

Office of Education
Division of Intramural Research

Fellows Newsletter

March 2014

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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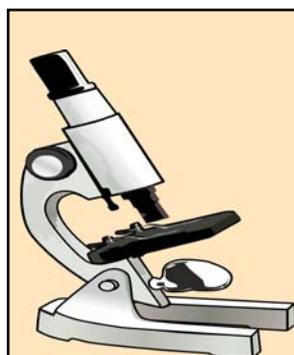
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From the Director of the Office of Education

March certainly came in like a lion! But the official start of Spring is less than 3 weeks away, so we can be sure that the snow will disappear soon. The OE and the Fellows Advisory Committee have several events planned for March, including the Career Development Seminar Series, the Tenure Track Seminar Series, and the St. Patrick's Day Dessert Party. We hope to see you all there.

Below you will find an announcement for "NHLBI DIR Research Day" to be held at Natcher Auditorium on June 6th. As you can see below, we've changed the name to accurately describe the purpose - a day to celebrate the research going on in DIR. Because it's on campus, we are encouraging posters from all the scientists in DIR - from postdocs to staff scientists and staff clinicians. The web site opens on April 1, so start writing your abstract!



NHLBI DIR Research Day 2014

June 9th

Natcher Conference Center and Auditorium

Registration opens April 1st

Meet the New Fellows



Dr. Chaochen Wang is a new Research Fellow in the Systems Biology Center under Dr. Keji Zhao. Dr. Wang earned his Ph.D. at the Chinese Academy of Sciences. His initial project at NIH is focusing on identifying synergetic factors of two histone modifiers Ezh2 and UTX during T cell differentiation.



Dr. Adam Brady is a new Postdoctoral Fellow in the Cell Biology and Physiology Center under Dr. Rosa Puertollano. Dr. Brady earned his Ph.D. at Cornell University. His initial project at NIH is to explore nutrient sensing and signaling at the lysosomes.

Sochacki, K. A., Shtengel, G., van Engelenburg, S. B., Hess, H. F., & Taraska, J. W. (2014). Correlative super-resolution fluorescence and metal-replica transmission electron microscopy. *Nat. Methods*. 10.

Photoactivated localization microscopy (PALM) is a superresolution technique that achieves a spatial resolution of the 10-20 nanometers, and is therefore suitable for the structural determination of macromolecules and the investigation of biological processes at close to the molecular scale. In PALM, sparse subsets of fluorescently labeled molecules are selectively switched on in a sequential manner. The activated molecules must lead to the consecutive emission of sufficient photons to enable localization of the molecule at nanometer-level precision coordinates before it is removed from the larger set of unactivated molecules by photobleaching. The process is repeated thousands of times until the molecular coordinates of all labeled molecules are obtained. The PALM image is a composite of all the single molecule coordinates and is two-dimensional. PALM, when combined with a single-photon multiphase interferometric scheme (iPALM), is able to provide sub-20-nm 3D protein localization with optimal molecular specificity. However, structural determination with PALM is limited by the labeling density and the lack of cellular context of the labeled molecules. Thus, PALM often is complemented by another technique called metal-replica transmission electron microscopy (TEM), which can determine the structural features of cells at 2nm resolution.

Previous efforts to reproducibly correlate super-resolution imaging data with EM at nanometer scale across large areas are hindered due to several reasons: fluorescent probes that are incompatible with EM sample preparation, structural deformation between imaging modes, and a lack of alignment markers that are stationary at the nanoscale. In this paper, the authors describe a technique that allows super-resolution 2D and 3D PALM imaging to be combined with metal-replica TEM, utilizing cell membrane grown on custom-designed gold nanoparticle-embedded coverslips. To validate this technique, the authors imaged single clathrin-coated structures

across the cell membranes and were able to achieve reproducible nanoscale correlation between PALM and TEM, as well as statistical analysis of protein localizations. Cells were grown on coverslips containing gold nanorod embedded under an ~20-nm layer of silica. The gold nanorods are visible in iPALM and extended above the flat surface of the coverslip, allowing them to be iPALM-TEM correlation markers in the xy plane. Proteins were marked by antibodies conjugated with Alesia Fluor 647 dyes (AF647) and membranes were labeled with myristoylated psCFP2, allowing for iPALM-TEM alignment in the z dimension. After mapping the PALM positions of AF647antibody-labeled clathrin heavy chain (clathrin-AF647) on the xy plane across the cell membrane onto the TEM images, a correlation between the localization of clathrin-AF647 obtained from PALM images and the 2D shapes of the clathrin-coated structures (CCSs) in TEM was established. Next, the authors aligned the iPALM z position of the myristoylated psCFP2 to the TEM membrane plane and attained correlation in the z dimension. Their results show that the shapes of the pits in the z dimension in iPALM images match the shapes of the corresponding pits in the TEM tomograms.

After validating the method with clathrin, the authors proceeded to apply the method on the endocytic protein epsin 1. Epsin colocalizes with clathrin and has been shown to be highly involved in multiple pathways such as membrane curvature formation, vesicle scission, etc.. However, the function of epsin in endocytosis remains unclear. The authors proposed that by revealing the physical location of epsin within clathrin structures at the nanometer scale, they would shed light onto epsin's role in endocytosis. First, the authors showed that epsin 1 is primarily located at the outer perimeter of most CCSs (81%). Only 18% of epsin1 was found in the center of CCSs. Then the authors constructed tomograms and analyzed the position of epsin 1 in the z dimen-

Recent Publications by NHLBI Fellows

Ahmad, S. M., Busser, B. W., Huang, D., Cozart, E. J., Michaud, S., Zhu, X., Jeffries, N., Aboukhalil, A., Bulyk, M. L., Ovcharenko, I., & Michelson, A. M. (2014). Machine learning classification of cell-specific cardiac enhancers uncovers developmental subnetworks regulating progenitor cell division and cell fate specification. *Development*. 141, 878-888.

Biesso, A., Xu, J., Muino, P. L., Callis, P. R., & Knutson, J. R. (2014). Charge Invariant Protein-Water Relaxation in GB1 via Ultrafast Tryptophan Fluorescence. *J. Am. Chem. Soc.* 136, 2739-2747.

Goswami, M., Hensel, N., Smith, B. D., Prince, G. T., Qin, L., Levitsky, H. I., Strickland, S. A., Jagasia, M., Savani, B. N., Fraser, J. W., Sadrzadeh, H., Rajkhowa, T., Ito, S., Jain, N. A., Battiwalla, M., Fathi, A. T., Levis, M. J., Barrett, A. J., & Hourigan, C. S. (2014). Expression of putative targets of immunotherapy in acute myeloid leukemia and healthy tissues. *Leukemia*. 10.

Gurnev, P. A., Yap, T. L., Pfefferkorn, C. M., Rostovtseva, T. K., Berezhkovskii, A. M., Lee, J. C., Parsegian, V. A., & Bezrukov, S. M. (2014). Alpha-Synuclein Lipid-Dependent Membrane Binding and Translocation through the alpha-Hemolysin Channel. *Biophys. J.* 106, 556-565.

Harmon, K. J., Bennett, E. E., **Gomella, A. A.,** & Wen, H. (2014). Efficient Decoding of 2D Structured Illumination with Linear Phase Stepping in X-Ray Phase Contrast and Dark-Field Imaging. *PLoS. One*. 9, e87127.

Kohr, M. J., Evangelista, A. M., Ferlito, M., Steenbergen, C., & Murphy, E. (2014). S-nitrosylation of TRIM72 at cysteine 144 is critical for protection against oxidation-induced protein degradation and cell death. *J. Mol. Cell Cardiol.* 10.

Konig, G., Pickard, F. C., Mei, Y., & Brooks, B. R. (2014). Predicting hydration free energies with a hybrid QM/MM approach: an evaluation of implicit and explicit solvation models in SAMPL4. *J. Comput. Aided Mol. Des.*

Liao, W., Spolski, R., Li, P., Du, N., West, E. E., **Ren, M.,** Mitra, S., & Leonard, W. J. (2014). Opposing actions of IL-2 and IL-21 on Th9 differentiation correlate with their differential regulation of BCL6 expression. *Proc. Natl. Acad. Sci. U. S. A.*

Martina, J. A., Diab, H. I., Li, H., & Puertollano, R. (2014). Novel roles for the MITF/TFE family of transcription factors in organelle biogenesis, nutrient sensing, and energy homeostasis. *Cell Mol. Life Sci.*

Neufeld, E. B., Zadrozny, L. M., Phillips, D., Aponte, A., Yu, Z. X., & Balaban, R. S. (2014). Decorin and biglycan retain LDL in disease-prone valvular and aortic subendothelial intimal matrix. *Atherosclerosis*. 233, 113-121.

Sochacki, K. A., Shtengel, G., van Engelenburg, S. B., Hess, H. F., & Taraska, J. W. (2014). Correlative super-resolution fluorescence and metal-replica transmission electron microscopy. *Nat. Methods*. 10.

Webster, B. R., Scott, I., Traba, J., Han, K., & Sack, M. N. (2014). Regulation of Autophagy and Mitophagy by Nutrient Availability and Acetylation. *Biochim. Biophys. Acta*. 10.

Wen, H., Gomella, A. A., Patel, A., Wolfe, D. E., Lynch, S. K., Xiao, X., & Morgan, N. (2014). Boosting phase contrast with a grating Bonse-Hart interferometer of 200 nanometre grating period. *Philos. Trans. A Math. Phys. Eng. Sci.* 372, 20130028.

Yi, J. H., Katagiri, Y., **Yu, P.,** Lourie, J., **Bangayan, N. J.,** Symes, A. J., & Geller, H. M. (2014). Receptor protein tyrosine phosphatase sigma binds to neurons in the adult mouse brain. *Exp. Neurol.* 10.

Yin, X., Subramanian, S., Hwang, S. J., O'Donnell, C. J., Fox, C. S., Courchesne, P., Muntendam, P., Gordon, N., Adourian, A., Juhasz, P., Larson, M. G., & Levy, D. (2014). Protein Biomarkers of New-Onset Cardiovascular Disease: Prospective Study From the Systems Approach to Biomarker Research in Cardiovascular Disease Initiative. *Arterioscler. Thromb. Vasc. Biol.*



Career Development Networking Session - Careers in Health Science Program Management

Presented by Fellows
Advisory Committee's Career Development Subcommittee

March 7th
1:30PM - 2:30PM
(50/2nd fl library)

Dr. Renee Wong - Program Officer in NHLBI Extramural Program to discuss her career transition.

Q&A with Investigator

Postdoc Kevin Ramkissoon interviews Dr. Caroline Fox, Senior Investigator, Laboratory for Metabolic and Population Health

Dr. Caroline Fox followed a B.A. in English with an M.P.H. in epidemiology from the University of Michigan. She was awarded her M.D. by the University of Pennsylvania in 1998 and went on to complete a residency in internal medicine, as well as a fellowship in Endocrinology, at the Brigham and Women's Hospital in 2001. The following year, Dr. Fox joined the NHLBI's Framingham Heart Study as a Medical Officer. She became a tenured Investigator in 2012 and in the brief



period since, has been recognized with a NHLBI Director's Award and two NHLBI Star Awards for her research and mentoring. She was also recently inducted into the American Society of Clinical Investigators. Dr. Fox currently holds a joint appointment as an Associate Clinical Professor of Medicine in the Brigham and Women's Hospital Department of Endocrinology where she combines epidemiology, biomarker research, genetics, and genomics research techniques to investigate how cardiovascular disease risk factors such as obesity and diabetes, influence the pathogenesis of both cardiovascular and chronic kidney disease. She currently serves as an associate editor for the journal *Circulation* and has published over 250 original scientific articles, in addition to several reviews and book chapters.

I see that you completed a bachelor's degree in English. What were the decisions that led you down the path to becoming a physician researcher?

I always had a tremendous sense of curiosity as well as a desire to question common assumptions. The physician researcher pathway gave me the ability to ask questions in the content of human health and disease. Training in English literature and writing provided me invaluable training in communication.

What do you enjoy most about being an NIH investigator?

The Intra-mural program is a fantastic opportunity to be a part of the innovative federal government program in biomedical research. The resources and research infrastructure provided by the NIH is an unparalleled opportunity to focus on high-risk high-reward research in a very nimble and flexible environment.

February was American Heart Month. We owe much of the progress made in our understanding cardiovascular disease in part to the NHLBI's Framingham Heart Study (FHS). What was your motivation for joining the FHS and what has it been like to be an integral part of such an influential and highly impactful study?

I feel so fortunate to be a part of the current investigative team at the Framingham Heart Study. I joined the study in 2001, and came in part because of the tremendous opportunities to work in genetic epidemiology. It is an honor to be a part of the FHS, and I have learned

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Q&A with Postdoc Dorothy Lerit

Postdoc Kevin Ramkissoon interviews Dr. Dorothy Lerit, Postdoc Fellow in the Cell Biology and Physiology Center

When did you decide that you wanted to become a scientist?

There were two formative courses that solidified my interest in the life sciences. The first was a high school Advanced Placement Biology class that motivated me to major in biology as an undergrad, and the second was an upper level undergraduate course that infected me with a strong interest in the cytoskeleton. I didn't really make up my mind to pursue science as a career until my junior year of college. This was in the early 2000's when money was still being thrown at research. At that time I was pursuing a second major in the English department, but reasoned that it would be easier making a living as a scientist than as a literary scholar.

What factors were most important in your decision to come to the NIH?

My initial postdoc search focused on the top centrosome/cilia labs across the country. I became geographically restricted when my partner accepted a job in northern Virginia and I refocused my search exclusively on the NIH, it being the preeminent research institute in the area. I had prior contact with Dr. Nasser Rusan, my current advisor, when I was a graduate student trying to prove mRNAs were trafficking toward centrosomes in *Drosophila* embryos. I set up an informational interview with him to get the inside scoop on life at the NIH and took up a position in his lab shortly afterward.

What do you enjoy most about your research here?

It was a big transition to go from a small graduate department working for an established PI to a very large institute working for a tenure-track PI. The timelines and the pressure are much more intense, but I've been rewarded with a few publications. Transitioning to a new biological system, the brain stem cells of the fruit fly, has also been rewarding. People get excited when you mention asymmetric cell division, neurodegeneration and tumors; and it's been fun to present my work at meetings.

What additional professional and career building activities have you participated in during your time at NIH?

I try to take full advantage of the various career development resources that are available to fellows. I applied for funding during my first year and was fortunate to be awarded the Lenfant Biomedical Fellowship through the NHLBI DIR. I've also participated in a number of the OITE workshops. I've enjoyed going to the NHLBI retreats and try to attend various seminars held across campus. Thanks to the WALs series, I have had lunch with a poet laureate and a Pulitzer Prize winner! More recently, I've served on a seminar committee where CBPC postdocs and grad students nominate and host outside speakers for our Thursday seminar series. We've hosted impressive PIs who delivered great talks and offered valuable career advice. It's been a fantastic experience!



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Featured Article

Beware the plagiarism checker!

By Herbert M. Geller, Ph.D.

An NHLBI lab recently sent in a revised manuscript to a respectable journal, and the next morning the manuscript was returned by the journal with the results from a “plagiarism checker” program, which detected overlaps with some published papers in about 7 or 8 sentences of the discussion. Needless to say, this was the first time the lab had ever encountered such an issue, and I was surprised when I learned about it.

So how could this happen? In writing the discussion, the first author, a visiting scientist at NHLBI, whose native language was not English, had altered general concluding sentences from these papers, which had found results parallel to their own but using different tissues. Most of these overlaps consisted of using the sentence construction of the original papers, but with alterations tailored to the actual results found in their paper. Others actually used whole introductory sentences. They did not actu-

ally refer to any data in the earlier paper, but accurately described their own data. So is this plagiarism or is it fair use?

Many web sites suggest that there is no fine line between plagiarism and fair use. The web site www.plagiarism.org defines several different kinds of plagiarism. The closest definitions include #1 cloning - Submitting another’s work, word-for-word, as one’s own. Clearly, this was not done. #2. Is called CTRL-C – Contains significant portions of text from a single source without alterations. Here, the operational word is “significant”. How much is significant? #3. Find - Replace – Changing key words and phrases but retaining the essential content of the source. This probably comes the closest, in that the key words that referred to the original tissue were gone, but the sentence structure remained the same. But one could argue that only a small portion of the submitted manuscript was copied, and an even smaller portion of the original paper, so this should be considered fair use. The program used by the journal does not actually take into account the nature of the overlap – just that there

is one, and therefore returned the paper.

In talking to others at NHLBI, we all admit that when we’re writing a paper, it’s relatively painless to paraphrase a sentence from some other paper, especially when it’s a generic phrase like “FGF-2 binds to HSPGs”. In fact, if you enter that phrase into Google Scholar, you get a hit, suggesting that there are just so many ways to express something that is common knowledge.

Fortunately, in this case, the journal merely requested that the offending sentences be rewritten and the manuscript sent back for review. But the take home lesson is very clear – even the slightest amount of copying is likely to be detected, and given the current awareness of scientific ethics, should not be part of your practice. The Fellows Editorial Board <http://ccr.cancer.gov/careers/feb/> offers free editing services, and is available to all at NIH. So even if you think that your English writing skills are weak, better to write an original sentence and have it edited, than to copy or paraphrase one.



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The Science Beat, continued

sion. Interestingly, the position of epsin in the CCSs in the z dimension resembles that of clathrin, indicating that epsin is distributed along the entire height of the CCSs during all stages of endocytosis, contradicting the previous notion that epsin 1 is only found at the bottom rim of CCSs. In summary, the methods described in this paper provide a useful tool for studying the comprehensive structure of all the proteins associated with the CCSs and their functions in endocytosis.

Q&A with Dr. Tiffany Powell-Wiley, continued

so much from the study team as well as the participants.

You have been recognized for your effectiveness as a mentor. What advice would you give to fellows and those who would serve as their mentors to foster mutually beneficial relationships?

I advise fellows that one of the most critical elements in selecting a research opportunity is to identify a great mentor. Setting clear expectations and mutual goals upfront is critical to a healthy mentoring relationship. I have weekly meetings with all of my fellows, and we always discuss short-term projects as well as longer-term career goals to ensure that fellows aren't just focusing on the present. Seeing fellows flourish and move on to great career opportunities provides me with tremendous satisfaction. I have learned a lot from my own mentors, and I am so fortunate to have had great guidance at every step of my career.

You have been the recipient of an NHLBI Director's award and multiple Star awards. What characteristic(s) of your personality

have been most influential to your success thus far?

Focus and determination are critical elements to being successful, particularly in the early stages of one's career. The NIH Intra-mural program is one of the best work environments to promote these two goals, since there are very few distractions beyond great science!

Had you not chosen a career in medical research, what career do you think you would have today?

The computer science and technology fields have grown beyond what any of could have imagined when we were making career choices. This would be an area that I would focus on if I hadn't chosen a career in medical research.

What hobbies or activities do you enjoy away from work?

I like to read, exercise, and bake. I also love to watch my 3 children play sports! I have learned a lot about baseball in the past few years.

NHLBI DIR St. Patrick's Day Bake-Off

**Tuesday, March 18th
3:00 PM - 4:00 PM
Building 10CRC, Room 2-3330**

**Please bring a dessert to share.
Must have green incorporated in the dish.
A prize will be given to the top voted dish.**



NHLBI DIR Seminar Series

Alex Mogilner, Ph.D.

Professor, Department of Neurobiology, Physiology and Behavior and Department of Mathematics
University of California, Davis

" Cell Protrusions from 2D to 3D "
Tuesday, March 18th
11:00 AM - 12:00 PM
Building 50, Room 1227/1233

Host: Jian Liu, Ph.D.

If interested in joining the speaker for lunch following the session, please RSVP to dirededucation@nhlbi.nih.gov
*limited spaces available

Sponsored by the NHLBI Office of Education and Tenure Track Faculty

Q&A with Dr. Dorothy Lerit, continued

Had you not chosen your current path, what career do you think you would have pursued?

I occasionally recall my undergrad experience and wonder what it would have been like had I gone down the other rabbit hole and completed my English degree. One of the aspects of science I enjoy most is writing, including grant and manuscript writing (cue the collective groan). I would say my favorite alternative career would be one where I write snappy little blurbs about high-impact science, or possibly scientific editor of an academic journal. I'm not sure how things will play out but I think it's important for everyone to have a backup plan (or two).

What hobbies or activities do you enjoy away from the lab?

I enjoy hiking in Shenandoah Valley when the weather is nice and try to find time to read and workout. I also enjoy cooking and have recently mastered making excellent pie dough! Overall I've found that if you don't take time for yourself it's easy to feel overwhelmed with the stresses of work. I similarly try to celebrate my major accomplishments. For example, I spent a month living in New Zealand after I defended my Ph.D. If you don't take the time to enjoy your own accomplishments who will?