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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.

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From the Director of the Office of Education

In last month's column, I wrote about how Grant Writing skills are transferable to many different kinds of writing. However, one of the major reasons to learn such skills it to actually write a grant, and I am happy to report that NHLBI set a record of 8 career transition grants, both K22 and K99, submitted in one deadline. NHLBI DIR has had an exceptionally high success rate for these applications, with almost all applications getting funded on the second try. So while the success rate is likely to drop because of the reduction in funding of NIH, these Career Transition Grants are still a great way to help you obtain an academic position.

Another form of grant writing is the Lenfant Fellowship program. This program, open to all fellows within the first two years at NHLBI, allows DIR postdocs to write an application that is identical to the NIH Ruth Kirschstein awards. The major difference is that, if you achieve a high priority score on your Lenfant application, your support continues from your lab's personnel budget, but you get an increase in your stipend at your next renewal. We will announce the results of the latest Lenfant competition in April, and the next deadline for submission will be sometime in June. If you are interested in submitting a Lenfant Fellowship application, watch for the opening announcement in your e-mail.

Too busy to think?

By Herbert M. Geller, Ph.D.

How busy are you? And is this good for your career? Many postdocs tell me that they are too busy in the lab to involve themselves in any other activity – that getting that next publication out is the most important thing for them and (perhaps) their lab chief. But is this true? And if so, is this the way to success?

While there is no question that hours in the lab can be important for success. Once, one of my colleagues told me that he was told by a security guard at Yale that he would be a successful scientist. When asked how he could predict this, the response was "I see you here a lot on nights and weekends". In fact, while he did work very hard at science, he was also an serious pianist and had many interests outside the lab. And his word did get published in the journals that we all respect. So while he was a dedicated scientist, he also knew that there are limits to how much time you can spend in the lab and that doing things other than lab work can actually enhance your productivity.

A story in the New York Times examined the effects of a reduced work week on productivity. A company in the Midwest decided that workers should work four days instead of five during the summer. What they found

was that productivity rose in the 32 summer hours as compared the 40 hours during the winter. A more recent article suggested that taking a 30 min break after 1.5 hours of work would similarly increase productivity.

Of course, scientific research is not producing widgets. We all know that research goes in cycles - the frustrating parts of getting an experiment going and doing the trouble shooting are followed by the rewards of actually collecting the data. Thus, once the experiment is working well, more hours at the bench might get you closer to the finish line, but more hours at the bench might not actually help you think through the issues that are stalling a project.

Another aspect is that there are just so many waking hours you have available. And your career is dependent upon learning skills other than simply writing papers - communication, both formal and informal, networking, and being aware of opportunities are all important and can be terribly short changed if all you do is stay in the lab.

As we approach nicer weather, I encourage you all to take advantage of it. For those who have never experience it, I suggest that the Cherry Blossom Festival, scheduled for the end of this month, is a great way to begin. In fact, the best Cherry Blossom viewing is in Bethesda, in the Kenwood neighborhood, not far from NIH. I hope to see you there!

NHLBI DIR Seminar Series

Guillermo Oliver, Ph.D.
Dept. of Genetics
St. Jude Children's Research Hospital
"How to Build a Lymphatic Vasculature in the Mammalian Embryo"

Tuesday, March 12
11:00 AM - 12:00 PM
Building 50, Room 1227/1233

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Miles Wilkinson, Ph.D.
Professor, Department of Reproductive Medicine
University of California, San Diego
"RNA Surveillence, MicroRNAs, and the Brain"

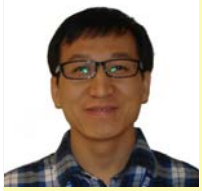
Tuesday, March 26
11:00 AM - 12:00 PM
Building 40, Room 1201/12303

Sponsored by the Office of Education
For more information, contact DIREducation@nhlbi.nih.gov

New NHLBI Fellows

Hiroyuki Kawagishi, Ph.D., is a new Visiting Fellow in the Center for Molecular Medicine under Dr. Toren Finkel. Dr. Kawagishi earned his Ph.D. from Nagoya University. Prior to the NIH, Dr. Kawagishi was a Research Fellow at the National Center for Geriatrics and Gerontology in Japan. His initial research project at the NHLBI is the analysis of biological function of primary cilia and relationship to cell metabolism.

Heather De Bari, Ph.D., is a new IRTA fellow in the Systems Biology Center under Dr. Robert Balaban. Dr. De Bari earned her Ph.D. in Biochemistry and Molecular Biology at SUNY Upstate Medical University. Her initial research project at the NHLBI is monitoring spectroscopic changes that are specific to cytochrome oxidase in whole mitochondria, and relating those changes to oxygen consumption.



Wenfei Jin, Ph.D., is a new Visiting Fellow in the Systems Biology Center under Dr. Keji Zhao. Dr. Jin earned his Ph.D. in Computational Biology at the University of Chinese Academy of Sciences. Prior to the NIH, Dr. Jin was a Research Associate at the Shanghai Institutes for Biological Services. His initial research project at the NHLBI is to study the histone modification and turnover of H2A.Z and H3.3.

Adrienne Campbell, Ph.D., is a new Visiting Fellow in the Cardiovascular Pulmonary Branch under Dr. Robert Lederman. Dr. Campbell earned her Ph.D. in Medical Physics and Bioengineering at University London College. Dr. Campbell was the recipient of the Commonwealth Scholarship in 2009. Her initial research project at the NHLBI is Low SAR (specific absorption rate, i.e. heating) imaging of passive devices for MR-guided inventions.

Christopher Jones, Ph.D., is a new IRTA Fellow in the Biochemistry and Biophysics Center under Dr. Adrian Ferre-D'Amare. Dr. Jones earned his Ph.D. in Biochemistry from Ohio State University. Dr. Jones was the recipient of the Edward F. Hayes Graduate Research Forum Award in Mathmatical and Physical Sciences. His initial research project at the NHLBI is the crystallization of an aminoglycoside-sensing RNA that senses the presence of antibiotics and thereby enables bacteria to destroy or export them.

Jacob Bitterman, Ph.D., is a new IRTA fellow in the Genetics and Developmental Biology Center under Dr. Jay Chung. Dr. Bitterman earned his Ph.D. in Pharmacology at Weill Cornell Medical College. Prior to the NIH, Dr. Bitterman was a TA at Weill Cornell while completing his Ph.D. coursework. His initial research project at the NHLBI is exploring whether HSP90 knockdown, or mutation to eliminate a phosphorylation site affects cAMP production.

Kleber Yotsumoto Fertin, Ph.D., is a new Visiting Fellow in the Hematology Branch under Dr. Greg Kato. Dr. Fertin earned his Ph.D. in Medical Pathophysiology School of Medicine at University of Campinas, Brazil. Dr. Fertin was the recipient of the 2012 American Society of Hematology Abstract Achievement Award. His initial project at the NHLBI is the optimization of an imaging flow cytometry assay for sickled cells in human blood samples to investigate mechanisms leading to overt sickling in an attempt to identify targets for therapy development.

Recent Publications by NHLBI Fellows

Baird N. J. and Ferre-D'Amare A. R. (2013) Modulation of quaternary structure and enhancement of ligand binding by the K-turn of tandem glycine riboswitches. *Rna-A Publication of the Rna Society* 19, 167-176.

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Castaing J. P., **Nagy A.**, Anantharaman V., Aravind L. and Ramamurthi K. S. (2013) ATP hydrolysis by a domain related to translation factor GTPases drives polymerization of a static bacterial morphogenetic protein. *Proc. Natl. Acad. Sci. U. S. A* 110, E151-E160.

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Kanter M. M., Kris-Etherton P. M., Fernandez M. L., **Vickers K. C.** and Katz D. L. (2012) Exploring the Factors That Affect Blood Cholesterol and Heart Disease Risk: Is Dietary Cholesterol as Bad for You as History Leads Us to Believe? *Advances in Nutrition* 3, 711-717.

Konig G., Bruckner S. and Boresch S. (2013) Absolute Hydration Free Energies of Blocked Amino Acids: Implications for Protein Solvation and Stability. *Biophys. J.* 104, 453-462.

Kumkhaek C., Aerbajinai W., Liu W., Zhu J., Uchida N., Kurlander R., Hsieh M.M., Tisdale J.F., Rodgers G.P. (2013) MASL1 Induces Erythroid Differenciation in Human Erythropietin-Dependent CD34+ cells through the Raf/MEK/ERK pathway. *Blood.*

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Ma J. H., Edlich F., **Bermejo G. A.,** Norris K. L., Youle R. J. and Tjandra N. (2012) Structural mechanism of Bax inhibition by cytomegalovirus protein vMIA. *Proc. Natl. Acad. Sci. U. S. A* 109, 20901-20906.

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Nagy A., Takagi Y., **Billington N.,** Sun S. A., Hong D. K. T., Homsher E., Wang A. B. and Sellers J. R. (2013) Kinetic Characterization of Nonmuscle Myosin IIB at the Single Molecule Level. *J. Biol. Chem.* 288, 709-722.

Oubrahim H., **Wong A.,** Wilson B. A. and Chock P. B. (2013) Mammalian Target of Rapamycin Complex 1 (mTORC1) Plays a Role in Pasteurella multocida Toxin (PMT)-induced Protein Synthesis and Proliferation in Swiss 3T3 Cells. *J. Biol. Chem.* 288, 2805-2815.

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Sochacki K. A., Larson B. T., Sengupta D. C., Daniels M. P., Shtengel G., Hess H. F. and Taraska J. W. (2012)

THE SCIENCE BEAT

By Zhiyun Ge, Ph.D.

Ma J. H.,Edlich F., **Bermejo G. A.,** Norris K. L., Youle R. J. and Tjandra N. (2012) Structural mechanism of Bax inhibition by cytomegalovirusproteinvMIA. *Proc. Natl. Acad. Sci. U. S. A* 109, 20901-20906.

Apoptosis, or programmed cell death, is a process that occurs in multicellular organisms. Apoptosis plays an essential role in the development and maintenance of the organism, as well as the host's defense against invading pathogens. The process of apoptosis is usually initiated by either extracellular or intracellular stress and is tightly regulated. The human protein Bax plays an essential role in apoptosis since its activation commits the cell invariably to apoptosis. Under normal conditions, Bax exists in both cytosolic and mitochondria-associated forms. Upon activation by proapoptotic proteins, Baxtranslocates to the mitochondria and undergoes dramatic conformational changes, which allows it to insert into the mitochondrial outer membrane (MOM) and to oligomerize.This in turn causes the release of cytochrome c that initiates the apoptotic signaling cascade. Bax function can be regulated by the Bcl-2 family proteins, including both pro- and antiapoptotic proteins.

Since apoptosis defends the host organism against infection, many viruses have developed mechanisms to inhibit host apoptosis. For instance, the human cytomegalovirus, encodes an antiapoptotic protein vMIA (viral mitochondria-localized inhibitor of apoptosis) that inhibits Baxand ultimately apoptosis. Interestingly, unlike the Bcl-2 family antiapoptoticproteins, vMIA recruits Bax to the mitochondria instead of inhibiting the mitochondrial localization of Bax. Although the interactions between Bax and the Bcl-2 proteins have been characterized, the molecular detains of the Bax-vMIA interaction remains unclear.

Bax adopts a α-helical structure in solution and previous studies have shown that helix α-9 is essential for the mitochondrial localization of Bax in normal cells. However, in cytomegalovirus-infected cells, the recruitment of Bax is via vMIA, indicating that vMIA binds Bax at a unique site to exert its antiapoptotic activity. To confirm this prediction, Ma et al. determined the structure of the complex between Bax and vMIA'sBax-binding domain (vMIA-BBD), using solution NMR. The BBD of vMIA used in this study encompasses residues 131-150 of the vMIA protein. The authors then mapped the vMIA-binding surface on Bax by the perturbation of signals from the heteronuclear single-quantum coherence (HSQC) spectrum of Bax when vMIA-BBD was added to Bax. The analysis revealed four regions in Bax(E44-D48, D84-D86, C126-T127, and a fourth region containing L181, A183, and I187-G192) that are close in space and form a distinct surface for vMIA-BBD binding. The authors observed rapid aggregation of Bax after the addition of vMIA-BBD, which allows only short experiments like the HSQC to be performed. As a result, HSQC-based paramagnetic relaxation enhancements (PREs) are required to accurately elucidate the exact position of vMIA-BBD relative to Bax. The results revealed that vMIA-BBD binds at a site that is previously unknown, which is the opposite to the BH1 and BH2 domain s of Bax. And the N-terminus of vMIA-BBD is close to the BH3 domain of Bax. The vMIA-BBD peptide is located in a pocket form by Bax helices α3-α4 and α5-α6. The residues V129, P130, L132, and I133 of Bax form a hydrophobic patch, which interacts with the L143 from vMIA-BBD. Further mutational analysis confirmed the above-mentioned residues as crucial residues for Bax-vMIA-BBD interaction. Finally, the authors assessed the effects of the mutations in the binding surface between Bax and vMIA-BBD in human cells. The subcellular localization of Bax and the release of cytochrome c upon apoptosis induction were quantified. The results suggest that vMIA binding to Bax prevents the unraveling of Bax that is need for its mitochondrial insertion and oligomerization, thus ultimately prevents apoptosis. In summary, this paper not only provides valuable insights in the function Bax in normal cells, but also establishes the basis for the development of drugs against human cytomegalovirus.

FARE is back for FY 2014!

NIH intramural trainees are invited to submit applications for the annual Fellows Award for Research Excellence (FARE) competition.

Winners will present their work at the 2013 NIH Research Festival, and serve as judges for the next FARE competition. Application and abstracts deadline is March 20.

For more information, please visit:
https://www.training.nih.gov/felcom/fare

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