

The NICHD Connection

June 2013

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Interesting Opportunity: The Health Education Outreach Program

By Pooja Modi and Cecilia Bahamon

Health Education Outreach Program (HEOP) is a community outreach project that was initiated by our friend Antonia Pusso, an NIAID postbaccalaureate fellow, in January 2012. We currently visit eight homeless shelters in Montgomery County, Maryland to discuss health issues with the medically underserved men, women, and children who live there. Given how vulnerable the homeless population is both to acute and to chronic diseases, our goal is to provide the shelter residents with current, evidence-based information about topics such as obesity, communicable diseases, and dental health. We also share useful resources to empower the homeless and help them make informed decisions about their health care with their physicians.

As members who have been involved in HEOP since the beginning, both of us have seen the project evolve into something bigger and better. Today, we have over 30 teachers, mostly NIH postbaccalaureate IRTA fellows, volunteering in small groups at the shelters. All of us have contributed countless hours building and refining lesson plans that we use as guidelines for our discussions. As a result of our hard work, we have built relationships we are proud of within the homeless communities.

Initially, however, we had many questions about how the residents at the shelters would react to HEOP. Both of us were fortunate to volunteer together at Carroll House, a shelter in Silver Spring for homeless adult men. Before approaching the men on our first day, we wondered if they would welcome a group of strangers who were approximately half their age. Would they want to open up to us and talk about their issues? Regardless of our concerns, we went in to the first class armed with a structured lesson plan on chronic pulmonary lung disease and smoking.

Although our first meeting with the men at Carroll House was successful and we were asked to come back for more lessons, we realized we needed to make the learning experience more interactive and engaging. After the first class, we let the residents' curiosity guide them in choosing the health topics we discussed with them. We incorporated more activities and chances for the residents to share their own experiences.

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Letter from the Editor

The NICHD Connection is celebrating its three-year anniversary! Over the past few years, fellows from across the institute have discussed their research, recapped numerous seminars and events, and expressed what their time at the NICHD has meant to them. From a simple idea to better connect the NICHD fellow community to a monthly publication by and for the fellows, I couldn't be happier with how this newsletter has developed over time.

Every month, I look forward to reading newsletter submissions and discussing articles with fellows. Truly, it's an honor to work with all of you in putting this together. This month's issue is no exception.

On our anniversary pages you'll find an "interesting opportunity" in the [Health Education Outreach Program](#), [award-winning research](#)

[from our postbac fellows](#), [plenty of photos](#) from recent NIH events, and a wonderful narration of the [Ninth Annual Fellows Retreat](#). Keep an eye out next month for the most popular questions asked at the retreat's roundtable career discussions.

On our anniversary issue, I want to write a special thank you to three people whose support for this project was and continues to be integral to its success: thank you to Dr. Guttmacher, Dr. Stratakis, and Brenda Hanning. Your support, as always, is very much appreciated.

Your Editor in Chief,
Shana R. Spindler, PhD

Questions, comments, or suggestions? Please send an email to Shana.Spindler@gmail.com.

The Health Education Outreach Program (continued from page 1)

For us, the most exciting parts of our lessons were when the residents opened up to each other about their health issues and debated about topics such as the benefits of prostate exams, low sodium diets, and mindfulness. We would like to think that these discussions are indicators that the shelter residents are more interested and invested in their wellbeing.

As we move forward with our mission in mind, we are eager for our third HEOP cycle to begin in October 2013. In addition to the health education we already provide, we are looking forward to initiating personalized, goal-setting meetings and cooking classes at the shelters. Although we went into the shelters with the notion that we were the teachers, we have learned far more from the shelter residents about health disparities. It has been a rewarding experience that will have a large hand at shaping our future service-oriented goals.

Because many of our members will leave for graduate school this summer, we are actively recruiting enthusiastic teachers who can contribute both time and new ideas. If you are interested in volunteering for the 2013-14 HEOP cycle or would like more information about HEOP, contact Pooja Modi at pdmodi14@gmail.com or Max Hockenbury at maxhockenb@gmail.com.



*Bottom row, starting from the left: Cecilia Bahamon, Sunny Huang, Pooja Modi, Antonia Pusso
Middle row: Brendan Miller, Ian Marpuri, Anthony Duong, Mary Ojukwu, Amy Ton, Amanda Krause
Back row: Max Hockenbury, Lindsay Matthews, Daniel Riggins*



Four NICHD Postbacs Receive OITE Poster Award

NIH Postbacs gathered in early May to share their research with the NIH community at the 2013 NIH Postbac Poster Day. Judges organized by the Office of Intramural Training & Education (OITE) evaluated each poster presentation, and postbacs scoring in the top 20 percent received an Outstanding Poster Award. *The NICHD Connection* is happy to announce that four NICHD postbacs received such an award. Continue below to learn about the exciting research from our winning postbacs!

STUDYING HUMAN METHYLATION DISORDERS IN FISH

By Brett Athans

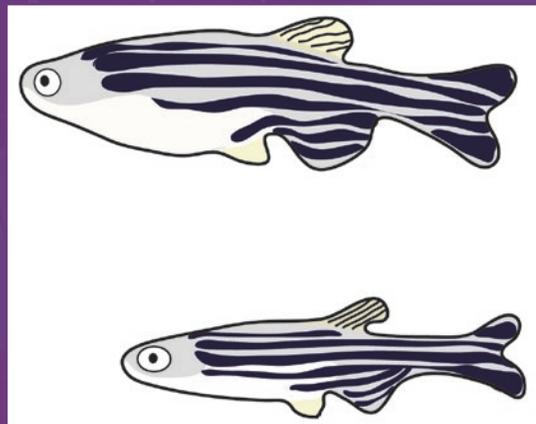
Mentor: Dr. Brant Weinstein

Epigenetic modifications to DNA—modifications that do not disrupt the actual DNA sequence—are known to affect gene expression. DNA methylation, the placement of methyl groups at certain places in the genome, plays a crucial role in gene expression regulation in normal development as well as disease, such as cancer.

To understand how DNA methylation regulates gene expression during embryonic development, we use zebrafish as a model organism to study DNA methyltransferases (Dnmts), the enzymes that methylate cytosine residues in DNA. There are zebrafish homologs for each human Dnmt gene, making it easy to study the roles of these genes in a vertebrate model system.

One of the human Dnmt genes, called Dnmt3b, is linked to ICF-1 syndrome, a disorder with defects in immune cells and craniofacial abnormalities. We isolated zebrafish Dnmt4, a homolog of human Dnmt3b, and characterized its role in hematopoietic development. Our results showed that Dnmt4 is expressed by developing hematopoietic stem cells (HSCs) in zebrafish embryos. Loss of Dnmt4 function in zebrafish leads to a gradual reduction in HSCs and downstream blood cell lineages, including immune cells.

To develop a zebrafish model for human ICF-1 syndrome, we have used a method that can target mutations to the Dnmt4 gene. We have now obtained several fish with mutations in Dnmt4, and we are currently analyzing these mutants for blood cell and craniofacial defects.



Cartoon representation of a zebrafish, provided by Brett Athans

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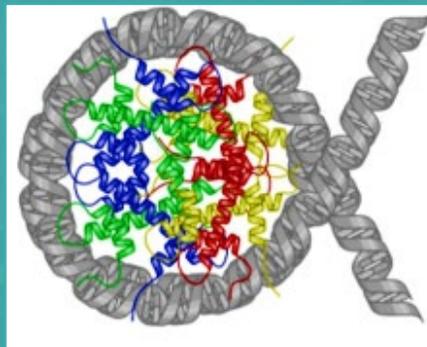
Four NICHD Postbacs Receive OITE Poster Award (continued from page 4)

HACKING HISTONES

By Ankur Narain

Mentor: Dr. Keiko Ozato

I examine how histones, proteins in the cell's nucleus that package DNA into an ordered structure, impact the regulation of innate immunity in macrophages. Specifically, I study histone H3.3, a replacement histone found in transcriptionally active genomic regions. Using a novel knock-in mouse model, I utilized biological tags to study how H3.3 is induced and deposited onto the genome after activation of macrophages by interferon- γ (IFN- γ), an important molecule within the innate and adaptive immune system.



Complete histone with DNA,
Creative Commons

I have found that H3.3 protein levels remain relatively unchanged after macrophage activation, despite a significant increase in H3.3 mRNA transcript levels. This indicates that H3.3 protein has a large endogenous pool that buffers against increases in protein levels via new translation. I also found that H3.3 was deposited towards the 3' end of genes that are activated by IFN- γ . The deposition of H3.3 was uncoupled to transcription, as H3.3 was primarily deposited after transcription of those genes had ended. This result may indicate a role for H3.3 in gene memory and reactivation of macrophages. Discovering this possible epigenetic role of H3.3 provides exciting opportunities for future research.



SEXUAL ACTIVITY MAY PROMOTE OVULATION

By Ankita Prasad

Mentor: Dr. Enrique Schisterman

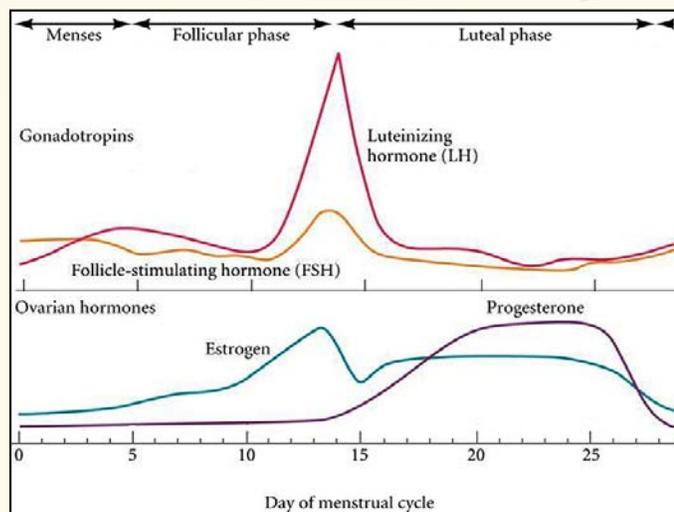
Characterizing the relationship among sexual activity, reproductive hormones, and ovulation can give us insight into female fertility. In our study, we found that women who were sexually active were less likely to have anovulatory cycles compared to women reporting no prior or current sexual activity. This relationship between sexual activity and ovulation remains even after taking into account age, race, body mass index (BMI), perceived stress level, and self-reported alcohol consumption.

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Four NICHD Postbacs Receive OITE Poster Award (continued from page 5)

We also observed significantly elevated levels of estrogen, luteal progesterone, and mid-cycle luteinizing hormone (LH), but not follicle stimulating hormone (FSH) or testosterone, in women who reported past or current sexual activity compared to women who reported never having been sexually active. These findings were from 259 women, aged 18-44, who participated in the BioCycle Study, which followed the women for ≤ 2 cycles and restricted participation in the study to women not attempting pregnancy or using hormonal contraception. Sexual activity, defined as vaginal intercourse, was self-reported via a daily diary.

Overall, sexual activity was associated with a lower probability of anovulation, concurrent with elevated estrogen, luteal progesterone, and mid-cycle LH concentrations, suggesting a possible correlation among sexual activity, reproductive hormones, and ovulation in humans.



Normal reproductive hormone variations across the menstrual cycle. Gilbert SF. Developmental Biology, 2006. Provided by Ankita Prasad.

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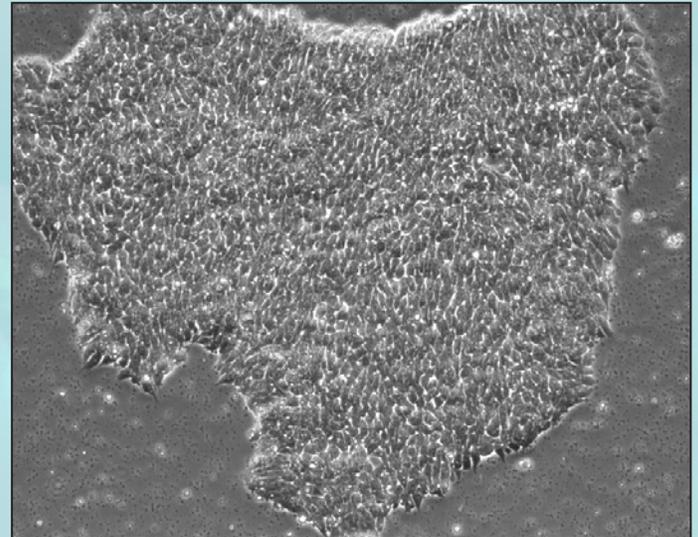
Four NICHD Postbacs Receive OITE Poster Award (continued from page 6)

CONGENITAL SYNDROME RAISES QUESTIONS ABOUT CELL FATE DECISIONS

By Amy Ton

Mentors: Kevin Francis, Karl Pfeifer, Forbes Porter

Cells are often situated in dynamic environments that contain external signals, prodding cells to activate, to extend, or simply, to function. The encapsulating and selectively permeable cell membrane acts as an initial communicator of signals to and from the cell. Our work explores how proper cell membrane integrity changes a cell's ability to respond to its environment.



Embryonic stem cell colony cultured without cholesterol, provided by Amy Ton

We are interested in how membrane integrity affects the ability of stem cells to self-renew, as stem cells use their environment to determine if they should maintain their stem-cell state or differentiate into a more mature cell type. To study this, we disrupted a stem cell's ability to synthesize cholesterol, a molecule that is highly enriched in specialized communication centers within the membrane and important for cell membrane fluidity.

We generated stem cells, called induced pluripotent stem cells, from skin cells of patients with Smith-Lemli-Opitz syndrome (SLOS), a congenital disorder characterized by defects in cholesterol biosynthesis. Additionally, we used a small molecule to disrupt cholesterol synthesis in normal human embryonic stem cells. Interestingly, when we cultured these cells in cholesterol-free conditions, the cells quickly differentiated toward neuroectodermal lineage, cells destined to become nervous system tissue. This led us to a slew of questions, such as what pathways could be driving this accelerated differentiation? Are these defects physiologically relevant? And, why are they choosing a neuroectoderm cell fate? We are currently pursuing answers to these questions—among many others.

Ninth Annual Fellows Retreat Recap

OPENING REMARKS, WITH DR. STRATAKIS
By Shana R. Spindler, PhD

“You know that I’m Greek, and I always try to give some Greek wisdom when I present,” said Dr. Constantine Stratakis as he opened the Ninth Annual NICHD Fellows Retreat. Dr. Stratakis, scientific director of the NICHD Division of Intramural Research, went on to recount the story of Mentor, a trusted companion of Odysseus in Greek mythology, who was tasked with advising and protecting Odysseus’ son, Telemachus, when Odysseus left for war. Dr. Stratakis likened the retreat to an event about mentorship and leadership. “You lead from the first time you go into a lab,” said Dr. Stratakis. A mentor is not just an advisor, but also someone who is trusted, he said.

Large round tables filled the room at the Smithsonian National Museum of the American Indian, and a scenic landscape painted the wall of glass windows to the right. Postdocs, graduate students, and support staff sat silently,

waiting to hear more words of wisdom, listening for that special recipe to obtain success even during difficult times; for it is no secret that budgets have tightened. Perhaps Dr. Stratakis could sense the anticipation. “Don’t view yourself as a victim of the times...as the weaker side of the equation” said Dr. Stratakis, “Seize the opportunity to lead!”

Attend retreats, talk to colleagues, participate in Office of Education activities, and network, network, network, he said. Submit abstracts, give talks, apply for outside funding, and—maybe most importantly—embrace learning, said Dr. Stratakis. “The secret to success is to find happiness in what you do.”



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Ninth Annual Fellows Retreat Recap

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SCIENCE, THE ARTS, & THE WORLD, WITH DR. JOHN BOHANNON

By *Erin Fincher*

Dr. John Bohannon is a scientist and an academic, just like many of us. He completed his doctoral degree in molecular biology, worked as a Fulbright scholar, and served as a Harvard visiting scholar. However, he hasn't allowed his scholarly pursuits to get in the way of having a really good time. In his keynote talk, Bohannon introduced us to the concept that science can—and should be—fun.

Dr. Bohannon presented ways to have fun with science, and regaled us with tales from his exciting career in science journalism. Bohannon encourages scientists to get out of the lab every now and then, to collaborate with others, and to find ways to combine science with other interests. He prompted us to apply our scientific knowledge and skill set to everyday questions that interest us (like whether we can distinguish pâté from dog food).

Dr. Bohannon emphasizes creativity as a way to convey science, pointing to his “Dance Your Ph.D.” competition as an example. Having fun is about engaging with the world, and Dr. Bohannon advocates going out and interacting with people. As proof that he follows his own advice: he collaborated on the award-winning “Green Porno” video series with Isabella Rossellini, an actress and artist he greatly admires.

Perhaps most importantly, he gives permission to be bizarre, to do something unexpected with our science. Not only is it fun, but it can make us stand out from the crowd. In today's competitive economic climate, being unique and memorable can be the key to getting that coveted position or funding.

Fun, Dr. Bohannon claims, is an undervalued commodity in science. Doing something interesting and exciting with your work can be a rewarding experience in itself, but can also have greater positive consequences for your growth as a scientist and ultimately, as a person. Dr. Bohannon's keynote speech was thought-provoking, inspiring, and, in keeping with his theme, an all around good time.

Learn more at <http://www.johnbohannon.org>.



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Ninth Annual Fellows Retreat Recap

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BREAKING BRAINS AND MONKEY WARS: FELLOW PRESENTATIONS 1 & 2

By Libby Barksdale, PhD

For the morning session of fellow presentations, we heard from two University of Washington alums: Dr. Megan Wyeth from the McBain lab, and Dr. Amanda Dettmer from the Suomi lab. Megan presented first with the monumental task of explaining how the auxiliary proteins Neto1 and Neto2 alter glutamate receptor expression at hippocampal synapses. But let's take a step back: when receptors (protein complexes embedded in the neuron's membrane responsible for receiving chemical signals from other neurons) don't function properly, the result is an imbalance of excitatory and inhibitory signals in the brain, which can lead to neuropathological conditions such as epilepsy.



Dr. Megan Wyeth

Research over the past decade has shown the importance of auxiliary proteins for normal synaptic function, and thus the maintenance of the excitation/inhibition balance. Using electron microscopy to examine two subsets of glutamate receptors (known as kainate and NMDA receptors) in wild type mice and mice lacking the Neto1 and Neto2 auxiliary proteins, Dr. Wyeth found that the



Dr. Amanda Dettmer

number of glutamate receptors she examined were altered in the absence of Neto1 and Neto2; kainate receptors decreased, while NMDA receptors increased. Using electrophysiology, Dr. Wyeth showed that eliminating Neto1 and Neto2 proteins resulted in reduced signal size in kainate receptors, and slower speeds of signaling in the NMDA type. Therefore, Neto proteins are necessary for proper synaptic, and ultimately brain, function.

Dr. Dettmer followed with some monkey tales, describing how she uses population studies of rhesus monkeys to investigate predictors

of infant mortality rates (IMR). Rhesus monkeys are a good model system for these studies, she explained, because the amounts of maternal and familial care necessary for an infant's survival are comparable to that needed for human infants. In 2009, an uprising at the NIH Animal Center in Poolesville, MD, resulted in the deposition of the historically dominant Family #1 and the promotion of Family #2 to top-dog (or top-monkey) status. This afforded Dr. Dettmer the opportunity to test the relationship between IMR and the stressful situations accompanying "warfare," with infant mortality defined as spontaneous abortions, still births, and infants that were culled within the first month after birth.

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Ninth Annual Fellows Retreat Recap

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Looking at three possible predictors (population density, chronic stress, and intra-group conflict), Dr. Dettmer identified a positive correlation between all three conditions and IMR. As population density increased—the tribe numbered over 100 monkeys for the first time ever in 2008—so did chronic stress, as measured via hair cortisol levels and the number of fight wounds. Since then, the population has been capped at 65-70 monkeys, and both stress levels and reported fight wounds have decreased—and importantly so has IMR. The take-home message: population-level events can, and do, affect individual mothers.



NICHD SCIENTIFIC UPDATE, WITH DR. “DENNY” PORTER

By Kevin Francis, PhD



While speakers earlier in the retreat agenda emphasized finding happiness or contentment in your career, the theme for the internal update by Dr. Denny Porter was finding fulfillment in your work. Denny is a board-certified pediatrician and clinical geneticist, senior investigator, and program head of NICHD's Program in Developmental Endocrinology and Genetics, as well as the NICHD clinical director. Dr. Porter shared his lab's recent basic science and translational clinical work on Niemann Pick, Type C1 (NPC) patients.

NPC is a rare disease characterized by mutations in the genes *NPC1* or *NPC2*, resulting in sphingolipid accumulation within patient cells and organs, causing toxicity and severe organ dysfunction. Using animal models and 2D gel electrophoresis, Dr. Porter's group identified a number of novel NPC biomarkers to provide readouts of therapeutic successes or failures. He followed up with a discussion of a potential therapy for NPC, (2-hydroxypropyl)-beta-cyclodextrin (simply known as cyclodextrin), which showed strong efficacy in animal models and subsequently moved to phase I clinical trials in the NIH Clinical Center.

Many issues arise when researchers move from the bench to bedside that must be planned for (or avoided). Dr. Porter concluded his presentation by discussing how we as scientists must balance risk versus efficacy when translating findings to patients. The time required for drug development and FDA approval, drug delivery mechanisms, and patient sample size were all problems that Dr. Porter and his group had to circumvent or overcome to move cyclodextrin toward the bedside. Dr. Porter's presentation provided excellent perspective both for basic and for clinical researchers on the successes and tribulations associated with translational science.

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Ninth Annual Fellows Retreat Recap (continued from page 11)

FLYING BLIND IN NAPPA: FELLOW PRESENTATIONS 3 & 4 By Celine Cluzeau, PhD

The afternoon fellow presentations included two fascinating topics: the neural substrates of color vision and high-throughput approaches to mapping host-pathogen protein interactions, presented by Dr. Krishna Melnattur and Dr. Kimberly Decker, respectively. Dr. Melnattur aims to explore the genetic basis of behavioral neural circuits. While in Dr. Chi-Hon Lee's lab at the NICHD, Dr. Melnattur has investigated the representation of color vision in the brain using the small fruitfly *Drosophila* as his model system.

Dr. Melnattur developed a novel aversive-conditioning behavioral assay to assess color discrimination in flies: an octagonal arena of blue and green LED panels with an infrared laser used as heat punishment to train the flies to avoid blue or green colors. Using this assay, he demonstrated that two specific photoreceptors, called R8 and R7 in *Drosophila*, are required for color vision. Furthermore, abolishing the synaptic input of two types of neurons, labelled Tm5a,b,c and Tm20, abolished the flies' color preference, implying that these specific neurons are required for perception of colors.

Next, Dr. Kimberly Decker shared her interests in identifying the mechanisms of virulence gene regulation by pathogenic bacteria. Her postdoctoral work in Dr. Matthias Machner's lab focuses on the interactions of *Legionella pneumophila*, the bacterium that causes Legionnaire's disease, and its host, the human macrophage. During the infection process, *L. pneumophila* injects about 300 effector proteins into macrophages, which appear to modify various cellular processes. However, only a few of these effector proteins have been characterized in detail.

Dr. Decker used Nucleic Acid Programmable Protein Array (NAPPA) technology, a process that immobilizes DNA templates on an array surface to generate proteins in situ just before experimentation, to screen host-pathogen, protein-protein interactions. She began her experiments with the well-studied LidA protein as proof-of-principle for this novel technique. In addition to some known targets of this bacterial protein, she identified an interesting novel target involved in negatively regulating mammalian cell growth.



Dr. Kimberly Decker

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Ninth Annual Fellows Retreat Recap

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NICHD SCIENTIFIC UPDATE, WITH DR. TODD MACFARLAN

By *Nazanin Ashourian, PhD*

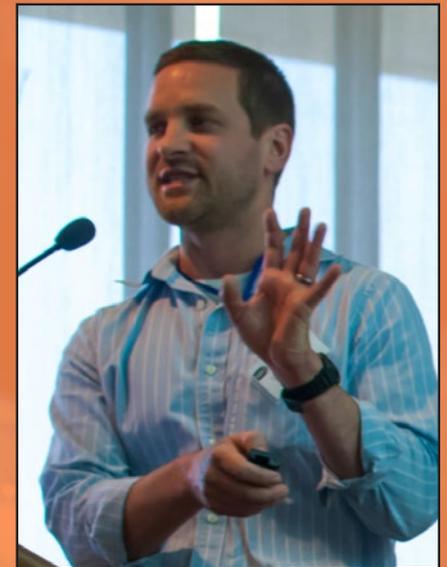
About 46 percent of the human genome is composed of transposable elements (TEs), segments of DNA that can independently replicate and change their positions in the genome, and their remnants. The debate on whether TEs have a symbiotic or a parasitic relation with our genome has been ongoing ever since their discovery by Barbara McClintock in the early 1950s, winning her the 1983 Nobel prize. While some of the initial models in the 1980s described TEs as selfish DNA, there has been growing evidence for their neo-functionalization and beneficial features in our genome.

Work by Dr. Todd Macfarlan has provided additional support for a synergetic relation between TEs and mammalian genomes. As an example of this positive relationship, Dr. Macfarlan and colleagues have shown that some of the cell fate genes essential for early mammalian embryonic development are later repressed using the regulatory sequences of retroviruses—a type of TE.

Some of Dr. Macfarlan's work centers on endogenous retroviruses (ERVs), retroviruses that have integrated their DNA into the host genome to be passed to the next generation. Macfarlan and his team found that ERVs seem to utilize preferential silencing mechanisms: i.e., the cellular mechanisms used to silence one class of retroviruses do not necessarily work on another.

To explain this observation, Dr. Macfarlan proposes a model in which universal repressor complexes target distinct ERV elements via direct interactions with zinc finger proteins (DNA binding proteins whose structures are maintained by zinc ions) that are specific for each ERV. The idea is that zinc finger proteins bind to specific (or a set of specific) sequences unique to each class of ERV elements and subsequently recruit universal repressor complexes.

Dr. Macfarlan's work is a view into the secretive world of transposable elements. Once thought to be the ultimate genomic parasites, we are learning that these DNA sequences may now be an integral part of normal development.



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Ninth Annual Fellows Retreat Recap

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KEY NOTE ADDRESS, WITH DR. SHIRLEY TILGHMAN

By Erin Fincher

Dr. Shirley Tilghman, president of Princeton University, was our second keynote speaker of the day. Dr. Tilghman gave a fascinating talk entitled "Educating a Biomedical Workforce in the 21st Century." She began by telling us about her time as a postdoctoral fellow at NIH.

When she first came to NIH in the late 1970s, the climate of postdoctoral training was very different than it is today. In 1980, it took on average of 9-12 months for investigators to secure their first NIH grant. Today, that number has skyrocketed to almost five years. The average age at which an investigator secures his or her first ROI grant is 42, and the average age of primary investigators is close to 50. In 1980, these numbers were much lower. All of this, Dr. Tilghman claims, is indicative of a deeply dysfunctional system of postdoctoral education and training. There is a clog in the educational pipeline, so to speak, but how do we fix it?

Dr. Tilghman offered a number of recommendations for changing the state of postdoctoral education in the biomedical sciences. She advocates changing the way graduate students are utilized and funded. Dr. Tilghman recommends that graduate students be treated as students, rather than cheap labor; education needs to be of primary importance during graduate training. And the training postdocs obtain needs to adequately prepare them for their next career moves.

Dr. Tilghman also advocates changing the way we fund fellowships, offering more training grants rather than research grants, capping the number of years that graduate students can be funded by NIH grants, increasing stipends for postdocs, and providing full benefits. Ultimately, Dr. Tilghman tells us, in order to unclog the educational pipeline, we need to change the culture of education in biomedicine. It may seem a monumental task, but Dr. Tilghman has provided us with some concrete steps in the right direction.



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2013 Fellows Retreat

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2013 *Fellows Retreat*

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Life Outside Lab

Earth Day
.....
Take Your Child
to Work Day
APRIL 25, 2013





Life Outside Lab

Earth Day
.....
Take Your Child
to Work Day

APRIL 25, 2013



June Announcements

A CALL FOR CLINICAL CONTRIBUTIONS

In the coming months, we'd like to highlight our clinical fellows and the work they do at the NICHD. If you would like to tell us your experience as a clinical fellow, share your research goals, suggest topics to cover, or simply give advice to younger trainees interested in clinical research, we'd love to hear from you! Please contact Shana Spindler at Shana.Spindler@gmail.com.

CALL FOR NIH CAREER SYMPOSIUM THOUGHTS

Did you attend the NIH Career Symposium on May 14? Did you have a eureka moment, where you thought, "Oh, I never knew that!"? Or did you find one fact particularly interesting or unexpected? If so, please consider sending a one- to two-sentence description of the surprising or interesting finding to the editor at Shana.Spindler@gmail.com.

June Events

MONDAY, JUNE 10, 11:30-1 PM

Town Hall meeting
Open to all members of the DIR
Building 31, room 6C6

WEDNESDAY, JUNE 26

Grantsmanship workshop
Please contact Yvette Pittman at Yvette.Pittman@mail.nih.gov in case spots open on the waitlist.