Advisory Council on Alzheimer's Research, Care and Services

Research Subcommittee: The Journey from Targets to Treatments

DHHS, Washington, DC
January 26, 2018

"Overview on NIA preclinical pipeline"

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

NIH National Institute on Aging

NIA Translational research pipeline for AD and ADRD The Team

Genetics and Epigenetics
ADSP, GCAD, NIGADS, ADGC
Marilyn Miller
millerm@nia.nih.gov

Target Discovery and Validation
AMP-AD Targets, M^{2}OVE-AD-AD, Resilience-AD
Suzana Petanceska
petanceskas@nia.nih.gov

Drug Discovery and Preclinical Drug Development
Drug development (U01), MODEL-AD, AlzPED, SBIR's
Lorenzo Refolo PhD
refolol@nia.nih.gov

Clinical Drug Development
AMP-AD Biomarkers, ABC-DS, ACTC, Clinical trials, DIAN-TU
Laurie Ryan PhD
ryanl@nia.nih.gov

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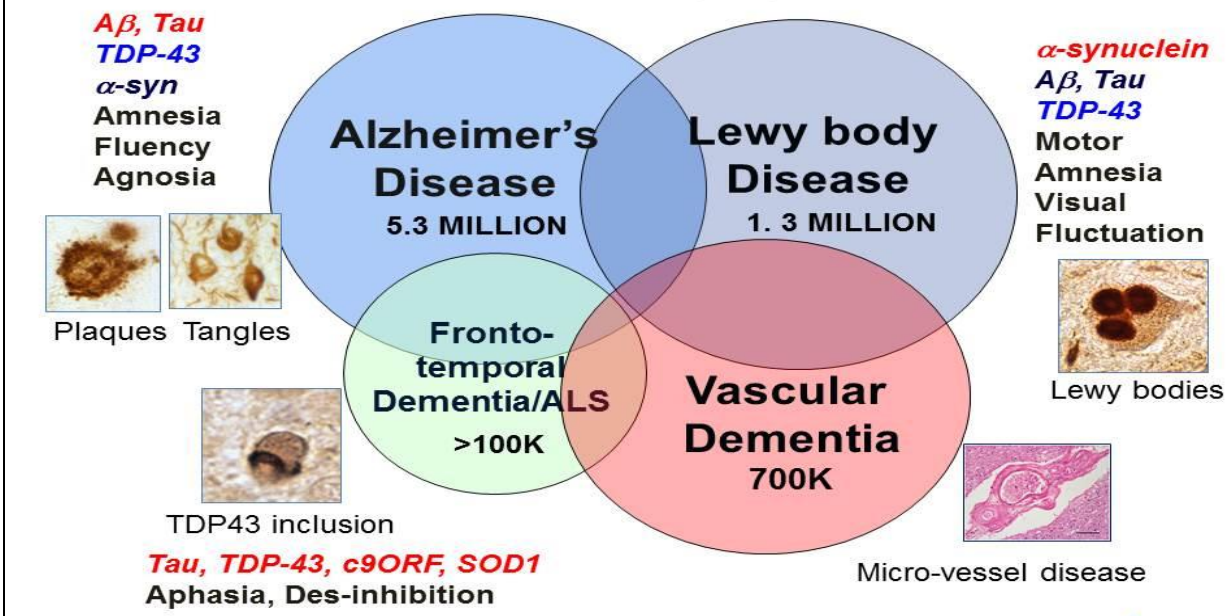
Dementias of the aging population



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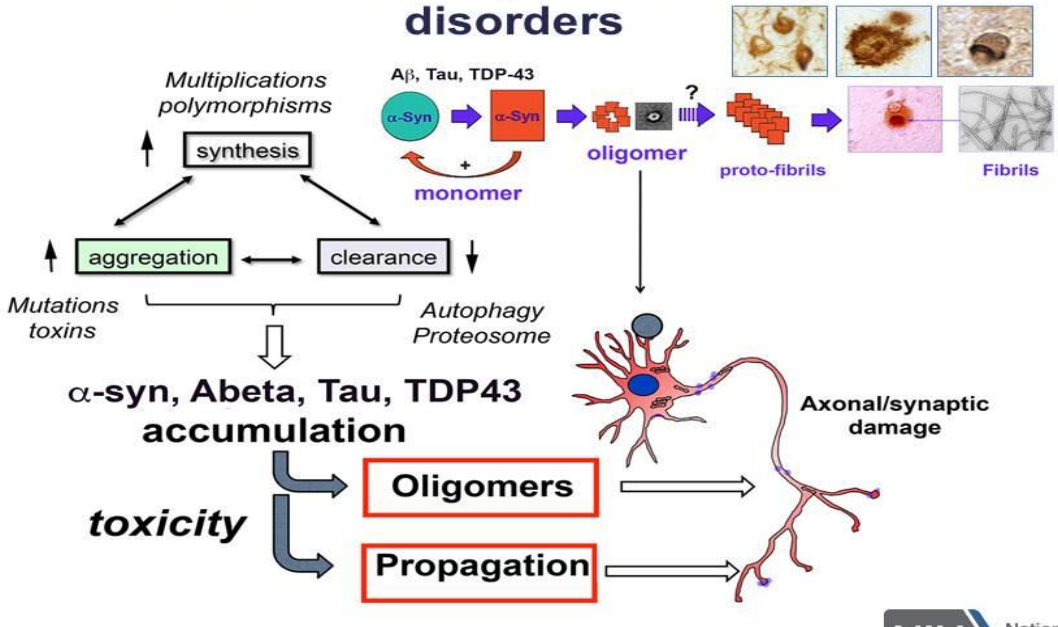
Mechanisms of toxicity in neurodegenerative disorders



Masliah and Valera MDS 2015

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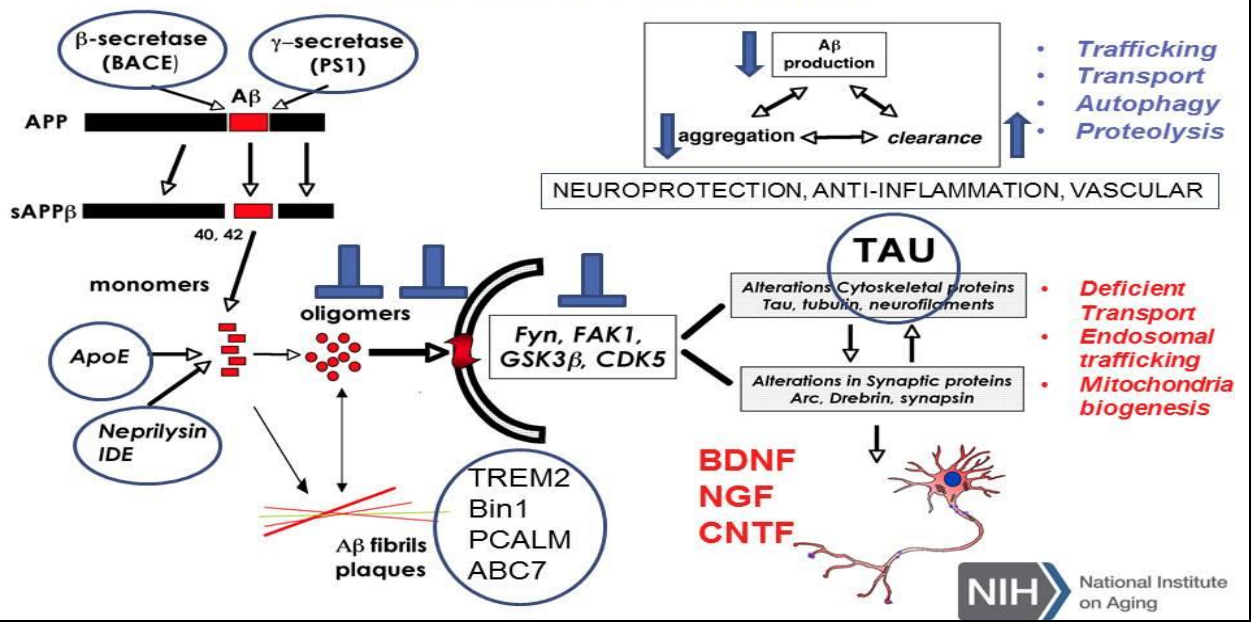
Mechanisms of neurodegeneration in Alzheimer's Disease



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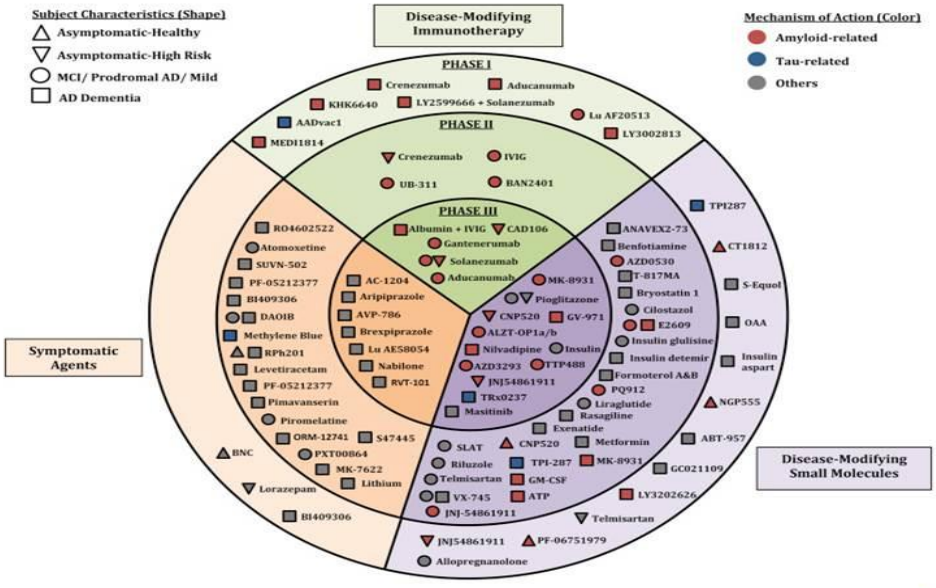
Alzheimer's Disease drug development pipeline-2017



Cummings et al Alz Dem 2017

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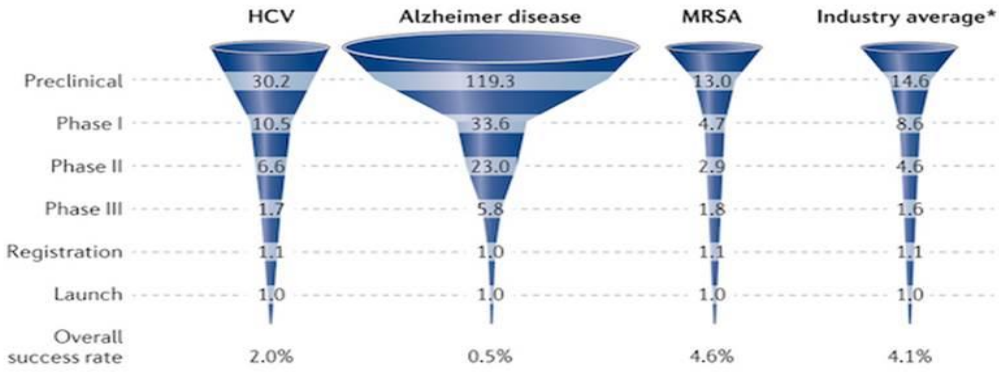
AD pipeline- how does it compare to others?



Nature Reviews | Drug Discovery

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Failure in the Clinic- where does the fault lie?

- **Too late?**
  - Drug interventions are started at the wrong stage of disease
- **Too little?**
  - May need greater drug effects
  - Insufficient dose
  - Lack of BBB penetration
- **Lack of target engagement**
  - Drugs do not engage with intended targets in patients
  - Lack of translatable pharmaco-dynamic biomarkers
- **Wrong target?**
  - We are targeting the wrong pathophysiological mechanisms
  - We need to target networks rather than single molecules
  - Unclear which toxic species to target

Sperling, Jack and Aisen, Science Translational Medicine, 2011

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Key AD Summits Recommendations

- ❑ 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.
- ❑ Support and enable open science.
- ❑ 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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Integrated NIA AD-Drug Development Program

- ADGC/NIAGADS
- ADSP

- SECONDARY PREVENTION TRIALS
- AD BIOMARKERS in DOWN SYNDROME
- AD CLINICAL TRIALS CONSORTIUM

- TRANSLATIONAL CENTERS FOR ANIMAL MODEL RESOURCES
- PRECLINICAL EFFICACY TESTING DATABASE
- TRANSLATIONAL BIOINFORMATICS AND SYSTEMS PHARMACOLOGY
- NEW CROSS-DISCIPLINARY TRAINING PROGRAMS AD/Data Science/Drug Discovery

- SYSTEMS AND NETWORK BIOLOGY

- OPTOGENETICS
- Human iPSC
- Next generation animal models

- INFLAMMATION
- PROTEOSTASIS
- METABOLIC AND VASCULAR ETIOLOGY

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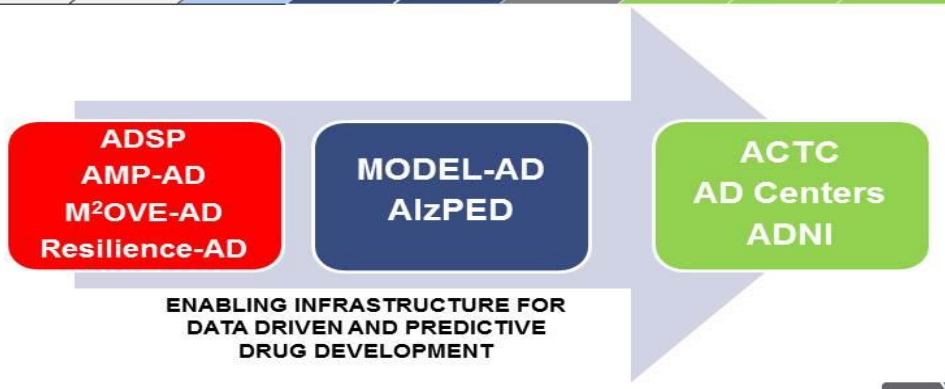
NIA and Trans-NIH translational pipeline for AD and ADRD



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adsp Alzheimer's Disease Sequencing Project

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

1. *New genomic variants* contributing to **Late-Onset AD (LOAD)**
2. *Identify genomic variants* contributing to **protection** against AD
3. *Provide insight* as to why individuals with known risk factor variants **escape developing AD**
4. Examine these factors in **multi-ethnic populations** to identify new pathways

- Associated Programs
  - **ADGC-** *Alzheimer's Disease Genetic Consortium*
  - **GCAD-** *Genome Center for AD*
  - **NIAGDS-** *NIA Genetics of AD storage site*

Now WGS in 10,000 controls and 10,000 AD, 10,000 diverse populations

PLCG2
ABI3
TREM2

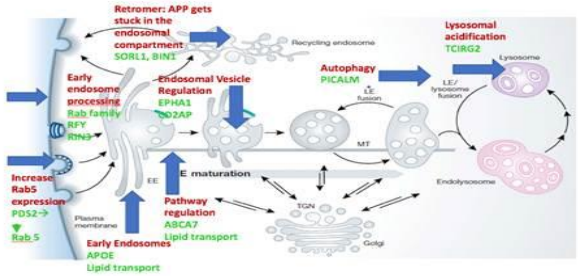

LETTERS

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

PSD2
TCIRG1
RIN3
RUFY1

JAMA Neurology | Original Investigation

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



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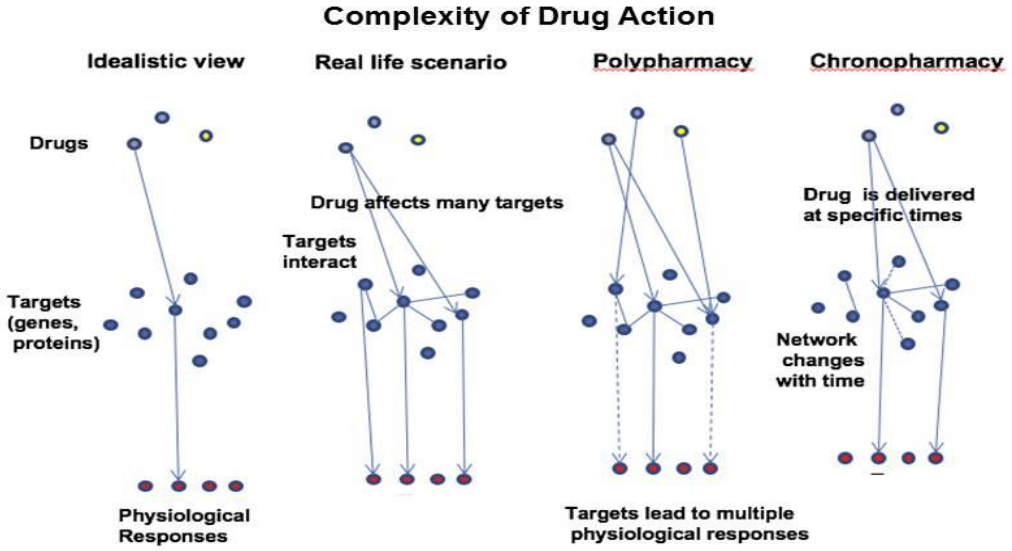
From single target to networks approach for AD-drug development



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ACCELERATING MEDICINES PARTNERSHIP (AMP)

Alzheimer's Disease Program

FNIH Foundation for the National Institutes of Health

Target Discovery and Preclinical Validation Project

NIA Contact: Suzana Petanceska

~2,500 brains

Sage Synapse BIONETWORKS

Clinical
Pathologic
Genomic
Epigenomic
RNAseq
Proteomic

Predictive Modeling

Data Integration

Experimental Validation

AMP-AD Knowledge Portal Sage Bionetworks

Portal launched on March 4, 2015

Rapid and Broad Sharing of Data

6 Academic Teams
– NIA grants –

Biomarkers Project

NIA contact: Laurie Ryan

tau PET imaging
novel fluid biomarkers

A4 DIAN API-ApoE4

Secondary Prevention Trials
anti-amyloid treatment

GAAIN alzheimer's association

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ACCELERATING MEDICINES PARTNERSHIP (AMP)

Progress over 4 years:

- Centralized data resource established
- All data deliverables/milestones met
- Over 100 novel targets discovered; currently undergoing data-driven prioritization for further preclinical validation
- A variety of experimental validation models developed
- Novel biomarker discovery initiated
- **AMP-AD Partners**

NIH National Institute of Neurological Disorders and Stroke · FDA · abbvie · Biogen · GlaxoSmithKline · Lilly · alzheimer's association · Alzheimer's Drug Discovery Foundation · US4against Alzheimer's · FNIH Foundation for the National Institutes of Health

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	

1. P. De Jager, D. Bennett
2. E. Schadt, B. Zhang, S. Gandy, J. Zhu, M. Ehrlich
3. T. Golde, N.Price, N. Ertekin-Taner, S. Younkin,
4. A. Levey, T. Montine, J. Troncoso, D. Geschwind
5. R. Kaddurah-Daouk
6. B. Yakner, L. Huei Tsai

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Secreted peptide *VGF* (non-acronymic)

Specifically expressed in a subpopulation of neuroendocrine cells, and is upregulated by nerve growth factor. The encoded secretory protein also shares similarities with the secretogranin/chromogranin family, however, its exact function is not known. **Multiple VGF peptides reported to be significantly decreased between converting and non-converting MCI patients (ADNI)** *Spellman et al. 2015* - NIH (FNIH) Biomarkers Consortium CSF Proteomics Project Team

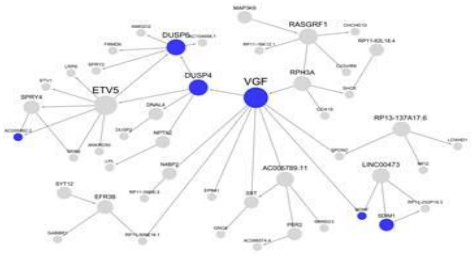
Differential Expression of VGF in Different Regions

VGF - Comparison	BM44 log2FC	BM44 AveExpr	BM44 t	BM44 p	BM44 adj.p	BM6 log2FC	BM36 AveExpr	BM61	BM36 p	BM36 adj.p	BM50 log2FC	BM10 AveExpr	BM101	BM10 p	BM10 adj.p	BM22 log2FC
CDR Demented vs NC	-0.49	4.33	-3.4	0.0073	0.781	-0.219	8.59	-1.55	0.122	0.89	-0.883	3.6	-1.45	0.146	0.854	-0.445
CDR Demented vs Nondemented	-0.357	4.33	-1.18	0.24	0.827	-0.154	8.59	-1.39	0.169	0.896	-0.466	3.6	-1.05	0.0434	0.708	-0.365
CDR NC vs Nondemented	0.143	4.33	0.882	0.41	1	0.062	8.59	0.041	0.808	0.957	0.185	3.6	0.54	0.59	0.957	0.0805
CERAD AD vs NL	-0.36	4.33	-1.7	0.0901	0.856	-0.154	8.59	-1.33	0.184	0.448	-0.341	3.6	-1.93	0.0549	1	-0.41
CERAD Definite+Prob vs NL	-0.444	4.33	-3.7	0.00758	0.443	-0.409	8.59	-3.47	0.0589	0.0678	-0.613	3.6	-3.3	0.00111	0.481	-0.711
PlaqueMean+Prob vs NoProb	-0.418	4.33	-3.82	0.00424	0.501	-0.361	8.59	-3.42	0.0583	0.0673	-0.545	3.6	-3.83	0.000135	0.0881	-0.644
Braak>=4 AD vs NL	-0.369	4.33	-3.63	0.00883	0.756	-0.319	8.59	-3.19	0.0598	0.155	-0.469	3.64	-3.64	0.00074	0.603	-0.595

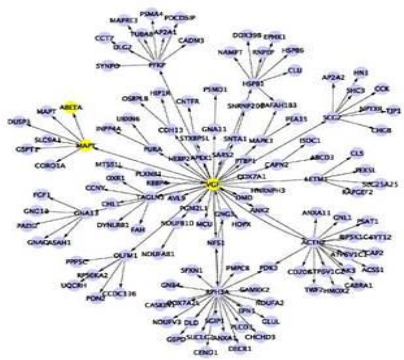
Correlation of VGF with Traits

VGF - trait	BM44 rho	BM44 p	BM44 adj.p	BM6 rho	BM36 p	BM36 adj.p	BM10 rho	BM10 p	BM22 rho	BM22 p	BM22 adj.p
CDR	-0.197	0.00259	1	-0.252	0.000135	1	-0.268	1.22E-05	0.257	-0.217	0.000727	1
CERAD	-0.184	0.00514	1	-0.204	0.00215	1	-0.234	0.000148	1	-0.269	2.38E-05	0.501
PlaqueMean	-0.175	0.00784	1	-0.215	0.00115	1	-0.261	2.16E-05	0.453	-0.286	6.92E-06	0.137
BraakScore	-0.305	3.32E-06	0.0698	-0.291	1.68E-05	0.341	-0.319	2.73E-07	0.00573	-0.384	1.71E-09	3.59E-05

Gene Causal Network



Protein Causal Network



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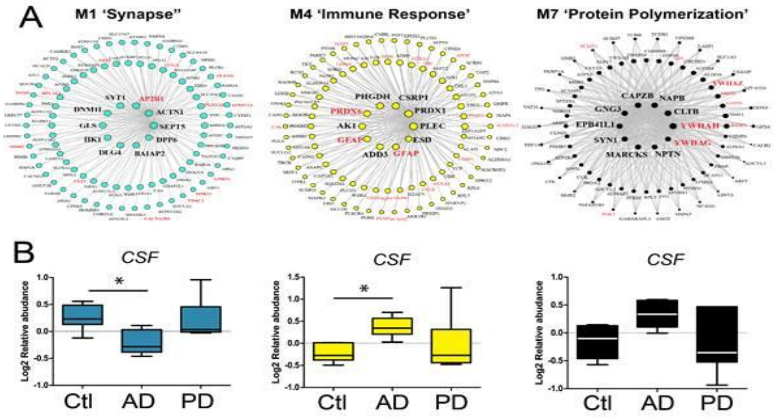
Protein Networks as Novel Biomarkers

AMP-AD Emory Team
PI: Allan Levey



Hub proteins from brain networks are found in human CSF and discriminate AD from control and PD patients. Hub proteins are defined as proteins with the highest intra-modular connectivity (i.e., proteins that are most central within the module) in the M1, M4 and M7 modules. Red symbols are proteins that were also identified in the CSF.

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Building on and expanding the AMP-AD Target Discovery Project

M²OVE-AD
Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease

NIA contact- Suzana Petanceska

- ~$30 million over 5 years to support cross disciplinary research teams:
- 5 research teams will generate various "omics" data from brain and peripheral fluids from individuals participating in several **natural history and population studies**
- Predictions about molecular mechanisms will be explored in **animal models** (AD models and models of vascular/metabolic risk factors).
- Goals and deliverables:
  - rapid and broad sharing of data
  - deeper understanding of the phenotypes of risk and the mechanisms linking vascular risk factors, cerebrovascular disease and AD
  - new disease-relevant therapeutic targets for prevention
  - molecular signatures that can be non-invasively measured and used for patient stratification

A collaboration between NIA and NINDS

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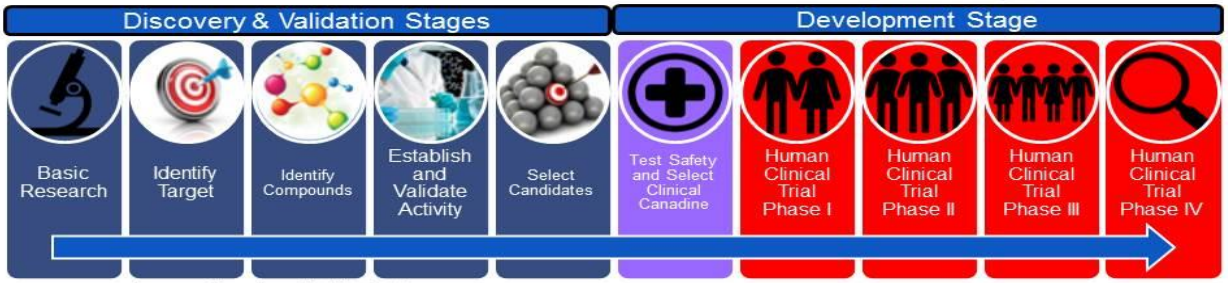
NINDS ADRD Translation Research Initiatives

In collaboration with NIA

NINDS contact: Roderick Corriveau (roderick.corriveau@nih.gov)

TAU CWOW	M²OVE	MarkVCID	Planning Grant -
VCID	FTD	LBD Biomarkers	Phase III Clinical
Mechanisms	Consortium	DetectingCID	Trials for LBD



----------Investigator Initiated----------

----------Blueprint Neurotherapeutics ----------

----------CREATE Bio----------

---------IGNITE---------

----------Exploratory Trial---------

----------NeuroNEXT----------

-Phase 3 Clinical Trial-

NIH National Institute of Neurological Disorders and Stroke

Some examples of NIA pipeline for AD and ADRD

AD Drug Development Program

PI	Institution	Project or Target
Tuszynski M	UCSD	BDNF Gene Delivery
Catalano C	Cognition Therapeutics, Inc	Receptor Antagonist CT0093
Lin CL	OSU	Activators of glutamate transporter EAAT2
Wagner S	UCSD	Soluble Gamma-Secretase Modulators
Ives J	Acumen Pharmaceuticals, Inc.	Amyloid-Beta Oligomer Selective Immunotherapy
Van Eldik L	U Kentucky	MW151, block cytokine
Agadjanyan M	Inst of Molecular Med	AV1959 anti-Amyloid vaccine
Thota G	Emory U	EP2 receptor antagonists
Watterson DM	Northwestern U	MAPK Inhibitors
Brinton R	USC	Allopregnanolone

Blueprint, Drug Discovery for CNS, and Preclinical Drug Development

PI	Institution	Project or Target
Rosenzweig-Lipson S	AgeneBio	GABA-A α5 agonists
Brunden K	U Penn	Microtubule-stabilizers for tauopathy
Zhang, S	VCU	Aβ oligomerization inhibitors
Pahan, K	Rush U	HEX, OCT and 3-hydroxy, 2, 2-dimethyl butyrate (HMB)
Bitan G	UCLA	'Molecular Tweezers' CLR01 as
Witt K	Southern Illinois U	Somatostatin-based therapeutics
Varghese J	UCLA	ApoE4-targeted therapeutics
LU K	Beth Israel Deaconess	pT231-tau mAbs
Stutzmann G	Rosalind Franklin Univ	Ryanodine Calcium Channels
Sung Ok Yoon	OSU	JNK3 inhibitors
Diamond M	Wash U	Anti-Tau Antibodies
Cai J	USF	anti-Aβ aggregation peptides

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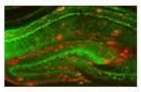
NIA Translational Center for Animal Model Resources
MODEL-AD

NIA contact, Larry Refolo



- **RFA AG16-014 (U54): Indiana University/Jax Labs/Sage Bionetworks (Bruce Lamb, PI) and UCI (Frank LaFerla)**
  - **Maximize human datasets to identify putative variants, genes and biomarkers for AD**
  - **Generate, phenotype and validate the next generation of Tg mouse models of AD**
    (50 new models over 5 years; deep, longitudinal phenotyping)
  - **Develop a preclinical testing pipeline that implements rigorous study design and data analysis**
  - **Make data and animal models available to the research community for use in therapy development without IP barrier.**

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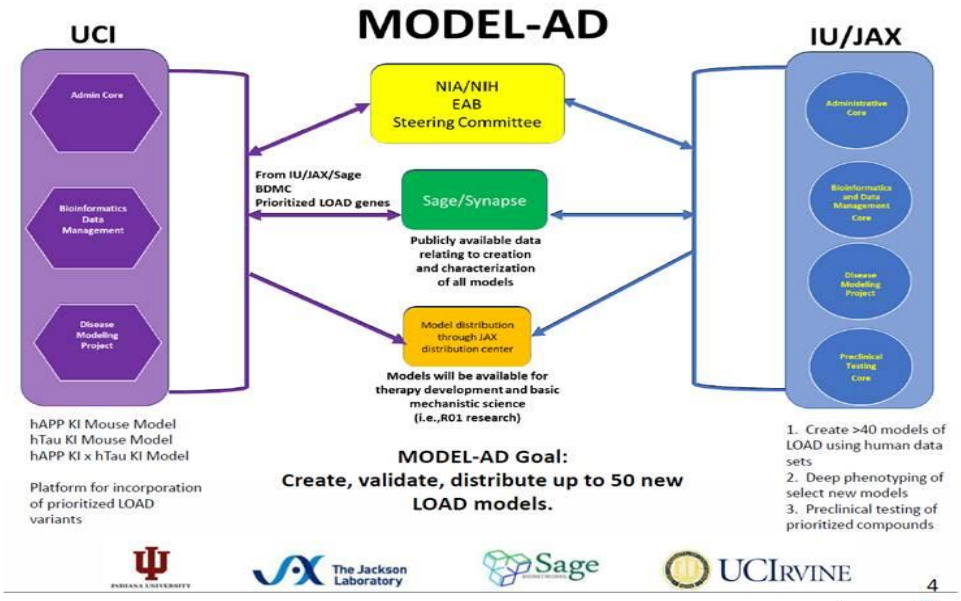
NIA Translational Center for Animal Model Resources



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Alzheimer's Disease Preclinical Efficacy Database

NIA contact, Larry Refolo

GETTING STARTED

- How to Enter Data
- Frequently Asked Questions
- Search Guides
- AlzPED Team
- Glossary of Terms

REPRODUCIBILITY GUIDELINES

- NIH Principles and Guidelines for Reporting Preclinica
- ARRIVE Guidelines (National Centre for the Replacem Refinement & Reduction of Animals in Research)
- Additional Reproducibility Guidelines

Current AlzPED Members:
NIA
NIH Library
ADDF
Alzheimer Association
Center for Open Science

https://alzped.nia.nih.gov/

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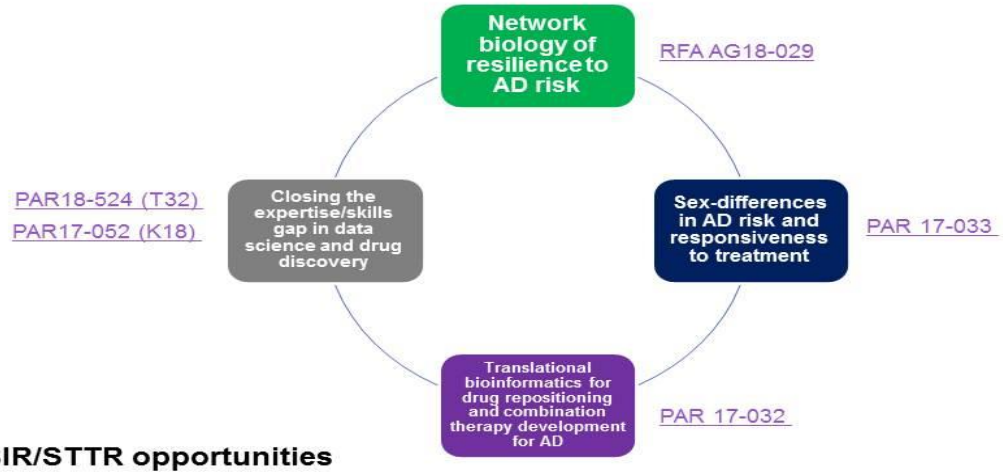
New* NIA funding opportunities for translation research



SBIR/STTR opportunities

- Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R41/R42/R43/R44)
- Tools for Clinical Care and Management of Alzheimer's Disease (AD) and its Comorbidities (R41/R42/R43/R44)
- Development of Socially-Assistive Robots (SARs) to Engage Persons with Alzheimer's Disease (AD) and AD-Related Dementias (ADRD), and their Caregivers (R41/R42/R43/R44)

https://www.nia.nih.gov/research/grants-funding/small-business-innovation-research-and-technology-transfer-programs

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Next steps toward developing an AD Translational pipeline

Attaining the Goal of Precision Medicine for AD

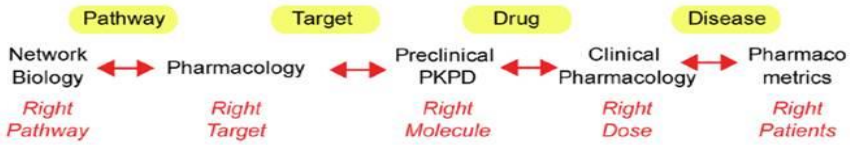

Figure 6. Areas in which QSP models will impact drug discovery. An alternative view of the impact of combined modeling and measurement approaches on key steps in drug discovery which range from identifying the right target to treating the right patients. (Courtesy of Piet Van Der Graaf, Pfizer Inc.)

www.ScienceTranslationalMedicine.org 30 November 2011 Vol 3 Issue 111

COMMENTARY

ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

Reisa A. Sperling,[1]* Clifford R. Jack Jr.,[2] Paul S. Aisen[3]

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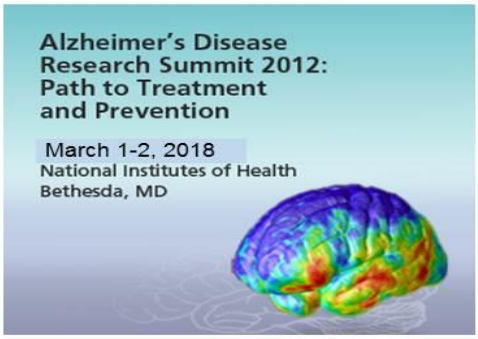
Alzheimer's Disease Summit Program- 2018



The 2018 Summit will build on the foundation laid by the NIH AD Research Summits held in 2012 and 2015. It will feature progress towards achieving the AD research implementation milestones and continue the development of an integrated multidisciplinary research agenda necessary to **enable precision medicine for AD treatment and prevention.**

- ❑ 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**
- ❑ Understanding the **Impact of the Environment to Advance Disease Prevention**
- ❑ Advances in **Disease Monitoring**, Assessment and Care
- ❑ Building an **Open Science Research Ecosystem** to Accelerate AD Therapy Development

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THANKS

January 26, 2018 -- Advisory Council Meeting #27

The meeting was held on Friday, January 26, 2018, in Washington, DC. The Research Subcommittee took charge of this meeting's theme, focusing on the process from targets to treatments. The Council heard speakers on the preclinical pipeline, the clinical trial pipeline, and the industry perspective. The meeting also included discussion of a driver diagram to guide the Council's future work, updates and a report from the October Care Summit, and federal workgroup updates. Material available from this meeting is listed below and is also available at https://aspe.hhs.gov/advisory-council-alzheimers-research-care-and-services-meetings#Jan2018.

Comments and questions, or alerts to broken links, should be sent to napa@hhs.gov.

General Information

Agenda	[HTML Version] [PDF Version]
Meeting Announcement	[HTML Version] [PDF Version]
Meeting Summary	[HTML Version] [PDF Version]
Public Comments	[HTML Version]

Handouts

Care Summit Report Themes	[PDF Version]
NAPA Driver Diagram Draft Examples	[PDF Version]
Outline for Care Summit Final Report	[PDF Version]

Presentation Slides

AbbVie's R&D Vision for Alzheimer's Disease	[HTML Version] [PDF Version]
Care Summit Report	[HTML Version] [PDF Version]
Clinical Subcommittee Update	[HTML Version] [PDF Version]
Initiatives, Partnerships and Collaboration to Help Patients with the Highest Unmet Need: Dominantly Inherited Alzheimer's Disease Trials Unit (DIAN-TU) as a Case Example	[HTML Version] [PDF Version]
Long-Term Services and Supports Committee Update	[HTML Version] [PDF Version]

NAPA Driver Diagram	[HTML Version] [PDF Version]
Overview of the Clinical Trial Pipeline for AD	[HTML Version] [PDF Version]
Overview on NIA Preclinical Pipeline	[HTML Version] [PDF Version]
Participating in an Alzheimer's Clinical Study: Perspectives on Involvement of a Person Living with Dementia and Her Study Partner	[HTML Version] [PDF Version]
Progress Since October	[HTML Version] [PDF Version]
Research Progress on Alzheimer's Disease and Related Dementias	[HTML Version] [PDF Version]
Research Subcommittee Agenda: The Journey from Targets to Treatments	[HTML Version] [PDF Version]

Videos

Updates since October meeting	[Video]
NAPA Driver Diagram	[Video]
Federal Updates	[Video]
Public Comments	[Video]
Research Subcommittee Agenda	[Video]
Care Summit Update	[Video]

Last Updated: 06/09/2018