The fifth of 10 listening sessions to gather feedback on the proposed Advanced Research Projects Agency for Health (ARPA-H) was held virtually on August 2, 2021. Advocates for research on addiction and alcoholism shared their opinions. The National Institutes of Health (NIH) is working closely with the White House Office of Science and Technology Policy (OSTP) to establish ARPA-H to focus on ambitious and innovative projects that will shape the future of health and medicine for all Americans.
Participants

White House Office of Science and Technology Policy (OSTP)
Max G. Bronstein, M.P.P., Assistant Director for Health Innovation
Tara A. Schwetz, Ph.D., Assistant Director for Biomedical Science Initiatives

National Institutes of Health (NIH)
Francis S. Collins, M.D., Ph.D., Director
Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director
George F. Koob, Ph.D., Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Nora D. Volkow, M.D., Director, National Institute on Drug Abuse (NIDA)

Stakeholders
Sandra D. Comer, Ph.D., Public Policy Officer, College on Problems of Drug Dependence (CPDD), Brentwood, TN; Professor of Neurobiology, Department of Psychiatry, and Director, Opioid Laboratory, Division of Substance Use Disorders, Columbia University, New York, NY
Raymond T. Chung, M.D., FAASLD, President, American Association for the Study of Liver Diseases (AASLD), Alexandria, VA; Director of Hepatology and the Liver Center, Vice Chief of Gastroenterology, Medical Director of the Liver Transplant Program, and the Kevin and Polly Maroni Research Scholar at Massachusetts General Hospital, Boston, MA.
Robert B. Huebner, Ph.D., Chairman, Friends of NIAAA (FNIAAA), Washington, DC
Jessica Hulsey, President and Chief Executive Officer, Addiction Policy Forum, North Bethesda, MD
Michael F. Miles, M.D., Ph.D., President, Research Society on Alcoholism (RSA), Austin, TX; Professor of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA
Kerry J. Ressler, M.D., Ph.D., President-Elect, American College of Neuropsychopharmacology (ACNP), Brentwood, TN; Chief Scientific Officer and James and Patricia Poitras Chair in Psychiatry, McLean Hospital, Belmont, MA; Professor of Psychiatry, Harvard Medical School, Boston, MA
Meeting Summary

Welcome and Opening Remarks
Lawrence A. Tabak, D.D.S., Ph.D., Principal Deputy Director, National Institutes of Health (NIH)
Francis S. Collins, M.D., Ph.D., Director, NIH
Max G. Bronstein, M.P.P., Assistant Director for Health Innovation, White House Office of Science and Technology Policy (OSTP)
George F. Koob, Ph.D., Director, National Institute on Alcohol Abuse and Alcoholism (NIAAA)
Nora D. Volkow, M.D., Director, National Institute on Drug Abuse (NIDA)

Dr. Tabak welcomed attendees and provided logistical information for the Q&A session that would occur at the end of the session. If approved, the Advanced Research Projects Agency for Health (ARPA-H) will be a new division within NIH, with a radically different culture and organization. The new agency will be designed to foster bold ideas that are largely use-driven and to conduct research that solves practical problems. The resulting platforms, capabilities, and resources will apply across many diseases and conditions. ARPA-H will also have a distinct focus on equity to ensure diversity in funding recipients and in the patient populations that will benefit from its breakthroughs.

Dr. Collins welcomed participants and attendees to the fifth of 10 listening sessions to gather feedback on the proposed ARPA-H. NIH is working closely with OSTP on ARPA-H, which is a high priority for the Biden administration. ARPA-H is designed to catalyze ambitious ideas and approaches that will shape the future of health and medicine for all Americans. The new agency, which will follow the Defense Advanced Research Projects Agency (DARPA) model, will focus on high-risk, high-reward projects and will be guided by visionary project managers. ARPA-H will recruit researchers who might otherwise not apply to NIH for support, and its projects will be driven by clearly defined milestones. OSTP and NIH wish to gather opinions from stakeholders, who will play a critical role in the establishment and success of ARPA-H. The 10 listening sessions will focus on specific research areas and will involve NIH Institute and Center (IC) directors who represent those areas.

Mr. Bronstein said that ARPA-H aims to fill gaps in the biomedical research ecosystem to which NIH supplies vital infrastructure. Advancing new ideas to improve human health and biomedical science will require a novel approach. The ARPA model has taken shape as the Advanced Research Projects Agency–Energy (ARPA-E), the Intelligence Advanced Research Projects Agency (IARPA), and DARPA; these examples show that the model works. It is now time to deploy the model for innovation in health.

Dr. Koob said that alcohol misuse and alcohol use disorder (AUD) inflict an enormous burden of suffering on society and an incredible toll on public health, costing the U.S. economy up to $250 billion annually from personal injury, loss of productivity, and the burden on the health care system. NIAAA works to address these issues in a setting of staggering incidence statistics for children with fetal alcohol spectrum disorder (FASD) and adults living with these disorders. If approved, ARPA-H could significantly advance
NIAAA efforts to diagnose, prevent, and treat AUD and alcohol-related problems, contributing significantly to improved overall health care in the nation. For example, wearable biosensors to measure blood alcohol levels in real time could facilitate diagnosis, monitor treatment, and help patients avoid relapse. Biomarkers or biomarker panels could aid diagnosis and improve understanding of vulnerability to AUD, facilitate prevention, direct individualized treatment, and help with monitoring and supporting long-term recovery. Finally, a social community challenge could help cause a paradigm shift in health care and make screening, intervention, and referral to treatment a core part of the basic approach to medicine in the United States. ARPA-H could provide the mechanism by which each person needing treatment for AUD, including those in underserved populations and underserved individuals, gets evidence-based, state-of-the-art treatment.

Dr. Volkow said that addiction devastates multiple organ systems and contributes to severe outcomes in a variety of health conditions, including a 40 percent higher risk of death from COVID-19. ARPA-H could provide innovation and translation of products that can address the major challenges of treatment and recovery. For example, there is a need to implement previously discovered treatments. Radical change is needed to get pharmaceutical companies interested in developing addiction treatments. ARPA-H could provide opportunities for properly trained basic scientists, investors, and partners to develop nonpharmaceutical treatment alternatives and models. ARPA-H could promote the implementation of addiction science that has been proven but unimplemented, tailored to specific groups, or inaccessible due to cost. Expanding access to treatment and developing individual interventions for substance use disorders (SUDs) will improve outcomes. Equity, stigma, and the lack of personalized treatments need to be addressed. NIDA supports the formation of ARPA-H and its promise of radicalizing and accelerating treatments that can help people prevent and treat SUDs.

**Comments from Invited Stakeholders**

Raymond T. Chung, M.D., FAASLD, President, AASLD, Alexandria, VA; Director of Hepatology and the Liver Center, Vice Chief of Gastroenterology, Medical Director of the Liver Transplant Program, and the Kevin and Polly Maroni Research Scholar at Massachusetts General Hospital, Boston, MA

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Kerry J. Ressler, M.D., Ph.D., President-Elect, ACNP, Brentwood, TN; Chief Scientific Officer and James and Patricia Poitras Chair in Psychiatry, McLean Hospital, Belmont, MA; Professor of Psychiatry, Harvard Medical School, Boston, MA

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On behalf of AASLD, Dr. Chung described alcohol-associated liver disease (ALD) as the most important medical consequence of AUD and the most common reason for liver transplantation in the United States. An alarming trend in hepatitis and cirrhosis, particularly among very young adults, has also led to a dramatic increase in liver transplantation rates, and COVID-19 has exacerbated the incidence of AUD and increased the number of ALD hospitalizations. ARPA-H projects could help characterize and address the multiple factors that contribute to severe ALD. Projects to characterize and develop biomarkers would benefit from clinical data-driven approaches, which have not historically been supported by NIH. Artificial intelligence (AI) and machine learning could be used to abstract behavioral, psychiatric, and social information from electronic health records and create interventions for high-risk patients. ALD would be eradicated with the elimination of AUD, so holistic treatment approaches are needed. ARPA-H projects could develop new tools for identifying high-risk AUD and prevent the development and relapses of serious ALD. AI could also be used to leverage population data to identify factors associated with the development or relapse of AUD, intensify preventive approaches, and promote abstinence with multidisciplinary psychosocial, behavioral, and pharmacologic approaches. Emerging technology, such as wearables and apps, could be used to monitor cravings and alcohol use or relapse. ARPA-H projects could catalyze cross-cutting, transformative approaches and stimulate interdisciplinary work between investigators who have been historically supported but siloed by NIH. If successful, these bold approaches could be applied to other causes of liver disease, including the highly prevalent nonalcoholic fatty liver disease and chronic viral hepatitis, a consequence of opioid use disorder. All share common pathways to fibrosis, cirrhosis, and cancer. ARPA-H could play a key role in efforts to identify druggable targets and develop agents to reverse liver fibrosis and prevent liver cancer. More funding is needed to support research in liver disease, so AASLD strongly advocates funding ARPA-H from new sources rather than from a redistribution of NIH funding. ASLD would like ARPA-H to focus on technologies and platforms that apply to a wide variety of diseases and organs, including the liver.

Dr. Huebner said that FNIAAA members had developed a long list of ARPA-H scientific and research opportunities. First, regarding comprehensive community-based interventions or multisystem approaches to reducing individual and community-level risk relevant to current causes of death and disability, these wide-scale prevention research efforts typically include budgets and timeframes beyond those allowed in NIH R01 grants. It has been difficult to find an NIH home for these types of studies, because prevention has cross-cutting outcomes. Within ARPA-H, such a project could initiate a culture of prevention, with evidence-based interventions that are studied and refined within a large-scale, long-term, multisystem, and multi-disease framework. Next, ARPA-H projects could accelerate and scale up evidence-based screening, brief intervention, and referral to treatment (SBIRT) for AUD within mainstream health care settings. Identifying alcohol problems early and providing brief advice and referral to treatment, if indicated, is a powerful tool for reducing the burden of the disease; however, uptake by
the health care system is lagging. An ARPA-H project that draws upon new technologies, implementation science, and the latest thinking on diffusion of innovations could boost the uptake of SBIRT at the individual, organizational, and system levels across our health care system. Another research opportunity for ARPA-H would be developing a better understanding of the dynamics of recovery. Innovative and feasible approaches for data collection, such as ecological momentary assessment and data analysis techniques like dynamic systems modeling, could be used to better understand trajectories of recovery, precipitants of relapse, and the neurobiological mediators and moderators of recovery. Finally, developing and refining digital health and web-based tools and mobile phone and wearable technology platforms has the potential to significantly increase initiation of treatment (a major issue in the addiction field) and boost the reach and access of treatment, especially among adolescents and young adults. For example, smart watches can monitor physiological data known to be associated with AUD, including heart rate variability. Mobile phone applications can use global positioning systems to remind users they are near settings that put them at risk for relapse. Virtual reality applications can train patients to cope with triggers and develop drink refusal skills. These suggestions fit well within the mission of ARPA-H: They are practical, user-driven issue areas that would benefit from nontraditional funding, timeframes, and structures. The treatment of AUD warrants fresh, novel, and multidisciplinary study.

Speaking on behalf of RSA, Dr. Miles said that the proposed ARPA-H program would be a perfect match for researching AUD, because it is a complex disease. Alcohol has specific molecular targets and marked promiscuity, affecting every organ system across the lifespan. It is the number one preventable cause of developmental cognitive impairment in conditions ranging from FASD to addiction to severe AUD, and it can lead to worsening cognitive decline in Alzheimer’s disease patients and to the onset of liver disease. Alcohol can also interact with other environmental factors, genetics, and comorbid nutritional or disease states to affect health. Potential areas of study and impact for ARPA-H include the need for development of novel, standardized, and dynamic outreach programs to identify, educate, and treat people living with AUD, particularly in traditionally hard-to-engage or diverse populations, and those at particular high risk, such as pregnant people. The dynamic planning of ARPA-H studies could be done with modern communication platforms, wearable monitoring, and flexible staffing approaches. Such outreach programs could have an immediate impact on disease burden, morbidity, and mortality (e.g., reducing deaths in college students from alcohol poisoning). Human and animal genetic and genomic studies are uncovering the complex genetic variants influencing AUD, but determining how that information can be integrated with life-stage and organ-specific mechanisms, together with other environmental data and social factors affecting disparities in health care, is an enormous challenge. Treatment of alcohol-related disease could benefit from innovative cross-disciplinary data science and AI predictive methodologies to improve prediction of disease, definition of disease heterogeneity, and identification of diverse therapeutic approaches. These types of studies would benefit many areas of mental health care and other complex diseases. Existing or over-the-horizon pharmacotherapies could benefit from novel medicinal chemistry modeling and deployment. For example, a recent report in *Nature* described the development and use of a novel peripheral blocker of drug action to reduce toxicity in
long-term drug treatment of alcohol consumption in a mouse model. The inertial barrier to transitioning academic research findings on AUD to industry means that there is a need for rapid and incentivized funding approaches at both the academic and industry levels, as was seen with recent work on COVID-19. Finally, novel molecular interventions for modifying behavior should be considered, as is being done with vagus nerve stimulation or deep brain stimulation for other disorders. For example, optogenetic and viral vector studies in animal models are localizing highly selective targets for manipulation of alcohol-related behaviors that might offer an alternative to pharmacotherapy or behavior treatment in humans for select cases. ARPA-H approaches could broadly affect the prevention, detection, management, and treatment of AUD.

Ms. Hulsey, representing the Addiction Policy Forum, said that it was critical to include addiction treatment in ARPA-H discussions because of the devastating effects (isolation, stress, anxiety, and loss) of the COVID-19 pandemic on addiction. ARPA-H projects could create change in addiction treatment by advancing and accelerating discovery, producing radical change, and inspiring innovation. Investment in scientists, researchers, and industry will advance discovery and add more tools to the toolbox to address addiction. Breaking down regulatory barriers and cutting through red tape are also high priorities. ARPA-H projects could develop new medications to treat stimulant disorders, such as cocaine and methamphetamine addiction, which are some of the most difficult addictions to treat. Long-term formulations are needed, as are medications for sedative use disorders, due to the increased use of benzodiazepine. Medications are also needed for polysubstance use disorder because most individuals struggling with addiction use more than one substance. ARPA-H projects could improve access to medications; because medications to treat AUD are woefully underutilized. ARPA-H could investigate precision medicine, new biomarkers, genetics, individualized treatments, and layer interventions. There is a need for increased understanding of the many intervention services and tools that patients need to reach long-term recovery, become stable, and develop happy, thriving lives. ARPA-H could work to advance the integration of addiction treatment into medicine; half of the adults in the United States do not recognize addiction as a health condition and do not know to connect with their physicians, pediatricians, general practitioners, or other medical professionals who can implement more immediate screenings and interventions. ARPA-H could also work to expand access through apps, digital tools, and wearables to make technology available for managing addiction as a chronic illness. ARPA-H projects could address the stigma around addiction, increasing access and utilization, improving health literacy, and encouraging individuals to pursue care sooner. Any large health initiative that focused on addiction would draw attention to its status as a health condition and bring patients into care sooner. ARPA-H efforts to address equity could improve access to gold-standard treatment for people from every race, ethnicity, region, and economic class. ARPA-H projects could accelerate implementation of new science and research, a gap that exists in ensuring that new tools, research, and discovery reach the patients, families, practitioners, and stakeholders who need them. If approved, ARPA-H could have a profound and cascading effect on understanding and treating addiction. New research, new discoveries, novel technologies, and useful tools can change how families feel about living with addiction.
Speaking on behalf of ACNP, Dr. Ressler said that he supported the development of an advanced research projects agency for mental health research. ACNP brings national and international leaders in neuroscience, prevention, and behavior together to advance the understanding of the psychiatric, neurological, and behavioral causes of SUD and AUD. Dr. Ressler posed the following questions for consideration in the development of ARPA-H projects:

- How can ARPA-H work with the Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative to accelerate the use of technologies that are emerging from the BRAIN Initiative to develop therapies for AUD and SUD? Can ARPA-H help the BRAIN Initiative team find private partners to implement their discoveries?
- Some big data approaches have been discussed. Can ARPA-H facilitate data science to address problems of SUD and AUD?
- Will there be opportunities for ARPA-H to incentivize work to reduce stigma and remove barriers to getting treatment to all individuals?
- Can ARPA-H better direct discovery science to translation and to implementation through additional academic and industry funding initiatives?
- Might there be opportunities for ARPA-H to create academic and industry initiatives to identify biological targets for intermediate phenotypes and digital phenotypes of psychiatric disorders, SUD, and AUD?
- Could ARPA-H facilitate Food and Drug Administration (FDA) consideration of biologically driven (as well as traditional, nosology-driven) neuropsychiatry targets? With co-morbidities, it is important to identify intermediate phenotypes for targets, which are critical for progress.
- Can ARPA-H leverage and integrate large-scale data collection from genomic approaches (e.g., Psychiatric Genomic Consortium, UK Biobank) with large-scale imaging (e.g., The ENIGMA Consortium, UK Biobank) and data consortia to further enhance these datasets for researchers and other users nationwide?
- Might ARPA-H be incentivized to integrate large-scale human biology data from preclinical model systems that promote understanding of the mechanisms of biology to enhance mechanistic studies of neuropsychiatric systems for AUD and SUD?

Dr. Comer said that CPDD recognized many research opportunities that could be catalyzed by the development of ARPA-H, including implementation research on therapeutic workplaces, where drug users who provided drug-free urine samples could be given access to gainful employment; using technology-based therapeutic tools to engage geographically or psychiatrically hard-to-reach patients; implementation research on contingency management, which rewards behaviors consistent with treatment goals; and developing major communications campaigns to reduce the stigma associated with drug and alcohol use. Incorporating precision medicine approaches into addiction treatment would also be incredibly important, along with enhancing systems for characterizing protein structures, applying AI and machine learning to libraries of interacting compounds to discover potential new treatments, and advancing nonabstinence outcomes across the translational spectrum. Significant gaps in the R&D enterprise that are slowing...
or impeding progress include a lack of industry knowledge about SUDs and lack of academic knowledge about the drug development process. An ARPA-H project could educate both groups. There are problems with the translation and implementation of research (from preclinical through clinical trials) into the community. Funding is needed to develop the best predictive models through all phases of development. There is a lack of engagement of implementation expertise across the treatment development process. It is important to better understand whether and how interventions work for all—or only for subgroups. Challenges in advancing research through to commercialization, implementation, and dissemination include the currently too-slow process for medication development and the lack of pharmaceutical company incentive to develop drugs for SUD. ARPA-H could implement partnership or collaboration strategies by expanding infrastructures that promote collaborations among pharmaceutical companies, contract research organizations, and academia and create new methods to facilitate the availability of real-time drug data, such as rapid postmortem toxicology results. ARPA-H could also develop infrastructure and partnerships to facilitate access to and interoperability of the vast amount of health data in the criminal justice, treatment, health care, and pharmacy sectors. These data sharing partnerships would include public and private institutions at the federal, state, and local levels. CPDD also supports the capitalization of the innovative technologies developed through the BRAIN Initiative and other initiatives, with a focus on the tech with the greatest applicability to diagnosing and treating SUDs. Finally, when planning ARPA-H, CPDD members strongly recommend the use of a two-step review process that involves submission of an initial one-page concept on rolling monthly deadlines that could be reviewed quickly; a full-length proposal would be submitted within 60 days if the initial concept were accepted.

Discussion

- How do we translate concepts from academic research into products that are developed by industry and become available to patients who need them? Dr. Volkow said that this problem has been studied extensively. The challenge is the risk for industry to not recover their investment. The National Academies of Sciences, Engineering, and Medicine has recommended policies to incentivize industry. Another model is to mandate the development of the initial compounds and then engage and promote the formation of small companies to develop them. A third strategy is a ladder initiative to lift treatments out of the “valley of death” by funding multiple researchers with specific ideas on how to advance a treatment. Finally, neuroscientists can be tutored in how to bring their ideas to market using venture capital. The need for innovation is hampered by limited resources. Dr. Koob said that the translation of animal models backward and forward is another strategy. The use of big data sets to identify targets that work in humans could be translated back to animal models for fine tuning and then back to humans. Another strategy is increasing the uptake of medicines that are available. For example, there are three FDA-approved medicines for the treatment of AUD, but no one is using them. Helping providers understand that they can help in this area would generate enthusiasm and pressure for new medications.
• How can we know if a project is radical, novel, or disruptive enough for ARPA-H? How is it different from existing NIH mechanisms? Dr. Schwetz said that ARPA-H will identify and fund bold and innovative efforts. Specific ideas will be solicited through broad agency announcements (BAA). These requests for proposals would outline specific criteria to include in the submitted proposals. Funded projects will be those where the investigators proposed to take a novel approach from point A to point B to achieve the goals outlined in the BAA. At least initially, it is likely there will also be broad, open, and investigator-initiated funding announcements. The details are still under development, and there is much work to be done. Dr. Tabak said that ARPA-H projects would likely be larger scale than those typically funded through the various NIH funding mechanisms. For example, R21s are more exploratory and have an appropriately smaller scale. ARPA-H projects will have a larger scale, more potential impact, and a rapid timeline. ARPA-H projects will have variable timelines, with some shorter and some longer projects.

• How will ARPA-H work with other existing governmental funding mechanisms? Will there be competition for funding? Dr. Schwetz said that partnerships, including those across federal agencies, will be critical for the success of ARPA-H. An interagency working group is being formed to discuss the mechanisms by which ARPA-H can efficiently and effectively build on and bolster ideas for collaboration across the federal government. Also, ARPA-H will complement, but not compete with, ongoing efforts of the NIH Institutes and Centers. To better understand the existing landscape of support for a particular area, program managers will conduct detailed landscape analyses and hold conversations with relevant stakeholders before planning programs that augment science without creating competing resources.

• How will ARPA-H conduct diversity research and address inequality? How will this focus be ingrained in the fundamental culture of the agency? What types of resources will be available to help fund inequality research for unmet medical needs? Dr. Schwetz said that health equity would be a critical component of ARPA-H and its work. Health equity will be built into each funded program, and it will be the main focus of some of the funded programs. Equity will be a critical element of ARPA-H’s hiring practices, bringing in diverse perspectives and lived experience. ARPA-H will also have someone whose key responsibility is to think about equity for the organization. Dr. Tabak added that the pandemic has taught NIH that it needs to engage individuals where they live and work within a community while proceeding at the speed of trust. This involves taking advantage of existing relationships within a community. Dr. Volkow said that innovations must provide accessible treatments and that high cost can be a barrier that creates inequities. The cost of health care can require new ways of thinking and providing quality care that is not so costly—particularly for addiction. Dr. Koob added that culturally specific treatments, diagnoses, and measurements need to be developed and implemented; after all, diverse forests are the strongest, and diversity is
needed at all levels of basic science and beyond.

- **Which specific wearable technologies could be meaningful to patients and transformative for medicine?** Dr. Volkow said that overdose deaths could be monitored and prevented with wearable devices that could automatically deliver naloxone. Another idea is using devices to inhibit cravings to prevent relapses. Wearable sensors can also measure the presence of blood alcohol in real time. Other blood alcohol measurement devices could be miniaturized to become wearable.

- **How will ARPA-H create industry collaborations?** Dr. Schwetz said that these collaborations would need to involve participation from a variety of stakeholders and be built on the strength of interagency relationships to help catalyze and facilitate the transition.

**Closing**

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

Dr. Tabak thanked participants and attendees for their interest in ARPA-H. ARPA-H is a work in progress, and OSTP and NIH will be hosting additional listening sessions to continue gathering information to help guide its establishment. Dr. Tabak invited attendees to send comments and questions to the ARPA-H comment box (ARPAHcomments@nih.gov) and to visit the ARPA-H webpage.