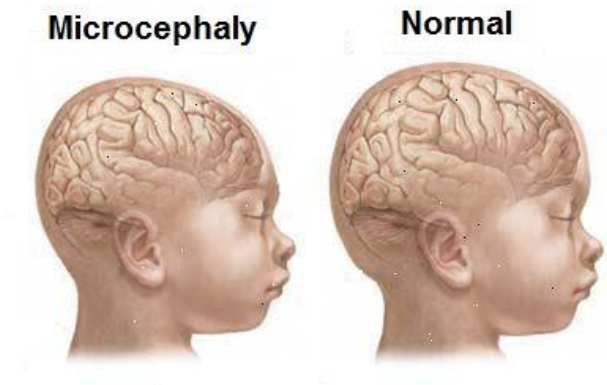
ERCC6 Gene & Cockayne Syndrome Type II

Zachary Beethem, Genetics 564

http://bluepurpleandscarlett.com/about-cs

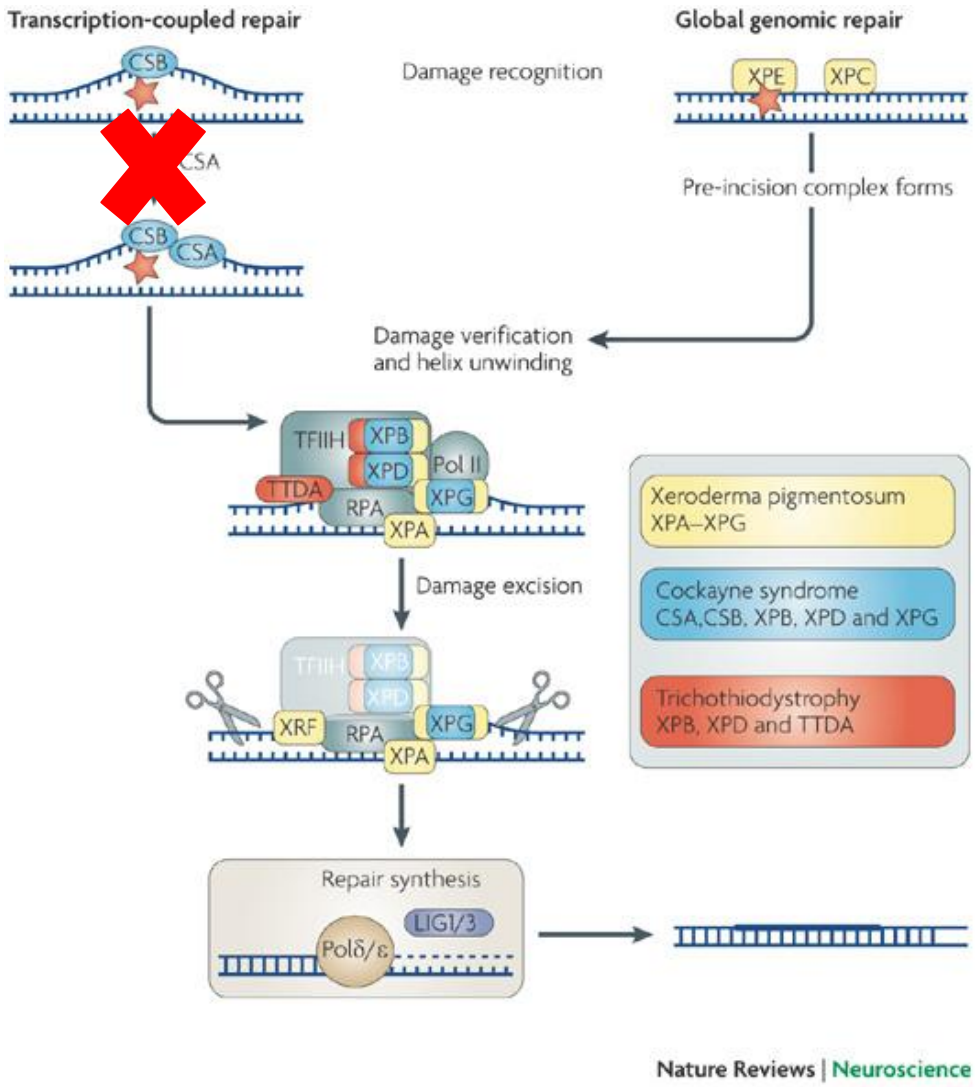
What is Cockayne Syndrome Type II?



https://www.emaze.com/@AFZQZLTO/Cockayne-Syndrome , https://www.aao.org/eye-health/diseases/what-are-cataracts , http://mytips10.blogspot.com/2016/01/microcephaly-definition-what-is-microcephaly.html

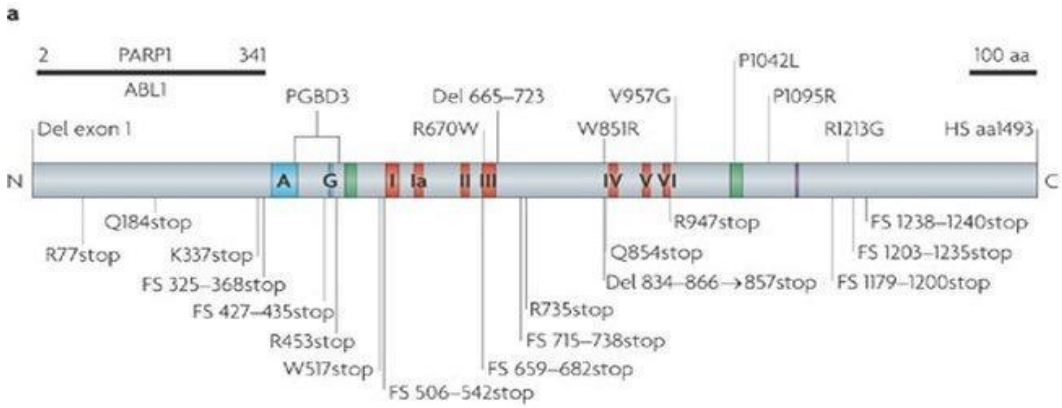
What causes CS Type II?

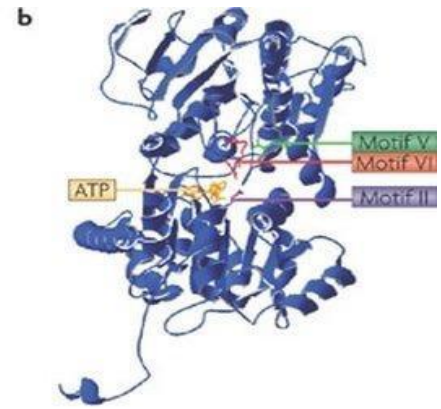
CSB = ERCC6
protein product



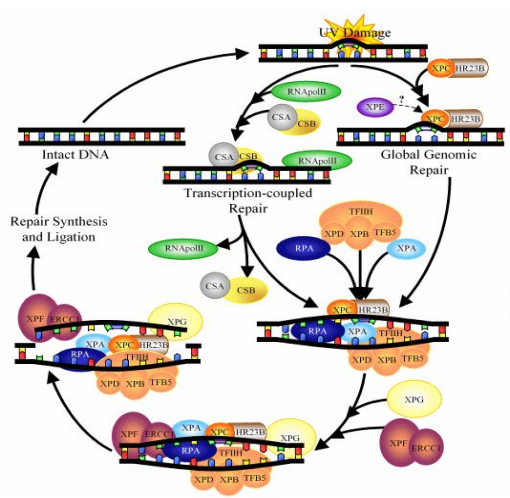
http://disorders.eyes.arizona.edu/disorders/cockayne-syndrome-type-ii

The ERCC6 Gene

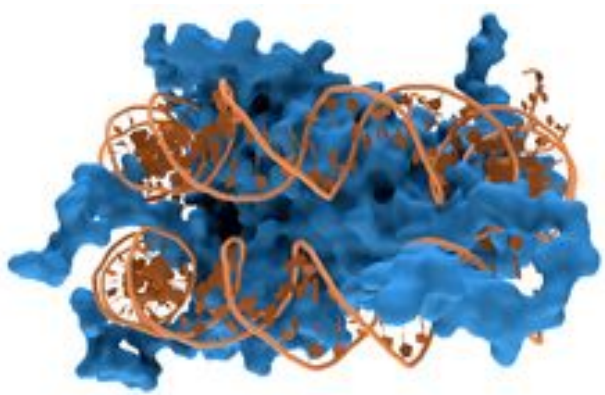




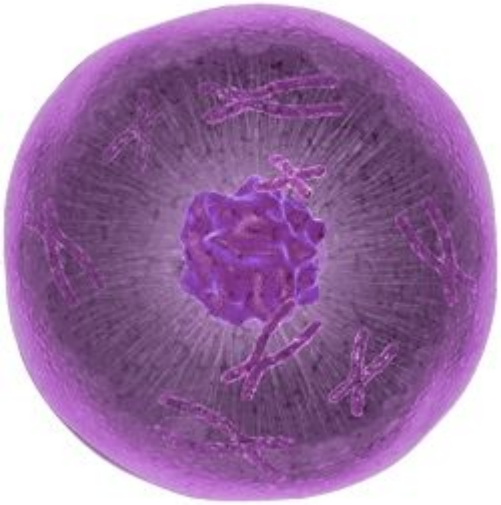
Biological Process



Molecular Function

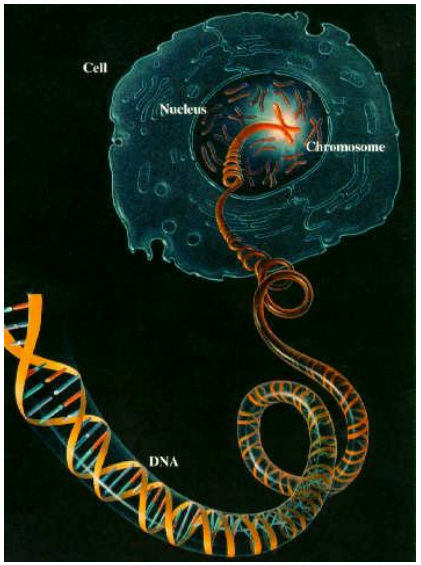


Cellular Component

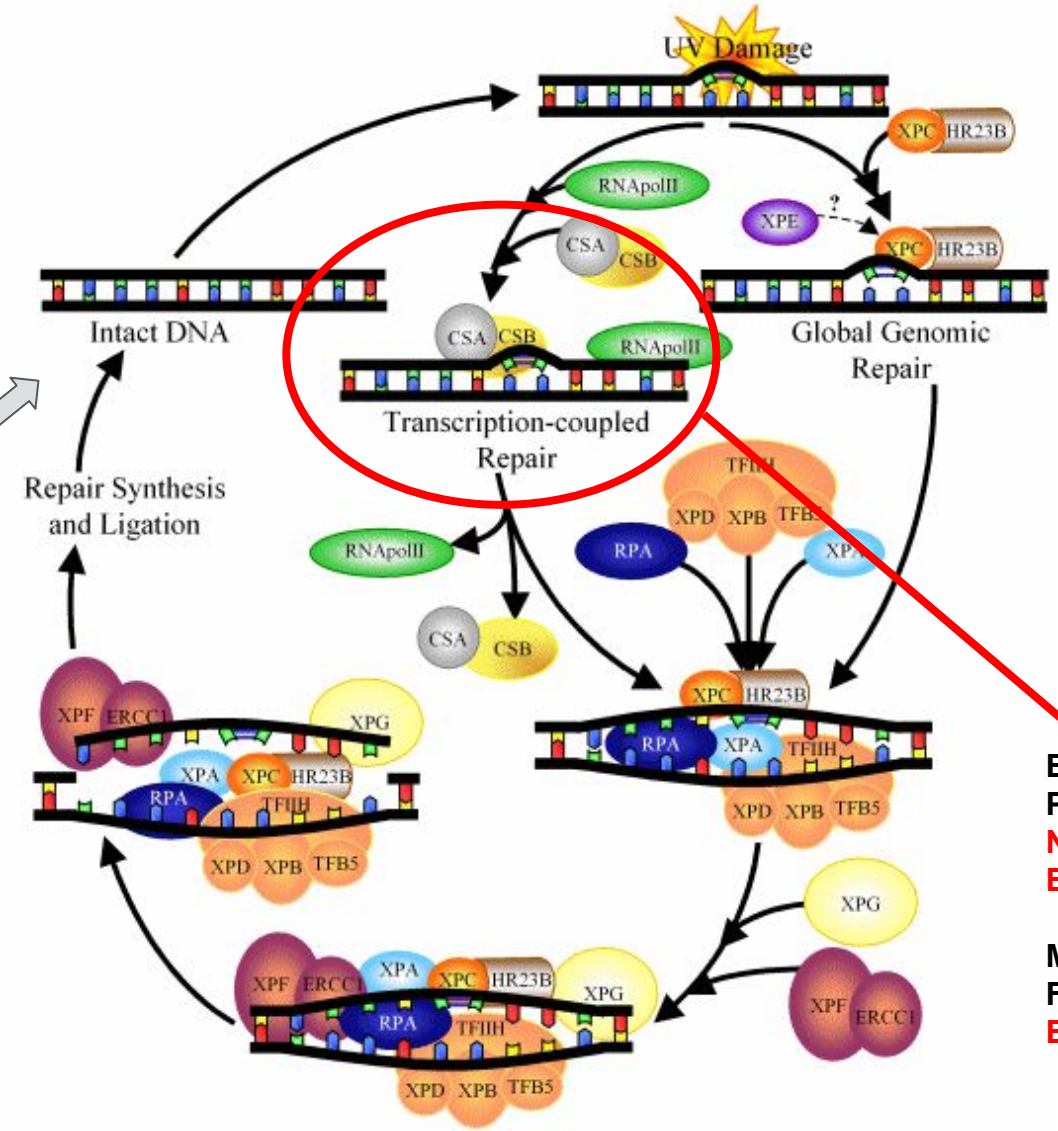


http://www.nature.com/nrg/journal/v10/n11/fig_tab/nrg2663_F2.html , http://stke.sciencemag.org/content/2007/415 , https://upload.wikimedia.org/wikipedia/commons/thumb/b/be/Nucleosome1.png/220px-Nucleosome1.png ,

What is ERCC6's role in the cell?



Cellular Component = Nucleus



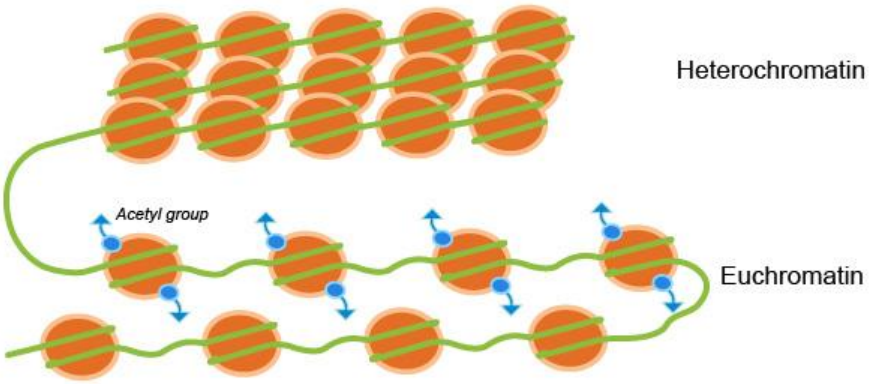
Biological Process = Nucleotide Excision Repair

Molecular Function = DNA Binding

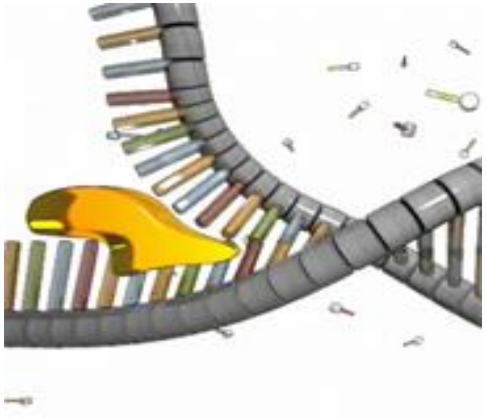
https://catalog.coriell.org/0/sections/collections/nigms/ner_pathway.aspx?PgId=256

What domains does ERCC6 have?

SNF2_N

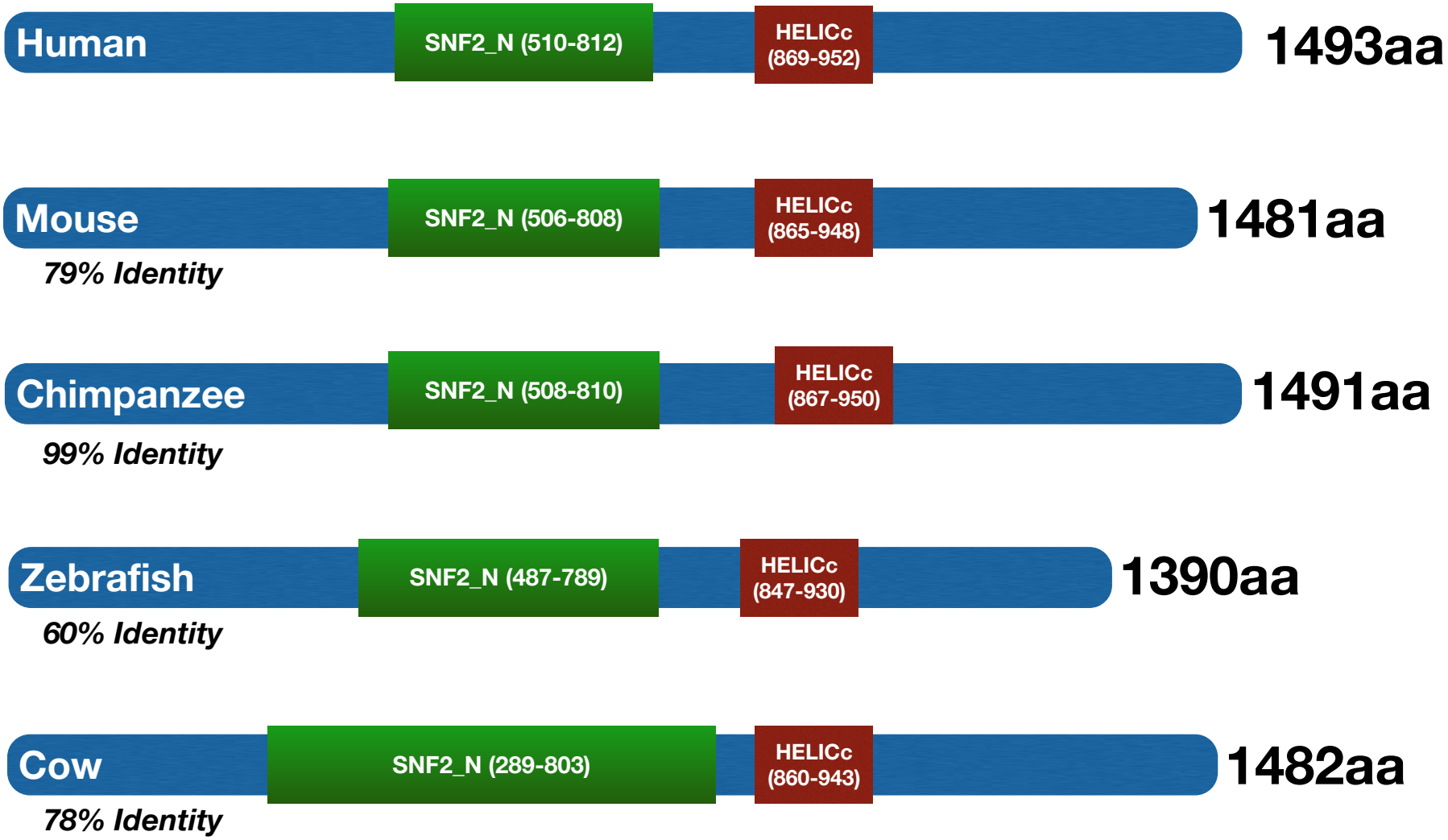


HELICc

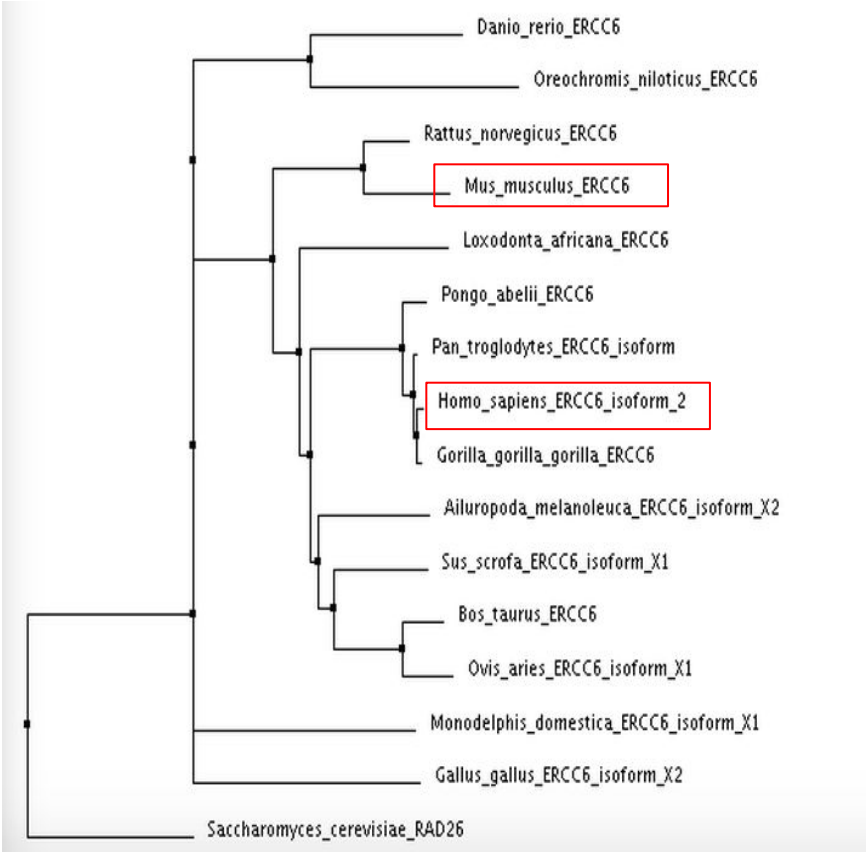


http://www.ebi.ac.uk/interpro/entry/IPR000330 , http://www.whatisepigenetics.com/chromatin-remodeling/ , https://www.nature.com/scitable/definition/helicase-307

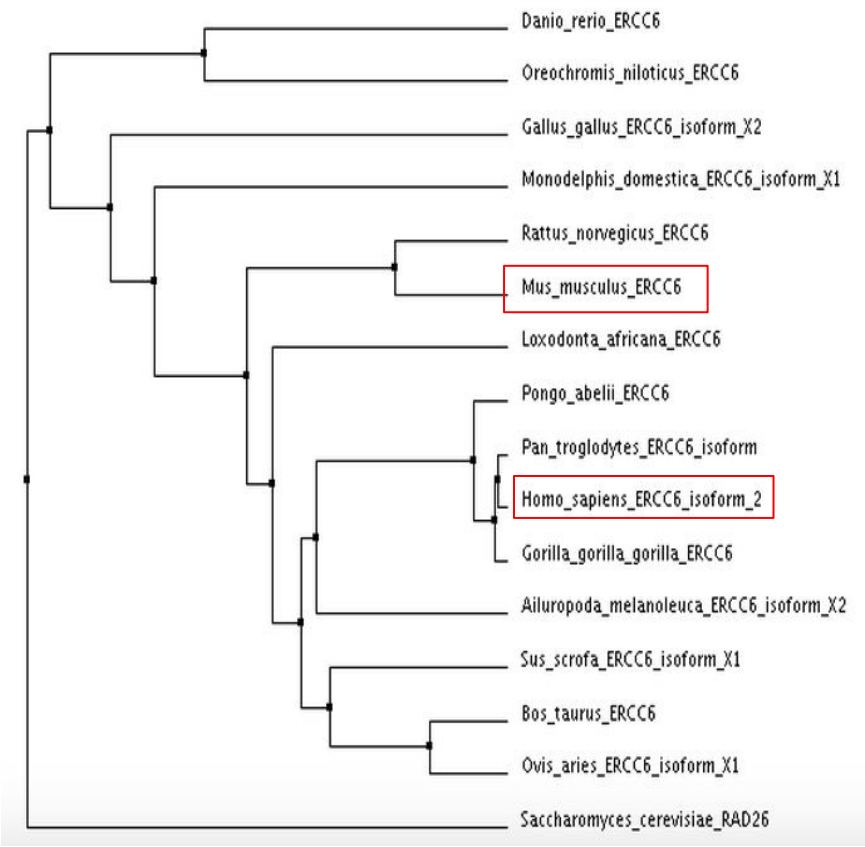
How well is ERCC6 conserved?



How are these homologs related?

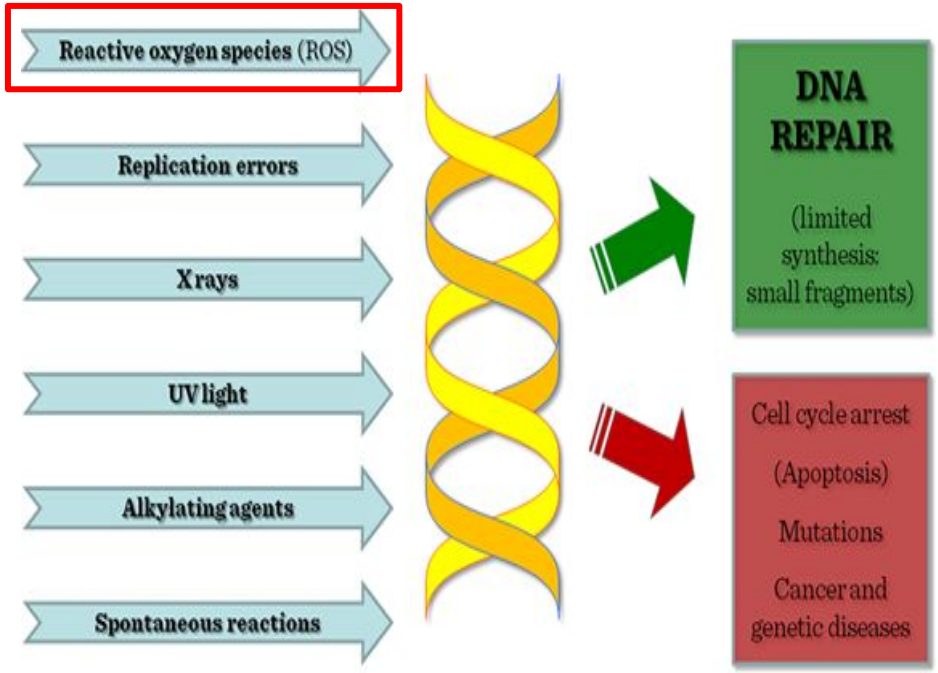


Percent Identity NJ



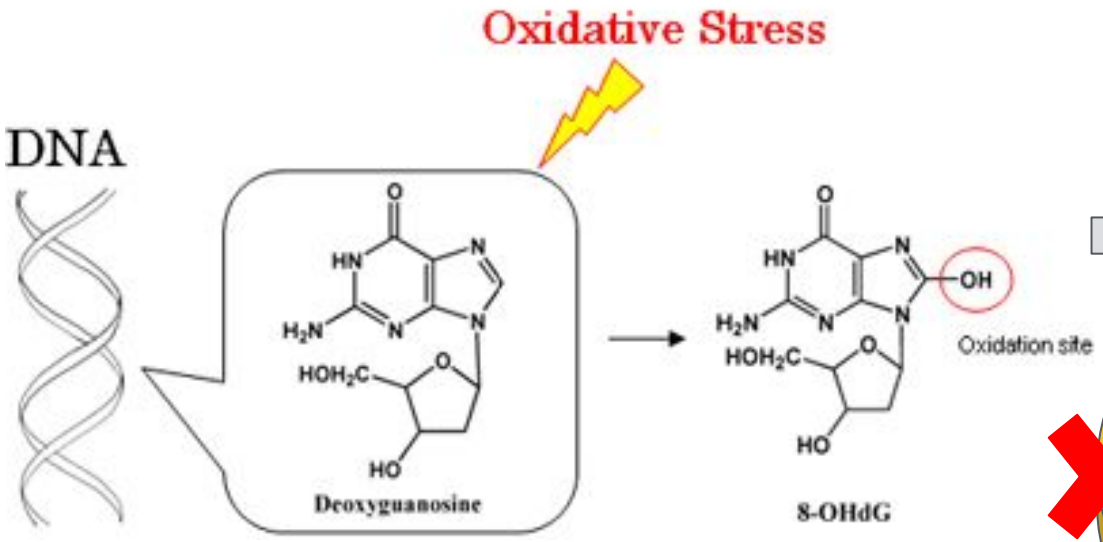
Percent Identity Average Distance

What is the gap?



http://www.tankonyvtar.hu/hu/tartalom/tamop425/0011_1A_Gerontologia_en_book/ch02s07.html ,
http://www.dailymail.co.uk/news/article-2385082/Coping-prematurely-aged-children-Families-Cockayne-Syndrome-kids-come-together.html

Gap in Knowledge

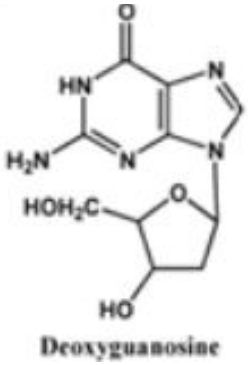


Oxidative Damage Accumulation
Premature aging symptoms

ERCC6/CSB
PROTEIN

Oxidative Damage
Base Excision Repair

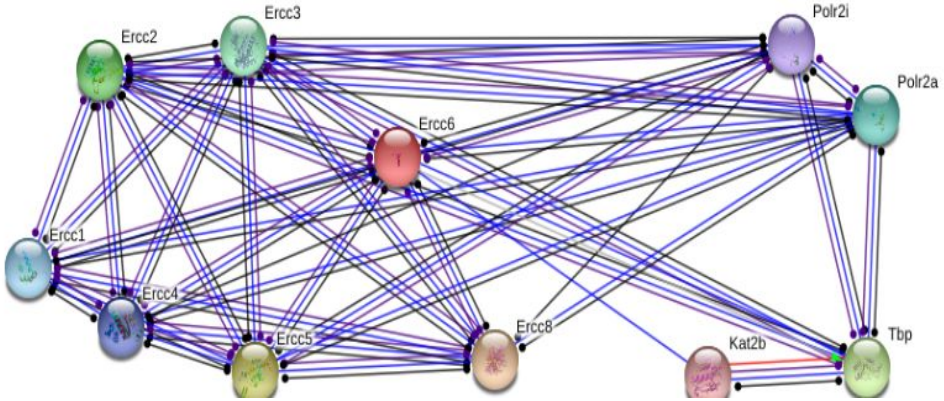
Healthy
DNA

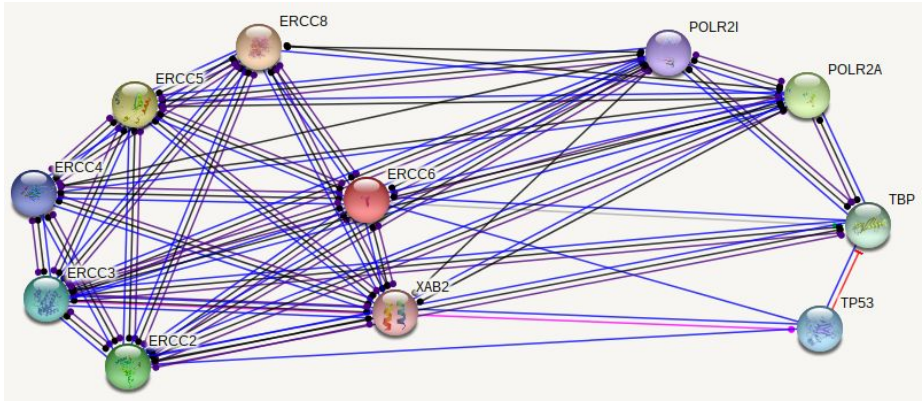


Primary goal: *To determine how ERCC6 regulates DNA damage repair after oxidative stress associated with aging.*

https://syndromespedia.com/cockayne-syndrome.html#.WP_buvQrJD8 , http://en.ori-japan.com/aboutfpp/about-fpp/

What model organism is best to study oxidative damage?





Mouse

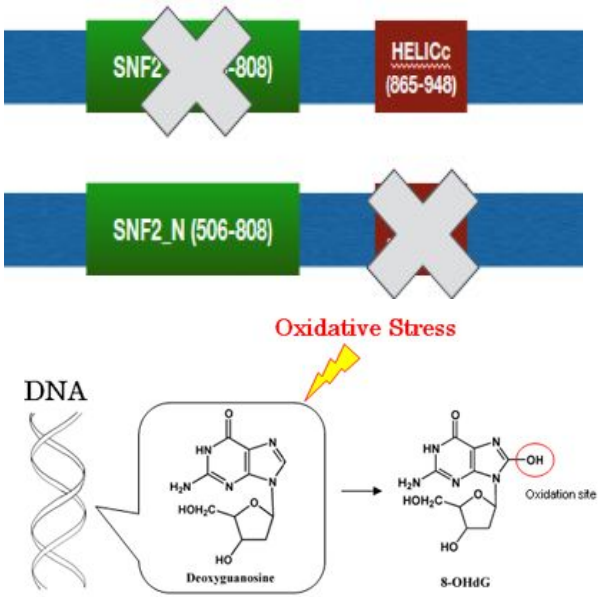
Human

http://www.victorpest.com/articles/house-mouse-facts-how-many-baby-mice-in-a-litter , http://progeriafamilycircle.blogspot.com/ , http://string-db.org/cgi/input.pl?UserId=pr2yjwXlURmS&sessionId=rLd6tI7IrE5T&input_page_show_search=on

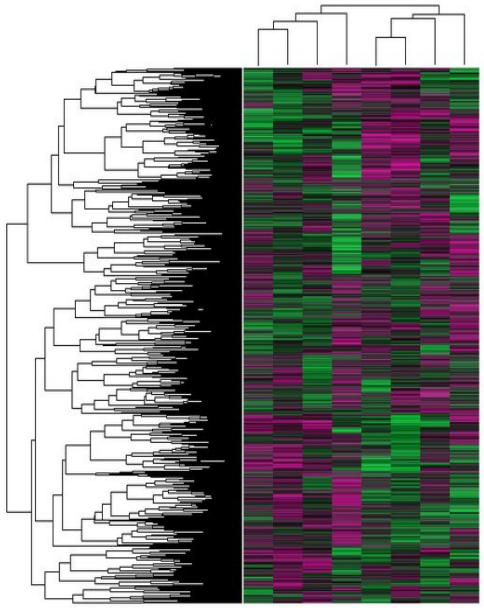
What is the central hypothesis?

ERCC6 loss leads to the aging phenotype in CS patients because oxidative damage cannot be regulated.

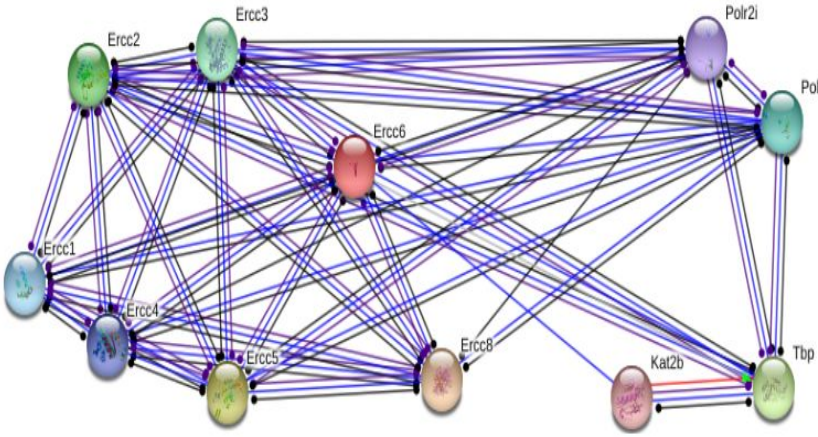
Aim 1



Aim 2

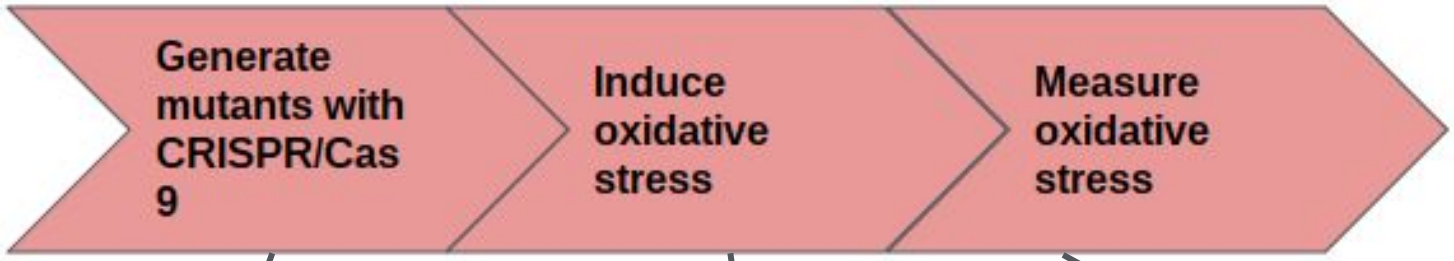


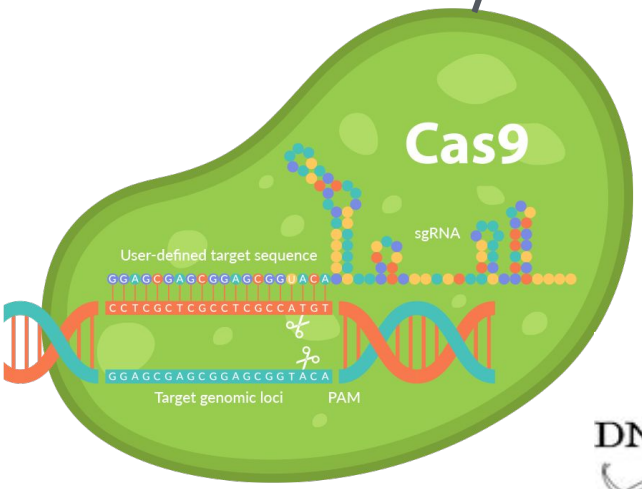
Aim 3

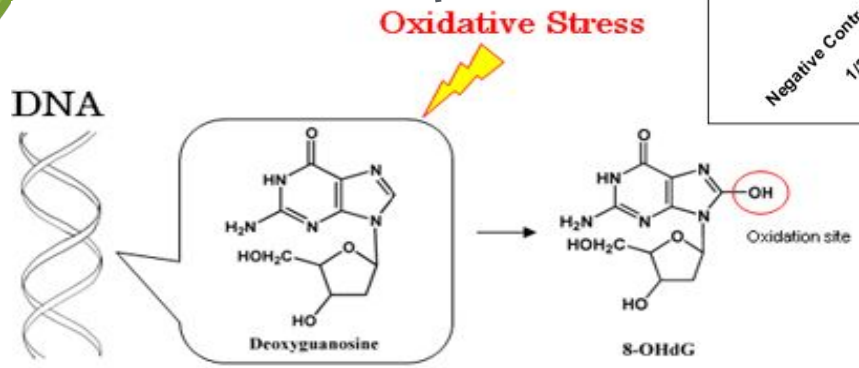


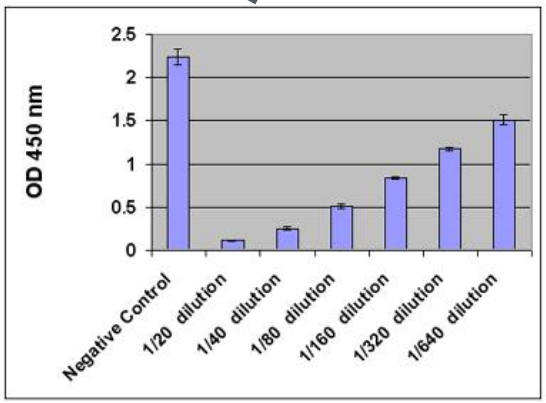
http://en.ori-japan.com/aboutfpp/about-fpp/ , https://www.ncbi.nlm.nih.gov/geo/gds/analyze/analyze.cgi?ID=GDS2176 , http://string-db.org/cgi/input.pl?UserId=pr2yjwXlURmS&sessionId=rLd6tI7IrE5T&input_page_show_search=on

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









http://en.ori-japan.com/aboutfpp/about-fpp/ , http://www.cellbiolabs.com/8-ohdg-dna-damage-elisa , https://www.synthego.com/crispr/

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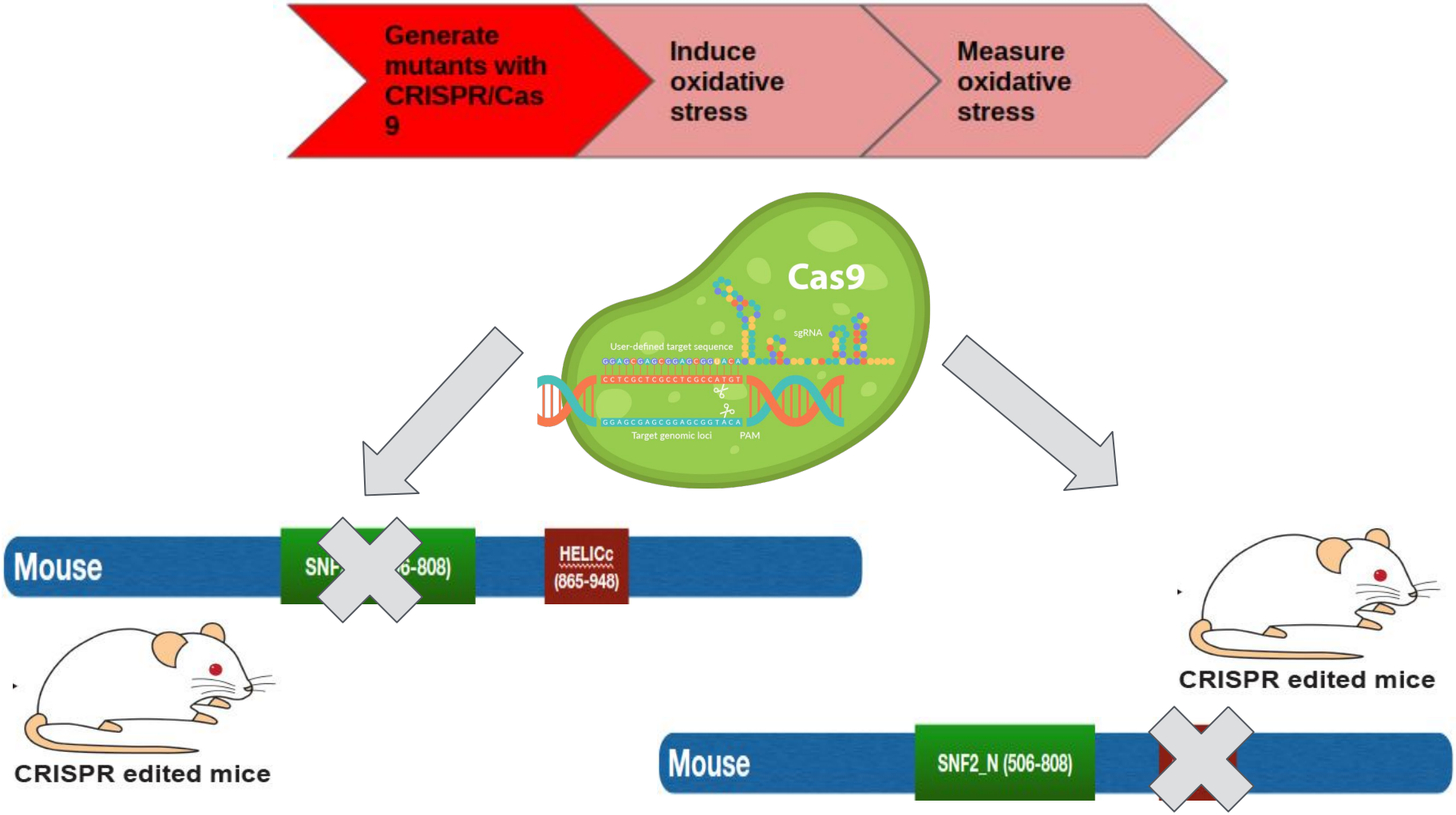

https://www.synthego.com/crispr/ , http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/

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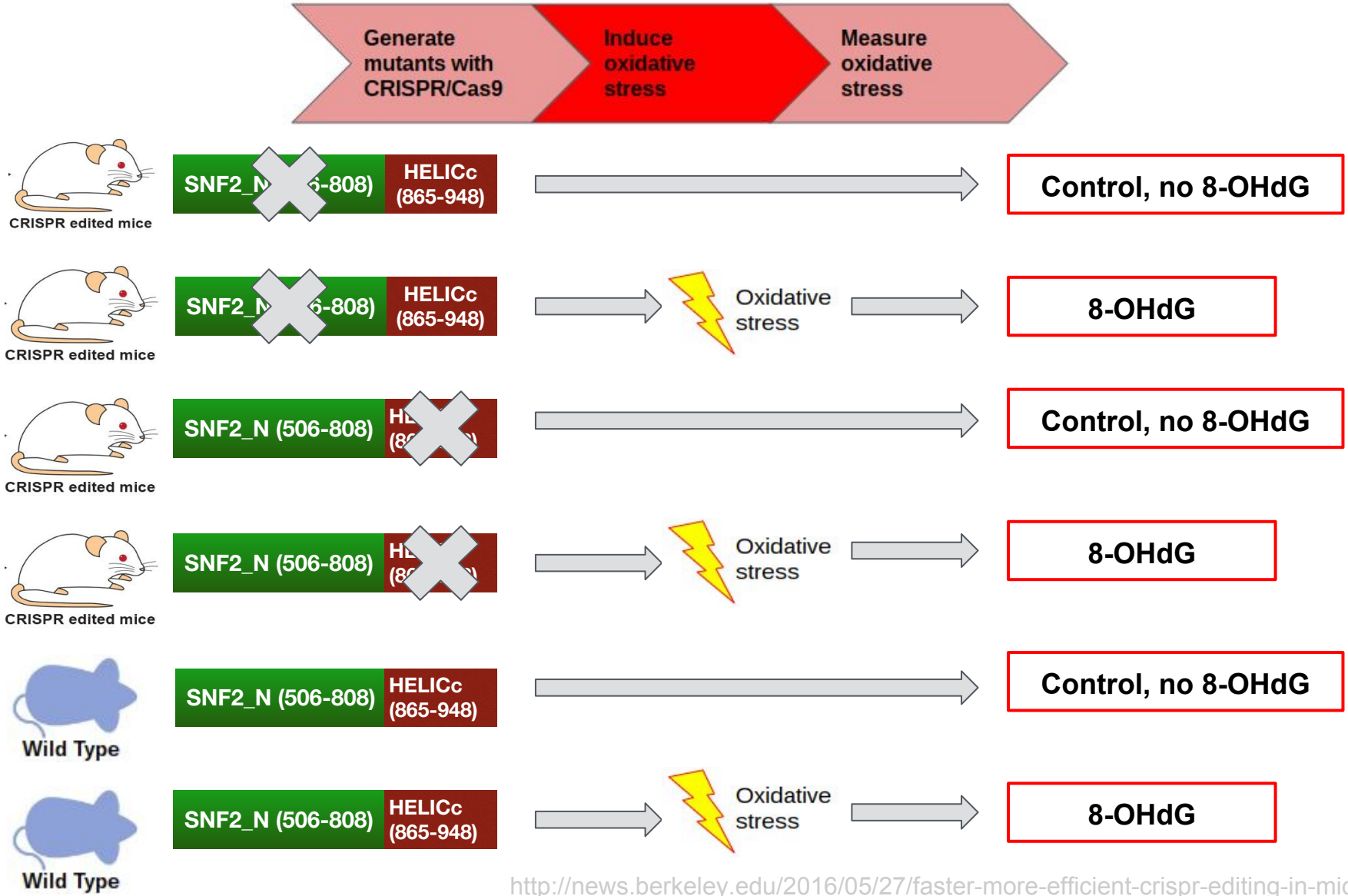

http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , http://www.cell.com/trends/cancer/fulltext/S2405-8033(16)30035-8

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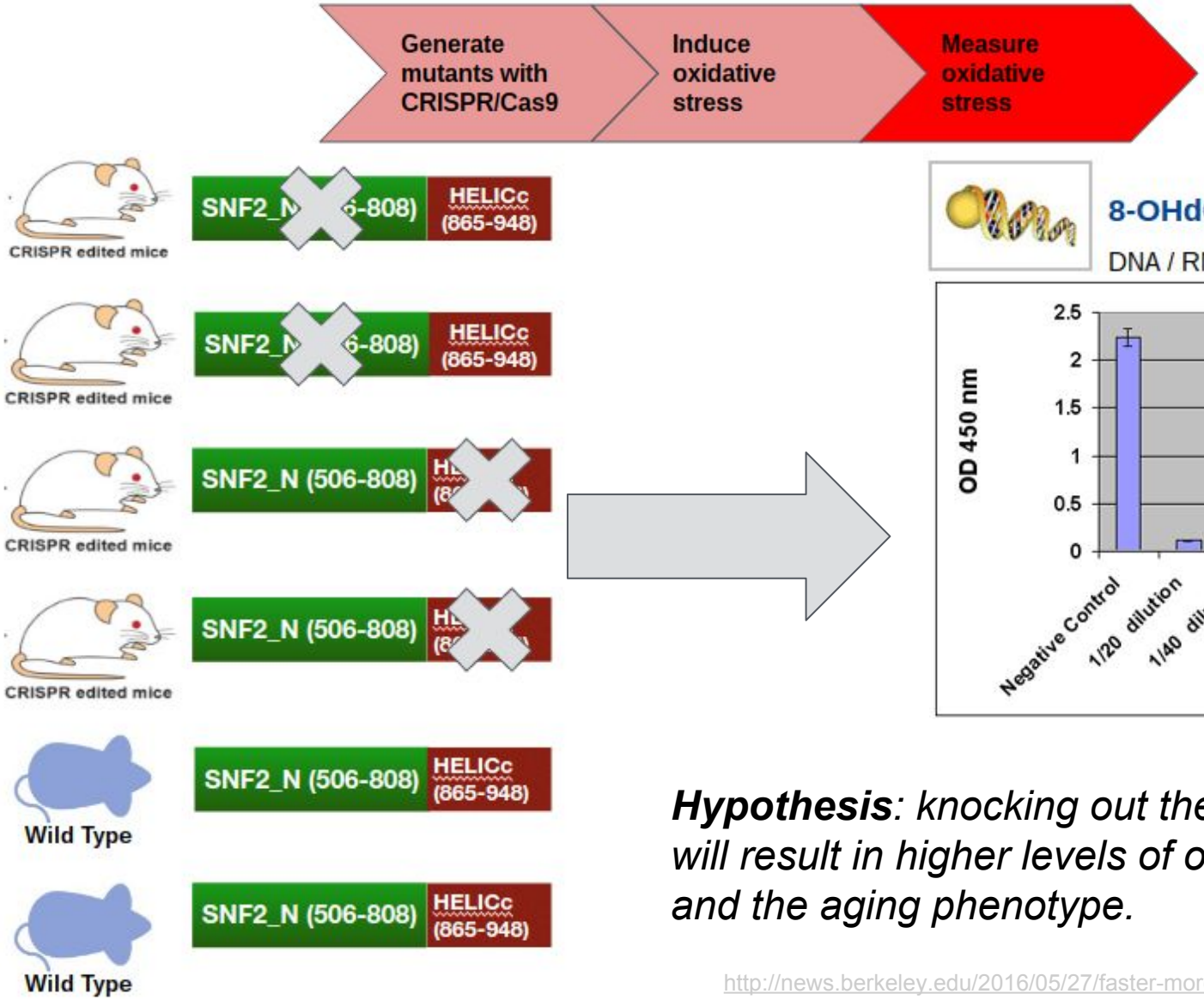
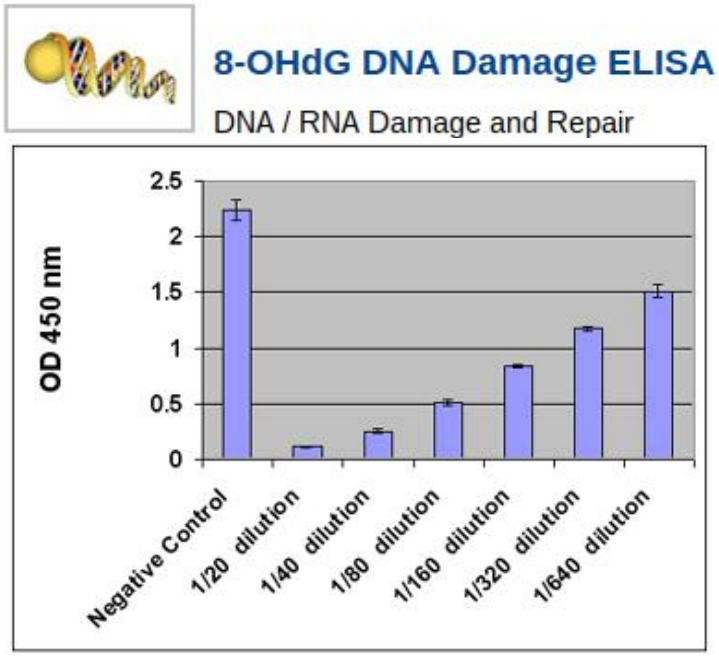
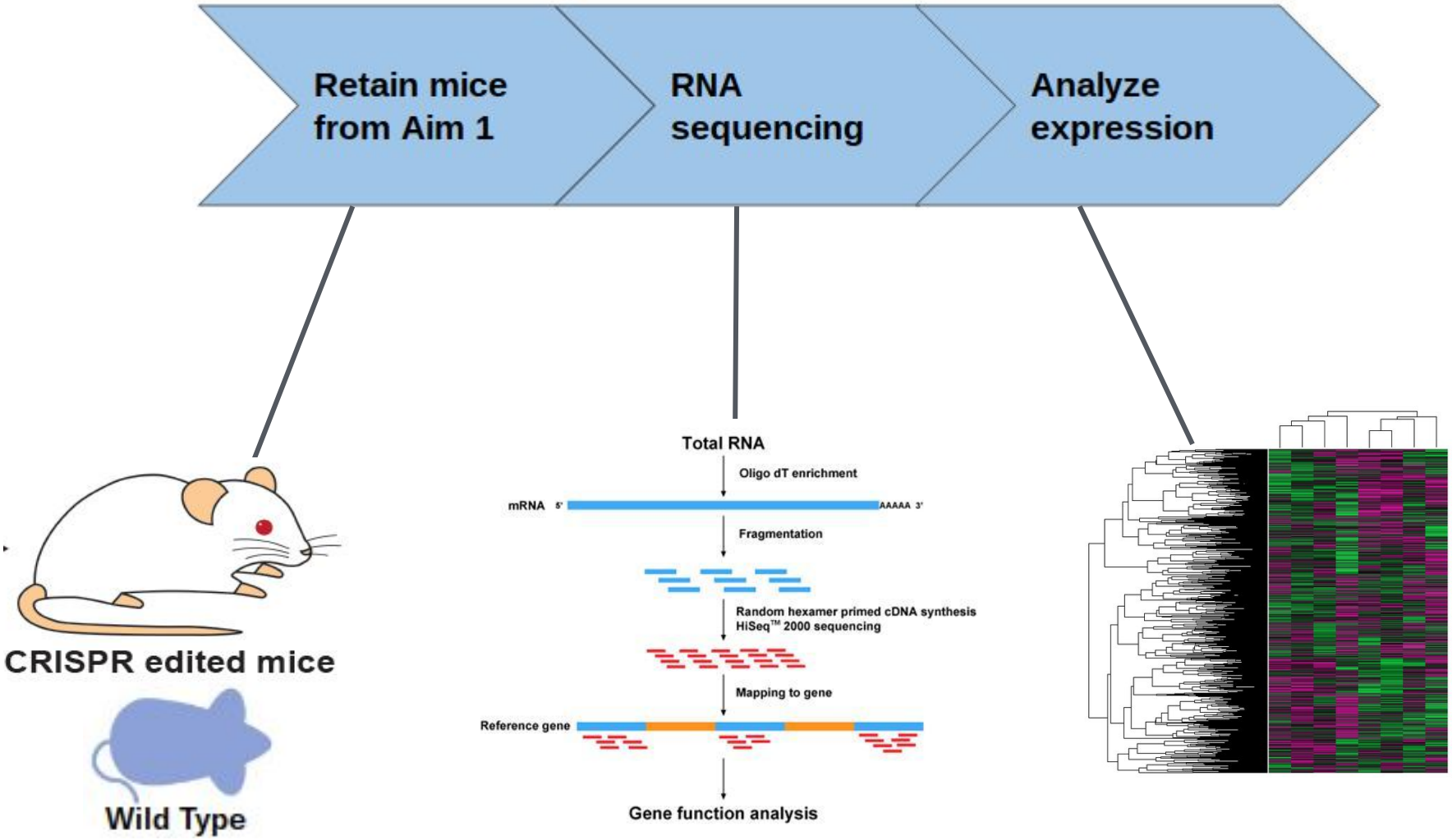




***Hypothesis**: knocking out the HELICc domain will result in higher levels of oxidative damage and the aging phenotype.*

http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , http://www.cell.com/trends/cancer/fulltext/S2405-8033(16)30035-8 , http://www.cellbiolabs.com/8-ohdg-dna-damage-elisa

Aim 2: Identify differentially expressed genes after oxidative stress in ERCC6 domain loss mutants from Aim 1



http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , ttps://www.ncbi.nlm.nih.gov/geo/gds/analyze/analyze.cgi?ID=GDS2176 , http://bio.lundberg.gu.se/courses/vt13/rnaseq.html

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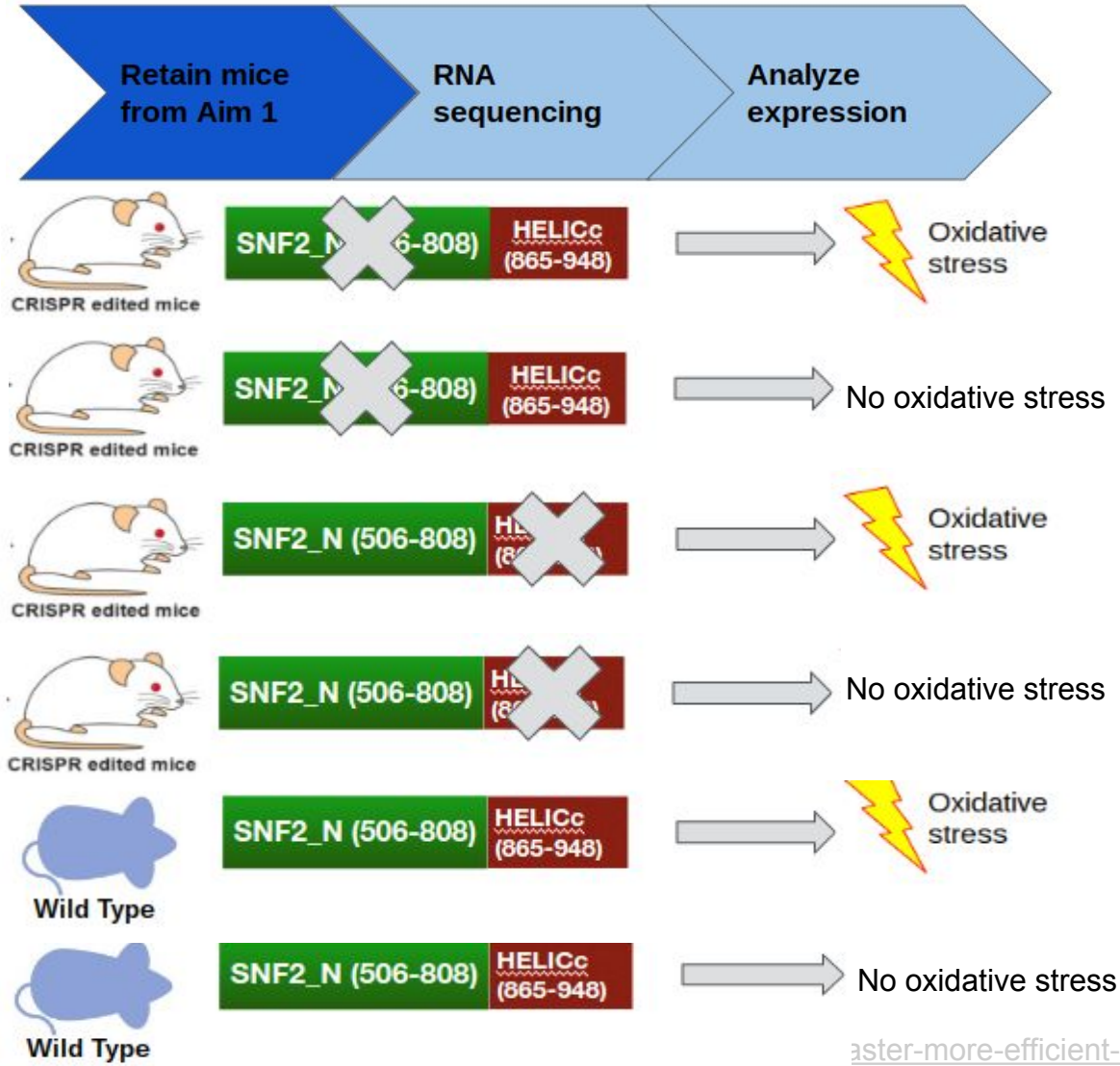

aster-more-efficient-crispr-editing-in-mice/ ,
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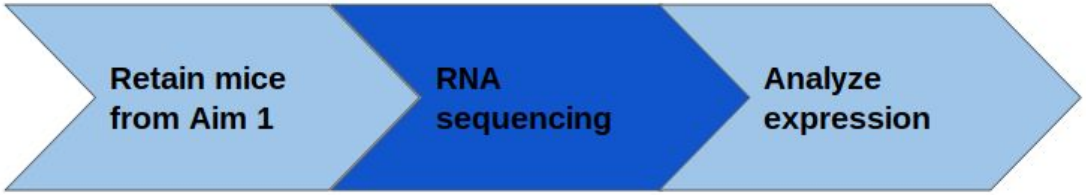
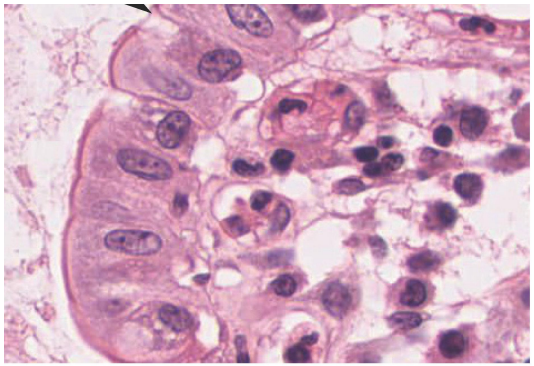
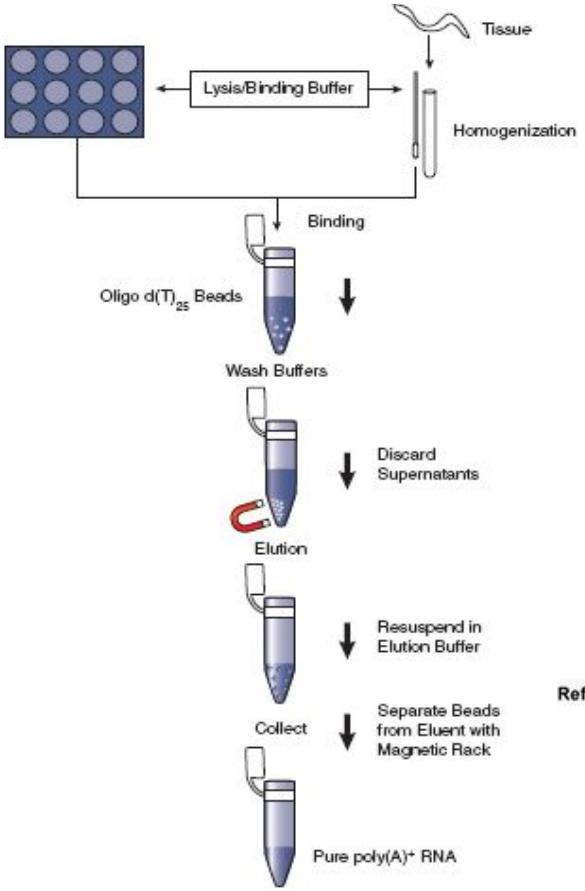
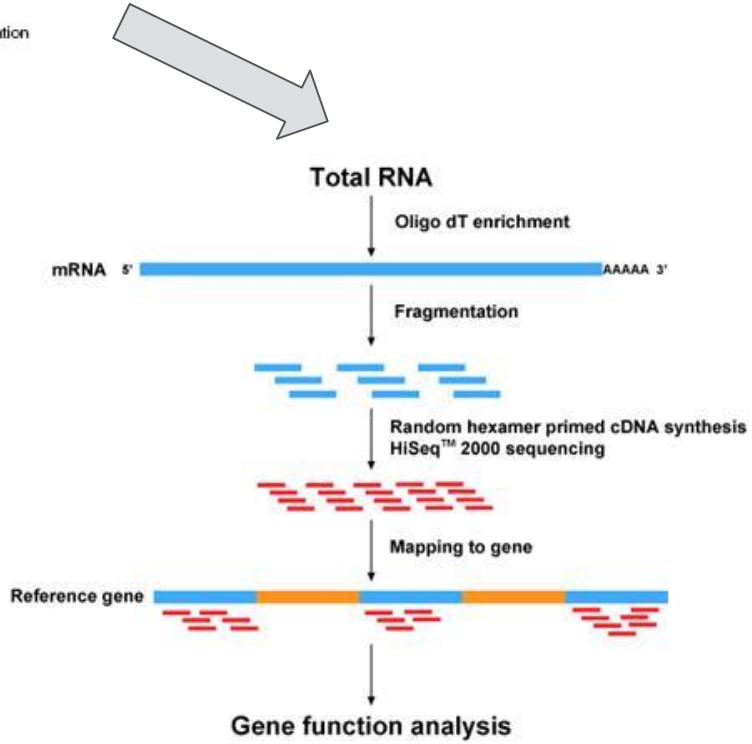




Tissue samples from 6 different mouse lines from Aim 1





https://www.neb.com/products/s1550-magnetic-mrna-isolation-kit , http://bio.lundberg.gu.se/courses/vt13/rnaseq.html , https://opentextbc.ca/anatomyandphysiology/chapter/4-2-epithelial-tissue/

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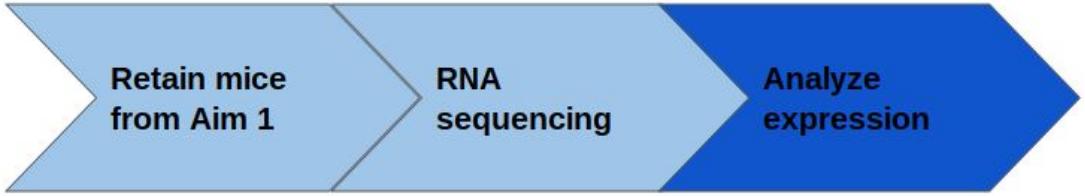
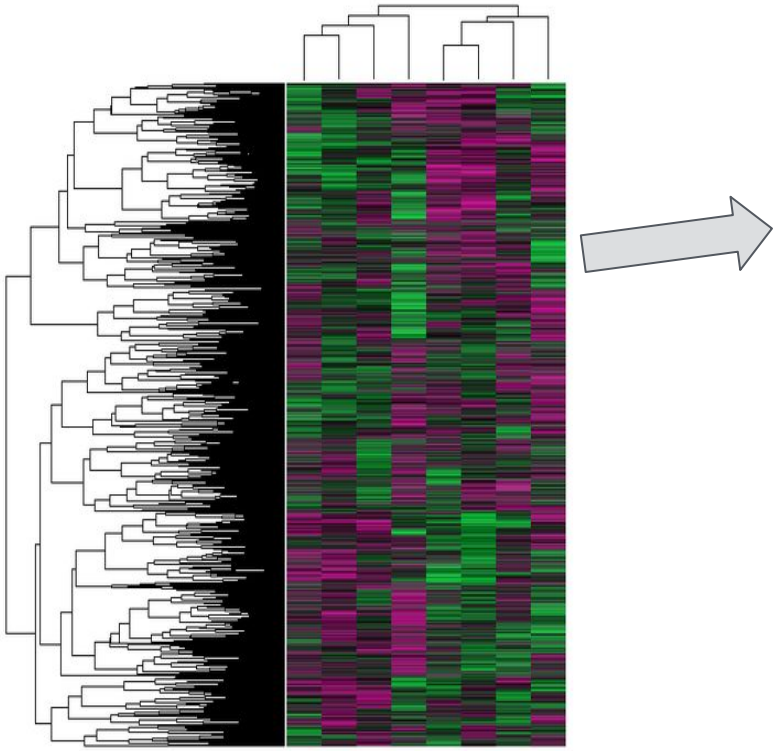
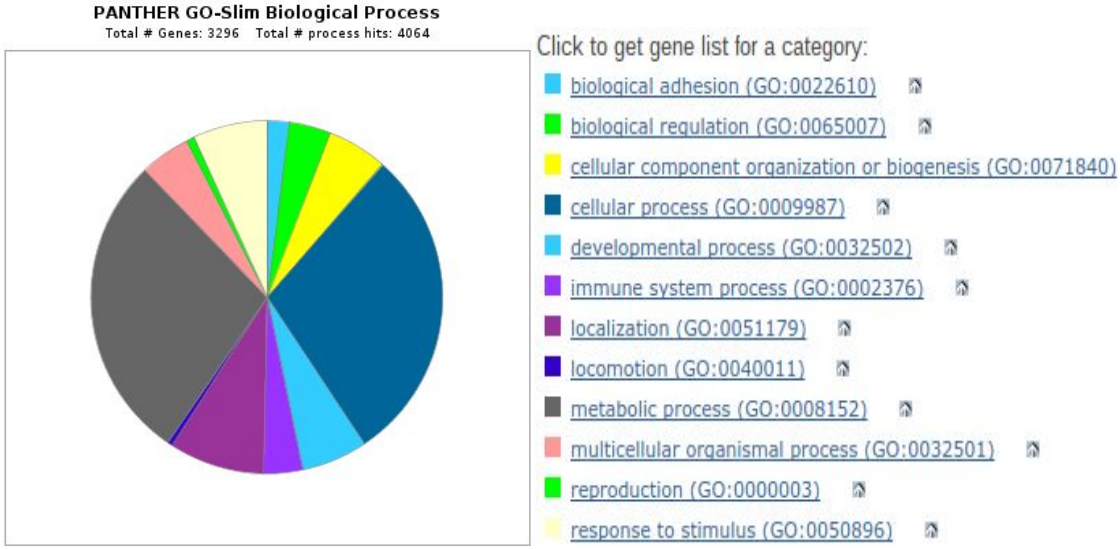


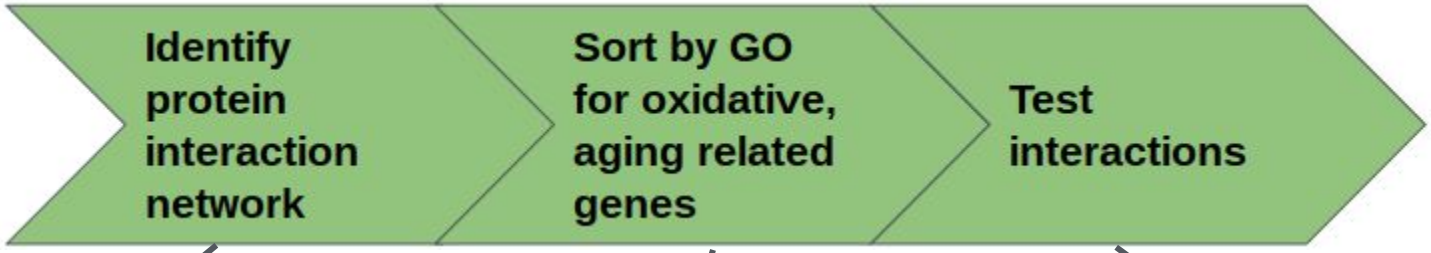


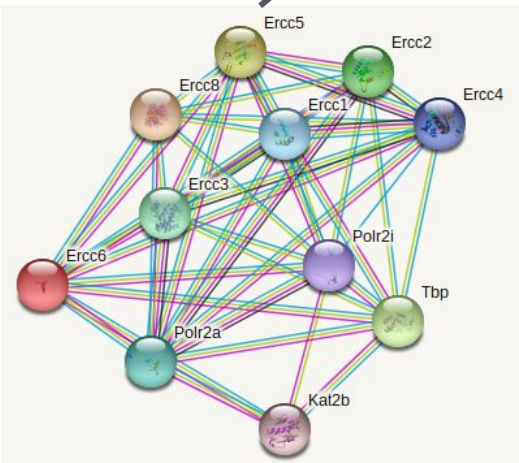


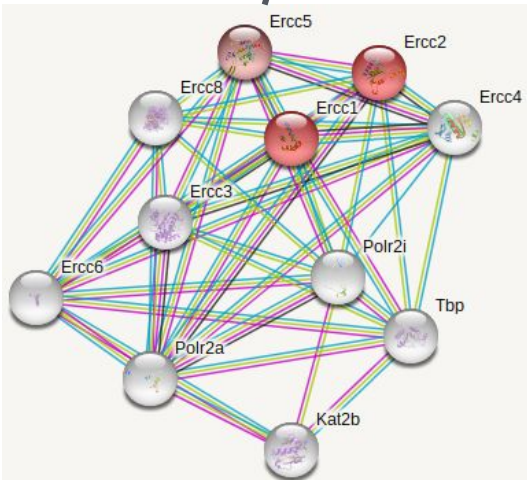
***Hypothesis**: loss of HELICc domain will lead to a downregulation of oxidative damage repair and aging associated genes.*

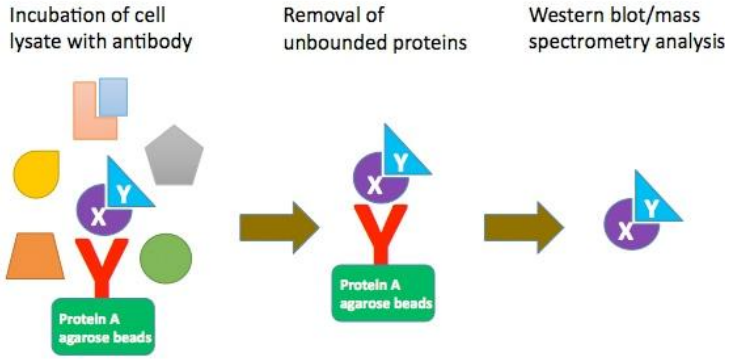
http://pantherdb.org/chart/pantherChart.jsp?listType=1&filterLevel=1&type=2&chartType=1&save=yes&basketItems=all&zoom=1&trackingId=FD8790585DFC3D222246F7D75802B001 , https://www.ncbi.nlm.nih.gov/geo/gds/analyze/analyze.cgi?ID=GDS2176

Aim 3: How does ERCC6 interact with proteins involved in oxidative damage regulation?



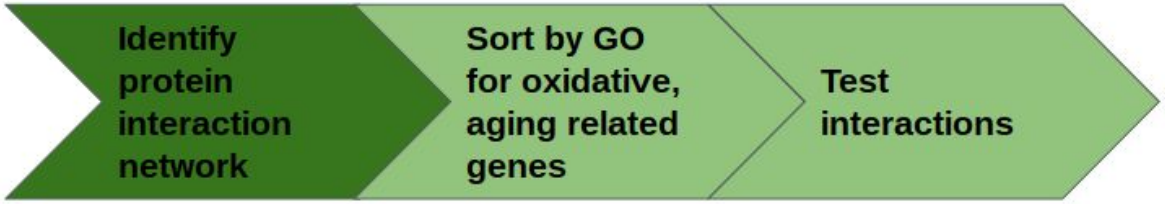


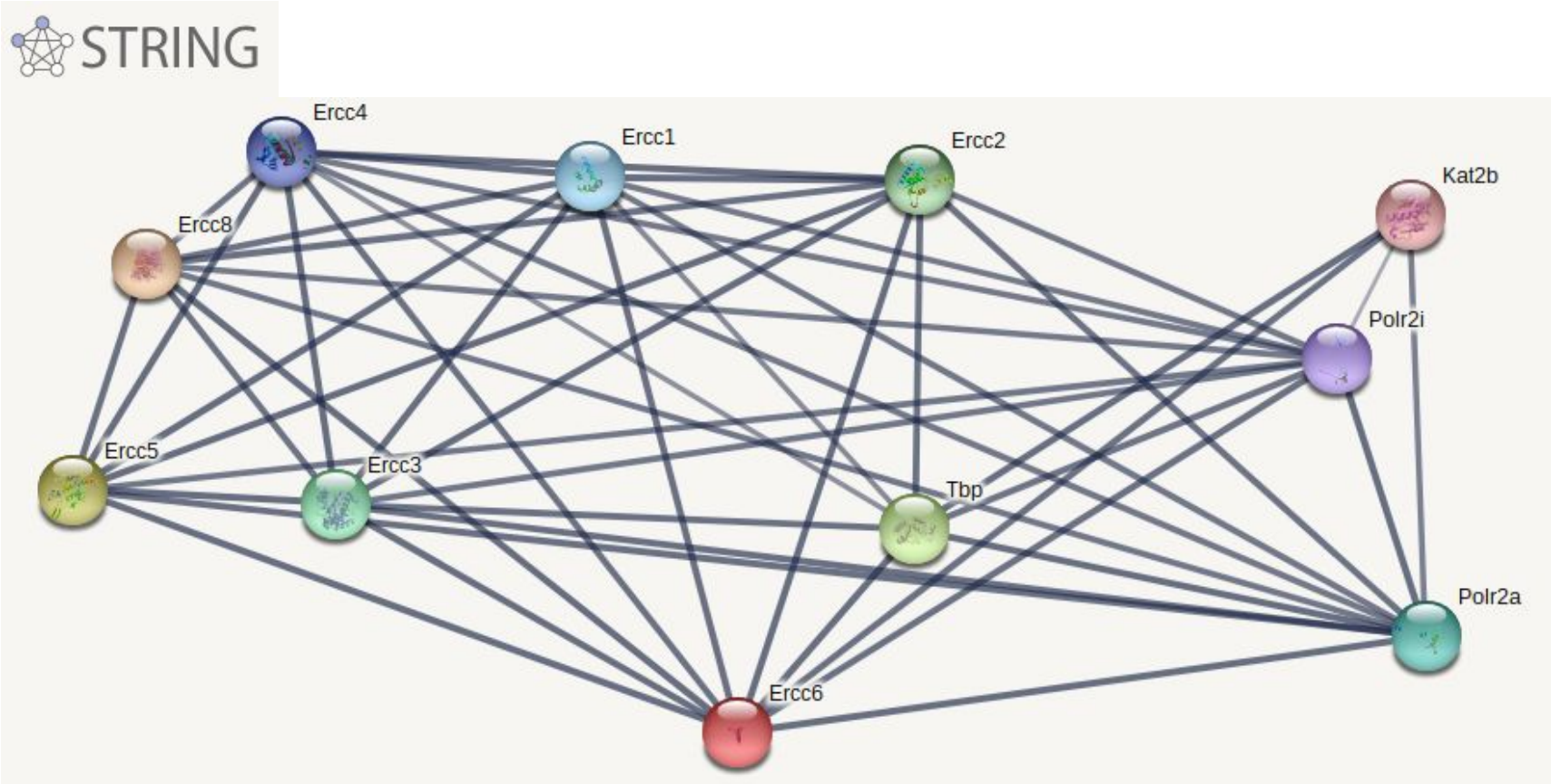




https://www.profacgen.com/Co-Immunoprecipitation-Co-IP.htm

Aim 3: How does ERCC6 interact with proteins involved in oxidative damage regulation?





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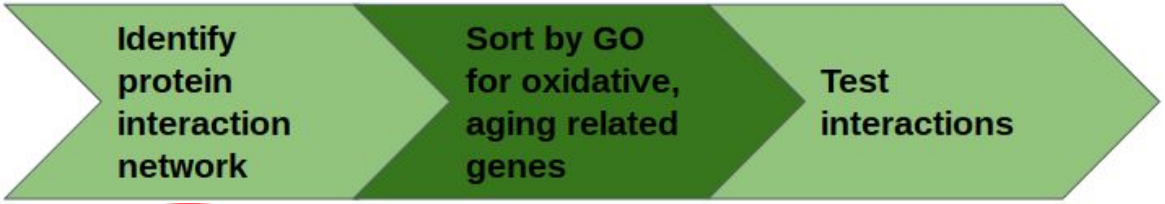
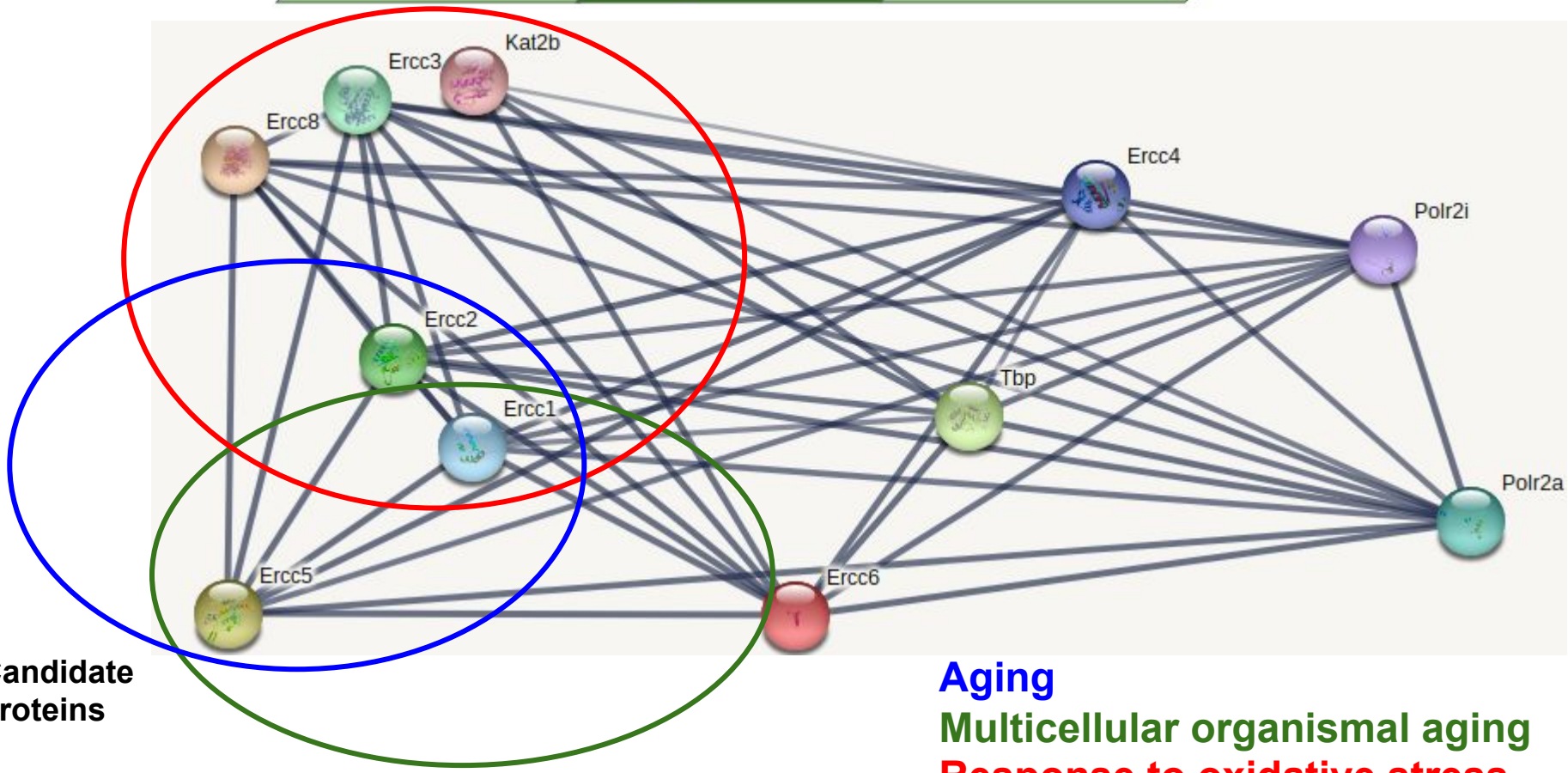
Aim 3: How does ERCC6 interact with proteins involved in oxidative damage regulation?





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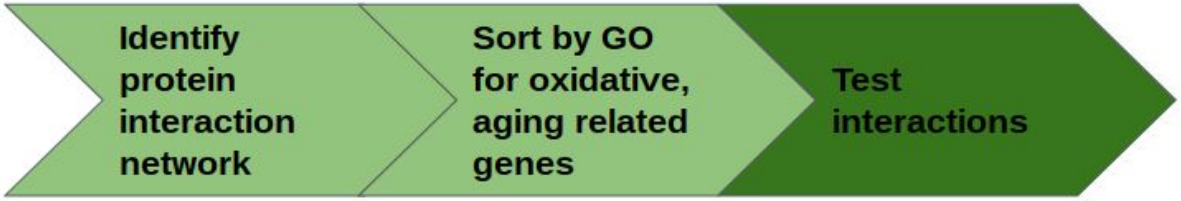
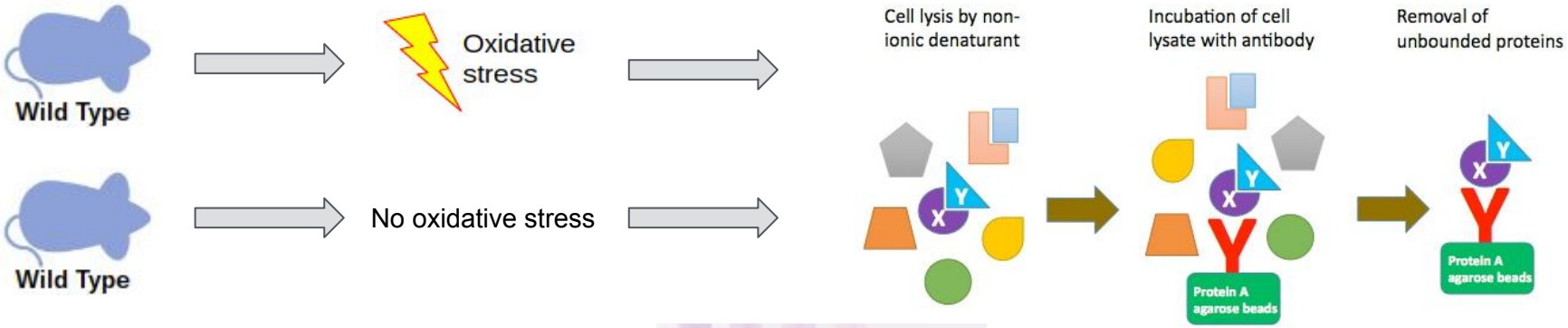
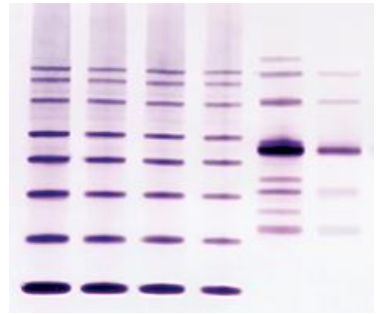
Aim 3: How does ERCC6 interact with proteins involved in oxidative damage regulation?





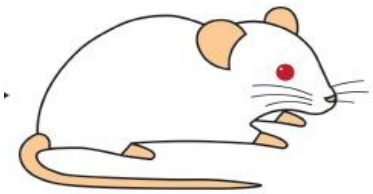


target proteins

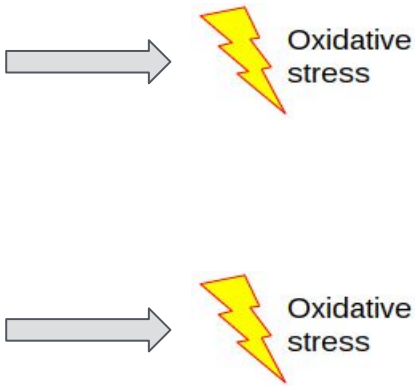
***Hypothesis**: ERCC6 will bind with proteins that have GO terms involving the oxidative damage repair pathway.*

https://www.profacgen.com/Co-Immunoprecipitation-Co-IP.htm , https://www.thermofisher.com/us/en/home/life-science/protein-biology/protein-assays-analysis/western-blotting/detect-proteins-western-blot/western-blot-imaging-analysis.html , https://www.tes.com/teaching-resources/blog/target-setting-secondary-students

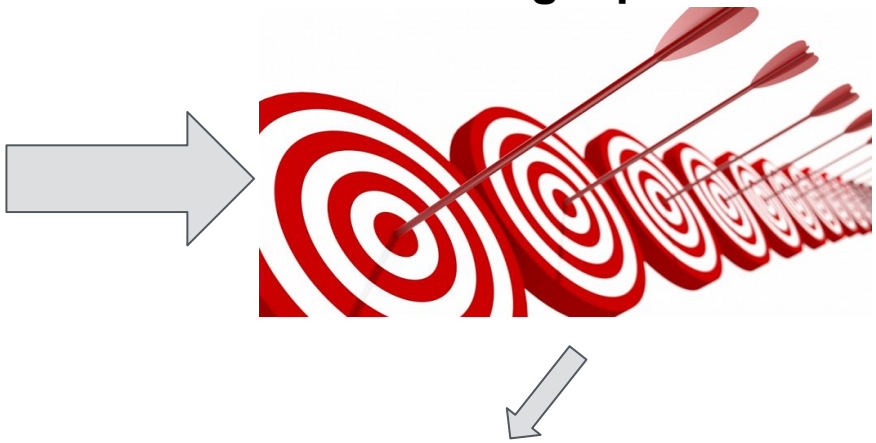
Future directions?



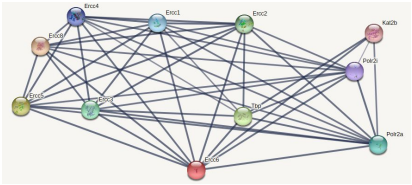
ERCC6 knockout



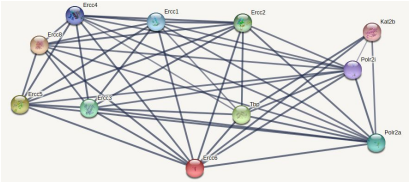
Aim 3 target proteins



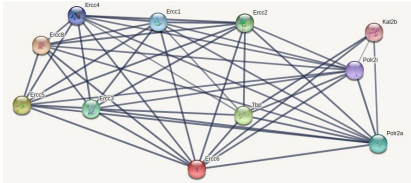
Target #1 network



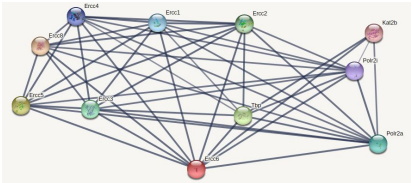
Target #2 network



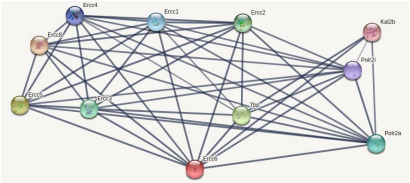
etc…..



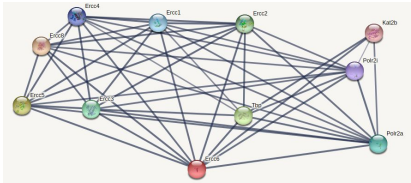
Target #1 network WT



Target #2 network WT



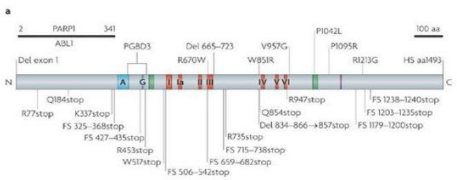
WT etc…..

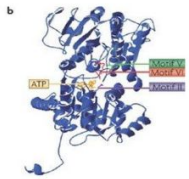


https://www.tes.com/teaching-resources/blog/target-setting-secondary-students , http://news.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ , http://www.cell.com/trends/cancer/fulltext/S2405-8033(16)30035-8 , http://string-db.org/cgi/network.pl?taskId=I59XitLI2uHN

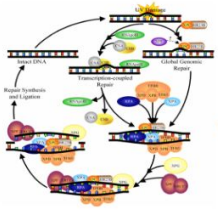
Conclusion

The ERCC6 Gene

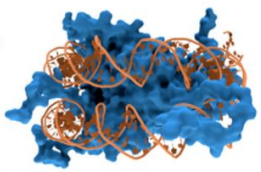




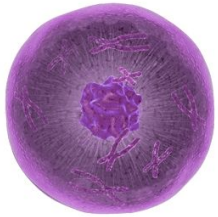
Biological Process

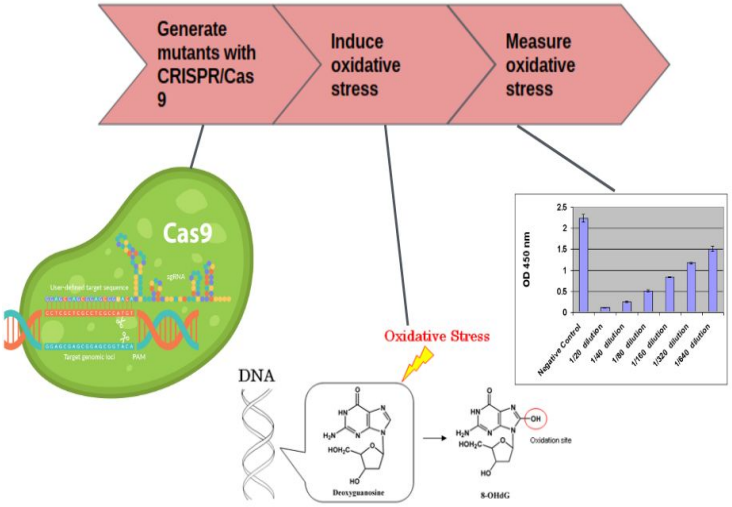


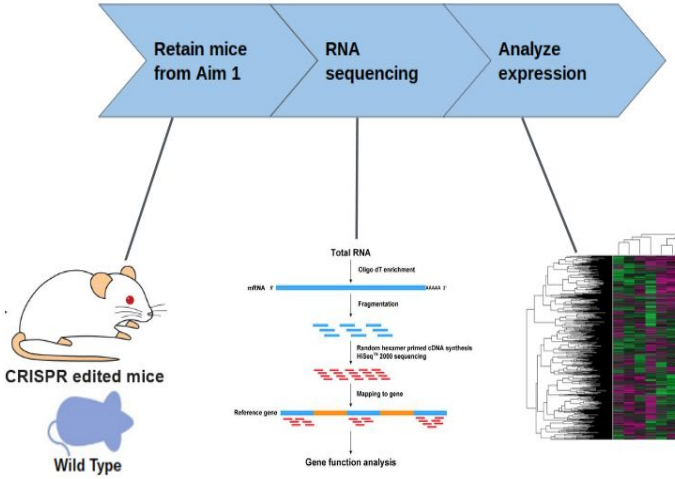
Molecular Function

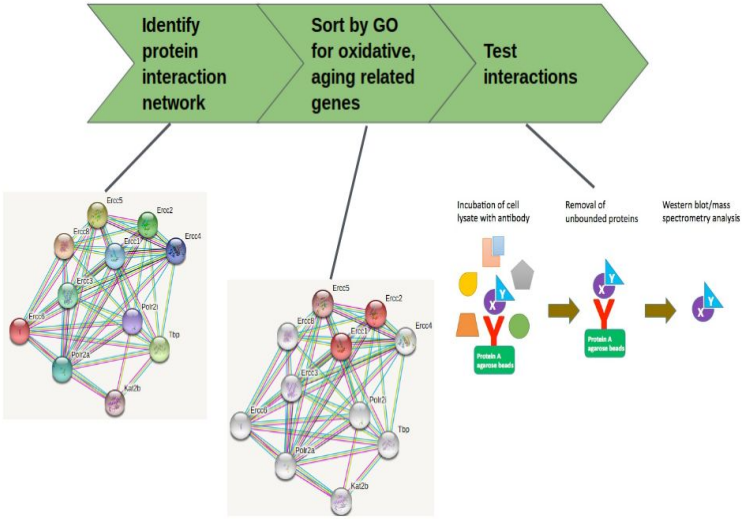


Cellular Component









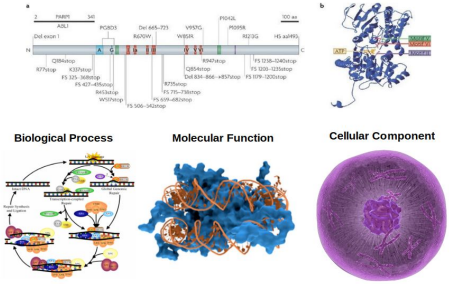
http://new.s.berkeley.edu/2016/05/27/faster-more-efficient-crispr-editing-in-mice/ . ttps://www.ncbi.nlm.nih.gov/geo/gdsbanalyze/analyze.cgi?ID=GDS2176 , http://bio.lundberg.gus.edu/courses/st13/rnaseq.html

Questions?

What is Cockayne Syndrome Type II?

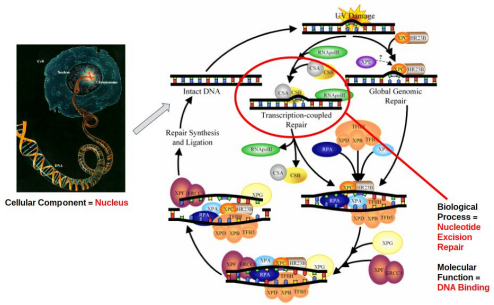
https://www.emaze.com/@AFZQZLTO/Cockayne-Syndrome , https://www.aao.org/eye-health/diseases/what-are-cataracts , http://mytips10.blogspot.com/2016/01/microcephaly-definition-what-is-microcephaly.html

The ERCC6 Gene



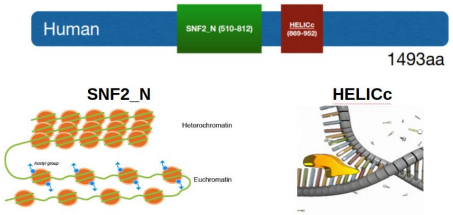
http://www.nature.com/mg/journal/v10/n11/fig_tab/nrg2663_F2.html , http://sike.sciencemag.org/content/2007/415 , https://upload.wikimedia.org/wikipedia/commons/thumb/b/be/Nucleosome1.png/220px-Nucleosome1.png

What is ERCC6's role in the cell?



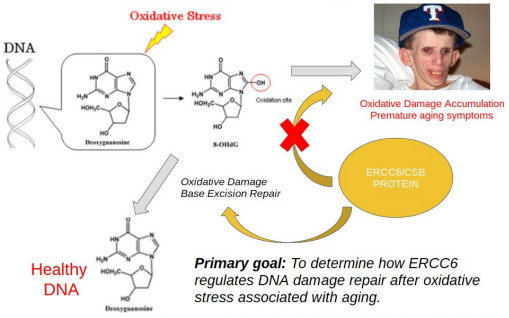
https://catalog.coriell.org/0/sections/collections/nigms/ner_pathway.aspx?PgId=256

What domains does ERCC6 have?



http://www.ebi.ac.uk/interpro/entry/IPR000330 , http://www.whatisepigenetics.com/chromatin-remodeling/ , https://www.nature.com/scitable/definition/helicase-307

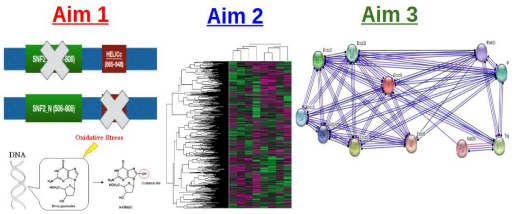
Gap in Knowledge



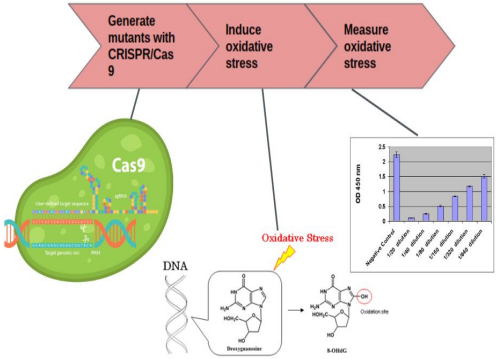
https://syndromespedia.com/cockayne-syndrome.html#.WP_bwKQrJD8 , http://en.ori-japan.com/aboutfpp/about-fppl

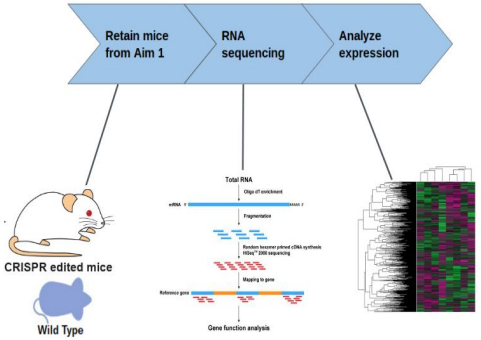
What is the central hypothesis?

ERCC6 loss leads to the aging phenotype in CS patients because oxidative damage cannot be regulated.

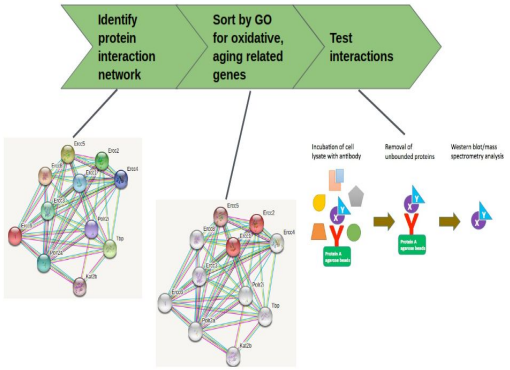


http://en.ori-japan.com/aboutfpp/about-fppl , https://www.ncbi.nlm.nih.gov/geo/gds/analyze/analyze.cgi?ID=GDS2175 , http://string-db.org/cgi/input.pl?UserId=prZyjwXUlRmS&sessionId=rLd6ll7lrEST&input_page_show_search=on





http://blog.s.berkeley.edu/2016/05/27/easier-more-efficient-crispr-editing-in-mice/ , ftp://ftp.ncbi.nlm.nih.gov/pub/geo/data/analyze/analyze.cgi?ID=GDS2175 , http://bio.lundbeg.gsu.edu/courses/4439/map-eq.html



References

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[2] ERCC6 Gene: Genetics Home Reference. https://ghr.nlm.nih.gov/gene/ERCC6#conditions

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[4] Cockayne Syndrome: Genetics Home Reference. https://ghr.nlm.nih.gov/condition/cockayne-syndrome#inheritance

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[8] Laugel, V., Dalloz, C., Durand, M. et al. 2010. Mutation update for the *CSB*/*ERCC6* and *CSA*/*ERCC8* genes involved in Cockayne syndrome. *Hum. Mutat*., 31: 113–126. doi:10.1002/humu.21154

[9] Wilson, B., T., Lochan, A., Stark, Z., Sutton, R. E. 2016. Novel missense mutations in a conserved loop between ERCC6 (CSB) helicase motifs V and VI: Insights into Cockayne syndrome. *Am. J. Med. Gen.* 170(3), 773-776. 10.1002/ajmg.a.37501