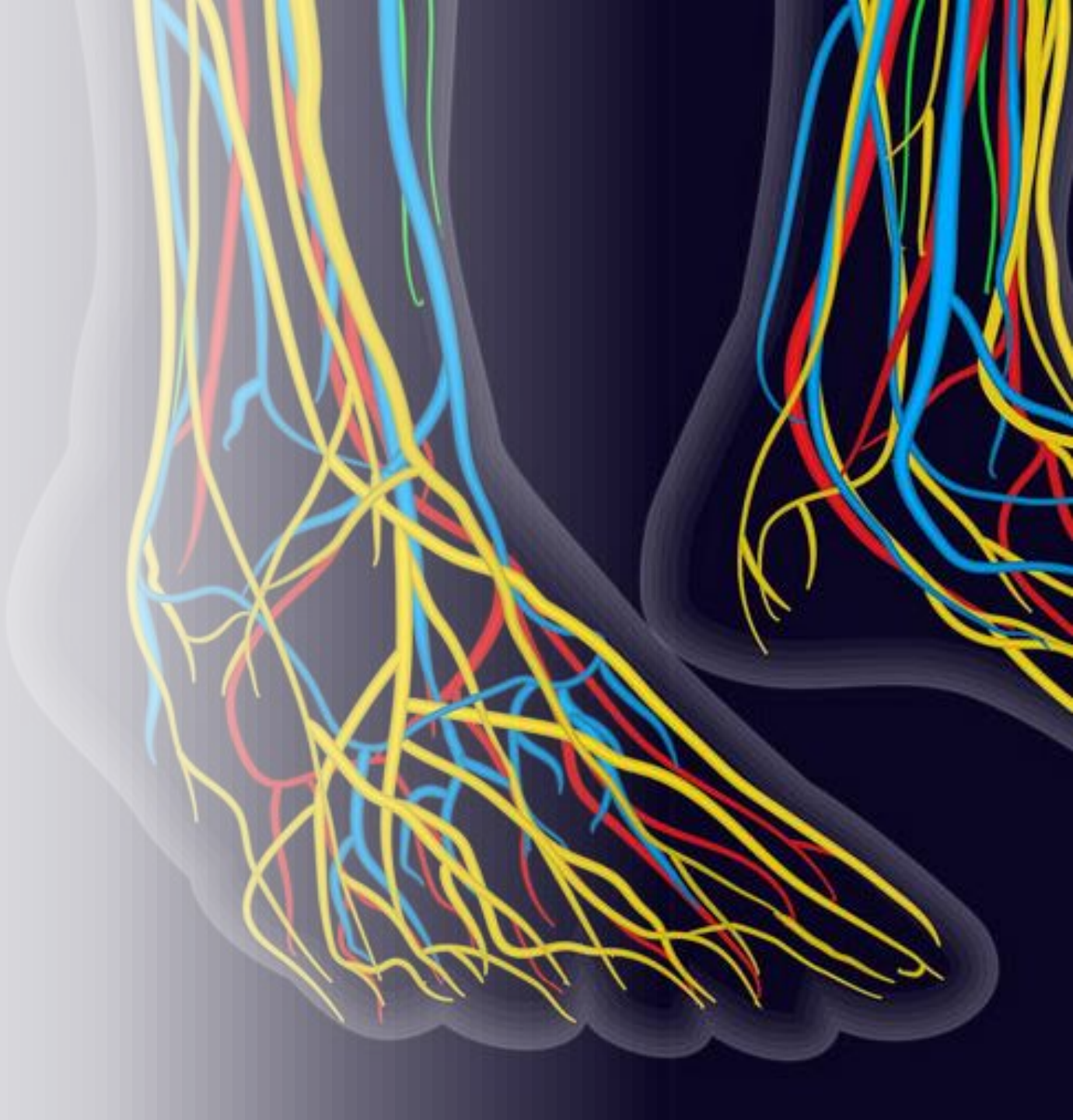
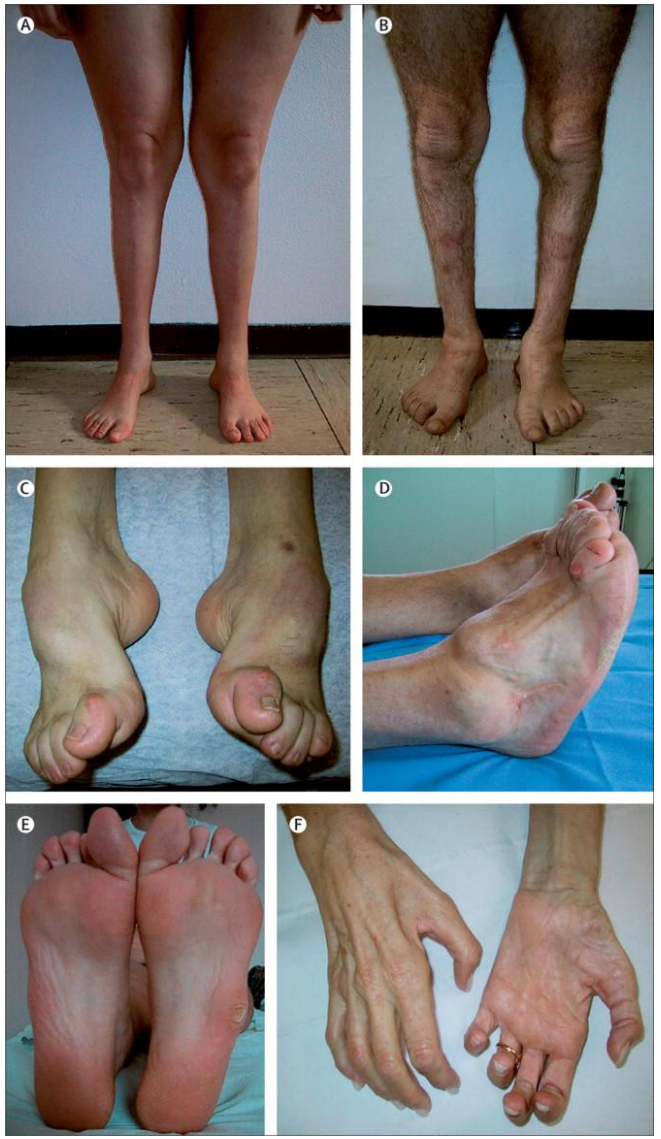
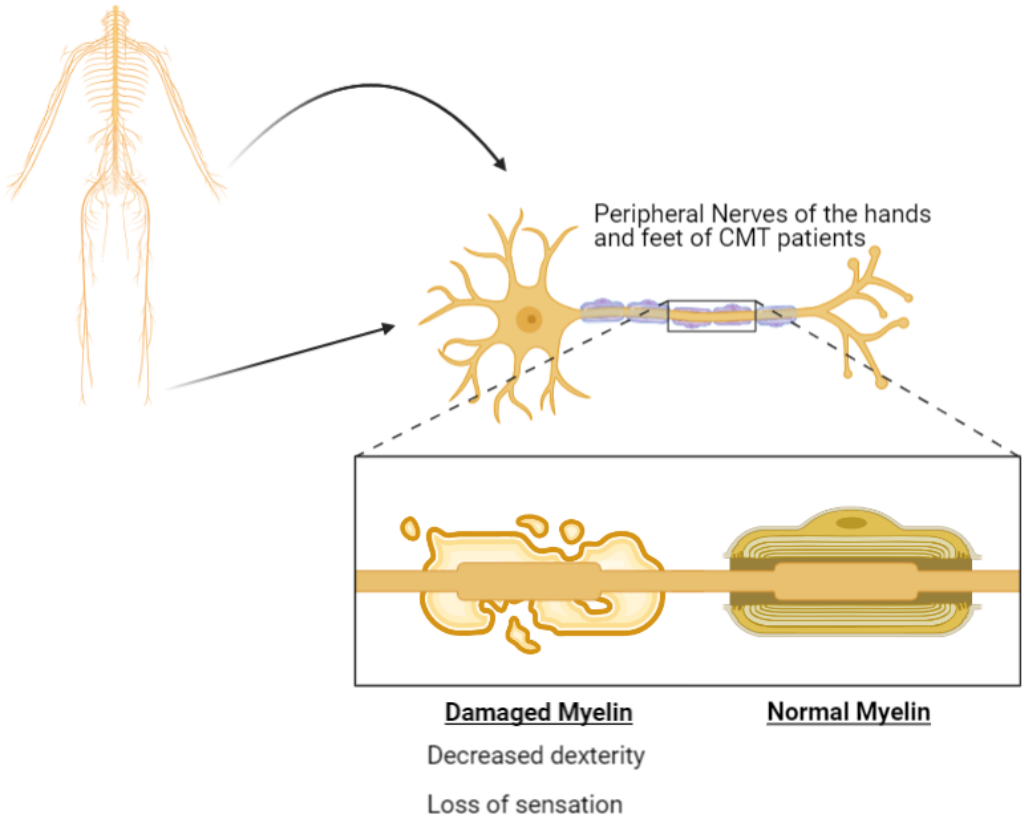
PMP22 and Charcot-Marie-Tooth Disease

Collin Nguyen



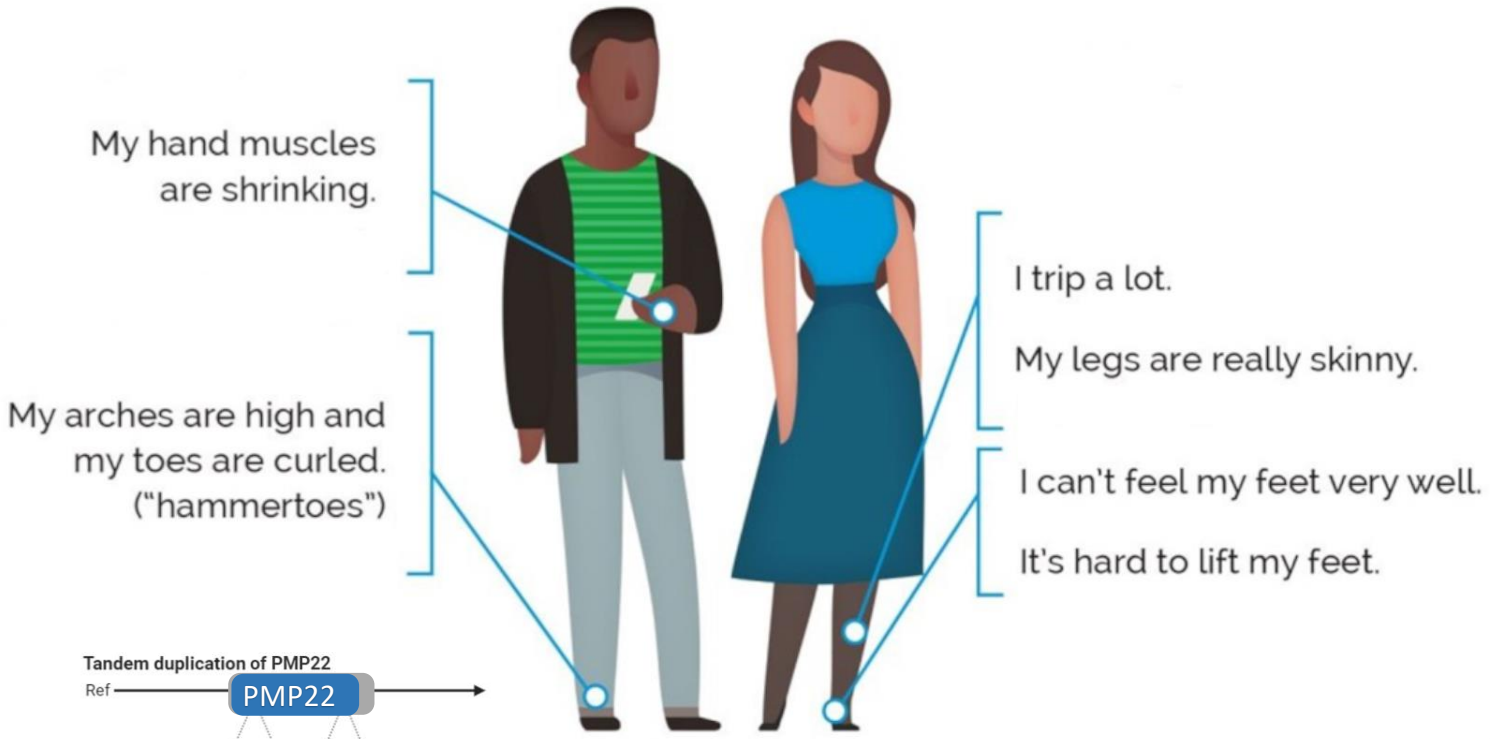
Charcot-Marie-Tooth is the most prevalent genetic disease of the peripheral nervous system

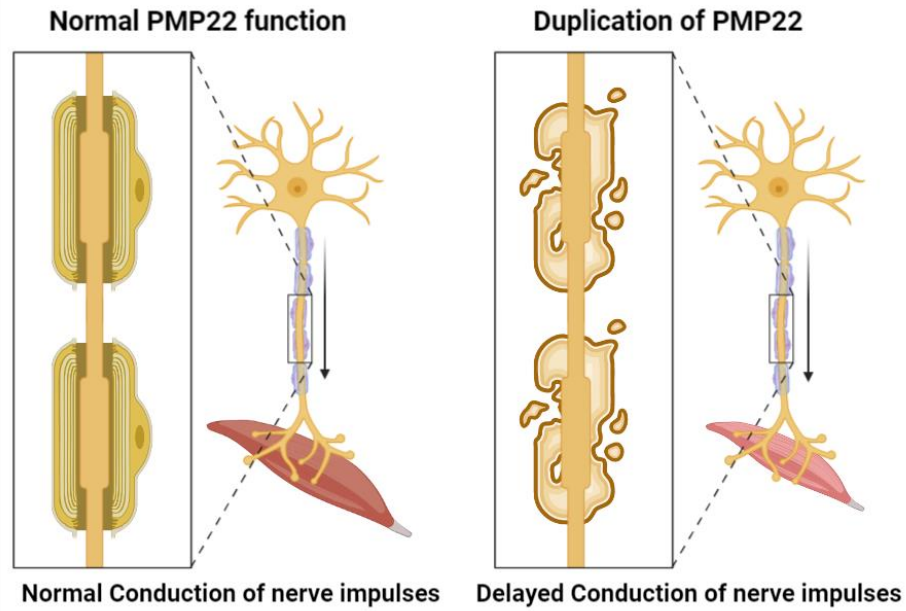


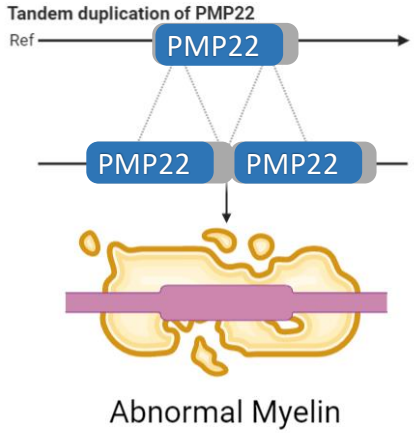


Diagnosis, natural history, and management of Charcot–Marie–Tooth disease
Pareyson, Davide et al.
The Lancet Neurology, Volume 8, Issue 7, 654 - 667

Symptoms are caused by a duplication of PMP22





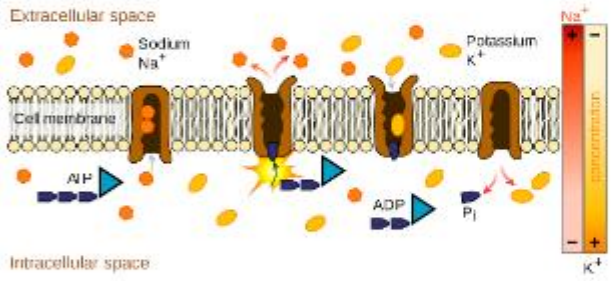


Reduced nerve signaling due to demyelination results in atrophy of muscles

Duplication of PMP22 causes abnormal myelination

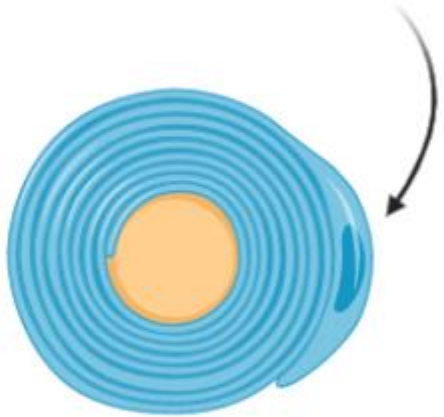
Human PMP22 Claudin 160 AA

Molecular Function



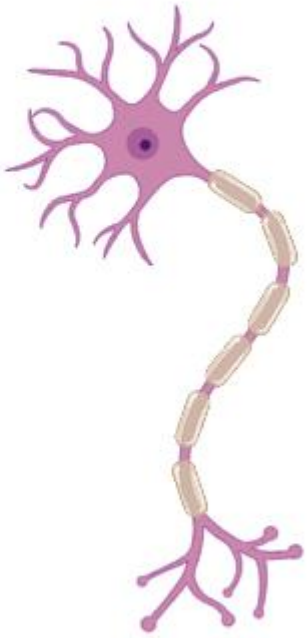
Nucleoside Triphosphatase Activity

Cellular Component



Scwann Cells

Biological Process

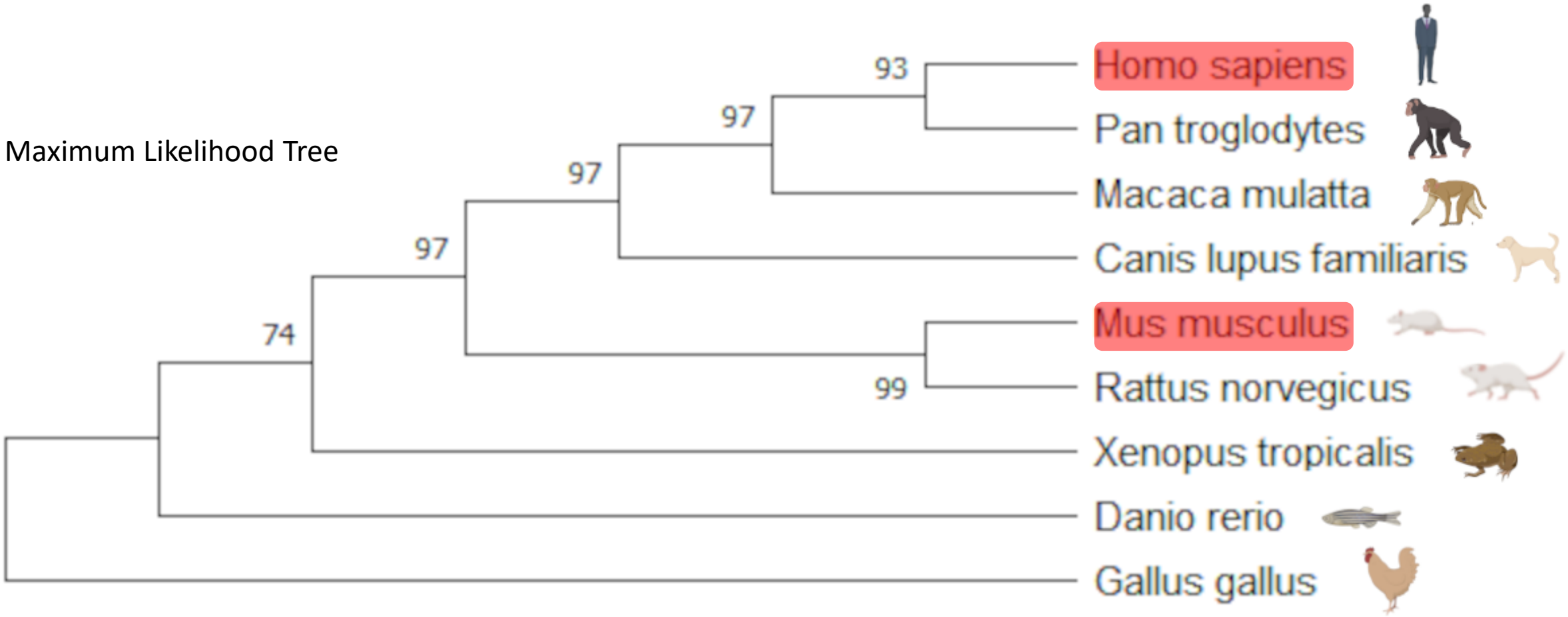


Myelination

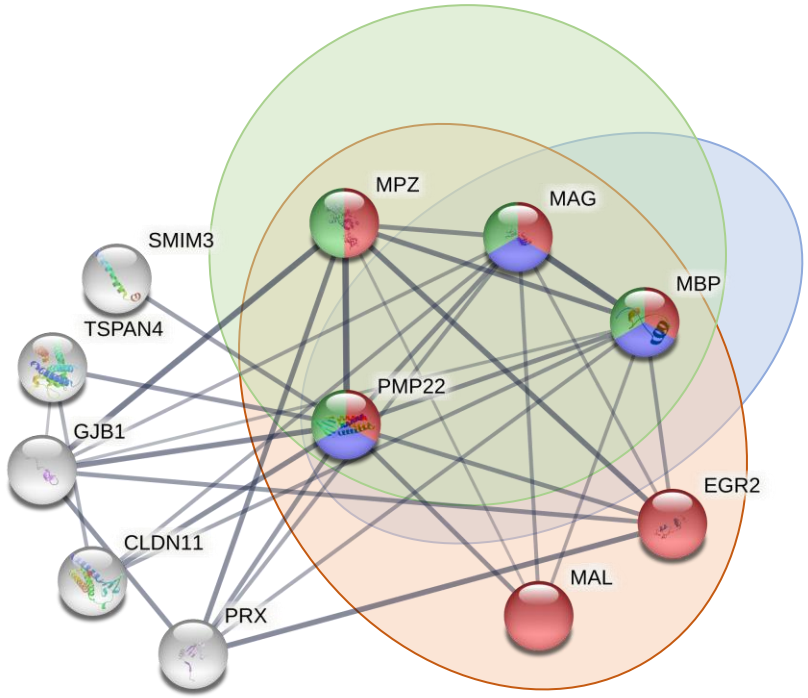
The PMP22 domain is highly conserved in model organisms

PMP22 is well conserved in species with peripheral nervous systems

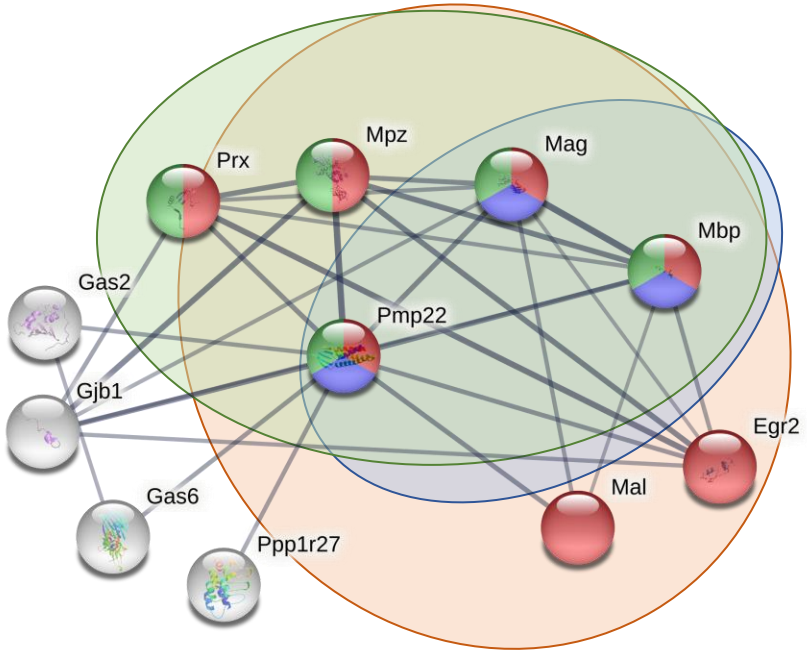
Maximum Likelihood Tree



PMP22 has several already identified protein interactions



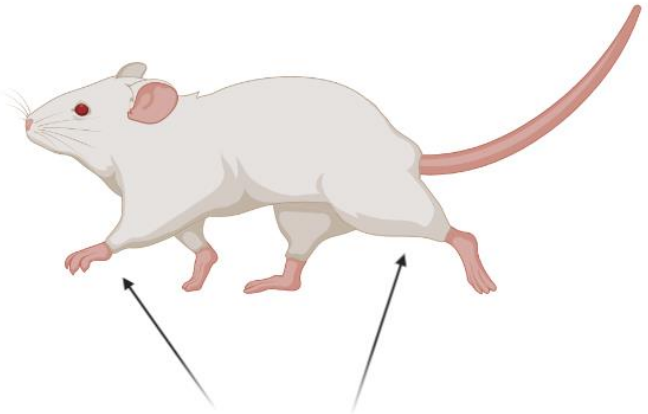
Human



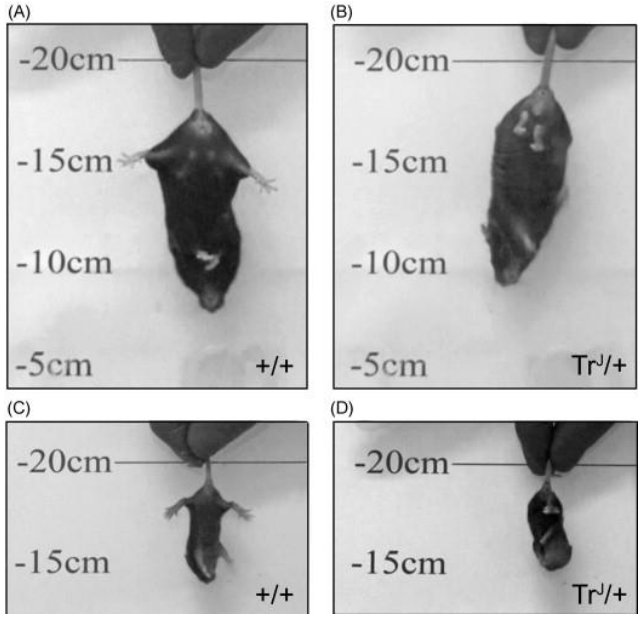
Mouse

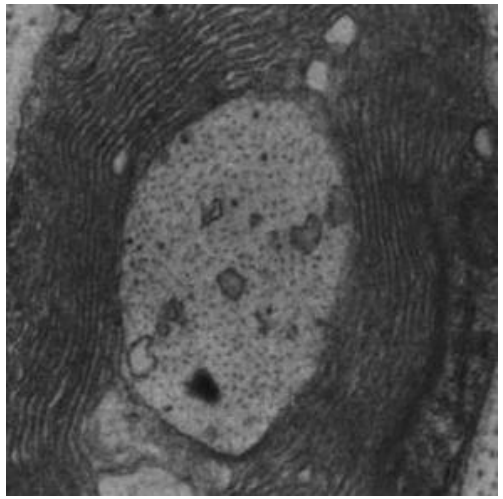
STRING can be used to find already known protein interactions in myelination, compact myelin and myelin sheath

Mice peripheral nervous systems act as good models for human disease

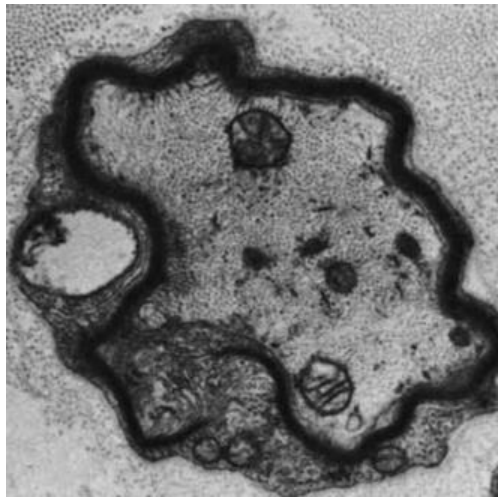


Demyelination results in abnormal gait and tremors of limbs

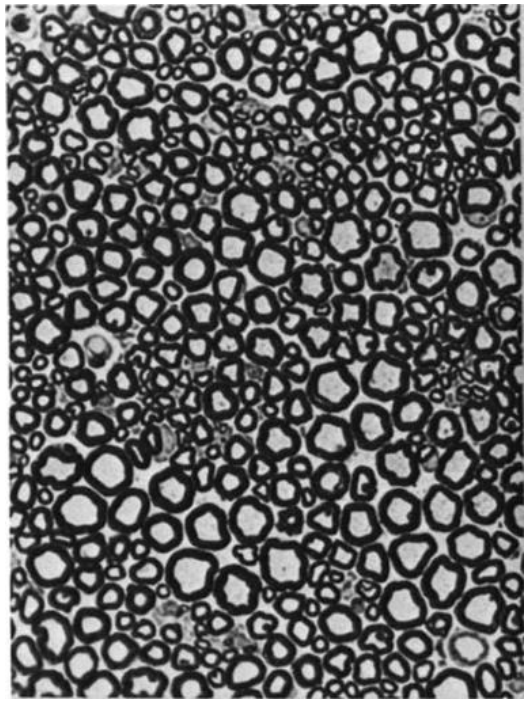




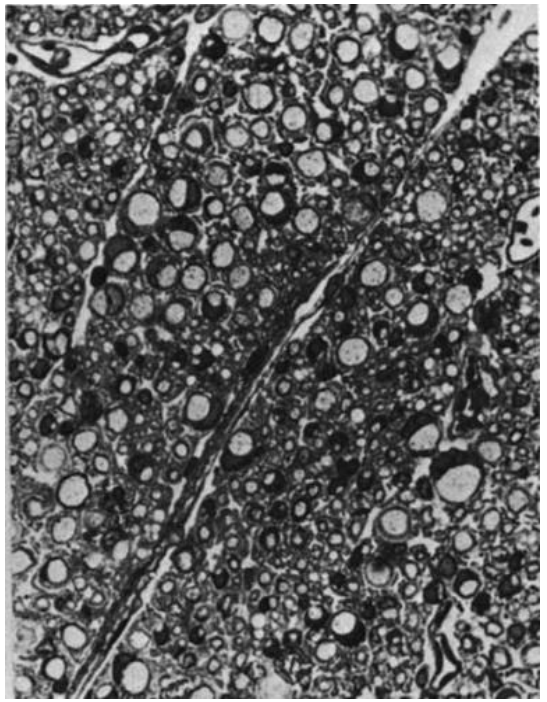
Normal Myelin



Abnormal Myelin

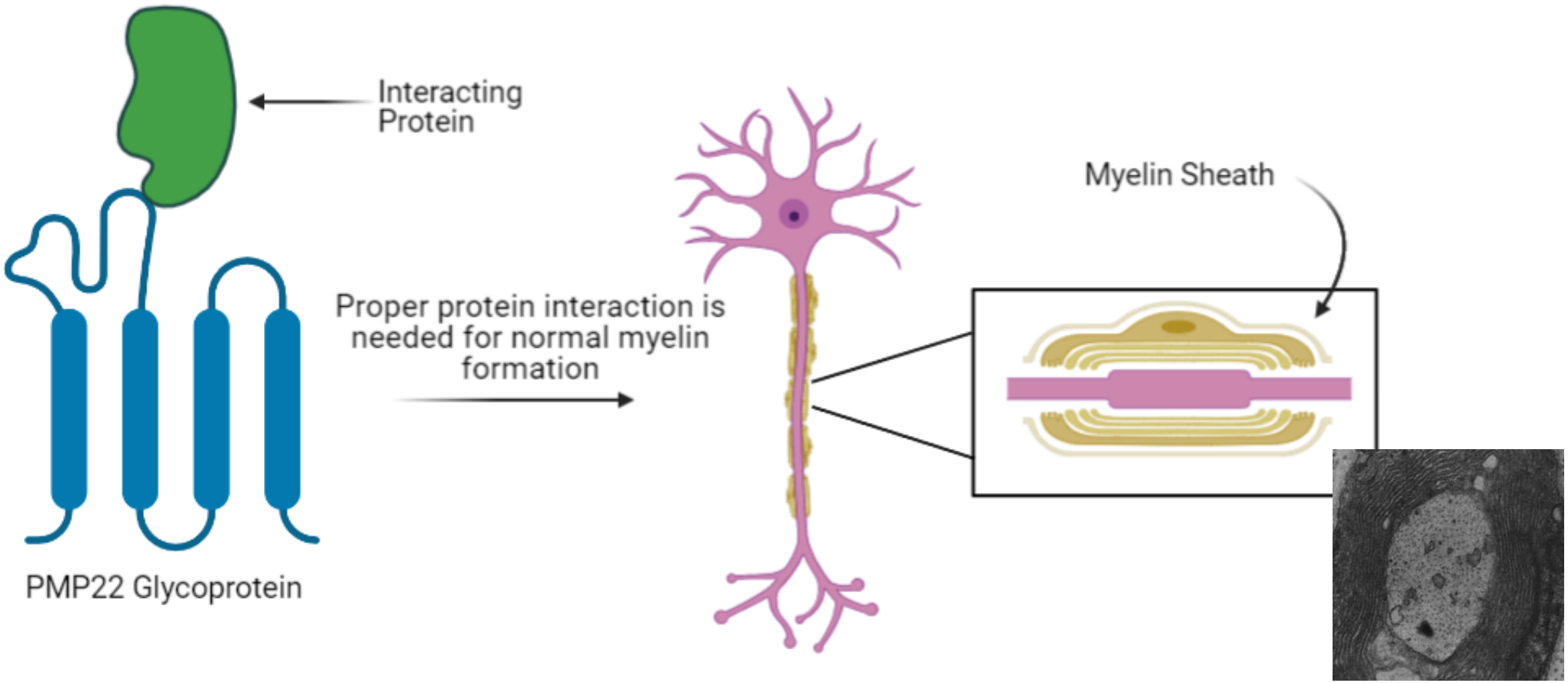


Normal Sciatic Cells



Demyelinating Sciatic Cells

It is unknown what role PMP22 plays in normal myelin formation



Hypothesis: The glycoprotein PMP22 in the peripheral nervous system plays a role in myelination through the protein-protein interactions with other proteins

Specific Aims

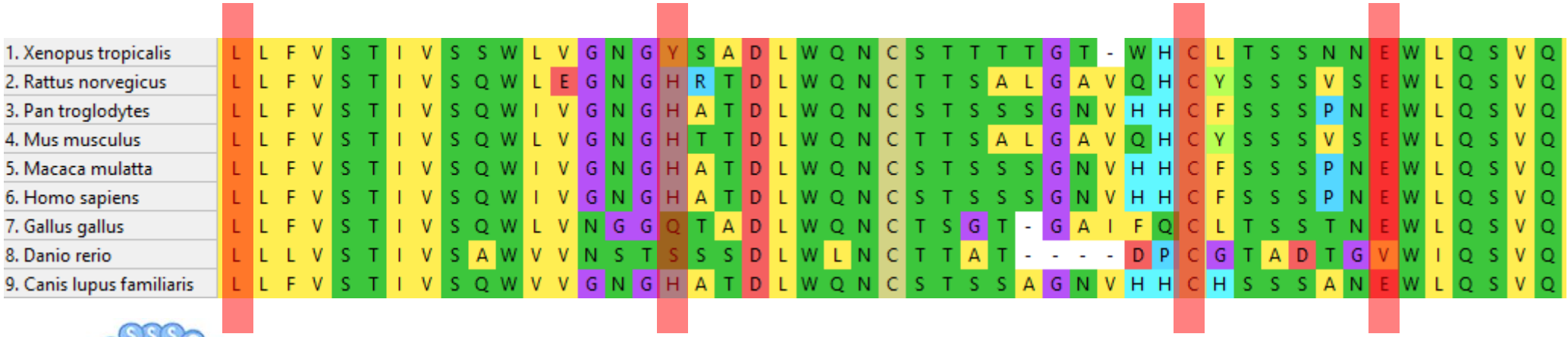
Goal: To determine the role of PMP22 in myelination in the peripheral nervous system

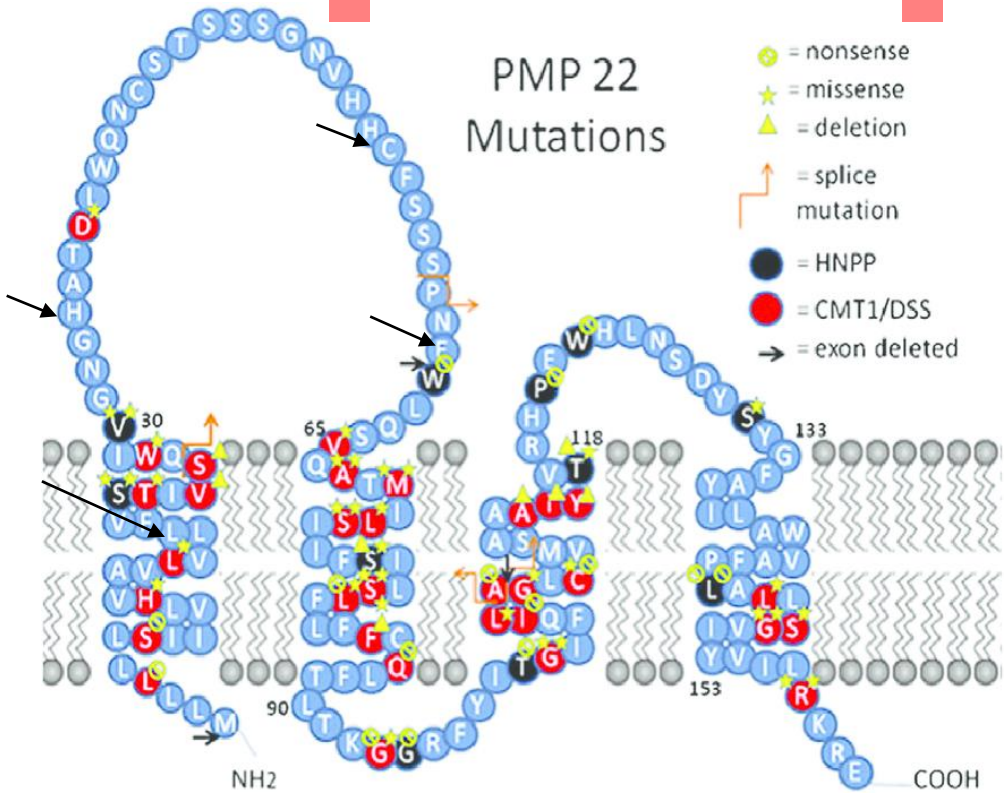
Aim #1: Identify conserved amino acids in PMP22 necessary for the regulation of Schwann cell growth and myelination.

Aim #2: Identify genes that are differentially expressed in in WT and PMP22 mutant myelinating Schwann cells.

Aim #3: Identify novel proteins important for myelination and cell proliferation.

Aim 1: Identity conserved amino acids in PMP22 necessary for myelination





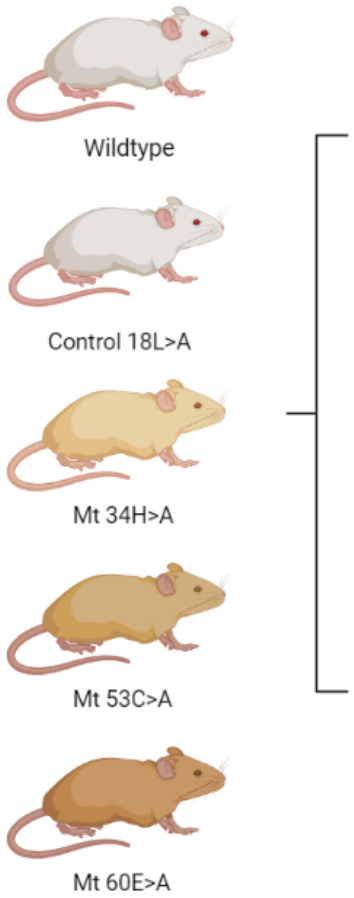
Amino Acids 34, 53, 60 may be involved in protein interactions and will be mutated. AA 18 will also be mutated and act as a control

Aim 1: Identity conserved amino acids in PMP22 necessary for myelination

Wildtype

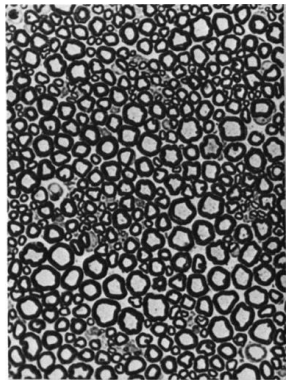
Identifying amino acids that impact Schwann cell growth and result in demyelination can give insight into how mutations of PMP22 may impact demyelination.

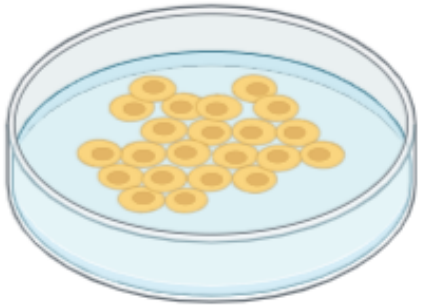
Aim 1: Identity conserved amino acids in PMP22 necessary for myelination



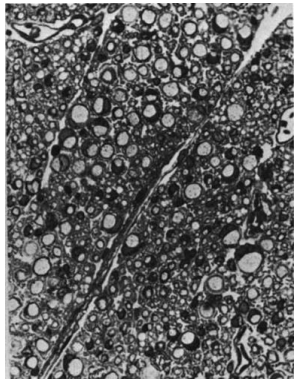
Hypothesis: Mice with mutations in conserved PMP22 amino acids in these extracellular loop regions will show demyelination in the peripheral nervous system

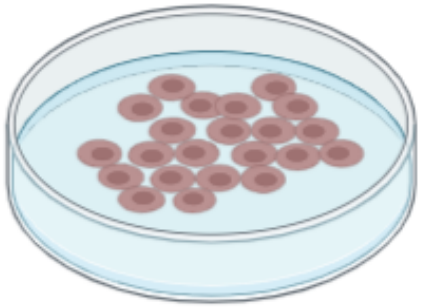
Aim 2: Mice with mutant phenotypes will show differential gene expression





Wildtype sciatic nerve sample

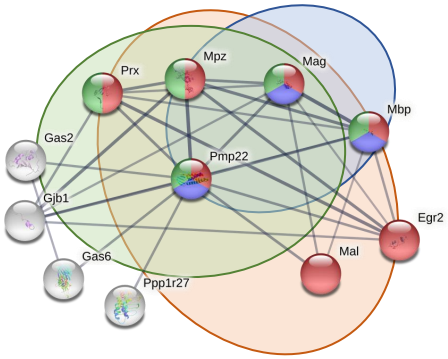




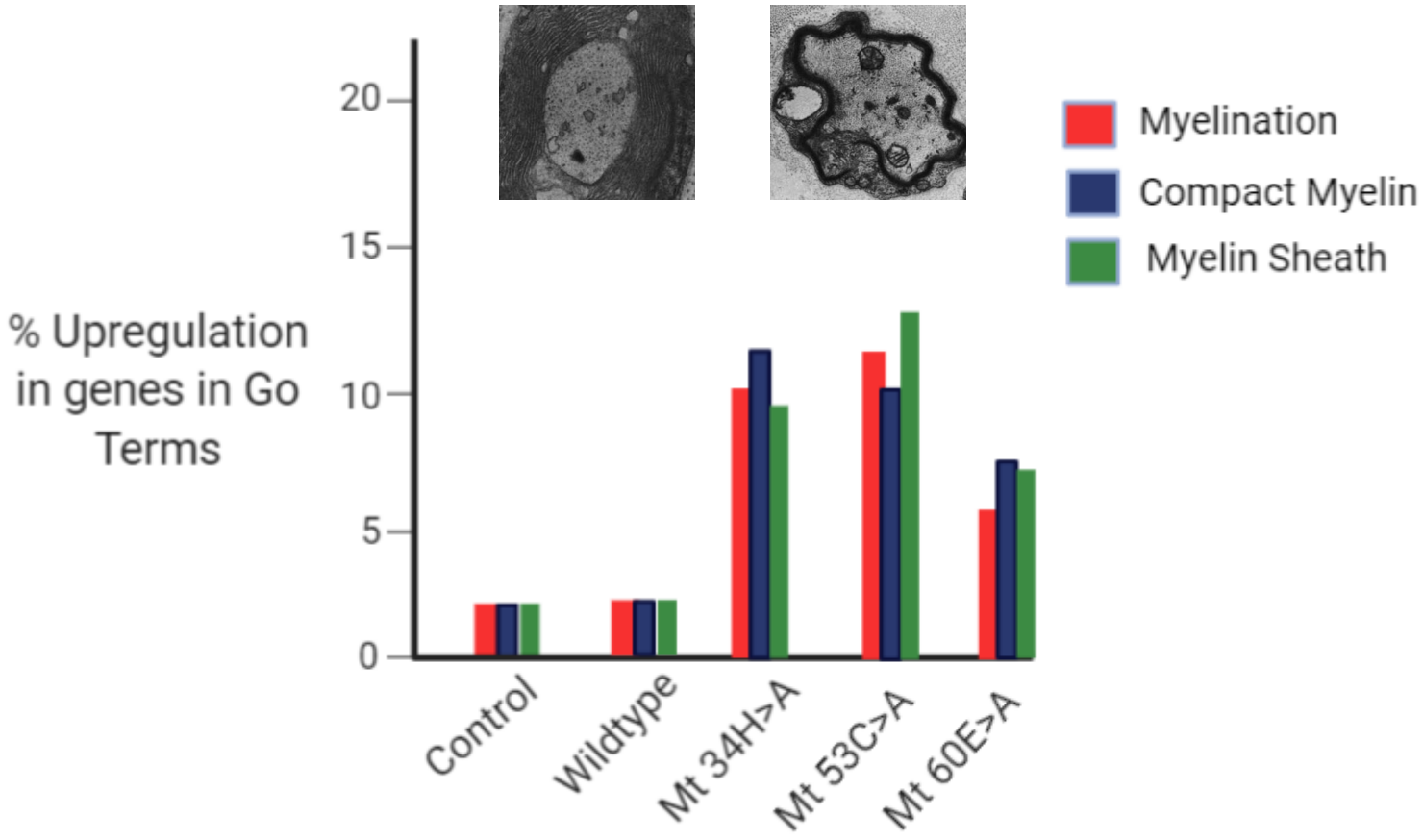
Mutant sciatic nerve sample

Identification of these differentially transcribed genes will aid in determining what genes and pathways PMP22 interacts with in myelination.

Aim 2: Mice with mutant phenotypes will show differential gene expression

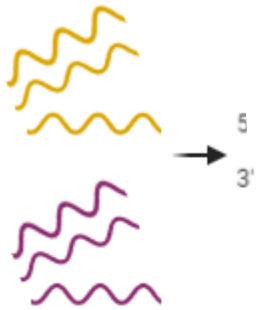


GENEONTOLOGY
Unifying Biology



Mice with PMP22 mutations will show abnormal levels of gene expression in pathways related to myelination.

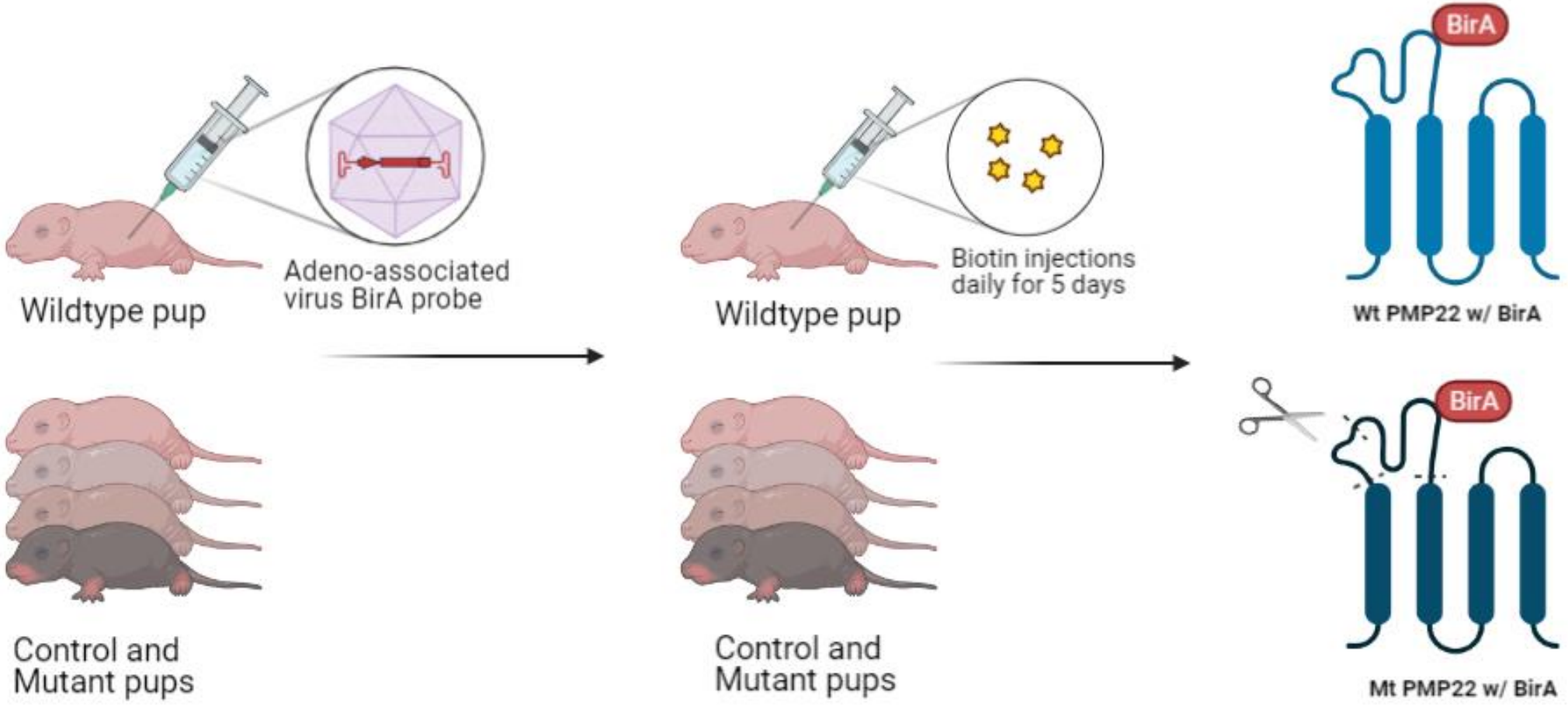
Aim 2: Mice with mutant phenotypes will show differential gene expression



Reverse transcriptase used to create respective cDNA

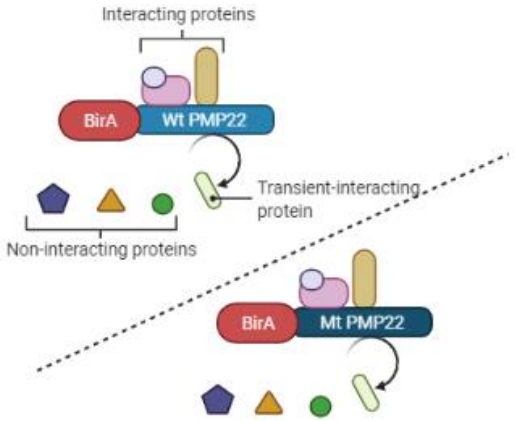
RT-qPCR can be used to validate results found in RNA-seq data

Aim 3: BioID will reveal novel and altered protein interactions in mutants



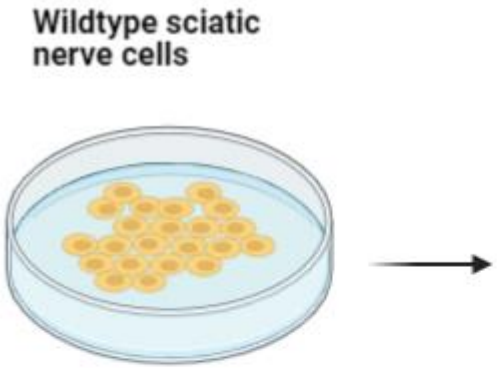
Discovery of new protein interactions that are impacted by PMP22 mutation can help enlighten the mechanisms by which PMP22 impacts myelination

Aim 3: BioID will reveal novel and altered protein interactions in mutants



Hypothesis: Analysis of M/Z data from BioID will elucidate new protein interactions and differences between wildtype & mutant PMP22 ability to interact with other proteins

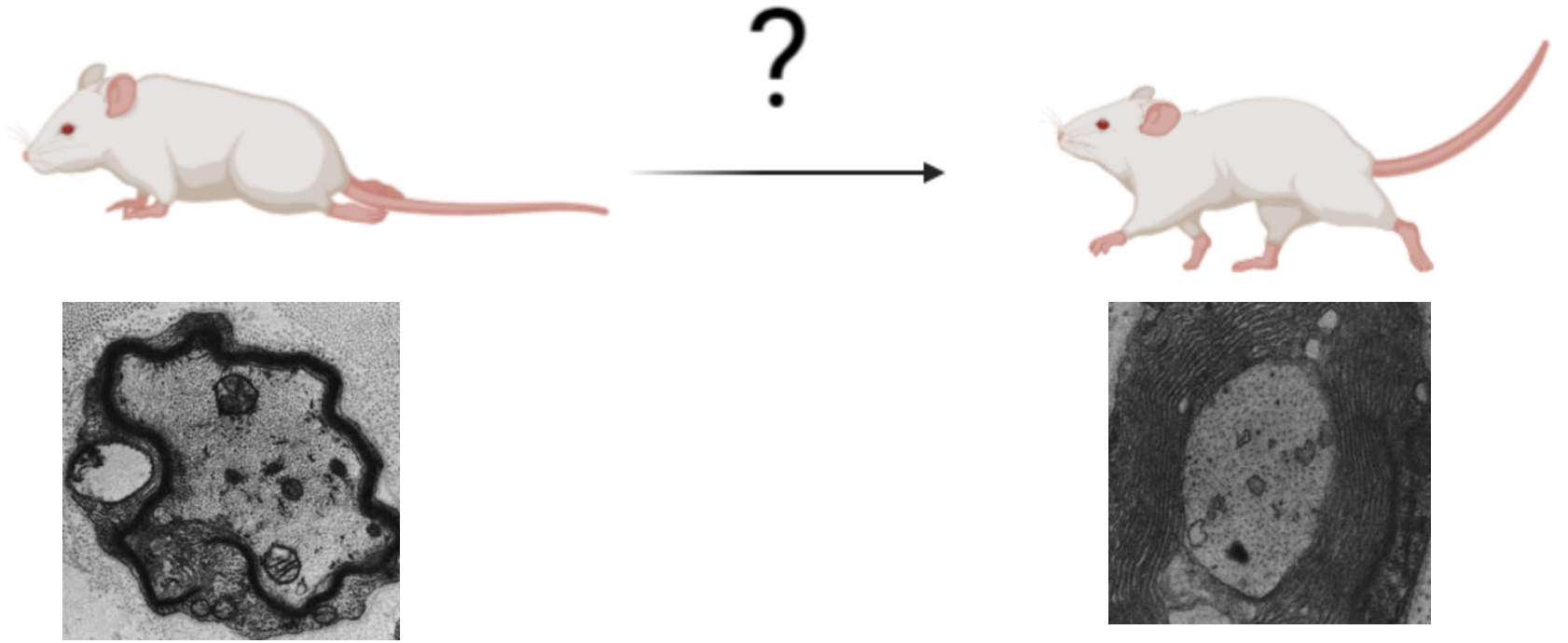
Aim 3: BioID will reveal novel and altered protein interactions in mutants



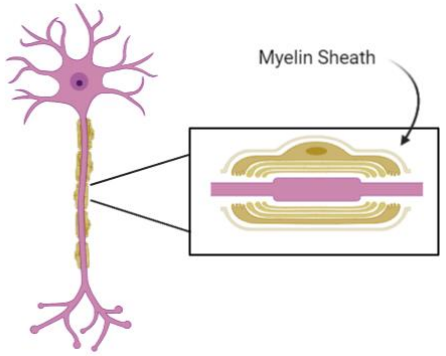
A western blot can be done to confirm the presence of the novel protein

Future Directions?

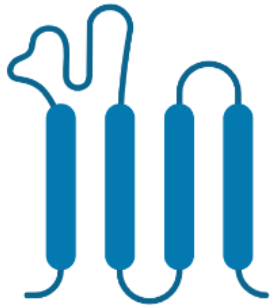
How can alterations in PMP22 associated protein interactions be rescued in vivo?



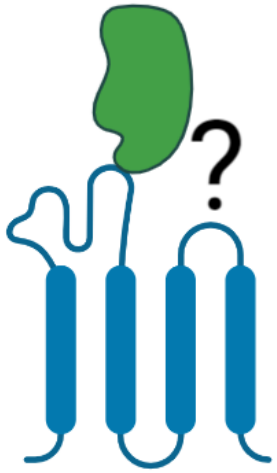
Conclusion



Charcot-Marie-Tooth Type 1A is a genetic disease of the peripheral nervous system resulting in demyelination



There is not cure for Charcot-Marie-Tooth 1A, however PMP22 is implicated in its demyelinating nature despite PMP22's role in myelination being unknown



Improved understanding of the protein interactions between PMP22 and other proteins can elucidate PMP22s role in myelination and contribute to a treatment

References

Biorender used to create images

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