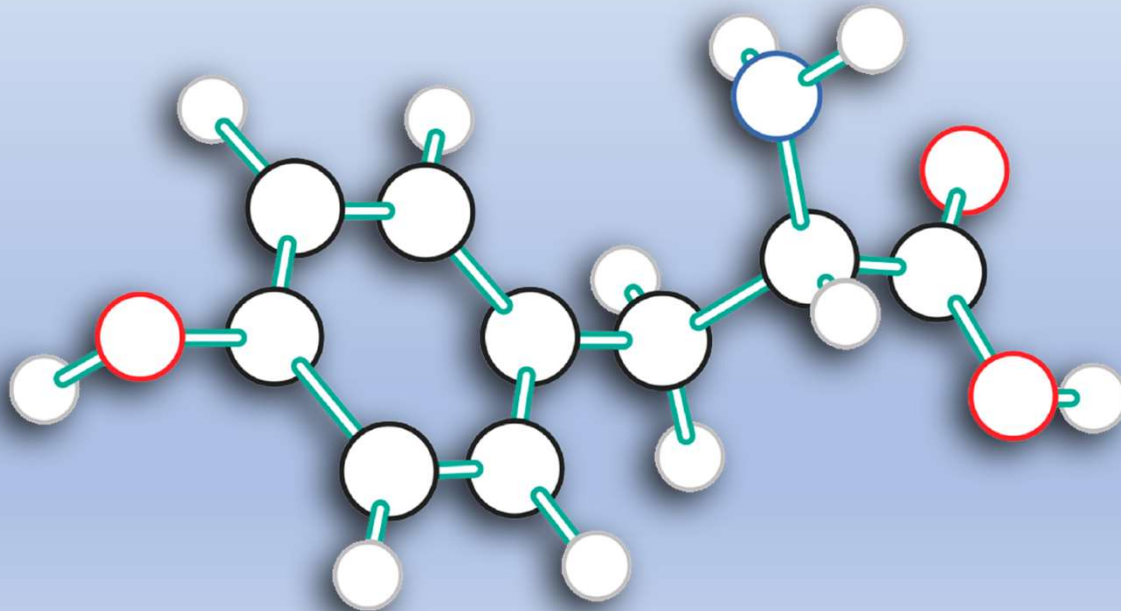


Inability to process tyrosine and phenylalanine: alkaptonuria and HGD



Will Rosenthal



WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

Genetics 564

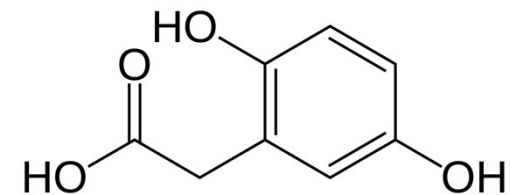
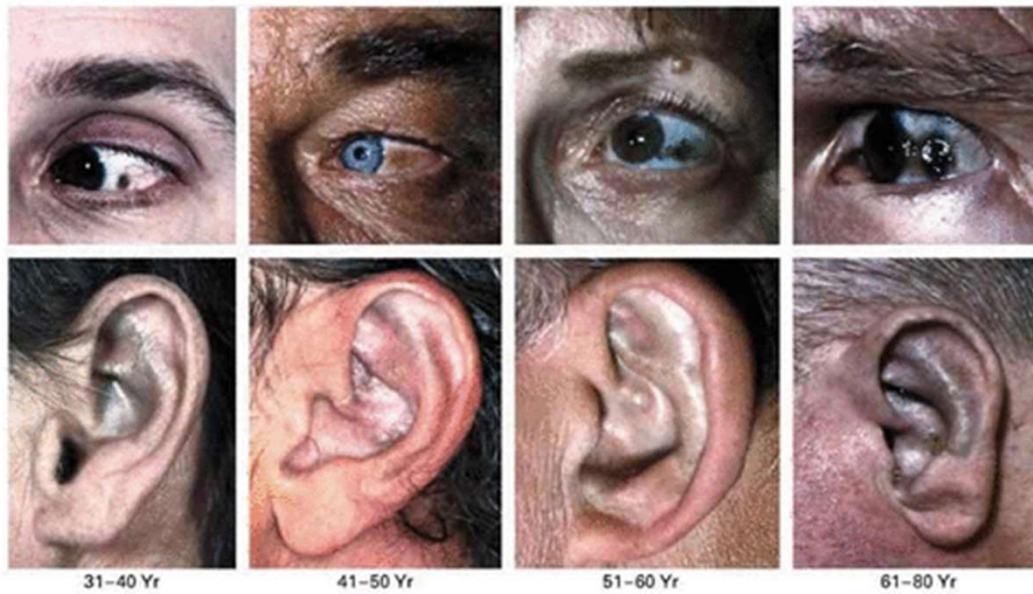
<http://nootropicgeek.com/wp-content/uploads/2017/10/tyrosine-molecule.jpg>

What are the symptoms of alkaptonuria?



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

What are the symptoms of alkaptonuria?

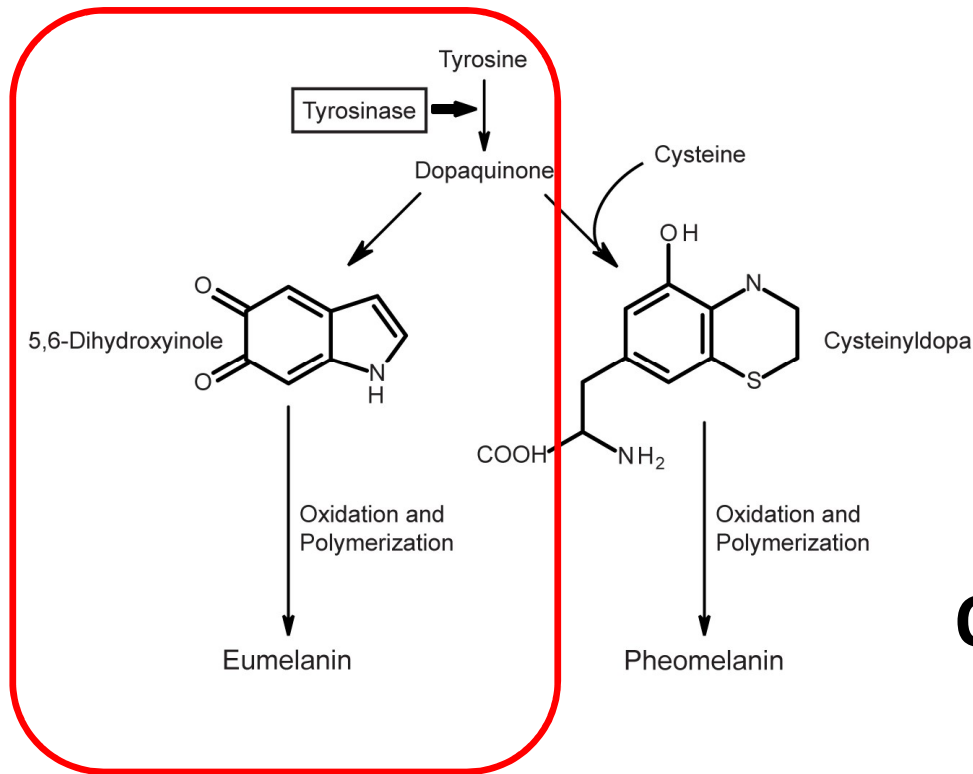


https://upload.wikimedia.org/wikipedia/commons/thumb/f/f1/Homogentisic_acid.svg/1200px-Homogentisic_acid.svg.png

<http://www.clinmedres.org/content/2/4/209/F3.large.jpg>

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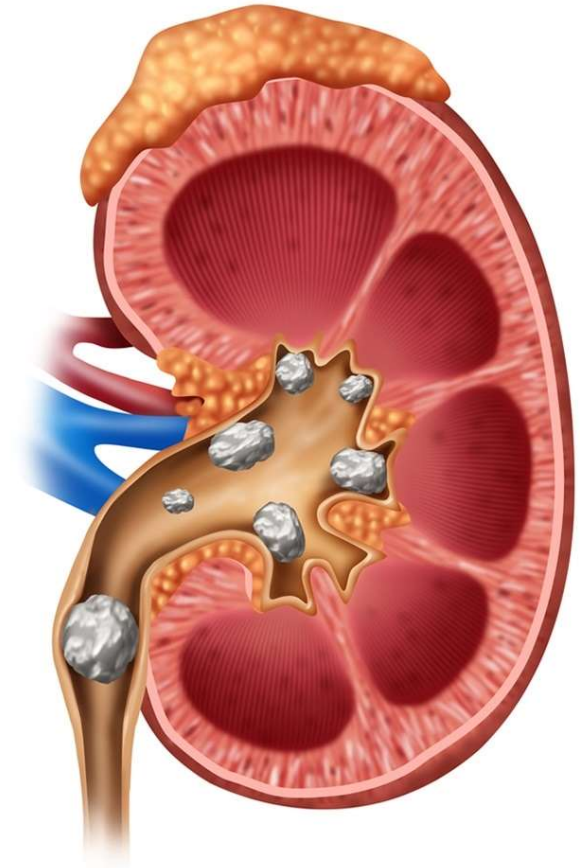
Acid buildup causes plaques



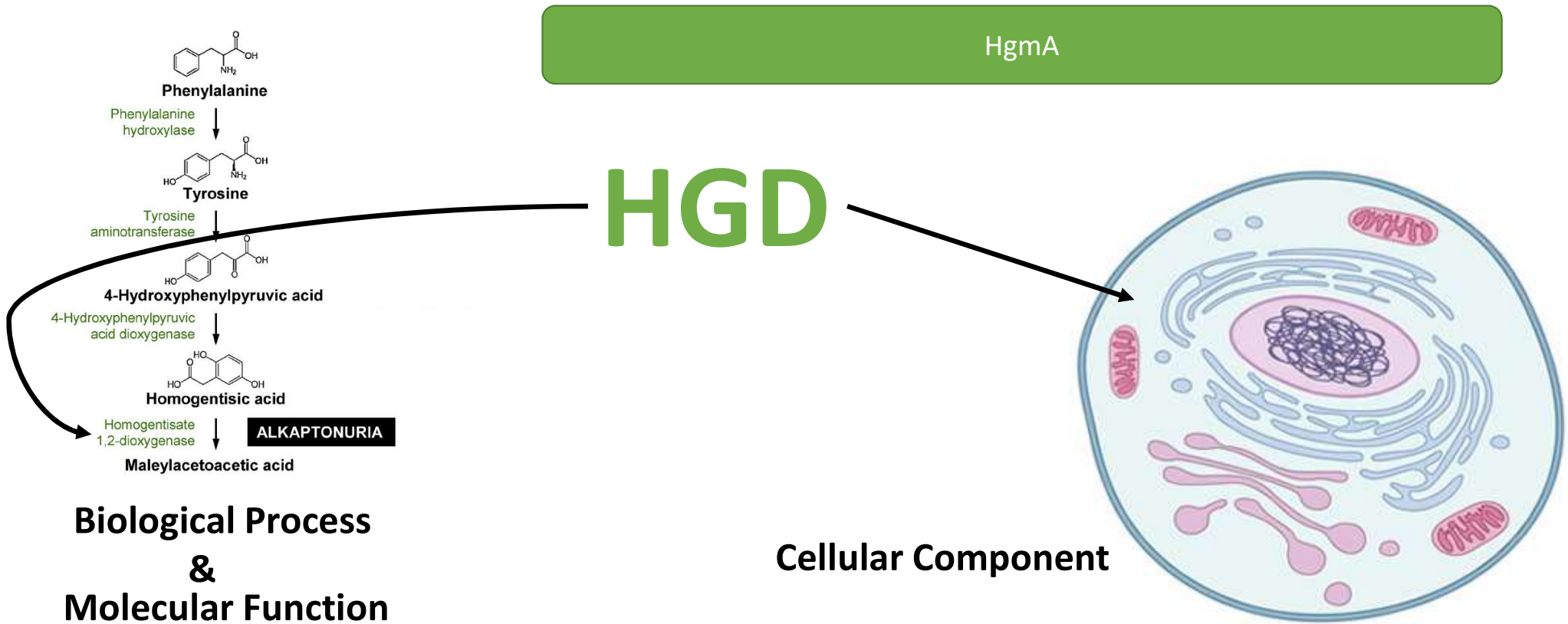
Organ function impaired

Stones everywhere!

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



What is HGD?



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



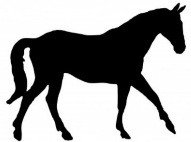
HgmA



HgmA

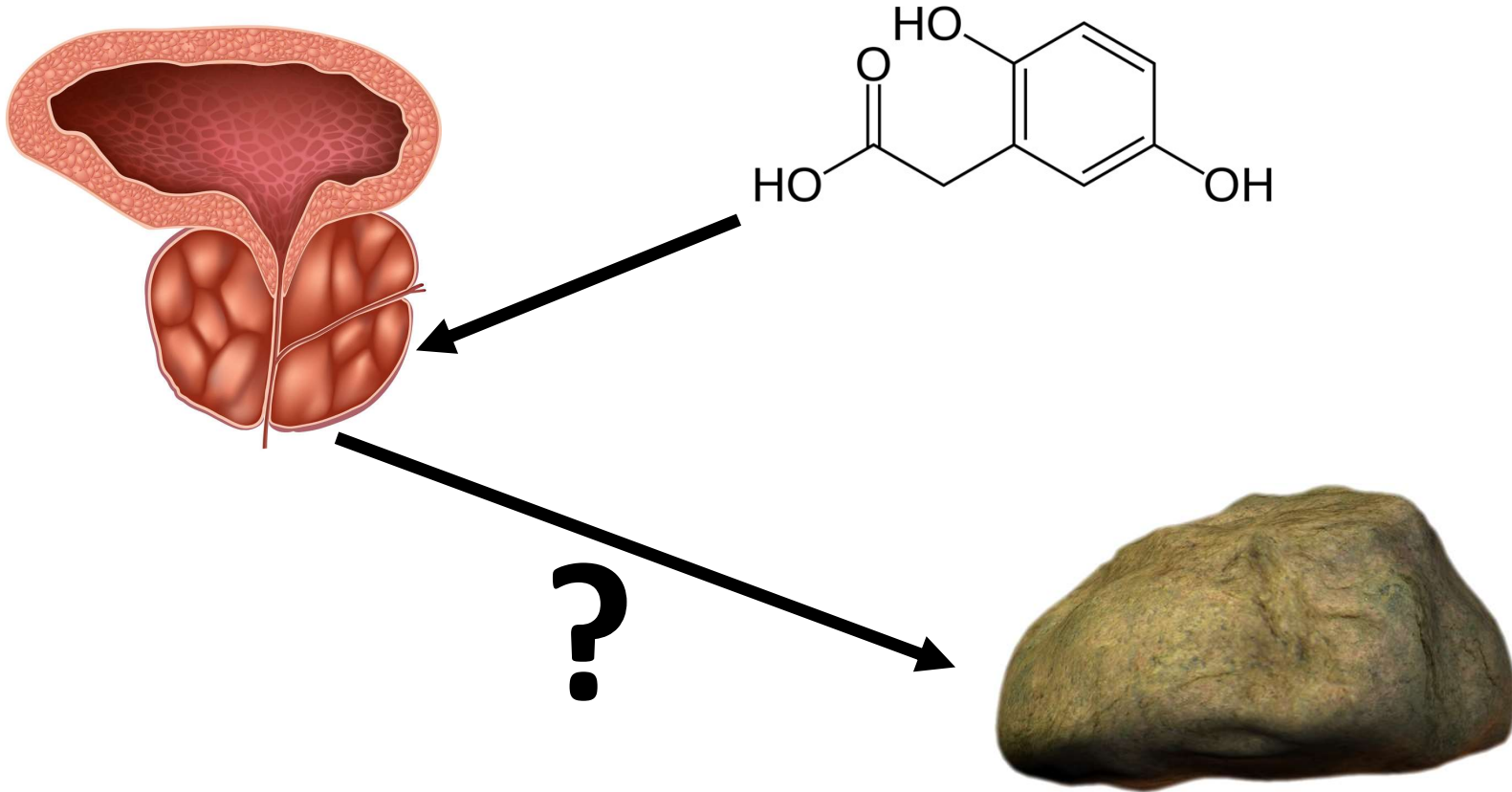


HgmA



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



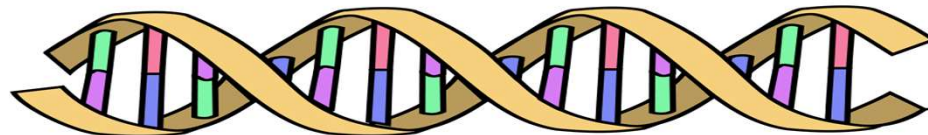
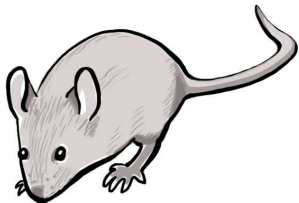
**Mice do not develop the
black plaques**

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

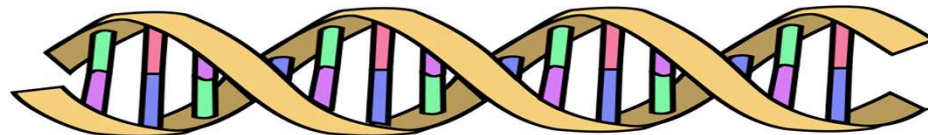
Aim 1

Identify conserved
protein regions



Aim 2

Characterize
prostate gene
expression

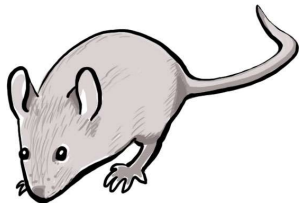


What is my primary goal?

Better understand how HGD functions in prostate amino acid metabolism

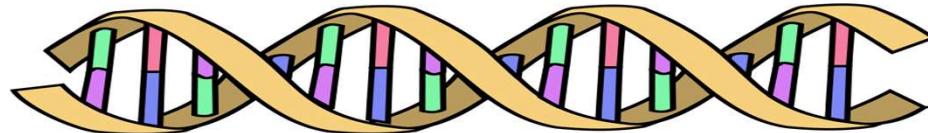
Aim 1

Identify conserved protein regions



Aim 2

Characterize prostate gene expression

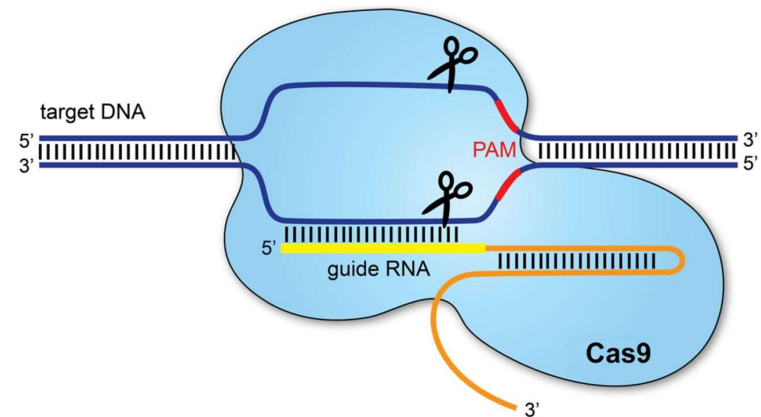


Aim 3

Understand the importance of phosphorylation sites

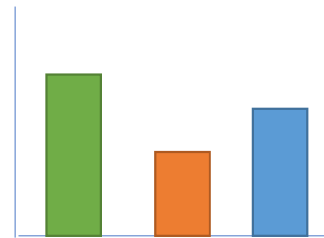
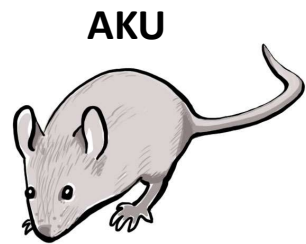
Aim 1: Identify conserved protein regions

1. Panda_(Ailuropoda_melanoleuca)	G L A N A R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
2. Zebra_finch_(Taeniopygia_guttata)	G L A N P R D F L V P V A W Y E D R Q V P G G Y T V I S K Y Q G
3. Cow_(Bos_taurus)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
4. Opossum_(Monodelphis_domestica)	G L A N P R D F L V P V A W Y E D R Q V P S C Y T V I N K Y Q G
5. Orangutan_(Pongo_abelii)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I D K Y Q G
6. Fugu_(Takifugu_rubripes)	G L A N P R D F L C P V A W Y E D R H V A A G Y T I I N K Y Q G
7. Tilapia_(Oreochromis_niloticus)	G L A N P R D F L C P V A W Y E D R K V P T G Y T V I N K Y Q G
8. Elephant_(Loxodonta_africana)	G L A N P R D F M I P V A W F E D R Q V P G G Y T V I N K Y Q G
9. Coelacanth_(Latimeria_chalumnae)	G L A N P R D F L T P V A W Y E D R K V P G G F M V I S K Y Q G
10. Platypus_(Ornithorhynchus_anatinus)	G L A N P R D F L V P V A W Y E D R Q A P G G Y T V L N K Y Q G
11. Dog_(Canis_lupus_familiaris)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
12. Horse_(Equus_caballus)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
13. Chicken_(Gallus_gallus)	G L A N P R D F L V P V A W Y E D R K I P G G Y T V I S K Y Q G
14. Bushbaby_(Otolemur_garnettii)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
15. Dolphin_(Tursiops_truncatus)	X X X X X X X X X I P V A W Y E D H Q A P G G Y T V I N K Y Q G
16. Turkey_(Meleagris_gallopavo)	G L A N P R D F L V P V A W Y E D R K I P R G Y T V I S K Y Q G
17. Sheep_(Ovis_aries)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K H Q G
18. Rabbit_(Oryctolagus_cuniculus)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
19. Duck_(Anas_platyrhynchos)	G L A N P R D F L V P V A W Y E D R Q V P G G Y T V I S K Y Q G
20. Llama_(Vicugna_pacos)	G L A N P R D F L I P V A W Y E D R Q M P S G Y T V I N K Y Q G
21. Wallaby_(Notamacropus_eugenii)	G L A N P R D F L V P V A W Y E D R Q V P G G Y T V I N K F Q G
22. Squirrel_(Ictidomys_tridecemlineatus)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
23. Rat_(Rattus_norvegicus)	G L A N P R D F L I P V A W Y E D R Q V P G G F T V I N K Y Q G
24. Zebrafish_(Danio_rerio)	G L A N P R D F Q T P V A W Y E D R T I A T G Y T I V N K Y Q G
25. Pig_(Sus_scrofa)	G L A N P R D F L I P V A W Y E D L Q V P G G F T V I N K Y Q G
26. C_elegans	G L A N P R D F E A P V A W F E D - - L D V E F T I I N K Y Q G
27. Fruitfly_(Drosophila_melanogaster)	G L A N P R D F E T P V A W F D D R D V K D - F Q V I S K F Q G
28. Gorilla_(Gorilla_gorilla_gorilla)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
29. Capuchin_(Cebus_capucinus_imitato)	G L A N P R D F L I P V A W Y E D R K V P S G Y T V I N K Y Q G
30. Chimpanzee_(Pan_troglodytes)	G L A N P R D F L I P I A W Y E D R Q A P G G Y T V I N K Y Q G
31. Mouse_(Mus_musculus)	G L A N P R D F L I P V A W Y E D R R V P G G Y T V I N K F Q G
32. Cat_(Felis_catus)	G L A N P R D F L I P V A W Y E D R Q V P G G Y T V I N K Y Q G
33. Arabidopsis_thaliana	G L A S R D F L A P T A W F E D G - L R P E Y T I V Q K F G G
34. Human_(Homo_sapiens)	G L A N P R D F L I P I A W Y E D R Q V P G G Y T V I N K Y Q G



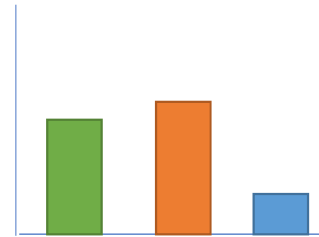
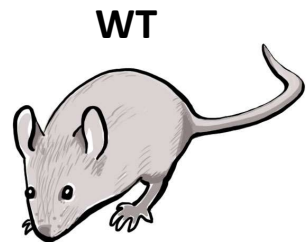
Mice fed a high-tyrosine diet, then assessed for prostate stones

Aim 2: Assess changes in gene expression



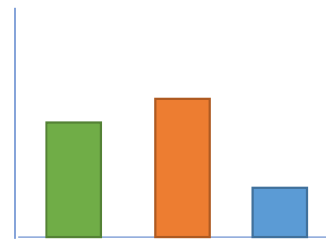
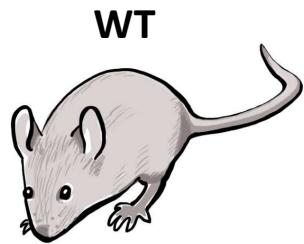
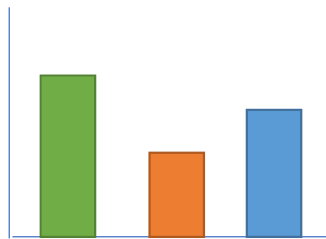
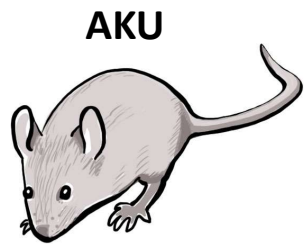
AKU mice will be lines created in the first aim

RNA sequencing

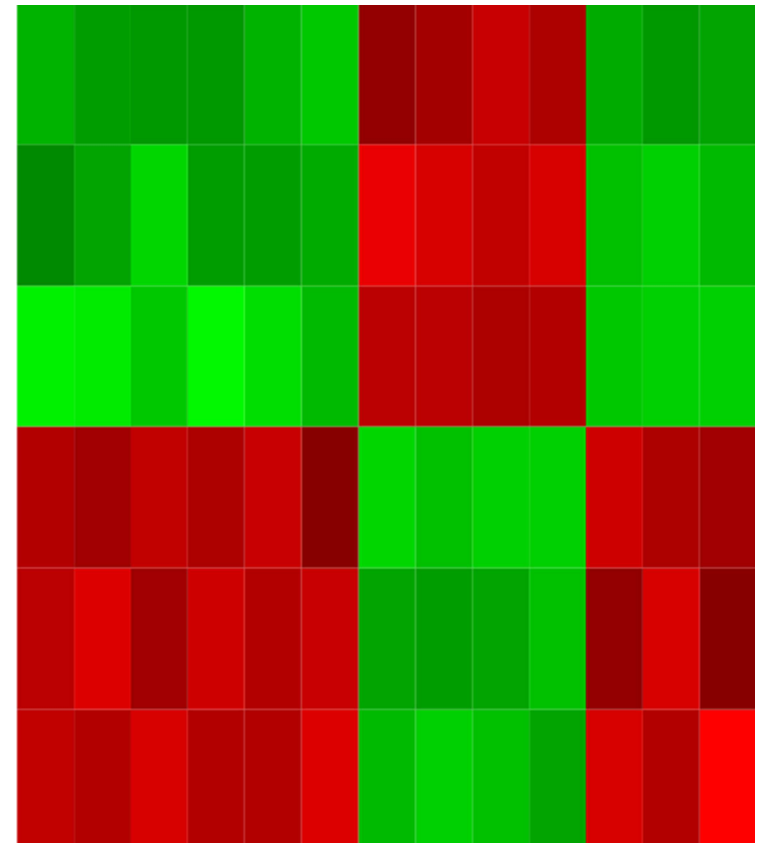


Mice fed a high-tyrosine diet

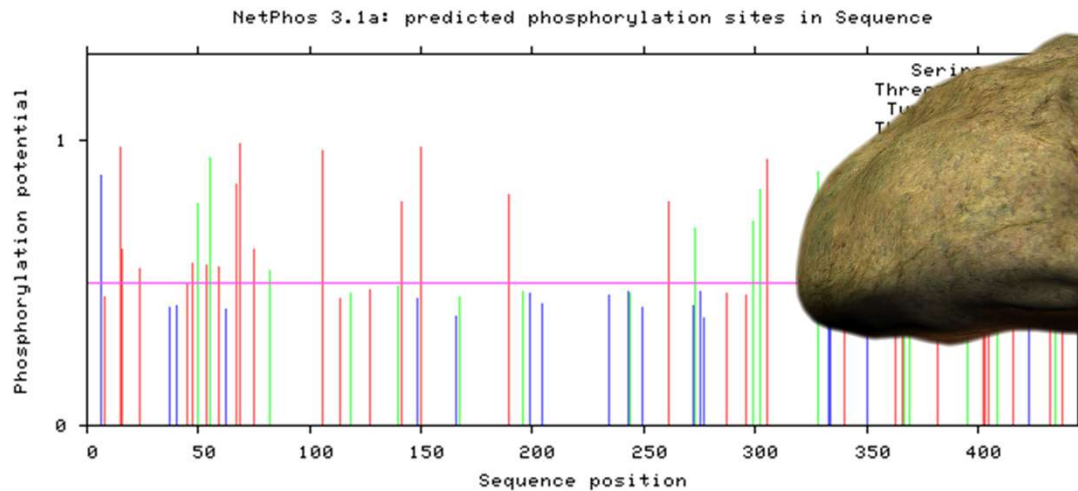
Aim 2: Assess changes in gene expression



GO terms involving detoxification and catabolism will be targeted

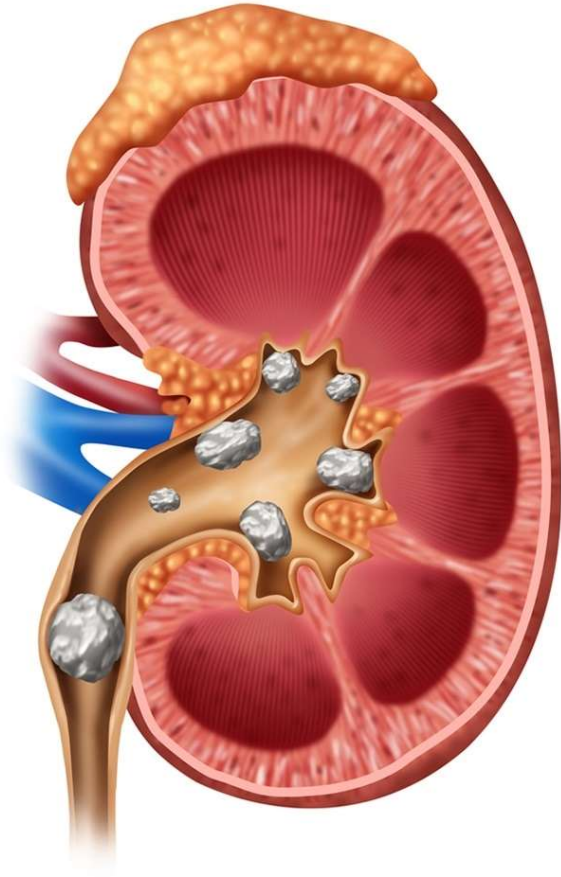


Aim 3: Characterize phosphorylation sites



1. Panda (<i>Ailuropoda melanoleuca</i>)	GLANARDFLIPVAWYEDRQVPGGYTVLNKYG
2. Zebra_finch (<i>Taeniopygia guttata</i>)	GLANPRDFLVPVAWYEDRQVPGGYTVLNKYG
3. Cow (<i>Bos taurus</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
4. Opossum (<i>Monodelphis domestica</i>)	GLANPRDFLVPVAWYEDRQVPSCYTVLNKYG
5. Orangutan (<i>Pongo abelii</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
6. Fugu (<i>Takifugu rubripes</i>)	GLANPRDFQCPVAWYEDRHYVAAGYTVLNKYG
7. Tilapia (<i>Oreochromis niloticus</i>)	GLANPRDFLCPVAWYEDRKKVPTGYTVLNKYG
8. <i>(Loxodonta africana)</i>	GLANPRDFMIPVAWFEDRQVPGGYTVLNKYG
9. <i>(Latimeria chalumnae)</i>	GLANPRDFLTPVAWYEDRKYVPGGFVMIKYG
10. <i>(Thrinorhynchus anatinus)</i>	GLANPRDFLVPVAWYEDRQAPGGYTVLNKYG
11. <i>(Sus familiaris)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
12. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
13. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
14. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
15. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
16. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
17. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
18. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
19. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
20. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
21. <i>(Sus scrofa)</i>	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
22. Squirrel (<i>Ictidomys tridecemlineatus</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
23. Rat (<i>Rattus norvegicus</i>)	GLANPRDFLIPVAWYEDRQVPGGFTVLNKYG
24. Zebrafish (<i>Danio rerio</i>)	GLANPRDFQTPVAWYEDRTIATGYTVLNKYG
25. Pig (<i>Sus scrofa</i>)	GLANPRDFLIPVAWYEDLQVPGGFVLNKYG
26. <i>C. elegans</i>	GLANPRDFEAPVAWFED - -LDVEFTVLNKYG
27. Fruitfly (<i>Drosophila melanogaster</i>)	GLANPRDFETPVAWFDRDVKD - FQVLSKFG
28. Gorilla (<i>Gorilla gorilla gorilla</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
29. Capuchin (<i>Cebus capucinus imitator</i>)	GLANPRDFLIPVAWYEDRKKVPSGGYTVLNKYG
30. Chimpanzee (<i>Pan troglodytes</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
31. Mouse (<i>Mus musculus</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
32. Cat (<i>Felis catus</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG
33. Arabidopsis (<i>thaliana</i>)	GLASRDFLAPVAWFEDG - LRPEYTVLNKYG
34. Human (<i>Homo sapiens</i>)	GLANPRDFLIPVAWYEDRQVPGGYTVLNKYG

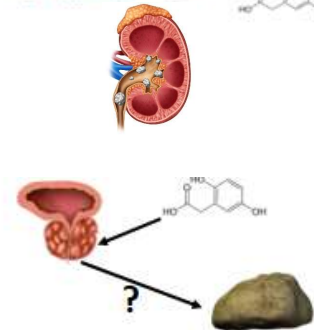
Future Directions



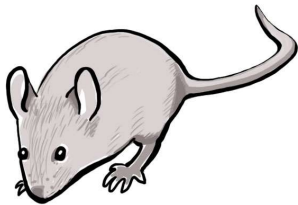
Summary



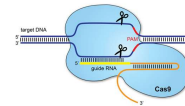
Symptoms



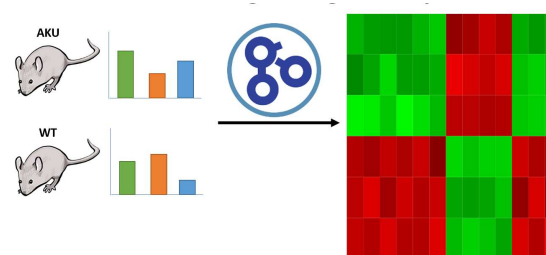
Stone cause unknown



Mice show only some symptoms



Specific aims



<https://westat1.gibsonresearch.com/a/77298333v-2308a-4>

References

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