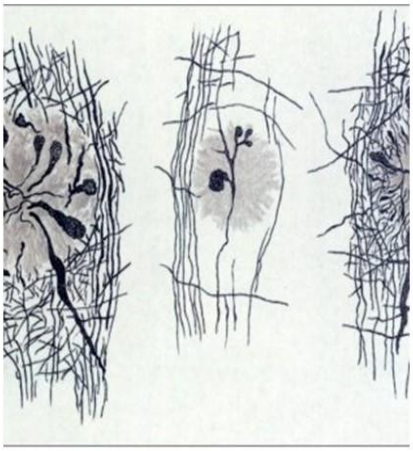
# Approaches to Alzheimer's and Related Dementias Therapeutics

Richard Hodes, Brad Hyman, and Allan Levey presenting for the
Research subcommittee

## 1906

Alois Alzheimer time.com

Alzheimer's drawings of tangles
In 1906



Alzheimer's drawings of plaques
In 1906

# Biochemistry

- Neurofibrillary tangles made primarily of tau protein
- Gene that makes tau (MAPT)
- Tau found in other neurodegenerative diseases like frontotemporal dementia and PSP
- MAPT mutations can lead to autosomal dominant frontotemporal dementia and PSP

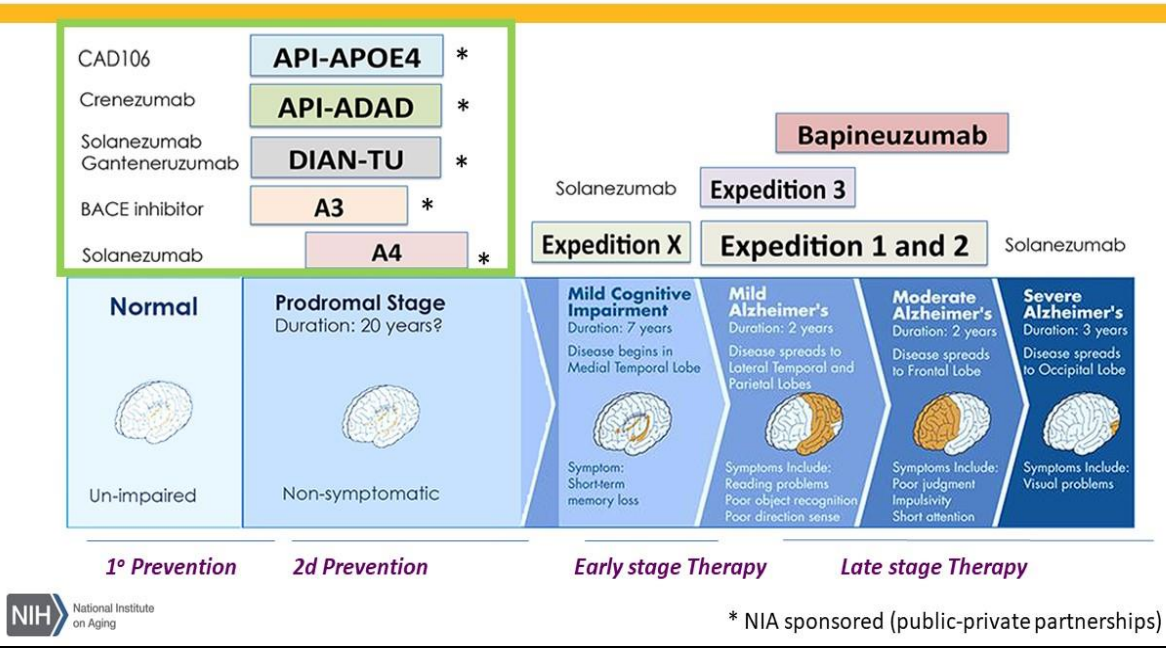
- Senile plaques made of amyloid
- Gene that makes amyloid precursor protein (APP) cloned
- Mutations in APP found to cause early onset autosomal dominant AD
- Down syndrome and other causes of genetic amplification of APP associated with early onset AD

# Therapeutics follow biochemical and genetic observations

- Early in phase III trials to study tau

- Multiple shots on goal for amyloid
- Recent highlights: inhibit the enzymes that make amyloid (e.g., BACE inhibitors)
- Clear the plaques away from the brain (e.g., immunotherapy)
- So far, no success in preventing further decline

# Alzheimer's Disease Immunotherapy Phase III Trials




NIH National Institute on Aging

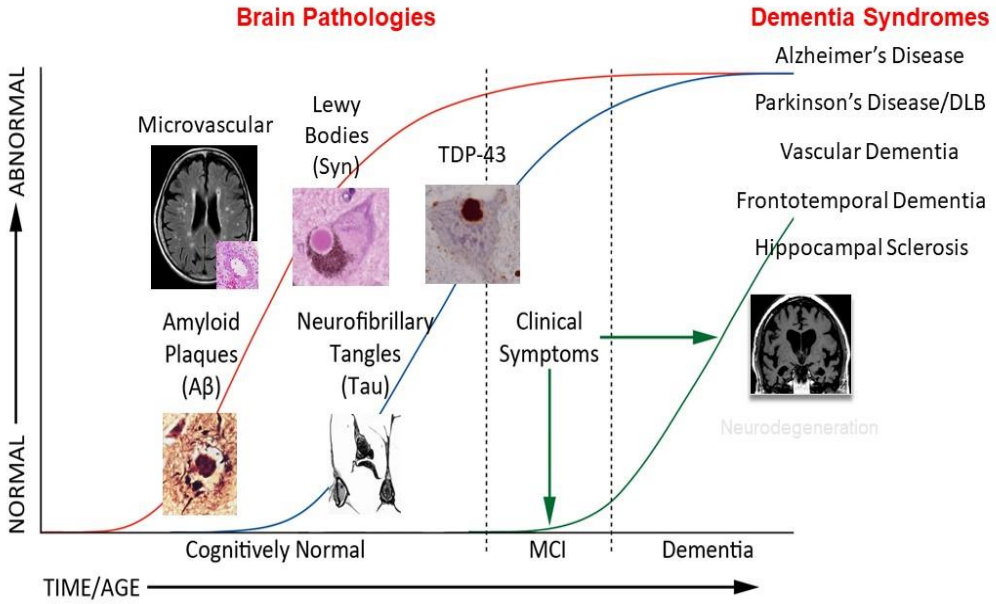
* NIA sponsored (public-private partnerships)

# Immunotherapy Clinical Trial for Individuals with Down Syndrome

**Active Immunotherapy for Cognitive Decline in Adults with Down Syndrome**

- **Rationale:** Trisomy 21 leads to increased levels of APP
- **Goal:** This study will investigate the safety, tolerability, as well as immunogenicity of an anti-amyloid vaccine in a Phase I clinical trial – in adults with DS aged 35-55.
- **Outcomes:** Effects on cognitive function and AD biomarkers will be secondary endpoints (Completion: 2021)

## The Progression of Alzheimer's Disease and Related Dementias




## Closer to a Blood Test for Alzheimer's Disease
## Amyloid-beta biomarkers & NfL

LETTER

doi:10.1038/nature25456

8 FEBRUARY 2018 | VOL 554 | NATURE | 249

**High performance plasma amyloid-β biomarkers for Alzheimer's disease**

Akinori Nakamura[1], Naoki Kaneko[2], Victor L. Villemagne[3,4], Takashi Kato[1,5], James Doecke[6], Vincent Doré[3,6], Chris Fowler[4], Qiao-Xin Li[4], Ralph Martins[7], Christopher Rowe[3,4], Taisuke Tomita[8], Katsumi Matsuzaki[9], Kenji Ishii[10], Kazunari Ishii[11], Yutaka Arahata[5], Shinichi Iwamoto[2], Kengo Ito[1,5], Koichi Tanaka[2], Colin L. Masters[4] & Katsuhiko Yanagisawa[1]

nature medicine

LETTERS

https://doi.org/10.1038/s41591-018-0304-3

**Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease**

Oliver Preische[1,2,21], Stephanie A. Schultz[1,21], Anja Apel[1,2,21], Jens Kuhle[4], Stephan A. Kaeser[1,2], Christian Barro[4], Susanne Gräber[1], Elke Kuder-Buletta[1], Christian LaFougere[1], Christoph Laske[1,2], Jonathan Vöglein[5,6], Johannes Levin[5,6], Colin L. Masters[7], Ralph Martins[8,9], Peter R. Schofield[10,11], Martin N. Rossor[12], Neill R. Graff-Radford[13], Stephen Salloway[14], Bernardino Ghetti[15], John M. Ringman[16], James M. Noble[17], Jasmeer Chhatwal[18], Alison M. Goate[19], Tammie L. S. Benzinger[3], John C. Morris[3], Randall J. Bateman[3], Guoqiao Wang[3], Anne M. Fagan[3], Eric M. McDade[3], Brian A. Gordon[3], Mathias Jucker[1,2*] and Dominantly Inherited Alzheimer Network[20]

ELSEVIER

Alzheimer's & Dementia 13 (2017) 841-849

Alzheimer's & Dementia

Theoretical Article

**Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis**

Vitaliy Ovod[a,b], Kara N. Ramsey[a,b], Kwasi G. Mawuenyega[a], Jim G. Bollinger[a], Terry Hicks[a], Theresa Schneider[a], Melissa Sullivan[a], Katrina Paumier[a], David M. Holtzman[a,b,c], John C. Morris[a,c], Tammie Benzinger[d,e], Anne M. Fagan[a,b,c], Bruce W. Patterson[e], Randall J. Bateman[a,b,c,*]

[a]Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA
[b]Department of Neurology, Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO, USA
[c]Department of Neurology, Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA
[d]Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA
[e]Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA

Research

JAMA Neurology | Original Investigation

**Performance of Fully Automated Plasma Assays as Screening Tests for Alzheimer Disease-Related β-Amyloid Status**

Sebastian Palmqvist, MD, PhD; Shorena Janelidze, PhD; Erik Stomrud, MD, PhD; Henrik Zetterberg, MD, PhD; Johann Karl, PhD; Katharina Zink; Tobias Bittner, PhD; Niklas Mattsson, MD, PhD; Udo Eichenlaub, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD

# NAPA playbook

- Discover new genes that contribute to AD and dementia
- Develop new information about the brain changes that occur before and during the disease process

Smithsonianmag.com

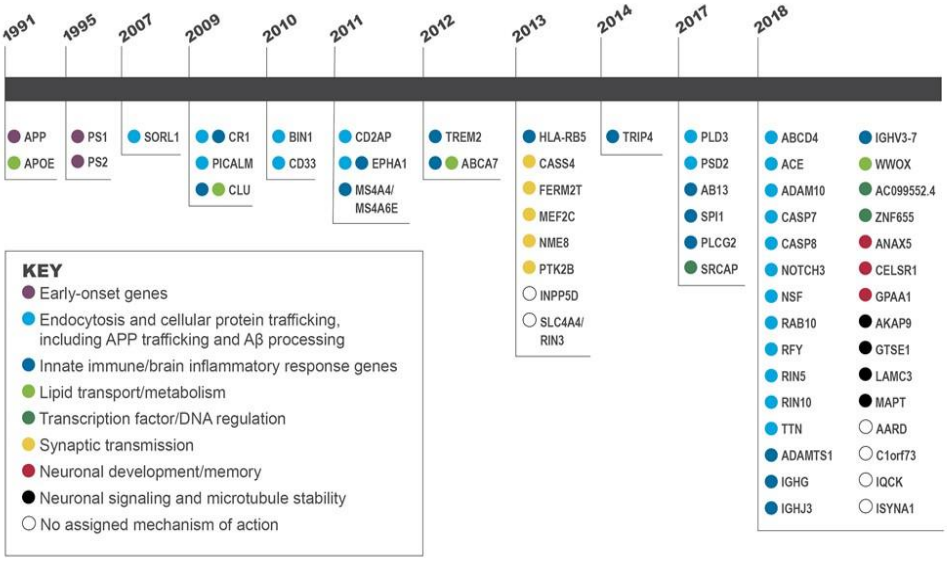
Clipart.com

- Tackle the disease at early stages and late stages, perhaps using different strategies at different stages
- Develop new targets and new approaches
- Find better ways of understanding person to person differences

## Genetic Regions of Interest in Alzheimer's Disease

By year of discovery

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



# 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**

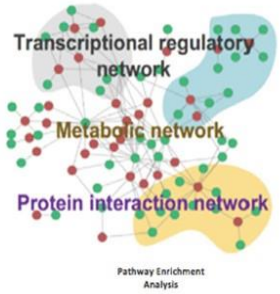
**6 Academic Teams – NIA U01/R01grants –**

www.synapse.org.ampad

Data
Network models
Code

**AMP-AD Knowledge Portal**

Sage BIONETWORKS Synapse




- 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 · gsk GlaxoSmithKline · Lilly · alzheimer's association · Alzheimer's Drug Discovery Foundation · US4against Alzheimer's · FNIH Foundation for the National Institutes of Health

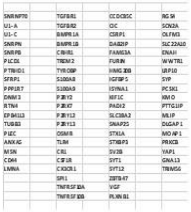
NIH National Institute on Aging

# ACCELERATING MEDICINES PARTNERSHIP (AMP)

**Progress over 4 years:**

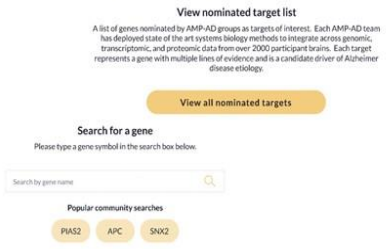
- Centralized data resource established- AMP-AD portal
- All data sharing deliverables met
- A variety of experimental validation models developed
- Novel biomarker discovery initiated
- Over 100 candidate targets nominated; currently undergoing data-driven prioritization for further preclinical validation

**Candidate Targets**



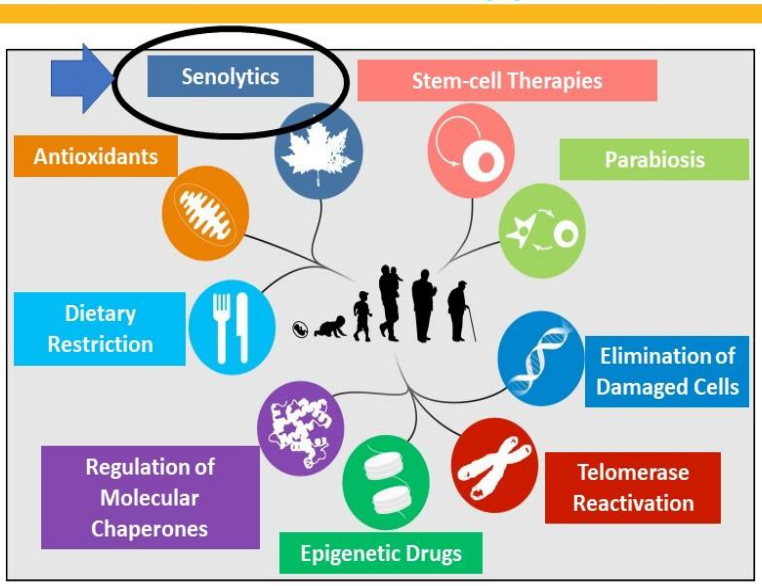
Agora

**agora.ampadportal.org**



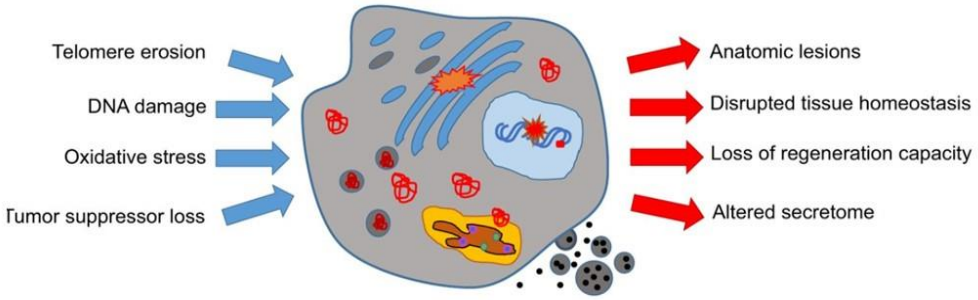

NIH National Institute on Aging

# Geroscience: Interventions and Approaches




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

# What is cell senescence?



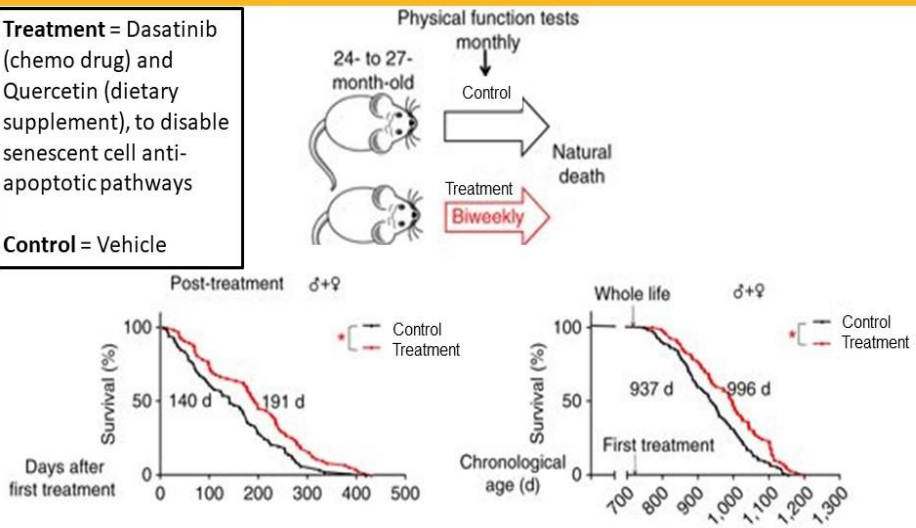

**Senescent cells secrete a large number of biologically active factors which affect the function of neighboring, non-senescent cells**

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

# Treatment with Senolytics Extends Lifespan in Older WT Mice

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

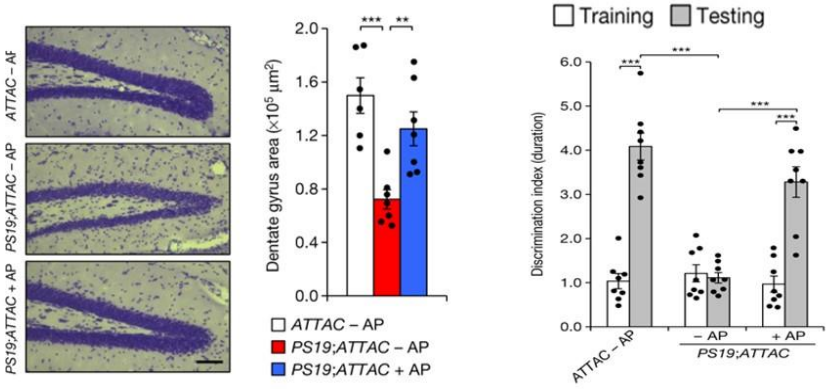
**Control** = Vehicle




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



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

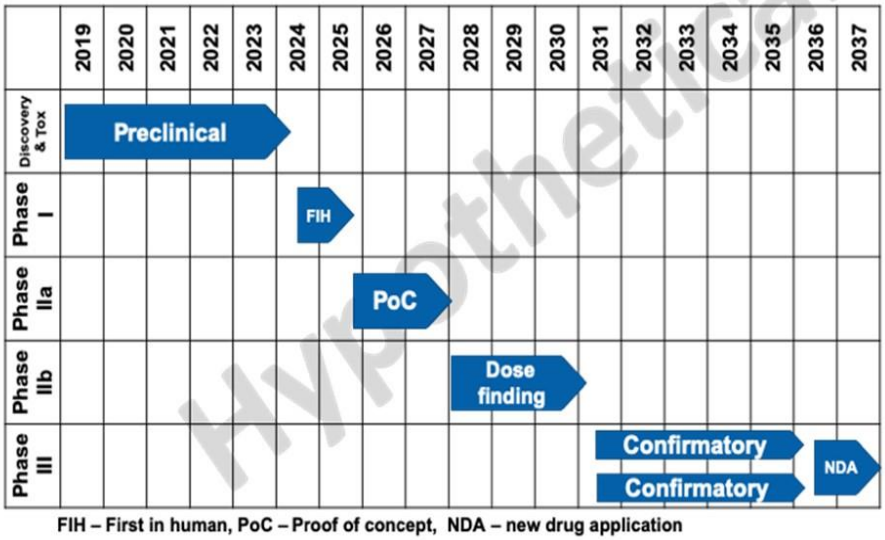



- **Senescent cells drive neurodegenerative disease**
- **Clearance of senescent cells through genetic manipulation or drug treatment decreases tau pathology and cognitive decline**

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

## Traditional Clinical Paradigm

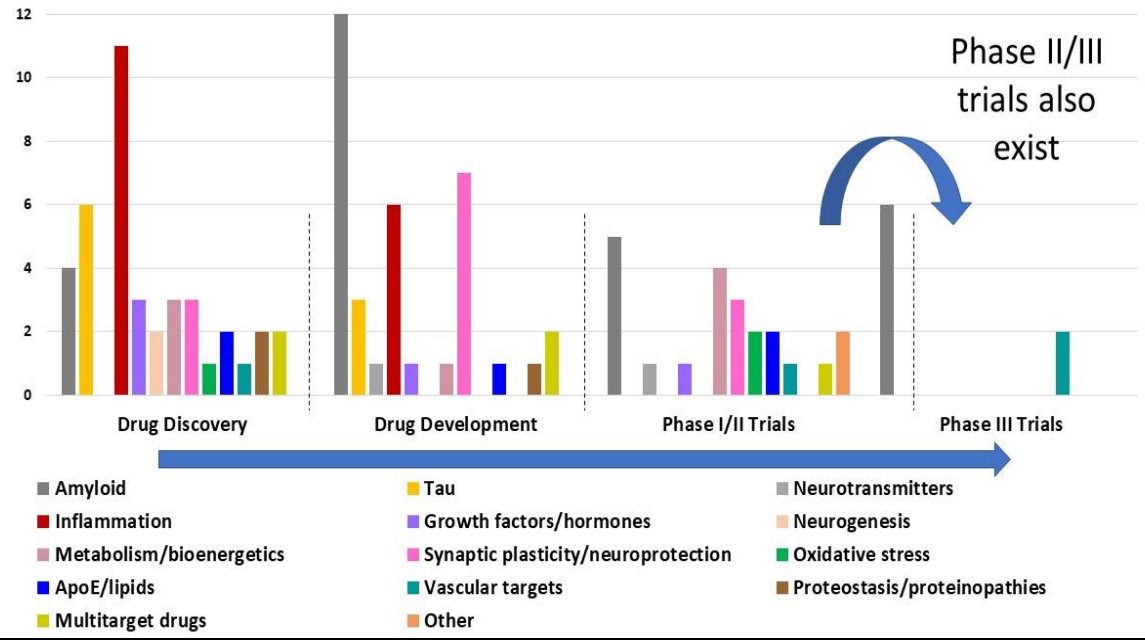
*Novel target (12 month endpoint) : 18++ years*



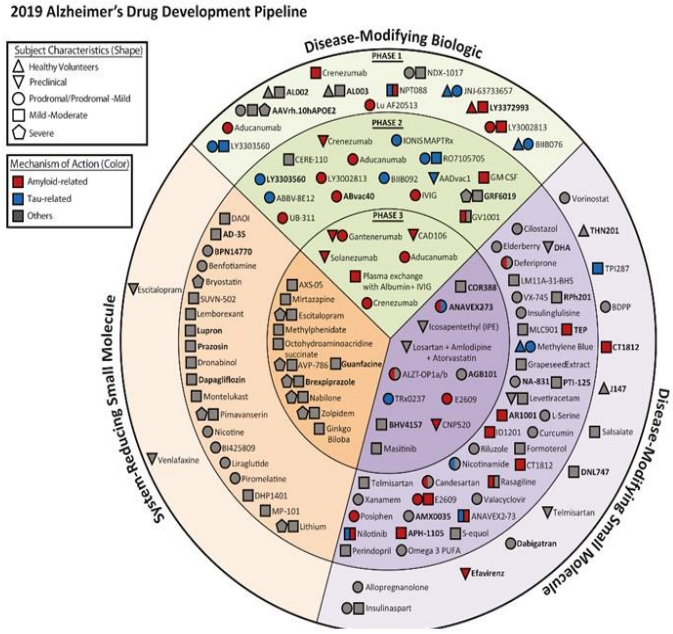

FIH – First in human, PoC – Proof of concept, NDA – new drug application

Courtesy of C Grosskreutz

## NIA Pipeline of Discovery

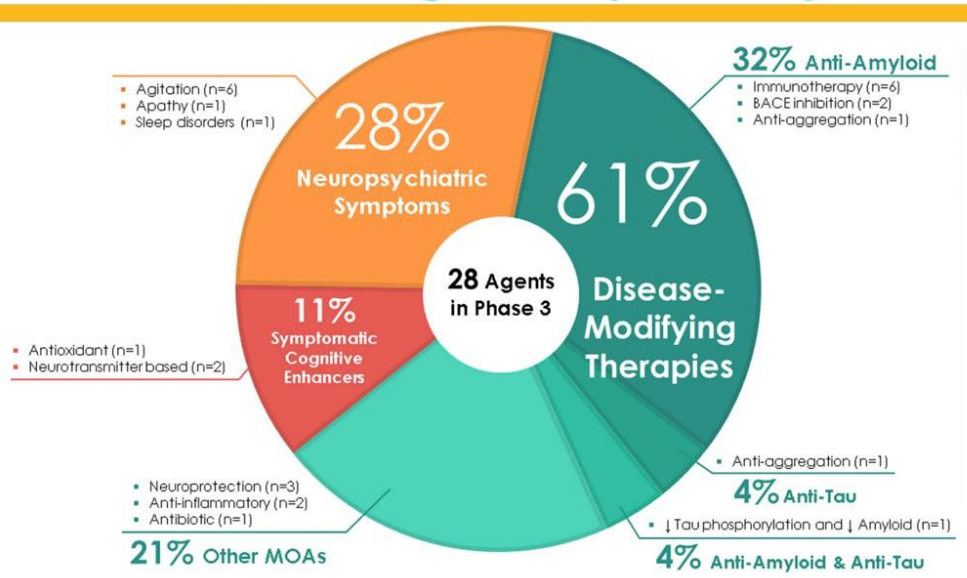


# Alzheimer's Disease Drug Development Pipeline - 2019



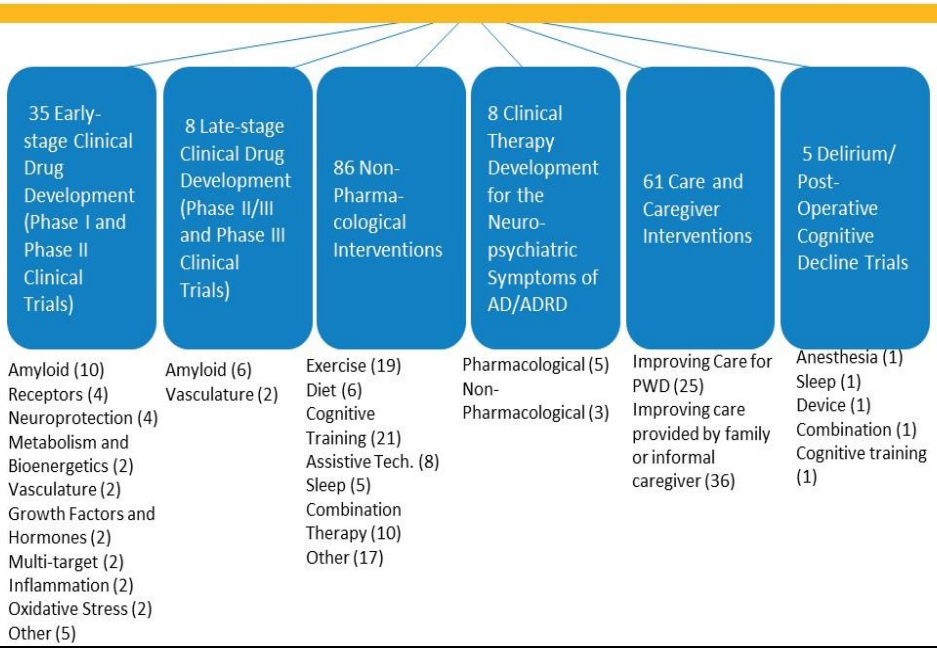

Cummings J., et al. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, Volume 5, 2019:272-293*

# Alzheimer's Disease Drug Development Pipeline - 2019




Cummings J., et al. *Alzheimer's & Dementia: Translational Research & Clinical Interventions, Volume 5, 2019:272-293*

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




21

# Physical Activity Clinical Trial for AD

**Exercise in Adults With Mild Memory Problems (EXERT)**

- **Goal:** Test effects of physical exercise on cognition, functional status, brain atrophy and blood flow, and cerebrospinal fluid biomarkers of Alzheimer's disease, in adults ages 65 to 89 year with MCI (Completion: 2022)

# Diet-Based Clinical Trial for AD

**MIND Diet Intervention to Prevent Alzheimer Disease**

- **Goal:** Test the effects of a 3-year intervention of the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) on cognitive decline and brain neurodegeneration among individuals 65+ years without cognitive impairment, who are overweight and have suboptimal diets (Completion: 2022)

# Cognitive Training Clinical Trial for AD

**Processing Speed Training to Preserve Driving and Functional Competencies in MCI**

- **Goal:** Test the capacity of an enriched version of processing speed training (PST) to preserve functional abilities in a clinical MCI population with quantified genetic and neuroimaging AD and comorbid cardiovascular disease biomarkers (Completion: 2020)

# World Wide FINGERS & POINTER

The FINGER trial is the first large, long-term RCT indicating that a multi-domain intervention with exercise, diet, cognitive and social stimulation and management of vascular/metabolic risk factors may benefit cognition in subjects at risk of dementia.

WORLD WIDE FINGERS
alzheimer's association

**U.S. POINTER:**
The Alzheimer's Association has initiated a study designed to replicate the results of the Finnish trial in the U.S. (to test the generalizability of the FINGER findings in American older adults).

U.S. POINTER is a two-year clinical trial to evaluate whether lifestyle interventions that simultaneously target many risk factors protect cognitive function in older adults who are at increased risk for cognitive decline.

# 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.

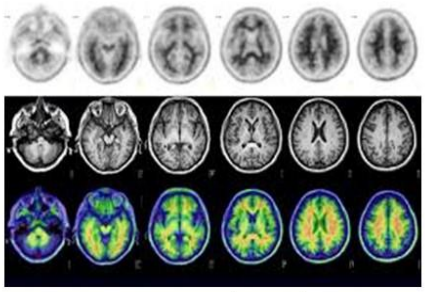
# SPRINT-MIND: Secondary Cognitive Outcome

- 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
- Participants assigned to the intensive treatment had a non-statistically significant reduction in all-cause probable dementia.

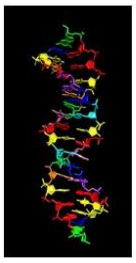
The SPRINT MIND Investigators for the SPRINT Research Group (2019). *JAMA, 321*(6):553–561.

# Important considerations in the next years

- Continued improvements in neuroimaging for AD related molecular changes
- Further understanding from genetics and other –omics research
- New drug trials and personalized medicine approaches; using our understanding of the heterogeneity of disease to enrich trials with more *homogeneous* groups of participants
  - Those with genetic risk factors, e.g., individuals with Down syndrome
  - Those with related dementias
  - Biomarker advances will inform these efforts
- Exploring diversity across all facets of disease research – including recruitment challenges, genetic variability, other factors influencing risk, differential treatment effects, and more



Ideasstudy.com



Nih.gov

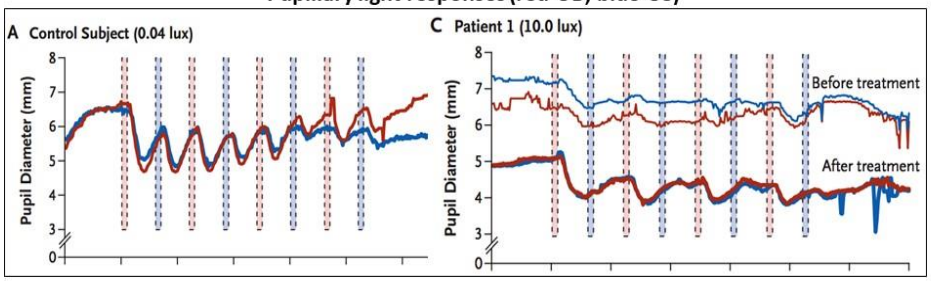
# Gene Therapy: a reality in treating devastating human diseases

N Engl J Med
2008;358:2240-8

## Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis

Albert M. Maguire, M.D., Francesca Simonelli, M.D., Eric A. Pierce, M.D., Ph.D., Edward N. Pugh, Jr., Ph.D., Federico Mingozzi, Ph.D., Jeannette Bennicelli, Ph.D., Sandro Banfi, M.D., Kathleen A. Marshall, C.O.T., Francesco Testa, M.D., Enrico M. Surace, D.V.M., Settimio Rossi, M.D., Arkady Lyubarsky, Ph.D., Valder R. Arruda, M.D., Barbara Konkle, M.D., Edwin Stone, M.D., Ph.D., Junwei Sun, M.S., Jonathan Jacobs, Ph.D., Lou Dell'Osso, Ph.D., Richard Hertle, M.D., Jian-xing Ma, M.D., Ph.D., T. Michael Redmond, Ph.D., Xiaosong Zhu, M.D., Bernd Hauck, Ph.D., Olga Zelenaia, Ph.D., Kenneth S. Shindler, M.D., Ph.D., Maureen G. Maguire, Ph.D., J. Fraser Wright, Ph.D., Nicholas J. Volpe, M.D., Jennifer Wellman McDonnell, M.S., Alberto Auricchio, M.D., Katherine A. High, M.D., and Jean Bennett, M.D., Ph.D.

**Pupillary light responses (red-OD, blue-OS)**




# Gene therapy success in infantile spinal muscular atrophy

WWW.CURESMA.ORG > NEWS > AVEXIS RECEIVES FDA APPROVAL OF ZOLGENSMA, A GENE THERAPY, FOR SPINAL MI
YEARS OF AGE

## AveXis Receives FDA Approval of Zolgensma, a Gene Therapy, for Spinal Muscular Atrophy for Patients Under Two Years of Age

BY CURE SMA | PUBLISHED ON MAY 24, 2019

Like Share Tweet

ZOLGENSMA HAS BEEN APPROVED BY THE FDA!

## New therapeutic approaches already leading to a sense of optimism despite recent disappointments

- Already here:
  - Earlier diagnosis and interventions
- On the way:
  - Gene therapy
  - Brain neuromodulation
  - Nonpharmacological interventions
  - New targets from genetic studies
  - New targets from AMP AD
  - New approaches to improve clinical trial design and hasten results
  - Numerous shots on goal…..