Department of Health and Human Services

National Institutes of Health

National Institute of Nursing Research

Minutes of the National Advisory Council for Nursing Research

September 13–14, 2016

The 90th meeting of the National Advisory Council for Nursing Research (NACNR) was convened on Tuesday, September 13, 2016, at 1:00 p.m. in Conference Room 620/630, Building 35, National Institutes of Health (NIH), Bethesda, Maryland. The first day of the meeting was an open session and adjourned that same day at 5:00 p.m. The closed session of the meeting, which included consideration of grant applications, was convened on Wednesday, September 14, 2016, at 9:00 a.m. and continued until adjournment at 1:00 p.m. Dr. Patricia A. Grady, Chair, NACNR, presided over both sessions of the meeting.

OPEN SESSION

I. CALL TO ORDER, OPERING REMARKS, COUNCIL PROCEDURES, AND RELATED MATTERS—Dr. Patricia Grady, Director, National Institute of Nursing Research (NINR)

Dr. Grady called the 90th meeting of the NACNR to order and welcomed all Council members, visitors, and staff. Dr. Grady recognized Dr. Jennifer Hatzfeld, new Council Member Ex Officio.

Conflict of Interest and Confidentiality Statement

Dr. Marguerite Kearney, Acting Executive Secretary, NACNR, and Director, Division of Extramural Science Programs, NINR, noted that the meeting was being recorded for purposes of the minutes and that audio recordings will be destroyed once the minutes are completed. She noted that NIH is a smoke-free campus. She asked Council members to update their addresses on the meeting roster that would be circulated during the meeting.

Minutes of the Previous NACNR Meeting

Council members received the minutes of the May 24–25, 2016, NACNR meeting via the electronic council book. A motion to accept these minutes was made, seconded, and approved unanimously. The

approved minutes of each NACNR meeting become part of the Institute's permanent record and are posted on the NINR website (www.ninr.nih.gov).

Dates of Future Council Meetings

Council members were asked to confirm their calendars for the following meeting dates and to contact Dr. Grady or Dr. Kearney about any conflicts or expected absences.

2017

January 24–25 (Tuesday–Wednesday)
May 23–24 (Tuesday–Wednesday)
September 12–13 (Tuesday–Wednesday)

2018

January 23–24 (Tuesday–Wednesday)
May 15–16 (Tuesday–Wednesday)
September 11–12 (Tuesday–Wednesday)

II. REPORT OF THE DIRECTOR, NINR—Dr. Patricia Grady, Director, NINR

The Director's report focused on activities and news from the Department of Health and Human Services (HHS), NIH, and NINR since the last Council meeting. Highlights included:

NINR is hosting a year of scientific symposia and scholarly events, which began with its "Advancing Science, Improving Lives" Scientific Symposium and will conclude with several events on the NIH campus and downtown DC this fall to celebrate its 30th anniversary.

Budget Update—Dr. Grady noted that the current fiscal year (FY) ends September 30, 2016. Congress must pass a new appropriations bill or a continuing resolution to continue to fund the government past September 30. Both the House and Senate Appropriations Committees have presented appropriations bills for FY2017 that provide funding increases for NINR and NIH.

Dr. Grady reviewed obligations for the Institute's FY2015 budget, noting that the majority of funding supports extramural research. Other NINR budget allocations include the intramural program research management services and training.

HHS News—Dr. Grady announced that Andrew Bindman, MD, was appointed Director of the Agency for Healthcare Research and Quality (AHRQ).

NIH News—The NIH Policy on the Use of a Single Institutional Review Board of Record for Multi-Site Research establishes the expectation that all sites participating in multisite studies involving non-exempt human subjects research funded by NIH will use a single Institutional Review Board (IRB) to conduct the ethical review required by HHS regulations for the Protection of Human Subjects. This policy will help standardize patient safety across the country. Pilots implementing this policy on the NIH campus have so far been successful.

In July, NIH announced $55 million in awards in FY2016 to build the foundational partnerships and infrastructure needed to launch the Cohort Program of the Precision Medicine Initiative (PMI). The awards will support a Data and Research Support Center, a Participant Technologies Center, and a network of Healthcare Provider Organizations (HPOs). The Mayo Clinic in Rochester, MN received an award earlier this year to build a biobank to support this effort. With these awards, NIH is on course to begin initial enrollment into the PMI Cohort Program in 2016, with the aim of meeting its enrollment goal by 2020.

NIH is hosting a Regional Seminar on Program Funding and Grants Administration October 26–28, 2016, in Chicago, IL. At the two-day seminar, more than 60 NIH and HHS policy, review, program, and grants management officials will share the latest updates and guidance on NIH-wide programs and policies and the NIH grants process.

Dr. Grady highlighted selected NIH-sponsored funding opportunities. Further details are available at: http://grants.nih.gov/grants/guide.

The following NIH staff news was noted:

- Dr. John Gallin, MD, has accepted the newly created dual position of NIH Associate Director for Clinical Research and Chief Scientific Officer for the Clinical Center. He will continue to serve in his current role as Director of the Clinical Center until a new Chief Executive Officer is selected.
- Dr. Joshua Gordon, MD, PhD, has been named Director of the National Institute of Mental Health (NIMH).
- Dr. Diana Bianchi, MD, has been named Director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Dr. Bianchi is expected to join NIH on October 31, 2016.

NINR News—As part of its continuing 30th Anniversary Events, NINR's 2016 Scientific Symposium ("Advancing Science, Improving Lives: A Window to the Future") will take place September 14, 2016. This scientific symposium will feature distinguished scientific speakers and include panel discussions on the topics of sleep and omics science. The final Anniversary Event will be the NINR Director's Lecture on November 1, 2016, where speaker Dr. Sandra Millon-Underwood will address "Evidence-based Interventions to Address Health Disparities in Cancer."

NINR's new five-year strategic plan will be released September 14, 2016, at NINR's Scientific Symposium and will be available shortly thereafter on the NINR website. The plan highlights areas of science NINR believes will have a significant impact on the health of the American people.

NINR recently participated in AcademyHealth's Annual Research Meeting, which brought together more than 2,600 researchers and interdisciplinary scientists. NINR's contributions were highlighted through a special session titled "30 Years of Nursing Research: The Past, Present, and Future of Nursing Science at the National Institute of Nursing Research." The session included the contributions of two scientists supported by NINR—Drs. Linda Aiken and Pamela Hinds. An NINR grantee, Dr. Mary Naylor of the University of Pennsylvania School of Nursing, received this year's Distinguished Investigator Award at the annual AcademyHealth meeting. The award recognizes investigators who have made significant and lasting contributions to the field of health services research through scholarship, teaching, advancement of science and methods, and leadership. Dr. Naylor developed the Transitional Care Model, an approach that seeks to improve care for older adults in the community.

NINR authored a follow-up to the NIH Symptom Science Model (NIH SSM) published last year. The latest paper, "National Institutes of Health Symptom Science Model Sheds Light on Patient Symptoms," was published online in May on the *Nursing Outlook* website. NINR held a Symptom Science Center Meeting in August 2016. The planning meeting was held with a small group of NIH and non-NIH experts to give guidance for moving forward with the development of the trans-NIH Symptom Science Center.

NINR authored a special paper entitled "The Spectrum of Caregiving in Palliative Care for Serious, Advanced, Rare Diseases: Key Issues and Research Directions" published in the July issue of the *Journal of Palliative Medicine*. The paper reports on an interdisciplinary workshop held in June 2015 that addressed the challenges of caregiving and palliative care for adults and children with rare diseases.

In July, the National Academies of Sciences launched a Roundtable on Quality Care for People with Serious Illness to foster an ongoing dialogue about critical policy and research issues to accelerate and sustain progress in care for people of all ages with serious illness. NINR is a Roundtable member and sponsor.

In August, NINR participated in an NIH-workshop "Advancing and Extending a Palliative Care Research Agenda in the Specialties." The workshop aimed to harness the growing interest and focus on advancing palliative care and provided a venue to synergize research goals, strategies, collaboration, and resources.

NINR recently released an animated video as part of its *Palliative Care: Conversations Matter*® campaign. The video provides an overview of pediatric palliative care for families, providers, and organizations. The new video and other campaign materials are available at: www.ninr.nih.gov/conversationsmatter.

NINR released a new series of videos titled "Building and Sustaining a Scholarly Career," which provide an overview of opportunities and dilemmas often encountered by midcareer scientists as they work to develop a sponsored project into a successful and sustained program of research. www.ninr.nih.gov/midcareervideos.

Selected NINR funding opportunity announcements are available at: www.ninr.nih.gov/ResearchAndFunding/DEA/OEP/FundingOpportunities/.

Training Opportunities—

- The 2016 Summer Genetics Institute (SGI) was held in June on the NIH Campus. This year's class included 25 participants representing universities across the country, which brings the total to over 350 graduates since 2000. This year, participants attended 42 lectures, which included presentations on topics such as genetic disorders, epigenetics, the microbiome, and stem cells. Two SGI alumni presented their research and career paths to illustrate how SGI training is incorporated into their programs of research.
- As part of the NINR Symptom Research Methodologies Series, the NINR Big Data in Symptoms Research Methodologies Boot Camp was held in July and included 160 participants from 75 institutions across the country. Participants engaged leaders in the areas of emerging "omics" technologies, protection of participant privacy, data sharing, and data science. The first day of the Boot Camp was videocast and is now archived on the NINR website.

- Applications for the 2017 Graduate Partnerships Program 2017 will be accepted at www.ninr.nih.gov/GPP through December 1, 2016.
- This summer, NINR's Division of Intramural Research (DIR) welcomed a new group of over 20 trainees, ranging from postdoctoral fellows and postbaccalaureate fellows to interns and special volunteers. Summer interns conducted their research for eight weeks, and some trainees are in NIH training programs such as the Community College Summer Enrichment Program (CCSEP), Graduate Summer Opportunity to Advance Research (GSOAR), and HiSTEP 2.0 (High School Scientific Training & Enrichment Program).

Dr. Grady provided an updated on the review of grant applications by the NIH Center for Scientific Review (CSR). NINR works closely with CSR to ensure the fair review of grant applications submitted to NIH and NINR by nurse scientists. Most of the applications submitted to NINR are reviewed by study sections organized by CSR. As part of ongoing efforts to enhance the review of these applications, CSR recently proposed several changes, including the creation of two to three predominantly "nursing" study sections and a new process for handling "orphan" applications, which are applications that are initially referred to study sections outside of those that typically review NINR grants. CSR and NINR will continue to work out the details of these new processes.

Dr. Grady noted the following NINR staff news:

- Dr. Patricia Brennan, who recently was named the new Director of the National Library of Medicine (NLM), has joined NINR's Division of Intramural Research as an Adjunct Investigator.
- Dr. Ann Cashion is Co-Chairing—along with Dr. Andy Griffith, Scientific Director of the National Institute on Deafness and Other Communication Disorders—the 2016 NIH Research Festival.
- Dr. Paule Joseph, an IRTA postdoctoral fellow in the Digestive Disorders Branch, and Ms. Kristen Weaver, a GPP predoctoral fellow also in the Digestive Disorders Branch, have been awarded the competitive Heilbrunn Nurse Scholar Award from Rockefeller University.
- Dr. Wendy Henderson, Chief of the Digestive Disorders Unit in NINR's DIR has been selected as a Fellow of the American Academy of Nursing.
- NINR researcher Dr. Jessica Gill, an NIH Lasker Clinical Research Scholar and Chief of NINR's Brain Injury Unit, Tissue Injury Branch, received the Johns Hopkins Distinguished Alumna Award.
- Dr. Katy Meilleur has accepted appointment as a Tenure Track Investigator in the Neuromuscular Symptoms Unit of the Tissue Injury Branch of the NINR DIR.

- Dr. Pamela Tamez has been named Deputy Training Director in the DIR Office of Training Programs.

III. PRECISION HEALTH FOR ALL: NIH'S PRECISION MEDICINE INITIATIVE® COHORT PROGRAM—Mr. Eric Dishman, Director, Precision Medicine Initiative Cohort Program

Mr. Dishman presented an overview of the Precision Medicine Initiative Cohort Program, which he has referred to as the Precision Health Initiative this landmark longitudinal research effort that aims to engage 1 million or more U.S. participants who volunteer to contribute their health data over many years to improve health outcomes, fuel the development of new treatments for disease, and catalyze a new era of data-based and more precise preventive care and medical treatment. The Program's mission is to accelerate science and breakthroughs that drive toward precision health for all.

The Program will feature a transformational approach to diversity, participation, and data access. The cohort will reflect the country's rich diversity to produce meaningful health outcomes for historically underrepresented communities. Participants will be true partners—not patients or subjects—in the research process. They will be involved in every step of program development, including what data are collected, what lab analyses are performed, what research is conducted, and how data are returned. Data sharing will be swift for both researchers and participants. The White House developed the Data Security Policy Principles and Framework to be incorporated into all PMI activities. Maintaining data security and privacy will be paramount to maintaining participants' trust and engagement.

The Program will employ two primary methods of engaging participants:

(1) Direct volunteers (anyone who can call an 800 number, go online, or use a mobile phone) across the continuum of people who range from having very little involvement in their own healthcare to those individuals who wear step counters daily
(2) Health provider volunteers through a partnership with the Veterans Administration and other healthcare providers.

Mr. Dishman outlined the current state of the Program. They are currently developing an interdisciplinary platform team among the 33 awardee partners, transition plans with multiple government agencies, and a robust community partners network. Work to test and pilot parts of the Program includes:

- Rolling out personas built upon ethnographic work in homes/focus groups

- Building a diverse 5,000-person community of beta testers
- Testing consent language and 5 survey modules, and defining the next 12 modules
- Obtaining feedback on content and design for educating the public and participants
- Experimenting with recruitment methods (e.g., church, mobile community visits)
- Drafting the full protocol for version 1 launch
- Cybersecurity testing of infrastructure.

A platform approach to implementation of the Program is being utilized. Multiple versions of the Program are being developed at once, with each release featuring new options for participants and researchers, scientific focus areas/measures, and data capture capabilities. Developers are following an iterative process to ensure that the first launch of the Program is not overloaded. Additional updates on the Cohort Program are available at: https://www.nih.gov/precisionmedicine.

IV. OVERVIEW OF THE NINR INTRAMURAL RESEARCH PROGRAM—Dr. Ann Cashion, Scientific Director, DIR, NINR

Dr. Cashion presented an overview of NINR's DIR program, the scientific focus of which is symptom science. To this end, DIR is focused on quantifying subjective symptom experiences, exploring underlying molecular mechanisms, determining environmental influences, recognizing individual variability, and employing clinical interventions.

Dr. Cashion summarized the NIH Symptom Science Model, which begins with the presentation of a symptom or cluster of symptoms. The symptom undergoes phenotypic characterization; biomarkers then are identified, which ultimately leads to clinical applications resulting in symptom reduction and improvement. The NINR DIR currently is incorporating this model into its individual research programs and the proposed Symptom Science Center to be led by NINR.

DIR is led by the Office of the Scientific Director, which directly oversees the Office of the Training Director and the Office of the Clinical Director. The Division's scientific research programs are divided into three branches: the Biobehavioral Branch, the Symptoms Management Branch, and the Tissue Injury Branch. With the addition of Dr. Patricia Brennan, DIR will be adding another branch.

Dr. Cashion provided an overview of each of the scientific branches. Biobehavioral Branch research focuses on the interplay of behavioral, biological, and environmental determinants of health and wellness across populations. Focus areas include brain-gut mechanisms in symptom distress related to digestive disorders and biobehavioral interventions to target digestive disorder symptoms.

The Symptom Management Branch conducts research on the underlying biological mechanisms of a range of symptoms, their effect on patients, and the bases for patient response to interventions. Research focus areas include weight gain biomarkers and prediction of patient outcomes, the nature and causes of fatigue in a variety of conditions, and the physiological role of nutrition in cardiovascular disease. There are three units within the Branch: the Symptom Biology Unit, the Cardiovascular Symptoms Unit, and the Genomic and Clinical Biomarkers Unit.

The Tissue Injury Branch researches mechanisms of tissue injury and identifies molecular targets and pathways for interventions. The Branch comprises the Brain Injury Unit, the Vascular Biology Unit, and the Neuromuscular Symptom Unit. Research focus areas include traumatic brain injury (TBI) and molecular mechanisms of comorbidity risks, interactions among nutrients and bioactive compounds that affect vascular function and symptoms, and novel clinical outcome measures and treatments in congenital myopathies and muscular dystrophies.

Dr. Cashion noted that none of the research conducted within DIR could be done without the cross-cutting genomics laboratory. The expertise and willingness of the lab's staff to learn the cutting-edge technologies and teach these approaches to NINR fellows and trainees have provided a stable foundation for the Division's programs.

V. EFFECTS OF CHRONIC STRESS ON MICROBIOTA-GUT-BRAIN AXIS—Dr. Wendy Henderson, Chief, Digestive Disorders Unit, Biobehavioral Branch, DIR, NINR

Dr. Henderson discussed the precision science approach to research at NINR and highlighted recent scientific discoveries on the effects of chronic stress on the microbiota-gut-brain axis using the NIH-Symptom Science Model. NINR-supported scientists are contributing research findings that can predict which people are most at risk for adverse symptoms and conditions, monitor treatment efficacy, and guide interventions to improve health and symptom outcomes.

Dr. Henderson noted the many ways chronic stress affects our lives, from gastrointestinal (GI) symptoms to hepatology and nutrition. Up to 20 percent of the U.S. population report stress-induced GI symptoms—they are the single most common reason for emergency room (ER) visits, are among the top ten reasons for outpatient visits, and cost the healthcare industry approximately $30 billion annually. Additionally, evidence suggests that chronic stress affects intestinal health across the lifespan. Dr. Henderson highlighted findings from NINR-supported research in the Digestive Disorders Unit.

The Brain-Gut Natural History study is examining the relationship between symptoms of chronic abdominal pain and intestinal inflammation by comparing the medical test results of normal-weight and overweight patients who have a history of chronic abdominal pain. It is often difficult to capture where patients feel pain and to quantify those findings. As such, the Gastrointestinal Pain Pointer was developed to capture in real time where and how much a patient feels pain and tracks those symptoms over time. The device also records heart rate and blood pressure. It is commercially available free of charge through NIH.

Researchers in Dr. Henderson's lab also have developed a protocol to experimentally induce GI stress symptoms using a test solution formulated by the NIH pharmacy. The solution is a mixture of absorbable and non-absorbable sugars (sucrose, lactulose, sucralose, and mannitol) that enables researchers to test for gastrointestinal permeability throughout the GI tract. Irritable bowel syndrome (IBS) patients exhibited decreased colonic permeability compared with healthy controls. Researchers were able to predict from a patient's oral microbiome how that patient would respond to the test solution. This method has been published in *Clinica Chimica Acta* and is being used in other hospitals.

In collaboration with University of Michigan researchers, Dr. Henderson's lab studied a murine model of chronic GI stress. They found similar butyric acid functioning in mice as in humans. Microbiota are associated with stressed animals; however more validation is needed to determine the effects of stress on epithelial cell barrier function and GI permeability.

In summary, NINR scientists have identified stress-induced GI symptoms, phenotypically characterized the effect of chronic stress on the GI tract, and developed personalized profiles—all leading to useful clinical applications of this research. Dr. Henderson highlighted other ongoing studies in this research area and noted that future studies will focus on symptoms diagnostics for patients experiencing these symptoms.

VI. TRAUMATIC BRAIN INJURIES AND THE ROLE OF TAU—Dr. Jessica Gill, Lasker Clinical Research Fellow, Tenure-Track Investigator, Brain Injury Unit, Tissue Injury Branch, DIR, NINR

Dr. Jessica Gill provided an overview of NINR's use of the NIH Symptom Science Model to elucidate the role of tau in traumatic brain injuries.

Traumatic Brain Injuries (TBIs) are incredibly common; over 1.5 million people are in emergency care due to these injuries each year, and roughly one-third of all U.S. military personnel who serve in combat operations experience at least one TBI. Individuals with TBI are more likely to experience ongoing complications such as postconcussive disorder (PCD), posttraumatic stress disorder (PTSD), and depression, and are also more likely to develop chronic traumatic encephalopathy (CTE)—progressive brain degeneration that leads to dementia following repetitive TBIs. However, there is currently no way to identify those who are at greatest risk for developing these chronic symptoms.

To help identify biomarkers to better pinpoint those at risk for chronic TBI symptoms, NINR researchers explored whether elevated levels of the protein tau were related to chronic neurological symptoms in military personnel who had experienced TBI. Tau is a microtubule protein that acts as a structural element in the axonal cytoskeleton. High concentrations of tau have been linked to mortality after severe TBIs and prolonged recovery. Using a new, ultrasensitive immunoassay technology, researchers could more easily measure tau and clarify its role in long-term complications of TBI. They found elevated tau levels in the blood samples of military participants with a history of TBI compared with participants who had never suffered a TBI. Total tau was found to be elevated even years later following multiple TBIs in young military personnel. These elevations may contribute to chronic symptoms and CTE. Future research on this protein will look at whether tau is related to recovery following a TBI and whether individual differences in tau activity shape recovery.

Dr. Gill and colleagues also looked at the concentrations of tau in athletes with concussions. Those athletes with concussions who do not have full neuronal damage are the most at risk for having chronic neuronal symptoms. The identification of biomarkers is needed to help inform when athletes are fit to return to play. Researchers collected preseason blood samples from collegiate athletes and healthy controls. They followed those athletes who had concussions and repeated the evaluation at seven days post injury. Results were compared over time—researchers found total tau levels to be lower in healthy controls who were not exercising. A six-hour change from baseline tau levels was found to be a prognostic biomarker of return to play. Researchers concluded that an evaluation of tau must include a

consideration of physical exercise and that tau may be related to CTE risk following concussion in athletes.

In closing, Dr. Gill highlighted the implications of this research. Peripheral biomarkers can be used to determine neuronal activity following brain injuries. Tau may serve as a prognostic biomarker and may be diagnostic in chronic cohorts. Larger prospective studies are needed to understand the role of tau in helping patients recover from brain injuries.

VII. A PRECISION MEDICINE-GUIDED APPROACH FOR FATIGUE ASSESSMENT AND MANAGEMENT IN A SYMPTOM SCIENCE CENTER—Dr. Leorey Saligan, Chief, Symptoms Biology Unit, Symptom Management Branch, DIR, NINR

Dr. Saligan described recent experiments completed by the Symptoms Biology Unit that were guided by precision medicine. The primary purpose of the Symptoms Biology Unit is to characterize distinct and shared functional pathways of fatigue in order to identify potential therapeutic targets to reduce the debilitating effects of symptoms.

Fatigue is a very common and costly symptom—costing $330 million annually across illnesses—yet little is known about the mechanisms of fatigue. Fatigue often co-occurs with depression, pain, sleep disturbance, and cognitive dysfunction. It interferes with daily function and negatively affects health-related quality of life, leading to poor treatment outcomes and disability. Dr. Saligan and colleagues are seeking to characterize the trajectory and causes of fatigue in specific conditions (e.g., cancer) using clinical and preclinical approaches.

The Clinical Natural History Study followed men with metastatic prostate cancer who were scheduled to receive radiation therapy. They were followed before treatment, weekly during treatment, and after treatment for up to one year. Researchers found that 30 percent of subjects developed chronic fatigue at one-year post treatment, which correlated with depressive symptoms, global pain, and urinary symptoms. This chronic fatigue did not correlate with anemia, body weight, or age. Based on these findings, NINR researchers are developing an algorithm that can predict individuals who will develop fatigue after completion of radiation therapy for cancer.

A full genome microarray was conducted on subjects at one-year post radiation therapy. Researchers were able to clearly delineate chronic fatigue predictive genes—genes that are related to glutamate receptors,

which are found on T-lymphocytes. Dr. Saligan and colleagues recently proposed that aberrant glutamate signaling has a role in fatigue pathogenesis, and cancer-related fatigue has always been linked to inflammatory processes. A clinical trial is now testing the hypothesis that mGluR in T cells mediates T-cell activation after radiation triggers release of inflammatory agents that influence the fatigue experience.

Next steps include continuing the mGluR clinical trial, examining RNA sequencing data to identify specific mGluR single nucleotide polypeptides (SNPs) that may be associated with fatigued individual, and validating associations of specific mGluR SNPs with fatigue through the NIH Symptom Science Center or extramural collaborations.

VIII. RYR1-RELATED MYOPATHY AND MALIGNANT HYPERTHERMIA: A CASE FOR PRECISION MEDICINE—Dr. Katy Meilleur, Assistant Clinical Investigator, Neuromuscular Symptoms Unit, Tissue Injury Branch, DIR, NINR

Dr. Meilleur presented research findings from the Neuromuscular Symptoms Unit within the Tissue Injury Branch, DIR. The overarching goals of the Unit are: development of clinical outcome measures/biomarkers to assess symptoms of congenital muscle disease; identification of novel genetic loci and elucidation of the relationship between genotype and phenotype in children with congenital muscle diseases; and clinical trial investigation of interventions to alleviate symptoms of congenital muscle disease, specifically Ryanodine Receptor 1-related myopathy (RYR1-RM).

RYR1-RM is the most common congenital myopathy (1/90,000), with a symptom spectrum including motor delay, muscle weakness, impaired ambulation, joint contractures, scoliosis, eye paralysis, respiratory failure, and susceptibility to malignant hyperthermia. RYR1 encodes a homotetrameric transmembrane ion channel, RyR1, which resides on the terminal sarcoplasmic reticulum in close proximity to the T-tubule. By releasing calcium from the sarcoplasmic reticulum into the cytosol in response to muscle fiber stimulation by the motor neuron at the neuromuscular junction, it mediates excitation-contraction coupling and functions as a regulator of cellular calcium concentrations and redox homeostasis. The latter mechanism recently was described in zebrafish and patient myotubes, showing that RYR1 mutations result in increased oxidative stress and that this is rescued in both models by treatment with N-acetylcysteine (NAC), a known antioxidant.

Based on preclinical results, Dr. Meilleur and colleagues now are conducting a clinical trial to test the safety and efficacy of NAC in a subgroup of RYR1-RM patients. The trial objectives are to determine

whether NAC reduces oxidative stress, fatigability, and fatigue. The study population includes both males and females 7 years of age and older. The study design has two phases. The first six-month phase includes natural history and outcome measures validation. The second six-month phase involves a randomized, double-blinded, placebo-controlled drug intervention trial. The primary outcome measures are blood glutathione for oxidative stress and six-minute walk test for fatigability.

Dr. Meilleur summarized baseline results of the trial. Forty-two patients enrolled in the study, 7 of whom have since withdrawn. Fifty-eight percent of the patients are adult females and 97 percent are Caucasian. Researchers found no significant difference in mean oxidative stress glutathione levels (GSH:GSSG) between children and adults. There was a significant difference in mean GSH:GSSG ratio between those in the current NAC trial and previously reported cases. The researchers found no difference between the zero- and six-month time points for measures of fatigability, which include a six-minute walk test, graded functional tests, and motor function tests. Muscle ultrasound is a useful mechanism to assess myopathic findings, but a more quantitative method to measure ultrasound results is needed than the physician rating currently being used. Muscle MRI results are pending, but researchers are finding up to 53 percent fat in the least affected upper leg muscle and up to 41 percent fat in the least affected lower leg muscle. If this clinical trial is successful, NAC would be the first Food and Drug Administration (FDA)-approved treatment available for RYR1-RM.

In closing, Dr. Meilleur noted that precision medicine approaches are being used to understand the role personal mutations play in channel function. Those individuals with a leaky calcium channel would be treated differently than those with a hypersensitive channel, a closed channel, or less protein altogether. Future research will focus on therapies specific to patients' individual mutations.

IX. ADJOURNMENT——Dr. Patricia Grady, Director, NINR

Dr. Grady thanked participants and attendees and adjourned the open session of the meeting at 5 p.m.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and Section 10(d) of the Federal Advisory Committee Act, as amended (5, USC Appendix

2). Members absented themselves from the meeting during discussion of and voting on applications from their own institutions or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

REVIEW OF APPLICATIONS

NACNR members considered 152 research and training grant applications on which NINR was the primary Institute; these applications requested a total of $44,410,769 (direct costs year 01). The Council also considered 434 applications on which another Institute/Center was primary and NINR was secondary. These applications requested a total of $309,155,441 (direct costs year 01). The Council concurred with the IRG recommendations on these 586 applications.

ADJOURNMENT

The 90th meeting of the NACNR was adjourned at 1:00 p.m. on September 14, 2016.

CERTIFICATION

I hereby certify that the foregoing minutes are accurate and complete.

Patricia A. Grady, Ph.D., R.N., F.A.A.N	Marguerite Kearney, Ph.D., R.N., F.A.A.N.
Chair	Acting Executive Secretary
National Advisory Council for Nursing Research	National Advisory Council for Nursing Research

COUNCIL MEMBERS PRESENT

Dr. Patricia A. Grady, Chair
Dr. Marguerite Kearney, Acting Executive Secretary
Dr. Cynthia Barnes-Boyd
Dr. Kathryn Bowles
Dr. Aaron G. Buseh
Dr. James Corbett
Dr. George Demiris
Dr. Donna Hathaway
Dr. Jennifer Hatzfeld, Ex Officio
Dr. Jillian Inouye
Dr. Deborah Koniak-Griffin
Dr. Bernadette Melnyk
Dr. Rita Pickler
Dr. Nancy Redeker
Dr. Meredeth Rowe

Dr. Alexa Stuifbergen
Dr. Jennifer Temel
Dr. Marjana Tomic-Canic

MEMBERS OF THE PUBLIC PRESENT

Mr. Randi Bates, The Ohio State University
Ms. Colleen McGovern, RN, MPH, The Ohio State University
Ms. Stephanie Sealschott, The Ohio State University
Ms. Kathy Sedgwick, NOVA Research Company
Dr. Guillermina Solis, University of Texas, El Paso
Ms. Stephanie Sealschott, The Ohio State University

FEDERAL EMPLOYEES PRESENT

Dr. Sarah Abbey, NINR/NIH
Dr. Lynn Adams, NINR/NIH
Mr. Brian Albertini, NINR/NIH
Dr. David Banks, NINR/NIH
Dr. Yvonne Bryan, NINR/NIH
Dr. Ann Cashion, NINR/NIH
Dr. Young Eun Cho, NINR/NIH
Mr. Matt Eliseo, NINR/NIH
Ms. Ana Ferreira, NINR/NIH
Mr. Gabriel B. Fosu, CSR/NIH
Dr. Nicolas Fourie, NINR/NIH
Dr. Lisa Gough, NINR/NIH
Dr. Chris Hafner-Eaton, NINR/NIH
Dr. Michelle Hamlet, NINR/NIH
Dr. Martha Hare, CSR/NIH
Dr. Rebecca Hawes, NINR/NIH
Dr. Wendy Henderson, NINR/NIH
Dr. Karen Huss, NINR/NIH
Ms. Mary A. Kelly, NINR/NIH
Ms. Diane Kuszewski, NINR/NIH
Ms. Alison Lemon, NINR/NIH
Dr. Yujing Lui, NINR/NIH
Dr. Martha Matocha, NINR/NIH
Dr. Jessica McIlvane, NINR/NIH
Dr. Katy Meilleu, NINR/NIH
Dr. Jeri Miller, NINR/NIH
Ms. Karyn Onyeneho, NINR/NIH
Dr. Ananya Paria, NINR/NIH
Ms. Sumiyya Rahem, NINR/NIH
Dr. Mario Rinaudo, NINR/NIH
Dr. Mary C. Roary, NINR/NIH
Ms. Regina Sheffield-Wright, NINR/NIH
Ms. Monique Shelton, NINDS/NIH
Dr. Pamela Tamez, NINR/NIH

Mr. Alex Trader, CSR/NIH
Dr. Lois Tully, NINR/NIH
Dr. Dan Wang, NINR/NIH
Ms. Kristen Weaver, NINR/NIH
Mr. Kevin G. Wilson, NINR/NIH
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