NINDS Fundamental Neuroscience Working Group

Public Webinar
July 27, 2023

National Institute of Neurological Disorders and Stroke

Agenda

1. Introductory Remarks
   Walter Koroshetz, MD
   Director, National Institute of Neurological Disorders and Stroke (NINDS)

2. FNWG Charge, Process and Timeline
   Lyn Jakeman, PhD
   Associate Director, Division of Neuroscience

3. FNWG Deliberations and Summary Recommendations
   Yishi Jin, PhD, FNWG Co-Chair;
      Distinguished Professor, Kavli Institute of Brain and Mind, UC San Diego
   Tim Ryan, PhD, FNWG Co-Chair,
      Professor of Biochemistry, Weill Cornell Medical College and HHMI

4. Q&A and Comments
   Please post your questions and comments in the Q&A box.

Why Did NINDS Convene a Fundamental Neuroscience Working Group of Council (FNWG)?

To Advance the NINDS Mission: Understanding the development, structure, and function of the normal nervous system is crucial for NINDS achieving its mission. *The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to improve neurological health for all people.*

To Address the NINDS 2021-2026 Strategic Plan: NINDS supports and performs a broad array of rigorous and important neuroscience research from fundamental studies of basic nervous system function to studies to improve treatments and prevent neurological disorders. *"NINDS will maintain its long-standing emphasis on investigator-initiated research, with targeted initiatives for individual investigators and teams to address opportunities or obstacles that investigator-initiated research is unlikely to address."*

NINDS Supports Fundamental Neuroscience Research

“Fundamental Neuroscience (FN) research is the engine of discovery - it generates new knowledge, drives innovation, and underlies many therapeutic breakthroughs. A more complete understanding of the development, the structure, and the function of the normal nervous system will benefit the entire neuroscience community.”

NINDS Fundamental Neuroscience Statement 2017

Fundamental Neuroscience Taskforce (FNT) Membership

Robert (Bob) Riddle, Ph.D.
Program Director
Neurogenetics Cluster

Crystal (Cris) A. Lee, Ph.D.
Health Program Specialist
Neurogenetics Cluster

Rebekah Corlew, Ph.D.
Patient Engagement Strategist
Office of Neuroscience Communications & Engagement (ONCE)

Karen David, Ph.D.
Program Director
Neurotechnology & Integrated Systems Cluster

Yejun (Janet) He, Ph.D.
Program Director
Systems & Cognitive Neuroscience Cluster

Nina Hsu, Ph.D.
Health Science Policy Analyst
ONCE

Lyn Jakeman, Ph.D.
Associate Director
Division of Neuroscience

Cristina Nigro, Ph.D., M.S.
Chief of Staff to the NINDS Director
Office of the Director

Leslie C. Osborne, Ph.D.
Program Director
Systems & Cognitive Neuroscience Cluster

Christine Torborg, Ph.D.
Health Science Policy Analyst
Office of Science Policy & Planning (OSPP)

William (Bill) Tyler, Ph.D.
Program Director
Neurogenetics Cluster

George Umanah, Ph.D.
Program Director
Channels, Synapses, and Circuits Cluster

Carlo Quintanilla, Ph.D. (former)
AAAS Science and Technology Policy Fellow
ONCE

NINDS Fundamental Neuroscience Taskforce (FNT)

- Evaluation of research funding by research type (2013-present)
- Evaluation of the NINDS Basic Research Program Announcement: Promoting Research In Basic Neuroscience *(2015-2020)*
- Director's message *(*February 2022): *Fostering Research in Fundamental Neuroscience*
- One stop webpage for current info and resources: Search NINDS and FN
- *Request for Information (RFI) on Advancing Research in Fundamental Neuroscience*
- Support the FN Working Group of Council to advise NINDS in its future planning

How Did NINDS Convene a Fundamental Neuroscience Working Group of Council (FNWG)?

NINDS invited a diverse group of FN researchers to form the *FN Working Group (FNWG)* to:

- ***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.
- ***Prepare a draft report*** of findings stemming from the above charge to the full NANDS Council on September 6, 2023.

FNWG Membership

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

Amita Sehgal, Ph.D.
University of Pennsylvania
Howard Hughes Medical Institute

Weiwei Wang, Ph.D.
University of Texas Southwestern Medical Center

Goals of the FNWG

FNWG will provide scientific recommendations to the NANDS Council 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.

FNT and FNWG Process

Public Request for Information

FNWG Co-Chairs Led Discussions and Draft Priorities

Public Webinar to Discuss Priorities

NINDS Advisory Council

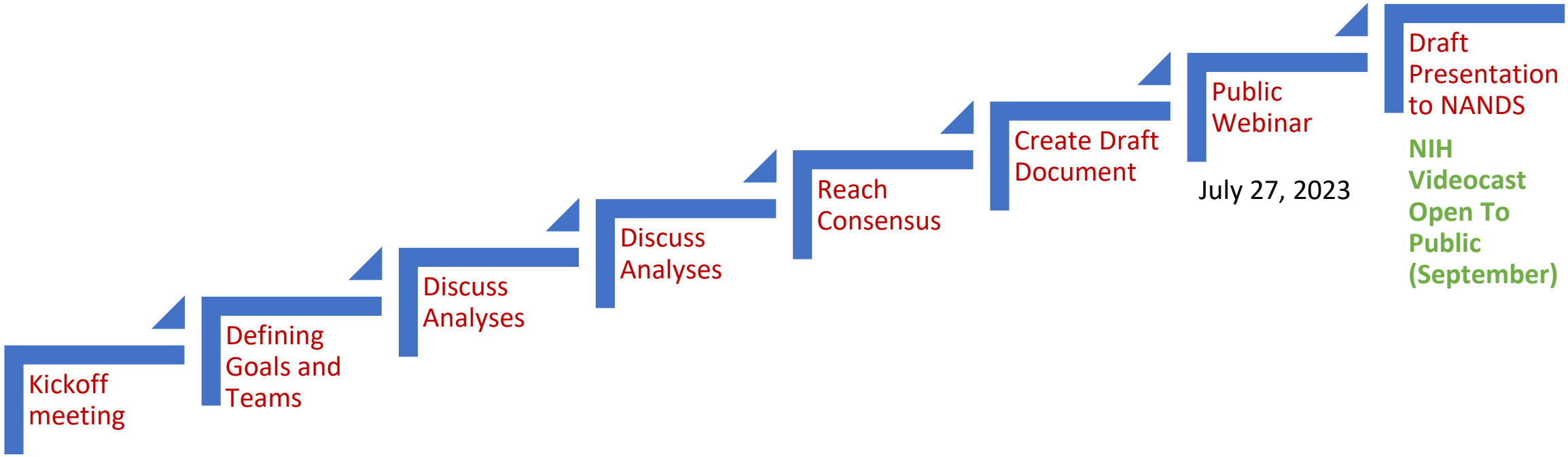
Feb-Aug 2022
- Responses shared with FNWG Co-Chairs

Dec 2022-June 2023
- Defined Focus Areas
- Discussed gaps and opportunities in subgroups and larger WG meetings

July 2023
- Public webinar for discussion and opportunity for questions and public comment
- Recommendations posted online for public comment through August 1, 2023

Sept 2023-
- Presentation, review and discuss ion of WG report
- Post final document
- Begin Implementation

FNWG Deliberations Process



Questions and/or Comments After Today?

The FNWG will complete their deliberations, including consideration of public input sent to fn@nih.gov by **August 1st**

Want to Watch the September 6th Presentation?

https://videocast.nih.gov/

Defining Focus Areas and FNWG Subgroups

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.

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

Subgroup Focus Questions

Each subgroup considered the following key questions:

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?

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Snapshot of the critical knowledge gaps identified by FNWG

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, to maintain and adapt to change in adults?
- The peripheral nervous system has been historically understudied.
- The need for better *in vivo* imaging of developmental processes over time and understanding which cells and signals coordinate development.

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?

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?

Snapshot of additional considerations identified by FNWG

2. How can we foster FN mechanistic investigation in the topic area?

- Prioritize the need to understand basic biology first, not focus on disease, emphasize basic cell biology, neuronal metabolism, *in vivo* electrophysiology…
- Foster collaboration between neuroscientists with biochemists, cell biologists, metabolism experts, engineers, function researchers, expert analyzers..., to support methodological development research.
- Encourage use of non-traditional model systems to study basic cell biological processes relevant to neurons, 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 them *in vivo* with function readouts for signaling events.

4. What are perceived funding difficulties?

- More experts for evaluating curiosity-driven, technology development, research
- Equitable access to state-of-the art imaging and core facilitates
- Sustained support for staff scientists

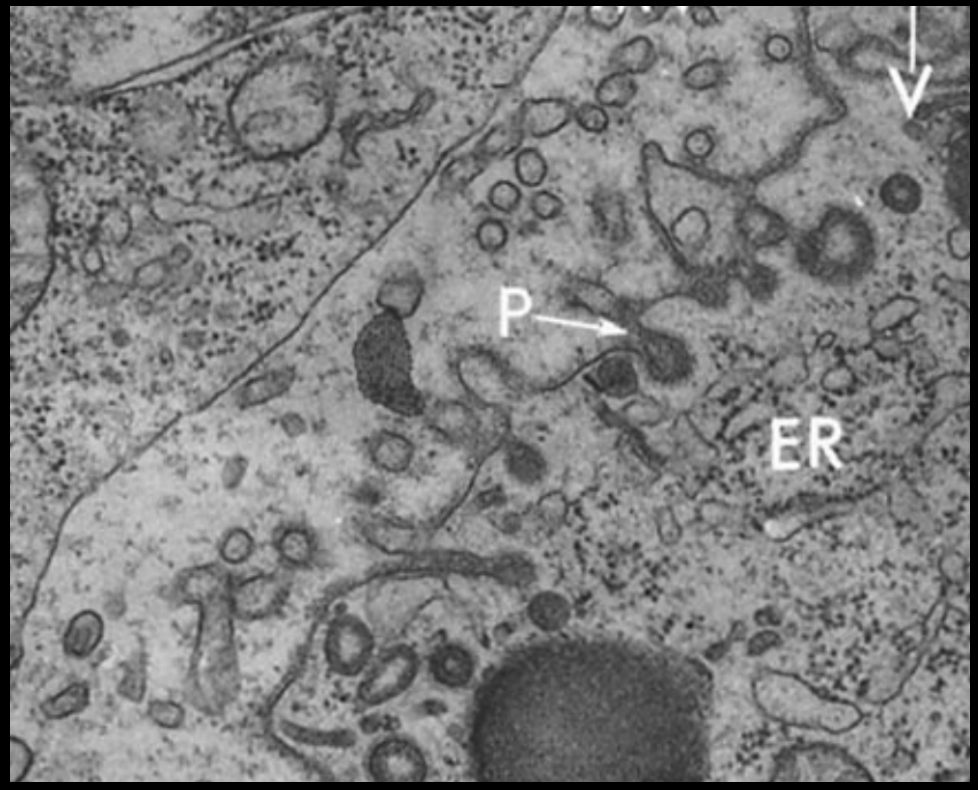
FNWG Summary Recommendations

1. Macromolecular Cartography: the organization of key protein machineries on the 1-1000 nm scale

Lessons from the 1950s: Electron microscopy revolutionized our think and sparked the imagination of scientists driving research for the next 50 years

Feeding a mosquito oocyte: 7 hours after a blood meal the appearance of “coated pits” on the surface of the oocyte :

The discovery of clathrin-mediated endocytosis



Roth & Porter JCB 1964

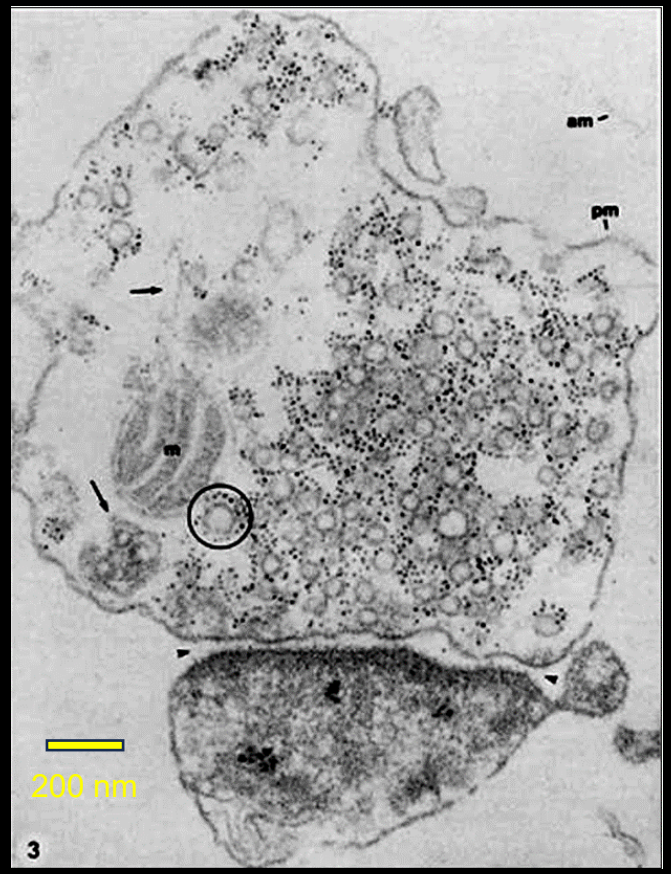
FNWG Summary Recommendations

1. Macromolecular Cartography: the organization of key protein machineries on the 1-1000 nm scale

The first molecular cartography of the nerve terminal

Immunogold labeling of synapsin providing definitive proof this is a synaptic vesicle associated protein

DeCamilli et al. 1983

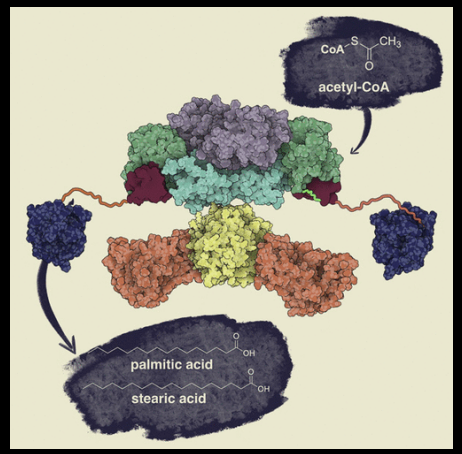


FNWG Summary Recommendations

1. Macromolecular Cartography: the organization of key protein machineries on the 1-1000 nm scale

How are key functional protein machineries organized within brain cells? Carrying out structure function analysis on the mesoscale

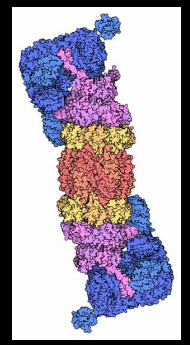
- **The machinery for building membranes**



The fatty acid synthesis complex

Paiva et al. Chem Reviews 2021

- **Protein turnover machineries**



26S Proteosome

FNWG Summary Recommendations

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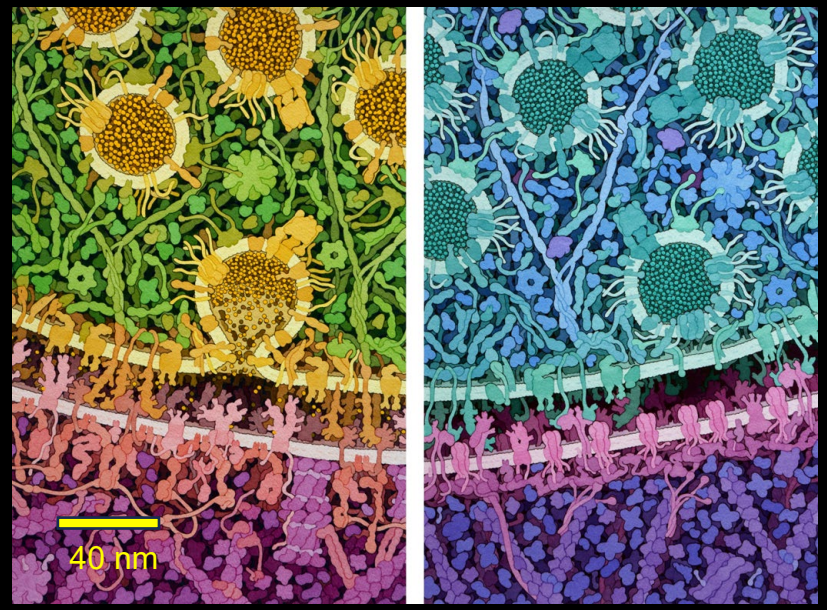
How are functional protein machineries organized within brain cells?
Carrying out structure function analysis on the mesoscale



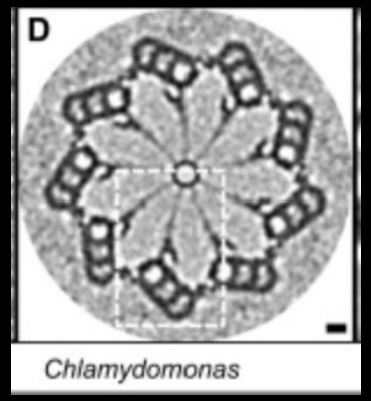
Prioritize research that fosters filling the information gap on the nm scale for molecular organization

FNWG Summary Recommendations

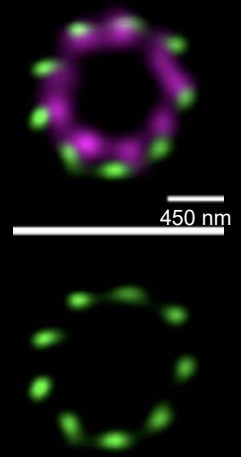
1. Macromolecular Cartography: the organization of key protein machineries on the 1-1000 nm scale

Macromolecular Cartography :
A coming frontier

Expansion & Super-resolution microscopy



Guichard et al Curr. Biol (2013)



α-tubulin

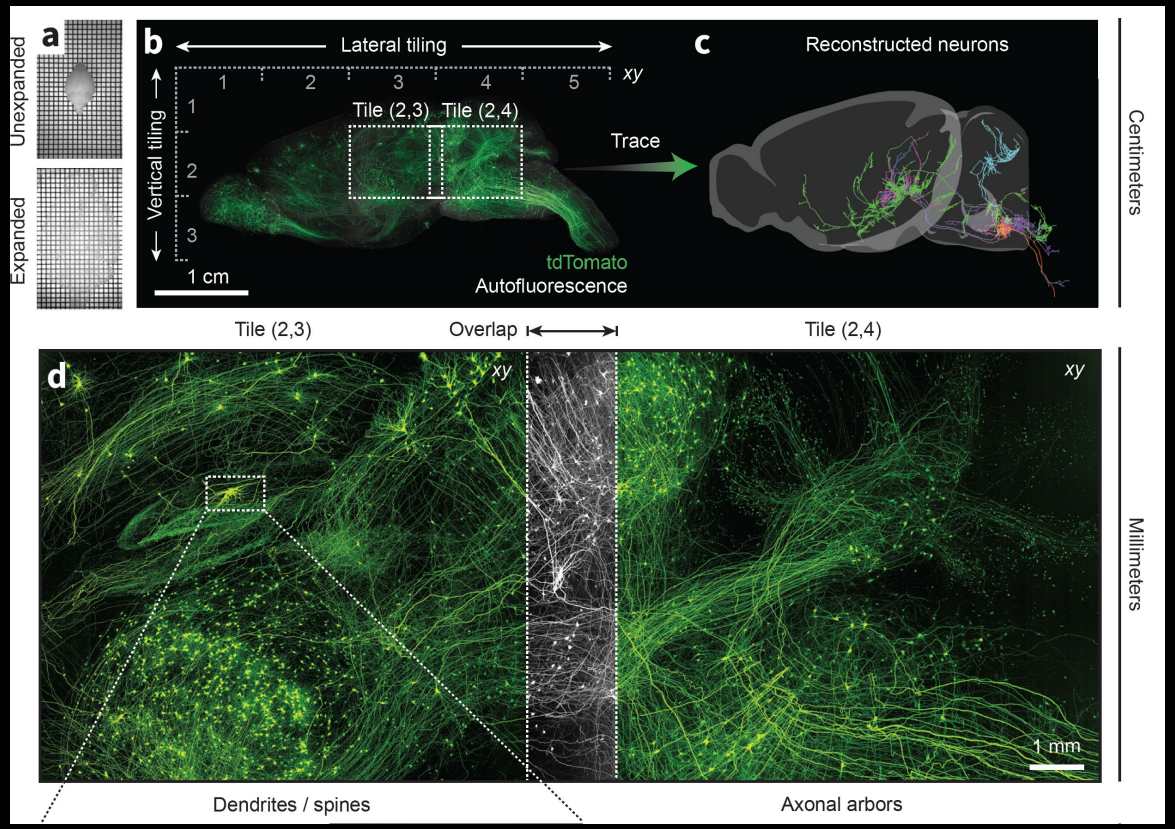
Polyglutamylated tubulin

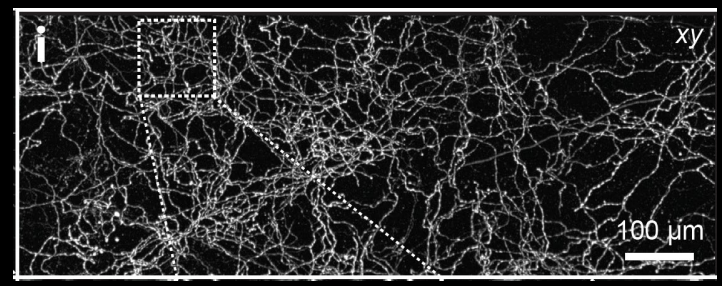
Gambarotto et al Nat. Comm (2019)

FNWG Summary Recommendations

1. Macromolecular Cartography: the organization of key protein machineries on the 1-1000 nm scale

Whole brain expansion microscopy: ExA-SPIM





Glaser et a. BioRxiv 2023

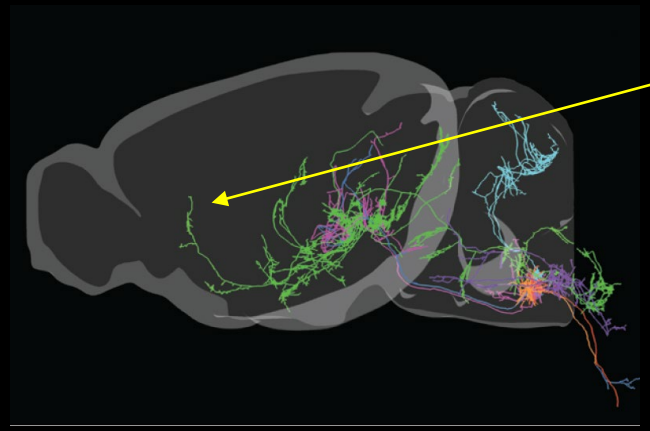
FNWG Summary Recommendations

2. Enable Quantitative approaches for studying protein turnover and how it is controlled in the brain

The brain contains the most geometrically complex cells in the body with process spanning distances that are 10000 x longer than typical cells and these cells typically must operate for 8-10 decades

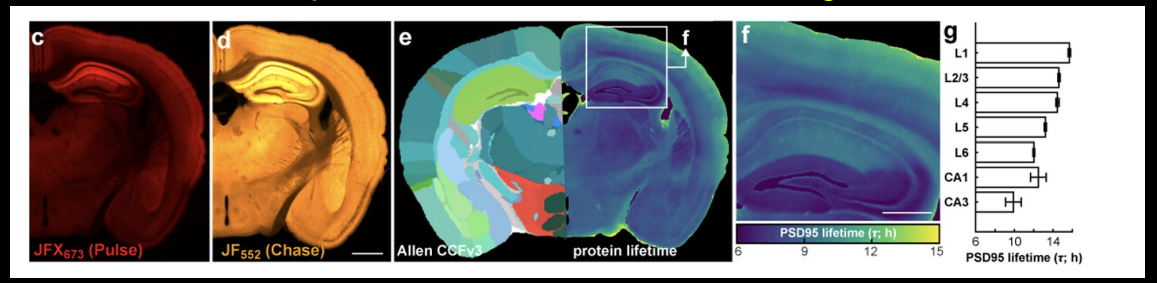
The protein machineries are constantly replaced with timescales that vary from hours to months

How do you ride the bicycle while needing to constantly change the parts?



This is far away from the cell body
What are the rules for replacing the proteins?

Map of PSD95 lifetimes across brain regions!



Mohar et al. BiorXiv 2023

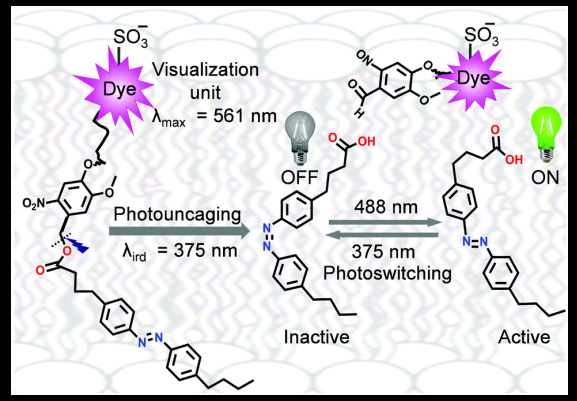
FNWG Summary Recommendations

3. Enable Quantitative approaches for tracking cellular activity (including *in vivo)*

e.g., lipid biology

The brain contains cells with the largest amount of membrane (e.g., oligodendrocytes, projection neurons)

What are the rules for lipid building, delivery & turnover? How does this intersect with signaling roles for lipids? Need new enabling technologies to tackle this problem

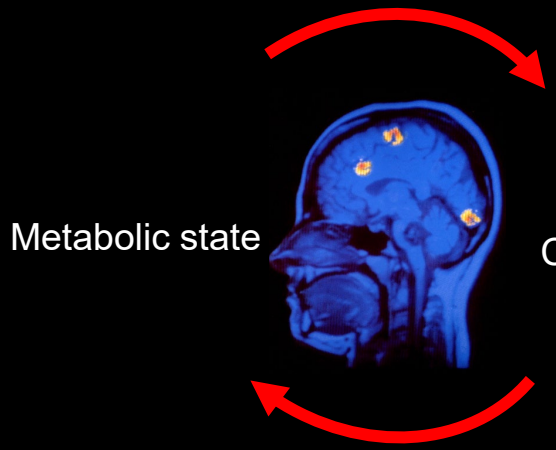


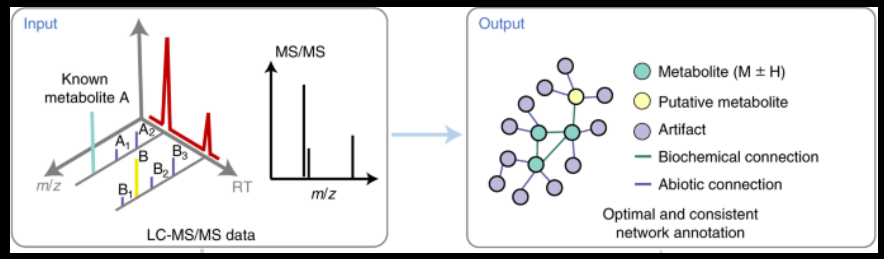
Caged photoswitchable signaling lipids
(Gaur et al., Chem. Commun, 2020)

FNWG Summary Recommendations

3. Enable Quantitative approaches for tracking cellular activity (including *in vivo)*

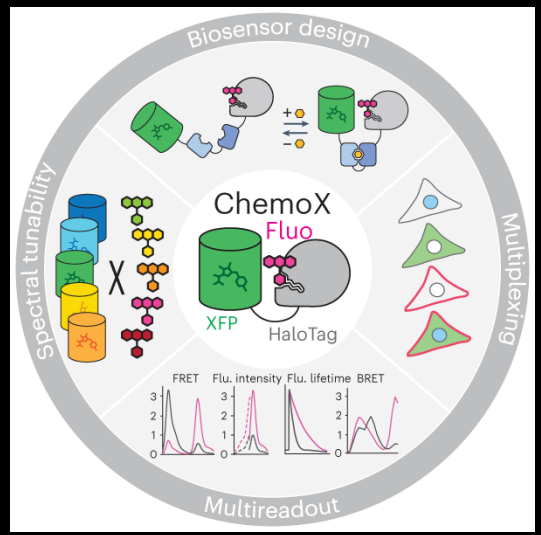
e.g., metabolism





"Standard" metabolic tracing approaches difficult to apply and interpret in complex tissues with mixed cell types and activity states

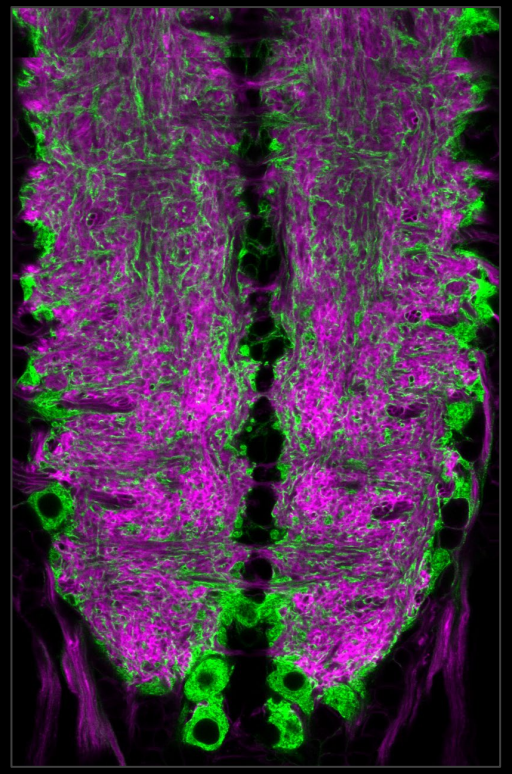
Enable tool development & optimization that can track important metabolites for the obvious (Bioenergetics, redox state) as well as intersection points between anabolism & catabolism at the single cell level



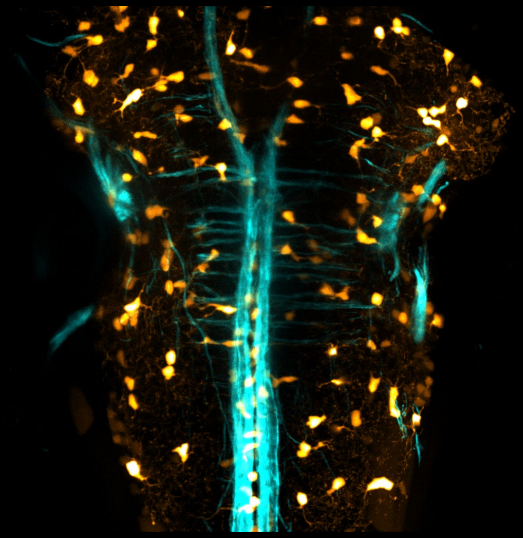
Hellwig et al. Nature Chemical Biolgy 2023

FNWG Summary Recommendations

4. Support approaches for capturing and imaging cell movement and cell-cell interaction during development of a (any) nervous system

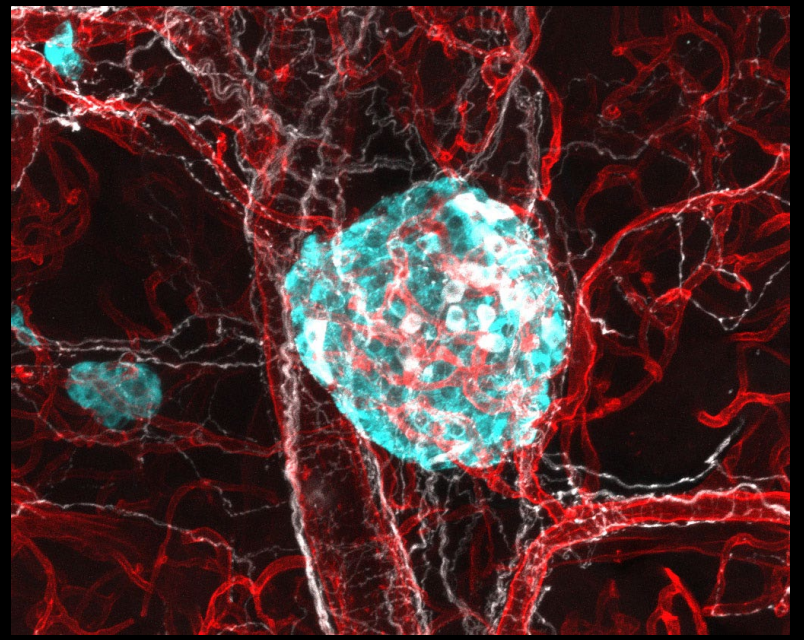


Astrocytes Neurons



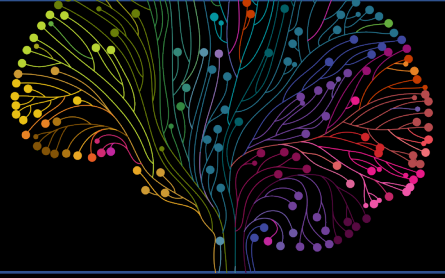
Oligodendrocytes
Axons

Sympathetic axon innervation of the heart



Pancreatic Islets
Sympathetic nerves
Blood vessels

FNWG Summary Recommendations



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

Novel collaborations with experts outside of neuroscience need to be incentivized, for example, through developing shared funding mechanisms

Sustained support for technical experts, such as scientists engaged in tool development or involved in supporting science infrastructure facilities, is also key for ensuring the continued success of fundamental neuroscience research.

What Do You Think?

Q&A and Feedback Session

National Institute of Neurological Disorders and Stroke

What's Next?

The FNWG will present their recommendations to NANDS Council for discussion and comment on September 6, 2023.

What Can You Do Now? Submit Your FN Applications!

- You don't need to wait for specific funding opportunity announcements to submit a research grant application on the FN research priorities or other FN research ideas.
- Contact NINDS to help you find the right program for your grant application. You can use the Program Director NINDS webpage to find the best contact. (Google NINDS and Program Director or use QR Code)
- Email fn@nih.gov

Thank You

Questions and/or Comments After Today?

The FNWG will complete their deliberations, including consideration of public input sent to fn@nih.gov by **August 1st**

Want to Watch the September 6th Presentation?

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The September 6th Council Meeting Agenda will be posted here:

https://www.ninds.nih.gov/news-events/events/national-advisory-council-nandsc-meeting-september-2023