

**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 SIXTY-SECOND MEETING
June 2, 2017**

NACCIH Members Present

Dr. Martin Blaser, New York, NY
Dr. Donald Brater, Indianapolis, IN
Dr. Alice Clark, University, MS¹
Dr. Lynn DeBar, Portland, OR
Dr. Tracy Gaudet, Washington, DC
Dr. Steven George, Durham, NC
Dr. Christine Goertz, Davenport, IA¹
Dr. Joel Greenspan, Baltimore, MD
Dr. Bin He, Minneapolis, MN¹
Dr. Patricia Herman, Santa Monica, CA
Dr. Steven Hersch, Charlestown, MA
Dr. Susmita Kashikar-Zuck, Cincinnati, OH
Dr. Janice Kiecolt-Glaser, Columbus, OH¹
Dr. Jean King, Worcester, MA
Dr. Helene Langevin, Boston, MA
Dr. Cynthia Price, Seattle, WA
Dr. Eric Schoomaker, Bethesda, MD
Dr. Reed Tuckson, Sandy Springs, GA¹

¹Telephone

SPEAKERS

Dr. John MacMillan, Dallas, TX
Dr. Mary Paine, Spokane, WA
Dr. Guido Pauli, Chicago, IL
Dr. Linda Porter, Bethesda, MD
Dr. Lawrence Tabak, Bethesda, MD
Dr. Richard van Breemen, Chicago, IL

NACCIH Members Not Present

Dr. Martin Blaser, New York, NY
Dr. Richard Niemtow, Alexandria, VA

Federal Staff Present

Adam Kuszak, ODS, NIH
Barbara Sorkin, ODS, NIH

Members of the Public:

Iris Aharonovich
Wei Liu
Breanne Van Nostrand
Amita Shukla

Closed Session

The first portion of the sixty-second 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 123 applications were assigned to NCCIH. Applications that were noncompetitive, not discussed, or were not recommended for further consideration by the scientific review groups were not considered by Council.

Council agreed with staff recommendations on 63 applications, requesting \$20,955,383 in total costs.

Informal Presentation

NCCIH Director Dr. Josephine Briggs made an informal presentation at 9:50 a.m., before the start of the open session, on four recent studies to which NCCIH contributed:

- Dr. Giulio Tonini and colleagues published a study on the neural correlates of dreaming that calls into question the classic assumption that dreaming occurs only during the rapid eye movement (REM) stage of sleep. By waking adults at various stages of sleep and asking them about their conscious mentation prior to awakening, they found evidence of processes similar to dreaming during non-REM sleep. In addition to calling a longstanding belief into question, this finding could be important in evaluating the potential adverse effects of benzodiazepine drugs on restorative sleep.
- Dr. Vitaly Napadow and colleagues demonstrated that acupuncture may produce local pain-relieving effects in carpal tunnel syndrome and may also affect the brain's pain centers. A novel finding of this study that contrasts with much of the literature on placebo was that acupuncture may have a direct effect on the wiring of the primary somatosensory cortex. This study needs to be replicated, but it may contribute to the ongoing effort to understand how acupuncture modifies pain states.
- Dr. Tor Wager and colleagues (including NCCIH intramural researcher Dr. Lauren Atlas) created a functional magnetic resonance imaging (fMRI)-based model that quantifies the cerebral contributions to pain beyond nociception. The question of whether imaging methods

can be used to determine the presence or absence of pain is one of the hottest current issues in pain research, and experts in the field consider this study an important contribution.

- Dr. Sheldon Cohen and colleagues used salivary cortisol measurements to investigate the relationship between marital status and perceived stress. They rigorously documented that happily married people had lower cortisol levels and found a good correlation between cortisol levels and perceived stress levels. Beyond its contribution to understanding the health benefits associated with marriage, this study is important because it demonstrates the usefulness of salivary cortisol measurements—if performed frequently enough and on a large enough sample—despite their substantial scatter.

Open Session

The open session convened at 10:00 a.m. Dr. Partap Khalsa, NACCIH Executive Secretary, called the meeting to order. The minutes of the February 2017 NACCIH meeting were approved unanimously.

I. NACCIH Director’s Welcome and Report to Council

Dr. Briggs announced that NACCIH Executive Officer Wendy Liffers will be retiring at the end of the summer. She will be greatly missed. Her deputy, Ginger Betson, will become acting executive officer.

Other staff changes include the recent retirement of Dr. Martin Goldrosen, former Director of the Division of Extramural Activities, who has been replaced by Dr. Partap Khalsa, and the departure of Alyssa Cotler, former Director of the Office of Communications and Public Liaison (OCPL), who has become Director of Communications and Marketing for the All of Us Research Program (formerly known as the Precision Medicine Initiative Cohort Study). Catherine Law is serving as the acting director of OCPL. Dr. Briggs welcomed Dr. Merav Sabri, a new program director in the Division of Extramural Research, whose expertise in neuroimaging will be particularly valuable to NACCIH.

NACCIH had anticipated a budget decrease in 2017 but actually received a modest increase of about 3 percent. The President’s budget for 2018 was presented on May 23. Dr. Briggs drew attention to comments made during House of Representatives hearings on the budget by Representative Rosa DeLauro of Connecticut and others about the importance of NIH as the Nation’s leading biomedical research agency.

Dr. Briggs thanked Council for their help in rapidly implementing an initiative to solicit applications to examine the impact of behavioral interventions on opioid use disorder; this initiative functions within the context of states’ plans for use of the Substance Abuse and Mental Health Services Administration (SAMHSA) opioid State Targeted Response (STR) grant funds authorized under the 21st Century Cures Act. Council input was very helpful in shaping the NACCIH funding opportunity by broadening it to include preventive modalities as well as the use of behavioral interventions as an adjunct to medication. NACCIH expects to receive applications in response to this funding opportunity in August.

II. Enhancing Stewardship: New Efforts To Promote a Stronger and More Stable Biomedical Research Workforce

NIH Principal Deputy Director Dr. Lawrence Tabak outlined steps that NIH is taking to enhance stewardship and support the careers of early stage and mid-career investigators. These efforts address the mandate in the 21st Century Cures Act that calls for the NIH Director to promote policies that provide opportunities for earlier independence and increased funding for the next generation of researchers.

NIH has already taken steps to increase the number of early stage investigators (ESIs), but is now increasing the flexibility of support for them as well. In addition, NIH is working to stabilize career trajectories by providing new support systems to nurture researchers who have been NIH principal investigators (PIs) for no more than 10 years.

Maximizing the impact of NIH funding requires a sophisticated approach that makes it possible to measure the interim influence of grant support on short-term outcomes. NIH has chosen to use a bibliometric measure, the Relative Citation Ratio (RCR), which addresses impact at the article level and is field independent. The RCR has been used to assess incremental research output according to the extent of grant support. The grant support index (GSI) used in these calculations includes only research project grants (RPGs). The results indicate that incremental returns from additional RPGs decrease as the number of RPGs held by an individual scientist increases.

To maximize the impact of NIH funding and ensure optimal stewardship, it makes sense to apply additional scrutiny to grant applications from those investigators who already have the most extensive NIH support. NIH has proposed a pilot program that involves placing a dynamic cap on the amount of support that any one investigator should have, using the GSI to inform decisions. The resources made available in this way can be used to support ESIs and mid-career investigators. Starting in the fall of 2017, all Institutes and Centers (ICs) will be asked (1) to proactively determine whether PIs with high GSIs should receive additional funding and (2) to provide written justification to the Office of the Director (OD) if a decision is made to award them additional funding. The OD will also track IC funding decisions related to ESIs and mid-career investigators to evaluate the uniformity of decisionmaking across NIH. These changes are expected to result in a shift of support to younger investigators; however, independent analyses will be conducted to assess the actual impact, and all actions will continue to be informed by stakeholder input.

Discussion: Dr. Briggs expressed support for the program described by Dr. Tabak, which could promote the transfer of leadership of projects to younger faculty, but noted that the details may pose challenges. She explained that NCCIH's research interests tend to attract younger and less heavily funded investigators, so the Center has always exceeded ESI targets. The proposed policy does not affect NCCIH's Research Centers, which are funded in a different way.

Dr. Schoemaker suggested expanding the concept of recruiting and retaining an outstanding workforce to include the social construct of leadership. Dr. George noted that the current funding system was built so that the most resilient would be successful in the end. Dr. Tabak said that having some sort of equilibrium, in which a steady state would exist for researchers at all stages of their careers, would make the most sense, and Dr. George suggested performing simulations to assess the impact of resilience.

Dr. King asked how the proposed pilot would affect racial diversity, productivity, and team science. Dr. Tabak said that supporting younger researchers would generally increase diversity because of the greater diversity of the scientific workforce in that age group. Productivity can best be assessed in the long term, when it can be seen whether RCR scores ultimately translate to new approaches to a disease or condition or other major accomplishments. The GSI has been designed in a way that would encourage PIs with multiple grants to take on younger co-PIs, and it may be possible to increase those incentives. Dr. King added that additional incentives for racial and ethnic diversity may also be needed, and Dr. Tabak pointed out that NIH has other initiatives aimed at achieving such diversity.

Dr. DeBar noted that colleagues have expressed a fear of the unknown in connection with this initiative and suggested that making more information available would help. Dr. Tabak explained that a report on the proposed pilot would be presented at a meeting of the Advisory Committee to the NIH Director the following week and information would be posted on the NIH Web site after that meeting. He thanked Council members for their input and insights.

III. Update of the NCCIH Intramural Program

Dr. Catherine Bushnell, scientific director of NCCIH's intramural pain program, briefly reviewed the timeline of the program, which began with her arrival at NIH in July 2012. Key milestones include the establishment of a memorandum of understanding with the National Institute of Neurological Disorders and Stroke for infrastructural support, hiring of core staff, renovation of space in the Porter Neuroscience Research Center and the Clinical Center, and recruitment of three tenure-track faculty members. The NCCIH intramural program is involved in many trans-NIH activities, notably a Special Interest Group on pain, which brings in speakers every year.

One focus of research in Dr. Bushnell's laboratory is the way in which chronic pain changes the brain in both animal models and human patients. Recently, her group was able to replicate in a rodent model a finding of reduced opioid binding in the brains of fibromyalgia patients and to confirm that this reflects fundamental brain changes that alter the brain's opioid system. These changes might explain the limited effectiveness of opioid therapy for chronic pain and provide insight into the link between pain and depression.

Discussion: Dr. Tuckson, a member of the Clinical Center's oversight committee, asked Dr. Bushnell whether she felt she was receiving the support of the newly enhanced Clinical Center infrastructure for her work. Dr. Bushnell responded that the Clinical Center's resources are limited, but her program is less affected than others because it does not use the most limited resources. There is a general feeling of nervousness about the changes in the scientific review process for clinical work because their impact is uncertain. Dr. Briggs, who serves on the Clinical Center's governing board, noted that NCCIH is making use of the Clinical Center for outpatient imaging studies, not inpatient work. She believes there is a strong commitment to focusing Clinical Center resources well, and pain should compete well in this tough environment.

In response to a question from Dr. King about gender differences in the brain's response to pain, Dr. Bushnell said that the initial studies in her laboratory used only male rats, but future animal and human studies will include both sexes.

IV. NCCIH Clinical Trials—Funding Opportunity Announcements, Submission, Review, and Oversight

Dr. Wendy Weber, Chief of the Clinical Research in Complementary and Integrative Health Branch in NCCIH's Division of Extramural Research, reviewed recent major changes in NCCIH's support of clinical trials.

In a recent publication in the *Journal of the American Medical Association*, NIH leadership emphasized the importance of ensuring that NIH-supported trials focus on high-priority mission-relevant questions that have the greatest likelihood to advance knowledge and improve health. Changes are being made throughout NIH to enhance the quality and efficiency of clinical trials. These changes involve the application and award process, which is being modified to enhance NIH's ability to evaluate the merits and feasibility of clinical trial applications, as well as improvements in oversight, transparency, and sharing of clinical trial results.

As part of this effort, NCCIH has implemented new policies related to the submission of grant applications for clinical trials. Such changes are to take place throughout NIH, but NCCIH has implemented them in advance of the deadline. One major change is that applications must be submitted in response to clinical trial-specific funding opportunity announcements (FOAs) rather than the Parent R01.

Clinical trials represent a substantial proportion of NCCIH's portfolio, and many of the interventions studied are widely used despite inadequate knowledge of their safety and efficacy. Interpreting the results of clinical trials on complementary health approaches has been challenging. Many trials have been conducted at single sites, which limits the generalizability of their results. Studies with negative results have been difficult to interpret because it is often unclear whether the intervention was delivered correctly, the product and dosage were appropriate, or an appropriate study population was selected. Frequently, large clinical trials have been conducted without the "building blocks"—the necessary preliminary data—to ensure that their results will be meaningful, and investigators have found it difficult to obtain funding to support the types of research needed to develop building block data.

Through the new clinical trial-specific FOAs, which are customized to different stages of clinical research, NCCIH will provide support for preliminary building block studies as well as definitive efficacy or pragmatic trials. Important features of the new FOAs include (1) requirements that applicants complete special attachments that provide details about the proposed study in a standardized way; (2) the use of cooperative agreement mechanisms for intermediate and advanced-stage clinical trials; and (3) a requirement that definitive efficacy trials be conducted at multiple sites, with independent data coordination. These requirements are intended to enhance rigor, reduce bias, and increase the generalizability of trial results. Special emphasis panels that NCCIH will establish will review applications for clinical trials.

NCCIH has conducted extensive outreach about the new clinical trial application process, including multiple posts on the Center's research blog, direct letters to professional organizations

and more than 3,000 previous applicants, a series of three webinars, and the publication of resources on the NCCIH Web site.

Discussion: In response to a question from Dr. Kashikar-Zuck, Dr. Weber explained that until January 2018, applications to NCCIH for purely mechanistic studies that fit the NIH definition of clinical trials can be submitted through the Parent R01. After that, NCCIH will find a new way for such applications to be submitted. Dr. Briggs said that NCCIH recognizes that studies involving markers or central measures fall within the NIH definition of clinical trials, but NCCIH distinguishes efficacy trials from mechanistic ones and is creating funding environments for both. Dr. Briggs also explained that NCCIH is anticipating that special panels within the Center rather than broader study sections will review clinical trial applications.

Dr. Gaudet asked how pragmatic trials fit into NCCIH's new approach to funding clinical trials. Dr. Weber explained that the types of feasibility data needed before launching a pragmatic trial are slightly different from those needed for an efficacy trial. For a pragmatic trial, investigators need to know that the intervention can be delivered in the desired way. Pragmatic trials typically are a very large investment, so good pilot or efficacy data are required before investigators move into that type of study and ask health care systems to act as partners in a large-scale project. Dr. Briggs added that the types of data needed before a pragmatic trial is initiated will be an important subject for ongoing debate. NCCIH is responsible for interventions that are being used despite a lack of strong efficacy data. Therefore, pragmatic effectiveness studies may be appropriate in some instances even if efficacy data are soft. Dr. DeBar commented that there may be times when it would be appropriate to move from a single-site efficacy trial to a pragmatic trial. Dr. Weber added that the UG3/UH3 FOAs will support efficacy, effectiveness, or pragmatic trial applications.

V. NCCIH Policy on Study Accrual and Retention

Dr. Catherine Meyers, Director of NCCIH's Office of Clinical and Regulatory Affairs, described a new policy for human subject research projects. Adopted by NCCIH at the beginning of 2017, this new policy requires PIs to submit a Study Accrual and Retention Plan (SARP) before they begin accruing participants.

To maximize the success and impact of funded work, it is essential to attain accrual and retention goals. The new policy will enable goals and expectations for recruitment and retention to be established in advance, and metrics (actual vs. expected start time, accrual progress over time, and retention over time) have been built into the policy to enable studies to be classified by performance level. The use of an automated electronic tool will enable NCCIH to monitor accrual proactively and work closely with investigators to meet challenges. Outreach activities to inform the community of the new policy have included a blog post, an e-mail to NCCIH investigators, and a webinar. NCCIH will continue to review the new process; thus far, it has been working well.

Discussion: In response to a question from Dr. DeBar, Dr. Meyers explained that variability in accrual throughout the year is to be expected. NCCIH expects accrual to be tracked monthly but asks investigators to report it every 4 months; NCCIH is interested primarily in monitoring cumulative accrual. Dr. Briggs explained that NCCIH has been proactive in monitoring accrual for a long time, but the new policy makes the process more formal. Throughout NIH, there is

concern about trials that never successfully accrue a sufficient number of participants or report results. NCCIH's statistics for accrual and reporting are either average or slightly better than average, but it is important to continue to pay close attention to this issue.

VI. Concept Proposal: Research Resource for Systematic Review of Complementary and Integrative Health

Dr. Weber presented a proposed initiative to support a research resource to continue to maintain an established database of controlled trials of complementary and integrative health interventions, increase outreach, and conduct or update a series of high-quality systematic reviews and meta-analyses on topics of high priority to NCCIH, particularly complementary mind and body interventions for pain conditions. Part of the initiative will involve working with the broader scientific community to enhance systematic review methods for nonpharmacologic interventions, interventions that cannot be blinded, interventions that have been evaluated in pragmatic trials, or interventions that cannot be studied in randomized trials. Dr. Briggs explained that NCCIH's philosophy for systematic reviews is to take a hands-off approach; the assessments must be performed by fully independent groups.

Discussion: Dr. Langevin commented that the NCCIH-funded individual subjects meta-analysis by Dr. Andrew Vickers and colleagues has had a transformative impact on acupuncture research. Support of additional projects of this type could be very valuable.

A motion to approve the concept was made, seconded, and passed unanimously.

VII. Moving the Needle in Natural Products Research: Where Are We? What Are the Next Steps

Introduction

In his introduction to this portion of the meeting, Dr. Craig Hopp, Deputy Director of NCCIH's Division of Extramural Research, pointed out that roughly half of NCCIH's extramural research funding goes to natural products. NCCIH's single biggest investment in natural products supports the Centers for Advancing Research on Botanicals and Other Natural Products (CARBON) program, co-funded with the Office of Dietary Supplements. The program has two components: the three Botanical Dietary Supplement Research Centers (BDSRC) and the two newer Centers for Advancing Natural Products Innovation and Technology (CANPIT). The speakers today are leaders of CARBON centers and of the NCCIH-funded Center for Excellence for Natural Product Drug Interaction Research.

UIC Botanical Dietary Supplement Research Center: Its Influence on the Commercial and Research Sectors

Dr. Richard van Breemen, PI of the BDSRC at the University of Illinois at Chicago (UIC), reviewed the accomplishments of the center since its founding in 1999. These accomplishments include 231 total publications and the education of 49 predoctoral graduates and more than 50 postdoctoral and visiting scholars.

Like the other BDSRCs, the one at UIC focuses on collaboration, education, and pilot projects that can become self-sustaining. The specific aims of the BDSRC program have changed over the years; the current area of emphasis is the impact of botanicals on resilience. The center at UIC has focused on botanicals for women's health, including alternatives to hormone therapy at menopause. Its three current projects focus on metabolomics design and standardization of extracts, modulation of estrogen carcinogenesis by resilient botanicals, and metabolism and safety of botanicals in women.

The UIC center has advocated for a stepwise framework for developing safe and effective botanical dietary supplements: (1) searching the scientific and ethnomedical botanical literature; (2) acquiring and authenticating plant material according to Good Agricultural and Collection Practices; (3) determining mechanisms of action, identifying active compounds, and investigating synergy and safety; (4) standardizing materials chemically and biologically; (5) investigating the metabolism and bioavailability of active compounds; (6) conducting *in vitro* assays of inhibition and induction of drug-metabolizing enzymes and transporters; (7) developing a formulation using current Good Manufacturing Practices (cGMP) for clinical evaluation; and (8) conducting clinical trials. Work performed at the UIC center has included all of these steps.

Dr. van Breemen stated that the greatest impact of the work done at the UIC center is the education of a new generation of experts. Graduates are now working in Government, industry, and academia. The development of the framework of steps to ensure the safety and efficacy of dietary supplements and the U.S. Food and Drug Administration's adoption of a cGMP requirement for dietary supplements are among the center's most important research impacts.

Discussion: In response to a question from Dr. Shurtleff, Dr. van Breeman explained that all botanicals used at the center are produced using cGMP and tested for safety. For example, the literature has suggested that red clover may have anticoagulant effects because it contains coumarins; therefore, special studies were conducted on this topic (no anticoagulant effects were found). Because there were reports of liver damage linked to black cohosh, clinical trial participants were monitored for liver damage; none was found. In response to a question from Dr. Hopp, Dr. van Breeman explained that the body responds to some substances in botanicals because it has evolved to defend itself against outside threats. Thus, cellular responses may be observed even if a substance is safe.

Center for High-Throughput Functional Annotation of Natural Products and Botanicals (HiFAN)

Dr. John MacMillan, PI of the HiFAN Center at the University of Texas Southwestern Medical Center, one of the CANPIT centers, described the objectives of his center's work: to develop new technologies for chemical and biological annotation of complex natural product mixtures, to create new generalizable informatics approaches to integrate chemical and biological datasets, and to build Web-based tools to allow open access to these new technologies. The anticipated 5-year outcomes of the center's work include a novel metabolomics platform for the comprehensive constitutional characterization of natural product extracts, high-resolution

platforms for unbiased characterization of the effect of small molecules on mammalian cell development, and generalizable informatics approaches for the prediction of compound activities directly from chemical and biological profiling data. Dr. MacMillan noted that the natural products field has not used bioinformatics well in the past, so the center's very active bioinformatics program is particularly valuable.

The HiFAN team, which includes researchers from multiple institutions, has been emphasizing work in functional signature ontology (FUSION) and cytological profiling, with the objective of completing and validating platforms of both types. Another current effort involves building bioinformatics tools to merge orthogonal biological datasets. Other goals include developing constitutional analysis methods for botanical extracts, creating bioinformatics methods to profile synergistic interactions, and developing a more accessible route to FUSION signature generation in individual laboratories.

Although HiFAN is a relatively new center, it has brought junior scientists into new areas of research. Fourteen junior scientists—five natural product chemists or analytical chemists, six cell biologists/biochemists, and three bioinformaticians—have been involved in the program so far. Three data integration working sessions that bring together scientists from various aspects of the program to work in pairs on coding and data interpretation have been held, and members of the group have moved on to postdoctoral fellowships and industry positions based on skill sets learned in the HiFAN program.

Discussion: In response to a question from Dr. King, Dr. MacMillan said that dihydrocaffeic acid, a substance being investigated in FUSION studies, comes from grape juice. Dr. Hopp pointed out that this substance is actually a product of microbial degradation of a grape juice component in the gut, and Dr. Briggs added that the microbial degradation of natural products is an area of interest.

Breaking Through the Noise: Raising the Bar for Natural Product–Drug Interaction Research

Dr. Mary Paine, co-PI of the NCCIH-funded Center of Excellence for Natural Product Drug Interaction Research, explained the reasons why research on natural product–drug interactions is needed and summarized the work being performed at her center.

Sales of natural products are rising, and people often seek out these products to supplement prescribed therapeutic regimens. However, taking natural products in conjunction with conventional medications can lead to adverse interactions. Understanding these interactions is more difficult than understanding drug–drug interactions because of the compositional variability of natural products, their complexity, the scarcity of human pharmacokinetic data for natural product constituents, and the lack of harmonized approaches to investigate potential interactions.

The goal of the center is to provide leadership in the study of natural product–drug interactions, with the ultimate goal of developing recommended approaches to determine the clinical relevance of pharmacokinetic interactions. Four high-priority natural products have been selected for study on the basis of a literature search and consumption patterns: green tea, cannabinoids, goldenseal, and licorice.

Substantial work has been completed on green tea (with Tazo brand green tea used as the test substance). The catechins in green tea have been identified as potential medicinal components. *In vitro* studies indicated that some green tea catechins interact with intestinal UDP-glucuronosyltransferases (UGTs) at clinically relevant levels of intake, which may influence the activity of drugs such as the selective estrogen receptor modulator raloxifene. However, preliminary results from a clinical study suggest that green tea does indeed interact with raloxifene but that inhibition of UGTs is not the mechanism of the interaction. One possible explanation for these findings is that green tea may be inhibiting an uptake transporter in the gut.

Discussion: In response to a question from Dr. DeBar, Dr. Paine explained that all of the work on green tea is being performed on samples from the same lot of product; therefore, the composition of the product is consistent. However, there is substantial variability in composition among green tea products produced by different companies. Dr. Brater pointed out that the results obtained with green tea illustrate the need for the type of research being undertaken because the *in vivo* results did not match the *in vitro* predictions. Dr. Briggs commented that there was much discussion about the value of *in vitro* screening during the planning of this initiative, that debate on this topic will continue, but that there will continue to be instances when human studies have surprising results. She added that there may be a general underestimation of transporter interactions.

Building a Stronger Natural Products Research Community

Dr. Guido Pauli, PI of the Center for Natural Products Technologies (CENAPT) at UIC, one of the CANPIT centers, described how his center is working to strengthen the field of natural product research through improved consolidation, coordination, and dissemination of research data and good research practices.

Natural products form a continuum from foods through functional foods, dietary supplements, and drugs. The investigation of these products is a challenge for researchers in many scientific fields, including biology, biochemistry, pharmacology, and medical sciences, and it involves basic, preclinical, and clinical research. Thus, natural products research is by its very nature multidisciplinary. CENAPT's activities include coordination, consolidation, and dissemination of research. The center serves as a resource for building natural products methodology, validating leads and markers, and developing new hypotheses. CENAPT is conducting technology demonstration projects in collaboration with other CARBON centers. Dissemination, including transparency and reproducibility, is a particularly hot topic in natural products research and is also a major focus of the center's activity.

Methods being used to study natural products include the knockout concept, in which a single compound is removed from a product through separation technology and the effects of its absence are assessed, and studies of putative active ingredients of natural products. CENAPT was contacted by a group in Minnesota to participate in investigations of curcumin, which led to the publication of a high-impact research paper.

VIII. Implementation of the National Pain Strategy

Dr. Linda Porter, director of NIH's Office of Pain Policy and Designated Federal Official for the Interagency Pain Research Coordinating Committee (IPRCC), presented an update of actions that have been taken to implement the National Pain Strategy (NPS).

The NPS is an outgrowth of the Affordable Care Act, which called for the formation of a committee to coordinate research on pain across the Federal Government. The IPRCC is that committee. In response to a 2011 report on pain from the Institute of Medicine (now the National Academy of Medicine), also called for by the Act, the IPRCC was asked to oversee the creation of a comprehensive, population health-level strategy for pain prevention, treatment, management, education, reimbursement, and research that includes specific goals, actions, time frames, and resources. This strategy is now known as the NPS.

An NPS report earlier this year presented a set of objectives in most of the requested areas. Coincidentally, the report was released the same week as the Centers for Disease Control and Prevention (CDC) opioid guidelines. The NPS report was overshadowed by the extensive publicity received by the CDC guidelines, but the two reports actually complement each other, because the opioid crisis cannot be controlled without improvements in pain care.

Actions that have been taken in the public and private sectors to help meet the NPS objectives include the following:

- Screening questions about high-impact chronic pain have been added to the 2016 and 2017 editions of the National Health Interview Survey. The CDC is currently analyzing the 2016 data.
- An objective to “decrease the prevalence of adults with high-impact chronic pain” has been added to *Healthy People 2020*, and additional pain-related objectives may be included in *Healthy People 2030*.
- The research agenda on opioids and pain management requested by the Secretary of Health and Human Services in 2016 includes plans for a pilot study to establish the feasibility and infrastructure for a nationwide population study to estimate the prevalence and costs of chronic pain in the general population and in diverse health care settings.
- NIH Centers of Excellence in Pain Education have developed case-based curriculum modules for pain care, and pain care experts have developed a set of core competencies for pain education for health care providers.
- The Office of the Assistant Secretary for Health has created an educational tool about pathways to safer opioid use for pain management.
- The Food and Drug Administration has developed an action plan to support better pain treatment and risk management.
- The American Pain Society has funded three grants related to pain management strategies.
- Federal agencies are conducting a nationwide study of insurance coverage for acute and chronic back pain treatment.
- The Agency for Healthcare Research and Quality is conducting systematic reviews of the literature on nonpharmacologic treatment for five major pain conditions in adults.
- A group of advocacy organizations has come together to fund a public awareness campaign about the benefits of comprehensive chronic pain care.
- A day-long NPS implementation stakeholders' meeting was held, and communications updates are being posted on the NPS Web site.

- The Department of Health and Human Services has included “Advancing the practice of pain management” as one of the five pillars of its Opioid Strategy.
- The Office of Pain Policy and the IPRCC have developed a set of 47 high-level research recommendations that have been released for public comment.

Discussion: Dr. Briggs said that NCCIH staff have been very involved in many of the activities that Dr. Porter described. Dr. Schoomaker complimented Dr. Porter and her colleagues for keeping the focus on pain as the genesis of the opioid crisis. Dr. Langevin pointed out that there is a difference between a strategy for pain that involves analgesia and one that involves addressing the underlying cause of pain. Preliminary evidence indicates that some modalities, such as acupuncture, can produce long-term improvement in pain. Dr. Porter said that this aspect of pain management is definitely being considered, as the focus of the NPS is on chronic pain and, therefore, on patient-centered, interdisciplinary care. Dr. Schoomaker mentioned the need to go beyond the traditional analog scale for pain to a more holistic approach. Dr. Briggs said that there is a need to move away from just addressing pain severity to focusing on pain interference with function.

IX. Public Comment and Adjournment

No public comments were offered.

The meeting was adjourned at 3:50 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

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