



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.

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From the Director of the Office of Education

Mark your calendars! As you can see from the announcement below, the NHLBI DIR Scientific Retreat will be held on May 20th 2013 at the Ronald Reagan Building on the National Mall. Although this will be a one-day retreat, we are planning a full day of events, including outside speakers, scientific talks and poster sessions by fellows, followed by a Happy Hour. Because the Reagan Building is easily accessible by Metro, and the retreat does not require an overnight stay, we are hoping to have nearly 100% participation of NHLBI DIR - Fellows, Staff Scientists, Technicians and Principal Investigators. Please watch for the opening of the Retreat web site for Abstract Submission and Registration in February.

The Holiday season is upon us, and we hope that while you are celebrating you reach out to help those who are less fortunate. Charitable contributions are a major way in which Americans provide support to the needy, and one easy way to do your share is by contributing to the Combined Federal Campaign. The CFC allows you to direct your contribution to a particular charity, or you can have the CFC allocate the funds according to their assessment of need. Complete information is on the CFC of the National Capital Area web Site <http://cfcnca.org/>. Please consider making a donation to help those in need. We wish you all a Happy Holiday season, and look forward to success for all in 2013.



THE SCIENCE BEAT

By Dinari Harris, Ph.D.

Shen X. Y., Li C. C., Aponte A. M., Shen R. F., Billings E. M., Moss J. and Vaughan M. (2012) Brefeldin A-inhibited ADP-ribosylation factor activator BIG2 regulates cell migration via integrin beta 1 cycling and actin remodeling. *Proceedings of the National Academy of Sciences of the United States of America* 109, 14464-14469.

Cell migration is a highly complex and regulated process, in which intracellular and extracellular signaling produce a coordinated response. It is a central process in the development and maintenance of multicellular organisms, and is an essential process during developmental morphogenesis. The migrating cell is highly polarized and relies on complex regulatory pathways involving the actin cytoskeletal system. A migrating cell must undergo well-defined and integrated steps in order to move including, front-to back polarization in response to extracellular cues, membrane extension by protrusion and adhesion, formation and cell-body translocation, adhesion disassembly, and rear retraction. Specifically, adhesion is mediated primarily by integrins, transmembrane receptors that bind extracellular matrix proteins outside the cell, and link actin cytoskeletal proteins and signaling pathways inside the cell. This physical linkage of integrins and actin provides traction for migration and several recent studies show the importance of this linkage in regulating adhesion organization and development. Actin polymerization orchestrates adhesion assembly near the leading edge of a migrating cell and the dynamic cross-linking of actin filaments promotes adhesion maturation.

The study by Shen *et al.* uncovered a role for the Brefeldin A-inhibited guanine nucleotide-exchange protein (BIG2) in regulating cell adhesion and cell migration through integrin $\beta 1$ recycling and actin remodeling, respectively. They used a combination of proteomics, motility assays, and localization experiments to identify proteins that are misregulated as a result of BIG2 inhibition. BIG2 is a guanine exchange factor (GEF) protein, responsible for activating the small GTPase, ADP-ribosylation factor (Arf), by accelerating the replacement of GDP for GTP in Arf complexes. The primary function of the family of Arf GTP-binding proteins are to regulate vesicle trafficking and, recruit coat proteins and adaptors from the cytosol to the plasma membrane (PM). Shen *et al.* used 2D difference gel electrophoresis and mass spectrometry (MS) to identify the unique cytosolic proteins that are misregulated as a result of

siRNA-mediated BIG2 inhibition in cells. Their proteomics analysis revealed two important findings about the role of BIG2 in these cells. First, most of the cytosolic proteins that increased in expression in BIG2-depleted cells were classified as binding proteins, consistent with BIG2 functions in activating Arf for recruitment of adaptor proteins. Second, MetaCore analysis, a proteomics program using high-throughput MS and genomic data to identify biological networks, suggests that these upregulated cytosolic proteins cluster into pathways involved in cell signaling and adhesion. Specifically, BIG2 depleted cells were enriched in proteins involved in integrin $\beta 1$ -extracellular matrix interactions on actin dynamics and cell motility.

Since depletion of BIG2 in cells resulted in an increase in cytosolic integrin $\beta 1$ -mediated signaling proteins, Shen *et al.* monitored the protein levels of integrin $\beta 1$ in BIG2-depleted cells. Immunoblotting and immunofluorescence experiments revealed an increase in cytosolic integrin $\beta 1$ and a decrease in surface integrin $\beta 1$ in BIG2-depleted cells. In control cells, BIG2 was localized juxtaposed to the nucleus, very reminiscent of trans-Golgi staining. Additionally, integrin $\beta 1$ was found to localize extensively with endogenous BIG2 in this perinuclear region, and also at the PM. In cells depleted of BIG2, integrin $\beta 1$ was more widely dispersed in the perinuclear region and was not clearly evident peripherally. These results suggested that that BIG2 depletion might be inhibiting integrin $\beta 1$ recycling from the trans-Golgi network to the PM. In order to determine if BIG2 depletion altered the localization of integrin $\beta 1$ because of defects in integrin recycling, Shen *et al.* monitored the return of internalized integrin $\beta 1$ to the cell surface in BIG2-depleted cells. Results suggested that significantly less internalized integrin $\beta 1$ recycled back to the PM and the return of internalized integrin $\beta 1$ to the cell surface is dependent on BIG2 function. Since integrin recycling is essential to cell migration, Shen *et al.* used wound healing and chemotaxis assays to find that BIG2 depletion decreases overall cell migration in both assays. The reduced cell mobility in BIG2-depleted cells was attributed to significant changes in actin dynamics. Normally, densely populated actin-rich membrane ruffles that act at the leading edge of migrating cells are reduced and irregular in BIG2-depleted cells. The localization of several of the cytosolic proteins upregulated in BIG2-depleted cells, indicated that Arp2, Arp3, cofilin-1, and phosphocofilin proteins showed reduced distribution at the leading edge of migrating cells. These results suggest that BIG2 is essential in regulating cycling of integrin $\beta 1$ to the PM, as well as components of Arp2/3 complex to the PM of the leading edge of migrating cells.

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

In addition to the known role of BIG2 in intracellular vesicle trafficking, Shen *et al.* uncovered a role of BIG2 in regulation of cell migration through mechanisms involving actin cytoskeleton rearrangements and integrin β 1 mediated membrane trafficking. They found that cells depleted of BIG2 results in decreased cell-surface integrin β 1, decreased cell migration, and reduced expression at the leading surface in migrating cells. The work by Shen *et al.* adds to a

growing line of evidence suggesting that the regulation of adhesion proteins are intimately involved in controlling overall cell migration. Further studies need to be conducted to identify specific adhesion proteins that might be required for cell migration on a variety of substrates (*eg.* collagen, fibrin, fibronectin).

A New Rotation Opportunity for NHLBI Fellows: The Tauri Group

By Joesph Laakso, Ph.D.

The growing number of postdoctoral Fellows interested in learning how to apply the skills developed during their scientific or medical training to areas outside of conventional bench science has not gone unnoticed by the NHLBI Office of Education. To provide opportunities for those Fellows strongly considering a transition away from bench science for the next step in their career, the NHLBI Office of Education has partnered with a number of organizations to offer 3-6 month rotation projects for NHLBI Fellows. These rotations, typically conducted at the end of a Fellow's tenure at the NIH, are full-time projects that help scientists demonstrate value to firms in fields such as industry or public policy. A particular career path that is increasingly of interest to M.D. and Ph.D. scientists is that of consulting (e.g., management or biotechnology consulting). For those Fellows who are investigating this particular type of career, The Tauri Group has expressed interest in exploring the opportunity to partner with the NHLBI Office of Education and provide rotation opportunities.

With demonstrated expertise in analytical consulting, The Tauri Group provides "a unique, multidisciplinary approach to problem-solving" for government agencies and private contractors. The company has been recognized for professional excellence by Washington Technology's Fast 50 list, and is also recognized as one of the "FANTASTIC 50 companies" by the Virginia Chamber of Commerce, among other awards. Projects at The Tauri Group sometimes call for subject matter expertise in chemistry, biology, drug development, medicine, and other areas in which advanced training in science or medicine could be beneficial. Recently Dr. Josh Henkin, Program Manager, at The Tauri Group, was on the NIH campus to discuss his work with the Department of Defense (DoD) developing medical countermeas-

ures against biological threats which often necessitates following the FDA Animal Rule, a pathway to licensure for candidate drugs and vaccines that cannot meet the requirements of traditional licensure because human efficacy studies are not possible for ethical reasons or because field studies to assess efficacy are not feasible.

Dr. Henkin holds a Ph.D. in Cell and Molecular Biology, and is enthusiastic about the prospect of NHLBI fellows learning how consulting works at The Tauri Group. He has characterized his work as "two steps away from the bench", meaning that consultants on his team provide advice and support at a level more removed from the scientists performing experiments. Beyond analytical consulting, a rotation project at The Tauri Group could serve as a way to learn more about how the DoD and FDA intersect during the drug development process, or how program management and project management in consulting differs from scientific project management. Rotation Fellows can also learn how consultants interact with clients in the public sector, and develop the soft skills that are increasingly valued by consulting firms looking to hire scientists who have already demonstrated strong quantitative and analytical capability through their education.

If you think a career in consulting could be a good fit for you, we strongly encourage you to consider a rotation project with The Tauri Group. Please note that due to the nature of the work, the ability to hold a DoD clearance is a requirement and therefore potential rotation positions are likely only available to US Citizens.

For additional information, please take a look at their webpage <http://www.taurigroup.com/> to become more familiar with their work. Alternatively, for specific questions, you may contact Josh Henkin at josh.henkin@taurigroup.com or 571-303-2138.

Recent Publications by NHLBI Fellows

- Aicher B. O., Haser E. K.,** Freeman L. A., Carnie A. V., Stonik J. A., Wang X. D., Remaley A. T., Kato G. J. and Cannon R. O. (2012) Diet-Induced Weight Loss in Overweight or Obese Women and Changes in High-Density Lipoprotein Levels and Function. *Obesity* **20**, 2057-2062.
- Ambatipudi K. S., **Swatkoski S.**, Moresco J. J., Tu P. G., Coca A., Anolik J. H., Gucek M., Sanz I., Yates J. R. and Melvin J. E. (2012) Quantitative proteomics of parotid saliva in primary Sjogren's syndrome. *Proteomics* **12**, 3113-3120.
- Arai A. E., **Leung S.** and Kellman P. (2012) Controversies in Cardiovascular MR Imaging: Reasons Why Imaging Myocardial T2 Has Clinical and Pathophysiologic Value in Acute Myocardial Infarction. *Radiology* **265**, 23-32.
- Barese C. N.,** Krouse A. E., Metzger M. E., **King C. A.,** Traversari C., Marini F. C., Donahue R. E. and Dunbar C. E. (2012) Thymidine Kinase Suicide Gene-mediated Ganciclovir Ablation of Autologous Gene-modified Rhesus Hematopoiesis. *Molecular Therapy* **20**, 1932-1943.
- Bell J. A., **Saikus C. E.,** Ratnayaka K., **Barbash I. M.,** Faranesh A. Z., Franson D. N., Sonmez M., Slack M. C., Lederman R. J. and Kocaturk O. (2012) Active delivery cable tuned to device deployment state: Enhanced visibility of nitinol occluders during preclinical interventional MRI. *Journal of Magnetic Resonance Imaging* **36**, 972-978.
- Covian R., **Chess D.** and Balaban R. S. (2012) Continuous monitoring of enzymatic activity within native electrophoresis gels: Application to mitochondrial oxidative phosphorylation complexes. *Analytical Biochemistry* **431**, 30-39.
- Douglass J., Gunaratne R., Bradford D., Saeed F.,** Hoffert J. D., Steinbach P. J., Knepper M. A. and Pisitkun T. (2012) Identifying protein kinase target preferences using mass spectrometry. *American Journal of Physiology-Cell Physiology* **303**, C715-C727.
- Ho J. E.,** Mahajan A., Chen M. H., Larson M. G., McCabe E. L., Ghorbani A., Cheng S., Johnson A. D., Lindgren C. M., Kempf T., Lind L., Ingelsson E., Vasani R. S., Januzzi J., Wollert K. C., Morris A. P. and Wang T. J. (2012) Clinical and Genetic Correlates of Growth Differentiation Factor 15 in the Community. *Clinical Chemistry* **58**, 1582-1591.
- Ho J. E.,** Liu C. Y., Lyass A., Courchesne P., Pencina M. J., Vasani R. S., Larson M. G. and Levy D. (2012) Galectin-3, a Marker of Cardiac Fibrosis, Predicts Incident Heart Failure in the Community. *Journal of the American College of Cardiology* **60**, 1249-1256.
- Jia J. L., Zheng X. B., **Hu G. Q.,** Cui K. R., Zhang J. Q., Zhang A. Y., Jiang H., Lu B. W., Yates J., Liu C. Y., Zhao K. J. and Zheng Y. X. (2012) Regulation of Pluripotency and Self-Renewal of ESCs through Epigenetic-Threshold Modulation and mRNA Pruning. *Cell* **151**, 576-589.
- Kim J. H., Wang A. B.,** Conti M. A. and Adelstein R. S. (2012) Nonmuscle Myosin II Is Required for Internalization of the Epidermal Growth Factor Receptor and Modulation of Downstream Signaling. *Journal of Biological Chemistry* **287**, 27345-27358.
- Konig G.,** Miller B. T., Borech S., Wu X. W. and Brooks B. R. (2012) Enhanced Sampling in Free Energy Calculations: Combining SGLD with the Bennett's Acceptance Ratio and Enveloping Distribution Sampling Methods. *Journal of Chemical Theory and Computation* **8**, 3650-3662.
- Li P., Spolski R., **Liao W., Wang L.,** Murphy T. L., Murphy K. M. and Leonard W. J. (2012) BATF-JUN is critical for IRF4-mediated transcription in T cells. *Nature* **490**, 543-+.
- Nie Z. Q., Hu G. Q., Wei G., **Cui K. R.,** Yamane A., Resch W., Wang R. N., Green D. R., Tessarollo L., Casellas R., Zhao K. J. and Levens D. (2012) c-Myc Is a Universal Amplifier of Expressed Genes in Lymphocytes and Embryonic Stem Cells. *Cell* **151**, 68-79.
- Rogers H., **Wang L.,** Yu X. B., Alnaeeli M., **Cui K. R.,** Zhao K. J., Bieker J. J., Prchal J., Huang S. M., Weksler B. and Noguchi C. T. (2012) T-cell Acute Leukemia 1 (TAL1) Regulation of Erythropoietin Receptor and Association with Excessive Erythrocytosis. *Journal of Biological Chemistry* **287**, 36720-36731.
- Schenk L. K., Bolger S. J., Luginbuhl K., Gonzales P. A.,** Rinschen M. M., **Yu M. J.,** Hoffert J. D., Pisitkun T. and Knepper M. A. (2012) Quantitative Proteomics Identifies Vasopressin-Responsive Nuclear Proteins in Collecting Duct Cells. *Journal of the American Society of Nephrology* **23**, 1008-1018.

New NHLBI Fellows

Amanda Lobell, Ph.D., is a new Postdoctoral IRTA in the Systems Genetics Lab under Dr. Susan Harbison. Dr. Lobell earned her Ph.D. in Anthropology at Harvard University. Prior to the NIH, she worked in the Molecular Evolution Lab at Harvard. Dr. Lobell's initial research project at NHLBI is to investigate the degree to which the genetic architecture of sleep is conserved between *Drosophila* and humans.



Heba Diab, Ph.D., is a new Postdoctoral IRTA in the Cell Biology and Physiology Center under Dr. Rosa Puertollano. Dr. Diab earned her Ph.D. in Biochemistry and Molecular Biology from SUNY Upstate Medical University. Prior to the NIH, she was a Graduate Research Assistant at the University. She also served as a tutor to teenage refugees. Her initial project at NHLBI is to assess the role of the transcription factor TFEB in regulation autophagy and lysosomal exocytosis in times of starvation.



Jenna DuMond, Ph.D., is a new Postdoctoral IRTA in the Systems Biology Center under Drs. Maurice Burg and Joan Ferraris. Dr. DuMond earned her Ph.D. in Chemistry from Wake Forest University. Prior to the NIH, she was an intern in an organic chemistry synthesis lab at Glaxo Smith Kline. Apart from science, she was a competitive figure skater for 11 years and coached figure skating for 15 years. Dr. DuMond's initial research project at the NHLBI is the proteomics analysis of identification of protein-protein interactions with NFAT5 transcription factor.

Recent Publications by NHLBI Fellows continued

Shen X. Y., Li C. C., Aponte A. M., Shen R. F., Billings E. M., Moss J. and Vaughan M. (2012) Brefeldin A-inhibited ADP-ribosylation factor activator BIG2 regulates cell migration via integrin beta 1 cycling and actin remodeling. *Proceedings of the National Academy of Sciences of the United States of America* **109**, 14464-14469.

Tao P., Wu X. W. and Brooks B. R. (2012) Maintain rigid structures in Verlet based Cartesian molecular dynamics simulations. *Journal of Chemical Physics* **137**.

Uchida N., Hargrove P. W., Lap C. J., Evans M. E., Phang O., Bonifacino A. C., Krouse A. E., Metzger M. E., Nguyen A. D., Hsieh M. M., Wolfsberg T. G., Donahue R. E., Persons D. A. and Tisdale J. F. (2012) High-efficiency Transduction of Rhesus Hematopoietic Repopulating Cells by a Modified HIV1-based Lentiviral Vector. *Molecular Therapy* **20**, 1882-1892.

Vaisman B. L., Andrews K. L., Khong S. M. L., Wood K. C., Moore X. L., Fu Y., Kepka-Lenhart D. M., Morris S. M., Remaley A. T. and Chin-Dusting J. P. F. (2012) Selective Endothelial Overexpression of Arginase II Induces Endothelial Dysfunction and Hypertension and Enhances Atherosclerosis in Mice. *Plos One* **7**.

**NHLBI DIR Holiday Dessert Potluck
Tuesday, December 18th
3-4 PM
Building 10, Room 2C116**

Bring a dessert and you will be entered to win the "Top Dessert" Prize.
All Fellows, Pl's, and Staff Scientists are invited.

**Farewell to OE Program Coordinator
Aurora Taylor**

The Office of Education bids a farewell to Aurora Taylor who has been on staff in the OE since 2007. Aurora started her time here as a part-time IRTA fellow while finishing her undergraduate degree at the University of Maryland. Upon graduation she became a Full-time member of the OE staff. We wish her the best and she will be greatly missed.

