# From Bench to Bedside: Exploring the Research Continuum at NIA

## UAB Integrated Aging Research Symposium


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Director
National Institute on Aging


National Institute on Aging

October 9, 2019

# 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

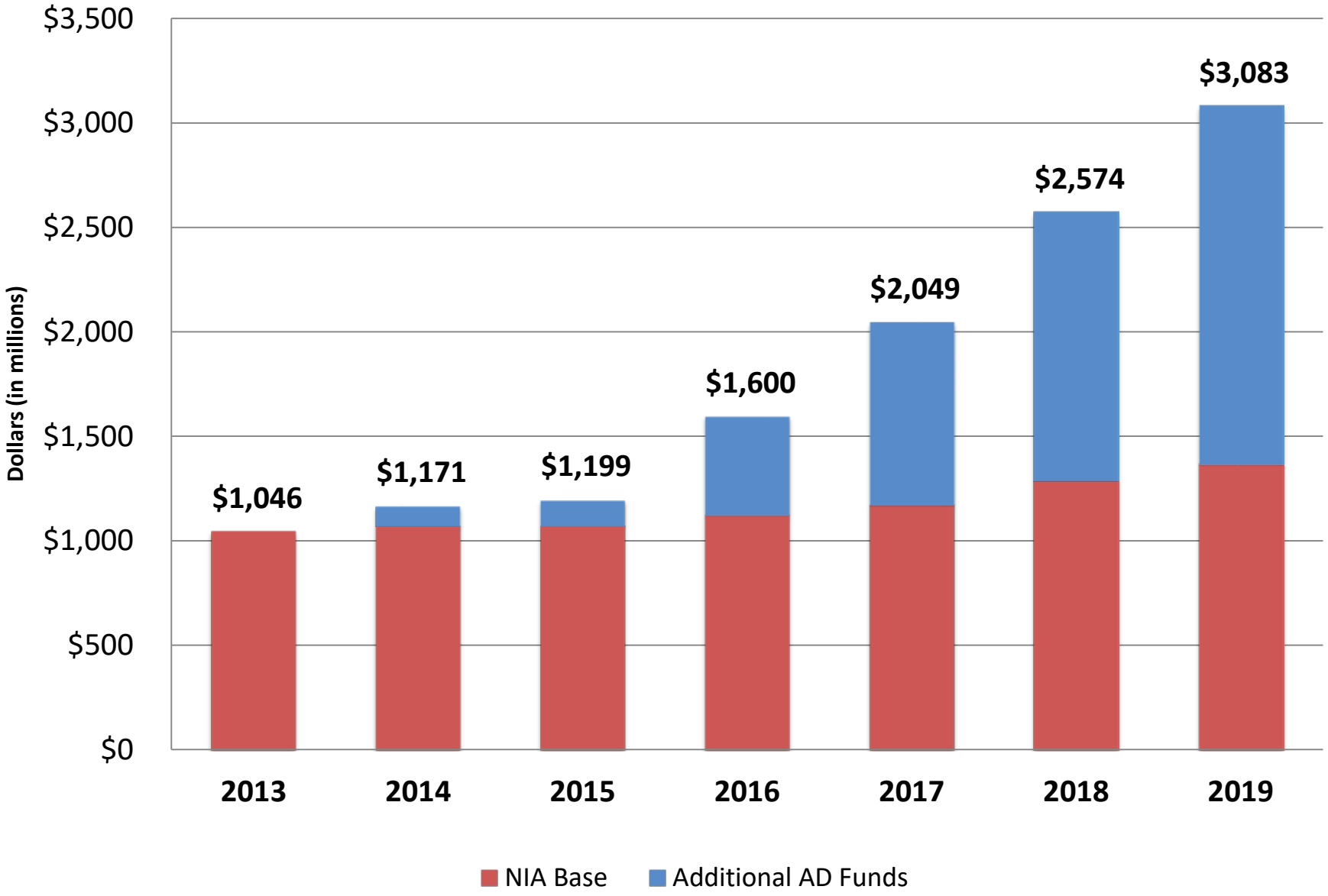
# FY20 Budget Status

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*



# Allocations for Competing Research Grant Awards, FY 2019

| CSR-reviewed Research Applications | | | | |
|---|---|---|---|---|
| | General Pay line, <$500k | General Pay line, =>$500k | AD/ADRD pay line, <$500k | AD/ADRD pay line, =>$500k |
| All applications except as noted below | 15 | 12 | 28 | 25 |
| N.I. R01s | 18 | 15 | 31 | 28 |
| E.S.I. R01s | 20 | 17 | 33 | 30 |

*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*

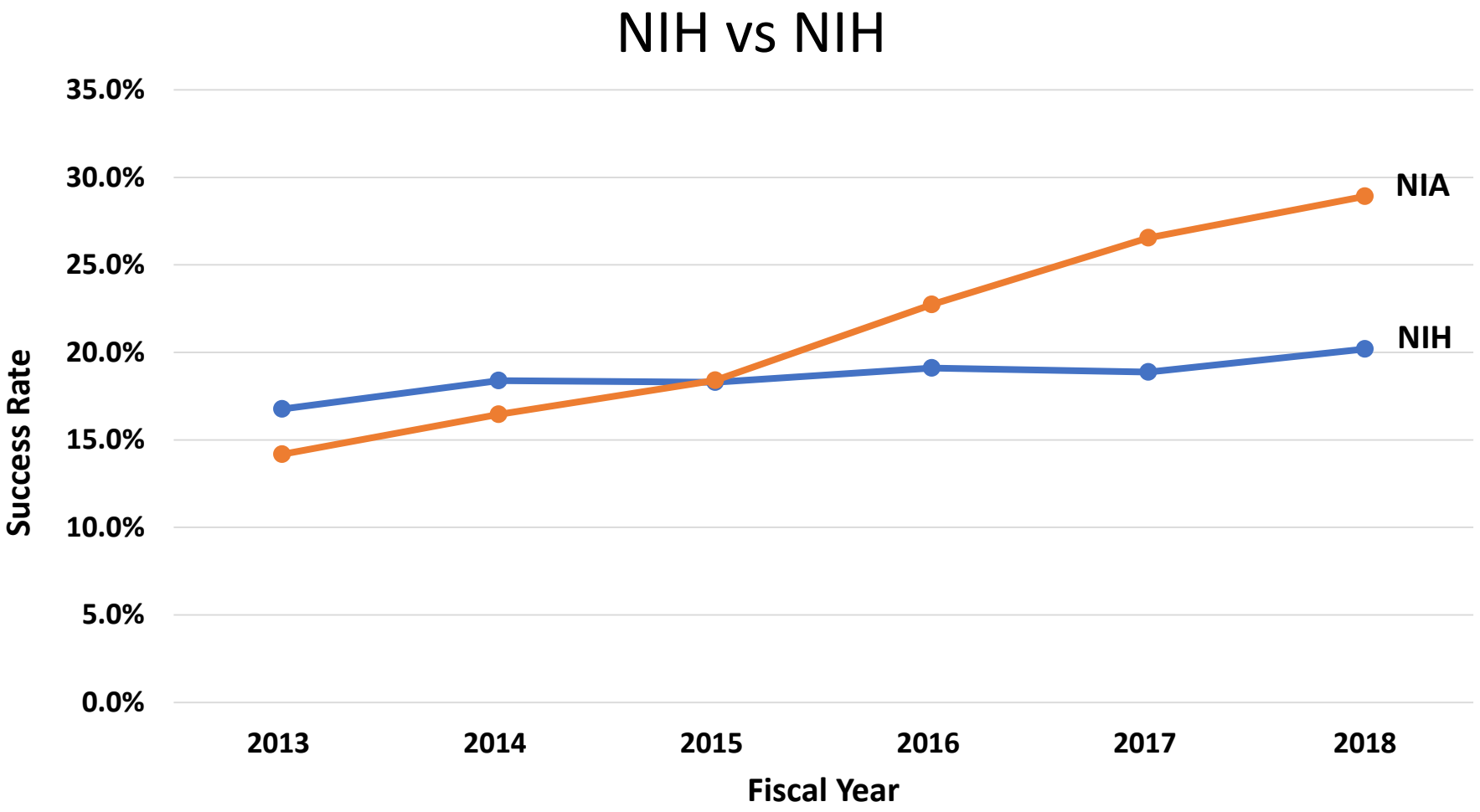
# FY 2019 Pay Lines

| NIA-reviewed Applications | | |
|---|---|---|
| | **General pay line** | **AD/ADRD pay line** |
| **Program projects (PO1)** | 20 | 38 |
| **Other NIA-reviewed research** | 20 | 38 |

# FY 2019 Pay Lines

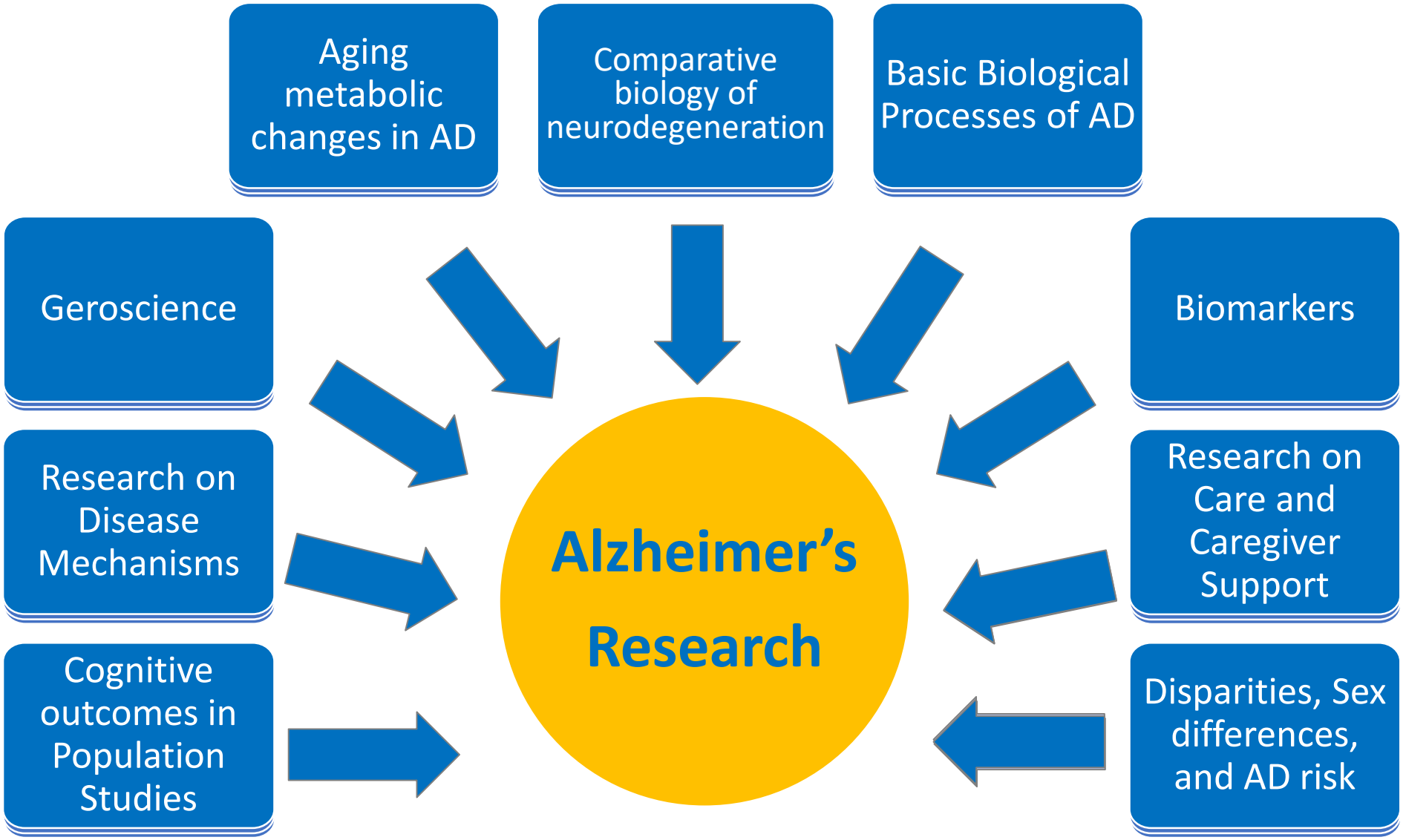
| Training-related Applications | | |
|---|---|---|
| | General pay line | AD/ADRD pay line |
| Training grants (T32, T35) | 21 | 35 |
| Career awards | 21 | 28 |
| Fellowships | 28 | 32 |

# RPG Success Rates Over Time



# Alzheimer's Disease & Related Dementias – Progress & Advances

# Diversity of AD/ADRD Research



# Alzheimer's and Related Dementias Research

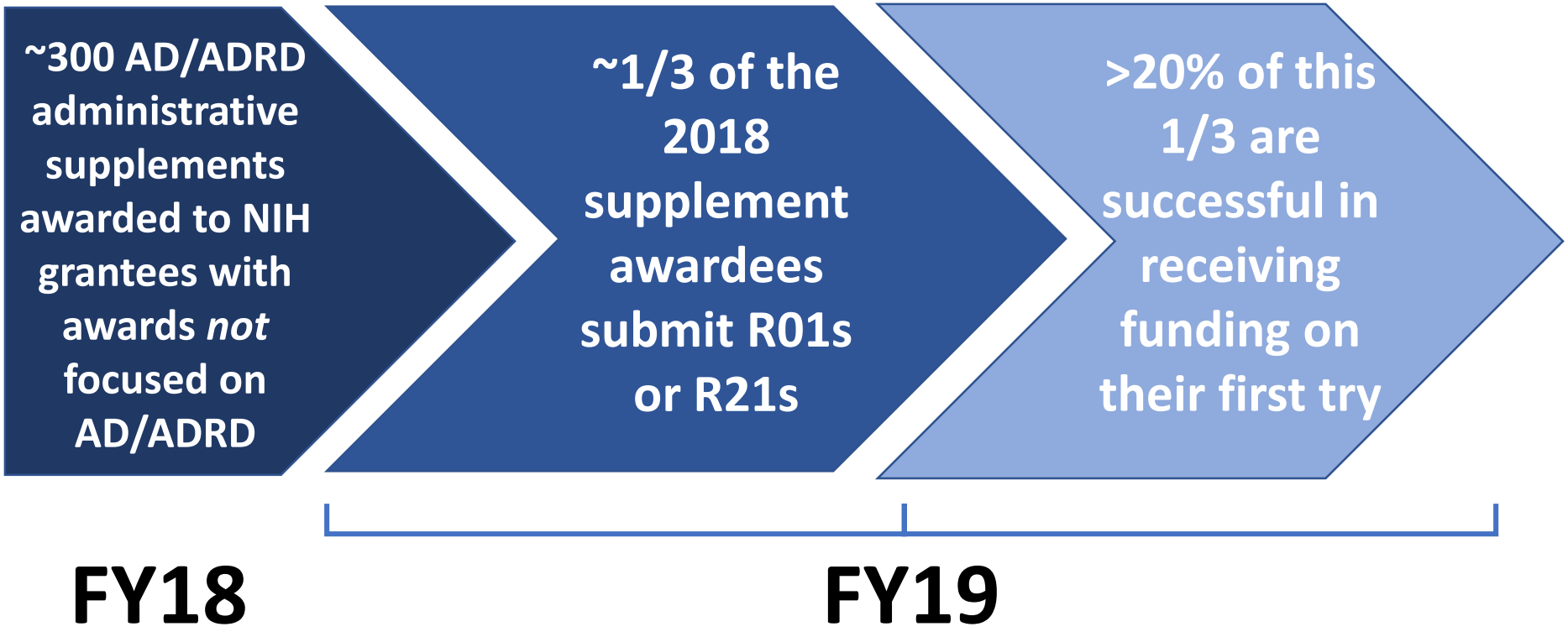
## *Growing the AD/ADRD workforce*

***From Fiscal Years 2015-2018:***

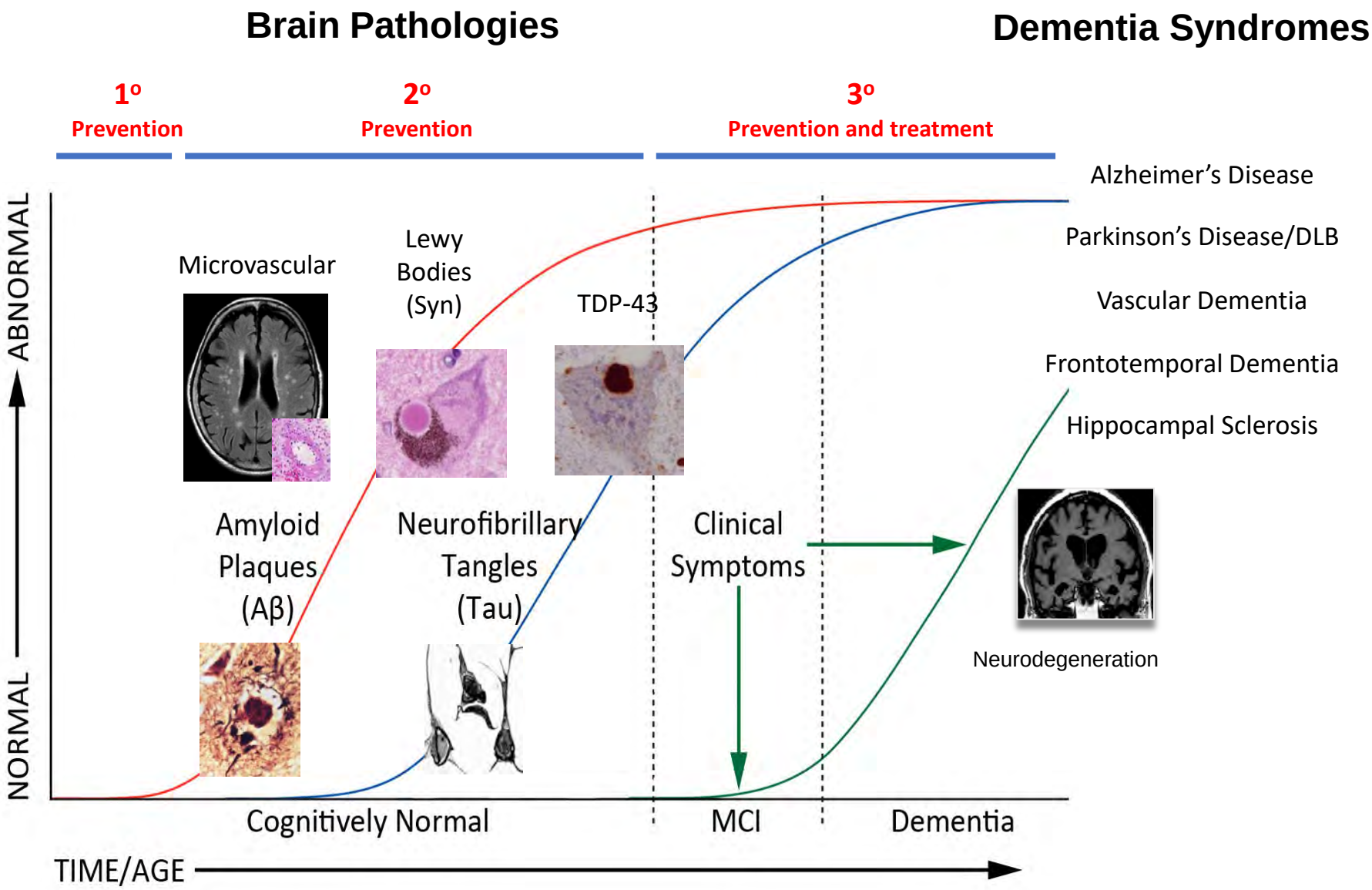
- ***~1/4*** of NIA's Alzheimer's and related dementias awardees were either *new or early stage* investigators

- ***~1/3*** of NIA's Alzheimer's and related dementias awardees were *new to the field*

# NIA AD/ADRD Administrative Supplements – Impact on Future Applications



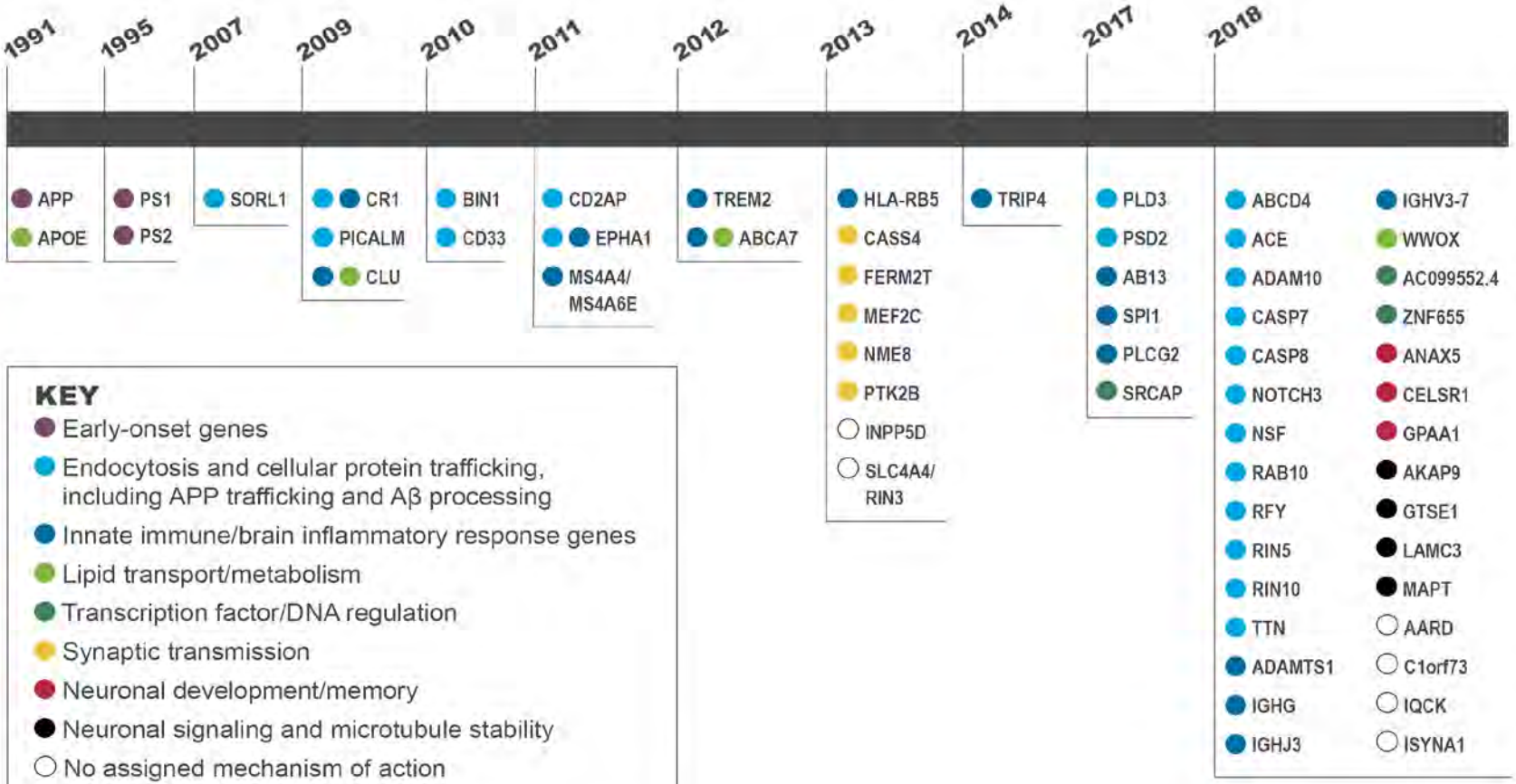
# The Progression of Alzheimer's Disease and Related Dementias



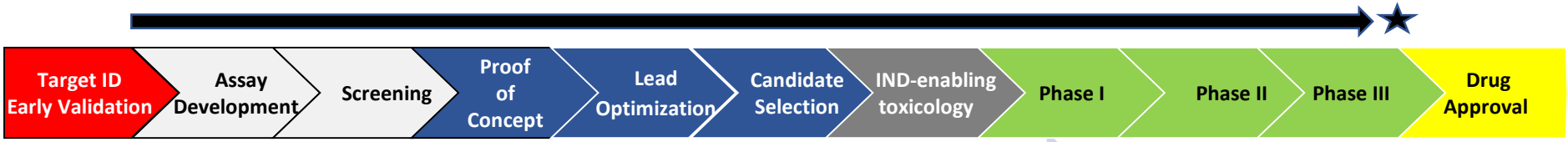
# Genetic Regions of Interest in Alzheimer's Disease

## By year of discovery

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



# NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline




**AMP-AD and Affiliated Consortia**

**AD Translational Centers for New Medicines**
***Launched October 2019***

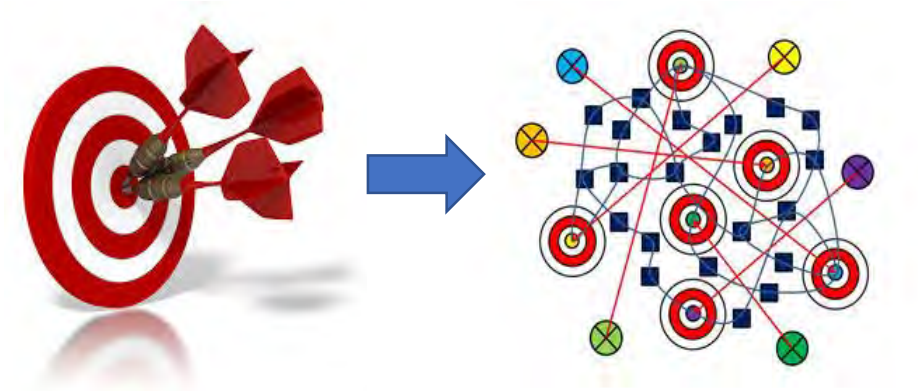
**MODEL-AD**
**AlzPED**

**ACTC**
**ADNI**
**AMP-AD Biomarkers**
**ABC-DS**

**ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT**

# NIA Alzheimer's Translational Research Program – since 2006
# Diversifying the Therapeutic Pipeline

**Next-gen anti-Aβ therapeutics:**
Sigma receptor – anti Aβ oligomer therapy
Gamma secretase modulators
Anti-Aβ oligomer immunotherapy
*A*β immunotherapy – DNA vaccine
Aβ aggregation inhibitors
Aβ catalytic antibodies



**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

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

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

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

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

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

**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

**Vasculature:**
Angiotensin II receptor
Mas receptor

# ACCELERATING MEDICINES PARTNERSHIP (AMP)

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**

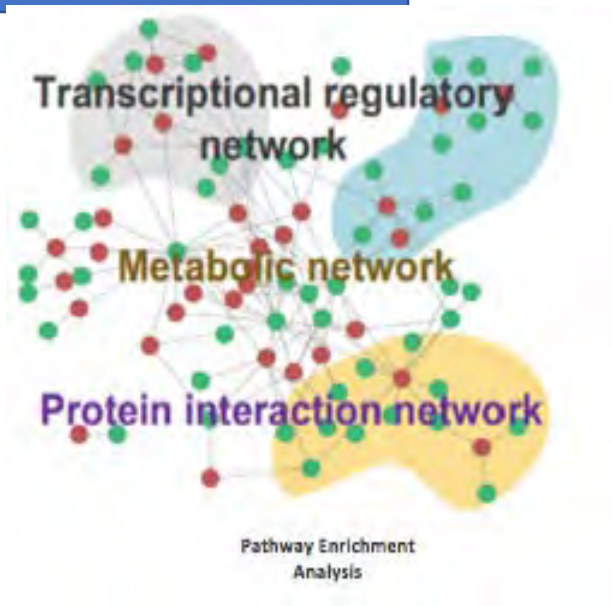
**6 Academic Teams**
**– NIA U01/R01grants –**

www.synapse.org.ampad

**Data**
**Network models**
**Code**

**AMP-AD Knowledge Portal**

Sage BIONETWORKS Synapse




**AMP-AD Partners**

- 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

NIH National Institute on Aging

# ACCELERATING MEDICINES PARTNERSHIP (AMP)

**Progress over 4 years:**

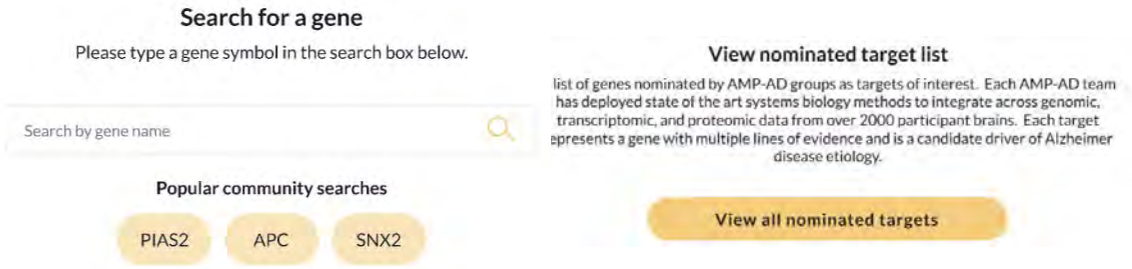
- Centralized data resource established- AMP-AD portal
- All data sharing deliverables met
- A variety of experimental validation models developed
- Novel biomarker discovery initiated
- Over 100 candidate targets nominated; currently undergoing data-driven prioritization for further preclinical validation

## Candidate Targets

| | | | | | | |
|---|---|---|---|---|---|---|
| SNRNP70 | | TGFBR1 | | CCDC85C | | RGS4 |
| U1-A | | TGFBR2 | | CIC | | SCN2A |
| U1-C | | BMPR1A | | CSRP1 | | OLFM3 |
| SNRPN | | BMPR1B | | DAB2IP | | SLC22A10 |
| SNRPB | | CRHR1 | | FAM63A | | ENAH |
| PLCD1 | | TREM2 | | FURIN | | WWTR1 |
| PTRHD1 | | TYROBP | | HMG20B | | LRP10 |
| SFRP1 | | S100A8 | | IGFBP5 | | SYP |
| PPP1R7 | | S100A9 | | ISYNA1 | | PCSK1 |
| DNM3 | | P2RY2 | | KIF1C | | KMO |
| RTN4 | | P2RX7 | | PADI2 | | PTTG1IP |
| EPB41L3 | | P2RY12 | | SLC38A2 | | MLIP |
| TUBB3 | | P2RY13 | | SNAP25 | | DLGAP1 |
| PLEC | | OSMR | | STX1A | | MOAP1 |
| ANXA5 | | TLR4 | | STXBP3 | | PRKCB |
| MSN | | CR1 | | SV2B | | YAP1 |
| CD44 | | CSF1R | | SYT1 | | GNA13 |
| LMNA | | CX3CR1 | | SYT12 | | TRIM56 |
| | | SPI1 | | ZBTB47 | | |
| | | TNFRSF10A | | VGF | | |
| | | TNFRSF10B | | PLXNB1 | | |

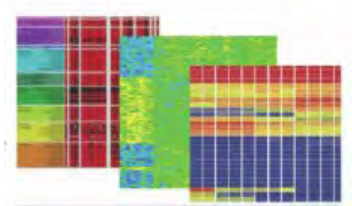
Agora

agora.ampadportal.org

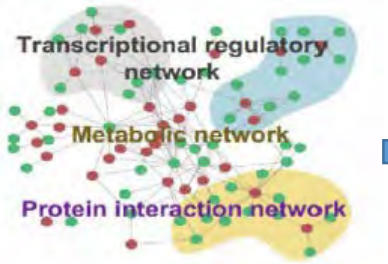



NIH National Institute on Aging

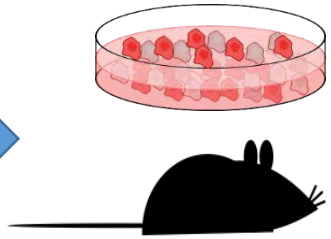
# Harnessing the power of Big Data to understand the complex biology of disease and discover new therapeutic targets



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



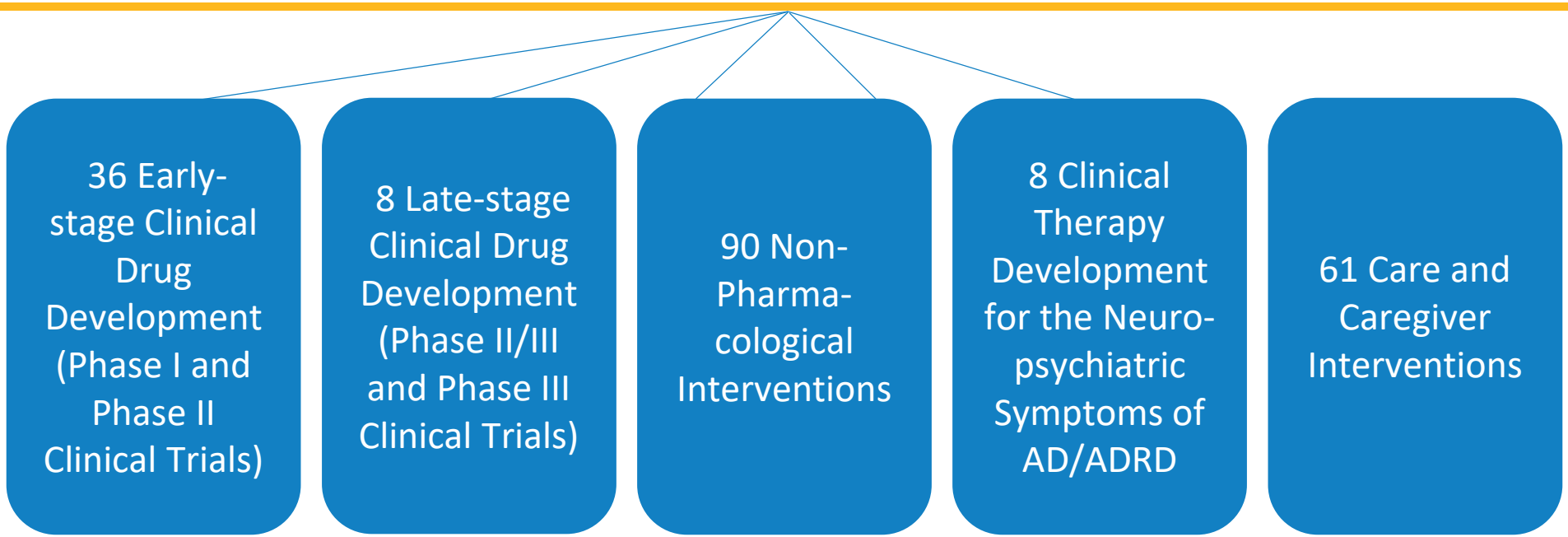

Computational modeling to identify novel therapeutic targets



Experimental validation in cell-based and animal models


Drug Discovery

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




www.nia.nih.gov/research/ongoing-AD-trials

# SPRINT-MIND Research Question

## SPRINT Memory and Cognition in Decreased Hypertension

***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
Systolic Blood Pressure Intervention Trial

The SPRINT MIND Investigators for the SPRINT Research Group (2019). *JAMA, 321*(6):553–561.

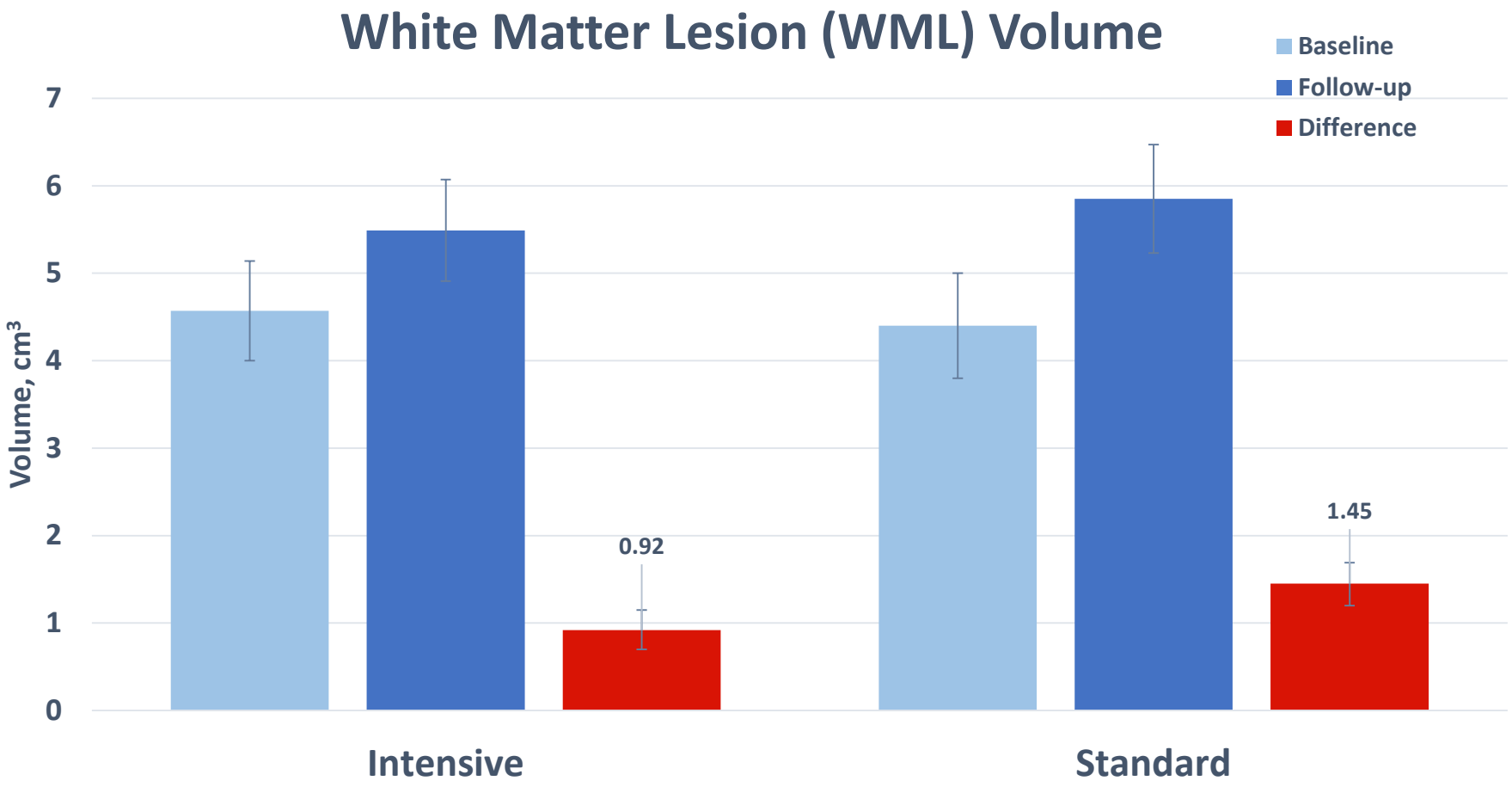
# SPRINT-MIND: Secondary Cognitive Outcome

- 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

The SPRINT MIND Investigators for the SPRINT Research Group (2019). *JAMA, 321*(6):553–561.

# SPRINT-MIND: Structural MRI Outcomes




Adapted from The SPRINT MIND Investigators for the SPRINT Research Group (2019). *JAMA, 322*(6), 524-534.

# Alzheimer's and Dementia Outreach, Recruitment, and Engagement Resources

www.nia.nih.gov/research/ADORE

**A searchable collection of materials for clinical trials recruitment and retention:**

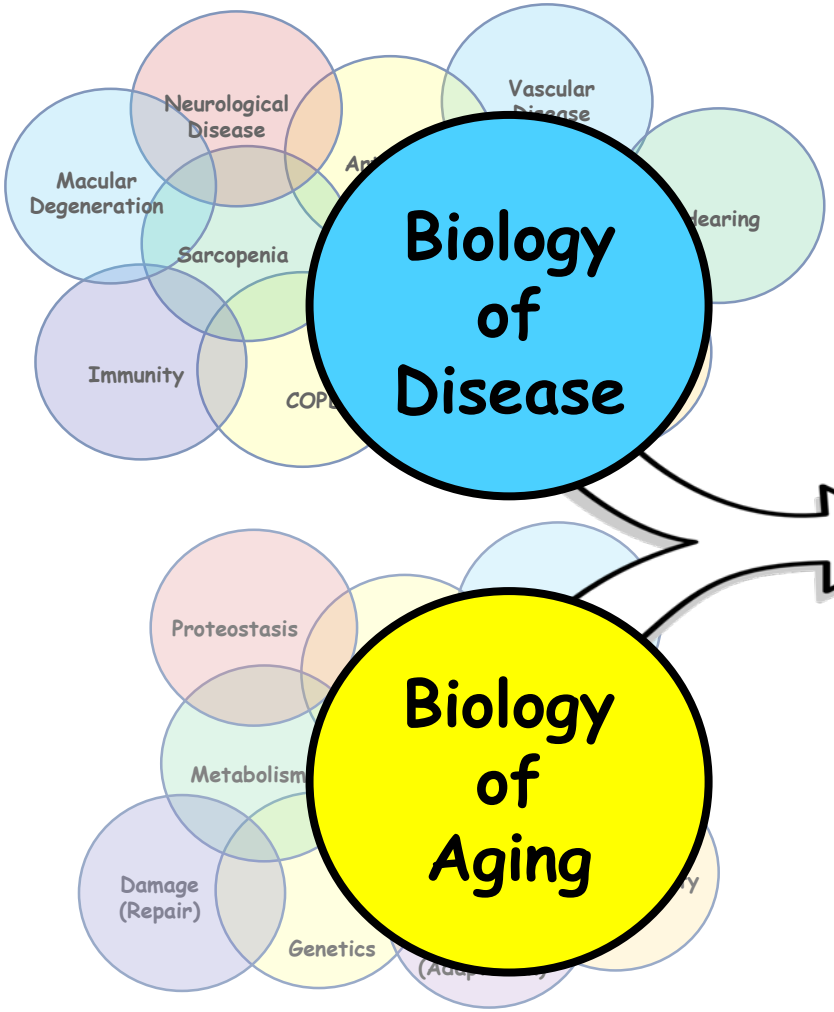
- **Find** flyers, toolkits, recruitment plans, and more from Alzheimer's Disease Research Centers, NIH, and others.
- **Browse** by goals, participant characteristics, and dozens of focused topics.
- **Get** tips for strategy from the Alzheimer's Disease and Related Dementias Clinical Studies Recruitment Planning Guide.
- **View, download, and share** participant testimonial **videos**.

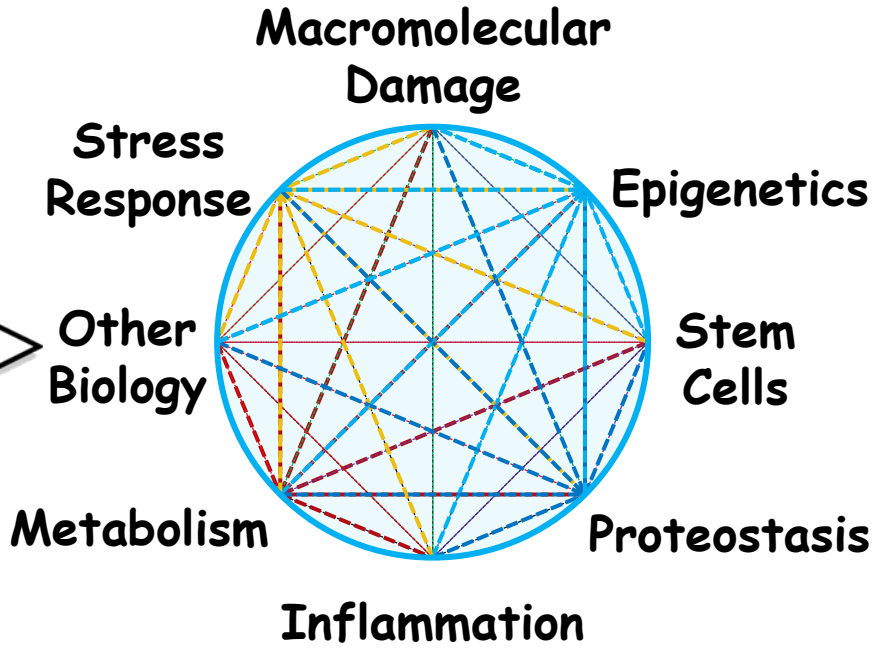
# New research collaboratory designed to spur innovation and improve dementia care


**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

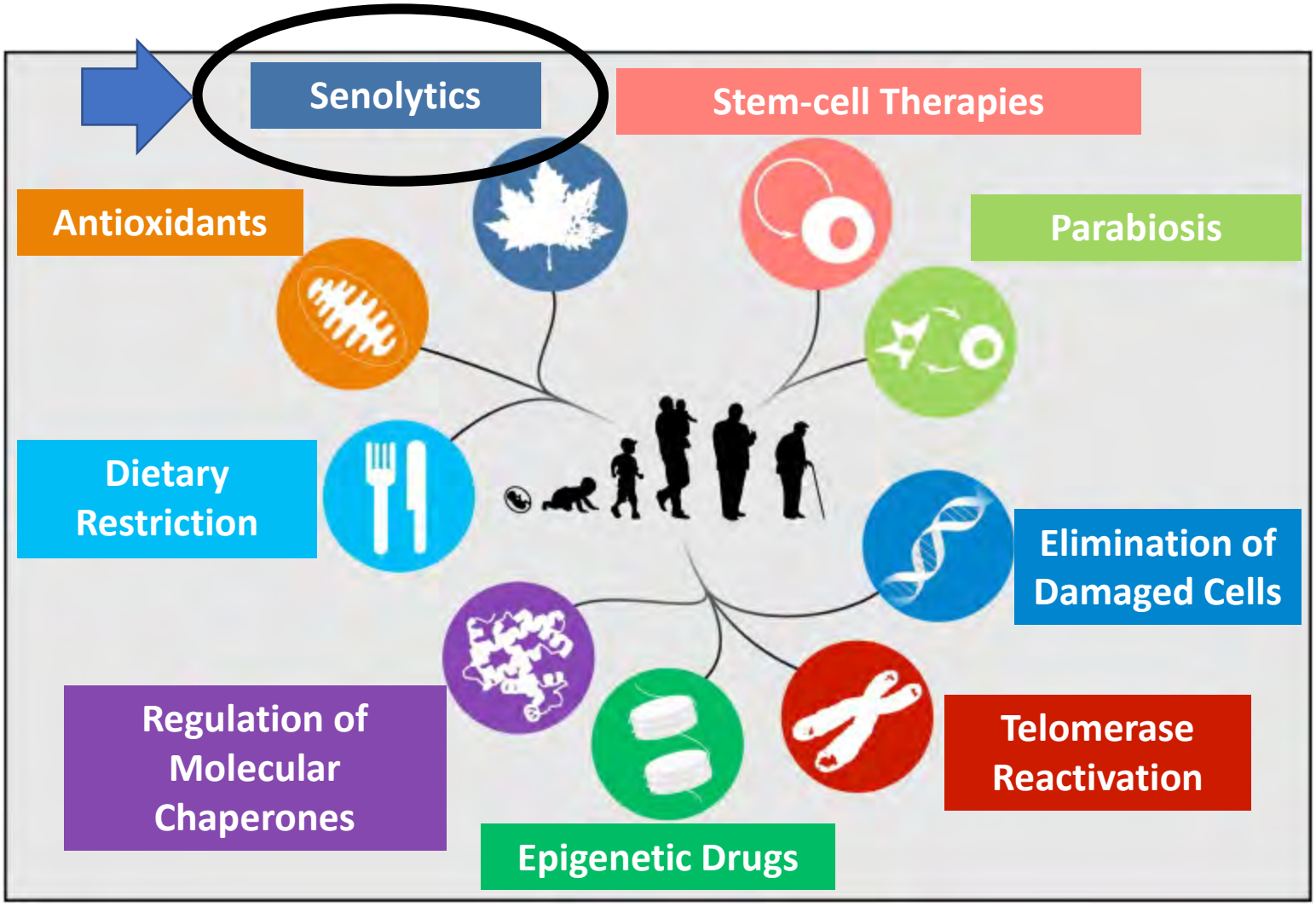



Sierra & Kohanski
J Gerontol June 2014

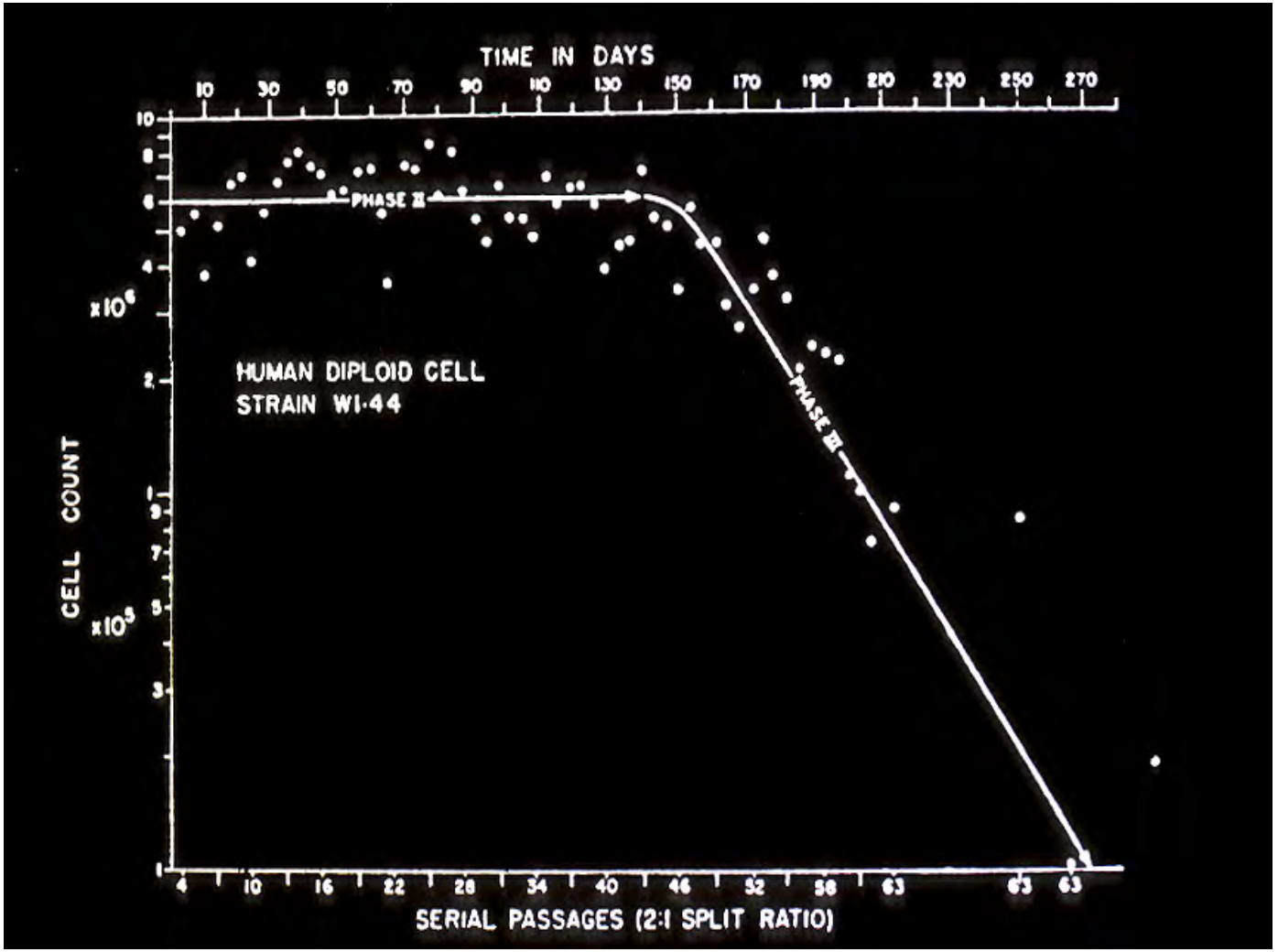
Kennedy *et al.*
Cell Nov 2014

# Geroscience: Interventions and Approaches

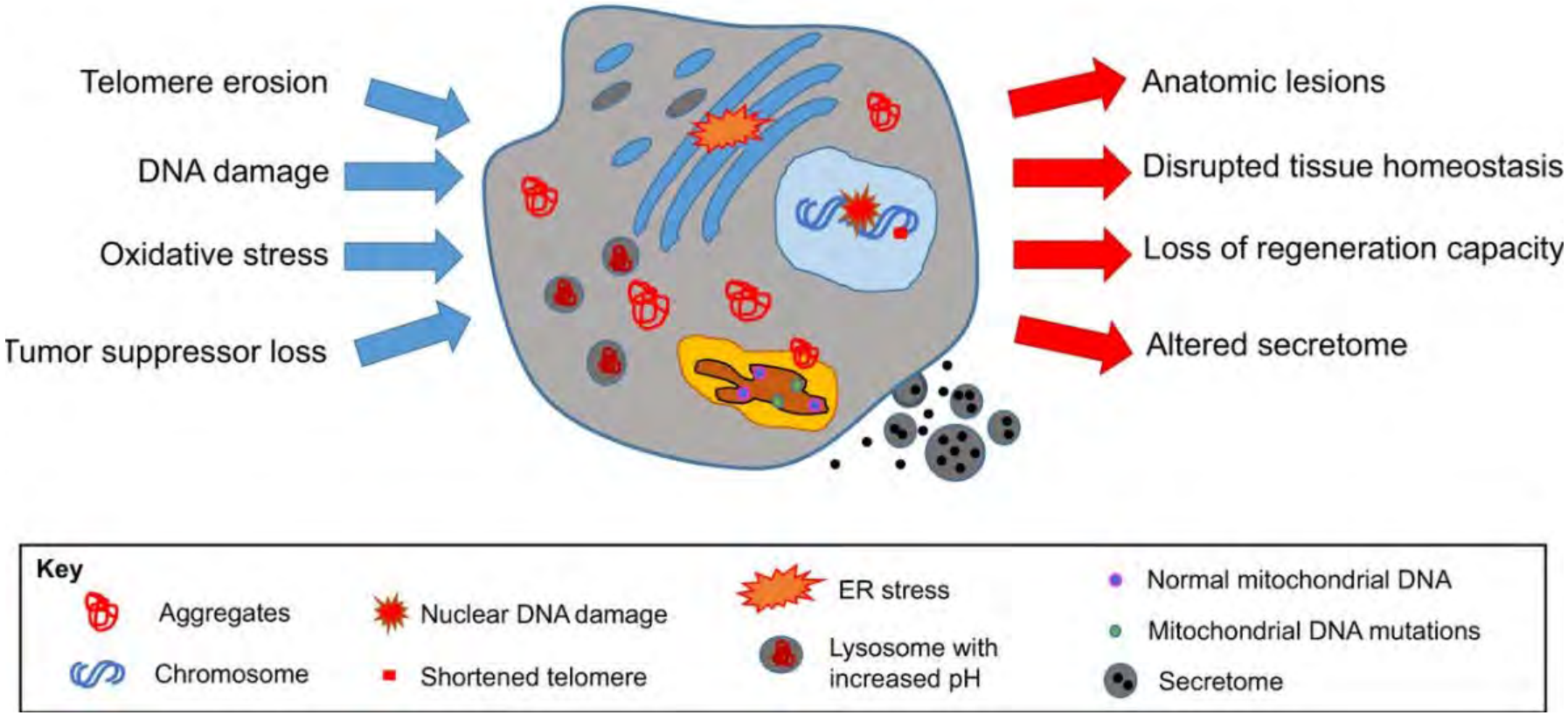



***Adapted from:*** López-Otín, C et al. (2013). *Cell* 153: 1194-1217.

# 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?

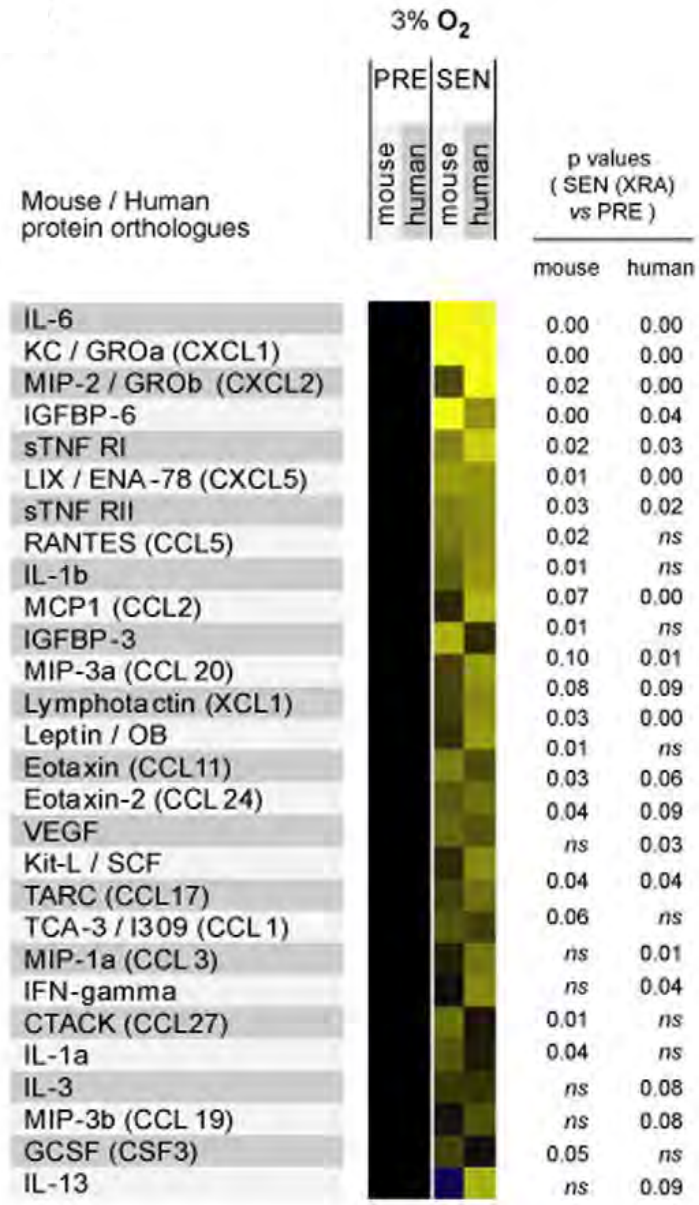



**Senescent cells secrete a large number of biologically active factors which affect the function of neighboring, non-senescent cells**

Ruan, L. et al. (2018). *J Cell Sci* 131.

# What is cell senescence?

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

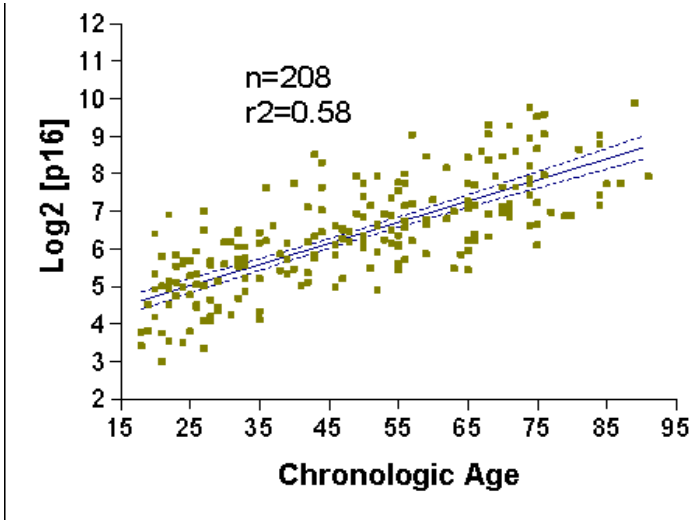



Coppe, J. et al. *PLoS One* (2010) 5(2):e918.

# A cell senescence marker for aging ($p16^{ink4a}$)

## Sharpless lab, University of North Carolina

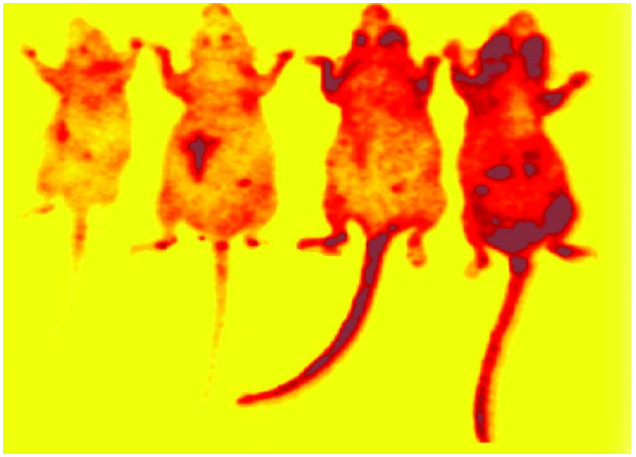
In Humans $p16^{ink4}$a expression in CD3+ T cells)




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

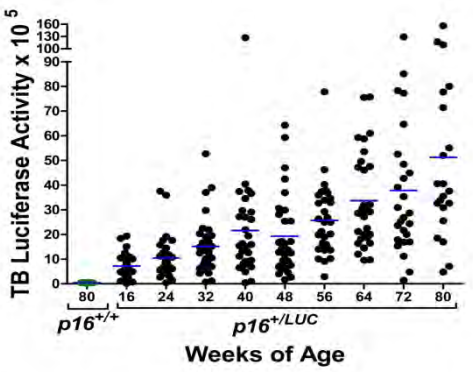
**Adapted from**
**Liu et al Aging Cell 8:439-448 (2009) – human studies**
**Burd et al. Cell 152: 340-351 (2013) – C57BL6 mouse model**

**In Mice,** a reporter of $p16^{ink4}$ expression in all cells of the body



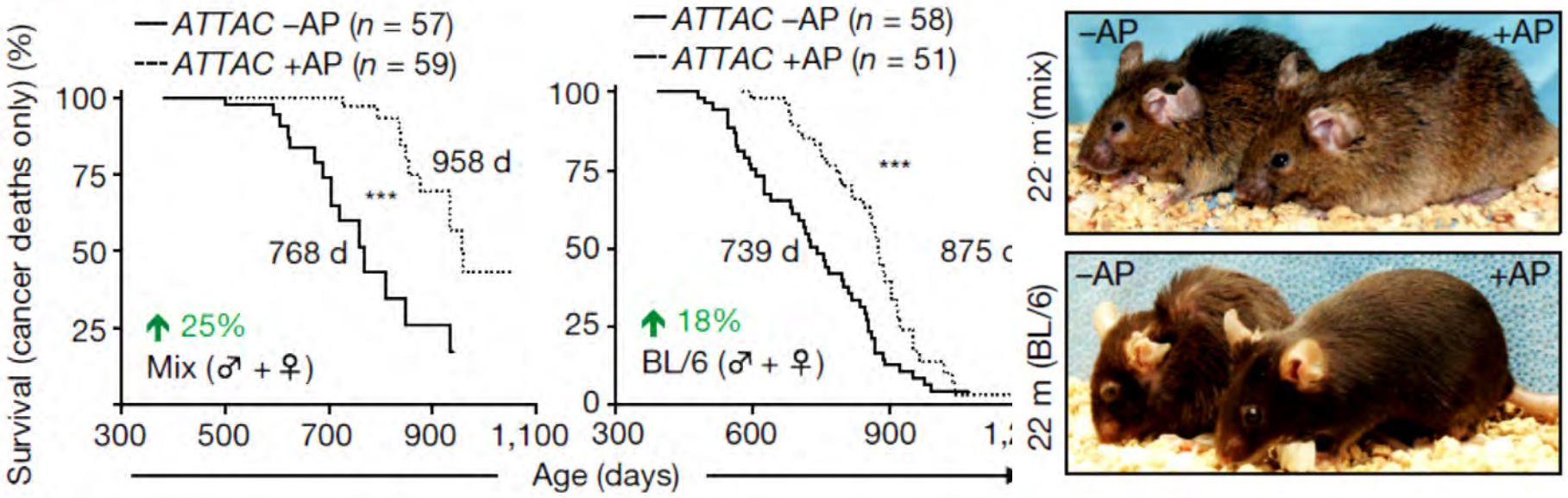
16 40 64 80

Weeks of age (one mouse)



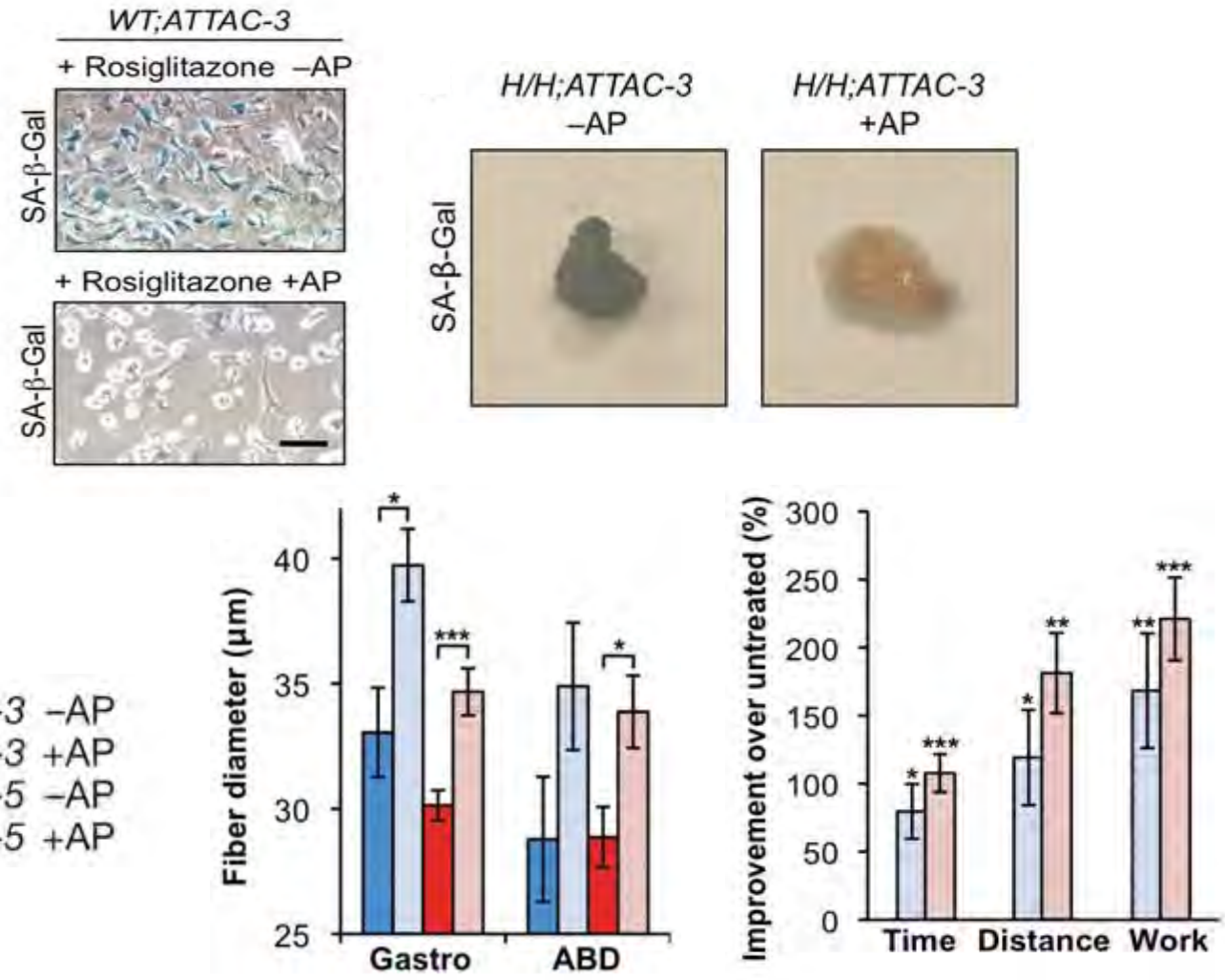

**( many mice )**

# Naturally occurring p16$^{Ink4a}$-positive cells shorten healthy lifespan



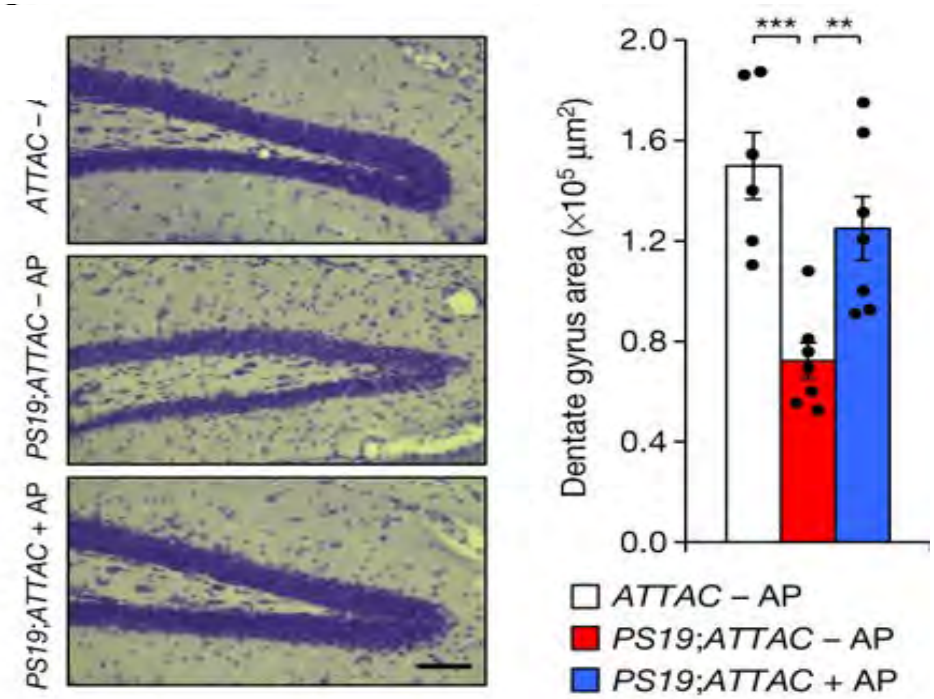

Baker DJ, et al. *Nature* (2016) 530(7589):184-9.

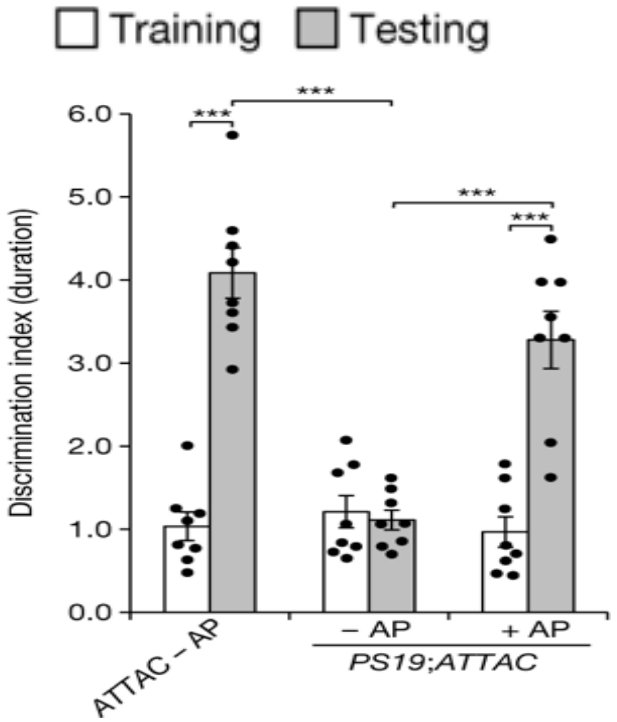
# Clearance of p16$^{Ink4a}$-positive senescent cells delays aging-associated disorders




Baker DJ et al. – Nature 479:232 (2011)

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



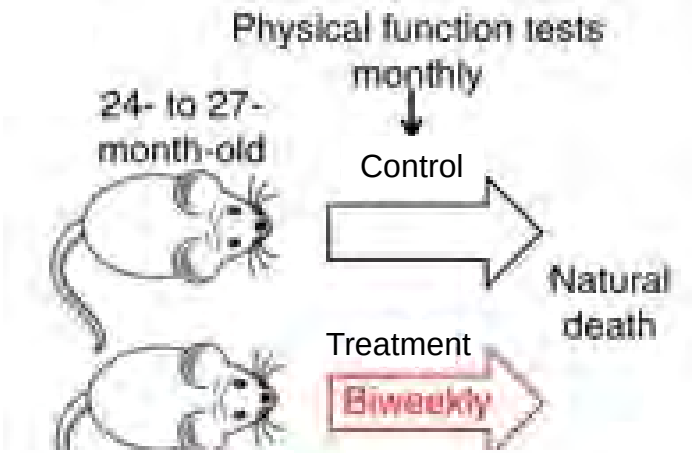

- **Senescent cells drive neurodegenerative disease**
- **Clearance of senescent cells through genetic manipulation or drug treatment decreases tau pathology and cognitive decline**

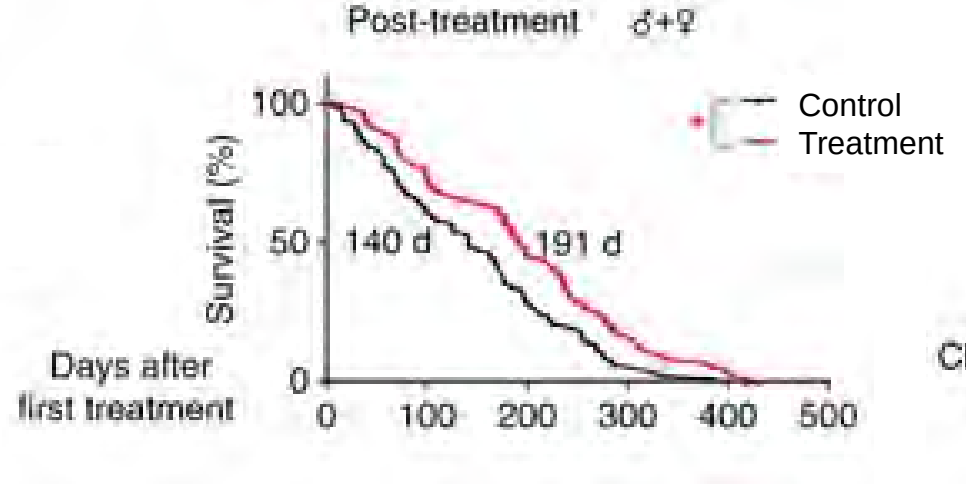
Bussian, T. et al. (2018*). Nature,* 562(7728): 578-582.

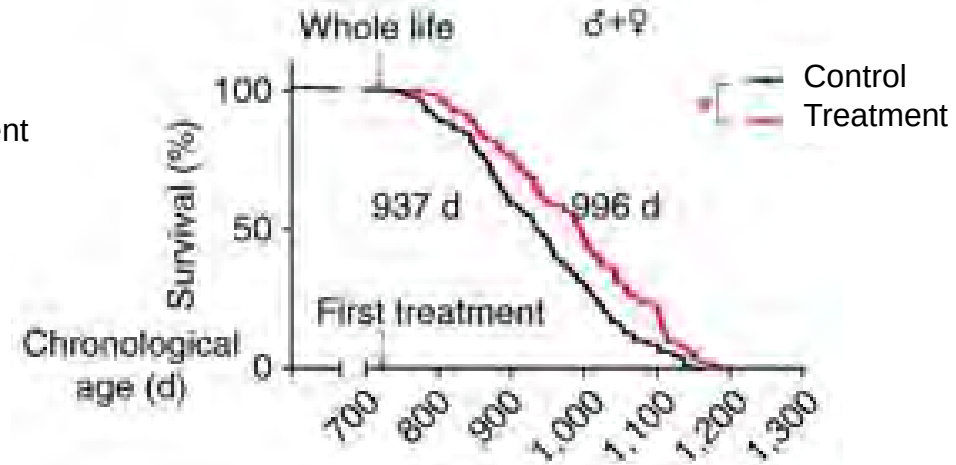
# Treatment with Senolytics Extends Lifespan in Older WT Mice

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

**Control** = Vehicle




Xu, M. et al. (2018*). Nature medicine,* 24(8):1246-1256.

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

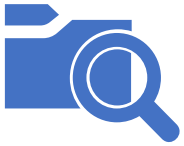
- Small Phase 1 studies on repurposed compounds (dasatinib + quercetin; navitoclax)
- *Conditions:*
  - Idiopathic pulmonary fibrosis (IPF) n=26 NCT02874989 (completed)
  - Alzheimer's disease n=5 NCT04063124
  - Diabetic chronic kidney disease n=16 NCT02848131
  - Osteoarthritis n=78 NCT03513016 (completed)
- Feasibility and tolerability results published for IPF Phase 1 study (Justice et al. (2019). EbioMedicine; 40:554-563)

# Translational Geroscience Network

**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.

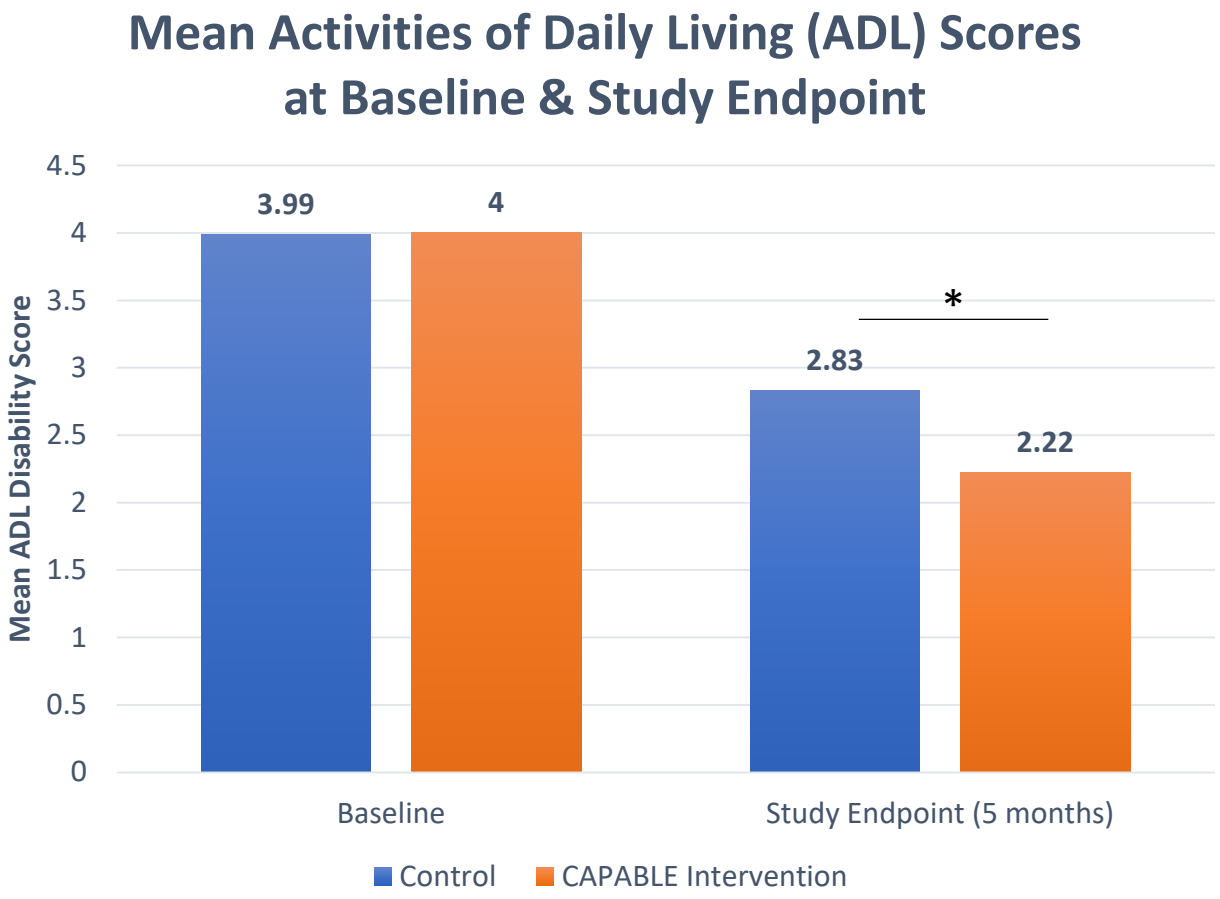


Support a data entry platform to facilitate cross-study comparisons.

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



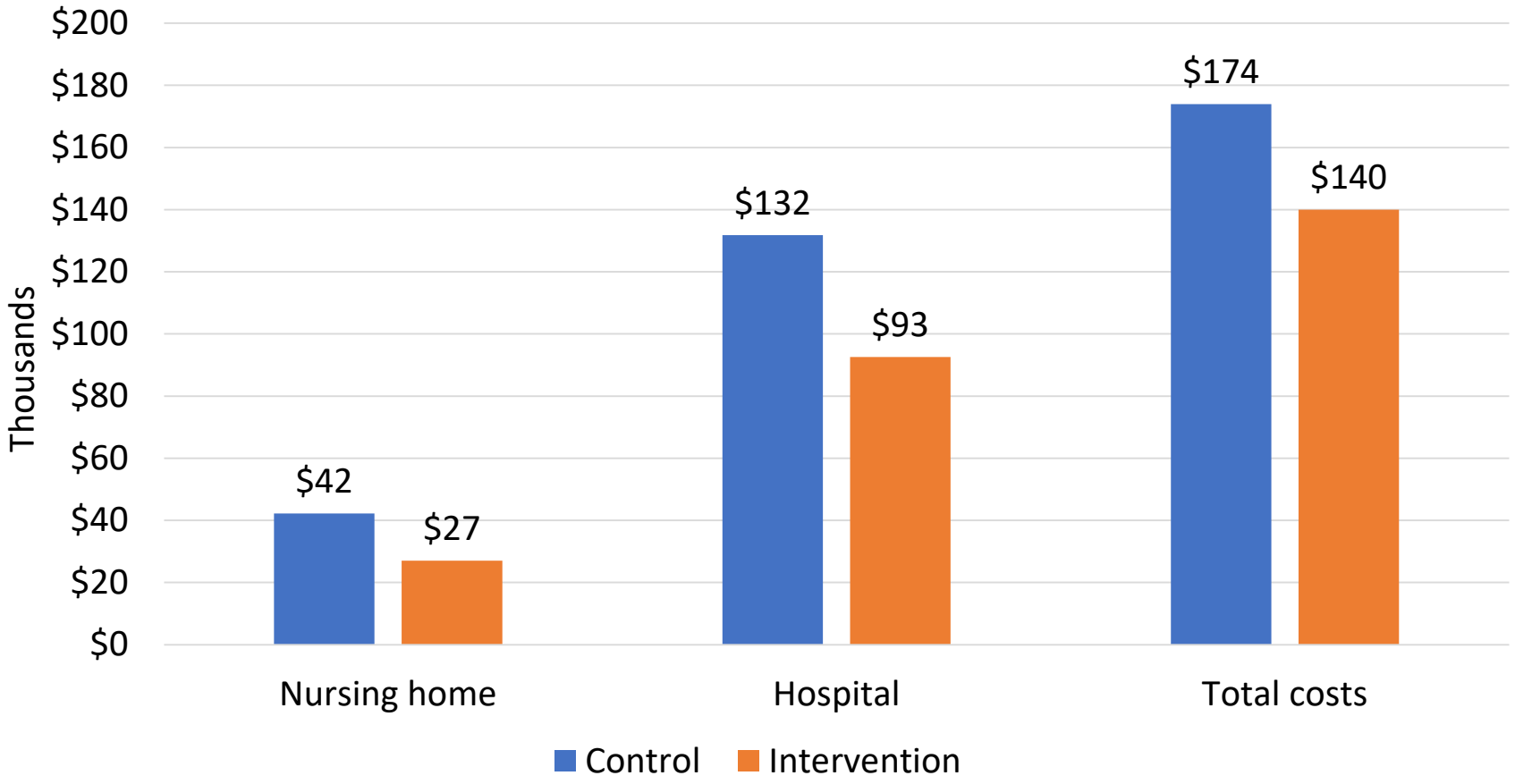

**Intervention** =

- 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.

Szanton, S.L., et al. (2019). *JAMA Intern Med.,179(2)*:204–211

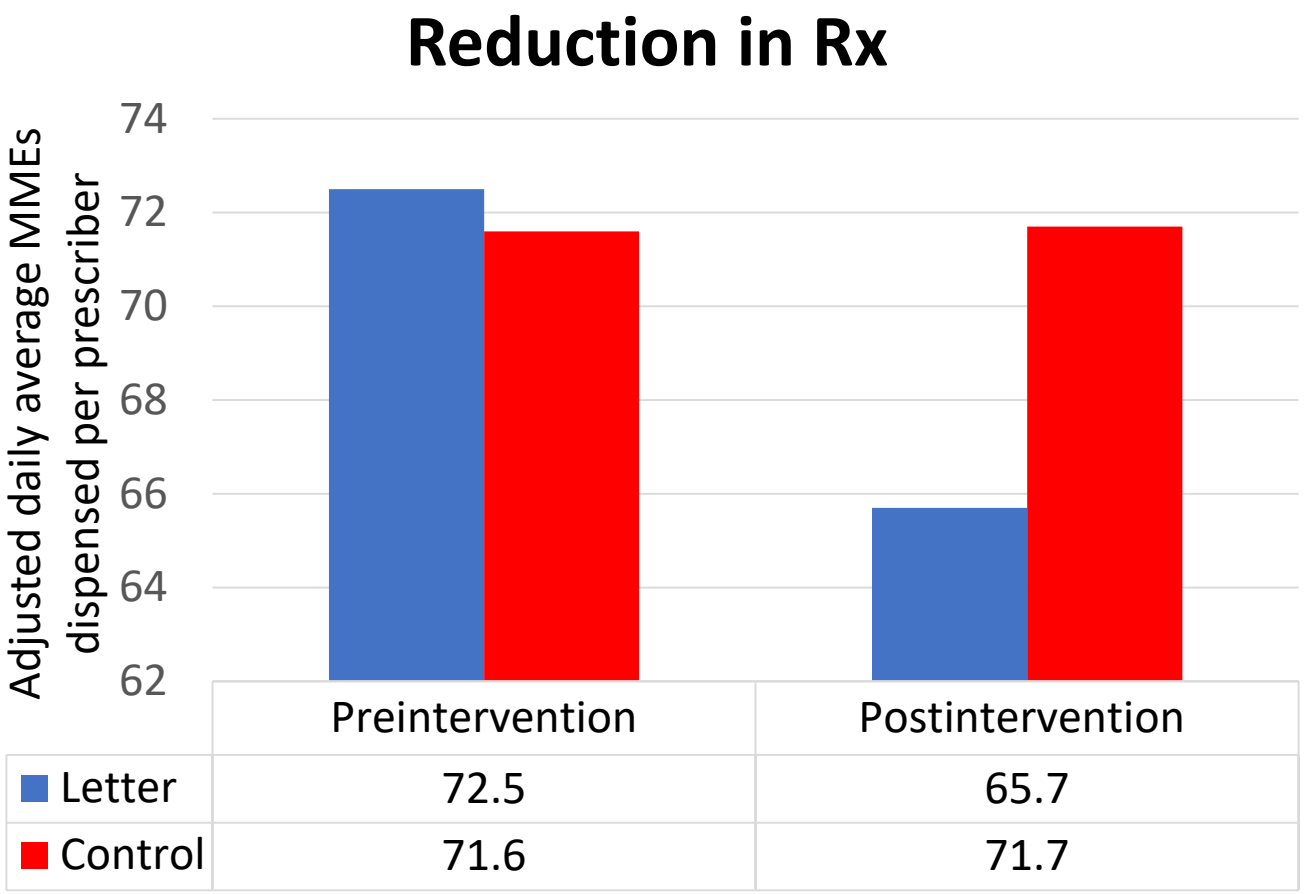
# Successful UTI Prevention Program in Nursing Homes Leads to Cost Reduction

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




Adapted from Hutton et al. (2018) *J AM Geriatr Soc* 66(4): 742-47.

# Notification of Patient Overdose Deaths Reduces Clinician Opioid Prescriptions




MME= milligram morphine equivalents

***MMEs in Rxs of letter recipients decreased by 9.7% after 3 months***

Doctor, J.N., et al. (2018). *Science, 361 (6402),* 588-590.

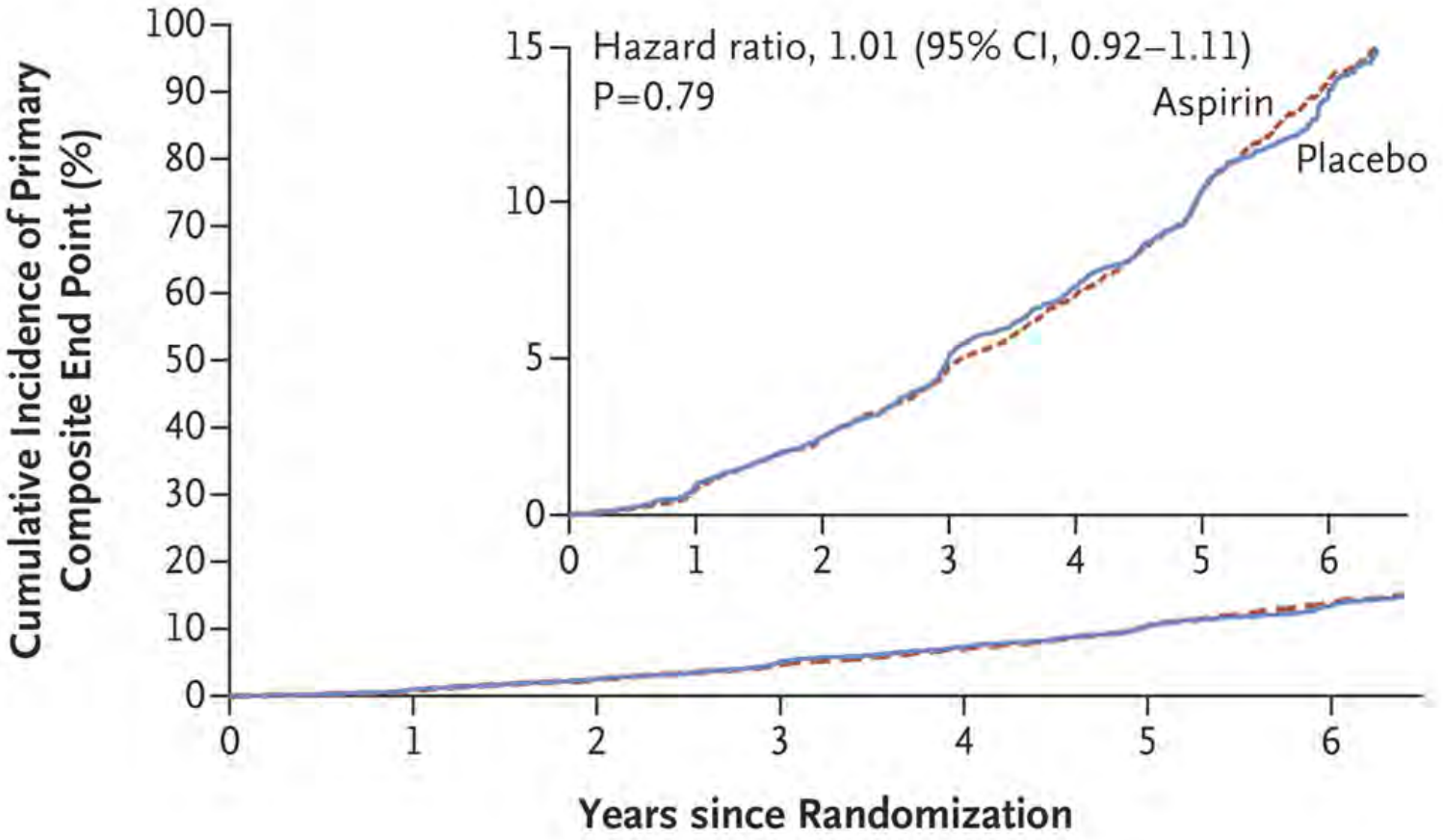
# Daily Low-Dose Aspirin Found to Have No Effect on Healthy Life Span in Older Adults

## 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




McNeill, J.J. et al. (2018). *NEJM 379*:1499-1508.

# 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**

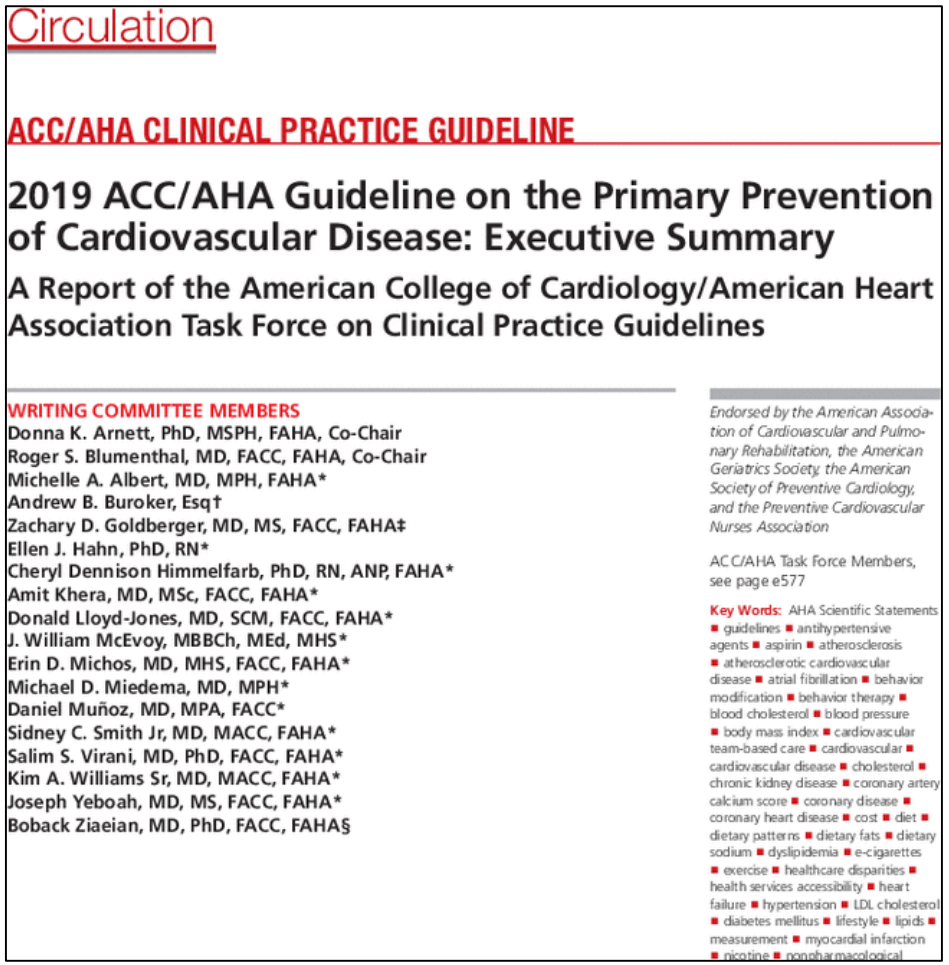
- **Cardiovascular**: No substantial reduction in risk of MI and stroke
- **Mortality**: Slightly higher – but not significant
- **Bleeding**: Significantly increased risk of serious bleeding
- **Physical disability**: No effect
- **Dementia**: No effect

McNeil, J.J. et al. (2018). *NEJM* 379:1499-1508.
McNeil, J.J. et al. (2018). *NEJM* 379: 1509-1518.
McNeil, J.J. et al. (2018). *NEJM* 379: 1519-1528.

# Change in ACC/AHA Clinical Practice Guidelines re: Aspirin for CVD Prevention

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association®
*Learn and Live*



Circulation

ACC/AHA CLINICAL PRACTICE GUIDELINE

## 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary

### A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines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*Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Geriatrics Society, the American Society of Preventive Cardiology, and the Preventive Cardiovascular Nurses Association*



ACC/AHA Task Force Members, see page e577



**Key Words:** AHA Scientific Statements ■ guidelines ■ antihypertensive agents ■ aspirin ■ atherosclerosis ■ atherosclerotic cardiovascular disease ■ atrial fibrillation ■ behavior modification ■ behavior therapy ■ blood cholesterol ■ blood pressure ■ body mass index ■ cardiovascular team-based care ■ cardiovascular ■ cardiovascular disease ■ cholesterol ■ chronic kidney disease ■ coronary artery calcium score ■ coronary disease ■ coronary heart disease ■ cost ■ diet ■ dietary patterns ■ dietary fats ■ dietary sodium ■ dyslipidemia ■ e-cigarettes ■ exercise ■ healthcare disparities ■ health services accessibility ■ heart failure ■ hypertension ■ LDL cholesterol ■ diabetes mellitus ■ lifestyle ■ lipids ■ measurement ■ myocardial infarction ■ nicotine ■ nonpharmacological

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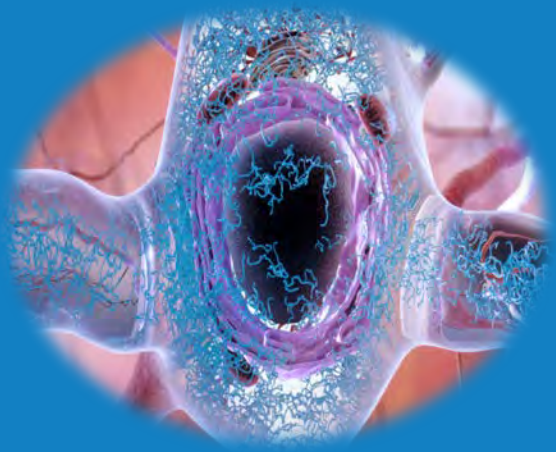

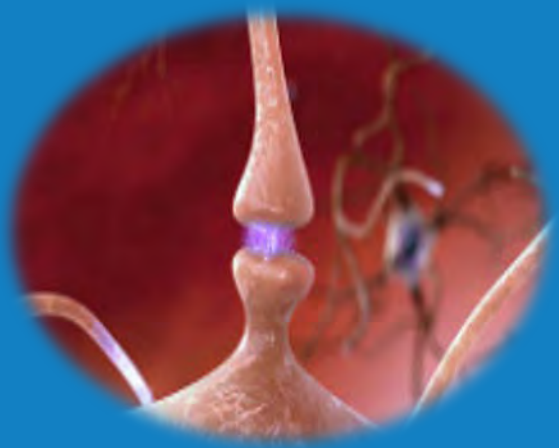

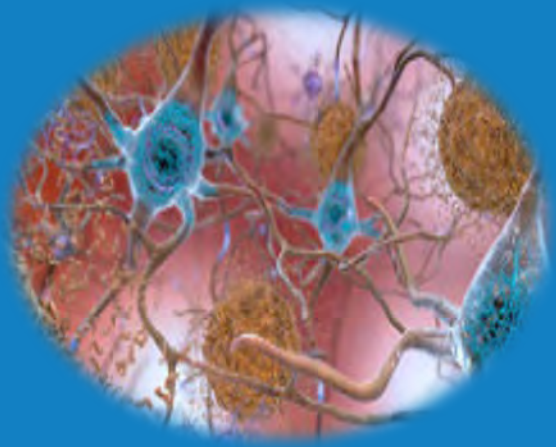

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