



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

We just returned from our retreat, and you can read a more complete report on the retreat and its environs in Cindy St. Hilaire's report below. Also new this year were presentations on the career histories of our fellows, and the results of the NIH Mentoring Survey, both of which were very illuminating.

Looking back over the last few years, we found that the average time for a fellow to be at NHLBI is dropping significantly from over 5 years to about 3.5 years. This is a good sign, since the postdoctoral fellowship was never intended to be permanent, but as a way of getting you to the next step. When we looked at the next positions of our fellows, we found that the largest percentage was faculty positions, either in the US or abroad, with over 1/3 of departing fellows in 2010 going this route. The next largest percentage was in government, primarily in the NIH intramural or extramural programs, followed by those who took second postdocs. Only a very few of our postdocs did not have another position after leaving here.

The results of the NIH mentoring survey are consistent with these results. The data indicate that an overwhelming percentage of NHLBI fellows are happy with their training here. Most NHLBI fellows have frequent access to their mentors, have a chance to develop their own ideas for research, and receive appropriate feedback about their progress. However, there are some fellows who are not getting what they want. It is to those fellows that the Office of Education extends an invitation to visit. Because your postdoctoral time is short, you need to make the most of it, and if your experience is not going well, you need to figure out your next move before you waste a lot of time. If you are in that situation, please remember that helping fellows achieve their goals is the primary mission of my office, so don't be afraid to take advantage of it.

9th Annual NHLBI DIR Scientific Retreat

By Cynthia St. Hilaire, Ph.D.

Our 9th annual NHLBI Division of Intramural Research Scientific Retreat was held at the Hyatt Regency

Chesapeake Bay, Cambridge, MD and over 200 NHLBI DIR Staff and Fellows attended. The location and lodgings were beautiful, while the food did not achieve distinction. One afternoon we snuck away and enjoyed some fresh oysters and a locally brewed IPA at the Blue Point Provision Company – who knew local oysters could be

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THE SCIENCE BEAT

By Daniel Kraushaar, Ph.D.

Vickers, K. C., Palmisano, B. T., Shoucri, B. M., Shamburek, R. D., & Remaley, A. T. (2011). MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nature Cell Biology* 13, 423-4182.

Recent advances in the field of cell signaling and cell physiology have added new examples of cell-to-cell communication to the classic 'textbook' modes of inter-cell communication that rely on secreted signaling molecules and gap junctions. For instance, membrane-derived vesicles, so-called exosomes, are shed from the cell surface and will carry bioactive molecules including proteins, mRNAs and miRNAs from donor cells to recipient cells. A current NHLBI study by Vickers *et al.* contributes to the growing list of inter-cell communication mechanisms by proposing that plasma high-density lipoprotein (HDL) takes miRNAs for a ride through blood plasma to recipient cells.

HDL is well known for its role as a delivery vehicle that transports excess cholesterol to the liver where it is destined for excretion. Curiously, Vickers and colleagues found abundant miRNA enriched in purified fractions of plasma HDL, suggesting that these short nucleic acids (22-26 nucleotides) associate with HDL. Microarray comparison of miRNA content from human HDL fractions of normal subjects with those suffering from familial hypercholesterolemia (FHC), a genetic disorder of the LDL receptor, revealed quantitative as well as qualitative differences in their HDL-miRNA profiles: FHC HDL contained a different set of miRNA species and their most prominent miRNAs were present at higher concentrations. The *Ldlr*^{-/-} FHC mouse model displayed similar differences in HDL-miRNA content compared to its wild type counterparts. Hence, a distinct and conserved

HDL-miRNA signature exists in the normal versus the disease state. Assays with nanogold-labeled miR-223, that was incubated with native HDL showed that HDL readily complexed with miRNAs *in vitro* without requirement for additional factors, in line with the idea that lipids such as phosphatidylcholine can form stable complexes with nucleic acids. Injection of recombinant HDL into mice and its subsequent retrieval from mouse plasma showed that HDL binds miRNAs *in vivo*, whereby rHDL-miRNA profiles differed between normal and mice with atherosclerosis. Experiments, aimed at elucidating, whether HDL acts as a *bona fide* deliverer of miRNAs, were carried out by loading native HDL with exogenous miRNAs. HDL-miRNAs were subsequently introduced to cultured hepatocytes, which were examined for intracellular miRNA content. Addition of HDL-miR-223 resulted in substantially elevated intracellular levels of miR-223 demonstrating intracellular delivery into hepatocytes. Short nucleotide miRNAs are non-coding post-transcriptional regulators of gene expression that target mRNAs and thereby repress gene expression.

Examination of mRNA levels of miR-223 targets revealed substantial reductions in transcript levels of the miR-223 targets, RhoB and Ephrin A1, suggesting that miRNAs delivered by HDL are biologically active. Treatment of hepatocyte cultures with endogenous HDL-miRNA from FHC subjects but not from normal subjects resulted in changes in gene expression of 217 genes, the majority of which represent direct targets of FHC HDL-miRNAs and were identified to play a role in lipid metabolism, inflammation and atherosclerosis. The discovery by Vickers *et al.* of HDL-mediated miRNA delivery and a distinct HDL-miRNA cargo may have implications not only for disease diagnosis but possibly also development of novel treatment strategies by means of HDL-delivery and targeted manipulation of genes important for pathophysiological processes.

New NHLBI Fellows

Suman Mitra, Ph.D. is a Visiting Fellow in the Laboratory of Molecular Immunology under Dr. Warren Leonard. Dr. Mitra earned his Ph.D. in Molecular Immunology from the University of Aberdeen, Scotland,

United Kingdom. He was the recipient of the 2010 Biochemistry Society United Kingdom travel grant to attend the American Association of Immunologist. Dr. Mitra's initial research project is to fine hnRNA inhibitors for IL-2.



Nathan Baird, Ph.D., is a new IRTA fellow in the Laboratory of RNA Biophysics and Cellular Physiology under Dr. Adrian Ferre-D'Amare. Dr. Baird earned his Ph.D. in Chemistry from the University of Chicago,

Illinois. Dr. Baird was a postdoc associate at the University of Chicago and at Fred Hutchinson Cancer Research Center before coming to NIH. His initial research project involves the structural and functional characterization of riboswitch RNA's.

so delicious! And on the way home Friday our lab filled up on some excellent French-inspired food at Mason's, located in the historic downtown of Easton, MD; I hope everyone was able sneak away and enjoy a non-science activity during the Retreat.

We had three major speakers. Our Keynote speaker was Dr. Tom Pollard of Yale University, who provided his viewpoint on the way to achieve success in science. Our two Scientific speakers came from Cambridge, MA - Dr. Don Ingber from Harvard and Dr. Forest White. .

The award for "best presentation" should go to Dr. Ingber, the inventor and proponent of the 'Tensegrity' theory of cellular behavior. He was thoroughly inspiring and exactly the kind of speaker the FAC was striving to find for the retreat. I think it is safe to say that everyone in attendance had at least one moment during his talk where they looked at their neighbor, jaw ajar, in awe. He is the epitome of the term "rock star scientist." Last week I had lunch with Dr. Karen Hirschi, a seminar speaker, who was a post-doc at Children's Hospital when Dr. Ingber was in the early stages of his career as a PI. She mentioned how everyone gave him a hard time about his 'Tensegrity' idea yet he continued to develop this concept and has become a leader in the field of mechanotransduction. His research attracted the attention of Hansjörg Wyss, who donated \$125 million to Harvard for the creation of the Institute for Biologically Inspired Engi-

neering, whose research mission is in part based on Dr. Ingber's "crazy" idea. It is the perfect example of how a long and challenging research trajectory can yield to a truly rewarding scientific career. Dr. White is less senior, and his talk was of special interest to the large number of NHLBI fellows doing proteomics. But he gave an important take-home message that using cell lines as surrogates for primary cells may not always be the correct approach.

We had some new components to this year's Retreat. The image contest was added and highlighted some of the beautiful microscopy work done at the NHLBI. This year's winner was Dr. Jean Yves Metias for his image of bone marrow repopulation. We hope to continue this contest at next year's retreat.

Another new component was the NHLBI Core Presentations. The goal of these presentations was to highlight the variety of expertise offered by NHLBI Cores, and to inspire you to think of new experiments using these facilities to further your research topic.

The last new addition to this year's retreat was the trivia game. We had seven teams of 5-8 players competing for the prize of an assortment of snacks from Trader Joe's. It was a lot of fun and we hope next year's Trivia will attract even more participants.

Finally, we want to congratulate this year's award winners, shown below.

Congratulations

2011 Outstanding Mentor Award

Dr. Elizabeth "Tish" Murphy



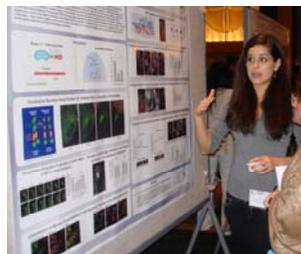
Poster winners

Jackie Douglass (not shown)

Lisa Bond, (bottom right)

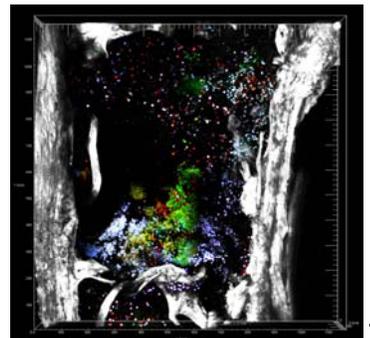
Sergey Plotnikov (bottom left)

Brian Busser (right)



NHLBI Image Contest Winner

Jean Yves Metias



Recent Publications by NHLBI Fellows

- Basuli, F., Wu, H. T., & Griffiths, G. L.** (2011). Syntheses of meta-[F-18]fluorobenzaldehyde and meta-[F-18]fluorobenzylbromide from phenyl(3-Formylphenyl) iodonium salt precursors. *J. Labelled. Compd. Rad.* *54*, 224-228.
- Feric, M., Zhao, B., Hoffert, J. D., Pisitkun, T., & Knepper, M. A.** (2011). Large-scale phosphoproteomic analysis of membrane proteins in renal proximal and distal tubule. *Am. J. Physiol. Cell Physiol.* *300*, C755-C770.
- Fernandes, F., Chen, K., Ehrlich, L. S., Jin, J., Chen, M. H., Medina, G. N., Symons, M., Montelaro, R., Donaldson, J., Tjandra, N., & Carter, C. A.** (2011). Phosphoinositides Direct Equine Infectious Anemia Virus Gag Trafficking and Release. *Traffic* *12*, 438-451.
- Kohr, M. J., Aponte, A. M., Sun, J. H., Wang, G. H., Murphy, E., Gucek, M., & Steenbergen, C.** (2011). Characterization of potential S-nitrosylation sites in the myocardium. *Am. J. Physiol. Heart Circ. Physiol.* *300*, H1327-H1335.
- Kuo, J. C., Han, X. M., Hsiao, C. T., Yates, J. R., & Waterman, C. M.** (2011). Analysis of the myosin-II-responsive focal adhesion proteome reveals a role for beta-Pix in negative regulation of focal adhesion maturation. *Nat. Cell Biol.* *13*, 383-U109.
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- Park, J. W., Piszczek, G., Rhee, S. G., & Chock, P. B.** (2011). Glutathionylation of Peroxiredoxin I Induces Decamer to Dimers Dissociation with Concomitant Loss of Chaperone Activity. *Biochem.* *50*, 3204-3210.
- Phillips, D., Aponte, A. M., Covian, R., & Balaban, R. S.** (2011). Intrinsic Protein Kinase Activity in Mitochondrial Oxidative Phosphorylation Complexes. *Biochem.* *50*, 2515-2529.
- Um, J. H., Pendergast, J. S., Springer, D. A., Foretz, M., Viollet, B., Brown, A., Kim, M. K., Yamazaki, S., & Chung, J. H.** (2011). AMPK Regulates Circadian Rhythms in a Tissue- and Isoform-Specific Manner. *Plos One* *6*.
- Vickers, K. C., Palmisano, B. T., Shoucri, B. M., Shamburek, R. D., & Remaley, A. T.** (2011). MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nat. Cell Biol.* *13*, 423-U182.
- Woodcock, H. L., Miller, B. T., Hodoseck, M., Okur, A., Larkin, J. D., Ponder, J. W., & Brooks, B. R.** (2011). MSCALE: A General Utility for Multiscale Modeling. *J. Chem. Theory. Comput.* *7*, 1208-1219.
- Yap, T. L., Pfefferkorn, C. M., & Lee, J. C.** (2011). Residue-Specific Fluorescent Probes of alpha-Synuclein: Detection of Early Events at the N- and C-Termini during Fibril Assembly. *Biochem.* *50*, 1963-1965.
- Yong, A. S. M., Stephens, N., Weber, G., Li, Y., Savani, B. N., Eniafe, R., Keyvanfar, K., Kurlander, R., Rezvani, K., & Barrett, A. J.** (2011). Improved outcome following allogeneic stem cell transplantation in chronic myeloid leukemia is associated with higher expression of BMI-1 and immune responses to BMI-1 protein. *Leukemia* *25*, 629-637.
- Zhou, Y. F., Wang, S. N., Yu, Z. X., Hoyt, R. F., Qu, X. A., & Horvath, K. A.** (2011). Marrow Stromal Cells Differentiate Into Vasculature After Allogeneic Transplantation Into Ischemic Myocardium. *Annals of Thoracic Surgery* *91*, 1206-1212.
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- Zhu, J. Q., Chin, K., Aerbajinai, W., Trainor, C., Gao, P., & Rodgers, G. P.** (2011). Recombinant erythroid Kruppel-like factor fused to GATA1 up-regulates delta- and gamma-globin expression in erythroid cells. *Blood* *117*, 3045-3052.

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