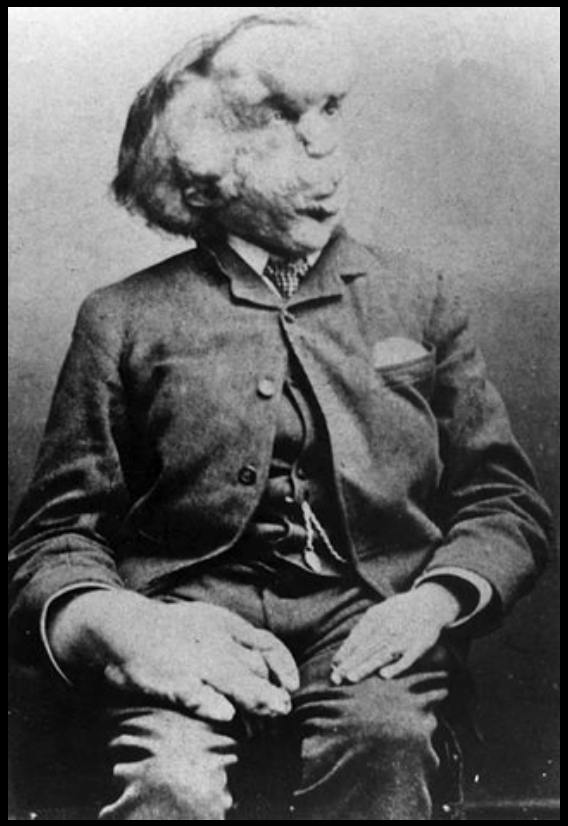
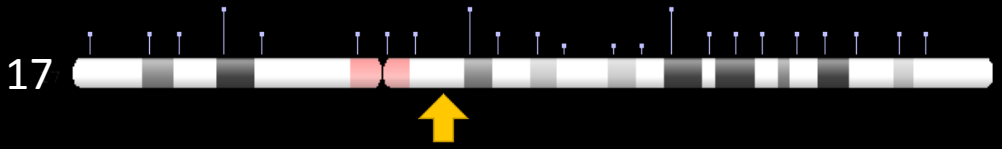
Neurofibromatosis Type 1

Laura Johnson

What is NF1?

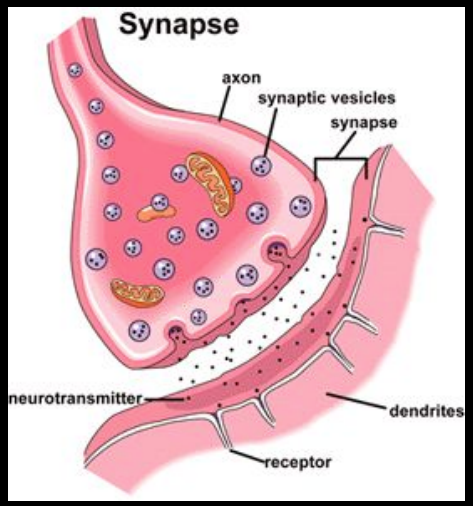
1/3,000



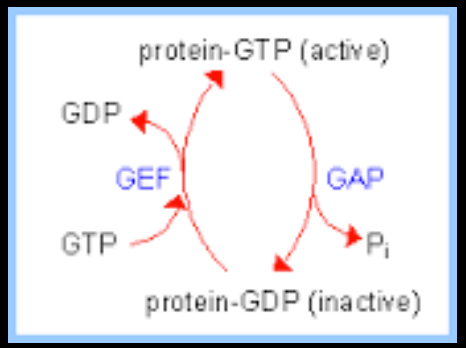


Neurofibromin

Cellular Component

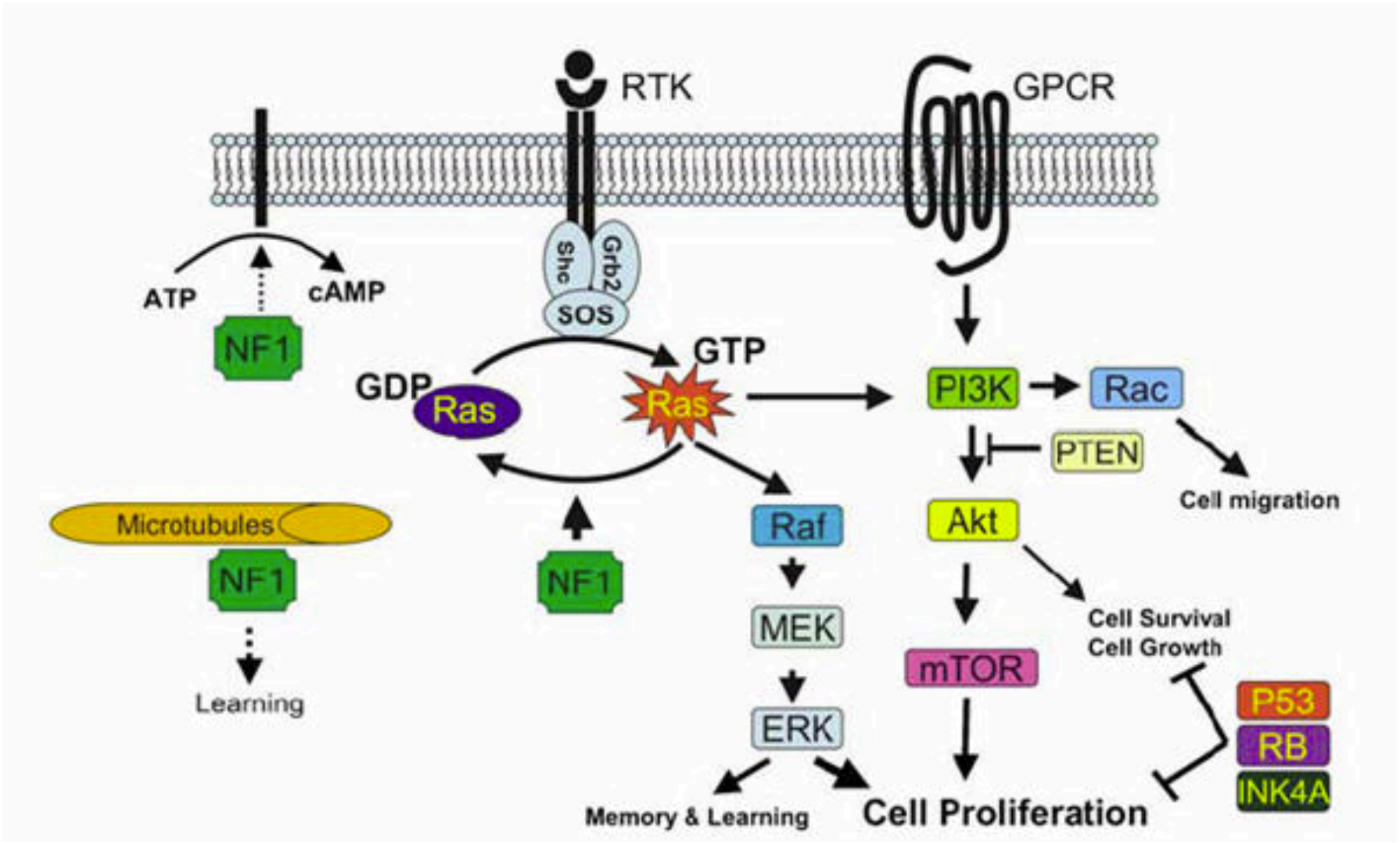


Molecular Function

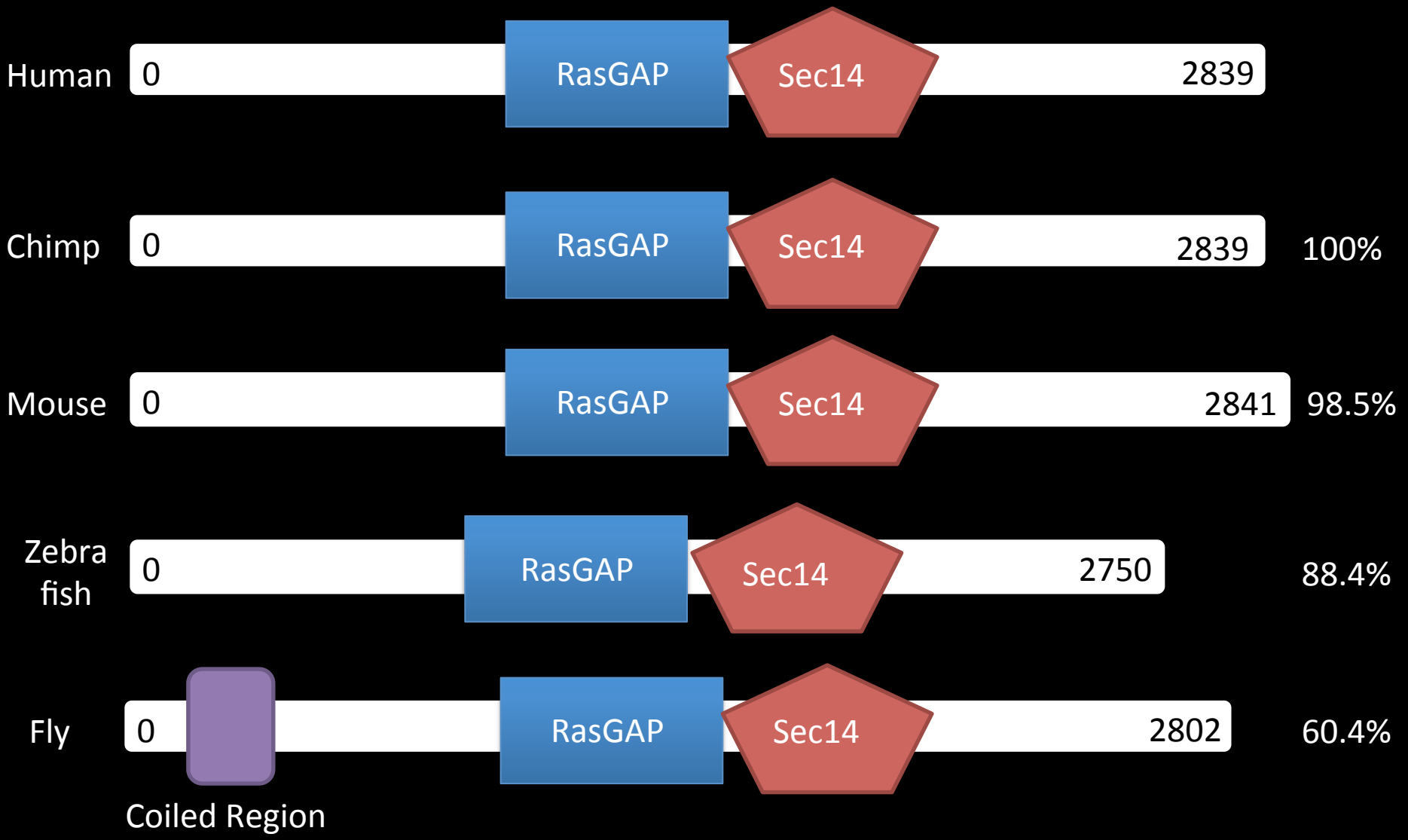


Biological Processes

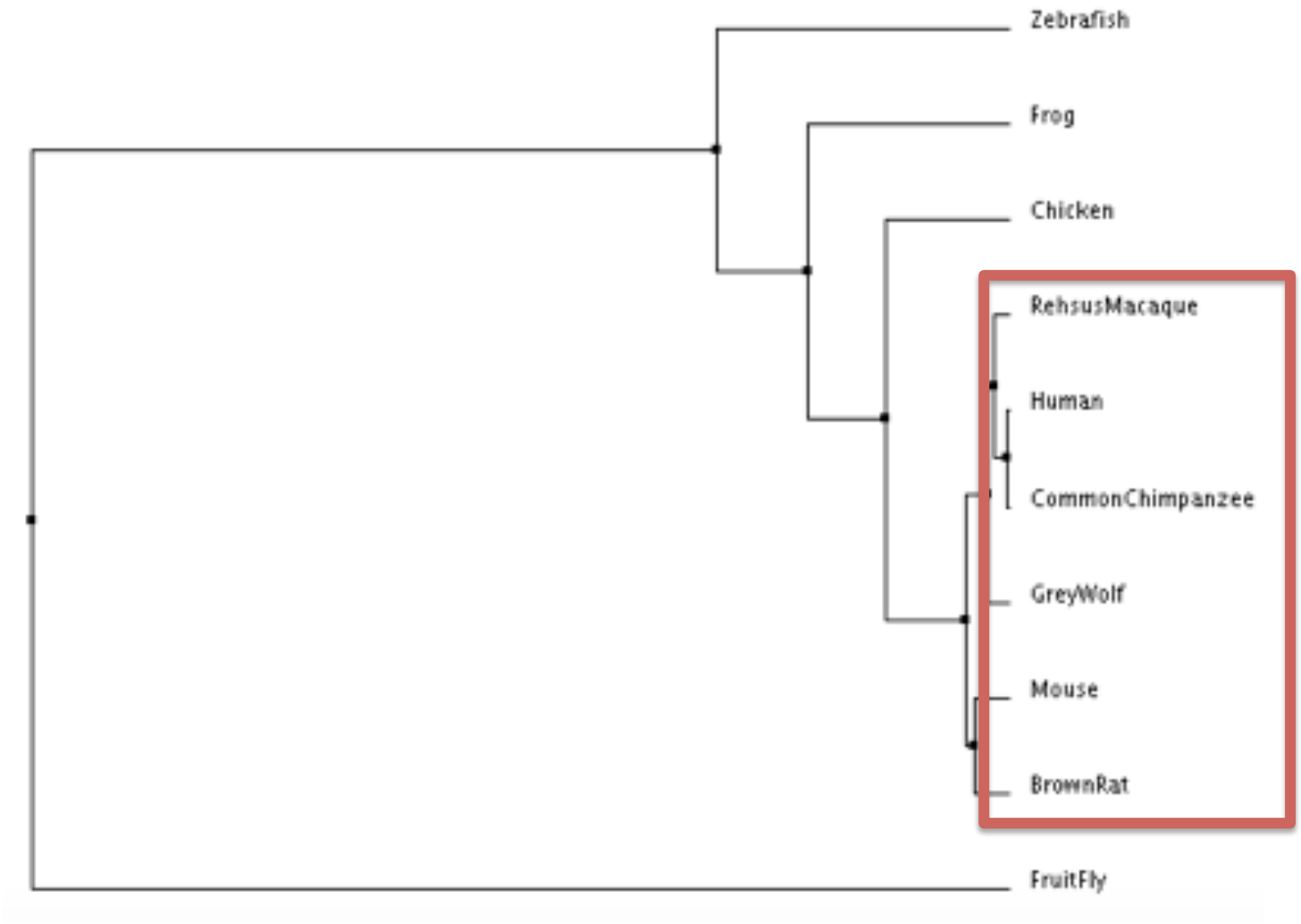
What Pathways does NF1 function in?



How well is NF1 conserved?



How well is neurofibromin conserved across mammals?

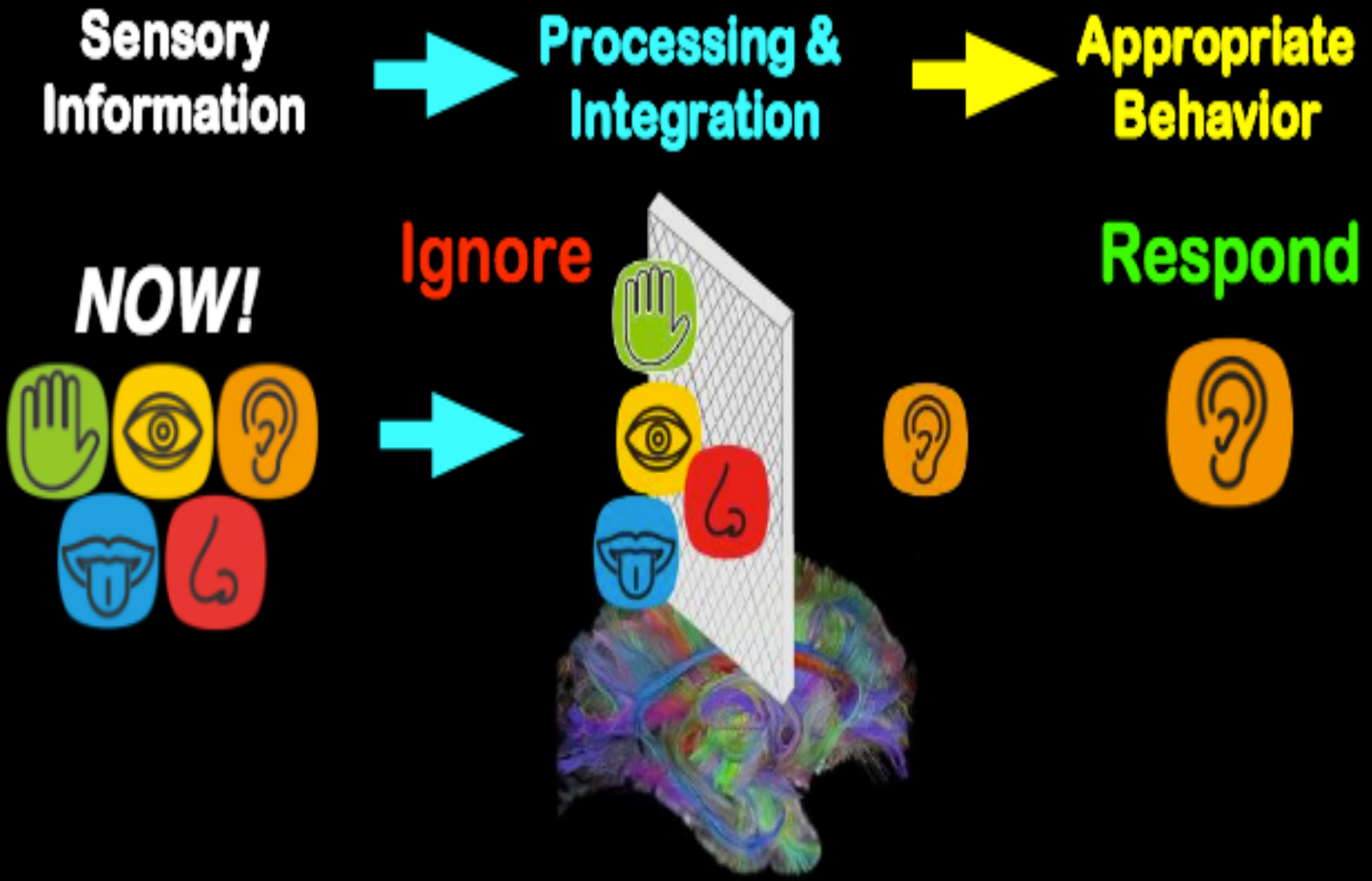


Average Distance Tree

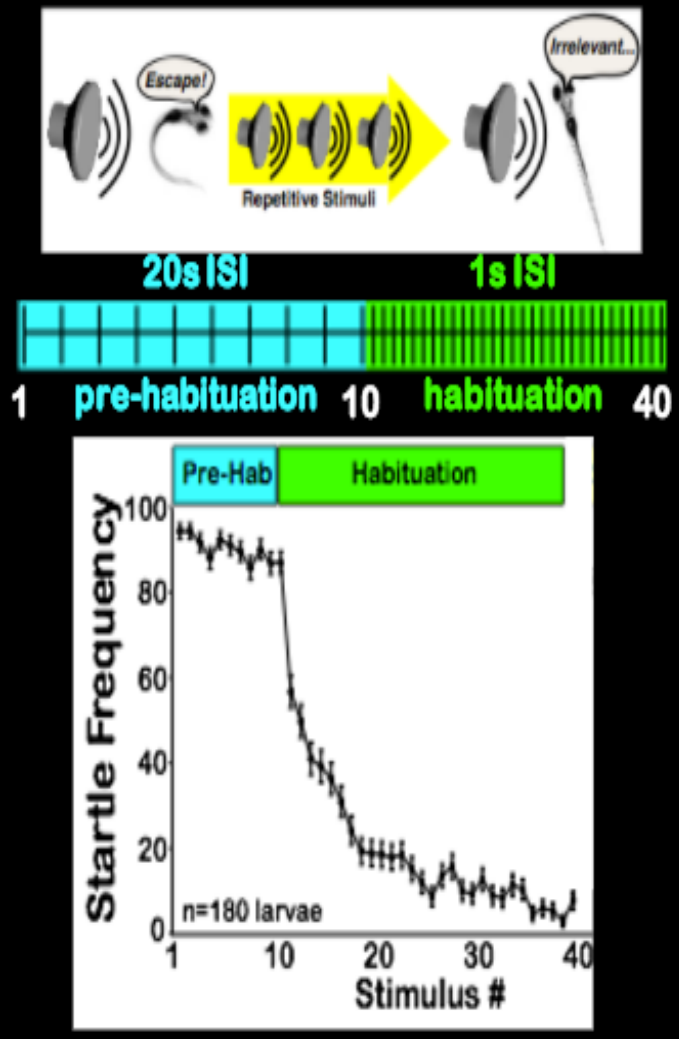
What does NF1 have to do with learning?

NF1 →  → 

How can learning be simulated?



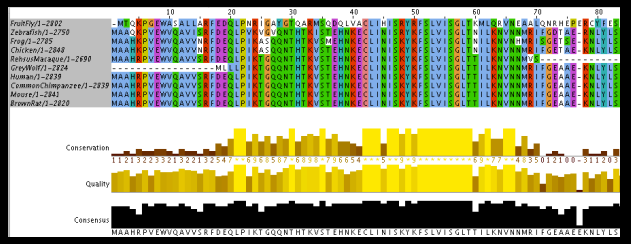
Can zebrafish learn?



What is the primary goal?
To understand how NF1 regulates learning.

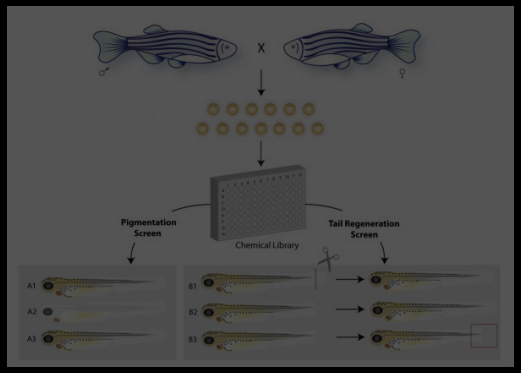
Aim 1

Identify which amino acids in NF1 are important for learning



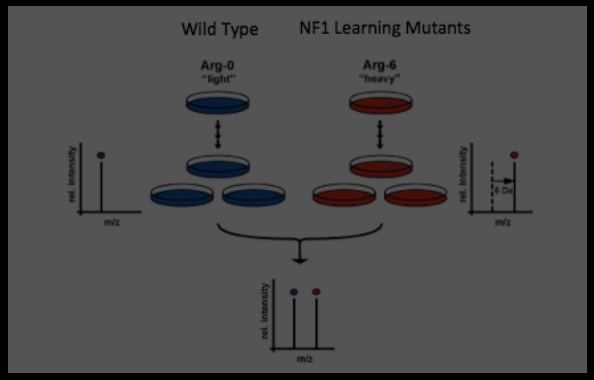
Aim 2

Determine small molecules that rescue learning deficits in NF1 zebrafish

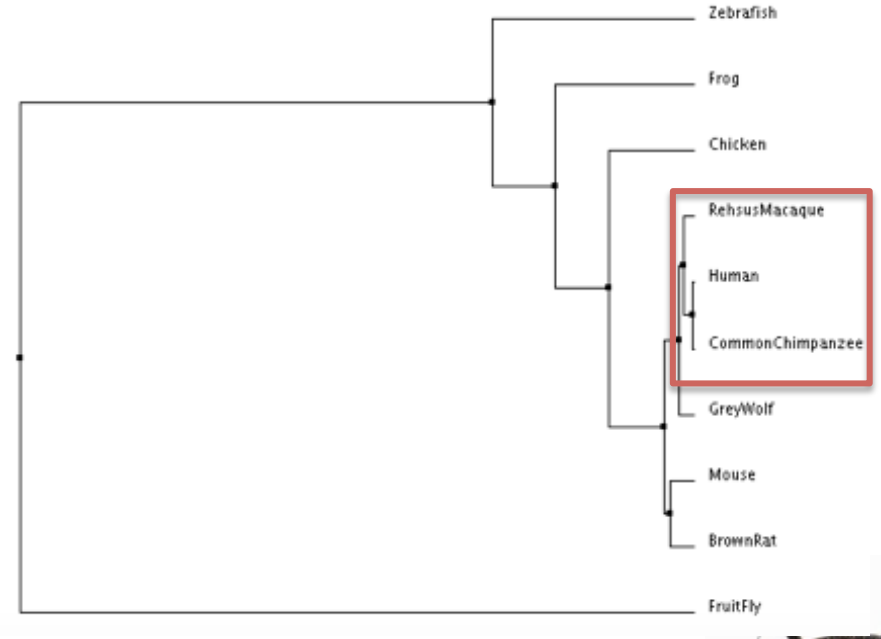


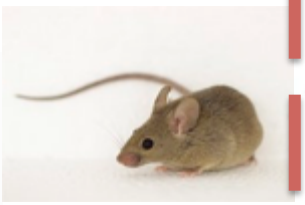
Aim 3

Determine protein phosphorylation levels in NF1 mutants in different tissues



Aim 1: What amino acids are necessary for learning?



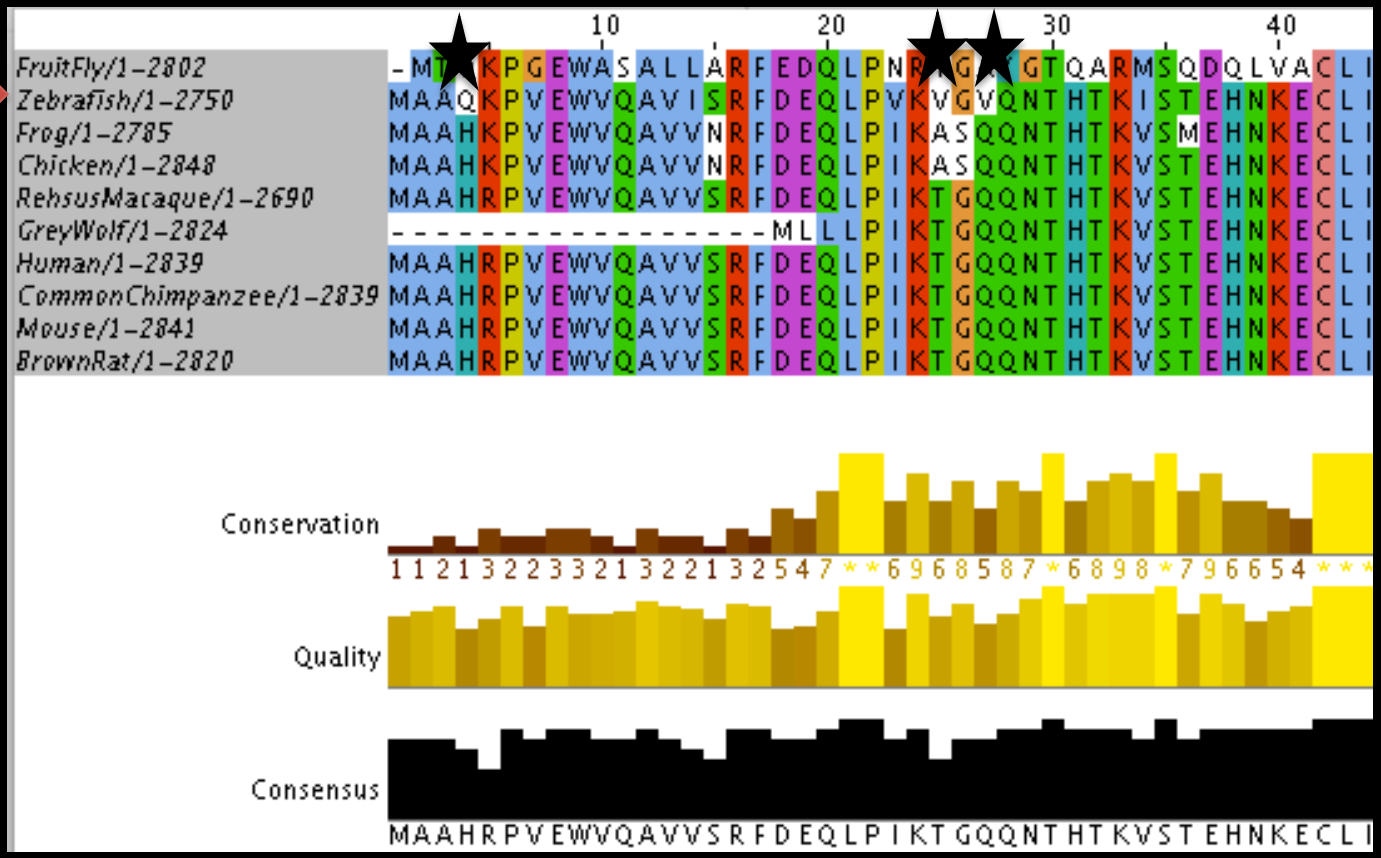


Simple | Advanced

Learning Ability

Aim 1: What amino acids are necessary for learning?

Clustal Omega analysis



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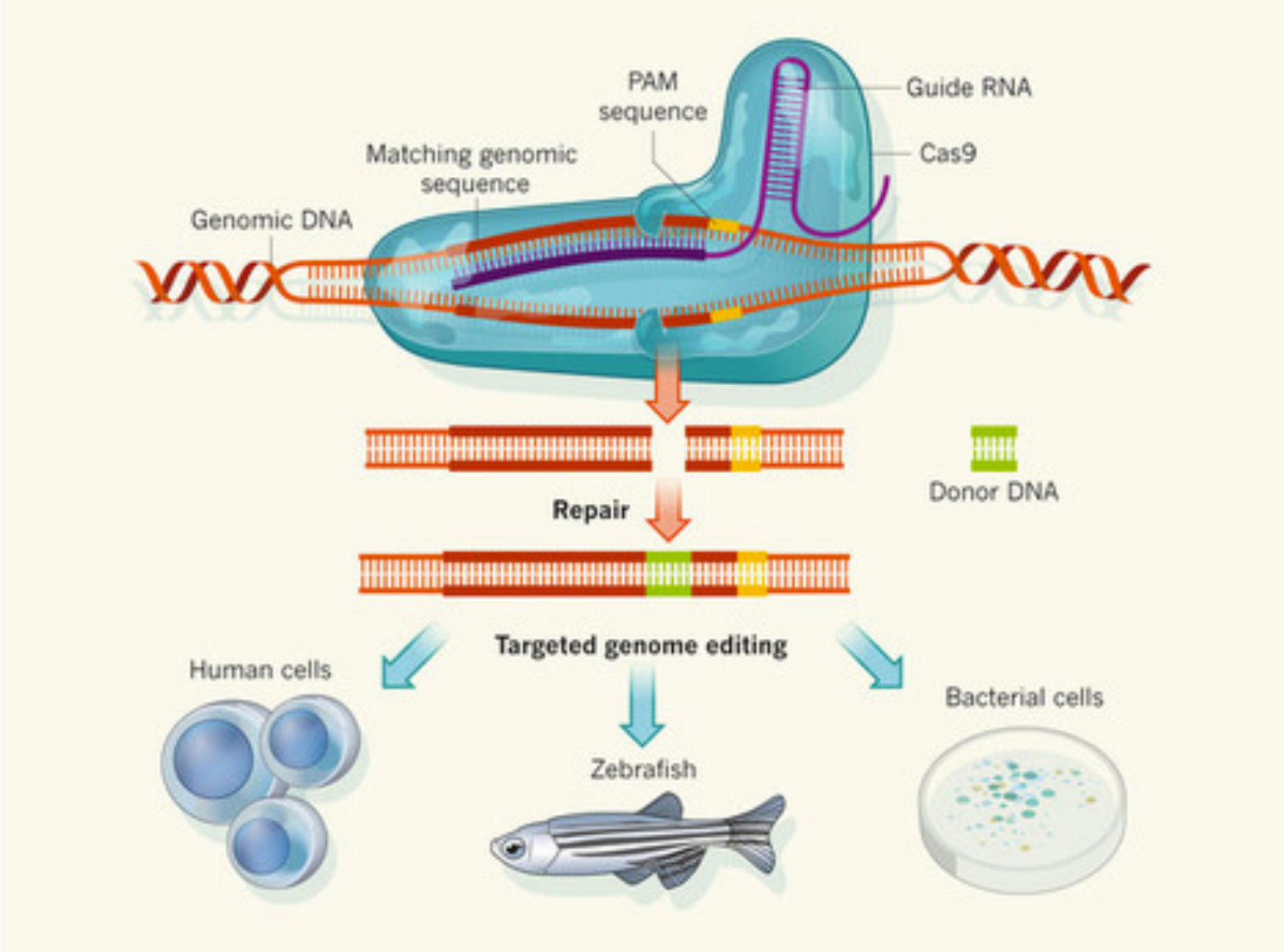

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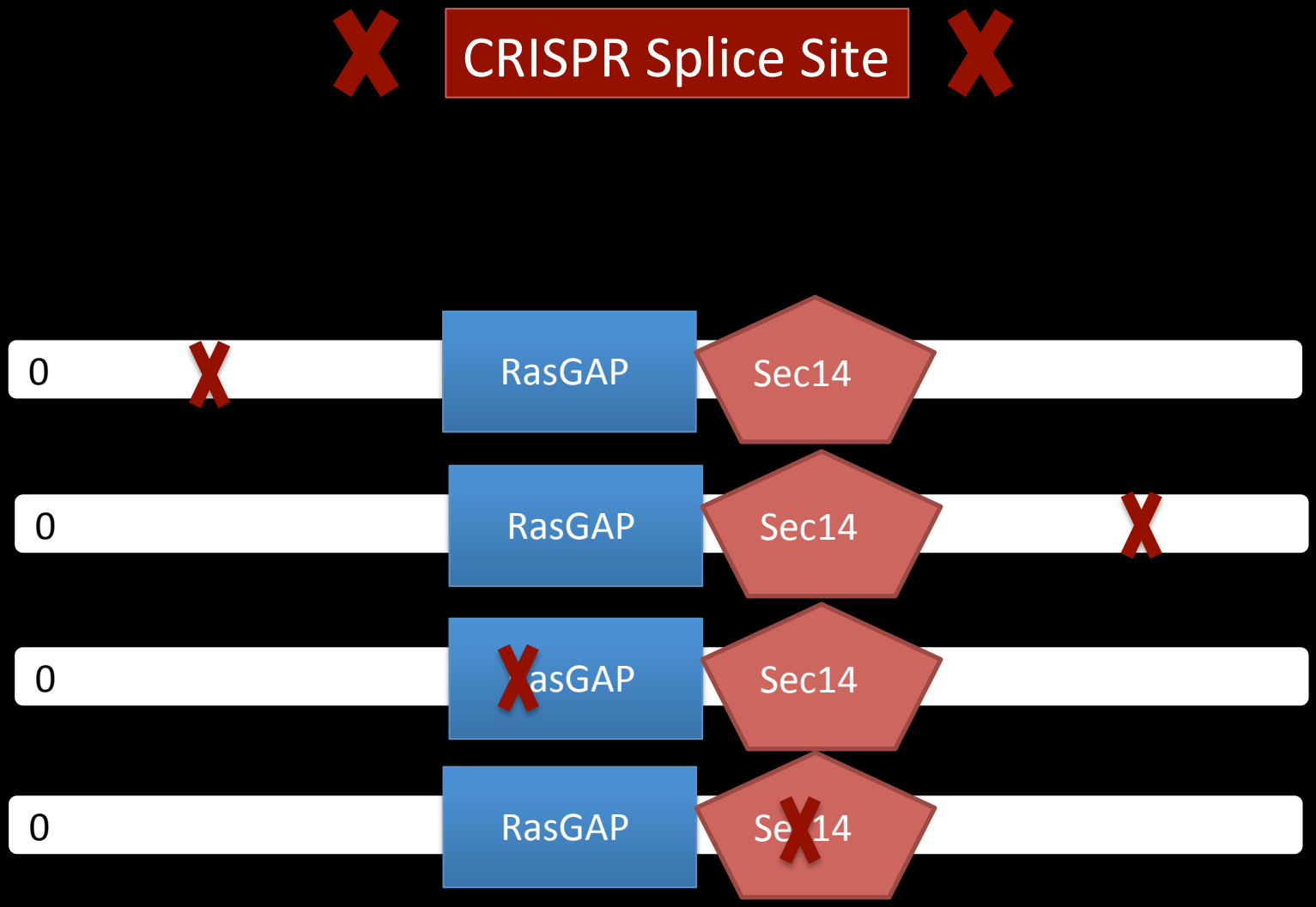
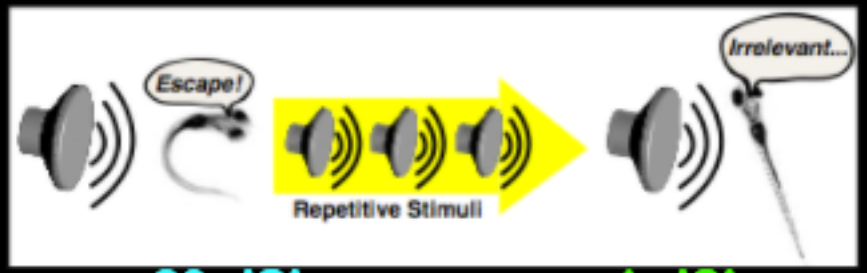
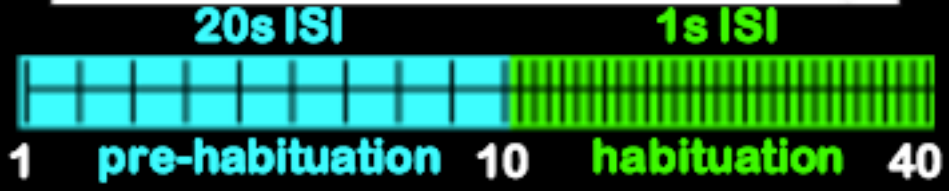
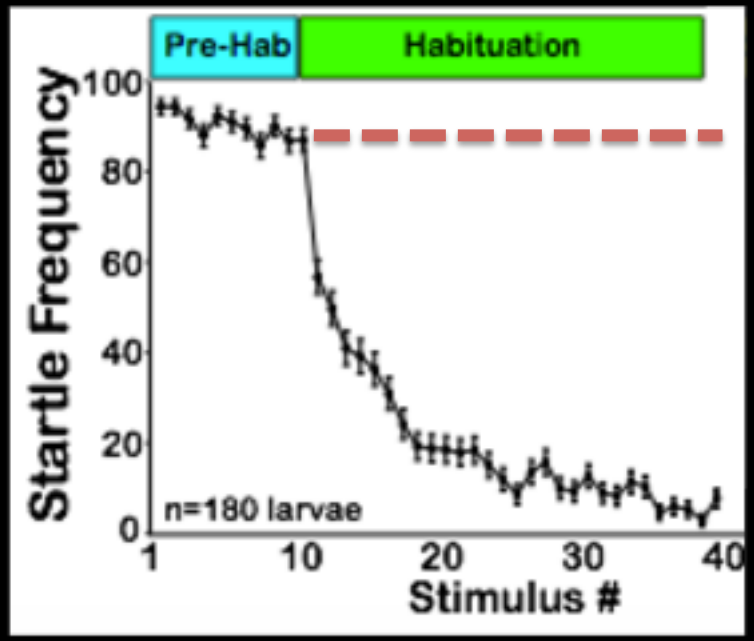


Aim 1
Hypothesis: CRISPER KO zebrafish will have reduced learning





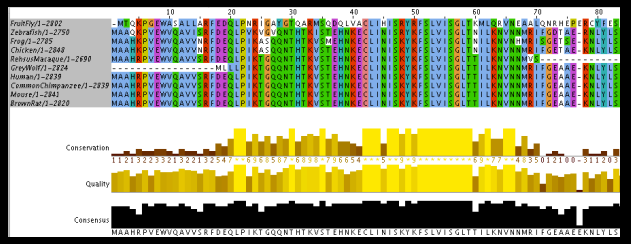


Mutant Learners

What is the primary goal?
To understand how NF1 regulates learning.

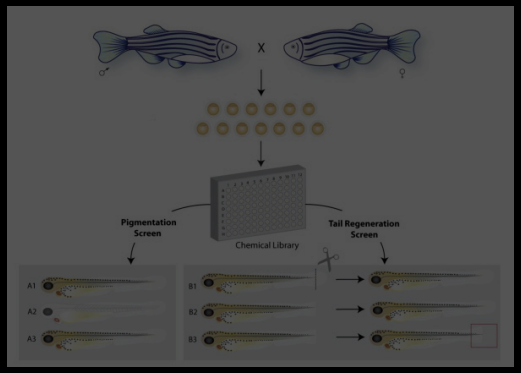
Aim 1

Identify which amino acids in NF1 are important for learning



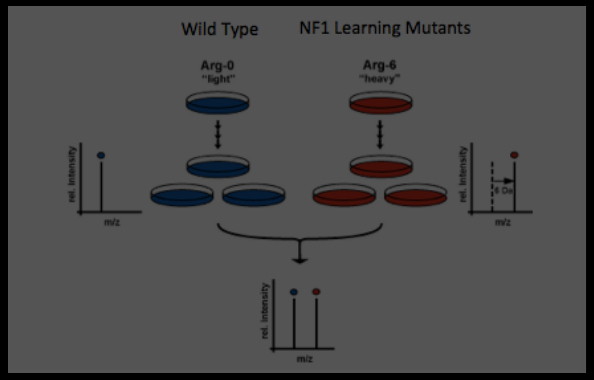
Aim 2

Determine small molecules that rescue learning deficits in NF1 zebrafish



Aim 3

Determine protein phosphorylation levels in NF1 mutants in different tissues



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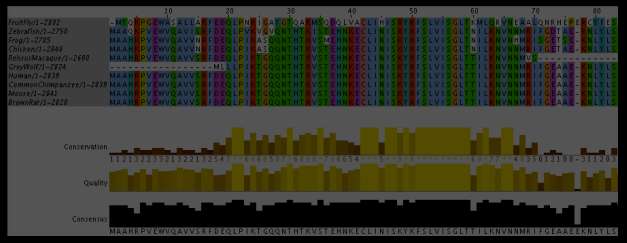

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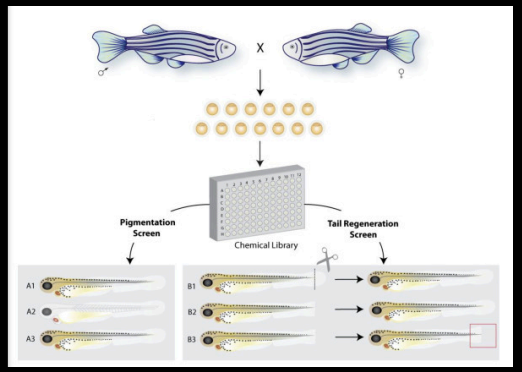

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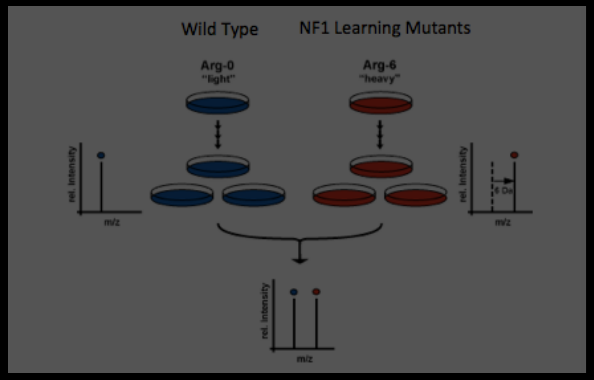

Aim 2: Are there small molecules that can rescue learning function?

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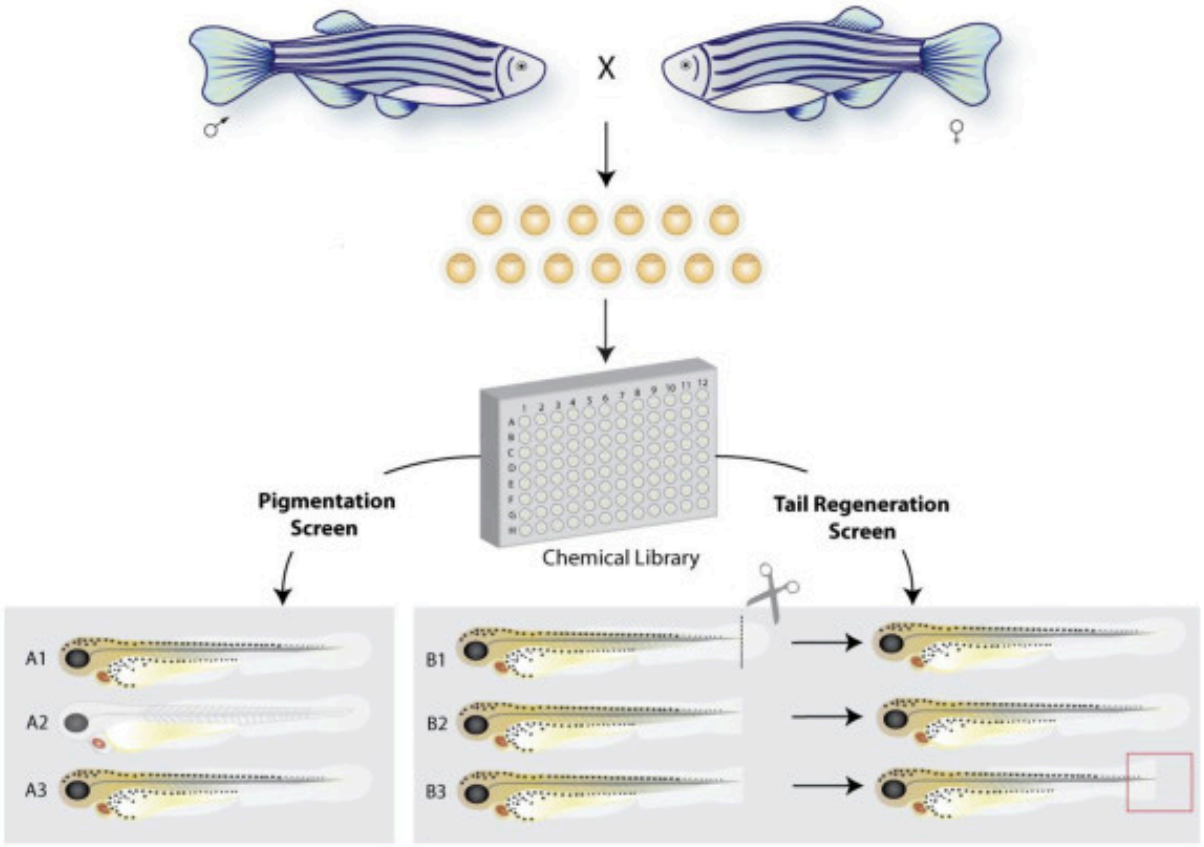
What phenotypes are relevant in this screen?



Aim 2: Do these phenotypes represent the connection between NF1 and learning?

NF1 →

→

Hypthesis: Learning function will be rescued in *Nf1* mutants by certain small molecule(s) associated with the cAMP pathway.

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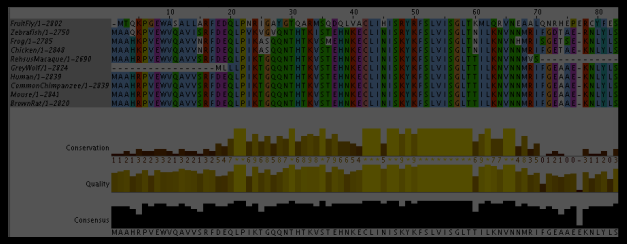

Aim 2

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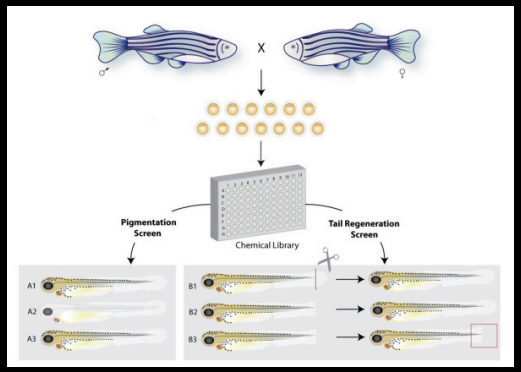

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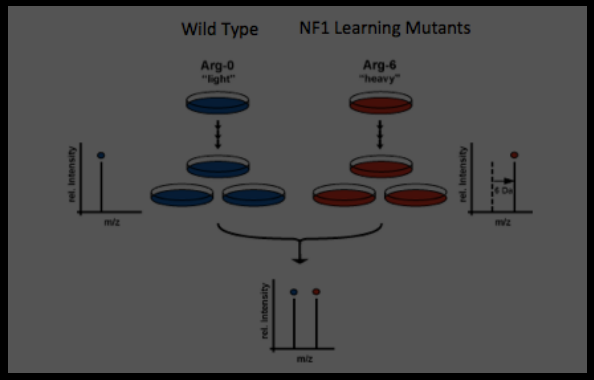

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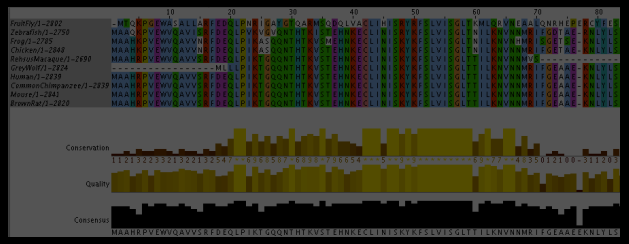

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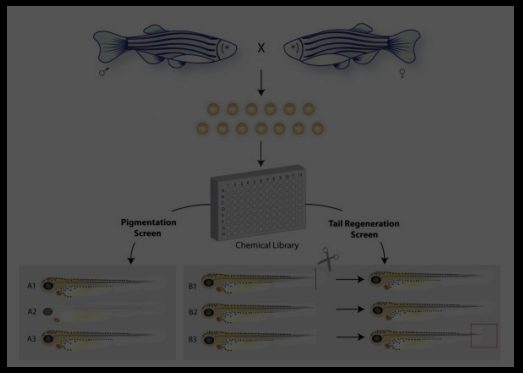

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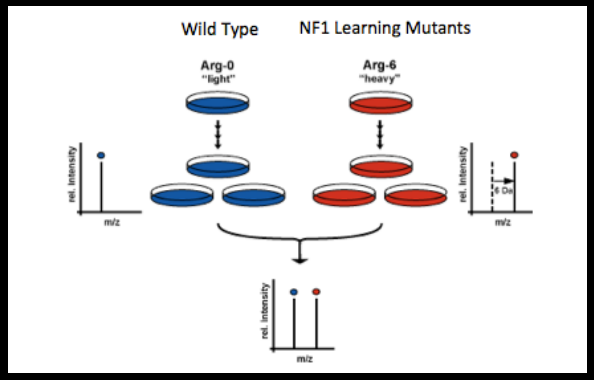
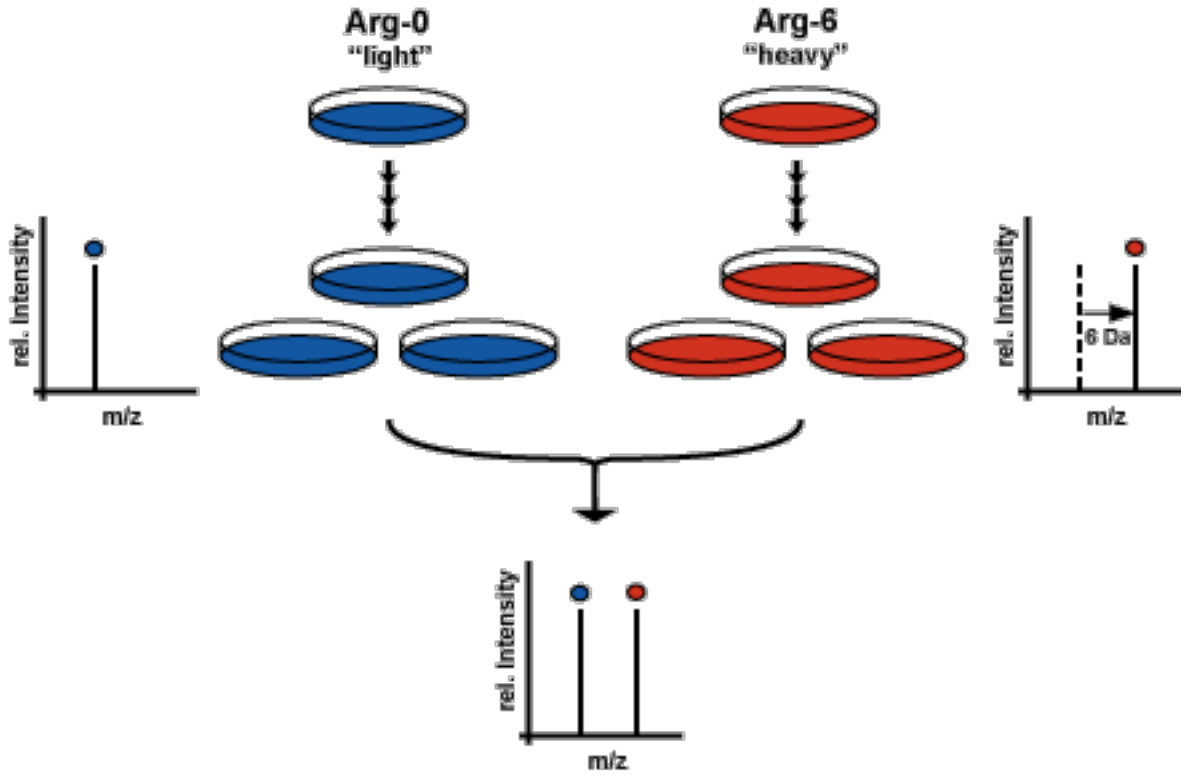
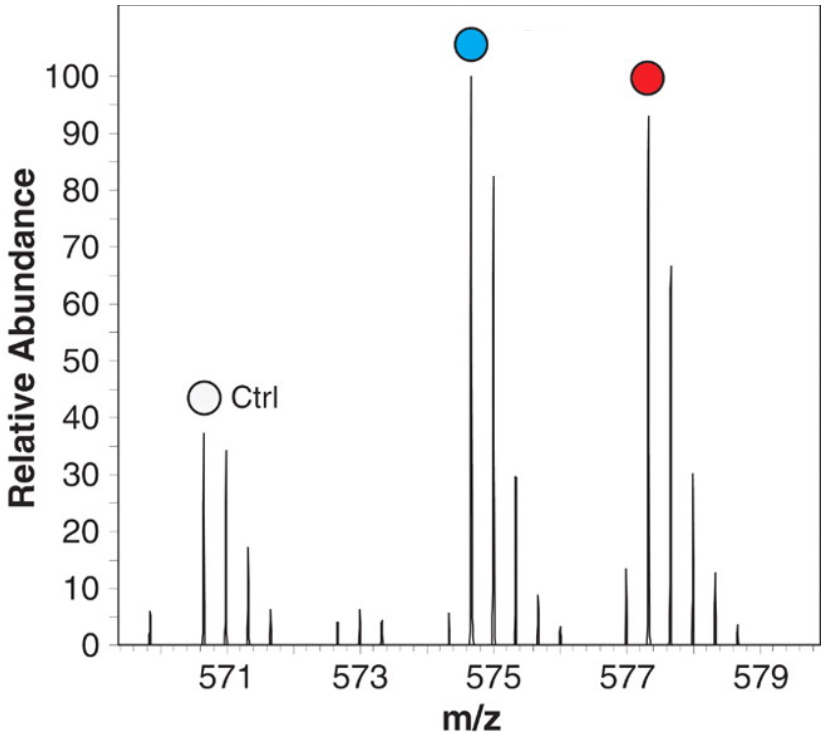


Aim 3: Determine protein phosphorylation levels in NF1 mutants in different tissues.

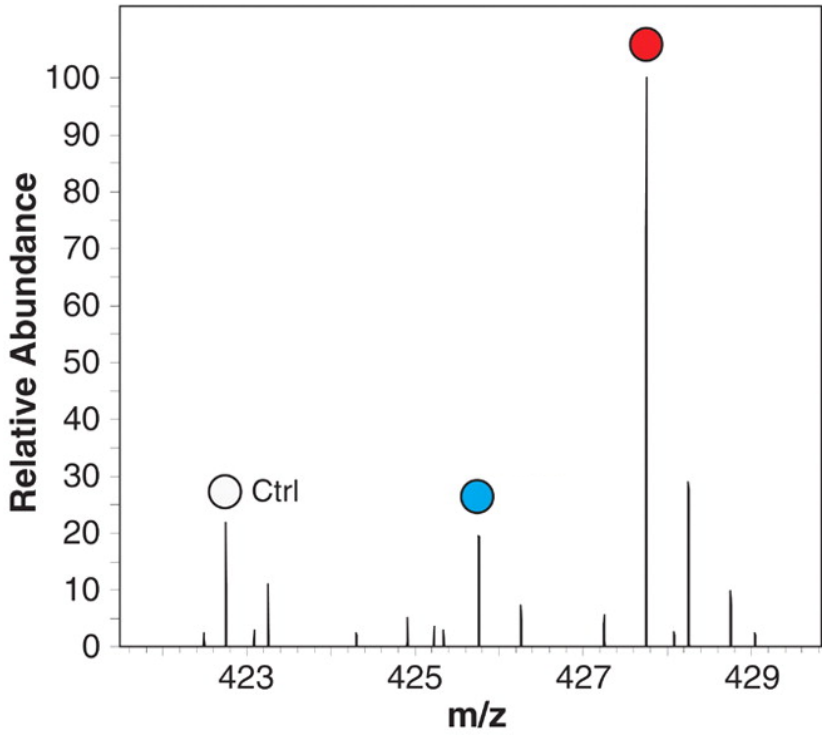
Wild Type NF1 Learning Mutants



Aim 3: Determine protein phosphorylation levels in NF1 mutants in different tissues.



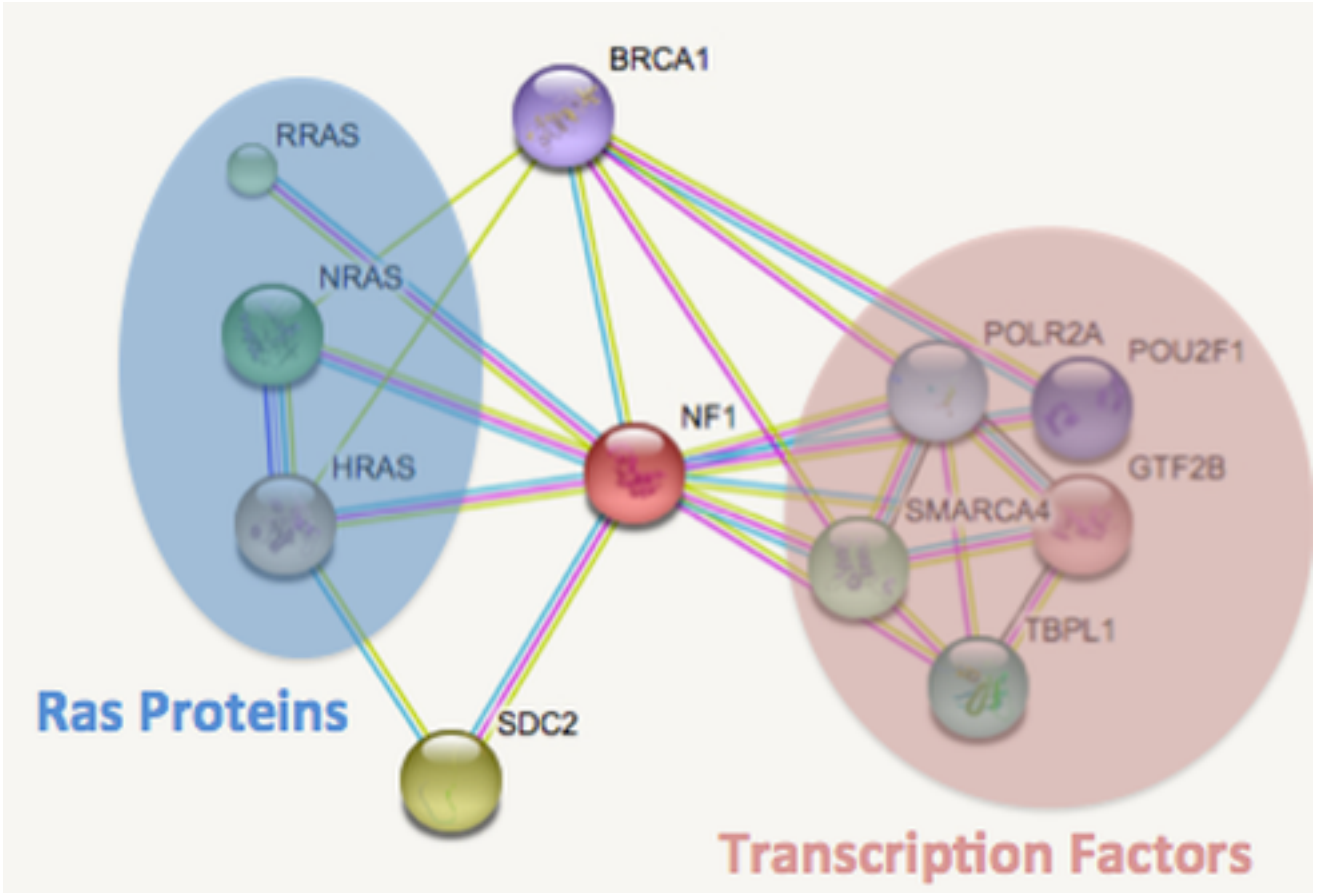
No change in phosphorylation



Change in phosphorylation:
Preform STRING analysis

Hypothesis: In *Nf1* learning mutants there will be lower phosphorylation levels in the cAMP pathway's proteins due to inactivation by the mutant NF1 protein

Aim 3: Determine protein phosphorylation levels in NF1 mutants in different tissues.



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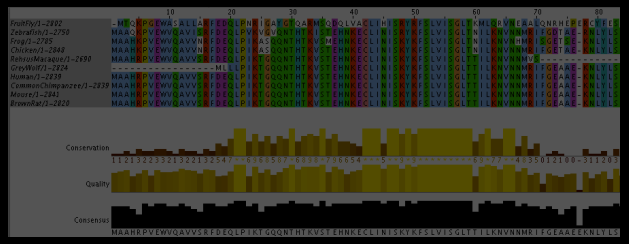

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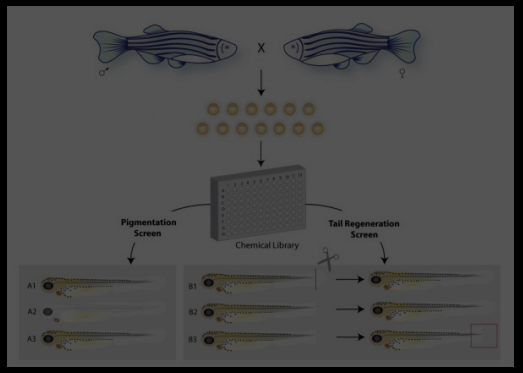

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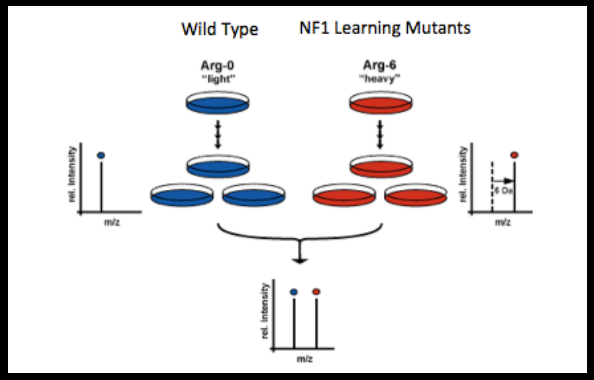

Future Directions

- Predictions on the severity of learning disabilities correlating to the position of the mutation on the NF1 gene.
- Drug trials for mice then humans for small molecules that are rescuing learning disabilities in NF1 zebrafish.

References

Pasmant E, Vidaud M, Vidaud D*, et al* Neurofibromatosis type 1: from genotype to phenotype *Journal of Medical Genetics* 2012;**49:**483-489

Shilyansky, C., Y.S. Lee, and A.J. Silva. "Molecular and Cellular Mechanisms of Learning Disabilities: A Focus on NF1." *Annual review of neuroscience* 33 (2010): 221–243. *PMC*. Web. 16 Mar. 2017.

Wolman MA, de Groh ED, McBride SM, Jongens TA, Granato M., Epstein JA. 2014. Modulation of cAMP and Ras Signaling Pathways Improves Distinct Behavioral Deficits in a Zebrafish Model of Neurofibromatosis Type 1. Cell Reports. 8(5):1265-70

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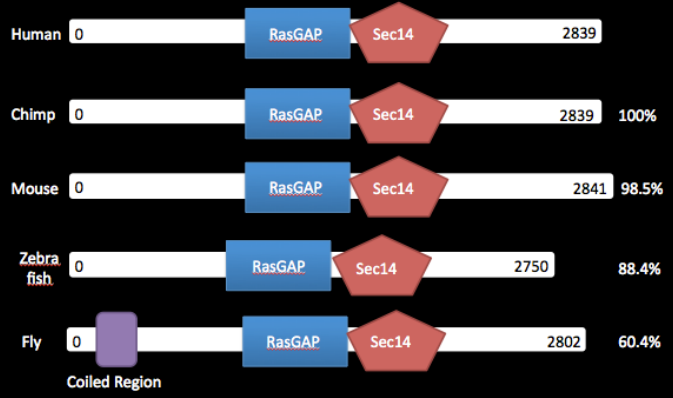
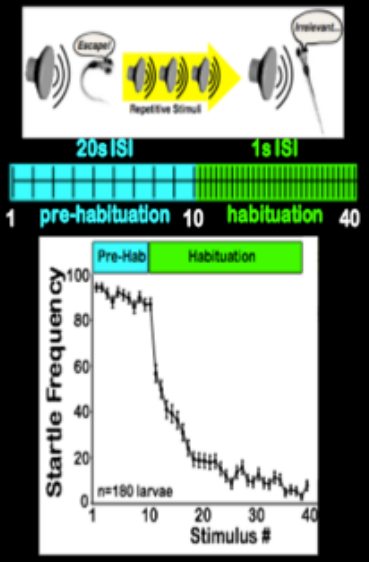
Questions?





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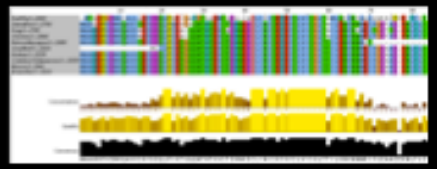

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