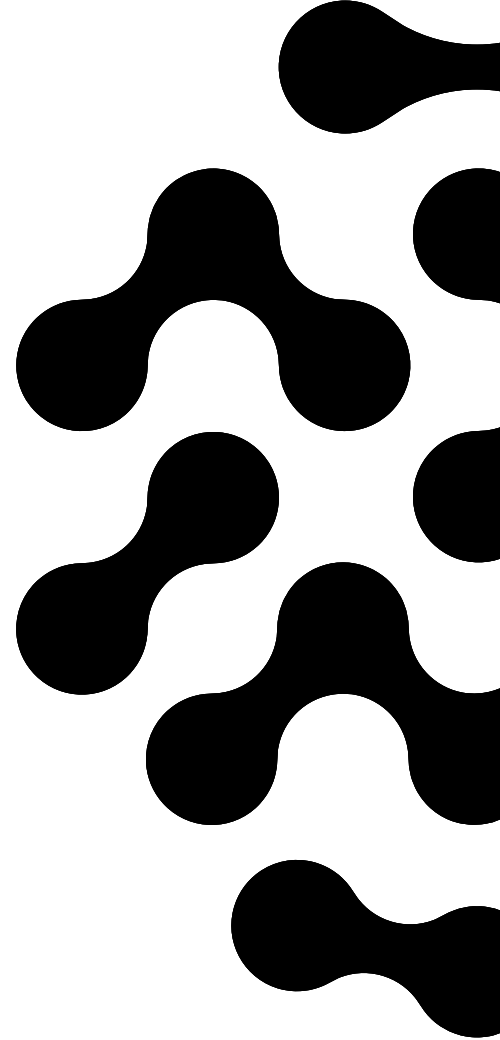


Discovering Dementia Discovery Research

Dementia Learning and Research Community

March 19, 2025

Francesca Alves & Scott Ayton



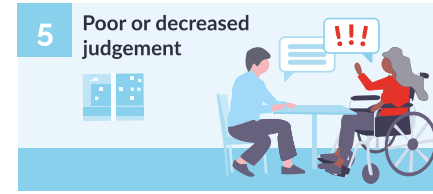
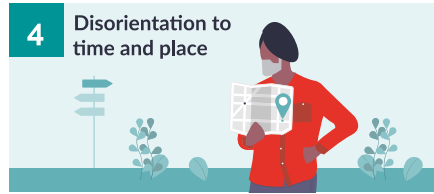
Outline

1. The priority of dementia
2. What goes wrong in Alzheimer's disease?
3. Hypothesis driven research:
 - Anti-amyloid therapies for Alzheimer's disease
4. Data driven research
5. The landscape of treatments for Alzheimer's disease

Dementia

- Loss of memory and/or other mental abilities severe enough to interfere with daily life
 - Gradual loss of brain cells
 - Insidious, chronic and persistent
-
- Alzheimer's disease (~ 60-80%)
 - Vascular dementia
 - Parkinson's disease
 - Dementia of the Lewy Bodies
 - Frontotemporal dementia
 - Huntington's disease





www.alzint.org

If these signs are new, they may be a sign of dementia.
Dementia is not a normal part of ageing.
Speak to your doctor or contact your dementia and Alzheimer association.

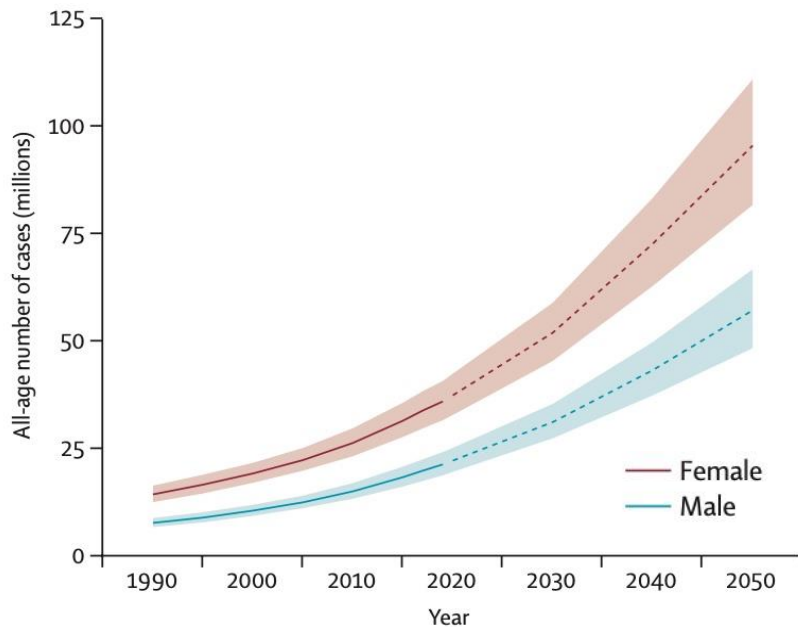
**Alzheimer's Disease
International**
The global voice on dementia

Dementia: the scale of the problem

THE TOP CAUSES OF DEATH IN AUSTRALIA
OVER THE PAST FOUR DECADES

	1977	1987	1997	2007	2017
1	Heart disease	Heart disease	Heart disease	Heart disease	Heart disease
2	Cerebrovascular disease (stroke)	Cerebrovascular disease	Cerebrovascular disease	Cerebrovascular disease	Dementia and Alzheimer's disease
3	Lung cancer	Lung cancer	Lung cancer	Lung cancer	Cerebrovascular disease
4	Car crashes	Lung disease	Lung disease	Dementia and Alzheimer's disease	Lung cancer
5	Lung disease	Bowel cancer	Bowel cancer	Lung disease	Lung disease
6	Bowel cancer	Car crashes	Dementia and Alzheimer's disease	Bowel cancer	Bowel cancer
7	Influenza and pneumonia	Breast cancer	Diabetes	Diabetes	Diabetes
8	Breast cancer	Suicide	Heart failure	Chronic kidney disease	Influenza and pneumonia
9	Diabetes	Diabetes	Suicide	Prostate cancer	Heart failure
10	Suicide	Prostate cancer	Breast cancer	Heart failure	Prostate cancer

Data: Australian Institute of Health and Welfare Note: Dementia was not listed as a cause of death until 1979 and heart failure was not listed as a cause of death until 1997



Lancet Public Health, 2022

Services and spending on dementia



Over half of people living in permanent residential aged care have dementia

623,300 scripts for dementia-specific medications were dispensed to almost **64,600 Australians** in 2019–20



People hospitalised for dementia **stayed 5 x longer** than the average hospitalisation



1 in 6 who completed a comprehensive assessment to use aged care services had dementia

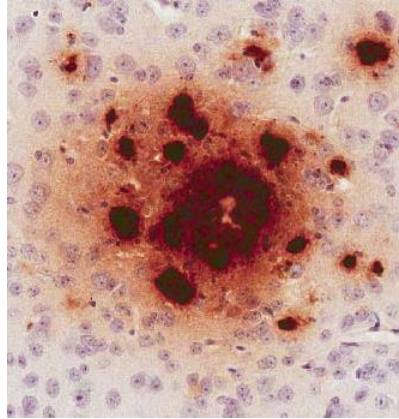


Between 2012–13 and 2019–20 there was a **43% increase** in the number of scripts dispensed for dementia-specific medications

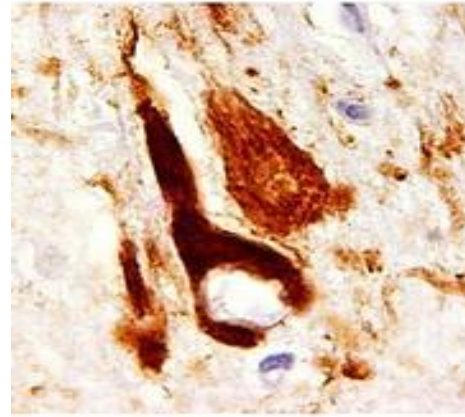
In 2018-19, \$3 billion was spent on health and aged care directly for dementia; **\$1.7 billion** was for permanent residential aged care



Alzheimer's disease is defined by abnormal deposits in the brain

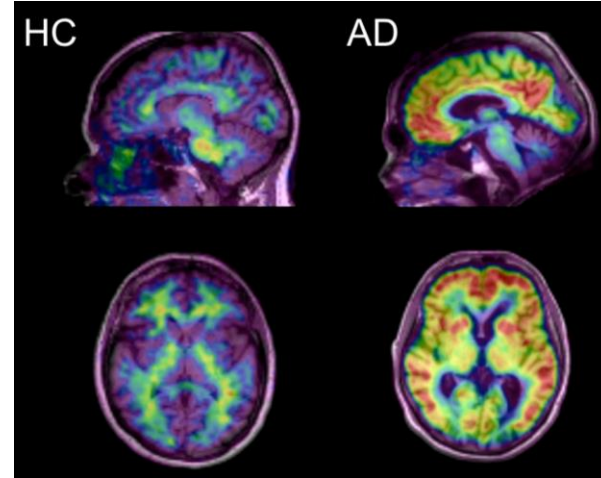


Amyloid plaque

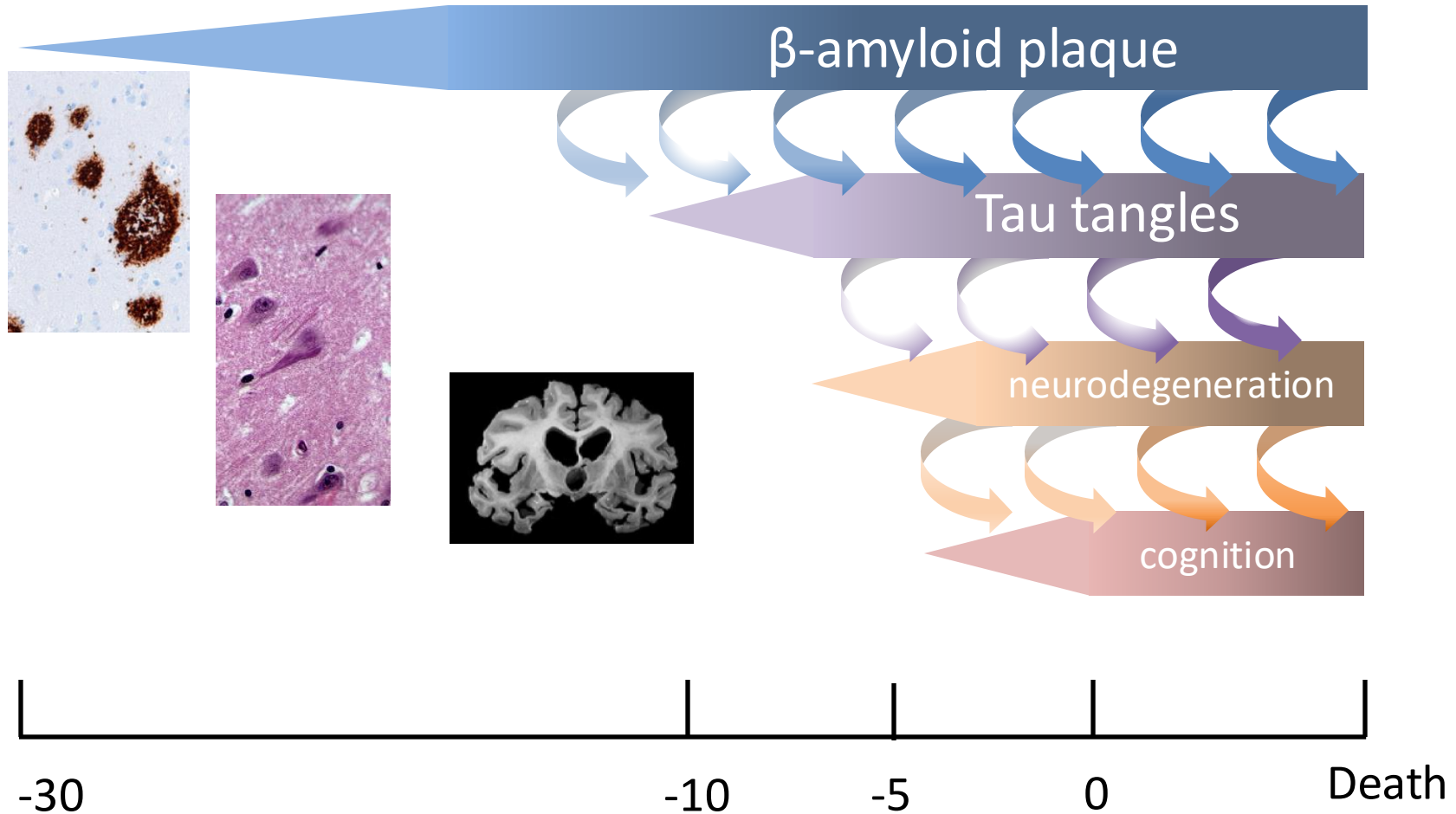


Neurofibrillary tangle

Alzheimer's Pathology imaging



Alzheimer's disease natural history



How does discovery science work?

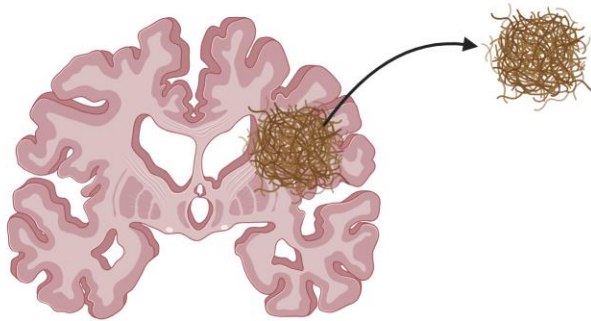
1 Hypothesis driven research
Amyloid hypothesis

2 Data driven research
My own research!

1

Hypothesis driven research

Hypothesis (noun): a supposition or proposed explanation made on the basis of limited evidence as a starting point for further investigation.



Amyloid is present in the brain

→ Amyloid is toxic and causes Alzheimer's disease



Amyloid is toxic and causes
Alzheimer's disease

How do we test a hypothesis?



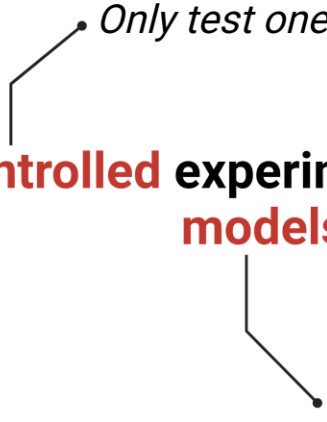
Amyloid is toxic and causes
Alzheimer's disease

How do we test a hypothesis?

Using **controlled** experiments in a range of
models

How do we test a hypothesis?

Using **controlled** experiments in a range of **models**

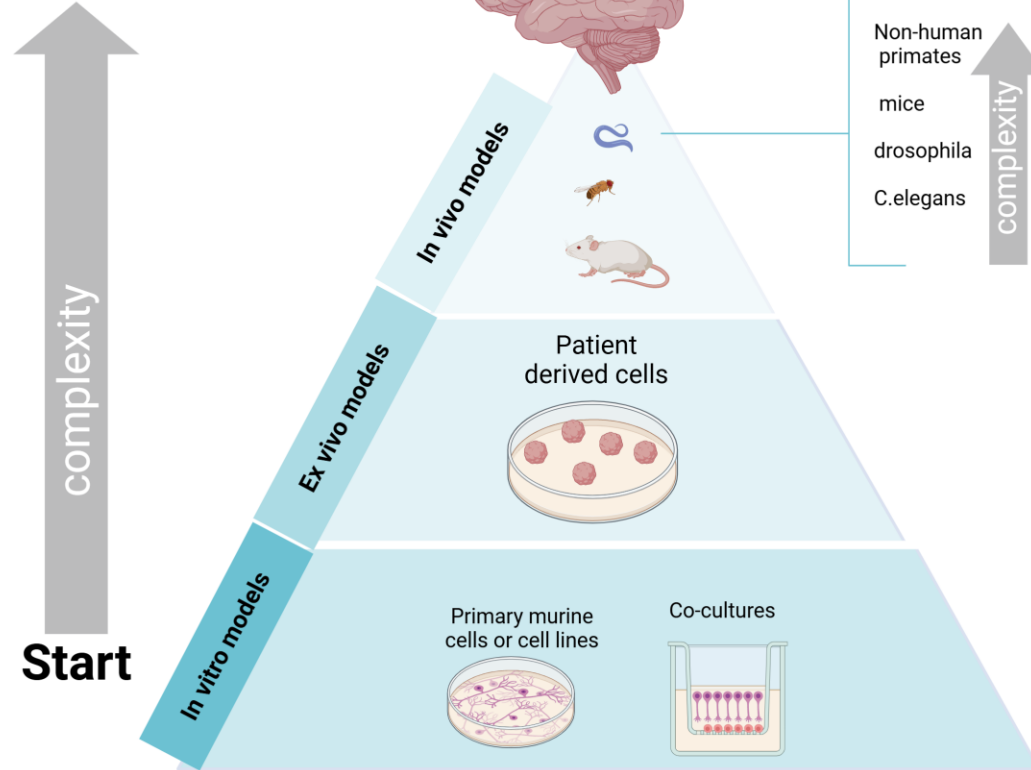


```
graph TD; A[Using controlled experiments in a range of models] --> B[Only test one thing at a time!]; A --> C[Can we recapitulate human disease?]
```

• Only test one thing at a time!

• Can we recapitulate human disease?

Models to use in discovery research

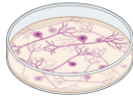


Neurodegenerative Preclinical Models

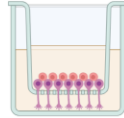
Advantages and Disadvantages

Generic cells

Cells
- Neurons



Co-cultures



Advantages

- Cost-effective
- Easily adaptable and augmented
- Direct way to study mechanisms
- Reproducibility

Disadvantages

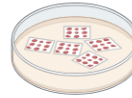
- Not representative of in vivo
- Long-term studies more challenging
- Requires in vivo confirmation

Patient derived cells/tissues

Cultured
organoids



Cultured
tissue explants



Advantages

- Long-term temporal studies
- May recapitulate disease defects
- Multicellular
- More material to work with

Disadvantages

- Not reproducible/high variability
- Lack of vascularization
- No peripheral immune components

In vivo models

Non-human primates, mice,
drosophila, C.elegans etc.



Advantages

- Long-term temporal studies
- More translational than cells alone
- Multicellular studies
- More material to work with

Disadvantages

- Ethical concerns
- High cost
- Not reproducible
- Not representative of human biology

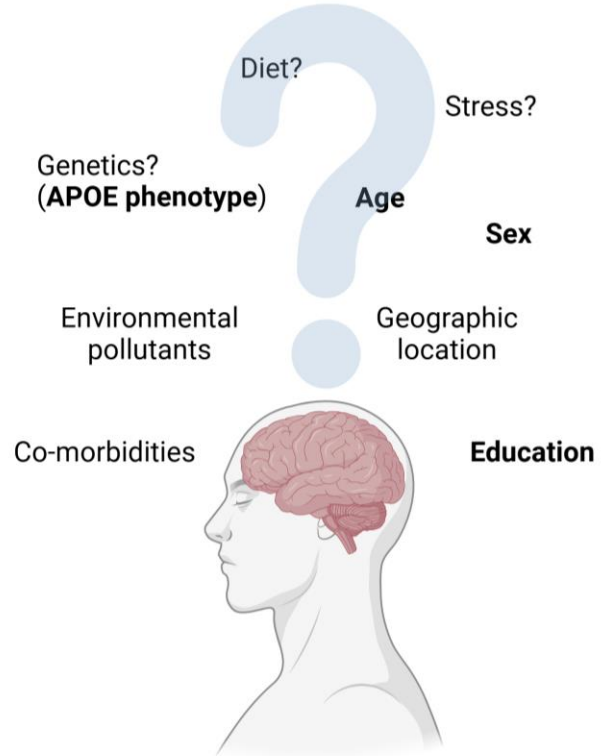
Using **controlled** experiments in a range of **models**

Humans and mice share a
high degree of genetic
similarity ~ 85%!

Why is human research so complex?



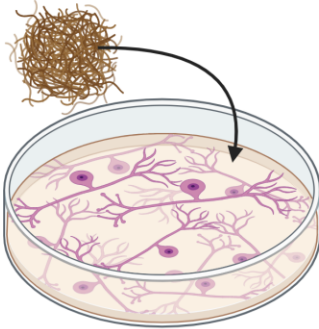
- Same genetic background
- Same environmental conditions
 - Housing
 - Diet
 - Stress
 - Age
 - Sex



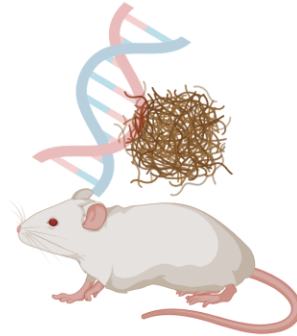
How do we test a hypothesis?

Amyloid is toxic and causes Alzheimer's disease

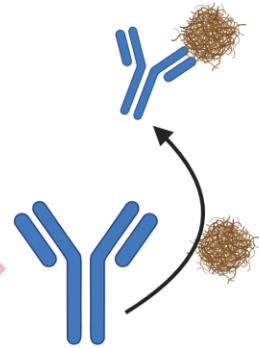
Testing in the
laboratory



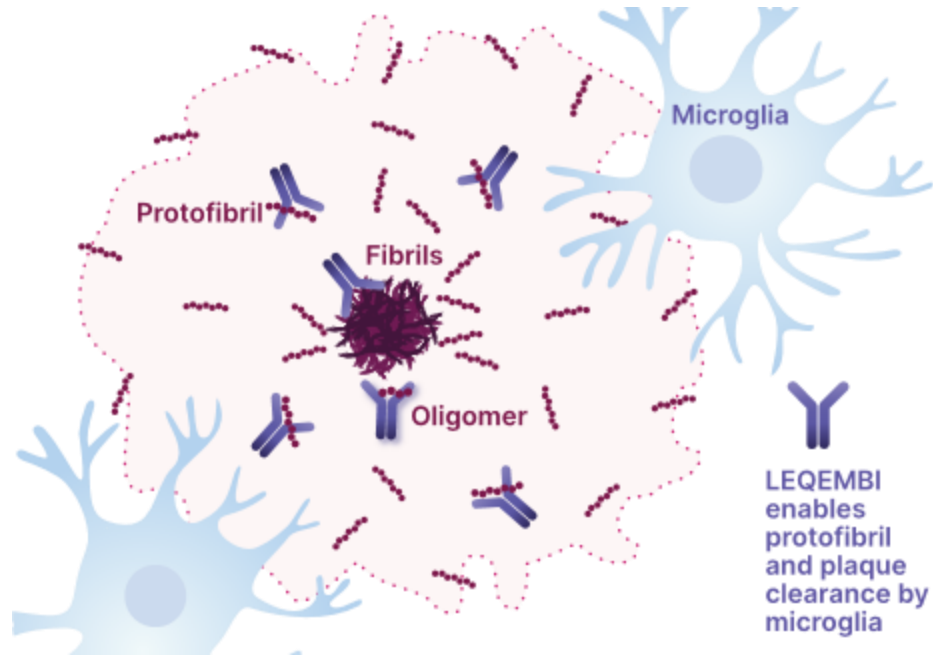
Testing in animal
models



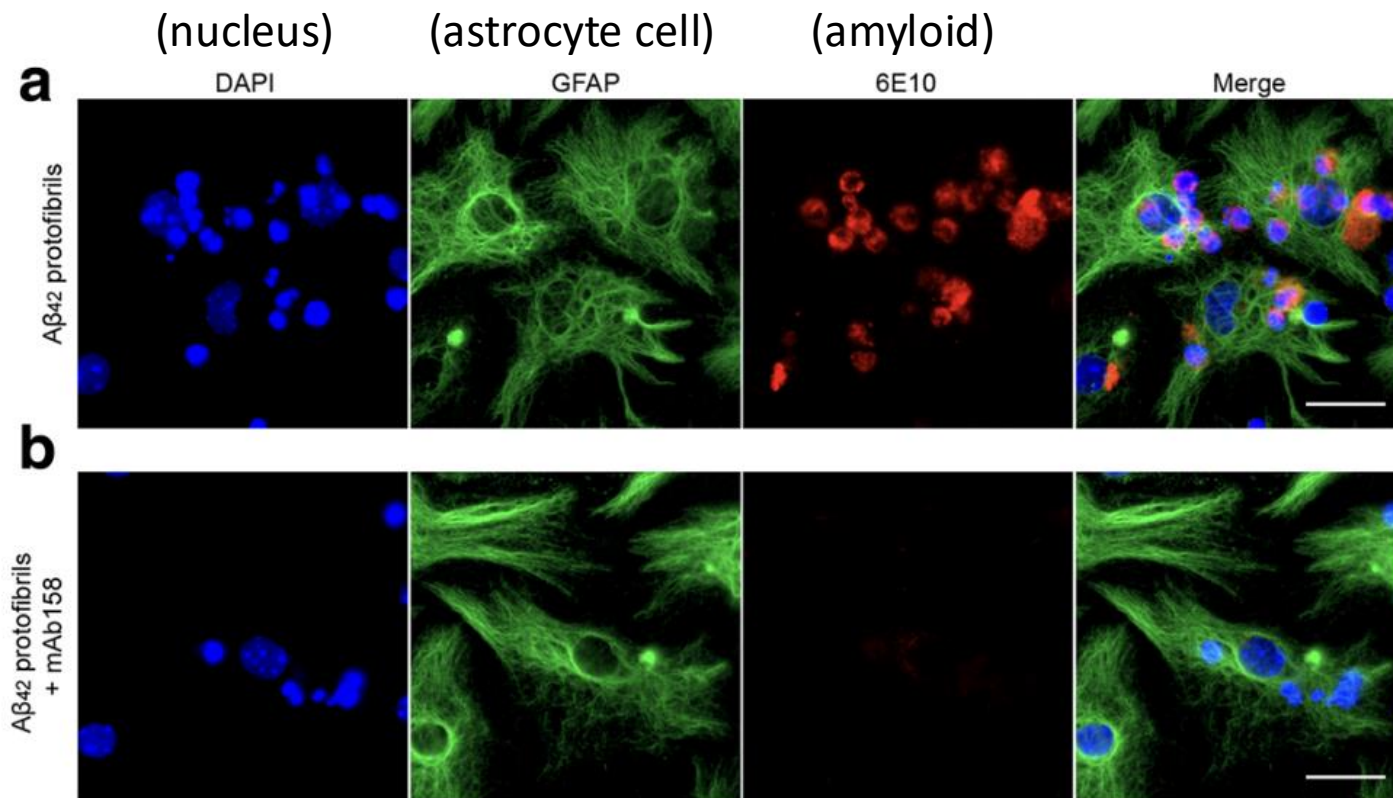
Development
of a drug



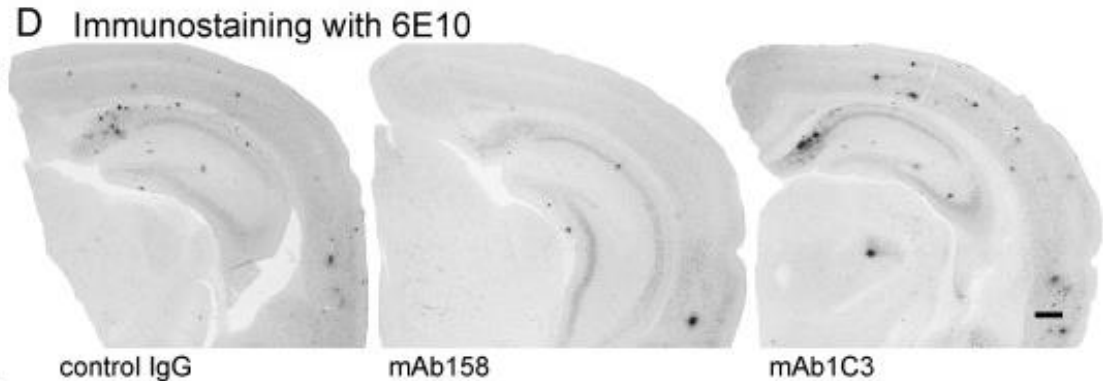
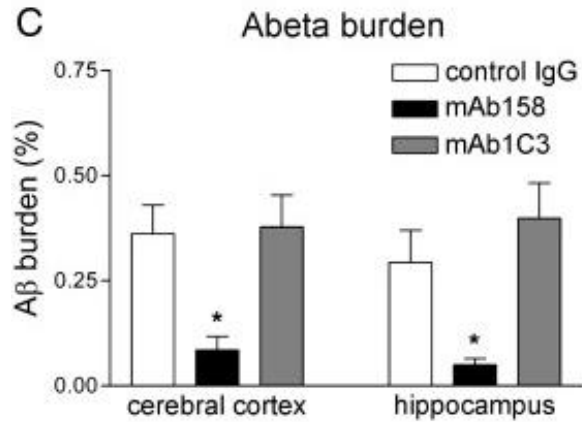
Lecanemab: antibody against amyloid



Testing a drug candidate in the lab



Testing a drug candidate in mice

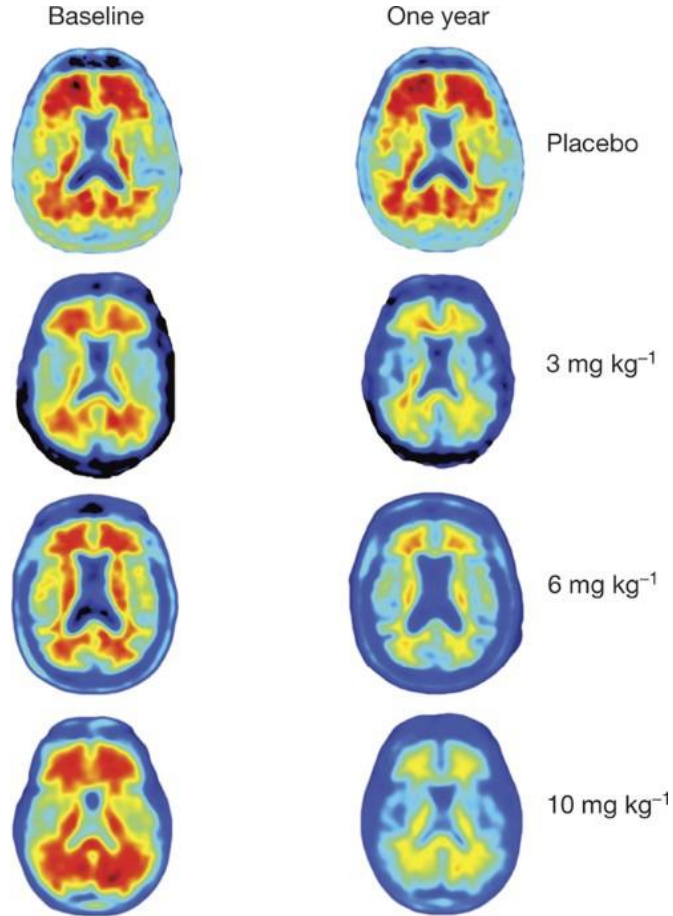


Drug development: The ultimate goal of discovery research

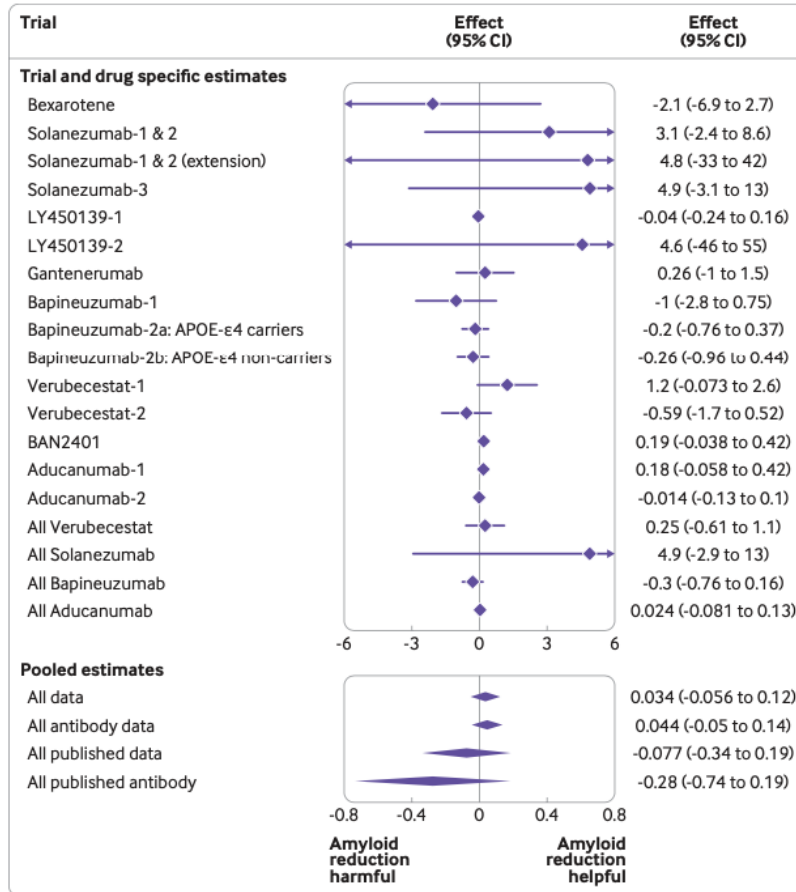


New drugs for Alzheimer's disease



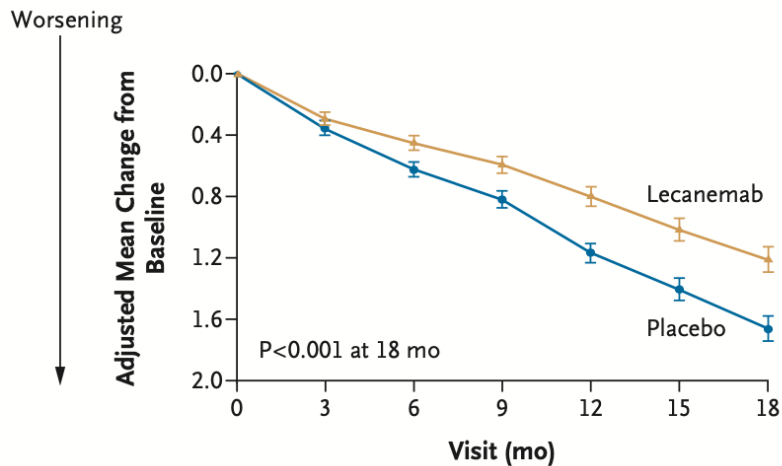


Current drugs are
very effective at
lowering plaque

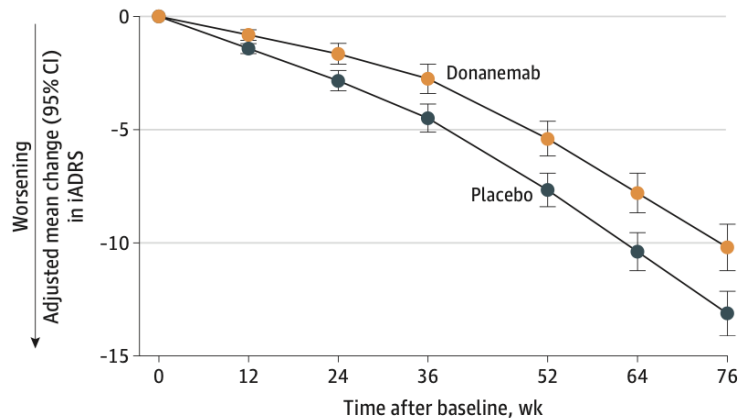


But do these drugs improve cognition?

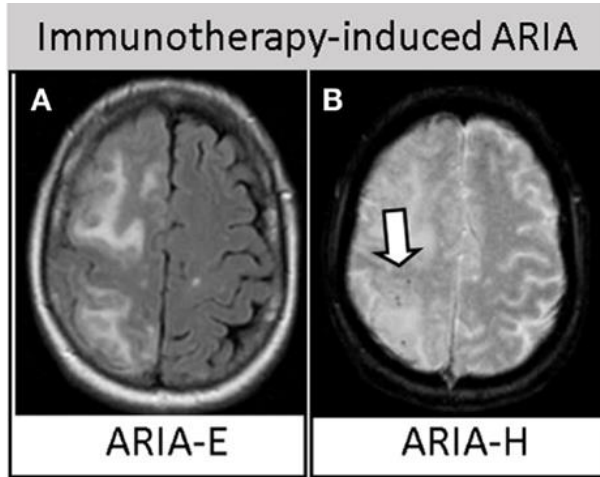
Lecanemab and Donanemab



B iADRS in combined population

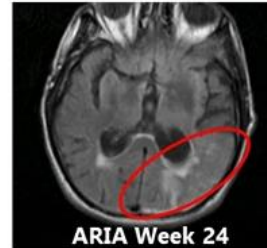


ARIA: Amyloid related Imaging Abnormality

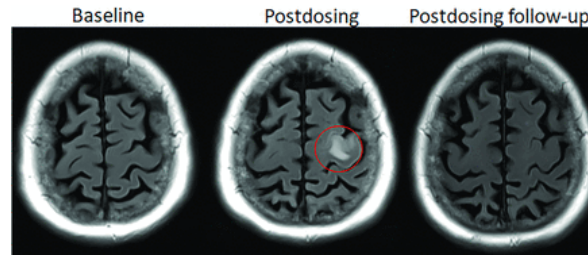


Severity: Area/number – often only reported as % prevalence

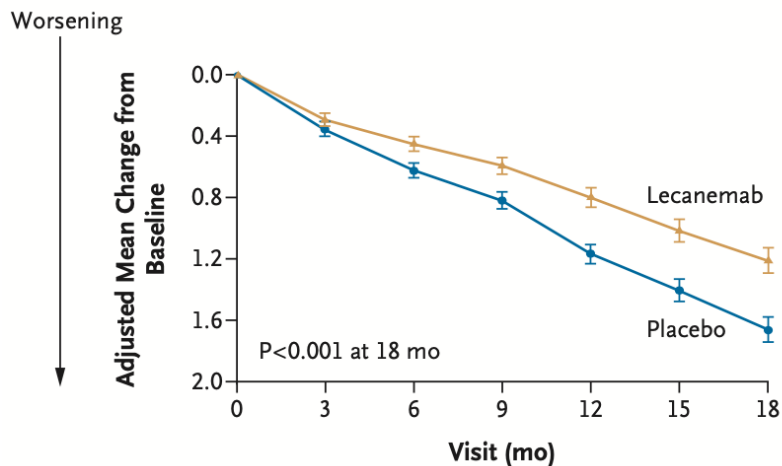
gantenerumab



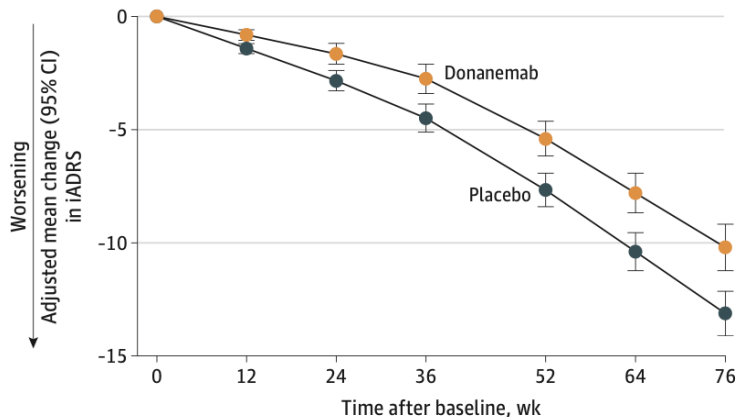
- Asymptomatic or symptomatic
- Can be severe: Deaths of several people attributed to ARIA
- Long-term clinical significance uncertain



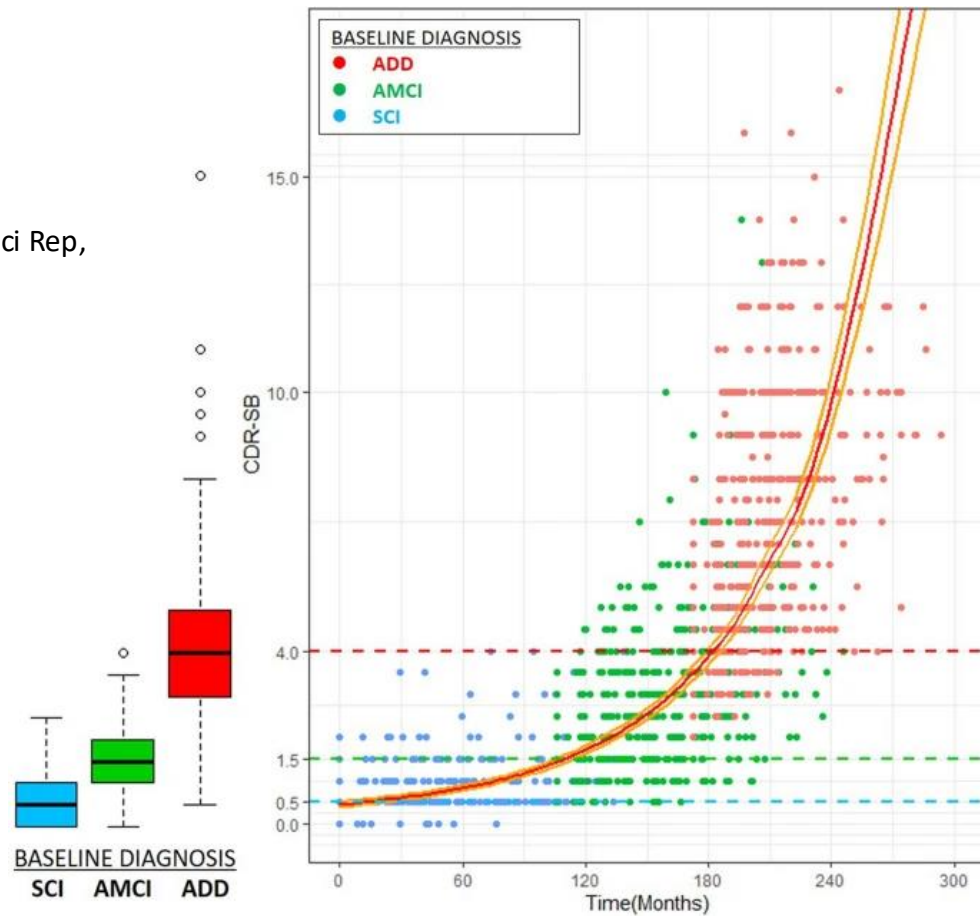
Will therapy lead to long term benefit?



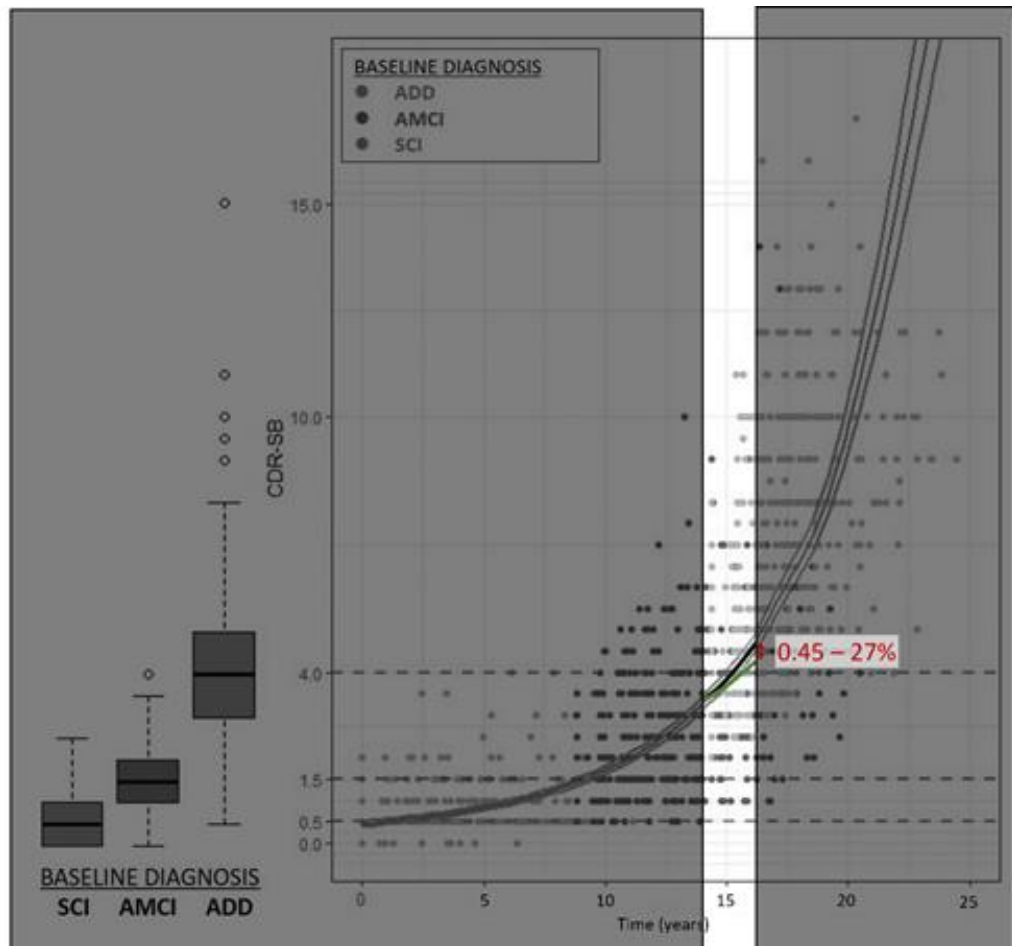
B iADRS in combined population



Kim et al., Sci Rep,
2020

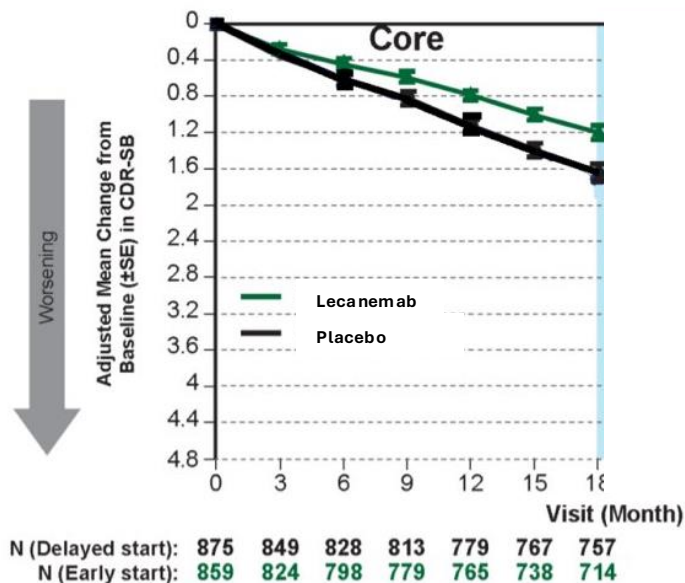


Kim et al., Sci Rep,
2020

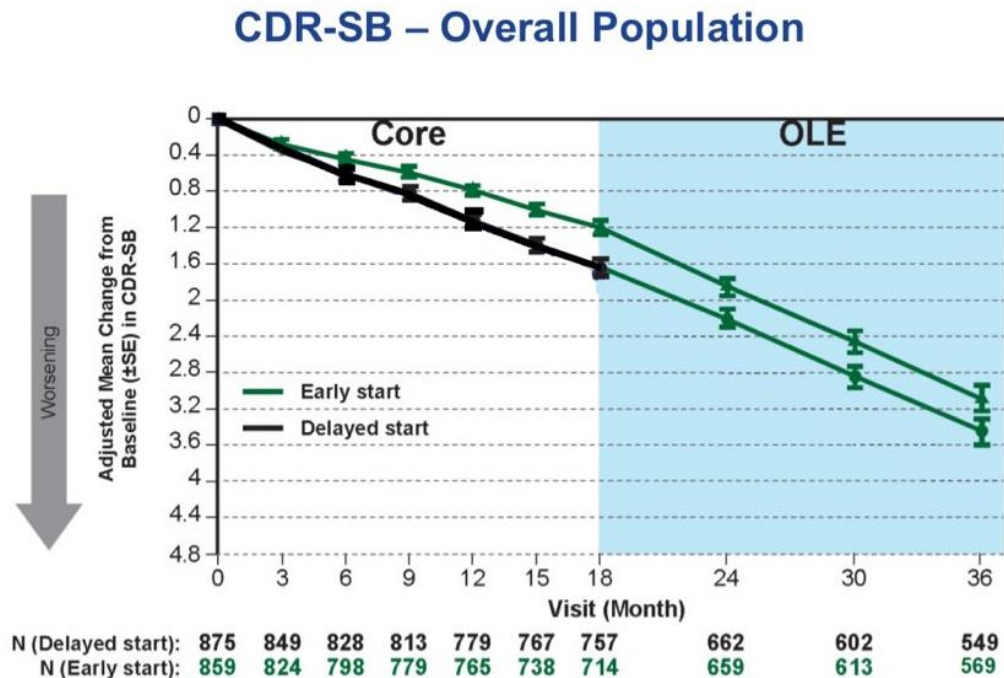


What is the long-term benefit of anti-amyloid drugs?

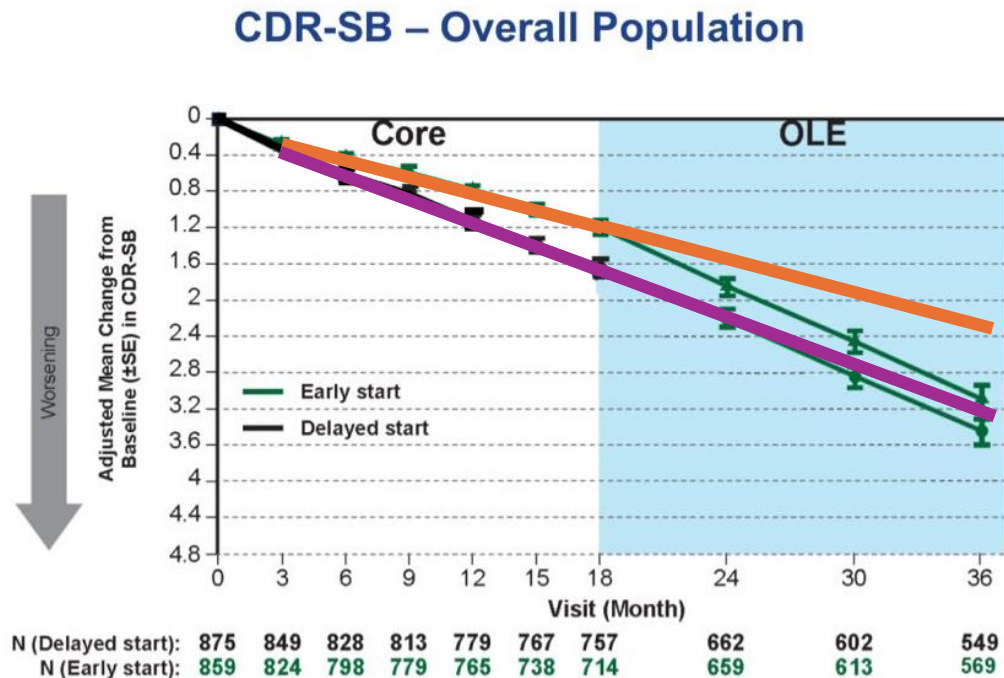
CDR-SB – Overall Population



What is the long-term benefit of anti-amyloid drugs?



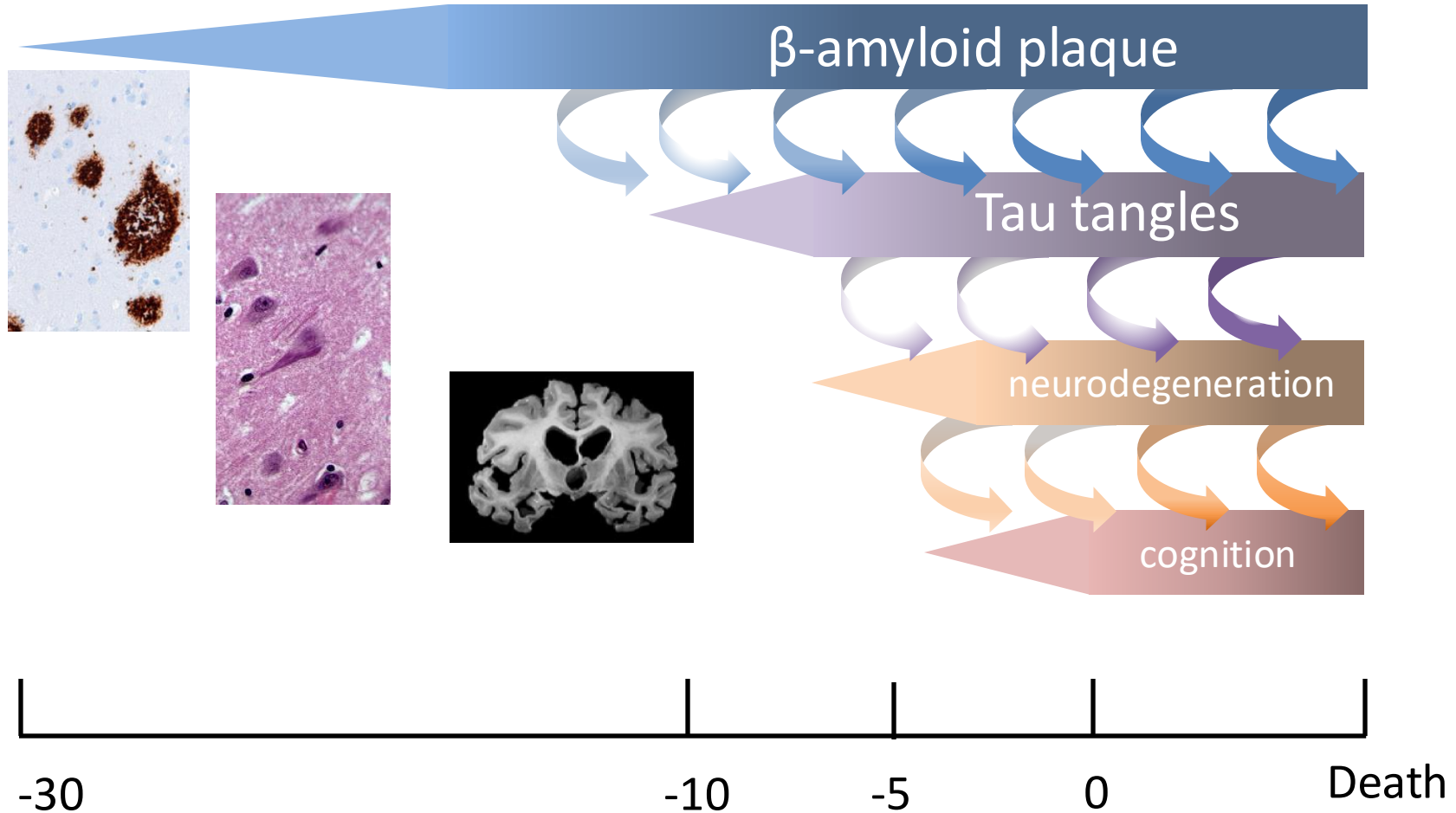
What is the long-term benefit of anti-amyloid drugs?



Anti-amyloid drugs in the approval process

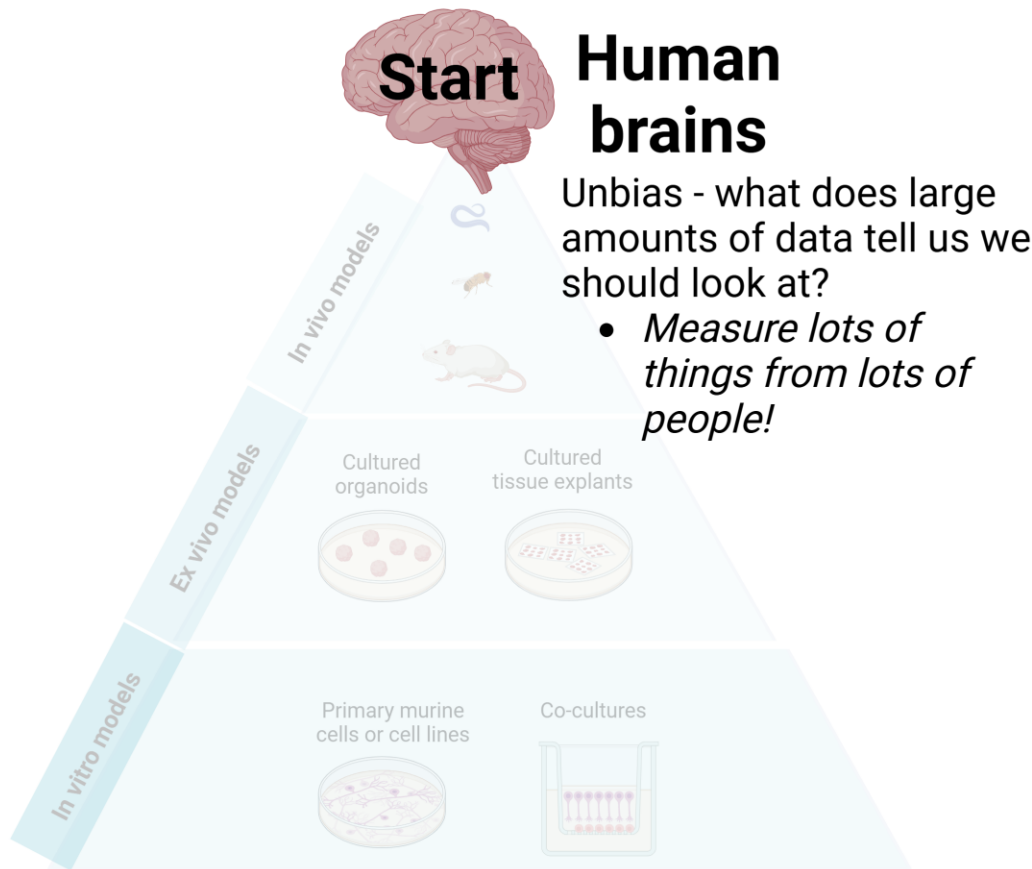
	aducanumab	lecanemab	donanemab
USA	Withdrawn	Approved	Approved
EU	Rejected	recommended	Under consideration
UK	Rejected	Approved (not reimbursed)	Approved (not reimbursed)
Aus	Rejected	Rejected	Under consideration

Alzheimer's disease natural history



2

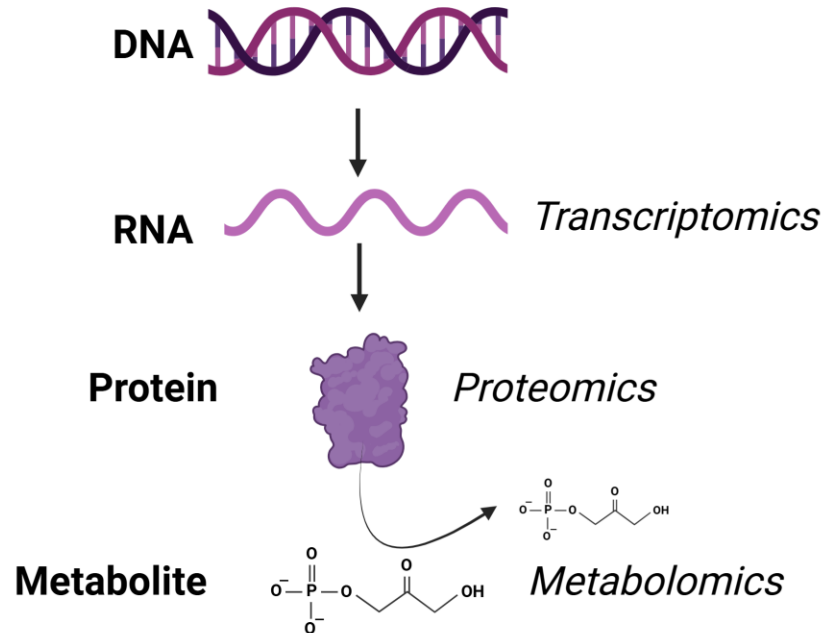
Data driven research



2

Data driven research: Omics technology

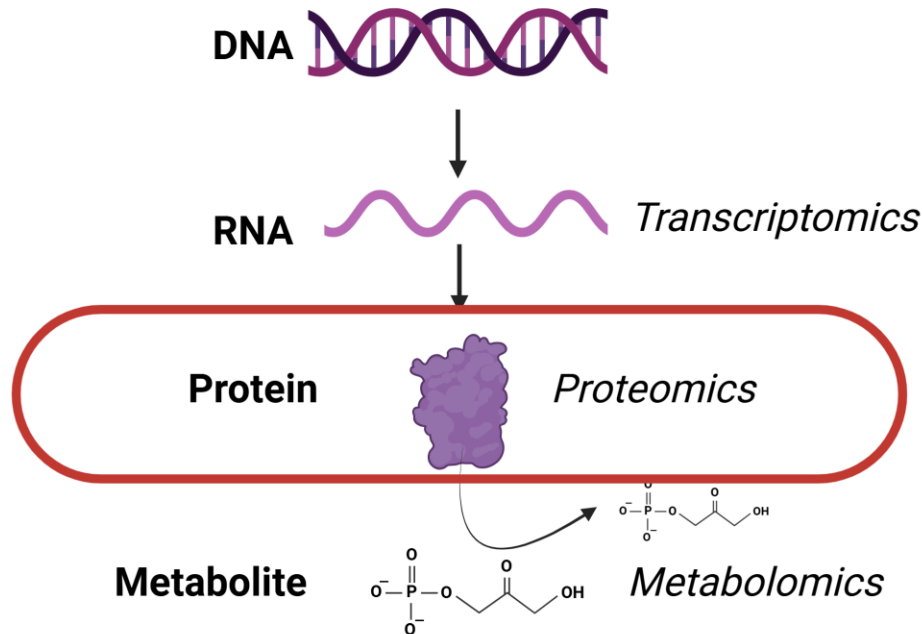
"*-omics*" is used to denote fields of study that focus on the complete or total set of a specific type of **biological molecule** or process



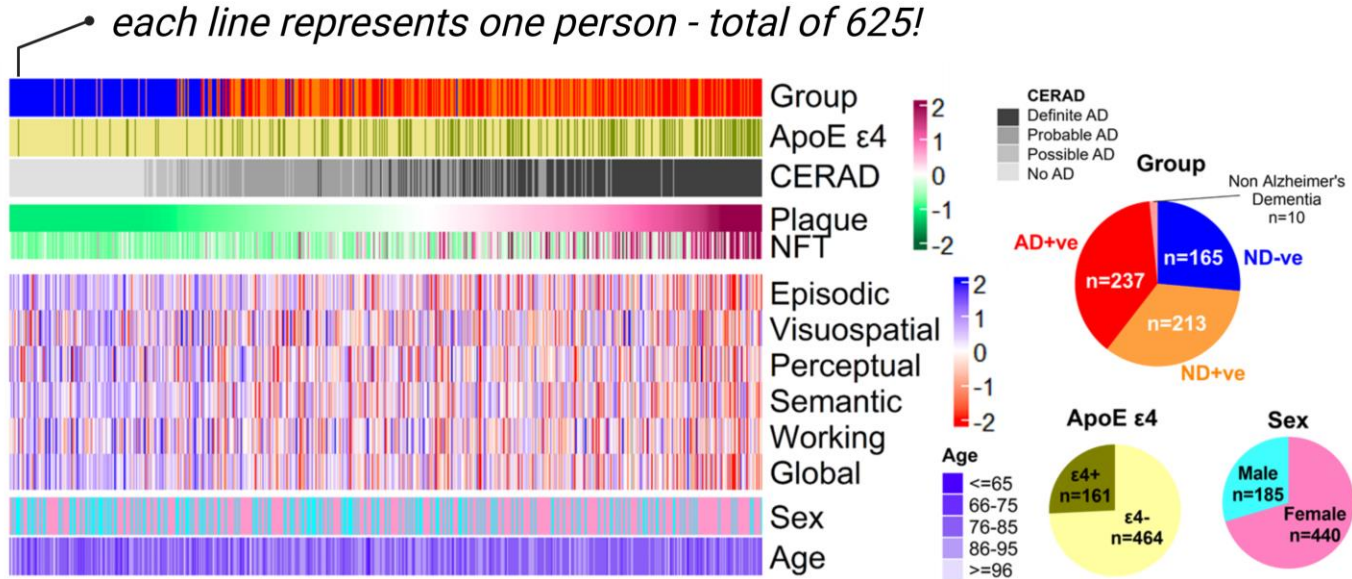
2

Data driven research: Omics technology

"-omics" is used to denote fields of study that focus on the complete or total set of a specific type of **biological molecule** or process

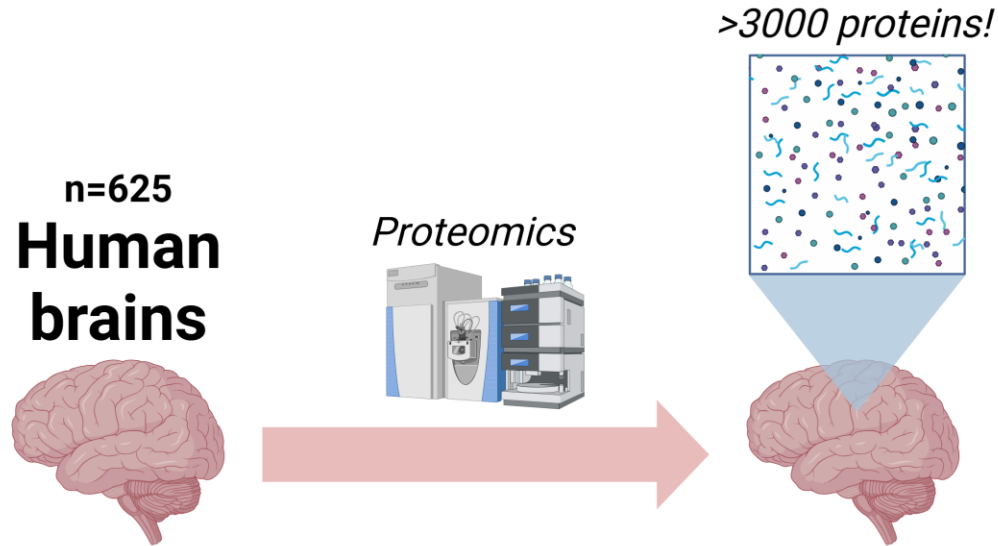


The Cohort: Memory and Aging project



2

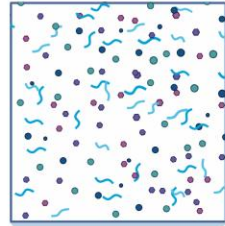
Data driven research - My own research!



*What does a complete view of all the
proteins in the human brain from
a large cohort tell us we should investigate?*

...3111 proteins from 625 people - now what?

>3000 proteins!



x 625



...3111 proteins from 625 people - now what?

Bioinformatics - A field of science that uses computers, databases, math, and statistics to collect, store, organize, and analyze large amounts of biological, medical, and health information.

= making sense of large data!

**Weighted gene co-expression network analysis
(WGCNA)**

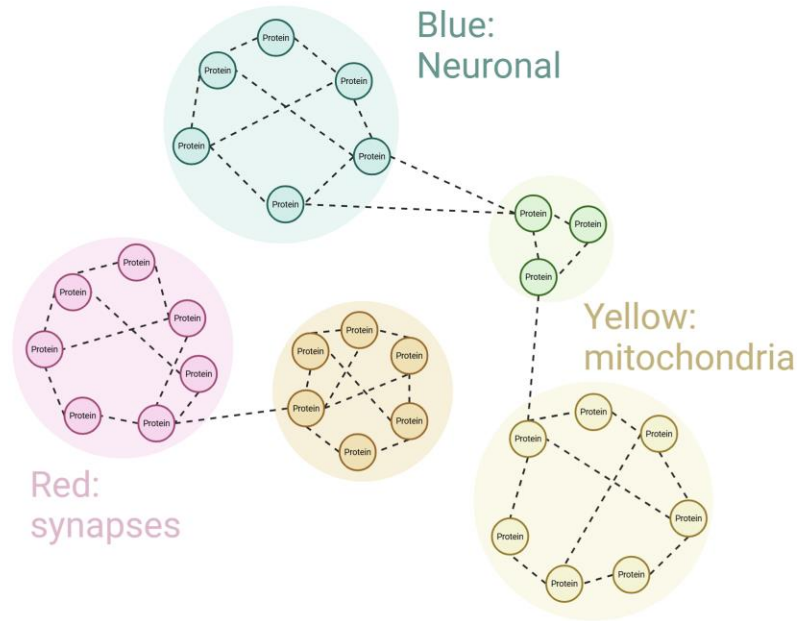
Weighted gene co-expression network analysis (WGCNA)

Clusters proteins into functional units 'cliques'
which can be ascribed biological functions

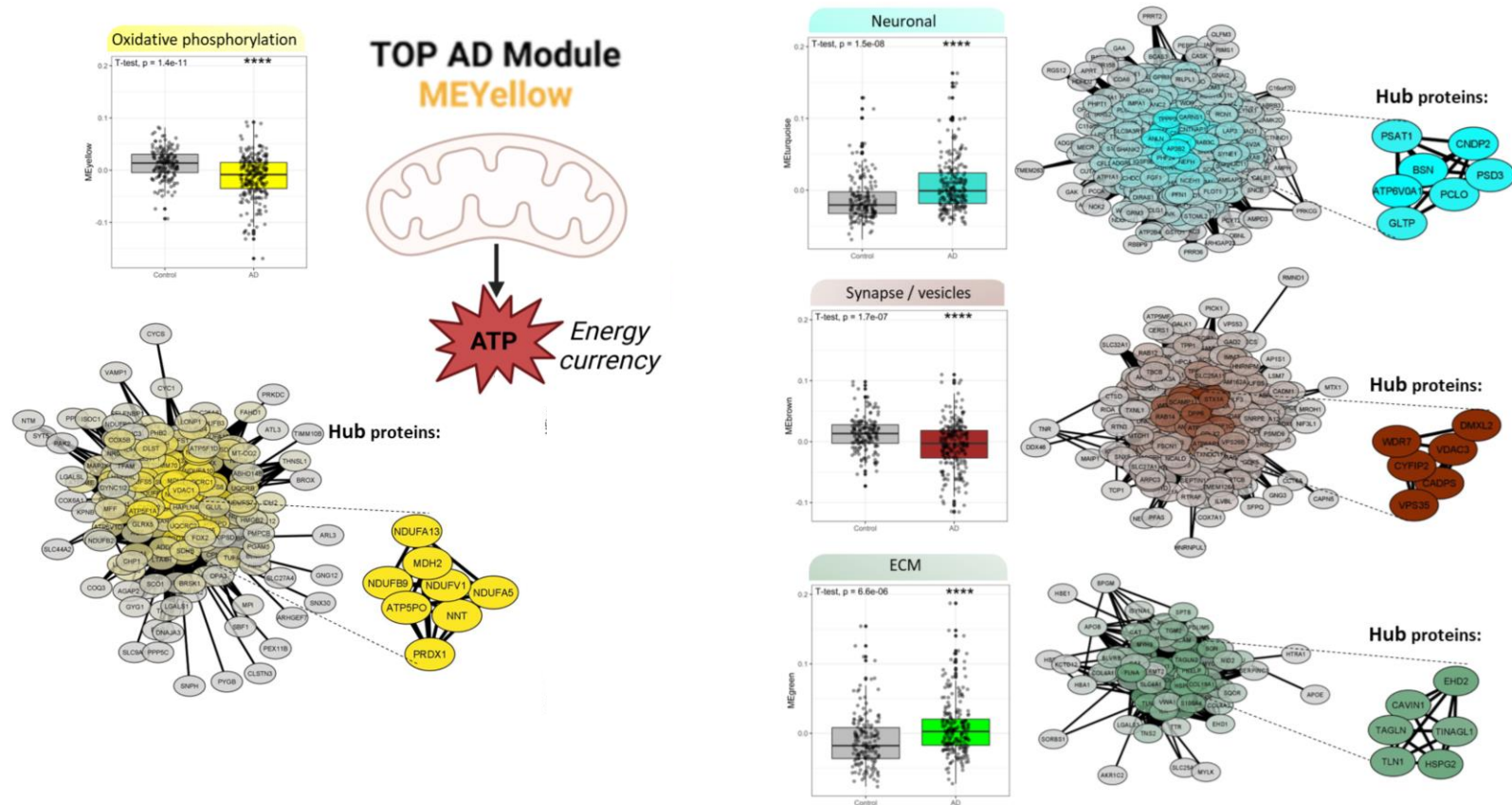


Weighted gene co-expression network analysis (WGCNA)

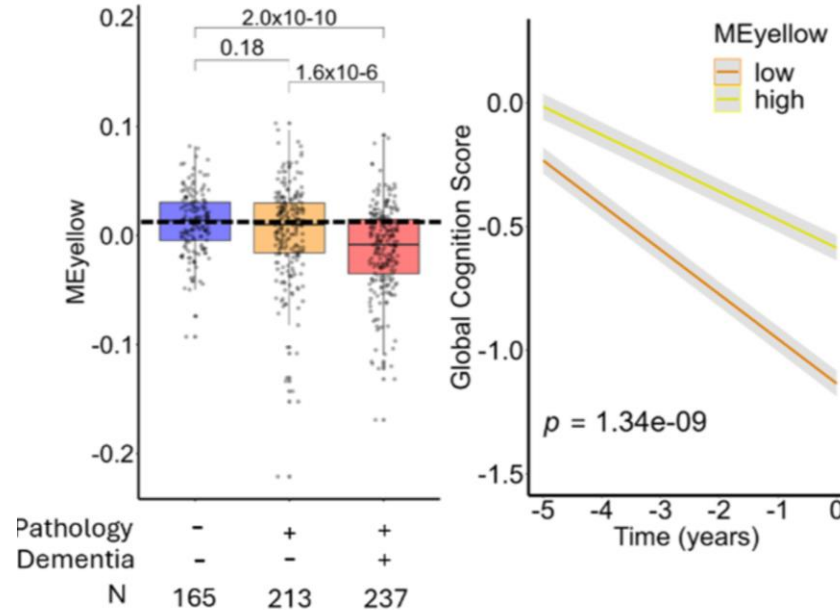
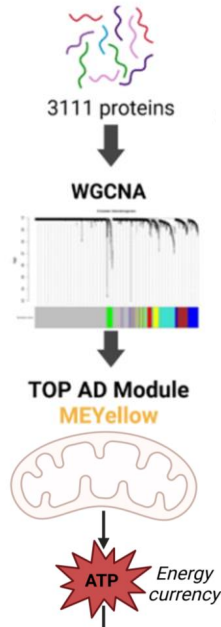
Clusters proteins into functional units 'cliques' which can be ascribed biological functions



Weighted gene co-expression network analysis (WGCNA)



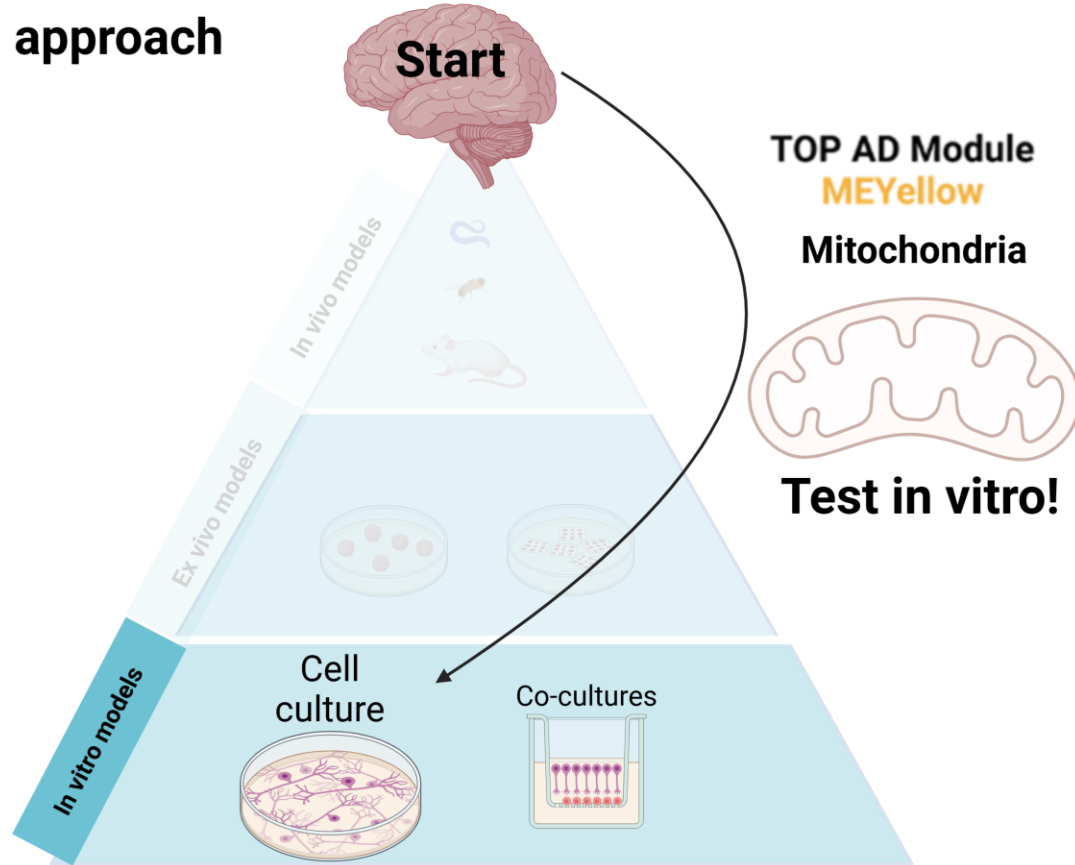
We should look into mitochondria changes (AKA. energy production)



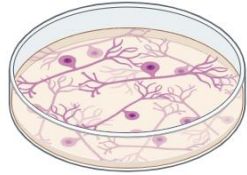
**A data driven
approach**

Human Brain

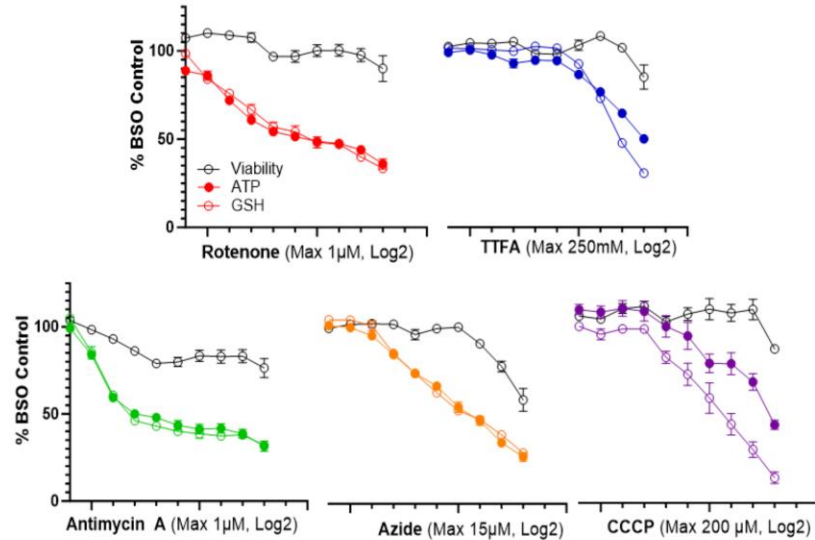
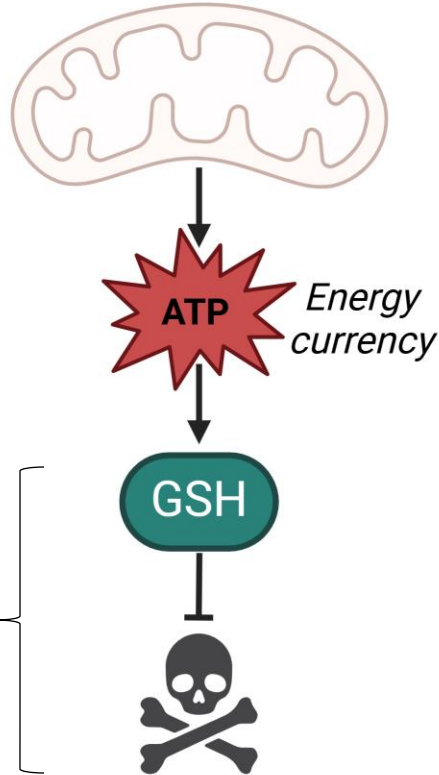
Start



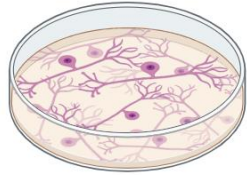
Cells
- Neurons



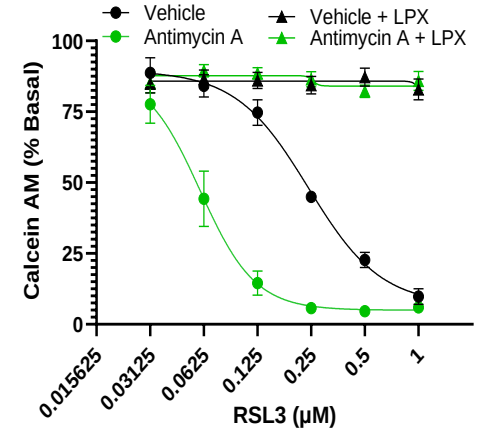
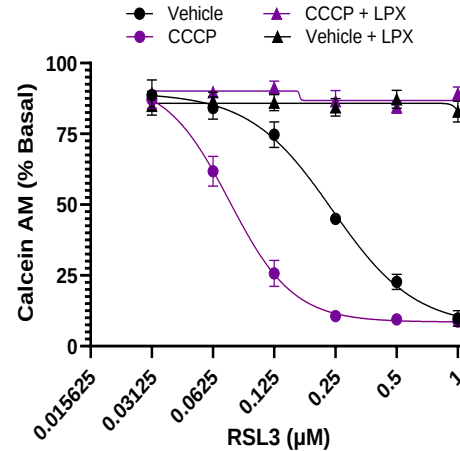
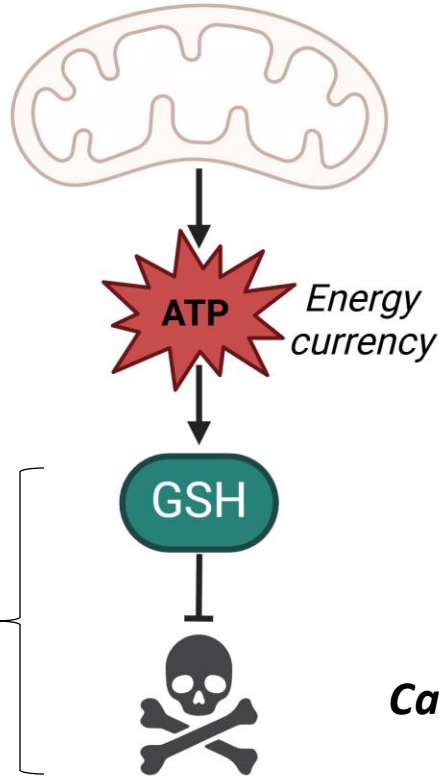
Targeting energy production to prevent neuronal cell death



Cells
- Neurons

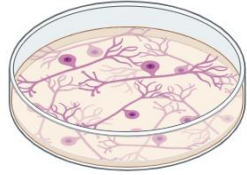


Targeting energy production to prevent neuronal cell death

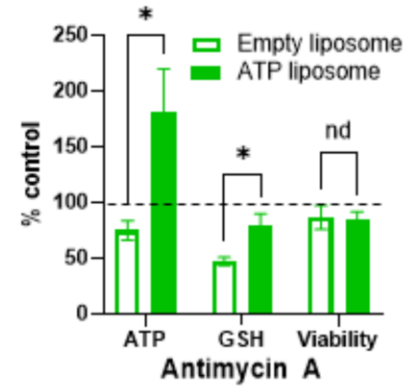
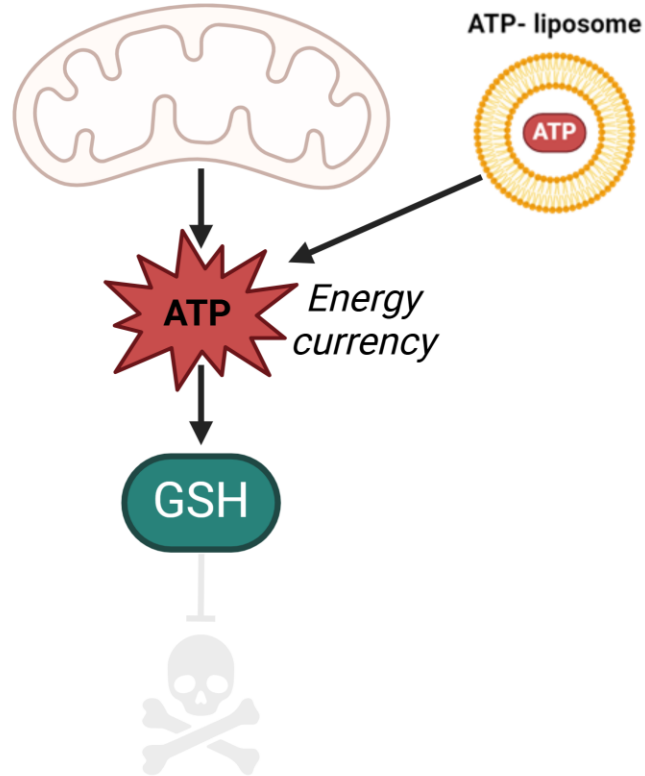


Low energy production = increased cell death!
Can we create a drug to increase energy and prevent cell death?

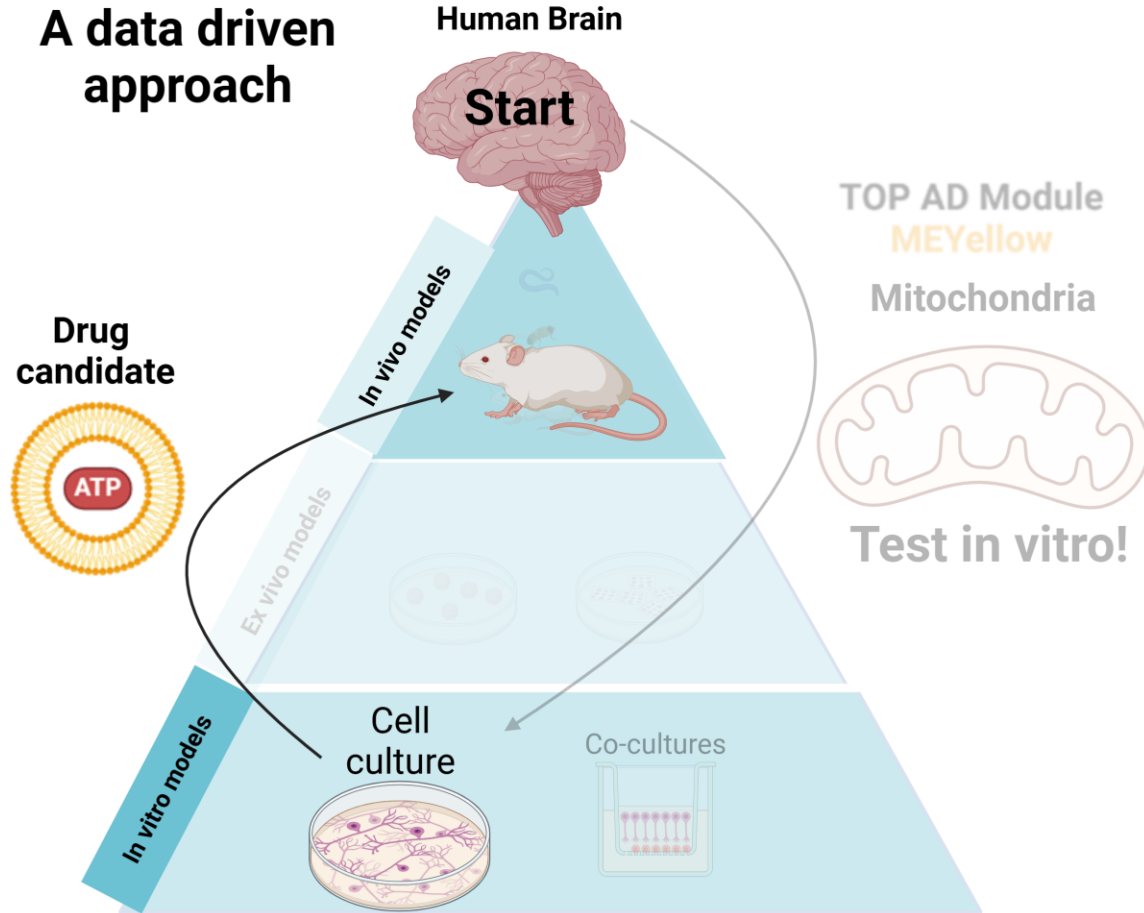
Cells
- Neurons



Therapeutic strategy: Increase ATP/Energy



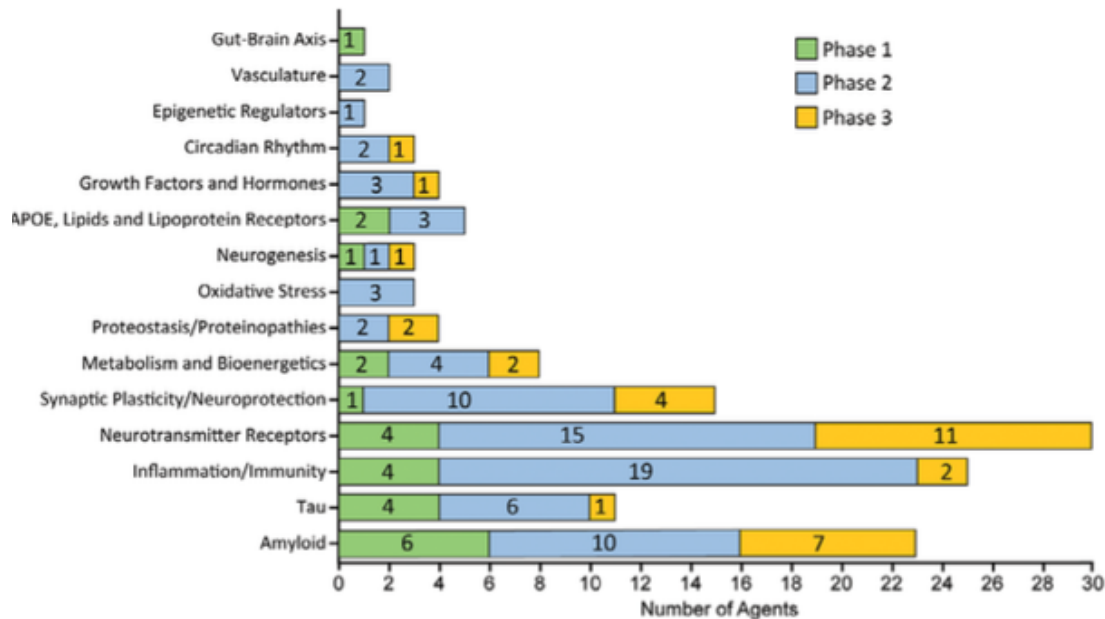
A data driven approach



New drug trials for Alzheimer's disease



New drug trials for Alzheimer's disease



Modifiable Risk Factors

Undertaking regular physical activity 	Keeping mentally stimulated 	Eating a healthy, balanced diet 	Reducing your alcohol intake 
 Maintaining an active social life	 Maintaining a healthy weight	 Quitting smoking	 Managing health conditions