



April 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

As of this writing, Congress has passed another short-term continuing resolution funding the U.S. Government through Thursday of this week. During that time, Congress needs to pass additional legislation which will provide funding through September, 2011, which is still a potential issue. It is still not clear how all this impacts the NIH, the NHLBI or the NHLBI Intramural Program.

Fortunately, the planning for the retreat on April 27-29 is complete. Over 220 fellows have registered to attend. We have nearly 100 posters in two poster sessions, and have identified some outstanding poster submissions for oral presentations. The nearly-final program is now available on the web. I look forward to seeing you there and learning about all the exciting research that we are doing here at NHLBI.

**9th Annual NHLBI DIR
Scientific Retreat
April 27-29, 2011
Cambridge, MD • Hyatt Regency**

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***

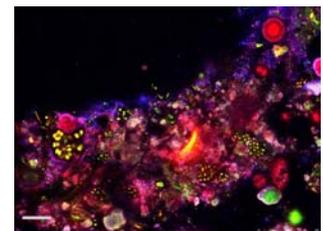
Donald Ingber, M.D., Ph.D.
***Professor of Bioengineering,
Harvard School of Engineering and
Applied Sciences***

NHLBI Image Contest

**Please vote for your
favorite image:**
<http://nhlbiretreat.shutterfly.com/>

***Voting will close on
Friday, April 15th***

The winner will be announced at
the NHLBI DIR Scientific Retreat



THE SCIENCE BEAT

By Nisha Narayan, Ph.D.

Yu M, Lam J, Rada B, Leto TL, Levine SJ (2011) Double-stranded RNA induces shedding of the 34-kDa soluble TNFR1 from human airway epithelial cells via TLR3-TRIF-RIP1-dependent signaling: roles for dual oxidase 2- and caspase-dependent pathways. J Immunol. 186(2):1180-8.

Tumor necrosis factors (or the TNF-family) are a family of cytokines that regulate inflammation, apoptosis and innate immunity among other essential processes in the cell. TNF or TNF-alpha is a monocyte-derived cytokine involved in systemic inflammation which exerts its effects by binding to two cell surface receptors, TNFR1 and TNFR2. This binding of TNF to TNFR1, the key receptor for TNF signaling, subsequently leads to the activation of MAPK and NF-kB signaling pathways, or alternatively results in caspase activation and apoptosis. Several stimuli including IL-1b, proteasome inhibitors, and Staphylococcal protein A can induce the proteolytic cleavage and shedding of soluble TNFR1 (sTNFR1). The authors of this study wanted to evaluate if ligands for TLRs can induce shedding of sTNFR1 as a mechanism to amend innate immune responses.

To do this, they use polyinosinic-polycytidylic acid [poly (I:C)], a viral dsRNA analogue to selectively induce the cleavage and shedding of sTNFR1 ectodomains but not the

release of full-length TNFR1, within exosome-like vesicles from human airway epithelial cells. Using RNA interference, they show that poly (I:C)-induced sTNFR1 shedding from NCI-H292 human airway epithelial cells is mediated by a TLR3-TRIF-dependent pathway that involves the downstream participation of the serine-threonine kinase and death mediator, RIP1. To deduce which pathway is mediating the effects, they use ERK and p38 inhibitors in conjunction with RNAi mediated knockdown of RIP1, and demonstrate that the shedding occurs independently of the MEK-, ERK-, p38-, or Akt pathways. Experiments were then performed to assess the function of Reactive Oxygen Species (ROS) signaling, and knocking down the expression of Duox2 and not Duox1 – both members of the NADPH oxidase family – inhibited poly (I:C)-induced TNFR1 shedding by 30%. Knocking both proteins down did not have a cumulative effect confirming the exclusivity of Duox-2 mediated ROS production in the activation of a TLR3-TRIF-RIP1 signaling pathway. They also show that poly (I:C)-induced sTNFR1 release from the human airway epithelial cells is dependent upon RIP1-mediated caspase activation by demonstrating reduced PARP cleavage in cells with a knockdown of RIP1.

In conclusion, this study has identified a mechanism by which signaling through the TLR3-TRIF-RIP1-dependent signaling pathway regulates the innate immune response to virus-induced airway inflammation. This is done through the shedding of soluble TNFR1, which then binds and potentially attenuates excessive TNF bioactivity.

Recent Publications by NHLBI Fellows

Andrade, M. V., **Iwaki, S.**, Ropert, C., Gazzinelli, R. T., Cunha-Melo, J. R., & Beaven, M. A. (2011). Amplification of cytokine production through synergistic activation of NFAT and AP-1 following stimulation of mast cells with antigen and IL-33. *European Journal of Immunology* 41, 760-772.

Biancotto, A., Fuchs, J. C., Williams, A., **Dagur, P. K.**, & McCoy, J. P. (2011). High dimensional flow cytometry for comprehensive leukocyte immunophenotyping (CLIP) in translational research. *Journal of Immunological Methods* 363, 245-261.

Bond, L. M., Peden, A. A., Kendrick-Jones, J., Sellers, J. R., & Buss, F. (2011). Myosin VI and its binding partner optineurin are involved in secretory vesicle fusion at the plasma membrane. *Molecular Biology of the Cell* 22, 54-65.

Cui, C., Chatterjee, B., Francis, D., **Yu, Q.**, SanAgustin, J. T., Francis, R., Tansey, T., Henry, C., Wang, B. L., **Lemley, B.**, Pazour, G. J., & Lo, C. W. (2011). Disruption of Mks1 localization to the mother centriole causes cilia defects and developmental malformations in Meckel-Gruber syndrome. *Disease Models & Mechanisms* 4, 43-56.

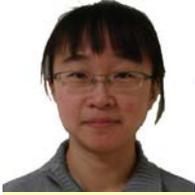
DeJesus, C. E., Egen, J., Metzger, M., Alvarez, X., Combs, C. A., Malide, D., Yu, Z. X., Tian, X., & Donahue, R. E. (2011). Transient neutropenia after granulocyte-colony stimulating factor administration is associated with neutrophil accumulation in pulmonary vasculature. *Experimental Hematology* 39, 142-150.

Duverger, O., Chen, S. X., Lee, D., **Li, T. W.**, Chock, P. B., & Morasso, M. I. (2011). SUMOylation of DLX3 by SUMO1 Promotes its Transcriptional Activity. *Journal of Cellular Biochemistry* 112, 445-452.

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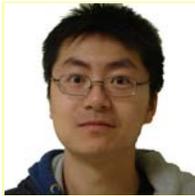
New NHLBI Fellows



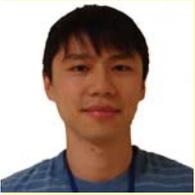
Jie Zhuang, Ph.D., is a Visiting Fellow in the Laboratory of Cardiovascular and Cancer Genetics under Dr. Paul Hwang. Dr. Zhuang earned her Ph.D. in Biophysics from the Chinese Academy of Sciences, Beijing, China. She was awarded the First-Class Scholarship, Academy chief scholarship of Chinese Academy of Sciences. Dr. Zhuang will be researching the function of p53 mutant in mitochondrial DNA damage and repair.



Jinwei Zhang, Ph.D. is a Visiting Fellow in the Laboratory of RNA Biophysics and Cellular Physiology under Dr. Adrian Ferre-D'amare. Dr. Zhang earned his Ph.D. in Biomolecular Chemistry from the University of Wisconsin, Madison, WI. He was the recipient of both the Travel Award and the Karavolas Scholarship at Wisconsin. Dr. Zhang's Initial research project involves the structural basis of tRNA-mediated antitermination by T-box riboswitch.



Xiaozhen (Shawn) Yu, Ph.D. is a Visiting Fellow in the Biochemistry and Biophysics under Dr. Justin Taraska. Dr. Yu earned his Ph.D. in Biochemistry from the University of Mississippi. He was a Rapid Diagnostics research intern at Becton, Dickinson and Company in San Diego, California. Dr. Yu's initial research project involves the FRET measurement of Maltose-binding protein (MBP).



Matt Lau, Ph.D. is a Visiting Fellow in the Laboratory of RNA Biophysics and Cellular Physiology under Dr. Adrian Ferre-D'amare. Dr. Lau earned his Ph.D. from Simon Fraser University, Burnaby, B.C., where he also completed his undergrad. He was the recipient of the Postdoctoral Croucher Foundation Fellowship in Hong Kong, China. Dr. Lau's initial research project is the selection of catalytic RNA's.



Ana Opina, Ph.D. is a Visiting Fellow in the Image Probe Development Center under Dr. Gary Griffiths. Dr. Opina earned her Ph.D. in Synthetic Chemistry from the University of Texas, Dallas. She was awarded the DA Secretary's Awards from the Department of Agriculture-Bureau of Agriculture Research in the Philippines. Dr. Opina's initial research project is to conjugate an MRI probe into the dendrimer to increase sensitivity of the MRI agent.

New NHLBI Principal Investigator



Adrian Ferre-D'Amare, Ph.D. is a new Principal Investigator in the Laboratory of RNA Biophysics and Cellular Physiology. Dr. Ferre-D'Amare earned his Ph.D. in Molecular Biophysics from the Rockefeller University in New York. He then completed his postdoctoral training at Yale University. Dr. Ferre-D'Amare is the recipient of many honors and awards including the Eli Lilly & Co. Research Award and the Distinguished Young Scholar in Medical Research award from W.M. Keck Foundation. Dr. Ferre-D'Amare was an Investigator at Howard Hughes Medical Institute before coming to NIH.

Recent Publications by NHLBI Fellows Continued

- Gallazzini, M., Heussler, G. E., Kunin, M., Izumi, Y., Burg, M. B., & Ferraris, J. D.** (2011). High NaCl-induced activation of CDK5 increases phosphorylation of the osmoprotective transcription factor TonEBP/OREBP at threonine 135, which contributes to its rapid nuclear localization. *Molecular Biology of the Cell* *22*, 703-714.
- Ganesh, S. K., Joo, J., Skelding, K., Mehta, L., Zheng, G., O'Neill, K., Billings, E. M., Helgadottir, A., Andersen, K., Thorgeirsson, G., Gudnason, T., Geller, N. L., Simari, R. D., Holmes, D. R., O'Neill, W. W., & Nabel, E. G.** (2011). Time course analysis of gene expression identifies multiple genes with differential expression in patients with in-stent restenosis. *Bmc Medical Genomics* *4*.
- George, A. K., Sonmez, M., Lederman, R. J., & Faranesh, A. Z.** (2011). Robust automatic rigid registration of MRI and X-ray using external fiducial markers for XFM-guided interventional procedures. *Medical Physics* *38*, 125-141.
- Ghysels, A., **Woodcock, H. L., Larkin, J. D., Miller, B. T., Shao, Y. H., Kong, J., Van Neck, D., Van Speybroeck, V., Waroquier, M., & Brooks, B. R.** (2011). Efficient Calculation of QM/MM Frequencies with the Mobile Block Hessian. *Journal of Chemical Theory and Computation* *7*, 496-514.
- Johnson, A. D. & Prakash, S.** (2011). Top Advances in Functional Genomics and Translational Biology for 2010. *Circulation-Cardiovascular Genetics* *4*, 94-97.
- Khositseth, S., Pisitkun, T., **Slentz, D. H., Wang, G. H., Hoffert, J. D., Knepper, M. A., & Yu, M. J.** (2011). Quantitative Protein and mRNA Profiling Shows Selective Post-Transcriptional Control of Protein Expression by Vasopressin in Kidney Cells. *Molecular & Cellular Proteomics* *10*.
- Kohr, M. J., Sun, J. H., Aponte, A., Wang, G. H., Gucek, M., Murphy, E., & Steenbergen, C.** (2011). Simultaneous Measurement of Protein Oxidation and S-Nitrosylation During Preconditioning and Ischemia/Reperfusion Injury With Resin-Assisted Capture. *Circulation Research* *108*, 418-U50.
- Leyva, F. J., Anzinger, J. J., McCoy, J. P., & Kruth, H. S.** (2011). Evaluation of transduction efficiency in macrophage colony-stimulating factor differentiated human macrophages using HIV-1 based lentiviral vectors. *Bmc Biotechnology* *11*.
- Lucas, H. R. & Lee, J. C.** (2011). Copper(II) enhances membrane-bound alpha-synuclein helix formation. *Metal-lomics* *3*, 280-283.
- Myers, K. A., Applegate, K. T., Danuser, G., Fischer, R. S., & Waterman, C. M.** (2011). Distinct ECM mechanosensing pathways regulate microtubule dynamics to control endothelial cell branching morphogenesis. *Journal of Cell Biology* *192*, 321-334.
- Saikus, C. E. & Lederman, R. J.** (2009). Interventional Cardiovascular Magnetic Resonance Imaging A New Opportunity for Image-Guided Interventions. *Jacc-Cardiovascular Imaging* *2*, 1321-1331.
- Sloand, E. M., Melenhorst, J. J., Tucker, Z. C. G., Pfannes, L., Brenchley, J. M., **Yong, A., Visconte, V., Wu, C., Gostick, E., Scheinberg, P., Olnes, M. J., Douek, D. C., Price, D. A., Barrett, A. J., & Young, N. S.** (2011). T-cell immune responses to Wilms tumor 1 protein in myelodysplasia responsive to immunosuppressive therapy. *Blood* *117*, 2691-2699.
- Xu, Z. X., **Wei, G., Chepelev, I., Zhao, K., & Felsenfeld, G.** (2011). Mapping of INS promoter interactions reveals its role in long-range regulation of SYT8 transcription. *Nature Structural & Molecular Biology* *18*, 372-U166.
- Yu, M., Lam, J., Rada, B., Leto, T. L., & Levine, S. J.** (2011). Double-Stranded RNA Induces Shedding of the 34-kDa Soluble TNFRI from Human Airway Epithelial Cells via TLR3-TRIF-RIP1-Dependent Signaling: Roles for Dual Oxidase 2-and Caspase-Dependent Pathways. *Journal of Immunology* *186*, 1180-1188.