

Office of Education
Division of Intramural Research**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 hope that all of you are enjoying the beginning of summer. The Summer Internship Program is a major feature of summer at NHLBI, and the Office of Education has several activities planned for our summer interns. First, we have the Summer Intern Lecture series, every other Wednesday at Noon. The next lecture in this series is by Dr. Jian Liu, whose work involves both theoretical approaches to cytoskeletal function. The complete schedule is given below. The next two events include a summer social event, and the Summer Intern Poster Day reception on August 8th. The web site is open for summer interns to submit their poster title, and we hope to see all interns and their mentors on Poster Day!

***NHLBI DIR Scientific
Retreat***

By Herbert M. Geller, Ph.D.

Over 200 DIR scientists attended and over 110 presented (the largest number ever for both) their results at the DIR Scientific Retreat on May 20th in the Ronald Reagan International Trade Center on the national mall. Dr. Robert Gahl chaired the morning session, which featured introductory talks by NHLBI DIR Scientific Director Robert Balaban and Office of Education Director Herbert Geller. Dr. Balaban delivered a provocative talk about the role of the journal impact factor on scientific practices. Dr. Geller then provided a summary of outcomes for the Fellows who left NHLBI in 2012 as well as the rotation opportunities for fellows in DIR. The chart of fellows outcomes is presented on Page 2 of this issue, and suggests that ~30% of fellows obtained academic positions. Lunch was provided by the generous

support of the FAES and the NHLBI Faculty.

The next part of the day was filled with oral scientific presentations by NHLBI DIR scientists – graduate students, postdoctoral fellows, biologists, and staff scientists – selected from abstract submissions by the Fellows Advisory Committee. The poster sessions were in the middle of the day, followed by another session of platform talks. The final session consisted of the awards ceremony which featured a talk by NHLBI Deputy Director Susan Shurin, at which the Fellows Award for Research Mentoring was presented to Keir Neuman, and awards for posters were presented to Natalia Dmitrieva and Zhiyun Ge in the category of Staff Scientist/Biologist and Post-Doc Fellow. At the end, several fellows and PIs participated in a Happy Hour.

Overall, many fellows said that this one-day retreat was the best they attended. While it may not have had the intensity of previous overnight retreats, it did provide an oppor-

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

tunity for many fellows to attend who would not normally go because of family commitments, as demonstrated by the attendance record. The Fellows Advisory Committee is currently planning the next retreat, and we welcome your suggestions to make the next retreat even better!

Figure 1: The largest fraction took positions in academia as Principal Investigators, either in the US or abroad. The next largest percentage went on to careers in Clinical Medicine, mostly in hospital-based practice, with the same numbers of fellows who left the NHLBI without a definite position.

Figure 1

35 Postdocs who left in 2012

Job Title	Number	%
PI outside US	2	7
PI in US Institution	7	21
Postdoctoral Fellow	3	10
Clinical Medicine	7	25
Research Assistant/SS	3	10
Fed. Gov. Other	1	3
Corporate Research	5	18
Looking for Work	7	25

Average Duration 3.6 yrs (↓) ; 1 yr-7 yrs

Award Recipients at the NHLBI DIR Scientific Retreat



Dr. Keir Neuman (above, left) and Dr. Herbert Geller (right)

Dr. Herbert Geller presents the NHLBI DIR Outstanding Mentor award to **Dr. Keir Neuman**, Principal Investigator of the Laboratory of Single Molecule Biophysics. This award is granted on the basis of Fellows nominations and written feedback. Congratulations to Dr. Neuman!

Dr. Natalia Dmitrieva (top right), from the Renal Cellular and Molecular Biology Section was the proud recipient of the Staff Scientist/Biologist Poster Award.



Dr. Zhiyun Ge (bottom right), from the Laboratory of Ribonucleoprotein Biochemistry lab was the proud recipient of the Post Doctorate Poster Award.

**Dr. Ge is also a writer of The Science Beat column.*



Poster Awards are determined by highest score in the areas of content and presentation.

**11th Annual
NHLBI DIR
Scientific
Retreat
May 20, 2013**



Recent Publications by NHLBI Fellows

- W. Aerbajinai, K. Lee, K. Chin, and G. P. Rodgers.** Glia Maturation Factor-gamma Negatively Modulates TLR4 Signaling by Facilitating TLR4 Endocytic Trafficking in Macrophages. *J Immunol.*, 2013.
- D. J. Chess, E. Billings, R. Covian, B. Glancy, S. French, J. Taylor, H. D. Bari, E. Murphy, and R. S. Balaban.** Optical spectroscopy in turbid media utilizing an integrating sphere: mitochondrial chromophore analysis during metabolic transitions. *Anal Biochem.* (13):10, 2013.
- S. Guzik-Lendrum, S. M. Heissler, N. Billington, Y. Takagi, Y. Yang, P. J. Knight, E. Homsher, and J. R. Sellers.** Mammalian Myosin-18A, a Highly Divergent Myosin. *Journal of Biological Chemistry* 288 (13):9532-9548, 2013.
- M. Halabi, K. Ratnayaka, A. Z. Faranesh, M. Y. Chen, W. H. Schenke, and R. J. Lederman.** Aortic Access From the Vena Cava for Large Caliber Transcatheter Cardiovascular Interventions Pre-Clinical Validation. *Journal of the American College of Cardiology* 61 (16):1745-1746, 2013.
- D. A. Lerit, J. T. Smyth, and N. M. Rusan.** Organelle asymmetry for proper fitness, function, and fate. *Chromosome Res.* 21 (3):271-286, 2013.
- W. Li and Y. S. Mukouyama.** Tissue-specific venous expression of the Eph family receptor EphB1 in the skin vasculature. *Dev Dyn.* :10, 2013.
- L. Maldonado-Baez, N. B. Cole, H. Kramer, and J. G. Donaldson.** Microtubule-dependent endosomal sorting of clathrin-independent cargo by Hook1. *Journal of Cell Biology* 201 (2):233-247, 2013.
- Z. McIver, J. J. Melenhorst, C. Wu, A. Grim, S. Ito, I. Cho, N. Hensel, M. Battiwalla, and A. J. Barrett.** Donor lymphocyte count and thymic activity predict lymphocyte recovery and outcomes after matched-sibling hematopoietic stem cell transplant. *Haematologica* 98 (3):346-352, 2013.
- K. J. Rosenquist, A. Pedley, J. M. Massaro, K. E. Therkelsen, J. M. Murabito, U. Hoffmann, and C. S. Fox.** Visceral and Subcutaneous Fat Quality and Cardiometabolic Risk. *JACC Cardiovasc Imaging.* (13):10, 2013.
- A. J. Sodt and R. W. Pastor.** Bending free energy from simulation: correspondence of planar and inverse hexagonal lipid phases. *Biophys J.* 104 (10):2202-2211, 2013.
- J. H. Um, A. L. Brown, S. K. Singh, Y. Chen, M. Gucek, B. S. Lee, M. A. Luckey, M. K. Kim, J. H. Park, B. P. Sleckman, M. Gellert, and J. H. Chung.** Metabolic sensor AMPK directly phosphorylates RAG1 protein and regulates V(D)J recombination. *Proc Natl Acad Sci U S A.*, 2013.
- K. C. Vickers, P. Sethupathy, J. Baran-Gale, and A. T. Remaley.** Complexity of microRNA function and the role of isomiRs in lipid homeostasis. *Journal of Lipid Research* 54 (5):1182-1191, 2013.
- K. C. Wood, M. M. Cortese-Krott, J. C. Kovacic, A. Noguchi, V. B. Liu, X. Wang, N. Raghavachari, M. Boehm, G. J. Kato, M. Kelm, and M. T. Gladwin.** Circulating Blood Endothelial Nitric Oxide Synthase Contributes to the Regulation of Systemic Blood Pressure and Nitrite Homeostasis. *Arterioscler Thromb Vasc Biol.*, 2013.
- B. Xu, N. Zhi, G. Hu, Z. Wan, X. Zheng, X. Liu, S. Wong, S. Kajigaya, K. Zhao, Q. Mao, and N. S. Young.** Hybrid DNA virus in Chinese patients with seronegative hepatitis discovered by deep sequencing. *Proc Natl Acad Sci U S A.*, 2013.

For the Summer Interns:**NHLBI DIR Summer Seminar Series**

"Two Actin Networks Dictate the Traction Force Oscillation with Single Focal Adhesions"

Jian Liu, Ph.D.

Wednesday, June 19th
11:45 AM- 1:30 PM
Building 10-CRC, Room 2-3330

THE SCIENCE BEAT

By Dinari Harris, Ph.D.

J. H. Um, A. L. Brown, S. K. Singh, Y. Chen, M. Gucek, B. S. Lee, M. A. Luckey, M. K. Kim, J. H. Park, B. P. Sleckman, M. Gellert, and J. H. Chung. Metabolic sensor AMPK directly phosphorylates RAG1 protein and regulates V(D)J recombination. *Proc Natl Acad Sci U S A.*, 2013.

The function and survival of all organisms is dependent on the dynamic control of energy metabolism, when energy demand is matched to energy supply. The AMP-activated protein kinase (AMPK) is an important integrator of signals that control energy balance through the regulation of multiple biochemical pathways in all eukaryotes. When a cell is low on fuel, AMPK shuts down processes that use energy and turns on processes that produce energy. Therefore, AMPK serves as an evolutionary conserved metabolic gauge/energy stress sensor and a homeostatic regulator of cellular ATP levels. Recently AMPK has been shown to play a central role in the regulation of body weight, systemic glucose homeostasis, lipid metabolism, and mitochondrial biogenesis, which has made it an attractive therapeutic target. Additionally, evidence is mounting that AMPK also plays a role in a number of pathways unrelated to energy metabolism. These discoveries uncover interesting and unexpected potential links between metabolic stress and a diverse number of seemingly unrelated biochemical processes. One such study by Um *et al.* identified a novel pathway that is regulated by AMPK and suggests a potential new link between metabolic stress and the development of B and T lymphocytes. In an attempt to find downstream targets of AMPK, the authors targeted the recombination-activating gene 1 (RAG1), a crucial factor for V(D)J recombination during lymphocyte development, as a strong candidate based on their bioinformatics searches.

V(D)J recombination, also known as somatic recombination, is a mechanism of genetic recombination in the early stages of immunoglobulin T cell receptors production in the immune system. This mechanism of V(D)J recombination can be separated into two distinct steps: (1) double-stranded DNA breaks (DSB) or cleavage induced by RAG1 and RAG2 protein complex; and (2) appropriate joining of pairs of coding ends. Since the proper regulation of V(D)J recombination is so essential for lymphocyte

development, it normally is under the control of the RAGs, which are themselves regulated through limited access to target loci controlled by chromatin remodeling proteins. Um *et al.* identified RAG1 through bioinformatics searches as containing a possible AMPK consensus motif and standard *in vitro* assays show that AMPK directly phosphorylates RAG1 at a single position, serine 258 (S258). To further this argument they showed the AMPK phosphorylates RAG1 at S258, using a phosphospecific antibody. The kinase activity of RAG1 and phosphospecific antibody binding to RAG1 was significantly reduced in the phosphoresistant alanine mutant, S258A. Additionally, *in vitro* assays using either AMPK activators in control cells or expression of a constitutively active form of AMPK in double knockout cells (AMPK DKO) results in phosphorylation of the RAG1 site.

After convincingly showing that RAG1 is a target of AMPK, Um *et al.* address the role of phosphorylation state on RAG1's ability to mediate DSB. In the first step of V(D)J recombination, the RAGs introduce a DSB precisely between a variable region gene-coding segment and an associated recombination signal sequence. This cleavage activity was monitored in an *in vitro* assay using both wildtype (WT) RAG1, the phosphoresistant alanine substitution (S258A), and two phosphoserine mimetic mutations (aspartic acid; S528D or glutamic acid; S258E). The extent of cleavage and rate of cleavage activity of RAG1 was increased in the phosphoserine mimetics (compared to WT), while the extent of DSB did not change in the phosphoresistant mutant. To investigate whether phosphorylation of RAG1 by AMPK could regulate cleavage activity *in vivo*, the authors tested the cleavage of an extrachromosomal substrate in WT and AMPK DKO cells and found that phosphorylation at S528 in RAG1 by AMPK augments cleavage activity.

Overall, Um *et al.* found that AMPK directly phosphorylates RAG1 at (S258), and the phosphorylation enhances the catalytic activity of the RAG complex, resulting in increased cleavage of oligonucleotide substrates *in vitro*, or increased recombination of an extrachromosomal substrate in a *in vivo* assay. These findings suggest that AMPK may link V(D)J recombination to metabolic stress. Further studies need to be conducted to determine whether AMPK-mediated phosphorylation of RAG1 may be involved in regulating lymphocyte development in response to changes in energy status.

New NHLBI Fellows



K. Maria Mills, Ph.D., is an IRTA Fellow in the Biochemistry and Biophysics Center under Dr. Keir Neuman. Dr. Mills earned her Ph.D. in Biophysics from the University of Michigan. Prior to the NIH, Dr. Mills was a Postdoctoral Fellow in the Structural Biology Department at the Memorial Sloan-Kettering Cancer Center. Her initial project at the NIH is single molecule studies of the dynamics of RecQ helicase and using single molecule FRET to study the conformational changes of the protein and magnetic tweezers to follow it unwinding DNA.



Sricharan Murugesan, Ph.D., is a Visiting Fellow in the Cell Biology and Physiology Center under Dr. John Hammer. Dr. Murugesan earned his Ph.D. in Biochemistry, Molecular and Cell Biology at Cornell University. Dr. Murugesan received the CALS Teaching Award for Outstanding Graduated Teaching Assistant in 2010. His initial project at the NIH is actin cytoskeletal organization at the immunological synapse in T cells.



Yubo Zhang, Ph.D., is a Visiting Fellow in the DNA Sequencing and Genomics Core under Dr. Guokai Chen. Dr. Zhang earned his Ph.D. in Hydrobiology Institute of Hydrobiology at the Chinese Academy of Sciences. Prior to the NIH, Dr. Zhang was a Postdoctoral Fellow at Lawrence Berkeley National Laboratory. His initial project at the NIH is setting up CHIA-PET in the DNA Sequencing and Genomics Core.



Susanne Winkler, M.D., is a Visiting Fellow in the Cardiovascular-Pulmonary Branch under Dr. Andrew Arai. Dr. Winkler earned her M.D. at University of Vienna Medical School. Prior to the NIH, Dr. Winkler was a resident in Internal Medicine/Cardiology at the Medical University of Vienna. Her initial project at the NIH is CAD compared in CT and MRI and myocardial perfusion dd.

Photo Album: The 11th Annual NHLBI DIR Scientific Retreat

