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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

The Office of Education is on the move! This is to be taken literally, as our new home, at least for the next few years, is in room 7N218, on the 7th floor of building 10. For those of you coming from Bldg. 50, this means you turn right on the North corridor after exiting the elevators rather than turning left. Please come and visit us in our new home.

Because of the NIH travel budget issues, our DIR Scientific Retreat on May 20 will have a new format, in which we feature more oral presentations by NHLBI fellows. The oral presentations will be chosen from the submitted abstracts and we hope to have presentations from each lab and branch. The decision by the Fellows Advisory Committee was made to maximize the time we have for interactions between NHLBI scientists, both in formal and informal interactions. The web site for registration and abstract submission will be open in March, so plan to send in your abstract soon!

The Ronald Reagan Building and International Trade Center

• Washington, DC •

Abstract submission opens next month

Grant Writing - A Transferable Skill

By Herbert M. Geller, Ph.D.

Just now, the largest number of NHLBI Fellows are about to submit their applications for a Career Transition Award. In parallel, we have the largest number of Lenfant Fellowship applications for review this cycle. While success at these grant writing would commonly be measured by getting a high priority score and funding, the skills you learn in writing a grant are directly transferable to many other kinds of writing.

The major purpose of a grant application is to convince the reviewer that you have a good idea and a way to approach it that will solve an important problem. There are many parallels to this situation. Thus, in industry you will often need to write a memorandum to your supervisor (or even higher) to justify a line of research that you feel will yield important benefits

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New NHLBI Fellows

Majid Kazemian, Ph.D., is a new Visiting Fellow in Immunology Center under Dr. Warren Leonard. Dr. Kazemian earned his Ph.D. in Computer Science at the University of Illinois at Urbana-Champaign. Prior to the NIH, he was a Research Assistant in the Department of Computer Science laboratory. Dr. Kazemian's initial research project at the NHLBI is analyzing data from whole exome sequencing.

Chen Glait-Santar, Ph.D., is a new Visiting Fellow in the Hematology Branch under Dr. Cynthia Dunbar. Dr. Glait-Santar earned her Ph.D. from the department of Cell and Developmental Biology at Sackler Faculty of Medicine from Tel-Aviv University. Prior to the NIH, she was a Postdoctoral Fellow at Weizmann Institute of Science. Dr. Glait-Santar's initial research project at the NHLBI is exploring the hematopoietic-stem cells niche in pathologic cases.

Scott Gordon, Ph.D., is a new IRTA Fellow in the Cell Biology and Physiology Center under Dr. Alan Remaley. Dr. Gordon earned his Ph.D. In Pathobiology and Molecular Medicine at the University of Cincinatti. Prior to the NIH, he was a teaching assistant at SUNY College at Brockport Department of Chemistry where he recieved the 2009 Academic Excellence Award for outstanding academic achievement in the Pathology and Molecular Medicince graduate program coursework. Dr. Gordon's initial research project at the NHLBI is developing novel mimetic peptides to modulate plasma lipid levels.

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

US Pharmacopeia– http://www.usp.org/

Center for Innovative Technology – http://www.cit.org/

Cont'd, page 1 to the company. In the area of nonprofit organizations, you may need to write an opinion piece that convinces the general public to support your cause. And any time you are applying for a job, you need to convince the hiring official that you are the best fit for the job.

Each of the above situations is an example of where clear, concise, focused writing will help your cause. My standard advice to grant writers is "if your mother can't understand what you are trying to do, then it will be hopeless for your intended reader". This is because you, the writer, are clearly the world's expert in the field, so you will not be able to find a reader who is equally familiar with your work or your ideas. A corollary of this, according to Dr. Barry Hoffer, former NIAAA Scientific Director is "you can never talk down to a reviewer".

Given all of the reasons above, even if you do not intend to go into an academic situation where grant writing is required, participating in the Office of Education Grant Writing Workshop and/or writing a Lenfant Grant application is going to payoff whatever your chosen career. I hope to see you all there!

Recent Publications by NHLBI Fellows

Sviridov D. O., Andrianov A. M., Anishchenko I. V., Stonik J. A., Amar M. J. A., Turner S. and Remaley A. T. (2013) Hydrophobic Amino Acids in the Hinge Region of the 5A Apolipoprotein Mimetic Peptide are Essential for Promoting Cholesterol Efflux by the ABCA1 Transporter. *J. Pharmacol. Exptl. Ther.* 344, 50-58.

Forman D. E., Fleg J. L., Kitzman D. W., Brawner C. A., Swank A. M., McKelvie R. S., Clare R. M., Ellis S. J., Dunlap M. E. and Bittner V. (2012) 6-Min Walk Test Provides Prognostic Utility Comparable to Cardiopulmonary Exercise Testing in Ambulatory Outpatients With Systolic Heart Failure. *J. Am. Coll. Cardiol.* 60, 2653-2661.

Kotani K., Sakane N., **Ueda M.,** Mashiba S., Hayase Y., Tsuzaki K., Yamada T. and Remaley A. T. (2012) Oxidized high-density lipoprotein is associated with increased plasma glucose in non-diabetic dyslipidemic subjects. *Clinica Chimica Acta* 414, 125-129.

Plotnikov S. V., Pasapera A. M., Sabass B. and Waterman C. M. (2012) Force Fluctuations within Focal Adhesions Mediate ECM-Rigidity Sensing to Guide Directed Cell Migration. *Cell* 151, 1513-1527.

Madenspacher J. H., Azzam K. M., Gong W. H., Gowdy K. M., Vitek M. P., Laskowitz D. T., Remaley A. T., **Wang J. M.** and Fessler M. B. (2012) Apolipoproteins and Apolipoprotein Mimetic Peptides Modulate Phagocyte Trafficking through Chemotactic Activity. *J. Biol. Chem.* **287,** 43730-43740.

Malide D., **Metais J. Y.** and Dunbar C. E. (2012) Dynamic clonal analysis of murine hematopoietic stem and progenitor cells marked by 5 fluorescent proteins using confocal and multiphoton microscopy. *Blood* 120, E105-E116.

Busser B. W., Huang D., **Rogacki K. R., Lane E. A.,** Shokri L., Ni T., **Gamble C. E.**, Gisselbrecht S. S., Zhu J., Bulyk M. L., Ovcharenko I. and Michelson A. M. (2012) Integrative analysis of the zinc finger transcription factor Lame duck in the Drosophila myogenic gene regulatory network. *Proc. Natl. Acad. Sci. U. S. A* 109, 20768-20773.

Park K. S., **Kim K. K.**, Piao Z. H., Kim M. K., Lee H. J., Kim Y. C., Lee K. S., Lee J. H. and Kim K. E. (2012) Olfactomedin 4 suppresses tumor growth and metastasis of mouse melanoma cells through downregulation of integrin and MMP genes. *Molecules and Cells* 34, 555-561.

Tao P., Hodoscek M., Larkin J. D., Shao Y. H. and Brooks B. R. (2012) Comparison of Three Chain-of-States Methods: Nudged Elastic Band and Replica Path with Restraints or Constraints. *J. Chem. Theory. Comput.* 8, 5035-5051.

Lee C., Hu J. Q., Ralls S., Kitamura T., Loh Y. P., Yang Y. Q., Mukouyama Y. and Ahn S. (2012) The Molecular Profiles of Neural Stem Cell Niche in the Adult Subventricular Zone. *Plos One* 7.

NHLBI DIR Seminar Series

Suzanne Pfeffer, Ph.D.

Professor of Biochemistry

Stanford University

"Membrane trafficking: Receptor and cholesterol import and export"

Tuesday, February 12th

11:00 AM - 12:00 PM

Building 50, Room 1227/1233

Sponsored by the Office of Education

For more information, contact DIREducation@nhlbi.nih.gov

THE SCIENCE BEAT

By Dinari Harris, Ph.D.

Sviridov D. O., Andrianov A. M., Anishchenko I. V., Stonik J. A., Amar M. J. A., Turner S. and Remaley A. T. (2013) Hydrophobic Amino Acids in the Hinge Region of the 5A Apolipoprotein Mimetic Peptide are Essential for Promoting Cholesterol Efflux by the ABCA1 Transporter. *J. Pharmacol. Exptl. Ther.* 344, 50-58.

Heart disease remains the leading cause of death in the United States. It has been found that plasma levels of high density lipoprotein (HDL) are negatively correlated with the incidence of atherosclerosis. However, there are beneficial effects of HDL on atherosclerosis and these effects have largely been attributed to its major protein, apolipoproteinA-I (apoA-I). Cholesterol efflux is the key step of reverse cholesterol transport and has become a therapeutic target against atherosclerosis. In particular, α-helical apoA-I is involved in the reverse cholesterol transport by facilitating two important steps in cholesterol transport: (1) stabilizing the HDL particle structure; and (2) interacting with the ABCA1 transporter. Use of apoA-I as a therapeutic intervention for atherosclerosis has been hampered by the fact that apoA-I is a large protein that is difficult to administer and expensive to manufacture. As a result of such an important role of apoA-I, more recently apolipoprotein mimetic peptides have become a target for pharmacologic development in the development of therapeutic agents for human atherosclerosis. One potent example is the bihelical apo-I mimetic peptide 5A, which was found to have significant anti-inflammatory and anti-atherogenic effects, increased HDL formation, increased cholesterol efflux, the conversion of pro-inflammatory HDL to anti-inflammatory HDL, and reduced lipoprotein oxidation.

ApoA-I mimetic peptides, like 5A have an amphipathic α-helical structure that recapitulates the secondary structure of the native apoA-I protein, which contains 10 amphipathic α helices. Amphipathic α helices, which are defined as having opposing polar and nonpolar faces oriented along the long axis of the helix, are an important structural motif of apolipoproteins(and mimetic peptides) that facilitate interactions with lipids. In ApoA-I the last helix is the most hydrophobic and critical in the ability of apoA-I to efflux cholesterol by the ABCA1 transporter. It has been proposed that during cholesterol efflux the last hydrophobic helix, which is largely excluded from the helical bundle and surface-exposed, makes the first critical contact with the lipid microdomains created by the ABCA1 transporter. Similar to the full-length protein, apoA-I mimetic peptides that contain amphipathic helices promote cholesterol efflux from cells by ABCA1-dependent pathway. The work by Sviridov *et al.* addressed the related question of how the apolipoprotein mimetic peptide 5A initially interacts with this ABCA1 transporter during cholesterol efflux. Using a combination of simulated annealing analysis and molecular dynamics, they modeled the lipid-free 5A peptide and confirmed that the structure does form a rigid bihelical amphipathic structure. More importantly, these two high affinity lipid α-helices, in the absence of lipids, is predicted to bury the hydrophobic faces of the two helices toward each other, therefore, shielding the majority the hydrophobic residues and stabilizing the entire structure. This bihelical structure was joined by an important hinge region which contains two essential hydrophobic residues predicted to be highly surface-exposed. Sviridov *et al.* hypothesized that the surface-exposed hydrophobic residues in the hinge region, phenylalanine at position 18 (F-18) and tryptophan at position 21 (W-21) play an important role in the initial interaction of the peptide with lipids similar to that proposed for the surface-exposed hydrophobic residues in the last helix of apoA-I.

To test the importance of the surface-exposed hydrophobic residues in the hinge of the ApoA-I mimetic peptide 5A, Sviridov *et al.* mutated these two hydrophobic residues (F-18 and W-21) to alanine (A; because it is uncharged/less hydrophobic) or glutamic acid (E; because it is charged) and monitored the effects on subsequent lipid binding and cholesterol efflux by the ABCA1 transporter. Using the series of 5A peptide analogs with mutations in the hinge regions, they observed that only the peptides that contain hydrophobic amino acids in either of the two positions were able to readily bind and solubilize phospholipid vesicles. In contrast, substitution of a charged residue in the hinge region almost completely blocked the ability of the peptide to bind phospholipid**s**. Next, Sviridov *et al.* tested the ability of the 5A peptide analogs to promote cholesterol efflux by the ABCA1 transporter. The pattern of cholesterol efflux by the 5A analogs was similar to the results from lipid binding assays, showing that cholesterol efflux was almost completely inactive when the peptide contained an E at either hinge position. In fact, they observed a direct correlation between the ability of the 5A peptide analog to bind phospholipids and the ability to efflux cholesterol by the ABCA1 transporter. Furthermore, work in mice, also confirmed the essential role of the hydrophobic residues in the hinge of the 5A peptide. Intravenous injection of 5A peptide analogs in mice increased plasma-free cholesterol and triglycerides only when the two hinge region residues were hydrophobic.

Overall the main finding from this study is that, in the case of bihelical amphipathic peptides like 5A, the hydrophobicity of residues in the hinge region appears to be critical in their ability to efflux cholesterol by the ABCA1 transporter. In addition, the work by Sviridov *et al* shows how experimental and computational studies can be combined to aid in the rational design of therapeutic agents for cardiovascular disease.