

# AMP-AD: Target Discovery and Preclinical Validation

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# AMP: Alzheimer's Disease (AD)

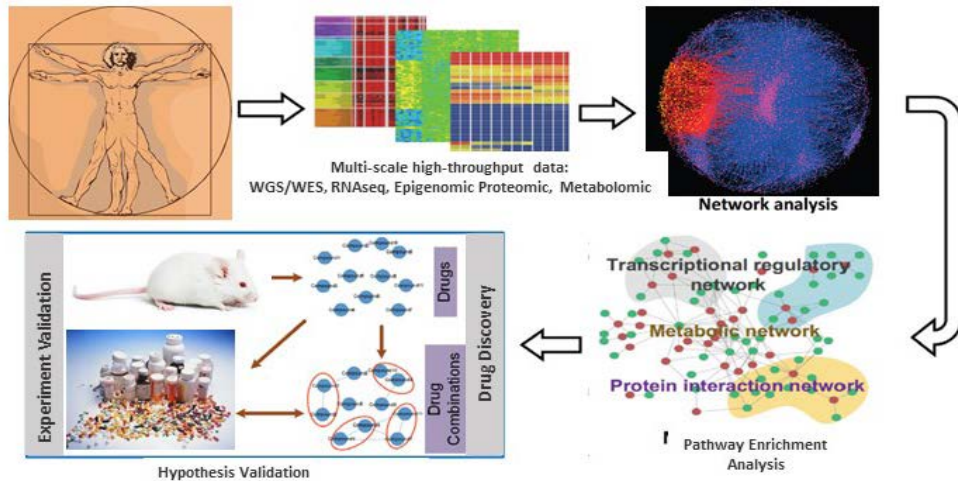
## TARGET DISCOVERY PROJECT:

Apply a systems biology approach to discover and validate the next generation therapeutic targets in an open science forum:

- ❑ Integrate multi-omics human data from well phenotyped cohorts to build network models of disease, followed by early target validation in multiple cell-based and preclinical models.
- ❑ Develop a data portal to enable rapid and broad sharing of data and analytical results.

### AMP-AD Target Discovery Project

-An Open Science Discovery Engine for Data Driven Drug Development-



AMP-AD Knowledge Portal

[www.synapse.org.ampad](http://www.synapse.org.ampad)



ACCELERATING MEDICINES PARTNERSHIP (AMP)

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ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

## 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/R01 grants –

Data  
Network models  
Code



[www.synapse.org.ampad](http://www.synapse.org.ampad)

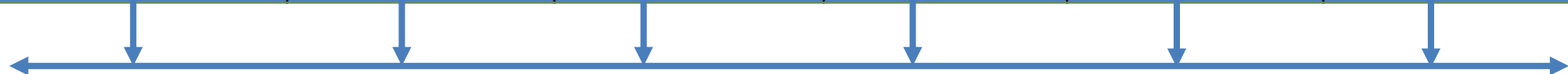
AMP-AD  
Knowledge  
Portal



# ACCELERATING MEDICINES PARTNERSHIP (AMP)

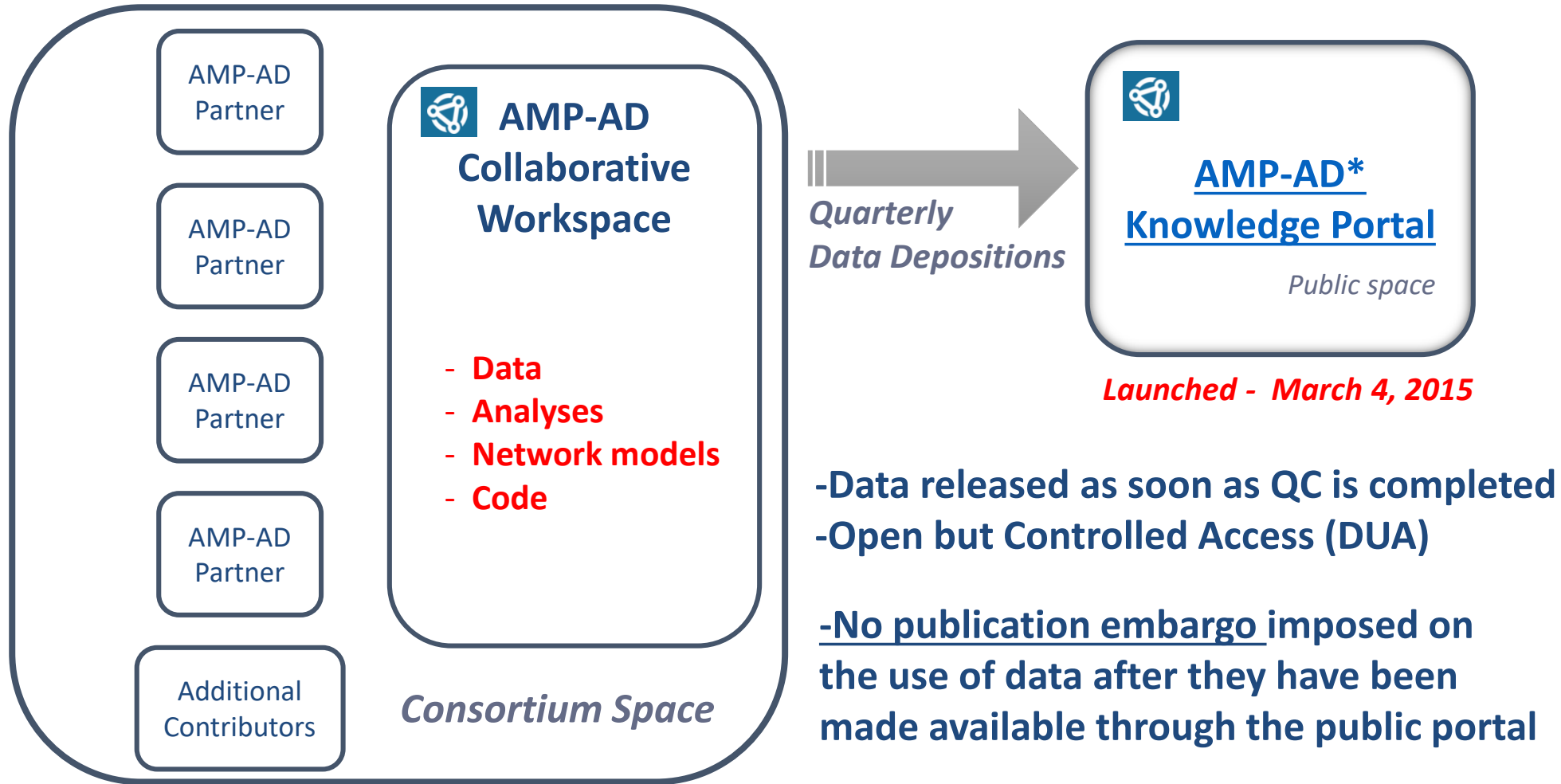
## ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

<b>Academic Teams</b>	<b>Broad-Rush</b>	<b>Mt Sinai</b>	<b>UFL/ISB /Mayo</b>	<b>Emory</b>	<b>Duke</b>	<b>Harvard/MIT</b>
<b>Principal Investigators</b>	<b>De Jager, Bennett</b>	<b>Schadt, Zhang</b>	<b>Golde, Price, Taner</b>	<b>Levey</b>	<b>Kaddurah-Daouk</b>	<b>Yankner, Tsai</b>
<b>Human Data source</b>	<b>ROSMAP</b>	<b>Mt Sinai Brain Bank</b>	<b>Mayo Brain Bank</b>	<b>All</b>	<b>ADNI</b>	<b>ROSMAP</b>
<b>Molecular Data Types</b>	<b>DNA-M, H3K9Ac, miRNA, RNAseq</b>	<b>RNAseq Whole exome seq</b>	<b>RNAseq</b>	<b>All Proteomics</b>	<b>Metabolomic</b>	<b>Txpn Factors</b>
<b>Target Identification</b>	<b>Bayesian networks</b>	<b>Bayesian networks</b>	<b>Innate Immunity Networks</b>	<b>Bayesian Networks</b>	<b>Systems analysis</b>	<b>REST</b>
<b>Validation</b>	<b>SRM Proteomics, iPSCs lines</b>	<b>iPSC, drosophila, mouse</b>	<b>mouse</b>	<b>Mouse, cell culture, drosophila</b>	<b>NA</b>	<b>mouse</b>



**Data Enablement and Coordination of Collaborative Analyses:  
Sage Bionetworks, Principal Investigator – Lara Mangravite**

# CENTRALIZED DATA RESOURCES



\*AMP-AD Knowledge Portal – [www.synapse.org/ampad](http://www.synapse.org/ampad)

# Quarterly Public Data Releases

**60,000 files** shared by **42 investigators** across **22 institutions** representing samples from **36 research studies**



**1309 total users\*** with **55 new users** per month

[www.synapse.org/ampad](http://www.synapse.org/ampad)

## What's in the portal?

15 human studies

3 rat models

22 model system studies

7043 human samples

10 drosophila models

17 mouse models

14 diagnoses

15 genomic data modalities

13 human cell models



# AMP-AD Knowledge Portal

## Rich Multi-Omics and Clinical Data from Antemortem Cohorts – ROS/MAP

### Genomics

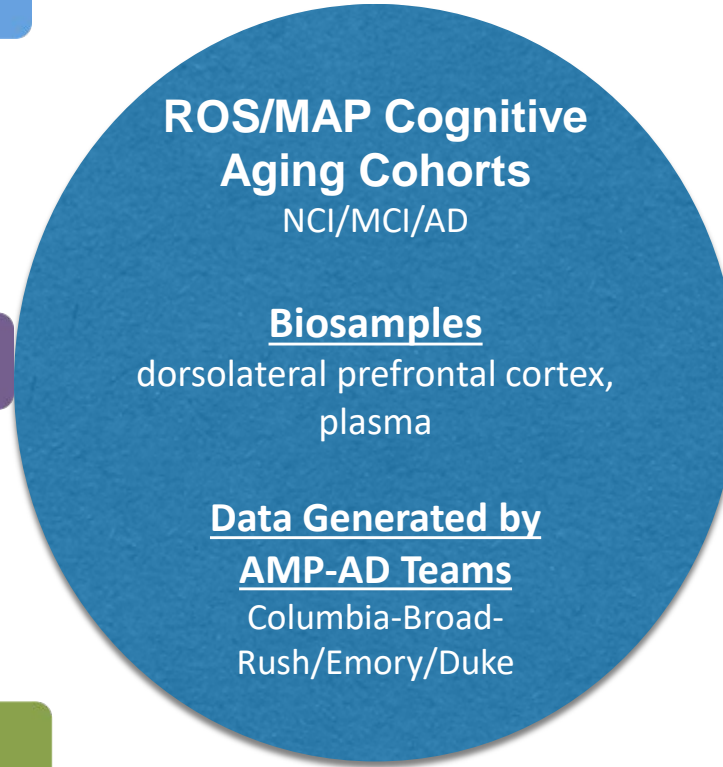
SNP genotypes  
WGS

### Transcriptomics

RNAseq  
mRNAarray  
miRNAarray

### Epigenomics

ChIPseq/H3K9ac  
Methylation array



### Clinical

age ad dx, age death, sex,  
edu, apoe, ethnicity, braak,  
ad reagan score, mmse,  
cerad. cogdx

### Proteomics

### Metabolomics

### Imaging

Full complement of phenotypic data

[www.radc.rush.edu](http://www.radc.rush.edu)

RADC Research Resource Sharing Hub





# Wall of Targets

## Standardized, aggregated evaluation of evidence

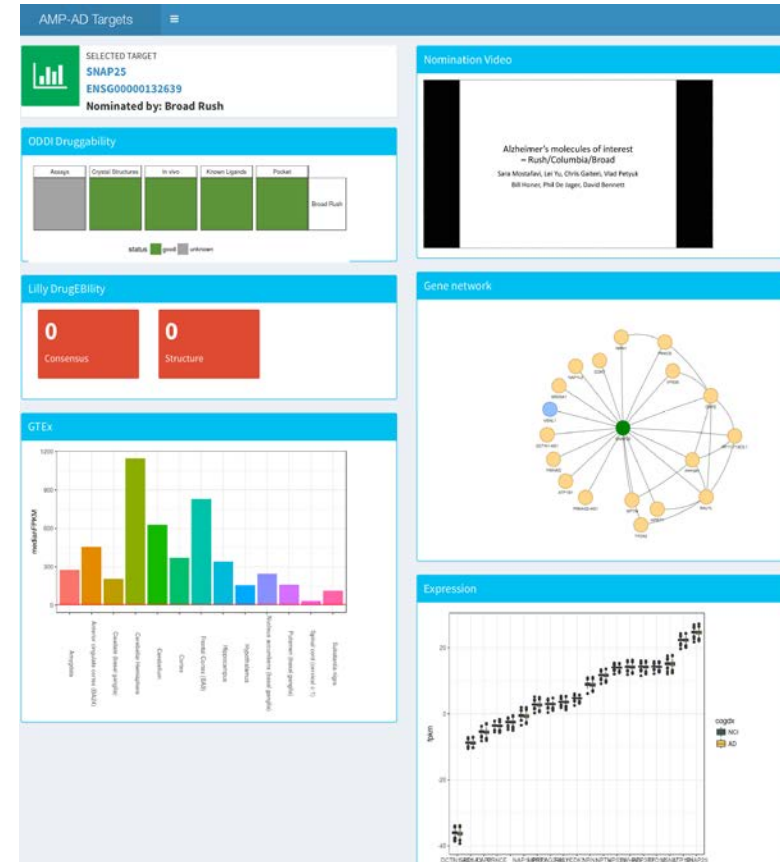
geneSynRegion	Layer1	Layer2	Layer3	Layer4	Layer5	RankScore_in_top_publicPubMed	Worm or Fly ortho	Mouse or Human	Ad mean	Ev mean	Mf mean	Nf mean	O1 mean	PS mean	PS mean	PS mean	PS mean					
PUXB3	BAZ2	7	38	200	227	274	535	0.407765	0	0	0	0	0.255189	0.622629	0.9044	1.179228	24.3594	29.8979	33.1262	NA		
WNR10A	BAZ5	8	58	122	240	362	433	0.282465	9	0	0	0	0.142423	0.249403	0.381949	0.538537	0.713539	0.835993	0.913749	NA		
PREP	BAZ5	7	45	141	254	368	465	0.244524	7	1	0.244523	0	0	0.130279	0.202229	0.290202	0.393577	0.477472	0.543208	0.597508	NA	
GABRG2	BAZ5	19	79	162	269	357	450	0.194019	5	1	0.208847	0.136105	0.205716	0.228117	0.421141	0.431952	0.446807	0.459322	0.470535	0.477472	0.487538	NA
OAT	BAZ5	17	70	158	256	352	451	0.162734	100	2	0.257645	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
CLTC	BAZ5	16	64	129	192	234	302	0.132651	54	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	TRUE
CSTF3	BAZ5	19	61	145	252	286	315	0.130401	69	3	0.270282	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
STAT3	BAZ5	33	105	162	221	271	321	0.131262	29	99	0.278362	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	TRUE
SRSF2	BAZ2	15	56	128	195	229	252	0.130839	2	1	0.265985	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
STESHA1	BAZ5	14	36	61	112	130	150	0.145659	73	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
MARNS	BAZ2	13	52	112	128	135	152	0.152725	56	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
TLN1	BAZ2	12	44	94	142	181	205	0.154022	27	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
PUM1B	BAZ5	16	49	100	140	160	177	0.162448	19	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
SYT1	BAZ5	11	27	59	94	126	152	0.238114	11	4	0.279234	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
SNRN	BAZ5	5	20	47	88	130	152	0.178157	88	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
STPBP1	BAZ5	9	48	108	140	152	152	1	1	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
IPCEP1	BAZ5	7	31	68	98	125	151	0.154333	51	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
PTPNC	BAZ5	21	48	79	105	117	122	0.154265	38	4	0.259403	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	TRUE
PARM1L	BAZ5	5	19	41	73	110	110	0.192465	32	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
DDIT1	BAZ5	15	48	81	97	108	109	0.19444	74	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
ITPA	BAZ5	14	45	86	81	84	84	0.235497	28	4	0.274652	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
BCL2	BAZ5	5	22	46	62	77	84	0.184023	48	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
VAP1	BAZ5	12	31	51	62	69	72	0.232663	40	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
FLJ4043	BAZ5	14	38	56	59	60	71	0.234065	67	NA	NA	NA	NA	NA	NA	0.035801	0.035801	0.035801	0.035801	0.035801	NA	
NHDL1	BAZ5	8	32	55	68	70	70	0.192558	41	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
GPX12L	BAZD	5	19	33	49	64	67	0.192558	41	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
LPD1	BAZ5	15	37	61	66	66	66	0.240791	10	1	0.273465	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
NPSP1	BAZ5	9	34	51	64	66	66	0.232534	42	9	0.285403	0.136413	0.200022	0.218307	0.354295	0.362497	0.362497	0.362497	0.362497	0.362497	0.362497	NA
WDR76	BAZ5	5	27	51	58	58	58	0.193941	34	0	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA
RPY5153B	BAZ5	12	31	51	56	57	57	0.190208	66	NA	0	0	0	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	0.035801	NA

High

Drugability Index



Low



Daily and Logsdon Sage Bionetworks

Release of AMP-AD preliminary target nominations AAIC 2018