ADC Directors meetings

National Institute on Aging

St Louis, MO

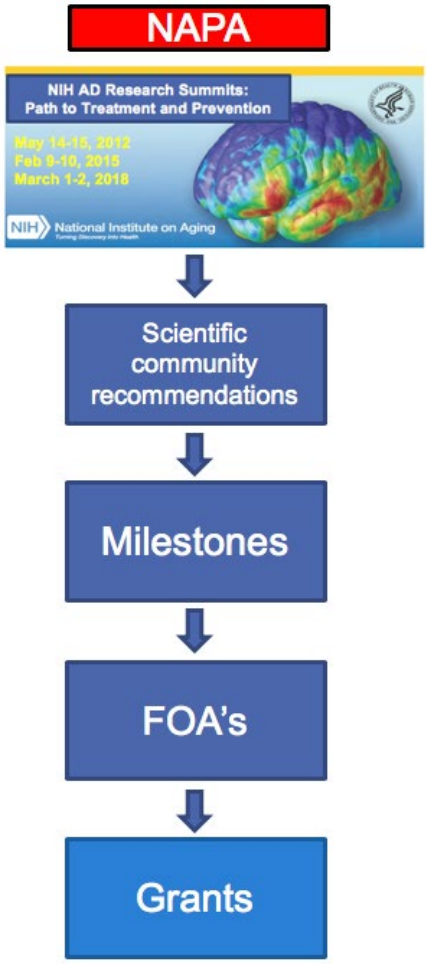
October 12, 2019

”NIA Division of Neuroscience Update"

Eliezer Masliah
Division of Neuroscience
NIA-NIH

NIH National Institute on Aging

Division of Neuroscience update FY19 toward advancing NAPA



- Over 150 milestones
- In FY19 DN funded over 1800 applications
- 800 new grants and 1000 non competitive (total 1.5B)
- Generated over 20 new FOA's

1. ***Senescence CNS Aging and AD (DiBattista, Opanashuk)***
2. ***Oscillatory Gene Expression AD (Mackiewicz)***
3. ***Infectious Etiology of AD (Mackiewicz, Anderson)***
4. ***Regulation Proteome Dynamics in AD (Yang)***
5. ***Increasing competitiveness of potential AD Centers (Silverberg, Elliott)***
6. ***Standardization AD imaging Biomarkers (Silverberg, Hsiao)***
7. ***Non-Invasive Neurostimulation in AD (McLinden, Ryan)***
8. ***Physician-Scientist Mentored Research in AD (Opanashuk)***
9. ***Stimulating Multidisciplinary Programs for AD (Elliott)***

January 2019 Council

1. *AD Sequencing Project (ADSP) Functional Genomics Program (FGP) (Yao and Miller)*
2. *Central and Peripheral Control of Balance in Older Adults (St.Hillaire-Clarke)*
3. *Glial Plasticity in the Aging Brain (Dibattista)*
4. *Harmonization of AD and ADRD Genetic, Epidemiologic and Clinical Data (Marilyn Miller)*
5. *Oligomer Seed bank Initiative - Austin Yang*
6. *Prodromal α-Synucleinopathies Consortium - Mackiewicz-Hsiao*

October 2019 Council

Concept Approvals: https://www.nia.nih.gov/approved-concepts

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Recent NIA collaborative programs in ADRD with NINDS and NHLBI

NINDS and **NIA** are funding natural history studies in FTLD

- *Study of individuals with a clinical diagnosis of FTD to help determine the clinical, genetic and biomarker profiles*
- *Study of families that have one of the three most common gene variants associated with FTD to learn more about the natural history*

ARIC Neurocognitive Study

The Atherosclerosis Risk in Communities Study (15,000 participants)

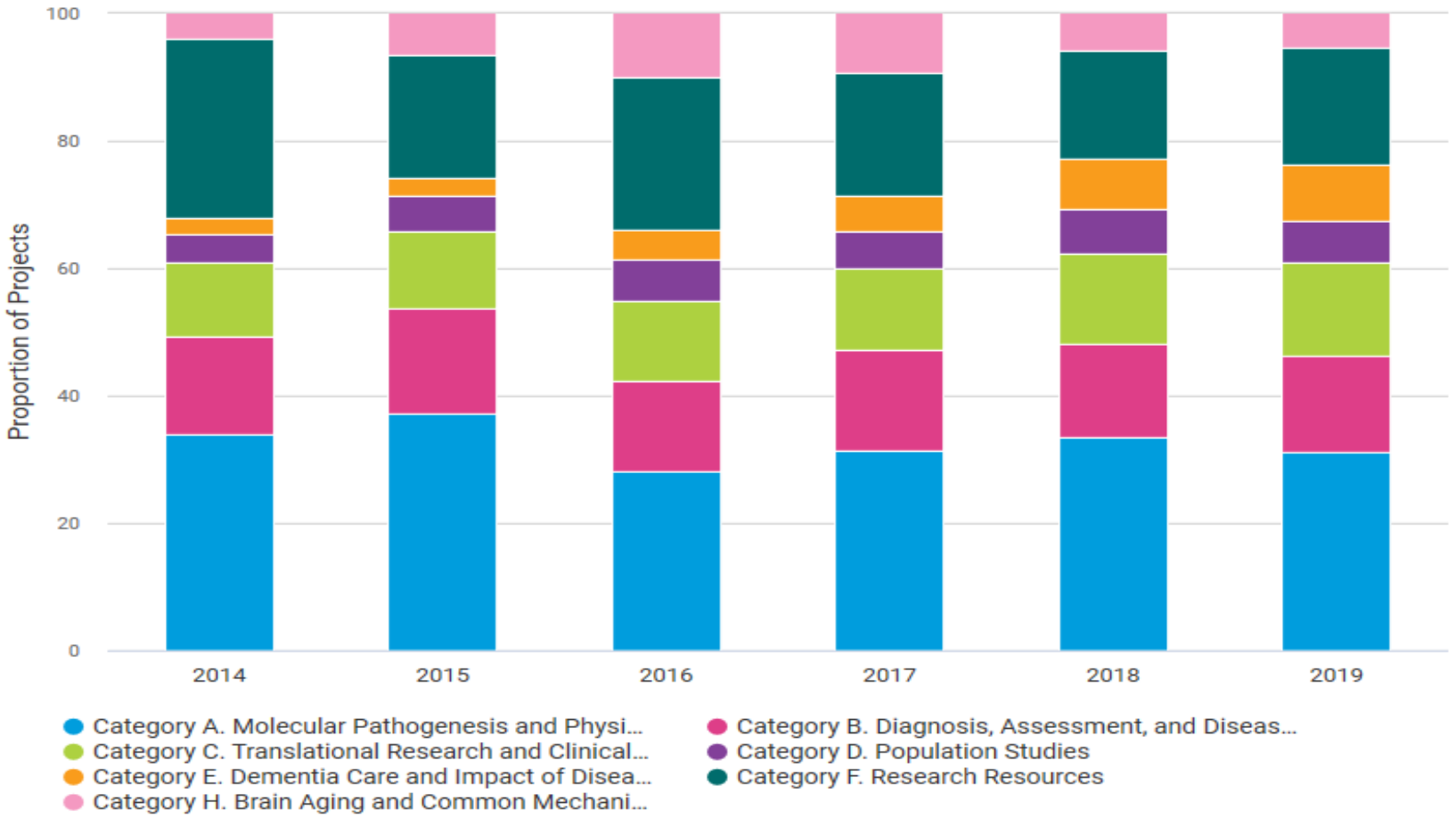
- *Midlife risk factors for cognitive decline, MCI and AD*
- *Resilience and Reserve*
- *Cognitive testing, brain imaging, accelerometry, hearing*

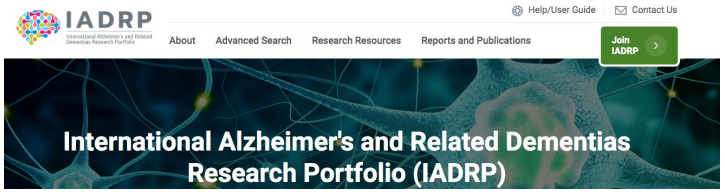
NIH National Institute of Neurological Disorders and Stroke

NIH National Heart, Lung, and Blood Institute

PAR-19-167: Development and Validation of Advanced Mammalian Models for Alzheimer's Disease-Related Dementias (ADRD) (R61/R33 Clinical Trial Not Allowed)

IADRP Project Summary – Proportion of NIA Projects by year across CADRO Categories – 2014 to 2019





https://iadrp.nia.nih.gov

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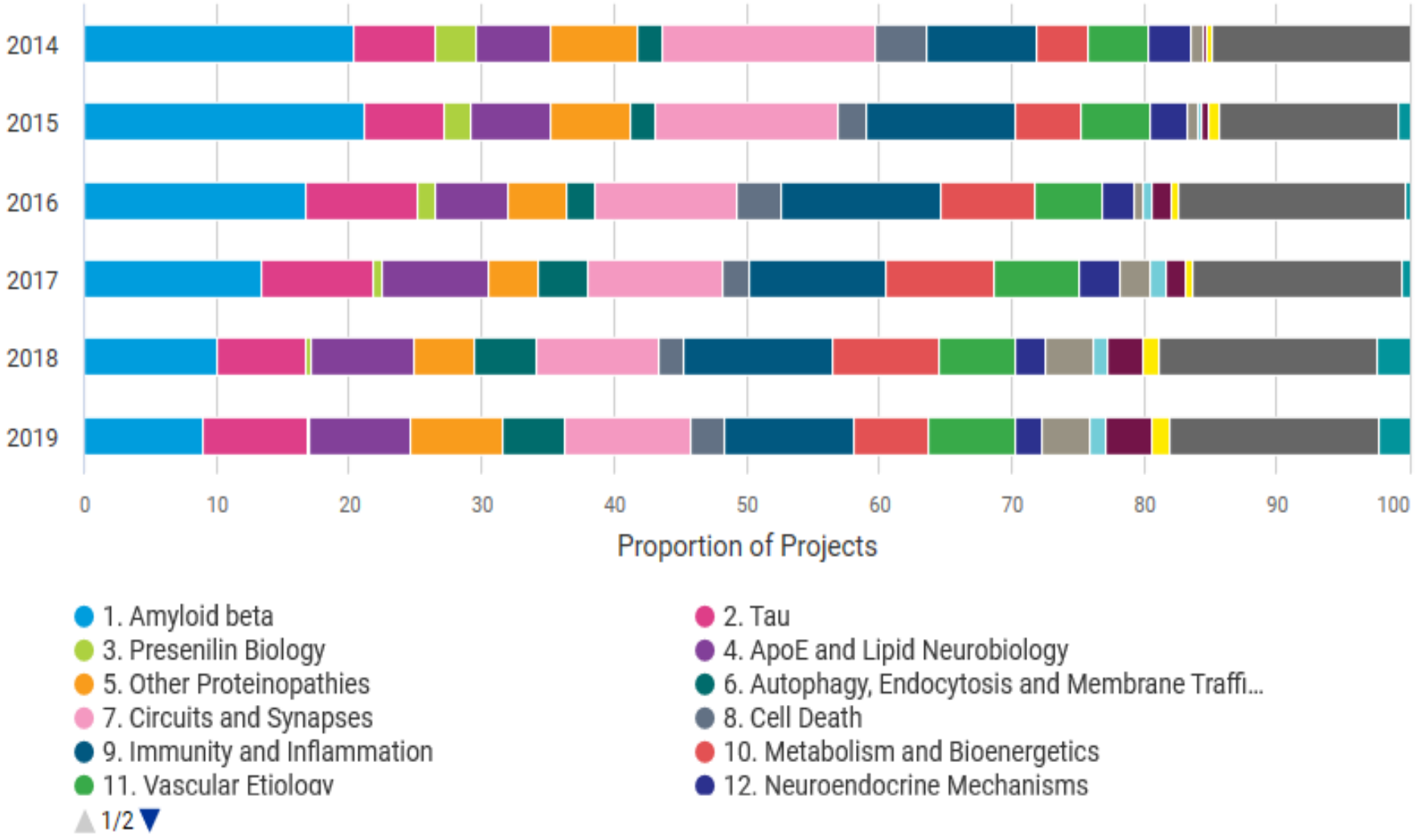
Comparison of NIA Projects by year (2014-2019)
Category A – Molecular pathogenesis



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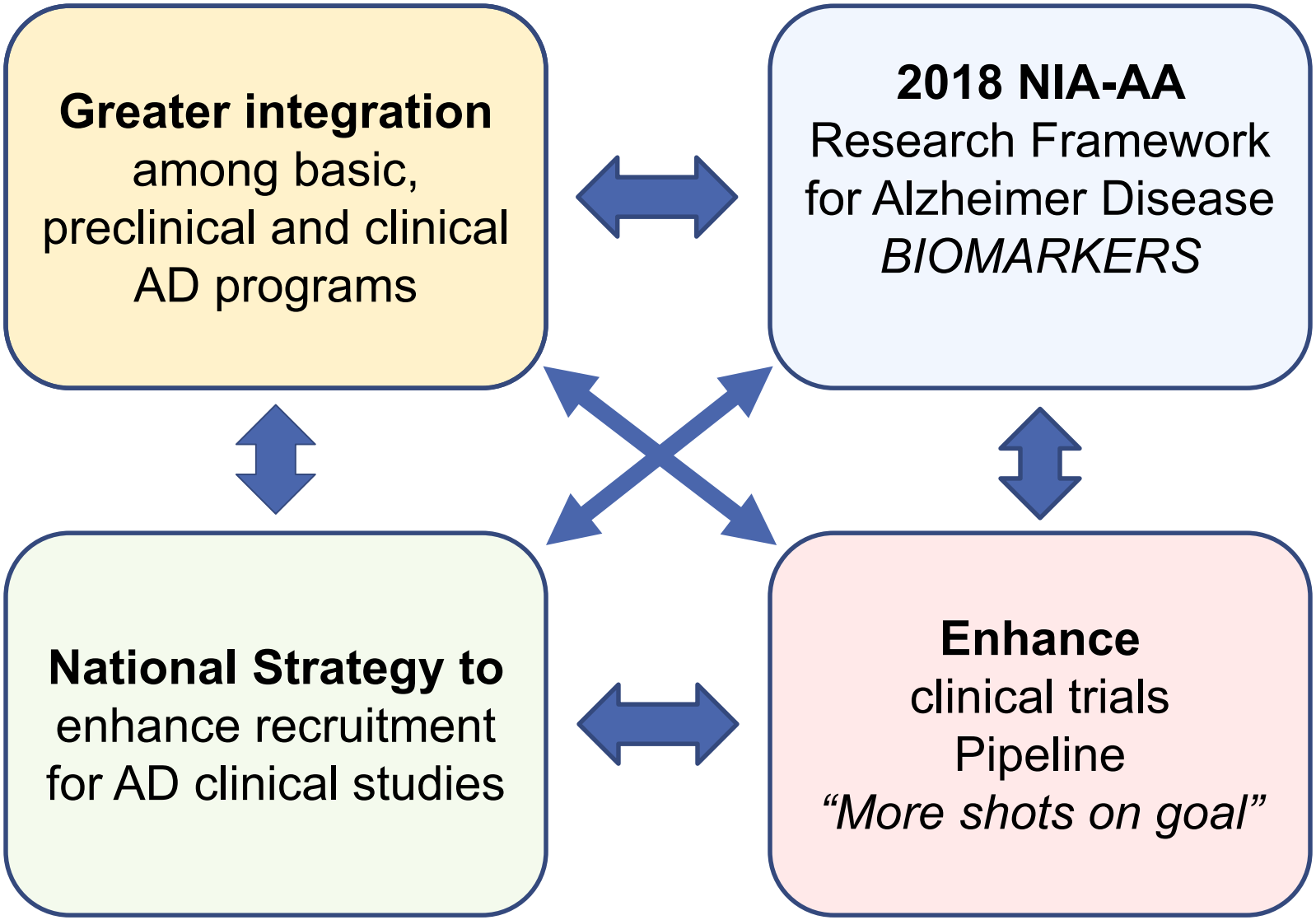
Some NIA-AD Research Priorities



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Understanding AD in the context of Aging

HIV-1, HHV, other pathogens

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

Aging

Proteinopathy

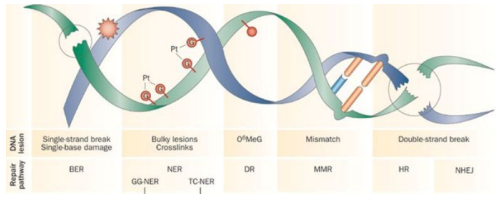
Proteostasis
Mitochondria
Inflammation
Endosomes
Growth Factors
Epigenetics
DNA damage
Senescent cells
Immune surveillance

Abeta
Tau
Synuclein
TDP43
Others

Synapse damage

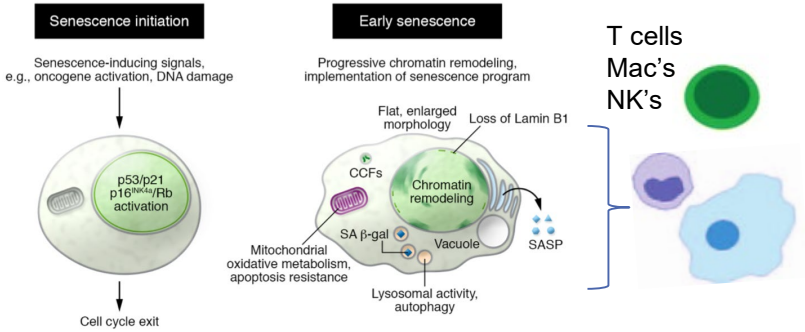
Neurodegeneration

DNA damage



Transposable elements

senescence/immune surveillance



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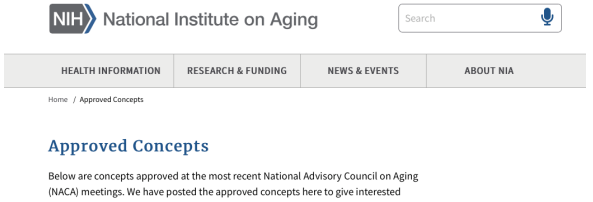
RFA-AG-18-025 Amyloid Protein Polymorphism Grantees Meeting, August 6-7, 2019, Bethesda, MD

NIA Program Director- Austin Yang

- *How many different polymorphs are there for each amyloid (Aß. Tau, a-synuclein and TDP43 amyloid?*
- *Are these polymorphs structurally homogeneous? How can homogeneity be assessed?*
- *How many of the polymorphs occur in vivo and are particular polymorphs specific to disease subtypes?*
- *Can the seeds be stored frozen?*
- *What are the best methods for standardizing the preparation of different amyloid polymorphs?*
- *What are the structural differences between oligomers and fibrils?*
- *Are polymorphs the sole basis of determination of prion-like strains?*

- Need to develop methods and reagents to validate the structure and purity of amyloid aggregates will for authentication of key reagents.
- ***These goals could potentially be best met by the establishment and operation of an amyloid aggregate seed bank.***



Outcomes of this initiatives might include:

1. Develop and analyze the structures of known and unknown oligomers and seeds isolated from both clinical and biological samples.
2. Detailed characterization of oligomers in terms of their sizes, structural homogeneities, morphology, image probe binding and immuno-reactivities.
3. Determine the optimal conditions to maintain, propagate, store and distribute these known and unknown oligomers/seeds.
4. Distribution of imaging, chemical and immunological probes to detect and quantify these oligomers and seeds along with protocols for verification and replication.

Scientific/Research Contact:

Austin Yang, Ph.D.

NIH National Institute on Aging

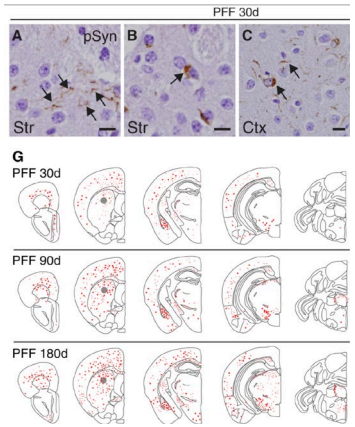
Seeding and spreading of amyloids involved in AD/ADRD

α-syn

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

Kelvin C. Luk, Victoria Kehm, Jenna Carroll, Bin Zhang, Patrick O'Brien, John Q. Trojanowski, Virginia M.-Y. Lee*

www.sciencemag.org SCIENCE VOL 338 16 NOVEMBER 2012



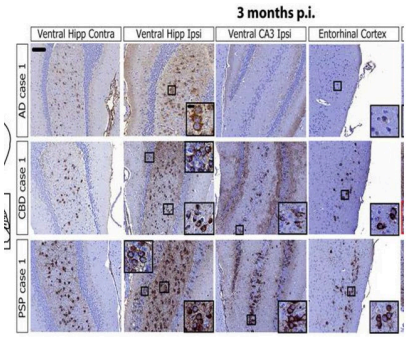
Tau

Neurobiology of Disease

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

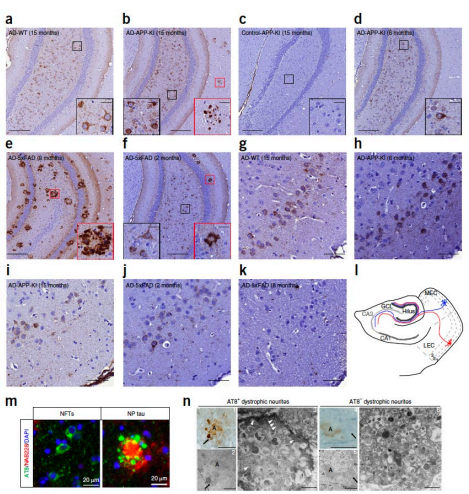


Aβ + Tau (AD)

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

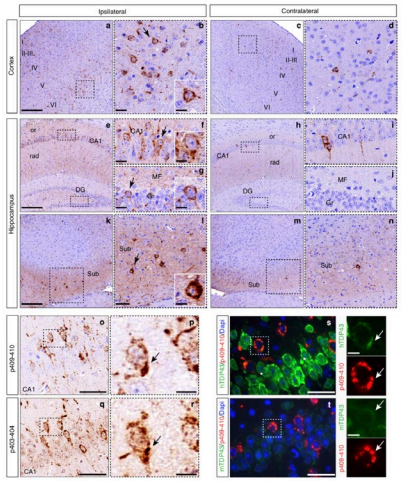
nature COMMUNICATIONS

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]



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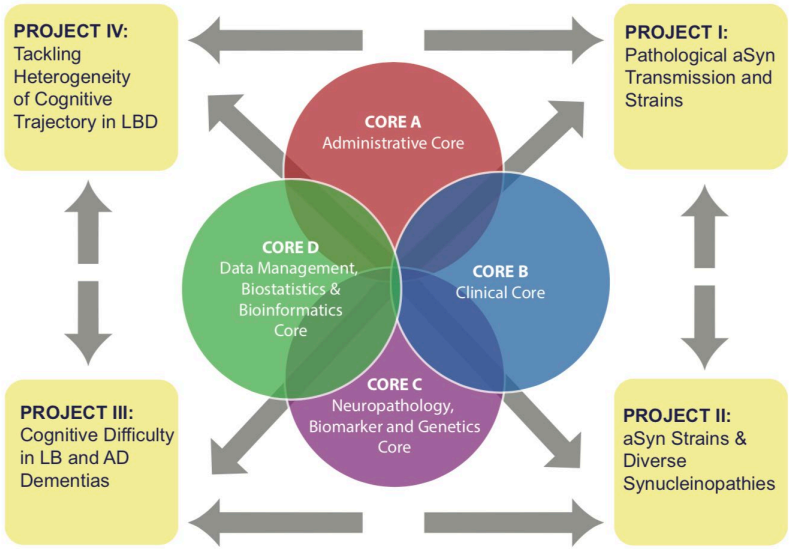
U19 Center On Alpha-synuclein Strains In Alzheimer Disease & Related Dementias

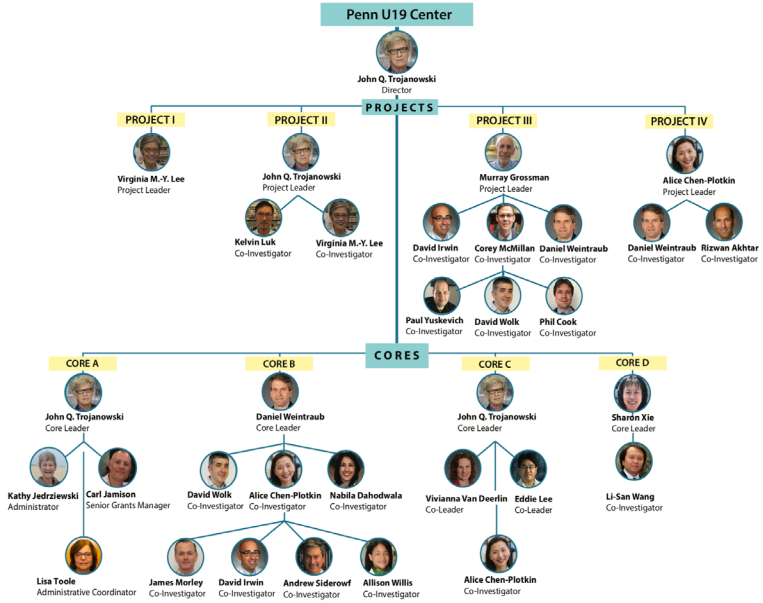
PI: John Q. Trojanowski

NIA Program Director: Lisa Opanashuk and Austin Yang

- Elucidate mechanisms of pathological aSyn-mediated neurodegeneration in AD+aSyn versus pure AD (AD-aSyn) compared with LBD as a function of aging and accumulations of aSyn aggregates as well as tau, Aβ and TDP-43 co-pathologies that influence different clinical manifestations of these disorders.

- Provide standardized PFF's derived from human brains, animal models, expertise.





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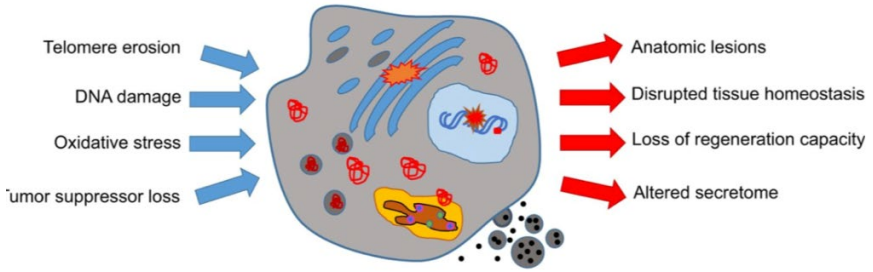
NIA Workshop on Senescence in Brain Aging and AD/ADRD September 18-19, 2019, Bethesda MD

NIA Program Director- Amanda Dibattista



1.Defining senescence in the brain. *Validate markers, promote transparency in methodology and develop a functional definition of senescence.*

2.Tool and resource development. *Better tools to facilitate basic studies on senescence in the brain.*

3.The aging secretome. *The importance of developing defined stages of brain aging—analogous to defined stages of AD.*

Session I. Systemic Factors, Senescence, and Brain Aging.

How does brain senescence compare to the rest of the body?

Could senescent cells be beneficial for the brain?

Session II. Non-Neuronal Cells, Senescence, and Brain Aging.

Is there overlap between biomarkers of senescence and aging?

Can post-mitotic cells (e.g., neurons) undergo a senescence-like phenotype in the human brain?

Session III. Senescence in AD/ADRD.

Does senescence contribute to AD, or vice versa?

Is there a role for targeting a dynamic process like senescence in precision medicine?

RFA-AG-20-025

Understanding Senescence in Brain Aging and Alzheimer's Disease

- Compare senescence **across brain cell types**, including endothelial cells, oligodendrocytes, astrocytes, microglia, neurons, and neural stem cells in aging and AD/ADRD;
- Clarify how the **interaction between brain cell types** contributes to senescent phenotypes during normal aging and AD/ADRD;
- Determine whether senescence **differentially affects brain regions** most vulnerable to neurodegeneration in normal aging; and
- Establish the relationship between **peripheral factors and brain** senescence during normal aging and AD/ADRD.

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NIA-NINDS Workshop on Viruses and Transposable elements in Neurodegenerative disorders

September 23-24, 2019, Bethesda MD

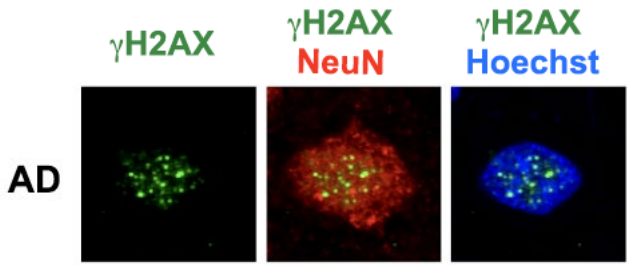
NIH leads- Avi Nath, Jean Tiong K, Alison Yao

Session I. *Mechanisms of Activation of TE in AD/ADRD*

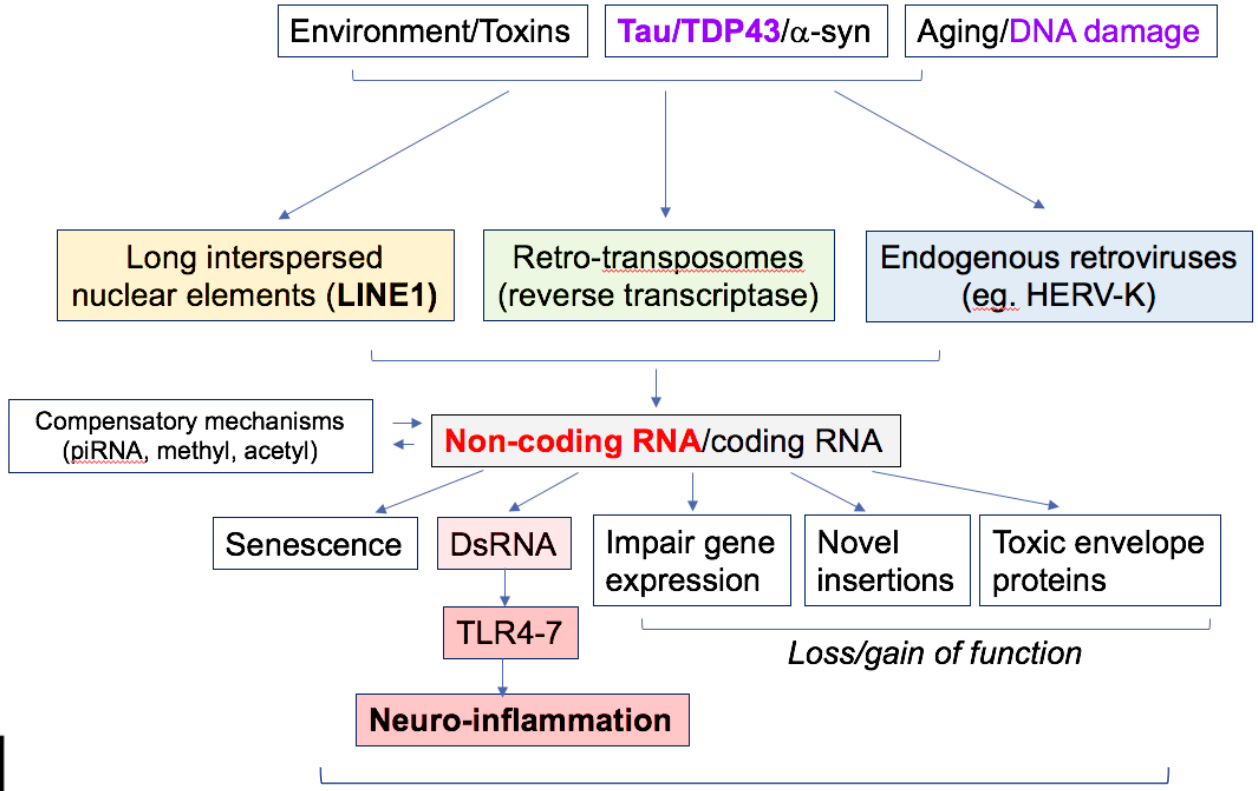
Session II. *Challenges on bioinformatics and sequencing of TE*

Session III. *Retroviral elements in Neurodegeneration*

Session IV. *TE in aging, infections inflammation in neurodegeneration*



Shanbhag et al ANC 2019



Anti-RV inhibitors
ASO's
TLR inhibitors

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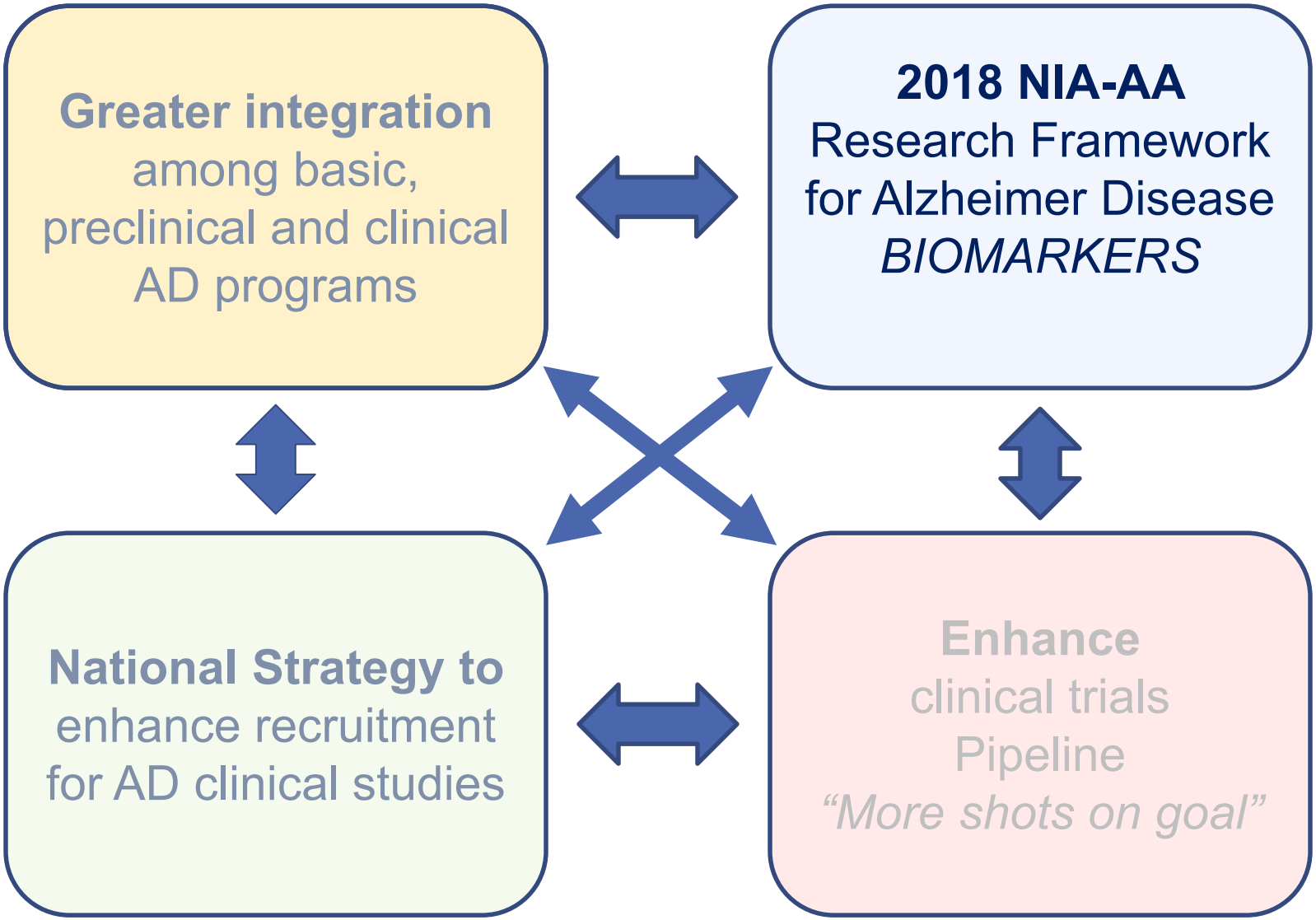
Some NIA-AD Research Priorities



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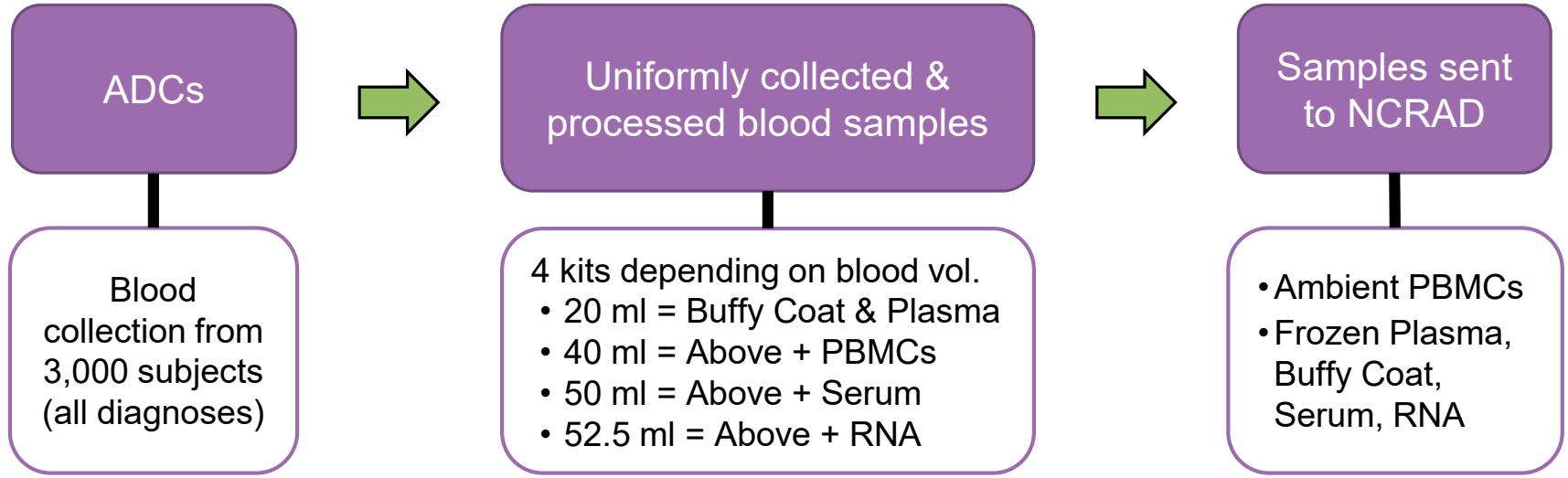
NCRAD Pilot Study: ADC Fluid Biomarker (ADCFB) Initiative



Fast Facts:

- Launched in June 2019
- Want to collect samples from 3,000 subjects by **June 2020**
- 19 Centers currently participating

Benefits to the Centers:

- Standardized collection protocol to facilitate cross center studies
- ADCs paid for sample collection
- Subset of a Center's biospecimens reserved and returned back to Center at no cost
- New grant being written to obtain data from these samples
  - Plasma assays, GWAS
  - Select routine labs (e.g. HbA1C)
- Future opportunities for training/education through the use of these samples

Want to join ADCFB?

Contact NCRAD:

Kaci Lacy
(lacy@iu.edu)
or
Kelley Faber
(kelfaber@iu.edu)

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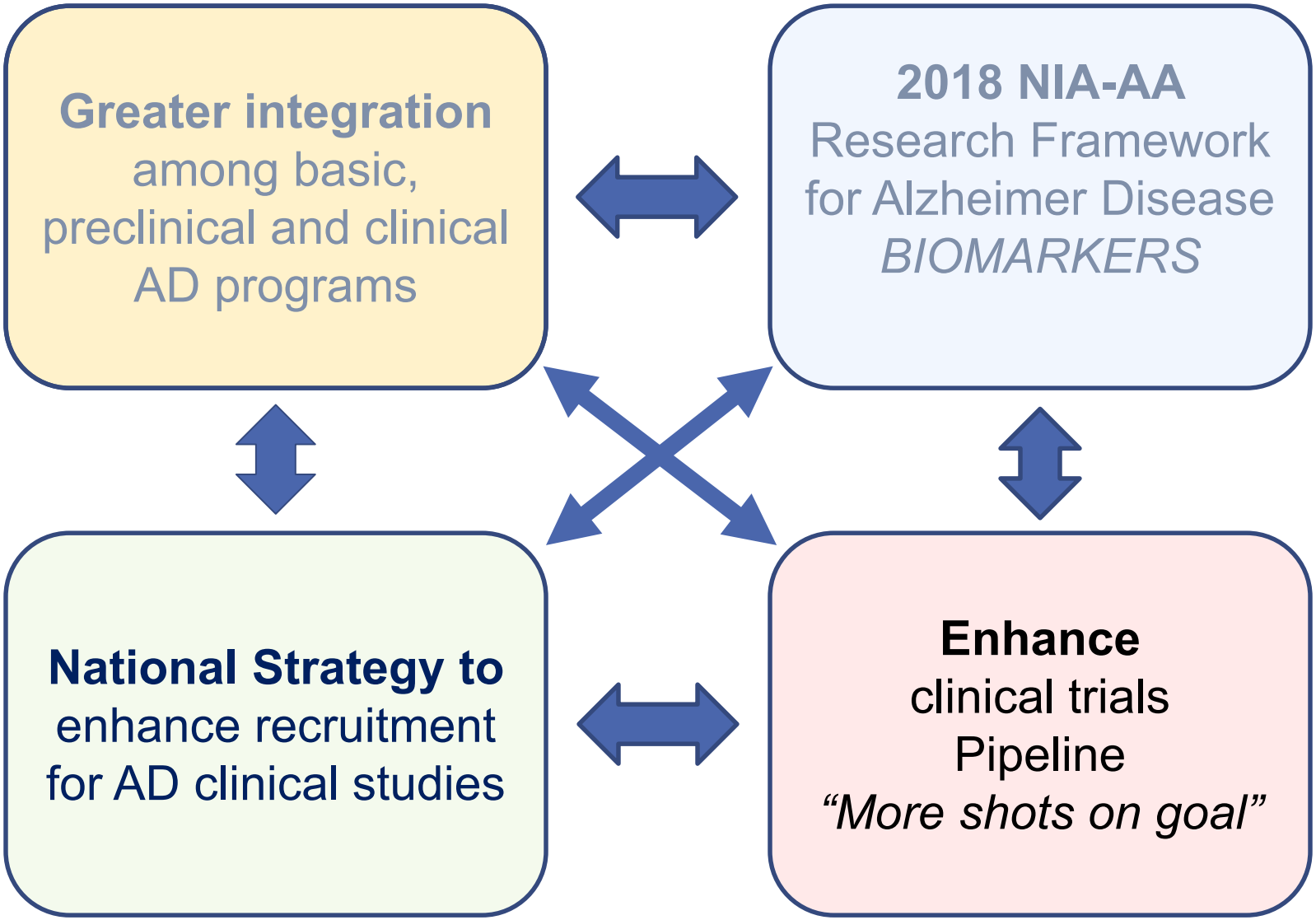
Some NIA-AD Research Priorities



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ACCELERATING MEDICINES PARTNERSHIP (AMP)

AMP-AD Target Discovery and Preclinical Validation Project 2.0 (RFA AG18-013 / RFA AG18-014)

FNIH Foundation for the National Institutes of Health

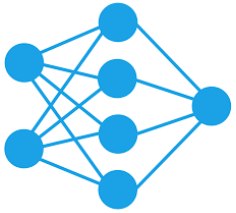
NIA Program Director: Suzana Petanceska

Generate

High-dimensional multi-omic data:
~2,500 human brains;~1000 blood samples

Integrate

Molecular profiling
Predictive Modeling
Experimental validation



Data
Network models
Code

www.synapse.org.ampad

AMP-AD Knowledge Portal

Sage BIONETWORKS Synapse

DATA SHARING

Duke U-Helmholtz U-U of Rotterdam
Icahn Institute at Mount Sinai
Arizona State University
Columbia-Rush
Emory-Baylor
UFL-Mayo-ISB

AMP-AD Data Coordinating Center (U24):
Sage Bionetworks

1. Sustain and expand the capabilities of the AMP-AD Knowledge Portal and the AGORA platform
2. Maximize the use of existing data and generate additional molecular profiling data (human and mouse) for use in target and biomarker discovery
3. Increase the bandwidth and develop new methods for functional validation of novel targets
4. Develop methods for integrative network analyses to discover patient stratification biomarkers and to enable disease sub-classification

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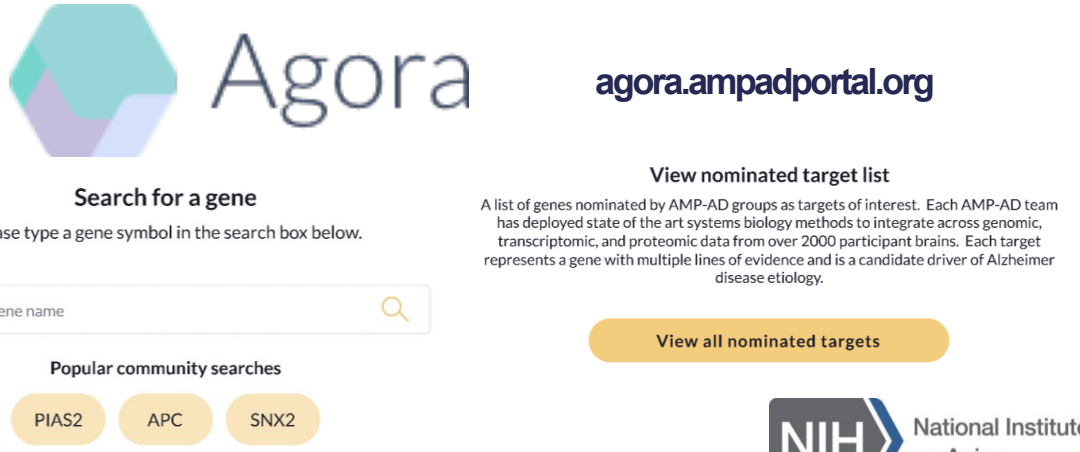
Progress over 4 years:

- Centralized data resource established- AMP-AD portal
- All data sharing deliverables met
- A variety of experimental validation models developed
- Novel biomarker discovery initiated
- Over **500** 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		



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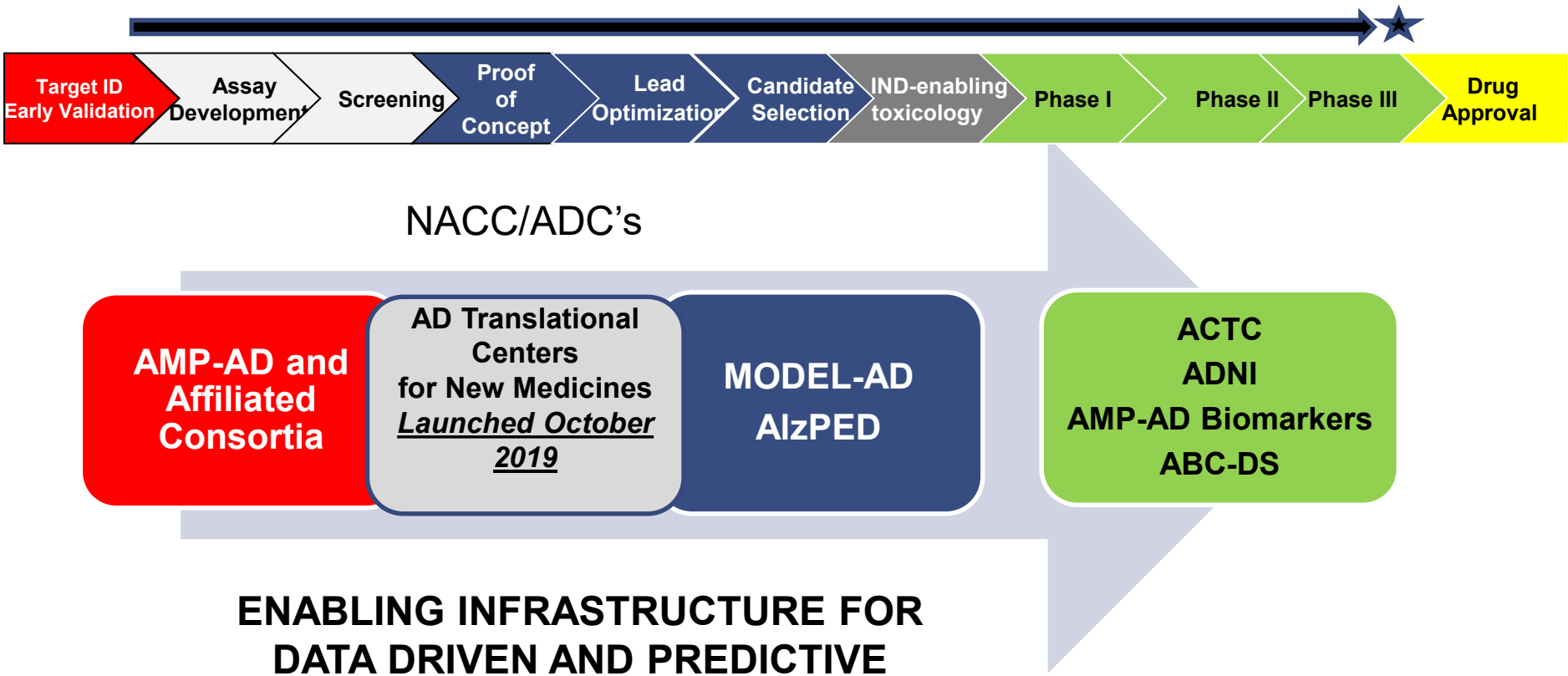
NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline



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AD Centers for Discovery of New Medicines - RFA AG 19-010

Bringing Open Science to AD Drug Discovery:
NIA Launches 2 New Translational Centers: $73M commitment over the next 5 years
https://www.nia.nih.gov/news/nih-funded-translational-research-centers-speed-diversify-alzheimers-drug-discovery

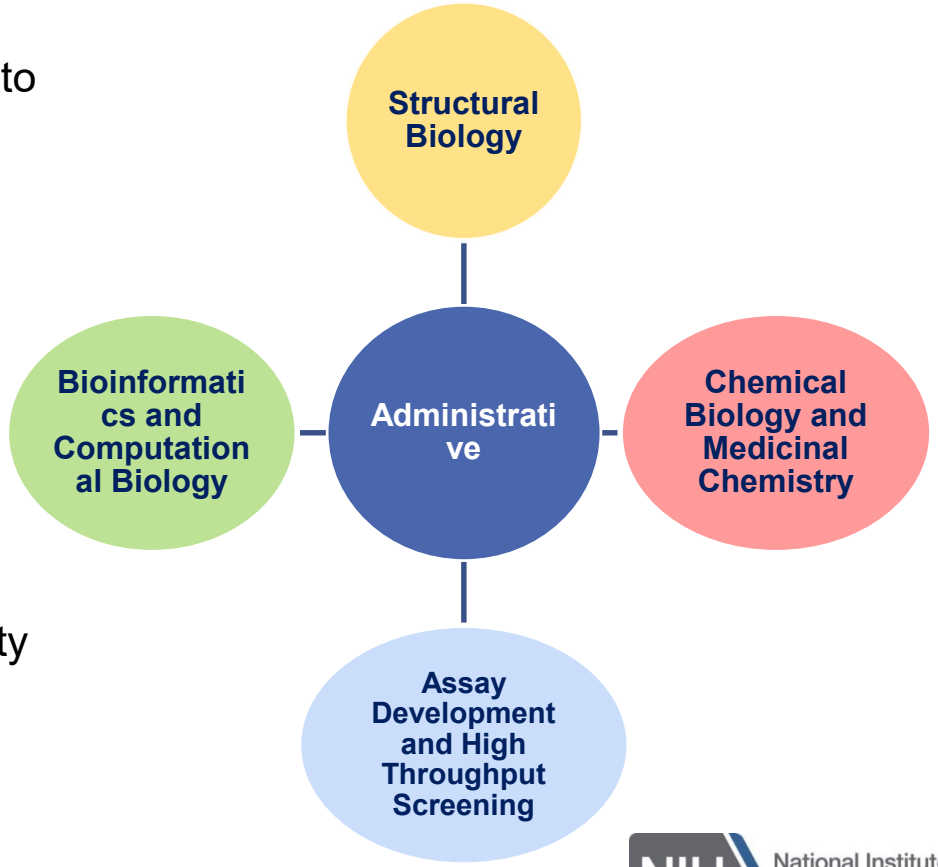
NIA Program Director: Larry Refolo

GOAL: Accelerate the validation of novel candidate targets delivered by AMP-AD through the development of open source tools, reagents, methods and by integrating the enabled targets into drug discovery campaigns.

Open Drug Discovery Center for Alzheimer's Disease (Open-AD)
Allan Levey, Emory University
Lara Mangravite, Sage Bionetworks
Aled Edwards, Structural Genomics Consortium

Alzheimer's Disease Drug Discovery center (ADDD)
Alan Palkowitz and Bruce Lamb, Indiana University and Purdue University

Center Structure



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Concept Approvals:
https://www.nia.nih.gov/approved-concepts

General FOAs:
https://www.nia.nih.gov/research/funding

Alzheimer's Disease and Related Dementias FOAs:
http://www.nia.nih.gov/AD-FOAs

Follow our "Inside NIA" blog:
https://www.nia.nih.gov/research/blog