2018 Spring ADC Meeting

DIRECTORS MEETING

Los Angeles, CA
April 21, 2018

”NIA/Division of Neurosciences UPDATE"

Eliezer Masliah, M.D.
Director, Division of Neuroscience,
National Institute on Aging, NIH

NIH National Institute on Aging

Key 2012/2015 AD Summits Recommendations

NAPA

Scientific community recommendations

Milestones

FOA's

Grants

- ❑ **Recognize the heterogeneity and the multifactorial nature of the disease.**
- ❑ **Support extensive molecular profiling of existing and establish new cohorts to fill the gaps in large-scale human data needed to build predictive models of disease and wellness.**
- ❑ **Employ new research paradigms such as systems biology and systems pharmacology.**
- ❑ **Enable rapid and extensive sharing of data, disease models, and biological specimens.**
- ❑ **Develop computational tools and infrastructure for storage, integration, and analysis of large-scale biological and other patient-relevant data.**
- ❑ **Build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate.**
- ❑ **Contribution of complex biology of Aging to AD.**
- ❑ **Develop new precompetitive public-private partnerships.**
- ❑ **Change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research.**
- ❑ **Engage patients, caregivers and citizens as direct partners in research.››**

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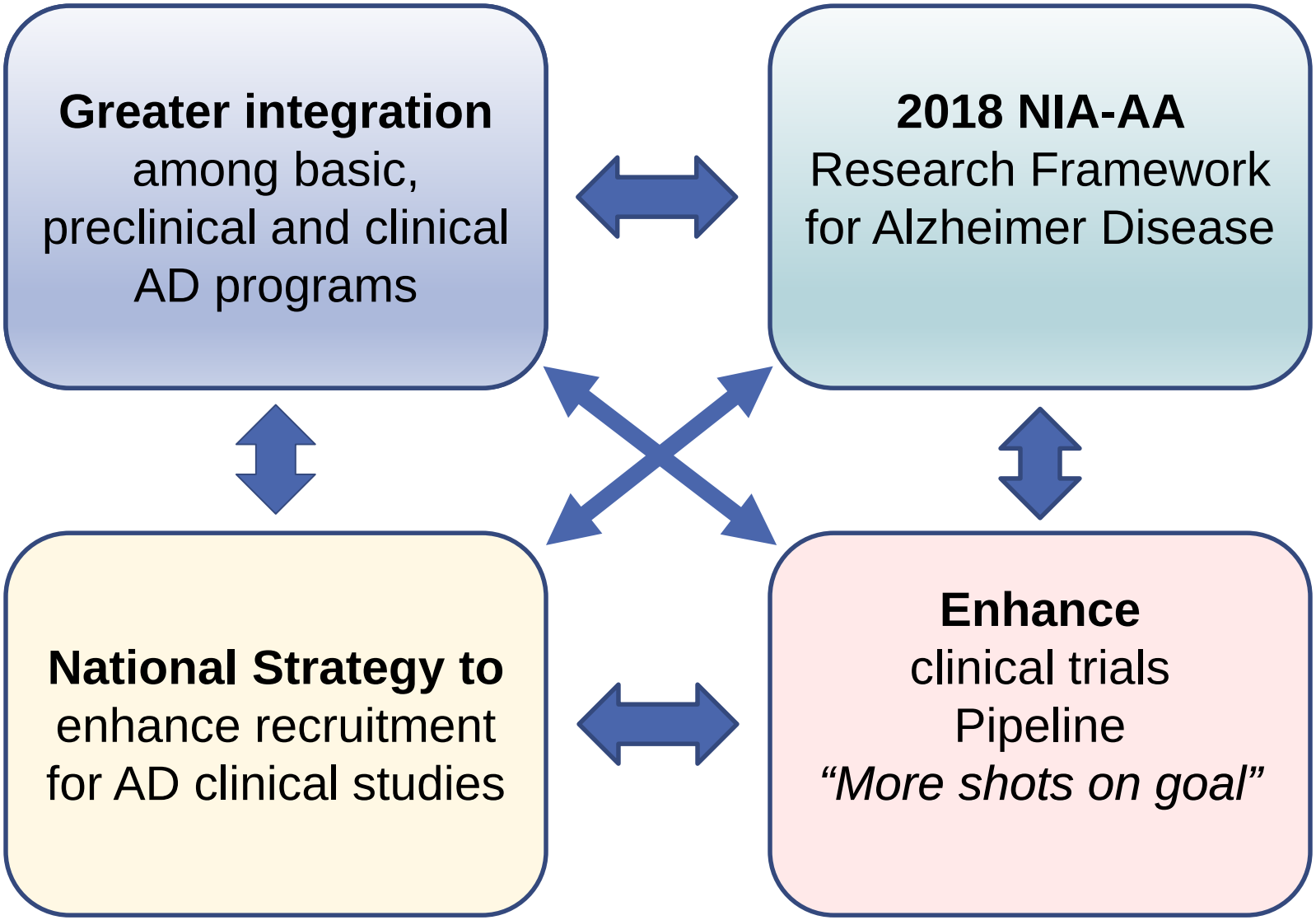
NIA-AD Research Priorities



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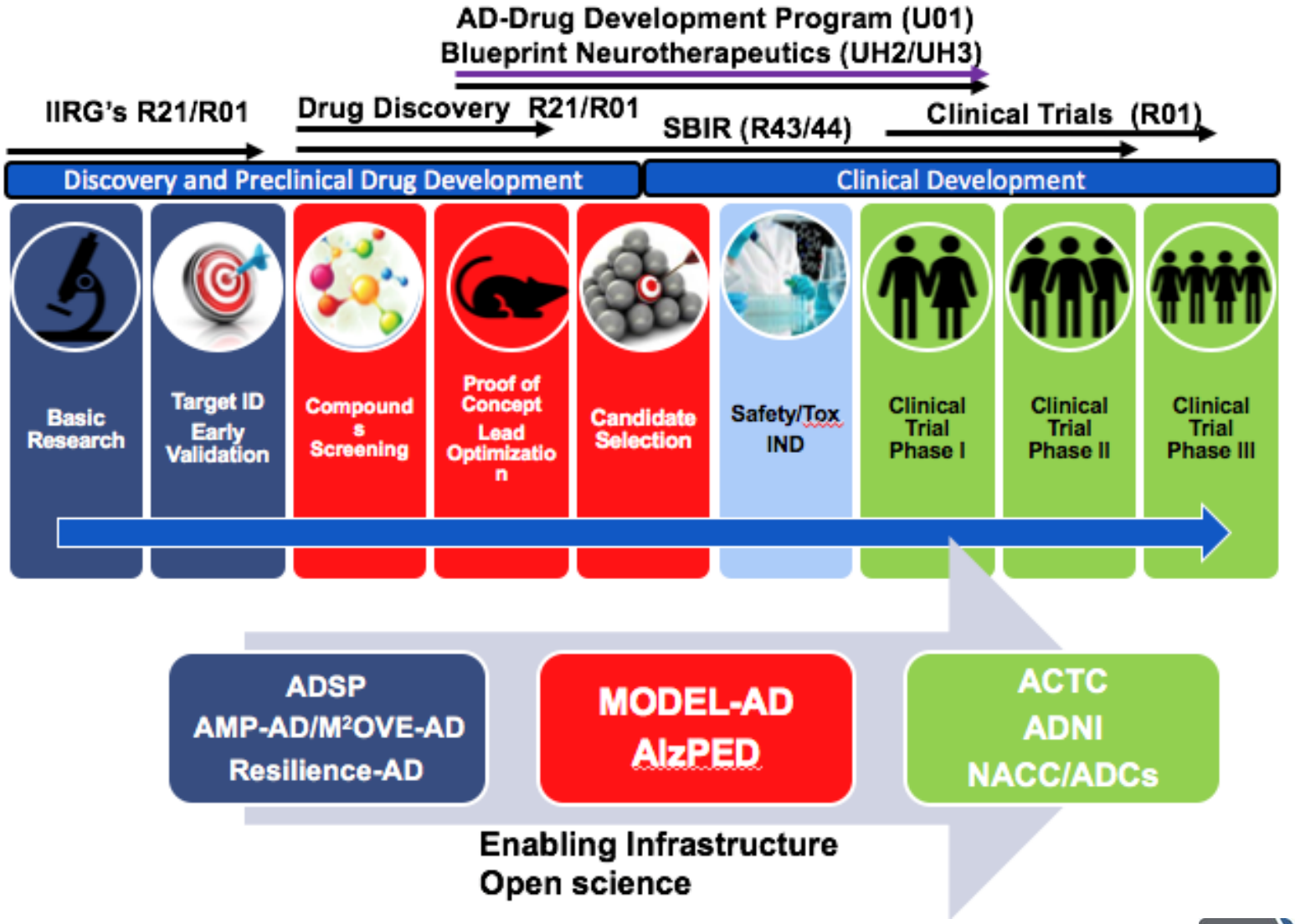
Greater integration of among AD programs



*NEW Funding opportunities (NOT-AG18-001)

- Disparities in Quality and Access to Dementia Care
- Improving the Lives of Persons with Dementia
- in vivo Synaptic Function in AD/ADRD
- Genetic Underpinnings of Endosomal Trafficking as a Pathological Hub in AD/ADRD
- ***Collaborative Studies on AD/ADRD (NIA Contact; Nina Silverberg)***
- ***Deciphering the Glycosylation Code of AD (NIA Contact; Austin Yang)***
- ***Data-Driven Approaches to Understand the Molecular Mechanisms of NPS in AD/ADRD (NIA Contact; Laurie Ryan and Suzana Petanceska)***

NIA-AD current priority research areas

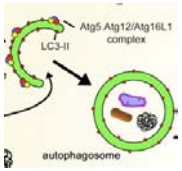
MOLECULAR BASIS FOR AD HETEROGENEITY

and mixed pathology

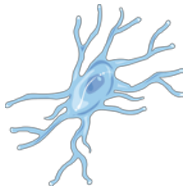
DYNAMIC INTERACTION BETWEEN PERIPHERAL SYSTEMS AND BRAIN AGING/AD

UNDERSTANDING NEURODEGENERATION IN THE CONTEXT OF AGING

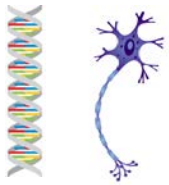
COMLEX BIOLOGY OF RESILIENCE



PROTEOSTASIS



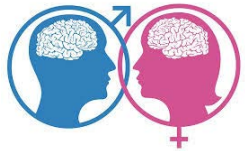
INFLAMMATION



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

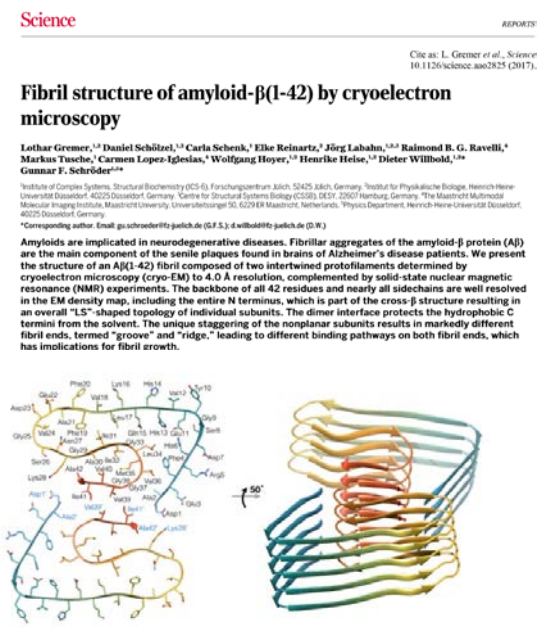
Initiatives in development:

- 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 Contact; Austin Yang**



Science

REPORTS

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

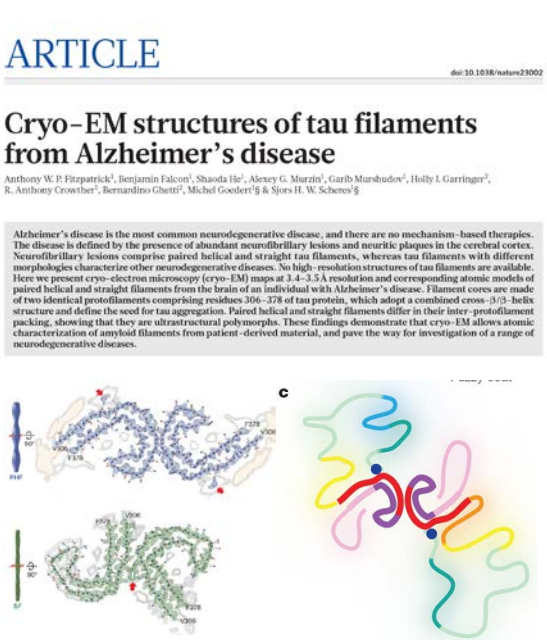
Fibril structure of amyloid-β(1-42) by cryoelectron microscopy

Lothar Gremer,[1,2] Daniel Schölzel,[1,2] Carla Schenk,[1] Elke Reinartz,[3] Jörg Labahn,[1,2,4] Raimond B. G. Ravelli,[4] Markus Tusche,[1] Carmen Lopez-Iglesias,[4] Wolfgang Hoyer,[1,5] Henrike Heise,[1,6] Dieter Willbold,[1,2]* Gunnar F. Schröder[2,5]*

[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: gu.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.



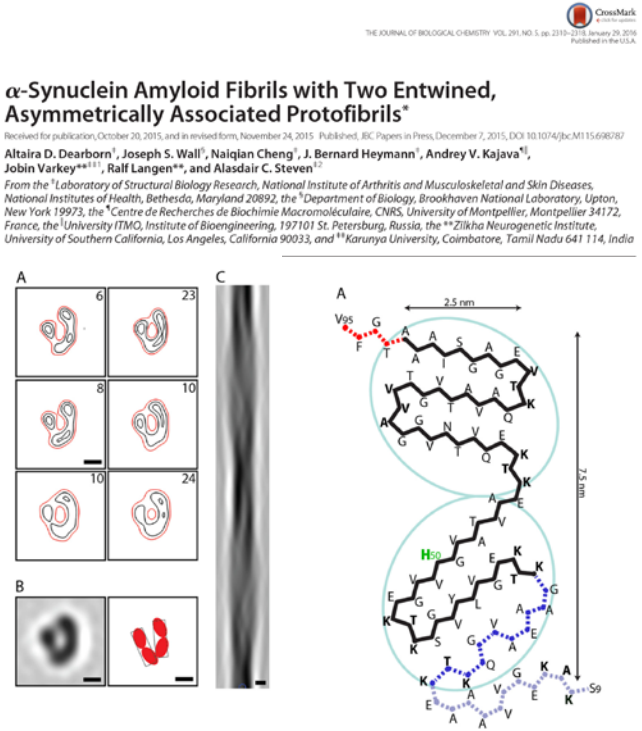
ARTICLE

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[2], 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.



CrossMark

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 291, NO. 5, pp. 2310–2318, January 29, 2016 Published in the U.S.A.

α-Synuclein Amyloid Fibrils with Two Entwined, Asymmetrically Associated Protofibrils*

Received for publication, October 20, 2015, and in revised form, November 24, 2015 Published, JBC Papers in Press, December 7, 2015, DOI 10.1074/jbc.M115.698787

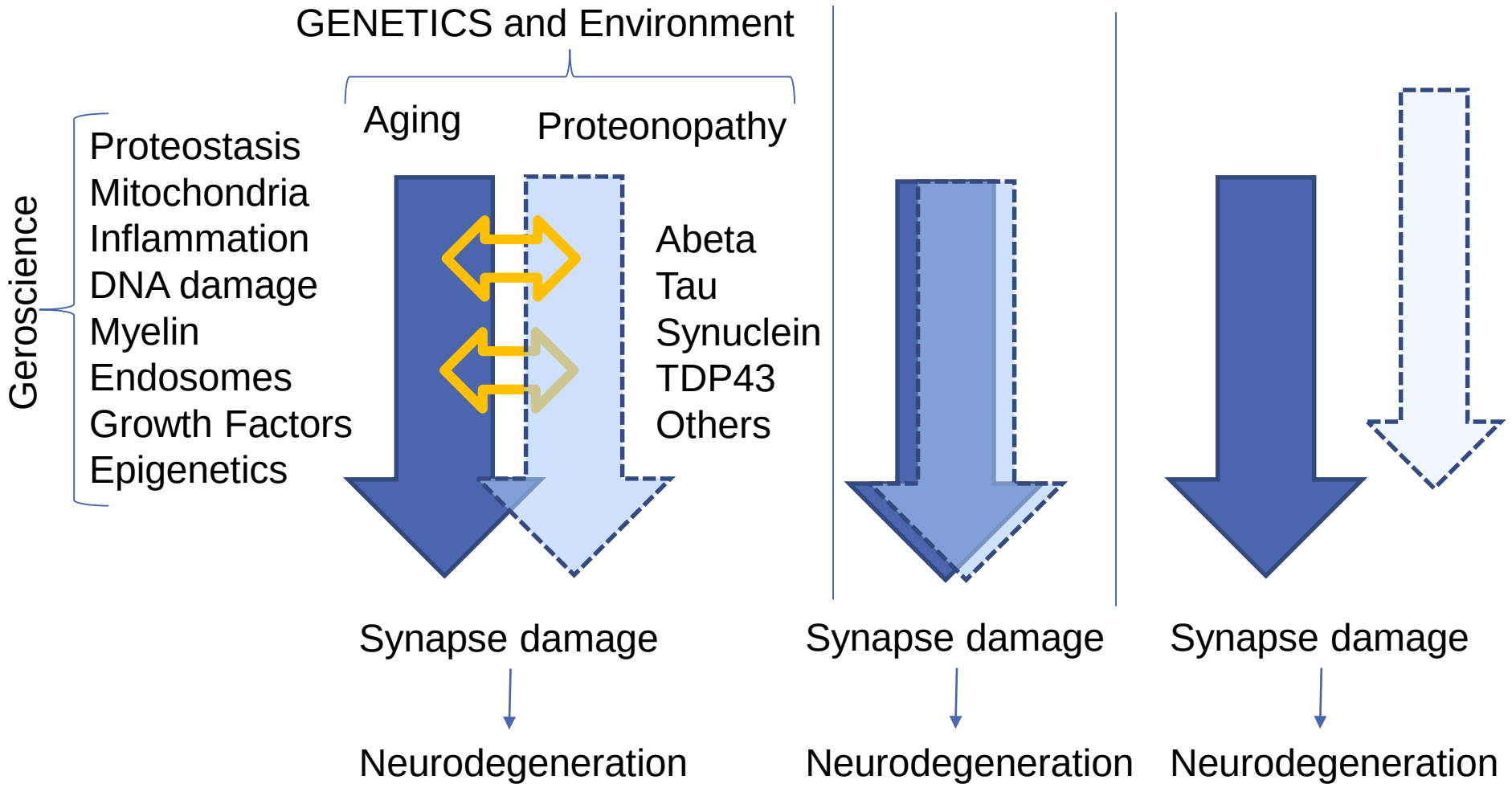
Altaira D. Dearborn[‡], Joseph S. Wall[§], Naiqian Cheng[‡], J. Bernard Heymann[‡], Andrey V. Kajava[¶], Jobin Varkey[**‡‡1], Ralf Langen[**], and Alasdair C. Steven[‡2]

From the [‡]Laboratory of Structural Biology Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland 20892, the [§]Department of Biology, Brookhaven National Laboratory, Upton, New York 19973, the [¶]Centre de Recherches de Biochimie Macromoléculaire, CNRS, University of Montpellier, Montpellier 34172, France, the [‖]University ITMO, Institute of Bioengineering, 197101 St. Petersburg, Russia, the [**]Zilkha Neurogenetic Institute, University of Southern California, Los Angeles, California 90033, and [‡‡]Karunya University, Coimbatore, Tamil Nadu 641 114, India

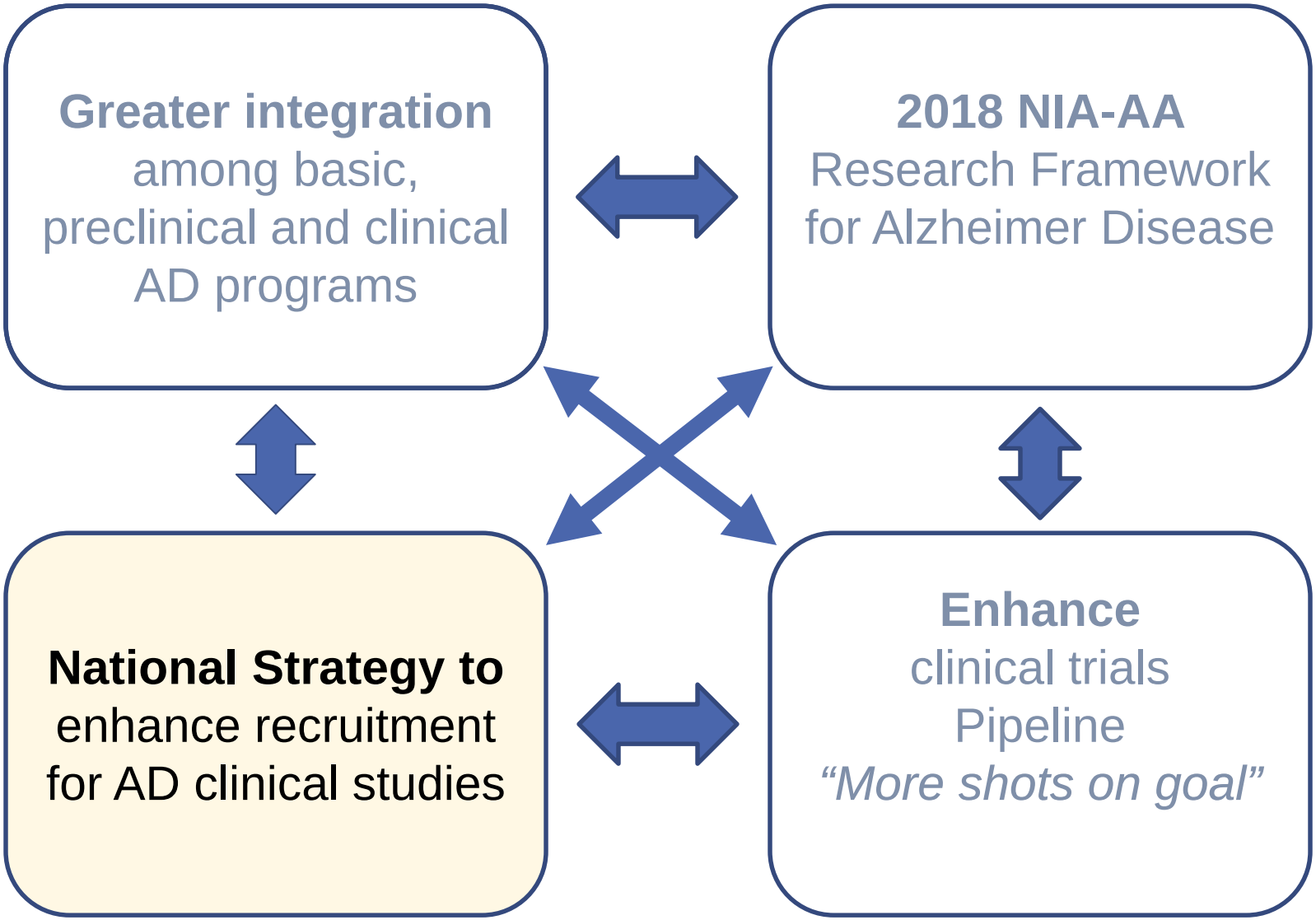
A beta **Tau** **alpha-synuclein**

National Institute on Aging

Understanding AD in the context of Aging



NIA- AD Research Priorities



NIH National Institute on Aging

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

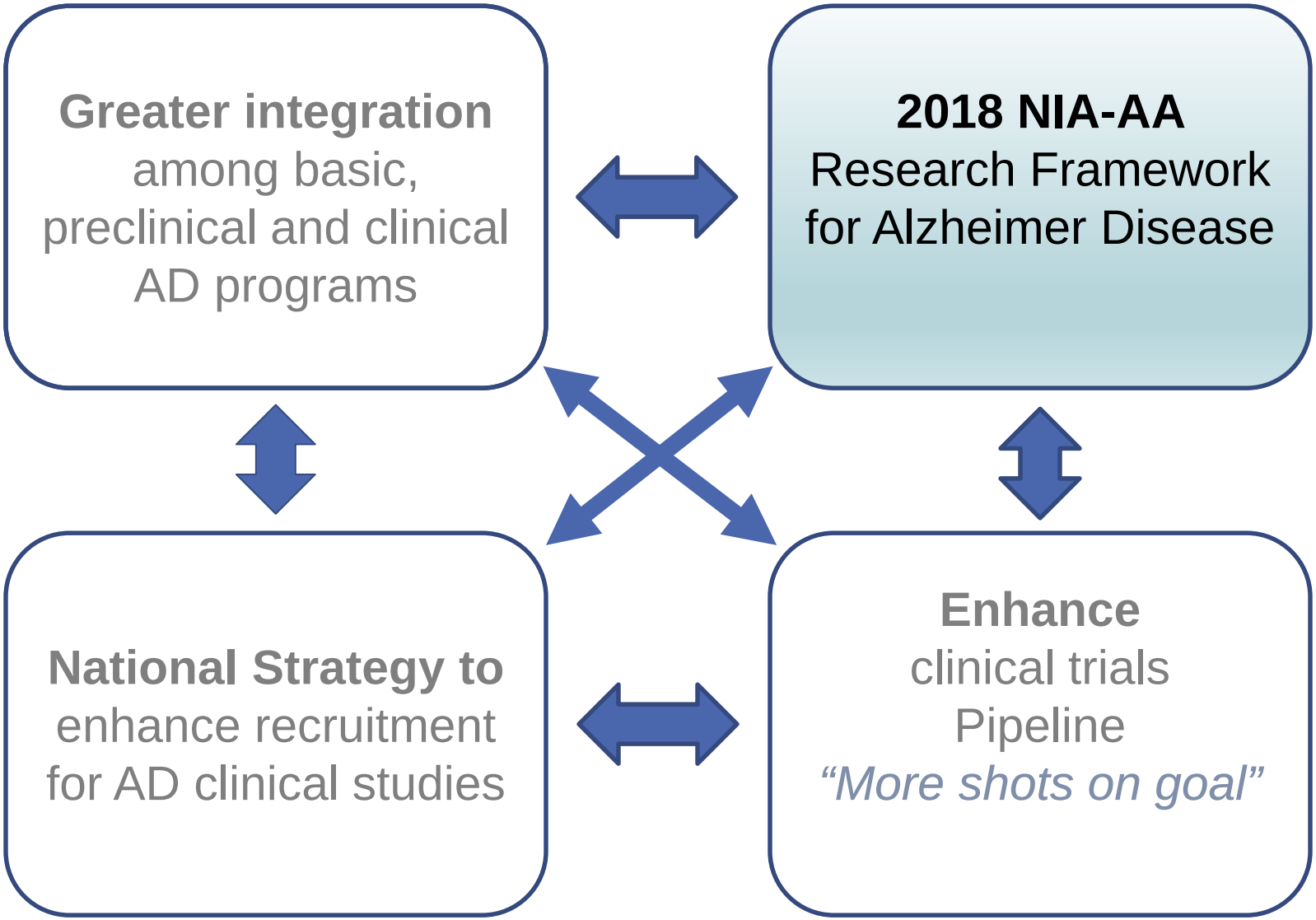
A. ***National Efforts-*** strategies that can lead to successful recruitment
B. ***Capacity building-*** bolster infrastructure to enhance recruitment
C. ***Connecting at the local level-*** best practices to build trusting relations

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

NIA-AD Research Priorities



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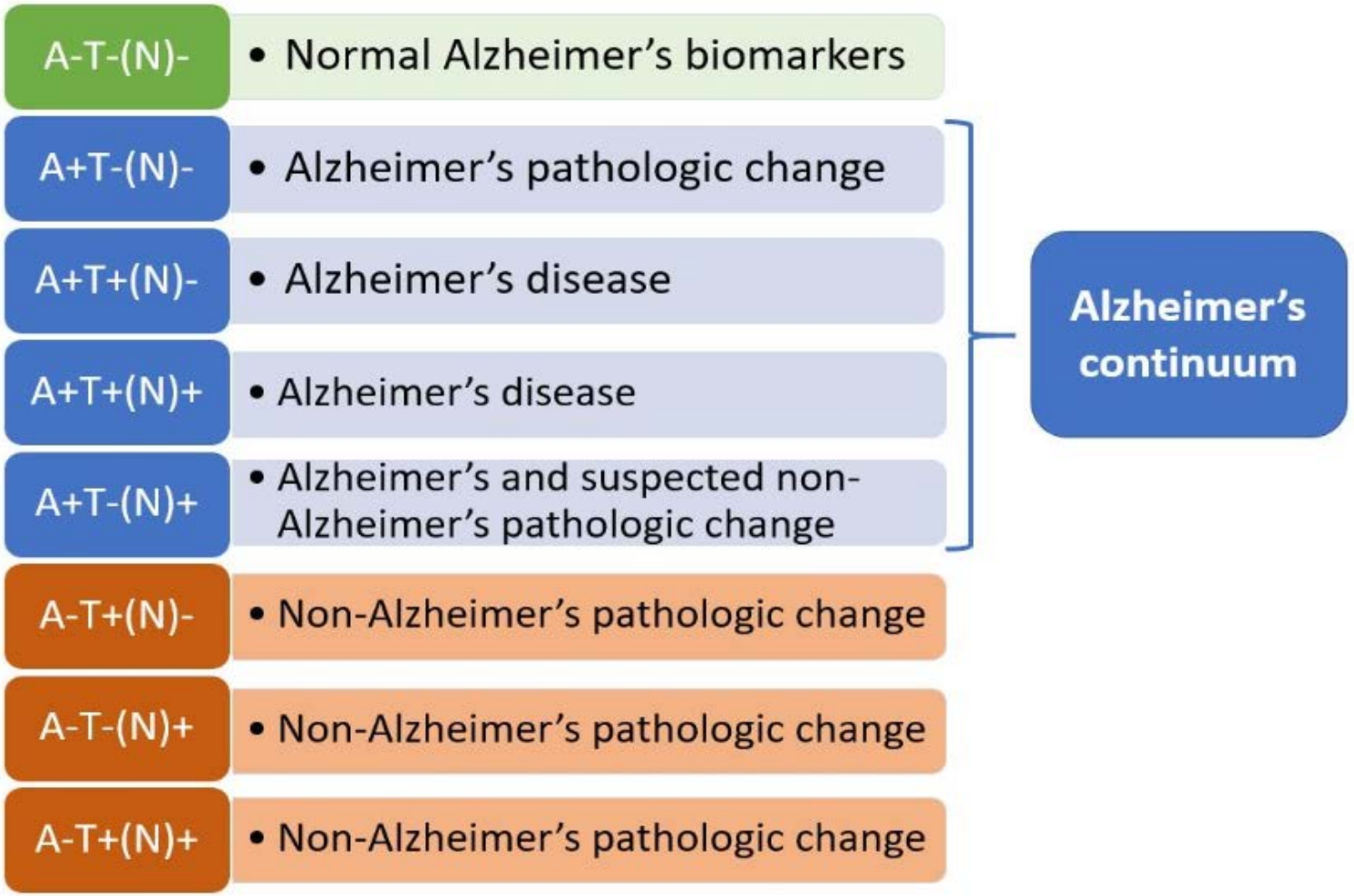
2018 NIA-AA Research Framework

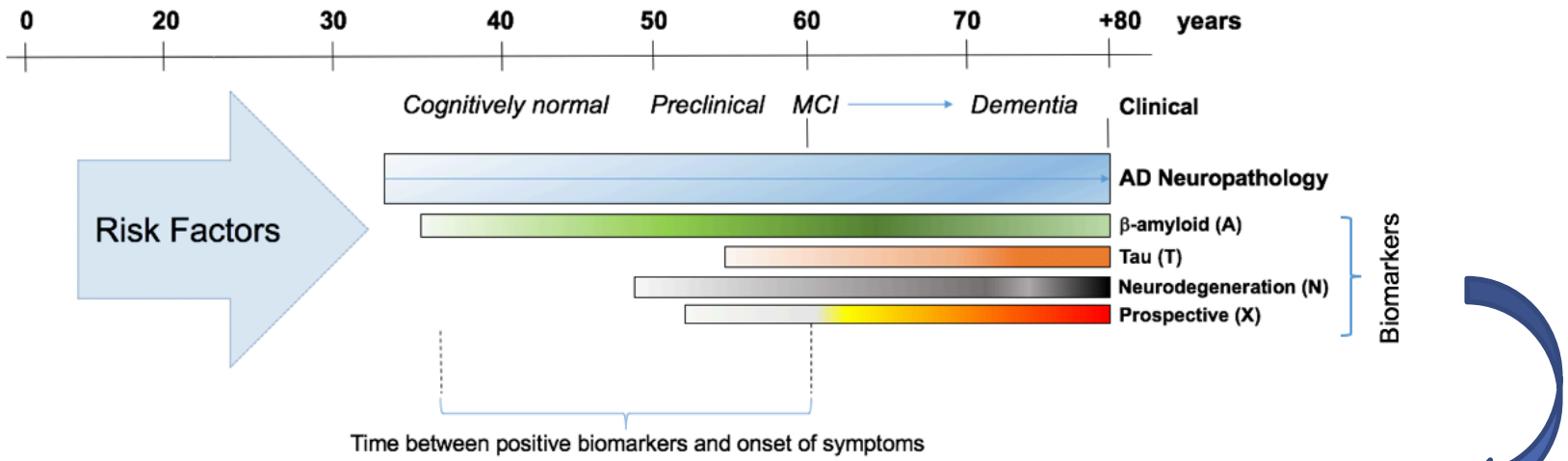


A = Amyloid; T = Tau;
N = Neurodegeneration

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

2018 NIA-AA Framework- Commentary

- Considers AD pathology separate from dementia
- Considers disease as a continuum including aging
- Very long incubation period between onset of pathology and cognitive impairment



The research framework is…	The research framework is NOT…
A testable hypothesis	A requirement for NIH grant submission
An approach that facilitates standardized research reporting	A statement about Alzheimer's pathogenesis or etiology
A common language and a reference point for researchers for longitudinal studies and clinical trials	An NIA policy, guideline or criterion for papers or grants
A welcome for other approaches	A disease definition for standard medical use
A welcome for other indicators of Alzheimer's and comorbidities	A fixed notion of Alzheimer's

NEW
ADC's Biomarkers Core

X= NEW

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*NEW Funding opportunities (NOT-AG18-001)

- Disparities in Quality and Access to Dementia Care
- Improving the Lives of Persons with Dementia
- ***in vivo Synaptic Function in AD/ADRD (NIA Contact; John Hsiao) (PAR-18-596)***
- ***Genetic Underpinnings of Endosomal Trafficking as a Pathological Hub in AD/ADRD (NIA Contact; Marilyn Miller)***
- Collaborative Studies on AD/ADRD,
- Deciphering the Glycosylation Code of AD,
- Geroscience Approaches to AD:
- Data-Driven Approaches to Understand the Molecular Mechanisms of NPS in AD/ADRD,

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

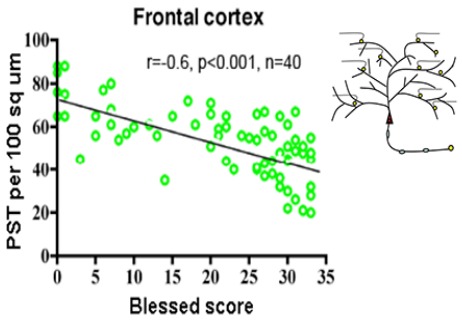
Chris Van Dyck (Yale U) CTAD 2017

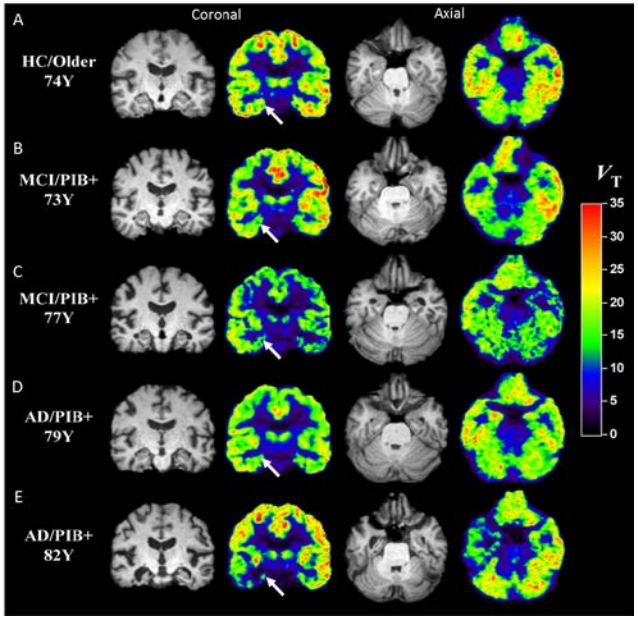
Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Robert D. Terry, MD,* Eliezer Masliah, MD,* David P. Salmon, PhD,* Nelson Butters, PhD,†
Richard DeTeresa, BS,* Robert Hill, PhD,* Lawrence A. Hansen, MD,* and Robert Katzman, MD*

We present here both linear regressions and multivariate analyses correlating three global neuropsychological tests with a number of structural and neurochemical measurements performed on a prospective series of 15 patients with Alzheimer's disease and 9 neuropathologically normal subjects. The statistical data show only weak correlations between psychometric indices and plaques and tangles, but the density of neocortical synapses measured by a new immunocytochemical/densitometric technique reveals very powerful correlations with all three psychological assays. Multivariate analysis by stepwise regression produced a model including midfrontal and inferior parietal synapse density, plus inferior parietal plaque counts with a correlation coefficient of 0.96 for Mattis's Dementia Rating Scale. Plaque density contributed only 26% of that strength.

Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580





RESEARCH ARTICLE

NEUROLOGY

Imaging synaptic density in the living human brain

Sjoerd J. Finnema,[1]* Nabeel B. Nabulsi,[1] Tore Eid,[2] Kamil Detyniecki,[3] Shu-fei Lin,[1]
Ming-Kai Chen,[1] Roni Dhaher,[2] David Matuskey,[1] Evan Baum,[1] Daniel Holden,[1]
Dennis D. Spencer,[4] Joël Mercier,[5] Jonas Hannestad,[5†] Yiyun Huang,[1] Richard E. Carson[1,6]

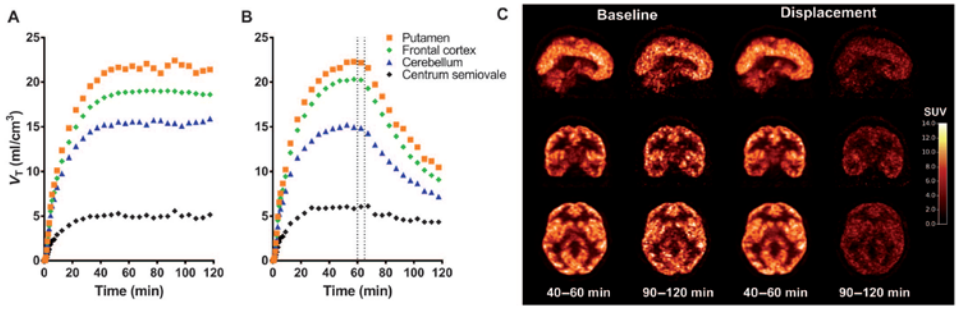
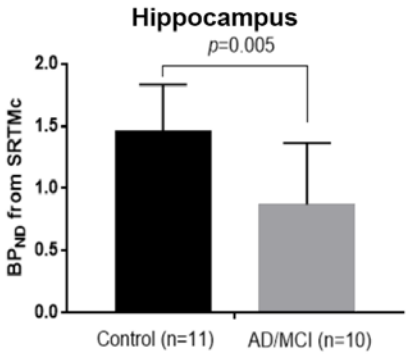


Fig. 3. [^{11}C]UCB-J binds to SV2A in the healthy human brain. (**A** and **B**) Regional TACs of V_T values in four brain regions after [^{11}C]UCB-J administration by a bolus plus constant infusion protocol in three control subjects under baseline (A) or displacement conditions in which levetiracetam (1500 mg) was intravenously infused 60 to 65 min after the start of [^{11}C]UCB-J infusion (B). Data are means (n = 3); the SD was not displayed for the sake of clarity. Individual subject data are shown in fig. S5. (**C**) PET summation images 40 to 60 min or 90 to 120 min after [^{11}C]UCB-J injection in subject 8. In the displacement study, levetiracetam (1500 mg) was intravenously infused 60 to 65 min after the start of [^{11}C]UCB-J infusion. Individual subject images are shown in fig. S6.



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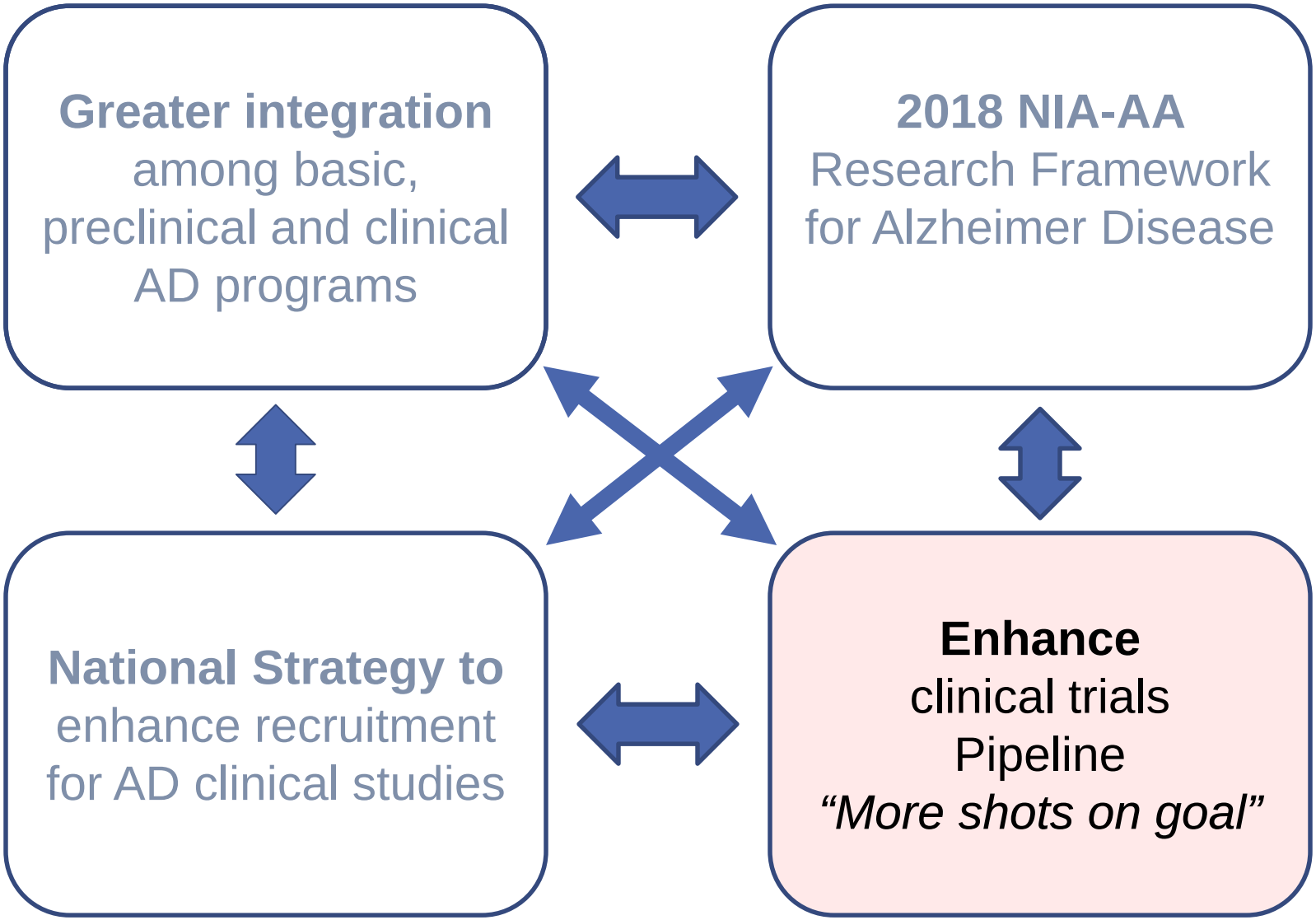
NIA-AD Research Priorities



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adsp
Alzheimer's Disease Sequencing Project

PI: G. Schellenberg; L. San U Penn; NIA Lead: Marilyn Miller

Genetic Underpinnings of Endosomal Trafficking as a Pathological Hub in AD/ADRD (NIA Contact; Marilyn Miller) (PAR-18-596)

PSD2
TCIRG1
RIN3
RUFY1

JAMA Neurology | Original Investigation

Early-Onset Alzheimer Disease and Candidate Risk Genes Involved in Endolysosomal Transport

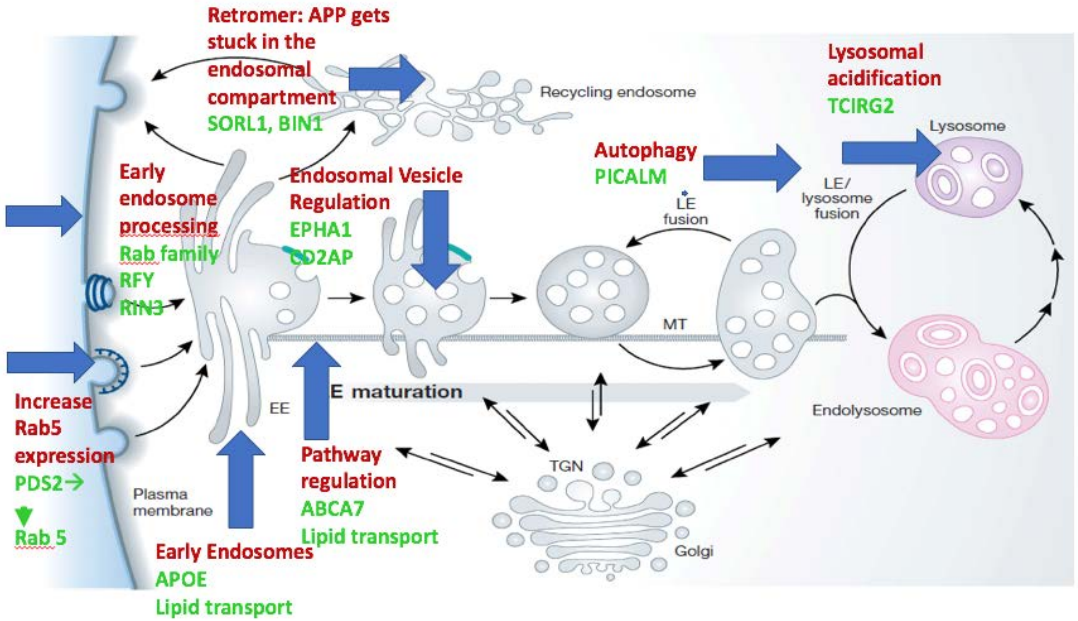
Brian W. Kunkle, PhD, MPH; Badri N. Vardarajan, PhD; Adam C. Naj, PhD; Patrice L. Whitehead, BS; Sophie Rolati, MS; Susan Slifer, MS; Regina M. Carney, MD; Michael L. Cuccaro, PhD; Jeffery M. Vance, MD, PhD; John R. Gilbert, PhD; Li-San Wang, PhD; Lindsay A. Farrer, PhD; Christiane Reitz, MD, PhD; Jonathan L. Haines, PhD; Gary W. Beecham, PhD; Eden R. Martin, PhD; Gerard D. Schellenberg, PhD; Richard P. Mayeux, MD, MSc; Margaret A. Pericak-Vance, PhD

PLCG2
ABI3
TREM2

LETTERS

NATURE GENETICS VOLUME 49 | NUMBER 9 | SEPTEMBER 2017 1373

Rare coding variants in *PLCG2*, *ABI3*, and *TREM2* implicate microglial-mediated innate immunity in Alzheimer's disease



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ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

NIA Lead: 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

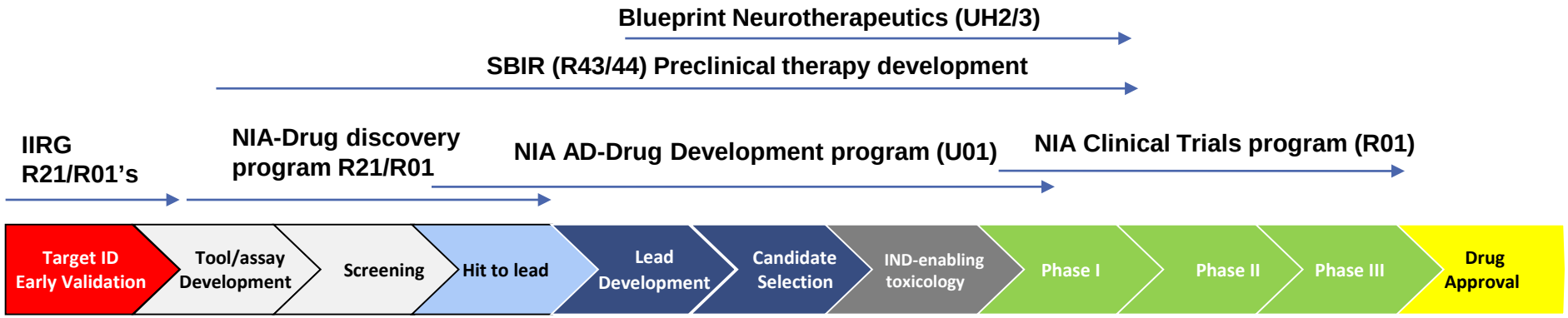
Progress over 4 years:

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

AMP-AD Teams
Candidate Targets: preliminary list

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		

NIA and Trans-NIH translational programs and infrastructure for AD



ADSP
AMP-AD
M²OVE-AD
Resilience-AD

MODEL-AD
AIzPED

ACTC
ADC/NACC
ADNI

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

OPEN SCIENCE

NIH National Institute on Aging

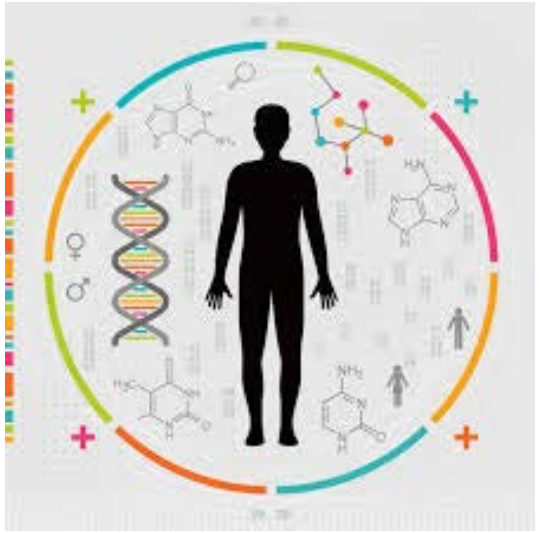
NIA- AD clinical trials pipeline toward 2025

NIA contact: Laurie Ryan and Kristina McLinden

- **Over 140 active trials**
- ***40*** *Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)*
  - Amyloid (9)
  - Neurotransmitter Receptors (3)
  - Metabolism and Bioenergetics (4)
  - Vasculature (3)
  - Growth Factors and Hormones (1)
  - Multi-target (6)- **Tau, inflammation, ApoE4, MAPK, JNK1**
  - Oxidative Stress (1)
- ***8*** *Late-stage Clinical Drug Development (Phase II/III and Phase III Clinical Trials)*
  - Amyloid (6)- **DIAN-TU, A4, API-ADAD, API-E4, others**
  - Vasculature (2)- **SPRINT-MIND, ASPREE**
- ***62*** *Non-Pharmacological Interventions*
  - Exercise (16)
  - Diet (2)
  - Cognitive Training (20)
  - Combination Therapy (11)
- ***7*** *Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD*
  - Pharmacological (5)- **lithium, methylphenidate, escitalopram, dronabinol, others**
  - Non-Pharmacological (2)- CAP, PATH
- ***37*** *Care and Caregiver Interventions*

2018 NIH Alzheimer's Disease Research Summit

Plans for the Future



March 1-2, 2018

- ❑ Novel Mechanistic Insights into the ***Complex Biology and Heterogeneity of AD***
- ❑ Enabling ***Precision Medicine for AD***
- ❑ Translational Tools and Infrastructure to ***Enable Predictive Drug Development***
- ❑ Emerging Therapeutics- ***novel targets***
- ❑ Understanding the ***Impact of the Gene-Environment to Advance AD Prevention***
- ❑ Advances in ***Disease Monitoring, Assessment and Care***
- ❑ Building ***Open Science Research Ecosystem to Accelerate AD Therapy Development***

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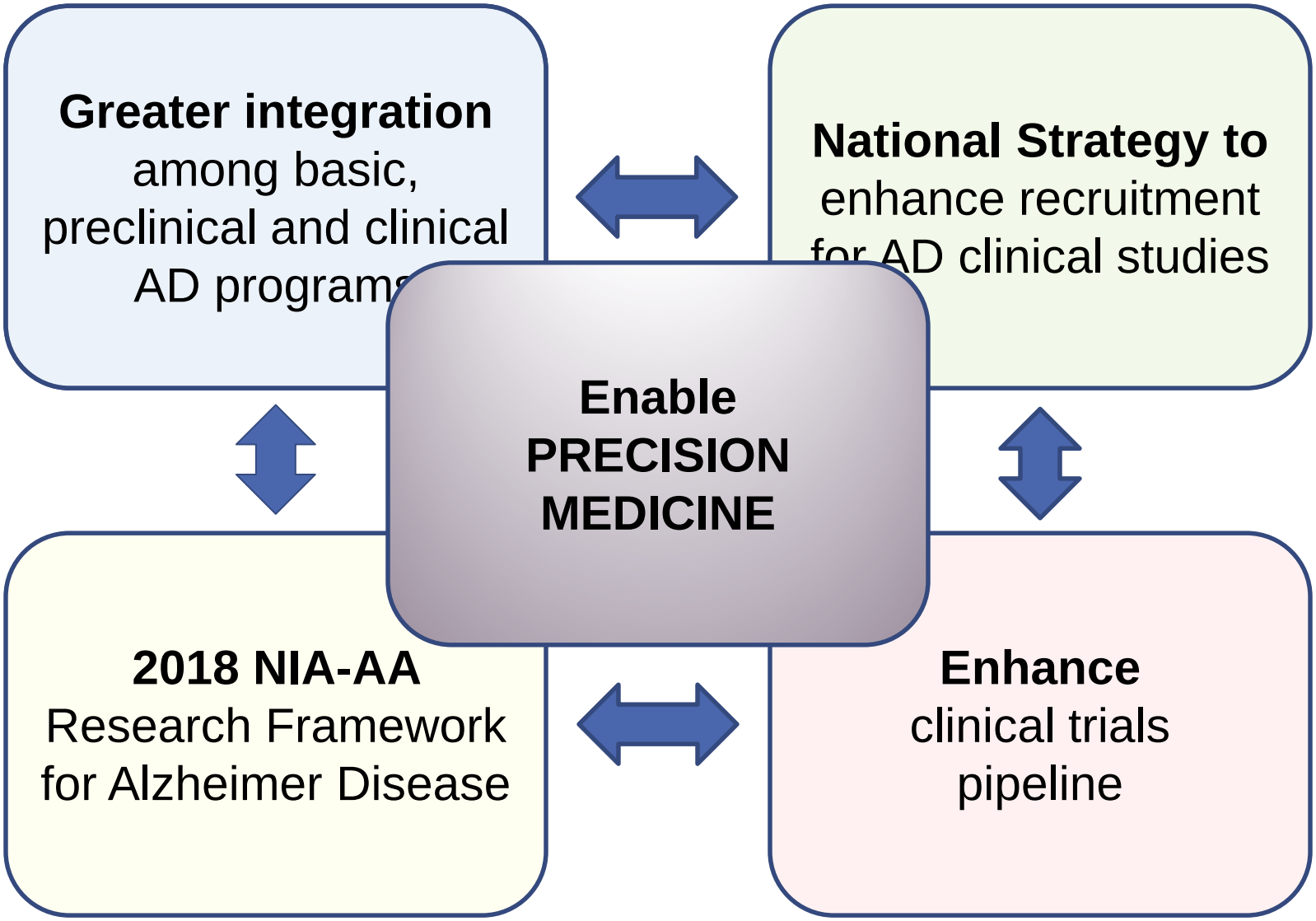
Research Priorities following 2018 AD Summit



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THANKS