

BMPR2 & Pulmonary Arterial Hypertension (PAH)

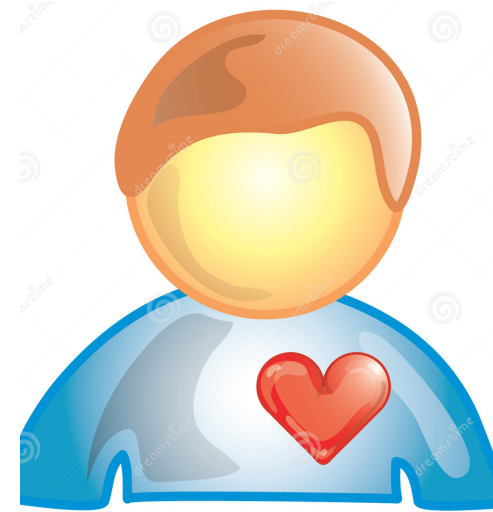
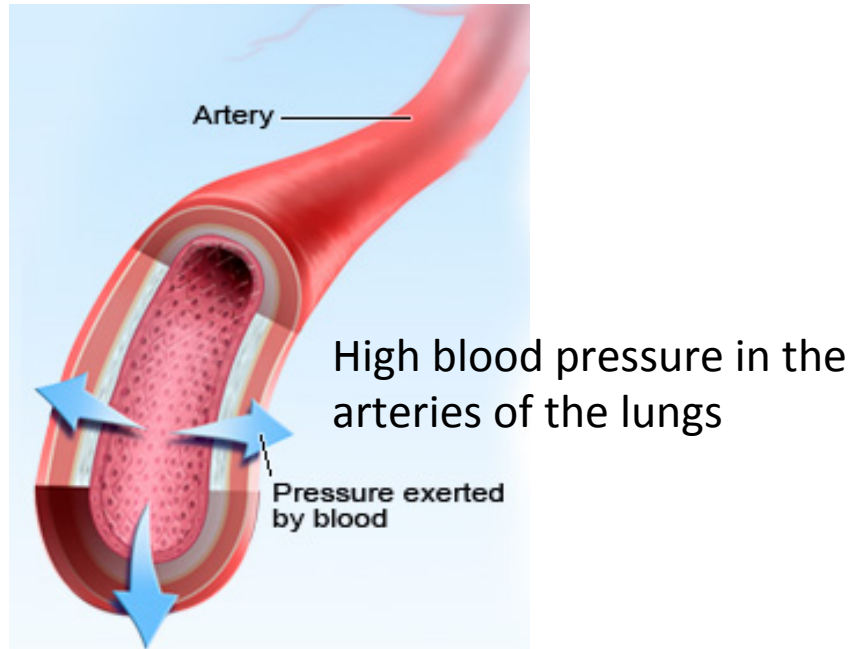


Genetics 564

Sunah Shin

BMPR2 = Bone Morphogenetic Protein Receptor type II

What is Pulmonary Arterial Hypertension (PAH)?



1,000 patients / year



2.8 years

What do the arteries in PAH patients look like?



Cell division  & Cell death 

PAH

Overgrowth of cells

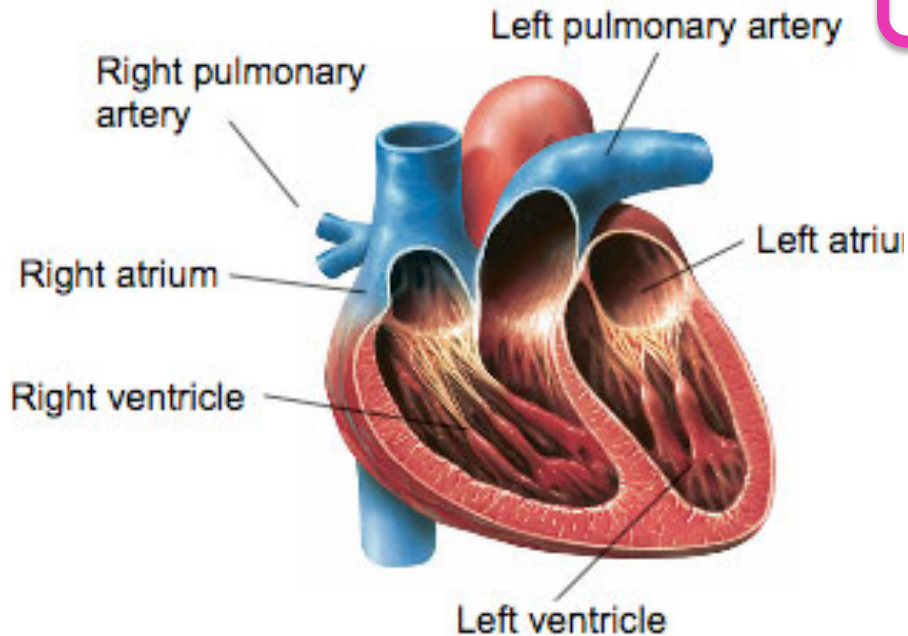
→ Pulmonary arteries narrow in diameter

→ Increasing the resistance to blood flow

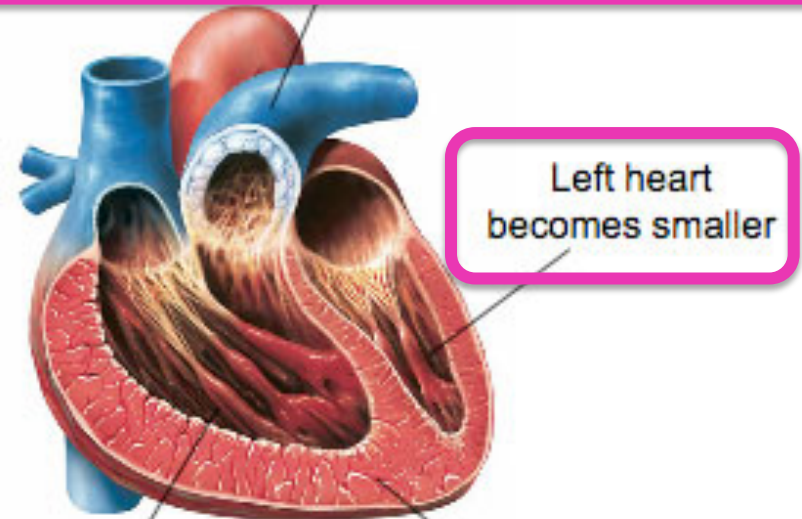
What does a PAH heart look like?

The narrowed pulmonary arteries
→ high resistance to blood flows to lungs

Pulmonary artery wall and its smaller vessels become
damaged, restricting blood flow to lungs

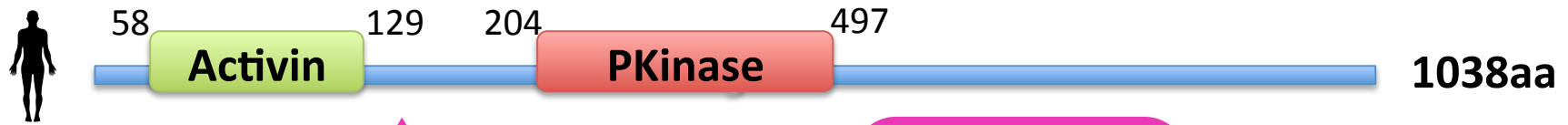


A Healthy Heart



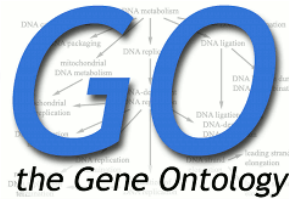
A Heart with PAH*

BMPR2 is mutated in PAH

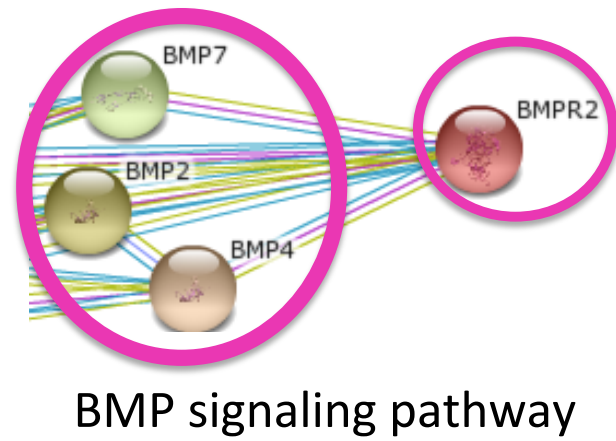
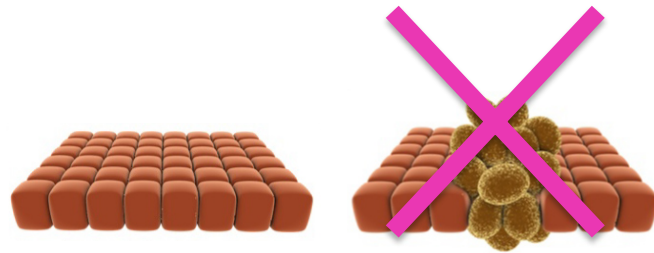
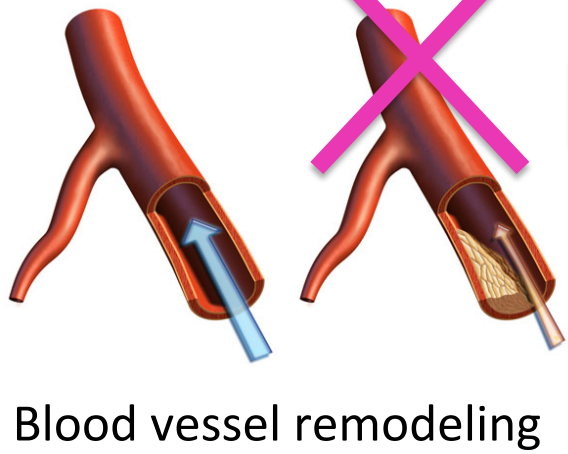


Frame shift / Nonsense / Missense

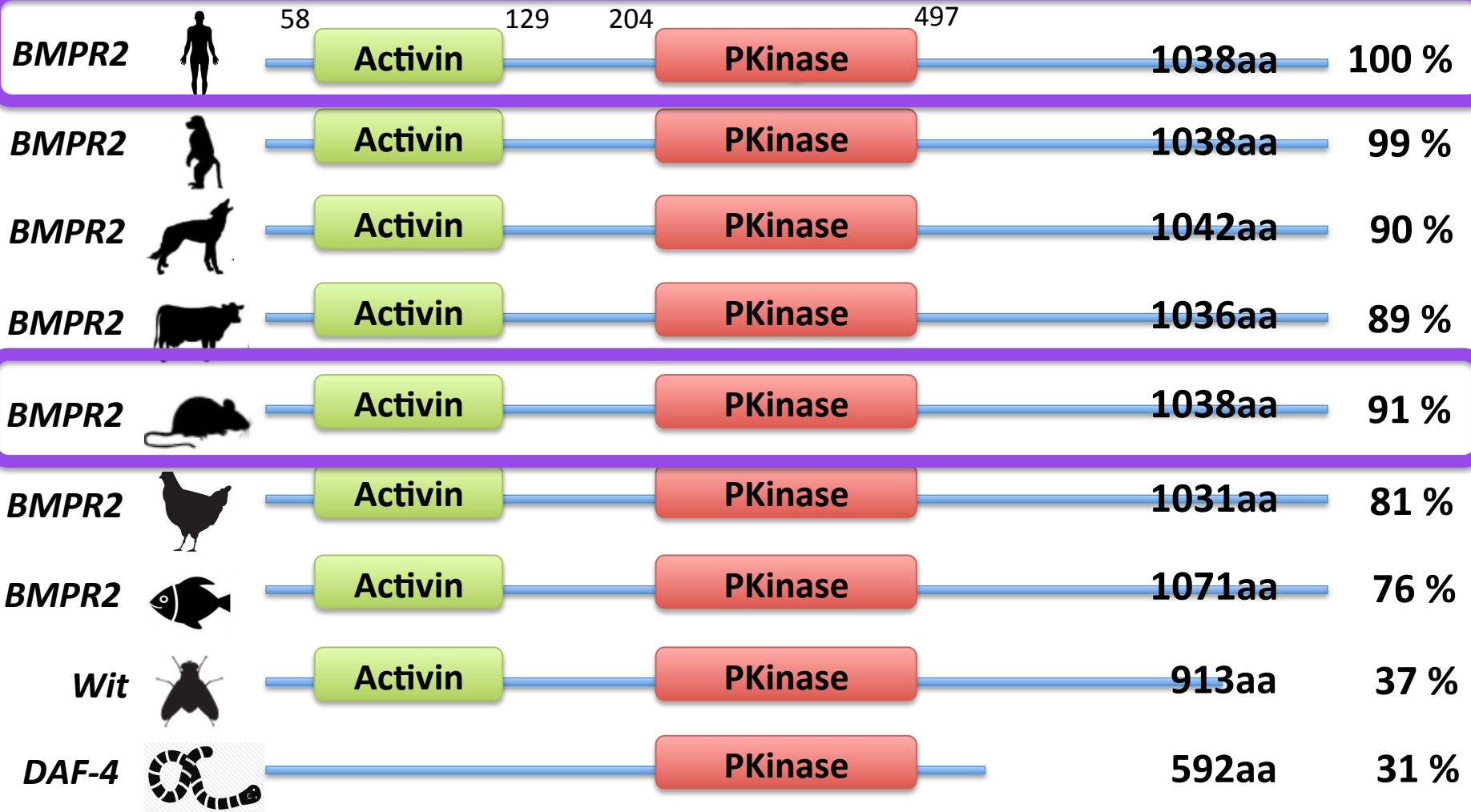
17% → developing PAH



Biological Process



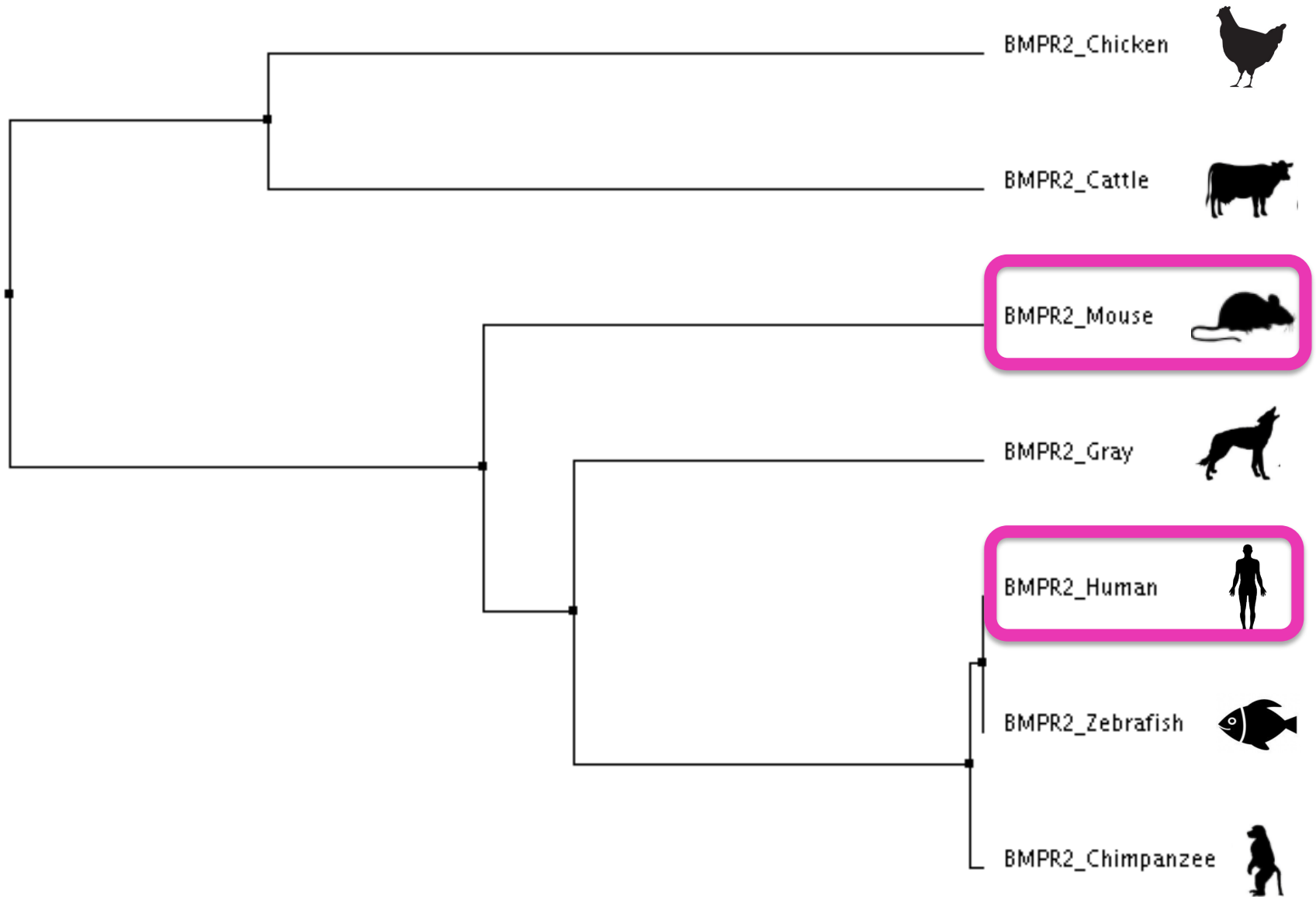
How well *BMPR2* is conserved?



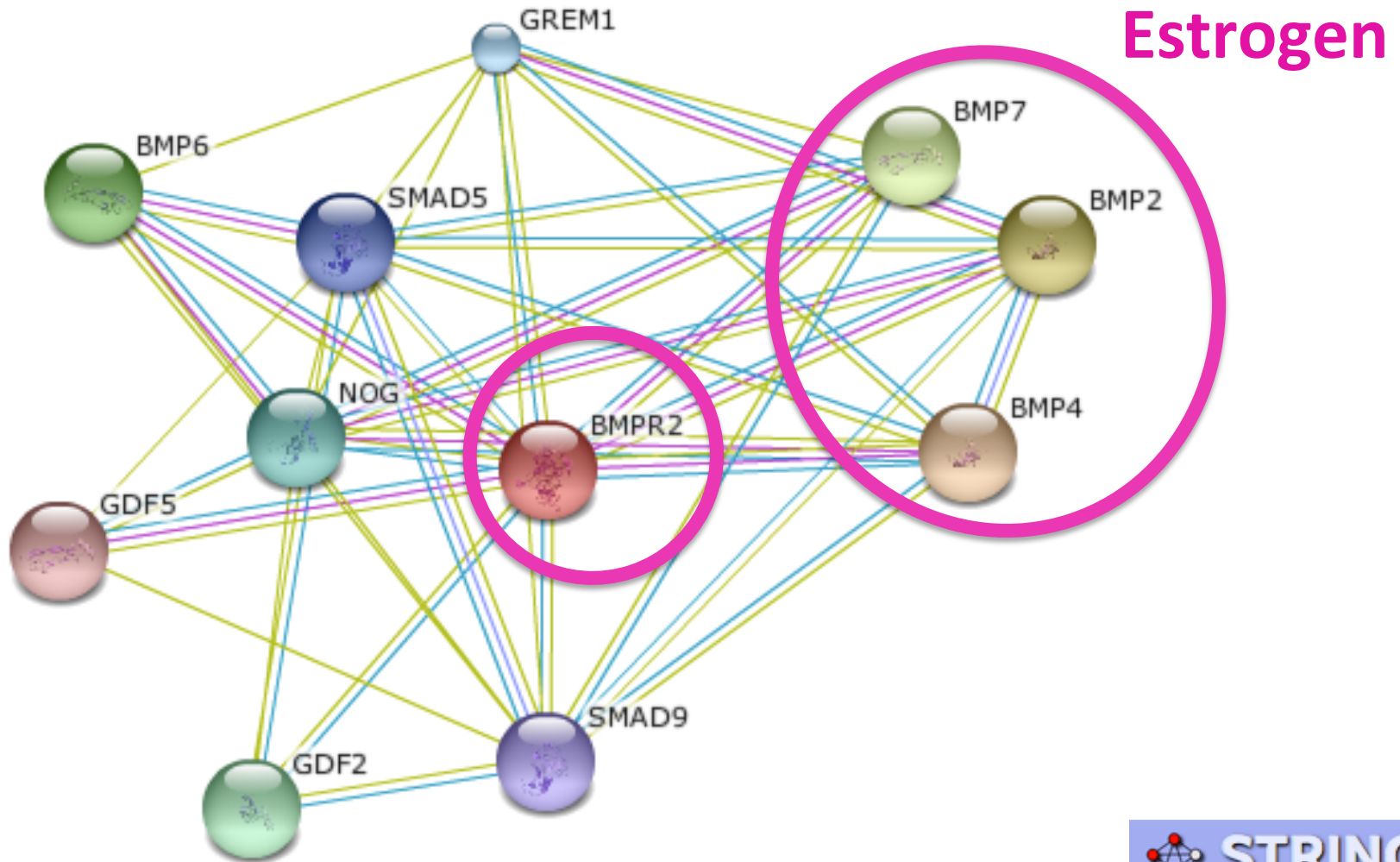
Activin receptor Domain

Protein Kinase Domain

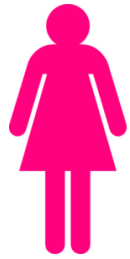
How does *BMPR2* Phylogeny look like?



How does *BMPR2* protein interact with other proteins?



Why is there a higher female prevalence for PAH?

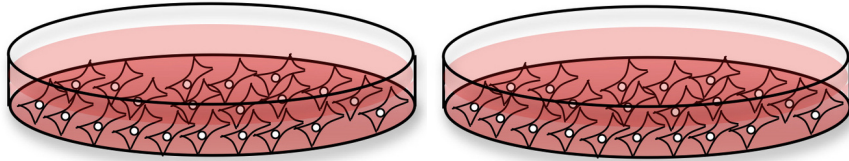


Hypothesis:

BMPR2 gene expression is **repressed** by higher levels of estrogen in the blood

Aim 1: To investigate how *BMPR2* gene is expressed at different levels in females and males in our *in vitro* study using adult human adipocytes

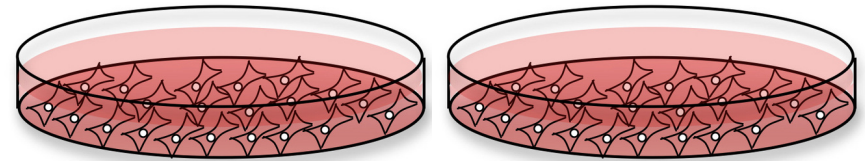
Female



Adipocytes with PAH
Mutant

Control Adipocytes
WT

Male



Adipocytes with PAH
Mutant

Control Adipocytes
WT

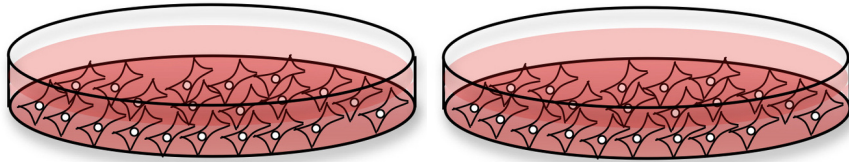
Why?

Different level of estrogen

→ Different level of *BMPR2* expression

Aim 1: To investigate how *BMPR2* gene is expressed at different levels in females and males in our *in vitro* study using adult human adipocytes

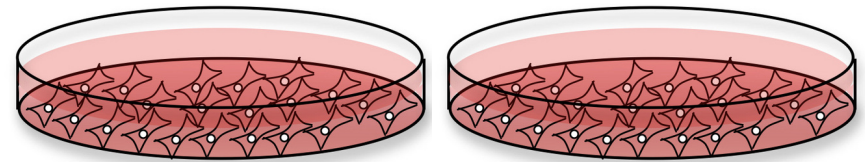
Female



Adipocytes with PAH
Mutant

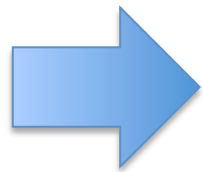
Control Adipocytes
WT

Male

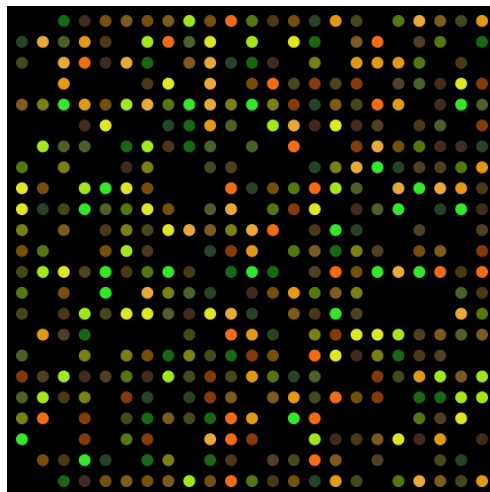


Adipocytes with PAH
Mutant

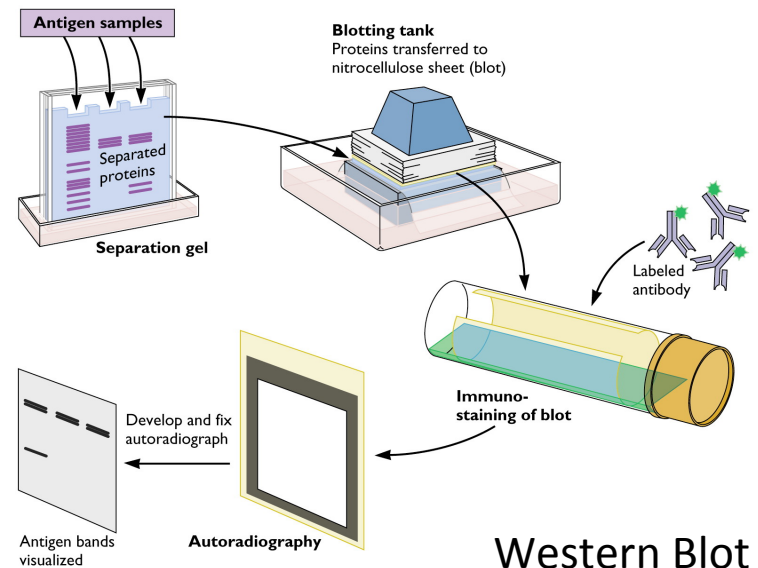
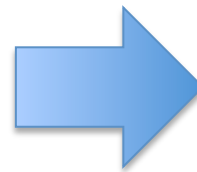
Control Adipocytes
WT



Measure *BMPR2*
gene expression
level
Identify *BMPR2*
gene → protein



DNA microarray



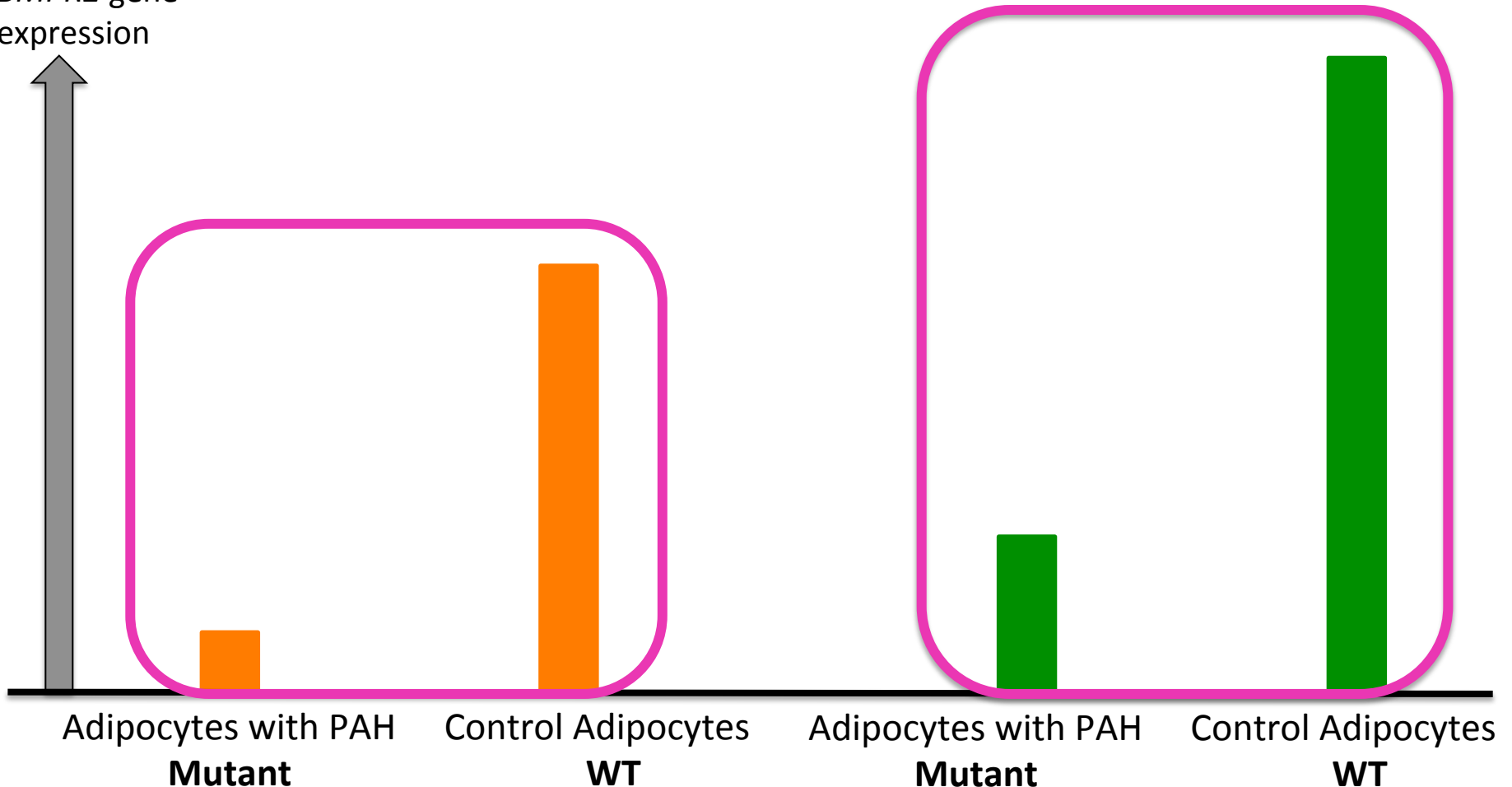
Detect the difference of *BMPR2* protein expression level

Expectation 1: Higher expression of estrogen in the blood in females represses the expression of *BMPR2*

The level of *BMPR2* gene expression

Females

Males



Aim 2: To determine if the level of estrogen in the blood regulates the expression of *BMPR2*

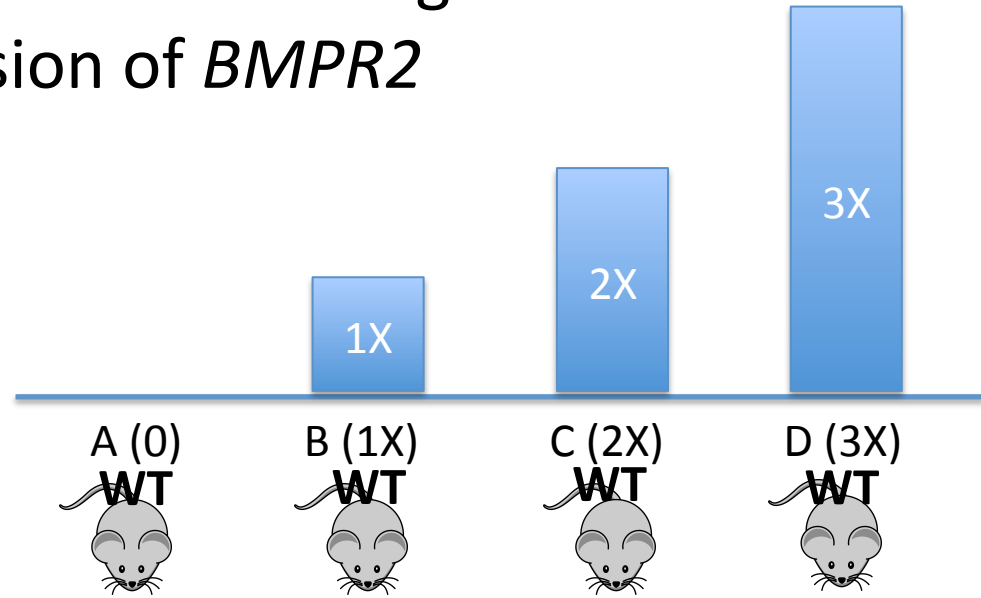
WHY?

Estrogen level ---???.--- *BMPR2* expression

Aim 2: To determine if the level of estrogen in the blood regulates the expression of *BMPR2*



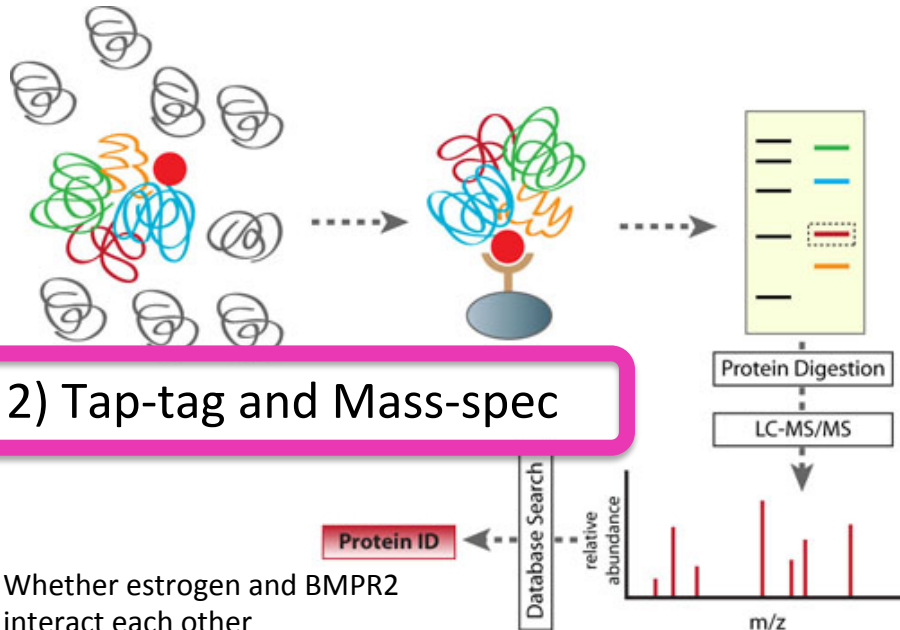
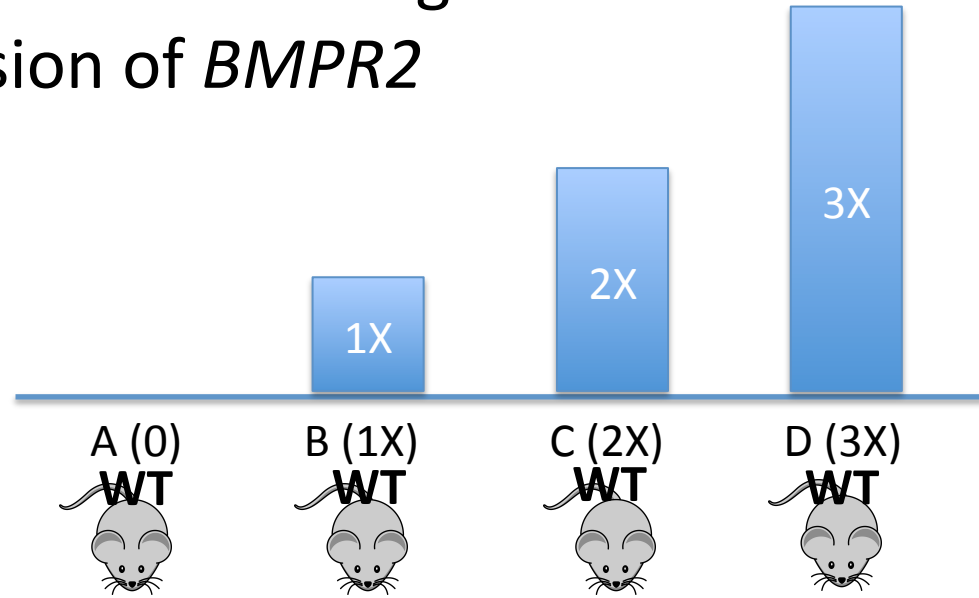
1) Inject different concentrations of estrogen to the WT female mice



Aim 2: To determine if the level of estrogen in the blood regulates the expression of *BMPR2*



1) Inject different concentrations of estrogen to the WT female mice

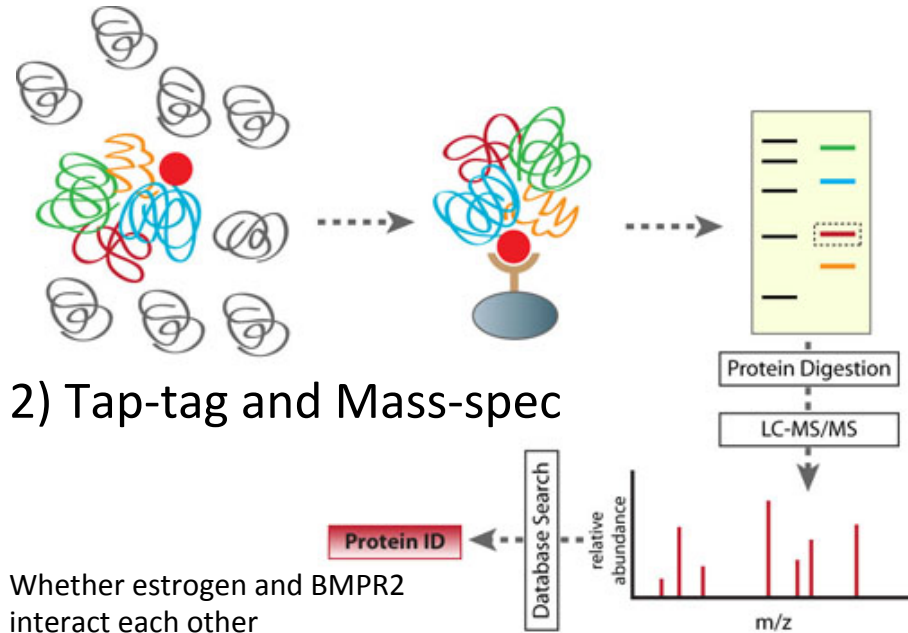
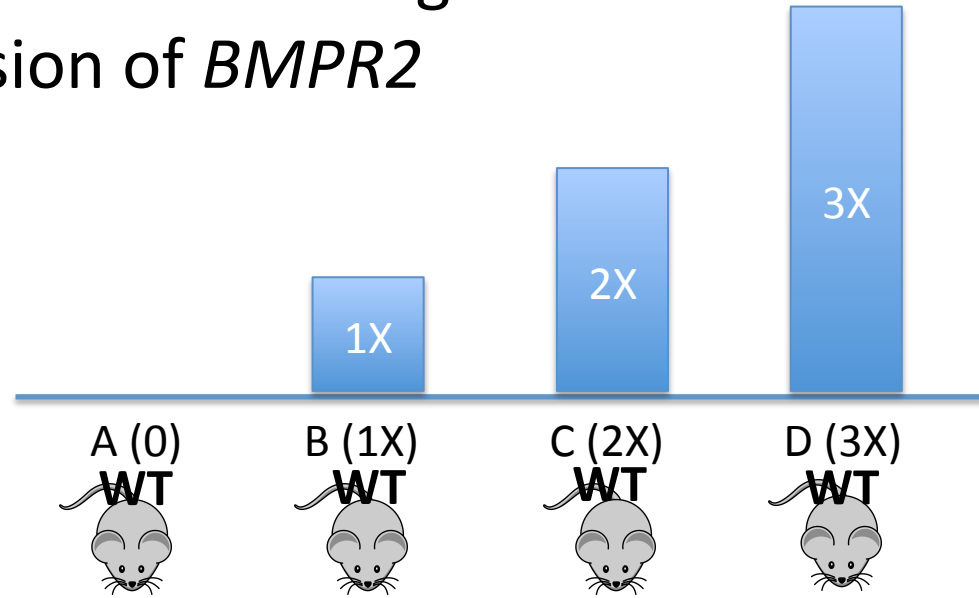


Whether estrogen and *BMPR2* interact each other

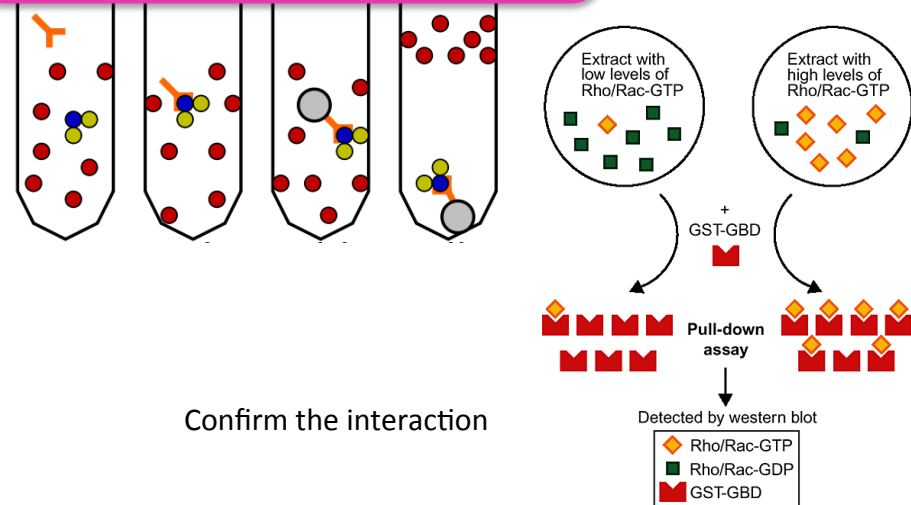
Aim 2: To determine if the level of estrogen in the blood regulates the expression of *BMPR2*



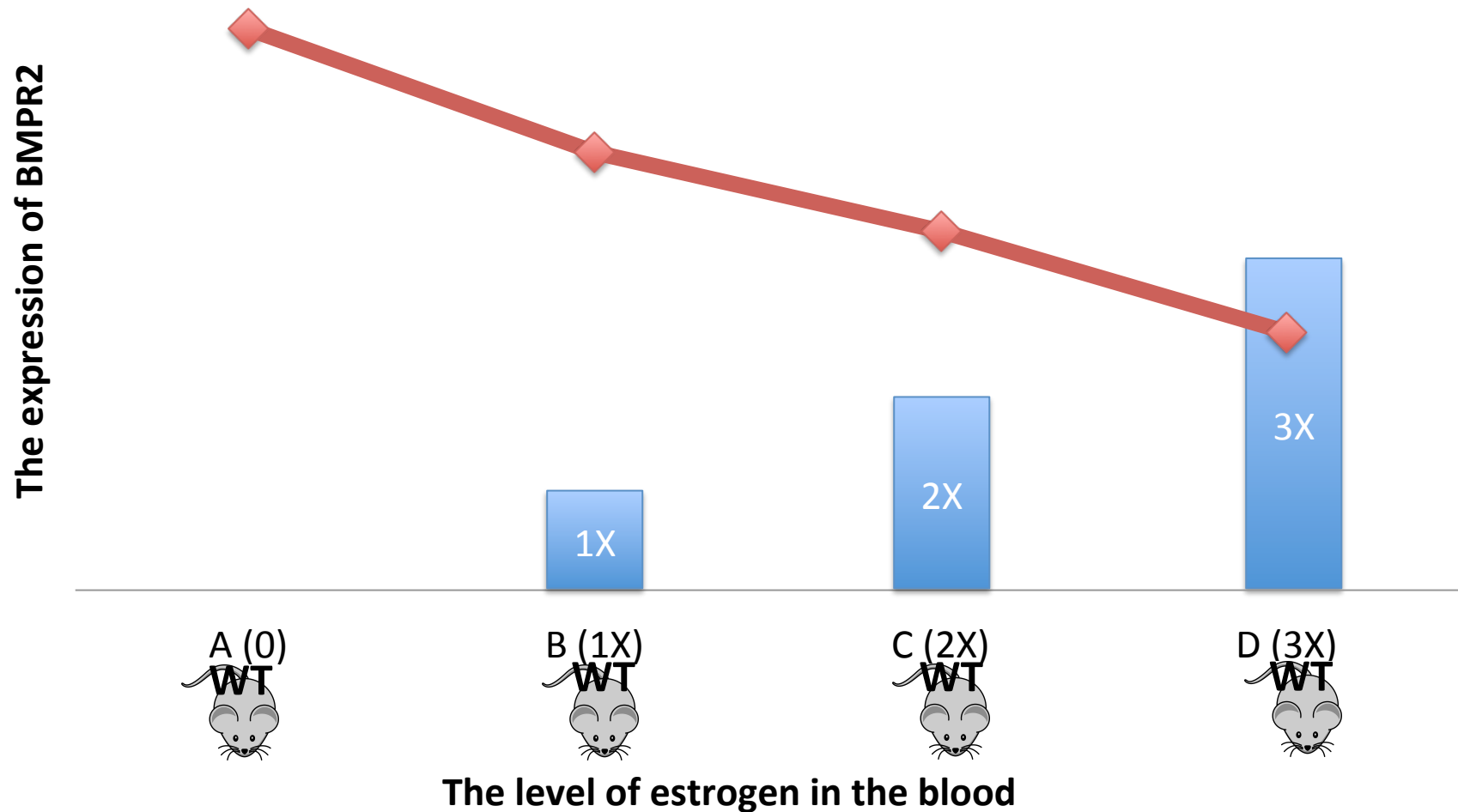
1) Inject different concentrations of estrogen to the WT female mice



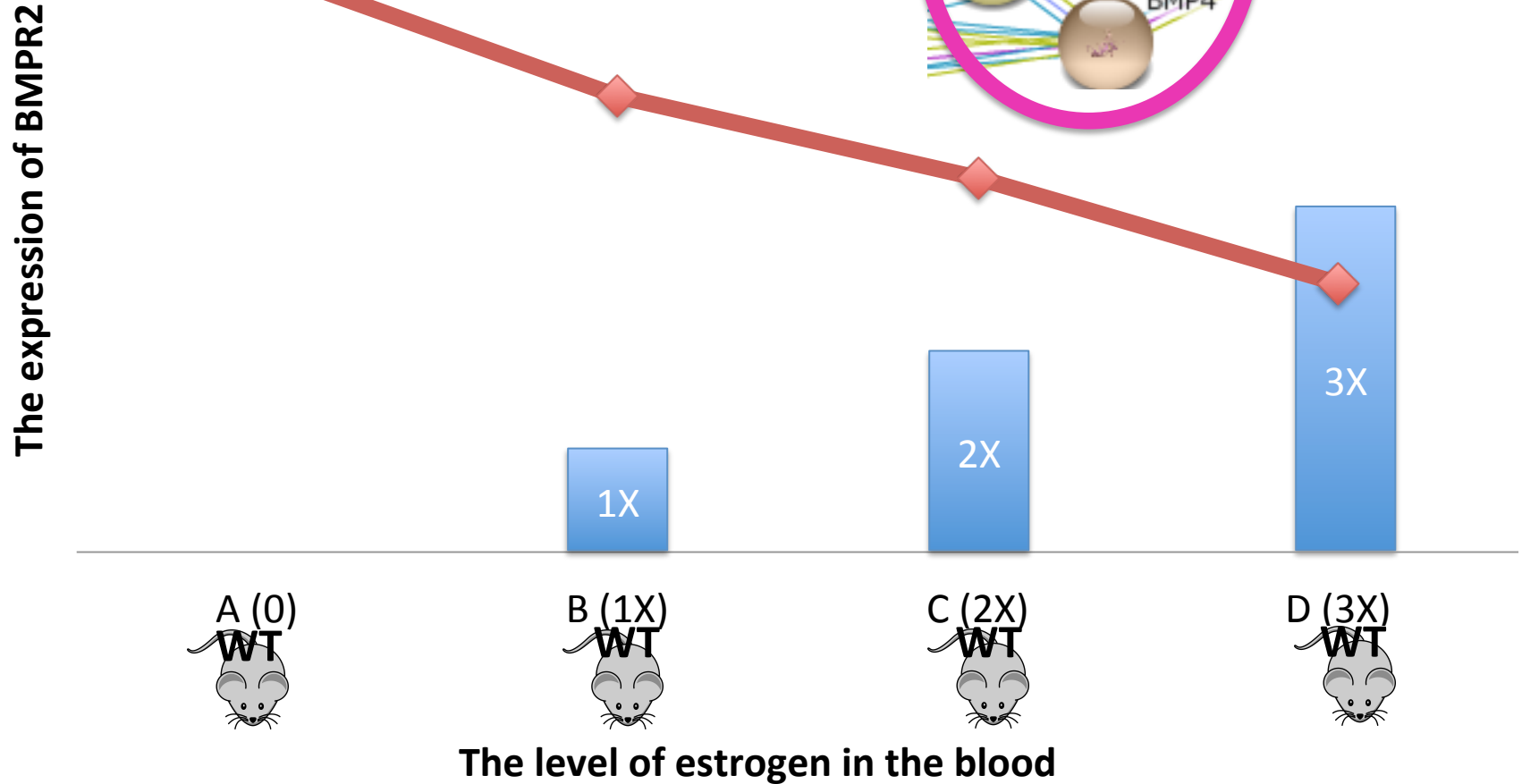
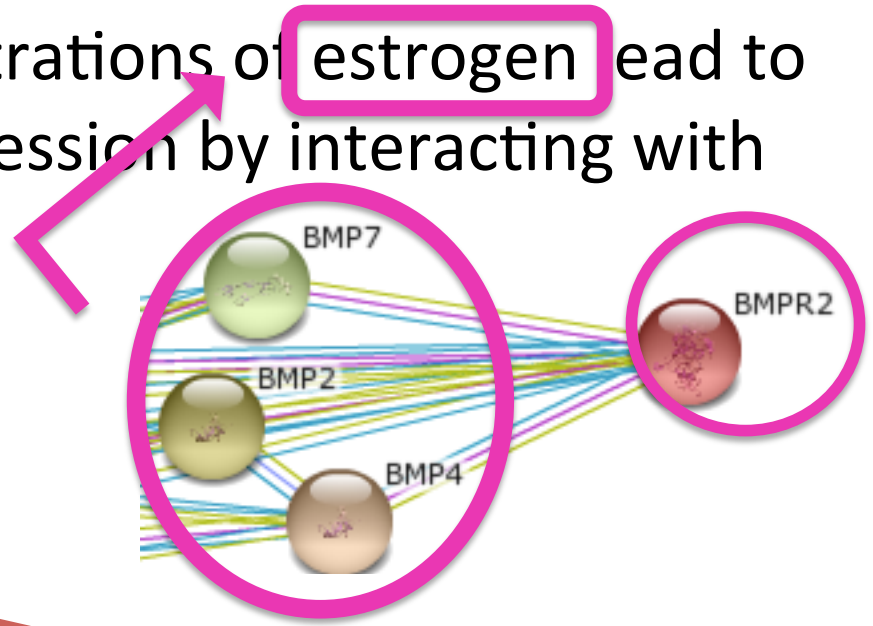
3) Immunoprecipitation or Pull-down assay



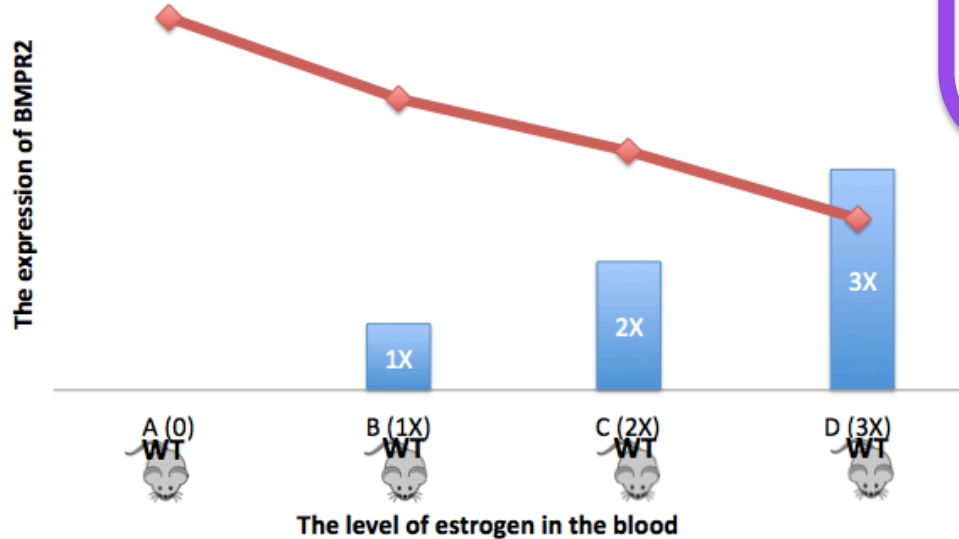
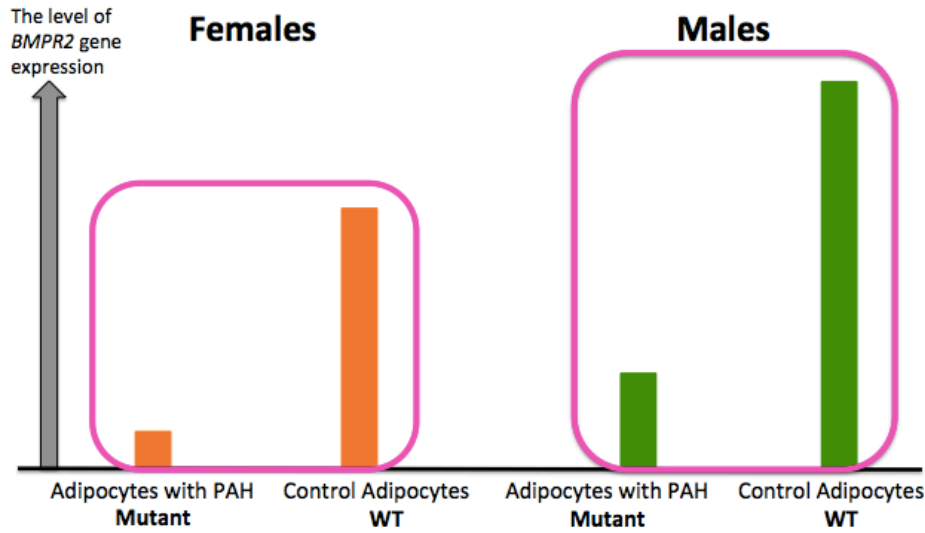
Expectation 2: High concentrations of estrogen lead to the repression of *BMPR2* expression by interacting with its potential partners



Expectation 2: High concentrations of **estrogen** lead to the repression of *BMPR2* expression by interacting with its potential partners



Conclusion



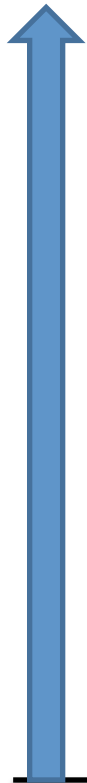
Female
Estrogen ↑
: *BMPR2* expression ↓

Future Direction

- 1) Determine the levels of estrogen in the blood in females from birth to death

The level of *BMPR2* gene expression

BMPR2
expression



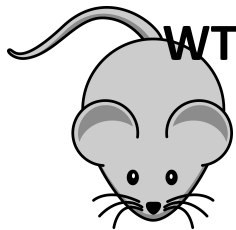
Age

2) Different diet on WT mice

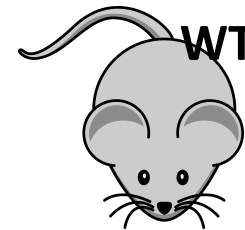


Repression of *BMPR2* gene expression

Salty Food



Non-salty Food

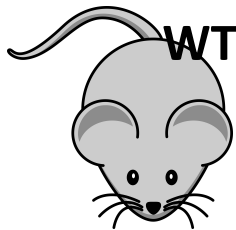


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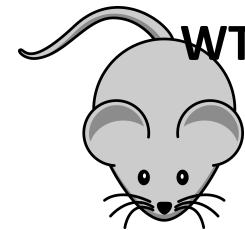


The level of *BMPR2* gene expression

Salty Food



Non-salty Food



References

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Questions?

