Down Syndrome:

The power of a single chromosome

WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

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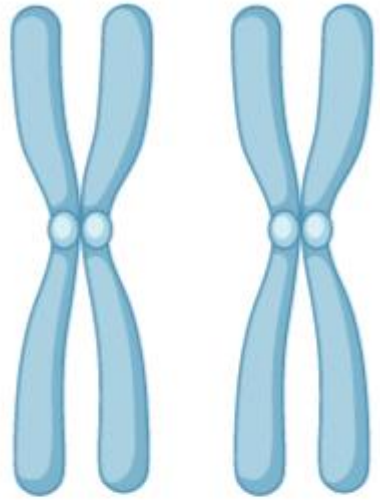
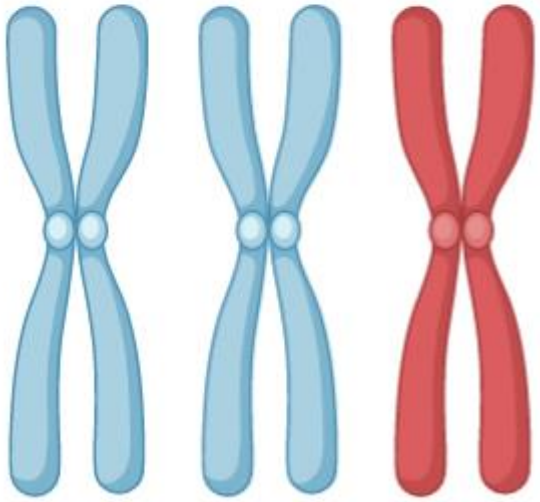
Genetics 564

What is Down Syndrome?





Caused by **trisomy** of chromosome 21

Down Syndrome Symptoms

Distinct **physical** features

Several **behavioral** & **neurodegenerative** symptoms

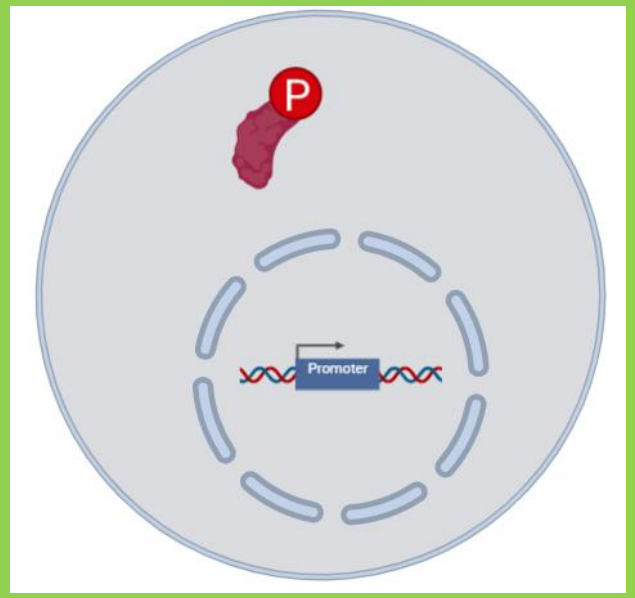
No single, standard treatment available

DYRK1A Gene Ontology

Biological Process

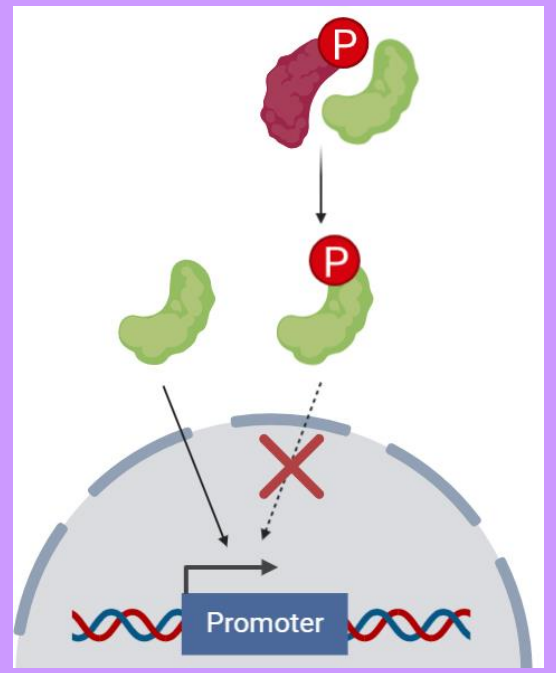
Regulate NPC proliferation and differentiation

Cellular Component



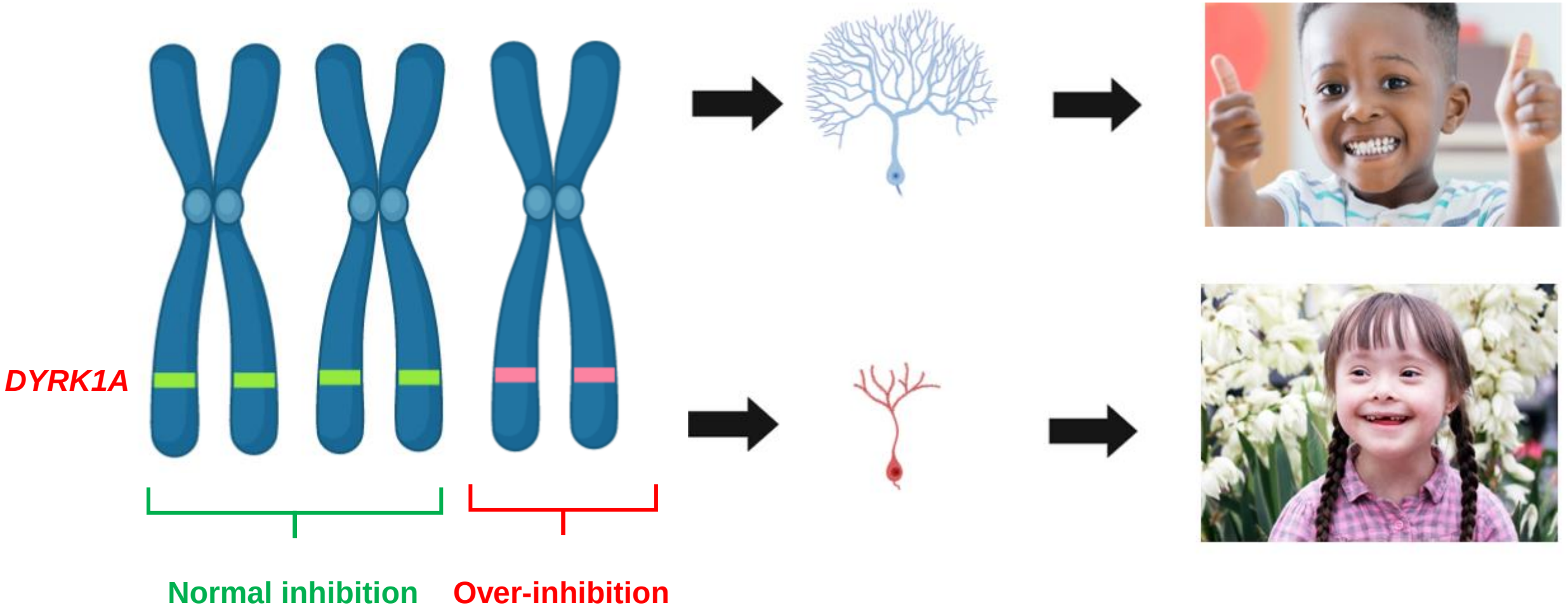
Localizes in the cytosol near the nuclear membrane

Molecular Function



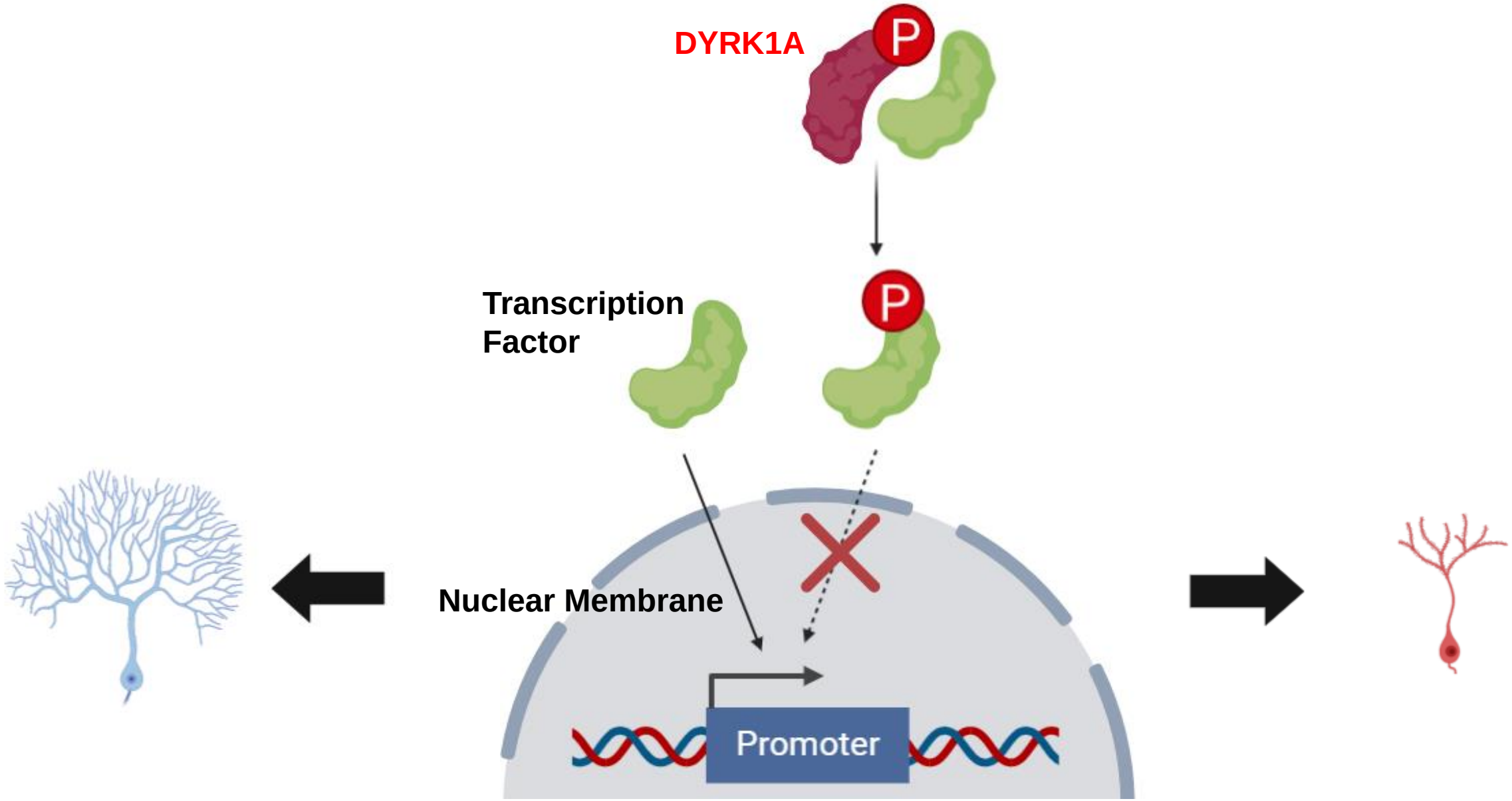
Kinase activity

Why does the extra chr 21 cause Down syndrome?



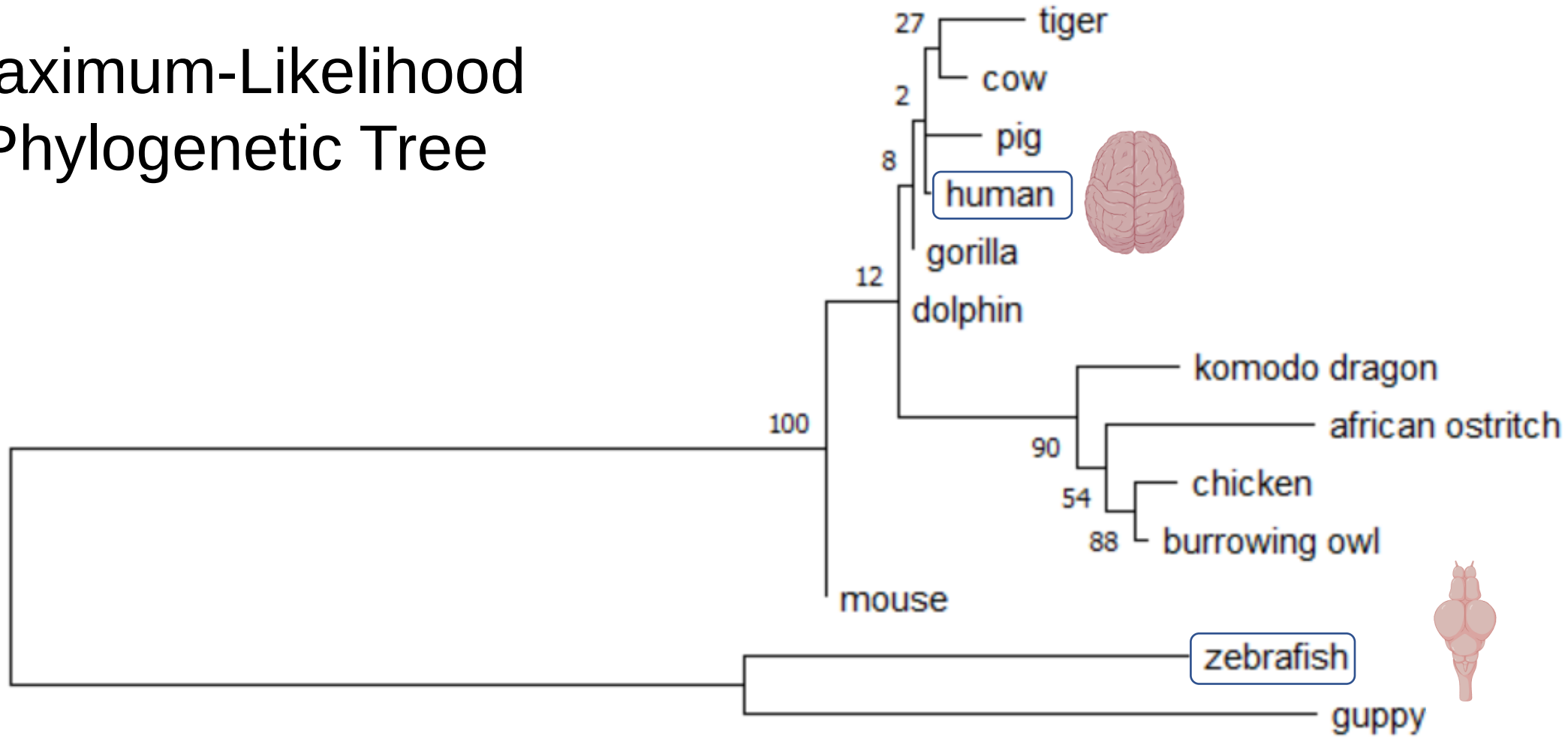
DYRK1A **plays a role in reduced neurogenesis and premature neuronal differentiation of neuro-progenitor cells**

Molecular mechanisms in which DYRK1A reduces neural proliferation?



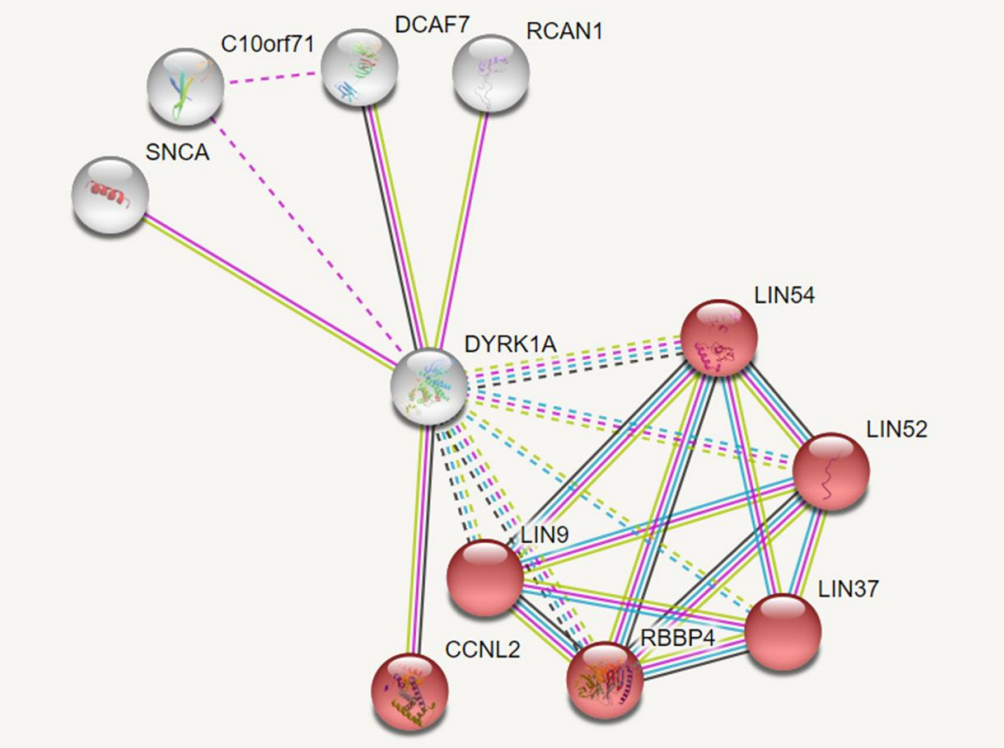
DYRK1A Homologs are evolutionarily related

Maximum-Likelihood Phylogenetic Tree

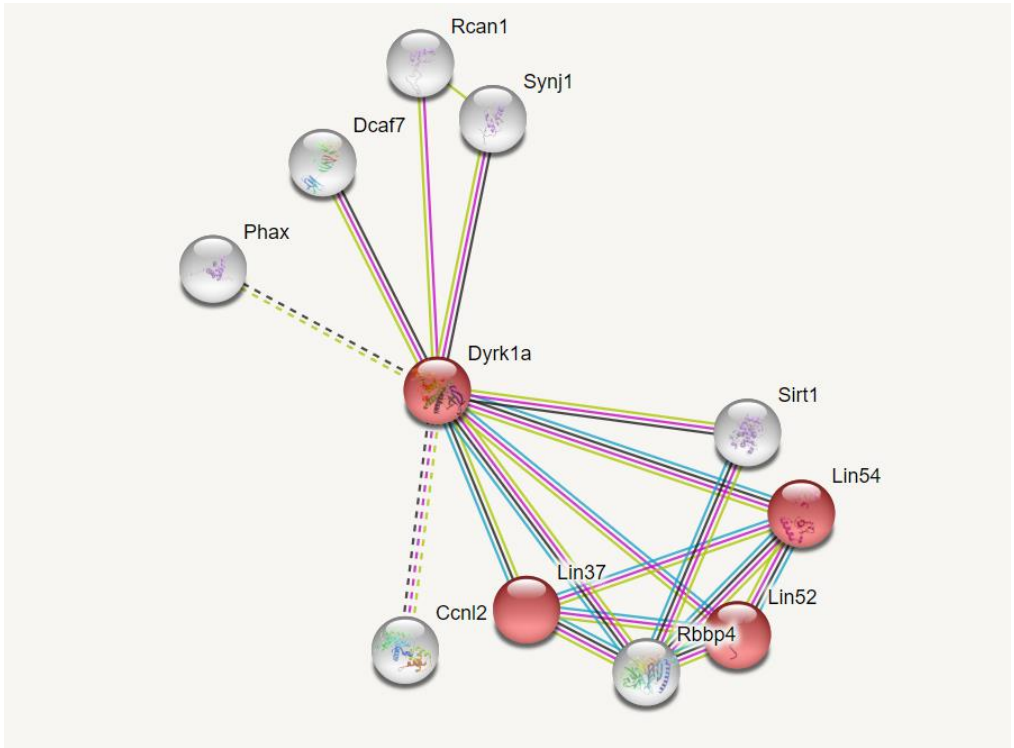


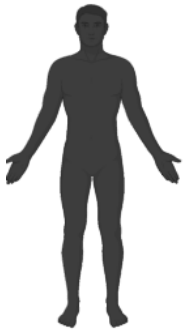
DYRK1A is a well conserved kinase

DYRK1A interacts with cell cycle regulators

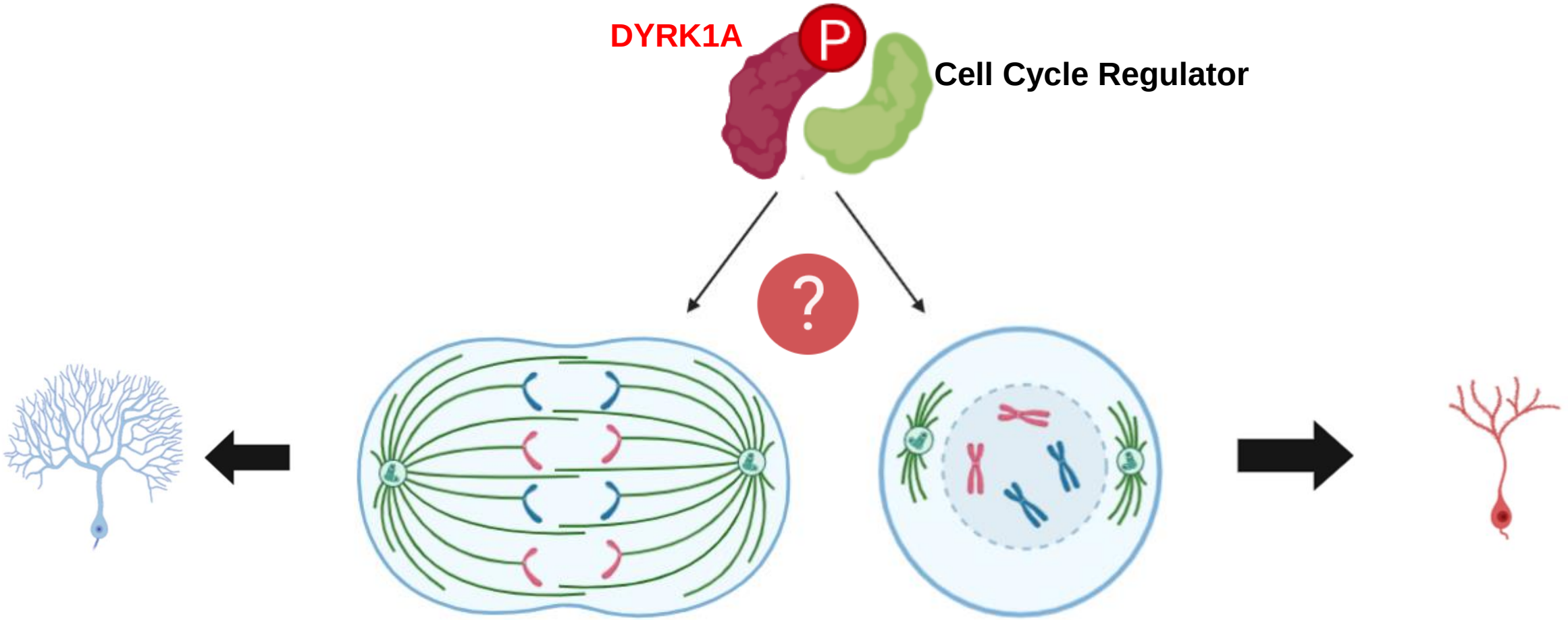


Cell Cycle Regulators



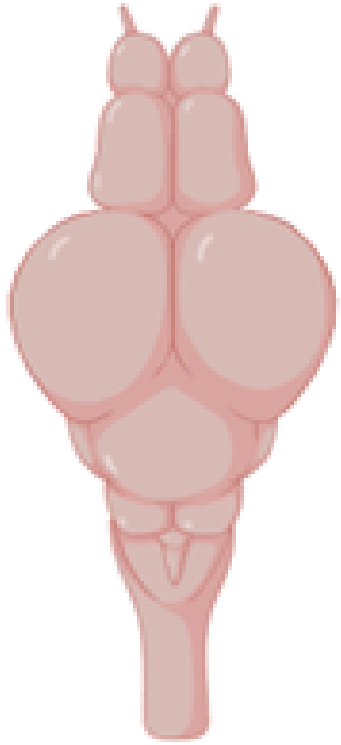


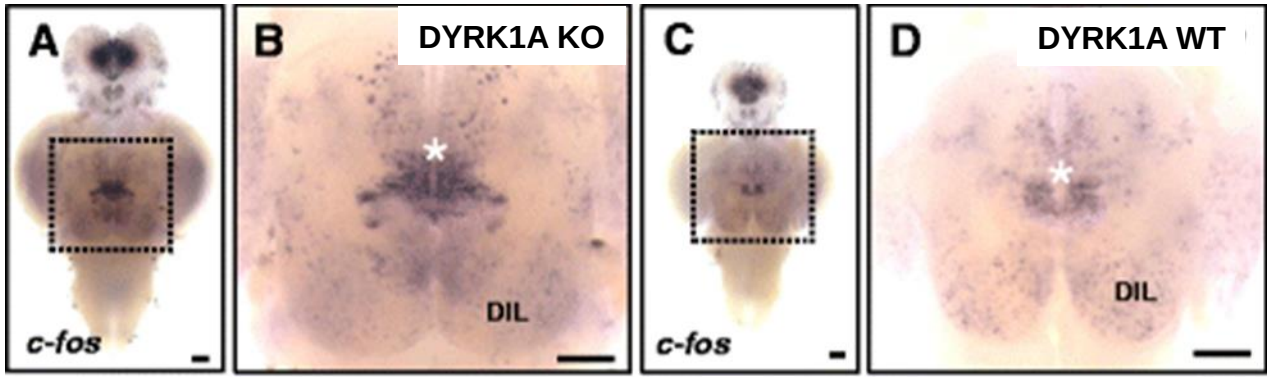
Knowledge Gap



It is unclear how DYRK1A protein **mediate cell division events** in the brain during neural development.

Zebrafish as a model organism for DYRK1A





Zebrafish are excellent model systems for understanding brain function and neuronal cell division

The Primary Goal

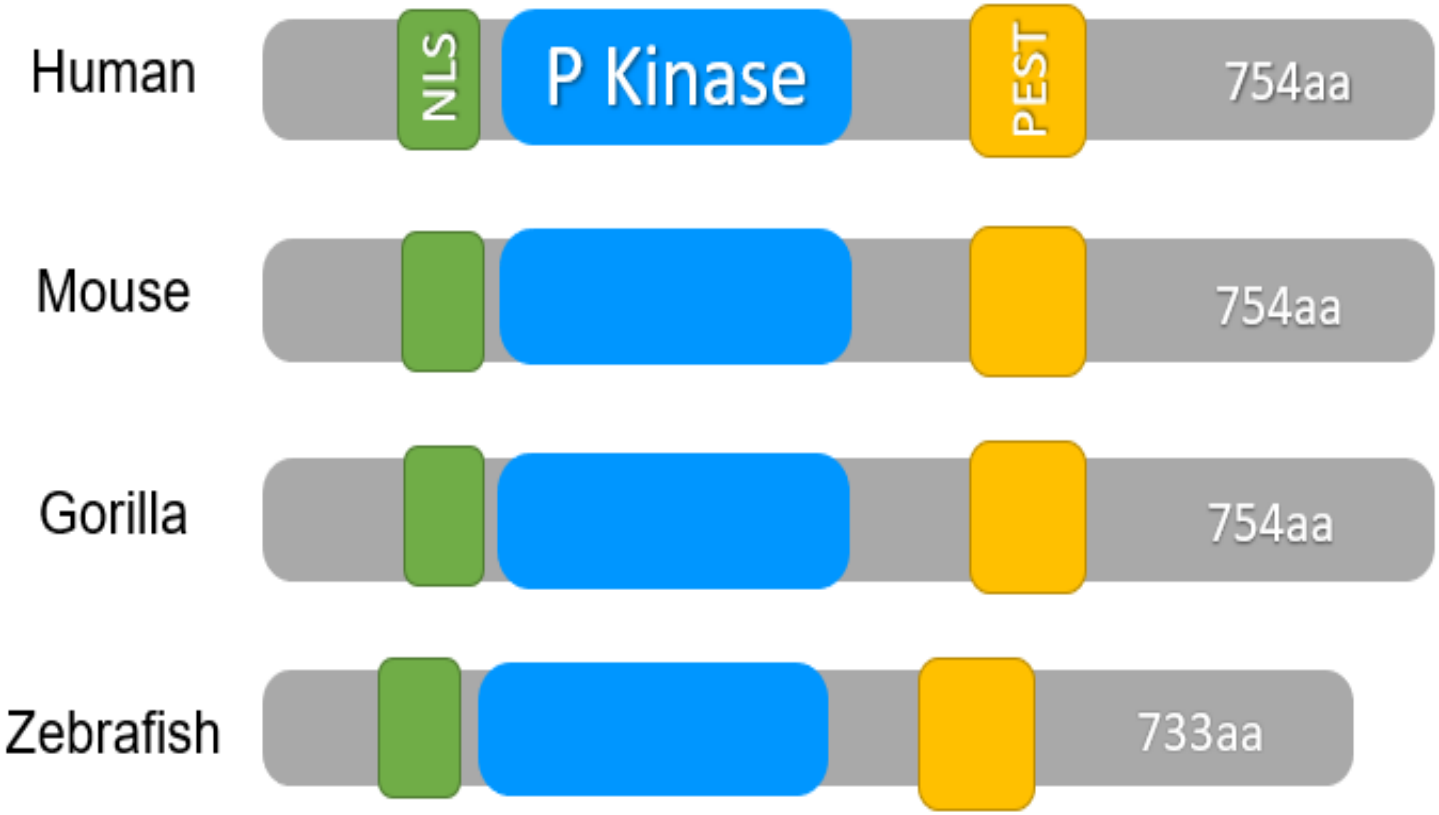
Determine how *DYRK1A* modulates the cell cycle during neural development

Aim 1:
Characterize and identify **DYRK1A domains** that are necessary for **cell cycle processes** in the brain

Aim 2:
Identify genes in the brain that are **expressed differently** with the DYRK1A mutants

Aim 3:
Determine DYRK1A **protein interactions** that regulate the **cell cycle** in neurons in the brain

Aim 1: Identify DYRK1A domains essential for inhibiting neural proliferation

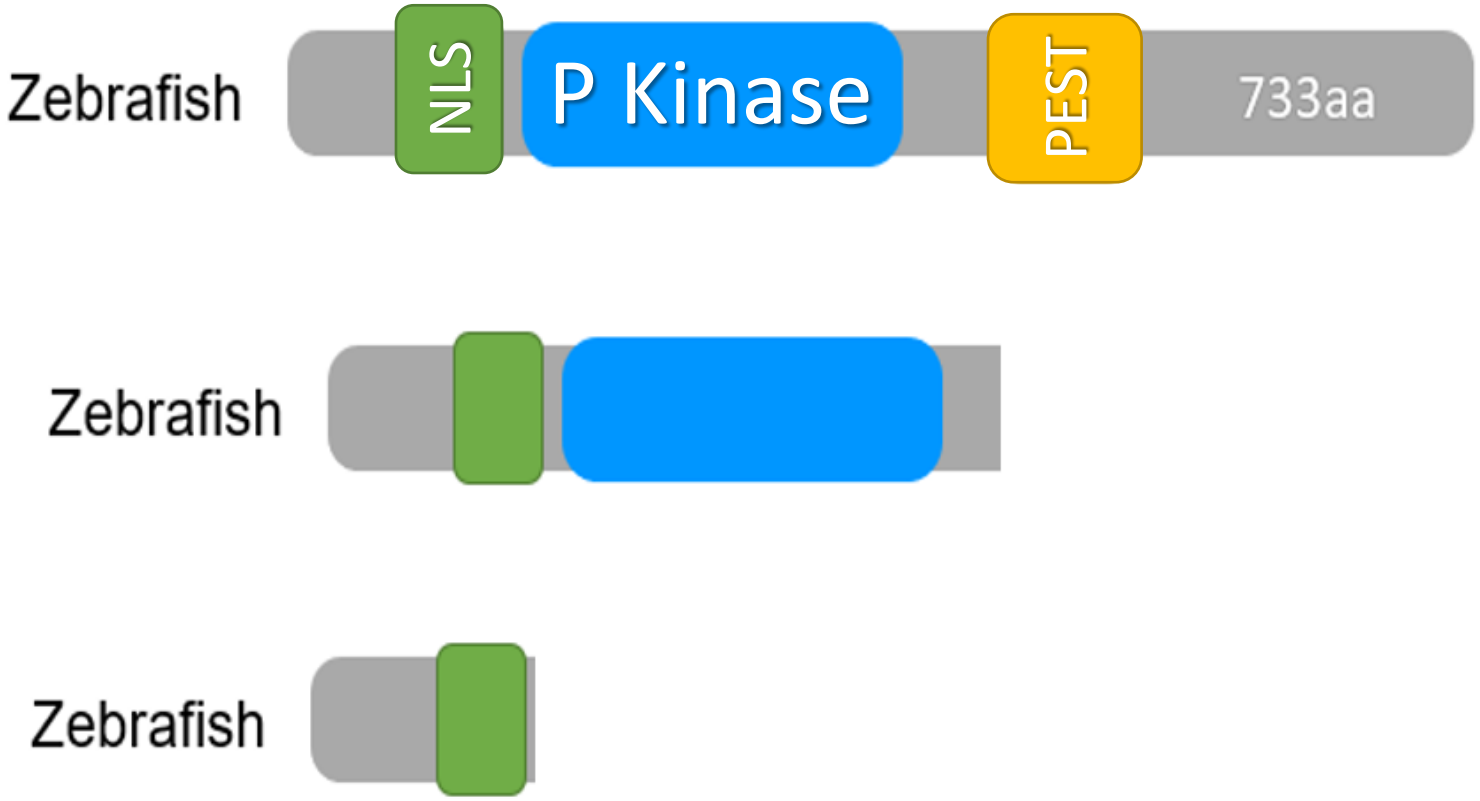


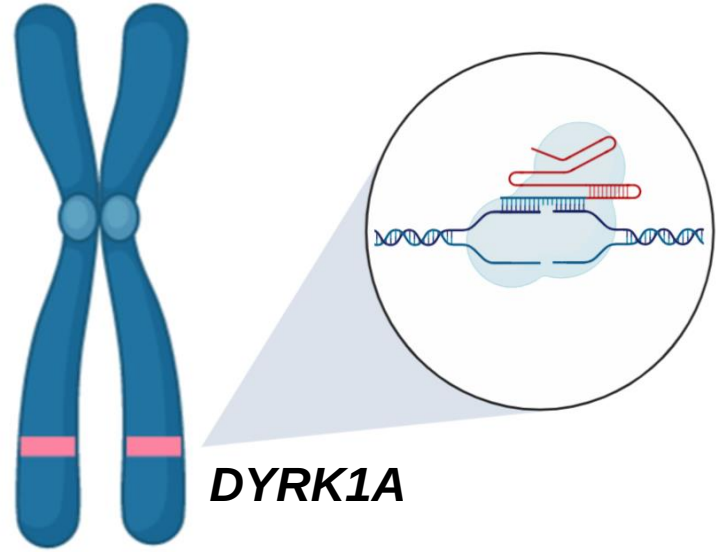
BLAST to obtain the protein sequences

Align with Clustal Omega

Confirm that the 3 main domains are well conserved

Aim 1: Identify DYRK1A domains essential for inhibiting neural proliferation



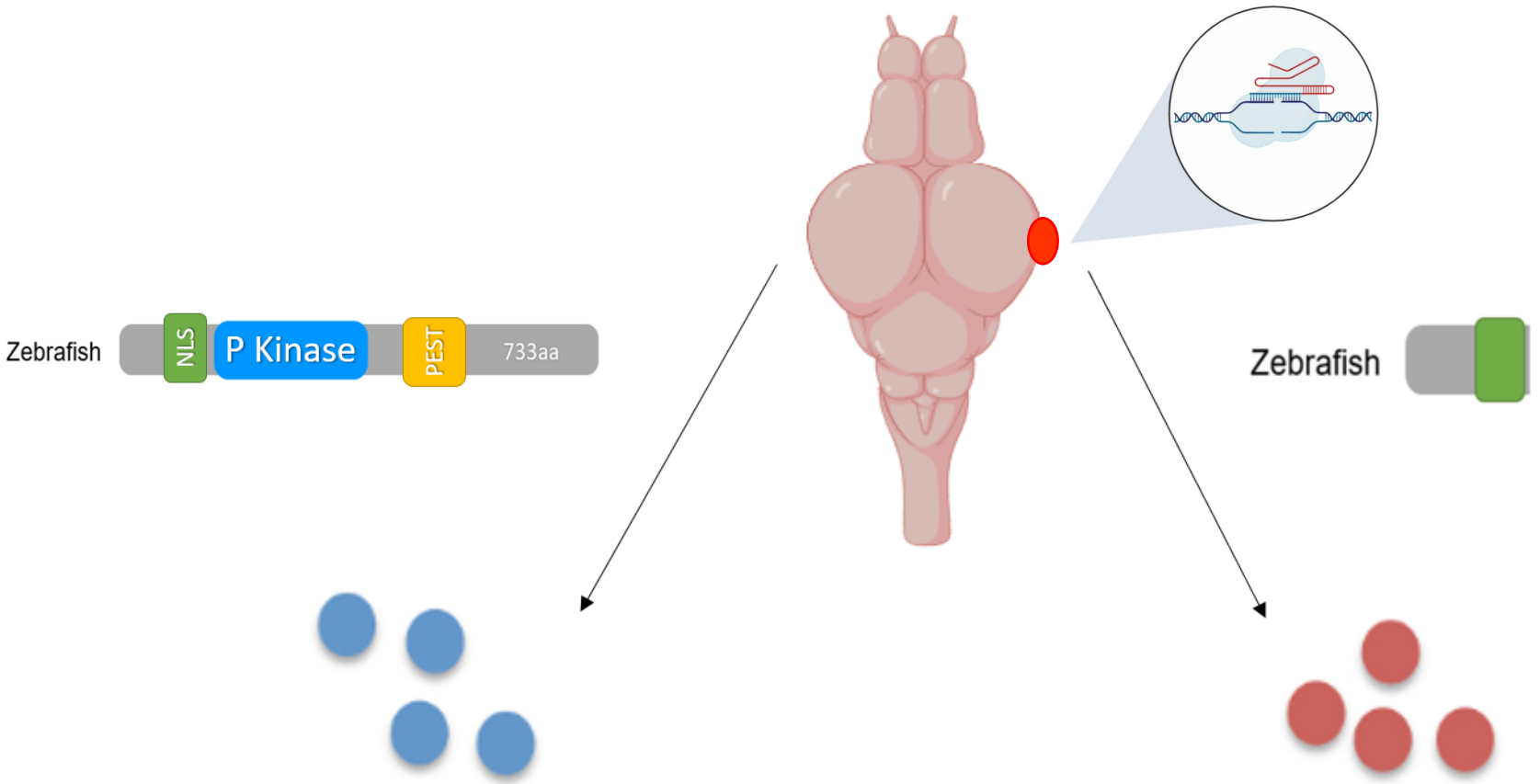


CRISPR/Cas9 to progressively knockout domains

Aim 1: Identify DYRK1A domains essential for inhibiting neural proliferation

Compare cell division patterns between the zebrafish

Aim 2: Identify differential gene expression in the brain in DYRK1A mutants

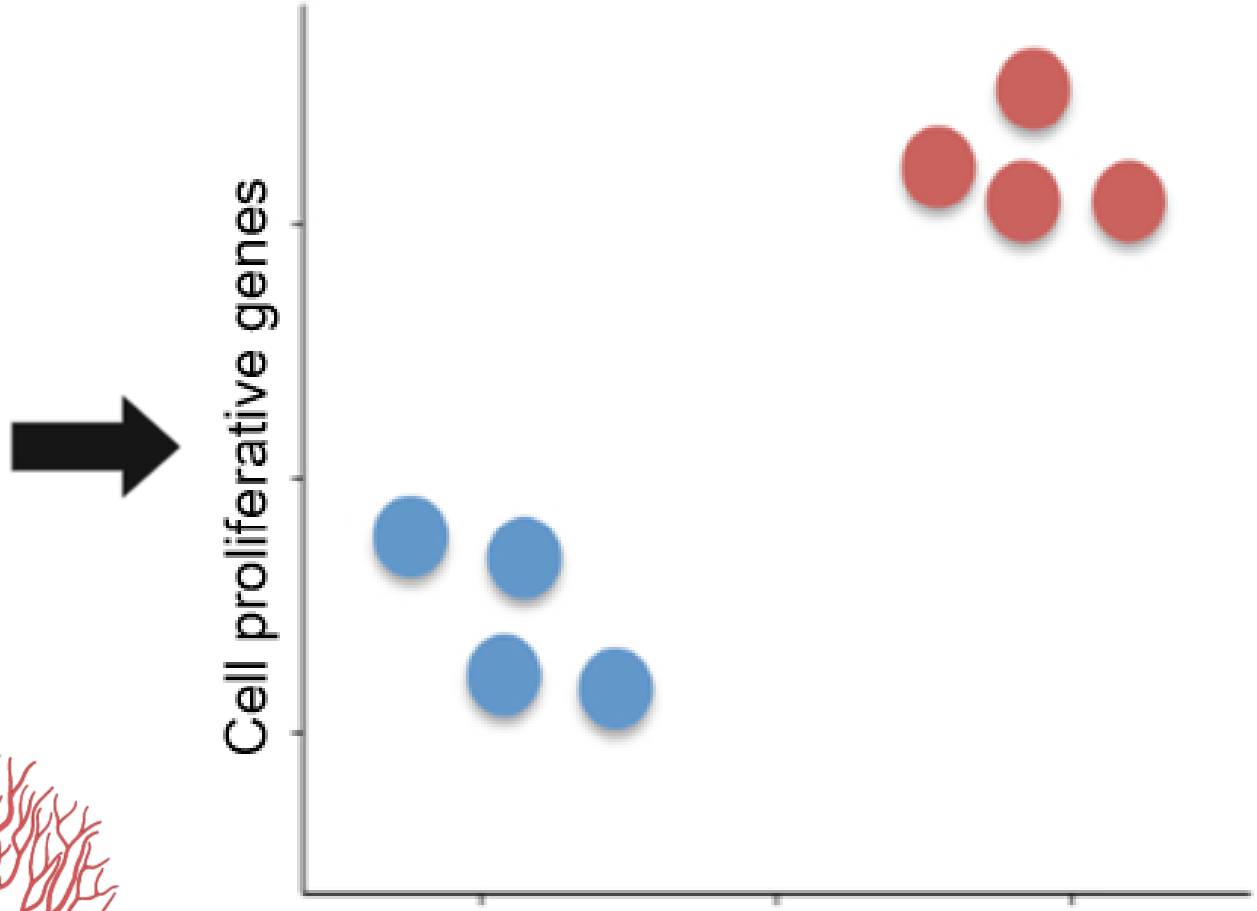


Delete the p-kinase domain of DYRK1A in a portion of the brain

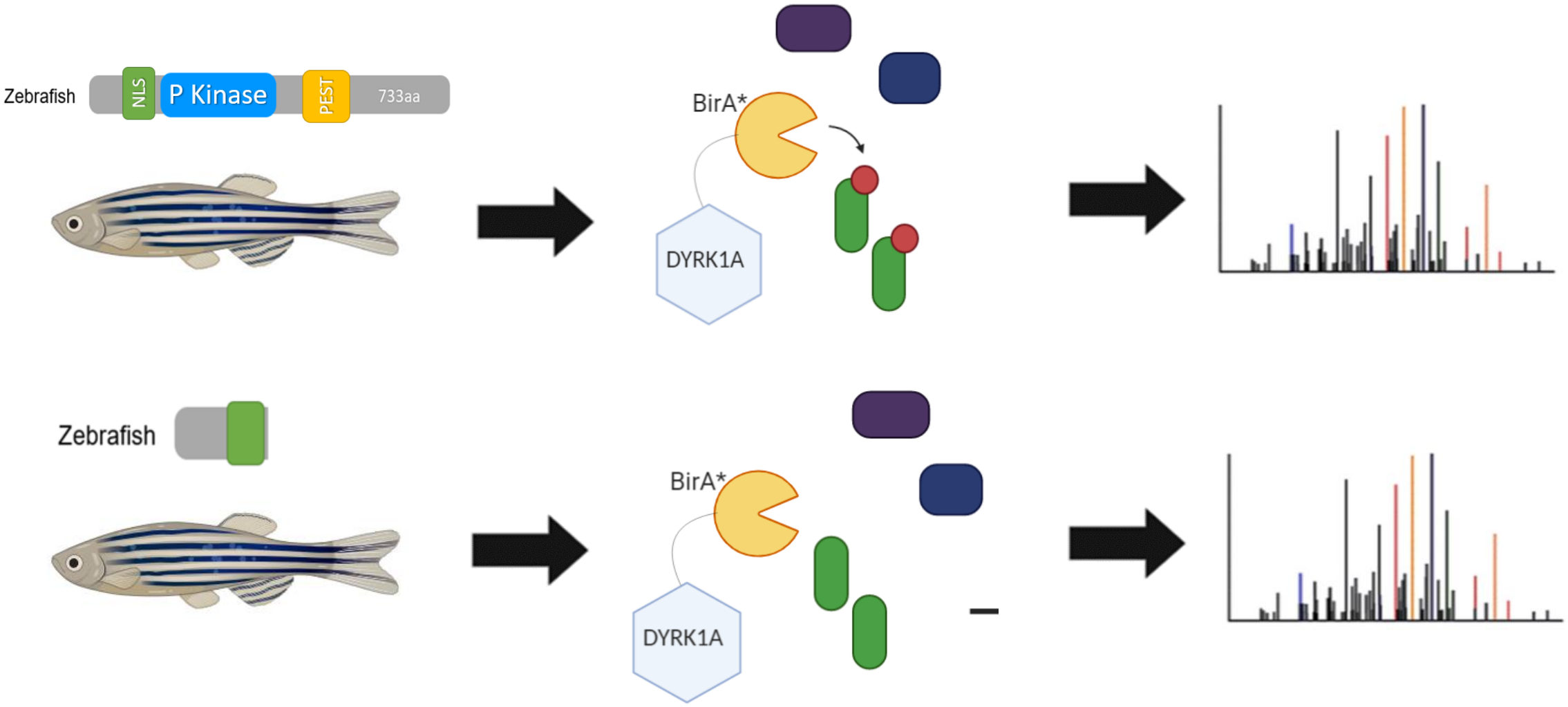
Aim 2: Identify differential gene expression in the brain in DYRK1A mutants

Cell proliferative genes

DYRK1A +/+ DYRK1A -/-

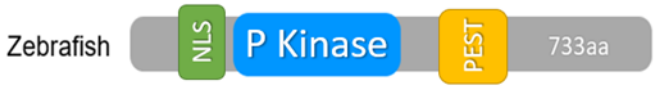


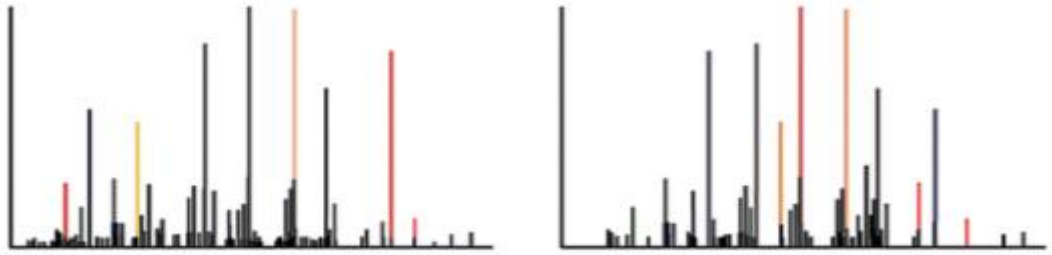
Aim 3: Determine DYRK1A protein interactions with Cell cycle regulators

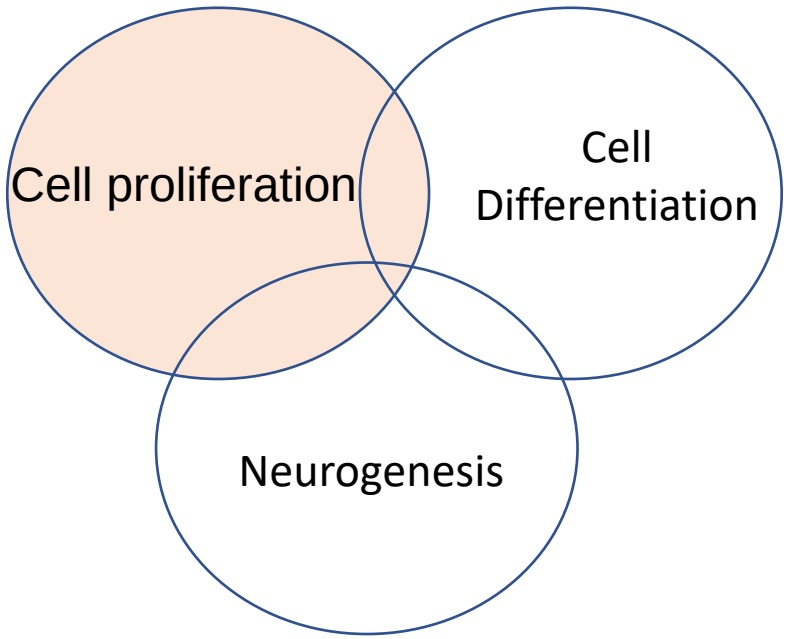


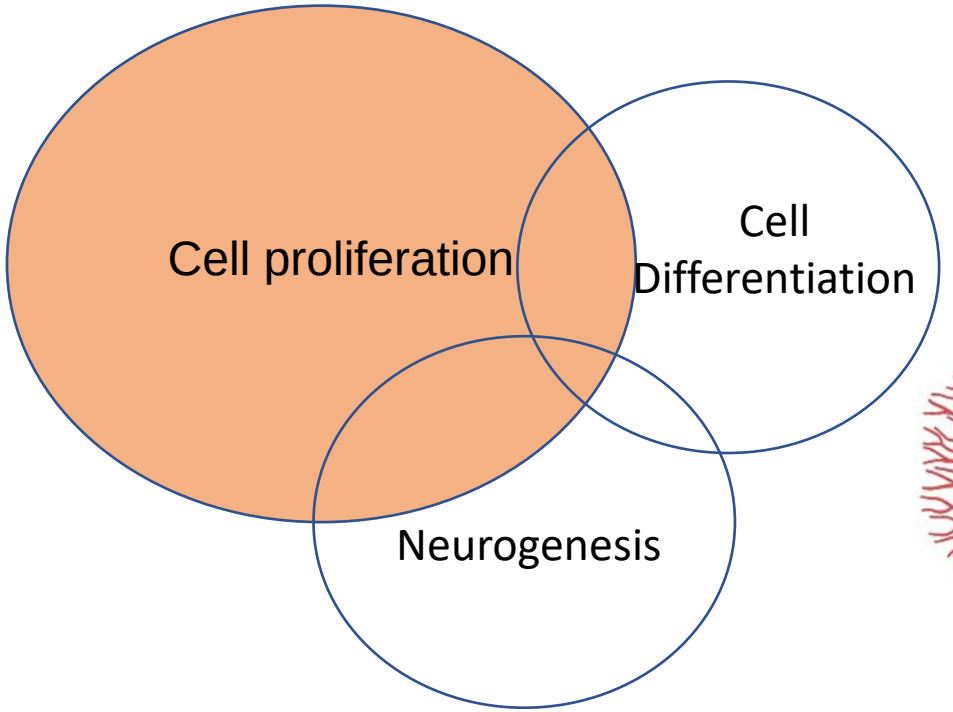
Biotinylate interacting proteins using BioID

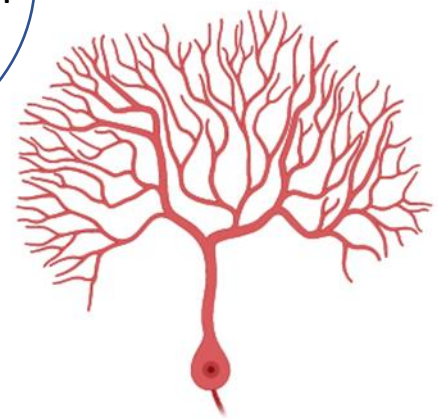
Aim 3: Determine DYRK1A protein interactions with Cell cycle regulators











Summary

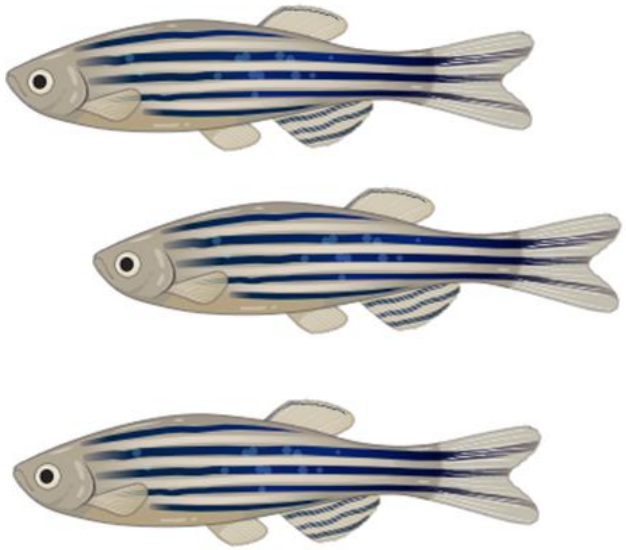
The P-kinase domain of DYRK1A is involved in regulating cell cycle processes.

DYRK1A modulates gene expression patterns of cell cycle regulators in neural brain cells.

DYRK1A protein interactions are important in understanding its role in cell division and neural proliferation in the brain.

Future Directions

DYRK1A



Future studies should focus on how DYRK1A impacts learning and behavioral phenotypes

References

1. Feki, A., & Hibaoui, Y. (2018). DYRK1A Protein, A Promising Therapeutic Target to Improve Cognitive Deficits in Down Syndrome. Brain sciences, 8(10), 187. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6210095/

2. Nguyen, Thu Lan et al. “Correction of cognitive deficits in mouse models of Down syndrome by a pharmacological inhibitor of DYRK1A.” Disease models & mechanisms vol. 11,9 dmm035634. 27 Sep. 2018. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5125364/?report=classic

3. Liu, Y., Lin, Z., Liu, M., Wang, H., & Sun, H. (2017). Overexpression of DYRK1A, a Down Syndrome Candidate gene, Impairs Primordial Germ Cells Maintenance and Migration in zebrafish. Scientific reports, 7(1), 15313. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5681638/

4. Thompson, B. J., Bhansali, R., Diebold, L., Cook, D. E., Stolzenburg, L., Casagrande, A. S., Besson, T., Leblond, B., Désiré, L., Malinge, S., & Crispino, J. D. (2015). DYRK1A controls the transition from proliferation to quiescence during lymphoid development by destabilizing Cyclin D3. The Journal of experimental medicine, 212(6), 953–970. https://doi.org/10.1084/jem.20150002

5. Olson L.E., et al. Down syndrome mouse models Ts65Dn, Ts1Cje, and Ms1Cje/Ts65Dn exhibit variable severity of cerebellar phenotypes. Dev. Dyn. 2004;230:581–589.

6. Liu, X, et al An AP-MS- and BioID-compatible MAC-tag enables comprehensive mapping of protein interactions and sub-cellular localizations. Nat Commun. 2018 Mar 22;9(1):1188. doi: 10.1038/s41467-018-03523-2.

7. Liu, X., Salokas, K., Tamene, F. *et al.* An AP-MS- and BioID-compatible MAC-tag enables comprehensive mapping of protein interactions and subcellular localizations. *Nat Commun* **9,** 1188 (2018). https://doi.org/10.1038/s41467-018-03523-2