Office of Education
Division of Intramural Research

Fellows Newsletter

June 2014

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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

Those of us who attended Research Day on Monday got a chance to experience the exciting science done in the NHLBI DIR. The quality of the science, both in oral presentations and in the posters, was exceptional. This was the first time we've held this event on the NIH campus, and the result was that many more PIs participated in the discussion, which made the day even more valuable. Relatively soon, the Fellows Advisory Committee will meet to discuss future plans, and so we'd like to hear your feedback on how you enjoyed this day and what we might do differently.

On Page 5 of this issue, I address the important issues of diversity and inclusion within the DIR. We all know how diverse the fellow population is, which means we have to make sure all are welcome, no matter their native language. That's why English must be used in conducting business within the lab environment. See my column for a longer explanation.

NHLBI DIR Research Day 2014

Meet the New Fellows

Nathan Hardy is a new Post-Baccalaureate Fellow in the Hematology Branch under Dr. Neal Young. Nathan earned his BA in Biology at Cornell University. His initial project at NIH is deep sequencing to find mutations in key exons indicated in Aplastic Anemia, MDS, & AML.

Patali Cheruku is a new Post-Baccalaureate Fellow in the Hematology Branch under Dr. Andre Larochelle. Patali earned her BA in Molecular and Cell Biology at Texas A&M University. Her initial project at NIH is to identify the difference in pathways activated by thrombopoietin and Eltrombopag, a thrombopooietin receptor agonist.

THE SCIENCE BEAT by Ling Yang, Ph.D.

Hong, S. G., Winkler, T., Wu, C., Guo, V., Pittaluga, S., Nicolae, A., Donahue, R. E., Metzger, M. E., Price, S. D., Uchida, N., Kuznetsov, S. A., Kilts, T., Li, L., Robey, P. G., & Dunbar, C. E. (2014). Path to the Clinic: Assessment of iPSC-Based Cell Therapies In Vivo in a Nonhuman Primate Model. Cell Rep. 7, 1298-1309.

Induced pluripotent stem cell (iPSC)-based cell therapies have great potential for regenerative medicine but are also potentially associated with tumorigenic risks. Current rodent models are not optimal predictors of efficiency and safety for clinical application. The rhesus macaque has been a very valuable model organism for development of novel cell and gene therapies, and analysis of the immune system. Physiological similarity including size and life span, phylogenetic similarity to humans, cross-reactivity of human cytokines and antibodies, completed genome sequencing, and knowledge gained from 3 decades of macaque immunologic studies stimulated by the HIV epidemic contribute to the utility of this model. Moreover, rhesus iPSCs resemble human iPSCs in terms of morphology, marker expression, and growth factor dependency to maintain their pluripotency.

In this study, the authors developed an autologous teratoma formation assay in the rhesus macaque, following a long process of optimization in vitro and in vivo, removing xenogeneic components such as Matrigel from the culture surface and implantation scaffolds because it will likely trigger rejection of the RhiPSCs or their progeny in an immunocompetent organism. Using this assay, they showed that undifferentiated iPSCs could indeed form teratomas in vivo. This method is simple and noninvasive and can be used for a variety of applications in the investigation and clinical development of tissue regenerative therapies. Up to 30 sites can be injected and harvested in a single macaque, without evident discomfort or clinical complications. It is noteworthy that although the autologous RhiPSCs did form mature teratomas in the macaques, the process was at least 20-fold less efficient on a per cell basis compared to teratoma formation following simultaneous injection of the same cells into NSG mice.

Mesodermal stromal cells, also termed BMSCs, are defined by adherent growth on plastic surfaces, typical fibroblastic morphology, and the potential to form skeletal tissues, including bone, cartilage, adipocytes, and hematopoiesis-supporting stroma. In their model, RhiPSC-SCs morphologically resembled BMSCs, expressed similar cell surface markers, and differentiated down the osteogenic lineage in vitro. By eight weeks, new bone had formed under the skin of implanted animal. Almost a year later no tumours had formed, and bone formation persisted. They also observed significant lymphocytic infiltrations in teratoma tissues derived from undifferentiated RhiPSCs, whereas no evidence of lymphocytic infiltrations in bone tissues derived from RhiPSC-SCs. This phenomenon might be due to low MHC class I expression on PSCs.

In conclusion, the authors developed a clinically relevant nonhuman primate model to assess the tumorigenic potential and in vivo efficacy of both undifferentiated and differentiated iPSCs in autologous settings without immunosuppression. The fact that none of the RhiPSC-SC implants showed any signs of tumor formation, and the low efficiency of teratomas derived from parental iPSCs indicates that the risk of these adverse events is calculable and probably can be further reduced by improved differentiation methods or safety switches such as suicide-gene technology. Therefore, the nonhuman primate model will be very valuable for evaluating a wide variety of iPSC-based treatment modalities.

Recent Publications by NHLBI Fellows

Beach, J. R., Shao, L., Remmert, K., Li, D., Betzig, E., & Hammer, J. A., III (2014). Nonmuscle Myosin II isoforms coassemble in living cells. *Curr. Biol. 24*, 1160-1166.

Burke, G. M., Wang, N., Blease, S., Levy, D., & Magnani, J. W. (2014). Assessment of reproducibility - automated and digital caliper ECG measurement in the Framingham Heart Study. *J. Electrocardiol. 47*, 288-293.

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de Messieres, M., Huang, R. K., He, Y., & Lee, J. C. (2014). Amyloid triangles, squares, and loops of apolipoprotein C-III. *Biochemistry. 53*, 3261-3263.

Escobar, T. M., Kanellopoulou, C., Kugler, D. G., Kilaru, G., Nguyen, C. K., Nagarajan, V., Bhairavabhotla, R. K., **Northrup, D.,** Zahr, R., Burr, P., Liu, X., Zhao, K., Sher, A., Jankovic, D., Zhu, J., & Muljo, S. A. (2014). miR-155 activates cytokine gene expression in th17 cells by regulating the dna-binding protein jarid2 to relieve polycomb-mediated repression. *Immunity.* 10.

Fujiwara, I., Remmert, K., Piszczek, G., & Hammer, J. A. (2014). Capping protein regulatory cycle driven by CARMIL and V-1 may promote actin network assembly at protruding edges. *Proc. Natl. Acad. Sci. U. S. A. 111*, E1970-E1979.

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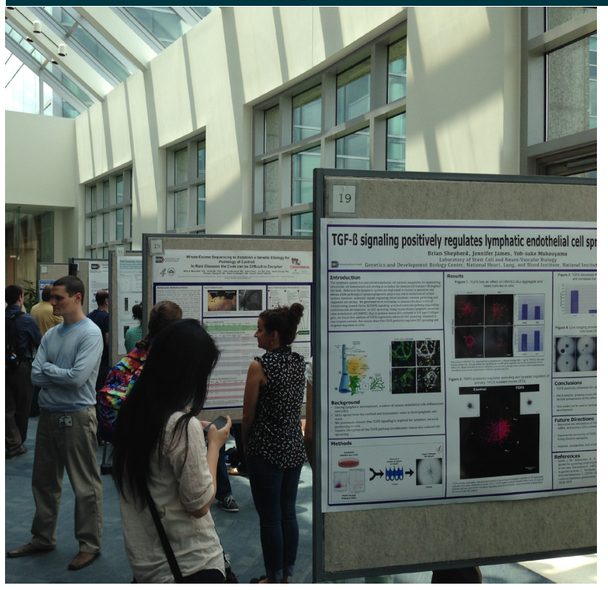
Hong, S. G., Winkler, T., Wu, C., Guo, V., Pittaluga, S., Nicolae, A., Donahue, R. E., Metzger, M. E., Price, S. D., Uchida, N., Kuznetsov, S. A., Kilts, T., Li, L., Robey, P. G., & Dunbar, C. E. (2014). Path to the clinic: assessment of ipsc-based cell therapies in vivo in a nonhuman primate model. *Cell Rep. 7*, 1298-1309.

Jain, N. A., Lu, K., **Ito, S.**, Muranski, P., Hourigan, C. S., Haggerty, J., Chokshi, P. D., Ramos, C., Cho, E., Cook, L., Childs, R., Battiwalla, M., & Barrett, A. J. (2014). The clinical and

NHLBI Research Day Recap



The Twelfth Annual NHLBI DIR Research Day was a great success! On June 9th, over 200 members of the NHLBI community came to Natcher Conference Center to participate in the annual demonstration of excellent work done throughout the DIR. Everyone from summer students to fellows to PIs attended. We were, of course, honored to have Dr. Susan Shurin give closing remarks to finish the day, and we wish her the best of luck in her retirement.

All in all, there were 15 speakers, 70 posters, and 14 Cores at Research Day. Every speaker, poster presenter, and Core helped make Research Day a success – so thank you! We would also like to thank Christina Farias and FAES for generously providing lunch. Christina has an open door policy and would love you hear your ideas! You can reach them at www.faes.org. Thanks again to everyone who attended, and we look forward to seeing you again next year!

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Q&A with Investigator

Postdoc Kevin Ramkissoon interviews Dr. Andrew Johnson, Investigator, Cardiovascular Epidemiology and Human Genome Branch

Dr. Andrew Johnson joined the NIH as postdoctoral fellow in 2007. He became a tenure track investigator in 2012, and currently leads a team of researchers employing population-scale approaches to understand the genetic and genomic underpinnings of the variability observed in patient responses to therapeutic interventions for cardiovascular disease. Prior to his arrival at the NIH, Dr. Johnson earned a B.S. in vertebrate physiology from Pennsylvania State University, and his Ph.D. in biomedical sciences from Ohio State University with dual emphases in bioinformatics and pharmacogenomics. He has served as a reviewer for more than 20 journals, with his own work resulting in more than 70 publications. Dr. Johnson has been recognized with numerous awards including the NHLBI Lenfant Fellowship and Genome Technology's Young Investigator Award. He was elected as a Fellow of the American Heart Association and is active on several committees of their Functional Genomics and Translational Biology Council.

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

It was gradual. I started out in Honors Engineering but late in my 1st undergraduate year found myself much more engaged in Biology than in matrix transformations, so I became a Physiology major. I did about 2 years of molecular research in Neuroscience and really enjoyed writing detailed protocols, troubleshooting techniques, teaching and exchanging skills, and being part of a larger research endeavor. Unfortunately the professor I worked with had a tough time with grant funding, did not get tenure, and left. In retrospect, his experience inhibited me from an immediate path to graduate school. I subsequently worked as a research tech/lab manager in 2 different model organism labs. This was the time I really got hooked on research. I presented at conferences, co-authored my first publications, was exposed to different mentoring styles, and saw more aspects to the business of science.

Can you briefly describe your experience as a postdoctoral fellow at the NIH?

Coming to the NIH as a postdoctoral fellow was a fantastic experience. I had multiple opportunities including "staying home" at my Ph.D. institution. The advice I received from mentors was to go away and get exposure to a different environment. That was great advice, but it was challenging on a

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Q&A with Postdoc Dr. Xiangbo Ruan

Postdoc Kevin Ramkissoon interviews Dr. Xiangbo Ruan, Laboratory of Obesity and Metabolic Diseases, Center for Molecular Medcine

What factors influenced your decision to come to the NIH?

I was first introduced to my current lab by a friend. The area of research is very attractive and the research environment and facilities are excellent. My interview went well and I got the impression that my mentor, Dr. Haiming Cao, would provide the necessary guidance and mentorship important towards my research career.

What is your current research focused on and how does it fit into your future plans?

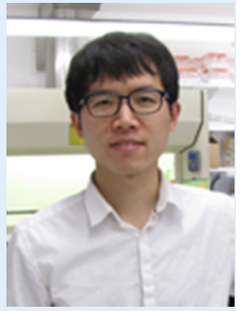
My current research is focused on the role that long non-coding RNA (lncRNA) plays in regulating metabolism. My plan is to transition to an independent investigator in the next 3 to 5 years with a research focus on metabolic diseases.

In addition to research, what professional/career building activities have you taken part in during your time as an NHLBI postdoc?

I have mentored two summer students in our lab. I enjoyed working with them a lot. I volunteered to be a lead judge for 2014 Graduate Partnerships Program (GPP) Symposium Poster Judging. I also serve as a writer for the NHLBI Fellows Newsletter, writing for the Science Beat and Q&A sections.

What advice would you give to a first year fellow entering the NHLBI training program?

My primary advice is to not rush into lots of experiments at the very beginning. It helps to take the necessary time to get a good understanding your lab and your project first. I also encourage fellows to talk with other scientists about their work.



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

When I was in high school my biology teacher was talking about how blood types were determined among different people. At the time, I thought that this process was so amazing and that there are so many secrets to be uncovered in the human body. From that point onward I wanted become a research scientist.

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

I like running. I just completed the 11th Annual Potomac River Run Marathon. I also play the guitar, which really helps me to relax.

Featured Article

NHLBI - A Diverse Environment
By: Herbert M. Geller, Ph.D.

The NHLBI, like all NIH institutes, celebrates diversity and inclusiveness. While "diversity" can cover many different facets of our lives, NIH is an especially diverse environment due to the presence of fellows from a large number of countries. This was highlighted in my talk at Research Day, where I presented a slide of NHLBI demographics. Although the majority of fellows are from the US, there are 28 other countries represented, with China being the most represented, with 46 fellows at NHLBI, India next with 11, Japan with 10 and Korea with 7.

Even though NHLBI is very diverse, this diversity is not uniform in every individual laboratory: some labs have a majority of Visiting Fellows from the same country, with a minority from other countries. In some of these labs, it has become the habit of the majority to use the language from their home country, rather than English, in talking to each other. It may seem that the use of a native language in the lab is helpful – research can be done sooner with the help of your colleagues. However, speaking a language other than English in the presence of fellows who do not speak that language creates a feeling of exclusion, which is contrary to the spirit and intent of the NIH to create a welcoming environment for all fellows.

The policy of NHLBI, like much of the world, is very clear – English is the international language for scientific communication. Moreover, speaking English in the lab serves two purposes: one, it allows for Visiting Fellows who are not proficient in English to improve, and two, it provides for a laboratory environment that celebrates diversity and inclusiveness. Use of another language in the lab does exactly the opposite. This does not mean that if you go to lunch with friends from your home country that you need to speak English, but it does mean that Visiting Fellows and their PIs need to be sensitive to creating a welcoming environment.

Q&A with Dr. Andrew Johnson, continued

personal level because it meant splitting up my family for 2 years. The NIH postdoc exposed me to cutting edge data and techniques in my field of population science, genomics and genetic epidemiology. At that crucial time (2007), there were few places in the world that had that level of data and expertise available, so it was a fortuitous choice. My mentor was well connected and respected amongst collaborators, which was particularly important in population sciences and genetics at the time. My mentor was also very supportive but gave enough latitude for me to take ownership of my projects.

How did your experience as a fellow influence your approach to mentoring NHLBI trainees?

My mentoring is a work in progress. I try to blend things that I like from prior mentors. The most important thing is regular meetings and clear 2-way communication wherein mentor and mentee both listen and can contribute ideas. I want mentees to have a balance of straightforward and challenging projects so they have a safety net for some success, while also having the potential to hit home runs. I also found the NIH PI course extremely helpful in thinking about how different personality and learning styles affect mentorship and research teams.

What were the most challenging and rewarding aspects of your transition to an independent investigator?

The most challenging aspects to me are recruiting/hiring and figuring out how to spend your research funds starting at Day 1. This goes hand in hand with one of the most rewarding aspects which is being able to determine the direction of the research program, and having the freedom to do that.

What advice would you give to fellows with aspirations of running their own lab to help them launch their independent careers?

Even if you dislike doing it, exploit all your available social networks, academic and non-academic. Do not be afraid to strike out into new areas or combine multiple areas of expertise or interest. At the same time know your target field(s). What are the relevant future questions for the next few years and what has largely been done? For all but the ultra-competitive genius, I think it is useful to identify niches and opportunities where you can make new contributions but hopefully not be under constant threat from competition.

You were a recipient of the Lenfant Fellowship. What advice would you give to NHLBI fellows towards preparing their own fellowship applications?

I believe the application process has become more involved since I initially applied so a recent awardee is probably in a better position to judge the current status and strategy. I think dem-

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Publications, continued

financial burden of pre-emptive management of cytomegalovirus disease after allogeneic stem cell transplantation-implications for preventative treatment approaches. *Cytotherapy.* 10.

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Ochi, F., **Fujiwara, H**., **Tanimoto, K**., **Asai, H**., **Miyazaki, Y**., Okamoto, S., Mineno, J., Kuzushima, K., Shiku, H., Barrett, J., Ishii, E., & Yasukawa, M. (2014). Gene-modified human alpha/beta-t cells expressing a chimeric cd16-cd3zeta receptor as adoptively transferable effector cells for anticancer monoclonal antibody therapy. *Cancer Immunol. Res. 2*, 249-262.

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Rogers, T. & Lederman, R. J. (2014). Right heart catheterization from the arm: back to first principles. *Catheter. Cardiovasc. Interv.* 10.

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Simmonett, A. C., **Pickard, F. C**., Schaefer, H. F., III, & Brooks, B. R. (2014). An efficient algorithm for multipole energies and derivatives based on spherical harmonics and extensions to particle mesh Ewald. *J. Chem. Phys. 140*, 184101.

Smirnov, M. S., Cabral, **K. A**., Geller, H. M., & Urbach, J. S. (2014). The effects of confinement on neuronal growth cone morphology and velocity. *Biomaterials.* 10.

Sodt, A. J. & Pastor, R. W. (2014). Molecular modeling of lipid membrane curvature induction by a peptide: more than simply shape. *Biophys. J. 106*, 1958-1969.

Trepiccione, F., Pisitkun, T., Hoffert, J. D., Poulsen, S. B., Capasso, G., Nielsen, S., Knepper, M. A., **Fenton, R. A.**, & Christensen, B. M. (2014). Early targets of lithium in rat kidney inner medullary collecting duct include p38 and ERK1/2. *Kidney Int.* 10.

Q&A with Dr. Andrew Johnson, continued

onstrating your productivity (i.e., quality and quantity of publications) and relative independent thought are important. From my recollection, the committee was focused on the oral presentation, ascertaining how much independence a candidate had, and what your future vision was for both your science and career. So I think having a coherent and interesting story to tell about where you've been, but probably more importantly where you think you, and your field, will be going are a major plus to the application.
You have been recognized with multiple awards for your early career research.

What characteristics of your personality have been most influential to your success thus far?

Natural curiosity – that drive to know more and not be dissuaded when I'm interested in a question. From an early age I had a strong collector and cataloger phenotype and this influences my research approach. Beyond that, being an honest, easy-going and no-nonsense person has helped me work with a variety of people in a highly collaborative area of science.

Had you not chosen your current path, what career do you think you be in today?

A computer science related job, or some type of architecture. I like to plan and design solutions to problems, synthesize inputs and create new things.

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

I have 2 great kids so hobbies suffer greatly to them (and science). If I had the time I would do more social juggling/club passing, biking, Nordic skiing, orienteering/racing, logic puzzles and board gaming, home brewing, and reading for pleasure.