

# Alzheimer's Disease and the influence of Presenilin 1

By Tony Cortez

# What is Alzheimer's Disease?

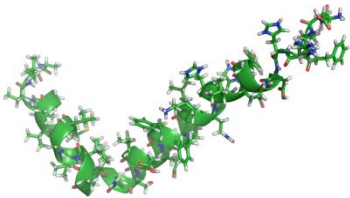


# How is *PSEN1* involved in Alzheimer's?



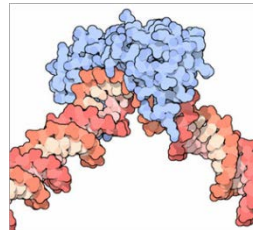
## Biological Process

- Beta-amyloid formation
- Cell differentiation
- Neurotransmission regulation
- Brain development



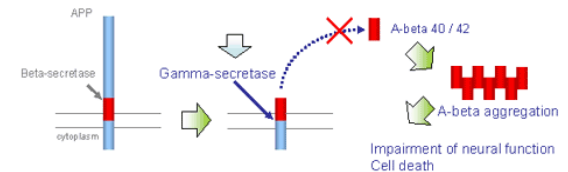
## Molecular Function

- Transmembrane transport
- Transcription factor binding
- Kinase activity

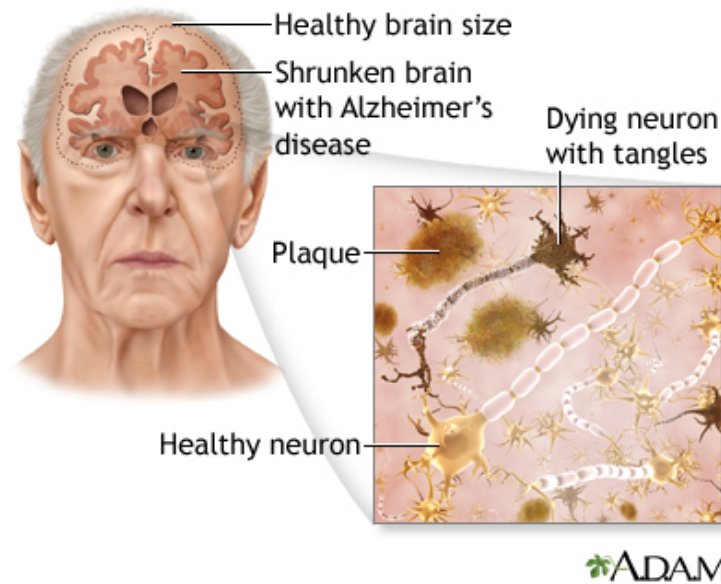
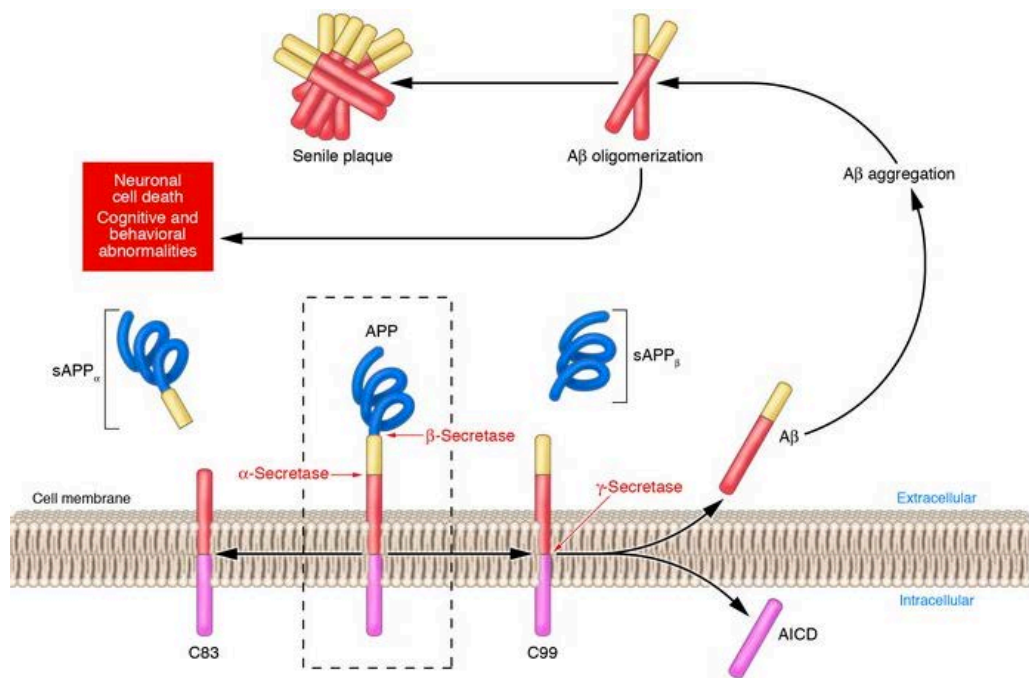


## Cellular Component

- Gamma-secretase complex
- Dendritic roots
- Regulatory protein complexes



# How is APP involved in Alzheimer's?

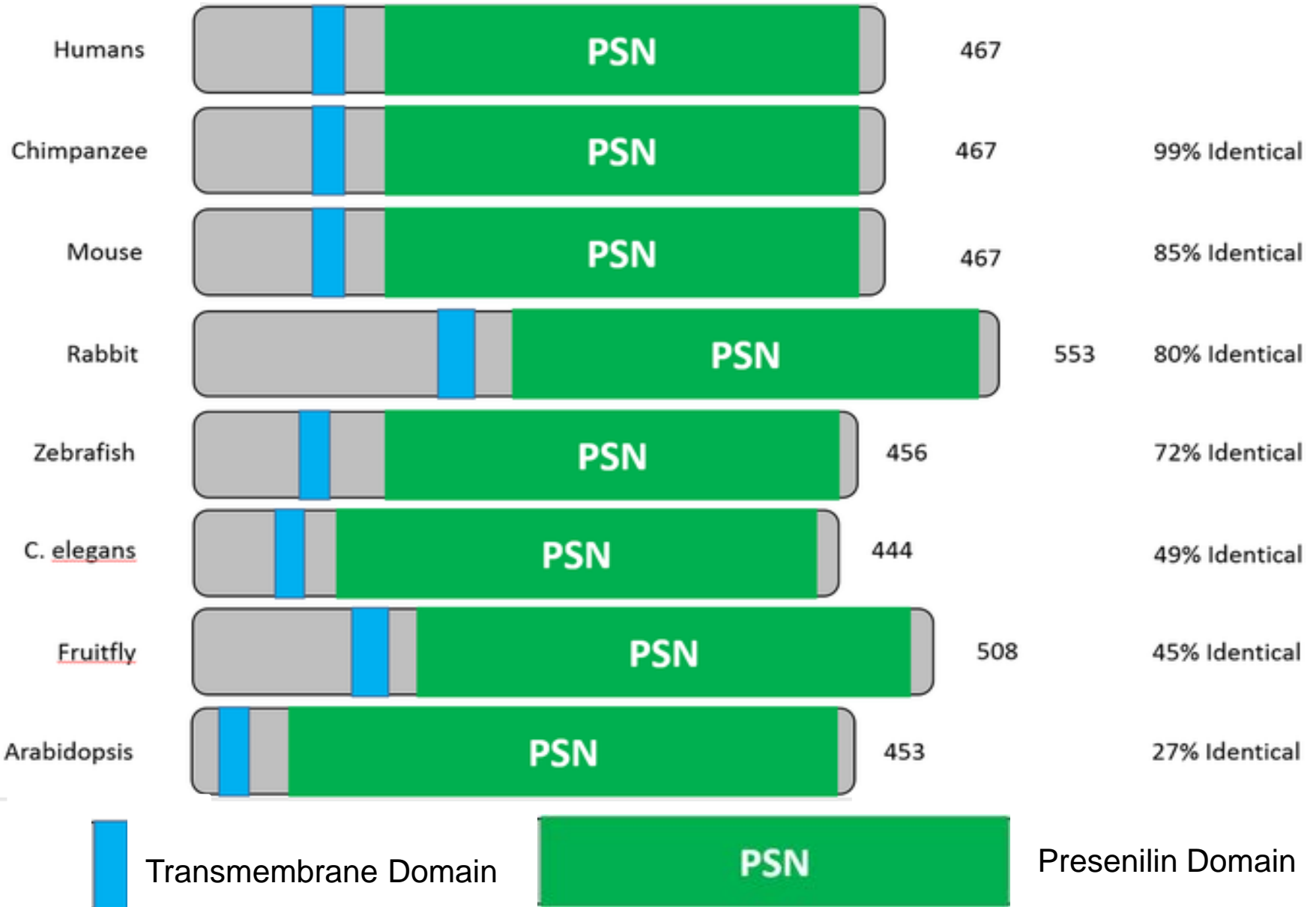


Memory loss

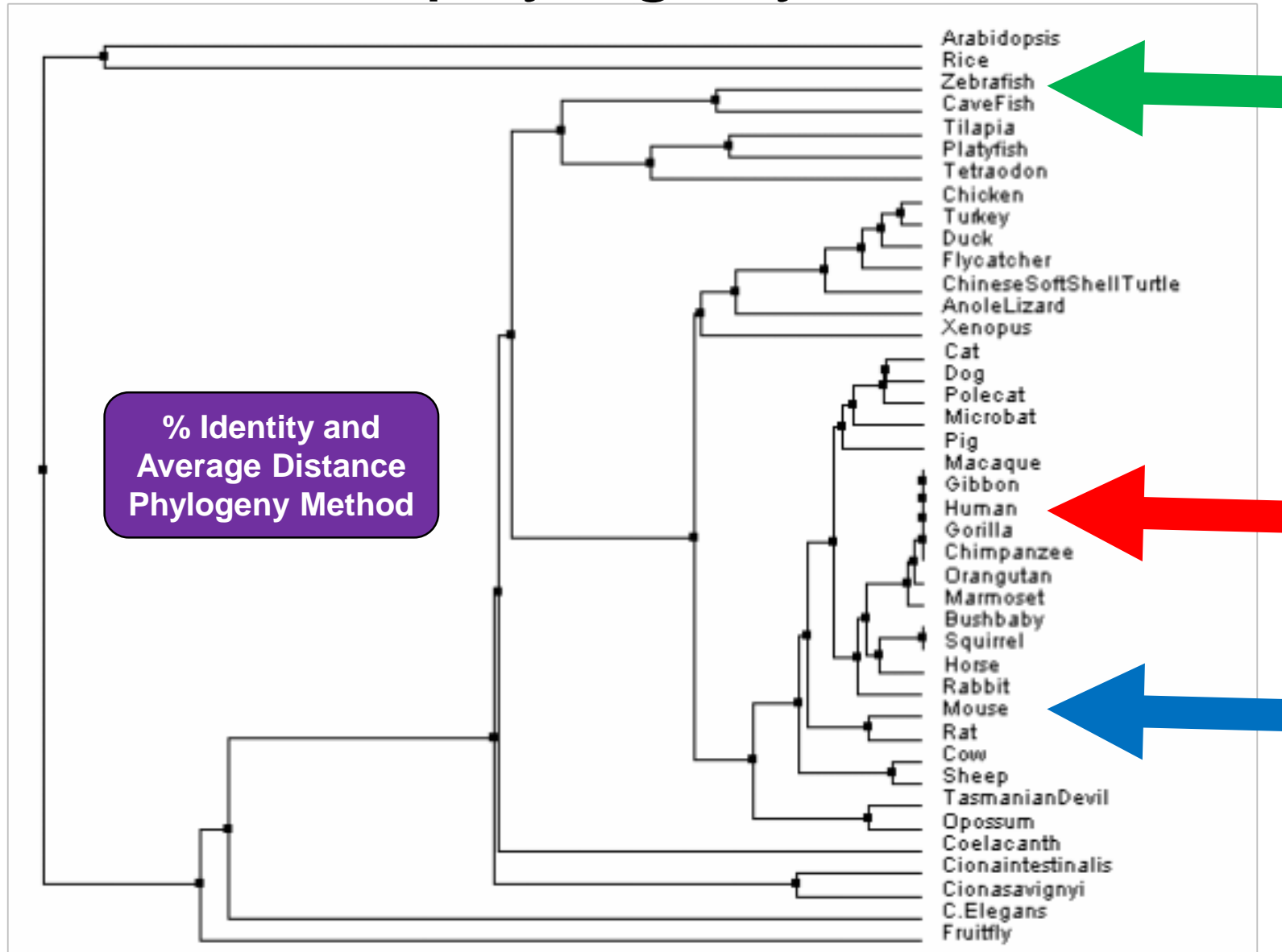
Speech impediment

Disorientation

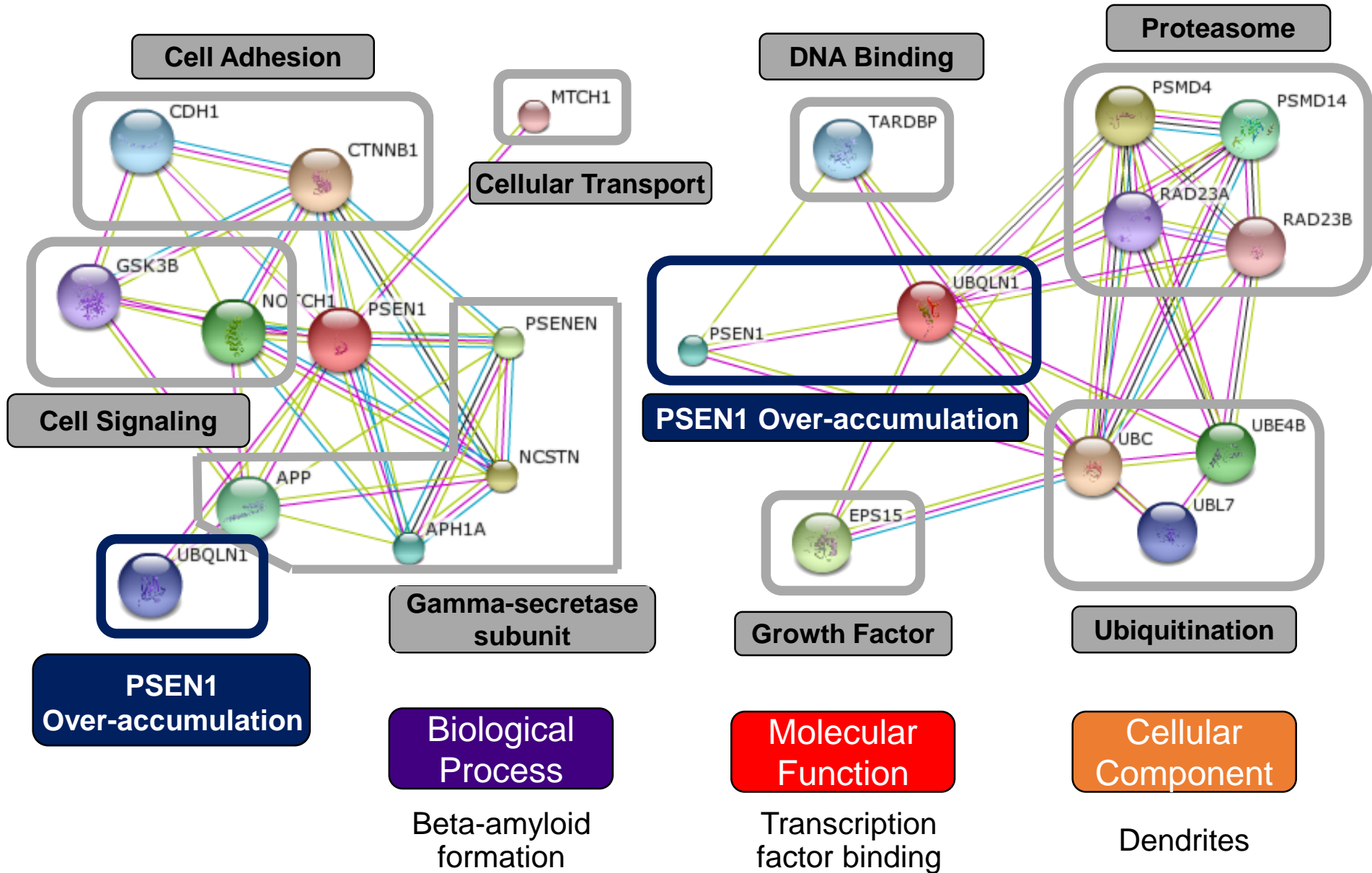
# How is **PSEN1** conserved across organisms?



# What is the phylogeny for PSEN1?



# What proteins interact with PSEN1?



# What is the gap in knowledge?

Unclear if the downregulation of **UBQLN1** mediates plaque formation

Alzheimer's Disease

Restored WT Function

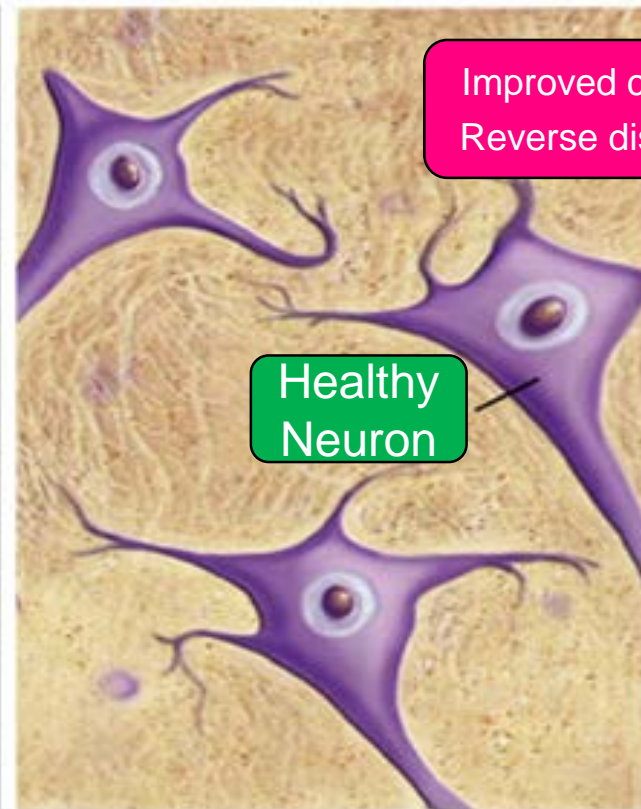
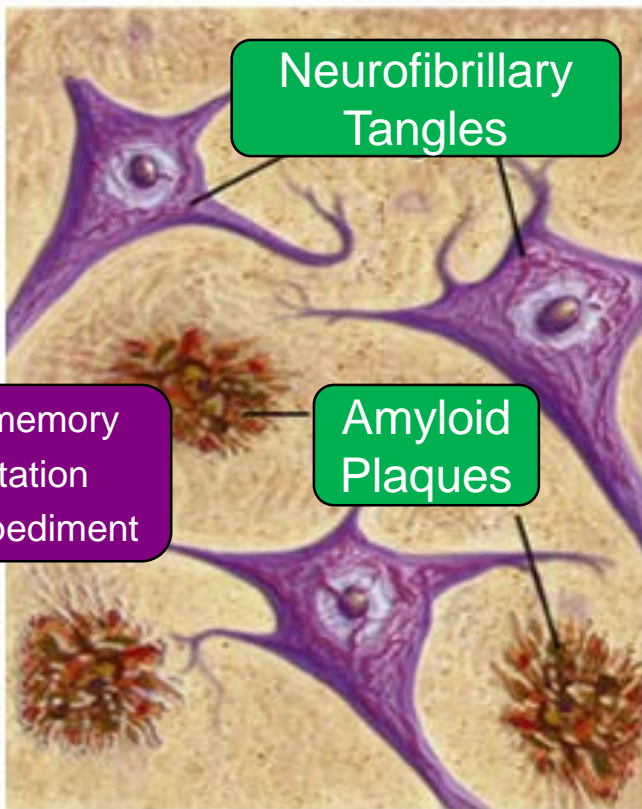
Neurofibrillary  
Tangles

Improved cognitive function  
Reverse disease symptoms

Amyloid  
Plaques

Healthy  
Neuron

Impaired memory  
Disorientation  
Speech impediment

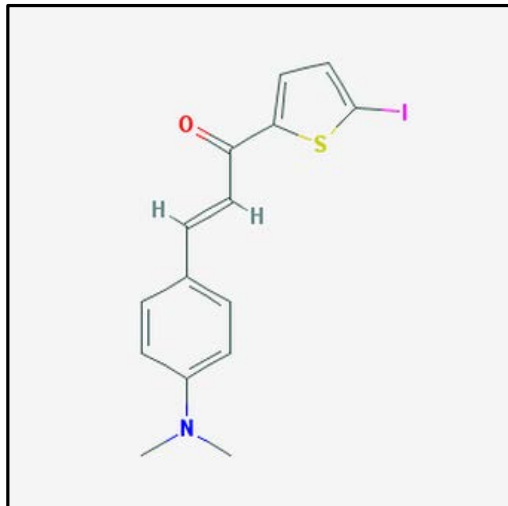




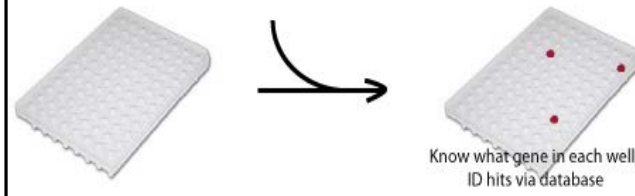
**Long Term Goal:** Discover if UBQLN1-mediated ubiquitination is required to regulate PSEN1 activity in regards to APP production.

**Aim 1:**

Identify a drug that inhibits UBQLN1 function of PSEN1 accumulation



Arrayed RNAi Library+ Cells (+ Treatment optional)

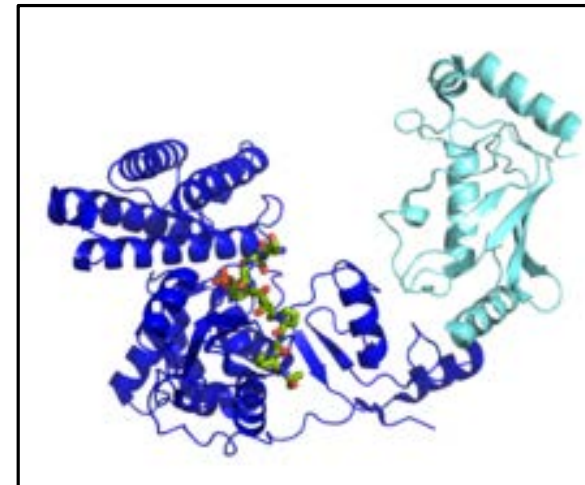


**Aim 2:**

Determine the importance of UBQLN1 and other ubiquitination-inducing proteins

**Aim 3:**

Identify phosphorylation sites in PSEN1 responsible for amyloid plaques



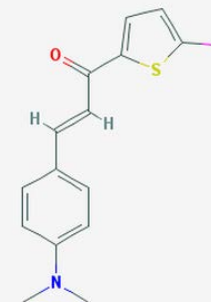
# Specific Aim 1:

Identify a drug that inhibits UBQLN1 function of PSEN1 over-accumulation

Approach:  
Chemical Genetic Database

UBQLN1

PubChem



Compound CID 17757413

(E)-3-[4-(dimethylamino)phenyl]-1-(5-iodothiophen-2-yl)prop-2-en-1-one

Hypothesis: Drugs that inhibit UBQLN1 will suppress PSEN1 accumulation, APP production and amyloid plaque formation.

# Specific Aim 1:

# Direct target drug testing results



	-Drug	-Drug Memory Test	+Drug	+Drug Memory Test
WT		Passed!		Failed!
Mutated PSEN1		Failed!		Passed!
Mutated UBQLN4		Failed!		Passed!

No amyloid plaques!

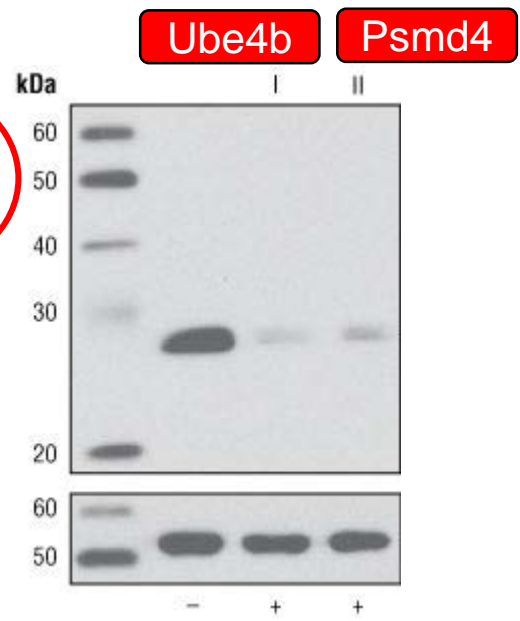
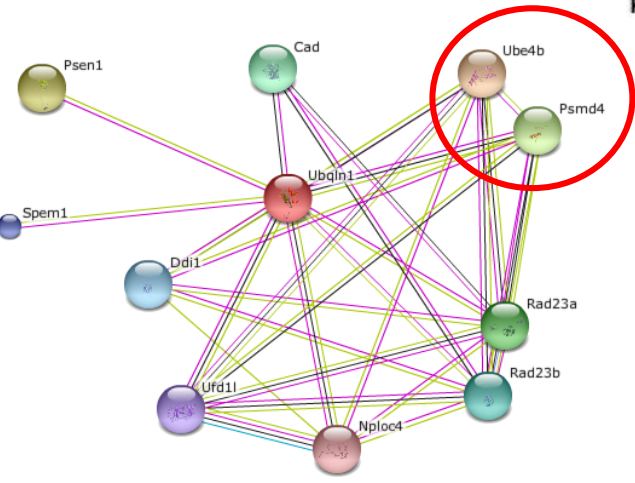
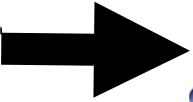
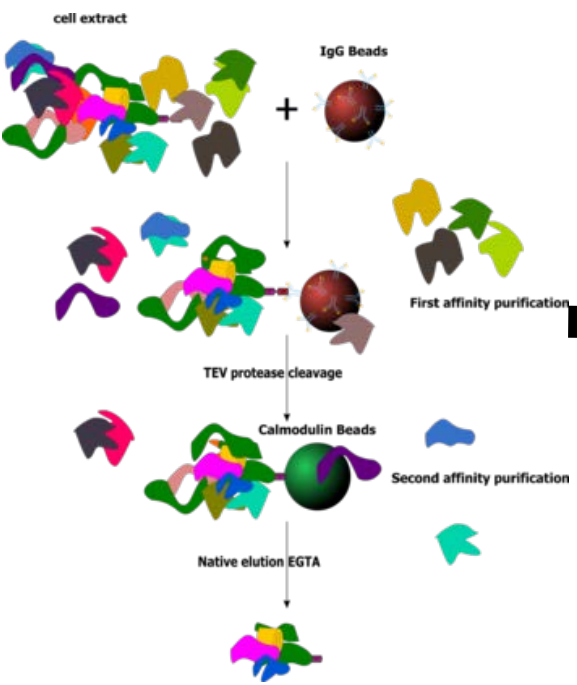
# Specific Aim 2:

Identify proteins that regulate PSEN1

**Approach:**  
Tandem Affinity Purification

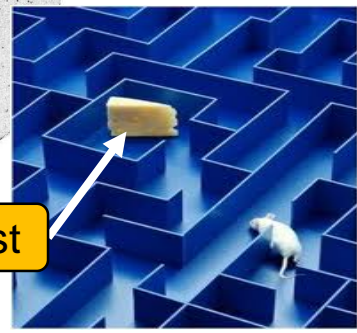
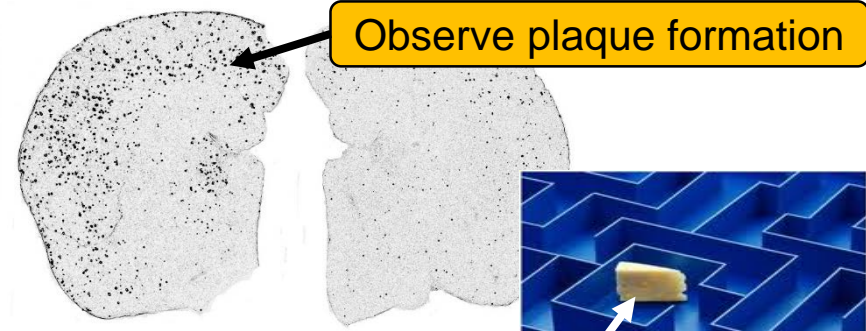
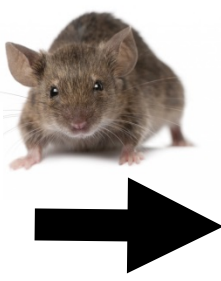
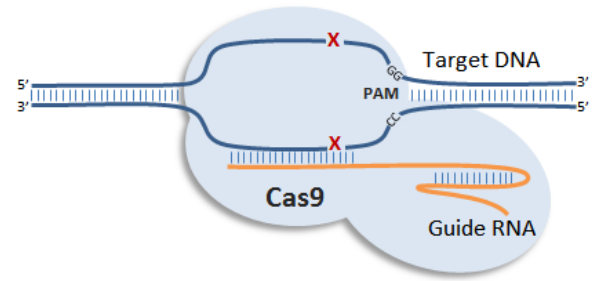
TAP-tag UBQLN1

Identify brain-specific candidate proteins



**Hypothesis:** UBQLN1 and other ubiquitination-inducing proteins will be found essential to amyloid plaque formation.

# Specific Aim 2:



Knockout UBQLN1 binding proteins

Perform memory test

Predicted Results

	WT Mice	Memory Test on WT	Mutated Psmc4	Memory Test on mutant
No Knockout		Passed!		Failed!
Knockout PSEN1		Failed!		Failed!
Knockout UBQLN1		Failed!		Failed!
Knockout Psmc4		Failed!		Failed!

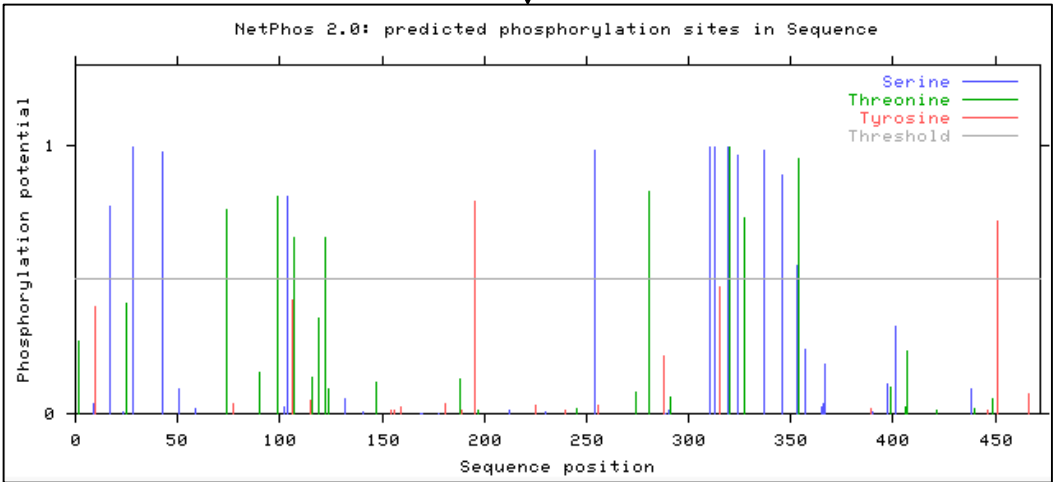
Amyloid plaques!

Amyloid plaques!

# Specific Aim 3:

Determine conserved post-translational modifications in PSEN1

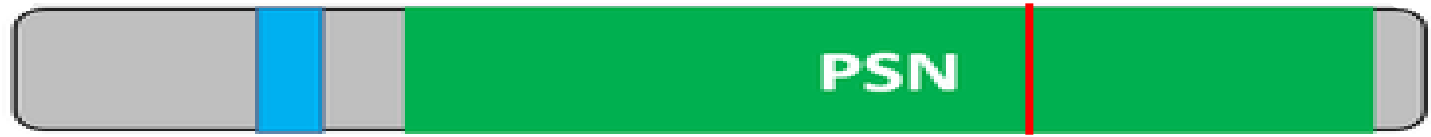
Clustal Omega



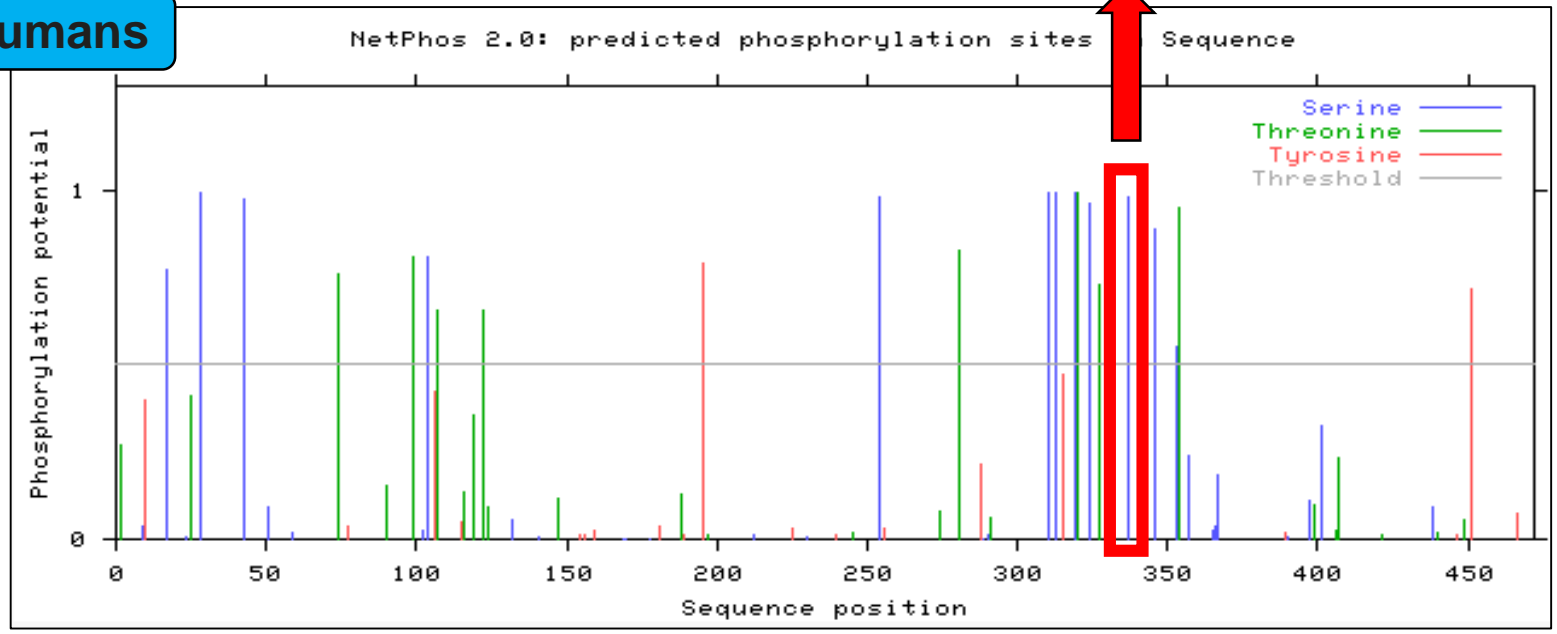
**Hypothesis:** Phosphorylation at certain amino acids are essential to regular PSEN1 function.

# Specific Aim 3:

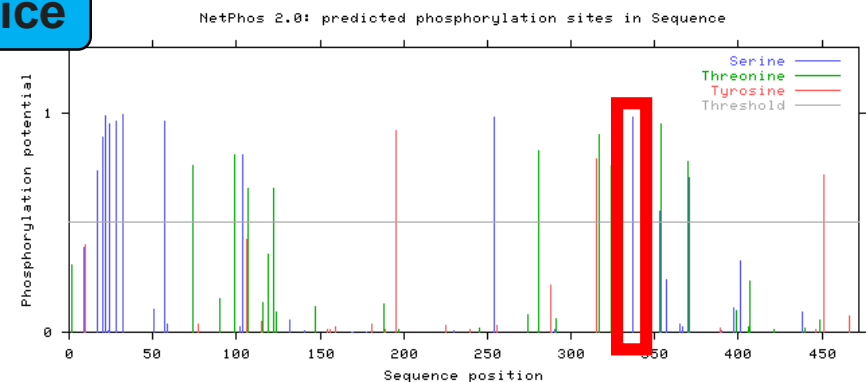
# Serine-320 is the most conserved PTM



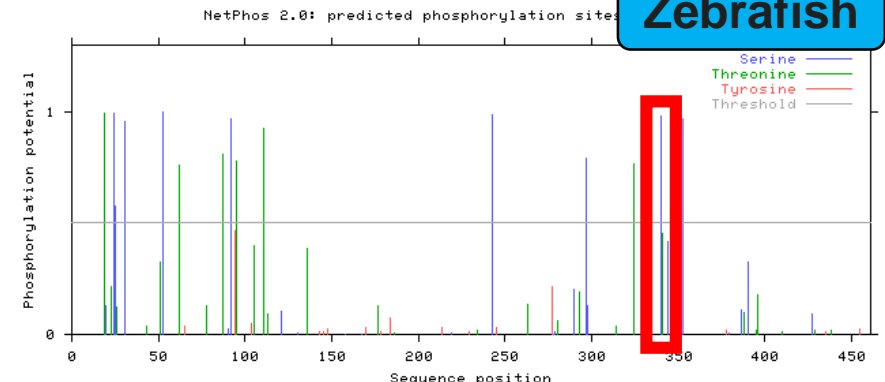
## Humans



## Mice

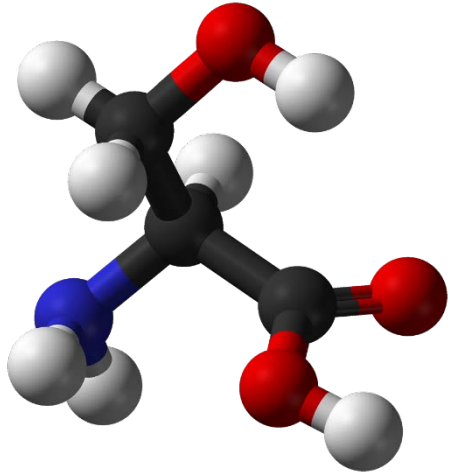


## Zebrafish

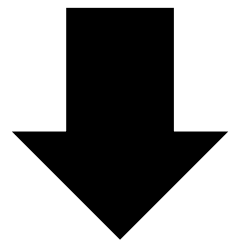


# Specific Aim 3:

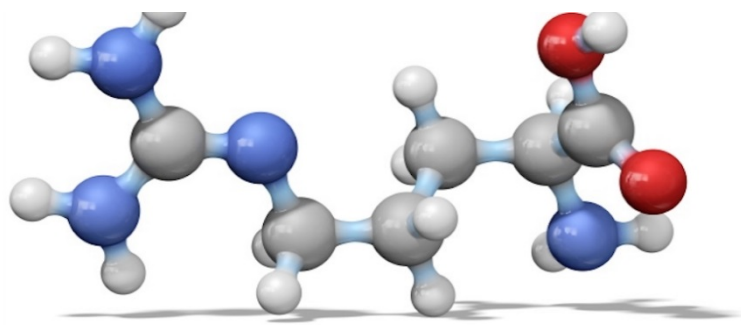
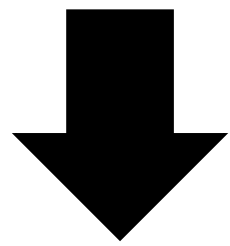
# Predicted Results



**Serine**



**CRISPR**

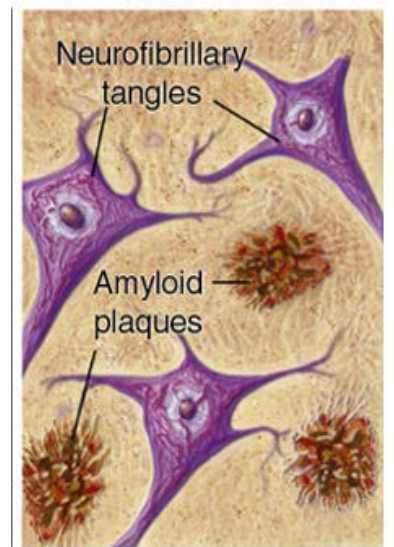


**Arginine**



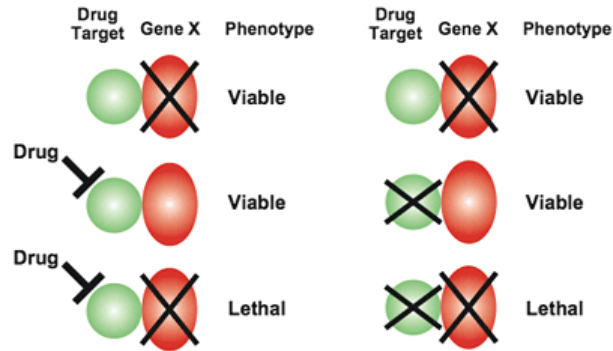
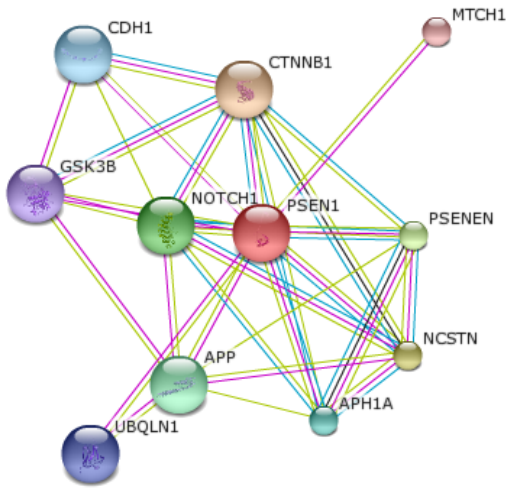
**Amyloid plaque formation!**

**Fail memory test!**





# Where does the future of **PSEN1** lead?



Further research on  
UBQLN1

Identify drug treatments for  
genes involved with Alzheimer's

Cure Alzheimer's Disease

# References

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**QUESTIONS?**