We seemed to have survived the Shutdown, and we hope that your research has returned to a productive state. While there is no budget deal yet, we hope that we won’t have a second shutdown on January 15th when the continuing resolution runs out.

The Holiday season is upon us, and while we take stock of all our achievements for 2013 and plan for 2014, we urge you to think of those amongst us who are less fortunate, and help through your contribution to the Combined Federal Campaign (CFC). The CFC website https://www.opm.gov/combined-federal-campaign/ provides lots of information about the organizations supported and how you can make either a designated or a general contribution to the CFC.

The Office of Education wishes you all a Happy Holiday season and a joyous, productive and successful 2014.

From the Director of the Office of Education

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The Fellows Newsletter is published monthly by the Office of Education, Division of Intramural Research, National Heart, Lung, and Blood Institute and distributed to NHLBI DIR members to promote the interest of DIR Fellows.

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The Science Beat
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NHLBI DIR Holiday Potluck

Wednesday, December 11th
3:00 - 4:00 PM
Building 10CRC, Room 5-2550

Please bring something to share.
A prize will be given to the top voted dish.
Meet the New Fellows

Andrew Simmonett, Ph.D., is a new Research Fellow in the Biochemistry and Biophysics Center under Dr. Bernard Brooks. Dr. Simmonett received his Ph.D. in Computational Quantum Chemistry from the University of Georgia. His initial project at the NHLBI is Deriving and implementing multiple moment terms into the CHARMM package.

Lo Lai, Ph.D., is a new Visiting Fellow in the Biochemistry and Biophysics Center under Dr. Rodney Levine. Dr. Lai received her Ph.D. in Cell and Molecular Biology from Rutgers University. Her initial project at the NHLBI is studying oxidative stress in cardiomyocytes.

Andrew Dittmore, Ph.D., is a new Postdoctoral IRTA in the Biochemistry and Biophysics Center under Dr. Keir Neuman. Dr. Dittmore received his Ph.D. in Materials from the University of California, Santa Barbara. His initial project at the NHLBI is constructing and characterizing the performance of a simple “magnetic tweezers” instrument.

THE SCIENCE BEAT by Dinari Harris, Ph.D.


Post-translational modifications play an important role in a wide range of cellular functions. One such reversible post-translational protein modification, termed poly-ADP ribosylation is catalyzed by the member of the poly(ADP-ribose) polymerase (PARP) enzyme family. Poly-ADP ribosylation influences DNA repair, transcription, centrosome duplication, and chromosome stability. Mechanistically, PARPs use NAD+ as a substrate to cleave off the nicotinamide moiety, followed by the covalent transfer of the ADP-ribose group to suitable acceptor proteins, like histones, DNA polymerases, topoisomerases, DNA ligases, transcription factors, and PARP1 itself. PARPs elongate chains by adding more ADP-ribose units to create a branched polymer, called poly(ADP-ribose) or PAR, which is subsequently degraded by poly(ADP-ribose) glycohydrolase (PARG) and ADP-ribosyl hydrolase 3 (ARH3). Because PAR metabolism is tightly regulated by these key enzymes and has been associated with brain ischemia, myocardial injury, Parkinson’s disease and diabetes, it has received considerable attention over the last few years as a potential therapeutic target. Reversible poly-ADP ribosylation is a pleiotropic regulator of various cellular functions but uncontrolled PARP activation may also lead to cell death. Results from several labs have shown that free PAR or PAR not covalently attached to acceptor proteins may contribute to parthanatos, a form of caspase-independent cell death. This parthanatos pathway is triggered by the release of apoptosis-inducing factors (AIF) from the mitochondria of cells. Specifically, PAR generated by PARP1 in the nucleus, translocates to the cytoplasm and binds to AIF on mitochondrial membranes. Following AIF cleavage and release from the mitochondria, AIF is translocated to the nucleus, whereby it induces large-scale DNA fragmentation and ultimately cell death.

The parthanatos cell death pathway mediated by poly-ADP in oxidatively stressed cells has been extensively studied for almost thirty years. However, the underlying molecular mechanism(s) and the exact roles of the metabolic enzymes responsible for PAR regulation (PARP1, ARH3, and PARG) have only begun to emerge relatively recently. In the study by Mashimo et al., the authors examined the role of ARH3 in the PARP1-mediated cell death pathway and demonstrated that ARH3 has a protective effect against the cytotoxicity induced by hydrogen peroxide (H2O2). To investigate the role of the PAR-degrading activity on ARH3 under oxidative stress induced by H2O2 exposure, the authors determined the subcellular localizations of ARH3 and found significant accumulations in the cytoplasm and to a lesser extent in the mitochondria and nucleus of cells. This distribution was disrupted in ARH3-/- knockout lines and subsequently conferred a protective effect against H2O2-induced cell death in ARH3 mutant lines. This protection against H2O2-induced cell death was associated with nuclear shrinkage and chromatin condensation, common characteristics of apoptotic cells. Since oxidative stress induced by H2O2 exposure causes DNA damage followed by PAR synthesis, the authors wanted to determine whether ARH3 deficiency caused a change in PAR levels after exposure. Using an anti-PAR antibody, they found that ARH3 did regulate both nuclear and cytoplasmic PAR accumulation in response to H2O2.

Exposure to H2O2 resulted in significant accumulation of nuclear PAR in ARH3-deficient cells lines compared to wild-type (WT) cell lines. Because these results suggested that the levels of PAR were altered in ARH3-/- mutant lines, the authors decided to examine the role of the other key metabolic enzymes involved in the regulation of PAR. Since, PARP1 and PARG are responsible for synthesis and turnover of PAR, respectively, Mashimo et al. investigated whether the higher PAR levels in ARH3-/- after H2O2 exposure was due to changes in activities of PARP1 and/or PARG. Using both small-molecule inhibitors and shRNA targeting PARP1, they found a reduced sensitivity in ARH3-/- cell lines to H2O2-induced cell death, decreased nuclear shrinkage and chromatin condensation, as well as decreased accumulation of nuclear PAR. These results taken...
Meet the New Fellows

Katherine Jones is a new Postbaccalaureate IRTA in the Genetics and Developmental Biology Center under Dr. Yosuke Mukoyama. Katherine is a recent graduate of Dartmouth College where she received her Bachelor of Arts in Biology.

Malkolm Graffe is a new Postbaccalaureate IRTA in the Biochemistry and Biophysics Center under Dr. Justin Taraska. Malkolm is a recent graduate Reed College where he received his Bachelor of Arts in Chemistry.

Brian Shepard is a new Postbaccalaureate IRTA in the Genetics and Developmental Biology Center under Dr. Yosuke Mukoyama. Brian is a recent graduate of Williams College where he received his Bachelor of Arts in Biology.

Recent Publications by NHLBI Fellows


**Q&A with Principal Investigator**

**Postdoc Kevin Ramkissoon interviews Dr. Nihal Altan-Bonnet, Principal Investigator, Laboratory of Host-Pathogen Dynamics**

**Kevin Ramkissoon (KR):** When did you decide that you wanted to become a scientist?

Nihal Altan-Bonnet (NAB): This may be cliché but I became interested in biomedical research when a close family member developed cancer while I was in high school. I had the youthful naïveté to think that I could find a treatment to help so in my free time, after classes I would read and try to understand scientific articles and attend seminars at Memorial Sloan Kettering Cancer Center (MSKCC). Throughout college I volunteered in basic science research labs at MSKCC and Mt. Sinai School of Medicine in labs headed by Dr. Robert De-lotto and Dr. Leslie Pick respectively. At that time both were early-career PIs and they did not have many people working with them - lucky for me! This gave me a wonderful opportunity to carry through entire projects by myself rather than having to work on things piece meal. As new PIs they spent a lot of their time at the bench doing experiments, which allowed for many impromptu and inspiring scientific discussions and enabled me to learn from them directly.

**KR: What are the most exciting aspects of working at the interface of host-pathogen interactions?**

NAB: The host-pathogen interface is a very exciting area of study right now. Thanks to cutting edge tools like bioinformatics, systems biology, super resolution light microscopy, intravital microscopy, siRNA, CRISPR and other genetic manipulation technologies we are beginning to shed light on just how critical how bacteria and viruses are for shaping life on this planet: from impacting how our bodies function under both normal and disease circumstances to modulating carbon dioxide storage in our oceans by regulating algae populations.

**KR: Can you briefly describe your experience as a post-doctoral fellow at the NIH?**

NAB: Having done my PhD studies with Dr. Sandy Simon at Rockefeller University I had already been bitten by the microscopy bug, to want to look at cells and their inner workings. I chose to come to Jennifer Lippincott-Schwartz’s lab (NICHD) for a post-doc not only because she was at the forefront of developing and applying fluorescent protein and imaging technologies to the study of living cells, but had (and still has) a reputation for challenging dogma and being bold in her thinking. I was not disappointed. Jennifer provided a very creative, stimulating and positive scientific environment where we were always encouraged to identify and go after the bigger, tougher and ultimately more rewarding questions. The years I spent in her lab were intellectually tremendously rewarding and exhilarating and gave me the tools and the confidence to enter a completely new field of study, host-pathogen interactions.

**KR: How has this experience influenced the way you train and mentor fellows in your lab?**

NAB: I encourage my students’ and post-docs’ creativity, they’re daring, and I try to get them to challenge themselves in their choices of areas to study and questions to pursue. I remind them almost daily that being at NIH gives them the freedom to take on risky but potentially high reward projects and to seek and foster interdisciplinary investigations and collaborations. In addition, I try to provide opportunities for them to present and discuss their work by sending them in my place to give talks at conferences. The ability to convey your ideas and experiments in public and to be able to thoughtfully answer questions about your research are critical for getting feedback and for disseminating your work.

**KR: Drawing on your experiences as both an NIH fellow and Investigator, what piece of advice would you give to NHLBI fellows for fostering positive relationships with their mentors?**

Cont’d on page 6

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**Dr. Nihal Altan-Bonnet, Bio in Brief**

Dr. Nihal Altan-Bonnet spearheads the Laboratory of Host-Pathogen Dynamics - a multidisciplinary team of investigators combining diverse techniques such as high-resolution imaging, molecular spectroscopy and high-throughput genetic screening to uncover the common mechanisms employed RNA viruses to hijack their human hosts. Schooled in NYC, Dr. Altan-Bonnet completed undergraduate degrees in biology and chemistry from Hunter College and a Ph.D. in cell biology from The Rockefeller University. She completed a post-doc at the NIH before heading back north for a faculty position at Rutgers University. A dynamic research program earned her numerous early-career awards, including a 2012 Presidential Early Career Award in Science and Engineering (PECASE), and brought her back to the NIH in 2013 as an Earl Stadtman Investigator. A strident proponent of applying basic research discoveries to public health, Dr. Altan-Bonnet along with her collaborators in the biotech industry, are actively translating results at the bench by developing and testing drugs designed to curtail viral replication, pathogenesis, and possibly the next pandemic.
Q&A with Postdoc Juliane Caviston

Juliane Caviston (JC): I had a great high school foundation in the life sciences. I took a Biochemistry class that really peaked my interest. I also worked as a technician for about 5 years in the yeast genetics lab of Dr. Erfei Bi at the University of Pennsylvania. It was a really great experience and definitely influenced my decision to go to graduate school. He regarded me as his first grad student and gave me every opportunity to grow as a scientist. Once, I gave a presentation to the department where I showed pictures of a dramatic morphological phenotype and the audience actually said “ooh.” I loved it! Wouldn’t?

KR: What factors influenced your decision to come to the NIH for a post-doc?

JC: There were multiple factors that factored into my coming to the NIH. I was trained as a cell biologist and studied the molecular motor protein dynein. I have always had a strong interest in protein trafficking, so coming to the Donaldson Lab in the Cell Biology and Physiology Center was a really good fit with both my prior training and where I wanted to go next. Another important consideration was that the MD/DC area offers good opportunities for couples pursuing dual science careers. My husband was recruited to the NIH and now works in NCATS. The area is also really family friendly – Montgomery County has some of the best public schools in the country and since we have 2 kids, this was a very attractive draw. Also, as an NIH fellow, I am eligible to use the NIH childcare center, for which there is a waiting list. I was lucky enough to have my youngest daughter attend a year of preschool here on campus with me and that was a wonderful, enriching experience for both of us!

KR: What do you enjoy most about the research environment and the people you work with?

JC: I had a strong training in cell biology and a significant part of that involved reading the publications and studying the research of some of the most prominent cell biologists, particularly scientists in the cytoskeleton and protein trafficking fields. My first scientific discussions with my current PI occurred over lunch while I was still in grad school at the University of Pennsylvania. I was part of a group of students that invited her to speak about her research. I really love the fact that I now work alongside her and many other high caliber scientists the likes of John Hammer, James Sellers and Edward Korn to name a few.

KR: Beyond your work in the lab, what experiences do you think have been beneficial to your training and development during your fellowship?

JC: There are so many opportunities here for fellows to participate in great scientific seminars and interest groups. I attend the protein trafficking interest group seminars and I am currently a member of the NIH Science Policy Discussion Group (SPDG). I enjoy the Fellows Retreat that we have every year. It is a great opportunity to meet everyone and learn about what research is going on in NHLBI. I have also been trying to take advantage of career development opportunities offered by the NHLBI Office of Education (OE), in part by joining the Fellows Advisory Committee (FAC). The Office of Intramural Training and Education (OITE) is also a wonderful resource for career development. I have taken the workplace dynamics course series which really opened my eyes to how strongly different personality types and backgrounds influence how well people work together, be it in a lab setting or otherwise.

KR: Had you not chosen your current path in research, what career do you think you would be in today?

JC: I love science and have a strong interest in writing and editing so I might have pursued a masters degree in science writing and communication.

KR: What advice would you give to a first year fellow just entering the NHLBI training program on helping achieve a good work/life balance?

JC: It’s a very personal thing, and it is probably quite different for everyone. Life in the lab can get very hectic and time consuming. Having a support structure outside of the lab is really helpful, be it friends or family. A big key to maintaining the work-life balance for me has been having a very supportive spouse. We completely share household and parenting responsibilities and he understands that sometimes things don’t go as planned in the lab! He is very patient and flexible, and I try to be the same. That’s the only way I know to stay “balanced."

NHLBI DIR SEMINAR SERIES

Hugo Bellen, Ph.D.
Investigator, Howard Hughes Medical Institute Professor, Baylor College of Medicine

“Mitochondria and Neurodegeneration”
Tuesday, December 10th
11:00 AM - 12:00 PM
Building 40, Room 1201/1203
new insight into the role that PARP1 and PARG play in the regulation of PAR metabolism.

During oxidative stress induced by hydrogen peroxide. Their results provide evidence for physiological functions of ARH3 and shed light on the release of AIF from the mitochondria and parthanatos. This research has identified the sequential action of PARG and ARH3 in PAR metabolism and its importance during oxidative stress induced by hydrogen peroxide. Their results provide evidence for physiological functions of ARH3 and shed new insight into the role that PARP1 and PARG play in the regulation of PAR metabolism.

In summary, the work by Mashimo et al. convincingly showed that PARG enhances PAR translocation by releasing protein-free PAR fragments from nuclear acceptor proteins. ARH3 lowers PAR levels in the nucleus and cytoplasm, preventing PAR translocation and parthanatos. This research has identified the sequential action of PARG and ARH3 in PAR metabolism and its importance during oxidative stress induced by hydrogen peroxide. Their results provide evidence for physiological functions of ARH3 and shed new insight into the role that PARP1 and PARG play in the regulation of PAR metabolism.

Together suggest that PARP1 is indeed responsible for the production of PAR and for the initiation of cell death in ARH3-/-- lines after H2O2 exposure, by preventing accumulation in the nucleus of excess PAR, and its translocation to the cytoplasm and mitochondria. It is well established that after PARP1 activation, excessive PAR production results in parthanatos, which is mediated by the release of AIF from the mitochondria and translocation to the nucleus. To examine the role of ARH3 in this pathway, Mashimo et al. showed that AIF did indeed accumulate much more in the nucleus of ARH3 deficient lines compared to WT lines after H2O2 exposure and this increase in AIF accumulation leads to parthanatos. In contrast, depletion of PARG protein protects ARH3-- lines from H2O2-induced cell death by suppressing PAR release from poly-ADP ribosylated PARP1 and its translocation to the cytoplasm and mitochondria. These results indicated that unlike, ARH3 deficiency, PARG depletions protected H2O2-induced parthanatos by preventing AIF release from the mitochondria.

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Between now and New Years, we consider this the Holiday season, a time for looking back and looking forward to the New Year. However, at NIH it’s also the time of year when the candidates for the Earl Stadtman Investigator positions come to campus for their interviews. As many of you know the Stadtman positions are named after Dr. Earl Stadtman, who was an NHLBI Lab Chief for many years before his sudden death several years ago. During his career, Dr. Stadtman trained many outstanding scientists, a few of whom went on to receive the Nobel prize. So it is quite fitting that this search for exceptional scientists and mentors should bear his name.

The candidates have been selected for interviews by field-specific committees based on the quality of potential excellence in their research as judged by their c.v., research proposal and letters of recommendation. However, the on campus interview is one of the most important steps in the process, and at NIH each field sponsors an all-day symposium for their candidates. This provides an exceptional opportunity for fellows who are interested in becoming a Principal Investigator to have an introduction to the interview process and learn about what to do and not to do. While these candidates all have significant achievements, each presenter will have their own style, and you can learn much from how they frame their seminar and how the audience responds. For example, the audience for these talks is comprised of NIH scientists, not all of whom will be experts in the field of the candidate. So you can see how they get their point across to this group. In addition, how they respond to questions is an important part of the process.

The first symposium was on Dec. 2nd, but you can find a full schedule here: https://ccrod.cancer.gov/confluence/display/NIHStadt/Stadtman+Presentation+Schedule+2013+-+2014;jsessionid=D6875E2177E6E24F40544E9A773A

Want an Academic Job:
Take Advantage of the Stadtman Searches
By Herbert M. Geller, Ph.D.

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