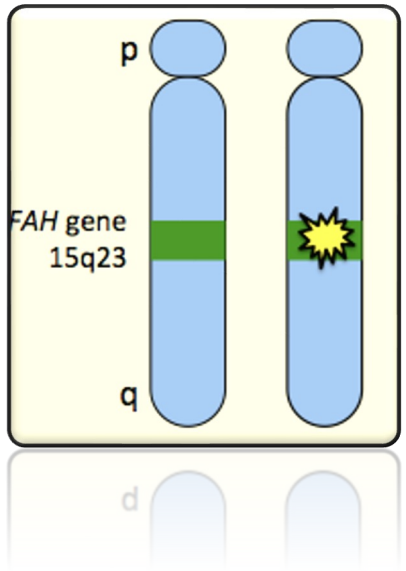
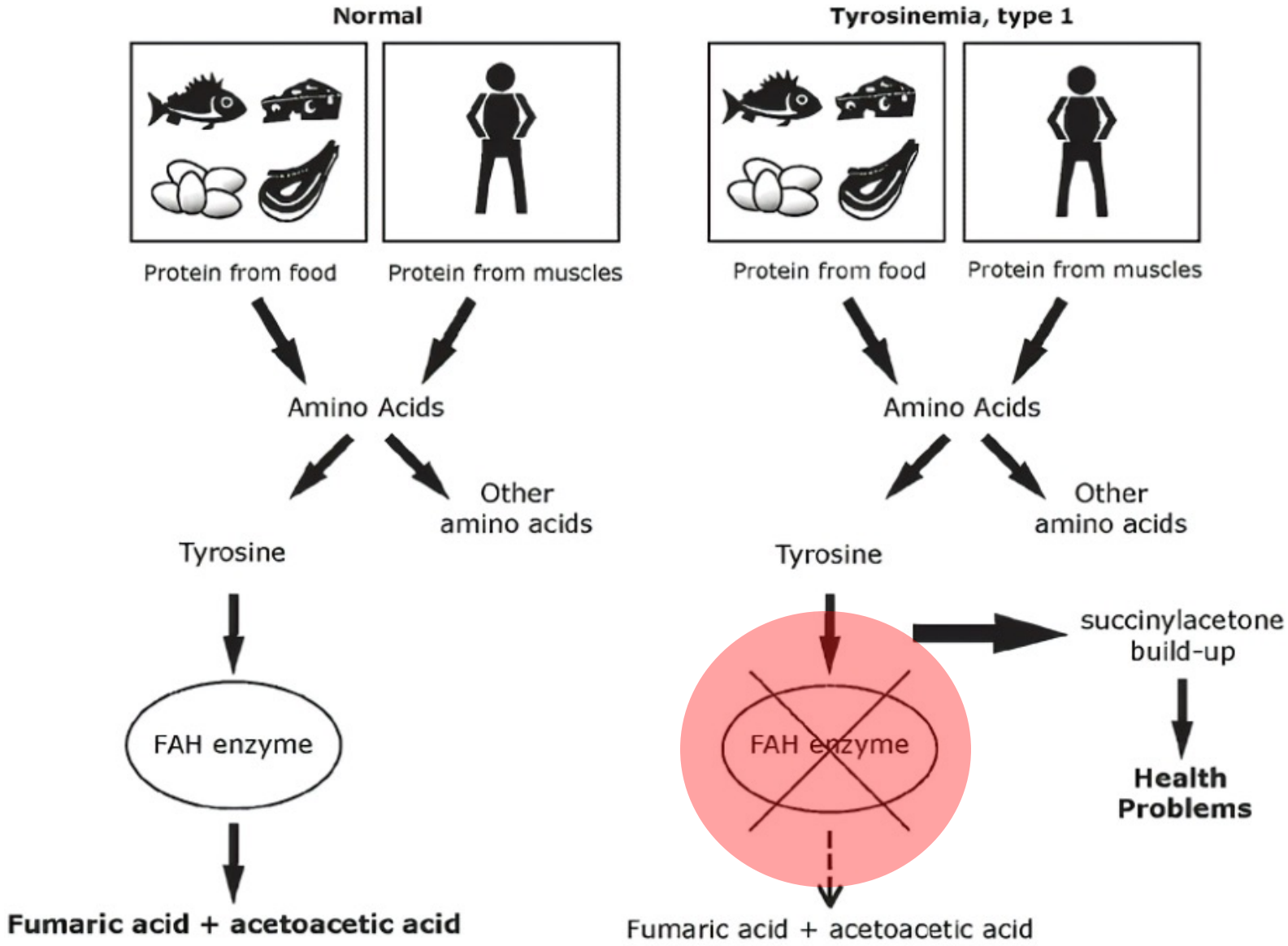
Tyrosinemia Type 1

Inability to break down tyrosine in the body

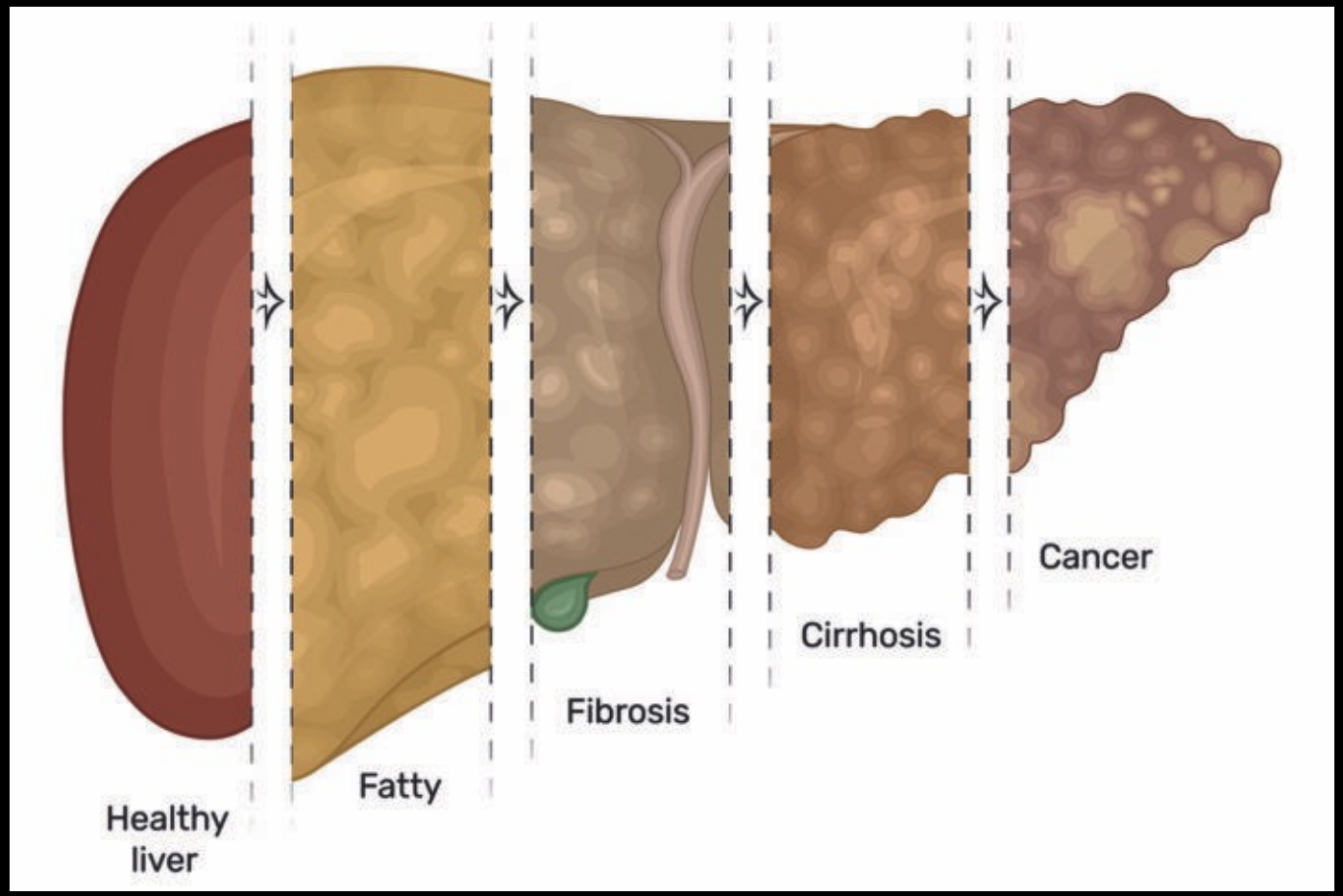
WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON
Brooke Fuerstenau

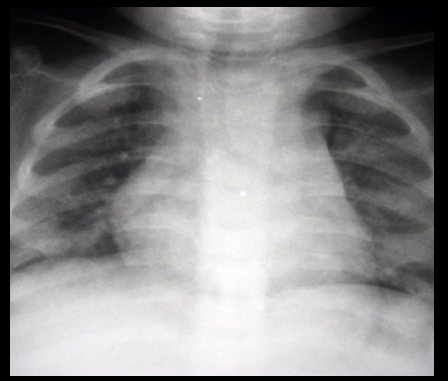
Tyrosinemia Type 1

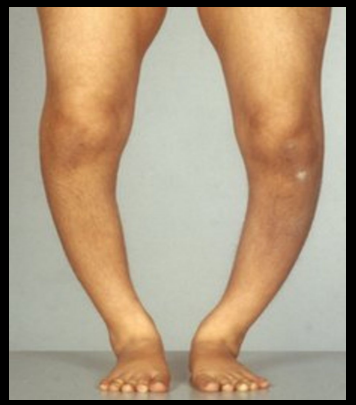


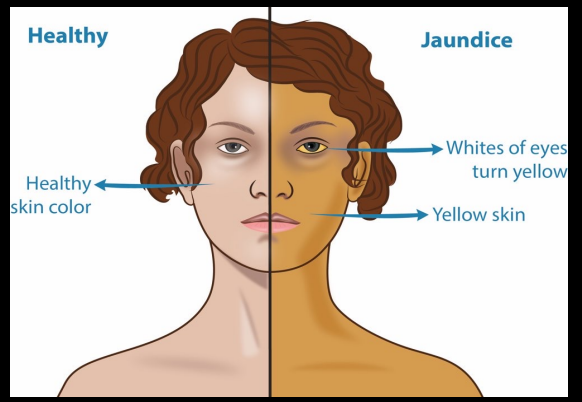


Symptoms and signs









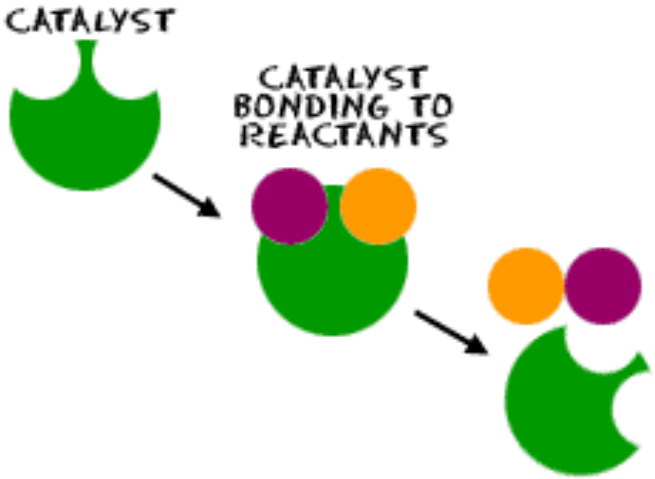
National Organization for Rare Disorders [2023]

Function of fumarylacetoacetase hydrolase

Human

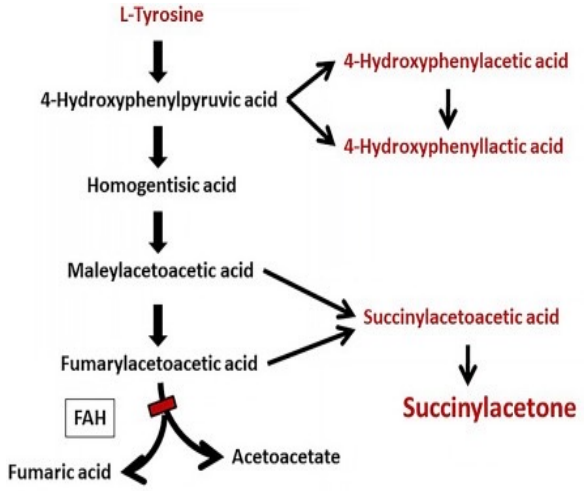
Gene Ontology

MOLECULAR FUNCTION



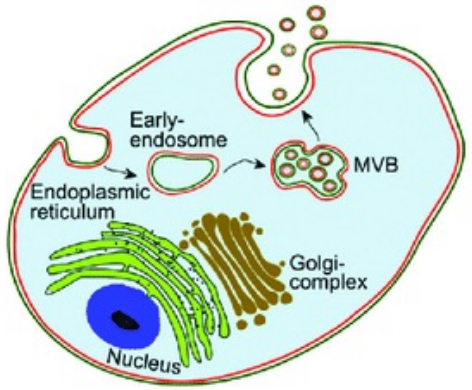
Catalytic activity

BIOLOGICAL PROCESS



Tyrosine metabolism

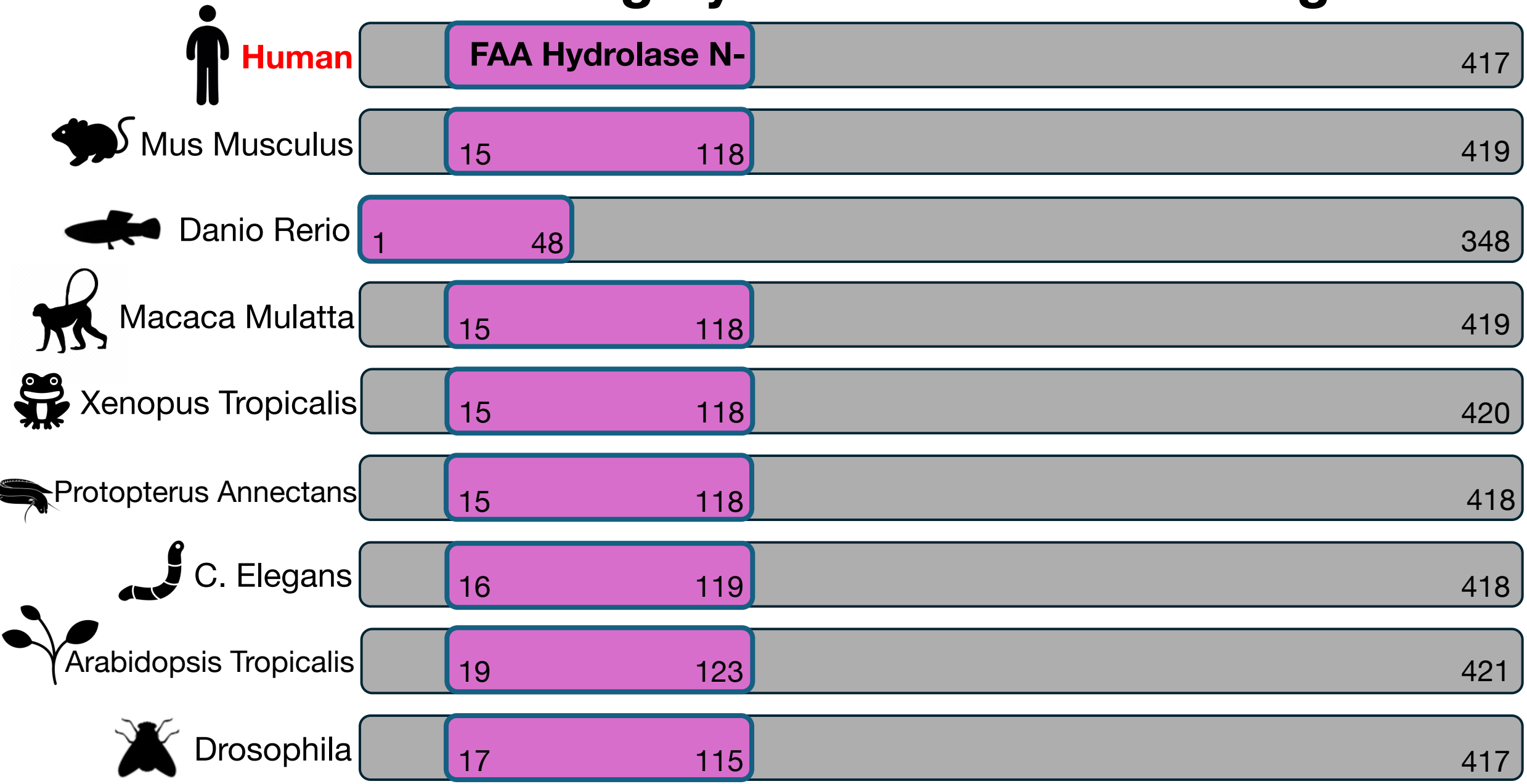
CELLULAR COMPONENT



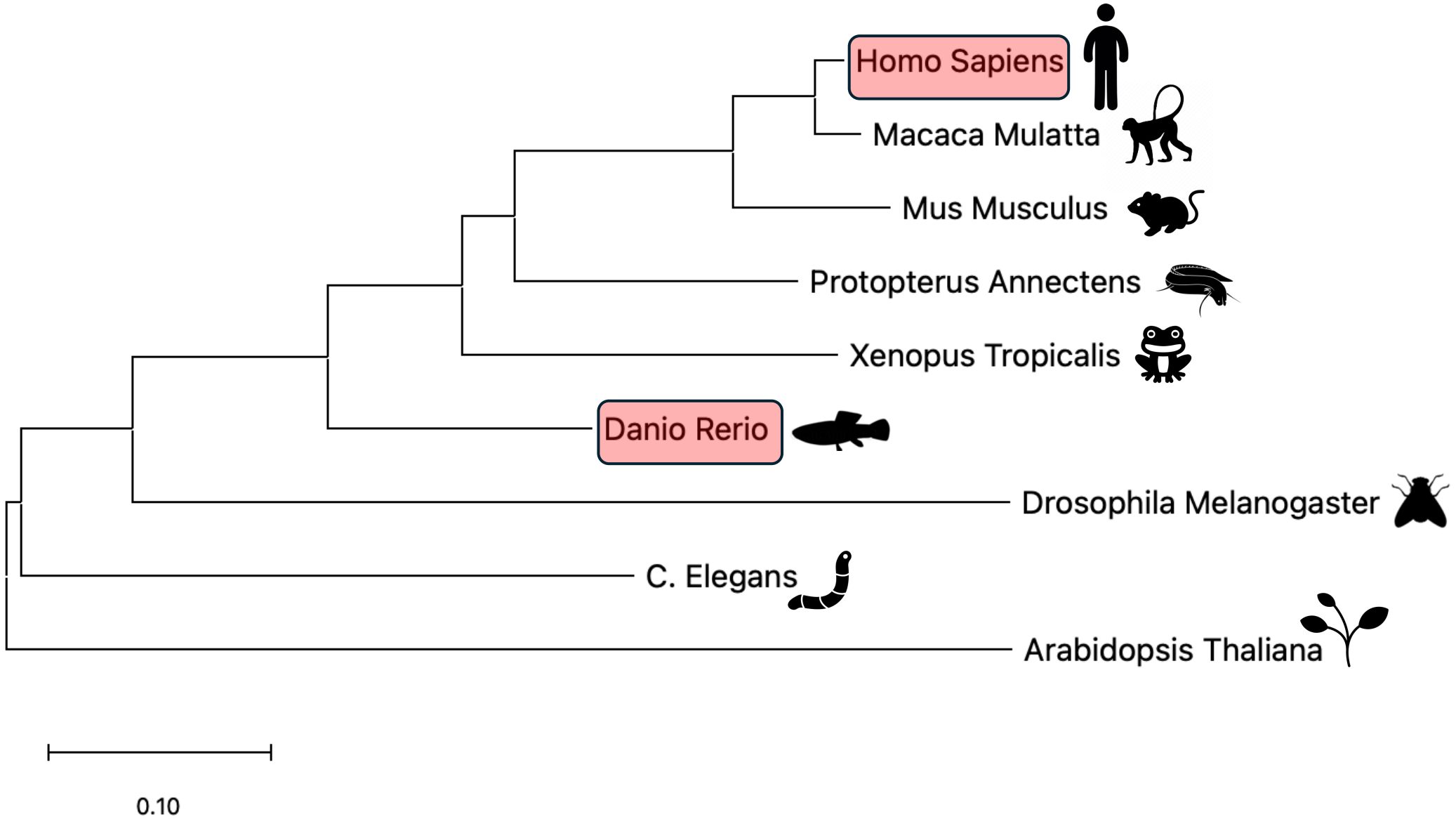
Extracellular exosome

The FAA domain is highly conserved across organisms

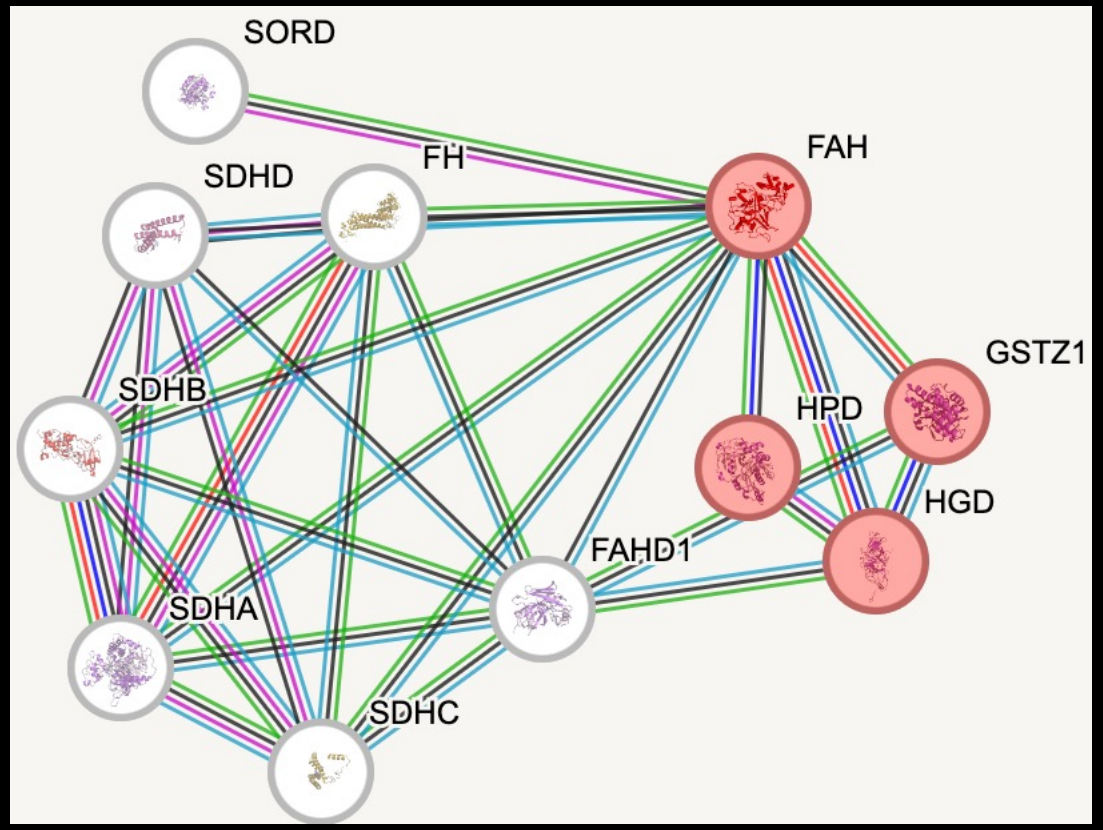
The FAA domain is highly conserved across organisms



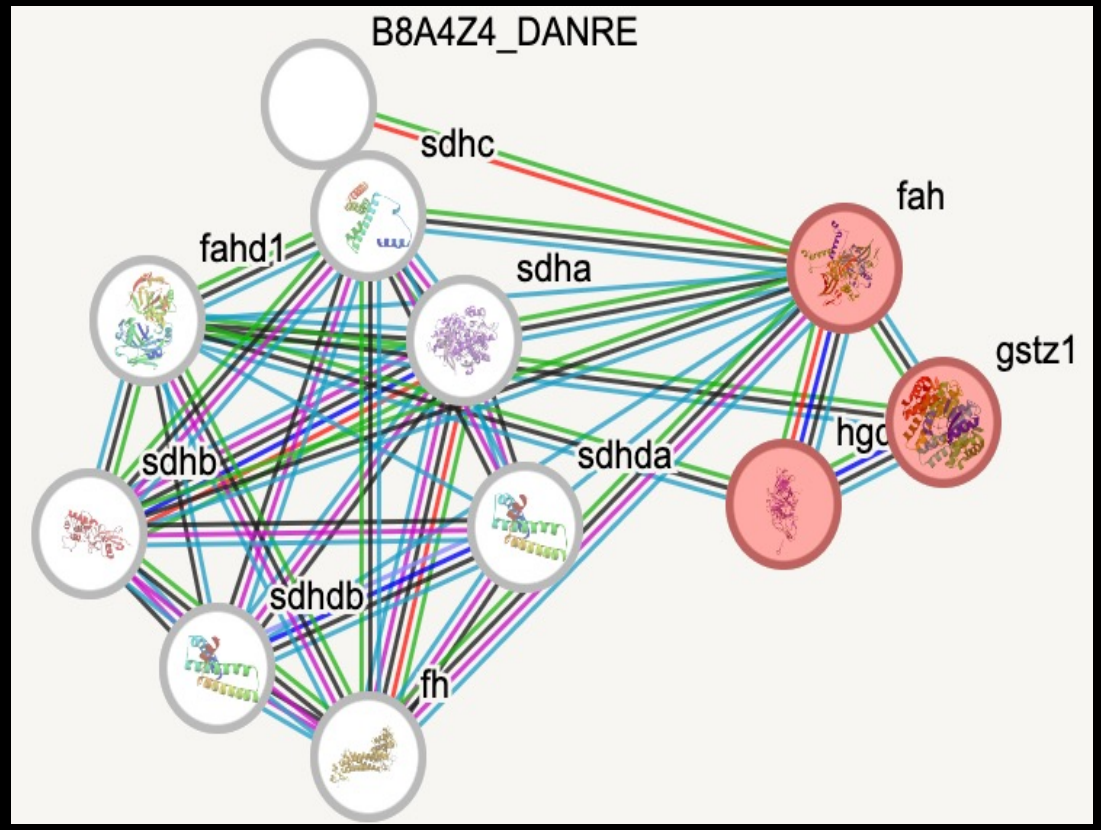
Phylogenetic tree



Protein interaction networks for FAA

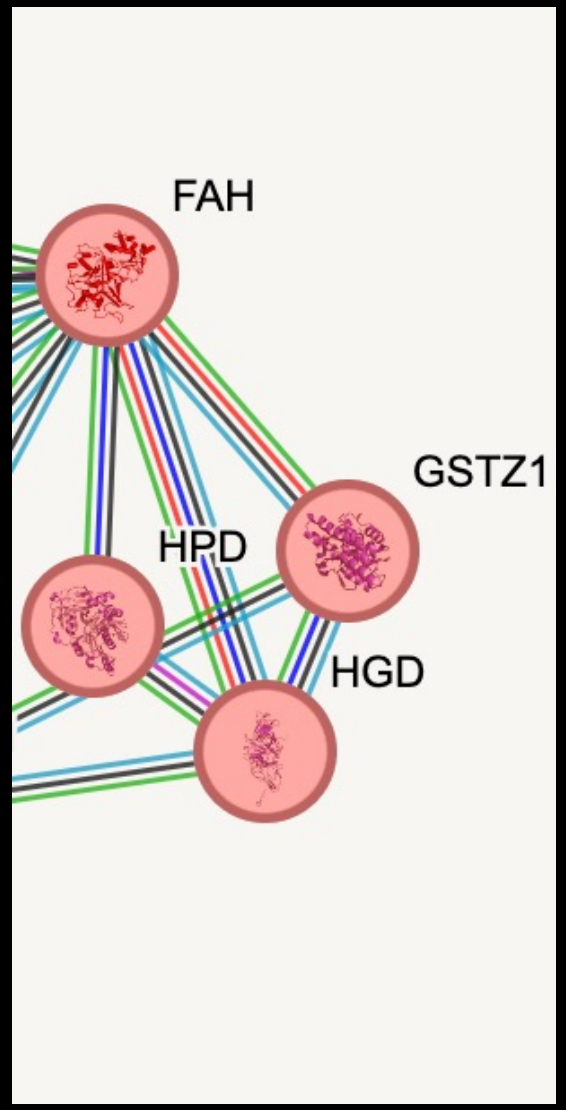


Homo sapiens

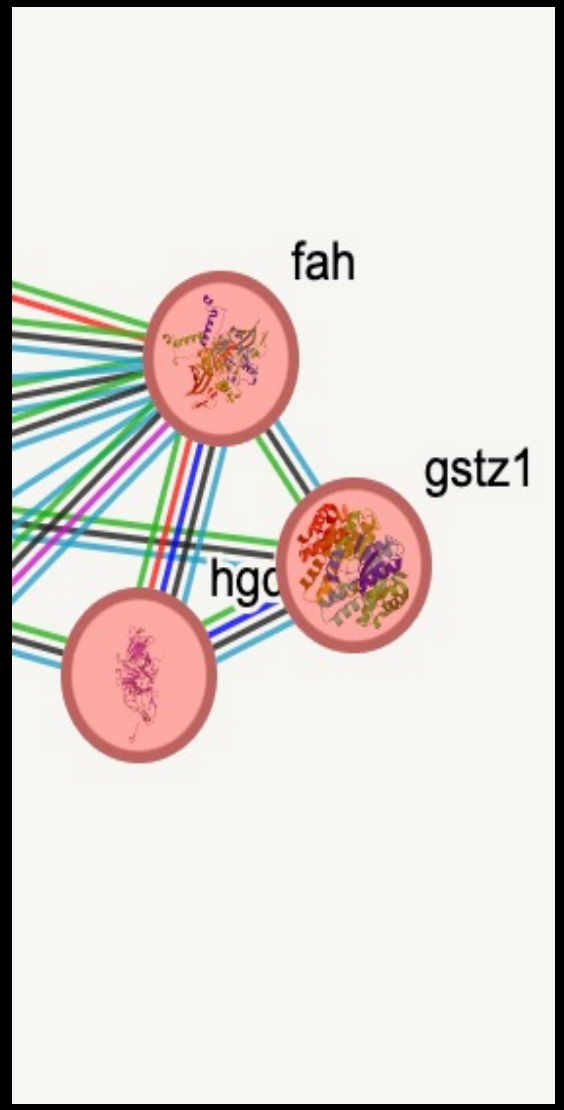


Danio rerio

Protein interaction networks for FAA



Homo sapiens

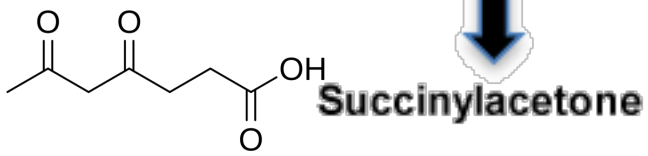


Danio rerio

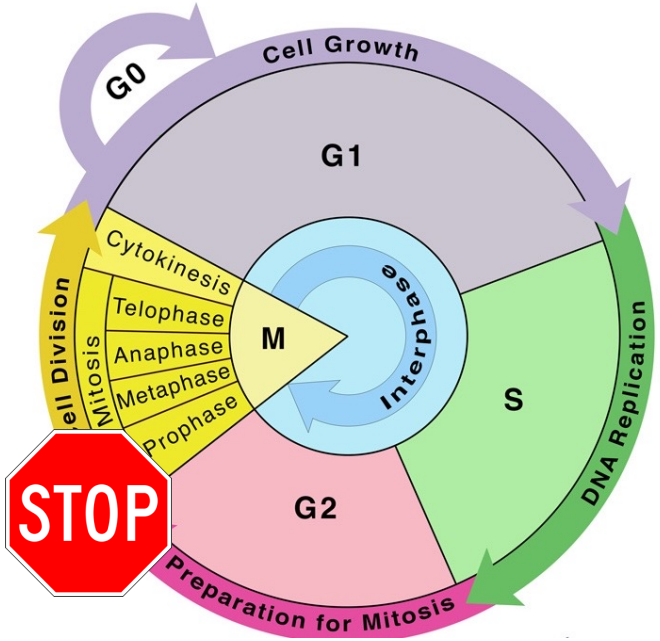
Tyrosine Catabolic Process

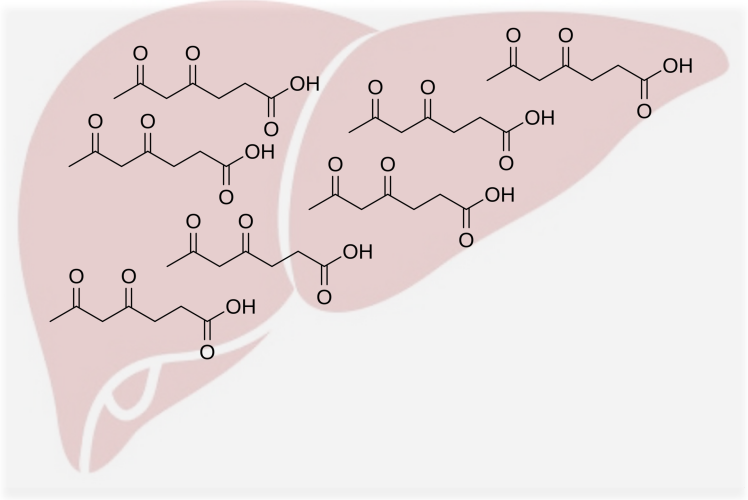
It is unknown what role FAA plays in hepatocyte apoptosis

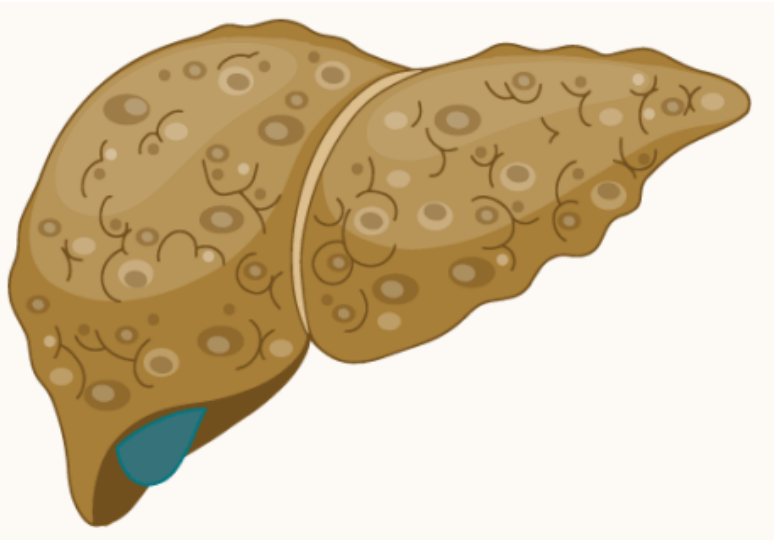
Tyrosine → 4 Fumarylacetoacetate → FAH →



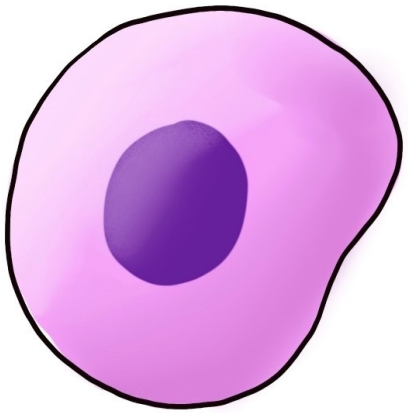
Succinylacetone

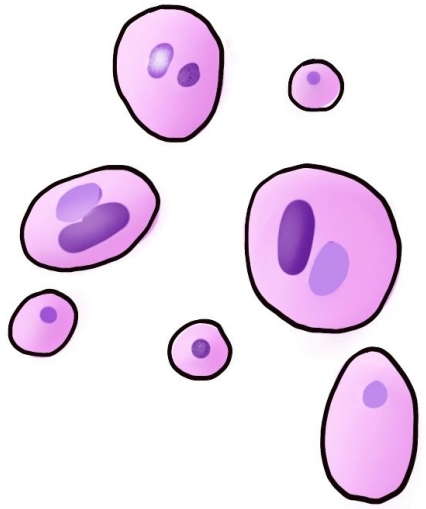






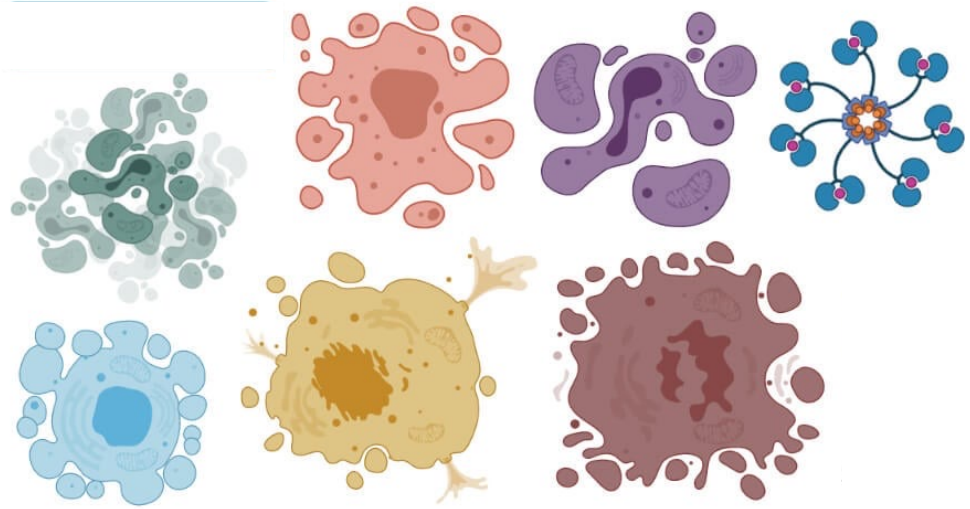
Histology analysis of apoptosis and apoptotic bodies

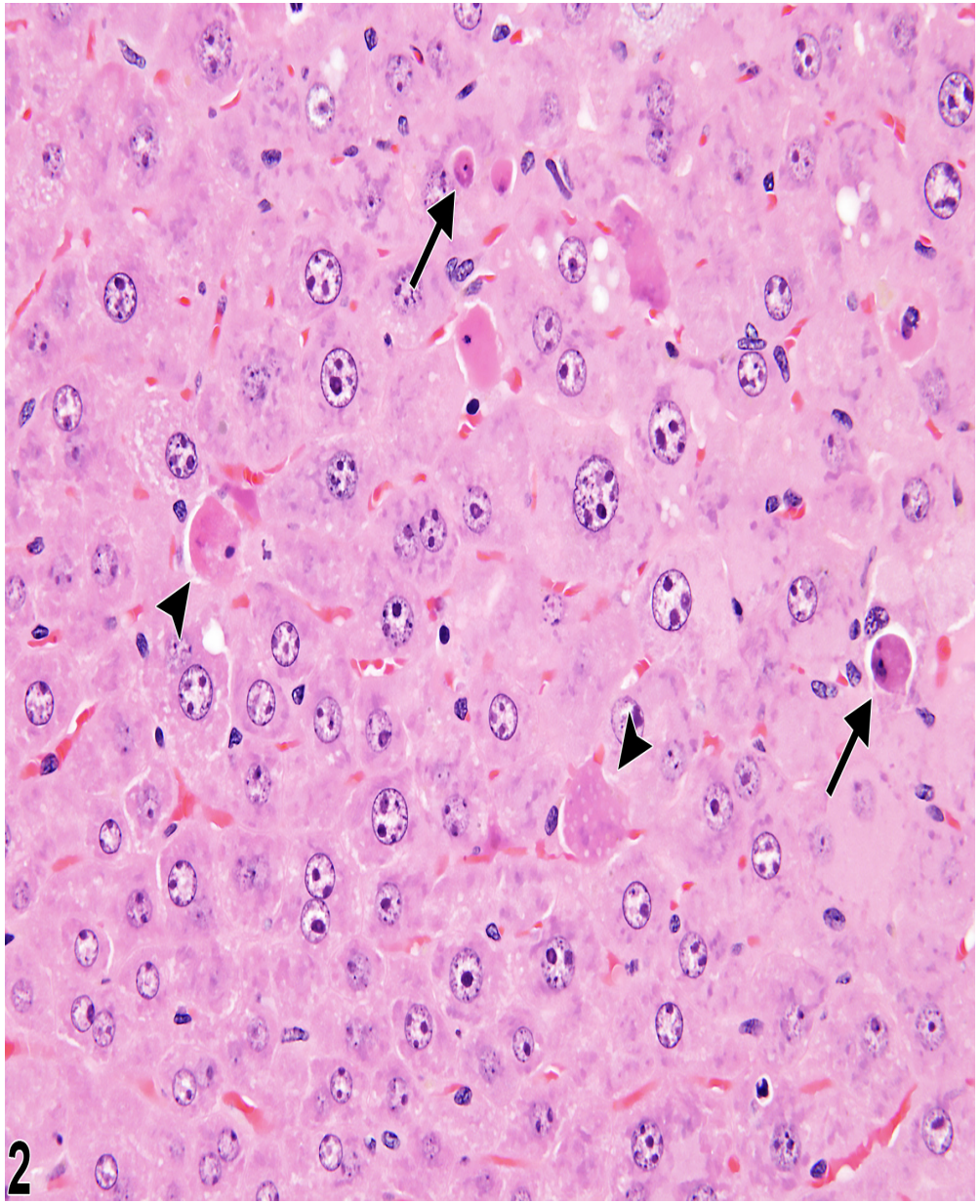




THE CELL HAS BROKEN INTO MANY SMALL PIECES CALLED "APOPTOTIC BODIES"

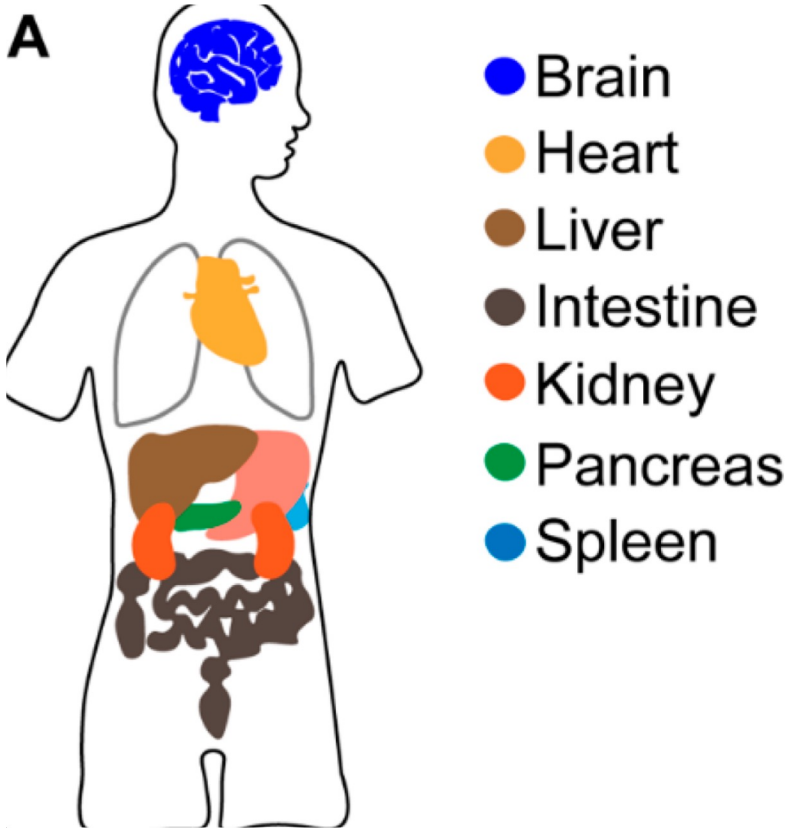
NORMAL, HEALTHY CELL → CELL AFTER APOPTOSIS



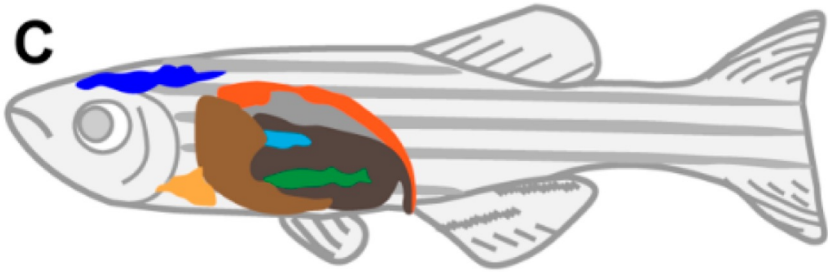


Danio rerio act as good models for liver diseases in humans

Zebrafish



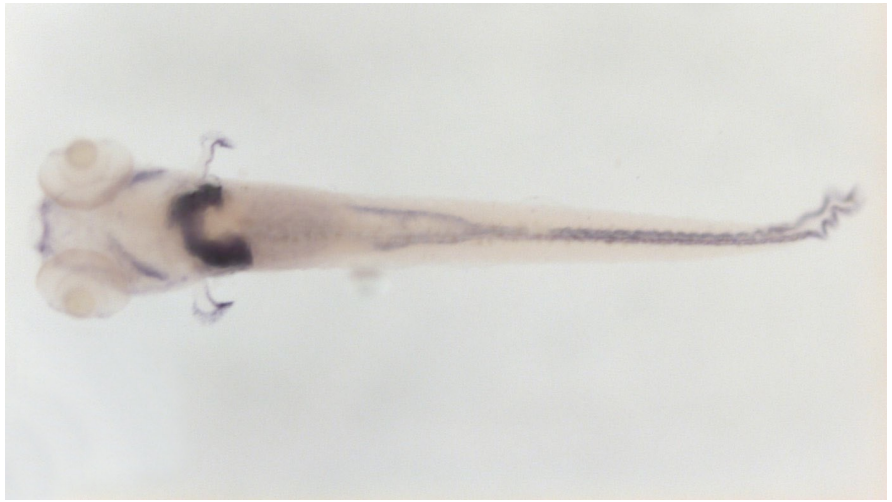
Larval zebrafish

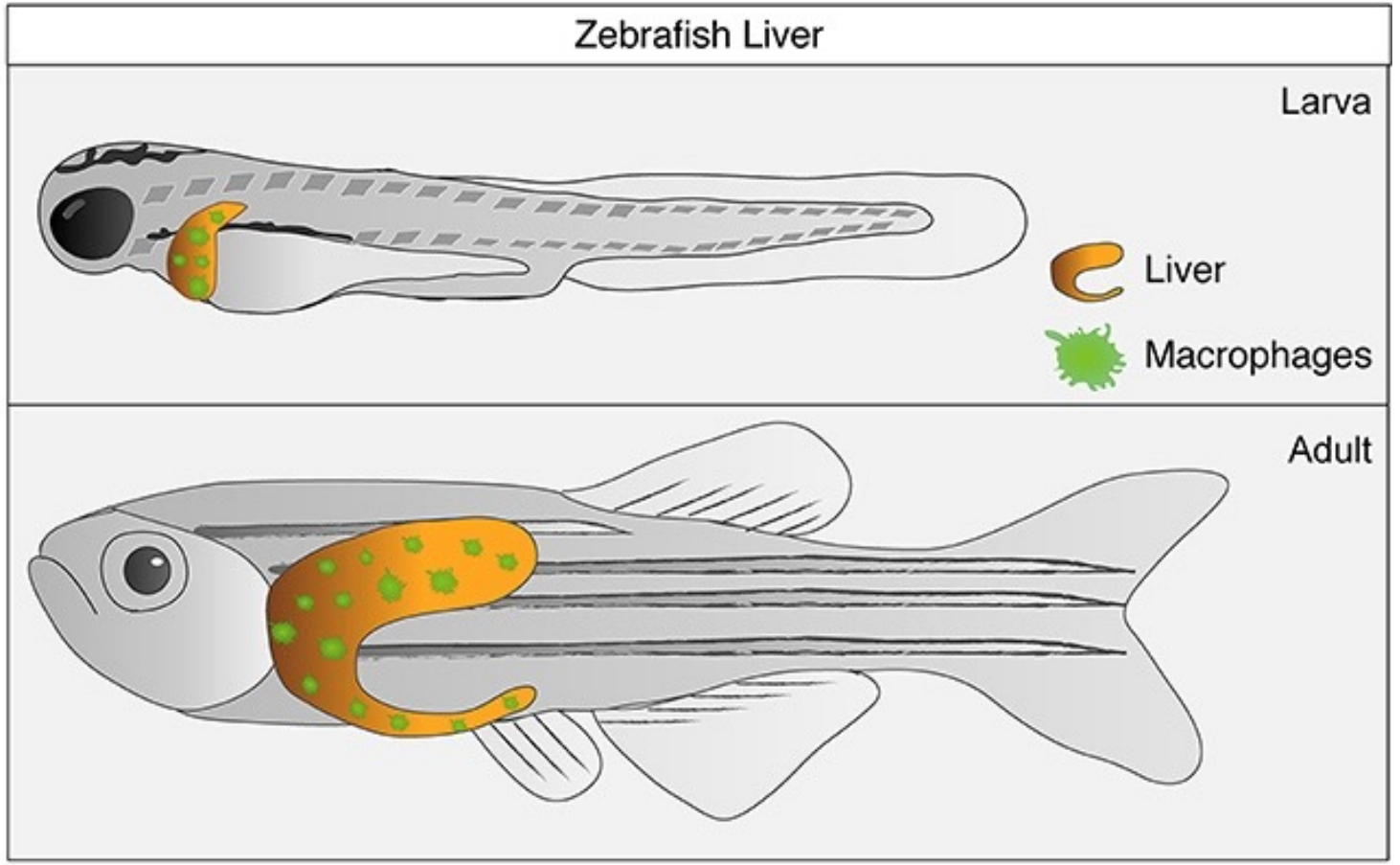


Adult zebrafish

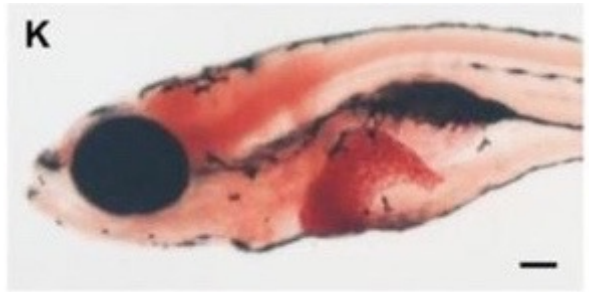
Danio rerio act as good models for liver diseases in humans

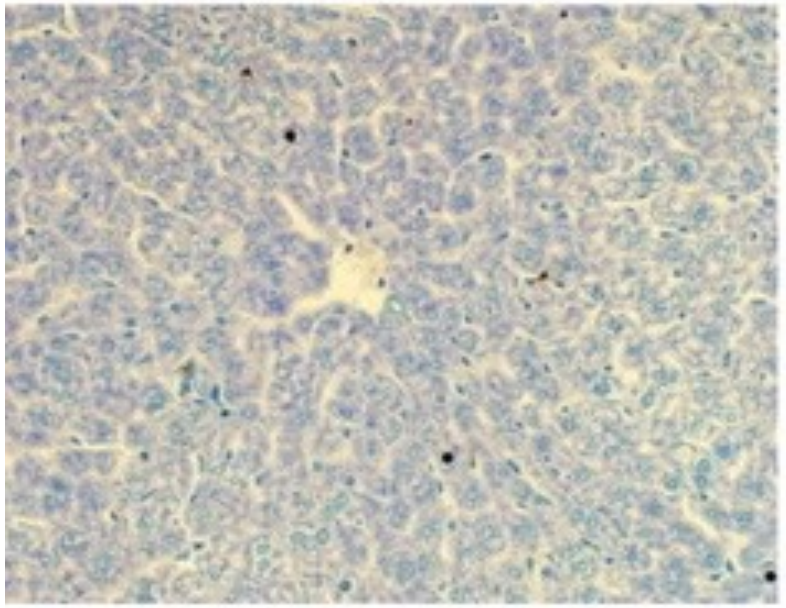
Zebrafish

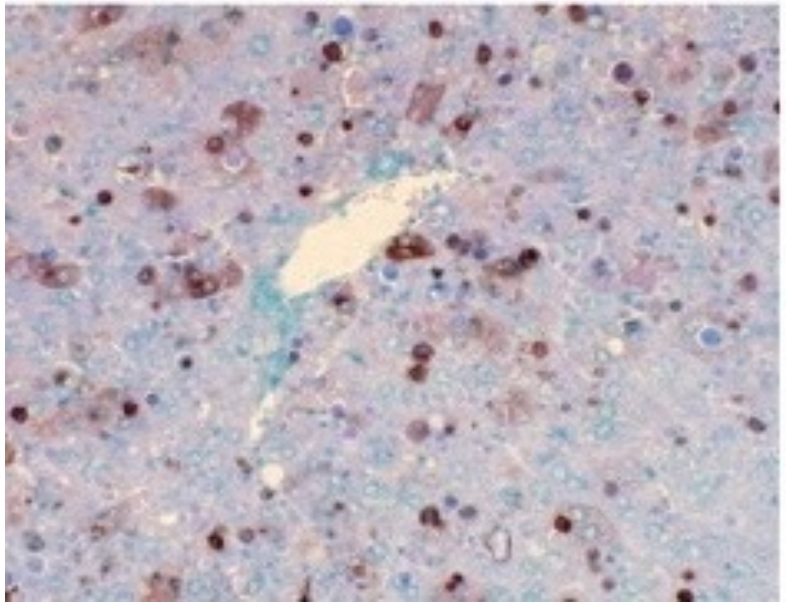




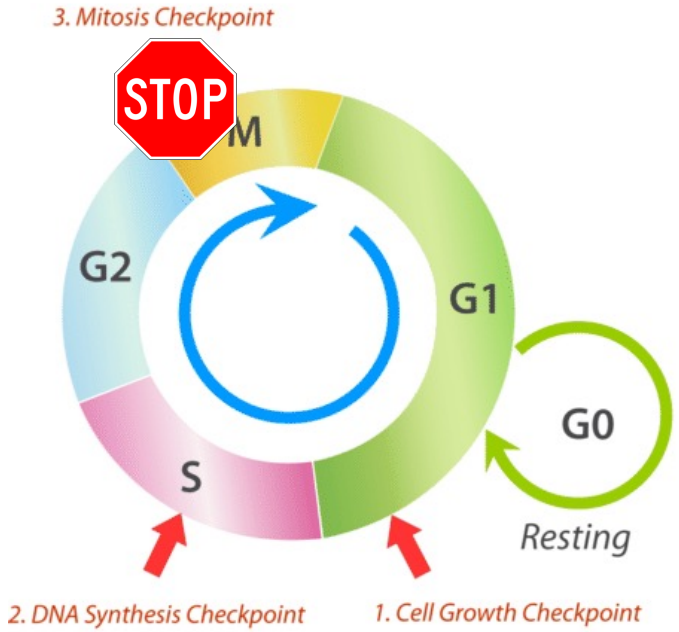
Danio rerio act as good models for liver diseases in humans







Primary goal of this research



HYPOTHESIS

The FAH gene regulates a key process involved in healthy cell progression and without this functioning gene, hepatocyte cells are stalled in the cell cycle, leading to increased apoptosis and in turn, cirrhosis of the liver.

Specific Aims

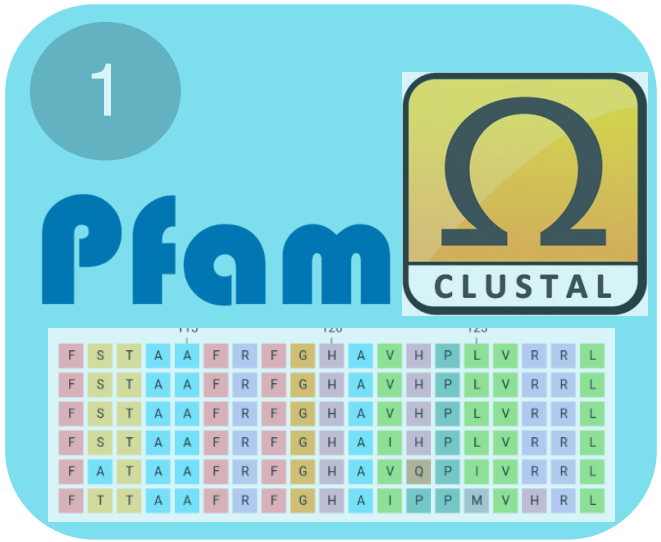
Goal : Understand how the absence of a functional FAH gene causes increased apoptosis of hepatocyte cells, leading to liver cirrhosis.

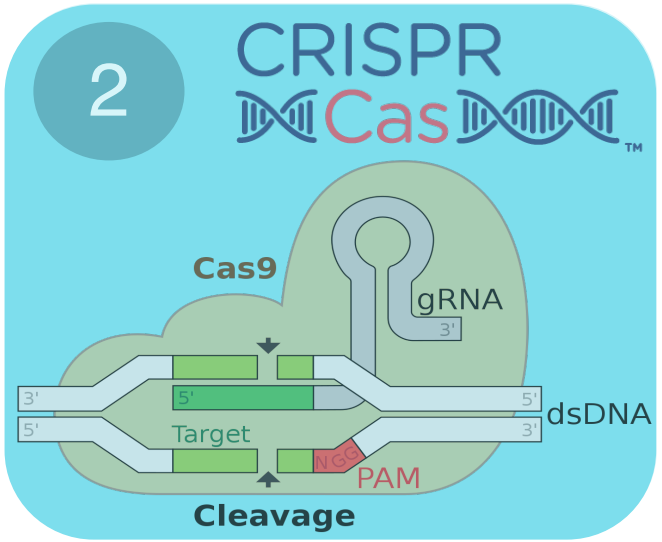
AIM 1	AIM 2	AIM 3
Identify conserved amino acids of FAH necessary for healthy cell progression.	Identify differentially expressed genes in WT and mutant FAH hepatocyte cells.	Quantify differentially expressed proteins in WT and mutant FAH hepatocyte cells.

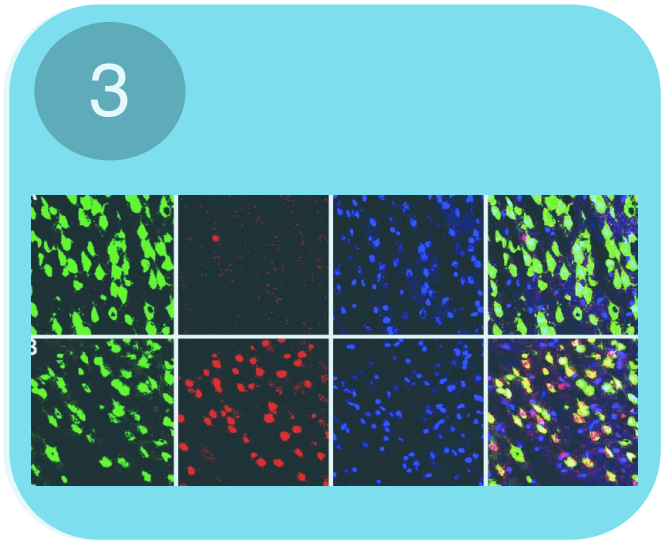
Long-term Goal : Further understand the mechanisms underlying this disorder in order to be able to effectively target symptoms with treatment drugs.

Aim 1 : Identify conserved amino acids of FAH necessary for healthy cell progression.

Rationale : Understanding how different amino acids within the FAH gene correlate to healthy cell progression and normal liver phenotype will allow for better assessment of treatment options.

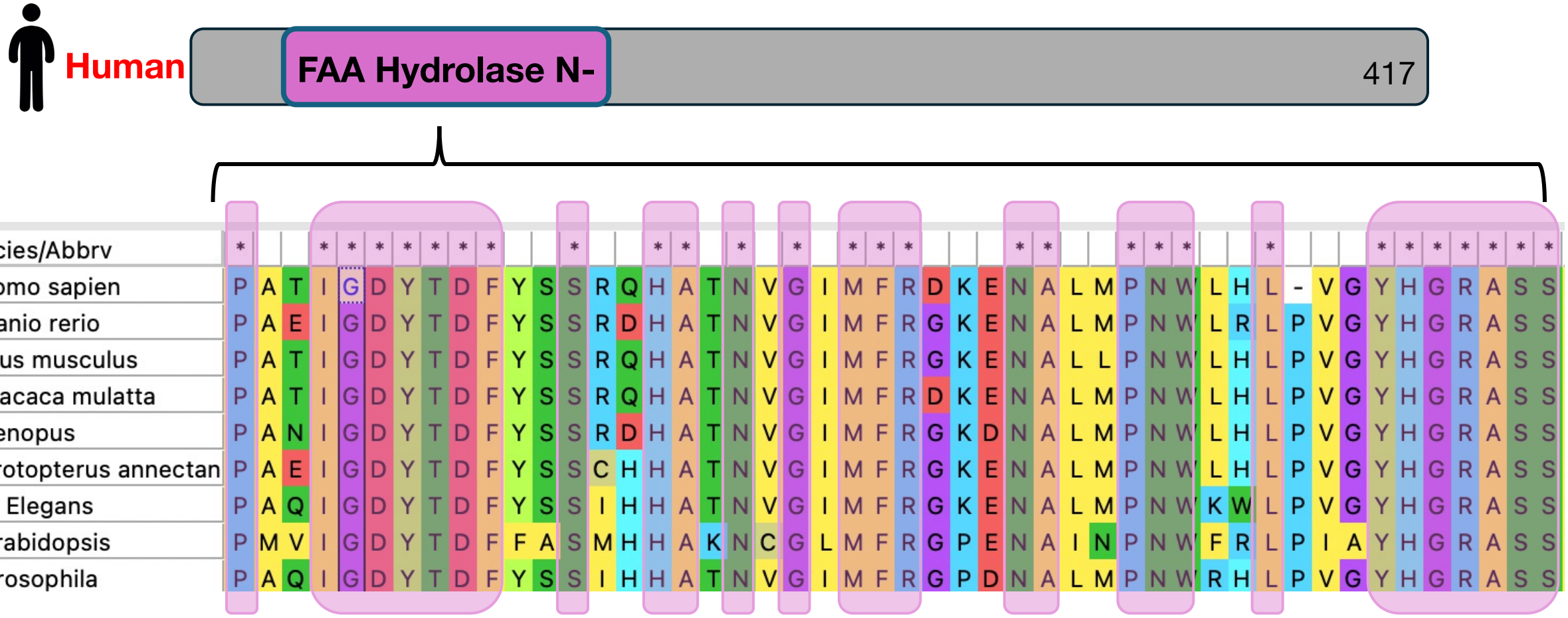




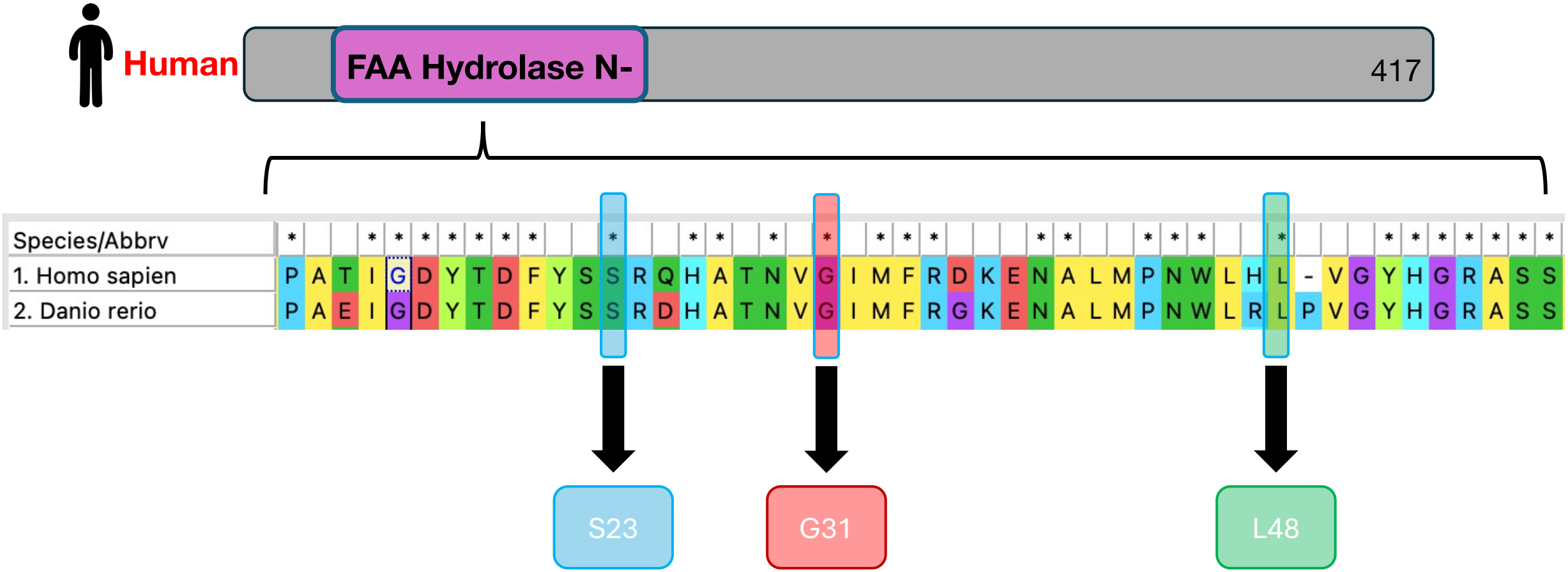


Hypothesis : Organisms with a mutated amino acid in the FAH gene will not progress as a healthy cell and will instead go through apoptosis at a checkpoint in the cell cycle.

Aim 1 : Identify conserved amino acids of FAH necessary for healthy cell progression.

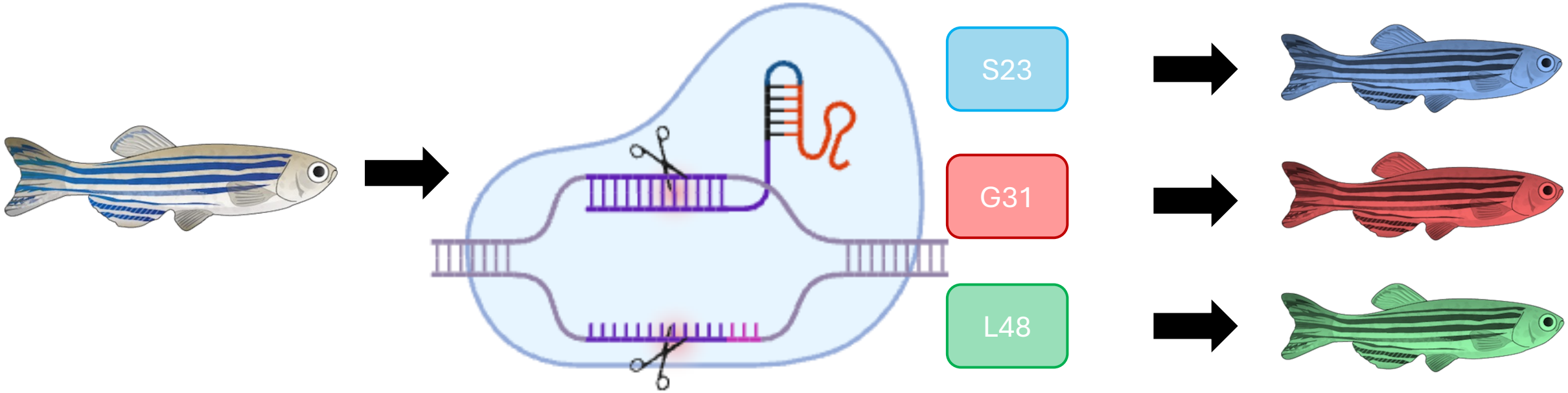


Aim 1 : Identify conserved amino acids of FAH necessary for healthy cell progression.



Domain Analysis | **CRISPR** | TUNEL assay

Aim 1 : Identify conserved amino acids of FAH necessary for healthy cell progression.

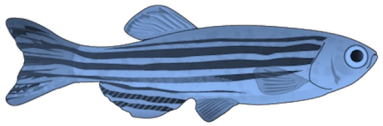


Domain Analysis | CRISPR | **TUNEL assay**

Aim 1 : Identify conserved amino acids of FAH necessary for healthy cell progression.

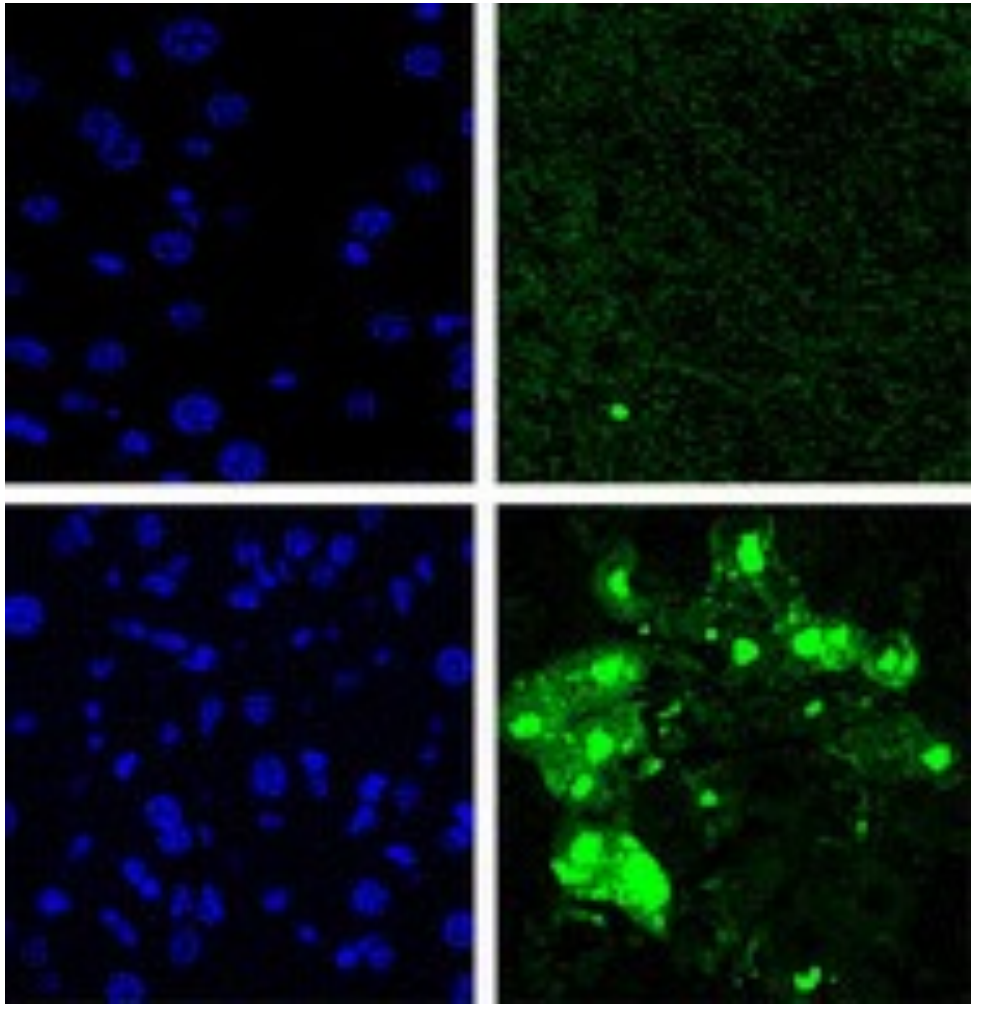
WT

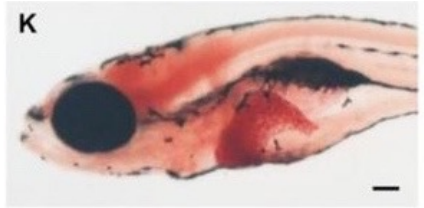
S23



G31

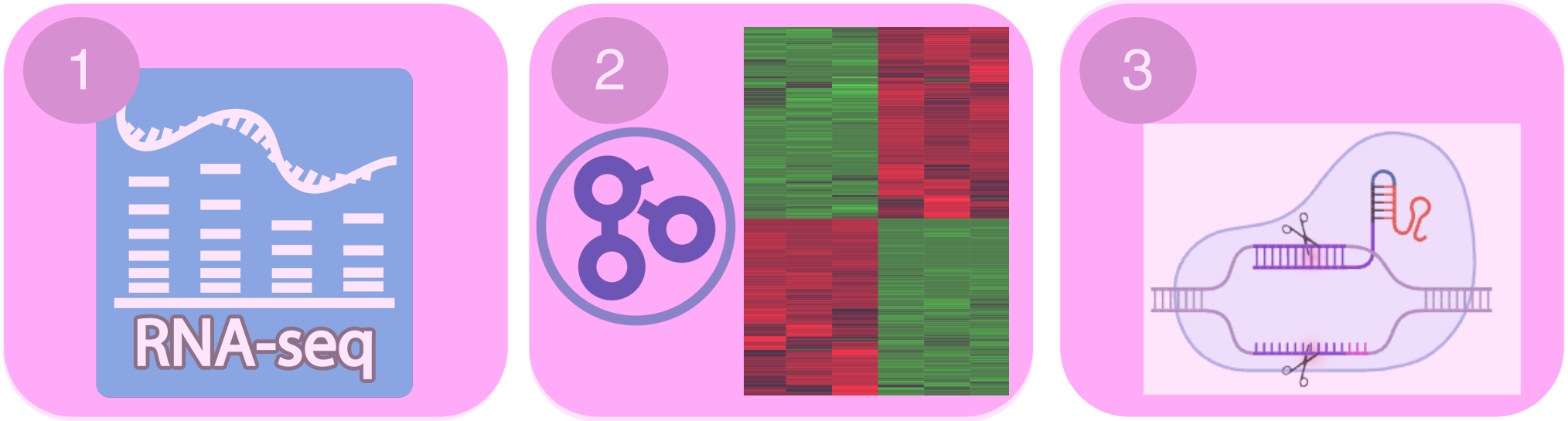
L48





Aim 2 : Identify differentially expressed genes in WT and mutant FAH hepatocyte cells that lead to apoptosis.

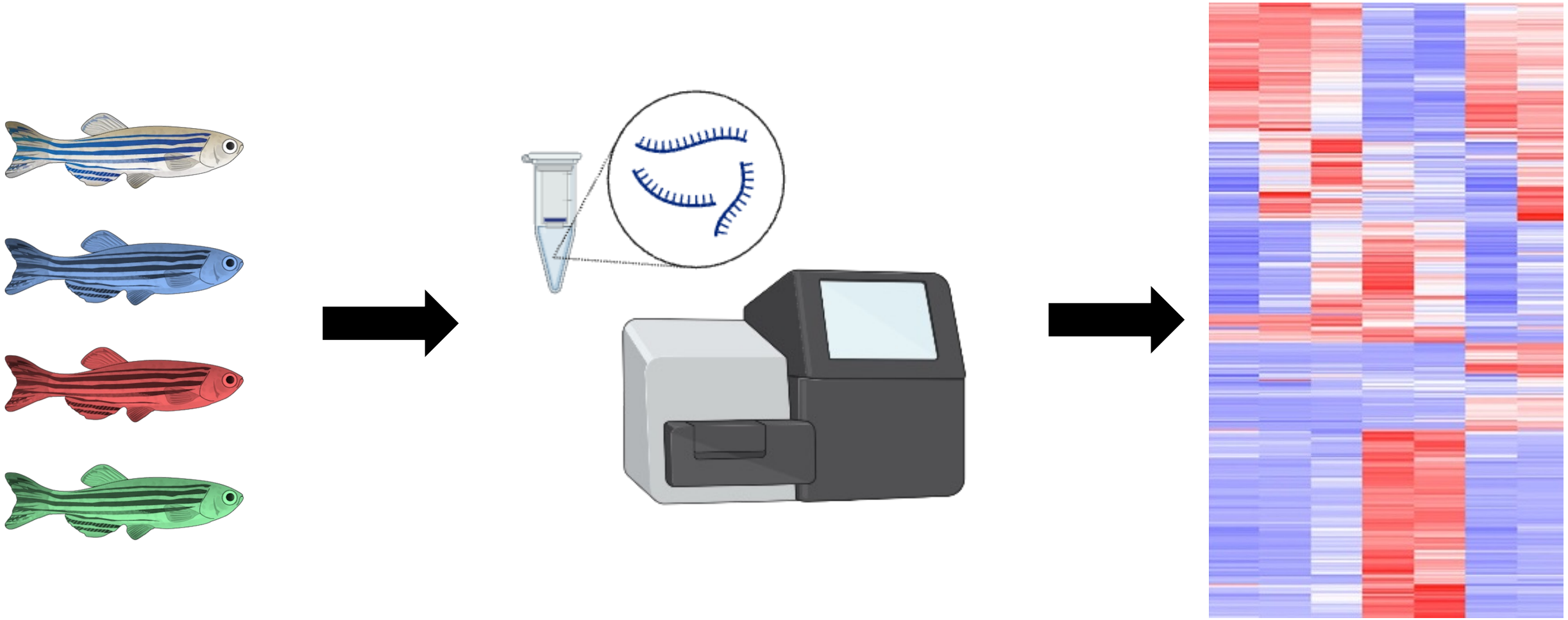
Rationale : Determining genes that are expressed / regulated differently in FAH mutant hepatocyte cells will allow for better understanding of cellular processes utilizing this gene and help fuel research into new targets for possible drug treatments.



Hypothesis : FAH mutant hepatocyte cells will have differentially expressed genes than WT hepatocyte cells, specifically in genes involved in tyrosine catabolism.

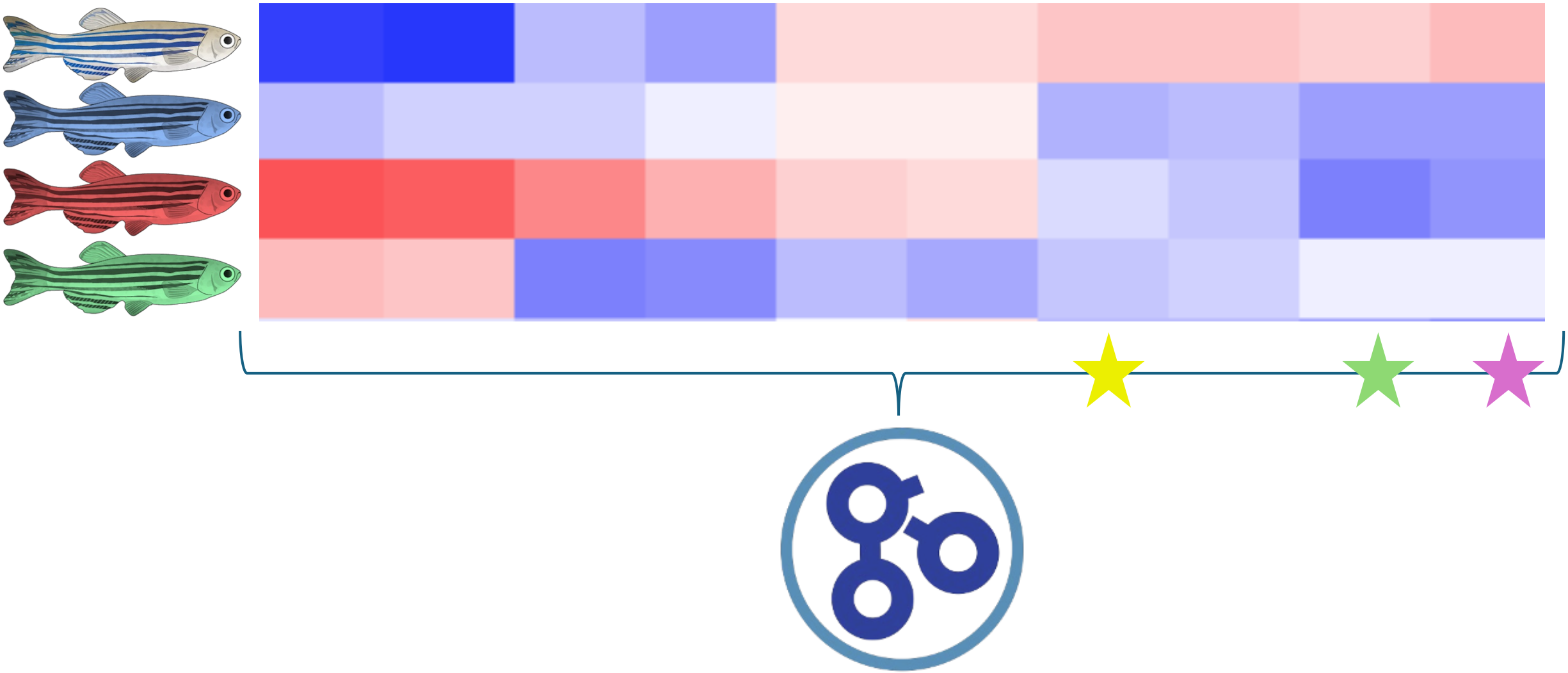
RNA-seq | Gene Ontology | Validation

Aim 2 : Identify differentially expressed genes in WT and mutant FAH hepatocyte cells that lead to apoptosis.



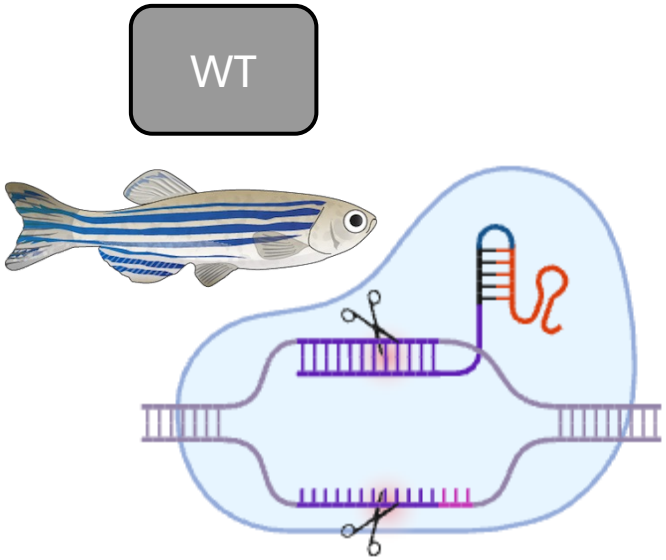
RNA-seq | **Gene Ontology** | Validation

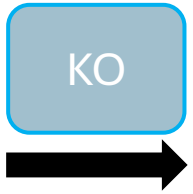
Aim 2 : Identify differentially expressed genes in WT and mutant FAH hepatocyte cells that lead to apoptosis.

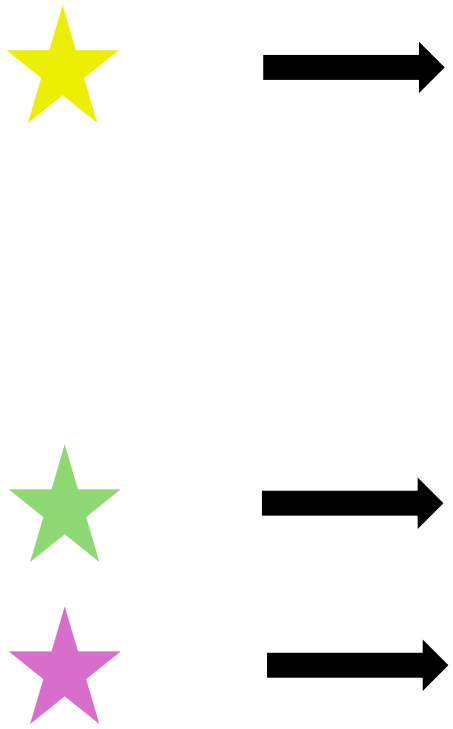


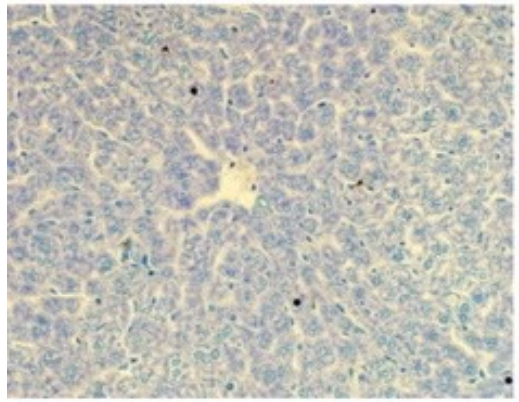
RNA-seq | Gene Ontology | **Validation**

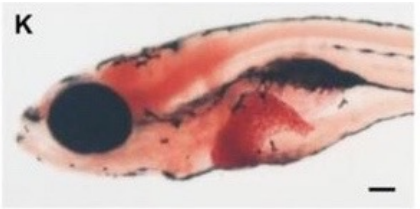
Aim 2 : Identify differentially expressed genes in WT and mutant FAH hepatocyte cells that lead to apoptosis.

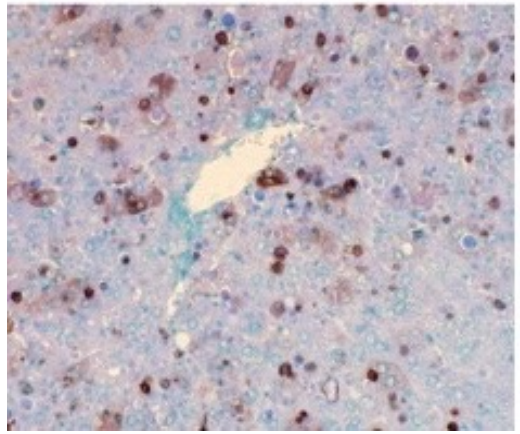






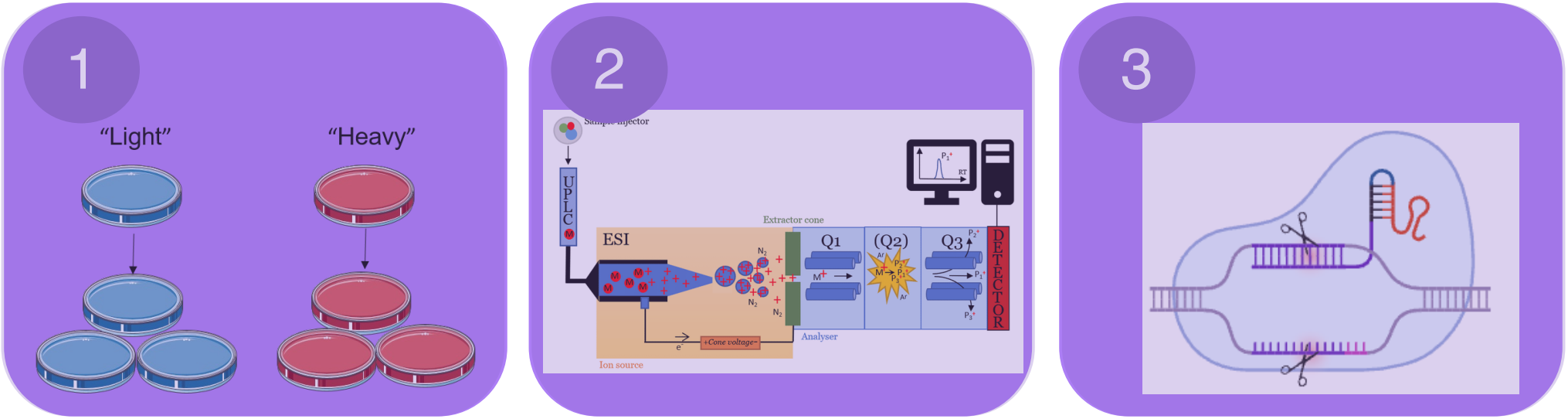






Aim 3 : Quantify differentially expressed proteins in WT and mutant FAH hepatocyte cells that lead to apoptosis.

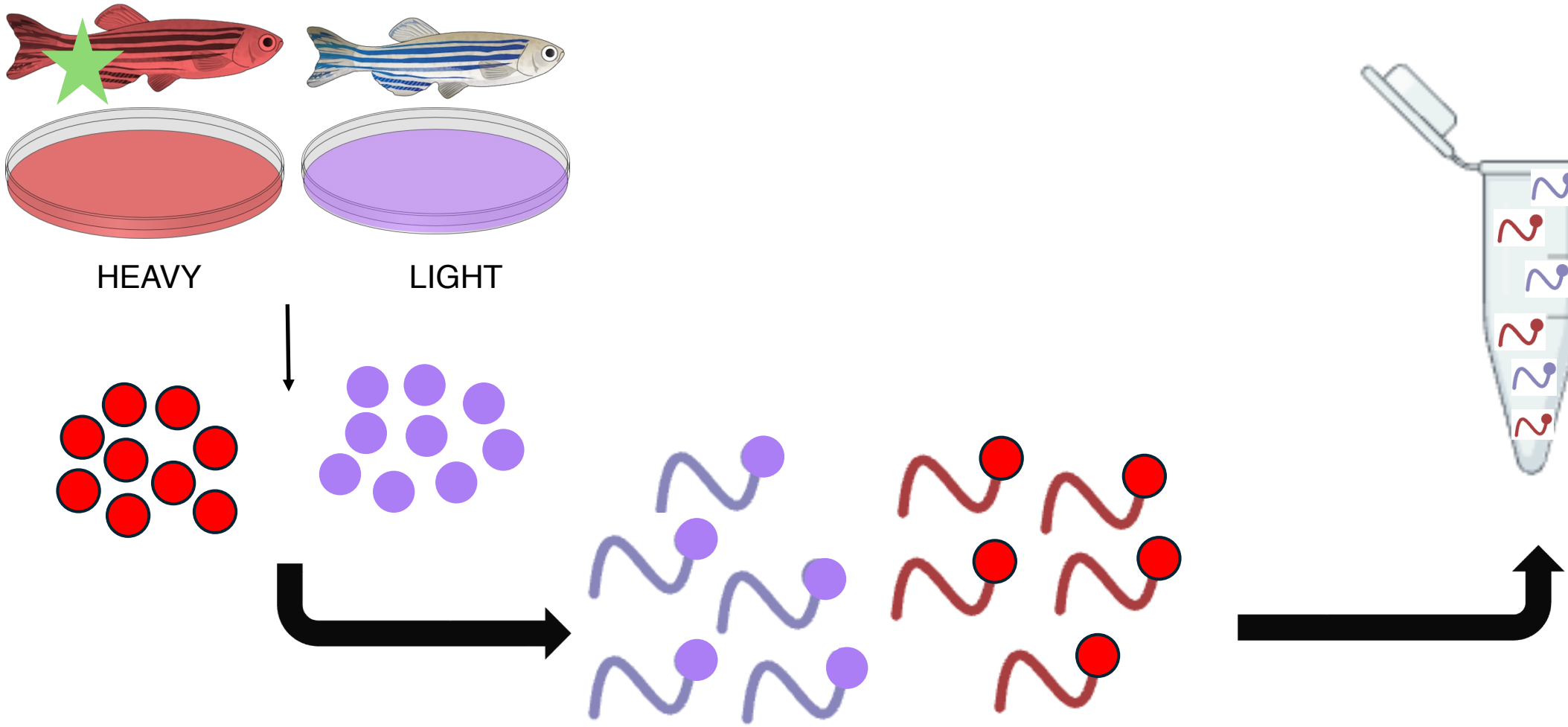
Rationale : Quantifying proteins expressed differently in WT and mutant FAH hepatocytes will allow for more understanding of the proteins involved in increased apoptosis and will allow for studies to be conducted to elucidate treatment options that target the pathways these proteins are involved in.



Hypothesis : Mutant FAH hepatocyte cells will have different protein expressions than WT cells, specifically in proteins that are involved in apoptosis of cells.

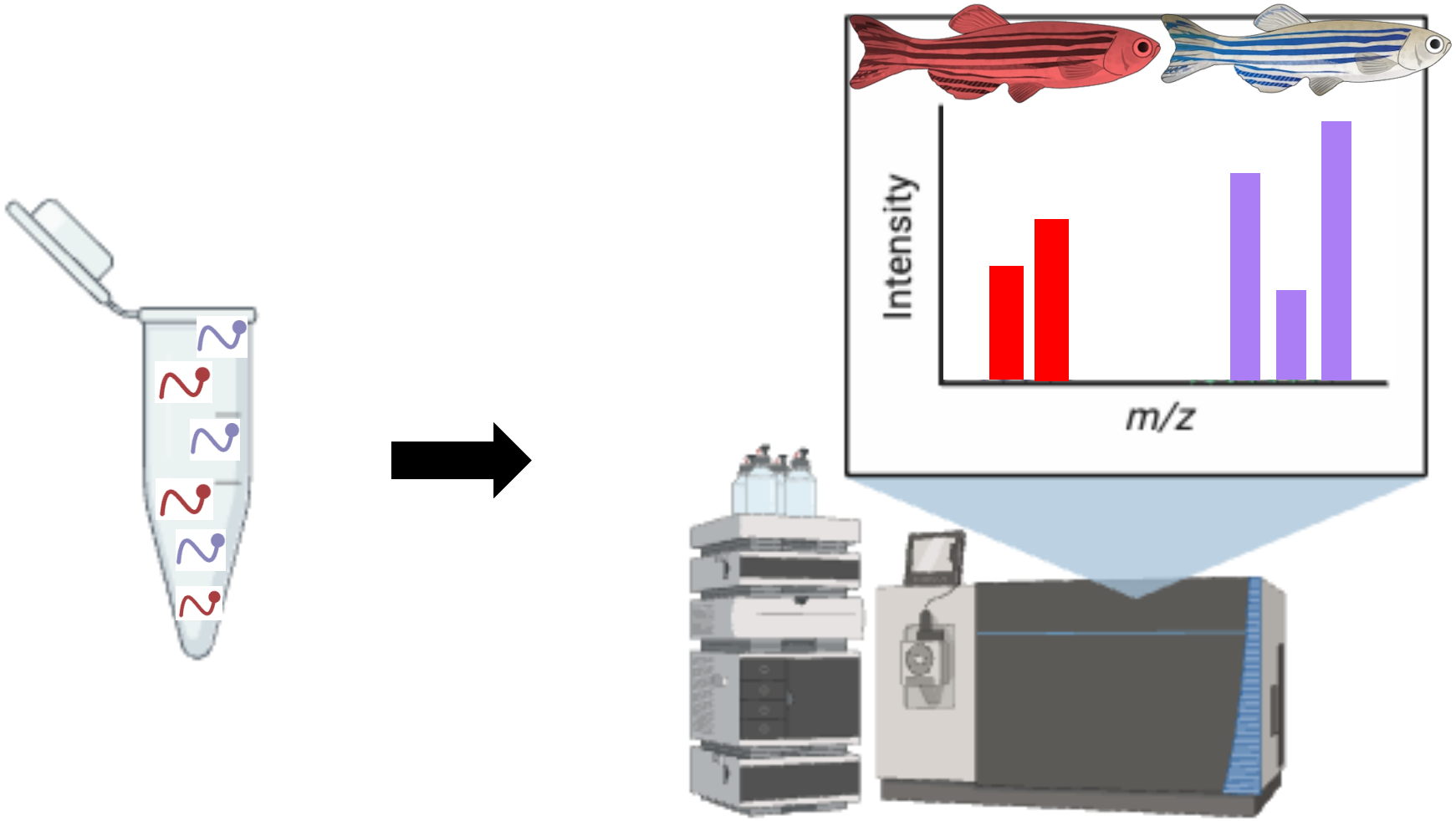
SILAC | LC-MS/MS | CRISPR

Aim 3 : Quantify differentially expressed proteins in WT and mutant FAH hepatocyte cells that lead to apoptosis.



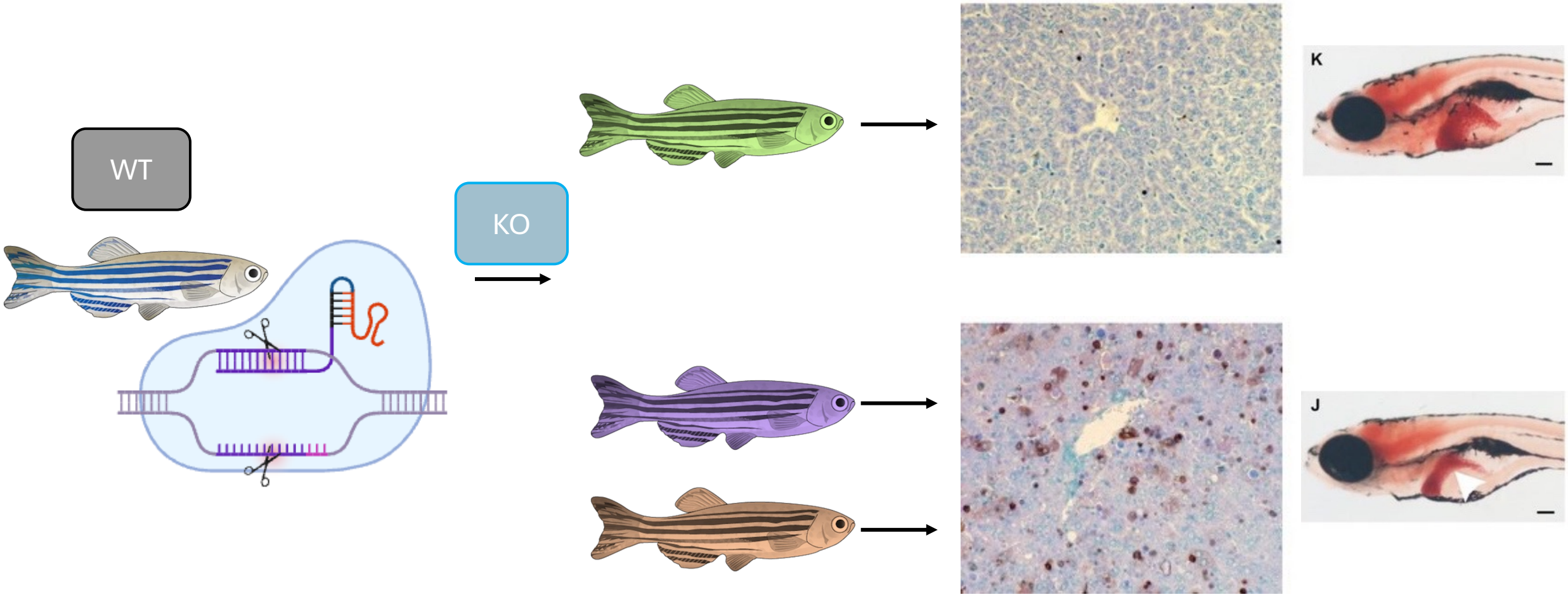
SILAC | **LC-MS/MS** | CRISPR

Aim 3 : Quantify differentially expressed proteins in WT and mutant FAH hepatocyte cells that lead to apoptosis.

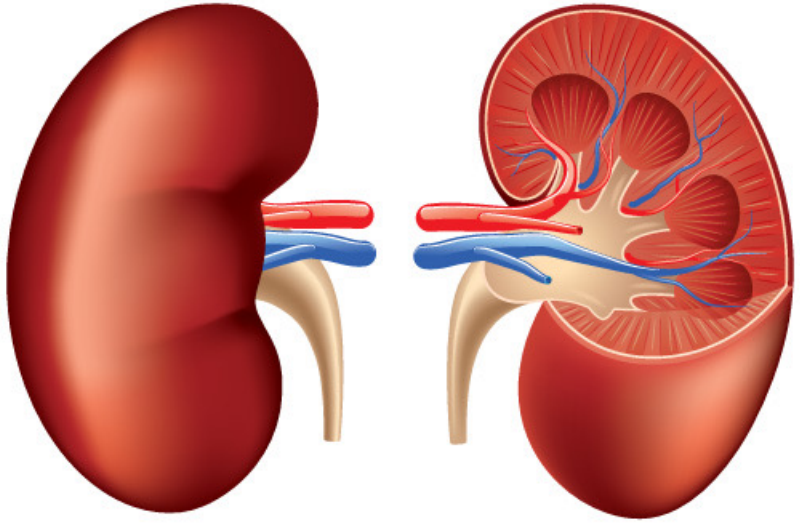


SILAC | LC-MS/MS | CRISPR

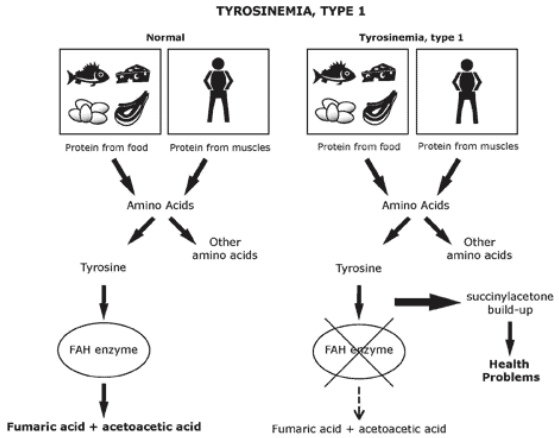
Aim 3 : Quantify differentially expressed proteins in WT and mutant FAH hepatocyte cells that lead to apoptosis.



Future research directions

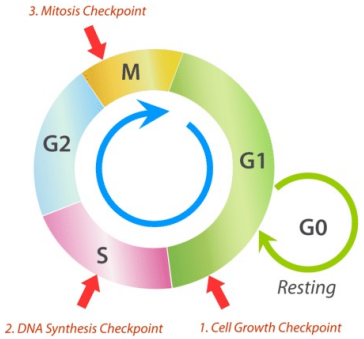


Summary



Tyrosinemia Type 1 is caused by a mutation in the FAH gene, when the enzyme fumarylacetoacetate hydrolase is not present and the body is unable to break down tyrosine, leading to buildup and health issues.

The FAH gene is very well conserved across many organisms, indicating it's evolutionary importance in function, which can best be modeled in zebrafish due to it's transparency and similarities to human function.



Researching increased liver apoptosis in zebrafish will allow for much more to be known about this disorder and the causes of it, hopefully leading to new treatment options.

References

Arranz JA, Pinol F, Kozak L, Perez-Cerda C, Cormand B, Ugarte M, Riudor E. Splicing mutations, mainly IVS6-1(G>T), account for 70% of fumarylacetoacetatehydrolase (FAH) gene alterations, including 7 novel mutations, in a survey of 29tyrosinemia type I patients. Hum Mutat. 2002 Sep;20(3):180-8. doi: 10.1002/humu.10084. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/122039 90)

Priestley, J. R. C., Alharbi, H., Callahan, K. P., Guzman, H., Payan-Walters, I., Smith, L., Ficicioglu, C., Ganetzky, R. D., & Ahrens-Nicklas, R. C. (2020). The Importance of Succinylacetone: Tyrosinemia Type I Presenting with Hyperinsulinism and Multiorgan Failure Following Normal Newborn Screening. *International journal of neonatal screening*, *6*(2), 39. https://doi.org/10.3390/ijns6020039

National Organization for Rare Disorders. (2023b, November 20). *Tyrosinemia type 1 - Symptoms, causes, treatment | NORD*. https://rarediseases.org/rare-diseases/tyrosinemia-type-1/

https://medicine.wustl.edu/news/study-reveals-links-between-fatty-liver-disease-liver-cancer/

https://www.sciencedirect.com/science/article/pii/S0166445X1730317X?via%3Dihub#fig0015
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3870180/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303001/

Elmore SA. 2007. Apoptosis: A review of programmed cell death. Toxicol Pathol 35:495-516. Abstract: https://www.ncbi.nlm.nih.gov/pubmed/17562483

https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=4762709_nihms758155f5.jpg