Alzheimer's Disease Centers Program

Fall Meeting

Atlanta, Georgia

October 20, 2018

” Division of Neuroscience Update"

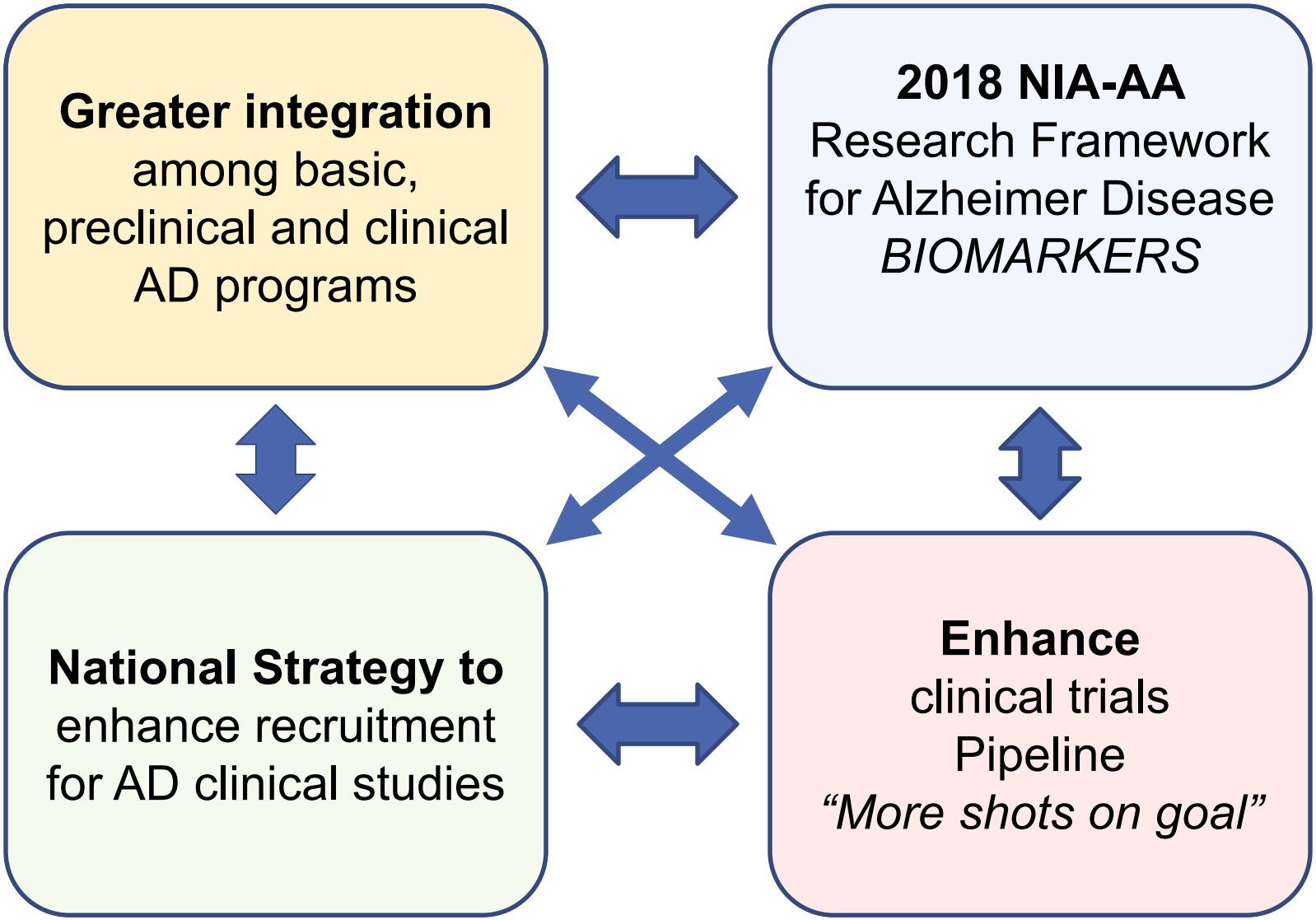
Eliezer Masliah, M.D.

Division of Neuroscience,

National Institute on Aging, NIH

NIH National Institute on Aging

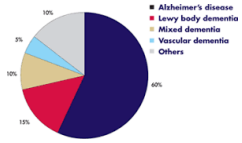
Some NIA-AD Research Priorities



NIH National Institute on Aging

Alzheimer's Disease and Related Dementias FOAs

http://www.nia.nih.gov/AD-FOAs

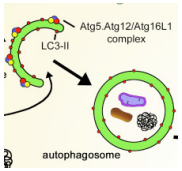


MOLECULAR BASIS FOR AD HETEROGENEITY
and mixed pathology

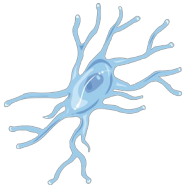
DYNAMIC INTERACTION BETWEEN PERIPHERAL SYSTEMS AND BRAIN AGING/AD

UNDERSTANDING NEURODEGENERATION IN THE CONTEXT OF AGING

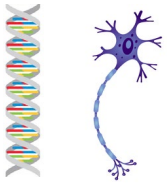
COMLEX BIOLOGY OF RESILIENCE



PROTEOSTASIS



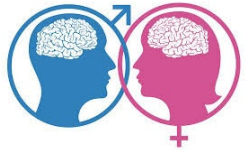
INFLAMMATION



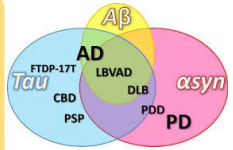
FUNCTIONAL VALIDATION OF GENETIC RISK FACTORS FOR AD

UNDERSTANDING THE COMPLEX BIOLOGY OF AD/ADRD

SEX DIFFERENCES AND AD RISK



COMMON MECHANISMS OF NEURODEGENERATION



MECHANISMS OF NPS IN AD

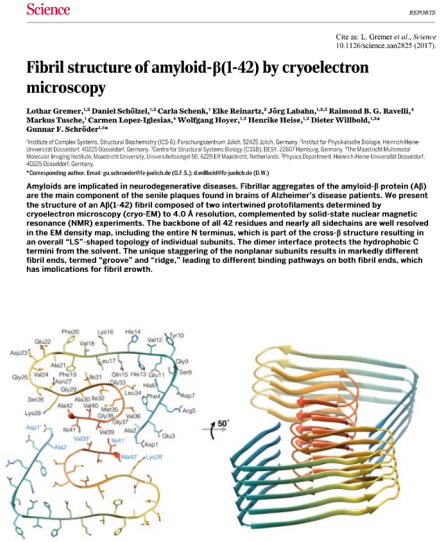
Initiatives in development:

- Microbiome in Aging;
- AD/Sleep and Circadian Rhythm;
- Selective neuronal vulnerability
- Amyloid fibril strains; glycobiology, endosome pathways,

NIH National Institute on Aging

New cryo-EM structure of amyloid fibrils might help develop new drugs and PET radioligands

RFA-AG-18-025 **Consequences of amyloid protein polymorphisms in Alzheimer's disease (R01) NIA lead; Austin Yang**


Science

REPORTS

Cite as: L. Gremer *et al.*, *Science* 10.1126/science.aao2825 (2017).

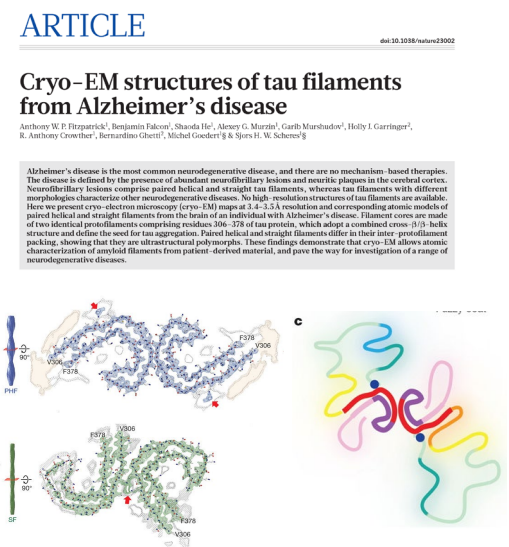
Fibril structure of amyloid-β(1-42) by cryoelectron microscopy

Lothar Gremer,[1,2] Daniel Schölzel,[1,2] Carla Schenk,[1] Elke Reinartz,[3] Jörg Labahn,[1,2,3] Raimond B. G. Ravelli,[4] Markus Tusche,[1] Carmen Lopez-Iglesias,[4] Wolfgang Hoyer,[1,2] Henrike Heise,[1,2] Dieter Willbold,[1,2]* Gunnar F. Schröder[1,2]*

[1]Institute of Complex Systems, Structural Biochemistry (ICS-6), Forschungszentrum Jülich, 52425 Jülich, Germany. [2]Institut für Physikalische Biologie, Heinrich-Heine-Universität Düsseldorf, 40225 Düsseldorf, Germany. [3]Centre for Structural Systems Biology (CSSB), DESY, 22607 Hamburg, Germany. [4]The Maastricht Multimodal Molecular Imaging Institute, Maastricht University, Universiteitssingel 50, 6229 ER Maastricht, Netherlands. [5]Physics Department, Heinrich-Heine-Universität Düsseldorf, 40225 Düsseldorf, Germany.

*Corresponding author. Email: ga.schroeder@fz-juelich.de (G.F.S.); d.willbold@fz-juelich.de (D.W.)

Amyloids are implicated in neurodegenerative diseases. Fibrillar aggregates of the amyloid-β protein (Aβ) are the main component of the senile plaques found in brains of Alzheimer's disease patients. We present the structure of an Aβ(1-42) fibril composed of two intertwined protofilaments determined by cryoelectron microscopy (cryo-EM) to 4.0 Å resolution, complemented by solid-state nuclear magnetic resonance (NMR) experiments. The backbone of all 42 residues and nearly all sidechains are well resolved in the EM density map, including the entire N terminus, which is part of the cross-β structure resulting in an overall "LS"-shaped topology of individual subunits. The dimer interface protects the hydrophobic C termini from the solvent. The unique staggering of the nonplanar subunits results in markedly different fibril ends, termed "groove" and "ridge," leading to different binding pathways on both fibril ends, which has imolications for fibril erowth.

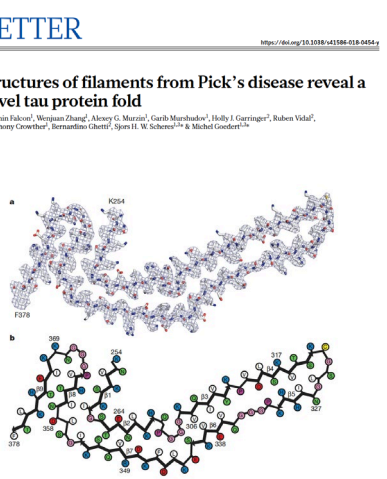

ARTICLE

doi:10.1038/nature23002

Cryo–EM structures of tau filaments from Alzheimer's disease

Anthony W. P. Fitzpatrick[1], Benjamin Falcon[1], Shaoda He[1], Alexey G. Murzin[1], Garib Murshudov[1], Holly J. Garringer[2], R. Anthony Crowther[1], Bernardino Ghetti[2], Michel Goedert[1]§ & Sjors H. W. Scheres[1]§

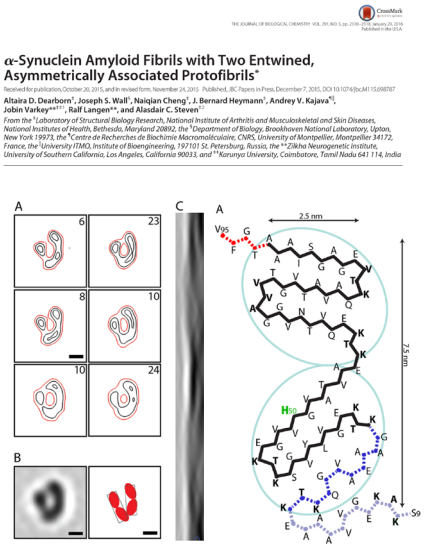
Alzheimer's disease is the most common neurodegenerative disease, and there are no mechanism-based therapies. The disease is defined by the presence of abundant neurofibrillary lesions and neuritic plaques in the cerebral cortex. Neurofibrillary lesions comprise paired helical and straight tau filaments, whereas tau filaments with different morphologies characterize other neurodegenerative diseases. No high-resolution structures of tau filaments are available. Here we present cryo–electron microscopy (cryo-EM) maps at 3.4–3.5 Å resolution and corresponding atomic models of paired helical and straight filaments from the brain of an individual with Alzheimer's disease. Filament cores are made of two identical protofilaments comprising residues 306–378 of tau protein, which adopt a combined cross-β/β-helix structure and define the seed for tau aggregation. Paired helical and straight filaments differ in their inter-protofilament packing, showing that they are ultrastructural polymorphs. These findings demonstrate that cryo-EM allows atomic characterization of amyloid filaments from patient-derived material, and pave the way for investigation of a range of neurodegenerative diseases.


LETTER

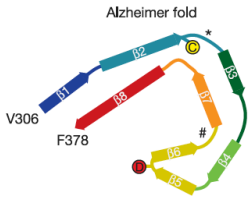
https://doi.org/10.1038/s41586-018-0454-y

Structures of filaments from Pick's disease reveal a novel tau protein fold

Benjamin Falcon[1], Wenjuan Zhang[1], Alexey G. Murzin[1], Garib Murshudov[1], Holly J. Garringer[2], Ruben Vidal[2], R. Anthony Crowther[1], Bernardino Ghetti[2], Sjors H. W. Scheres[1,3]* & Michel Goedert[1,3]*



Aβ **4RTau (AD)** **3RTau (Pick's)** **α-synuclein**



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Seeding and spreading of amyloids involved in AD/ADRD

Tau

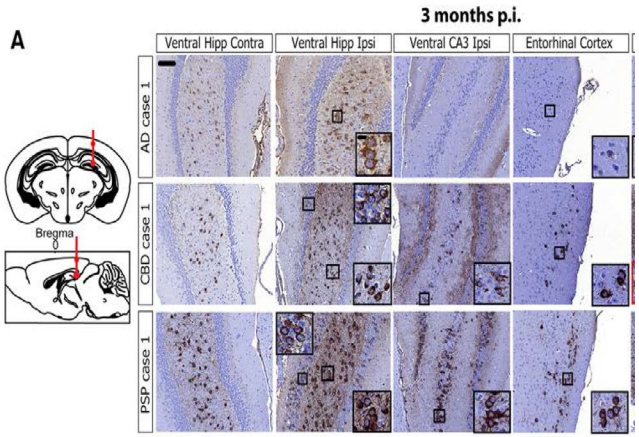
Neurobiology of Disease

The Journal of Neuroscience, Month XX, 2017 • 37(XX):XXXX–XXXX • 1

Pathological Tau Strains from Human Brains Recapitulate the Diversity of Tauopathies in Nontransgenic Mouse Brain

Sneha Narasimhan, Jing L. Guo, Lakshmi Changolkar, Anna Stieber, Jennifer D. McBride, Luisa V. Silva, Zhuohao He, Bin Zhang, Ronald J. Gathagan, John Q. Trojanowski, and Virginia M.Y. Lee

Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104

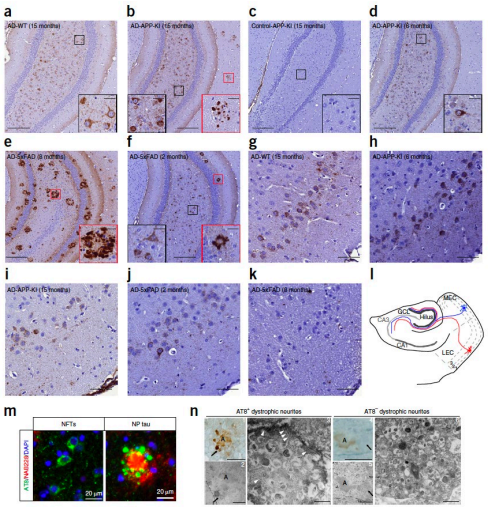


Aβ + Tau (AD)

nature medicine

Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation

Zhuohao He[1], Jing L Guo[1], Jennifer D McBride[1], Sneha Narasimhan[1], Hyesung Kim[1], Lakshmi Changolkar[1], Bin Zhang[1], Ronald J Gathagan[1], Cuiyong Yue[2], Christopher Dengler[2], Anna Stieber[1], Magdalena Nitla[1], Douglas A Coulter[2,3], Ted Abel[4], Kurt R Brunden[1], John Q Trojanowski[1] & Virginia M-Y Lee[1]



TDP-43

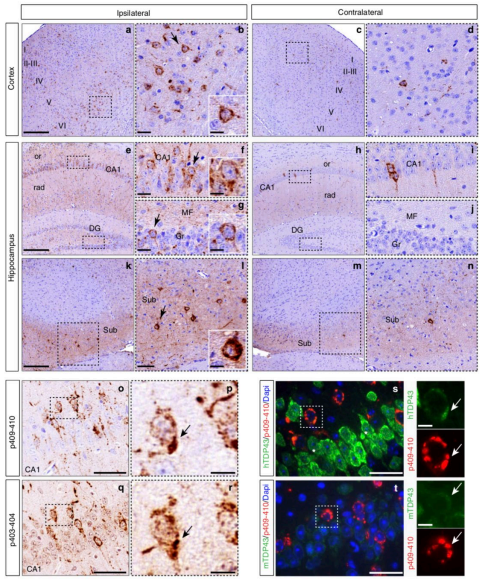
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06548-9 OPEN

Patient-derived frontotemporal lobar degeneration brain extracts induce formation and spreading of TDP-43 pathology in vivo

Silvia Porta[1], Yan Xu[1], Clark R. Restrepo[1], Linda K. Kwong[1], Bin Zhang[1], Hannah J. Brown[1], Edward B. Lee[2], John Q. Trojanowski[1] & Virginia M.-Y. Lee[1]



Understanding AD in the context of Aging

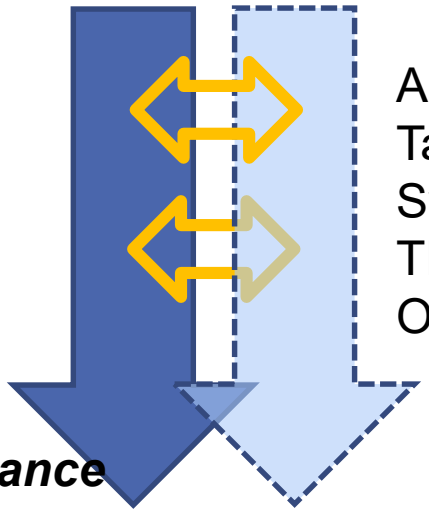
Trauma, chemicals radiation, radicals, stress, metabolic, **viruses**

GENETICS and ***Environment***

Aging

Proteonopathy

Proteostasis
Mitochondria
Inflammation
Endosomes
Growth Factors
Epigenetics
DNA damage
Senescent cells
Immune surveillance

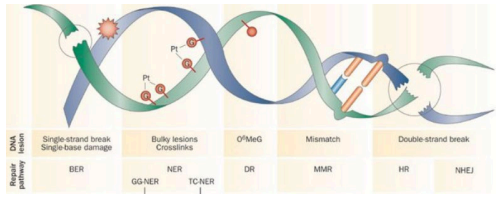


Abeta
Tau
Synuclein
TDP43
Others

Synapse damage

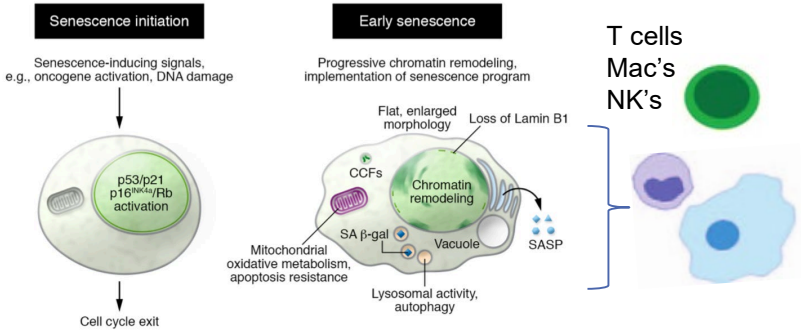
Neurodegeneration

DNA damage



Transposable elements

senescence/immune surveillance



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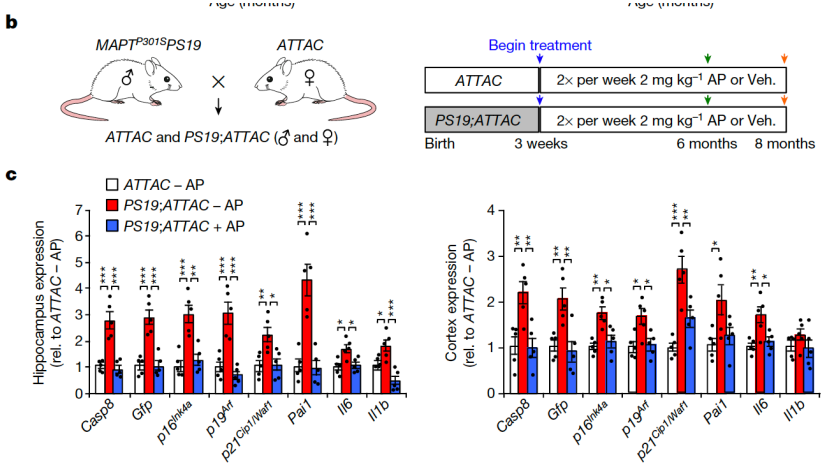
Eliminating senescent cells in Tau models

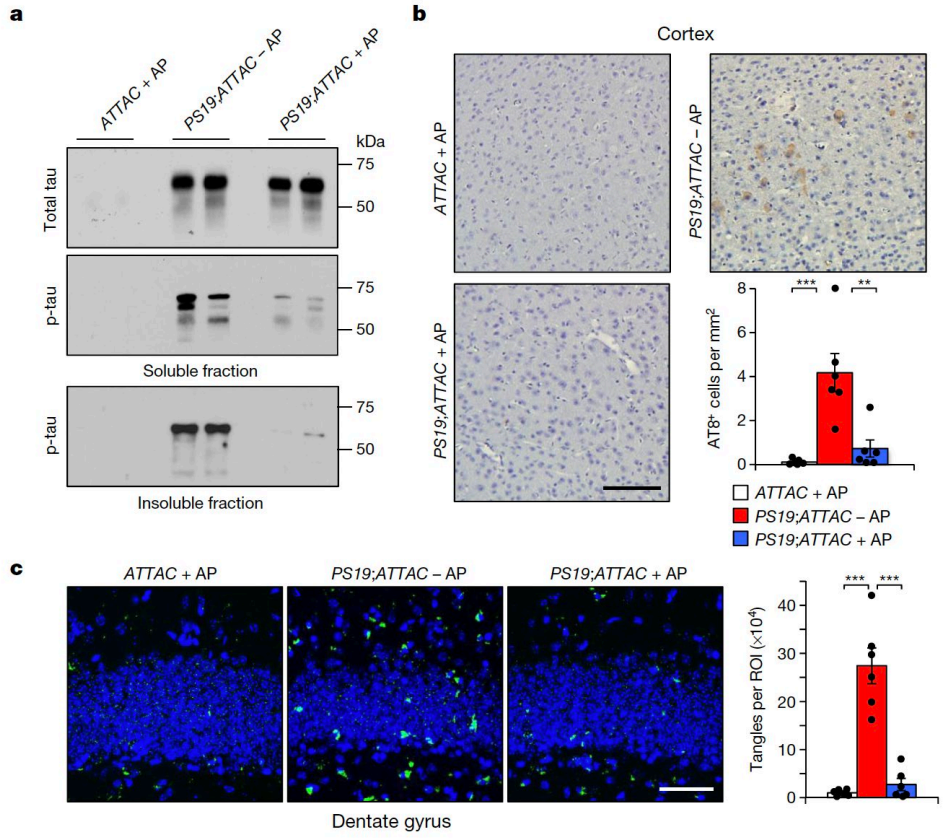
LETTER

https://doi.org/10.1038/s41586-018-0543-y

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

Tyler J. Bussian[1,3], Asef Aziz[2,3], Charlton F. Meyer[2], Barbara L. Swenson[2], Jan M. van Deursen[1,2] & Darren J. Baker[1,2]*





INK-ATTC (apoptosis through targeted activation of caspase), a transgene expresses the p16 promoter-driving ATTC fusion protein (caspase 8 fused to the FK506-binding protein).

Upon the administration of the inducer AP20187, the fusion protein dimerizes, activating caspase 8, and p16-positive senescent cells are specifically killed by apoptosis.

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Understanding AD in the context of resilience

J Neuropathol Exp Neurol
Vol. 76, No. 6, June 2017, pp. 458–466
doi: 10.1093/jnen/nlx030

ORIGINAL ARTICLE

Resistance to Alzheimer Disease Neuropathologic Changes and Apparent Cognitive Resilience in the Nun and Honolulu-Asia Aging Studies

Caitlin S. Latimer, MD, PhD, C. Dirk Keene, MD, PhD, Margaret E. Flanagan, MD, Laura S. Hemmy, PhD, Kelvin O. Lim, MD, Lon R. White, MD, MPH, Kathleen S. Montine, PhD, and Thomas J. Montine, MD, PhD

Published Ahead of Print on March 28, 2018 as 10.1212/WNL.0000000000005303

VIEWS & REVIEWS

Resistance vs resilience to Alzheimer disease

Clarifying terminology for preclinical studies

Eider M. Arenaza-Urquijo, PhD, and Prashanthi Vemuri, PhD

Neurology® 2018;0:1-9. doi:10.1212/WNL.0000000000005303

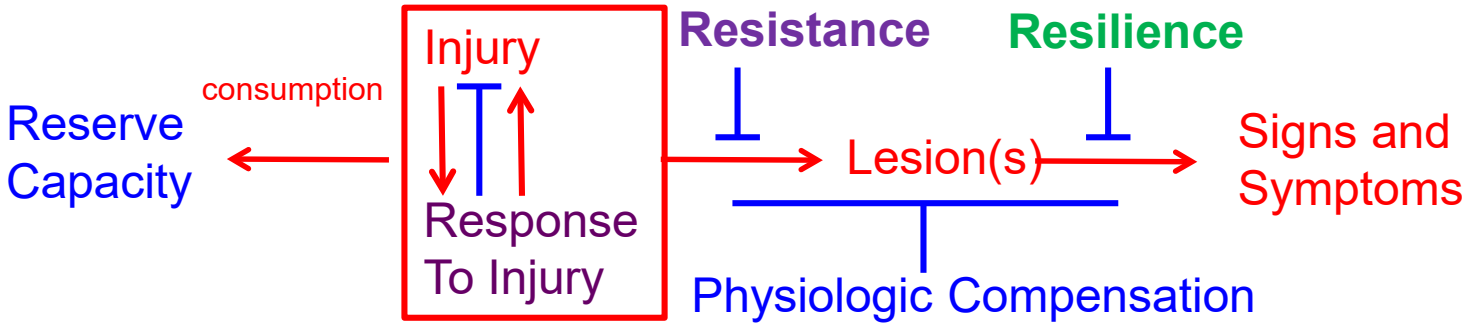
Correspondence
Dr. Arenaza-Urquijo
eiderarenaza@gmail.com

Acta Neuropathologica (2018) 136:377–388
https://doi.org/10.1007/s00401-018-1872-5

ORIGINAL PAPER

Non-Alzheimer's contributions to dementia and cognitive resilience in The 90+ Study

John L. Robinson[1] · Maria M. Corrada[2] · Gabor G. Kovacs[1,3] · Myrna Dominique[1] · Carrie Caswell[4] · Sharon X. Xie[4] · Virginia M.-Y. Lee[1] · Claudia H. Kawas[5] · John Q. Trojanowski[1]



Montine and Keene

Resistance (High cog perform; no/low AD path)
Resilient (High cog perform, high AD path)

Conclude that: Sex, ethnicity, and lifestyle factors may significantly influence resistance to developing brain injury with age.

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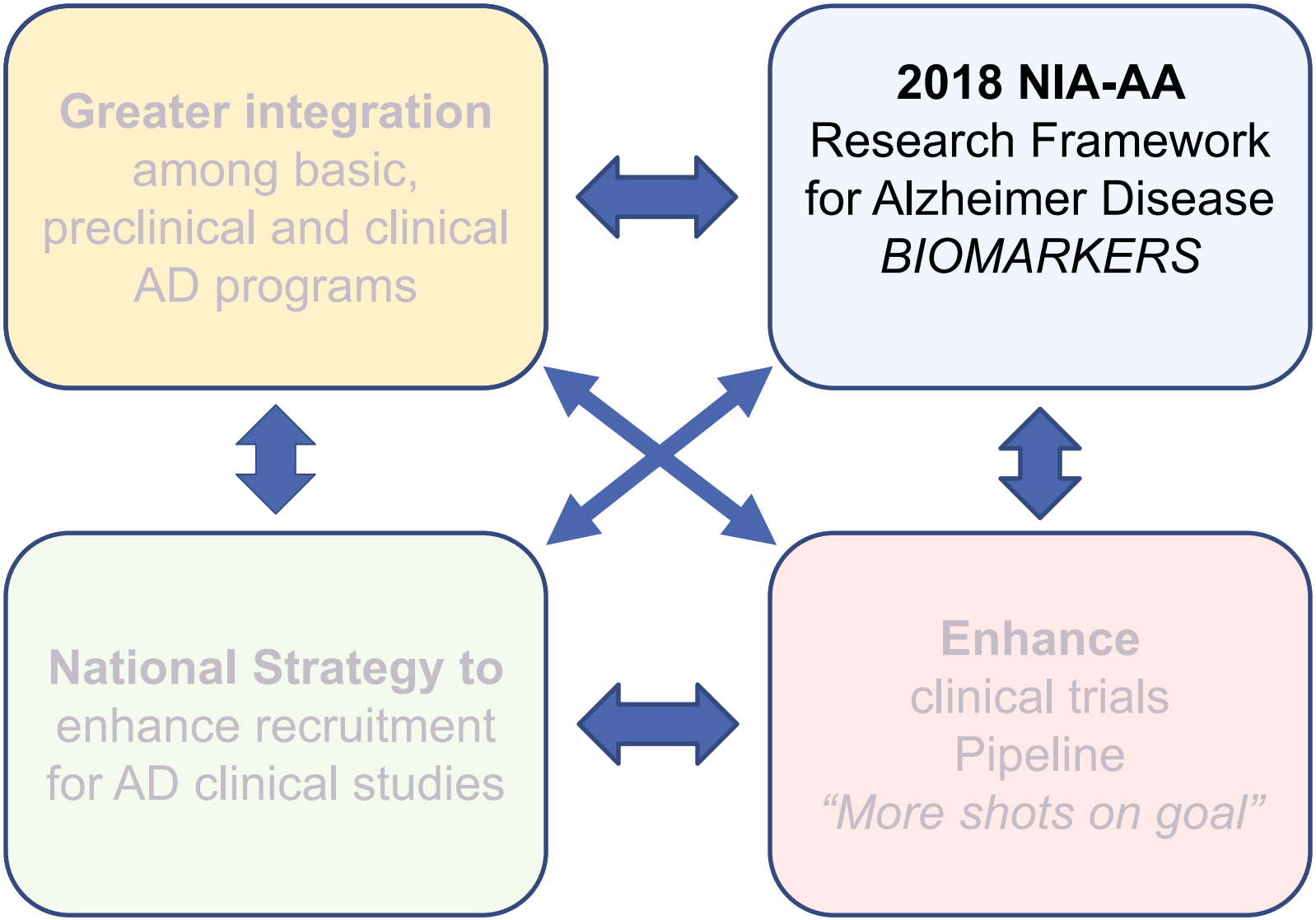
Some NIA-AD Research Priorities



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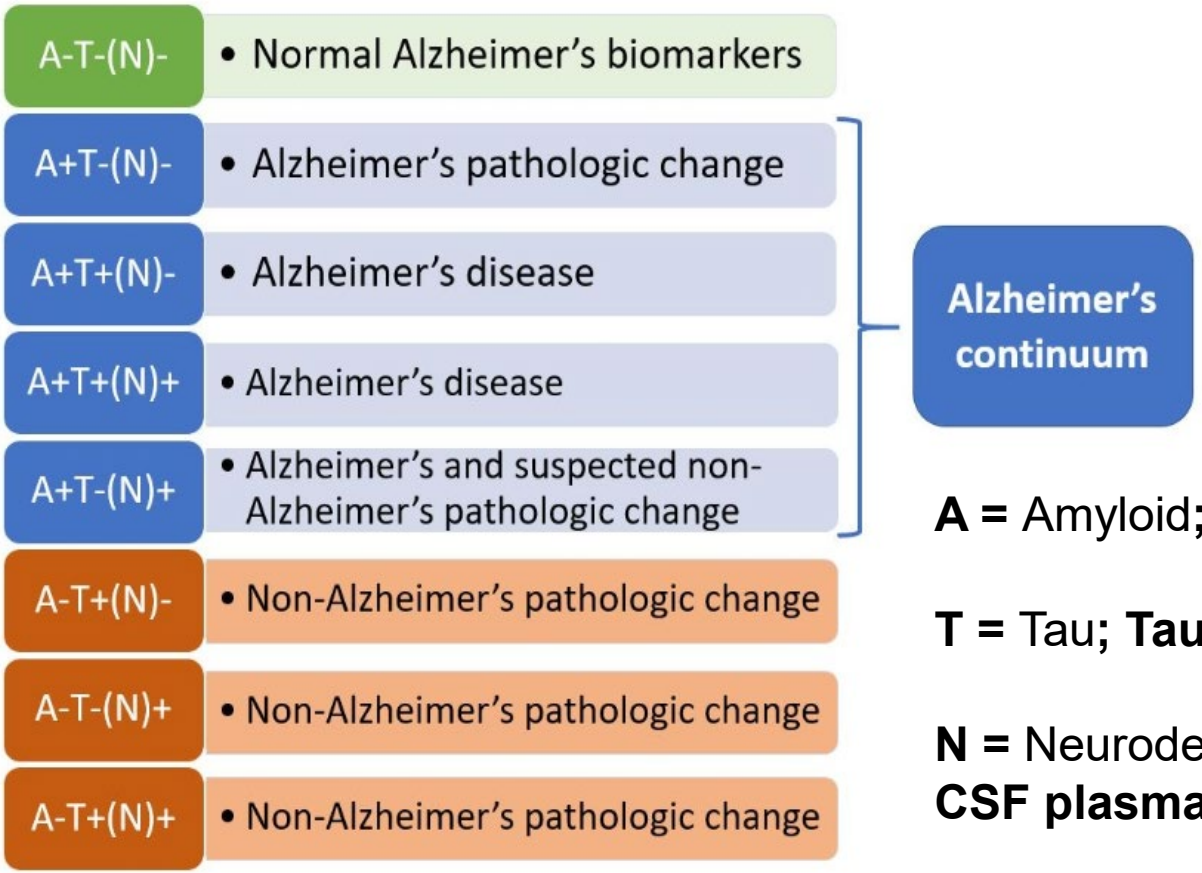
2018 NIA-AA Research Framework



A = Amyloid**; Abeta PET, CSF, plasma**

T = Tau**; Tau PET, pTau CSF**

N = Neurodegeneration; **FDG-PET, MRI, CSF plasma Neurofilament**

X = synapses, vascular, synuclein, TDP43, inflammation

Adapted from Jack et al., *Alzheimer's & Dementia* (2018) 14(4): 535-562.

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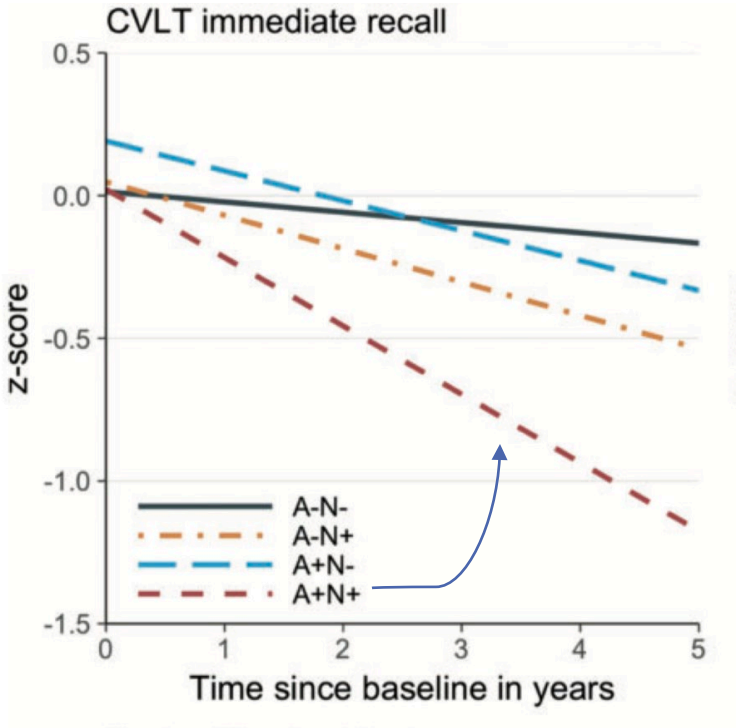
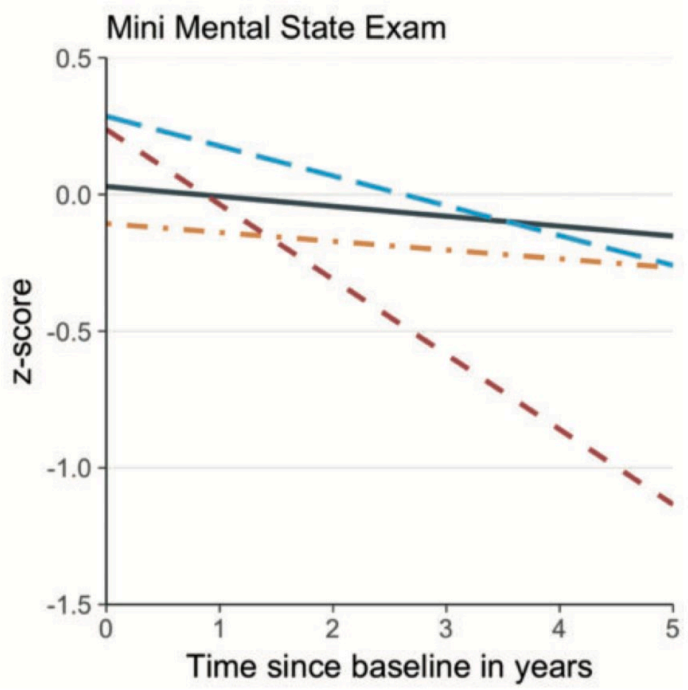
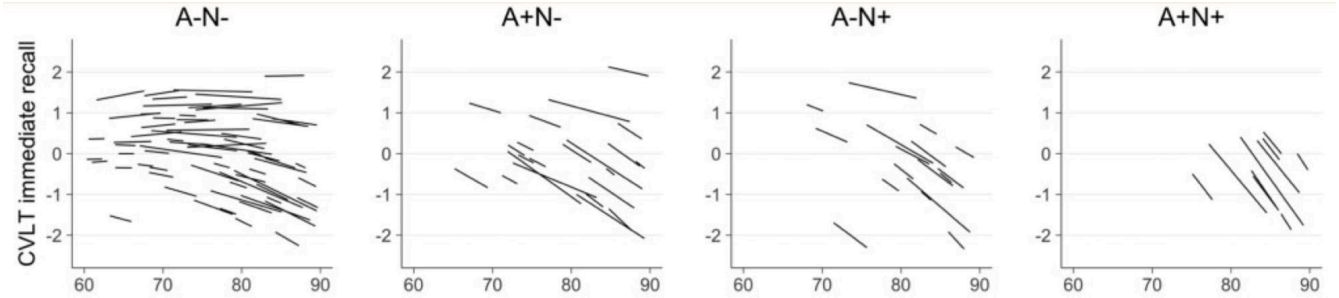
Testing the 2018 NIA-AA Research Framework (A) and (N) are associated with cognitive decline







Bilgel et al. (2018). *Brain* 28: 2475–2485.

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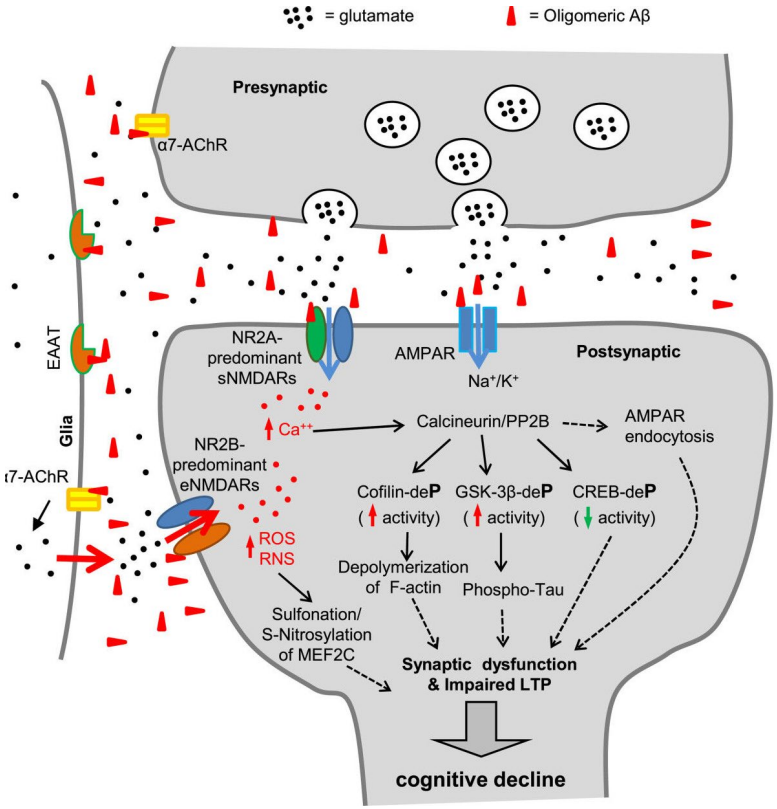
Live imaging of synapses in AD with the SV2A radioligand ^{11}C-UCB-J

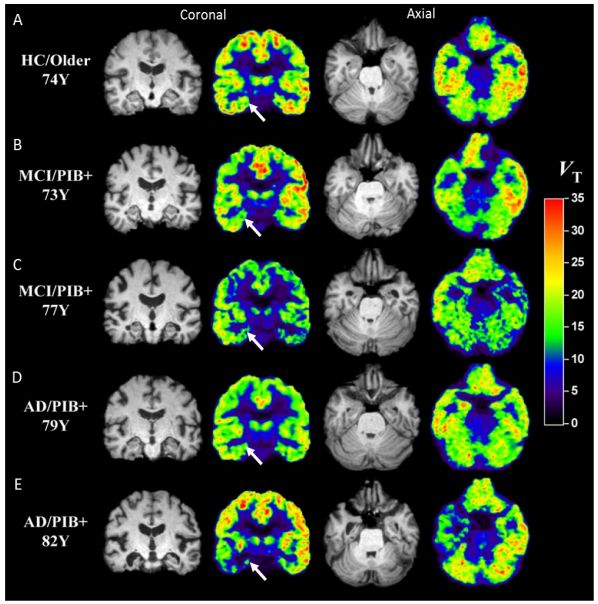


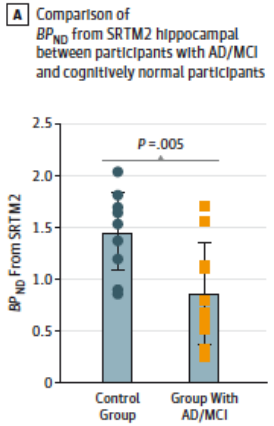
Tu *et al. Molecular Neurodegeneration* 2014, **9**:48
http://www.molecularneurodegeneration.com/content/9/1/48

JAMA Neurology | Original Investigation

Assessing Synaptic Density in Alzheimer Disease With Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging

Ming-Kai Chen, MD, PhD; Adam P. Mecca, MD, PhD; Mika Naganawa, PhD; Sjoerd J. Finnema, PhD; Takuya Toyonaga, MD, PhD; Shu-fei Lin, PhD; Sohella Najafzadeh, MS; Jim Ropchan, PhD; Yihuan Lu, PhD; Julia W. McDonald, BA; Hannah R. Michalak, BA; Nabeel B. Nabulsi, PhD; Amy F. T. Arnsten, PhD; Yiyun Huang, PhD; Richard E. Carson, PhD; Christopher H. van Dyck, MD



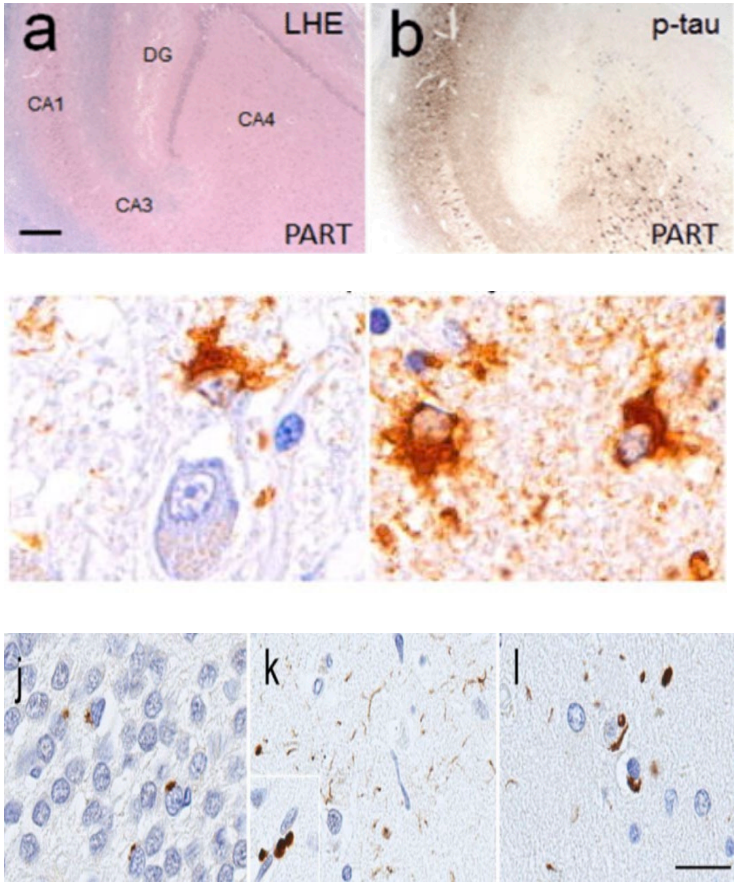


***in vivo* Synaptic Function in AD/ADRD**
(NIA Contact; John Hsiao) (PAR-18-596)

NIH National Institute on Aging

Emerging neuropathological entities relevant to the 2018 NIA-AA Framework

- A (-), T (-/+), N (+)
  - **PART**, primary age related taupathy
  - **ARTAG**, aging related tau astrogliopathy
  - **L**imbic predominant **A**ge related **TDP** diseas**E** (**LATE**)



Meeting report 10/18 to 10/19 2018

Limbic-predominant age-related TDP disease (LATE)

Diagnostic autopsy results:
LATE Neuropathologic Change (LATE-NC)

- Study of community-based autopsy cohorts show that LATE-NC is the second-largest associative contribution (among neurodegenerative conditions) to amnestic cognitive impairment in the aging population, with the same order of magnitude as AD plaques and tangles.

- Autopsied individuals with LATE-NC tend to have been diagnosed as AD in the clinical setting -- the disease preferentially affects episodic memory but may culminate in dementia.

- This disease is probably a large component of "SNAP" (suspected non-amyloid pathology) and in particular cases with "T-N+" biomarker profile. Hopefully, future studies will develop specific biomarkers for LATE-NC.

Planning committee
Pete Nelson (co-chair); Nina Silverberg (co-chair); Dennis Dickson, Julie Schneider, John Trojanowski, Helena Chui

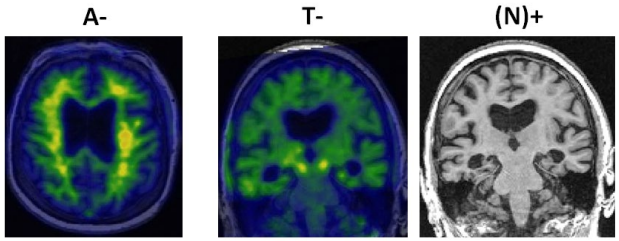
Meeting participants

Rosa Rademakers, Clifford Jack, Eliezer Masliah, Bud Kukull, C. Dirk Keene, Gabor Kovacs, Gregory Jicha, Irina Alafuzoff, Konstantinos Arfanakis, Linda Van Eldik, Patricia Boyle, Tom Montine, William Seeley, Melissa Murray, Robert Rissman, Margaret Flanagan, Allan Levey

Off-site participants

Su Nag, Lei Yu, Dave Fardo, Reisa Sperling, Shigeo Murayama, Keith Josephs, Claudia Kawas

86 yo, F, progressive amnestic dementia. Clinic Dx "AD".



New correct autopsy diagnosis:
LATE-NC with hippocampal sclerosis

Courtesy of Dr. Cliff Jack

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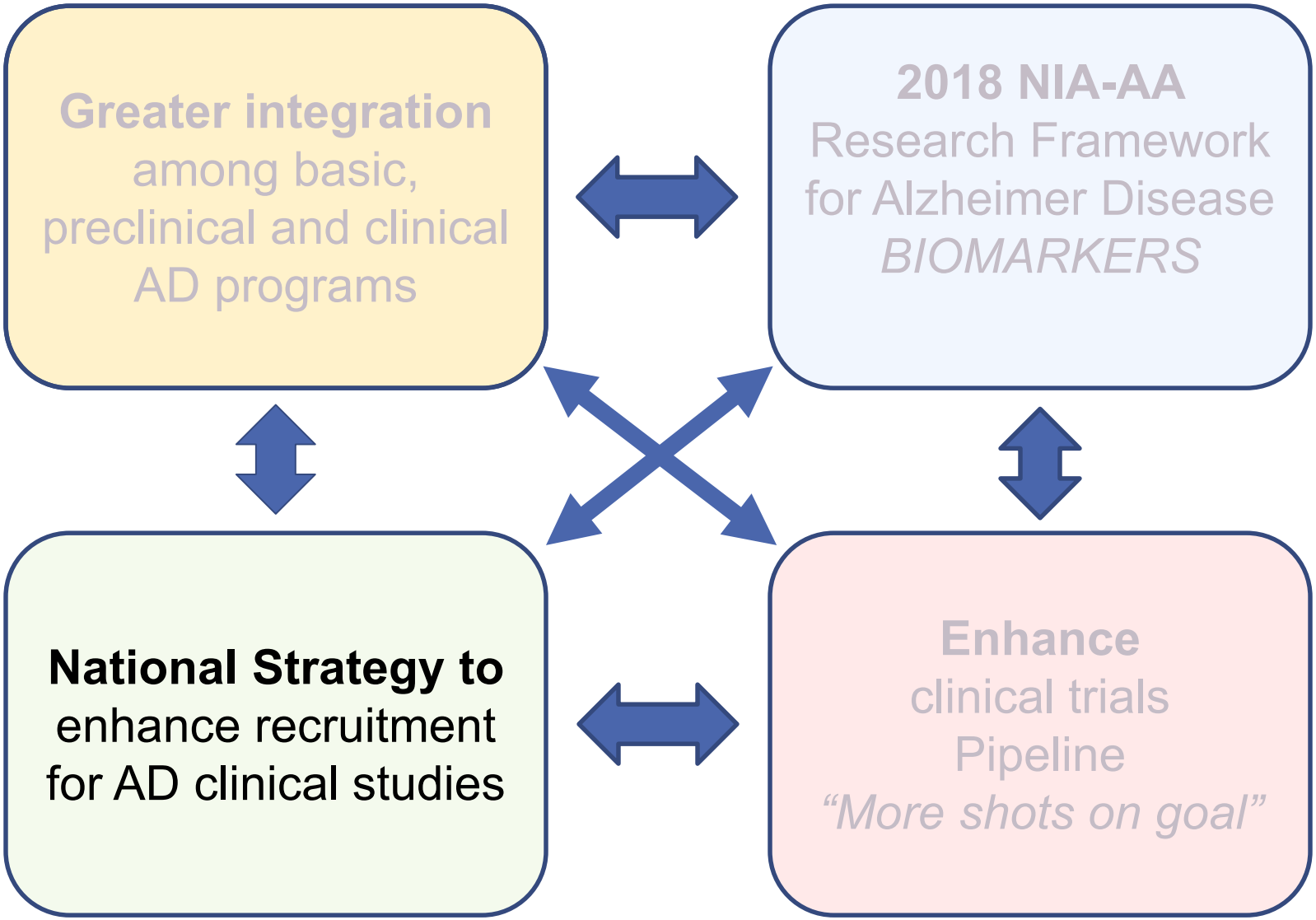
Some NIA-AD Research Priorities



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National Strategy for Alzheimer's Disease Recruitment and Participation in Clinical Research (ADRP)

A. ***National Efforts-*** strategies that can lead to successful recruitment
B. ***Capacity building-*** bolster infrastructure to enhance recruitment
C. ***Connecting at the local level-*** best practices to build trusting relations

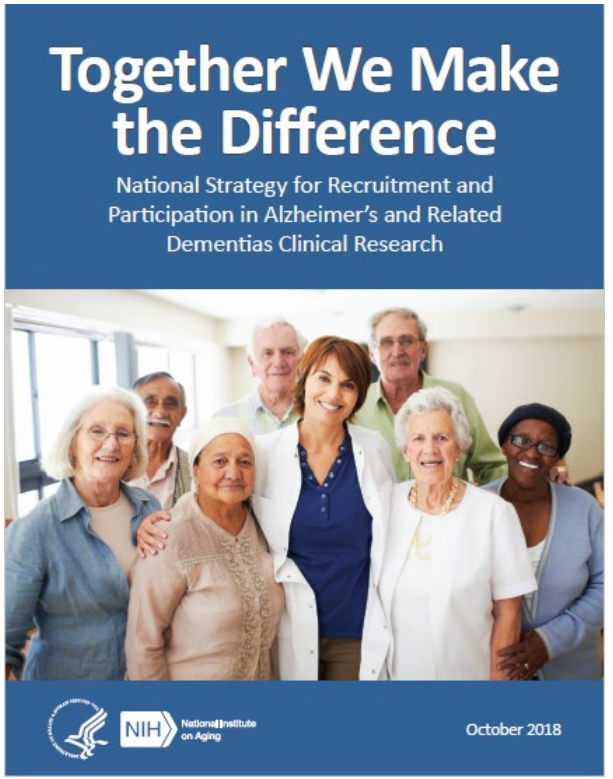
Funding Opportunity Title	Examining Diversity, Recruitment and Retention in Aging Research (R24 Clinical Trial Not Allowed)
Activity Code	R24 Resource-Related Research Projects
Announcement Type	New
Related Notices	None
Funding Opportunity Announcement (FOA) Number	PAR-18-749

NIA Contact; Cerise Elliott

NIH National Institute on Aging

National Strategy for Recruitment & Participation in Alzheimer's & Related Dementias Research

- Released 10/19 at NAPA
- Developed with facilitation by Alzheimer's Association, input of working groups, & public
- Next steps: implementation – how can we work together?
- 10/23 #ResearchDiversity day on social media



www.nia.nih.gov/research/recruitment-strategy

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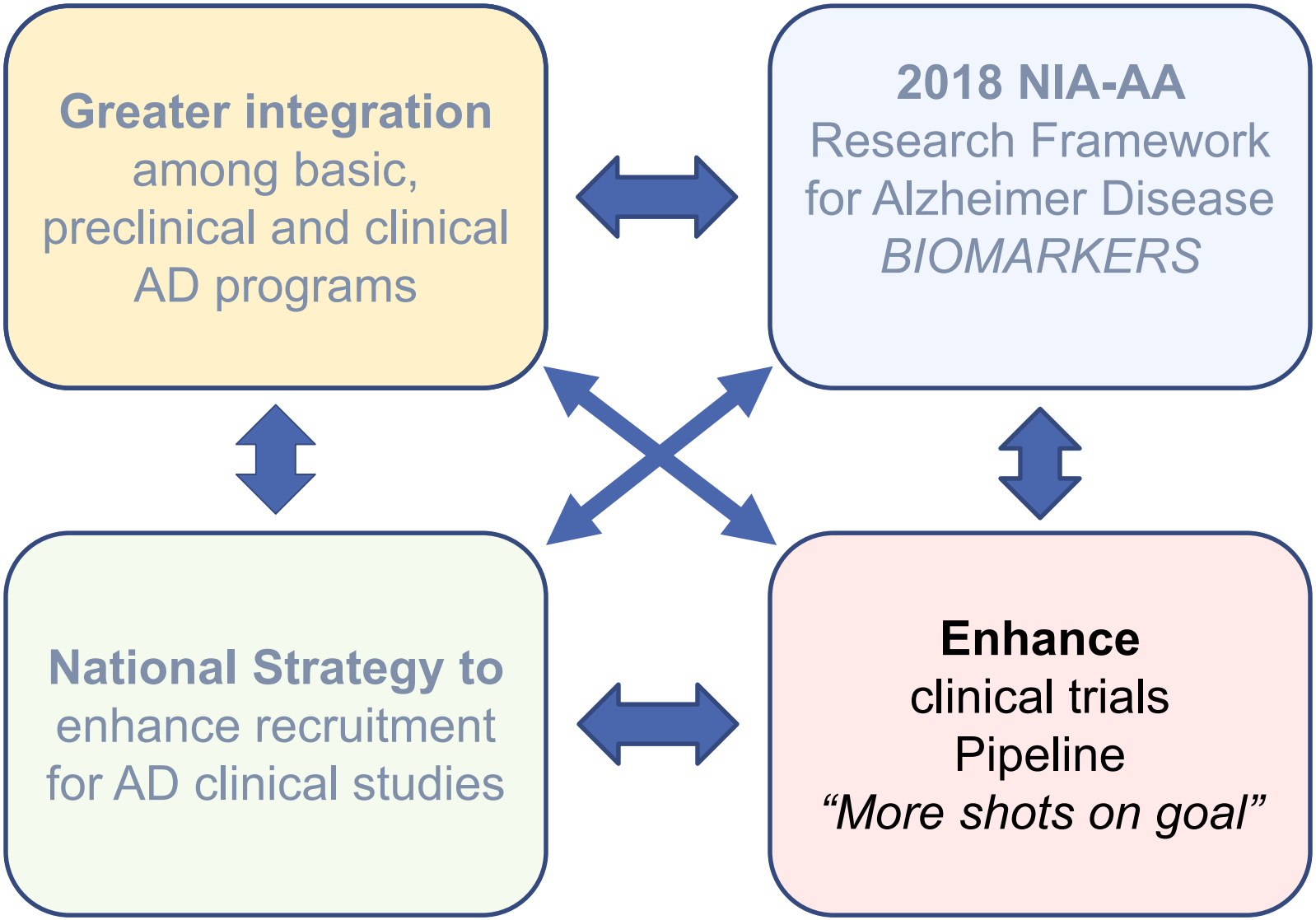
Some NIA-AD Research Priorities



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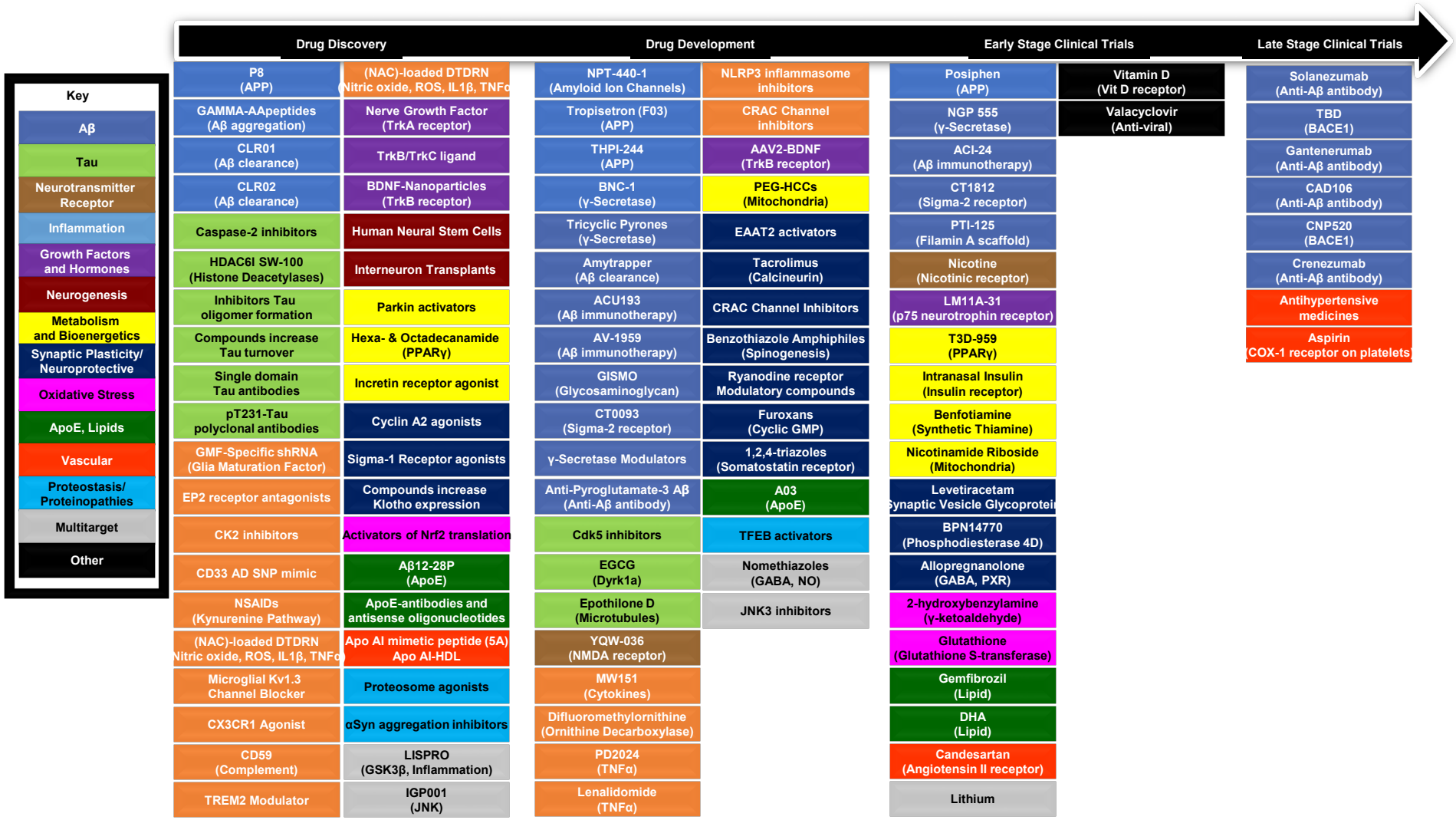
NIA- AD drug development pipeline toward 2025



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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

View nominated target list

A list of genes nominated by AMP-AD groups as targets of interest. Each AMP-AD team has deployed state of the art systems biology methods to integrate across genomic, transcriptomic, and proteomic data from over 2000 participant brains. Each target represents a gene with multiple lines of evidence and is a candidate driver of Alzheimer disease etiology.

View all nominated targets

Search for a gene

Please type a gene symbol in the search box below.

Search by gene name

Popular community searches

PIAS2 APC SNX2

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Open for business!

Partnerships with NGO's

Trans-NIH collaborations

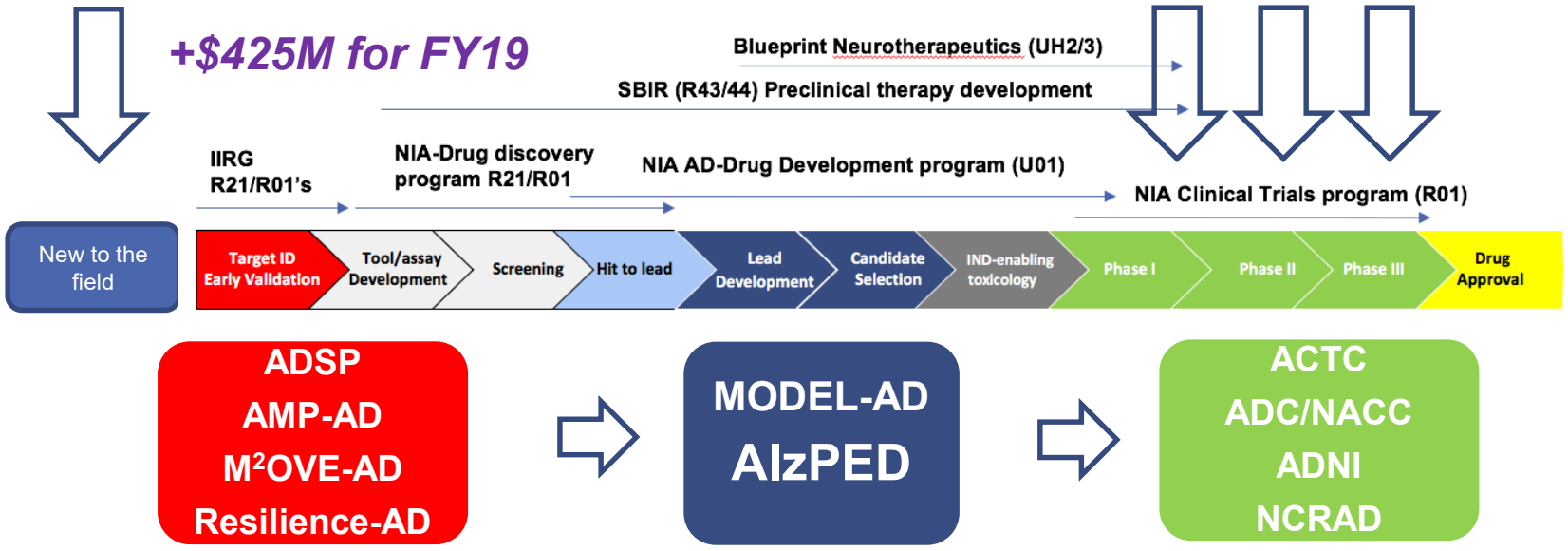
Public private partnerships

Open science/data sharing

Enabling precision medicine

New PI's, early career, junior faculty training

Pre-clinical to Phase I-II (translation gap)



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Turning Discovery Into Health

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Health Scientist Administrator

Position Series/number: General Health Science Series, 0601

Grade Scale: GS-7, 9, 11 - 15, SES, Title 42, SBRS and Commissioned Corps

JOB DESCRIPTION

Health Scientist Administrators at the NIH are responsible for the initial administrative, scientific and technical review of NIH research grant applications pertaining to the scientific and technical fields. The duties and responsibilities of the Health Scientist Administrator include, but are not limited to; organizing and managing peer-review groups to evaluate research proposals on the basis of their scientific merit; managing extramural research and research training programs, and identifying research areas warranting either increased or decreased funding emphasis; developing requests for applications (RFAs) and Requests for Proposals (RFPs) designed to elicit research grant and contract proposals from the scientific community; providing technical assistance to applicants and grantees; serving as project officer on research contracts and program administrator/director on research grants; conducting site visits to applicant and grantee institutions to

Video Spotlight

- Biologist
- Health Science Administrator - Scientific Review Officer
- Health Science Administrator - Program Officer

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