



Office of Education, Division of Intramural Research
National Heart, Lung, and Blood Institute
FELLOWS NEWSLETTER

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.

Office of Education, DIR, NHLBI

Herbert M. Geller, Ph.D., Director
Angela N. Theofilos, Program Coord.
Aurora J. Taylor, Program Coord.

DIREDucation@nhlbi.nih.gov

Building 10, Room 2N242

Tel: 301-451-9440

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From the Director of the Office of Education

I interact with many fellows who are doing a job search or thinking about future careers. When I direct them to our web site, I often get the response "I didn't know there was so much information on the Office of Education intranet site ". While you all have gotten a tour of the OE intranet site when you arrived, I'd like to remind you that this is not a static web site: we are constantly updating the information to enhance your training experience. This information is targeted towards your career development, with many links to web sites that have specific job listings as well as web sites that have information on preparing your C.V. or resume, writing a cover letter, and even how to prepare your NHLBI business cards. We are continually adding rotation opportunities for fellows. Even if you are not directly involved in a job search, I'd suggest that you make periodic visits to the web site, <http://dirintranet.nhlbi.nih.gov/oe>, to check out the latest updates. In addition, if you encounter a useful web site, please let us know so we can link to it from our web pages.

I hope that your summer is going well. The newsletter is taking a summer vacation in August, so look for your next newsletter at the beginning of September.

***Making the Most of your
NHLBI Fellowship
Experience***

By Mark Stevens, Chair,
Fellows Advisory Committee

In the busy world of a post-doctoral fellow at the NIH, it is sometimes easy to overlook the fact that we are here to obtain essential training for success in our future careers. We have to design and run experiments, analyze data, give presentations, and write papers. Additionally, we may have to help train summer students or other fellows. It is no wonder why we may consider skipping "career development" activities, especially if we would like some time for ourselves or our fami-

(cont'd on p.4)

**NHLBI Summer Students:
Lunchtime Seminar Series**

*Seminars held in Building 10,
Room 7S235 from 12:00-1:30

7/14

**Nico Tjandra, Ph.D.
Laboratory of Molecular
Biophysics**

**"Structural Studies of Actin
Cytoskeleton Regulation"**

7/28

**Michael Sack, M.D., Ph.D.
Translational Medicine Branch
"Diabetes, Mitochondria, and
Insights Gained from 'Anti-Aging'
Research"**

Featured CORE: The Animal MRI/Imaging Core **Stasia Anderson, Ph.D.**

The Animal MRI/Imaging Core performs magnetic resonance imaging (MRI) of small animal models in the NHLBI. Our goals are to develop and optimize MRI methods for cardiovascular imaging of mice and rats, determine solutions for project needs, and perform the studies.

MRI provides high resolution anatomic images of the heart and large vessels as well as detailed functional information such as ejection fraction, cardiac output, ventricular volumes and wall thicknesses. We have also performed studies of kidneys, skeletal muscle, and fixed embryos. I have a particular interest in MR microscopy, or high resolution tissue imaging. The studies undertaken in the Core include myocardial infarction, genetic mutations affecting the heart, atherosclerosis, kidney disease, myocardial fibrosis, myocardial infarction, obesity and diabetes.

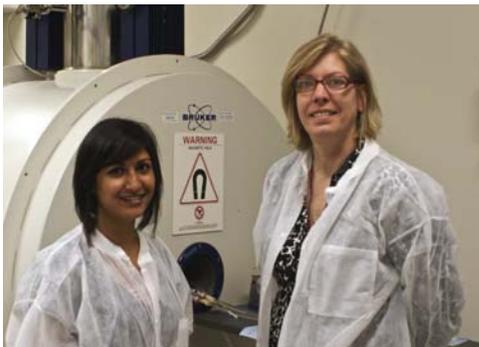
The Imaging Core primarily operates within the NIH Mouse Imaging Facility (MIF), a MRI, ultrasound, CT, and optical imaging facility for small animals that is a NIH-wide resource. Our oversight committee is chaired by

Dr. Andrew Arai, and Aneeka Chaudhry is a research assistant to provide expert help with your animals. All live animal imaging and some ex vivo tissue imaging is performed within the MIF. The Core has dedicated magnet time on a 7.0T Bruker Pharmascan. We also have access to a 7.0T Bruker vertical bore microimaging system for tissue imaging sited in Building 14. In addition to MRI, which is the main focus of the Core, we can incorporate additional techniques available through the MIF such as computed tomography, ultrasound and bioluminescence. The most commonly used additional method is ultrasound, and fellows are normally trained to perform the ultrasound exam themselves.

To initiate a new study, I meet with the PI and fellows to determine their needs and formulate an experimental plan, using standardized or custom-designed methods. Planning for number and timing of animal imaging usually requires any time-sensitive aspects of the experiment to be coordinated with the imaging timing. This may include staggering groups for surgery or treatment. I advise about how to initiate a study, beginning with amendment to the Animal Care and Use Committee (ACUC) protocol, and provide methods for protocols. Additional proce-

dures are required for the MIF such as safety training for lab staff and meeting with the MIF veterinarian. I help coordinate these and MIF-specific administrative needs such as forms and housing facility health reports. All administrative needs to initiate an animal imaging study take approximately a month to complete.

Typically the lab fellows bring the animals to the MIF as scheduled and return them to housing after imaging, and fellows are welcome, though not obligated, to be involved in all aspects of the imaging process. Learning to perform independent imaging requires longer training than is usually encountered in a short study, but experience can be gained in all aspects. Training opportunities include animal handling, setup, and anesthesia, performance of the MRI experiment, theory and background of the MRI experiment, and data processing. After a short period of training, fellows can perform their own data processing of standard cardiac function. The accuracy of the analysis is a priority for the Core, and we oversee all data processing, and we perform much of it. We are very interested and committed to the success of our research projects and welcome your inquiries if you think an imaging study may help your research project.



Aneeka Chaudhry and Stasia Anderson

Animal MRI/Imaging Core
Building 10 Room BID49C

New NHLBI Fellows

Jing Chen, Ph.D., is a Visiting Fellow in the Biochemistry and Biophysics Center under Dr. Jian Liu. Dr. Chen earned her Ph.D. in Mathematical Modeling of Bacterial Motility from the University of California, Berkeley. Her current research project is the modeling of mechanochemical regulation in metaphase/anaphase transition in mitosis.



Recent Publications by NHLBI Fellows

Chiang, Y. J., Calado, R. T., Hathcock, K. S., Lansdorp, P. M., Young, N. S., & Hodes, R. J. (2010). Telomere length is inherited with resetting of the telomere set-point. *Proceedings of the National Academy of Sciences of the United States of America* 107, 10148-10153.

Johnson, A. D., Bhimavarapu, A., Benjamin, E. J., Fox, C., Levy, D., Jarvik, G. P., & O'Donnell, C. J. (2010). CLIA-tested genetic variants on commercial SNP arrays: Potential for incidental findings in genome-wide association studies. *Genetics in Medicine* 12, 355-363.

Kim, G., Cole, N. B., Lim, J. C., Zhao, H., & Levine, R. L. (2010). Dual Sites of Protein Initiation Control the Localization and Myristoylation of Methionine Sulfoxide Reductase A. *Journal of Biological Chemistry* 285, 18085-18094.

Kitajiri, S., Sakamoto, T., Belyantseva, I. A., Goodyear, R. J., Stepanyan, R., Fujiwara, I., Bird, J. E., Riazuddin, S., Riazuddin, S., Ahmed, Z. M., Hinshaw, J. E., Sellers, J., Bartles, J. R., Hammer, J. A., Richardson, G. P., Griffith, A. J., Frolenkov, G. I., & Friedman, T. B. (2010). Actin-Bundling Protein TRIOBP Forms Resilient Rootlets of Hair Cell Stereocilia Essential for Hearing. *Cell* 141, 786-798.

Klauda, J. B., Venable, R. M., Freites, J. A., O'Connor, J. W., Tobias, D. J., Mondragon-Ramirez, C., Vorobyov, I., Mackerell, A. D., & Pastor, R. W. (2010). Update of the CHARMM All-Atom Additive Force Field for Lipids: Validation on Six Lipid Types. *Journal of Physical Chemistry B* 114, 7830-7843.

Lagranha, C. J., Deschamps, A., Aponte, A., Steenbergen, C., & Murphy, E. (2010). Sex Differences in the Phosphorylation of Mitochondrial Proteins Result in Reduced Production of Reactive Oxygen Species and Cardioprotection in Females. *Circulation Research* 106, 1681-1686.

Lucas, H. R., DeBeer, S., Hong, M. S., & Lee, J. C. (2010). Evidence for Copper-dioxygen Reactivity during alpha-Synuclein Fibril Formation. *Journal of the American Chemical Society* 132, 6636-+..

Metais, J. Y., Topp, S., Doty, R. T., Borate, B., Nguyen, A. D., Wolfsberg, T. G., Abkowitz, J. L., & Dunbar, C. E. (2010). Feline leukemia virus integrase and capsid packaging functions do not change the insertion profile of standard Moloney retroviral vectors. *Gene Therapy* 17, 799-804.

Salcido, C. D., Larochelle, A., Taylor, B. J., Dunbar, C. E., & Varticovski, L. (2010). Molecular characterisation of side population cells with cancer stem cell-like characteristics in small-cell lung cancer. *British Journal of Cancer* 102, 1636-1644.

Xie, J. J., Larochelle, A., Maric, I., Faulhaber, M., Donahue, R. E., & Dunbar, C. E. (2010). Repetitive Busulfan Administration After Hematopoietic Stem Cell Gene Therapy Associated with a Dominant HDAC7 Clone in a Nonhuman Primate. *Human Gene Therapy* 21, 695-703.

THE SCIENCE BEAT

By Nisha Narayan, Ph.D.

[Lagranha CJ, Deschamps A, Aponte A, Steenbergen C, Murphy E. Sex differences in the phosphorylation of mitochondrial proteins result in reduced production of reactive oxygen species and cardioprotection in females. *Circulation Research* \(2010\) Jun 11;106\(11\):1681-91.](#)

Heart disease is the number one cause of death in women in the United States. A vast number of epidemiological studies show that premenopausal women have a much lower risk of acquiring cardiovascular disease compared to

men and to post-menopausal women. Thus the obvious protection offered by the hormone estrogen, is thought to act in a variety of ways, from alteration of gene expression brought about by the binding of estrogen, to estrogen receptors or by alterations in post-translational modifications mediated by signaling events. There are also studies that support the role of altered mitochondrial function in this process.

In this study, the authors test the hypothetical role of differences in mitochondrial protein levels or post-translational modifications in cardio-protection conferred to females. To do so, they use rats as a model and first

demonstrate that the females demonstrate less ischemia/reperfusion related injury, better post-ischemic recovery and less necrosis compared to males. They then compared ovariectomized (ovx) female rats with normal female rats and found the ovx females to have poorer recovery and more necrosis. With the model established, they then sought to examine sex differences in mitochondrial proteins through proteomics – mitochondria from male and female hearts were separated by 2D fluorescence difference Gel Electrophoresis (DIGE) and the differences in peptide patterns were analysed using the Progenesis Software. The proteins showing significant differences were extracted, investigated using MALDI TOF/TOF and were identified to be proteins involved in metabolic processes. They then identified the post-translational modifications as shown by multiple locations of the same protein, which they also confirmed as phosphorylation by ProQ Diamond staining. Aldehyde Dehydrogenase-2 (ALDH2) was one of these proteins that showed higher phosphorylation in females compared to males or ovx females. They then go on to show that the higher phosphorylation levels of ALDH2 in female mice is attributed to the kinase Protein Kinase C (PKC) and that this phosphorylation coincides with increased ALDH activity. These baseline phosphorylation changes observed in female rats were also apparent during Ischemia/Reperfusion.

Male/female differences were also observed in α -KGDH and its phosphorylation was confirmed in female mice using an antibody that recognized PKC-specific phosphorylation sites. α -KGDH has been shown to generate ROS (Reactive Oxygen Species) under conditions of high NADH/NAD. Consequently, the addition of NADH to permeabilised mitochondria and two α -KGDH substrates - α -ketoglutarate and the reduced form of Coenzyme A – caused a prominent increase in ROS in males compared to females, suggesting that α -KGDH in female mitochondria is less susceptible to generation of ROS. The same was true also under conditions of anoxia and reoxygenation. Finally, to assess whether the phosphorylation of α -KGDH alters ROS generation, α -KGDH was phosphorylated with PKC and phosphorylated α -KGDH exhibited significantly less ROS production when CoA, α -KG and NADH are added. The addition of PKC and PI3K inhibitors to the hearts before Ischemia further confirmed the cardioprotective role of ALDH2 and α -KGDH phosphorylation in females versus males.

The study succeeds in elucidating stochastic mechanisms by which female rats show cardioprotection as opposed to males by the regulation of ROS and oxidative metabolism through the differential phosphorylation of the mitochondrial enzymes, ALDH2 and α -KGDH (alpha-Ketoglutarate Dehydrogenase).

lies every once and awhile. On the other hand, constantly avoiding such events may not be beneficial to our future. By missing a seminar, you might lose out on making an important contact, or by not attending a career session, you might not be aware of everything you are qualified to do or what you need to do to be a stronger candidate for a certain position.

The mission of the NHLBI Fellows Advisory Committee (FAC) is to help NHLBI trainees by organizing events that will provide training and career opportunities. The annual NHLBI Fellows Retreat is one example. The FAC is also aware of more widespread opportunities at the NIH through contacts in the NIH Fellows Committee (FELCOM), and will assist in communicating these to the NHLBI community.

In addition, any NHLBI fellow is encouraged to share comments and/or suggestions about activities that either hinder or improve your experience at NHLBI or the NIH. This type of information is very important to making our training environment the best that it can be. Finally, participation in the committee allows you to gain leadership experience.

One item that the committee would like to address at NHLBI is community building. We have all come from university settings where we attended graduate student lunches, happy hours, athletics, and other social events. These allowed us to meet other students, post-docs, or professors that we may not frequently come into contact with and even make new friends. If anyone has ideas on activities in our

institute that could achieve these goals with maximum attendance, we are happy to involve NHLBI fellows in any or all of our activities, and would like to hear your ideas either by e-mail or in person.

As Chair of the FAC, I understand that we cannot attend every seminar, panel discussion, or other such events, but I urge you to take advantage of the ones that are relevant to you. It will only make your training experience better and the people you meet may be valuable contacts for the future.

Please, feel free to contact me (Mark, stevensmv@nhlbi.nih.gov) or Dr. Geller (gellerh@nhlbi.nih.gov) regarding any aspect of your NHLBI training experience. Thank you for your continued participation.