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

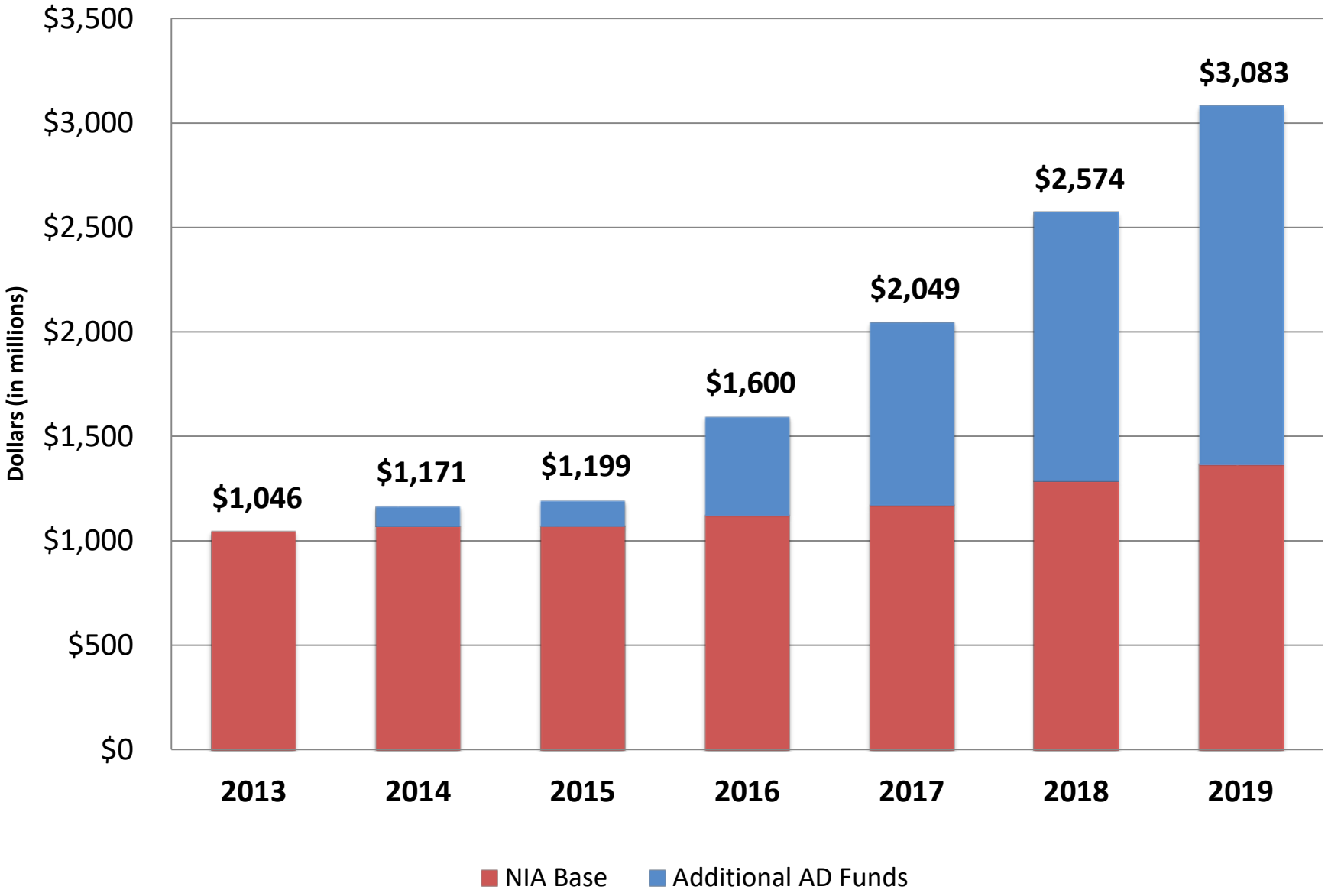
FY20 Budget Status

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

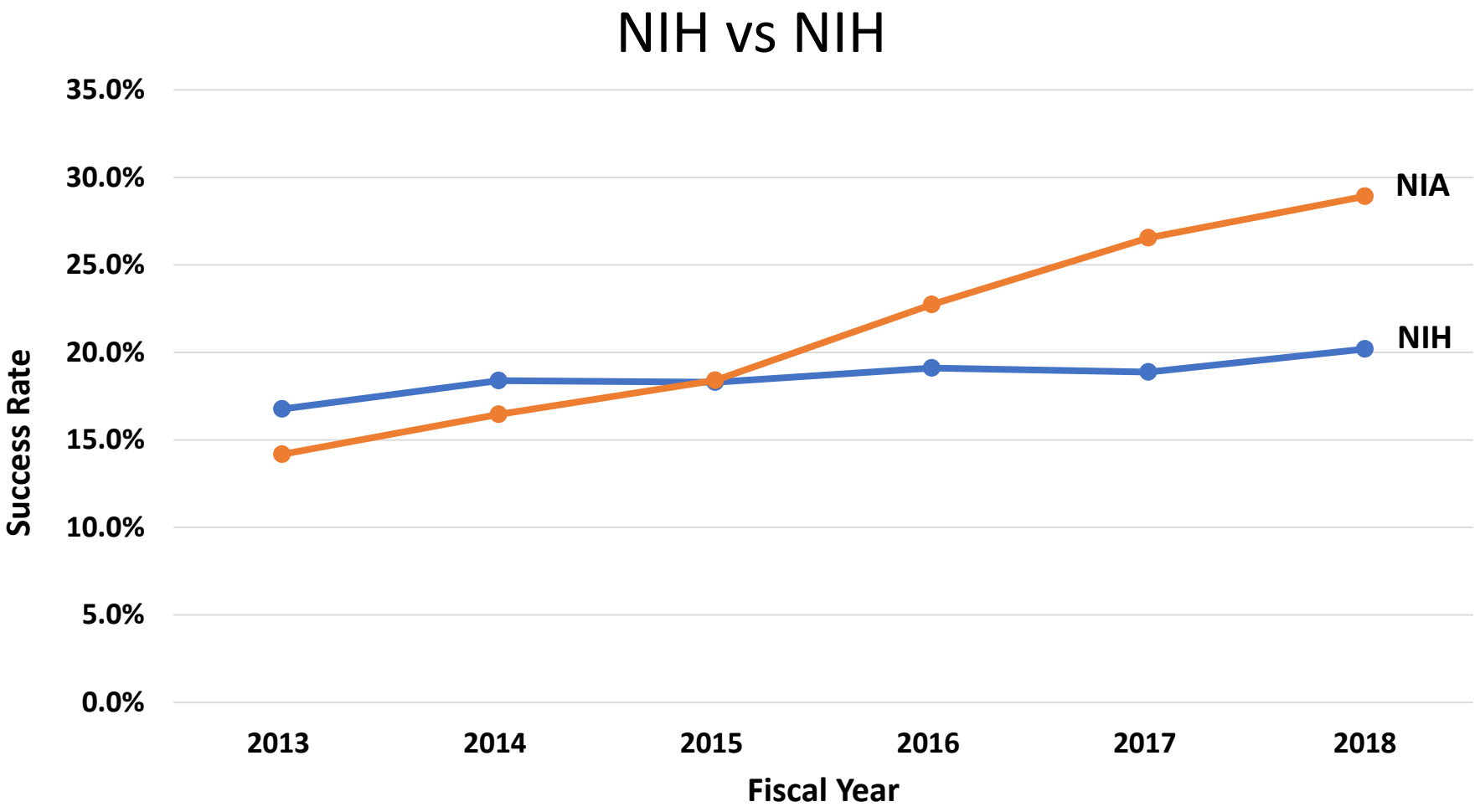
FY 2019 Pay Lines

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

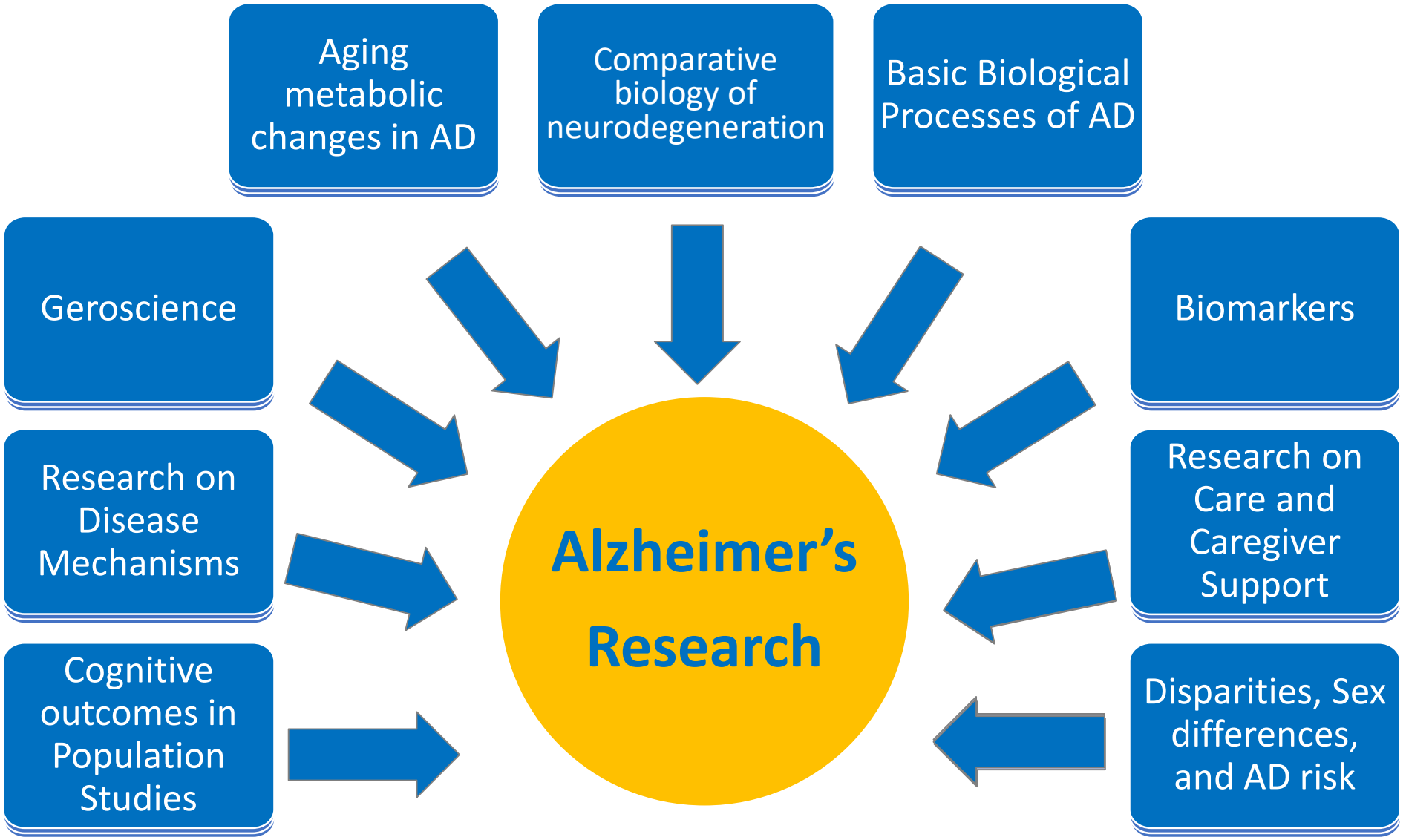
Training-related Applications		
	General pay line	AD/ADRD pay line
Training grants (T32, T35)	21	35
Career awards	21	28
Fellowships	28	32

RPG Success Rates Over Time



Alzheimer's Disease & Related Dementias – Progress & Advances

Diversity of AD/ADRD Research



Alzheimer's and Related Dementias Research

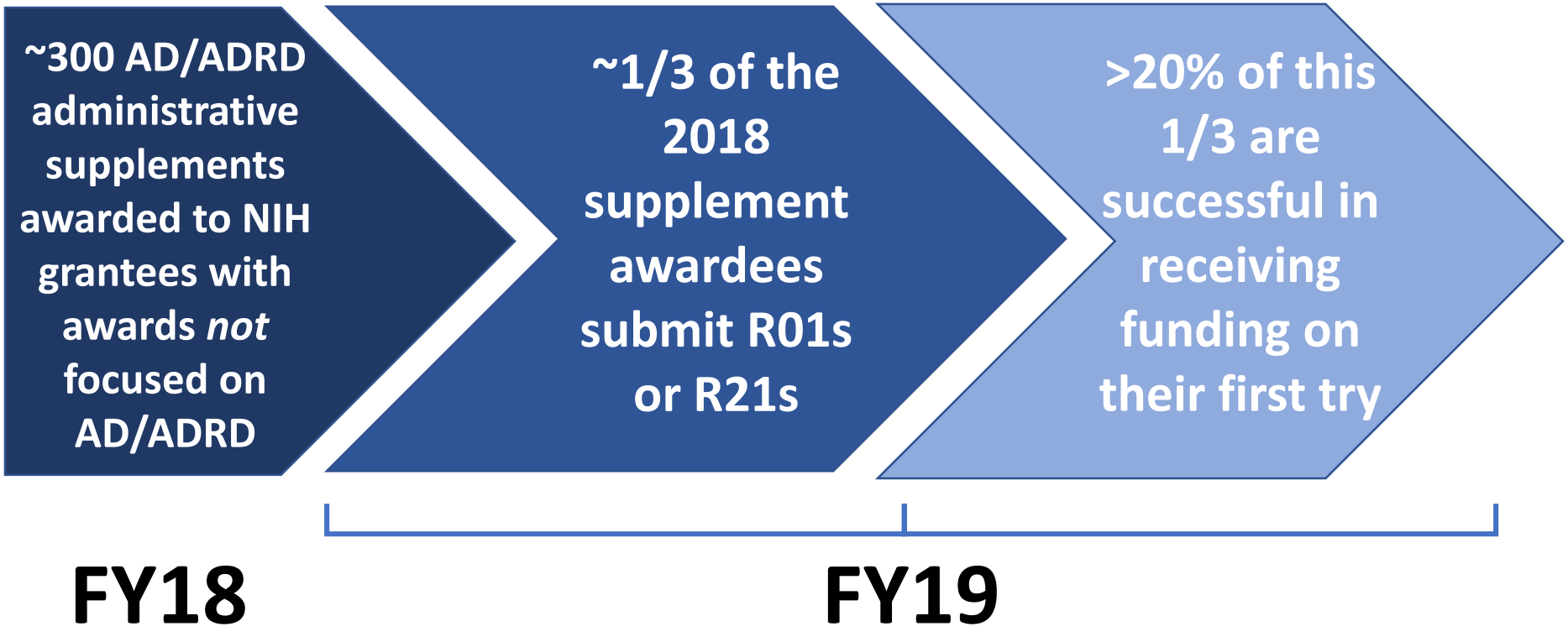
Growing the AD/ADRD workforce

From Fiscal Years 2015-2018:

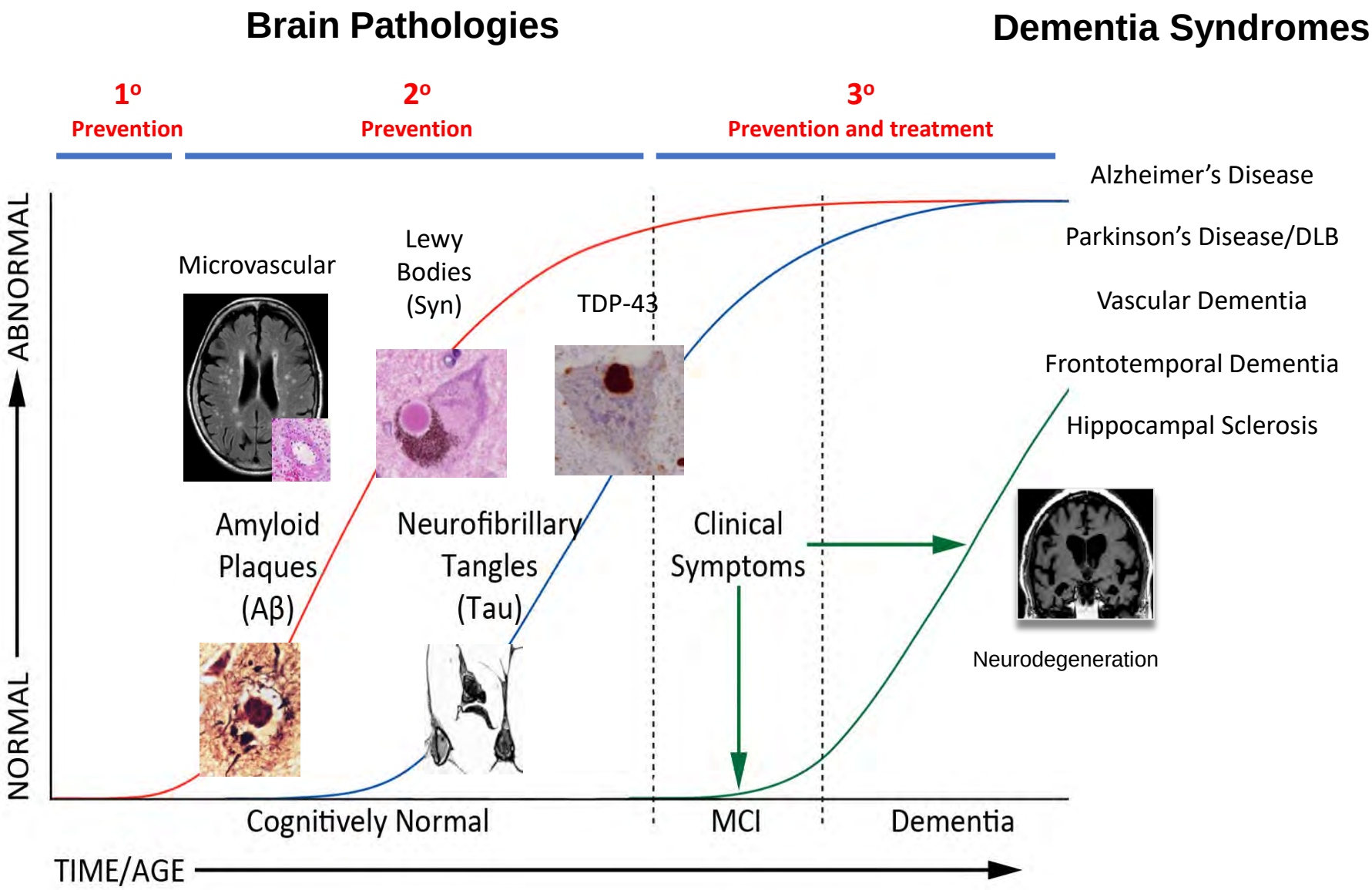
- ***~1/4*** of NIA's Alzheimer's and related dementias awardees were either *new or early stage* investigators

- ***~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



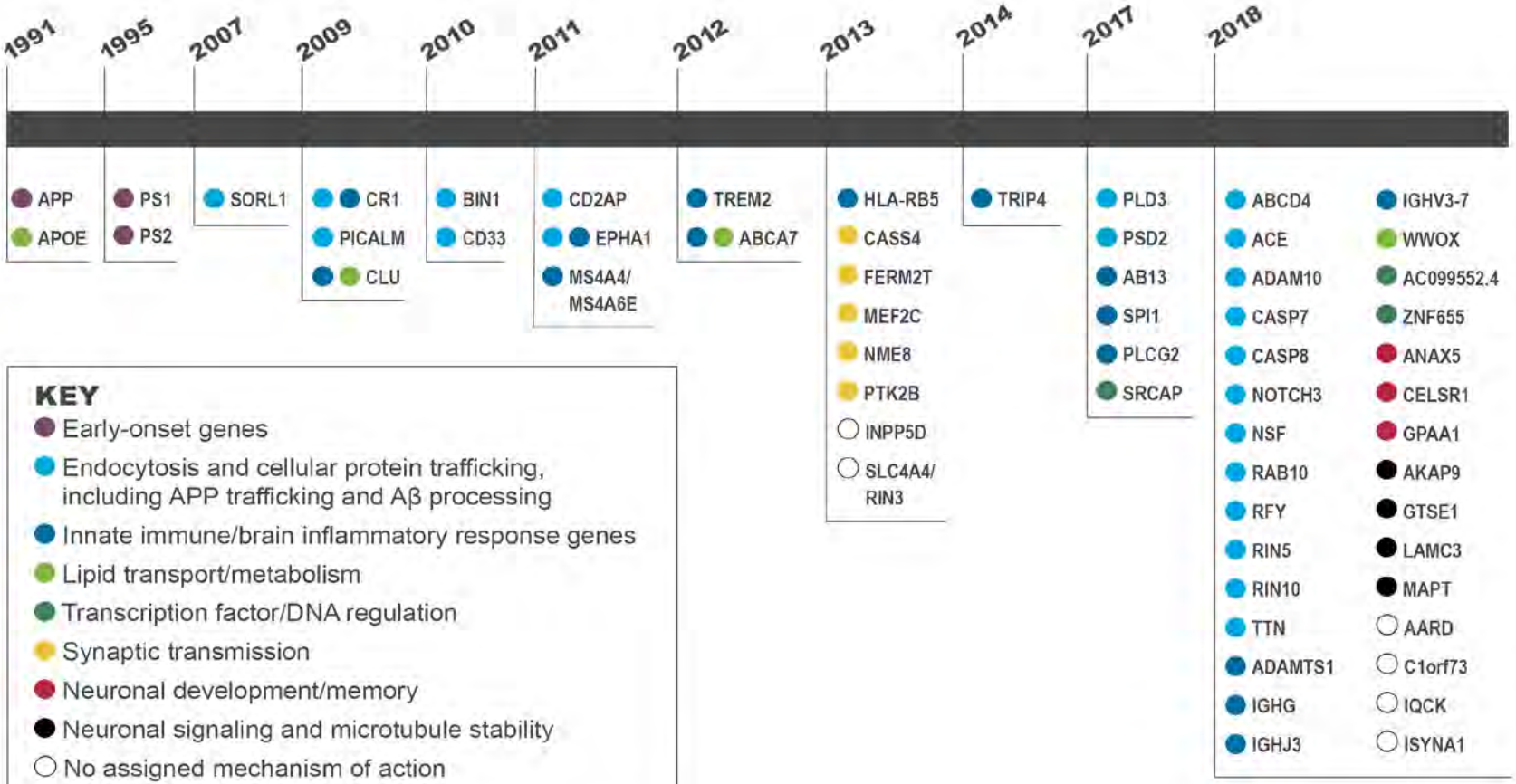
The Progression of Alzheimer's Disease and Related Dementias



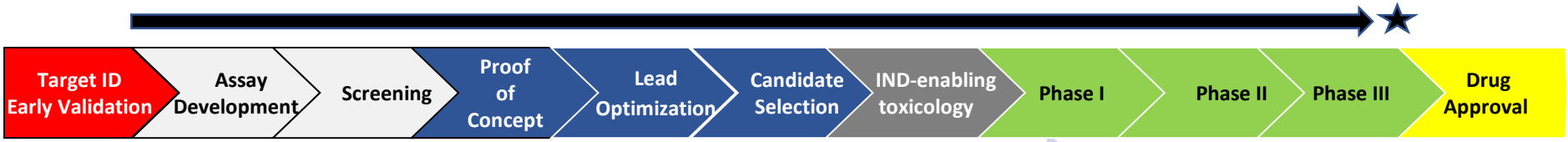
Genetic Regions of Interest in Alzheimer's Disease

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

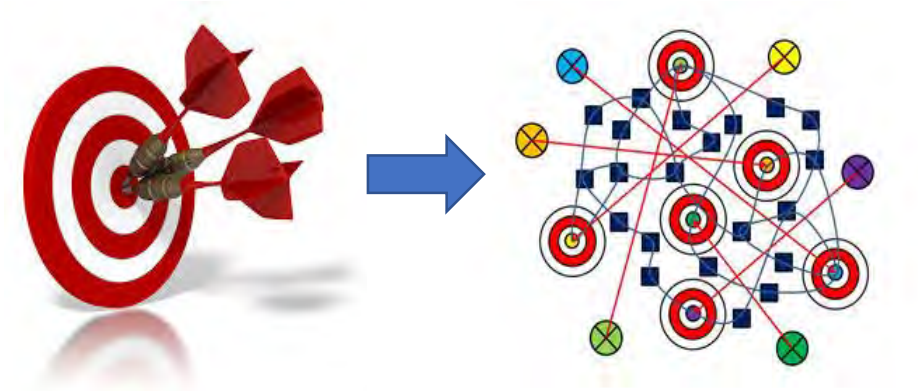
MODEL-AD
AlzPED

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

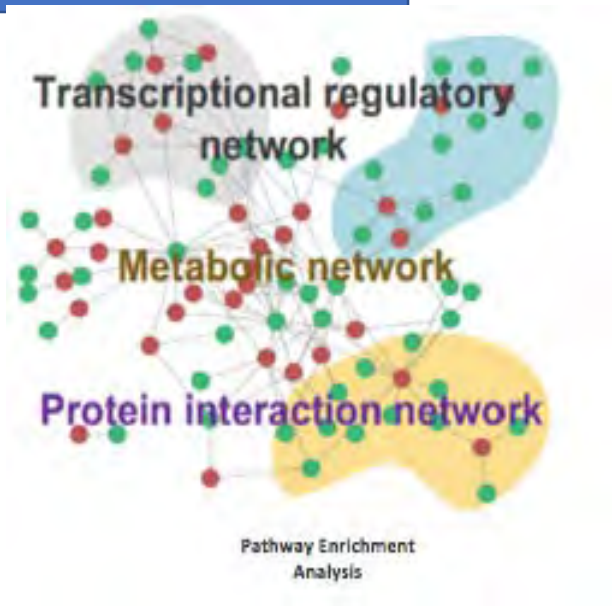
Molecular profiling
Predictive Modeling
Experimental validation

6 Academic Teams
– NIA U01/R01grants –

Data
Network models
Code

AMP-AD Knowledge Portal

Sage BIONETWORKS Synapse



- 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 Partners

NIH National Institute of Neurological Disorders and Stroke · FDA · abbvie · Biogen · GlaxoSmithKline · Lilly · alzheimer's association · Alzheimer's Drug Discovery Foundation · US Against Alzheimer's · FNIH Foundation for the National Institutes of Health

NIH National Institute on Aging

ACCELERATING MEDICINES PARTNERSHIP (AMP)

Progress over 4 years:

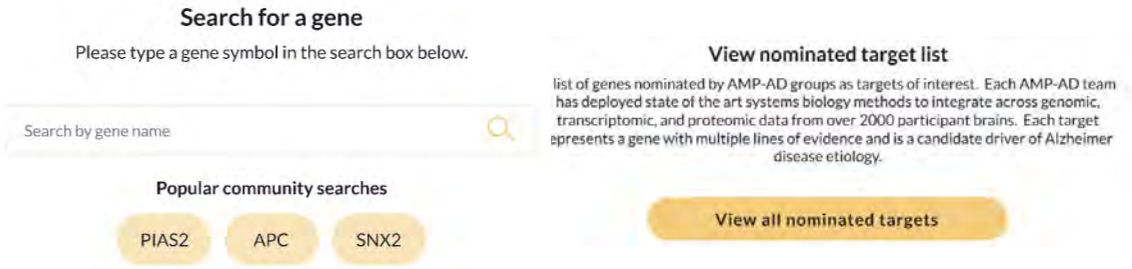
- Centralized data resource established- AMP-AD portal
- All data sharing deliverables met
- A variety of experimental validation models developed
- Novel biomarker discovery initiated
- Over 100 candidate targets nominated; currently undergoing data-driven prioritization for further preclinical validation

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		

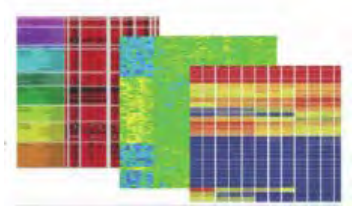
Agora

agora.ampadportal.org

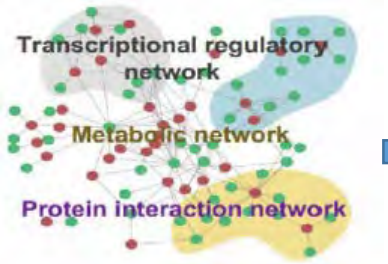


NIH National Institute on Aging

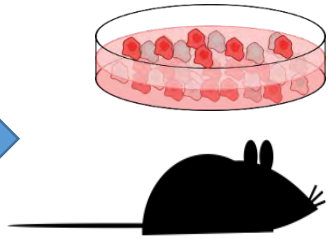
Harnessing the power of Big Data to understand the complex biology of disease and discover new therapeutic targets



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



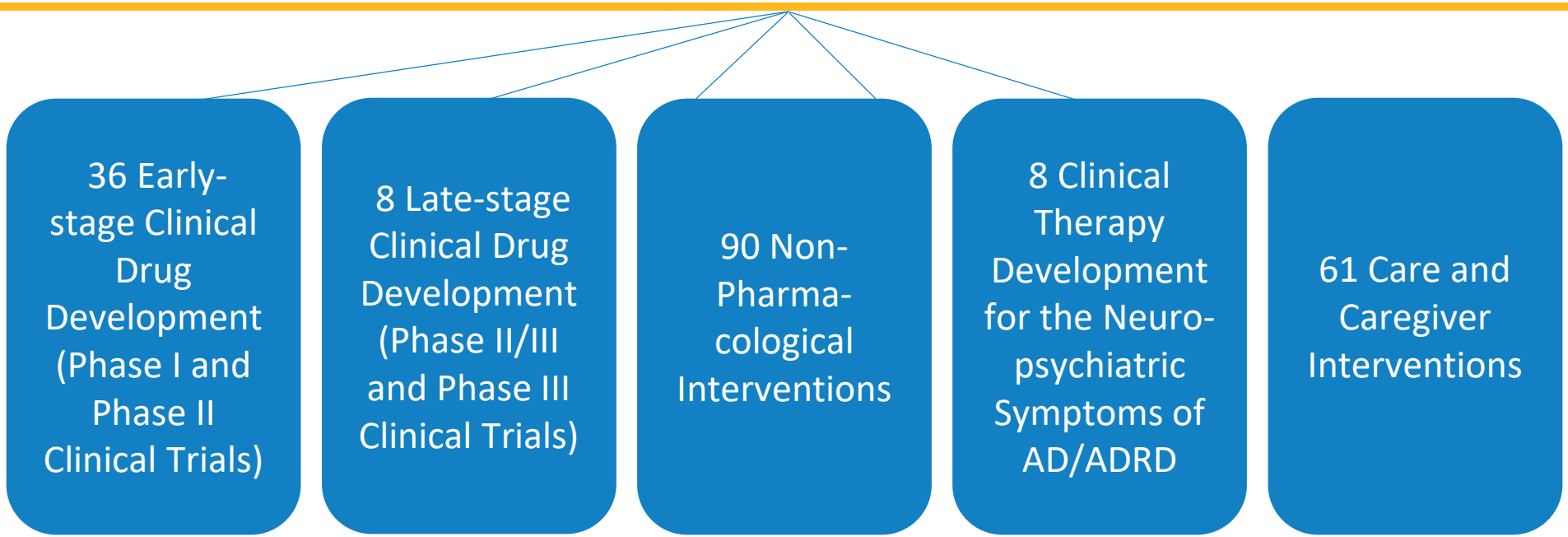
Computational modeling to identify novel therapeutic targets



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.

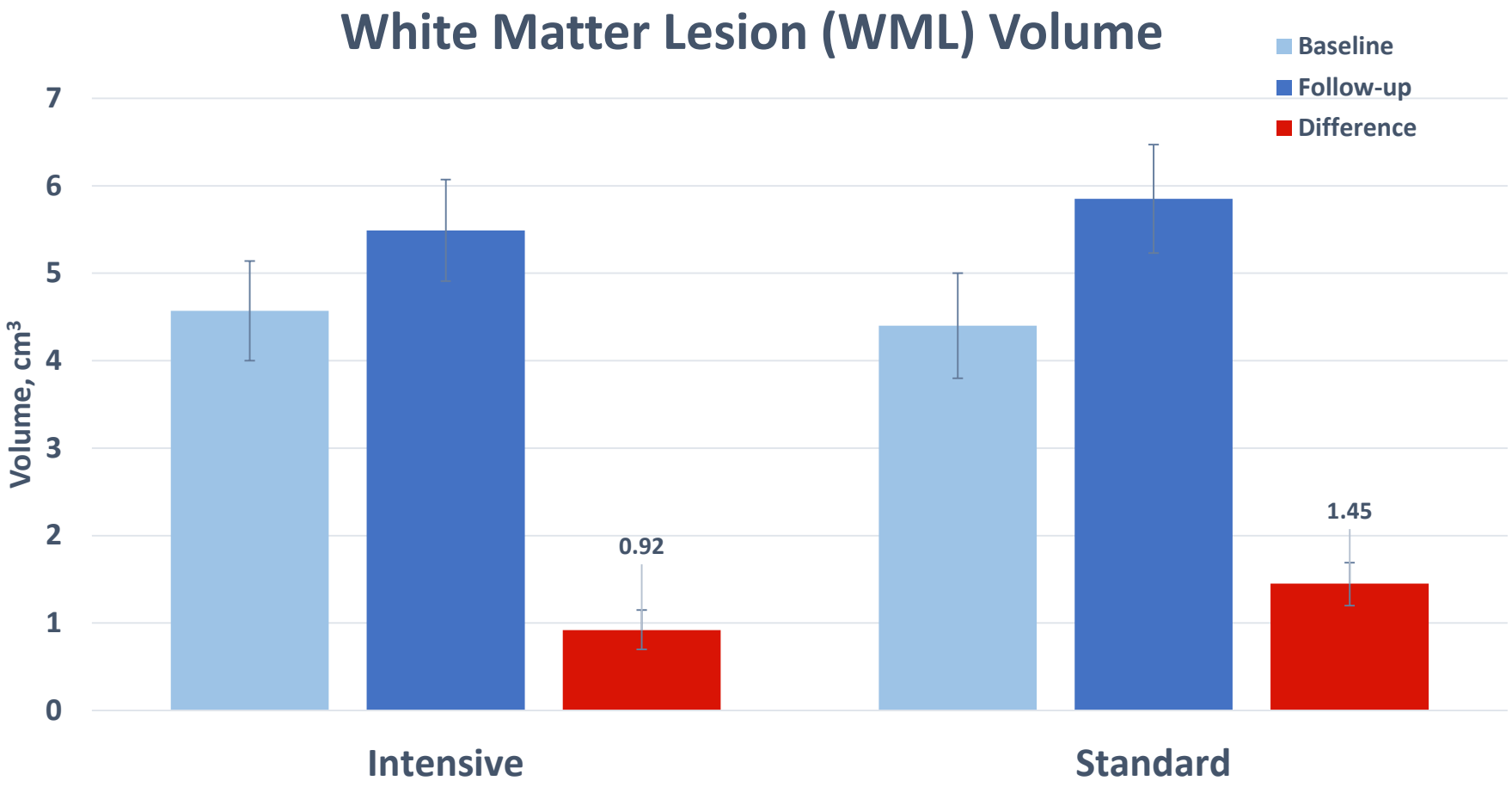
SPRINT-MIND: Secondary Cognitive Outcome

- 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:

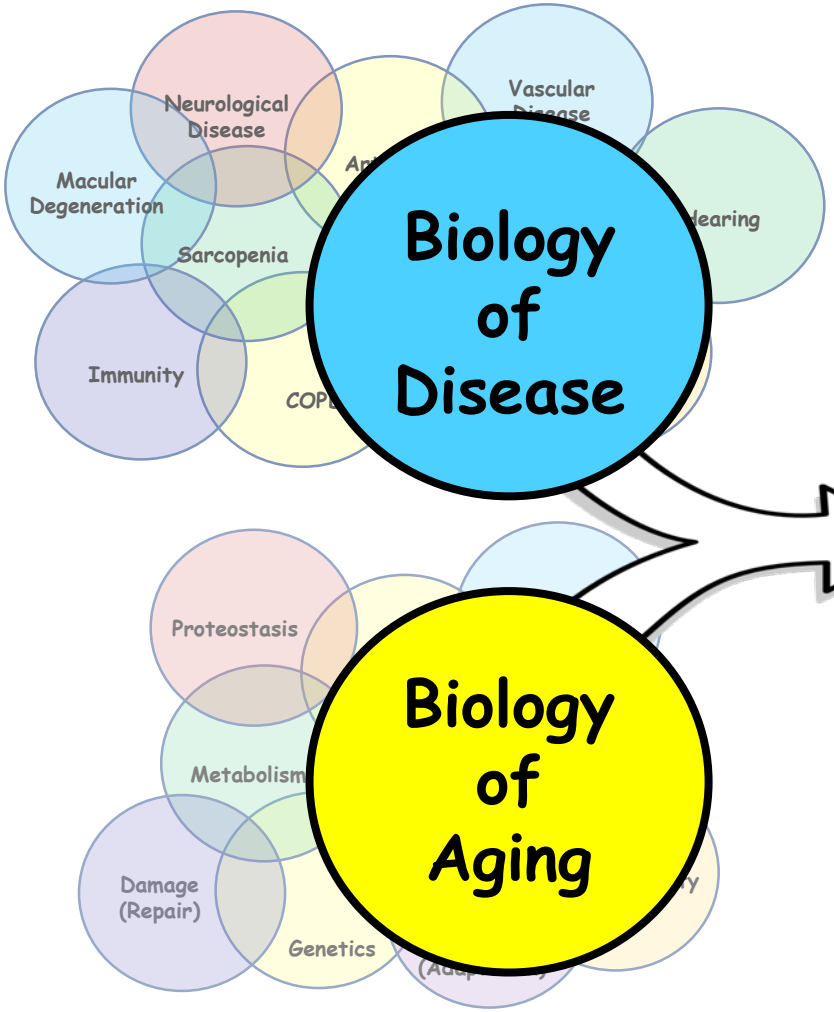
- **Find** flyers, toolkits, recruitment plans, and more from Alzheimer's Disease Research Centers, NIH, and others.
- **Browse** by goals, participant characteristics, and dozens of focused topics.
- **Get** tips for strategy from the Alzheimer's Disease and Related Dementias Clinical Studies Recruitment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

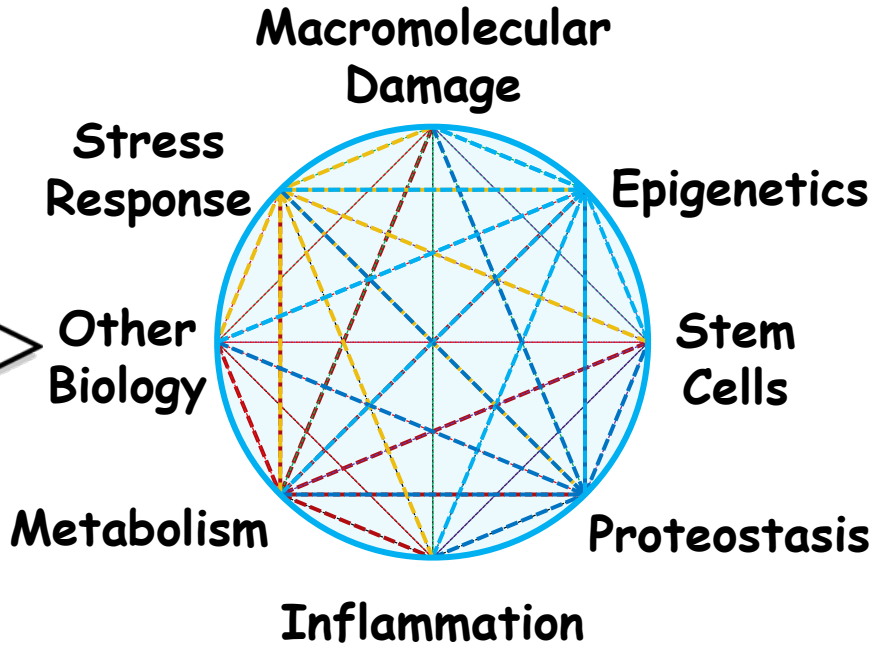
New research collaboratory designed to spur innovation and improve dementia care

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

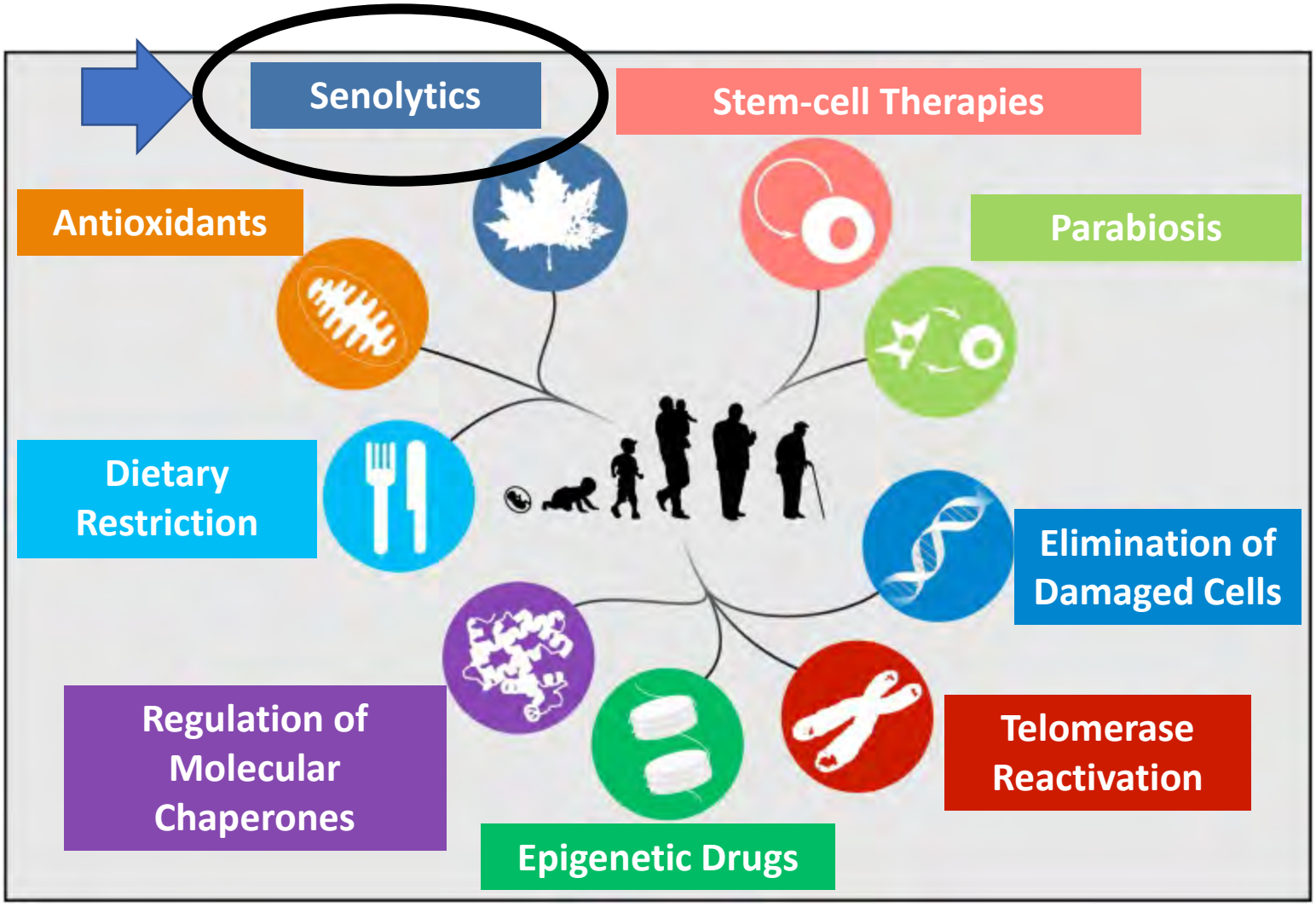




Sierra & Kohanski
J Gerontol June 2014

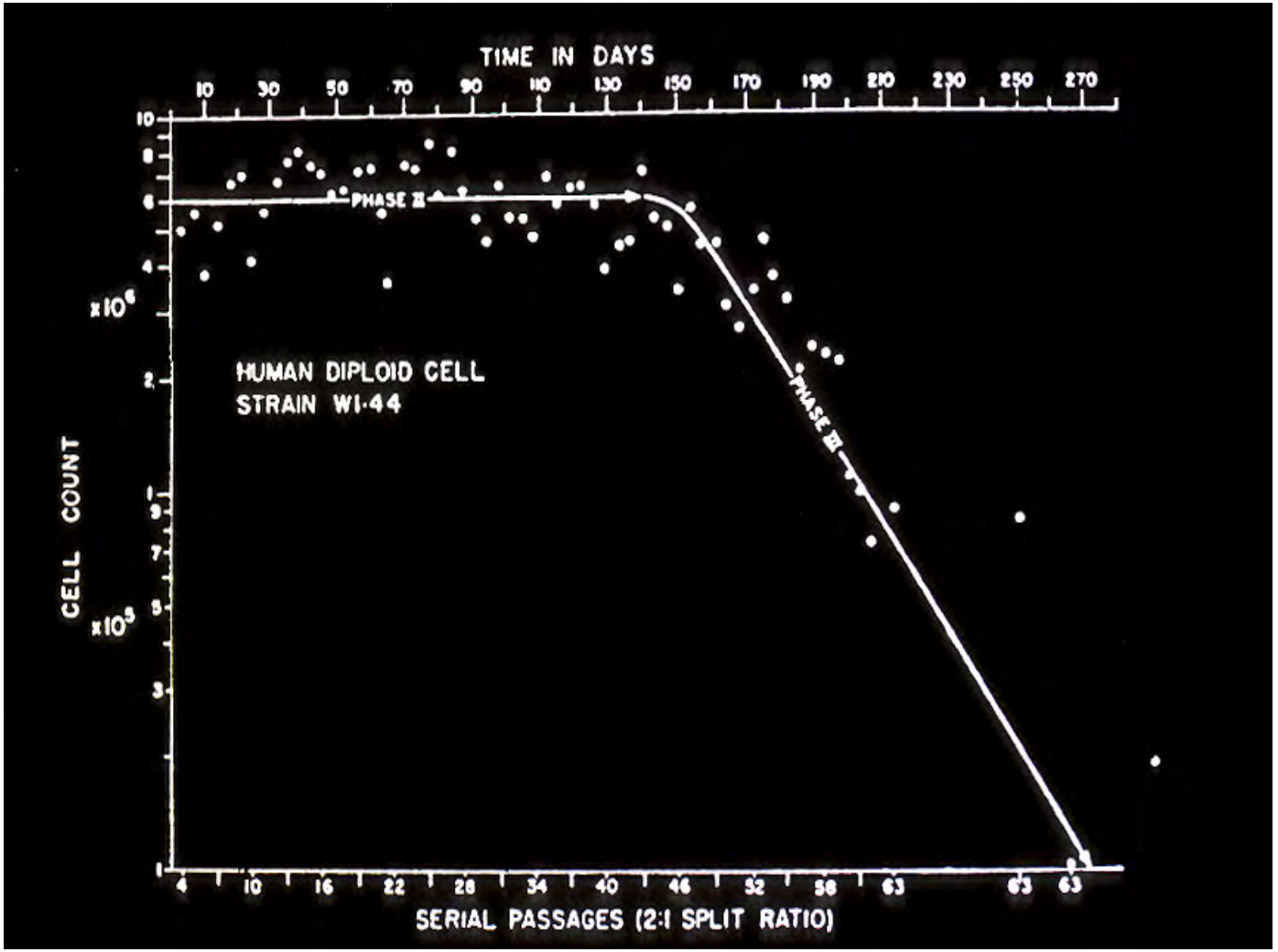
Kennedy *et al.*
Cell Nov 2014

Geroscience: Interventions and Approaches

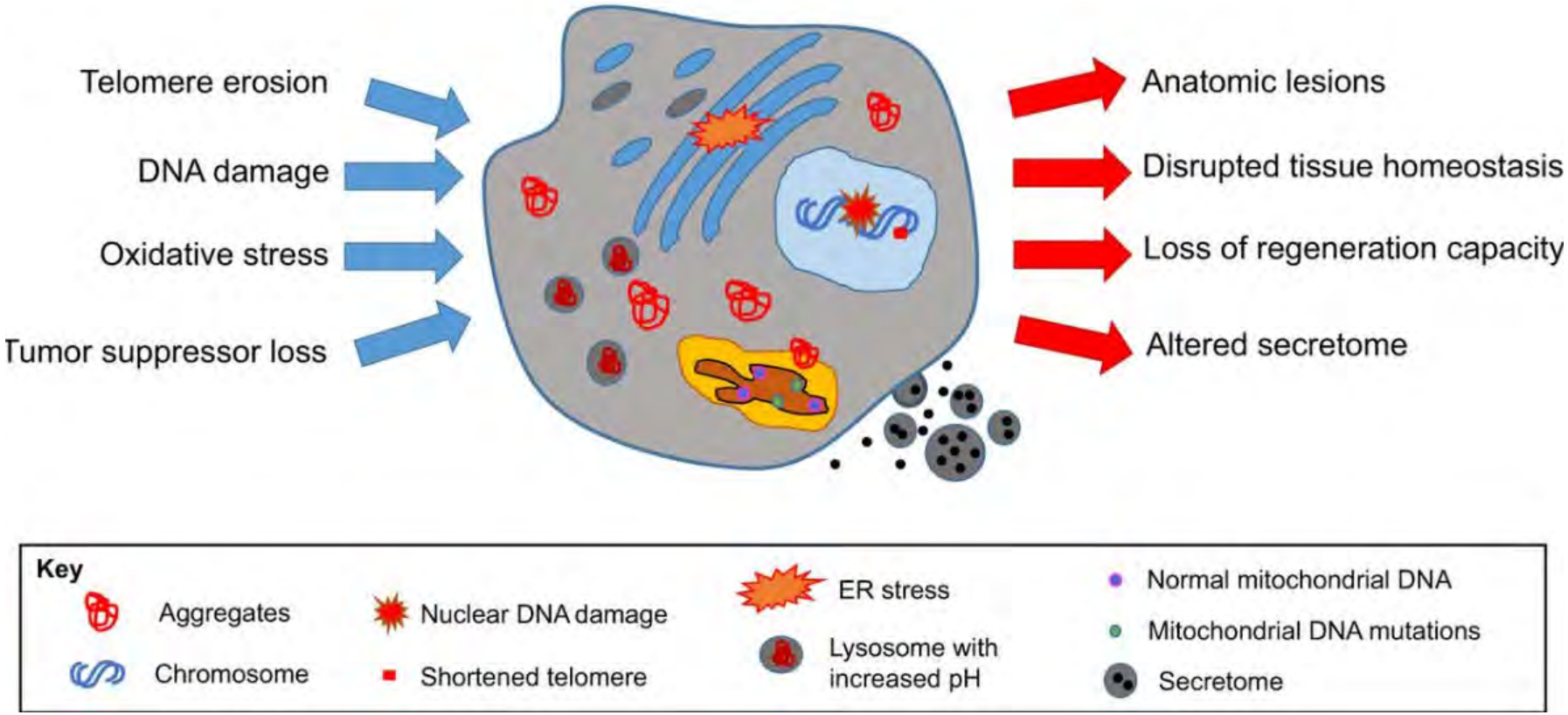


Adapted from: López-Otín, C et al. (2013). *Cell* 153: 1194-1217.

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?

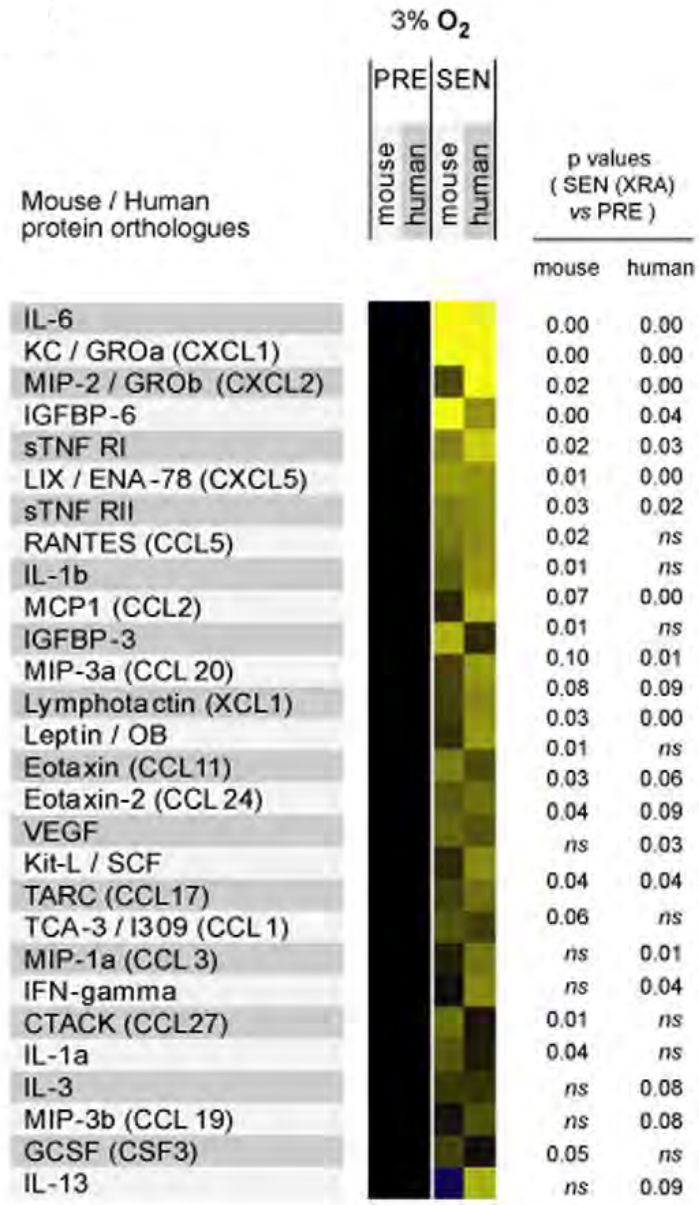


Senescent cells secrete a large number of biologically active factors which affect the function of neighboring, non-senescent cells

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

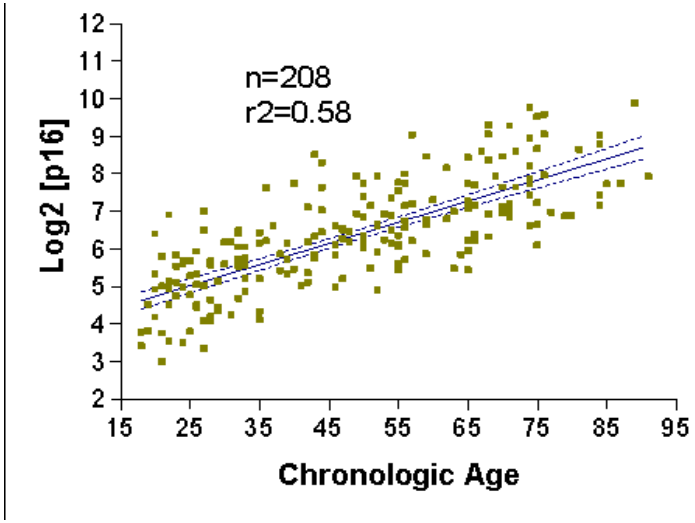


Coppe, J. et al. *PLoS One* (2010) 5(2):e918.

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

Sharpless lab, University of North Carolina

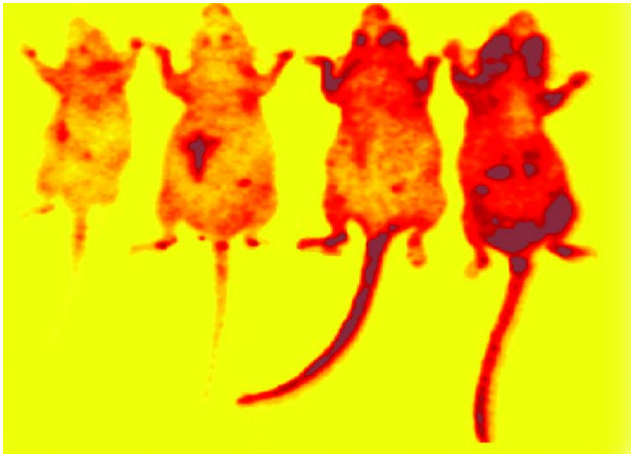
In Humans $p16^{ink4}$a expression in CD3+ T cells)



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

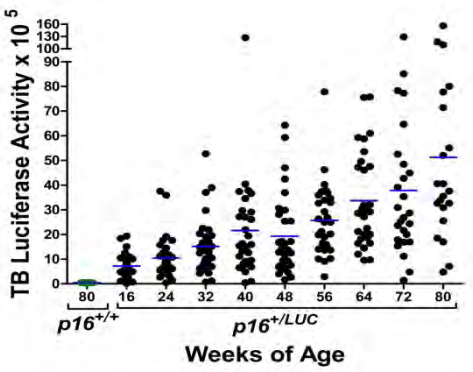
Adapted from
Liu et al Aging Cell 8:439-448 (2009) – human studies
Burd et al. Cell 152: 340-351 (2013) – C57BL6 mouse model

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



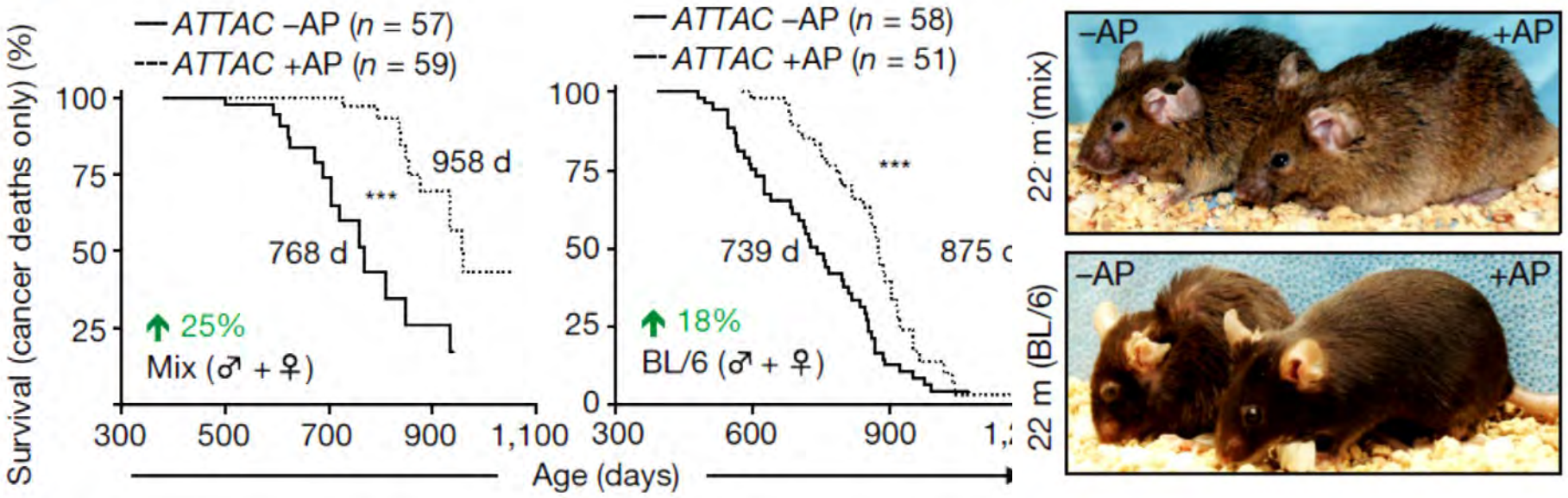
16 40 64 80

Weeks of age (one mouse)



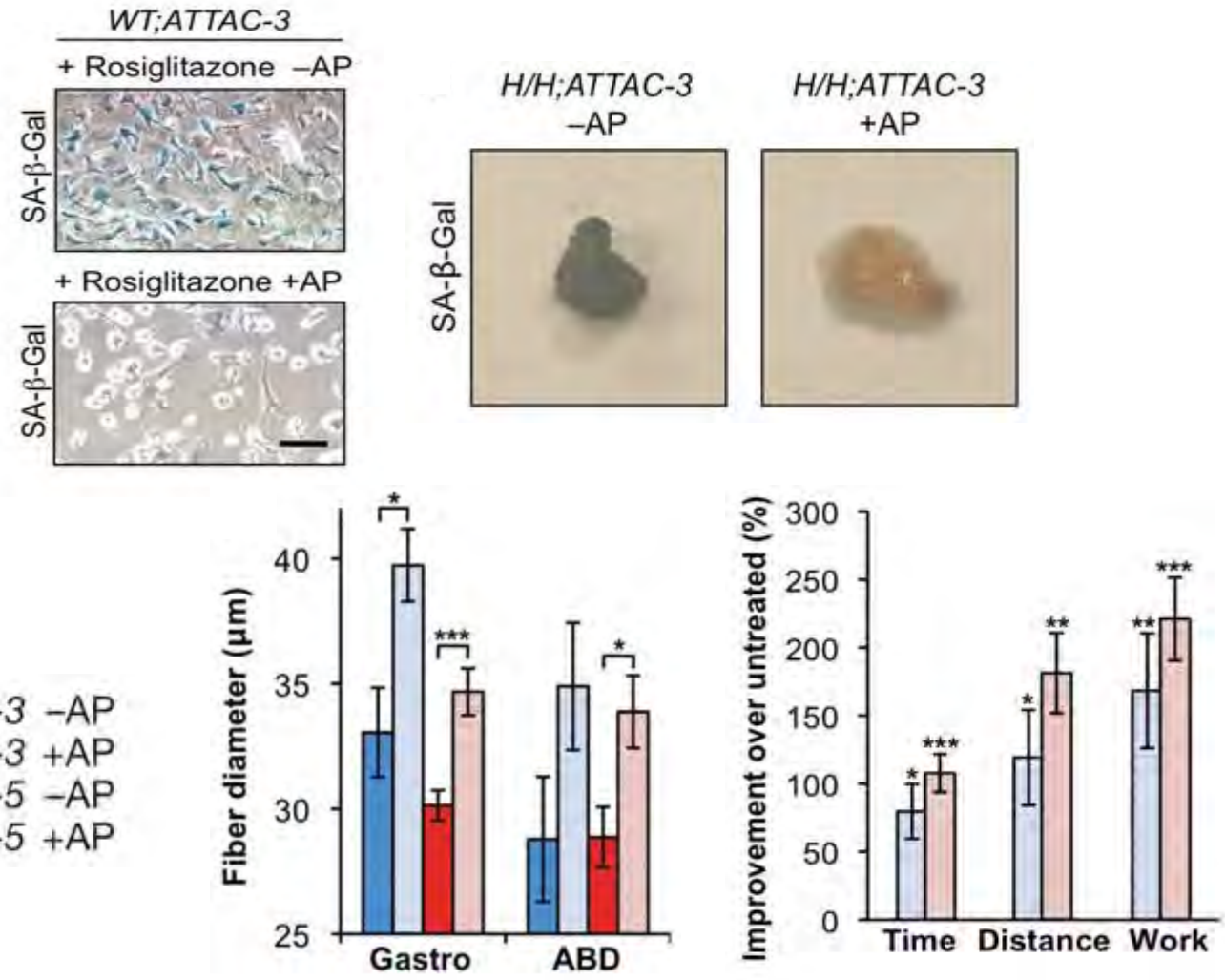
(many mice)

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



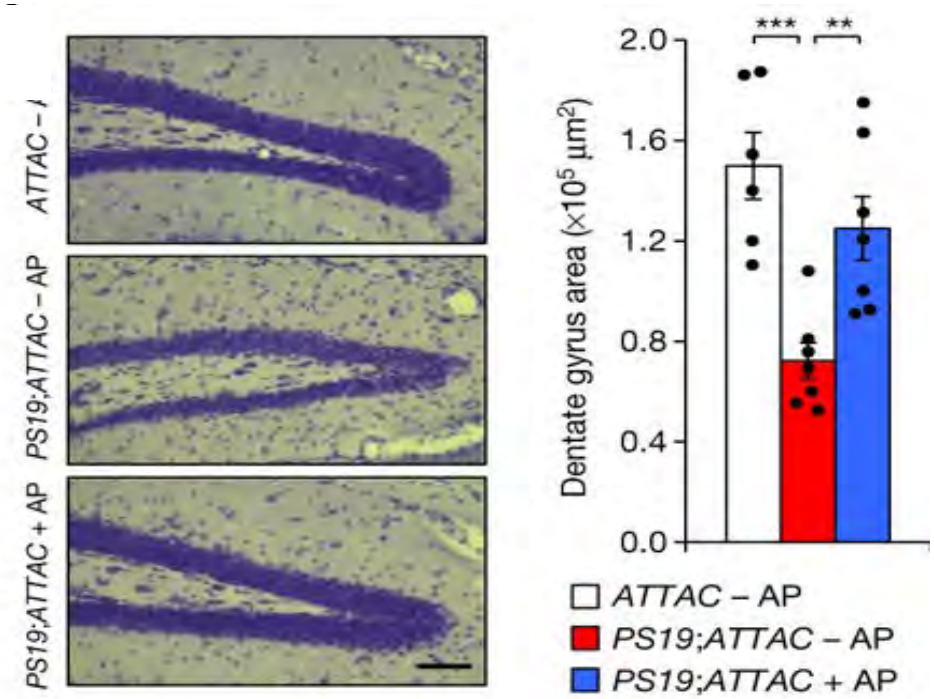
Baker DJ, et al. *Nature* (2016) 530(7589):184-9.

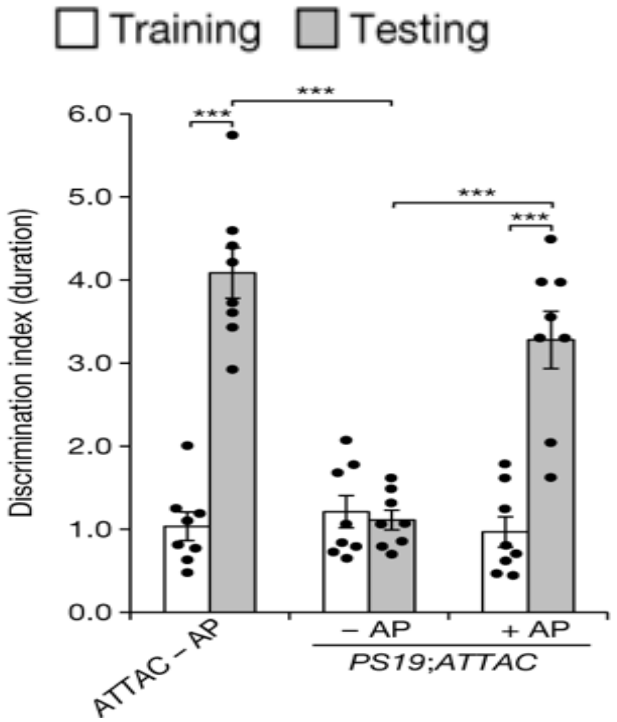
Clearance of p16^{Ink4a}-positive senescent cells delays aging-associated disorders



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

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





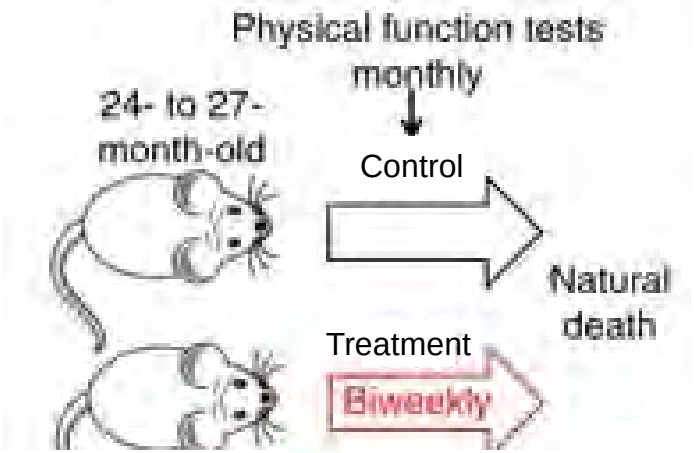
- **Senescent cells drive neurodegenerative disease**
- **Clearance of senescent cells through genetic manipulation or drug treatment decreases tau pathology and cognitive decline**

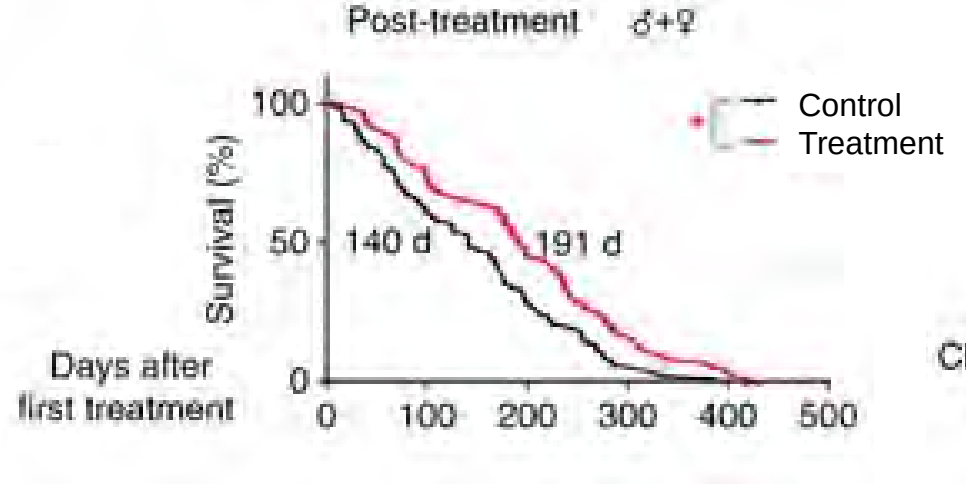
Bussian, T. et al. (2018*). Nature,* 562(7728): 578-582.

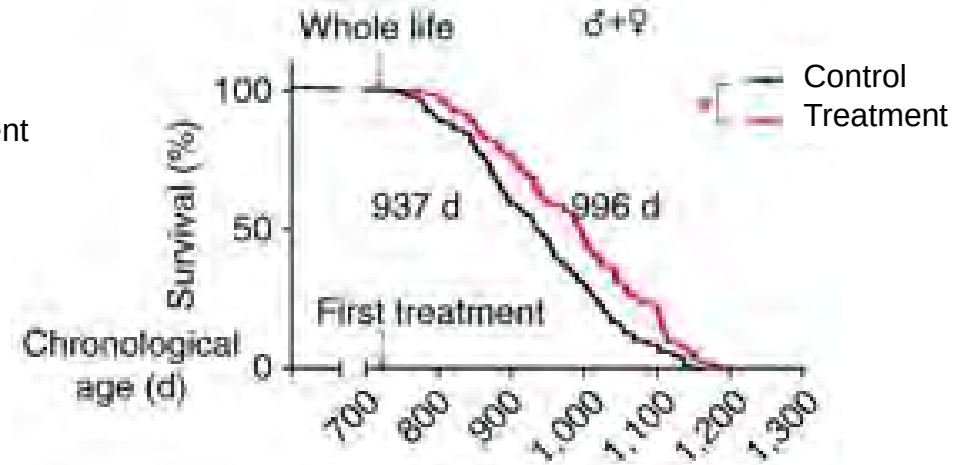
Treatment with Senolytics Extends Lifespan in Older WT Mice

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

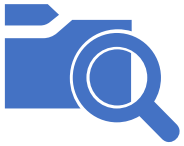
- Small Phase 1 studies on repurposed compounds (dasatinib + quercetin; navitoclax)
- *Conditions:*
  - Idiopathic pulmonary fibrosis (IPF) n=26 NCT02874989 (completed)
  - Alzheimer's disease n=5 NCT04063124
  - Diabetic chronic kidney disease n=16 NCT02848131
  - Osteoarthritis n=78 NCT03513016 (completed)
- 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.

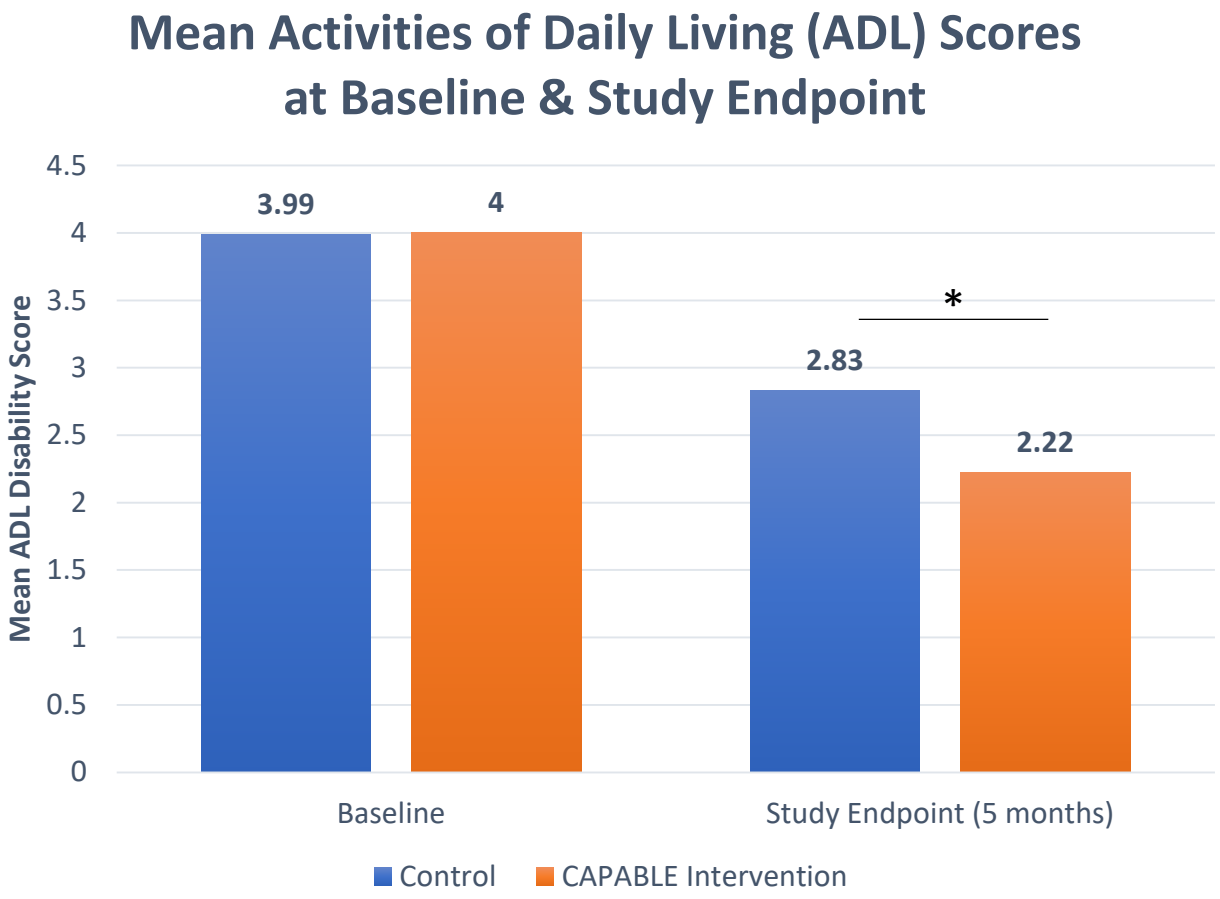


Support a data entry platform to facilitate cross-study comparisons.

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



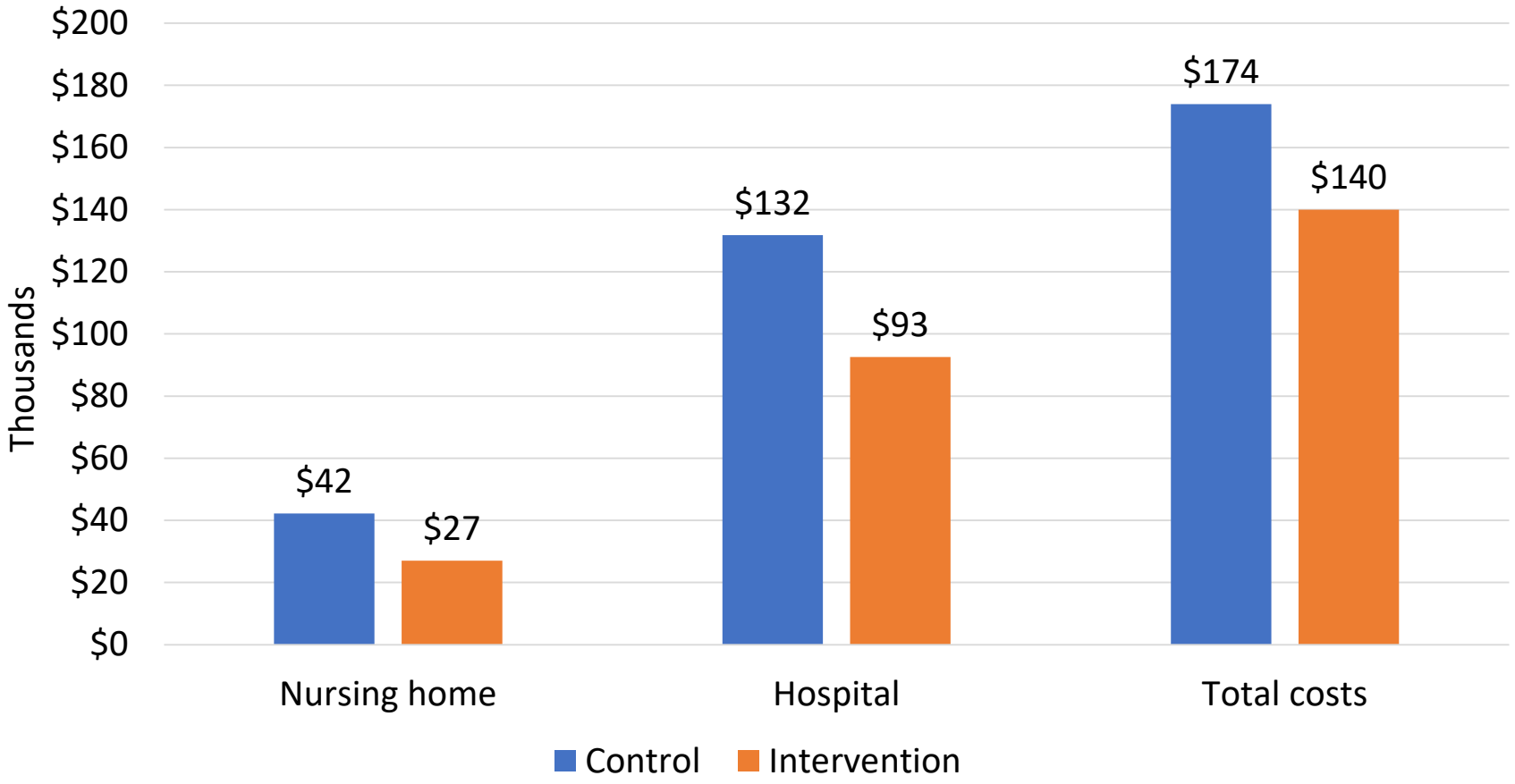
Intervention =

- 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

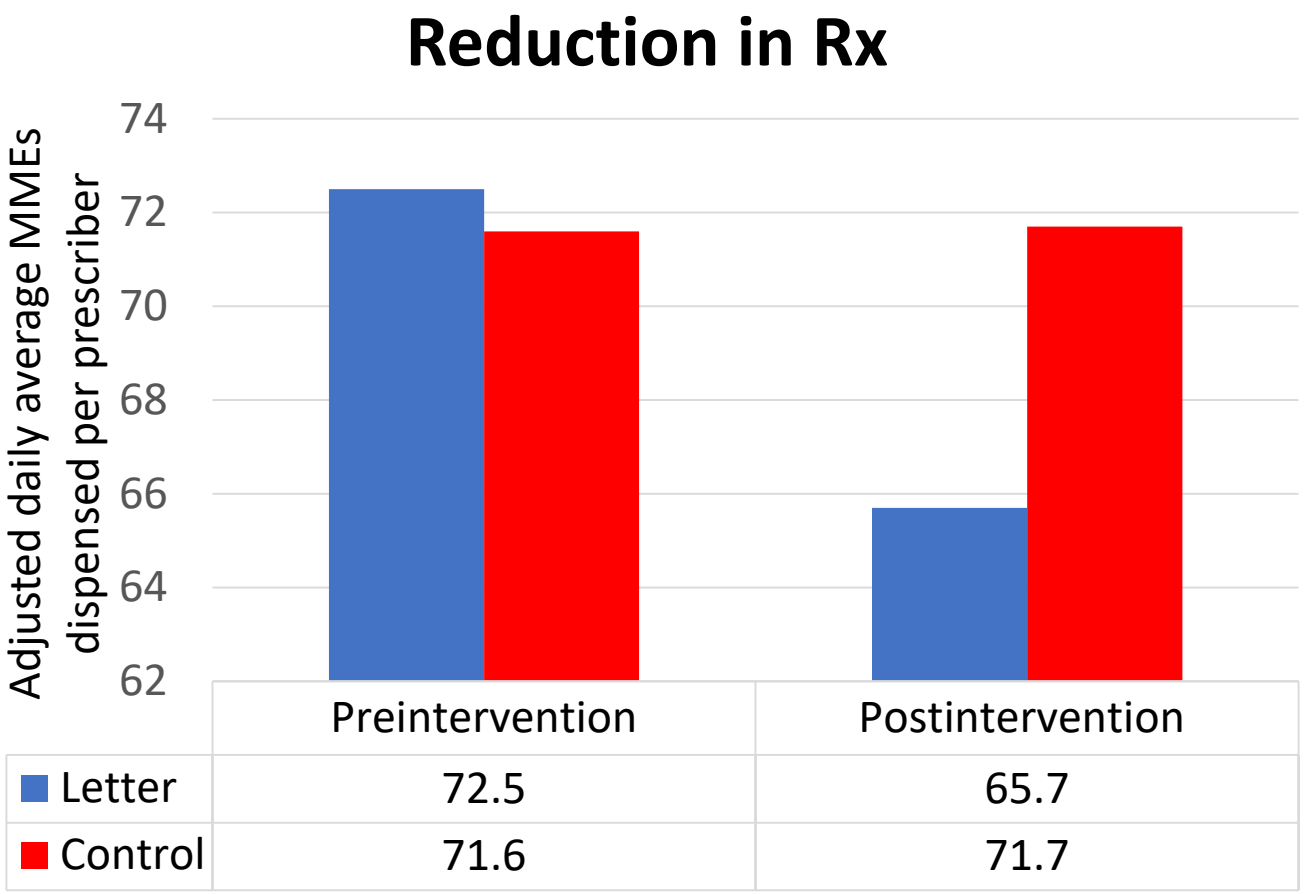
Successful UTI Prevention Program in Nursing Homes Leads to Cost Reduction

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.

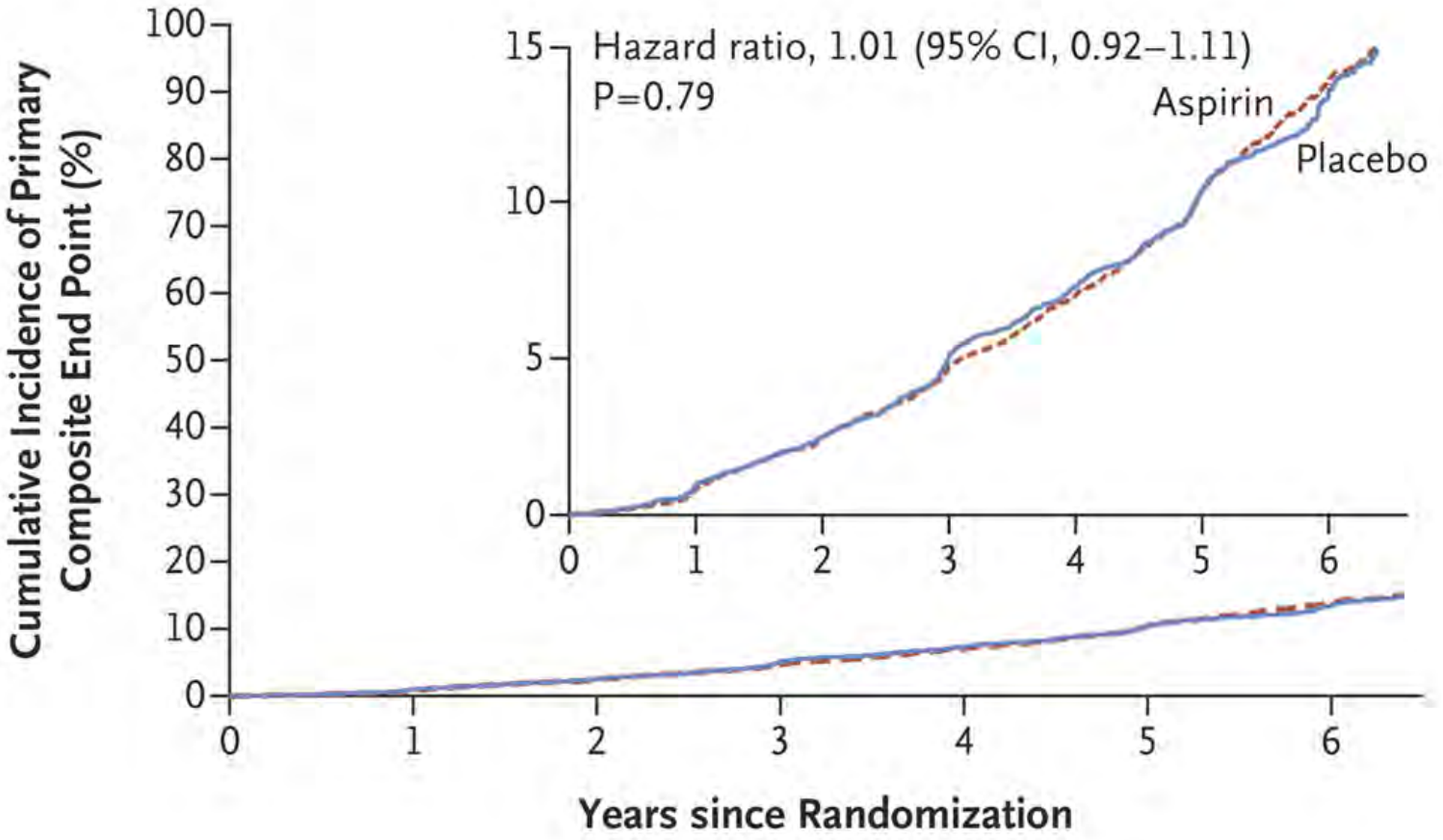
Daily Low-Dose Aspirin Found to Have No Effect on Healthy Life Span in Older Adults

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**

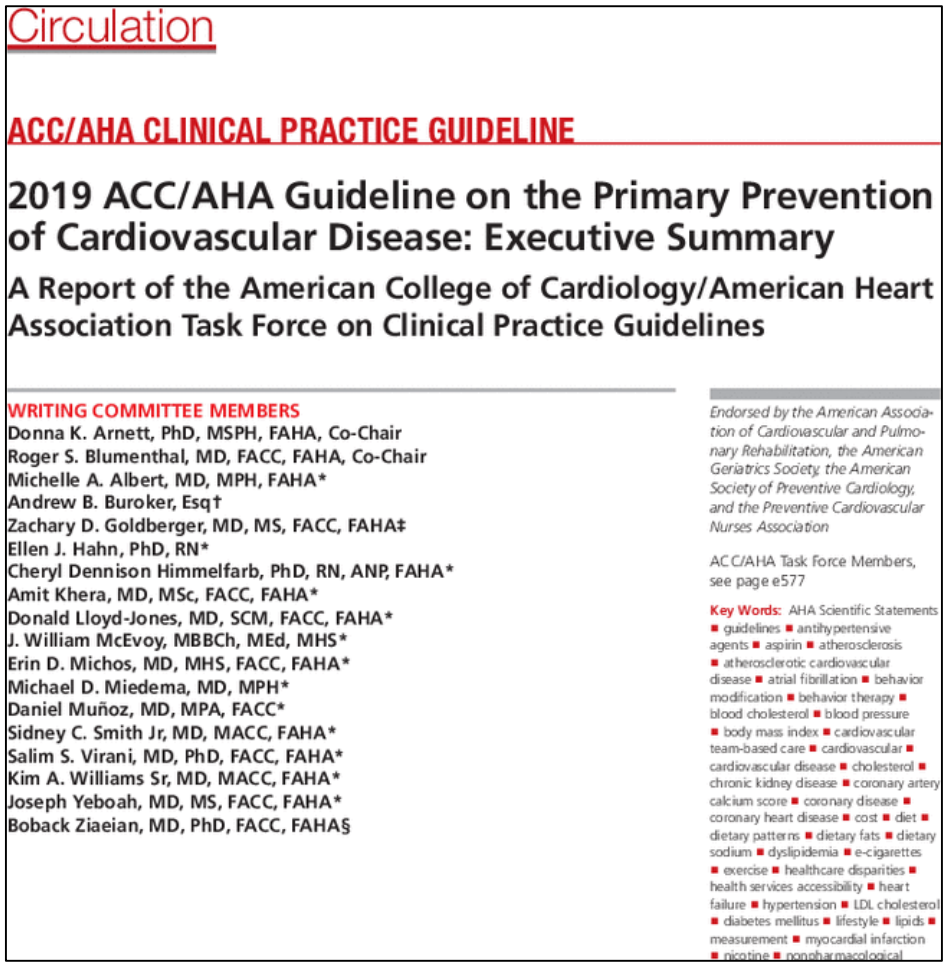
- **Cardiovascular**: No substantial reduction in risk of MI and stroke
- **Mortality**: Slightly higher – but not significant
- **Bleeding**: Significantly increased risk of serious bleeding
- **Physical disability**: No effect
- **Dementia**: No effect

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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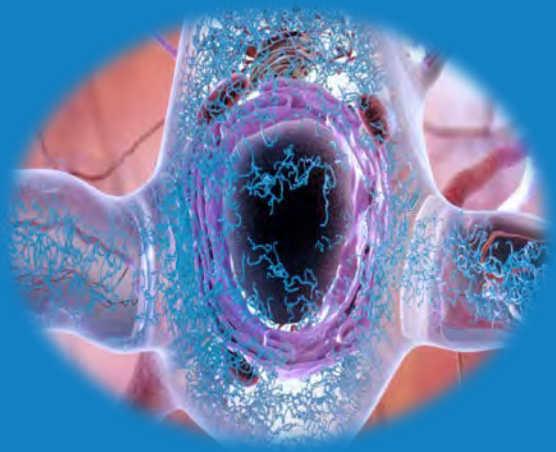

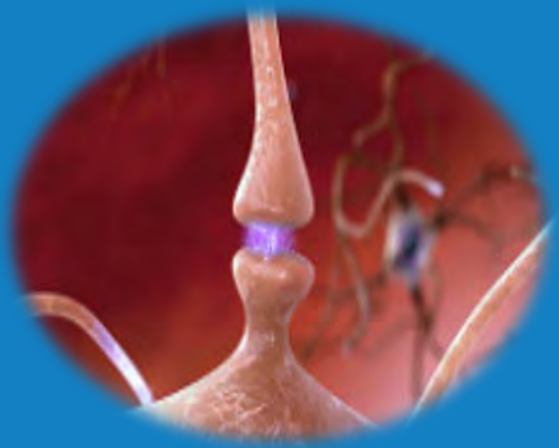

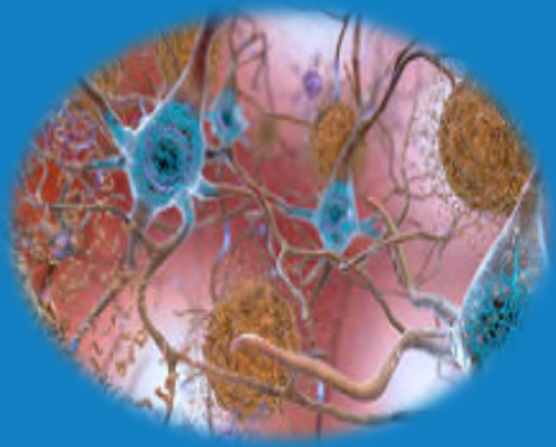

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