

Office of Education
Division of Intramural Research

Fellows Newsletter

September 2013

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

Herbert M. Geller, Ph.D.,
Director
Angela N. Theofilos,
Program Coordinator
Marie N. Nguyen,
Program Analyst

The Science Beat

Zhiyun Ge, LRB
Dinari Harris, LMCI

**Fellows Advisory
Committee**

Jacob Bitterman, LOAG
Juliane Caviston, MBS
Jue Chen, PFDS
Pradeep Dagur, HB
Robert Gahl, LSB
Scott Gordon, LMS
Kira Holmstron, LMB
Zhiping Jiang, LPCD
Daniel Kraushaar, LEB
Cory Lago, TMB
Kang Le, LMR
Elizabeth Mushaben, LALI
Kevin Ramkissoon, ESBL
Toby Rogers, CIP
Cynthia St. Hilaire, MMC
Javier Traba Dominguez, LMBM
Lu Wang, LMI
Chad Williamson, MBS
Yingfan Zhang, LMC
Hang Zhao, LB



- In this issue:
- Welcome Letter....P.1
 - The Science Beat....P.2
 - Feature column by NHLBI Scientific Director, Dr. Robert Balaban....P.2
 - Q&A with DIR Investigator...P.3
 - New NHLBI Fellows Bios....P.2&3
 - Recent Publications by NHLBI Fellows....P.4
 - Q&A with Postdoc.....P.4
 - Feature column by NHLBI DIR Scientific Director....P.5

From the Director of the Office of Education

As you can see, the Newsletter has a new look and some new content as well. While we are continuing the Science Beat and new fellows biographies, we have several new monthly features, including interviews with PIs and fellows telling about their experiences in NHLBI, and information about new postdocs. In addition, this month, we feature a column by Dr. Robert Balaban, our Scientific Director, adapted from a recently published editorial, about how research is evaluated in the DIR, especially how one should not conflate publication in a High Impact Journal (HIJ) with a High Impact Publication.

We also welcome several new members of the Fellows Advisory Committee (FAC), listed on the left. As you know, the FAC serves a very important role in helping the Office of Education best serve our fellows. Most importantly, the FAC has established a Career Development Subcommittee, which is busy planning several events to enhance the NHLBI Postdoctoral Experience. The initial objective of this committee is presented on Page 6. Serving on the FAC or subcommittees is an ideal way to get to know other NHLBI fellows, and can provide valuable evidence of being able to tackle problems outside the lab.

POSTDOCTORAL SEMINAR

“Acetylation and Mitochondrial Quality Control”

Iain Scott, Ph.D.
Laboratory of Mitochondrial Biology and Metabolism

September 12, 2013
1:30 PM-3:00 PM
Building 10, Room 7N119

Your feedback at this seminar is much appreciated. *This is a prelude to a Job Talk.*

Meet the New Postdocs



Nuo Sun, Ph.D., is a new Visiting Fellow in the Center for Molecular Biology under Dr. Toren Finkel. Dr. Sun earned his Ph.D. in the Department of Microbiology & Immunology at Georgetown University Medical Center. His initial project at NIH is on signals that control liver cancer in mammals.



Adam Trexler, Ph.D., is a new Postdoctoral IRTA in the Biochemistry and Biophysics Center under Dr. Justin Taraska. Dr. Trexler earned his Ph.D. in Molecular Biology and Biochemistry at Yale University. His initial project at NIH is on investigating the localization and arrangement of proteins involved in exocytosis of dense core vesicles in PC12 cells.



Tania Nguyen, Ph.D., is a new Visiting Fellow in the Biochemistry and Biophysics Center under Dr. J. Robert Hogg. Dr. Nguyen earned her Ph.D. in Biochemistry at University of Oxford. Her initial project at NIH is to set up a system to observe single mRNP molecules and analyze their composition/kinetics and interactions of these components.

I.Thievessen, P.M.Thompson, S.Berlemont, K.M.Plevock, S.V.Plotnikov, A.Zemljic-Harpf, R.S.Ross, M.W.Davidson, G.Danuser, S.L.Campbell, C.M.Waterman. Vinculin-actin interaction couples actin retrograde flow to focal adhesions, but is dispensable for focal adhesion growth, J Cell Biol. 202 (2013) 163-177.

Cell movement is a complex phenomenon primarily driven by the actin network beneath the cell membrane. Cell migration can be divided into three general components: (1) Cell protrusion of the leading edge; (2) adhesion of the leading edge and de-adhesion at the cell body and rear; and (3) cytoskeletal contraction to pull the cell forward. Each of these steps is driven by physical forces generated by networks of cytoskeleton proteins. In particular, the leading edge senses the extracellular environment using adhesion receptors, also known as integrins, linked to the intracellular actin cytoskeleton through a complex network of regulatory proteins that work together to form focal adhesions (FA). In migrating cells, polymerizing filamentous actin pushes the leading edge forward, while at the same time being pushed back, causing retrograde flow. This retrograde flow is an important factor that determines translocation rates of a cell via the various mechanical forces imposed on it by various adhesion proteins. At the leading edge of migrating cells, actin assembly and membrane protrusion are closely coupled with the formation of integrin-based FAs that attach to the extracellular matrix. Thievessen et al. uncovered that the FA protein vinculin acts as part of a “molecular clutch” that engages actin flow to coordinate actin and FA dynamics.

The association between the cells translocation rate and retrograde flow can be explained by the existence of a “molecular clutch” composed of vinculin, talin, and other adhesion complexes. This “molecular clutch” determines the extent to which the cytoskeleton and the underlying ECM can interact. Through this interaction, the clutch controls the transmission of the cytoskeletal contractile forces to the ECM and the rate of cell translocation. In line with this model, Thievessen et al. showed that cell mobility occurs through the interactions be-

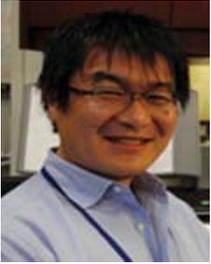
tween protein vinculin and the cytoskeletal lattice formed by the protein actin. By physically binding the actin that makes up the cytoskeleton, vinculin operates as a form of “molecular clutch” transferring force and controlling cell motion. Using vinculin-deficient primary mouse embryonic fibroblast (Vcl-KO MEFs), Thievessen et al. convincingly showed that F-actin flowed significantly faster in the leading edge of cells compared to control MEFs. To further emphasize the role of vinculin on actin dynamics, the researchers showed that a mutation (I997A) that interfered with the ability of vinculin to bind actin was unable to fully rescue the effects of vinculin deficiency on actin retrograde flow in add-back experiments in Vcl-KO MEFs.

Next Thievessen et al. examined the role of vinculin and its associated actin-binding activity affected FAs. They found that as well as slowing actin dynamics, depleting vinculin (Vcl-KO MEFs) resulted in a decrease in the number of nascent FAs in the lamellipodia and increased the proportion of mature FAs in the lamellae, indicating that the vinculin promotes the formation and turnover of nascent FAs and inhibits the maturation of FAs. The results from the add-back experiments using various vinculin mutants expressed in Vcl-KO MEFs showed that vinculin needed to be activated and able to bind F-actin in order to restore formation and turnover of nascent FAs in lamellipodia. Additionally, research showed that Vcl-KO MEFs exhibited a lower ECM traction stress generated by associated FAs and that the growth rate of FAs correlated positively with F-actin retrograde flow velocity in both control and Vcl-KO MEFs. This finding suggests that growth of FAs is dependent on the speed of actin flow, rather than force.

At the leading edge of a migrating cell, vinculin engages F-actin, and this clutch action slows retrograde flow. In turn, this reduces the tension on [Cont'd on page 6](#)

Q&A with NHLBI DIR Investigator

Many thanks to Dr. Yosuke Mukoyama for answering our questions this month.



Introduction:

I am Yosuke Mukoyama (Yoh-suke Mukouyama when publishing), a tenure-track investigator in the Laboratory of Stem Cell and Neuro-Vascular Biology, Genetics and Developmental Biology Center. I completed my PhD in March 1999 at the University of Tokyo, Japan, where I studied cytokine regulation of early hematopoiesis in mouse embryos. I joined David Anderson's lab at Caltech in September 1999 and studied cellular and molecular basis for neuro-vascular wiring and neural stem cell maintenance.

Since January 2006, I've been conducting the lab at NIH, where I have extended my studies at Caltech to patterning mechanisms of tubular branching networks during organogenesis.

What do you like the best about working at the NIH?

The collegial and mutually supportive environment.

What has been the highest point of your career thus far?

Well...difficult question. I guess it is the time when I found a beautiful congruence of arteries and sensory nerve branching patterns in the confocal microscopy room, at midnight, at Caltech. This finding leads to a Cell paper and subsequently helps me get an academic job!

Favorite place to eat in Bethesda?

I always take speakers to Satsuma, a Japanese Restaurant in Bethesda.

Best piece of career advice you have received?

I don't remember who gave me this career advice, but I've followed it: "if you focus on doing good science, then everything else will take care of itself"

When you are not busy working, what do you enjoy doing?

Playing tennis with my family and friends! I enjoy watching football games with my 6-year old son, and enjoy chatting with my two ladies: ? year old wife and 9 year old daughter.

Meet the New Postbacs



Kathleen Vaughan is a new Postbaccalaureate IRTA in the Genomic Medicine Section headed by Dr. James Taylor. Kathleen

is a recent graduate of Hamilton College where she received her Bachelor of Science degree in Chemistry and Hispanic Studies.



Alexandra Selby is a new Postbaccalaureate IRTA in the Cell Biology Section headed by Dr. Neal Young. Alexandra is a recent graduate of Emory

University where she received her Bachelor of Science degree in Biology.

INTRAMURAL FELLOWS FORUM WITH DR. GARY GIBBONS

All NHLBI DIR Fellows are invited to a dialogue and information sharing forum with the NHLBI Director, Dr. Gary Gibbons

September 20, 2013
12:30 PM- 1:30 PM
Building 50, Room 2328

This meeting will open with a few brief remarks regarding NHLBI leadership and trans-NHLBI activities and will reserve the remaining portion for open discussion.

FELCOM Announcements

Come celebrate
NIH Postdoc Appreciation Day

Tuesday, September 17th
3PM - 4PM
Building 1, Front Lawn

Meet fellows from other
institutes, take a group photo,
and enjoy an
afternoon refreshment.

Recent Publications by NHLBI Fellows

Bat T, Steinberg SM, Childs R, Calvo KR, Barrett AJ, Battiwalla M, Baird K, Zhang D, Pulanic D, Dunbar CE, Pavletic SZ (2013) Active thrombopoiesis is associated with worse severity and activity of chronic GVHD. *Bone Marrow Transplant*10.

Diaw L, **Youngblood V**, Taylor JG (2013) Introduction to next-generation nucleic acid sequencing in cardiovascular disease research. *Methods Mol Biol* 1027:157-79.

Gahl RF, Tekle E, Tjandra N (2013) Single color FRET based measurements of conformational changes of proteins resulting from translocation inside cells. *Methods*10.

Gomella A, Martin EW, Lynch SK, Morgan NY, Wen H (2013) Low dose hard x-ray contact microscopy assisted by a photoelectric conversion layer. *AIP Adv* 3:42121.

Heissler SM, Liu X, Korn ED, Sellers JR (2013) Kinetic characterization of the ATPase and actin-activated ATPase activities of *Acanthamoeba castellanii* Myosin-2. *J Biol Chem*.

Lee IH, Finkel T (2013) Metabolic regulation of the cell cycle. *Curr Opin Cell Biol*10.

Maldonado-Baez L, **Williamson C**, Donaldson JG (2013) Clathrin-independent endocytosis: A cargo-centric view. *Exp Cell Res*10.

Maunakea AK, Chepelev I, Cui K, Zhao K (2013) Intragenic DNA methylation modulates alternative splicing by recruiting MeCP2 to promote exon recognition. *Cell Res*10.

Mishra A, Yao X, Levine SJ (2013) From bedside to bench to clinic trials: identifying new treatments for severe asthma. *Dis Model Mech* 6:877-888.

Plotnikov SV, Waterman CM (2013) Guiding cell migration by tugging. *Curr Opin Cell Biol*10.

Sellers SE, **Dumitriu B**, Morgan MJ, **Hughes WM**, Wu CO, Raghavachari N, Yang Y, Uchida N, Tisdale JF, An DS, Chen IS, Hematti P, Donahue RE, Larochelle A, Young NS, Calado RT, Dunbar CE (2013) No impact of lentiviral transduction on hematopoietic stem/progenitor cell telomere length or gene expression in the rhesus macaque model. *Mol Ther*10.

Thievensen I, Thompson PM, Berlemont S, Plevock KM, **Plotnikov SV**, Zemljic-Harpf A, Ross RS, Davidson MW, Danuser G, Campbell SL, Waterman CM (2013) Vinculin-actin interaction couples actin retrograde flow to focal adhesions, but is dispensable for focal adhesion growth. *J Cell Biol* 202:163-177.

Youngblood V, Taylor JG (2013) Sequencing PCR-Amplified DNA in lipoprotein and cardiovascular disease research. *Methods Mol Biol* 1027:139-55.

Zhang J, Ferré-D'Amaré AR (2013). Co-crystal structure of a T-box riboswitch stem I domain in complex with its cognate tRNA. *Nature*. 500(7462):363-6.

Q&A about Extramural Rotation

Many thanks to Postdoc Cory Lago from the Laboratory of Cardiovascular and Cancer Genetics for answering our questions this month.



Explain the rotation you participated in.

I participated in an rotation at the NHLBI Office of Technology Transfer and Development (OTTAD). I was there for about 4 months but only 8hrs/week. Some weeks it was one full day, others it was two mornings just depending on my experiments. I initially taught myself the basics of patent law and the technology transfer process by putting together a power point presentation summary on the topic. Once I was familiar with the basics, I began helping a few technology development specialists in the office with their daily tasks.

What was your favorite part of the program?

My favorite part of the program was getting to learn about a variety of new technologies. It was fun to sit down with a few different employee invention reports, all on different topics most of which I was unfamiliar with, and learn how to search the literature and prior art to see if these inventions were novel. I also really enjoyed communicating with the scientists who developed the technologies to learn more about their invention, why they thought it was novel, how it was different from what was out there, etc.

What did you find most challenging?

I found the transition from being in that lab, where you are up walking around and talking to people all day, to sitting at a desk with a computer to be the most challenging. But, as I saw a couple of people in the office do, you don't have to be sedentary. You can choose to go meet with investigators and have face-to-face meetings instead of doing everything via email and phone if you choose. The nice thing about this career is that depending on how you work best you can set up a situation that is optimal for you.

[Cont'd on next page](#)

From the NHLBI DIR Scientific Director

Review of Scientific Productivity and Excellence in the National Heart Lung and Blood Institute Division of Intramural Research



Robert S. Balaban, Ph.D.
Scientific Director, National Heart Lung and Blood Institute (NHLBI)
(Adapted from a recent editorial)

The DIR is composed of a broad group of investigators working on basic structural biology and cell biology to clinical research within the Clinical Center on the Bethesda Campus and regional hospitals. Investigators are reviewed every 4 years by an external Board of Scientific

Counselors (BSC) as specified for all NIH intramural research programs. Each Institute accomplishes this task in slightly different manner. At NHLBI, the review is a Bethesda campus site visit involving BSC members chairing an expert panel of ad hoc experts to evaluate the scientific accomplishments over the last 4 years. Prior to the visit, the investigator provides an extensive written report on recent work and available resources. At the meeting, the investigator makes a brief presentation before a question and answer session where the strengths and weakness of the program are explored. Any program weakness revealed in the BSC report must be discussed in this open question period. After the site visit, the BSC members working with the information provided by the ad hoc members create a draft report provided to the investigator. The investigator can then write a rebuttal or request a formal meeting with the entire BSC to review the report and finalize the recommendations to the NHLBI Director and Council. Through this process an investigator has their "day in court" as well as an appeal processes.

The retrospective nature of this review is one of the important aspects of this process focusing on the previous 4 years. This makes the review rather straight forward in simply reviewing scientific accomplishments rather than the more difficult task of speculating what might happen in the future. Based on this retrospective criterion, the determination of the productivity and impact of the investigators over the 4 year period is a critical element of the review. In this task, we ask the ad hoc reviewers to provide their judgment of the investigators contribution to science based on their publications, write-up, presenta-

tion and response to questions during the review. However, in the last decade or so I have noted a disturbing trend to equating impact in the field with the journal a work is published in rather than the substance of the work. This sometimes resulted in a more careful evaluation of the journals published in, rather than the science performed. It was developing that a publication in a handful of "high impact journals" (HIJ), with usually a broad scope of interest, was becoming the bench mark for a successful research program rather than the science itself. The old phase of "publish or perish" is changing to "publish in HIJ or perish". This practice has sometimes minimized the consideration of the investigators development of novel insights, technologies or new hypothesis for the BSC to consider. Indeed, reducing the review to impact factors or similar metrics could make the whole peer review process unnecessary, simply calculate your impact and rely on the journal review process. In response to this trend, our current charge to the BSC, and ad hoc members, is asking the reviewers to bring their judgment of the scientific contribution to the table, not the editorial practices of a few journals. I am very pleased to report that our ad hoc reviewers and BSC has taken this charge very seriously and excellent discussions of the science produced in the DIR have evolved. In addition to our review boards, numerous other investigators share the opinion that the science content is more important than the journal in which it is published. A few of those investigators recently generated a document entitled San Francisco Declaration on Research Assessment: Putting science into the assessment of research at the recent American Society of Cell Biology annual meeting with many points that I present in this discussion concerning the emphasis on where one publishes rather than what is published.

What is the nature of this biomedical publication "funnel" we have begun to create? As the NIH and other grant awarding agencies pay-line dips down to the ~10% region it is clear to our community that any scientific review process attempting to cull the best 10% is difficult and many outstanding proposals are going unfunded. I believe that most investigators would argue that a pay-line even at 20% is difficult to defend in capturing the best work presented. In a recent article in Nature on the issues of low percentage acceptance of grants entitled Research funding: Making the cut Dr. Dick McIntosh, emeritus at the University of Colorado stated, "That's in a range (~20%) where you have lost discrimination." The chairman of the American Cancer Society grant review panel agreed stating, "Deciding between the top grants, I don't want to say [Cont'd on page 6](#)

Rotation, continued

Would you recommend it to others?

Yes, I would recommend this rotation to other fellows who are interested in a career in technology transfer. The director is very friendly and helpful and willing to work with you to make sure that you get what you want out of the internship. I went in with an idea of what I wanted to learn and once he felt that I was caught up to speed with the basics, he helped me transition into the areas that I wanted to learn about. I would recommend that you are familiar with the field and have taken an FAES course or two related to technology transfer before you do this internship though.

Do you have any advice for other postdocs interested in participating in a rotation?

If I had the opportunity to do it over again, I would have just stuck to 1 full day/week for the rotation. I also would have asked to shadow/work with more people in the office who preferred to do their interactions with investigators in person simply because I am a people person and work better that way.

it's arbitrary, but it's not really based on strong criteria". This low acceptance rate has generally been described as a major impediment to furthering biomedical research. However, when I look at the HIJ published acceptance rates (when available from the web) I find that most of these journals are operating well below a 10% acceptance rate we find so troubling in evaluating research grants. Thus, one could argue that outstanding work is not being published in the HIJ simply based on the flaws of a scientific review when only a small fraction of the work is being accepted independent of the rigor of the review. Using this system that accepts less than 10% of the manuscripts submitted as an absolute gateway to a successful review is at best, problematical, and just as distressing as the current pay lines for grants. Thus, it is unclear why we should rely on the review processes of journals with a couple of reviewers in most cases and when a full open grant review panel operating at even a higher acceptance levels gives us concerns with regard to missing outstanding science. It is important to note that the "journal funnel" is a creation of our biomedical research community and we are capable of opening this reduced aperture while the research grant pay line is not; being simply dependent on the economics of the grant awarding agencies. On a personal level, I had a fellow take an academic position after a post-doc in my lab and we were reflecting on what it would take to be successful in their academic position. Surprisingly, the fellow identified the acceptance rates in the HIJ journals as the biggest, or first, barrier rather than the NIH grant. Why? First the start up funds from the academic program was adequate to start and early career awards were available from NIH

and other sources. The impression of the fellow was that without a track record of publications in HIJ that they would not get the larger R01 grant or promotion at their institution. This is an opinion shared by many of the junior faculty I interact with. Again, the importance of HIJ publications is a self-inflicted wound created by many review processes generated by the biomedical research community and not a government bureaucracy or group of deans. I fear the most negative impact of this virtual funnel will be on the attraction of new and success of existing junior investigators. Again, we created this implied requirement of the HIJ publications; we can remove it as well.

It is laudable if a manuscript is published in an HIJ and likely to get more attention than in a more focused journal, however, we must realize that using the HIJ review system as our gateway to judging the scientific performance of a program is flawed. Again, my issue here is nothing specific about the process, editors or funding mechanism of the journals, it is simply requiring a successful trek through almost any review process that judges scientific merit within the top 10% should not be the gateway to continued scientific support and recognition. Thus, I have asked our intramural review process to broaden the "funnel" to give credit for papers published in specialty journals that provide a rigorous review of the science presented and that the work has had a major positive impact on the development of a given field. In presenting this charge to our review panels, it has generally been accepted as an excellent and appropriate goal of the research program and vigorous scientific discussions have emerged in the reviews.

Beat, continued

ECM-associated integrin but generates traction, and promotes the formation and turnover of nascent FAs. This tension, along with reducing the actin-flow dependent growth of FAs, facilitates cell migration. The work by Thievensen et al. identified an important role of vinculin in controlling cell movement, which will ultimately allow research to create drugs and therapies that finely target these protein interactions. Cell movement and mobility play a crucial role in cancer research because of metastasis in tumor development, therefore, this type of research is setting the fundamental groundwork and foundation upon which research can begin targeting specific aspects of cell movement and force transduction.

Introducing Career Development Small-Group Meetings



Attention postdocs! Do you know what you are doing after your fellowship contract ends?

Now is the time to be investigating potential careers, networking, and learning how to tailor your resume to your future employer. The Fellows Advisory Committee wants to help make these tasks more manageable by offering monthly career development sessions.

Beginning in November we will be inviting local professionals representing divergent scientific career tracks to come discuss their jobs, answer questions, and network with NHLBI fellows. Using a small group format will be a convenient way to learn about the diversity of jobs available to postdocs ending their tenure at NHLBI, and allow for personal interactions with invited professionals - a great way to start to build relationships with local employers!

Please participate in our online survey, which will be emailed to you later this month, to help us gauge participant interest and identify career topics of greatest appeal.

-The Fellows Advisory Committee