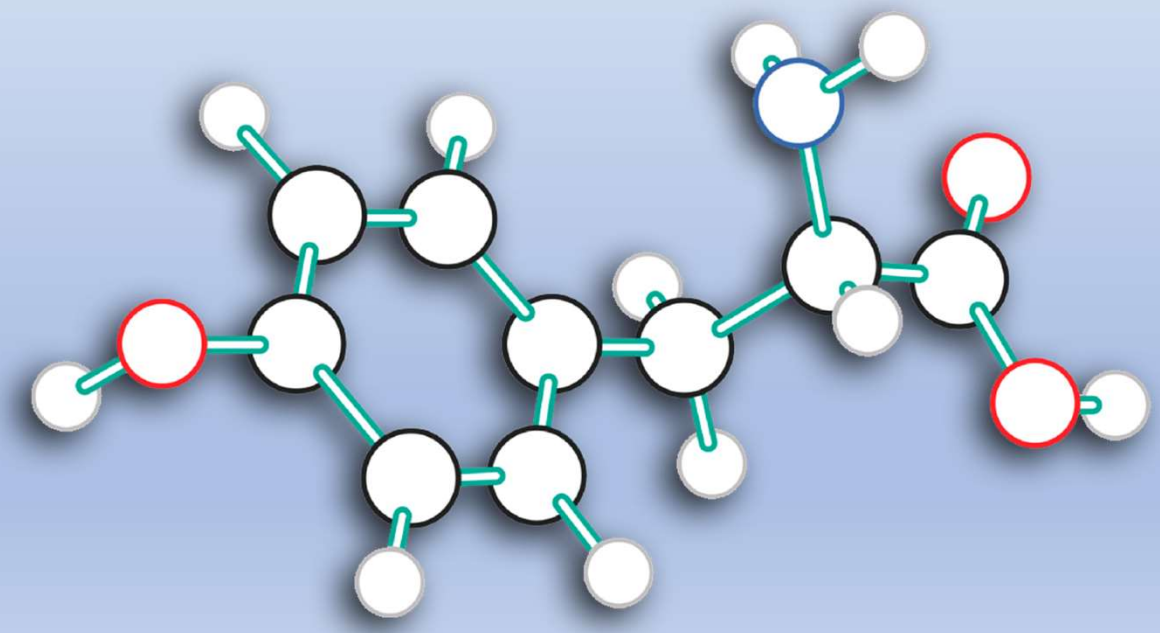
Inability to process tyrosine and phenylalanine: alkaptonuria and HGD



http://nootropicgeek.com/wp-content/uploads/2017/10/tyrosine-molecule.jpg

Will Rosenthal

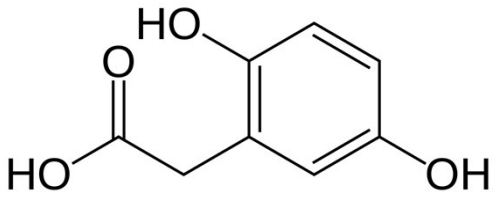
WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

Genetics 564

What are the symptoms of alkaptonuria?

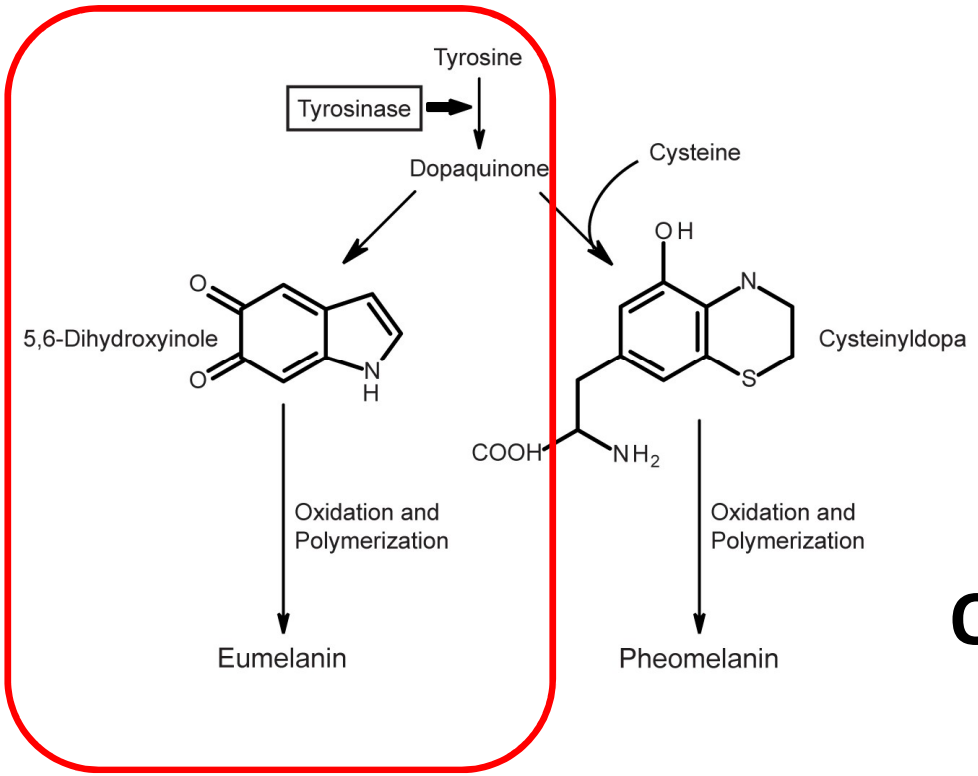
https://www.jointhealthmagazine.com/wp-content/uploads/2012/01/arthritis-leg-pain.jpg

What are the symptoms of alkaptonuria?



https://upload.wikimedia.org/wikipedia/commons/thumb/f/f1/Homogentisic_acid.svg/1200px-Homogentisic_acid.svg.png
http://www.clinmedres.org/content/2/4/209/F3.large.jpg
http://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/2002/nejm_2002.347.issue-26/nejmoa021736/production/images/medium/nejmoa021736_f3.gif

Acid buildup causes plaques

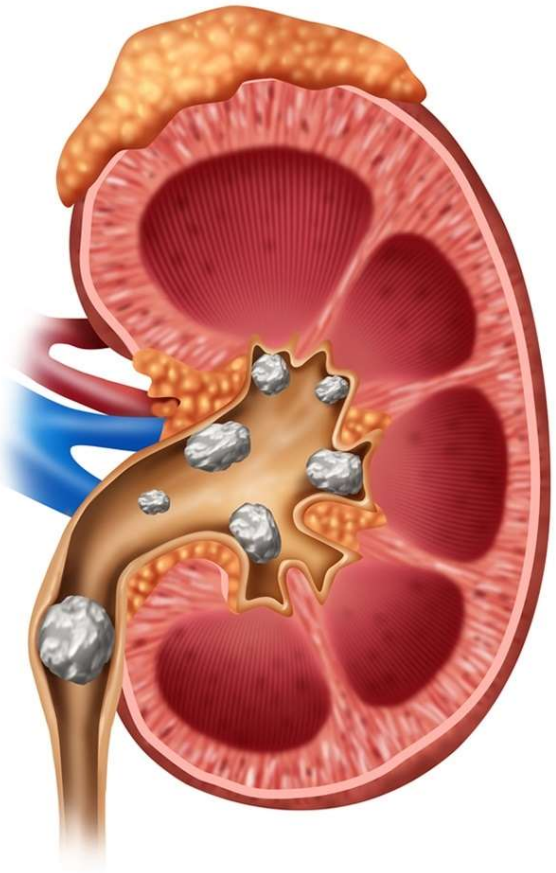


Organ function impaired

https://i.stack.imgur.com/9QyDk.png

http://cdn2.stylecraze.com/wp-content/uploads/2013/07/2646-Vitamin-C-Deficiency-ss.jpg

Stones everywhere!

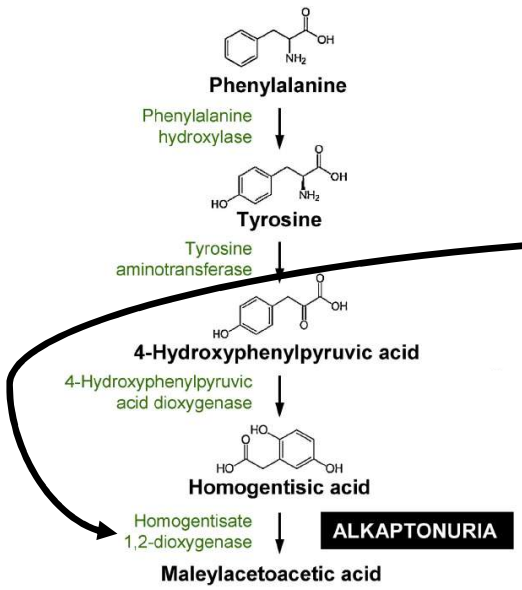


Kidney stones, gallbladder stones, and prostate stones all occur more frequently

https://www.news-medical.net/image.axd?picture=2017%2f9%2fshutterstock_409736524.jpg

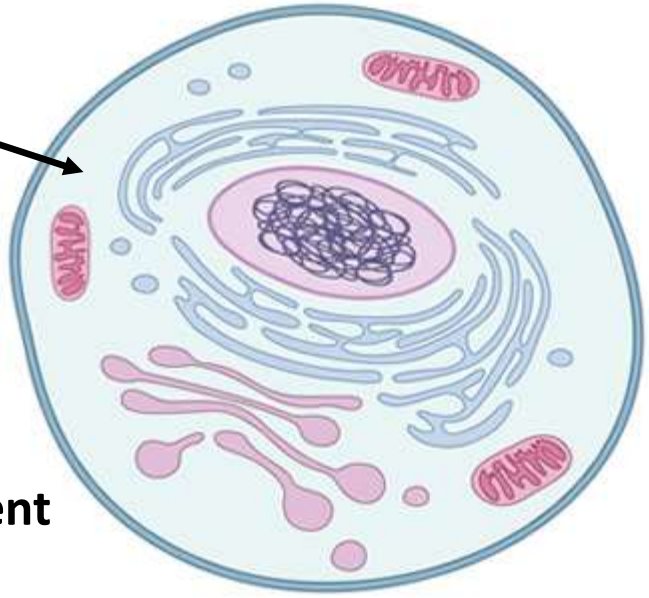
What is HGD?

HgmA



Biological Process & Molecular Function

HGD



Cellular Component

http://www.nature.com/scitable/content/ne0000/ne0000/ne0000/ne0000/14704902/U1CP1-5_ProkvsEukCell_ksm.jpg
https://www.researchgate.net/profile/Andrew_Davison2/publication/263239383/figure/fig1/AS:296045096521736@1447594059502/Tyrosine-degradation-pathway-showing-the-enzyme-defect-in-alkaptonuria-Nitisinone-blocks.png

How conserved is HGD?

How conserved is HGD?


HgmA

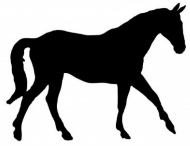

HgmA


HgmA

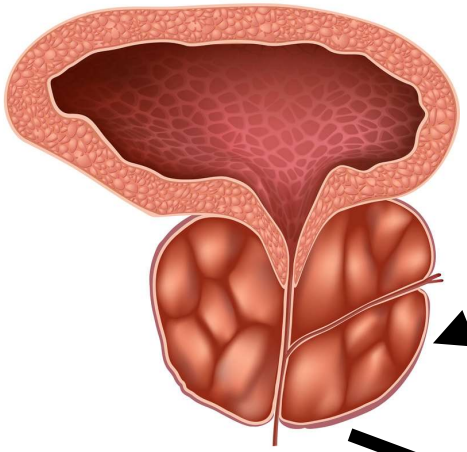

HgmA

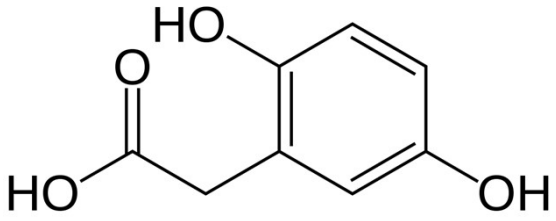

HgmA


HgmA


HgmA

What is the gap in knowledge?





?

https://healthprep.com/wp-content/uploads/2017/03/BPH.jpg
https://upload.wikimedia.org/wikipedia/commons/thumb/f/f1/Homogentisic_acid.svg/1200px-Homogentisic_acid.svg.png

Mice are special

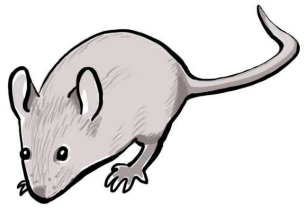
Mice do not develop the black plaques

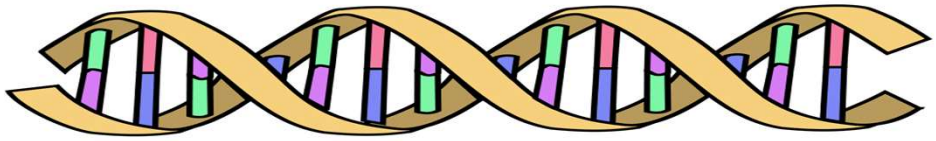
What is my primary goal?

Better understand how HGD functions in prostate amino acid metabolism

Aim 1

Identify conserved protein regions



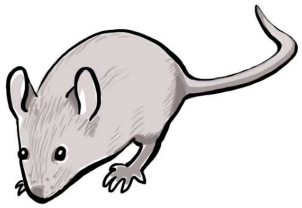


What is my primary goal?

Better understand how HGD functions in prostate amino acid metabolism

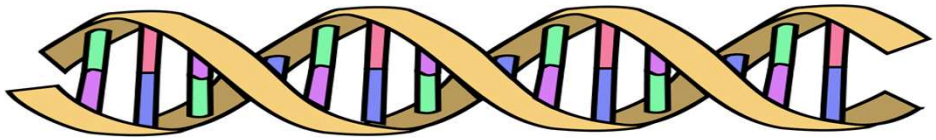
Aim 1

Identify conserved protein regions



Aim 2

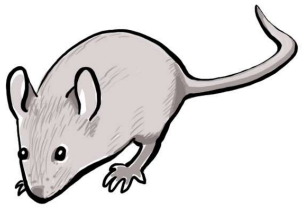
Characterize prostate gene expression

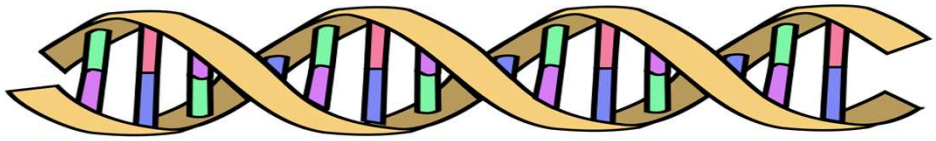


What is my primary goal?

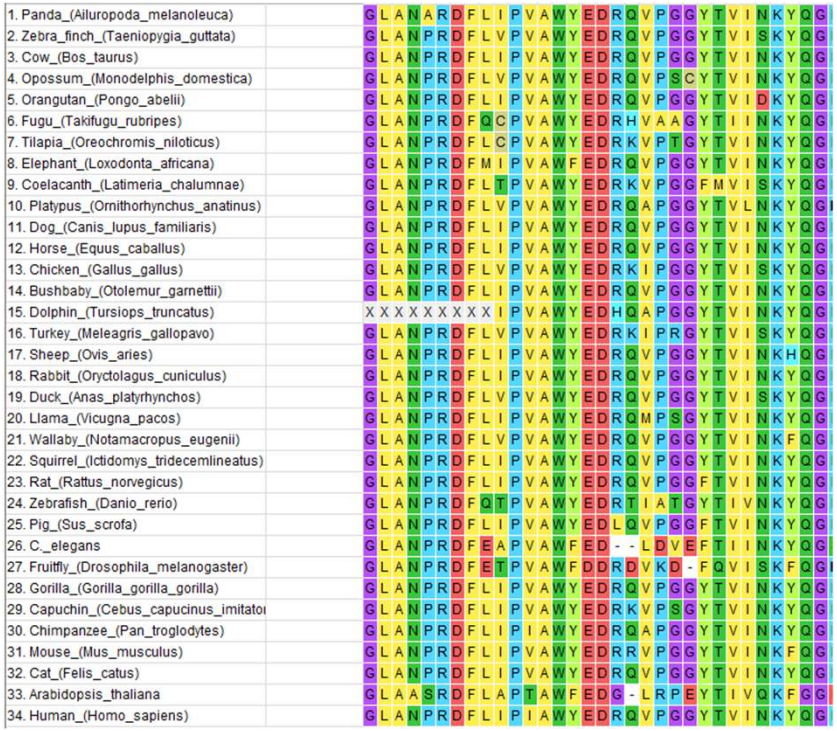
Better understand how HGD functions in prostate amino acid metabolism

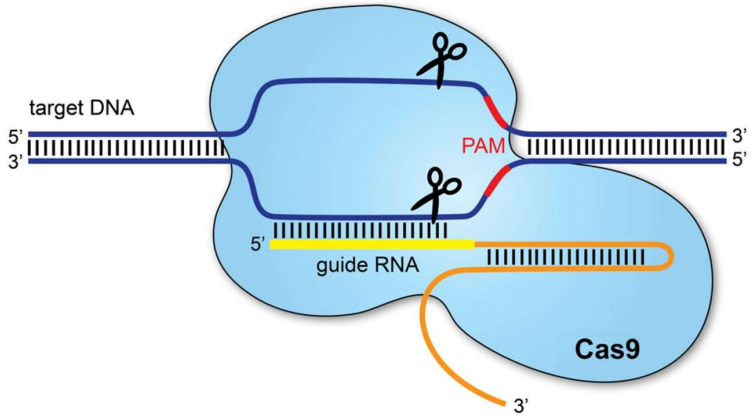
Aim 1	Aim 2	Aim 3
Identify conserved protein regions	Characterize prostate gene expression	Understand the importance of phosphorylation sites





Aim 1: Identify conserved protein regions



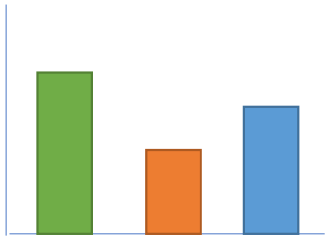


Mice fed a high-tyrosine diet, then assessed for prostate stones

http://ep.bmj.com/content/edpract/101/4/213/F1.large.jpg

Aim 2: Assess changes in gene expression

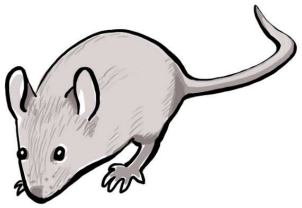
AKU

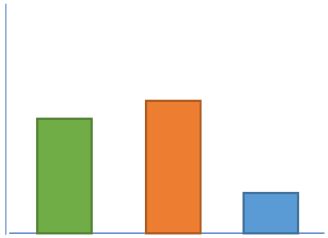


AKU mice will be lines created in the first aim

RNA sequencing

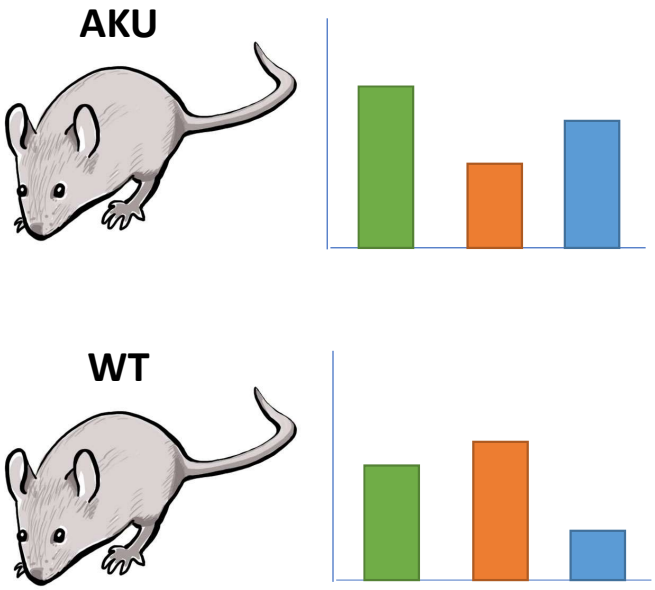
WT

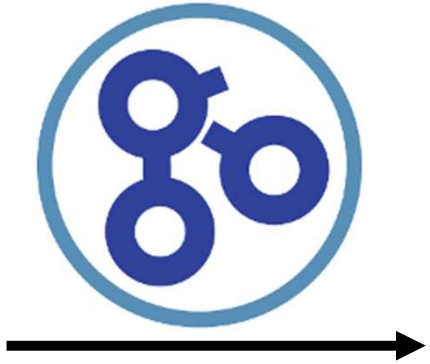


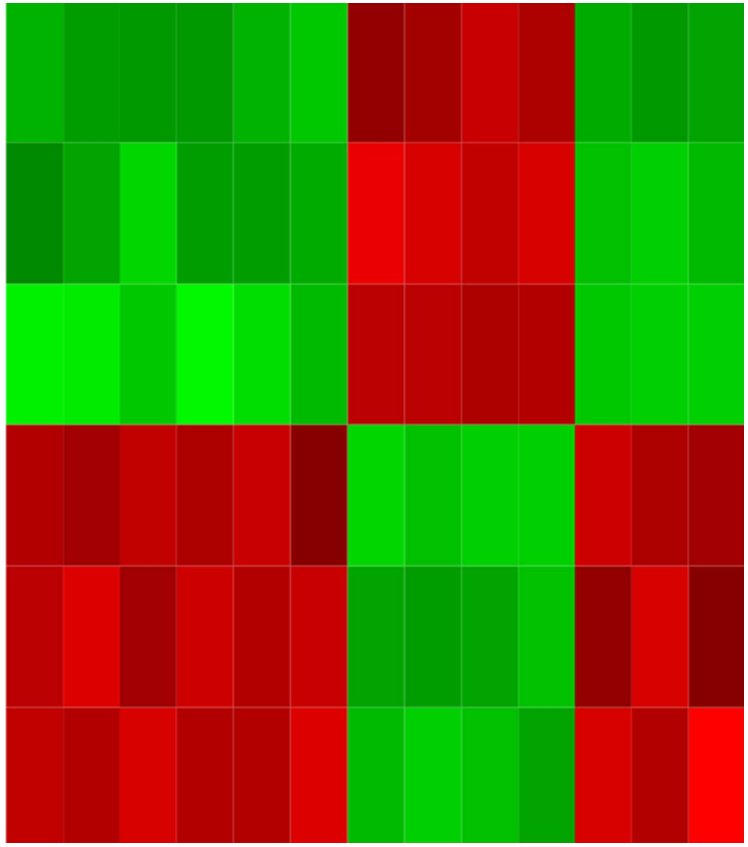


Mice fed a high-tyrosine diet

Aim 2: Assess changes in gene expression





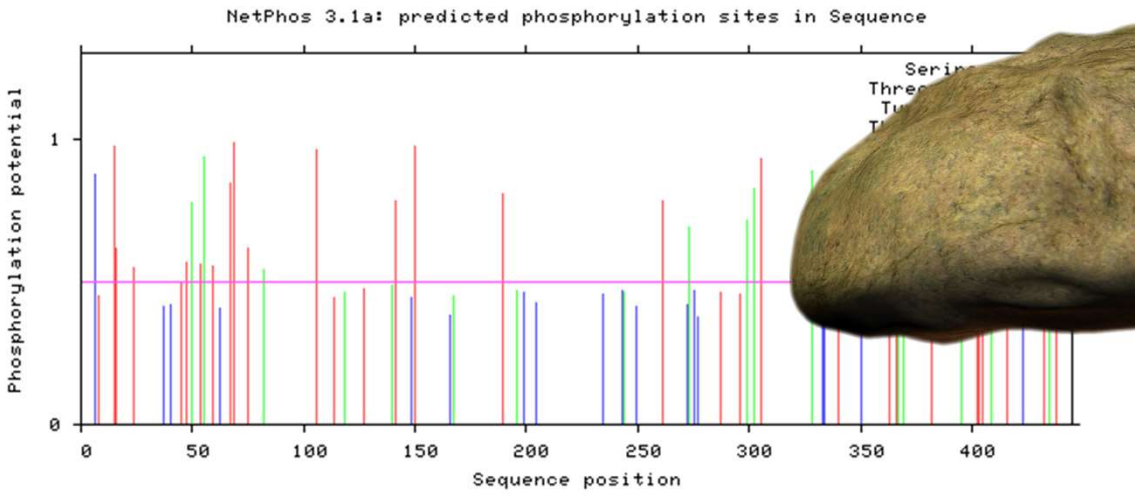


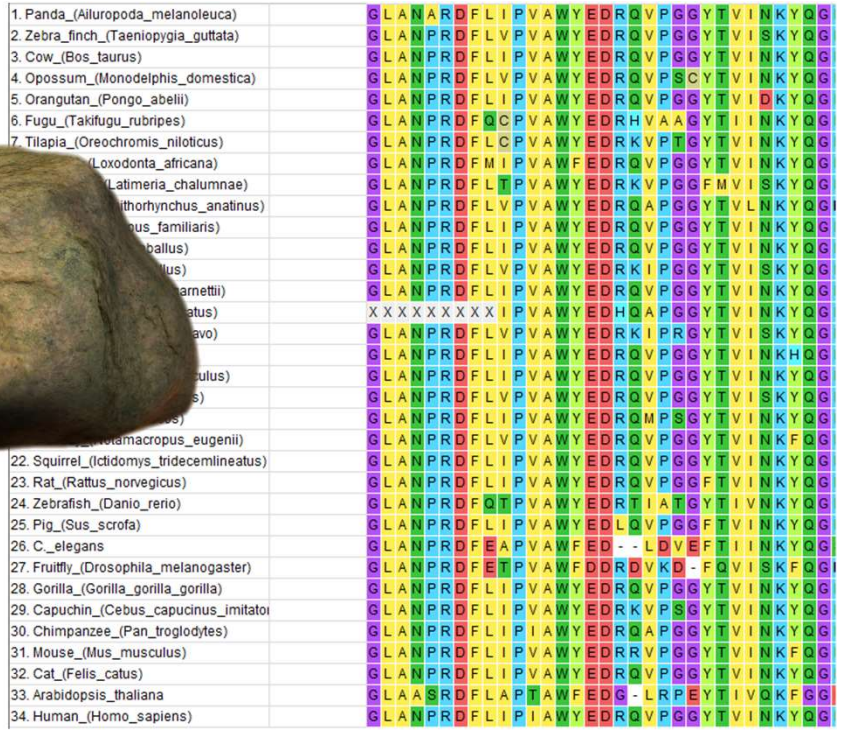
GO terms involving detoxification and catabolism will be targeted

https://avatars1.githubusercontent.com/u/7750835?s=200&v=4

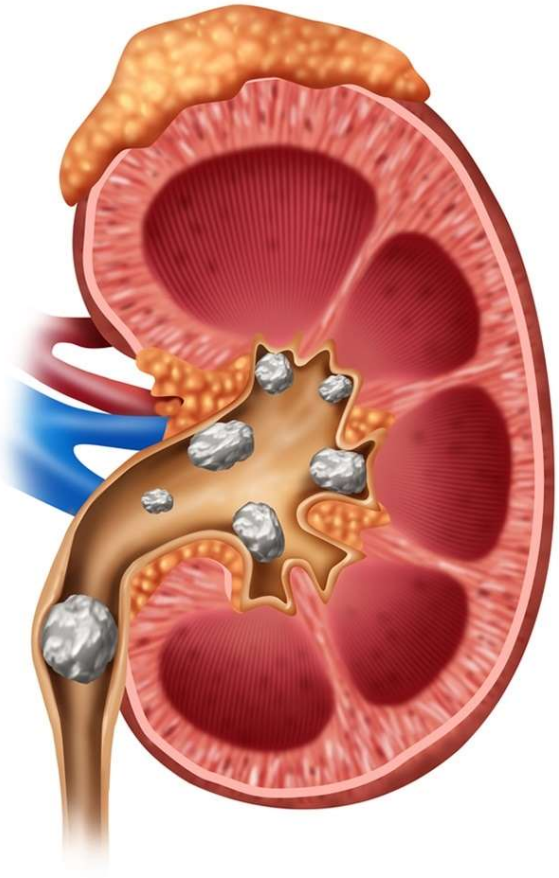
https://s24.postimg.org/5hbw04xh1/Sham2_T00d4h.png

Aim 3: Characterize phosphorylation sites

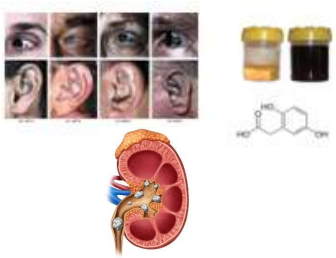




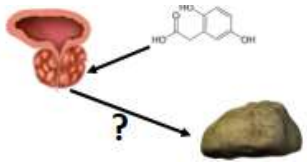
Future Directions



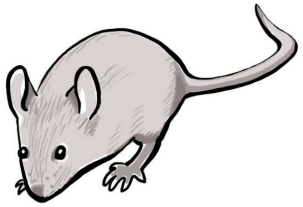
Summary



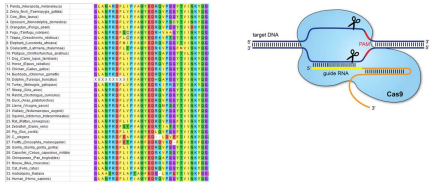
Symptoms



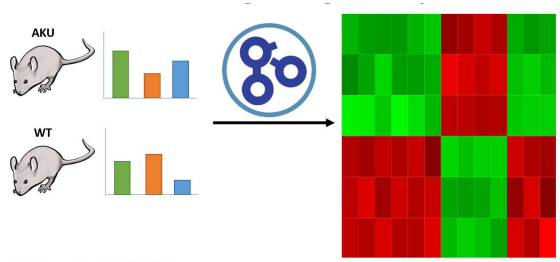
Stone cause unknown



Mice show only some symptoms



Specific aims



References

Ranganath, Lakshminarayan R., Jonathan C. Jarvis, and James A. Gallagher. "Recent advances in management of alkaptonuria (invited review; best practice article)." *Journal of clinical pathology* (2013): jclinpath-2012.

Kumar, Sudhir, Glen Stecher, and Koichiro Tamura. "MEGA7: molecular evolutionary genetics analysis version 7.0 for bigger datasets." *Molecular biology and evolution* 33.7 (2016): 1870-1874.

Cong, Le, et al. "Multiplex genome engineering using CRISPR/Cas systems." *Science* (2013): 1231143.

Blom, Nikolaj, Steen Gammeltoft, and Søren Brunak. "Sequence and structure-based prediction of eukaryotic protein phosphorylation sites1." *Journal of molecular biology*294.5 (1999): 1351-1362.