ERCC6 Gene & Cockayne Syndrome

by Zachary Beethem

https://www.emaze.com/@AFCWWORI/Cockayne

What is Cockayne Syndrome?

A rare, autosomal recessive, neurodegenerative disorder

Invariably fatal

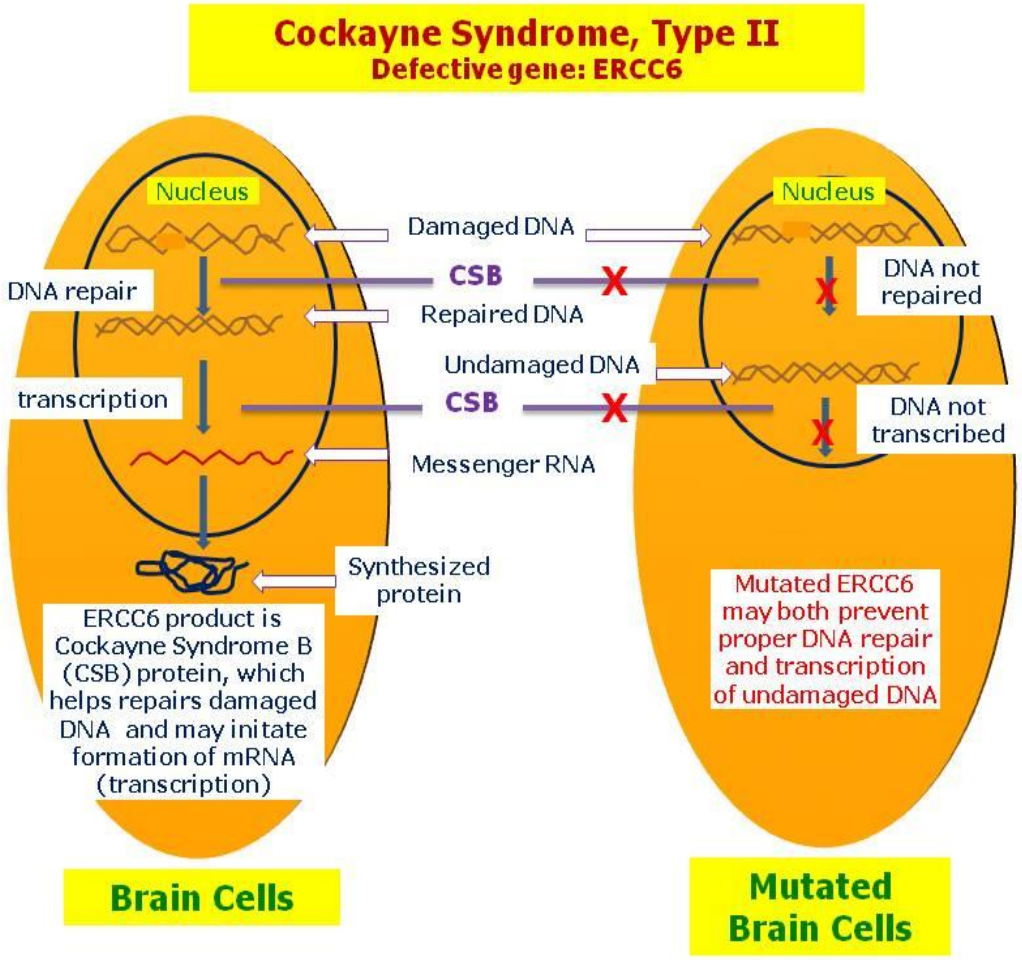
Wide range of symptoms

Four types: I, II, III, and xeroderma pigmentosum (XP-CS)

Cockayne Syndrome Type II

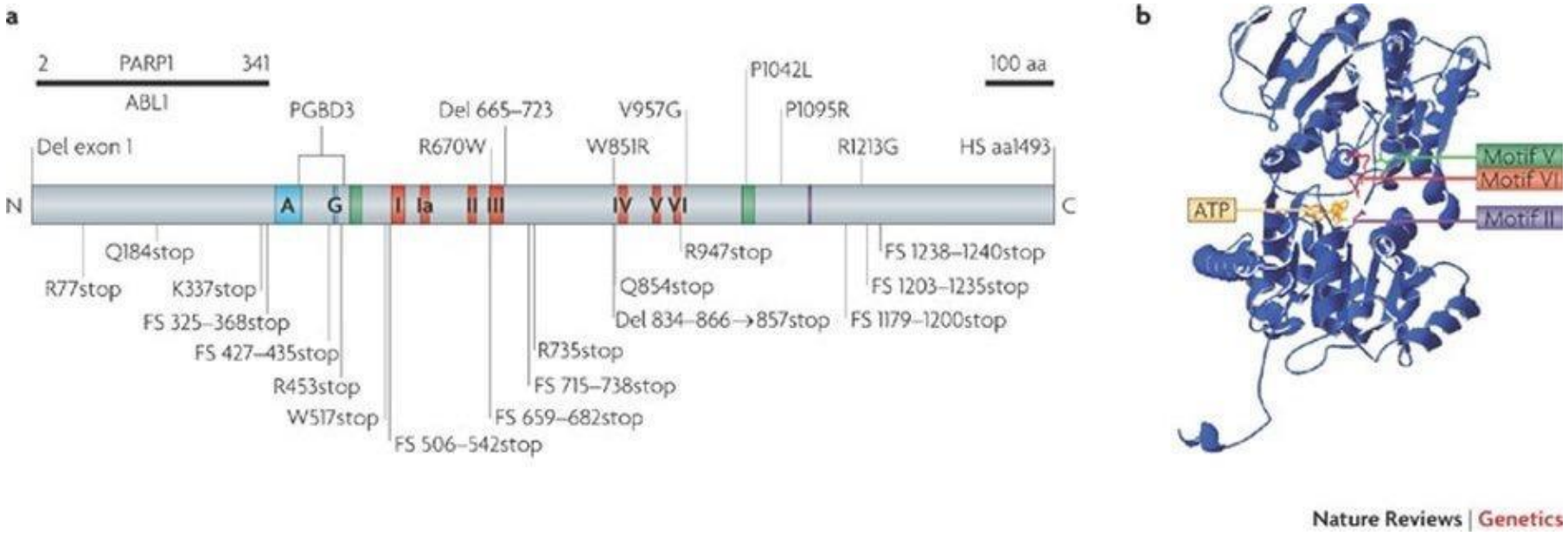
http://bluepurpleandscarlett.com/about-cs

What causes CS Type II?



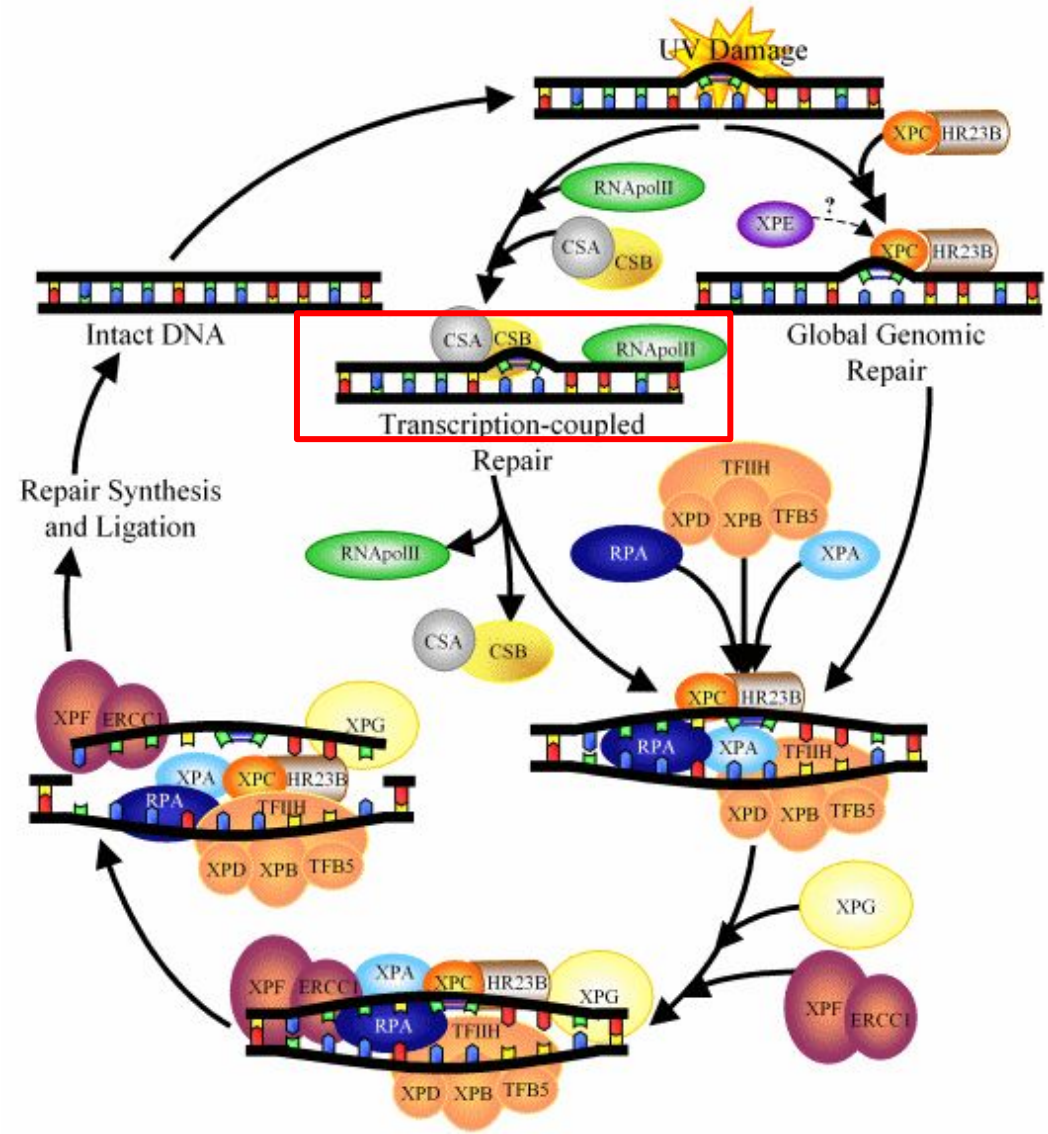
http://disorders.eyes.arizona.edu/disorders/cockayne-syndrome-type-ii

The ERCC6 Gene



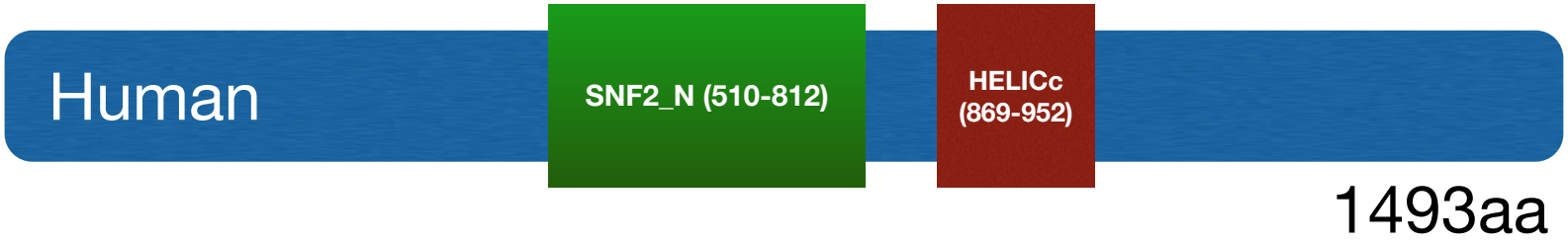
http://www.nature.com/nrg/journal/v10/n11/fig_tab/nrg2663_F2.html

What is ERCC6's role in DNA repair?



https://catalog.coriell.org/0/sections/collections/nigms/ner_pathway.aspx?PgId=256

What domains does ERCC6 have?

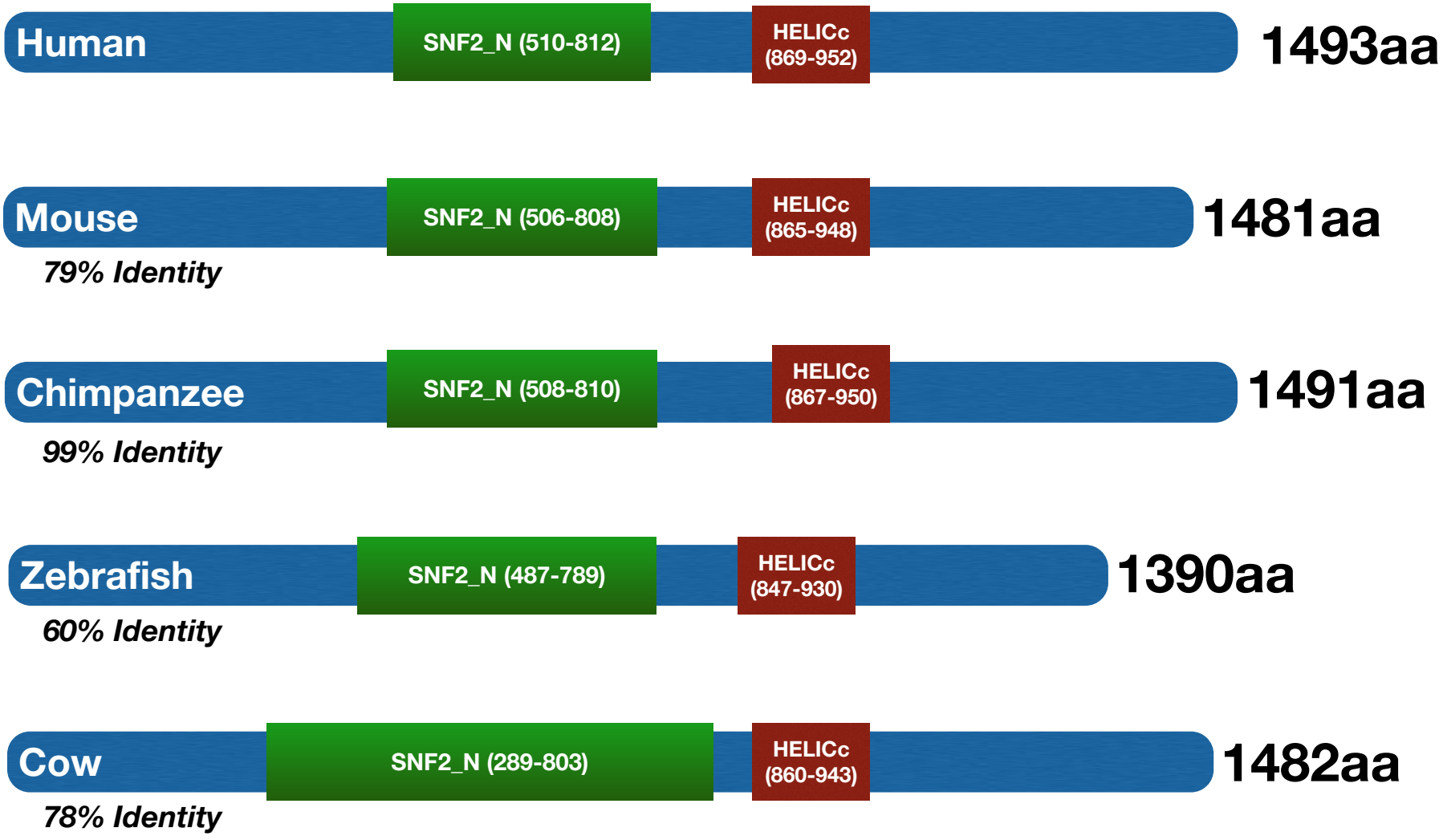


SNF2_N: Molecular function is to bind ATP. Proteins with this domain can disrupt histone-DNA interactions.

HELICc: C-terminal domain helicase. Molecular function is ATP binding and helicase activity.

http://www.ebi.ac.uk/interpro/entry/IPR000330
http://www.uniprot.org/uniprot/Q60ER9

What do common ERCC6 homologs look like?



How similar are the common homologs?

Orangutan, 97.98% identity

Gorilla, 99.13% identity

Chimpanzee, 99.46% identity

Mouse, 79.07% identity

Cow, 78.27% identity

Zebrafish, 59.86% identity

Rat, 78.97% identity

Wild Boar, 84.88% identity

Elephant, 82.19% identity

Panda, 84.61% identity

Sheep, 81.77% identity

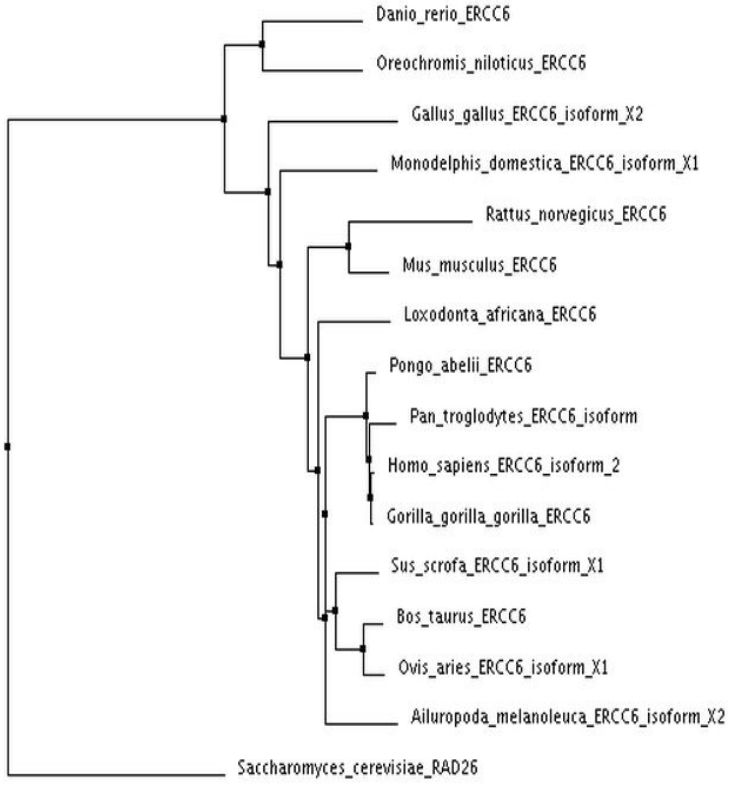
Red Junglefowl, 64.55% identity

Tilapia, 56.65% identity

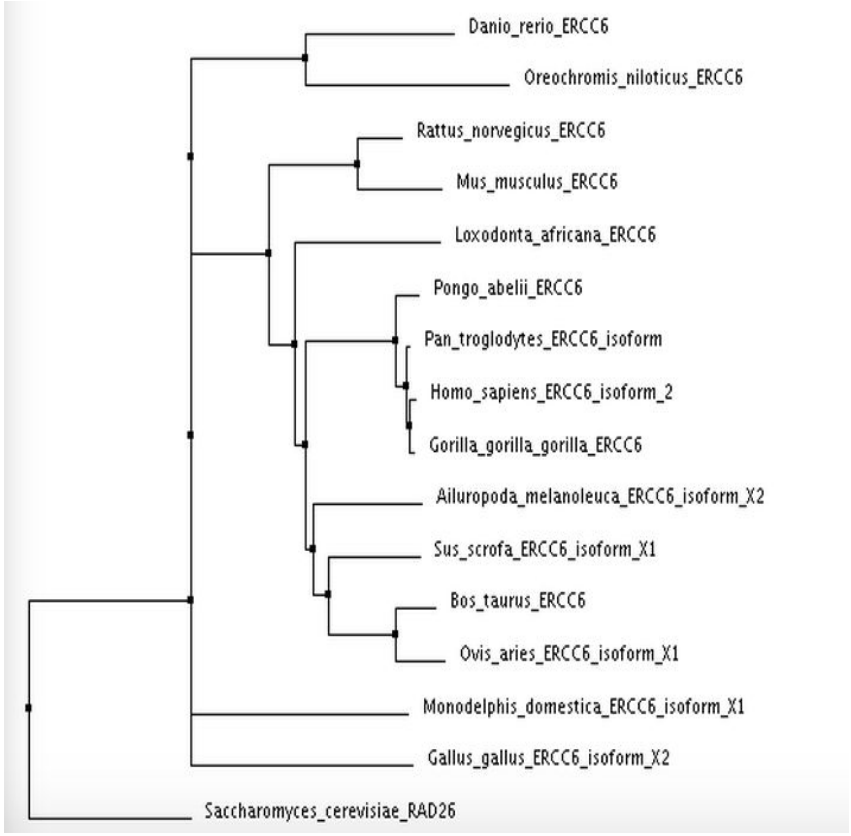
Possum, 69.24% identity

Saccharomyces cerevisiae, 38.52% identity

How are these homologs related? (NJ)

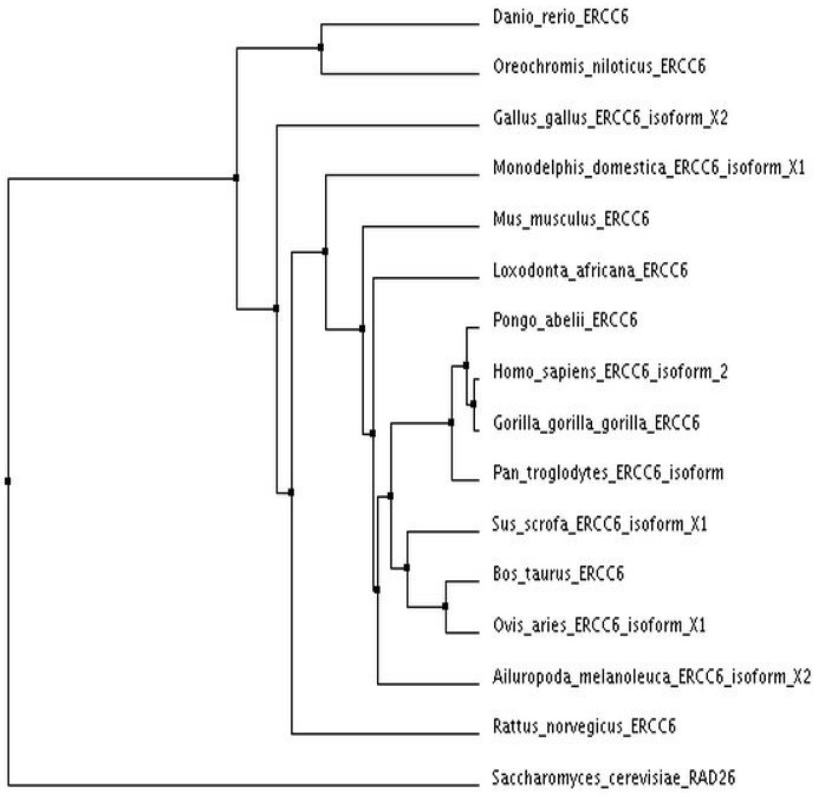


BLOSUM62 NJ

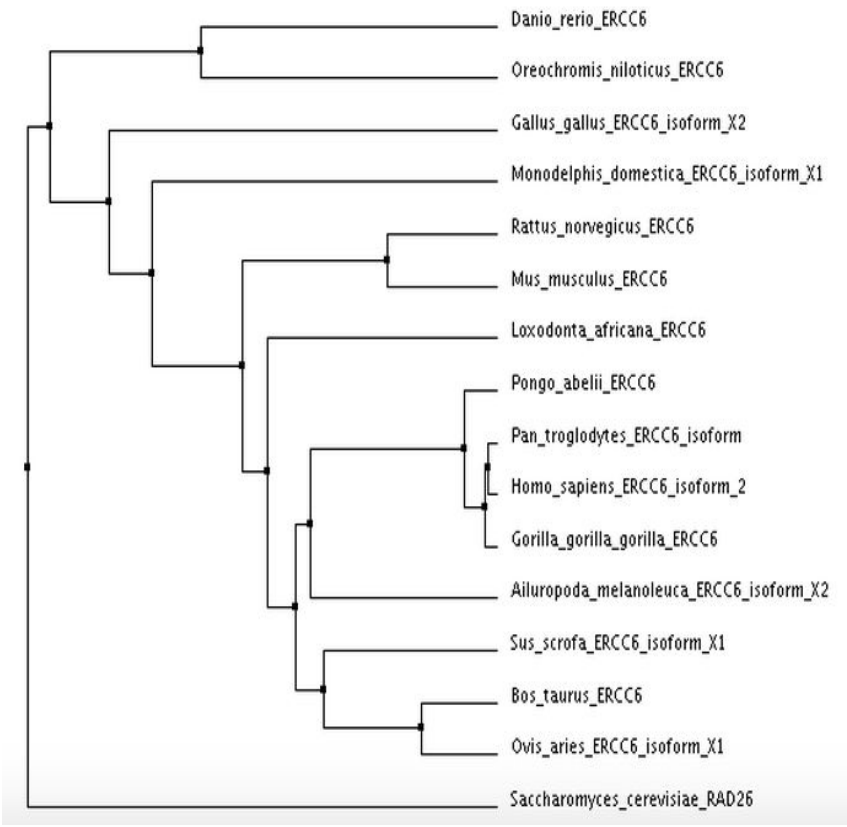


Percent Identity NJ

How are these homologs related? (AD)



BLOSUM62 Average Distance



Percent Identity Average Distance

What is not known?

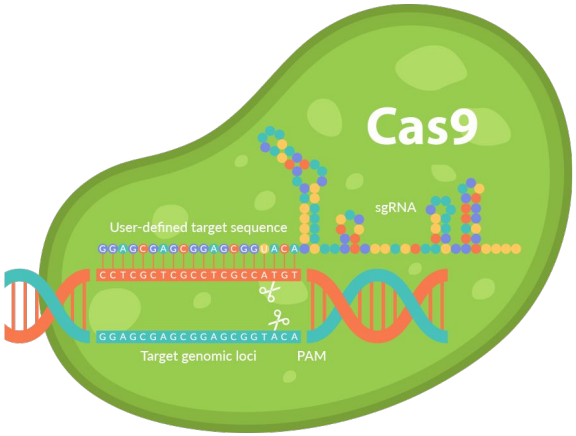
http://www.tankonyvtar.hu/hu/tartalom/tamop425/0011_1A_Gerontologia_en_book/ch02s07.html

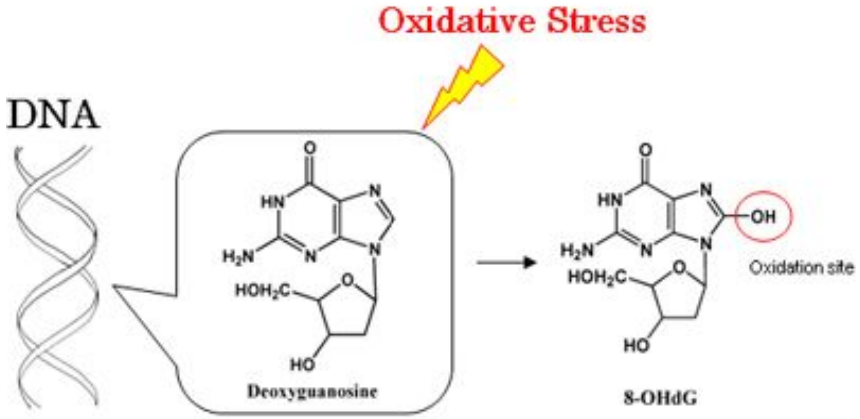
Gap in Knowledge

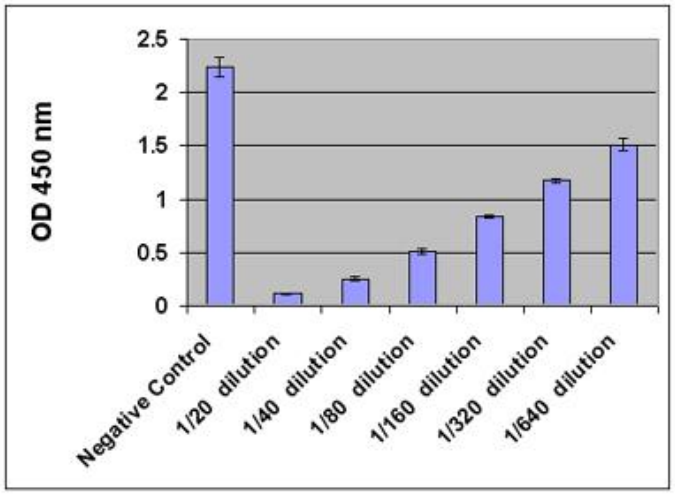
A major symptom of CS is progeria, or premature aging. Aging is caused by oxidative damage. ERCC6 is thought to play a molecular role in processing and possibly fixing oxidative damage. *What is this role?*

What is the ideal model organism for studying oxidative damage?

Aim 1: Which protein domains are important for managing oxidative stress?

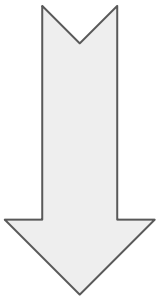






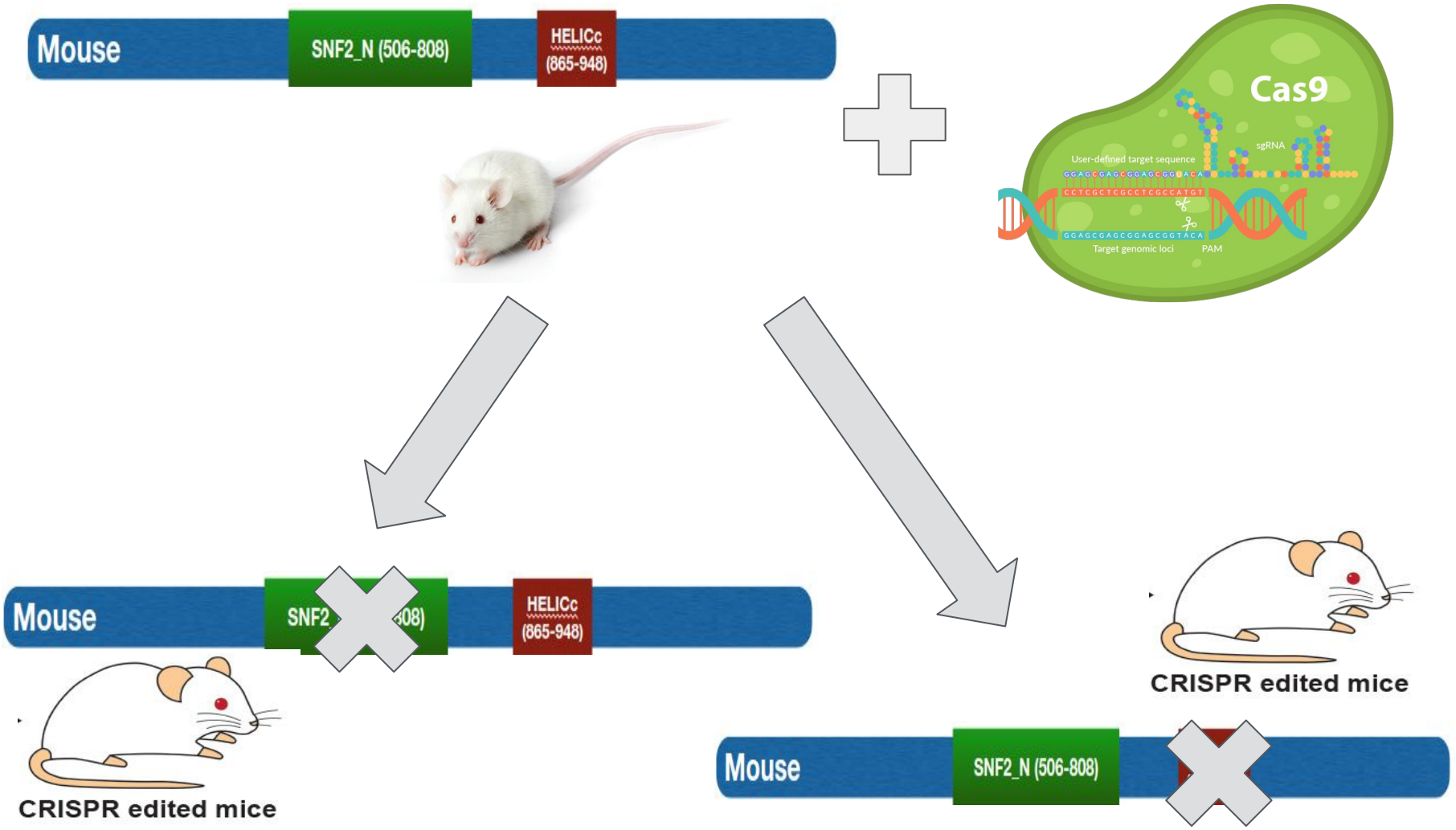
http://pfam.xfam.org/ , http://smart.embl-heidelberg.de/ , http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , http://en.ori-japan.com/aboutfpp/about-fpp/ , http://www.cellbiolabs.com/8-ohdg-dna-damage-elisa

Aim 1, Step 1: Identify



http://pfam.xfam.org/ , http://smart.embl-heidelberg.de/

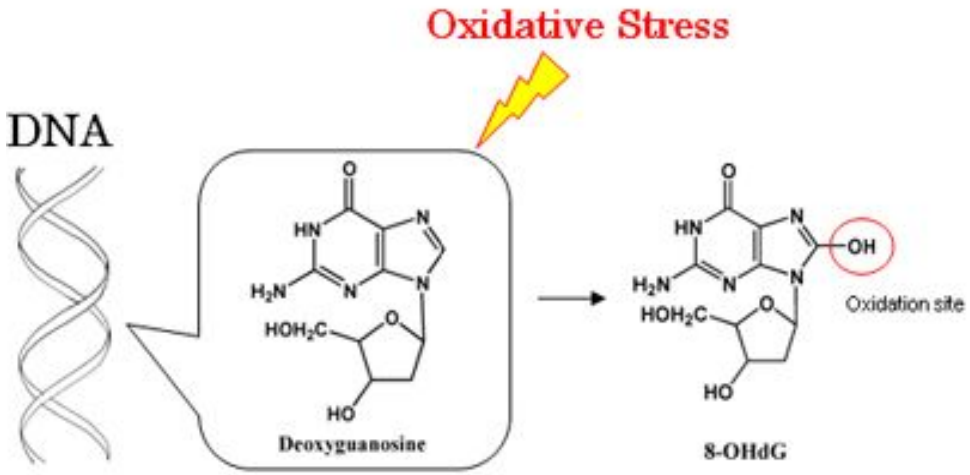
Aim 1, Step 2: Edit



http://www.thomasgoetz.com/blog/2014/5/20/where-the-white-lab-mouse-came-from , https://www.synthego.com/crispr/ , http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/

Aim 1, Step 3: Induce Stress

CRISPR edited mice



Produces 8-OHdG

http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , http://en.ori-japan.com/aboutfpp/about-fpp/

Aim 1, Step 4: Measure 8-OHdG in CRISPR mice models

CRISPR edited mice

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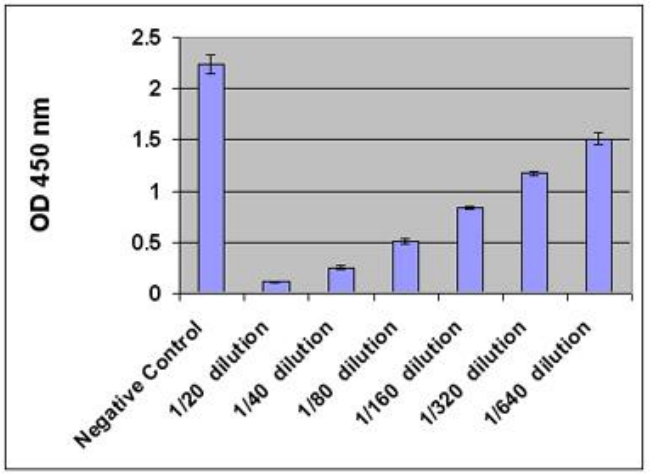
Creating Solutions for Life Science Research

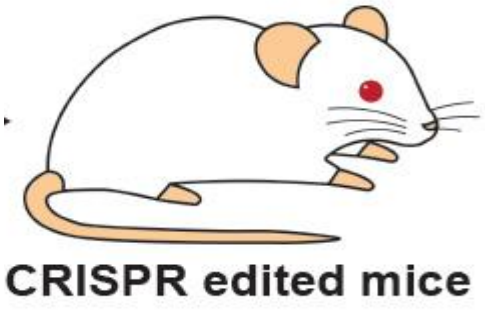
8-OHdG DNA Damage ELISA
DNA / RNA Damage and Repair

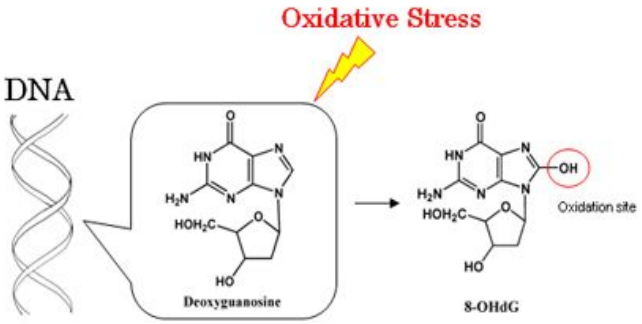


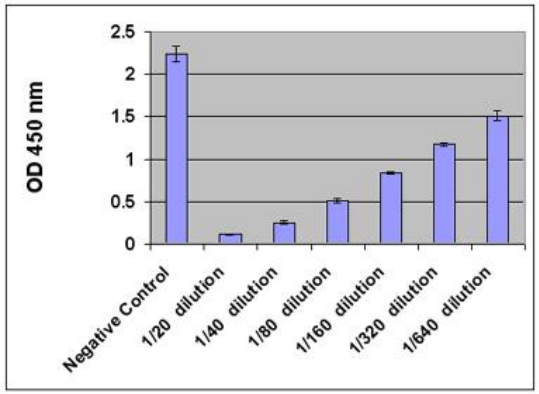
8-OHdG levels in urine. High levels = successful processing of oxidative damage

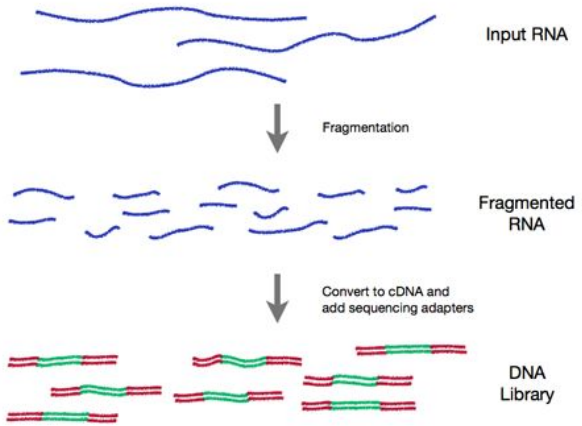
http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , http://www.cellbiolabs.com/8-ohdg-dna-damage-elisa

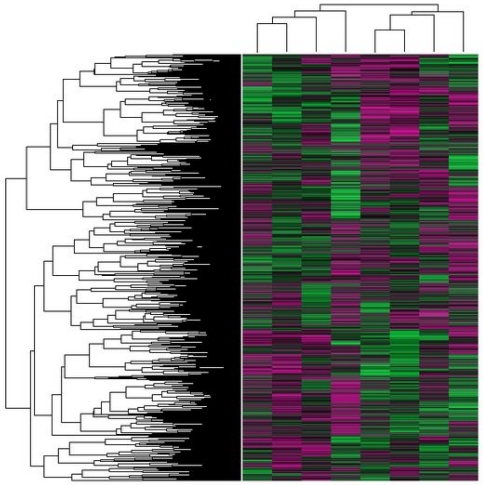
Aim 2: What genes does ERCC6 interact with when fixing oxidative damage, and do certain genes compensate for the loss of ERCC6?











Click to get gene list for a category:

- biological adhesion (GO:0022610)
- biological regulation (GO:0065007)
- cellular component organization or biogenesis (GO:0071840)
- cellular process (GO:0009987)
- developmental process (GO:0032502)
- immune system process (GO:0002376)
- localization (GO:0051179)
- locomotion (GO:0040011)
- metabolic process (GO:0008152)
- multicellular organismal process (GO:0032501)
- reproduction (GO:0000003)
- response to stimulus (GO:0050896)

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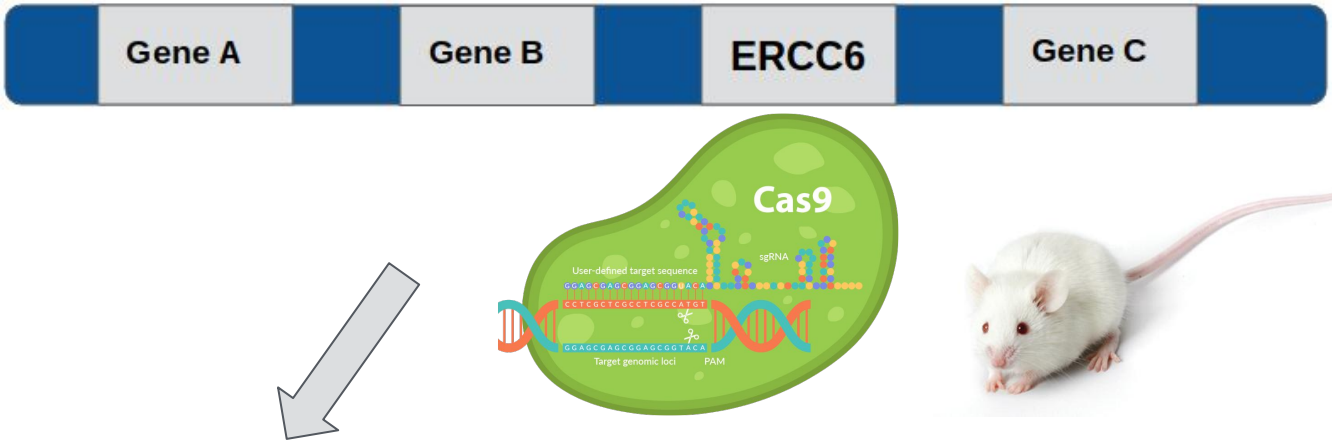
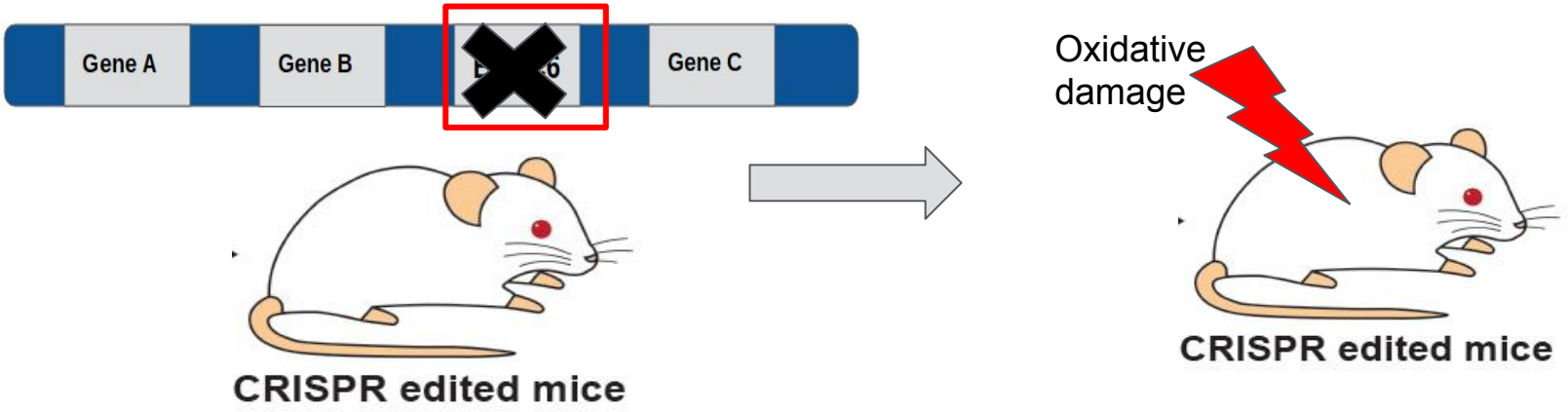
Aim 2, Step 1: CRISPR & Oxidative Stress





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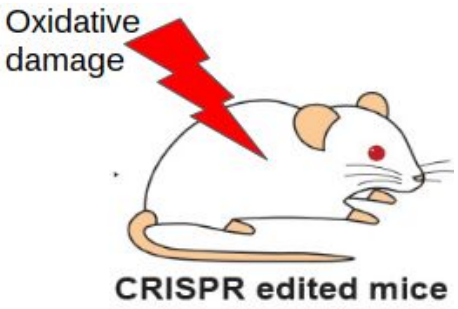
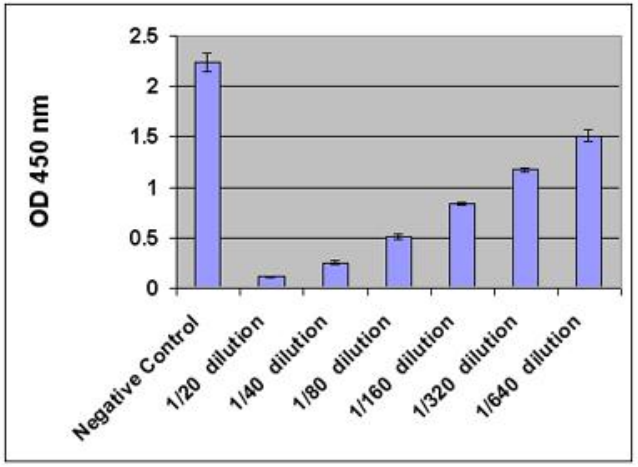
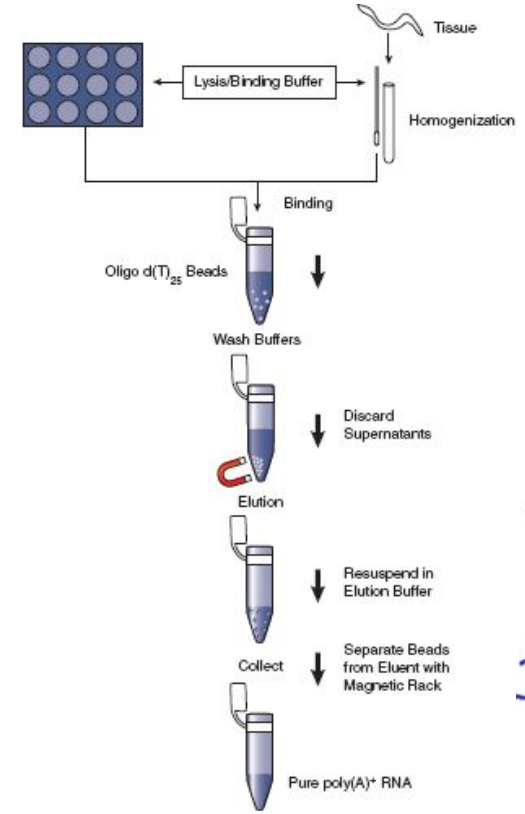
Aim 2, Step 2: Measure and RNA-Seq

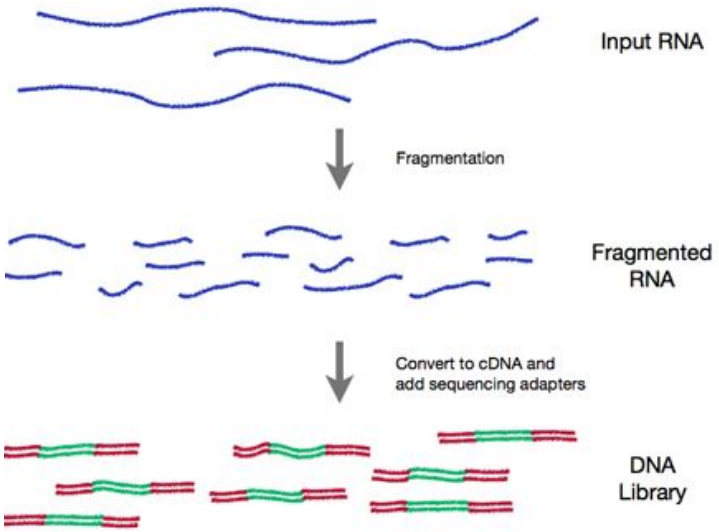


8-OHdG DNA Damage ELISA

DNA / RNA Damage and Repair







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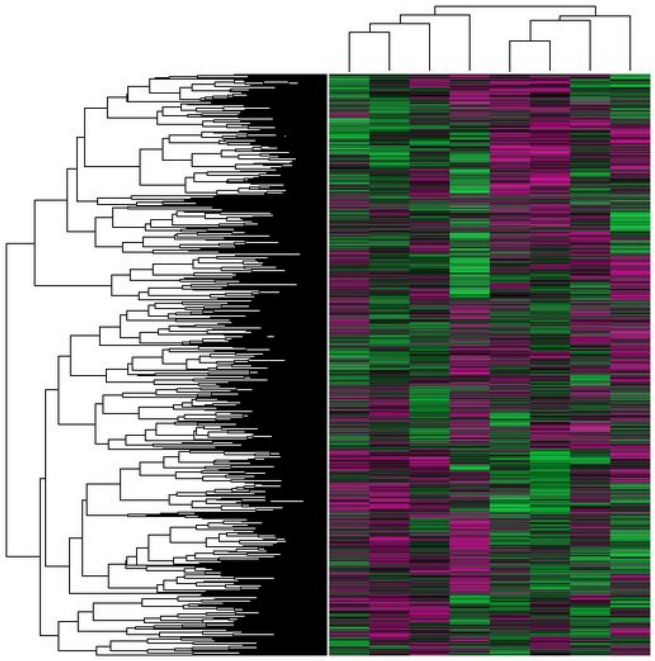
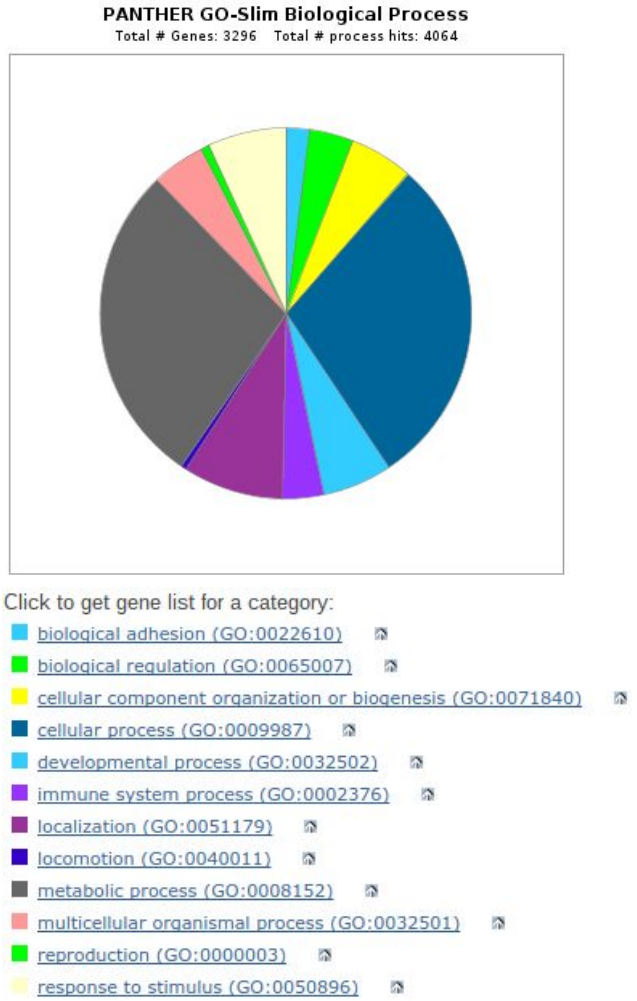
Aim 2, Step 3: Measure expression, identify processes





http://pantherdb.org/chart/pantherChart.jsp?listType=1&filterLevel=1&type=2&chartType=1&save=yes&basketItems=all&zoom=1&trackingId=FD8790585DFC3D222246F7D75802B001 , https://www.ncbi.nlm.nih.gov/geo/gds/analyze/analyze.cgi?ID=GDS2176

References