NIH Priorities for Alzheimer’s Disease and Down Syndrome

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Global Down Syndrome Research and Medical Care Roundtable
June 27, 2019
New Trans-NIH Down Syndrome Initiative
Congressional Directive for DS

• In the FY 2018 budget legislation for NIH:
  ▫ “Develop a new trans-NIH initiative ... to study trisomy 21, with the aim of yielding scientific discoveries to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for:
    • Alzheimer's disease
    • cancer
    • cardiovascular disease
    • immune system dysregulation
    • and autism,
    • among others...”

• Unique double benefit: understanding both Down syndrome and shared common conditions (risks or resiliencies)

Protected from:
• Many solid tumors
• Atherosclerosis and heart attacks
INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE)

3 Components:

1. Conduct targeted, high-risk, high-reward basic science studies on chromosome 21. Emphasis on studies that can inform the other two components

2. Assemble a large cohort of individuals with Down syndrome across the lifespan for comprehensive phenotyping and biomarker analysis.

3. Include individuals with Down syndrome in existing and future clinical trials.
The INCLUDE Project: A Trans-NIH Initiative

National Cancer Institute (NCI)
National Eye Institute (NEI)
National Heart, Lung, and Blood Institute (NHLBI)
National Human Genome Research Institute (NHGRI)
National Institute on Aging (NIA)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
National Institute on Deafness and Other Communication Disorders (NIDCD)
National Institute of Dental and Craniofacial Research (NIDCR)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute of Environmental Health Sciences (NIEHS)
National Institute of Mental Health (NIMH)
National Institute on Minority Health and Health Disparities (NIMHD)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute of Nursing Research (NINR)
National Center for Advancing Translational Sciences (NCATS)
National Center for Complementary and Integrative Health (NCCIH)
Office of the Director/Office of Research Infrastructure Programs (ORIP)
Office of the Director/Office of Strategic Coordination (Common Fund)

20 different NIH institutes, centers, and offices involved!
NIH Funding for Research on Down Syndrome
FY 2008 - FY 2018

INCLUDE funding
FY2018 INCLUDE Funding

- ~$23 M supported 49 supplements to existing NIH grants
- Distributed among 14 Institutes
- All 3 components addressed
- Data sharing expectation
- Leverage DS-Connect®: The Down Syndrome Registry when possible

https://www.nih.gov/include-project
FY2018 AD-Related INCLUDE Supplements

- Treating with gamma-secretase modulators to prevent neurodegeneration in mouse models of DS and AD – Component 1

- Enhanced metabolomics in ABC-DS (Alzheimer’s Biomarkers Consortium – DS) – Component 2

- Lifestyle factors in ABC-DS – Component 2

- Role of midlife cardiovascular disease on AD pathology and cerebrovascular reactivity – Component 2

- Down Syndrome module for AD Centers (National Alzheimer’s Coordinating Center - NACC) – Components 2 & 3

- Building AD-DS clinical trials infrastructure within Alzheimer’s Clinical Trials Consortium (ACTC) – Component 3
Future Directions: FY2019-FY2022

• Continue support in FY2019 to fully launch the INCLUDE project

• Focus on new Requests for Applications (RFAs) to the greatest extent possible but also support additional supplements in FY2019 to further leverage existing infrastructure

• It is anticipated that this level of support will be maintained in FY2020 through FY2022

• Scientific workshops are planned for FY2019 and FY2020
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Ongoing NIA/NIH Translational Initiatives and Resources for Research on Alzheimer’s Disease in Down Syndrome
A Pipeline of NIA and Trans-NIH Translational Research Funding Initiatives

AMP-AD Targets
M²OVE-AD
Resilience-AD

MODEL-AD
AlzPED

ACTC
ADNI
AMP-AD
Biomarkers
ABC-DS

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT
Alzheimer’s Biomarkers Consortium - Down Syndrome (ABC-DS)

Exploring the Connection Between Down Syndrome and Alzheimer’s Disease

The ABC-DS study is a joint study conducted by two groups of research collaborators — Neurodegeneration in Aging Down Syndrome (NIAD) and Alzheimer’s Disease in Down Syndrome (ADDS) — and is supported by the National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), both part of NIH.

https://www.nia.nih.gov/research/abc-ds
ABC-DS

- $46M consortium - Two multi-institutional, cross-disciplinary research teams (Contact PIs: NiAD - Ben Handen, ADDS - Nicole Schupf) collaborating and harmonizing measures and procedures

- Biomarkers to track AD-related changes in the brain and cognition for ~400 adults with Down syndrome (25-85 years old)

- Measures include PET (Amyloid and Tau), MRI, CSF and blood markers, DNA for GWAS, cognitive/memory tests

- Data will be available in a public database via LONI/ATRI, pre-publication; samples will be made available to qualified investigators via the National Centralized Repository for Alzheimer’s Disease and Related Dementias (NCRAD)
ABC-DS Deliverables

- Develop valid assessment procedures for tracking clinical progression

- Determine proteomic, metabolomic and CSF biomarker profiles associated with different clinical profiles and track biomarker profile changes over the course from normal aging to MCI to AD onset and progression

- Identify multimodal MRI, amyloid and tau PET profiles associated with AD onset and progression

- Determine critical factors that link cerebral Aβ deposition to neurodegeneration

- Identify genetic signatures influencing AD risk

- Compare findings with other populations having high and low risk for AD
ABC-DS Performance Sites

NiAD Sites
- University of Pittsburgh (coordinating center)
- University of Wisconsin, Madison
- University of Cambridge
- Washington University

ADDS Sites
- Columbia University (coordinating center)
- Harvard University
- University of California, Irvine
ABC-DS Planned Enrollment

NiAD
- 180 Subjects with DS (10% with AD)
- 40 Sibling controls
- age 25 and older

ADDS
- 200-225 Subjects with DS (25% with AD)
- Age 40 and older
Alzheimer's Disease Research Centers

- The NIA ADCs are NIH Centers of Excellence, established in 1984

- Areas of investigation range from:
  - the basic mechanisms of disease to
  - managing the symptoms and helping families cope with the effects

- ADC researchers conduct basic, clinical, translational and behavioral research and train scientists
ADC Diverse Populations

- **Underrepresented Groups**
  - Rural (Oregon, Wash U, Wisconsin)
  - African American (e.g., Rush, Kentucky, Wash U)
  - Asian (UCSF)
  - Hispanic (e.g., UC Davis, Penn, Columbia)
  - Native American (Arizona, Wisconsin, UW, Wake Forest)

- **Specific Populations**
  - *Down Syndrome* (Columbia, UC Irvine, Kentucky)
  - Dominantly Inherited Alzheimer’s Disease (DIAN study - Wash U)
  - FTLD (UCSF, Indiana, Mayo, Northwestern)
  - Oldest Old (UC Irvine)
  - English as a Second Language (Northwestern)
Alzheimer’s Disease Research Center

Structure

Administrative Core

Biomarker Core

Neuropathology Core

Optional Cores

Research Education Component

Alzheimer’s Disease Research Center

Clinical Core

Developmental Projects

Outreach, Recruitment and Engagement Core

Data and Statistics Management Core

Research Education Component


National Alzheimer’s Coordinating Center Database of Uniform Data Set

**Unique features of ADC Program**

- Very large number of geographically diverse, well-characterized, annually followed participants
- Longitudinal f/u
- Neuropathological data
- Many with imaging and genetic data also
- **Two modules have been added to the UDS** — 1) frontotemporal lobar degeneration (FTLD Module, implemented March 2015) and 2) Lewy body disease (LBD Module, implemented August 2017)

**Down Syndrome Module (DS Module) under development***

*INCLUDE Supplement  
https://www.alz.washington.edu/WEB/data_descript.html
Alzheimer's Clinical Trials Consortium (ACTC) (U24)

- Awarded December 2017; ~$70 M

- PIs: Paul Aisen, Alzheimer’s Therapeutic Research Institute (ATRI), San Diego; Reisa Sperling, Brigham and Women’s Hospital and Massachusetts General Hospital, Boston; Ronald Petersen, Mayo Clinic, Rochester, Minnesota (U24AG057437)

- Includes multiple clinical trial sites with dedicated support

- A separate NIA Funding Opportunity Announcement (FOA) is soliciting applications for clinical trials to be managed and supported by the ACTC (PAR-18-513)

ACTC Goals:

• Conduct clinical trials (early to late stage) of promising pharmacological and non-pharmacological interventions for cognitive and neuropsychiatric symptoms in individuals with AD and other age-related dementias across the spectrum from pre-symptomatic to more severe stages of disease.

• Provide a state-of-the-art clinical trial infrastructure to facilitate rapid development and implementation of protocols, including a centralized Institutional Review Board (IRB).

• Provide leadership in innovative trial design methods, outcomes and analyses as well as recruitment strategies, particularly in diverse populations.

• Enable broad sharing of procedures and methods, as well as trial data and biosamples.
Leverage the extensive breadth and depth of expertise within ACTC and ABC-DS to efficiently conduct AD clinical trials in the DS population

1) Augment ACTC units with insights from leading experts in DS, including ABC-DS and European groups

2) Develop and facilitate sites capable of conducting AD clinical trial protocols in individuals with DS

3) Develop an electronic database for the ACTC-DS network that is harmonized with ABC-DS data standards
Other NIA/NIH Alzheimer’s and Related Dementias Clinical Trial Mechanisms

• Early Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01) PAR-18-877
  ▫ Phase I and II, pharmacological and non-pharmacological interventions
  ▫ Studies on trial design and methods

• Late Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01) PAR-18-878
  ▫ Phase II/III, III, pharmacological and non-pharmacological interventions

• Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD): R43/R44 PAS-18-187 & R41/R42 PAS-18-188
A Randomized, Placebo-Controlled, Dose-Escalating, Multicenter, Phase 1b Clinical Trial of the Anti-Amyloid Vaccine ACI-24 in Adults with Down Syndrome
3 Star Study

- AG047922 - supported by NIA, LuMind Foundation and AC Immune

- ACI-24: Anti-amyloid active vaccine; currently in phase 2 for sporadic AD in Europe

- Aims to stimulate the immune system (without concomitant pro-inflammatory T cell activation) to produce antibodies that specifically target the oligomeric and fibrillar Abeta proteins to prevent plaque accumulation and to enhance plaque clearance

- 3 clinical trial sites – Barrow, MGH, UCSD

- The first (low-dose) and the second (high-dose) cohorts fully enrolled
3 Star Study Design

- Phase I (safety and tolerability)

- Participants aged 25-45 with DS, IQ>40

- 2 cohorts (low dose, high dose) of 8 subjects each (n=16, 12 active treatment, 4 placebo)

- 12 months treatment and 12 months safety follow-up

- All participants have been able to complete all study procedures

- Topline results expected late 2020

- Optional cohort 3 expansion: additional 8 subjects based on safety, tolerability, immunogenicity or target engagement data

Slide courtesy of Michael Rafii with modifications
Thank You!

Welcome to Alzheimers.gov

The Federal Government portal to information on Alzheimer’s disease and related dementias care, research, and support.

- Get answers about Alzheimer’s, dementia, and caregiving
- Join a clinical trial
- Stay up to date with research news
- Find resources for healthcare professionals

DS-Connect® is a powerful resource where people with Down syndrome and their families can:

- Connect with researchers and health care providers.
- Express interest in participating in clinical studies on Down Syndrome, including studies of new medications and other treatments.
- Take confidential health-related surveys. These surveys are aimed at better understanding the health of people with Down Syndrome across their lifespans.

Join the Registry  Set up a Professional Account  Información en español