

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
NATIONAL INSTITUTES OF HEALTH  
NATIONAL CENTER FOR COMPLEMENTARY  
AND INTEGRATIVE HEALTH**

**NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY  
AND INTEGRATIVE HEALTH  
MINUTES OF THE SEVENTIETH MEETING  
June 7, 2019**

**NACCIH Members Present**

Dr. Belinda Anderson, West Long Branch, NJ  
Dr. Lynn DeBar, Seattle, WA  
Dr. Roni Evans, Minneapolis, MN  
Dr. Diana Fishbein, University Park, PA  
Dr. Steven George, Durham, NC  
Dr. Joel Greenspan, Baltimore, MD  
Dr. Richard Harris, Ann Arbor, MI  
Dr. Kendi Hensel, Fort Worth, TX  
Dr. Patricia Herman, Santa Monica, CA  
Dr. Tammy Born Huizenga<sup>2</sup>, Grand Rapids, MI  
Dr. Susmita Kashikar-Zuck, Cincinnati, OH  
Dr. John MacMillan, Santa Cruz, CA  
Dr. Cynthia Price, Seattle, WA  
Dr. Eric Schoomaker<sup>3</sup>, Bethesda, MD  
Dr. Justin Sonnenburg<sup>1</sup>, Stanford, CA  
Dr. Barbara Timmermann, Lawrence, KS  
Dr. Gloria Yeh, Boston, MD<sup>1</sup>

<sup>1</sup>Telephone

<sup>2</sup>Ad-hoc

<sup>3</sup>Ex-officio

**NACCIH Members Not Present**

Dr. Tracy Gaudet<sup>3</sup>, Washington, DC  
Dr. Bin He, Pittsburgh, PA  
Dr. Jean King, Worcester, MA

**Speakers**

Dr. James Anderson, Bethesda, MD

Dr. Susan Weiss, Bethesda, MD  
Dr. Alia Crum, Stanford, CA  
Dr. Peter Strick, Pittsburgh, PA

### **Non-NCCIH, Federal Staff Present**

Dr. Barbara Sorkin, Office of Dietary Supplements, NIH

### **Members of the Public**

Dr. Christine Girard, Portland, OR  
Dr. Sonia de Quateli Doi, Bethesda, MD

## **I. Closed Session**

The first portion of the 70th meeting of the National Advisory Council for Complementary and Integrative Health (NACCIH) was closed to the public, in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

A total of 136 applications were assigned to NCCIH for consideration of funding. Applications that were noncompetitive, were not discussed, or were not recommended for further consideration by the scientific review groups were not considered by Council.

Council concurred with staff recommendations on 66 scored applications, which requested \$32,097,859 in Year 1 total costs.

## **II. Open Session—Call to Order**

The open session was convened at 10:00 a.m. by Dr. Partap Khalsa, NACCIH Executive Secretary,. A motion was made and seconded to approve the minutes of the February 2019 Council meeting; there were no revisions and no discussion, and the motion was approved unanimously.

## **III. NCCIH Director's Report**

Dr. Langevin reported on two recent policy issues to which NIH is giving much attention: (1) an initiative to fight sexual harassment against women in the biomedical workplace, both at NIH and its funded institutions, and (2) issues related to certain scientists with links to foreign institutions and/or governments who have engaged in practices that violate federal law, regulations, NIH Policy, and/or standards in the American research enterprise. The second problem could potentially affect some studies' integrity. NIH has emphasized that it is not singling out any particular group, ethnicity, etc., in its investigation.

Recent NCCIH staff changes include: Dr. Slava Soldatenkov, Division of Extramural Activities, who retired, and Dr. Magdalena Naylor, Division of Intramural Research (DIR). Dr. Brian Walitt has been appointed Acting Clinical Director of DIR. Ms. Catherine Law, who had been serving as Acting Director of the Office of Communications and Public Liaison (OCPL), has been named Director of OCPL. Dr. Langevin welcomed Dr. Tammy Born Huizenga as a new member of Council.

There is broad bipartisan support for increases to the NIH and NCCIH budgets for FY 2020. Dr. Langevin explained that the Center received an increase in total funding in FY 2019 as it did in FYs 2018 and 2017. In 2019, NCCIH was able to increase its spending on research grants.

Dr. Langevin presented several examples of impactful NCCIH-funded research results from studies on:

- Plant medicines used in the Civil War era that today are showing promise against drug-resistant bacteria
- The human microbiome (specifically, the vaginal microbiome in relation to preterm birth, the gut microbiome in inflammatory bowel diseases, and host-microbe dynamics in prediabetes)
- The effects of manual therapy on pain-related biology
- Trends in the prevalence of, and health care use for, noncancer pain in the United States.

Applications have been received in response to NIH HEAL (Helping to End Addiction Long-term<sup>SM</sup>) Initiative funding opportunity announcements (FOAs) for “Pragmatic and Implementation Studies for the Management of Pain To Reduce Opioid Prescribing” (PRISM1, PRISM2) and “Behavioral Research To Improve Medication Assisted Treatment” (BRIM) of opioid use disorder. These applications will be brought to the August 2019 Council meeting. NCCIH is actively involved in NIH HEAL activities: Dr. Langevin is on the executive committee; Dr. David Clark, Division of Extramural Research (DER), is cochair of the Implementation Science in Opioid Addiction group; and Drs. Wendy Weber, DER, and Robin Boineau, DER and Office of Clinical and Regulatory Affairs, are members of the Clinical Research in Pain Management group. Two HEAL FOAs, in which NCCIH participates, have upcoming receipt dates: RFA-NS-18-043 and RFA-NS-18-042. Applications for RFA-AT-19-001, under the Sound Health initiative (which is supporting research on music and health), will be brought to the August 2019 Council meeting, as will applications for two FOAs on cannabinoids, RFA-AT-19-008 and RFA-AT-19-009.

NCCIH played major roles in recent scientific workshops on cannabinoids; acupuncture for cancer symptom management, pain, and substance abuse; interoception and nervous system disorders; and natural products to treat pain. Dr. David Shurtleff, NCCIH Deputy Director, and Dr. Emmeline Edwards, DER Director, will cochair a workshop at the annual meeting of the College on Problems of Drug Development. A workshop led by NCCIH on “Neurocircuitry of Force-Based Manipulations” will be held at NIH in September 2019. The FDA held a public hearing on “Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds” and is accepting comments through July 2.

NCCIH is marking its 20th anniversary in 2019. To celebrate, the Center will hold a 1-day scientific symposium, “NCCIH at 20: A Catalyst for Integrative Health Research,” on September 23 in Lipsett Amphitheater. It will include the 2019 Stephen E. Straus Distinguished Lecture in the Science of Complementary Therapies by Dr. Lorimer Moseley of the University of South Australia. Panels will address (1) research by early-stage investigators, (2) pain in military members and veterans, and (3) natural products. NCCIH is sponsoring three lectures in spring 2019 on the gut microbiome. The NIH Health Care Systems Research Collaboratory held a meeting and workshop in May and just participated in a workshop, “Essentials of Embedded Pragmatic Clinical Trials,” prior to the AcademyHealth Annual Research Meeting. Dr. Langevin has been representing NCCIH at a number of conferences and on various advisory bodies inside and outside NIH—e.g., by delivering the keynote address at the American Pain Society Scientific Meeting. She has launched a Twitter account, @NCCIH\_Director.

**Discussion:** Dr. Hensel asked about the goal of the music and health initiative. Dr. Langevin said that it is to study music as a treatment and its effects on health enhancement and health promotion. Dr. Edwards added that this activity is a trans-NIH one, with a working group. The first effort focused on how music impacts the brain, in terms of both basic science and the potential therapeutic effect of music as a modality. Understanding what is going on in the brains of the performers and what music provides to their well-being is integrated with this. The Performing Arts Medicine Association has scheduled a conference at which Dr. Shurtleff will speak. Dr. Langevin said that the topic of the health of performing artists is an important one.

#### **IV. Annual Report on the NCCIH Division of Intramural Research**

Dr. Catherine Bushnell, Scientific Director of DIR, explained that DIR conducts basic, clinical, and translational research focusing on the role of the brain in perceiving, modifying, and managing pain, with an emphasis on mechanistic studies. The Division is an integrated basic and clinical research team that uses state-of-the-art research tools and resources and collaborates with other NIH intramural neuroscience, imaging, and mental and behavioral health research programs. DIR has two branches, each with three sections.

Dr. Bushnell heads DIR's Pain and Integrative Neuroscience Branch, which has three sections:

- The Section on Behavioral Neurocircuitry and Cellular Plasticity is headed by Dr. Yarimar Carrasquillo. It works to identify anatomical, molecular, and cellular mechanisms that underlie pathological pain states—with a focus on the amygdala, a structure in the limbic brain system. The amygdala has not been as deeply researched in relation to pain as has the spinal cord. Among Dr. Carrasquillo's achievements is a major paper currently under review at *Neuron*.
- The Section on Sensory Cells and Circuits, headed by Dr. Alexander Chesler, investigates the neurons and circuits of the somatosensory system and their changes during injury and inflammation. Among his activities are his second NIH Board of Scientific Counselors pretenure review (upcoming) and publication of many papers.
- The Section on Affective Neuroscience and Pain is headed by Dr. Lauren Atlas and focuses on characterizing the psychological and neural mechanisms by which expectations and other cognitive and affective factors influence pain, emotional experience, and clinical outcomes. Among Dr. Atlas's achievements have been having numerous papers published, accepted, or invited for revision; election to the NIH Assembly of Scientists; and appointment as an adjunct investigator with the National Institute of Mental Health.

In the Clinical Investigations Branch (CIB), the focus is on mechanistic clinical research targeted at understanding the development and maintenance of chronic pain, as well as nonpharmacologic treatment modalities such as cognitive behavioral therapy (CBT), meditation, and music. The CIB provides a clinical setting and the medical expertise to evaluate people with a wide range of painful disorders. Dr. Walitt is the Acting Director.

Among the new hires at DIR is Dr. Yuanyuan (Kevin) Liu of Harvard University, who will be a Stadtman Tenure-Track Investigator cross-appointed between NCCIH and the National Institute of Dental and Craniofacial Research. This kind of collaborative approach is a good way for NCCIH to expand despite limited resources.

NCCIH is the lead agency on the pain center being developed at NIH. The project is in a holding pattern until a full-time DIR Clinical Director is hired. In the interim, Drs. Bushnell, Walitt, and Atlas are coleading the project. The mission is to create a pain phenotyping platform within the NIH Clinical Center to better understand mechanisms of diverse pain states and to recommend personalized therapies to prevent the development of chronic pain and opioid abuse. At present, resources include common methodological approaches that staff can use in their studies and in NIH intramural collaborations, such as quantitative sensory and autonomic testing units; anatomical and functional magnetic resonance imaging (MRI) and combined positron emission tomography/MRI; core questionnaires; funding for a fellow; and genetic sequencing. NCCIH, the National Heart, Lung, and Blood Institute, and the National Institute of Nursing Research have provided the resources. In an era of very tight space on campus, DIR has been given extra rooms in the Clinical Center and a house in The Quarters area, both of which Dr. Bushnell said indicate a high level of interest.

The program's studies include a phenotyping protocol, clinical study 16-AT-0077, "Clinical and Scientific Assessment of Pain and Painful Disorders." This is a broad protocol with Dr. Bushnell as the principal investigator and many associate investigators. Study participants (the capacity is currently 10,000) have a core evaluation. Staff have a number of phenotyping measures from which to choose, allowing flexibility. All data obtained go into a common database, and the team is following the data sharing plans that are evolving at NIH.

DIR's ongoing collaborative projects at NIH include:

- Examination of mechanisms of chronic pain in patients with sickle cell disease, using a hematopoietic stem cell transplant model
- Study of psychosocial and neural factors that shape responses to third molar extraction surgery and could predict postsurgical pain and opioid use
- Research on patients with rare somatosensory processing disorders (such as congenital insensitivity to pain) to uncover new mechanisms in pain genetics and neurobiology.

Additional collaborations are being developed.

**Discussion:** Dr. Kashikar-Zuck called the pain center a "fantastic" idea. She asked whether the concept is more bottom-up or top-down, including in funding. Dr. Bushnell described the project as a mixed model in which the idea is to have the facility available—sometimes with a for-pay structure, although the funding details need to be worked out. Everyone with whom Dr. Bushnell has communicated about the pain center project has appeared to be on board with and excited about it. She described interest as top-down—for example, when Secretary of Health and Human Services Alex Azar visited NIH, he and NIH Director Dr. Francis Collins chose DIR as one of his tour sites, where they met a patient with a rare pain condition. Dr. Bushnell sees much interest in the project at the highest NIH levels. There has been increased media interest in DIR's work.

Dr. Shurtleff described the NIH intramural community as very collaborative and the movement toward the pain center as a grassroots effort. Dr. Langevin said that integrative health is playing a leadership role in pain both intramurally and extramurally and that people are looking to NCCIH for leadership—a situation that has changed a great deal over the past 10 years and of which NCCIH should be proud. Dr. Schoemaker commended Dr. Bushnell on her work on this "interagency, collaborative effort" that could be enduring and shared. The program might help settle questions about chronification of pain in specific populations. He noted how diverse the study outcomes are in the literature; could the pain center help by

adopting standardized tools, measures, etc.? Dr. Bushnell responded that her team has all the major questionnaires in their topic area available to them, which creates a comprehensive approach. With a rare disease, there is a related pain phenotype, and by collecting data using these tools they may be able to find which ones are best. She agreed it would be beneficial to develop standard tools.

Dr. Harris asked what Dr. Bushnell will do to leverage the results from the pain center for the long term. Dr. Bushnell said DIR's unique opportunity is rare disease states and the related pain phenotypes. The focus will be to use this to better understand mechanisms from animal and human models and leverage collaborations and the access they bring. DIR does not have access to extramural research funds.

Dr. Shurtleff suggested that a theme within HEAL, the transition from acute to chronic pain, is one where DIR could have a role. Dr. Bushnell agreed and mentioned DIR's unique models. Dr. Langevin said that HEAL is in the process of giving a very large amount of support to pain science, including to DIR's work in this area, and HEAL is lifting the pain field overall and enabling crossfertilization. The pain center may create a gathering point. Dr. Bushnell said that NCCIH has the expertise and can lead this project, but it needs to have other ICs involved. Dr. DeBar suggested looking at synergies across FOAs and the science to see if there are opportunities to marry some of the extramural and intramural work. Dr. Bushnell described programs at NIH that offer those opportunities.

Dr. Greenspan asked whether there are any plans to develop a database "of all comers," whether the pain conditions studied are rare or common, and if so, could it be mined in other contexts? Dr. Bushnell said this is of interest but the specifics will depend on the resources. The present plan is that the data on all patients who come in through the pain center and in the phenotyping protocol (including healthy people) will be stored in a common place and format. How much the team could move beyond these patient populations is not yet determined. The team also provides access to nonpharmacologic, nonopioid treatment options such as transcranial magnetic stimulation (e.g., targeted to sickle-cell disease), vagal nerve stimulation, or yoga, providing an opportunity for testing and to add to knowledge.

## **V. Concept Clearances**

### **Concept on Natural Products and Pain**

Dr. Craig Hopp, Deputy Director of DER, presented a concept on natural products and pain. Much input had been received from staff, the NIH community, and the extramural community. Throughout history, people have made medicines from things around them and made pharmacopoeias, including for pain, but lacked a sense of how or why these products might be effective. Today, we have a better sense of how analgesics work, often because natural products have shed light on the receptors and pathways involved. NCCIH thinks it makes sense to focus on nature again for new sources of analgesic compounds.

The Center's thinking and efforts on this topic began pre-HEAL, and recently, NCCIH presented a workshop on natural products and pain. The workshop recommendations included a need for more repositories, as both physical and digital archives, and a call for more support for and investment in early-stage discovery science. Some pain research at NCCIH is being done in the context of HEAL, and the Center does not want to duplicate HEAL efforts. However, there are areas not covered under HEAL that NCCIH is well suited to support. NCCIH could then leverage HEAL to support additional natural product research. NCCIH and its partners have developed a comprehensive platform with many components, which could be executed in parallel. Objectives are as follows:

- Mining of existing literature and other resources to compile a robust list of understudied natural products with evidence of analgesic activity (to eventually form an information hub).
- Collection of plants or other natural product sources from around the world with reported analgesic activity that are not available in existing repositories. (In general, anything collected needs to be able to be added to NCI's freely available natural products library.)
- High-throughput screening of natural product libraries in established pain targets or phenotypic assays, especially those leveraging existing repositories and ongoing NIH screening infrastructure. Examples might be libraries of academic labs or companies within industry.
- Discovery, identification, and characterization of natural products with promising analgesic activity.
- Leveraging initiatives under HEAL as potential avenues for translational development of promising nonaddictive analgesic natural products.

**Discussion:** Dr. Timmermann supported this concept, stated there is a need for it, and asked whether NCCIH was proposing to have a central repository at NIH or whether investigators would keep individual collections at their institutions. Dr. Hopp responded that to the extent researchers are making new collections, those items should be included in the NCI repository. NCCIH will work with NCI, which would be open to new additions as long as the researchers abide with its library's policies.

Dr. MacMillan asked how NCCIH will handle agreements with foreign countries. Dr. Hopp said that as far as he knows, with regard to NCI, the investigators work out agreements with the source countries if they find something. NCI's model is well established. Dr. MacMillan agreed that NCI has its particular approach, but if individual investigators are to do this work, that is viewed from a very different perspective. For example, there can be major problems within review, even if one possesses a "reasonable permit" from officials in the foreign country; renegotiation to reach a higher NIH standard may be required. He recommended that NCCIH make this clear and perhaps talk to the State Department. Dr. Hopp said Dr. Flora Katz at NIH's Fogarty International Center has much experience with such agreements, but NCCIH wants to ensure it has its "ducks in a row."

Dr. MacMillan suggested including details about the capabilities and resources of the National Center for Advancing Translational Sciences (NCATS) within the initiative. Dr. Hopp said the concept is not of a fixed "menu" but of a flexible one, and NCCIH will be clear about its information on NCATS, including to avoid duplication. One issue that keeps coming up, Dr. MacMillan said, is that NCI's collection is too large to screen in a cost-effective manner. Will there be a requirement to use that library, how would it be used, and if used, would everyone receive the same set of plates? He thought the concept should move ahead but has daunting logistical aspects. Dr. Wen Chen, DER, commented that one of the Center's efforts will be to try to find a way to narrow the database down.

Dr. Timmermann suggested doing some ethnobotanical database screening ahead of collecting samples. Dr. Hopp agreed and said these activities could be done in sequence or parallel. In response to a question from Dr. George regarding evidence of analgesic activity, Dr. Hopp said one approach is to add narrowing filters to determine which candidates have the most promising activity. The concept was unanimously passed, with the exception of one vote to be obtained after the meeting.

### **Concept on Mechanisms Underlying Modulation of the Glymphatic and Lymphatic Systems by Complementary and Integrative Health Approaches**

Dr. Yisong Wang, DER, presented this concept. The glymphatic (glial-lymphatic) system and the meningeal lymphatic system have critical roles in the body and brain. For example, they are key players in removing solutes and waste products from the brain, such as amyloid beta (A $\beta$ ), tau, lactate, and proinflammatory cytokines. The glymphatic system also contributes to brainwide nutrient delivery. The meningeal lymphatic system shares similar functions to the peripheral lymphatic system in carrying out tissue homeostasis and immune trafficking/surveillance.

The glymphatic system has been implicated as having a role in medical conditions such as Alzheimer's disease, cortical spreading depression–associated migraine aura, traumatic brain injury, subarachnoid hemorrhage/ischemic stroke, multiple microinfarcts, diabetes-associated cognitive impairment, chronic stress, and the aging brain. Experimental disruption of the meningeal lymphatic system exacerbates A $\beta$  deposition and cognitive impairment in mice. More understanding is needed of how the glymphatic and lymphatic systems are regulated. This could help in the development of therapeutic strategies to prevent or delay many diseases and disorders, including brain dysfunction, as well as inform health promotion and disease prevention.

Both systems have some evidence of being modulated by nonpharmacologic approaches. Physical exercise, continuous theta burst stimulation (cTBS), and deep inhalation–mediated thoracic pressure reduction have been shown to regulate brain lymphatic flows. Osteopathic lymphatic pump manipulations and lymphatic drainage massage can regulate peripheral lymphatic flows. In a study in mice, omega-3 fatty acids were seen to promote A $\beta$  clearance through facilitation of a glymphatic function in mice (the aquaporin-4, or AQP4, function). However, significant knowledge gaps remain.

Many complementary and integrative health approaches are widely used by the public for conditions related to the lymphatic and glymphatic systems. This initiative would stimulate rigorous research on the effects of these approaches as well as the underlying mechanisms. The Center would encourage studies on diseases and disorders of high programmatic interest, such as pain, Alzheimer's disease, anxiety, and depression, and/or promotion of health and well-being. Preclinical studies using relevant animal models and human mechanistic studies would be appropriate.

**Discussion:** In response to a question from Dr. Harris, Dr. Wang said he thought, in general, the initiative would be intended to stimulate a research study. Dr. Edwards added that NCCIH does not usually talk about specific mechanisms at this stage, but there are various options, and NCCIH will take into account the status of the field as it develops an initiative. Dr. Greenspan asked whether the NCCIH portfolio includes any current studies about the lymphatic system. Dr. Wang said he knew of one.

The concept was passed unanimously except for one vote to be obtained after the meeting.

### **Concept on mHealth and Remotely Delivered Complementary and Integrative Interventions**

Dr. Lanay Mudd, DER, presented a concept for a proposed initiative to promote research on mHealth for integrative approaches in relation to fostering health promotion and disease prevention and improving care for hard-to-manage symptoms. This initiative would also address one of NCCIH's top priorities, innovative clinical trial designs. Dr. Mudd defined "mHealth" or "mobile health technologies" as referring to the use of mobile phones and other wireless technology, including web-based platforms and video technologies, in medical care or health research. The approaches in the concept would be fully remotely delivered, with no in-person contact with research staff.



Potential advantages of mHealth include capability to improve scalability and reach of interventions—supporting the ability to conduct nationwide recruitment from a single site, which would help to improve generalizability of results—and to also potentially reach populations with rare conditions. This approach may also be cheaper and easier to implement. Some disadvantages include potential dilution of the intervention components; lack of a personal connection, which may be important with some complementary approaches; and safety considerations. Many commercial mHealth tools—e.g., on meditation or yoga—are being used without much evidence on their usefulness or safety for different conditions. Scientific interest in mHealth is increasing, and Dr. Mudd showed several examples of illustrative projects from the NCCIH portfolio. While these are examples of first steps, she said, NCCIH needs to consider how to support this kind of research moving forward into the effectiveness/efficacy/pragmatic trial stages. Currently, the Center’s FOAs require investigators to use multisite approaches to improve generalizability of findings, whereas this concept uses a single site coordinating a nationwide effort. NCCIH does not have a current FOA that supports this kind of work.

**Discussion:** Dr. Price expressed enthusiasm for the concept and asked about going fully remote vs. partially remote (e.g., by having flexibility for at least one in-person meeting, which could be critical for many populations). Dr. Mudd responded that that might indeed be the case with some populations, conditions, etc., and in those cases she thinks the current FOAs with a multisite requirement are appropriate. With this concept, NCCIH is trying to support research on fully remotely delivered interventions because of advancing technology, even in terms of collecting biosamples, and for greater reach. An in-person visit may not be needed. For example, a study on CBT for insomnia that directly compared a fully remotely delivered option with an in-person option found comparable results. Not many investigators or interventions are ready to immediately go forward with this approach, but there are those who are, and NCCIH has a gap there.

Dr. Schoemaker was supportive but also concerned that mHealth programs have already been in use, e.g., in the Department of Defense (DoD), and recommended that NCCIH leverage what has already been learned by large health care systems. Such programs may be used at times without knowledge of the degree of traction with the individual user and/or without outcome studies to demonstrate utility. He added that “the first connection is vital” in the complementary and integrative health space. Yet engaging with the millennial and Gen Z populations requires addressing questions of mHealth, so he is glad NCCIH is looking at them. The DoD started doing psychological and psychiatric counseling by telemedicine more than a decade ago, and he has seen that younger people actually prefer that approach to person-to-person, especially for very intimate questions. Dr. DeBar commented there may be places where having enough touch and tailoring would be desirable. Her organization has been studying the topic and found the opposite of what Dr. Schoemaker said—i.e., respondents want high touch. She could see a mechanism having a remote app but also ways to touch people, as by telephone or video.

In response to a question from Dr. Price about the nature of comparative designs relative to the concept, Dr. Mudd clarified that comparisons with in-person delivery would be best suited for NCCIH’s FOAs that require multisite work; here, the approach could be compared to other app deliveries or remotely delivered interventions. A fully remotely delivered intervention can have fully nationwide recruitment and data collection from one center and in addition generalizability in delivering results on efficacy and effectiveness. If there are one or more visits, then to obtain a generalizable sample, multiple sites are needed. Dr. Kashikar-Zuck said one key would be to fund projects that have appropriate control groups. She cautioned that the CBT world, for example, has been doing this for a long time, and in well-controlled, published studies remote-to-remote, it is hard to find a difference in effect sizes. She

encouraged learning what has been going on with other types of interventions, making comparisons explicit, and ensuring NCCIH will learn something scientifically. Dr. Mudd agreed and made further comments on the choice of comparator group and the complexities when working with remote delivery. These applications would have gone through feasibility testing before moving into the efficacy design.

The concept passed unanimously minus one abstention, with one vote to be obtained after the meeting.

## **VI. Symposium on the NIH/NCCIH High-Risk, High-Reward Research Program**

Dr. Edwards provided brief background on how NCCIH has used and continues to use the High-Risk, High-Reward (HRHR) Program. In her experience, the Center has seen the benefits of leveraging this program to bring excellent, innovative investigators to its portfolio and to leverage resources from the NIH Common Fund. Awardees do research in areas highly relevant to the NCCIH mission, and the Center has engaged with them in other ways—e.g., in its lecture series and as workshop panelists at national meetings. In short, NCCIH sees its participation in the program as a win-win situation.

### **NIH High-Risk, High Rewards Program**

Dr. James Anderson, Director of the Division of Program Coordination, Planning, and Strategic Initiatives, NIH Office of the Director, gave an overview of the NIH Common Fund and specifically the HRHR Program. The program supports exceptionally creative scientists proposing high-risk, high-impact research and is designed to stimulate innovation in biomedical and health-related fields, as well as provide unique opportunities for scientists to propose transformative ideas without the need for preliminary data. He added that a fundamental goal is to encourage very creative scientists to pursue high-risk work that would not fare well in standard peer review. Topics of applications can be in any area of the NIH portfolio.

Dr. Anderson explained each of the four types of awards (full details are at <https://commonfund.nih.gov/highrisk>). The Pioneer Award allows creative and productive researchers to explore new scientific directions; the New Innovator Award provides innovative early-stage investigators with the opportunity to pursue novel research ideas; the Transformative Research Award gives teams or individual principal investigators latitude to investigate “trailblazing” scientific ideas without budget limits; and the Early Independence Award allows young scientists to “skip the postdoc” and pursue transformative independent research careers earlier. A working group of the NIH Advisory Committee to the Director will be releasing a report on its review of the HRHR program. One area that needs more work is obtaining more applications from women.

### **The Avant-Garde and Avenir Programs of the National Institute on Drug Abuse (NIDA)**

Dr. Susan Weiss, Director of the Division of Extramural Research, NIDA, discussed two NIDA programs that are similar to the HRHR program. Among the topics Dr. Weiss addressed were application requirements, budgets, review, success rates, and recent awardees and their publications.

The Avant-Garde Award Program for HIV/AIDS and Drug Use Research supports individual scientists of exceptional creativity who propose high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. No detailed budget is required.

NIDA's Avenir Awards are grants to early-stage investigators who propose highly innovative studies and represent the future of addiction science. NIDA has two Avenir programs, one on HIV/AIDS and the other on the genetics and epigenetics of substance abuse. Awardees' average numbers of publications have been relatively large, and Relative Citation Ratio scores tend to be 2 or higher. For the genetics/epigenetics track, NIDA encourages scientists from other ICs who would be interested in working in NIDA's area, as well as candidates who are in the early stages of their careers and show promise as future leaders, to apply.

### **Harnessing Mindset in 21st-Century Health Care**

Dr. Alia Crum, assistant professor of psychology at Stanford University (lab page: <https://mbl.stanford.edu/>) discussed the research she has been doing related to the placebo effect and mindset under an NCCIH-administered New Innovator grant.

She described several of her team's published studies done in lab and/or clinical settings. One in the latter led to interesting findings about how a health care provider's perceived demeanor, warmth, and competence, which had been presented to the participants in degrees ranging from low to high, affected the size and the healing of a minor allergic reaction to a pinprick containing allergen. Differing social contexts in the study had effects as well. In sum, it appears that how well a treatment works appears to depend on mindset, and mindset hinges on social context. Mindsets matter, including in shaping treatment outcomes.

Dr. Crum's current projects include a longitudinal study delivering remote interventions to patients diagnosed with cancer, in the form of video stories told by cancer survivors about how mindsets related to illness and treatment have mattered to them. The second is a training, "Medicine Plus Mindset," being delivered throughout the Stanford Primary Care System, to help providers establish useful mindsets in their jobs and value what they do, and in turn to influence patients in this useful and positive way.

Dr. Crum said that her HRHR grant was a fit because she had a novel, unprecedented approach, a lack of preliminary data, and broad aims, and used interdisciplinary methods. Her application might not have been successful in review elsewhere at NIH. The New Innovator Award has been essential to enable Dr. Crum to engage in novel impactful projects.

**Discussion:** Dr. B. Anderson expressed concern about the impact upon people of receiving negative information on their health risks and outcomes, especially if and when they are already receiving that kind of negative information, e.g., via technology. Dr. Crum agreed and added that, in her opinion, many of our technological advances and personal health apps are doing more harm than good, and there is much evidence to back up that view. Information for information's sake is not necessarily beneficial if we do not help people to understand or interpret it. Also, if we try to tell people to do something specific for their health so that they do not get sick or sicker, the evidence is that most people do not change their behaviors—rather, they end up with a mindset constantly making them feel unhealthy. Perceived health is a stronger predictor of mortality than objective markers of health. Her group is also studying approaches to public health messaging.

Dr. Schoemaker suggested that one major reason we have not exploited the placebo effect is because it does not sell many drugs, devices, hospitalizations, etc. Dr. Crum agreed that we have not figured out yet how to make the placebo effect a standard or how to do the financial piece, e.g., in the insurance and

health payment systems. Dr. Langevin said that many things we do are about preventing disease, but we can also talk about health restoration, which is a big shift in thinking.

In response to Dr. Hensel's question on how Dr. Crum trains primary care providers, Dr. Crum said that it starts as a 2-hour, live training delivered to the entire clinic staff. This piece has been empowering and helped staff realize everyone has a role in shaping mindset. Lectures, group work, and a 1-hour followup 1 month later are included. The training focuses on her model, the research, and four mindsets: those related to treatment, illness, the body, and the health care team. Her team is working with a studio to turn this program into an online training and potentially into continuing medical education.

### **Insights on an NIH Transformative Research Award (T-R01)**

Dr. Peter Strick, scientific director of the University of Pittsburgh Brain Institute and distinguished professor and chair of neurobiology (lab page: <https://www.neurobio.pitt.edu/faculty/strick.htm>), discussed highlights from his research, including work under his NIH Director's Transformative Research Award, to establish a structural framework for the brain-body connection—the neural circuits that connect the cerebral cortex with peripheral organs. Disturbance in the brain connection has been thought to contribute to problems in functioning and development of illness. A focus in Dr. Strick's talk was the neural substrate of functional disorders, including many that are widely considered intractable, such as irritable bowel syndrome and fibromyalgia. Progress in this line of research could inform research on new treatments and the way we view and manage such disorders.

Dr. Strick described a novel technique he developed of using live virus to overcome blocks in studying multisynaptic circuits. He has found that actual neural connections are involved for which there are biological substrates. He sees psychosomatic illnesses as neither irrational or imaginary; they are real, and they are indeed “all in your head,” because the brain is in the head. If a medical phenomenon such as a disease is happening inside a person's head, that does not mean it is not real. Dr. Strick's team has also discovered, for example, a biological explanation for why movement reduces stress.

With regard to his HRHR award, Dr. Strick said he initially received some skepticism from a mentor on his idea to develop a virus technique. Dr. Strick received one of the early HRHR awards, persisted, and later published the first evidence in the field that scientists can use neurotropic viruses to trace neural pathways. He also proved that, against prevailing belief, it is not impossible to sort out transport, reveal neural networks, and infer functional meaning from tracing through as many as six synaptic steps. He described the HRHR program as very key to his progress and as allowing scientists to take risks and do experiments that most people would say they would never do under any circumstances. HRHR is the only way he could have done his science.

**Discussion (including on the symposium as a whole):** Dr. Schoemaker said that the DoD's Defense Advanced Research Projects Agency (DARPA) is also a setting in which there is high risk that the science will fail. The symposium showed remarkable work and a theme of success. However, should NCCIH (a relatively small IC) move farther into this area of deliberate risks, substantial investments, and high chances of failure? Dr. Weiss said that not all of NIDA's HRHR grantees have achieved what they set out to do. Also, NIDA funds many applications under the BRAIN Initiative that have relatively poor scores compared to other projects it supports. However, NIDA sees a need to take risks. One should examine failures carefully. Dr. Strick described projects that took years and involved some failures along the way.

Dr. J. Anderson said that the Common Fund staff does think about the risk issue a great deal. It has done several projects in parallel with DARPA. There are designs that create failure. He recommended tracking pivots to learn how often they happen and what they mean. Dr. Langevin said that with NCCIH's phased awards (which contrast with HRHR, e.g., by having clear milestones), about half the awards do not transition because they cannot pivot. Dr. Shurtleff said that with HRHR the Center is investing in the investigator rather than the project.

Dr. Crum suggested reexamining the term "High-Risk, High Reward." Her work is closer to terms like "paradigm-shifting," "complex," and "messy" than "risky." She has a goal but does not know how the process will look, which is figured out along the way.

Dr. Schoomaker said that he sees this concept as high-reward but a different kind of risk, and the approach as "more of a Myers-Briggs P than a J....the reward is out there." NCCIH would be endorsing a new stratagem to come at high-reward science with a different kind of risk mitigation. Dr. Edwards commented that behavioral science researchers are not well represented in applications NCCIH sees from the HRHR pool. She hopes Council members will encourage their communities to apply in the complementary and integrative health subject area, and invited their feedback on topics to target.

Dr. Fishbein said that these programs enable movement away from traditionalist reviewers and from models that are not necessarily forward thinking or transdisciplinary. They encourage experimentation and the opening of minds to new paradigms not only in the field but when designing and critiquing research. She suggested reviewers receive training to help them think out of the box. Dr. DeBar said that many of these HRHR projects are crossdisciplinary and "unsiloing." Questions to consider include how to get better measures of impact beyond citations and how to incubate people so they will be better positioned to do this kind of crossdisciplinary work.

Dr. Price asked whether, if a program were developed at NCCIH similar to HRHR, it would have a specific focus. Dr. Edwards said that NCCIH has discussed at various points whether to identify a gap area and offer this kind of program. Dr. Price said that her preference would be to have the program be more broad and open as far as topics. Dr. B. Anderson wished to see the HRHR name kept the same; as an applicant, she would find it suggestive of developing something out of the box. Dr. Harris thought diversifying and having resources in multiple pots (including to invest in investigators to help them get to their next step) makes sense. Dr. Kashikar-Zuck asked whether NCCIH could offer more communication to researchers of examples of scientists who have received HRHRs, e.g., via the Center's website, Twitter, and workshops and conferences. Dr. Edwards responded with an example of having done so—with Dr. Isaac Chiu of Harvard Medical School—and supported the idea of featuring this topic more on the NCCIH website. Dr. J. Anderson said that the Common Fund features all its funded investigators on its website, and in addition, Dr. Collins often highlights their study findings in his blog. Dr. Anderson offered to talk with NCCIH about pulling the Fund's information over.

Dr. Timmermann said she thinks NCCIH has a very important role in the United States, and she would like to see in what ways NCCIH-funded researchers' work could be highlighted more to the public, scientists, and others, e.g., through the media. Dr. Fishbein agreed that the work is impactful to the public, described a few of her activities in this area, and added that this NCCIH information, along with what the evidence says, should be translated to the public. Dr. Langevin praised the NCCIH OCPL team, its efforts, and the Center's website. Ms. Law commented that NCCIH's website is considered to be well designed for the public, but there is always room for improvement. There are ways, such as linking to the Common Fund materials already available, to help people understand the value of this kind of

program and how it can be an exciting generator for science. Dr. Timmermann mentioned television advertisements. Ms. Law said that she, Ms. Irene Liu, and the Center’s web team could talk with members of the DER team about the goals for an effort; the target audiences; and optimal approaches. Dr. Edwards added that whenever NCCIH puts out an initiative, it is not a static but rather an interactive process, including with webinars for applicants. Uptake of NCCIH initiatives has greatly increased from these efforts. Dr. B. Anderson suggested the Center tie messaging to value-based reimbursement, in which there is a lot of current interest.

## **VII. Public Comment and Adjournment**

Dr. Christine Girard, incoming president of the National University of Natural Medicine (NUNM), Portland, Oregon, introduced herself and her university. She also introduced Dr. Sonia de Quateli Doi, a board member of NUNM. Dr. Girard expressed as one of her priority interests to expand NUNM’s involvement in research and its engagement with the scientific community in complementary and integrative health. The university has received various NIH grants and is a clinical research site for one. Its teaching clinic for naturopathic and Chinese medicine students provides primary care. NUNM is eager to collaborate and has experience in this. Dr. Girard saw NUNM’s strengths as in early-phase natural products research, and mind and body research in conditions of clinical importance. She expressed appreciation of (1) NCCIH and the Council shining a scientific light on systems and practices of health care that she saw as too often underrepresented in the current paradigm, and (2) NCCIH’s research support to NUNM. NCCIH’s work, she said, contributes to broadening the range of health care options available to the public, encourages patient self-efficacy, and builds the evidence. She praised “thinking differently.”

The meeting was adjourned at 3:20 p.m.

We hereby certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.

Partap Khalsa, D.C., Ph.D., D.A.B.C.O.  
Executive Secretary  
National Advisory Council for  
Complementary and Integrative  
Health

Helene Langevin, M.D.  
Chairperson  
National Advisory Council for  
Complementary and Integrative  
Health