

***Eunice Kennedy Shriver* National Institute of Child Health and Human
Development Division of Intramural Research
BOARD OF SCIENTIFIC
COUNSELORS MINUTES
June 2, 2017 Building 31,
Room 2A48**

Members Present: Dr. Scott A. Rivkees (chair), Dr. Kate Ackerman (nominee), Dr. Jeanne Brooks-Gunn, Dr. Frances Jensen (nominee), Dr. Deborah L. Johnson (nominee), Dr. Kojo A. Mensa-Wilmot (nominee), Dr. Antonios Mikos, Dr. Yoel Sadovsky, Lilianna Solnica-Krezel, Dr. Susan S. Taylor, Dr. Eric Vilain, Dr. Martha Werler (nominee), and Dr. Michelle A. Williams.

Federal Employees Present: Dr. Constantine A. Stratakis, Dr. Charles Dearolf, Ms. Francie Kitzmiller, 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 previous meetings, as Dr. Bianchi, Director, NICHD, would not be able to join the meeting in person, however she recorded a video message for the group.

Dr. Stratakis welcomed two new BSC members to the group, Dr. Johnson and Dr. Werler. He thanked departing members, Dr. Solnica-Krezel and Dr. Williams for their years of service and presented them with certificates.

Dr. Stratakis introduced Dr. Bianchi's video message.

Director's Video Message

Dr. Bianchi thanked the BSC for their time and service to the institute and apologized for not being able to be present in person. She was attending an annual meeting on campus between NIH and the Bill and Melinda Gates Foundation at which Bill Gates himself was speaking. She asked members to write down any questions they had during her presentation and she would provide a response by email.

The outline for her talk included important issues related to NIH funding in FY17 and FY18, important themes of advocacy for NICHD, building bridges with other organizations both intramural and extramural, training, shared resources, grant support index (GSI), and NICHD's participation in the 21st Century Cures legislation.

In FY16, NICHD's direct appropriations totaled \$1.338B, including \$1.04B in extramural funding, \$124M in intramural funding, \$45M in research management support (RMS) which are the

administrative costs for running the institute, and \$127M in taps to central NIH. As percentages, this breaks down to 77.7% extramural, 9.3% intramural, 3.4% RMS, and 9.5% taps (across all mechanisms). The FY16 direct appropriations for extramural only were shown separately: non-competing research program grants (RPGs) at 47%, competing RPGs at 18%, centers and networks at 14.7%, training at 6.8%, contracts at 6.1%, other research at 3.8%, and Small Business Innovation Research/Small Business Technology Transfer at 3.5%.

Dr. Bianchi went on to explain the importance of NIH-Congress interactions and shared a photo of herself meeting with Representative Barbara Lee of California. Establishing relationships with Congress is important because Congress ultimately determines the appropriations for the NIH. In the most recent legislation, Congress passed the FY17 omnibus budget resulting in an additional \$40.5M for NICHD.

The President's detailed budget proposal for FY18 was released on May 23, 2017 and, if passed, NIH would absorb a \$5.8B dollar cut, bringing its overall funding to \$25.9B. NICHD's budget would be reduced by nearly 25%, or \$340M. The proposal also calls for a reorganization of the 27 NIH institutes and centers with the elimination of the Fogarty International Center and move of the Agency for Healthcare Research and Quality to NIH as a separate institute. Dr. Bianchi reminded the BSC that Congress sets NIH's budget and that NIH enjoys bipartisan support.

Dr. Bianchi then spoke about her vision for NICHD. "Despite our name," she said, "NICHD only funds about 18% of child health research at NIH and NICHD also dedicates large parts of its portfolio to rehabilitation, women's health, and reproductive health." NICHD needs to better-define "our brand" by communicating the message and through an updated, more user-friendly website. Another important element is to listen to the voice of the patient and advocate for personalized medicine in pediatrics, obstetrics and rehabilitative medicine, three areas that have not been well-articulated in the *All of Us* program. NICHD also needs to build bridges with other NIH institutes and other organizations, work to catalyze innovation, analyze the best way to identify the trainees who are most likely to succeed, stress the importance of data science and sharing to leverage our prior investments, integrate obstetrics and pediatrics research at NICHD, and emphasize the critical role of the Advisory Council members.

The Friends of NICHD is a loose organization of professional groups that have interests that are aligned with NICHD's. Dr. Bianchi and Lisa Kaeser, Director of the Office of Legislation and Policy Analysis, meet with the Friends of NICHD regularly. In the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network, the patient advocacy groups really inform the areas on which NCATS works, a model that Dr. Bianchi would like to use more in NICHD.

The precision medicine initiative, started by President Obama, has been renamed the *All of Us* and is currently in beta testing mode. NICHD has been meeting with Dr. Eric Dishman, the Director of *All of Us*, and his Deputy Director, Dr. Stephanie Devaney, to bring children into the conversation. We're happy to announce that Dr. Tina Cheng, Chair of Pediatrics at Johns Hopkins University, has been named to the top-level advisory committee, and she will be providing expertise on getting children enrolled into the *All of Us* program.

Dr. Bianchi spoke about building bridges and the importance of integrating obstetrics and pediatrics research at NICHD. For instance, the NICHD Maternal-Fetal Medicine Units Network (MFMU) includes 12 enrollment sites and the Neonatal Research Network has 15 enrollment sites, eight sites of which overlap but are administered separately. We are working on a pilot to integrate these networks and hopefully save some costs but, more importantly, result in more data and more long-term analysis of the babies whose mothers were enrolled in the MFMU.

Another important collaboration for NICHD is with the National Human Genome Research Institute (NHGRI). The two institutes have a number of ongoing collaborations but held a very productive meeting on May 18, 2017 to discuss additional opportunities for collaboration including the need to have more emphasis on pediatric pharmacogenomics. There is an opening in NICHD's Maternal Pediatric Pharmacologic Branch and this would be an opportunity to recruit an additional staff member with expertise in pharmacogenomics to begin to build that bridge. Ongoing collaborations with NHGRI include the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, the Gabriella Miller Kids First Pediatric Research program which is sequencing cohorts of children for defects, the Undiagnosed Disease Network, and the ClinGen.

Dr. Bianchi presented a graph on Training and Career Development Awards as a percentage of total expenditures between 1983-2015. This 30-year analysis showed that the percent of the NICHD extramural budget devoted to training has consistently been between 5 and 7 percent. NICHD plans to continue to contribute 5 to 7 percent of our budget to training. A large piece of the training budget, 38.3%, is devoted to institutional K awards. NHLBI has the next highest level of institutional K awards at 11.2%. The success rate of individual K awards, either K08 or K23, had declined considerably since 2007. A long-term analysis of trainees who received K funding of their subsequent success applying and receiving funding for predominantly R-series grants showed that MDs may need some additional time for training and experience in order to successfully compete with PhDs and MD-PhDs. While NICHD plans to continue to fund training awards at the same level, there will be a shift toward funding more individual K awards.

Dr. Bianchi emphasized a commitment to shared resources such as the Data and Specimen Hub (DASH) and the Placental Atlas Tool, both publicly available resources for data and specimens. DASH is a centralized resource for researchers to store and access de-identified data from studies supported by NICHD, which can help investigators meet NIH's data sharing requirements for their own studies and find others' study data for secondary analyses. By supporting data sharing through DASH, NICHD aims to accelerate scientific findings and improve human health. DASH was launched in August 2015 and currently includes 37 studies available in DASH, 7,767 users, 591 registered users, and 45 DASH data requests. One paper on racial and socioeconomic disparities with cervical length has already been published using the DASH resource.

NIH is trying to level the playing field for junior investigators. Over the last 25 years, success rates of early-stage investigators have declined, were going up over the early part of the millennium but are now declining for mid-career investigators, and have continued to rise for more senior investigators. An analysis across NIH extramural programs has shown that 10 percent of principal investigators get over 40 percent of the funding and that research impact tends to flatten out for investigators who are funded at the equivalent of three R01s. This has led NIH to propose the

Grant Support Index (GSI), a measure of a PI's grant support. PIs would be allowed to review a maximum of 21 points, benchmarked to an R01 which is worth seven points.

The 21st Century Cures Act was the last piece of legislation signed by President Obama. NICHD has a prominent role in each of the following aspects of the 21st Century Cures Act: the task force on research specific to pregnant and lactating women for which NICHD will serve as the lead institute, the national pediatric research network, global pediatric research, the inclusion of children in clinical research, and medical rehabilitation research. In response to the 21st Century Cures Act, the NIH Inclusion in Research Workshop was held on June 1, 2017 with the goals to (1) ensure women, children, and racial/ethnic minorities are appropriately represented in clinical research studies; (2) assemble clinical research data on women, minorities, and "relevant" age categories, including pediatric and older populations; and, (3) improve research related to sexual and gender minority populations.

Dr. Bianchi ended her talk with emphasizing the "A" for advice from the advisory councils to that NICHD can leverage the collective expertise and wisdom of Council and the BSC. She posed three specific questions of whether NICHD should undergo a strategic planning process, what the institute's funding priorities should be, and whether there are strategic partnerships NICHD should make.

Dr. Bianchi thanked the BSC for their time and for listening to this presentation. She again invited members to send her any questions by email.

Scientific Director's Presentation

Dr. Stratakis welcomed four new members of the BSC: **Dr. Vanessa Auld**, from the Department of Zoology at the University of British Columbia, and **Dr. Elizabeth Bonney**, director of research at the Department of Obstetrics and Gynecology at the University of Vermont, will be joining the BSC at the next meeting in December; he introduced and welcomed **Dr. Deborah Johnson**, from the Department of Molecular and Cellular Biology at Baylor College of Medicine and **Dr. Martha Werler**, professor and chair of the Department of Epidemiology at Boston University.

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 visits 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. Each investigator of the DIR is reviewed at least every four years utilizing ad hoc review committees chaired by members of the BSC. 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 and that the main evaluation is retrospective, rather than prospective, at least for tenured investigators. Site visit scores allow for prioritization between laboratories, as well as between projects within a laboratory.

To maintain excellence within the intramural program all laboratories are reviewed rigorously. Dr. Stratakis added that to maintain the vitality of the DIR, existing resources need to be re-allocated to allow for the continued recruitment of new tenure-track investigators. In recent years, the NICHD DIR has also set aside 1.5-2% of our allocation for competitive awards. All investigators are also encouraged to apply for outside funding opportunities.

NICHD DIR's staff currently numbers around 950, including 56 tenured and 6 tenure-track investigators. Two tenure-track investigators were recruited to the DIR in 2016 and a third in early 2017. A fourth tenure-track investigator was hired in a joint recruitment with DIPHR. More than 80 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 DIR's new organizational structure was approved and has been in place since October 1, 2015 so we are now entering our second year under the new structure. 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 within the six building clusters, 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. There are two additional ASDs, **Dr. Mary Dasso**, who serves as the ASD for Budget and Administration, and **Dr. Tracey Rouault**, the ASD for Recruitment, Retention, and Diversity. **Dr. Chris McBain** continues to serve as Deputy Scientific Director. Scientifically, the laboratories have self-assembled into intellectual affinity groups, with some having secondary affiliations in addition to their primary groups. Each group elects an Affinity Group Head but this individual does not have a supervisory or administrative role. Memberships of the GSA and affinity groups were presented. A propos of rehabilitation medicine, a recommendation was made that members of the National Center for Medical Rehabilitation Research (NCMRR) could interact with the Neuroscience affinity group as adjunct members. The issue of recruitment by affinity groups was raised at the site visit the previous day and Dr. Stratakis explained that Dr. Rouault's role is to seek advice from all of the affinity groups to help set priorities. However, the DIR may only be able to recruit one new tenure-track investigator for every two or three who leave because of the budget situation. The BSC encouraged the affinity groups to have their own intermittent internal reviews to assess the quality of the science as well as for strategic planning to look for research opportunities that aren't currently being covered. Affinity Group Heads also organize the NICHD DIR's Annual Scientific Retreat. This year's retreat will be held on September 25, 2017 and BSC members are invited to attend.

The NICHD has an overall budget of more than \$1.3B, of which approximately 14% goes to supporting the DIR, including 5% for taps and 9% for operations. Of the approximately \$181M the NICHD DIR received for FY17, 30% is allocated toward personnel, 28% toward consumables, 20% toward the NIH Office of Research Services to cover buildings, maintenance, etc., and 16% will be paid in support of the NIH Clinical Center. The DIR renovation costs for FY17 are currently estimated to be ~\$3.4M as part of a years-long effort to provide new or renovated space to more than 80% of the investigators. Animal care costs are currently approximately \$2M. Under the FY17 appropriations bill signed by the President in May, the NICHD DIR will receive an

additional allocation of \$4.4M over the FY16 budget which is not included in these estimates. We anticipate using most of this funding to support capital equipment requests.

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 \$1.7M in assessments (the latter mostly for IT support).

As the purchasing power of the NICHD DIR has decreased over the past several years, the number of personnel has also decreased. The number of trainees has fallen to 265, following a trend seen across NIH, where labs have tended to hire more permanent support staff as budgets have gotten tighter. A number of senior investigators have retired including Dr. Igor Dawid in December 2016 and Dr. Thomas Sargent in January 2017. Both Drs. Dawid and Sargent were part of the developmental biology group.

Despite the budget difficulties, the NICHD DIR has recruited three new tenure-track investigators, between late 2016 and early 2017: Dr. Katie Drerup, a developmental biologist, Dr. Claire Le Pichon, a neuroscientist, and Dr. Timothy Petros, also a neuroscientist. Dr. Petros will present later in the meeting. The DIR also supported DIPHR in the recruitment of Dr. Fasil Tekola-Ayele whose primary appointment is with DIPHR and he has a secondary appointment with the DIR. Dr. Fasil Tekola-Ayele started the summer of 2016. Two ongoing recruitments for tenure-track or mid-level investigators in translational research and in cellular and developmental neurobiology have been put on hold because of the hiring freeze. The next Lasker Program search has been announced but again there is uncertainty about whether the NICHD DIR would be able to hire if a strong candidate were identified. The program provides support for 5-7 years at NIH followed by up to 3 years at an extramural research facility.

Dr. Stratakis then reviewed the activities of the Office of Education. The NICHD DIR training population currently totals 265, including 180 postdocs, 51 postbaccalaureate fellows, 18 graduate students and 16 clinical fellows. The fellows put together their own monthly newsletter in addition to organizing an annual fellows retreat.

The Office of Education, along with the Scientific Director, support a number of initiatives to increase diversity. The Developing Talent Scholars program supported two recruitments at the postbaccalaureate level in 2017: Ms. LaTaijah Crawford in the Shi lab and Mr. Carlos Echeverria in the Dasso lab. Two alumni, Rim Mehari and Nicolas Johnson recently were accepted into medical school. At the postdoc level, Dr. Alejandra Garcia in the Stopfer lab was recruited with the support of the Fellows Recruitment Incentive Award and will start in November 2017. In 2017, the DIR will also centrally support 15 summer student positions for individuals from groups traditionally underrepresented in science or from disadvantaged backgrounds.

The Office of Education is continuing initiatives aimed at public speaking, teaching, and grantsmanship. The third annual Three-minute Talks (TmT) Competition will be held on June 27, 2017 to promote the effective communication of science. The Office of Education also

successfully implemented an online annual progress reporting system for postdocs. The reports are provided at the time of the site visit to help assess mentoring and are already beginning to produce good data. The DIR is also currently vetting an extensive list of grant opportunities to confirm intramural fellows' eligibility for competitive funding from outside organizations. Dr. Sara Young in the Dever lab, Dr. Abhi Subedi in the Burgess Lab, and Dr. Jim D'Amour in the McBain lab received Postdoctoral Research Associate (PRAT) Fellowships awards in 2017. With these additions, NICHD will host six PRAT fellows out of 20 slots available across NIH. The Intramural Research Fellowship is a new award opportunity for NICHD DIR postdocs and clinical fellows which will provide training on how to write an NIH grant. Awards will be for \$30K for one year and applications will be reviewed by the BSC.

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

NICHD continues to be successful in receiving NIH Bench-to-Bedside awards, having received more awards between 2006-2015 than any other institute proportionate to its size. For the FY17-FY18 cycle, three awards were made to NICHD investigators.

The DDIR Innovation Awards is a new opportunity to provide seed money for innovative and high-impact research, and to stimulate interactions among investigators across NIH's intramural research program. Decisions on the first cycle of awards are expected in June 2017.

Successful awards from second cycle of the NICHD DIR Director's Awards were presented, 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.

NICHD DIR investigators also had the opportunity to compete for NIH Intramural-to-Russia funding through the NIH Office of AIDS Research and for Office of AIDS Research Strategic Funding made available by the NICHD Office of the Director. The successful awards were presented.

A number of DIR investigators were honored this year. Dr. Gigi Storz received the Biomedical Research Exemplar award from the Washington University of St. Louis Research Exemplar Project and was bestowed the 2017 Ruth Kirschstein Mentoring Award, a very prestigious award across NIH. Dr. Storz also was selected by the women scientists association at NIH to give the 2017 Anita Roberts lecture. Dr. Forbes Porter also received a Biomedical Research Exemplar award.

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

Presentation on DIPHR

The Division of Intramural Population Health (DIPHR) is focused on the health and wellbeing of populations and is organized into three branches: the Epidemiology Branch, the Biostatistics and Bioinformatics Branch, and the Health Behavior Branch. DIPHR is made up of 27 staff and 35-40 trainees. Its FY17 operating budget was \$9M, less than 5% of NICHD's intramural budget.

DIPHR celebrated its 50th anniversary on May 15-16, 2017.

DIPHR hosted two Medical Research Scholars this year: Daniel Kuhr, from the University at Buffalo Jacobs School of Medicine of Biomedical Sciences, and Ukpebo Rebecca Omosigho, from the University of Tennessee Health Science Center College of Medicine.

Several scientific advances from each of the three branches were presented. Between 2016-2017, press releases from DIPHR were viewed by 5.7 billion people globally. Dr. Buck Louis presented two graphics showing the scientific areas DIPHR has covered over its 50-year history.

Currently, there is a search for a new Chief of the Biostatistics and Bioinformatics Branch following the return of Dr. Paul Albert to NCI. This is in addition to three open positions for biostatisticians and bioinformaticians that are affected by the hiring freeze. It was clarified that the hiring freeze does not affect postdocs and most other trainee positions.

Dr. Stratakis thanked Dr. Buck Louis.

Following a brief recess, Dr. Stratakis introduced the next speaker, Dr. Petros. Dr. Petros is our most recent tenure-track recruit, who started March 1, 2017.

Staff Presentations

Timothy Petros, PhD, Investigator and Head, Unit on Cellular and Molecular Neurodevelopment

Mechanisms regulating the differentiation and maturation of distinct interneuron subtypes

Research Vision: Proper cortical function requires a balance between excitatory projection neurons and inhibitory GABAergic interneurons, an extremely heterogeneous population with distinct morphologies, connectivity and neurochemical markers. Abnormal development and function of interneurons has been linked to the pathobiology of brain diseases such as schizophrenia, epilepsy and autism. Many genes implicated in brain disorders are enriched in young interneurons. Dr. Petros' central hypothesis is that the protracted period of interneuron development represents a vulnerable window during which insults can result in psychiatric disease. He believes that a detailed characterization of the genetic and environmental mechanisms that regulate interneuron development is critical for understanding normal development and the etiology of brain diseases, and this will be the focus of his research into the near future. He is exploring the role of extrinsic environmental influences in regulating interneuron diversity and maturation by challenging interneuron precursors into new environments. Additionally, his laboratory will utilize

novel strategies he has developed to characterize gene expression profiles of specific interneuron subgroups at multiple developmental stages and link this information with mature interneuron subtypes. These studies will uncover critical knowledge regarding interneuron differentiation and maturation, and will act as a springboard for my future research.

Goal 1. Exploring how the environment regulates interneuron diversity and maturation

The extent to which most interneuron characteristics (location, morphology, electrophysiological properties, etc.) are intrinsically genetically ‘predefined’ or determined by environmental interactions is unknown. To explore this issue, Dr. Petros harvested early postnatal interneuron precursors from the cortex and hippocampus (donor), and transplanted them homotopically (Ctx-to-Ctx) or heterotopically (Ctx-to-Hip, Hip-to-Ctx) into age-matched WT hosts. By harvesting more mature interneuron precursors that have completed tangential migration and are residing in their final location (yet with minimal synaptic integration), they are able to analyze how malleable these cells are after heterotopic transplantations. Their evidence indicates that the proportion of interneuron classes occupying a specific brain region is largely determined by the host environment, but some specific interneuron subtypes seem to be more genetically ‘hardwired’ and resistant to environmental influences. In the future, Dr. Petros hopes to perform single-cell RNAseq experiments on transplanted cells to determine how their transcriptome changes upon homo- or heterotypic transplantation, whether the transcriptome resembles interneurons from the host or donor region, etc. He would also like to expand this approach to striatal interneurons, as their profile is even more distinct from cortical and hippocampal interneurons. This type of multifaceted, in depth analysis of transplanted cells will provide insight into the intrinsic and extrinsic mechanisms that regulate interneuron maturation.

Goal 2. Identify fate-determining genes by ‘time-stamping’ the transcriptome of interneuron progenitors

Previous screens attempting to identify interneuron subtype-specific genes were confounded because (1) most neurochemical markers that characterize mature interneuron subgroups are not expressed in medial ganglionic eminence (MGE) progenitors and (2) the MGE contains diverse progenitors that give rise to different cell types (not just interneurons) that occupy many brain regions. To understand interneuron differentiation and maturation, novel strategies must be developed to overcome current limitations. Dr. Petros’ lab aims to identify actively transcribed genes in MGE progenitors while retaining the capacity to identify the mature fate of these cells in the postnatal brain. Dr. Petros presented their work on developing an inducible form of DNA adenine methyltransferase (Dam) identification (DamID) that will label actively transcribed genes in a temporally and spatially restricted manner. This approach allows us to ‘time-stamp’ a cell’s transcriptome at a specific stage of development for future analysis; essentially, they can view a cell’s transcriptional history. Inducible DamID overcomes the challenge of how to study the transcriptome of fate-committed precursors in a heterogeneous environment such as the MGE. The utility of this approach will be broad and can be utilized to query the transcriptome of specific neuronal subgroups at distinct developmental timepoints. In the future, Dr. Petros can envision crossing DamID mice with mouse models of interneuron-relevant psychiatric diseases (or integrate the DamID cassette into mESCs derived from

these mice) to compare the transcriptome of specific interneuron subgroups between normal and disease models. Thus, the approach for inducibly ‘time-stamping’ the transcriptome of specific cell types with inducible DamID is extremely versatile and critical for understanding cell diversity and connectivity.

Long-term Outlook: The projects outlined above aim to answer critical questions regarding interneuron development that are challenging to address with existing strategies. Dr. Petros has developed approaches to define the genomic and environmental influences on interneuron precursors during their differentiation and maturation. He believes with these aims as a starting point, he will be well positioned to make critical contributions to the field of interneuron development. As the number of genes linked to human diseases continues to grow, he will pursue a link between candidate disease-related genes with dysfunction in specific aspects of interneuron development.

A few questions by BSC members followed. The BSC also commented on the appropriateness of this work to be done in the intramural program.

Dr. Stratakis then asked Dr. Forbes Porter to introduce the next two presenters, Dr. Simona Bianconi and Dr. An Dang Do. Both Drs. Bianconi and Dang Do are trained in pediatrics and human clinical genetics. In addition to their research, they both provide support to the genetics clinical programs and serve as co-ward chiefs for pediatrics.

Simona Bianconi, MD, Staff Clinician

Observational studies and small clinical trials at NICHD in rare diseases

Dr. Bianconi has been a staff clinician since October 2016. In this role, she offers clinical support to teams that are running observational or clinical trials at NICHD. Her training as a pediatrician and clinical geneticist allows her to actively engage in this research environment.

Clinical research: Dr. Bianconi is an associate investigator in observational studies and clinical trials, and a primary investigator for the NIH-CC site of a multicenter trial. Her work on Niemann Pick Disease Type C includes (1) the evaluation of biochemical markers and clinical investigation of Niemann- Pick Disease Type C which is ongoing; (2) a Phase 1/2 Study of Vorinostat therapy in Niemann Pick Disease, Type C; (3) a Phase 1 Cyclodextran Trial: Intrathecal 2-Hydroxypropylbetacyclodextrin in patients with Niemann Pick Disease Type C1 which has been completed; and (4) a Phase 2b/3 prospective, randomized, double-blind, sham controlled trial of VTS270 in subjects with neurological manifestations of Niemann Pick Type C1 Disease which is ongoing. Dr. Bianconi’s work on Smith-Lemli-Opitz Syndrome includes both clinical and basic investigations. She is also involved in an observational study of males with Creatine Transport Deficiency (CTD).

Education/ Training: Dr. Bianconi has enjoyed the opportunity to train and mentor medical students that have participated in research or clinical rotations at NIH/NICHD.

Professional Development: Dr. Bianconi's professional goal is to continue providing excellent care in rare diseases, all the while identifying appropriate biomarkers and outcome measures. Her overall goal is to improve the therapeutic landscape in rare diseases by specializing in small clinical.

An Ngoc Dang Do, MD, PhD, Staff Clinician

Supporting and furthering NICHD's clinical, research, and teaching missions

Dr. Dang Do was drawn to the Staff Clinician position at NICHD for the opportunities to integrate her training as a physician scientist, an internist and pediatrician, and a clinical and biochemical geneticist into an excellent model of patient-oriented research. She is interested in the neuropsychiatric and neurodevelopmental manifestations of disorders of inborn errors of metabolism. Her long-term research endeavors focus on exploring mechanisms that produce a clinically recognizable phenotype, yet allow a wide variation in expression in terms of age of onset and disease manifestations. Since starting in December 2016, Dr. Dang Do joined and initiated projects that align with NICHD's missions and visions, and with my professional interests.

Clinical research

Dr. Dang Do is an associated investigator on observational and interventional protocols that focus on conditions of inborn errors of metabolism, including Niemann-Pick type C (NPC1) [PI: Forbes Porter] and Creatine transporter deficiency (CTD) [PI: Simona Bianconi], where defects in neurodevelopment is a key phenotype. NPC1 is an autosomal recessive disorder of cholesterol transport and abnormal lysosomal storage. Disease presentation varies from fatal neonatal or infantile hepatobiliary involvements, to childhood oculomotor and gross motor impairments, to adult psychiatric illnesses. CTD is an X-linked recessive disorder of abnormal cerebral energy metabolism. Main neurological symptoms of intellectual disability, seizures and autistic spectrum disorder are more prominent in males, but may also be present in female carriers.

Dr. Dang Do is revising the observational protocol for Osteogenesis Imperfecta (OI) [PI: Joan Marini], with two major additions: inclusion of newly identified collagen-related forms of OI and extension of the age limit of study participants to monitor adult-related health issues in individuals with OI.

Education/Service

In support of NICHD's goal to further integration of genetics and genomics into the institute's working missions, Dr. Dang Do has proposed and received support from NICHD and NHGRI leaderships to start an NICHD Genetics Elective. The main objectives for the elective are adding valuable training exposures to rare genetic conditions for NHGRI trainees and facilitating potential collaborative opportunities between NICHD investigators and NHGRI trainees.

Professional development

Improving her ability to be a productive physician scientist is a continuing goal. Using Dr. Porter's Bench-to-Bedside award, Dr. Dang Do is initiating an observational protocol to study Juvenile Neuronal Ceroid Lipofuscinosis (CLN3). CLN3 is an autosomal recessive lysosomal storage disease with an insidious neurodegenerative clinical course. The bedside objectives aim to identify clinical or biochemical markers for disease monitoring and use as future therapeutic outcome measures, and to collect biosamples for research. The initial bench objectives will focus on using multiple -omic screens to identify potential biochemical markers.

Questions followed.

Dr. Deena Zeltser is the latest staff clinician hired in this reorganization of the clinical program and she will be asked to present to the BSC during their next meeting in December.

After a brief recess, Dr. Stratakis asked Dr. Buck Louis to introduce the last two speakers of the morning session: Drs. Pauline Mendola and Zhen Chen. Dr. Mendola is a tenure-track investigator in the Epidemiology Branch and Dr. Chen is a tenure-track investigator in the Biostatistics and Bioinformatics Branch.

Pauline Mendola, PhD, Investigator, Epidemiology Branch, DIPHR

Asthma and Pregnancy: Adverse outcomes and susceptibility to ambient air pollution

Dr. Mendola is a reproductive epidemiologist with a long-standing interest in environmental influences on reproductive health. She came to NICHD in 2011 after serving as a researcher and branch chief at the Environmental Protection Agency and the National Center for Health Statistics. Her work at NIH builds on her past experiences, including two early studies of air pollution and pregnancy outcomes, and her interest in research that can inform clinical practice to improve outcomes for pregnant women with chronic disease. Asthma is common among reproductive-aged women and approximately 10% of pregnancies are complicated by maternal asthma. Using a nationwide US obstetric cohort with delivery-admission electronic medical records, she observed significant increases in adverse obstetric and neonatal outcomes associated with maternal asthma. In that same cohort, modified Community Multi-scale Air Quality models estimated exposure to criteria air pollutants and air toxics for all pregnancies. Air pollution is known to exacerbate asthma and has been independently associated with poor pregnancy outcomes. She studied the interaction of asthma and air quality and found that women with asthma appeared to have a greater risk for preterm birth and preeclampsia compared to non-asthmatics at the same exposure levels. Her ongoing pregnancy cohort study (Breathe – Wellbeing, Environment, Lifestyle and Lung Function; B-WELL-Mom) builds on these findings, with clinical exams and biologic specimens collected during each trimester of pregnancy and four-months post-partum among three groups of women: poorly-controlled asthmatics, well-controlled asthmatics and non-asthmatics. Asthma symptoms can worsen, stay the same, or improve during pregnancy, suggesting that the maternal immune response to pregnancy impacts disease expression. This variation in asthma control during

pregnancy is not well understood and B-WELL-Mom is designed to investigate a comprehensive set of predictors including demographic, biologic, genetic and environmental factors among women with well-characterized asthma control prior to enrollment. Improving prediction of poor asthma control can be used to target intervention strategies where they can have the greatest impact.

A few questions by BSC members followed.

Zhen Chen, PhD, Investigator, Biostatistics and Bioinformatics Branch, DIPHR

Novel statistical methods in diagnostic accuracy and chemical mixtures modeling, with applications in maternal and child health research

Dr. Chen's current methodological research interests lie within the arenas of diagnostic accuracy and chemical mixtures modeling. In the former, he develops novel statistical procedures for estimating multiple ROC curves using data with no gold standard, with *a priori* constraints, or having missing data; in the latter, he proposes innovative framework for estimating associations between exposures to environmental pollutants and health outcomes when the number of exposures is large, when exposures are subject to limit of detections, or when repeated (e.g., familial) data are collected. Collaboratively, Dr. Chen has been serving as the principal statistician in several NICHD studies, including ENDO that studies the natural history, diagnosis and outcomes of endometriosis and B-Well-Mom that investigates factors of poor asthma control during pregnancy. He served as the Principal Investigator in the Physician Reliability Study that examines accuracy of endometriosis diagnosis by different groups of physicians using different combinations of clinical information. Dr. Chen joined NICHD as a staff scientist in 2008 and as a tenure track investigator in 2009. Prior to that, he was an Assistant Professor in Biostatistics (non-tenure-track) at the University of Pennsylvania School of Medicine from 2003 to 2008 and a Research Fellow at the Biostatistics Branch in the National Institute of Environmental Health Sciences from 2001 to 2003. He received his Ph.D. degree in statistics in 2001 from the University of Connecticut and was the recipient of the Young Investigator Award in the American Statistical Association in 2002 and NIH Merit Awards in 2009 and 2012.

A few questions by BSC members followed.

The open session concluded at 12:10 pm.