



June 2012

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

While the official start of summer is still two weeks away, summer has already begun for the NHLBI. We are welcoming over 70 summer students to our laboratories, most of whom have already arrived. The Office of Education is once again sponsoring a series of pizza lunches for our summer students, the first of which is on Wednesday, June 13th. A complete schedule of summer seminars, along with a complete list of summer students is on the NHLBI web site at: <https://intramural.nhlbi.nih.gov/Offices/OSD/OE/Pages/InfoforSummerStudents.aspx>. We encourage all of our students to attend these lectures to get a flavor of the types of research going on at NHLBI.

A Strategy for Success

On Thursday, May 24th, New York Times columnist Tom Friedman presented his insightful observations on the state of the U. S. economy and competitiveness in the world today. Much of his message is directed at success in business, but there are some observations that apply for each of us to be successful.

He presented four points for success, many of which are intrinsic to our behavior as scientists: 1) Think like an immigrant; 2) Act like an artisan; 3) Be entrepreneurial; 4) Act like a waitress.

The first: As we look around campus, we recognize that immigrants are a major fraction of the NIH scientific workforce, and so NIH is already ahead

of the pack. He noted that what makes the immigrant mentality so special is that immigrants have no legacy to fall back on: they are hungry to make it on their own, and they don't want to lose for themselves and for their children. So this means that they constantly search for opportunities and are continually being optimistic about their future here. With this is the pressure to have their children be successful. So the take home message here is for all of us to act like we can lose it all without hard work and imaginations

The second: artisans were the norm before the industrial revolution. They produced items one by one for their clients, and their success was based on their own hands, with no large organization to shield them

[Cont'd on page 3](#)

**The Fellows Advisory Committee
seeks new members**

If your lab is not represented (see left), please join our next meeting:
Monday, June 11th, 4pm
Building 10-CRC/5-2550

New NHLBI Fellow

Min Ren, Ph.D., is a Research fellow in the Laboratory of Molecular Immunology under Dr. Warren Leonard. Dr. Ren earned her Ph.D. in Molecular Pharmacology from the Albert Einstein College of Medicine, Bronx, New York. She previously worked as a postdoc in cancer research at the University of Chicago, where she later held an assistant professor position. Dr. Ren's initial research project will be to measure the phenotypic differences of the Th 1, 2, 8, 17 differentiation in inbred mouse strains and combining phenotypic and computational genomics analysis to identify new elements that involved in Th cells differentiation.

Lunchtime Seminar Series

*for summer interns

Justin Taraska, Ph.D.
Laboratory of Molecular and Cellular Imaging

"Imaging the nanometer-scale structure of exocytosis and endocytosis"

Wednesday, June 13
12:30 PM-2:00 PM
10CRC/2-3750

Recent Publications by NHLBI Fellows

- Busser, B. W., Taher, L., Kim, Y., Tansey, T., **Bloom, M. J.**, Ovcharenko, I., & Michelson, A. M. (2012). A Machine Learning Approach for Identifying Novel Cell Type-Specific Transcriptional Regulators of Myogenesis. *Plos Genetics* 8.
- Calado, R. T., Cooper, J. N., **Padilla-Nash, H. M.**, Sloand, E. M., Wu, C. O., Scheinberg, P., Ried, T., & Young, N. S. (2012). Short telomeres result in chromosomal instability in hematopoietic cells and precede malignant evolution in human aplastic anemia. *Leukemia* 26, 700-707.
- Chapman, C. M.**, **Sun, X. M.**, Roschewski, M., Aue, G., **Farooqui, M.**, Stennett, L., **Gibellini, F.**, Arthur, D., **Perez-Galan, P.**, & Wiestner, A. (2012). ON 01910.Na Is Selectively Cytotoxic for Chronic Lymphocytic Leukemia Cells through a Dual Mechanism of Action Involving PI3K/AKT Inhibition and Induction of Oxidative Stress. *Clin. Cancer Res.* 18, 1979-1991.
- Dickendesh, T. L., Baldwin, K. T., Mironova, Y. A., Koriyama, Y., Raiker, S. J., Askew, K. L., Wood, A., Geofroy, C. G., Zheng, B. H., **Liepmann, C. D.**, Katagiri, Y., Benowitz, L. I., Geller, H. M., & Giger, R. J. (2012). NgR1 and NgR3 are receptors for chondroitin sulfate proteoglycans. *Nature Neuroscience* 15, 703-712.
- George, A. K.**, Faranesh, A. Z., Ratnayaka, K., Derbyshire, J. A., Lederman, R. J., & Hansen, M. S. (2012). Virtual Dye Angiography: Flow Visualization for MRI-Guided Interventions. *Magn. Reson. Med.* 67, 1013-1021.
- Kovacic, J. C.**, Mercader, N., Torres, M., Boehm, M., & Fuster, V. (2012). Epithelial-to-Mesenchymal and Endothelial-to-Mesenchymal Transition From Cardiovascular Development to Disease. *Circulation* 125, 1795-1808.
- Lin, J. X., **Li, P.**, Liu, D. L., Jin, H. T., He, J. P., Rasheed, M. A. U., **Rochman, Y.**, **Wang, L.**, Cui, K. R., Liu, C. Y., Kellsall, B. L., Ahmed, R., & Leonard, W. J. (2012). Critical Role of STAT5 Transcription Factor Tetramerization for Cytokine Responses and Normal Immune Function. *Immunity* 36, 586-599.
- Phillips, D.**, Covian, R., Aponte, A. M., **Glancy, B.**, Taylor, J. F., **Chess, D.**, & Balaban, R. S. (2012). Regulation of oxidative phosphorylation complex activity: effects of tissue-specific metabolic stress within an allometric series and acute changes in workload. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 302, R1034-R1048.

Lenfant Award Recipient



Congratulations to Postdoc Dorothy Lerit, recipient of the Lenfant Biomedical Fellowship, a competitive award which recognizes and provides additional support to those fellows committed to pursuing a career in research. Dorothy has been a PostDoctoral IRTA in the laboratory of Molecular Machines and Tissue Architecture since Summer of 2011. Dr. Lerit earned her Ph.D. in Molecular Biology from Princeton University.

Science Rotations for NHLBI Fellows

Have you thought about leaving the bench? Are you interested in a career which takes advantage of your scientific and analytical skills? If so, you may be interested in participating in NHLBI DIR Rotations with any of the organizations listed below. Rotations typically last 3 – 6 months, most often full-time, and are scheduled at the end of your NHLBI fellowship. Rotations or details can also be arranged for displaced Staff Scientists.

Contact the Office of Education if you are interested.

Fellows Rotation in Extramural Research –

<http://dir-intranet.nhlbi.nih.gov/oe/document.aspx?frer.htm>

- With the NHLBI Extramural Program to focus on Research Administration or Review

Battelle National Laboratories – <http://dir-intranet.nhlbi.nih.gov/oe/documents/battelle.htm>

- With any of several National Labs administered by Battelle

The FASEB Public Policy Research Fellows Program – www.faseb.org

- With the FASEB in Bethesda to focus on Science Policy

Research!America – www.researchamerica.org

- To focus on Science Policy Research in Alexandria, Virginia

from their customers. And artisans signed their work. In some ways, practicing science is very much in this tradition, as we, as authors, sign our work. But the general rule is that it is essential to have work of the highest quality that you want associated with your name.

The third: entrepreneurial. For Tom Friedman, this means that one should never rest on ones laurels – every achievement, every experiment, every result, is only an intermediate result on the way to progress. If we are ever finished with a project, so that we have no more avenues to pursue, then we ourselves are finished. For most of us, this is not an issue, as it is hard to actually complete one publication with-

out opening up several new areas of investigation.

The fourth: a waitress? Here he related a story of a breakfast that he had at his favorite Perkins Pancake house, where the waitress served their meals, with the comment "I added a little extra fruit to your plate of pancakes". So what does this gesture mean? It means that the waitress, despite working to discrete tasks, figured out what she could do on her own that would reward her, in this case in the form of a bigger tip. In fact, this is probably the one piece of universal advice that applies to each of us – if we put in that extra effort we can make ourselves more distinguishable.

One of his long-standing tenets is that the world is flat and it is hyper-connected. Because it is flat, you need to stand above the crowd to gain recognition or employment. And because of the connectivity, you also need to recognize that your ideas will not be kept in isolation for long. So you need to act on them now, before someone else does. And you can only do this if you consciously seek to excel.

One point that he made is that immigration is one of the major forces that made the U.S. economy strong, and that we should welcome immigrants as contributors rather than ask people to go home after their period of training here.

THE SCIENCE BEAT

By Daniel Kraushaar, Ph.D.

Chapman, C. M., Sun, X. M., Roschewski, M., Aue, G., Farooqui, M., Stennett, L., Gibellini, F., Arthur, D., Perez-Galan, P., & Wiestner, A. (2012). ON 01910.Na Is Selectively Cytotoxic for Chronic Lymphocytic Leukemia Cells through a Dual Mechanism of Action Involving PI3K/AKT Inhibition and Induction of Oxidative Stress. *Clin. Cancer Res.* 18, 1979-1991.

Chronic lymphocytic leukemia (CLL) is the most common leukemia of the Western World and is a malignancy of mature B-cells. CLL is currently incurable with chemotherapy probably due to signals that emanate from cells of the cancer microenvironment and continue to support leukemic cell survival and proliferation. ON 01910.Na is a non-ATP competitive multikinase inhibitor that has been tested in advanced clinical trials for myelodysplastic syndrome. The current NHLBI study by Chapman *et al.* examined whether ON 01910.Na possesses additional anti-cancer activity against CLL cells *in vitro*. To this end, PB mononuclear cells were isolated from CLL patients and subsequently subjected to ON 01910.Na treatment. By means of annexin V staining, cytotoxicity as a result of drug-induced apoptosis was detected in B-cell but not T-cell populations of CLL patients. Furthermore, the dose- and time-dependent effect on viability was observed only in B-cells of CLL patients but barely in B-cells of healthy patients. Drug-induced reduction in viability was accompanied by loss of mitochondrial membrane potential and activation of pro-apoptotic factors including BAK, BAX and caspase-3 demonstrating the activation of apoptotic pathways. The LD₅₀ was determined to be at around 1-2 μM/L for most patients, a concentration that can be realistically achieved *in vivo*.

Microarray and gene ontology analyses showed that drug-induced changes in gene expression were significantly related to inhibition of the PI3K/AKT pathway and prompted further examination of this signaling pathway. Activation of PI3 kinase (PI3K) leads to phosphorylation and activation of AKT, which in turn phosphorylates and thereby inactivates forkhead transcription factors. Conversely when PI3K is inhibited, forkhead transcription fac-

tors translocate to the nucleus and initiate the expression of pro-apoptotic genes. Examination of AKT showed that ON 01910.Na-treated cells carry reduced levels of AKT phosphorylation and increased expression of several forkhead transcription factors, in line with the idea that ON 01910.Na is a potent inhibitor of the PI3K/AKT pathway. Additional analysis of gene expression changes triggered by ON 01910.Na treatment indicated that a significant number of genes controlled by the activating protein -1 (AP-1) transcription factor was upregulated. AP-1 forms as homo or heterodimers composed of Jun, Fos and others, upon activation by c-Jun N-terminal kinase (JNK), which in turn is induced by radical oxygen species (ROS). Examination of the JNK/AP-1 pathway showed that ON 01910.Na induces an increase in ROS and downstream phosphorylation of JNK concomitantly with the upregulation of JNK pro-apoptotic target genes including ATF-3 and NOXA. In keeping with the idea that ON 01910.Na induces a ROS-mediated stress response, an antioxidant, N-acetylcysteine, was able to offset the cytotoxic effect of ON 01910.Na. As mentioned previously, the cellular microenvironment plays a pivotal role in leukocytic cell survival by providing signals that enhance CLL proliferation and survival. In order to mimic the stromal microenvironment, CLL cells were co-cultured with stromal dendritic HK cells and exposed to ON 01910.Na. As expected co-culture with HK cells substantially increased the viability of CLL cells. This effect was completely abrogated by treatment with ON 01910.Na with similar cytotoxic efficacy between co-culture and medium alone. In conclusion, ON 01910.Na has been identified as a highly specific drug with anti-mitotic activity that induces apoptosis and reduces viability of CLL cells even when cultured in conditions that mimic its stromal microenvironment. Chapman *et al.* deciphered that ON 01910.Na acts through inhibition of the PI3K/AKT pathway and triggers an oxygen-stress induced response, both which ultimately lead to cell death. The results of this and other studies have led to the commencement of the first clinical trial with ON 01910.Na in patients with lymphoid malignancies and have highlighted the importance of pre-clinical studies that help to characterize the underlying mechanisms of drug-induced anti-cancer activities.