Advancing Fundamental Neuroscience Research: Report of the Fundamental Neuroscience Working Group of the National Advisory Neurological Disorders and Stroke (NANDS) Council

September 22, 2023

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Executive Summary

Research on the development, structure and function of the normal nervous system, or fundamental neuroscience (FN), is the foundation of the NINDS mission. In 2022, NINDS convened a Fundamental Neuroscience Working Group (FNWG) to discuss key issues in FN and prepare recommendations to the National Advisory Neurological Disorders and Stroke (NANDS) Council. The enclosed report is aimed to inform NINDS approaches and plans to support and advance research in FN. The Working Group was charged in January of 2023 to: 1) look to the future of FN by identifying critical gaps, key unanswered questions, and new opportunities in FN research, 2) evaluate the effectiveness and potential of current NINDS programs to support the breadth of FN research, and 3) propose and prioritize concepts and strategies with the potential to enhance the overall impact of NINDS FN research over the next 5-10 years.

The FNWG was encouraged to focus their deliberations on the biggest unanswered questions of basic neuroscience, and to identify areas where timely stimulus or activities led by NINDS might effectively catalyze neuroscience research across the board. The Co-Chairs, in consult with NINDS staff, focused on cellular and molecular questions in the core recommendations in recognition that this area has not been included in ongoing, existing initiatives, but is one where catalytic opportunities could accelerate discovery across neuroscience. After extensive deliberations and obtaining feedback during a public webinar held in July 2023, the recommendations here were presented to the NANDS Council on September 6, 2023.

Four of the six recommendations emphasize gaps in availability of transformative resources and tools to inform understanding of the mechanisms of neurobiological processes of brain development and function at the molecular and cellular level. FNWG recommends support for the concept of "Macromolecular Cartography" to map and track subsets of proteins known to be part of functional subcellular units. The working group also recommends support for quantitative approaches to characterize protein and molecule turnover timescales, development of approaches for capturing and imaging cell movement and cell-cell interactions, and resourcing of tool development for in vivo measurement of cellular activity. Such approaches would serve to advance mechanistic studies of the central and peripheral nervous system, including investigator-initiated studies of neuronal, glial, and immune cells, spanning across the lifespan and using many different model systems. The final recommendations highlight additional opportunities to ensure the health of FN research. These include promotion of interdisciplinary team science and collaborations with technical expertise across diverse disciplines, and importantly, supporting mentoring of the next generation of FN researchers.

Purpose of the Fundamental Neuroscience Working Group

The mission of the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH), is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease for all people. Research on the development, structure, and function of the normal nervous system, or fundamental neuroscience (FN), is the foundation for achieving that mission.

To address this important component of the research portfolio, NINDS convened a Fundamental Neuroscience Working Group (FNWG) of the National Advisory Neurological Disorders and Stroke (NANDS) Council to hold a series of meetings to discuss key issues and prepare a report to the NANDS Council with recommendations to inform NINDS approaches and plans to support and foster FN research.

Working Group Charge

The Fundamental Neuroscience Working Group (hereafter referred to as the FNWG) was tasked to provide scientific guidance via NANDS Council to NINDS on how best to advance FN research.

The charge of the FNWG was to:

- **Look to the future of FN** by identifying critical gaps, key unanswered questions, and new opportunities in FN research.
- **Evaluate the effectiveness and potential of current NINDS programs** to support the breadth of FN research.
- **Propose and prioritize concepts and strategies** with the potential to enhance the overall impact of NINDS FN research over the next 5-10 years.

Working Group Roster

The Working Group included two members of the NANDS Council* and other investigators with expertise in fundamental neuroscience research.

Yishi Jin*, Ph.D. (Co-Chair), *Kavli Institute of Brain and Mind, University of California, San Diego*
Timothy Ryan*, Ph.D. (Co-Chair), *Weill Cornell Medical College, Howard Hughes Medical Institute*
Bruce Bean, Ph.D., *Harvard Medical School*
David Clapham, M.D., Ph.D., *Janelia Research Campus, Howard Hughes Medical Institute*
Marc Freeman, Ph.D., *Vollum Institute, Oregon Health & Science University*
José E. García Arrarás, Ph.D., *University of Puerto Rico, Río Piedras Campus*
Alicia Dione Guemez-Gamboa, Ph.D., *Northwestern University*
Shantá Hinton, Ph.D., *William & Mary*
Oliver Hobert, Ph.D., *Columbia University, Howard Hughes Medical Institute*
Sarah Kucenas, Ph.D., *University of Virginia*

Rejji Kuruvilla, Ph.D., *Johns Hopkins University*
Wendy Macklin, Ph.D., *University of Colorado*
Kelsey Martin, M.D., Ph.D., *Simons Foundation*
Linda Richards, AO, FAA, FAHMS, Ph.D., *Washington University in St. Louis*
Amita Sehgal, Ph.D., *University of Pennsylvania, Howard Hughes Medical Institute*
Weiwei Wang, Ph.D., *University of Texas Southwestern Medical Center*

Timeline

The FNWG met monthly via Zoom over 8 months in 2023. Meetings occurred:

1. January 27 (kickoff meeting)
2. February 17 (defined goals and formed subgroups)
3. March 17 (subgroup discussion)
4. April 21 (subgroup discussion)
5. May 19 (reached consensus - identified common themes, gaps, and opportunities)
6. June 16 (created draft recommendations)
7. July 27 (public webinar followed by closed session to consider input received at the public webinar)
8. August (The FNWG completed their formal deliberations, including consideration of public input sent to fn@nih.gov by August 1, 2023, via email)

On September 6, the FNWG presents its draft report and recommendations to the NANDS Council.

Process and Deliberations

The FNWG addressed the following specific goals:

- Identify opportunities that NINDS could take to facilitate innovation and enable discoveries that are not currently addressed in FN.
- Consider specific recommendations to optimize or enhance current NINDS programs in support of the FN research mission.
- Evaluate how NINDS might support the development, refinement, dissemination, and broad use of next generation technologies, approaches, or resources to open new areas of exploration.
- Present a report of findings stemming from the above charge to the full NANDS Council on September 6, 2023.

Fundamental neuroscience encompasses a broad area of research interests and levels of study and NINDS actively supports all these areas. With an eye towards new advances, the FNWG decided to focus on the areas of cellular and molecular neuroscience as the most suitable for making a meaningful impact (elaborated below). After establishing this focus, subgroups of the FNWG considered key questions across seven topic areas as part of the FNWG deliberations (see Table 1).

Table 1. FNWG-considered topic areas and subgroup members

Topic area	Subgroup members
1. Development	Linda Richards, Rejji Kuruvilla, Shantá Hinton
2. Genomic organization and regulation	Alicia Guemez-Gamboa, Oliver Hobert
3. Inter-tissue interaction	Marc Freeman, José García Arrarás, Sarah Kucenas
4. Metabolism	Tim Ryan, Amita Sehgal
5. Lipid stasis	Yishi Jin, Wendy Macklin
6. Atomic organization of machinery	Bruce Bean, Weiwei Wang
7. Subcellular organization of machinery	Kelsey Martin, David Clapham

Each subgroup considered the following four key questions (See Table 2):

1. What are the critical knowledge gaps in the topic area?
2. How can we foster FN mechanistic investigation in the topic area?
3. What are the technology choke points in the topic area?
4. What are perceived funding difficulties?

Table 2. Snapshot of FNWG subgroup deliberations and findings

Key questions	Subgroup deliberations and findings
1. What are the critical knowledge gaps in the topic area?	• **Development, inter-tissue interaction** – How do all cell types interact and communicate to shape the fate of other cells and to maintain and adapt to change in adults? – How to promote increased study of the peripheral nervous system? – How can improved *in vivo* imaging of developmental processes over time elucidate which cells and signals coordinate development? • **Genomic organization and regulation** – How do multiple molecular pathways interact to change the function of a system? – How to promote or generate more productive action on big "lists" generated from genomics data? • **Metabolism, lipid stasis** – What are the metabolic rules that govern brain functions and subsequent animal behavior? – How is metabolism integrated with key signaling pathways? – How does lipid signaling *in vivo* drive neural function (e.g., synaptic plasticity)? – What are the decision points that trigger building or arresting lipid membrane recruitment to support healthy neuronal function? • **Subcellular organization, atomic organization**

	– What are the protein networks that produce coordinated subcellular organization? – How can they be identified at high resolution within cells to measure protein interactions over time? – How is compositional spatial specificity achieved in higher-order ion channel/receptor clusters?
2. How can we foster FN mechanistic investigation in the topic area?	• Prioritize the need to understand basic biology first rather than, focus on disease by, emphasizing basic cell biology, neuronal metabolism research, and *in vivo* electrophysiology. • Foster collaboration of neuroscientists with biochemists, cell biologists, metabolism and function researchers, engineers, and other experts to support methodological development research. • Encourage use of non-traditional model systems to study basic cell biological processes relevant to neurons and embrace more exploratory science.
3. What are the technology choke points in the topic area?	• Robust and accurate indicators with good temporal and spatial resolution to measure and track signaling cascades. • Sensors for every pathway, particularly genetically encoded sensors, and tools to manipulate sensors *in vivo* with functional readouts from signaling events.
4. What are the perceived funding difficulties?	• More experts for evaluating curiosity-driven technology development and research. • Equitable access to state-of-the art imaging and core facilities. • Sustained support for staff scientists.

Subsequently, the full FNWG convened to incorporate the subgroups' recommendations and to identify cross-cutting themes. The full FNWG discussed research and resource gaps common across the different fundamental cellular and molecular neuroscience topic areas. FNWG deliberated on crucial unanswered neuroscience questions, current FN resources, the state of the FN research enterprise, promoting career opportunities in FN, current NINDS funding strategies, and challenges to obtaining steady support for FN research. Meeting summaries were used to create the initial draft recommendations, which were discussed and revised by the full FNWG.

Recommendations

How the nervous system develops, functions, and is maintained over the life of an organism has fascinated scientists for centuries. Despite the tremendous progress made in deciphering arguably the most complex organ system, the FNWG identified many remaining gaps in fundamental knowledge. In particular, the FNWG focused on information gaps at the cellular and molecular scales, including: 1) How is metabolism regulated in the brain at the cellular and network level and how does it integrate with key signaling pathways? 2) How do macromolecules interact with each other within cells to form higher-order conformations and how does this architecture modulate function? 3) How do the many

cell types in the nervous system interact? and 4) How does the nervous system change over organismal lifespan and evolutionary timescales? These cellular and molecular gaps in turn hinder understanding of cellular physiology in its native context, i.e., the living brain/organism.

Why Cellular & Molecular Neuroscience?

The Working Group's choice to focus on cellular and molecular questions in our core recommendations is based in part on what we perceive as areas where we expect technological breakthroughs to make dramatic advances in the coming years and in part because existing initiatives (for example The *Brain Research Through Advancing Innovative Neurotechnologies*® [BRAIN] Initiative) are already catalyzing advances in other areas of neuroscience research. For example, progress in systems neuroscience research has dramatically accelerated thanks to a confluence of technical advances over the last decade, including emerging technologies to control single cell activity (channel-rhodopsins, DREADDS, etc.) and to record activities on large scales (GCaMP, Neuropixels, GRIN lens-based microscopes and mesoscopes). Within this framework, the accurate interpretation of systems research requires a deeper understanding of the organization of those circuits (i.e. what cells form synaptic connections with each other). This question is the motivation for mapping the connectome of various brain regions.

Technology Development and Cross-Disciplinary Approaches

Inspired by how technology has driven new approaches in systems neurosciences, we feel the time is ripe to similarly propel cellular and molecular neuroscience research. Advances in genetically-encoded optical sensors have led to many more investigators designing and deploying sensors for a myriad of analytes. The accelerating pace of technological improvements in sensor design and utility suggests that many previously unattainable measures of intracellular analytes will become feasible. However the precise interpretation of intracellular recordings requires a detailed understanding of how protein machineries are organized on their operational spatial scale. The organization of proteins, RNAs, metabolites, and lipids within the specialized architecture of any resident cells of the nervous system is poorly understood and makes interpretation of genetic clues associated with diseases challenging. A better understanding of cell physiology, and the origins and consequences of its dysregulation, necessitates that its organization and functional principles be understood at different length scales, from tens of nanometers to millimeters and centimeters, as well as at different timescales, from physiological processes to an organism's lifespan.

To achieve these goals, the FNWG agrees that the development of new tools, together with enhancing cross-disciplinary interactions with experts in cell biology, protein chemistry, biophysics, metabolism, and other fields, are essential to enable mechanistic leaps in our understanding of the development and function of the nervous system. The FNWG also identifies several opportunities to enable significant advancements in FN research and recommends dedicated efforts in the following areas: macromolecular cartography; quantitative approaches to characterize protein/molecule turnover timescales and location *in vivo*; capturing and imaging cell movement and cell-cell interaction during nervous system development; and tool development for *in vivo* measurement of cellular activity. Two additional recommendations call for the incentivization of collaborations with experts outside of

neuroscience, paired with sustained support for technical experts and shared resources, and support for mentoring the next generation of FN researchers.

1. **Prioritize research into the organization of macromolecular complexes within cells from a few nanometers to one micron in length by developing tools and research programs to create a dynamic Macromolecular Cartography that analyzes subsets of proteins known to be part of functional subcellular units.**

   When electron microscopy emerged as a tool in cell biology seven decades ago, the first images of organelles on the mesoscopic subcellular scale fueled the next generation of experiments with a new intellectual framework of how to understand the cellular milieu. Three decades later, the first sets of synaptic proteins were identified through biochemical purification and the identification of their geographic location within neurons fueled discovery. However, we lack detailed knowledge of how molecules are organized on the mesoscale for much of the proteome of nervous system cells. An information gap persists regarding the organization of macromolecular complexes within cells in the few nanometers to one micron length scale. This gap leads to a "black box" view of the cell in which researchers must infer the functional role of protein complexes, signaling cascades, and pathways without understanding their supramolecular organization, providing an often incorrect or incomplete understanding.

   Knowledge of the detailed distribution of a given molecule or protein is central to unravelling how it coordinates cellular functions, so much insight can be gained from carrying out a detailed mapping of molecules on cellular structures and interrogating their functionality in brain cells, referred to as Macromolecular Cartography. Analogously to how electron microscopy propelled novel thinking about cell biology, the FNWG anticipates that Macromolecular Cartography will shepherd in a new era of molecular understanding of the nervous system.

   Mapping the organization of molecules on the several nanometer scale in the context of cells that span millimeters or centimeters has traditionally been an intractable problem. In the last decade, however, advances in several complementary technologies have made accessing this level of information possible. These advances include better molecular engineering tools (CRISPR), affinity reagents (Halo and SNAP tags, as well as custom-designed nanobody antigens), proximity ligation assays, and super-resolution and expansion microscopy, as well as efficient methods for combining fluorescence approaches with electron microcopy (CLEM).

   For Macromolecular Cartography, the FNWG recommends the analysis of subsets of proteins that are known to be part of functional units with the ultimate goal of understanding how molecular organization enables function, and how this dynamically changes in different physiological contexts *in vivo*. Ideally, the initial focus would be in cell types where these proteins have a known physiological role amenable to deep functional analyses. Below are several examples of functional units that could be approached in this way,:

a) Cell signaling and/or ion channel complexes at the membrane such as examining the detailed subcellular distribution of G-protein-coupled receptors, and downstream G-proteins and modulators

b) Bioenergetic and other metabolic enzymes such as a detailed mapping of the distribution of key enzymes used for glycolysis and the pentose phosphate pathway and their relative positioning with respect to mitochondria or other organelles within specific subcellular milieus, such as dendrites, spines, axons, nerve terminals. and how this compares with glial cells

c) The fatty acid synthesis enzymes, triglyceride assembly machinery, and lipases

d) The machinery for protein and organelle turnover such as autophagy enzymes and proteosomes

For all these units, it is critical to understand not only their static subcellular localizations but also changes in localization. This will require the development of technologies to visualize the dynamics of molecular interactions and trafficking within cells.

2. Enable quantitative approaches to characterize protein and molecule turnover timescales and location *in vivo* to advance understanding of molecular interactions their contribution to cellular stability and plasticity.

Cells in the nervous system, particularly neurons, have very little, if any, turnover. How these cells integrate and stabilize different molecules and macromolecular complexes remains a mystery. To understand how cells and circuits are stabilized or structurally plastic and the role of protein-protein interactions in these events, the field needs rich spatial quantitative protein information across developmental stage and cell types, as well as during cell-cell signaling. Recently, the first estimates of how the neuronal protein PSD95 turns over in different brain regions has been determined using a combination of CRISPR tagging and self-labeling Halo tags that use pulse chase fluorescent labels of different colors. This approach demonstrates that it is possible to obtain estimates of local protein turnover over time in a spatially defined fashion. The FNWG encourages further technical development in this area that will allow this approach to be deployed as broadly as possible. Integrating this information with Macromolecular Cartography will enhance fundamental knowledge of cellular stability and plasticity.

3. Support approaches for capturing and imaging cell movement and cell-cell interaction during development of the nervous system.

The cellular and physiological complexity of the nervous system is remarkable and daunting. Understanding how the development of the central nervous system's neurons, glia, vascular and immune cells, and other supporting cells is coordinated across spatial- and timescales is an unmet and crucial goal. A more comprehensive understanding of the cellular mechanisms that drive development, coordinate morphogenesis by signaling to other cells, and assemble neural tissue is essential.

The FNWG notes that this same understanding is required of the peripheral nervous system, which has been historically understudied. Its connection to the central nervous system and integration of all sensory modalities makes it an intriguing system in which to study how the two halves of the nervous system develop and function and how they differ in their capacities for plasticity and regeneration. Improved understanding of the peripheral nervous system will also provide new insight into how innervation is coordinated with organogenesis during development and how the nervous system controls bodily functions.

Additionally, the FNWG emphasizes that researchers who work with model, simple, or non-canonical system, are poised to rapidly elucidate key early developmental processes in the central and peripheral nervous systems and use those findings to illuminate evolutionarily conserved mechanisms in humans. Visualizing these *in vivo* developmental processes, such as neural crest migration, developmental apoptosis, axon pathfinding and branching, circuit formation, and formation of structures like the blood brain barrier, is necessary to provide the foundation for hypothesis-driven mechanistic studies on developmental regulation. The FWNG also recognizes that although techniques such as single cell-transcriptomics have vastly improved our understanding of neural development, these studies should be followed by mechanistic studies to define the specific molecular pathways that underlie the development of neuronal populations and their interactions with other cell types.

4. Ensure adequate resourcing of tool development for *in vivo* measurement of cellular activity.

To make fundamental discoveries about the nervous system and gain mechanistic insight into how it develops, functions, and is maintained, novel tools need to be developed to give researchers unprecedented access to the cellular physiology of the *in vivo* brain. The toolkit for imaging neuronal activities has expanded significantly during the last decade with the development of genetically encoded sensors for Ca^{2+}, cAMP, and voltage, as well as several fast- and slow-acting neurotransmitters. The development of GCaMP for imaging neuronal activity is an example of successful collaboration between tool developers and users that enabled rapid improvement in GCaMP design, validation, *in vivo* experimental use. These imaging tools need to be complemented by "ground-truth" electrophysiological recording of activity in developing brains that provides greater fidelity than EEG measurements. These recordings are technically challenging and will require the development of new types of recording apparatus and techniques. Moreover, as described below, there are limited tools and sensors for many processes across whole cells or cellular compartments. The FNWG recommends that greater time and financial resources should be invested to foster interdisciplinarity between neuroscientists and biochemists, cell biologists, metabolism researchers, engineers, geneticists and other experts working on non-canonical model organisms. Collaborations with other Institutes, such as the National Institute of Biomedical Imaging and Bioengineering (NIBIB), could be necessary to such a tool-building effort. The FNWG further considers that developing transformative new tools to track metabolites and lipid flux could be essential for fundamental molecular breakthroughs:

4.1. Encourage the development of tools for tracking metabolites in the brain.

Metabolism is closely intertwined with cognitive states as human brains are acutely sensitive to interruptions in fuel supply. Molecules that were previously thought of as simple bioenergetic intermediates are now also appreciated as crucial signaling molecules. Altered brain metabolism is also considered a precursor to the eventual onset of neurodegeneration. Yet, metabolism in neural tissue is much less understood than in other tissues owing in part to the architectural and cell type complexity in the brain and in part to the relative inaccessibility of the nervous system. Thus, standard metabolic measurement techniques are difficult to deploy and interpret in brain tissue. The development of genetically encoded sensors for a suite of key metabolites which, when successful, will allow subcellular tracking of metabolites of individual cells in intact or semi-intact brains is ripe for technical advances. Although some sensors for glycolytic metabolites such as glucose, ATP, pyruvate, lactate, and NAD+ have been developed, these are limited in scope and in general require significant optimization to allow for both accurate quantification and unambiguous interpretation of signals. In addition to the metabolites mentioned above, the toolkit should be expanded to allow real-time detection of metabolites that are known to serve as critical intersection points between anabolic and catabolic pathways, or cell signaling pathways. Examples include: phosphogluconate, now thought to provide feedback signals between glycolysis and the pentose phosphate pathway; NADPH, a critical regulator of redox control; and intermediates of the TCA cycle that lie at the intersection of anaplerosis and cataplerosis such as citrate, fumarate, α-ketoglutarate, and oxaloacetate.

4.2. Encourage the development of *in vivo* sensors for tracking lipids in cellular compartments.

Like metabolites, lipids play essential roles not only in building cellular architecture but also in cellular signaling and repair. Identifying lipid species and composition in each cell type is challenging. Recent technological advances in spatial lipidomics offer some hope and further development should be encouraged. Neurochemists are developing photoflippable lipids that use azobenzene bonds and can be driven to specific cellular localization via SNAP-tag and “click chemistry.” This could begin to address the unknown mechanisms underlying intracellular lipid signaling. Tools for tracking lipid flux *in vivo* with subcellular resolution are also limited. Available sensors for several phospholipids are somewhat useful and may be optimized and expanded to other lipid species. Fluorescently tagged cholesterol derivatives are currently available for fixed tissue, but novel cholesterol derivatives are needed for *in situ* analysis; for example, alkyne-cholesterol analogs that can be labeled with fluorophores by click chemistry. As most lipid sensors have only been tested *in vitro* or in cell lines, close collaborations between neuroscientists and chemists would be beneficial and necessary in this tool-building effort.

5. **Promote interdisciplinary team science and collaborations with technical expertise across diverse disciplines.**

   Much of the proposed research work will require team science involving neuroscientists, chemists, engineers, and others who can develop novel approaches to understanding the development and function of the nervous system. In this endeavor, sustained support for technical experts, such as scientists engaged in tool development or in supporting science infrastructure facilities, was also identified as key to ensuring the continued success of FN research. Such investigators can identify crucial technical and other non-hypothesis driven approaches to understanding the nervous system and must be supported by both NIH funding and recognition at their home institutions. To incentivize collaborations with outside experts, shared funding mechanisms could be developed with other NIH Institutes and the use of high-end equipment core facilities could be expanded.

6. **Support the mentoring of the next generation of FN researchers.**

   The rapid creation of knowledge in the field of neuroscience mandates that we must cultivate and expand the training that supports the FN enterprise. The field's ability to address basic questions of the development, maintenance, and function of the nervous system needs scientists with diverse perspectives and skill sets. Sustaining an innovative workforce for any discipline requires cultivating and trusting the next generation to bring their authentic selves and understanding that this is how excellence is achieved. It will be vital to allow these young researchers to continue being interdisciplinary by reaching across disciplines to solve problems and develop new technologies to address basic, translational, and clinical questions about the brain and the nervous system.

   Many undergraduates start their research career as a scientist at a liberal arts institution and are exposed to various disciplines. However, once they matriculate into graduate programs they immediately must specialize; so much so that they are forced to leave behind questions that cut across academic disciplines in innovative ways. It is these interdisciplinary questions and perspectives that are needed to make profound leaps forward in our understanding of the brain. For this reason, the FNWG recommends that NINDS invest in a diverse pipeline of future FN researchers and leaders that are broadly trained across disciplines, including at the undergraduate level. This will build and empower a nimble and creative workforce of the future capable of asking and answering questions that lead to transformative advances in human knowledge.

Concluding remarks

Description is the foundation of scientific endeavors, and descriptive analyses have always been a critical element of biology. It is also the first step towards developing a mechanistic understanding of biological processes. The FNWG recommends that parallel efforts be made in the coming years to deepen our descriptive abilities in exploring the molecular mesoscale of the cellular milieu of the cells of the nervous system, and to develop better tools that allow us to measure molecular perturbations as well as the dynamics of key cellular analytes. We foresee that the technical advances of the last decade will help spur progress towards a fundamental mechanistic understanding of the cellular and molecular machineries that make up the nervous system.

NANDS Council Deliberation

The Working Group Co-Chairs presented the findings and recommendations in this report during the open session meeting of the NANDS Council on September 6, 2023. All Council members voted to accept the report's recommendations. In their discussion, Council members provided feedback in support of the FNWG's thoughtful deliberations and overall recommendations. Council members also echoed the importance of highlighting FN and supporting trainees to pursue FN research. In addition, Council members posed several challenging ideas for NINDS to consider while formulating plans for implementation. Some Council members felt that targeting aspects of cellular and molecular neuroscience, or any specific research area, should not detract from NINDS' clear focus on investigator curiosity-driven research approaches that are spontaneous and untargeted. A suggestion was made to change the title of the report to clarify the focus on cellular and molecular research. There was overall consensus that while considering this report NINDS should also continue to message clearly that all areas of neuroscience are important, regardless of whether the research could be directly translational. Another concern raised was that the compiled recommendations call for emphasis on descriptive research studies and whether that approach can be reconciled with the need for hypothesis testing to answer key biological and mechanistic questions. Finally, Council members noted the potential costs of implementing all the proposed recommendations, and discussed how NINDS might balance financial support for tool development with support for open research approaches in an era of potential budget constraints in the coming years.

Appendices

I. FN topics covered in the NINDS Division of Neuroscience

Fundamental Neuroscience (FN) research, defined here as research to understand the structure and functions of the normal nervous system over the lifespan, is the cornerstone for scientific advances underlying neurological health and therapeutic development and clinical care for all neurological conditions and diseases. The NINDS supports hundreds of research grants and programs each year in FN, with an emphasis on investigator-initiated proposals that do well after scientific review. FN topics are covered in the Division of Neuroscience, while disease related topics are covered in the Division of Neuroscience, the Division of Translational Research, and the Division of Clinical Research at NINDS.

The Division of Neuroscience supports grant applications on a broad range of FN topics, including:

- Molecular determinants of normal neurodevelopment and function including early embryonic neural development; neural crest and neural tube development; neurogenesis and cell fate determination; cell migration; axonal guidance; and neurotrophic factor signaling.
- Cellular and molecular studies of nervous system signaling in relation to electrical excitability and inter-cellular communication.
- Structural and functional studies of molecules underlying neural signaling, including ion channels, neurotransmitter receptors and transporters, synaptic vesicle and synaptic scaffolding proteins, and intracellular signal transduction cascades.
- Cellular and molecular mechanisms of synaptic transmission, synaptic modulation and plasticity, and synapse formation and development.
- Neural plasticity in the adult nervous system.
- Stem and progenitor cell biology in the development and repair of the nervous system.
- Basic studies of chromatin, and transcriptional and translational regulation in the central nervous system (CNS).
- Oligodendrocyte and Schwann cell development, function, and myelination
- Role of glial cells (e.g. astrocytes, microglia, oligodendrocytes) and other non-neuronal cells (e.g. endothelial cells, invading cells of immune origin) on the structure and function of the nervous system, including glial cell biology in model organisms.
- Integrative and quantitative approaches in systems neuroscience.
- Studies of neural circuits and systems that mediate motor control, sensory processing, nociception, and cognitive activities.
- Research on neurological mechanisms including quantitative studies of neurological processes that can impact complex behaviors such as language, cognition, sensation, perception, movement, sleep, and response to pain.
- Research in homeostatic regulation of cyclic and appetitive behaviors such as sleep, activity, feeding, and drinking.

- Studies of the blood-brain-barrier, neurovascular unit, and basic cerebrovascular biology, including mechanisms of blood-brain and brain-CSF barrier functions and the entry and exit of cells, factors, molecules, and compounds via the intact and compromised barrier.
- Vascular mechanisms of CNS function and blood flow regulation.
- Technology development for neural signaling research, including genetic models, tools for analyzing or manipulating gene expression and function, tools for manipulating cell signaling, and new techniques for structural studies of membrane proteins and protein interactions.
- Development and use of neurotechnology for sensing and modulating neural activity.
- Application of novel tools and methodologies for system approaches, including optical recording, optogenetic control of neural circuits, neuroimaging, neuroinformatics, advances in *in vivo* recording and stimulation techniques, and methods for analysis of complex neural signals.

II. Overview of NINDS FN Research Funding Trends over Time

The vast majority of NINDS funding for FN Research is supported through Investigator Initiated applications that are submitted to open Research Project Grant (RPG) Funding Opportunities. Standard RPG applications are assigned to subject area Integrated Review Groups in the Center for Scientific Review, where they receive an impact score from the assigned Study Section. Funding recommendations are made as annual appropriations allow, based heavily on the impact score and percentile as described on the NINDS funding strategy website.

The percentage of funded NINDS grants that support FN (basic / basic) research has remained stable since 2012.

All funded NINDS grants are manually coded by Program staff using the following Basic/Applied Coding Definitions and Usage Rules:

1. **Basic Research:** Aimed at understanding the structure and function of the nervous system.
   - **Basic / Basic Research:** Research to understand the normal nervous system, whether in vitro, in animals, or in humans.
   - **Basic / Disease-Related:** Research on understanding disease and disease mechanisms, and research that derives its primary rationale from diseases whether in vitro, in animals, or in humans.

2. **Applied Research:** Research to develop or test diagnostics, therapeutics, or preventive interventions, whether in animals, humans, or in vitro. Includes all stages of development from proof of concept in disease models to human clinical trials.
   - **Applied / Translational Research:** All studies up to (but not including) first in human studies.
   - **Applied / Clinical Research:** All applied research in humans from first in human studies through phase III trials.

Usage Rules:

Program staff categorize the research types within each application. The data are reported in 25% increments for each award and % are based on the goal of each specific aim with respect to the four Basic/Applied subcategories. More details on this coding approach and methods can be found here.

Figure 1

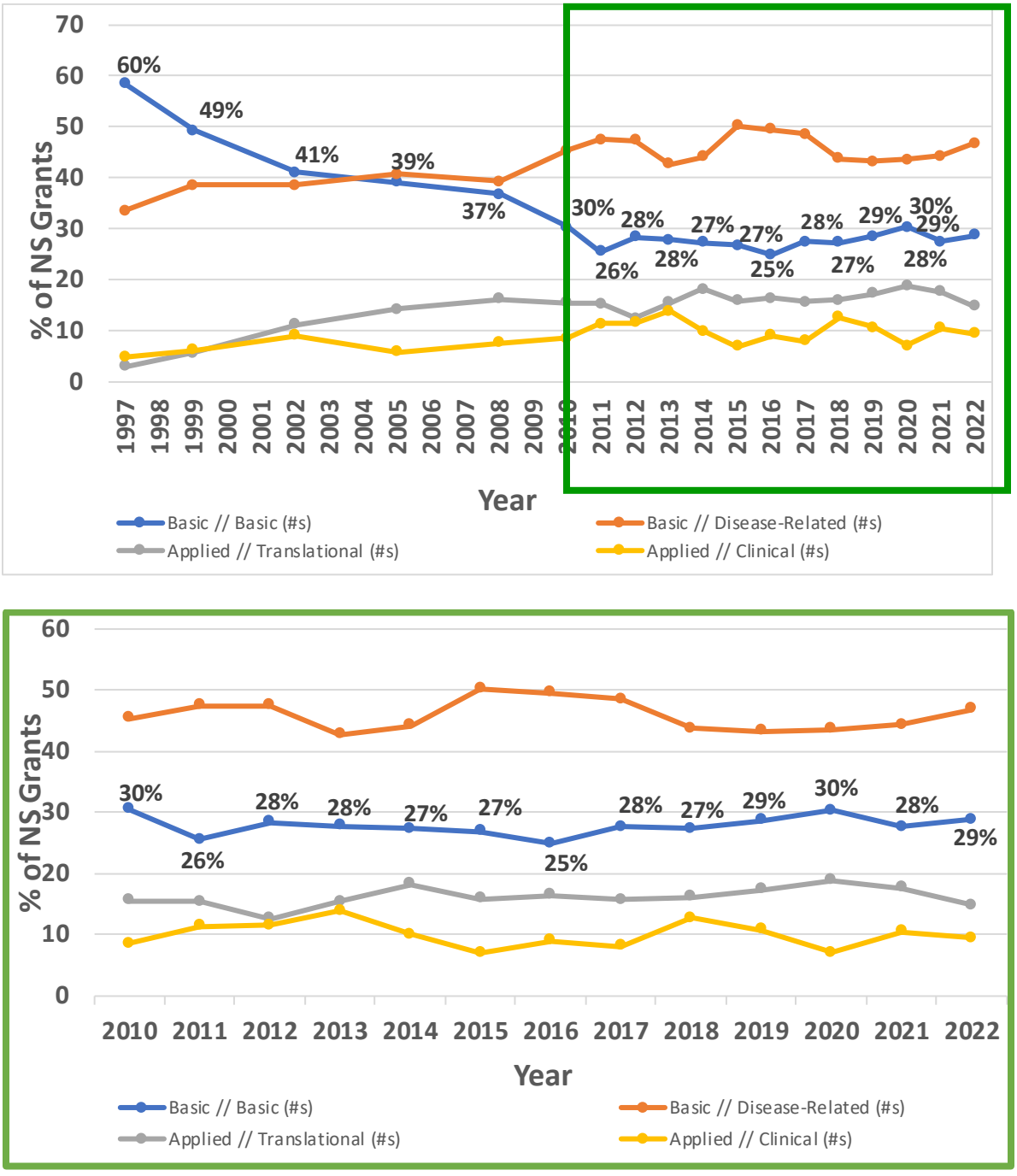

Figure 1: The Percentage of Funded Basic / Basic RPGs has remained Relatively Stable since 2012. The percentage of NINDS competing awards in each of the four coding subcategories from 1997 to 2022. Coded basic / basic research as a % of the total showed a steep decline from 1997 to 2011 from almost 60% to less than 30%, while the percentage of awards issued for basic / disease and applied research categories increased. The relative funding for basic / basic research has been steady at 25-30% of total awards since 2012. Data includes all RPGs (R01 and RF1 (~49-62%), R21 (~20-26%), others (~16-25%). For last 10 years (2013-2022) NINDS has awarded an average of 896 RPG awards each year.

III. NINDS Funding Opportunities that Support FN Research

1. NINDS supported FN through a targeted program announcement with Set Aside Funds (PAS) from 2016-2022

Promoting Research in Basic Neuroscience, PAS 15-029, and its reissue PAS 18-483, extended the typical NINDS pay line for R01 awards that were 100% basic / basic by 2-4%, from 2016 -2022 (the last receipt date was for October council 2021). The goal of this Program Announcement with Set-aside Funds (PAS) was to stimulate research addressing fundamental questions in basic neuroscience. Proposed projects could address any area of neuroscience within the mission of NINDS that focused on understanding the development, the structure, and/or the function of the normal nervous system. Although fundamental basic research often generates insights relevant to disorders of the nervous system, this PAS was not intended to stimulate research that is explicitly disease related. Tool development was of secondary importance. All applications went to standing study sections. $5 million was set aside annually, which funded approximately 12-15 additional R01s that were 100% basic / basic and scored outside of the typical NINDS pay line. For each council, NINDS R01 applications were considered if they responded directly to the PAS or to the parent R01 announcement and were 100% basic / basic and 5-6% outside of the typical NINDS pay line.

Figure 2

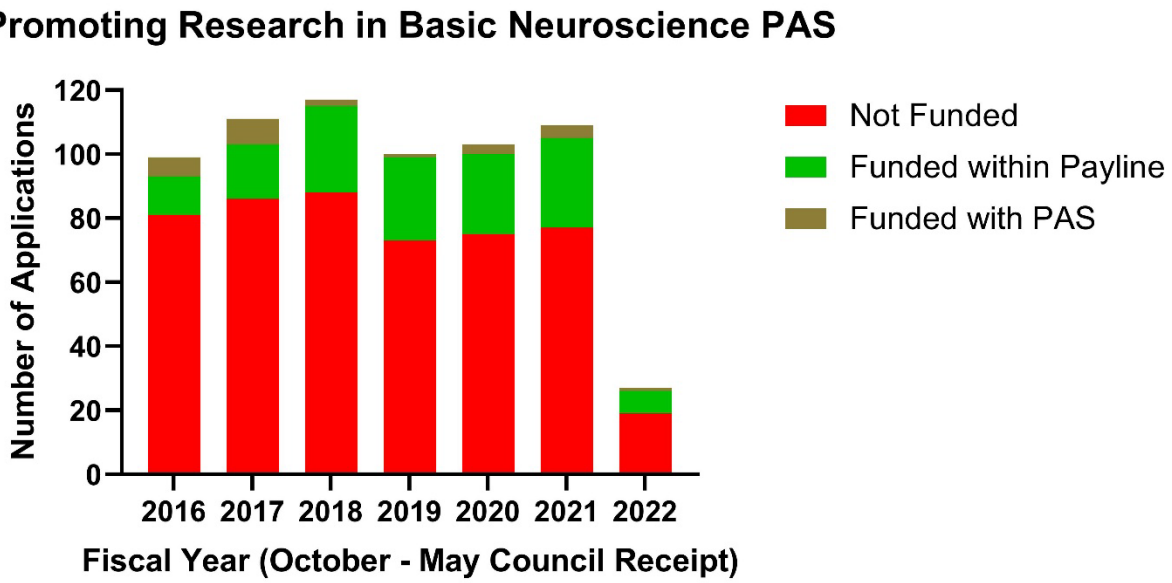

Figure 2: The Promoting Research in Basic Neuroscience PAS Extended the Typical NINDS Pay Line by 2-4% to Fund Additional R01s that were 100% Basic / Basic from 2016-2022. On average, NINDS received ~107 applications each year responding to the PAS Funding Opportunity. The red bars show those applications submitted to the PAR that were not funded. Applications scoring within the NINDS pay line (green bar) were paid according to normal funding policies and additional meritorious applications that scored beyond the pay line were funded using the set aside funds (gold bar).

2. NINDS support of FN across a wide range of funding opportunities and grant mechanisms

Basic / Basic coded research is supported by the Activity Codes listed in the following Table. Each Activity Code is associated with specific NIH or NINDS funding guidelines to ensure appropriate review and level of funding for many types of research studies.

Table 3

Activity Code	Description	Years of Support	Maximum $ Allowed
DP1	**NIH Director's Pioneer Award** - OD (Office of the NIH Director) High Risk High Reward	≤ 5	$700K DC/year
DP2	**NIH Director's New Innovator Award Program** - OD High Risk, High Reward, ESIs	3 + 2	$300K DC/year
P01	**Program Project Grant** – Collaborative research programs, can be renewed once	≥5	$1 million DC/year
P20	**Exploratory Grant Program–** planning grants for developing Research Centers	≤ 4	$250K DC/year

R01	**Research Project Grant Program** - Renewable, requires preapproval if >$500K DC/year	≤ 5	Fit to project
R15	**Research Enhancement Award** - Lower resourced Institutions only (Also called AREA or REAP)	3	$300K DC/3 years
R21	**Exploratory/Developmental Research Grant Award** - Cannot be renewed	2	$275K DC/2 years
R24	**Resource-Related Research Projects** - Dissemination or provision of resources	≤ 4	≤$700K DC/4 years
R25	**Research Education Programs for Residents & Fellows** - Research education and training of clinical residents and fellows to foster careers as physician-scientists	≤ 5	Salary plus fringe for 80% full-time professional effort
R35	**Research Program Award** - No Specific Aims. Track record and potential success considered	8	$750 DC/year
R37	**Javits Neuroscience Investigator Award** – Competitive R01s nominated by NINDS Staff and NANDS Council to recognize investigator with history of exceptional performance	4 + 3	Fit to project
R56	**High Priority, Short-Term Project Award** - R01 applications with priority scores or percentiles that fall just outside the funding limit and nominated by NINDS Staff	1	Fit to project, capped at $350k DC
RF1	**Multi-Year Funded Research Project Grant** - An R01 that has been multi-year funded	≤ 5	Fit to project
U01	**Research Project Cooperative Agreements** - Support a discrete, specified, circumscribed project and with substantial Federal programmatic staff involvement	Solicited funding opportunities for various programs. Duration and maximum $ vary.	
U19	**Research Program Cooperative Agreements** – Multidisciplinary, team science, multiple projects towards a major objective, and with substantial Federal programmatic staff involvement	Solicited funding opportunities for various programs. Duration and maximum $ vary.	
U24	**Resource-Related Research Projects Cooperative Agreements** - Support research projects contributing to improvement of the capability of resources to serve biomedical research	Solicited funding opportunities for various programs. Duration and maximum $ vary.	
UF1	**Multi-Year Funded Research Project Cooperative Agreement** - Multi-year funded equivalent of the U01	Solicited funding opportunities for various programs. Duration and maximum $ vary.	
UG3	**Phase 1 Exploratory/Developmental Cooperative Agreement** – Supports first phase; larger budget than UH2 mechanism	Solicited funding opportunities for various programs. Duration and maximum $ vary.	
UH3	**Exploratory/Developmental Cooperative Agreement Phase II** - Second phase for the support for innovative exploratory and development research activities initiated under the UH2 mechanism	Solicited funding opportunities for various programs. Duration and maximum $ vary.	

Table 3: Table of NINDS Funding Mechanisms that Support Basic/FN Research. Description of grant activity codes for NINDS awards including basic / FN research during the period 2018-2022.

3. NINDS success rates for common investigator-initiated funding mechanisms that support FN

Several grant mechanisms are used to support labs or teams of investigators with research projects submitted in response to "Parent" Notices of Funding Opportunities (NOFOs). The most appropriate mechanism depends on factors including the scope, breadth, or structure of the proposed project, or the career stage or institutional eligibility of the applicant. Four activity codes comprise the primary grant types for FN as supported by NINDS. For more information about these types of grants, see: Research Project Grants | National Institute of Neurological Disorders and Stroke (nih.gov).

Success rate data for each type of grant activity and for each NIH Institute and Center (IC) are publicly available. Success rates are defined as the percentage of reviewed grant applications that receive funding. They are computed on a fiscal year basis and include applications that are peer reviewed and either scored or unscored. For additional information see NIH Success Rate Definition.

Table 4

Activity Code	Number of Applications Reviewed	Number of Applications Awarded	2022 Success Rate	Total Funding	Success Rate Range (Mean) 2013-2022
R01	2,519	495	20%	$260,925,199	16-23% (20%)
R21	1,031	210	20%	$73,272,079	14-25% (18%)
R15	75	20	27%	$8,421,647	5-27% (15%)
R35	57	9	16%	$6,124,991	2-100% (20%*)

Table 4: FY 2022 Success Rates for NINDS R01s, R21s, R15s, and R35 Grant Mechanisms. These data can be found at NIH RePORT. Success rates vary year to year and can be particularly wide-ranging for activity codes with a small number of applications. *For R35s, the first two years (2016-2017) of funding were excluded from the mean because the success rates were skewed (2% and 100%) as this new funding mechanism was initiated.

4. Representation of Basic/ FN Research for the most common NINDS Funding Mechanisms

Different funding mechanisms show a slightly different distribution of research types at NINDS. Proportions of the four Basic / Applied research types for the most common research mechanisms are illustrated in the following pie graphs.

4.1 Research project grant (R01)

An R01 provides support for up to 5 years and funding sufficient to conduct an independent research project. [NIH Research Project Grant Program (R01) | grants.nih.gov]

Figure 3

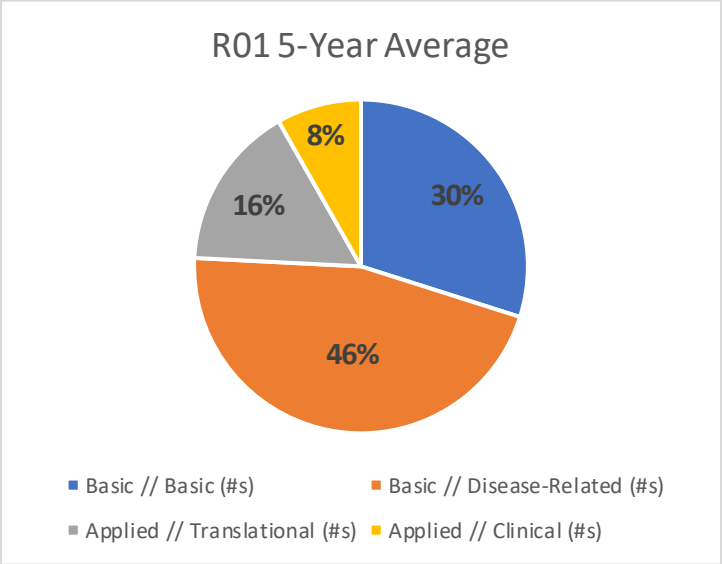

Figure 3: Average percentage of NINDS R01 Awards from 2018 – 2022 in Each of the Four Basic / Applied Funding Categories. The average percentage of basic / basic R01 awards in the last 5 years is 30%. The NINDS pay line from 2018-2022 ranged from 14% to 16%, with an average of 520 R01 grants funded each year. The average success rate of R01 awards from 2018-2022 was 21%.

4.2 Exploratory / developmental research grant award (R21)

The R21 grant mechanism is intended to encourage exploratory/developmental research by providing support for early and conceptual stages of project development. The NIH has standardized the Exploratory/Developmental Grant (R21) application characteristics, requirements, preparations, and review procedures in order to accommodate investigator-initiated (unsolicited) grant applications. Investigators may request a project period of up to two years and their R21 cannot be renewed. [NIH Exploratory/Developmental Research Grant Award (R21) | grants.nih.gov]

Figure 4

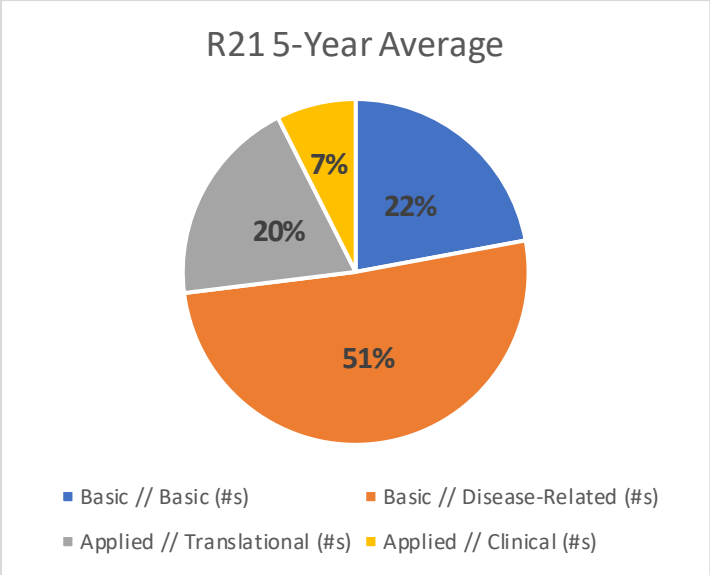

Figure 4: Average percentage of NINDS R21 Awards from 2018 – 2022 in Each of the Four Basic / Applied Funding Categories. The average percentage of basic / basic R21 awards in the last 5 years is 22%. The NINDS pay line from 2018-2022 ranged from 14% to 16%, with an average of 223 R21 grants funded each year. The average success rate of R21 awards from 2018-2022 was 20%.

4.3 Academic research enhancement award (AREA, REAP – R15)

The R15 mechanism is intended to support small-scale research projects at educational institutions that provide baccalaureate or advanced degrees for a significant number of the Nation's research scientists but that have not been major recipients of NIH support. R15s come in two forms: AREA and REAP. [NIH Research Enhancement Award (R15) | grants.nih.gov]

1. Academic research enhancement award (AREA) for undergraduate-focused institutions
2. Research enhancement award program (REAP) for health professional schools and graduate schools

Figure 5

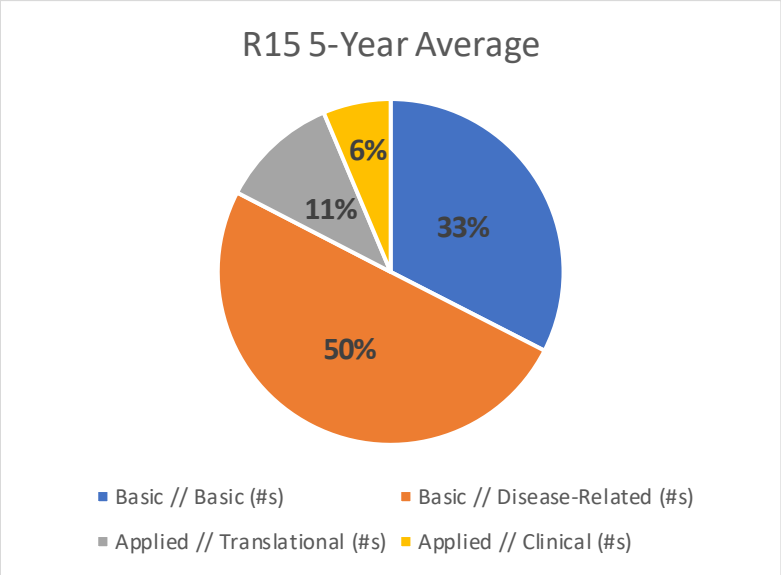

Figure 5: Average percentage of NINDS R15 Awards from 2018 – 2022 in Each of the Four Basic / Applied Funding Categories. The average percentage of basic / basic R15 awards in the last 5 years is 33%. The NINDS pay line from 2018-2022 ranged from 14% to 16%, with an average of 16 R15 grants funded each year. The average success rate of R15 awards from 2018-2022 was 17%.

4.4 Research program award (R35)

The NINDS Research Program Award (RPA) aims to support the NINDS-related research of an investigator's laboratory or research group for a sustained period of up to 8 years. The award is intended to increase funding stability, reduce the time investigators spend writing grant applications, and facilitate a more flexible research environment. The goal of the R35 is to help investigators make meaningful contributions to neuroscience by providing greater funding stability, flexibility, and support for your overall research project. The R35 RPA is a funding mechanism that supports research efforts by: providing stable funding of up to $750,000 per year (direct cost funding) for up to eight years; allowing investigators to focus on their work rather than spending valuable time continuously applying for funding; allowing investigators to conduct long-term, rewarding research that is not tied to specific aims; and providing flexibility to pivot as needed to emerging and timely topics. Because of the lack of specific aim, the R35 is not often used to support clinical research programs. RFA-NS-22-038; funding started in FY 2016 – current.

Figure 6

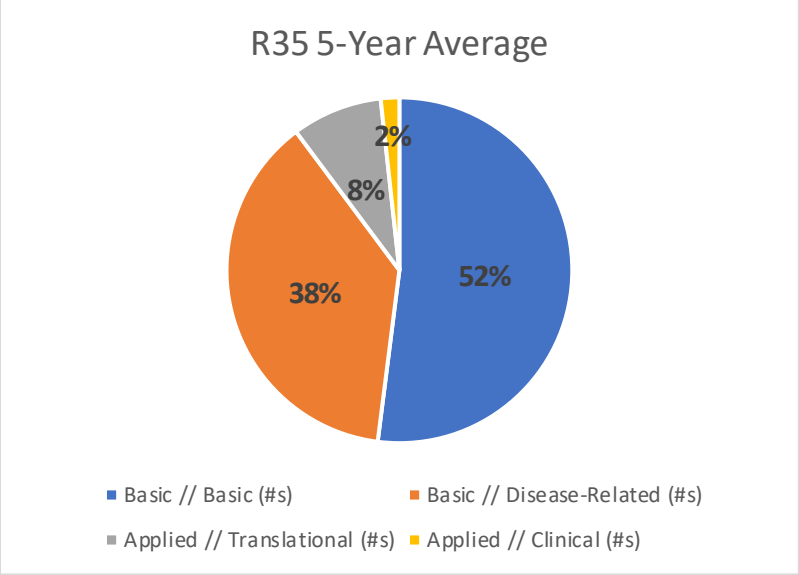

Figure 6: Average percentage of NINDS R35 Awards from 2018 – 2022 in Each of the Four Basic / Applied Funding Categories. The average percentage of basic / basic R35 awards in the last 5 years is 52%. The NINDS pay line from 2018-2022 ranged from 14% to 16%, with an average of 14 R35 grants funded each year. The average success rate of R35 awards from 2018-2022 was 20%.

5. NINDS funding mechanisms for trainees and early career faculty

Although most NIH-funded trainees (post-baccalaureate students, graduate students, and post-doctoral fellows) are supported through R01 grants to their advisors or through T32 training grants to an institution, NINDS provides Individual Fellowships (F awards) to trainees at the graduate and postdoctoral levels and Career Development Awards (K awards) to scientists and clinician-researchers at the postdoctoral and early career faculty stages.

Table 5

Training Award	Description
F30	**Individual NRSA for Dual-Doctoral Degree Students in non-MSTP Institutions** – Predoctoral training
F31	**Individual NRSA for PhD Students & MD/PhD Students from MSTP Institutions** - Predoctoral training
F32	**NINDS Postdoctoral NRSA Fellowship** – Early postdoctoral training
F99	**Individual Predoctoral to Postdoctoral Fellow Transition Award** – For predoctoral students in their 3-4 year of training to facilitate transition into postdoctoral appointments

K01	**NINDS Postdoctoral Career Development Award** – Mentored postdoctoral research with a comprehensive career development plan that will enable the start of an independent research program
K02	**Independent Scientist Award** - Early to mid-career clinician-scientists in need of additional protected time committed to research
K08	**Mentored Clinical Scientist Research Career Development Award** - Mentored awards for clinicians
K12	**Neurosurgeon Research Career Development Program (NRCDP)** - Mentored research career development for junior neurosurgeon faculty at institutions nationwide that support neurological research
K22	**Career Transition Award for NINDS Intramural Clinician-Scientists** – For clinician-scientists to receive mentored research in the NINDS intramural program, followed by independent research
K23	**Mentored Patient-Oriented Research Career Development Award** - Mentored awards for clinicians
K99	**Pathway to Independence Award** - Mentored postdoctoral research (K99) followed by independent research (R00)

Activity Code	Number of Applications Reviewed	Number of Applications Awarded	2022 Success Rate	Total Funding	Success Rate Range (Mean) 2013-2022
F30	21	7	33%	$293,617	9-37% (20%)
F31	463	112	24%	$4,672,977	17-30% (25%)
F32	83	20	24%	$1,402,978	19-39% (29%)
F99	62	35	57%	$1,481,371	41-73% (56%)
K01	25	8	32%	$1,634,344	11-40% (24%)
K02	1	0	0%	$0	0-38% (18%)
K08	55	19	35%	$3,731,365	26-47% (35%)
K12	1	1	100%	$3,202,476	0-100% (71%)
K22	2	0	0%	$0	0-67% (26%)
K23	72	24	33%	$4,534,972	15-40% (28%)
K99	133	29	22%	$3,506,704	9-29% (19%)

Table 5: The FY 2022 Success Rates of NINDS F30s, F31s, F32s, F99s, K01s, K02s, K08s, K12s, K22s, K23s, and K99s. The success rates of NIH Training and Research Career Development Programs are available for each IC and can be found at NIH RePORT. Data for success rates of NINDS funding mechanisms for trainees and early career investigators for FY 2022 are shown. Total funding for each activity code and the success rate range and mean from 2013-2022 are also shown. The success rates vary year to year and can be particularly wide-ranging for activity codes with a small number of applications.

5.1 Individual fellowships for pre-doctoral and post-doctoral trainees (F30, F31, F32, F99)

NINDS individual fellowships provide research training opportunities to trainees at the graduate, and postdoctoral levels. Predoctoral (F30, F31 and F32) and postdoctoral (F32) programs were combined below. For details on training, see Individual Fellowships | National Institute of Neurological Disorders and Stroke (nih.gov).

Figure 7

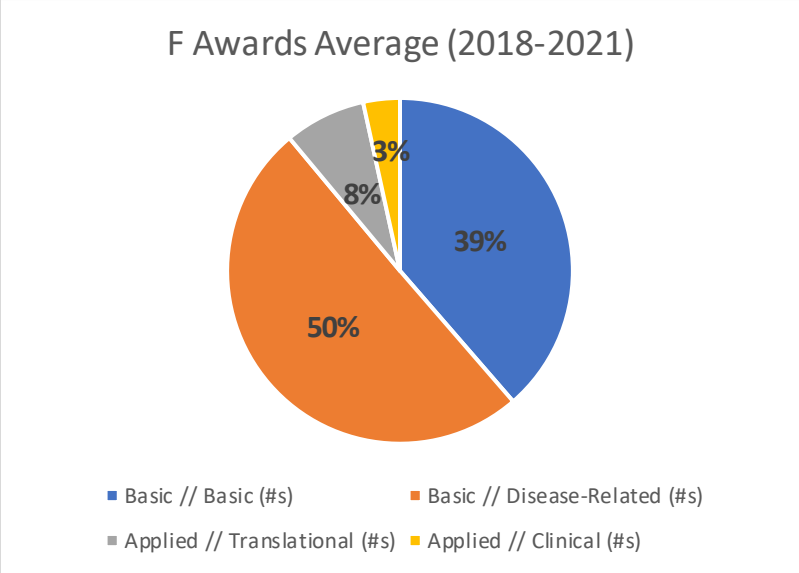

Figure 7: Average percentage of NINDS Fellowship (F) Awards from 2018 – 2021 in Each of the Four Basic / Applied Funding Categories. The average percentage of basic / basic F awards in the last 4 years is 39%. An average of 152 F awards are funded each year (of those awards 2% are F30s, 62% are F31s, 19% are F32s and 16% are F99s).

5.2 Career development awards (K01, K02, K08, K12, K22, K23, K99)

NINDS career development awards provide research training opportunities to scientists and clinician-researchers at the postdoctoral and early career faculty levels. Career Development Awards | National Institute of Neurological Disorders and Stroke (nih.gov)

Figure 8

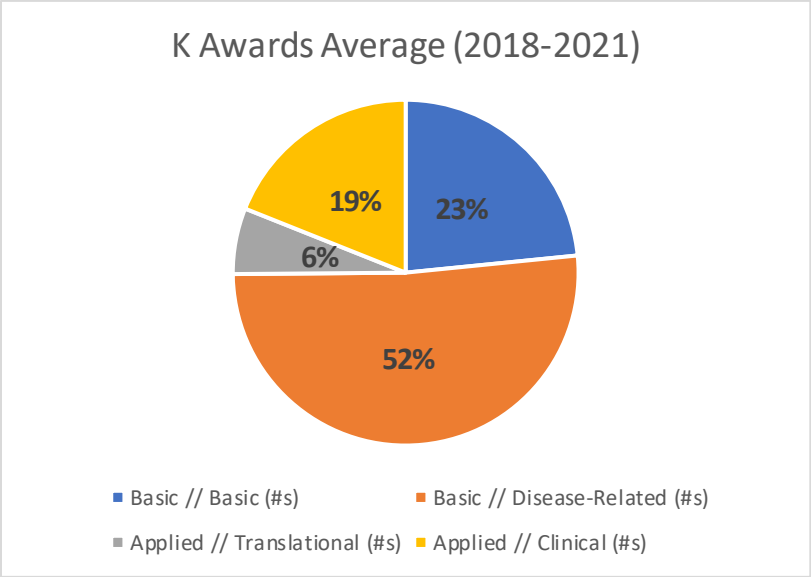

Figure 8: Average percentage of NINDS Career Development (K) Awards from 2018 – 2021 in Each of the Four Basic / Applied Funding Categories. The average percentage of basic / basic K awards in the last 4 years is 23%. An average of 67 K awards are funded each year (of those awards 7% are K01s, 2% are K02s, 28% are K08s, 1% are K12s, 5% are K22s, 27% are K23s, 1% are K24s* and 29% are K99s). *K24s are specific to the HEAL Initiative and the first year of K24 funding started in 2021.

6. NINDS supports team science research.

While virtually all research is collaborative, sometimes the goals or scale of highly impactful projects benefit from a specific collaborative program or team science approach. NINDS supports the use of the following specific collaborative funding mechanisms when appropriate. Team or Multi-Component | National Institute of Neurological Disorders and Stroke (nih.gov)

1. Multiple PI Research Project Grants: The multi-PD/PI option (also referred to as an MPI application) is available for most funding mechanisms supported by NIH and NINDS. The MPI option allows applicants and their institution to identify more than one PD/PI on a single grant application. The goal is to encourage collaboration among equals when that is the most appropriate way to address a scientific problem. These proposals must have a clear leadership plan and are subject to the same budgetary requirements as a single PI application. Collaborative FN projects are often submitted as MPI R01s. MPI applications submitted to the Parent R01 NOFO typically have a single set of Specific Aims and are usually reviewed in standing CSR study sections.

2. Research Program Project Grants (P01): The NINDS P01 NOFO (PAR-21-181) solicits grant applications that propose to conduct innovative research within the mission of the NINDS via a synergistic collaboration between scientists who might not otherwise collaborate. The program project grant is designed to support research in which the funding of several interdependent highly meritorious projects as a group offers significant scientific advantages over support of these same projects as individual research grants. The awards are often multidisciplinary, with groups of investigators working on three or more research projects that contribute to the overall program objectives. Each project has its own set of Specific Aims, and the projects, in combination, must be synergistic to the goals of the P01. Each P01 must also have at least one administrative core and one additional resource core. Applications are reviewed by an NINDS review panel. They may be renewed one time, given a limit of a 10-year cycle. NINDS typically places a $1M direct cost cap on these awards.

3. Research Project Cooperative Agreements (U01): The U01 mechanism is one of several "U" mechanisms, or Cooperative Agreement funding activities, used by NINDS. The U01 is available to support discrete, specified, circumscribed projects to be performed by investigator(s) in an area representing their specific interests and competencies. Similar in scope to an R01, the U01 is used when substantial programmatic involvement is anticipated between the awardee and NINDS staff. However, unlike the R01, no NIH "Parent" U01 mechanism exists for unsolicited investigator-initiated projects. NINDS has not typically used this mechanism for FN research projects. Instead, the U01 mechanism is more often used for research programs that require achievement of specific programmatic milestones, such as larger translational and clinical studies.

4. NINDS Interdisciplinary Team Science Grants (RM1): This newly utilized NINDS 5-year award funding opportunity (RFA-NS-22-036) solicits interdisciplinary teams of experts that seek to cross technical and conceptual boundaries through collaboration to achieve ambitious goals for basic, translational, and/or clinical research. NINDS expects that the goal of an RM1 will be bold, impactful, and challenging. RM1 projects have a single defined goal that is difficult to achieve by an individual or parallel efforts and can only be achieved by the combined efforts of 3-6 multiple Principal Investigators, functioning as co-equals and sharing leadership, each with a distinct background necessary to accomplish the project. Although there are no budget limitations, the budget must be well justified. These are reviewed by an NINDS scientific review panel.

IV. Summary of Responses to the FN Request for Information (RFI)

Beginning in February 2022, NINDS directly asked the community to provide comments and advice on the opportunities and obstacles for FN research to accelerate our understanding of the normal development, structure, and function of nervous systems through a Request for Information (RFI). The RFI was advertised via NANDS Council, a NINDS Director's Message, emails from the NINDS Director,

Dr. Walter Koroshetz, to Department Chairs and Societies, an OPEN Stage Webinar, and individual NINDS Program Director outreach. The RFI was open through September 1, 2022. NINDS received 20 responses to the FN RFI.

The input sought by NINDS included, but was not limited to, comments addressing any or all the following areas of interest:

- New ways that NINDS could better support FN.
- Noteworthy cases in which FN research programs were exceptionally successful and the unique aspects in their design.
- Issues that present obstacles or opportunities for the advancement of new areas of FN.
- Whether mechanistic and/or discovery-based research proposals are adequately fostered and ideas to better advance these types of FN research.
- The ability of present NINDS grant mechanisms (e.g., R01, R21, P01, R35, etc.) to advance all areas of FN research, their strengths and weaknesses, and potential for improvement.
- The value of team science approaches to advance FN research.
- The utility, gaps, obstacles, and potential opportunities for using NIH provided tools and resources (e.g., Alliance or IMPC).
- The need for a strategic planning process (akin to the BRAIN Initiative) for any aspect of FN research.
- Topic ideas for an NINDS FN workshop.
- The decision process (including any concerns) to submit an application on any specific area of FN research.
- Any additional comments related to FN.

Responses Broken out by RFI-identified Topic Area of Interest

New ways that NINDS could better support FN

- "…mechanistic studies in basic systems such as cultured cells (not even neuronal) are needed to develop tools and ideas to extend into neurons and the brain."
- Set aside some amount (e.g., 10%) of the budget for FN research with dedicated review.
- "Emphasis…on research programs that use novel technologies…or advantageous models (especially non-mammalian models) for the analysis of processes at high resolution directly *in vivo* in the living organism."
- *[alternative to previous bullet above]* "…Emphasize theory and frameworks above technology. Tool development is wonderful and necessary, but all too often is rewarded above new ideas."
- Embrace cell biologists that want to study the unique cell biology of neurons and glia.
- Support the creation of better conceptual frameworks for executing and interpreting brain perturbation experiments.
- Fund/create more interdisciplinary teams.

Noteworthy cases in which FN research programs were exceptionally successful and the unique aspects in their design

- Sometimes the most successful science is that where you don't know where the road will ultimately lead you.
- Optogenetics - in the early years it was done as a side project and didn't get R01 funding until it had matured. This is a common story for new directions.
- Examples taken from 'If Neuroscience Needs Behavior, What Does Behavioral Science Need?' by Nora Newcombe, December 29, 2017
- A description of an RM1 approach (Teams Science)

Issues that present obstacles or opportunities for the advancement of new areas of FN

- Overemphasis on rodent models, easy circuits, and histology.
  - Developing new tools/models.
  - Use of *in vivo* living (behaving) systems.
- Lack of consensus on what to focus on.
- Funding stability, hyper competitiveness.

Whether mechanistic and/or discovery-based research proposals are adequately fostered and ideas to better advance these types of FN research

- Discovery based research is harder to support than hypothesis-driven mechanistic research.

The ability of present NINDS grant mechanisms (e.g., R01, R21, P01, R35, etc.) to advance all areas of FN research, their strengths and weaknesses, and potential for improvement

- Consider effective use of PAS or RFA with type set aside.
- Support larger (non-modular) budgets for FN.
- Consider DP2-like approaches.

The value of team science approaches to advance FN research

- Important and necessary.
- But not the whole solution.
  - Can impose selection bias.
  - Can limit innovation.

The utility, gaps, obstacles, and potential opportunities for using NIH provided tools and resources (e.g., Alliance or IMPC)

- No responses.

The need for a strategic planning process (e.g., BRAIN) for any aspect of FN research

- One respondent pointed out gaps in the BRAIN Initiative's scope.

- "I think if planning were to occur around FN, it shouldn't be to pick out major areas to fund. The point of FN research is to figure out what we don't yet know. And it's impossible to know where the next big discovery will be. I think highlighting broad areas that are encouraged, like development, is helpful. But I think the messaging needs to be that any new discovery is important for FN and later clinical work."

Topic ideas for an NINDS FN workshop

- "A workshop exploring what it is that we are trying to achieve in fundamental neuroscience with regard to understanding 'What causes what?', and its relationship to laying the foundations for interventions in the longer term would be valuable for guiding fundamental neuroscientists toward research that will be impactful in the long-term."
- "Using cross-species paradigms to advance research. How might researchers broaden the number of species we study and use as model organisms? How to better match the species to the problem and compare species, while considering natural ecologies of adaptation?"

The decision process (including any concerns) to submit an application on any specific area of FN research

- Per previous answers, general concern of reviewer and group (Study Section) biases.
    - Mixing FN and more translational grants in the same study section can skew scores.
    - Discovery vs. Hypothesis Testing.
    - Overemphasis on large projects and large teams.
        - e.g., BRAIN recommendations of what disciplines should be included.