NINDS Strategic Planning Discussion Panel

Therapy Development Panel Meeting Summary

October 7, 2020

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Introduction

The purpose of this discussion group was to gather perspectives from a panel of 16 translational scientists to define the challenges and opportunities for therapy development that NINDS will address over the next 5 to 10 years.

The panel first convened on September 16, 2020, to become familiar with the goals of the discussion group. After that orientation meeting, panelists submitted suggested topics for discussion; suggestions ranged from early preclinical to late clinical areas. The panel co-chairs organized suggestions into five broad types of "gaps" in the field: scientific, biomarker, training, process, and partnership.

The panel began preliminary discussion of these gaps on September 24, 2020. Panelists then reconvened on October 7, 2020, for the main discussion, during which they organized gaps and opportunities into three categories centered on the theme of precision in therapy development: seeing (i.e., measuring/phenotyping) more precisely, intervening more precisely, and testing more precisely. The panel took care to note that although some topics were relegated to specific categories during discussion, considerable overlap and interaction exists across all three categories. Ultimately, the suggestions raised by this discussion group represent ways in which NINDS can help to get "the right care to the right patients at the right time."

Measuring and Phenotyping

During the main discussion, the panel defined the goal for the measuring and phenotyping category:

> "The goal here is to develop biomarkers and other technologies to help understand important types of patients with both common and rare diseases that may interact with therapy. Types in this sense would be interpreted broadly to include understanding biology (including genotypes [and] phenotypes), patient disease factors, variety of symptoms, outcomes and disease burden, temporal aspects of disease evolution in an individual, as well as the range of social determinants of health factors impacting disease manifestation and progression."

The panel discussed what it means to truly measure more precisely in the world of therapy development, and agreed that a key factor is precise measurement of the intersection between therapeutic action and the key biological processes that drive the disease in question. To achieve this measurement, patients must be carefully "typed" (i.e., sorted or categorized based on a quality such as phenotype or genotype) so that the underlying target biology for any given patient group (e.g., mechanism, rate of progression) is relatively homogeneous in order to maximize chances and magnitude of therapy success; one panelist noted explicitly that "typing" and grouping by target biology did not require a homogeneous patient population in terms of demographics. The panel further recognized that precise "typing" of patients does not imply the generation of ever smaller groups until the individual is itself a unique group, but rather grouping patients by meaningful biological metrics.

The panel prioritized natural history studies as among the highest priority opportunities in this category for NINDS to consider. Natural history studies with frequent, consistent measurements

represent a key data source that will help the field to better understand various measurements—including biomarkers—as they pertain to disease progression and outcomes as well as patient experiences. This enhanced understanding allows for "typing" of patients according to more meaningful criteria and may enable precise early intervention in pre-symptomatic populations. Furthermore, insights gleaned from natural history studies can form a "backbone" upon which new and improved clinical criteria, biomarkers, endpoints, and socioeconomic determinants of health can be validated. The panel acknowledged that support for natural history studies would likely necessitate strategic selection of disease areas in which NINDS should invest; partnerships with industry and advocacy groups may help to offset associated costs.

The panelists also prioritized data standardization and aggregation as fundamental to therapy development. This priority was viewed by the panelists as directly related to natural history studies, because aggregation of data from natural history studies is an area in which NINDS can provide great benefit to the field; panelists cited the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer's Network (DIAN) as exemplars. NINDS can play a key role in mitigating the challenges that currently arise in data sharing environments. For example, patient-facing portals for the aggregation of data into registries can provide a wealth of data and yet still fail to capture critical elements because of a lack of standardization. NINDS can work to implement structural requirements and a universal lexicon for nervous system disorders to help resolve this problem. Moreover, a centralized repository of standardized data would facilitate machine learning approaches to therapy development. Panelists also believed that data—including clinical trial or experimental data, methods, and samples—should be shared openly, and that NINDS can make open data sharing a requirement of funding.

Panelists expressed that enhanced leveraging of biomarkers will likely play a critical role in the advancement of therapy development over the next 5 to 10 years. Furthermore, the panel acknowledged that the term "biomarker" itself is vast and that NINDS can play a leading role not only in developing new and novel biomarkers but also in more concretely defining biomarkers as a concept so that investigators and other stakeholders can speak a common language on this important topic. The FDA definitions of biomarker may be useful in this endeavor, because they are well publicized.

In the realm of measuring and "typing" patients more precisely, the panel highlighted biomarkers that can be used for prognostic, diagnostic, or quantitative purposes; these may include genetic and imaging analyses (among many other examples) insofar as they help to define "types" of patients. Biomarkers related to protective factors (e.g., qualities identified in individuals with highly penetrant genetic mutations who do not manifest the illness) are also a valuable area of study, as well as characterization of all biomarkers in healthy populations.

Intervening and Altering

During the main discussion, the panel defined the goal for the intervening and altering category:

> "The goal here is [to] design and engineer interventions with mechanisms and delivery that [are] more targeted. This is about learning how, when, where, and on whom to intervene with a disease process to improve the focus of intervention where it is most effective and rational. It

might include gene therapy, immunotherapy, focused molecular targets, goal-directed dosing or timing, or more adaptive systems of delivery. Intervening more precisely must include intervening safely."

The panel recognized that more precise measuring is intimately related to more precise intervening and altering; as biological mechanisms are measured more precisely, interventions may become more targeted, efficacious, and safe. In this spirit, the panelists agreed that biomarker development is thus a high priority for intervening and altering neurological and neuropsychiatric diseases—specifically biomarkers of target engagement, target response, and pharmacodynamics. Biomarker development includes the characterization of invasive biomarkers of target engagement and pharmacodynamics (e.g., a quantifiable metabolite that can validate the penetration of new agents into the brain), which can then be used as benchmark points of comparison for commonly employed noninvasive biomarkers (e.g., imaging) to confirm that the proper target is being measured and/or altered.

Panelists discussed the importance of early intervention—often before symptoms appear—in diseases of the nervous system given the substantial neuronal loss that has already occurred once symptoms arise, as well as the role that biomarkers will likely play in making early intervention more possible. However, early treatment carries its own ethical challenges, including the risk of subjecting patients to potential adverse treatment effects unnecessarily; thus, improving the timing of intervention is not merely a matter of indiscriminately treating identifiable pre-symptomatic patients early but rather at the *right* time for that patient, thereby requiring precise patient population identification and ethical considerations that are built into protocols.

The panel also emphasized the need for NINDS to fund focused studies and interventions on social determinants of health (including neurologically-specific ones such as the placebo effect) as well as to develop nonpharmacologic interventions more broadly (e.g., game-style therapies). This entails rigorous implementation and de-implementation science that holistically evaluates an intervention in context of use with other existing therapies. NINDS could also facilitate implementation science in the context of community neurology practices, for example by allowing community-based physicians to apply for grants in collaboration with academic centers. These studies—which the panel noted may have difficulty finding funding elsewhere but are nonetheless critical—will enable incorporation of precise nonpharmacologic interventions into currently defined outcomes or endpoints.

The panel further identified a variety of therapeutic intervention types as important for the advancement of the field, including antisense oligonucleotides (ASOs) and gene therapies, regenerative implantable materials, precision small molecules and biologics, and nanotechnologies (e.g., for drug delivery). Partnerships and collaborations with industry and advocacy groups—including for "high-risk high-reward" investments that are supported early on by NIH—were also appreciated by the panel for their value in facilitating precise intervention development. Requests for proposals (RFPs) that mandate such partnerships may be beneficial, because some panelists pointed out that grant applications with collaborative components are sometimes rejected by study sections on the basis that industry partners should foot the bill. The panel cited ADNI and the FNIH Accelerating Medicine Partnerships (AMPs) as exemplary partnership models.

Panelists also discussed funding mechanisms to support the development of precision interventions and was largely supportive of translational center grants such as the U54 mechanism or the FDA Pediatric Device Consortia Grants Program. These sorts of mechanisms would fund centers that in essence serve as accelerators, providing core services and supports to candidate interventions at the center's discretion more quickly and efficiently than traditional funding mechanisms. Unlike Small Business Innovation Research (SBIR) or Small Business Technology Transfer (STTR) grants, this funding would be available to a broader group of intervention developers (e.g., academic researchers). The panel took special note that these funding mechanisms must be widely disseminated to encourage diversity of applicants and ideas.

Testing and Evaluating

During the main discussion, the panel defined the goal for the testing and evaluating category:

> "The goal here is [to] design clinical trials, big data analytics (including deep learning and machine learning), and other experiments that leverage more advanced strategies to evaluate efficacy of interventions in ways that illuminate efficacy not just in the aggregate, but in ways that better explore the impact on patients, including setting, dose, [and] timing. It might include things like bucket, platform, or other adaptive trials; n of 1 trials; implementation and de-implementation studies; and identifying gaps in outcome determination across phases."

Regarding testing and evaluating more precisely, panelists discussed types of "human and pre-clinical studies that iteratively leverage advanced strategies to evaluate efficacy and effectiveness of interventions." The panel emphasized that innovative trial designs—including master protocols for bucket, umbrella, platform, or other adaptive trials—should be a priority for upcoming NINDS efforts for therapy development. N of 1 studies that leverage intrapatient evaluations (e.g., pre- and post-treatment tests) were similarly recognized as useful by the panel and as related in essence to the natural history studies that the panel promoted. Currently, inherent constraints on adaptive clinical trial designs exist by virtue of the requirement that grant applications present the "most expensive version" of how the trial may proceed; thus, more flexible funding mechanisms (e.g., funding with milestone requirements) are warranted to promote the adoption of these designs.

The panel also agreed that one crucial way in which NINDS can assist with more precise testing and evaluation during therapy development is to establish standardized endpoints that will be referenced across industry, academia, and the FDA. This universal agreement will assist with comparisons of trials across populations and investigators.

The panel emphasized that thorough training in scientific methods and rigor will be essential to the success of these innovative trial designs and that the community must take care not to allow pragmatic trials to become a "euphemism" for less rigorous. Full discussion of training considerations was omitted because it was considered to be the primary charge of other NINDS Strategic Plan Discussion Groups (i.e., Training and Diversity); however, the panel noted that such considerations were highly relevant to all suggestions that arose during these discussions and could be a limiting factor for success at every stage of therapy development.

Finally, the panel noted that the inclusion of preclinical studies in the scope of its suggestions for more precise testing and evaluating of therapy development encompasses standardization of animal models. Multiple panelists expressed hesitation at allowing the field to overly rely on animal models for therapy development and would prefer more methods for performing safe and effective experiments in patients directly. However, overall the panel agreed on the importance of not creating an "artificial division of pre-clinical and clinical" work in this domain, because they should mutually inform each other in an iterative fashion.

The panel supported establishment of more preclinical screening centers of excellence to improve the transition of therapy development from the preclinical to the clinical stage, and believed that NINDS could leverage its current funding of animal model development to this end. These centers can give investigators in academia and industry access to appropriately relevant animal models that they might not otherwise have. Furthermore, these centers can help to mitigate the reproducibility problem because animal models can be evaluated, calibrated, and standardized in an unbiased and centralized manner. In addition, these centers can be a hub for developing and disseminating guidance regarding best practices and use cases of animal models within therapy development, as well as a home for training programs in statistical and scientific rigor and experimental design.

Therapy Development Panel Roster

Frank Bennett, PhD
Executive Vice President & Chief Scientific Officer
Ionis Pharmaceuticals

Lucie Bruijn, PhD
Senior Director, Translational Medicine, EMEA
Novartis Gene Therapy GTX

Doug Cole, MD
Managing Partner
Flagship Pioneering

Nita Farahany, JD, PhD
Robinson O. Everett Professor of Law
Professor of Philosophy
Duke Law School

Christopher Flores, PhD
Vice President, Neuroscience Therapeutic Area
Janssen Pharmaceutical Companies of
Johnson & Johnson

Elizabeth Garofalo, MD
Principal
EAG Pharma Consulting

Rebecca Hammond, PhD
Director, Scientific Communications & Research Operations
Sage Therapeutics

Duncan Maitland, PhD
Stewart & Stevenson Professor I
Department of Biomedical Engineering
Texas A&M University

Ingo Mellinghoff, MD
Acting Co-Chair & Vice Chair for Research
Department of Neurology
Memorial Sloan Kettering Cancer Center

Dominique Pichard, MD
Chief Scientific Officer
Rettsyndrome.org

Rema Raman, PhD
Professor of Neurology
Director, Biostatistics Core
Alzheimer's Therapeutic Research Institute
University of Southern California

Alfred Sandrock, MD, PhD
Executive Vice President, Research & Development
Biogen

Robert Silbergliet, MD
Professor
Department of Emergency Medicine
University of Michigan Medical School

Susan Slaugenhaupt, PhD
Scientific Director
Mass General Research Institute
Professor of Neurology
Harvard Medical School

Barbara Slusher, PhD
Director, JHU NIMH Therapeutics Core
Professor of Neurology
Johns Hopkins University

Olajide Williams, MD
Associate Professor
Department of Neurology
Columbia University