

***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
Division of Intramural Research
BOARD OF SCIENTIFIC COUNSELORS
MINUTES
June 3, 2016
Building 31, Room 2A48

Members Present: Dr. Jerome F. Strauss (chair), Dr. Rita J. Balice-Gordon (by phone, closed session only), Dr. Jeanne Brooks-Gunn (by phone, closed session only), Dr. P. Michael Conn, Dr. Laurinda Jaffe, Dr. Frances Jensen (nominee), Dr. Antonios Mikos, Dr. Tarun B. Patel, Dr. Scott A. Rivkees, Dr. Yoel Sadovsky, Dr. Joan A. Steitz, Dr. Susan S. Taylor, Dr. Eric Vilain (nominee), and Dr. Michelle A. Williams.

Federal Employees Present: Dr. Constantine A. Stratakis, Dr. Catherine Spong, Dr. Charles Dearolf, Ms. Brenda Hanning, and at various times additional members of the NICHD staff participated in the meeting.

I. OPEN SESSION

The meeting convened at 8:05 a.m. Dr. Stratakis started by saying that the agenda for this meeting would be different than previously, as Dr. Spong, Acting Director, NICHD, would not be able to join the meeting until later in the morning, and, thus, other presentations would precede that of the Director of the Institute.

To introduce the first two speakers, Dr. Stratakis provided an overview of the recent NICHD Division of Intramural Research (DIR) reorganization that included a number of changes to the Office of the Clinical Director (OCD). Clinical support staff members are now supervised by the OCD; their services are assigned to investigators according to need.

Dr. Stratakis introduced two of the newly hired (2015) staff clinicians, Drs. Jenny Blau and Andrew Demidowich, who would be presenting. Dr. Blau is the Associate Director, Inter-Institute Endocrinology Training Program (IETP) and Co-Chief of Internal Medicine. Dr. Demidowich is Co-Chief of Internal Medicine and serves as the NICHD Liaison for the Medical Research Scholars, a program from which he graduated. Both Drs. Blau and Demidowich completed their clinical fellowships with the Inter-Institute Endocrinology Training Program.

Staff Presentations

Jenny E. Blau, M.D., Staff Clinician & Co-Chief, Internal Medicine, NICHD and Associate Director, Inter-Institute Endocrinology Training Program

Associate Program Director [0.5 FTE] and Co-Chief, Internal Medicine [0.3 FTE]

After less than a year serving as the Assistant Deputy Program Director, Dr. Blau has been appointed as the Associate Program Director for the IETP. In addition, as Co-Chief, her role involves several complementary functions, including:

1. Teaching and mentoring
 - a. Didactic lectures on a variety of endocrine topics including: endocrine emergency management, rare and common bone disease, anorexia nervosa, pregnancy-related hormone physiology and pathophysiology, reproductive endocrinology, etc.
 - b. Organize and facilitate Research Oversight Career Development quarterly meetings
 - c. Semi-annual clinical and research evaluations of fellows
2. Overseeing clinical care of patients
 - a. Principal investigator of *T-CH-1021* “Evaluation of Adults with Endocrine-Related Conditions” to facilitate endocrine-related evaluations of adults to advance the clinical skills of fellows and to provide stimuli for new clinical research initiatives
 - b. Quality assurance review of surgical cases as a part of Protection of Human Subjects Research within NICHD
 - c. Consult service attending for patients admitted to other institutes; oversee fellows taking care of patients admitted to NICHD protocols in 5NW and 5SW Day Hospital
 - d. Lead multidisciplinary rounds with NICHD, NIDCR, NCI, and NIDDK faculty
3. Strategic leadership of the program
 - a. Created and executed a new IETP training program website, which reflects the program goals, structure, and highlights the current research of faculty, fellows, and prominent alumni
 - b. Retention and recruitment strategies

Research Interests [0.2 FTE]

Dr. Blau’s research has focused on the side effects and safety issues associated with of a new class of oral anti-diabetic drugs called sodium glucose co-transporter 2 (SGLT2) inhibitors, which target renal glucose reabsorption. She has approached this by studying pharmacodynamic effects to gain insight into the pathophysiological mechanisms mediating the adverse effects of the drugs. She has had two high impact journal publications reviewing the literature and proposing mechanisms accounting for adverse effects on bone as well as ketoacidosis.

SGLT2 inhibitors have demonstrated favorable and exciting benefits including reduction of major adverse cardiovascular events and improvement in diabetic kidney disease, yet have also been associated with increased treatment-emergent bone fractures. This prompted the FDA to require changes in the label for the first in class drug, canagliflozin. Dr. Blau is the lead investigator in a randomized crossover design to study healthy adults during two sequential 5-day inpatient stays with daily serial blood and urine testing. The

primary end-point was the mean of 9 determinations of plasma intact FGF23 immunoactivity between 24-72 hr. The results from a pre-planned interim analysis (n=10) demonstrated that canagliflozin significantly increased serum phosphate within 12hr. probably triggered by the increase in phosphate, mean FGF23 (24-72 hrs) increased by 30.8 ± 8.9 pg/mL (+36%; $p=0.007$, paired t-test). Associated with increases in FGF23 and/or phosphate, 1,25-dihydroxyvitamin D levels decreased significantly (Days 2-5). Furthermore, PTH increased (Days 4-5), providing evidence of secondary hyperparathyroid physiology. The findings of this research suggest approaches to mitigate and/or prevent treatment-emergent bone effects, which could be particularly important for youth with type 2 diabetes (or possibly type 1 diabetes, if approved) who may be on this drug for many years. This data will be presented during an oral panel presentation at the American Diabetes Association 2016 Annual Meeting.

A few questions by BSC members followed. A propos of whether the IETP slots are going unmatched, Dr. Blau noted that NIH's program is different from others in academe because of the additional research component, so it attracts different candidates; there have been no unmatched slots. However, Dr. Stratakis added that he wants to ensure the trainees are a good fit for NIH's physician scientist training programs, even if that means that spots may go unfilled, as the percentage of trainees interested in a physician scientist's career declines.

Dr. Stratakis then introduced the next speaker, Dr. Demidowich.

Andrew P. Demidowich, M.D., Staff Clinician & Co-Chief, Internal Medicine, NICHD and Liaison, NICHD Medical Research Scholars Program

Dr. Demidowich joined NICHD upon completion of his Adult Endocrine Fellowship at the NIH in July 2015. As a staff clinician, his responsibilities are divided, 80% clinical and 20% research. His clinical duties include being the 5NW NICHD Ward Co-Chief along with Jenny Blau, MD, as well as the Internal Medicine consultant for other NICHD protocols. As the 5NW Ward Co-Chief, he is on-call 38 weeks of the year overseeing the clinical care that the first-year endocrine fellows provide to patients admitted under NICHD protocols. Typically, four to eight patients are admitted each week, and his duties include rounding with and teaching the fellows, ensuring that the correct orders (and tests) are placed, identifying errors or complications that may have been missed, and acting as backup resource in case the Primary Investigator is unavailable. In this role, he has created disease-specific templates and calculators for the first-year endocrine fellows to help in the interpretation and analysis of the work-up of Cushing's Syndrome and Hyperaldosteronism, a daunting task for novice endocrinologists. Moreover, he reviews all NICHD cases scheduled to go to the OR to ensure that they are medically cleared and are clinically appropriate for surgery.

As the internal medicine consultant, Dr. Demidowich is available to help with adult patients normally seen under NICHD pediatric or genetics protocols. Specifically he has been consulted on adult subjects with Niemann-Pick Disease Type C who have had acute complications of their disease, as well as evaluations of adults with osteogenesis imperfecta. Lastly, he has acted as the primary attending for subjects admitted to the

NIH Clinical Center under the Familial Sarcolemmal Musculodystrophy protocol (13-CH-0112).

Dr. Demidowich has been actively involved in several research projects, but his primary interest is investigating obesity-induced inflammation and mitigating its effects on metabolic syndrome (MetS). Innate immunity is activated in obesity by circulating molecules such as fatty acids and cholesterol crystals by binding to nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3 (NLRP3) receptors in adipocyte tissue macrophages. This binding stimulates NLRP3 oligomerization, inflammasome formation, and proinflammatory cytokine activation, which in turn leads to insulin resistance and decreased pancreatic beta-cell reserve. Several mouse models and human studies have shown that the suppression of this chronic low-level inflammatory state improves metabolic dysregulation and may impede the onset of diabetes and cardiovascular disease. As there are limited medical therapies to ameliorate obesity-related metabolic dysregulation, he has created a randomized, double-blinded, placebo-controlled pilot trial (14-CH-0119) investigating the effects colchicine, a potent inhibitor of the NLRP3 inflammasome, in forty obese adults with MetS, under the tutelage of Dr. Jack A. Yanovski. Outcomes measured include changes in insulin resistance, beta-cell reserve, systemic inflammation, and stool microbiome. Using adipose tissue obtained from biopsies, the lab is also studying colchicine's local effects on inflammation and insulin resistance.

Dr. Demidowich is also working with Dr. Yanovski to investigate the effects of the *MC3R* T6K+V81I double mutation in obese adults (13-CH-0097). They have found that homozygosity for this haplotype is associated with greater adiposity. Despite their greater adiposity, it seems as though these individuals are protected from a pro-inflammatory state, the reasons for which they are still investigating.

In addition, Dr. Demidowich is working with Dr. Stratakis to investigate disorders of the adrenals, including hyperaldosteronism, primary macronodular adrenal hyperplasia (PMAH), and Carney's Complex. Specifically he is examining whether individuals with hyperaldosteronism and germline mutations in *ARMC5* have a unique laboratory profile during adrenal venous sampling (AVS), and whether nationally accepted cut-offs for AVS should be revised. He also participates in other clinical projects within the Stratakis lab.

Questions followed. Dr. Stratakis thanked both speakers and asked Dr. Jack Yanovski to introduce the next presenter. Dr. Yanovski then introduced the next speaker, Dr. Dezmound Taylor-Douglas, a graduate student in his Section of Growth and Obesity supported by the NICHD Developing Talent Program. Dr. Taylor-Douglas was recently awarded his Ph.D. from Howard University and presented some data and results from his thesis work to the BSC.

Dezmound Taylor-Douglas, Ph.D., NICHD Scholar, Section on Growth and Obesity

Exploring Adipocyte Metabolic Processes to Explain the Obese phenotype of the Human Melanocortin 3 Receptor Homozygous C17A+G241A Knock-in Mouse

Background: In children, homozygosity for the *MC3R* C17A + G241A partially inactivating “double mutation” is associated with obesity. No prior studies have evaluated the mechanisms associated with the expansion of the white adipose tissue (WAT) associated with the *MC3R* C17A + G241A haplotype.

Methods: To elucidate the phenotype of *MC3R* C17A + G241A, the lab created homozygous knock-in mice, replacing *Mc3r* with human wild type *MC3R* (*MC3R^{hWT/hWT}*) or with human *MC3R* C17A + G241A (*MC3R^{hDM/hDM}*). To investigate the mechanisms for the expansion of WAT in *MC3R^{hDM/hDM}*, Dr. Taylor-Douglas assessed WAT gene expression using microarray analysis. Activated lipolysis was assessed by treating isolated adipocytes from *MC3R* knock-in epididymal fat pads with 50nM isoproterenol or 100µM forskolin to measure cAMP generation, and glycerol and free-fatty acid release. Adipocyte phosphorylated-HSL and lipid droplet colocalization was also examined with fluorescent microscopy.

Results: *MC3R^{hDM/hDM}* mice had greater body weight and fat mass (p’s < 0.01). The much larger WAT and fat cell diameter of *MC3R^{hDM/hDM}* demonstrated impaired isoproterenol-induced lipolysis in comparison to *MC3R^{hWT/hWT}*. Compared with *MC3R^{hWT/hWT}*, *MC3R^{hDM/hDM}* had a significant downregulation of genes that promote lipolysis (p<.0001). *MC3R^{hDM/hDM}* WAT exhibited significantly decreased mRNA and protein expression of lipolytic enzymes including ATGL and HSL. *MC3R^{hDM/hDM}* adipocytes that were activated with isoproterenol had, relative to *MC3R^{hWT/hWT}* mice, somewhat impaired activation of adenylyl cyclase, as demonstrated by a significant decrease in cAMP production. However, *MC3R^{hDM/hDM}* had a much more marked decrease in glycerol and FFA release of glycerol after isoproterenol-stimulated activation of lipolysis. *MC3R^{hDM/hDM}* MSCs differentiated into adipocytes demonstrated decreased lipid droplet/p-HSL colocalization after isoproterenol-stimulated activation of lipolysis.

Conclusion/Discussion: The human *MC3R* C17A + G241A haplotype appears to stimulate an expansion of adipose tissue that is at least partially due to impaired beta-adrenergic stimulated lipolysis. How *MC3R* coordinates lipolytic signaling processes in WAT warrants further investigation.

Questions followed. The BSC praised Dr. Taylor-Douglas on his nice presentation. When asked about his plans, Dr. Taylor-Douglas indicated that he would be starting a postdoctoral fellowship at the Gladstone Institutes in San Francisco in the laboratory of Dr. Eric Verdin.

Scientific Director’s Presentation

Dr. Stratakis began his presentation by noting that there were a number of outgoing BSC members following this meeting, as well as some new members of the BSC. He thanked Drs. Jaffe, Patel, Steitz, and Strauss for their years of service. Three new members have been recruited and will join the BSC at the next meeting on December 2, 2016. They are **Dr. Kate Ackerman**, a developmental biologist, geneticist, and pediatrician from the University of Rochester Medical School, **Dr. Serdar Bulun** from Northwestern University who will provide

expertise in endocrinology, obstetrics and gynecological research, and **Dr. Sophia Tsai**, a molecular and developmental biologist from Baylor College of Medicine. The fourth nomination is pending and Dr. Stratakis invited the BSC to submit any recommendations of potential candidates. **Dr. Scott Rivkees** will serve as the next chair of the BSC. **Dr. Michelle Williams**, who was just named the next dean of the Harvard T.H. Chan School of Public Health, has agreed to serve on the BSC for one more year until June 2017. It was also announced that **Dr. Rita Balice-Gordon** has accepted a new position as head of the Neuroscience Research Unit at Sanofi. Dr. Stratakis congratulated both Drs. Williams and Balice-Gordon and thanked them for their continuing service to the BSC, despite their new and highly demanding roles.

Dr. Stratakis then reviewed the tasks of the BSC to evaluate the research of NICHD DIR and advise institute leadership on programmatic decisions and resource allocations. The goal of the intramural program is to promote high-risk, high-impact laboratory and clinical investigation that could not be readily supported in the extramural environment. The BSC reviews site visit reports and tenure-track investigators on an ongoing basis, and meets twice a year, each June and December. The NICHD DIR Guidelines for Site Visit Reviews is a dynamic (i.e. continuously updated) policy document that has been in effect since 2010. While the NICHD DIR uses a scoring system similar to that used in extramural study sections, the review of an intramural laboratory differs in that it covers the whole research portfolio of an investigator, not just a single project. Site visit reviews allow for prioritization between laboratories but also between projects within a laboratory. To maintain excellence within the intramural program, all laboratories must be rigorously reviewed.

The tenure process was then reviewed. For tenure consideration, both site visit and BSC reviews are required. If both are positive, an individual will move forward for review by the institute's Tenure and Promotions Committee. NICHD's Tenure and Promotions Committee is chaired by the deputy scientific director, Dr. Chris McBain. Finally, the case is reviewed by the NIH Central Tenure Committee.

This is the process that will be followed for Dr. Ruzong Fan, from the Division of Intramural Population Health Research (DIPHR), who was reviewed in December 2015 and for whom a decision on whether to move him forward for tenure consideration is needed.

Dr. Stratakis added that to maintain the vitality of the DIR existing resources need to be reallocated to allow for the recruitment of new tenure-track investigators. All investigators are also encouraged to apply for outside funding opportunities.

NICHD DIR's staff currently numbers around 1000, including 59 tenured and 4 tenure-track investigators as of October 1, 2016. More than 100 clinical protocols are run by NICHD, two-thirds of them at the NIH; five accredited graduate medical education programs train clinical fellows, some in collaboration with other ICs (e.g., Medical Genetics run by NHGRI). The NICHD has an overall budget of more than \$1.3B, of which approximately 14% goes to supporting the DIR. Of the approximately \$180M the NICHD DIR received in FY16, 34% was allocated toward personnel, 21% went toward consumables, 20% went toward the NIH Office of Research Services to cover buildings, maintenance, etc., and 15% was paid in support of the NIH Clinical Center. Dr. Stratakis noted that the operating budget has increased by 2%, from 19% to

21%, as a percentage of the whole, under his leadership as a scientific director despite a \$5M increase in school tax to the Clinical Center and a \$3M increase in management fund (NIH assessment) over the same period. This was accomplished by the closure of certain projects and the related savings in personnel salaries. Since FY10, the DIR has undertaken a huge effort to co-localize laboratories into five or six research hubs around the Bethesda NIH campus. The cost of these renovations and moves will be approximately \$4.8M in FY16, with costs expected to taper off after FY17. Animal care costs are currently \$4.6M, including ~\$2M in support of the Poolesville facility. Dr. Stratakis reminded the BSC that NICHD is currently phasing out its presence at the Poolesville facility and expects this money to be added to the consumables budget. It is expected that approximately \$5M will be spent in FY16 on capital equipment. The Perinatology Research Branch, headed by Dr. Roberto Romero, is supported by a \$15.5M contract with Wayne State University in Detroit, MI, and the program receives an additional sum of approximately \$1.5-\$1.7M for operating costs from the DIR. In addition to the discussed DIR allocation, DIPHR has a budget of approximately \$9M including \$7M for operating costs and \$1.9M in assessments.

As the purchasing power of the NICHD DIR has decreased over the past several years, the number of personnel has also decreased. The total staff has decreased from 1073 in FY12 to 980 in FY16. A number of senior investigators have retired including Drs. Mark Mayer and Ralph Nossal. Dr. Jennifer Lippincott-Schwartz left NIH in February 2016 to take a position as a Group Leader at the HHMI Janelia Farm Research Campus but will continue to work with the NICHD DIR one day a week as a scientist emerita. Dr. James Russell retired in April 2016 and his nomination as a scientist emeritus is pending. Dr. Igor Dawid has announced his intention to retire at the end of 2016. Dr. Stratakis also informed the BSC of the passing of both Dr. Donald Rau and Dr. Kuo-Ping Huang. Dr. Rau's lab had focused on elucidating the interconnections of forces, structures, and dynamics of biologically important assemblies. Dr. Huang, who had retired and was appointed a scientist emeritus, was known for his contributions to our understanding of the body's control of metabolism, cell signaling, and brain function.

Dr. Stratakis then presented a number of personnel changes related to the reorganization of the Office of the Clinical Director.

- Dr. **Jenny Blau** was hired in July 2015 as a staff clinician who serves as Co-Chief of the Internal Medicine Ward as well the Assistant Deputy Program Director, Inter-Institute Endocrinology Training Program. She presented to the BSC earlier in the meeting.
- Dr. **Andrew Demidowich** was hired in July 2015 as a staff clinician who serves as Co-Chief of the Internal Medicine Ward and also serves as NICHD Liaison to the NIH Medical Research Scholars Program. Dr. Demidowich also presented to the BSC earlier in the meeting.
- A third staff clinician, Dr. **Simona Bianconi**, who specializes in genetics, was hired in November 2015 and will be asked to present to the BSC in December 2016 or June 2017.

Several honors and awards were also presented.

- Dr. **Mihaela Serpe** was awarded tenure on February 1, 2016 by the NIH Central Tenure Committee. In response to a question, Dr. Stratakis told the BSC that investigators get additional resources once they receive tenure.
- Dr. **Matthias Machner** was awarded tenure on March 21, 2016 by the NIH Central Tenure Committee.
- Dr. **Jack Yanovski** received a Bench to Bedside Award of \$50K/year for two years to study *Attention Bias Retraining in Adolescents with Loss of Control Eating*.

An update was provided on the efforts to open up the NIH Clinical Center to extramural investigators through collaborations with intramural researchers. NICHD continues to participate in this opportunity, which is beginning its fourth cycle of applications.

As part of the Human Placenta Project, the NICHD Office of the Director allowed intramural investigators to compete for funding. Two awards were made in FY16 to (1) Dr. Amir Gandjbakhche for *Real Time Oximetry of Anterior Placenta Using Near Infrared Spectroscopy*, a renewal of previous funding, and (2) Dr. Todd Macfarlan for *Quantifying Placental Gene Expression from Maternal Plasma-isolated Cell-free Nucleic Acids for Real-time Monitoring of Placental Health*.

Investigators also had the opportunity to compete for the second cycle of the NICHD DIR Director's Awards, which provides two years of funding in FY16-FY17. Twenty-five applications were received and \$2M was awarded supporting eight different projects. This opportunity was created based on the recommendation of the Blue Ribbon Panel to foster new collaborations within the DIR. The application was based on a modified R-21 and an external review committee of NICHD and NIH extramural staff conducted the reviews.

As part of NICHD's efforts to advance our understanding of how the Zika virus infection affects reproduction, pregnancy, and the developing fetus, the NICHD Office of the Director gave DIR investigators the opportunity to compete for Zika Virus Research Awards. Two awards were funded, to (1) Drs. Leonid Chernomordik and Joshua Zimmerberg to study *Zika Virus Entry into the Cells: Assays and Mechanisms*, and (2) Dr. Leonid Margolis to study *Pathogenesis and Transmission of Zika Virus in Human Tissue ex vivo*.

The NICHD DIR is currently recruiting for up to four tenure-track or mid-level investigators in the areas of clinical and translational research in pediatric or women's health, cell/development biology, and basic or translational neuroscience. Two tenure-track investigators have already been recruited: Drs. Katie Drerup and Claire Le Pichon. Dr. Drerup is expected to begin working October 1, 2016 with the developmental biology group. Dr. Le Pichon, a neuroscientist, will start sometime during the summer/fall 2016. Both will be invited to present to the BSC in the coming year. The Lasker Clinical Research Scholars Program was established in 2011 to create career research opportunities for physician-scientists. BSC members were asked to encourage prospective candidates from their institutions to apply for the Lasker Program by the

August 26, 2016 deadline. The Lasker program provides support for 5-7 years at NIH followed by up to 3 years at an extramural research facility.

The NICHD DIR's new organizational structure was approved and has been in place since October 1, 2015. A number of Associate Scientific Director (ASD) positions were created to serve the needs of PIs such as managing maintenance contracts, shared equipment, and administrative staff, but ASDs do not participate in budget and personnel negotiations. The ASDs represent their functional areas on the Group of Senior Advisors (GSA), which meets monthly. On April 7-8, 2016, the GSA met to set the FY17 budgets for each laboratory in a fair and transparent process based on site visit scores, current personnel, and previous budget allocations. Scientifically, the laboratories have self-assembled into intellectual affinity groups, with some having secondary affiliations in addition to their primary groups. Membership of the GSA and affinity groups was presented. Following the reorganization, the DIR is currently redesigning all of its websites.

Dr. Stratakis announced the Inova Translational Medicine Institute (ITMI) - NICHD Fellowship Program. The program will provide a graduated genetics fellow with two to three years support to do research at the NICHD while they receive clinical genetics training at Inova Fairfax Hospital. The program is currently recruiting and BSC members were asked to encourage prospective candidates to apply.

The DIR currently has 277 trainees including 187 postdoctoral fellows, 52 postbaccalaureate fellows, 16 clinical fellows, and 22 graduate students. The fellows put together their own monthly newsletter in addition to organizing an annual fellows retreat. This year's retreat was held on April 22, 2016 and featured talks by Dr. Eric Betzinger and Dr. Jorge Cham. The third annual Three-minute Talks (TmT) Competition is currently underway to promote the effective communication of science. In 2016, NICHD postdocs and graduate students will again participate in a live competition with trainees from NHGRI and NIDCR. The winner will be announced at the December meeting. The Office of Education is continuing initiatives aimed at public speaking and teaching, grantsmanship, and increasing diversity through the Fellows Recruitment Incentive Award and Developing Talent Scholars Program. Dr. Stratakis reminded the BSC that Dr. Desmond Taylor-Douglas, whom they heard from earlier, was a Developing Talent Scholar. The DIR is also working to create an online annual progress reporting system for postdocs, with plans to provide reports at the time of the site visit to help assess mentoring. The career paths of postdocs from the DIR are similar to those from academia, and postdocs are encouraged to apply for K99 awards for which there has been some success. A number of postbacs have been accepted to medical and graduate schools and a list of the institutions where they are going was presented. The Office of Education has also reformed the way fellows are trained on the responsible conduct of research (RCR).

A propos of the Red Team Report and the reorganization of the NIH Clinical Research Center (CRC), Dr. Stratakis said NICHD is somewhat at a disadvantage since a permanent director of the institute has yet to be named. Dr. Stratakis has had conversations with NIH leadership about the future of supporting pediatric research at the CRC but further discussions will have to wait until the new leadership of the CRC is in place. Dr. Strauss will raise the concerns and support

of the BSC for the future of pediatric and women's health research at the CRC during the BSC chairs meeting later in June.

Dr. Stratakis then introduced Dr. Germaine Buck Louis to provide an update on DIPHR.

DIPHR is made up of 29 staff and 38 trainees organized into the Office of the Director and three Branches, the Epidemiology Branch, the Biostatistics and Bioinformatics Branch, and the Health Behavior Branch, that use a team science approach. Dr. Stephen Gilman was recruited as the acting chief of the Health Behavior Branch about a year ago from the Harvard School of Public Health. The branch is actively working to develop a new mission and vision under its new leadership. The entire division is also working to develop their own five-year strategic plan. The division staff will move to new space at 6710 Rockledge Drive on June 6, 2016. In 2017, the division will celebrate the 50th anniversary of its inception and plans to mark the occasion with a scientific symposium.

The members of DIPHR have also received numerous honors in the past six months and Dr. Buck Louis highlighted a few from the Epidemiology Branch. Dr. Enrique Schisterman received the 2016 Mentoring Award from the Society of Pediatric and Perinatal Epidemiologic Research; Dr. Emily Mitchell, a postdoc, received 2015 Article of the Year from the American Journal of Epidemiology and Society for Epidemiologic Research. Another postdoc, Dr. Rose Radin, received the Society for Epidemiologic Research Lilienfeld Postdoctoral Prize Paper Award. Dr. Yeyi Zhu, a postdoc, has received three travel awards to date in 2016 from the American Heart/Stroke Association, the Epidemiology Congress of the Americas, and the Society of Pediatric and Perinatal Epidemiologic Research.

DIPHR is committed to science communication. Since January 2016, they have had eight press releases. The staff undergoes formal media training annually to ensure they can effectively communicate with the press to get their message out.

A propos of whether DIPHR will redirect any of its research to the Zika virus, Dr. Buck Louis indicated that because of the nature of the division's studies, projects are funded five years out so there would not be much flexibility until FY2018.

Dr. Stratakis thanked Dr. Buck Louis.

Dr. Stratakis and Dr. Spong then presented the outgoing members, Drs. Jaffe, Patel, Steitz, and Strauss with certificates. They offered their thanks to the members for their outstanding service to the NICHD DIR and for their wise counsel.

Following a short recess, Dr. Stratakis introduced the next speaker, Dr. Anton Simeonov, the newly appointed scientific director of the National Center for Advancing Translational Sciences. Dr. Stratakis reminded the BSC that they had approved plans to merge the NCATS clinical program with that of NICHD, under the leadership of the NICHD Office of the Clinical Director; this has now been accomplished. The agreement has been in place for several months.

Presentation on the National Center for Advancing Translational Sciences (NCATS)

Anton Simeonov, Ph.D., Scientific Director, National Center for Advancing Translational Sciences

The Intramural Division of the National Center for Advancing Translational Sciences (NCATS): A Collaborative Vehicle to Catalyze Therapeutic Discovery

The mission of the National Center for Advancing Translational Sciences (NCATS) is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of interventions across a wide range of human diseases and conditions. There are several thousand known diseases affecting humankind and treatments are available for only several hundred of them, with new drugs taking more than a decade and costing over one billion dollars to develop. NCATS is directly addressing this problem by discovering new technologies and other approaches that could greatly accelerate the process of developing and deploying therapeutic solutions. A description of the Center's intramural operations was presented, focusing on the use of advanced assay and chemistry technologies to address the wide range of needs associated with early discovery space. Further, examples were provided of programs aimed at progressing lead agents through later stages of preclinical development.

Questions followed.

Dr. Stratakis then invited Dr. Spong to provide an update on the institute to the BSC.

Acting Director's Remarks

Dr. Catherine Spong presented several NIH-wide updates:

- Dr. Eric Dishman was appointed Director of the Precision Medicine Initiative (PMI) Cohort Program to lead NIH's effort to build the landmark PMI longitudinal study of one million or more U.S. volunteers. Dr. Dishman came to NIH from Intel Corporation's Health and Life Sciences Group where he served as Vice President and Intel Fellow.
- NIH has announced the first award for the biobank to support the PMI. The award, made to the Mayo Clinic, includes \$142 million over five years to establish a research cohort biobank and to provide the infrastructure to store, to analyze, and to make available to all the researchers the anticipated 35 million biospecimens and related data.
- Dr. Matthew Gillman was named the Environmental Influences on Child Health Outcomes (ECHO) Program Director beginning in July 2016.
- Dr. Patricia Flatley Brennan will be the new Director of the National Library of Medicine beginning in August 2016.

- Dr. Maureen Goodenow will join NIH in July 2016 as the NIH Associate Director for AIDS Research and Director of the NIH Office of AIDS Research.
- A blue ribbon panel has been named to help guide Vice President Biden's national cancer moonshot initiative. The panel serves as a working group to the presidentially appointed National Cancer Advisory Board. They are currently soliciting ideas from the public and scientific community online at www.CancerResearchIdeas.cancer.gov through July 1, 2016.
- The Advisory Council for the Director's (ACD) Working Group on the Clinical Center, known as the Red Team, made recommendations on reducing risk and promoting patient safety at the NIH Clinical Center. Their report will be discussed during the ACD meeting on June 9-10 and will be open to the public. The Red Team recommended centralizing authority for intramural clinical care and research and reorganizing leadership under a physician CEO to add expertise and experience in hospital management and patient care. In response to the report, the NIH is (1) establishing a hospital board led by Dr. Laura Forese, (2) establishing an NIH Office of Research Support and Compliance with Dr. Kathryn Zoon serving as its interim director, and (3) retaining two companies specializing in quality assurance for manufacturing and compounding.
- Under the Fair Labor and Standards Act, a new rule was established raising the overtime pay exemption to \$47,476 effective December 1, 2016. As a result, NIH will increase postdoctoral NRSA stipends to levels at or above the new threshold.
- NIH recently published a paper in *Science* (Vol. 351, Issue 6280 pg. 1405) reaffirming its support of basic science research.
- The Common Fund's Gabriella Miller Kids First Pediatric Research Program issued its FY16 initiative. The focus is to identify samples for whole genome sequencing that will help elucidate the genetic contribution to childhood cancers and the genetic etiology of structural birth defects. The program will develop a data resource for the pediatric research community of well-curated phenotype and sequence data.
- The Bill and Melinda Gates Foundation and NIH held their third annual consultative workshop on April 18, 2016 at the Porter Neuroscience Research Center. NICHD staff participated in numerous discussions including those on maternal child health and Zika virus.

Dr. Spong continued her update to the BSC with NICHD news, first reviewing the budget. NICHD saw a 7% increase in grant applications in FY16, consistent with other institutes across NIH. This increase can be partially attributed to the fact that grant applications can now be resubmitted indefinitely. With the increase in applications, the success rate has declined. R01 and R21 submissions have increased in volume, while R03 submissions have been declining. Extramural funding makes up 65% of NICHD's budget. Of this, approximately 36% of went to investigator initiated R01s. Contracts, centers, R21, and P01 grants each received 6% of the funding. Cooperative agreements make up 4%, and R03's are 1% of the budget. Approximately

half of the institutes declare paylines, including NICHD. NICHD's payline is currently 9%, as with NCI's, and just above NIA's 8%. In analyzing its scored applications, 65% of the applications received by NICHD are for human studies and 35% for animal studies while overall NIH receives significantly more animal study applications than human studies. Since human studies are more expensive, the requested direct cost on NICHD applications is higher than NIH overall. When comparing the cost of NICHD funded human studies to those done across NIH, the average cost is higher in NICHD since these are often dealing with vulnerable populations such as small children, pregnant women, or people needing rehabilitation. The scores of NICHD applications are similar to the scores in other institutes so it appears that the higher number of more expensive human studies is a major factor. The BSC pointed out that the institutional cost sharing on such studies is also higher. An internal group has been working to identify opportunities to ensure that NICHD is funding the best science, and discussions took place during the January 2016 Advisory Council meeting. Ideas include being more strategic about award mechanisms, funding large programs or grants, funding investigators with numerous awards or those receiving over \$1M in funding, and participation in funding opportunity announcements. Efforts are also being made to be more flexible in discretionary funding by identifying priorities more clearly. NICHD anticipates seeing results of these changes in FY18.

NICHD has also reviewed its training portfolio. To improve the success rate of individual K and F awards, support will be shifted from institutional K12 to individual K awards. Compared with other institutes, NICHD supports a disproportionately high number of K12 awards and relatively few individual K awards. Beginning in FY17, NIH has increased the salaries for K08 and K23 career development awards so additional funds will be needed to support these awards. Dr. Spong emphasized that NICHD is not diminishing its interest in training but rather trying to improve outcomes by reallocating existing resources.

Dr. Spong then provided an update on NICHD's involvement in the Zika virus response. The mosquito-borne flavivirus was first discovered in Uganda in 1947. On February 1, 2016, the World Health Organization declared the Zika virus an international public health emergency. There are numerous associated pregnancy outcomes with Zika virus, including fetal loss, miscarriage, stillbirth, fetal brain abnormalities, eye abnormalities, neuromuscular problems, and speech problems. Most of the current literature relates to women who were symptomatic and children with microcephaly but approximately 80% of infected individuals are asymptomatic. An FOA for rapid funding for research on Zika virus and its complications was issued and will accept applications on a rolling basis from March 20, 2016 until March 1, 2019. A multi-site, multi-country prospective observational cohort study will also be conducted to specifically study Zika virus in pregnancy by providing supplemental funding to existing sites in Zika endemic areas. Enrollment in this cohort study is expected to begin in June 2016.

The Human Placenta Project (HPP) is a collaborative effort involving multiple researchers, institutions, and funding sources, with the ultimate goal to understand human placental development, structure, and function in real time. The Third Human Placenta Project Meeting was held April 14-15, 2016 in Bethesda, MD focusing on imaging, bioinformatics, and technology.

The National Center for Medical Rehabilitation Research (NCMRR), under the leadership of Dr. Alison Cernich, has done a remarkable job coordinating a research plan for rehabilitation research across NIH. The NCMRR profile includes two 2016 Presidential Early Career Awards for Scientists and Engineers (PECASE) awardees, Drs. Elizabeth Skidmore and Ervin Sjedic. The *Rehabilitation Research at NIH: Moving the Field Forward* meeting was held May 25-26, 2016 with over 400 participants to identify gaps, discuss infrastructure needs, and emphasize training and career development opportunities.

NICHD is committed to data sharing and making information available to researchers through its Data and Specimen Hub (DASH), launched in early 2016. The National Children's Study (NCS) Archive opened March 1, 2016 and includes data and biologic and environmental samples from the NCS. The NCS archive will ultimately be merged with the DASH system. DIPHR also has its own data sharing site, the Biospecimen Repository Access and Data Sharing (BRADS).

The Office of Health Equity (OHE) was recently evaluated as part of a review of the NICHD Office of the Director. To better align the OHE to meet its goals, the grants have been transferred to the division of extramural research and a working group has formed to identify areas of focus. Dr. Jean Flagg-Newton was appointed acting director of OHE after the departure of Dr. Regina James to the National Institute of Minority Health and Health Disparities.

In legislative news, the FY17 Presidential Budget Request included \$33B for NIH, with \$1.338B for NICHD. The final budget has not been set and congressional negotiations are ongoing.

Dr. Spong then invited questions. A propos of P01 program grants, Dr. Spong noted that many institutes no longer accept these awards and they may not be optimal to fund the best science given that multi-PI R01s are now available unless there is a specific area of need. With regard to intramural funding, approximately 14% of NICHD's budget is spent on the DIR compared to an average of about 11.5% across NIH. This is largely due to a contract with Wayne State University to support the Perinatology Research Branch, headed by Dr. Roberto Romero – this support was provided by the OD directly, until 2012 when it was transferred to the DIR line.

A propos of the impact of the CRC reorganization on budget, Dr. Stratakis answered the question and agreed that it is not likely to be budget-neutral but that it has been implied that the current "school tax" system will be replaced. If the new system is based upon usage, NICHD will benefit since its clinical PIs are currently underutilizing the CRC relative to the current school tax.

The open session concluded.