



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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**The Science Beat**

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Dinari Harris, LMCI

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***From the Director of the Office of Education***

We in the Office of Education hope that your New Year is off to a great start. Planning is well underway for the NHLBI DIR Retreat, which this year will be held on May 20th at the Ronald Reagan Building. Though this is a more subdued event, we hope that the benefit of having a one-day retreat in a great setting on the national mall will allow all DIR researchers to attend. Because the retreat is also later than usual, we will open abstract submission at the beginning of March.

In December, the Advisory Committee to the NIH Director released their report on the future of the Biomedical Research Workforce. Obviously, this is important to all of you as trainees with long careers ahead of you. I have summarized some of the important points in this report below, and welcome your feedback about ways to improve training within DIR. I especially encourage you to come and join the Fellows Advisory Committee which helps plan the activities and advises the Office of Education on how we can make your time here more rewarding.

***New NIH Policies on the Future of the Biomedical Research Workforce***

By Herbert Geller, Ph.D.

In early 2012, the NIH Director charged the Advisory Committee to the Director (ACD) to develop recommendations that would enhance the Biomedical Research Workforce in the future. The final report of the Advisory Committee was released in December, and it contains many recommendations that impinge upon the future training of NHLBI graduate students and postdocs.

One problem that was addressed was that traditional training is aimed at preparing students and postdocs for academic research careers, and has not recognized the fact that most trainees do not obtain faculty positions at re-

search-intensive institutions. So the first recommendation was to enhance training of graduate students and post-doctoral researchers, first by establishing a grants program that would support innovative approaches to complement traditional research training, and second, by encouraging the adoption of individual development plans for all trainees. As to the first recommendation, the DIR is already ahead of the curve, as exemplified by the existence of the Office of Education and the Career Development Activities supported by the OITE. In terms of the second, we have established mechanisms for each Fellow in DIR to formulate an Individual Development Plan (IDP), but we have not yet required one. The Annual Fellows Progress Report closely tracks the issues that are ad-

Cont'd on page 2

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

**FelCom needs representatives for NHLBI.  
Please contact the Office of Education if you are  
interested in attending their monthly meeting.**

Cont'd from page 1 dressed in an IDP, so we are in compliance with the spirit of the recommendation. So I am asking for your feedback as to whether we need to implement a more rigorous approach to the IDP. You can either communicate with me or with your lab/branch/center representative on the Fellows Advisory Committee as to how you feel about enhancing this process.

The next recommendations addressed how to accelerate the development of independent research careers, including NIH Pathway to Independence Awards (K99/R00) and Early Independence Awards. The major recommendation here is that NIH should increase the amount of money that supports these early programs. At the same time, to further speed up the transition, it was recommended that the eligibility for K99/R00 awards be reduced to four years of postdoctoral training, rather than the current five. It is not at all clear how this change would impact DIR Fellows, so it would be helpful to hear your feedback as to whether you consider this change positive or negative.

The next recommendation is that all training institutions identify and track more comprehensively all graduate students and postdoctoral researchers to provide a sound basis for assessing workforce needs and planning future training activities. More comprehensive career outcomes data also would help to inform prospective graduate students and postdoctoral researchers contemplating careers in biomed-

cal research. Tracking our alumni has always been a difficult issue, especially if a fellow chooses a career that does not involve publication. We do collect this information for our departing fellows, but it is hard to track fellows if they change jobs. For this reason, we established the NIH Fellows and Alumni Group on LinkedIn, but the success of this method depends upon the fellow joining LinkedIn and then signing up for the Group. Another proposal is that researchers should be assigned a unique Researcher ID, and that this ID would be included in publications. This would definitely address issues of scientists with common names. However, such a system would not be able to keep track of alumni if they did not publish. So it is not clear how successful any mechanism would be.

One final recommendation is that assessment of the biomedical research workforce be an ongoing project, including a proposed follow-up study on clinician scientists. The DIR is already addressing the issue of increasing the clinician-scientist program through the Assistant Clinical Investigator and the Lasker Clinical Research Scholars Program. Both of these programs are in their relative infancy, and so it is too early to assess their long-term success rate.

I urge all of you to learn more about the report by visiting the web site at:

<http://www.nih.gov/news/health/dec2012/od-07.htm>



## **11th Annual NHLBI DIR Scientific Retreat**

**May 20, 2013  
The Ronald Reagan Building  
Washington, DC**

**THE SCIENCE BEAT**

By Zhiyun Ge, Ph.D.

**Narayan N., Lee I. H., Borenstein R., Sun J. H., Wong R., Tong G., Fergusson M. M., Liu J., Rovira I. I., Cheng H. L., Wang G. H., Gucek M., Lombard D., Alt F. W., Sack M. N., Murphy E., Cao L. and Finkel T. (2012) The NAD-dependent deacetylase SIRT2 is required for programmed necrosis. *Nature* **492**, 199-+.**

Necrosis is a form of cell death caused by external factors to the cell or tissue. It is characterized by the disruption of cell membrane integrity and subsequent uncontrolled release of the products of cell death into the intracellular space. Although necrosis was initially viewed as an unregulated process, emerging evidence suggests that some forms of necrosis are programmed. The programmed necrosis is also termed necroptosis and is involved in various pathological forms of cell death, including ischemic brain and injury, neurodegenerative diseases and viral infections. Necroptosis occurs following the activation of receptor-interacting protein 1 (RIP1) in response to the ligands, such as tumour necrosis factor receptor (TNFR) and the formation of a RIP1-RIP3 complex. It is known that the formation of RIP1-RIP3 complex is essential for necrosis to occur. However, the molecular mechanism that mediates the RIP1 and RIP3 interaction remains largely elusive.

In this paper, Narayan et al. described the role of the NAD-dependent deacetylase SIRT2 as a central regulator of programmed necrosis. SIRT2 is one of the seven known mammalian sirtuin isoforms and its functions remained uncharacterized. Therefore, the authors set out to explore the roles of SIRT2 through the identification of its cellular interacting partners. Interestingly, one of the identified interacting proteins of SIRT2 is RIP3, potentiating a role of SIRT2 in programmed necrosis. The authors were able to validate the interaction between SIRT2 and RIP3 using either epitope-tagged proteins or endogenous proteins. The authors also showed that SIRT2 interacts with the carboxy terminus of RIP3 *in vitro*.

Next the authors hypothesized that SIRT2 may play a role in regulating the RIP1-RIP3 interaction and the overall necrotic response. Necrotic stimulus led to RIP1-RIP3 formation in wild-type mouse embryonic fibroblasts (MEF), while *Sirt2*<sup>-/-</sup> MEFs failed to produce RIP1-RIP3 complexes upon receiving the necrotic stimulus. Consistent with this observation, the authors also observed defects in pro-

grammed necrosis in cells lacking SIRT2. Inhibition of SIRT2's deacetylase activity using a pharmacological inhibitor AGK2 also resulted in defects in RIP1-RIP3 complex formation, as well as programmed necrosis in multiple cell lines following necrotic stimulation. These results not only confirm the role of SIRT2 in modulating RIP1-RIP3 complex formation and programmed necrosis, but also suggest that the deacetylase activity of SIRT2 is playing a role in the necrotic pathway. The authors then showed that the SIRT2-dependent deacetylation of RIP1 is required for the RIP1-RIP3 interaction. Existing evidence suggests that necrotic stimulus brings RIP1 and the already formed RIP2-SIRT2 complex in close proximity to each other, thus facilitating the deacetylation of RIP1 by SIRT2 and the subsequent formation of RIP1-RIP3 complex. The authors then sought to identify the lysine residues of RIP1 for SIRT2-dependent deacetylation. Since RIP1 and RIP3 interacts through the RHIM domain and the formation of RIP1-RIP3 complex is dependent on the deacetylation of RIP1 by SIRT2, lysine close to the RHIM domain (Lysine 530) in RIP1 may be the target of SIRT2. It was then shown that Lysine 530 in RIP1 is indeed acetylated and SIRT2 is able to deacetylate peptides encompassing residues 529-546 of RIP1, indicating that acetylated Lysine 530 in RIP1 is a substrate of SIRT2. To further explore the function of Lysine 530 and obtain evidence that SIRT1-dependent deacetylation of RIP1 regulates RIP1 function, the authors utilized gain (RIP1, K530Q) or loss (K530A, RIP1) of function mutants of RIP1 to demonstrate that the deacetylation of Lysine 530 of RIP1 by SIRT2 is essential for the interactions between RIP1 and RIP3 and eventually for ligand-dependent programmed necrosis. Finally, the authors elucidated the physiological importance of SIRT2 and showed that inhibition of SIRT2 prevents necrosis in ischaemia-reperfusion injury, leading to improvement of functional recovery after the injury.

In summary, SIRT2 plays a central role in modulating programmed necrosis through regulating the RIP1-RIP3 complex formation. Inhibition of SIRT2 function genetically or pharmacologically may be of great clinical value for treating various diseases where necrosis is playing a significant role.

**Recent Publications by NHLBI Fellows**

- Narayan N., Lee I. H., Borenstein R., Sun J. H., Wong R., Tong G., Fergusson M. M., Liu J., Rovira I. I., Cheng H. L., Wang G. H., Gucek M., Lombard D., Alt F. W., Sack M. N., Murphy E., Cao L. and Finkel T. (2012) The NAD-dependent deacetylase SIRT2 is required for programmed necrosis. *Nature* **492**, 199-+.
- Abeykoon A. H., **Chao C. C.**, Wang G. H., Gucek M., Yang D. C. H. and Ching W. M. (2012) Two Protein Lysine Methyltransferases Methylate Outer Membrane Protein B from *Rickettsia*. *J. Bacteriol.* **194**, 6410-6418.
- Ring A. M., Lin J. X., Feng D., **Mitra S.**, Rickert M., Bowman G. R., Pande V. S., Li P., Moraga I., Spolski R., Ozkan E., Leonard W. J. and Garcia K. C. (2012) Mechanistic and structural insight into the functional dichotomy between IL-2 and IL-15. *Nature Immunol.* **13**, 1187-+.
- Bond L. M.**, Arden S. D., Kendrick-Jones J., Buss F. and Sellers J. R. (2012) Dynamic Exchange of Myosin VI on Endocytic Structures. *J. Biol. Chem.* **287**, 38637-38646.
- Li J. X., Ferraris J. D., Yu D. N., Singh T., **Izumi Y.**, Wang G. H., Gucek M. and Burg M. B. (2012) Proteomic analysis of high NaCl-induced changes in abundance of nuclear proteins. *Physiol. Genomics* **44**, 1063-1071.
- Biancotto A., **Feng X. M.**, Langweiler M., Young N. S. and Mccoy J. P. (2012) Effect of anticoagulants on multiplexed measurement of cytokine/chemokines in healthy subjects. *Cytokine* **60**, 438-446.
- Zhao B. Y.**, Pisitkun T., Hoffert J. D., Knepper M. A. and **Saeed F.** (2012) CPhos: A program to calculate and visualize evolutionarily conserved functional phosphorylation sites. *Proteomics* **12**, 3299-3303.
- Bolger S. J.**, Hurtado P. A. G., Hoffert J. D., **Saeed F.**, Pisitkun T. and Knepper M. A. (2012) Quantitative phosphoproteomics in nuclei of vasopressin-sensitive renal collecting duct cells. *Am. J. Physiol. Cell Physiol.* **303**, C1006-C1020.
- Izumi Y.**, Li J. X., **Villers C.**, Hashimoto K., Burg M. B. and Ferraris J. D. (2012) Mutations that reduce its specific DNA binding inhibit high NaCl-induced nuclear localization of the osmoprotective transcription factor NFAT5. *Am. J. Physiol. Cell Physiol.* **303**, C1061-C1069.
- de Latour R. P., Calado R. T., Busson M., **Abrams J.**, Adoui N., Robin M., Larghero J., Dhedin N., Xhaard A., Clave E., Charron D., Toubert A., Loiseau P., Socie G. and Young N. S. (2012) Age-adjusted recipient pretransplantation telomere length and treatment-related mortality after hematopoietic stem cell transplantation. *Blood* **120**, 3353-3359.
- Mitra A., Luo J., **Zhang H. M.**, Cui K. R., Zhao K. J. and Song J. Z. (2012) Marek's disease virus infection induces widespread differential chromatin marks in inbred chicken lines. *BMC Genomics* **13**.
- Van Itallie C. M., Tietgens A. J., **LoGrande K.**, Aponte A., Gucek M. and Anderson J. M. (2012) Phosphorylation of claudin-2 on serine 208 promotes membrane retention and reduces trafficking to lysosomes. *J. Cell Sci.* **125**, 4902-4912.
- Keyvanfar K., **Weed J.**, **Swamy P.**, Kajigaya S., Calado R. T. and Young N. S. (2012) Interphase Chromosome Flow-FISH. *Blood* **120**, E54-E59.

As many of you know, there are severe restrictions on travel and meeting-related expenses at NIH. However, we realize that it is very important for fellows to travel to meetings in order to advance your scientific career. Towards that end, if you find that you cannot attend a meeting that is important for your career, please inform the Office of Education so that we can address this important issue.

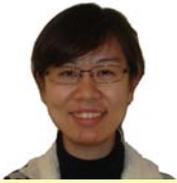
## New NHLBI Fellows



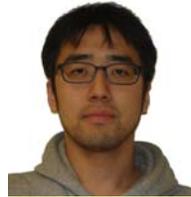
**Huiqing Li, Ph.D.**, is a new Visiting Fellow in the Cell Biology and Physiology Center under Dr. Rosa Puertollano. Dr. Li earned her Ph.D. in Developmental Biology at the University of Maryland. Prior to the NIH, she was a Postdoc at the Johns Hopkins University School of Medicine. Dr. Li's initial research project at the NHLBI is detecting the function of tfeb during zebrafish development.



**Kira Holmstrom, Ph.D.**, is a new Visiting Fellow in the Center for Molecular Medicine under Dr. Toren Finkel. Dr. Holmstrom earned her Ph.D. in Cognitive and Behavioral Neuroscience from Eberhard-Karis University. Prior to the NIH, she was a Postdoctoral Fellow in the Department of Molecular Neuroscience. Dr. Holmstrom's initial research project at the NHLBI investigates the effects of Ethe 1 in programmed necrosis.



**Xueting Jin, M.D.**, is a new Visiting Fellow in the Center for Molecular Medicine under Dr. Howard Kruth. Dr. Jin earned her M.D. from Fudan University. She has volunteered at the 4th & 5th Annual China Symposium on Stem Cell Transplantation and was in charge of volunteers at the 80<sup>th</sup> Anniversary of Shanghai Medical College. Dr. Jin's initial research project at the NHLBI is figuring out the effect of Apo-AI and HDL on M-CSF cultured macrophages from mice.



**Juyong Lee, Ph.D.**, is a new Visiting Fellow in the Biochemistry and Biophysics Center under Dr. Bernard Brooks. Dr. Lee earned his Ph.D. in Chemistry from Seoul National University. Prior to the NIH, he was a Postdoctoral Fellow at the Korean Institute for Advanced Study. Dr. Lee's initial research project at the NHLBI is developing sampling methods for accurate free energy calculation.



**Florentina Tofoleanu, Ph.D.**, is a new Visiting fellow in the Biochemistry and Biophysics Center under Dr. Bernard Brooks. Dr. Tofoleanu earned her Ph.D. in Biophysics at University College Dublin. She was the recipient of the "Embark Initiative" Postgraduate Scholarship by the Irish Research Council for Science, Engineering and Technology. Dr. Tofoleanu's initial research project at the NHLBI focuses on coarse grained and Langevin dynamics simulations.

## Top Chef: Elizabeth Mushaven

**Congratulations to Elizabeth Mushaven whose Raspberry Cheesecake won "Top Dessert" at the NHLBI DIR Holiday Dessert Potluck**



## Philip Clifford, Ph.D.

**"Play to Your Strengths: Creating an Individual Development Plan"**

**Thursday, January 17th  
9:00 AM- 10:00 AM  
Building 50, Room 1227/1233**

*Dr. Clifford is Associate Dean of the Graduate School of Biomedical Sciences Medical College of Wisconsin. He will discuss data on scientific careers, becoming familiar with a process to evaluate career options, and a new science-specific resource for career planning, [myIDP.sciencecareers.org](http://myIDP.sciencecareers.org).*