Dani Dumitriu Becomes the First Female Resident in the U.S. to Secure R01 During Training

In 2014, facing rapid decline of physician-scientists entering academia, the NIH tasked the Physician-Scientist Workforce Working Group (PSW-WG) with root cause analysis of this trend. Around the same time, Dr. Dani Dumitriu, having just completed the MD/PhD program at Mount Sinai, was battling an important career decision. During the previous two years, she had developed a mouse model to tackle her long-term goal of identifying neurocircuits of resilience and was excited about spearheading this research. Simultaneously, she found herself loving clinical medicine and could not imagine leaving her physician-half behind while continuing to advance her scientist-half. The conundrum: going the traditional route of residency followed by fellowship meant being away from the bench for a minimum of 3-5 years. Would the field of Neuroscience wait for her to finish residency? Would she have the stamina to return to this work following prolonged emersion into the clinical realm? The answer to both, according to the PSW-WG: probably not.

To solve this conundrum, Dr. Dumitriu developed a radical third alternative: integrate post-graduate clinical and basic science training. Following her match into the Pediatric Residency at Mount Sinai, she approached the departments of Pediatrics, Environmental Health, and Neuroscience with an ambitious but clearly outlined plan: interweave residency requirements with a research fellowship in Pediatric Environmental Health over the course of five years, with the goal of developing an independent research program. A faculty position in a non-clinical department would enable applying for funding.

Within a year of this custom-tailored residency, Dr. Dumitriu encountered another major challenge outlined by the PSW-WG: a complete lack of suitable funding mechanisms. Counterintuitively, the only grant she qualified for was an R award, for which “any individual with the skills, knowledge, and resources necessary to carry out the proposed research” is eligible. In contrast, K awards require a minimum of 75% research time, an unrealistic allocation during residency. In year three, Dr. Dumitriu applied for an R01 which was discussed but scored outside the fundable range. In year four, she received the award on resubmission, becoming the second resident in the country, and the first female, to secure R dollars during training. This important milestone is underscored by another finding from the PSW-WG: females comprise only 22% of NIH Research Project Grant physician-scientist awardees.

Perhaps not by coincidence—both Dr. Dumitriu and Dr. Kafui Dzirasa (the first resident awarded an R01) study the neurobiological basis of resilience. To date, research has primarily focused on the pathophysiology of disease. Very little is known about the flipside: resistance to developing disease. Yet even highly heritable disorders show incomplete penetrance. In the lab, this can be studied at the mechanistic level. For example, the Dumitriu lab examines differences in the structural connectomes of stress-activated neurons in resilient versus susceptible mice (Fig). Putative pathways can then be tackled at the developmental and environmental levels, with the goal of identifying interventions that subtly nudge the circuit toward resilience. Analogously, post-graduate physician-scientist training programs might benefit from studying index cases of successful nontraditional residencies.
A Comprehensive Meta-Analysis Shows That Sperm Concentration Has Dropped More Than 50 Percent in 40 Years

In a systematic review and meta-analysis of trends in sperm count published in July 2017 in Human Reproduction Update, Shanna H. Swan (Department of Environmental Medicine and Public Health and member of the Mindich Child health and Development Institute), together with researchers from the Hebrew University-Hadassah Braun School of Public Health and Community Medicine and researchers at the Icahn School of Medicine at Mount Sinai reported a significant decline in sperm concentration and total sperm count among men from Western countries.

Scientists have been debating whether sperm count has been going down ever since researchers in Denmark published a study in 1992 showing a 50 percent drop in sperm count between 1940 and 1990. Shanna Swan and colleagues decided to return to this question 25 years after that alarm by conducting a state-of-the-art review of the subject. To conduct the current review and meta-analysis, they searched PubMed/MEDLINE and EMBASE for English language studies of human sperm count (SC) and total sperm count (TSC) published 1981-2013. To deal with a very large number of potentially relevant articles (7518 abstracts and 2510 articles) reporting primary data on SC they assembled a team of seven researchers and worked with a research librarian and a meta-analysis expert. All selected abstracts and articles were reviewed following a predefined protocol, following PRISMA guidelines. After exclusions of articles not meeting eligibility criteria the meta-analysis included 244 estimates of SC and TSC from 185 studies of 42,935 men who provided semen samples 1973-2011. Slopes were examined within broad geographic groups (North America, Europe and Australia, called “Western” and within two categories of subjects (those who had proven their fertility and those who were not selected by fertility). The slopes of SC and TSC were estimated as functions of sample collection year using simple linear regression and weighted meta-regression models. The latter models were adjusted for covariates and modification by fertility and geographic group. SC declined significantly between 1973 and 2011 (slope in unadjusted models =-0.70 x million/ml/year; 95% CI -0.72 to -0.69; p<0.001; slope in adjusted meta-regression models =-0.64; -1.06 to -0.22; p=0.003). Slopes were modified by fertility and geographic group, with a steeper slope among Unselected Western (-1.58; -2.02 to -0.74; p<0.001; 52.4% overall) vs. Fertile Western (-0.68; -1.51 to -0.05; p=0.053). Trends for TSC were similar to those for SC and results changed minimally in sensitivity analyses. This comprehensive analysis reports a significant decline in sperm count (as measured by SC and TSC) between 1973 and 2011, with a 50-60% decline among men unselected by fertility from North America, Europe and Australia.

In this comprehensive analysis, sperm count (whether measured by SC or TSC) declined significantly among men from North America, Europe and Australia during 1973-2011, with a 50-60% decline among men unselected by fertility. These findings strongly suggest a decline in male reproductive health, plausibly linked to changing environment and modern lifestyle. This major current public health challenge should be addressed. Research on causes and implications of this decline is urgently needed.

Niels Skakkebæk, a Danish pediatrician and researcher whose 1992 paper with Elisabeth Carlsen reporting large long-term declines in human sperm count kicked off over 20 years of debate, commented: “Most worryingly [in Denmark] is that semen quality is in general so poor that an average young Danish man has much fewer sperm than men had a couple of generations ago, and more than 90 percent of their sperm are abnormal.”
**Amy Kontorovich, MD, PhD**

**Amy R. Kontorovich**, MD, PhD is an Assistant Professor of Medicine in Cardiology and is the Medical Director of Adult Cardiovascular Genetics in the Zena and Michael A. Wiener Cardiovascular Institute. Dr. Kontorovich received a BSE in Bioengineering from the University of Pennsylvania where she studied biomechanical effects on endothelial cells in atherosclerosis. She fulfilled the MD and PhD degrees from Stony Brook University. Her doctoral work with Dr. Ira Cohen involved developing a novel quantum-dot nanoparticle-based method for tracking stem cells after delivery to the heart. Dr. Kontorovich completed both the Internal Medicine residency and fellowship in Cardiology at the Icahn School of Medicine at Mount Sinai. Her research is focused on myocarditis, an inflammatory condition of the heart that can lead to sudden cardiac death and cardiomyopathy. She studies genetic factors that mediate this rare and potentially fatal outcome of infection by common viruses.

**Recent Publications:**


**Ke Hao, ScD**

**Dr. Ke Hao** is a tenured Associate Professor in the Department of Genetics and Genomic Sciences, and a member of the Icahn Institute for Genomics and Multiscale Biology. He received his undergraduate degree in Biological Sciences and Technology at Tsinghua University, China. He graduated with a Doctor of Science degree at Harvard University, focusing on algorithm development and analysis of genetics and genomics data. In 2012, he was recruited to the Icahn Institute for Genomics and Genomic Sciences, and a member of the Icahn Institute for Genomics and Multiscale Biology. He received his undergraduate degree in Biological Sciences and Technology at Tsinghua University, China. He graduated with a Doctor of Science degree at Harvard University, focusing on algorithm development and analysis of genetics and genomics data. In 2012, he was recruited to the Icahn Institute for Genomics and Genomic Sciences, and a member of the Icahn Institute for Genomics and Multiscale Biology. He invented an integrated system, Bio3Air, to measure the amount of ambient PM$_{2.5}$ inhaled over a long period of time with very high spatial and time resolution. The system is now applied in environment epidemiology studies in China led by Dr. Hao. He was also involved in a large number of genetics studies, including linkage scans, genome-wide association studies (GWAS) and whole-exome/whole genome studies (NGS) on many disease areas (e.g COPD and IBD). Dr. Hao led projects to systematically characterize genetic control of transcriptome and proteome (i.e., eQTLs and pQTLs) in human tissues and also construct gene networks. The xQTLs were integrated with GWAS or NGS to provide insight on the molecular mechanism underlying disease genetic predisposition.

**Recent Publications:**

Trainee Pilot Projects: 2017 Awardees

Project Title: “Cell-type specific transcriptome profiling in umbilical cord blood”

Investigator: Michael S. Breen, PhD, Postdoctoral fellow, Seaver Autism Center for Research and Treatment, Department of Psychiatry and Genetics and Genomics Sciences

Primary Mentor: Joseph D. Buxbaum, PhD, Department of Psychiatry and Genetics and Genomics Sciences

Secondary Mentors: Dan J. Stein, PhD (University of Cape Town) and Meaghan Jones, PhD (University of British Columbia)

Abstract: Several recent reports, including preliminary data from our large prospective longitudinal mother-infant cohort, the Drakenstein Child Health Study in South Africa, support the utility of gene expression in umbilical cord blood (UCB) to identify the molecular changes associated with prenatal exposures to adverse in utero environments. However, cellular heterogeneity in UCB has not been fully appreciated. Failure to account for cellular composition in gene expression studies of bulk tissue can result in both widespread false positive and false negative results. Moreover, there is a dearth of studies exploring the gene expression profiles within specific UCB cell subsets, which will enable the identification of UCB cell-type specific markers that could drive the discovery of cellular or molecular differences that are potentially masked by bulk UCB sampling techniques. This project will 1) perform genome-wide RNA-sequencing on seven flow-cytometry sorted UCB cell subsets, including monocytes, NK cells, CD4+ and CD8+ T cells, B cells, neutrophils and nucleated red blood cells. Subsequently, 2) cell-type specific gene expression signatures will be used to develop computational tools for predicting frequencies of multiple cell types in gene expression profiles of bulk UCB samples, which will be validated using cell frequencies determined by flow cytometry on paired samples. These data will be 3) applied to our already existing mother-infant studies of UCB gene expression and will provide an open-resource for in silico estimation of the relative proportion of each cell type in bulk UCB, which will also benefit other researchers.

Trainee Investigator: Oscar Rodriguez, PhD Candidate, Department of Genetics and Genomics Sciences

Primary Mentor: Andrew Sharp, PhD, Department of Genetics and Genomics Sciences

Secondary Mentor: Ali Bashir, PhD, Department of Genetics and Genomics Sciences

Abstract: Expansions of tandem repeats (TRs), most commonly triplet repeats, are known to underlie >20 different human neurological diseases. While several of these, e.g. Huntington's disease, are usually adult onset disorders, many repeat expansion disorders such as Friedreich's ataxia, myotonic dystrophy and Spinobulbar muscular atrophy often show childhood onset. Furthermore, expansion of the FMR1 locus represents the most common cause of congenital intellectual disability in males. Although recent advances enable TR loci to be genotyped from high-throughput sequencing, short-read technologies are limited for the study of TRs. Specifically, only TR tracts that can be completely spanned by a single read can be reliably genotyped. As pathogenic repeat expansions that underlie neurological disease are typically larger than a 150bp Illumina read, the identification of expanded TRs is intractable to short-read sequencing, and therefore this class of mutation remains essentially undetectable with current sequencing technologies.

We have shown that long-read sequencing technology can detect previously missed structural variants such as large TR expansions. Combined with novel algorithms that we developed that allow the accurate genotyping of very large TRs, we propose that the application of Pacific Biosciences sequencing to carefully selected cohorts has the potential to identify novel pathogenic repeat expansions underlying a number of human neurological diseases.

To generate pilot data for a larger project, this proposal lays out a framework to develop the necessary background datasets and perform long-read sequencing to identify a putative novel tandem repeat expansion using a rare family with a history of dominant ataxia.

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Trainee Highlights

MCHDI Trainee Leadership Committee in Second Year of Enhancing Training Environment

The Trainee Leadership Committee (TLC), now in its second year, was formed with the goal of building a community of young scientists focused on child health. In the first year, they consolidated a trainee mailing list, hosted a social, organized workshops on negotiation and policy, and established a trainee pilot grant program. The winners of the inceptive pilot grant were Oscar Rodriguez and Michael S. Breen, PhD. Oscar is a PhD candidate in the labs of Ali Bashir and Andrew Sharp. He will perform long-read sequencing to identify novel tandem repeat expansions in a family with a history of dominant ataxia. Michael is a postdoctoral fellow in Joseph Buxbaum’s lab and his pilot project will measure cell type specific transcriptome profiles from umbilical cord blood in order to build more effective models for extracting cell subset-specific information directly from heterogenous samples. Congratulations!

This year, the TLC again brought together over 50 predocs and postdocs for our annual kick-off social. In addition to providing a venue where trainees can get to know each other, they also surveyed the attendees on workshops they would like to see in the coming year. In contrast to last year’s more focused results, the interests were across the board: how to give a job talk, science “speed dating,” accessing the Mount Sinai Data Warehouse, working with the IRB, and science and/or healthcare policy. Their first official event was on October 3rd—they organized a grant writing panel (featuring trainees with funded grants) as part of the Child Health Research seminar series. The TLC are looking forward to workshops in the winter and spring, and are open to suggestions!

Finally, the committee would like to welcome the two newest TLC members, Allison Kann and Maya Deyssenroth.

Jeanette Stingone, PhD, MPH—
Postdoctoral Fellow, Department of Environmental Medicine and Public Health

Maya Deyssenroth, PhD—DrPH,
Postdoctoral Fellow, Department of Environmental Medicine and Public Health

Felix Richter—MD/PhD Student, Graduate School of Biomedical Sciences

Allison Kann—PhD Student, Graduate School of Biomedical Sciences

Allison is a PhD student in Dr. Rob Krauss’s lab, studying the role of cell adhesion proteins in the muscle stem cell niche. Maya is a postdoctoral fellow in Dr. Jia Chen’s lab focusing on placental epi/genomic analyses in relation to intrauterine metal exposures and postnatal health effects.

Jeanette Stingone, PhD, MPH
Postdoctoral Fellow, Department of Environmental Medicine and Public Health

Maya Deyssenroth, PhD
Postdoctoral Fellow, Department of Environmental Medicine and Public Health

Felix Richter
MD/PhD Student, Graduate School of Biomedical Sciences

Allison Kann
PhD Student, Graduate School of Biomedical Sciences

Save the Date
Children’s Health Seminars and Workshops hosted by the TLC
February 6, April 3, and May 15, 2018 • 12–1 pm in Room L6-14 of the Icahn Building
Feel free to contact Allison, Felix, Jeanette or Maya with suggested topics and/or speakers.


5th Annual MCHDI Retreat

Save the Date
5th Annual MCHDI Retreat

Date: November 28, 2017
Time: 8:30 am – 5:15 pm
Location: Harmonie Club Ballroom, 1st Floor
4 E 60th St, New York, NY 10022