NINDS Funding Strategy
-
NIH Research on Multiple Sclerosis

National Institute of Neurological Disorders and Stroke

NASEM – Committee for the Assessment of NIH Research on Autoimmune Diseases
February 1, 2021

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Program Director

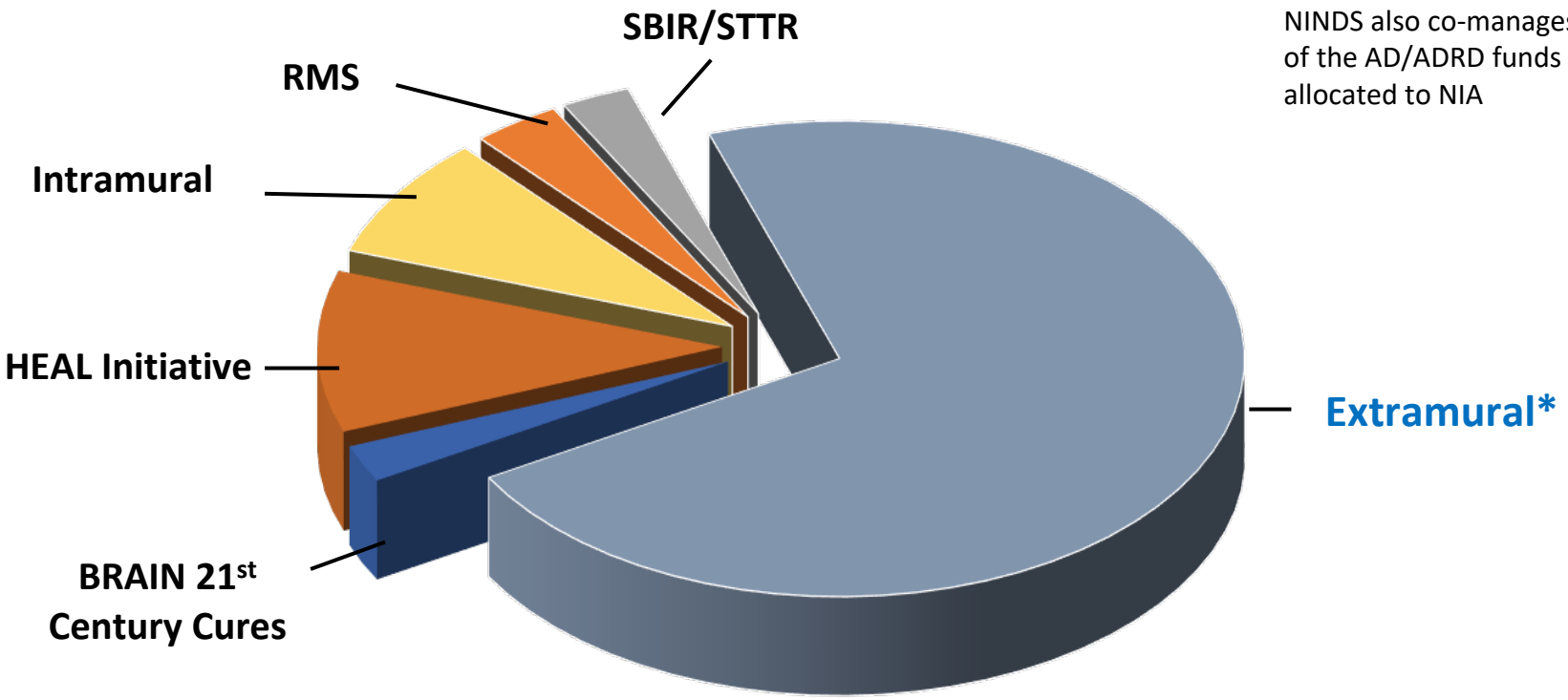
NINDS - Mission

To seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease

- 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

NINDS - Budget

FY 2019: $2.274 B



NINDS also co-manages parts of the AD/ADRD funds allocated to NIA

- 6,399 applications received / 1,409 new grants awarded
- 4,469 active grants
- Supported 4,271 PIs from 457 organizations

NINDS mission covers a wide range of neurological disorders

NIH National I Neurologi and Stroke

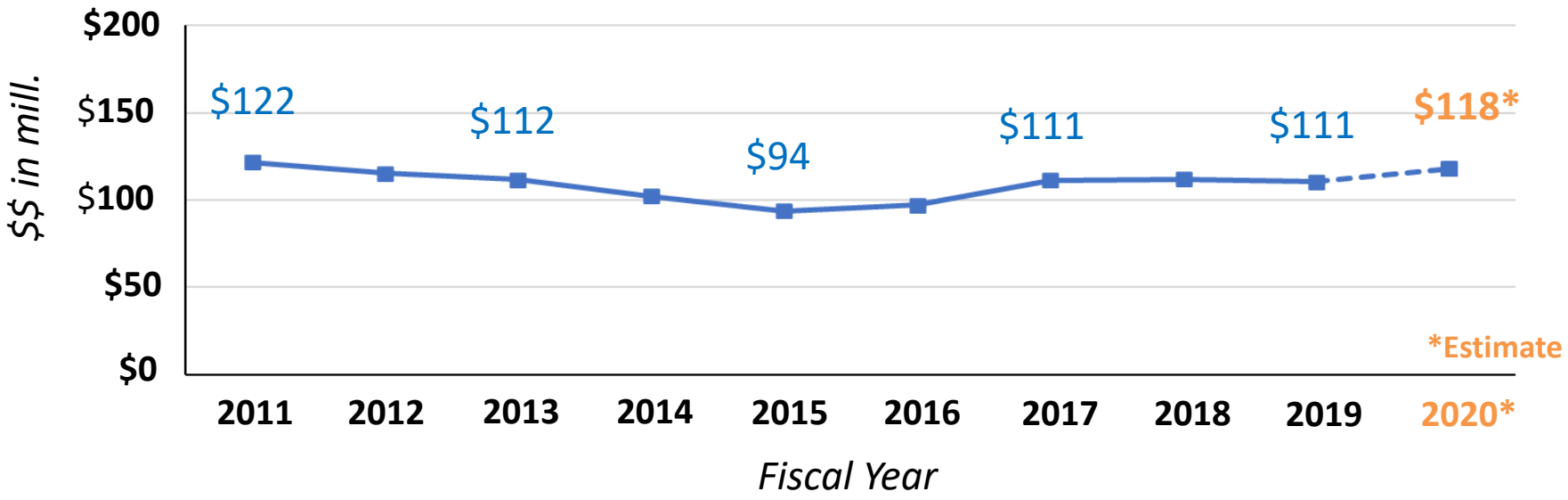
Autoimmune Disease at NINDS

- **Multiple Sclerosis**
- Neuromyelitis Optica
- MOG-Antibody associated disorders
- Myasthenia Gravis
- Guillain-Barré syndrome
- Autoimmune encephalitis (ie. Anti-N-methyl D-aspartate R)
- Transverse myelitis
- Acute disseminated Encephalomyelitis
- Paraneoplastic Syndromes

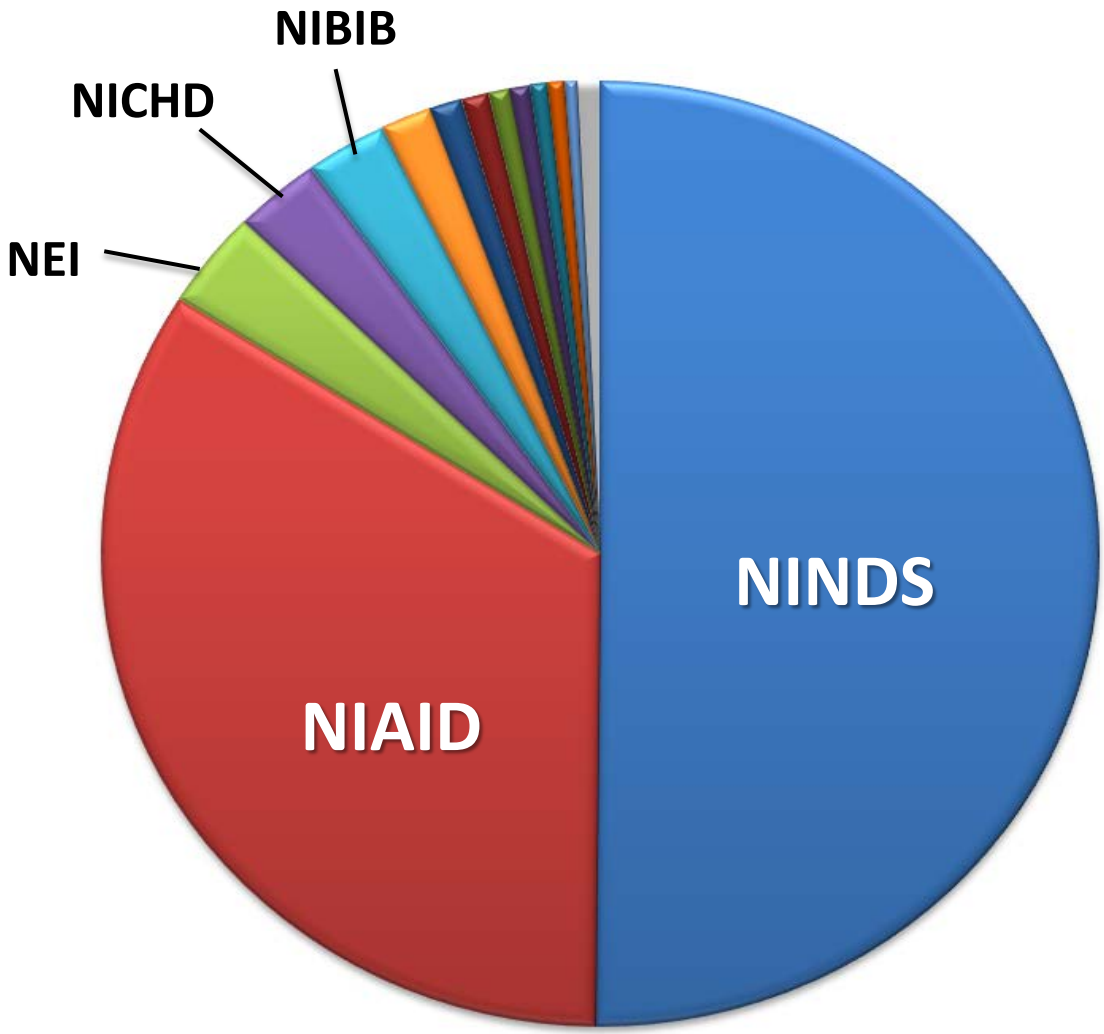
NIH MS Budget Trends

MS category constant over time

MS category represents ~11% of NIH AD category



NIH Multiple Sclerosis funding by IC

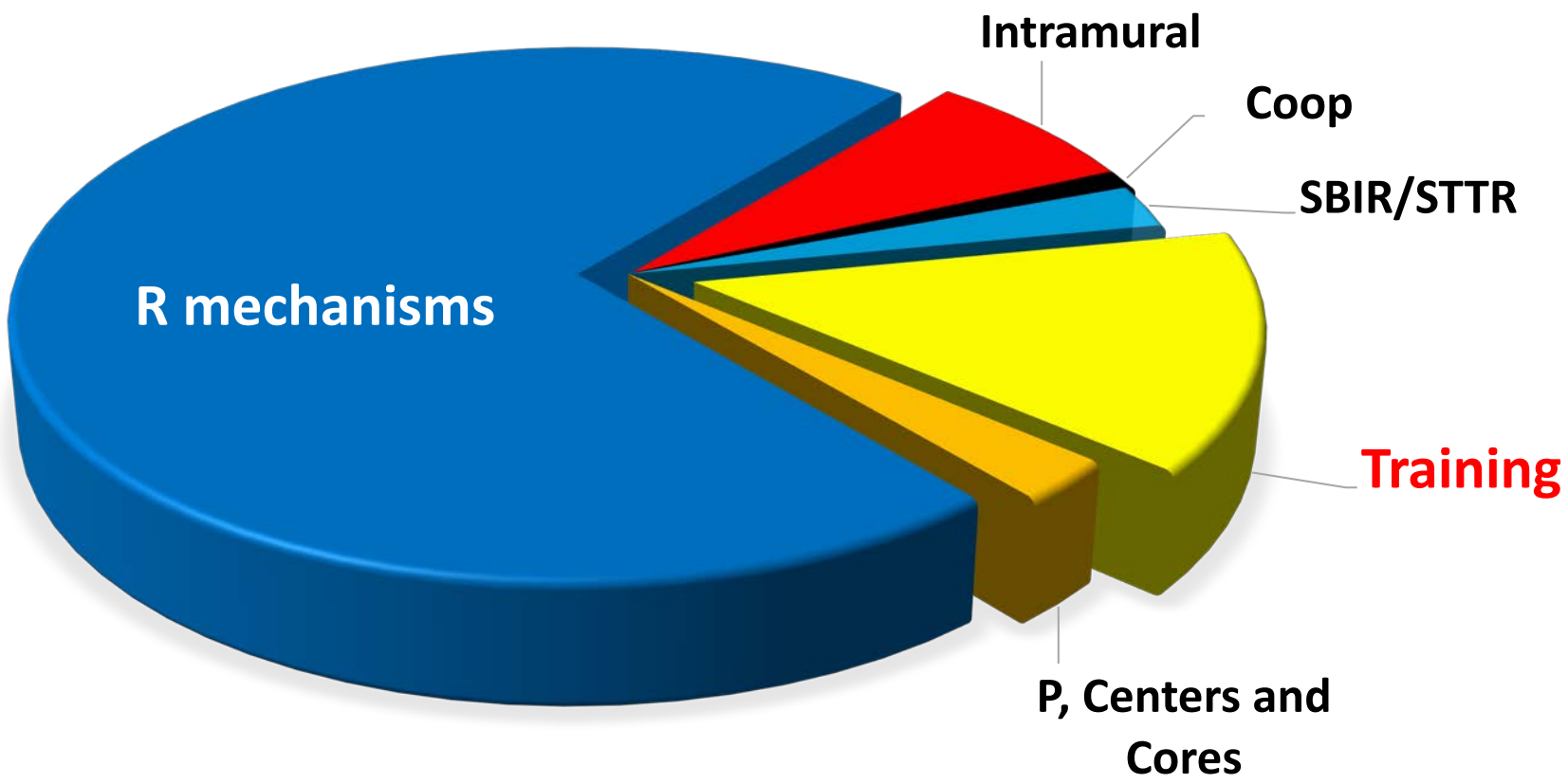


FY 2019
NIH: $110.6M

NINDS	$55.50M
NIAID	$37.50M
NEI	$3.70M
NICHD	$3.10M
NIBIB	$2.90M
NCI	$1.84M
NIA	$1.15M
NIGMS	$0.97M
NCATS	$0.78M
NIEHS	$0.73M
NIDDK	$0.62M
NINR	$0.61M
OD	$0.44M
NIDA	$0.30M
NIMHD	$0.19M
NIMH	$0.16M
NCCIH	$0.13M
NIDCD	$0.03M

NIH MS Projects by Grant Mechanism

FY2019
271 Projects



NIH Intramural Research Program

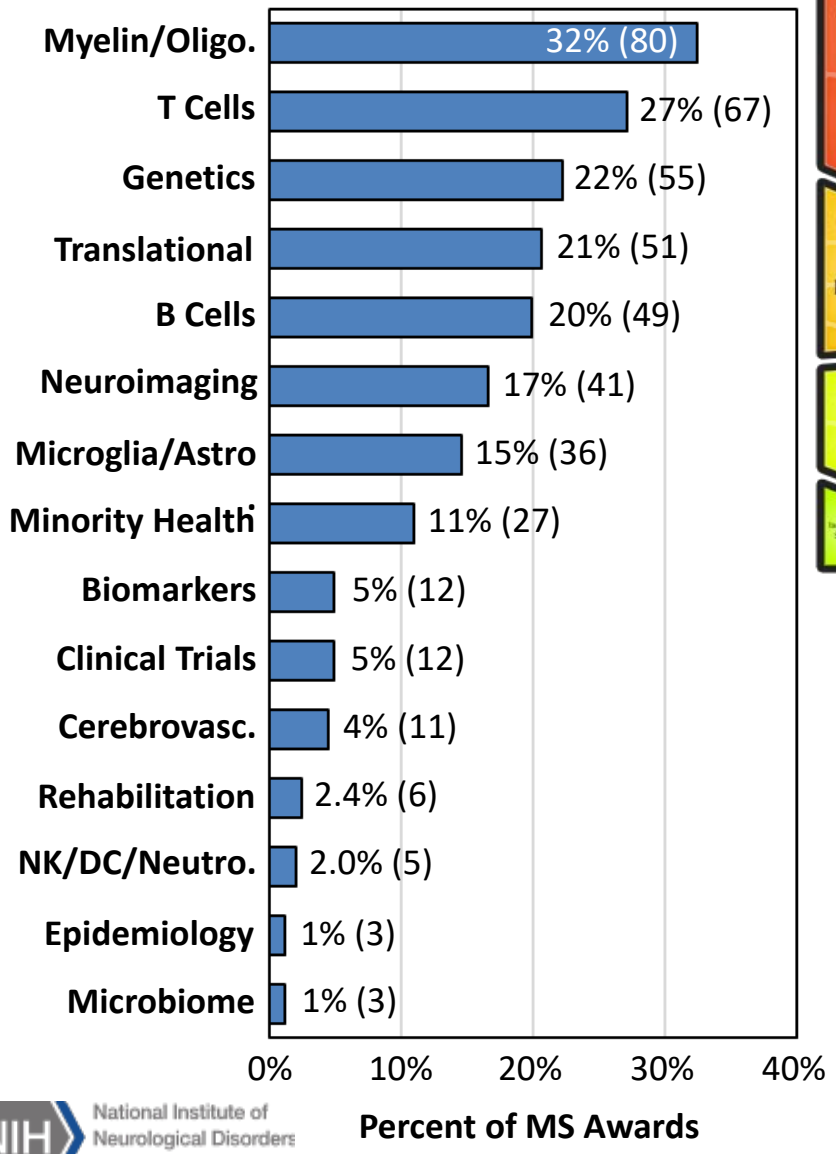
Daniel Reich, MD, PhD

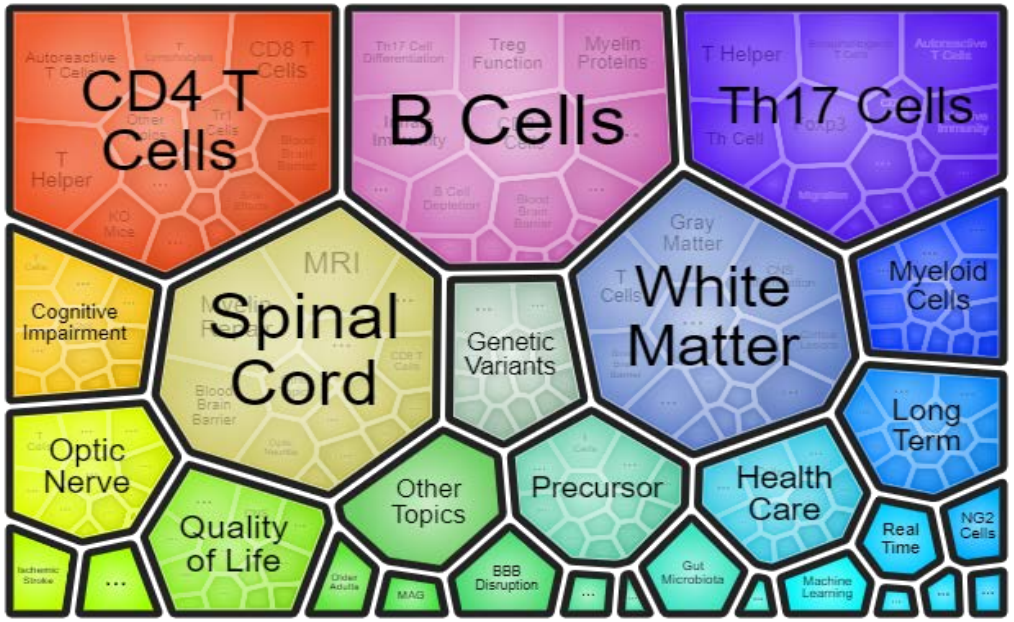
NINDS, Translational Neuroradiology Section. Use of advanced MRI techniques to understand the sources of disability in MS and on ways of adapting those approaches for research trials and patient care. Noninvasive imaging modalities to dissect biological mechanisms of tissue damage.

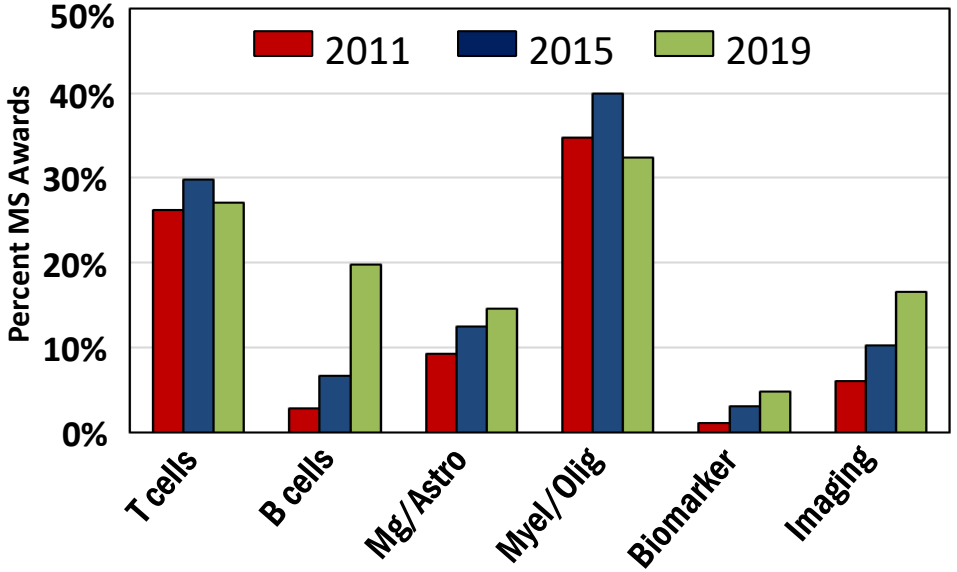
Bibiana Bielekova, MD

NIAID, Neuroimmunological Diseases Unit. CNS pathophysiological processes in MS with a focus on aberrant immune activation targeting CNS tissues. Combination trials supported by biomarker studies and mathematical modeling with the goal of developing precision medicine for diagnosis, prediction of disease progression and therapy response on an individual patient level.

FY2019 NIH Multiple Sclerosis portfolio







National Institute of Neurological Disorders and Stroke

MS research at NIH covers a wide range of topics and disciplines

- Innate and adaptive immune function and its dysregulation
- Glial cell types, their single cell heterogeneity and cross talk between astro, oligo, microglia ect
- Role of oligodendrocytes in de/remyelination/antigen presentation/myelin repair
- Cells and factors involved in axonal degeneration and neuroprotection
- Role of neuroinflammation/signaling pathways
- BBB and mechanisms of cell migration
- Development of novel imaging methods and their application
- Genetic and environmental risk factors
- Sex differences, hormonal impact
- Role of the gut microbiome and of diet
- Cognitive impairment and cognitive reserve
- Studies on MS symptoms such as fatigue, bladder dysfunction, pain, depression, etc.
- Impact of co-morbidities and aging on MS
- Health disparities (in disease manifestation and outcome)
- Improved outcome measures, CDEs
- Biomarker research
- Rehabilitation and Quality of Life
- Animal model development
- Ophthalmologic changes/optic neuritis/RNFL/OCT/VEP
- ……

We have made substantial progress – with much still to do

Identified over 200 genetic variants associated with MS – MSHapMap (1st NINDS complex genetic disorder)

- Research into gene functions; whole exome sequencing, miRNA and gene regulation, single cell RNASeq linked with anatomical location

Over two dozen medications for MS to chose from, most approved within the past 5-10 years.

- Most are immunomodulatory - need for neuroprotective/repair agents!
- Need for phase II outcome measures to advance drug development in progressive disease

Identified environmental and life-style risk factors in MS (obesity, smoking, Vitamin D deficiency, impact of diet) and the impact of co-morbidities

- Characterize prodromal phase/Prognosis for RIS and CIS
- Ultimate goal: prevention trials

Advances in neuroimaging (7T, sophisticated postprocessing of images and development of algorithms, novel PET tracers, small animal imaging, ability to image without Gd injections, machine learning, BRAIN Connectome

- Validation of utility for predicting disease course and therapeutic monitoring

Technological advances such as opto-genetics, CRISPR, 2-photon microscopy, all applied to MS.

Several feasible biomarkers are in testing and validation stages

- additional discovery/validation efforts such as VEP/OCT; Use for discovery of underlying pathology

Progress in the understanding of pediatric MS

- Clinical trials in this population

Identified repair pathways and therapeutic interventions

- Move forward into drug development pipeline and early clinical trials

Improvements in Telehealth, rehabilitative and wellness interventions/Wearable technologies

Diagnosis for MS happens faster and is more accurate

Appreciation of heterogeneity of MS and differences to related disorders

A multitude of consortia have formed, and longitudinal cohorts were established.

Advances towards precision medicine/Individualized therapy

NINDS - Programs

- Most NINDS programs are disease agnostic
- Funding is based on merit as determined by peer-review
  - Limited opportunities for special pay and Bridge awards based on programmatic priorities and other factors
- Specific programs undergo NINDS “in-house” custom review
    - **Training programs (K awards, T32)**
    - **Research Centers and Cores**
    - **Translational/Drug development***
    - **Clinical trials/Clinical networks***

* milestone-driven

NINDS - Translation
Bridge the Gap to Clinical Trials

Development Programs

NIH Blueprint for Neuroscience Research

NIH National Institutes of Health

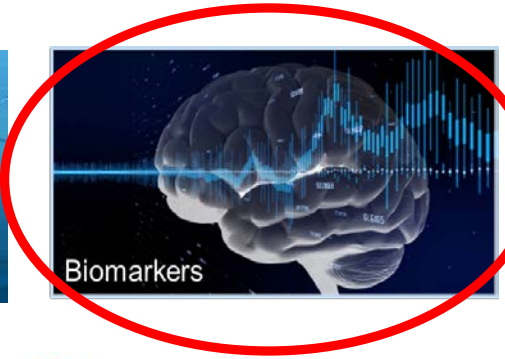
CREATE Bio

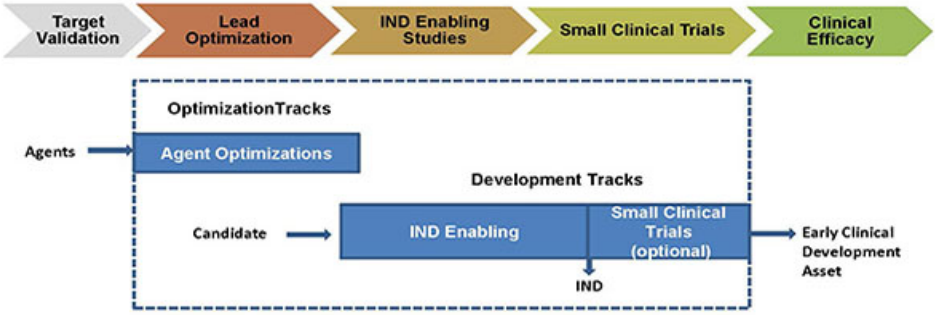
Translational Neural Devices

SBIR · STTR
America's Seed Fund

Feasibility Programs and Contract Resources

IGNITE
Innovation Grants to Nurture Initial Translational Efforts





Training

ADME/Tox.

Chemistry

Manufacturing

Clinical

Biomarkers: Discovery and Validation

Analytical Validation of a Candidate Biomarker for Neurological Disease
PAR-18-550, PAR-18-549

Clinical Validation of a Candidate Biomarker for Neurological Disease
PAR-18-664, PAR-18-548

Two MS projects were the first funded validation projects under this new program

- ***Validation of Serum Neurofilament Light Chain as a Prognostic and Monitoring Biomarker in Multiple Sclerosis***

Can NfL determine ongoing neuro-axonal damage prior to permanent disability?
Serum NfL as a prognostic and monitoring biomarker in large, demographically diverse patient cohorts

- ***Central Vein Sign: a Diagnostic Biomarker in Multiple Sclerosis***

Can evaluation for CVS hasten accurate diagnosis in individuals with typical presentations of an initial demyelinating event.
Can it be an accurate test for MS among individuals with atypical presentations of a suspected demyelinating disease.

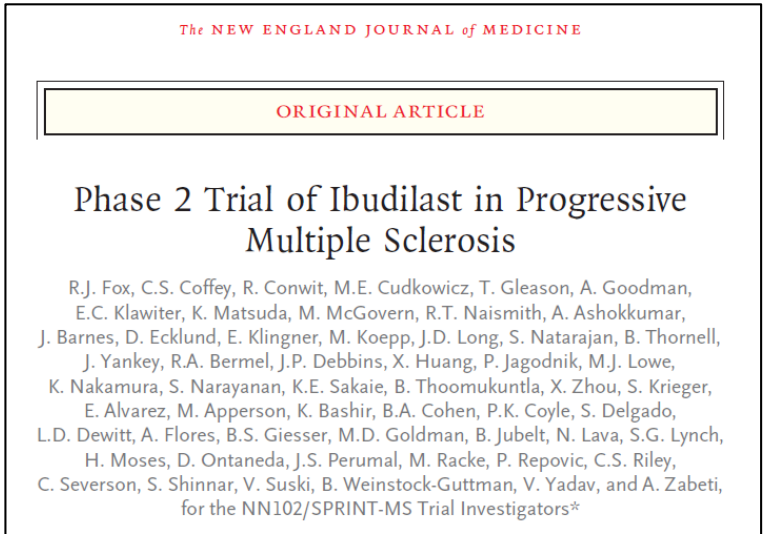
NINDS – Clinical Trials Programs

- **Common Data Elements – MS was one of the first 5 diseases we tackled**
- **First in Human Trials**
- **CT Readiness for Rare Neurological and Neuromuscular Diseases**
- **NINDS Exploratory Clinical Trials**
- **NINDS Efficacy Clinical Trials**
- **Comparative Effectiveness Research:** comparing the benefits and harms of different existing interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings
- **NINDS Clinical Trials Networks**
  - Early Phase Pain Investigation Clinical Network (EPPIC-Net)
  - Stroke Trials Network (NIH StrokeNet)
  - **Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)**
  - SIREN (Strategies to Innovate EmeRgENcy Care Clinical Trials Network)
  - Neurological Emergencies Treatment Trials (NETT) Network

SPRINT-MS: Ibudilast in Progressive MS

SPRINT-MS: First funded trial in the new NeuroNEXT network

- 96-week, 28-site, phase II trial in the NeuroNEXT network
- Primary Outcome: brain atrophy
- Secondary outcomes: additional imaging measures
- Main findings:
  - 48% slowing in progression of brain atrophy
  - Strong safety/tolerability
- Funding NINDS, MediciNova, NMSS



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis

R.J. Fox, C.S. Coffey, R. Conwit, M.E. Cudkowicz, T. Gleason, A. Goodman, E.C. Klawiter, K. Matsuda, M. McGovern, R.T. Naismith, A. Ashokkumar, J. Barnes, D. Ecklund, E. Klingner, M. Koepp, J.D. Long, S. Natarajan, B. Thornell, J. Yankey, R.A. Bermel, J.P. Debbins, X. Huang, P. Jagodnik, M.J. Lowe, K. Nakamura, S. Narayanan, K.E. Sakaie, B. Thoomukuntla, X. Zhou, S. Krieger, E. Alvarez, M. Apperson, K. Bashir, B.A. Cohen, P.K. Coyle, S. Delgado, L.D. Dewitt, A. Flores, B.S. Giesser, M.D. Goldman, B. Jubelt, N. Lava, S.G. Lynch, H. Moses, D. Ontaneda, J.S. Perumal, M. Racke, P. Repovic, C.S. Riley, C. Severson, S. Shinnar, V. Suski, B. Weinstock-Guttman, V. Yadav, and A. Zabeti, for the NN102/SPRINT-MS Trial Investigators*

National Institute of Neurological Disorders and Stroke

NINDS Collaborative Efforts

- DoD - Congressionally Directed Medical Research Programs – MS Integration Panel
- CDC – 21st Century Cures Act, National Neurological Conditions Surveillance System – MS and PD selected as pilot projects
- FDA/NINDS WG on CNS drug developments/Cell therapies
- PCORI – Advised PCORI on MS funding announcements/ integration of PCORI-funded projects in biomarker efforts
- NIAID/NINDS/NCI "HLA/KIR consortium"
- NIAID Autoimmune Centers of Excellence
- NIAID Immune Tolerance Network/Co-funding of clinical trials
- NCMRR/NINDS Joint workshop on "NIH Pathways to Prevention Workshop: Can Physical Activity Improve the Health of Wheelchair Users?"
- Joint projects with the National MS Society
- **NINDS holds an annual 2-day conference with our patient advocacy groups**

Thank you