



February 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

We are pleased to announce that registration and abstract submission for the DIR Scientific Retreat will be open this week and close March 2nd. While the exact venue is not certain, each of our potential sites is interesting and we are planning the best retreat ever. Watch for an e-mail very soon that will give you all the information you need.

When you are looking for a job, many employers will want to know that you are capable of supervising other people. Mentoring a summer student is a great way to begin to get this supervisory experience. Right now, each PI is getting many requests for summer students, and so please talk to your PI and collaborate on selecting one that will help your research and provide you with valuable mentoring experience.

***The Future of the
Biomedical Workforce***

By Herbert Geller, Ph.D.

**9th Annual NHLBI DIR
Scientific Retreat**

March 28-30, 2012

Location: TBD

Keynote Speaker:

-Dr. Nancy Andrews, Duke

Scientific Speakers:

-Dr. Alexandra Newton, UCSD

-Dr. Zena Werb, UCSF

**An email with the abstract
submission website will be sent
this week.**

Earlier this year, the Advisory Committee to the NIH Director began an effort to assess the future needs for biomedical research personnel. The first step in this process was collecting information on several issues that relate to graduate and postdoctoral training as well as future careers for trainees. A public comment period was established where anyone could go on line to comment on several issues, including of special interest to NIH Fellows and Investigators: The balance between supply, including the number of domestic and foreign trained PhDs and post-docs, and demand, i.e. post-training career opportunities.

- Characteristics of PhD training
- Characteristics of clinician-research training including issues such as
 - The balance between MDs and MD/PhDs

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

Recent Publications by NHLBI Fellows

- Anzinger, J. J.**, Chang, J., Xu, Q., Barthwal, M. K., Bohnacker, T., Wymann, M. P., & Kruth, H. S. (2012). Murine bone marrow-derived macrophages differentiated with GM-CSF become foam cells by PI3K gamma-dependent fluid-phase pinocytosis of native LDL. *J. Lipid Res.* 53, 34-42.
- Begum, N., **Shen, W. X.**, & Manganiello, V. (2011). Role of PDE3A in regulation of cell cycle progression in mouse vascular smooth muscle cells and oocytes: implications in cardiovascular diseases and infertility. *Curr. Opin. Pharmacol.* 11, 725-729.
- Cherkasova, E.**, Malinzak, E., Rao, S., **Takahashi, Y.**, Senchenko, V. N., Kudryavtseva, A. V., Nickerson, M. L., Merino, M., Hong, J. A., Schrupp, D. S., Srinivasan, R., Linehan, W. M., Tian, X., Lerman, M. I., & Childs, R. W. (2011). Inactivation of the von Hippel-Lindau tumor suppressor leads to selective expression of a human endogenous retrovirus in kidney cancer. *Oncogene* 30, 4697-4706.
- Dagur, P. K.**, Biancotto, A., Wei, L., Sen, H. N., Yao, M., Strober, W., Nussenblatt, R. B., & McCoy, J. P. (2011). MCAM-expressing CD4(+) T cells in peripheral blood secrete IL-17A and are significantly elevated in inflammatory autoimmune diseases. *Journal of Autoimmunity* 37, 319-327.
- Kim, I., **Kim, Y. J.**, **Metais, J. Y.**, Dunbar, C. E., & Larochelle, A. (2012). Transient silencing of PTEN in human CD34(+) cells enhances their proliferative potential and ability to engraft immunodeficient mice. *Exp. Hematol.* 40, 84-91.
- Meguro, A., **Ozaki, K.**, Hatanaka, K., Oh, I., Sudo, K., Ohmori, T., Matsu, H., Tatara, R., **Sato, K.**, Sakata, Y., Nakae, S., Leonard, W. J., & Ozawa, K. (2011). Lack of IL-21 signal attenuates graft-versus-leukemia effect in the absence of CD8 T-cells. *Bone Marrow Transplant* 46, 1557-1565.
- 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. *J Cell Biol.* 192(2):321-34.
- Nacif, M. S., Turkbey, E. B., Gai, N., Nazarian, S., van der Geest, R. J., Noureldin, R. A., Sibley, C. T., **Ugander, M.**, Liu, S. T., Arai, A. E., Lima, J. A. C., & Bluemke, D. A. (2011). Myocardial T1 Mapping With MRI: Comparison of Look-Locker and MOLLI Sequences. *J. Magn. Reson. Imaging* 34, 1367-1373.
- Pisitkun, T., Hoffert, J. D., **Saeed, F.**, & Knepper, M. A. (2012). NHLBI-AbDesigner: an online tool for design of peptide-directed antibodies. *Am. J. Physiol. Cell Physiol.* 302, C154-C164.
- Vaisman, B. L., Demosky, S. J., Stonik, J. A., **Ghias, M.**, Knapper, C. L., Sampson, M. L., **Dai, C. L.**, Levine, S. J., & Remaley, A. T. (2012). Endothelial expression of human ABCA1 in mice increases plasma HDL cholesterol and reduces diet-induced atherosclerosis. *J. Lipid Res.* 53, 158-167.

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

THE SCIENCE BEAT

By Daniel Kraushaar, Ph.D.

Cherkasova, E., Malinzak, E., Rao, S., Takahashi, Y., Senchenko, V. N., Kudryavtseva, A. V., Nickerson, M. L., Merino, M., Hong, J. A., Schrupp, D. S., Srinivasan, R., Linehan, W. M., Tian, X., Lerman, M. I., & Childs, R. W. (2011). Inactivation of the von Hippel-Lindau tumor suppressor leads to selective expression of a human endogenous retrovirus in kidney cancer. *Oncogene* 30, 4697-4706.

Around 50,000 new cases of kidney cancer are diagnosed in the US alone each year. Kidney cancer is an unusual cancer in that it is susceptible to an immune response. In this sense it is not surprising that immunotherapies are considered standard treatment options for patients with advanced metastatic kidney cancer. Despite immunotherapies, only few target antigens that mediate T-cell recognition and initiate kidney tumor regression have been identified in the past. One of them, the human endogenous retrovirus type E (HERV-E), has been the focus of the recent NHLBI study by Cherkasova *et al.* Endogenous retroviruses represent sequences of the human genome that are remnants of exogenous infections that have been passed on over many generations. Due to negative selection HERVs become silenced or mutated, but in a number of tumors including renal cell carcinomas, HERVs may become reactivated and elicit antitumor immunity.

Analyzing primary renal cell carcinoma (RCC) tumors, the study revealed that HERV-E is specifically detected in the 'clear cell' or ccRCC histological kidney tumor subtype and is expressed in the earliest and late stages of carcinogenesis. Gene expression analysis further showed that the tumor suppressor gene 'von Hippel-Lindau' (VHL) is inactivated in all ccRCC cell lines in most cases owing to mutations or deletions in one of the three VHL exons. Re-expression of transgenic VHL in VHL-deficient ccRCC cell lines significantly suppressed the expression of HERV-E and suggested that inactivation of VHL is a requirement for proviral HERV-

E expression. Bisulfite sequencing of cell lines that do not express HERV-E transcripts including those of other cancer types and normal tissues revealed that the 5'LTR region of HERV-E transcripts was hypermethylated. On the other hand, VHL-deficient ccRCC cell lines that express HERV-E displayed a hypomethylated 5'LTR. Hence, DNA methylation appears to be an important mechanism for keeping HERV-E silent and also suggests that VHL expression is accompanied by changes in chromatin that allow for HERV-E expression. The authors continue their investigation by testing the role of a candidate transcription factor named HIF-2 α in the regulation of proviral expression. All VHL-deficient cell lines exhibited elevated expression of HIF-2 α showing a negative correlation between it and VHL expression. Knockdown of HIF-2 α in ccRCC cell lines reduced the expression of HERV-E, demonstrating a direct functional link between HIF-2 α and HERV-E expression, whereby HIF-2 α activates HERV-E transcription. Further support for this was gleaned from HIF-2 α alpha binding studies using chromatin immunoprecipitation with an antibody against HIF-2. HIF-2 bound to HIF response elements (HREs) within the 5'LTR of HERV-E transcripts. Comparisons between cell lines with varying levels of DNA methylation at binding sites revealed that HIF-2 α only bound at hypomethylated 5'LTRs. In consequence, treatment of ccRCC cell lines that contained relatively high levels of DNA methylation at the HERV-E locus, with a demethylating agent or a deacetylase inhibitor resulted in upregulation of HERV-E. Therefore HERV-E expression levels show direct dependence on a permissive chromatin state that allows for binding of transcription factors such as HIF-2 α .

In summary, Cherkasova *et al.* elucidated the mechanisms by which proviral HERV-E expression is regulated during kidney carcinogenesis. As such, inactivation of the tumor suppressor gene VHL, will result in aberrant HERV-E expression. Studies such as this, will improve our understanding of how oncogenic expression of antigens is controlled and will prove useful for kidney cancer therapies that aim at boosting human immunity.

New NHLBI Fellows

Erin West, Ph.D., is a new Post Doc fellow in the Immunology Center under Dr. Warren Leonard. Dr. West earned her Ph.D. in Immunology and Molecular Pathogenesis from Emory University in Atlanta, Georgia.

She was the recipient of the 2011 Immunology and Molecular Pathogenesis Student of the Year award. Dr. West is currently researching the role of the cytokine TSLP on CD4 and CD8 T cell differentiation and homeostasis.



Christopher Hourigan, Ph.D., is a new Clinical Fellow in the Hematology Branch under Dr. Charles Bolan. Dr. Hourigan earned his Ph.D. in Clinical Medicine from the University of Oxford. He is a former

research fellow of the Immunology and Immunotherapy Research program at Johns Hopkins. Dr. Hourigan's will be researching the human immune response to myeloid leukemias in long term survivors.



Alice Sun, Ph.D., is a Visiting Fellow in the Biochemistry and Biophysics Center under Dr. Keir Neuman. Dr. Sun earned her Ph.D. in Biomedical Engineering from University of Michigan, Ann Arbor, Michigan. She received the 2011 Rackham Student Travel Grant from the University of Michigan. Dr. Sun's current research project is the study of single-molecule human RecQ helicases using magnetic tweezers.

- Career development of clinician-researchers
 - Recommendations for changes to the curricula for training clinician-researchers.
- Length of Post-doctoral training.
- Possibilities for professional/staff scientist positions and the level of training required for such positions (e.g. PhD or MSc degrees).
- Issues related to the attractiveness of biomedical research careers (e.g. salary, working conditions, availability of research funding)

A report was issued on January 31st that summarized the feedback on these issues, and also noted that several other issues were raised by the respondents:

- Funding. Uncertainty and lack of funding, distribution of funding, restricted paylines, success rates, and excessive competition
- Multi-disciplinary. Need for multi/inter/ trans-disciplinary research training to prepare individuals for a wide range of academic and non-academic career opportunities
- Salary. Inadequate compensation and benefits

- Length of Training. Amount of training time too long to be feasible for majority
- Non-US Citizens. Foreign students and post-doctoral fellows
- Career appeal. Working conditions (e.g. heavy workload, perception of being perceived as cheap labor, long work hours)
- Mentoring. Quality of career development and the need for pre-college preparation
- Diversity. Under-represented minority post-doctoral, fellows and junior faculty.

Commenters were asked to rank these issues in order of importance. Not unexpectedly, Supply and Demand, the characteristics of Ph.D. Clinical, and Postdoctoral Training, and Biomedical Research Career Appeal were ranked the highest, followed by Diversity. This order of responses was the same overall or when the responders were individuals; interestingly, when the responders were representing institutions, Supply and Demand and Career Appeal were pushed down the list, suggesting that there may be a real dichotomy between current trainees and potential employers as to what the is-

ues are. Issues that are important to our trainees include:

Supply and Demand Many of the comments suggested that the system needs to be better balanced, either by reducing the number of graduate slots, reducing the number of trainees per PI, and perhaps increasing the number of permanent positions in science while reducing the number of trainees. Some commenters felt that the influx of foreign trainees was diminishing the opportunities for domestic applicants, but overall it was felt that these scientists ultimately benefit the US economy. Two recommendations were made to address these issues:

- Reduce the number of students and post-doctoral fellows supported, and improve awareness and understanding of the branching career path available to new scientists (supply-side).
- Increase total funding and revise current funding structures to promote wider distribution of funds (demand-side).

While there is no concerted effort to reduce the number of fellows in the DIR, the Office of Education is committed to providing opportunities for our

fellows to explore many different career paths other than bench research.

Postdoctoral Training Comments were made that the salary and benefits for Postdocs were, in general, inadequate. Other comments addressed the issue of the postdoctoral fellow being in a holding pattern, while others felt that it did not make sense to limit the number of years of postdoctoral training when permanent jobs are hard to find. Many commenters felt that more career transition awards would help move fellows to permanent jobs. Finally, there was a general consensus that most postdoctoral fellows do not engage in enough career development activities and that mentoring was not adequate. In response, these recommendations were made:

- Increase the availability and length of transition funding for senior post-doctoral fellows.
- Raise the NRSA post-doctoral stipend and mandate that all NIH-supported post-doctoral fellows (whether

directly or indirectly supported) receive this amount.

- Require better documentation and monitoring of training progress and career planning.

The DIR already pays stipends that are higher than the NRSA, and we endeavor to make sure that fellows are adequately rewarded. We also offer our fellows two options for transition awards: the K99/R00 which is open to all postdocs, and the K22, which is only open to NHLBI fellows; we have had a high degree of success with both mechanisms. Finally, the DIR is committed to continued monitoring of postdoctoral progress, and we are exploring new ways to do this, including the requirement that fellows file an individual development plan, an instrument that outlines their goals for the postdoctoral training period and allows for continued self-assessment.

Clinician Characteristics. Interestingly, the major issue here was that commenters felt that there is a decline

in the number of MD recipients conducting clinical research in academia. Many commenters agreed that this decline is due to the pressures they face to be profitable in clinical practice. This led to one predictable recommendation:

- Provide mechanisms to support protected time for clinician research.

The DIR and NIH are actively addressing this issue through the establishment of the Assistant Clinical Investigator Position as well as through the Clinical Research Scholars.

Finally, the other major issue was **Biomedical Research Career Appeal**. In general, this was considered important, but the proposed solutions are all contained within the other more general issues, such as low salary, long time until independence, and the competition for funding.

I urge you all to read the full report, which is available on the web at: http://acd.od.nih.gov/BWF_RFI.PDF

FARE Award

NHLBI intramural trainees are invited to submit applications for the annual NIH Fellows Award for Research Excellence (FARE) competition. Winners will receive recognition for their work**, present their work at a scientific meeting and the 2012 NIH Research Festival, and serve as judges for the next FARE competition. Application and abstracts must be submitted online between February 22 and March 22. Winners will be notified in June.

To apply for the award, go to: <https://www.training.nih.gov/felcom/fare>