U.S. Department of Health and Human Services
National Institutes of Health (NIH)
Office of the Director (OD)
Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)

Council of Councils Meeting
May 18, 2018

Meeting Minutes

I. CALL TO ORDER AND INTRODUCTIONS

James M. Anderson, M.D., Ph.D., Director, DPCPSI, welcomed participants, NIH staff members, and members of the public to the meeting of the Council of Councils. The meeting began at 8:15 a.m. on Friday, May 18, 2018, in Building 31, Conference Room 10, on the NIH Campus in Bethesda, Maryland.

Dr. Anderson welcomed members and noted that Drs. Charles Mouton, Bruce Ovbiagele, and John Postlethwait were unable to attend. The meeting attendees are identified below.

Following introductions and announcements from Franziska B. Grieder, D.V.M., Ph.D., Executive Secretary for the NIH Council of Councils, Dr. Anderson reviewed the day's agenda.

A. Attendance

1. Council Members

Council Members Present
Chair: James M. Anderson, M.D., Ph.D., Director, DPCPSI
Executive Secretary: Franziska B. Grieder, D.V.M., Ph.D., Director, Office of Research Infrastructure Programs (ORIP), DPCPSI
Maria L. Acebal, J.D., Food Allergy Research & Education, Inc., Washington, DC
Maria Rosario G. Araneta, Ph.D., M.P.H., University of California, San Diego, La Jolla, CA
Eric Boerwinkle, Ph.D., The University of Texas Health Science Center at Houston, Houston, TX
Melissa Brown, M.D., M.N., M.B.A., Thomas Jefferson University, Philadelphia, PA
Jonathan Epstein, M.D., Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
Rick Horwitz, Ph.D., Allen Institute for Cell Science, Seattle, WA
Patricia D. Hurn, Ph.D., R.N., University of Michigan, Ann Arbor, MI
R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
Paul J. Kenny, Ph.D., Icahn School of Medicine at Mount Sinai, New York, NY
Sachin Kheterpal, M.D., M.B.A., University of Michigan Medical School, Ann Arbor, MI
Gary A. Koretzky, M.D., Ph.D., Weill Cornell Medical College, New York, NY
Michael D. Lairmore, D.V.M., Ph.D., University of California, Davis, Davis, CA
Jian-Dong Li, M.D., Ph.D., Georgia State University, Atlanta, GA
Terry Magnuson, Ph.D., The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
Edith P. Mitchell, M.D., FACP, Thomas Jefferson University, Philadelphia, PA
Jean E. Schaffer, M.D., Washington University School of Medicine, St. Louis, MO

Scout, Ph.D., The Torvus Group, Beverly Hills, CA
Bruce J. Tromberg, Ph.D., University of California, Irvine, Irvine, CA
J. Leslie Winston, D.D.S., Ph.D., Procter & Gamble Global Oral Care, Mason, OH
Nsedu Obot Witherspoon, M.P.H., Children's Environmental Health Network, Washington, DC
Gail Yokote, M.S., University of California, Davis, Davis, CA

Council Members Absent
Jorge L. Contreras, J.D., The University of Utah, Salt Lake City, UT
Charles P. Mouton, M.D., M.S., The University of Texas Medical Branch, Galveston, TX
Bruce Ovbiagele, M.D., M.Sc., MAS, Medical University of South Carolina, Charleston, SC
John Postlethwait, Ph.D., University of Oregon, Eugene, OR

2. Liaisons

Rachel Ballard, M.D., M.P.H., representing **David M. Murray, Ph.D.,** Director, Office of Disease Prevention (ODP), DPCPSI
Joseph Betz, Ph.D., representing **Paul M. Coates, Ph.D.,** Director, Office of Dietary Supplements, ODP, DPCPSI
Janine A. Clayton, M.D., Director, Office of Research on Women's Health, DPCPSI
Maureen M. Goodenow, Ph.D., Director, Office of AIDS Research, DPCPSI
Karen Parker, Ph.D., M.S.W., Director, Sexual and Gender Minority Research Office (SGMRO), DPCPSI

William Riley, Ph.D., Director, Office of Behavioral and Social Sciences Research, DPCPSI
Elizabeth L. Wilder, Ph.D., Director, Office of Strategic Coordination (OSC), DPCPSI
David R. Wilson, Ph.D., Director, Tribal Health Research Office, DPCPSI

3. *Ex Officio* Members Absent

Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, NIH

4. Presenters

Patricia Labosky, Ph.D., Program Leader, OSC, DPCPSI
R. Paul Johnson, M.D., Emory University School of Medicine, Atlanta, GA
Terry Magnuson, Ph.D., Vice Chancellor for Research, Sarah Graham Kenan Professor of Genetics, The University of North Carolina at Chapel Hill School of Medicine
Michael Nader, Ph.D., Professor of Physiology & Pharmacology and Radiology, Director, Center for the Neurobiology of Addiction Treatment, Co-Director, Center for Research on Substance Use and Addiction, Wake Forest School of Medicine
George Santangelo, Ph.D., Director, Office of Portfolio Analysis (OPA), DPCPSI
Nora Volkow, M.D., Director, National Institute on Drug Abuse (NIDA), NIH

5. NIH Staff and Guests

In addition to Council members, presenters, and Council Liaisons, others in attendance included NIH staff and interested members of the public.

B. Announcements and Updates

Dr. Grieder reviewed the following:

- Council members are Special Government Employees during the days of Council meetings and are therefore subject to the rules of conduct governing federal employees.

- Each Council member submitted a financial disclosure form and conflict-of-interest statement in compliance with federal requirements for membership on advisory councils. The financial disclosures are used to assess real and perceived conflicts of interest, and Council members must recuse themselves from the meeting during discussions of any items for which conflicts were identified.

- Time is allotted for discussion between the Council members and presenters, but time for comments from other meeting attendees is limited. The public may submit comments in writing; instructions are available in the *Federal Register* notice for the meeting, which was published on April 13, 2018.

- Minutes from the January 26, 2018 meeting are posted on the DPCPSI website. The minutes from this meeting also will be posted there.

C. Future Meeting Dates

The final Council meeting of 2018 will be held on September 7 at the NIH Cloisters, rather than the current conference room, because of renovations to Building 31.

II. EVALUATING THE "BROADENING EXPERIENCES IN SCIENTIFIC TRAINING (BEST)" AWARDS

Patricia Labosky, Ph.D., an OSC program leader, explained that assessment of the current biomedical research workforce—including principal investigators (PIs), graduate students, and those in postdoctoral programs—showed that current training programs seldom train researchers for careers other than academic research, yet less than a quarter of the trainees ended up in tenure-track positions. The BEST program addresses this by facilitating trainee exposure to more career options while maintaining robust scientific training. Practical strategies, such as building infrastructure to support novel training opportunities and ensuring that trainees are provided the necessary information to pursue their career paths, will support broad changes in the culture of biomedical research training.

To support catalysis of new ideas, the BEST awards are time limited and nonrenewable; although not required, the awardees cooperate as a consortium. Sites are both geographically and organizationally diverse, and the models used to execute BEST programs also vary widely. Many sites initially offered the program components to a select group of trainees and expanded over the course of the award to saturate the campus, including programs outside biomedical research. Mentoring programs are included at almost all sites, and sites incorporate internal steering committees, external advisory boards, and trainee feedback, as well as partnerships outside academia.

Common programmatic elements include career and professional development tools, experiential learning components, and expanded mentorship opportunities. Dr. Labosky noted that although a mentor may passively help with career or professional skills, their role is primarily research-focused, so programs in non-science topics are needed. Expanding experiential learning options can help trainees avoid the significant time commitment of an internship that often turns out to be a poor match, and instead the

programs provide shorter and more varied options, such as site visits or job shadowing, to help trainees narrow down which career paths most interest them.

Some common philosophical approaches from the consortium have been articulated. To support the BEST program's goal of instilling a commitment to building research skills and career preparation in line with the current job market, all U.S. research institutions focused on graduate and postdoctoral education should establish offices dedicated to professional career development. Transparency is critical in evaluation and recruiting, including clear information about how many students and postdoctoral scientists become PIs and pursue other career paths, and there is universal encouragement within the consortium to view nonacademic careers as desirable options for many trainees rather than failures. Ultimately, the BEST program aims to give trainees increased confidence to pursue their ideal career paths, which hopefully will decrease training times and reduce the number of trainees who default to postdoctoral training in the absence of a specific career path.

The NIH is collecting data to assess trainees' agency, ability to make career choices, and time to the first non-training job, as well as measuring the sustainability of activities and infrastructure at sites. Early data indicate that most BEST awardee's training programs are offering information about a greater number of career paths, and the most popular method for providing this information is through single-day workshops. Many sites are adding courses to their curricula, including certificate programs, as well as peer and professional mentorship programs and externships, internships, and job shadowing experiences.

Dr. Labosky explained that the overarching goal—culture change—can be hard to measure, especially because a control group cannot be defined and attendees at many popular activities are hard to count. Trainees who have attended a few events without being associated with their sites' BEST programs can be considered as a comparison group in the absence of a control. Actual participation likely is much larger than these data due to the prevalence of events at which exact attendance cannot be tracked, such as open seminars.

When trainees were polled regarding how they think about various career paths, research in industry remained the most popular intended path for graduate students, followed by the PI track. Those in postdoctoral positions indicated that the research PI path is their top choice—which Dr. Labosky noted is expected for those already in a postdoctoral program—but a significant percentage indicate no desire to become a PI. Many graduate students and postdoctoral researchers were extremely confident in their ability to follow their chosen career path. Trainees using the BEST program found it very helpful, with helpfulness increasing with more exposure to the program components. Integrating BEST program offices closely with graduate programs or departments helps ensure that all trainees have access to program components and supports sustainability. Although measuring how long researchers spend in postdoctoral positions is difficult, Dr. Labosky noted that BEST program components are not supposed to increase the time required to earn a degree or finish a postdoctoral experience.

Most sites have multiple sources of funding, so program components are likely to be sustainable. Although some sites have begun publishing papers on outcomes, Dr. Labosky stressed that current NIH data incorporate only a small fraction of trainees who are and will be part of the program. As more data are gathered, a strong evidence base can show which strategies work and for whom, which will help institutions recruit the best and brightest in the midst of a changing culture.

Discussion Highlights

- Although participation in postdoctoral programs can increase the transdisciplinarity of trainees' education, they should not feel obligated to go through postdoctoral training if they want to follow a career path for which it is not required. The BEST program aims to let trainees take charge of their own career paths.

- When asked about the diversity of the workforce, Dr. Labosky explained that BEST was developed to be open to all trainees. Current data suggest that trainees from underrepresented minorities participate slightly more often than expected, but the program focuses more on easing processes for all trainees. The Common Fund's Diversity Program Consortium has a program specifically focused on diversity—Building Infrastructure Leading to Diversity (BUILD)—which works to establish partnerships with universities that serve large populations of students from underrepresented minorities. Although recent published data suggest that the transition from postdoctoral to PI roles is the point at which researchers from underrepresented minorities are most likely to drop out of the pipeline, Dr. Labosky reiterated that the BEST program encourages trainees to make their own choices at all stages. Council members recommended investing in additional diversity efforts.

- In response to a question about whether PI and mentor cultures have become more supportive of trainees' preferred career paths regardless of their effect on PIs' research, Dr. Labosky commented that faculty have been happy that BEST program components reduce their responsibility to advise trainees on career paths so they can focus on the science. She emphasized that trainees vote with their feet and will choose to work in locations that are supportive.

- When asked about the bias toward academic research among training grant committees, Dr. Labosky suggested that reviewers often are faculty members and may prioritize academic paths. Dr. Labosky and Council members agreed that BEST should continue to emphasize the value of nonacademic careers.

- Dr. Labosky agreed that data gathered for these studies reveal that the workforce is not well understood; she emphasized that BEST's taxonomic efforts are ongoing. Transparency and tracking individuals' career paths are practices that are beginning to permeate the academic community in all disciplines, including both sciences and the humanities, but dissemination takes time.

III. NIDA UPDATE

Nora Volkow, M.D., the director of NIDA, emphasized the severity of the opioid crisis. Opiate receptors are present in the brain's pain network, reward center, and breathing regulation areas; opioids thus inhibit sensations of acute pain, stimulate sensations of reward, and inhibit the neurons responsible for breathing, which causes most overdose deaths. Tolerance to opioids' analgesic and rewarding effects occurs rapidly, and a higher dose is required for the same level of reward and pain relief. However, the breathing center may develop its tolerance more slowly, which complicates the use of opioids to manage chronic pain because the dose required to ease pain may be higher than the tolerance level of the breathing center. This increases the likelihood of addiction and overdose for those more tolerant to pain inhibition than breathing inhibition. Opioids are some of the most potent, rewarding, and addictive drugs known, and repeated administration produces not only tolerance, but also neural adaptations in the dopaminergic system of the brain, which drives behavioral motivation. D1 dopamine receptors motivate an individual to movement or rewards; in opposition to this, D2 dopamine receptors modulate that proactivity. The D2 receptor is significantly reduced by repeated administration of drugs, leading to an inability to self-regulate and a propensity for impulsive and compulsive behaviors.

Dr. Volkow commented that the epidemic was unintentionally started by the health care system; well-meaning providers overprescribed opioids as a pain treatment without sufficient knowledge of their effects or infrastructure to support treatment. Many people who became addicted through prescriptions would not otherwise have been exposed to opioids, and many transitioned to classical addictive drugs in

the absence of continued prescriptions. Although opioid prescriptions have decreased recently, fatal overdoses continue to increase, in part because of the addition of newer drugs, including fentanyl, which crosses the blood-brain barrier rapidly, has an affinity for opioid receptors that makes it more than 50 times as potent as heroin, and depresses breathing thus decreasing oxygen delivery to the brain very quickly. Reversal strategies are available for heroin overdose, but the effects of fentanyl alone or in combination with other drugs—such as heroin, alcohol, or benzodiazepines—are more complicated and less understood. Synthetic fentanyl, one of the most potent agonists known, dramatically increases overdose mortality when used to lace other drugs. Only a small volume of synthetic fentanyl is needed to produce the same effect as larger volumes of other opioids, which allows drug smugglers to make more money with smaller amounts. Dr. Volkow noted that opioid use is spreading like an infectious disease, but the addition of the profit motive from the drug dealers complicates the patterns.

Additional research focuses on several avenues. Pain management research must address the needs of the many Americans with chronic pain to prevent these patients from turning to the black market to obtain opioids. Research also must address the needs of those currently addicted to opioids by improving the understanding of addiction mechanisms, developing treatments for addiction, and determining how to prevent addiction and overdoses. Improving the fundamental understanding of how these drugs interact with receptors can improve development of pain treatment as well. Pain is heterogeneous and must be treated on the individual level. Advances in structural biology enable improved study of receptor structure and the modifications of various ligands; promising areas of research include the development of bias agonists for opioid receptors and greater understanding of signaling differences between endogenous peptides and exogenous ligands in terms of developing tolerance.

Dr. Volkow pointed out that only three effective classes of medication for opioid addiction are available, adding that clinicians would not be content with so few treatments for any other disease. The stigma of addiction has been an obstacle to medication development and use—medication-assisted treatment (MAT) is effective but difficult to access for many of those who need it. Addiction is a chronic disease that requires sustained care, and the lack of sufficient infrastructure causes many people to fall out of the care system; many who begin MAT do not continue in care, but because the changes to the brain persist for months or years, those who stop MAT have an extremely high risk of death from overdose. Expanded access to MAT and the development of new medications are needed urgently.

Dr. Volkow emphasized that researchers cannot afford to design the perfect treatment that will take years to affect the population—someone dies from an opioid overdose every 12 minutes. The U.S. Food and Drug Administration recently approved a 6-month buprenorphine implant to protect against relapse, although the approved dosage is not sufficient to occupy the necessary receptors, particularly for those with severe addiction—Dr. Volkow emphasized that the promise of this product is tempered by the limited number of people it can benefit. She touched on many strategies that can be addressed immediately, such as development of other extended-release formulations for existing medications, which can help people maintain compliance with addiction treatment. Drug combinations, new targets, and new delivery methods are in development, as is a potential vaccine for opioid addiction. The health care system can be engaged to expand access to treatment, initiate those who come to the emergency room into treatment, and provide linkage to care. Treatment also could be expanded to those within the criminal justice system, who often must go “cold turkey” when in prison and thus are at a much higher risk of relapse into drug taking and overdose within the first few days of release. Dr. Volkow added that research into the fundamental neurocircuitry of the dopaminergic system has increased the understanding of how this system interacts with motivation and why addictions often are comorbid with mental health disorders; further research into this system can lead to treatments for the multitude of diseases in which this system is involved. Dr. Volkow closed with a mention of the Helping to End Addiction Long-term (HEAL) Initiative, which adds significant funds to NIH’s current research to address the opioid crisis and includes components related to both pain and opioid use disorders.

Discussion Highlights

- In response to a question about partnerships with other NIH Institutes and Centers (ICs) or providers, such as dentists, who may encounter drug-seeking individuals, Dr. Volkow described several partnerships with ICs to address the complex issues involved in this crisis—every IC is involved in fighting the opioid crisis in some way. Partnerships with outside groups could be more complicated to implement, but providers (dentists as well as others) could be educated in screening patients for addiction and providing linkage to care.

- Council members stressed the need for new pain treatments, particularly for those with a legitimate need for pain relief who have been stigmatized by the opioid crisis. Dr. Volkow commented on the balance between proactively developing novel concepts, translating existing components, and supporting valuable basic science. Training the next generation of scientists can help advance basic discoveries and facilitate translation, and providing physicians and trainees with better education about pain treatment and addiction screening is a critical strategy with a large impact that can be implemented quickly.

- Dr. Volkow recognized the need to partner with the device industry to develop nonpharmacologic interventions. Devices could be developed to provide auto-delivery of opioid overdose rescue, support MAT in rural communities, or incorporate stimulating treatments for mental illnesses; devices also often are approved more quickly than medications.

- When asked whether the Council can help establish any structural changes to help combat the crisis, Dr. Volkow suggested that Council members could brainstorm alternative models of execution. Dr. Anderson added that the prize model, although not effective for every project, could be used more often to find ideas that disrupt traditional systems.

IV. INTRODUCTION TO THE USE OF NON-HUMAN PRIMATES (NHPs) IN ADDICTION RESEARCH

R. Paul Johnson, M.D., the director of the Yerkes National Primate Research Center, provided background on NHPs and other animal models, emphasizing that although models contribute to scientific advances, all are approximations with certain limitations. Rodent models have been useful in substance abuse research, but their distant phylogenetic relationship to humans may lead to significant differences in pharmacokinetics and drug metabolism, and their shorter lifespans make modeling the chronicity of addiction challenging. NHPs are genetically closer to humans, and the progressive development of the cerebral cortex is similar, with conservation of key neurochemical pathways involved in substance abuse. Procedures for drug self-administration, longitudinal studies, and imaging are easier to establish and conduct, and paradigms of stress and social dominance are well established. Additionally, homologous reward and testing strategies between NHPs and humans have been validated. Small sample sizes and the inability to preselect individuals to develop drug abuse limit NHP studies, and psychiatric comorbid effects are difficult to study. However, NHP genetic data have become more available and less expensive; future directions for NHP research include learning to leverage genetic data to better inform experiments, validating and translating NHP models for human studies, defining molecular mechanisms *in vivo*, and expanding the focus on novel approaches to prevention and treatment of opioid abuse.

V. NHP MODELS OF DRUG ADDICTION

Dr. Johnson introduced Michael Nader, Ph.D., a professor of Physiology & Pharmacology and Radiology, the director of the Center for Neurobiology of Addiction Treatment, and the co-director of the Center for

Research on Substance Use and Addiction at Wake Forest School of Medicine. Dr. Nader's laboratory uses intravenous self-administration of cocaine by macaques—which are phylogenetically, anatomically, and neurohormonally similar to humans—to study vulnerability to chronic drug use, as well as maintenance and treatment, over a number of years. Rhesus monkeys are studied when the research question concerns individual phenotypes, and cynomolgus monkeys are used for studies of social interaction.

Dr. Nader emphasized the importance of understanding the many factors that affect an individual's susceptibility to drug use, including prior history, environment, sex, and social context. He explained that cocaine blocks the action of transporters that remove dopamine from the synapse, increasing dopamine binding to both D1-like and D2-like receptors. The prevalence of receptors changes throughout the cycle of substance use disorder, and personalized medicine strategies likely will be required to treat substance use effectively. Determining biomarkers to predict which individuals respond to each treatment will be necessary. Dr. Nader's team used drug-naïve macaques to confirm an inverse relationship between the number of D2-like receptors and an individual's vulnerability to stimulant abuse. A hierarchical social housing model was used to assess whether vulnerability could be changed; subordinate monkeys, as models of chronic social stress, self-administered cocaine at higher rates, and dominant monkeys, as models of environmental enrichment, showed increases in dopamine receptor availability and lower rates of cocaine self-administration.

This study, as with many foundational studies of human substance abuse, used only male subjects; female macaques are an appropriate model for humans because of similarities in the menstrual cycle, which must be taken into account as a study variable. When Dr. Nader's team studied vulnerability to substance abuse of subordinate and dominant female monkeys, dominant females and males both showed increases in receptor availability, but dominant males became less susceptible to cocaine and dominant females became more susceptible. Dr. Nader reiterated that although dopamine receptor availability is a trait that is known to influence vulnerability, the relationship appears to be negative in males and positive in females.

Dopamine receptor availability also can decrease over time depending on cocaine dosage, but abstinence studies in male monkeys showed differences in how fast each individual recovered to baseline receptor availability. Half of male monkeys recovered their baselines quickly, but half did not, and the cause of this variability has not yet been determined. Sex also affects recovery—female monkeys abstinent for at least 9 months did not recover their receptor baselines.

Monkeys given a choice between cocaine at various dose levels and food rewards chose food when cocaine doses were low, but chose cocaine when doses were high. Treatment with a receptor agonist affected these choices positively (i.e., decreased cocaine choices at the high doses), but a receptor antagonist produced negative outcomes (i.e., increased cocaine choices at the low doses). To understand the relationship between environmental enrichment and stress, Dr. Nader's team tested behavioral outcomes by exposing one monkey to a new social group as an intruder. When the intruder monkey was dominant in its own social group, this exposure acted as enrichment, which decreased self-administration of cocaine and increased activity in brain areas related to social reward. When subordinate monkeys were removed from the social group and introduced as an intruder in another social group, increases in cocaine self-administration were observed. Other environmental manipulations attempted that would be hypothesized to be enriching included larger pen sizes; this decreased cocaine self-administration, as hypothesized, but the effects did not last long. In another study, pair-housing these male monkeys with female monkeys in an attempt to relieve stress actually increased stress. Dr. Nader emphasized that whether monkeys find environmental manipulations as enriching or stressful cannot be predicted in the absence of changes in behavior (in this case, cocaine self-administration).

Dr. Nader's team also studied the efficacy of existing medications and found rank-related differences in male monkeys and sex-related differences in dominant monkeys—no medication had the same effects in all groups. This suggests that clinical trials to evaluate pharmacotherapies likely would show low levels of efficacy, because too many variables affect how well each medication works. Dr. Nader suggested that the ideal goal is to determine why each strategy works the way it does in various individuals and provide clinicians with a toolbox of strategies incorporating both pharmacological and environmental variables.

As a final point, Dr. Nader pointed out that macaques are ideal animal models for prenatal drug exposure, and studies show that adult monkeys who were exposed to cocaine prenatally remain more impulsive and vulnerable to cocaine than control monkeys. Current studies are testing whether a dopamine D3 receptor compound can block the reinforcing effects of an opiate without reducing its analgesic effects; pharmacotherapies for people who are currently dependent on opiates will be more complicated to develop. Dr. Nader emphasized that interactions between genes, environment, and drug history produce equivocal outcomes and recommended that substance abuse research aim to understand the biological basis for individual differences and sex-specific treatment strategies.

Discussion Highlights

- When asked whether any biomarkers for dominance have been found, Dr. Nader explained that testosterone serves this role for males, but no predictive hormones or other markers have been found in females.

- Dr. Nader acknowledged the challenge in maintaining the resources to support a macaque colony for a long observational period, especially under cyclical funding periods. He noted that some grant reviewers might not appreciate the difficulty NHP researchers face when asked to make small changes before resubmitting applications for this kind of study.

- Dr. Nader expressed a willingness to collaborate with others to study components outside his area of expertise, such as the role of serotypes, but he emphasized that the current NHP models are the best and most homologous animal models for drug abuse. Dr. Johnson added that determining how to translate technologies between animal models is critical, but funding such studies can be challenging if the models are not yet established.

- Attendees discussed the difficulty in sharing data, such as sequenced NHP chromosomes, given the complex correlation of such other factors as social rank, drug history, and sex.

VI. REVIEW OF GRANT APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).[1] Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Council would represent a real or perceived conflict of interest. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect. The *en bloc* vote for concurrence with the initial review recommendations was affirmed by all Council members present. During the closed session, the Council concurred with the review of 78 ORIP applications with requested first-year direct costs of $28,070,218. The Council also

[1] For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to *en bloc* actions.

concurred with the review of 1,010 Common Fund applications with requested first-year direct costs of $1,749,577,092.

VII. REPORT FROM THE WORKING GROUP ON ASSESSING THE SAFETY OF RELOCATING AT-RISK CHIMPANZEES

Dr. Anderson explained that the report written by this working group, which was established by the Council at the previous meeting, can be accepted or rejected by the Council but not altered. After the vote, suggestions from the Council will be gathered, and Dr. Anderson will format them into a letter for delivery to the NIH director, following Dr. Magnuson's review. The report has been posted to the Council website and will be available for public comment for 60 days, after which the NIH director will use comments from the Council and the public to make a final decision about how to implement the report's recommendations.

Terry Magnuson, Ph.D., Council member and chair of the working group, explained that all NIH-owned or -supported chimpanzees became eligible for retirement in 2015 to the federal sanctuary system operated by Chimp Haven, Inc. Many of these chimpanzees already have been moved to the sanctuary, but others remain supported in other facilities. Dr. Magnuson stressed the complexity of deciding whether to relocate these chimpanzees to the sanctuary, taking into account the available sanctuary space and existing social groups, as well as the health and welfare of individual chimpanzees, many of whom are geriatric. Laws and regulations prohibit a licensed veterinarian from issuing a health certificate for an animal that would be endangered by transportation and prohibit carriers from transporting clearly ill or distressed animals.

The relocation process begins with an assessment and preparation before the trip. The sending and receiving facilities assess space, transport conditions, social groupings, and each chimpanzee's health and behavior. Physical examinations may require as many as four anesthesia events and considerable stress. The chimpanzees are assessed for their potential to harbor communicable diseases that could endanger animals at the receiving site; whether transport and relocation would endanger each chimpanzee's health; and the potential effects of anesthesia, stress, and new social groups. The U.S. Department of Agriculture (USDA) requires that a licensed veterinarian certify each chimpanzee's health prior to transport. During transit, the chimpanzees might be subjected to additional sedation or particularly long travel times. When the chimpanzees arrive at the receiving facility, they undergo a quarantine, integration into a new social group, and medical tests and physical examinations, which might require additional sedation.

The working group, composed of specialists in human and NHP health, was formed to determine guidance for assessing each chimpanzee's fitness for relocation given the complications of age and chronic health conditions. The NIH charged the working group with providing advice and recommendations on factors to be considered by the attending veterinarian staff when deciding whether to relocate NIH-owned or -supported at-risk chimpanzees from federally supported facilities to the sanctuary. To fulfill this charge, the working group reviewed summaries of the published literature on factors related to the process and relevant laws, regulations, and policies, and interviewed staff at the facilities and outside veterinary experts, including ethicists. The group developed a points-to-consider report and a risk-based selection matrix focused particularly on ambiguous circumstances. Dr. Magnuson listed the deliberation considerations used to create the recommendations, including how health status should factor into relocation decisions, how facilities determine which animals are at-risk, which factors would disqualify an animal from relocation, whether facilities suggest risk-management strategies, what standard operating procedures exist, what data are used to inform the decision-making, and the respective roles of the sending and receiving facilities. The working group used the physical status scale developed by the American Society of Anesthesiologists, which had been previously adapted for veterinary use. It

includes five risk classes; chimpanzees who are likely to experience severe adverse events because of the relocation process likely will fit into the two highest risk classes ("high-risk" or Category 4 and "extremely high-risk" or Category 5) and are significantly compromised by disease or exhibit behavioral problems that restricts their integration into new social groups.

The working group offered seven recommendations. **Recommendation 1** is to relocate all chimpanzees unless relocation is extremely likely to shorten their lives; chimpanzees considered "at-risk" should be considered for relocation to avoid separating social groups. If risk-management strategies will not offset the hazards of sending an entire social group, the group should be reconfigured to remove the fragile chimpanzee so that the healthier animals can be relocated. **Recommendation 2** is that the NIH should oversee development of standardized approaches to assess each chimpanzee based on the five classes of risk on the anesthesia scale. Animals classified as high-risk according to this scale should be assessed for relocation on a case-by-case basis, taking into account their health and social needs and the ability of the receiving sanctuary to provide adequate individualized care; extremely high-risk animals should not be relocated. **Recommendation 3** is that all facilities use the same assessment system and share veterinary records. **Recommendation 4** is for facilities to collaborate to expand technical assistance available to the receiving facility and to scale up the veterinary capacity and specialized care that chimpanzees will require as they age. **Recommendation 5** is for facilities to develop shared relocation standard operating procedures that describe appropriate risk-mitigation strategies, and **Recommendation 6** is to resolve disagreements with the help of independent veterinary experts. Dr. Magnuson noted that the sending and receiving facilities usually agree, but external veterinarians could help navigate any disagreement; he emphasized that this external expert should not be the same veterinarian who issues the health certificate for transit. **Recommendation 7** is that facilities should share data with the NIH, allowing the NIH to undertake actuarial and demographic analyses of the chimpanzee population. Dr. Magnuson emphasized the importance of considering this issue now as the chimpanzees continue to age into the geriatric category.

Discussion Highlights

- In response to a question about the budgetary expenses incurred by the recommended actions, Dr. Magnuson explained that the working group was directed not to consider factors outside its charge, including budgets and whether any facilities currently in use cannot provide adequate care.

- Council members asked for a description of the receiving sanctuary. Working group members Drs. Gwendalyn Maginnis and Marisa St. Claire explained that the sanctuary has multiple housing areas of various sizes, including two large forested areas through which social groups are rotated; additional forested areas are under construction to provide adequate space for current and new social groups.

- When asked whether a process was in place to evaluate the success of a move, Dr. Magnuson described the quarantine and physical exam process but emphasized that extreme reactions following transport often are not predictable. Dr. Maginnis added that the large number of chimpanzees at the sanctuary provides each individual with more options to improve its social situation. Dr. Magnuson noted that end-to-end transportation care is recommended whenever possible so that familiar caregivers can help chimpanzees adjust to the new environment.

- A Council member pointed out that the phrasing "extremely likely to shorten their lives" in Recommendation 1 was not well defined within the recommendation; the assessment matrix is more detailed, but vague phrasing in the recommendation could compromise a veterinarian's ability to assess the chimpanzee's safety. Dr. Magnuson explained that the health of chimpanzees

classified as Category 4 varies widely, but veterinarians at the sending facilities are familiar with individuals and can assess their fitness subjectively. Dr. Maginnis noted that many of the clinical conditions of concern are those in which the animal becomes decompensated under stress. Dr. Sachin Kheterpal, Council member and working group member, explained that the working group was responsible for adhering to statutory language that prioritizes movement to the sanctuary, but recommendations for alternate language that balances the prioritization of both movement and chimpanzee health should be considered for inclusion in the letter to the NIH director.

- In response to a question about worst-case scenarios, Dr. Magnuson noted that a death at a sanctuary is the responsibility of the sanctuary, and the sending veterinarian is not considered responsible for deaths during transit. Dr. St. Claire explained that many conditions that may cause death in transit can be identified prior to transport; animals in Category 4 may have only a few months of life left regardless of whether they are transported. She emphasized that transportation is always a judgment call taken seriously and all possible precautions are utilized. Dr. Maginnis added that losses are likely in a group of relatively frail animals, but veterinarians make the most informed decisions they can and will examine all parameters of any bad outcomes to inform future decisions.

- When asked about support for existing centers as chimpanzee populations decrease, Dr. St. Claire and Dr. Maginnis explained that most facilities have other sources of funding and likely would continue to operate without chimpanzees.

The Council voted to accept the report. The following recommendations were added:

- Determine more accurate language for the working group's recommendations, particularly the phrase "extremely likely" in Recommendation 1 and the kinds of data intended to be collected in Recommendation 7.

- Emphasize that sending sites must maintain the appropriate quality of care as their chimpanzee populations diminish.

- Include specific guidelines related to adverse events. Dr. Maginnis and Dr. St. Claire explained that the USDA does not have reporting requirements for adverse events, but such events would be assessed, preventive measures would be implemented, and a report would be made to the Office of Laboratory Animal Welfare (OLAW). Council members suggested that OLAW consider creating a data safety board to review circumstances where there are adverse events and refine practices.

VIII. UPDATE FROM THE OFFICE OF PORTFOLIO ANALYSIS (OPA)

George Santangelo, Ph.D., the director of OPA, emphasized the need to find ways to decrease the interval between scientific research and subsequent improvements in health. Clinical trials are attempts to improve human health and, as such, can represent the translation of research into potential practice. Citation of biomedical research publications by clinical trials or guidelines (clinical articles) can be considered a representation of translation and a publication's value to the improvement of human health; identifying publications likely to be cited in future trials could help reduce the interval between research and translation to practice.

OPA built a machine-learning model that incorporated the data profiles and citation dynamics of all papers in PubMed and assigned each paper a score estimating the likelihood of future translation.

Whenpapers published since 1995 were assessed,publications with human components to their research—identified by the presence of medical subject heading (MeSH) terms that map solely within the Human branch of the MeSH ontology—accumulate citations by a clinical article at a faster rate than those with no human components to the research. Dr. Santangelo explained that the ratio of MeSH categories can be used to locate each paper on a triangular map of human, animal, and molecular/cellular relevance. Thepapers most often cited by clinical articles are clustered near the pole of exclusively human research, and the papers least often cited by clinical articles are molecular/cellular-focused.

After the machine-learning algorithm is trained on data profiles for each publication, the model it generates can predict any paper's potential to be cited in future clinical research based on its data profile. OPA's algorithm was able to predict the likelihood of citation within 2 years of publication, and its predictionswere in general more successful than those of expert reviewers. To further assess the algorithm's abilities, the contribution of different variables to the translation probability score can be ranked. For human-focused articles, the yearly citation rate—which reflects the amount of interest a paper generates—is the variable that most affects the probability score. The most important variable for fundamental articles is whether they had been cited by human-focused papers, followed by citation by papers with disease- or drug-related MeSH terms. Using these variables as part of a score's "genetics," the team "mutated" some variables and discovered that adding citations from papers with MeSH terms exclusively related to molecular/cellular science decreases the likelihood of translation; the likelihood increases slightly with citation by papers with animal-related MeSH terms, and showed the largest increase when cited by human-related papers that also include the specific MeSH terms "disease," "therapeutic," and "chemicals" or "drugs."

Dr. Santangelo used a real-world example to assess whether the algorithm accurately predicts the actual citation rate. Although a higher percentage of *Salmonella* papers were funded by the NIH than the average, very few were cited by clinical articles. However, papers on cancer biomarkers were rarely funded by the NIH, but both the overall number of papers and citations by clinical articles are increasing. The scores produced by the algorithm show an even more dramatic prevalence for clinical citation of papers on cancer biomarkers, and this study could have implications for data-driven management of the NIH portfolio.

In summation, Dr. Santangelo reiterated that fundamental research articles take longer to be cited by a clinical article, that citations within 2 years of publication are sufficient to predict the likelihood of future citation by a clinical article, and that citation by molecular/cellular-focused papers decreases the likelihood that a paper will be relevant to clinical research in the future, whereas citation by human-focused papers with disease, therapeutic, and chemical/drug MeSH terms increases the probability of future citation by a clinical article. Algorithms such as this that can describe the kinds of data profiles likely to exhibit bench-to-bedside knowledge flow might help identify emerging areas of translation.

Discussion Highlights

- Journal impact factor was not considered in this analysis.

- Council members suggested that some articles may have shown skewed ratios of human to animal tags due to the nature of the tagging system. Dr. Santangelo responded that the map shows little subject-matter bias.

- When asked whether this method could demonstrate how NIH research supported impactful therapeutic approaches, Dr. Santangelo commented that one critical function of OPA is to

demonstrate the value of biomedical research and characterize NIH investments essential for advances that improve human health.

- Council members disagreed that citation in clinical trials or guidelines represents translation and cautioned against using such terminology without caveats. Dr. Santangelo suggested that clinical trials are the first step along the path that leads to advances in improving human health but agreed that highlighting caveats is important. Dr. Anderson pointed out that no other such theoretical work with the NIH portfolio was being conducted.

- Council members reiterated that more fundamental papers might be cited less frequently than those immediately preceding a therapeutic discovery, and Dr. Santangelo explained that his team is exploring pathways of discovery that would more accurately include papers cited earlier in the translation process.

- A Council member recommended that a future meeting consider the controversy around the definition of clinical trials.

IX. CLOSING REMARKS

Dr. Anderson thanked the Council members and speakers for their contributions at this meeting. He reminded the members that the next Council meeting is scheduled for September 7, 2018.

X. ADJOURNMENT

Dr. Anderson adjourned the meeting at 4:08 p.m. on May 18, 2018.

XI. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing summary minutes are accurate and complete.

James M. Anderson -S

Digitally signed by James M. Anderson -S
Date: 2018.06.19 10:35:29 -04'00'

James M. Anderson, M.D., Ph.D.
Chair, NIH Council of Councils
Director, DPCPSI, OD, NIH

Date

Franziska B. Grieder -S

Digitally signed by Franziska B. Grieder -S
Date: 2018.06.19 10:54:30 -04'00'

Franziska B. Grieder, D.V.M., Ph.D.
Executive Secretary, NIH Council of Councils
Director, ORIP, DPCPSI, OD, NIH

Date