the purpose of PIO, including who our audience is and how we can better

disseminate information about basic physiological function. Suggestions included adding more visual elements (e.g., infographics), adding citations to the information that's currently provided, and using the PIO content to more prominently support the I Spy Physiology blog.

The committee agreed to look at three more sections of PIO by July 15 to determine whether the information is still current and accurate. Volunteers were:

- Pascale – Renal
- Audrey – Respiratory
- Ben – Muscular

### *AAAS Mass Media Fellowship«*

Jonathan Wosen, a PhD candidate at Stanford University, was the committee's top choice for the 2017 AAAS Mass Media Fellowship. He was selected for the fellowship and will be spending his summer at STAT News, a news organization focused on in-depth coverage of health and medicine. We will keep Council updated on his progress.

### *Video Outreach Project*

The committee's Council liaison at EB 2017, Bill Yates, conveyed to us Council's objective to constrain new project costs due to the large costs related to Society-wide strategic planning, the APS website rebuild, and other high-priority initiatives. Therefore, we are not presenting an action item related to creating a high-impact video outreach project to Council at this time. However, the committee is still in support of this idea. A summary of this project from our previous report is detailed below:

In summer 2016, the committee requested funds to work with video production vendor Explainr to create a six-video series of short, high-impact videos on interesting physiological concepts. Council responded that they would have liked for us to get bids from other companies. Since Explainr is the innovator in the science video space – creating popular videos and series for the American Chemical Society, and recently the American Society for Pharmacology and Experimental Therapeutics and others – competitors who could offer a similar caliber were few.

However, as a follow-up, the committee viewed presentations at its winter meeting from both Explainr and Leading Authorities, Inc., who have experience creating promotional videos for APS and others in the association space. Both companies presented bids for the work. Explainr cost less (6 videos for $45K) than LAI (3–4 videos depending on concept for $31K–$42 K). Overall, the committee unanimously thought Explainr would be better able to present physiology in a fun and unique way.

The Committee hopes to be able to move forward with this project in the near future.

Committee Chair Barb Goodman is available to answer any questions.

*Council accepted the report of the Communications Committee.* ●

# Conference Committee


David M. Pollock, Chair

The APS Conference Committee (APSCC) continued its effort toward reviewing and overseeing the conference program beyond EB and joint meetings with other societies. We held a face-to-face meeting at APS headquarters in October of 2016, where we reviewed reports from recent conferences as well as updates from pending conferences that were submitted by APS members. In the coming years, we have approved the following conferences.

### 2017

***Cardiovascular and Aging: New Frontiers and Old Friends*** will be at the Westin Westminster Hotel, August 10–14, 2017.

***Physiological Bioenergetics: Mitochondria from Bench to Bedside*** will be at the U.S. Grant Hotel in San Diego, CA, August 30 – September 2, 2017.

***Physiology and Pathophysiology Consequences of Sickle Cell Disease*** will be at the Embassy Suites Convention Center Hotel in Washington, DC, November 6–8, 2017.

### 2018

***Institute of Teaching and Learning*** will be held at the Convourse Hotel in Madison, WI, June 18–22, 2018.

***Cardiovascular, Renal and Metabolic Diseases: Gender-Specific Implications for Physiology*** is to be held in Knoxville, TN, September 30 – October 3, 2018.

***Intersociety Meeting: Comparative Physiology*** was approved for 2018 and will be held in Austin, TX.

### 2019

***Aldosterone and ENaC in Health and Disease: The Kidney and Beyond*** will be held at the Stanley Hotel in Estes Park, CO, October 2–6, 2019.

For the first time, the committee also met for a breakfast meeting at the EB meeting in Chicago. The new strategic plan will have a major impact on the APSCC's activities, and so it was important to discuss how the strategic plan may impact the committee's activities. It is clear that scientific conferences are viewed as extremely valuable to the membership and the society at large. However, there has been long-standing concern about the financial cost of having small conferences, so we conducted a review of how finances have been managed in recent years. This resulted in a decision by the Meetings Department along with the Business Office that the APSCC will be managing the budgets in coordination with the conference organizers going forward. The APSCC and Meetings Department are also working with the Development Office to discover new ways of gaining financial support for specific conferences. This includes applications for NIH funding. Most recently, we were able to obtain a R15 grant from the National Heart, Lung and Blood Institute to support trainee and early career investigator travel to the 2017 APS conference on sickle cell disease.

Importantly, one of the new strategic priorities identified in our new strategic planning process is that APS needs to expand the influence of the Society through conferences. Therefore, in the coming year, the conference committee will be reviewing how this can be achieved not only by increasing the number of conferences and developing a stronger brand identity, but also by developing a long-term strategy for addressing our members' needs and bringing the conference program into context with larger meetings such as EB. We look forward to receiving your conference proposals and ideas to strengthen the value of this critically important aspect of physiological research and discovery.

*Council accepted the report of the Conference Committee.* ●

## Distinguished Physiologists Committee


Peter K. Lauf, Chair

The Distinguished Physiologists Committee consists of 10 members. One of the primary duties of each committee member is to "develop and maintain liaison with emeritus members and members about to retire." This liaison is accomplished by submitting, on behalf of the Society, a personal 70th, 80th, 90th, or 100th birthday greeting. Each greeting includes an invitation for the senior recipient to inform APS about his or her current activities, interests, and whereabouts, and requests "words of wisdom" for younger colleagues. The historical and philosophical commentaries evoked by this invitation provide the material subsequently published in "News from Distinguished Physiologists" in each issue of *The Physiologist*. By the end of 2016, the Senior Physiologist Committee members sent birthday wishes to 127 members reaching age 70, 80 members reaching age 80, 53 members reaching age 90, and 7 members reaching the age of 100! Five response letters were received and published in *The Physiologist*.

Another responsibility of the Senior Physiologists Committee is to review applications and recommend to Council the annual awardees of the $500 G. Edgar Folk, Jr., Senior Physiologists Award. This award is designed to support the scientific activities of a senior member. In 2016, we received and awarded one application: Robert Wurster of Loyola University Medical Center.

*Council accepted the report of the Distinguished Physiologists Committee.* ●

## Education Committee


Jeffrey L. Osborn, Chair

The 2016–2017 fiscal year was very busy and filled with numerous accomplishments, including launching a new undergraduate physiology majors initiative. The committee awarded the ADInstruments Macknight Early Career Innovative Educator Award to APS member Katherine Wilkinson of San Jose State University for her novel lab titled "An Hypothesis-Driven Laboratory Component for an Upper-Division Undergraduate Neurophysiology Course." Her application and innovative teaching approach combines an authentic research experience with an active-learning classroom and provides a strong "systems approach" to the department's physiology curriculum. The EB 2017 Refresher Course titled "Curricular Innovation in Sex and Gender-Based Medical Physiology Education" was once again well attended and received very strong reviews. This year's course was headed by Education Committee member Karie Scrogin and featured Virginia Miller of the Mayo Clinic, Todd Vanderagh of the University of Arizona, Kent Thornburg of Oregon Health & Sciences University, and Marjorie Jenkins of Texas Tech University. The Education Office expanded the professional skills "online" training courses to include publication ethics. Summer field testers deemed this new course highly popular and needed. In keeping with expansion of undergraduate physiology majors, the committee and APS again sponsored keynote addresses at the Human Anatomy and Physiology Conference (M. Harold Laughlin) and the National Association of Biology Teachers (Larry Kenney). Undergraduate research activities at EB17 continued to grow. APS renamed the undergraduate abstract awards the "Barbara A. Horwitz and John M. Horowitz Outstanding Undergraduate Abstract Awards" in recognition of a generous gift from APS members Barbara A. Horwitz and John M. Horowitz, longtime supporters and mentors of undergraduate researchers. There were 91 applications reviewed, with 30 of these being named Barbara A. Horwitz and John M. Horowitz Outstanding Undergraduate Abstracts. In the final competition of these 30 awardees, Janine DeBlasi from the University of South Florida was awarded

the David Bruce Award for best undergraduate poster presentation. In all, 115 undergraduates presented their research at the EB 2017 undergraduate poster session. The NIH-funded Frontiers in Physiology: Integrating Programs to Build Communities of Practice (R25 OD016492) continues to train teachers in inquiry-focused instruction using first a year-long online program followed by a summer laboratory research experience and attendance at the spring EB meeting for additional training in workshop activities. Two regional APS chapters (Michigan and Puerto Rico) are in the process of developing regional communities to support K-12 science education. These regional pilot programs provide the foundation for future integration of the program into other APS chapters. APS PhUn week completed its 11th consecutive year of outreach, reaching 14,189 school children in 2016 and utilizing 608 volunteer scientists nationwide. PhUn Week 10-year participation awards were presented to Barb Goodman, Andrea Gwosdow, and Lisa Bernard-Harrison. The Education Committee has begun expansion of recognizing and supporting undergraduate programs in physiology that serve as exemplars in preparing students for physiology careers. Significant information and data are being gathered to bring forth to the membership where we believe there will be substantial impact on physiology graduate programs and careers in the immediate and distant future. A formal subcommittee has examined the availability of undergraduate physiology programs in U.S. institutions and produced a list of "best practices as defined for the development and delivery of undergraduate degrees/programs /curriculum/courses in physiology for the 21st century." The first Physiology Majors Interest Group (P-MIG) meeting was held May 18–19 at Michigan State University and hosted by Erica Wehrwein. The meeting was highly innovative and successful, with the group agreeing to expand on the contents for 2018 and holding an even larger conference at the University of Arizona, hosted by Claudia Stanescu. It is clear that this next arena for the discipline of physiology is critical to defining and branding of the Society as a whole. The committee is deeply committed and invested in making undergraduate physiology a major focus for APS both now and in the future. We strongly believe that an undergraduate physiology focus will provide the future of the APS membership through expanded numbers of students pursuing physiological and biomedical science research careers.

*Council accepted the report of the Education Committee.* ●

## Finance Committee

Meredith Hay, Chair

### Action Item: Approve the 2016 Audit Report

On June 1, 2017, the Finance Committee met via conference call with Marina Polyakova of Rogers & Company, the Society's audit firm. Rogers explained that fieldwork for the 2017 audit was performed by Rogers & Company from April 24, 2017 through April 28, 2017 at the APS office in Bethesda. Based on their work, Rogers & Company rendered an unqualified opinion (i.e., clean opinion) on the Society's financial statements, affirming that the statements presented fairly, in all material respects, the financial position of the Society at December 31, 2016 and 2015. The 2016 audit report noted no material internal control weaknesses or other areas of concern with respect to the Society's financial processes.

Polyakova discussed the audit report and an accompanying letter to the Finance Committee, Council, and Management of APS (board letter). The board letter is a required communication from the audit firm to the client. Rogers explained that the Society's financial statements were audited in accordance with generally accepted auditing standards. The 2016 audit did not include a review of the Society's records, in accordance with government auditing standards, because the Society's income from federal grants was less than $750,000. Only organizations with federal grant (or contract) income of $750,000 require such an audit.

Polyakova discussed all sections of the audit report, including her analysis of the financial statements. She

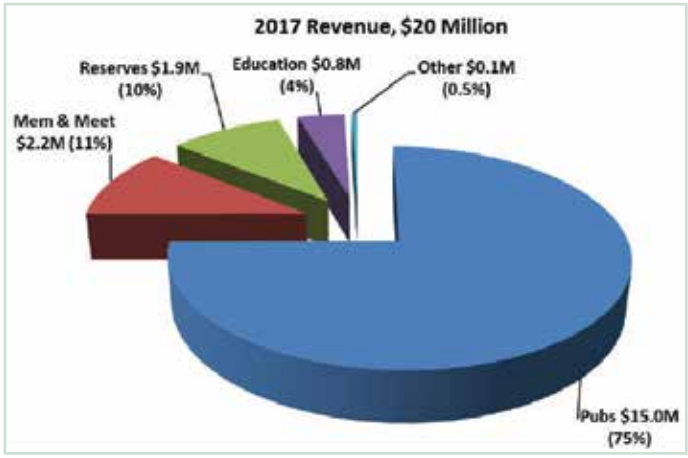
explained that the statements reflected a surplus of $1.34 million, which was the result of $2.31 million net investment income and a $961,000 net operating loss.

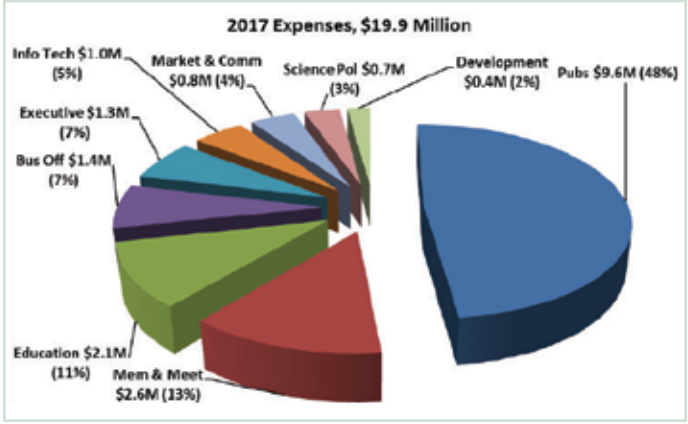
After several questions from the committee, a motion was made and seconded to accept the 2016 audit report by Rogers & Company. The motion carried unanimously.

## APS Budget

The Finanee Committee met in March to review 2016 financial activity and review the Society's 2017 budget. 2016 revenue was $19.8 million, which included $1.6 million in support from reserves, and expenses over the same period were $18.7 million, resulting in a surplus for the year of $1.1 million.

The 2017 operating budget has revenue of $20.0 million, expenses of $19.9 million, and a surplus of $91,500. The charts below represent the sources of revenue and the allocation of expenses, respectively, in the 2017 operating budget. The 2016 report and 2017 budget were approved by Council at its spring meeting.




## Investments

The Society's long-term invested funds at December 31, 2016 totaled $65 million. Of those invested funds, approximately $40 million is set aside as reserves, a portion of which is used to support the annual operating budget. The remaining $25 million is used to support the Society's numerous award programs and sections. The chart below reflects the overall growth of the Society's investments from 2012 to 2016 and the allocation between reserves and the award programs and section funds.


## Development Office

The development program, now in its third year of operation, has been seeking and cultivating additional philanthropic support for the numerous programs and awards offered by the Society. The development team, including John Van Ness and Megan Mitzelfelt, continues to work with the Society's leadership and staff to build relationships with individuals, corporations, and private foundations so that gifts and grants can be solicited for the Society's current endeavors and, ultimately, build the Society's endowed funds. The Development Office has built a full fundraising program with formal annual fundraising plan, including programs to seek annual, major, and planned gifts from APS members and corporate, foundation, and government grants and sponsorships.

### *2016 Annual Report*

The Development Office has produced the third APS Annual Report, which reviews the Society's 2016 accomplishments, finances, and lists all donors.

### *Strategic Partnership with ADInstruments*

At the end of 2016, ADInstruments signed an agreement to participate in a strategic partnership with APS for the next 3 years. As part of the agreement, ADInstruments will provide $111K over 3 years to support the Macknight Award, Claude Bernard Distinguished Lecture, section/group awards, and the 2018 Institute on Teaching and Learning. ADInstruments has also expressed interest in providing additional support for the LifeSciTRC, although this is not currently part of the partnership agreement.

### *Major & Planned Giving*

Significant progress had been made in identifying, contacting, and cultivating major and planned gift prospects. At present, we've identified and researched 440 individual members who may have interest in considering a gift. Personal calls on 168 prospects have been made to introduce them to the giving opportunities and to discuss their particular interests and philanthropic objectives. See the pipeline report below for a summary of these activities as of June 2017. Two planned gift commitments have been made thus far in 2017, and one major gift agreement is pending. Donor engagement and solicitation plans have been made for 11 individuals who appear ready for gift solicitation.

| Prospect Stage | As of June 2017 | As of June 2016 |
|---|---|---|
| Identified | 440 | 213 |
| Contacted | 300 | 158 |
| Visited | 168 | 73 |
| Promising prospects | 40 | 31 |
| Gift commitments | 5 | 3 |

### *Development Task Force*

Several APS members have been invited to serve on the new Development Task Force, and all have accepted the position. The first task force teleconference is planned for July and a full in-person meeting for sometime this fall.

### *Donor Surveys*

Development sent out a survey to current and past donors in early 2017 to assess donor satisfaction with and interests in giving to the Society. Past donors were also asked the reason(s) for discontinuing giving to APS in the past year. Results from the surveys show that the majority of respondents are satisfied with the services that APS provides to donors. There was some dissatisfaction with difficulty in giving online. Donors express the most interest in giving to support advocacy for federal research funding, to increase the general public's knowledge of physiology, and to section/group activities. Past donors cited changes in financial circumstances, support for another organization, or simply forgetting as the top reasons for not continuing their support in 2016.

## Information Technology

The IT Office recently began three projects that will significantly enhance the Society's ability to serve its members and all other constituents. IT recently added a staff person, Christine Zhou, who is experienced in the implementation, modification, and support of websites and customer-facing online applications. Christine's experience in leading such projects will be very helpful.

### *APS Connect (collaboration software): Enhancements and Relaunch*

APS leadership has voiced numerous concerns about APS Connect as it is currently designed. The current APS Connect communities are not providing or promoting the collaboration as intended. The plan is to *1)* improve the organization, appearance, and functionality of the communities' homepages; *2)* facilitate and promote opportunities for collaboration through use of communities; and *3)* implement reporting on participation and engagement metrics. Per the recommendation of APS Council, the IT and Membership Departments are in the early stages of working with SAC to determine what their requirements are with respect to the use of APS Connect. From the meetings, IT will develop a requirements document to guide them through the implementation of an improved APS Connect. IT hopes to roll out several new configurations and/or select changes to the functionality to address existing issues. Then they hope to relaunch a redesigned APS Connect at the end 2017 that can effectively promote community and collaboration.

### *APS Website Redesign and New Content Management System (CMS)*

The APS website is outdated and does not serve APS well as the central source of information about the Society or as a hub for its community. The APS CMS lacks the functionality of modern CMSs and is no longer

being enhanced and supported. IT has begun working with all the departments to identify current website users (both APS members and non-members). IT will go through the RFP process to identify the contractor best able to assist the Society in this major effort. The preliminary target launch date for the new website is the end of 2018.

### *Implement Informz (Marketing Automation Platform)*

APS would like to be able to more effectively capture and use data to carry out a strategic marketing and communications plan. The Informz marketing automation platform will provide the Society the capabilities necessary to implement and manage such a plan. Specifically, Informz will allow the Society to *1)* capture data on the interactions of our customers with our online services to both better understand our customers and their needs, and the level of usage for our various online services and products; *2)* provide the tools to develop and execute sophisticated marketing campaigns, including features like A/B message testing, personalized content, e-mails triggered by customer actions; and *3)* use marketing automation tools that can also be used for customer notifications and to improve recruitment and retention of members, subscribers, meeting attendees, etc. The Minding Your Business communications and strategic planning efforts are providing guidance to this effort. By July 31, 2017, IT hopes to complete the migration of existing e-mail marketing information to the Informz marketing automation platform while also collecting new customer information related to user activity related to e-mail sent by the Society and user visits to our websites. For the remainder of 2017, IT will roll out the new marketing automation capabilities to enhance current marketing of APS products and services, implement a corporate communications plan, and provide better tools for running select marketing campaigns.

*Council accepted the report of the Finance Committee.* ●

## International Physiology Committee


Eric Lazartigues, Chair

The role of the International Physiology Committee (IPC) is to assist APS by identifying and implementing ways in which APS can best serve its international members, achieve globally its goals of fostering education, scientific research, and dissemination of information in the physiological sciences, and raise its global stature.

The IPC assists APS in the review of international awards programs. The International Early Career Physiologist (IECP) travel awards program provides support for students, trainees, and junior faculty working outside the U.S. to attend Experimental Biology (EB). The IPC reviewed 45 applications and recommended support of $1,000 be given to the top 12 ranking applications.

The IPC also reviewed applications for APS travel awards to attend the International Union of Physiological Sciences – Rio de Janeiro. The IPC reviewed 78 applications for the 2017 IUPS Congress Travel Award and recommended support of the top 53 ranking applications, of which 12 were from the U.S.

The International Opportunity Program aims to strengthen ties between APS and international societies on a global level, with a particular emphasis on underrepresented regions. The committee recommended five applications from the following individuals, each receiving $7,500:

- Alberto Dorta-Contreras, Havana Medical Sciences University, Havana, Cuba.
- Mangala Gunatilake, University of Colombo, Colombo, Sri Lanka.
- Celia Sladek, University of Colorado, Aurora, CO.
- Fernanda Marcondes, Piracicaba Dental School, University of Campinas, Sao Paulo, Brazil.
- Gabor Tigyi, University of Tennessee Health Science Center, Memphis, TN.

The deadline for IOP support applications for 2018 was extended to September 8, 2017.

*Council accepted the report of the International Physiology Committee.* ●

## The John F. Perkins, Jr. Memorial Award for International Physiologists Committee


Paul Davenport, Chair

The John F. Perkins, Jr. Memorial Award for International Physiologists promotes cultural exchange and scientific collaborations by providing supplementary aid to families of foreign scientists working for a minimum of 3 months in the U.S. In this way, young scientists are able to bring spouse and children, and thus make full use of the cultural exchange as well as the scientific benefits associated with an international collaboration. This award is intended to support the spouse's and children's visit to the U.S. for postdoctoral fellows and junior faculty from overseas. Application for the Perkins Award must be made jointly by the host, who must be an APS member, and the visiting scientist. The recipient receives funds generally not exceeding $5,000.

Applications for the Award are accepted in the spring and fall, with application deadlines of April 15 and October 15. For the October 2016 deadline, the committee received two applications and funded both applications. Susumu Hosokawa will be working at the University of Arizona in the lab of Jason X. J. Yuan. Mirza Beig will be working at the University of North Texas Health Science Center in the lab of Steve Mifflin. For the April 2017 deadline, the committee received two applications and funded one applicant. Supaporn Kulthinee will be working at Tulane University Health Science Center in the lab of Luis Gabriel Navar.

*Council accepted the report of the John F. Perkins, Jr. Memorial Award for International Physiologists Committee.* ●

## Joint Program Committee


Robert Hester, Chair

### Experimental Biology 2017

The 2017 EB Meeting was held in Chicago from April 22 to April 26. Participating societies were APS, AAA (anatomy), ASBMB (biochemistry), ASIP (pathology), ASN (nutrition), and ASPET (pharmacology). The APS hosted five guest societies: the Microcirculatory Society (MCS), the Biomedical Engineering Society (BMES), American Federation for Medical Research (AFMR), and The Physiological Society (Physoc). Overall paid scientific registrants across all societies was 12,527, with 1,504 ancillary registrants. APS had 395 sessions in total: 249 poster sessions, 62 symposia, 51 featured topics, 19 lectures, 2 workshops, 1 refresher course, 2 awards sessions, and 9 special sessions.

The meeting opened with several unique sessions on Saturday, April 22, including the traditional *Refresher Course* this year on "Curricular Innovation in Sex and Gender Based Medical Physiology Education." APS sponsored two unopposed Techniques and Technology in Physiology Workshops on Saturday, April 22, titled "Choosing the Right Diet for Your Animal Model" and "Using Ultrasound to Teach Cardiovascular Physiology and Anatomy" (cosponsored by American Association of Anatomists). Saturday featured *Physiology in Perspectives: The Walter B. Cannon Memorial Award Lecture* presented by Michael Welsh from the Howard Hughes Medical Institute at the University of Iowa. The lecture was followed by an EB-wide opening reception free to all registrants.

APS also held the *Henry Pickering Bowditch Memorial Award Lecture* featuring Brant Isakson of the University of Virginia and 12 section-sponsored distinguished lectures. APS also sponsored four integrative symposia systems:

- Hypoglycemia: Neural Pathways of the Glucose Counter-Regulatory Response, Hypoglycemia Unawareness and Its Treatment
- Engineering for Health: Integrating Engineering and Physiology to Combat Disease
- Exercise Intolerance in Metabolic, Pulmonary and Cardiovascular Diseases: Did We Forget the Brain?
- Impact of Exosomes on Muscle Atrophy, Hypertrophy and Myogenesis

The APS President's Symposium Series was organized by Jane Reckelhoff around the theme *Research Advances in Sex/Gender and Developmental Programming of Chronic Diseases* and included three symposia and one lecture:
- Women and Health Research
- Sex Differences in Physiology and Pathophysiology
- Developmental Programming of Diseases
- Nobel Prize in Physiology or Medicine Lecture "The Road to Stockholm: A Nobel Mission" presented by Louis Ignarro, UCLA School of Medicine

The Nobel lecture was followed by a ticketed closing banquet open to physiologist registrants.

A total of 8,389 abstracts, 7,525 regular and 864 late-breaking, were programmed by the six EB 2017 sponsoring societies. Total abstracts submitted for EB 2017 increased by 8% over EB 2016, which received a total of 7,761 abstracts.

There were 8,389 abstracts submitted to EB 2017, with APS members submitting 2,478. EB 2017 represented 1,291 greater registrants than EB 2016. The total number of undergraduate/high school members, teachers, and students was 2,286, an increase of 367. Exhibitor registration decreased by 148, a continual trend. There also has been a continual decrease in number of exhibitor booths and companies over the last 4 years.

## Experimental Biology 2018

The Joint Program Committee (JPC) met at EB 2017 on Saturday, April 22 to begin organizing EB 2018 to be held Saturday, April 21 through Wednesday April 25 in San Diego.

The JPC summer meeting was held on June 19–20, 2017 in Crystal City, VA, to schedule rooms by day and time for the platform sessions, and to minimize scientific overlap.

At EB 2017, Council finalized several decisions that affected EB 2018 programming. APS Council voted to remove Wednesday from the scientific sessions starting in EB 2019. Therefore, in anticipation of EB 2019 scientific sessions being on Sunday through Tuesday, we modified the schedule for EB 2018 as follows (with Council approval):

- Career session by the Women in Physiology Careers and Trainee Committees will occur from 7 to 8 AM. Maytas is developing this schedule, which is expected to occur in multiple rooms across multiple days.

- All oral sessions will be 90 minutes in length and will be from 8:30 to 10:00 AM, 1:30 to 3:00 PM, and 3:30 to 5:00 PM on Sunday through Wednesday. The 3:30 to 5:00 session on Wednesday will be the Nobel lecture.

- Poster sessions will run from 10 AM to 12 PM each day. There will be no oral sessions occurring concurrently with the poster.

- The lunch break will hopefully allow members to visit the exhibitors.

- To have a cross-society open ceremony, the Tang Lecture will be Saturday from 6 to 7 PM followed by a meeting-wide reception.

- The Cannon Lecture will be moved to Sunday from 5:30 to 6:00 PM.

- The Bowditch Lecture will be Monday from 5:30 to 6:00 PM.

We had 24 section and interest group JPC reps attend the meeting. We developed 20 tracks for the EB 2018 meeting and then programmed the scientific sessions. JPC representatives were informed that speakers and chairs were not allowed to speak in or chair multiple sessions. JPC reps will contact session and FT chairs about correcting this issue. The online submission program for symposia and featured topics has been developed but will have some changes implemented to improve the ease of use. For EB 2019, all symposia and featured topics will be submitted online. This will allow for sections to easily review all submissions to determine possible scientific overlap. The program will allow for tracking speakers speaking multiple

years in a row. Programming of posters from received abstracts will be performed electronically in December or January. Abstract submission dates have not been determined. Several APS sections and interest groups added "Nutrition" to abstract categories to attract other members of EB to APS sections.

Translational Physiology Interest Group will again be selecting translational abstracts for an unfunded session where investigators will provide 5-minute presentations on translational physiology. The meeting will also feature sessions organized by the APS Publications, Careers in Physiology, Public Affairs, Women in Physiology, Trainee Advisory, Physiologists in Industry, and Education Committees.

At the Fall 2015 Council Meeting, Council approved JPC's goal to decrease the number of abstract categories to foster scientific interactions across sections and interest groups. Due to all of the other issues with shortening the meeting by 1 day, this has not been completed.

Due to changes in personnel in the Office of Scientific Meetings at FASEB, which handles the meeting planning, there has been no projections as to the attendance or cost for EB 2018.

The deadline for Call for Abstracts will be December 7, 2017.

The JPC received 11 integrative physiology symposium proposals for EB 2018, of which the following have been selected. Each of the selected symposia was vetted by the members of the JPC and some changes were suggested.

- Remote Ischemic Preconditioning, Hypoxic Preconditioning, Vital Organ Protection
- Bioartificial Organs: Using Donor and Synthetic Scaffolds
- Tissue-Distributed Control of Sex Differences in Diabetes and Cardiovascular Disease
- Extracellular Matrix Remodeling and Integrin Signaling in Metabolic Diseases

In addition, two workshops are scheduled on the first day of EB 2018:

- Sex as Biological Variable (Yosten)
- Wearable Devices (Sandberg)

The President's Symposium Series, organized by Dennis Brown and titled *Exosomes: The New Frontier,* will feature a series of three symposia and a Nobel Lecture:

- Cell Biology of Exosomes
- Exosomes in Diagnostics and Therapeutics
- Pathophysiology of Exomes
- Nobel Prize Award Lecture: Undetermined at this time

The Cannon Lecture will be given by Ole H. Petersen. The Bowditch Lecture will be given by Yatrik M. Shah.

At the end of the meeting, JPC had a general discussion about possible changes in EB 2019. With the loss of Wednesday, there will need to be major changes. Two options were presented:

*1)* There is a decrease in the number of oral sessions, anywhere from 20 to 25 sessions.

*2)* Increase the number of rooms each day. Adding two rooms each day will still require a cut of ~5 sessions. The concern is that adding rooms would increase the scientific overlap of oral sessions.

No clear preference was reached.

Additionally, there was a discussion concerning the JPC meeting that occurs Saturday at EB. It was recommended and approved by JPC that at EB 2018 the JPC would meet Tuesday at noon to have a general discussion about EB 2018, such as hot topics for EB 2019, room sizes, and any other items that would affect EB 2019 programming. It was then recommended that, in EB 2019, the Saturday JPC meeting would be moved to Thursday morning to provide time for more detailed discussions, such as about symposia/featured topics for EB 2020, in an attempt to minimize scientific overlap and possibly develop a shared oral session.

*Council accepted the report of the Joint Program Committee.* ●

# Membership and FAPS Committee


Robert Brock, Chair

A continued priority of the APS is to actively attract, meet the needs of, engage, and retain the entire membership. The new Fellow of the APS (FAPS) Program has been implemented to play an active role in engaging members of the Society. As the committee proceeded through the annual FAPS review process, there was a need to further fine-tune the approval process. As a result, a subcommittee was established to evaluate the rigor of the FAPS applicant criteria and suitability of application scoring.

## Membership

The total number of members is 10,711 (compared with 10,830 from a year ago). [Note: 1,197 (752 regular) members were dropped on 04/01/2016 as a result of unpaid dues.] There was a net gain of 251 regular, 281 graduate student, and 61 undergraduate student members since the fall 2016 status report. The current retention rate is 88% for all members; 92% for regular members.

During the previous year, there has been an on-going interaction with APS Marketing toward promotional campaigns to more effectively recruit and retain membership. The following efforts have been productive and will be continued:

*1)* Solicited non-member editorial board members and EB invited speakers.
- 43 editorial board members applied; 27 renewed for 2017.
- 8 non-member invited speakers applied; 6 renewed for 2017.

*2)* APS exhibited at competing meetings, placed advertisements in related journals, and posted marketing items to various social media outlets.

*3)* Authors publishing in APS journals who are non-members are solicited to join.

*4)* APS provided staff and a connected computer to receive membership applications and dues payments at APS Exhibit booth and kiosk during meetings.
- 39 new members.

*5)* Members can place credit cards on file for auto-renewal of subsequent year's dues.

A decade ago, the Finance Committee recommended and Council approved increasing APS membership dues $15 every year until 2018, when the regular membership dues hit $200. As a result of the challenges encountered by the current financial, regulatory, and academic climates, standing APS membership dues and criterion were reviewed. The committee recommended that the cost of membership remain at current rates. The committee also endorsed an adjustment in benefits so that affiliate members may also be eligible for membership meeting registration discount(s).

Moreover, in addition to the auto-renewal option for payment of membership dues, the committee recommended that payments be permitted on a multi-year basis. These multi-year payments should be made in the amount of the current year's rate. Individuals who pay in advance will not incur additional charges should dues increase in future years, but if a member chooses to resign with dues having been prepaid, then the remaining balance will not be refunded.

Last, it is believed that the transition of a graduate student to regular membership should be aligned to the date of the degree, not a time-limit on the graduate student membership. As a consequence, the current graduate student membership requirements should now read as follows:

> Graduate student membership is open to any student working toward a terminal graduate degree in physiology or related field and who is actively engaged in physiological work. Graduate student membership is limited to 5 years or upon receipt of the graduate terminal degree, whichever is sooner.

*Council accepted the report of the Membership and FAPS Committee.* ●

# Physiologists in Industry Committee

Matthew R. Zahner, Chair

## EB 2017 Physiologists in Industry Committee Symposium

The 2017 symposium titled "Nitric Oxide Pathway Modulation for Therapeutic Intervention and Exercise Enhancement" was organized and chaired by John Mattson and co-chaired by Kavaljit Chhabra (postdoctoral recipient of 2016 Physiologists in Industry Committee Novel Disease Award). The session was co-sponsored with the EEP section. Attendance was excellent, with more than 300 attending, and Mattson was invited to submit the symposium as an invited manuscript to the *Journal of Applied Physiology*.

## EB 2017 Novel Disease Awards

This award recognized a graduate student and a postdoctoral fellow whose investigations have been designated by the Physiologists in Industry Committee as outstanding examples of experimental research. The winner of the postdoctoral award was T. Dylan Olver (University of Missouri, Columbia) for the project titled "Elucidating the Mechanisms of Pial and Paraenchymal Cerebral Small Vessel Disease in a Novel Porcine Model of HFpEF." The winner of the predoctoral award was Kasi McPherson (University of Mississippi Medical Center) for the project titled "Treatment with Lisinopril Delays the Early Progression of Proteinuria in a Novel Model of Prepubertal Obesity."

In an effort to broaden the award focus to include more areas of research that is translatable to industry, the Physiologists in Industry Committee was approved to change the name of the award from "Novel Disease Model" to "Translational Research Award." Briefly, this award recognizes one predoctoral and one postdoctoral trainee whose area of experimental research is translatable to industry applications. Applicants will be evaluated on their first-author EB meeting abstract, supplementary description of their project, and career goals.

## Physiologists in Industry Committee Mixer

The 15th annual Physiologists in Industry Committee Mixer was held on Sunday, April 23, 6:45–8:00 PM at the Chicago Hyatt Regency McCormick Place. The annual Physiologists in Industry Committee Mixer is traditionally a great opportunity to network with industry and academic APS members alike. The mixer is designed to attract trainees and engage them in discussion about careers, research, and opportunities in industry positions. This year, we included a cash bar and free hors d'oeuvres. The mixer was well attended and provided a great chance for meaningful industry career opportunity discussions.

## EB 2018 Physiologists in Industry Committee Symposium

To foster greater interaction among sections, academia, and industry, the 2018 Physiologists in Industry Committee symposium will focus on basic sciences topics with preclinical stages of development and translation that have broad appeal to cross-sectional APS members. The title of 2018 PIC symposium is "Biosensors Advancing Health and Disease Research." The session will be coordinated and chaired by Brandon Bucher and co-chaired by T. Dylan Olver. Boucher is an active member of the committee, and Olver is our 2017 Novel Disease Model Award recipient at the postdoctoral level. We are looking forward to seeing you all at the EB 2018 events and Physiologists in Industry Committee Symposium on Monday, April 23, 2018, 1:30–3:00 PM.

*Council accepted the report of the Physiologists in Industry Committee.* ●

# Porter Physiology Development and Minority Affairs Committee


Layla Al-Nakkash, Chair

## 50th Anniversary of the Porter Physiology Development Program

APS is celebrating the 50th anniversary (1967–2017) of this groundbreaking fellowship program (described below), with various commemorations and an EB 2017 brunch event. The success of this 50th anniversary celebration was a testament to the hard work of the Porter 50th Anniversary Honorary Committee: Pamela Gunter-Smith, Nelson-Escobales, Rayna Gonzales, H. Maurice Goodman, Jean A. King, Keisa Williams Mathis, Nathanial G. Pitts, Annabell C. Segarra Marreno, and Martin Frank, along with APS Staff. A commemorative plaque was made, including the names of all Porter Fellows in the first 50 years of the program; the plaque will be hung in the APS offices this fall. An online and printed compendium of Porter Fellows with a description of their research was produced; attendees at the 50th anniversary celebration brunch received a copy of the booklet. This booklet includes interviews with selected Porter Fellows, highlights all Porter Fellows from 1967 to 2017, and recognizes the pioneers of the Porter Fellowship (William Townsend Porter, A. Clifford Barger, Eleanor Ison-Franklin). A wonderful glass commemorative plaque was also given to all Porter Fellows.

A celebratory 50th Anniversary Champagne Brunch was organized during EB 2017 to provide visibility of the program accomplishments to both Porter Fellows and potential funders. The 50th anniversary of this landmark program provided an opportunity both for the Society to celebrate its success in promoting diversity among physiologists and to garner recognition for its long-term support of diversity efforts. The anniversary provided an important opportunity to highlight the program to a wider audience (members and funders). All past Porter Fellows were invited, along with the APS leadership and local and regional foundation staff for fundraising purposes. Current Porter Fellows, Porter mentors, as well as Porter Committee members were also invited. Martin Frank gave a talk on the history and success of the Porter Fellows in APS, Pamela Gunter-Smith gave a talk about A. Clliford Barger, Layla Al-Nakkash presented the inaugural A. Clifford Barger award to Caroline Appleyard, and A. Clifford Barger's daughter also spoke about her father's influence. Approximately 115 Fellows, guests, donors, and staff attended this successful celebration.

## A. Clifford Barger Underrepresented Minority Mentorship Award

The Porter Physiology Development and Minority Affairs Committee (PPD-MAC) was pleased to present the inaugural A. Clifford Barger Underrepresented Minority Mentorship Award (*www.the-aps.org/barger*) at the 50th anniversary celebration brunch during EB 2017. The award promotes and embodies the APS goal of broad diversity among physiologists by recognizing mentoring as a highly valued professional activity that makes significant impacts on diversity in physiology. In its first year, the award received numerous outstanding applications. The committee selected Caroline Appleyard from the Ponce School of Medicine and Health Sciences in Puerto Rico as the inaugural awardee.

## The Porter Physiology Development Fellowship Program

This program encourages diversity among students pursuing full-time studies toward the PhD in the physiological sciences as well as encouraging their participation in the APS by providing 1- to 2-year full-time graduate fellowships and professional development activities. The program is open to underrepresented ethnic minority applicants who are citizens or permanent residents of the U.S. or its territories. Fellows are expected to be/become APS members, participate in EB, complete professional development activities, and participate in K-12 outreach. Since 1967, the program has provided more than 238 fellowships to 132 trainees. For 2017–2018, the PPDMAC selected eight fellowships to be awarded. The committee noted the high quality of applications received. The stipend paid to the Porter Fellows for 2017–2018 will again be $28,300, consistent with the NIH scale. Victoria Parker (University of Iowa)

was designated as the Eleanor Ison-Franklin Fellow for having the highest-ranked renewal application. In spring of 2017, the Porter Physiological Development Fund received the following contributions: $85,500 from the William Townsend Porter Foundation and $80,000 from the APS. The committee sincerely appreciates the continued support of the William Townsend Porter Foundation, APS member contributions, and the APS Council that makes these fellowships possible.

## Society for the Advancement of Chicanos & Native Americans in Science (SACNAS) National Conference

SACNAS provides conference activities for students, postdocs, educators, administrators, and researchers in all disciplines of science, mathematics, and engineering. In 2016, the theme for the SACNAS annual conference was "STEM Diversity and Public Understanding." APS exhibited at this October conference in Long Beach, CA. Over 4,120 attendees participated in the conference. Most attendees were undergraduates. Adrienne Bratcher (PPD-MAC Member) and Joshua Sheak (K-12 Minority Outreach Fellow) staffed the APS booth to promote APS diversity programs, K-12 resources and materials, and Undergraduate Summer Research Fellowships, as well as other APS awards, grants, and fellowships, trainee and career information, and APS membership.

## Annual Biomedical Research Conference for Minority Students (ABRCMS)

Now in its 16th year, ABRCMS continues to be the largest, professional conference for minority students to pursue advance training in science, technology, engineering, and mathematics (STEM). More than 4,050 individuals attended the 2016 ABRCMS in Tampa, November 9–12. The APS exhibited at the 2016 meeting to promote undergraduate programs, graduate study in physiology, and the APS programs for minority students. The APS was pleased to again provide $2,500 for cash awards for the most outstanding undergraduate presentations in physiology research. APS was represented by Carmen De Miguel (University of Alabama Medical Center; K-12 Minority Outreach Fellow) and Corey Reynolds (PPD-MAC Member). Fourteen undergraduate students received APS-sponsored awards for the best oral (3) and poster (11) presentations in the physiological sciences. Awardees were added to the APS Minority Physiologists and APS Trainee communities in APS CONNECT.

## K-12 Minority Outreach Fellows Program

The APS K-12 Minority Outreach Fellowship fosters communication between minority graduate and postdoctoral students and middle/high school minority life sciences students. Outreach Fellows must be past Porter Fellows or Minority Travel Fellows. The 2017–2018 Minority Outreach Fellow is Lindsey Stavola (Yale University). Stavola, a past Porter Fellow, attended EB 2017 and will attend ABRCMS later this year.

## Local Undergraduate Research Awards in Physiology (LURAP)

The Local Undergraduate Research Awards in Physiology (LURAP; *www.the-aps.org/LURAP*) offers members additional opportunities to promote physiology on their home campuses and aims to ensure awareness of, and advocacy for, the discipline of physiology. APS member Lorraine Turcotte presented a LURAP award (APS certificate, APS membership, and APS t-shirt) to Sarah Wong (junior in biological sciences) at the University of Southern California (April 12, 2017).

## Minority Travel Fellows Program

The PPD-MAC reviewed and recommended 42 award recipients for Minority Travel Fellowships to attend EB 2017. This year, 10 of those 42 travel fellows were supported with funding from Janssen Pharmaceutical Companies of Johnson & Johnson. This additional funding was largely the outcome of efforts made by past Porter fellow Raul Camacho, a scientist at Janssen. Since its inception in 1987, the APS Minority Travel Fellowship Program has awarded 995 travel fellowships to 612 undergraduate students, graduate students, and postdoctoral fellows, and to faculty members at minority institutions.

In addition to travel support, the Travel Fellows Program provides meeting mentors, an EB meeting orientation session, the Porter Reception (networking), a networking breakfast, and a luncheon with a guest speaker that honors the Travel Fellows. This year, PPD-MAC had a successful networking breakfast during EB. APS President-elect Dennis Brown actively participated in the networking breakfast. The Travel Fellows

Luncheon was held on Wednesday of the EB meeting. The Fellows heard from keynote speaker John Solaro (Director, University of Illinois Chicago Center for Cardiovascular Research). Solaro's talk, "What It Takes to Make the Passage into a Tenure Track Appointment," provided insights on dos and don'ts for entrance to successful tenure positions. His presentation can be viewed at *http://bit.ly/2eOghcS*.

### APS Minority Physiologists Facebook Fan Page

The APS Minority Physiologists page, managed by the PPD-MAC, has over 460 people who have viewed, liked, and received the page's weekly updates. PPD-MAC members submit monthly page postings covering topics including information about summer research programs, APS-sponsored workshops, mentoring, the National Research Mentoring Network (webinars), APS Living History project videos, and URM publishing, among many other postings. The direct link to the page is *www.facebook/APSMinorityPhysiologists*.

The PPD-MAC encourages all those interested in participating in these programs to contact the committee or the APS Education Office.

*Council accepted the report of the Porter Physiology Development and Minority Affairs Committee.* ●

## Publications Committee

Curt D. Sigmund, Chair

### Editor-in-Chief Appointments and Reappointments

At the March 21–23, 2017, meeting, the Publications Committee interviewed candidates for the editorship of the *American Journal of Physiology-Lung, Cellular* and *Molecular Physiology* and *Physiological Reviews*.

Rory E. Morty [Department of Lung Development and Remodeling, Max Planck Institute for Heart and Lung Research and Department of Internal Medicine (Pulmonology), University of Giessen and Marburg Teaching Hospital] was appointed editor-in-chief of *AJP-Lung*, succeeding Sadis Matalon. His term begins January 1, 2018.

Sadis Matalon (Distinguished Professor, Alice McNeal Endowed Chair Director, Division of Molecular and Translational Biomedicine, Vice Chair for Research Department of Anesthesiology and Perioperative Medicine, Director, Pulmonary Injury and Repair Center, The University of Alabama at Birmingham) was appointed editor-in-chief of *Physiological Reviews*, succeeding Dennis Brown. His term begins January 1, 2018.

The first terms of editors-in-chief Josephine Adams *(AJP-Cell Physiology)* and Bill Yates *(Journal of Neurophysiology)* were evaluated for reappointment to a second 3-year term, effective July 1, 2017. The Publications Committee unanimously reappointed each editor-in-chief to a second and final 3-year term. At the fall 2017 meeting, the Publications Committee will evaluate the third term of Barbara Cannon (European Committee Chair, *Physiological Reviews*).

Sue C. Bodine (University of Iowa) was appointed editor-in-chief of *Journal of Applied Physiology*, succeeding Peter Wagner, as of July 1, 2017.

The Joint Managing Board of *Physiological Reports*, representing the Publication Committees of the American Physiological Society and The Physiological Society, appointed Thomas R. Kleyman (Chief of the Renal-Electrolyte Division of the Department of Medicine at the University of Pittsburgh) to succeed Susan Wray as editor-in-chief of *Physiological Reports* as of January 1, 2018. Kleyman has served as deputy editor-in-chief of *Physiological Reports* since the journal's launch in 2013 and is a former editor-in-chief of *AJP-Renal Physiology*.

Morten Bækgaard Thomsen (Department of Biomedical Sciences at the University of Copenhagen) has been appointed as deputy editor-in chief, succeeding Thomas

Kleyman. Thomsen has served as an associate editor of the Journal since July 2015.

## 2017 Subscription Pricing

The Publications and Finance Committees accepted the recommended subscription and Legacy pricing for 2018, which was approved by Council at its spring meeting.

| | Tier 1 | Tier 2 | Tier 3 |
|---|---|---|---|
| Online | 1.0% | 2.0% | 4.5% |
| Print + Online | 5.0% | 5.0% | 5.0% |
| Print | 5.0% | 5.0% | 5.0% |

Individual and Member rate: 2%.

Legacy content follows Tier 3 online-only pricing.

## Discussion

### *A. From the Joint EIC Publications Committee Meeting: Enhanced Reproducibility: Where Should We Go in Another Year?*

It was recommended that the APS refer to the STAR Methods Guide from Cell Press (*http://www.cell.com/pb-assets/journals/research/cell/methods/Methods%20Guide.pdf* and *http://www.cell.com/star-methods*).

- The STAR Methods format is required for acceptance for Cell Press journals. It is not required for initial submission, but it is encouraged.
- The guide contains three main components: general instructions for authors, a file checklist for authors, and a reference sheet for editors for use during peer review
- Discourages "as previously reported"

It was recommended to

- Replace bar graphs with box and whisker plots
- Require full Western blots submitted as supporting data
- Offer more education about the ARRIVE guidelines
- Apply guidelines across journals; i.e., avoid separate guidelines by journal, but ok to pilot
- Consider enhanced reporting guidelines for humans

### *B. Conference Proceedings Initiative Assessment*

The Conference Proceedings initiative took effect with APS-sponsored meetings held from 2015 to 2016 for up to two meetings per year, by agreement between editor-in-chief and conference organizer, on a first-come, first-served basis. The plan called for assessment of the plan by the Publications Committee at its spring 2017 meeting to determine whether the initiative should be continued.

The key components of this initiative are:

- Selected participants are invited to submit short reviews or original research.
- Submission length up to 4 printed pages, 2 figures (or 1 table/1 figure), one in color.
- Standard ethical/scientific considerations apply. Overall impact is not a criterion. Extensive revisions or additional experiments should not be requested.
- Articles included in standard journal issue and appear in a separate, dedicated online TOC.
- Host editor-in-chief is in agreement with organizers on all details established for the conference articles.
- No author charges apply; publication costs are supported by APS.

**Uptake of the Initiative**

***AJP-Regulatory, Integrative and Comparative Physiology***

**Conference:** Cardiovascular, Renal and Metabolic Diseases: Physiology and Gender Conference, Annapolis, MD, November 17–20, 2015.

**Submitted, accepted, published:** 17 review articles were commissioned and submitted, 2 rejected, 1 revised, 5 published. Additionally, a Call for Papers on the topic was issued with a deadline of June 30, 2016.

**Articles submitted/published:** 15 articles submitted, 2 rejected, 1 in revision, 6 published as of this writing.

**Editorial:** An editorial describing the series was published in the November 2015 issue of *AJP-Regu* (*http://dx.doi.org/10.1152/ajpregu.00417.2015*).

The dedicated web page created to showcase these articles is at *http://ajpregu.physiology.org/gender.*

***Advances in Physiology Education***

**Conference:** Institute on Teaching and Learning Workshop held in Madison, WI, June 2016.

**Articles commissioned:** 8.

**Articles submitted/published:** 4 submitted / 2 accepted; 2 published.

**Editorial:** An editorial by Barbara E. Goodman and Marsha Lakes Matyas was published in *Advances* in June 2016: "What is the American Physiological Society's ITL and Who Are the Members of PECOP?" (*http://dx.doi.org/10.1152/advan.00045.2016*).

***AJP-Heart and Circulatory Physiology***

**Conference:** Inflammation, Immunity and Cardiovascular Disease Conference, Westminster, CO, August 2016.

**Commissioned:** Open Call for Papers issued from speakers from the conference; submission deadline of December 31, 2016.

**Submitted/accepted/published:** As of January, 2017: 9 submitted, 4 rejected, 3 in revision, 1 published.

**Decision**

The committee deemed that the Conference Proceedings initiative has increased the visibility of both conference and the journals and therefore has been successful. The committee was unanimous in determining that the initiative should continue as a pilot for another 2 years, with the following criteria:

- Invitations to speakers should be supplemented and coordinated with an open call in advance of the meeting. All papers would continue to be peer reviewed prior to acceptance.
- Journals should track the citations of the articles published that were derived from the meeting

## Scientific Impact/Attractiveness to Authors

### *Impact Factor*

The 2015 Journal Impact Factors (IF) published in Journal Citation Reports by Thomson Reuters in 2016 has APS Journals generally holding their rankings. *AJP-Lung* and *AJP-Endo* all increased their rankings slightly, and *Comprehensive Physiology* fared well in second full-year IF at 6.364. *Physiological Reviews* once again ranked no. 1 in the field of physiology, with an IF of 30.924. See *http://www.the-aps.org/mm/Publications/Journals/Impact-Factors.html.*

**Note:** In October 2016, Clarivate Analytics (*www.clarivte.com*) was formed from an acquisition of Web of Science (from Thomson Reuters), the website that hosts the Journal Citation Report's key metric, the Journal Impact Factor.

### *Manuscripts Received*

Manuscript submissions in 2016 decreased overall by 2% vs. 2015 across all original research journals and all manuscript types. (There was a 1% decrease in 2015 vs. 2014.) Submissions to *AJP-Lung* increased by 22%; to *AJP-Renal* by 13%; and to *Physiological Genomics* by 12% compared with 2015.

### *Supplemental Material*

A total of 420 data supplements were published in 2016, 144 of which contained video files. This represents an 11% increase in total data supplements from 2015 and a 3% increase in video files specifically. Figure and table supplements increased by 23%. A total of 167 data supplements have been published so far in 2017 (January to May).

### *Podcasts*

In 2016, *AJP-Heart* released 32 podcasts *JAPPL* released 15. *JN* released 17 and *AJP-Cell* released 1 podcast highlighting published articles. So far in 2017 (January to May), 23 podcasts have been published (*Heart* 17, *JAPPL* 7, *JN* 5, and *Cell* 1).

### *Time to First Decision*

Time to first decision averaged 22 days in 2016 across all of the original research journals, 0.8 days more compared with 2015. *AJP-Cell* time to first decision was fastest at 17 days, followed by *AJP-GI&L* and *AJP-Heart* both at 19 days. The average time to first decision YTD May 2017 is 23 days.

### *Peer Review System*

Enhancements to the peer review system are made as requested by the editors-in-chief and as needed by staff. These enhancements are ongoing. In 2016, there were approximately 30.

## *Annual Reviews* Award for Scientific Reviewing

The *Annual Reviews* Award for Scientific Reviewing was introduced in 2012. The award is given for excellence

in providing systematic, periodic examinations of scholarly advances and provoking discussion that will lead to new research activity. The award recognizes an APS member who has written scientific reviews and has helped provide an enhanced understanding of the area of physiology reviewed. The successful candidate, chosen by the Publications Committee, is awarded $2,000 and up to $2,000 reimbursement toward travel to attend the annual Experimental Biology meeting to receive the monetary award and a recognition plaque.

The 2017 award was presented to David G. Harrison (Director, Division of Clinical Pharmacology, School of Medicine, Vanderbilt University).

*Annual Reviews* has informed the APS that they will not renew the award after 2017.

## Publications Integrity and Policy

### *NSF Grant*

In 2012, the Publications and the Education Departments jointly submitted a successful application to the NSF for the development of modular course materials on publication ethics. The materials are to be used in Responsible Conduct of Research courses in STEM graduate programs. Additional collaborators on the project are the Biomedical Engineering Society (BMES) and the Society of Biological Engineers (SBE). The amount of the grant was $400,000 awarded over a 3-year period. Currently, the grant is on its second 1-year, no cost extension through summer 2017 to complete the grant goals and submit the final report.

### *NIH Grant*

In fall 2014, the Publications and the Education Departments jointly submitted a grant proposal, solicited by NIH, to develop a training module to enhance data reproducibility (RFA-GM-15-006). The proposal, titled "Controls in Animal Studies Professional Skills Course," utilizes APS expertise in developing professional skills training courses and the expertise of its advisory board in designing animal studies. The proposed module focuses on the general factors that a researcher should consider when designing, analyzing, and reporting results from animal studies. Topics include sex, longitudinal studies, drug treatments, large animal models, and surgery. The proposal was well received and funded ($150,000). The 3-year grant period began on September 18, 2015.

### *Ethics Cases*

After a spike in 2011 (251 cases), the total number of ethics cases arising during peer review and production has decreased to 94 cases in 2016 and 86 cases projected for 2017. The decrease is due primarily to presentation errors that are fixed before early publication. Other cases were categorized as duplication of data, duplicate publication, human/animal subject protocol, conflict of interest, and plagiarism.

In 2016, 73% of all cases were identified in the accepted stage before manuscripts were sent to AiPS. This compares to 71% in 2015. In 2016, the percentage of cases identified in AiPS was 4% (vs. 2% in 2015). The percentage of case concerns identified in the submitted/review stage in 2016 was 14% compared with 17% in 2015. In 2016, 8 cases (9%) were identified after final publication compared with 13 cases (10%) in 2015. Sanctions were applied to five cases. Location of corresponding authors' institutions of 2016 ethics cases was split nearly 50-50 between U.S. vs. non-U.S. institutions, which follows the trend.


*2017 total through May. Projected total for year = 86.

## Publication Ethics Policy Updates

In 2016, APS Ethics Policy was amended as follows:

- **January 2016:** Ended exception to prior publication policy for *Journal of Neurophysiology* manuscripts posted on preprint servers.
- **May 2016:** Returned the *Journal of Neurophysiology* preprint server exception to the prior publication policy, trial through April 2017; see footnote at *http://www.the-aps.org/mm/Publications/Info-For-Authors/Ethical-Policies*.
- **November 2016:** Updated language throughout ethics policy

- **November 2016:** Updated COI section to note potential COI's for Editorial Focus articles.

## Changes to Instructions to Authors

- **March 2016:** Updated copyright section to include policy on posting articles to websites (*http://www.the-aps.org/mm/Publications/Info-For-Authors/Copyright*).
- **July 2016:** Added Cores of Reproducibility in Physiology (CORP) Invited Review as an article type (*http://www.the-aps.org/mm/Publications/Journals/J-Appl-Physiol/Article-Types*).
- **August 2016:** Added new section on "Promoting Transparent Reporting in APS Publications to Enhance Data Reproducibility" (*http://www.the-aps.org/mm/Publications/Info-For-Authors/Promoting-Transparent-Reporting*) and the companion webpage "Experimental Details to Report in Your Manuscript" (*http://www.the-aps.org/mm/Publications/Info-For-Authors/Experimental-Details-to-Report*).
- **December 2016:** Updated Data Repository Standards section to encourage deposit of data that underlie the conclusions into public repositories. Added a table to highlight the main data repositories (*http://www.the-aps.org/mm/Publications/Info-For-Authors/Data-Repositories*).
- **February 2017:** Added Computer Simulation guidelines to the section on Promoting Transparent Reporting in APS Publications.

In March 2017, the NIH issued an announcement stating, "The NIH encourages investigators to use interim research products, such as preprints, to speed the dissemination and enhance the rigor of their work. This notice clarifies reporting instructions to allow investigators to cite their interim research products and claim them as products of NIH funding."

APS policy has considered posting a manuscript to a preprint server as prior publication and has prohibited it (with a trial exception for *JN*). In consideration of the new NIH announcement, the Publications Committee, in consultaton with the editors-in-chief, has revised this policy to allow APS authors to submit original research to preprint servers. The new policy requires (as did the *JN* exception) that the authors declare on submission whether or not the manuscript or a version had been posted to a preprint server to identify the server and the DOI. See the policy at *http://www.the-aps.org/mm/Publications/Info-For-Authors/Policy-on-Posting-to-Preprint-Servers-Prior-to-Submission-to-APS-Journals.html*.

## Eighth International Congress on Peer Review and Scientific Publication (Chicago, September 10–12, 2017)

Christina Bennett and Rita Scheman submitted an abstract titled "Assessing the Outcomes of Introducing a Digital Image Quality Control Review into the Publication Process for Research Articles" to the Eighth International Congress on Peer Review and Scientific Publication (*http://www.peerreviewcongress.org/index.html*), which was accepted for session presentation. The abstract summarizes the work that has been done since 2011 in achieving appropriate digital image presentation and publication of images in APS journals as originally captured.

The congress is organized by JAMA and the BMJ, and takes place every 4 years with the aim ". . . to encourage research into the quality and credibility of peer review and scientific publication, to establish the evidence base on which scientists can improve the conduct, reporting, and dissemination of scientific research."

## Finance

### *Subscription Pricing and Sales*

In 2012, a tiered pricing model was implemented for journals and the Legacy Content. Tiers were assigned based on the value of the journal to the institution. The goal was to have a pricing variance of 10% between tiers 1, 2, and 3 by 2014, which has been achieved.

The online-only 2016 price for tier 1 was set at 0% increase; the tier 2 price was set at 3% increase; and the tier 3 price was set at 5% increase. Print and online journal prices for 2016 were set at a 2.5% increase for tier 1, a 5.5% increase for tier 2, and a 7.5% increase for tier 3. The print-only price increased by 10%. Subscription count decreased in 2016 by 3% compared with 2015. APS continues to respond to requests from consortia of libraries or multi-site institutions, offering custom pricing for tiers 4 and 5 online subscriptions, if we are not losing subscription dollars by doing so. There were 1,531 tier 4 and 5 subscription orders in 2016, and 6 unit sales of Legacy Content, the latter of which is sold at a one-time price of $2,550 for tier 1, $2,990 for tier 2, and $3,430 for tier 3. Based on our institutional

market analysis, APS has arranged for sales agency representation in regions globally that were identified as having growth potential. Sales representation covers Europe, the Mideast, Brazil and Latin America, India, and China. The APS offers digital single article pay-per-view sales.

### Color Figures

Authors continue to take advantage of the benefit of scientifically warranted color made free of charge to first or last authors of original research articles who are APS members. (Scientifically necessary color is published free of charge in all review articles.) The number of color figures in research articles published in 2016 decreased by 7.6%, from 5,288 in 2015 to 4,888 in 2016, of which 2,695 (55%) were free to APS members.

### Advertising

The APS sells commercial advertising in its online and print journals through AdNet, a FASEB-managed advertising group.

### Author Fees

The author survey conducted by the Publications Department in 2014 raised several important issues that resulted in recommendations from the Publications and Finance Committees to implement the following revenue neutral revisions to author fees, which were applied to manuscripts submitted as of January 1, 2016:

- Submission fees were eliminated.
- Page charges were increased from $75 to $85 to incorporate submission fee and achieve revenue neutrality.
- Color fees for nonmembers have been reduced to $200 per figure from $400 per figure, made possible through cost savings from production changes and renegotiation of the APS contract with its composition and printing vendor.
- Elimination of page charges for the *AuthorChoice* option, whereby only the fixed fee ($2,000 for original research articles or $3,000 for review articles) is payable.

### APS AuthorChoice

The APS *AuthorChoice* program was introduced to all APS research journals in July 2007. For a fee of $2,000 ($3,000 for review articles) in addition to other author fees, an article is made freely available immediately upon payment and is delivered by the APS on behalf of the author to PMC, to be uploaded upon publication. Starting with manuscript submissions in 2016, author page charges that were additional to the $2,000 (or $3,000 for review articles) were eliminated. This change brings APS within community norms. In 2016, APS received 91 requests for the option vs. 57 requests in 2015, which represents approximately 2.3% of all published articles during 2016 vs. 1.3% in 2015.

As of 2013, to enable authors to comply with the policies of many funding agencies, APS has instituted the application of the CC-BY Creative Commons attribution license (*http://creativecommons.org/licenses/*) to *AuthorChoice* articles governing reuse in place of standard copyright.

### Copyright and Permissions

Since 2011, the Copyright Clearance Center (CCC) has administered on behalf of APS permissions for reuse of APS copyrighted materials in electronic format. The CCC is the primary provider to academic publishers of copyright permissions services; APS has been working with this organization for many years for administration of print copyright permissions.

### Editor Budgets

The estimated expense for running the editors' offices remains at $150 per manuscript. Almost all editors are in alignment, and some realize savings. Publications continue to clarify and simplify expense guidelines with editors. The ability to make office funds "fungible" for other specific purposes was implemented as a 2-year trial as of 2013. The guidelines were reviewed and revised by the Publications Committee at its March 2014 meeting and again at its 2015 meeting, wherein it was agreed:

- Editors may use their expense budget to benefit the journal as they see fit.
- EICs are asked to include in their reports to the Publications Committee at each March meeting as to how their EIC and AE fungible budgets were used to benefit their journal.

## Online Journals Hosting

### Hosting Platform

The APS contract with HighWire for hosting the published journal articles runs until the end of 2017.

During 2016, APS conducted an RFP to research prospective hosts and selected Atypon's Literatum platform as the next home for our journals. The new site will be launched at the beginning of January 2018. APS conducted a website survey at the end of 2016, sent to the full editorial boards of all journals, to collect feedback regarding priorities and preferences for the presentation and navigation of the journals' content websites. This feedback is being consulted to improve the user experience for the next iteration of the site.

## Editorial Initiatives

### Reviewer CME

Since 2013, APS has offered Continuing Medical Education (CME) credit to eligible reviewers; i.e., U.S.-based medical doctors, who serve as manuscript reviewers and meet qualitative criteria that have been set by our editors. Reviewer CME was introduced in *AJP-Endo,* administered by The Endocrine Society (TES), and intended to roll out to all interested APS journals. Since July 2015, CME has been offered by *AJP-Heart* and *JAPPL* to eligible reviewers, and, as of 2016, by *AJP-Lung* and *AJP-Renal,* administered by the Washington University School of Medicine CME Department. Washington University was brought in because TES subsequently determined that APS titles other than *AJP-Endo* were out of scope for their mission. As of 2017, administration of the program has been consolidated at the Washington University School of Medicine. Details about manuscript review CME are at *http://www.the-aps.org/mm/Publications/Journals/Reviewer-Guidelines.html#CME*.

In 2016, CME credit for manuscript reviewing was awarded to 165 reviewers for reviewing 274 papers as follows: 13 reviewers for 13 papers in *AJP-Endo;* 45 reviewers for 81 papers in *AJP-Heart;* 37 reviewers for 65 papers in *JAPPL;* 27 reviewers for 47 papers in *AJP-Lung;* 39 reviewers for 68 papers in *AJP-Renal.* CME credits for manuscripts reviewing to year to date, May 31, 2017, were awarded to 6 reviewers for 7 papers in *AJP-Endo;* 3 reviewers for 3 papers in *AJP-Heart;* 28 reviewers for 57 papers in *AJP-Renal;* and 6 reviewers for 7 papers in *JAPPL.* Beginning July 1, the CME program will add two additional journals, *AJP-Cell* and *AJP-GI,* and will move from a paper-based system to a more efficient online platform that will make it easier for editors to complete and manage their conflict-of-interest statements and for reviewers to receive their CME certificates.

### Data Reproducibility in APS Journals

Since 2014, NIH and other funders have raised concerns about the lack of experimental reproducibility in research. In response, NIH is making changes to graduate student education, grant preparation, and publishing guidelines in an effort to promote better experimental design, analysis, and reporting (*https://www.nih.gov/research-training/rigor-reproducibility*).

In 2015, FASEB hosted three roundtable discussions on experimental reproducibility, of which APS was an active participant. As a result of these meetings, FASEB prepared a set of recommendations to the scientific community, published in January 2016 (*www.faseb.org/Portals/2/PDFs/opa/2016/FASEB_Enhancing%20Research%20Reproducibility.pdf*). In particular, they encouraged society publications committees and journal boards to increase rigor and transparency in the journals, in part by providing more detailed guidelines for reporting methods and reagents in research articles.

In 2016, recommendations from the editors-in-chief to the APS Publications Committee resulted in the development of enhanced guidelines for reporting experiments in APS journals. In August 2016, the guidelines were posted online in "Information for Authors" to encourage better reporting of animal experiments, antibody validation, and experimental details in figures and legends. Guidelines for articles based on original computer simulation software were posted online in January 2017.

Two webpages were created to highlight the guidelines (see below) and others were updated:

- "Promoting Transparent Reporting" (*http://www.the-aps.org/mm/Publications/Info-For-Authors/Promoting-Transparent-Reporting*).
- "Experimental Details to Report" (*http://www.the-aps.org/mm/Publications/Info-For-Authors/Experimental-Details-to-Report*).

### Statistics Review

APS collaborated with the American Statistical Association to identify a small group of statisticians that were interested in serving as statistics reviewers for APS journals. As of December 2016, seven statisticians have agreed to participate in this effort. After 6 months of participation as a statistics reviewer, formal invitations

to join the editorial board(s) may be extended at the discretion of the Editors in Chief.

### *Module on Best Practice in Peer Reviewing*

The author survey conducted by the Publications Department in 2014 raised several important issues, which the Publications Committee agreed to address. One of these issues was the creation of educational materials to support best practice for APS reviewers. To achieve this, a working group of editor-in-chief volunteers [Irv Zucker (Chair), Sadis Matalon, Rick Samson, and Peter Wagner] was established, which developed these materials. The materials represent the basic principles for peer reviewing. The goal established is for each editor-in-chief to host webinars for their associate editors and editorial boards on a regular basis.

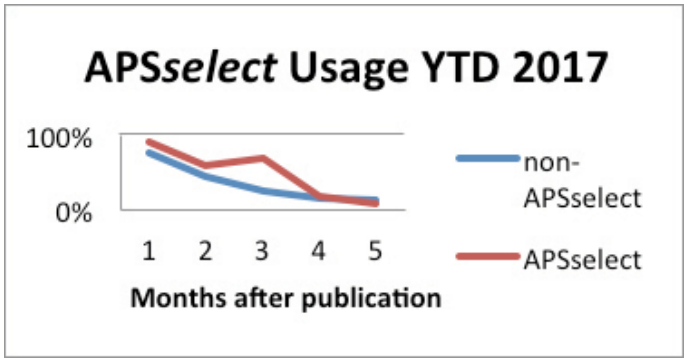
The working group developed and the Publications Committee reviewed and edited the module. The PPT module is complete and has been distributed to the editors-in-chief for use with their editorial boards. This module, along with a version narrated by Irv Zucker (editor-in-chief, *AJP-Heart*) is available at *http://www.the-aps.org/mm/Publications/Journals/Reviewer-Guidelines.html*.

## Recent Publications

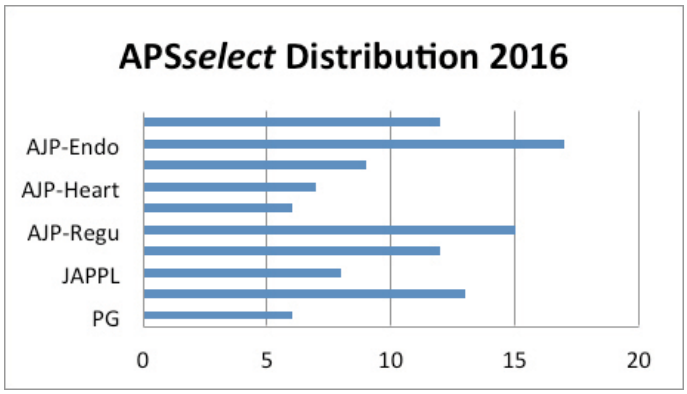
APS*select* (*http://apsselect.physiology.org/*), launched in January 2014, highlights and promotes the top APS original research papers that are published each month across all 10 APS original research journals. APS*select* is edited by Joe Metzger (editor-in-chief) and Linda Samuelson (associate editor). A certificate is awarded to the authors of each selected article. The monthly selection process is:

- The editors-in-chief of each of the 10 journals nominate two recent articles.
- A Selection Board, representative of disciplines within physiology, chooses the final articles, using a 10-point rating system, similar to that of NIH grant peer review.
- APS staff manages the nomination/selection and posts the winning list to the website.

Usage data show that articles chosen for APS*select* experience a spike in usage on publication vs. non-APS*select* articles (see graph below).




Average usage for selected vs. non-selected original research articles, The data have been normalized across all 10 research journals. Values are given as a relative percentage of the maximum amount of usage that an average non-selected or selected article received during this 5-month period.




APSselect articles in 2016 as represented across all APS original research journals. AJP-Endo had the highest representation of APSselect articles (17).

### *Comprehensive Physiology*

*Comprehensive Physiology* (*www.comprehensivephysiology.com*), edited by David Pollock, is a digital update of the *Handbook of Physiology*. The first issue, published in January 2011, included all content of the most recent edition of the printed *Handbook* digitized and presented as "Classic Content," plus 25 new articles. *Comprehensive Physiology* is published by Wiley on behalf of the APS.

*Comprehensive Physiology* is published quarterly. As of June 1, 2017, 884 articles have been invited, of which 451 have been accepted, 30 are in review or revision, and 423 have been published. The invited articles are from 11 of the 13 sections, covering 25 topics; "topics" correspond to a volume of the *Handbook*.

To maximize use and appeal for teaching, *Comprehensive Physiology* has added teaching materials for newly commissioned and updated articles. As of fall 2016,

teaching material is provided by the authors in two parts and displayed on a separate tab in the article:

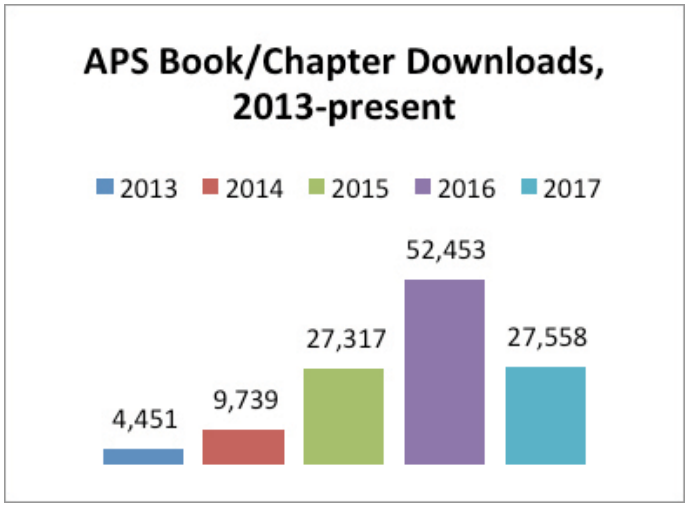
1) A brief (<150 words) didactic synopsis is included in the article, after the abstract.

2) Additional figure legends that are geared toward students accompany the figures.

### Book Monograph Series

In June 2011, the APS and Springer signed an agreement for Springer to publish books in the APS Monograph Series on behalf of the APS. These series are: Perspectives in Physiology, Methods in Physiology, Physiology in Health and Disease. As part of the program, 33 backlist monograph titles have been digitized and are now freely available to APS members.

Twelve books have been published in the program to date for a total of 80,679 full text downloads.




- All new titles are published in electronic format as part of Springer's "Physiology eBook Collection" and are available in print.
- All ebooks published in the program, both new and backlist titles, are freely available to APS members via login at the APS website at *www.the-aps.org/mm/Publications/Books*. The books are hosted on the Springer website and can be downloaded as a PDF or viewed in the reader's browser.
- The hardcover print version of each new title is available to APS members at the special price of $40.

### Physiological Reports

*Physiological Reports* is a general physiology open access journal owned jointly by the APS and The Physiological Society and published on their behalf by Wiley. The journal is tasked to achieve a quick time to publication while upholding a quality standard of sound research that constitutes a useful contribution to the field. The journal uses a "cascading peer review model," whereby manuscripts considered unsuitable for publication in an APS/TPS journal, but yet deemed to be of publishable value, are "referred" to *Physiological Reports,* with author agreement to "transfer" the manuscript and reviewer agreement to transfer the manuscript reviews. The journal also accepts de novo submissions, whose peer review process is comparable to that of APS journals.

**Article Types.** The journal accepts original research articles, reviews, and commissioned editorial focus articles. In July 2015, the journal began accepting a new article type, Case Reports, which are clinical cases that must have a physiological focus (see *http://physreports.physiology.org/author-guidelines*).

**Joint Managing Board.** *Physiological Reports* is managed by a joint managing board composed of representatives from both societies.

**Editors.** Susan Wray (University of Liverpool) is editor-in-chief and Thomas Kleyman (University of Pittsburgh) is deputy editor-in-chief, and, in June 2015, the JMB reappointed both to a second and final 2-year term.

**Journal Business Model.** The journal is funded by an author processing charge (APC) of $1,500, paid by the author upon acceptance. There are waivers in place for submissions from authors based in countries that cannot afford the fees (as there are for all APS journals). The APC for Case Reports is $1,000; all Case Reports accepted for publication through 2016 (initiated August 2015) were free.

**Editorial Status.** *Physiological Reports* launched in March 2013. The first article appeared online in May 2013, and the first issue was compiled in June 2013, Articles are published as they are ready, and issues are compiled monthly. From January to May, 2017, 172 articles were published, with the cascading peer review model accounting for ~75% of the total submissions, and ~94% of these articles accepted for publication.

***Acta Physiologica.*** Currently, the majority of published papers have come from transferred manuscripts. In recognition of this success, and to further broaden international appeal of the journal, in June 2015, the societies signed an agreement with The Scandinavian Physiological Society to include their journal, *Acta Physiologica*, as a supporter journal to *Physiological Reports*, from which suitable manuscripts are referred.

## Community Publicity Initiative: Societies Collaboration Project: "Scientific Society Publisher Alliance (SSPA), by Scientists for Science

In summer 2015, Mark Johnston (editor-in-chief of *Genetics*, published by the Genetics Society of America) organized a meeting of executive and publication directors of scientific membership societies to consider working together to reassert the profile of the value of society "peer edited" journals – journals edited by active scientists and published by non-profit societies that represent the researcher community. The Society-Sponsored Journals Consortium was formed by 10 scientific societies, including the APS. A MoU was signed, and seed funding was contributed by each.

The consortium (now "SSPA") worked with a marketing firm to deploy qualitative market research strategies to determine motivations and provide the foundation for the development of key attributes, positioning, audience segments, and recommendations for future marketing efforts that will push the message into the community (*phase I*). Key research findings include:

- Confirmation how different factors influence author behavior in publication choices and how these change along the career path.
- Perceptions of society vs. commercial titles.
- Value of the scientist as editor – preferred, but few have given it much thought.

*Phase 1* (conceptual phase) established a position statement:

> "Published by practicing scientists for science, society journals give authors the opportunity to publish in a prestigious title with direct access to a targeted audience. These publications advance research by providing peer validation and author support and by reinvesting in the community as part of their not-for-profit commitment."

*Phase 2* is the practical and implementation phase.

The SSPA has embarked on *phase 2*, led by a small working group of members, including Rita Scheman of the APS. We continue to work with marketing and now design consultants to establish a website for the SSPA as the face of a campaign to promote the positioning statement. The website will launch August 1, 2017.

## Marketing and Communications

The following 2017 report reflects the concerted efforts of the APS Communications Office to share more APS journal articles in both traditional (press) and social (APS National Facebook and Twitter feeds) media outlets.

### *Press Releases*

The APS Communications Office issued 35 press releases between January and May 2017, of which 19 were related to APS journal articles. APS journal press releases received 32,957 views from the media on our press release distribution website (Newswise) from January 1 to May 31, 2017. The top five most popular journal releases addressed:

- Effects of eating vs. fasting before exercise on gene expression of fat tissue (*AJP-Endo:* 1,871 views).
- The ratio of dietary potassium to sodium that may reduce heart and kidney disease (*AJP-Endo:* 1,766 views).
- Protective effect of caffeine on oxygen-induced lung injury in premature newborns (*AJP-Lung:* 1,416 views).
- Identification of a protein that regulates a gene associated with schizophrenia (*JN:* 1,370 views).
- Changes in gut microbiota in response to diet and antibiotic use (*AJP-GI:* 1,264 views).

### *Social Media*

The Communications Office posts daily on APS National Facebook and Twitter feeds, targeting a wide variety of journal-related content, such as monthly APS*select* articles, Articles in PresS, news articles that mention research published in the APS journals, and posts shared from the journal-specific social media feeds. We post 10–15 journal-related posts each month on Facebook and 20–25 on Twitter. Journal-related posts are some of the most popular on the APS National social feeds, with total views in the tens of thousands. APS

journal articles were also featured in 10 Dr. Dolittle blog posts and 6 *I Spy Physiology* blog posts from January 1 to May 31, 2017.

### *APS PublicationsTwitter Account*

The Publications Department started a Twitter feed (*https://www.twitter.com/APSPublications*) at the end of 2015. In 2016, after 544 tweets, the number of followers reached a respectable 432. As of June 2017, we have 583 followers. Topics include newly posted research, freely available research articles of timely interest from the archives, articles in the news and social media, and new APS*select* titles.

*Council accepted the report of the Publications Committee.*

## Science Policy Committee

Laura McCabe, Chair

### SPC Meetings

The Science Policy Committee (SPC) held its face-to-face meeting in Bethesda, MD on October 26–27, 2016. Because 2016 was an election year and the meeting was held just weeks before the Presidential election, the committee did not go to Capitol Hill. Instead, the SPC had a working session focused on developing tools for improving rigor and reproducibility that will be made available on the APS website in conjunction with the EB symposium on the same topic. The committee also reviewed future advocacy plans and a number of relevant policy topics, including FOIA regulations and NIH's use of other transactional authority (OTA).

### EB 2017 Public Affairs Symposium

The SPC sponsored the Public Affairs Symposium for EB 2017 in Chicago. Committee members Roy Sutliff and Alicia Schiller chaired the session, titled, "Why Scientific Rigor Matters and How to Improve It." The session was very well attended. Kristine Willis gave an overview of the NIH perspective on rigor and reproducibility; Brad Yoder shared his experience with the UAB graduate training program on rigor; Curt Sigmund discussed how APS publications are addressing the need to improve rigor and transparency; and Tracey Weissgerber discussed the need to develop better statistical methods for data analysis and visualization. The session was audio-recorded and will be available with the PowerPoint slides on the APS website.

### SPC Advocacy Activities

#### *APS Leadership Visits Capitol Hill with FASEB*

On March 9, 2017, I joined five other APS members to participate in FASEB's annual Capitol Hill Day. Representing APS were FASEB Board Member Hannah Carey, FASEB Past-President J.R. Haywood, APS President Jane Reckelhoff, APS representative to the FASEB SPC Kevin Kregel, and APS member Christopher Waters.

#### *APS Statements*

In January 2017, the Trump Administration presented a plan to restrict travelers from certain countries from coming to the U.S. Because of concerns about the effect this plan would have on the sciences, the APS issued a statement (*http://www.the-aps.org/CoreValues*) affirming the Society's core values, which include "fostering a diverse and inclusive scientific workforce encompassing the best and brightest minds from around the world."

In May, the Trump Administration proposed a FY 2018 budget that would cut the budgets of the NIH (–21%), NSF (–11%), NASA (–3%), and the VA Medical and Prosthetic Research Program (–5%). APS issued a statement calling on Congress to reject this plan to cut research.

Both statements were sent directly to the membership through APS Connect, as well as posted on the APS Science Policy website, and distributed via social media accounts.

### *APS Early Career Advocacy Fellows*

The APS received six eligible applications for the APS Early Career Advocacy Fellowship (ECAF). The committee selected two awardees: Amanda Marie James, a postdoctoral fellow at Emory University School of Medicine, and Eric George, an assistant professor of physiology and biophysics at the University of Mississippi Medical Center. The APS Council approved these selections, and James and George joined the second-year fellows, Heidi Medford and LaShauna Evans, in the ECAF program. The fellows were invited to attend the committee's meeting at EB in Chicago, where an orientation luncheon provided the fellows with an opportunity to interact with members of the committee, Society leadership, past fellows, and staff.

### *Chapter Advocacy Outreach Program*

This program was developed to help physiologists become more effective advocates by providing speakers at APS Chapter meetings. It is a joint project of the APS Science Policy and Animal Care and Experimentation Committees. The Office of Science Policy provides information to the Chapter Advisory Committee each year concerning the program and providing a list of sample topics. Chapter representatives are invited to request a speaker, with the APS covering that person's travel expenses. We received three requests in 2013; two in 2014; one in 2015; and three in 2016. To date, no requests have been received in 2017.

## Leadership Interactions with FASEB

The APS is currently represented on the FASEB Board of Directors by Kevin Kregel, who took over for Hannah Carey when she began service as Vice President-elect for Science Policy of FASEB in July. I currently serve as the APS representative to the FASEB Science Policy Committee (SPC).

Kevin attended the FASEB Board meeting in June, which focused on the future of FASEB, including the sale of the campus, and FASEB's plans to develop an open-access journal. The board also heard from NIH Deputy Director Larry Tabak about NIH's plans to implement limits on support to individual investigators. The FASEB SPC meeting was also held in conjunction with the board meeting, and the symposium was on "Incorporating Convergence Science into the Research Enterprise."

APS is represented on various FASEB SPC subcommittees by the following individuals: Hannah Carey, John Chatham, Gaylen Edwards, JR Haywood, Katie Wilkinson, Kevin Kregel, Bill Talman, Tim Musch, Bill Yates, Virginia Miller, Carrie Northcott, Gina Yosten, Tom Pressley, Chris Westby, TanYa Gwathmey-Williams, Amy Davidoff, Brooks Robey, and Phil Clifford.

## @SciPolAPS

@SciPolAPS is the Twitter feed the APS Office of Science Policy uses to disseminate information about science policy issues, including animals in research. The staff typically puts out about six tweets per day, and about 90% of these tweets typically get some kind of response, i.e., a retweet or a comment. As of June, 2017, @SciPolAPS had nearly 2,500 followers, and some of these individuals are well known in the fields of science policy and science communications. Nearly 18% of those who follow @SciPolAPS have at least 1,000 followers of their own, while 5.8% have at least 5,000 followers. In addition, five of those who subscribe to the feed have over 1 million followers.

*Council accepted the report of the Science Policy Committee.* ●

# Section Advisory Committee

Wolfgang M. Kuebler, Chair

Since the previous report of the Section Advisory Committee (SAC), presented at the Summer 2016 Council meeting, SAC has had two face-to-face meetings (SAC only) on November 8, 2016 in San Antonio, and at the 2017 Experimental Biology meeting in Chicago, April 21, 2017, as well as a joint meeting with Council on November 9, 2016 in San Antonio. Other communications have been through telephone conferences and e-mails.

## Synposis from SAC Meetings and Annual Section Reports

### *SAC Membership and Oversight*

On an annual basis, SAC undergoes changes in membership. In the past year, Sean Stocker [central nervous system (CNS)], Timothy Musch [exercise and environmental physiology (EEP)], Joseph Brozinick [endocrinology and medicine (EM)], Donald Kohan [renal (RENAL)], Larissa Shimoda [respiration (RESP)], and Jonathan Kibble [teaching of physiology (TEACH)] completed their service as section chairs. We recognize and thank Sean, Tim, Joe, Don, Larissa, and Jonathan for their leadership and dedication to the APS. Concomitantly, we welcome Kirsteen Browning (CNS), Bruce Gladden (EEP), Gina Yosten (EM), John Imig (RENAL), Greg Funk (RESP), and Lynelle Golden (TEACH) as new section chairs to SAC.

Wolfgang Kuebler will finish his service as chair of SAC on December 31, 2017, and will be replaced by Sean Stocker as new chair of SAC.

### *Communication Between SAC and Council*

In November 2016, SAC and Council held their third joint meeting outside the regular EB meetings in San Antonio, TX. At the joint meeting, Council and SAC discussed the Society's Strategic Plan, the joint initiative between Joint Program Committee (JPC) and SAC to review and optimize APS programming at the EB meeting, and the role of SAC in CoC operations and the identification and recruitment of suitable candidates to committees.

In February 2017, Council and SAC held their strategic planning meeting in Houston, TX, and worked with Minding Your Business (MYB) to identify future strategic goals and strengths/weaknesses of current focus areas and allocation of resources.

SAC unanimously welcomes the opportunity for a regular exchange with Council and strongly supports the continuation of the joint fall meetings. Section chairs have suggested to further expand these meetings to discuss important topics in "work groups" or "brainstorm" sessions.

A joint SAC-Council meeting has again been scheduled for fall 2017 (location TBD). SAC members also appreciated the opportunity to get involved in the ongoing branding and strategic refocusing initiative with MYB, and it was felt important that the sections as a direct representation of the APS membership are well represented in these initiatives.

### *Communication via APS Connect*

Various section chairs raised concerns regarding communication with their membership via the APS Connect system. Despite extensive efforts to familiarize their membership with APS Connect, sections found that they lost communication with members, resulting in poor response rates to calls for nominations or session proposals. This was considered a very serious issue by SAC and was brought to Council. In response to these concerns, a Working Group has been established by Marty Frank and Wolfgang Kuebler to bring together APS staff and some of the current or previous section chairs (Declan McCole, Eric Lazartigues, William Jackson, Donald Kohan, Kirsteen Browning) to work on ways to best address these issues. A first conference call has been scheduled for the end of July 2017. In the mean time, SAC requested the ability for Section Steering Committee members to send directs e-mails to their membership, bypassing the daily digest/APS Connect.

### *Programming of Experimental Biology Meeting*

In close cooperation with the JPC and JPC Chair Robert Hester, SAC has discussed extensively about ways to increase the attractiveness and diversity of our scientific program at the EB meeting and to leverage

on the unique strengths of our Society. To this end, the Hester was invited to attend the past SAC meetings as guest, and Wolfgang Kuebler, as chair of SAC, attended the meeting of the JPC in Crystal City in June 2016. A task force consisting of the chairs of SAC and JPC, as well as members of SAC (Donald Kohan, Sean Stocker) was established and discussed future options for EB programming in a series of telephone conferences and online discussions. As a first result from these discussions, abstract categories and topics for future EB meetings have been harmonized in an attempt to combine the best science within a specific field and to avoid intersection competition for abstract submissions.

Overall plans and options for EB reprogramming were presented to Council during the fall 2016 meeting by Robert Hester and Wolfgang Kuebler, and Council encouraged JPC and SAC to move forward with these discussions and to think broadly, i.e., to put all options to the table. As a direct result, programing for EB 2018 will have a series of changes compared with prior meetings, with individual sessions being generally reduced from 120 to 90 min to make room for poster sessions that will no longer be scheduled to overlap with lunch break, but daily from 10 AM to 12 PM instead. This change was implemented to directly address the recent decline in overall attendance at poster sessions and to specifically strengthen the communication of novel science and the interaction with junior faculty and trainees. Shifting poster sessions to the mornings will also free time for attendees to visit the industry exhibition, which is an important part both for the exchange with industry partners and vendors as well as a financial basis of the EB meeting. To further emphasize the Society's strength with a focus on young rising investigators and top novel research, sections were encouraged to increase the number of featured topics and decrease the number of symposia when scheduling for EB 2018. Symposia and Featured Topics will each receive $3,000 plus complimentary registration for speakers/chair(s) (in case of symposia) or three complimentary registrations (for Featured Topics), and funds will be distributed by the session chair, as approved by the section JPC and SAC rep. Overall allocation of sessions, however, will not change.

For 2019, JPC and SAC plan to reduce scientific programing to Saturday to Tuesday in the attempt to eliminate programing on Wednesday, thus responding to the growing constraints in terms of both time and finances of APS members when attending a 5-day meeting. Various models for such a scenario have been developed over the past year and will be discussed with Council at upcoming meetings.

SAC has been due to review session allocations for the 2017 EB meeting; however, in view of the ongoing changes in EB programing, SAC decided to keep session allocations unchanged for the time being and to work with Council to develop novel metrics for session allocation once the new EB programing plan has been finalized and rolled out.

### *Awards*

Overall, sections continue to see a continuous increase in applications for their awards. In response, many sections have increased their number of awards, as well as award endowments, to adjust for increased travel and housing expenses, and several sections have established APS endowed matching funds accounts to sustain the funding of existing awards or increase the number of awards for established programs. In addition, several sections have implemented new ways to recognize outstanding presenters and presentations, and to increase their visibility, e.g., RENAL added 10 new posters to the Posters and Professors Session, who were giving "Recognition Presentations" and received certificates at the Renal Dinner. Cell and molecular physiology (CaMP) increased the number of Robert Gunn Awards to six (grad and undergrad) to accommodate a larger pool of worthy applicants, and increased the dollar amount of the awards from $300 to $500 to adjust for increased expenses. CaMPS also created an International Trainee Travel Award of $750 to provide trainees with funds to attend meetings outside the U.S. RESP installed a total of 20 industry-sponsored poster presentation awards 2 years ago, and funds have been secured to continue this program. CNS is working to grow the endowmenet for the Graduate Student Van Harreveld Award to increase the number of awards from one to two.

### *Engaging Members in Section Operations*

Sections communicate with their members through newsletters, ListServ e-mails, personal contacts, and in-

creasingly through social media. APS Connect is used by all sections but is considered very problematic, and many section chairs feel it has in fact hurt their communication with membership (see "Communications Between SAC and Council" for details). In general, improved communications with membership are among the top priority goals of several sections.

Most sections have established Trainee Committees/Trainee Development Committees/Trainee Advisory Committees to support trainee participation in the meeting and section operations with very positive results and enthusiastic feedback from trainees. Some sections have established "Mentoring Clubs" where trainees are matched with mentors by the trainee subcommittee to form novel interactions that will be helpful from both a scientific and a career development perspective. In addition, sections increasingly develop opportunities for trainees to meet and exchange with the sections' distinguished speaker in an informal setting.

### Interactions with Other Sections

Interactions between sections are considered very good/excellent and have resulted in increased programming of cross-sectional symposia and combined featured topics in recent years. Sections have also been actively involved in the creation and implementation of the new Interest Groups Nutrition Physiology or Sex Gender Research.

### Interactions Between Sections and APS Journals

The interaction between the section and the APS journals is unanimously considered to be very positive. Many of the journal editors are members of or included in Programming and Steering Committees. Some sections organize special EB symposia based on a hot topic theme published in the corresponding AJP journal; other sections issue coordinated "Calls for Papers" for sessions programmed at EB with the corresponding journal. In many instances, distinguished lecturers, symposia speakers, and new investigator or trainee abstract awardees receive subsequent invitations to publish reviews or mini-reviews in the corresponding journals, with the dual goal to increase the visibility and profile of the section and concomitantly to cover hot topics in the journals. Some sections also receive financial support for symposia from journals.

### How Can SAC and APS Better Serve Your Section?

Overall, the sections feel well supported by both APS and SAC. Areas identified for potential further improvement relate to

- communications with membership (see "Communication Between SAC and Council")
- real-time information via a central database on which members receive awards or recognition from APS to prevent "double-dipping" from different sections
- better APS website to score or rank abstracts submitted for different section awards
- coordinate fundraising efforts by open communication between APS and SAC
- installation of formal poster session facilitators into the program to increase visibility and trafficking at the poster sessions
- better communication between APS and section chairs regarding qualifications and expectations for APS leadership prior to the time nominations are solicited by the sections.

### Section Finances

Most sections consider their finances as solid; however, finances remain an important concern, and for some sections expenses have exceeded income in the past years. Major cost factors remain the social events/banquets at the EB meeting and the support for trainee activities. Several sections expressed the need for help in obtaining long-term funding to maintain their current level of membership services.

### Section Social Events

Due to considerable increases in costs for the section dinners and banquets, several sections have switched to less formal, less expensive events. To foster interaction, some sections have adopted the idea of a trainee-investigator networking "bingo" from CaMP, and several sections foster the interaction between the distinguished lecturer and trainees through breakfast events and post-seminar receptions.

### APS Matching Funds Initiative

Most sections have developed matching-funds endowment programs, which are commonly aimed for trainee awards or the exact use of which remains to be determined. RESP and RENAL have completed their initial endowment funds of $50,000 and successfully applied to APS to increase the amount APS will match

to $50,000, which they hope to reach over the next 12 24 months. Gastrointestinal and Liver Physiology and Neural Control and Autonomic Regulation have developed new APS matching funds programs, which were approved by Council at the EB 2017 meeting.

### Action Item Requests for Council

None.

*Council accepted the report of the Section Advisory Committee.*

## Trainee Advisory Committee

Erica Dale, Chair

### TAC Trainee Survey

A full analysis of the 2010 survey results, analyzed by educational level, was provided to Council in 2011, and a TAC subcommittee is working on a manuscript to publish the 2010 survey results. At the fall 2013 TAC meeting, the committee approved moving from a survey every 3 years to every 5 years to align this process with the APS Strategic Planning process, which is currently done every 5 years. The TAC began planning for the 2014 survey, including discussion of topics and objectives. However, with the change in timeline for APS Strategic Planning, TAC has put the finalization of the survey on hold to coordinate with Council planning activities.

### EB Symposia

The EB 2017 TAC Symposium was titled, "Kick Start Your Funding: Looking Beyond NIH and NSF," and was organized Jennifer Steiner and Kristi Streeter. The goal of this symposium was to help trainees and early career scientists identify additional funding opportunities to support their research as well as provide them with information on how to apply and write successful applications. There were speakers from the following four categories: *1)* private foundation, *2)* military, *3)* crowd sourcing/kickstarter, and *4)* industry. The TAC symposium for EB 2018 is titled, "Do It Again: How to Achieve Rigorously Reproducible Research." There are four confirmed speakers for four topics: experimental design (Sean Stocker from Penn State); data recording and analysis (Bill Yates from University of Pittsburgh); publishing results (Kim Barrett from University of California-San Diego); and data management and storage (David Mellor from Center for Open Science). This symposium will be chaired by Ryan Downey and Melinda Engevik.

### Career Webinar Series

The first webinar in this series (Rudy Ortiz) was produced and is ready for coordinated dissemination. All stakeholders in the webinar series (COPC, TAC, and Porter committees) have chosen primary and secondary participants for the 2017 webinar recordings. We anticipate production of all webinars for 2017 taking place over the summer months and are prepared for coordinated dissemination through early 2018.

### APS Trainee Facebook Site and Twitter

As of June, 2017, The APS Trainee Facebook page currently has 2,173 Facebook "likes" (up from 404 in 2014, a 438% increase), and the Twitter account has 223 followers (up from 110 in 2014, a 103% increase). Postings come from staff, TAC members, and APS Twitter feeds, providing regular communication (multiple postings per week, on average) to trainees from the APS and the TAC. At the annual fall meeting, TAC establishes monthly topics relevant to trainees and assigns members responsible for posting materials. Monthly reminders are sent out to TAC members reminding them to post. Staff will work together to send more Twitter messages out to increase the numbers on that platform.

### Dale J. Benos Early Career Professional Service Award

The committee is extremely pleased to note that the applicant pool for this ninth year of the award was again highly competitive. Although all five candidates were worthy of the award, the committee agreed that Patricia Silveyra (Assistant Professor at Penn State College of Medicine) was the most outstanding candidate. Silveyra has demonstrated a remarkable

level of professional service, outreach, and mentoring/teaching activities with students at the graduate/professional, undergraduate, and K-12 levels, as well as with members of her community. Silveyra has also utilized her unique background to include outreach to underserved, minority, international, and female scientists. In addition to her scientific accomplishments, she has won numerous awards for her mentoring and outreach throughout her career to date. The Council approved this selection, and Silveyra received the award at EB 2017. She will also prepare an article for a future issue of *The Physiologist*.

The TAC has begun to follow up with past award winners to determine whether they have continued their service activities and to ask about the impacts of receiving the award on their careers and professional activities. The first recipient of this award was surveyed at the end of 2013, and the fifth recipient will be surveyed this year.

## TAC Outreach

TAC members continue to use social media tools (Facebook and Twitter) along with the APS website and newsletter to engage both undergraduate students and physiology trainees. TAC members attended the EB 2017 Undergraduate Poster Session and engaged many of the undergraduate students in discussions of their research, encouraged them to become APS members, and promoted the APS social media sites (Facebook, etc.). The TAC also collaborated with the COPC on the 2017 EB Undergraduate Orientation Session, with Daria Ilatovskaya presenting a portion of the orientation talk.

## Undergraduate Research Advisory Board

To gain a broader perspective of the involvement of undergraduates in APS, the TAC sent a survey to all undergraduates that submitted an abstract to a physiology topic at the EB 2016 meeting. As an incentive to increase participation, the undergraduates were given the opportunity to receive a certificate recognizing them as members of the Undergraduate Research Advisory Board. Almost half of the undergraduate students presenting at EB 2016 responded to the survey. A manuscript has been published with these results in *Advances in Physiology Education*.

## APS Graduate Student Ambassador Program

The GSA subcommittee (Kristi Streeter, Jennifer Steiner, and Stephen Copp) has kicked off the GSA Program. Candidates have been chosen, notified, and met with the GSA leads at EB 2017. The subcommittee has created *1)* a GSA APS Connect Community for the GSAs to have access to documents as well as communicate with one another, *2)* a survey for each GSA to complete after their site visit (APS is working on making this into a Survey Monkey survey), *3)* a benefit/expectation checklist reviewed at the EB training, and *4)* a physiology/APS PowerPoint template for the GSAs to use during their site visits.

## Communication with Sections

TAC representatives updated their section activity information in 2015–2016 and shared information with their Section Steering Committee. The most common trainee activities for sections were research awards for trainees and junior faculty, discounted banquet tickets for trainees, involvement of junior faculty as symposia speakers, and e-media use. About two-thirds of the sections have a trainee section in their newsletter and have trainees co-chair symposia or featured topics at EB, and some sections also include trainee-driven sessions at EB, trainee subcommittees within the section, and awards for undergraduate students.

## Communication with APS Committee Trainee Members

Council approved funding for a breakfast meeting at EB for all trainees who are members of the APS standing committees and APS Chapter Steering Committees. The idea of this breakfast is to maintain contact with these trainees to understand their needs and concerns in regard to committee service. Attendance at these meetings has steadily climbed each year. In addition, the TAC has begun to develop a survey that has been distributed to trainees on APS committees.

*Council accepted the report of the Trainee Advisory Committee.* ●

# Women in Physiology Committee


Caroline Rickards, Chair

## Modified Duties of the Women in Physiology Committee

The charge of the Women in Physiology (WIP) Committee was modified during our 2016 Strategic Planning Meeting and approved by APS Council in December 2016. The new charge is:

*1)* To promote excellence in mentoring.

- Administer the Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award.

*2)* To provide mentoring support/resources/guidance to trainees (female and male) in physiology.

- Administer a mentoring program for junior physiologists.
- Administer the Caroline tum Suden/Frances Hellebrandt Professional Opportunity Awards.

*3)* To promote and raise the visibility of female physiologists across all career stages (trainees, early/mid-career, and established career).

*4)* To highlight and promote the success of female physiologists.

*5)* To promote the activities of the WIP Committee.

- Submit reports of APS and FASEB activities for publication in *The Physiologist*.

*6)* To coordinate activities with other committees on women within the FASEB organization and those of other scientific societies.

- Nominate women APS members for the annual FASEB Excellence in Science Award.
- Chair serves as APS representative on FASEB's Excellence in Science Award Committee.

## Strategic Planning Meeting

The WIP Committee and invited guests met at APS headquarters May 2–3, 2016, for a Strategic Planning Meeting. In accordance with our request for funding to Council in July 2015, the primary objective of this meeting was to develop a 5-year strategic plan for the WIP committee to:

- Increase gender equality among APS membership.
- Increase recruitment and retention of female students in physiology.
- Promote the success of women physiologists across career stages.

Nine WIP Committee members, two invited guests, and four APS staff were in attendance. We had an exceptionally productive meeting where we were able to thoroughly review our current charge and committee activities, and explore potential new initiatives for the advancement of women within the Society and the wider scientific community, including extensive discussion of options for new mentoring programs within the Society. The final meeting report was approved by APS Council in December 2016. Specific items addressed by Council included:

- Addition to the WIP Committee charge activities that may address the needs of the LGBTQ community.

- Delay distribution of a formal survey to APS membership to assist in developing mentoring initiatives until after the Society completes the Strategic Planning process.

- Approval of an annual WIP Committee Fall Meeting to facilitate the management of current activities and new initiatives arising from our Strategic Planning Meeting.

## Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award

Seven excellent nominations were received for the 2017 Bodil M. Schmidt-Nielsen Distinguished Mentor and Scientist Award. The WIP Committee selected Kurt Albertine (Professor of Pediatrics at the University of Utah School of Medicine) as the awardee. During the EB meeting, Albertine gave an excellent talk, providing an overview of his best tips on mentoring that he has developed over his prestigious career. The multimedia presentation (slides and audio) from Albertine's presentation will be posted on the APS website. The lecture was followed by an afternoon tea

reception, attended by APS presidents (current, past, incoming), WIP Committee members, APS trainee award winners, APS staff, and guests specified by the awardee. Albertine will also develop a Mentoring Forum column based on his lecture to be published in *The Physiologist* over the next year.

## APS Professional Opportunity Awards: Caroline tum Suden/Frances Hellebrandt, Steven M. Horvath, Fleur L. Strand, and Gabor Kaley Awards

The WIP Committee received 95 initial applications for the 2017 tum Suden Professional Opportunity Awards, which is lower than the number of applications in 2016 (117). The committee was able to fund 50 tum Suden Awards, 2 Horvath Awards (awarded to the top two URM applicants), and 1 Strand Award (awarded to the top overall applicant) for an overall funding rate of 56% (53 awards in total).

## Mentoring Programs

### *Mentoring Forum*

Over the past 12 months, the WIP Committee has coordinated the development of six new Mentoring Forum columns published in *The Physiologist*. These columns cover a wide range of topics, from lessons on resilience and science careers in the federal government to professional service, connecting with women in science, mentoring guidance, and teaching practice. Each article has related bulletin board discussion topics at the mentoring website and on LifeSciTRC.

### *Online Mentoring Programs*

The WIP Committee continues to provide information about MentorNet on the APS website, and the APS is also a Scientific & Professional Society partner with the National Research Mentoring Network (NRMN) (*https://nrmnet.net/*), which provides comprehensive mentoring services for APS members, including a "Virtual Mentoring Program," similar to the MentorNet approach. A variety of mentoring resources are also available on the APS website under the "Career Development & Mentoring" link. During the Strategic Planning Meeting, the WIP Committee explored a number of innovative options that would provide much needed mentoring experiences across career stages without incurring the logistical and fiscal expenses of establishing and maintaining a formal mentoring program, such as MentorNet, or a similar APS-specific program. These program ideas will be developed further during the WIP Committee 2017 fall meeting.

### *WIP Committee Facebook Page*

The WIP Committee has a very active Facebook page, with 691 "likes" and many posts reaching more than 300 views. The specific goals of this page are to share information that is relevant to the mission of the WIP Committee with both men and women, including content on gender issues in science, promotion of physiology to early career scientists, and mentoring. Please visit and "Like" the WIPC Committee Facebook page at *https://www.facebook.com/APS.WIPC.*

## Experimental Biology Mentoring Workshop

For EB 2017, the workshop was titled "Choosing the Right Lab and Personnel for Your Career." The workshop was held on Sunday from 10:30 AM to 12:30 PM and was attended by approximately 125 participants! Twenty-one attendees (~49%) completed a survey, and, based on these responses, the audience was primarily made up of trainees (high school students, undergraduate students, graduate students, postdoctoral fellows); however, there was a wide range of audience members, including junior and established investigators, and laboratory technicians. The speaker presentations received very high ratings (average of 4.5 out of 5.0), and the subsequent 40-minute panel discussion resulted in an informative and lively dialogue between the speakers and audience members.

## Representation of Women in APS and Scientific Community Leadership

One of the charges of the WIP Committee is to support advancement of women in APS and in the scientific community at large. The WIP Committee annually reviews the number of women serving on APS Committees and Section Steering Committees. Of the members who include sex in their membership profile ($n$ = 7,411), women currently comprise 31% of the APS membership [28% of the regular membership ($n$ = 6,203) and 48% of the graduate/undergraduate student membership ($n$ = 1,208)]. Most of these numbers either remain the same or have increased slightly from last year.

In reviewing the membership of the APS Section Advisory Committee (SAC) and other Society

committees, we found that the representation of women on the general Society committees continues to be very good. The WIP Committee commends the CoC for its ongoing attention to diversity on APS-appointed committee positions. The committee is also pleased to note that, in 2017, the APS Council has four women of nine elected regular members (44%) as well a woman in the past-president position. Thus, overall, 5 (42%) of the 12 elected members of Council are women. The committee contends that this continues to reflect the increasing role of women in the Society as a whole and especially in committee leadership positions, which provide important visibility and service opportunities. In 2017, the SAC also has 4 women representatives out of 13 (31%); we continue encouraging all sections to involve women in their leadership positions, particularly as section chairs.

In reviewing the Section Steering Committees, on average, we found the same proportion of women as last year (38%). Currently, all but three sections (CNS, EEP, Respiration) have steering committees where at least 25% of the members are women, and 6 of the 12 sections have steering committees where at least 40% of the members are women. Similarly, 20 of 22 APS committees are comprised of at least 25% women members; this is compared to 15 of 22 committees last year. Women are also chairs of seven of these APS committees (32%). The WIP Committee encourages the Committee on Committees and the Section Steering Committees to continue their efforts to identify and select women members for APS Committees.

Historically, there have been very few women selected for the major APS awards. At EB 2017, only 1 of the 15 (7%) distinguished lectures was given by a woman; this is down from 3 lectureships in 2016 and 6 lectureships in 2015. The committee continues to strongly encourage sections to include women on their slate of candidates for their distinguished lectureships in the future.

## Concluding Remarks

The WIP Committee continues to work to promote women within the Society and the scientific community, and to provide mentoring for early career investigators and trainees. We look forward to additional involvement in new APS programs and activities, and we will strive to remain instrumental in the implementation of the New Strategic Plan developed by Council.

*Council accepted the report of the Women in Physiology Committee.* ●

# Experimental Biology

## Experimental Biology 2018 Distinguished Lectures

### Physiology in Perspective: The Walter B. Cannon Memorial Award Lecture

**Ole H. Petersen**

Cardiff University

*The Roles of $Ca^{2+}$ and ATP in Pancreatic Physiologi and Pathophysiology*

Sunday, April 22, 2018, 5:30 PM

*Supported by Sucampo*

### Henry Pickering Bowditch Memorial Award

**Yatrik M. Shah**

University of Michigan

*Oxygen Sensing Pathways: A Critical Link Between Inflammation and Cancer*

Monday, April 23, 2017, 5:30 PM

### Robert M. Berne Distinguished Lectureship of the APS Cardiovascular Section

**Jason Yuan**

University of Arizona Health Sciences

*Mechanisms of Pulmonary Vascular Disease: Pathogenic Role of Ion Channels*

Tuesday, April 24, 2018, 3:30 PM

### Hugh Davson Distinguished Lectureship of the APS Cell and Molecular Physiology Section

**Paul Quinton**

University of California, San Diego

*Confessions of a Long-Term Extra-Marital Affair with Bicarbie*

Sunday, April 22, 2018, 3:30 PM

### Joseph Erlanger Distinguished Lectureship of the APS Central Nervous System Section

**Wolfram Schultz**

University of Cambridge

*Getting the Best Reward: Neuronal Mechanisms for Utility Maximisation*

Monday, April 23, 2018, 3:30 PM

### August Krogh Distinguished Lectureship of the APS Comparative and Evolutionary Physiology Section

**Stanley S. Hillman**

Portland State University

*Anuran Amphibians as Models for Understanding Extreme Dehydration Tolerance*

Tuesday, April 24, 2018, 3:30 PM

*Supported by Novo Nordisk Fonden*

### Solomon Berson Distinguished Lectureship of the APS Endocrinology and Metabolism Section

**Erik A. Richter**

August Krogh Institute

*The BIG story: the Beautiful, Integrative, Glucose Metabolism and Exercise*

Monday, April 23, 2018, 3:30 PM

### Edward F. Adolph Distinguished Lectureship of the APS Environmental and Exercise Physiology Section

**David Poole**

Kansas State University College of Veterinary Medicine

*Muscle Microcirculation: Gateway to Function and Dysfunction*

Monday, April 23, 2018, 1:30 PM

### Horace W. Davenport Distinguished Lectureship of the APS Gastrointestinal and Liver Physiology Section

**Jerold R. Turner**

Brigham and Women's Hospital

Tuesday, April 24, 2018, 3:30 PM

### History of Physiology Group Lecture

**Peter B. Raven**

University of North Texas Health Science Center

*Bengt Saltin, MD, DSci (1935–2014): Exercise is Medicine*

Tuesday, April 24, 2018, 1:00 PM

### Carl Ludwig Distinguished Lectureship of the APS Neural Control and Autonomic Regulation Section

**David Paterson**

University of Oxford

*Heart Meets Brain: Brain Meets Heart: Therapeutic Opportunities*

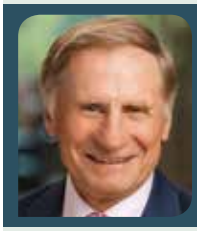
Monday, April 23, 2018, 1:30 PM

### Carl W. Gottschalk Distinguished Lectureship of the APS Renal Section

**Lisa M. Satlin**

Icahn School of Medicine at Mount Sinai

Monday, April 23, 2018, 3:30 PM



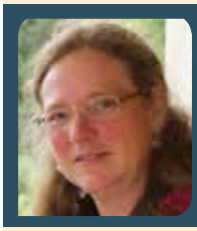
### Julius H. Comroe, Jr. Distinguished Lectureship of the APS Respiration Section

**Bert Forster**

Medical College of Wisconsin

*Interdependence of Neuromodulators in the Control of Breathing*

Tuesday, April 24, 2018, 3:30 PM



### Claude Bernard Distinguished Lectureship of the APS Teaching of Physiology Section

**Jenny L. McFarland**

Edmonds Community College

Sunday, April 22, 2018, 3:30 PM

Supported by ADInstruments

### Ernest H. Starling Distinguished Lectureship of the Water and Electrolyte Homeostasis Section

**David L. Mattson**

Medical College of Wisconsin

*Diet, Inflammation and Hypertension*

Sunday, April 22, 2018, 3:30 PM

## APS Nobel Prize Award Lecture

**Leland Hartwell**

The Biodesign Institute, Arizona State University

Wednesday, April 25, 2018, 3:30 PM

# Experimental Biology 2018

## April 21–25, 2018, San Diego, CA

## PHYSIOLOGY PLATFORM SESSIONS

### Saturday, April 21, 2018

| Room | Times as Indicated | | |
|---|---|---|---|
| 20A | 8:00 AM–12:00 PM<br>*Education Committee Refresher Course*<br>GI Physiology: Not Just the Gut Anymore<br>**Sasser/Merritt** | 2:15 PM–5:15 PM<br>*WEH Section Award Session*<br>WEH Trainee Award Finalists and Data Diuresis<br>**O'Conner/Polichnowski** | |
| 22 | | | 3:00 PM–5:00 PM<br>*NCAR Section*<br>Data NCARNation |
| 24 | 9:30 AM–11:30 AM<br>*MCS President's Symp* | 1:00 PM–3:00 PM<br>*MCS Abstract-based Symp* | 3:30 PM–5:30 PM<br>*MCS Abstract-based Symp*<br><br>6:00 PM–8:00 PM<br>*MCS Poster Discussion* |
| 25A | 9:00 AM–5:00 PM<br>ETG Pre-Meeting | | |
| 25B | | 1:00 PM–2:30 PM<br>*ACE Committee Symp*<br>Avoiding Common Pitfalls in Preclinical Animal Research Design<br>**Michele** | |
| 25C | | | 3:00 PM–4:30 PM<br>*Communications Committee Symp*<br>Social Media for the Professional Scientist<br>**Goodman** |
| 26 | | 1:00 PM–3:00 PM<br>*Techniques Workshop*<br>Sex and Age as Biological Variables in Physiology Research<br>**Yosten/Kolar** | 3:00 AM–5:00 AM<br>*Techniques Workshop*<br>Transformative Technologies Enabling Ecological Assessment of Human and Wildlife Physiology<br>**Sandberg/Crossley** |
| 27 | | 1:00 PM–2:30 PM<br>*AFMR Symp*<br>The Role of TIEG1 in Disease Processes: From Bench to Bedside<br>**Rajamannan/Hawse** | 3:00 PM–4:30 PM<br>*AFMR Symp*<br>The Mevalonate Pathway: A Fundamental Player in Human Disease<br>**Zeki/Ghavami** |
| 28A | | 1:00 PM–5:15 PM<br>*PGG Special Session*<br>5th Annual Physiological Genomics Conference | |

## Sunday, April 22, 2018

| Room | 8:30–10:00 AM | 1:30–3:00 PM | 3:30–5:00 PM |
|---|---|---|---|
| 20A | *IPSS Symp*<br>Ischemic and Hypoxic Conditioning: Potential for Protection of Vital Organs<br>**Rickards/Sprick** | *APS President's Symp Series*<br>Exosomes: The New Frontier. Cell Biology of Exosomes | *MCS Lecture*<br>MCS Landis Award Lecture and Business Meeting<br><br>5:30 PM–6:30 PM<br>*APS Cannon Lecture* Supported by Sucampo AG<br>**Petersen** |
| 22 | *MBG Symp*<br>Maintenance and Remodelling of the Neuromuscular Junction in Health and Disease<br>**Ljubicic** | *CV Section Symp*<br>American Journal of Physiology Heart and Circulatory Physiology Editors Symp<br>**Zucker/Lindsey** | 3:30 PM–5:00 PM<br>*CV Section FT*<br>Kaley Award FT: Cerebral Vascular Dysfunction and Impaired Cognitive Function<br>**Roman** |
| 23 | *CV Section Symp*<br>Of Mice and Men: What Have We Really Learned About the Regulation of Coronary Vascular Function in Health and Disease?<br>**Phillips/Goodwill** | *GIL Section FT*<br>Cell Plasticity and Repair and Disease Mechanisms in the Stomach, Liver and Intestine<br>**Powell** | 3:30 PM–4:30 PM<br>*WEH Section*<br>*Starling Lecture*<br>**Hinojosa-Laborde**<br><br>4:30 PM–5:30 PM<br>*WEH Section*<br>New Investigator Award Lecture<br>**Hinojosa-Laborde/Madhur** |
| 24 | *CV Section FT*<br>Role of the Microbiome in Cardiovascular Disease<br>**Buys** | *CV Section FT*<br>Innate and Adaptive Immunity in Cardiovascular Physiology<br>**Madhur** | |
| 25A | 7:00 AM–8:00 AM<br>*TAC Symp*<br>Do it Again: How to Achieve Rigorously Reproducible Research I<br>**Downey/Obi**<br><br>8:30 AM–10:00 AM<br>*ETG Symp*<br>Building Epithelial Organs In Vitro to Study Physiology and Pathogenesis of Disease<br>**Nørregaard/Dixon** | *Renal Section Symp*<br>ENaC Proteins As Mechanosensors in Endothelial and Vascular Smooth Muscle Cells<br>**Drummond/Ashley** | *Resp Section FT*<br>Communication and Miscommunication in Lung Injury and Repair<br>**Koval/Birukov** |
| 25B | 7:00 AM –8:00 AM<br>*Careers Symp*<br>2018 Careers in Physiology Symp I<br>**Brandauer/Becker**<br><br>8:30 AM–10:00 AM<br>*Translational Physiology Interest Group FT*<br>Translational Physiology Showcase: TBD<br>**Young** | *EEP Section FT*<br>Exploring Novel Mechanisms to Improve Exercise Tolerance in Health and Disease<br>**Harris/Barnes** | *EEP Section Symp*<br>Epigenetic Memory of Environmental Exposure: a Physiological Perspective<br>**Murashov/Clanton** |

| | | | |
|---|---|---|---|
| 25C | 7:00 AM–8:00 AM<br>*WIPC Symp*<br>Recognizing and Responding to Implicit Bias in Science I<br>**Kendra Wallace/Ho**<br><br>8:30 AM–10:00 AM<br>*EEP Section Symp*<br>Too Hot to Handle: Controversies in Exertional Heat Stroke Prevention and Treatment<br>**Laitano/King** | *CEP FT*<br>Comparative and Evolutionary Physiology Section Trainee-Driven FT<br>**Crossley** | *NCAR Section FT*<br>Psychological Stress Disorders: Novel Concepts and Mechanisms<br>**Sabharwal** |
| 26 | *NCAR Section FT*<br>NCAR Young Investigator Awards<br>**Moraes/Poglitsch** | *CNS Section Symp*<br>Sex Differences in Central Circuits<br>**Wainford/Browning** | *Teaching Section*<br>*Bernard Lecture*<br>Supported by ADInstruments<br>**McFarland** |
| 27 | *WEH SectionSymp*<br>Inflammation and Sodium Reabsorption<br>**Lee/Pai** | *Resp Section Symp*<br>Non-Canonical Functions of the Lung in Immunity and Hemostasis<br>**Kuebler/Juss** | *Cell Section Davson Lecture*<br>**Quinton** |
| 28A | *Renal Section FT*<br>Renal Section Young Investigator Award FT<br>**Pluznick** | *Cell Section Symp*<br>Organoids: Modelling Cell Physiology and Disease in 3D<br>**Bradbury/Ameen** | *CNS Section Symp*<br>Intersection of Central Pain and Reward Circuitry in CNS Disorders<br>**Edwards/Roberto** |
| 28B | *Teaching Section Symp*<br>Addressing Higher Levels of Bloom's Taxonomy in the Teaching and Learning of Physiology<br>**Clements-Jewery/Hopper** | *PGG FT*<br>From Gene to Function of Complex Traits: Analysis of Genes Identified in Human GWAS and Animal Models<br>**Solberg Woods** | *Resp Section FT*<br>Microglia as Effectors of Respiratory Plasticity in Health and Disease<br>**Kinkead/Powell** |
| 28DE | *PGG Nonfunded FT*<br>Physiological Genomics Trainee Highlights | *SfRBM Symp*<br>Redox Biology: A Unifying Theme in the Etiology of Human Diseases<br>**Case/Kevil** | *GIL Section*<br>John Forte GIL Plenery Session<br>**Uno/Frey** |

## Monday, April 23, 2018

| Room | 8:30–10:00 AM | 1:30–3:00 PM | 3:30–5:00 PM |
|---|---|---|---|
| 20A | *IPSS Symp*<br>Bioartificial Organs: Using Donor and Synthetic Scaffolds<br>**Harrison-Bernard** | *President's Symp Series*<br>Exosomes: The New Frontier. Pathophysiology of Exosomes | |
| 22 | *Sex Group Symp*<br>Impact of Sex-Specific Size of the Normal and Failing Left Ventricle: Studies in Humans and Mice<br>**Kerkhof/Miller** | *CV Section Symp*<br>CV Section – Young Investigator Symp<br>**Goulopoulou/Belin de Chantemele** | *CV Section FT*<br>Protective Mechanisms in the Vasculature: Wiggers Award Session<br>**Sigmund** |
| 23 | *Hypoxia Group Symp*<br>Novel Physiologic-Based Approaches to Treating Sleep Apnea<br>**Dempsey/Bates** | *GIL Section Symp*<br>Identification of Novel Drug Targets For the Modulation of Gastrointestinal Motility<br>**Uray/Perrino** | *CV Section Symp*<br>Brown Adipose Tissue and Cardiovascular Function: Insulin Resistance, Vascular Tone, and Cardioprotective Effects<br>**Stanford/Scherrer-Crosbie** |

## Monday, April 23, 2018, continued

| | | | |
|---|---|---|---|
| 24 | *NCAR Section FT*<br>Novel Insights on Sympathetic Activation in Kidney Disease: From Animal Models to Clinical Trials<br>**Park/Becker** | *NCAR Section Ludwig Lecture*<br>**Paterson** | *Renal Section Gottschalk Lecture*<br>**Satlin**<br><br>5:30 PM–6:30 PM<br>*APS Bowditch Lecture*<br>**Shah** |
| 25A | 7:00 AM–8:00 AM<br>*TAC Symp*<br>Do It Again: How to Achieve Rigorously Reproducible Research II<br><br>8:30 AM–10:00 AM<br>*PGG FT*<br>Non-coding RNA Regulation of Inflammation in Cardiovascular, Kidney, and Respiratory Diseases<br>**Kriegel/Rogers** | *ETG FT*<br>Hans Ussing Lecture of the Epithelial Transport Group<br>**Akiba** | *Resp Section FT*<br>Molecular, Cellular and Systems-Level Mechanisms Driving Ventilation and CO2 Sensitivity during Acute and Chronic Hypercapnia<br>**Hodges/Hawkins** |
| 25B | 7:00 AM–8:00 AM<br>*Careers Symp*<br>**Brandauer**<br><br>8:30 AM–10:00 AM<br>*Renal Section Symp*<br>New Concepts in JGA Physiology<br>**Peti-Peterdi/Buckley** | *Renal Section FT*<br>Advances in Renal Physiology I<br>**Ortiz** | *Translational Group Symp*<br>Altering Phenotype Without Genotype<br>**Sones/Reijnders-Most** |
| 25C | 7:00 AM–8:00 AM<br>*WIPC Symp*<br>Recognizing and Responding to Implicit Bias in Science III<br><br>8:30 AM–10:00 AM<br>*Cell Section FT*<br>Ion Channels and Transporters in Health and Disease<br>**Worrell** | *Cell Section Symp*<br>Biophysical and Metabolic Regulation of Stem Cells<br>**Rehman/Shin** | *CEP Section Symp*<br>Comparative Perspectives on Maximal O2 and CO2 Transport in Animals<br>**Hedrick** |
| 26 | *Nutrition Symp*<br>The Physiology of Personalized Nutrition<br>**Voy/Anthony** | *PIC Symp*<br>Biosensors in Health and Disease<br>**Bucher** | *CNS Section Erlanger Lecture*<br>**Schultz** |
| 27 | *CV Section FT*<br>Regulation of Blood Flow in Health and Disease<br>**Ohanyan** | *EEP Section Adolph Lecture*<br>**Poole** | *EM Section Berson Lecture*<br>**Richter** |
| 28A | *EM Section FT*<br>Gut-Brain Interactions and Control of Feeding Behavior<br>**Stein** | *EM Section Symp*<br>The role of REDD1 in the Regulation of Skeletal Muscle Metabolism<br>**Steiner** | *WEH Section FT*<br>Impact of Diet on Blood Pressure Regulation<br>**Greene/Stodola** |
| 28B | *Teaching Section FT*<br>Abstract-Driven FT<br>**Osborne** | *History Group Symp*<br>The Physiological Challenges of Escaping Extreme Environments: DIsabled Subs and Stratospheric Bailouts<br>**Ryan/Dean** | *Teaching Section Symp*<br>Synergizing Teaching and Scholarship<br>**Harris** |

## Tuesday, April 24, 2018

| Room | 8:30–10:00 AM | 1:30–3:00 PM | 3:30–5:00 PM |
|---|---|---|---|
| 20A | *IPSS Symp*<br>Tissue-Distributed Control of Sex Differences in Diabetes and Cardiovascular Disease<br>**Stafford** | *President's Symp Series Symp*<br>Exosomes: The New Frontier. Exosomes in Diagnostics and Therapeutics | 5:30 PM–7:00 PM<br>*APS Business Meeting* |
| 22 | *EM Section Symp*<br>Mechanisms Underlying Skeletal Muscle Adaptation in Health and Disease<br>**Lang** | *CV Section Symp*<br>Steroid Receptor Signaling in Cardiovascular Health and Disease<br>**Hamblin/Clayton** | *MBG FT*<br>Exercise and Skeletal Muscle as Key Regulators of Whole Body Aging<br>**Jackson/Brooks** |
| 23 | *NCAR Section Symp*<br>Neuro-Immune Interactions in Inflammatory Homeostasis<br>**Marvar** | *GIL Section FT*<br>GI and Liver Physiology and Disease<br>**TBD** | *GIL Section Davenport Lecture*<br>**Turner** |
| 24 | *Cell Section Symp*<br>Molecular Mechanisms for Salt-induced Cardiovascular Disease<br>**Kirbo/Osborn** | *Resp Section Comroe Lecture*<br>**Forster** | |
| 25A | 7:00 AM–8:00 AM<br>*TAC Symp*<br>Do It Again: How to Achieve Rigorously Reproducible Research<br><br>8:30 AM–10:00 AM<br>*Renal Section FT*<br>Advances in Renal Physiology II<br>**Inscho** | *Cell Section FT*<br>Epithelial Mechano-Sensitivity in Health and Disease<br>**Beyder/Chebib** | *ETG FT*<br>Hebert Lecture of the Epithelial Transport Group<br>**Subramanya** |
| 25B | 7:00 AM–8:00 AM<br>*Careers Symp*<br>**Brandauer**<br><br>8:30 AM–10:00 AM<br>*EEP Section FT*<br>Getting Blood to Where it Needs to Go: Emerging Mechanisms Regulating Skeletal Muscle Blood Flow in Health and Disease<br>**Romero/Hearon** | *Resp Section FT*<br>Cell Plasticity: Calcium, cAMP and Beyond<br>**Mehta** | *WEH SectionFT*<br>Adaptations in Fluid Balance and Blood Pressure Regulation during Pregnancy<br>**Denton** |
| 25C | 7:00 AM–8:00 AM<br>*WIPC Symp*<br>WIPC Symp 2018: Recognizing and Responding to Implicit Bias in Science<br><br>8:30 AM–10:00 AM<br>*CEP Section FT*<br>The Effects of Environmental Challenges on Performance and Metabolism<br>**Williams/Hindle** | *EEP Section Symp*<br>Molecular Transducers of the Physiological Adaptations to Exercise and Aging<br>**Seals/Martens** | *EEP Section Symp*<br>Respiratory and Limb Skeletal Muscle Weakness in Disease: Mechanisms and Treatments<br>**Bowen/Ferreira** |
| 26 | *Resp Section Symp*<br>Neuroplasticity of Airway Reflexes<br>**Bolser/Pitts** | *Hypoxia Group FT*<br>**Harris/Moya Cespedes** | *CEP Section Krogh Lecture*<br>Supported by Novo Nordisk Fonden<br>**Hillman** |

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|---|---|---|---|
| 27 | *CV Section FT*<br>Novel Discoveries in Vascular Physiology<br>**Jaggar/Earley** | *WEH Section FT*<br>Origins of Cardiovascular Disease: Does Metabolic Disease Always Come First?<br>**Spradley/De Souza** | *CV Section Berne Lecture*<br>**Yuan** |
| 28A | *CNS Section FT*<br>Interrogating Neuronal Circuits Mediating Body Fluid Homeostasis<br>**Krause/TBA** | *CV Section Symp*<br>The Vasculome: An Integrated Exploration of Vascular Reactivity, Lineage, and Specialization<br>**Galis/Yin** | *Cell Section FT*<br>Cell Signaling: Proteins, Pathways, and Mechanisms<br>**Hamilton** |
| 28B | *CV Section FT*<br>Endothelial Cell Contraction or Retraction (Insights Into Barrier Function and Permeability)<br>**Webb/Wenceslau** | *NCAR Section Symp*<br>Sympathetic Neurovascular Transduction in Humans: Are we there yet?<br>**Shoemaker** | *NCAR Section FT*<br>Battle of the Reflexes: Chemo- vs. Baroreflexes during Physiological Stressors, Aging and Cardiovascular Disease<br>**Kellawan** |
| 28DE | | *Renal Section Symp*<br>Structure and Function of Renal Epithelial Cilia<br>**Bell/Satlin** | |
| TBD | | 1:00 PM–2:00 PM<br>*History Group Lecture*<br>**Raven** | |

## Wednesday, April 25, 2018

| Room | 8:30–10:00 AM | 1:30–3:00 PM | 3:30–5:00 PM |
|---|---|---|---|
| 20A | *IPSS Symp*<br>Extracellular Matrix Remodeling and Integrin Signaling in Metabolic Diseases<br>**Wasserman** | | 3:30 PM–4:30 PM<br>APS Nobel Prize Award Lecture |
| 22 | *CV Section Symp*<br>Chemotherapy Induced Vascular Toxicity: Do Small Things Matter? Cosponsored by AJP - Heart and Circulatory Physiology<br>**Beyer/Croce** | *WEH Section FT*<br>Stress, Sleep, Circadian Rhythms and Blood Pressure Regulation<br>**Gumz/Johnston** | |
| 23 | *Physoc Symp*<br>Epithelial Crosstalk and Innate Immunity<br>**Garnett** | *APS/Physoc Symp*<br>DAMPs and Inflammasomes: A Clear and Present Danger<br>**Khan** | |
| 24 | | *WEH Section FT*<br>Immune Modulation of Blood Pressure and Vice Versa<br>**Ryan** | |
| 25A | *GIL Section Symp*<br>Bile Acids in the Small Intestine and Colon, Physiology, Pathophysiology, and Therapeutic Opportunities<br>**Keely/Lajczak** | *SFiB Pan-American Symp*<br>Pan-American Symp<br>**Campagnole-Santos** | |

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|---|---|---|---|
| 25B | *CV Section FT*<br>Post-translational modifications in cardiovascular disease<br>**Scott** | *EEP Section FT*<br>AMPK-mediated control of mitophagy<br>**Hood/Yan** | |
| 25C | *CEP Section FT*<br>Comparative Models of Disease<br>**Pamenter** | *EM Section Symp*<br>Cardiac Metabolism Moving Center Stage: New Insights Enabling Metabolic Modulation Therapy<br>**Wende/Glatz** | |
| 26 | *MBG FT*<br>Role and Importance of Mitophagy in Skeletal Muscle in Health and Disease<br>**Beaudry/Deldicque** | *CV Section FT*<br>Mechanotransduction in Cardiovascular Function<br>**Thodeti/Lindsey** | |
| 27 | *Resp Section FT*<br>The Influence of State on Cardiorespiratory Control Mechanisms<br>**Cummings/Dutschmann** | | |
| 28A | *EM Section FT*<br>Brain - Gut Microbiota Interactions in Cardiovascular and Metabolic Control<br>**Collister** | *CNS Section FT*<br>The Gut-Brain Axis<br>**Torres-Reveron/Appleyard** | |
| 28B | *WEH SectionFT*<br>Novel Approaches and Techniques in Water and Electrolyte Research<br>**Smith** | *Resp Section FT*<br>Resp Section Abstract-Driven FT<br>**Prakash/Koval** | |

# APS News

## Physiology and Biotechnology: The 7th AAPS Congress, Lagos, Nigeria

Bolanle Iranloye, Yemi I. Olatunji-Bello, and Frank B. O. Mojiminiyi

The 7th Congress of the African Association of Physiological Sciences (AAPS) was held at the Welcome Centre Hotel, Lagos, Nigeria, September 5–8, 2016. It was organized by the AAPS and the Physiological Society of Nigeria (PSN). The following societies participated: the Sudanese Physiological Society (SPS), the Physiology Society of Southern Africa (PSSA), the Egyptian Society of Physiological Sciences (ESPS), the American Physiological Society (APS), the International Union of Physiological Sciences (IUPS), and the Physiological Society of Nigeria (PSN).

The objectives of the Congress included the following:

- Sharing emerging techniques in the development and dissemination of knowledge in research, learning, teaching, and the training of future physiologists.
- Building capacities of young African physiologists by updating their knowledge and improving their communication and presentation skills.
- Providing information on teaching and research funding opportunities for Africans.
- Building scientific collaborations among African physiologists and also between African and non-African physiologists.
- Enhancing the organizational structure of the AAPS and convincing more national physiological societies to join as members.
- Enhancing communication among AAPS members.

### The Program

The Congress was declared open by Yemi Osinbajo, the Vice President of the Federal Republic of Nigeria, through a representative. In attendance at the opening ceremony was President of the IUPS, Sir Denis Noble, who also served as the president of the 7th AAPS congress. Also present was Gary Sieck, a former president of the APS, Jide Idris, the representative of the Governor of Lagos state, and a host of other dignitaries.

The program included:

- Three plenary sessions. The speakers at these sessions were Sunny Ohia, the thematic lecturer Kennedy Erlwanger, and Gary Sieck.
- Two panel discussions of four panelists each were held on "Developing Curricula in Applied Physiology and Teaching'' and ''Research Funding Opportunities for Africans."
- AAPS/ADInstruments "Training the Trainers'' workshop that ran for three sessions. This was anchored by Tony MacKnight, Abhor Ighoroje, Rob Carroll, Penny Hansen, and two younger physiologists: Lamis Kaddam and Adesina Arikawe.
- The cardio-metabolic syndrome workshop, which ran for a whole day with five invited speakers and five oral communications from submitted abstracts related to cardio-metabolic syndrome. This workshop

Some delegates at the opening ceremony

Sir Denis Noble and Dr. Gary Sieck arriving for a session

Yemi Olatunji-Bello, the AAPS 2016 LOC Chair, and Mrs. Bolanle Iranloye, the LOC Treasurer


Gary Sieck, Tony Ebeigbe, and Faadiel Essop with some young physiologists

was organized by Faadiel Essop and was generously sponsored by the APS.
- 18 oral presentations in two parallel sessions.
- 125 poster presentations.

## Participants

The participants and their respective countries of origin are shown in Table 1.

**Table 1. Participants and countries of origin**

| Country | No. of Participants |
|---|---|
| Sudan | 6 |
| Egypt | 1 |
| South Africa | 2 |
| Zimbabwe | 2 |
| U.S. | 5 |
| Canada | 1 |
| UK | 1 |
| New Zealand | 1 |
| Nigeria | 211 |
| **Total** | **230** |

## Outcomes of the Congress

The congress had the following outcomes.

***1)*** **Election of AAPS executives.** Emeritus Professor Soga Sofola emerged as the new President of the AAPS, with Faadiel Essop (President of the PSSA) as the vice president. Gary Sieck served as the electoral officer.

***2)*** **Strengthening of the AAPS and its constituent societies.** The pervasive enthusiasm that was palpable at the Lagos meeting suggests that AAPS has come of age. However, there should be no room for complacency. There is also the need to bring on board again the entire East African subregion as well as other countries – besides Nigeria – from West Africa. These challenges are already being addressed by the AAPS executive committee. Indeed, there are already plans to hold a meeting in East or Central Africa as a way of resuscitating the chapters there before the next AAPS congress in Sudan in 2020.

***3)*** **Networking between physiologists from Africa and invited (non-African based) physiologists.**

***4)*** **Training of African physiologists on sourcing for research grants.**

***5)*** **36th PSN Annual General Meeting was held.**

## A Constructive Engagement at EB 2016 in San Diego!

This write-up will not be complete without mentioning a meeting between the APS Council and AAPS representatives at Experimental Biology 2016, which was held in San Diego, CA. Notable on the APS team were the then-APS President Patricia Molina, APS Past-President David Pollock, the then-President-Elect Jane Reckelhoff, Mike Hill, the current APS President Dennis Brown, and Martin Frank. On the AAPS team were Yemi Olatunji-Bello, Alexander Adelaiye, Akin Alada, and Frank Mojiminiyi. Since this meeting was crucial to the planned Nigerian AAPS congress, Yemi Olatunji-Bello, the chair of the LOC AAPS 2016 congress, hopped onto

Amal Saeed, the then AAPS President, making a comment

Faadiel Essop, the Vice President of the AAPS, making a comment at the AGM

the next available plane to San Diego and fortunately arrived in time for the joint meeting. Far-reaching decisions were taken concerning APS/AAPS relations. Aside from a humongous amount of benefits available to the AAPS from the rich repertoire of the APS, one of the immediate benefits was financial support from the APS to facilitate the attendance of 50 young African scientists at the AAPS congress. The AAPS executive committee intends to continue the dialogue with the APS so that the far-reaching decisions taken at the meeting will be actualized.

The 7th AAPS congress was, undoubtedly, a successful event. The atmosphere was exciting, and the sessions were very well organized and proceeded in orderly fashion. They teemed with young enthusiastic physiologists who were bowled over by the sight of giants of physiology such as Sir Denis Noble, Gary Sieck, Penny Hansen, Rob Carroll, Amal Saeed, Soga Sofola, Prem Gathiram, Faadiel Essop, Ojuka, Kennedy Erlwanger, and others. They scrambled to take pictures with them!

To sum up, the 7th AAPS congress was a pointer to what Africa can do. This suggests that the AAPS is coming of age and that it is determined to stand up and be counted among the important continental physiological societies on the globe. The success was brought about by a very determined and enterprising LOC that refused to take "no" for an answer, and cooperation within the AAPS council and also between the national physiological societies that make up the AAPS. In addition, there was strong encouragement from the IUPS, the APS, and The Physiological Society (London). It is hoped that such a conducive milieu will continue so physiology will not just survive in Africa but really prosper, as it is doing elsewhere. ●

Tony MacKnight of ADInstruments and Penny Hansenthe

Sir Denis Noble making a comment after an oral presentation by another delegate at a symposium

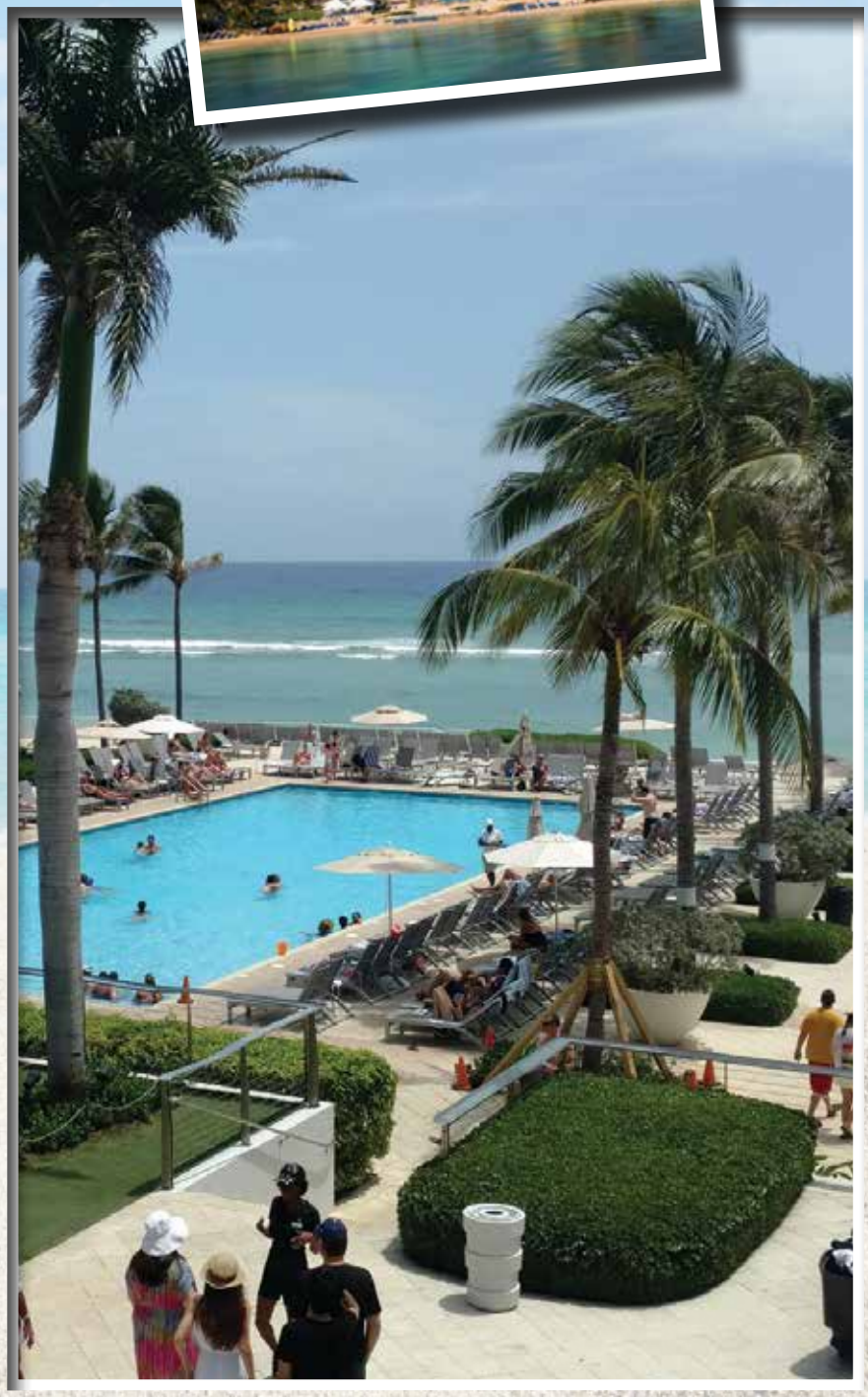
The generous support of the APS, ADInstruments, Wellcome Trust, The Lagos State Government, and The Physiological Society, London, is gratefully acknowledged. The APS sponsored the symposium on cardiometabolic diseases in Africa and attendance of 50 young African scientists. The strong moral support of Sir Denis Noble and that of the entire APS council, especially Patricia Molina and Martin Frank, is gratefully acknowledged. We thank Sonny Ohia, Gary Sieck, and Kennedy Erlwanger the main speakers; as well as Rob Carrol, Penny Hansen, Tony MacKnight, Ahbor Ighoroje, Lamis Kaddam, and Adesina Arikawe for organizing the teaching workshop. The organizers and speakers at the panel on ''Research Funding Opportunities for Africans'' are also gratefully acknowledged. We remain eternally grateful to everyone who contributed to the success of AAPS Congress 2016 in Lagos, Nigeria!

# Chair/Program Director Leadership Retreat Announced

Chairs or leaders of a Department, Division of Physiology, or Program of Physiology in any form, in any type of school (medical, graduate, undergraduate, veterinary, osteopathic, dentistry, etc.) are cordially invited to attend the Association of Chairs of Departments of Physiology's (ACDP) annual Leadership Retreat. The meeting will be held on November 30 to December 3, 2017 at the Hilton Rose Hill Resort in Montego Bay, Jamaica.

Come connect with fellow leaders and hear about the latest in research, biomedical funding, and other issues of interest in a beautiful, relaxing setting. ACDP President Charles E. Wood (University of Florida College of Medicine) has developed a quality program for attendees along with numerous opportunities for networking and discussion of relevant issues.

Wood has announced that the 2017 Distinguished Service Awardee is Hershel Raff (St. Luke's Medical Center/Medical College of Wisconsin), and the 2017 Arthur Guyton Distinguished Lecturer is R. John Solaro (University of Illinois Chicago Medical College). Presentations will be made by both awardees.



**For more information about the meeting, see http://acdponline.org/Home/Meetings/2017-Leadership-Retreat.**

**Mark your calendars and plan to attend!**

# 2018 Arthur C. Guyton Educator of the Year Award Announcement

The 2018 Arthur C. Guyton Educator of the Year Award supported by Elsevier ($1,000 cash prize plus reimbursement of the advanced registration fee, a framed, inscribed certificate, up to $750 in travel reimbursement to the Experimental Biology meeting, and a complimentary ticket to the Section Dinner) recognizes a full-time faculty member of an accredited college or university and member of the APS who has independent evidence of *1)* excellence in classroom teaching over a number of years at the undergraduate, graduate, or professional levels; *2)* commitment to the improvement of physiology teaching within the candidate's own institution; and *3)* contributions to physiology education at the local community, national, or international levels. The awardee is requested to write an essay on his/her philosophy of education for publication in *The Physiologist*.

The typical nominee will have shown excellence in teaching and have made significant contributions in student advisement, graduate education, and/or curriculum design and reform at their institution. The activities that distinguish a candidate in the rankings include outreach activities at the state, national, or international level, and contributions to education through APS activities, peer-reviewed educational journal articles, and widely disseminated publications such as commercially produced textbooks, lab manuals, or software. Unsuccessful nominees may be reconsidered for the award during the subsequent year with notification to the nominee and the nominator and receipt of updated information. The award winner is announced at the APS Business Meeting during Experimental Biology.

## Nominations Process

Each nominee must be nominated by a member of APS. All candidate materials must be sent by December 1, 2017 to Beth Beason-Abmayr (Chair, Guyton Awards Selection Committee) at *bbeason@rice.edu*. ●

# Chapter News

## Michigan Physiological Society Fourth Annual Meeting

**Valerie VanRyn (Secretary-Treasurer), Michigan State University**
**Karen L. Ball (President), Alma College**
**Patrick J. Mueller (Past-President), Wayne State University School of Medicine**

As one high school teacher put it so powerfully, shortly after her students attended our annual meeting:

> "They loved interacting with people who also love research. The students did not know 'things like this existed,' and it truly has opened their eyes into the field of research in physiology. To provide a setting like this for high school students to participate both in the meeting and in presenting 'high school' research projects was such a good idea, and it is making the highlight reels here at my high school. My principal is even going to have the students who came to the MPS meeting receive special recognition during her speech at graduation Thursday! GO MPS! Several of my students want to continue with the MPS and possibly mentor other high school students for the years to come. At my school, the word has spread to the students taking both AP Biology and Applied Medical Research next year. I've had 10 students stop by and ask if we are doing MPS meeting next year. It created a social buzz! Imagine that . . . science chatter among teenagers!"
>
> – *Sue Speirs, Grosse Point North High School, Grosse Point, MI*

Prior to receiving the comment above, the Fourth Annual Meeting of the Michigan Physiological Society (MPS) began on June 8, 2017, and was hosted by Alma College in Alma, MI. An additional event related to the conference, the inaugural Michigan Physiology Quiz (MiPQ), was held 1 day prior on Wednesday, June 7. The meeting hosted 142 attendees, representing 20 institutions of secondary and higher level education including Alma College, Alma High School, Central Michigan University, Ferris State University, Grosse Pointe North High School, Hope College, Lumen Christi Catholic School, Michigan State University, Michigan Technological University, Michigan Youth Challenge Academy, Northern Michigan University, Northville High School, Oakland University, St. Clair County Community College, The University of Michigan-Ann Arbor, The University of Michigan-Flint, Western University (Ontario), Wayne County Community College District, Wayne State University, and Western Michigan University. Five educators from the high schools mentioned above also participated in our second annual Life Sciences Teacher Workshop offered in conjunction with the annual meeting on Friday, June 9. Twenty-three high school students also participated in programming from the Life Sciences Program, the annual meeting itself, and activities programmed specifically for them.

Registration began Thursday afternoon, June 8, and during the opening session Patrick Mueller (MPS President, Wayne State University) and Karen Ball (MPS President-Elect, Alma College) greeted MPS members, special attendees, and guests. On behalf of Alma College, Michael Selmon (Provost and Vice President for Academic Affairs, Alma College), welcomed the membership to the Alma College campus. To bring a close to the welcome and meeting opening, Bruce McAttee, the Mid-Michigan Regional Director from the Honorable Gary Peters' office (U.S. Senator, Michigan), discussed how his office views the public's perceptions of research, research funding, and how MPS members can advocate for research to help maintain or increase funding for research.

The Society then welcomed Keynote Speaker J. Kevin Shoemaker of Western University, School of Kinesiology in London, Ontario, Canada. Shoemaker's keynote address was titled "Forebrain Neurocircuitry Associated with Autonomic Function in Humans." A short question-and-answer period followed the keynote lecture, with Shoemaker kindly providing career advice specifically to trainees who were in attendance.

As in years past at annual meetings, trainees presented all of the other oral presentations. These trainees included high school, undergraduate, medical, and graduate students, as well as postdoctoral fellows. Trainees gained valuable experience by taking

advantage of opportunities to serve as session co-chairs, introducing speakers and moderating discussion periods following each talk. The Awards Committee selected presenters based on the quality of their abstract submissions. Trainees gave approximately 10-minute presentations followed by a 5-minute question-and-answer period. The question-and-answer sessions were guided by the trainee session co-chairs, who encouraged trainees in the audience to ask questions rather than faculty who accommodated this opportunity. This format enabled trainees to practice asking questions similar to those occurring at national meetings. Each oral presentation was judged by volunteer faculty to help determine the awards for the top presentations. There were 19 total oral presentations over the 2-day conference and included 3 research-oriented symposia and 1 education-based symposium.

The first oral session covered cardiovascular and renal physiology studies and was co-chaired by trainees Amelia Glazier (University of Michigan) and Guodong Pan (Henry Ford Hospital). The symposium featured five excellent talks by Enshe Jiang (postdoctoral fellow, Michigan Technological University); Janice Diaz-Otero (graduate student, Michigan State University); Timothy Bryson (graduate student, Wayne State University/Henry Ford Hospital); Keyona King-Medina (graduate student, Wayne State University/Henry Ford Hospital); and Melanie Flaherty (undergraduate student, Northern Michigan University).

The evening activities began with a strolling dinner, allowing attendees to view trainee research projects during the first of two poster sessions. The first poster session included roughly half of the 66 total posters. Poster abstracts were selected in advance by the Awards Committee to determine which posters would be further judged at the meeting. Poster presentations were also scored by a panel of volunteer faculty. Following the poster session, a Welcome Reception was held on the Hogan Quad and featured lawn games and local music from the "10-¢enters". Trainees were encouraged to network with attendees from other Michigan institutions on a more informal basis.

On Friday, June 9, after the morning announcements, the second oral session began. The session was themed around endocrinology and physiological genomics and was co-chaired by trainees Ian M. Greenlund (Michigan Technological University) and Nguyen Truong (Michigan State University). The session featured excellent talks by six individuals: Leena Kadam (postdoctoral fellow, Wayne State University); Xingfa Han (graduate student, University of Michigan); Naiomy Rios-Arce (graduate student, Michigan State University); Anne Tonson (postdoctoral fellow, Michigan State University); Juliette Brown (graduate student, Michigan State University); and Joseph Bires (undergraduate student, Oakland University).

Three concurrent breakout sessions focused on trainee development were scheduled during mid-Friday morning. The highlighted topics were "Joining a Professional Society" organized by Susan Barman (Michigan State University), "Elevator Pitches for Trainees: Implementing the 3 Minute Thesis in Our Department" organized by Charles Chung (Wayne State University), and "Searching for a "Postdoc" organized by Isola Brown (Michigan State University). Several trainees and students served on panels during these breakout sessions. Posters were available for further previewing during this period as well.

After the trainee breakout sessions, the third oral session contained talks about neurophysiology and respiratory physiology, and was chaired by trainees Mohamad El Chami (Wayne State University) and Alexandra Cara (University of Michigan). Five excellent presentations were given by Cameron Kortes (medical student, Central Michigan University); Ninotchska Delvalle (graduate student, Michigan State University); Yuan Fan (graduate student, Michigan Technological University); Vladimir Grubisic (postdoctoral fellow, Michigan State University); and Isola Brown (graduate student, Michigan State University).

Following a lunch break, the fourth oral session began and was themed around physiology education. This session was co-chaired by trainee Ross Michaels (Michigan Technological University) and Trevor Gohl (Michigan State University). This session featured excellent talks by Christine Klingert (medical student, Wayne State University) and Valerie VanRyn (post-baccalaureate, Michigan State University) as well as a particularly inspirational presentation given by Soumya Kulkarni (high school student, Northville

High School), who started her own high school neuroscience club. Keynote speaker Steve Elmer rounded out the symposium by presenting a talk titled "The Two Hour Marathon: What Do Students Think?" After the last oral session, attendees assembled on the front steps of the Heritage Center for a group photo (Figure 1).

**Figure 1.** 2017 MPS Annual Meeting.

In a parallel session on Friday, a Life Sciences Teacher Workshop was offered. The APS Chapter Program and APS staff partnered with the MPS for the second year in a row to host the model program Regional Professional Learning Communities (RPLC). The full-day workshop consisted of 6 Life Science teachers with interactions involving up to 23 of the high school students. Several sessions and panels were tailored specifically at the high school level, including a separate keynote lecture by Shoemaker, breakout sessions, interactive demonstrations, and exposure to APS-related activities, e.g., K-12 outreach activities and the APS Frontiers program. The high school teachers were also encouraged to attend posters presented by the high school students occurring during the general meeting poster session. They also attended the educational symposium (see above). The MPS K-12 Co-Chairs Sue Speirs (Grosse Pointe North High School) and Monica McCullough (Western Michigan University) coordinated these activities, and sessions were moderated by Sue Speirs. Shoemaker gave a stimulating lecture titled "Effect of Exercise Training on Brain Health" to both the teachers and the high school students in attendance. A number of MPS members served on a career panel, and the Society thanks Travis Wakeman (graduate student, Michigan Technological University) and Naveen Sharma (assistant professor, Central Michigan University) for their time with the teachers in this capacity (Figure 2). Additionally, two hands-on learning activities took place in the Human Performance Lab, featuring blood flow dynamics and cardiovascular control during lower body negative pressure, forearm blood flow, and blood pressure regulation. The Society thanks Steward Jensen (Associate Professor of Physics, Alma College) and John Davis (Professor of Integrative Physiology and Health Science, Alma College) for their time invested in educating the teachers in this capacity.


**Figure 2.** Life Sciences Teacher Workshop Career Panel MPS members (from *left* to *right*): Naveen Sharma (assistant professor, Central Michigan University) and Travis Wakeham (graduate student in Biological Sciences from Michigan Technological University).

All members and guests reconvened for the Business Meeting on Friday afternoon. Secretary-Treasurer Valerie VanRyn (MSU) discussed the budget, expenses, and donations from the previous year. Subsequently, MPS President Patrick Mueller announced the date of the next annual meeting at Michigan Technological University as June 14–15, 2018. He then offered thanks to the outstanding members of the executive board who completed terms: Erica Wehrwein (MSU, Past-

President) and Sue Barman (MSU, Membership and Fundraising Chair) (see Figure 4). An electronic ballot was distributed at the meeting, and a popular vote was taken to elect new members. The results were tallied, and a current member of the executive board, John Durocher (MTU), was chosen as President-Elect. The meeting concluded with the Awards Ceremony. Awards were funded by generous donations of participating institutions as well as a number of individual members. Of the 19 total oral presentations, 4 trainees were honored with an award certificate and a $250 check (Figure 3). Of the 68 total poster presentations, 6 trainees were honored with an award certificate and a $100 check (Figure 3).

**Figure 3.** Oral and poster presentation winners, MPS members (from *left* to *right*): Mohamad El-Chami, Soumya Kulkarni, Naiomy Rios-Arce, Travis Wakeham, Vladimir Grubisic, Trevor Gohl, Christopher Occhiuto, and Isola Brown. Awardees not pictured: Ryan Mack and Mohammad Mustafa Ahmadzai.

**Figure 4.** MPS executive board: Kevin Gordish (website coordinator), John Durocher (Awards Committee chair), Isola Brown (Trainee Committee, co-chair), Karen Ball (President-Elect), Erica Wehrwein (Past President), Valerie VanRyn (Secretary-Treasurer), Sue Barman (Membership and Fundraising Chair), and Patrick Mueller (President). Not pictured: Monica McCullough (K-12 outreach co-chair), Sue Speirs (K-12 outreach co-chair), and Ankita Jaykumar (Trainee Committee, co-chair).

The MPS was extremely pleased with the robust member turn-out for the 2017 Annual Meeting. In addition, for the first time the meeting:

- Hosted an undergraduate Michigan Physiology Quiz (MiPQ).
- Included participation by the Michigan state legislation by welcoming Bruce McAttee, Regional Director from the Honorable Gary Peters' office (U.S. Senator from Michigan).
- Invited its first international Keynote Speaker from Ontario, Canada.

We owe many thanks to the Planning and Executive Committee (Figure 4) and local volunteers for the execution of this meeting. We are very grateful to The APS for their continuous support. We also appreciate the financial support of our generous sponsors: Michigan State University College of Human Medicine (William D. Strampel, Dean), Office of the Vice President for Research (Stephen Lanier, Vice President), Henry Ford Health System (Margot LaPointe, Vice President for Research), Michigan State University College of Natural Sciences (R. James Kirkpatrick, Dean), Michigan Technological University Graduate School (Pushpa Murthy, Dean), Department of Kinesiology & Integrative Physiology (Jason Carter, Chair), and Department of Biological Sciences (Shekhar Joshi, Chair), Wayne State University, School of Medicine (Jack Sobel, Dean), Wayne State University, School of Medicine, Department of Physiology (J.-P. Jin, Chair), Michigan State University, Graduate School (Judith Stoddart, Interim Dean), Michigan State University, Office of the Vice President for Research & Graduate Studies (Stephen Hsu, Dean), Wayne State University, School of Medicine, Research Office (Linda Hazlett, Interim Vice Dean), Wayne State University,

School of Medicine, Graduate Programs (Dan Walz, Associate Dean),Wayne State University Graduate School (Ambika Mathur, Dean) and Mayo Graduate School Biomedical Engineering & Physiology Program (Carlos Mantilla, Program Consultant). ●

All photos are courtesy of Mohammad El-Chami (Wayne State University).

# Michigan Physiological Society Introduces an Undergraduate Physiology Quiz Team Competition at Their Annual Meeting

**Valerie VanRyn, Erica A. Wehrwein, and Susan M. Barman**
*Michigan State University, East Lansing, Michigan*

## Background on IMSPQ

Nearly 15 years ago while on sabbatical as a Professor of Physiology of the Faculty of Medicine at the University of Malaya in Kuala Lumpur Malaysia, Hwee-Ming Cheng pondered ways to encourage medical students to get excited about learning physiology (2, 5). The outcome of his creative reflection was the development of the first Intermedical School Physiology Quiz (IMSPQ) in 2003. He recruited teams of three to five students from eight Malaysian medical schools to compete in an oral quiz held before a live audience at the University of Malaya. Cheng served as Quizmaster and asked questions that covered nearly every organ system. The top performing team was awarded with a trophy named in honor of Prof. A. Raman, the first Malaysian Professor of Physiology at the University of Malaya, who died suddenly of cardiac arrest in 1998.

Within 5 years, the IMSPQ had grown to become an international event; IMSPQ 2008 included 39 teams, 26 coming from outside of Malaysia. By 2014, IMSPQ had grown to include teams from 90 medical schools (21 from Malaysia, 69 from elsewhere). The growth in participation led to the need to establish a two-phase competition, since including all teams would create huge time constraints, and this way teams are competing at the highest level. On *day 1,* there was a 100-question, true-false quiz to whittle down the number of teams that would participate in the oral competition on *day 2*.

In addition to several hundred medical students converging at the University of Malaya, each team brought one or more faculty mentors. To keep these mentors occupied while their students were taking the true-false quiz, Cheng invited a physiologist to lead a refresher course in their area of expertise. To date, these instructors have been from the U.S. and include Richard E. Klabunde [Professor of Physiology, Marian University College of Osteopathic Medicine, Indianapolis IN (2014)], Kim E. Barrett [Distinguished Professor of Medicine, University of California-San Diego (2015)], Susan M. Barman [Professor, Michigan State University, East Lansing, MI (2016)], and Walter F. Boron [Professor, Case Western Reserve University, Cleveland OH (2017)]. Both Barrett and Barman have reported on their positive experience with IMSPQ (1, 4).

Having been a part of IMSPQ 2016, one of us (Barman) can testify to the high energy level in the auditorium during the oral competition. The audience is packed with students and faculty cheering on their favorite team. The competitors on the stage are very intent on answering questions and will challenge the Quizmaster if they are convinced they answered a question correctly but were deemed to have provided a wrong answer. This meant a small panel of judges, including the refresher course instructor and faculty who did not have a conflict of interest, had to trust their own knowledge of physiology to make a final decision. This added to the intensity of this event. The final round of the oral quiz is a match between the top three scoring teams in the other rounds. In the end, one realizes that all the participants are winners since they have displayed an incredible level of competency in cellular and systems physiology. This should serve them well when they become physicians.

## Planning for a U.S. Team to Participate in IMSPQ

In addition to the increased number of teams participating in IMSPQ, as described by Cheng (5), many of the faculty who have brought a team of medical students to participate in the IMSPQ in Malaysia have been inspired by the dynamics of the program and have developed a similar quiz in their home country. In at least some cases, winners of the regional competition have gone on to participate in the IMSPQ.

Refresher course instructors have returned to the U.S. in awe of what they have witnessed: several hundred medical students who were driven to prepare extremely well in an effort to be recognized as the team that demonstrates the greatest proficiency in physiology. In fall 2016, Barman and Barrett began a campaign to send a U.S. team to the next IMSPQ. They came up with the plan to have the competition start at the APS Chapter level.

The majority of the teams that participate in IMSPQ are comprised of students who enter medical school straight out of high school. When Barrett and Barman were strategizing about the format for a U.S. team, Kim wisely suggested that we recruit undergraduates who are enrolled in physiology majors or specializations or even students who simply have taken and enjoyed a physiology course. After discussing this idea with the IMSPQ founder, Cheng agreed that the academic profile of this pool of students would be equivalent to that of the IMSPQ competitors. Cheng also advised that 7–10 teams would be ideal for an inaugural event.

After much discussion and strategizing, a decision was made to have the Michigan Physiological Society (MPS) host a quiz. We (VanRyn, Wehrwein, and Barman) prepared a proposal that Barman submitted to APS Council for their consideration. The plan was to recruit teams of undergraduate students from various Michigan universities or colleges and to hold a competition at the MPS annual meeting. We also requested that the winning team be allowed to travel to Malaysia to compete in IMSPQ with financial support from the APS. Although the APS Council denied the request as submitted, they encouraged Barman to have MPS hold a competition at their 2017 annual meeting and to use this as a stepping stone to entice other APS Chapters to follow suit. The hope is that once more chapters include a competition in conjunction with their annual meeting, then the U.S. may set up a competition among chapter winners (perhaps held in advance of the EB Meeting) to send the overall winning team to compete in the IMSPQ later that year.

### *Planning for the Inaugural U.S. Quiz Modeled after IMSPQ*

The inaugural event was named the Michigan (Mi) Physiology Quiz (MiPQ, pronounced "my physiology quiz") and was held at Alma College (Alma, MI) during the afternoon of June 7, 2017, the day before the start of the annual chapter meeting. We initially fell short of our goal of at least seven teams by just one, so we planned to run the event with six recruited teams of undergraduate students. However, one team had to bow out at the last-minute due to scheduling conflicts. The five remaining teams (Ferris State University, Michigan State University, Michigan Technological University, Oakland University, and Wayne State University) were each comprised of three to five enthusiastic students, eager to face the challenge to see which school comes out on top, and a faculty mentor who helped them prepare ahead of time and served as a coach at the event. Barman served as Quizmaster for the inaugural MiPQ.

For the inaugural event, we chose questions from a book of questions and associated ideal answers compiled by Cheng (3). All faculty mentors were provided an electronic copy of this book for them to use when prepping their team for the MiPQ. Teams were also told that the format for the quiz would be for students to provide short answers to questions. As Quizmaster, Barman selected questions covering a range of topics (cardiovascular, neural, renal, and respiratory physiology) for each round of the event. These questions were of course not shared with anyone. Moving forward, the plan is to develop a bank of questions from instructors across Michigan who teach physiology. In fact, if the quiz expands beyond Michigan as hoped, we can get a much larger bank of questions by requesting submissions from physiology instructors across the U.S.

## Format for the Oral Quiz

The rules and format described below followed as close as possible the original oral quiz format fine-tuned by Cheng for IMSPQ. The total number of sessions needed to complete a round will depend on the number of teams participating. For purposes of this description, we will assume 10 teams will participate.

Round 1 of the competition will be divided into two sessions, each with representatives of five teams (three to five students / team).

In each session, any *three* members of a team will compete. The composition of the competing team can only be changed at the beginning of each subsequent round except in acute illness afflicting a member.

In each session, *one* member of each team will step forward to answer questions. If there are five teams in a session, five students will step forward.

*Question 1* will be directed to the first student (sequence of teams determined randomly). The question will be read twice. The student will be given 15 seconds to respond. A correct answer will earn 3 points. There will be no penalty for a wrong answer.

If this first response is wrong or there is no response in 15 seconds, the question is open to the other four students only after the Quizmaster has announced, "The answer is wrong." or the 15-second timer has sounded. The first student to hit a buzzer after this will be given a chance to answer. Premature use of the buzzer will be penalized. No excuse will be allowed for unintentional use of the buzzer. A correct second response will earn 2 points. An incorrect second response will be penalized 1 point.

*Question 2* will then be directed to the second of five students, and the student will be instructed to respond within 15 seconds. The procedure that follows is repeated until question 5 is directed at the fifth student.

After the first cycle of five students is completed, the next five students – one from each team – will step forward to replace their team members. The quiz will proceed as above until the 10th question has been asked in the second cycle.

The third cycle of competition between the last five students completes the session. Each session of five teams will thus have a total of 15 questions (30 questions total).

This format will be repeated for the second group of five teams to complete *round 1.*

The team with the most points in each session of *round 1* automatically goes to the semifinal round. In addition, the four teams with the next highest scores from among the remaining eight teams will also advance to the semifinal round. Thus the semifinal round will include six teams.

For the semifinal round, there will again be two sessions, each including representatives from three teams. The format will follow that of *round 1;* a total of nine questions will be asked in each session within the semifinal round (18 questions total).

The team with the most points in each session of the semifinal round automatically goes to the final round. In addition, the one team with the next highest score from among the remaining four teams will also advance to the final round. Thus the final round will include three teams.

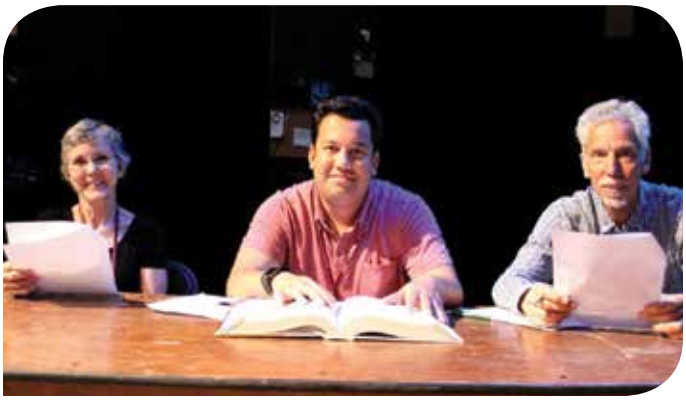
For the final round, the format will be the same as for other rounds but only one session will be needed. The final round will include a total of nine questions.

First place, second place, and third place winners will be determined based on the scores earned by each team in the final round.

Quizmaster Sue Barman

Several faculty or staff were recruited in advance of the event to help with the logistics of the quiz. In addition to the Quizmaster, three judges, who did not have a conflict of interest since they were not affiliated with a participating institution, were selected. When called on by the Quizmaster, the judges were used to decide

whether an answer was correct in the event that it differed from the ideal answer. For this, they were provided with a number of physiology textbooks, as well as the question and answer key. Additionally, two time-keepers were selected and placed at a table with scoring equipment and timers. The time keepers were responsible for enforcing the time restraints on the question answers and determining which team buzzed in first. Last, two individuals served as score keepers, who kept an ongoing written tally of scores, mutually agreed on these scores, and then projected the scores on a large display screen of a PowerPoint slide (with the layout of a scoreboard that included all school mascots and scores), updated in real time for the audience to see.



Judges Adele Denison, Naveen Sharma, and John Davis

Alma College hosted the event in a large auditorium; the seats of the auditorium welcomed peers, instructors, friends of the participants, as well as several early arriving MPS conference attendees. Three members of each team were seated at five individual tables in a half-moon formation on the stage; the Quizmaster was at a podium to their left near the front of the stage, and three judges were at a table to the left of the Quizmaster. We were fortunate to be able to borrow ADInstruments teaching hardware (PowerLab, push-button switches) and software (LabChart version 8.1.5), courtesy of Michigan State University Department of Physiology, to create a multi-input buzzer system that was connected to a monitor. Two time-keepers who handled the PowerLab equipment were at a table directly in front of the competitors. Two score keepers were in the upper audio-video room at the rear of the auditorium. Between the individual team tables and the scoring equipment, five microphones were set up, one for each team. These were placed in close proximity of the scoring equipment so that the microphones and the buzzers could both be easily


Michigan Physiology Quiz

accessible to the respondent. Each team had one representative at their designated microphone at any given time while the other team members remained at the table. In the instance that the student who was assigned the question either did not answer or answered incorrectly, the Quizmaster and/or judges verbally deemed the answer "incorrect," and the question was opened to the other teams. The buzzer system allowed two time-keepers to immediately determine which person was the first to respond, with the accuracy of a millisecond.

## Rewarding the Participants

In keeping with naming the IMSPQ winning team members for a distinguished Malaysian physiologist, members of the first place MiPQ team were honored as the Warren Plimpton Lombard Award recipients. Lombard was one of the first professors of physiology in the state of Michigan (University of Michigan, 1892–1923) and the eighth APS President (*http://www.the-aps.org/fm/About/presidents/introwpl.html*).

All participants of MiPQ were treated to a pizza party, which also served as an awards ceremony. Members of the first-, second-, and third-place teams for MiPQ (Wayne State University, Michigan State University, and Oakland University, respectively; received certificates recognizing their accomplishments. Thanks to the generous contributions of some Michigan Physiological Society members, they also received a monetary award. Members of the first-, second-, and third-place teams each received $75, $50, and $25, respectively. All students participating in the MiPQ received a copy of the 25th edition of *Ganong's Review of Medical Physiology*, compliments of McGraw-Hill.

## Future Plans

As mentioned above, teams were comprised of undergraduate students from Michigan universities and colleges for the inaugural MiPQ. We allowed students to participate as long as they were undergraduate students in the spring of 2017 and had taken a physiology course at some point in their college career, even if they graduated by the time the MiPQ event was held in June. For the first time at an IMSPQ, in 2017, Cheng allowed students enrolled in a masters degree program to participate. This will be discussed as an option for future MiPQ events.

## Are You Interested in Starting a Physiology Quiz at Your Next Chapter Meeting?

If you are thinking about including this engaging event at your annual meeting, it is advisable to form a subcommittee of faculty and staff who can help with the logistics, including helping to recruit teams, soliciting questions from participating institutions

Wayne State University Team (1st place)

Michigan State University Team (2nd place)

Oakland University Team (3rd place)

(and others if possible), identifying time keepers, score keepers, and judges, and soliciting donations. Barman reached out to individuals in Michigan who have had leadership roles in APS or the Chapter for soliciting donations. In addition, someone needs to assume the role of Quizmaster, who will need to identify the questions that will be included in the various rounds of the oral quiz.

Ferris State University Team

Michigan Technological University Team

Teams that participate should work with their faculty mentors to prepare for the competition, perhaps even meeting weekly to practice answering questions.

If you are interested in starting a quiz for your APS Chapter, you are welcome to attend the MiPQ event to be held at Michigan Tech in conjunction with the fifth annual MPS meeting (June 14 – 15, 2018). Contact us for more information. Also, we welcome more in-state and even out-of-state teams and their faculty mentor/coach to participate in the second annual MiPQ.

Contact Sue Barman if you have any questions (*barman@msu.edu*). ●

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# People and Places

## Meet APS Awardees

APS hands out more than $1 million in the field of physiology each year as part of our mission to advance scientific discovery, understand life, and improve health. Deadlines are fast approaching for a number of our awards, including section and abstract-based awards for Experimental Biology 2018. We are proud to provide support to the careers of many physiological researchers, including the bright young investigators profiled here. Read on to learn more about these awardees and check out the wide range of awards available to APS members of all career levels in our Special Awards Edition of the APS News Update (*http://www.the-aps.org/mm/hp/Audiences/Public-Press/Awards-Special-Edition-September-2017.html*).

### Justin Grobe: Advancing Research in Cardiometabolic Physiology

Justin Grobe

It was early in middle school that Justin Grobe realized that he didn't have to limit himself to learning from textbooks – he could actually participate in the process of scientific discovery. "After a few years of working on Science Olympiad projects every day after school with my science teachers, I couldn't imagine a career outside of science," Grobe said.

His undergraduate research mentor, Christopher Barney, a physiologist at Hope College in Michigan, made the largest impact on Grobe's career trajectory. Grobe worked with Barney for 4 years as an undergraduate and participated in research during all three of his summers in college. One of these summers was spent in the laboratory of Michael J. Katovich at the University of Florida's Department of Pharmacodynamics. "It was here that I really started to appreciate how chemistry impacts our biology," Grobe said. "I was hooked, and after graduation I immediately enrolled in graduate school in Mike's lab to pursue training in physiology and pharmacology."

Grobe's current research program focuses on how the brain controls blood pressure and resting metabolic rate via hormones in the brain's renin-angiotensin system. He is also investigating how perturbations in this system can result in diseases like hypertension and obesity. His work has shown that angiotensin receptors in the hypothalamus play an important role in energy balance. He has also discovered that a neurohormone called arginine vasopressin may be involved in preeclampsia, a complication of pregnancy characterized by high blood pressure.

Grobe's research into the brain's control of resting metabolic rate has required him to develop new technologies to measure metabolic rate in mice. These new technologies have allowed him to accurately measure the energy flux of animals as well as the small, but physiologically important, energy flux of gut microbes.

"Together, these research foci have led to an array of breakthrough ideas in cardiometabolic physiology," Grobe said.

Grobe was awarded the 2017 APS Arthur C. Guyton Award for Excellence in Integrative Physiology. The $30,000 award recognizes young investigators who demonstrate outstanding promise based on their research program in feedback control systems, quantitative modeling, and integrative physiology.

Now a faculty member at the University of Iowa, Grobe received tenure in July 2017. "There is little doubt in my mind that my receipt of the 2017 Guyton Award – an internationally recognized accomplishment that only goes to one early career physiologist each year – contributed to the positive review of my tenure application packet," Grobe said.

"In addition, the research grant that is associated with this award has already permitted my laboratory to purchase new equipment and perform preliminary studies to support outgoing research grant and graduate student fellowship applications," he said. "Thus, this 'investment' in my laboratory by the American Physiological Society is already helping us move our research program in exciting new directions, and to train the next generation of physiologists."

## Declan McCole: Breaking Ground in Gut Physiology


Declan McCole

Declan McCole is a physiologist studying the intestinal epithelium, the lining of the gut that separates the outside from the inside of the body. The barrier can become "leaky," leading to inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis. McCole is interested in understanding exactly why the epithelium becomes leaky – and how to fix it.

McCole began his research career at University College Dublin, Ireland, studying the host response to liver fluke infection in cattle. The parasite triggers chloride secretion from the cow's intestinal epithelium, an attempt to protect the body by flushing away the parasite. During his PhD, McCole worked to figure out how the chloride secretion response by the epithelium was regulated and how different gut immune cells responded over the course of infection. While based in the department of pharmacology, he spent the final year of his PhD studies at the university's veterinary school, working closely with researchers,veterinary nurses, and surgeons. He completed University College Dublin's first PhD to be jointly awarded by two different schools (science and veterinary medicine).

After his PhD, McCole went to the University of California, San Diego (UCSD), for a postdoctoral fellowship in a mucosal immunology laboratory. There, he studied a human parasite called *Cryptosporidium*, which can cause diarrhea or even death in immunocompromised patients. He then moved to the lab of Kim Barrett, the former president of APS, also at UCSD, where he studied the molecular signaling mechanisms that regulate chloride secretion in the gut epithelium.

Now leading his own lab at University of California, Riverside (UC Riverside), McCole is focused on studying how the epithelium forms a barrier, and how the barrier becomes disrupted in IBD (Crohn's disease and ulcerative colitis) and other inflammatory conditions. He has identified genes that make the epithelial barrier in the gut weaker and is studying the mechanisms involved, as well as therapeutic approaches to correct these barrier defects.

In 2014, a year after moving to UC Riverside, McCole received the S&R Foundation Ryuji Ueno Young Investigator Award, which recognizes an individual demonstrating outstanding promise in a select area of physiology. McCole used the funds from the award to develop a novel mouse model that carries a mutation in a particular gene in the intestinal epithelium. Developing a new mouse model is costly, and it's not usually something that a federal agency like NIH will pay for. "Generally, they want to see that you have a mouse model and that it works before they'll fund you," he explained. "That's why funds like this [the Ueno Award] are very important."

In July 2017, McCole received notice that his NIH R01 grant had been renewed – a satisfying vote of confidence in his research program, and a pot of money that will support his lab for the next 4 years.

"Certainly, the Ueno Young Investigator Award was helpful from a monetary perspective because it allowed me to invest in new technology in my lab," McCole said. "The recognition also helped increase my visibility within APS and tangibly helped with respect to my successful tenure application," he added.

## Nicole Nichols: Developing New Models to Study Breathing


Nicole Nichols

When Nicole Nichols was little, her grandmother and a family friend both passed away from lung disease after developing respiratory failure. That's how she became interested in understanding how the lungs work and how breathing is controlled by the brain and spinal cord. In college, Nichols was initially interested in medicine but found satisfaction in articulating questions and seeking answers. "That's when I knew I wanted to pursue a research career," she said.

Her work as a graduate student at Wright State University in Ohio looked at how nerve cells in the brain stem respond to varying levels of carbon dioxide and oxygen, and then regulate breathing accordingly. She discovered that the nerve cells adapt to the changing environment to keep breathing normal. Later, as a postdoc at the University of Wisconsin in Madison, she worked to understand how motoneurons compensate to regulate breathing when other neurons are dying, such as what occurs in amyotrophic lateral sclerosis (ALS).

One of the challenges of studying breathing regulation in the rat model of ALS is that the rats didn't just have breathing problems – they also had limb weakness and other motor deficits. So, as an assistant professor at the University of Missouri, Nichols developed a rat model in which only breathing was affected and where she could control the amount and rate of motoneuron death. This model will be used to identify pharmacological targets to restore breathing, she explained.

For developing this model, she received the 2015 APS Giles F. Filley Young Investigator Award, which is given annually to recognize an early career respiratory physiologist. The award enabled Nichols to purchase crucial laboratory equipment to measure respiratory output. That was important because federal grants typically support supplies and personnel, not equipment.

"These awards are extremely important to young investigators, not only to help them financially as they are establishing independence," she said. "The recognition is also important because it can help early career investigators attract trainees to the lab."

## Jennifer Pluznick: Trusting Serendipity on a Path to Discovery


Jen Pluznick

Jennifer Pluznick always knew she wanted to be a scientist, although she didn't always know what kind. As an undergraduate, she took a course in a different biological discipline every semester. "The semester I took genetics, I told my roommates that I was going to be a geneticist," Pluznick said. "The semester I took cell biology, I told them I was going to be a cell biologist. And the last course in the sequence was physiology," which could explain why she became a physiologist.

Now associate professor of physiology at Johns Hopkins University in Baltimore, Pluznick studies olfactory receptors in the kidney. She is pursuing the idea that these chemical receptors allow the kidney to monitor the levels of certain metabolites in the blood. She happened upon these receptors by chance when she was a postdoc studying polycystic kidney disease. At the time, the microarrays she used to measure gene expression in cells in response to a stimulus showed changes in a suite of olfactory receptor genes. At first, she thought it was proof that the array wasn't working, but a few confirmatory experiments showed her that she had stumbled on something interesting. At that point, she realized that "this is way cooler than the thing I thought I was going to do – so I'm going to do this instead."

For her work elucidating the role of olfactory receptor 78, which is expressed in the kidney and is important for regulating blood pressure, Pluznick received the 2015 Wang Young Investigator Award and the 2016 Mandel Young Investigator Award. She discovered that the receptor is exclusively activated by metabolites produced by bacteria that live in the gut. These metabolites cross the gut and enter the bloodstream where they can be detected by the kidneys. "The role of the microbiome was really unexpected," she said.

The awards have benefited Pluznick in a couple of ways. They provided an influx of funds at a time "when the funds were really really tight for me," she said. The money enabled her to keep some key experiments running. In addition, the recognition from peers was meaningful, and having the awards to list on her CV helped with promotions and grant applications. "These awards are really important. For new PIs, the monetary value and professional recognition can really help in a tough funding climate," she said.

## Robert Hester and UMMC Colleagues Trademark HumMod Technology

Robert Hester

APS Program Committee Chair Robert Hester and his colleagues at the University of Mississippi Medical Center (UMMC) recently received a registered trademark for their HumMod technology, which "simulates human physiology under normal and pathological situations." According to a press release on the UMMC website, "Dr. Robert Hester's laboratory has no pipettes or microscopes, no test tubes or cell lines. Instead, there are computers. Those computers contain people – lungs breathing, hearts beating – or at least the closest replicas one can build with code and equations and variables." HumMod technology is part of a legacy project at UMMC started by professors Arthur Guyton and Thomas Coleman, who started hand-drawing an electrical circuit-like model of the cardiovascular system in the 1960s. Hester, the Billy S. Guyton Distinguished Professor of Physiology and Biophysics at UMMC, calls the model one of the "best, most complete, mathematical models of human physiology ever created." Read more at *https://www.umc.edu/news/News_Articles/2017/July/math,-medicine-converge-with-hummod.html*. ●

## Jennifer Pluznick Presents at TEDMED

Jennifere Pluznick

Jennifer Pluznick presented the TED talk "You Smell with Your Body, Not Just Your Nose" at the 2016 TEDMED meeting in Palm Springs, CA. Pluznick is an assistant professor of physiology at the Johns Hopkins School of Medicine. TED talks are short, invited speeches that focus on "ideas worth spreading." They are hosted by the nonprofit TED (which stands for Technology, Entertainment and Design) and take place at their conferences, including TEDMED, several times each year. Pluznick's talk was related to her research on olfactory receptors and the "sense of smell" present in unexpected places, such as organs and body parts other than the nose. To watch her talk, which has been viewed more than 1 million times to date, visit *https://ted.com/talks/jennifer_pluznick_you_smell_with_your_body_not_just_your_nose?utm_source=tedcomshare&utm_medium=email&utm_campaign=tedspread*. ●

# Charles Tipton Recognized by American College of Sports Medicine


Charles Tipton

APS member Charles Tipton, an emeritus professor at the University of Arizona, was recently recognized by the American College of Sports Medicine with a symposium titled *Exercise is Medicine: Current Insights from C. M. Tipton's Scientific Grandchildren*. APS members Kenneth Baldwin and Ronald Terjung chaired the session. Presentations were by select former students ($n = 22$), grandchildren ($n = 91$), and great grandchildren ($n = 46$). Their collective publication record was ~3,000 manuscripts. ●

# Education

## Report from the Inaugural Physiology Majors Interest Group Meeting

Valerie VanRyn, Jennifer Rogers, Jeffrey Osborn, Claudia Stanescu, and Erica Wehrwein

### History

Physiology Majors Interest Group (P-MIG) is a consortium of individuals from institutions with undergraduate degree programs in physiology or with an emphasis in physiology. The purpose of this group is to provide a mechanism for peer institutions to discuss best practices for degree programs in physiology, including appropriate course sequencing, programmatic learning objectives, career development, and more. P-MIG was founded in 2014 by John Halliwill (University of Oregon), Erik Henriksen (University of Arizona), Dan McCann (Gonzaga University), and Erica Wehrwein (Michigan State University). The first official event for P-MIG was at EB in 2015 with an APS Teaching Section symposium titled "What's Your Major? The Rise of the Undergraduate Physiology Degree." In 2016–2017, P-MIG hosted networking sessions at EB that were sponsored by the APS education office. With these sessions being well attended, the group hosted its first stand-alone conference dedicated to physiology undergraduate programs and curricula in May 2017 at Michigan State University. A report of that meeting is below.

### Inaugural Conference Planning Committee

The members of the inaugural conference planning committee were as follows: Erica Wehrwein (Michigan State University), Claudia Stanescu (University of Arizona), Jennifer Rogers (University of Iowa), Jeff Osborn (University of Kentucky), and Valerie VanRyn (Michigan State University).

### Inaugural Conference

The inaugural meeting of the P-MIG was hosted on May 18–19, 2017, at Michigan State University in East Lansing, Michigan.

Due to generous sponsorship, the event, including registration and meals, was run at no cost to participants (see acknowledgements below). Participants were only responsible for covering their personal travel expenses. Without this generous funding, the meeting could not have taken place, since the majority of the attendees stated their attendance was contingent on the limited cost.

This stand-alone meeting generated a lot of interest across the world with in-person and web-based participation from five different countries, including the U.S., Canada, England, Australia, Portugal, and Nigeria. In total, 45 individuals from 34 institutions were in attendance over the course of the 2-day meeting. The timing of the meeting was not well aligned with teaching schedules, near to the end of the semester for most, so 25 additional individuals specifically requested to attend but were unable to due to scheduling conflicts with teaching. Therefore, the 2018 meeting will take place June 28–29 to improve attendance.

### Characteristics of Programs in Attendance

Following are some of the characteristics of the programs that attended.

- 71% self-classified as human physiology, 42% as systems/integrative, 33% as exercise physiology, 13% as cellular/molecular, 8% as animal/comparative, 4% as plant, 4% as nutrition, and 4% as other. (Note: more than one possible primary focus of their major was allowed).
- 56% of programs were >10 years old, 12% were 5–10 years, 9% were 0–5 years, 13% were renamed to physiology recently, 4% were developing, and 4% attended with a goal of starting a program in the future (aspirational).
- 40% were from a biology or life sciences department, and 43% were from a physiology department.
- 89% were from an undergraduate college or university.
- 87% listed APS as one of the professional societies that they refer to for issues regarding undergrad physiology education, with the next highest being HAPS at 13%.
- Graduating class size in spring 2017: 0–25 was 24%, 26–50 was 19%, 51–75 was 19%, 76–100 was 9%, 101–200 was 5%, 201–300 was 24%.

- Total enrollment size in spring 2017: 0–50 was 18%, 50–100 was 9%, 100–200 was 14%, 200–300 was 9%, 300–400 was 23%, 400–500 was 4%, 500+ was 23%.

## Meeting Agenda

The meeting commenced with a welcome from MSU Department of Physiology Chair Lee Cox and an introduction of Erica Wehrwein (meeting coordinator and founding member of P-MIG). The following goals of the meeting were presented.

*1)* To build a community of peer undergraduate physiology programs.

*2)* To facilitate networking among those programs.

*3)* To discuss and establish minimum requirements for a physiology major.

*4)* To establish a regular conference for P-MIG institutions.

The first day highlighted the works of an array of stimulating and thought-provoking individuals.

- Joel Michael (Rush Medical School) was invited to discuss his recent publication and area of study on the core concepts of physiology related to creating core competencies as a tool of contemplating what is important to be included in a program and what should be universally common across all programs.
- Kevin Haudek and Mark Urban-Lurain (professors of biochemistry and engineering, Michigan State University) discussed their NSF-funded AACR project, LeaP UP, to show how principle-based reasoning develops in undergraduates, how design assessments aligned with learning progression, how to develop automated scoring models for short-text responses, and how to map national trends in levels of achievement.
- Jeff Osborn (University of Kentucky) outlined his role as the chair of the APS Education Committee and how the role of undergraduate education and involvement is highly relevant on both local and national fronts.
- Jason Carter (Michigan Technological University) shared his experience with establishing curriculum standards for the American Kinesiology Association (AKA) and offered advice to P-MIG on the process of identification of a set of core ideas and skills considered central to the discipline.

The first day concluded with full introductions by individuals in attendance and self-selected concurrent breakout sessions related to new and developing programs, programs with enrollment of >500, exercise/physical therapy-based programs, biology-based programs, school of medicine-based programs, and programs that use combined anatomy and physiology coursework.

The second day focused on career development.

- Erica Wehrwein opened with an introduction of career development and desires for physiology degree holders.
- Phil Gardner (Director of Career Services, Michigan State University) led an enlightening discussion regarding the transition from college to career, market trends, and workforce readiness.
- Joel Michael continued his workshop on the core concepts in physiology.
- Lori Seischab (Michigan State University) imparted her expertise as an academic advisor for the physiology major as well as an instructor for a new course based in awareness and developmental advising at MSU titled "PSL101: Frontiers in Physiology."
- Anthony Paganini (Director of Integration and Innovation, Michigan State University College of Human Medicine) shared his experience as a medical educator, the ongoing curricular and content review they are undergoing, as well as the ideals for a bachelor of science degree holder entering medical school.
- Wehrwein presented on programmatic assessment resources that exist and how to maximize resources such as Bio-MAPS, PHYS-MAPS, PULSE, NRC Interpersonal Skills, and many others.

## Data Collection

Extensive information was collected through detailed pre- and post-meeting surveys from all attendees. The post-survey was authored in collaboration with the APS Education Office, which will also serve as external meeting evaluators. The pre-survey data were made available to all attendees and were used as a guide for conference planning. The pre- and post-survey data are being prepared for publication. The meeting planning committee would gladly share any data with interested parties prior to publication.

**Summary**

The meeting was well attended, informative, and energizing. The gathering allowed for dissemination of ideas, general shared discussion among all attendees, and smaller group discussions based on program type and topic. The meeting post-survey was very positive, indicating a successful meeting and a strong desire among the group to meet again; therefore, planning has started for the 2018 meeting at the University of Arizona on June 28–29, 2018. ●

## Acknowledgements

The planning committee thanks the generous sponsors who came forward in support of this event: APS, The Association of Chairs of Departments of Physiology (ACDP), Michigan State University (MSU) Department of Physiology, the University of Oregon Department of Human Physiology, the University of Arizona College of Medicine Department of Physiology, MSU College of Natural Sciences, and MSU Office of the Associate Provost for Undergraduate Education. We also are grateful to the MSU Physiology Department Staff, especially Kim Crain, for hard work with meeting logistics.

P-MIG attendees dove into discussion regarding physiology undergraduate education

# Diversity and Higher Education Awards for EB

## Education Office Awards

To apply for any of these awards, go to *the-aps.org/awardapps*.

### *Minority Outreach Fellowships*

**Application Deadline:** December 1, 2017

*the-aps.org/minorityoutreach*

The APS Minority Outreach Fellowship seeks to foster communication between minority graduate and postdoctoral students and middle / high school minority life sciences students. Applicants must have received a Porter Fellowship or a Minority Travel Fellowship Award to be eligible. Program activities include year-long outreach fellowships for senior graduate students and postdoctoral fellows to visit K-12 classrooms, help conduct teacher professional development workshops, and attend scientific meetings. Funds are provided to attend two EB meetings and one fall conference (ABRCMS or SACNAS), a value of $5,400.

### *ADInstruments Macknight Early Career Innovative Educator Award*

**Application Deadline:** December 1, 2017

*the-aps.org/adi*

The ADInstruments Macknight Early Career Innovative Educator Award honors an early career APS member who demonstrates the greatest potential for incorporating innovative teaching techniques and effectively utilizing technology resources in engaging undergraduate students in physiology education. The awardee receives $1,500, up to $2,000 in travel expense reimbursement, and complimentary advanced registration to attend the EB meeting and an institutional grant providing the awardee's institution with a PowerLab PTB4152 Physiology Teaching Bundle or equivalent. Applicants must be a member of the APS Teaching Section (first, second, or third affiliation).

### *Translational Research Awards for Predoctoral Students and Postdoctoral Fellows*

**Application Deadline:** December 7, 2017 (coincides with EB abstract deadline)

*the-aps.org/mm/awards/Other-APS-Awards*

This award recognizes a postdoctoral fellow ($800 award) and a predoctoral student ($500 award) whose area of experimental research is translatable to industry applications (treatment development or improvement, diagnosis, mechanism of action, health and wellness). Applicants will be evaluated on their first-author EB meeting abstract and a supplementary one-page (maximum) description of *1)* the translational nature of their project and its potential utility for future research, *2)* their contribution to the work, and *3)* their career goals. Applicants do not have to be APS members, and there are no restrictions on how the award is spent; however, their sponsor must be an APS member in good standing at the time of application.

### ■ *Caroline tum Suden/Frances A. Hellebrandt Professional Opportunity Awards*
### ■ *Steven M. Horvath Professional Opportunity Awards*
### ■ *Fleur L. Strand Professional Opportunity Award*

**Application Deadline:** December 7, 2017 (coincides with EB abstract deadline)

*the-aps.org/mm/awards/Other-APS-Awards*

To be considered for these awards, the applicant must be either a graduate student or a postdoctoral fellow, the first author of an abstract submitted to APS, and a member of APS in good standing at the time of application (either Student or Regular Member). To receive the award, recipients must attend EB, present a poster at the meeting, and attend the APS Business Meeting. The top applicant will be designated as the Fleur L. Strand Awardee and will receive $1,000. The top two underrepresented racial/ethnic minority recipients will be designated as Steven M. Horvath Awardees. The awardees receive $500 and complimentary EB registration. Awardees will be allowed to only receive a tum Suden, Strand, or Horvath Award once as a predoctoral student and once as a postdoctoral fellow.

### ■ *Barbara A. Horwitz and John M. Horowitz Undergraduate Research Awards*

**Abstract Deadline:** December 7, 2017

**Application Deadline:** January 12, 2018

*the-aps.org/eb-undergrad*

The Barbara A. Horwitz and John M. Horowitz Undergraduate Research Awards are presented annually to undergraduate students who submit a first-author abstract to the EB meeting and present their research at the meeting. There are two types of Horwitz/Horowitz Undergraduate Awards that students can apply for through a single application. See the website for more details and apply online at *the-aps.org/awardapps*.

**Outstanding Undergraduate Abstract Awards**

These awards provide $100 and a 2-year complimentary APS membership. The student must be enrolled as an undergraduate at the time of the abstract submission, be the first author on an EB abstract, and be working with an APS member. Selection of awardees is based on the abstract, letter of application, and letter of support from the research host. Receipt of the award is contingent on presenting the research at EB.

**Excellence in Undergraduate Research Awards**

To be considered for this award, students must be an Outstanding Undergraduate Abstract Awardee and must attend and present a poster at the EB meeting. The recipients receive $400 and a certificate. The highest ranked awardee receives an additional $250, thanks to the generous contribution of an APS member. Selection of awardees is based on the quality of the poster and oral presentation of the poster to the Award Selection Committee.

### ■ *Minority Travel Fellowship Awards*

**Application Deadline:** December 14, 2017

*the-aps.org/minoritytravel*

The APS is offering travel awards to attend EB 2018. The Minority Travel Fellowship is designed to increase their active participation in, and networking at, scientific meetings.

The APS Minority Travel Fellowship Awards are open to underrepresented minority (URM) graduate students, postdoctoral fellows, and early career faculty (recently transitioned or within 5 years of receiving a PhD); and graduate students, postdoctoral fellows, and early career faculty (recently transitioned) with disabilities. See website for full eligibility details.

Awardees will receive up to $1,800 in expense reimbursement for registration, housing, meals, air and ground transportation, and tips. These awards do not provide funds for international travel.

### Graduate Student Ambassadors

**Application Deadline:** December 15, 2017

*www.the-aps.org/gsa*

The Graduate Student Ambassador (GSA) program seeks to foster communication between current APS graduate trainees and undergraduates in your geographic area. The 2-year GSA fellowship includes travel support to attend EB, web-based training, and local outreach activities involving visits to primarily undergraduate institutions to promote careers in biomedical sciences and APS membership, programs, and awards. The APS Trainee Advisory Committee (TAC) is recruiting a passionate and dedicated group of graduate students to become part of the next class of Graduate Student Ambassadors.

### Porter Physiology Development Fellowships

**Application Deadline:** January 15, 2018

*the-aps.org/porter*

The goal of the Porter Physiology Development Program is to encourage diversity among students pursuing full-time studies toward a PhD in the physiological sciences and to encourage their participation in APS.

The Porter Fellowship provides a full-time graduate fellowship ($28,300 during the academic year) to students in programs leading to the PhD in the physiological sciences at U.S. institutions. The program is open to underrepresented racial and ethnic minority applicants who are citizens or permanent residents of the U.S. or its territories and are student members of APS. The applicant's mentor/PI must also be an APS member.

### Dale J. Benos Early Career Professional Service Award

**Application Deadline:** January 24, 2018

*the-aps.org/benos*

The Dale J. Benos Early Career Professional Service Award honors an early career stage (graduate student, postdoctoral fellow, assistant professor or equivalent position) member of APS. The award will honor someone who is judged to have made outstanding contributions to the physiology community and demonstrated dedication and commitment to furthering the broader goals of the physiology community. This can be by serving on professional committees, participating in K-12 education outreach, participating in scientific advocacy and outreach programs, or otherwise strengthening and promoting the physiology community. See the website for more details and apply online at *the-aps.org/awardapps*.

### Undergraduate Summer Research Fellowships

**Application Deadline:** February 1, 2018

*the-aps.org/summerresearch*

APS is proud to offer four fellowship programs (IOSP, STRIDE, UGREF, and UGSRF) that allow undergraduate students the opportunity to participate in a summer of research. Fellows spend an average of 10 weeks in the laboratory of an established scientist and APS member. Each fellow receives a $4,000 stipend plus additional funds for travel to present his or her research at the EB meeting. Research hosts receive funds for student lab supplies. See the website for more details about each of the four programs.

# Create a Short Physiology Video and You Could Win a Cash Prize and EB Travel Award

**Application Deadline:** December 15, 2017
*www.the-aps.org/video*

APS Physiology Video Contest: "Function Follows Form" encourages undergraduate, graduate and professional students to creatively connect with physiology and engage with the broader public through a short video contest.

First-place awardee(s) receives a total of $750 and up to $1,000 in travel funds to attend the EB 2018 meeting to accept the award. The award-winning video is selected by members of the Career Opportunities in Physiology Committee.

Viewer's Choice awardee(s) receives a total of $250 (determined by total views on YouTube site as of the first day of the EB meeting).

Videos should creatively demonstrate and/or explore a specific physiological function in 5 minutes or less (including credits). The target audience is the general public. Video can be staged as a short play, commercial, news broadcast, talk show, music video, documentary, etc. No professional assistance can be provided to produce the video in any manner. Copyrighted material may only be used if proper permission is attained before the application is submitted. Videos are uploaded to YouTube for viewing. Application materials are submitted online to APS.

To view previous award-winning videos and find more information, visit *www.the-aps.org/video*.

Start filming now and submit your award-winning video by December 15 at *www.the-aps.org/awardapps*.

# Science Policy

## Opposition to VA Research Restrictions Continues to Grow

On July 26, the House of Representatives approved a measure that would halt VA research with dogs even when the animals receive the same kind of anesthesia, analgesia, and post-operative care provided to pets and human patients undergoing surgery. Rep. Dave Brat (R-VA) offered the provision as an amendment to a bill that included the VA's FY 2018 appropriations. The amendment was approved by voice vote. Brat said the measure was a response to controversy generated by the White Coat Waste Project, which wrote to the VA Inspector General in March alleging "egregious transparency and accountability failures and animal welfare abuses in controversial dog experimentation" at the Hunter Holmes McGuire VA Medical Center in Richmond.

APS President Dennis Brown rebutted the White Coat Waste Project's accusations in letters to the chairs of the House and Senate Appropriations subcommittees responsible for VA funding. Underscoring the importance of research with dogs as part of efforts to develop treatments for serious medical conditions affecting veterans, Brown urged Congress to strike the Brat amendment from the final version of the bill. Brown noted that the problems at the Richmond VA had been promptly identified and corrected. "We therefore believe that these incidents should not be allowed to define a program that has done so much to support the health and quality of life of our nation's veterans," Brown wrote.

Opposition to the Brat amendment spread rapidly among organizations representing veterans and the research community. On September 12, U.S. Secretary of Veterans Affairs David Shulkin published an op-ed in *USA Today,* in which he said that the amendment threatened the VA's mission to "push the envelope constantly in search of medical advancements that will help improve the lives of disabled veterans." Shulkin called on Congress to "preserve humane and carefully supervised canine research at the VA."

Sherman Gillums, Jr., the Executive Director of the Paralyzed Veterans of America, pointed out in an interview in *Stars and Stripes* that the importance of the research was never considered during the Brat debate on the House floor. "The catastrophically disabled veteran population, I think, might give balance to this discussion that they had without us in the room," Gillums told *Stars and Stripes.* In an earlier opinion column published in *The Hill,* Gillums noted that the lives of paralyzed veterans "will never be the same as our lives before service, but advances in research will help us experience lives with less pain—and more hope."

The American Legion also went on record against the Brat amendment. "Stopping VA research that can only be done with dogs will mean accepting that the care we offer our veterans must be limited to what we can do now in those areas," American Legion National Commander Denise H. Rohan said in a letter to Senate Appropriations Committee Chairman Thad Cochran. Rohan urged that the VA be permitted to "continue research vital to advancing the medical well-being of our nation's veterans." ●

# Fiscal Year 2018 Federal Funding Update

On September 8, 2017, President Trump signed legislation to extend current funding levels for all federal agencies and programs through December 8, 2017. Passage of the continuing resolution (CR) avoided the threat of a shutdown that was looming if Congress failed to meet the October 1 deadline for completing fiscal year (FY) 2018 appropriations bills. The legislation also temporarily suspended the debt ceiling and replenished a disaster relief account needed to deal with the aftermath of Hurricanes Harvey and Irma.

With the threat of a government shutdown avoided for the time being, Congress continues to work toward completion of FY 2018 appropriations legislation. Committees in both the House of Representatives and the Senate have proposed funding levels for research at the NIH, NSF, VA, and NASA (see Table 1).

Of particular note, appropriators in both chambers proposed sizable increases for the NIH for what would be the third consecutive year. The Senate bill also included language that would prohibit the agency from making changes to facilities and administrative (F&A) cost reimbursement rates. That was a response to the Trump Administration's FY 2018 budget proposal to cap NIH's F&A reimbursement to research institutions at 10%. The Senate also added language to require NIH to determine whether fetal tissues obtained from spontaneous abortions and still births would be adequate for research needs. This is in contrast to the House version of the NIH funding bill, which would prohibit funding for research using tissues obtained from induced abortions. Because the House and Senate language differs, compromise fetal tissue language will have to be worked out in negotiations between the two legislative bodies.

The Medical and Prosthetic Research Program at the VA would receive a significant increase in FY 2018 under the proposals from both the House and the Senate (see also "Opposition to VA Research Restrictions Continues to Grow" on p. 397).

Unfortunately, appropriators were less generous with funding for the NSF and NASA. In budget hearings earlier this year, appropriators had noted that the current budget caps prevent them from proposing larger increases. These caps were put in place by the Budget Control Act of 2011 (BCA), with the goal of restraining discretionary spending over a period of 10 years. If Congress approves spending bills that exceed the limits in the BCA, sequestration is triggered and funding for federal programs will be reduced to the level specified in that year's cap. In recent years, Congress acted to raise the caps to increase funding for priority programs. Given the current political dynamics, it will likely need to do so again to finalize FY 2018 spending. ●

**Table 1.** ***House and Senate Spending Levels***

| Agency | Current Level (FY 2017) | House-Proposed Level | Senate-Proposed Level |
|---|---|---|---|
| NIH | $34.08 B | $35.41 B (+3.2%) | $36.23 B (+5.6%) |
| NSF | $7.47 B | $7.34 B (–1.8%) | $7.31 B (–2.2%) |
| NASA | $19.65 B | $19.87 B (+1.1%) | $19.59 B (–0.6%) |
| VA Medical and Prosthetic Research | $673 M | $698 M (+3.7%) | $722 M (+7.3%) |

# NIH Issues New Policies for Early and Mid-Career Investigators

On August 31, 2017, the National Institutes of Health (NIH) released new policy guidance supporting the Next Generation Researchers Initiative. The goals of the initiative are to help investigators establish and maintain independent research programs at an earlier age; stabilize the biomedical research workforce; and enhance diversity. The policy directs institutes and centers to prioritize funding for qualifying, meritorious applications from Early Stage Investigators (ESIs) and Early Established Investigators (EEIs). NIH adopted this approach after it abandoned plans announced earlier this year to institute a grant support index (GSI). The GSI would have effectively limited the amount of funding that an individual investigator could receive so that NIH's resources could be more evenly distributed across the research community.

The new policy defines ESIs as those who have completed their research degrees within the last 10 years and have not held a substantial NIH research award, such as an R01. EEIs are defined as individuals who received their first substantial NIH award within the past 10 years. To be eligible for prioritized funding, EEIs must be supported by only one active award or else must be at risk for losing all NIH research support without a successful competing grant application. Each institute and center will develop its own strategies for implementing the new policy. The Office of the Director will centrally track an updated census of ESI and EEI grantees, and develop metrics to assess the outcomes of the policy.

The NGRI program is set to begin in the current fiscal year (FY 2017), with the goal of providing grant support to an additional 200 researchers in each category compared with the number funded in FY 2016. The expected cost is $210 million for the first year, with an additional $210 million added in each of the next 4 years to achieve a steady-state cost of approximately $1.1 billion per year.

For more information on the new policy and links to related information, see the NIH's Next Generation Researchers Initiative webpage (*https://grants.nih.gov/ngri.htm*). ●

# Membership

## New Regular Members

***transferred from student membership**

**William Adams**
Univ. of North Carolina at Greensboro, Greensboro, NC

**Bruce G. Allen**
Montreal Heart Inst., Montreal, QC, Canada

**Francisco Javier Altamirano**
UT Southwestern Med. Ctr., Dallas, TX

**John Andrew Baugh**
Univ. Coll. Dublin, Dublin, Ireland

**Dan Berkowitz**
Johns Hopkins Univ., Baltimore, MD

**Peter James Blair**
Univ. of Nevada-Reno, Reno, NV

**Julie Bossuyt**
UC Davis, Davis, CA

**Steven L. Brody**
Washington Univ. Sch. of Med., Saint Louis, MO

**Robert William Caldwell**
Med. Coll. of Georgia, Augusta, GA

**Chris Cartwright**
Stanford Univ. Sch. of Med., Stanford, CA

**Indra Chandrasekar**
Sanford Research, Sioux Falls, SD

**Ta-Yuan Chang**
Geisel Sch. of Med. at Dartmouth, Hanover, NH

**Aihua Chen**
East China Normal Univ., Shanghai, China

**Geoffrey Edward Ciarlone**
U.S. Navy, Rockville, MD

**Fayssal El Husseini**
CARDIF, Paris, France

**Davide Filingeri**
Loughborough Univ., Loughborough, United Kingdom

**Alexandra Garvin**
Univ. of Arizona Coll. of Med.-Phoenix, Phoenix, AZ

**David D. Gibbons**
Milligan Coll., Milligan College, TN

**Kathleen M. Gilmour**
Univ. of Ottawa, Ottawa, ON, Canada

**Zachary Aaron Graham**
James J. Peters VA Med. Ctr., Bronx, NY

**Silvia Guatimosim**
UFMG, Belo Horizonte, Brazil

**Raquibul Hasan**
Univ. of Tennessee, Memphis, TN

**Brad G. Hill**
Univ. of Louisville Sch. of Med., Louisville, KY

**Mu Huang**
Inst. for Exercise and Environmental Med., Dallas, TX

**Polly Husmann**
Indiana Univ., Bloomington, IN

**Makoto Kanzaki**
Tohoku Univ Sendai-City Miyagi Japan

**Danielle Jin-Kwang Kim**
Pennsylvania State Univ. Coll. of Med., Hershey, PA

**Heidi Kloefkorn**
Emory Univ., Atlanta, GA

**Noriyuki Koibuchi**
Gunma Univ. Graduate Sch. of Med., Maebashi, Japan

**Rian Landers-Ramos**
Univ. of Maryland Sch. of Med., Columbia, MD

**Maxime Mickael Mahe**
Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

**Daniel Ryan Moore**
Univ. of Toronto, Toronto, ON, Canada

**Amy Elizabeth Oakley**
Univ. of Michigan, Ann Arbor, MI

**Rennolds Ostrom**
Chapman Univ. Sch. of Pharmacy, Irvine, CA

**Mikhail Papisov**
Massachusetts General Hosp. & Harvard Med. Sch., Boston, MA

**Jordan Patik**
The Univ. of Texas at Arlington, Austin, TX

**Maria Puigbonet**
Georgian Coll., Barrie, ON, Canada

**Gautam Rishi**
Inst. of Hlth. and BioMed. Innovation, Brisbane, QLD, Australia

**Joseph Kraft Ritter**
Virginia Commonwealth Univ., Richmond, VA

**Gracious Ross**
Aurora Res. Inst., Milwaukee, WI

**Rahul Sharma**
Univ. of Virginia, Charlottesville, VA

**Patricia J. Sime**
Univ. of Rochester, Rochester, NY

**Demetris Soteropoulos**
Newcastle Univ., Newcastle Upon Tyne, United Kingdom

**Yu-Yo Sun**
Emory Univ. Sch. of Med., Atlanta, GA

**William James Turbitt**
Univ. of Alabama at Birmingham, Birmingham, AL

**Adam John Wells**
Univ. of Central Florida, Orlando, FL

**Luke Xie**
Genentech, South San Francisco, CA

**Ling Xin**
Univ. of Mississippi, University, MS

**Jian Xu**
USC, Los Angeles, CA

## New Graduate Student Members

**Wonmo Ahn**
Univ. of North Colorado, Greeley, CO

**Jason Au**
McMaster Univ., Hamilton, ON, Canada

**Devika Bagchi**
Univ. of Michigan Med. Sch., Ann Arbor, MI

**Jorge Silva Barcellos**
URV, Porto Alegre, Brazil

**Krystal Diaz Belmonte**
LSU Hlth. Sci. Ctr., New Orleans, LA

**Jamelle Brown**
Univ. of Alabama at Birmingham, Birmingham, AL

**Jacob Levi Brown**
Univ. of Arkansas-Fayetteville, Fayetteville, AR

**Amanda Buch**
Weill Cornell Graduate Sch. of Med. Sci., New York, NY

**Latoya E. Campbell**
Asu/Mayo Clinic Arizona, Scottsdale, AZ

**Jenny Cheng**
Univ. of Wisconsin-Madison, Madison, WI

**Aikaterini Christogianni**
Loughborough Univ., England, Loughborough, United Kingdom

**Daniel Cook**
Univ. of Iowa, Iowa City, IA

**Spencer Craig**
Cushen Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX

**Gean Domingos Da Silva Souza**
Univ. of São Paulo, Gainesville, FL

**Elizabeth Anne Davis**
Univ. of Illinois at Urbana-Champaign, Urbana, IL

**Robert Marcus Fuchs**
LSUHSC New Orleans, Reno, NV

**Ria Christian Fyffe-Freil**
Virginia Commonwealth Univ., Richmond, VA

**Kelly Gavião**
Univ. of Campinas, Campinas, Brazil

**Jonique Catherine George**
Boston Univ., Boston, MA

**Abigail Vaughan Giles**
National Inst. of Hlth., Bethesda, MD

**Ronee Harvey**
Mayo Clinic Coll. of Med., Rochester, MN

**Alexandra Elizabeth Hochstetler**
IUPUI, Indianapolis, IN

**Christopher Horn**
Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX

**Jeffrey John Hsu**
UCLA, Los Angeles, CA

**Hyun Tae Hwang**
Univ. of California-Davis, Davis, CA

**Megan Jones**
Univ. of Northern Colorado, Greeley, CO

**Suyash Narendra Joshi**
Technical Univ. of Denmark, Lyngby, Denmark

**Danica Jurcakova**
Commenius Univ., Bacuch, Slovakia (Slovak Republic)

**Manish Kar**
London Sch. of Hygiene and Tropical Med., Ajax, ON, Canada

**Sergio M. Laranjo**
Univ. de Lisboa, Lisbon, Portugal

**Komal Marwaha**
Maharishi Univ. of Management, Fairfield, IA

**Mykola Matsyuk**
Detroit Med. Ctr., Warren, MI

**Allan Joseph Medwick**
Western Michigan Univ., Kalamazoo, MI

**Pedro Augusto Carvalho Mira**
Federal Univ. of Juiz de Fora, Juiz De For a, Brazil

**Jacob C. Monroe**
Purdue Univ., West Lafayette, IN

**Dianna Huyen-Tram Nguyen**
UNT Hlth. Sci. Ctr., Arlington, TX

**Christopher Nguyen Miguel Pastrana**
Univ. of North Texas Health Sci. Ctr., Fort Worth, TX

**Crystal Miranda Reynaga**
Univ. of California-Irvine, Irvine, CA

**Lauren Elise Rispen**
Western Sydney Univ., Sydney, NSW, Australia

**Gabrielle Rowe**
Univ. of Louisville, Louisville, KY

**Adam Russell-Hallinan**
Univ. Coll. Dublin, Belfield, Ireland

**Afton Seeley**
Univ. of Miami, Miami, FL

**Ninette Shenouda**
McMaster Univ., Mississauga, ON, Canada

**Israel Soto**
LSU Hlth. Sci. Ctr. Shreveport, Shreveport, LA

**Kalyn Specht**
Virginia Tech, Blacksburg, VA

**Megan Sylvester (ahern)**
Univ. of Arizona, Tucson, AZ

**Lais Tono Tono Cardozo**
Univ. of Campinas, Piracicaba, Brazil

**Patrick Türck**
Federal Univ. of Rio Grande Do Sul, Porto Alegre, Brazil

**Denis James Wakeham**
Cardiff Metropolitan Univ., Cardiff, United Kingdom

**Gregory Tyler Williams**
Liberty Univ., Waco, GA

**Subhi Talal Younes**
Univ. of Mississippi Med. Ctr., Flowood, MS

## Undergraduate Student Members

**William Castillo-González**
Univ. de Ciencias Médicas de la Habana, La Habana, Cuba

**Cristóbal González-Losada**
Univ. de Ciencias Médicas de la Habana, La Habana, Cuba

**Marilyn Steyert**
Univ. of California San Francisco, Columbia, MD

**Maureen Ann Walsh**
Slippery Rock Univ., Slippery Rock, PA

**Jose Daniel Zazueta Leon**
Univ. de Monterrey, Culiacan, Mexico

## Affiliate Members

**Jessica Drews**
Sparrow Hosp., Lansing, MI

**Peter Van Schaick**
Peter Van Schaick, LLC, Poughkeepsie, NY

# Publications

## Current Calls for Papers

### Physiological Genomics

- -Omic Approaches to Understanding Muscle Biology
  *Submission deadline: November 30, 2017*
- Genetics of Metabolic Syndrome
  *NEW DEADLINE: June 30, 2018*
- Single Cell Analysis
  *NEW DEADLINE: May 31, 2018*

### Journal of Neurophysiology

- Progress in Motor Control
  *Submission deadline: June 30, 2018*
- Neuroscience at the 38th World Congress of the International Union of Physiological Sciences
  *Submission deadline: June 30, 2018*
- The Role of Eye Movements in Perception, Cognition, and Action
  *Submission deadline: June 30, 2018*
- Working Memory: Neural Mechanisms
  *Submission deadline: December 31, 2017*
- 50 Years of Microneurography: Insights into Neural Mechanisms in Humans
  *Submissions deadline: December 31, 2017*
- Control of Coordinated Movements
  *Submission deadline: December 31, 2017*

### Advances in Physiology Education

- Historical Perspectives and Living Histories

### Journal of Applied Physiology

- Vascular Aging
  *Submission deadline: January 31, 2018*

### American Journal of Physiology – Cell Physiology

- Applications of Advanced Cell Culture in Cell Physiology: Co-culture, Organoids, Stem Cells
  *Submission deadline: December 31, 2017*
- Ion-sensitive Cell Signaling
  *Submission deadline: December 31, 2017*
- Pathogenic Roles of Ion Channels and Transporters
  *Submission deadline: December 31, 2017*

### American Journal of Physiology – Gastrointestinal and Liver Physiology

- Mechanisms of Host and Microbiome Interactions
  *Submission deadline: December 1, 2017*
- Appetite, Satiation, and Obesity
  *Submission deadline: December 1, 2017*
- Gastrointestinal Motor, Secretory, and Sensory Functions
  *Submission deadline: December 1, 2017*
- Gastrointestinal Aging
  *Submission deadline: December 1, 2017*
- Enteric Nervous System Interactions
  *Submission deadline: December 1, 2017*
- Gastrointestinal and Liver Development and Organogenesis
  *Submission deadline: December 1, 2017*
- Immune Mechanisms of Gastrointestinal Cancer
  *Submission deadline: December 1, 2017*

### American Journal of Physiology – Heart and Circulatory Physiology

- Novel Mechanisms of Myocardial Ischemia, Ischemia-Reperfusion, and Protection by Myocardial Conditioning
  *Submission deadline: February 1, 2018*
- Cardiac Regeneration and Repair
  *Submission deadline: February 1, 2018*
- Extracellular Matrix in Cardiovascular Pathophysiology
  *Submission deadline: February 1, 2018*

### American Journal of Physiology – Lung Cellular and Molecular Physiology

- Age-Related Dysfunction in Lung Barrier Function in Health and Disease
- Biomarkers in Lung Diseases: From Pathogenesis to Prediction in New Therapies
  *Submission deadline: December 31, 2017*
- Ion Channels and Transporters in Lung Function and Disease
- Translational Research in Acute Lung Injury and Pulmonary Fibrosis
  *Submission deadline: December 31, 2017*

### American Journal of Physiology – Regulatory, Integrative and Comparative Physiology

- G Protein-Coupled Receptor Signaling in Metabolic Disease
  *Submission deadline: December 31, 2017*
- Oxygen Signaling
  *Submission deadline: December 31, 2017*
- Cardiovascular and Metabolic Consequences of Sleep and/or Circadian Disruption
  *Submission deadline: May 1, 2018*

### American Journal of Physiology – Renal Physiology

- Inflammation and Inflammatory Mediators in Kidney
  *NEW DEADLINE: December 31, 2017*
- Renal Control of Mineral Homeostasis
  *Submission deadline: December 31, 2017*
- Newer Therapies for Diabetic Nephropathy and Their Cardiovascular Effects
  *Submission deadline: December 31, 2017*
- Microbiome in Kidney and Bladder Diseases
  *Submission deadline: December 31, 2017*
- Molecular Mechanism of Renal Tubule Transport
  *Submission deadline: December 31, 2017*

For a complete list of current Calls for Papers, visit the APS website.

## Books Received

***The Biology of Exercise***

**Edited by Juleen R. Zierath, Michael J. Joyner, and John A. Hawley**
**New York: CSHL Press, 2017, 396 p., 46 color & 28 B/W illus., $79 (paperback)**
**ISBN: 978-1-621822-85-1**

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# News from Distinguished Physiologists

## Letter to Lois Heller

**Edith Hendley writes:** "I am approaching my 90th birthday in a few weeks, finding myself, improbably, still a practicing physiologist. It started when I was a sophomore at Hunter College of the City of New York, when I took my first physiology course and fell in love with our discipline. Over the following 70 or so years since then, I have witnessed profound changes in both what we consider physiology and what it has meant to watch the progress of women who enter science careers.

"In the 1940s through 1970s, courses in physiology included elaborate student 3-hour labs, usually carried out in anesthetized dogs obtained from the animal shelter, where they otherwise would be euthanized. We routinely learned to manage a safe level of anesthesia, to perform tracheotomy, cannulation of major arteries and veins, surgical procedures on the GI tract, brain lesioning, etc. This of course all stopped as animal rights activists eventually prevailed in their fight against the use of animals in the laboratory. Still, those skills were invaluable during the rest of my career.

"The physiology course we taught in our medical schools until very recently consisted of lectures based on the system of the body: cardiovascular, respiratory, GI, endocrinology, reproduction, renal, central nervous system, etc. Graduate students were enrolled in the same course as the medical students. Today, we teach the physiology of a particular organ as part of an integrated curriculum that includes its anatomy, gross and micro, imaging, pharmacology, cell and molecular biology, embryology, and pathophysiology. In my medical school, the University of Vermont Larner College of Medicine, we are phasing out lectures completely, and by 2020 all of our preclinical training, including the physiology component, will be interactive as well as integrative, as indeed we are even converting our traditional classroom seating to small group tables of eight students working at their tablets. Our graduate students, on the other hand, do continue learning physiology in a traditional lecture-based course, separate from the medical course.

"Departments of Physiology such as mine no longer recruit faculty that bear any resemblance to those recruited in the past. Mine now consists of biophysicists, molecular biologists, structural biologists, X-ray crystallographers, cryo-electron microscopists, and yeast geneticists rather than the blood-and-guts physiologists I "grew up" with in my career. As such, they are not likely to seek membership in the APS, and this is something I feel we have lost.

"My own career started out with a master's degree at Ohio State University, where I studied an extract of the adrenal cortex, labeled as "the sodium factor" by my adviser, Frank Hartman, a pioneer in discovering the multiple physiological actions of adrenal cortical extracts. I recorded its effects on sodium excretion in the dog and learned decades later that the sodium factor I studied was aldosterone.

"In those days, it was very easy to obtain fellowships for doctoral programs as the sputnik era, post-WWII, resulted in generous funding by the federal government to advance science training in the U.S. One had the pick of many universities eager to recruit returning war veterans on the GI bill as well as any women entering science careers. I chose to study cardiovascular physiology at the University of Illinois College of Medicine. My adviser was Alfred Schiller, who tragically died 1 year after I received the Ph.D. in his laboratory, studying the role of hypoxemia on capillary permeability.

"After marriage and the birth of my three children, I had no choice but to stay at home with them since no child care was available in those days, and preschool was only available after potty-training. Furthermore, nepotism rules in most universities forbade recruiting husband and wife as faculty, in addition to a not-too-easily disguised practice of avoiding hiring mothers of young children. Despite these barriers for women pursuing academic careers, I was able, with household help, to work part-time over a period of about 6 years in a sort of perpetual post-doc status, which I never regretted, since it kept me academically involved while raising my children. This brought me to a part-time research associateship with Solomon Snyder, a brilliant young neuropharmacologist at Johns Hopkins University College of Medicine in Baltimore, where my husband's full-time position as a biochemist determined where we would reside and work. In Sol Snyder's exciting lab, I spent 5 years and published eight papers and two book chapters, albeit at half-time,

and at a very low salary. This prolific, exhilarating period of my life laid the foundations for my lifelong interest in the neurochemistry of catecholamines, and it led to my recruitment to the University of Vermont College of Medicine at a time when the fields of brain neurochemistry and neuroscience were rapidly expanding. Amazingly, I went from the lowest academic rank, a research associateship, to a tenure-track, associate professorship, by-passing the ranks of instructor and assistant professor altogether. I attribute this to my beloved former Chair of Physiology at UVM, the late Norman R. Alpert, who was well ahead of his time in promoting the careers of women and racial minorities at a time when both were scarce in academe. After Alpert's death, our current chair, David Warshaw, continued valuing my presence in his department, despite the pressures to restrict precious office space to only those generating grant-based overhead income to the university. My contributions to the department currently are the teaching I do in the first-year medical curriculum. I no longer conduct grant-based research of my own but continue to consult on an informal basis in other grant-funded projects.

"Over the past 20 or so years, I have developed and maintained two inbred strains of rats derived from the spontaneously hypertensive (SHR) rat: one expressing the hypertension of the SHR, without the hyperactivity and reactivity to stress that had inadvertently been inbred along with the hypertensive trait. The other inbred strain developed in my laboratory expresses the behavioral characteristics of the SHR, but not the hypertension, making this an interesting strain for studying hyperactivity and reactivity to stress, their neurochemical correlates, and genetic basis. I was able to make the two strains available to the scientific community when I could no longer maintain them by donating them for cryopreservation of their embryos at the NIH facility for inbred rat and mouse strains, housed at the University of Missouri, Columbia, MO, Rat Resource and Research Center.

"The other aspect of my career that defines me is my participation in promoting the welfare and opportunities for women in science, I was there at the beginning of the modern era of women's liberation in the early 1970s, and the few of us who were practicing careers in biological sciences formed the organization that became the Association for Women in Science (AWIS). A gathering of about 30 women biologists founded AWIS during a national meeting of the Federation of American Societies of Experimental Biology (FASEB). AWIS made heady progress during the mid-1970s, with the passage of the Women in Science and Technology Act sponsored by Senator Ted Kennedy. Even more effective was the addition of the Higher Education Amendments, Title VII and Title IX, to the Civil Rights and Voting Rights Acts enacted during the Johnson administration. Title VII mandated that women in academe be given the same opportunity and pay in employment decisions, and Title IX guaranteed that women students achieve equality in admissions to academic programs, in athletic facilities, in scholarships, in financial aid, etc. Any institutions not in compliance with these mandates were subjected to withholding of federal funding and grants, a most effective threat that resulted in the rapid rise in the advancement of women in academe. We felt this keenly in my university. Within a few years, admission of women to the medical school increased from 10% to over 50%. Even more dramatically, facilities in the OR were expanded for women students to scrub up in rather than in the nurses' quarters where there was no opportunity to interact with the male-only surgical faculty during their training.

"At UVM, I served on the President's Commission on the Status of Women; the Women's Caucus; establishment of the Women's Center; formation of a chapter of AWIS, etc. It was gratifying to witness the astonishing increase in the number of tenured women in the College of Medicine. We were only four when I joined the faculty in 1973, and now we have women as chairs, deans, even chief residents in surgical specialities!

"In closing, I would like to thank the APS for this opportunity to reminisce on the huge changes I have witnessed over 70 years, gratified that we old-timers still have something to contribute to the generations that follow us." ●

# Letter to Lois Heller

**Robert L. Hazelwood writes:** "My sincere apology for the tardy reply to your kind letter of congratulations on my 90th birthday, which arrived precisely on the day of my wife and me moving from our comfortable home here in Georgetown, TX to a senior retirement community nearby. The sheer chaos associated with downsizing and moving after all these years prevented my usual quick reply to letters such as yours.

"My journey in physiology was a sheer joy. My training at University of California, Berkeley, under Leslie Bennett in the Herbert M. Evans Institute of Endocrinology prepared me well to face the uncertainties of academic life that confront one just starting their career. And with these guidelines and goals, I worked hard to instill in my students a love for physiology, not just a way of life. In my work at Boston University School of Medicine and later at University of Houston, I was blessed by having administrators who believed in my efforts, by colleagues who guided yet challenged me, and by continuous funding – and, most of all, by my students who stimulated me to do better. These students, always welcome in our house to test my wife Barbara's culinary talents, worked indiviually and as an harmonious group in planning and executing experiments directed toward animal models of Type 2 diabetes. These early experiments led us to a very exciting collaboration with the late Joe Kimmel of University of Kansas Medical School and the serendipitous discovery of the first pancreatic polypeptide (APP) and ulimately other workers to the so-called PP family and its role in vascular, appetite, and obesity regulation.

"It was an exciting journey, to say the least, but very rewarding in that each student, while learning to design a worthwhile experiment, to establish significant controls, and to value so-called "failed experiments" as a valid learning experience, left his or her mark on our laboratory – and on me as their mentor. Today they are successful as a result of their own imagination and work, their perserverance, not mine. I only gave them the opportunity to explore, to freely exchange ideas, to thoroughly search the literature associated with their projects. Each has made his/her mark in the field of physiology, and I speak of Michael Goodman, Charlie Blake, Marian Walters, Martin Adamo, Steve Naber, and Jerry Colca, to mention but a few who passed through my laboratory. I now stand by, at age 90, in total admiration of their contributions and success. And I have the warm feeling that they are students no more, but rather they are friends, colleagues, and leaders in their fields of physiology.

"It was the same diligent work of these students that led to awards given to me – but actually reflected their efforts and their success and advancement as young investigators – such as quality teaching, significant and relevant research, Fulbright, and the highest award given at the University of Houston, the Farfel award. Parts of 24 years at Chiang Mai Medical School in northern Thailand as the Visiting Professor in Physiology was a most pleasant 'side award.'

"Thank you Dr. Heller for your remembrance card and the opportunity to express my thoughts. God Bless!" ●

# Positions Available

**Assistant/Associate/Full Professor:** The College of Pharmacy in Gainesville, FL invites applications tenure-track positions at the rank of assistant, associate or professor in the Department of Pharmacodynamics. The College of Pharmacy is seeking faculty to strengthen and expand its research in understanding mechanisms of disease and developing new therapeutics. The ideal candidate will have a record of research, teaching, and scholarly accomplishments commensurate with the rank at hire. Associate and full professor applicants are expected to have experience in graduate education and in mentoring graduate students, and to have a strong record of research funding and research accomplishments. The department is highly integrative and collaborative, with a strong focus in cellular and systems physiology and pharmacology. The College of Pharmacy has a strong commitment to attain even greater prominence among the top tier of pharmacy programs. The college is located at the main campus of the University of Florida in Gainesville, the flagship AAU academic research institution of the State of Florida. The college is based in one of the largest integrated academic health centers in the country, with Colleges of Medicine, Nursing, Dentistry, Public Health and Health Professions, and Veterinary Medicine, as well as UF Health and the Veterans Affairs Medical Center, situated on a university campus serving over 50,000 students. Applicants should have a doctoral degree in an appropriate field. Successful candidates will have evidence of research funding appropriate to their current status, a proven track record of publication in journals, and the ability to contribute to professional and graduate education. Criminal background check is required. Candidates should have a record of research, teaching, and scholarly accomplishments. The Search Committee will accept applications until the positions are filled and will begin reviewing applications immediately. Interested applicants should apply online at *https://jobs.ufl.edu*. A cover letter, CV, brief summary of research accomplishments, funding and current research, and a list of three references are required. References will not be contacted without the applicant's permission. To request further information, please contact Dr. Joanna Peris (*Peris@cop.ufl.edu*), Search Committee Chair, University of Florida College of Pharmacy, PO Box 100474, Gainesville, FL 32610. The University of Florida is an equal-opportunity institution dedicated to building a broadly diverse and inclusive faculty and staff. If an accommodation due to a disability is needed to apply for this position, please call 352-392-2477 or the Florida Relay System at 800-955-8771 (TDD). Searches are conducted in accordance with Florida's Sunshine Law. The final candidate will be required to provide an official transcript to the hiring department upon hire. A transcript will not be considered "official" if a designation of "Issued to Student" is visible. Degrees earned from an education institution outside of the U.S. are required to be evaluated by a professional credentialing service provider approved by National Association of Credential Evaluation Services (NACES), which can be found at *http://www.naces.org/*.

**Assistant/Associate/Full Professor:** The newly established Seton Hall-Hackensack Meridian School of Medicine invites applications for multiple open rank positions in basic science disciplines including: physiology, anatomy/histology/embryology, and neurosciences. Successful candidates will join a cohort of medical educators in the Department of Medical Sciences. Faculty appointments will be made at the appropriate level (assistant, associate, professor) based on the candidate's experience. Faculty members will participate in the planning, direction, and implementation of the School of Medicine's medical education program, which will feature an integrated 3 + 1 curriculum that allows students to develop an individualized fourth year program following a 3-year core curriculum. Active learning techniques, including team-based and problem-based learning, will be utilized. The successful candidate will also be expected to provide service to the School of Medicine and professional communities, to assist in LCME accreditation activities, and to engage in innovative scholarship and research to advance medical knowledge. *Minimum qualifications and abilities:* Terminal degree (PhD, MD, DO) with specialization in a basic science field listed above. Evidence of excellence in teaching in an undergraduate medical education (UME) and/or other health science settings. Demonstrated scholarship (e.g., presentations, publications, patents, extramural grant-funding, etc.) in a relevant professional field. Documented ability to mentor and motivate students and peers. *Highly preferred qualifications:* Experience in team-based, problem-based, or case-based learning. Demonstrated ability in leading the development and implementation of courses integrating biomedical, social, population health, and behavioral sciences in a UME setting. Skills necessary to contribute to the establishment and

formation of a Department of Medical Sciences at a developing allopathic medical school. Experience in LCME accreditation activities and development of new medical schools. The Seton Hall-Hackensack Meridian School of Medicine is currently seeking preliminary accreditation from the Liaison Committee on Medical Education (LCME) with plans to matriculate the first class of students in Fall 2018. The School of Medicine will be located in Nutley, NJ, approximately 10 miles west of New York City. The interprofessional campus will house the School of Medicine as well as The Seton Hall University College of Nursing and School of Health and Medical Sciences. For more information about the School of Medicine, please visit our website at *http://www.shu.edu/medicine/*. Individuals wishing to apply should submit an application, including a cover letter, statement of teaching philosophy, curriculum vitae, and list of professional references via the Seton Hall Employment Opportunities website at *http://jobs.shu.edu/cw/en-us/job/492721/assistantassociatefull-professor-basic-sciences*. Seton Hall University is an equal opportunity/affirmative action employer. It honors diversity and respects the religious commitments of all its employees. In turn, its employees respect Catholic beliefs and values, and they support its mission as a Catholic institution of higher education.

**Postdoctoral Fellow:** A postdoctoral research fellowship is available July 2017 on a NIH-funded T32 training grant focused on providing multi-disciplinary multi-modality training in molecular and translational cardiovascular imaging for highly qualified fellows holding either a MD or/and PhD, in preparation for academic careers as independent investigators in the highly clinically relevant field of cardiovascular imaging. Postdoctoral fellowship training will be 2–3 years in duration. There are three primary research focuses in the postdoctoral training: *1)* cardiovascular molecular imaging, *2)* cardiovascular imaging technologies and analyses, and *3)* translational cardiovascular imaging. Applicants will have full access to resources available through the Yale Translational Research Imaging Center, including small and large animal surgical suite, fluoroscopy suite, 3D ultrasound, 64-slice SPECT/CT, micro-SPECT/-CT, micro-CT, and optical imaging, along with other institutional resources, including PET/CT and MRI. Participation is in ongoing NIH-funded projects. Applications will be encouraged from clinical, engineering, and basic science departments, with particular attention to the recruitment of minority, disabled, and disadvantaged candidates. Candidates fellows must hold either a MD or/and PhD. Candidates must be U.S. citizens or hold a green card. Please contact Albert Sinusas for more information: office: 203-785-5005; e-mail: *Albert.Sinusas@yale.edu*.

**Postdoctoral Fellow:** The Center for Translational Medicine at the Lewis Katz School of Medicine is currently seeking postdoctoral scientists to work in the laboratory of Director Dr. Walter J. Koch. We are looking for motivated people who have an interest in cutting-edge translational cardiovascular research. Currently, several projects are ongoing dealing with novel aspects of G-protein-coupled receptor kinases (GRKs) and p-arrestins in heart failure and metabolic disorders. You will join a large dynamic lab where you can have the freedom to also start independent projects. Studies involve small animal models to advance novel therapeutics for heart and metabolic diseases. Applicants just completing their PhD is preferred. Grant writing will also be emphasized in first 2 years. Please send letters of interest and CVs to Walter J. Koch, PhD, Director Center for Translational Medicine Temple University School of Medicine, 3500 N Broad St., MERB 941, Philadelphia, PA 19140; e-mail: *walter.koch@temple.edu*.

**Postdoctoral Fellow:** The Hood lab at Auburn University is hiring two (2) postdoctoral scholars to *1)* evaluate the role of oxidative stress and mitochondrial function in life history tradeoffs and *2)* evaluate the effects of genetic variation in the intracellular stress response on reproductive fitness and mitochondrial performance. Projects will be completed in wild-derived house mice and deer mice, respectively. Both projects are funded by the National Science Foundation. A strong background in ecology/evolutionary biology and physiology and excellent communication, organizational, and leadership skills are required. Applicants with strong lab skills will be given preference. Preferred skills include isolating mitochondria and measuring mitochondrial respiration, running Western blots, and performing ELISAs. Postdocs will be expected to assist with training graduate students in the lab, develop synergistic projects, write grants, and produce first-authored papers and contribute to co-authored papers. These are 1-year positions with the possibility of renewal for a total of 2 or 4 years, pending satisfactory

work. Information about Hood lab and abstracts for funded projects can be found at *thehoodlaboratory.com*. This work will be completed in collaboration with Dr. Andreas Kavazis, School of Kinesiology at Auburn (*http://www.education.auburn.edu/initiatives/muscle-biochemistry-lab-dr-andreas-kavazis/*) and Dr. Hippokratis Kiaris, School of Pharmacy, University of South Carolina (*http://sccp.sc.edu/Hippokratis_kiaris*). Applicants must have a PhD in an appropriate field. The candidate selected for this position must be able to meet eligibility requirements to work in the U.S. at the time the appointment is scheduled to begin and to continue working legally for the proposed term of employment. Women and minorities are strongly encouraged to apply. This announcement is informal in nature, and candidates of interest will be asked to submit a formal application for complete consideration after initial screening. If interested, please send a CV and a statement of interest with a list of relevant skills to Wendy Hood at *wrhood@auburn.edu* (please note our mail system is limited to 25-Mb messages). Receipt of application will be confirmed within 3 days. Review of applications will begin August 7, 2017, and continue until a suitable applicant is found.

**Postdoctoral Fellow:** A postdoctoral scientist position is available in the University of South Florida Department of Molecular Pharmacology & Physiology to study ion channels in the physiology and pathophysiology of the heart rhythm. The appropriate candidate will have a PhD degree or its equivalent. Experience in the field of electrophysiology is required. Experience with one or more of the following techniques are preferred: animal surgery, conventional molecular and cellular biology, optical mapping, and patch clamp. Interested candidates should send their CV, a brief research statement, and a list of 3 references to Dr. Sami Noujaim at *snouiaim@health.usf.edu*.

**Postdoctoral Fellow:** A postdoctoral position is available in the laboratory of Dr. Toni R. Pak in the Department of Cell and Molecular Physiology, Loyola University Chicago. The project will focus on ligand-independent signaling of nuclear receptors in the aged brain, with an emphasis on alternative RNA splicing and proteomics. Molecular biology techniques, including viral vector construction, ChIP and RIP assays, nuclear run-on assays, qPCR, and ability to work with both whole animal and in vitro models, are required. In addition, experience with HPLC and MS/MS using targeted approaches to detect posttranslational modifications is preferred. The successful candidate will be highly motivated, have strong oral and written communication skills, and have a PhD in the field of RNA biology, molecular biology, endocrinology, and/or neuroscience. Interested applicants should send a cover letter describing their experience and interests, CV, and names of 3 references. The packet should be sent as a single pdf file to *tpak@luc.edu*.

**Postdoctoral Fellow:** The Department of Medicine, Division of Cardiology at the Lewis Katz School of Medicine is currently seeking postdoctoral scientists to in work in the laboratory of Arthur M. Feldman, MD, PhD, the Laura H. Carnell Professor of Medicine. We are looking for motivated scientists who have an interest in pursuing cutting-edge translational cardiovascular research. Our ongoing work is focused on the role of BAG3 in cardiovascular disease with particular interest in its role in autophagy, apoptosis, excitation-contraction coupling, and regulation of nuclear proteins. The work spans studies in animal models that harbor mutations in BAG3 to the molecular genetics of BAG3 mutations in patient populations, with the long range goal of advancing novel therapeutics for heart and skeletal muscle disease. We seek individuals who have recently completed their PhD degrees and those with experience in molecular biology and biochemistry, and either mouse hemodynamics or gene editing and gene therapy. All applicants should currently reside in the U.S. Grant writing will also be emphasized within the first 2 years of the position. The postdoctoral fellow duties will include, but are not limited to, organizing and implementing complex research plans, the development of new methods, testing and data collection, analysis and interpretation of data, writing detailed scientific reports, and mentoring graduate and undergraduate students. The candidate will be expected to possess superior communication skills and present their research findings on a regular basis to both peers within the center and at national and international meetings. No teaching will be required of this position. Competitive salary and benefits such as health insurance and paid vacation are provided. To apply for this position please e-mail a cover letter, curriculum vitae, and 2–3 letters of reference to Dr. Arthur M. Feldman at *Arthur.Feldman@tuhs.temple.edu*.

**Postdoctoral Fellow:** An NIH postdoctoral research fellowship is available in Dr. Donald R. Menick's laboratory at the Medical University of South Carolina to study epigenetic regulation in cardiovascular disease. The main project will deal with examining the role of histone deacetylases (HDACs) in the regulation of macrophage phenotype and early resolution of inflammation in the post-MI heart. We and others have shown that treatment with HDAC inhibitors preserves LV function and myocardial remodeling in the post-MI heart. Our work shows that inhibition of HDACs results in the early recruitment of reparative macrophages in the post-MI heart and correlates with improved ventricular function and remodeling. Here, we will use nanoparticle delivery of HDAC inhibitors to determine whether targeted delivery of a class I HDAC inhibitor to inflammatory monocytes attenuates MI injury. We are also determining whether treatment with a class I selective HDAC inhibitor in a model of chronic inflammation commonly seen in patients with atherosclerosis results in reduced deleterious remodeling and preservation of ventricular function. Our objective is to test whether inhibition of class I HDACs in activated monocytes is sufficient to reprogram macrophage phenotype in the post-MI heart, reduce deleterious remodeling, and preserve ventricular function. Our study has identified a very promising therapeutic opportunity to manage macrophage phenotype and enhance resolution of inflammation in the post-MI heart. Applicants should have a doctorate in biochemistry, immunology, molecular biology, cell biology, physiology, or a closely related discipline and be a U.S. citizen or permanent resident eligible for NIH grant support. Successful applicants must have a strong publication record and excellent communication and laboratory skills. The fellow will be expected to participate in experimental design, data collection, analysis and interpretation, and preparation of oral and written scientific reports. The fellow will be a part of our NIH T32 program, which provides a rich environment in training and career mentoring, with workshops and individualized mentoring team to maximize our trainees' success toward an independent research career. Salary is commensurate with experience according to NIH stipend levels. Please submit a cover letter describing research interests and experience, a curriculum vitae, and copies of recent research publications along with name, address, and phone number of three references. Direct all correspondence and recommendations to Donald R. Menick, PhD, Professor of Medicine, Director of Gazes Cardiac Institute, 114 Doughty St., MSC773 Medical University of South Carolina, Charleston, South Carolina 29425; e-mail: *menickd@musc.edu*.

**Research Scientist:** The Molecular Cardiology Research Institute (MCRI) of Tufts Medical Center seeks an outstanding candidate for the position of Mouse Physiology Core Surgeon. This position will involve learning and mastering a variety of cardiovascular surgical procedures in small rodents with the eventual goal of performing unsupervised procedures for a large research group. Additional key responsibilities include assisting in administration of the Mouse Core facility and coordinating the scheduling of procedures in a multiple Principal Investigator Institute. The position provides the opportunity to work initially under the general supervision of a senior surgeon, which over time will progress to unsupervised work. The Mouse Cardiovascular Physiology Core Facility has developed a number of models for studying the cardiovascular system, including mouse myocardial infarction (heart attack), mouse cardiac electrophysiology studies, models of pressure overload-induced heart failure (transaortic constriction), and mouse carotid artery injury. Cardiac phenotype assessment techniques include echocardiography, invasive hemodynamic analysis, and implantable telemetry. Although prior experience with microsurgery is desired and exceptional skills with mice are requisite, the ideal candidate will possess a strong interest in, and aptitude for, learning from an established and highly skilled senior surgeon, with the goal of producing reproducible surgical models. We are seeking candidates who can commit to a long-term "core" position. The position requires: minimum of Master's degree; excellent writing and communications skills; prior experience in molecular biology and/or in animal physiology. The Molecular Cardiology Research Institute (MCRI) is an internationally known institute with several principal investigators studying diverse topics of molecular medicine. Please visit our website at *www.tuftsmedicalcenter.org/mcri*.

**Research Scientist:** The Molecular Cardiology Research Institute (MCRI) of Tufts Medical Center seeks a highly motivated researcher with experience working with rodents to coordinate and perform experimental studies of pharmacological treatments for heart failure. The successful applicant will work closely with the principal

investigators on a variety of research projects using state-of-the-art mouse models of cardiac hypertrophy and failure, as well as biochemical, molecular, and cell-biological assays, and to address clinically relevant questions in cardiovascular biology. The research team's goal is to identify new therapeutic targets to prevent or treat cardiovascular diseases in humans. As needed, the individual will be required to develop protocols independently and establish new methodologies in the laboratory. Competitive applicants will ideally hold an advanced scientific degree (MS or above) and be able to commit to a long-term position. *Principal Duties and Responsibilities:* Work as part of one or more project teams, and remain proficient in designing, managing and performing experiments. Perform cardiac function studies including echocardiography in mice. Drug administration to mice by oral gavage and intraperitoneal injection. May perform model mouse surgery in collaboration with the MCRI animal surgeon. Collect and analyze data, and deliver experimental research reports when necessary with guidance from the PIs for collaborative research projects. With guidance from the PIs, produce scientific manuscripts for publication in peer-reviewed journals, and present research data in house and in scientific conferences. Write as well as assist in the preparation of applications for external grants for research and fellowships. Assist in general lab organization and maintenance, supply ordering, and liaising with infrastructure departments. Learn new skills such as vascular function studies in mouse models using wire and pressure myography. *Knowledge, Skills, and Abilities:* Minimum of MS in biochemistry, cell biology, microbiology, or bioscience degree program. Experience in molecular biology techniques and animal research experience is desired. Excellent organizational and communication skills are essential. Desire and ability to learn new procedural skills in mouse, such as ex vivo vascular function studies and cardiac myocyte isolation. Ability to coordinate and organize in vivo protocols and studies with large numbers of mice. The Molecular Cardiology Research Institute (MCRI) is an internationally known institute with several principal investigators studying diverse topics of molecular medicine. Please visit our website at *www.tuftsmedicalcenter.org/mcri*.

**Research Scientist:** Miromatrix is a Minnesota-based biotechnology company engaged in the development of fully biological human organs to solve the chronic shortage of transplantable organs, utilizing its patented perfusion decellularization/recellularization technology, as well as organ-derived biological products such as MIROMESH® and MIRODERM® for soft-tissue reinforcement and advanced wound care, respectively. This is a unique opportunity to join a growing company with novel products. Miromatrix has an immediate opening for a highly motivated individual who wants to join our team in a fast-paced, results-oriented work environment. We are looking for a talented Senior Development Scientist to lead our Kidney Team in the development of a novel recellularized kidney graft for the treatment of kidney failure. In this role, primary responsibilities will be experiment planning, decellularization of kidneys, cell culture, bioreactor seeding, characterization of kidney function, and preclinical studies. *Required Qualifications.* Miromatrix seeks an individual with at least a BS degree in one of the sciences or engineering disciplines including tissue or biomedical engineering. The successful candidate will be highly proficient in tissue engineering, cell biology, and cell culture. Applicants should have at least 5 years of relevant experience. Excellent organizational, verbal, written, and interpersonal skills are essential, as well as enthusiasm for a collaborative work culture. *Desired Qualifications.* Preference will be given to those with prior tissue engineering experience and a background in regenerative medicine, either industry or academic related. Additional experience in the characterization of kidney function, primary cell culture, extracellular matrix, and/or endothelial cell culture are definite pluses, as well as an MS or PhD in a biology or engineering discipline, or an MD. We encourage those with industrial regenerative medicine or tissue engineering experience to apply. Miromatrix offers a competitive compensation package with great growth potential. The company is committed to providing a safe, fair, and enjoyable work environment. Job offer will be contingent upon a pre-employment background check and drug screening. Miromatrix Medical, Inc. is an equal-opportunity employer. To apply, e-mail your resume and cover letter to *dseetapun@miromatrix.com*.

# Meetings & Congresses

## 2017

*November 2*

**Mitochondria in Health and Disease,** The New York Academy of Sciences, NY. *Information:* Internet: *http://www.nyas.org/Mitochondria2017/*

*November 6-8*

**APS Conference: Physiology and Pathophysiology Consequences of Sickle Cell Disease,** Washington, DC. *Information:* Internet: *http://www.the-aps.org/mm/Conferences/APS-Conferences/2017-Conferences/Sickle-Cell*; *#SickleCell17*

*November 9-11*

**4th European Biopharma Congress,** Vienna, Austria. *Information:* Internet: *http://biopharmaceutics.pharmaceuticalconferences.com/europe/*

*November 12-15*

**Keystone Symposia: Frontiers of Serotonin Beyond the Brain,** Park City, UT. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18T5*

## 2018

*January 14-18*

**Keystone Symposia: Heart Failure–Crossing the Translational Divide,** Keystone, CO. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18A1*

*January 14-18*

**Keystone Symposia: State of the Brain–Genetic Dissection of Brain Circuits and Behavior in Health and Disease,** Keystone, CO. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18A2*

*February 17-21*

**Biophysical Society 62nd Annual Meeting,** San Francisco, CA. *Information:* Internet: *http://www.biophysics.org/2018meeting/Home/tabid/7117/Default.aspx*

*February 25-March 1*

**Keystone Symposia: Vascular Biology and Human Diseases–From Molecular Pathways to Novel Therapeutics, joint with the meeting on Uncomplicating Diabetes: Reducing the Burden of Diabetes Related End-Organ Injury,** Santa Fe, NM. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18J8*

*February 25-March 1*

**Keystone Symposia: Endoderm Development and Disease–Cross-Organ Comparison and Interplay,** Taos, NM. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18C3*

*March 25-29*

**Keystone Symposia:** iPSCs–A Decade of Progress and Beyond, Olympic Valley, CA. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18C7*

*April 21-25*

**Experimental Biology,** San Diego, CA.

*June 13-16*

**Keystone Symposia: Novel Aspects of Bone Biology,** Snowbird, UT. *Information:* e-mail: *info@keystonesymposia.org*; Internet: *http://www.keystonesymposia.org/18E3*

*July 7-11*

**11th FENS Forum of Neuroscience,** Berlin, Germany. *Information:* Internet: *http://forum2018.fens.org/*

*September 5-8*

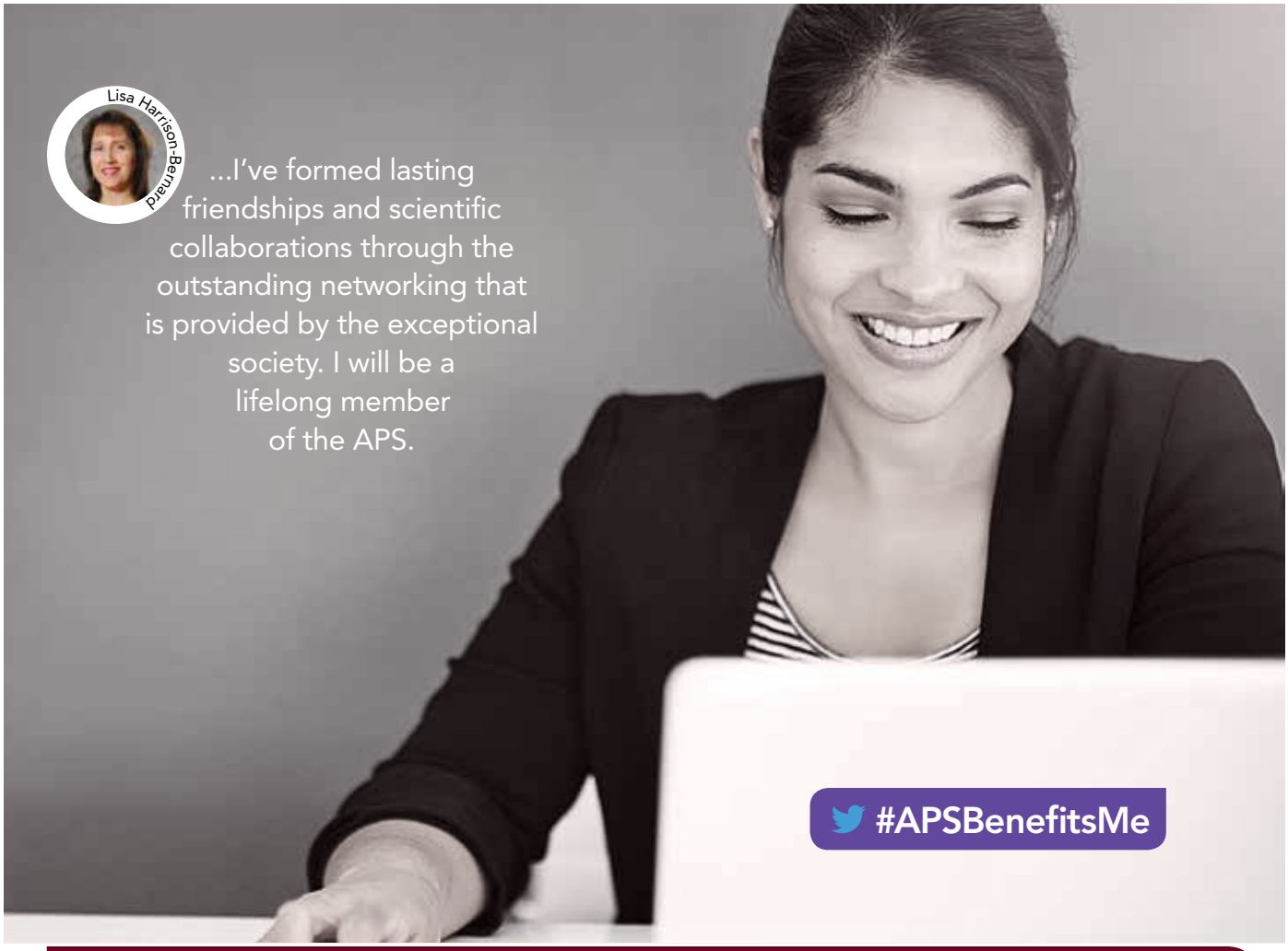
**8th International Congress of Pathophysiology,** Bratislava, Slovakia. *Information:* internet: *http://www.icp2018.com*

*October*

**The 17th International Biochemistry of Exercise Conference (IEBC),** Beijing, China. *Information:* Organized by the Chinese Association of Exercise Physiology and Biochemistry

*October 18-21*

**34th World Congress of Internal Medicine,** Cape Town, South Africa. *Information:* internet: *http://www.wcim2018.com*

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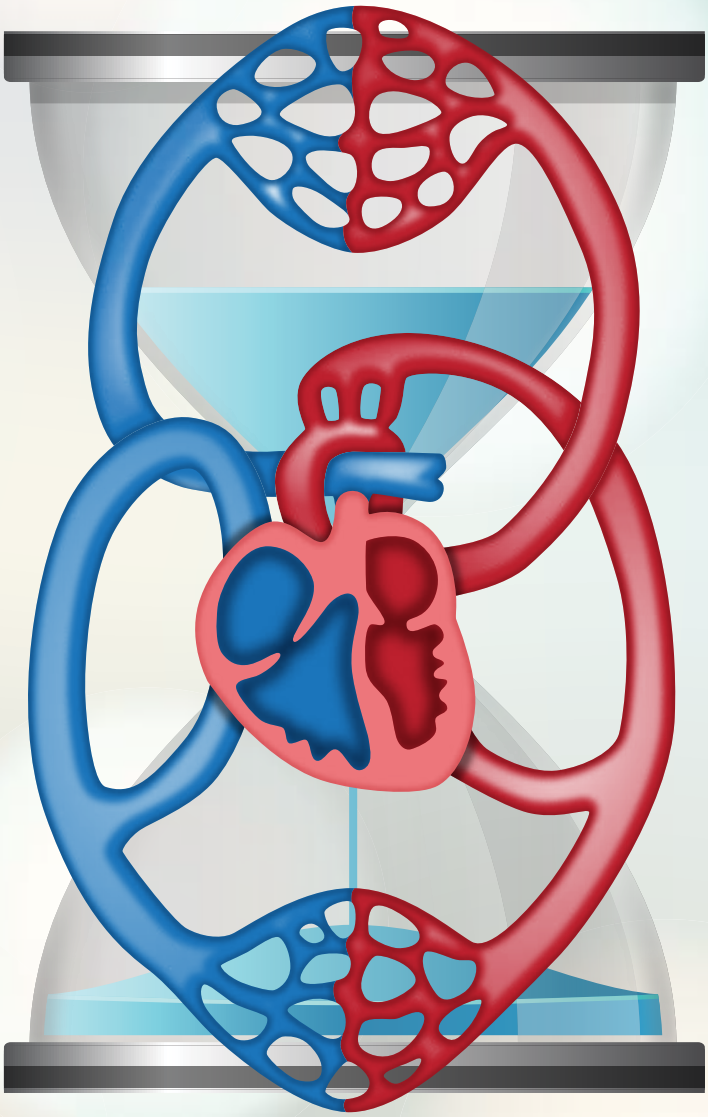
# Cardiovascular Aging: New Frontiers and Old Friends

Westminster, Colorado • August 11-14, 2017



# Conference Program & Abstracts

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**2017 APS CONFERENCE**
**CARDIOVASCULAR AGING: NEW FRONTIERS AND OLD FRIENDS**
**AUGUST 11-14, 2017, WESTMINSTER, COLORADO**

**ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS**

# 2017 APS Conference
# Cardiovascular Aging: New Frontiers and Old Friends
# August 11-14, 2017, Westminster, Colorado

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## Acknowledgements

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# 2.0 LECTURE

**2.1**

## STRATEGIES FOR OPTIMAL CARDIOVASCULAR AGING

**Douglas Seals[1]**

**[1]Integrative Physiology, University of Colorado Boulder, 354 UCB, Boulder, CO, 80309**

Cardiovascular diseases (CVD) remain the leading causes of morbidity and mortality in the U.S., and aging is by far the greatest risk factor for CVD. Much of the increase in CVD risk with aging is driven by adverse changes to arteries, most prominently large elastic artery stiffening and endothelial dysfunction, which, in turn, induce secondary detrimental effects on the heart and systemic circulation. Arterial dysfunction also contributes to many other common conditions of aging including cognitive/motor disorders and metabolic and kidney diseases. Altered vasoactive signaling featuring reduced nitric oxide bioavailability and modifications in the expression and architecture of structural proteins in the arterial wall are key characteristics of arterial aging. Two mechanistic Old Friends responsible for these changes are chronic oxidative stress and low-grade inflammation (inflammaging). As such, identifying the upstream processes that contribute to oxidative stress and inflammation is one of the New Frontiers of arterial aging research. Presently there is evidence for mitochondrial dysfunction, impaired autophagy/mitophagy, dysregulated energy-sensing pathways and sex hormone deficiency playing important roles. However, other fundamental mechanisms of biological aging, including cellular senescence, reduced stress resistance, genomic instability, telomere attrition, reduced proteostasis, stem cell dysfunction and/or epigenetic modifications, along with gut dysbiosis, also may contribute. Strategies for which there is extensive experimental evidence of benefit may be considered preventive and/or therapeutic Old Friends for arterial aging, and include healthy lifestyle practices such as regular aerobic exercise, limiting energy intake, and healthy diet composition. These strategies act to maintain arterial function and health with aging by favorably modulating one or more of the above processes to suppress oxidative stress and inflammation. Several novel strategies represent New Frontiers, but presently lack evidence for efficacy, particularly in humans. These include alternative exercise training regimens (e.g., high-intensity interval training); behavior (intermittent fasting) or pharmacological (sirtuin-activating and NAD+-boosting compounds) based chronic energy restriction-mimicking paradigms; healthy diet composition-inspired nutraceuticals (supplements, functional foods); and environmental stress-leveraged interventions (e.g., heat therapy).

# 4.0 SYMPOSIUM: COUNTERMEASURES TO CARDIOVASCULAR AGING

**4.1**

## RAPAMYCIN AND ELAMIPRETIDE (SS-31): INTERVENTIONS TO REVERSE CARDIAC AGING BY ENHANCING MITOCHONDRIAL FUNCTION

Peter Rabinovitch[1]

[1]Pathology, Univ. of Washington, 1959 NE Pacific St., Box 357705, Seattle, WA, 98195

Aging is associated with significant declines in skeletal and cardiac muscle function and a higher incidence of cardiovascular disease. Even in healthy individuals, aging results in increased prevalence of sarcopenia, left ventricular hypertrophy, impaired diastolic function and reduced myocardial performance. These same changes are seen in aging mice, making them a useful model for studies of muscle healthspan. We were able to show that transgenic mice expressing mitochondrial catalase (mCAT), displayed delayed cardiac aging. Subsequently, we have been interested in whether shorter term pharmacologic treatments might be able to reverse the functional deficits of skeletal and cardiac muscle aging in old mice. The mitochondrial protective SS-31 peptide (elamipretide) offers similar benefits as mCAT in models of pressure overload-induced cardiac hypertrophy and failure. This agent has recently been shown to bind to cardiolipin and improve the electron carrying function of cytochrome c, while reducing its peroxidase activity. We have now found that 24 month old mice receiving SS-31 for 8 weeks have improved skeletal muscle energetics, function and endurance, enhanced cardiac diastolic function, improved myocardial performance, reduced cardiac hypertrophy and increased exercise endurance. The cardiac improvements are persistent after removal of the drug, with a half-time of approximately 2 weeks. Continuing this theme, we found that 8 week rapamycin treatment can also reverse established cardiac aging, inducing proteomic and metabolic remodeling that improves mitochondrial energy metabolism. Interestingly, rejuvenation of cardiac function by 8 week rapamycin treatment is persistent for longer than 8 weeks after the drug treatment is withdrawn. Results with both rapamycin and SS-31 indicate that short-term treatments can enhance mitochondrial function and reverse muscle aging phenotypes in old mice and that these benefits can be long-lasting. Thus, interventions that target mitochondrial function can have a high translational potential, with late-life treatments conferring healthspan improvements with persistent benefits. Support: NIH grants P01AG001751, P30 AG013280, R01 AG038550.

**4.2**

## LATE-LIFE EXERCISE TRAINING REVERSES AGE-RELATED MICROVASCULAR DYSFUNCTION: *A ROLE FOR ADIPONECTIN*

Judy Muller-Delp[1]

[1]Biomedical Sciences, Florida State University, 1115 West Call Street, Tallahassee, FL, 32306-4300

Coronary microvascular function and blood flow responses to acute exercise are impaired in the aged heart, but can be restored by exercise training. Age impairs myogenic responsiveness of coronary arterioles; however, even at an advanced age, exercise training restores myogenic responses of coronary arterioles. Adiponectin has also been implicated

in maintenance of optimal cardiovascular function due to 1) enhancement of endothelial function and stimulation of angiogenesis, and 2) regulation of smooth muscle differentiation and prevention of atherosclerosis. We assessed contractile function and vascular smooth muscle phenotypic changes, as well as adiponectin signaling in coronary arterioles from young and old Fischer 344 rats that either underwent 10 weeks of treadmill exercise training or remained sedentary. Contractile function was impaired in coronary arterioles from aged rats, and vascular smooth muscle shifted from a differentiated, contractile phenotype to a secretory phenotype with associated hypertrophy of smooth muscle in the arteriolar wall. Circulating adiponectin and arteriolar expression of downstream signaling molecules, adenosine monophosphate-activated kinase (AMPK) and smooth muscle myosin heavy chain, were decreased in aged rats, whereas expression of the synthetic protein, ribosomal protein S6 (rpS6) and phosphorylated rpS6 was increased. Exercise training improved contractile function in coronary arterioles from old rats and restored a contractile phenotype to arteriolar smooth muscle. Exercise training increased circulating adiponectin, restored arteriolar expression of AMPK and smooth muscle myosin heavy chain, and decreased the level of rpS6 and phosphorylated rpS6 in coronary arterioles from old rats. Thus, age-induced contractile dysfunction and emergence of a secretory smooth muscle phenotype in coronary arterioles are reversed by late-life exercise training, possibly through increased adiponectin signaling.

**4.3**

**MODULATORY INFLUENCES OF SEX HORMONES ON VASCULAR AGING**

Kerrie Moreau[1,2]

[1]Medicine, University of Colorado Anschutz Medical Campus, Mail Stop B179, 12631 E. 17th Ave, Room 8111, Aurora, CO, 80045, [2]Geriatric Research Education and Clinical Center, Eastern Colorado Veterans Affairs, 1055 Clermont St, Denver, CO, 80220

Vascular aging, featuring endothelial dysfunction, is a major risk factor for developing age-associated cardiovascular diseases (CVD). In women, the decline in endothelial function is attenuated until menopause, whereafter the rate of decline accelerates to match that seen in men. Sex differences in the decline in endothelial function have been attributed to changes in gonadal hormones with aging. In women, we have demonstrated a progressive impairment in endothelial function across the stages of the menopause transition, related in part, to declining estradiol (E2) levels. Additionally, we and others demonstrate that endothelial function can be improved with E2 treatment in postmenopausal women. In contrast to women, little is known about the impact of declining testosterone (T) levels on endothelial function in men, but some evidence suggest greater endothelial dysfunction in men with low T compared to men with higher T. Our research employs short-term gonadal suppression models to manipulate sex hormones in an acute and reversible manner to distinguish the independent mechanisms of action of gonadal hormones from other factors (e.g., adiposity) that may influence vascular function during more chronic sex hormone withdrawal. Our preliminary observations demonstrate that short-term lowering of E2 and T in women and men, respectively, impairs endothelial function, and that oxidative stress is a key mechanism underlying this impairment. The underlying causes of the oxidative stress and endothelial dysfunction are unknown, but may be related to impairments in endothelial nitric oxide synthase and mitochondrial function. Further investigations into the defects that intersect vascular and gonadal aging will inform effective sex-specific intervention strategies to preserve vascular health and prevent CVD. Support: NIH R01s AG027678, AG22241, AG049762, R56HL114073, K01AG20683, P30 DK048520 and UL1 TR001082, and University of Colorado Denver (UCD) Center for Women's Health Research, and Eastern Colorado VA Geriatric Research, Education, and Clinical Center

**4.4**

**INTRAVENOUS ADIPOSE-DERIVED CELL THERAPY IMPROVES CARDIOVASCULAR PERFORMANCE IN AGED RATS**

Amanda LeBlanc[1], Natia Kelm[1], Jason Beare[1], Monika George[1], Charles Shofner[1], Jacob Dale[1], Joseph Tinney[2], Bradley Keller[2], James Hoying[1]

[1]Physiology, University of Louisville, 302 E. Muhammad Ali Blvd, Louisville, KY, 40202, [2]Pediatrics, University of Louisville, 302 E. Muhammad Ali Blvd, Louisville, KY, 40202

Over 50% of adult women presenting with symptoms of ischemic heart disease have "clear" coronary artery angiograms. Additional testing indicates coronary microvascular dysfunction contributes to the coronary perfusion deficits in these women. Current therapies for this condition, called microvascular angina, are relatively ineffective. Our previous research demonstrated that tissue-resident macrophages within the therapeutic cell preparation derived from the stromal vascular fraction (SVF) of adipose tissue improved peripheral small artery function. Delivered IV, these SVF-derived macrophages migrate to the walls of small vessels and reset vasomotor tone. Therefore, we hypothesized that IV delivery of SVF cells could reverse coronary microvascular dysfunction. Using the aged female Fisher-344 rat (22 mos. of age) as a model of coronary microvascular dysfunction without coronary artery involvement, combined with high-resolution ultrasound and indwelling chronic telemetry, we evaluated cardiac function and coronary flow reserve (CFR) in aged animals receiving fluorescently tagged GFP+ SVF cells from syngeneic young rats (6 x $10^6$ cells/rat) via the tail vein at one-week and four-weeks post-injection. At the time of explant, the location of injected SVF cells was determined via confocal microscopy, and isolated coronary arteriole preparations were used to evaluate vasoactivity. Injected GFP+ SVF cells had incorporated into the coronary vasculature one-week post-injection and remained there at 4 weeks. While coronary blood flow was improved in animals receiving the cell therapy, vasoreactivity of isolated arterioles to flow, pressure, bradykinin, and endothelin was unaffected. Measures of heart function such as maximal CO, percent HR increase, and LV EDD and EDV - which are all compromised in aged animals - were significantly improved in response to a dobutamine

challenge compared to pre-SVF measurements. The cell therapy did not lead to arrhythmias or increased mortality. Our findings indicate that IV-delivered adipose SVF cells disseminate to the aging heart and incorporate into the microvascular wall and perivascular spaces of the coronary vasculature. The presence of the therapeutic cells in the heart is associated with improved coronary perfusion and concomitant cardiac function. Funding: NIH RO1 AG053585 (AJL) and P30 GM103507 (UofL), Jewish Heritage Fund for Exellence (AJL), Gheen's Foundation (AJL).

## 5.0 POSTER SESSION I

### 5.1

### MITOQ SUPPLEMENTATION IMPROVES VASCULAR ENDOTHELIAL FUNCTION IN HEALTHY LATE MIDDLE-AGED AND OLDER ADULTS

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Vascular endothelial dysfunction, as assessed by a decline in endothelium-dependent dilation (EDD), is a primary contributor to increased cardiovascular disease (CVD) risk with age. A key mechanism of reduced EDD with age is decreased bioavailability of the vasodilatory and vasoprotective molecule nitric oxide (NO) secondary to increased oxidative stress. Excessive reactive oxygen species production by mitochondria (mtROS) is emerging as a significant cause of vascular oxidative stress and reduced NO bioavailability with aging. Consistent with this concept, preclinical findings from our laboratory demonstrate that decreasing mtROS with the mitochondria-targeted antioxidant MitoQ restores NO-mediated EDD in old mice. The purpose of the current study was to translate our preclinical findings to humans by conducting a randomized, placebo-controlled, double-blind, crossover clinical trial to assess the efficacy of 6 weeks of oral MitoQ (20 mg/day) vs. placebo supplementation for improving EDD in healthy, late middle-aged and older adults (n=18, 60-79 yrs). EDD, measured by brachial artery flow-mediated dilation ($FMD_{ba}$), was increased by 48% with MitoQ vs. placebo ($P<0.01$), whereas endothelium-independent dilation (dilation with sublingual nitroglycerin) was unaffected ($P>0.05$). Additionally, MitoQ supplementation abolished tonic mtROS-mediated suppression of EDD, evaluated in a subset of subjects (n=7), as indicated by a 69% increase in $FMD_{ba}$ with acute oral administration of 160 mg of MitoQ ($P<0.05$) under placebo conditions, but no change in $FMD_{ba}$ with acute MitoQ ($P>0.05$) following 6 weeks of MitoQ supplementation. Participant characteristics were unaffected by MitoQ (all $P>0.05$). Collectively, these data suggest that MitoQ and other therapeutic strategies targeting mtROS may hold promise for treating vascular endothelial dysfunction and reducing CVD risk with aging.

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### 5.2

### PROGRESSION OF ALZHEIMER'S DISEASE: THE ROLE OF NITRIC OXIDE BIOAVAILABILITY IN CEREBRAL AND PERIPHREAL CIRCULATION.

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**Background.** In aging, cerebral and systemic circulation decline likewise to cognitive decline. Also, reduced availability of nitric oxide (NO) in both cerebral and peripheral blood vessels results in further alterations of circulation. Therefore, changes in circulation and NO bioavailability may contribute to the development of Alzheimer's disease (AD). However, role of NO bioavailability in the control of extracranial blood flow, cerebral, and systemic circulation during AD progression have not been so far fully elucidated.

**Methods.** We assessed cortical circulation (partial volume correction) with arterial spin labeling (PVC-CBF), and measured internal carotid (CA), and femoral (FA) artery blood flow in young (YG), healthy old (OLD), patients with mild cognitive impairment (MCI), and in patients at 1st ($AD_1$), 2nd ($AD_2$), and 3rd ($AD_3$) phase of AD. NO was determined via plasma NO metabolites (nitrite and nitrate concentrations), passive limb-movement (PLM) induced hyperemia was used to assesses both NO bioavailability and systemic vascular function.

**Results.** Ninety-eight individuals (10 YG, 14 OLD, 19 MCI, 24 $AD_1$, 20 $AD_2$, and 11 $AD_3$) were included in this study. PVC-CBF, CA, and FA blood flow were significantly (all $p<0.05$) reduced across the range from YG to OLD, MCI, $AD_1$, $AD_2$, $AD_3$ subjects. Plasma level of nitrates was significantly reduced ($p<0.05$) among the 6 groups, with values of 67.8±4.2 µM in the YG, 58.1±5.1 µM in OLD, 51.1±3.0 µM in MCI, 45.1±3.7 µM in $AD_1$, 39.2±3.7 µM in $AD_2$, and 36.1±23.3 µM in $AD_3$. Similarly, PLM was significantly decreased ($p<0.05$) in the 6 groups, with values of 439±59 ml⋅min$^{-1}$ in YG, 298±38 ml⋅min$^{-1}$ in OLD, 233±41 ml⋅min$^{-1}$ in MCI, 202±25 ml⋅min$^{-1}$ in $AD_1$, 155±19 ml⋅min$^{-1}$ in $AD_2$, and 117±24 ml⋅min$^{-1}$ in $AD_3$. Significant

correlations were retrieved between plasma nitrates and PLM, PVC-CBF, CA, as well as FA blood flow.

**Conclusions.** These results suggest that AD-related circulation impairment is progressive and not limited to the brain cortex, but it is likely the consequence of a systemic vascular dysfunction. The link between cardiovascular and the central nervous system degenerative processes during the progression of AD is likely related to the depletion of endogenous NO.

**5.3**

**ACUTE AND CHRONIC EFFECTS OF E-CIGARETTE VAPOR EXPOSURE ON VASCULAR FUNCTION: NEW FRIEND OR OLD FOE?**

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**Background:** Proponents for electronic cigarettes (E-cigs) claim they are a safe alternative to smoking tobacco-based cigarettes, however little is known about the acute and/or long-term effects of E-cig vapor exposure, particularly in the context of vascular (dys)function. We hypothesize that acute and chronic E-cig exposure would result in similar vascular dysfunction that has been observed with cigarette smoking.

**Methods:** Data were obtained from C57BL/6 female mice that were, either acutely (one 5 minute exposure, N=4) or chronically exposed (4 h/day, 5 d/wk for 8 months, N=6) to cappuccino flavored E-vapor (18 mg/ml nicotine). Intravital microscopy was used to assess arteriolar reactivity following acute exposure, and in-vivo Doppler ultrasonography was used to assess aortic stiffness (pulse wave velocity) at 3 times points (pre, during, post) with chronic exposure. After chronic exposure, the thoracic aorta was dissected, sectioned into rings and mounted onto an ex-vivo wire tension myograph system. Force transduction was used to measure the changes in aortic tension in response to vasodilatory compounds.

**Results:** Acute E-cigarette exposure resulted in no significant changes in baseline arteriolar vessel diameter; however 60-min post exposure arteriolar diameters were decreased by an average of 31% ($p<0.001$) and acetylcholine (ACh)-induced vasodilation was reduced by 9% ($p<0.001$) and 7% ($p<0.05$) 0 and 60 minutes, respectively. In chronically exposed mice, aortic stiffness increased 2.5 times greater in E-cig vs filtered-air exposed control mice (1.14±0.24 m/s 0.45±0.20 m/s, $P<0.05$, respectively). The maximal aortic relaxation achieved to methacholine was 90% in air exposed mice, and reduced to 70% in chronic E-cig exposed mice ($P<0.05$). No differences were noted in sodium nitroprusside dilation between the groups.

**Conclusion:** Our data provides the first evidence showing a single acute exposure has negative effects on *in vivo* vascular function, and that chronic exposure significantly accelerates age-associated increase in aortic stiffness, and significantly impairs aortic endothelial-dependent vasodilation. Endothelial-independent vasodilation was not alter with chronic E-cig exposure. These data indicate that E-cigs should not be considered safe, and that they induce significant deleterious effects on endothelial function in the central and peripheral vasculature.

**5.4**

**CONTRADICTORY INDICATORS OF ARTERIAL STIFFENING DURING LONG-DURATION SPACEFLIGHT**

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Removal of the normal head-to-foot gravitational vector during spaceflight alters several of the stimuli affecting arterial structure and function: there is a chronic relative hypertension in arteries above heart-level, elevation of hormones of the renin-angiotensin-aldosterone system, and marked reductions in daily physical activity with development of insulin resistance. Recently, we have studied changes in arterial properties in 17 astronauts in response to 6-months spaceflight. In the first study (Vascular) of 8 astronauts (4 women), we reported an increase in carotid artery stiffness that was similar to changes observed with aging ~20 years, and pulse wave transit time was reduced (Am J Physiol H628-38, 2016). In another recent study (Vessel Imaging), carotid artery intima-media thickness increased ~12% from pre-flight baseline (Aerosp Med Env Physiol 87: 449-53, 2016), and we found an increase from 0.48±0.07 mm to 0.55±0.1 mm (mean±SD, n=10, p=0.08) from pre- to post-flight. In a subsequent study of 9 male astronauts (BP Reg), we measured cardiac output by rebreathing (Q_RB) and finger arterial pulse contour analysis with Modelflow (Q_MF) in an upright seated position before flight and during flight. Q_RB increased 48% from pre- to inflight (4.76±0.67 to 7.00±1.40 L/min, $p<0.001$) while Q_MF was unchanged (6.60±1.95 to 5.91±1.16 L/min). Concurrent with the measures of Q_RB, brachial arterial pulse pressure was not different from pre- to inflight (63.3±10.5 to 57.2±15.9 mmHg); however, estimated arterial compliance (stroke volume/pulse pressure) increased from 1.24±0.21 to 2.23±0.90 mL/mmHg (p=0.004). Different methods in the two spaceflight studies resulted in different conclusions regarding changes in arterial stiffness. Local stiffness and wall thickness of the carotid artery increased comparing before to immediately after spaceflight. In contrast, overall arterial compliance increased inflight compared to pre-flight. Because Q_MF was unreliable with

spaceflight, and we measured Q_RB only seated, there was not an opportunity to compare supine posture with spaceflight. We hypothesize that the inability of Q_MF to track change in cardiac output and the increase in arterial compliance with spaceflight result from similar marked increases in vascular conductance in the splanchnic vascular bed. Increased stiffness of the carotid arteries is primarily related to the chronic elevation in arterial pressure above the heart while in space, a cerebral hypertension, with potential contributions from hormonal changes and physical inactivity with chronic weightlessness. Supported by Canadian Space Agency.

**5.5**

**LEUKOCYTE TELOMERE LENGTH AND ARTERIAL STIFFENING ACROSS THE STAGES OF THE MENOPAUSE TRANSITION**

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Background: Large artery stiffening is a consequence of vascular aging and increases the risk for cardiovascular disease (CVD). The age-associated increase in arterial stiffness is augmented in women after menopause, presumably due to estrogen deficiency. Telomeres, specialized DNA complexes at the ends of chromosomes, protect DNA and preserve the genome during replication. Longer leukocyte telomere length (LTL) is associated with longevity and resistance to CVD. Estrogen may regulate telomerase, the reverse transcriptase that adds telomeres to the ends of chromosomes, preserving LTL. We determined whether increased arterial stiffening across the stages of menopause is related to LTL shortening.

Methods: Participants were 124 healthy women (19-70y) classified as premenopausal (pre; n=36, 34±8y; mean±SD), early perimenopausal (early peri; n=24, 49±3y), late perimenopausal (late peri; n=25, 50±4y), or postmenopausal (post; n=39, 59 ± 5y). LTL was measured from genomic DNA isolated from peripheral blood mononuclear cells using quantitative real-time polymerase chain reaction. Arterial stiffness was measured using carotid artery compliance (inverse of stiffness) with ultrasound.

Results: Arterial compliance was progressively reduced across the stages of menopause (pre 1.24±0.30; early peri 0.95±0.32; late peri 0.96±0.27; post 0.82±0.32 $mm^2/mmHgx10^{-1}$, $p<0.001$). LTL tended to be shorter across menopause stages (pre 88±25; early peri 88±23; late peri 75±21; post 79±18 kilobases/diploid genome, p=0.06). LTL was positively correlated with arterial compliance (r=0.21, p=0.02), and inversely correlated with menopause stage (r= -0.19, p=0.04) and age (r= -0.19, p=0.04). The correlation between LTL and arterial compliance did not persist after controlling for menopause stage (r=0.14, p=0.13) or age (r=0.12, p=0.19).

Conclusion: These results suggest a potential mechanistic link between arterial stiffening and LTL across the stages of menopause. Future studies should investigate how estrogen regulates telomere length, including its effects on telomerase function, and how telomere shortening may mediate vascular aging. Longitudinal studies are needed to determine the effects of the changing hormonal environment with menopause, independent from those of age, on telomeres.

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**5.6**

**EFFECT OF AGE ON CEREBRAL BLOOD FLOW DYNAMICS FOLLOWING ACUTE RESISTANCE EXERCISE**

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Aging decreases cerebral blood flow and increases cerebral pulsatility, an alteration that is associated with a greater prevalence of brain lesions and cognitive impairment. Resistance exercise (RE) is recommended for older adults for improving cardiovascular and metabolic risk factors. High-intensity RE is a potent stimulus that acutely increases blood pressure (BP) and reduces cerebral blood flow velocity (CBFv), resulting in greater flow pulsatility in cerebral circulation, which may damage cerebral microvasculature. Understanding the relationship between aging and cerebrovascular function in response to a physiological stress, like RE, in older adults is essential to help understand how to reduce the risk of cerebrovascular events. **PURPOSE:** To examine the effect of age on cerebral blood flow dynamics following acute RE in older adults compared with young adults. **METHODS:** Young (n=32, 26yrs, BMI: 24.0 $kg/m^2$) and older (n=13, 58yrs, BMI: 29.3 $kg/m^2$) adults performed maximal leg-extension/flexion RE (3x10 reps), with measurements at pre- and post-RE (Immediate, 5, 30-min). Heart rate (HR), BP (SBP, DBP, MAP), cardiac output (Q), CBFv of the middle cerebral artery, and end-tidal $CO_2$ were collected. **RESULTS**: Mean and diastolic CBFv increased immediately post-RE in the young group (interaction, $p<0.01$) and decreased below baseline at 5-min post-RE ($p<0.01$) in both groups. CBFv pulsatility increased post-RE ($p<0.01$) in both groups, but continued to rise at 5-min post-RE in the young group (interaction, $p<0.01$). MAP was higher in the older group and increased immediate post-RE ($p<0.01$) in both groups. **CONCLUSION**: RE increased arterial BP in both groups; however, differential responses in the cerebral and systemic hemodynamics occurred between the young and older adults. Despite obtaining higher BP during RE in the older group, mean and diastolic CBFv did not increase post-RE. This differential age response indicates reduced cerebral hemodynamic responsiveness to RE with aging.

Table 1. Mean ± SD, *Exercise, †Group, ‡Interaction, p<0.05.

| | | Baseline | Immediate | 5-min | 30-min |
|---|---|---|---|---|---|
| HR (bpm)*†‡ | Young (Y) | 66±9 | 87±12 | 75±11 | 73±9 |
| | Older (O) | 62±8 | 75±6 | 67±7 | 68±8 |
| Q (L/min)*‡ | Y | 5.1±0.9 | 8.0±1.3 | 6.2±1.2 | 5.4±0.9 |
| | O | 5.4±1.5 | 7.4±2.3 | 5.5±1.3 | 4.9±1.3 |
| SBP (mmHg)*†‡ | Y | 124±9 | 138±13 | 125±11 | 125±9 |
| | O | 143±22 | 166±25 | 140±21 | 145±19 |
| DBP (mmHg)* | Y | 72±7 | 76±8 | 71±7 | 75±6 |
| | O | 72±7 | 77±7 | 72±7 | 76±6 |
| MAP (mmHg)*† | Y | 93±7 | 100±10 | 93±8 | 96±6 |
| | O | 100±10 | 110±11 | 98±10 | 103±9 |
| CBFv Systolic (cm/s)* | Y | 96±18 | 116±26 | 96±17 | 91±16 |
| | O | 94±26 | 108±23 | 89±21 | 88±23 |
| CBFv Diastolic (cm/s)*‡ | Y | 43±10 | 46±10 | 37±9 | 42±9 |
| | O | 41±13 | 37±14 | 35±10 | 39±12 |
| CBFv Mean (cm/s)*‡ | Y | 62±13 | 71±19 | 57±12 | 59±12 |
| | O | 62±17 | 64±15 | 55±15 | 58±16 |
| CBFv Pulsatility Index*‡ | Y | 0.87±0.12 | 1.01±0.19 | 1.05±0.18 | 0.85±0.13 |
| | O | 0.90±0.21 | 1.15±0.28 | 1.01±0.24 | 0.85±0.19 |
| End-Tidal CO2*‡ | Y | 4.7±0.6 | 5.6±0.7 | 4.5±0.5 | 4.4±0.6 |
| | O | 4.8±0.38 | 5.4±0.3 | 4.7±0.4 | 4.6±0. 5 |

**5.7**

## EFFECT OF L-CITRULLINE ON EXERCISE BLOOD FLOW IN OLDER WOMEN AND MEN

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Chronic L-citrulline (CIT) supplementation increases plasma L-arginine, and possibly nitric oxide bioavailability. Past studies have demonstrated improved NIRS-derived muscle oxygenation patterns during leg exercise following CIT supplementation in young men, but it is unknown if a similar finding would be observed in older adults. The purpose of this study was to test the hypothesis that exercise blood flow (BF) would be improved with CIT in older adults. Healthy older women (n=13, 70.2 ± 1.6y; mean ± SEM) and men (n=12, 71.1 ± 1.5y) completed a placebo controlled, double-blind, crossover trial. Participants were randomized to oral CIT (6 g/day) or placebo for 14 days, and switched to the other treatment for another 14 days after washout. The BF response to calf muscle exercise was measured in the right superficial femoral artery using Doppler ultrasound. Comparison was made between treatments on the change in BF from pre-to-post supplementation with adjustment for sequence and period effects. The change in exercise BF was not different between treatments in women (CIT: -14.6 ± 17.5 vs. placebo:23.2 ± 31.0 mL/min, p=0.51), but differed between treatments in men (CIT: 61.0 ± 21.3 vs. placebo:-19.7 ± 23.6 mL/min, p=0.01) such that the BF response to exercise was increased following CIT (pre: 447.8 ± 37.7 vs. post: 508.8 ± 47.8 mL/min, p=0.01) with no significant change following placebo (pre: 480.6 ± 37.9 vs. post: 460.9 ± 44.2 mL/min, p=0.42). These findings show a positive effect of L-citrulline on exercise-induced blood flow in older men, but not in women.

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**5.8**

## INFLUENCE OF GENDER ON HYDRATION, LEAN MASS, STRENGTH, AND BLOOD PRESSURE IN OLDER ADULTS

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Overnight when intake is low, muscle can be depleted by fluid shifts to maintain blood pressure. This loss of intramuscular water may influence muscle function. We explored overnight changes in hydration, body composition, strength and blood pressure in 23 older adults (75.8 ± 1.3 years).

**Methods:** Men (n=9) and women (n=14) completed two testing sessions: mid-day euhydrated (Day 1) and early next morning dehydrated (Day 2). Hydration and body composition were measured with multi-frequency bioelectrical impedance. Strength was measured with hand grip dynamometry, arm curls, and chair stands. Blood pressure was measured lying, sitting, and standing.

**Results:** On Day 1, men had greater *body weight* (80.6±5.0 vs 68.5±3.3 kg, $p<0.05$), *lean mass* (59.8±3.0 vs 40.0±1.5 kg, $p<0.001$) and *upper body strength* (handgrip: 41.6±3.5 vs 22.2±1.6 kg, $p<0.001$; arm curls: 18±1.3 vs 14.9±0.8 curls, $p<0.05$) compared to women. This was accompanied by greater ($p<0.001$) *total body water* (47.0±1.5 vs 33.2±0.9 L), *extracellular water* (19.8±0.7 vs 15.8±0.4 L), and *intramuscular water* (25.5±1.2 vs 17.5±0.6 L). However, there were no gender differences in positional changes in *systolic* (lying-sitting: +6.4±5.6 mmHg; sitting-standing: -7.6±2.1 mmHg) or *diastolic* (lying-sitting: -4.4±2.8 mmHg; sitting-standing: -7.3 ± 2.3 mmHg) *blood pressure*. On Day 2, men and women experienced similar overnight losses in *body weight* (-0.9±0.1 kg, $p<0.001$), *lean mass* (-0.6±0.2 kg, $p<0.01$), and *upper and lower body strength* (hand grip: -1.6±0.4 kg, $p<0.01$; arm curls: -1.2±0.5 curls, $p<0.05$; chair stands: -1.1±0.5 stands, $p<0.05$), with a trend for loss of *total body water* (-0.4±0.2 L, $p=0.08$). Positional blood pressure was stable overnight except the change in *systolic blood pressure* between lying and sitting, which was significantly different on Day 1 than on Day 2 (+6.4±5.6 vs -4.4±2.8 mmHg, $p<0.05$), with a trend on Day 2 for less stability in men than women (-9.6±2.4 vs -1.1±4.2 mmHg, $p=0.06$).

**Conclusion:** In these older adults, both men and women had significant overnight loss of body water, lean mass, and strength, while positional blood pressure remained relatively stable. Based on these preliminary findings, greater lean mass does not influence the extent of overnight fluid loss or related loss of lean mass and strength, as loss did not differ by body size or muscle volume. The difference in positional systolic blood pressure observed on Day 2 is clinically non-significant and may be an anomaly.

**5.9**

## DECREASED AGE-RELATED AUTONOMIC FUNCTION POSES A RISK FOR UNSTABLE CARDIOVASCULAR DYNAMICS: MONITORING CHANGES IN CIRCULATING BLOOD VOLUME

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**Introduction:** Autonomic function is important in the initial compensatory mechanism during blood volume changes and is important in monitoring a patient's condition. However, few studies have investigated the effect of the aging on autonomic function and cardiovascular dynamics throughout changes in circulating blood volume. **Objective:** We examined the influence of aging on changes in autonomic function and cardiovascular dynamics, according to changes in circulating blood volume. **Methods:** We recorded the blood pressure (BP) and electrocardiographic data of 70 patients (mean age, 57.0 ± 14.2 years; 70.0% males) who were maintained in the supine position throughout autologous blood donation (200–400 mL; less than 10% of the circulating blood volume), as a model blood volume decrease. We subsequently administered fluid therapy with lactated Ringer's solution, using a volume equivalent to the volume of blood donated, as a model of blood volume increase. We analyzed heart rate variability parameters, including high frequency (HF) power spectra and the ratio of low frequency (LF) to HF power (LF/HF), to estimate parasympathetic and sympathetic nerve activity. Patients were divided into two groups based on a cut-off of 65 years, according to the World Health Organization's definition of elderly people. The Tohoku University Graduate School of Medicine's Ethics Committee approved this study (2014-1-378), which was conducted in conformance with guidelines for experimental procedures as set forth in the Declaration of Helsinki. **Results:** The LF component and HF component at rest decreased with age. In the ≥ 65-years group (n = 25), the LF component, HF component and LF/HF at rest were lower than in the < 65-years group (n = 45). During blood volume changes, the HF component and LF/HF in the ≥ 65-years group remained lower than those in the < 65-years group. The rate of change in heart rate (HR) and BP in the ≥ 65-years group fluctuated more than in the < 65-years group, throughout blood volume changes. **Conclusion:** These results show that aging decreases autonomic function at rest and influences it continuously during a blood volume change of approximately 10% of the circulatory blood volume. This may cause increased fluctuation in HR and BP. These findings suggest that there is an underlying risk of circulatory failure in elderly people during the early stages of blood volume changes.

**5.10**

## BENEFICIAL ROLE OF PALM OIL DERIVED-TOCOTRIENOLS IN CARDIOVASCULAR AND METABOLIC HEALTH

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Vitamin E is comprised of a group of two closely related compounds, tocopherol (TP) and tocotrienol (T3). Vitamin E's biological activities and its resultant health benefits have almost exclusively been attributed to alpha-tocopherol (α-TP). However, T3s are now known to exhibit 40-60 times stronger antioxidant activities than α-TP. In addition, T3s also display anti-inflammatory and cholesterol lowering properties which is not found in α-TP. Here we demonstrate the beneficial role of T3 in promoting cardiometabolic health.

*In vitro* studies using human hepatoma cells (HepG2) showed that γ/δ-T3 downregulated the protein expression of factors involved in cholesterol and triglyceride biosynthesis. On the other hand, γ/δ-T3 upregulated LDL receptor (LDLr), a lipoprotein to improve the uptake and clearance of LDL particles. *In vivo* experiments using LDLr deficiency mice (LDLr-/-) showed that γ/δ-T3 was able to reduce triglyceride and LDL levels significantly without affecting the HDL level. The inclusion of α-TP did not manifest this lowering effect. In another animal study, all the Vitamin E compounds tested (α-TP, α-, γ- and δ-T3) reduced collagen deposition and inflammatory cell infiltration in the heart in the rats supplemented with a high-fat diet. An eight week human study with borderline-high cholesterol showed that the administration of γ/δ-T3 isomers was able to lower triglyceride levels significantly, with no changes in LDL and HDL levels.

The data presented here should improve the understanding of the role of T3 in cardiometabolic health with profound implications in ageing-associated cardiovascular diseases.

**5.11**

## DEFECTIVE VASCULAR AUTOPHAGY IMPAIRS EXERCISE-INDUCED ACTIVATION OF ENDOTHELIAL NITRIC OXIDE SYNTHASE IN MICE

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Molecular mechanisms regulating age-related changes in vascular function are only partly understood. Impairment of autophagy, the ubiquitous lysosomal trafficking pathway that regulates nutrient and redox homeostasis, is a common feature of aging at the cellular level. Earlier we showed that genetic or pharmacologic inhibition of autophagy in cultured bovine aortic endothelial cells (ECs) reduces shear stress-induced endothelial nitric oxide (NO) synthase (eNOS) activation and NO production. It is unknown whether aging impairs agonist-induced activation of autophagy and eNOS in the vasculature. Arteries from 2, 6, 17, and 24 month old C57Bl6 mice displayed a reduction in LC3 II : GAPDH protein expression and an increase in p62 : GAPDH accumulation, suggesting an age-associated decline in autophagy. While 14 h fasting increased LC3 II : GAPDH in arteries of 6-month old mice

vs. random-fed controls, the upregulation was not observed in 24-month old animals. Acute exercise i.e., 60-min treadmill-running, increased LC3 II : GAPDH and p-eNOS$^{S1177}$ : total eNOS in arteries from 6-month old mice, but 24-month old animals were refractory to this stimulus. Collectively, these data suggest that aging impairs agonist-induced activation of autophagy and eNOS in the vasculature. Next we explored how limited autophagic flux in ECs might precipitate reduced eNOS activation. In preliminary studies we observe that inhibiting autophagy in ECs impairs glycolytic ATP production to an extent that limits purinergic receptor signaling to PKC-δ, an established positive regulator of eNOS. As a first step to determine translational relevance of this mechanism, 2-month old C57Bl6 mice were treated ± 3-methyladenine (3MA; 30 mg/kg IP), a class III PI3K inhibitor that blocks autophagosome formation. Thirty-min later mice completed 60-min treadmill running or were sedentary. Relative to the respective sedentary condition, acute exercise increased beclin-1 and Atg3 accumulation, p62 degradation, and increased GLUT1, p-PKCδ$^{T505}$, and p-eNOS$^{S1177}$ in arteries from vehicle-treated but not 3-MA treated mice. These data provide strong proof of concept that impaired vascular autophagy might compromise purinergic mediated eNOS activation. Supported by AHA 16GRNT31050004, NIH AGO52848, University of Utah College of Health, Center on Aging, and Diabetes and Metabolism Center.

**5.12**

## PREHYPERTENSION ACCELERATES VASCULAR AGING ACROSS THE MENOPAUSAL TRANSITION IN HEALTHY WOMEN

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**Background**: Endothelial dysfunction, characterized by impaired endothelial-dependent vasodilation, is a key feature of vascular aging and increases the risk for cardiovascular disease. We have previously shown that endothelial function is reduced across the stages of menopause in healthy women, presumably due to loss of estrogen. Pre-hypertension (120-139/80-89mmHg) similarly exacerbates vascular aging. In women, pre-hypertension may create an age/disease interaction that, combined with the loss of ovarian hormones, may further accelerate vascular aging. Therefore, we compared endothelial function in healthy normotensive and pre-hypertensive women across the stages of the menopause transition. Within the perturbations of a pre-hypertensive vasculature, we expected to see a more negative impact in pre-hypertensive women than in normotensive women as estrogen declines.

**Methods**: Endothelial function (brachial artery flow-mediated dilation; FMD) was measured in 192 healthy women (19-70y) classified as premenopausal (n=51, 34±8y; mean±SD), early perimenopausal (n=24, 49±3y), late perimenopausal (n=26, 50±4y), early (≤5y) postmenopausal (n=40, 55±3y), or late (>5y) postmenopausal (n=51; 60±4y). Women were further classified as normotensive (<120/80mmHg, n=120) or pre-hypertensive (120-139/80-89mmHg, n=72).

**Results**: Brachial artery FMD was progressively reduced across stages of menopause (P<0.001). At each stage, FMD was lower in pre-hypertensive vs normotensive women (P<0.001: premenopausal (10.7±3.3 vs 9.3±1.8); early perimenopausal (8.7±2.9 vs 7.5±2.1); late perimenopausal (7.5±2.1 vs 5.8±1.6); early postmenopausal (6.0±1.8 vs 5.1±1.8); late postmenopausal (5.4±1.5 vs 4.5±2.0). Adjusting for age did not influence the main effects of menopausal stage (P=0.003) or blood pressure category (P=0.004).

**Conclusion:** These data demonstrate that prehypertensive women experience proportionally greater declines in endothelial function across the stages of menopause than their normotensive peers. This suggests that prehypertension may contribute to an age-disease interaction in healthy women. Future investigations should evaluate lifestyle interventions and whether maintaining or improving blood pressure, particularly during the menopause transition, slows the progression of vascular aging and prevents cardiovascular disease.

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**5.13**

## OXIDATIVE STRESS CONTRIBUTES TO AGE-ASSOCIATED REDUCED LEFT VENTRICULAR DIASTOLIC FUNCTION IN MEN

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**Introduction**: Left ventricular (LV) diastolic function declines with age, even in healthy adults. A possible mechanism for the age-related decline in LV diastolic function may be a functional maladaptation to an imbalance between reactive oxygen species (ROS) generation and endogenous antioxidant defenses (i.e., "oxidative stress"). Whether oxidative stress contributes to reduced LV diastolic function in aging men is unknown. Methods: LV diastolic function (transthoracic echocardiography; peak early [E] to late [A] mitral inflow velocity ratio [E/A], and peak early [E] mitral inflow velocity to peak early [e'] mitral annular velocity ratio [E:e']) was measured during intravenous infusion of saline (control) and during supraphysiological

intravenous infusion of the potent antioxidant Vitamin C in healthy young (n=12, 30±5 yrs; mean±SD) and older men (n=7, aged 65±6 yrs). Results: Compared to young men, older men had a ~45% lower mitral valve E/A ratio (1.24±0.13 vs 2.26±0.23, p<0.01) and a ~40% higher septal E:e' and lateral E:e' (10.4±0.9 vs 6.1±0.4, p<0.01, and 7.4±0.8 vs 5.4±0.4, p<0.03, respectively). Septal E:e' decreased ~20% during Vitamin C (to 8.3±0.6, p<0.05) in older men, indicating a tonic suppression of LV diastolic function by ROS. Vitamin C did not change septal E:e' (6.0±0.4, NS) in young men. There was no significant effect of Vitamin C on the mitral valve E/A ratio (1.1±0.2,NS) in older men, however E/A ratio decreased during Vitamin C infusion in young men (to 1.95±0.16, p<0.01), indicating a decrease in LV diastolic function possibly related to a disruption and shift in redox balance to a pro-oxidant state. Conclusion: These preliminary findings support oxidative stress as a potential mechanism for the age-related decline in LV diastolic function in men. Future studies should determine the mechanisms by which ROS alters LV diastolic function and whether chronic exposure to endogenous antioxidants attenuates or reverses the decline in LV diastolic function with aging. Support: NIH R01AG049762, P30 DK048520, UL1 TR001082; Eastern Colorado VA Geriatric Research, Education, and Clinical Center

**5.14**

**EXTRACELLULAR MATRIX REMODELING PROTEASES AS A FUNCTION OF MENOPAUSE STAGE: IMPACT ON VASCULAR AGING**

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Background: Vascular aging, featuring large artery stiffening and endothelial dysfunction, is accelerated in women during the menopause transition. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) impact vascular aging by regulating extracellular matrix (ECM) turnover and remodeling. We determined whether MMPs and TIMPs are mechanistically related to vascular aging across menopause stages. Arterial stiffness (carotid artery compliance with ultrasound), endothelial function (brachial artery flow-mediated dilation, FMD), and serum MMP2, MMP9, TIMP1 and TIMP2 concentrations were measured in 144 healthy women categorized as premenopausal (N=38, 34±8yr, mean±SD), early (N=24, 49±3yr) and late (N=24, 50±3 yr) perimenopausal, and early (N=27, 55±3 yr) and late (N=31, 61±5 yr) postmenopausal. Results: Arterial compliance and FMD were reduced across menopause stages. MMP9 was different across menopause stages (P=0.003), with higher concentrations in late perimenopausal compared to premenopausal women, and lower concentrations in both early and late postmenopausal compared to late perimenopausal women (all P<0.05). There were no significant differences in MMP2, TIMP1, or TIMP2 concentrations. MMP9/TIMP1 ratio (marker of net MMP activity, proteolytic potential, and ECM degradative capacity) was different across menopause stages (P=0.005), with a lower ratio in late postmenopausal women compared to late perimenopausal (P<0.05), indicating reduced proteolytic activity. FMD was inversely correlated with MMP2 (r=-0.19, P=0.025) and TIMP2 (r=-0.21, P=0.018). Circulating estrogen concentrations were positively correlated with MMP9 (N=97, r=0.39, P<0.01) and MMP9/TIMP1 ratio (N=91, r=0.38, P<0.01). Age was positively correlated with TIMP2 (r=0.19, P=0.025). Conclusion: These data suggest that the menopause transition is associated with alterations in ECM remodeling proteases, favoring greater ECM accumulation. These ECM proteases may play a role in endothelial dysfunction in vascular aging. Whether serum MMPs and TIMPs reflect concentrations at the local vascular level, and whether and how they are mechanistically linked to vascular aging across the menopause transition, warrants further study. Support: NIH R01s AG027678, AG22241, AG049762, R56HL114073, K01AG20683, P30 DK048520 and UL1 TR001082, University of Colorado Denver (UCD) Center for Women's Health Research, and Eastern Colorado VA Geriatric Research, Education, and Clinical Center.

**5.15**

**ACUTE NITRATE SUPPLEMENTATION ATTENUATES PROGRESSIVE ISCHEMIC EXERCISE-INDUCED PRESSOR RESPONSES IN POSTMENOPAUSAL WOMEN**

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Older (postmenopausal) women have exaggerated blood pressure (BP) responses during static exercise, as well as during post-exercise circulatory arrest (PECA), suggesting an enhanced metaboreflex and altered autonomic control of BP. These BP responses are prognostic for future hypertension, adverse cardiovascular events, and mortality. Intriguingly, dietary nitrate supplementation has shown beneficial effects on contracting muscle perfusion (Casey et al., 2015) and metabolite accumulation (Bailey et al., 2010; Bailey et al., 2009). However, its effects on the regulating BP in postmenopausal women have not been investigated. **PURPOSE:** We tested the effects of acute nitrate supplementation on reflex increases in BP evoked by progressively restricting blood flow to the exercising forearm in healthy postmenopausal women. We hypothesized that dietary nitrate supplementation would attenuate the increases in BP during graded muscle ischemia and metaboreflex isolation. **METHODS:** In a randomized, double-blind, crossover study, eight healthy postmenopausal women (60 ± 1 years) consumed a concentrated beetroot juice supplement ($BR_{nitrate}$; 140 mL Beet-It Organic, James White Juice

Company) or nitrate-depleted beetroot juice as a placebo ($BR_{placebo}$; 140 mL nitrate-depleted Beet-It Organic, James White Juice Company) on separate visits at least 7-days apart. On each visit, subjects performed low intensity intermittent handgrip exercise (10% of MVC, 30 contractions/min) until volitional fatigue followed by 3-min of PECA. During the exercise, muscle blood flow was restricted progressively as follows: After 4-min of free flow exercise period, a BP cuff on the subject's upper arm was progressively inflated starting from 20 mmHg at a rate of 20 mmHg/min. BPs and HR were recorded continuously throughout the experiment. **RESULTS:** Acute dose of $BR_{nitrate}$ raised plasma $NO_3^-$ and $NO_2^-$ compared to $BR_{placebo}$ (all $p<0.05$). BPs steadily increased with exercise during both visits ($p<0.05$), and time course of peak BP responses tended to increase with $BR_{nitrate}$ (vs. $BR_{placebo}$; P=0.17). Moreover, $BR_{nitrate}$ attenuated percent ΔMAP at volitional fatigue (25±3% vs. $BR_{placebo}$ 30±5%; $p<0.05$). During PECA period, no intervention effect was observed on the reductions in HR and SBP. DBP during PECA decreased to a greater extent with BRnitrate, but it didn't reach significance (vs. $BR_{placebo}$; P=0.18). **CONCLUSION:** These results suggest that acute nitrate supplementation alters reflex increases in BP at fatigue during progressive ischemic forearm exercise, and warrant continued investigation of nitrate supplementation and reflex control of the circulation during exercise in postmenopausal women.

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**5.16**

**THE IMPACT OF MENOPAUSAL STAGE AND AEROBIC FITNESS ON ENDOTHELIAL FUNCTION AND RESPONSES TO ACUTE EXERCISE**

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Cardiovascular disease risk increases with menopause; however, whether this change effects endothelial function and if fitness modulates any effects on endothelial function remains largely unexplored. **PURPOSE:** To determine if there are differences in endothelial function before and after acute exercise in healthy peri- and post-menopausal women with disparate levels of aerobic fitness. **METHODS:** High and low fit (HIGH, n=15; LOW, n=15) peri- and postmenopausal women (PERI, n=16; POST, n=14) completed 30min of treadmill exercise at 60-64% $VO_{2peak}$. Brachial artery flow-mediated dilation (FMD) was measured twice before and after exercise. Artery diameter and blood flow were continuously measured during 2min of baseline, 5min of forearm blood flow occlusion (200mmHg), and 4min post-occlusion. FMD was calculated as ($Diameter_{peak}$-$Diameter_{baseline}$)/ $Diameter_{baseline}$ x 100. Shear rate area-under-the-curve (SR AUC) to peak dilation and time to peak dilation (TTP) were calculated. Data was analyzed for differences by group (PERI vs. POST), condition (HIGH vs. LOW), and time (pre- vs. post-exercise) using ANOVAs and is expressed as mean±SEM. FMD data on LOW PERI and POST was previously published. **RESULTS:** Overall, FMD was higher in PERI compared with POST (PERI: 6.9±1.0% vs. POST: 5.0±1.0%, p=0.03), independent of fitness. There was a main effect of fitness on FMD (p=0.024), with no difference in pre-exercise FMD (HIGH: 5.0±1.7% vs. LOW: 6.5±1.3%, p=0.205) but lower FMD in HIGH after acute exercise (HIGH: 5.0±1.1% vs. LOW: 7.3±1.4%, p=0.05). Before exercise, FMD did not differ by fitness in PERI (p=0.271), but was lower in HIGH compared to LOW POST (HIGH: 3.3±1.5% vs. LOW: 6.5±0.5%, p=0.038). Repeated FMD trials lead to a lower FMD response in LOW POST (pre-exercise 1: 7.7±1.1%, pre-exercise 2: 5.3±1.0%, post-exercise 1: 7.8±1.5%, post-exercise 2: 4.5±1.0%, p=0.03) but not HIGH POST (pre-exercise 1: 2.1±1.0%, pre-exercise 2: 4.6±2.2%, post-exercise 1: 4.3±1.6%, post-exercise 2: 4.0±1.0%, p=0.486). Reported differences in FMD were independent of SR AUC and baseline diameter. There was a main effect of menopausal status on TTP (p=0.03), with higher TTP in POST before (PERI: 45.4±5.5s vs. POST: 65.9±10.4s, p=0.05) but not after acute exercise (PERI: 54.2±9.0s vs. POST: 65.3±13s, p=0.273). **CONCLUSION:** Endothelial function appears to worsen with menopause, independent of fitness; however, fitness may improve endothelial responsiveness to repeated FMD trials and appears to modulate the response to acute exercise. FMD in HIGH POST was low despite few CVD risk factors in this group. Further investigation is warranted to understand the impact of fitness on endothelial function in aging women.

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**5.17**

**VAGAL MODULATION OF HEART RATE BY THE ARTERIAL BAROREFLEX IN MIDDLE-AGED WOMEN: A POTENTIAL INFLUENCE OF REPRODUCTIVE AGE.**

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Measures of cardiac autonomic function are reduced with advanced *chronological* age in both sexes (Laitinen et al., 1998; Tank et al, 2000), and this reduction may partly explain the increased cardiovascular morbidity and mortality observed in older adults. In women, however, the potential for *reproductive* aging to contribute to the age-related decline in vagal modulation of cardiac activity has remained largely under-examined. Thus, the **PURPOSE** of the present study was to investigate whether cardiovagal baroreflex sensitivity (BRS) is influenced by menopause transition stage in a sample of healthy middle-aged women. **METHODS:** Women (41 – 59 yrs.) were categorized into early perimenopausal (n =12), late perimenopausal (n = 8), and early postmenopausal (n = 9) stage groups based on self-

reported bleeding history using the Stages of Reproductive Aging Workshop criteria. Beat-to-beat arterial blood pressure (Finometer midi) and heart rate (ECG) were continually collected during 10 minutes of spontaneous breathing while resting in the supine position. Cardiovagal BRS was subsequently determined by averaging the regression coefficients of corresponding sequences of increasing and decreasing systolic blood pressure and R-R interval. **RESULTS:** There was an overall influence of menopause transition stage on cardiovagal BRS ($p = 0.018$). Specifically cardiovagal BRS values were lower across menopause stage groups with statistically significant differences observed between the early perimenopausal and early postmenopausal women ($p = 0.017$). In the combined sample of women, cardiovagal BRS was best explained by a model containing systolic blood pressure and a marker of reproductive aging (follicle-stimulating hormone; $r^2 = 0.57$, $p < 0.001$). **CONCLUSIONS:** Collectively, these findings provide evidence that *reproductive* aging may contribute, at least in part, to the age-associated decline in cardiovagal BRS in women.

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**5.18**

**MORE ACCURATE SYSTOLIC BLOOD PRESSURE MEASUREMENT FOR IMPROVED HYPERTENSION MANAGEMENT IN ELDERLY**

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Since excessive lowering of blood pressure can lead to adverse side-effects, its accurate measurement is essential for safe control. However, currently available automatic blood pressure measurement devices, based on oscillometry, are prone to significant errors (errors of 10-15 mmHg are common), mainly due to indirect determination of the blood pressure from the oscillometric air-pressure waves. Erroneous measurement by 10-15 mmHg can lead to a similar unintended reduction of systolic blood pressure and may adversely affect patients treated to a systolic blood pressure of 120-130 mmHg. In particular, in the elderly, inaccurate systolic blood pressure measurement can lead to excessive blood pressure lowering, increase the risk of hypotension and consequently lead to hypo-perfusion to vital organs, including the brain. A novel technique for systolic blood pressure measurement, based on photoplethysmography, was found to be more accurate than the available automatic oscillometric technique, enabling more precise automatic systolic blood pressure measurements, in the home and clinic. More accurate systolic blood pressure measurement allows both optimal and safer control of blood pressure.

## 6.0 SYMPOSIUM: NOVEL MECHANISMS OF BLOOD FLOW CONTROL AND MICROVASCULAR FUNCTION WITH AGE

**6.1**

**SKELETAL MUSCLE OXYGEN TRANSPORT DURING EXERCISE: EFFECTS OF AGING AND HEART FAILURE.**

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Chronic heart failure (CHF) represents a "perfect storm" of multiple organ dysfunction that impacts critically the $O_2$ transport system (↑ $O_2$ requirements, ↓ $O_2$ availability), culminating in impaired muscle function and exercise intolerance. CHF afflicts over 5 million Americans the vast majority of whom are aged 65+ years. However, within established CHF animal models there is a dearth of investigations examining aged individuals - the condition of most direct relevance to human health. Whereas CHF in the aged may be a pathophysiologically different disease than in younger counterparts both manifestations are characterized by reduced nitric oxide (NO) bioavailability. Within skeletal muscle, CHF and aging impair arteriolar vasodilation and perturb capillary hemodynamics disrupting the $O_2$ delivery-to-utilization/requirement balance. The predations of both CHF and aging coalesce at $O_2$'s final frontier – the blood-myocyte interface – to reduce microvascular $O_2$ pressure and $O_2$ diffusing capacity. This $O_2$ transport deficit is resistant to current traditional therapies. However, increasing NO bioavailability via dietary nitrate supplementation elevates skeletal muscle blood flow and vascular conductance whilst simultaneously reducing the $O_2$ cost of exercise. This therapeutic strategy is targeted towards muscles and muscle regions with low microvascular $O_2$ pressures and reduced pH (both of which impair endogenous NO synthase function). We present evidence that nitrate supplementation can restore capillary hemodynamics in CHF and improve contracting muscle microvascular $O_2$ pressures and $O_2$ diffusing capacity. This strategy has great potential to improve the efficacy of cardiac rehabilitation and patient quality of life and reduce morbidity and mortality in CHF. Support: HL-108328 and AHA 4350011. REFERENCES: Ferguson, S.K., C. T. Holdsworth, T.D. Colburn, J.L. Wright, J.C. Craig, A.J. Fees, A.M. Jones, J.D. Allen, T.I. Musch, and D.C. Poole. Dietary nitrate supplementation: Impact on skeletal muscle vascular control in exercising rats with chronic heart failure. J Appl Physiol. 121:661-9, 2016.

**6.2**

**REGULATION OF SKELETAL MUSCLE BLOOD FLOW DURING EXERCISE IN AGING HUMANS**

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The regulation of blood flow and oxygen delivery to contracting skeletal muscle is complex and involves the mechanical effects of muscle contraction; local metabolic, red blood cell and endothelium-derived substances; and the sympathetic nervous system (SNS). With advancing age in humans, skeletal muscle blood flow is typically reduced during dynamic exercise and this is due to a lower vascular conductance, which could ultimately contribute to age-associated reductions in aerobic exercise capacity, a primary predictor of mortality in both healthy and diseased aging populations. Recent findings from our laboratory and others have highlighted the role of impaired endothelial control of blood flow to contracting muscle of older adults. In this context, impaired nitric oxide availability due to scavenging by reactive oxygen species, in conjunction with elevated vasoconstrictor signaling via endothelin-1, reduces the local vasodilatory response to muscle contraction in older adults. Additionally, aging impairs the ability of contracting skeletal muscle to blunt sympathetic vasoconstriction (i.e. "functional sympatholysis"), which is critical for the proper regulation of tissue blood flow distribution and oxygen delivery, and could further reduce skeletal muscle perfusion during high intensity and/or large muscle mass exercise in older adults. More recently, observations from our laboratory strongly suggest that initiation of endothelium-dependent hyperpolarization (EDH) is the underlying signaling event necessary to properly modulate sympathetic vasoconstriction in contracting muscle, and that age-associated impairments in red blood cell adenosine triphosphate release and stimulation of EDH may explain impairments in both local vasodilation and functional sympatholysis with advancing age in humans.

**6.3**

## THE IMPACT OF AGE AND HYPERTENSION ON CUTANEOUS MICROVASCULAR FUNCTION

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Microvascular dysfunction, characterized by attenuated endothelium-dependent vasodilation, augmented vasoconstriction, and eutrophic remodeling occurs via distinct mechanisms in primary human aging vs. hypertensive pathology. The human cutaneous circulation is an accessible model for examining mechanisms underly microvascular dysfunction in humans. Impaired vasoreactivity in the cutaneous microcirculation is detectable prior to impairments in condiut artery function, and occurs to a similar magnitude and via the same mechanisms as microvascular damage to the coronary, renal, and skeletal muscle circulations. Thermal and pharmacological stimuli, combined with traditional biochemical approaches, provide a powerful *in vivo* bioassay allowing for the targeted pharmaco-dissection of distinct mechanisms underlying cutaneous microvascular dysfunction as well as a tool for examining the potential impact of lifestyle and pharmacological intervention strategies. Emerging data in the human cutaneous circulation indicate that enzymatically produced hydrogen sulfide ($H_2S$) is an important endothelium-derived hyperpolarizing factor. There are multiple enzymatic sources of $H_2S$ in the cutaneous microvasculature including cystathione γ-lyase, and 3-mercaptopyruvate trans-sulferase. $H_2S$ is capable of modulating vascular function through extensive cross talk with the NO signaling pathway at multiple regulatory points. Further, the $H_2S$ and NO pathways appear to be differentially regulated in primary aging vs. hypertension. Emerging data suggest that points along the $H_2S$ enzymatic pathway may be specific molecular targets for the development of treatment strategies for age and hypertensive vascular pathology. Additionally, new putative targets for pathology-associated vascular remodeling will be discussed. NIH HL093238
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**6.4**

## MICROVASCULAR ADAPTATIONS DURING AGING: OPPORTUNITIES FOR NEW MODELS AND DISCOVERIES

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Microvascular network growth and remodeling are common denominators for most age-related pathologies. In multiple pathologies (cancer, retinopathies, rheumatoid arthritis) blocking microvascular growth, termed angiogenesis, would be beneficial. In others (myocardial infarction, stroke, hypertension), promoting angiogenesis would be desirable. Most therapies, however, are developed using adult animal models. This approach is problematic and does not account for the impaired angiogenesis and the inherent network structure changes that might result from age. Considering the common conception that angiogenesis is impaired with age, a need exists 1) to study the causes and mechanisms of angiogenesis in aged scenarios and 2) to develop new tools to enable comparison of aged versus adult responses to therapy. The objective of this presentation will be to introduce novel cell changes along aged microvascular networks and a new angiogenesis ex vivo tissue culture model for aging research. Immunolabeling of mesenteric microvascular networks harvested from Aged (24 mo.) versus Adult (9 mo.) male Fischer 344 rats identified an increased vascular pericyte coverage along capillaries in aged networks. This finding suggests a novel hypothesis that pericytes might play a role in aging impaired angiogenesis and motivates the need to probe spatio-temporal pericyte-endothelial cell interactions. Culturing the rat mesenteric tissues potentially provides such a model as both cell types remain viable and functional across the hierarchy of intact networks. Our results will highlight the opportunity for advancing our scientific tools and understanding of how and why microvascular network growth is altered in aged tissues.

This work is supported by NIH AG049821. REFERENCE: Sweat, RS, Sloas DC, Stewart SA, Czarny-Ratajczak M, Baddoo M, Eastwood JR, Suarez-Martinez AD, Azimi MS, Burks HE, Chedister LO, Myers L, and Murfee WL. (2017). Aging is associated with impaired angiogenesis, but normal microvascular network structure, in the rat mesentery. *Am J Physiol Heart Circ Physiol*. 312(2):H275-H284.

# 8.0 SYMPOSIUM: NOVEL IMPLICATIONS FOR BLOOD FLOW AND VASCULAR DYSFUNCTION IN NON-CARDIOVASCULAR RELATED DISEASES

## 8.1

### IMPLICATIONS FOR BLOOD FLOW IN PROSTATE CANCER: TUMOR/SYSTEMIC INTERACTIONS, CENTRAL AND PERIPHERAL CARDIOVASCULAR FUNCTION

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Cancer is considered an accelerated model of aging, largely due to a reduced aerobic capacity at any point after treatment (e.g., 10+ years) compared to healthy age-matched counterparts. The reduced aerobic capacity is attributed to the deleterious effects of cancer treatment(s). Exercise training has been shown to benefit cancer patients, largely by mitigating the side effects of treatment and increasing therapy tolerance. We are interested in investigating 1) how exercise can impact tumor/systemic interactions and the subsequent effect on tumor oxygenation as the first step in understanding how exercise training may impact cancer treatment, and 2) whether cancer itself, independent of treatment, can impact indices of aerobic capacity and the regulation of skeletal muscle blood flow at rest and during exercise. In pre-clinical models of prostate cancer, during exercise there is a large increase in tumor blood flow that is associated with a down-regulation of several vasoconstrictor pathways of the tumor resistance vasculature. When comparing skeletal muscle (soleus) blood flow at rest and during exercise, cancer did not affect resting muscle blood flow, but significantly reduced the change in muscle blood flow to moderate-intensity exercise (reduced rest-exercise muscle perfusion), indicating potential vascular dysfunction within the periphery. When looking at fatigue and central indices of cardiovascular function, time-to exhaustion in a treadmill exercise test was reduced with cancer, and tumor mass was significantly correlated with reduced LV function (i.e., LV DP/DT). These data suggest that 1) exercise may be a useful intervention to modulate tumor hypoxia and blood flow and, 2) cancer, independent of treatment, hastens the onset of fatigue, likely due to reduced central and peripheral cardiovascular function. Given the multifaceted negative impact of aging on the cardiovascular system, it is likely that cancer induced cardiovascular dysfunction is potentiated in aging subjects. (American Cancer Society (RSG-14-150-01-CCE to BJB) McCullough, D.J., J.N. Stabley, D.W. Siemann, B.J. Behnke. Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise. *J. Natl. Cancer Inst.* Apr; 106(4):dju036. Doi 10.1093/jnci/dju036.

## 8.2

### ENDOTHELIAL DYSFUNCTION IN THE ADIPOSE: A KEY REGULATOR OF AGE RELATED METABOLIC DYSFUNCTION?

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While once thought to be an inert site of energy storage, the adipose tissue is now appreciated as a dynamic endocrine organ that, when dysfunctional, contributes to both metabolic and cardiovascular disease risk. The adipose tissue contributes to metabolic homeostasis by buffering plasma free fatty acids, limiting ectopic lipid accumulation and secreting adipokines and cytokines that can influence metabolism, inflammation, and appetite. It is well appreciated that adipose dysfunction is a consequence of obesity. This dysfunction, characterized in part by adipose hypertrophy and inflammation, is known to contribute to the tissue and systemic metabolic dysfunction that occur in obesity. Less is known, however, about the consequences of aging on the function of the adipose and its interlaying vasculature or their role in age-associated metabolic dysfunction. Like obesity, advanced age also leads to adipose tissue dysfunction and inflammation that is concomitant with metabolic impairments, but in contrast, this occurs despite a reduction in adipose mass. Although the mechanisms underlying reduced adipose tissue mass and the concomitant adipose dysfunction with advancing age are incompletely understood, dysfunction of the arteries within the adipose tissue may be a significant factor. With aging, both endothelial function and angiogenic capacity are impaired in the adipose tissue and this arterial dysfunction may contribute to tissue inflammation and hypoxia that characterizes adipose dysfunction. A better elucidation of the mechanisms underlying adipose artery dysfunction with advancing age may provide important insight into treatment strategies to reduce metabolic and vascular diseases in older adults.

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# 11.0 SYMPOSIUM: NOVEL MECHANISMS UNDERLYING VASCULAR IMPAIRMENTS IN THE AGING BRAIN

## 11.1
## PULSE PRESSURE IN THE AGING BRAIN

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The major cause of peripheral arterial stiffening is aging, and this is accelerated by sedentariness, hypertension, diabetes and atherosclerosis; in these conditions, the biomechanics of the cerebral arteries are poorly understood. When combined, sedentariness, hypertension, obesity, elevated glucose and lipids are associated with a 2- to 4-fold rise in the risk of brain infarction. Furthermore, physical inactivity alone is a greater risk factor for stroke than for myocardial infarction and there is evidence that sedentariness increases dementia. A major benefit of regular exercise, which can acutely increase blood pressure to 200 mm Hg, is the maintenance of the cerebrovascular endothelial function and wall structure. Increase in aortic stiffness has been reported to be associated with increased carotid flow augmentation (blood acceleration during systole) and pulsatility of blood flow in the middle cerebral artery (MCA). In human, chronic increases in systemic pulse pressure are associated with cerebrovascular damage, leading to the so-called pulse-wave encephalopathy. Several studies have established a link between peripheral arterial stiffness responsible for the sustained increase in pulse pressure and brain microvascular diseases such as cerebral small vessel disease, cortical gray matter thinning, white matter atrophy and cognitive dysfunction in older individuals, hypertensive and diabetic patients. In addition, the higher pulsatility of CBF is positively correlated with the loss of white matter integrity. Finally, the rarefaction of white matter is strongly associated with MCA pulsatility that is strongly dependent on aortic pulse pressure and large artery stiffness. Thus, physiopathological conditions characterized by an increase in peripheral artery stiffness and thus pulse pressure, are associated with brain damage and structural changes.

## 11.2
## AGING INCREASED BLOOD PRESSURE AND ALTERS THE BIOMECHANICAL PROPERTIES OF THE POSTERIOR CEREBRAL ARTERIES AND THE PARENCHYMAL ARTERIOLES

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Artery dysfunction is an important determinant of cardiovascular diseases such as hypertension, atherosclerosis and cerebral artery disease which are major causes of mortality in the elderly. Cerebral artery remodeling, described as a change in artery structure, could also play an important role in dementia development. To assess the effects of aging on the biomechanical properties and structure of the cerebral vasculature and we elected to study two artery types, the posterior cerebral arteries (PCAs) and parenchymal arterioles (PAs). The PCAs are relatively large pial arteries while the PAs are smaller arterioles that dive into the brain parenchyma, these smaller vessels regulate the perfusion of the microcirculation where nutrient and gas exchange occurs. The biomechanical properties of the PCAs and PAs from young (3-5 months old) and aged (22-24 months old) were assessed by pressure myography. Significantly different ($p<0.05$) data are presented as mean ± SEM; young vs old (n=9 in each group). In the PCA, older mice had increased outer (155.6 ± 3.2 vs 169.9 ± 3.2μm) and lumen (116.4 ± 3.6 vs 137.1 ± 4.7μm) diameters. Wall stress (375.6 ± 35.4 vs 504.7 ± 60.0 dynes/cm$^2$) and artery stiffness (β-coefficient: 5.2 ± 0.3 vs 7.6 ± 0.9) were also increased. However, wall strain (0.8 ± 0.1 vs 0.6 ± 0.1) was reduced with age. In the PAs from old mice, wall thickness (3.9 ± 0.3 vs 5.1 ± 0.2 μm), and area (591.1 ± 95.4 vs 852.8 ± 100μm$^2$) were increased while stress (758.1 ± 100.0 vs 587.2 ± 35.1dynes/cm$^2$) was reduced. Blood pressure was measured by telemetry in a small group of young (n=3) and aged (n=4) mice. Aging increased mean arterial (104.6±0.25 vs 118.5±0.24mmHg) and pulse pressures (0.36.57±1.84 vs 47.83±0.36mmHg). Preliminary studies suggest that the aged mice also exhibited artery rarefaction, and increased calcium and collagen deposition. We conclude that age-associated remodeling occurs in large cerebral arteries and arterioles and may increase the risk of cerebrovascular disease.

## 11.3
## HUMAN CEREBRAL ARTERY FUNCTION AND AGING

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Aging is associated with vascular dysfunction, elevated cardiovascular disease risk, and increased Alzheimer's disease (AD) pathology. In addition, aging reduces cerebral perfusion and cerebral arterial function, and is associated with brain atrophy. Understanding the effects of physiological aging on cerebral blood flow and brain structure may help to determine effective strategies to mitigate these effects on the population. Currently, cerebral blood flow regulation during midlife is poorly understood, making it difficult to distinguish age-related physiology from AD-related pathophysiology. Furthermore, age-related changes in the vasculature may accelerate pathophysiological increases in neurodegeneration and AD neuropathology. Understanding how cerebral arterial function changes, especially during midlife, is important because this is the critical period where lifestyle and pharmacological intervention can modify the risk of future cognitive impairment. Exercise may be one strategy to prevent or delay cognitive decline. Regular exercise has been shown to improve cognition, likely through beneficial adaptations in cerebral arterial function. Additional interventions initiated during midlife that are directed at improving cerebral perfusion and cerebral arterial function are necessary.

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**11.4**

**ROLE OF ENDOTHELIAL NNOS IN AGE-RELATED MICROVASCULAR IMPAIRMENTS**

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Endothelial cells have been shown to express endothelial (eNOS) and neuronal (nNOS) isoforms of nitric oxide synthase. Although eNOS has been extensively studied in aging vasculature, we know very little about the expression, the pathophysiological role, or the regulation of nNOS in the brain microvessels in aged animals. For the first time, we have identified the expression of nNOS in the primary cultured brain microvascular endothelial cells from mice, rats, and humans; and the freshly isolated rat brain microvessels. Lack of nNOS expression in endothelial cells in the nNOS knockout mice further confirmed the presence of nNOS in the endothelial cells. Inhibition of nNOS by pharmacological and RNAi approaches showed that endothelial nNOS is constitutively active and does not produce NO but instead produces superoxide. Interestingly, inhibition of nNOS by the same pharmacological inhibitors in primary cultured cortical neurons showed that nNOS of neuronal origin produces NO but not superoxide. Thus, endothelial nNOS is distinct from nNOS of neuronal origin as well as eNOS. The impact of aging on the endothelial nNOS was examined in the freshly isolated brain microvessels from young (10 weeks) and middle aged Sprague Dawley (18 month) rats. Although the expression levels of nNOS was found to be not significantly different, endothelial nNOS in the aged microvessels does not produce superoxide. Furthermore, supplementation of tetrahydrobiopterin attenuated the endothelial nNOS activity suggesting that it exists physiologically in an uncoupled state possibly localized in a subcellular compartment lacking access to tetrahydrobiopterin. Therefore, we examined the effects of pharmacological inhibition of nNOS on the mitochondrial respiration by measurements of oxygen consumption rate in the isolated heart mitochondria. We found that nNOS inhibitors enhanced the proton leak and reduced the ATP production in isolated heart mitochondria of young rats which were lost in the middle-aged rats. Thus, aging is associated with the alterations of endothelial and mitochondrial nNOS activity. This work is supported by: NIH grant (NS094834) and AHA Scientist Development Grant (14SDG20490359).

## 12.0 SYMPOSIUM: CELLULAR SENESCENCE AND GENOMIC INSTABILITY: IMPLICATIONS FOR CARDIOVASCULAR DISEASE

**12.1**

**CELLULAR SENESCENCE AND SENOLYTIC AGENTS IN AGE-RELATED DYSFUNCTION AND CHRONIC DISEASES**

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Senescent cells, which are resistant to apoptosis, can secrete a range of pro-inflammatory cytokines and chemokines, matrix-destroying proteases, factors that cause stem cell dysfunction, and hemostatic factors, the senescence-associated secretory phenotype (SASP). We developed senolytic agents – drugs that selectively eliminate senescent cells by inhibiting the pro-survival Senescent Cell Anti-apoptotic Pathways (SCAPs) that protect these cells from apoptosis due to their own SASP. Decreasing senescent cell abundance by intermittent treatment with senolytic drugs decreased frailty in progeroid mice, enhanced cardiac ejection fraction, improved aortic vascular reactivity, and reduced hemostatic factors in old mice, alleviated impaired gait in mice following leg irradiation, reduced lung fibrosis and enhanced pulmonary function in mice with bleomycin-induced lung dysfunction, reduced insulin resistance in diet-induced obese mice, and decreased vascular calcification, increased vascular reactivity, and decreased atherosclerosis in hypercholesterolemic mice. Thus, senolytic drugs are a new intervention that may delay, prevent, or treat multiple age- and chronic disease-related disorders. Support: NIH grant AG013925, the Connor Group, and the Ted Nash and Glenn Foundations. REFERENCE: Zhu, Y., Tchkonia, T., Pirtskhalava, T., Gower, A., Ding, H., Giorgadze, N., Palmer, A.K., Ikeno, Y., Borden, G., Lenburg, M., O'Hara, S.P., LaRusso, N.F., Miller, J.D., Roos, C.M., Verzosa, G.C., LeBrasseur, N.K., Wren, J.D., Farr, J.N., Khosla, S., Stout, M.B., McGowan, S.J., Fuhrmann-Stroissnigg, H., Gurkar, A.U., Zhao, J., Colangelo, D., Dorronsoro, A., Ling, Y.Y., Barghouthy, A.S., Navarro, D.C., Sano, T., Robbins, P.D., Niedernhofer, L.J., Kirkland, J.L. The Achilles' heel of senescent cells: From transcriptome to senolytic drugs. Aging Cell 14:644-658, 2015.

**12.2**

**AGE-RELATED ARTERIAL ALU ELEMENT INSTABILITY AND SURVIVAL IN MELANOMA PATIENTS**

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**Background:** Highly repetitive short interspersed ALU elements are hot-spots for genomic structural mutations. In cancer patients, age-related ALU element instability in arteries could contribute to arterial functional changes that promote cancer progression and increase mortality rates.

**Objective:** To determine if ALU element instability occurs with advancing age in arteries from patients with non-metastatic melanoma and influences risk for mortality from metastatic disease during a 5-year follow-up period in a subgroup of age-matched patients.

**Methods:** ALU element instability was assessed in 88 small feed arteries obtained from routine sentinel lymph node biopsies by measuring ALU element content per genome by qPCR. ALU element damage was assessed by the DNA break marker, serine 139 phosphorylated histone γ-H2A.X (γ-H2), at ALU elements by ChIP. Apoptotic signaling was assessed by p53 bound to the BAX gene promoter by ChIP.

**Results:** ALU element content decreased with advancing age ($r = -0.22$; $P < 0.02$) in arteries from melanoma patients. Patients with lower ALU element content had a higher 5-year mortality rate from metastatic disease than those with higher ALU element content (Hazard Ratio (HR) = 4.45; $P < 0.01$). ALU element damage was not correlated with age ($r = 0.14$; $P = 0.10$), but was negatively correlated with ALU element content ($r = -0.32$; $P < 0.01$). Patients with greater amounts of ALU element damage had a higher 5-year mortality rate from metastatic melanoma than those with less ALU element damage (HR = 2.91; $P < 0.04$). Apoptotic signaling was not correlated with age ($r = 0.13$; $P = 0.09$), but demonstrated a positive correlation with ALU element content ($r = 0.25$; $P = 0.01$). Apoptotic signaling was not predictive of mortality from metastatic disease (HR = 0.66; $P = 0.22$).

**Conclusions:** ALU element instability occurs with advancing age in arteries and is linked to disease progression and lower survival in melanoma patients. DNA damage is associated with age-related ALU element instability and mutant arterial cells may escape apoptosis to promote maladaptive effects in arteries. These findings highlight the relevance of genomic instability in arteries to melanoma pathogenesis.

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**12.3**

**VASCULAR TELOMERE DYSFUNCTION: ASSOCIATION WITH AGING AND FUNCTIONAL IMPLICATIONS**

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In recent years, the relation between altered telomere function and cardiovascular disease risk has become appreciated. Although epidemiology and physiology studies have typically focused on mean telomere length, there are other features of telomere dysfunction that appear to confer greater physiologic significance, such as the uncapping of telomere ends. Telomeres form specialized structures called t-loops that protect chromosome ends. The loss of this loop, known as uncapping, leads to the recognition of telomere ends as double-stranded DNA breaks and initiates a DNA damage response. This DNA damage response causes activation of p53 and p21-mediated cellular senescence. Only a few uncapped telomeres within a cell are needed to trigger a DNA-damage response and telomere uncapping can occur irrespective of changes in mean telomere length.

In human resistance arteries, markers of telomere uncapping and p53/p21-induced senescence increase with advancing age. Importantly, telomere uncapping, but not mean telomere length, is related to markers of cellular senescence in arterial tissue with aging. These age-related changes in telomere uncapping and senescence appear to be greater in women than men, indicating a possible additive effect of menopause and advancing age. To assess the effect that telomere uncapping *per se* has on vascular function, we utilized a mouse model of induced knockdown of telomeric repeat binding factor 2 (TRF2), a key protein involved in t-loop maintenance. When *Trf2* knockout is induced in all cells, there is increased telomere uncapping and p21-mediated senescence in arteries. Whole body *Trf2* knockout leads to increased blood pressure and impaired endothelial function, as indicated by reduced endothelium-dependent dilation associated with reduced nitric oxide bioavailability and increased oxidative stress. Knockout of *Trf2* induced specifically in endothelial cells also leads to impaired endothelial function characterized by an increase in vascular permeability, indicative of a dysfunctional endothelial barrier.

Thus, advancing age is associated with greater arterial telomere uncapping and cellular senescence. Proof-of-concept studies indicate that induced telomere uncapping can lead to endothelial cell dysfunction. As such, interventions that target the telomere uncapping pathway may be able to prevent or reverse age-related vascular dysfunction and cardiovascular disease risk.

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## 13.0 POSTER SESSION II

**13.1**

**MYOFILAMENT AND BIOCHEMICAL RESPONSES OF THE RIGHT VENTRICLE TO HYPOXIA-RELATED CARDIAC DYSFUNCTION IN AGING**

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Heart failure (HF) is a major public health concern, particularly within aging populations. In age-related left-

sided HF as well as other clinical contexts, *right* ventricular (RV) function is the strongest predictor of survival. However, despite the clear link between RV dysfunction and mortality, little is known about the impact of age on RV function, and no RV-directed therapies exist. Accordingly, the purpose of this investigation was to assess the impact of age on RV function under control conditions and in response to stress using a model of hypobaric hypoxia (HH) (pulmonary hypertension), a highly significant and translationally important disease in cardiovascular aging. We exposed young (3-4 month) and old (~20 months) mice to HH (~17,000 feet; $PO_2$ 10%) and assessed myofilament-mediated changes in cardiac contractile function. In HH, cardiopulmonary morbidity and mortality were significantly accelerated in aged mice, with all HH challenged mice dying within 4 weeks (compared to 0% of young mice). In addition, aged mice exposed to HH had higher lung and RV weights compared to young mice, indicative of more severe pulmonary edema and RV hypertrophy. Assessment of isolated RV cardiomyocyte contractile behavior demonstrated no differences in young versus old control mice. However, cardiomyocytes from old mice exposed to HH demonstrated higher RV myocyte contractile force alongside diminished myofilament cooperativity and a trend towards decreased calcium sensitivity, changes which are directionally similar to those seen in young animals exposed to HH. Since sarcomeric protein biochemistry is a major regulator of the mechanical behavior of cardiac tissue, we quantified phosphorylation of myofilament proteins. Phosphorylation of the inhibitory subunit of the troponin complex (cTnI) was increased at Ser150 in young models of HH exposure and in old RV exposed to HH, albeit less robustly in old animals compared to young. Phosphorylation of cTnI at this site is predominantly modulated by AMP-activated protein kinase (AMPK), which is diminished with aging. AMPK activators are promising targets for HF therapy, thus ongoing investigations will elucidate the impact of AMPK activators on myofilament contractility and cardiac function in the aging and HH-exposed right heart.

**13.2**

**AGING-ASSOCIATED UPREGULATION OF CARDIAC B3-ADRENERGIC SIGNALING IS AN IMPORTANT CAUSE OF CARDIAC AGING**

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Aging-Associated Upregulation of Cardiac β3-Adrenergic Signaling is An Important Cause of Cardiac Aging

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Background. Myocardial aging leads to diminished inotropic response to β-adrenergic receptor (AR) stimulation. The molecular mechanism remains unclear. We hypothesize that upregulation of cardiac $\beta_3$-AR with resultant enhanced negative modulation on β-adrenergic signaling plays a critical role in this age-related event. Thus, aging-induced desensitization of cardiac β-adrenergic signaling may be attenuated or prevented in $\beta_3$-AR knockout ($\beta_3$KO) aged mice.

Methods. We compared cardiac $\beta_3$-AR gene expression and myocyte contractile and $[Ca^{2+}]_i$ transient ($[Ca^{2+}]_{iT}$) responses to isoproterenol (ISO, $10^{-6}$ to $10^{-8}$ M), a non-selective β agonist, and BRL-37,344 (BRL, $10^{-8}$ M), a selective $\beta_3$ agonist, in isolated left ventricular (LV) myocytes obtained from 2 young (Y)(~3-4 mo) and 2 aged (A) (~18-24 mo) groups (6/group) of wild-type (WT) and $\beta_3$KO mice, respectively.

Results. Compared with YWT myocytes, AWT myocytes showed about 30% decline in basal cell contraction ($dL/dt_{max}$, 85.6 vs 122.1 μm/s) and relaxation ($dR/dt_{max}$, -61.9 vs -89.9 μm/s) with decreased $[Ca^{2+}]_{iT}$ (0.18 vs 0.21) ($p<0.05$). There were significantly increased $\beta_3$-AR mRNA (27%, 0.15±0.01 vs 0.12±0.01) and protein levels accompanied by contrast alterations on myocyte response to β- and $\beta_3$-AR stimulation. In AWT myocytes, ISO ($10^{-8}$ M) caused much less increases in $dL/dt_{max}$ (AWT:30% vs YWT:72%), $dR/dt_{max}$ (25% vs 56%), and $[Ca^{2+}]_{iT}$ (13% vs 26%); in contrast, BRL produced a much greater decrease in $dL/dt_{max}$ (17.9% vs 6.9%) and $[Ca^{2+}]_{iT}$ (28.2% vs 18.7%). Compared with YWT, Y$\beta_3$KO, which did not alter basal contraction of myocytes, markedly improved the ISO concentration-response curve. Importantly, in contrast to AWT mice, myocytes obtained from A$\beta_3$KO mice showed significantly improved basal cell contraction and relaxation with nearly preserved ISO-stimulated positive inotropic effect. Compared with Y$\beta_3$KO, in A$\beta_3$KO mice, ISO caused similar increases in $dL/dt_{max}$ (78% vs 84%) and $[Ca^{2+}]_{iT}$ (32% vs 34%).

Conclusion. Cardiac aging is associated with upregulation of $\beta_3$-AR, which is a critical determinant to the diminished positive modulation of β-adrenergic signaling, and directly contributes to age-associated deficits in LV myocyte functional performance.

**13.3**

**CARDIAC MYOSIN BINDING PROTEIN-C PHOSPHORYLATION IMPROVES LONGEVITY AND PRESERVES HEART FUNCTION IN AGING HEARTS**

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**Introduction:** In 2014, ≥65Yr population constituted 14.5% (46.2M) of US population. By 2060 this number will double. Heart failure prevalence will increase from 6.5M in 2017 to >8M in 2030 due to the aging population. Cardiac myosin binding protein-C (cMyBP-C), a heart muscle thick filament protein, can regulate cross-bridge

attach/detachment process by its phosphorylation status. cMyBP-C phosphorylation is decreased in heart failure.

**Hypothesis:** phosphorylated cMyBP-C supports normal heart function during aging.

**Results:** We test this idea by aging mouse models of phosphorylation deficient cMyBP-C(S273A, S282A, S302A)-(t3SA), phosphorylation mimetic cMyBP-C(S273D, S282D, S302D)-(t3SD), and WT-control cMyBP-C(tWT). t3SD mice showed enhanced survival (Kaplan Meier at 18 months: tWT: 91.8%$^{\#}$; t3SA: 80.9%*$^{\#}$; t3SD: 95.8%*, Log Rank test $p<0.05$). t3SD hearts maintained an EF >45% throughout aging and exhibited enhanced contractility with faster tissue Doppler of myocardial contraction velocity during systole, s'. Conversely, loss of cMyBP-C phosphorylation (t3SA) caused heart failure and systolic dysfunction (EF: tWT: 41±4, t3SA: 31±5*$^{\#}$, t3SD: 48±2), (s': tWT: 17.05±0.92$^{\#}$; t3SA: 15.52±2.09$^{\#}$; t3SD: 23.83±1.10*). Additionally, t3SD hearts showed enhanced myocardial relaxation velocity during early diastole, e', and smaller blood flow Doppler to e' ratio (E/e'); meanwhile, t3SA hearts exhibited impaired relaxation (e': tWT: 16.66±1.39$^{\#}$, t3SA: 14.04±1.01$^{\#}$, t3SD: 33.06±0.01*), (E/e': tWT: 34.06±3.99$^{\#}$; t3SA: 37.73±2.23$^{\#}$; t3SD: 18.49±1.46*). We use peak relaxation rate $(-dF/dt)_{min}$ to peak force generation rate $(+dF/dt)_{max}$ ratio (dFR) to compare lusitropy of intact papillary muscles. t3SD muscles show increased dFR, meaning enhanced relaxation (at 1.5 Hz: tWT: 0.56±0.06$^{\#}$; t3SA: 0.45±0.02$^{\#}$; t3SD: 0.70±0.04*). Single negative exponential was used to calculate $[Ca^{2+}]_i$ decay rate constant $k_{Ca}$. All models show similar $k_{Ca}$; therefore, enhanced relaxation in t3SD is attributed to cross-bridge cycling but not differences in $[Ca^{2+}]_i$ handling. Mean±SEM; *$p<0.05$ vs tWT; #$p<0.05$ vs t3SD.

**Conclusion:** Better cardiac function contributed to enhanced survival in t3SD mice. Simultaneous force and $[Ca^{2+}]_i$ measurements on papillary muscles showed that t3SD enhancement of relaxation occurs independently of $[Ca^{2+}]_i$. Therefore, acceleration of cross-bridge cycling due to phosphorylation of cMyBP-C can be translated into novel treatments for age related cardiac dysfunction.

### 13.4

### EARLY CELL-CELL COUPLING IMPAIRS TRANSPLANTED STEM CELL RETENTION AND EFFICACY IN THE ISCHEMIC CARDIOMYOCYTE AND MURINE HEART

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**Background:** Bone marrow-derived mesenchymal stem cells (BM-MSC) are reported to induce beneficial effects in the heart following ischemia but a loss of these cells within hours of administration could significantly diminish their long-term effect. We hypothesized that early coupling between BM-MSC and ischemic cardiomyocytes through gap junctions (GJ) may play an important role in stem cell survival and retention in the acute phase of myocardial ischemia.

**Methods:** We seeded HL-1 cardiomyocytes in either normoxic (Nx) or ischemic (Isc) conditions for four hours. Subsequently, murine BM-MSC (mBM-MSC) were seeded on top of the HL-1 monolayer and the co-cultures were returned to incubation under previous conditions (Group 1, Nx, Group 2, Isc) or switched to ischemia-reoxygenation (Group 3, Isc/Nx) for an additional two hours. For the final two-hour co-culture period a GJ inhibitor (Carbenoxolone, CBX; 100 uM) was added to half of the culture plates in each of the three groups. Co-cultures were labeled with Annexin V, Sytox Red, and Sca-1 (mBM-MSC), to identify apoptotic cells and distinguish between HL-1 and mBM-MSC with flow cytometry. To determine the effect of GJ inhibition on mBM-MSC *in vivo*, we induced ischemia in mice by 90-minute LAD occlusion followed by reperfusion for 24 hours. mBM-MSC, CBX-treated mBM-MSC, or CBX+vehicle alone were injected in the left ventricular apex at the end of the 90 min ischemic period and the mice were allowed to recover. Twenty-four hours after cell injection, left ventricular diastolic and systolic function was assessed by pressure-volume loop analysis with an indwelling LV catheter.

**Results:** Ischemia induced a greater proportion of dead mBM-MSC in co-culture compared to the Nx group. Isc/Nx resulted in significantly higher early apoptotic but fewer dead mBM-MSC. The presence of the GJ inhibitor CBX in the co-culture reduced the number of dead and apoptotic cells in Isc and Isc/Nx groups by 3-5 fold ($p<0.05$). Isc/Nx caused impaired cardiac function that was attenuated by mBM-MSC injection. CBX-treated mBM-MSC led to further improvement in cardiac function (mBM-MSC vs. mBM-MSC+CBX: $E_{es}$ 7.3 ± 1.66 vs. 15.0 ± 5.81; $E_{max}$ 18.8 ± 6.50 vs. 27.5 ± 9.33; PRSW 49.5 ± 9.89 vs. 99.4 ± 17.4; mean ± SD; $p\leq0.05$; n = 6) while CBX alone did not.

**Conclusions:** While functional GJ are critical for long-term integration of stem cells within the myocardium, early GJ communication may represent a novel paradigm whereby ischemic and apoptotic cardiomyocytes induce a "bystander effect" when coupled to newly transplanted mBM-MSC and thus impair cell retention and functional benefits.

### 13.5

### DNA-REPAIR IN CARDIOMYOCYTES IS CRITICAL FOR MAINTAINING CARDIAC FUNCTION

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**Background:** DNA in every cell is continuously damaged and DNA repair systems are essential for protection from DNA damage-induced cancer and aging-related diseases. Here we studied the role of DNA repair in cardiomyocytes in maintaining normal cardiac function. DNA repair-deficient *Xpg*$^{-/-}$ and cardiomyocyte-specific

*Xpg*$^{c/-}$ (*αMHC-Xpg*$^{-/-}$) mice were used to study left ventricular (LV) geometry and function.

**Methods:** *Xpg*$^{-/-}$ (n=39), *αMHC-Xpg*$^{-/-}$ (n=26) and control wildtype (WT, n=28) mice were sacrificed at age 16 wks. LV geometry and function were measured and hypertrophy marker genes were determined. Superoxide ($O_2^-$) production was studied using lucigenin-enhanced chemiluminiscence. Molecular imaging was performed to determine early apoptosis in the *in vivo* heart using near infrared fluorescent Annexin V probe, combined with contrast-enhanced microCT for anatomical reference. Late apoptosis was determined via TUNEL assay in LV sections.

**Results:** *Xpg*$^{-/-}$ mice showed reduced growth, followed by body weight loss and shortened lifespan (19 wks). *αMHC-Xpg*$^{-/-}$ mice exhibited normal growth and body weight gain, but also showed reduced lifespan (28 wks). At 16 wks, LV function was deteriorated in both groups compared to WT, demonstrated by decreases in fractional shortening (*Xpg*$^{-/-}$ 38±2, *αMHC-Xpg*$^{-/-}$ 28±2 vs. WT 49±2%; both $p<0.05$) and $LVdP/dt_{P30}$ (*Xpg*$^{-/-}$ 4020±370, *αMHC-Xpg*$^{-/-}$ 5380±280 vs. WT 9380±380 mmHg/s; both $p<0.05$) and increases in relaxation time constant tau (*Xpg*$^{-/-}$ 10.5±0.7, *αMHC-Xpg*$^{-/-}$ 11.7±1.5 vs. WT 7.7±0.3 ms; both $p<0.05$). The relative RNA expression level of atrial natriuretic peptide was increased in both groups, but particularly in *αMHC-Xpg*$^{-/-}$ (*Xpg*$^{-/-}$ 3.6±0.3 and *αMHC-Xpg*$^{-/-}$ 8.6±1.5 fold change; both $p<0.05$). Total $O_2^-$ production was only increased in *Xpg*$^{-/-}$ (*Xpg*$^{-/-}$ 49±6, *αMHC-Xpg*$^{-/-}$ 29±1 vs. WT 26±2 RLU/g; $p<0.05$). Both Xpg-deficient models displayed marked increases in *in vivo* myocardial apoptosis (*Xpg*$^{-/-}$ 3.7±0.9, *αMHC-Xpg*$^{-/-}$ 2.8±0.3 vs. WT 1.0±0.2 pmol/g heart weight normalized to WT; both $p<0.05$) as well as in late myocardial apoptosis (*Xpg*$^{-/-}$ 2.5±0.2, *αMHC-Xpg*$^{-/-}$ 1.7±0.1 vs. WT 1.0±0.1 positive nuclei ‰ normalized to WT; both $p<0.05$).

**Conclusion:** Mice with (cardiomyocyte-restricted) loss of DNA-repair protein XPG display a heart failure phenotype, demonstrating that intact DNA repair in cardiomyocytes is critical for maintaining normal cardiac function.

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**13.6**

## THE EFFECTS OF AGING ON PATHOLOGIC LEFT VENTRICULAR REMODELING AND DYSFUNCTION DEPEND CRITICALLY ON THE UNDERLYING PATHOLOGY

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**Purpose:** The aging heart undergoes a number of non-pathological structural and functional alterations which are reminiscent to the changes observed in the failing heart, and which thus may increase cardiac vulnerability to develop heart failure in response to mechanical overload. Consequently, we studied the effect of aging on left ventricular (LV) remodeling and dysfunction in response to mechanical overload.

**Methods:** C57BL6J mice were subjected to pressure overload by transverse aortic constriction (TAC) or myocardial infarction (MI) at 3 or 24 mo of age. Eight weeks after TAC or MI, LV geometry and function were assessed and isometric force was studied in single permeabilized cardiomyocytes.

**Results:** Aging resulted in sham-operated animals in increases in LV weight (26%), LV end-diastolic lumen diameter (7%) and passive isometric myofilament force (Fpas, 44%) and in decreases in $LVdP/dt_{P40}$ (22%) and $LVdP/dt_{min}$ (22%) in 24 vs. 3 mo (all $p<0.05$). TAC and MI produced LV hypertrophy, LV dysfunction and backward failure in all age groups. Interestingly, the relative TAC- and MI-induced increases in LV weight (compared to age-matched shams) were blunted (TAC: 92% at 3 mo, 60% at 24 mo; MI: 34% at 3 mo, 7% at 24 mo). In TAC, the blunted LV hypertrophy was associated with aggravated LV dysfunction, demonstrated by further decreases in $LVdP/dt_{P40}$ (31%) and $LVdP/dt_{min}$ (30%) and increases in lung fluid and RV weight (28%) in 24 vs. 3 mo (all $p<0.05$). In contrast, the blunted MI-induced LV hypertrophy was associated with a trend towards ameliorated LV diastolic dysfunction, demonstrated by reductions in tau (33%) and LV end diastolic pressure (55%) in 24 vs. 3 mo. Furthermore, the survival rate after 8 wk of MI in 24 mo was higher compared to 3 mo (resp. 83% vs. 71%). This was contrary to the survival rate after 8 wk of TAC (70% in 24 mo vs. 88% in 3 mo). The TAC-induced LV dysfunction at 3 mo was accompanied by elevated cardiomyocyte maximal force development (Fmax, 51%), whereas the MI-induced LV dysfunction was accompanied by reduced Fmax (33%), compared to age-matched sham (both $p<0.05$). Conversely, Fpas was markedly increased in TAC (157%),but unchanged in MI. Aging in TAC resulted in reductions of Fmax and Fpas to baseline sham levels, which were not altered in MI.

**Conclusion:** These observations indicate that the effects of aging on the cardiac response to hemodynamic overload depend critically on the underlying pathology.

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**13.7**

## ADVANCE AGE AND CIRCULATING MIR423 ARE INDEPENDENT PREDICTORS OF POSTOPERATIVE ATRIAL FIBRILLATION

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**Objective:** Postoperative atrial fibrillation (PoAF) is a common complication after surgery. Identification of patients at risk of PoAF is difficult in patients undergoing surgery with no prior history of atrial fibrillation (AF) or severe ventricular dysfunction. Circulating miRNAs have been proposed as biomarkers for myocardial dysfunction, but their role in predicting PoAF over clinical predictors is not known. We therefore sought to determine whether miRNA involved in cardiovascular disease can identify those patients who developed PoAF with no prior history of AF and determined the incremental value of miRNA over clinical predictors of AF.

**Methods:** Preoperative blood from patients undergoing coronary artery bypass graft (CABG) surgery with no previous history of AF, supraventricular or ventricular tachycardia, or severe ventricular dysfunction was used for RNA isolation. Differences in the relative levels of miRNA between those who did and did not develop PoAF were assessed using qPCR. Area under the curve was used to assess the incremental value of adding miRNAs to clinical predictors on receiver operating characteristics.

**Results:** Out of 77 patients, 41 developed PoAF (53%). Patients who developed PoAF were older (mean age 69.7± 8.8y vs. 64.4 ±10.2y, p=0.02) and 53% were male; there were no differences in prevalence of hypertension, diabetes, hyperlipidemia, previous myocardial infarction, heart failure, stroke, COPD, sleep apnea, LVEF, or cardiac medications. Out of 12 miRNAs analyzed, only miR423 was significant at the univariate level in predicting patients who developed PoAF [OR 1.12, 95% CL (1.04-1.25), p=0.012]. Multivariate analysis showed that age [OR 1.07, 95% CL (1.01-1.13), p=0.024] and miR423 [OR 1.14, 95% CL (1.04-1.30), p=0.018] were independent predictors of PoAF; male sex, MI, diabetes, CHF, and hypertension were not significantly associated with PoAF (p>0.05). Adding miR423 to clinical predictors improved the C statistics from 0.66 (95% CL 0.54-0.78) to 0.77 (95% CL 0.66-0.88).

**Conclusion:** In patients undergoing CABG surgery, incorporation of circulating levels of miR423 as a biomarker to clinical predictors improves identification of patients at risk for PoAF and selection for prophylactic intervention to reduce this common complication.

### 13.8

### STORE-OPERATED CA2+ INFLUX IN HUMAN VENTRICULAR FIBROBLASTS INCREASES BY AGE

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**Objective:** Senescence-induced changes, including excessive fibrosis, contribute to impaired cardiac function in the elderly. Pro-fibrotic processes like fibroblast (FB) proliferation, activation, secretion of extracellular matrix and cytokines are intracellular $Ca^{2+}$-dependent. However, the effect of advancing age on the $Ca^{2+}$ mobilization processes of human ventricular fibroblasts (hVF) is unclear. Therefore, we tested the hypothesis that aging promotes pro-fibrotic changes within hVFs by altering the intracellular $Ca^{2+}$ release and store-operated $Ca^{2+}$ influx (SOC).

**Methods:** Primary hVF cultures, obtained from cardiac disease-free trauma victims of different ages from 2 to 60 years, were used. Cytosolic free $Ca^{2+}$ imaging was performed in hVF preloaded with fluo-3 AM (confocal microscopy). Thapsigargin (2.5 μM) was used to release and deplete intracellular $Ca^{2+}$ stores in $Ca^{2+}$-free KRH solution, and then $CaCl_2$ (2 mM) was added to assess SOC-$Ca^{2+}$-influx. Ionomycin (2 μM) was used for maximal $Ca^{2+}$ normalization. Expression of genes related to SOC and fibrosis – STIM1, Orai1, TRPC1, TRPC3, COL1A1, COL1A2, COL3A1, MMP1, MMP2, MMP3, TIMP3 and GAPDH – were assessed by quantitative reverse transcription polymerase chain reaction. Age-related transdifferentiation of hVFs was determined by immunoblotting for α-smooth muscle actin. Collagen secretion/deposition after 48 h culture of hVFs was assayed using a Sircol™ kit. Data were analyzed by age group comparison <50 (n=3-5) vs ≥50 years (3-4) by unpaired Student's t-test or by regression analysis of the sample population (n=9).

**Results:** $Ca^{2+}$ release from intracellular stores by thapsigargin was not different (p=0.12) between <50 (15±1%) and ≥50 groups (24±5%), but SOC-$Ca^{2+}$-influx was significantly (p=0.04) elevated in the ≥50 group (60±12%) vs the <50 group (32±3%). Regression analysis showed an age-dependent increase in SOC-$Ca^{2+}$ influx of hVFs ($R^2$=0.5). Age did not significantly alter the expression of genes related to SOC or fibrosis and the status of hVF transdifferentiation to myofibroblasts. The secretion/deposition of soluble collagen by hVFs tends to increase by age ($R^2$=0.4).

**Conclusions:** Aging-related increase in hVF collagen secretion is associated with increased SOC-$Ca^{2+}$ influx with no change in the magnitude of intracellular $Ca^{2+}$ release or the expression of related genes. Regulatory mechanisms that enhance SOC-$Ca^{2+}$ influx with aging need to be defined to identify specific targets for prevention of excessive fibrosis and myocardial dysfunction in the elderly.

### 13.9

### CARDIAC TROPONIN T AND ENDOTHELIAL CELL DYSFUNCTION IN AGING AND ALZHEIMER'S DISEASE

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Alzheimer's Disease (AD) is an age-related disorder characterized by progressive cognitive decline and dementia. Growing evidence suggests that the neurodegenerative process is initiated by chronic cerebral hypoperfusion caused by aging related vascular dysfunction. Given that the endothelial cell senescence and apoptosis has severe impact on vascular function in aging, a concerted effort is required to understand the mechanisms underlying

vascular endothelial dysfunction in aging and AD to identify novel treatments.

Troponin T (TnT), a key regulator of the muscle contractile machinery, has three isoforms, TnT1, TnT3, and TnT2, which are expressed in slow-, fast-twitch skeletal muscle, and cardiac muscle, respectively. TnT2, or "cardiac" troponin T (cTnT), is also expressed in several noncardiac tissues, including skeletal muscle, smooth muscle and adipose tissue. Its gene expression was also detected in several microvessel endothelial cells from various human tissues, including choroid, retina, and lung. In addition, its protein expression was detected on the surface of cultured primary tumor endothelial cells.

Given that non-myofilament associated cTnT could induce apoptosis in non-muscle cells, we hypothesize that cTnT expression in vascular endothelial cells will increase with aging and AD pathogenesis, which subsequently affects endothelium integrity and function. In the current study, using aging and AD mouse models and cultured mouse brain vascular endothelial cells, we reveal (1) cTnT mRNA expression in mouse brain increases with aging and AD pathogenesis; (2) cTnT protein is expressed in brain vascular endothelial cells and its level increases with aging and AD pathogenesis; (3) a higher level of apoptosis exists in the brain of old or AD mice, which is mainly found in cTnT positive cells; and (4) adeno-associated virus serotype 2 (AAV2) is efficient in cultured endothelial cells, while AAV9-mediated cTnT gene expression driven by CMV (universal) or tMCK (skeletal muscle specific) promoter is only successful in cultured C2C12 skeletal muscle cells, but not in cultured brain vascular endothelial cells. Our findings indicate that cTnT may be a potential target to prevent aging and AD associated decline in vascular endothelium function. In addition, AAV2-mediated gene delivery will be an appropriate tool for vascular endothelial cell cTnT targeting.

**13.10**

## SIRT-1 OVEREXPRESSION MITIGATES LARGE ARTERY STIFFENING WITH ADVANCING AGE

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Advancing age is associated with large artery stiffening that is accompanied by lower expression of the cellular deactylase, sirtuin-1 (SIRT-1). Interventions such as lifelong caloric restriction prevent much of the age-related increase in larger artery stiffness while preserving SIRT-1 expression. The aim of this study was to determine if lifelong overexpression of SIRT-1 would attenuate age-related large artery stiffening. Aortic pulse wave velocity (PWV), the gold-standard measurement of large artery stiffness, was measured in SIRT-1 transgenic ($SIRT^{TG}$) overexpressing and wild-type (WT) littermate control mice developed on a C57BL/6 background. PWV measurements were performed at 3 month intervals from 3-24 months of age. Histological assessment of elastin and collagen content of the aortic wall was completed in young (5-6 mo), middle-age (10-12 mo) and old (22-24 mo) $SIRT^{TG}$ and WT mice (n=3-15/group). Elastin and collagen content were normalized to young WT mice. All animal procedures were in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the University of Utah and Salt Lake City Veterans Affairs Medical Center. Although aging was strongly correlated with PWV in both WT and $SIRT^{TG}$ mice (R=0.72 and 0.60, respectively, P<0.0001), there was a significantly greater rate of large artery stiffening with age in WT mice (slope±SEM: 3.5±0.3 $cm \cdot s^{-1} \cdot mo^{-1}$) compared to $SIRT^{TG}$ mice (2.3±0.3 $cm \cdot s^{-1} \cdot mo^{-1}$; P<0.05). Compared to young and middle-age WT mice, elastin content was ~17-18% lower and collagen content was 34-43% higher in old WT mice (P<0.05). Unlike WT mice, there was no age-related change in elastin or collagen in $SIRT^{TG}$ mice (P>0.05). These results demonstrate that SIRT-1 overexpression mitigates age-related large artery stiffening and this is concomitant with the prevention of age-related changes in aortic wall elastin and collagen content.

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**13.11**

## ADVANCED AGE DOES NOT AFFECT THE MAGNITUDE OF CURRENTS THROUGH CAV1.2 VOLTAGE-GATED $CA^{2+}$ CHANNELS IN SMOOTH MUSCLE CELLS FROM MURINE SUPERIOR EPIGASTRIC ARTERIES

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Smooth muscle cells (SMCs) from superior epigastric arteries (SEAs) of male C57BL/6 mice display spontaneous transient outward currents (STOCs) and their amplitude is elevated at positive membrane potentials in Old (24 mo) vs. Young (3 mo). The purpose of this study was to test the hypothesis that aging was also associated with an increase in CaV1.2 voltage-gated $Ca^{2+}$ channel (VGCC) current density that might account for the increase in STOC amplitude. Using whole-cell perforated patch recording in SEA SMCs isolated from Young or Old, the CaV1.2 VGCC blocker nifedipine (1μM) decreased the frequency of STOCs at a holding potential of +30 mV. In Young, this effect was from 4.1±0.7 to 2.5±0.6 Hz (n=9, p<0.05) and in Old from 3.5±1 to 1.8±0.5 Hz (n=10, p<0.05). There was no significant effect on STOC amplitude in either age group (p>0.05). Similarly, the CaV1.2 VGCC agonist, BayK8644 (50nM) increased STOC frequency from 6±0.8 to 9.4±1.6 Hz (n=10, p<0.05) in Young and from 5.9±1.4 to 9.8±1.7 Hz (n=10, p<0.05) in Old, again with no effect on STOC amplitude (p>0.05). Thus, $Ca^{2+}$ influx through CaV1.2 VGCCs controls

STOC frequency, but not STOC amplitude. Nifedipine-sensitive $Ba^{2+}$ current densities at +30 mV were -0.48±0.3 pA/pF (n=13) in SMCs from Young and -0.85±0.26 pA/pF (n=13) in SMCs from Old (p>0.05 vs. Young). Similarly, BayK8644-stimulated current densities at +30 mV were -3.9±0.6 pA/pF (n=16) in SMCs from Young and were -4.0±0.7 pA/pF (n=16) in SMCs from Old (p>0.05 vs. Young). Our data refute the hypothesis that increased currents through CaV1.2 VGCC account for the increased STOC amplitude that is observed in SEA SMCs from Old. Supported by NIH R01HL086483.

**13.12**

**T CELL DEPLETION IMPROVES ARTERIAL FUNCTION IN BOTH LARGE ELASTIC ARTERIES AND RESISTANCE ARTERIES OF OLD MICE**

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T cells have been shown to mediate arterial dysfunction in experimental hypertension. Both large arteries and resistance vessel beds exhibit a marked increase in infiltrating T cells in old mice. To determine whether T cells directly mediate age-related arterial dysfunction, we depleted T cells in old mice (22-24 months) using anti-CD3 F(ab'2) fragments (150µg, i.p. every 7 days for 28 days), control mice received isotype control antibody fragments (n = 9/group). Mice treated with anti-CD3 F(ab')2 exhibited an ~50% reduction in circulating and splenic T cells compared to mice receiving isotype control. T cell numbers in both the aorta and mesentery were >60% lower in anti-CD3 F(ab')2 treated mice compared to controls as assessed by flow cytometry. To determine whether T cell depletion influences large elastic artery stiffness, we assessed pulse wave velocity (PWV) before and after 28 days of treatment with anti-CD3 F(ab')2 or isotype control. Before initiation of treatment (day 0), PWV was similar compared to the isotype control group (319 ± 4 vs. 328 ± 5 cm/s). At day 28, PWV was modestly elevated in control mice and decreased ~15% in anti-CD3 F(ab')2 treated mice (347 ± 12 vs. 298 ± 5 cm/s). These changes were independent of altered systolic blood pressure as measured at 28 day by tail cuff (F(ab')2: 147±4 vs. Isotype: 140±6 mmHg). To determine whether T cells play a role in resistance artery dysfunction with aging, we assessed acetylcholine mediated endothelium-dependent dilation (EDD) in isolated, cannulated 2nd order mesenteric arterioles. Arterioles from old anti-CD3 F(ab')2 treated mice exhibited improved EDD compared to old controls (44 ± 6% vs. 29 ± 4% maximal dilation). These differences were abolished in the presence of the nitric oxide (NO) synthase inhibitor L-NAME (22 ± 7% vs. 17 ± 4% maximal dilation), suggesting that the improvement in EDD with T cell depletion was due to improvements in NO bioavailability. In summary, after pharmacological T cell depletion, old mice exhibited decreased PWV and increased resistance vessel EDD and NO bioavailability. Collectively, these data suggest an important causal link between T cells and both age-related large artery stiffening and impaired EDD in resistance arteries.

**13.13**

**MECHANISMS OF IMPAIRED DEOXYGENATION-INDUCED RED BLOOD CELL ATP RELEASE IN OLDER ADULTS: ROLES OF CELL DEFORMABILITY AND CAMP**

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Red blood cells (RBCs) release ATP upon deoxygenation, which binds to endothelial purinergic receptors and stimulates conducted vasodilation. As local tissue metabolic demand increases, ATP release increases in direct proportion to the degree of hemoglobin (Hb) deoxygenation, thus allowing RBCs to both detect and initiate a vascular response to imbalances between oxygen supply and demand. We have recently demonstrated that RBC ATP release is impaired in older adults, but the underlying mechanism is unclear. Using isolated RBCs from young (Y) and older (O) adult humans, we tested the hypothesis that changes in RBC deformability (Y: 23±1 yrs, n = 13-15; O: 65±3 yrs, n = 10-14) and cAMP signaling (Y: 27±1 yrs, n = 9; O: 65±2 yrs, n = 9) contribute to age-related impairments in ATP release during Hb deoxygenation. Isolated RBC ATP release during normoxia ($PO_2$ ~112mmHg) and hypoxia ($PO_2$ ~20mmHg) was quantified using the luciferin-luciferase technique following RBC incubation with either Y-27632 (Rho-kinase inhibitor to increase deformability), diamide (cell-stiffening agent), cilostazol (phosphodiesterase 3 (PDE3) inhibitor), or vehicle control (saline or dimethylformamide). RBC transit time (RCTT), an index of deformability where lower values indicate greater deformability, was measured using a blood filtrometer to determine the effects of age and drug on RBC deformability (Y-27632 and diamide; n = 9 per age group). On average, the relative change in ATP release from normoxia to hypoxia in vehicle control conditions was significantly less in RBCs from O compared with Y (~50% vs ~120%; $P<0.05$). RBCs from O were also less deformable than from Y (RCTT: 8.541±0.050 vs. 8.234±0.098 (a.u.), respectively, $P<0.05$). Y-27632 improved RBC ATP release (111.7±17.2%) and deformability (RCTT: 8.228±0.083) in O adults such that neither were different from the Y control ($P>0.05$), whereas diamide decreased RBC ATP release (67.4±11.8%) and deformability (RCTT: 8.955±0.114) in Y adults such that they were similar to O control. Cilostazol did not change ATP release vs. control in O (69.1±12.3%) or Y (145.1±28.3%) adults ($P>0.05$), thus the impairment with age persisted. We conclude that decreased RBC deformability, but not altered cAMP hydrolysis via PDE3, is a primary contributor to age-related impairments in RBC ATP release, and that this may have implications for impaired vascular control with advancing age.

Support HL119337, F31HL126377

13.14

## AGING ENHANCES ATRIAL FIBRILLATION INDUCIBILITY IN ATHEROSCLEROTIC HOSTS

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Introduction and Rationale Advanced age is the most critical factor for the development of atrial fibrillation (AF); 10% of patients in their 80s have AF and 50% of patients with AF are 80 years of age or older (Kannel WB et al). Atherosclerosis, a chronic inflammatory condition, is also associated with AF but whether this is due to a direct inflammatory alteration or indirectly via atrial remodeling and fibrosis from associated conditions such as hypertension is not known. However, the interplay between aging, atherosclerosis, and AF has not been explored. Here, we examined the effects of a high fat diet (HFD), intended to promote atherosclerosis, and aging on AF inducibility in *Ldlr*$^{-/-}$ mice.

Methods and Results After programmed electrical stimulation in the right atrium via intravenous catheterization, only 4/10 young (2-4 months of age) chow-fed *Ldlr*$^{-/-}$ mice exhibited AF, whereas 9/10 young HFD-fed *Ldlr*$^{-/-}$ mice exhibited AF (Figure 1). Interestingly, 2 of 10 young *Ldlr*$^{-/-}$ mice fed a HFD exhibited sustained AF (2 hrs), suggesting that a minority of mice fed a HFD for 2 months not only exhibit AF inducibility but sustainability. Under the same protocol, only 1/6 young chow-fed *Ldlr*$^{-/-}$ mice exhibited AF, in striking contrast to aged (15-16 months of age) chow-fed *Ldlr*$^{-/-}$ mice that exhibited AF in 4/6 mice (Figure 2). Atrial cardiomyocytes from old, but not young *Ldlr*$^{-/-}$ mice, exhibited delayed after depolarizations (DADs) and increased propensity for spontaneous calcium release. We next generated bone marrow chimeras of young and aged *Ldlr*$^{-/-}$ mice by lethally irradiating mice and infusing them with aged-matched or mismatched bone marrow from *Ldlr*$^{-/-}$ donors, as reported in our prior work (Du W et al). Intriguingly, 3 of 4 young chow-fed *Ldlr*$^{-/-}$ mice that received aged bone marrow exhibited AF inducibility, whereas transplantation of young bone marrow into aged chow-fed *Ldlr*$^{-/-}$ mice reduced AF inducibility to 1/6 mice (Figure 2).

Conclusions Atherosclerosis and aging enhance AF inducibility, likely due to hematopoietic factors, in atherosclerotic-prone hosts.

References: Kannel WB, et al., *Am J Cardiol* 1998. Du W, et al. *Aging Cell* 2016, 15:766-777

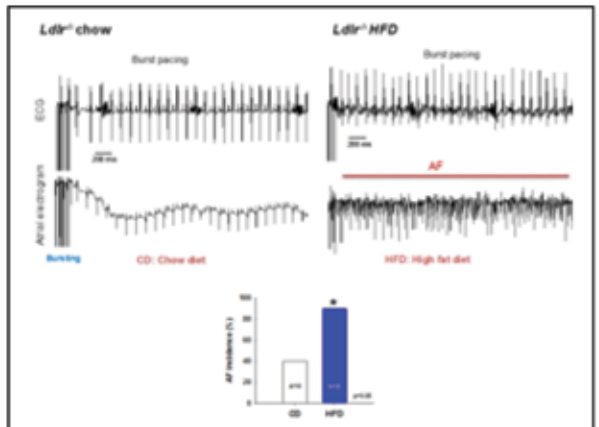


**Figure 1. HFD induces AF susceptibility in young *Ldlr*$^{-/-}$ mice.** Young (2 mo of age) *Ldlr*$^{-/-}$ mice were fed a HFD diet for 2 mo or maintained on a chow diet. At this point, mice underwent electrical stimulation of the R atria and surface and intra-atrial ECG were recorded. Bottom: significantly increased AF inducibility in mice on HFD vs Chow.

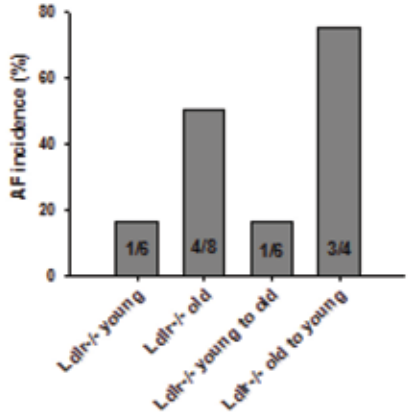


**Figure 2. AF incidence is greater in aged than young *Ldlr*$^{-/-}$ mice, AF incidence is greater in aged than young *Ldlr*$^{-/-}$ mice,** but young mice with old bone marrow have increased AF incidence, whereas old mice with young bone marrow have reduced AF incidence.

13.15

## MECHANISMS OF IMPAIRED SKELETAL MUSCLE HEMODYNAMICS DURING CONTINUOUS NON-STEADY STATE EXERCISE AND RECOVERY IN AGING HUMANS

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Blood flow to exercising skeletal muscle is typically reduced with age; however, our understanding of this impairment in humans is largely limited to investigations of steady-state hemodynamics. Here, we continuously measured forearm blood flow (FBF; Doppler ultrasound) and calculated forearm vascular conductance (FVC; FBF/mean arterial pressure) in 14 young (23 ± 1 yrs) and 14 older (67 ± 2 yrs) adults during 3 min of rhythmic handgrip exercise and 2 min of recovery. Subjects performed two randomized, continuous, non-steady state exercise trials: 90 sec at either a low or high workload (10% or 20% of maximum voluntary contraction) followed immediately by transition to the other workload for 90 sec. Thus, subjects completed a low-to-high (L2H) and a high-to-low (H2L) intensity transition. FBF and FVC were quantified in 3 sec bins and cumulative area under the curve (AUC) was calculated throughout. In the L2H trial, vasodilation during the initial workload was reduced ~40% in older compared with young adults (FVC AUC: 72 ± 10 vs. 117 ± 11 ml·100 mmHg$^{-1}$), and the impairment persisted throughout transition to the high workload (236 ± 30 vs. 373 ± 35 ml·100 mmHg$^{-1}$) and recovery (353 ± 49 vs. 550 ± 58 ml·100 mmHg$^{-1}$; all $P$<0.05). A similar age impairment was observed during the first H2L workload (FVC AUC older: 123 ± 13; young: 212 ± 24 ml·100 mmHg$^{-1}$), which continued through the low workload (289 ± 35 vs. 454 ± 49 ml·100 mmHg$^{-1}$) and recovery (357 ± 43 vs. 557 ± 63 ml·100 mmHg$^{-1}$; all $P$<0.05). After 90 sec of exercise, FBF was 30 to 60 ml (L2H and H2L, respectively) lower in older adults and the cumulative age-related deficit increased to ~130 ml by the end of recovery in both trials. In follow-up studies, 2 g of oral ascorbic acid did not improve FBF or FVC in older adults (n=8) during exercise or recovery, and local inhibition of nitric oxide (NO) and prostaglandins (PGs) in young adults (n=12; intra-arterial L-NMMA and ketorolac, respectively) did not affect FBF or FVC beyond the first minute of exercise. We conclude that impaired vasodilation and the magnitude of the blood flow deficit in older adults performing non-steady state exercise increase over time and are not explained by NO or PGs. These findings may have implications for muscle perfusion during activities of daily living in older adults, and the primary mechanisms underlying this age-related impairment remain to be determined.

Supported by NIH HL119337.

**13.16**

**METABOLIC SYNDROME AND ADVANCING AGE ALTER CORONARY SMOOTH MUSCLE CELL CALCIUM HANDLING SIMILARLY IN OSSABAW MINIATURE SWINE**

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**Introduction:** Age is a non-modifiable risk factor for coronary artery disease (CAD). Other modifiable risk factors such unhealthy diet can lead to metabolic syndrome (MetS), which is associated with a greater risk of developing CAD. $Ca^{2+}$ regulation is pivotal to coronary smooth muscle (CSM) function. Our lab recently found that calcium handling in CSM is dysregulated in CAD in a biphasic manner, with sarcoplasmic reticulum (SR) $Ca^{2+}$ store increased in early CAD and decreased in late CAD. Aging is associated with increased $Ca^{2+}$ influx and a greater SR store, similar to $Ca^{2+}$ handling changes observed in CAD. However, $Ca^{2+}$ handling in aging and MetS-induced CAD have yet to be compared. Using Ossabaw miniature swine with MetS-induced CAD, we tested the hypothesis that calcium handling in aged lean swine will more closely resemble calcium handling in young swine with MetS vs. young lean swine.

**Methods:** Young Ossabaw swine (age 2-3.5 years) were placed on either a lean diet or an atherogenic diet. Young swine and aged lean Ossabaw swine (age 7-13 years) were euthanized and coronary arteries were excised from the hearts. CSM cells were enzymatically dispersed from freshly dissected conduit coronary arteries, loaded with the fluorescent $[Ca^{2+}]_i$ indicator fura-2, and $Ca^{2+}$ handling studied in a constant-flow superfusion chamber. Membrane depolarization with an 80 mM $K^+$ solution induced $Ca^{2+}$ influx via voltage-gated calcium channels (VGCCs) and loaded the SR store. Caffeine-induced SR store release and undershoot after removal of caffeine (SR $Ca^{2+}$ pump [SERCA] activity) were measured. Extrusion by plasmalemmal transporters was determined by examining the time to restore $[Ca^{2+}]_i$ levels to half of the caffeine-induced peak. VGCC activity was calculated as the slope of $Ba^{2+}$ influx during superfusion with a 2 mM $Ba^{2+}$ solution.

**Results:** Young MetS swine had significantly higher body weight and cholesterol levels than young lean swine and aged lean swine, indicating MetS. IVUS analysis also revealed that disease severity was comparable in young MetS swine and aged lean swine. However, young MetS swine showed significantly higher SR store release as compared to young lean controls. This difference was exacerbated in lean aged swine. Aged swine also had significantly attenuated SERCA activity than both young lean swine and young MetS swine, while young MetS swine only trended towards impaired SERCA function when compared to young lean swine. Both young MetS and aged lean swine had significantly higher $Ca^{2+}$ influx when compared to young lean swine. However, extrusion mechanism function as measured by time to half recovery did not differ between groups.

**Conclusion:** Overall, aged lean swine show more similar $Ca^{2+}$ handling to young MetS swine, rather than young lean swine. In fact, many of the $Ca^{2+}$ handling changes are exacerbated in aged lean swine, indicating that age may be a greater factor in CAD-related $Ca^{2+}$ handling dysfunction than modifiable cardiometabolic risk factors that give rise to MetS-induced CAD.

**13.17**

**HEALTHY AGING CONVERGES ON A CONSERVED KLF-AUTOPHAGY PATHWAY**

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A hallmark of aging is loss of organelle quality control and proteostasis secondary to reduced autophagy. While autophagy, a fundamental mechanism involved in degradation and recycling of dysfunctional cellular components has established pro-longevity effects, our understanding of molecular mechanisms governing autophagy under diverse aging paradigms remains incompletely understood. Here we show that a family of transcriptional regulators termed Kruppel-like factors (KLFs), are both necessary and sufficient to determine lifespan through control of autophagy in C. elegans and modulate mammalian vascular age-associated phenotypes. Overexpression of C. elegans klf-1 and klf-3 is sufficient to extend lifespan in an autophagy-dependent manner. Additionally, KLFs are necessary for lifespan extension and autophagy across mechanistically distinct longevity models. We further identify a mammalian KLF, KLF4, which also regulates autophagy in mouse embryonic fibroblasts (MEFs), and demonstrate that a KLF4-autophagy pathway may have functional consequences for mammalian longevity. Specifically, increased levels of endothelial restricted KLF4 attenuates age-related loss of vessel compliance, a characteristic age-associated phenotype in mammals, and this effect is dependent on autophagy. Finally, we provide evidence that transcript abundance of KLF4 in human vessels decreases with age. Thus, the KLFs are nodal regulators of autophagic activity and have longevity promoting effects during the aging process.

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**13.18**

**ESTROGEN TREATMENT AND CELLULAR SENESCENCE ON PROTEOSTASIS MAINTENANCE IN ENDOTHELIAL CELLS**

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The heat shock response (HSR) is an important cytoprotective mechanism necessary to maintain normal protein homeostasis, and an essential protective response to cellular stress and injury. While a reduction in the HSR in senescent cells has been previously reported, work has been limited to senescent fibroblasts. Given the prevalence of oxidative injury in the aging cardiovascular system, we investigated whether senescent human coronary artery endothelial cells have loss of the HSR and impaired proteostasis, and whether the cytoprotective hormone, 17-beta estradiol (E2), which we previously have found to indirectly increase HSP expression, can mitigate these changes. We found that the senescent (SEN) endothelial cells had a diminished HSR, and also had more protein aggregates than young, early passage (EP) cells. In addition, although E2 treatment did not affect the amount of protein aggregates in either EP or SEN cells, it was able to increase the HSR in EP cells. However, the HSR in senescent cells was unaffected by E2. In sum, aging and senescence in adult human EC is accompanied by a blunting of the HSR and an increase in protein aggregation. E2 did not mitigate these changes in the aging endothelial cells.

**13.19**

**REDUCED GLYCOLYSIS AND INCREASED OXYGEN CONSUMPTION WITH AGING IN ENDOTHELIAL CELLS**

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Age-associated vascular endothelial dysfunction is a hallmark of cardiovascular disease (CVD) and is known to be associated with increased arterial oxidative stress. The mitochondria are believed to be an important source of superoxide contributing to age-associated endothelial dysfunction, however the effect of aging on vascular endothelial mitochondrial function *per se* is not clear. In this present study, we utilized Seahorse$^{TM}$ technology to assess mitochondrial respiration, via changes in the oxygen consumption rate, and glycolysis, via the extracellular acidification rate. We studied cultured primary lung endothelial cells (ECs) from *young and old C57BL/6 mice* as well as in early (P3) and late (P17) passage human umbilical vein endothelial cells (HUVEC), a cell culture model of aging. *We found that* old primary ECs demonstrate a 36% higher rate of oxygen consumption ($p<0.0001$), 11% higher basal respiration ($p<0.01$), 92% higher proton leak

($p<0.0001$), and 74% higher spare respiration ($p<0.0001$) compared with young primary ECs. In contrast, ATP production was 27% ($p<0.0001$) lower in old compared with young primary ECs. We further demonstrated that mitochondrial extracellular acidification rate is 47% lower ($p<0.0001$) and maximal glycolytic capacity was 21% lower ($p<0.0001$) in old compared with young primary ECs. We found similar differences for all variables in late vs. early passage HUVECs as for old vs. young primary ECs. Taken together, our findings suggest that there is a shift in energy production away from glycolysis toward a greater reliance on the mitochondria in old ECs. This higher mitochondrial oxygen consumption in concert with lower rates of ATP production in old ECs may contribute to increased mitochondrial superoxide production and subsequent endothelial dysfunction, a possibility requiring further elucidation.

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**13.20**

**ALTERED MITOCHONDRIAL RESPONSES TO NITRIC OXIDE SYNTHASE INHIBITORS IN ISOLATED CARDIAC MITOCHONDRIA FROM YOUNG AND AGED RATS.**

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Mitochondria have been shown to express a unique nitric oxide (NO) producing nitric oxide synthase (NOS) enzyme named mtNOS. However, the exact pathophysiological role of mtNOS has not been examined. Furthermore, the impact of aging on mtNOS is unclear. The objective of the present study was to examine the impact of aging on the mitochondrial effects of NOS inhibitors. Mitochondria from the hearts of young (10 weeks) and middle-aged Sprague Dawley (18 month) rats were isolated by gradient separation. ARL-17477, pharmacological inhibitor of neuronal NOS (1 μmol/L) and NIO, pharmacological inhibitor of eNOS (0.5 μmol/L) were utilized. Mitochondrial oxygen consumption rates by the Seahorse Bioscience Analyzer in isolated cardiac mitochondria were measured in response to ATP synthase inhibitor (Oligomycin, 4 μmol/L), ionophore (FCCP, 4 μmol/L), and electron transport inhibitors (antimycin and rotenone; □8mol/L and 4 μmol/L each). Isolated mitochondria from old rat hearts showed increased basal respiration (oxygen consumption rate, OCR pmol/min; 95±10 vs 60±12), proton leak (72±24 vs 23±6), decreased maximal respiration (371±54 vs 552±70) accompanied by reduced reserve respiratory capacity (372±50 vs 536±75) compared to that of young rats suggesting increased uncoupling in the aged mitochondria (n=6 pairs of animals each). ARL treatment did not affect mitochondrial basal respiration in both young and aged rats but significantly increased proton leak (110±25 vs 23±6) and decreased ATP production (235±26.5 vs 149±23) in mitochondria only from young rats. ARL treatment tends to correct the decreased maximal respiration (480±55 vs 371±54) and reserve respiratory capacity (451±51 vs 373±50) in mitochondria from aged rats. NIO treatment exerted similar effects as that of ARL, except it increased proton leak from both the young and aged mitochondria. Thus, mtNOS was sensitive to both eNOS and nNOS inhibitors and possibly mediate the transition to aging mitochondrial phenotype.

This work is supported by: NIH grant (NS094834) and AHA Scientist Development Grant (14SDG20490359).

**13.21**

**ACUTE LYSYL OXIDASE INHIBITION AUGMENTS ENDOTHELIUM-DEPENDENT VASODILATION IN YOUNG, BUT NOT MIDDLE-AGED, MEN AND WOMEN.**

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The lysyl oxidase family of enzymes (lysyl oxidase (LOX) and the lysyl oxidase-like (LOXL) 1-4 isoforms) catalyzes the formation of collagen cross-linking in the vasculature. LOX is regulated within a narrow physiological window where upregulation of LOX increases vascular stiffness, making LOX a potential molecular target in vascular remodeling, while downregulation of LOX is associated with endothelial dysfunction. *In vivo* human research on the LOX family is scarce due to the risks associated with prolonged systemic LOX inhibition. The cutaneous microvasculature is a safe and appropriate vascular bed to examine LOX inhibition *in vivo,* due to the localized techniques to facilitate delivery of compounds directly to the skin microvasculature (intradermal microdialysis). Further, age-associated changes in endothelial function are observable in the cutaneous microvasculature and representative of systemic microvascular endothelial dysfunction in both mechanism and magnitude. Our objective was to locally inhibit LOX and LOXL 1-4 in the cutaneous microvasculature to delineate (1) the role of LOX in microvascular endothelial function and (2) age-associated changes in LOX function. Two intradermal microdialysis fibers were placed in the forearm of 10 young (24±1 y) and 10 middle-aged (50±2 y) healthy men and women. Sites were continuously perfused with (1) BAPN to inhibit LOX and LOXL 1-4 and (2) lactated Ringer's to serve as control; a dose response to the endothelium-dependent agonist acetylcholine (ACh: $10^{-10}$-$10^{-1}$ M) was performed. Red cell flux was measured via laser Doppler flowmetry and normalized to cutaneous vascular conductance (CVC: flux•MAP$^{-1}$) and expressed as a percentage of site-specific maximum vasodilation (%$CVC_{max}$; sodium nitroprusside 50 mM + local heating to 43°C). Data were curve modeled as four parameter logistic regressions and the Log EC50's compared to determine a change in vasodilator sensitivity. LOX inhibition increased sensitivity to ACh in the young group (LogEC50 ACh: -3.65, ACh + BAPN: -4.34; $p=0.03$). In contrast, there was no change in sensitivity to ACh in the middle-aged group with BAPN (LogEC50 ACh: -3.41, ACh + BAPN: -3.74; $p=0.47$). These *in vivo* human data

demonstrate that LOX plays a role in attenuating vasodilator sensitivity to ACh in young men and women, but this effect is lost by middle age. This suggests that the LOX family of enzymes play a functional role in the cutaneous microvasculature and that the actions of LOX are age-dependent.

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**13.22**

**THE EFFECTS OF TWO WEEKS OF REDUCED DAILY ACTIVITY ON THE SKELETAL MUSCLE MICROVASCULAR FUNCTION OF ELDERLY MEN**

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The prolonged lack of physical activity in elderly adults increases the risk for the development of chronic metabolic diseases including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Even short-term periods of inactivity can significantly impair glycemic regulation and cause obvious muscle loss (sarcopenia). It is now apparent that the skeletal muscle microvasculature plays a critical role in establishing insulin sensitivity by controlling both delivery and access of insulin and glucose to the musculature, however, the effect of these periods of inactivity on skeletal muscle capillary recruitment is relatively unknown. The purpose of the present study was to determine if a two-week reduction in daily step count, in elderly individuals, would induce alterations in measures of skeletal muscle microvascular perfusion and whether unilateral resistance exercise (EX) countermeasures, completed during the step reduction (SR) period, could prevent possible microvascular impairments. Healthy, elderly male participants (age= 69 ± 3 years; N=17) were assessed following two weeks of daily step count reductions to ~1500 steps/day. Unilateral lower limb resistance exercise was performed every second day during the period of reduced activity. After the 2 week intervention, simultaneous assessment of vastus lateralis microvascular function was completed simultaneously in both legs using contrast enhanced ultrasound (CEUS). Interestingly, there were no detectable differences between the two legs (SR vs EX) at rest when analyzed for total area under the curve (785±88 vs 889±95), wash-in slope (0.19±0.02 vs 0.19±0.02 dB/s), peak wash-in slope (0.41±0.05 vs 0.44±0.07 dB/s), peak intensity (9.2±1.0 vs 10.6±1.1 dB) and time to peak (64.0±6.7 vs 61.1±4.6 s). These results suggest that for elderly men resistance training countermeasures were unable to enhance capillary perfusion. The vascular assessments were completed at rest, without a specific microvascular stimulus, such as insulin or acute exercise, and this could have resulted in the underestimation of overall vascular function. Further investigation is required to determine the level and type of activity required to maintain long-term vascular health in elderly individuals exposed to periods of inactivity for an extended length of time.

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**13.23**

**EFFECT OF INTRALUMINAL PRESSURE ON VASCULAR SMOOTH MUSCLE CONTRACTILITY IN AGED SKELETAL MUSCLE RESISTANCE ARTERIES**

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Objective: We tested the hypothesis that exposure to an acute increase in intraluminal pressure improves vascular smooth muscle (VSM) contractility in aged skeletal muscle resistance arteries.

Methods: Soleus muscle feed arteries (SFA) from young (4 mo) and old (24 mo) Fischer 344 rats were cannulated with glass micropipettes and endothelial cells were removed (denuded) by passing 5 ml of air through the lumen of the vessel. SFA were then pressurized to 90 $cmH_2O$ or 130 $cmH_2O$ for 1 h. At the end of the 1-h treatment, intraluminal pressure in all arteries was set to 90 $cmH_2O$ for examination of VSM contractile function. Contractile responses were assessed using increasing whole log doses of norepinephrine (NE; $10^{-9}$-$10^{-4}$ M), angiotensin II (Ang II; $10^{-11}$-$10^{-7}$ M), and phenylephrine (PE; $10^{-9}$-$10^{-4}$ M). To assess the role of the RhoA pathway, VSM constrictor responses were assessed in the absence or presence of a RhoA-Kinase inhibitor (Y27632; $10^{-6}$ M).

Results: Constrictor responses of denuded SFA to PE and Ang II were significantly impaired in Old SFA relative to young SFA, whereas constrictor responses to NE were preserved. In the presence of Y27632, to inhibit Rho Kinase, constrictor responses to NE, Ang II, and PE were significantly blunted in young and old denuded SFA. In addition, the age-group difference in constrictor responses to Ang II was eliminated. Treatment of old SFA with an acute (1h) increase in intraluminal pressure resulted in impaired (not improved) VSM constrictor responses to NE, PE and Ang II.

Conclusion: The results of this study indicate that VSM contractile function declines with age due, in part, to impaired RhoA-signaling. Contrary to our hypothesis, treatment with an acute increase in intraluminal pressure did not improve VSM contractile function in aged SFA.

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**13.24**

## SIRT1 NEGATIVELY REGULATES INFLAMMATION AND AGING-INDUCED ENDOTHELIAL BARRIER DYSFUNCTION

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Aging is a major risk factor for endothelial barrier dysfunction and vascular hyperpermeability, which contributes to the development and progression of cardiovascular disease. Aging is associated with chronic low-grade systemic inflammation and inflammatory signaling leads to increased endothelial barrier permeability. Sirtuins, NAD-dependent deacetylases, are tightly associated with aging and longevity from yeast to mammals. Deletion of Sirtuin 1 (Sirt1) results in upregulation of acetylated NFκB and increased inflammatory responses, while SIRT1 activators reverse age-related vascular endothelial dysfunction and inflammation. Despite an established relation between SIRT1 and vascular aging, how sirtuins regulate endothelial barrier function is poorly understood. To study the role of sirtuins in endothelial permeability with aging, we examined primary mouse lung endothelial cells (MLECs) isolated from young (4-6 months) and old (24 months) SIRT1 transgenic overexpressing ($SIRT1^{TG}$) and wildtype (WT) littermate mice with electric cell-substrate impedance sensing (ECIS), an in vitro continuous monitoring system that quantifies attachment and spreading of cells. In WT mice, MLECs from old mice were 80% more permeable than MLECs from young mice ($p<0.0001$). Whereas MLECs from young $SIRT1^{TG}$ mice were 18% less permeable than MLECs from age-matched WT mice ($p<0.005$). To examine the impact of aging and SIRT1 overexpression on the cytokine-induced impairments in barrier function, MLECs were incubated with TNFα (2ng/ml; 20 hrs) or IL-1β (10ng/ml; 40 hrs). TNFα-induced permeability was 5% greater in MLECs from old compared with young mice ($p<0.001$). SIRT1 overexpression appears to protect against the age-associated increase in cytokine-induced endothelial permeability, as IL-1β induced EC permeability was 47% lower in MLECs from young $SIRT1^{TG}$ mice compared with age-matched WT mice ($p<0.001$). To further confirm the role of Sirt1 in regulation of endothelial barrier function, MLECs from young WT mice were treated with the NAD+ precursor, nicotinamide mononucleotide (NMN), a Sirt1 activator. NMN treatment inhibited IL-1β induced EC permeability by 30% ($p<0.0001$). Our findings suggest that Sirt1 protects against age-related endothelial cell barrier dysfunction at baseline and in response to inflammatory stimuli.

**13.25**

## ENDOTHELIAL CELL AUTOPHAGY MAINTAINS SHEAR-STRESS-INDUCED NITRIC OXIDE GENERATION VIA GLYCOLYSIS-DEPENDENT PURINERGIC SIGNALING TO ENOS

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Endothelial cell autophagy and nitric oxide (NO) generation are compromised by aging but a mechanistic link has not been defined. Earlier we reported that genetic and pharmacological approaches that limit autophagy in bovine arterial endothelial cells (ECs) prevent shear-stress induced p-$eNOS^{S1177}$ and NO production. We sought to determine the responsible mechanism. Upon autophagy compromise in ECs exposed to shear-stress, impaired EC glucose uptake and EC glycolysis attenuated ATP production. We hypothesized that decreased glycolysis-dependent purinergic signaling via P2Y-1 receptors prevents shear-induced NO generation. Maneuvers that restore glucose transport and glycolysis (e.g. overexpression of GLUT1) or purinergic signaling (e.g. addition of exogenous ADP) rescue shear-induced p-$eNOS^{S1177}$ and NO production in ECs with impaired autophagy. Conversely, GLUT1 siRNA, impairing purinergic signaling via ectonucleotidase-mediated ATP/ADP degradation (e.g. apyrase), or by pharmacological (e.g. MRS2179) or genetic (e.g. P2Y1-R siRNA) inhibition of P2Y-1 receptors, inhibits shear-induced p-$eNOS^{S1177}$ and NO generation in ECs with intact autophagy. Supporting a central role for $PKC\delta^{T505}$in relaying the autophagy-dependent purinergic-mediated signal to eNOS, we find that: (i) shear-stress induced activating phosphorylation of $PKC\delta^{T505}$is negated by inhibiting autophagy; (ii) shear-induced p-$eNOS^{S1177}$ and NO generation are restored in autophagy-impaired ECs via pharmacological (e.g. bryostatin) or genetic (e.g. CA-PKCδ) activation of $PKC\delta^{T505}$; and (iii) pharmacological (e.g. rottlerin) and genetic (e.g. PKCδ siRNA) PKCδ inhibition prevents shear-induced p-$eNOS^{S1177}$ and NO generation in ECs with intact autophagy. Importantly, key nodes in this signaling pathway are recapitulated in human arterial endothelial cells with suppressed autophagy, and in mice with temporal deletion of Atg3 specifically in ECs. Targeted reactivation of purinergic signaling and/or PKCδ has strategic potential to restore compromised EC NO generation in the context of aging-associated autophagy suppression.

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**13.26**

## ROLE OF DAMPS IN DEVELOPMENT OF MICROVASCULAR DYSFUNCTION IN HUMAN CORONARY ARTERY DISEASE

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**BACKGROUND:** Despite decades of intense research, cardiovascular diseases associated with aging remain the leading cause of death in the western world. Microvascular endothelial dysfunction is an early indicator of future adverse cardiac events, even before onset of large vessel damage. We have shown that in subjects with coronary artery disease (CAD), microvascular flow-mediated dilation (FMD) switches from a NO-mediated to a $H_2O_2$-mediated mechanism with corresponding elevations in mitochondrial reactive oxygen species ($_{mt}$ROS). Interestingly, patients with CAD display increased mitochondrial DNA ($_{mt}$DNA) damage. We hypothesized that increased levels of circulating $_{mt}$DNA fragments, termed Damage Associated Molecular Patterns ($_{mt}$DAMPs), are responsible for the endothelial dysfunction in CAD by activating Toll Like Receptor 9 (TLR9), increasing ROS formation, and decreasing NO production.

**METHODS:** We examined the effect of increased $_{mt}$DAMPs on the mechanism of FMD in isolated human microvessels (~200µm) from patients without CAD. We also evaluated $H_2O_2$ levels (Amplex red) and eNOS (Nitric Oxide Synthase) expression in cultured endothelial cells (EC) after exposure to $_{mt}$DAMPs or a TLR9 agonist. Finally, Mito-Dendra2 mice (mitochondria-localized fluorescent protein) were used to evaluate endothelial mitochondrial fission/fusion.

**RESULTS:** Exposure to $_{mt}$DAMPs switched the mechanism of FMD from NO to $H_2O_2$ in non-CAD vessels (% Max Diameter: Control 84.7±8.2; + L-NAME: 89.4±5.5; + Peg-Cat 35.4±10.8*; N=3); increased $H_2O_2$ production; and decreased eNOS phosphorylation (Ratio Phospho/Total eNOS: Vehicle 1.60±0.27 vs $_{mt}$DAMPs: 0.04±0.004, N=4). Similar patterns were observed following treatment with a TLR9 agonist. $_{mt}$DAMPs promoted mitochondrial fission (Mitochondrial Fragmentation Count: $_{mt}$DAMPs 21.67 ± 1.31 vs. vehicle 9.8 ± 0.4; $p<0.0001$; Form Factor/ Aspect Ratio: $_{mt}$DAMPs 1.62 ± 0.04/1.77±0.02 vs. Vehicle 2.55 ± 0.08/2.54 ± 0.06; $p<0.0001$) compared to the vehicle.

**CONCLUSION:** Our data suggest that $_{mt}$DAMPs increase mitochondrial fission, increase $H_2O_2$ levels, and shift the mechanism of FMD from NO- to $H_2O_2$-dependent. We conclude that elevated $_{mt}$DAMPs are sufficient to produce a microvascular CAD phenotype.

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**13.27**

## BLOOD PRESSURE IN ELDERLY KIDNEY TRANSPLANT RECIPIENTS

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**Background:** Hypertension is a high prevalence in elderly. The association between age and hypertension after kidney transplantation and pattern of blood pressure in elderly kidney transplant recipients are unclear.

**Methods:** This is a retrospective, closed cohort study conducted in kidney transplantation recipients during 12-month period. A total of 70 patients were divided into 2 age groups: < 60 and ≥60 years old. Post-transplant hypertension is defined by systolic or diastolic blood pressure (SBP or DBP) ≥140 or 90 mmHg, respectively.

**Results:** Of all 70 patients, mean age±SEM was 52.66±1.43 years. The majority of the patients were male (41 patients, 58.6%). Since there are many variability in blood pressure measurement during early post-transplant period, blood pressure was started reviewed from 4 weeks post-transplant and then at 12, 24, 36, and 48 weeks post-transplantation. Relative risk was used to measure the association between the patients' age and hypertension (Table 1). Older age group appears to have greater risk of systolic hypertension then younger age group (except at 4 weeks post-transplantation); whereas, they had lower risk for diastolic hypertension. Although, the elderly-hypertension association during different time post-transplant were not statistically significant, the association of elderly and post-transplant hypertension both systolic and diastolic were significant at 24 weeks post-transplantation as well as systolic hypertension at 36 weeks post-transplantation. By using heterogeneity effects method, body mass index (BMI) is a potential effect measure modification between old age and post-transplant hypertension.

**Conclusion:** Compared to younger age kidney transplant recipients, older age patients are at higher risk for systolic hypertension and appear to have lower DBP. This pattern seems to be similar to non-transplant elderly patients.

**Table 1:** Association between 2 different patient groups stratified by age and hypertension.

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; RR, relative risk; SBP, systolic blood pressure

* Statistical significance

# Stratum-specific estimates of relative risk by body mass index

| Post-transplant (weeks) | SBP | | | DBP | | |
|---|---|---|---|---|---|---|
| | RR | CI | P-value | RR | CI | P-value |
| 4 | 0.875 | 0.398-1.922 | 0.787 | 0.156 | 0.022-1.103 | 0.027 |
| 12 | 1.286 | 0.681-2.428 | 0.587 | 0.361 | 0.093-1.555 | 0.199 |
| 24* | 1.985* | 1.107-3.560 | 0.048 | 2.695* | 1.697-4.280 | 0 |
| - BMI < 25 | 1.600 | 0.472-5.420 | 0.587 | 0 | | |
| - BMI ≥ 25 | 2.133 | 1.069-4.258 | 0.055 | 0.640 | 0.206-1.991 | 0.503 |
| 36 | 1.686 | 0.840-3.384 | 0.225 | 0.265 | 0.037-1.914 | 0.262 |
| 48* | 2.166* | 1.095-4.282 | 0.065 | 0.265 | 0.037-1.914 | 0.262 |
| - BMI < 25 | 2.333 | 0.300-18.146 | 0.465 | | | |
| - BMI ≥ 25 | 1.968 | 0.965-4.016 | 0.101 | | | |

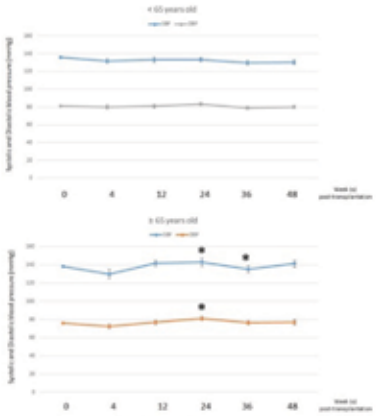

Figure 1: Mean and SEM for SBP and DBP in patients age <65 and ≥ 65 years old after kidney transplantation
* Statistical significance

# 14.0 SYMPOSIUM: MITOCHONDRIA: THE EPICENTER OF AGING RELATED CARDIOVASCULAR DEFECTS

## 14.1

### THE REQUISITE ROLE OF MITOCHONDRIA IN INTERACTIONS BETWEEN CARDIAC MYOCYTES AND THE CORONARY VASCULATURE

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Mitochondrial dysfunction in obesity and diabetes can be caused by excessive production of free radicals, which can damage mitochondrial DNA. Because mitochondrial DNA plays a key role in the production of ATP necessary for cardiac work, we hypothesized that mitochondrial dysfunction, induced by mitochondrial DNA damage, uncouples coronary blood flow from cardiac work. Myocardial blood flow (contrast echocardiography) was measured in Zucker lean (ZLN) and obese fatty (ZOF) rats during increased cardiac metabolism (product of heart rate and arterial pressure, i.v. norepinephrine). In ZLN increased metabolism augmented coronary blood flow, but in ZOF metabolic hyperemia was attenuated. Mitochondrial respiration was impaired and ROS production was greater in ZOF than ZLN. These were associated with mitochondrial DNA (mtDNA) damage in ZOF. To determine if coronary metabolic dilation, the hyperemic response induced by heightened cardiac metabolism, is linked to mitochondrial function we introduced recombinant proteins (intravenously or intraperitoneally) in ZLN and ZOF to fragment or repair mtDNA, respectively. Repair of mtDNA damage restored mitochondrial function and metabolic dilation, and reduced ROS production in ZOF; whereas induction of mtDNA damage in ZLN reduced mitochondrial function, increased ROS production, and attenuated metabolic dilation. Adequate metabolic dilation was also associated with the extracellular release of ADP, ATP, and $H_2O_2$ by cardiac myocytes; whereas myocytes from rats with impaired dilation released only $H_2O_2$. Mitochondrial function plays a seminal role in connecting myocardial blood flow to metabolism, and integrity of mtDNA is central to this process.

## 14.4

### NON CANONICAL TELOMERASE AS REGULATOR OF MITOCHONDRIAL HEALTH AND ENDOTHELIAL FUNCTION

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The catalytic subunit of the Telomerase holoenzyme, TERT, counteracts telomere shortening. Recently a non-canonical role in attenuating formation of mitochondrial reactive oxygen species (mtROS) in coronary arterioles from subjects with coronary artery disease (CAD) has been identified. We demonstrated that activation of TERT can reverse the mechanism of flow-induced endothelium-dependent dilation (FMD) from H2O2- to NO, restoring the phenotype to one observed in subjects without CAD. mtROS is known to promote development of arteriolosclerosis and endothelial dysfunction, predisposing individuals to vascular complications. NO has a well-known inhibitory effect on mtROS generation and has also been demonstrated to increase telomerase.

The underlying mechanism how mitochondrial TERT asserts its protective effects are not know. We have observed that the dominant negative splice variant β del TERT is elevated in subjects with CAD, while overall amounts of TERT are decreased. β del TERT elevates mitochondrial DNA damage leading to an increase in ROS production.

Telomerase is also known to be a key factor in initiation of autophagy, a critical regulator of cellular homeostasis via recycling damaged proteins and organelles. Decreased telomerase levels are known to impair autophagy resulting in decreased stress response and elevated ROS levels.

During pathological stress elevated levels of ROS can attenuate endothelial function and shear-induced NO formation. Superoxide is also produced with physiological stimuli (e.g. shear) but any damaging effects are held in check by endogenous cellular systems including autophagy. Autophagic flux is necessary for shear-induced release of NO in isolated human microvessels while mal-adapted autophagy results in excess oxidative stress and greater susceptibility to oxidant-induced injury. Whether nuclear or mitochondrial

telomerase activity contributes to these changes is not established. We developed novel decoy peptide that prevent nuclear (nucXTERT) or mitochondrial (mitoXTERT) translocation of TERT allowing us to differentiate the roles of nuclear and mitochondrial telomerase in mediating vascular protective phenotypes.

We hypothesize that mitochondrial telomerase plays a protective role by preventing mtDNA damage in normal conditions and promoting autophagy. Expression of β del TERT in disease suppresses this protective effect and elevates vascular cellular oxidative stress to induce the conversion from NO to H2O2 as the mediator of FMD.

## IATE BREAKING ABSTRACTS

**LB001**

**EXERCISE PREVENTS CARDIOMETABOLIC DYSFUNCTIONS IN ANGIOTENSIN II-INDUCED RAT MODELS OF METABOLIC SYNDROME**

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**Background:** Skeletal muscle insulin resistance frequently occurs with glucose intolerance, hyperinsulinemia, dyslipidemia, essential hypertension, and central obesity. These metabolic and cardiovascular abnormalities are known as insulin resistance syndrome, a major risk factor of diabetes and cardiovascular diseases. Angiotensin II (ANGII) is a potent vasoactive peptide that has been demonstrated to be one of the causes of insulin resistance condition. Multiple cardiometabolic abnormalities including hypertension, dyslipidemia, and impaired insulin sensitivity developed in rats that infused with ANGII. Even though physical exercise is known to attenuate risks of cardiovascular diseases in humans and animals that consumed high-calorie diet, it remains to be elucidated whether exercise could relieve cardiometabolic conditions induced by chronic ANGII infusion.

**Objectives:** This study assessed the protective effects of physical exercise by voluntary wheel running (VWR) in ANGII-infused rats.

**Methods:** Adult male Sprague-Dawley rats were randomly assigned to sedentary or VWR groups. After a 6-wk period of sedentary or VWR, rats in each group were subdivided and subcutaneously administered with either normal saline or ANGII (100 ng/kg/min) for 14 days. Following 10 days, an oral glucose tolerance test was performed to determine whole body insulin sensitivity. 4 days later, animals were terminated and skeletal muscle glucose transport activity were measured in isolated soleus muscles.

**Results:** We found that VWR decreased body weight, fat weight, and systolic blood pressure as well as improved serum lipid profiles in ANGII-infused rats. Moreover, insulin resistance of glucose transport and impaired insulin signaling molecules were not observed in the soleus muscle of ANGII-infused rats that underwent VWR. The soleus muscle of VWR rats was associated with significant increases in GLUT-4 protein abundance (109%) and the level of AMPK $Thr^{172}$ (43%) and decreases in oxidative stress marker (31%) and the levels of insulin-induced p38 MAPK $Thr^{180}/Tyr^{182}$ (45%) and SAPK/JNK $Thr^{183}/Tyr^{185}$ (25%).

**Conclusions:** The present investigation demonstrated that prior voluntary exercise could prevent the progression of cardiometabolic syndrome in insulin-resistant rats induced by chronic ANGII administration as well as improve cardiometabolic profile in rats with normal insulin sensitivity.

This work was supported by grants from The Thailand Research Fund (TRF) through the Royal Golden Jubilee (RGJ) Ph.D. Program (Grant PHD/0228/2552)

**LB002**

**ROLE OF VASCULAR AGING IN LUNG REGENERATION**

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Aging is associated with impaired organ function and increased susceptibility to various chronic diseases, including chronic obstructive pulmonary disease (COPD). Impairment of lung regeneration and repair contributes to the pathogenesis of COPD. While compensatory lung growth after pneumonectomy (PNX) is highly induced in lungs of juvenile people, aging reduces the regenerative ability of the lungs in humans and mice. Angiogenesis – the formation of new blood capillaries- plays a key role in lung regeneration and is impaired in aging animals. However, the age-related changes in angiogenesis and how these changes contribute to lung epithelial morphogenesis have not been examined before. The objective of this study is to elucidate the mechanism by which vascular aging impairs lung regeneration. Wnt signaling is a key regulator in lung vascular and alveolar regeneration. We have found that the expression of Wnt ligand co-receptor, low-density lipoprotein receptor-related protein 5 (LRP5) and angiogenic factor, vascular endothelial growth factor receptor (VEGFR2), is significantly lower in endothelial cells (ECs) isolated from aged mouse lungs. Knockdown of LRP5 in lung human microvascular endothelial (L-HMVE) cells inhibits EC sprouting and epithelial budding formation *in vitro*. Recently, we developed a unique method to implant fibrin gel on the mouse lung, which enables the precise analysis of blood vessel formation and interaction between ECs and epithelial cells in the mouse lung. When fibrin gel is implanted on the aged mouse lung, vascular and alveolar formation in the implanted gels is suppressed. Importantly, compensatory lung growth after unilateral PNX is impaired in telomerase reverse transcriptase (TERT) knockout mice, in which telomerase activity is inhibited. These results suggest that vascular aging is involved in the suppression of lung regeneration and that rejuvenation of angiogenesis through LRP5-VEGFR2 signaling will lead to the development of new and better strategies for age-related lung diseases including COPD.

This study is supported by MCW start-up funds.

**LB003**

**HIGHER PLASMA CONCENTRATIONS OF THE GUT-DERIVED METABOLITE TRIMETHYLAMINE N-OXIDE IS CORRELATED WITH IMPAIRED ARTERIAL AND COGNITIVE FUNCTION IN YOUNG AND OLDER HEALTHY ADULTS**

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Aging is associated with impaired arterial endothelial function and stiffening of the large elastic arteries, which contribute to the development of other age-related disorders, including impaired cognitive function. One underlying cause of this impaired arterial function may be age-related alterations in the gut microbiome, including increased production of adverse gut-derived metabolites, such as trimethylamine N-oxide (TMAO). Elevated TMAO has been linked to atherosclerosis and Alzheimer's disease; however, whether TMAO contributes to impairments in function that precede clinical disease is unknown. PURPOSE: We sought to determine if plasma TMAO increases with aging in humans and if such increases in circulating TMAO are related to impaired arterial and/or cognitive function. METHODS: Plasma was collected from healthy young (N=12; 22±1yr) and middle-aged to older (MA/O; N=49; 65±7yr) adults who also underwent baseline arterial testing to assess endothelial function (brachial artery flow-mediated dilation, FMD) and arterial stiffness (carotid-femoral pulse wave velocity, PWVc-f). Cognitive function was assessed in a subset of MA/O adults (N=36) using the NIH Toolbox. Relations between plasma [TMAO], analyzed using liquid chromatography-mass spectrometry, and arterial and cognitive function outcomes were determined using linear regression models, unadjusted and adjusted for cardiovascular (CV) risk factors. RESULTS: Compared to young adults, plasma [TMAO] was >4-fold higher in MA/O adults (4.8±2.3 vs. 1.1±0.4 μM, $p<0.001$), FMD was ~50% lower (4.1±2.1 vs. 8.3±2.4%, $p<0.001$), and PWV was ~40% higher (857±182 vs. 611±49 cm/sec, $p<0.001$). In unadjusted models, higher plasma [TMAO] was related (inversely) to FMD ($r2=0.29$, $p<0.001$) and (positively) to PWVc-f ($r2=0.13$, $p=0.03$). These relations remained, and were actually strengthened, when controlling for age, cardiorespiratory fitness (VO2max), body mass index, and serum low-density lipoprotein cholesterol (FMD: $r2=0.36$, $p=0.001$; PWVc-f: $r2=0.37$, $p=0.01$). Higher plasma [TMAO] was also related (inversely) to Fluid Cognition Composite Score, which includes measures of executive function, episodic and working memory, and processing speed (unadjusted: $r2= 0.13$, $p=0.03$; adjusted for CV risk factors: $r2=0.30$, $p=0.049$). CONCLUSIONS: Circulating levels of TMAO are increased in MA/O adults and are related to impaired endothelial function, arterial stiffness, and impaired cognitive function.

Supported by R01 HL134887

**LB004**

**AGE AND TIME DEPENDENCE OF POST-OVARIECTOMY ESTRADIOL TREATMENT ON CARDIOVASCULAR REGULATION IN DAHL SALT-SENSITIVE RATS**

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**Objective**: To assess the mechanisms for differences in regulation of the cardiovascular system of Dahl salt-sensitive (DS) rats to estradiol (E2) treatment as a function of time following ovariectomy as a model for women who initiate E2 replacement therapy post-menopausally or post-oophorectomy.

**Methods**: DS rats were ovariectomized (OVX) at 4.5 mo (DS-$OVX^Y$) or 7 mo of age (DS-$OVX^O$). At 7 mo, OVX DS rats in each group were treated with E2 for 4 weeks (DS-$OVX^Y$+E2, DS-$OVX^O$+E2) or vehicle. Mean arterial blood pressure (MAP) was measured telemetrically in all groups from 7-8 mo. Body weight (BW) was measured throughout the experiment and plasma angiotensin II (AngII) concentration was measured at time of sacrifice (8mo) by RAS-Fingerprint™ (Attoquant). Brain morphometric and receptor autoradiographic determinations of angiotensin II receptor determinations are in process.

**Results**: As reported concurrently (Council for High Blood Pressure, 2017), E2 treatment at 7 mo did not alter MAP in DS-$OVX^y$, but it did prevent the ovariectomy-induced increase in MAP in the DS-$OVX^O$. E2 treatment reduced BW in both the DS-$OVX^y$ group and the DS-$OVX^O$ groups. E2 treatment reduced plasma AngII in both DS-$OVX^Y$ and DS-$OVX^O$ groups by ~40% compared to their vehicle-treated controls. Brain AT1 angiotensin receptor expression has been shown to be reduced in the solitary tract nucleus of OVX-DS versus SHAM-DS rats (Society for Neuroscience, 2017) and assays are in process to determine if E2 treatment will alter this change. Additionally, the ventricles of the DS rats tend to be enlarged compared to other rat strains suggestive of disturbed fluid balance in the DS female brain.

**Conclusions**: E2 replacement attenuates the increase in MAP in 7 mo old DS rats when treatment begins immediately post-ovariectomy, but not when initiated 3.5 mo post-OVX in young DS rats. The E2-induced change in BW and plasma AngII concentration did not differ with time of initiation of treatment post-ovariectomy, suggesting that changes in brain Ang II receptor expression may explain the differential blood pressure responses. These findings are relevant to treatment of ovarian hormone-deficient women with E2. Funding sources: NIH HL- 121456 and Peptide Radioiodination Shared Resource, Georgetown University.

**LB005**

## $O_2$ AVAILABILITY AND METABOLIC RESERVE: EVIDENCE OF DIFFERENT SKELETAL MUSCLE PHENOTYPES IN COPD

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Exertional dyspnea and exercise intolerance are hallmark manifestations of chronic obstructive pulmonary disease (COPD). However, despite the debilitating consequences of the disease, the pathophysiological mechanisms that underpin the loss of exercise capacity and mobility in patients with COPD are still unclear. Overall, the literature suggest that patients with COPD exhibit anomalies of both peripheral $O_2$ transport and muscle bioenergetics which have the potential to limit exercise capacity. However, their actual contribution to exercise intolerance is still debated, likely in part, due the pathophysiological heterogeneity of COPD. Therefore, the purpose of this study was to determine the physiological determinants of muscle aerobic capacity in COPD patients. Specifically, we examined whether a brief ischemia during exercise followed by reactive hyperemia (RH) would affect peripheral $O_2$ supply and mitochondrial function in patients with COPD. 18 patients with moderate to severe COPD performed plantar flexion exercise while phosphorus magnetic resonance spectroscopy, near-infrared spectroscopy, and Doppler ultrasound were used to assess muscle metabolism and peripheral hemodynamics. In 8 subjects, "responders", convective (free-flow area under the curve, AUC FF: 0.18±0.15 $L.min^{-1}$; RH: 0.34±0.20 $L.min^{-1}$) and diffusive $O_2$ delivery were significantly increased in RH, resulting in significantly higher mitochondrial phosphorylation capacity (FF: 18±8 $mM.min^{-1}$; RH: 31±9 $mM.min^{-1}$). In 10 subjects, "non-responders", neither convective (AUC FF: 0.23±0.10 $L.min^{-1}$; RH: 0.32±0.09 $L.min^{-1}$) and diffusive $O_2$ delivery, nor mitochondrial phosphorylation capacity (FF: 29±12 $mM.min^{-1}$; RH: 23±7 $mM.min^{-1}$) were significantly different between conditions. In conclusion, the current integrative study revealed two subgroups of COPD patients with different muscle phenotypes. Nearly half of the patients with COPD appeared to exhibit a metabolic reserve in the plantar flexor muscles whereas the other half demonstrated a loss of convective and diffusive $O_2$ delivery reserve, potentially combined with intrinsic limitation of the mitochondrial capacity to synthesize ATP. Together, our findings clearly highlight the importance of identifying the different phenotypes within the wide spectrum of COPD when exploring the effectiveness of novel therapeutic treatments.

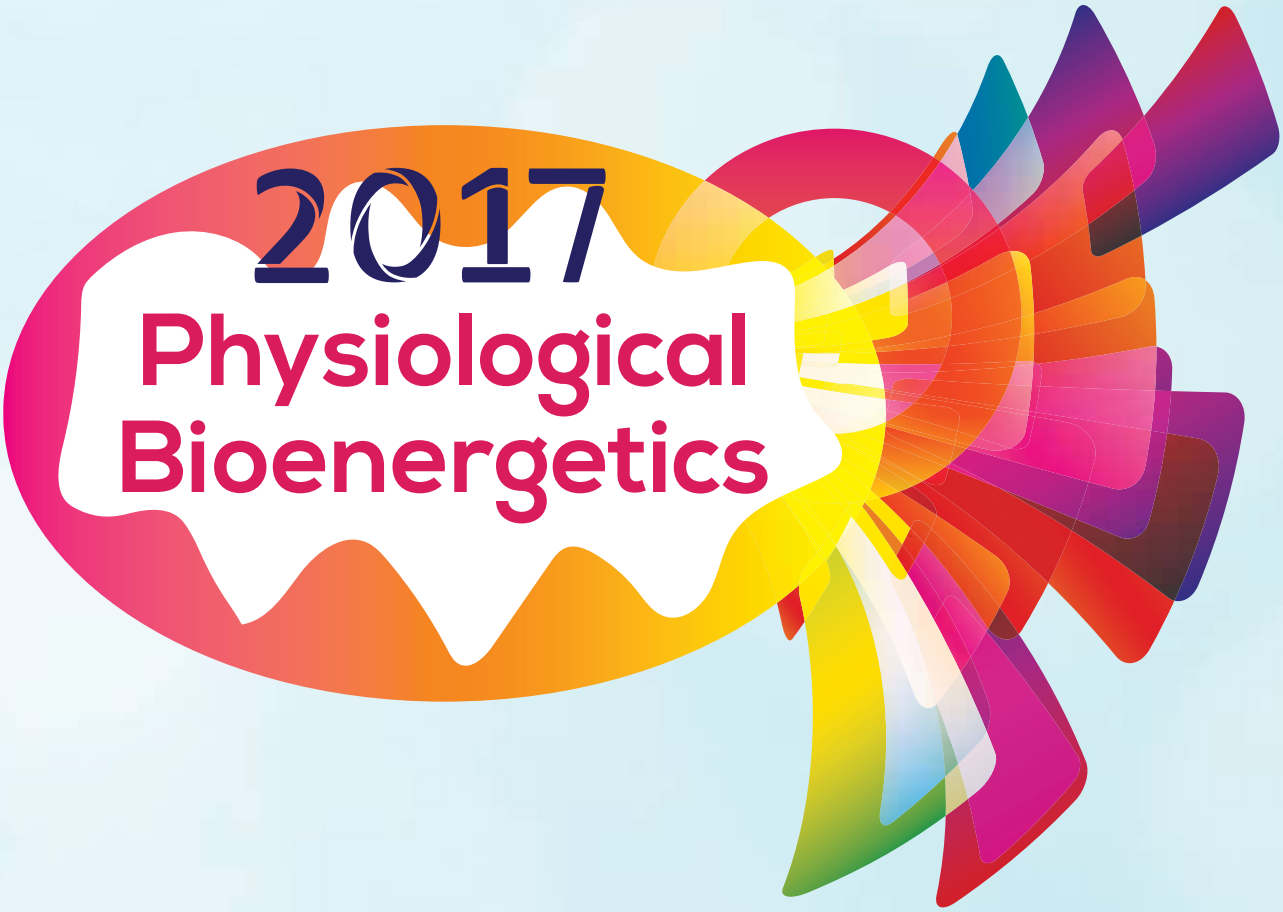
**2017 APS Conference:**
**Cardiovascular Aging: New Frontiers and Old Friends** **Author Index**

*** indicates invited speaker**

# Physiological Bioenergetics: Mitochondria from Bench to Bedside

San Diego, California • August 27-30, 2017

# Conference Program & Abstracts

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2017 APS Conference
**Physiological Bioenergetics**
**Mitochondria from Bench to Bedside**
August 28-30, 2017, US Grant Hotel, San Diego, California

## ABSTRACTS OF INVITED AND VOLUNTEERED PRESENTATIONS

2017 APS Conference
**Physiological Bioenergetics**
**Mitochondria: From Bench to Bedside**

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## 1.0: KEYNOTE LECTURE

### 1.1
### THE MITOCHONDRIA RETICULUM OF MUSCLE CELLS

**Robert Balaban**[1]

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Recently both 3D high resolution and functional studies in muscle cells have revealed a tightly coupled mitochondria reticulum (MR) to rapidly distribute potential energy, in the form of the mitochondrial membrane potential (MMP), throughout skeletal muscle and heart cells. Herein the structural aspects of the MR are described using 3D Focused Ion Beam Scanning Electron Microscopy (FIB-SEM) and presented in muscle cells. A large portion of the MR conductivity is dependent on direct mitochondrial matrix continuity while in some regions of the muscle the connectivity is proposed to occur via poorly characterized electron dense regions (EDR) between adjacent mitochondria. Using a photo-activated mitochondrial uncoupler to regionally perturb the MMP, we have demonstrated that large regions of the MR are electrically coupled via a shared matrix as well as EDR structures between the mitochondria. In murine skeletal muscle cells a large fraction of the mitochondrial volume is located in regions close to capillary indentations in the cell structure. These embedded capillaries are surrounded by large pools of mitochondria near the plasma membrane that have narrow tubes which run along the I-Bands (I-Band Mitochondria Segments (IBMS)) deep into the muscle cell. It has been proposed that these IBMS serve to distribute the MMP from the large sub-sarcolemma mitochondrial pool to the more central ATP-consuming myofibril region of the muscle cell. Consistent with this notion was the observation that there is a 3-fold enhancement of MMP generating oxidative phosphorylation complex in comparison to MMP utilizing ATP synthesis enzymes in the periphery of the muscle cell when compared to central regions near the muscle ATPase activity. In cardiac cells, no IBMS exist and the coupling is exclusively through large mitochondria structures and numerous EDR connections. These data are consistent with a mitochondria reticulum in muscle cells that couples large numbers of mitochondria together providing a rapid and uniform potential energy source throughout the cell to support ATP production. (NHLBI Division of Intramural Research).

REFERENCES: Glancy, et al., 2005, Nature, 523, 617-20. doi: 10.1038/nature14614.; Glancy et al., 2017, Cell Reports 19, 487–496 April 18, 2017 http://dx.doi.org/10.1016/j.celrep.2017.03.063.

## 2.0: ENERGY SCHOOL I

### 2.1
### MITOCHONDRIA-TARGETED MOLECULES: TOOLS AND THERAPIES

**David Brown**[1]

[1]Human Nutrition, Foods, and Exercise, Virginia Tech, 1035 Integrated Life Science Building, 1981 Kraft Drive, Virginia Tech Corporate Research Center, Blacksburg, VA, 24060

Mitochondrial dysfunction is noted across numerous pathologies. Interventions that target cellular bioenergetics have enormous potential to mitigate disease burdens. This presentation has two major objectives. The first is to give an overview of various mitochondria-targeting strategies in development. The opportunities and challenges of targeting mitochondria will be presented. A selection of mitochondria-targeted compounds currently in clinical trials, as well as promising pre-clinical therapies in development, will be addressed. Emerging approaches that utilize peptide sequences as delivery vectors for mitochondrial cargo will also be discussed. The second objective is to describe ongoing work in my research laboratory using a series of cell-permeable peptides to treat heart disease. Several different peptides that improve cardiac mitochondrial function have been discovered, and their effects on various aspects of cellular bioenergetics will be presented. Funding support: NIH R01 HL123647.

### 2.2
### THE INS AND OUTS OF MITOPHAGY AND QUALITY CONTROL

**Roberta Gottlieb**[1]

[1]Heart Institute, Cedars-Sinai Medical Center, 127 S. San Vicente Ave., AHSP9313, Los Angeles, CA, 90048

Mitochondria are born from pre-existing mitochondria like Athena from Zeus's forehead. However, in a homeostatic system, before new mitochondria are formed, space must be made for them by clearing some of the old mitochondria through mitophagy. In this presentation, I will cover key mechanisms for mitochondrial quality control, as well as factors regulating mitochondrial biogenesis. Mitochondrial quality control involves multiple pathways including the ubiquitin-proteasome system - particularly for outer membrane proteins; intrinsic mitochondrial proteases - required for processing many imported mitochondrial proteins; mitochondrial-derived vesicles; the mitochondrial unfolded protein response; and mitophagy. Mito-biogenesis involves a transcriptional pathway governed largely by PGC-1alpha, but we have recently demonstrated a translationally controlled response in the human heart. Mitochondrial turnover can lead to metabolic reprogramming, which may alter cellular function and gene expression - this may be adaptive or maladaptive. Impaired quality control can lead to accumulation of damaged or dysfunctional mitochondria which may generate increased reactive oxygen species, exhibit diminished ATP production or impact cell function due to metabolic inflexibility. Damaged mitochondria can release damage-associated molecular patterns (DAMPs) that trigger innate immunity and can lead to systemic inflammation, or can activate apoptotic or necrotic cell death pathways. Finally, conditions that enhance or impair mitochondrial quality control will be discussed.

Funding: NIH P01 HL112730.

## 3.0: MOVING MITOCHONDRIA NETWORKS AND QUALITY CONTROL

### 3.1

### NON-CANONICAL ROLE OF DYNAMIN-RELATED PROTEIN DRP1 IN REGULATING BIOENERGETICS OF CARDIAC MUSCLE CELLS

**Shey-Shing Sheu**[1]

[1]Department of Medicine, Center for Translational Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, 1020 Locust St, Philadelphia, PA, 19107-6731

Mitochondrial dynamics, including fission, fusion, and movement, is a fundamental mechanism in regulating mitochondrial function. Dynamin-related protein 1 (Drp1) is the major GTP hydrolyzing protein that is responsible for fission. Studies have shown that Drp1 is abundantly expressed in adult cardiac myocytes. Paradoxically, compared to numerous cell types, adult cardiac myocytes exhibit very low frequency in mitochondrial fission. This dichotomy between the abundance of Drp1 and scarcity of mitochondrial fission has prompted us to investigate the non-canonical roles of Drp1 in cardiac muscle cells. Using multiple approaches encompass biochemical, genetic, and confocal, super-resolution, and electron microscopy, we have obtained results showing that mitochondrial Drp1 is preferentially localized in the mitochondria-associated sarcoplasmic reticulum (SR) membrane fraction (MAM), the region that bridges $Ca^{2+}$ release site (SR) with energy producing site (mitochondria). Increased cytosolic $Ca^{2+}$ transients promote translocation of Drp1 to mitochondria. Moreover, inhibition of Drp1 significantly decreases mitochondrial respiration with a modest increase in mitochondrial elongation. Drp1 inhibition also leads to a decrease in the frequency of transient and stochastic opening of the mitochondrial permeability transition pore (mPTP) which triggers mitochondrial flash. This leads us to propose an intriguing hypothesis that Drp1, through its induction of transient or subconductance flickering of mPTP openings, may cause physiological oscillations of mitochondrial membrane potential ($\Delta\Psi_m$). This in turn can trigger the oscillatory bursts of mitochondrial respiration and thus ATP generation, as shown previously. We have also obtained data further show that stressing the heart with chronic β-adrenergic receptor (β-AR) stimulation leads to a significant increase in CaMKII-dependent Drp1 phosphorylation and translocation to mitochondria, which causes excessive mPTP opening, reactive oxygen species (ROS) generation, cardiac hypertrophy, and ultimately, heart failure. In conclusion, our results show that Drp1 is strategically accumulated in the MAM in order to sense the localized high $Ca^{2+}$ in the SR-mitochondria junctions during cardiac excitation-contraction coupling. The activation of Drp1 leads to enhanced mitochondrial respiration for ATP generation through mPTP transient openings as such the heart can maintain the balance between energy demands and supplies. However, excessive Drp1 activation leads to persistent mPTP opening and excessive ROS generation that causes cell injury and death. Support: NIH 2R01HL093671, 1R01HL122124, 1RO1114760. REFERENCES: Zhang H, Wang P, Bisetto S, Yoon Y, Chen Q, Sheu SS, Wang W. A novel fission-independent role of dynamin-related protein 1 in cardiac mitochondrial respiration. *Cardiovasc Res.* 113(2):160-170, 2017.

### 3.3

### MITOCHONDRIAL DYNAMICS IN THE BRAIN

**Sarah Berman**[1]

[1]Dept of Neurology and Pittsburgh Institute for Neurodegenerative Disease, University of Pittsburgh, 3471 Fifth Avenue, BST3, Rm 7037, Pittsburgh, PA, 15213

Increasing evidence links dysregulation of mitochondrial dynamics and quality control to neurodegenerative diseases. In neurons, mitochondrial biogenesis, degradation through mitophagy, fission, fusion, and axonal transport are critical for maintaining mitochondrial function, protection of mitochondrial DNA, cell death mechanisms, and proper distribution of mitochondria to synapses and synaptic functioning. Neurons have specific features that likely contribute to the critical nature of proper function and regulation of mitochondrial dynamics: they do not replicate, and mitochondrial turnover is thought to be slower than in most other cell types; they have unique anatomy, with long, highly energy-requiring axons with specific compartmentalization of function; and they are highly dependent on adequate mitochondrial respiration. Evidence implicating dysregulation of mitochondrial dynamics and quality control is particularly strong in Parkinson's disease (PD), directly linking both genetic and neurotoxic models of PD, and suggesting that this may be a common pathogenic mechanism of PD neurodegeneration. In PD, the degenerative process starts in distal axons, where mitochondrial dynamics are particularly important. In addition, the selectively vulnerable neurons that degenerate in PD throughout the brain share common features of being long, highly energy-requiring axons with sprouting terminals, and vulnerable neurons may contain fewer mitochondria. We study regulation of mitochondrial dynamics specifically in neurons and have found differences in dynamic processes such as mitophagy, compared to other cell types, in part due to bioenergetic differences. We also find early changes in neuronal mitochondrial dynamics in PD-relevant models, including early reversal of mitochondrial axonal transport in PD-vulnerable dopamine neurons *in vivo*. In addition, discovery of compartmentalized changes in mitochondrial density in PD-relevant neuronal models have led to studies to characterize neuroanatomical compartmentalization of mitochondrial biogenesis in cell bodies, axons, and dendrites. Better characterization of mitochondrial dynamics and quality control mechanisms in compartmentalized neurons will be important for understanding the role of dysregulation of these processes in neurodegenerative disease.

### 3.4

### ELIMINATION OF PATERNAL MITOCHONDRIA IN MAMMALIAN EMBRYOS

**David Chan**[1]

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Maternal inheritance is a signature feature of mitochondria. Sperm contribute mitochondria to the zygotes, but these paternal mitochondria are eliminated, so that inheritance of mitochondria and their DNA is uniparental. A role for mitophagy (the autophagic degradation of mitochondria) in the elimination of paternal mitochondria has been shown in early nematode embryos. It is not clear if a similar mechanism exists in mammalian embryos. To study the elimination of paternal mitochondria, we tracked the fate of sperm mitochondria in mouse embryos after fertilization. *PhAM* mice ubiquitously express mito-Dendra2, a photo-convertible fluorophore localized to the mitochondrial matrix. When *PhAM* males are mated to normal females, the resulting embryos contain fluorescently labeled mitochondria that can be tracked by fluorescence microscopy. We found that paternal mitochondria do not fuse with other mitochondria, eventually lose their membrane potential, and are selectively eliminated from the embryo by 80 hours after fertilization. In contrast, maternal mitochondria are stable and fusion-active. To test the role of specific genes in paternal mitochondria elimination, we used lentivirus encoding shRNA to disrupt the function of genes in the early embryo.

## 4.0: TRANSLATING THE MITOCHONDRIA: TAKING IT TO THE CLINIC

### 4.1

### MUSCLE BIOENERGETICS IN EXERCISE AND BED REST

**Bret Goodpaster**[1]

[1]Translational Research Institute for Metabolism and Diabetes, Florida Hospital, 301 East Princeton Street, Orlando, FL, 32804

Prolonged inactivity due to hospitalization or injury causes profound skeletal muscle atrophy and weakness. Preclinical models have suggested cross-talk between the regulatory circuits that control muscle mitochondrial function and muscle mass, but the role of mitochondrial energetics in disuse atrophy in humans is not known. We have identified potential links in the coordinate control of muscle mass and energetics that occur with inactivity. We performed unbiased gene-expression analysis (RNA-seq) in muscle biopsies from individual subjects before and after 10 days of complete bed rest. Multiple mitochondrial pathways including fatty acid oxidation and oxidative phosphorylation were downregulated following bed rest. Concordantly, upstream regulatory analysis revealed important transcriptional regulators of energy metabolism including PPAR**α**, ERR**α**, and PGC-1**α** as being deactivated with bed rest. We measured protein markers of mitochondrial content (OXPHOS), dynamics (MFN2, OPA1, FIS1, DRP1), autophagy (Beclin1, LC3B, BNIP3), and atrophy (poly-ubiquinated proteins (poly-ub) by Western blot. Fatty acid composition of several lipid classes in skeletal muscle was measured by infusion-MS analysis. Maximal coupled respiration assessed by high-resolution respirometry decreased following bed rest in conjunction with muscle atrophy. These data suggest the early and sustained de-activation of gene regulatory circuits controlling mitochondrial biogenesis occur concomitantly with the atrophy process. This circuit is also activated with exercise and may serve as a therapeutic target for the recovery of muscle from disuse atrophy

### 4.2

### PLATELET BIOENERGETICS AS A BIOMARKER FOR MITOCHONDRIAL DYSFUNCTION IN HUMAN DISEASE

**Sruti Shiva**[1]

[1]Vascular Medicine Institute; Department of Pharmacology & Chemical Biology, Center for Metabolism and Mitochondrial Medicine, University of Pittsburgh, 200 Lothrop St, 1240E BST, Pittsburgh, PA, 15261

It is well established that bioenergetic dysfunction plays a role in the pathogenesis of numerous "non-metabolic" diseases in all organ systems. However, this dysfunction remains poorly characterized in patient populations due to the invasiveness of obtaining tissue for mitochondrial studies. Here we hypothesize that measurements of bioenergetics in circulating blood platelets can be utilized as a biomarker of global bioenergetic dysfunction in human disease. We demonstrate that platelet bioenergetic profile remains stable over time in healthy humans and is uniquely altered in different pulmonary and vascular disease states. Additionally, we show data demonstrating bioenergetic variability among different natural cohorts including the aging population and differences in race and gender. Notably, we show that changes in mitochondrial function correlate with clinical parameters of disease and that platelet bioenergetic function is significantly correlated with bioenergetic parameters in other organs including the lung and skeletal muscle. Collectively, these data suggest that platelet bioenergetic profile is a robust and useful marker for assessing mitochondrial function in healthy humans and patients with disease. The implications of utilizing this method as well as of platelet bioenergetic dysfunction in the progression of pathology will be discussed.

### 4.3

### MITOCHONDRIAL DNA DAMAGE AS A BLOOD-BASED BIOMARKER FOR EARLY PARKINSON'S DISEASE

**Evan Howlett**[1], **Nicholas Jensen**[1], **Catherine Corey**[2], **Andrea Weinstein**[3], **Kirk Erickson**[4], **Samuel Goldman**[5], **Caroline Tanner**[5], **Marie Armentero**[6], **Fabio Blandini**[6], **JT Greenamyre**[1], **Samay Jain**[1], **Sruti Shiva**[2], **Laurie Sanders**[7]

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Parkinson's disease (PD) is the most common neurodegenerative movement disorder and the diagnosis of living patients is primarily based on clinical criteria, which can lead to misdiagnoses. The validation of reliable biomarkers for PD remains a major unmet need and is critical towards therapeutic development. Here, for the first time we investigated mitochondrial DNA (mtDNA) damage as a systemic biomarker of PD. We used our novel PCR-based methodology to measure blood-based mtDNA damage in PD, Alzheimer's disease (AD) and healthy subjects. Strikingly, mtDNA damage levels in idiopathic early PD were significantly increased in blood buffy-coat samples compared to healthy controls. Interestingly, we found in a different cohort, that mtDNA damage is increased in the peripheral blood mononuclear cells (PBMCs) from PD subjects, indicating persistent mtDNA damage in circulating immune cells. In archived DNA samples from two additional cohorts, we were able to replicate these findings of increased mtDNA damage in buffy-coat and PBMCs in PD patients compared to healthy subjects. To address whether changes in mtDNA damage are found in other neurodegenerative diseases, we evaluated mtDNA damage between AD subjects and healthy controls in buffy-coat derived DNA – and found no differences, suggesting that mtDNA damage is not a peripheral broad-based neurodegenerative biomarker. Our data raises the possibility that mtDNA damage might form the basis of a blood-based biomarker of PD that could be used for patient stratification in clinical trials. Furthermore, we propose that levels of mtDNA damage can identify a subset of PD patients that are amenable to specific molecular targeting. Funding sources include: William N. and Bernice E. Bumpus Foundation Innovation Award, Mitochondria, Aging and Metabolism/Basic Biology Aging Pilot Project Program, Alzheimer's Disease Research Center Seed Monies Grant Program and Pittsburgh Claude D. Pepper OAIC.

**4.4**

## INTEGRATED APPROACHES TO TRANSLATIONAL REDOX BIOLOGY AND BIOENERGETICS

**Victor Darley-Usmar[1]**

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Bioenergetic Health is a new concept which captures the experimental finding that translational research in metabolism must embrace the metabolic plasticity inherent in human populations to define what is normal. This is an essential first step in establishing the range of normal metabolic and bioenergetic parameters so that pathological indications can be clearly recognized. The data is now emerging from studies of bioenergetics and metabolomics in cells or platelets isolated from human blood. This is important since Bioenergetics is now at the forefront of our understanding of pathological mechanisms, new therapies and as a biomarker for the susceptibility of disease progression in metabolic diseases, neurodegeneration, cancer and cardiovascular disease. A key concept is that the mitochondrion can act as the "canary in the coal mine" by serving as an early warning of bioenergetic crisis in patient populations. Furthermore, cellular mitochondrial function is known to vary between populations due to differences in genetic background and in response to lifestyle changes including diet and exercise. It is clear that we urgently need new clinical tests to monitor changes in bioenergetics in patient populations. This is now possible due to the development of high-throughput assays to measure cellular energetic function in the small numbers of cells that can be isolated from human blood or from tissue biopsy samples. The sequential addition of well characterized inhibitors of oxidative phosphorylation allows a bioenergetic profile to be measured in cells isolated from normal or pathological samples. This profile can define the extent to which these cells utilize mitochondrial oxygen consumption to produce ATP, are using protons for other processes or leak and the maximal respiration. Non-mitochondrial oxygen consuming pathways are also measured and are likely indicative of a pro-inflammatory state. Taken together we propose these parameters are a measure of bioenergetic health of a cell population. We therefore propose the development of the Bioenergetic Health Index (BHI), which is a single value that defines bioenergetic health based upon the analysis of cellular mitochondrial profiles in cells isolated from human subjects. This is now being related to metabolomic and lipidomics analysis in platelets which has the potential to both define the molecular basis for individual variation in human populations and predict the response to stress. Ultimately, BHI has the potential to be a new biomarker for assessing patient health of (or for) both prognostic and diagnostic value.

## 5.0 POSTER SESSION I

**5.1**

## METABOLIC REGULATION OF EXERCISE-INDUCED CARDIAC GROWTH

**Andrew Gibb[1,2,3], Paul Epstein[4], Shizuka Uchida[5], Yuting Zheng[1,2], Lindsey McNally[1,2], Patrick Trainor[1,2], Daniel Conklin[1,2], Kenneth Brittian[1,2], Michael Tseng[6], Steven Jones[1,2], Aruni Bhatnagar[1,2], Bradford Hill[1,2]**

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**University of Louisville, 302 E. Muhammad Ali Blvd, Louisville, KY, 40202, [6]Department of Anatomy and Neuroscience, University of Louisville, 511 S. Floyd, Louisville, KY, 40202**

***Background:*** Exercise training promotes metabolic changes in the heart that are associated with physiologic cardiac growth; however, it is not known whether or how physical activity-induced changes in cardiac metabolism modulate myocardial remodeling. In this study, we tested whether exercise-mediated changes in cardiomyocyte glycolysis regulate the physiologic cardiac growth program.

***Methods:*** We used radiometric, immunologic, metabolomic, and biochemical assays to measure changes in myocardial glucose metabolism in mice subjected to acute and chronic treadmill exercise. As tools to determine the relevance of changes in glycolytic activity, we determined how cardiac-specific expression of mutant forms of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK2) affect cardiac structure, function, metabolism, and gene programs relevant to cardiac remodeling. Metabolomic and transcriptomic screening were employed to identify metabolic pathways and gene sets regulated by glycolytic activity.

***Results:*** Acutely, exercise reduced PFK2 phosphorylation, thereby decreasing myocardial glycolysis; however, after 4 weeks of exercise training and in the fully recovered state, myocardial PFK2 activity and glycolysis were increased compared with sedentary controls. Cardiac-specific expression of a kinase-deficient PFK2 transgene ($Glyco^{Lo}$ mice) lowered glycolytic rate and regulated the expression of *Cebpb* and *Cited4*, known to govern the physiologic cardiac-growth program. Correspondingly, $Glyco^{Lo}$ hearts, in the absence of exercise, showed a form of cardiac growth similar to the exercise-adapted heart, replete with larger myocytes, enhanced cardiac function, and higher capillary-to-myocyte ratios. Expression of phosphatase-deficient PFK2 ($Glyco^{Hi}$ mice) increased glucose utilization and promoted mild cardiac hypertrophy characterized by mild left ventricular dilatation, depressed cardiac function, and absence of activation of the physiologic growth program. Nevertheless, polarization of myocardial metabolism by both transgenes caused modest mitochondrial damage. Transcriptomic analyses indicated that myocardial metabolism coordinates key genes relevant to cardiac remodeling.

***Conclusions:*** We conclude that PFK2-mediated decreases in glycolytic activity are a stimulus for physiologic cardiac growth and that metabolic flexibility is important to maintain mitochondrial health in the heart.

**5.2**

## MITOCHONDRIAL FUNCTION AND TRANSCRIPTIONAL REGULATION DURING DENERVATION-INDUCED SKELETAL MUSCLE ATROPHY.

**Gavin Pharaoh[1,2], Kavithalakshmi Sataranatarajan[1], Constantin Georgescu[3], Niran Hadad[4], Bumsoo Ahn[1], Rojina Ranjit[1], Kaitlyn Riddle[1], Willard Freeman[2,4], Jonathan Wren[3], Holly Van Remmen[1,2,5]**

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Age-related declines in muscle mass and function reduce quality of life. The mechanisms underlying these changes are still not defined, but loss of innervation and increased mitochondrial reactive oxygen species (ROS) generation are proposed to play a key role. The goal of this study was to measure the changes in mitochondrial function and gene expression that occur following loss of innervation. Mice were exposed to sciatic nerve transection on one limb, sham surgery on the other, and then sacrificed at 0.5, 1, 2, 4, 7, and 14 days post-transection. The gastrocnemius muscle, innervated by the sciatic nerve, was collected for RNA isolation and measurement of ROS generation in isolated mitochondria (fluorometer) and permeabilized muscle fibers (Oroboros O2K). Gastrocnemius mass was significantly reduced at 4 days post-transection and was reduced 42% by 14 days. ROS production was significantly increased at 4 days post-transection, and the elevated ROS production was correlated with the decrease in muscle mass ($r^2$=0.3246, p=0.0008). RNAseq analysis showed that approximately 450 transcripts were differentially regulated post-transection with most changes occurring at 7 and 14 days. The biological processes of the differentially regulated transcripts at 12-24 hours and 2-4 days primarily involve stress responses, while those occurring at 7 and 14 days are characterized by a disruption in homeostasis of metabolic, cellular, and contractile functions. Four transcripts (RCS, Gadd45a, Gdf5, and Myog) were upregulated at all time points and are involved in calcium signaling, growth arrest, and stimulation of muscle reinnervation. The motifs for the transcription factors Mef2a-d were significantly enriched in the promoters of differentially regulated transcripts beginning at 4-7 days suggesting a fiber type shift to slow-twitch. Known age-related atrophy pathways (ATF4, UCP1) are induced by loss of innervation. Denervation causes muscle atrophy, increased ROS production, an acute stress response, a chronic dysregulation of metabolic, cellular, and contractile homeostasis, and induction of fiber type shift.

Funding: 1R01AG050676-01A1 Defining the Relative Roles of Pre- and Post-Synaptic Events in the Initiation and Progression of Sarcopenia. Oklahoma Medical Research Foundation Pre-doctoral Scholarship

**5.3**

## NITRO-OLEIC ACID PROTECTS MICE FROM DIET-INDUCED HEPATIC STEATOSIS AND INSULIN RESISTANCE

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Obesity is the number one risk factor for the development of non-alcoholic fatty liver disease (NAFLD). Steatosis, the hallmark of NAFLD, is an accumulation of fat within the liver. Mitochondria play a central role in liver metabolism by tightly controlling the high rates of fatty acid oxidation (FAO). During the development of NAFLD, mitochondria are able to adapt to the increased lipid load in hepatocytes by increasing the rate of FAO. However, reactive oxygen species (ROS) generation is increased, which damages hepatocytes, and in turn induces inflammation. Evidence suggests that hepatic mitochondrial dysfunction lies at the core of the pathogenesis of NAFLD, although the underlying mechanisms responsible for this are still poorly understood. Current understanding supports that suppressing both inflammation and ROS promotes both anti-diabetic and improved NAFLD. Additionally, it has recently been reported that electrophilic nitro-oleic acid ($OA\text{-}NO_2$) has potent anti-inflammatory and antioxidant signaling actions. Therefore, it was hypothesized that mitochondrial dysfunction, ROS production and inflammation could be attenuated by systemic administration of $OA\text{-}NO_2$ in a high fat diet-induced murine model of insulin resistance and NAFLD. Mice on HFD (60% kcal from fat) for 20 wk displayed increased adiposity, insulin resistance and hepatic steatosis compare to mice on normal chow (NC). The HFD mice had mitochondrial dysfunction characterized by lower hepatic mitochondrial complex I, IV and V activity compared to mice on NC. Treatment with $OA\text{-}NO_2$ for the last 6.5 wk (out of 20) abrogated the HFD-mediated decrease in hepatic mitochondrial complex I, IV and V activity. The RCR of the mice on HFD (3.1±0.2) was significantly decreased compared to NC (5.8±0.4) whereas $OA\text{-}NO_2$ treatment prevented the HFD-mediated decrease in hepatic RCR. This data suggests that $OA\text{-}NO_2$ improves hepatic mitochondrial function during obesity although the mechanism of action is still being investigated. Administration of $OA\text{-}NO_2$ restored glucose tolerance and significantly reversed hepatic steatosis, as indicated by the normalization of hepatic triglycerides as well as a decrease in liver xanthine oxidoreductase activity, pro-inflammatory cytokine levels and markers of oxidative stress. These observations support that the broad signaling actions of electrophilic fatty acids represent a therapeutic strategy for limiting the complex pathogenic events that are instigated by obesity.

## 5.4
## MECHANISMS OF MITOCHONDRIAL DYSFUNCTION AND IMPAIRED CARDIAC BIOENERGETICS IN RAT OFFSPRING EXPOSED TO MATERNAL DIABETES AND HIGH-FAT DIET

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**Background:** Infants born to diabetic or obese woman are at risk of heart disease. While excess circulating fuels are recognized risk factors, the mechanism of pathogenesis is not understood. We showed that newborn rats exposed to diabetes and high-fat diet during pregnancy had poorer diastolic/systolic cardiac function, mitochondrial dysfunction and impaired cellular bioenergetics. This study aimed to determine the underlying mechanism.

**Methods:** Sprague-Dawley rats were fed either control or high-fat diet. On day 14 of pregnancy, dams were injected with citrate buffer or streptozotocin to induce diabetes then treated with twice daily insulin. Dams delivered offspring from four groups: controls, diabetes-exposed, diet-exposed, and combination-exposed. Hearts were harvested and neonatal rat cardiomyocytes (NRCM) were isolated and analyzed by Western blot, mitochondrial imaging, and extracellular flux analyses which included fuel preference and respiratory complex function of permeabilized cells. Group comparisons were by two-way ANOVA for diabetes, diet and interaction effect. Significance was set at $p \leq 0.05$.

**Results:** Diabetes-exposed NRCM had fewer fusion and fission events, shorter mitochondria, lower mitochondrial copy number and decreased glycolytic and respiratory capacity. High-fat diet-exposed NRCMs have shorter mitochondria, higher mitochondrial copy number, increased expression of PGC1α and more oxidative stress. Mechanisms of altered dynamism appear to be sex specific. Exposed females have less OPA-1 protein expression while males have less MFN2 and MFF. Both sexes have lower DRP1 expression, especially following diet exposure. Diet-exposed females have a lower expression of Complex I (NDUFA2) and III (Cox5B) proteins. Permeabilized NRCMs from combination-exposed females also have a lower OCR with various complex I and III fuels including pyruvate, palmitoyl-carnitine and duroquinol.

**Conclusions:** Maternal diabetes and high-fat diet impair mitochondrial dynamism and respiratory complex function in cardiomyocytes from developing newborn offspring. Findings demonstrate the role of maternal conditions in mitochondrial health and cardiac disease in the developing fetus and uncover mechanisms of fuel-mediated cardiomyopathy.

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## 5.5
## DECREASED MITOCHONDRIAL OXIDATIVE CAPACITY IN PERIPHERAL BLOOD MONONUCLEAR CELLS AFTER CHRONIC AMINO ACID SUPPLEMENTATION IN OLDER ADULTS WITH HYPERTRIACYLGLYCEROL-AEMIA

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**Background:** Reports that skeletal muscle mitochondrial respiratory capacity is lower in older adults than in young adults implicates mitochondrial dysfunction in the aging process. Blood-cell bioenergetics has been suggested as an indicator of systemic mitochondrial health. We have shown that supplementation with essential amino acids (EAAs) plus arginine decreases plasma and liver triacylglycerols in older adults. The impact of such supplementation on mitochondrial respiration of circulating cells is unknown. Thus, we sought to assess the effect of eight weeks of EAAs + arginine supplementation on circulating cell bioenergetics in older adults with hypertriacylglycerolaemia.

**Methods:** Six (two men) older adults underwent testing before and after 8 weeks of supplementation with EAA + arginine (11g of EAAs ingested twice daily). A skeletal muscle biopsy as well as peripheral blood mononuclear cells (PBMC; n=4), and platelets (n=4) were collected pre- and post-supplementation. Mitochondrial respiration was determined in permeabilized myofibers from the m. vastus lateralis using Oroboros, and in intact PBMC and platelets using a Seahorse.

**Results:** Maximal coupled respiration (respiration linked to ATP production) in muscle was not significantly changed by 8 weeks of EAA supplementation. However, ATP-linked respiration, maximal respiration and reserve capacity were significantly decreased in PBMC following 8 weeks of EAA supplementation. While no significant differences in mitochondrial respiration were observed for platelets, the glycolytic capacity of platelets was decreased after EAA supplementation. No significant alterations in glycolysis were observed in PBMC.

**Conclusions:** These results indicate that EAA supplementation may lower respiration rates in PBMC. The mechanisms underlying these changes may include that by lowering lipids, as we previously observed, cellular stress is reduced and ATP demand is reduced, or that the substrate pool is altered and thus metabolism shifted. Future studies are needed in order to elucidate mechanisms and understand the implications of these novel findings.

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**5.6**

## DIMINISHED VASCULAR FUNCTION IN OLD MEN CORRELATES WITH ELEVATED MITOCHONDRIAL RESPIRATION IN PERIPHERAL BLOOD MONONUCLEAR CELLS

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Background: Vascular aging, featuring endothelial dysfunction related to oxidative stress, precedes an increased risk of cardiovascular disease (CVD). Mitochondrial activity is paramount to optimal vascular health, and its dysfunction is thought to play a role in oxidative stress-mediated vascular aging. Adenosine monophosphate-activated protein kinase (AMPK) is a cellular regulator of nitric oxide synthase activity, upstream of both vasodilation and mitochondrial function; decreased AMPK activity observed in aging impacts many physiological functions. We hypothesized that vascular endothelial dysfunction observed in old men is associated with mitochondrial abnormalities in peripheral blood mononuclear cells (PBMCs), mediated by AMPK activity. Methods: Endothelial function (brachial artery flow-mediated dilation, FMD) and PBMC mitochondrial respiration (Oroboros) were measured in 18 healthy men, either young (N=10, 30±5yr, mean±SD) or old (N=8, 62±7yr). Expression of pAMPK and eukaryotic translation initiation factor 4E-binding protein 1(4E-BP1, a marker of cellular signaler mTOR) were measured in PBMCs using Western blot analysis (young N=3 and old N=7). Results: FMD was lower in old compared to young men (5.2±0.6% vs. 8.1±0.9%, p=0.02). PBMC lipid respiration in state 3 trended higher in old compared to young men (33.1±5.3 pmol/sec/1 x $10^6$ cells, mean±SEM vs. 18.4±2.5 pmol/sec/1 x $10^6$ cells, p=0.09). Respiratory control ratio (RCR, state 3:state 4, a measure of mitochondrial efficiency) was also greater in old compared to young men in lipid respiration (3.4±0.2 vs. 2.3±0.33, p=0.01). FMD was inversely correlated with both carbohydrate (r=-0.52, p=0.03) and lipid respiration (r=-0.54, p=0.02) uncoupled states, and lipid respiration RCR was inversely correlated with 4E-BP1 protein content in the pooled population (r=-0.66, p=0.03). There were no correlations with pAMPK protein levels. Conclusions: The greater mitochondrial respiration in old men correlative with diminished vascular function may be compensatory and indicative of early mitochondrial maladaptation. As mitochondrial dysfunction is associated with the generation of reactive oxygen species, known to deplete endothelial function, altered redox state in the vasculature is the focus of ongoing investigation in our

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**5.7**

## SKELETAL MUSCLE MITOCHONDRIAL DYSFUNCTION AND IL-33 RECEPTOR (ST2) GENE DELETION IN A MOUSE MODEL OF PULMONARY HYPERTENSION

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Pulmonary arterial hypertension (PAH) is a progressive, incurable disease of the pulmonary vasculature leading to right ventricular failure. Cytokines have been implicated in pulmonary resistance vessel remodeling, and an elevated serum IL-33-to-IL-33 receptor (ST2) ratio is a biomarker of PAH. Whether cytokines contribute to skeletal muscle pathology and disease progression is unknown. We hypothesized that muscle mitochondrial dysfunction occurs in PAH skeletal muscle through an IL-33-dependent cytokine pathway.

To test this hypothesis we used the Sugen/hypoxia (SuHx) model of pulmonary hypertension and adult WT and IL-33 receptor gene ablated ($ST2^{-/-}$) mice. Diaphragm and soleus mitochondrial function were measured under maximal ADP-stimulated respiration ($J_{O2max}$), and uncoupled electron transport system capacity (ETS) conditions with glutamate, malate, and succinate as substrates. Regulators of mitochondrial fusion (Mfn2, Mfn1) and biogenesis (PGC1α) and muscle protein ubiquitination (MuRF1) were measured in gastrocnemius by Western blot.

Males: Diaphragm $J_{O2max}$ was lower in WT-SuHx vs. WT-CON (112±33 vs 193±80 pmol.s.mg$^{-1}$; $p<0.05$), but not in $ST2^{-/-}$-SuHx (207±109 pmol.s.mg$^{-1}$). Soleus $J_{O2max}$ was also lower in WT-SuHx vs WT-CON (89±38 vs 138±39 pmol.s.mg$^{-1}$; $p<0.05$), but not in $ST2^{-/-}$-SuHx (122±71 pmol.s.mg$^{-1}$). Gastrocnemius Mfn1/2 was lower ($p<0.05$) in WT-SuHx and $ST2^{-/-}$-SuHx vs WT-CON. MuRF1 was not different across treatment or genotype ($p>0.05$). PGC1α was lower in WT-SuHx vs WT-CON ($p=0.057$), but was not different when comparing $ST2^{-/-}$-SuHx vs $ST2^{-/-}$-CON.
Females: Diaphragm $J_{O2max}$ was unaffected by SuHx. However, ETS was lower in both WT-SuHx and $ST2^{-/-}$-SuHx vs. WT-CON (162±8 and 157±107 vs 256±41 pmol.s.mg$^{-1}$; $p<0.05$). Soleus $J_{O2max}$ was unaffected by SuHx. Mfn1/2, MuRF1, and PGC1α were not affected in the gastrocnemius of SuHx females.

In male mice, SuHx conditions result in a profound reduction in skeletal muscle mitochondrial oxidative capacity associated with lower levels of fusion proteins. Global gene deletion of the IL-33 receptor (ST2) prevented a reduction in diaphragm/soleus mitochondrial respiration independent of fusion protein levels. Conversely, females exhibited a modest change in muscle mitochondrial function and no difference in the level of mitochondrial regulators. Inflammatory cytokines, such as IL-33, may play a role in skeletal muscle maladaptation to PAH and this appears to be sex-dependent. *Support: US Department of Veterans Affairs and SDSU University Grants Program.*

**5.8**

## EFFECT OF LACTATE ON MITOCHONDRIAL RESPIRATORY FUNCTION IN SKELETAL MUSCLE

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Lactate is now recognized as not merely a metabolic substrate. We previously reported that single administration of lactate up-regulated genes related to oxidative metabolism including *Ppargc1a* and *Ucp3* in mouse skeletal muscle. To examine the role of lactate as a signal for improving mitochondrial function, we first investigated whether repeated lactate administration alters mitochondrial enzyme activity. C57BL/6J male mice daily received 1 g/kg of sodium lactate by i.p. injection for one week. We found that COX activity was increased in skeletal muscle after one week of lactate administration. There was a trend toward increased lactate transporter MCT4 protein content. The peak blood lactate concentration after the injection was declined on the last day (day 7) compared with that on the first day (day 1), which suggests that lactate is taken up by tissues and oxidized in mitochondria. Next, we measured mitochondrial respiration using a Seahorse extracellular flux analyzer. For this analysis, C2C12 myotubes were treated with 20 mM lactate for 24 hours. However, there were no effects of lactate on either basal or maximal oxygen consumption rates. Further studies using different concentration and/or duration of lactate treatment are required. In this study, we demonstrate that repeated lactate administration increases lactate clearance and mitochondrial enzyme activity in mouse skeletal muscle.

**5.9**

## HETEROGENEITY OF ENERGY TRANSFORMATION IN PULMONARY ENDOTHELIAL CELLS: A LOOK AT THE MECHANICAL WORK

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Biological cells are no exception to the laws of physics. One such law is the law of energy conservation. Following this law, the cell transforms its energy currency to engage in three types of work: chemical, transport, and mechanical. While chemical and transport work is studied in great details, the mechanical work of the cells has never been quantified. Quantitative assessment of cellular mechanical work will be crucial to identify physical laws that govern processes such cell reorientation, barrier function, and migration. Using Monolayer Stress Microscopy, a novel in vitro platform to measure local mechanical forces around a cell, we have quantified mechanical work that each cell in an advancing monolayer does on its substrate as well as on its neighbors.

We measured mechanical work for three cellular systems: pulmonary artery endothelial cells (AECs), pulmonary microvascular endothelial cells (MECs), and pulmonary vein endothelial cells (VECs). These three cellular systems are known to exhibit remarkable functional and molecular heterogeneity. Here we found that over 940 minutes, although the cellular monolayers have an advancing front, the AECs with their uniform cobblestone morphology and negligible motion were most quiescent and VECs with their non-uniform mesenchymal morphology and non-coherent motion were least quiescent. The farther the cells were from being quiescent, the more strongly the cells were engaged in mechanical work. Across these cellular systems, the relative difference in the mechanical work on the substrate (WS) was not same as the relative difference in the mechanical work on the neighboring cells (WC). The cells that are known to have strongest barrier properties – the MECs – had the highest value for the ratio WS/WC, and the cells with weakest barrier properties – the AECs – had the lowest value for the ratio WS/WC. Moreover, the mechanical work of the fastest and most coherently moving cells – the MECs – was least sensitive to the cellular size, distance from the advancing front and their state of jamming. Taken together, this study presents a first quantitative assessment of cellular mechanical energies and opens new avenues for the mechanobiological assessment of pulmonary vascular diseases.

**5.10**

## ROCK2 MODULATES SKELETAL MUSCLE MITOCHONDRIAL FUNCTION

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ROCK2 Modulates Skeletal Muscle Mitochondrial Function

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Background: Rho-associated coiled-coil containing kinase (ROCK) is a ubiquitous serine/threonine kinase with established clinical relevance in wide range of pathologies including metabolic diseases such as Type 2 Diabetes and muscular disorders. Previous studies have attempted to investigate ROCK's role in skeletal muscle function but outstanding conflicts exists due to absence of isoform specific knockdowns and lack of tissue specificity with chemical inhibitor treatments. Similarly, while literature exists on ROCK's effect on mitochondrial driven apoptosis, there is a gap in knowledge on isoform specific ROCK2 effect on skeletal muscle mitochondria.

Methods and Results: To study ROCK2 role in the skeletal muscle, we have generated a novel genetic mouse model with a skeletal muscle-specific deletion of ROCK2 (hereby known as Myo R2KO). To characterize *in vivo* phenotype, we first subjected mice to Forced Endurance Treadmill Test and discovered that Myo R2KO mice had decreased endurance performance compared to control. In addition, we discovered that after 6 week exercise stimulus, our Myo R2KO exhibited an increased heat production quantified by metabolic cages. Consequently, we wanted to measure energy utilization on a tissue level. We found no difference in glycolysis as measured by lactate readings, glucose uptake assay and Seahorse glycolysis stress test. However, we did delineated that primary myofibers isolated from Myo R2KO animals had poorer oxidative phosphorylation ability as measured by Seahorse Mitochondria Stress Test. Next we determined *in vitro* that Myo R2KO mitochondria had dysfunctional mitochondria function represented by increased ROS production, decreased ATP luminescence and decreased membrane potential measured through TMRE staining. We are currently validating potential molecular signaling mechanisms. Preliminarily, we have found an increase in UCP3 levels in mRNA isolated from our Myo R2KO animals compared to control.

Conclusion: In conclusion, skeletal muscle ROCK2 is a critical regulator of mitochondria function. When skeletal muscle ROCK2 is knocked out mitochondria dysfunction occurs which leads to *an in vivo* phenotype of abnormal heat production and decreased motor performance. These

findings suggest that skeletal muscle ROCK2 may be a viable target to treat mitochondria dysfunction with long term implications for multiple diseases including Type 2 Diabetes and skeletal muscle atrophy.

**5.11**

**SINGANLING MECHANISMS OF DRP1 TRANSLOCATION TO THE MITOCHONDRIA-SR ASSOCIATIONS IN ADULT MURINE CARDIOMYOCYTES**

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Mitochondrial dynamics, including fission, fusion, and movement, is a fundamental mechanism in regulating mitochondrial function. The high level of Drp1 in the heart seems to be at odds with numerous studies showing that mitochondrial dynamics in adult ventricular myocytes occurs rather infrequently. Electron micrographs show that in adult mammalian cardiac myocytes, the majority of inter-myofibrillar mitochondria appear to be fragmented and tethered to the sarcoplasmic reticulum (SR) near the dyads. We tested the hypothesis that Drp1 is strategically accumulated at the mitochondria-SR associations (MAM) and that during continuous excitation-contraction coupling processes (e.g. heartbeats), the localized high $Ca^{2+}$ in the SR-mitochondria junction further increases translocation of nearby cytosolic Drp1 to the MAM. **Methods and results:** Western blots analysis shows a Drp1 presence in the SR and crude mitochondria fractions. Furthermore, pure mitochondria and MAM fractions were obtained via Percoll purification of crude mitochondria. Proteomic results show that Drp1 is mostly presented and enriched in the purified MAM but not in the pure mitochondrial fraction. To confirm this biochemical data, the distance between SR (RyR2) and Drp1 (labelled with immunofluorescent antibodies) in adult cardiac myocytes was quantified in nanometer scale by using ZeissLSM880 confocal microscope-Airy-scan detector. Intriguingly, over 80% of Drp1 is located within 200 nm radius of RyR2. Similar results can be observed in preparations by using immunogold TEM. Moreover, Drp1 distribution along the dyads was studied by the localization of the Drp1 along the transversal side of the mitochondria (TOM20). A significantly increased translocation of Drp1 to the transversal sides was observed upon 15min-2Hz electric field stimulation in freshly isolated adult ventricular myocytes superfused with isoproterenol+$Ca^{2+}$ (1mM) in comparison to myocytes incubated with quasi-$Ca^{2+}$-free (2.5 μM) buffer. Finally, isolated hearts form rat retrogradely perfused (Langendorff) with Krebs buffer supplemented with isoproterenol+$Ca^{2+}$ (1.8mM) showed a significantly elevated Drp1 accumulation at the MAM fraction vs. those perfused with quasi-$Ca^{2+}$-free (2.5 μM) Krebs buffer. **Conclusion:** According to these results, we conclude that Drp1 is preferentially positioned at the mitochondria-SR associations and its recruitment likely involves $Ca^{2+}$ signaling and/or beta-adrenergic activity.

**5.12**

**THE MITOCHONDRIAL CIRCUIT BREAKER: NETWORK SECURITY IN THE SKELETAL MUSCLE MITOCHONDRIAL RETICULUM**

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The skeletal muscle mitochondrial reticulum is a large, grid-like network of physically and electrically coupled mitochondria. While network connectivity allows for rapid communication and distribution of energy throughout the cell, this connectivity puts the entire network at risk as localized dysfunction can also quickly spread throughout the cell. We hypothesized there must be protective mechanisms in place to minimize spread of dysfunction throughout the skeletal muscle mitochondrial reticulum. To test this hypothesis, a photoactivatable mitochondrial uncoupler (MitoPhotoDNP) was loaded into isolated mouse soleus muscle fibers to enable precise control over mitochondrial depolarization within specific regions of the cell upon UV irradiation. The electrical response to localized mitochondrial depolarization was followed by monitoring the mitochondrial membrane potential (TMRM) through a confocal microscope. The structural response was evaluated by imaging muscle fibers containing a genetically encoded, photoswitchable (green-to-red) mitochondrial fluorescent protein (MitoDendra2). Immediately (<400 ms) upon irradiation of MitoPhotoDNP in the center of a muscle cell, there was a shared depolarization of the membrane potential in the irradiated and the surrounding regions consistent with electrical network connectivity. However, shortly thereafter, electrical separation between the irradiated and surrounding regions occurred where the irradiated region continued to depolarize while the non-irradiated region repolarized back to baseline levels with a time constant of 7.9±0.3 seconds. Mitochondria within the irradiated region began to physically disconnect from the network ~30 seconds after depolarization. Physical separation occurred through retraction of branched, elongated mitochondria into consolidated structures resulting in 32±4% fewer, but 33±8% larger mitochondria inconsistent with mitochondrial fission. Indeed, mitochondrial fission inhibitors, mdivi-1 or dynasore, did not prevent the physical separation mechanism. These data suggest dysfunctional mitochondria can be quickly electrically sequestered through a circuit breaker-like mechanism while damaged mitochondria are physically separated through a consolidation process that likely facilitates repair or replacement through mitophagy.

These rapid alterations in mitochondrial connectivity allow skeletal muscle fibers to quickly respond to local dysfunction within seconds and restore energy distribution to the remainder of the muscle cell.

**5.13**

**EXERCISE COMBINED WITH CALORIE RESTRICTION-INDUCED WEIGHT LOSS, BUT NOT WEIGHT LOSS ALONE, IMPROVES MITOCHONDRIAL RESPIRATORY CAPACITY IN SKELETAL MUSCLE OF OLDER OBESE SUBJECTS**

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**Background:** Skeletal muscle mitochondrial capacity has been linked to deranged energy metabolism in aging, obesity and type 2 diabetes. Calorie restriction has been shown to have "anti-aging" effects in animal models, and calorie restriction-induced weight loss (CRWL) and exercise can both improve several aspects of cardiometabolic health in human obesity. The effects of CRWL in older obese humans, however, are not known. The aim of this study was to investigate the effect of 6-month diet-induced weight loss intervention with or without the addition of exercise training on skeletal muscle mitochondrial respiratory capacity.

**Methods:** Twenty-six older adults with obesity were randomized to one of the following 6-month intervention: Health education (CON: n=9, 5M/3F, age=70±5yrs, BMI=35±5.8kg/m$^2$), Calorie restriction-induced weight loss (CRWL: n=7, 2M/5F, age=71±5yrs, BMI=35.8±5.0kg/m$^2$), or Weight-loss and exercise (WLEX: n=10, 5M/5F, age=68±3yrs, BMI=37.7±6.2kg/m$^2$). CON subjects participated in biweekly health education sessions with no specific exercise/dietary advice. CRWL and WLEX participants had a goal of 10% weight-loss through calorie restriction. Subjects in the WLEX group completed a supervised exercise program. A percutaneous muscle biopsy of the vastus lateralis was collected pre and post interventions. Mitochondrial respiratory capacity of permeabilized myofibers was evaluated by high-resolution respirometry. Complex I+II supported leak respiration, complex I+II supported maximal oxidative phosphorylation (OXPHOS), and maximal uncoupled respiration were evaluated. Additionally, titration of ADP was performed to evaluate ADP sensitivity.

**Results:** While mitochondrial respiration was unchanged in the CON and CRWL groups after the 6-month intervention ($p>0.05$), subjects in the WLEX group presented an increased leak (PRE: 65.4±18.8 vs. POST: 79.1±29 pmol/s*mg; $p=0.05$), maximal OXPHOS (PRE: 258.4±40.6 vs. POST: 307±68.2 pmol/s*mg; $p=0.04$) and a trend to higher uncoupled respiration (PRE: 301.3±39.6 vs. POST: 346.8±79 pmol/s*mg; $p=0.06$) after the exercise training. Additionally, while Km was unchanged in the three groups after intervention, there was a trend for increased Vmax in the exercise group after training (PRE: 255±43 vs. POST: 304±66; $p=0.08$).

**Conclusions**: Exercise is required to improve mitochondrial respiratory capacity in skeletal muscle of older obese human subjects undergoing calorie restriction-induced weight loss.

**5.14**

**WITHDRAWN**

**5.15**

**LONGITUDINAL FOLLOW-UP OF EQUINE MUSCLE MORPHOMETRICS AND ASSOCIATED METABOLIC PROPERTIES INDUCED BY 8 WEEKS OF TREADMILL TRAINING**

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***Reasons for performing the study:*** Aquatraining is increasingly incorporated into equine training and rehabilitation programs. However, little is known about the physiological responses to this type of training. Our research group previously reported the morphometric changes in 15 skeletal muscles of horses subjected to 8 weeks of aquatraining. ***Objectives:*** (1) to compare muscle morphometric changes induced by dry treadmill training with those induced by aquatraining, (2) to identify changes in muscle metabolic properties induced by treadmill training. ***Materials and Methods:*** seven healthy untrained horses completed an 8-week treadmill training program (20 min/session, 5 days/week, belt speed 1.25 m/sec). Morphometric assessment of 15 strategically chosen muscle groups was performed on 3 occasions (start, after 4 weeks and at finish) using transcutaneous ultrasound (B-mode Esaote, macroconvex, 5-7.5 MHz). Muscle biopsies were harvested at start and finish of the study, at rest, from the M. Pectoralis profundus (PP) and Vastus lateralis of the M. quadriceps femoris (QF). Principal Component Analysis was performed on the metabolomics results. ***Results:*** (1) there was a significant increase in muscle mass of the M. Trapezius cervical part (+57%), the M. PP (+29%), the M. Trapezius thoracic part (+26%), the M. Brachiocephalicus (+10%) and a significant decrease in muscle mass of the QF muscle (-18,8%), the M. Erector spinae lumbal part (-

8,8%) and the M. Semitendinosus (-6,7%) after treadmill training; (2) treadmill training significantly increased levels of long chain and significantly decreased levels of medium chain acylcarnitines in both muscle groups. Early (glucose, glucose-6-phosphate and fructose-6-phosphate) and late stage (pyruvate and lactate) glycolytic intermediates and pentose-phosphate pathway intermediates were significantly increased in the QF muscle. A significant increase in oxidized glutathione and intermediates of the glutamine/glutamate metabolism and a significant decrease in glycine and acetyl-glycine was found in the PP muscle. ***Conclusions:*** treadmill training clearly influences different skeletal muscles when compared to aquatraining[1]. Comparison of the metabolite profiles reveals an upregulation of fat oxidation and glycolysis in QF muscle (decreasing muscle mass) versus an upregulation of fat oxidation and amino acid metabolism in PP muscle (increasing muscle mass).

[1]Morphometric Changes in 15 Skeletal Muscles of Horses After 8 Weeks of Aquatraining. *Equine Veterinary Journal 2016, 48*, 30.

**5.16**

**THE ROLE OF PARKIN IN AGE-DEPENDENT PLATELET MITOCHONDRIAL AND THROMBOTIC DYSFUNCTION**

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Aging is one of the greatest risk factors for thrombosis and gives rise to conditions such as deep vein thrombosis, myocardial infarction and stroke. However, the mechanisms underlying age-related increased thrombosis remain unclear. Platelets are anucleate circulating cells that when activated, aggregate and catalyze thrombus formation. Prior studies have shown age-dependent increases in platelet activation, but the molecular mechanisms that lead to this activation remain unclear. Though platelets are anucleate, they contain functional mitochondria and an active ubiquitin-proteosome system (UPS). Given that age related declines in mitochondrial function and the UPS have been documented in other cell types, we hypothesized that age-dependent dysfunction in the UPS leads to increased mitochondrial reactive oxygen species (mtROS) production, which stimulates platelet activation leading to thrombosis. Herein, we demonstrate that platelets from healthy middle aged (36-70 years) and elderly (>75 years) human subjects show a decrease in UPS activity as well as decreased expression of the E3 ubiquitin ligase Parkin, a key regulator of mitochondrial proteins. This was accompanied by an increase in mitochondrial oxidant production compared to healthy young subjects (18-35 years). These results were recapitulated in a mouse model of healthy aging in which old (1.5 years) mice showed decreased time to occlusion in a ferric chloride thrombosis model, concomitant with increased production of platelet mitochondrial ROS and decreased UPS activity. Ongoing studies in wildtype and parkin knockout mice are testing whether decreased UPS activity directly leads to mitochondrial ROS production and whether these changes result in platelet activation.

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**5.17**

**IMPACT OF EXERCISE TRAINING AND AGING ON THE SKELETAL METABOLISM IN RATS WITH LOW/HIGH INTRINSIC AEROBIC CAPACITY**

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**PURPOSE:** Low exercise capacity is a strong and independent predictor of cardiovascular disease and early mortality[1]. Exercise training is widely known to be beneficial to human health in different ways. Low intrinsic capacity runners (LCR) is a rat model which is especially useful to study the effect of altered energy metabolism and the effect of different interventions. Nuclear magnetic resonance (NMR) based metabolomics has been widely used to investigate metabolic change. The purpose of this study was to explore the metabolic profiles of LCR and high capacity runners (HCR) rats and to investigate the impact of exercise training in muscles metabolism by NMR based metabolomics.

**METHODS: Animal model:** LCR and HCR rat models were artificially selected by generations 29 and 30 as previously described[1]. The maximal oxygen consumption (VO2max) was recorded to measure running capacity. Selected rat models were divided into two rounds according to the age difference (Round 1: 9 months age; Round 2: 18 months age) and performed training regimes. **MR experiments:** Rat soleus muscle were extracted with dual-phase extraction protocol. To perform NMR study. Raw MR spectra were pre-processed before multivariate analysis. **Statistics:** Partial least square discriminative analysis (PLS-DA) was used to the main metabolic differences between the groups. Three-way ANOVA was used to compare the mean difference of VO2max across the LCR and HCR groups with or without exercise training.

**RESULTS:** HCR rats showed a 54% and 30% higher VO2max compared with LCR rats without training, in Round 1 and Round 2 respectively. Exercise training did not change VO2max significantly in the LCR group, while it induced a significant increase (34%) in the HCR group in Round 1. PLS-DA discriminated LCR sedentary group from HCR sedentary group in both Round 1 and Round 2.

Exercise training also influenced metabolic profiling in both Round 1 and Round 2 of LCR groups. The loading plots demonstrate the metabolites (glutamine, glutamate, creatine, lactate, taurine) associated with discriminations.
**CONCLUSION:** Exercise training increased VO2max in HCR rats, but not in LCR. The results of this study suggest a strong interaction between the exercise training and the intrinsic exercise capacity, as evidenced by alteration in VO2max and metabolic profiles. Metabolomics analysis can potentially predict the impact of exercise training and aging on LCR rats. Some of the influential metabolites are detectable by clinical MRS examination.
Reference: 1. Koch, L,etc. *Circulation Research*. 2011.

**5.18**
**MULTIMERIC METABOLIC ENZYME COMPLEXES IN THE CYTOSOL OF THE ADULT MAMMALIAN HEART**

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**Background:** Multimeric complexes composed of metabolic enzymes can facilitate channeling of metabolic intermediates in the mitochondrion; however, it is unclear whether analogous complexes coordinate the glucose metabolic network in the cytosol of the mammalian heart. We used native-gel approaches to identify multimeric metabolic enzyme complexes in the heart and determined how changes in metabolic activity affect their formation.
**Methods:** We used blue-native gel electrophoresis (BN-PAGE) to examine high molecular mass enzyme complexes in the cytosol of hearts with known differences in glycolytic rate, i.e., exercise (EXE)-adapted hearts and hearts expressing kinase-deficient or phosphatase-deficient phosphofructokinase 2 (termed here as $Glyco^{Lo}$ or $Glyco^{Hi}$, respectively). The identity of the complexes was assessed by mass spectrometry and immunoblotting. Myocardial glucose utilization was quantified in perfused hearts by measuring the formation of $^3H_2O$ derived from metabolism of [5-$^3$H]-glucose.
**Results:** Compared with hearts from sedentary wild-type (WT) controls, myocardial glucose utilization was ~60% higher in both WT EXE and sedentary $Glyco^{Hi}$ hearts and was 40% lower in $Glyco^{Lo}$ hearts ($p<0.05$; n=5–8/group). Separation of myocardial multimeric complexes in the cytosol by BN-PAGE yielded several bands greater than 720 kDa. Discernable mass shifts in two bands in $Glyco^{Hi}$ samples suggested a potential multimeric complex responsive to glycolytic activity. By mass spectrometry, this complex was found to contain all enzymes in the glycolytic pathway with the exception of hexokinase 1/2, phosphoglycerate kinase, and phosphoglycerate mutase. This complex also appears to harbor acetyl CoA carboxylase 2 and fatty acid synthase. In WT EXE hearts, BN-PAGE immunoblotting demonstrated a 5-fold increase in tetrameric lactate dehydrogenase (LDH) B compared with hearts from sedentary WT, $Glyco^{Lo}$ or $Glyco^{Hi}$ hearts ($p<0.05$; n=3/group).
**Conclusions:** The cytosol of the mammalian heart harbors multimeric, metabolic enzyme complexes that are modulated by glycolysis and exercise. Future studies are focused on understanding how they contribute to metabolic pathway activity, the mechanisms that regulate their formation, and how they contribute to cardiac health.

**5.19**
**MITOCHONDRIAL DYNAMICS IN SKELETAL MUSCLE IN PATIENTS ON MAINTENANCE HEMODIALYSIS**

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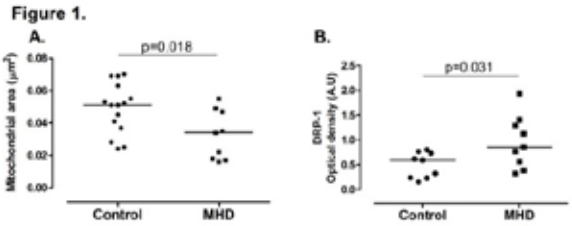
Frailty and sarcopenia are commonly present in patients on maintenance hemodialysis (MHD) and increase the risk of morbidity and mortality. Mitochondria, as the principal source of energy, are important for proper muscle function. Mitochondria are dynamic organelles that are constantly undergoing either fusion or fission. Mitochondrial fusion leads to enlarged mitochondria and maximizes the oxidative capacity. Mitochondrial fission results in smaller mitochondria and is crucial for the segregation and elimination of damaged mitochondria. Oxidative stress, commonly present in patients on MHD, may damage the mitochondria. We have previously described reduced mitochondrial content and ultrastructural mitochondrial abnormalities in patients with chronic kidney disease on MHD. Thus, we now evaluate the hypothesis that mitochondrial fission is increased in patients on MHD, as a mechanism to remove damaged mitochondria. For this purpose, we evaluated mitochondrial dynamics in skeletal muscle biopsies from 10 patients on MHD and 15 controls with no history of CKD. The groups were matched by age, gender, and race. We measure mitochondrial size using transmission electron microscopy. We also measured OPA-1, Fis-1 and DRP-1, markers of mitochondrial dynamics, by western blot. The groups were also comparable in self-reported activity. Controls and patients on MHD were similar in terms of age (52.8±8.7 vs. 50.3±15.1), BMI (30.6±7.3 vs. 29.0±5.1), and gender. We found that mitochondria are smaller in patients with ESRD compared to individuals with no history of CKD (Figure 1A). We did not find any difference in the abundance of either OPA-1 or Fis-1 between the groups. We did find an increased content of DRP-1 in patients on MHD (Figure 1B). Smaller mitochondria may indicate a preferential mitochondrial fission in skeletal muscle from patients on MHD. Damaged mitochondria may be segregated and eliminated by mitophagy. This is consistent with our previous finding of increased mitophagy in patients on MHD. Future studies are required to evaluate how changes in mitochondrial dynamic and function may impact frailty and sarcopenia in patients on MHD.




**5.20**

**LOCALIZED PROTON-COUPLING BIOENERGETICS IN MITOCHONDRIA**

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Recently, we have preliminarily made a major breakthrough in understanding proton-coupling bioenergetics over the Nobel-prize work of Peter Mitchell's chemiosmotic theory. The decades-longstanding energetic conundrum of alkalophilic bacteria as to how they are able to synthesize ATP has now, for the first time, been clearly elucidated using a newly modified proton motive force (pmf) equation based on the new proton electrostatic localization theory [Lee JW (2015), Bioenergetics 4: 121. doi:10.4172/2167-7662.1000121]. This work may have fundamental implications to better understand the bioenergetics in many other biological systems including mitochondria. For example, the pmf value reported previously with the Mitchellian equation in the last 50 years may need to be revisited for possible significant updates in mitochondria. Notably, with the conventional chemiosmotic theory, one would have to "adjust" the Delta pH values to get an energy efficiency <100% in mitochondria (Silverstein TP (2014) J Bioenerg Biomembr 46:229–241). This "elephant-in-room" scientific problem could now be addressed with the newly developed pmf equation. This presentation will show that the true total pmf value (including the local pmf) may be significantly larger than those previously reported in mitochondria, as they all used the classic Mitchellian pmf equation, which misses an important contribution from the localized protons. This finding may have far-reaching implications on many biological systems including human health and possibly also related to the fundamentals of human memory.

**5.21**

**MITOCHONDRIAL REGULATION PROTECTS THE TURTLE HEART FROM OXIDATIVE DAMAGE AFTER REOXYGENATION**

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Reintroducing oxygen after a period of anoxia causes oxidative damage to tissues by production of reactive oxygen species (ROS). Freshwater turtle hearts (*Trachemys scripta*) are remarkably resilient to oxidative damage and suffers no damage from reoxygenation even after months of anoxia during winter hibernation. Preventing ROS production from mitochondria might be key to this resilience. In the mouse, inhibition of mitochondrial complex I by the post-translational modification S-nitrosation has been shown to inhibit ROS production upon reoxygenation. In this study, we tested the hypothesis that turtles prevent oxidative damage after anoxia/reoxygenation by limiting ROS production via S-nitrosation of complex I. We acclimated turtles to low temperature and anoxia or normoxia and analysed isolated heart mitochondria for respiration rate, ROS production, enzyme activity and S-nitrosation of mitochondrial proteins. We also used the mitochondria specific S-nitrosating agent MitoSNO to analyse the effect of S-nitrosation on turtle heart mitochondria *in vitro*. We found that anoxia acclimation does reduce ROS production and respiration rate of purified mitochondria, and that S-nitrosation of complex I inhibits activity and ROS production after anoxia/reoxygenation *in vitro*. However, activity and S-nitrosation of turtle complex I was not affected by anoxia acclimation *in vivo*. Instead, lower activity of the mitochondrial marker enzyme citrate synthase and lower maximal respiration rate of anoxic turtle mitochondria indicates down-regulation of the content of mitochondria in the turtle heart during anoxia. Reducing the content of mitochondria in the turtle heart during prolonged anoxia may prevent ROS production upon reoxygenation and protect against oxidative damage.

**5.22**

**12 WEEKS RESISTANCE TRAINING INCREASED SKELETAL MUSCLE MOTS-C, A MITOCHONDRIALLY ENCODED PEPTIDE, IN MEN WITH IMPAIRED GLUCOSE REGULATION**

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Beyond all well-known retrograde signals, studies have identified mitochondria-linked factors that influence the cellular and extracellular environments, including mitochondria-derived peptides and mitochondria-localized proteins (1-3). The first described mitochondria-derived peptide was humanin (4), and recently another small peptide also encoded from the mtDNA called MOTS-c (mitochondrial open reading frame of the 12S rRNA-c) was discovered (5). MOTS-c has been shown to regulate glucose metabolism by activating AMPK and the glucose

transporter type 4 (GLUT 4) (5,6). Whether human skeletal muscle MOTS-c expression is influenced by exercise is not known.

**Purpose:** This study aimed to investigate whether endurance or resistance training over a 12-week period could induce changes in levels of MOTS-c protein in men with IGR both in skeletal muscle and in serum. The hypothesis was that MOTS-c is an exercise-responsive mitokine. **Methods:** Male subjects (n=48) with impaired glucose regulation (IGR) were randomly assigned to resistance training (RT), Nordic walking (NW) or a control group (C). The training was performed 3 times/week during 12 weeks. Biopsies from the *m. vastus lateralis* and serum samples were obtained before and after the intervention. Skeletal muscle and serum protein and mRNA levels of MOTS-c were analyzed along with factors involved in metabolic regulation such as MEF2A, RIP140, PGC-1a and GLUT4. **Results:** Skeletal muscle MOTS-c protein increased in the RT group ($p<0.05$, $n=15$), but did not change in the NW or C group. There were no significant changes of MOTS-c serum levels over time or between the groups. However, correlation analysis revealed a negative correlation between âˆ†MOTS-c protein in serum and âˆ†RIP140 protein in skeletal muscle ($r=-0.513$, $p<0.01$). Interestingly, a positive but weak correlation between of âˆ†MOTS-c protein in serum and âˆ†GLUT4 mRNA in skeletal muscle was detected ($r=0.359$, $p=0.015$). **Conclusion:** In this study it is shown, for the first time, that MOTS-c protein levels increase in human skeletal muscle following 12 weeks of resistance training in men with IGR. This study also highlights the importance of studying mitochondria-derived peptides to further understand and improve mitochondrial and exercise related medicine.

**5.23**

## ATF5 IS REQUIRED FOR MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE-MEDIATED CARDIOPROTECTION DURING ISCHEMIA-REPERFUSION INJURY

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**Introduction:** The mitochondrial unfolded protein response (mtUPR) is a compartment-specific, stress-induced retrograde signaling pathway. In *C. elegans*, the transcription factor ATFS-1 plays a central role in the mtUPR. Under mitochondrial proteotoxic stress, ATFS-1 enters the nucleus and upregulates a variety of genes including those for mitochondrial chaperones and proteases to reestablish mitochondrial proteostasis.

ATF5 has been proposed to be the mammalian ortholog of ATFS-1, but only recently was it shown that ATF5 can rescue the mtUPR response in *C. elegans* lacking ATFS-1. Here, we use a mouse model to examine if induction of the mtUPR can convey cardioprotection in ischemia-reperfusion (IR) injury and if ATF5 is essential for this effect.

**Methods:** An ATF5 knockout mouse model on a C57BL/6J background was used with age- and gender-matched controls from the same colony, complying with NIH guidelines. Langendorff-perfused hearts were exposed to 30 min of ischemia followed by 60 min of reperfusion. IR injury was quantified by functional recovery of the rate × pressure product during reperfusion, and by infarct size measured by tetrazolium chloride staining. The mtUPR was induced using oligomycin, doxycycline, or chloramphenicol administered by intraperitoneal injection 6 h prior to Langendorff-perfusion.

**Results:** $Atf5^{-/-}$ mice had a 67% neonatal death rate, similar to previous reports, so mice of both genders were used in this study. In untreated mice, neither genotype ($Atf5^{+/+}$, $Atf5^{+/-}$, or $Atf5^{-/-}$) nor gender had an effect on recovery from cardiac IR injury. However, when $Atf5^{+/+}$ or $Atf5^{+/-}$ mice were treated with oligomycin, doxycycline, or chloramphenicol, there was a significant increase in functional recovery and a significant reduction in infarct size. This cardioprotective effect of mtUPR induction prior to IR injury was absent in $ATF5^{-/-}$ mice.

**Conclusions:** This study shows that the *in vivo* pharmacologic induction of the mtUPR conveys cardioprotection after IR, with this effect requiring ATF5. Furthermore, the loss of ATF5 did not alter the susceptibility of untreated hearts to IR injury, as expected from the mtUPR signaling pathway being a transcriptional regulator. The results herein provide strong supporting evidence of the hypothesis that ATF5 is the mammalian ortholog of ATFS-1.

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**5.24**

## PROTEIN KINASE CΔ (PKCΔ) CONTROLS BASAL MITOCHONDRIAL BIOENERGETICS IN DOPAMINERGIC NEURONAL CELLS: RELEVANCE TO MITOCHONDRIAL DYSFUNCTION IN NEURODEGENERATIVE DISEASES

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Mitochondria dictate both physiological and pathological processes in the nervous system. Mitochondrial dysfunction has been widely implicated in the pathogenesis of various neurodegenerative diseases, including Parkinson's disease (PD). Previously, we demonstrated that protein kinase Cδ (PKCδ) is an oxidative stress-sensitive kinase that preferentially expresses in dopaminergic neurons and plays a key role in mediating dopaminergic neuronal apoptosis via caspase-3-mediated proteolytic activation of the kinase. We also demonstrated that dopaminergic neurotoxic insults trigger PKCδ translocation from the cytosol to

mitochondria. Nonetheless, the functional roles of PKCδ in modulating basal mitochondrial functions remain elusive. In the current study, we developed a CRISPR/Cas9-based PKCδ knockdown N27 dopaminergic neuronal stable neuronal cells to investigate the relevance of PKCδ in basal mitochondrial function by comparing it with the Control CRISPR/Cas9 N27 cells. Surprisingly, PKCδ knockdown dopaminergic neuronal cells exhibit higher basal levels of total reactive oxygen species (ROS) and mitochondrial superoxides as compared to the control CRISPR/Cas9 N27 dopaminergic cells. Further characterization of cellular bioenergetics in PKCδ knockdown cells by the Seahorse XFe24 Bioanalyzer revealed a striking impairment in basal oxygen consumption rate (OCR), ATP-linked linked respiration and spare capacity. A significant reduction in mitochondrial activity and mtDNA copy number was also observed in the PKCδ knockdown cells. Image analysis using the 3D-confocal microscopy revealed significant mitochondrial structural damage in the PKCδ knockdown N27 cells as compared to control cells. Collectively, our results implies that the redox sensitive PKCδ plays an obligatory role in regulating basal bioenergetics capacity of dopaminergic neuronal cells. Grant support: (NIH NIEHS R01ES026892 and R01ES027245 and The W. Eugene and Linda Lloyd Endowed Chair).

Key Words: mitochondrial respiration, PKCδ, pesticides, Parkinson's disease.

**5.25**

## BIOENERGETIC CHARACTERIZATION OF MULTIDRUG RESISTANT BREAST CANCER CELLS

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Multidrug resistance (MDR) is a common resistant mechanism of cancer cells to cytotoxic drugs in systemic therapy. MDR is characterized by increased expression of ATP-dependent drug exporting pumps (e.g. P-glycoprotein) which remove cytotoxic compounds from the cytosol. However, the mechanism whereby cancer cells rapidly respond to this increased ATP demand is not fully understood. There have been repeated reports suggesting highly glycolytic nature of MDR phenotype. However, recent studies have suggested that mitochondrial modulators have a significant role in preventing development of MDR phenotypes. It has been shown that MCF7Dox, a MDR variant of the MCF7 breast cancer cell line has highly glycolytic phenotype with increased glucose uptake/consumption rate *in vitro* and *in vivo*. To further analyze the glycolytic pathway, we developed a new approach to quantifying glycolytic rate using extracellular acidification. We confirmed that in MCF7Dox cells, glycolytic rate under basal conditions is significantly increased compared to MCF7 cells. Furthermore, MCF7Dox cells have a significant increase in compensatory glycolysis when mitochondrial ATP production is blocked. This metabolic profile switch is accompanied by a decreased dependency on glutamine to fuel mitochondrial respiration and increased tolerance of the MCF7Dox cells to glutamine deprivation as compared to the MCF7 cells. We performed calcein efflux studies in MCF7 and MCF7Dox cells to characterize ATP-dependent pump activity responsible for the MDR phenotype. MCF7Dox cells can export cytosolic calcein-AM fluorescent probe in contrast with MCF7 cells that retain it in the cytosol, confirming the difference in ATP-dependent pump activity of the cell variants. When MCF7Dox cells were pre-incubated with 2-deoxy-D-glucose to inhibit glycolytic ATP production, no effect on calcein efflux was observed. However, when cells were pretreated with the mitochondrial ATP-synthase inhibitor oligomycin, calcein efflux was completely blocked despite increased glycolytic activity observed under this condition, strongly suggesting that MDR mechanism relies on mitochondrial generated ATP for maintaining the chemoresistance phenotype. These findings have potential therapeutic relevance in the context of specific modulation of mitochondrial ATP production to prevent therapy resistance.

**5.26**

## INACTIVATION OF MITOCHONDRIAL DEACETYLASE SIRT3 LEADS TO SOD2 HYPERACETYLATION, PROMOTES VASCULAR OXIDATIVE STRESS, INCREASES ENDOTHELIAL DYSFUNCTION, EXACERBATES HYPERTENSION AND TREATMENT WITH SOD2 MIMETICS RESCUE SIRT3 DEPLETED PHENOTYPE

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Mitochondria play an important role in redox cell signaling. Metabolic dysfunction and antioxidant depletion lead to dysregulation of redox signaling and oxidative stress which contribute to cardiovascular disease. Sirt3 is a key regulator of mitochondrial function and it activates major mitochondrial antioxidant enzyme SOD2 by deacetylation of specific lysine residues and Sirt3 depletion increases oxidative stress. We hypothesized that loss of vascular Sirt3 activity increases vascular oxidative stress and endothelial dysfunction promoting hypertension and end organ damage. The role of vascular Sirt3 was studied in human subjects with essential hypertension, wild-type C57Bl/6J mice, $Sirt3^{-/-}$, tamoxifen-inducible endothelium specific Sirt3 knockout mice ($Ec^{Sirt3KO}$) and tamoxifen-inducible smooth muscle specific Sirt3 knockout mice ($Smc^{Sirt3KO}$) using angiotensin II model of hypertension (0.7 mg/kg/day). Analysis of human subjects with essential hypertension showed 2.6-fold increase in SOD2 acetylation and 1.4-fold decrease in Sirt3 while SOD2 expression was not affected. Western blot analysis of mouse aorta showed 30% reduction of vascular Sirt3 and increased SOD2 acetylation by 2-fold after onset of angiotensin II-induced hypertension. Hypertension was markedly increased in $Sirt3^{-/-}$ mice in response to angiotensin II (0.7 mg/kg/day) compared with wild type mice and treatment with mitoTEMPO (1.5 mg/kg/day) normalized the blood

pressure and vascular relaxation in Sirt3$^{-/-}$ mice. Deletion of Sirt3 in smooth muscle exacerbated hypertension (165 mm Hg vs 155 mm Hg in wild-type) and significantly increased mortality in angiotensin II infused Smc$^{Sirt3KO}$ mice (30% vs 3% in wild-type) which was associated with higher rate of aortic aneurysm formation (75% vs 10% in wild-type). Ec$^{Sirt3KO}$ mice had elevated basal blood pressure by 12 mm Hg and hypertension was exacerbated in Ec$^{Sirt3KO}$ mice. This was accompanied by impaired vascular relaxation, reduced production of endothelial nitric oxide supporting the pathological role of endothelial Sirt3 deficiency. Decrease in NO is a hallmark of endothelial dysfunction in hypertension due to vascular oxidative stress. Angiotensin II infusion increased vascular $O_2^{\bullet}$ by 2-fold in wild-type 3-fold in increase in $O_2^{\bullet}$ in Smc$^{Sirt3KO}$ mice which exacerbated endothelial dysfunction (4-fold decrease in NO). Angiotensin II induced hypertension was associated with Sirt3 S-glutathionylation and scavenging of mitochondrial $H_2O_2$ in mCAT mice prevented Sirt3 inactivation, reduced SOD2 acetylation and diminished hypertension. These data indicate that hypertension is associated with reduced Sirt3 expression and redox inactivation of Sirt3. This leads to SOD2 hyperacetylation and SOD2 inactivation which promotes vascular oxidative stress, increases endothelial dysfunction, exacerbates hypertension, increases end-organ-damage and mortality. It is conceivable that Sirt3 agonists and SOD2 mimetics may have therapeutic potential in cardiovascular disease.

**5.27**

**ESTROGEN TREATMENT AFFECTS MITOCHONDRIAL COMPLEX I KINETICS AND $H_2O_2$ EMITTING CAPACITY DIFFERENTLY IN LIVER VS. SKELETAL MUSCLE OF OVARIECTOMIZED MICE**

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The use of estrogen (E2) therapies (ET) prevents many of the metabolic health challenges brought by surgical or natural menopause, including insulin resistance, metabolic syndrome and type 2 diabetes. However, the molecular mechanism(s) by which E2 affects metabolic tone across different tissues remains not well understood. We have previously shown ET protects cellular redox balance and insulin sensitivity in skeletal muscle (SM) of ovariectomized (OVX) mice, by modulating mitochondrial electron transfer efficiency. The liver comprises not only a key tissue for glucose homeostasis, but is also the main processing organ of exogenously-administered E2. Thus, the goals of this study were: 1) to further elucidate the mechanism(s) by which E2 protects mitochondrial function in SM, with a emphasis on the kinetics and $H_2O_2$ emitting capacity and topology (sites of $O_2^{\bullet-}/H_2O_2$ leak) of complex I (C I), and 2) to compare the effects of OVX and ET on such parameters in liver mitochondria. 10 week-old C57BL/6N mice were OVX, and received +/- 2 weeks of ET via a subcutaneous mini-osmotic pump (1µg/day). In SM, ovarian E2 withdrawal decreased maximal NADH oxidation capacity (-43%, $p<0.05$), and increased $J_{H_2O_2}$ emitting potential of C I at the Flavin site ($I_F$) by three-fold ($p<0.005$). E2 treatment *in vivo*, as well as E2 exposure *in vitro* fully reversed these effects. In liver, OVX did not alter C I function or $J_{H_2O_2}$ emitting capacity. However, E2 treatment *in vivo* was associated with a reduction in supercomplex levels (-33%, $p<0.05$) and a higher NADH oxidation capacity (+40%, $p<0.05$) without concomitant changes in the capacity of quinone reduction, suggesting C I may be prone to $O_2^{\bullet-}/H_2O_2$ leak from the quinone binding site ($I_Q$). Accordingly, exposure of liver OVX mitochondria to E2 *in vitro* led to a two-fold higher $J_{H_2O_2}$ emitting potential at site $I_Q$ ($p<0.005$). Given that C I decreased function and increased $H_2O_2$ production have been associated with the pathophysiology of non-alcoholic fatty liver disease, these results raise concerns on the safety of ET for women with, or at risk of, liver disease. The present findings provide novel insights for the development of alternative safer therapeutic strategies for naturally- and surgically-induced menopausal women. R01 DK096907

**5.28**

**PERM1 (PGC-1 AND ERR-INDUCED REGULATOR, MUSCLE 1) IS REQUIRED FOR EXERCISE–INDUCED MITOCHONDRIAL BIOGENESIS AND ENHANCES OXIDATIVE CAPACITY IN SKELETAL MUSCLE**

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Skeletal muscle mitochondrial content and oxidative capacity are important determinants of muscle function and whole body health. Mitochondrial content and function are enhanced by endurance exercise, and impaired in states or diseases where muscle function is compromised, such as myopathies, muscular dystrophies, neuromuscular diseases and age-related muscle atrophy. Hence, elucidating the mechanisms that control muscle mitochondrial content and oxidative function can provide new insights into states and diseases that affect muscle health. In past studies, we identified *Perm1* (PGC-1 and ERR-induced Regulator, Muscle 1) as a gene induced by endurance exercise in skeletal muscle, and regulating mitochondrial oxidative function in cultured myotubes. The capacity of Perm1 to regulate muscle mitochondrial content and function *in vivo* is not yet known. In this study, we use adeno-associated viral (AAV) vectors to increase or decrease Perm1 expression in skeletal muscles of adult mice. Compared to control vector, AAV1-Perm1 leads to significant increases in mitochondrial content and oxidative capacity. Moreover, AAV1-Perm1 transduced muscles show increased capillary density and resistance to fatigue (Cho et al., 2016). By

contrast, AAV1-shPerm1 decreased basal oxidative phosphorylation (OXPHOS) protein content and citrate synthase activity and attenuated mitochondrial biogenesis induced by exercise training. To gain insights into the pathways by which Perm1 remodels skeletal muscle, we next assessed the phosphorylation levels of kinases known to be important for mitochondrial biogenesis and other aspects of skeletal muscle oxidative function. We found that loss of Perm1 leads to decreases in phosphorylation of p38 and CaMKII. By contrast increased Perm1 expression enhances phosphorylation levels of p38 and CaMKII.
Conclusion: Taken together, our findings suggest that Perm1 is required for exercise–induced mitochondrial biogenesis and enhances oxidative capacity in skeletal muscle through modulation of p38 and CaMKII activity.

**5.29**
**ATP PRODUCTION CAPACITY AND PARTITIONING BETWEEN GLYCOLYSIS AND OXIDATIVE PHOSPHORYLATION IN CELLS CATABOLIZING SINGLE SUBSTRATES**

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The majority of cellular ATP production is shared between glycolysis and oxidative phosphorylation. This partitioning is highly dynamic, changing in response to substrates and to alterations in the activities of each production pathway; e.g., inhibition of electron transport will cause glycolytic ATP production to increase, given a suitable substrate. This dynamic relationship is driven not by transcriptional alteration or post-translational enzyme modification, but rather by the kinetic regulation that maintains a steady state intracellular ATP/ADP ratio. The sum of the bioenergetic capacities of each pathway defines a theoretical maximum rate at which the cell can generate ATP, defining the upper limit of ATP demand that can be placed on the cell before energetic collapse. We have previously described a method for calculating ATP production rates using extracellular flux measurements of oxygen consumption and acidification, and the resulting ATP production characteristics of C2C12 myoblasts using glucose as the sole exogenous substrate, including the total rate of production, its partitioning (the Glycolytic Index), the change in partitioning when glucose is added (the Crabtree Index) and when mitochondrial respiratory chain activity is altered (the Pasteur Index), and the theoretical range of ATP supply over which the cell can utilize either glycolysis or oxidative phosphorylation to meet ATP demand (the Supply Flexibility Index)(1). Here, we demonstrate how these characteristics are influenced by different exogenous substrates. This research was funded in part by NIH R15 ES025917-01A1 to SM.
(1) Mookerjee, S. A., Gerencser, A. A., Nicholls, D.G., and Brand, M.D. (2017) Quantifying intracellular rates of glycolytic and oxidative ATP production and consumption using extracellular flux measurements. *J. Biol. Chem. (2017) 292(17) 7189 –7207*

**5.30**
**METABOLIC REGULATION OF NEUROINFLAMMATION**

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Inflammation is an important physiological mechanism accompanying ischemic injury. The inflammatory response starts within minutes, and lasts weeks or months after ischemic injury. In stroke, the detrimental effects of pro-inflammatory activation of microglia, the resident macrophages of the brain, are underscored by the evidence that suppression of microglial activation limits cerebral injury. An increasing body of evidence suggests a link between cell metabolism, mitochondrial function and proinflammatory cytokine generation by immune cells. We previously demonstrated that that lipopolisaccharide (LPS)-induced activation promotes significant metabolic changes suppressing mitochondrial function and increasing glycolysis in microglial BV-2 cells. On the other hand, enhancement of mitochondrial function attenuated the LPS-induced oxidative and metabolic responses, and suppressed proinflammatory activation of microglia. In this study we investigated the modulation of the LPS-induced inflammatory response of microglial BV-2 cells by inhibition of miR-338. Several studies have demonstrated the potential of miR-338 inhibition to enhance and protect mitochondrial function through upregulation of mitochondrial proteins. Inhibition of miR-338 attenuated the LPS-induced oxidative and metabolic responses, and suppressed proinflammatory activation, which depended on HIF-1□ mechanisms. Thus, miR-338 suppression provides a novel strategy to modulate proinflammatory cytokine production of relevance to inflammation-associated pathologies.

**5.31**
**ACUTE MANEB EXPOSURE DISRUPTS BOTH GLYCOLYSIS AND MITOCHONDRIAL FUNCTION IN SK-N-AS NEUROBLASTOMA CELLS**

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Maneb (MB), a manganese-containing fungicide, in combination with the herbicide paraquat (PQ) has been reported as an environmental risk factor for Parkinson 's disease (PD), as chronic MB exposure causes pathology similar to that of PD in mouse models. Although the mechanism of PQ toxicity through redox cycling and oxidative stress has been highly researched, MB's contribution has not been fully described. MB has been

shown to preferentially inhibit complex III *in vitro* causing reduced mitochondrial function. More recently it has been shown that MB acts as a cysteine thiol modulator, acting on proteins with redox regulation through protein thiol adduction. Additionally, several proteins involved in cellular energy pathways have been shown to react through redox signaling and cysteine thiol regulation. Understanding the mechanisms of these compounds in neurons and their effect on mitochondrial function and energy pathways may aid in better characterization of PD pathology. In this study, the neuroblastoma SK-n-AS cell line was analyzed with acute maneb exposure using the Agilent Seahorse XFp Analyzer. Briefly, basal oxygen consumption and extracellular acidification rate were first measured, then 50uM MB was injected and a glycolysis stress test and mitochondrial stress test were conducted. The glycolysis stress test showed significantly decreased glycolysis rate and glycolytic capacity in cells exposed to 50 uM MB. Furthermore, the investigation of mitochondrial stress showed significantly decreased ATP production in the MB treated cells. These results support the hypothesis that enzymes involved in ATP production and glycolysis are disrupted through modification of protein thiols. Further investigation into these redox regulated proteins may lead to therapeutic targets and mechanistic understanding that can be applied to pathology and development. Funding: NIH/NIEHS (ES027593)

**5.32**

**PRESYNAPTIC ENERGY UTILIZATION DURING HIGH-FREQUENCY SYNAPTIC TRANSMISSION AT THE CALYX OF HELD**

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Maintenance of cellular energy as ATP is important in neurons, which are energetically expensive and consume ~20% of an organism's energy at rest. While a considerable amount of energy is expended to regenerate the electrical polarization of neurons, efficient release and recycling of neurotransmitter consumes nearly half of the presynaptic neuronal energy budget. In general, mitochondria are the major suppliers of cellular energy in neurons, generating ATP via oxidative phosphorylation. However, the specific utilization of energy from cytosolic glycolysis and/or mitochondrial respiration at the presynaptic terminal, a spatially and functionally isolated compartment within neurons, remains unclear. We use a synapse amenable to physiological investigation and specialized for high frequency transmission in mice, the calyx of Held, to test the sources of energy utilized to support energy maintenance during activity-dependent neurotransmission. We show that acute inhibition of either glycolysis or mitochondrial respiration alters excitatory postsynaptic currents (EPSCs) during high frequency activity at this mammalian synapse before the onset of hearing. However, in mature calyx synapses tuned for sustained high frequency transmission, these differences are absent. Our data suggest a specific metabolic profile exists to support high-frequency information transmission, which changes over the course of postnatal synaptic maturation due to a greater reserve of ATP and enhanced ATP production following synaptic activity. As a result, the mature terminal is capable of firing for minutes in the absence of glycolysis or mitochondrial respiration.

## 6.0 ENERGY SCHOOL II

**6.2**

**MTDNA STRUCTURE AND SIGNALING**

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By virtue of its endosymbiotic origins, the eukaryotic cell represents a co-evolution between nuclear and mitochondrial genomes. The mitochondrion is a descendent of an a-proteobacteria, and the majority of its genes have been transferred the to the host nucleus, leaving a remnant of the original a-proteobacterial genome residing inside the organelle. In mammals, this mitochondrial DNA (mtDNA) encodes 13 polypeptides, 22 tRNAs, and 2 rRNAs that are essential for proper cellular bioenergetic function and metabolism. Because changes in bioenergetics have become key features in several types of metabolic diseases, it has been suggested that mtDNA sequence variation can alter mitochondrial – nuclear interactions that influence cell function, and thus, disease susceptibility. To directly test this hypothesis, Mitochondrial – Nuclear eXchange (MNX) mouse models have been developed to determine the impact of different mtDNA – nuclear genome (nDNA) combinations upon common disease susceptibility, using cardiac disease and cancer models. Results from these studies are consistent with the hypothesis that different mtDNA – nDNA combinations change cellular bioenergetics and importantly, disease susceptibility. While these studies are focused upon basic factors germane to specific diseases, they also challenge current concepts concerning the basis for genetic susceptibility and thus, precision medicine. Further, they are relevant to mitochondrial gene therapies currently being pursued for pathogenic mtDNA mutation. (NIH HL103859, HL109785, & DoD W81XWH-07-1-0540). Fetterman, J., Zelickson, B., Johnson, L., Moellering, D.R., Westbrook, D.G., Pompilius, M., Sammy, M.J., Salman, E.D., Johnson, M., Dunham-Snary, K.J., Cao, X., Bradley, W.E., Zhang, J., Wei, C.C., Chacko, B., Schurr, T.G., Kesterson, R.A., Dell'Italia, L.J., Darley-Usmar, V.M., Welch, D.R., Ballinger, S.W. Mitochondrial genetic background modulates bioenergetics and susceptibility to acute cardiac volume overload. *Biochemical Journal – Metabolism* 455: 157-167 2013. Feeley, K.P., Bray, A.W., Westbrook, D.G., Johnson, L.W., Kesterson, R.A., Ballinger, S.W., Welch, D.R. Mitochondrial genetics regulate breast cancer tumorigenicity and metastatic potential. *Cancer Research* 75: 4429-4436, 2015. Dunham-Snary, K.J., Ballinger, S.W. Mitochondrial DNA mismatch matters. *Science* 349: 1449-1450, 2015. Kesterson, R.A., Johnson, L.W., Lambert, L.J.,

Vivian, J.L., Welch, D.R., Ballinger, S.W. Generation of Mitochondrial – Nuclear eXchange Mice via Pronuclear Transfer. *Bioprotocol* 6 (20): e1976, 2016.

## 7.0 MITOCHONDRIAL ADAPTATION AND RESPONSES TO STRESS

### 7.2

### MITOCHONDRIAL ACETYLATION IN HEART FAILURE

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Mitochondrial dysfunction has been implicated in several pathologies that culminate in heart failure. Under non-ischemic conditions the heart derives over 90% of its energy from oxidative phosphorylation, making mitochondrial fuel substrate metabolism a key node for potential disruption. As such, there is currently strong interest in characterizing mechanisms that regulate fuel metabolism in the heart. Lysine acetylation has been shown to regulate metabolic enzymes in a number of tissues, and recent research has suggested that cardiac mitochondrial energy metabolism pathways may also be regulated by this post-translational modification. Acetylation uses acetyl-CoA derived from fuel metabolism as a co-factor, thereby linking cellular nutrient availability to mitochondrial bioenergetic output. This aspect is of particular importance, as several forms of cardiac disease (e.g. heart failure, ischemia, diabetic cardiomyopathy) are characterized by alterations in the availability and utilization of fuel substrates. In most cases, protein acetylation status is controlled by the opposing activities of acetyltransferase and deacetylase enzymes. Using several methods to inhibit normal cardiac function, we are currently investigating the role of the acetyltransferase-related protein Gcn5l1 in regulating cardiac fuel metabolism. Our current data suggests that acetylation promotes fatty acid oxidation in the heart, and that this modification is regulated in part by Gcn5l1 activity. Driving fat oxidation under pathological conditions via this mechanism may reduce cellular bioenergetic efficiency, limiting overall cardiac output and promoting disease progression. (NIH K22HL116728 & R56HL132917).

### 7.4

### TARGETED DELETION OF MNSOD IN MOUSE SKELETAL MUSCLE LEADS TO ELEVATED SUPEROXIDE AND INCREASED OXIDATIVE STRESS, MITOCHONDRIAL DYSFUNCTION AND REDUCED FORCE GENERATION BUT DOES NOT INITIATE MUSCLE ATROPHY

**Bumsoo Ahn**[1], **Rizwan Qaisar**[1], **Shylesh Bhaskaran**[1], **Gavin Pharaoh**[1], **Rojina Ranjit**[1], **Kaitlyn Riddle**[1], **Holly Van Remmen**[1,2]

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Our previous work has demonstrated that loss of innervation and disruption of the neuromuscular junction (NMJ) in skeletal muscle results in mitochondrial dysfunction and increased mitochondrial ROS that are associated with muscle atrophy and weakness. To directly test the role of mitochondrial dysfunction and ROS generation in this series of events independent of loss of innervation we generated a muscle specific knockout mouse model in which MnSOD, the primary superoxide anion scavenger in the mitochondrial matrix, was deleted using a Cre-Lox approach. The expression of Cre was driven by a constitutively active human skeletal actin promoter (HSA-Cre) and effected a greater than 90% deletion of the protein in skeletal muscle (m*Sod2*KO mice). We measured mitochondrial ROS production and respiration using permeabilized fibers from red gastrocnemius muscle in wild type and m*Sod2* KO female mice at 7-8 months of age. ROS generation was elevated by ~5 fold in the m*Sod2* KO mice, and significant defects in mitochondrial respiration were observed (50% reduction in complex I-medicated respiration; 40% decrease when complex II-mediated). Mitochondrial calcium retention capacity was also decreased by 70% in m*Sod2* KO mice. To determine the effect of reduced MnSOD and increased superoxide on muscle function, we measured *in situ* contractile function in gastrocnemius muscle. Maximum isometric specific force was decreased by ~30% in mutant mice with direct stimulation on muscle, but the reduction in force was greater (~50%) after stimulation of the sciatic nerve. Surprisingly, gastrocnemius mass was not different between wild type and m*Sod2* KO mice. Our findings suggest that increased mitochondrial ROS generation and oxidative stress play an important role in regulation of contractile function of skeletal muscle but do not appear to directly increase muscle atrophy. This result supports the concept that mitochondrial ROS and dysfunction are not critical mediators of denervation-induced atrophy.

### 7.5

### ADAPTATION TO LOSS OF THE MITOCHONDRIAL PHOSPHATE CARRIER IN SKELETAL MUSCLE

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The mitochondrial phosphate carrier (PiC), encoded by the nuclear gene *SLC25A3*, was purified more than 30 years ago. PiC is widely believed to serve as the primary means of inorganic phosphate (Pi) uptake into mitochondria for oxidative phosphorylation (oxphos) and for transporting Pi that buffers the vast amount of calcium that mitochondria can take up. However, it is only recently that the direct study of PiC *in vivo* has become feasible. This is due to the recent discovery of mutations in human PiC and the development of a PiC floxed mouse. Human *SLC25A3*

mutations produce a severe clinical phenotype at birth and with striated muscle as a key affected tissue, and mice with cardiac-specific PiC loss eventually develop abnormal cardiac function. Yet, evidence of ample mitochondrial ATP and near normal organ function despite PiC depletion in humans and mice suggest that PiC expression far exceeds Pi needs and/or that functional compensation can be substantial, including the mitochondrial uptake of Pi through alternate pathways. To explore these possibilities we generated mice with Tamoxifen(Tam)-inducible skeletal muscle (Skm) PiC knockdown (Tam+Cre+); 3 weeks after Tam, PiC protein was <5% of control in Skm mitochondria. Despite minimal PiC, Tam+Cre+ mice gained weight normally and performed as control mice on a treadmill at slow speed. Though Tam+Cre+ mice fatigued faster during an incremental endurance treadmill test, they could still sustain some level of aerobic exercise. This provides *in vivo* evidence for compensatory Pi provisioning to PiC-depleted Skm mitochondria. Bioenergetics analysis in Skm mitochondria revealed that oxphos in PiC-depleted mitochondria ranges from zero to ~40% of control, and that this is robustly substrate-dependent. These observations along with other, more circumstantial, evidence such as lower weight of fat stores in Tam+Cre+ mice, suggest that PiC-depleted Skm mitochondria adopt a "work-around" in which compensatory Pi uptake occurs via the dicarboxylate carrier, at the expense of Krebs cycle cataplerosis, and with fatty acids as a preferred substrate. Yet, despite the ability to engage a "work-around" to supply ATP, endurance performance of Tam+Cre+ mice declines after several weeks of PiC loss, suggesting that the "work-around" is maladaptive or that it is offset by parallel stress signaling. Ongoing studies explore these possibilities. Funding: United Mitochondrial Disease Foundation; Thomas Jefferson University.

## 8.0 MITOCHONDRIAL SIGNALING: ATP AND BEYOND

### 8.1
### MITOCHONDRIAL ROS IN NEURONAL SIGNALING

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Mitochondria are a main site of reactive oxygen species (ROS) production. The overproduction of mitochondrial ROS can cause oxidative damage to proteins, lipids and DNA, and is associated with a diverse range of disease pathologies. However, ROS also play a role in an organism's physiology and mitochondrial ROS contributes to cell signaling pathways. Despite the dual role of ROS in health and disease, there are no means to simultaneously control the timing, quantity and site of ROS generation. To address this limitation, we use an optogenetic approach in *C. elegans* to investigate how ROS microdomains contribute to ROS damage or signaling. Novel genetically-encoded ROS generating proteins produce ROS in response to light and allow for the spatial and temporal control of ROS production. I will highlight ongoing studies from my laboratory that investigate ROS microdomains and their impact on physiologic outputs. Research supported by NIH R01 NS092558.

### 8.2
### MITOCHONDRIA AS SIGNALING ORGANELLES

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For decades, the mitochondria have been primarily viewed as biosynthetic and bioenergetic organelles generating metabolites for the production of macromolecules and ATP, respectively. Our work has elucidated that mitochondria have a third distinct role whereby they release reactive oxygen species (ROS) and metabolites such as L-2HG to initiate physiological and pathological processes including hypoxic activation of HIFs, cellular differentiation, T cell activation and cancer cell proliferation. I will discuss our recent findings on how mitochondria as signaling organelles control cell fate and function.

### 8.3
### MITOCHONDRIAL PROTEIN IMPORT AND SIGNALING

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Modulation of the mitochondrial protein import pathways can have regulatory effects on mitochondrial function. We have conducted chemical genetic screens to identify modulators for the TOM-TIM23, TIM22, and MIA protein import pathways. Neurodegenerative diseases such as Parkinson's have been linked to a dysfunctional mitochondrial quality control system that is maintained by the proteins PINK1 and Parkin. Whereas mitophagic pathways are becoming well-characterized, little is known about the molecular mechanisms for Pink1 trafficking in mitochondria. We have used two probes to characterize Pink1 translocation. MB-12 promotes the accumulation of PINK1 on the mitochondrial surface without dissipating the mitochondrial membrane potential and Parkin is subsequently recruited. Conversely, MB-10 inhibits the accumulation of PINK1 on dysfunctional mitochondria. MB-10 likely targets TIMM44. Normal PINK1 import is not dependent on TIMM44, but the subsequent anchoring of PINK1 to the mitochondrial outer membrane upon insult requires TIMM44. Thus, we have new tools for dissecting Pink1/Parkin trafficking and studying the induction of Pink1-dependent mitophagy in cell and animal models. REFERENCES: Miyata, N., J. Steffen, M.E. Johnson, S. Fargue, C.J. Danpure, and C.M. Koehler. 2014. Pharmacologic rescue of an enzyme-trafficking defect in primary hyperoxaluria 1. *Proc Natl Acad Sci U S A.* 111:14406-14411; Miyata, N., Z. Tang, M.A. Conti, M.E. Johnson, C.J. Douglas, S.A. Hasson, R. Damoiseaux, C.A. Chang, and C.M. Koehler. 2017. Adaptation of a genetic

screen reveals an inhibitor for mitochondrial protein import component Tim44. *J Biol Chem*. In Press.

**8.4**

**THE RELEASE OF MITOCHONDRI AS DAMAGE ASSOCIATED MOLECULAR PATTERN**

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Mitochondria are organelles present in eukaryotic cells in charge of energy supply and control of cell death. Intriguingly, mitochondria share with bacteria multiple features, such as their outer and inner membrane content in cardiolipin, and a circular genome containing hypomethylated CpG DNA motifs (mtDNA). While damaged organs and activated cells can extrude their mitochondria, which are suggested to trigger innate immunity, we observed that blood platelets could also release their mitochondria, both as free organelles or encapsulated in plasma membrane vesicles, known as microparticles. Mitochondrial release by platelets is initiated by different triggers (e.g. thrombin, collagen, immune complexes), and by storage under blood bank conditions, suggesting that mitochondrial damage associated molecular patterns (DAMP) might contribute to inflammation that prevails in diseases implicating activated platelet and to transfusion adverse reactions. The monitoring of extracellular mitochondria in blood in chronic inflammation and in blood transfusion products may provide indications on mechanisms underlying systemic inflammation and may reduce transfusion-induced adverse reactions.

**8.5**

**MITOCHONDRIAL SIGNALING IN MYOFIBROBLAST TRANSDIFFERENTIATION AND FIBROSIS**

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When the heart is injured, fibroblasts transition from a structural role into contractile, synthetic myofibroblasts. This is crucial for scar formation after myocardial infarction to prevent ventricular rupture, but excessive fibrosis is maladaptive and leads to heart failure. Recent reports have identified an elevation in intracellular calcium ($_{i}Ca^{2+}$) as an important second messenger driving myofibroblast formation. While $_{i}Ca^{2+}$ signaling appears to be necessary for both TGF -dependent and -independent fibrotic signaling pathways, other $Ca^{2+}$ domains, such as mitochondrial calcium ($_{m}Ca^{2+}$), have not been explored. $_{i}Ca^{2+}$ signaling is rapidly integrated into the mitochondrial matrix via the mitochondrial calcium uniporter channel, a mechanism theorized to integrate cellular energetic demand with metabolism and respiration. We've discovered that alterations in $_{m}Ca^{2+}$ uptake are essential to myofibroblast transdifferentiation. I will discuss how genetic approaches revealed this novel signaling pathway and present data to support the notion that alterations in mitochondrial metabolism are crucial for the conversion of fibroblasts to myofibroblasts and the fibrotic response to injury.

## 9.0 POSTER SESSION II

**9.1**

**CALCULATING MUSCLE OXIDATIVE ATP SYNTHESIS *IN VIVO* DURING HIGH INTENSITY CONTRACTIONS USING 31-PHOSPHOROUS MAGNETIC RESONANCE SPECTROSCOPY: ADJUSTING FOR CHANGES IN $V_{MAX}$**

**Miles Bartlett[1], Rajakumar Nagarajan[2], Liam Fitzgerald[1], Ellen Chow[1], Jane Kent[1]**

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Noninvasive and continuous 31-phosphorous magnetic resonance spectroscopy ($^{31}$P MRS) measures can be used to calculate the rate of oxidative ATP synthesis ($ATP_{ox}$) during skeletal muscle work under steady state conditions. However, the assumptions related to steady state energetics precludes the use of this approach during high-intensity contractions. Thus, the purpose of this study was to develop a method for calculating $ATP_{ox}$ during non-steady state conditions. The vastus lateralis muscle of 16 young adults (23.5±2.3yr, 8 women) was examined during contractions in a Siemens 3T whole-body scanner using a dual-tuned surface coil ($^{1}$H/$^{31}$P, 6 x 8cm). Muscle oxidative capacity (rate of phosphocreatine (PCr) recovery, $k_{PCr}\cdot s^{-1}$) following a brief, 24-s maximal contraction was determined and compared with $k_{PCr}\cdot s^{-1}$ following an incremental contraction protocol to fatigue. The protocol consisted of five 2-min stages of maximal isokinetic knee extensions (120°·s$^{-1}$, 30° range of motion), starting with a contraction frequency of 0.1 Hz and increasing to 0.125, 0.2, 0.25 and 0.5 Hz. MRS measurements were collected continuously and metabolites were quantified in jMRUI using AMARES. $ATP_{ox}$ was calculated assuming $ATP_{ox}= V_{max}/(1+(Km/([ADP][Pi]/[ATP]))$; where $K_m$=0.11 and $V_{max}=k_{PCr}\cdot(PCr_{rest})$. We then modified this method by adjusting $V_{max}$ and $K_m$ to account for the observed declines in $k_{PCr}$ at fatigue, and compared ATPox calculated by both methods at the end of the ramp protocol to the initial rate of PCr recovery ($Vi_{PCr}$). ATP production by glycolysis and the creatine kinase reaction were also determined and used to calculate total ATP production for each stage. At the end of the fatigue protocol, $ATP_{ox}$ calculated by our new method was not different from $Vi_{PCr}$ (0.72 ±0.21 vs 0.70±0.14mM·s$^{-1}$, respectively, p=0.7), but $ATP_{ox}$ calculated by the traditional method was faster than $Vi_{PCr}$ (0.85±0.17 vs 0.70±0.14 mM·s$^{-1}$, respectively, p<0.01). Moreover, total ATP cost of contraction was lower when calculated by our new method compared to the traditional method (0.89±0.22 vs 1.02±0.22 mM·s$^{-1}$, p<0.05). Collectively, these results suggest that steady state MRS methods overestimate $ATP_{ox}$ during high intensity

contractions by not accounting for transient impairments in oxidative capacity, which subsequently inflates calculations of total ATP cost.

Funding: Institute for Applied Life Sciences and the Commonwealth Honors College

**9.2**

**INTEGRATED MEASURES OF CELLULAR BIOENERGETICS AND MITOCHONDRIAL FUNCTION IN HUMAN PLATELETS IN THE DIAGNOSIS OF METABOLIC DISEASE**

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Mitochondrial respiratory chain disorders comprehend a spectrum of mitochondrial genetic defects, which affect approximately 1 in 5000 individuals. The diagnosis is difficult due to the diverse clinical presentations that can be associated with a specific molecular defect in metabolism. The current approach relies on the detection of mitochondrial DNA (mtDNA) mutations or on the assessment of mitochondrial complex activities in tissue biopsies or cultured cells, which are time-consuming and lack standardized protocols suitable for clinical evaluation. In the present study we used specific inhibitors of mitochondrial complexes I, II, IV and V in platelets in order to validate the mitochondrial stress test (MST) in intact platelets and the complex activity assay in permeabilized platelets using the extracellular flux analyzer. For this purpose, platelets are pretreated with: rotenone (complex-I inhibitor), TTFA (complex-II inhibitor), oligomycin (ATP synthase inhibitor) or azide (complex-IV inhibitor) in a dose-response manner. Then, the activities of specific complexes were determined (CI, CII, CIV), as well as the MST. As expected the platelets pretreated with inhibitors (rotenone and TTFA) demonstrated a dose-response decrease in mitochondrial respiration with an associated increase in glycolytic flux. We present the results from two confirmed mitochondrial disease patients and compare them to healthy adults. Our results provide a framework for the diagnosis of mitochondrial respiratory chain disorders based on blood platelets mitochondrial complexes activities evaluation. This method requires a simple blood draw and is minimally invasive; the analysis can be automated, and takes less than four hours. *This work was supported by a donation from Agilent-Seahorse Bioscience and the Foundation for Mitochondrial Medicine (to UAB).*

**9.3**

**TEMPERATURE-INDUCED CHANGES IN GLYCOLYTIC RESERVE AND MITOCHONDRIAL SPARE RESPIRATORY CAPACITY IN COLORECTAL CANCER AND HUMAN T-CELL LINES**

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Thermotherapy, as an approach for manipulating cellular bioenergetics, has recently attracted considerable attention from basic and clinical investigators working in the area of cancer, organ transplant and diabetes research. A number of studies and clinical trials have shown that thermotherapy can be successfully used as a standalone or combined therapy for various metabolic conditions. However, the impact of temperature treatment on cancer or T-cell bioenergetics has not been studied in detail with a real time, microplate-based, label-free detection approach. The present study investigates how changes in temperature affect the bioenergetic characteristics (mitochondrial function and glycolysis) of three colorectal cancer (CRC) cell lines and primary human T-cells utilizing Seahorse XF96 technology. Experiments were performed at 32°C, 37°C and 42°C using assay medium conditions and equipment settings adjusted to produce equal oxygen and pH levels ubiquitously at the beginning of all experiments. The results suggest that temperature significantly changes multiple components of the glycolytic and mitochondrial function of all cell types tested. Under hypothermia conditions (32°C), the extracellular acidification rates (ECAR) of CRC cells were significantly lower compared to the same basal ECAR levels measured at 37°C. In primary human T cells, the ECAR/OCR rates increased at 42°C. Interestingly, the FCCP dose response at 37°C vs 42°C showed significant shifts in profiles, suggesting that single dose FCCP experiments might not be sufficient to characterize the mitochondrial metabolic potential when comparing groups, conditions or treatments. These findings provide valuable insights into the metabolic and bioenergetic changes of CRC and human T-cells under hypo- and hyperthermia conditions that could potentially lead to the development of better-targeted and personalized strategies for patients with cancer, metabolic disorders, diabetes or transplanted organs. **Support:** NCI and Markey Cancer Center, University of Kentucky.

**9.4**

**GENETIC VARIATION IN MITOCHONDRIAL COMPLEX I ACTIVITY AMONG INBRED STRAINS OF MICE**

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Mitochondrial dysfunction has been shown to link to metabolic diseases, such as obesity, NAFLD, and diabetes. To dissect the genetic control of mitochondrial functions and its physiological role, we employed a panel of >100 strains of inbred mice, termed Hybrid Mouse Diversity Panel (HMDP), which allows for high resolution mapping. Previously, we have shown that when fed a high fat/high sucrose obesogenic diet, HMDP mice exhibited large variations in obesity, insulin resistance and hepatic steatosis which are dependent on their genetic background. We isolated mitochondria from 287 livers from 102 strains of male mice. Complex I activity was measured and normalized to citrate synthase activity. A 10-fold difference was observed between the extreme strains. We found that complex I activity was negatively correlated with obesity traits: body weight, body fat percentage, fat mass response to diet. It was also inversely correlated with subcutaneous fat mass but not fats from other depots. Parallel to the obesity connection, complex I activity was inversely correlated with food intake and HOMA-IR. These data show that complex I activity is tightly associated with body composition and insulin action. Metabolomic analysis revealed a negative correlation between complex I activity and plasma gamma-aminobutyric acid (GABA). In the liver, complex I activity showed a negative correlation with 4-aminobutyrate aminotransferase (Abat), an enzyme that catalyzes GABA catabolism and is involved in the mitochondrial nucleoside salvage pathway. Our finding is consistent with previous report that human subjects harboring homozygous ABAT missense mutation displayed increased GABA level and reduced mtDNA in the brain. These data suggest that GABA may be a useful plasma biomarker for mitochondrial function. Genome wide association mapping identified two significant loci on chromosomes 8 and 13. The chromosome 8 peak spans ~1.4Mb and contains 18 genes whereas the chromosome 13 peaks is ~1.7 Mb wide containing 4 genes. The identification and validation of causal genes in these loci will provide novel insight into the regulation of complex I function by nuclear genes.

**9.5**

## COMMON AND CONTRASTING MECHANISMS OF MITOCHONDRIAL QUALITY CONTROL AND OXIDATIVE STRESS IN PROLIFERATING AND POST-MITOTIC CELLS

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It has been long observed that oxidative stress, in particular mitochondrial damage, is associated with many chronic diseases, including atherosclerosis, cancer, diabetes, cardiovascular diseases, arthritis, hypertension and neurodegenerative disorders. The mechanisms of mitochondrial quality is control involve regulation of mitochondrial redox homeostasis, mitochondrial fission/fusion, mitochondrial biogenesis and degradation. 1) A few years ago, we have made the initial observation that differentiation of SH-SY5Y cells leads to increased mitochondrial membrane potential, increased mitochondrial reserve capacity, resistant to oxidative stress-induced cell death, and significant remodeling of mitochondrial electron transport chain proteins with increase of complex IV proteins without changes of other complexes or mitochondrial mass as assessed by citrate synthase activity and mtDNA/nDNA ratio. 2) Following this study we have investigated the relationship of mitochondrial respiration, we have investigated the impact of Sirt3 knockout, which is associated with MnSOD inhibition and increase of mitochondrial reactive oxygen species, on mitochondrial respiration. Interestingly, Sirt3-/- cells exhibit normal mitochondrial respiration in the stress test. However, in response to starvation, Sirt3 knockout led to increased JNK activation, more severe decrease of maximal and reserve capacity oxygen consumption rate and more cell death. Despite that autophagic flux is upregulated in Sirt3 knockout cells, inhibition of autophagy exacerbates cell death, indicating that insufficient autophagy activation contributes to starvation-induced cell death. 3) In proliferation breast cancer cells, attenuated autophagic flux in response to GABARAPL1 knockout is associated with increased HNE-protein adducts and increased mtDNA damage. However, these oxidative stress phenotypes did not result in cell death, but an increase of GSH, increased mitochondrial number, increased mitochondrial protein VDAC, increase of mitochondrial basal OCR, membrane potential and total cellular ATP, and resistance to exogenous HNE-induced cell death. 4) In contrast to proliferating cells, we recently found that primary neuron mitochondria exhibit increased mtDNA damage when autophagy is inhibited, with associated attenuation of mitochondrial respiration and decreases of TCA cycle metabolites. Furthermore, mitochondrial fragmentation, increased mitochondrial peroxynitrite, and inhibition of mitochondrial respiration occur upon HNE exposure. Further inhibition of autophagy exacerbates mitochondrial respiratory deficits and initiates mitochondrial remodeling. In total, these studies demonstrate common and contrasting mechanisms of mitochondrial quality control and cellular responses to endogenous and exogenous oxidative stress in proliferating and post-mitotic cells.

**9.6**

## NATURAL KILLER CELLS CONTRIBUTE TO PLACENTAL MITOCHONDRIAL DYSFUNCTION IN RESPONSE TO PLACENTAL ISCHEMIA IN REDUCED UTERINE PERFUSION PRESSURE (RUPP) RAT MODEL OF PREECLAMPSIA

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**Introduction:** Preeclampsia (PE), is characterized by new onset hypertension and is associated with immune activation and placental oxidative stress. Placental ischemia is believed to be the initial event in the development of PE. Cytolytic Natural Killer (NK) cells are elevated in the placentas of PE women. One mechanism of cytotoxicity of NK cells is release of proteins modulating mitochondrial dysfunction and oxidative stress which may play a role in the pathophysiology of PE. We have shown that placental ischemia induces NK cell activation in the reduced uterine perfusion pressure (RUPP) rat model of PE. Thus, we hypothesize that NK cell depletion could improve oxidative stress, mitochondrial function and blood pressure in RUPP rats. **Methods:** Sprague Dawley rats were divided into three groups; normal pregnant (NP), RUPP and RUPP+NK cell depletion rats (RUPP+NKD). On gestational day (GD) 14, RUPP surgery was performed, and NK cells were depleted with Anti-asialo GM1 antibodies (7µg/100µL, i.p) on Gday 15 and Gday 17. On GD19 blood pressure (MAP) was measured and placental mitochondria were isolated. Mitochondrial function was assessed by studying respiration and Complex I activity. Data are expressed as mean±SEM, statistical analysis included one way ANOVA and Bonferroni post hoc test. **Results:** MAP was elevated in RUPP (n=9) compared to NP rats (n=10) (125±3 mmHg vs. 109±2 mmHg, $p<0.05$) which was normalized in RUPP+NKD (n=3; 106±6 mmHg). State 3 (313±16 vs. 423±15 pmol/sec/mg, $p<0.05$) and uncoupled (244±13 vs. 300±11 pmol/sec/mg, $p<0.05$) respiration rates were reduced in RUPP (n=7) vs. NP (n=8) but improved in RUPP+NKD (n=3; 398±28 pmol/sec/mg, $p<0.05$ vs RUPP). However, there was no change in uncoupled respiration. Respiratory control ratio (state 3/state 4) was significantly reduced in RUPP (n=7) vs. NP (n=8) (7±1 vs 11±1, $p<0.05$) but was improved in RUPP+NKD (n=3; 12±2, $p<0.05$ vs. RUPP). Complex I (12±3 vs. 23 ± 2 nmol e-/min/mg, $P<0.05$) was drastically reduced in RUPP compared to NP but was increased in RUPP+NKD (n=3; 24±6, $p=0.1349$ vs RUPP) but did not reach statistical significance. **Conclusion:** The reduction in mitochondrial respiration and complex I activity were improved with NK cell depletion in RUPP rats indicating the importance NK cells play in causing placental mitochondrial dysfunction and pathophysiology in response to placental ischemia of pregnancy. Funding: RO1HD067541(BL)/Office of Research, UMMC.

**9.7**

## ALPHA SYNUCLEIN AND ATP SYNTHASE - A FAIRY TALE WITHOUT A HAPPY END.

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Despite a wealth of publications about misfolded α-synuclein in Parkinson's disease, very little has been reported about this protein's physiological function in health and the mechanism of its toxic gain of function in disease. This current study established an important function for α-synuclein in the regulation of ATP synthase activity. Using mice lacking α, β and γ-synuclein, and a combination of biochemical, live cell imaging and mitochondrial respiration analysis we report that synuclein deficiency results in reduced ATP synthase efficiency and lower ATP levels. Application of extracellular monomeric α-synuclein shows that monomers enter the cell and localise to mitochondria, interact with ATP synthase and increases its efficiency. It is therefore capable of rescuing the mitochondrial phenotype observed in synuclein-deficient mice. These data suggest that monomeric α-synuclein is a previously unrecognised physiological regulator of mitochondrial bioenergetics through its ability to interact with ATP synthase and aid its efficiency.

In Parkinson's disease (PD), α-synuclein aggregation and mitochondrial dysfunction are central players in its pathogenesis. Here we show how the beneficial physiological function of monomeric α-synuclein switches to a pathological effect, in the presence of oligomeric forms. This study shows that toxic oligomers maintain their interaction with the ATP synthase, which has also been proposed to be a key component of the mitochondrial permeability transition pore (mPTP), but lose the ability to aid its efficiency. Oligomers, but not monomers, directly induce mPTP in isolated mitochondria and intact cells, and lower the threshold for calcium induced and ROS induced mPTP opening. We propose that the uniquely redox active oligomers induce the conversion of ATP synthase to the mPTP leading to neuronal cell death which can be prevented by the inhibition of mPTP. These findings were validated in patient derived iPS neurons with an α-synuclein triplication in which increased levels of α-synuclein cause early onset PD.

This study highlights a beneficial physiological effect of monomers and the mechanism by which oligomers exert a toxic gain of function leading to neurodegeneration.

**9.8**

## MITOCHONDRIAL (DYS)FUNCTION: CAUSE OR CONSEQUENCE OF TYPE 2 DIABETES

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The relationship between insulin resistance (IR) and type 2 diabetes (T2DM) with mitochondrial dysfunction is controversial. Our laboratory has found mitochondrial dysfunction and impaired cerebrovascular function of young (10 - 12 w old) Zucker Obese (ZO) rats compared with their Zucker Lean (ZL) controls, when the ZO rats were IR but not hyperglycemic. However, mitochondrial respiration was normal in the arteries from ZO rats. The development of T2DM in 14 w old Zucker Diabetic Fatty Obese (ZDFO) rats resulted in a significantly decreased mitochondrial basal respiration rate and proton leak as well as altered protein expression of the voltage dependent anion chanel (VDAC) and manganese superoxide dismutase (MnSOD) in large cerebral arteries of ZDF compared with Leans (ZDFL). The level of superoxide was significantly increased in cerebral blood vessels of ZDFO rats compared with ZDFL rats. In this study, we examined prolonged T2DM effects on cerebrovascular mitochondrial function.

Cerebral microvessels and large cerebral arteries, isolated from 21 w old, male ZDFO and ZDFL animals, maintained on high fat diet, were used to determine mitochondrial and non-mitochondrial protein expression using Western blot and mitochondrial oxygen consumption rate (OCR) measured by the Seahorse Bioscience Analyzer.

We found that levels of mitochondrial proteins for the Dynamin Related Protein-1, VDAC, Complexes II, III, and V, acetylated MnSOD, and for the non-mitochondrial, phosphorylated and total endothelial nitric oxide synthase were similar between the ZDFO and ZDFL rats in microvessels. Surprisingly, the calculated components of mitochondrial respiration in large cerebral arteries, including the non-mitochondrial respiration, ATP production, proton leak, basal respiration, maximal respiration, and spare capacity were similar between the ZDFL and ZDFO groups.

Our data suggest that the early stages of IR and T2DM results in selective mitochondrial dysfunction but that mitochondrial respiration and protein levels become normal with prolonged T2DM. More research is needed to determine and understand this compensatory mechanism and its implications in treatment of diabetic patients. Funding: NIH (DWB: HL-077731; HL093554; PVK: NS094834), LA Board of Regents (DWB), AHA (PVK: 14SDG20490359; IR: 15POST23040005; 17SDG33410366; VNS: PRE31450006). [1]I Merdzo et al. PMID28095372. [2]I Merdzo et al. PMID26873973.

**9.9**

## TREATMENT OF MITOCHONDRIAL $CA^{2+}$ OVERLOAD IN HEART FAILURE: A NEW STRATEGY BASED ON NANOMEDICINE

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Heart failure (HF) is the clinical syndrome causing the highest adult death rate in industrialized countries, with an annual death rate of 20-40% of the diagnosed cases, and a 50% survival chance 5 years from initial diagnosis. Among its complex etiology and pathophysiology, intracellular $Ca^{2+}$ dysregulation has been recognized as one of the key manifestations of HF. Such intracellular $Ca^{2+}$ dysregulation leads to a decrease in ATP and an increase of reactive oxygen species mediated by mitochondrial dysfunction. In patients with advanced HF it has been found an overexpression of the protein in charge of $Ca^{2+}$ uptake into the mitochondria, the mitochondrial calcium uniporter (MCU). The modulation of MCU activity, like with the use of $Ru_{360}$ could be a potential therapy against $Ca^{2+}$ overload in HF. However $Ru_{360}$ has a low cell membrane permeability. To overcome this limitation, the use of nanovectors has been explored with the objective to increase the bioavailability of intracellular $Ru_{360}$ with a controlled release.

In this work, $Ru_{360}$ was encapsulated in a polymeric nanovector. This nanovector was characterized in terms of size distribution, surface charge, and loading capacity of $Ru_{360}$. H9c2 cells were used to study the internalization of the nanovectors by confocal microscopy and to study the modulation of $[Ca^{2+}]_m$ transport. Results obtained show that the nanovector has an average diameter of 100 nm with a negative surface charge and a loading capacity of 40 nmole/mg of nanovector. Internalization into H9c2 cells is dose dependent and the nanovector can reduce the $[Ca^{2+}]_m$ transport after 24 hours of incubation better than free $Ru_{360}$.

**9.10**

## VASCULAR ENDOTHELIAL MITOCHONDRIAL FUNCTION PREDICTS DEATH OR PULMONARY OUTCOMES IN PRETERM INFANTS

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**Rationale**: Vascular endothelial mitochondrial dysfunction contributes to the pathogenesis of several oxidant stress associated disorders. Oxidant stress is a major contributor to the pathogenesis of bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity that often leads to sequelae in adult survivors. **Objectives**: This study was conducted to identify whether differences in mitochondrial bioenergetic function and oxidant generation in HUVEC (human umbilical venous endothelial cells) obtained from extremely preterm infants were associated with risk for BPD or death before 36 weeks post-menstrual age.

**Methods**: HUVEC oxygen consumption and superoxide and hydrogen peroxide generation were measured in 69 infants. **Results**: When compared to HUVECs from infants who survived without BPD, HUVEC obtained from infants who developed BPD or died had lower maximal OCR (mean ± SEM in pmol/min/30,000 cells, 107 ± 8 vs. 235 ± 22, $p < 0.001$), produced more superoxide after exposure to hyperoxia (mean ± SEM in MitoSox Red fluorescence units: 89807 ± 16616 vs. 162706 ± 25321, $p < 0.05$) and released more hydrogen peroxide ($H_2O_2$) into their supernatant after hyperoxia exposure (mean ± SEM in resorufin arbitrary fluorescence units, 1879 ± 278 vs. 842 ± 119, $p < 0.001$). **Conclusions**: Our results indicating that endothelial cells of premature infants who later develop BPD or die have impaired mitochondrial bioenergetic capacity and produce more oxidants at birth suggest that the vascular endothelial mitochondrial dysfunction seen at birth in these infants persists through their postnatal life and contributes to adverse pulmonary outcomes and increased early mortality.

**9.11**

## NANO-PARTICULATE EXPOSURE IMPACTS THE ADAPTIVE RESPONSE IN 6-MONTH AND 21-MONTH OLD FEMALE MICE

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Environmental toxicants, can act as an accelerator of protein damage, with excess accumulation of protein aggregates promoting the aging process. To counteract, cells rely upon a plethora of stress-responsive enzymes, including the mitochondrial Lon protease and the cytosolic 20S proteasome, both of which degrade damaged proteins. However, with age, their efficiency decreases. Our objective is to understand the age-related changes of the adaptive stress response associated with non-toxic amounts of nanoparticulate matter (nPM) in young (6 month) and middle-aged (21 month) female mice.

The adaptive stress response, or as recently coined 'adaptive homeostasis,' is a phenomenon, wherein exposure to non-damaging amounts of an oxidant triggers heightened expression of multiple stress-inducible enzymes, including the mitochondrial Lon protease and the 20S proteasome. Earlier invertebrate studies have shown a robust increase in the stress response in young organisms, which is lost with age. Here we explore a novel approach to assess the adaptive response in a mammalian model. Female mice were exposed to either ambient air or reaerosolized particulate matter (nPM) collected from the 110 Freeway (Southern California). 3 month and 18 month female mice were exposed for 5 hours a day, 3 days a week, for 10 weeks. Afterwards, heart, liver, and lung tissue was collected and protein expression, activity, and oxidation was assessed.

Our findings suggest nPM exposure and age impact the mitochondrial Lon protease and the proteasome expression and activity. More interestingly, is its impact upon indirect tissues (heart and liver). In all three tissue types, nPM exposure in young females, triggered a strong increase in Lon and the 20S proteasome. Yet, inducibility was lost in an age- and nPM-dependent manner. Interestingly, Nrf2, the transcriptional activator of the proteasome, showed age-related increases, accompanied by an age-related increase in its transcriptional suppressors, Bach1 and c-Myc. Thus our findings indicate the age- and nPM-related loss of the adaptive response. Moreover, this approach is first-of-its-kind in presenting a mammalian model of the adaptive stress response. Together, this work offers a clearer understanding of the effects of air pollution on aging and its impact on the adaptive stress response.

**9.12**

## POTENTIAL LOCAL ADAPTATION OF MITOCHONDRIAL AND NUCLEAR PROTEIN DEGRADATION TO STRESS MEASURED IN LON PROTEASE AND PROTEASOME ACTIVITY IN A WIDELY DISTRIBUTED INTERTIDAL MARINE ORGANISM

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Evolution has crafted a diversity of phenotypes resulting in many organisms that are locally adapted to respond to the rigors of their native environment. In a widely distributed intertidal marine crustacean, *Tigriopus californicus*, previous studies have shown a longitudinal cline in thermal tolerance between separate populations. In this experiment, protein degradation patterns are compared between a southern population from San Diego with a higher thermal tolerance and a northern population from Santa Cruz with a lower heat tolerance. This study examines the how the major actors of protein degradation and by extension protein homeostasis, the Lon Protease in the mitochondria and the Proteasome in the cytoplasm respond to heat stress in locally adapted populations. This study aims to understand how evolutionary forces have shaped the patterns of protein regulation. Lon Protease activity was measured by the degradation of tritium labelled aconitase and Proteasome activity was measured by the degradation of a fluorogenic substrate and measured on a fluorometer. The impact of heat stress on protein degradation is different between the southern and northern population. Furthermore, the when these populations experience temperatures similar to the maximum temperature experienced in their environment, their protein degradation patterns are different than when they simply experience a sublethal heat stress, which indicates a potential local

adaptation of protein degradation to particular thermal regimes. Understanding how the pattern of protein degradation is modulated between these two populations could shed light on how this highly conserved process can be adjusted to a particular environment and how those adjustments can contribute to an organism's greater fitness.

**9.13**

**AGE-DEPENDENT ALTERATIONS IN MITOCHONDRIAL ENERGETICS IN HUMAN ATRIA**

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**Objective:** Mitochondrial dysfunction in the senescent heart has been documented; however, the molecular bases for the aging-associated decline in energy metabolism in the human heart are not fully understood. We examined transcription profiles of genes coding for mitochondrial proteins in atrial tissue from aged (≥65 years old) and comorbidities-matched adult (<60years old) patients with preserved left ventricular function. We also correlated changes in functional activity of mitochondrial oxidative phosphorylation (OXPHOS) complexes with protein and gene expression changes.

**Methods:** Atrial appendage tissue from well-matched adult (50±8 years, n=23) and aged (73±6 years, n=25) patients undergoing elective coronary artery bypass graft surgery was used. Oxygen consumption rate (OCR) was measured in isolated mitochondria. Functional activity of individual OXPHOS complexes I-V was measured spectrophotometrically in tissue homogenates. Protein expression level of corresponding OXPHOS protein subunits was determined by Western blot. Gene expression profiling was performed using Affymetrix Human Genome U133 Plus 2.0 microarrays and RT-PCR.

**Results:** Isolated mitochondria from senescent hearts demonstrated a significant decrease in uncoupled OCR in the presence of carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone (r=0.94, p=0.01) and state3/state 4 (r=0.84, p=0.04) when oxidized glutamate and malate. There was no age-dependent change in OCR in mitochondria oxidizing succinate or ascorbate with N,N,N',N'-tetramethyl-p-phenylenediamine. The functional activity of the individual OXPHOS complex I was significantly reduced with age (r=0.42, p=0.01). No age-dependent correlation was observed for functional activities of the remaining four OXPHOS complexes. This was associated with a significant reduction in complex I (*NDUFB8* subunit) protein expression level (p=0.01). Of 78 genes that code for subunits of complexes I to V, the expression of 8 genes was significantly reduced in aged atria. These included 5 genes coding for subunits of complex I (*NDUFA6*, *NDUFA9*, *NDUFB5*, *NDUFB8*, *NDUFS2*, $p<0.01$) and one gene each for complexes II (*SDHD*, p=0.04), III (*UQCRC2*, p=0.01), IV (*COX7A2L*, p=0.04), and V (*ATP5G1*, p=0.03).

**Conclusion:** Aging is associated with a selective decline in activity of OXPHOS within the broader transcriptional downregulation of genes regulating mitochondrial energetics, providing a substrate for reduced energetic efficiency in the senescent human atria.

**9.14**

**MITOCHONDRIAL COUPLING AND OXIDATIVE PHOSPHORYLATION CAPACITY DIFFERS WITH LIFE HISTORY STRATEGIES IN THE WING DIMORPHIC CRICKET, *GRYLLUS FIRMUS***

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An individual's life history strategy is defined by differential allocation of resources between growth, maintenance, activity, and reproduction, which results in variation in daily metabolic demands. Individuals also vary in their ability to efficiently produce ATP via oxidative phosphorylation (OXPHOS). Here, we sought to determine if variability in energy production and demand are correlated and test the hypothesis that differences in mitochondrial function occur concomitantly with variation in life history energy demands. Morphs of the wing dimorphic cricket (*Gryllus firmus*) specialize in either dispersal or reproduction. Compared to reproductive morphs, adult dispersal morph mitochondria were predicted to have higher OXPHOS capacities to support high metabolic demands of flight. Using an Oxygraph-2k high resolution respirometer (Oroboros Instruments, Innsbruck, Austria) we characterized rates of OXPHOS of isolated mitochondria from adult day five dispersal and reproductive morphs when stimulated by four separate substrate combinations: 1) pyruvate and malate, 2) glutamate and malate, 3) palmityolcarnitine and malate, 4) succinate and rotenone. Regardless of substrate, average state 3 respiration rates were higher in dispersal morphs suggesting an increased oxidative phosphorylation capacity associated with this life history tactic. Notably, despite both supporting entry into complex 1 of the electron transport chain, OXPHOS differed markedly when stimulated by pyruvate and malate (dispersal-465.8 ± 63.6 $pmolO_2/s/mg$; reproductive-223.2 ± 56.7 $pmolO_2/s/mg$) compared to glutamate and malate (dispersal-97.6 ± 11.9 $pmolO_2/s/mg$; reproductive-72.8 ± 8.4 $pmolO_2/s/mg$). Morphs did not differ in state 4 respiration rates. Consequently, dispersal morphs have more coupled mitochondria with higher respiratory control ratios (RCR, state 3/state 4) and could be operating at a higher membrane potential. Reactive oxygen species (ROS) production increases exponentially with increases in membrane potential and when the redox

environment of the mitochondria is highly-reductive. While the enhanced respiratory capacities may be necessary to produce sufficient ATP for dispersal, this may come with the associated cost of increased ROS. Future experiments will quantify both morph's membrane potential and ROS generation. Overall, our findings provide evidence for a link between life history tactics and mitochondrial function. Funded by the Hellman Family Foundation

**9.15**

**BUTYRATE ENHANCES MITOCHONDRIAL FUNCTION IN AUTISM LYMPHOBLASTOID CELLS UNDER PHYSIOLOGICAL STRESS**

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Background: Butyrate (BUT) is a short-chain fatty acid derived from the enteric microbiome that positively modulates mitochondrial function, including enhancing oxidative phosphorylation and beta oxidation. BUT has been associated with autism spectrum disorder (ASD), a disorder that involves mitochondrial dysfunction. We have developed a lymphoblastoid cell line (LCL) model of ASD, with a subset of ASD LCLs demonstrating mitochondrial dysfunction (ASD-A) and others demonstrating normal mitochondrial function (ASD-N). Given the positive modulation of BUT on mitochondrial function, we hypothesized that BUT would have a preferential positive effect on ASD-A LCLs. To this end, we measured mitochondrial function and expression of key genes involved in mitochondrial responses to stress in ASD and age and gender-matched control LCLs following 24 and 48 h treatment with BUT (0-1mM) both with and without an acute increase in reactive oxygen species (ROS).

Results: In control LCLs, respiratory parameters linked to ATP production were attenuated by BUT at 1mM. In contrast, BUT significantly increased respiratory parameters linked to ATP production in ASD-A LCLs but not in ASD-N LCLs. In the presence of acute ROS, BUT increased respiratory parameters linked to ATP production for all groups. Analysis of individual LCL responses demonstrates that BUT modulated mitochondrial respiration to a final common set point. Gene expression analysis revealed that the highest concentration of BUT (1mM) increased expression of genes involved in mitochondrial fission (PINK1, DRP1, FIS1) and physiological stress (UCP2, mTOR, HIF1a, PGC1a) as well as genes thought to be linked to cognition and behavior (CREB1, CamKinase II).

Conclusions: These data show that the enteric microbiome derived short-chain fatty acid BUT can have beneficial effects on the mitochondria, which are dependent on dose and the intracellular redox state and vary depending on the underlying mitochondrial function of the cell. In general, these data suggest that BUT can enhance mitochondrial function in the context of physiological stress and/or mitochondrial dysfunction, and may be an important metabolite that can help rescue energy metabolism defects in ASD. This research was supported by the Arkansas Biosciences Institute (Little Rock, AR) to REF, and GoodLife Children's Charities, Autism Canada and Autism Research Institute to DFM.

**9.16**

***IN VIVO* SKELETAL MUSCLE ENERGETICS AND FATIGUE ARE NOT DIFFERENT IN MEN AND WOMEN DURING INCREMENTAL DYNAMIC KNEE EXTENSION WORK**

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Sex-based differences in human skeletal muscle energetics and fatigue have been shown during isometric contraction protocols, but less is known about energetic differences during fatiguing dynamic contractions. We hypothesized that men would fatigue more, accumulate more intracellular proton ($H^+$) and inorganic phosphate (Pi), and rely more on glycolytic ATP production *in vivo* than women. Muscle oxidative capacity (rate of phosphocreatine recovery, $k_{PCr}$, $s^{-1}$)), and changes in cytosolic high-energy phosphates, pH and rates of ATP synthesis were measured in the vastus lateralis muscle of 8 women and 7 men (22.5±2.2 and 24.9±1.8 yrs, respectively) using 31-phosphorus magnetic resonance spectroscopy (MRS). Participants performed a 5-stage fatigue protocol consisting of maximal isokinetic contractions ($120°\cdot s^{-1}$, 30° range of motion) inside the bore of a Siemens 3T MR system. MRS measurements were collected continuously (2-s temporal resolution, 6x8 cm $^1H/^{31}P$ dual tuned coil). Contraction frequency increased every 2-min from 0.1 to 0.125, 0.2, 0.25 and 0.5 Hz. Fatigue was quantified as the decline in peak power observed at the end of each stage and expressed as a percentage of baseline. MRS data were quantified in jMRUI 6.0beta using AMARES. Relative concentrations of PCr, Pi, ATP, and phosphomonoesters were determined, and rates of ATP production by the 3 energy pathways (creatine kinase reaction, glycolysis, and oxidative phosphorylation) were calculated (Lanza et al., 2005, *J Appl Physiol*). No sex-based differences were observed for any study measures, including muscle oxidative capacity ($p>0.05$, all). Peak power at the end of stage 5 declined to 69.5±5.5 and 72.8±11.5 % of baseline for men and women, respectively. At the end of stage 5, [Pi] was 34.6±5.5 and 34.6±2.7mM, and pH was 6.76±0.16 and 6.78±0.12 in men and women, respectively. Fatigue at each stage was directly associated with [Pi] ($r^2=0.87$) and [$H^+$] ($r^2=0.98$), and

indirectly related to oxidative capacity ($r^2$=0.43); $p \leq 0.02$ for all. Notably, there were no sex-based differences in ATP flux through the 3 pathways. These results indicate that men and women experienced comparable metabolic and contractile perturbations during energetically-costly dynamic contractions, and, in both sexes, the development of fatigue was related to intracellular energetics, including oxidative capacity.

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**9.17**

**MITOCHONDRIA PROMOTE PROINFLAMMATORY MACROPHAGE FUNCTION IN CORONARY ARTERY DISEASE**

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There is evidence that mitochondria play a regulatory role in effector macrophages. We found that mitochondrial gene expression pattern in CAD macrophages is different from healthy control macrophages indicating changes in their functions. We hypothesized that mitochondria-dependent signaling regulates cytokine production in proinflammatory CAD macrophages. We used monocyte-derived macrophages from CAD patients and healthy subjects to characterize basic mitochondrial functions. In fact, we found that resting (M0) and activated (M1) macrophages show significant differences in metabolism and mitochondrial functions. CAD macrophages had a higher metabolic activity associated with a higher rate of glycolysis and mitochondria activity. We found that CAD macrophages had a higher rate of respiration, membrane potential, and mitochondrial ROS production. Increased mitochondrial ROS production in CAD macrophages depleted reduced glutathione. We found that CAD macrophages have distinctive fragmented mitochondria when compared to controls indicating functional alterations. Next, we analyzed detailed molecular mechanisms behind observed dysfunctions and identified a regulatory mechanism in the mitochondria responsible for the overproduction of ROS. Our data indicate that increased ROS production and mitochondrial metabolism induced a proinflammatory phenotype in CAD macrophages, including elevated Il-6 and Il-1b production. Targeting mitochondrial hydrogen peroxide reversed proinflammatory phenotype in CAD macrophages. Correcting mitochondrial hyperactivity by pharmacological intervention also reversed the proinflammatory phenotype in CAD macrophages. Taken together our study suggests a critical role for mitochondria in the regulation of effector functions and a proinflammatory phenotype in CAD macrophages.

**9.18**

**MITOCHONDRIAL GENETIC BACKGROUND INFLUENCES CELLULAR BIOENERGETICS AND MITOCHONDRIAL DNA DAMAGE IN HUMANS AT BIRTH**

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Cardiovascular disease (CVD) is the leading cause of death in the United States. African-Americans have a higher mortality rate from CVD than non-Hispanic whites; although the mechanisms underlying this disparity are not known. One factor often overlooked is the contribution of mitochondrial genetics to disease susceptibility. Mitochondria are both sources and targets of oxidative stress, which has been shown to contribute to endothelial dysfunction and CVD. Mitochondrial DNA (mtDNA) damage and changes in bioenergetics have also been associated with diseases of aging including CVD. We postulate that individuals with distinct mitochondrial haplogroups will have differing bioenergetic profiles and basal mtDNA damage levels which will result in differential susceptibility to CVD. Specifically, we hypothesize that individuals with African haplogroups will have different bioenergetics and higher basal mtDNA damage levels than Eurasian haplogroups.

To test this, bioenergetics and mtDNA damage were assessed in newborn cord blood and human umbilical vein endothelial cells (HUVECs) belonging to mtDNA haplogroups H and L, representing north Eurasian and African maternal ancestries, respectively. Newborn cord blood and endothelial cells were used in order to provide a "baseline" for mitochondrial function (from an individual with a relatively naive exposure history to CVD risk factors). Assessment of bioenergetics in cord blood cells is desirable as cells isolated from blood samples could serve as surrogates of systemic vascular health. Also, this approach enables assessment of mitochondrial function in a non-invasive manner in individuals throughout life for measuring various indices of mitochondrial health. This may be of potential utility in determining individual CVD risk and/or prognosis in CVD patients.

HUVECs from haplogroup L used less oxygen for ATP production and had increased levels of mtDNA damage compared with those in haplogroup H. HUVECs belonging to haplogroup L also had decreased basal and maximal bioenergetic capacities compared with haplogroup H. No significant difference was observed in bioenergetics assessed in cord blood cells, but experiments are ongoing in order to increase sample size. In conclusion, mitochondrial genetic background affects cellular bioenergetics and mtDNA damage in endothelial cells, and may contribute to CVD susceptibility.

*This research was conducted with IRB approval and in conformance with the Declaration of Helsinki.

**9.19**

**EFFECTS OF EPA INTAKE ON DENERVATION-INDUCED MITOCHONDRIAL ADAPTATION OF SKELETAL MUSCLE**

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Eicosapentaenoic acid (EPA) is a kind of omega-3 polyunsaturated fatty acid that is abundantly contained in fish oil. EPA intake is effective for such as anti-inflammation and anti-obesity. We investigated the effects of EPA intake on denervation-induced mitochondrial adaptation in mice skeletal muscle. ICR mice (male, 8 weeks old) were daily administrated Olive Oil (Control oil) or EPA at a dose of 300 mg/kg body weight by gavage for 4 weeks. After 2 weeks of oil intake, mice underwent unilateral sciatic nerve transection surgery. The hindlimb without denervation surgery served as the sham-operated control. Body and gastrocnemius muscle weight were not different between Olive Oil and EPA. PGC-1αand mitochondrial respiration proteins were decreased by denervation in both groups. Those proteins were higher in EPA group than those in Olive Oil group. In addition, EPA group contained higher levels of mRNA and protein related to mitochondrial fusion than Olive Oil group. Our results indicate that EPA intake rescues denervation-induced loss of mitochondria and enhances the expression of mitochondrial fusion molecules in mice skeletal muscle. This study was supported by a High Performance Project (Japan Sports Agency).

**9.20**

**HEXOKINASE-II DISSOCIATION FROM MITOCHONDRIA TRIGGERS MITOPHAGY IN CARDIOMYOCYTES**

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**Introduction:** There is emerging evidence that the metabolic pathway interplays with the survival pathway to preserve cellular homeostasis. Hexokinases (HKs) catalyze the first committed step of glucose metabolism and hexokinase-II (HK-II) is the predominant isoform in the heart. Our recent study revealed that HK-II positively regulates general autophagy in the absence of glucose. Mitochondrial HK-II (mitoHK-II) is regulated by Akt and provides mitochondrial protection against oxidative stress, while it is known to be decreased in the ischemic heart.

**Hypothesis:** We evaluated the hypothesis that mitoHK-II dissociation triggers mitochondria specific autophagy (mitophagy).

**Results:** mitoHK-II levels were significantly decreased in neonatal rat ventricular myocytes (NRVMs) subjected to simulated ischemia, in the perfused mouse heart subjected to global ischemia and in the heart subjected to myocardial infarction. To assess the role of mitoHK-II dissociation, mitoHK-II dissociating peptide (15NG) was expressed in NRVMs and in the adult heart using adenovirus or adeno-associated virus serotype 9 (AAV9). 15NG expression significantly decreased mitoHK-II levels in NRVMs and in the adult mouse heart. Remarkably 15NG expression induced Parkin translocation to mitochondria, robust ubiquitination of mitochondrial proteins and mitophagy assessed by Mito-Keima in NRVMs. These responses were reversed by the recovery of mitoHK-II by co-expression of HK-II but not by that of mitochondria binding deficient mutant of HK-II. Interestingly, 15NG expression did not induce mitochondrial membrane depolarization nor PINK1 stabilization at mitochondria, suggesting that the effects of mitoHK-II dissociation is not dependent on the well established mitochondria depolarization/PINK1 pathway. Modest dissociation of mitoHK-II did not induce mitophagic responses but enhanced ischemia-induced mitophagic responses and provided survival effects against ischemic stress.

**Conclusions:** These results suggest that mitoHK-II dissociation induced by ischemia can regulate Parkin dependent mitophagy, in conjunction with depolarization dependent mechanisms and that HK-II could confer cardioprotection by initiating mitophagy during ischemia.

**9.21**

**REVISITING THE OPA1 FUNCTION FOR ENERGETIC MAINTENANCE**

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The protein optic atrophy 1 (OPA1) is a dynamin-related large GTPase associated with the inner mitochondrial membrane. OPA1 is a critical factor connecting mitochondrial morphology and energetics by functioning in mitochondrial inner membrane fusion and cristae maintenance. Inner membrane-anchored long OPA1 (L-OPA1) undergoes proteolytic cleavage to form short soluble OPA1 (S-OPA1) lacking the transmembrane domain. Upon mitochondrial dysfunction associated with depolarization, apoptosis, or permeability transition, L-OPA1 is cleaved to form S-OPA1, which is suggested to prevent fusion of dysfunctional mitochondria. While the fusion activities of L- and S-OPA1 have been investigated, their roles in energetic maintenance are poorly understood. It is often thought that S-OPA1 is a functionally insignificant proteolytic product of L-OPA1 because OPA1 cleavage is observed with mitochondrial fragmentation and dysfunction. Nevertheless, cells contain a mixture of L- and S-OPA1 in normal conditions, suggesting the functional significance of maintaining both L- and S-OPA1. We used cells exclusively expressing L-, S-OPA1, or both and evaluated the differential functions of L- and S-OPA1. Our mitochondrial fusion assay elaborated that L-OPA1 has an intrinsic activity for mitochondrial fusion whereas the fusion activity of S-OPA1 is insignificant. Remarkably, we found that S-OPA1 alone without L-OPA1 is capable of maintaining OXPHOS function, as judged by growth in OXPHOS-requiring media, respiration measurements, and respiratory complex levels. Most

strikingly, S-OPA1 alone maintains normal cristae structure, which has been commonly ascribed to the function of OPA1 oligomers containing both L- and S-OPA1. Furthermore, we found that GTPase activity of OPA1 is critical for maintaining cristae tightness, and thus energetic competency. Our data demonstrate that, contrary to conventional notion, S-OPA1 is fully competent for maintaining energetics and cristae structure.

**9.22**

**NITRITE INHIBITS MITOCHONDRIAL PHOSPHODIESTERASE AND ACTIVATES CAMP-PKA-AKAP1 SIGNALING TO MODULATE MITOCHONDRIAL FUNCTION IN NORMOXIA**

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Nitrite is an established signaling molecule that regulates mitochondrial function in hypoxia by inhibiting respiration and mitochondrial oxidant production, but its effects on mitochondrial function in normoxia remain unclear. We previously showed that nitrite increases protein kinase A (PKA) activity in the heart during non-hypoxic conditions. However, the mechanism by which nitrite increases PKA activity and its consequences on mitochondrial function are unknown. Here, we demonstrate that in normoxic conditions nitrite (unlike nitric oxide) increases cAMP levels in H9C2 cardiomyocytes and in isolated mitochondria, leading to PKA activation. This increase in cAMP levels is due to nitrite-dependent inhibition of the mitochondrially localized phosphodiesterase 2A (PDE2A), which degrades cAMP. In addition to increasing PKA activation, we observed that nitrite increases the expression of A-kinase anchoring protein (AKAP1), which tethers PKA to the mitochondrial membrane. Consistent with the mitochondrial targeting of PKA, we show that nitrite induces the phosphorylation of Ser58 on mitochondrial complex IV-1 (a known PKA target) and increases its activity by 86%, leading to augmented basal and maximal respiration (48% and 29%, respectively compared to control). Pharmacological inhibition of PKA attenuates nitrite-dependent increase in respiration, complex IV activity and phosphorylation. These data demonstrate that nitrite is a unique signaling molecule able to increase cAMP levels in normoxia and show a novel mechanism by which nitrite selectively modulates mitochondrial PKA-dependent signaling through the inhibition of PDE2A. Further, these data show that nitrite is a versatile signaling molecule that not only modulates nitrogen dependent post-translational modification, but also modulates phosphorylation.

**9.23**

**NITRITE REGULATES MITOCHONDRIAL DYNAMICS TO INHIBIT VASCULAR SMOOTH MUSCLE CELL PROLIFERATION & RESTENOSIS**

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Nitrite, a dietary constituent and endogenous signaling molecule previously thought to be a biologically inert product of endogenous nitric oxide oxidation, has recently been shown to regulate a myriad of biological processes. For example, nitrite has been shown to inhibit smooth muscle proliferation and attenuate restenosis after vascular injury. However, the mechanism of nitrite-dependent inhibition of smooth muscle proliferation remains elusive. Nitrite is an established regulator of mitochondrial morphology and function, and mitochondrial dynamics have been previously shown to regulate cell cycle progression. Thus, we hypothesized that nitrite modulates mitochondrial dynamics and function to inhibit cell cycle progression and attenuate smooth muscle cell proliferation. Using rat aortic smooth muscle cells (RASMCs) we demonstrate that nitrite inhibits RASMC proliferation induced by platelet derived growth factor (PDGF) in a concentration dependent manner. This phenomenon is associated with mitochondrial fusion dependent on the upregulation of mitofusin-1 (Mfn1). Further, nitrite treatment upregulates the cyclin dependent kinase inhibitor p21, an effect that is abolished in Mfn1 deficient RASMCs. Upon preliminary investigation, we also show that nitrite treatment concomitantly inhibits chymotrypsin-like activity of the 20S proteasome. Ongoing studies are focused on determining the mechanism by which nitrite inhibits the proteasome to upregulate Mfn1 and thereby stimulate mitochondrial fusion while increasing p21 expression. These data have important implications for dietary and pharmacological modulation of vascular health and uncover a novel potential physiological mechanism for the regulation of smooth muscle cell number.

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**9.24**

**PRESYNAPTIC LOSS OF DYNAMIN-RELATED PROTEIN 1 PROFOUNDLY ALTERS SYNAPTIC VESICLE RELEASE AND RECYCLING AT THE CALYX OF HELD**

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Sustained transmitter release is essential for proper interneuronal communication. Impaired mitochondrial function is implicated in many neurodegenerative diseases, and likely affects neurotransmission prior to cellular loss. Synaptic transmission at glutamatergic synapses during repetitive trains of stimuli is affected when presynaptic

mitochondrial function or localization is disrupted, but the underlying mechanism is poorly understood. In this study, we investigate the role of mitochondria in synaptic vesicle (SV) recycling, by eliminating Dynamin-Related Protein-1 (DRP1) selectively in the presynaptic terminal at the calyx of Held synapse.

Floxed-DRP1 (DRP1fl/fl) mice were injected with AAV-cre-GFP at postnatal day 1(P1) to inhibit DRP-1 expression presynaptically, and used for the study at P16 – P18. Infected (GFP-positive) cell soma in the ventral cochlear nucleus, and their respective calyx of Held presynapses in the contralateral medial nucleus of the trapezoid body, showed loss of DRP1 protein via antibody staining, thus generating a presynaptic-specific DRP1-KO (DRP1-preKO). Conditional DRP1-KO was confirmed by Western Blot of DRP1 from AAV-cre-GFP infected neuronal cultures. Volumetric reconstruction of the VCN cell body and calyx terminal showed significant increase in mitochondrial particle size in DRP1-KO somata and calyx presynaptic terminal.

Using postsynaptic voltage-clamp recording from calyx synapses, we find that DRP1-preKO exhibited enhanced basal evoked response (response to 0.1Hz stimulation) and a 3-fold increase in spontaneous synaptic activity (mEPSC). Standing readily-releasable pool (RRP) size was significantly reduced in DRP1-preKO, suggesting an important role for mitochondria in maintenance of SV modality at presynaptic terminal. Additionally, DRP1-preKO synapses have profoundly altered kinetics of the RRP: faster depression, increased initial release probability, and slower recovery after pool depletion were all observed. DRP1-preKO also showed a significant reduction in synaptic transmission delay. These results indicate that the proper functioning of mitochondria is essential for the regulation of synaptic vesicle release during activity, and selectively affect vesicle release during a train of stimuli. Ongoing experiments aim to determine the specific mechanism underlying the presynaptic defect in SV release.

**9.25**

## MITOCHONDRIAL ALTERATIONS IN RIGHT VENTRICULAR DYSFUNCTION SECONDARY TO CHRONIC PRESSURE OVERLOAD

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**Objective:** The objective of this study is to characterize the effects of right ventricular dysfunction (RVD) on fatty acid oxidation (FAO) and mitochondrial biogenesis.

**Methods:** RVD was created in 8-week old male Wistar rats using pulmonary artery banding (PAB). Rats with sham surgery were used for comparison. Increases in ejection time (ET) and estimated pressure gradient across the constriction (ΔP) demonstrated RVD in PAB rats by serial echocardiography. 8 weeks post-surgery, invasive hemodynamics were measured and RV tissues were harvested for Western blot and RT-qPCR analysis of peroxisome proliferator-activated receptor alpha (PPARa), a marker for FAO, and PPAR-gamma coactivator 1-alpha (PGC-1a), a master regulator of mitochondrial biogenesis. All procedures were approved by the UW-Madison IACUC and conform with the APS "Guiding Principles in the Care and Use of Animals."

**Results:** Chronic pressure overload as well as diastolic and systolic RVD were confirmed in PAB rats by invasive measurements (Table1). Also, RV tissues from RVD showed a 3.3-fold increase in FAO and 0.5-fold decrease in mitochondrial biogenesis, suggesting a shift toward FAO metabolism and increased fatty acid uptake. Protein expression levels of PGC-1a and PPARa showed the same trends but did not reach statistical significance.

**Table 1.** Invasive hemodynamics and mitochondrial function-related gene expression in sham and RVD rats.

| Parameter | Sham (n=8) | RVD (n=6) |
|---|---|---|
| $P_{es}$ (mmHg) | 27 ± 6 | 77 ± 9* |
| *Diastolic indices* | | |
| Tau Weiss (ms) | 5 ± 1 | 11 ± 2* |
| $dP/dt_{min}$ (mmHg/s) | -1816 ± 137 | -2717 ± 348* |
| *Systolic indices* | | |
| $dP/dt_{max}$ (mmHg/s) | 2444 ± 124 | 4252 ± 546* |
| EF (%) | 69 ± 5 | 40 ± 7* |
| CO (mL/min) | 108 ± 22 | 37 ± 11* |
| *Fold change in mitochondrial gene expression* | | |
| PPARa | 1.23 ± 0.02 | 3.37 ± 1.32* |
| PGC-1a | 0.71 ± 0.08 | 0.50 ± 0.03* |

Data expressed as mean ± SEM. $P_{es}$, end-systolic pressure. $dP/dt_{min}$, minimum rate of pressure rise. $dP/dt_{min}$, maximum rate of pressure rise. EF, ejection fraction. CO, cardiac output. *$p<0.05$ vs Sham.

**Conclusion:** RVD due to chronic pressure overload alters the mitochondrial balance between FAO and glycolysis, which may implicate increased fatty acid accumulation in mitochondria (i.e., lipotoxicity) as a disease mechanism in RV failure secondary to chronic pressure overload.

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**9.26**

## MICRORNA-338 REGULATES MITOCHONDRIAL FUNCTION FOLLOWING CEREBRAL ISCHEMIA BY TARGETING COX4I1 IN ASTROCYTES

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MicroRNAs (miRs) play a central role in regulating gene expression by inhibiting translation of target genes. Brain-enriched microRNA-338 (miR-338) is known to play an important role in mitochondrial and neuronal function,

however the role of miR-338 in stroke remains unknown. MiR-338 targets cytochrome-c oxidase subunit 4I1 (COX4I1), which plays an essential role in controlling ATP production and mitochondrial biogenesis. Astrocytes are critical regulators of neuronal homeostasis following stroke, and we have previously shown that interventions aimed at preserving astrocyte mitochondrial function following injury can be neuroprotective. This study investigated the effect of miR-338 inhibition on *in vivo* injury outcome following transient focal cerebral ischemia and on astrocyte function following *in vitro* ischemic injury. Pre-treatment of mice with intracerebroventricular injection of miR-338 antagomir 24 h prior to middle cerebral artery occlusion significantly reduced infarct size and improved neurological score after 24 h of reperfusion. As predicted, brain levels of COX4I1 were increased in miR-338 antagomir-treated mice. *In vitro*, primary astrocyte cell cultures subjected to glucose deprivation demonstrated decreased cell death when pre-treated with miR-338 inhibitor, and greater cell death when miR-338 levels were increased by mimic pre-treatment. Decreases in miR-338 were associated with increased ATP production, augmented cytochrome c oxidative activity and attenuated reduction of mitochondrial membrane potential, with preserved COX4I1 mRNA expression. Protection induced by inhibition of miR-338 was diminished by knockdown of COX4I1. In summary, miR-338 inhibition targets astrocyte mitochondrial function to improve outcome following stroke at least in part by regulating mitochondrial function and targeting COX4I1. MiR-338 therefore represents a potential therapeutic target for the treatment of ischemic stroke and other injury or disease states where mitochondrial function is impaired.

**9.27**

## EFFECT OF AGE ON SKELETAL MUSCLE MITOCHONDRIAL FUNCTION: INSIGHT FROM NEAR-INFRARED SPECTROSCOPY

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Age is the greatest risk factor for chronic disease, and is associated with a marked decline in functional capacity and quality of life. A key factor contributing to loss of function in aging, is the decline in skeletal muscle function. While the exact mechanism remains incompletely understood, age-related mitochondrial dysfunction is thought to play a major role. To explore this question further, we recruited eight community-dwelling seniors (age: 74±4 years; m/f: 2/6; BMI: 24 ± 4) and eight young volunteers (age: 24±2 years; m/f: 5/3; BMI: 24 ± 2). Skeletal muscle oxidative capacity (i.e. mitochondrial function) was determined from the recovery kinetics of muscle oxygen consumption. Following a brief bout of handgrip exercise at 50% of one's maximal voluntary contraction, a series of rapid, supra-systolic, arterial cuff occlusions were performed in conjunction with near-infrared spectroscopy placed over the flexor digitorum profundus (i.e. the primary muscle responsible for handgrip exercise). Muscle oxygen consumption was then calculated for each cuff occlusion, as the slope of change in oxygenated hemoglobin minus deoxygenated hemoglobin, and the maximal oxidative capacity was calculated from the recovery kinetics of muscle oxygen consumption. As expected, we observed a marked reduction in the initial rate of skeletal muscle oxygen consumption immediately post-exercise with age: -0.98±0.46 vs. -1.91±1.88 $\mu M \cdot 1^{-1}$, P=0.02, old vs. young, respectively. Remarkably, this group difference persisted even when the workload was matched for absolute force (n = 5). In contrast to our hypothesis however, the rate constant of oxidative recovery following exercise, fit to a monoexponential recovery curve, was not found to be different with age: 56.5±7.4 sec vs. 50.6±7.5 sec, P=0.59, old vs. young, respectively. Taken together, we interpret these findings to reflect an overall reduction in mitochondrial content with age, rather than a frank impairment in mitochondrial function per se. However, a larger sample size is needed to confirm these results.

**Funding:** This work was supported by a UT Arlington Interdisciplinary Research Program grant.

**9.28**

## PHOSPHOFRUCTOKINASE COORDINATES MITOCHONDRIAL AND ANCILLARY BIOSYNTHETIC PATHWAY ACTIVITIES IN THE CARDIOMYOCYTE

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***Background:*** The heart is an omnivorous organ, using a myriad of substrates for both catabolism and anabolism. While the catabolism of glucose via glycolysis for energy provision is fairly well understood, it is less clear how the ancillary pathways of glucose metabolism, critical for synthesizing cellular building blocks and modulating stress responses, are regulated.

***Methods:*** We used radiometric glycolytic assays, [$^{13}C_6$]-glucose isotope tracing, and extracellular flux analysis to understand how phosphofructokinase (PFK)-mediated changes regulate glucose carbon partitioning into catabolic and anabolic pathways. As tools to determine the relevance of PFK-mediated changes in glycolysis, we determined how transduction of mutant forms of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK2) affect cardiac myocyte catabolism and anabolism *in vitro*.

***Results:*** Expression of kinase-deficient ($Glyco^{Lo}$) or phosphatase-deficient ($Glyco^{Hi}$)-PFK2 in neonatal rat cardiac myocytes coordinately regulated glycolytic rate and lactate production. Interestingly, in all groups, >40% of

glucose taken up by the cell was not catabolized to pyruvate, providing a substantial amount available for entry into the ancillary pathways (e.g. pentose phosphate, hexosamine biosynthetic, glycerolipids). Stable isotope resolved $^{13}C$ isotopologue fractional enrichment patterns suggest that PFK activity regulates glucose carbon incorporation into the ribose and glycerol moieties of purines and phospholipids, respectively. However, under conditions of high PFK activity, low $^{13}C$ incorporation into pyrimidines, UDP-N-acetylhexosamine, and fatty acyl chains of triglycerides suggest limitations in mitochondrial-derived oxaloacetate, acetyl-CoA, and fatty acids. Consistent with this idea, high glycolytic rates diminished mitochondrial activity and the coupling of glycolysis to glucose oxidation.

***Conclusions:*** These findings suggest that PFK coordinates the activities of ancillary pathways of glucose metabolism by directly modulating glycolytic intermediate entry into such pathways and by indirectly regulating mitochondrial cataplerosis.

**9.29**

**CORRELATION BETWEEN MITOCHONDRIAL FUNCTION AND MORPHOLOGY AFTER ISCHEMIA-REPERFUSION**

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We have shown that mitochondria-derived vasodilation of middle cerebral arteries (MCAs), was retained 48 h after middle cerebral artery occlusion (MCAO) compared with arteries from the contralateral (contra) side or with MCAs from sham rats[1]. Although the magnitude of the mitochondria-derived vasodilation of ipsilateral (ipsi) MCAs was intact, the overall vasoreactivity, including the endothelium-dependent vasodilation[1] and $Ca^{2+}$ sparks activity[2], was significantly reduced when compared with contra and sham MCAs. In addition, ipsi mitochondria respired at an energetically inappropriate level compared with contra or sham MCAs[2]. However, the correlation of these changes in mitochondrial function in relation to mitochondrial morphology in ipsi MCAs remains unclear. Therefore, we examined mitochondrial morphology in ipsi, contra, and sham MCAs, using transmission electron microscopy, from age-matched, male, Sprague Dawley rats, randomly exposed to MCAO or sham surgery.

MCAO had distinctive effects on mitochondrial morphology and density of ipsi but not contra MCAs. Mitochondria appeared damaged with areas of disrupted internal structures such as the sarcoplasmic reticulum in the vascular smooth muscle cells (VSM) of ipsi MCAs. Extensive mitochondrial fields, typically seen in naïve MCAs, were reduced in area. In contrast, mitochondria in endothelial cells (EC) in ipsi MCAs appeared more prevalent than in sham MCAs and lacked evidence of mitoptosis, seen in VSM cells. Mitochondria in EC cells of ipsi MCAs were in close approximation of adjacent mitochondria, which is suggestive of fission. Mitochondrial morphology, density, and relationship to other cellular structures in sham MCAs were similar to naïve arteries. Typical mitochondrial fields were present in VSM cells of contra MCAs and mitochondria in EC did not exhibit any characteristics distinct from sham or naïve MCAs.

Our data indicate that the altered mitochondrial function in ipsi MCAs corresponds to cell specific vulnerability of VSM and resiliency of EC to ischemic stress. Thus, given the critical role of mitochondria in promoting cell protection, mitochondria in cerebral vascular EC might represent an important therapeutic target in stroke patients. Funding: NIH (DWB: HL-077731; HL093554), LA Board of Regents (DWB; and PVK: LEQSF(2014-17)-RD-A-11), AHA (PVK: 14SDG20490359; IR: 15POST23040005; 17SDG33410366). [1]I Rutkai et al. PMID25063798. [2]I Rutkai, et al. FASEB J April 2017 31:1080.16.

**9.30**

**ASPARTATE IS NOT THE SOURCE OF SUCCINATE IN MYOCARDIAL ISCHEMIA.**

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**Background:** Ischemia-reperfusion injury is the underlying pathology of acute myocardial infarction. The metabolite succinate accumulates during ischemia and is rapidly consumed at reperfusion, driving the generation of reactive oxygen species. Despite this detrimental role at reperfusion, ischemic succinate accumulation is evolutionarily conserved across diverse tissues and species, suggesting that it may serve a beneficial role in ischemia. Elucidating the pathway of succinate accumulation will provide insights into ischemic metabolism that could be leveraged for novel therapeutics.

Ischemic succinate is proposed to be derived from aspartate that is converted to fumarate via the malate/aspartate shuttle or purine nucleotide cycle. Fumarate is then reduced to succinate via a functional electron transport chain (ETC) of Complexes (Cx) I and II (Cx I-II ETC). Herein, we used a targeted metabolomics approach to test these hypotheses in a mouse cardiac model of ischemia.

**Methods**: Experiments complied with the NIH Guide for Care and Use of Laboratory Animals. Ischemic succinate accumulation was investigated in mouse heart mitochondria, cardiomyocytes, and perfused hearts. Metabolites were resolved using HPLC/photo-diode array. Metabolomic flux analyses were performed using heavy isotope tracking by LC-MS/MS.

**Results:** Hypoxic mitochondria generated succinate via a Cx I and II dependent mechanism. However, in both cardiomyocyte and perfused heart models, ischemic succinate accumulation was not sensitive to Cx I, Cx II, or Krebs cycle inhibitors. Appropriate inhibition of Cx I and

Cx II was confirmed spectrophotometrically. Neither malate/aspartate shuttle inhibition nor purine nucleotide cycle inhibition lowered ischemic succinate levels. Additionally, [U-$^{13}$C]aspartate infusion to perfused hearts did not increase the labelling of succinate in ischemia. Of all interventions tested, only glucose-free perfusion significantly diminished ischemic succinate accumulation.
**Conclusions:** Herein, we show that while hypoxic mitochondria are capable of generating succinate *in vitro* via the Cx I-II ETC, this was not the mechanism for ischemic succinate accumulation in cardiomyocytes and intact hearts. Additionally, in contrast with previous findings, ischemic succinate is not derived from aspartate *in situ*. The role of glycolysis in ischemic succinate accumulation is the subject of ongoing investigations.
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## 10.0 MITOCHONDRIAL GENETICS AND OMICS

### 10.1
### NOVEL METHODS TO MODULATE MTDNA HETEROPLASMY

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The human mitochondrial DNA (mtDNA) is present in multiple copies per cell and codes for 13 polypeptides, 22 tRNAs and 2 rRNAs, all of which required for oxidative phosphorylation (OXPHOS) activity. A large number of mutations (>200) in the mtDNA have been associated with clinical syndromes. However, only when their levels exceed a certain threshold, a bioenergetics defect ensues. Therefore, if the levels of mutant genomes could be reduced, the cell should recover its normal OXPHOS function.

We developed mitochondria-targeted TALEN (mitoTALEN) directed against a point mutation in the mtDNA of a heteroplasmic mouse model. This point mutation in the tRNA alanine gene (nt 5024 C>T) destabilizes the tRNA alanine, causing a mitochondrial protein synthesis defect in cells with high levels of the mutation. The mouse with approximately 70-80% mutant mtDNA develops a mild phenotype, developing a cardiomyopathy later in life (around 1 year of age). Experiments with cells from the mouse showed that the mitoTALEN designed was highly efficient against the mutant mtDNA. The two mitoTALEN monomers were expressed from AAV9 particles and injected in the Tibialis Anterior (TA) muscle of the right leg muscle. AAV9 coding for only one monomer was injected in the left TA. Mice were sacrifice 6, 12 and 24 weeks after injection. DNA analysis showed a reduction in the percentage of mutant mtDNA in the right TA at all time points. We did not detect a depletion in mtDNA nor significant levels of deletions, which were previously associated with mtDNA double-strand breaks. In addition, the decrease in mutant mtDNA load in the TA was accompanied by an increase in the levels of tRNA alanine, which is decreased by the 5024 C>T mutation.

In parallel, we are also designing smaller mitochondria-targeted DNA editing enzymes, with could facilitate in vivo gene therapy for mitochondrial diseases.

### 10.2
### DNA DAMAGE DRIVES AGING VIA SUPPRESSION OF THE MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE AND DAF-16/FOXO3A ACTIVITY

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DNA damage is implicated in the aging process, yet the mechanism by which it drives aging is not fully elucidated. To address this, we screened DNA repair-deficient *ercc-1* worms, with increased endogenous nuclear DNA damage, for dysregulation of lifespan modulating pathways. Surprisingly, the mitochondrial unfolded protein response was suppressed, while DAF-16/FOXO3A was activated. The former was required for energy optimization and the latter to mitigate the accompanying increase in oxidative stress. However, the period of protection conferred by DAF-16/FOXO3A activation was limited and correlated with organismal dysfunction, in a CEP-1/P53 dependent manner. These DAF-16/FOXO dynamics were recapitulated in DNA repair-deficient primary cells and mice, as well as, wild-type mice, demonstrating that this is a conserved response. Collectively these data suggest that it is the mitochondrial reprogramming and failure to maintain the appropriate cellular stress responses in the face of chronic DNA damage that promotes age-related decline.

### 10.3
### MITOCHONDRIAL FUNCTION AND THE EPIGENETIC LANDSCAPE

**Oswaldo Lozoya[1], Inmaculada Martinez-Reyes[2], Dagoberto Grenet[1], Tianuyan Wang[1], Jianying Li[1], Pierre Bushel[1], Navdeep Chandel[2], Richard Woychik[1], Janine Santos[1]**

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Mitochondria are well-recognized for their role in ATP and reactive oxygen species generation, in addition to producing intermediate metabolites through the TCA (tricarboxylic acid) cycle. The crosstalk between metabolism and epigenetic modifications in the nucleus is becoming increasingly evident but the extent to which mitochondrial metabolites are required for these effects

remains largely unknown. We recently showed using a cell culture model of acute mitochondrial DNA (mtDNA) depletion that electron flow sustains a functional oxidative TCA cycle, which in turn is necessary to maintain histone acetylation in the nucleus. Following this work, we have interrogated genome-wide locus specific changes in histone acetylation and in DNA methylation, and the extent to which these regulate gene expression. The time-wise progression and the signals associated with these events will be discussed. Lozoya et al., submitted. This work was supported by the NIH intramural program.

**10.4**

**MITOCHONDRIAL TARGETED OXIDANTS AND DNA DAMAGE**

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Mitochondria dysfunction is associated with human pathophysiologies including: aging, cancer, cardiovascular disease and neurodegeneration. We sought to develop a targeted method for causing oxidative mitochondrial dysfunction in the absence of damage to other regions of the cell to test the controversial hypothesis that dysfunctional mitochondria generate sufficient flux of ROS to cause nuclear damage. A novel mitochondrial-targeted fluorogen-activating-peptide (mito-FAP) and a malachite green dye analog, which specifically targets singlet oxygen to Complex IV when irradiated with 660 nm light, induced rapid mitochondrial dysfunction in HEK293 cells. By controlling the amount of dye and light exposure we found conditions to reduce mitochondrial respiration to 10% of control within 4 hrs of damage, as measured by Seahorse Bioanalyzer. Within 4 hrs of damage, mitochondria displayed a fragmented appearance by STED microscopy. This singlet oxygen damage to the mitochondrial electron transport chain (ETC) caused a second wave of mitochondria-generated superoxide and loss of Complex I, III, and IV activities. Damage was abrogated by pretreatment with sodium azide, a singlet oxygen quencher or N-acetyl cysteine a ROS scavenger. Rho zero cells, lacking respiration, were refractory to the second wave of superoxide production. These data are consistent with mito-FAP + dye + light causing rapid singlet oxygen damage to the ETC, followed by dysfunctional ETC production of superoxide. This persistent mitochondria-induced ROS caused a loss of mitochondrial membrane potential and inhibition of cell growth, without apoptosis. Cell cycle arrest was accompanied by a loss in DNA replication and appearance of a replication stress marker, phospho-RPA32. Our experiment with nuclear-targeted HyPer, which is a fluorescent sensor specific for measuring hydrogen peroxide present in the nuclease, indicated appreciable hydrogen peroxide flux 24 hrs after the initial mitochondrial injury with singlet oxygen. Fragile telomeres were present 48 hr after mito-FAP damage supporting the concept that a flux of mitochondria-generated ROS can cause nuclear DNA damage. Finally, we have used this system to successfully ablate mitochondrial function in 5-day old zebrafish embryos expressing mito-FAP in the central nervous system. Together these results indicate a novel approach for studying the effects of mitochondrial damage in living cells and model organisms.Support: NIH grant R21ES025606.
REFERENCE: He J, Wang Y, Missinato MA, Onuoha E, Perkins LA, Watkins SC, St Croix CM, Tsang M, Bruchez MP. A genetically targetable near-infrared photosensitizer. *Nat Methods.* 2016 13(3):263-8.

## LATE BREAKING ABSTRACT SUBMISSIONS

**LB1**

**MITOCHONDRIAL ADAPTATIONS ASSOCIATED WITH THE LOSS OF HEMOGLOBIN AND MYOGLOBIN MAY CONSTRAIN CARDIAC PERFORMANCE OF ANTARCTIC FISHES**

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The loss of expression of hemoglobin (Hb) and myoglobin (Mb) in Antarctic icefishes is associated with extensive mitochondrial remodeling in cardiac muscle. Mitochondrial density is 36.5 % in hearts of species that lack Hb and Mb, compared to 15.9 – 25.0 % in species that express the proteins, and mitochondria are enlarged due to a proliferation of phospholipids, but not proteins. We sought to determine how alterations in mitochondrial structure impact function, particularly in response to warming. The red-blooded species, *Notothenia coriiceps* and icefish, *Chaenocephalus aceratus*, were held at ambient temperature and exposed to acute heat stress. The maximal activities of citrate synthase (CS) and lactate dehydrogenase (LDH), respiration rates of isolated mitochondria, adenylate levels, and changes in mitochondrial protein expression were quantified from hearts of animals held either at ambient temperature and following acute heat stress. Cardiac mitochondria of icefishes are extremely well coupled, but in response to warming, proton leak increases to a greater extent in icefishes compared to red-blooded species. The ratio of cytochrome *c* oxidase activity-to-state 3 respiration rate is significantly higher in mitochondria of +Hb/ +Mb species, suggesting a greater capacity to enhance flux through the respiratory chain when needed. Consistent with this, levels of ATP and energy charge are higher in hearts of +Hb/+Mb species at both ambient temperature and following acute heat stress. Maximal activity of CS is also higher in +Hb/+Mb species. Finally, proteomic analysis indicates that mitochondrial protein expression of aerobic metabolic enzymes and antioxidants increases in hearts red-blooded species but not the icefish in response to acute thermal stress. Together, these data suggest that cardiac performance at elevated temperature may be constrained by mitochondrial function in Antarctic icefishes. Funding was

provided by a grant from the National Science Foundation (ANT 1341663 to KOB).

**LB2**

**AGE-RELATED CHANGES IN MYOGENIC CAPACITY OF EQUINE SATELLITE CELLS**

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Myogenic stem cells (satellite cells, SC) aid in muscle repair and growth during postnatal life. In response to injury or a growth stimulus, SC are activated, proliferate, and subsequently differentiate and fuse to form mature myofibers. As subtle myofiber injuries can occur routinely during daily muscle activity, continuous muscle repair is essential for muscle maintenance throughout life. However, the ability to regenerate muscle and replace damaged myofibers declines with age. The poor regenerative capacity of aged muscle is reportedly due to changes of the SC microenvironment, but intrinsic changes within an aged SC may also impair its function. Here, we examined differences in the intrinsic myogenic capacity and mitochondrial function between skeletal muscle SC from young and aged American Quarter Horses. Muscle biopsies were taken from the Gluteus medius (GLU) and the Triceps brachii (TRI) of young (2-4 yr; n=4) and aged (20-27 yr; n=4) horses. Satellite cells were isolated, proliferated in growth medium, and differentiated in serum-depleted medium. Satellite cells derived from aged compared to young TRI tended to display compromised proliferative capacity (P=0.062, day 4), and significantly lower differentiation (P=0.017) and fusion capacity (P=0.023). Satellite cells isolated from aged GLU exhibited a significant decline in proliferative rate (P=0.015, day 4) and a tendency for a decrease in differentiation capacity (P=0.079). During SC differentiation, gene expression of mitochondrial (mt) DNA encoded subunits of the electron transport system, ND1 (P=0.007, day1; P=0.043, day 2) and COX1 (P=0.031, day 1; P=0.017, day 2), was lower in SC from aged compared to young TRI, despite a higher mt DNA copy number in aged SC (P=0.033, ND1 primer; P=0.021, COX1 primer). Interestingly, differentiating SC from aged compared to young TRI also showed decreased gene expression of mt biogenesis regulators PGC-1α (P=0.059), NRF1 (P=0.05) and TFAM (P=0.008); and differentiating SC from aged compared to young GLU displayed a decrease in expression of PGC-1α (P=0.024). Accumulation of autophagy cargo protein p62 (P=0.038) and autophagosome-bound protein LC3II (P=0.034) in differentiating SC from aged TRI suggested impaired autophagic activity. Collectively, our study suggest that age was associated with impaired mt function, biogenesis and possibly quality control in SC from equine skeletal muscle.

**LB3**

**TARGETING MITOCHONDRIAL FISSION RESTORES INSULIN SIGNALING AND BIOENERGETICS IN SKELETAL MUSCLE INSULIN RESISTENCE**

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Previous data from our lab suggests that phosphorylation of dynamin-related protein-1 (Drp1) at serine residue 616 is reduced by 12 weeks of endurance exercise training in obese individuals with prediabetes. Moreover, the changes in Drp1 phosphorylation were associated with changes in whole body fat oxidation and peripheral insulin sensitivity, suggesting that mitochondrial fission may be altered in insulin resistance. In order to test the potential of Drp1 as a therapeutic target for prevention of skeletal muscle insulin resistance, we treated C2C12 cells with glucose free DMEM containing either 500 µM BSA-conjugated palmitic acid (PA) or oleic acid (OA). 1% BSA in DMEM served as the treatment control. 100 nM insulin was added to appropriate wells 15 minutes before the end of the treatments for assessment of insulin signaling. Drp1 activation at Ser616, along with insulin signaling at Akt Thr308 were assessed by Western blot. The XF24 analyzer was used to assess functional bioenergetic changes. PA treatment, but not OA, increased Drp1 Ser616 activation and basal oxygen consumption, and reduced spare respiratory capacity, mitochondrial coupling efficiency, and insulin stimulated Akt Thr308 phosphorylation (all $P<0.05$). Inhibition of mitochondrial fission by 150 µM mDivi1 for 1 hour, or knockdown of Drp1 by shRNA, restored insulin signaling and cellular bioenergetics ($P<0.05$), suggesting that alterations in insulin sensitivity and cellular bioenergetics induced by saturated fatty acids can be abrogated by targeting the mitochondrial fission pathway. Grant support: 1R01DK108089

**LB4**

**CARDIAC ISCHEMIA IMPAIRS EVERY STEP OF THE OXIDATIVE PHOSPHORYLATION PATHWAY**

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Despite numerous investigations examining the effects of ischemia on the ability of cardiac mitochondria to produce ATP, it is still unclear the degree to which ischemia affects each component of mitochondrial energy transduction pathway. The present study examined mitochondrial function at respiration rates between resting and maximal and utilized force-flow analysis to determine the effect of ischemia on each step of the oxidative phosphorylation pathway.

Mitochondria were isolated from rat hearts subjected to either 60 minutes of control coronary flow or 60 minutes of

no flow ischemia. Driving forces (extramitochondrial phosphorylation potential, mitochondrial membrane potential, and NADH redox status) and flux (oxygen consumption and reactive oxygen species (ROS) production rates) were determined. Force-flow analysis was used to determine the interaction between energetic driving forces and flux to calculate the effective activity of each step within the oxidative phosphorylation pathway.

Ischemia reduced mitochondrial oxygen consumption rates at high phosphorylation potentials (300 ± 27 vs 161 ± 13 nmol $O_2$/nmol cytochrome a/min) but had much less of an effect at low phosphorylation potentials (76 ± 10 vs 55 ± 5), however ischemia diminished mitochondrial membrane potential (~11 mV) across all phosphorylation potentials. Force-flow analysis revealed ischemia decreased 1) the conductance of the electron transport chain (ETC) and 2) the combined activity of ATP synthase and the adenine nucleotide translocase both by ~50%. Indeed, the contributions of each pathway to the total mitochondrial resistance to energy transfer did not differ between control and ischemia, with fuel transport contributing ~15%, the ETC contributing ~25%, and ATP synthase contributing ~60% to the total resistance. ROS production was linearly related to driving force down the ETC (from redox potential to membrane potential) in both control and ischemic mitochondria, however ROS production rates were 2.3-fold higher in ischemic mitochondria.

The decreases mitochondrial ATP production capabilities caused by ischemia are distributed throughout the oxidative phosphorylation energy production pathway and high mitochondrial respiration rates are the most severely inhibited. Neither reductions in ETC or ATP synthase activity alone are responsible for ischemia-induced impairments, and to improve respiration at higher workloads, the function of the entire pathway must be improved.

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**LB5**

## SKELETAL MUSCLE MITOCHONDRIAL UNCOUPLING ACTIVATES THE INSULIN SIGNALING PATHWAY

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Obesity is an epidemic effecting nearly 100 million individuals in the United States. Upwards of $210 billion dollars are spent yearly treating acute and chronic conditions of obese patients. As such, therapeutic approaches aimed at reducing obesity and its related symptoms are highly warranted. Mitochondrial uncoupling agents are well known for their effects on enhancing metabolic rate and energy expenditure. By collapsing the proton gradient, energy is dissipated as heat, resulting in weight loss. Uncoupling agents have been used in the treatment of obesity since the 1930's. However, the underlying mechanisms driving uncoupling-induced thermogenesis and its interactions with lipid metabolism remain poorly understood. To investigate the role of uncoupling in skeletal muscle metabolism and insulin resistance, fully differentiated C2C12 myotubes were treated with 20 uM of carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone (FCCP) for 4 hours. Furthermore, cells were differentially treated with 500 uM palmitic acid (PA) (18 hours), FCCP (4 hours), and insulin (10 minutes). Changes in mitochondrial dynamics and insulin signaling were assessed via Western blot. Treatment with FCCP significantly uncoupled ($P<0.05$) OXPHOS as demonstrated by OPA1 proteolytic processing. At 30 minutes and extending through the 4 hour time course, FCCP significantly increased AKT (t308 and s473) and AS160 phosphorylation ($P<0.05$). Treatment with PA significantly reduced OPA1 expression ($P<0.05$), as well as activation of the insulin signaling pathway ($P<0.05$). Insulin recovered proteolytic degradation of L-OPA1 in control and PA treated cells. The combined effects of FCCP and insulin significantly differed in PA-treated cells ($P<0.05$), suggesting an interaction-effect between FCCP and palmitate. Thus, skeletal muscle mitochondria act as energy sensors, acting through canonical signaling pathways in order to maintain homeostasis. Lipotoxicity appears to ablate this response, by both deteriorating communication within the mitochondria and intracellularly. These findings provide mechanistic insight into how lipids may contribute to mitochondrial dysfunction and insulin resistance in skeletal muscle. *This study was funded by the NIH (R01-DK108089).*

*indicates invited speaker