From Bench to Bedside: Exploring the Research Continuum at NIA

UAB Integrated Aging Research Research Symposium

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Director
National Institute on Aging

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Appropriations and Funding
FY 2019 Budget

$39 Billion for the NIH

- $40M for universal flu vaccine
- $29M increase for BRAIN
- $86M increase for All of US
- $425M increase for AD/ADRD

- $3.1B for the NIA
- $84M increase for NIA research; percent increase comparable to other ICs

- All NIA divisions will benefit
  - Behavioral and Social Research
  - Aging Biology
  - Neuroscience
  - Geriatrics and Clinical Gerontology
FY19 enacted level for NIA was $3.083B

- **Senate committee draft includes:**
  - An additional $3B for NIH above FY19 funding levels
  - $3.606B (16.9% increase) for NIA; this figure includes $350M for AD/ADRD research

- **House passed bill (HR 2740) includes:**
  - An additional $2B for NIH above FY19 funding levels
  - $3.356B (8.8% increase) for NIA

- HR 4378 signed on 9/27/19 – funds the Federal government (at FY19 levels) through November 21, 2019
NIA Appropriations
Fiscal Years 2013-2019

Dollars (in millions)

- 2013: $1,046
- 2014: $1,171
- 2015: $1,199
- 2016: $1,600
- 2017: $2,049
- 2018: $2,574
- 2019: $3,083

Legend:
- NIA Base
- Additional AD Funds
## Allocations for Competing Research Grant Awards, FY 2019

<table>
<thead>
<tr>
<th>CSR-reviewed Research Applications</th>
<th>General Pay line, &lt;$500k</th>
<th>General Pay line, =&gt;$500k</th>
<th>AD/ADRD pay line, &lt;$500k</th>
<th>AD/ADRD pay line, =&gt;$500k</th>
</tr>
</thead>
<tbody>
<tr>
<td>All applications except as noted below</td>
<td>15</td>
<td>12</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>N.I. R01s</td>
<td>18</td>
<td>15</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>E.S.I. R01s</td>
<td>20</td>
<td>17</td>
<td>33</td>
<td>30</td>
</tr>
</tbody>
</table>

New investigator: An applicant who has not received a prior R01 award or its equivalent.

Early-Stage Investigator: A new investigator who is within 10 years of finishing research training.

First-time renewing; A former new or early-stage investigator’s first renewal application when the investigator has no other NIH grant support.

ADRD: Research on Alzheimer's disease and on Alzheimer's-related Dementias
## FY 2019 Pay Lines

### NIA-reviewed Applications

<table>
<thead>
<tr>
<th></th>
<th>General pay line</th>
<th>AD/ADRD pay line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program projects (PO1)</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>Other NIA-reviewed research</td>
<td>20</td>
<td>38</td>
</tr>
</tbody>
</table>
# FY 2019 Pay Lines

## Training-related Applications

<table>
<thead>
<tr>
<th></th>
<th>General pay line</th>
<th>AD/ADRD pay line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Training grants</strong></td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>(T32, T35)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Career awards</strong></td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td><strong>Fellowships</strong></td>
<td>28</td>
<td>32</td>
</tr>
</tbody>
</table>
RPG Success Rates Over Time

NIH vs NIH

Success Rate

Fiscal Year

2013 2014 2015 2016 2017 2018

NIH

NIA
Alzheimer’s Disease & Related Dementias – Progress & Advances
Diversity of AD/ADRD Research

- Aging metabolic changes in AD
- Comparative biology of neurodegeneration
- Basic Biological Processes of AD
- Geroscience
- Research on Disease Mechanisms
- Cognitive outcomes in Population Studies
- Biomarkers
- Research on Care and Caregiver Support
- Disparities, Sex differences, and AD risk

Alzheimer’s Research
Alzheimer’s and Related Dementias Research

Growing the AD/ADRD workforce

From Fiscal Years 2015-2018:

- \(\sim \frac{1}{4}\) of NIA’s Alzheimer’s and related dementias awardees were either new or early stage investigators

- \(\sim \frac{1}{3}\) of NIA’s Alzheimer’s and related dementias awardees were new to the field
~300 AD/ADRD administrative supplements awarded to NIH grantees with awards not focused on AD/ADRD

~1/3 of the 2018 supplement awardees submit R01s or R21s

>20% of this 1/3 are successful in receiving funding on their first try
The Progression of Alzheimer’s Disease and Related Dementias

**Brain Pathologies**

1° Prevention
- Microvascular
- Amyloid Plaques (Aβ)
- Neurofibrillary Tangles (Tau)

2° Prevention
- Lewy Bodies (Syn)
- TDP-43

3° Prevention and treatment
- Clinical Symptoms
- MCI
- Neurodegeneration

**Dementia Syndromes**
- Alzheimer’s Disease
- Parkinson’s Disease/DLB
- Vascular Dementia
- Frontotemporal Dementia
- Hippocampal Sclerosis

**Cognitively Normal**

**TIME/AGE**

**ABNORMAL**
**Genetic Regions of Interest in Alzheimer's Disease**

By year of discovery

NOTE: Color indicates mechanism of action in the body. See key below.

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**KEY**
- *Early-onset genes*
- Endocytosis and cellular protein trafficking, including APP trafficking and Aβ processing
- Innate immune/brain inflammatory response genes
- Lipid transport/metabolism
- Transcription factor/DNA regulation
- Synaptic transmission
- Neuronal development/memory
- Neuronal signaling and microtubule stability
- No assigned mechanism of action
NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline

AMP-AD and Affiliated Consortia

AD Translational Centers for New Medicines

MODEL-AD AlzPED

ACTC ADNI AMP-AD Biomarkers ABC-DS

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT
**Next-gen anti-Aβ therapeutics:**
- Sigma receptor – anti Aβ oligomer therapy
- Gamma secretase modulators
- Anti-Aβ oligomer immunotherapy
- Aβ immunotherapy – DNA vaccine
- Aβ aggregation inhibitors
- Aβ catalytic antibodies

**Cytoskeleton/Tau:**
- Microtubule stabilizers
- CDK5-tau phosphorylation
- Calpain Inhibitors
- Tau aggregation inhibitors
- DYRK1A

**Oxidative Stress:**
- Nrf2
- γ-ketoaldehyde
- Glutathione S-transferase

**Vasculature:**
- Angiotensin II receptor
- Mas receptor

**αSyn**
- Heavy chain αSyn antibodies
- αSyn aggregation inhibitors

**Multi-target therapeutics:**
- p38αMAPK
- GABA Receptor and NO production
- Neurogenesis
- Proteostasis

**Neuroinflammation:**
- EP2 receptor
- P38 MAPK
- CRAC Channel
- NLRP3 Inflammasome
- TNFα

**Neurotransmitter Receptors and Growth Factors:**
- mGluR5 Receptor
- GABA Receptor A alpha5
- TrkB
- P75 Neurotrophin Receptor

**Synaptic Plasticity/Neuroprotection:**
- Calcineurin
- Ryanodine Receptor
- Excitotoxic Amino Acid Transporter
- Somatostatin Receptor subtype-4

**Metabolism and Bioenergetics:**
- Insulin Receptor
- Mitochondria

**ApoE4**
- ApoE-antibodies
- Antisense oligonucleotides

**Heat Shock Proteins:**
- HSP 90

**Cell therapies:**
- Neural Stem Cell transplantation

**Cell Death:**
- CDK4/6
- OMA1
ALZHEIMER’S DISEASE - Target Discovery and Preclinical Validation Project

NIA Program Director: Suzana Petanceska

**Generate**

High-dimensional multi-omic data:
~2,500 human brains; ~1000 blood samples

**Integrate**

Molecular profiling
Predictive Modeling
Experimental validation

6 Academic Teams – NIA U01/R01 grants –

- P. De Jager, D. Bennett
- E. Schadt, B. Zhang, S. Gandy, J. Zhu, M. Ehrlich
- T. Golde, N. Price, N. Ertekin-Taner, S. Younkin,
- A. Levey, T. Montine, J. Troncoso, D. Geschwind
- R. Kaddurah-Daouk
- B. Yakner, L. Huei Tsai

AMP-AD Knowledge Portal

Synapse

AMP-AD Partners

NIH
FDA
abbvie
Biogen

Foundation for the National Institutes of Health
Progress over 4 years:

- Centralized data resource established - AMP-AD portal
- All data sharing deliverables met
- A variety of experimental validation models developed
- Novel biomarker discovery initiated
- Over 100 candidate targets nominated; currently undergoing data-driven prioritization for further preclinical validation
Harnessing the power of Big Data to understand the complex biology of disease and discover new therapeutic targets.

Genomic, proteomic, metabolomic data from human brain and plasma samples

Computational modeling to identify novel therapeutic targets

Experimental validation in cell-based and animal models

Drug Discovery
Ongoing NIA AD/ADRD and Related Intervention and Prevention Trials (~200)

36 Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)
- Amyloid (10)
- Receptors (4)
- Neuroprotection (4)
- Metabolism and Bioenergetics (2)
- Vasculature (2)
- Growth Factors and Hormones (2)
- Multi-target (2)
- Inflammation (2)
- Oxidative Stress (2)
- Other (6)

8 Late-stage Clinical Drug Development (Phase II/III and Phase III Clinical Trials)
- Amyloid (6)
- Neuroprotection (2)

90 Non-Pharmacological Interventions
- Exercise (19)
- Diet (6)
- Cognitive Training (22)
- Assistive Tech. (9)
- Sleep (5)
- Combination Therapy (11)
- Other (18)

8 Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD
- Pharmacological (5)
- Non-Pharmacological (3)

61 Care and Caregiver Interventions
- Improving Care for PWD (25)
- Improving care provided by family or informal caregiver (36)

www.nia.nih.gov/research/ongoing-AD-trials
Does intensive blood pressure control compared with standard control reduce the occurrence of dementia?

Randomized Controlled Trial Target Systolic Blood Pressure

- Intensive Treatment
  Goal SBP < 120 mmHg
  \( n = 4,278 \)

- Standard Treatment
  Goal SBP < 140 mmHg
  \( n = 4,285 \)

SPRINT-MIND: Secondary Cognitive Outcome

- The Intensive Treatment Group experienced a statistically significant reduction in the rate of developing MCI (19% reduction) as compared to the Standard Treatment Group.

- The Intensive Treatment Group experienced a statistically significant reduction in the rate of composite MCI and probable dementia (15% reduction) as compared to the Standard Treatment Group.

SPRINT-MIND: Structural MRI Outcomes

White Matter Lesion (WML) Volume

Adapted from The SPRINT MIND Investigators for the SPRINT Research Group (2019). JAMA, 322(6), 524-534.
A searchable collection of materials for clinical trials recruitment and retention:

- **Find** flyers, toolkits, recruitment plans, and more from Alzheimer’s Disease Research Centers, NIH, and others.
- **Browse** by goals, participant characteristics, and dozens of focused topics.
- **Get** tips for strategy from the Alzheimer’s Disease and Related Dementias Clinical Studies Recruitment Planning Guide.
- **View, download, and share** participant testimonial videos.
New research collaboratory designed to spur innovation and improve dementia care

NIA IMPACT will:

- Develop and disseminate technical, policy, and best practices
- Enhance research development and investigator capacity:
  - Fund/guide pilot ePCTs, support transformation into full-scale ePCTs.
  - Resource for NIA-funded investigators conducting ePCTs in PLWD.
  - Support training through career award, workshops, and on-line modules.
- Engage stakeholders
Geroscience - Convergence

Biology of Disease

Biology of Aging

Macromolecular Damage

Epigenetics

Stem Cells

Proteostasis

Inflammation

Stress Response

Other Biology

Metabolism

NNeurological Disease

Vascular Disease

Macular Degeneration

Sarcopenia

Immunity

COPD

Heart Disease

Immunity

Vascular Disease

Macromolecular Damage

Epigenetics

Stem Cells

Proteostasis

Inflammation

Stress Response

Other Biology

Metabolism

Sierra & Kohanski
J Gerontol June 2014

Kennedy et al.
Cell Nov 2014

Biology of Disease

Biology of Aging

Geroscience - Convergence
Geroscience: Interventions and Approaches

In 1961, L. Hayflick proposed that the limited replicative lifespan of cells in culture represented the phenomenon of aging at the cellular level.
What is cell senescence?

Senescent cells secrete a large number of biologically active factors which affect the function of neighboring, non-senescent cells

Senescent cells secrete a large number (and large amounts) of biologically active factors with the potential of affecting cellular physiology / responses in neighboring, non-senescent cells.

A cell senescence marker for aging (p16\textsuperscript{ink4a})
Sharpless lab, University of North Carolina

In Humans  \( p16^{\text{ink4a}} \) expression in CD3+ T cells

- increases 1.4-fold per decade => 16-fold over 8 decade adult lifespan.
- Increase seen well before ‘aging’ is apparent.

Adapted from
Naturally occurring p16\textsuperscript{Ink4a}\textsuperscript{-}positive cells shorten healthy lifespan

Clearance of p16^{ink4a}-positive senescent cells delays aging-associated disorders

Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline

- Senescent cells drive neurodegenerative disease
- Clearance of senescent cells through genetic manipulation or drug treatment decreases tau pathology and cognitive decline

Treatment with Senolytics Extends Lifespan in Older WT Mice

**Treatment** = Dasatinib (chemo drug) and Quercetin (dietary supplement), to disable senescent cell anti-apoptotic pathways

**Control** = Vehicle

Senolytics are Being Tested in the Clinic Against a Handful of Diseases

- Small Phase 1 studies on repurposed compounds (dasatinib + quercetin; navitoclax)

- **Conditions:**
  - Idiopathic pulmonary fibrosis (IPF) n=26 [NCT02874989](https://clinicaltrials.gov/show/NCT02874989) (completed)
  - Alzheimer’s disease n=5 [NCT04063124](https://clinicaltrials.gov/show/NCT04063124)
  - Diabetic chronic kidney disease n=16 [NCT02848131](https://clinicaltrials.gov/show/NCT02848131)
  - Osteoarthritis n=78 [NCT03513016](https://clinicaltrials.gov/show/NCT03513016) (completed)

- Feasibility and tolerability results published for IPF Phase 1 study (Justice et al. (2019). EbioMedicine; 40:554-563)
**Goal:** Accelerate the development of interventions designed to treat chronic conditions (e.g., diabetes, heart disease, Alzheimer’s disease) as a group by targeting biological aging.

- Support “use case” trials using repurposed drugs to harmonize recruitment and analytic procedures.
- Expand an assay facility to analyze biospecimens across the network.
- Support a data entry platform to facilitate cross-study comparisons.
- Develop a biobanking and repository network for samples from clinical trials to permit future analyses.
NIA Science – Making an Impact
CAPABLE Intervention Reduced Disability in Activities of Daily Living by 30% for Low-income Baltimore Older Adults

Intervention =
- Up to 6 Home visits by OT, RN
- Implementation of personal plan based on assessments and participant goals
- Home repairs (up to $1300)
- Significant reduction in ADL disability scores compared with participants in control group. Adjusted Effect Size: 0.70 (0.54-0.93), $p = .01.$

Successful UTI Prevention Program in Nursing Homes Leads to Cost Reduction

One-Year Health and Cost Outcomes for a Representative 120-Bed Nursing Home

<table>
<thead>
<tr>
<th></th>
<th>Nursing home</th>
<th>Hospital</th>
<th>Total costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>$42</td>
<td>$132</td>
<td>$174</td>
</tr>
<tr>
<td>Intervention</td>
<td>$27</td>
<td>$93</td>
<td>$140</td>
</tr>
</tbody>
</table>

Notification of Patient Overdose Deaths Reduces Clinician Opioid Prescriptions


<table>
<thead>
<tr>
<th></th>
<th>Preintervention</th>
<th>Postintervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Letter</strong></td>
<td>72.5</td>
<td>65.7</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>71.6</td>
<td>71.7</td>
</tr>
</tbody>
</table>

MME= milligram morphine equivalents

MMEs in Rxs of letter recipients decreased by 9.7% after 3 months
Daily Low-Dose Aspirin Found to Have No Effect on Healthy Life Span in Older Adults

ASpirin in Reducing Events in the Elderly (ASPREE) - **Background**

- International randomized double-blind placebo trial that started in 2010
- 19,114 participants (16,703 in Australia and 2,411 in the United States)
- Participants were aged 70 years or older (U.S. Hispanics and African-Americans were enrolled at age 65 years or older)
- Participants were followed for an average of 4.7 years

**Will a daily dose of 100 mg enteric-coated aspirin extend the duration of disability-free (including onset of dementia, total mortality, or persistent disability) life in healthy older adults?**
ASPREE –
Primary Composite Endpoint

Daily Low-Dose Aspirin Found to Have No Effect on Healthy Life Span in Older Adults

ASPirin in Reducing Events in the Elderly (ASPREE) - Results

• **Cardiovascular**: No substantial reduction in risk of MI and stroke
• **Mortality**: Slightly higher – but not significant
• **Bleeding**: Significantly increased risk of serious bleeding
• **Physical disability**: No effect
• **Dementia**: No effect

Change in ACC/AHA Clinical Practice Guidelines re: Aspirin for CVD Prevention
Ways to Stay Informed and Connected

Search all active NIA funding opportunities:
https://www.nia.nih.gov/research/funding

Review the latest approved concepts:
https://www.nia.nih.gov/approved-concepts

Subscribe to our blog and stay up to date on the latest NIA news:
https://www.nia.nih.gov/research/blog
NIA
The Leader in Aging Research