Office of Education
Division of Intramural Research

Fellows Newsletter

January 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

Happy New Year to all from the Office of Education. We hope you all have a productive and successful year. While 2013 was unsettling for those of us inside NIH, it seems that 2014 will be much less stressful, with (at least for now) no talk of shutting down the government once again

On January 17th at 11 AM in Lipsett Auditorium, the NHLBI DIR will have the Orloff Awards ceremony to honor outstanding research achievements of DIR scientists, including many Fellows. Later that same day, in Bldg. 50 the Fellows Advisory Committee of the Office of Education is sponsoring a get-together with Dr. Zheng You, a former NHLBI fellow now working at DuPont to discuss research in industry. Both of these programs promise to be interesting and informative.

This issue of the newsletter features an interview with Dr. Greg Alushin, who has just recently started as a Principal Investigator at NHLBI, after one year as a postdoc here. His research is sponsored by a new NIH grant program for early career investigators, called the NIH Directors Early Independence Award, which provides startup funds for those who want to short-circuit their postdoc years and go directly to a PI position. He is the first intramural recipient of this prestigious award.

NHLBI DIR SEMINAR SERIES

Michael Lederman, M.D.

Scott R. Inkley Professor of Medicine Professor of Biomedical Ethics, Pathology, Microbiology and Molecular Biology
Case Western Reserve University

"Residual Immune Dysregulation Syndrome in Treated HIV infection"
Tuesday, January 14th 11:00 AM - 12:00 PM
Builing 50, Room 1227/1233

Meet the New Fellows

Dr. Hyun Jun Jung is a new Visiting Fellow in the Systems Biology Center under Dr. Mark Knepper. Dr. Jung earned his Ph.D. Kyungpook National University. His initial project at NIH is to analyze the binding sites of transcription factors, which are responsive to vasopressin in kidney collecting duct cells using ChIP-seq.

Dr. Kohei Hosokawa is a new Visiting Fellow in the Hematology Branch under Dr. Neal Young. Dr. Hosokawa earned his M.D. at Kanazawa University School of Medicine and Ph.D. at Kanazawa University Graduate School of Medical Science. His initial project at NIH is to clarify the immune pathophysiology of bone marrow failure, such as aplastic anemia and myelodysplastic syndrome.

THE SCIENCE BEAT by Zhiyun Ge, Ph.D.

***Kraushaar DC**, Zhao K (2013) The Epigenomics of Embryonic Stem Cell Differentiation. Int J Biol Sci 9:1134-1144.*

Embryonic stem cells (ESCs) are cells derived from the inner cell mass of a blastocyst, an early-stage embryo. ES cells possess two distinctive properties: pluripotency and self-renewal ability. Pluripotency means ESCs are able to differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm. In addition, ESCs are capable of propagating themselves indefinitely under defined conditions. Thus, ESCs not only can serve as a great model for studying early development, but can also be employed as useful tools for regenerative medicine. The plasticity and pluripotency of ESCs ultimately results from an open and highly dymamic chromatin landscape. Each different cell type displays unique gene expression profile (transcriptome) and epigenetic signature (epigenome). During the transition of ESCs to a more developmentally restricted cell type, the global transcription profile changes, resulting in silencing of pluripotency genes and activation of lineage-specific genes. Extracellular signals, intracellular transcription factors, as well as regulators of chromatin states and epigenetic modifiers all contribute to the changes in the gene expression profile required for cell differentiation and lineage specification. The epigenome of ESCs must ensure the transcription of genes that maintain their pluripotency and, upon lineage commitment, facilitate cell-type specific activation of developmental genes. Genome-wide maps of epigenetic factors in ESCs revealed their unique epigenetic signature, which contributes to their plasticity. In this review, the authors summarize the current view of the global epigenetic landscape of ESCs and the roles epigenetic factors play in the maintenance of ESC pluripotency and in ESC differentiation during development.

ESCs overall exhibit higher transcription levels than somatic cells, due to elevated transcription of sequences that are silent in differentiated cells and genes that constitutively express in both ESCs and differentiated cells. The hyper-transcriptional activity in ESCs results from an open and plastic chromatin configuration. During differentiation, heterochomatic foci increase and mobility and turnover of chromatin-associated protein, such as histones, decrease. Genome-wide analyses of histone marks reveal different abundance of active and repressive histone marks in ESCs and differentiated cells. Interestingly, a number of developmental genes are bivalently modified by both active and repressive histones, priming them for activation prior to ESC differentiation. Furthermore, while some bivalently modified genes resolve to monovalently modified genes or carry no marks during differentiation, lineage-related genes retain bivalency to remain poised for expression at later developmental stages. The achievement of bivalent chromatin marks depends on two groups of functionally opposing proteins: the Polycomb (PcG) and Trithorax (Trx)/MML proteins. Gene bivalency allows the unstable state of gene repression to rapidly switch to gene activation when developmental stimuli are presented. The authors then describe the mechanism that fine-tunes the regulation of bivalent domains, including histone acetylation, ATP-dependent chromatin remodeling, histone methylation and heterochomatin, histone variants, and DNA methylation.

Histone acetylation is regulated by two families of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs remove acetyl groups from histone tails and repress transcription by preventing rapid acetylation and PolII binding to promoters. In ESCs, HDACs may be involved in both positive and negative regulation of gene expression. They repress the expression of lineage-specific genes that need to be silenced and activate genes that prevent excessive acetylation. HATs in ESCs have been implicated in regulating pluripotency factors.

ATP-dependent chromatin remodeling factor Brg1 plays a critical role in the pluripotency of ESCs. The function of Brg1 is high context-dependent and it facilitates both gene activation and repression by modulating nucleosome stability and pluripotency-associated chromatin competence.

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Q&A with Postdoc Brian Glancy

Postdoc Kevin Ramkissoon interviews Dr. Brian Glancy, Postdoctoral Fellow in the Systems Biology Center

Kevin Ramkissoon (KR): When did you decide that you wanted to become a scientist?

Brian Glancy (BG): I decided to become a scientist during my junior year of college. Prior to that, I had planned on becoming a high school physical education teacher. However, after working at a social science research agency for a couple of years, I realized that I would get more enjoyment out of a more academic career. My undergraduate degree is actually in sport science with an emphasis in sport pedagogy, but I finished all those requirements by the end of my junior year and spent my senior year taking all the science courses necessary to pursue a graduate education in exercise physiology.

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

BG: To be honest, prior to coming here, I had little idea about all the benefits to being a postdoc at the NIH. I just knew that, as a graduate student, when I thought of the best possible places to continue to study skeletal muscle mitochondrial energetics, Dr. Balaban's lab was at the top of the list. This was the first and only position I inquired about, and, fortunately, I was able to join the lab.

KR: What do you enjoy most about the research environment here?

BG: I absolutely love the research environment here. Perhaps the most enjoyable part is the ability to follow your research questions wherever they may lead. This is due in large part to the access to so many different types of equipment in our lab and the various core facilities, as well as the ability to interact with world-renowned experts from a wide variety of fields.

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

BG: I'm currently in my fifth year here and it's been great so far. The first half of my fellowship was spent significantly expanding studies on the control of skeletal muscle mitochondrial function in vitro that I began as a graduate student. Over the last few years, I have been learning how to examine skeletal muscle mitochondria in live animals using multi-photon microscopy and optical spectroscopy. I believe learning these cutting edge techniques will serve me well as I look towards an academic position at a university.

KR: In addition to research, have you participated in additional professional/career building activities during your time at NIH? Were these experiences beneficial and would you recommend them to other fellows?

BG: I probably haven't participated in as many career building activities as I should have. Traveling to conferences once or twice a year has been a great way to see what's on the cutting edge of science at the moment as well as to network with people from universities where I may want to apply for a position at or setup collaborations with in the future. I would also highly recommend the grant writing workshop through the Office of Education with Dr. Geller. It offers a lot of help with what can seem like a daunting task to a first-time grant writer.

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

BG: I would pass on the advice that was given to me when entering the program: figure out what you want to do when you leave your fellowship (academia, industry, advocacy, another fellowship, medical school, etc.) and design your fellowship to meet those goals. Many PIs are very experienced at helping fellows transition to their next positions and there also many opportunities offered for additional scientific and career development training by the NHLBI and NIH.

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

BG: I love playing competitive sports. That's the main reason why I study muscle energetics. In addition to playing sports locally, I've participated in a lot of regional and national racquetball and flag football tournaments over the last several years. Recently, I've also gotten in to rock climbing thanks to my wife. My life is really pretty simple: sports, science, and good food.

NHLBI Fellows Career Development & Networking Session - Research Scientist in Biotech

Friday Jan. 17, 2014, 4PM - 5PM
Bldg. 50, Rm. 2328

The NHLBI Office of Education is offering a career development and networking opportunity for fellows interested in learning more about jobs in the biotech industry. Dr. Zheng You will visit the NIH main campus Friday January, 17th to discuss her 2010 transition from an NHLBI postdoctoral fellow in Dr. Rodney Levine's lab, where she studied the modification and repair of proteins involved in oxidative stress, to her current position as a Research Investigator at DuPont. Her current research focus at DuPont is developing biocatalysts for producing chemicals from renewable sources. Dr. You will share her experience and offer tips on finding an industry position, building a competitive resume, and making a successful transition. If you have questions about life in biotech, want to learn more about the transition process, or just want to make a new contact, please come join us from 4-5pm on Jan. 17th for this small group event.

Recent Publications by NHLBI Fellows

Cai Z, Jitkaew S, Zhao J, Chiang HC, Choksi S, Liu J, Ward Y, Wu LG, Liu ZG (2014) Plasma membrane translocation of trimerized MLKL protein is required for TNF-induced necroptosis. Nat Cell Biol 16:55-65.

Carnie A, Lin J, **Aicher B, Leon B**, Courville AB, Sebring NG, de JJ, Dellavalle DM, Fitzpatrick BD, Zalos G, Powell-Wiley TM, Chen KY, Cannon RO, III (2013) Randomized trial of nutrition education added to internet-based information and exercise at the work place for weight loss in a racially diverse population of overweight women. Nutr Diabetes 3:e98. doi: 10.1038/nutd.2013.39.:e98.

Desmond R, Townsley DM, **Dumitriu B,** Olnes MJ, Scheinberg P, Bevans M, Parikh AR, Broder K, Calvo KR, Wu CO, Young NS, Dunbar CE (2013) Eltrombopag restores tri-lineage hematopoiesis in refractory severe aplastic anemia which can be sustained on discontinuation of drug. Blood.

Kraushaar DC, Zhao K (2013) The Epigenomics of Embryonic Stem Cell Differentiation. Int J Biol Sci 9:1134-1144.

Lu K, Cheng MJ, Ge X, Berger A, Xu D, Kato GJ, Minniti CP (2013) A Retrospective Review of Acupuncture Use for the Treatment of Pain in Sickle Cell Disease Patients: Descriptive Analysis From a Single Institution. Clin J Pain.

Maldonado-Baez L, Donaldson JG (2013) Hook1, microtubules, and Rab22: Mediators of selective sorting of clathrin-independent endocytic cargo proteins on endosomes. Bioarchitecture 3.

Porat-Shliom N, Weigert R, Donaldson JG (2013) Endosomes derived from clathrin-independent endocytosis serve as precursors for endothelial lumen formation. PLoS One 8:e81987.

Saeed F, Hoffert JD, Knepper MA (2013) CAMS-RS: Clustering Algorithm for Large-Scale Mass Spectrometry Data using Restricted Search Space and Intelligent Random Sampling. IEEE/ACM Trans Comput Biol Bioinform.

Scott I, Webster BR, Chan CK, Okonkwo JU, Han K, Sack MN (2013) GCN5-like protein 1 (GCN5L1) controls mitochondrial content through coordinated regulation of mitochondrial biogenesis and mitophagy. J Biol Chem.

West EE, Kashyap M, Leonard WJ (2012) TSLP: A Key Regulator of Asthma Pathogenesis. Drug Discov Today Dis Mech 9:10.

Collaborative Faculty Positions in Molecular and Cell Biology

The Department of Anatomy in the College of Medicine at Howard University is seeking to hire two faculty members at the rank of Instructor/Assistant Professor. This program is unique, in that those hired will experienced postdocs who will spend their first two years splitting their time between teaching at Howard (25%) and continuing their lab research in their current lab at NIH. During that time, Howard will pay for the salary and renovate a lab, after which the fellow would then transition to a full-time tenure track position at Howard.

Candidates will be expected to teach cell biology and microscopic anatomy in courses offered to students in the College of Medicine and Dentistry as well as graduate students. The selected candidates will be expected to participate in one or two histology laboratories per week.

Applicants may send or e-mail to:

Dr. Donald Orlic, Professor and Chairman, Department of Anatomy, College of Medicine, Howard University, 520 W St. N.W. Washington D.C. 20059 (donald.orlic@howard.edu)

The Science Beat, continued

Histone methylation is associated with heterochromatin and transcription repression. Upon lineage commitment of ESCs, their chromatins become less dynamic, due to the increased global levels of heterochromatic marks and heterochromatin-associated proteins. One histone methylation mark, H3K9me3 is involved in the terminal silencing of lineage specific genes during differentiation, and the repression of lineage-specific genes in undifferentiated ESCs.

The presence and incorporation of histone variants into nucleosomes adds an additional layer of regulation. Canonical histones are primarily expression during the S phase, while non-canonical histones express throughout the cell cycle. The incorporation of histone variants is tightly regulated. Histone variants may serve as replacement histones when canonical histones are in short supply. More interestingly, histone variants, such as H3.3 may also have unique modification signatures and functional roles. Evidence suggests that H3.3 is playing a role in ESC pluripotency. Another histone variant, H2A.Z, regulates the accessibility of developmental genes and affects their expression in a context-dependent manner.

DNA methylation often leads to gene silencing through several different mechanisms: preventing binding of transcription factors to their target sites, interfering with histone modifications that associate with gene activation. In ESCs, de novo DNA methylation has been suggested to be required for the silencing of pluripotency genes and eventually cell type commitment.

Featured Article

Good News!

By Herbert M. Geller, Ph. D.

Good news for Asian fellows!

The NIH budget has always been the bellwether for the US commitment to medical research. An significant number of new medical and pharmaceutical developments can be traced to origins in NIH funding. We have all been reading articles and have felt the effects of the sequester on the NIH budget and our own research, but an article just published in the Jan 2nd issue of the New England Journal of Medicine entitled "Asia's Ascent – Global Trends in Biomedical R & D Expenditures" actually quantifies this decline in US expenditures over the past five years, but also highlights the flip side of the equation: as US and Canadian expenses have declined (paralleled by a decline in Europe), many Asian nations have increased their expenditures on Biomedical R & D.

In their article, the authors show that, over the period of time from 2007-2012, the total US R & D budget has declined from $131 billion to $119 billion, while the world's total has increased from $227 billion to $268 billion. What is especially interesting is that they broke down totals for each country into public expenditures and expenditures by private industry. For example, in the US, public expenditures actually increased by about $900 million, but private expenses by industry declined precipitously by 15%, from $83.3 to 70.4 billion. This data supports what we have been seeing in the cutbacks in the US pharmaceutical industry.

But the good news is that the Asian nations are increasing their expenses at an amazing rate. As you might expect, China had the largest annual growth rate in Biomedical R & D, 32%. The next leading countries are South Korea, Singapore, Australia, India, Japan and Taiwan, with annual growth rates between 5-11%. China's growth is particularly interesting, from $2 billion in 2007 to $8.4 billion in 2012 – with most of that increase coming from the private sector, $1.5 billion to $6.3 billion, while the public sector grew from $0.6 to $2.0 billion. South Korea nearly doubled their research expenditures from $3.5 billion to $5.0 billion. Japan, despite its economic problems, managed to increase expenditures over that time from $28.2 billion to $37.2 billion, with a constant 75% from industrial research.

While it is impossible to predict the future, it seems likely that this trend will continue for some time to come. If so, it portends a real opportunity for those from the Asia to take advantage of this growth.

FELCOM ANNOUCEMENTS

Changes in health insurance for IRTA and Visiting Fellows.
Starting Jan. 1:

Medical network is shrinking by 3-4%. Dental plan costs are increasing. Check with your doctor and dentist about coverage.

Contact FAES with any additional questions
(301-496-8063)

Q&A with Investigator

Postdoc Kevin Ramkissoon interviews Dr. Gregory Alushin, Ph. D. , Early Independent Scientist, Laboratory of Macromolecular Interations

Bio in brief

Dr. Gregory Alushin came to the NHLBI in 2012 as a postdoctoral fellow in the Cell Biology and Physiology Center after completing a B.A. in biochemistry at Columbia University and his Ph.D. in biophysics at the University of California, Berkeley. He has received multiple honors for his early career research including the Harold M. Weintraub Graduate Student Award from the Fred Hutchinson Cancer Research Center and the Norton B. Gilula Award from the American Society for Cell Biology. A 2013 Early Independence Award from the NIH marked his transition to an independent scientist and allowed him to establish an interdisciplinary research program within the NHLBI DIR. Dr. Alushin employs cutting-edge light and electron microscopy to study the three-dimensional arrangements formed by the components of the cytoskeleton in vitro and in cells with molecular resolution. His work thus far has provided insights into cellular dynamics in areas such as cell division and further aims to impact human health by elucidating fundamental biophysical mechanisms of mechanosensation, which influences stem cell differentiation and cancer metastasis.

Kevin Ramkissoon (KR): When did you decide that you wanted to become a scientist?

Gregory Alushin (GA): I was actually a bit of a late bloomer in deciding that I wanted to become a scientist compared to a lot of other stories that I hear. When I was in high school I was much more interested in the humanities and thought that I would become a journalist. However, I had always enjoyed chemistry, and when I started my undergraduate studies at Columbia I was fortunate to enroll in an organic chemistry course for first year students taught by an amazing lecturer. Although difficult, I found the material much more engrossing than the humanities courses I was taking at the time. So I suppose the primary driver for becoming a researcher in my case was simple curiosity, which led me to take more and more chemistry, and eventually biology courses, and to start working in the lab of Prof. Alex Tzagoloff the summer after my sophomore year.

KR: Can you briefly describe your experience as an NHLBI postdoctoral fellow?

GA: I was a postdoctoral fellow for a year in Clare Waterman's lab, here in the Cell Biology and Physiology Center. Having spent my Ph.D. exclusively doing in vitro and computational work for the structural analysis of protein complexes by

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cryo-electron microscopy, I really wanted to learn how to do some cell biology since studying the behavior of a protein in a physiologically relevant setting really enhances ones ability to interpret structural results, and vice-versa. Clare was a natural choice due to her reputation as an outstanding microscopist and our joint interests in the relationship between forces and the cytoskeleton. Clare was an amazing mentor. She really believed I deserved to make the transition to independence and was extremely supportive during the entire process of my Early Independence Award application. I don't know too many PIs who would give up a postdoc so quickly just because they thought it was the right thing to do to move science forward.

KR: What have been the most challenging and rewarding aspects of your transition from postdoc to PI?

GA: My first staff members are arriving this week, so that transition is, I suppose, still underway. Logistics have never been my strongest suit, so that has been the greatest challenge for me thus far: the nuts and bolts of assembling a lab. I never imagined I would spend so much time thinking about which particular shaking incubator to buy, or the square-footage occupied by a refrigerator but this type of activity occupies a substantial portion of my day. Learning to not let it completely take over and still dedicate time every day to thinking about science and doing research is an ongoing challenge.

I enjoy working with others, and so I anticipate a particularly rewarding aspect will be getting to work on problems I am excited about with people that I am excited about. Having spent a lot of time planning, gathering resources, and interviewing people, it is super exciting to suddenly throw everything into the mix and see what happens. As the lab takes on a life of its own who knows what sort of stuff we will come up with.

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

GA: The right mixture of a willingness to try new things and follow my intuition and a very high, perhaps even extreme, level of persistence, both in terms of following a particular scientific thread and individual experiments. For example, much of my most important work in cryo-electron microscopy involved spending, say, sixteen hours sitting silently in a dark basement collecting data without knowing whether or not it was good, and usually it wasn't. Fortunately new automation tools are obviating the need for such endeavors, but being passionate about your experiment and believing in the potential importance of its results is generally critical for doing high-impact work.

KR: What advice would you give to current fellows aspiring to build a career at high-caliber research institutions such as the NIH?

GA: My own career path has been unusual in that I obtained my position contingent upon winning an Early Independence Award from the NIH Common Fund. I am happy to provide advice to anyone who would be interested in applying for this grant; however one can only apply within one year of finishing the Ph.D. Anyone who would like to discuss it should definitely contact me.

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

GA: I must admit my number of hobbies has been decreasing, but recently because of my fiancée's initiative I have taken up climbing. I also quite enjoy hiking and camping, cooking, reading fiction for pleasure, and playing with our cat, Alexa.

KR: Had you not chosen a career in scientific research, what do you think you would be doing today?

GA: I would guess that younger people in the current climate have pretty much all thought about alternative careers at some point, and I did too before deciding to pursue a postdoc. I considered a career in science writing or editing and wrote for, and eventually ran, a graduate student popular science magazine called the Berkeley Science Review. Although I didn't end up pursuing that path, I gained a lot of very valuable experience in management and science communication for a broad audience, both of which are definitely highly relevant for a research career. Even if it does not result in a career change, it is certainly my experience that spending some time doing these types of "extra-curricular" activities often leads to the acquisition of skills that will enhance one's research career.

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