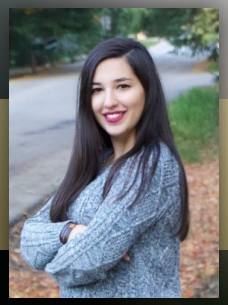
Sanfilippo Syndrome

A rare lysosomal storage disorder



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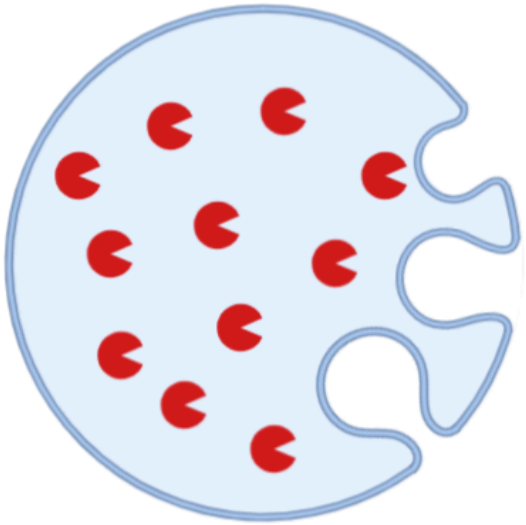
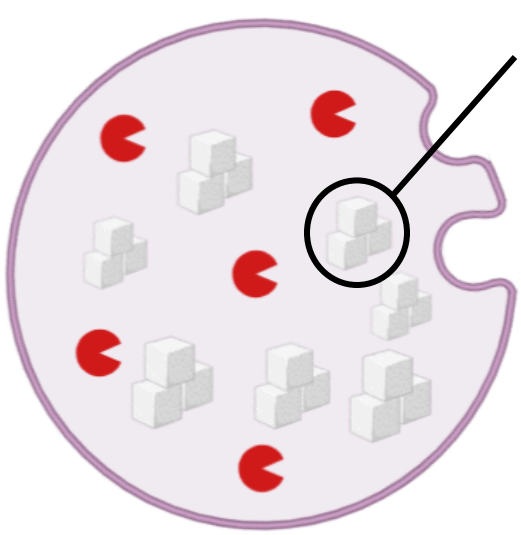
What is Sanfilippo syndrome?



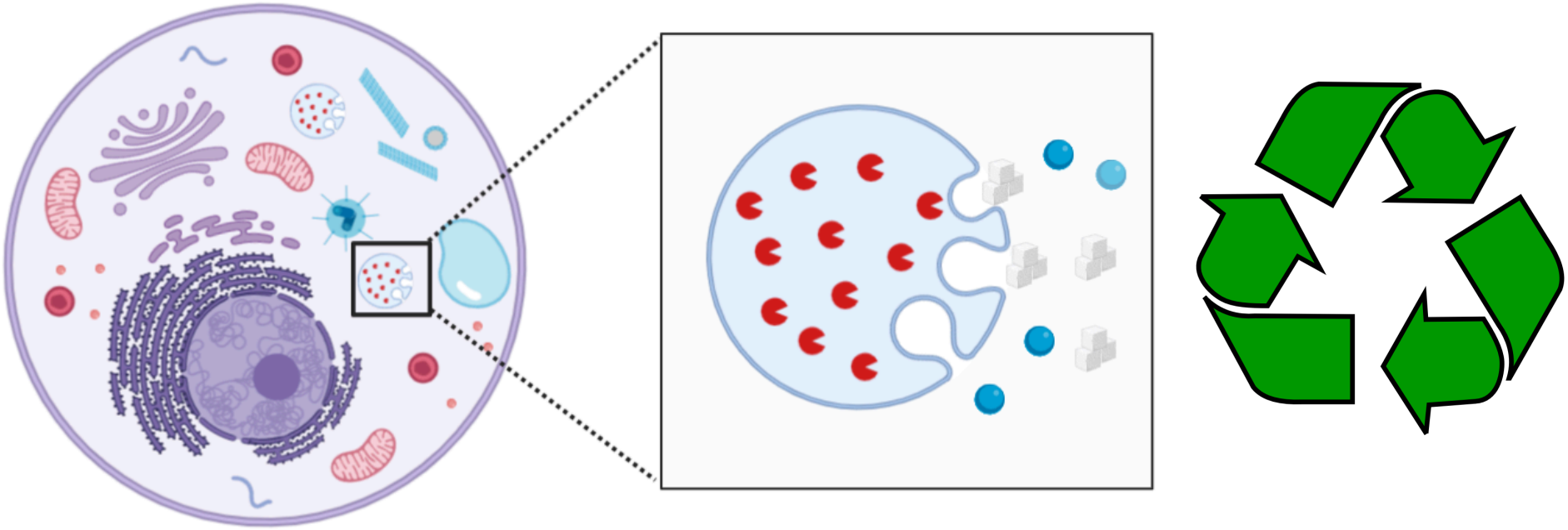
Healthy lysosome



Diseased lysosome

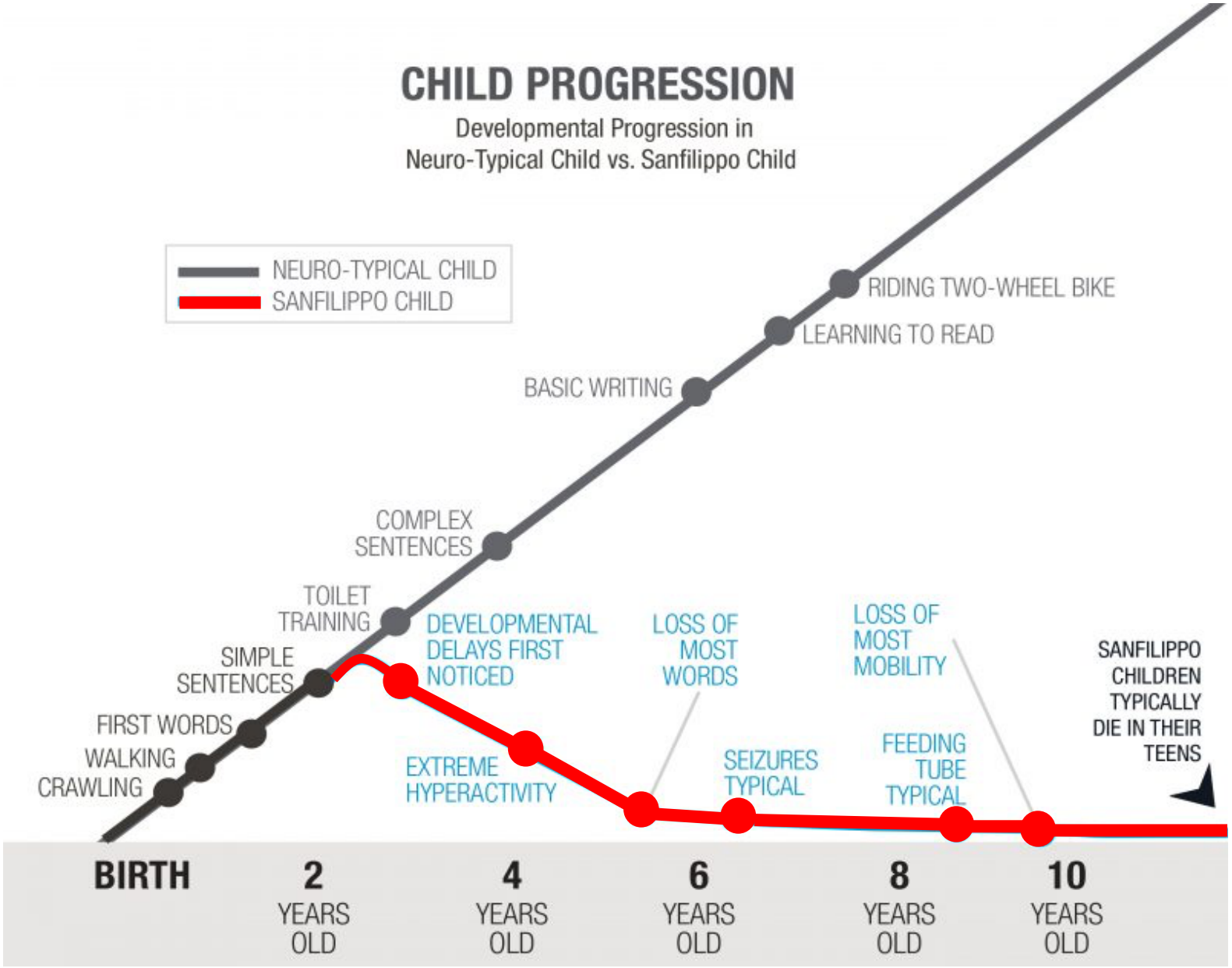
Autosomal recessive lysosomal storage disorder

Lysosomes: The recyclers of cells



Lysosomes break down unwanted macromolecules

Sanfilippo symptoms progress over time

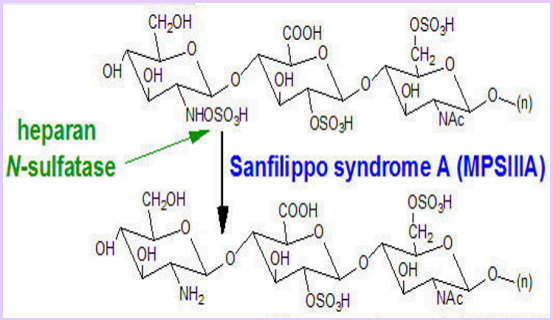


The causes of Sanfilippo syndrome

Sanfilippo Types	Gene	Missing Enzyme
A	SGSH	Heparan N-sulfatase
B	NAGLU	N-acetyl-alpha-D-glucosaminidase
C	HGSNAT	Acetyl-CoA:alpha-glucosaminide acetyltransferase
D	GNS	N-acetylglucosamine-G-sulfate sulfatase

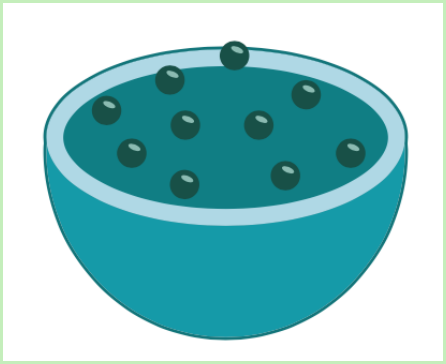
SGSH gene causes Sanfilippo syndrome type A

Molecular function



Enzyme regulation
Catalytic activity

Cellular component

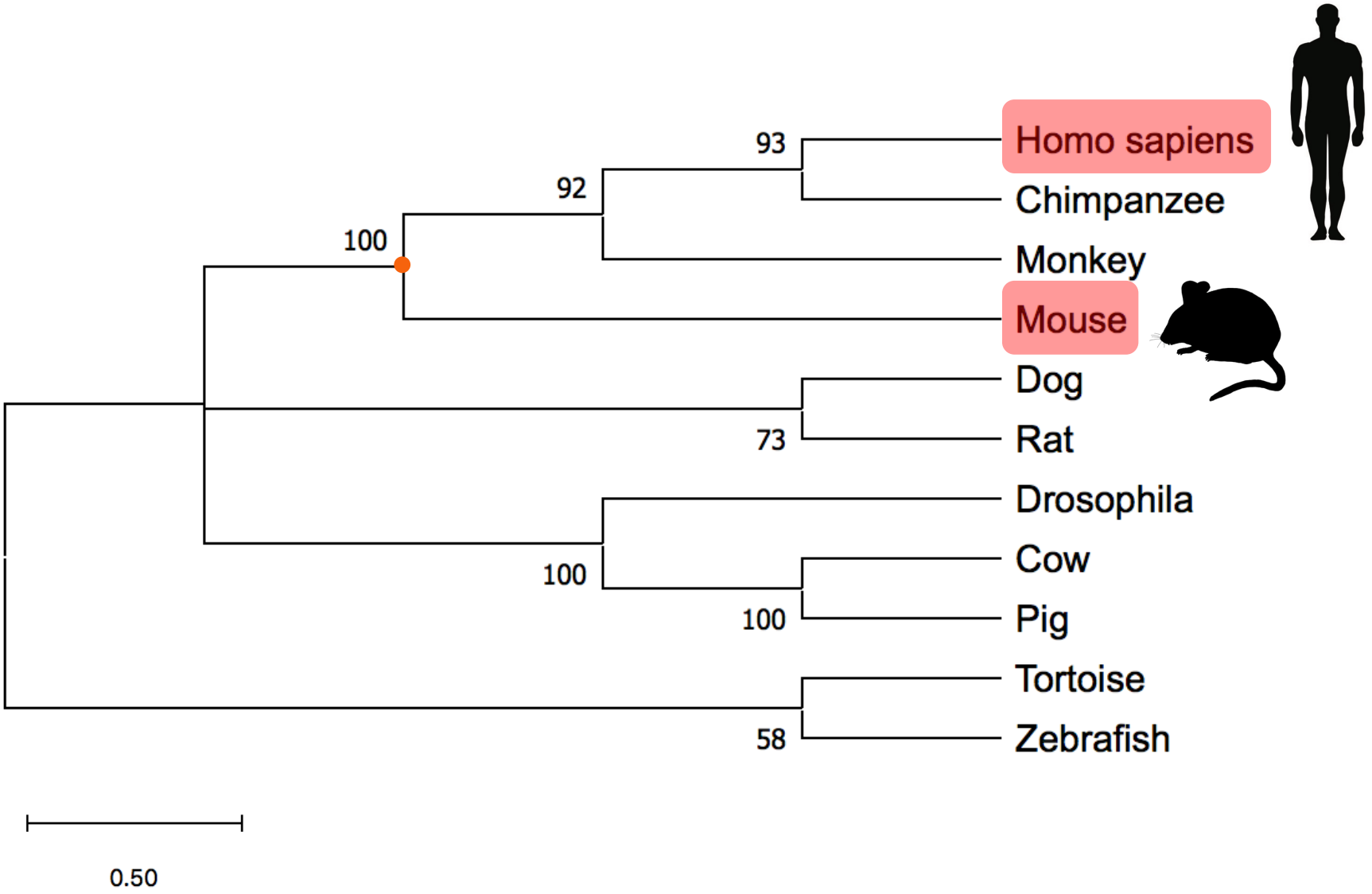


Lysosome
Extracellular exosome

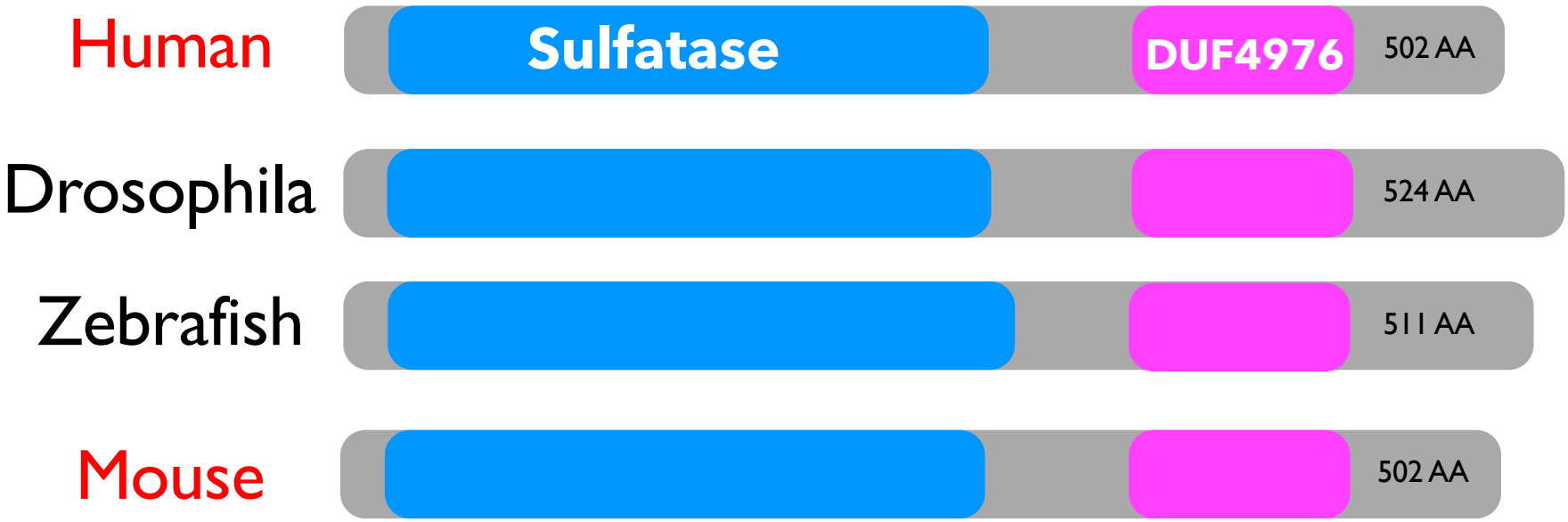
Biological process

Catabolism
Brain development

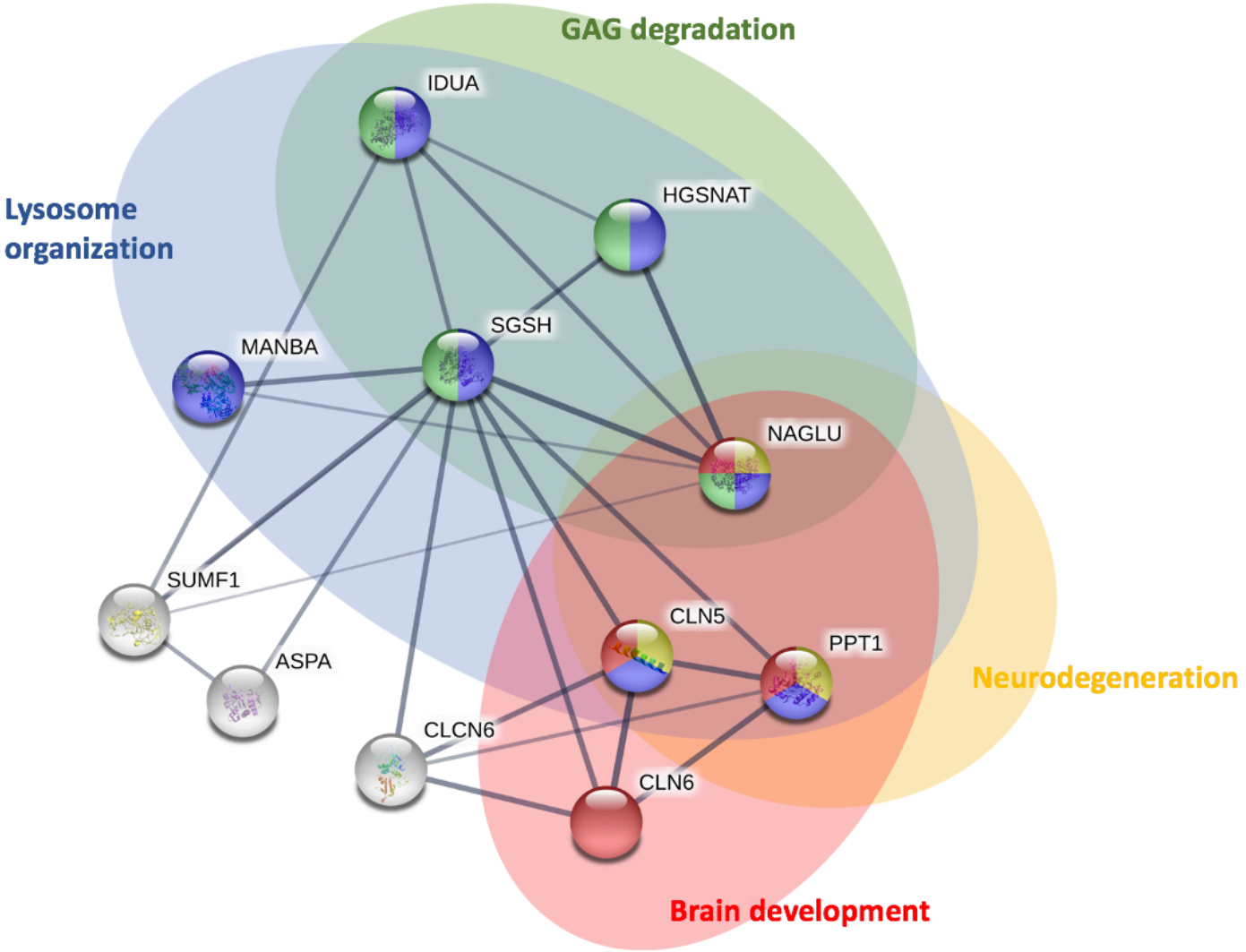
SGSH is well conserved across species



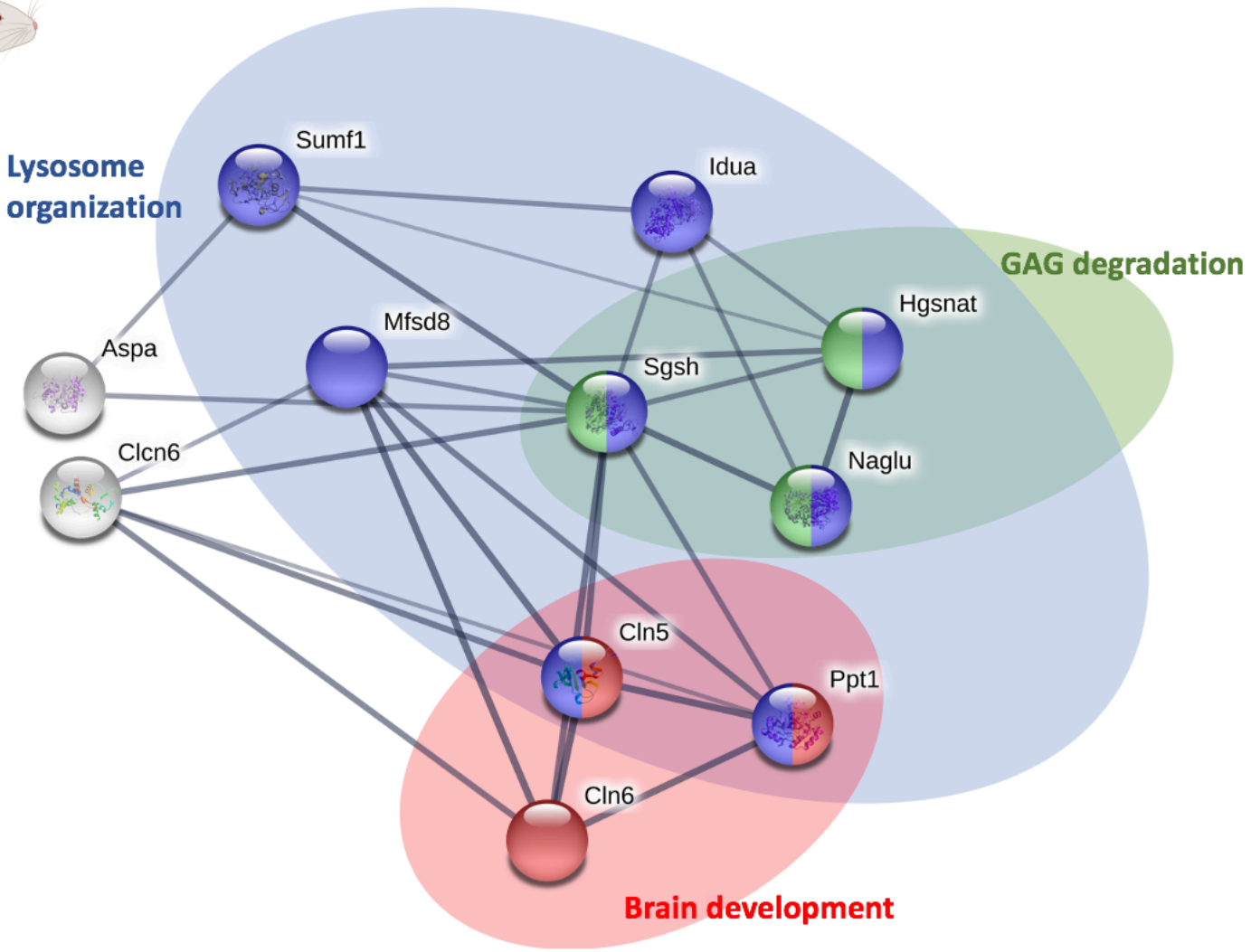
SGSH domains are well conserved



SGSH interaction network reveal possible functions in brain development



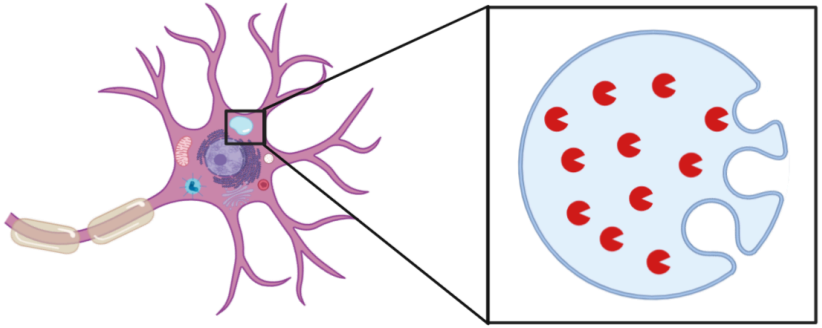
Similar SGSH interaction network in mice

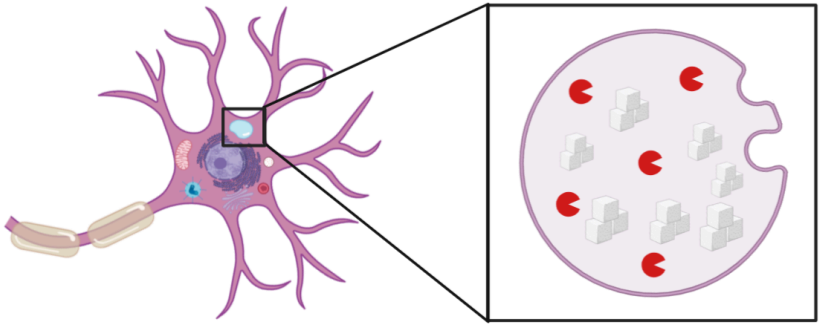


Mice as model organisms

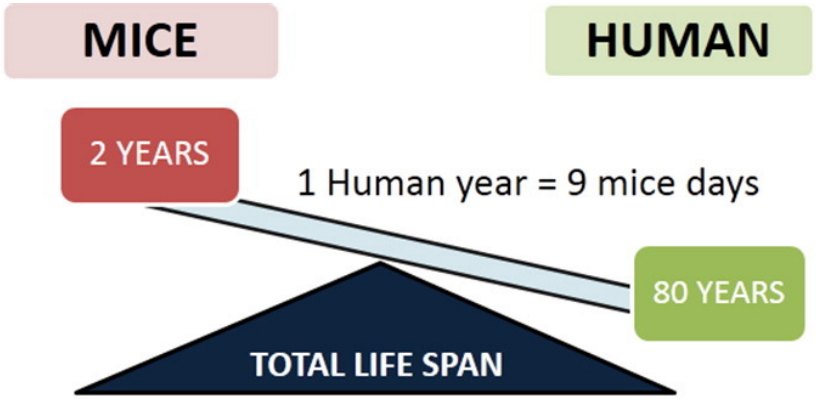
Wildtype mouse

SGSH mutant mouse





Mice are good models for studying lifespan



2yr 6yr 15yr

Wt-28 days

Wt-42 days

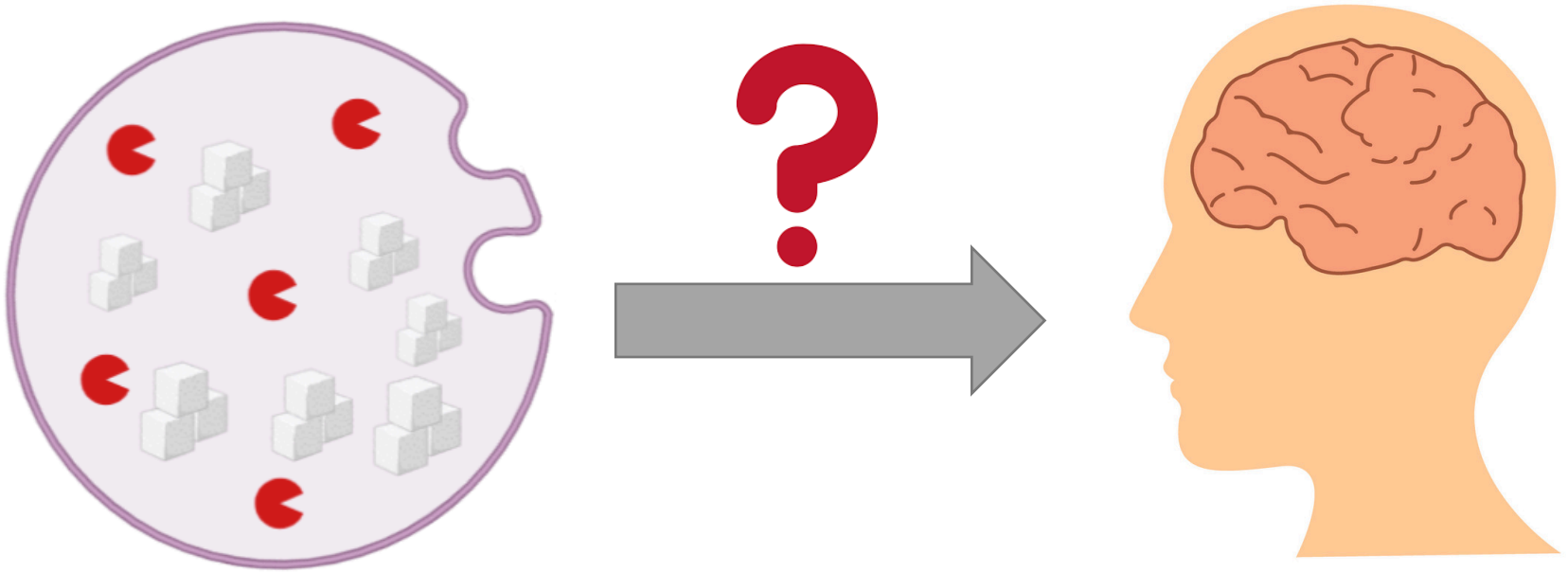
Wt-70 days

Mt-28 days

Mt-42 days

Mt-70 days

It is unclear how sugar accumulates in the lysosomes of neurons in SGSH mutants

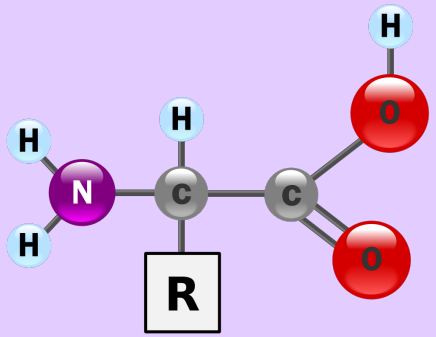


The Primary Goal

Determine how sugar accumulates in lysosome of brain.

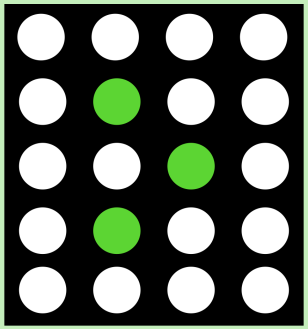
Aim 1

Identify amino acids important for GAGs accumulation in neurons



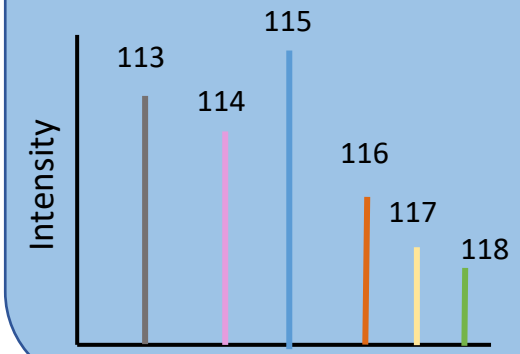
Aim 2

Identify small molecules that rescue neurodegeneration in SGSH mutants



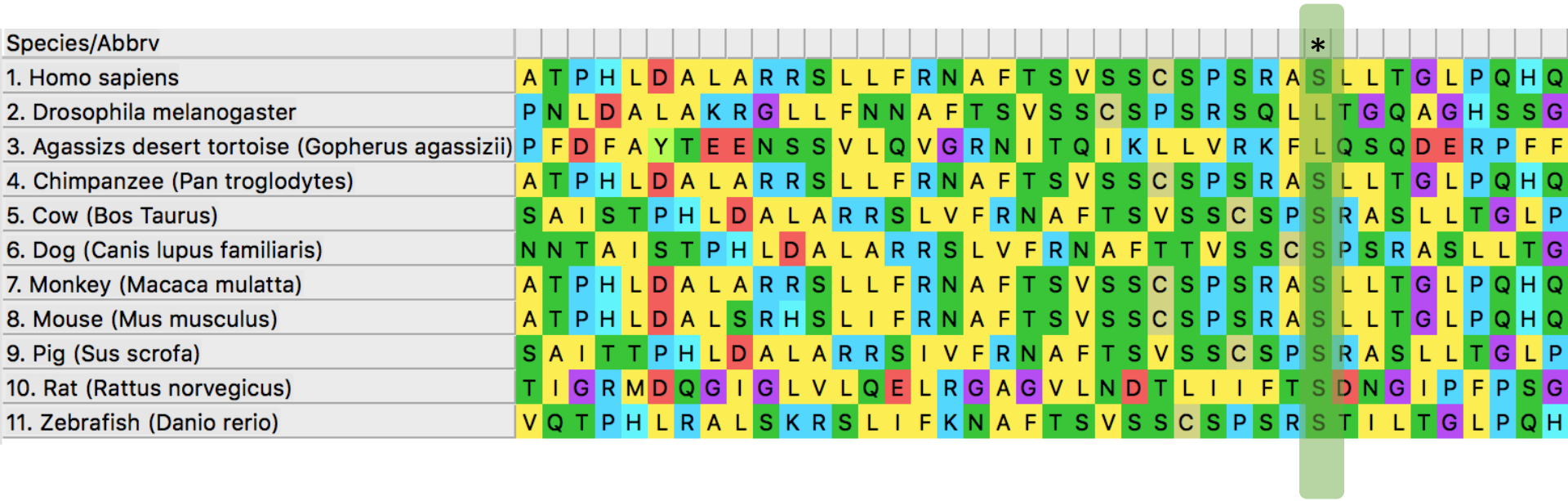
Aim 3

Quantify proteins associated with neurodegeneration and lysosomal degradation



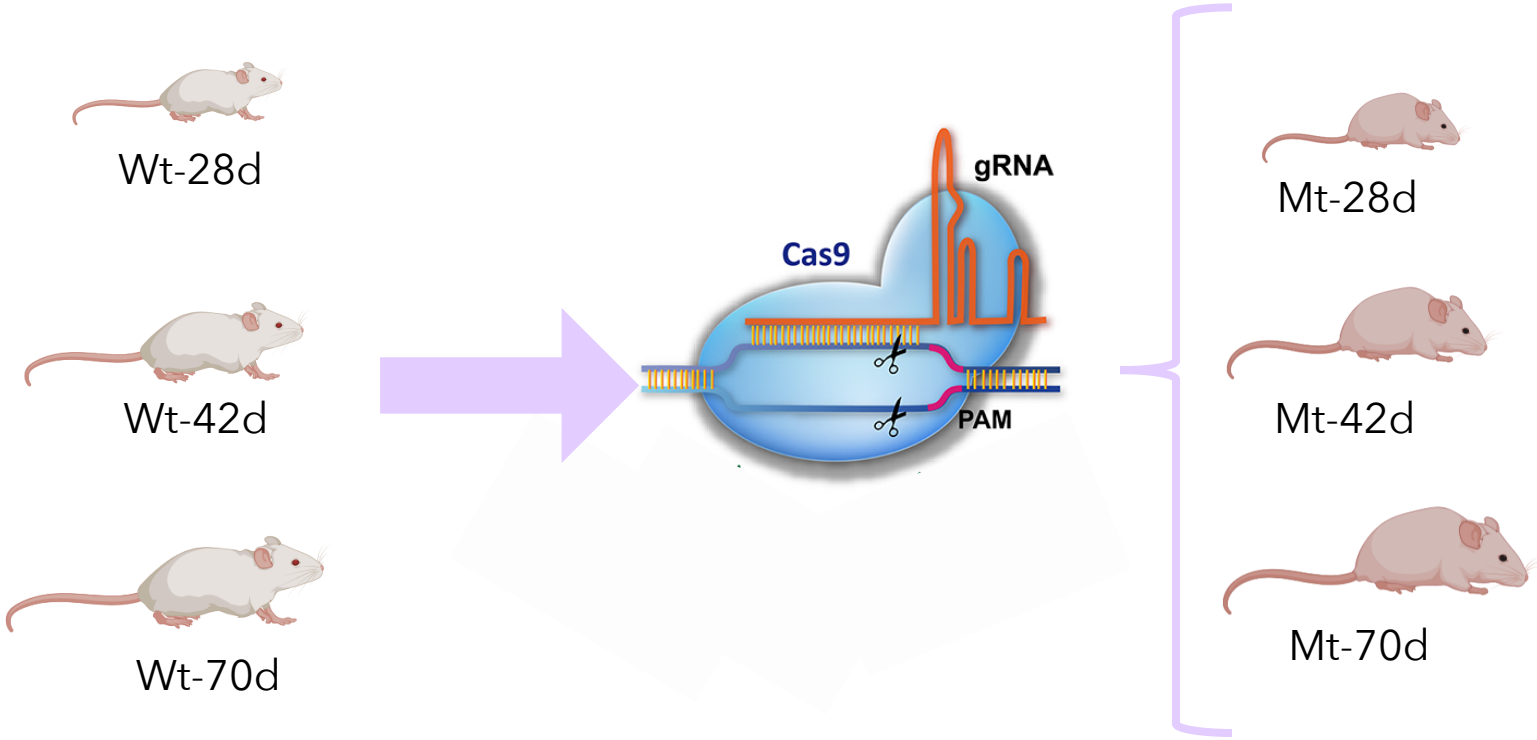
Hypothesis: Sugar accumulations in the lysosome is mediated by SGSH during early development

Aim 1a: Identify conserved amino acids of SGSH that are important for removal of sugar in the neurons over time



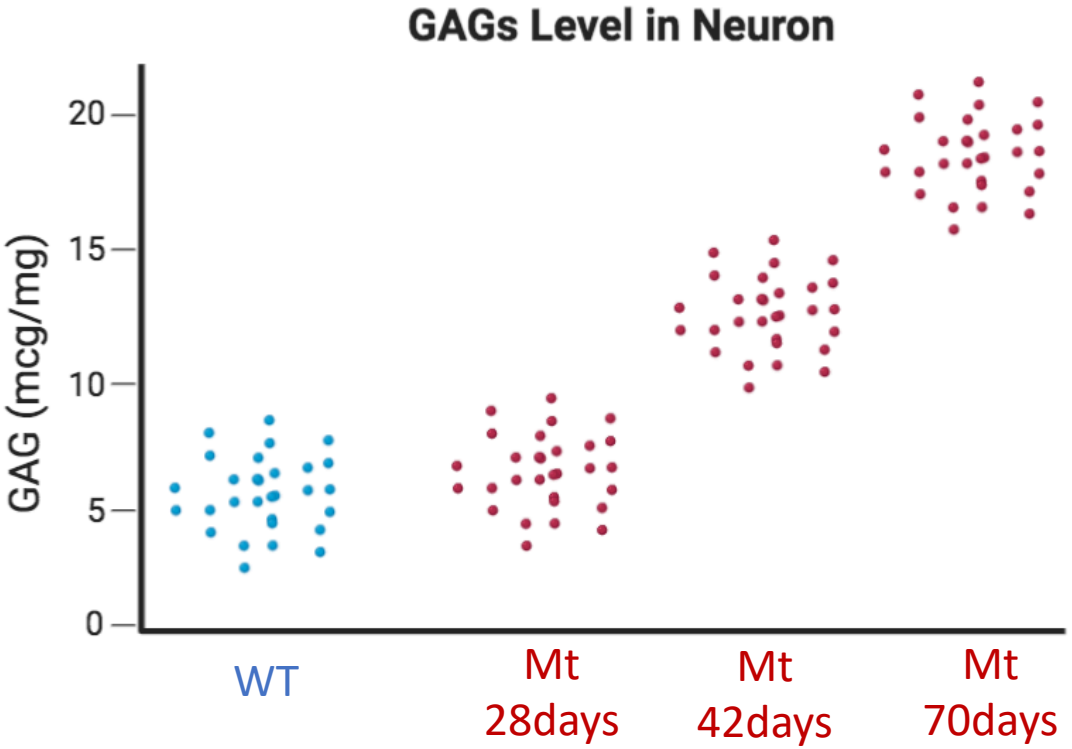
BLAST and ClustalOMEGA → CRISPR/Cas9 → GAGs Assay

Aim 1b: Use CRISPR/Cas9 to create SGSH mutant mice



BLAST and ClustalOMEGA → CRISPR/Cas9 → GAGs Assay

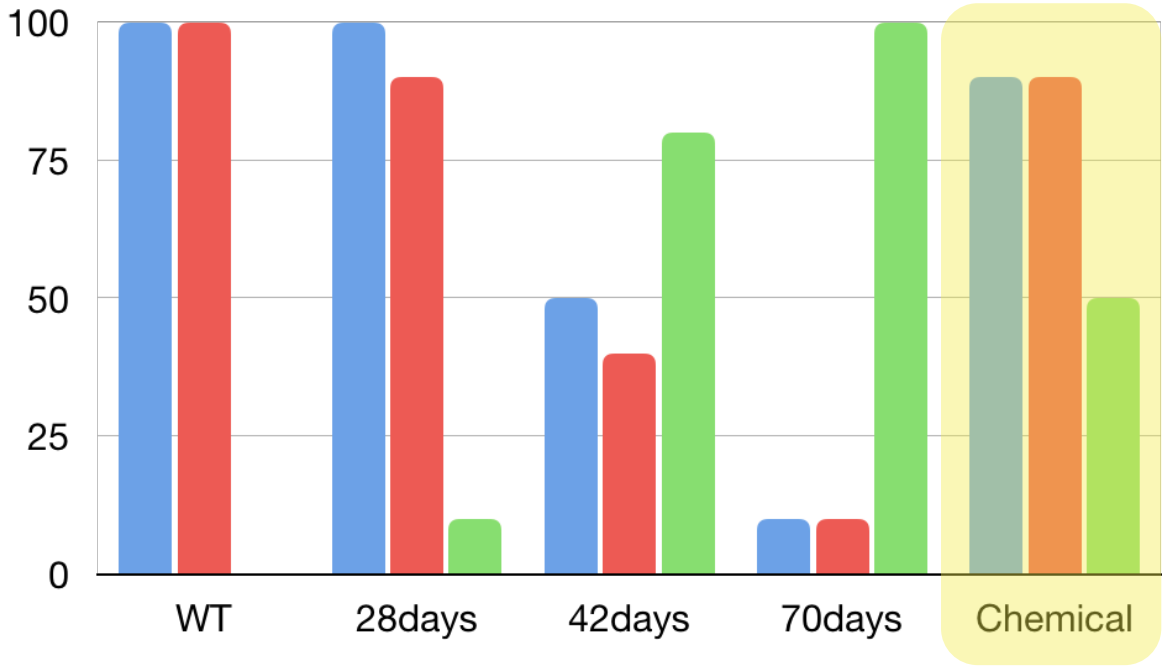
Aim 1c: Quantify sugar levels in brain over time

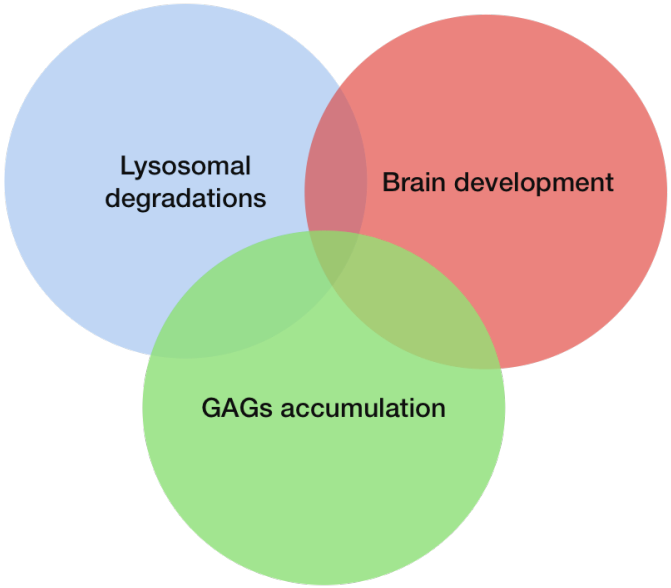


Hypothesis: Mutated mice show higher levels of GAGs in the lysosomes of neurons and the accumulation increases with age.

BLAST and ClustalOMEGA → CRISPR/Cas9 → GAGs Assay

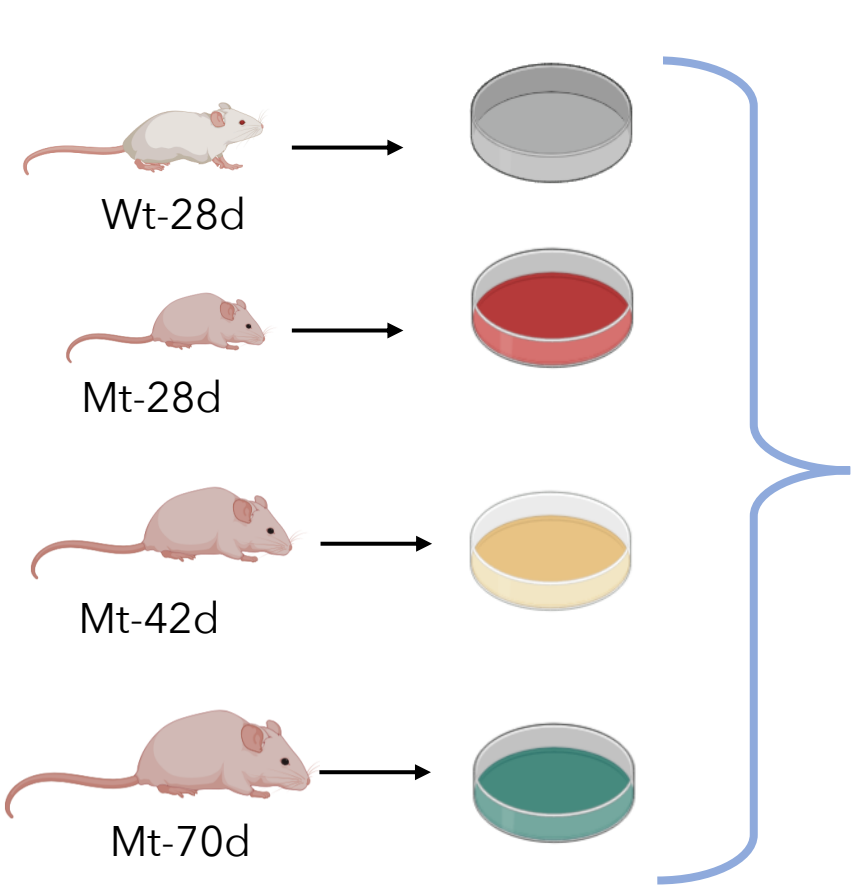
Aim 2: Identify small molecules that rescue phenotypes in SGSH mutants

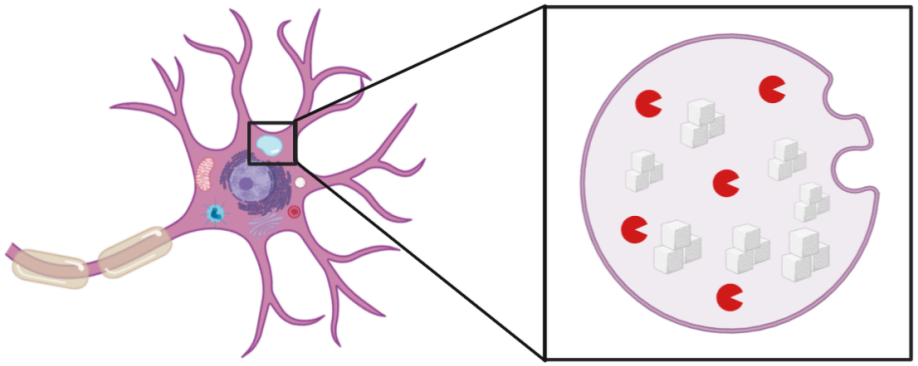


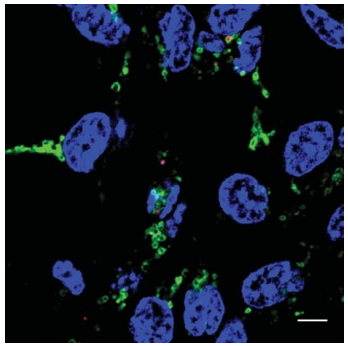


Hypothesis: Molecules associated with upregulation of lysosomal degradation and brain development will rescue phenotypes in mutant mice.

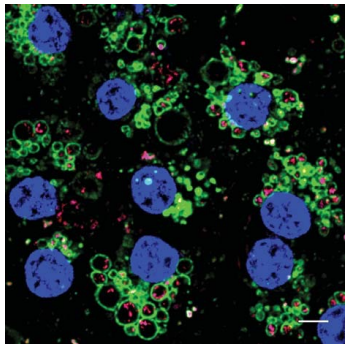
Aim 2a: Prepare neuronal cell cultures of SGSH mutant mice







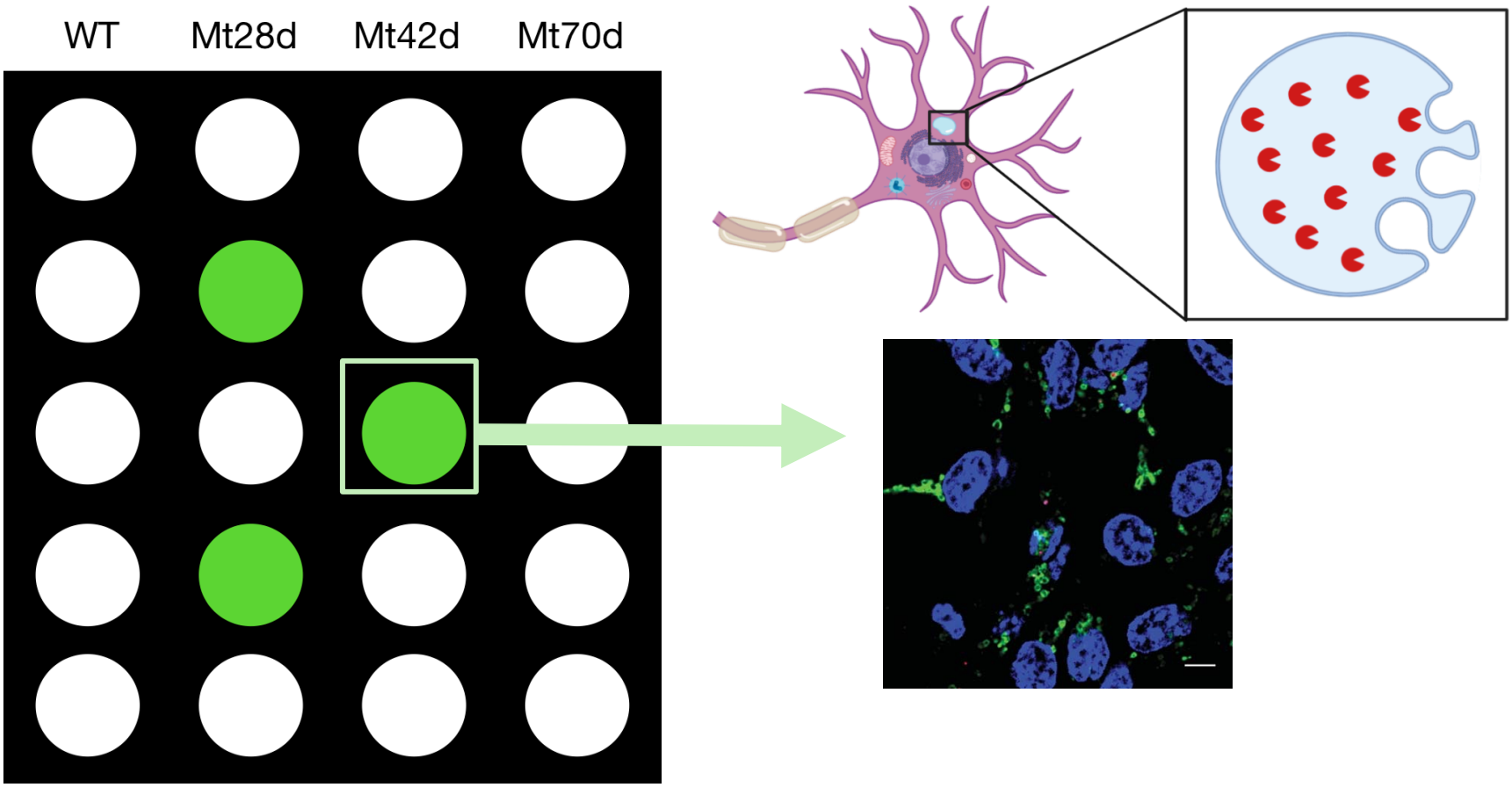
Wildtype



Mutant

Neuronal cell cultures → Chemical genomics screen → Screen phenotype rescues

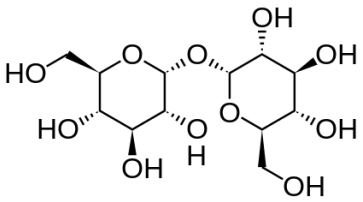
Aim 2b: Perform chemical genomics screen to find molecules that rescue phenotype



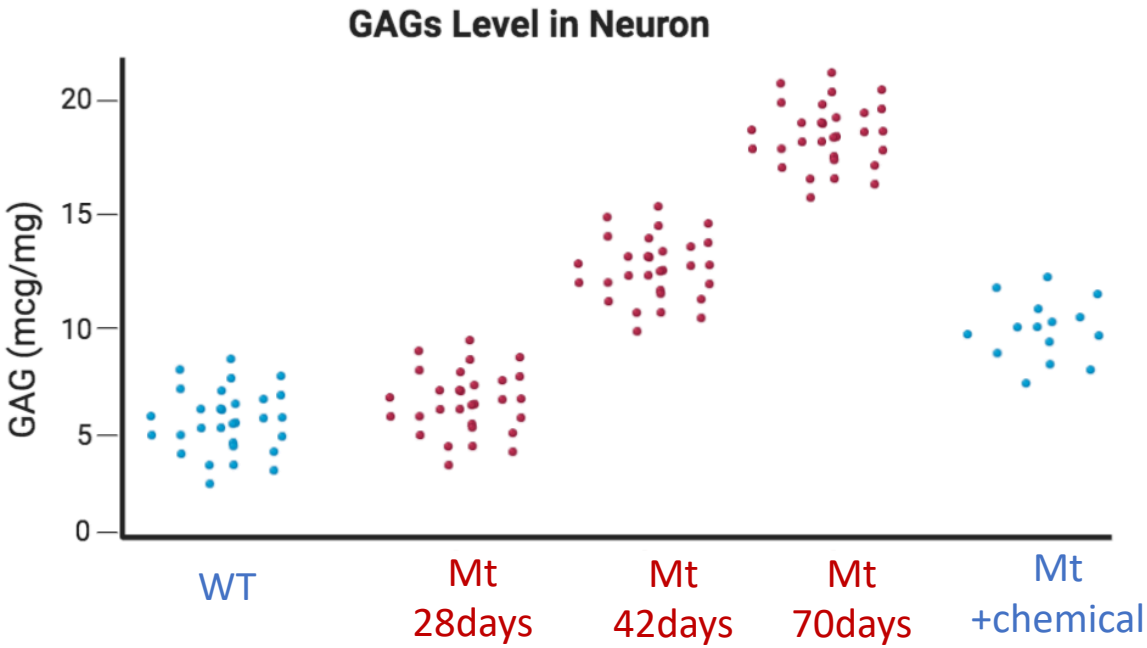
Neuronal cell cultures → Chemical genomics screen → Screen phenotype rescues

Aim 2c: Determine molecules that rescue sugar accumulation

Mt-42 days



Wt-42 days

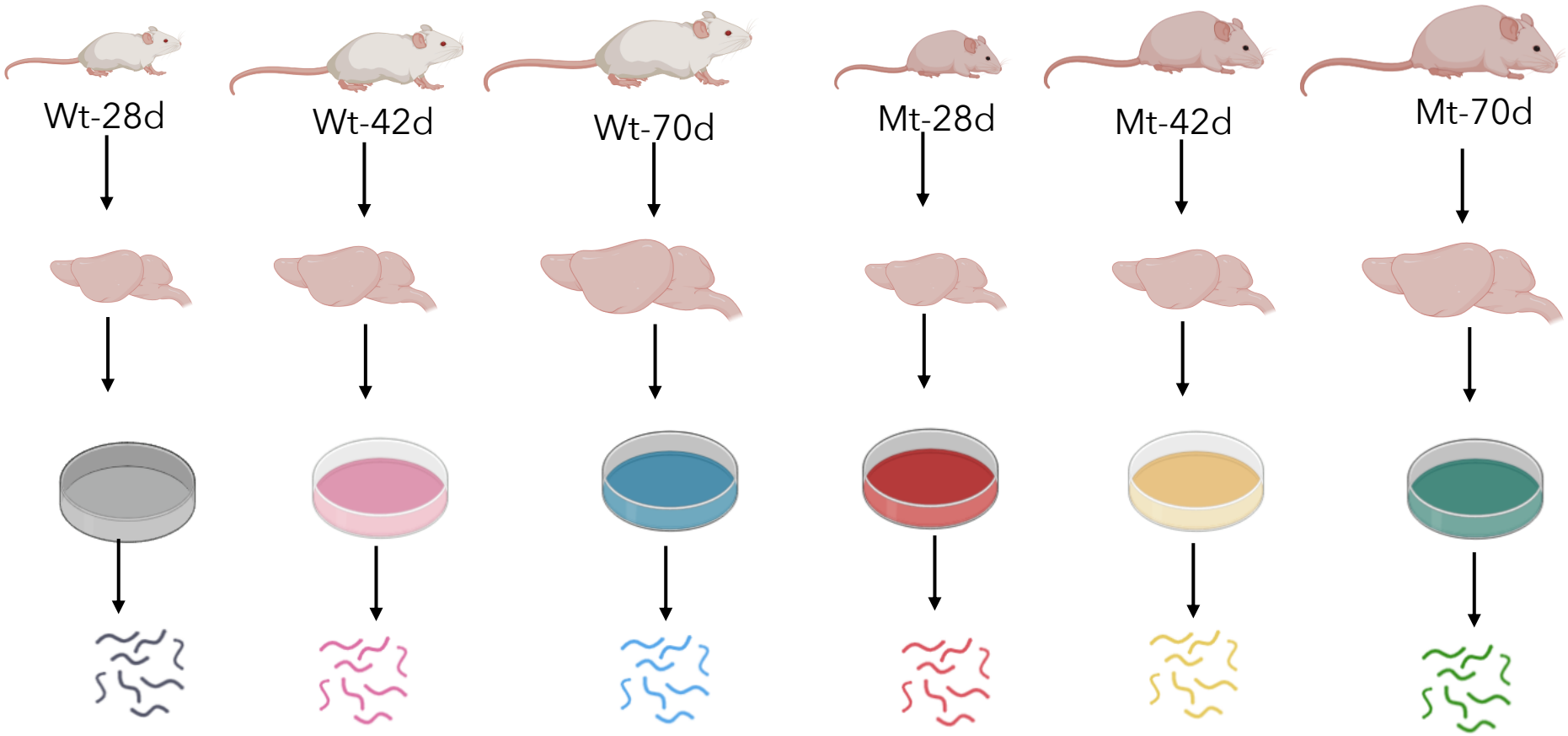


Neuronal cell cultures

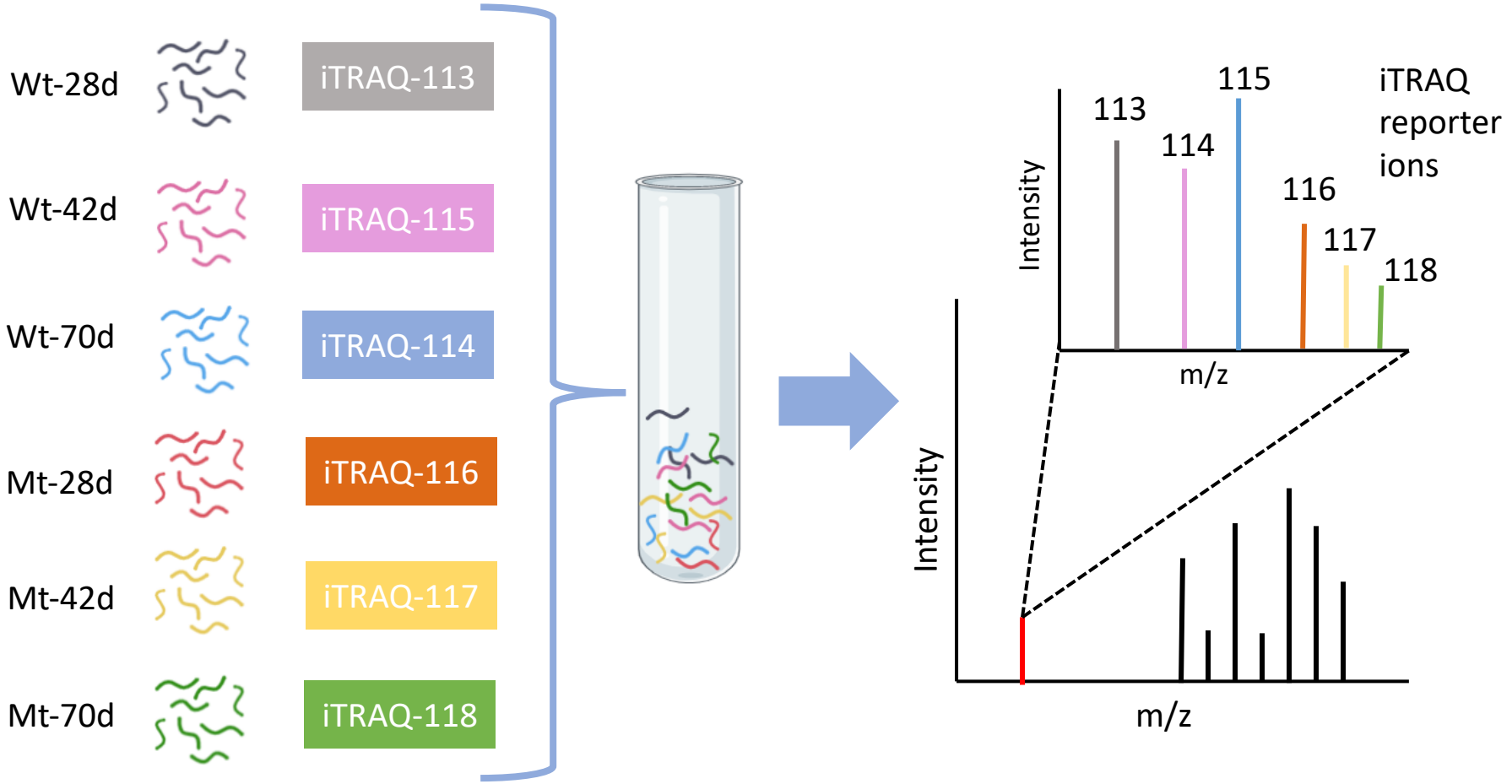
Chemical genomics screen

Screen phenotype rescues

Aim 3a: Identify other protein interactions associated with SGSH and brain development



Aim 3b: Quantify proteins associated with brain development and sugar accumulation

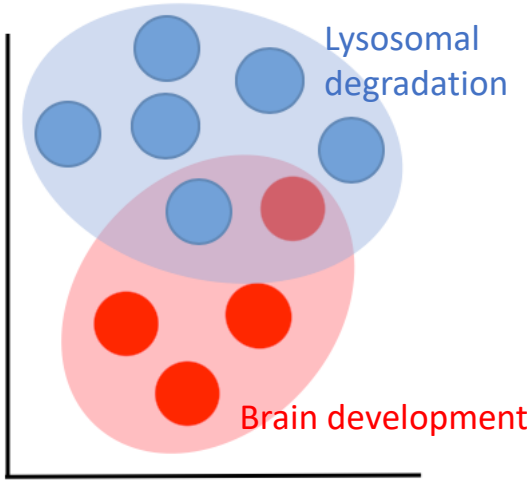


Tissue isolation and protein extraction

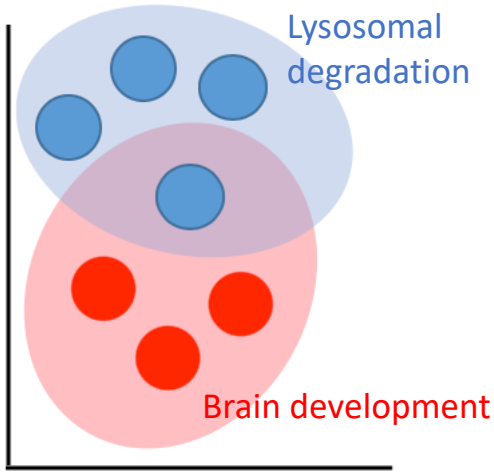
iTRAQ and mass spectrometry

Gene ontology

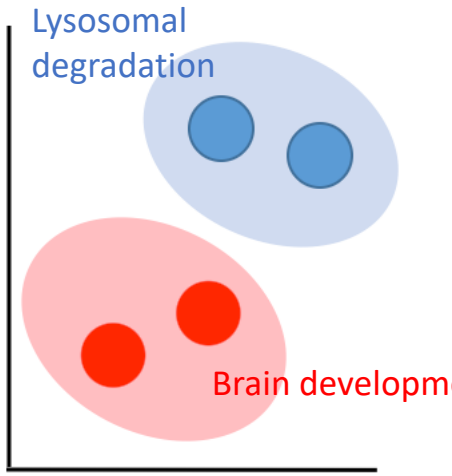
Aim 3c: Categorize proteins associated with SGSH



Wt-42

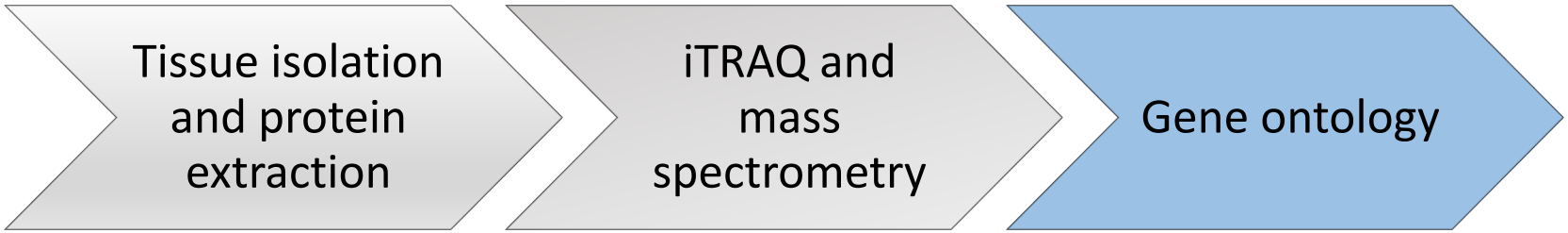


Mt-42d

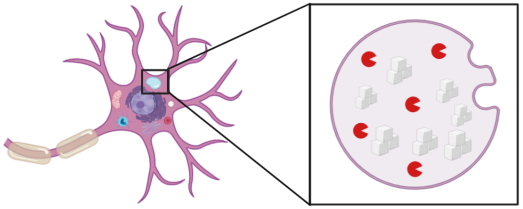


Mt-70d

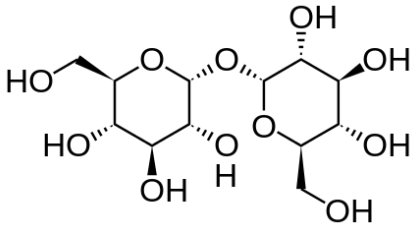
Hypothesis: Proteins involved in brain development and lysosomal degradation will be more abundant in the wildtype than mutant mice



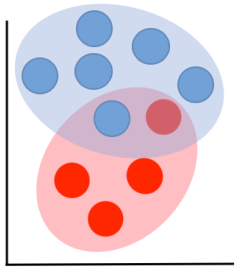
Summary



Sanfilippo syndrome type A is a lysosomal storage disorder caused by SGSH mutation that affects brain development.

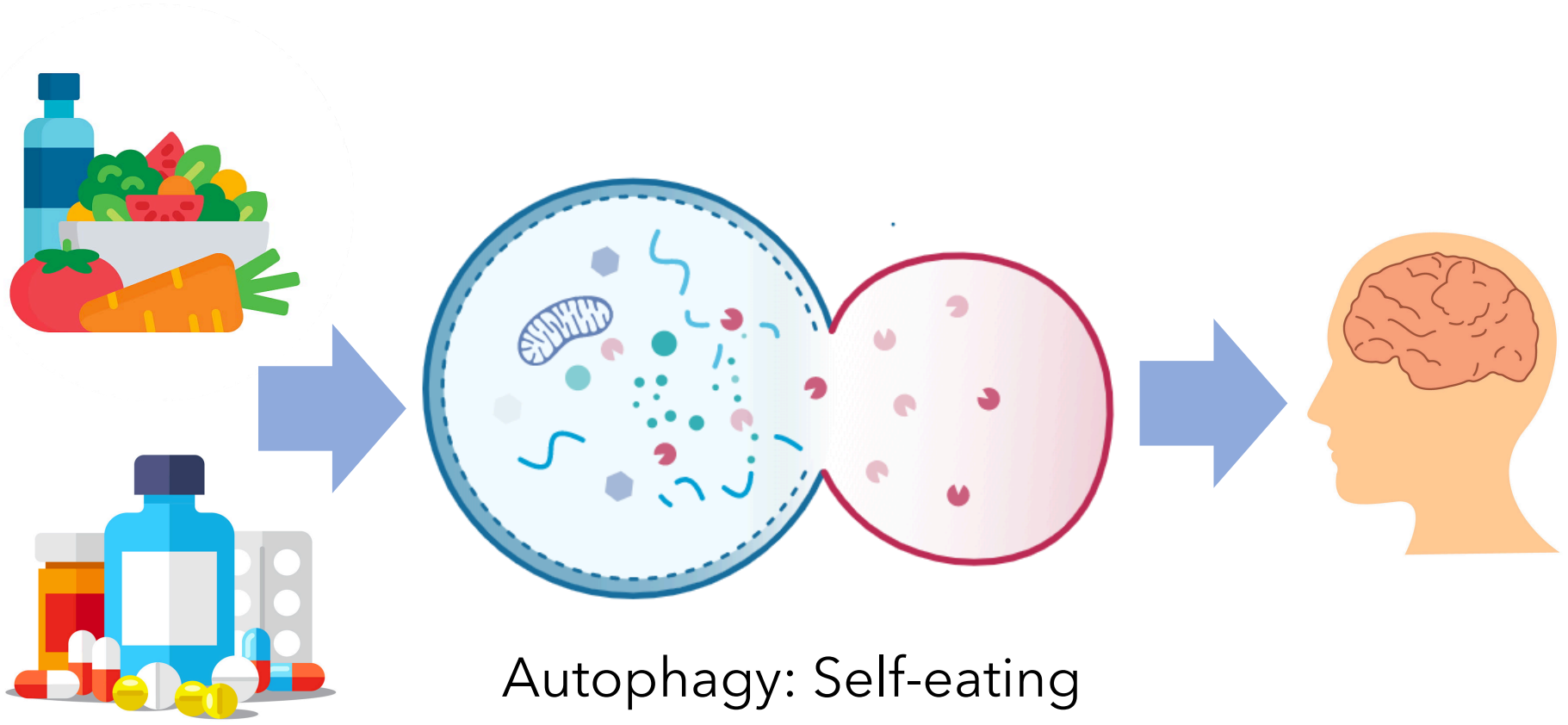


There is still no cure for this disease, but finding molecules interacting with SGSH can be a potential target for drug therapy.



SGSH interacts with other proteins that may play a role in brain development and lysosomal degradation.

Future Directions



Autophagy: Self-eating

References

Cure Sanfilippo Syndrome Foundation. Retrieved from: https://curesanfilippofoundation.org/what-is-sanfilippo/
Fedele A. O. (2015). Sanfilippo syndrome: causes, consequences, and treatments. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4664539/

Gilkes JA, Heldermon CD. Mucopolysaccharidosis III (Sanfilippo Syndrome)- disease presentation and experimental therapies. (2014). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25345095

Images:
Title: https://i1.wp.com/researchaustralia.org/wp-content/uploads/2016/11/sanfilippo.jpg?w=2048&ssl=1

Lysosome: https://www.Biorender.com

Symptoms: https://curesanfilippofoundation.org

Cellular and biological: https://biorender.com

Molecular function: https://themedicalbiochemistrypage.org/largeglycandegradation.php

Human: https://www.1001freedownloads.com/free-vector/free-vector-human-silhouette

Mouse: https://www.pinclipart.com/downpngs/ibJmhw_cute-mouse-silhouette-mouse-silhouette-transparent-background-clipart/

Brain: https://www.vectorstock.com/royalty-free-vector/flat-design-human-brain-in-head-icon-vector-20044653

Neuron: https://socratic.org/questions/as-every-cell-has-organelles-what-type-of-organelles-are-located-in-the-neuron