Effects of LM11A-31 on longitudinal cerebrospinal fluid biomarkers of pathophysiology in Alzheimer's disease

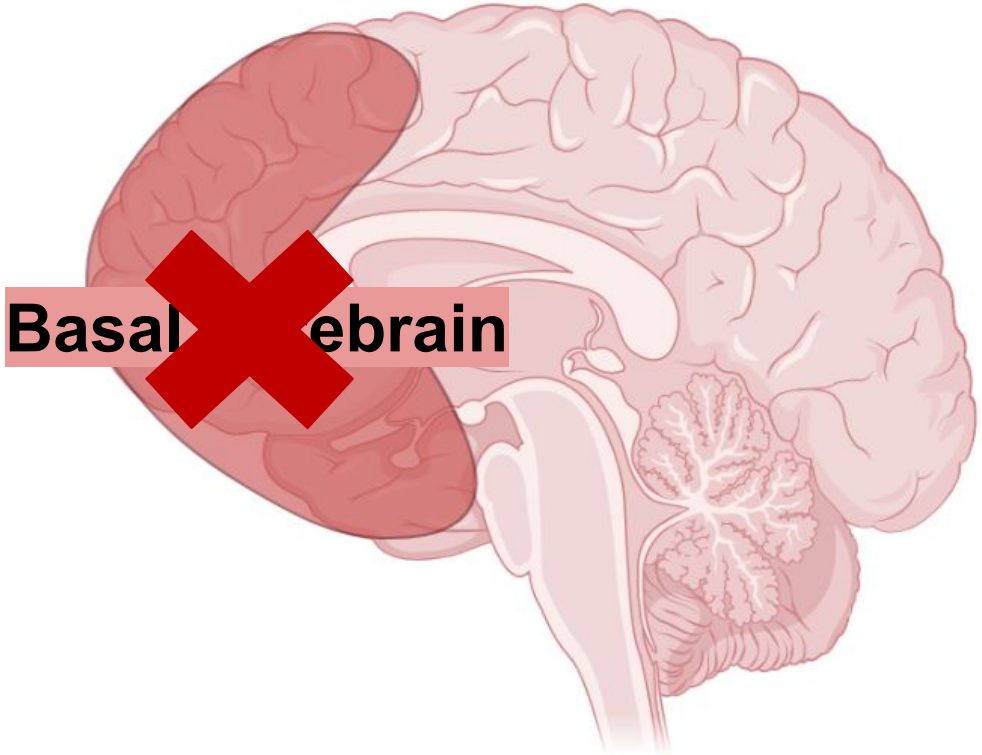
Lucy Hui
Supervisor: Dr. Taylor Schmitz

Schulich MEDICINE & DENTISTRY

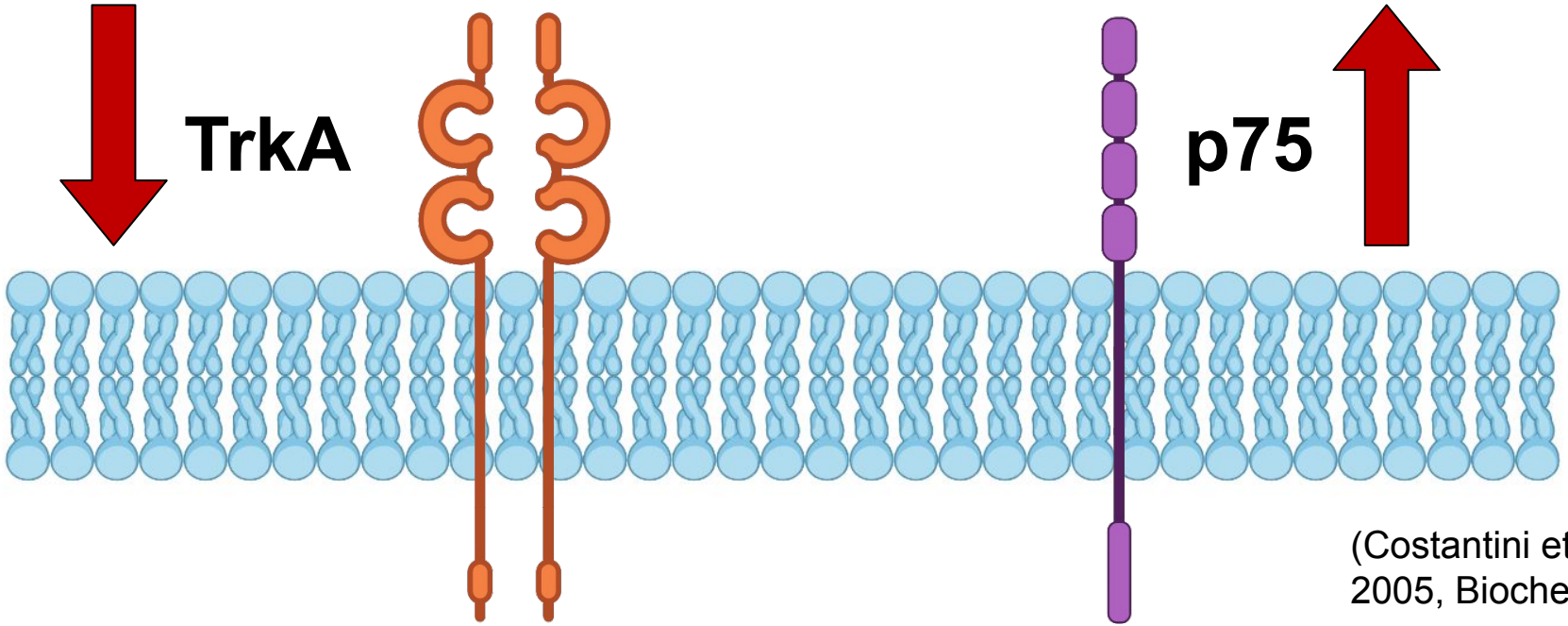
Western

Introduction

Alzheimer's Disease (AD)

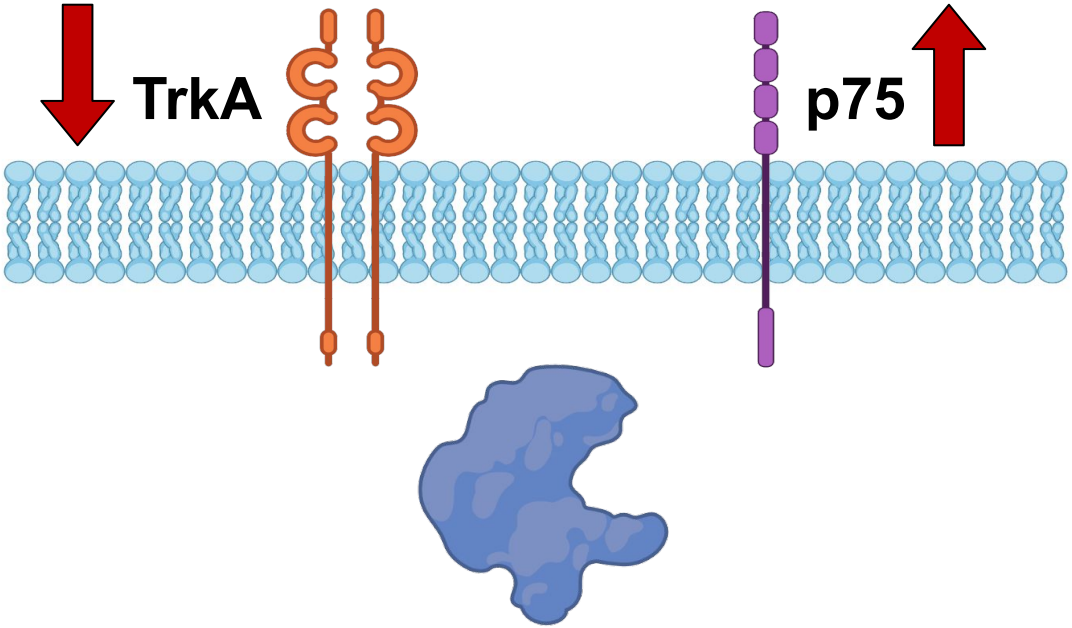


Alzheimer's Disease (AD)



(Costantini et al., 2005, Biochem J)

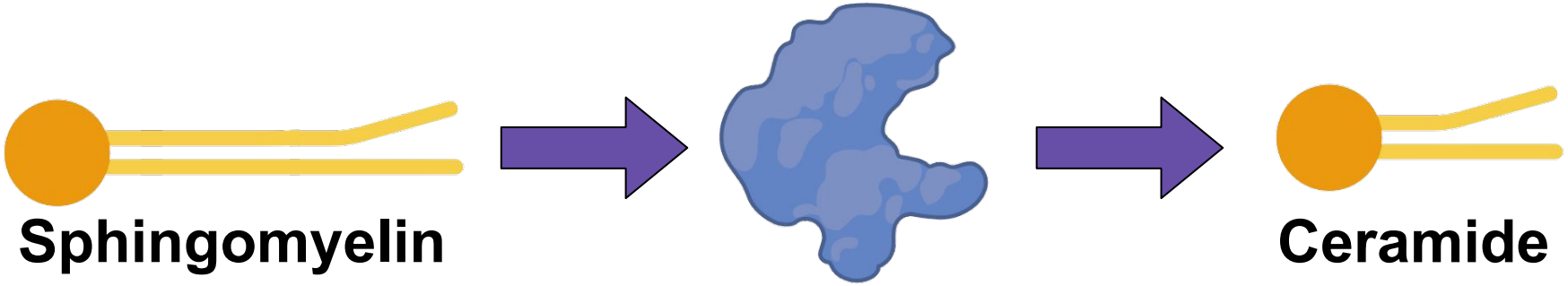
Alzheimer's Disease (AD)



Sphingomyelinase

(Costantini et al., 2005, Biochem J)

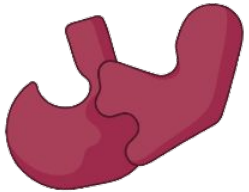
Alzheimer's Disease (AD)



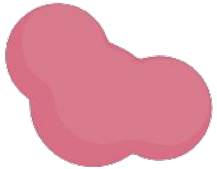
(Costantini et al., 2005, Biochem J)

Alzheimer's Disease (AD)

β secretase



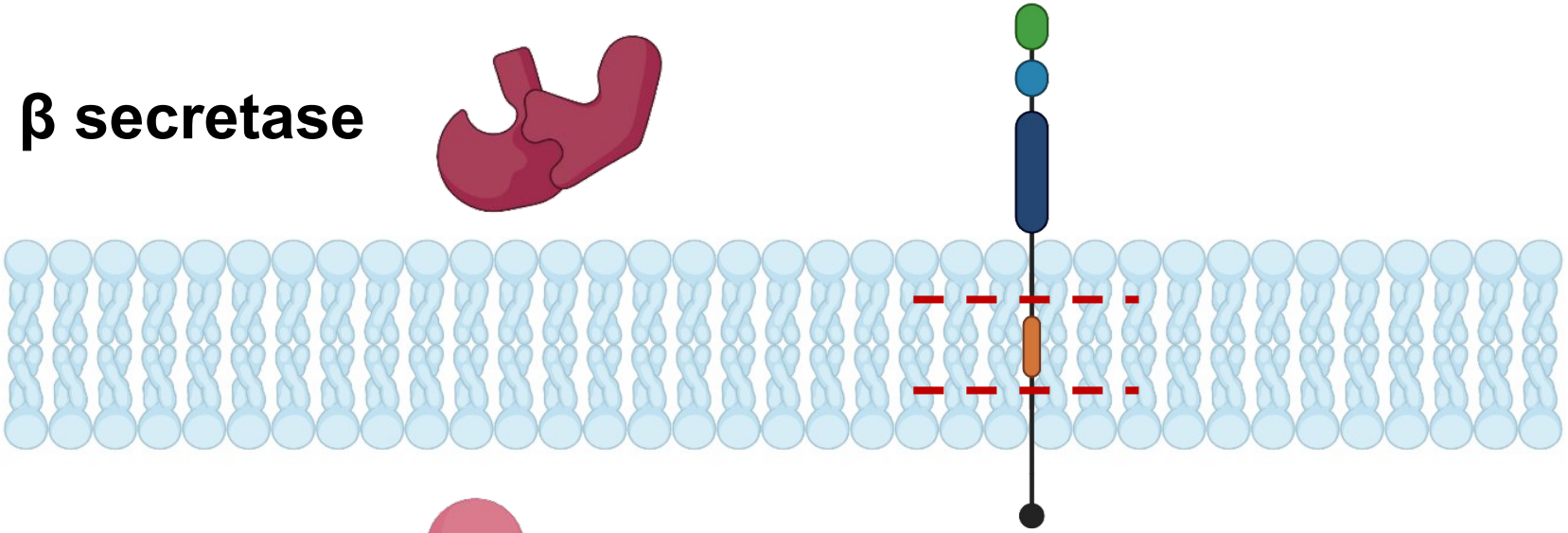
γ secretase



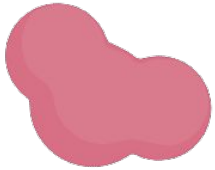
(Takasugi et al., 2015, Biochem Biophys Res Commun)

Alzheimer's Disease (AD)

β secretase

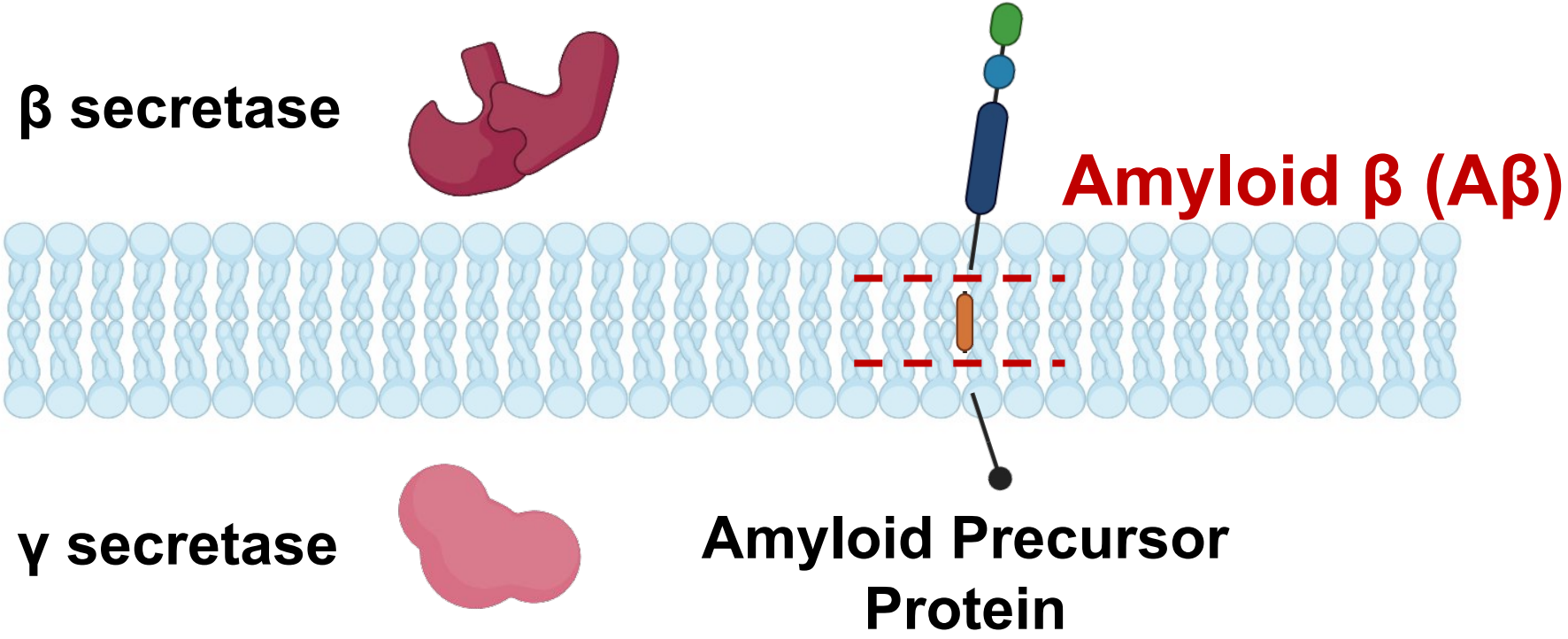


γ secretase

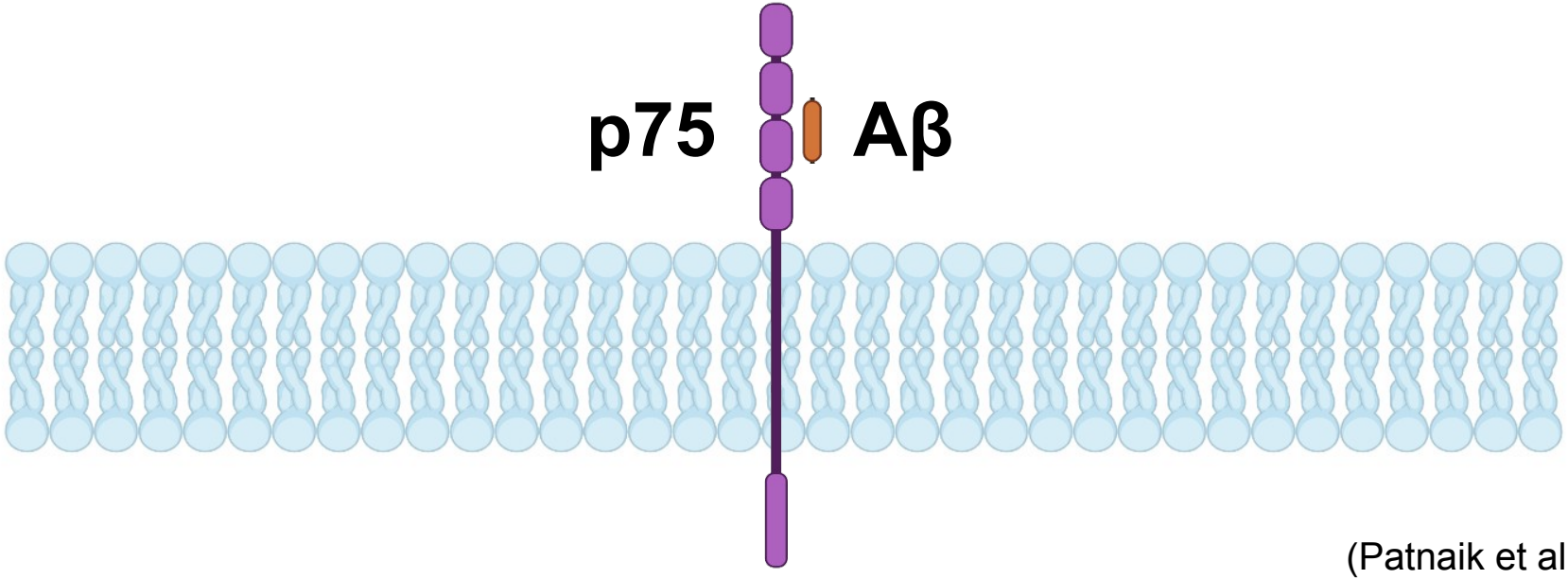


Amyloid Precursor Protein

Alzheimer's Disease (AD)

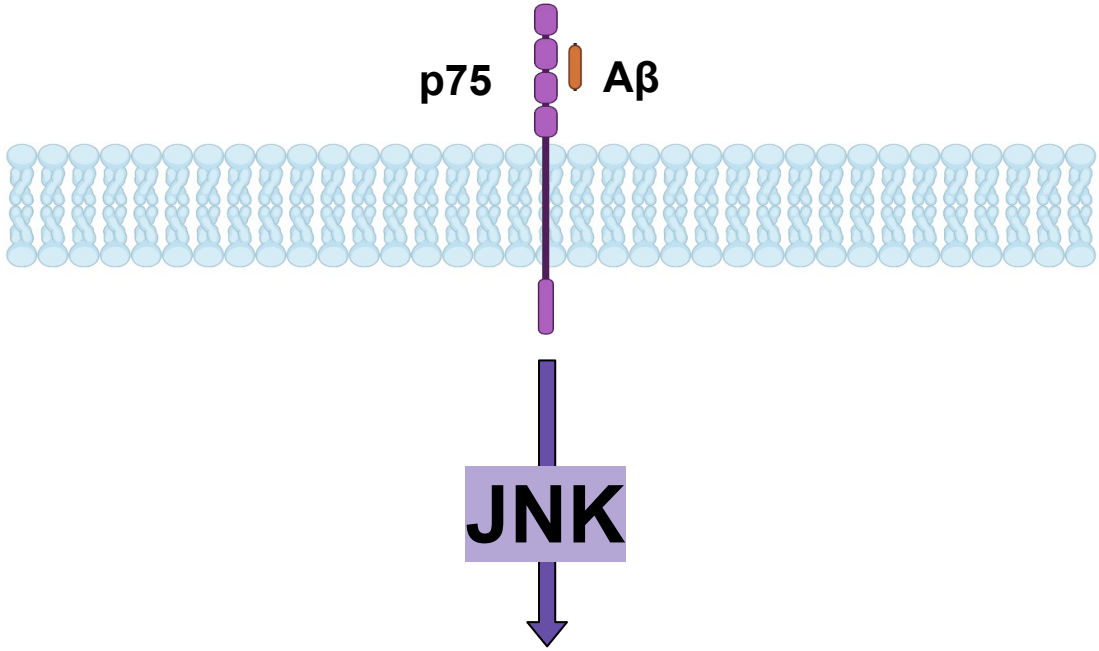


Alzheimer's Disease (AD)



(Patnaik et al., 2020, Nature)

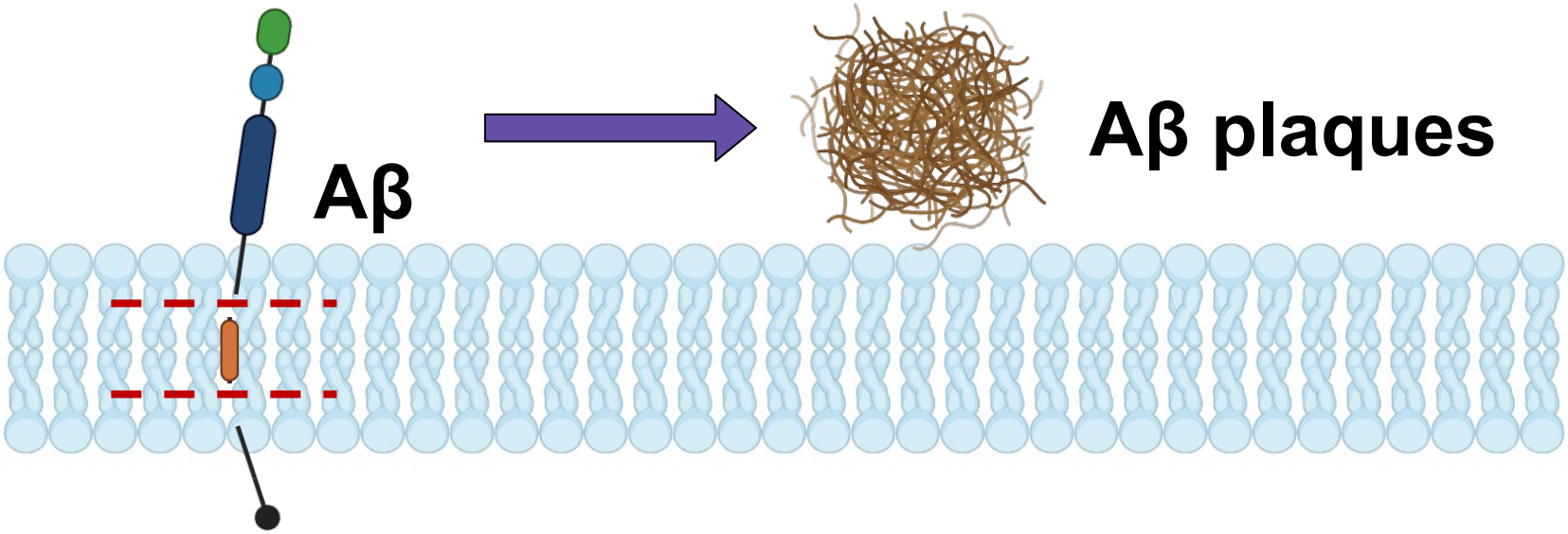
Alzheimer's Disease (AD)



(Patnaik et al., 2020, Nature)

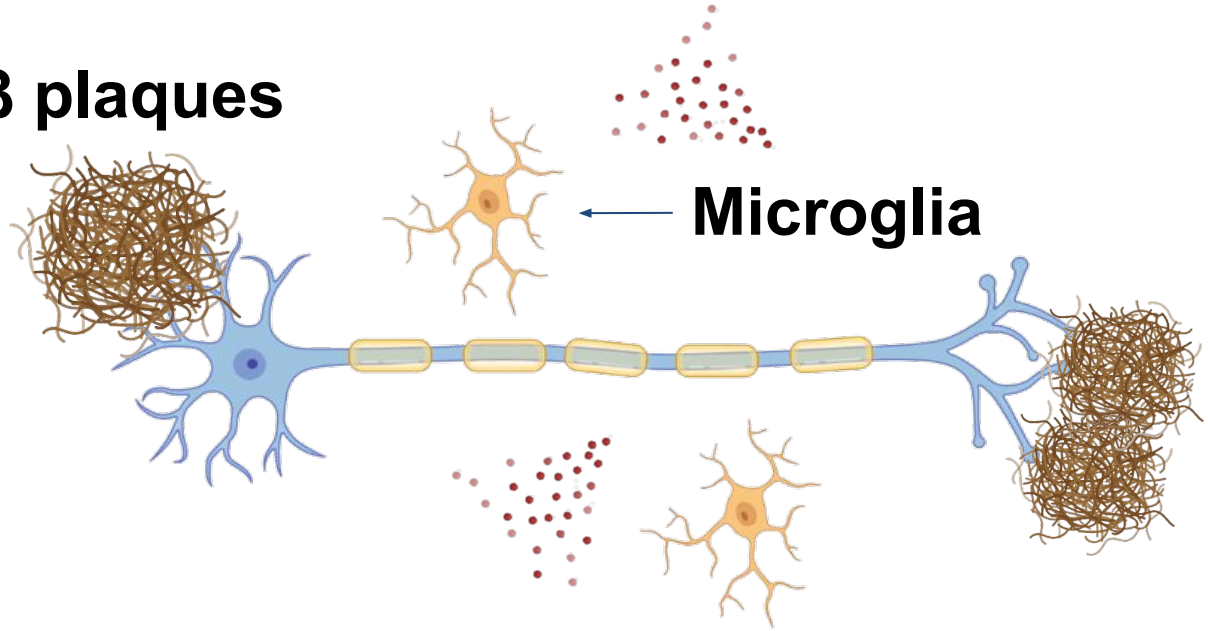
CELL DEATH

Alzheimer's Disease (AD)



Amyloid Precursor Protein

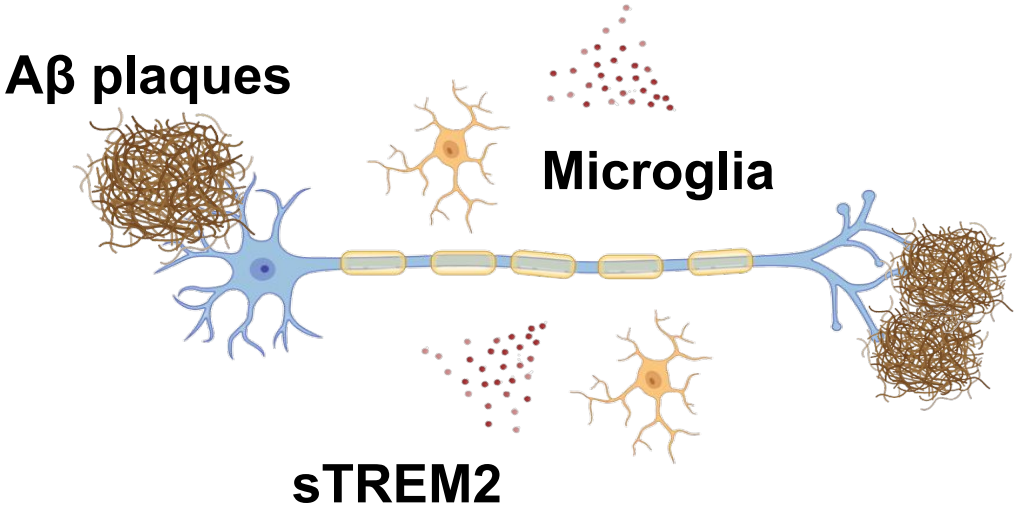
Alzheimer's Disease (AD)



sTREM2

(Kinney et al., 2018, Alzheimers Dement)

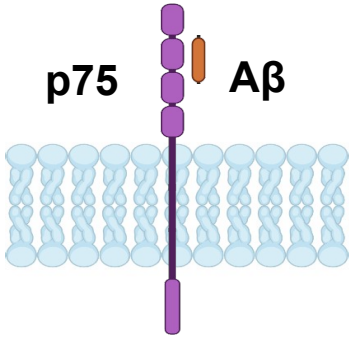
Alzheimer's Disease (AD)

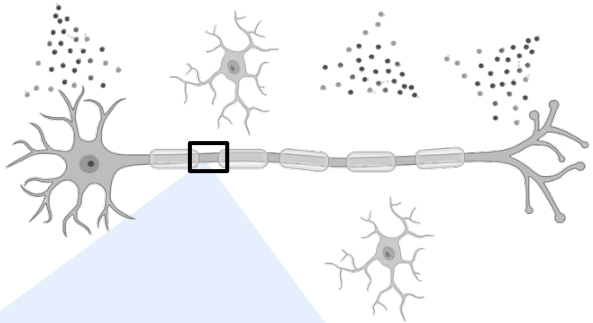


CELL DEATH

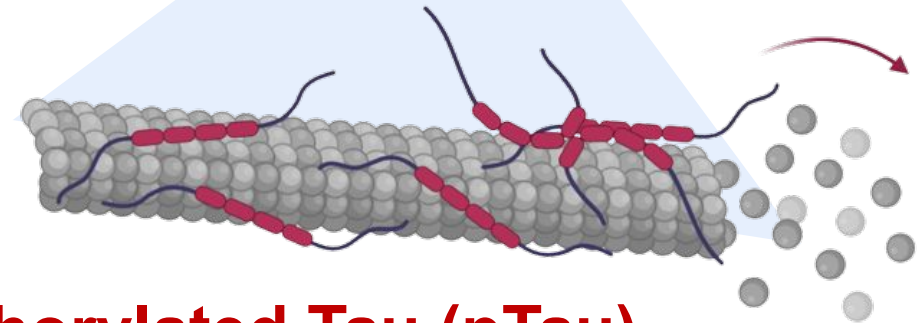
(Kinney et al., 2018, Alzheimers Dement)

Alzheimer's Disease (AD)



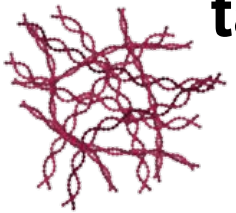


(Shen et al., 2019, Neurobio dis)

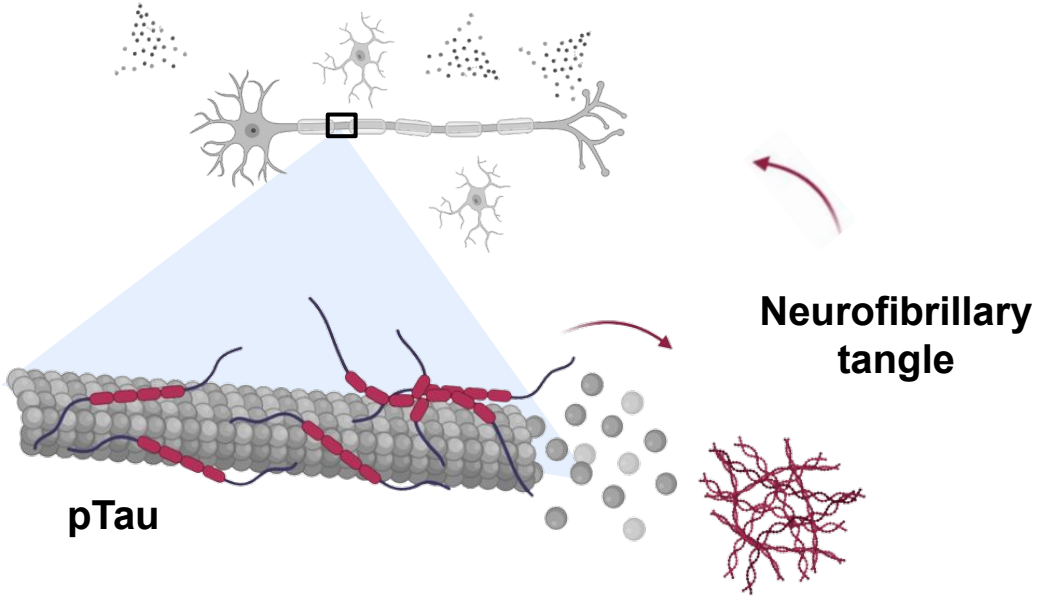


phosphorylated Tau (pTau)

Neurofibrillary tangle

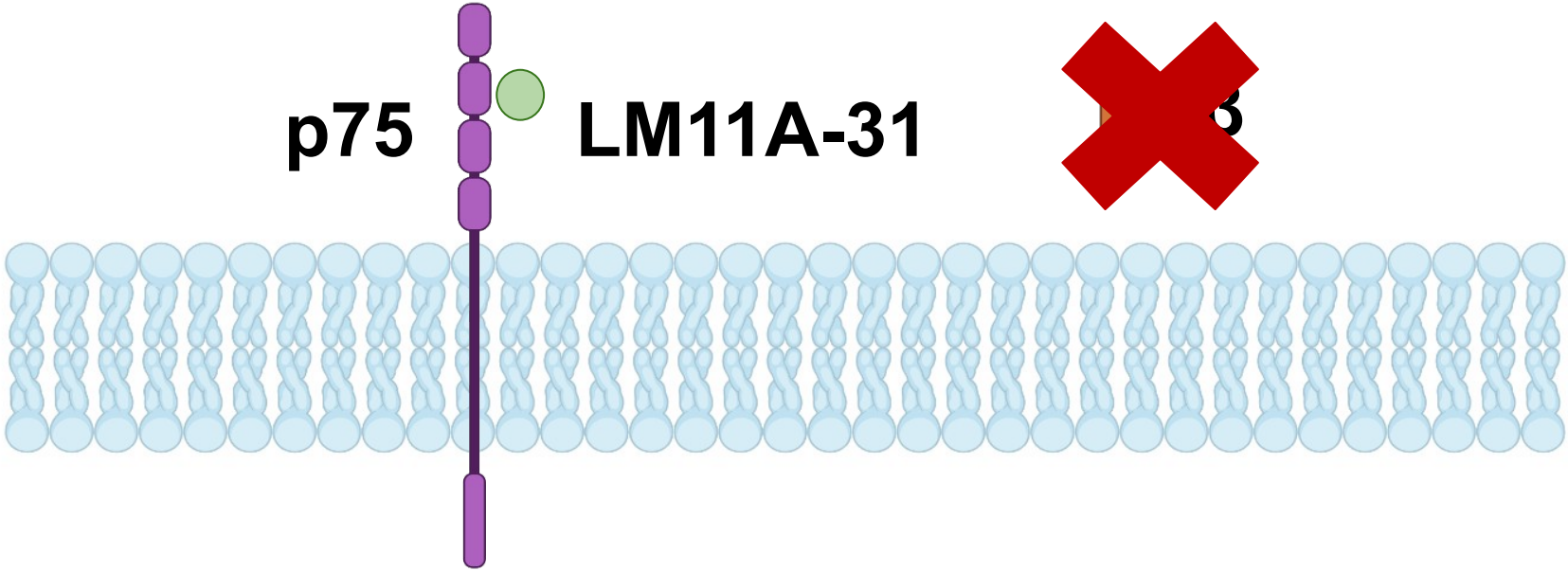


Alzheimer's Disease (AD)



CELL DEATH

Alzheimer's Disease (AD)

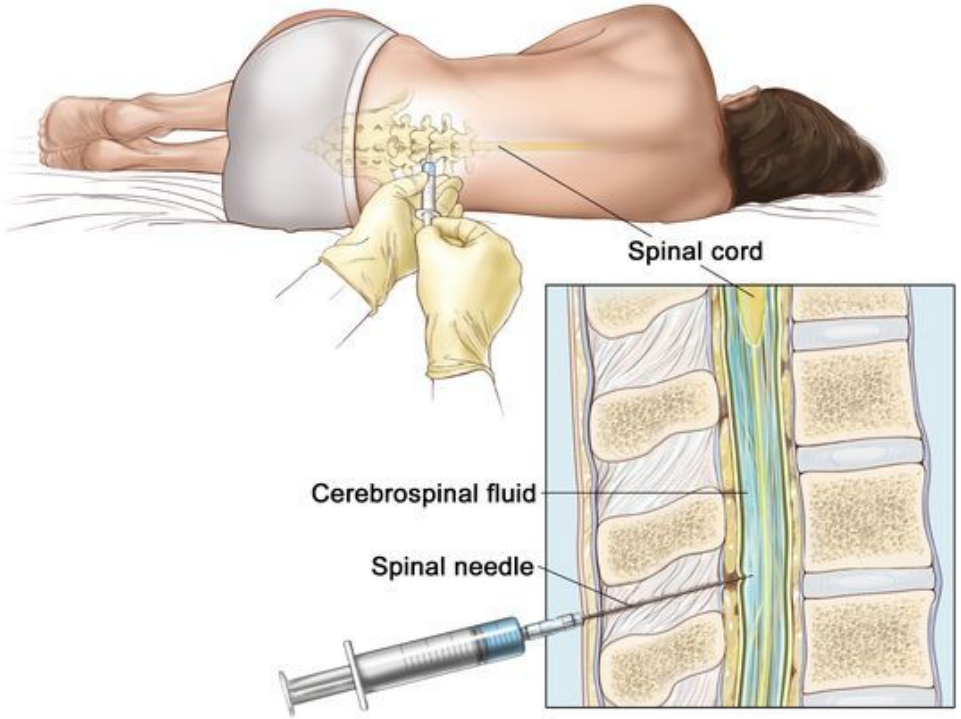


CELL SURVIVAL

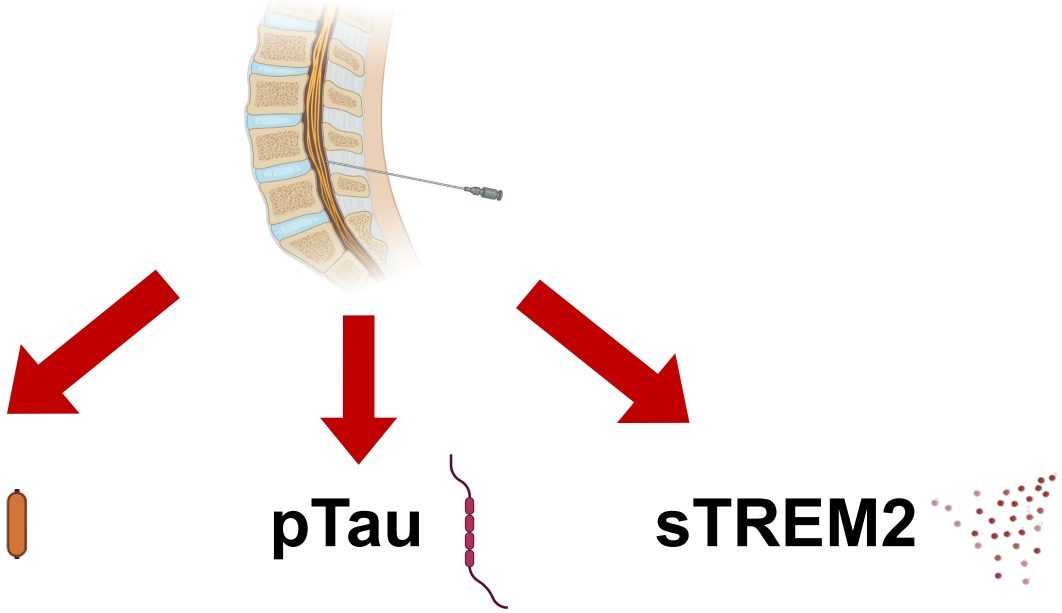
(Simmons et al., 2014, PLoS One)

Cerebrospinal fluid (CSF)

Cerebrospinal fluid (CSF)

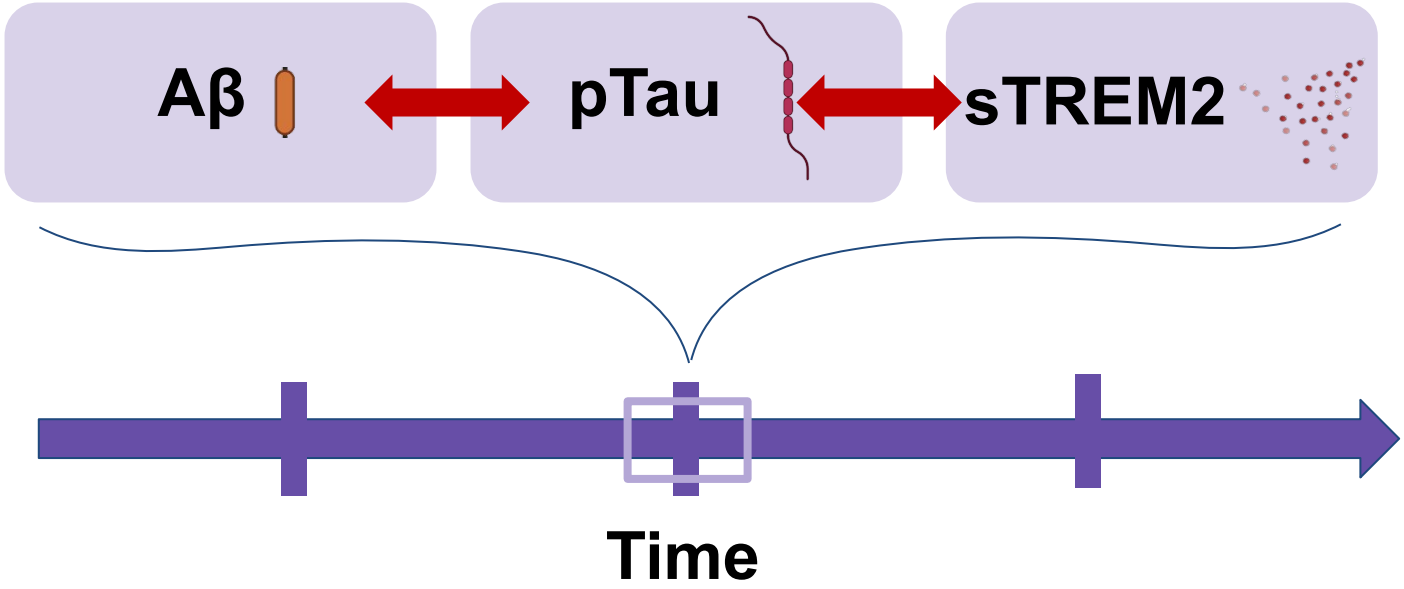


Cerebrospinal fluid (CSF)



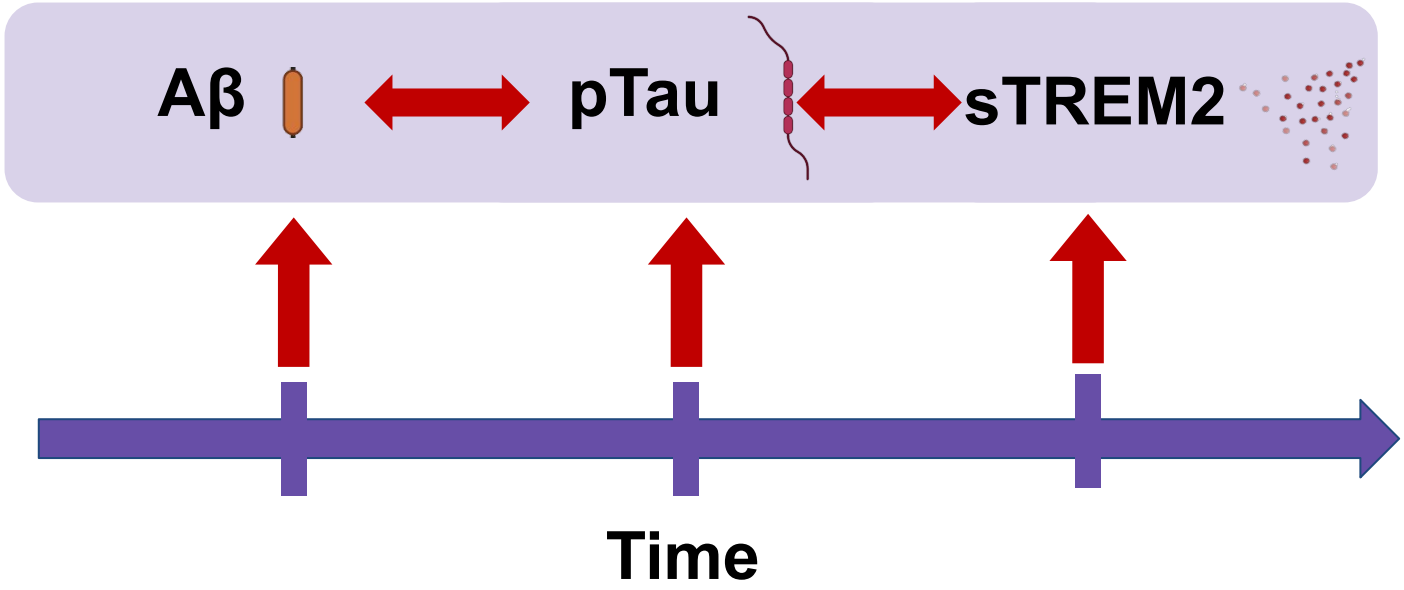
TREATMENT EFFECTIVENESS

Rationale

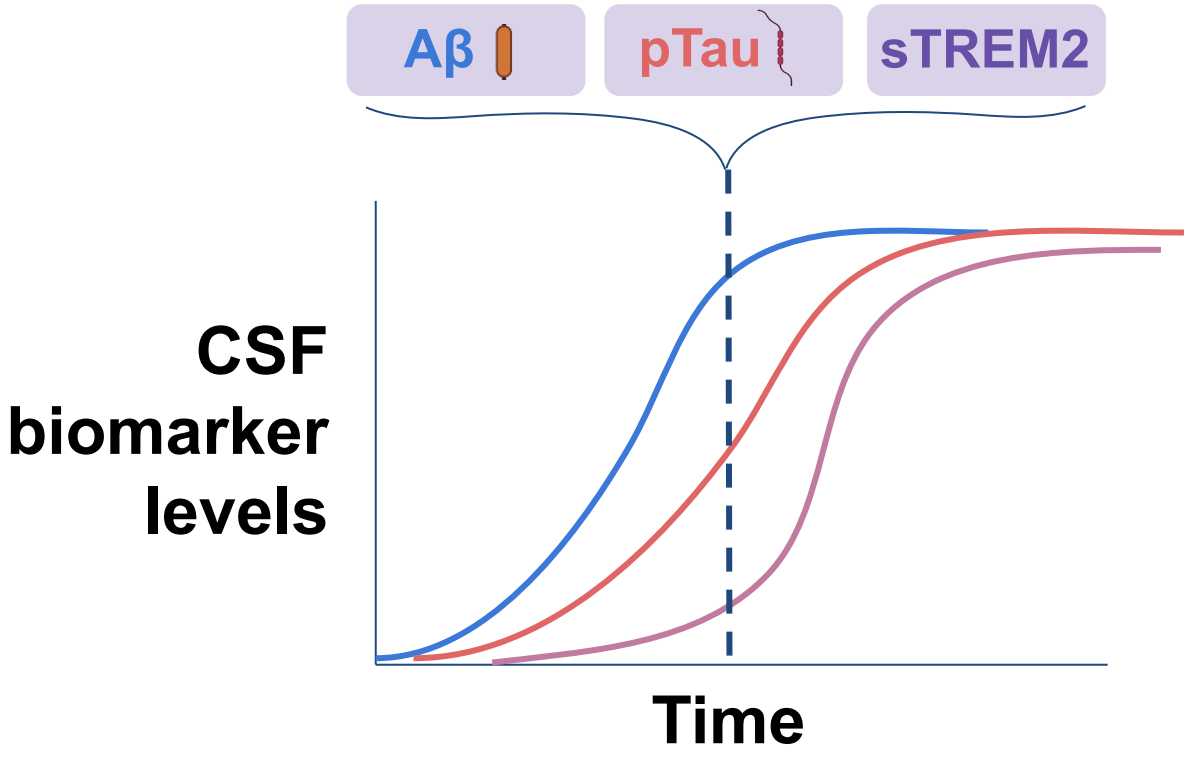


UNIVARIATE & CROSS-SECTIONAL

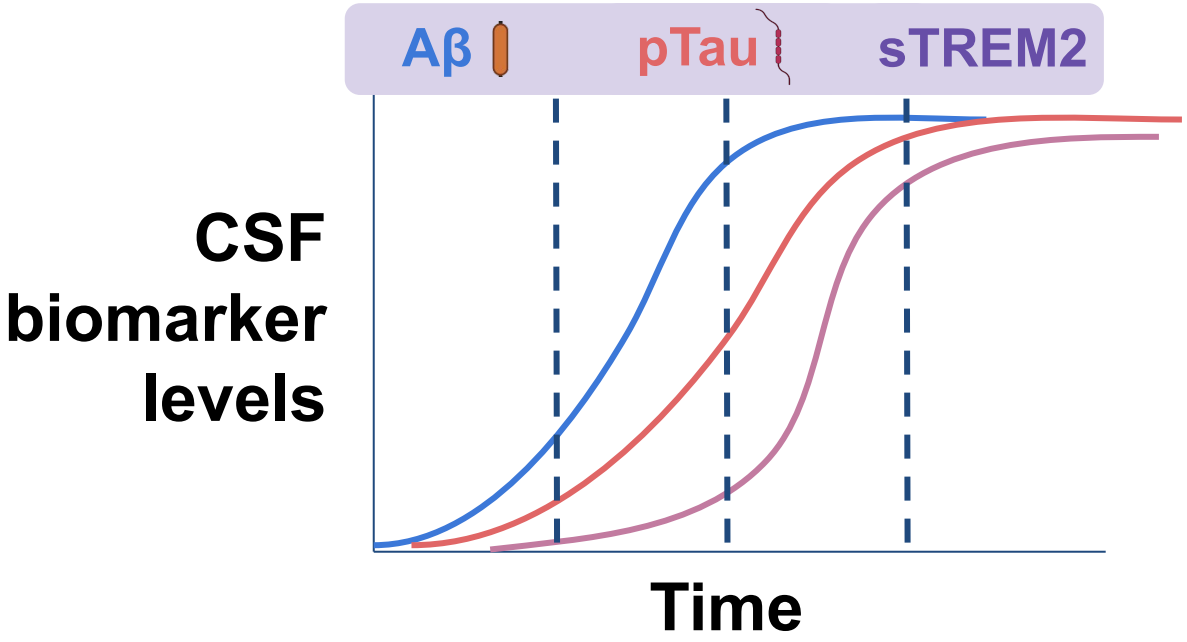
Rationale



Rationale



Rationale



MULTIVARIATE & LONGITUDINAL

Hypothesis

Longitudinal multivariate analysis of CSF biomarkers will detect distinct phenotypes of biomarker interactions and trajectories associated with the treatment responder group in comparison to the treatment non-responder group.

LM11A-31

Methods

Clinical Trial Dataset n = 150

Baseline

Placebo

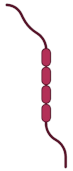
Treatment

After

Placebo

Treatment

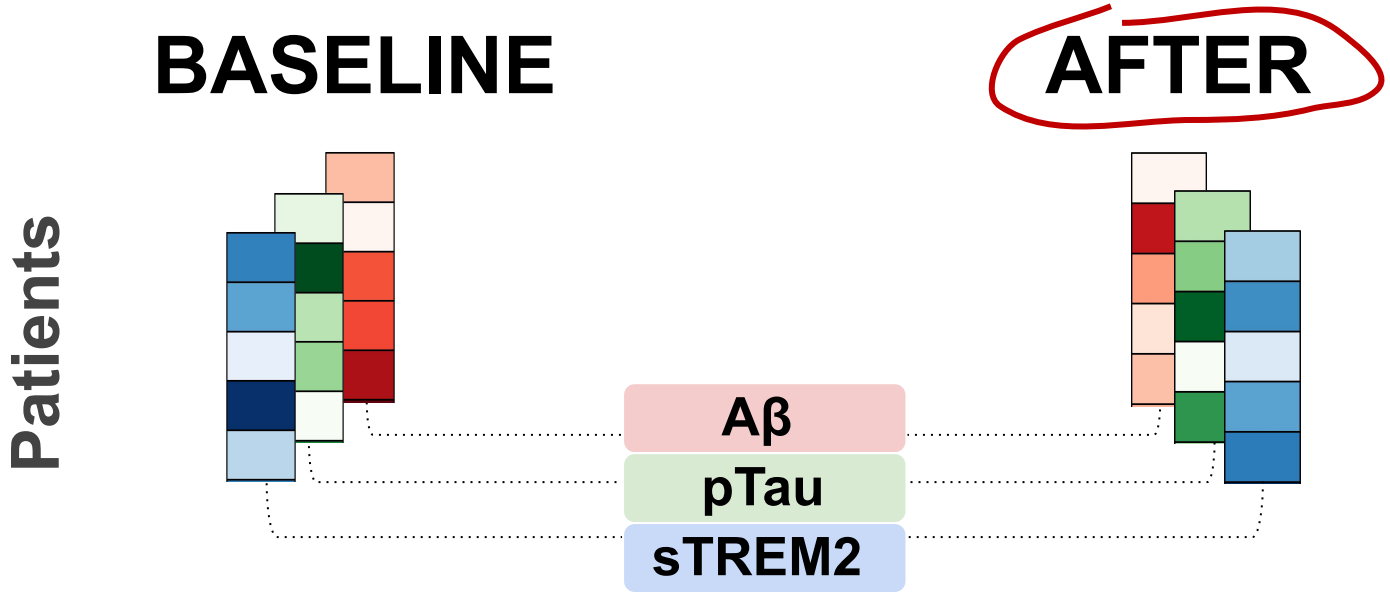
Aβ

pTau 

sTREM2

Similarity Network Fusion (SNF)

Step 1: Original Data



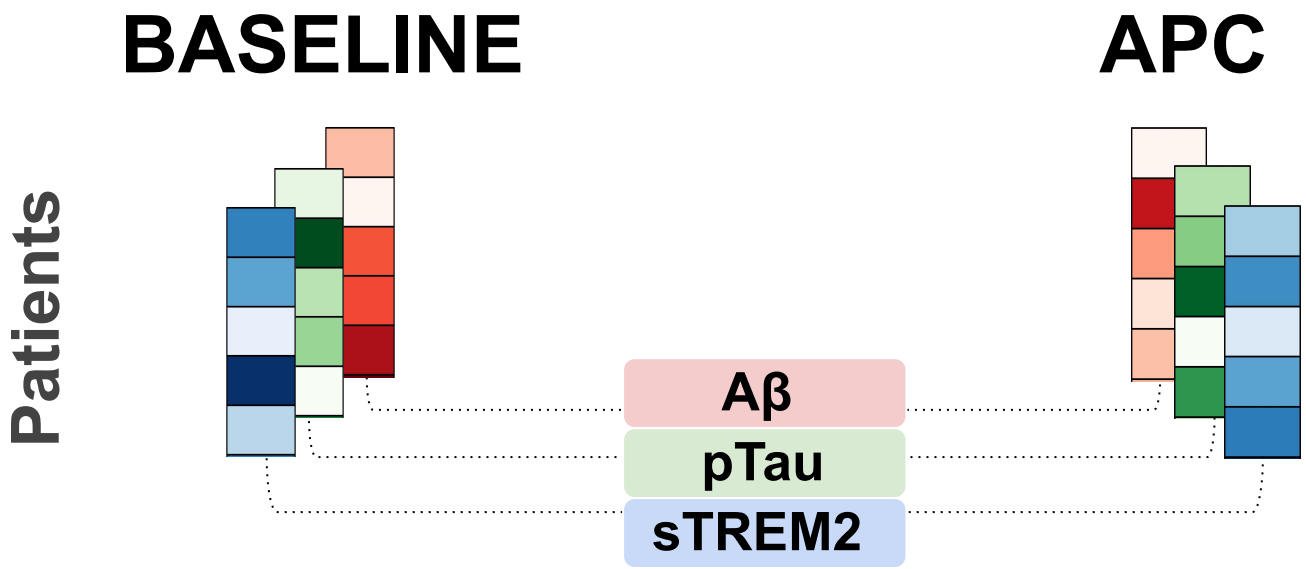
Similarity Network Fusion (SNF)

Step 1: Original Data

$$APC = \left[\left[\frac{\text{Time 2}}{\text{Time 1}} \right]^{\frac{365}{\text{Intervals}}} - 1 \right] X\ 100$$

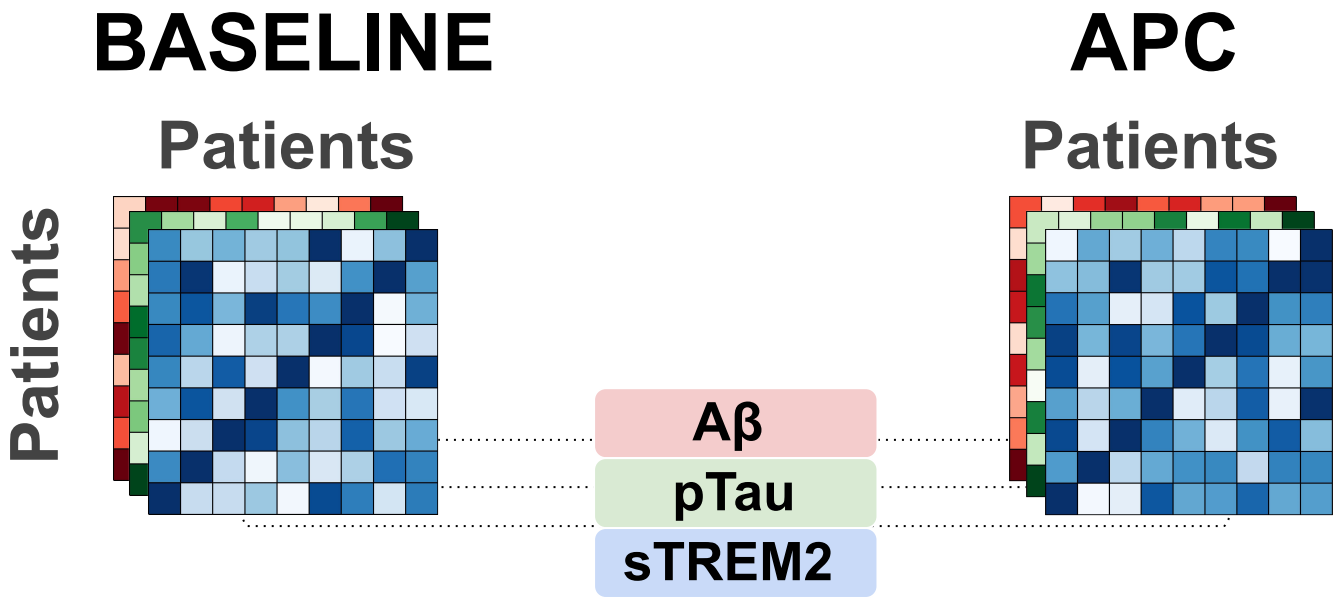
Similarity Network Fusion (SNF)

Step 1: Original Data



Similarity Network Fusion (SNF)

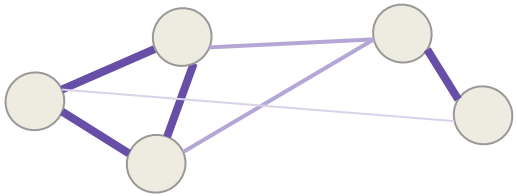
Step 2: Patient Similarity Matrices



Similarity Network Fusion (SNF)

Step 3: Patient Similarity Networks

BASELINE



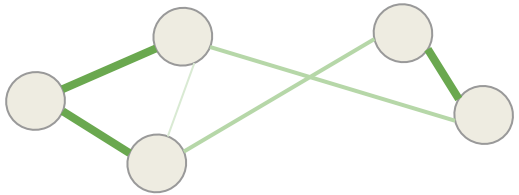
x 3

Aβ

pTau

sTREM2

APC



x 3

Similarity Network Fusion (SNF)

Step 4: Patient Network Fusion

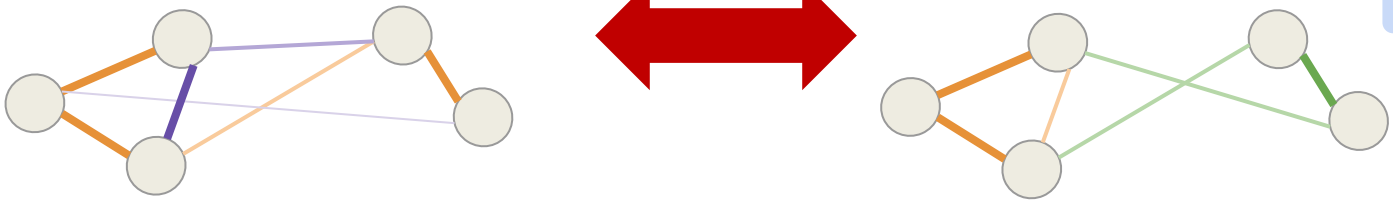
BASELINE

APC

Aβ

pTau

sTREM2



x 3

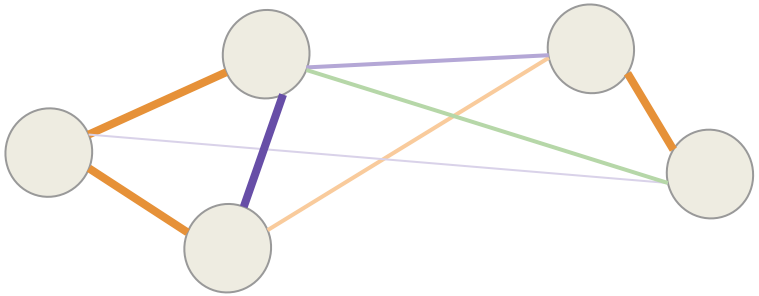
Supported by all data

x 3

Similarity Network Fusion (SNF)

Step 5: Fused Patient Similarity Network

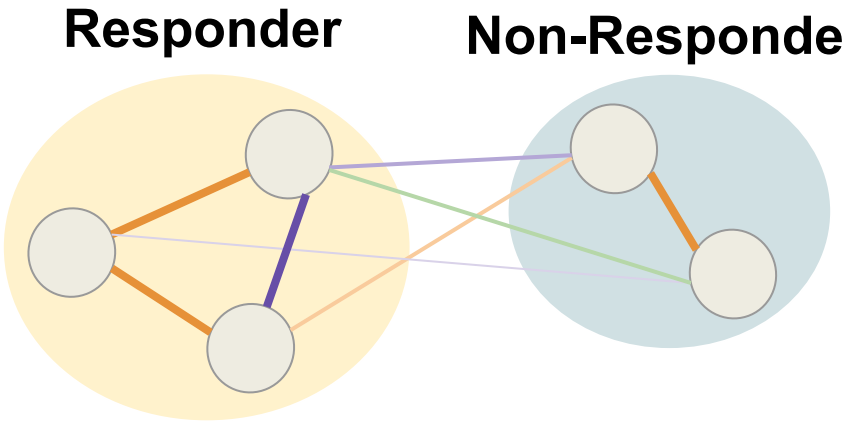
Responder Non-Responder



Baseline APC Supported by all data

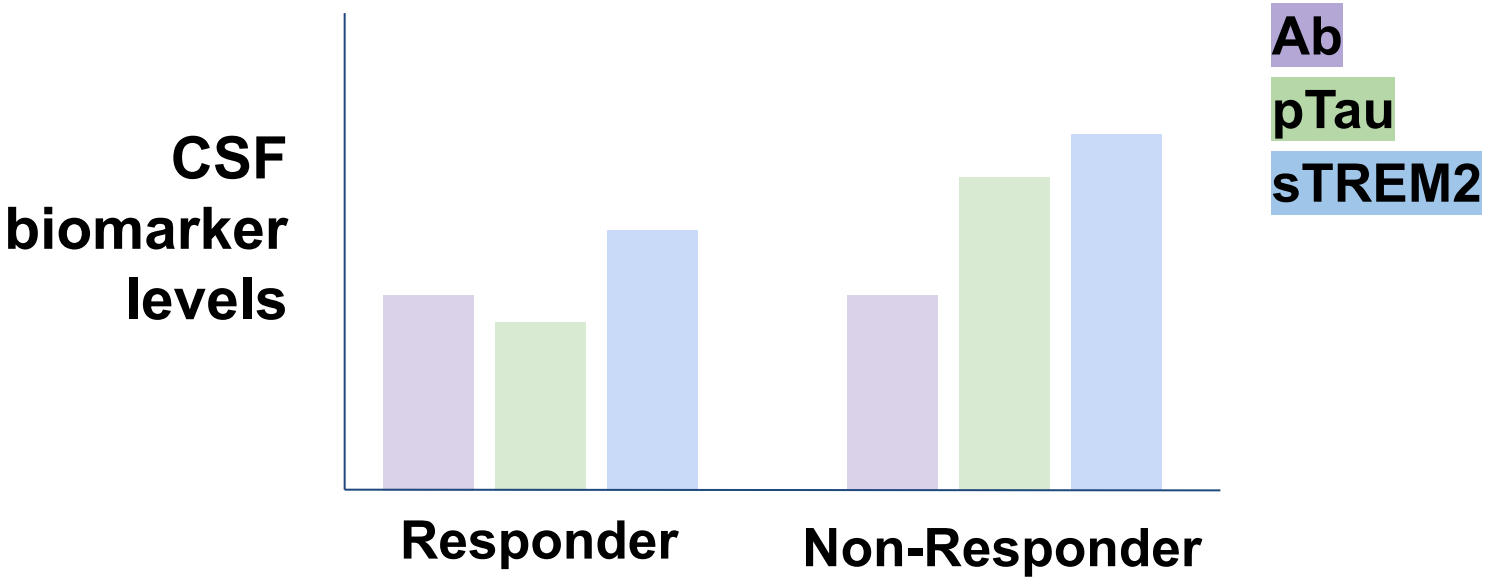
Similarity Network Fusion (SNF)

Step 6: Spectral Clustering



Baseline APC Supported by all data

Post-Hoc Analysis



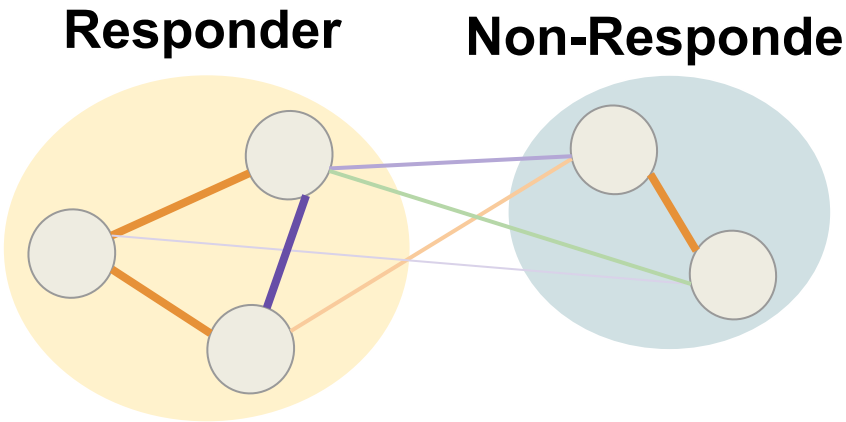
Anticipated Results

Schulich MEDICINE & DENTISTRY

Western

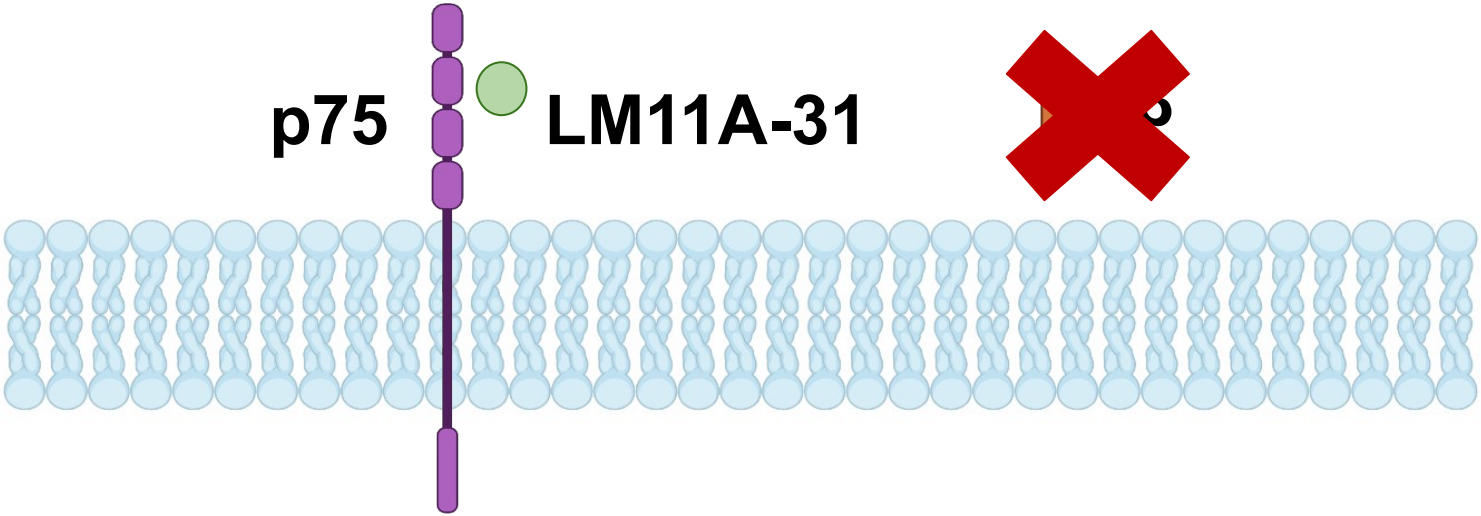
Clustering

(Blennow, 2005, Front. Neurosci)



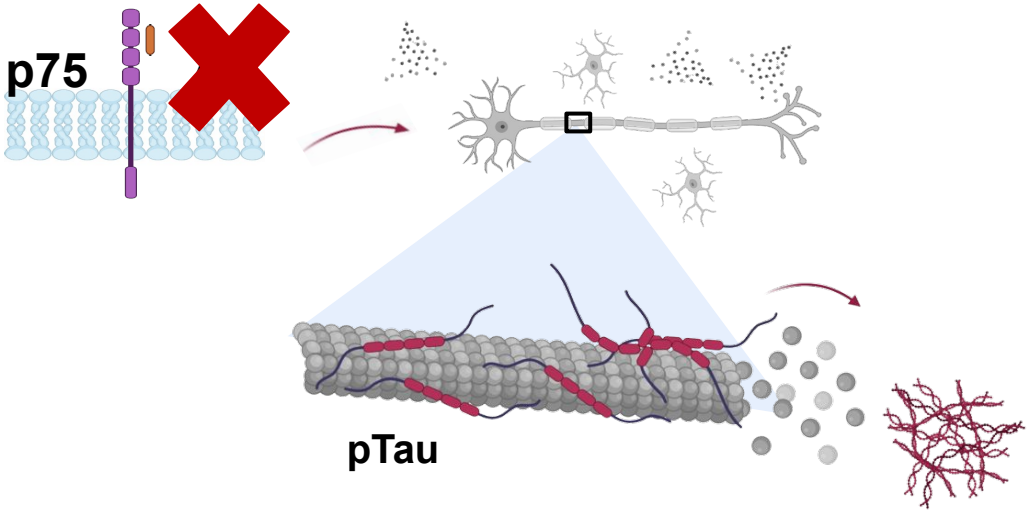
Before **After** **Supported by all data**

Aβ



No significant difference between treatment response groups

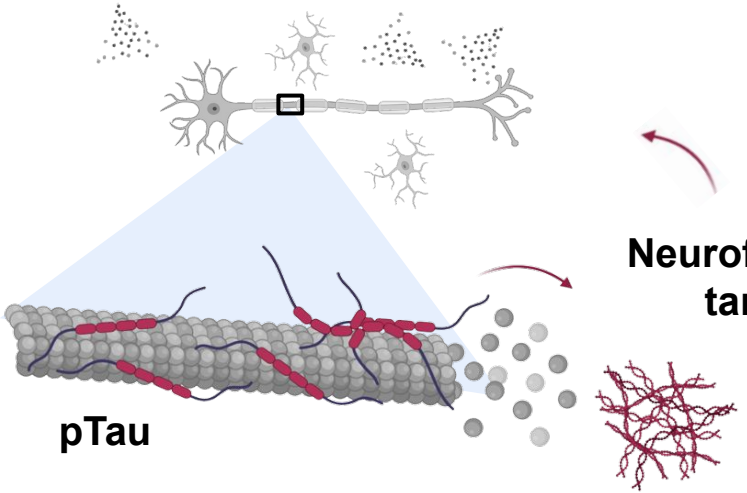
pTau



(Manucat-Tan et al., 2019, Aging)

Significantly decreased in response group

sTREM2



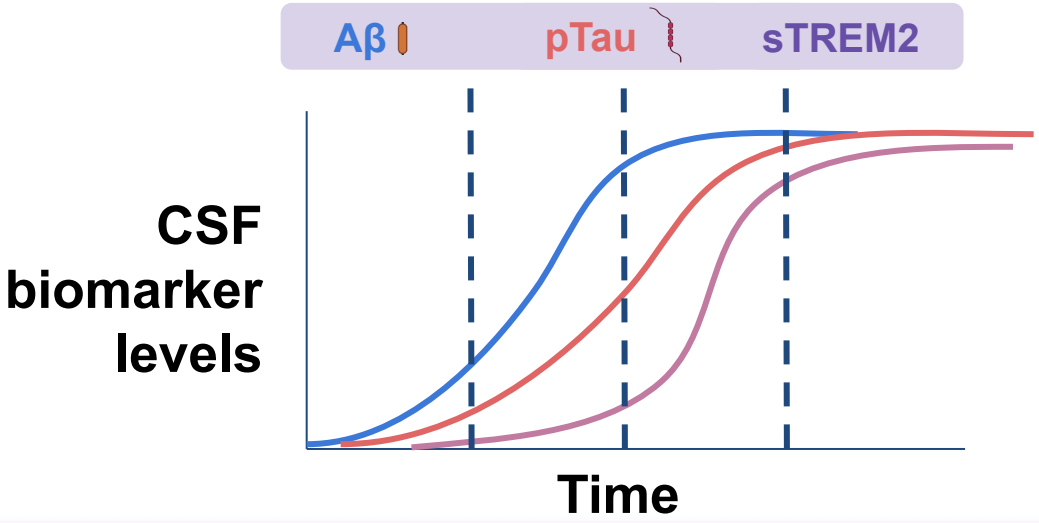
(Elshaer et al., 2019, Diabetologia)

Significantly decreased in response group

Significance

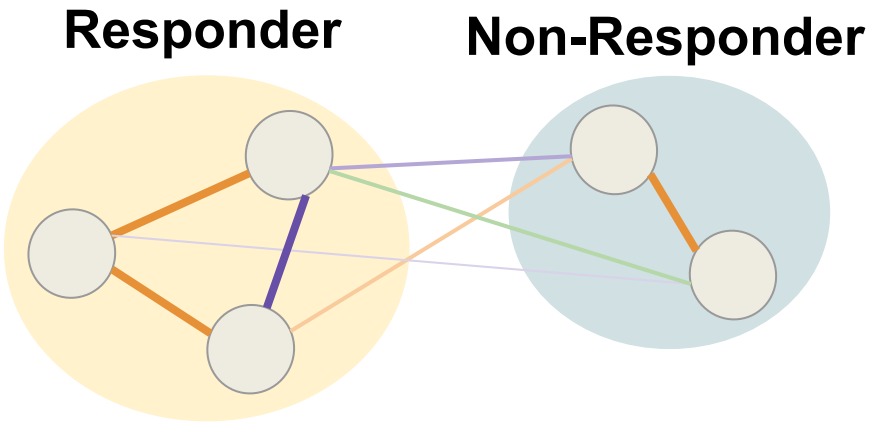
Significance

1 Longitudinal & Multivariate



Significance

2 Novel Phenotypes



Significance

3 Advance Precision Medicine