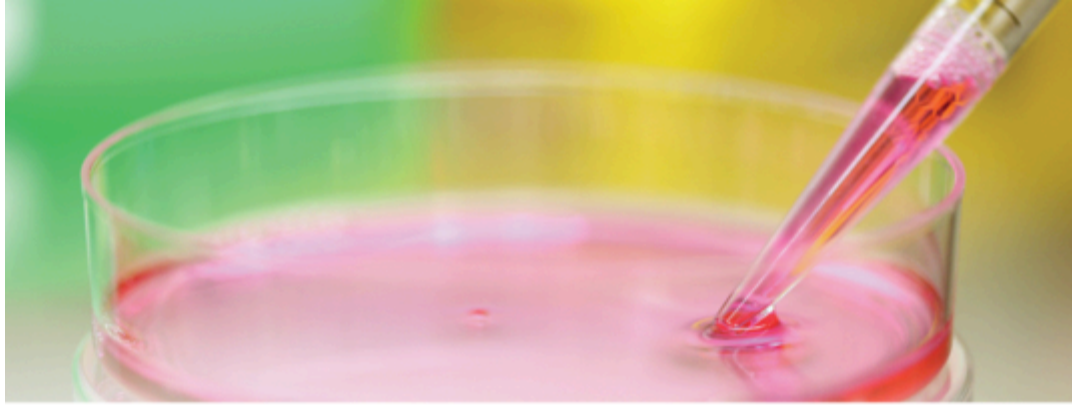
National Institute of Neurological Disorders and Stroke

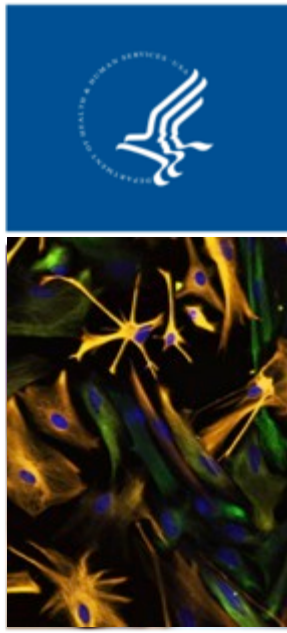
NINDS Initiatives and Neurodegeneration Research

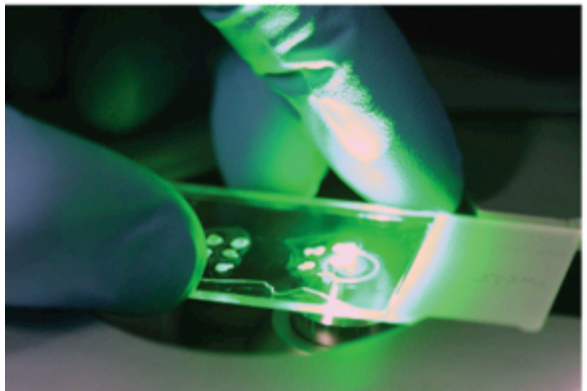
CIRM Brainstorming Neurodegeneration

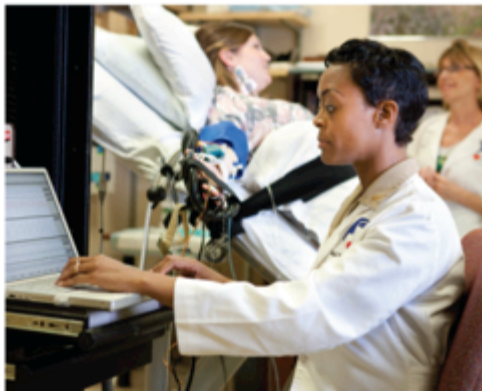
April 16, 2019

Walter Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke, NIH



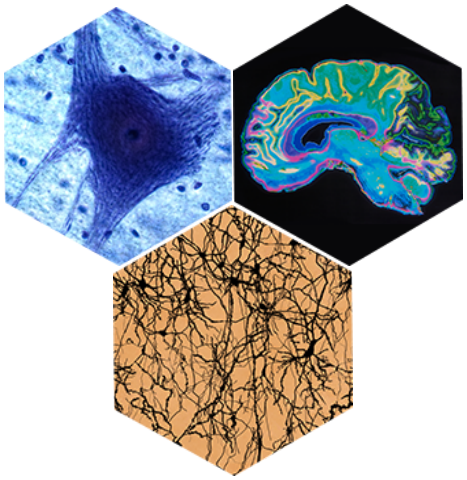






The National Institute of Neurological Disorders and Stroke (NINDS)

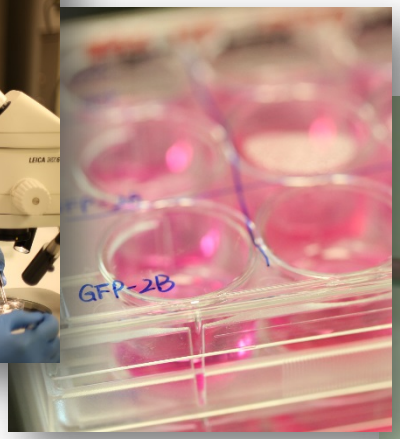
The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease

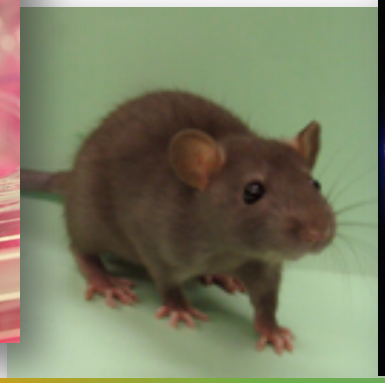


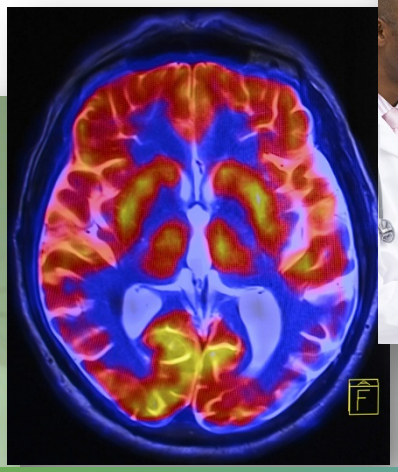
Strategies:

- Invest in basic, translational and clinical research
- Identify gaps in research and public health needs
- Train a talented and diverse research workforce
- Support development of tools and resources to enable discoveries
- Communicate and collaborate with all stakeholders, including the public
- Evaluate and continuously improve all NINDS programs

NINDS Invests Across the Research Spectrum







Basic	Translational	Clinical
Fundamental Neuroscience Disease-Focused Research	*Pipeline through to FDA IND/IDE*	*Phase I, II, III Trials FDA Review*

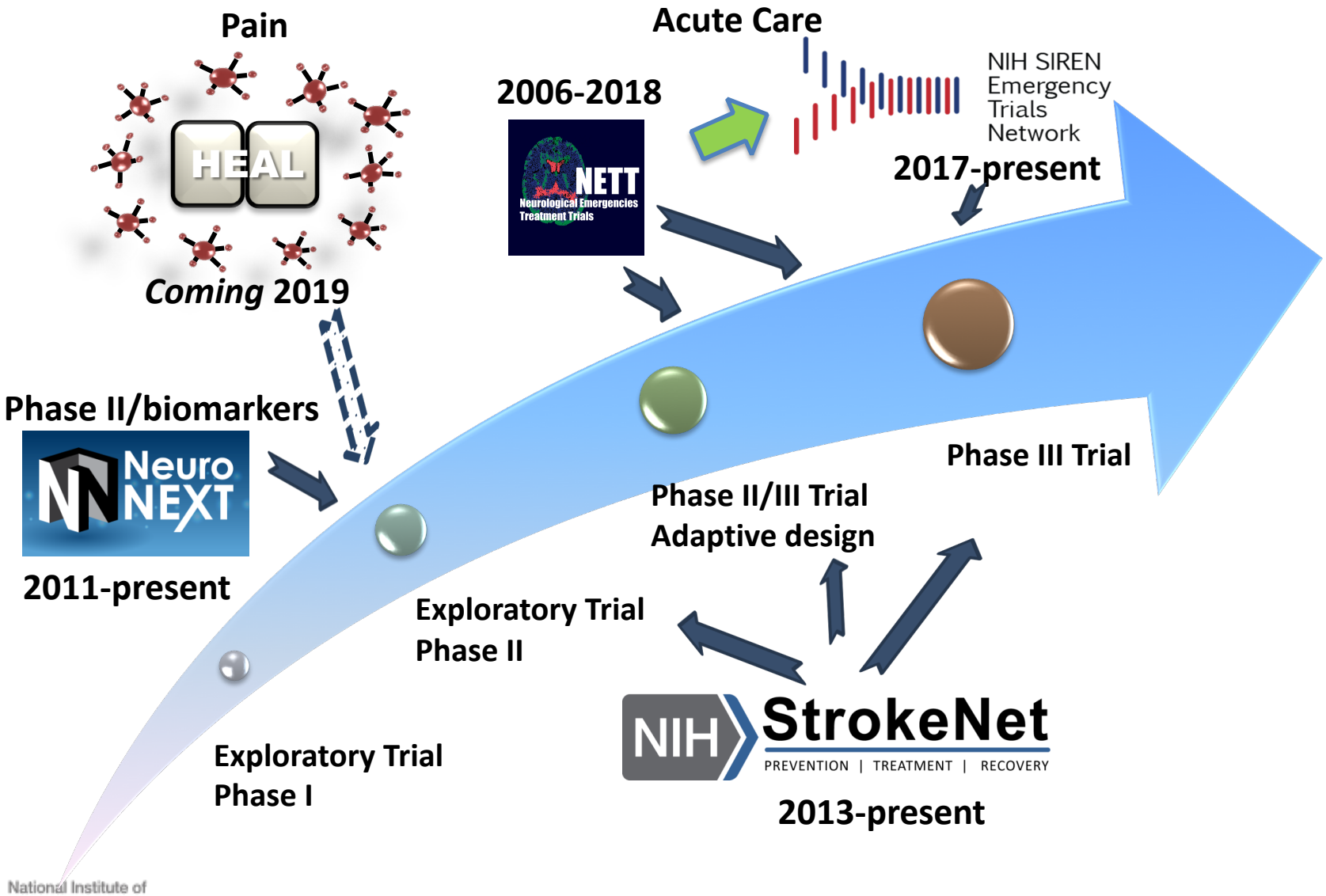
Division of Neuroscience

Division of Translational Research

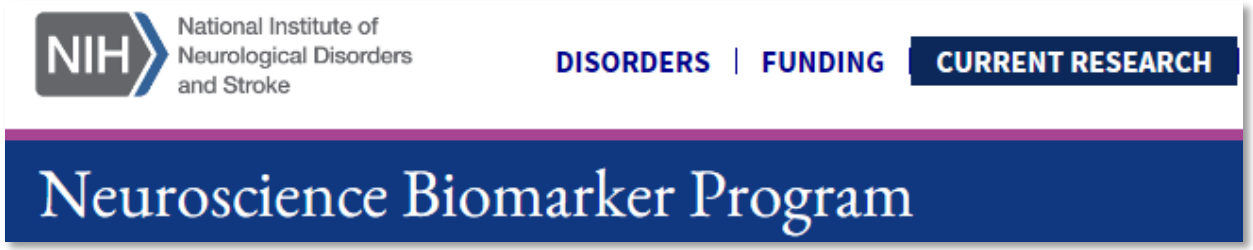
Division of Clinical Research

Division of Extramural Activities (includes Training)

NINDS Clinical Networks



NINDS Biomarker Strategy



Goal: Facilitate the development of high quality biomarkers to improve the quality and efficiency of clinical research and trials (Phase II and beyond)

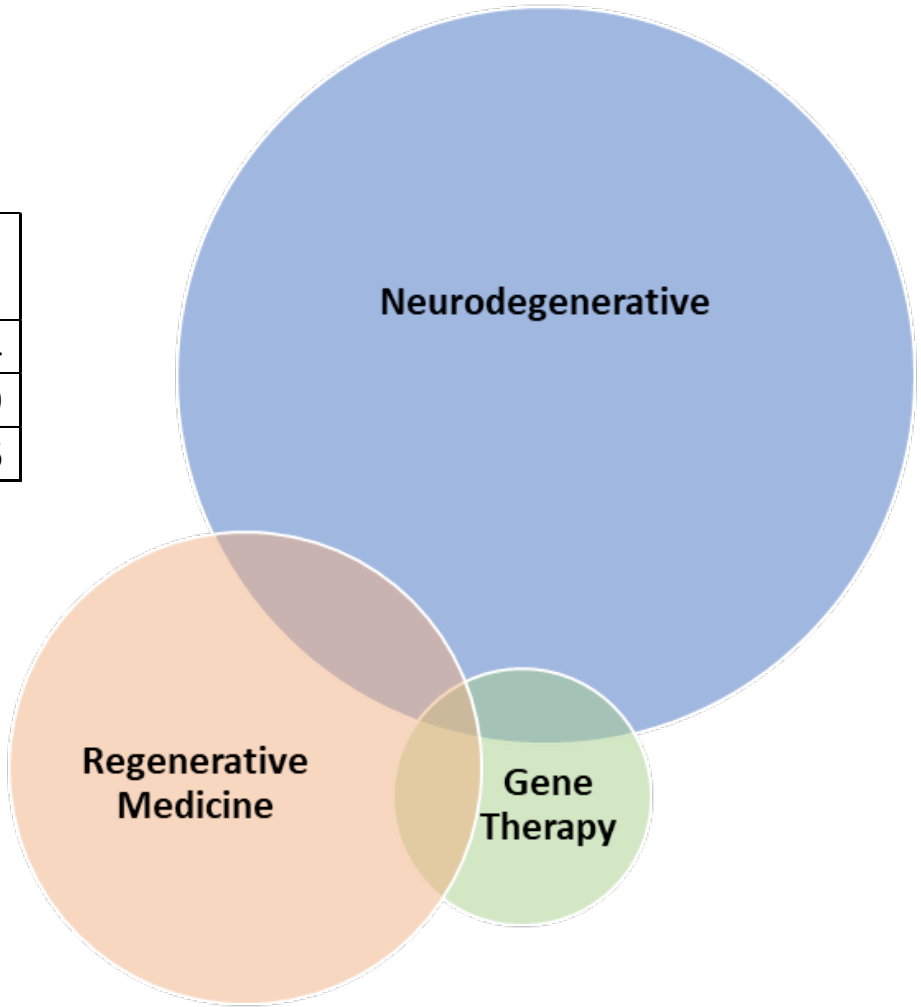
NINDS is coordinating across research to build a new, comprehensive approach for biomarker development and validation

- Promote analytical and clinical validation of existing candidate biomarkers
- Catalyze biomarker research through centralized information on NIH biosample and imaging repositories, data collections, and best practice consensus standards/methods

NIH Support for Neurodegeneration, Regenerative Medicine, and Gene Therapy Research

Research Areas ($ in millions)	FY15	FY16	FY17
Neurodegenerative	$ 1,662	$ 2,058	$ 2,554
Regenerative Medicine	$ 862	$ 886	$ 939
Gene Therapy	$ 238	$ 265	$ 266

*Based on RePORT RCDC Categories



Estimated overlap of FY18 research funding

All of Us

Common Fund: Somatic Cell Genome Editing

BRAIN Initiative

NOTABLE NIH-WIDE INITIATIVES

NEUROLINCS

NeuroLINCS is a NIH-funded collaborative effort between multiple research groups across the country with **expertise in patient-derived iPSC technology, disease modeling, OMICS methods, and computational biology** with a goal to understand the causes of neurological diseases and develop new therapies

NIH Common Fund Program: Somatic Cell Genome Editing Program

Program Components

https://commonfund.nih.gov/editing

1. **Testing Gene Editing Reagents and Delivery Systems in Better Animal Models**
2. **Assessing Adverse Biological Consequences of Genome Editing**
3. **Improving *In Vivo* Delivery of Genome Editing Machinery**
4. **Expanding the Human Genome Engineering Toolkit**
5. **Dissemination and Coordinating Center (e.g., via SCGE Toolkit)**

SCGE Toolkit

Envisioned as a Community Resource to enable future preclinical studies of genome editing therapies

Resources may include (but are not limited to):

- genome editing delivery systems developed by the Consortium, along with detailed characteristics and associated validation data
- genome editors developed by the Consortium, along with detailed characteristics and validation data
- biological platforms and assays to monitor and measure the adverse effects of genome editing in human cells
- small and large animal models for assessing the efficacy of various genome editing approaches
- methods and best practice protocols

Cell therapy
Science Advances - Friedreich's Ataxia

Friedreich's ataxia

Stephanie Cherqui, PhD
UCSD/Rady Children's Hospital

- One-time transplantation of autologous hematopoietic stem and progenitor cells (HSPCs) that have been genetically modified (via lentivirus transduction) to express the frataxin gene at physiological levels

SCIENCE TRANSLATIONAL MEDICINE | REPORT

NEURODEGENERATIVE DISEASE

Transplantation of wild-type mouse hematopoietic stem and progenitor cells ameliorates deficits in a mouse model of Friedreich's ataxia

Celine J. Rocca,[1] Spencer M. Goodman,[1] Jennifer N. Dulin,[2] Joseph H. Haquang,[1] Ilya Gertsman,[1] Jordan Blondelle,[3] Janell L. M. Smith,[1] Charles J. Heyser,[2] Stephanie Cherqui[1]*

Adrenoleukodystrophy

Florian Eichler, M.D.
Mass General Hosp

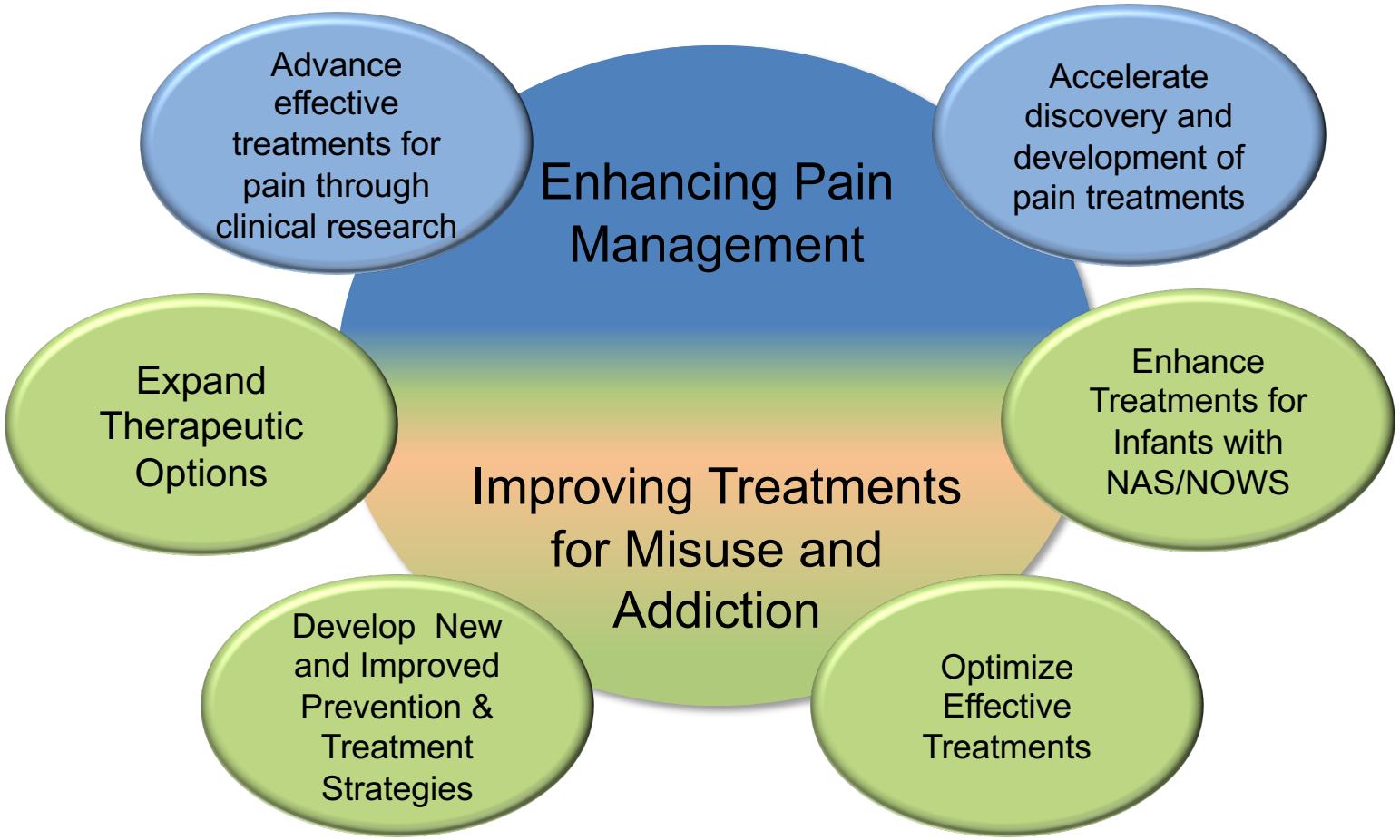
ORIGINAL ARTICLE

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Paul J. Orchard, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Myriam Armant, Ph.D., Colleen Dansereau, M.S.N., R.N., Troy C. Lund, M.D., Weston P. Miller, M.D., Gerald V. Raymond, M.D., Raman Sankar, M.D., Ami J. Shah, M.D., Caroline Sevin, M.D., Ph.D., H. Bobby Gaspar, M.D., Paul Gissen, M.D., Hernan Amartino, M.D., Drago Bratkovic, M.D., Nicholas J.C. Smith, M.D., Asif M. Paker, M.D., Esther Shamir, M.P.H., Tara O'Meara, B.S., David Davidson, M.D., Patrick Aubourg, M.D., and David A. Williams, M.D.

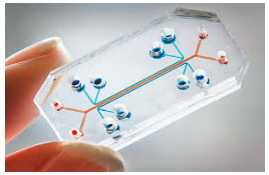

HEAL
NIH · Helping to End Addiction Long-term

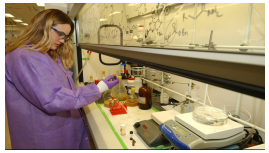
HEAL Initiative Research: Pain *AND* Opioid Misuse/Addiction



Develop Human Cell-based Screening Platforms and Novel Drugs to Treat Pain, Addiction, and Overdose

Nat'l Center for Advancement of Translational Science (NCATS)

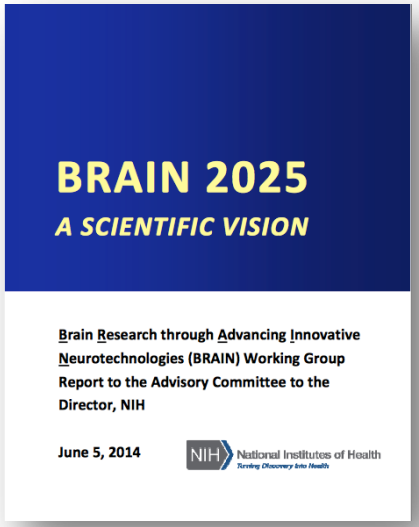




- Support preclinical optimization and development of safe, effective, and non-addictive small molecule and biologic therapies to treat pain.
- Develop human cell/tissue models
  - Peripheral and central nervous system
  - Normal and disease states
  - iPSC-derived neurons, 3D printed organoids, tissue chips
- Advance investigational drugs for new targets
  - Human tissue constructs to identify new probes/drug leads
  - Automated chemical synthesis
  - Artificial Intelligence to identify new chemical structures
  - IND-enabling studies: Optimization of Non-addictive Therapies [Small Molecules and Biologics] to Treat Pain

THE BRAIN INITIATIVE®

NIH: Focus on Structure and Function of Brain Circuits

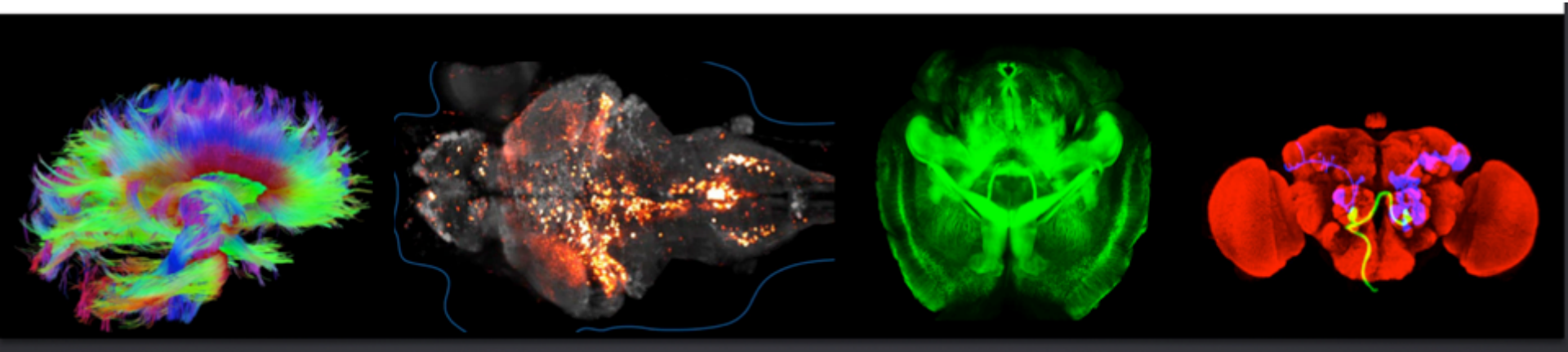


Goal: See the circuits in action by developing new tools to understand:

- How the brain controls how we move, plan, execute, and remember
- How to monitor/manipulate circuits for improved function
- How disordered brain circuits cause neuro/mental/substance use disorders

FIRST FIVE YEARS — Emphasize technology development

SECOND FIVE YEARS — Emphasize discovery driven science



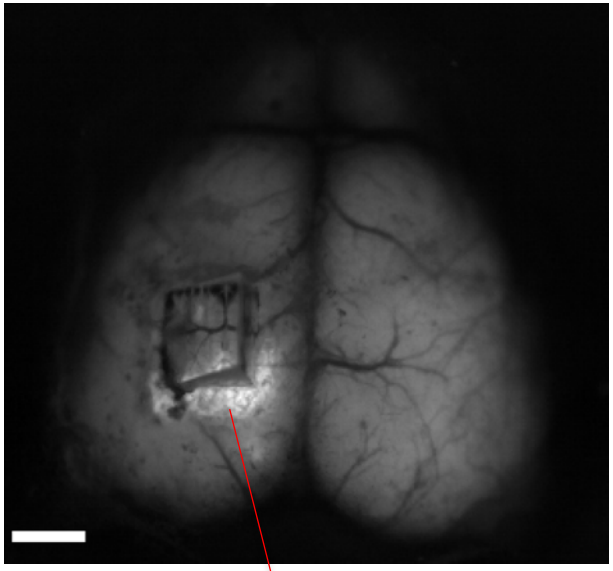
THE BRAIN INITIATIVE®

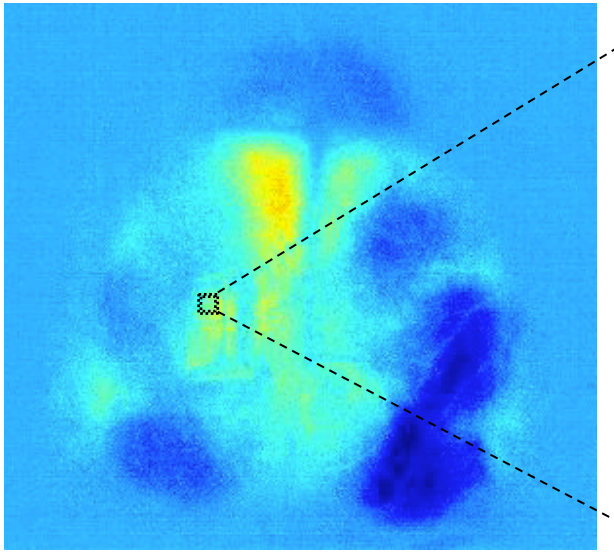
Microscope Reveals Activity at Multiple Scales Simultaneously

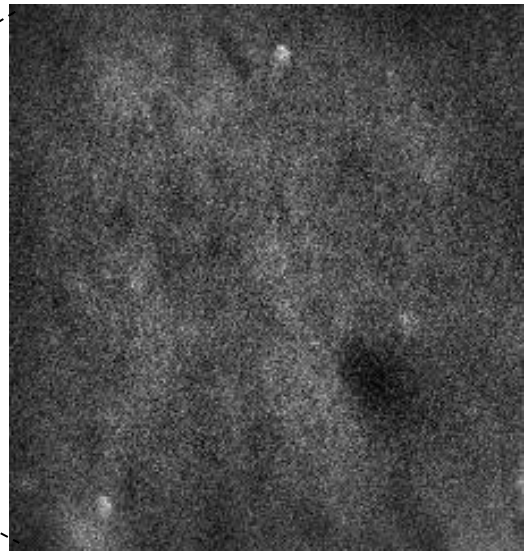
Brain activity measured while mice run on a treadmill:

Cortex-wide Activity

Single Cell Activity







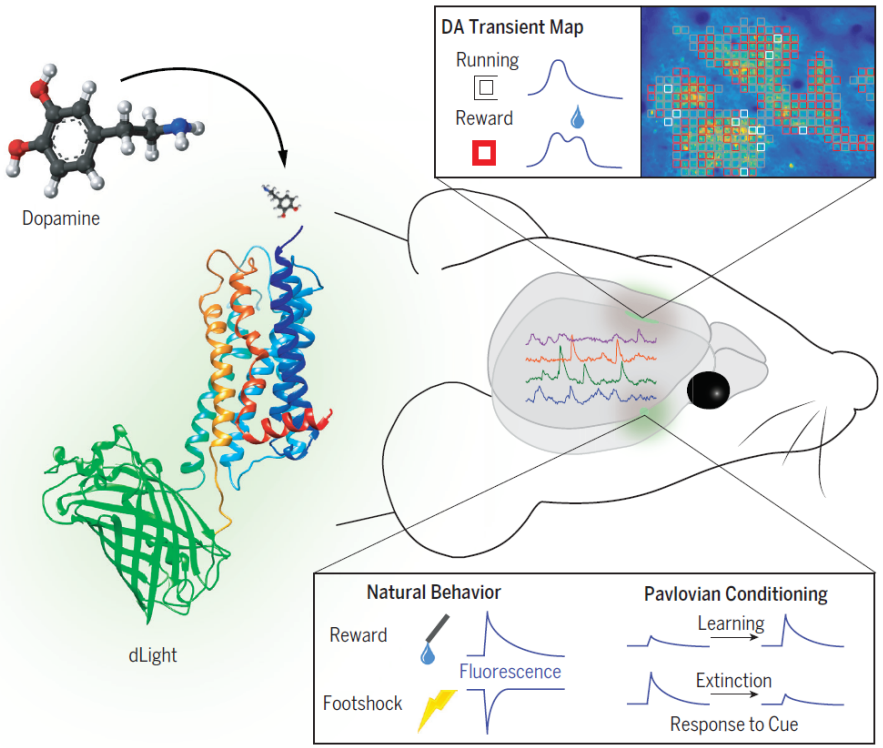
200 X 200 μm

Prism of Mesoscope

From the laboratory and collaborations of Dr. Michael Crair, Yale University
Barson, Hamodi et al. Funded FY15

NIH National Institutes of Health
Turning Discovery Into Health

New Class of Genetically-Encoded Sensors Permit Ultrafast Imaging of Dopamine Activity in the Brain

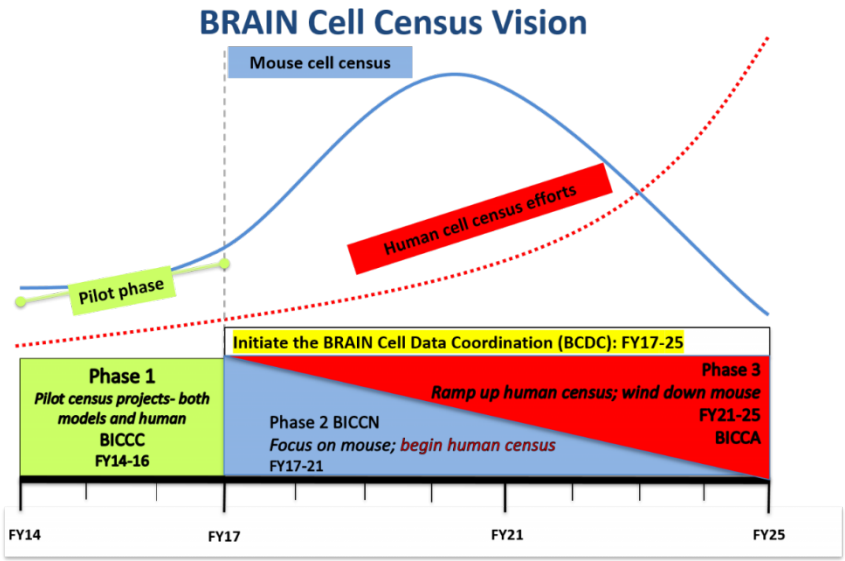


- New: intensity-based genetically encoded dopamine indicator (dLight1)
- dLight1 allowed dynamic recording of dopamine activity at the cellular level within milliseconds
- Activity visualized in live animals during behaviors, like reward learning and running
- Sensor design platform can be used to develop norepinephrine, serotonin, melatonin, and opioid neuropeptide indicators

Patriarchi et al., *Science,* 2018

THE BRAIN INITIATIVE®

BRAIN Initiative Cell Census Network (BICCN)



Cell Types Circuits

Theory/Data Analysis Human Neurosci

NEWS RELEASES

Monday, October 23, 2017

NIH BRAIN Initiative launches cell census

$250 million effort will catalog "parts list" of our most complex organ.

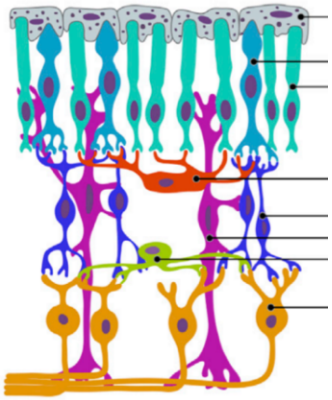
- Provide a comprehensive reference of all cell types in human, monkey, and mouse brain to provide genomic access to map, monitor and modulate activity in a cell type specific manner.
- 9 funded projects to support 4 parts of the network:

Brain Cell Data Center

Mouse Brain Cell Census Center

Mouse Brain Cell Census Collaboratory

Human and Nonhuman Primate Brain Cell Census Collaboratory

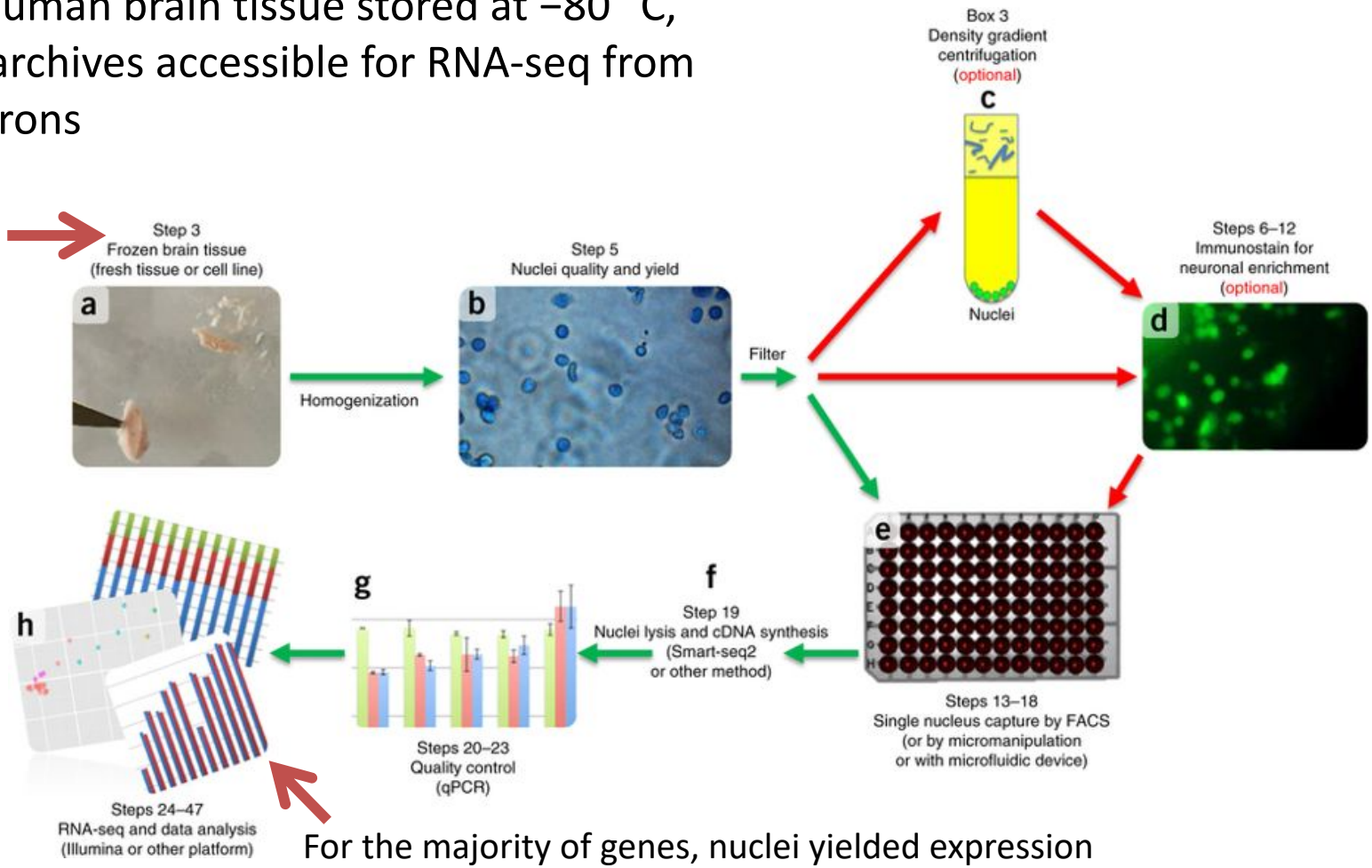


NIH National Institutes of Health
Turning Discovery Into Health

Sequencing the Transcriptome of Cell Nucleus

Advance: Nuclear transcriptomes can be obtained from postmortem human brain tissue stored at −80 °C, making brain archives accessible for RNA-seq from individual neurons

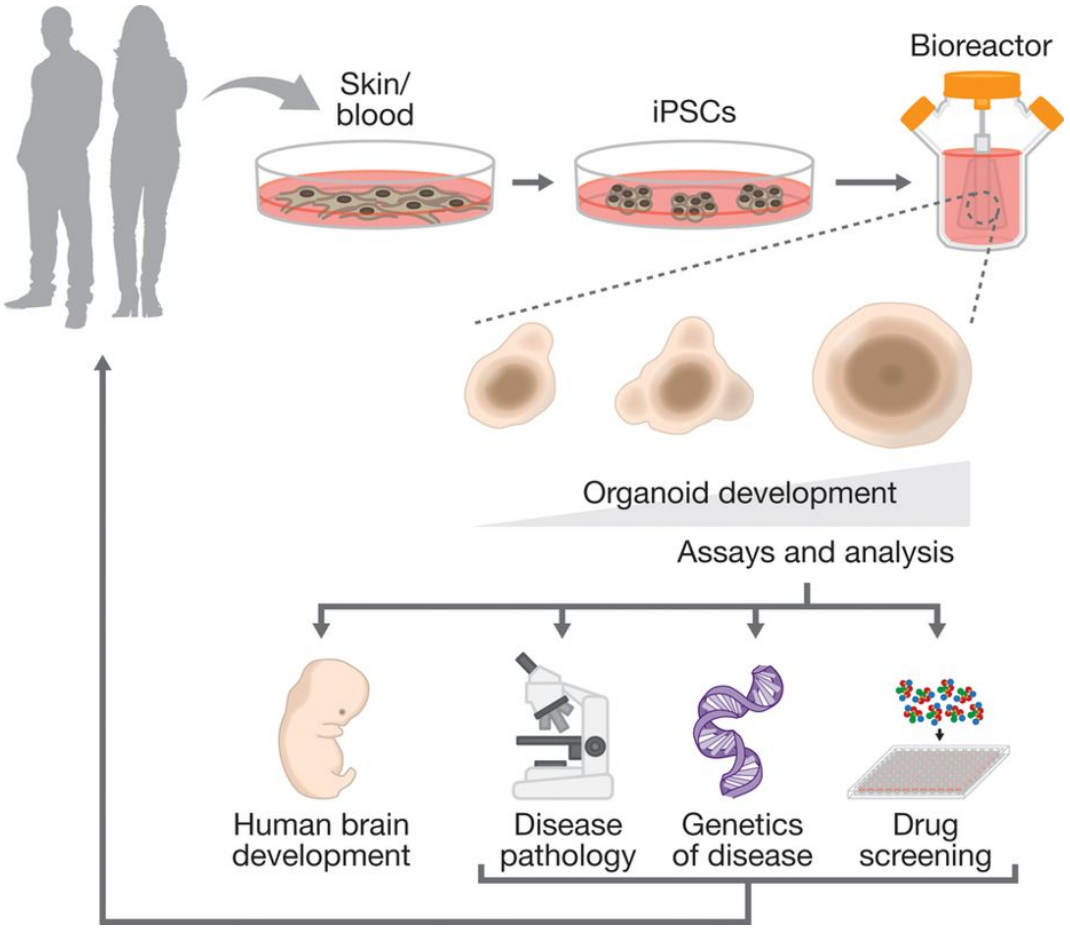
Isolating nuclei at 4 °C from tissue homogenates causes minimal damage



For the majority of genes, nuclei yielded expression signatures similar to whole-cell controls.

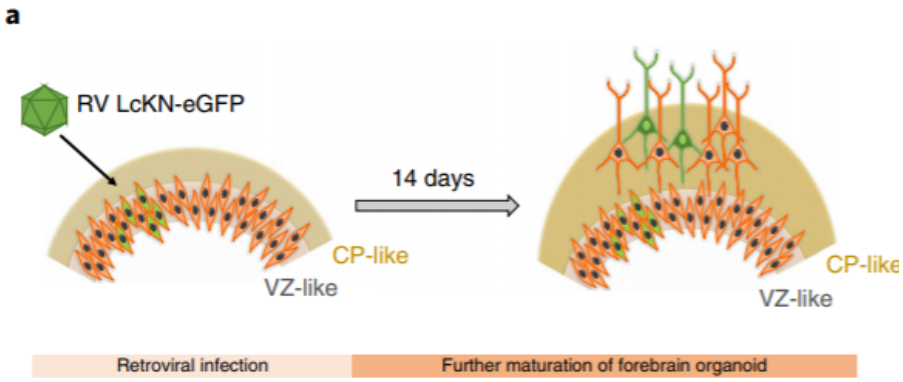
Krishnaswami et al., *Nature Protocols* **volume 11**, pages 499–524 (2016)

Organoids required! A new path to understanding human brain development and disease



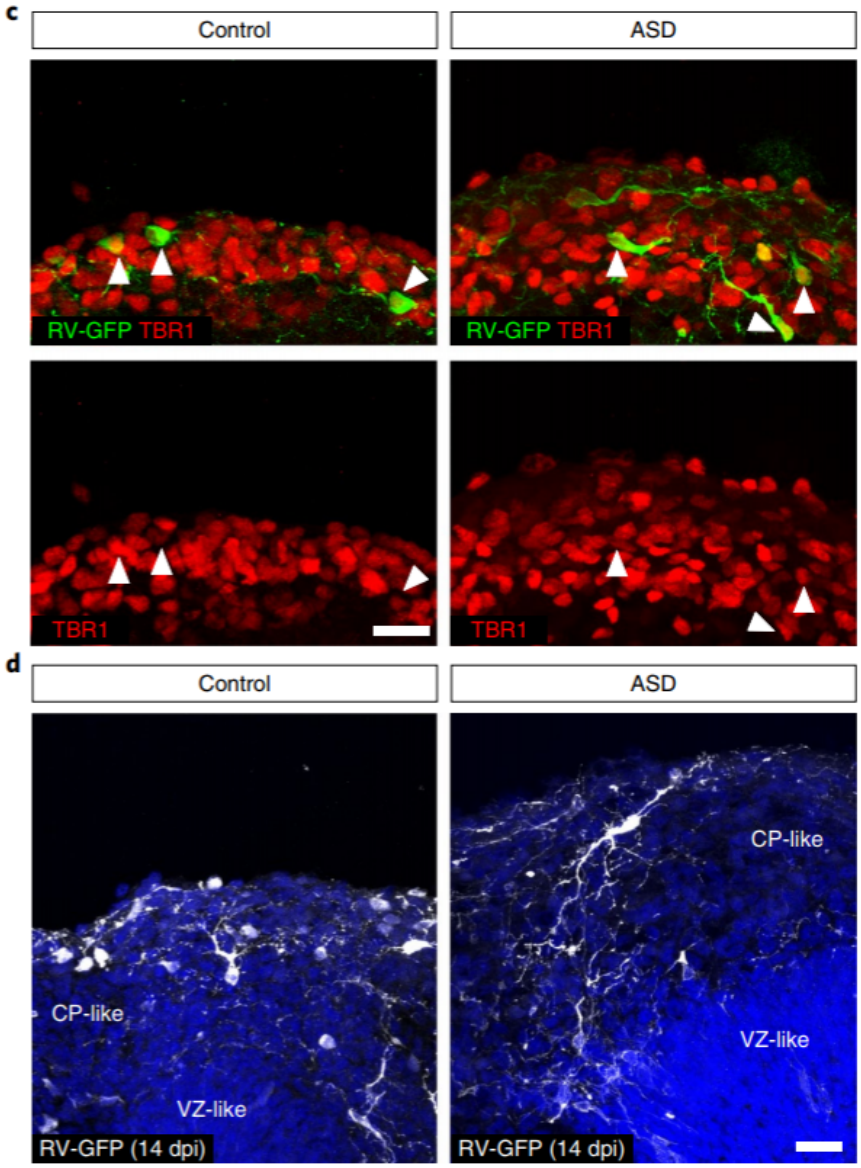
Paola Arlotta, Nature Methods, 15:27-29, 2018

Science Advances in Stem Cell Modeling *Autism*



- Labeled dividing radial glial-like cells in organoids for lineage tracing
- No difference in overall cell fate commitment
- **Differences in timing:** Early-born ASD cortical neurons had aberrantly complex neurite structures

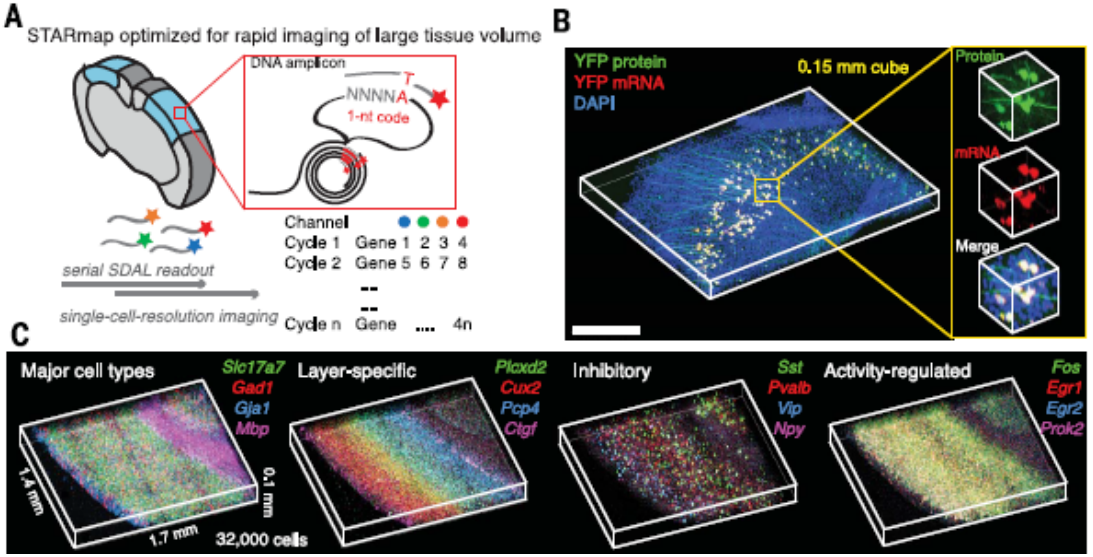
Schafer et al, Nat Neuro, 2019



National Institute of Neurological Disorders and Stroke

STARmap: 3D Intact-tissue Sequencing of Single-Cell Transcriptional States

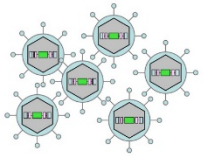
- Dr. Karl Diesseroth and colleagues at Stanford have developed STARmap: spatially-resolved transcript amplicon readout mapping.
- Cellular RNAs are labelled by pairs of DNA probes followed by enzymatic amplification (amplicons).

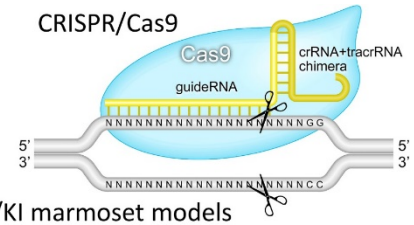


X. Wang et al., *Science,* 2018

- Tissue is transformed into 3D hydrogel DNA chip by anchoring DNA amplicons.
- To identify RNA species manifested by DNA amplicons, each species is encoded as a five-base barcode and read out by in situ sequencing method that decodes DNA sequence in multicolor fluorescence.

Marmosets as a Model System for Neurological Disorders

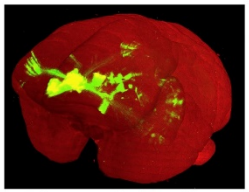




Transgenic/ target gene KO/KI marmoset models

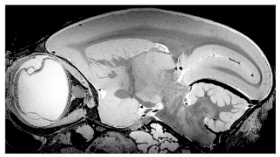
GM marmoset

9.4 T MRI

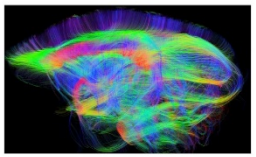


Tracer Injection
(Registration with MRI)

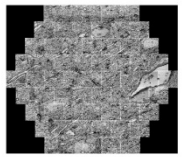
SEM



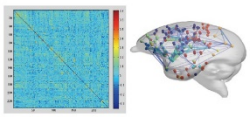
High Resolution MRI



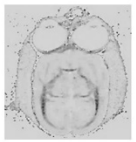
Diffusion Tensor Image



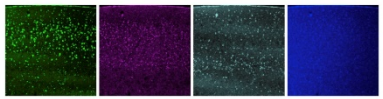
Micro-connectome



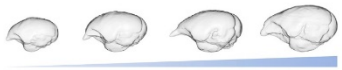
rs-fMRI



Myelination map



Correlative analysis



Developmental Standard brain

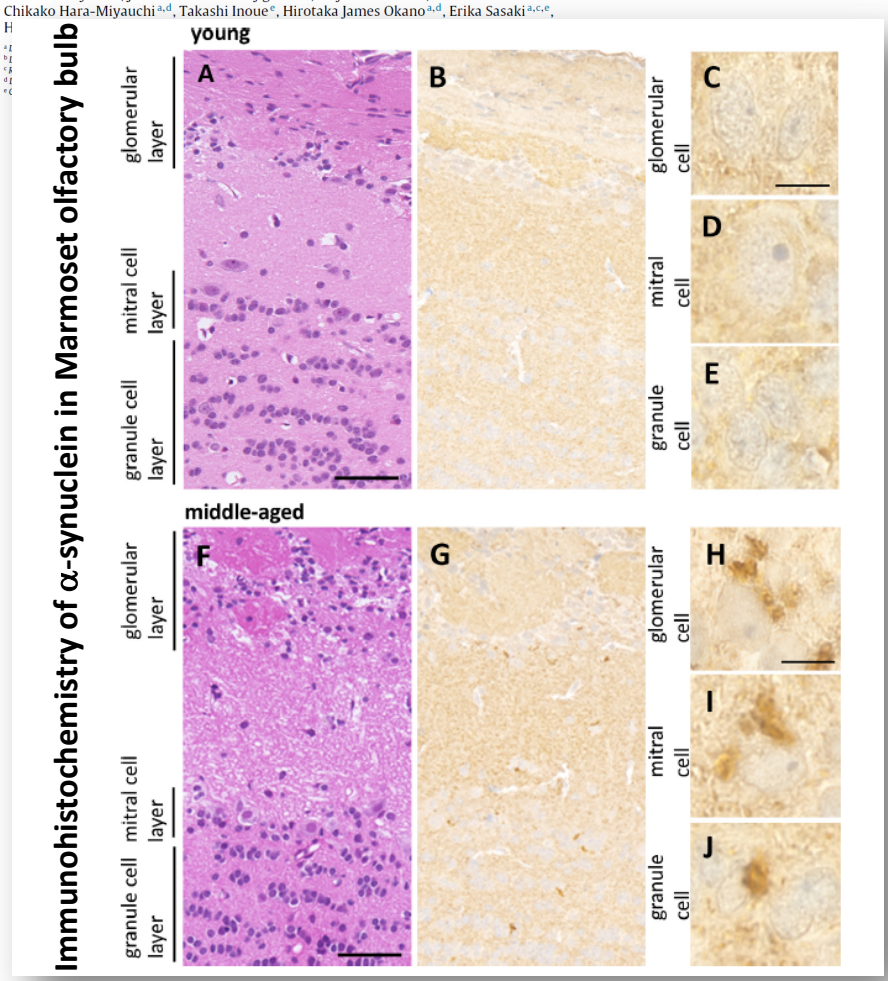
Okano, H., et al., (2016) Neuron
Volume 92, Issue 3, Pages 582-590

Example of a recent PD advance

Contents lists available at ScienceDirect
Neuroscience Research
journal homepage: www.elsevier.com/locate/neures

α-Synuclein aggregation in the olfactory bulb of middle-aged common marmoset

Reona Kobayashi[a], Junko Takahashi-Fujigasaki[b], Seiji Shiozawa[a,c], Chikako Hara-Miyauchi[a,d], Takashi Inoue[e], Hirotaka James Okano[a,d], Erika Sasaki[a,c,e],



NINDS Human Cell and Data Repository (NHCDR)

NeuroBioBank

NEUROREPOSITORIES

Repository Resources at NINDS

NINDS Human Biomarkers Biospecimen and Data Repository*

- ✓ CSF, DNA, Plasma, RNA, Serum, other types possible

BioSEND

NINDS Human Genetics Resource Center

- ✓ DNA and lymphoblastoid cell lines

NINDS Human Cell and Data Repository

- ✓ Fibroblast and iPSC lines

Parkinson's Disease Data Management Resource*

- ✓ Stores data for the PDBP

NIH Neurobiobank

- ✓ Post-mortem brain tissue

Federal Interagency TBI Research*

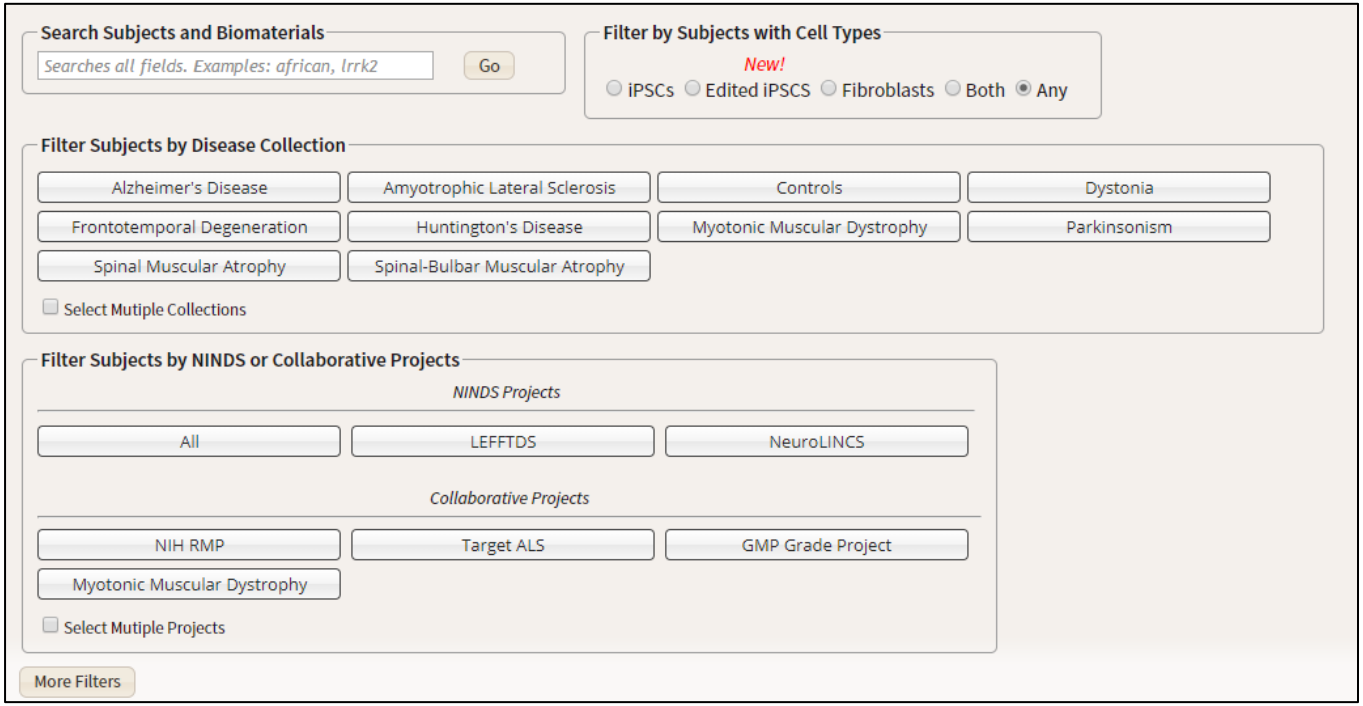
- ✓ May be used as a common data platform (imaging, omics, RNA Seq., etc.)

Applicants may also leverage other resources if sharing and rigor requirements are met

** Shared data structures*

NINDS Human Cell and Data Repository (NHCDR)

RUTGERS
THE STATE UNIVERSITY
OF NEW JERSEY



Jennifer Moore, PhD
Scott Saccone, PhD

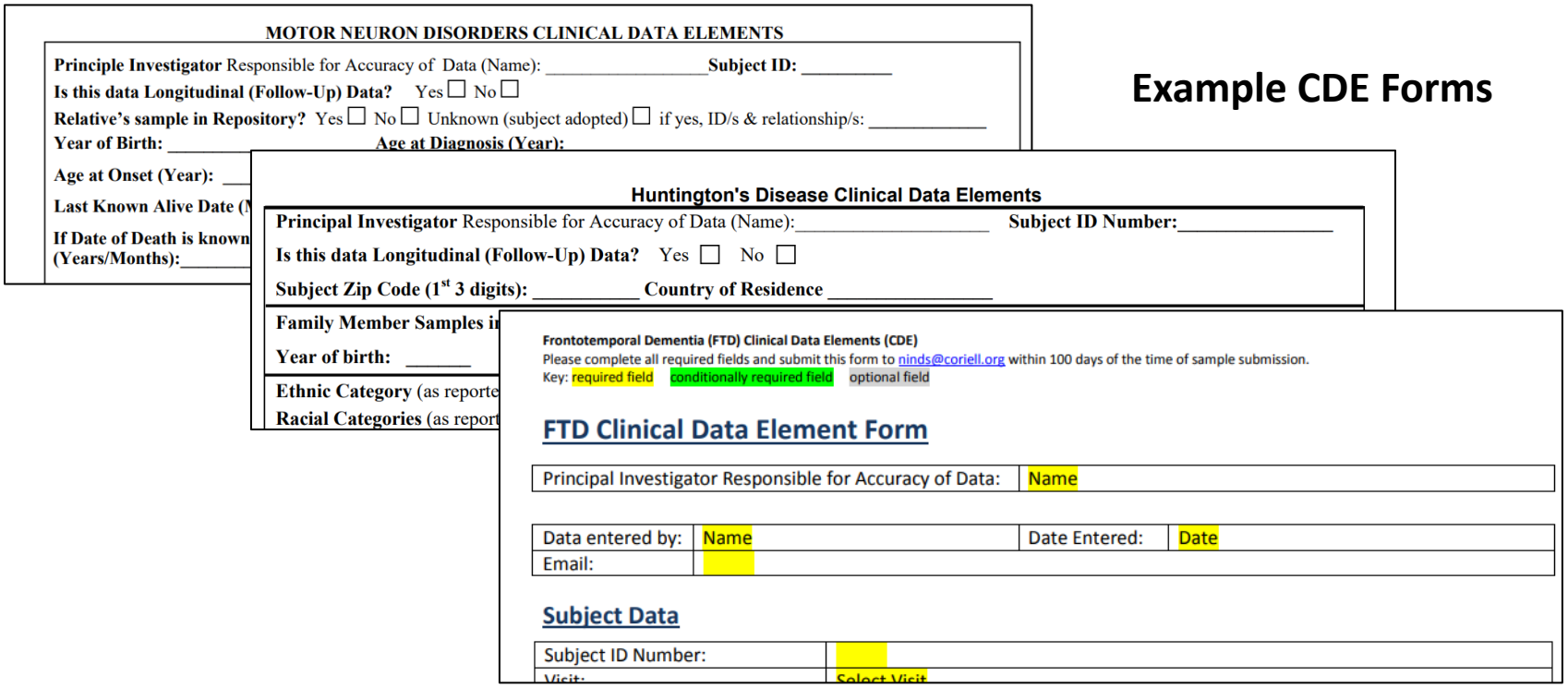
To date:

- Distributed over 1800 fibroblast lines and 600 iPSC lines

https://nindsgenetics.org/

NHCDR clinical data

- Interactive, sortable table for navigating the entire catalog
- Currently, each line has a clinical dataset derived from Common Data Elements (CDEs)
- Looking to the future: more extensive clinical data (e.g., dbGaP)

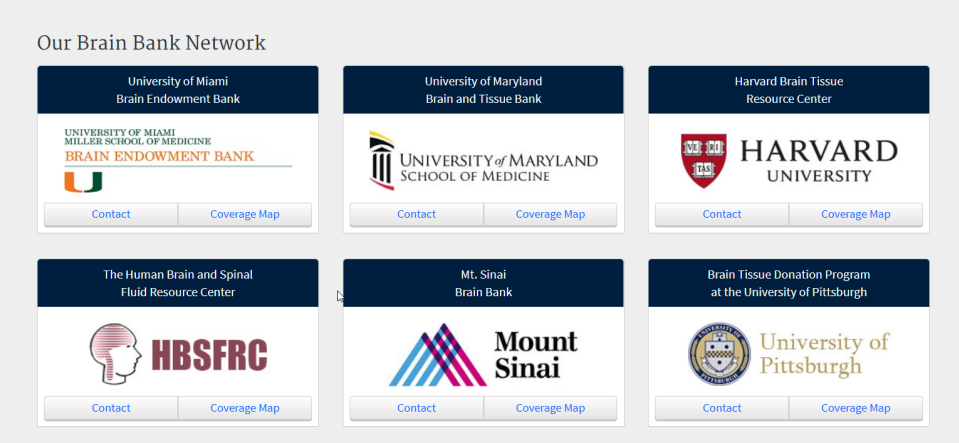


Example CDE Forms

https://nindsgenetics.org/

NIH NeuroBioBank

NeuroBioBank
Facilitating Research and Creating Awareness



- 12,600+ cases in inventory
- 2,100+ donors banked
- 400 + disorders represented
- 870+ requests submitted
- 560+ investigators served

By the numbers:

- Collaboration between NINDS, NIMH, NICHD, and NIA
- Current neurodegenerative disease subjects (as of 3/1/19)
  - Alzheimer's Disease = 1755 subjects, 1755 specimens
  - Parkinson's = 590 subjects, 588 specimens
  - Huntington's = 555 subjects, 551 specimens
  - ALS = 231 subjects & specimens
  - LBD = 271 subjects & specimens
  - Vascular dementia = 143 subjects & specimens

AD + ADRD

ALS

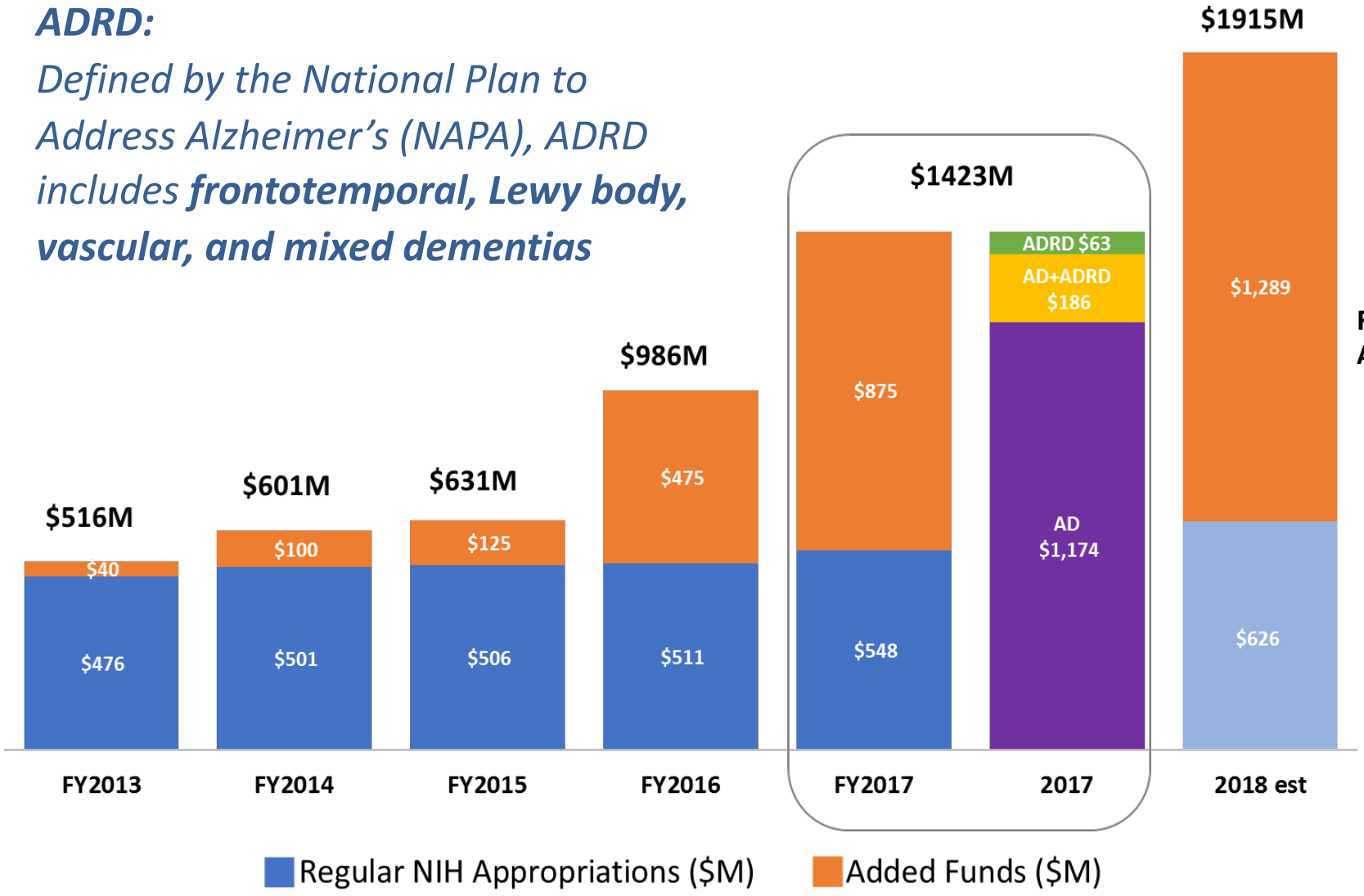
Parkinson's Disease

INITIATIVES IN NEURODEGENERATION

AD/ADRD Research Funding Increases at NIH

ADRD:

Defined by the National Plan to Address Alzheimer's (NAPA), ADRD includes ***frontotemporal, Lewy body, vascular, and mixed dementias***



FY19 Appropriations:

- **$2.3 B ($425 M increase)**

NINDS AD/ADRD Research Opportunities for FY 2019

***ADRD**: Types of dementias that share cognitive and pathological features with Alzheimer's and/or commonly co-occur with typical Alzheimer's pathology*

Vascular Dementias

VCID

- **RFA-NS-19-012** Prospective clinical research to determine the stroke and events and comorbidities that increase risk for or cause **Cognitive Impairment and Dementia in Post-Stroke Populations** (Application Deadline: Thursday, April 18, 2019)

Lewy Body Dementia (LBD)

LBD

- **PAR-19-170 Progression Markers for Cognitive Impairment** in Parkinson's Disease Dementia (PDD) (Application Deadline: Wednesday, May 8, 2019)
- **Lewy Body Dementia Center without Walls** to systematically and comprehensively characterize alpha-synuclein and amyloid-beta subspecies

Fronto-temporal Degeneration (FTD)

FTD

- Collaboration with the NIA for **FTD Natural History, Biomarker, and Genetics Studies**

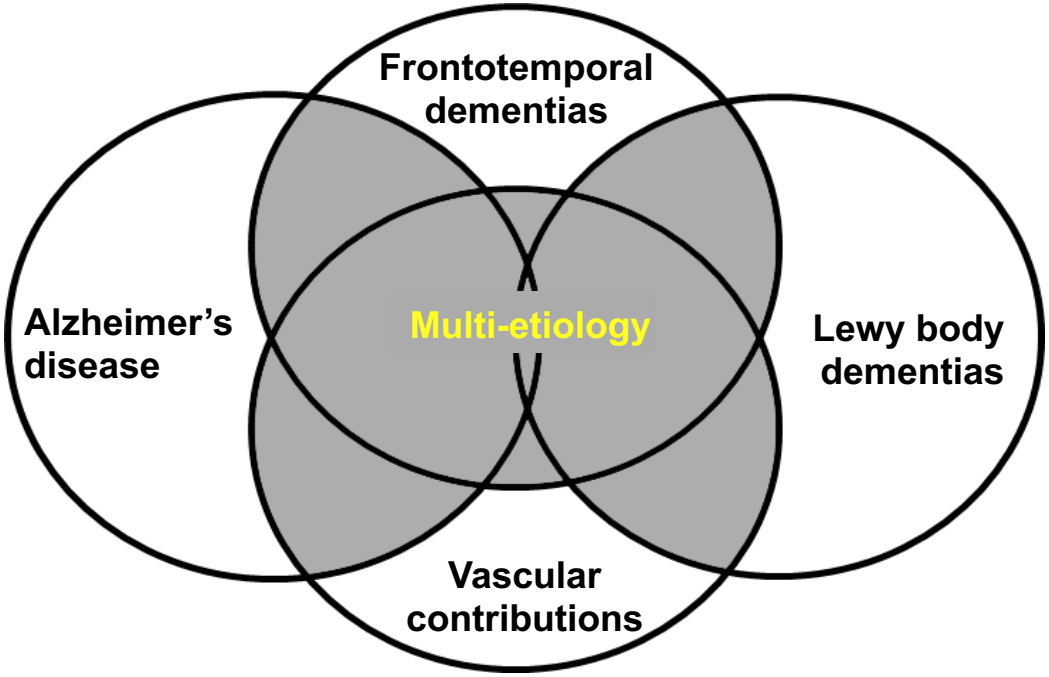
MED & AD/ADRD Cross Cutting

MED & HD

- **Advanced ADRD Animal and Cellular Models**
- **PET Ligand Development** to identify ADRD proteinopathies or pathological processes
- Studies on the **Clinical Research** and **Pathological Mechanisms of AD/ADRD in CTE/TBI**
- **RFA-NS-19-015** Validate novel **ADRD Druggable Targets** for development of pharmaceutical interventions (Application Deadline: Tuesday, May 7, 2019)
- **AD/ADRD Training Supplements** to mentor the researchers from underrepresented groups

Alzheimer's Disease-Related Dementias (ADRD)

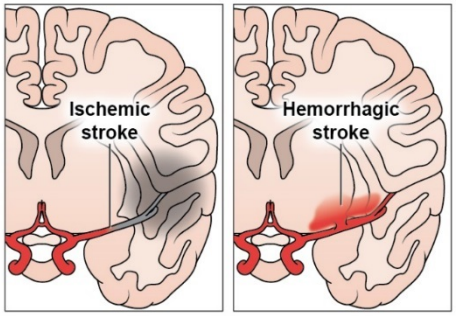
Dementia is a spectrum of diseases with multiple and often mixed etiologies



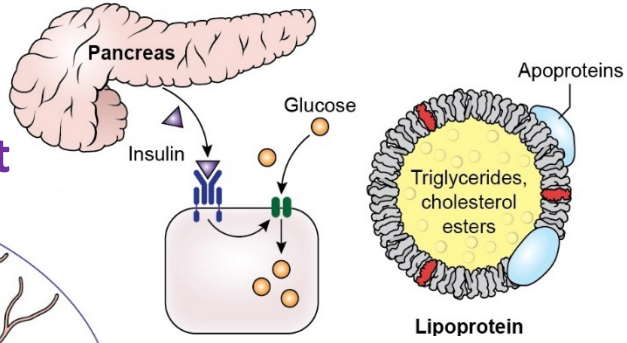
- How can we understand the different drivers at the cell, tissue and organ level
- How they are related?
- Can we prevent initial triggers?
- Can we slow disease processes?

The Science of Neural Degeneration

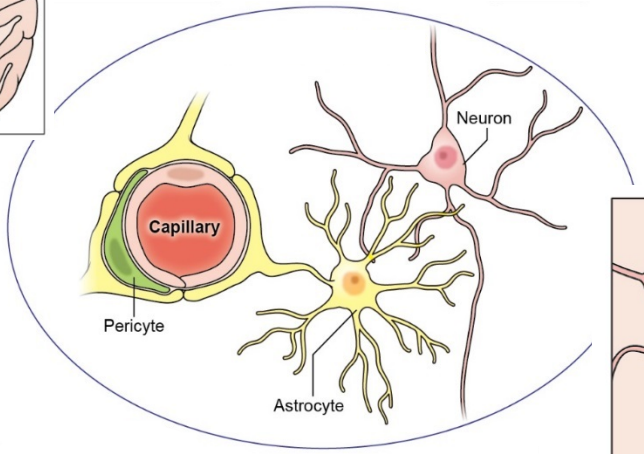
Cerebro- & Cardio-Vascular Biology

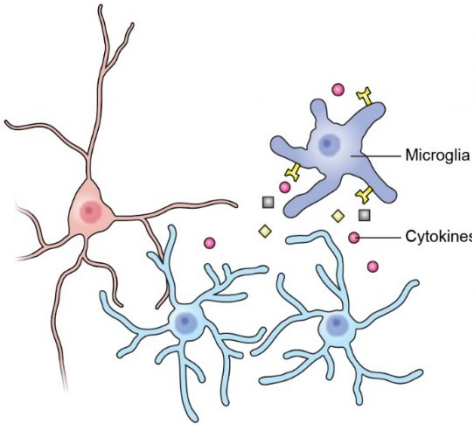


Metabolism

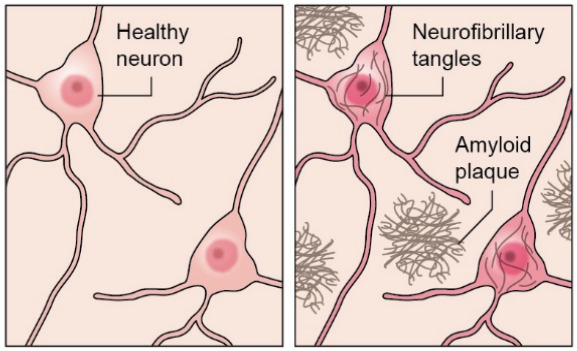


Neurovascular Unit





Immune Function



AD Biology

Mechanism-oriented dementia research is best described as the neuro-glial-immune vascular unit integrating proteinopathy, synaptopathy, metabolism, immune, small vessel.

NINDS ADRD Research Initiatives and Programs

supported by the additional AD/ADRD funds

REasons for Geographic and Racial Disparities in Stroke (REGARDS)

REGARDS

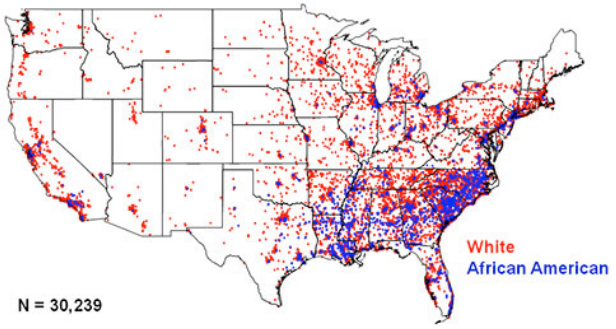


Image: UAB website

MarkVCID

National Consortium of 7 sites and 1 coordinating center **to develop and validate biomarkers for vascular contributions to cognitive impairment and dementia (VCID)**

NINDS ADRD Research Initiatives and Programs

supported by the additional AD/ADRD funds

Tau Center without Walls

Investigates molecular mechanisms that contribute to abnormal, toxic forms of tau that are found commonly in the brains of people with FTD, PSP and AD

West cWOW | East cWOW

Tau Center Without Walls

FTD Sequencing Consortium

Aims to discover and validate genetic factors (e.g., gene mutations) that increase FTD risk in active collaboration with NGOs, and researchers at NIH

NINDS ADRD Research Initiatives and Programs

supported by the additional AD/ADRD funds

The Lewy Body Dementias Biomarkers Initiative

Leverages the NINDS Parkinson's Disease Biomarkers Program (PDBP) to **support biomarker discovery studies for LBD** by adding data and biospecimens from patients with LBD

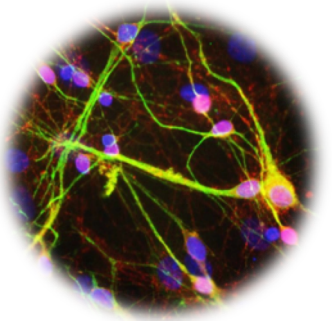
DetectCID

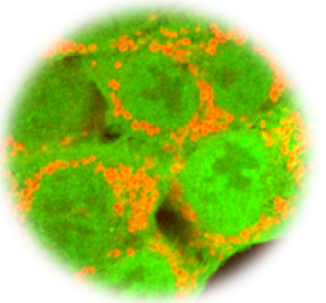
3 research teams are developing standardized, simple-to-use cognitive tests and detection tools that take 5 minutes or less **to increase accurate detection of cognitive impairment and dementia in primary care**

Image from UAB news

NINDS Supports Wide Range of PD Research

- **Basic science**: molecular mechanisms, synuclein spreading, genetic and environmental risk factors
- **Udall Centers of Excellence**
- **Clinical research**
  - Environmental triggers- microbiome, toxin
  - Clinical trials identify successful (DBS, Tai Chi) and unsuccessful (CoQ10, creatine, pioglitazone) therapies
  - Trials underway:
    - SURE-PD3 (Study of URate Elevation in Parkinson's Disease)
    - STEADY-PD III (Efficacy of Isradipine in early Parkinson Disease)
    - SPARX (Study in Parkinson's Disease of Exercise)
    - AAV2-GDNF for Advanced Parkinson's Disease
- **Biomarkers are critical if going to increase probability of identifying treatments**
  - PD Biomarkers Program (PDBP)
  - BioFIND
  - Accelerating Medicines Partnership (AMP-PD)





Parkinson's Disease Biomarker's Program (PDBP) Goals

- **PDBP promotes discovery of biomarker candidates for early detection and measurement of disease progression**
- **PDBP coordinates the efforts of multiple stakeholders through a common Data Management Resource and web portal**
- **PDBP is a multi-faceted platform for**:
  - Integrating existing biomarker efforts
  - Standardizing data collection and management across these efforts
  - Accelerating the discovery of new biomarkers
  - Fostering and expanding collaborative opportunities for all stakeholders

Accelerated Medicines Partnership in Parkinson's Disease (AMP-PD)

Public Private Partnership to identify and validate diagnostic, prognostic, and progression biomarkers

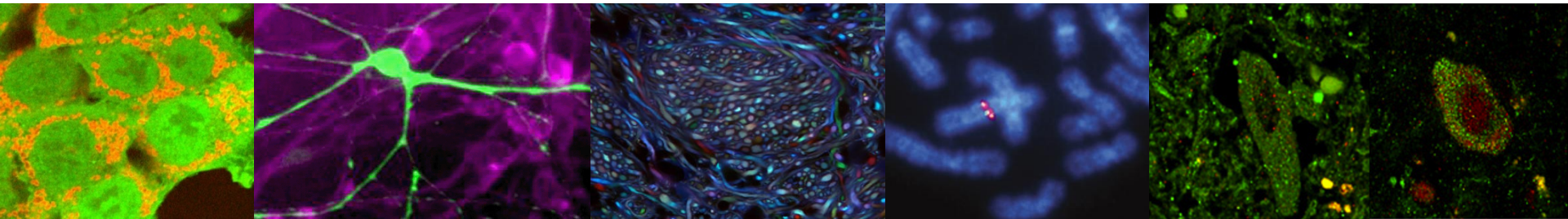
Partners: Celgene, GSK, MJFF, Pfizer, Verily, Sanofi, NINDS, FDA

Cohorts: PPMI, BioFIND, PDBP, HBS

FNIH
Foundation for the National Institutes of Health

$24M project aims to:

- Standardize clinical data vin PPMI, PDBP, HBC, BioFind
- Conduct standardized assays on thousands of existing biosamples, incorporating existing clinical, imaging, genetic data
- Clinical data with transcriptomics, epigenomics, whole genome sequencing, metabolomics, proteomics for wide research use.
- Dissect new targets, disease subtypes; track, predict disease progression



AMP-PD Research Plan

Stage 1	Stage 2	Stage 3
$2.3-3 M	$10-15 M	$3-6 M
0 – 14 months	12 – 48 months	36 – 60 months

- **Establish Working Groups**

Data working group will be the Central organizing unit

  – Transcriptomics

  – WGS

- **Develop operation and data processing SOPs**
- **Harmonization datasets**

  – PPMI (MJFF)

  – PDBP, HBS, BioFIND

3,000 PD cases & and 1,000 ctrls
Biosamples: 3313 CSF, 15,430 RNA, 10,392 plasma 4,000 DNA, PBMCs

verily

Launch AMP-PD Knowledge Portal

WGS, RNA seq, clinical data

Adaptive Design

F2F Meeting to finalize strategy for Stage 2

Plasma | **Serum** | **CSF**

Platform Analysis

- **Extracellular RNA (exRNA) seq**
- **Proteomics**
- **Metabolomics**

Brain Platform

- **Feasibility Study**
- **Single cell RNA seq**

GO → **RFA(s)/ Contracts/ Prize Challenge**

RFAs/contracts/Prize Challenge

GO →

- Longitudinal cohort analysis of successful platforms from Stage 2
- RFA for data analysis, tool development, disease modeling

NINDS Clinical Trial Data

- Add data from 2 Phase III clinical trials to AMP-PD knowledge portal
- WGS
- Plasma samples

FNIH Foundation for the National Institutes of Health | Accelerating Medicines Partnership

Thank You!

Walter J. Koroshetz, M.D.

Director

National Institute of Neurological Disorders and Stroke

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Website: http://www.ninds.nih.gov/

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