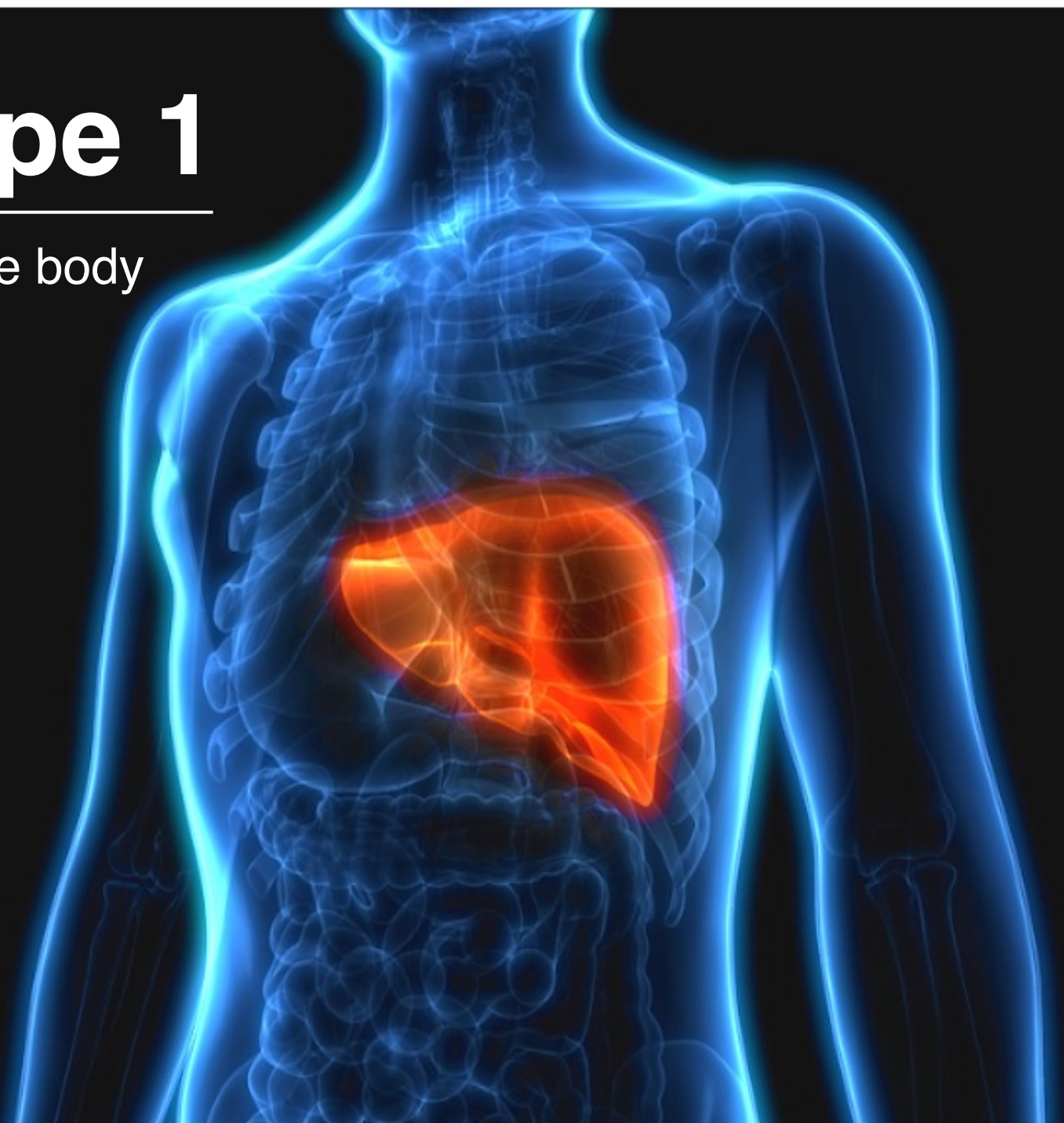


Tyrosinemia Type 1

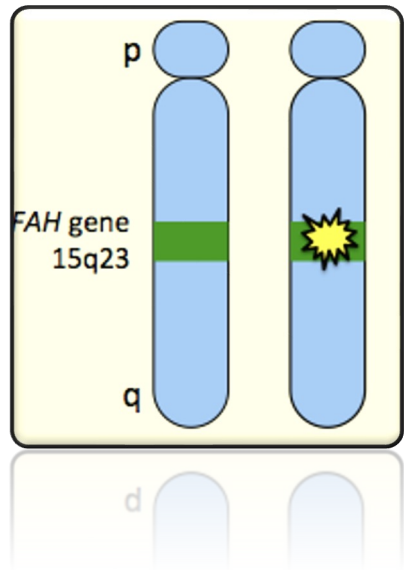
Inability to break down tyrosine in the body



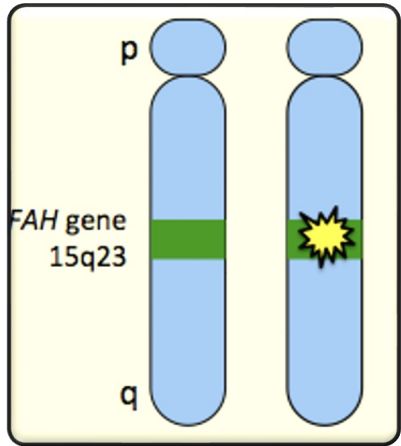
WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

Brooke Fuerstenau

Tyrosinemia Type 1



Tyrosinemia Type 1



Protein from food



Protein from muscles

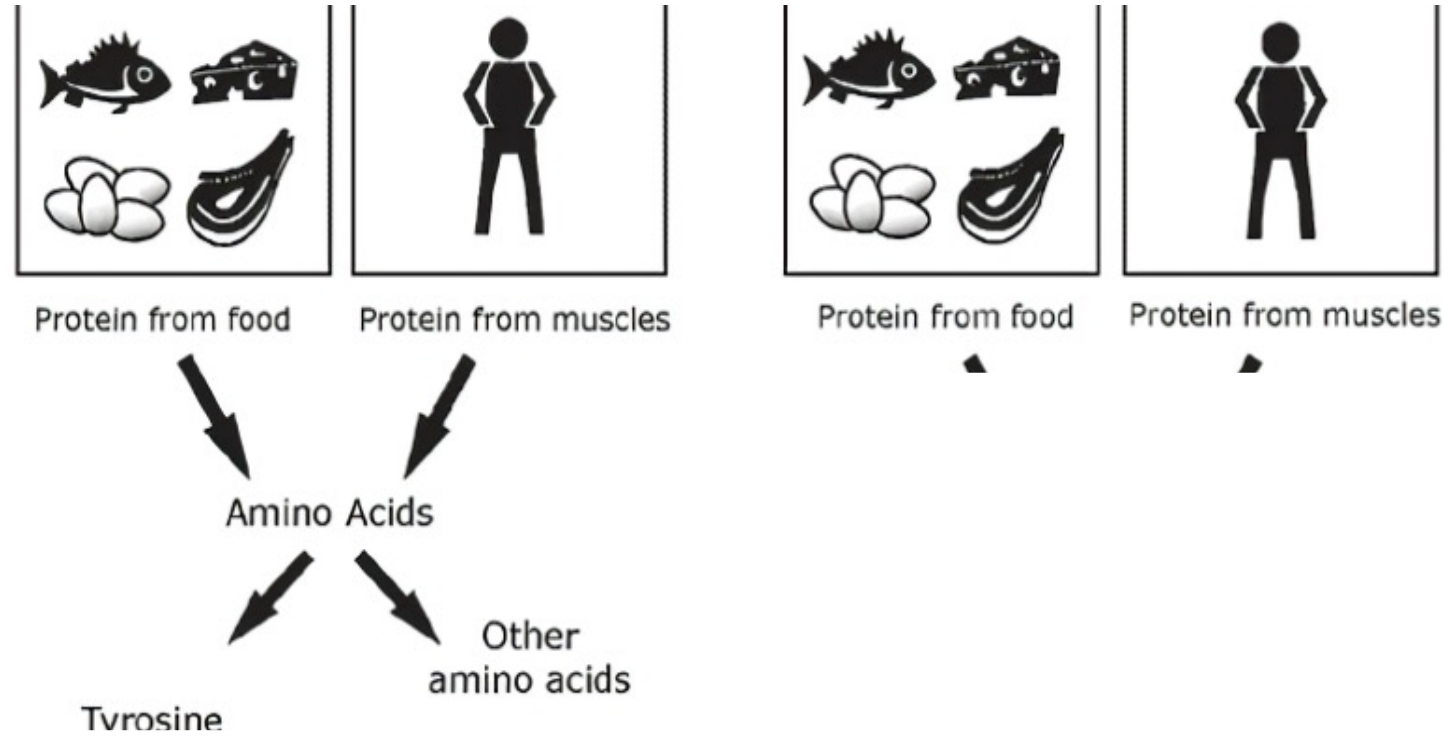
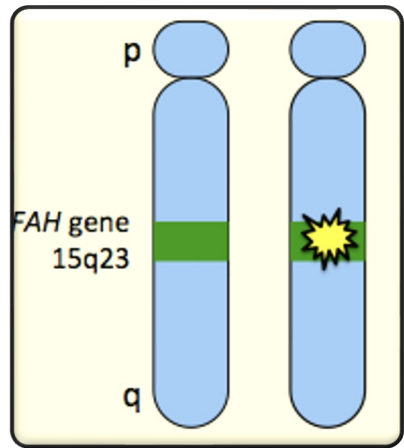


Protein from food

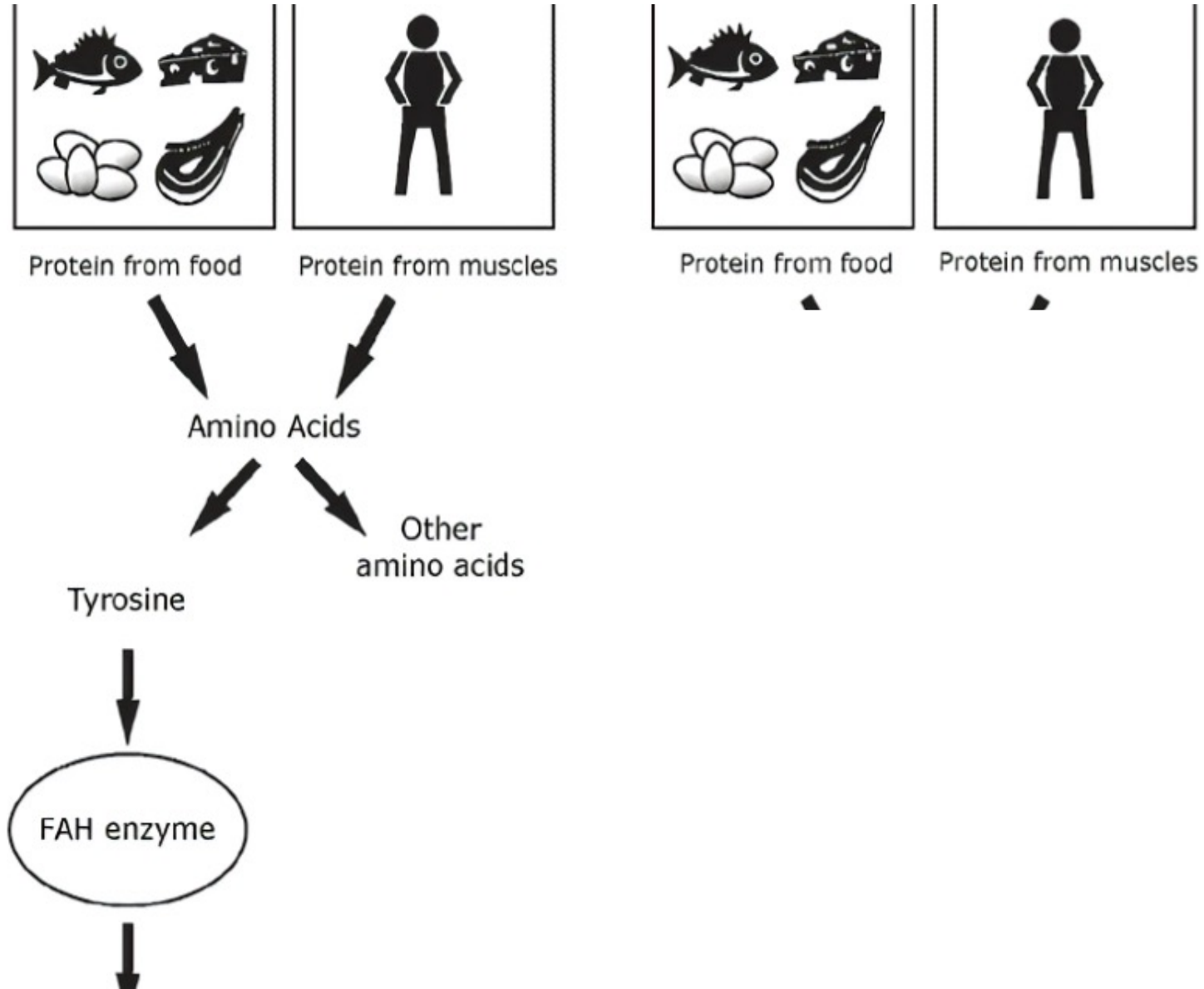
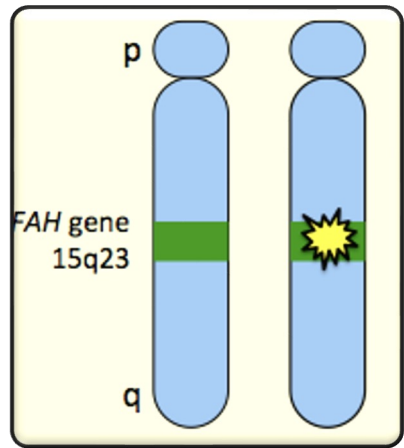


Protein from muscles

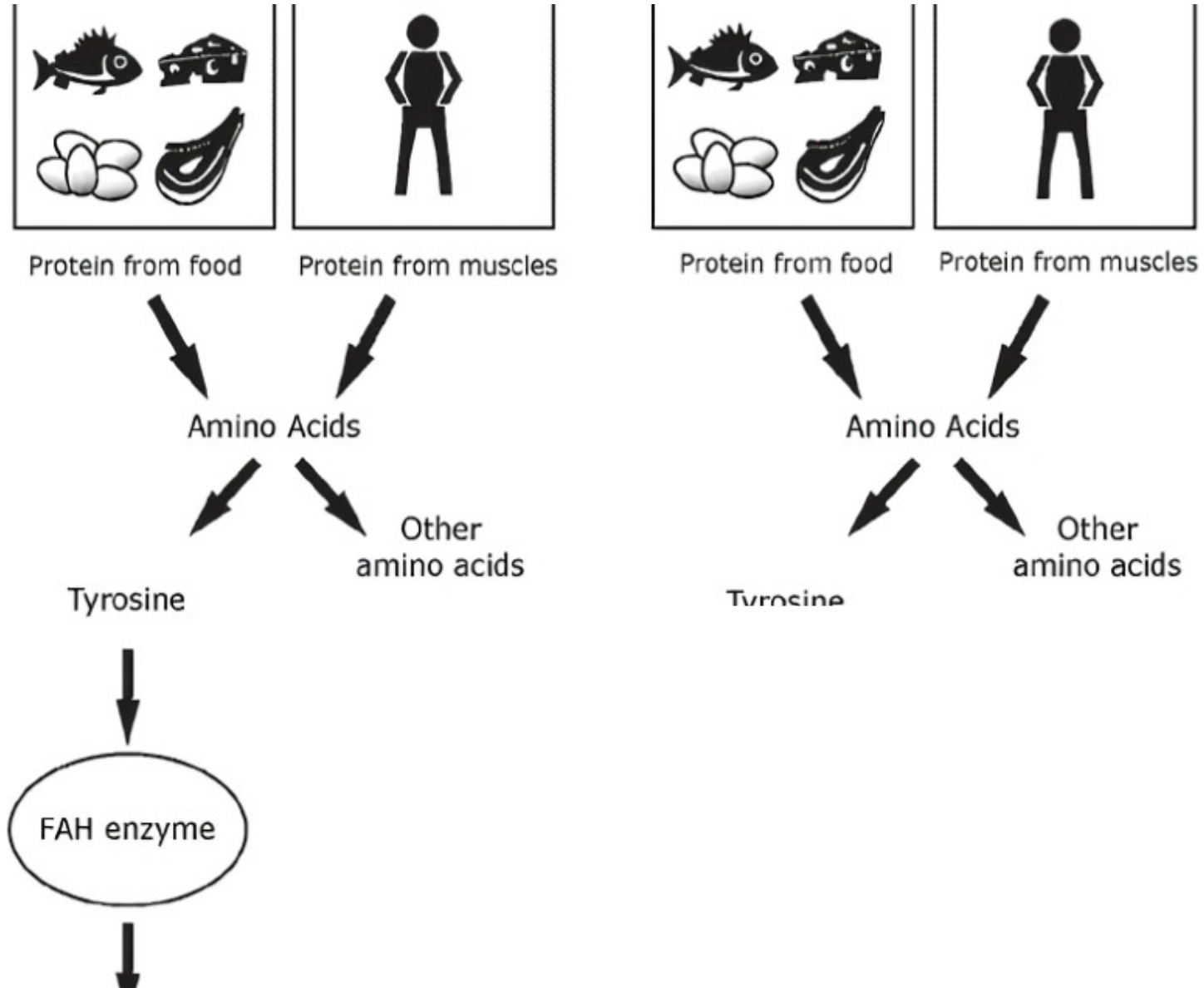
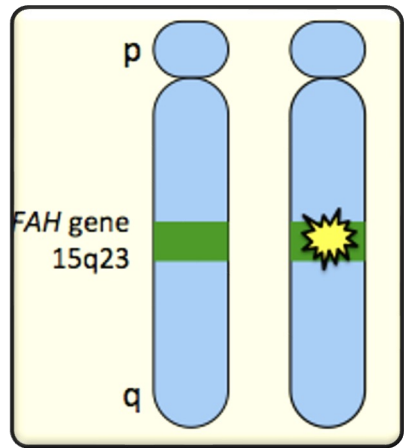
Tyrosinemia Type 1



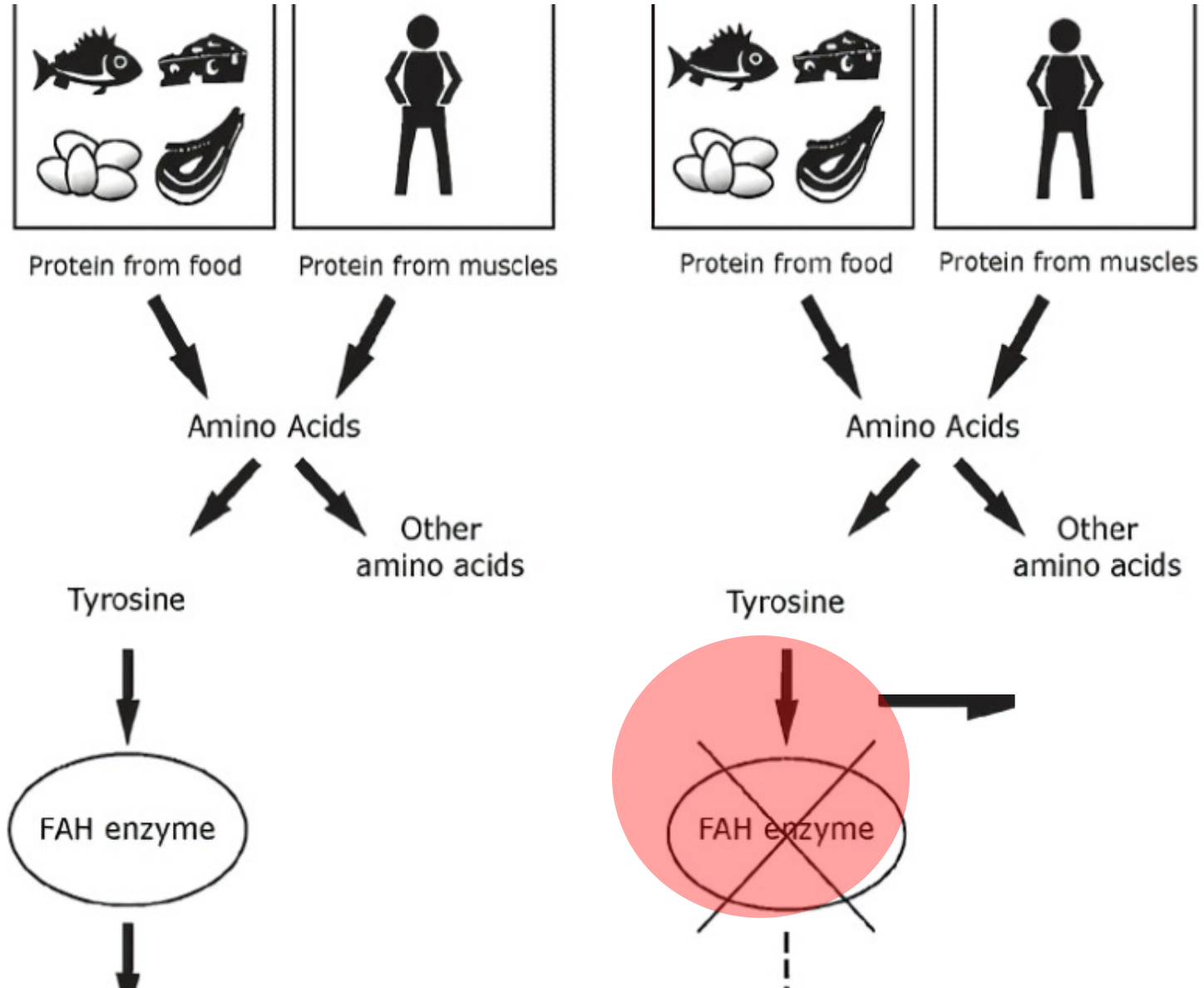
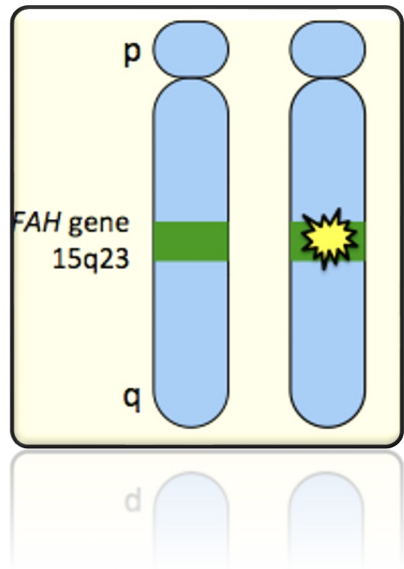
Tyrosinemia Type 1



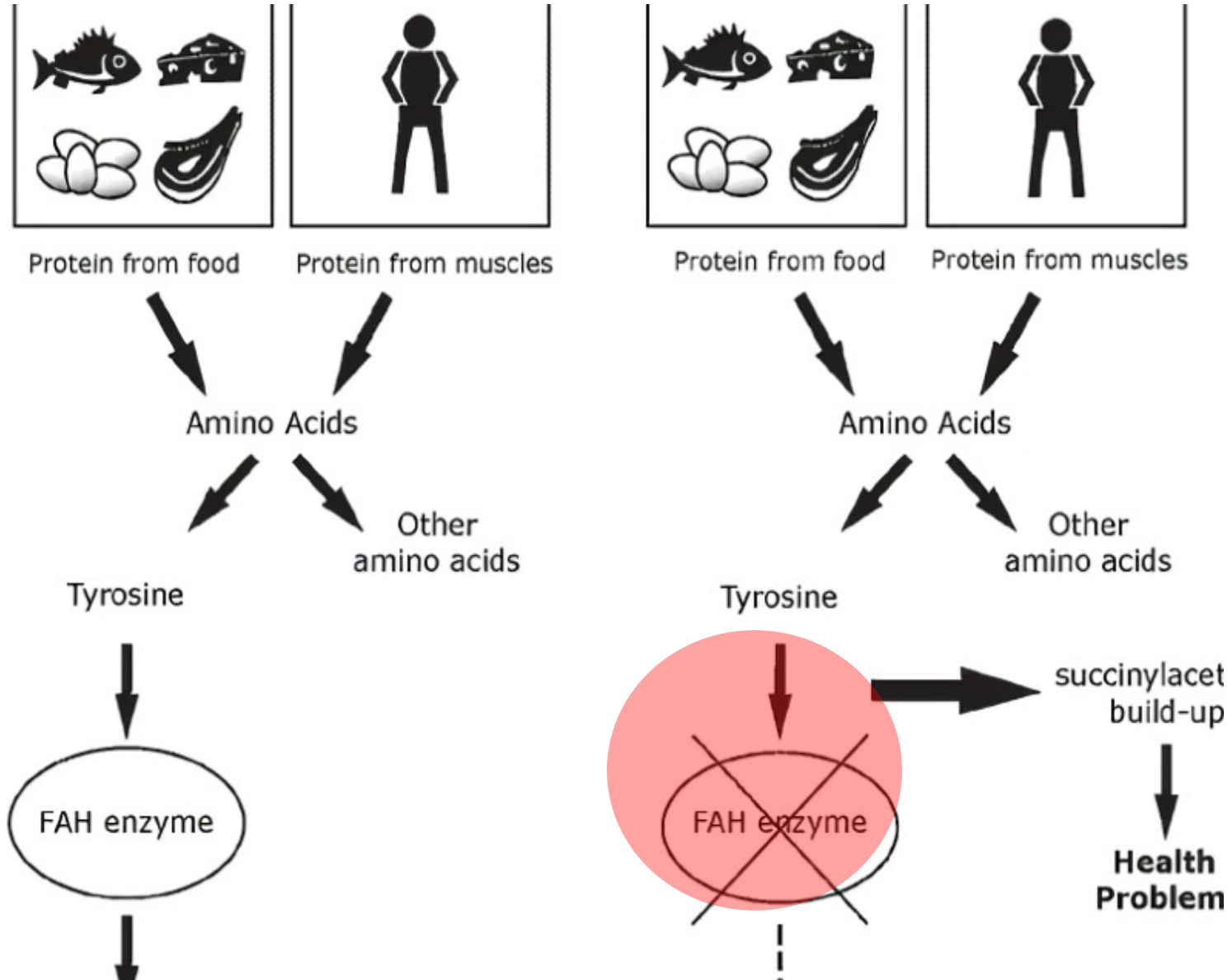
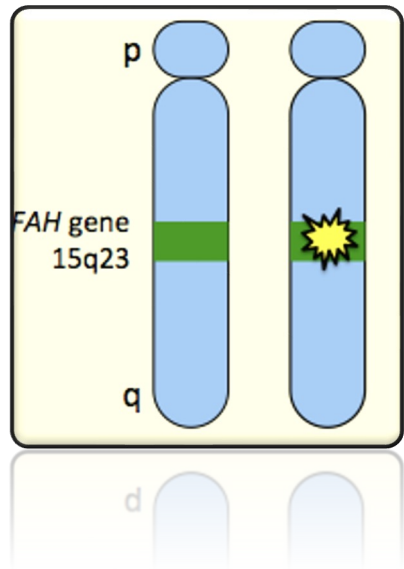
Tyrosinemia Type 1



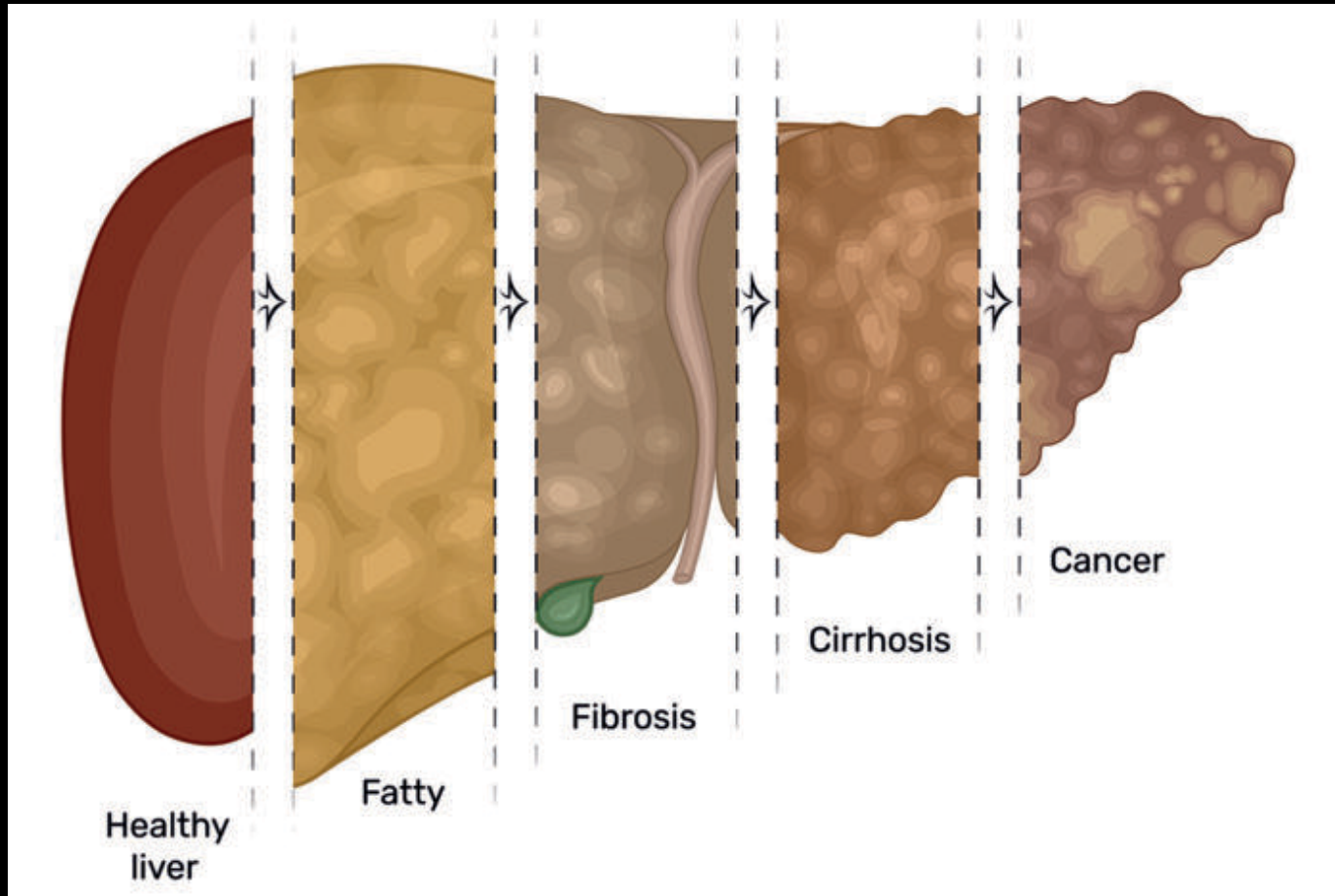
Tyrosinemia Type 1



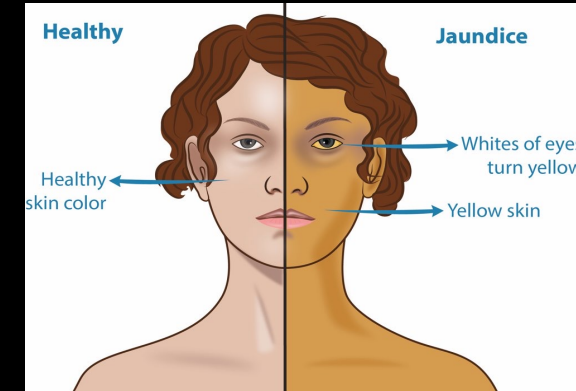
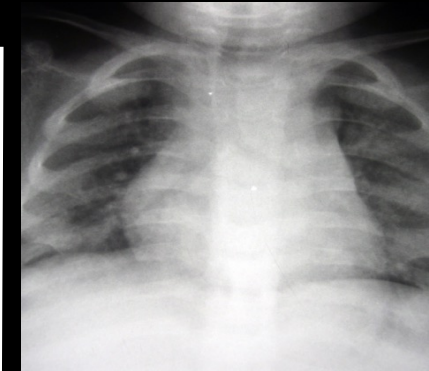
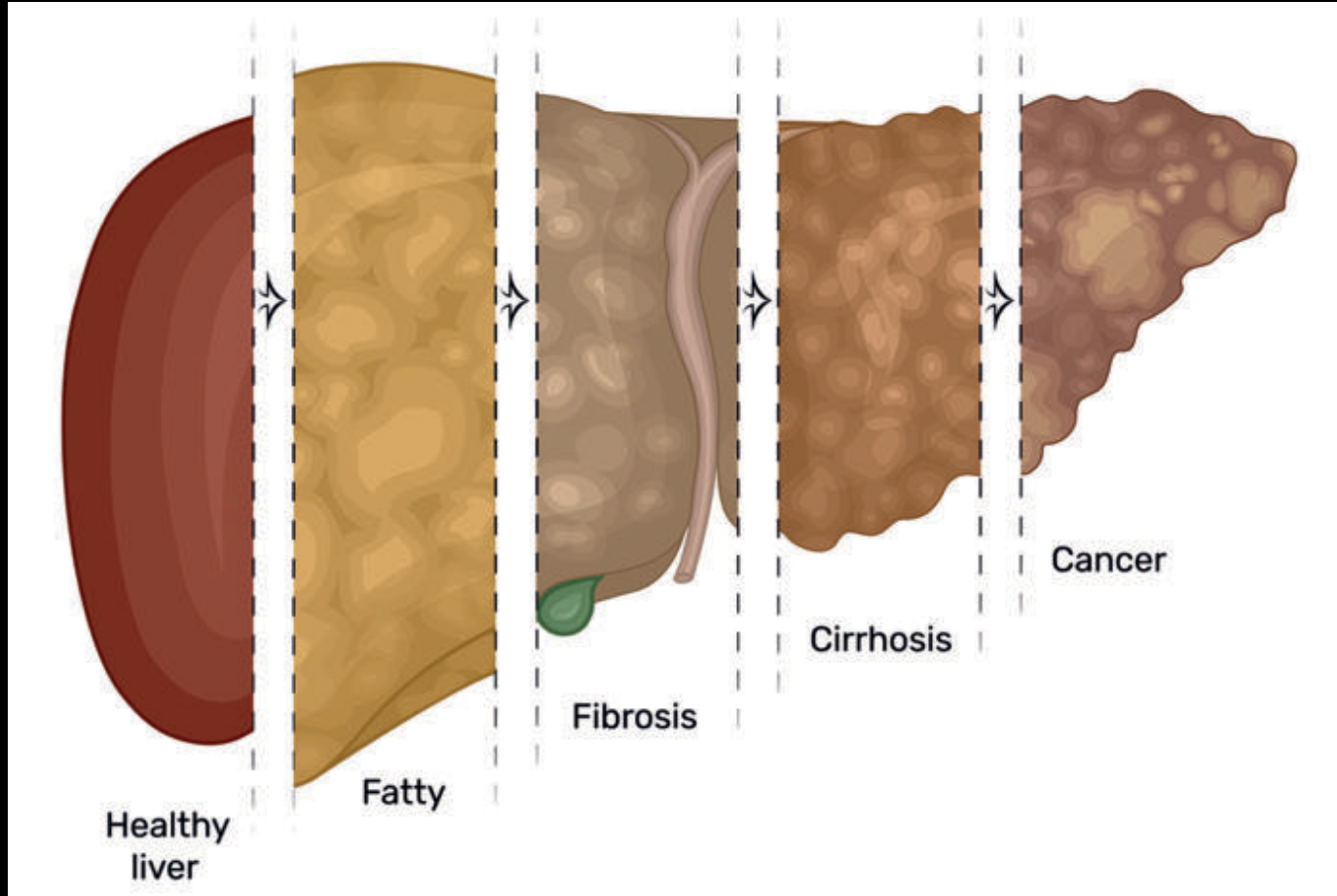
Tyrosinemia Type 1



Symptoms and signs



Symptoms and signs

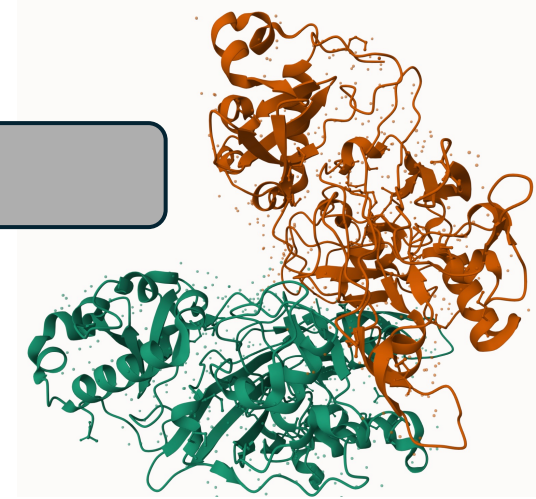


Function of **fumarylacetoacetase hydrolase**



Human

FAA Hydrolase N-terminus



Function of **fumarylacetoacetase hydrolase**



Human

FAA Hydrolase N-terminus

Gene Ontology



Function of **fumarylacetoacetase hydrolase**



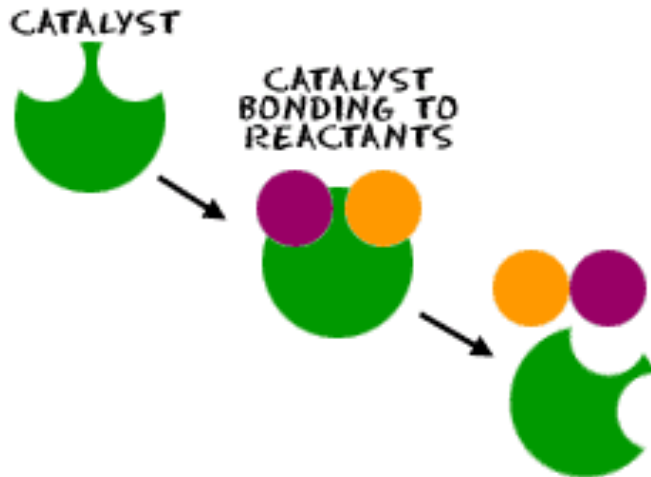
Human

FAA Hydrolase N-terminus



Gene Ontology

MOLECULAR FUNCTION



Catalytic activity

Function of **fumarylacetoacetase hydrolase**



Human

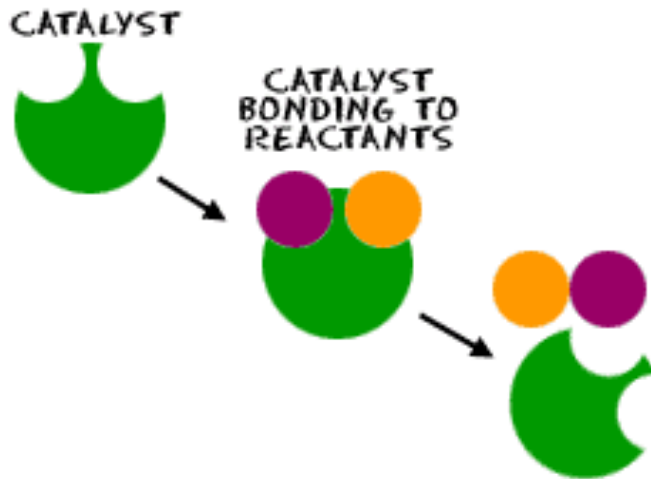
FAA Hydrolase N-terminus



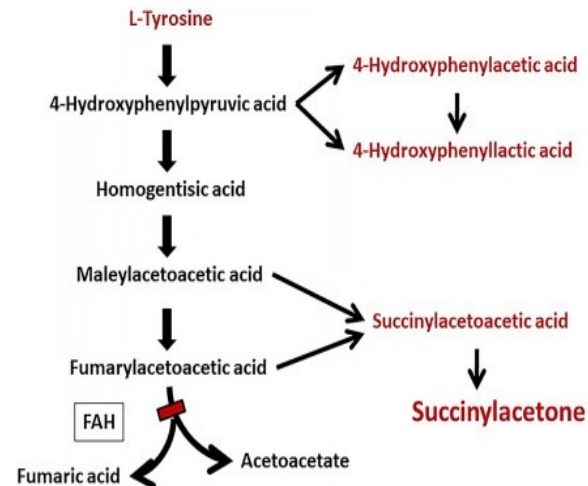
Gene Ontology

MOLECULAR FUNCTION

BIOLOGICAL PROCESS



Catalytic activity



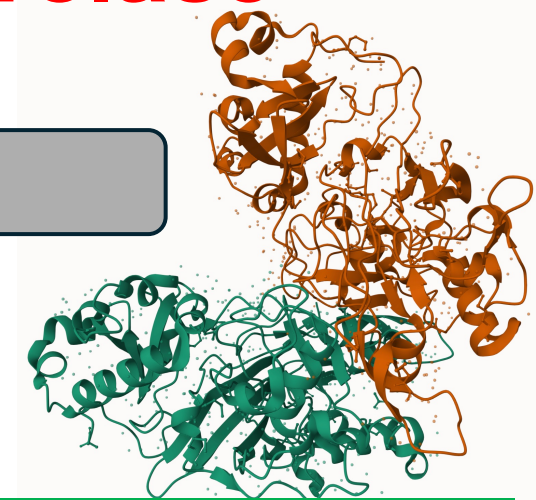
Tyrosine metabolism

Function of **fumarylacetoacetase hydrolase**



Human

FAA Hydrolase N-terminus

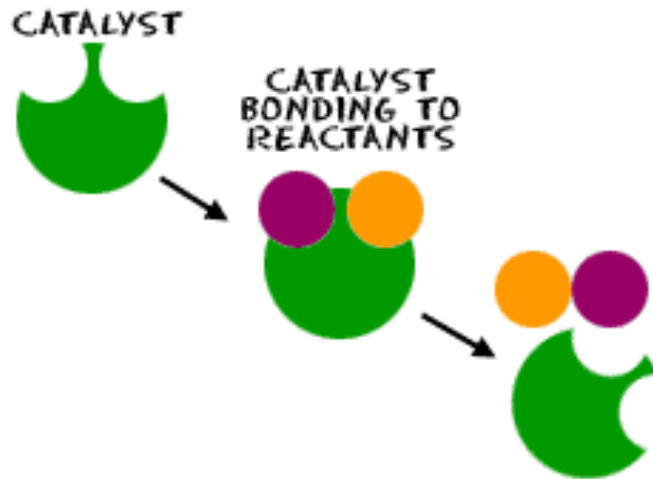


Gene Ontology

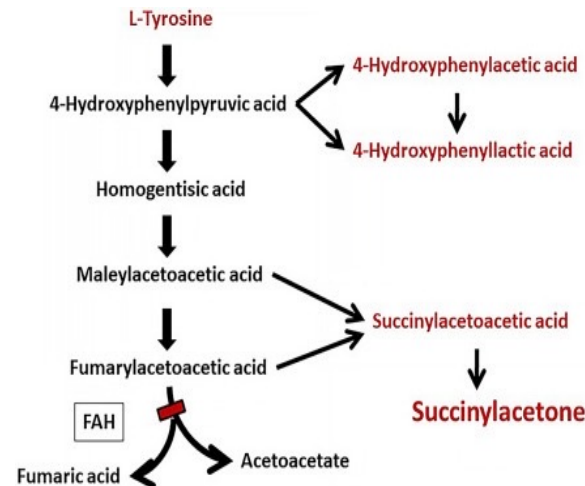
MOLECULAR FUNCTION

BIOLOGICAL PROCESS

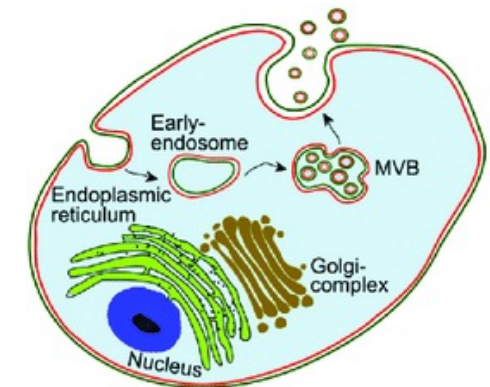
CELLULAR COMPONENT



Catalytic activity



Tyrosine metabolism



Extracellular exosome

The **FAA** domain is highly conserved across organisms

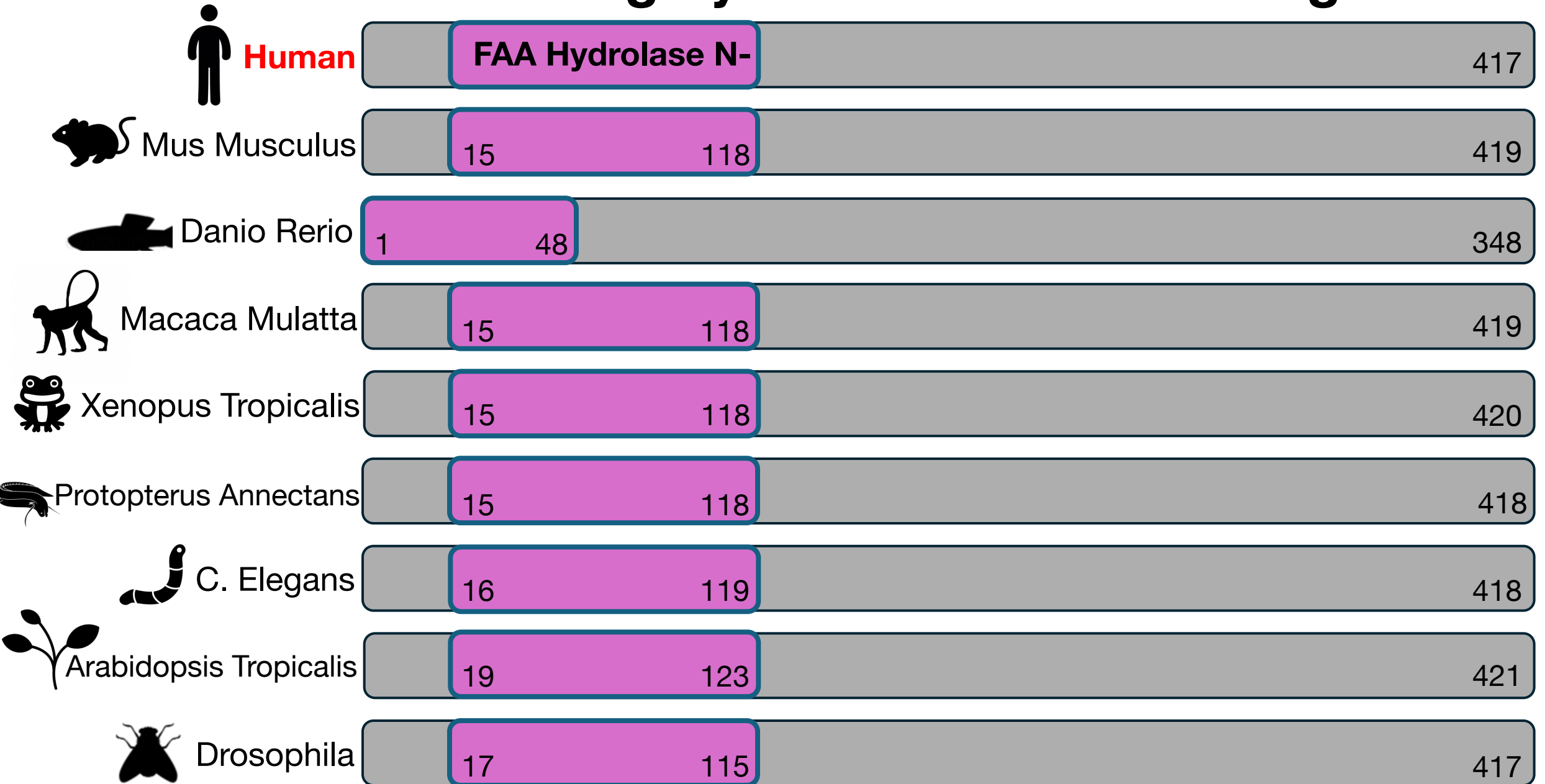


Human

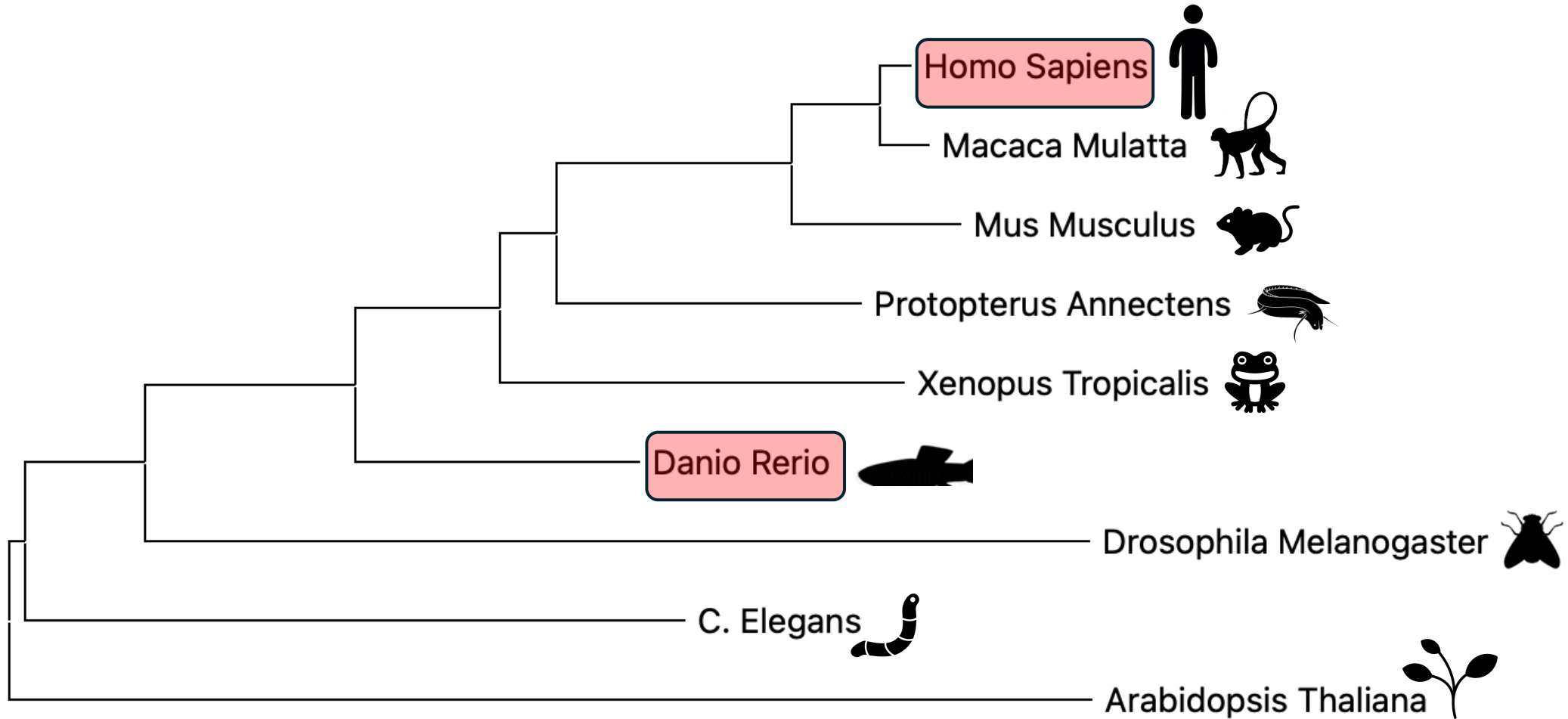


417

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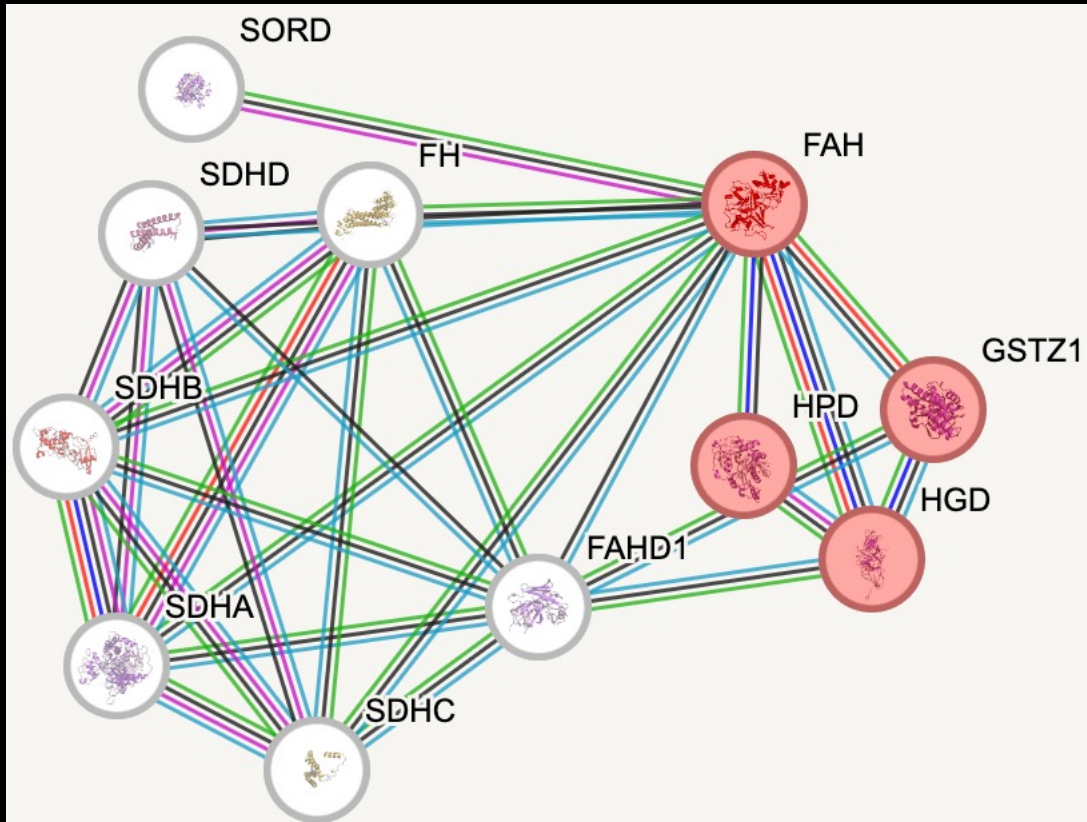


Phylogenetic tree

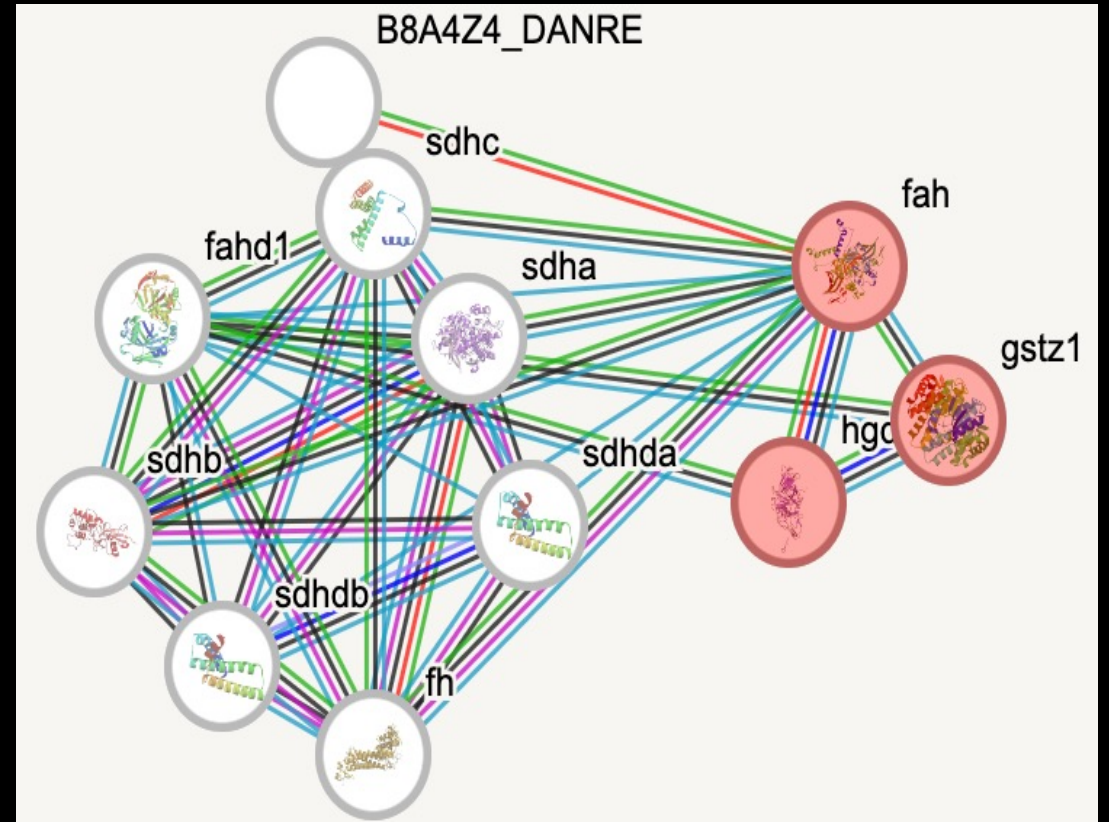


0.10

Protein interaction networks for FAA

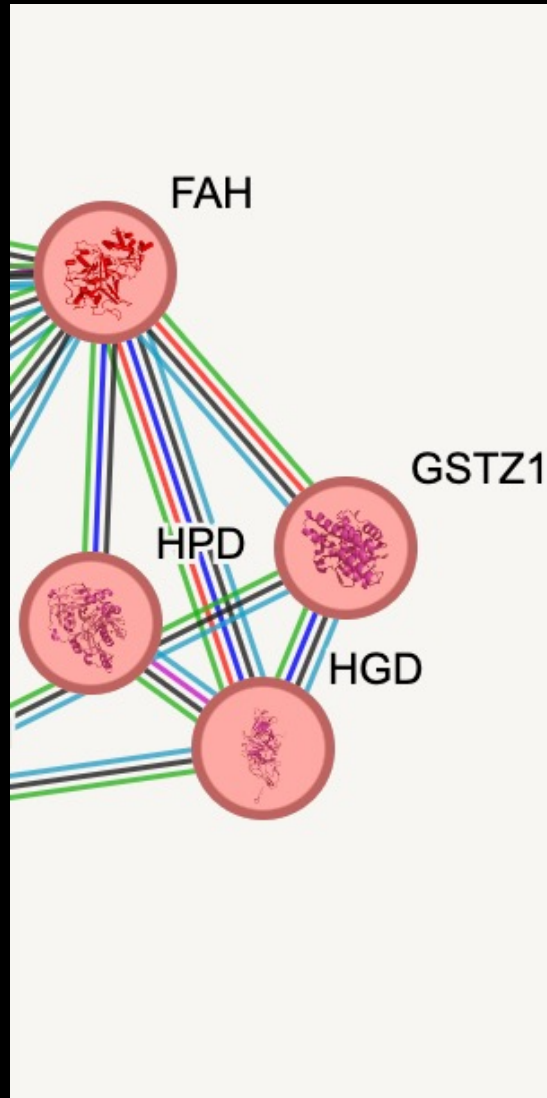


Homo sapiens

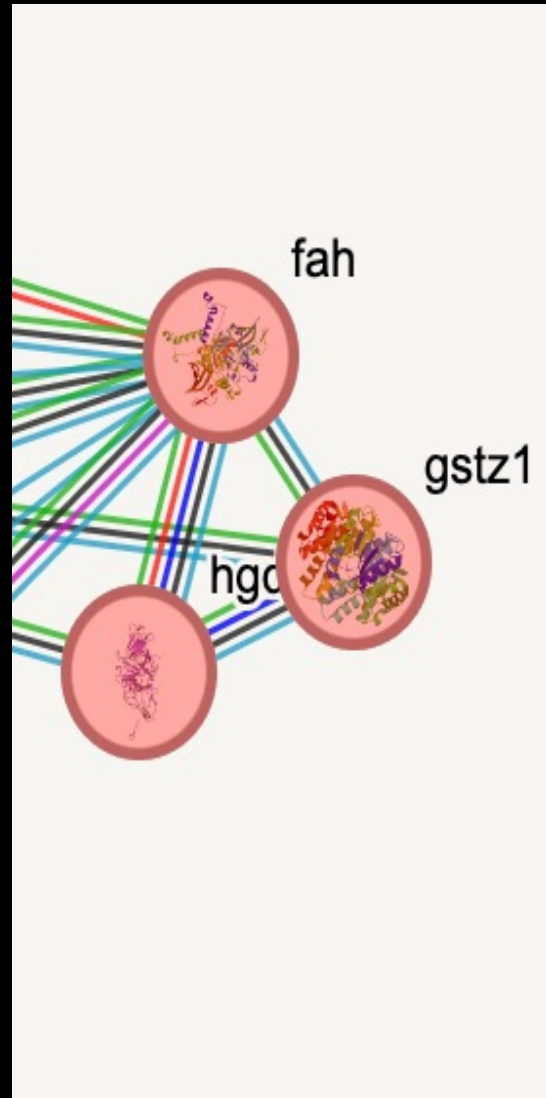


Danio rerio

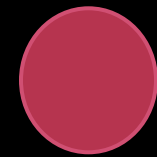
Protein interaction networks for FAA



Homo sapiens



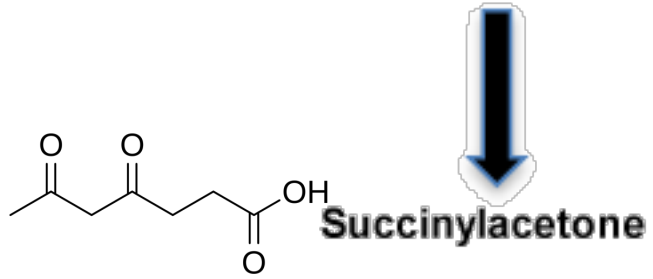
Danio rerio



Tyrosine Catabolic Process

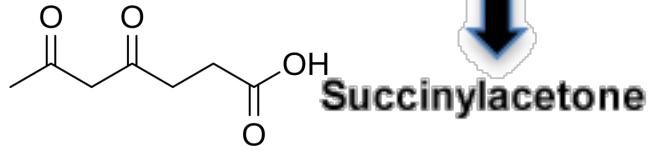
It is unknown what role **FAA** plays in hepatocyte apoptosis

Tyrosine → 4 Fumarylacetoacetate → FAH →



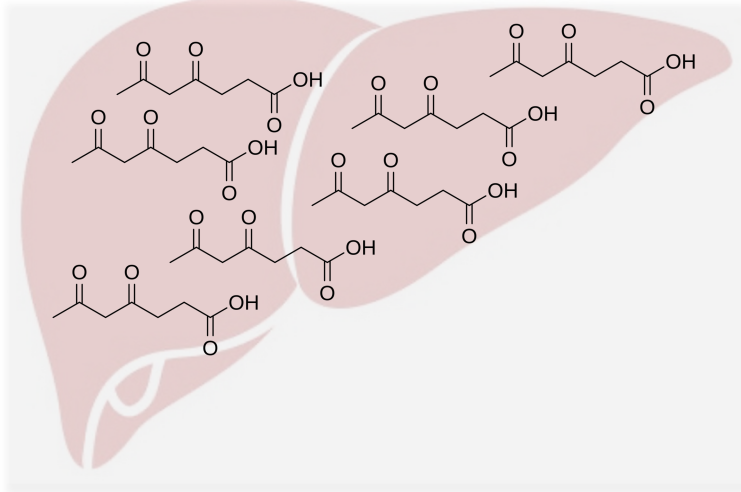
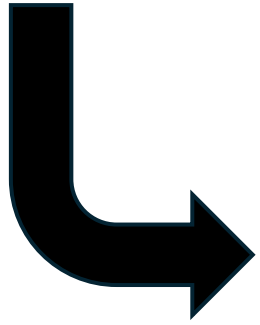
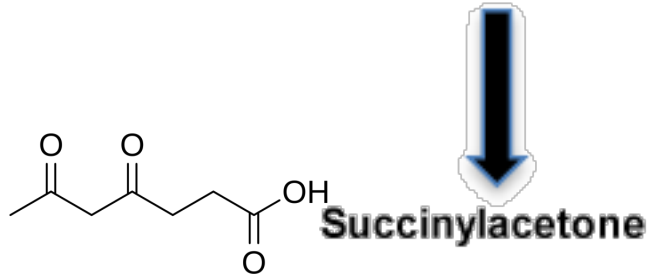
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Tyrosine → 4 Fumarylacetoacetate → ~~FH~~ →



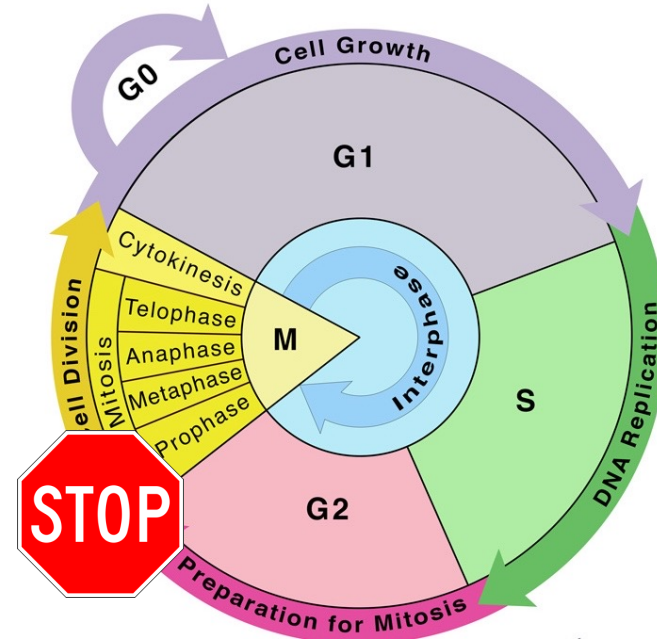
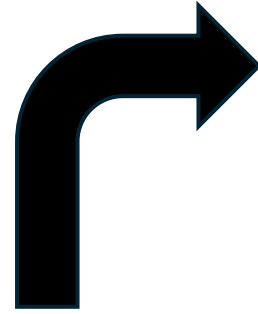
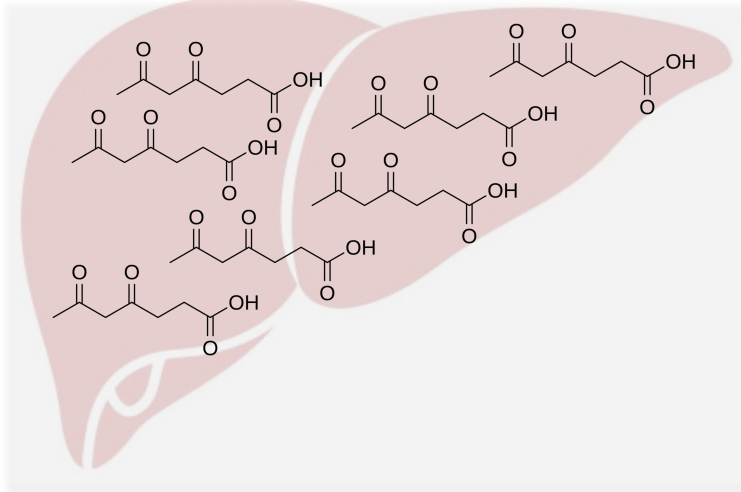
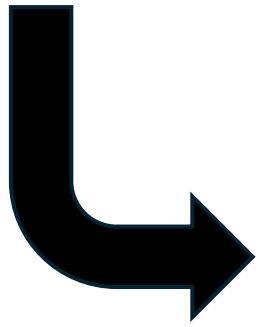
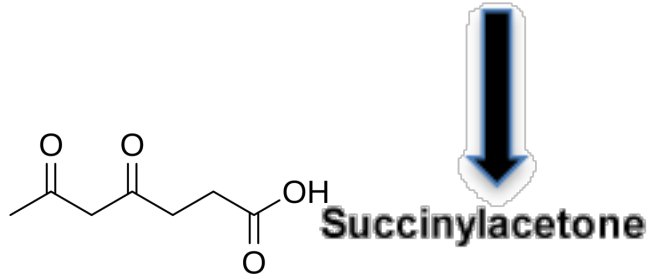
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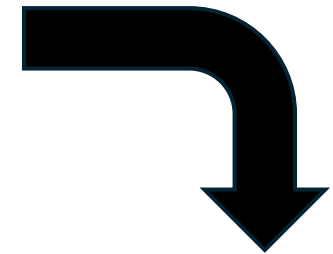
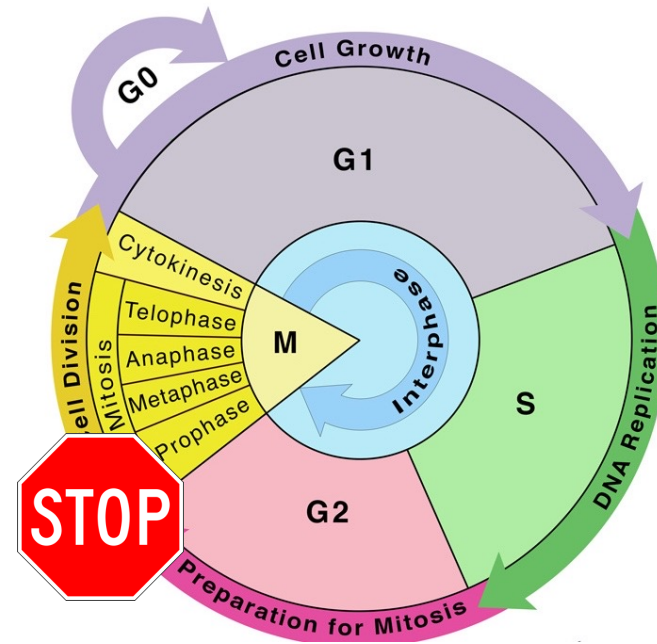
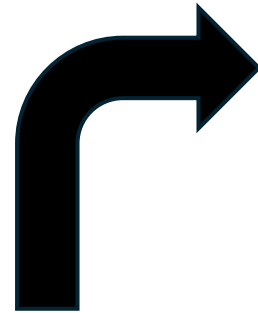
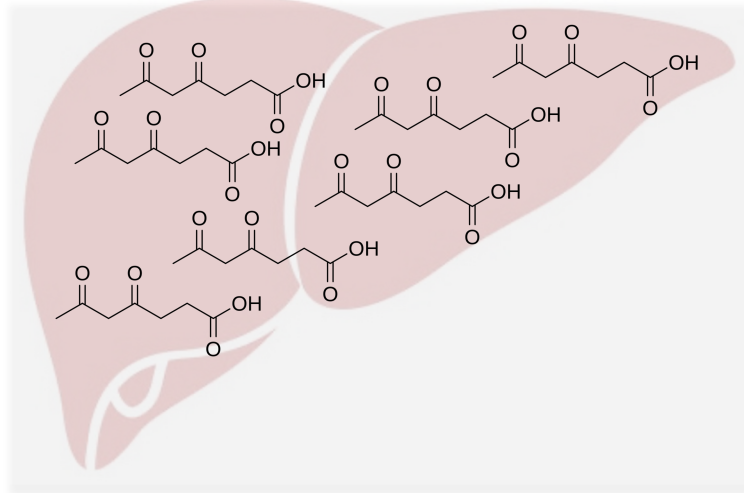
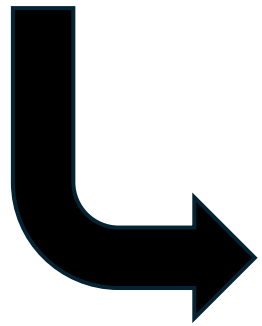
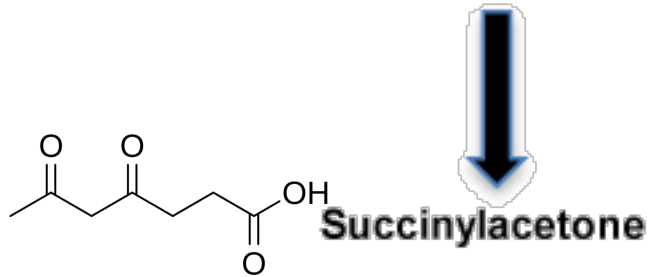
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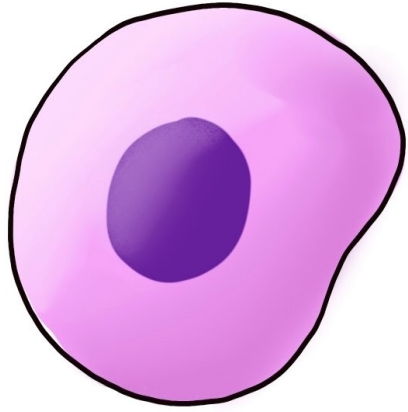


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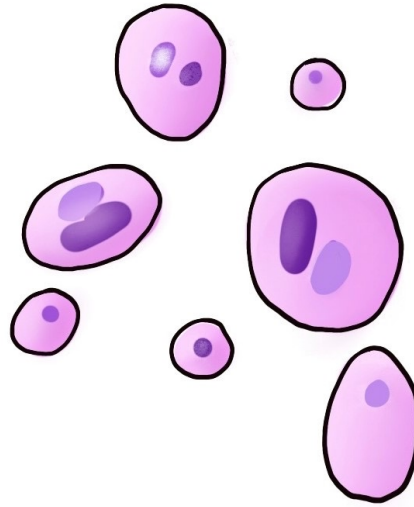
Tyrosine → 4 Fumarylacetoacetate → **FAA** →



Histology analysis of apoptosis and apoptotic bodies



NORMAL, HEALTHY
CELL

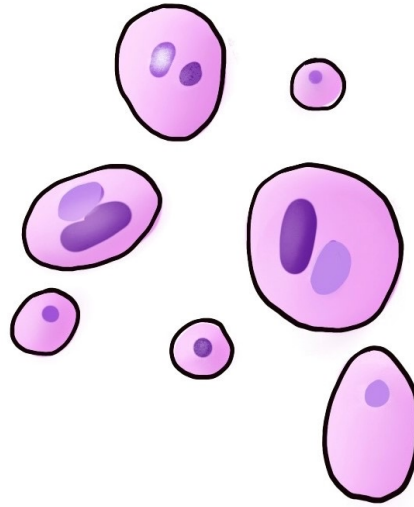
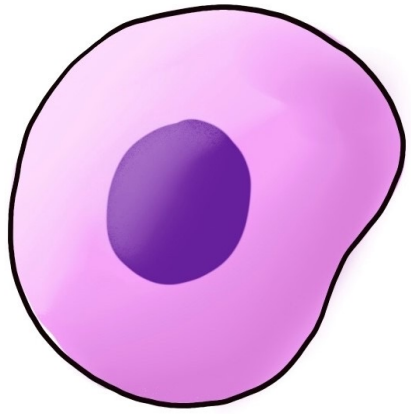


CELL AFTER APOPTOSIS

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

ZGoralski
1997 PATHOLOGY BY PAPER, CA

Histology analysis of apoptosis and apoptotic bodies



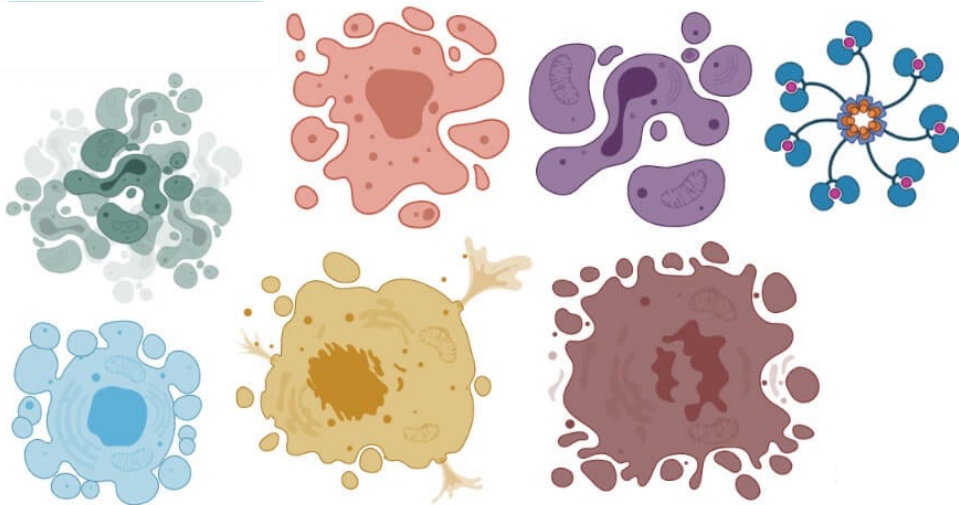
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ZGoralski
HISTOLOGY BY ZGORALSKI

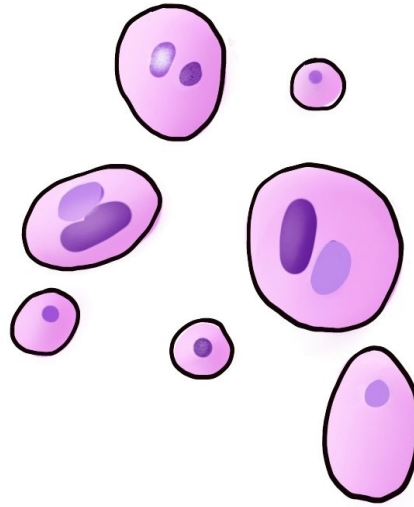
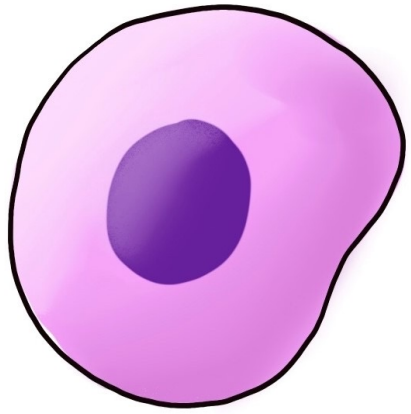
NORMAL, HEALTHY
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CELL AFTER APOPTOSIS



Histology analysis of apoptosis and apoptotic bodies



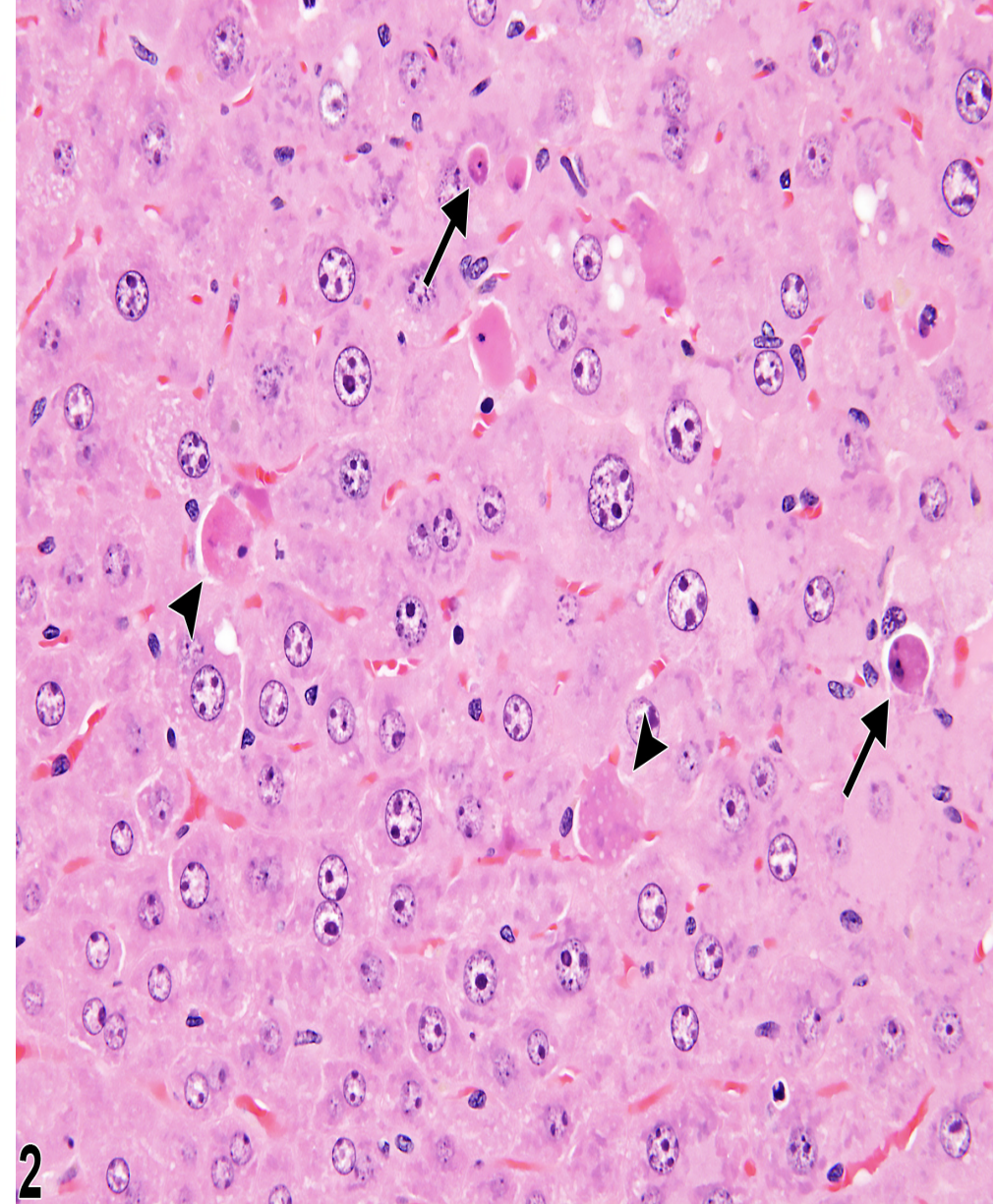
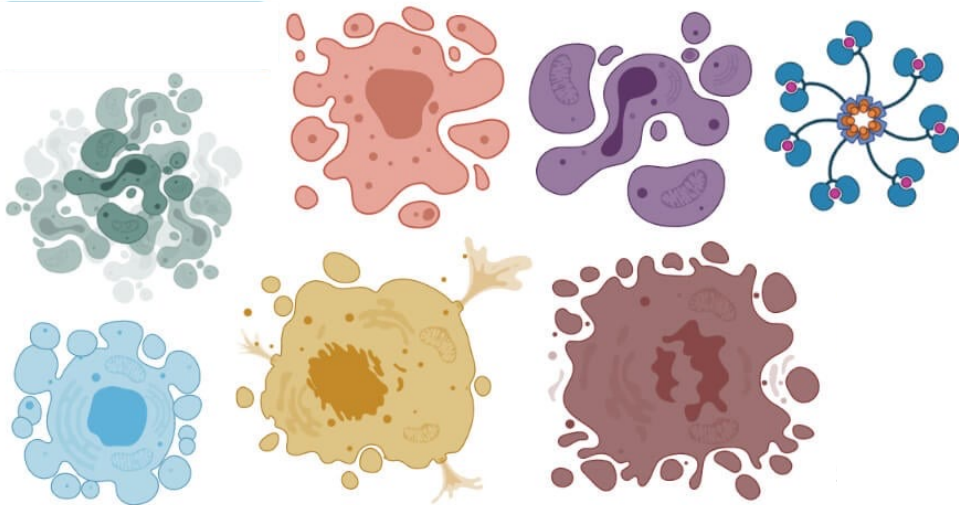
THE CELL HAS BROKEN INTO MANY SMALL PIECES CALLED "APOPTOTIC BODIES"

ZGorak's
HISTOLOGY RESOURCE, LLC

NORMAL, HEALTHY CELL



CELL AFTER APOPTOSIS



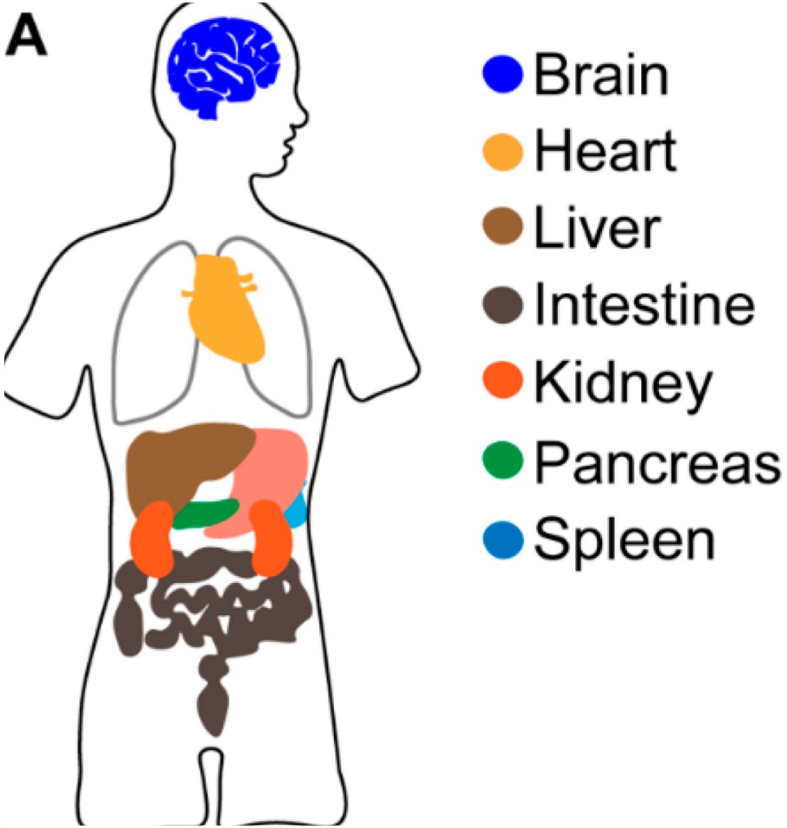
***Danio rerio* act as good models for liver diseases in humans**

Zebrafish



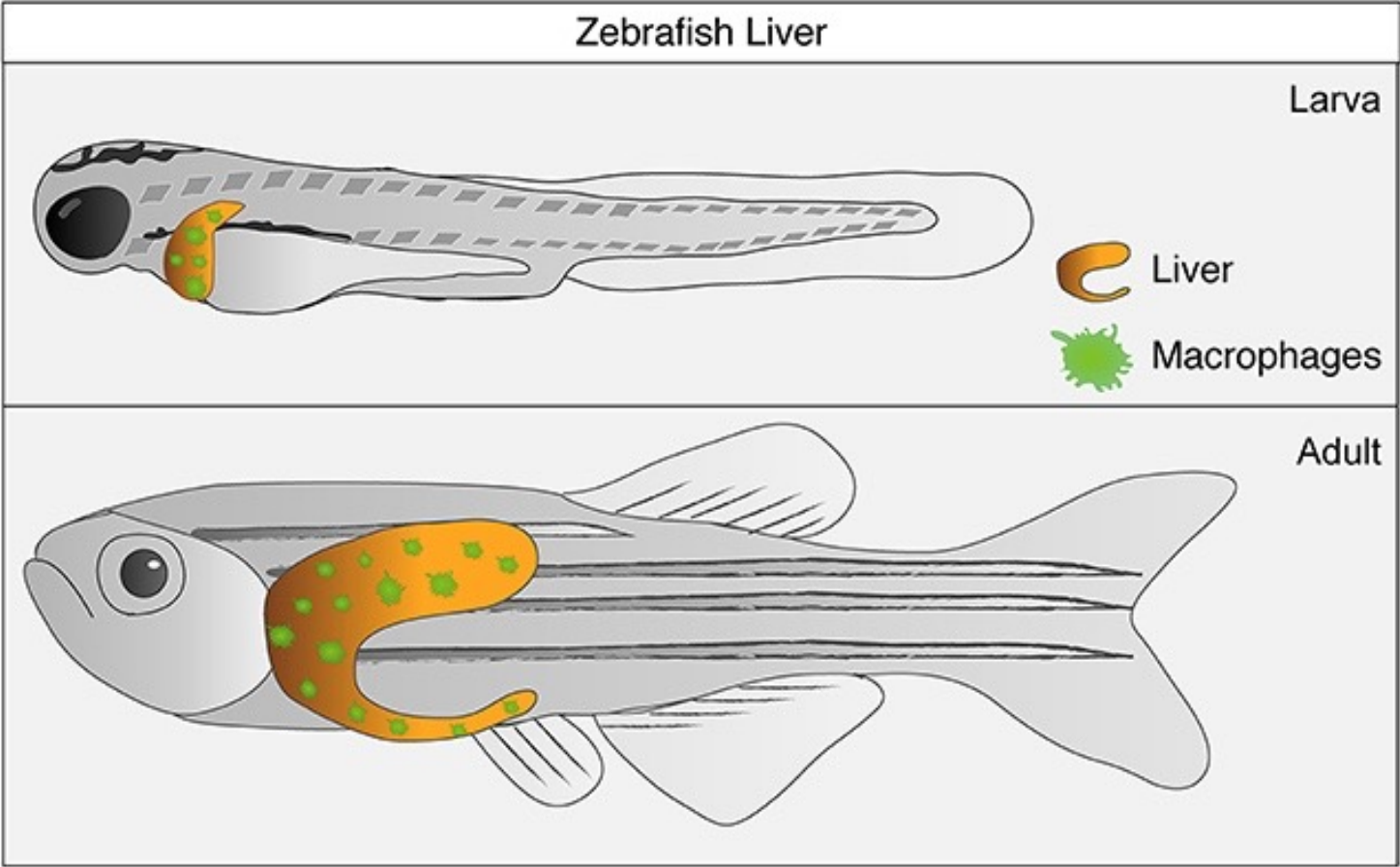
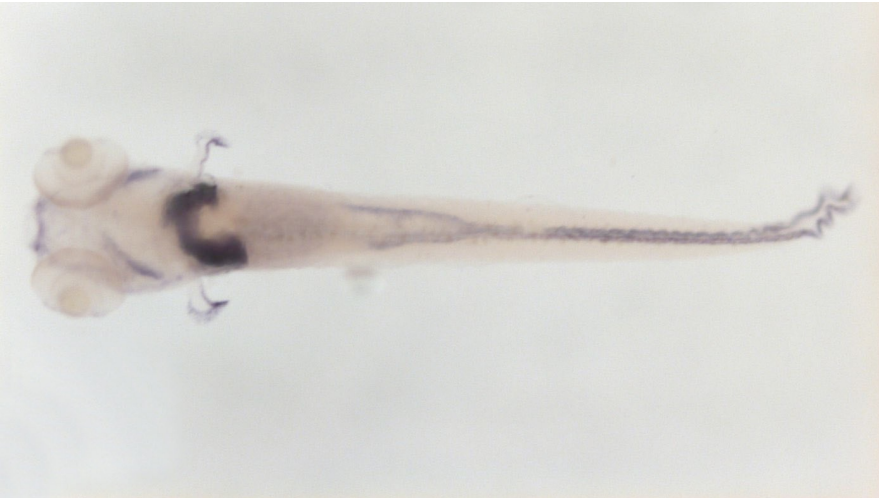
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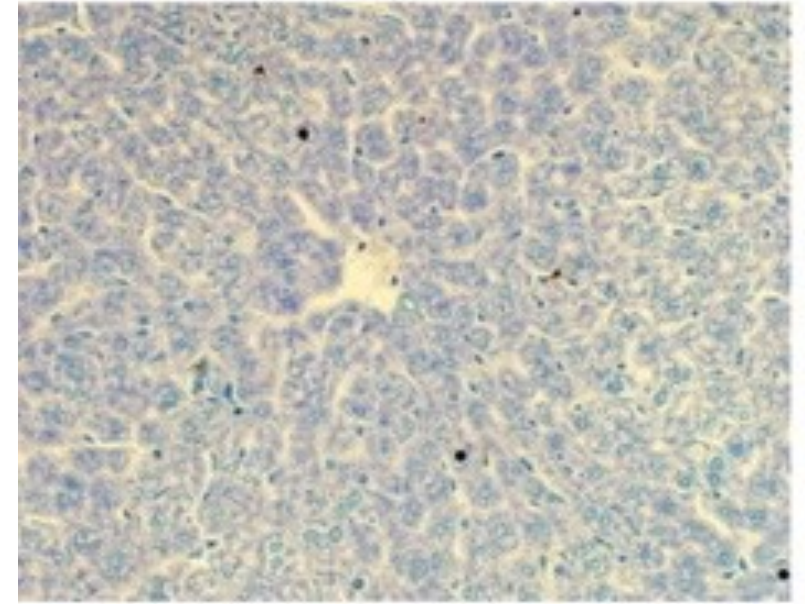
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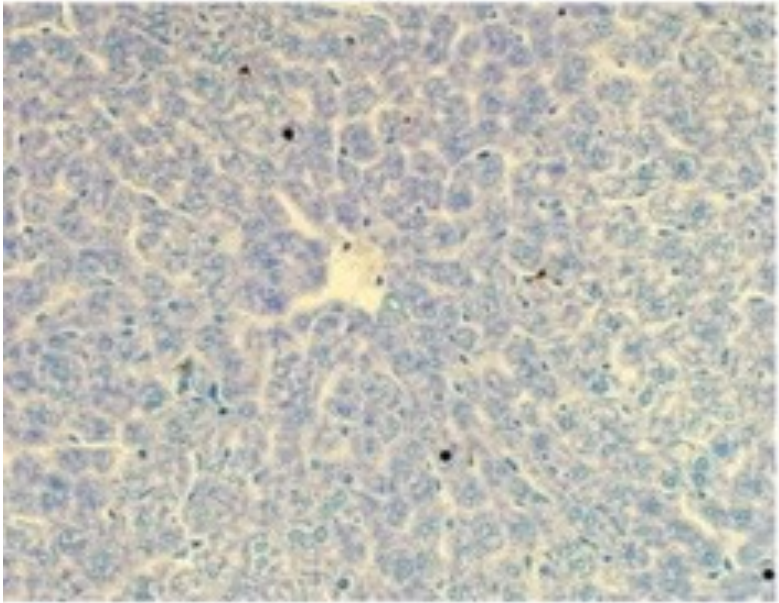
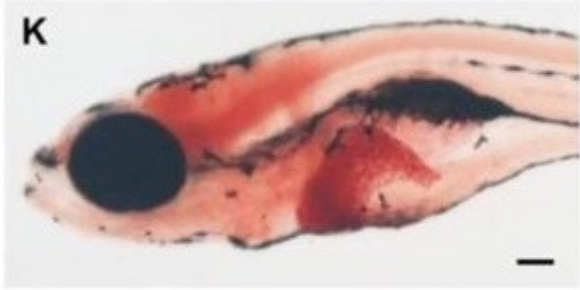
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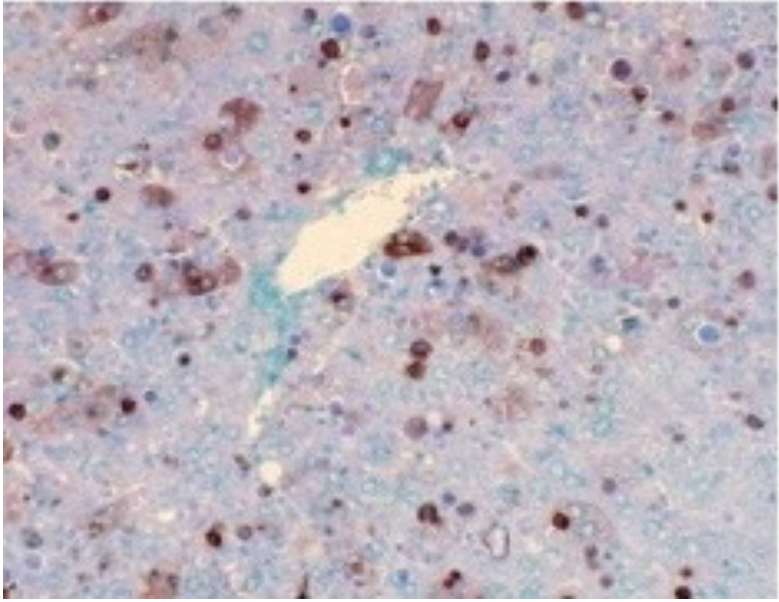
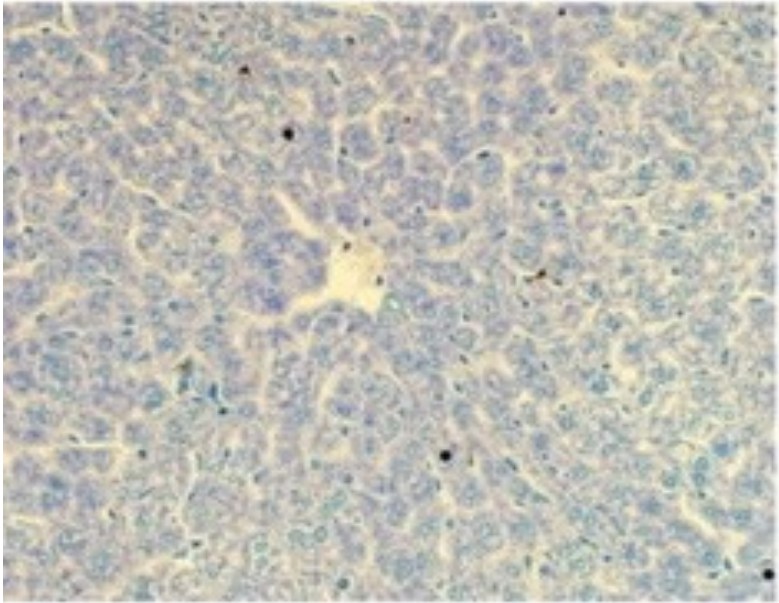
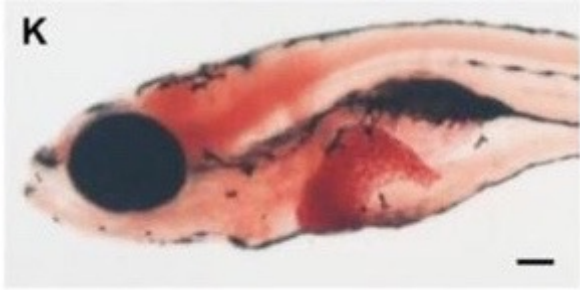
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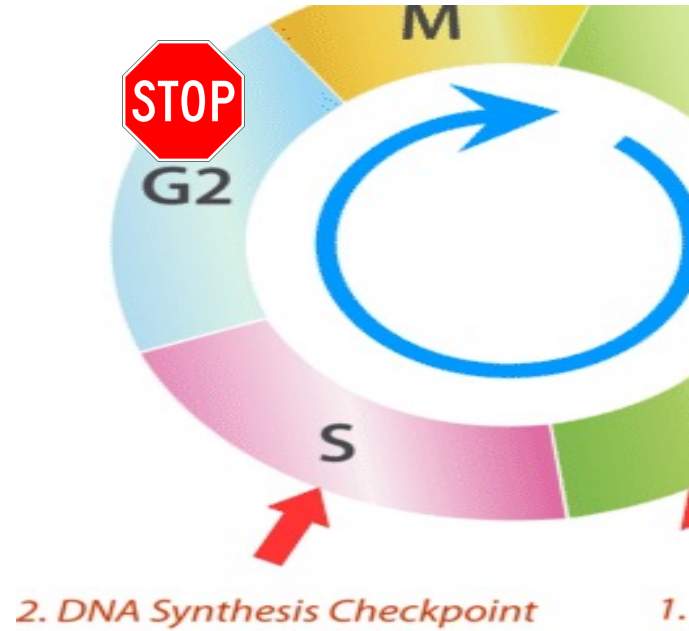
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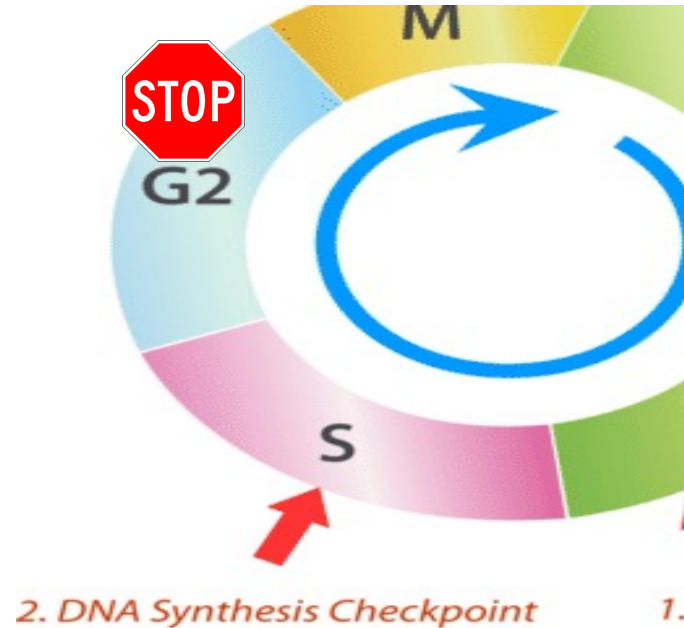
Danio rerio act as good models for liver diseases in humans



Primary goal of this research



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.

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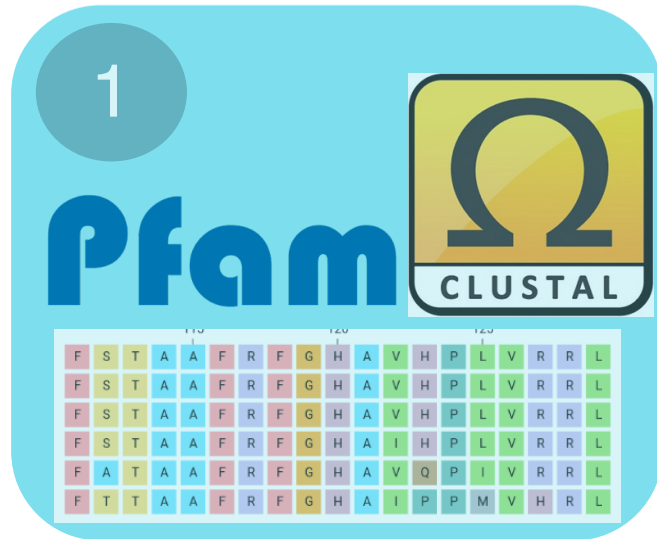
Long-term Goal : Further understand the mechanisms underlying this disorder in order to be able to effectively target symptoms with treatment drugs.

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.

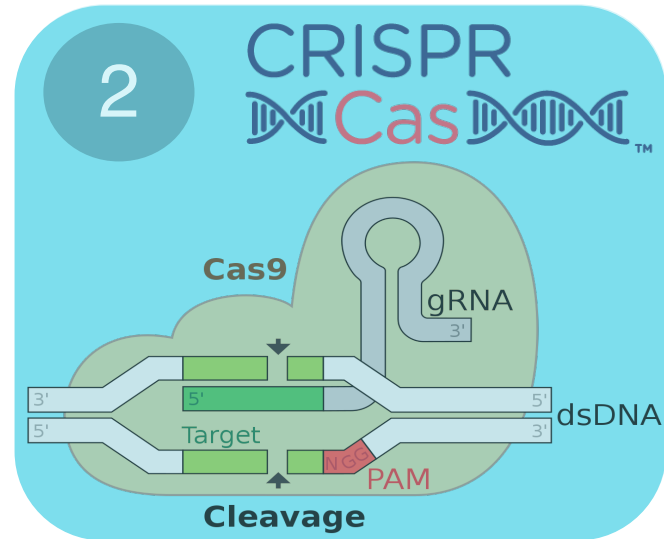
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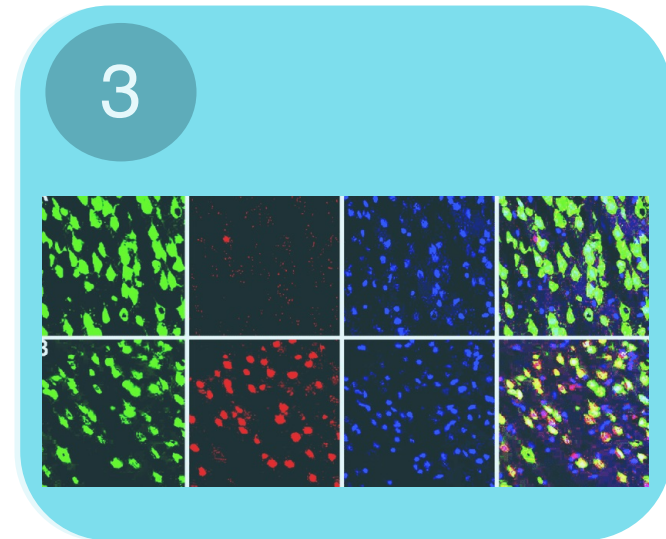
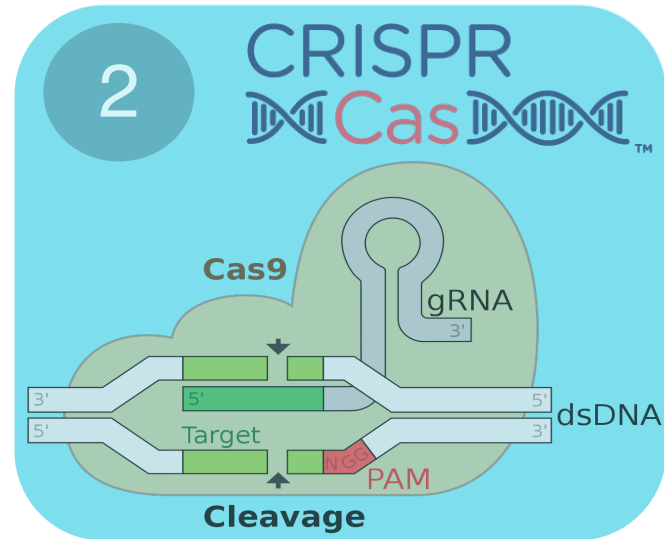
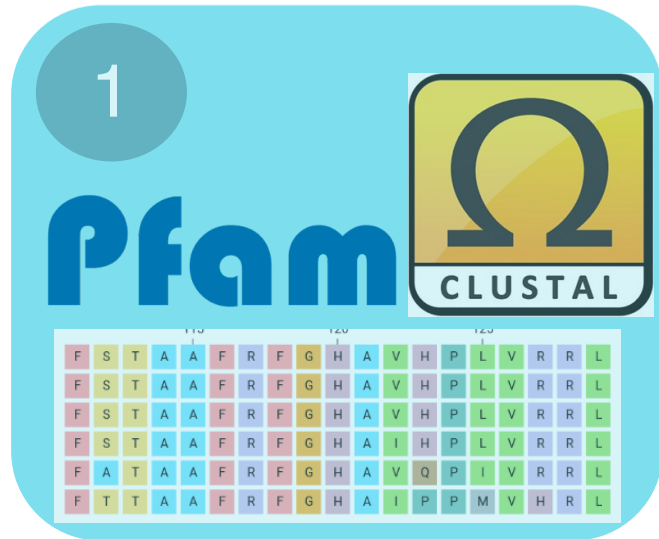
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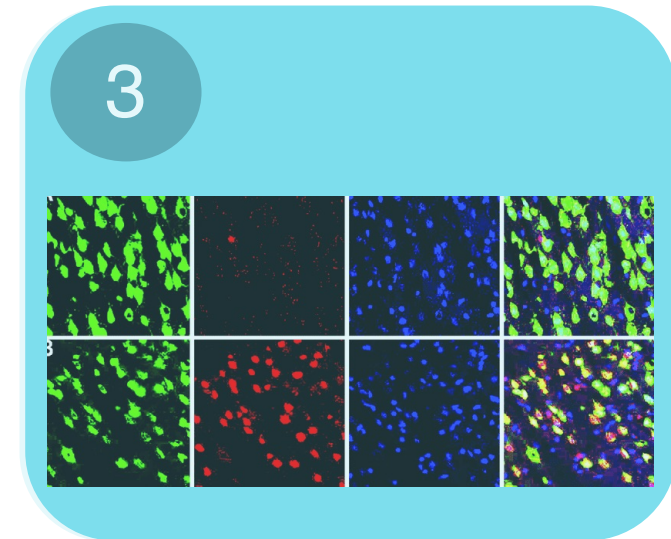
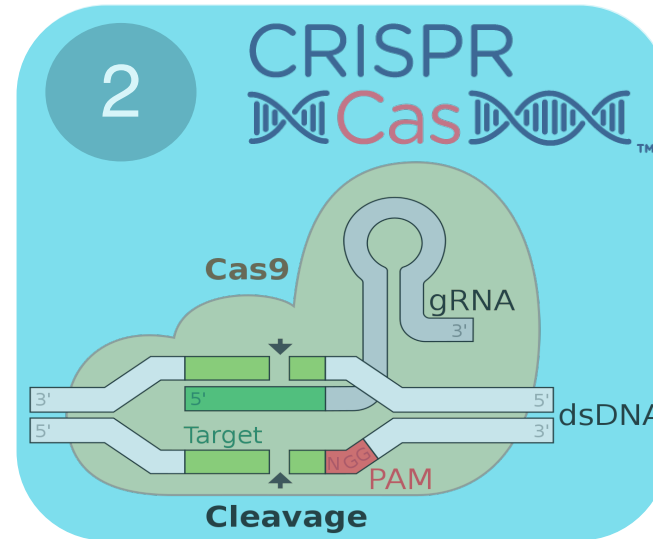
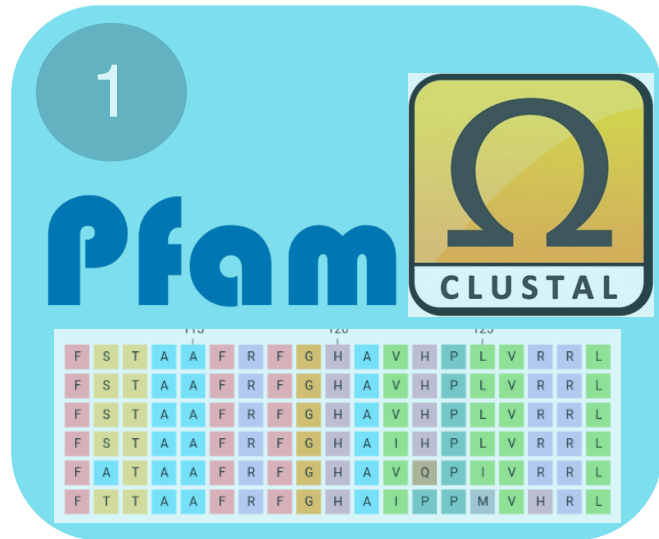
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Rationale : Understanding how different amino acids within the FAH gene correlate to healthy cell progression and normal liver phenotype will allow for better assessment of treatment options.



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.

Domain Analysis

CRISPR

TUNEL assay

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



Human

FAA Hydrolase N-

417

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



Human

FAH Hydrolase N-

417

Species/Abbrv	*		*	*	*	*	*	*	*		*		*	*	*	*	*	*	*		*	*		*	*	*		*		*	*	*	*	*	*	*	*											
1. Homo sapien	P	A	T	I	G	D	Y	T	D	F	Y	S	S	R	Q	H	A	T	N	V	G	I	M	F	R	D	K	E	N	A	L	M	P	N	W	L	H	L	-	V	G	Y	H	G	R	A	S	S
2. Danio rerio	P	A	E	I	G	D	Y	T	D	F	Y	S	S	R	D	H	A	T	N	V	G	I	M	F	R	G	K	E	N	A	L	M	P	N	W	L	R	L	P	V	G	Y	H	G	R	A	S	S
3. Mus musculus	P	A	T	I	G	D	Y	T	D	F	Y	S	S	R	Q	H	A	T	N	V	G	I	M	F	R	G	K	E	N	A	L	L	P	N	W	L	H	L	P	V	G	Y	H	G	R	A	S	S
4. Macaca mulatta	P	A	T	I	G	D	Y	T	D	F	Y	S	S	R	Q	H	A	T	N	V	G	I	M	F	R	D	K	E	N	A	L	M	P	N	W	L	H	L	P	V	G	Y	H	G	R	A	S	S
5. Xenopus	P	A	N	I	G	D	Y	T	D	F	Y	S	S	R	D	H	A	T	N	V	G	I	M	F	R	G	K	D	N	A	L	M	P	N	W	L	H	L	P	V	G	Y	H	G	R	A	S	S
6. Protopterus annectan	P	A	E	I	G	D	Y	T	D	F	Y	S	S	C	H	H	A	T	N	V	G	I	M	F	R	G	K	E	N	A	L	M	P	N	W	L	H	L	P	V	G	Y	H	G	R	A	S	S
7. C. Elegans	P	A	Q	I	G	D	Y	T	D	F	Y	S	S	I	H	H	A	T	N	V	G	I	M	F	R	G	K	E	N	A	L	M	P	N	W	K	W	L	P	V	G	Y	H	G	R	A	S	S
8. Arabidopsis	P	M	V	I	G	D	Y	T	D	F	F	A	S	M	H	H	A	K	N	C	G	L	M	F	R	G	P	E	N	A	I	N	P	N	W	F	R	L	P	I	A	Y	H	G	R	A	S	S
9. Drosophila	P	A	Q	I	G	D	Y	T	D	F	Y	S	S	I	H	H	A	T	N	V	G	I	M	F	R	G	P	D	N	A	L	M	P	N	W	R	H	L	P	V	G	Y	H	G	R	A	S	S

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



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FAA Hydrolase N-

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Species/Abbrv	*		*	*	*	*	*	*		*		*	*	*		*	*		*	*		*	*	*		*		*	*	*	*	*	*	*														
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5. Xenopus	P	A	N	I	G	D	Y	T	D	F	Y	S	S	R	D	H	A	T	N	V	G	I	M	F	R	G	K	D	N	A	L	M	P	N	W	L	H	L	P	V	G	Y	H	G	R	A	S	S
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8. Arabidopsis	P	M	V	I	G	D	Y	T	D	F	F	A	S	M	H	H	A	K	N	C	G	L	M	F	R	G	P	E	N	A	I	N	P	N	W	F	R	L	P	I	A	Y	H	G	R	A	S	S
9. Drosophila	P	A	Q	I	G	D	Y	T	D	F	Y	S	S	I	H	H	A	T	N	V	G	I	M	F	R	G	P	D	N	A	L	M	P	N	W	R	H	L	P	V	G	Y	H	G	R	A	S	S

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



Human

FAH Hydrolase N-

417

Species/Abbrv

1. Homo sapien

2. Danio rerio



Domain Analysis

CRISPR

TUNEL assay

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

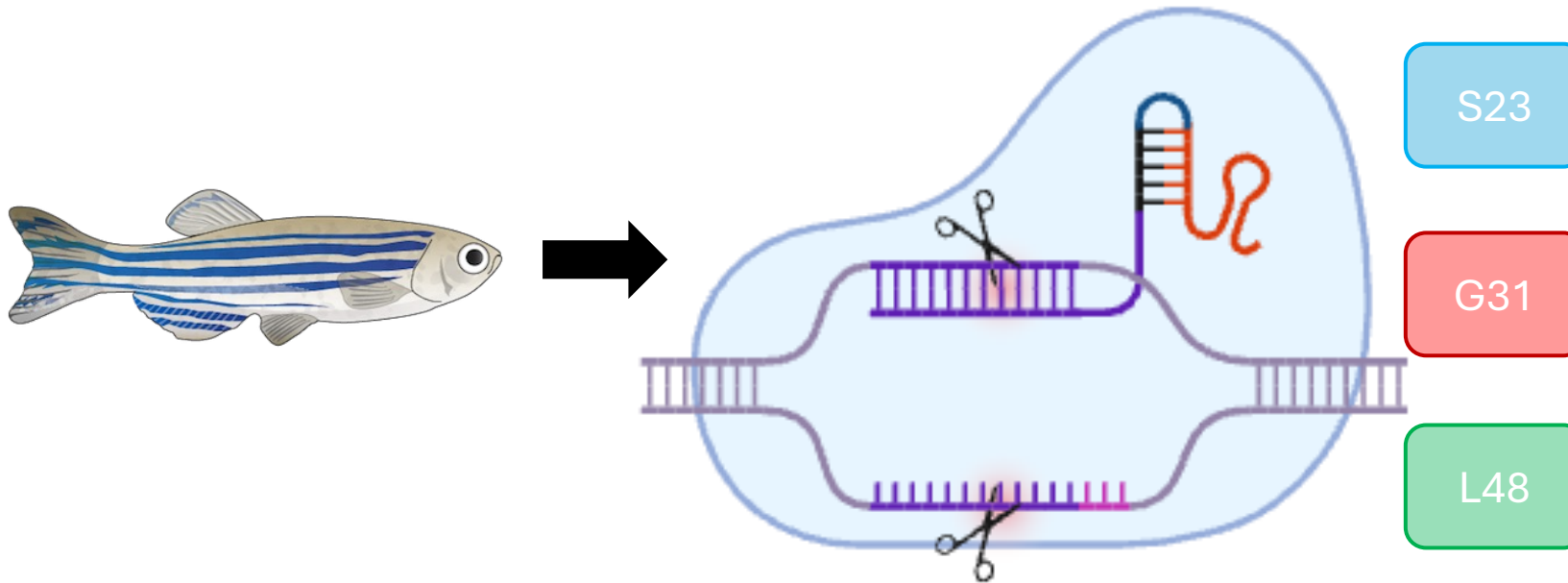


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CRISPR

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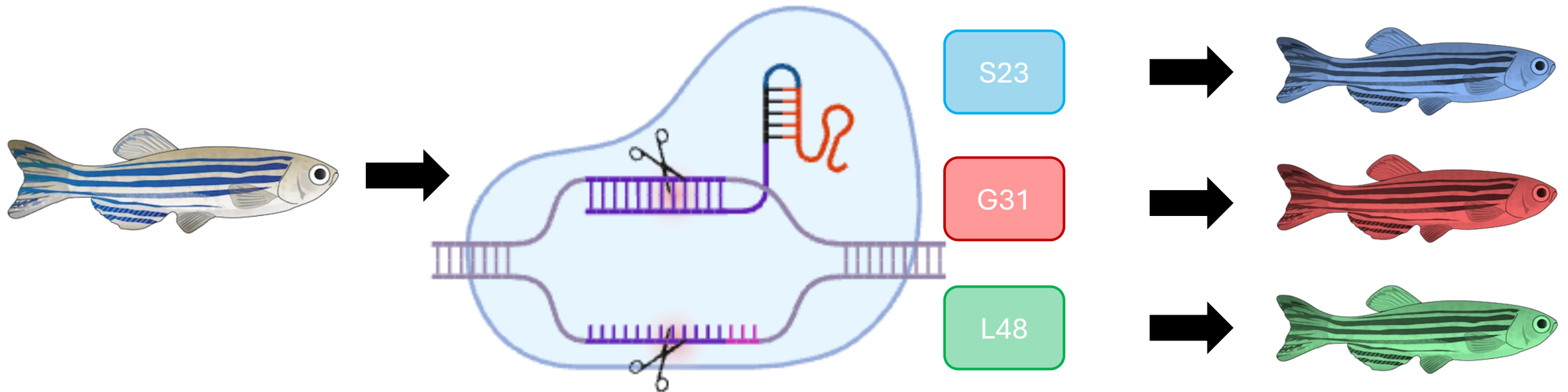


Domain Analysis

CRISPR

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Domain Analysis

CRISPR

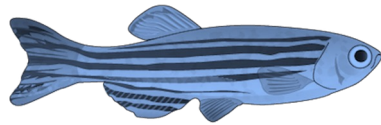
TUNEL assay

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WT



S23



G31

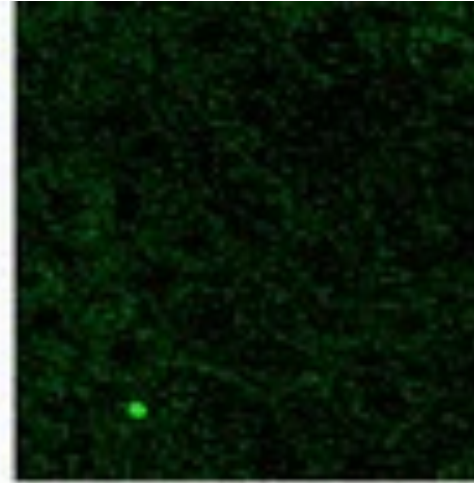
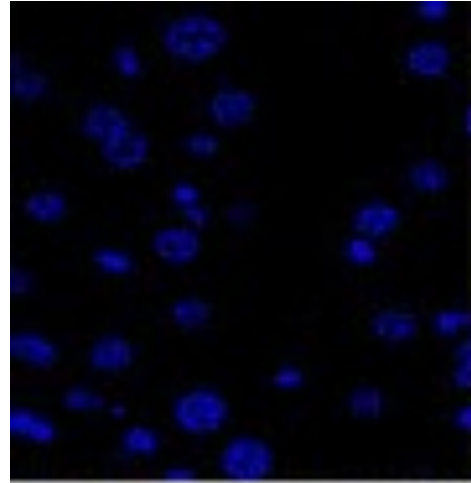


L48

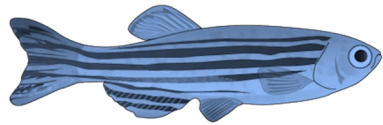


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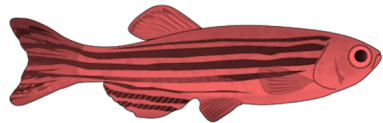
WT



S23



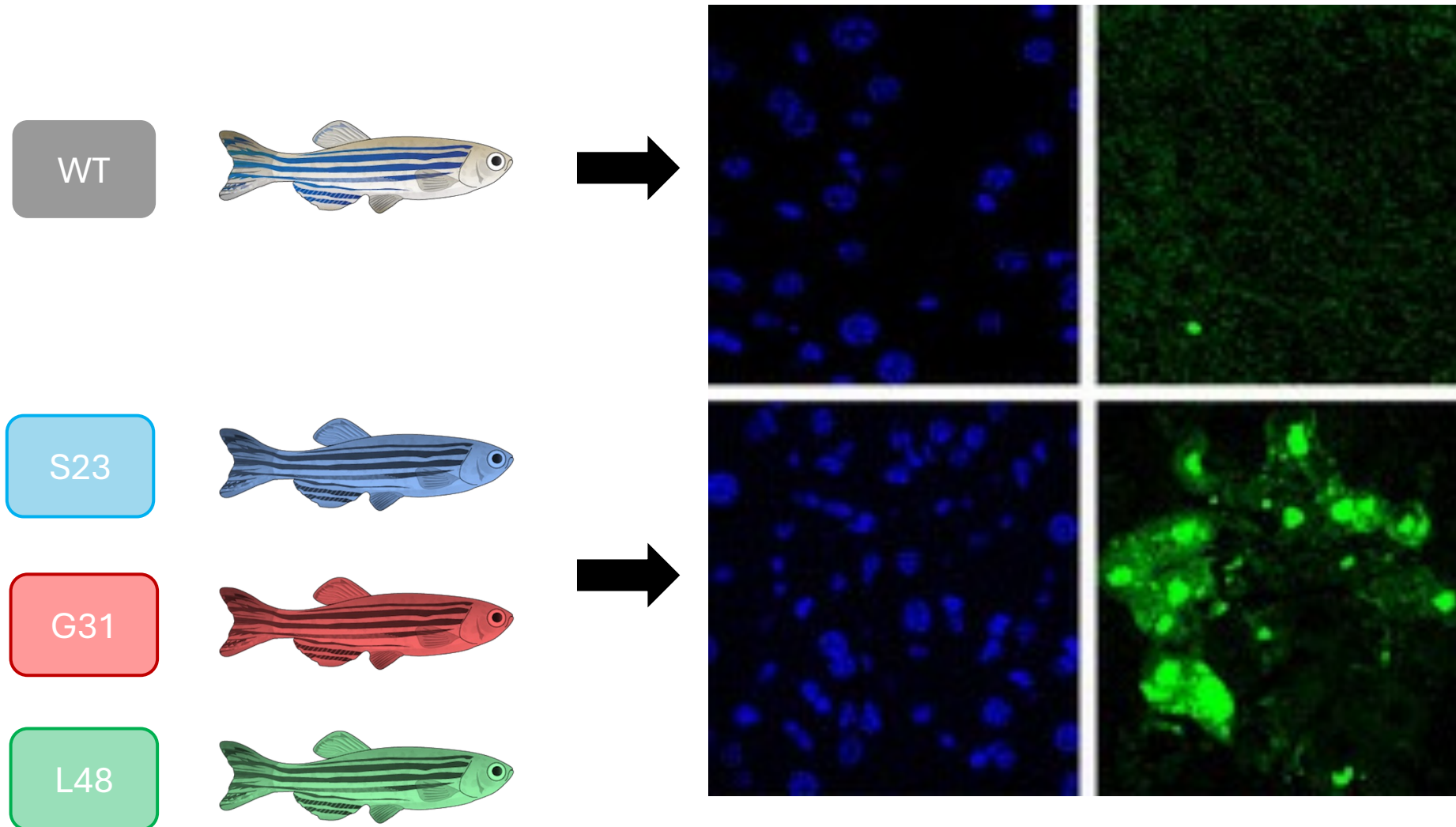
G31



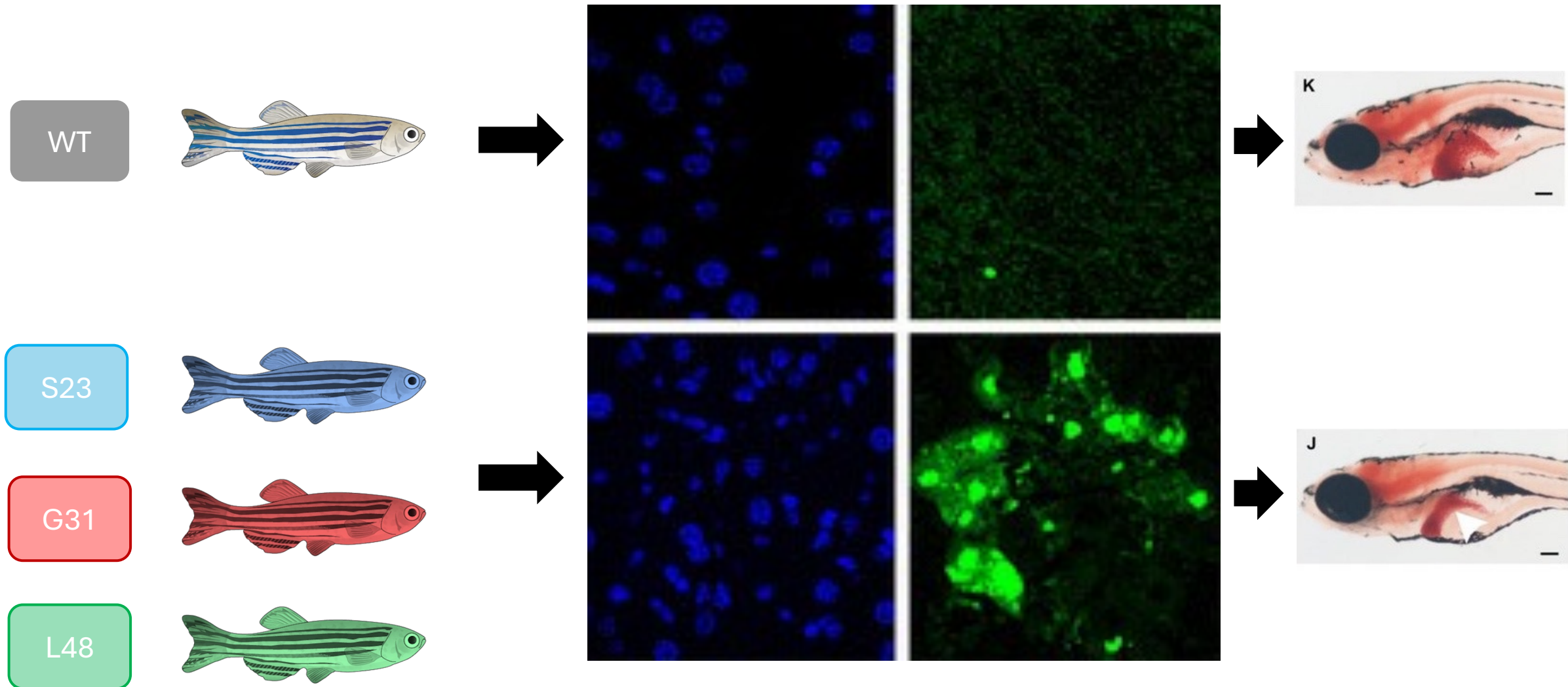
L48



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



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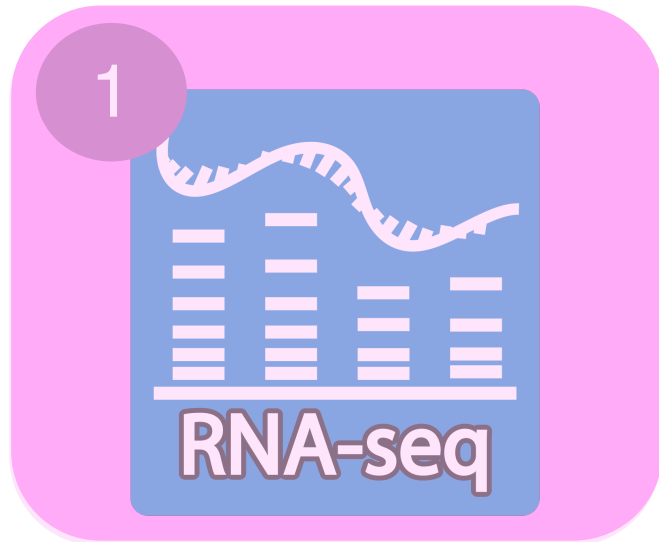


Aim 2 : Identify differentially expressed genes in WT and mutant FAH hepatocyte cells that lead to apoptosis.

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.

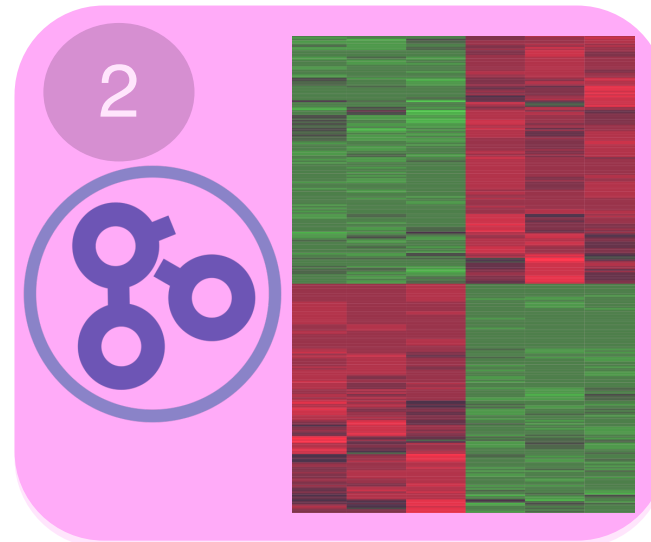
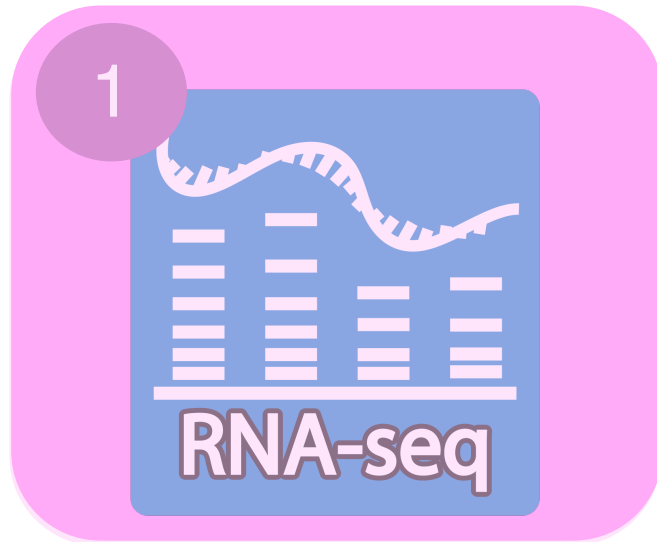
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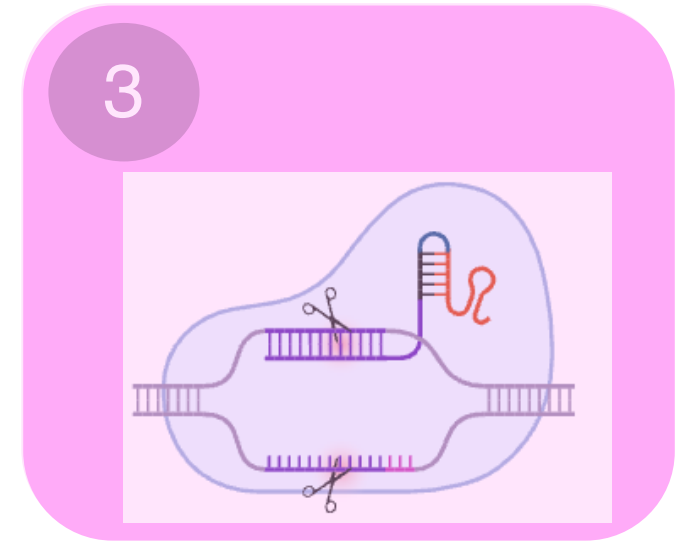
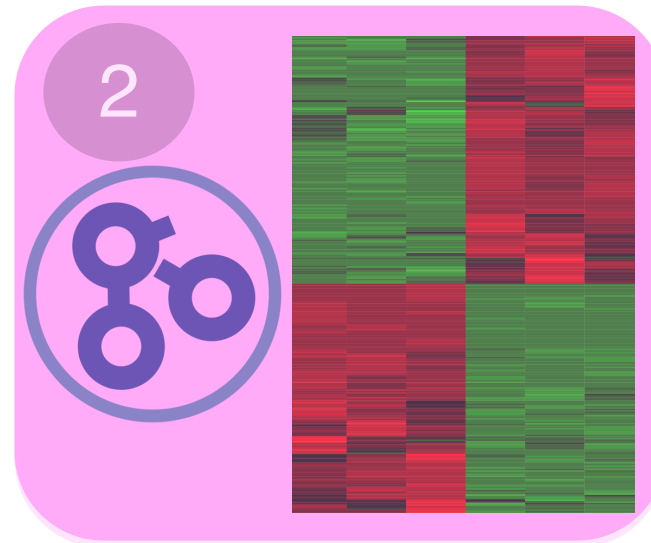
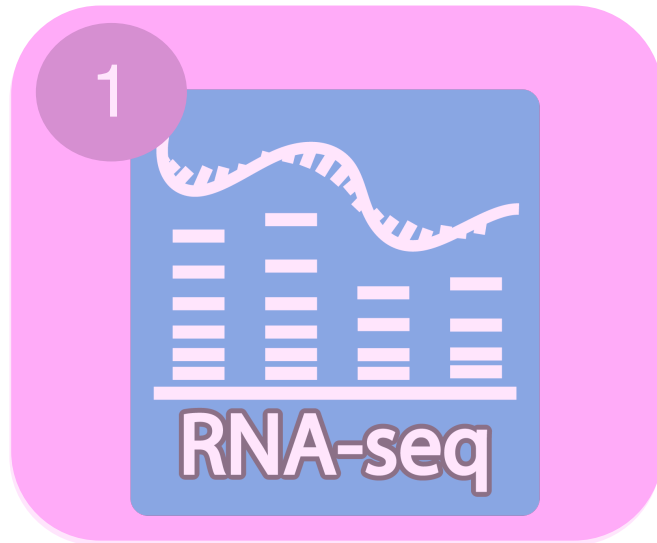
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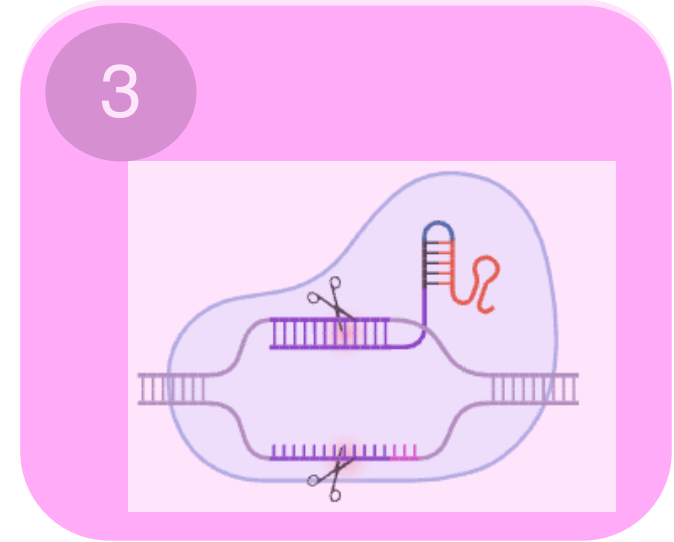
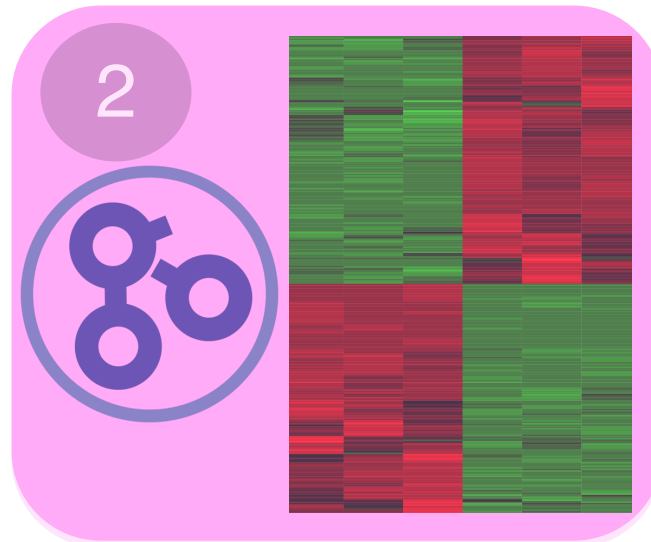
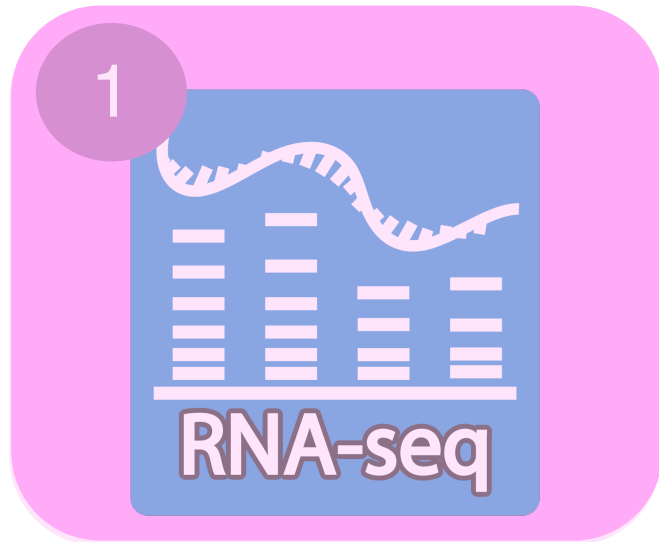
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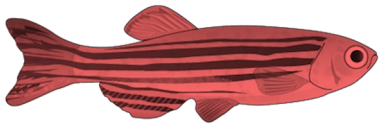
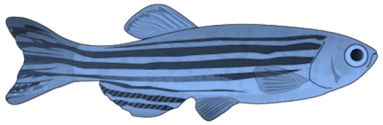
Hypothesis : FAH mutant hepatocyte cells will have differentially expressed genes than WT hepatocyte cells, specifically in genes involved in tyrosine catabolism.

RNA-seq

Gene Ontology

Validation

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

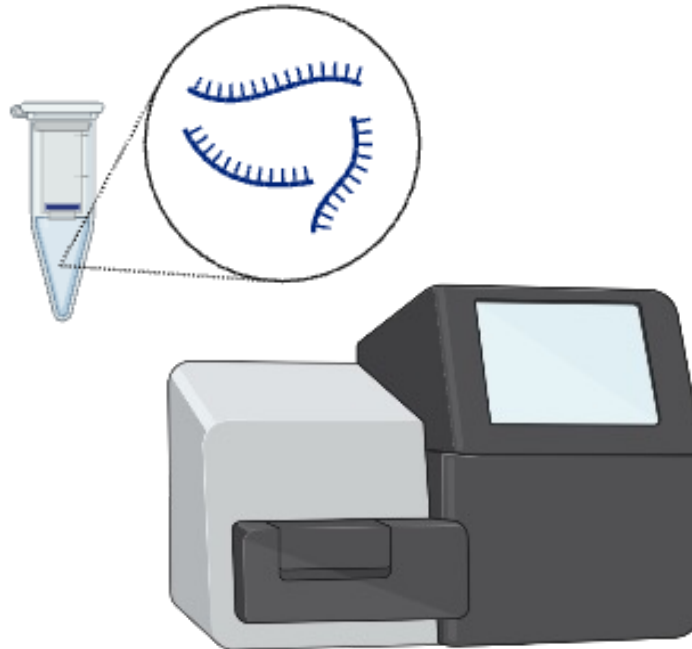
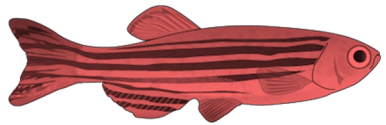
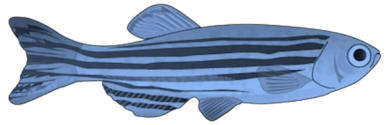


RNA-seq

Gene Ontology

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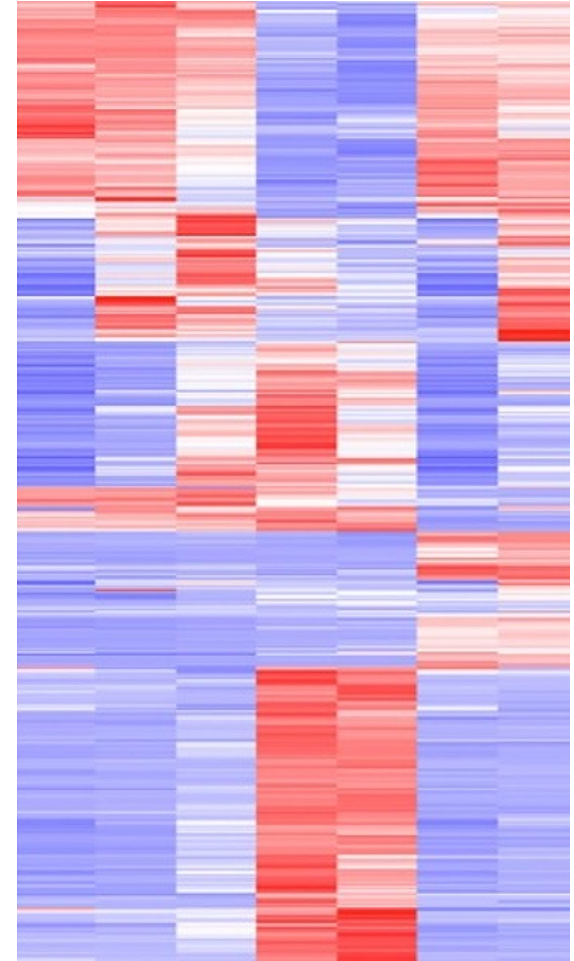
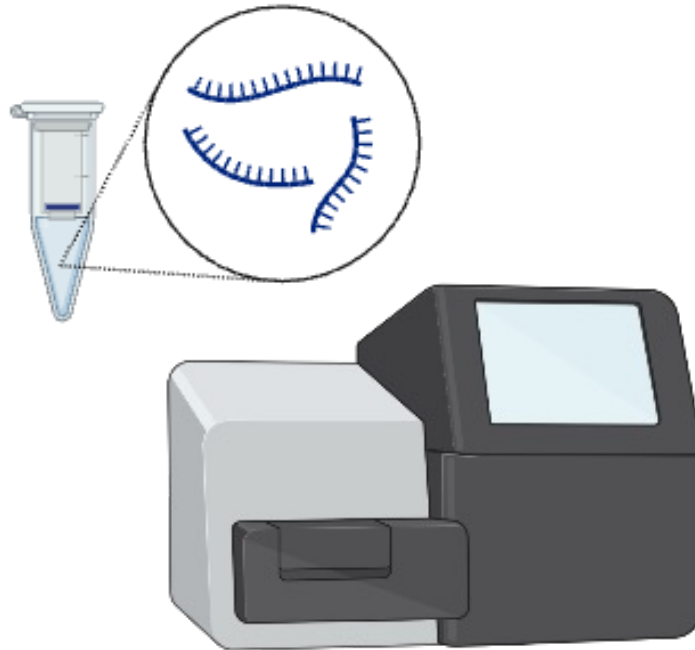
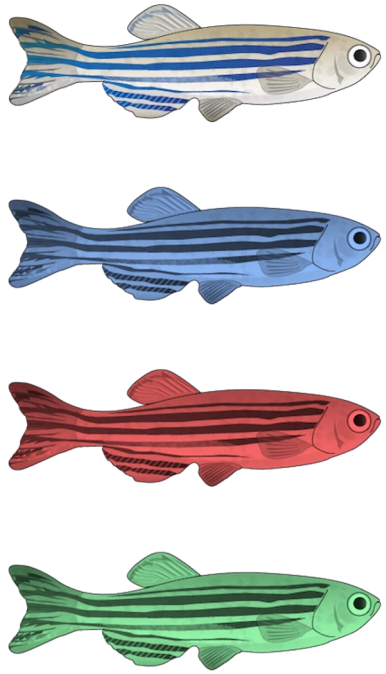


RNA-seq

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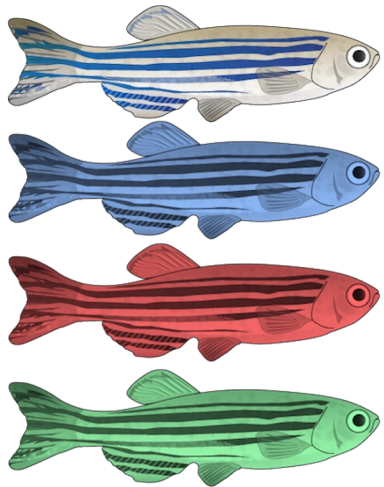


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Gene Ontology

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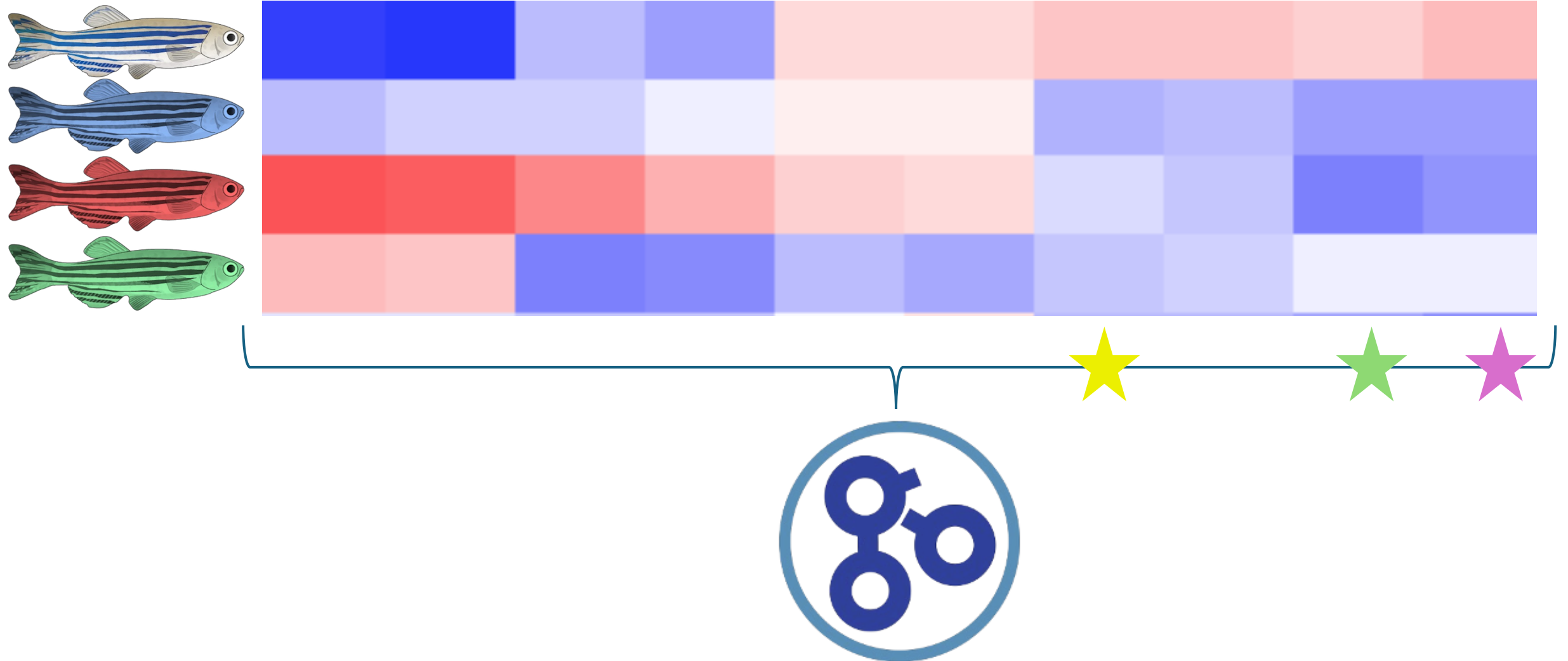


RNA-seq

Gene Ontology

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RNA-seq

Gene Ontology

Validation

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

WT

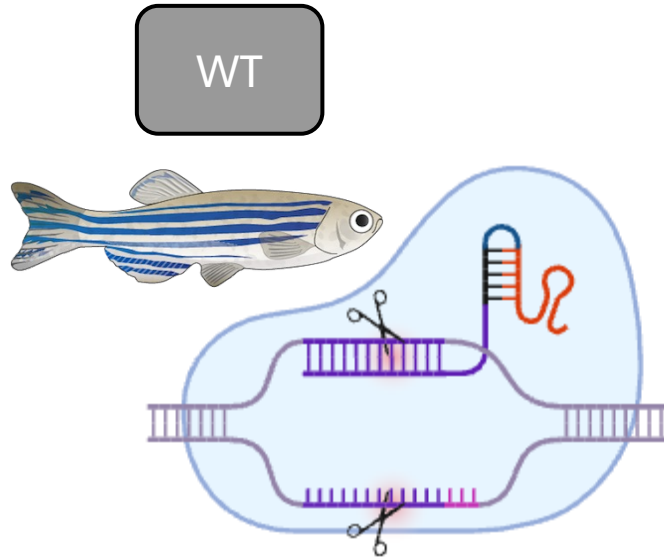


RNA-seq

Gene Ontology

Validation

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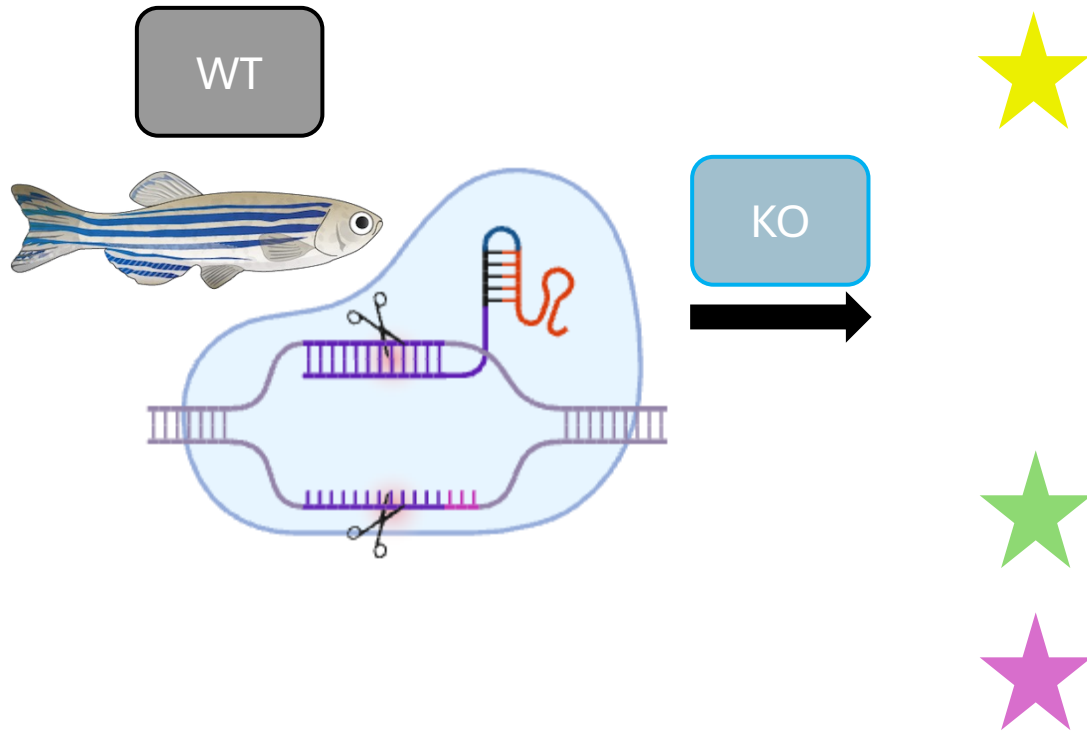


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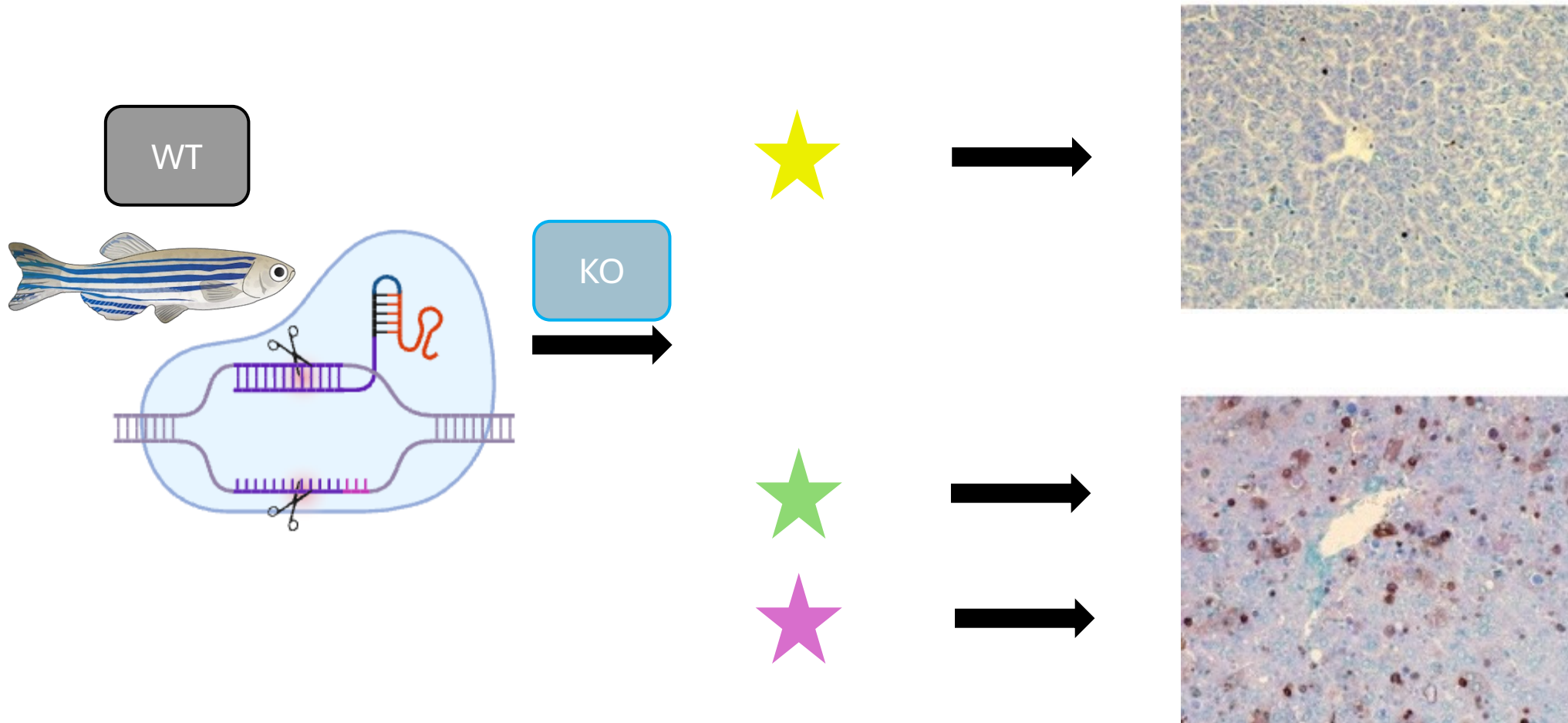
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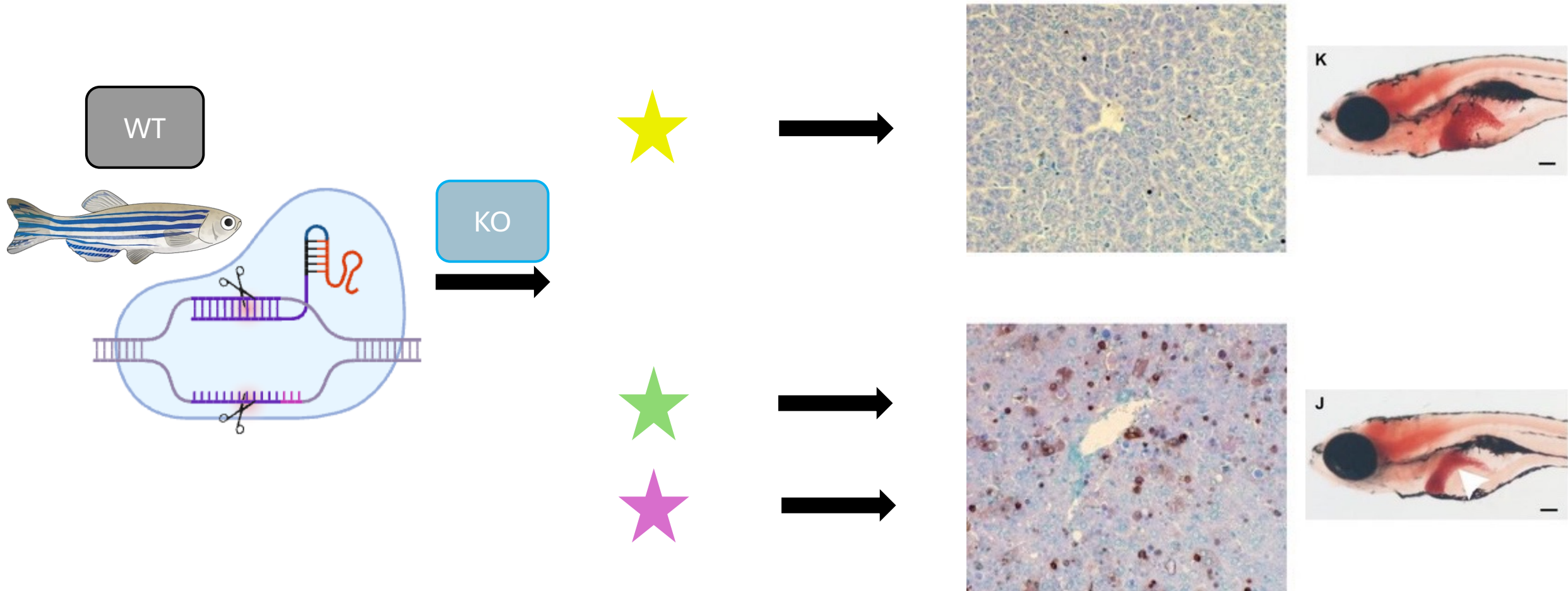


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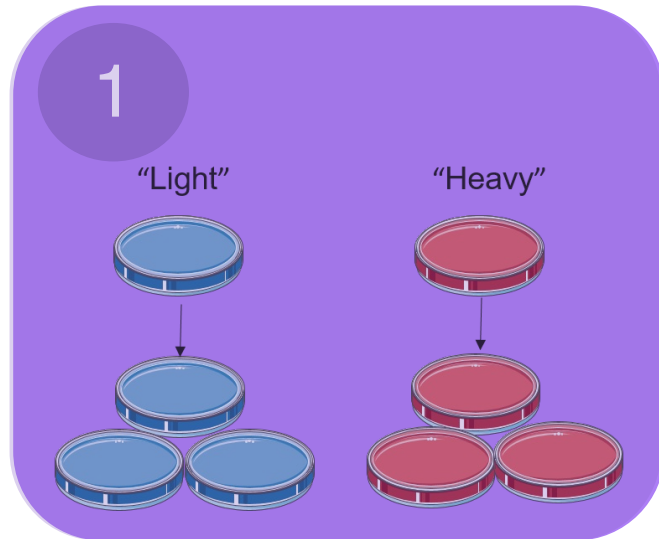


Aim 3 : Quantify differentially expressed proteins in WT and mutant FAH hepatocyte cells that lead to apoptosis.

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.

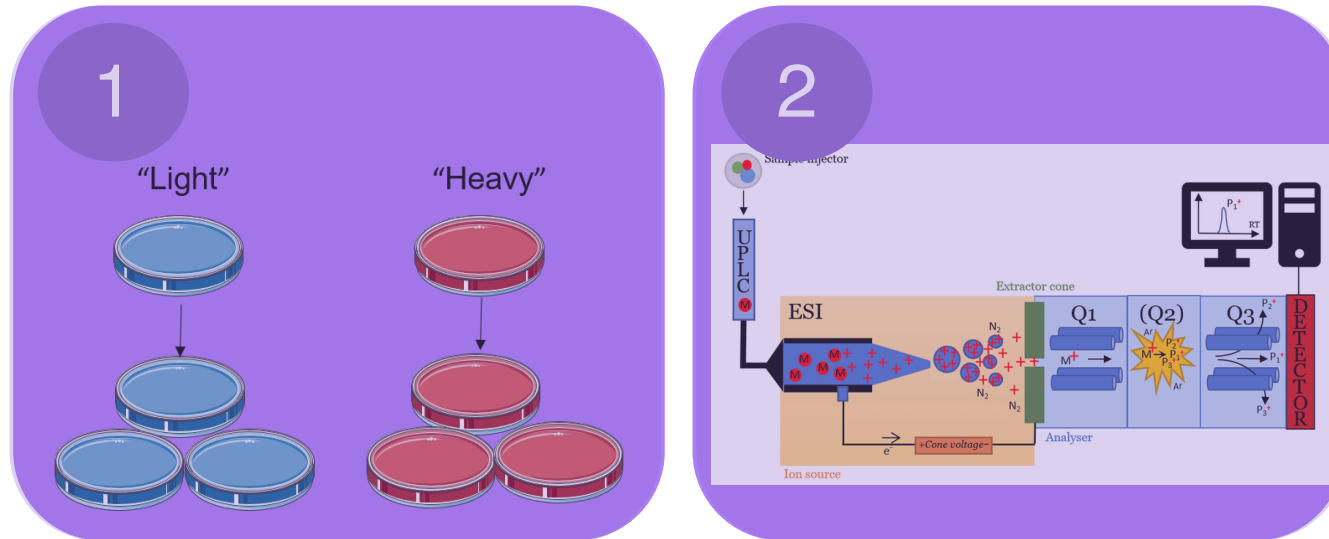
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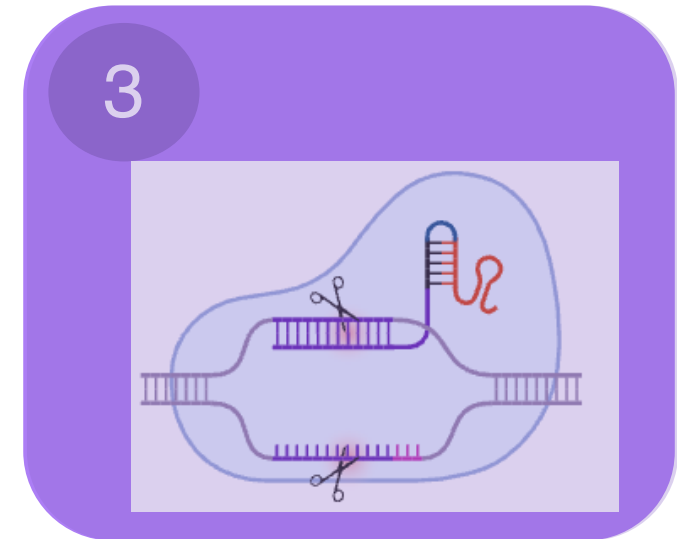
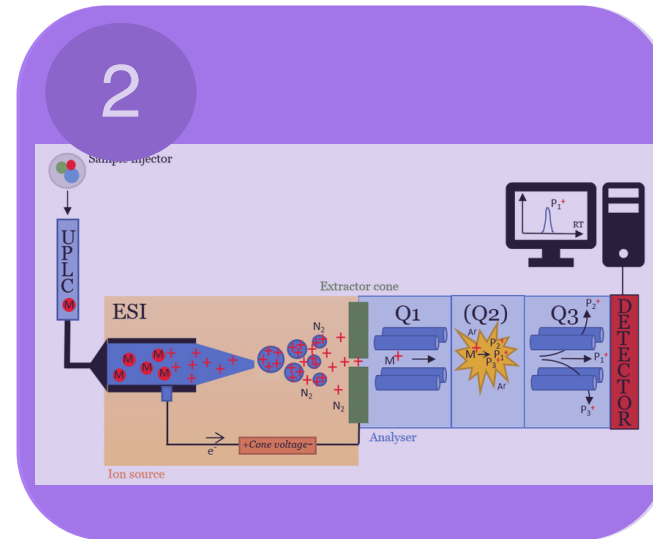
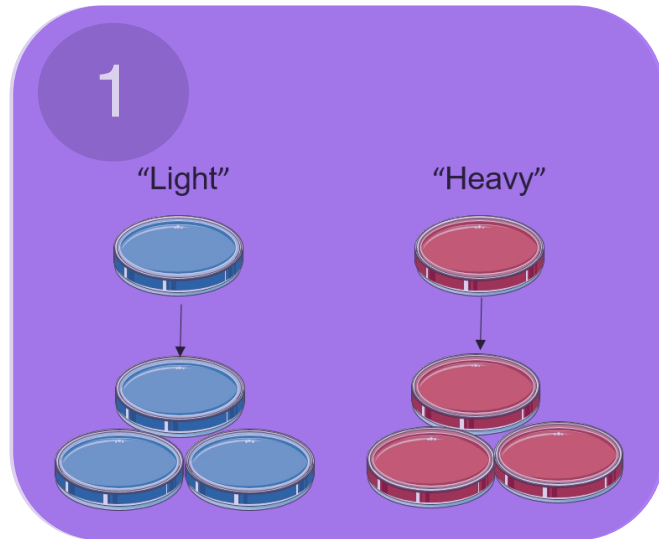
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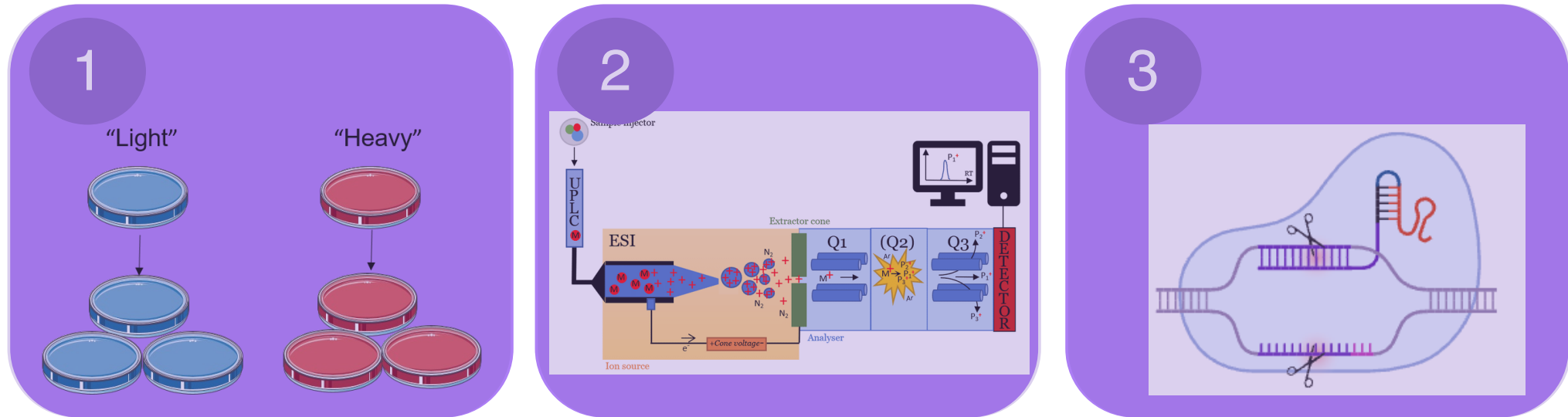
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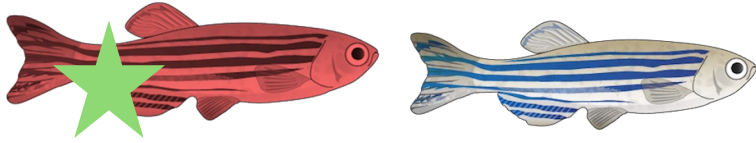
Hypothesis : Mutant FAH hepatocyte cells will have different protein expressions than WT cells, specifically in proteins that are involved in apoptosis of cells.

SILAC

LC-MS/MS

CRISPR

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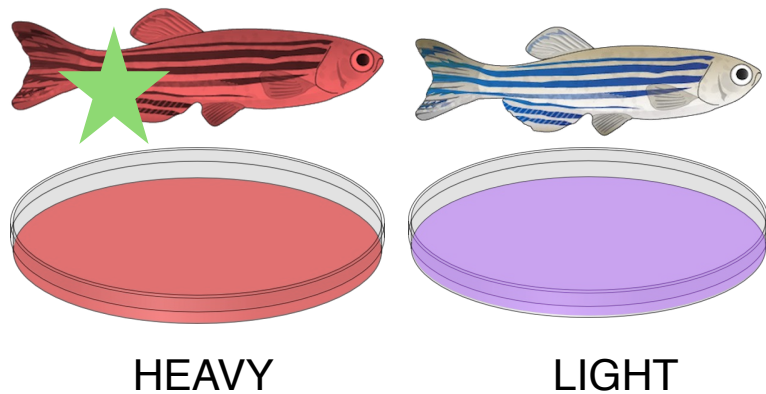


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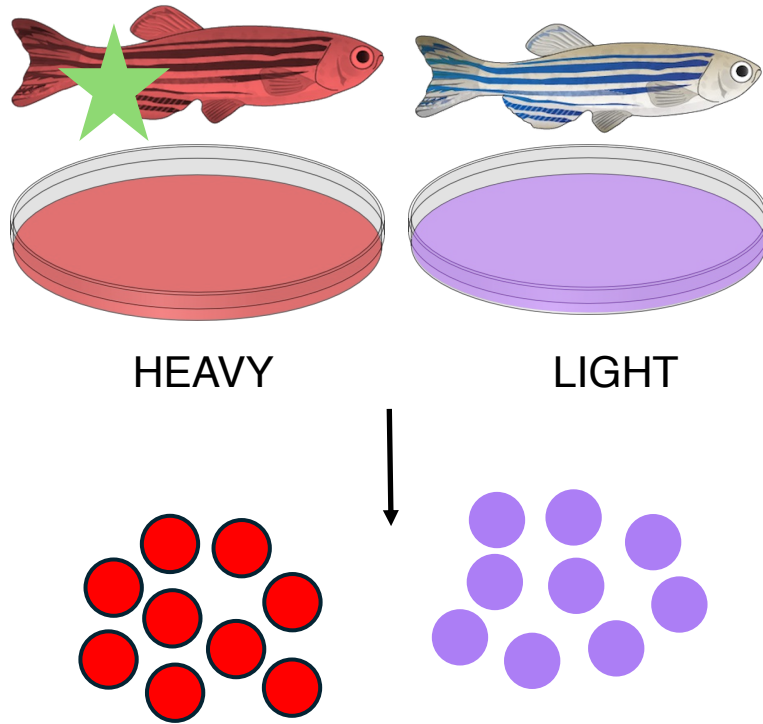


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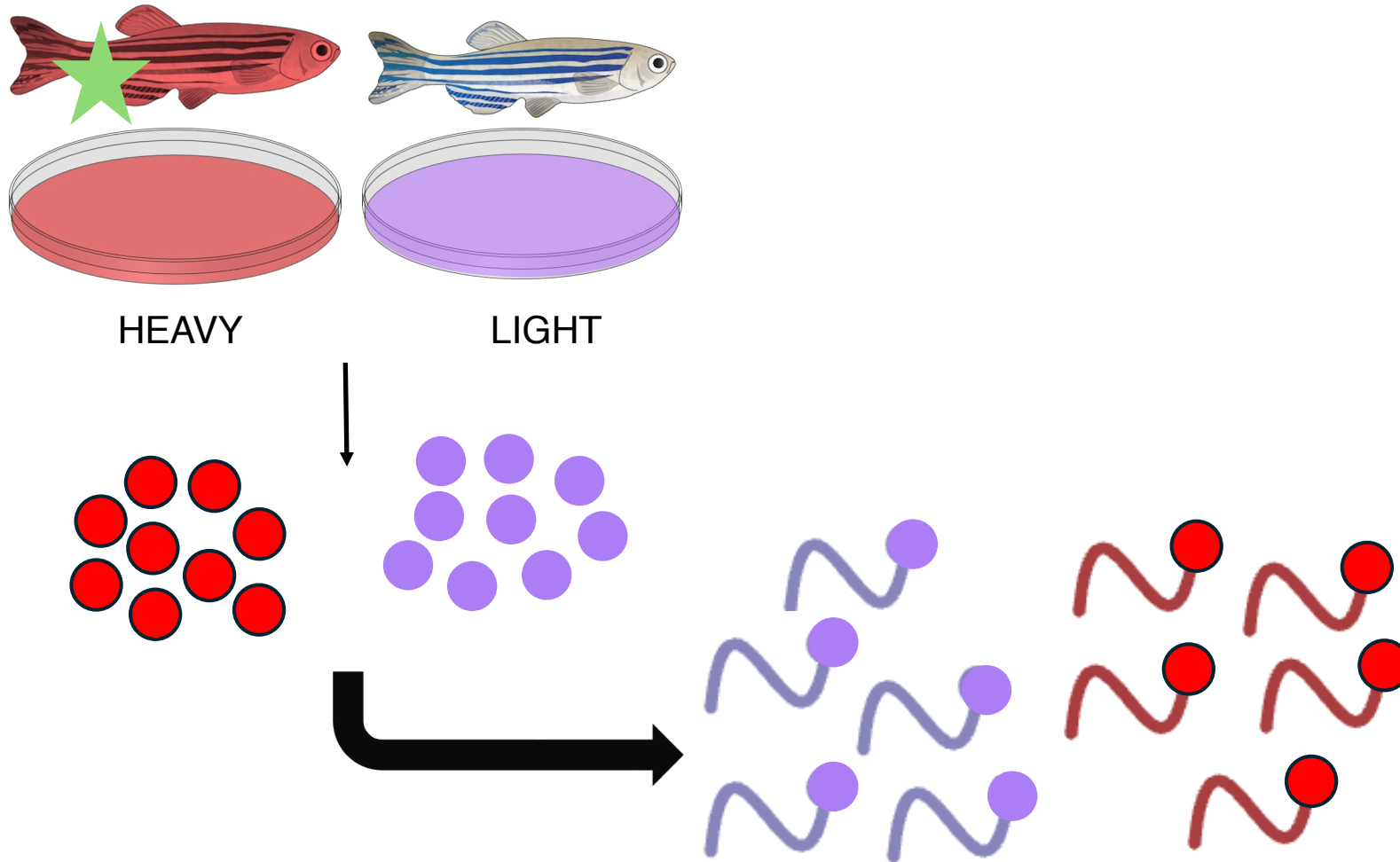


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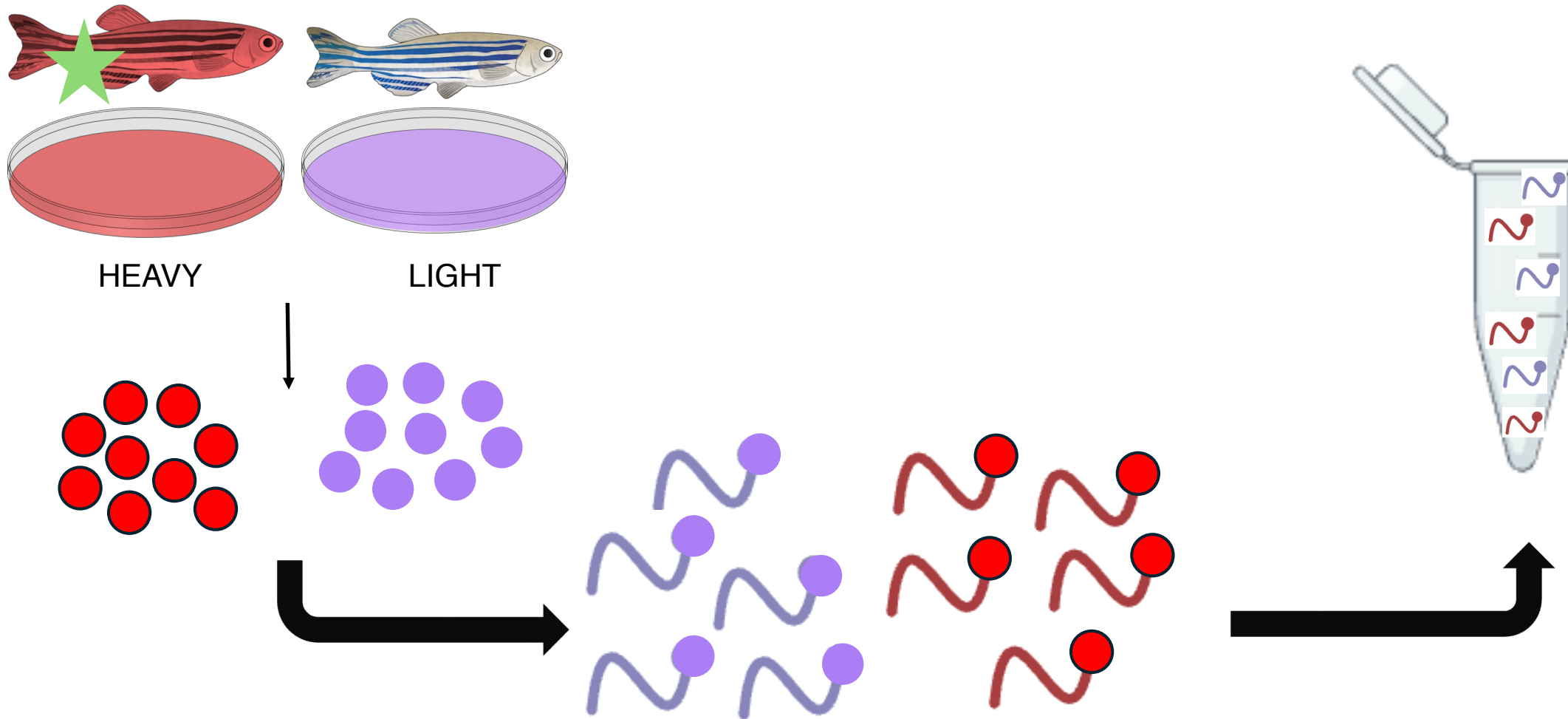


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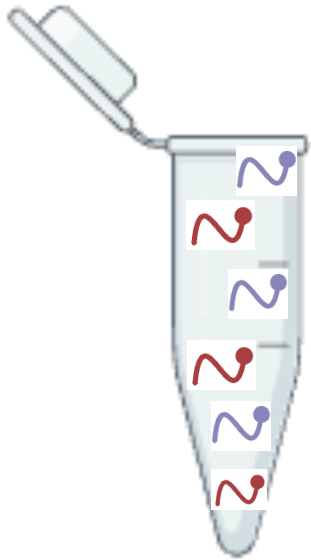


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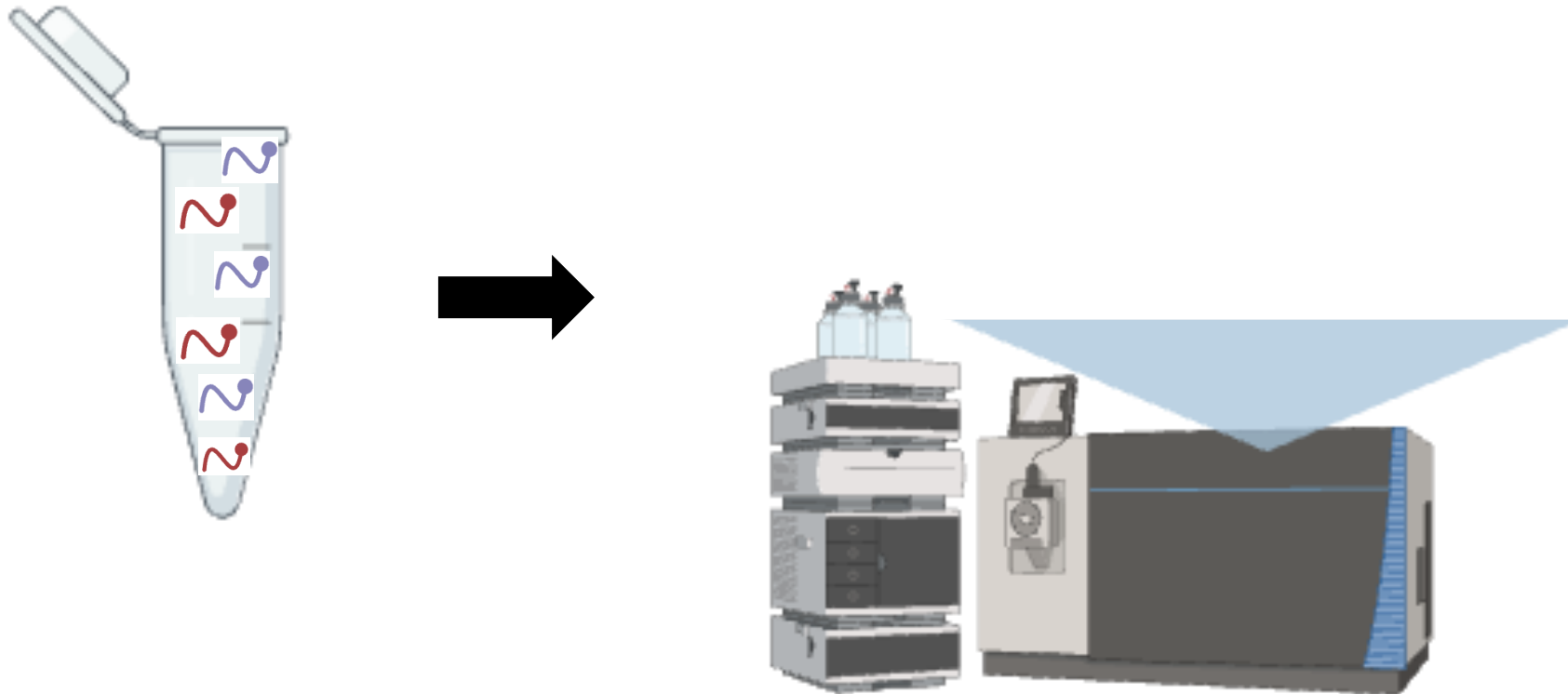


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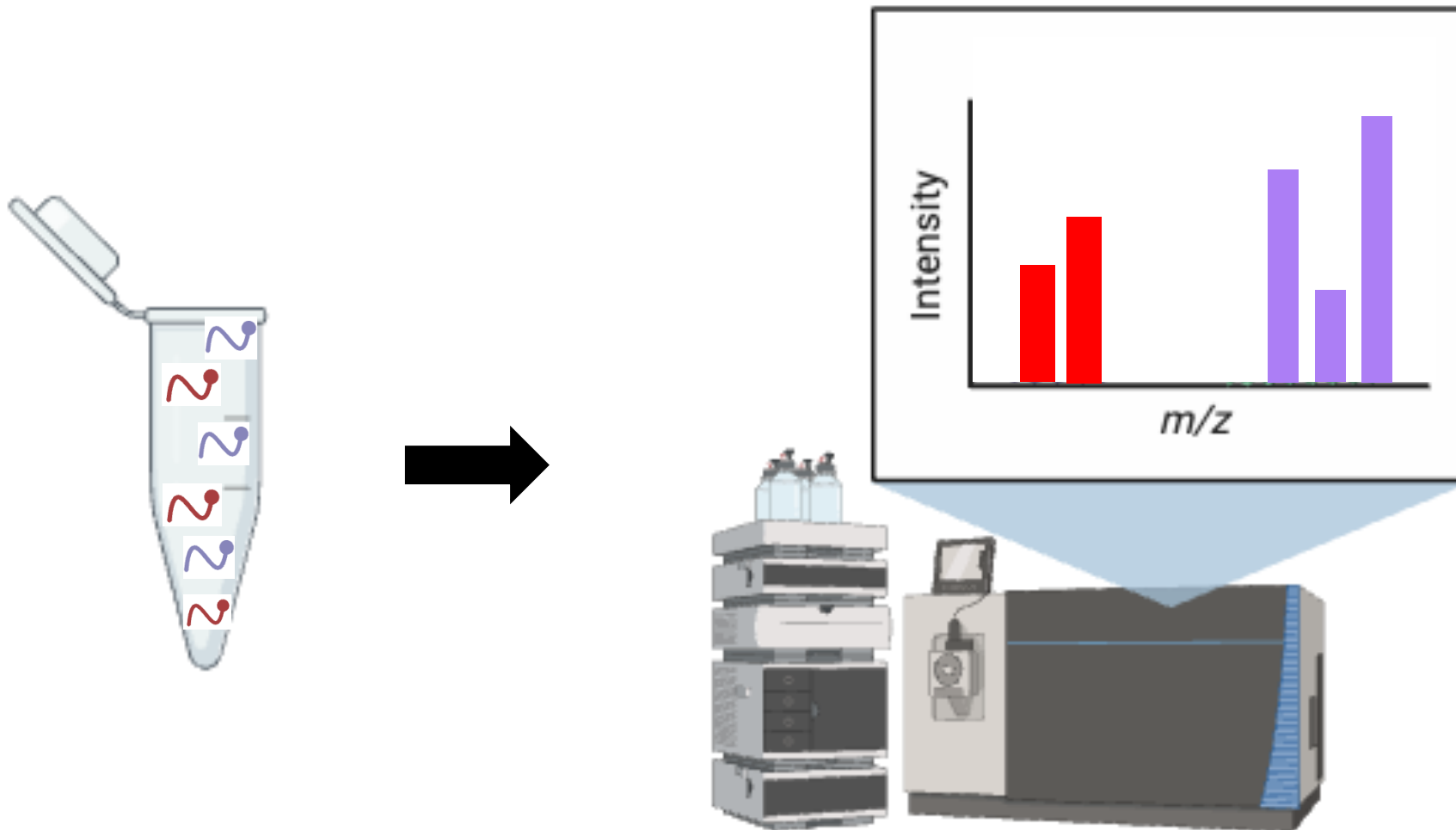


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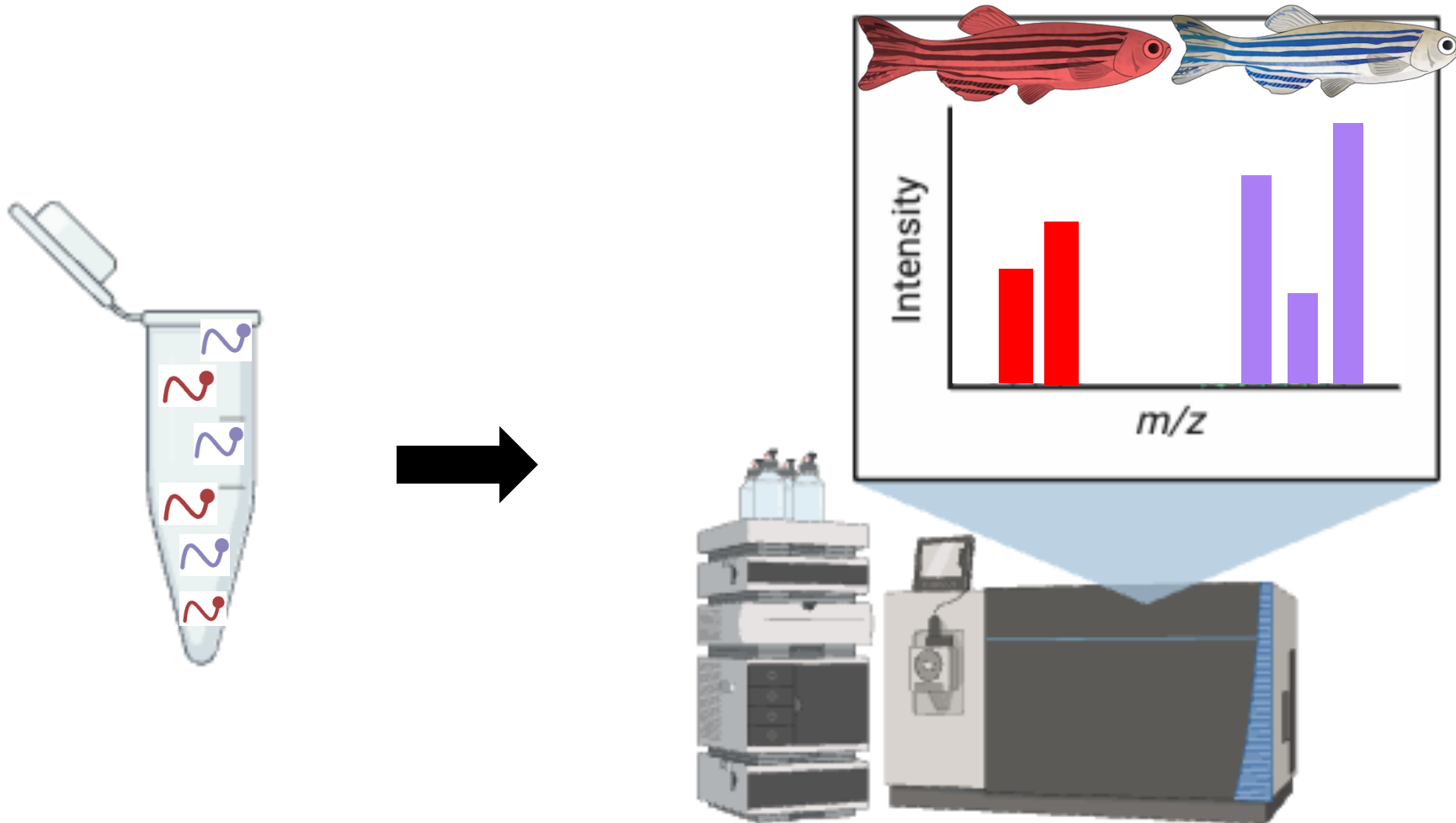


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SILAC

LC-MS/MS

CRISPR

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

WT

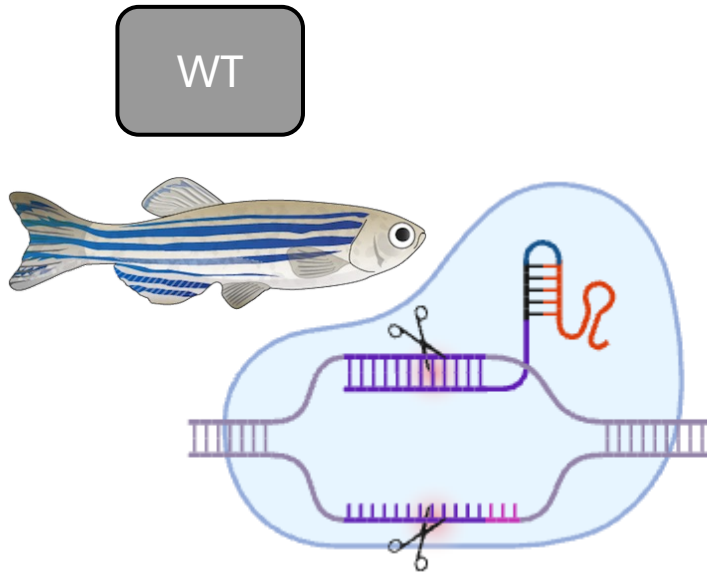


SILAC

LC-MS/MS

CRISPR

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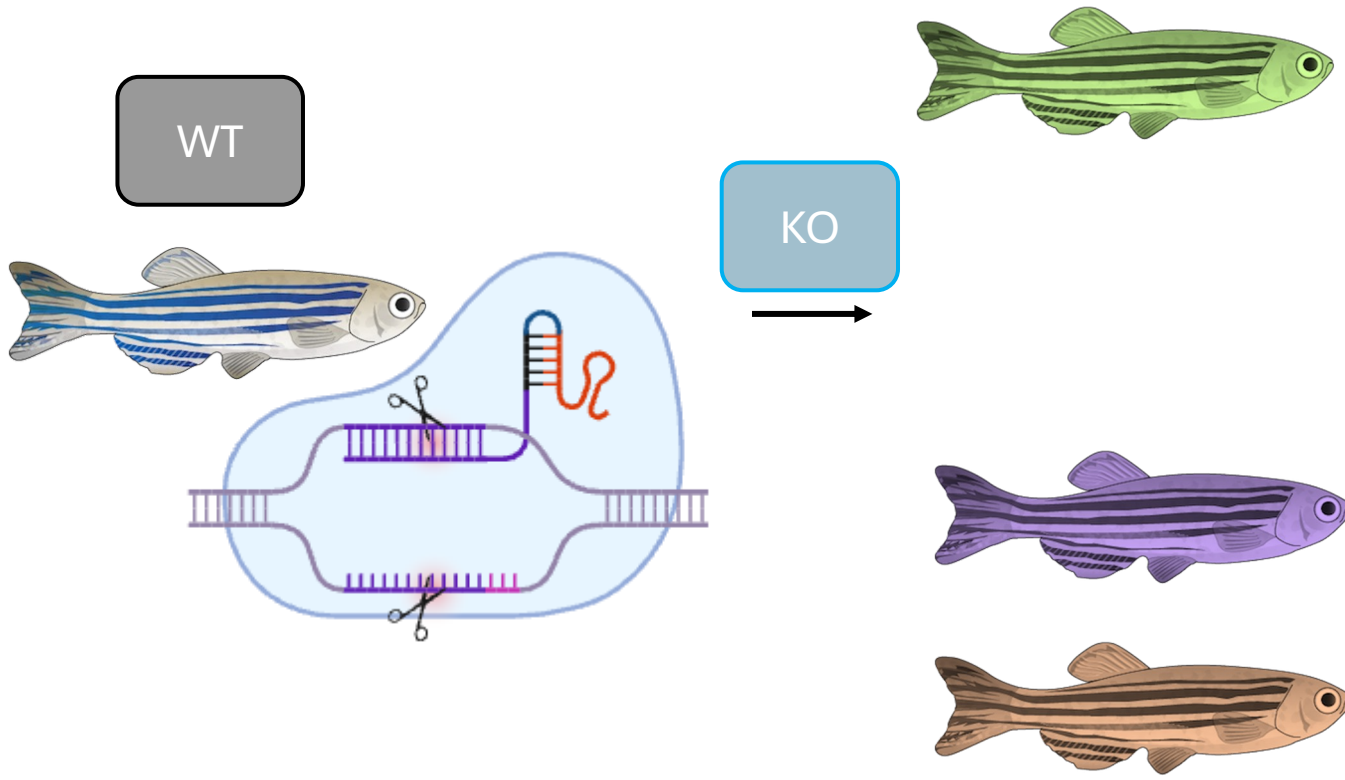


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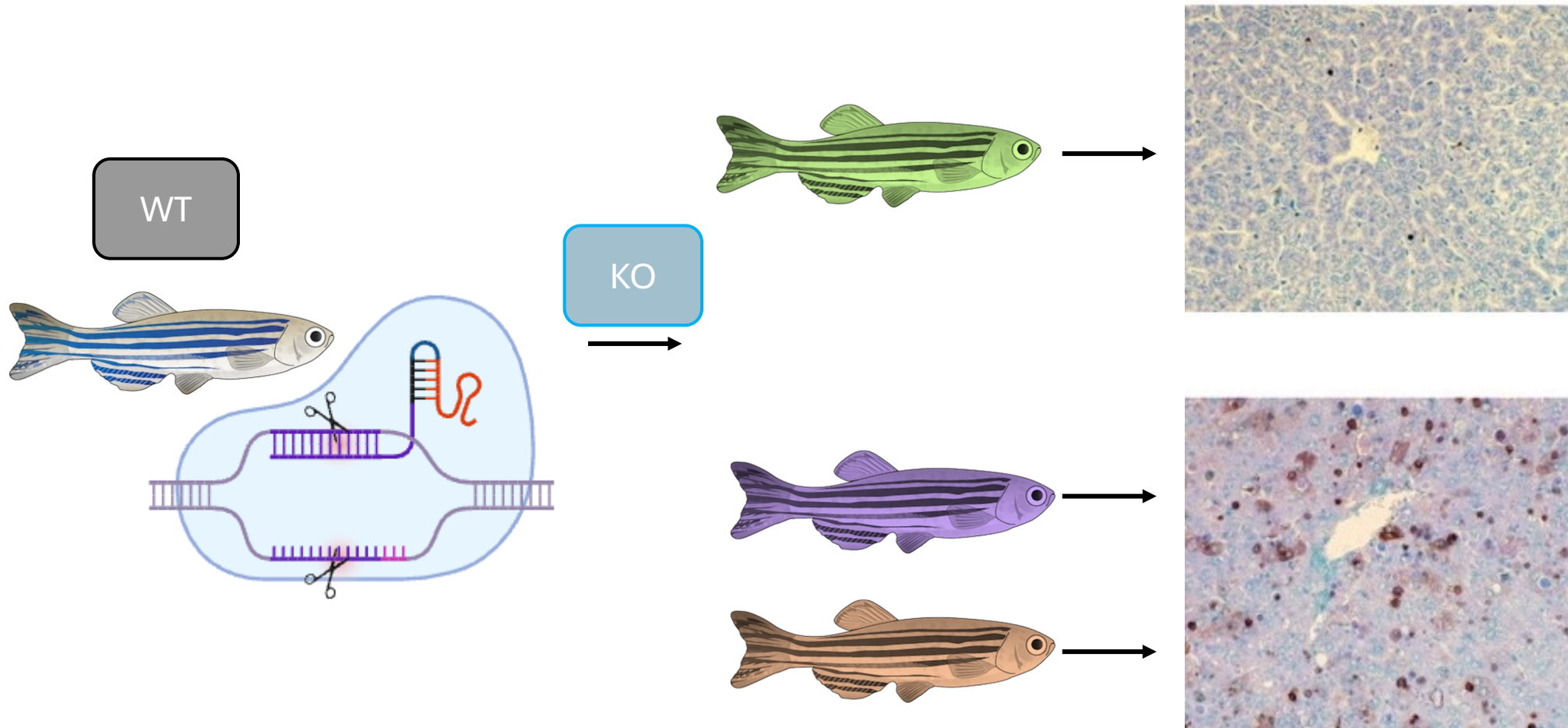


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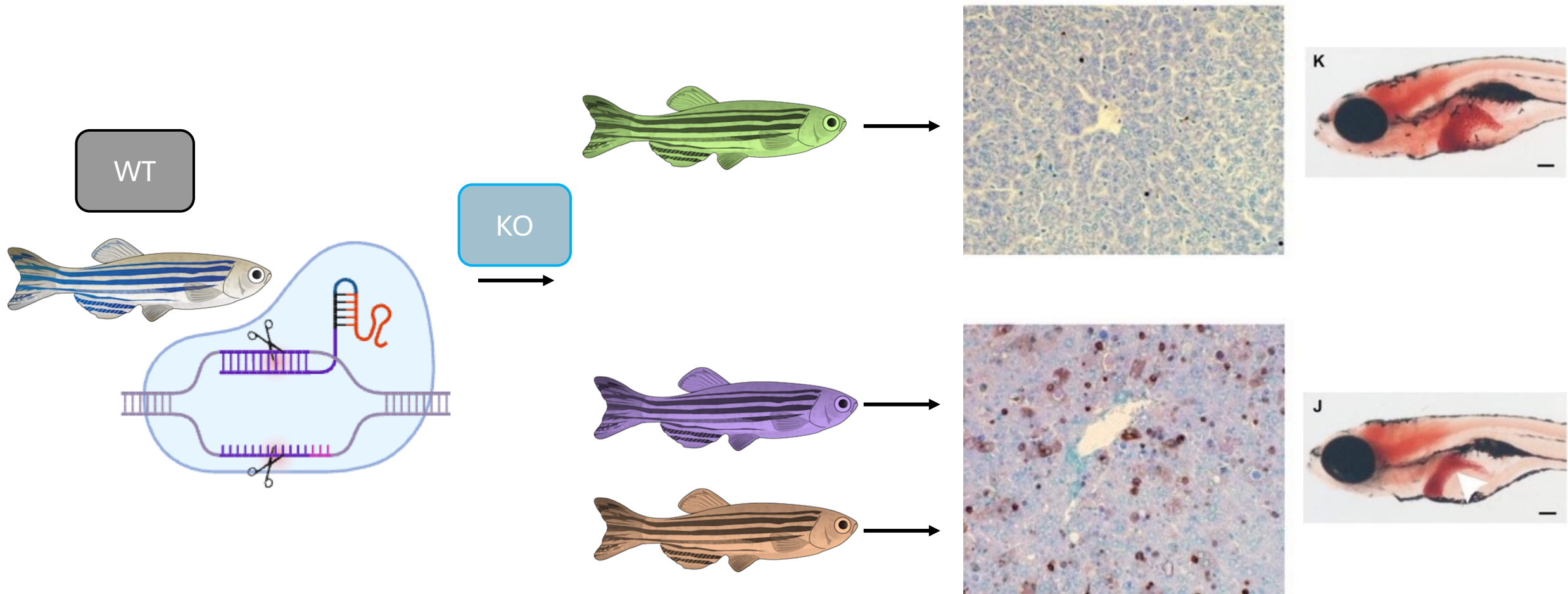


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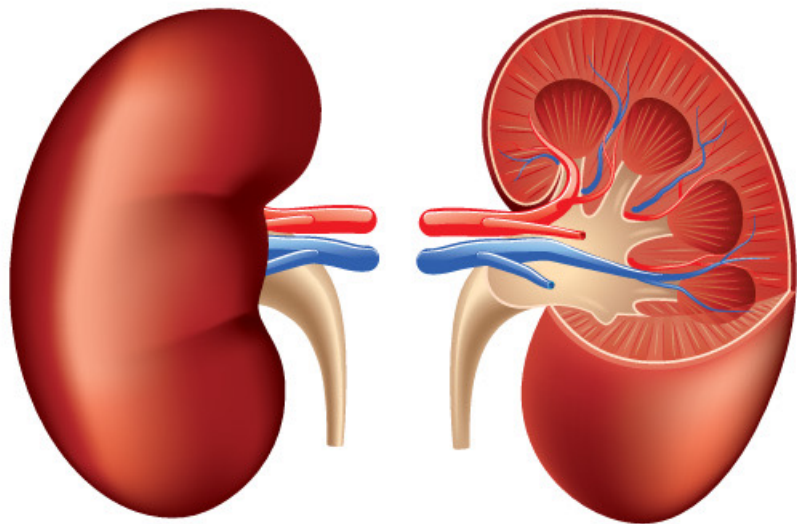


Future research directions

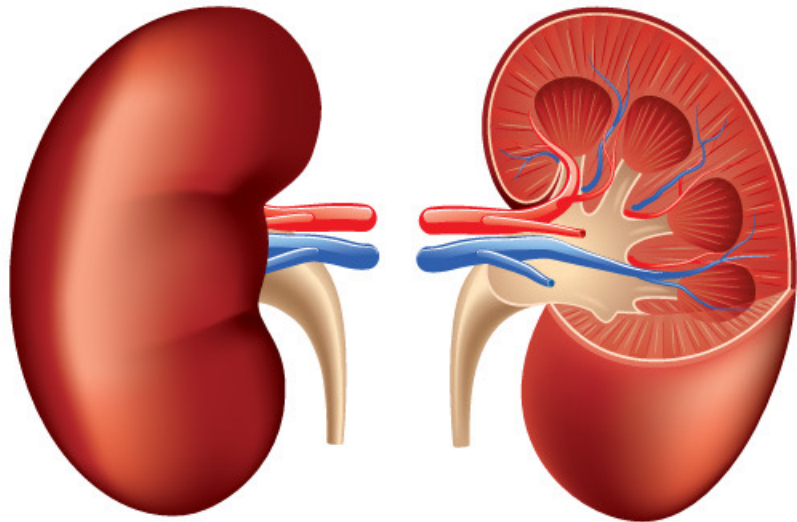
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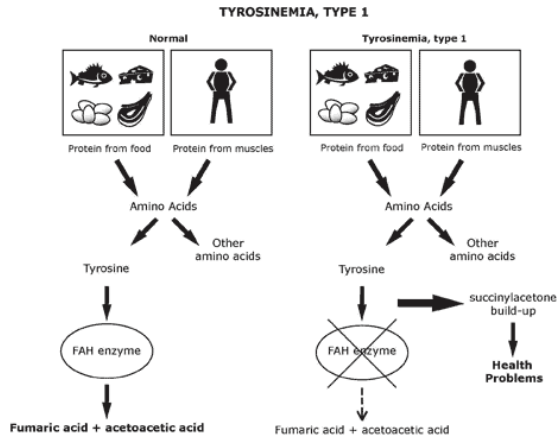


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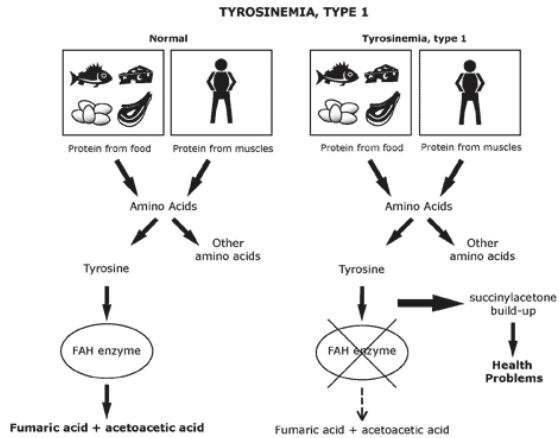
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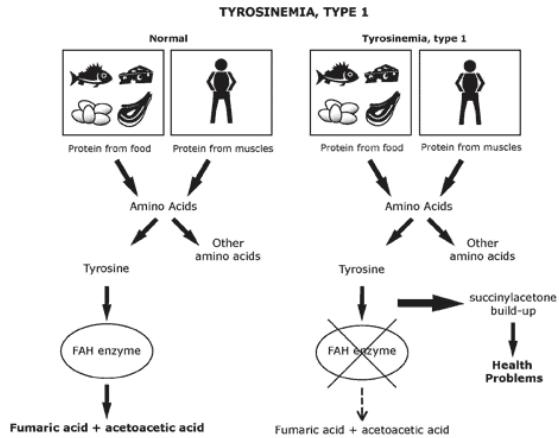


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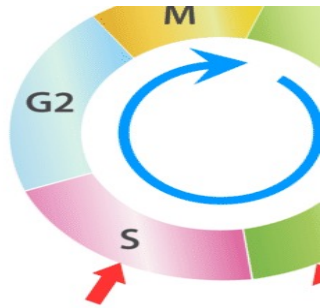
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Researching **increased liver apoptosis** in zebrafish will allow for much more to be known about this disorder and the causes of it, hopefully leading to new treatment options.

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