

Lynch Syndrome and MSH6

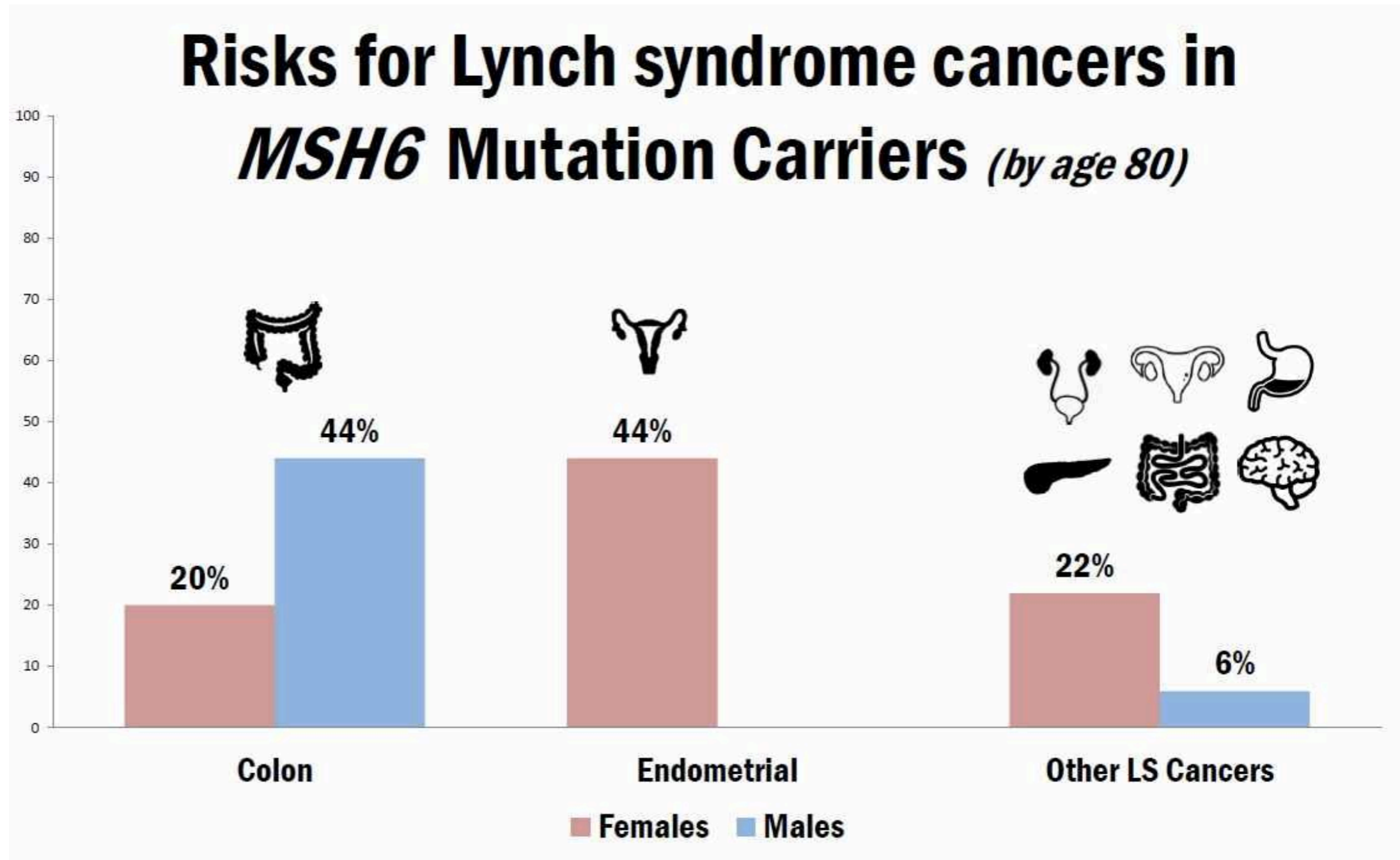


WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

Laura Williams



What is Lynch Syndrome?



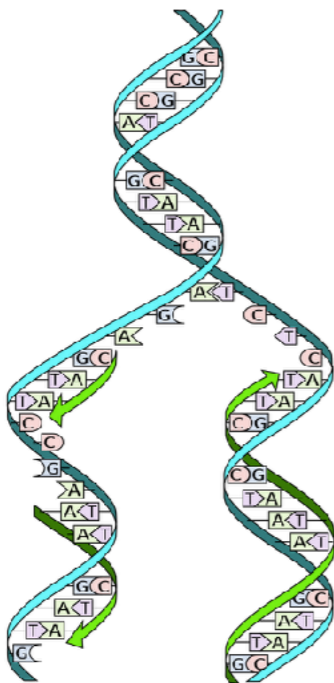
What does MSH6 do?

PWWP

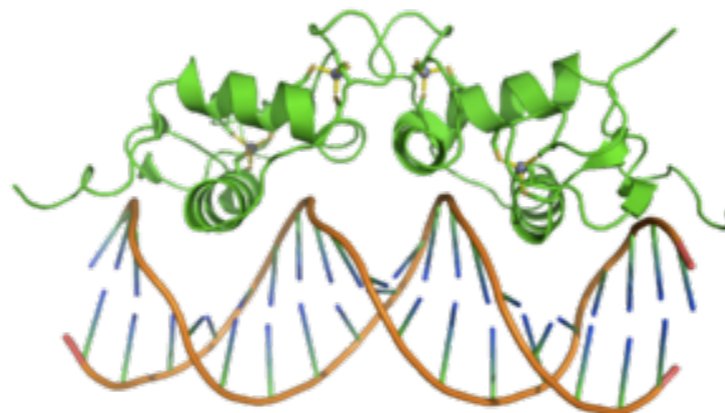
MUTSd

MUTSac

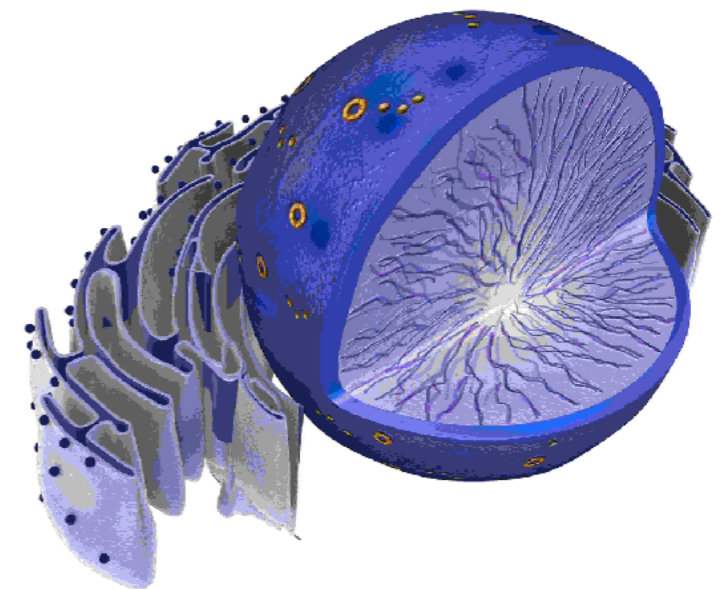
Biological Process



Molecular Function



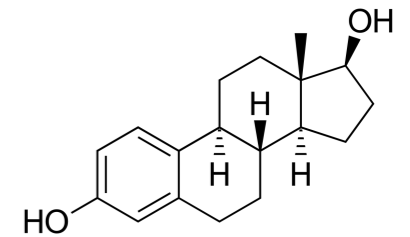
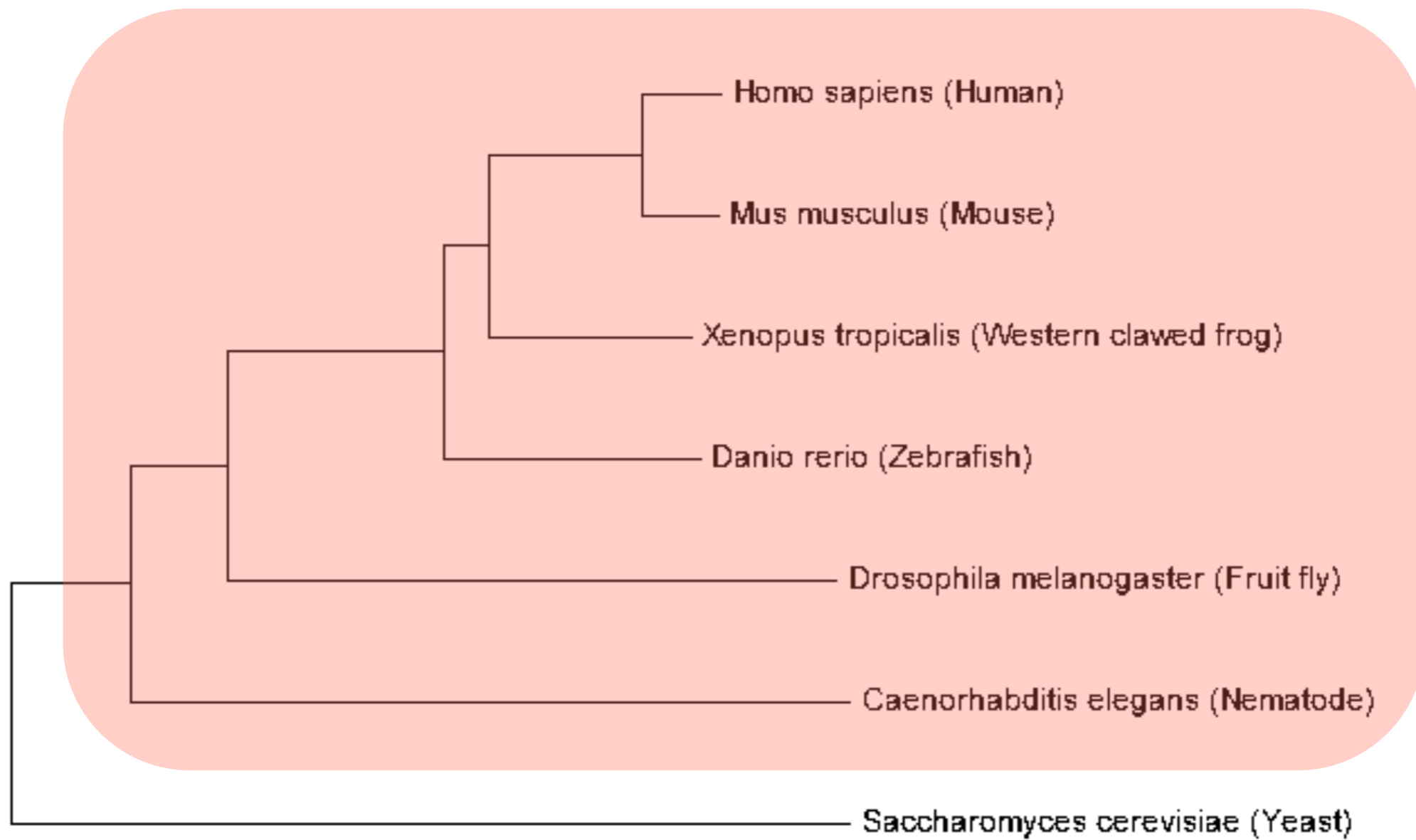
Cellular Component



MSH6 is well conserved across species

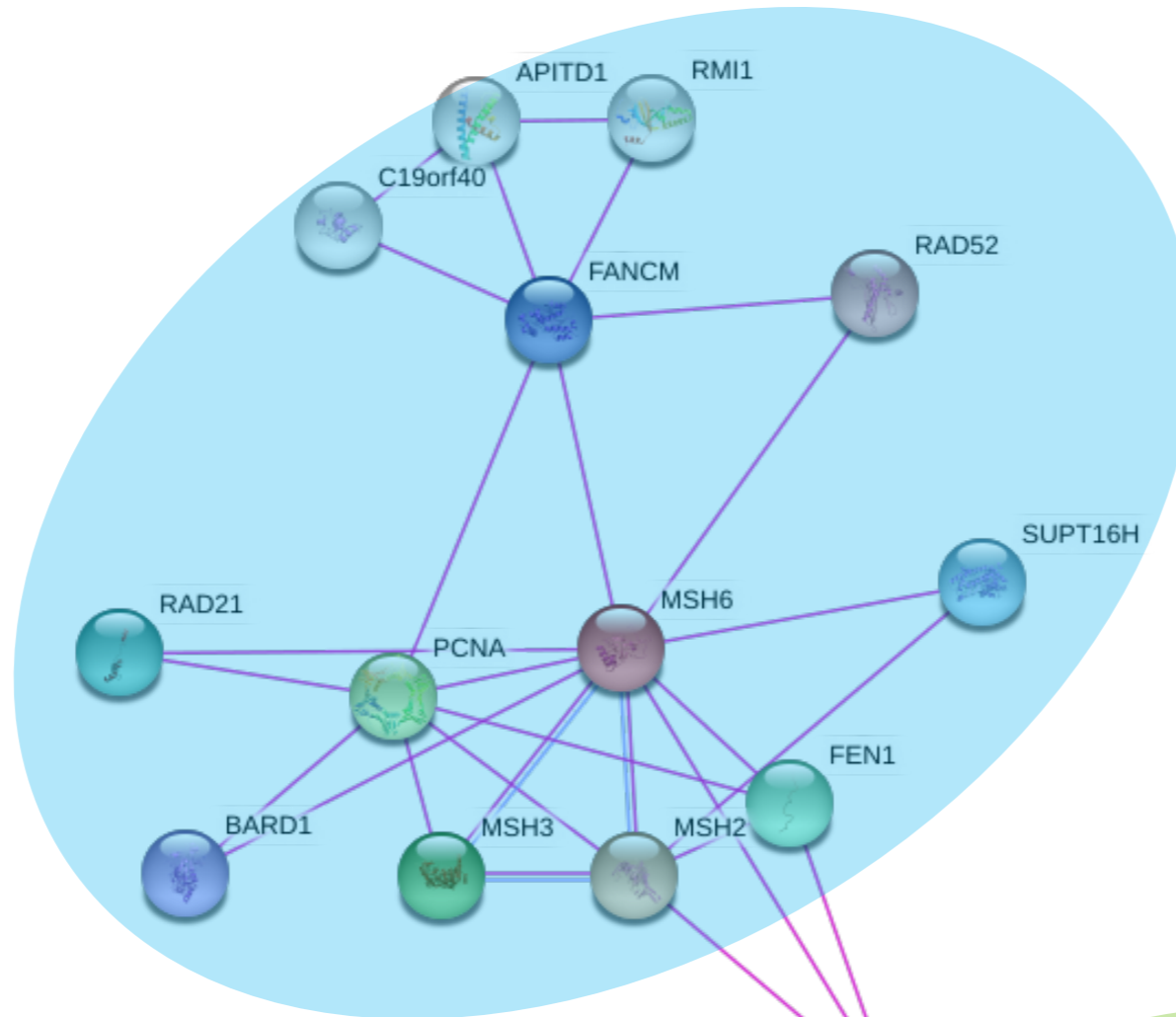


MSH6 Phylogeny

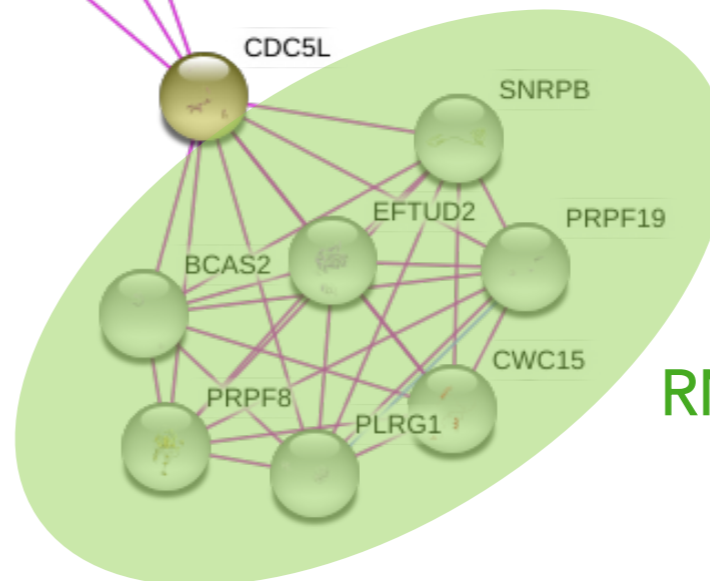


MSH6 Protein Interactions

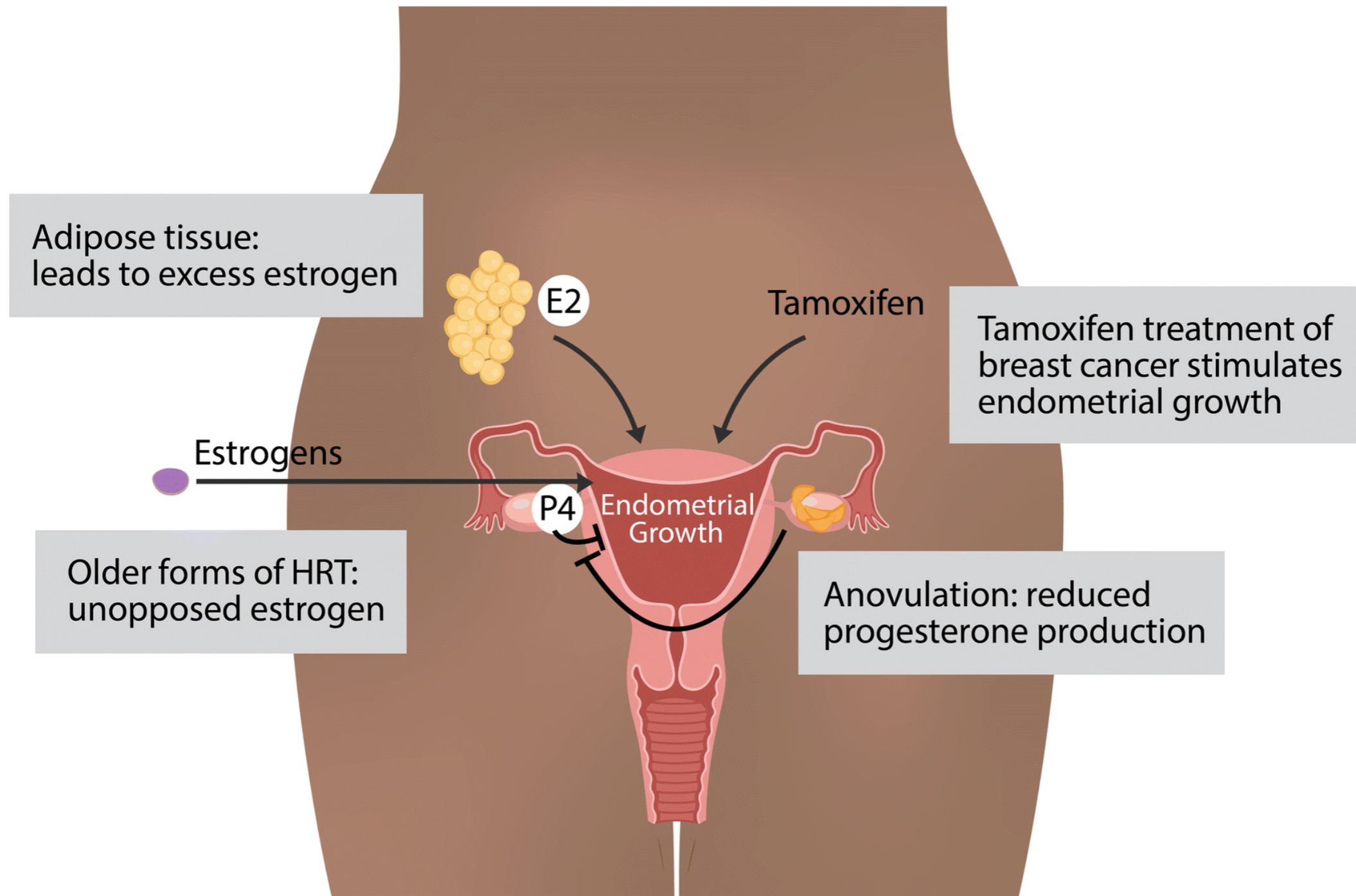
DNA Repair



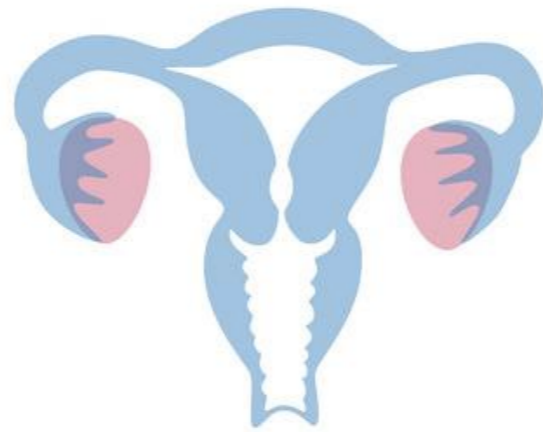
RNA Splicing



Estrogen and Endometrial Cancer



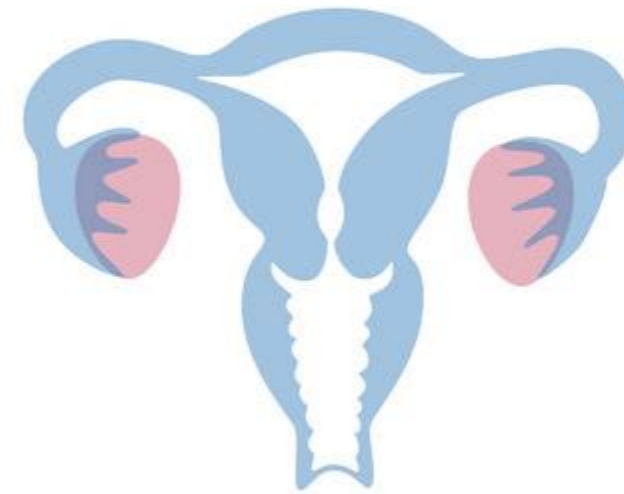
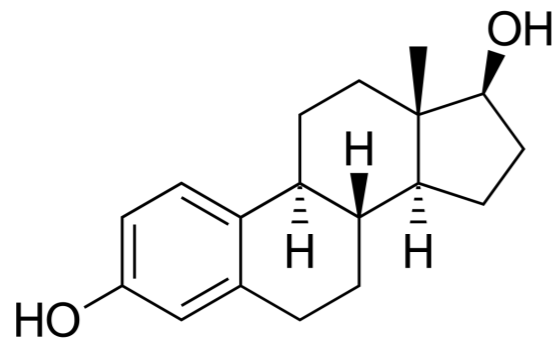
What model organism can we use to study Lynch syndrome?



Mice with mutated MSH6 exhibit endometrial cancer

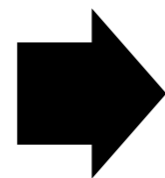
Primary goal

Determine whether estrogen receptor signaling in cells with an MSH6 mutation contributes to the development of endometrial cancer



Aim 1

Identify ER interaction motifs in MSH6



Aim 2

Determine how estrogen interaction with MSH6 affects the transcriptome



Aim 3

Determine how estrogen interaction with MSH6 impacts protein expression

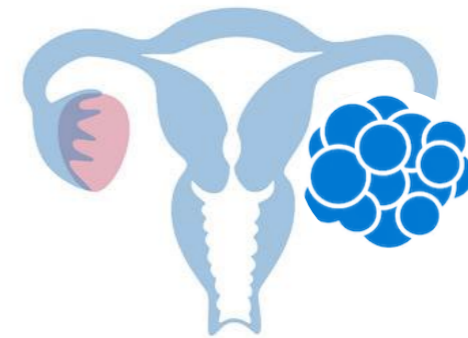
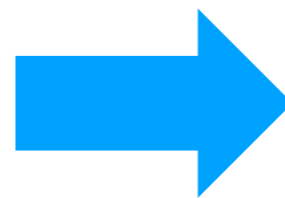
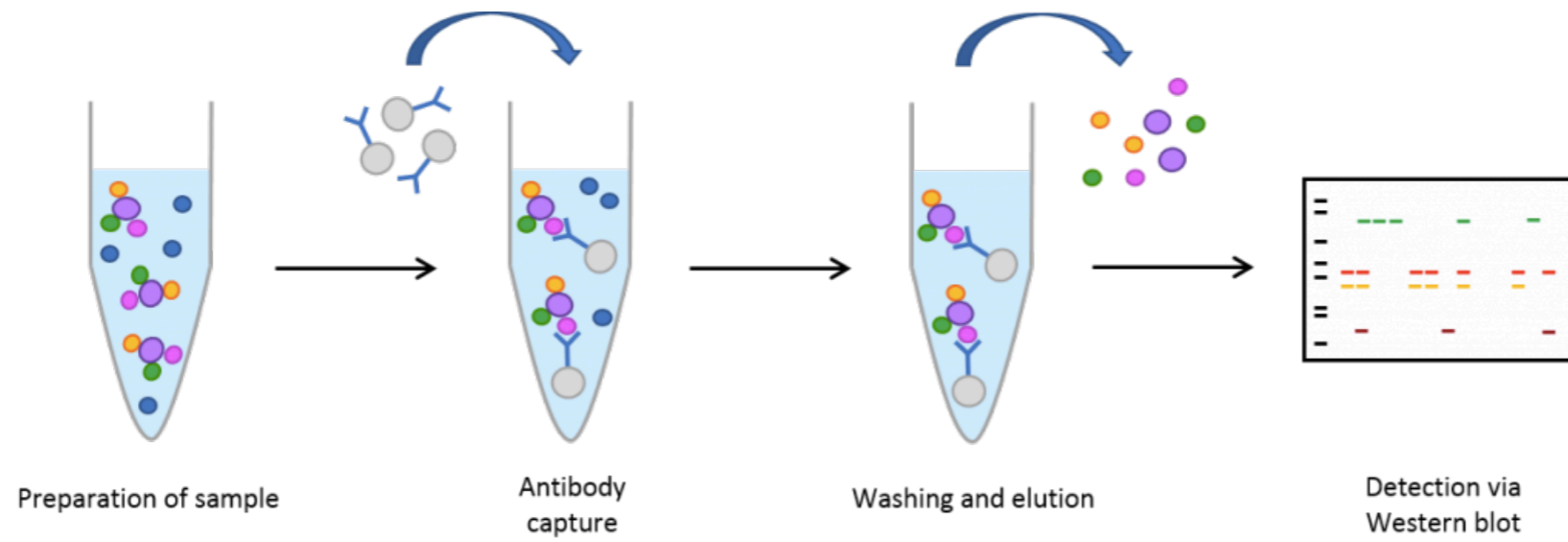
Aim 1: Identify ER interaction motifs in MSH6

Caenorhabditis	TPGHRQWWTMKSQHFDTILLFKVGKPYETYHMDAVEVVRALNIAFM---RGSYAHAGFPE	307
Drosophila	SPGVRQWWVLKSDNYDCVLPFKVGKPYELYHMDADVGVNELGFTYM---RGEFAHSGFPE	318
Homo	TPGMRKWWQIKSQNFDLVICYKVGKPYELYHMDALIGVSELGLVFM---KGNWAHSGFPE	463
Mus	TPGMRKWWQLKSQNFDLVIFYPYKVGKPYELYHMDAVIGVSELGLIFM---KGNWAHSGFPE	462
Saccharomyces	TPFEKQYWEIKSKMWDCIVFPKKGKPFELYEKDALLANALFDLKIAGGGRANMQLAGIPE	371
Arabidopsis	SASQKQYWSVKSEYMDIVLFPFKVGKPYELYELDAELGHKELDWKMTMSGVGKCRQVGISE	327

The MEME Suite

Motif-based sequence analysis tools

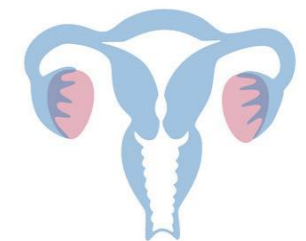
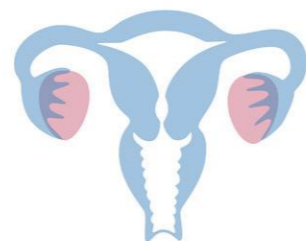
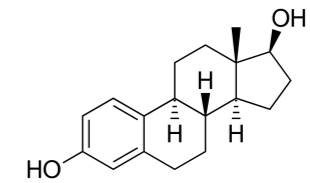
Aim 1: Identify ER interaction motifs in MSH6



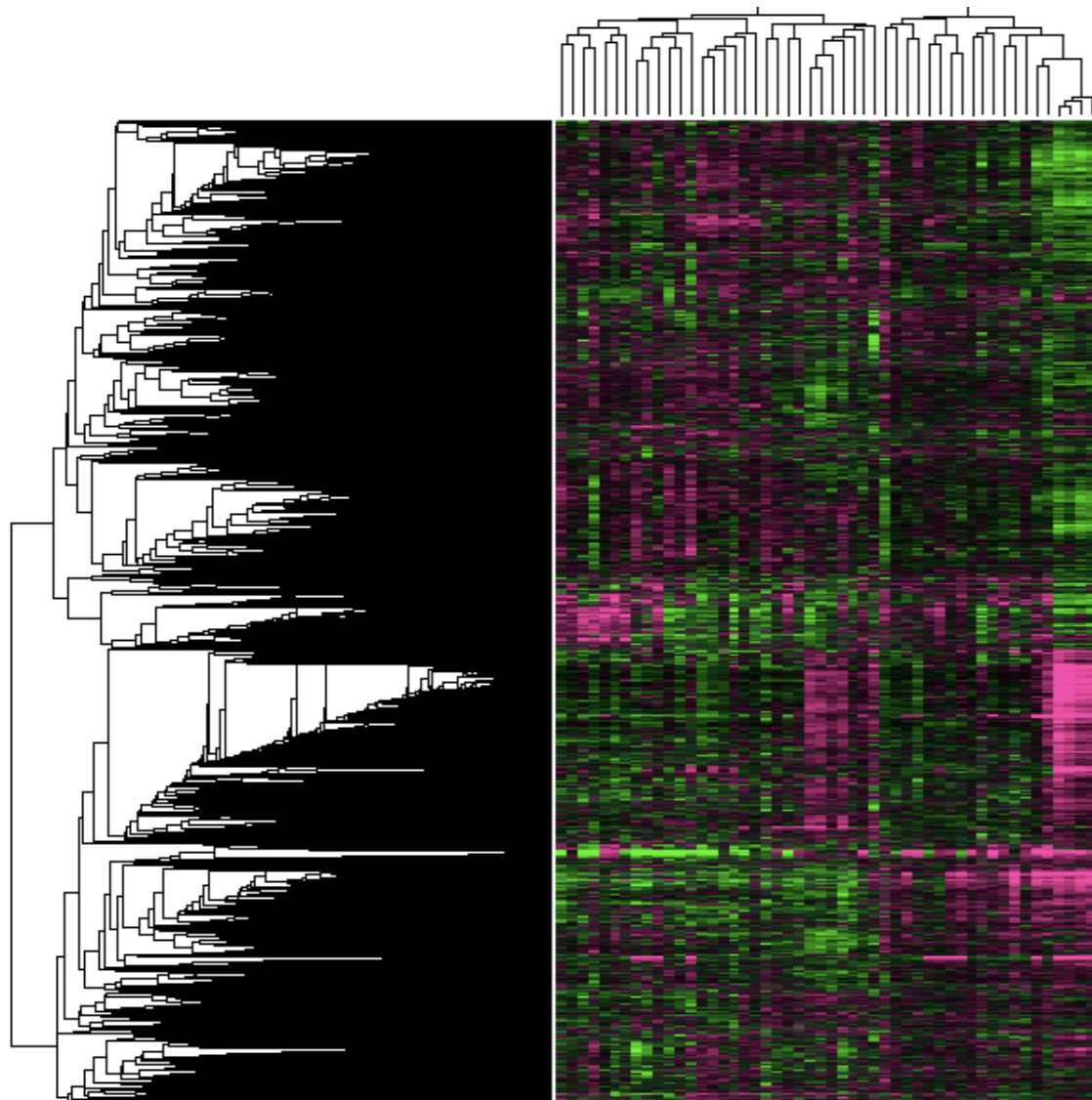
Aim 2: Determine how estrogen interaction with MSH6 affects the transcriptome

No Estrogen

Estrogen



Aim 2: Determine how estrogen interaction with MSH6 affects the transcriptome

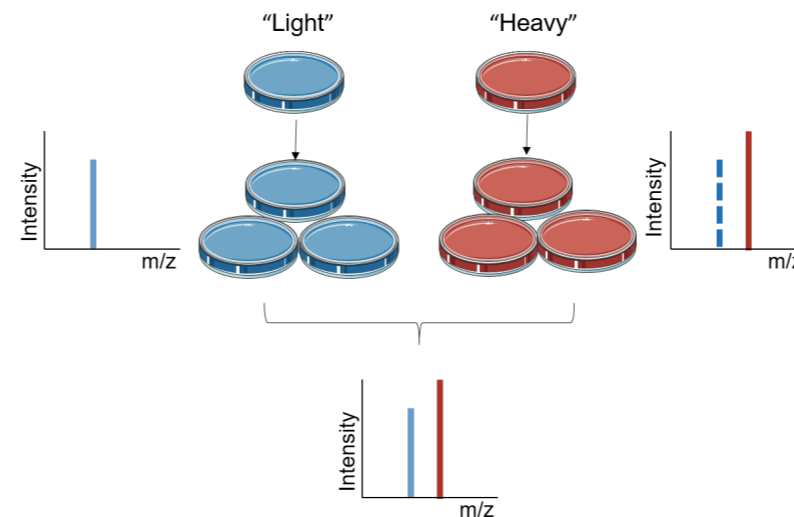
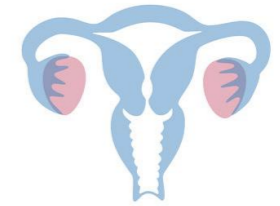
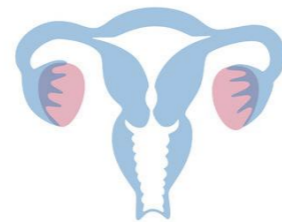
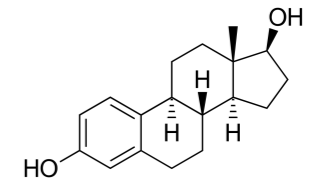


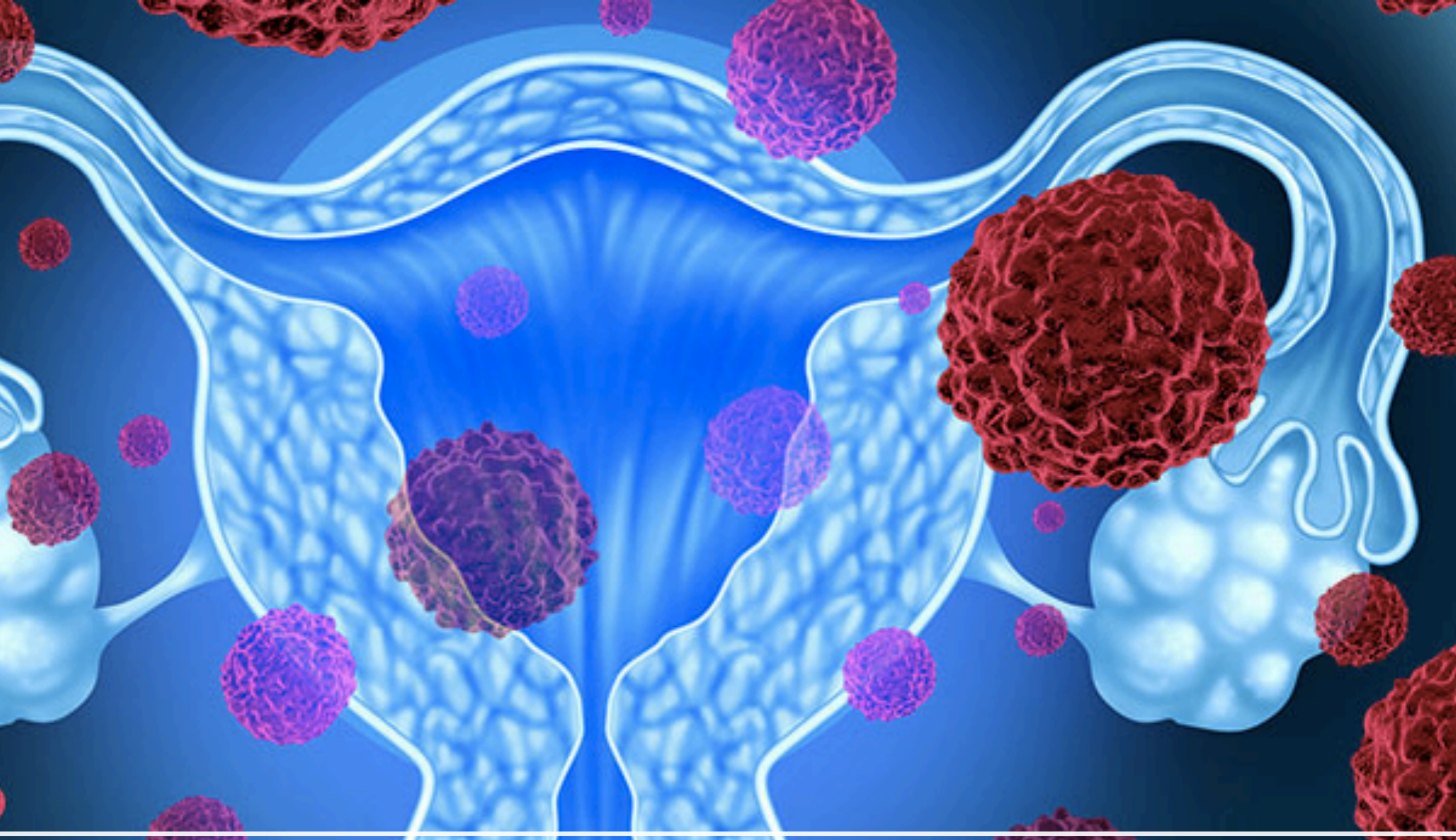
GENEONTOLOGY
Unifying Biology

Aim 3: Determine how estrogen interaction with MSH6 impacts protein expression

No Estrogen

Estrogen



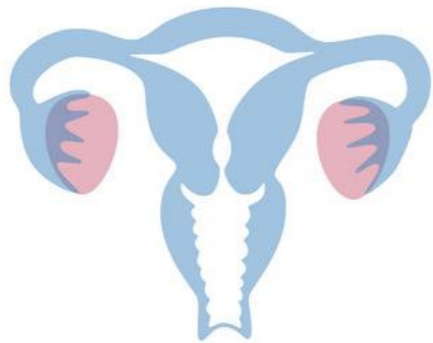


Future Directions

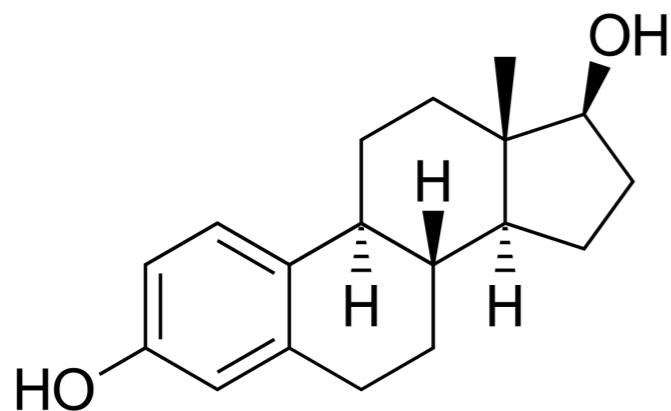
Conclusions



Lynch syndrome is a hereditary cancer disorder that can be caused by mutation of MSH6



Estrogen causes proliferation of endometrial cells which can lead to endometrial cancer



Understanding how estrogen interacts with MSH6 can help develop treatments for endometrial cancer

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Images

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