



February 2011

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

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From the Director of the Office of Education

While we are still within the throes of winter, there are constant reminders that spring is not far ahead. One of these reminders is the opening of registration for the NHLBI DIR Scientific Retreat on April 27-29 on February 14th. We encourage all NHLBI DIR scientific staff to participate at the retreat. For Fellows and Staff Scientists, this means we encourage you to share your research with others by presenting a poster. For Investigators, we hope you will participate as a poster judge. Whatever your role, I am sure you will have a great time, as we have an outstanding list of speakers and presenters.

We also are soliciting your nominations for the NHLBI DIR Mentoring Award for Investigators and Staff Scientists. Nominations can be made anonymously on the retreat web site. The process is that all nominations are considered, and then we solicit feedback on the nominee from all current and former lab personnel as criteria for the award.

For those of you who need a little something else to brighten your lab day, I suggest that you look at the "Bad Project" YouTube video (see story on page 2). And if you feel that you have one, I have provided some advice on how to deal with it. Remember, that the Office of Education is here to assist all NHLBI scientific personnel in their career development issues.

9th Annual NHLBI DIR Scientific Retreat

April 27-29, 2011

Cambridge, MD • Hyatt Regency

****Registration opening February 14th***

Keynote Speaker:

Thomas Pollard, M.D.

***Sterling Professor of Molecular, Cellular,
and Developmental Biology***

Yale University

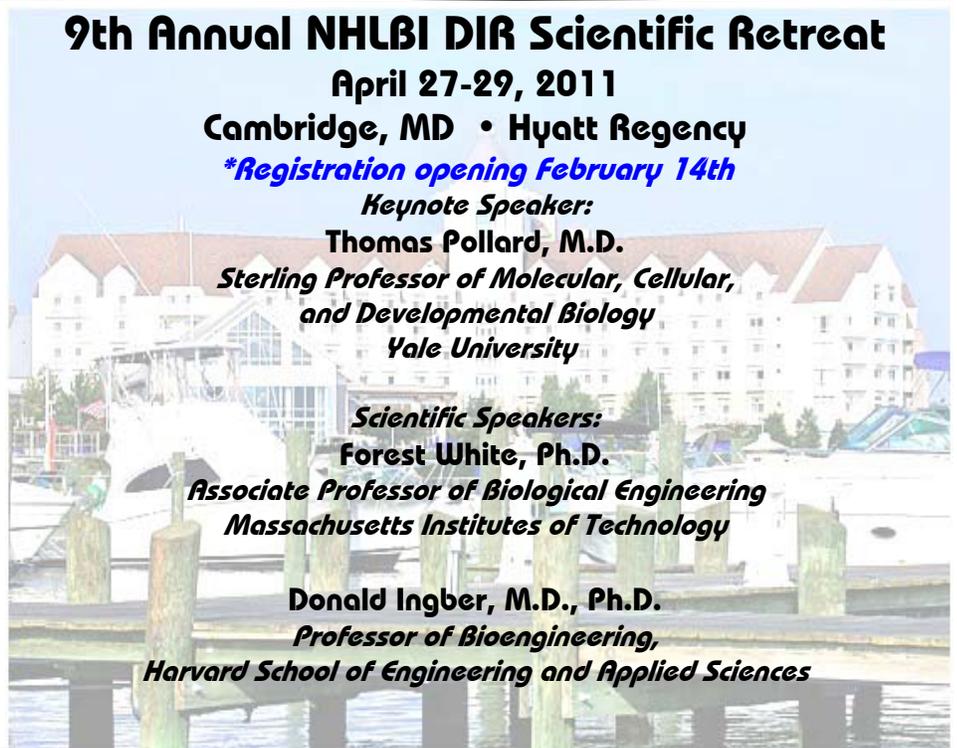
Scientific Speakers:

Forest White, Ph.D.

***Associate Professor of Biological Engineering
Massachusetts Institutes of Technology***

Donald Ingber, M.D., Ph.D.

***Professor of Bioengineering,
Harvard School of Engineering and Applied Sciences***



<http://dir-intranet.nhlbi.nih.gov/oe/>

Lady Gaga's "Bad Romance" turns into "Bad Project"

By Herbert Geller, Ph.D.

The screen shots to the right are taken from an incredibly entertaining video entitled "Bad Project" (<http://www.youtube.com/watch?v=Fl4L4M8m4d0>), a Lady Gaga sendoff created by the Zheng lab at Baylor based on the travails of a graduate student. While the costumes and music are captivating, the basic themes of the video – that there are bad projects, and it takes too long to get out of graduate school – are very real. So what's a graduate student or postdoc to do if they feel trapped in such a situation?

The first approach is communication: a frank discussion with the PI of the laboratory, where each of you presents your reasons for either continuing or ending the project. There are many reasons for either decision: is the project not working because of technical difficulties that seem insurmounta-

ble? Does it require reagents or techniques that are not yet available (such as a transgenic mouse) or too expensive (like deep sequencing) that will take an extended period of time to acquire? Or are the experiments not working due to lapses in experimental



design, such as positive and negative controls that would help troubleshoot the issues? In the latter case, better

planning before doing that Western blot might actually help things go faster.

One issue that arises frequently is how much data are needed for a publication? Many Investigators here at NIH aim for the "prestige" journals. However, it's not only the data that get you in, it's also the question that you are addressing and its newsworthiness. Thus, it's not always a good strategy to keep collecting more data and doing more experiments in the hope that you can get that paper into Cell. All the authors in the lab need to aim for a strategy, especially if the research involves students or postdocs, for publications that will appear in a time frame that will advance the career of the trainee. This means that a project that takes five years from start to finish is inappropriate for a postdoc, unless they have a backup project (a "good" project) that can provide more immediate results. Of course, if you read the comments on the YouTube site, you'll see that many have outlasted a "bad project" to actually achieve that publication.

The Chronicle of Higher Education- A Career Resource for Academic Job Seekers

By Herbert Geller, Ph.D.

When I began Graduate School, I also began my lifelong addiction to Science and Nature. The rates for a student subscription were low, and I didn't have to wait several weeks for the lab copy to reach my desk. At the beginning, I read them from front to back, a natural sequence. But something happened as I neared completion of my Ph.D. – I began by reading the job ads at the back, even before the hot science in the front, in the hopes of locating that "ideal" postdoctoral and later faculty position. While these jour-

nals are the primary place to look for a research position, they are not the primary source of information for jobs in Academia, especially jobs at smaller colleges and universities that emphasize a balance of teaching and research. So where should you look?

The Chronicle of Higher Education is a weekly newspaper that has a print edition and a strong presence on the Web. Each week, many different positions are advertised either by specialty or as large ads from a particular institution listing their anticipated vacancies for the coming year. Each of these ads is also on their web site <http://chronicle.com/jobs/> which is free and searchable. Thus, a search of jobs in "Biology" found 198 positions at

places as diverse as Colby College in Maine, the University of Minnesota, Morris, to Virginia Commonwealth University in Richmond.

In addition to this search feature, each job-seeker can create a free account that allows for creation and storage of resumes/c.v.s and cover letters. These can then be sent electronically to respond to the particular advertisement.

The Office of Education is available to help you navigate these employment issues.

E-mail direducation@nhlbi.nih.gov to schedule an appointment.

Recent Publications by NHLBI Fellows

- Ho, J. E.**, Levy, D., Rose, L., **Johnson, A. D.**, Ridker, P. M., & Chasman, D. I. (2011). Discovery and replication of novel blood pressure genetic loci in the Women's Genome Health Study. *J. Hyperten.* 29, 62-69.
- Ikeda, Y.**, Taveira-DaSilva, A. M., Pacheco-Rodriguez, G., Steagall, W. K., **El-Chemaly, S.**, Gochuico, B. R., May, R. M., Hathaway, O. M., Li, S. W., Wang, J. A., Darling, T. N., Stylianou, M., & Moss, J. (2011). Erythropoietin-driven proliferation of cells with mutations in the tumor suppressor gene TSC2. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 300, L64-L72.
- Kemble, C. K.**, Auxier, J., **Lynch, S. K.**, Bennett, E. E., Morgan, N. Y., & Wen, H. (2010). Grazing angle Mach-Zehnder interferometer using reflective phase gratings and a polychromatic, un-collimated light source. *Optics Express* 18, 27481-27492.
- Miriyala, S., Subramanian, T., Panchatcharam, M., Ren, H. M., **McDermott, M. I.**, Sunkara, M., Drennan, T., Smyth, S. S., Spielmann, H. P., & Morris, A. J. (2010). Functional Characterization of the Atypical Integral Membrane Lipid Phosphatase PDPI/PPAPDC2 Identifies a Pathway for Inter-
- conversion of Isoprenols and Isoprenoid Phosphates in Mammalian Cells. *J. Biol. Chem.* 285, 13918-13929.
- Ni, T.**, **Tu, K.**, Wang, Z., Song, S., **Wu, H.**, Xie, B., Scott, K. C., Grewal, S. I., Gao, Y. A., & Zhu, J. (2010). The Prevalence and Regulation of Antisense Transcripts in *Schizosaccharomyces pombe*. *Plos One* 5.
- Noh, O. J., Park, Y. H., **Chung, Y. W.**, & Kim, I. Y. (2010). Transcriptional Regulation of Selenoprotein W by MyoD during Early Skeletal Muscle Differentiation. *J. Biol. Chem.* 285.
- Sloand, E. M., **Olnes, M. J.**, **Shenoy, A.**, Weinstein, B., Boss, C., Loeliger, K., Wu, C. O., More, K., Barrett, A. J., Scheinberg, P., & Young, N. S. (2010). Alemtuzumab Treatment of Intermediate-1 Myelodysplasia Patients Is Associated With Sustained Improvement in Blood Counts and Cytogenetic Remissions. *Am. J. Clin. Oncol.* 28, 5166-5173.
- Wagner, W.**, Brenowitz, S. D., & Hammer, J. A. (2011). Myosin-Va transports the endoplasmic reticulum into the dendritic spines of Purkinje neurons. *Nat. Cell Biol.* 13, 40-U101.

New NHLBI Fellows



Du Ning, Ph.D., is a Visiting Fellow in the Immunology Center under Dr. Warren Leonard. Dr. Ning earned her Ph.D. in Veterinary/Pathology at the Veterinary College, China Agriculture University. She was a Post Doctoral Fellow at the Chinese National Influenza Center before coming to NIH. Dr. Ning's initial research project will be evaluating the efficacy of reassortant influenza virus vaccine in mice models.



Sarah Heissler, Ph.D., is a Visiting Fellow in the Cell Biology and Physiology Center under Dr. James Sellers. She earned her Ph.D. in Biochemistry from Gottfried Wilhelm Leibniz University Hannover, Germany. Her thesis was "Functional Analysis of Human Myosin-Motordomains" under Dr. Dietmar Manstein. Her current research project is the regulation of non-muscle myosin.

New NHLBI Principal Investigator



Haiming Cao, Ph.D. is a new Investigator in the Molecular Medicine Center. He earned his Ph.D. in Medicine from the University of Nevada. Dr. Cao completed his Postdoctoral training in the School of Public Health at Harvard University. He collaboratively worked to gain three provisional patents within the last three years. Dr. Cao was the recipient of the Accelerator Grant and also has a long history in teaching and mentoring.

THE SCIENCE BEAT

By Daniel Kraushaar, Ph.D.

Wagner, W., Brenowitz, S. D., & Hammer, J. A. (2011). Myosin-Va transports the endoplasmic reticulum into the dendritic spines of Purkinje neurons. Nat. Cell Biol. 13, 40-U101.

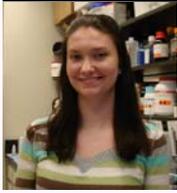
Dendritic spines are actin-rich protrusions on neuronal dendrites that serve as sites of excitatory synaptic input. The endoplasmic reticulum (ER) extends into all cerebellar Purkinje neuronal spines and functions in the local release of Ca²⁺, which is triggered upon activation of the metabotropic glutamate receptor (mGluR). The mechanisms that ensure the correct distribution of ER into neuronal spines are currently not understood but were subject to investigation in the NHLBI study by Wagner *et al.* who examined the role of myosin-V in this process. Class V myosins are motor proteins that are involved in the intracellular transport of organelles, mRNA and proteins along actin filaments. Myosin-V has been shown to mediate the localization of organelles along actin in lower organisms that include the fungi *Saccharomyces cerevisiae* and *Dictyostelium discoideum*, yet its role in metazoan organisms has remained unclear. Mutant mice, null in *dilute* (*Myo5a*), which encodes the heavy chain of mouse myosin-Va, display a striking ER localization defect with ER missing from dendritic spines of cerebellar Purkinje neurons and may suggest a role of myosin-Va in ER targeting. Using laser scanning confocal microscopy and live imaging of fluorescently tagged markers, Wagner *et al.* visualized and recorded the dynamics of ER localization in wild type and *dilute-lethal* (*d1201/d1201*) Purkinje neurons in order to gain insight into the role of myosin-Va in ER movement.

During 2-photon laser glutamate uncaging, glutamate is released at single Purkinje dendritic spines of cerebellar slices and triggers the release of a Ca²⁺ transient that was visualized with the Ca²⁺ indicator Fluo-4. A Ca²⁺ transient was elicited and recorded at control Purkinje spines, which was completely abolished by treatment with an mGluRI antagonist. In contrast, mutant *d1201/d1201* Purkinje spines failed to evoke a Ca²⁺ transient, demonstrating a physiological role of myosin-Va in mGluR-dependent Ca²⁺ release. To test whether mislocalization of the ER may underlie the failure of Ca²⁺ release, cell volume and ER of Purkinje neurons were visualized by transfection with plasmids encoding

for fluorescently tagged marker proteins and ER movement was traced by live confocal imaging. Spine growth and extension of protrusions started at around 10 days *in vitro* (DIV) with around 13% of protrusions filled with ER and all spines becoming loaded with ER by DIV 15 in wild type Purkinje neurons. The presence of ER in mutant *d1201/d1201* was restricted to dendrites and completely absent in spines of DIV 10 and DIV 15 neurons. Further quantification of ER insertion events from time lapse recordings showed that ER insertion rates were reduced by 30-fold in *d1201/d1201* mutant neurons compared to littermate controls, suggesting that ER movement into Purkinje spines requires myosin-Va.

The authors further examined whether myosin-Va acts in cell-autonomous fashion by expressing GFP-tagged myosin-Va in *d1201/d1201* Purkinje neurons. Interestingly, expression of exogenous myosin-Va completely restored ER targeting to spines and myosin-Va localized to the tips of *d1201/d1201* Purkinje spines. Co-culture with wild type cerebellar neurons was not able to rescue ER distribution and further indicates that myosin-Va acts cell-autonomously. A time series that recorded myosin-Va and ER dynamics during spine growth demonstrated that myosin-Va co-localizes with the leading tip of ER tubules as both move into the spine indicating that direct transport by myosin-Va targets the ER to dendritic spines. Wagner *et al.* confirmed that ER movement requires the motor function of myosin-Va by introducing mutant forms of myosin-Va into the *d1201/d1201* background of Purkinje neurons. Expression of exogenous myosin-Va mutants that display decreased processivity or lack of ATPase activity reduced both efficiency and velocity of ER localization into Purkinje spines. These results suggest that myosin-Va actively transports ER into Purkinje protrusions and does not simply act to tether ER to actin filaments. Given that microtubule-based transport plays an important role in ER distribution in neuronal dendrites, the authors also examined whether MTs may mediate the transport of ER in Purkinje neurons. However, disruption of microtubule formation by treatment with nocodazole had no effect on steady-state ER loading to spines. Together, the study by Wagner *et al.* elucidated that ER movement into Purkinje spines does not significantly depend upon transport along MTs and instead depends on what appears to be an evolutionary conserved mechanism of actin-based transport by the myosin motor myosin-Va.

Congratulations to The Graduate Research Symposium Poster Winners



Lindsay Case (Biochemistry category)
Engagement of Integrins Downstream of Ventral Actin Waves
Laboratory of Cell and Tissue Morphodynamics
Research Advisor: Dr. Clare Waterman



Ryan Harrison (New Proposal category)
Unraveling Helicase Dynamics One Molecule at a Time: Case Studies In RecQ and UvrD
Laboratory of Molecular Biophysics
Research Advisor: Dr. Keir Neuman



Candace Pfefferkorn (Structural Biology category)
The Yin and Yang of Amyloids: Insights from alpha-Synuclein and the Pmel17 Repeat Domain
Laboratory of Molecular Biophysics
Research Advisor: Dr. Jennifer Lee

**The Fellows Award for
Research Excellence (FARE)
will be accepting
applications from
February 22-March 22.**

**For more information
and/or submit an application,
please visit:
<http://felcom.od.nih.gov/subCommittee/fare.aspx>**

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