NINDS Strategic Planning Discussion Panel

Basic Science Panel Meeting Summary

October 2, 2020

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Introduction

The purpose of this discussion group was to gather perspectives from a panel of 14 neuroscientists to define the challenges and opportunities for basic science research that NINDS should consider addressing over the next 5- to 10-year period. These perspectives are one source of input that NINDS will use to develop their 5-year strategic plan and to guide implementation of that plan.

The panel first convened on September 15, 2020, for an orientation meeting designed to introduce panelists to each other, identify co-chairs to lead the panel discussion, and to give the group their charge. NINDS asked the panelists to submit 2-3 key challenges or great opportunities for basic neuroscience research, focusing either on science or process issues. Panel co-chairs organized these suggestions into five broad themes to guide the discussion: funding mechanisms, unmet challenges in neurological disease and disorders, clinical-basic science interface, scientific community responsibility, and data sharing. Below is a summary of that discussion, which took place on October 2, 2020.

Funding Mechanisms

Many panelists expressed that the current funding mechanism structure (e.g., R model grants) has been successful. One area of potential optimization is to incorporate more ways to extend the research time beyond the typical 5 years of funding for inherently longer-term projects (e.g., study of a neurodegeneration model or neural maturation). Such funding could be a continuation or expansion of the R35 mechanism, which provides funding beyond this 5-year window and includes a checkpoint to ensure that adequate progress has been made to warrant the continuation of the grant. An important consideration for longer-term funding mechanisms is how best to define the metrics of success at that midpoint check-in; the traditional metric of success is publication record, but the first half of a long-term project may not produce many publications. Panelists suggested that these metrics and milestones could be defined in the grant application by the applicants, and furthermore that there should be some degree of flexibility to revise those milestones as circumstances change over time. The group took care to note that definitions of success should not be rooted in supporting the initial hypothesis, because this will encourage applicants to generate more conservative hypotheses.

Although the panelists expressed enthusiastic support for longer-term funding mechanisms, they noted that it would require strong timeline justification criteria and careful management of the NINDS portfolio to avoid inadvertent exclusion of cohorts of new investigators because too much money in a funding cycle is already accounted for by projects with long timelines. It is also important to prevent bias of these longer-term grants awards against younger investigators, because a current requirement for the R35 stipulates that the applicant have already received one cycle of NINDS funding; however, multiple members of the group expressed that a bias in favor of awarding R35 grants to more senior researchers does not appear to exist at this time.

Panelists also expressed support for smaller funding mechanisms that can be used to support a full- or part-time technician for long time periods to provide specific expertise or develop technologies that are intended to continually operate in a lab or core facility. Such funding would provide job stability for talented staff scientists who fall outside of the typical research career track beyond the 5-year grant

cycle, save valuable time spent training new personnel, and may encourage team science by supporting experts in shared core facilities.

Unmet Challenges in Neurological Disease and Disorders

In light of increasing evidence that there are numerous non-brain influences on brain activity (e.g., gut-brain interactions), the panelists supported a shift beyond studying single brain regions or single organs and toward "whole organism" approaches to interrogating neurological diseases and disorders. One panelist expressed that a potential hindrance to this shift is the confidence (or lack thereof) that study sections may have in an investigator's ability to move outside of their area of expertise (i.e., a neuroscientist's ability to conduct rigorous work outside the nervous system). Many panelists believed that this concern should be addressed through collaboration, including initiatives funded across NIH Centers (e.g., issuance of a joint request for applications [RFA] supported by NINDS and NHLBI to study cardiovascular influences on brain function). Existing programs such as the Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program may also serve as an exemplar for such a collaborative effort in this area.

The panelists addressed the prevalence of large qualitative data sets in neuroscience. Although these data sets contain a wealth of information, many believe that they are not currently leveraged to their full potential, particularly in a way that will progress beyond descriptive goals toward identifying more causal relationships in the field. Given the large investment that is required for de novo generation of large data sets, panelists expressed support for funding mechanisms that will incentivize data mining efforts on existing data sets, acknowledging the fact that these efforts may be more exploratory than hypothesis driven—a quality that often is less favorable to reviewers. NINDS could play a central role in "matchmaking" data analysis projects with existing data sets so that data may be reused by multiple groups to answer unique questions. Numerous concerns related to such data mining efforts were expressed by the panel—including the user-friendliness of the data sharing interface and attribution concerns for resulting publications—and are explored further in the Data Sharing section of this meeting, where they were discussed in depth.

Panelists also discussed the types of data that could be generated to advance the field. One panelist suggested a funding mechanism to support the collection of longitudinal data on biological variables that are linked to clinical outcomes in neurological disease. This panelist further suggested the creation of a database of Food and Drug Administration (FDA)-approved drugs for drug repurposing studies, which NINDS could support by creating a centralized repository for labs to acquire aliquots of drugs without going through the lengthy material transfer agreement process with the drug manufacturer. Additionally, an RFA to incentivize studies of the blood–brain barrier without an explicit disease focus could assist drug repurposing efforts. All of these efforts would simultaneously support the clinical–basic science interface goals discussed at this meeting.

Clinical–Basic Science Interface

The panel discussed the challenges involved in fostering connections between basic and clinical scientists—a goal for which there is much enthusiasm in the field but has not yet been widely achieved.

The panel acknowledged the value of medical scientist training programs (MSTPs) in this arena; these programs generate an MD/PhD workforce that brings both fundamental basic research knowledge and clinical experience to the table. However, one panelist who completed an MSTP program noted that once these researchers return to the clinic, many face resistance to starting their own basic research labs.

Rather than reliance on clinician-scientists to bridge the gap between clinical and basic research, the panel expressed broad support for collaborative efforts that include both clinicians and basic scientists in funded partnerships. As one panelist described it, basic scientists and clinicians operate on different timescales—for example, the validation studies needed to translate a basic science finding into a clinical environment not easily achieved within the standard basic science funding cycle or even the tenure of many lab members (e.g., graduate students and postdocs). As a result, basic scientists are ill-equipped to tackle such translational projects on their own. Likewise, the panel recognized that clinical training does not equal clinical research experience, and furthermore clinicians may struggle to find protected time for research at their home institution. Thus, a strong dialog between these groups is essential.

The panel expressed mixed perceptions of the current ease with which funding can be secured for clinicians and basic scientists on the same grant, but generally supported mechanisms that would have a mixture of basic (i.e., in animal models) and clinical (i.e., in humans) aims. Some panelists endorsed a mechanism in which basic scientists may propose a translational application for their discovery, but rather than fund the proposal in the traditional sense, NINDS could support the proposal by taking that discovery through the regulatory and preclinical aspects of the process that are generally outside the scope of basic research labs.

Several panelists also acknowledged the value of involving patient advocacy groups in this space. These groups can bring a patient-centered focus to research questions and inspire collaboration between basic scientists and clinicians; as one panelist described it, engagement with patients and families may represent an opportunity to combine advocates with clinicians and basic researchers to form a “three-legged stool” that “may stand better” with this added source of support. Patient-Centered Outcomes Research Institute (PCORI) grants may serve as an exemplary model of incorporating patient and care partner engagement in research funding opportunities.

Scientific Community Responsibility: Sociology and Grant Review

The panelists discussed the ethos of the neuroscience community with regard to how reviewers contemplate and evaluate the projects that are proposed for funding. The conversation centered on the community’s definition of what it means for science to be truly innovative. For many, the term

"innovation" carries the implication of tool or methods development, so much so that tool development has become overemphasized in the review process and may be considered more innovative than a concept-driven project. The panel therefore discussed ways in which the community may change its approach to the idea of innovation.

Several panelists endorsed evaluating grant applications on their "originality" in place of grading "innovation"—a simple change in reviewer terminology that may shift value toward conceptual frameworks capable of moving the field forward by changing the way researchers think about fundamental questions. The panel also believed that NINDS and other funding agencies must communicate a clear message to reviewers on how to properly weight these aspects of technique-driven and theory-driven innovation in their overall evaluation. One panelist noted that reviewers who do not weight these factors fairly can potentially bias the review process in favor of institutions that are already flush with resources; researchers in labs without the resources to build a "shiny new tool" may instead propose a novel and logical extension of previous work, but be judged as proposing merely incremental rather than transformative work and find less success with reviewers.

The panel also considered how the neuroscience community evaluates the use of different model organisms. The conversation focused on how models are chosen for specific projects—for example, is the model the best option for the central question at hand, or is it the model that is most readily available and familiar to the researcher? One panelist conveyed that the evaluation of model fitness is an area in which study sections already excel. The panel generally believed that NINDS should continue to facilitate this discussion of model fitness, perhaps by funding opportunities to characterize the relationships between model organisms with a focus on their utility for answering fundamental neurobiological questions (e.g., which cell types are found in which organisms)—a task that might otherwise be outside the scope of single grants.

Although the panel did not have sufficient time to thoroughly discuss the topic, several panelists noted workforce considerations in their suggestions related to how NINDS can contribute to the scientific community. For example, one panelist suggested that the timeline for K99 awards should be adjusted so that deserving scientists are not disqualified for personal reasons (e.g., time off for maternity leave). This panelist also noted that many immigrant physician scientists are unable to pursue independence grants (e.g., K12, K08, K23) because they are restricted to U.S. nationals and green card holders—eliminating approximately 25% of the entire physician population in this country from eligibility.

Data Sharing

The panelists agreed that data sharing is an essential form of collaboration. Reuse of existing data enables labs to perform analyses with a volume or variety of data that may otherwise be impossible given their resources, and furthermore can save time, money, and in many cases animal lives that would otherwise be spent generating redundant data de novo. However, the panel also acknowledged that data sharing is not occurring on the scale that many believe it should.

A critical step toward effective and widespread data sharing is accessibility. This is more than merely publishing data; data sets must be packaged and published in a user-friendly way on platforms that are

regularly maintained, have support available, are not prohibitively expensive to use, and employ standard formats or common data elements that other researchers can navigate easily. Integration of data formatting for reuse with existing data acquisition or analysis software may encourage data sharing by reducing the effort needed to make data accessible. The panelists believed that NINDS—and NIH more broadly—could play a leadership role in ensuring that these qualities are achieved when data are published for reuse.

The panel also discussed "carrot" and "stick" approaches (i.e., incentives and consequences) to promoting data sharing and reuse. Many panelists believed believe that there is a lack of incentive to devote energy to a large data set because investigators do not receive credit when the data are reused by others; as one panelist described this attribution problem, "there is no H index associated with [sharing data]." To reward researchers for making quality data publicly available, the panel supported recognition of the data generator in the form of authorship credit that is competitive with the boost that publications add to a researcher's portfolio; this could take the form of a new class of authorship (e.g., "corollary author") for those who did not contribute intellectually to a project but whose data made the project possible. Panelists noted that in the basic science arena, first author graduate students or postdocs are especially incentivized by this authorship potential, and one panelist suggested that for some number of years after the publication of a data set that first author can be made responsible for providing support to reusers of that data. In line with these incentives, the panel suggested that value be placed on data sharing contributions (e.g., additions to GitHub, generation of new animal models) similar to that which is already assigned to publication record when researchers are considered for grants or career promotions.

The upfront and continued cost of making data available is a barrier to data sharing. Funding opportunities can help labs overcome this hurdle by offsetting this cost. As a grant is ending, it would be useful if researchers could apply for supplementary funds from NINDS that are specifically allocated to preserving data for reuse (e.g., to cryopreserve a newly developed mouse line at Jackson Laboratories, or to fund a partnership—perhaps with a company—to assist with formatting data). Panelists also supported funding mechanisms to encourage data mining and reuse, such as the secondary analysis grants offered by the BRAIN Initiative.

As several panelists noted, some researchers commit to share data related to a project (e.g., upon submission of a manuscript to certain journals) but fail to ultimately do so. Panelists believed that consequences for failure to follow through on data sharing commitments should be enforced. NINDS can enlist program officers to assist with ensuring accountability for researchers who commit to share their NIH-funded data, and failure to share promised data can result in a negative impact on future fundability for that grantee; multiple panelists agreed that this kind of "stick" approach is warranted and that it "has to be about the money." The panel further noted that universities could promote data sharing efforts (e.g., NIH could require NIH-funded universities to set data sharing standards).

Training, Diversity, and Communications

The panelists submitted several written suggestions relevant to Training, Diversity, and Communications. In the interest of time, the co-chairs, in consultation with NINDS, decided to not

include these topics in the agenda for the Basic Neuroscience Research Discussion Panel because there are other Discussion Panels that are entirely focused on these topics. These written suggestions were sent verbatim to the relevant Discussion Panels and are summarized here.

Panelists expressed concern about the very small numbers of minorities in faculty positions in basic neuroscience despite the many programs to foster the move of minorities into academics. Several panelists offered specific suggestions for promoting diversity, equity and inclusion. One suggestion was to overhaul authorship, award and PI attribution models to promote justice and career sustainability for future generations of scientists. Another panelist suggested providing greater transparency in funding outcomes to inspire greater trust among investigators and the broader community given recent controversy and concerns about racial and gender equity in funding. Another panelist advocated for allowing every new professor to attend one study section discussion panel to level the playing field among new assistant professors who have varying degrees of senior help.

Panelists were enthusiastic about maintaining diversity fellowships (both F and K programs), the K99/R00 program, and the K programs for clinician scientists. A few suggestions for improving these programs included extending the eligibility timeline for women who have to interrupt research due to maternity leave, increasing opportunities for non-nationals residing in the United States to pursue pathway to independence grants for physician scientists, developing a "fast-track" pathway to encourage neurosurgeons to pursue basic science projects. Another panelist suggested developing a more integrated approach to neuroscience education that instills in the next generation of neuroscientists the skills, knowledge, and desire to "think big and synthesize"[1].

[1] Buzsaki, G., *The Brain From Inside Out*. 2019, New York: Oxford University Press. 441.

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