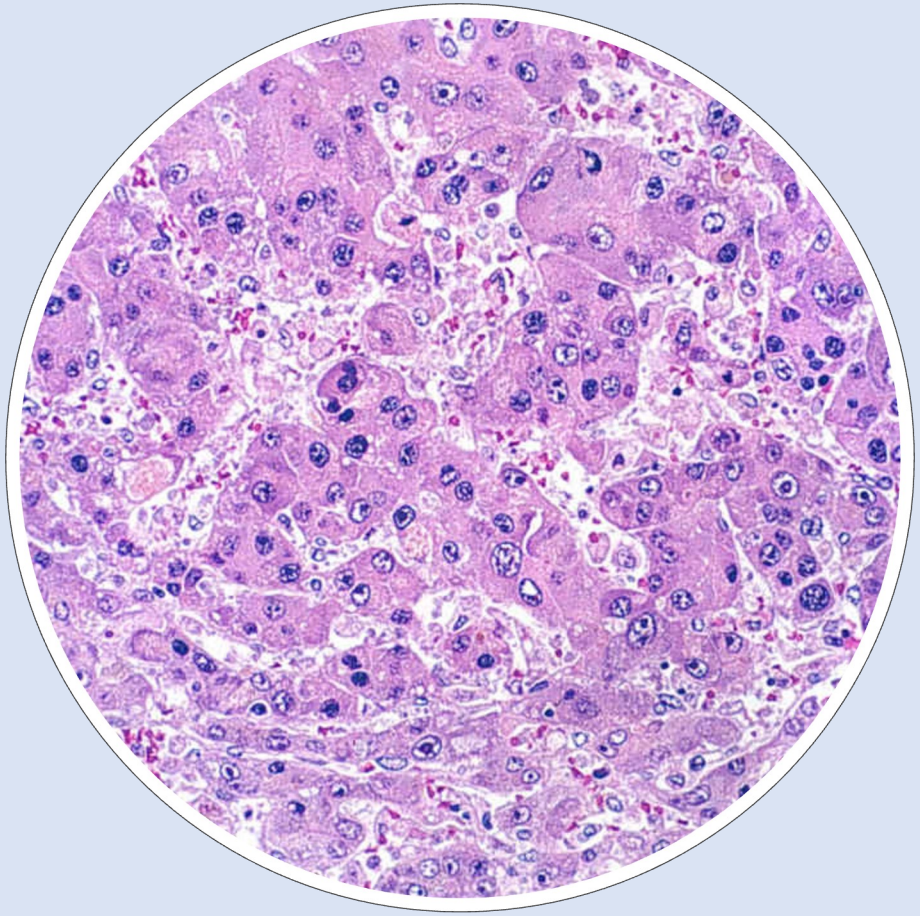
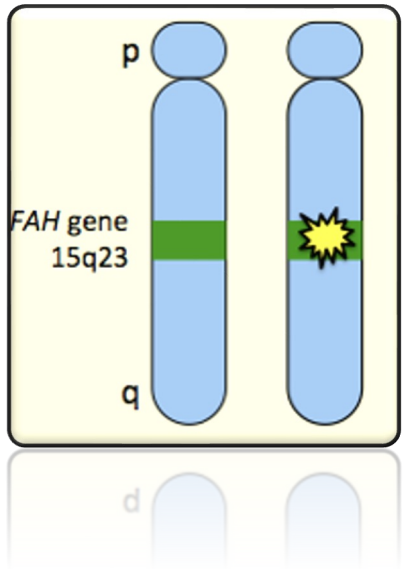
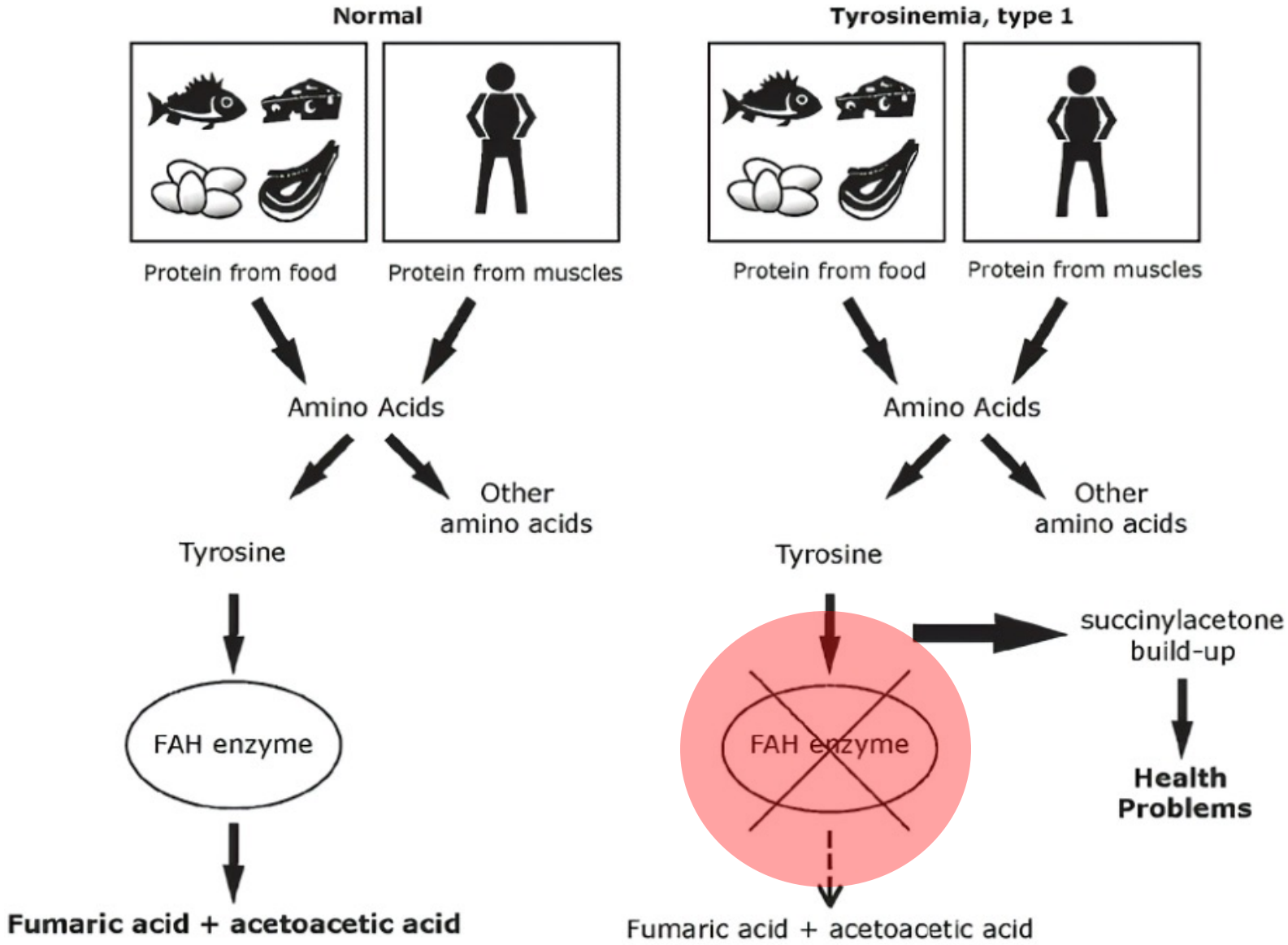
Tyrosinemia Type 1

Brooke Fuerstenau

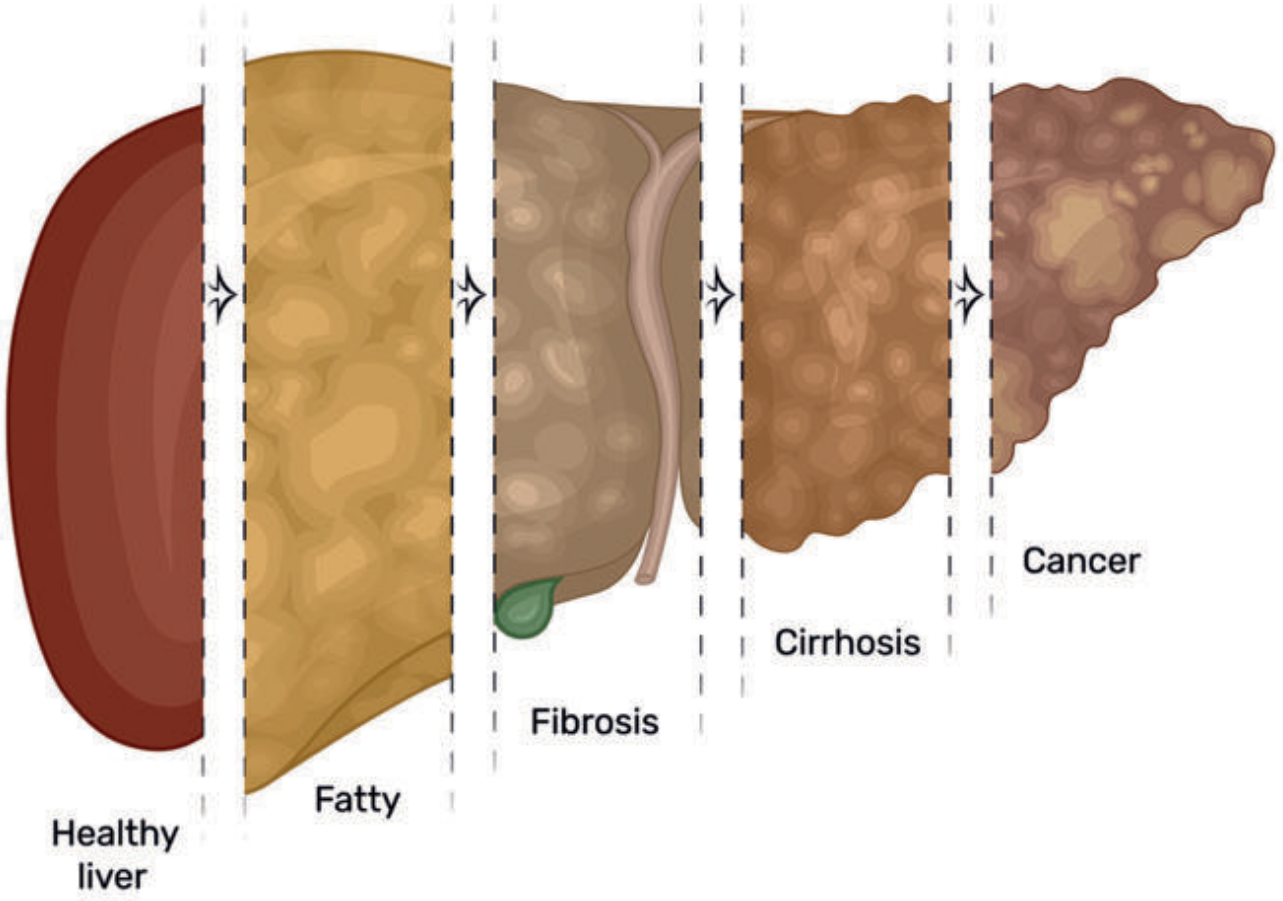


What is Tyrosinemia Type 1?

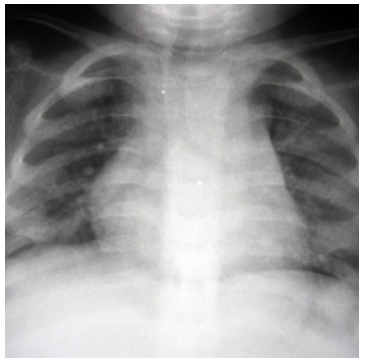


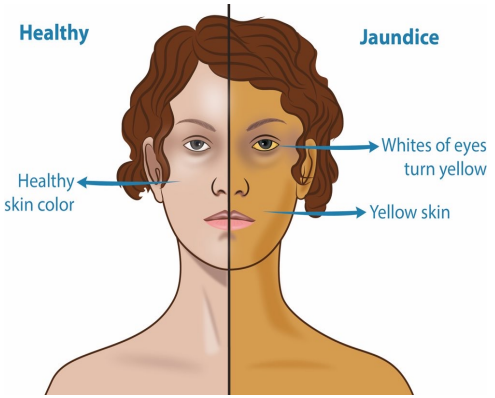


Symptoms and Signs

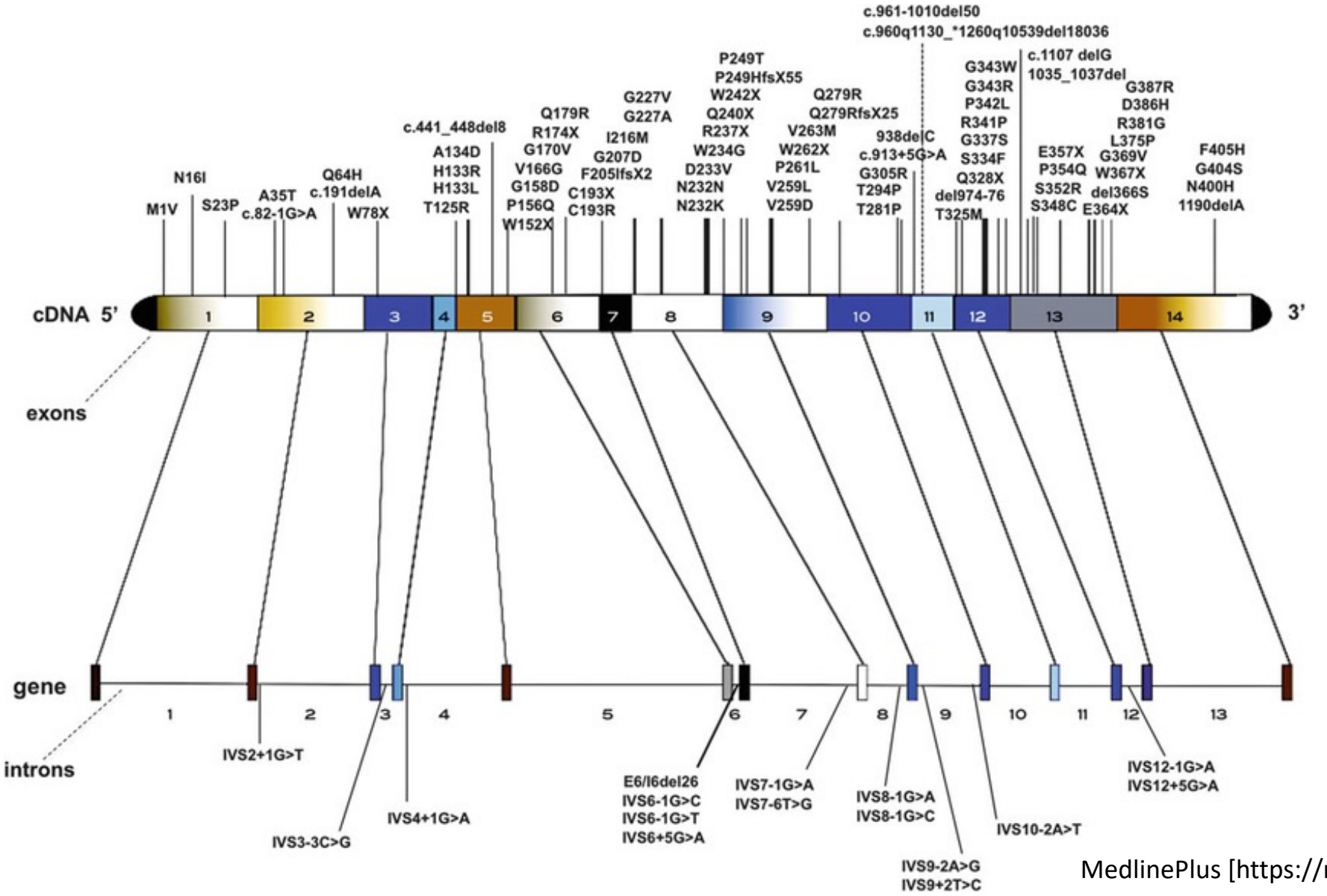


National Organization for Rare Disorders [2023]





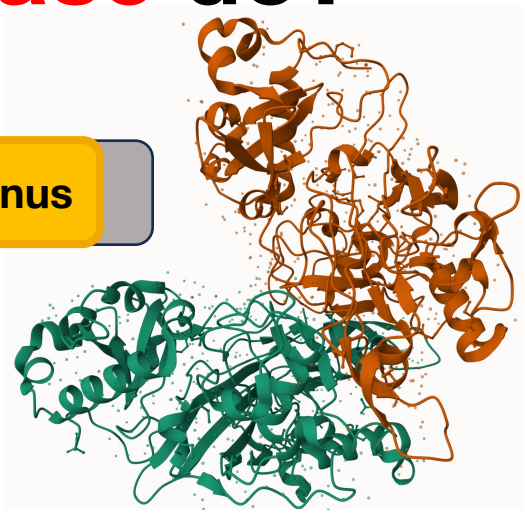
What is the FAH gene?



- Encodes for the enzyme fumarylacetoacetase hydrolase
- Enzyme found in liver and kidneys
- Enzyme used to break down tyrosine (amino acid)

MedlinePlus [https://medlineplus.gov/download/genetics/gene/fah.pdf]

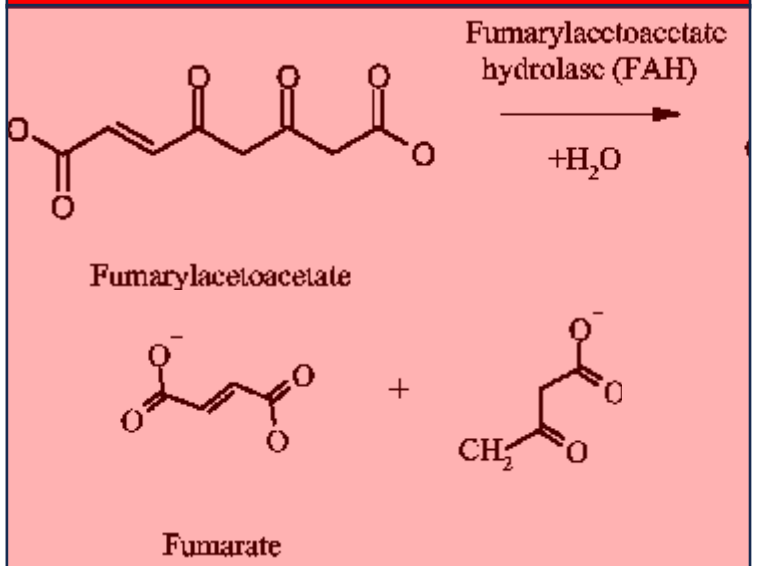
What does fumarylacetoacetase hydrolase do?



Human

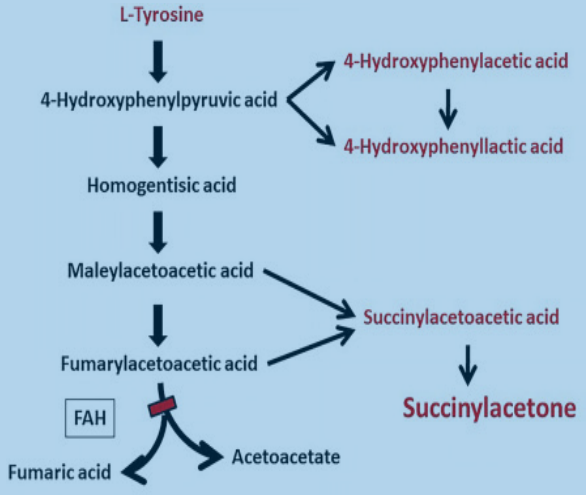
Gene Ontology

MOLECULAR FUNCTION



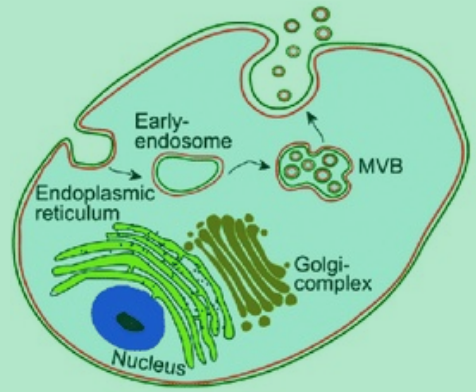
Catalytic activity

BIOLOGICAL PROCESS



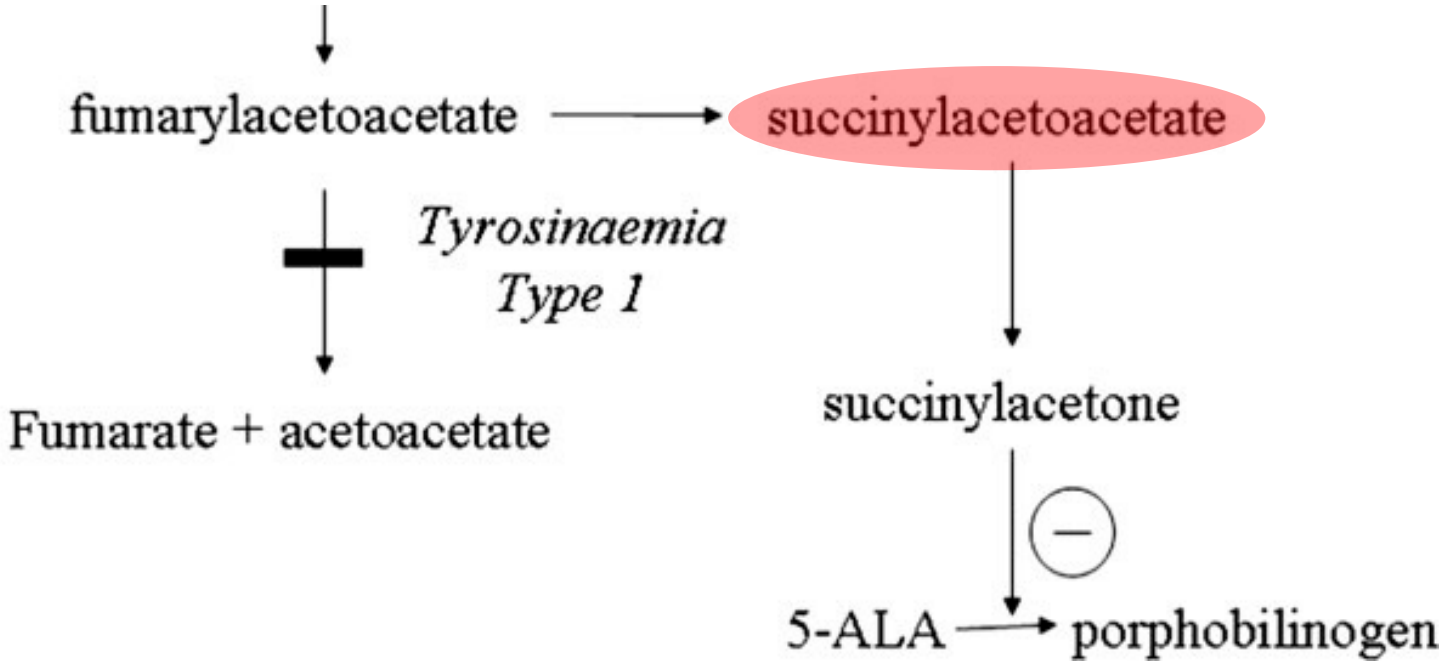
Tyrosine metabolism

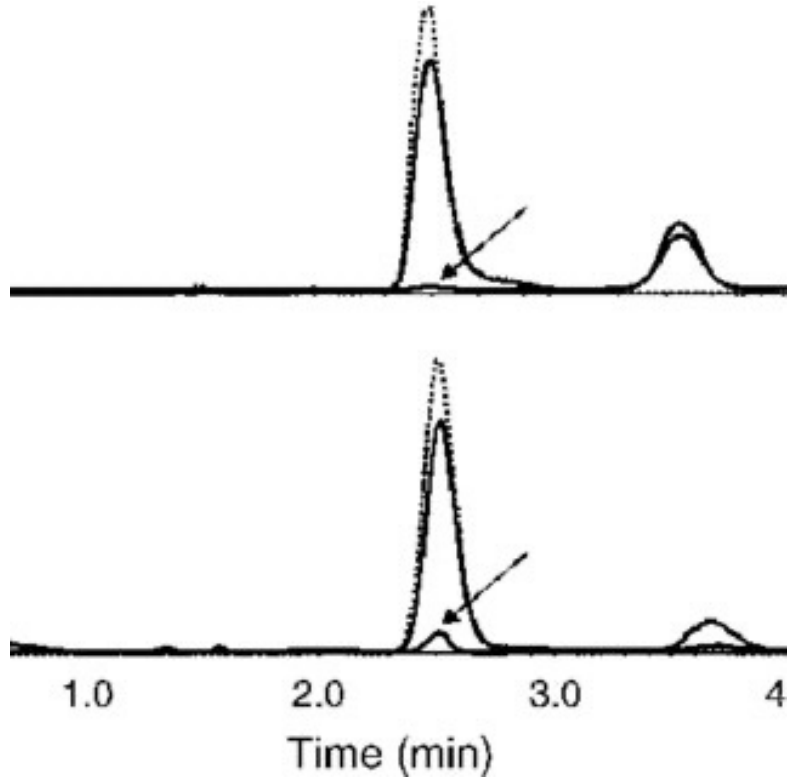
CELLULAR COMPONENT



Extracellular exosome

What happens when fumarylacetoacetase hydrolase is not present?

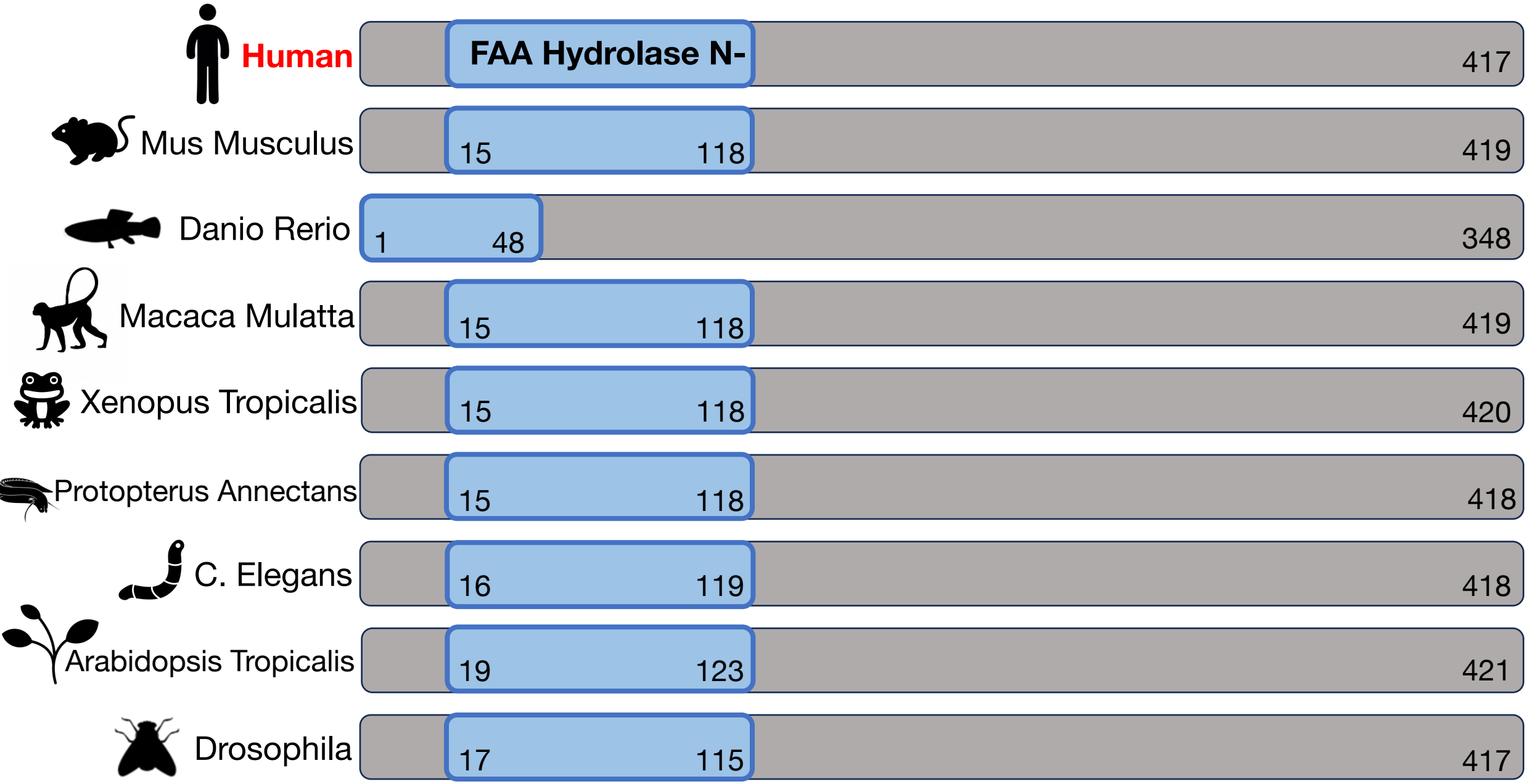




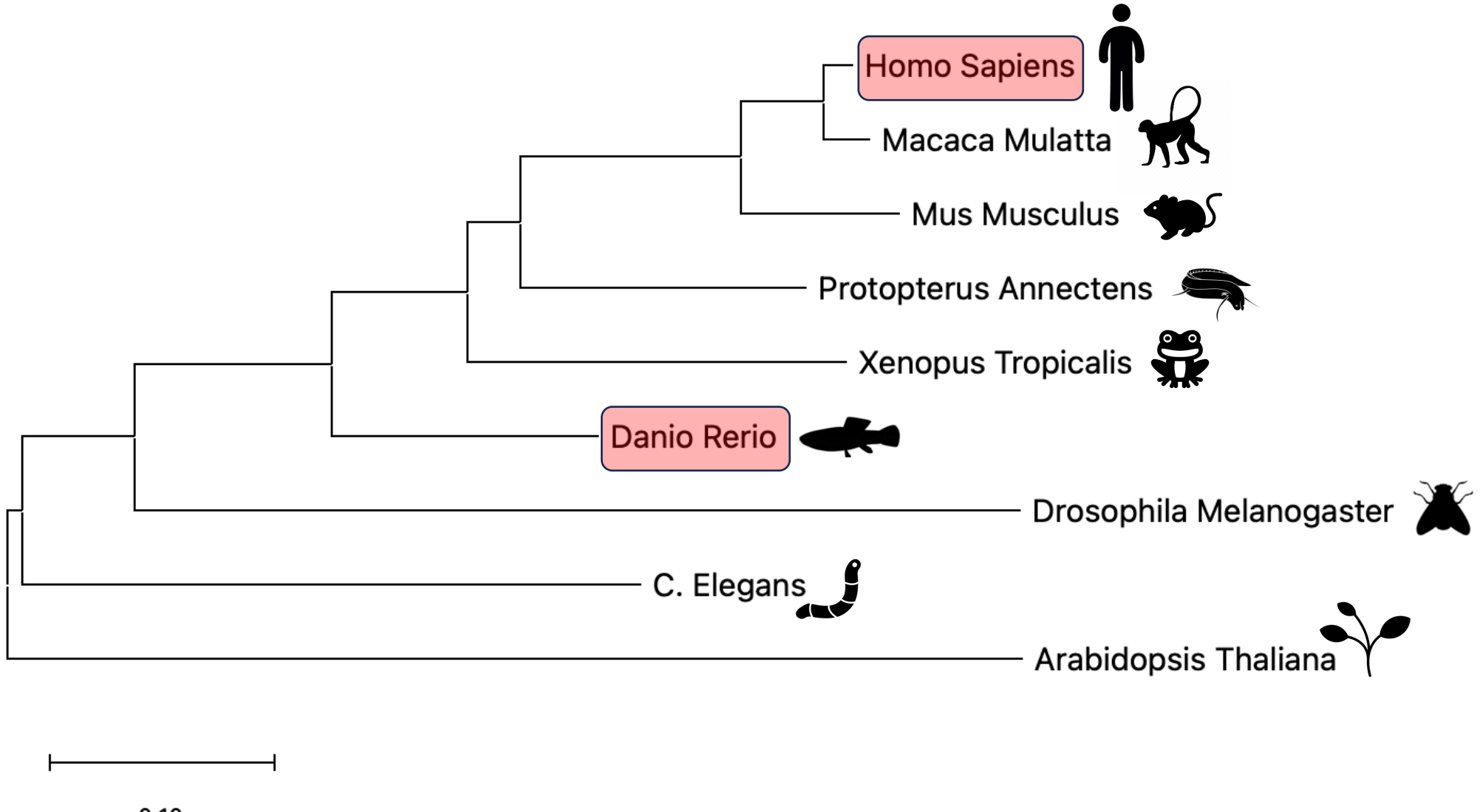
** detection in blood spots and urine tests

Priestly Et al. [2020]

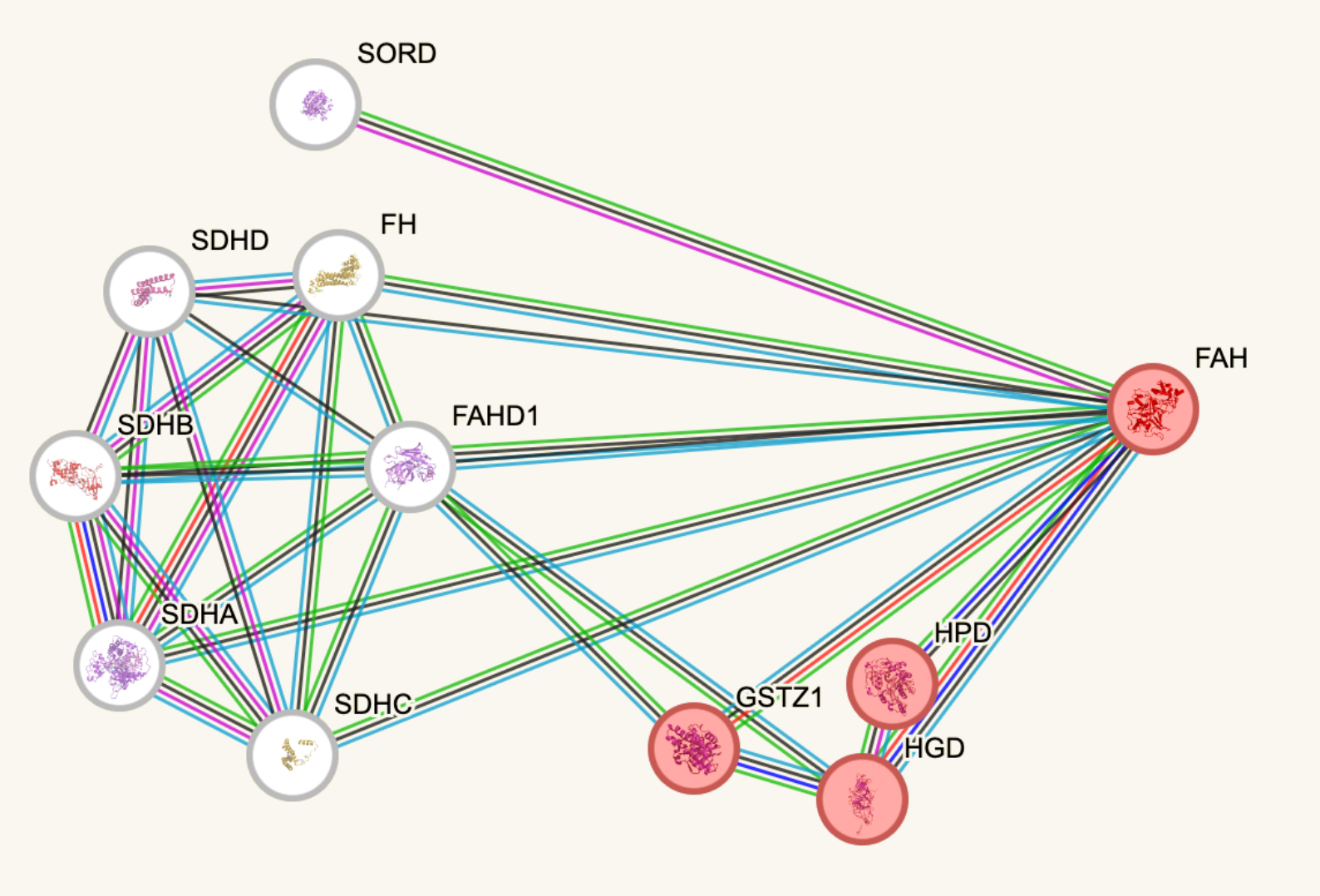
How well conserved is the FAA enzyme across organisms?



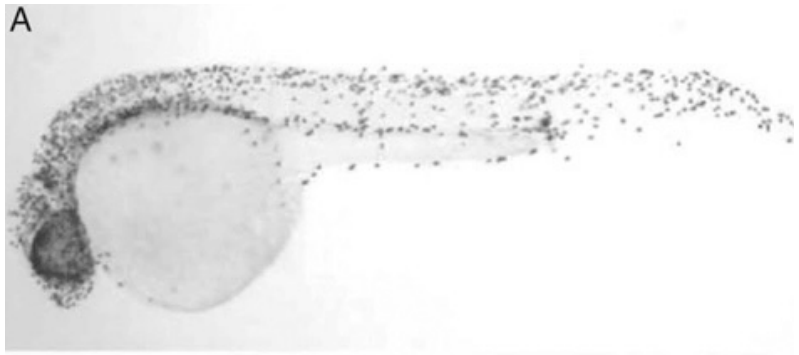
Phylogenetic Tree

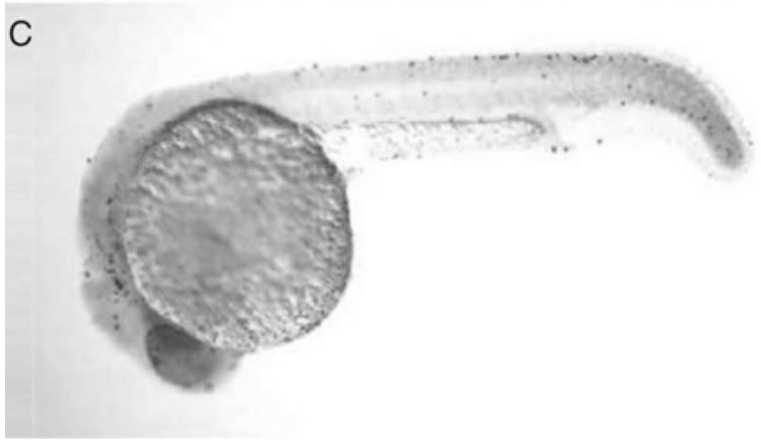


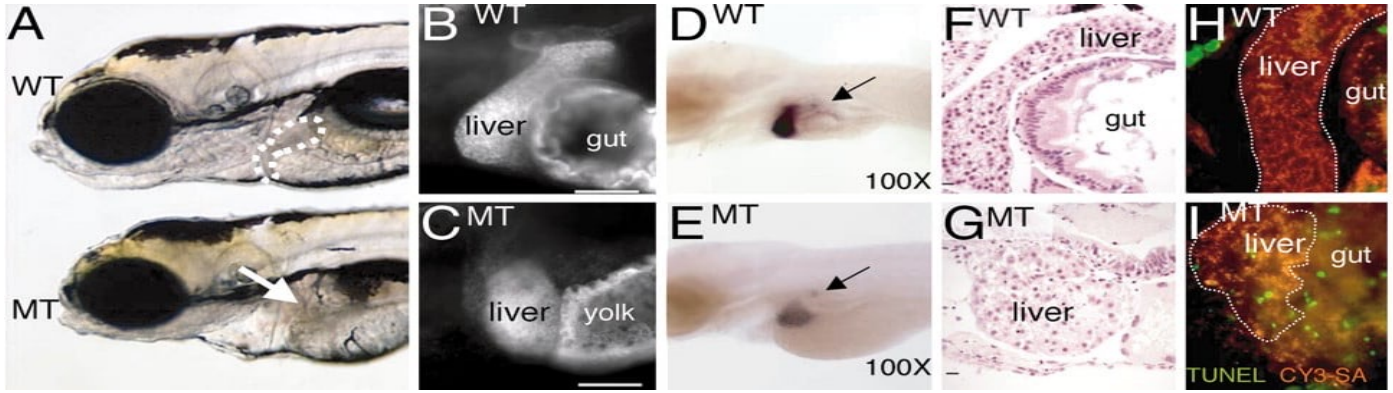
Protein interaction network



What model organism can best represent Tyrosinemia?





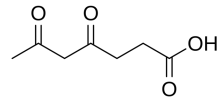


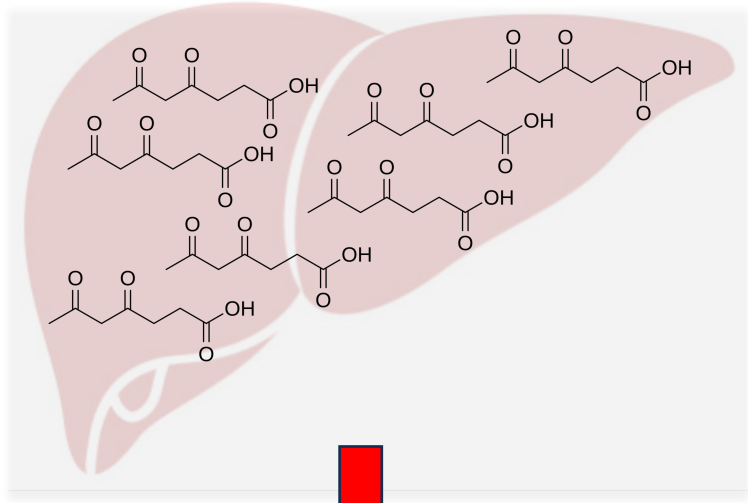
Danio Rerio

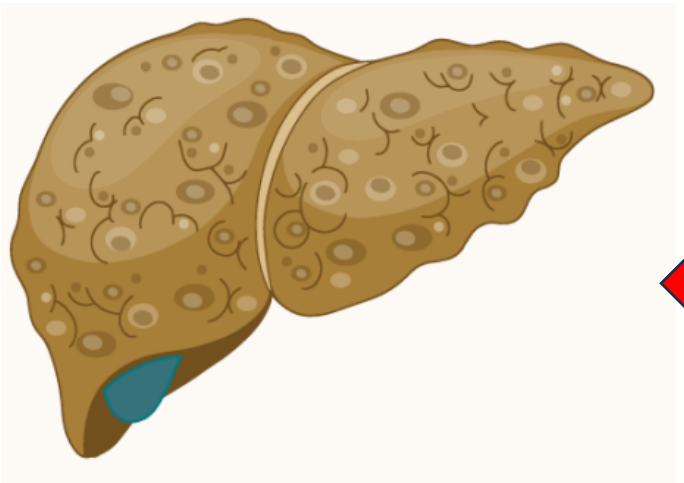
What is the gap in knowledge?

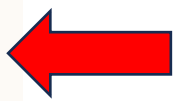
Tyrosine → 4 Fumarylacetoacetate → FAH →

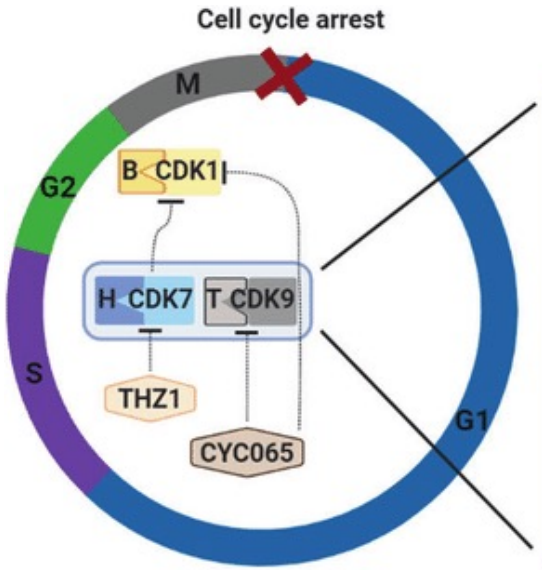
Succinylacetone

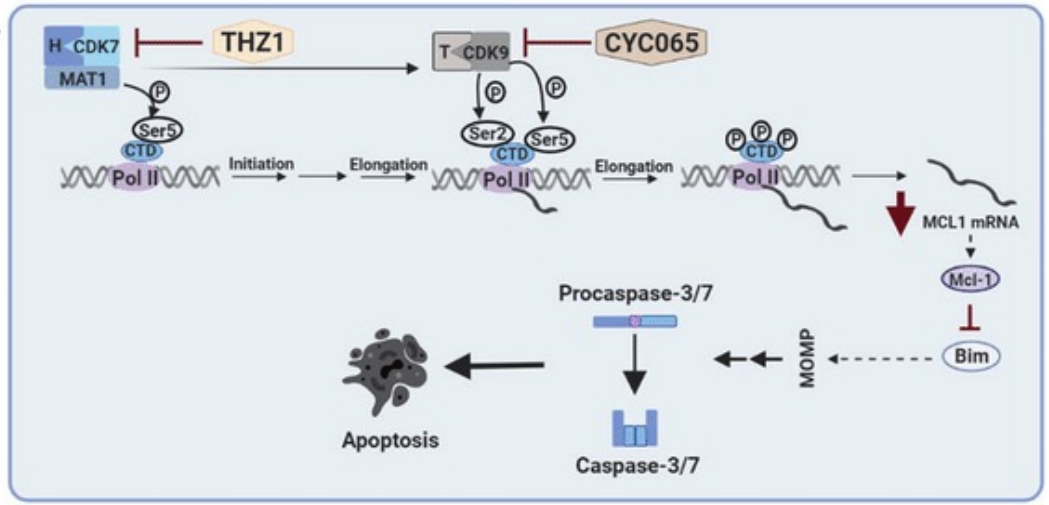




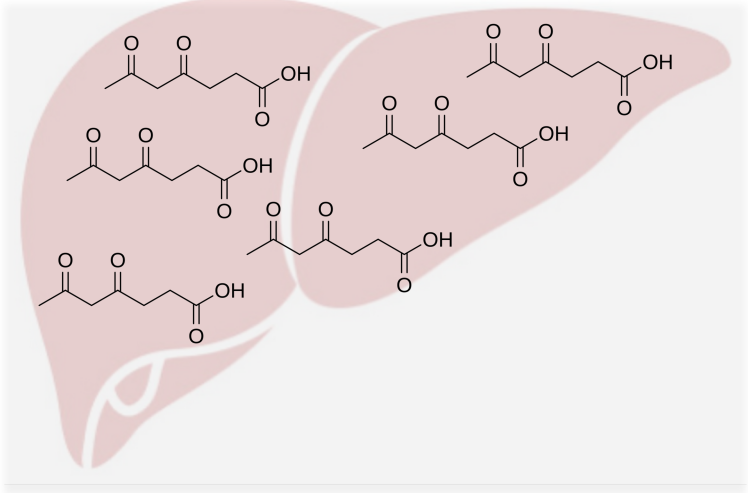


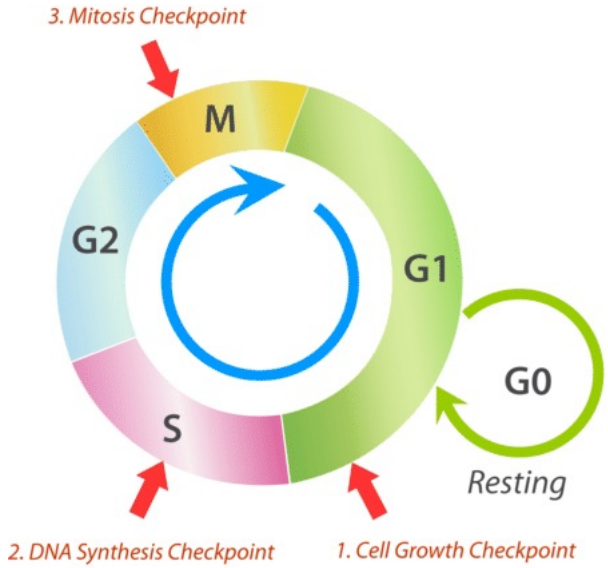






What is the primary goal of this research?

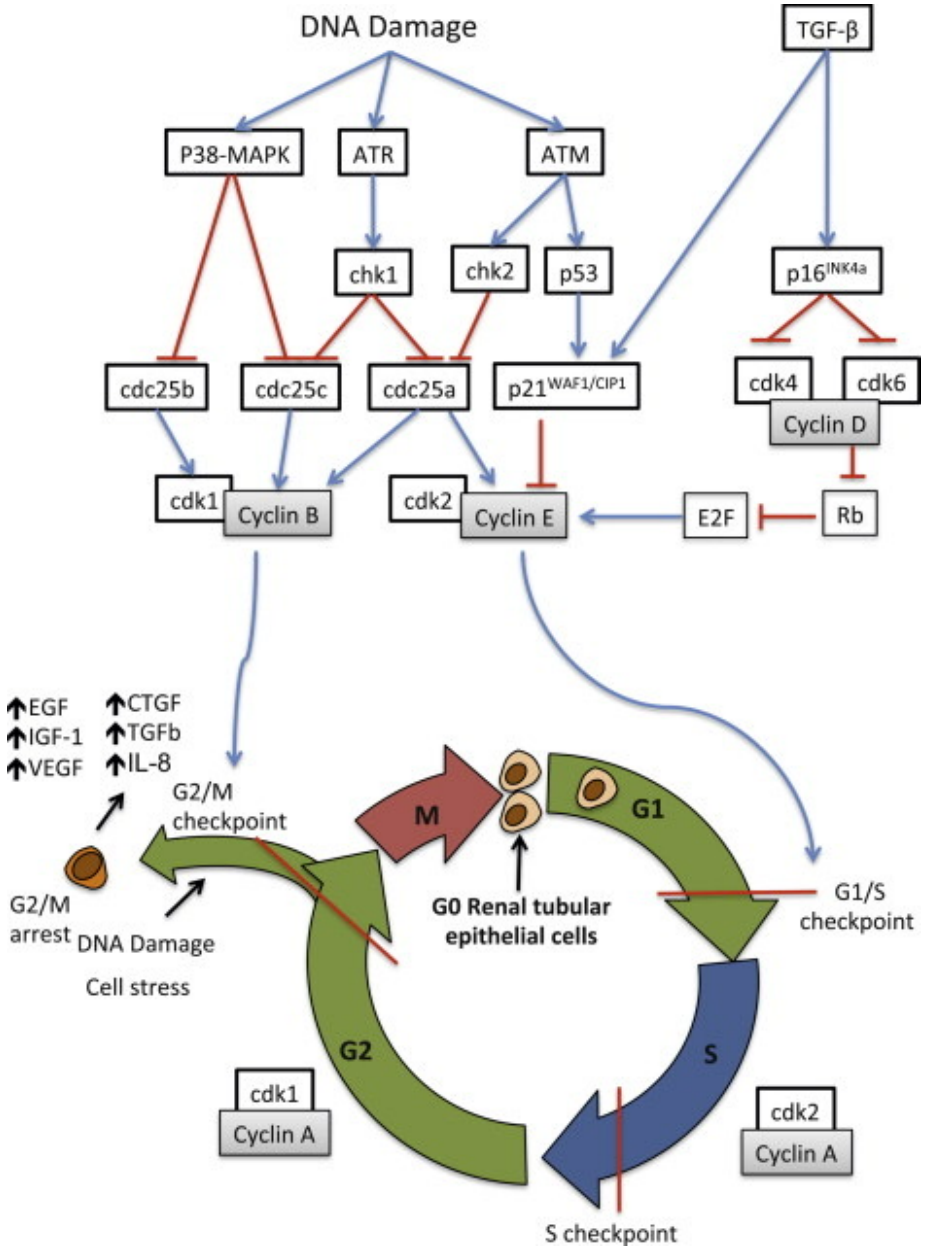




HYPOTHESIS

Excess succinylacetoacetate disrupts a pathway present in a normal functioning liver, causing hepatocyte cells to be stalled in the cell cycle, leading to increased apoptosis and in turn, cirrhosis of the liver

Aim 1 : Identify amino acids important for cell cycle arrest in the liver.



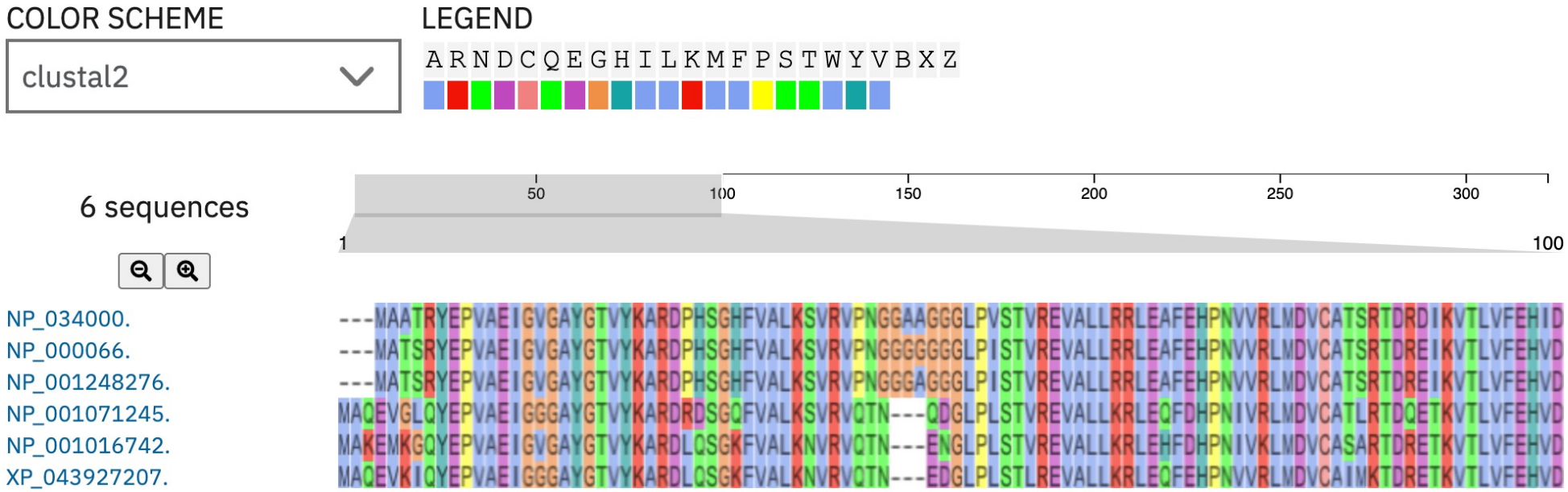
	Species	Gene	Architecture	aa
☐	*Homo sapiens* human	CDK4 cyclin dependent kinase 4		303
☐	*Mus musculus* house mouse	Cdk4 cyclin dependent kinase 4		303
☐	*Rattus norvegicus* Norway rat	Cdk4 cyclin-dependent kinase 4		303
☐	*Danio rerio* zebrafish	cdk4 cyclin dependent kinase 4		297
☐	*Bos taurus* cattle	CDK4 cyclin dependent kinase 4		303
☐	*Macaca mulatta* Rhesus monkey	CDK4 cyclin dependent kinase 4		303
☐	*Pan troglodytes* chimpanzee	CDK4 cyclin dependent kinase 4		303
☐	*Canis lupus familiaris* dog	CDK4 cyclin dependent kinase 4		303
☐	*Sus scrofa* pig	CDK4 cyclin dependent kinase 4		303
☐	*Xenopus tropicalis* tropical clawed frog	cdk4 cyclin-dependent kinase 4		319

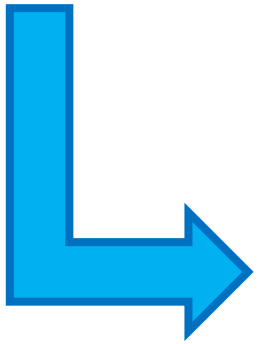
Cyclin D (cdk4 and cdk6)

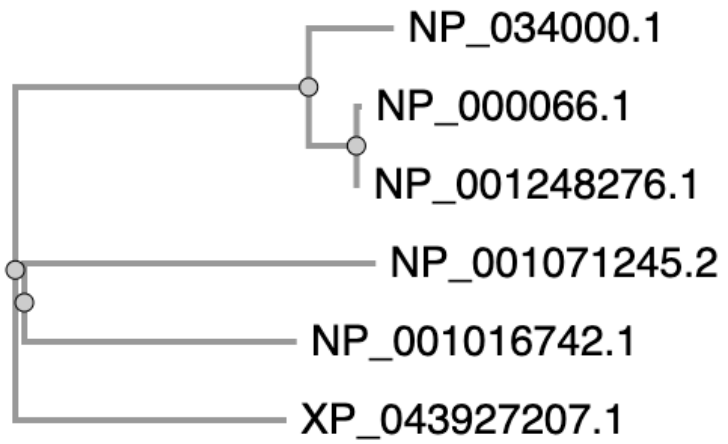
repeat

RB, p53, E2F

Aim 1 : Identify amino acids important for cell cycle arrest in the liver.



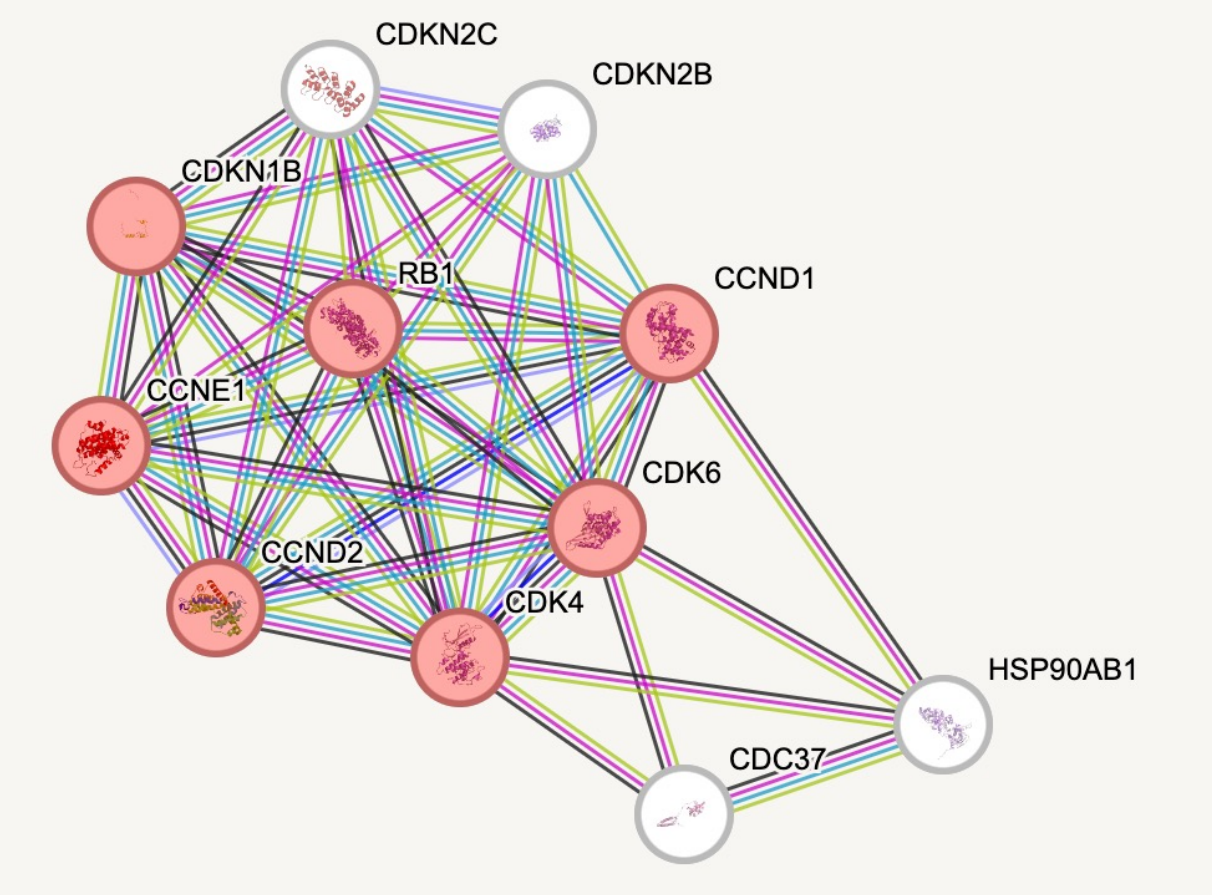




Aim 1 : Identify amino acids important for cell cycle arrest in the liver.

UniProt

InterPro



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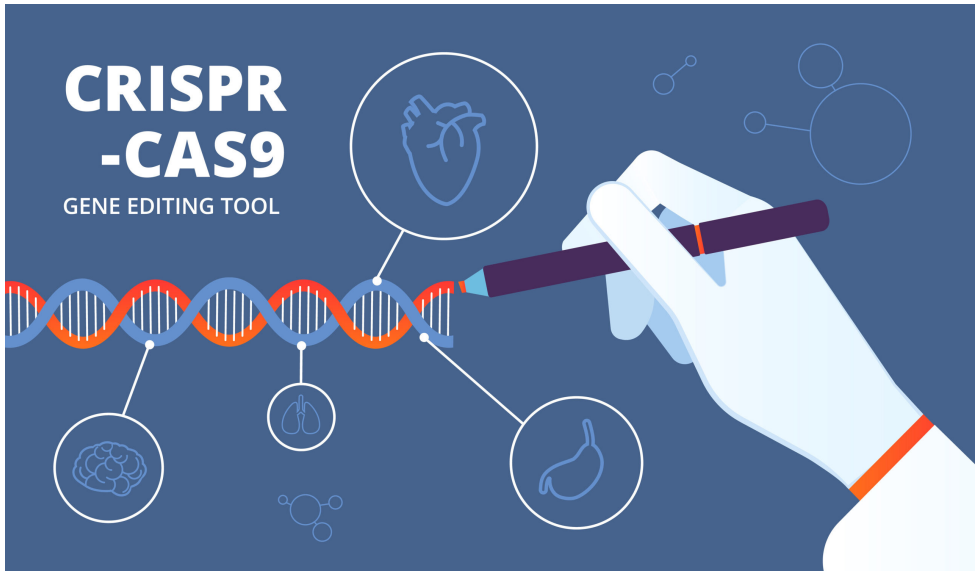
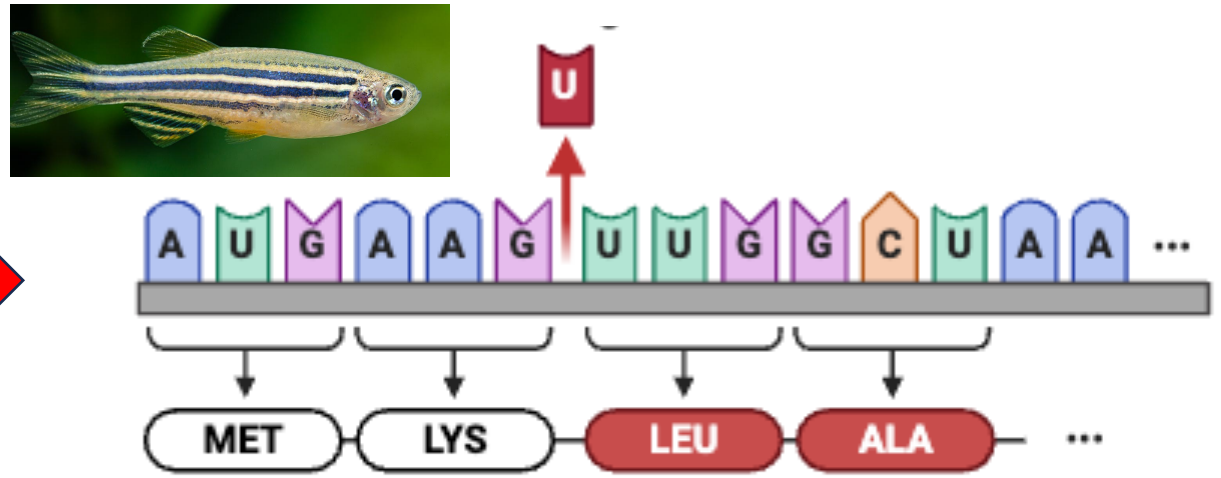
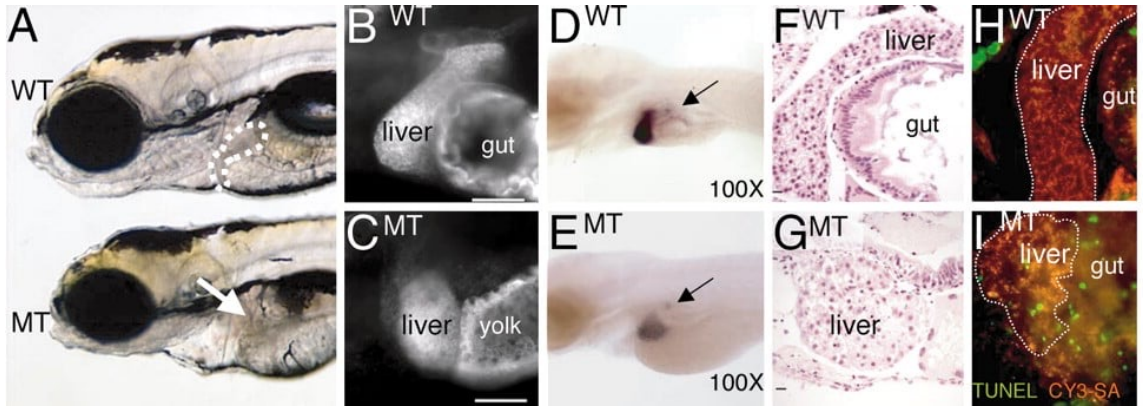
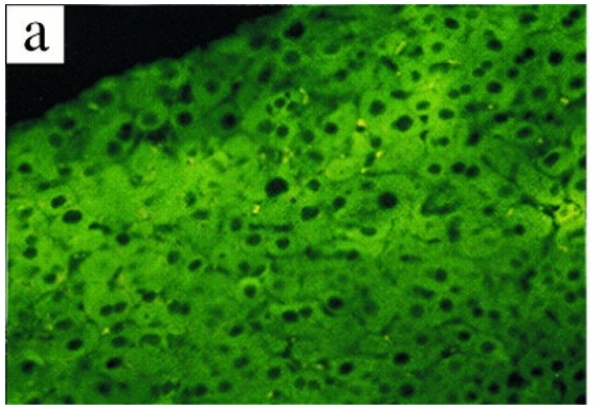
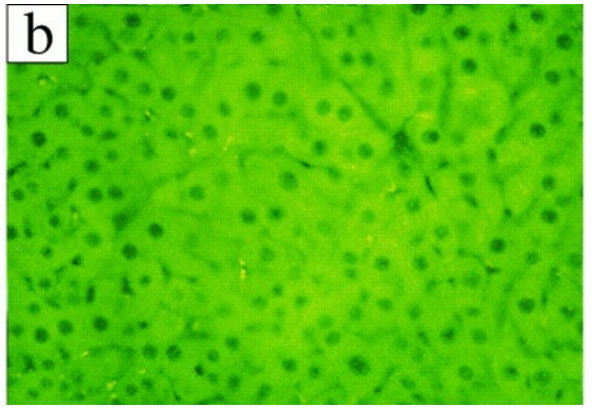




Observe phenotypic differences between WT and mutant







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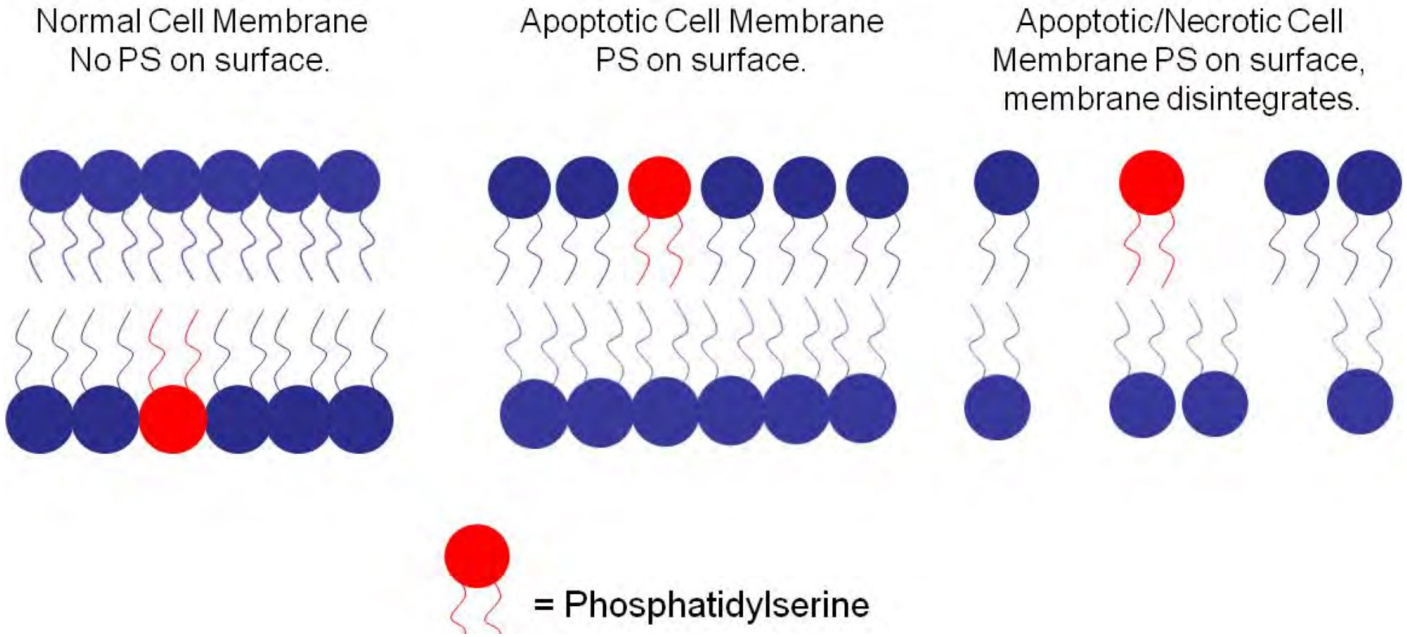
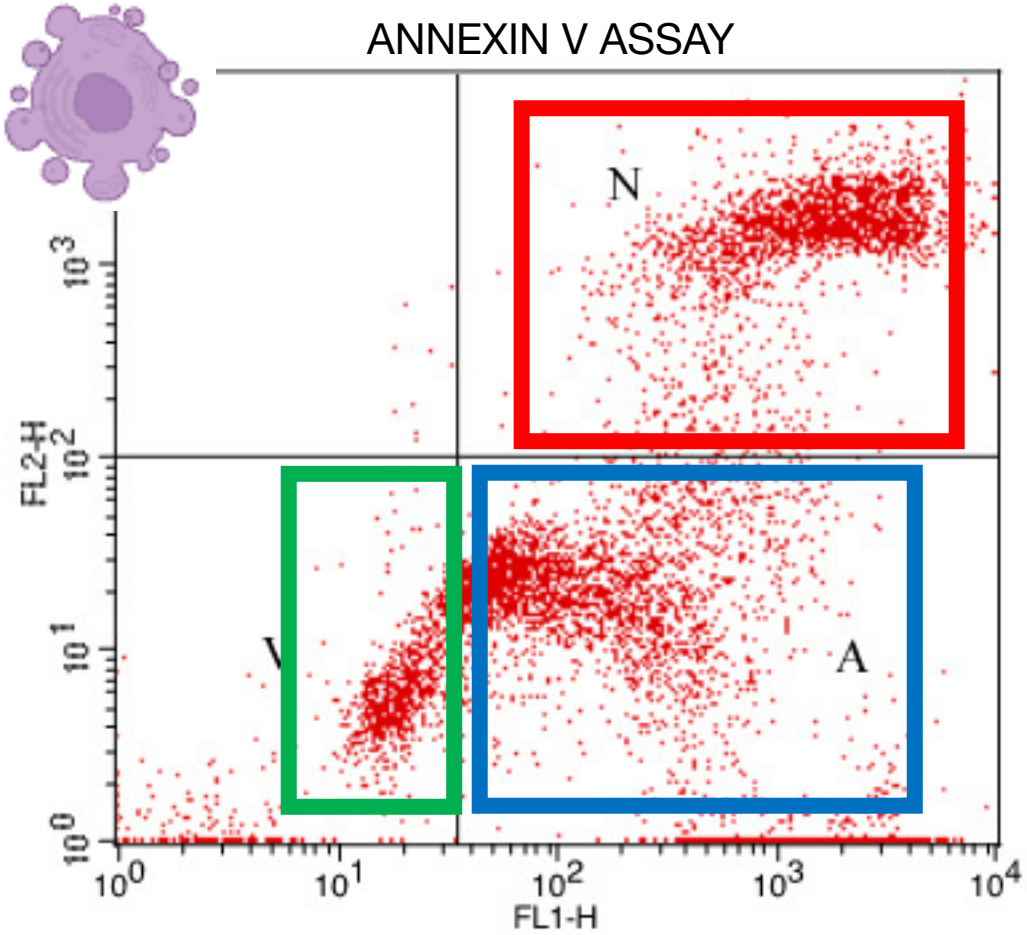


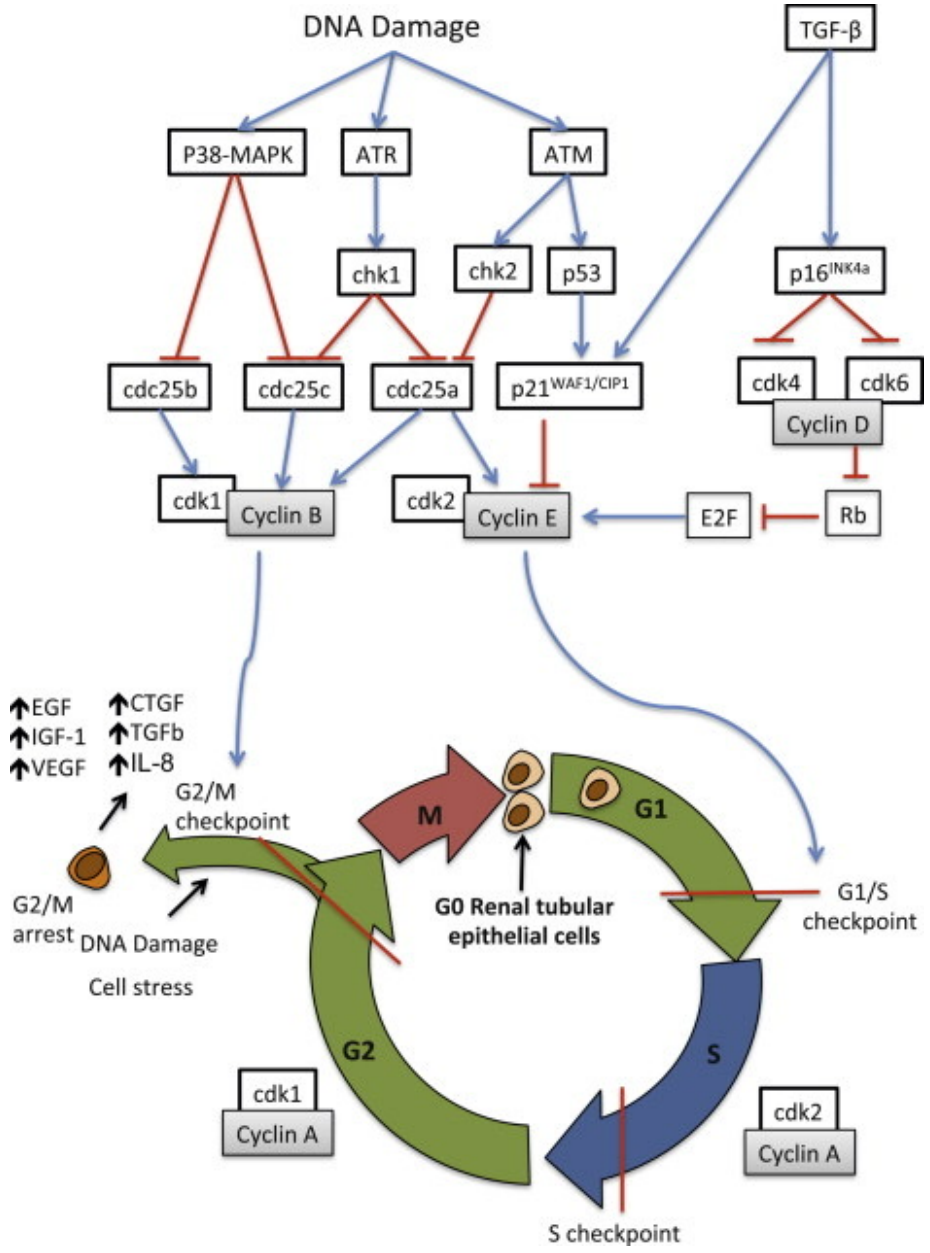


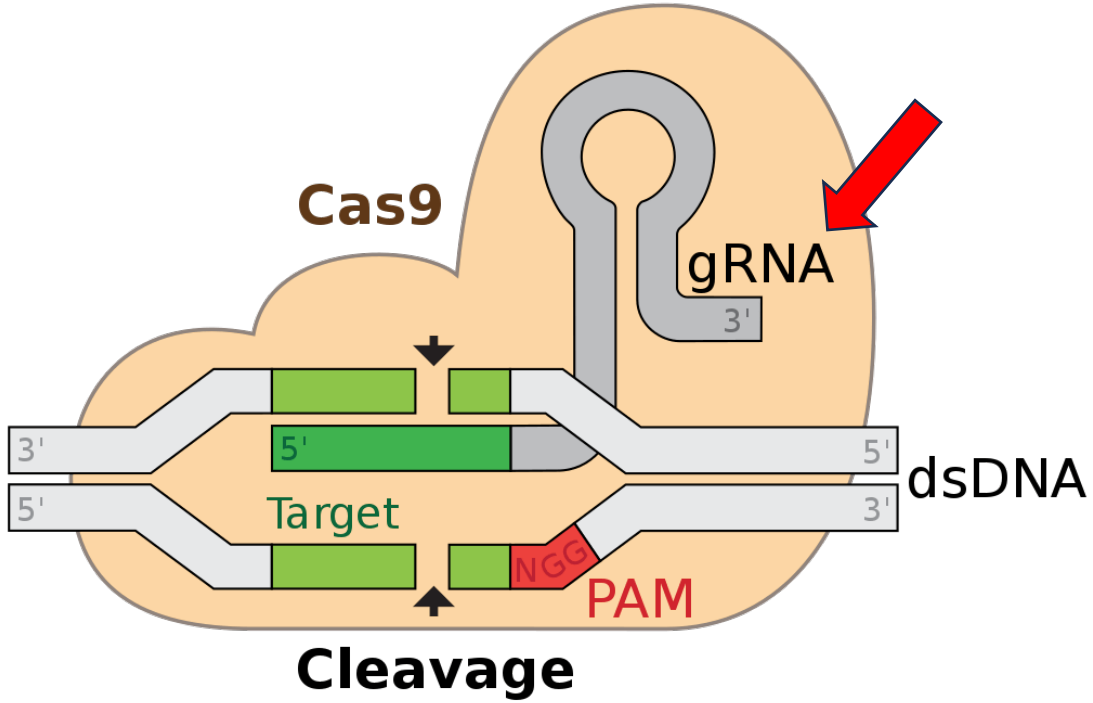
live cells

early apoptotic cells

late apoptotic cells

Aim 2 : Identify genes important for cell cycle regulation in the liver in zebrafish.





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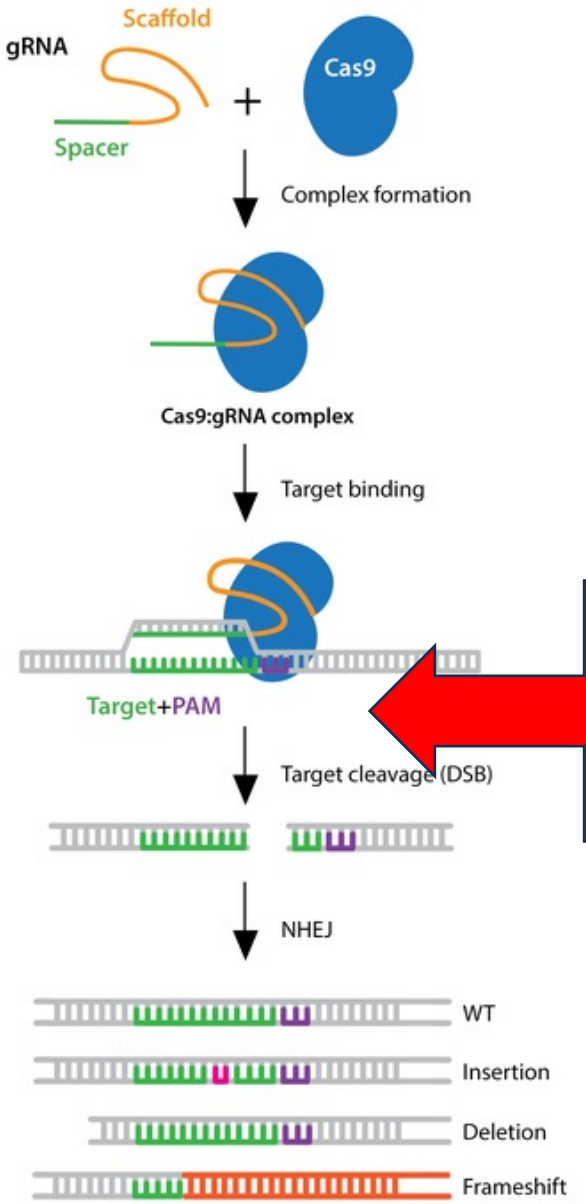
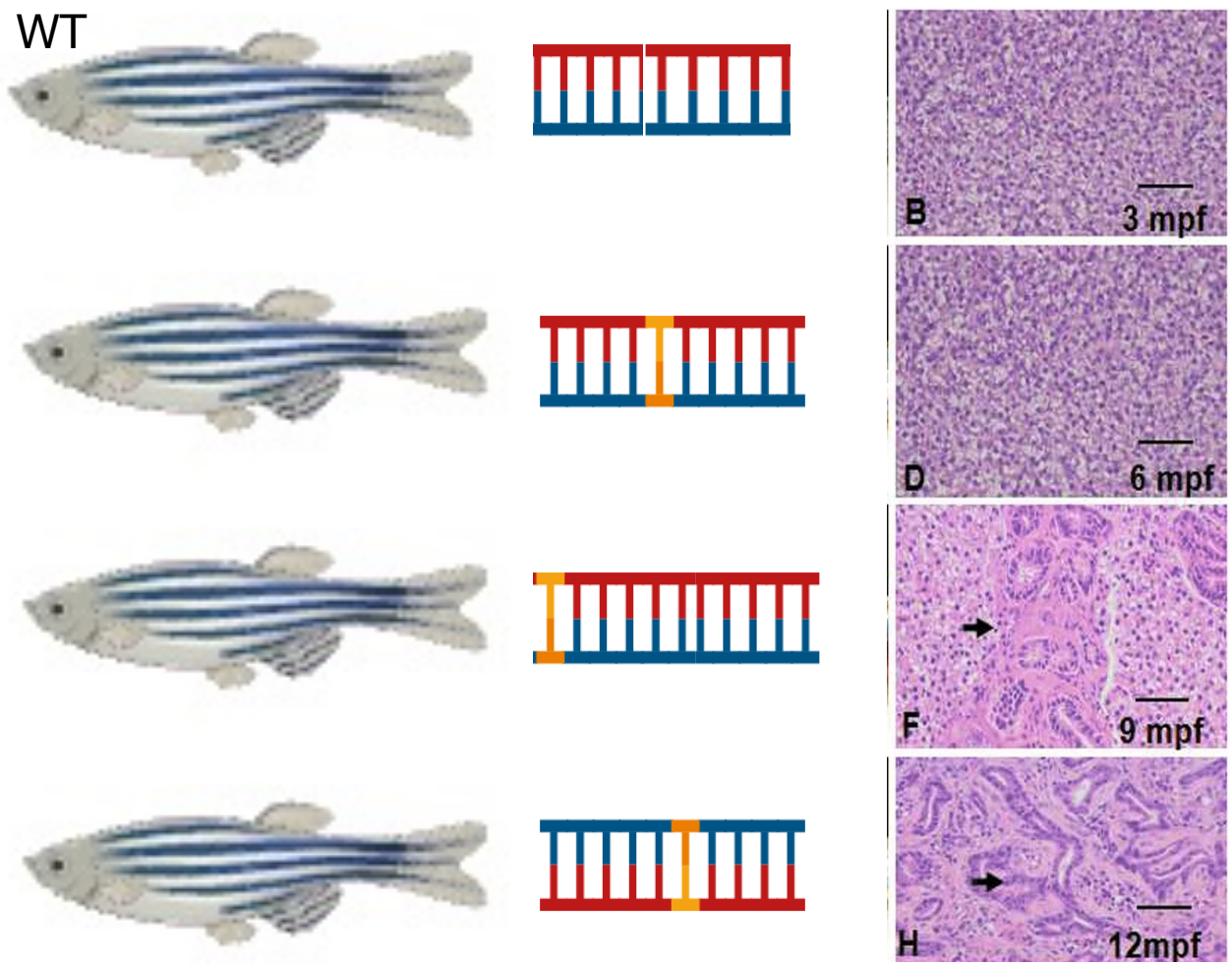


Mutagenesis of identified genes by gRNAs in zebrafish



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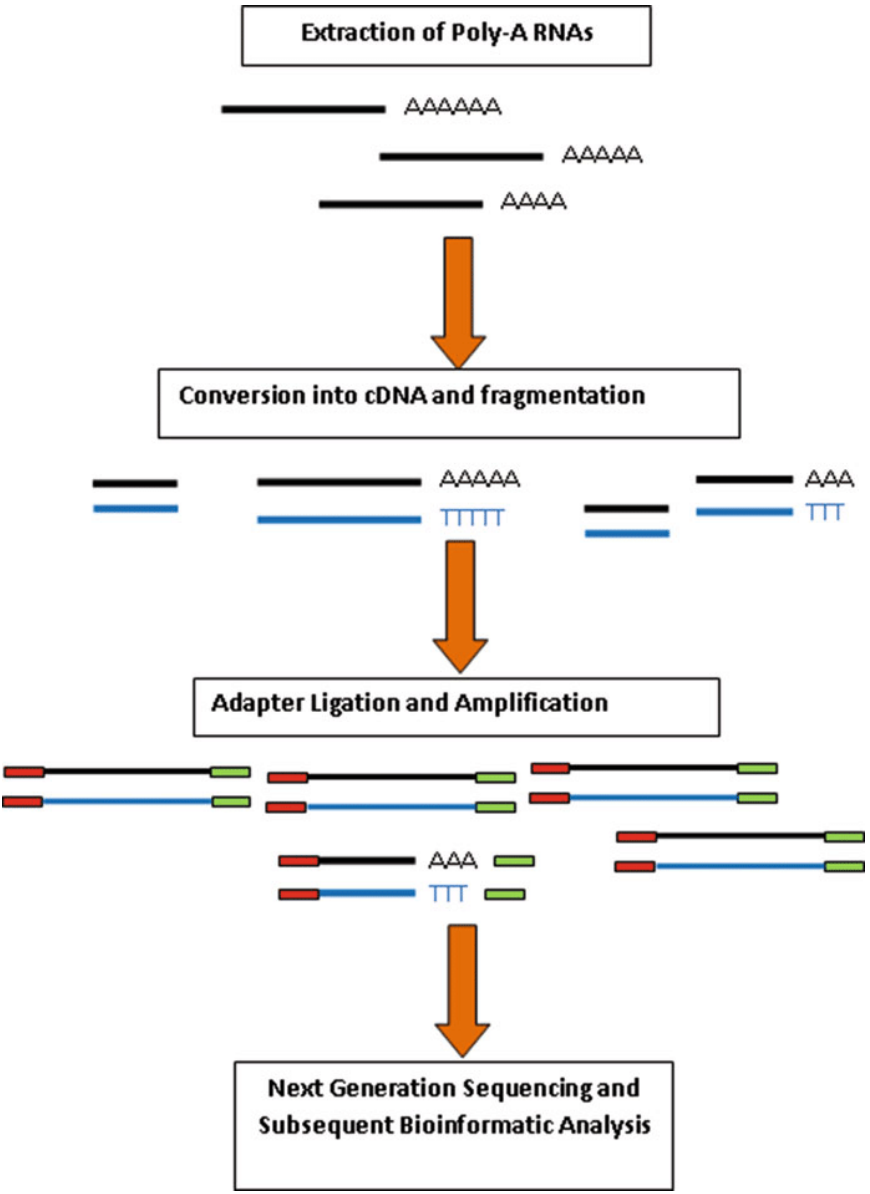
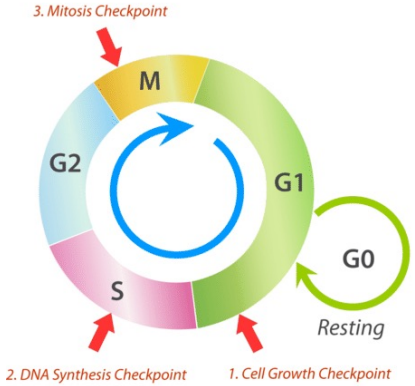
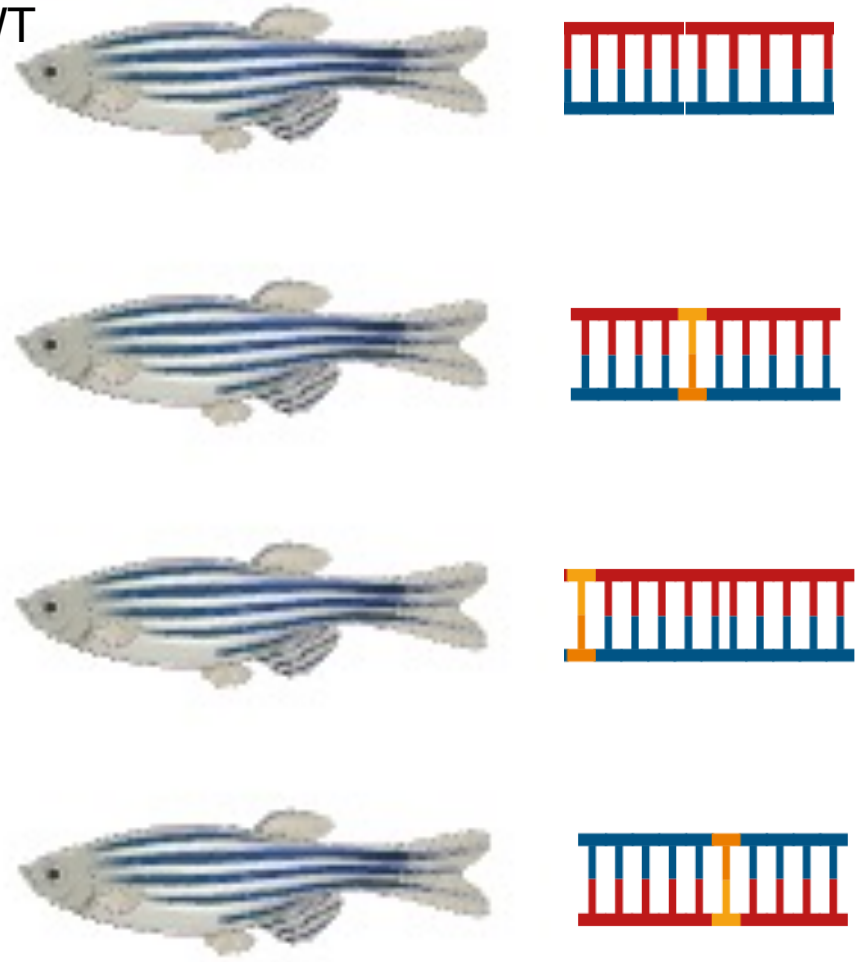


Taken at different points in the cell cycle

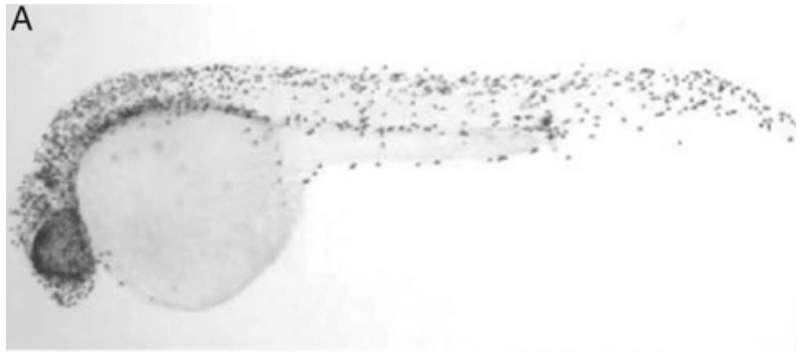


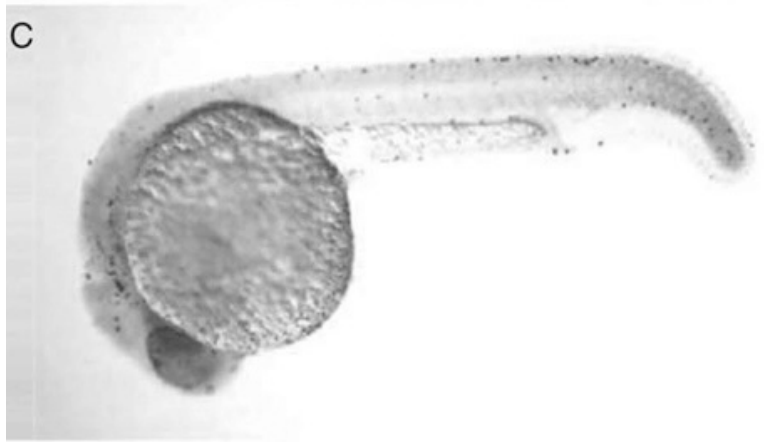
WT

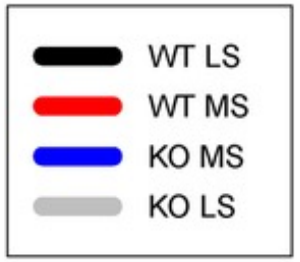


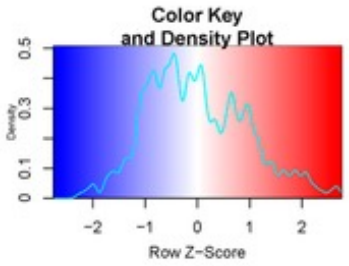
Aim 2 : Identify genes important for cell cycle regulation in the liver in zebrafish.

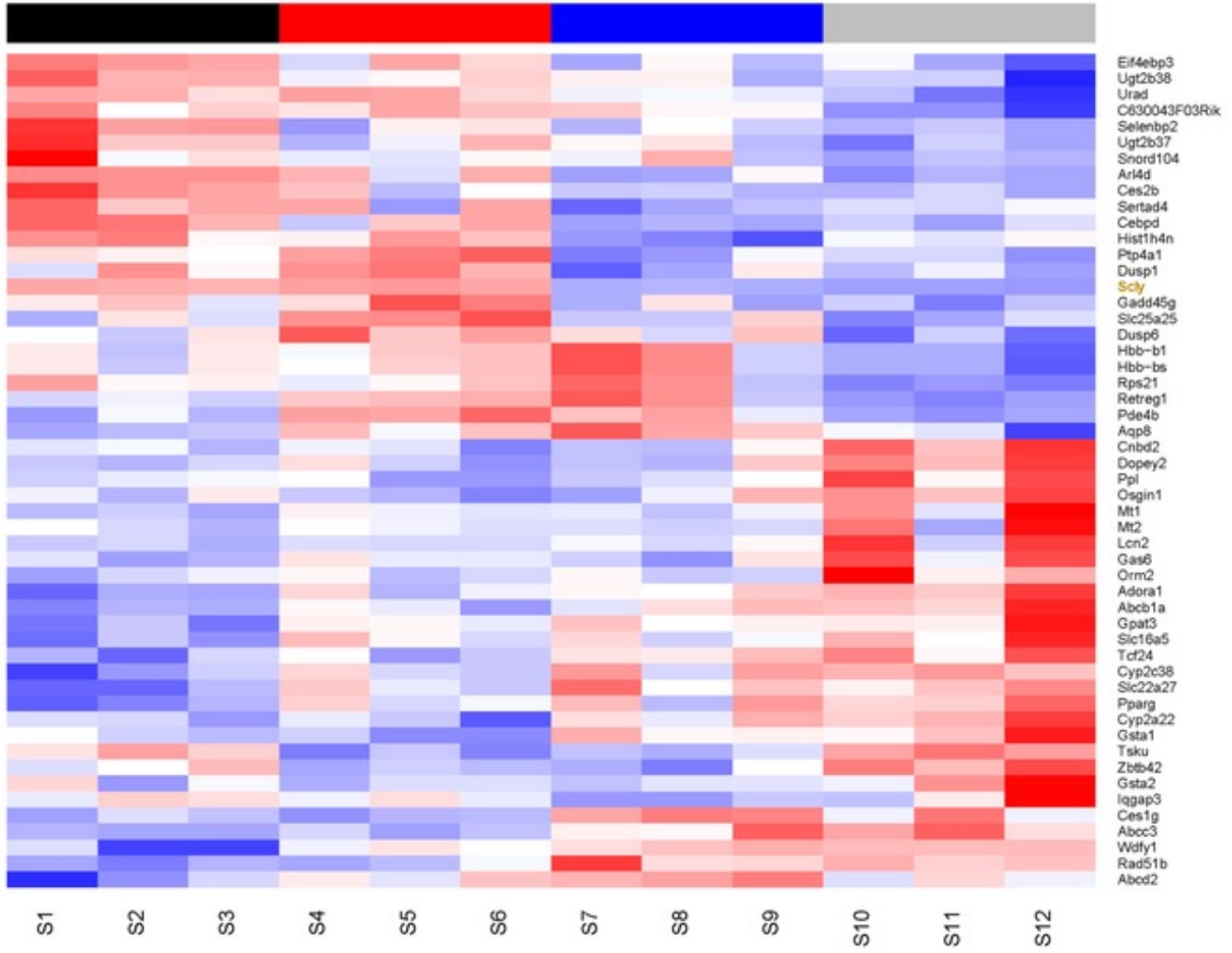
Analyze phenotypes from different gene mutations



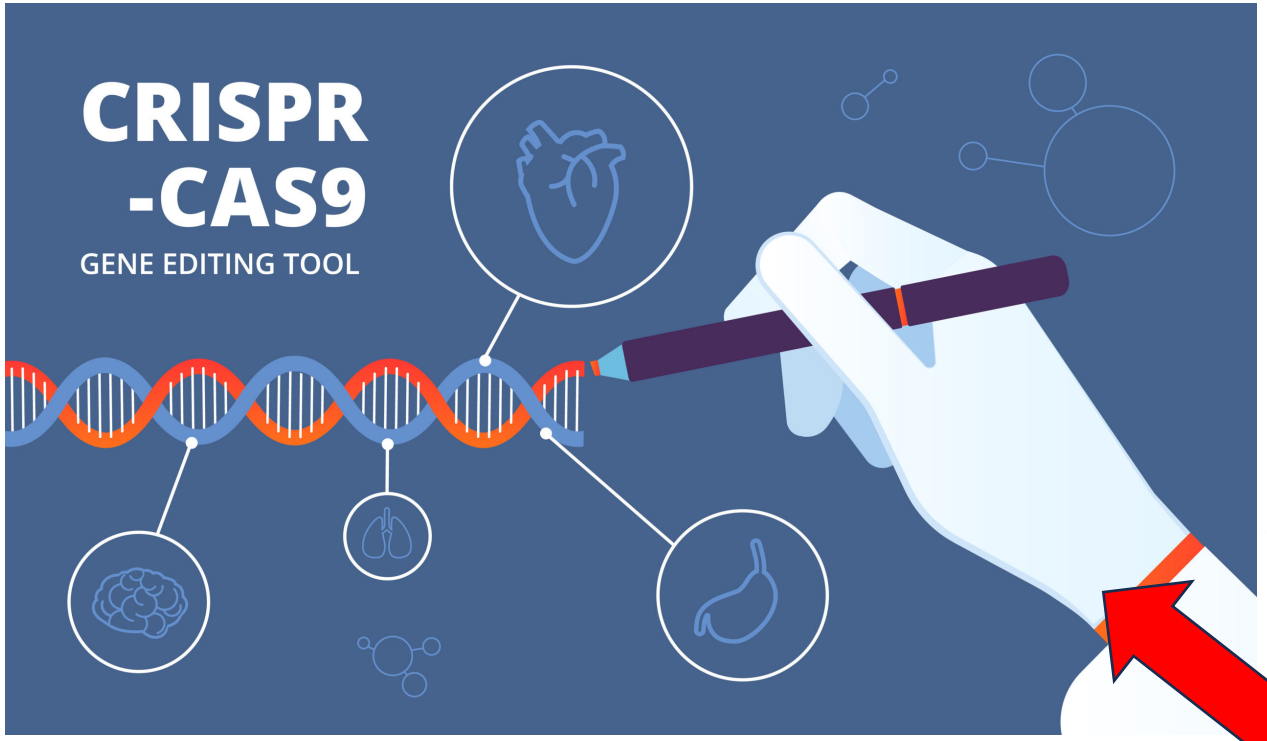




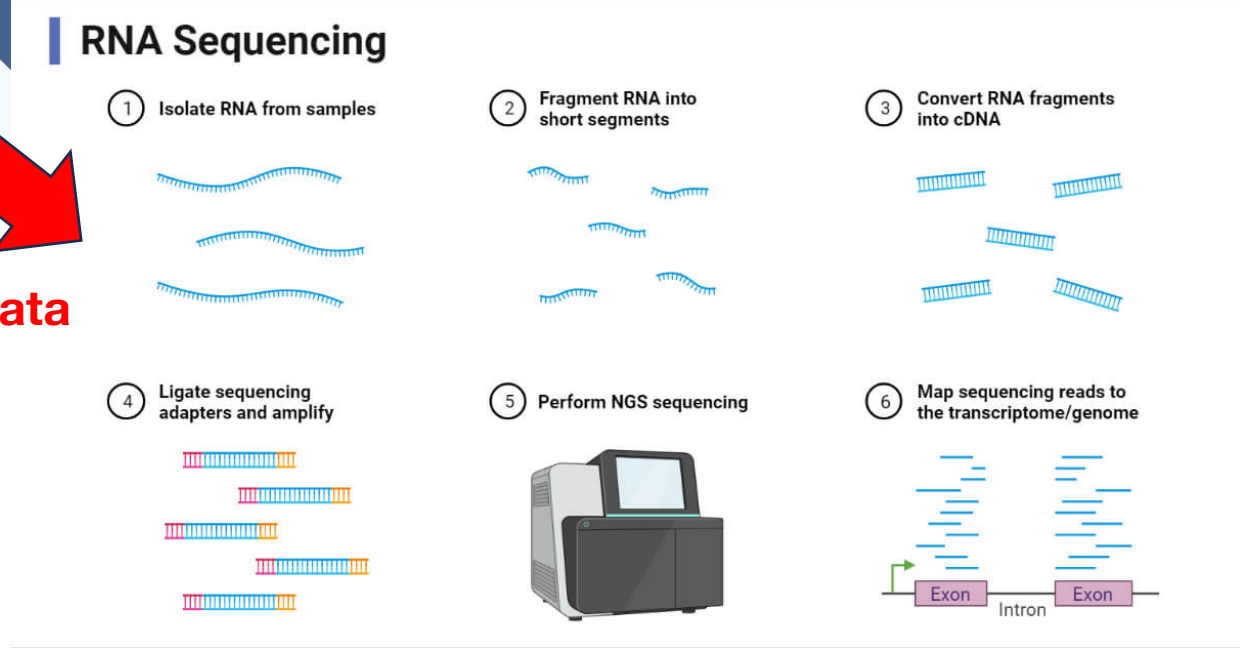




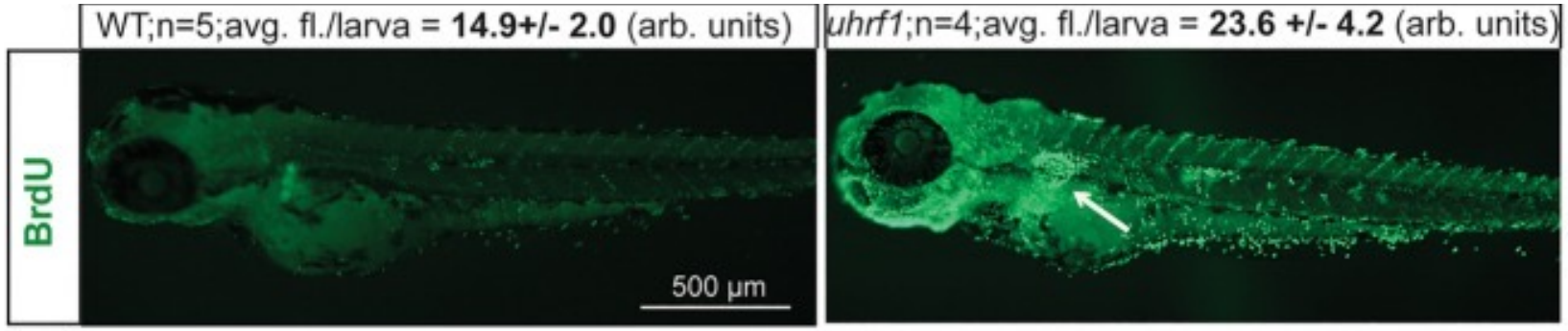
Aim 2 : Identify genes important for cell cycle regulation in the liver in zebrafish.

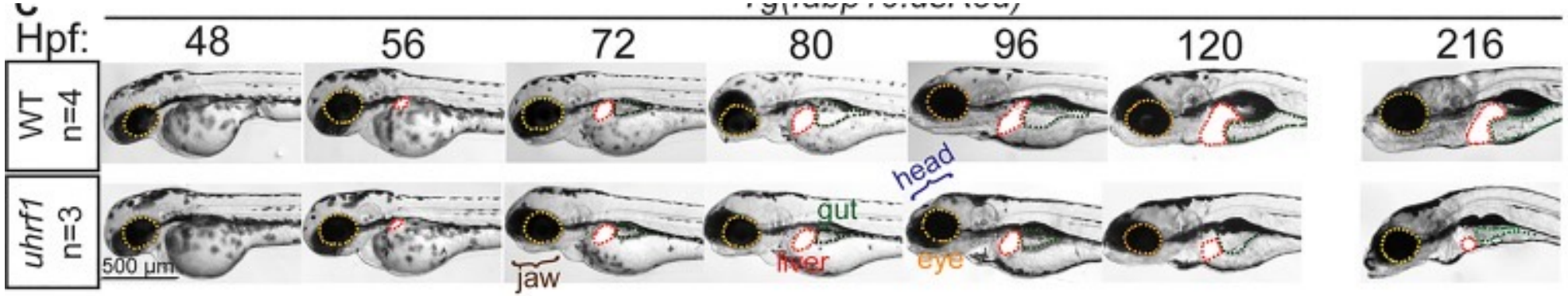


Integrate data

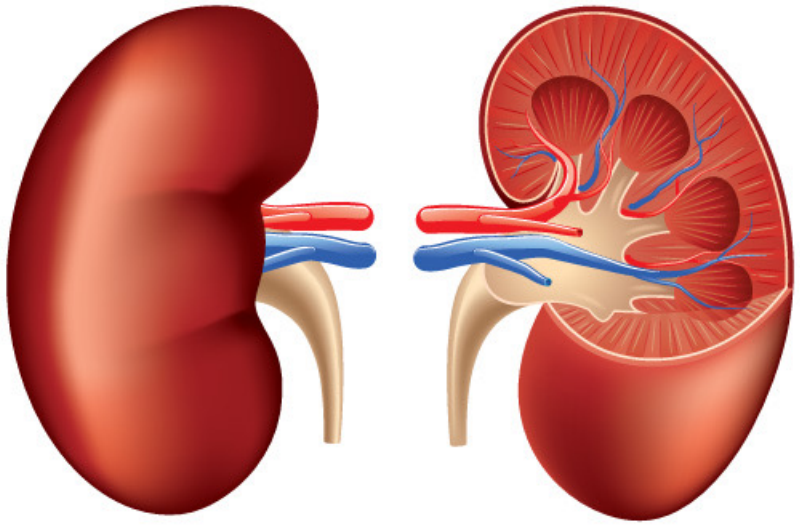


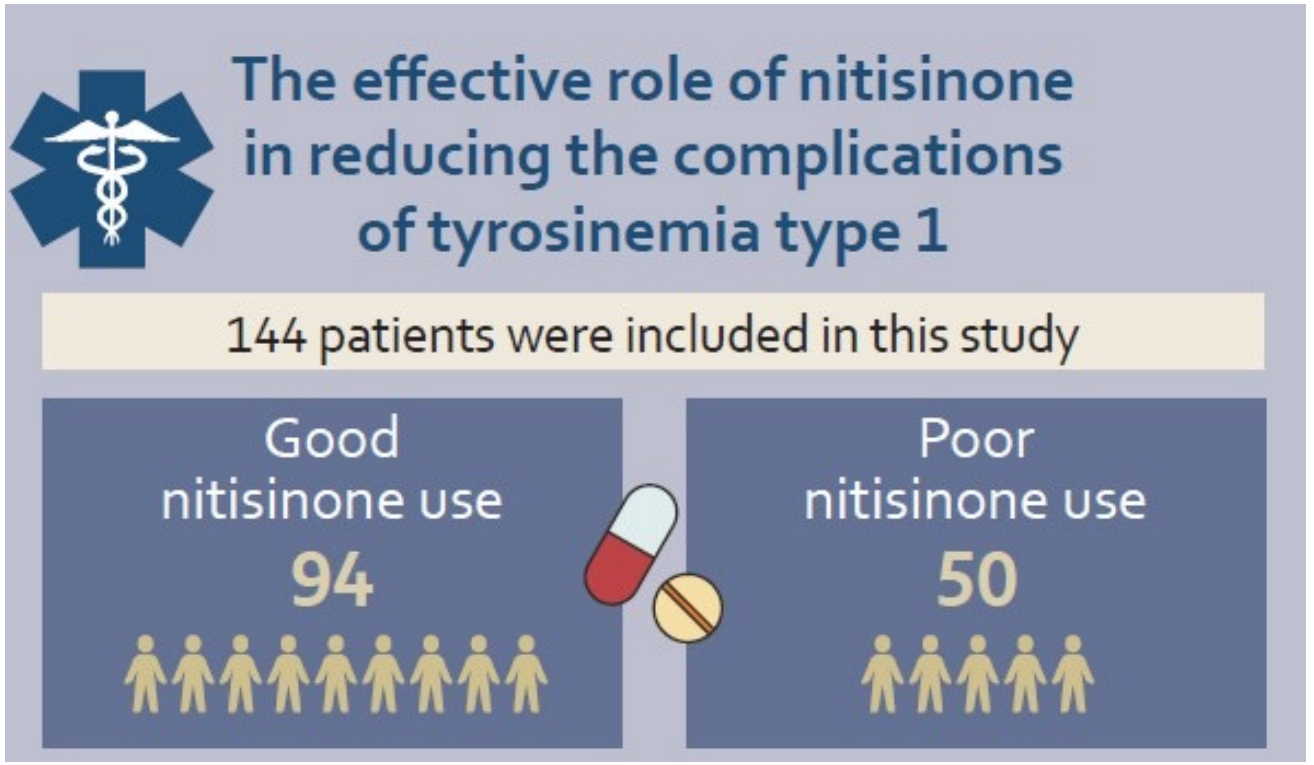
Aim 3 : TBD


WT;n=5;avg. fl./larva = **14.9+/- 2.0** (arb. units)
uhrf1;n=4;avg. fl./larva = **23.6 +/- 4.2** (arb. units)
BrdU
500 µm

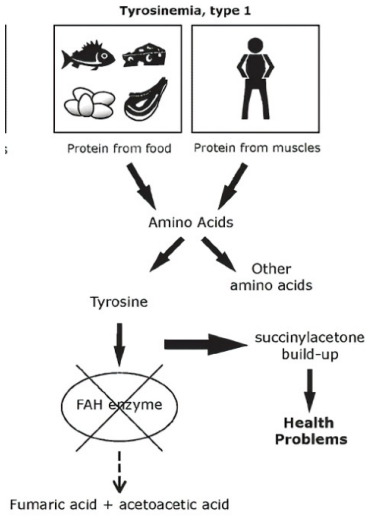

Hpf:
48
56
72
80
96
120
216
WT n=4
uhrf1 n=3
500 µm
jaw
liver
gut
head
eye

Future research directions …



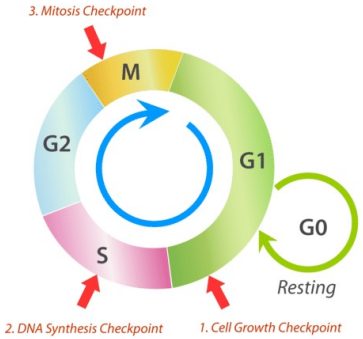


Summary



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.



Researching cell cycle arrest and 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.

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