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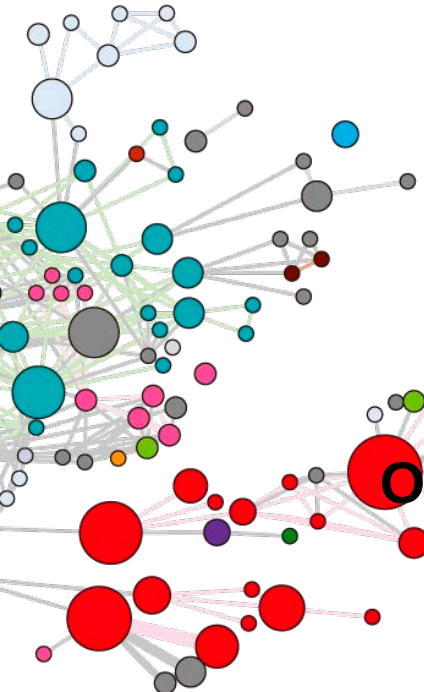
Genomic Medicine Institute

Using Artificial Intelligence for Alzheimer's Disease Drug Repurposing

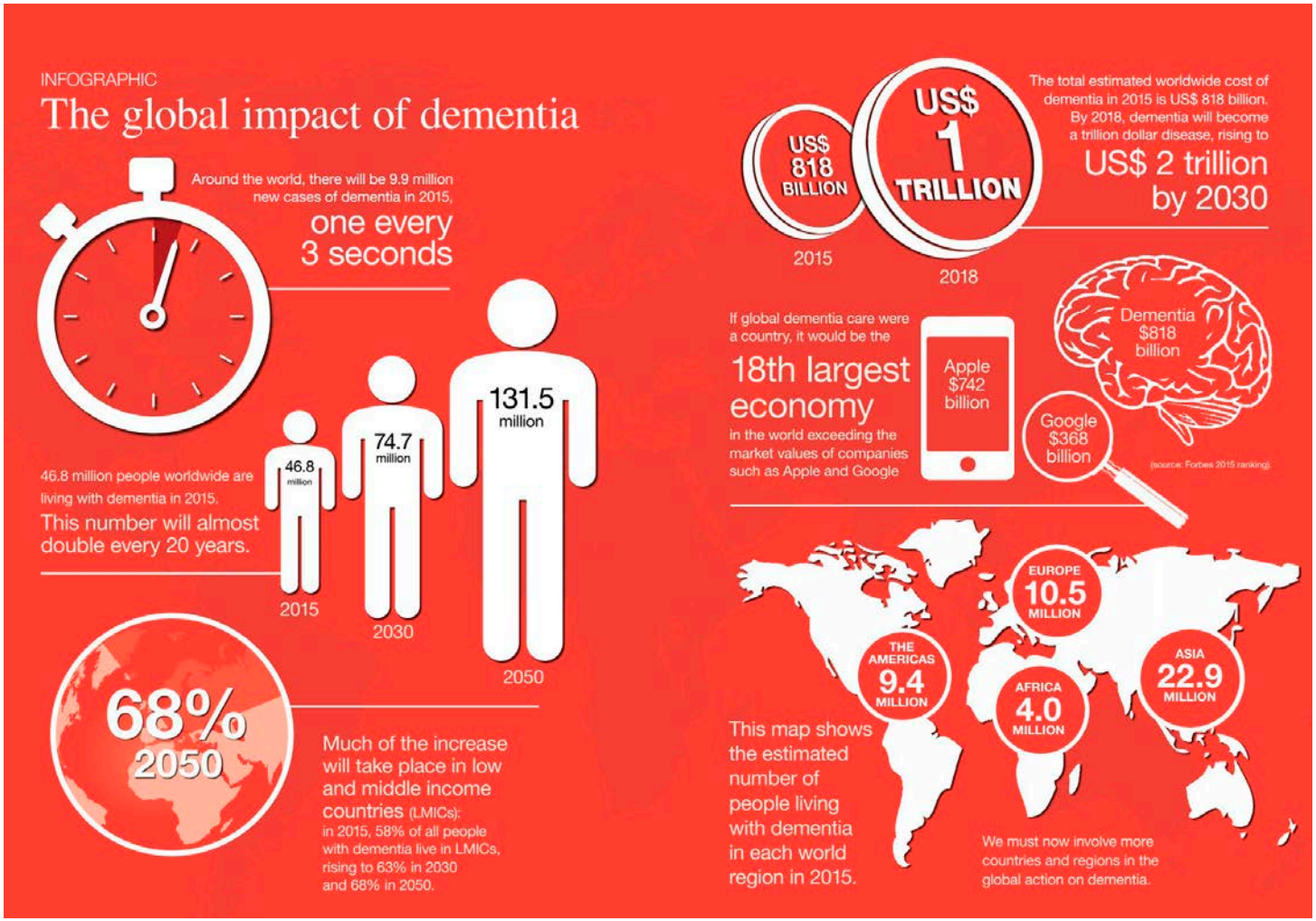
3 R01 AG066707-02S1

Feixiong Cheng, PhD
Assistant Professor



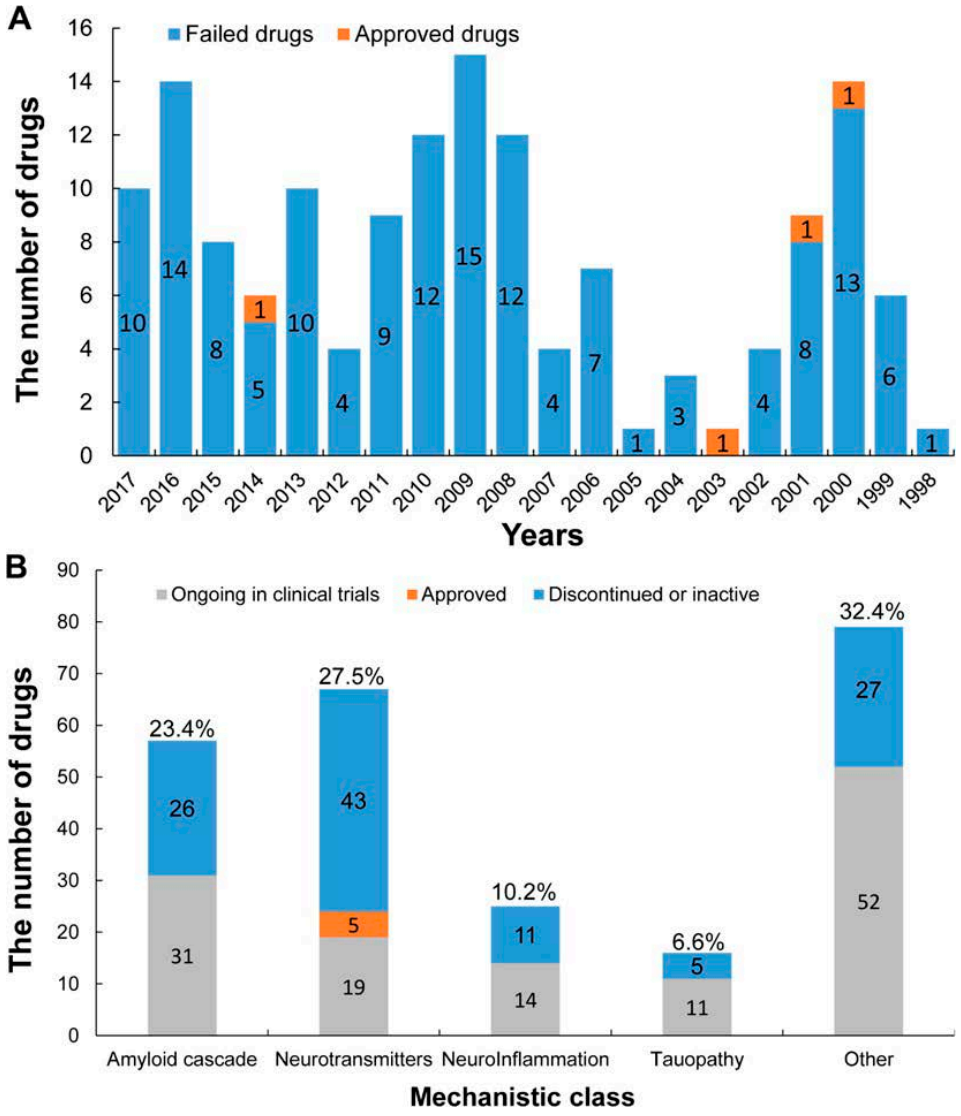
ODSS AI Supplements Closeout Meeting
Room 1, October 31, 2022

Alzheimer's Disease



46.8 million patients in 2015; 16 million patients in U.S. (2050)

Emerging Challenges in Alzheimer's Drug Discovery



The attrition rate for AD clinical trials (2002-2012) is estimated at **99.6%**

Currently 5 available drugs approved by the U.S. Food and Drug Administration (FDA) to alleviate its **symptoms**.

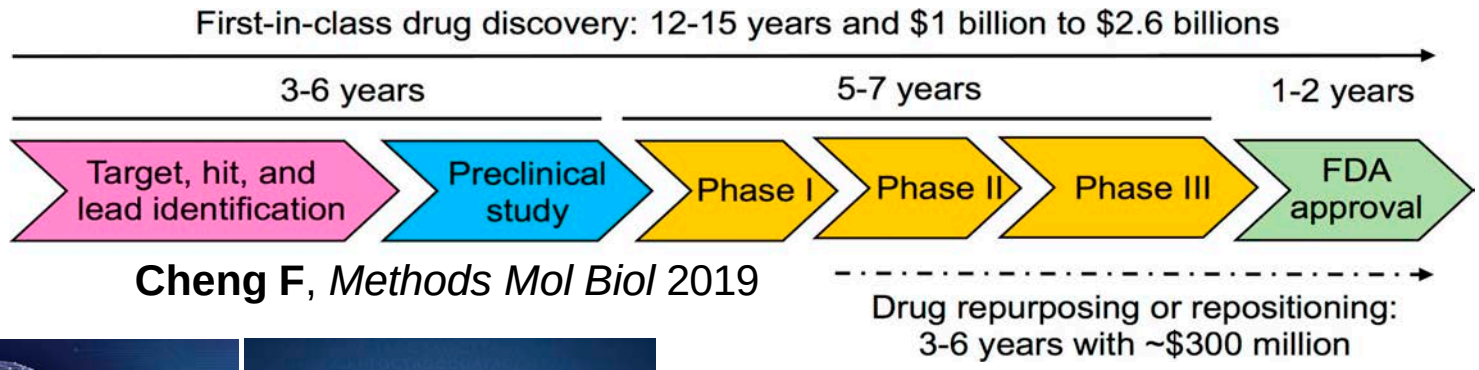
Aducanumab (June/2021)

Anti-amyloid antibody

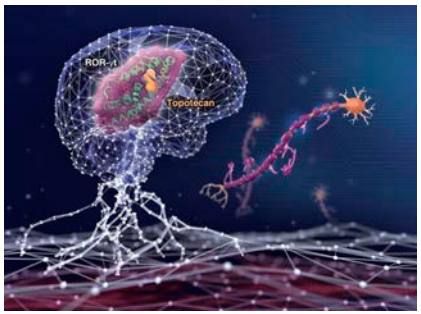
(controversial approval)

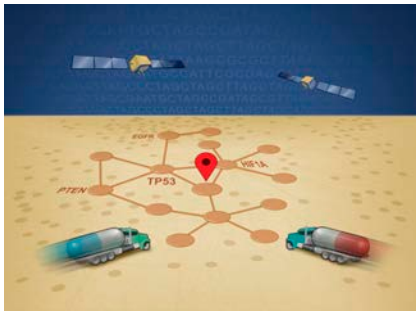
Fang et al., *Med Res Rev.* 2020

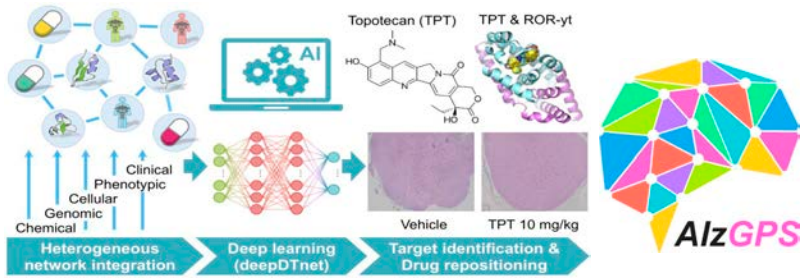
Drug Repurposing/Repositioning

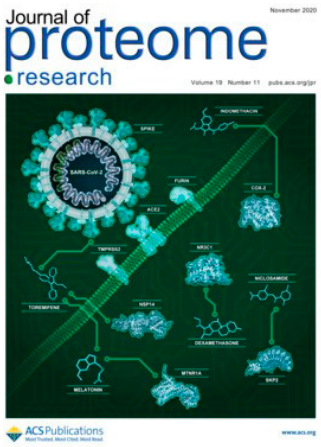


Cheng F, *Methods Mol Biol* 2019









Cell Metabolism 2015; *J Med Chem* 2017; *Oncogene 2017*; *JCI Insights* 2018; *Cancer Res* 2018; *Cell Chemical Biology* 2019; *Chemical Science* 2020 (Cover); *Bioinformatics 2019 2020 and 2021; Nature Genetics* 2021; *Cell* 2021; *PLOS Medicine* 2021; *STTT* 2021; *Aging Cell* 2022

Nature Commun 2018; 2019a; 2019b, *Pharmacological Reviews* 2020 (Cover); *Cell Discovery* 2020; *JPR* 2020a *and* 2020b (Cover), *BMC Medicine* 2020; *Lancet Digital Health* 2020 (Cover)*; PLOS Biology* 2020; *Genome Biology* 2021; ***Genome Research* 2021; *Alzheimer's Research & Therapy* 2021a, 2021b, and 2022; *Nature Aging* 2021; *Nature Biotechnology* 2022, *Cell Reports Medicine* 2022, *Nature Machine Intelligence* 2022**

Challenge to translate genetic (GWAS) and WGS findings for drug target discovery

ARTICLES
https://doi.org/10.1038/s41588-019-0358-2
nature genetics

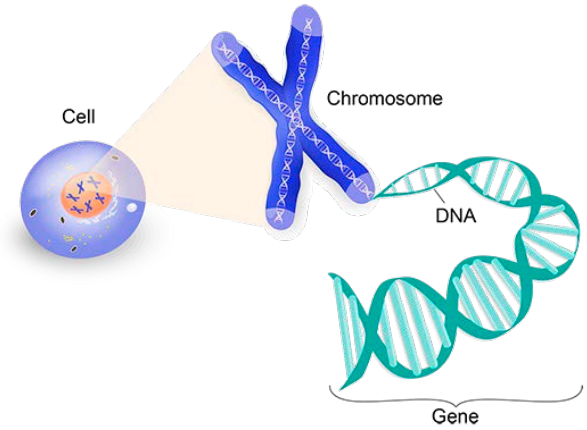
Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing

nature genetics
ARTICLES
https://doi.org/10.1038/s41588-018-0311-9

Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk

nature genetics
ANALYSIS
https://doi.org/10.1038/s41588-020-00776-w
Check for updates

Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes



nature genetics
LETTERS
https://doi.org/10.1038/s41588-020-00773-z
Check for updates

Integrating human brain proteomes with genome-wide association data implicates new proteins in Alzheimer's disease pathogenesis

95% loci located in non-coding regions?

Likely causal genes for each loci??

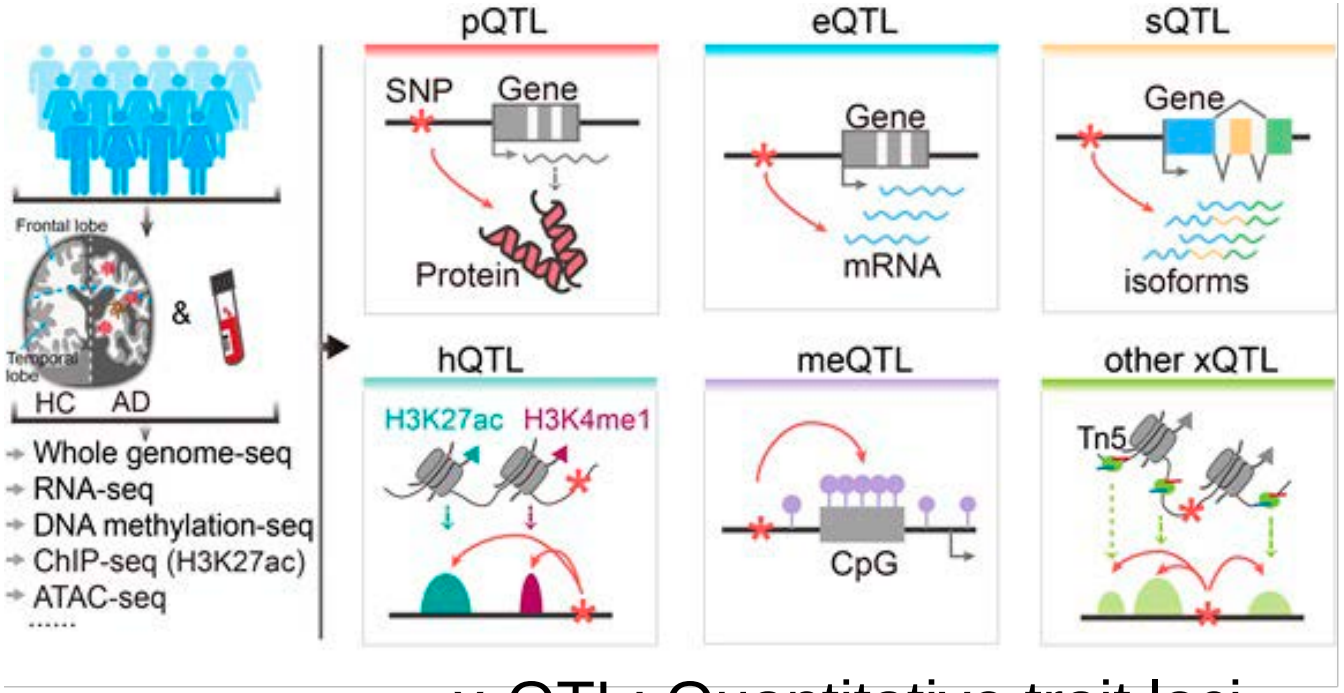
Opportunities to translate non-coding genome findings to drug discovery

adsp Alzheimer's Disease Sequencing Project

NIAGADS

AD Knowledge Portal
AMP-AD

AlzGPS



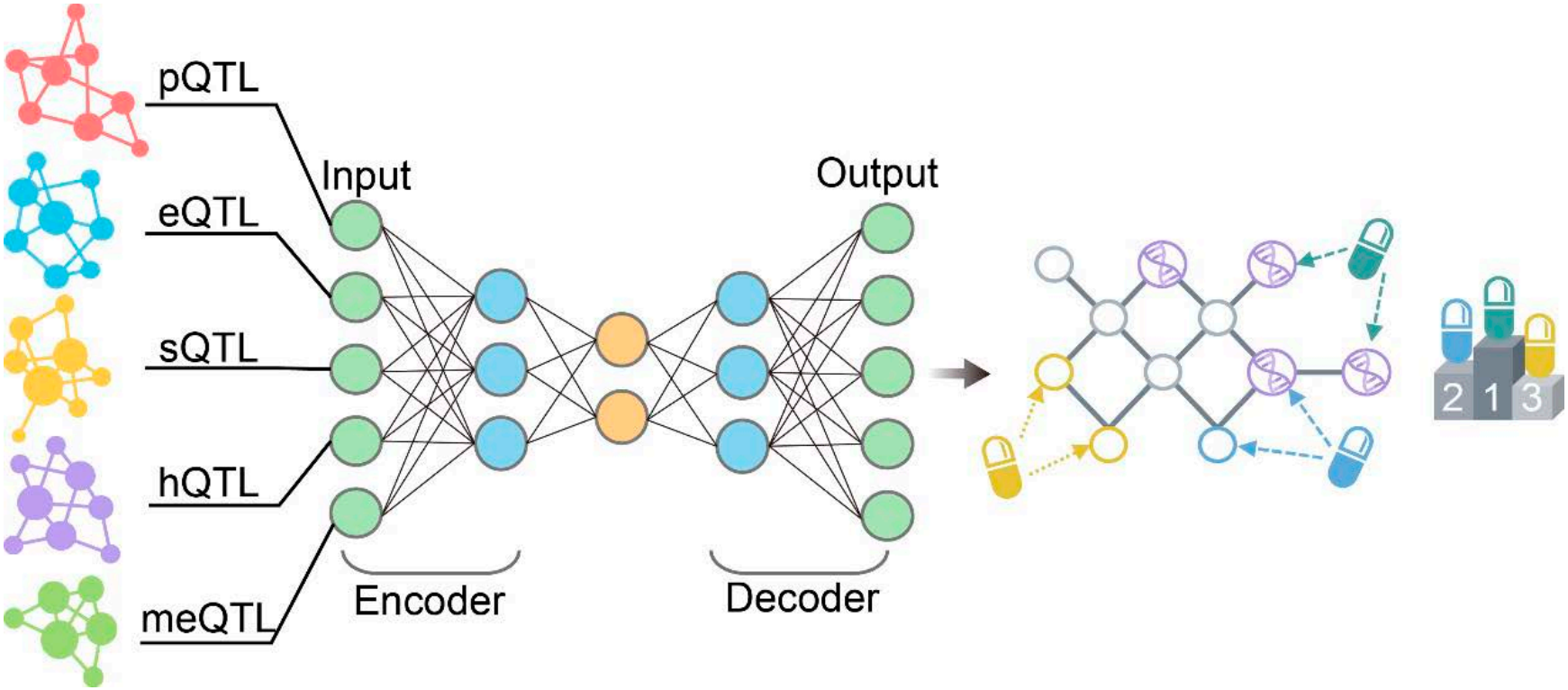
The Alzheimer's Cell Atlas
A Single-Cell Type Transcriptomics And Network Pathobiology Map For Target Identification

Zhou et al., *Alzheimer Res Ther* 2021;
Alzheimer & Dementia 2022

x-QTL: Quantitative trait loci (**e**xpression, **p**rotein, **s**plicing, **me**thylation, **h**istone, others)

Bykova et al., *Human Molecular Genetics* 2022

Hypothesis: Translate multi-omics findings to rapid therapeutic development using AI\ML approaches

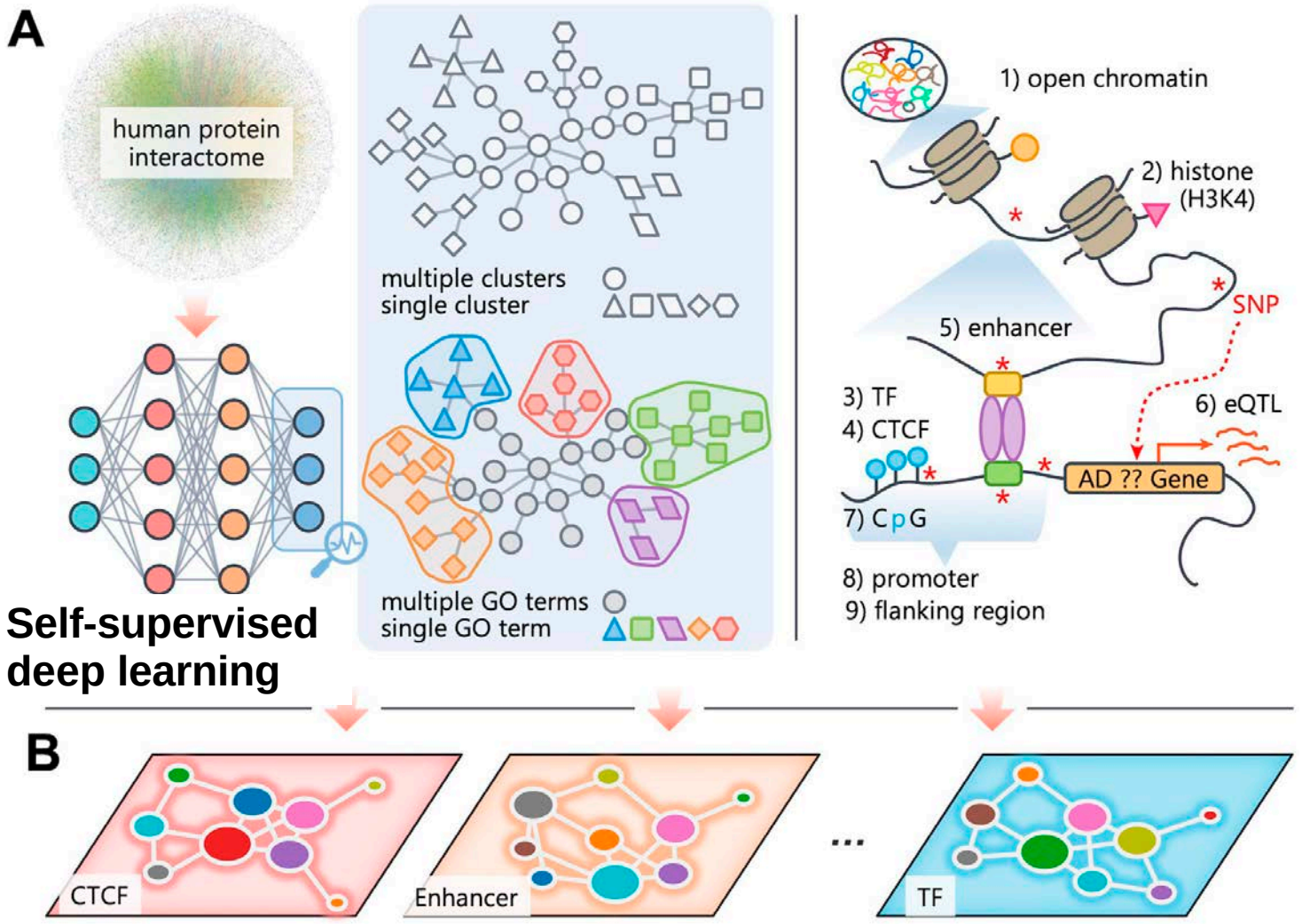


Hypothesis: AI\ML approaches enable utilize multi-omics data for identifying likely risk genes for better understanding of disease mechanisms and drug targets in Alzheimer's disease (AD).

Bykova et al., *Human Molecular Genetics* 2022

Multi-omics informed target identification

NETTAG: **net**work **t**opology-based deep learning framework to identify AD-**a**ssociated **g**enes



Xu et al., *Cell Reports* 2022, in press

Codes: https://github.com/ChengF-Lab/NETTAG

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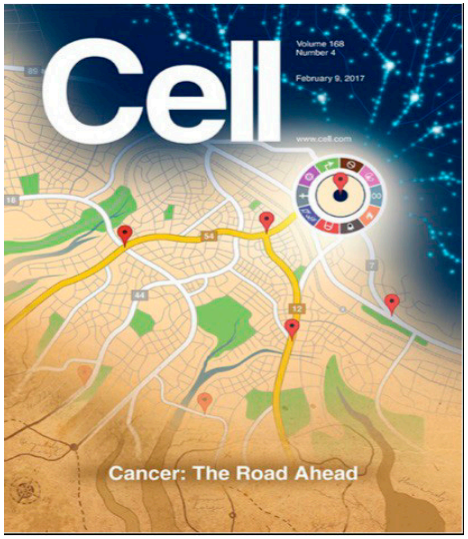
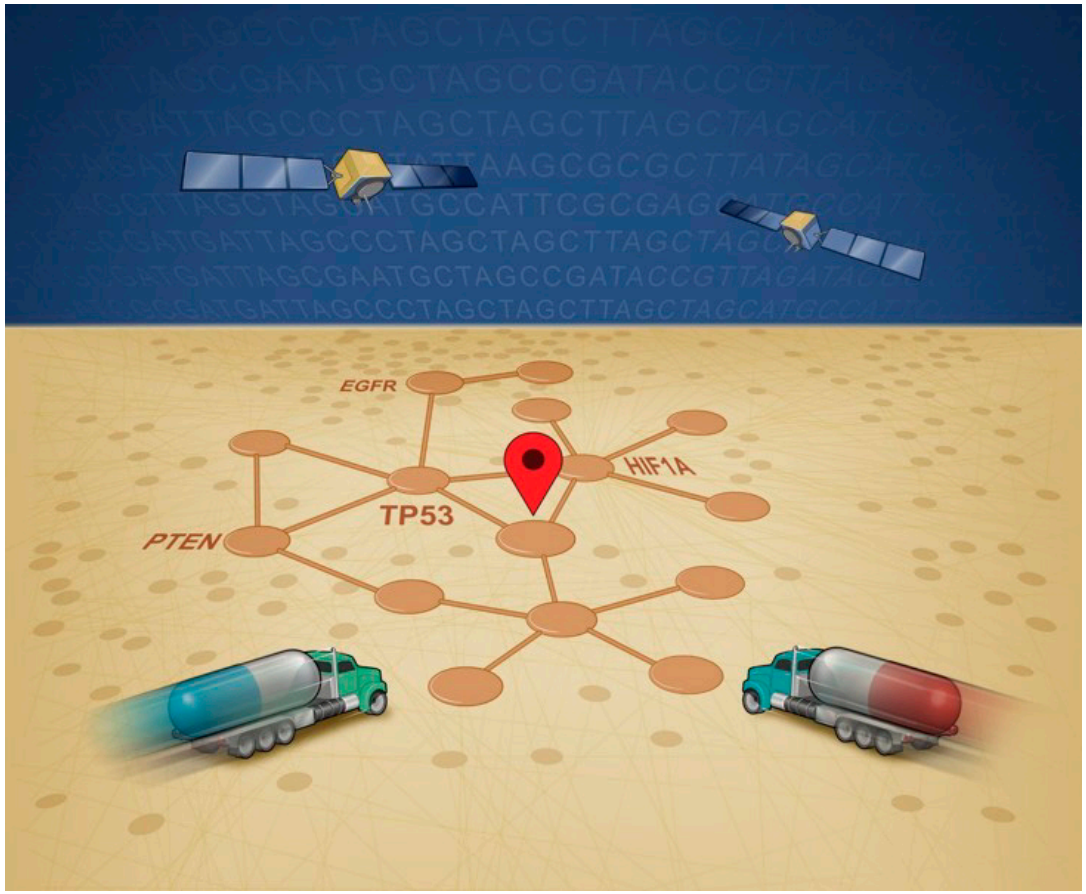
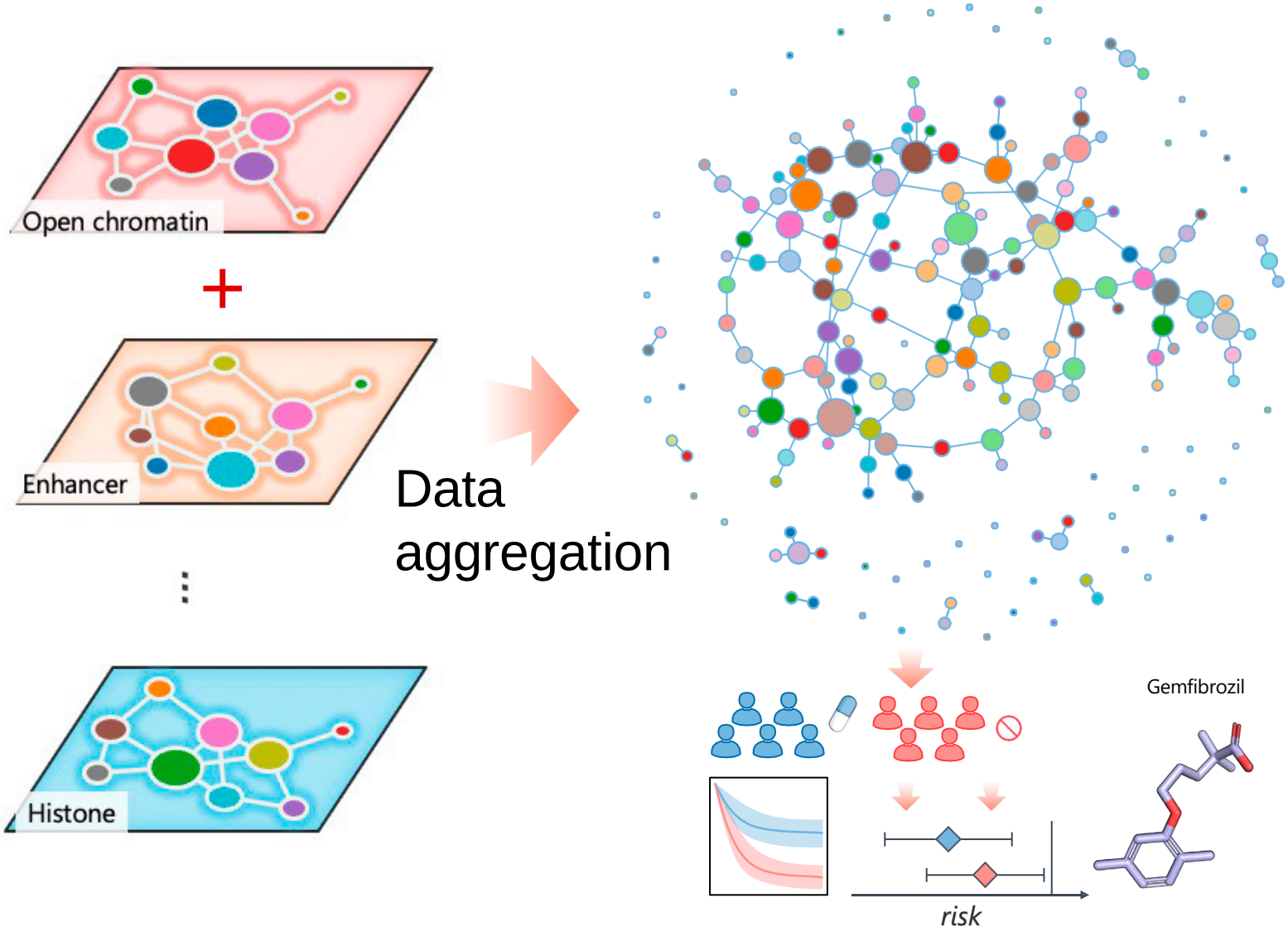
Interpretability of PPI network impacted by disease mutations





GPSnet: Cheng et al., *Nature Commun* 2019
Xu et al., *Genome Research* 2021

Interpretability of NETTAG



Xu et al., *Cell Reports* 2022, in press

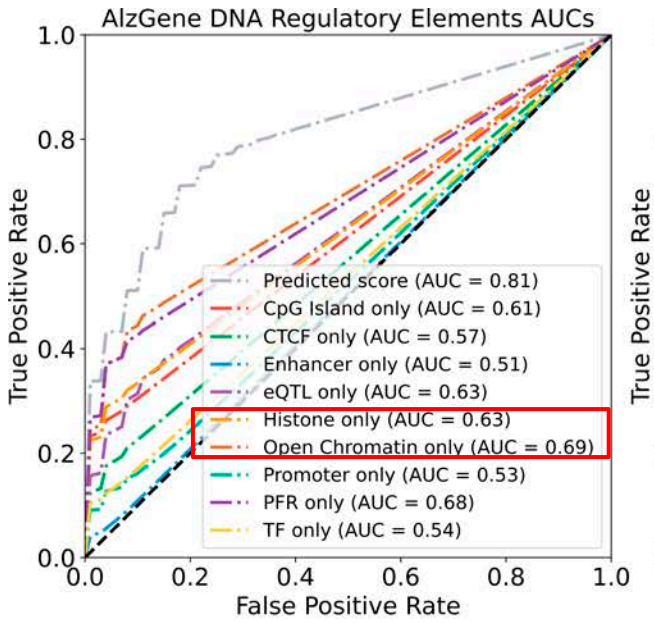
Codes: https://github.com/ChengF-Lab/NETTAG

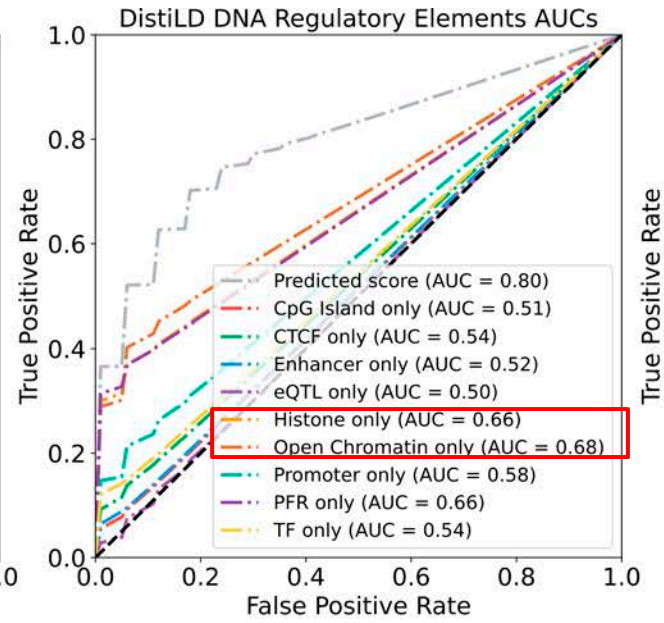
AD GWAS from NIAGADS

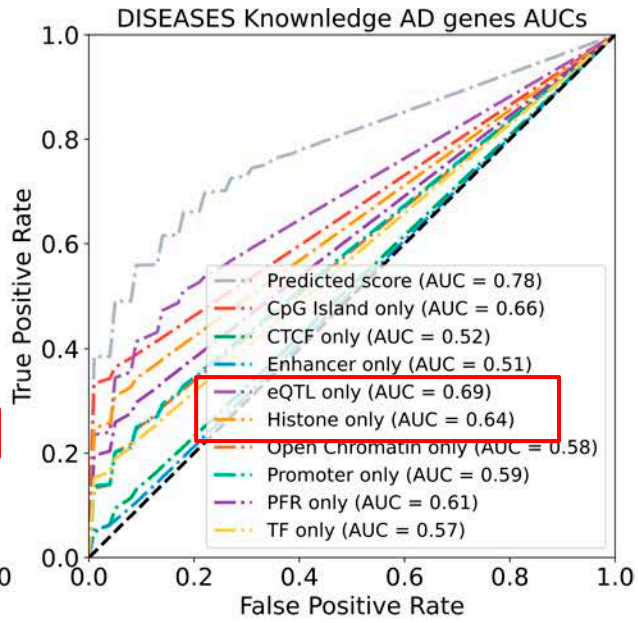
ID	Ethnic	# of SNPs	# of Sample size (case/control)	# of SNPs ($P<10^{-5}$)	Reference
1	USA ,UK	17,343	1,808/2,062	2	PMID:17317784
2	USA	313,504	2,391/2,464	11	PMID:19136949
3	USA, Europe	529,205	5,964/10,188	44	PMID:19734902
4	Europe	537,029	6,010/8,625	53	PMID: 19734903
5	USA, Europe	2,540,000	5,038/19,970	10	PMID: 20460622
6	USA	483,399	2,269/3,107	11	PMID: 20885792
7		565,336	2,465/2,564	11	PMID: 21379329
8	USA, Europe	496,763	19,870/39,846	61	PMID: 21460840
9	USA	2,324,889	11,840/10,931	169	PMID: 21460841
10	USA	1,016,423	4,167/4,336	12	PMID: 22005931
11	African American		1,968/3,928	4	PMID: 23571587
12	Europe	191,777	3,129/119,777	1	PMID: 23150908
13	Europe	7055881;11632	25,580/48,466	20	PMID: 24162737
14	European ancestry	180,882	143,706/766,756	50	PMID: 30617256
15	Non-Hispanic Whites	36,648,992	35,274/59,163	56	PMID: 30820047

eQTLs, pQTL, histone-QTLs, and TF-QTLs from GTEx, NIH RoadMap, FANTOM5, and NIH 4D Nucleome. **Brain-specific and AD-specific functional genomics: MetaBrain, ROSMAP, MSBB, Mayo (NIA-funded AD Knowledge portal)**

Performance (AUC) Evaluation of NETTAG







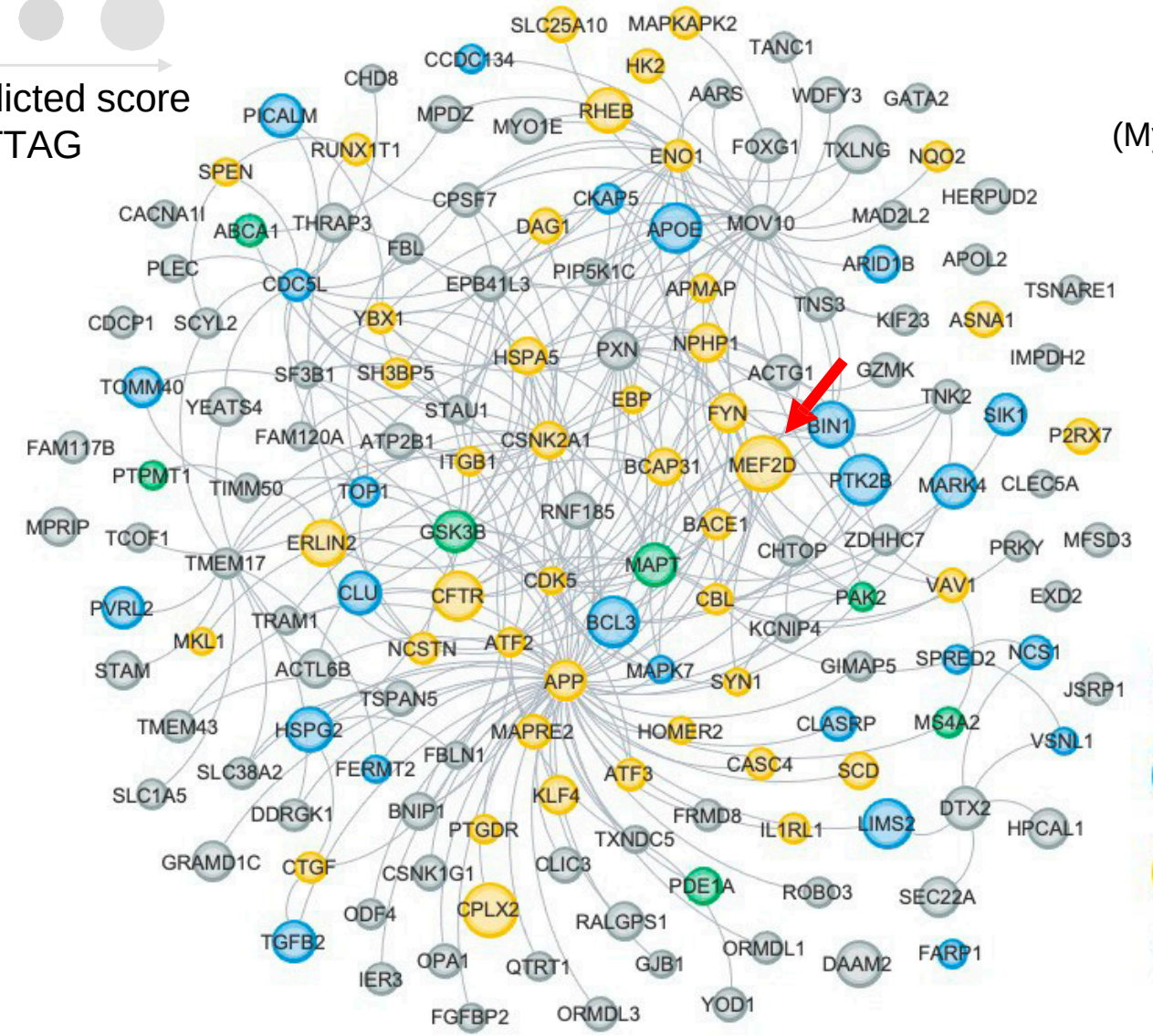
Test/Validation Sets of AD-associated genes collected from four public databases: Alzgene, DistilD, DISEASES, TIGA

Integration of functional genomic (multi-omics) data improve accuracy (AUC) by 10%-25%

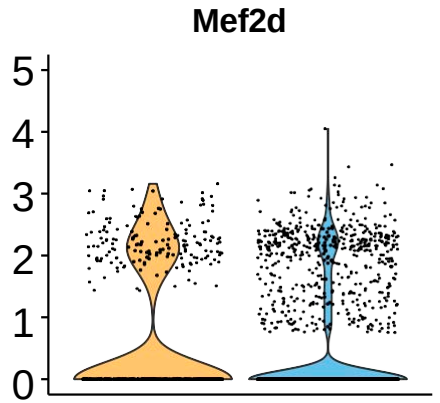
Xu et al., *Cell Reports* 2022, in press

PPI network module of 156 predicted AD genes

predicted score
NETTAG



MEF2D
(Myocyte Enhancer Factor 2D)



GWAS Catalog, no regulatory evidence

GWAS Catalog, with single/multiple regulatory elements

alzRGs with other evidence

other predicted alzRGs

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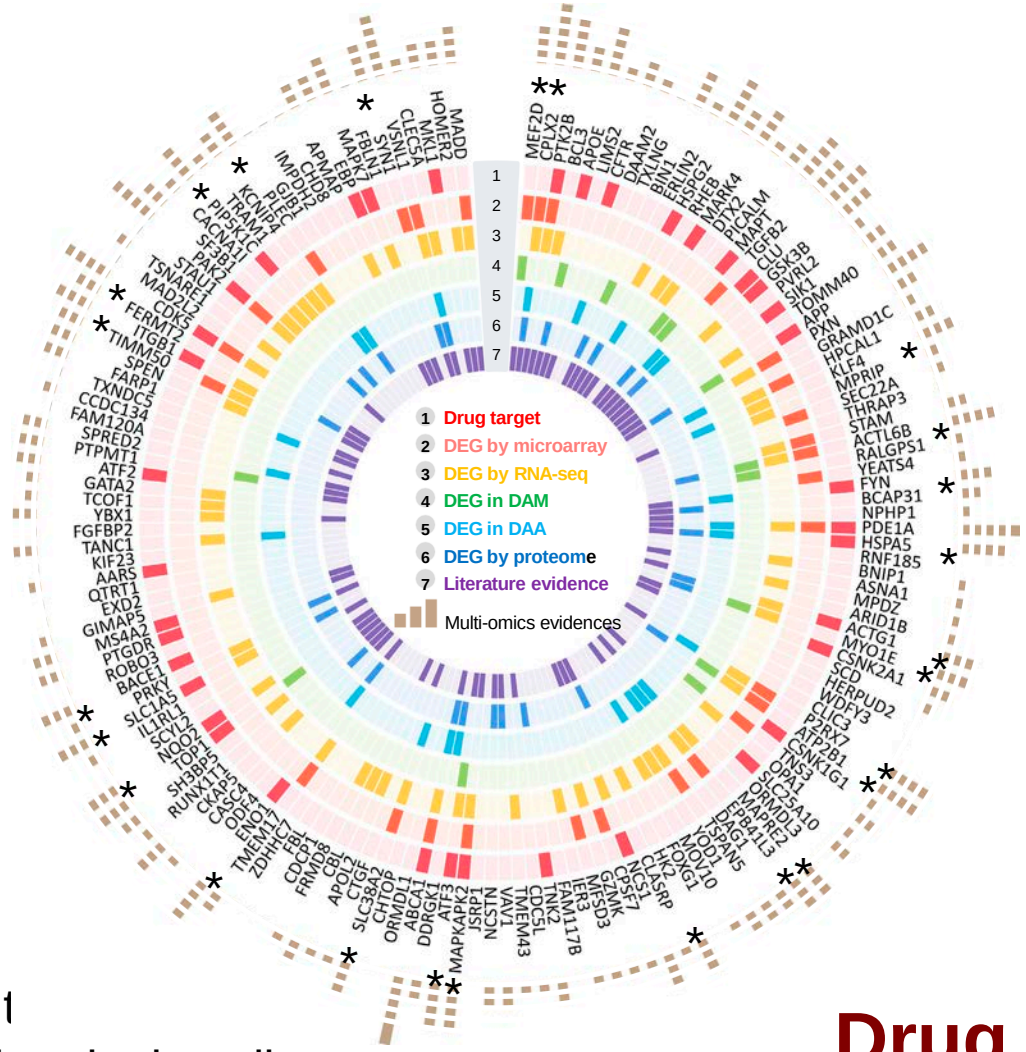
Xu et al., *Cell Reports* 2022, in press

Multi-omics validation of 156 predicted AD genes



DEG: differentially expressed genes/pro
DAM: disease-associated microglia
DAA: Disease-associated astrocyte

Drug targets

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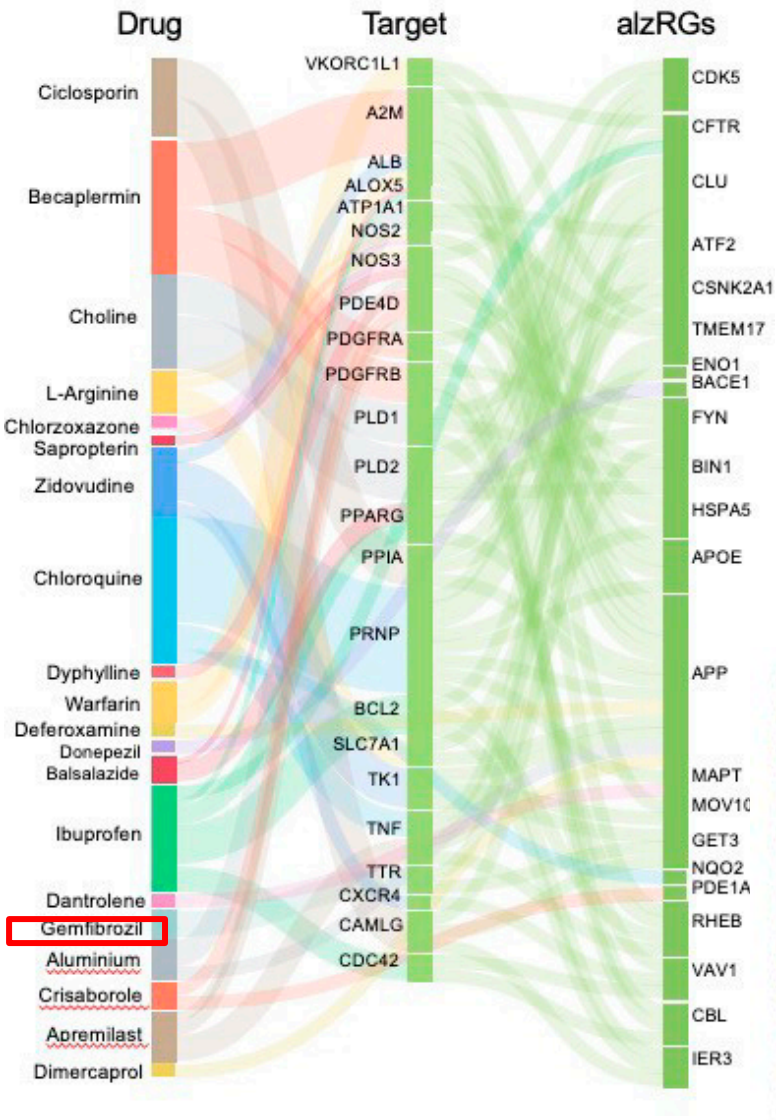
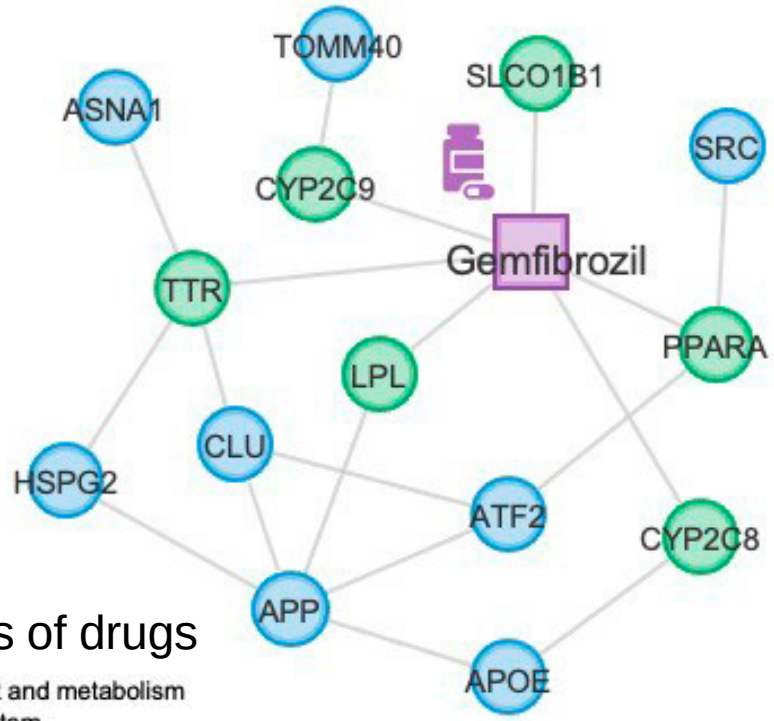
Xu et al., *Cell Reports* 2022, in press

Identifying Repurposing Drugs via Targeting AD Risk Genes





ATC codes of drugs

- Alimentary tract and metabolism
- Respiratory system
- Dermatologicals
- Blood and blood forming organs
- Various
- Genito-urinary system & sex hormones
- Sensory organs
- Cardiovascular system
- Antiparasitic products
- Antiinfectives for systemic use
- Nervous system
- Systemic hormonal preparations
- Musculo-skeletal system
- Antineoplastic and immunomodulating
- Not available

drug

drug target only

module node only

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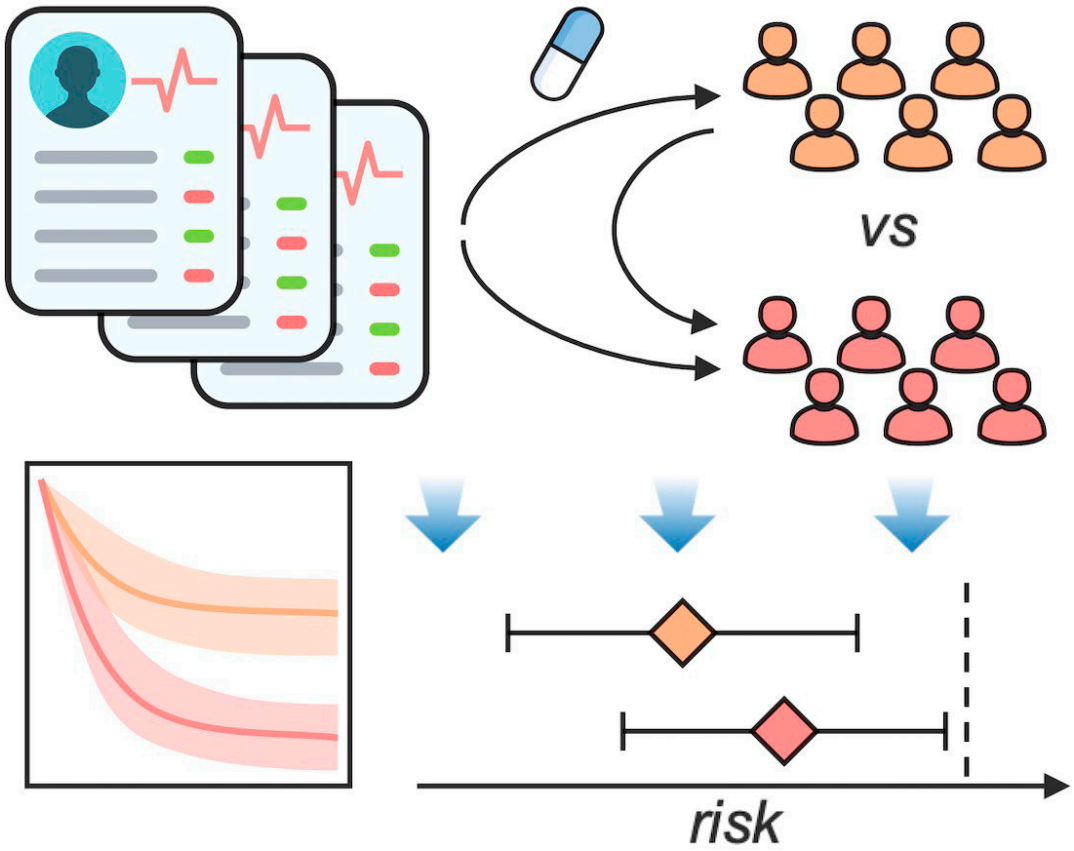
Xu et al., *Cell Reports* 2022, in press

Drug-Cohort Design using Real-world Patient Data



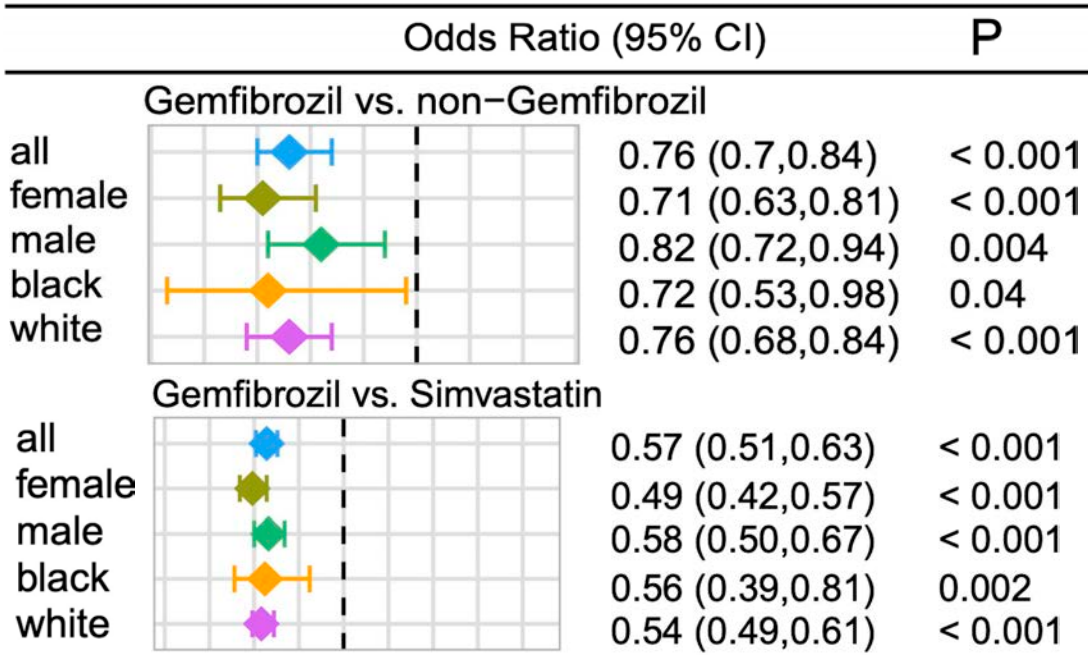
Gemfibrozil users vs. non-Gemfibrozil users

Active comparator design

Propensity score matching cohort studies adjust various confounding factors (age, sex, race, disease comorbidities, etc).

Cheng et al., *Nature Commun* 2018; Fang et al., *Nature Aging* 2021; Xu et al., *Genome Res* 2021; Zhou et al., *Nature Biotechnology* 2022

Gemfibrozil is associated with 40% reduced risk of Alzheimer's Disease in Real-World EHR data (10 million patients)



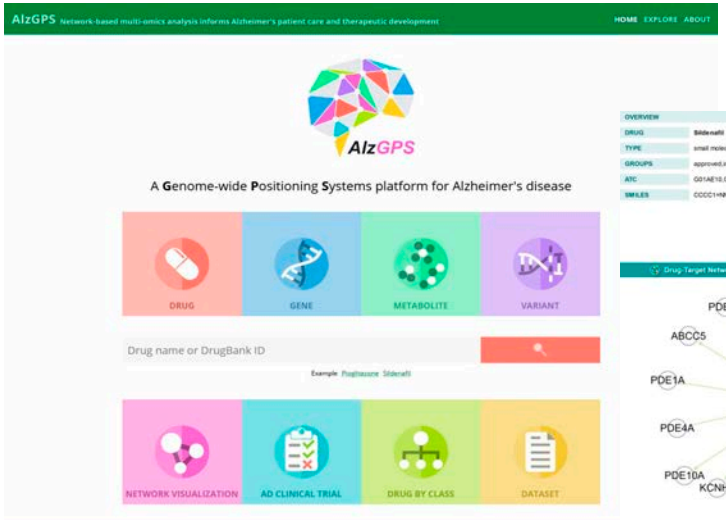
Propensity score matching cohort studies reveals that **gemfibrozil** (anti-lipid medicine) is significantly associated with 43% reduced risk of AD compared to **Simvastatin** (an anti-lipid drug in a Phase II AD clinical trial [NCT00486044 and NCT00939822]) (10 million patients from Northwestern University EHR systems)

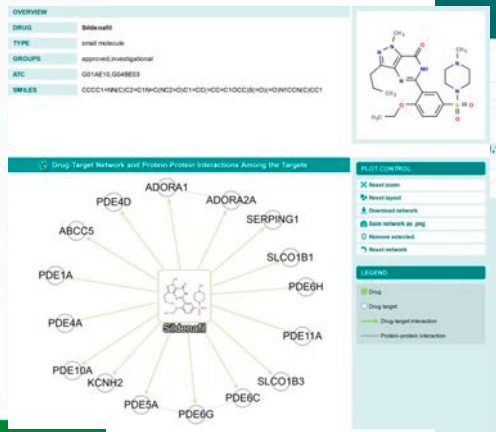
Xu et al., *Cell Reports* 2022, in press

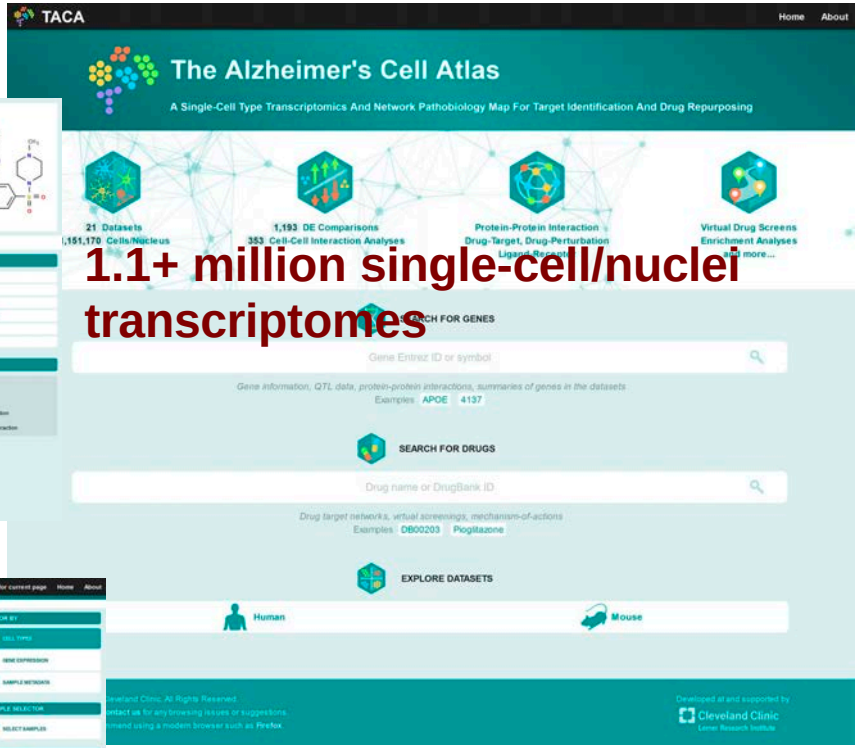
Preliminary Summary

- We demonstrated that AL\ML approaches offer powerful tools to identify risk genes and drug targets in Alzheimer's disease
- Unique integration of brain-specific functional genomics (xQTL) data synergistically improve performance in prediction of risk genes in AD.
- We identified **gemfibrozil** as a candidate drug for AD.
- More functional and clinical validation of **gemfibrozil** using Alzheimer's disease models and patients are highly warranted.

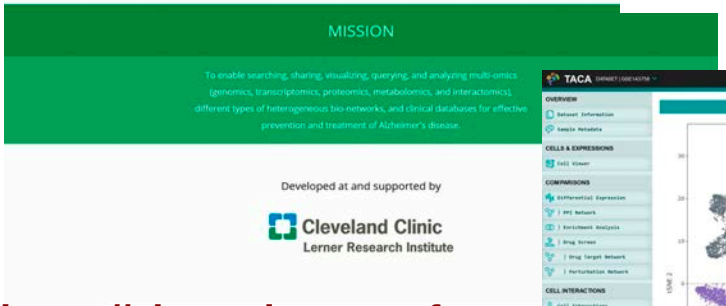
Open Science and Data Sharing (AI\ML Supplement)

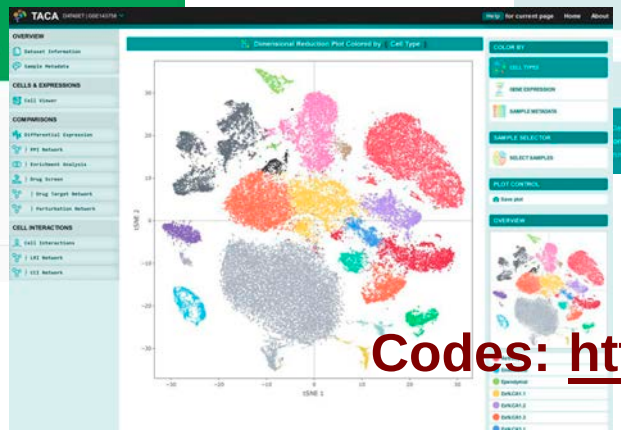






1.1+ million single-cell/nuclei transcriptomes





https://alzgps.lerner.ccf.org

TACA: https://taca.lerner.ccf.org

Codes: https://github.com/ChengF-Lab

To enable utilize multi-omics data to identify/validate drug targets and disease mechanisms for AD via AI\ML tools.

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Zhou et al., *Alzheimer's Research & Therapy* 2021; Zhou et al., *Genome Biology* 2021
Zhou et al., *Alzheimer's & Dementia 2022, in press*

Acknowledgements

Cheng Lab

- **Jielin Xu**
- Yuan Hou
- Yadi Zhou
- William Martin
- Jessica Castrillon
- Yunguang Qiu
- Yayan Feng
- Dhruv Gohel
- Marina Bukova
- Lijun Dou
- Yichen Li

- Lab Alumni
- Jiansong Fang
- Yin Huang

Cleveland Clinic

- **Jeffrey Cummings**
- **James Leverenz**

CWRU

- Andrew Pieper
- Jonathan Haines

Indiana University

- Pengyue Zhang

Northwestern ADRC

- Margaret Flanagan
- Yuan Luo
- **Chengsheng Mao**

3 R01 AG066707-02S1

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NIH National Heart, Lung, and Blood Institute

hhmi Howard Hughes Medical Institute

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