

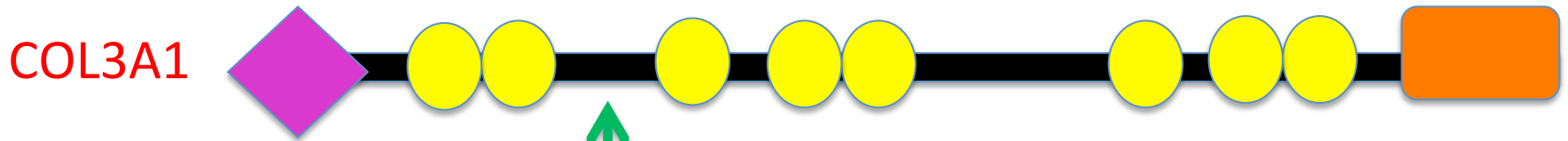
# Ehlers-Danlos Syndrome (EDS) and COL3A1

By: Kelly Morgan

# What is Ehlers-Danlos Syndrome?

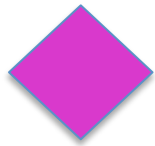


# What gene is mutated in Vascular EDS?



COL3A1

Glycine Substitutions



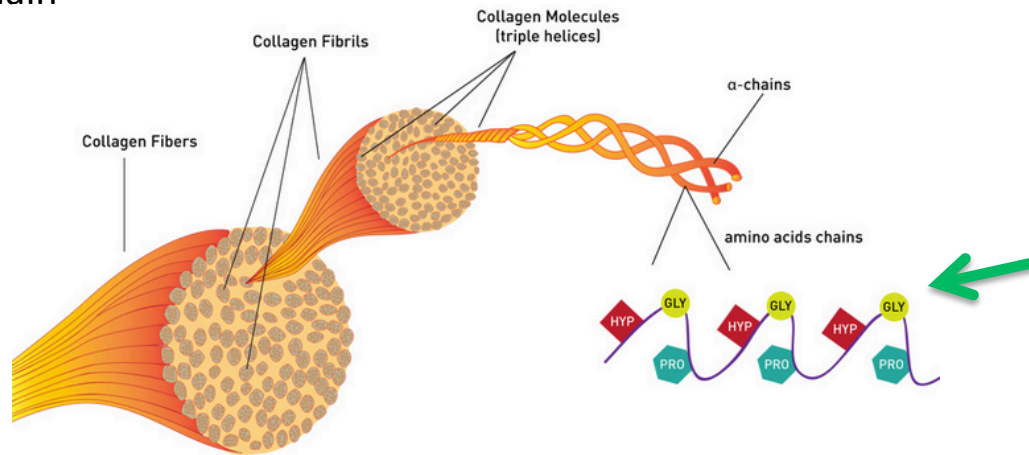
VWF Type 3 domain



Collagen helix



Fibrillar collagen C-terminal domain



Biological Process

Molecular Function

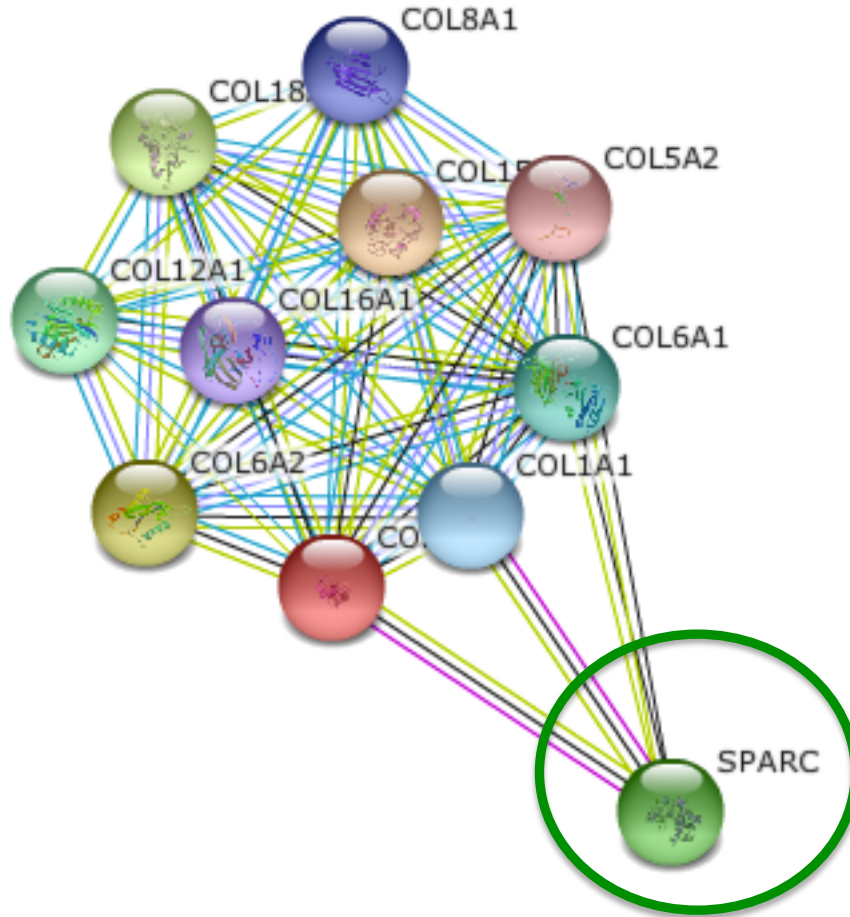
Cellular Component

Integrin binding  
Metal ion binding

**Heart development**  
Organ wall development

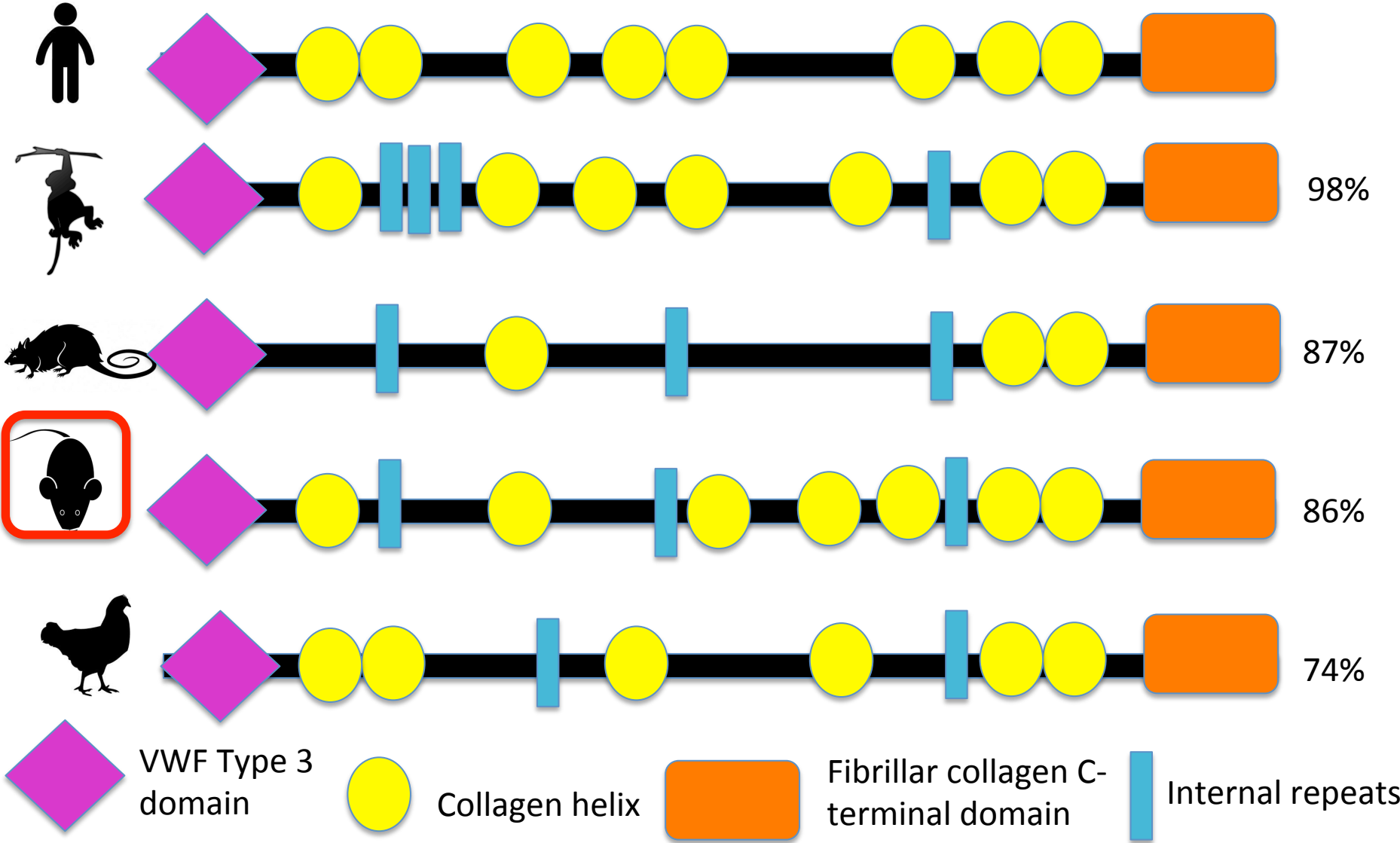
Extracellular Matrix

# What proteins interact with COL3A1?



Cell growth

# How well conserved is COL3A1?



# Why use mice as a model organism?

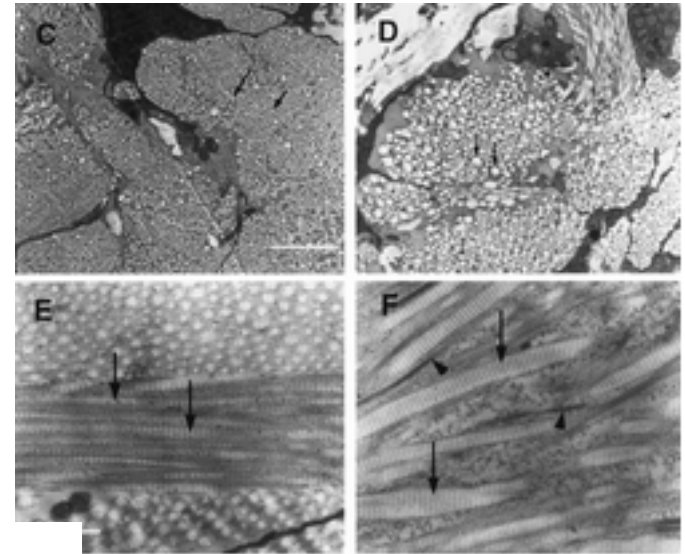
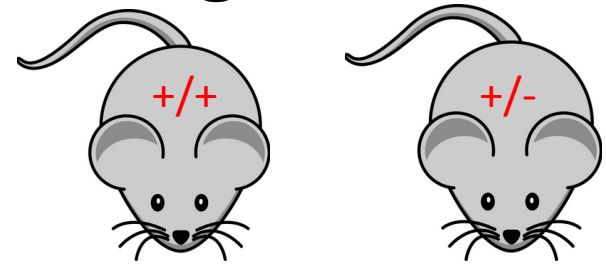
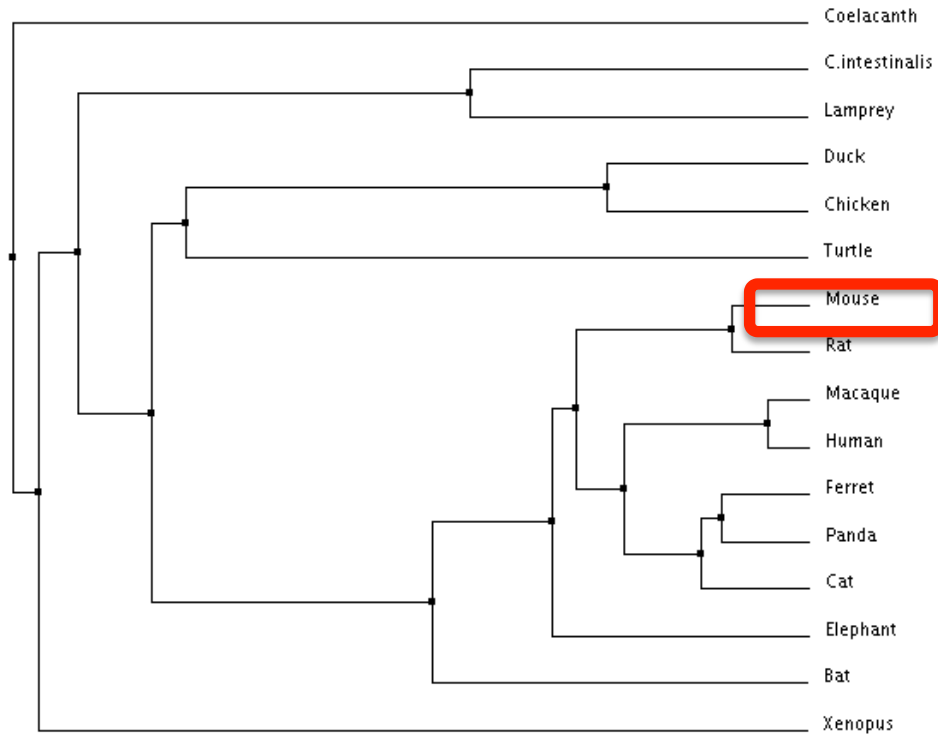
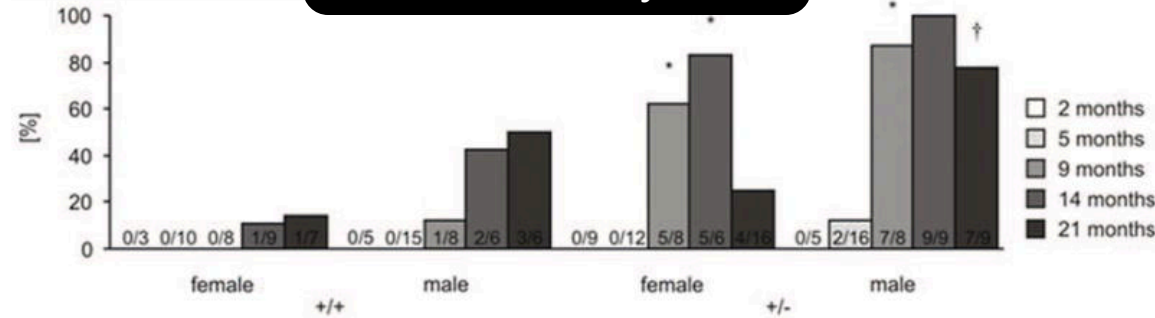


Figure 6

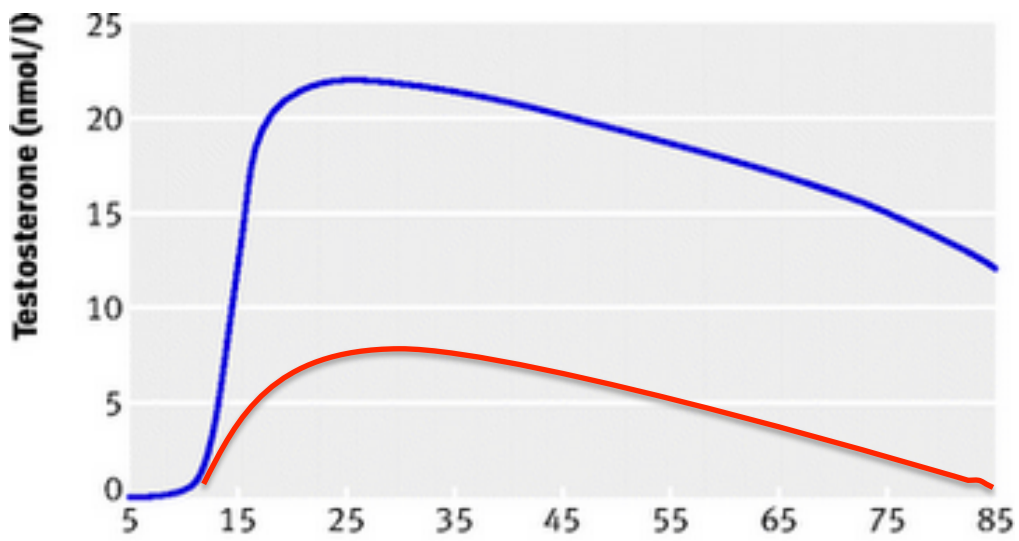
Average Distance  
% Identity



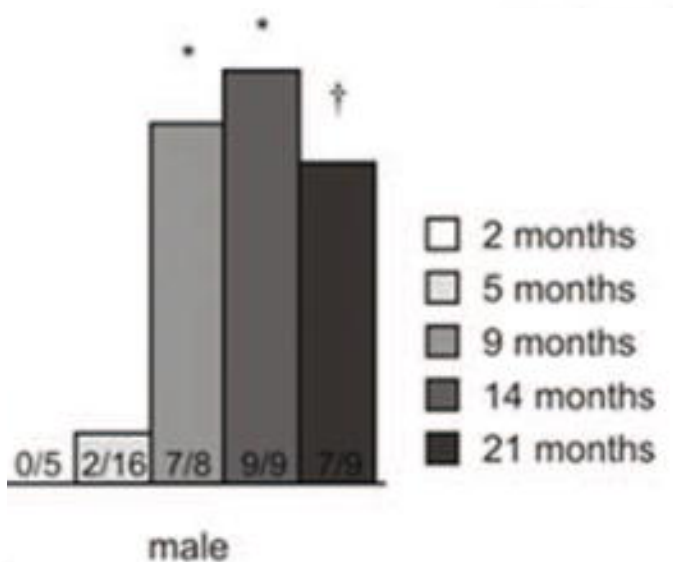
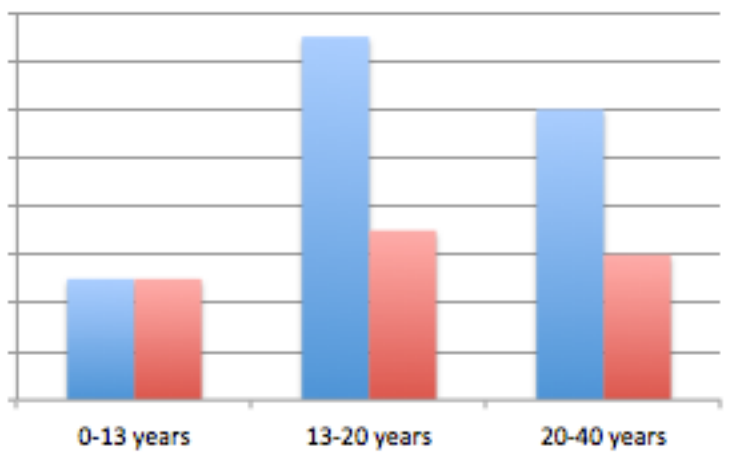
Aortic lesions

COL3A1  
Haploinsufficient mice

# Gap in Knowledge: Why is Vascular EDS more lethal in males than females?

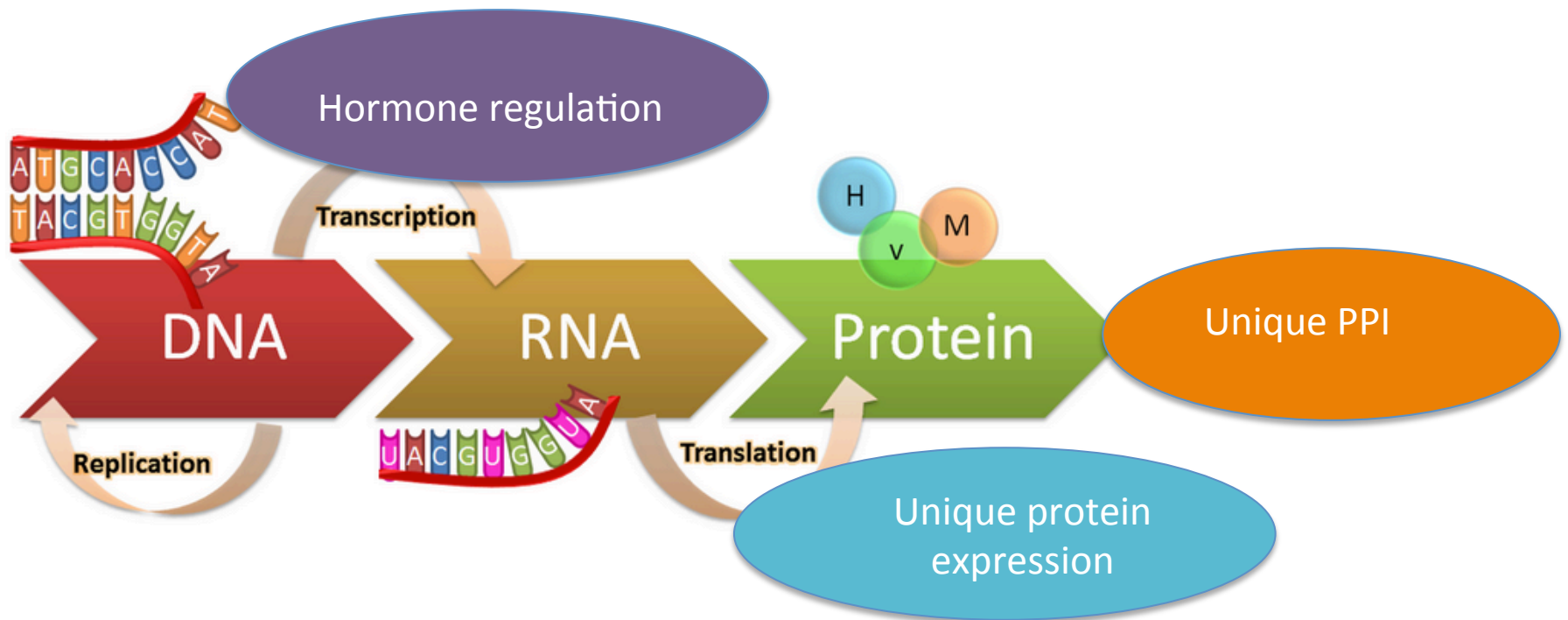


Collagen Production



# Goal: Identify factors that contribute to male-biased lethality

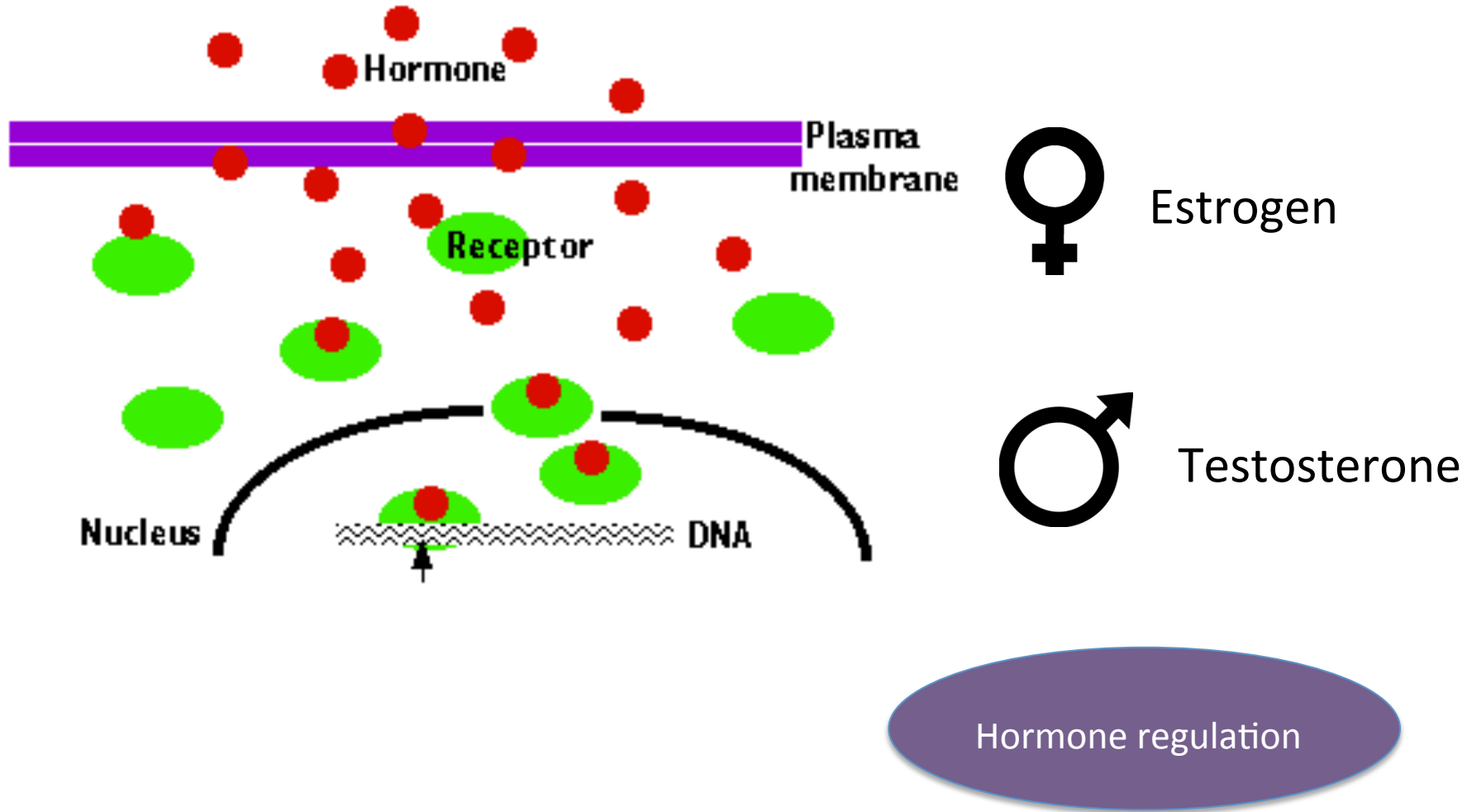
## Hypothesis



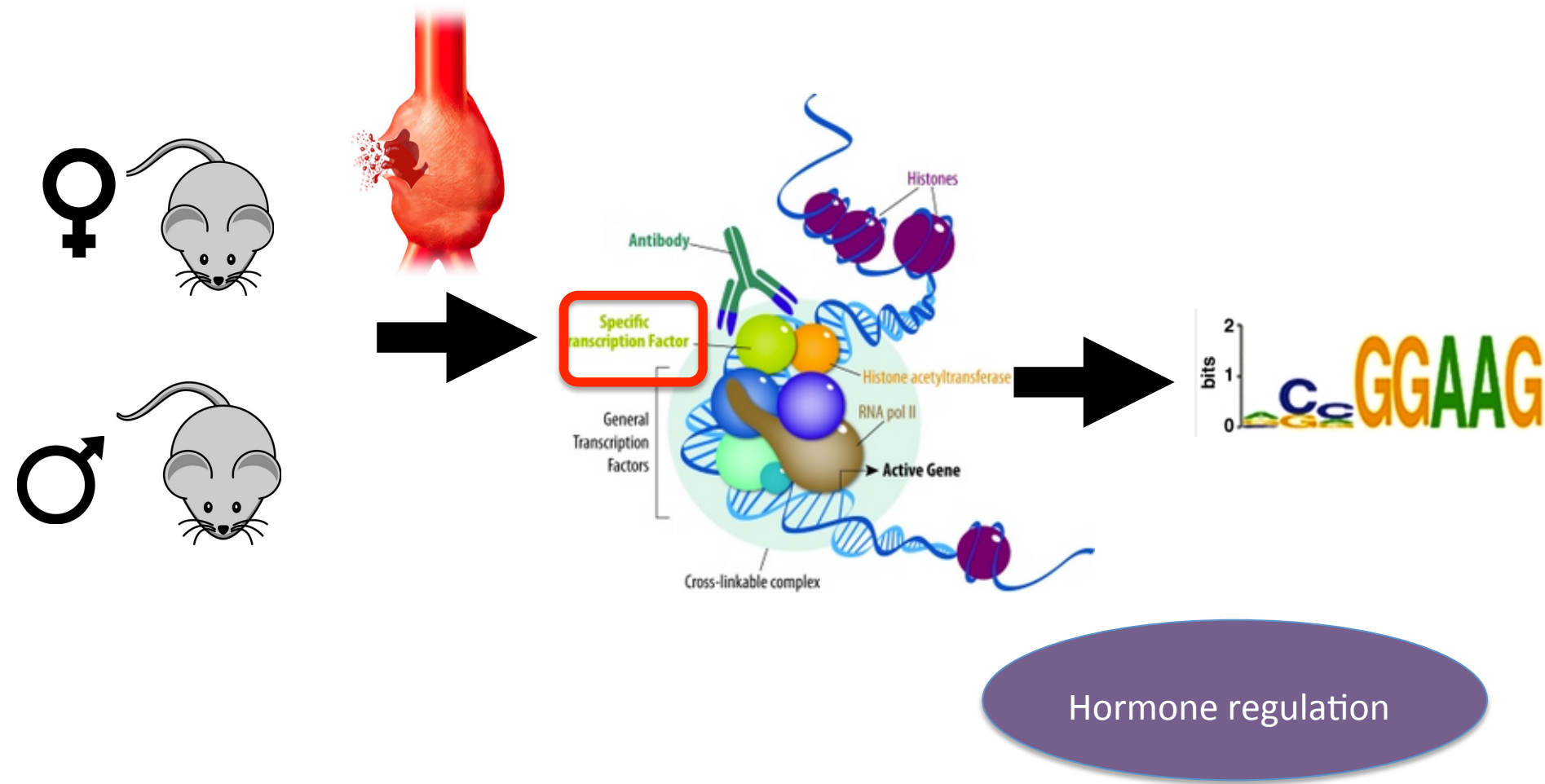
*Hormonal differences between the sexes lead unique protein expression and interactions of **COL3A1** and other proteins with similar Gene Ontology*



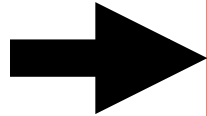
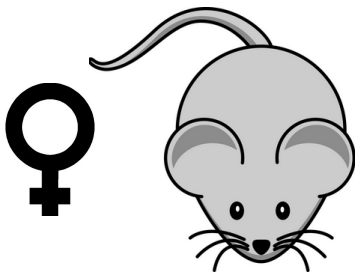
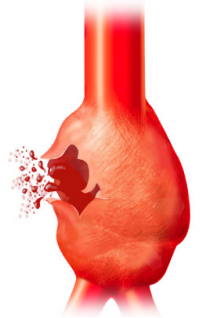
# Aim 1: Identify transcriptional targets of testosterone and estrogen receptors



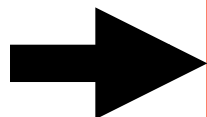
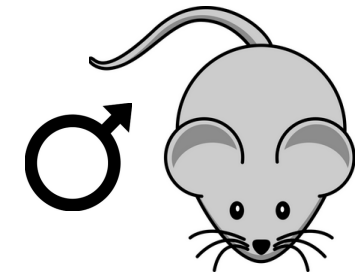
# How will transcriptional targets be identified?



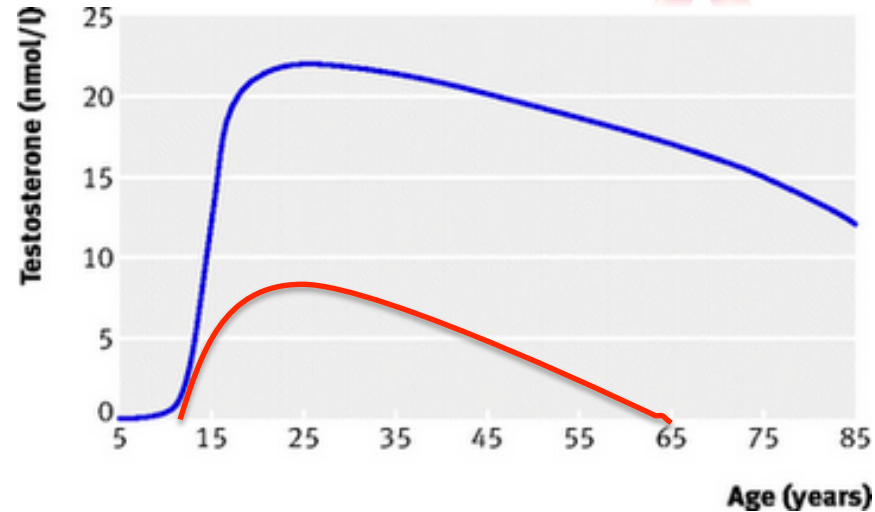
# What genes are under hormonal regulation in mice hearts?



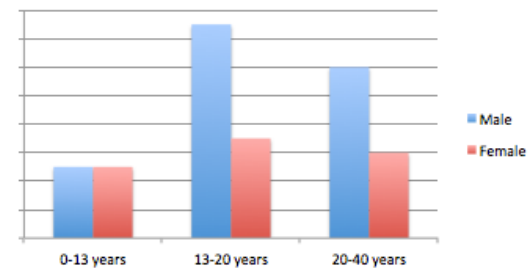
Genes under estrogen regulation will **not** include **COL3A1**



Genes under testosterone regulation will include **COL3A1**



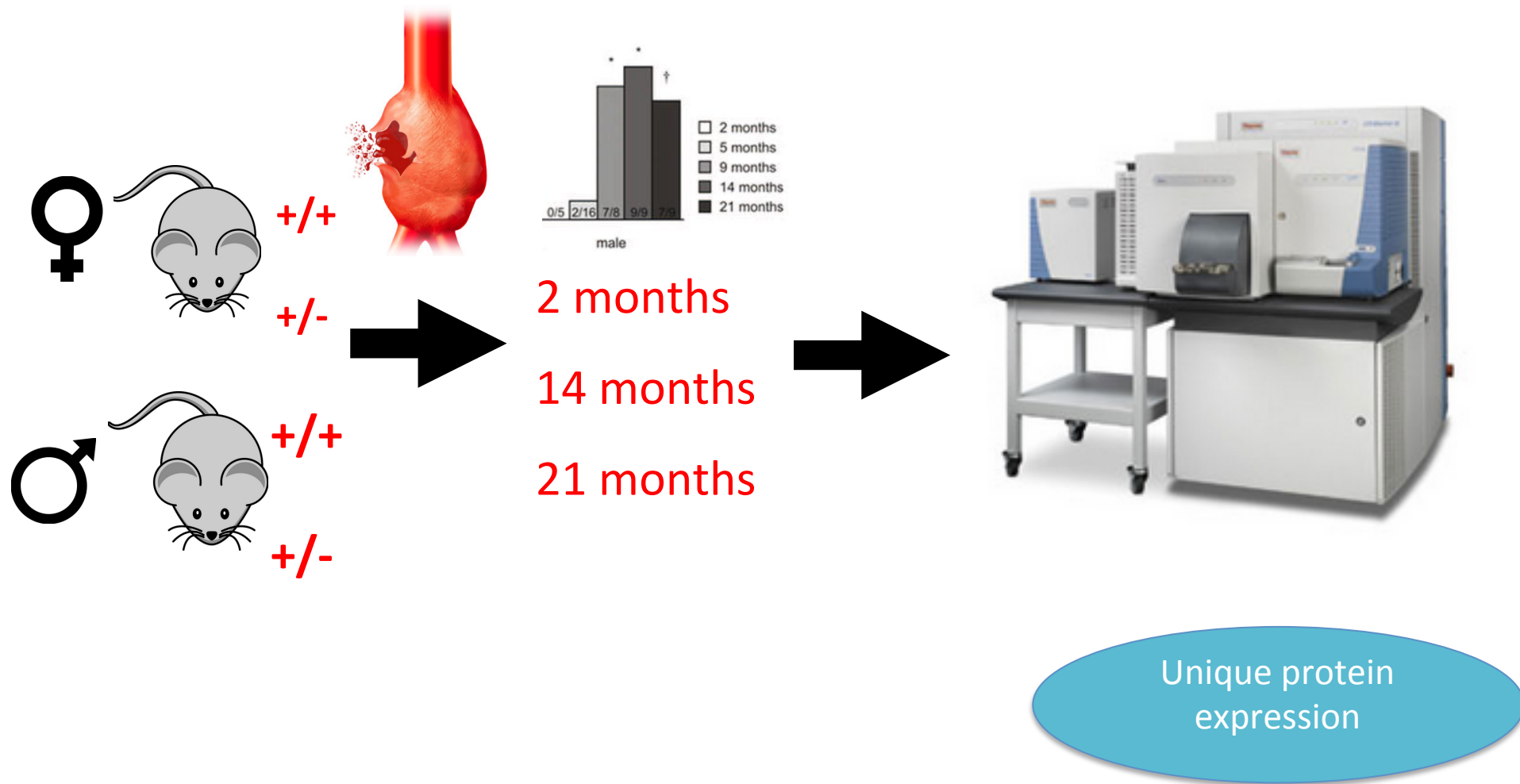
Collagen Production



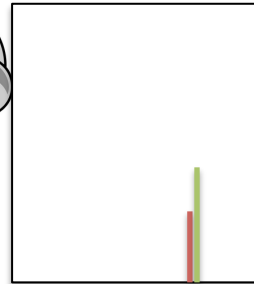
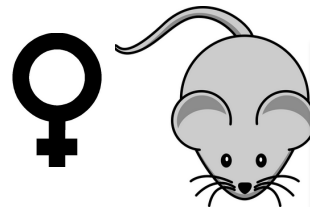
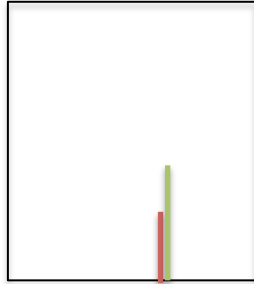
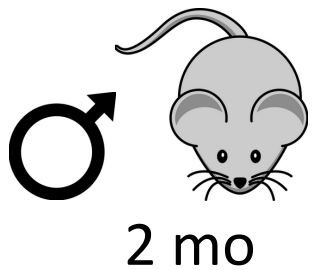
*Testosterone targets will include **COL3A1** and Estrogen will not*

Hormone regulation

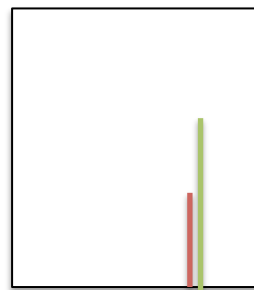
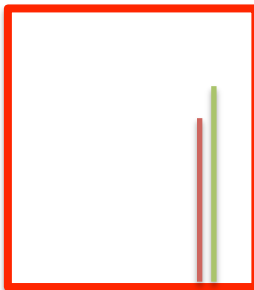
# Aim 2: Identify proteins in the heart of male and female mice at different time points in development



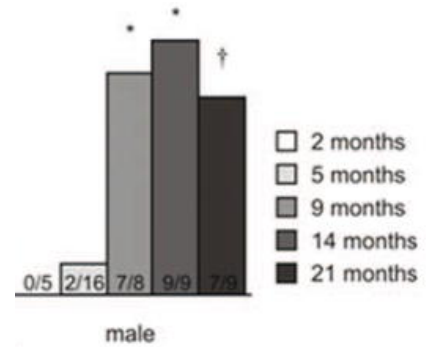
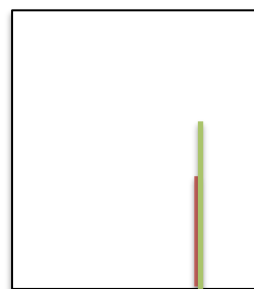
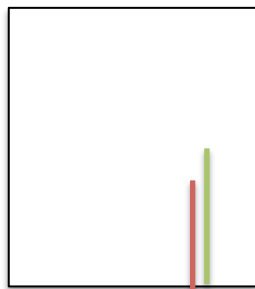
# What proteins will be expressed in the heart and when?



14 mo



18 mo



Wild type  
COL3A1

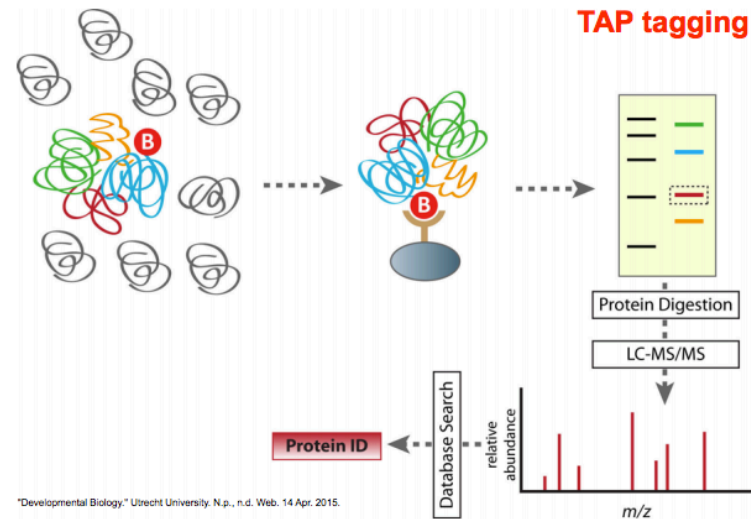
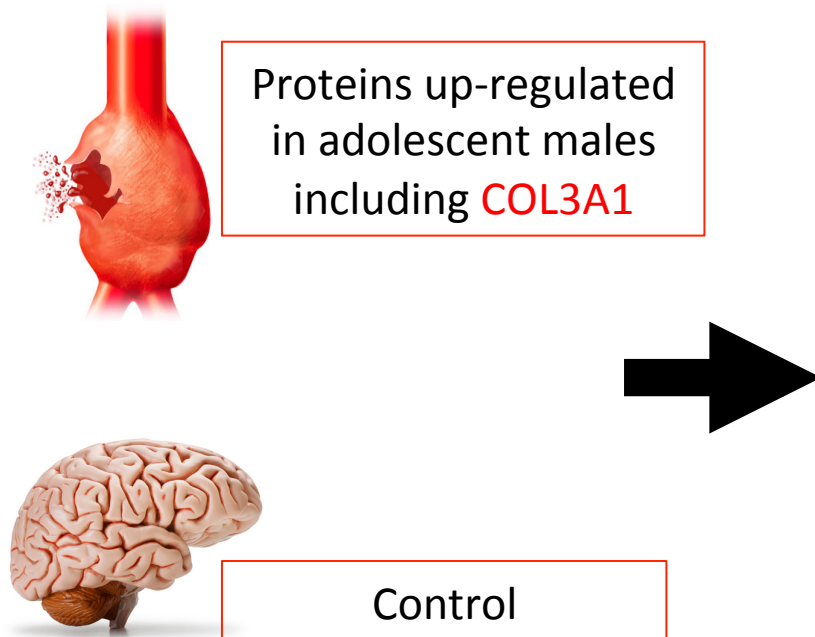


Mutant  
COL3A1

*COL3A1 will be expressed highest healthy in adolescent males and show significant decrease in mutants*

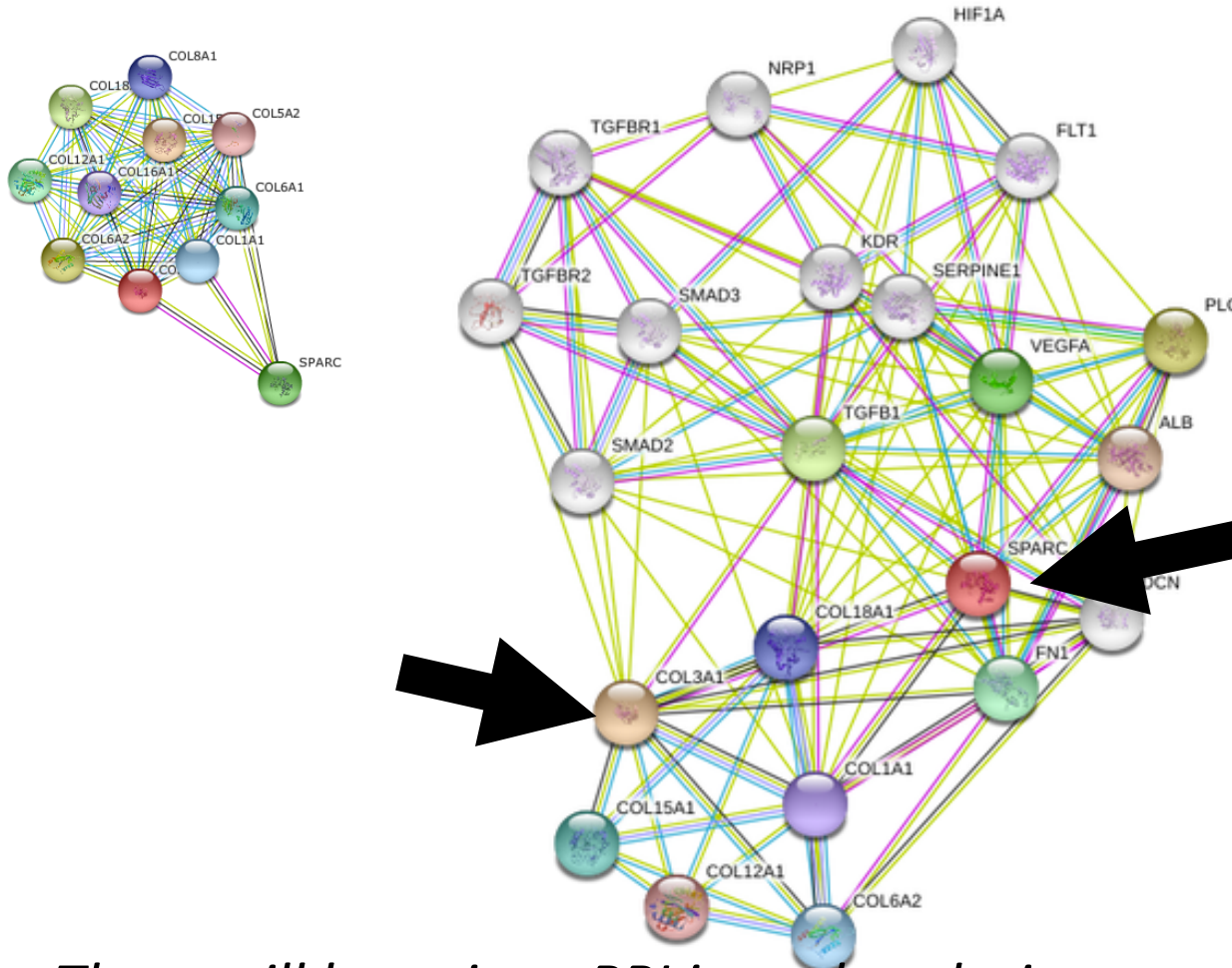
Unique protein expression

# Aim 3: Identify protein protein interactions (PPI) in male hearts during adolescence



Unique PPI

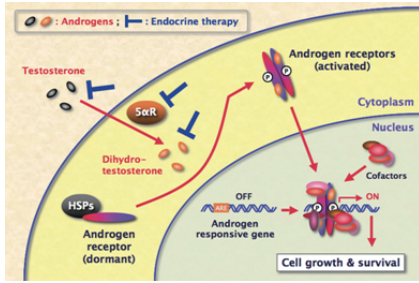
# What proteins do we expect to interact?



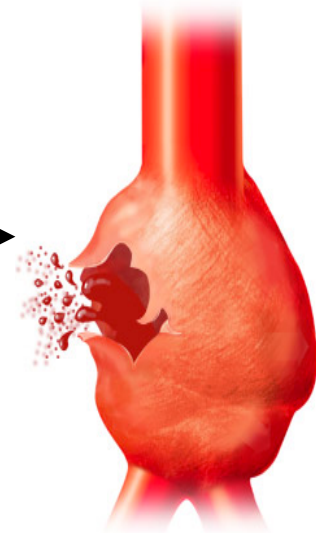
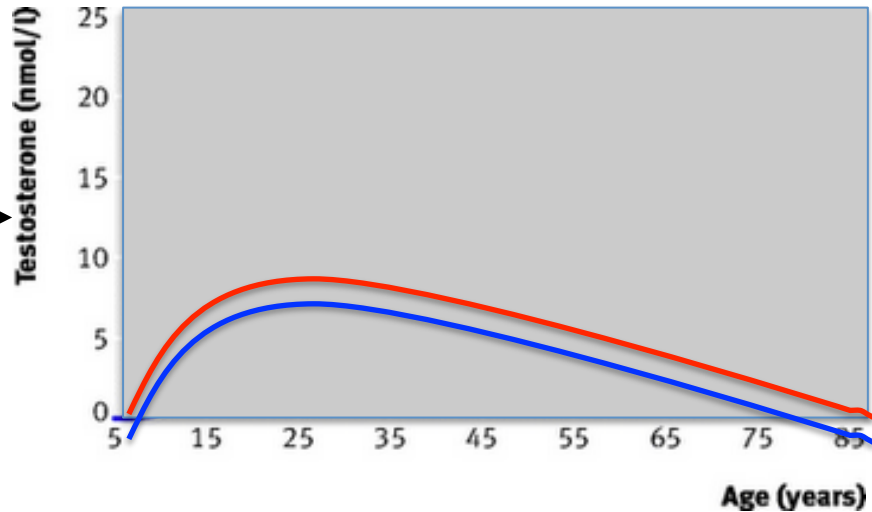
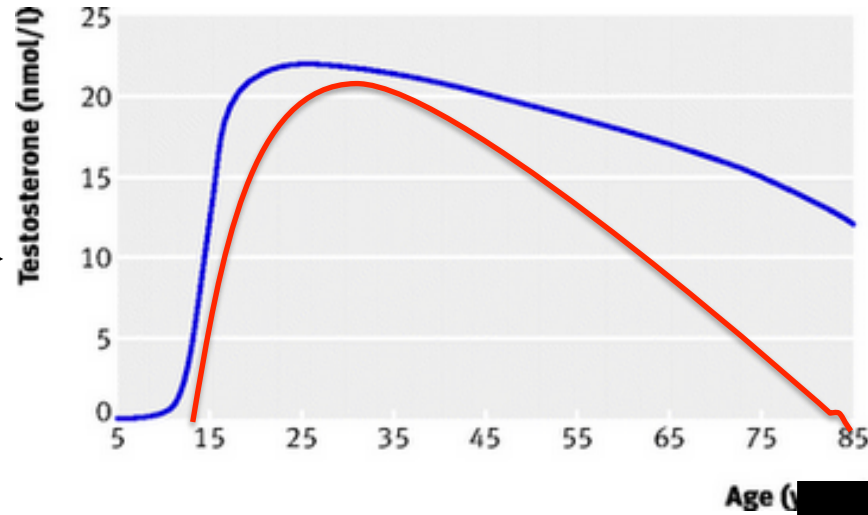
STRING 10

*There will be unique PPI in males during adolescence as a result of the protein expression that is under hormonal regulation*

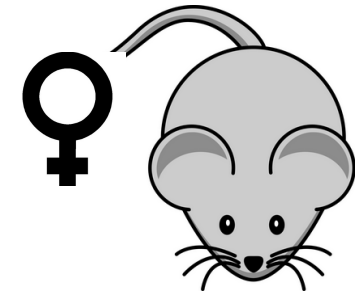
Unique PPI



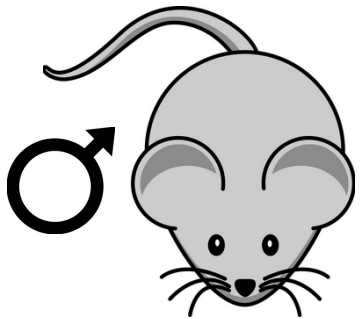
# Future directions



Male  
Female



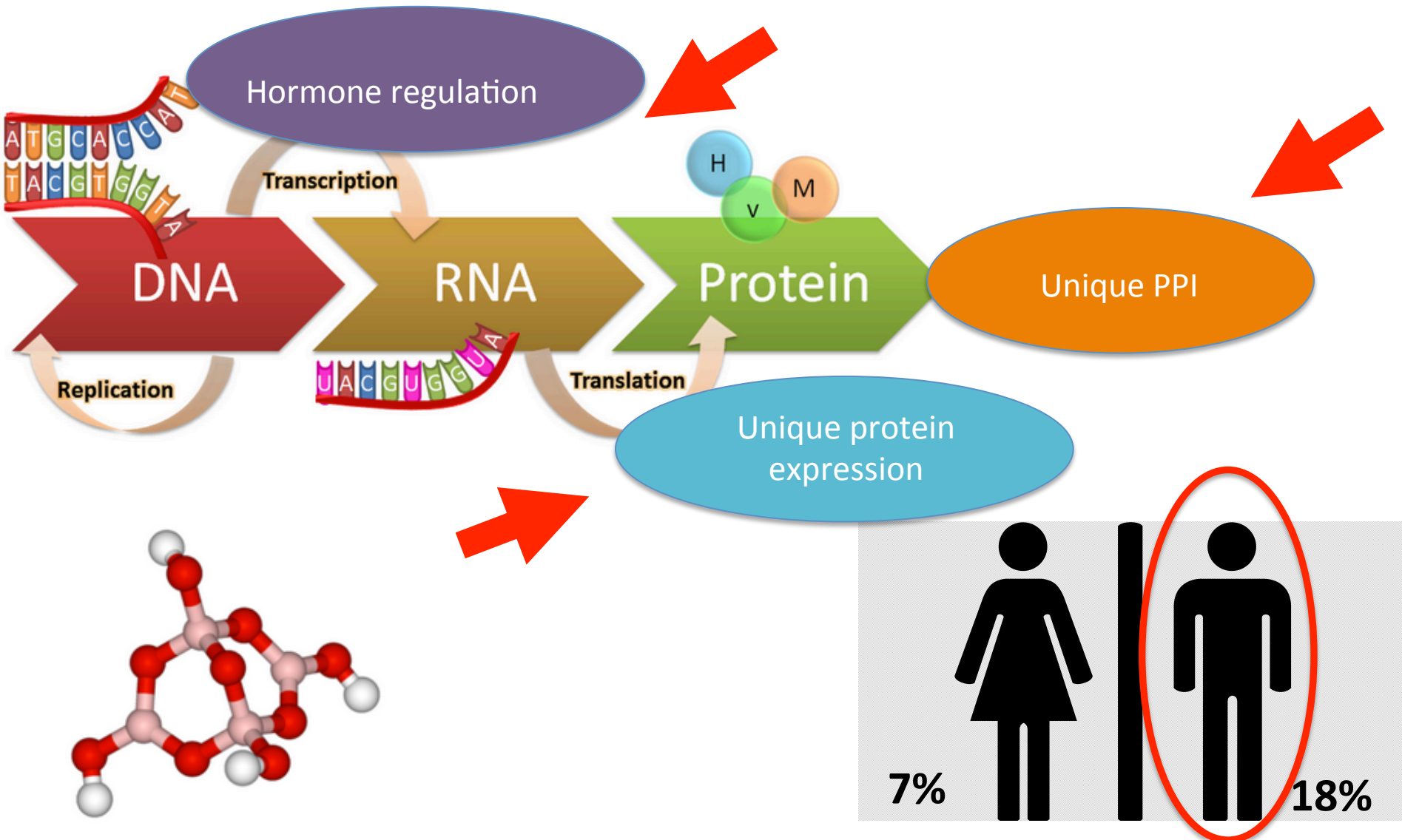
+/-



+/-



# Long Term Goal: Decrease the male biased lethality of Vascular EDS



Questions?

# References

- 1) Taj FT, Sajjan VV, Singh D. Ehlers-Danlos syndrome. Indian Dermatology Online Journal 2014;5(Suppl 1):S68-S70. doi: 10.4103/2229-5178.144554.
- 2) Pauker, Susan P., and Joan Stoler. "Clinical Manifestations and Diagnosis of Ehlers-Danlos Syndromes." UpToDate. Ed. Peter H. Scher and Paul L. Romain. Wolters Kluwer, 12 Nov. 2014. Web. 20 Feb. 2015. <<http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-ehlers-danlos-syndromes>>.
- 3) "Ehlers-Danlos Syndrome." Genetics Home Reference. U.S. National Library of Medicine, 16 Feb. 2015. Web. 19 Feb. 2015. <<http://ghr.nlm.nih.gov/condition/ehlers-danlos-syndrome>>.
- 4) Pepin, Melanie G. "Ehlers-Danlos Syndrome Type IV." GeneReviews. University of Washington, Seattle, 3 May 2011. Web. 20 Feb. 2015. <<http://www.ncbi.nlm.nih.gov/books/NBK1494/>>.
- 5) "COL3A1 Gene." Genetics Home Reference. U.S. National Library of Medicine, May 2006. Web. 20 Feb. 2015. <<http://ghr.nlm.nih.gov/gene/COL3A1>>.
- 6) <http://path.upmc.edu/cases/case504/dx.html>
- 7) Ong, KT, J. Perdu, J. Backer, E. Bozec, P. Collignon, J. Emmerich, AL Fauret, JN Feissinger, DP Germain, G. Georgesco, JS Hulot, A. De Paepe, H. Plauchu, X. Jeunmairte, S. Laurent, and P. Boutouyrie. "Result FEffect of Celiprolol on Prevention of Cardiovascular Events in Vascular Ehlers-Danlos Syndrome: A Prospective Randomised, Open, Blinded-endpoints Trial.ilters." Lancet (2010): 1476-484. PubMed. U.S. National Library of Medicine, 30 Oct. 2010. Web. 20 Feb. 2015. <<http://www.ncbi.nlm.nih.gov/pubmed/20825986>>.
- 8) Pepin, Melanie G., Ulrike Schwarze, Kenneth M. Rice, Mingdong Liu, Dru Leistriz, and Peter H. Byers. "Survival Is Affected by Mutation Type and Molecular Mechanism in Vascular Ehlers–Danlos Syndrome (EDS Type IV)." Genetics in Medicine Print.