

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

Members Present: Dr. Scott A. Rivkees (chair), Dr. Kate Ackerman (nominee), Dr. Jeanne Brooks-Gunn (by phone, closed session only), Dr. Serdar Bulun (nominee) Dr. Frances Jensen (nominee), Dr. Kojo Mensa-Wilmot (nominee), Dr. Antonios Mikos, Dr. Yoel Sadovsky, Dr. Lilianna Solnica-Krezel, Dr. Eric Vilain, and Dr. Michelle A. Williams.

Federal Employees Present: Dr. Constantine A. Stratakis, Dr. Diana Bianchi, Dr. Arlyn Garcia-Perez, Ms. Brenda Hanning, and at various times additional members of the NICHD staff participated in the meeting.

I. OPEN SESSION

The meeting convened at 8:00 a.m.

Scientific Director's Presentation

Dr. Stratakis started by announcing that Dr. Diana Bianchi started as Director of NICHD on November 6, 2016. Dr. Bianchi was previously the Founding Executive Director of the Mother Infant Research Institute and the Vice Chair for Pediatric Research at the Floating Hospital for Children and Tufts Medical Center. Her laboratory will be hosted by NHGRI, with funding provided by NICHD, and will be physically housed in the Porter Neurosciences Research Center (PNRC).

Dr. Stratakis shared the sad news that Dr. P. Michael Conn passed away suddenly on November 26, 2016. Dr. Conn had served as the Senior Vice President for Research at Texas Tech University Health Sciences Center since 2013 and had been a member of the BSC since 2015. He was a prolific author who was instrumental in helping us understand how G protein-coupled receptors mediate many of the neuronal pathways. Dr. Conn was a great scientist and magnificent person who will be sorely missed.

Two members, Dr. Lilianna Solnica-Krezel and Dr. Michelle Williams, are nearing the end of their terms on the BSC in June 2017. Dr. Stratakis invited their input as well as input from other members of the Board on potential successors. He also welcomed new members **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. Kojo Mensa-Wilmot**, a cell biologist from the University of Georgia.

Dr. Stratakis then offered his congratulations to both Drs. William and Vilain for the following: **Dr. Michelle Williams** was elected to the National Academy of Medicine; and, **Dr. Eric Vilain** was named the next Director of the Center for Genetic Medicine Research at Children's National Health System's Children's Research Institute, a position he will assume in July 2017.

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. 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 59 tenured and 5 tenure-track investigators. Two tenure-track investigators were recruited to the DIR in 2016 and a third in a joint recruitment with DIPHR. The DIR has one additional recruit starting in 2017 and an ongoing recruitment effort to identify two more tenure-track investigators. 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 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 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. Scientifically, the laboratories have self-assembled into intellectual affinity groups, with some having secondary affiliations in addition to their primary groups. Memberships of the GSA and affinity groups were presented.

The NICHD has an overall budget of more than \$1.3B, of which approximately 14% goes to supporting the DIR. Of the approximately \$181M the NICHD DIR received in FY16, 32% was allocated toward personnel, 21% went toward consumables, 21% went toward the NIH Office of Research Services to cover buildings, maintenance, etc., and 14% was paid in support of the NIH Clinical Center. The DIR spent approximately \$4.3M for renovations in FY16 as part of a years-

long effort to provide new or renovated space to more than 80% of the investigators. Renovation costs peaked in FY16 and are expected to taper off by FY18, freeing up additional funds for recruitment. Animal care costs are currently \$4.7M, 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.

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 (the latter mostly for IT support).

The budget for FY17 has not been set and the NIH is currently operating on a continuing resolution through March 2017. The NIH Clinical Center (CRC) needs has added a more than \$3M emergency assessment for FY17 to implement the recommendations of the Red Team report for the NIH CRC. The additional tap will result in a cut to the capital equipment budget.

As the purchasing power of the NICHD DIR has decreased over the past several years, the number of personnel has also decreased. Between FY12 and FY16, the number of labs decreased from 90 to 65, the number of trainees is down to 277 from 350, and the total staffing has decreased from 1073 to 963. A number of senior investigators have retired. 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 was appointed a scientist emeritus. Dr. Igor Dawid has announced his intention to retire at the end of 2016 and Dr. Thomas Sargent will retire in January 2017. Both Drs. Dawid and Sargent were part of the developmental biology group and there may be the opportunity to recruit a developmental biologist in FY18. Ms. Brenda Hanning, Deputy Director, Liaison and Training, will be retiring on December 31, 2016. Dr. Yvette Pittman will continue to support the Office of Education as Associate Director. Dr. Stratakis also informed the BSC of the passing of Dr. Carolyn Bondy, who had retired and was appointed a scientist emerita. Dr. Bondy had been instrumental in understanding many of the genes that cause Turner syndrome before her retirement in 2012.

Despite the budget difficulties, the NICHD DIR has recruited new tenure-track investigators, two of whom began in fall 2016: Dr. Katie Drerup, a developmental biologist, and Dr. Claire Le Pichon, a neuroscientist. Dr. Timothy Petros, another neuroscientist, has been recruited and is expected to start in March 2017. The DIR also supported DIPHR in the recruitment of Dr. Fasil Tekola-Ayele. Dr. Tekola-Ayele's primary appointment is with DIPHR and he has a secondary appointment with the DIR.

Drs. Drerup, Le Pichon, and Tekola-Ayele will all present later in the meeting.

There are also two ongoing recruitments for tenure-track or mid-level investigators in translational research and in cellular and developmental neurobiology. A hiring freeze has been announced that

is expected to go into effect around January 20, 2017 but the parameters of what will be included and how long it is expected to last are not known.

BSC members were asked to encourage prospective candidates from their institutions to apply for the Lasker Program, which 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 DIR has an active mentoring program, supporting a number of clinical fellowships and graduate students through affiliations with academic centers. 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 including the NICHD Developing Talent Scholars. The Developing Talent Scholars program supported two recruitments at the postbaccalaureate level: Mr. Oluwadamilola Bankole in the Levin lab and Ms. Amber Simmons in the Basser lab. At the postdoc level, Dr. Anna Roberts-Pilgrim in the Leikin lab was recruited with the support of the Fellows Recruitment Incentive Award. The third annual Three-minute Talks (TmT) Competition was held in 2016 to promote the effective communication of science. Two of the winning videos will be shown during the break. The Office of Education is continuing initiatives aimed at public speaking, teaching, and grantsmanship. Dr. Amber Stratman of the Weinstein lab received a K99 award from NHLBI in 2016 and NICHD had two PRAT fellows in 2015. The Office of Education also successfully implemented an online annual progress reporting system for postdocs. The reports will be provided at the time of the site visit to help assess mentoring and are already beginning to produce good data.

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.

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 complete 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*.

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 29 staff and 35-40 trainees. DIPHR's FY16 budget was \$8.8M, approximately 4.6% of NICHD's intramural budget. Since June 2016, division staff completed their move to new space at 6710 Rockledge Drive, welcomed their newest Earl Stadtman tenure-track investigator Dr. Fasil Tekola-Ayele, completed their site visit review on October 20-21, and had numerous scientific advances.

Dr. Tekola-Ayele completed his undergraduate and master's training in Ethiopia before receiving his PhD from the University of Sussex in the United Kingdom. Prior to his appointment as an Earl Stadtman Investigator, Dr. Tekola-Ayele had been a research fellow in NHGRI. In addition to DIPHR and DIR, his recruitment was also supported by NIMHD, NIDDK, and the NIH Office of Equity, Diversity, and Inclusion. His research focuses on statistical genetics and health disparities.

Several scientific advances from each of the three branches were presented. The Health Behavior Branch focuses on normal adolescent and child development, risky behaviors, and the early origins of health disparity. Dr. Stephen Gilman, acting director of the Health Behavior Branch, will present later in the agenda. During the 2012-2016 review cycle, DIPHR completed a number of large research initiatives including the CHEF Trial, Diabetes and Women's Health, EAGeR Trial, NEXT study, NICHD Fetal Growth, and Upstate KIDS. DIPHR is committed to data sharing and developed the BRADS website in addition to participating in the NICHD-wide data sharing site, DASH. Data was presented from an analysis conducted by the NIH Division of Library Services showing the impact of DIPHR's work. Out of 210 papers published in 2012-2013, 25% were among the top 10% in the field in terms of citations. Between 2012-2015, DIPHR investigators published 509 papers, delivered 260 talks, had 26 press releases seen by 4.5 billion people globally, and had 8,902 statistical software downloads. The NICHD Fetal Growth Studies are being leveraged by extramural scientists who will be following the infants born in the study through childhood, as a part of the NIH ECHO Study.

In 2017, DIPHR will be celebrating its 50th anniversary and plans to host a scientific symposium to commemorate the event.

Dr. Stratakis thanked Dr. Buck Louis before introducing the next speaker, Dr. Howard.

Staff Presentations

Bruce Howard, M.D., Senior Investigator, Developmental Biology Group

The hypothesis that postnatal development and aging are ultimately driven by epigenetic clocks is controversial, but of considerable interest. This hypothesis makes strong predictions that evidence for net development- and age-associated epigenome change will be demonstrable, and that such change will be linked to shifts in gene expression patterns. Yet age-related increases or decreases in histone marks reported to date are not widely believed to play a causal (clock-like) role in lifespan progression. Here, Dr. Howard introduces a new, chromatin topology-based approach to explore epigenome structure in the contexts of differentiation and development. He shows that this approach reveals an extensive, and previously non-described, mode of epigenome remodeling for large repressive H3K27me3-enriched (Polycomb) domains. Dr. Howard further shows that such remodeling can be linked statistically to shifts in expression patterns of domain-embedded genes. His findings are important not only for the new avenue of epigenome study that they open, but also because (it can be argued) the epigenome change described is of a form more likely to play a causal role in postnatal development and aging than that previously reported.

A few questions by BSC members followed. A propos of what kind of techniques he plans to apply in the future, Dr. Howard indicated that he would not be applying any since he currently has no laboratory or budget and is just asking to continue in his current status.

Dr. Stratakis then introduced the next speaker, Dr. Tekola-Ayele, an Earl Stadtman Investigator jointly recruited by DIPHR and the DIR.

Fasil Tekola-Ayele, Ph.D., M.P.H., Earl Stadtman Investigator, Epidemiology Branch, DIPHR

Cardiometabolic diseases are major contributors to mortality and morbidity globally. African ancestry populations are experiencing a growing burden of cardiometabolic diseases, including diabetes, dyslipidemia, hypertension, obesity, coronary heart disease and stroke. These complex disorders are caused by multiple, potentially interacting, environmental and genetic factors. Although considerable progress has been made in the identification of the socio-cultural, demographic and lifestyle risk factors for cardiometabolic diseases, many genetic factors that underlie individual susceptibility to these diseases remain largely unknown. Progress in genomic technologies has enabled identification of cardiometabolic disease susceptibility genetic variants in European and Asian ancestry populations; however, limited progress has been made in African ancestry populations. In this presentation, Dr. Tekola-Ayele showed recent examples of genomic and functional studies in African populations leading to discoveries of novel African ancestry-specific as well as ancestry-shared genetic loci associated with cardiometabolic diseases. These studies demonstrate that population differences in genetic structure, ancient environmental pressures that shape the human genome, and early life environmental adversities contribute to disparities in global cardiometabolic diseases.

Precision public health and medical care will benefit all individuals only if diverse populations are involved in the early phases of knowledge generation.

Questions followed.

Following a brief recess, Dr. Stratakis showed the two winning TmT videos.

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

Director's Remarks

Dr. Bianchi began her remarks by thanking the BSC for their time and service to the institute.

She described herself as a passionate advocate of NICHD, having served as an Advisory Council member from 2012-2016, taken part in the 2010 visioning process, and participating and moderating workshops as part of the Human Placenta Project. Dr. Bianchi's appointment as NICHD's director began on November 7, 2016.

Following the recent presidential election, Dr. Bianchi highlighted some of the goals of the new administration that align with the NIH mission including to "advance research and development in healthcare."

Dr. Bianchi then provided a legislative update. The FY17 budget has not been set and we are currently operating under a continuing resolution, which was expected to be extended through April 2017. While under a continuing resolution, NICHD will keep a conservative pay line and delay big programmatic decisions until the budget is known. The House of Representatives recently passed the 21st Century Cures Act. Among other things, the Act reauthorizes NIH for 2018-2020; provides an additional \$4.8B to NIH over 10 years for the PMI, Cancer, and BRAIN Initiatives; provides \$1B of additional funding to states to supplement opioid abuse prevention and treatment; provides \$500M of additional funding to the FDA; calls for improving medical rehabilitation research at NIH; establishes a task force on research specific to pregnant and lactating women; and requires NIH to continue to support the National Pediatric Research Network.

Dr. Bianchi continued her update to the BSC with NICHD news. An analysis of NICHD funding conducted by the Office of Extramural Research has shown that paylines have been declining while there is an increasing number of applications for funding. There has been no change over time in the scores. Compared to other institutes, NICHD receives more applications for human subjects studies, with fewer applications for animal studies, and the requested budgets are higher because human subjects research is more expensive to conduct. While serving as acting director, Dr. Catherine Spong, along with Dr. Della Hann, Director of Extramural Research, took steps to increase the flexibility for discretionary funding and to be more strategic with our investments, which led to increased paylines in FY16. The increase in the R01 payline from 9 to 10% represents a \$10M increase in funding. A propos of institutional T32 grants, Dr. Bianchi indicated that there was an NIH-wide effort to reduce the number of institutional grants in favor of individual funding.

At the annual NIH Institute and Center Directors Leadership forum, one of the focuses was on using better metrics to evaluate grant applications. The Relative Citation Ratio (RCR) measures the impact of individual articles and normalizes impact for the field of study. A paper was published in September 2016 in *PLoS Biology* explaining the metric and how it can be calculated at <https://icite.od.nih.gov/>. The RCR metric has been validated by other groups and some institutions, such as Wellcome Trust, have already adopted it. Another metric is the Research Commitment Index (RCI), which could be used to help ensure more PIs are funded at earlier career stages. Several studies have shown that as labs get more funding, productivity starts to flatten or decrease. There are currently no funding caps in place but the NICHD Advisory Council reviews all labs that receive more than \$1M in funding.

NICHD recently completed a review of our Office of Health Equity. Recommendations from the review focused on three main areas including the portfolio of health disparities research, creating a diverse workforce, and on communications within and outside NIH. NICHD is currently recruiting a new director for the Office of Health Equity to lead these efforts.

Dr. Bianchi then provided an update on NICHD's involvement in the Zika in Infants and Pregnancy (ZIP) cohort study. The study will include nine sites throughout North, Central, and South America. The study plans to follow 10,000 women to determine the risks of Zika infection during pregnancy on maternal and fetal outcomes while controlling for potential confounders and patient enrollment has already begun. The study is supported by NICHD, NIAID, NIEHS, and the Oswaldo Cruz Foundation. A workshop was held in Bethesda on September 22-23, 2016 to identify strategies for evaluation, management, and treatment of the Zika virus and outline future research needs. The meeting report will be published in *JAMA Pediatrics*.

The NIH-wide Precision Medicine Initiative has been named *All of Us*. Dr. Bianchi has met with the initiative's director, Dr. Eric Dishman, who provided assurances that children included in the study. The goal is to enroll at least one million participants over the next three to four years under a national centralized IRB. Pregnant women and people with physical disabilities will be enrolled in version 1 and children will be enrolled in version 2, beginning around summer 2017. The initiative includes support for a data and research support center, a biobank, a participant technologies center to support enrollment, and to various health care provider organizations who will engage patients and help in building research plans. Dr. Bianchi saw opportunities to link this effort with NICHD's PregSource initiative.

The Environmental Influences on Child Health Outcomes (ECHO) program is the successor to the National Children's Study and seeks to investigate the longitudinal impact of prenatal, perinatal, and postnatal environmental exposures on pediatric health outcomes with high public health impact. Dr. Matthew Gillman was recruited from Harvard to serve as the Program Director. ECHO plans to harness existing cohorts to study the effects of early environmental exposures on obesity, respiratory disease, neurodevelopment, pre/peri/post-natal outcomes, and on child health. In FY2016, as part of the redirection of National Children's Study funds, NIH created the IDeA States National Pediatric Clinical Trials Network to address access gaps for rural children embedded at IDeA locations. The network includes 23 states and Puerto Rico. The IDeA network infrastructure could lend itself to the ECHO study, while providing better healthcare access to children in rural areas.

The Common Fund's Gabriella Miller Kids First Pediatric Research Program seeks to develop a resource of well-curated phenotype and sequence data for the pediatric research community that will help elucidate the genetic contribution to childhood cancers and the genetic etiology of structural birth defects. A number of R03 funding opportunities for analysis of the data were announced.

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. A research plan on rehabilitation was published on September 14, 2016 with the concurrence of the 17 participating institutes and centers focusing on rehabilitation through the lifespan, family and community, technology and device development, research design and methodology, translation of research, and building research capacity. Dr. Bianchi and Dr. Cernich will take part in a Congressional briefing on December 8, 2016 related to this effort.

Staff Presentations

Dr. Stratakis introduced the next speaker, Dr. Drerup, who was recently recruited to the DIR's Developmental Biology Group.

Catherine M. Drerup, Ph.D., Investigator and Head, Unit on Neuronal Cell Biology

The pathogenesis of many developmental and degenerative diseases of the nervous system includes defects in the formation and maintenance of long axonal processes. One of the primary intracellular processes important for axon structure and activity is the transport of proteins and organelles between the neuronal cell body and various axonal regions. While anterograde (cell body to axon terminal) transport utilizes a superfamily of kinesin motor proteins, retrograde axonal transport relies on a single motor protein complex, cytoplasmic dynein. How this single motor transports a variety of cargo in a regulated fashion is still largely unknown. The primary goal of the Drerup lab is to understand how cargo-specific retrograde transport is mediated and, in turn, how disruptions in this process lead to disease states. For this work, the lab uses forward and reverse genetic approaches, in vivo imaging and biochemistry in zebrafish embryos and larvae. Using a forward genetic screen, Dr. Drerup has identified several mutant lines with phenotypes indicative of inhibited retrograde cargo transport in axons. Of particular interest was one mutant which contained a loss of function mutation in Actin related protein 10 (Actr10). Actr10 mutants display a selective accumulation of mitochondria in swollen axon terminals, a phenotype not observed in other mutant lines isolated. In vivo analyses of mitochondrial transport demonstrated that this accumulation in actr10 mutants was due to disrupted retrograde transport of this organelle. Mitochondrial fractionation studies revealed that, in the absence of Actr10, mitochondria fail to attach to the dynein retrograde motor protein complex, identifying the root cause of the transport disruption. Using a mass spectrometry approach, the lab has identified candidate proteins that may function with Actr10 to regulate retrograde mitochondrial transport. The short-term goal of the Drerup lab is to identify which of these proteins partner with Actr10 in mitochondrial transport and gain insight into how this interaction is regulated. This will further our understanding of how this important

organelle is properly positioned in axons. Long-term, the lab will use the genetic and imaging advantages of the zebrafish to dissect the mechanisms of retrograde axonal transport of discreet cargo with the goal of bridging the gap in our understanding of how transport disruptions impact to disease states.

Questions followed. Several members complimented Dr. Drerup on her very clear and articulate presentation. A propos of her resources, Dr. Drerup said that she is excited to have access to the zebrafish facility and that she has plenty of space to perform her screenings.

Dr. Stratakis then introduced the next speaker, Dr. Le Pichon. Dr. Le Pichon was recently recruited from NINDS where she was a senior research fellow. Her recruitment was also supported by NEI, NINDS, and NCCIH.

Claire E. Le Pichon, Ph.D., Investigator and Head, Unit on Development of Neurodegeneration

By the time neurodegenerative diseases become symptomatic, considerable irreversible neuronal loss has already occurred. Dr. Le Pichon's research plan centers on investigating the early biochemical and cellular events involved in pathogenesis. Neurodegenerative disease is believed to be caused by a combination of genetic and environmental stressors (e.g. in the most simplistic case, a disease-causing genetic mutation). Her hypothesis is that regardless of the specific triggers, diverse neurodegenerative diseases converge on common cellular programs that govern neuronal fate. If true, understanding and suppressing the downstream programs directing neurodegeneration offers a powerful approach to prevent the degeneration and death of neurons. Dr. Le Pichon's previous work showed that dual leucine zipper kinase or DLK (Map3k12) is an essential regulator of neurodegeneration and that its genetic deletion or pharmacological inhibition is protective in multiple mouse models of neurodegenerative disease. Having noted striking similarities between the neuronal response to acute nerve injury and to chronic neurodegenerative disease stressors, she extended this work to show that DLK deletion or inhibition is protective in mice with sciatic nerve injury, preventing the development of neuropathic pain. She established that DLK is a master regulator of the neuronal response to injury in pain by controlling the induction of colony stimulating factor 1 (Csf1). This cytokine has been shown to be secreted at the spinal cord terminal of the sensory neurons where it recruits microglia that are essential to the development of neuropathic pain. That DLK signaling can induce local microglial recruitment is a key discovery, which provides a mechanistic link between neuronal stress and neuroinflammation, both in acute nerve injury and in chronic disease.

In future work, Dr. Le Pichon will follow up on these findings by crossing mouse models of neurodegeneration to a novel reporter mouse of DLK pathway activity that she is currently generating using a CRISPR-Cas9 knock-in strategy. With the resulting mouse, she can predict the neurons that will degenerate and gain genetic access to them. Dr. Le Pichon will define transcriptomic signatures of early pathology in the pre-degenerating neurons by FACS sorting them. She will localize these neurons and characterize them using light sheet Ultramicroscope imaging of whole brain and spinal cord tissues. She is developing a genetic platform that will allow her to test the reversibility of neuronal stress

once these pathways are engaged. Dr. Le Pichon's work also investigates the role of neuroinflammation, in particular the cellular interplay between stressed neurons and glia, which she has evidence are closely linked within disease pathogenesis and progression. These overarching goals are driven by the idea that the better we understand the cellular events that initiate pathology, the earlier one could theoretically intervene and with better therapeutic outcomes.

Questions followed.

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

Stephen E. Gilman, Sc.D., Investigator and Acting Branch Chief, Health Behavior Branch, DIPHR

Socioeconomic disparities in mood disorders have been observed in clinical and population samples for more than a century. More cases of the disorders exist amongst the lower socioeconomic groups. The recent emergence of life course approaches in the field of psychiatric epidemiology, along with cohorts of children established in the 1950s and 1960s that have been followed into adulthood, has shaped our understanding that disparities reflect in large part the causal influences of socioeconomic circumstances on the vulnerability experience mood disorders.

In this presentation, Dr. Gilman reviewed his program of research investigating the role of early life socioeconomic circumstances on the risk of mood disorders over the life course. Based partly in the New England Family Study birth cohort, findings from this program of research demonstrate that adverse socioeconomic circumstances during childhood increase lifetime risk for mood disorders, both first onset of disorders as well as for their long-term chronicity. His team has pursued several paths to understand the underlying mechanisms. They have investigated the psychological sequelae of early life circumstances, and shown that children exposed to adversity are more vulnerable to stress-induced mood disorders in adulthood than children not exposed. These findings led to their recent work on the neurodevelopmental consequences of early life adversity; this has revealed neurodevelopmental deficits associated with adversity, deficits that increase risk for the severity of mood disorders including suicidal behaviors. Current efforts target the effects of adversity during the prenatal period and its implications for long-term mental health among offspring. Dr. Gilman closed by discussing directions for new research initiatives in the Intramural Research Program concerning the developmental origins of suicide and health disparities.

Questions followed.

The open session concluded at 12:15 pm.