

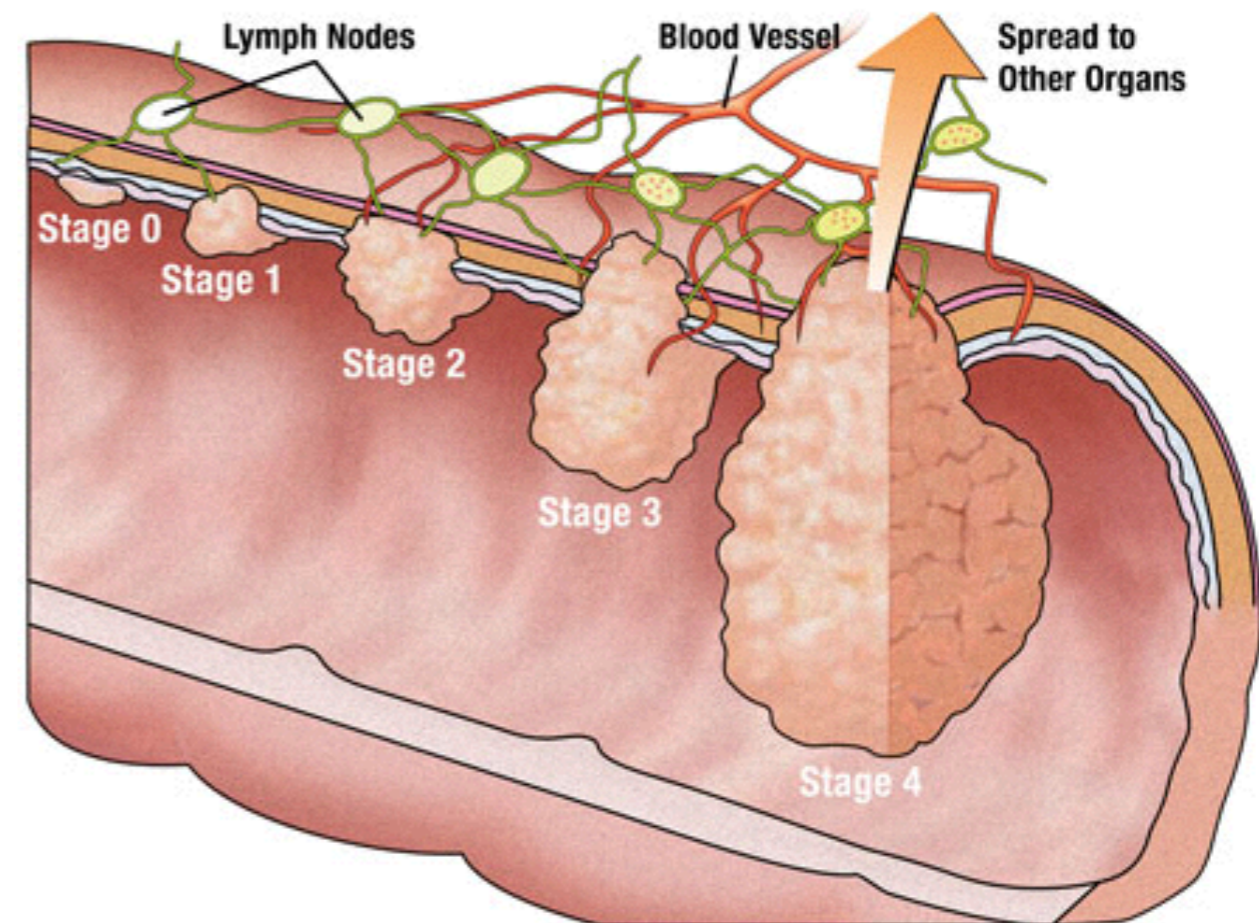
Role of 14-3-3sigma in Colorectal Cancer

Mikayla Simons

What is Colon Cancer?



Lifetime Risk: 1 in 20
Third leading cause
of cancer deaths



- 50,310 deaths expected in 2015
- 136,830 new cases of Colon/Rectal Cancers

What are the warning signs of colorectal cancer?



Blood in the Stool

Stomach Aches

Vomiting

Nausea

The importance of studying colorectal cancer

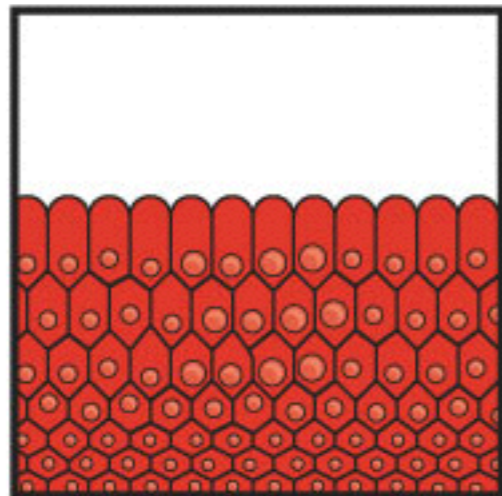
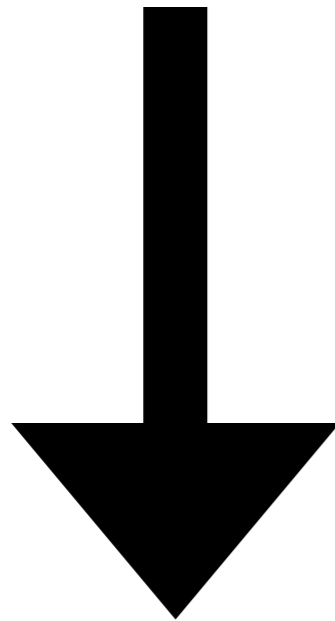


What is one of the genes that affects colon cancer?

hyper-methylation
at the promoter



Stratifin (SFN), HME1

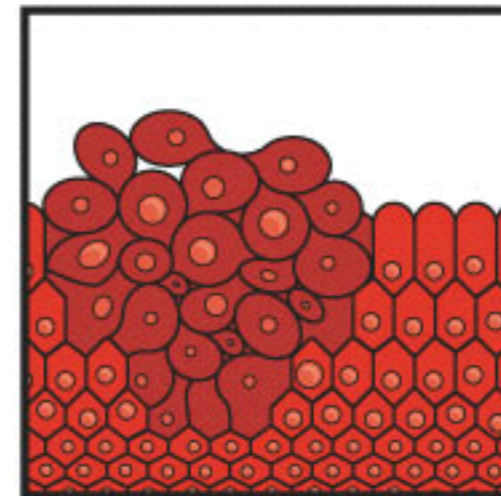


Normal cells

Occurs in
Keratinocytes



Causes:
UV Radiation
Cell Cycle Damage



Cells forming a tumour

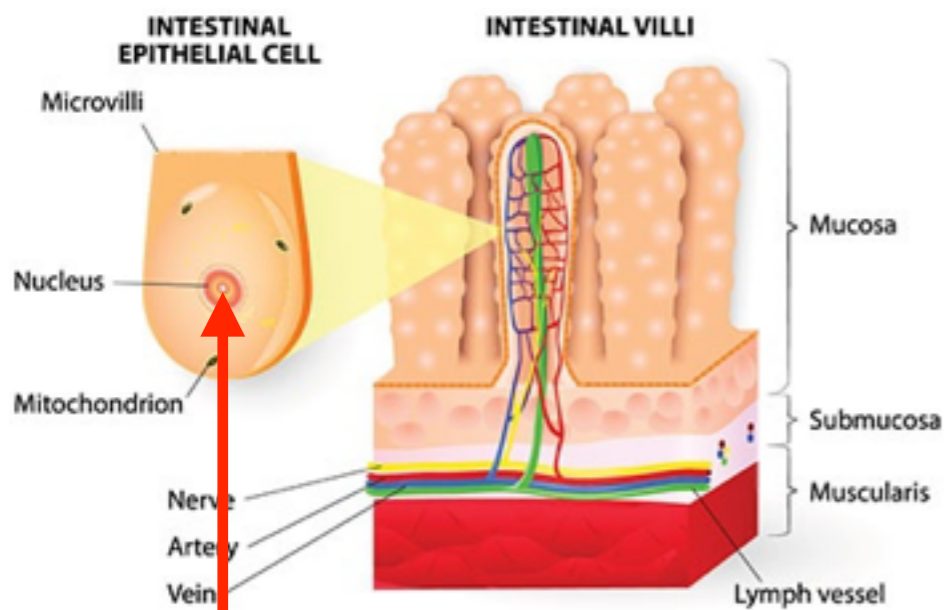
14-3-3sigma is well conserved



Where and how does 14-3-3sigma function?

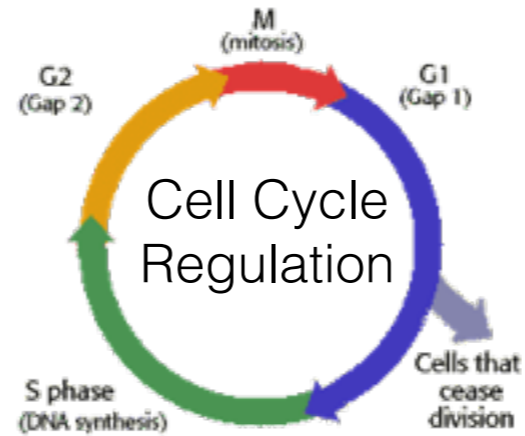
Cellular Components

Epithelial Cells

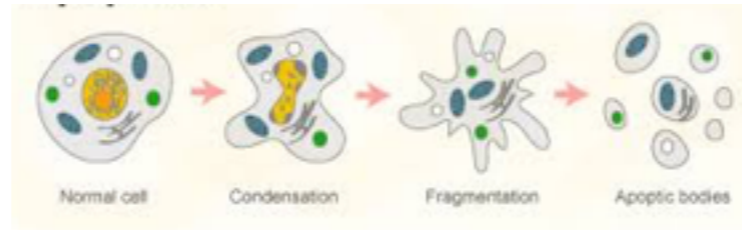


Nucleus

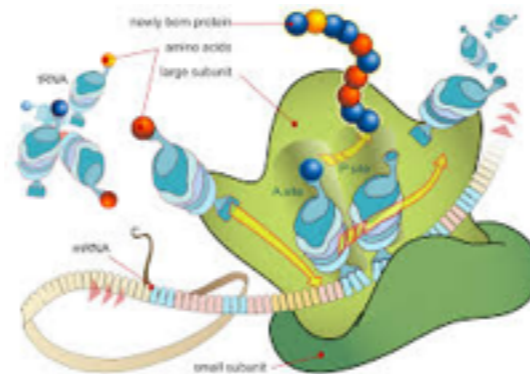
Biological Process



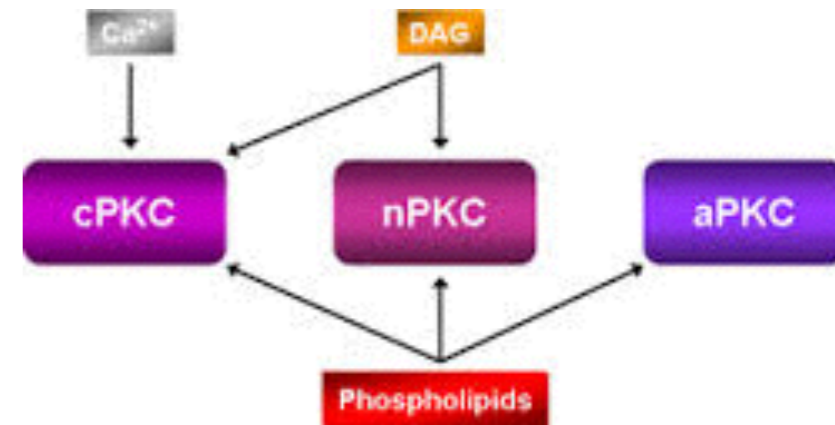
Apoptosis



Translation



Molecular Function



Protein Kinase C inhibitor activity

[http://en.wikipedia.org/wiki/Translation_\(biology\)](http://en.wikipedia.org/wiki/Translation_(biology))

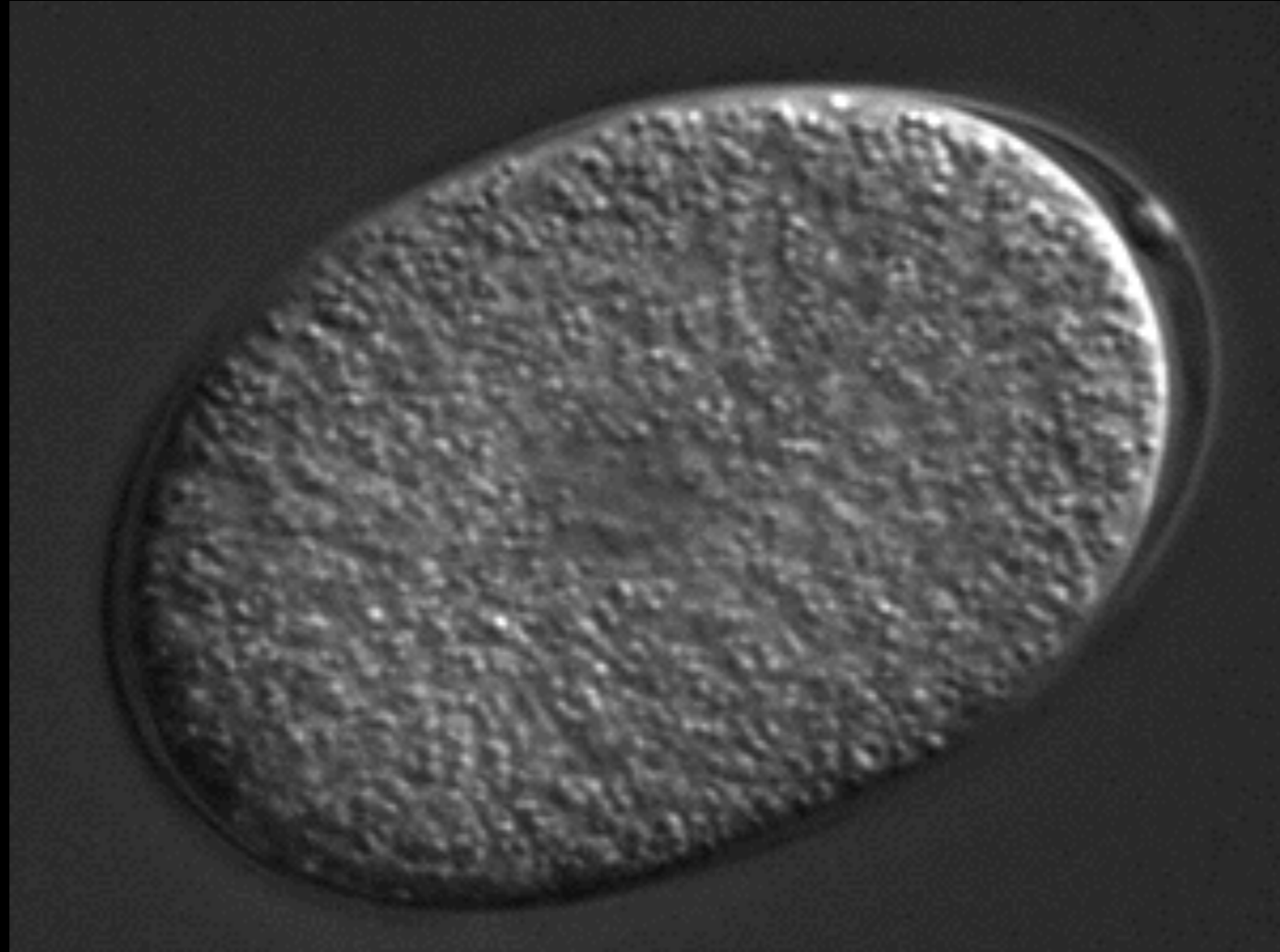
http://www.biology.arizona.edu/cell_bio/tutorials/cell_cycle/cells2.html

<http://www.buzzle.com/articles/simple-columnar-epithelium-labeled-diagram-and-function.html>

<http://www.abnova.com/support/resources.asp?switchfunctionid=%7BCBB86AB6-2EA6-422F-BBBD-1CB8B9DCE6FA%7D>

What is still unknown?

Though much is known about the role of 14-3-3 σ in translation, its role in **Cell Division** as it relates to colorectal cancer is unclear.



Hypothesis: 14-3-3 σ /PAR-5 and its binding partners regulate the activity proteins necessary for cytokinesis by binding to serine/threonine sites.

What is PAR-5 and how does it function?

Worm

14-3-3

248 aa

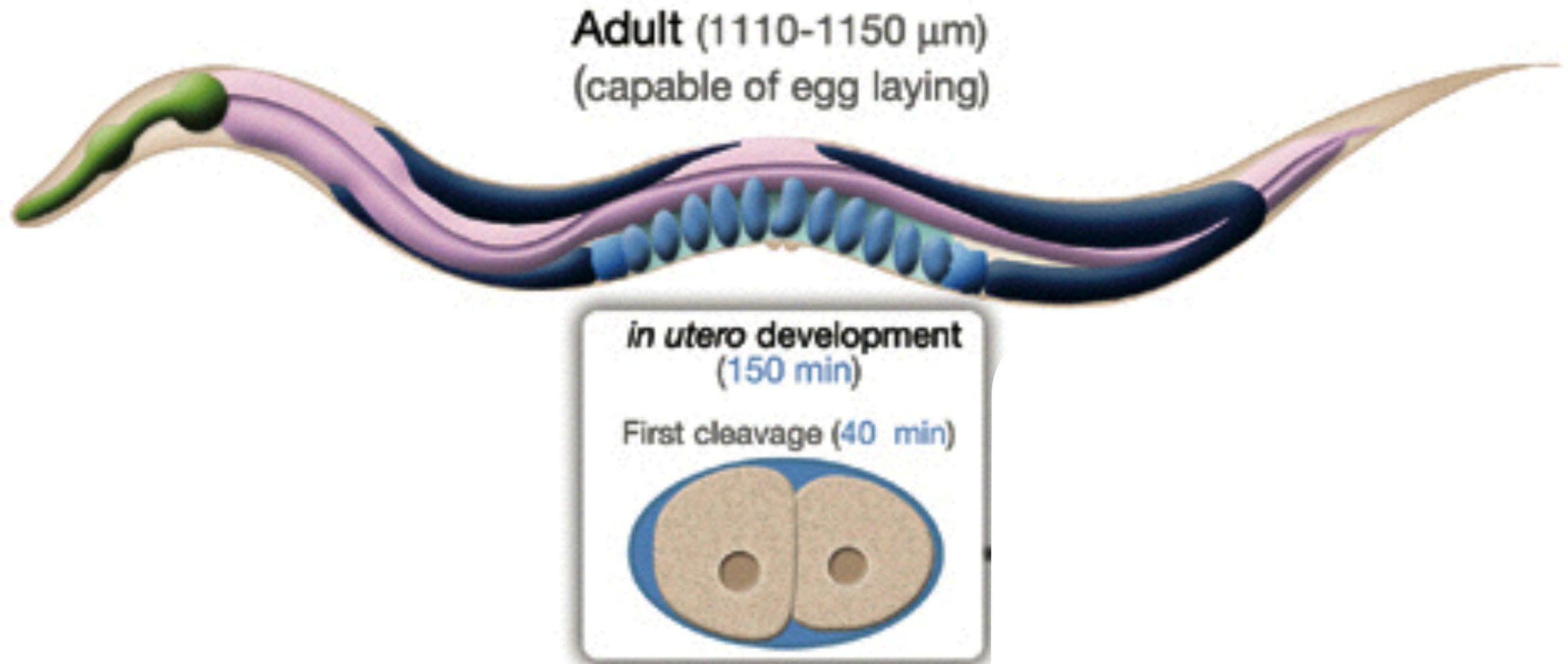
GO TERMS:

Partitioning defective protein

Zygotic asymmetric cell division

Essential for early embryonic development

Why *C. Elegans*?



Prolific, Transparent, Easy to Image and Study

Aim 1: To identify and sort the functions of PAR-5 and 14-3-3sigma interacting partners and determine if they play a role in translation or cell division.

Approach:

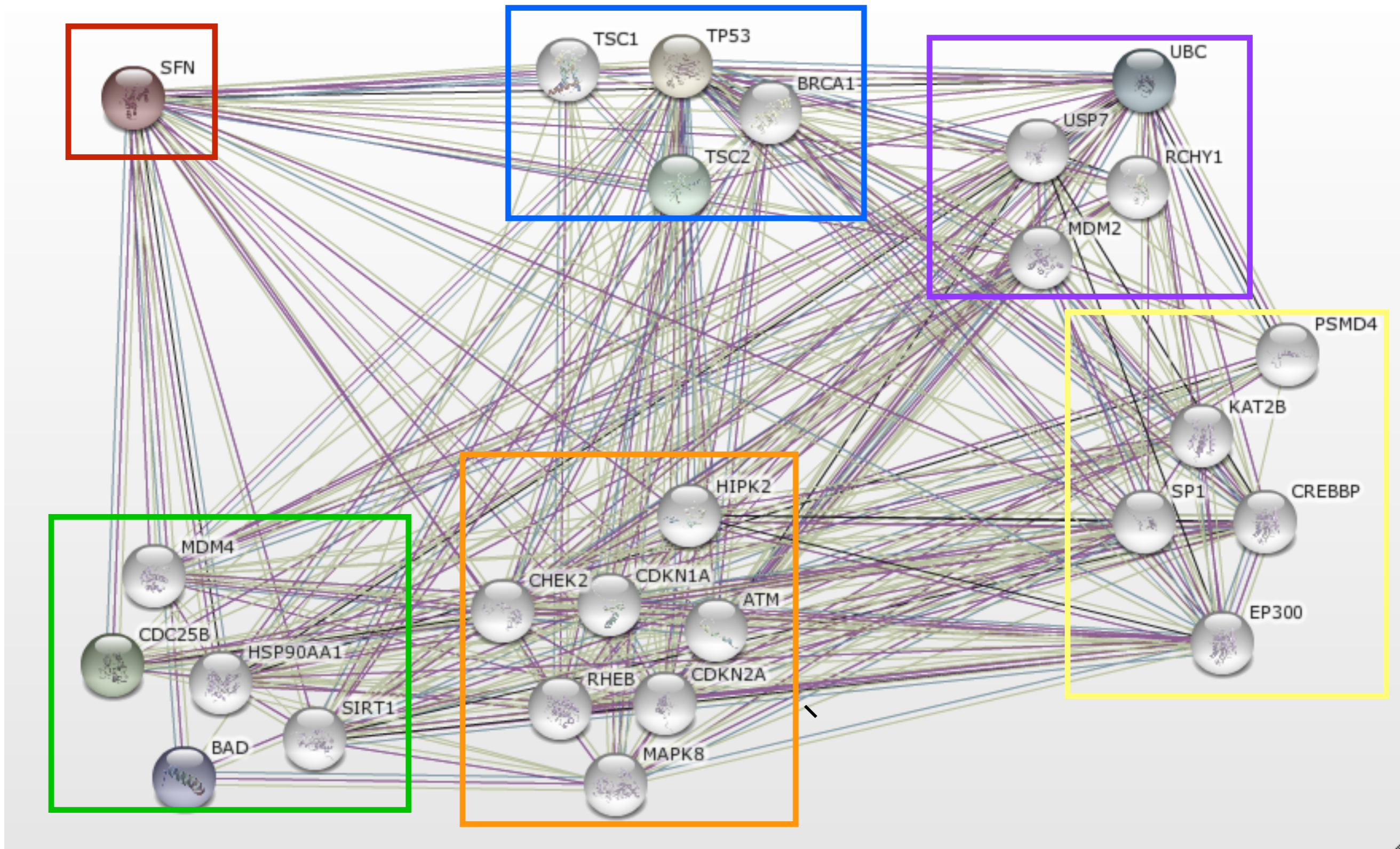
STRING









SMART

GO
the Gene Ontology

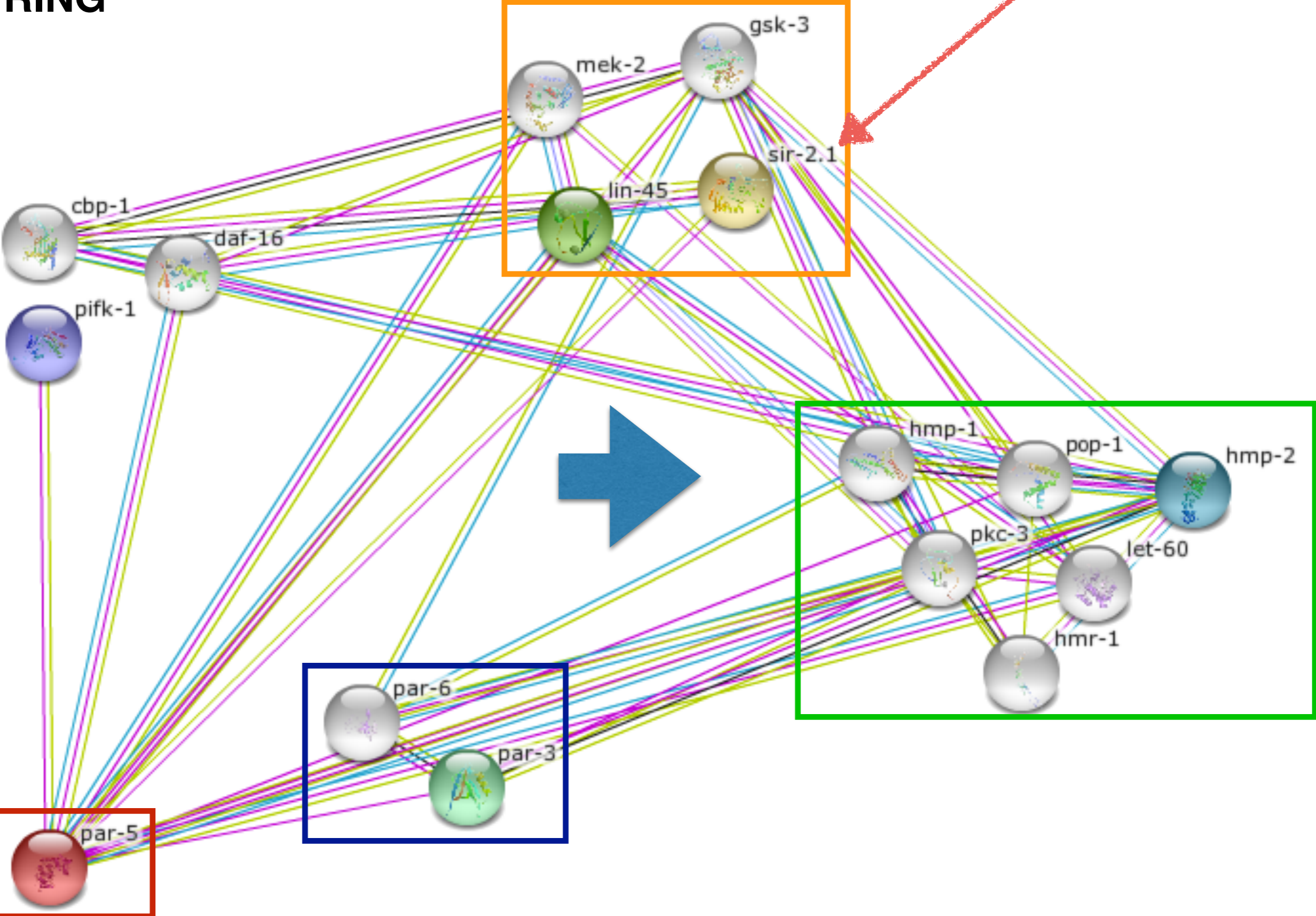
Rationale: Determine which proteins will be useful for research




- | | | | | | |
|------------------------------------------------------------------------------------|----------------------|-------------------------------------------------------------------------------------|-----------------|---------------------------------------------------------------------------------------|----------------------------------|
|  | Tumor Suppressor |  | Ubiquitination |  | Serine/Threonine Phosphorylation |
|  | Cell Cycle Mediation |  | 14-3-3 σ |  | Transcription Factors |

STRING

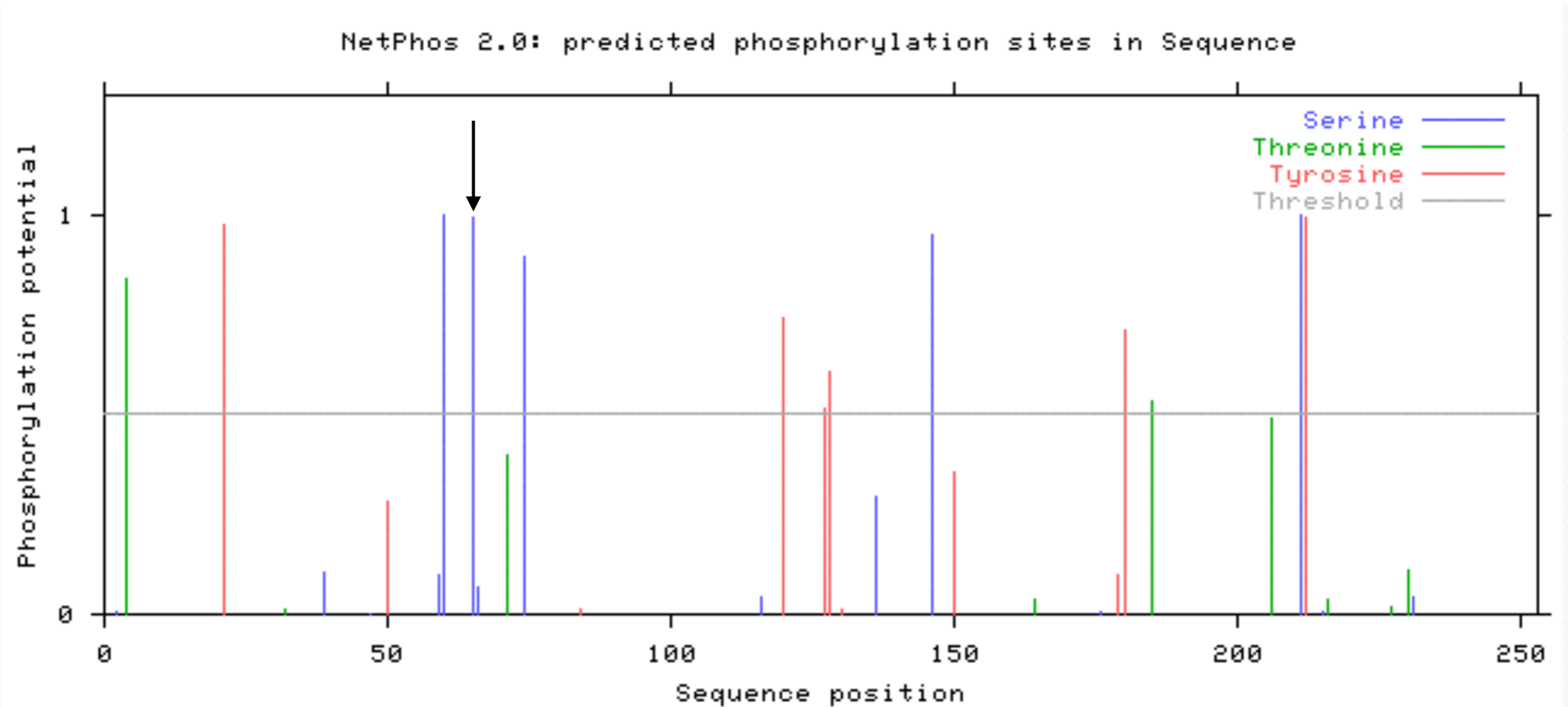
STRING



-  Phosphorylation/Protein Kinases
-  Cell Polarity
-  Cell Migration & Shape
-  PAR-5

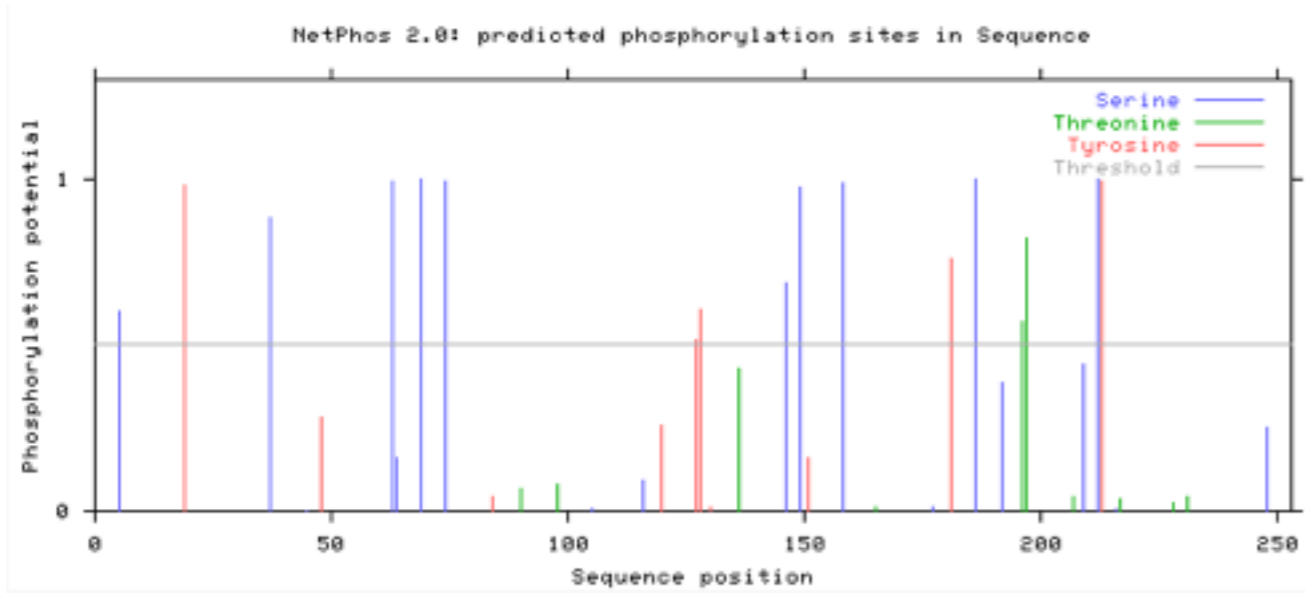
Aim 2: To identify conserved serine/threonine phosphorylation sites on PAR-5 that function during cell division.

NetPhos 2.0 for C. Elegans



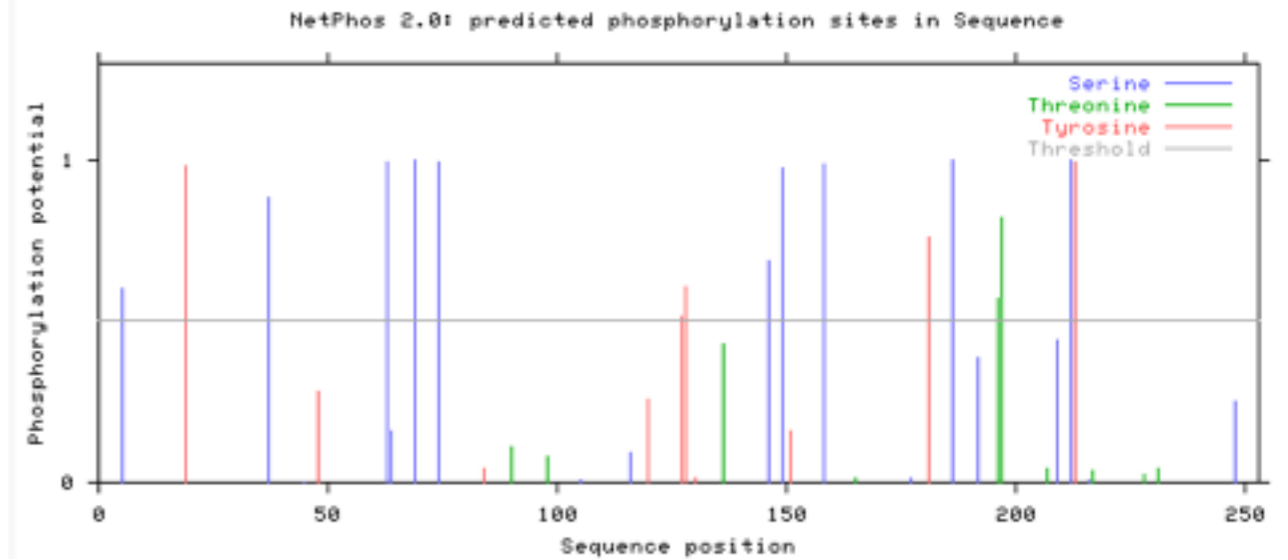
Rationale: To determine the well-conserved sites between organisms.

PTM sites are well-conserved across multiple organisms.

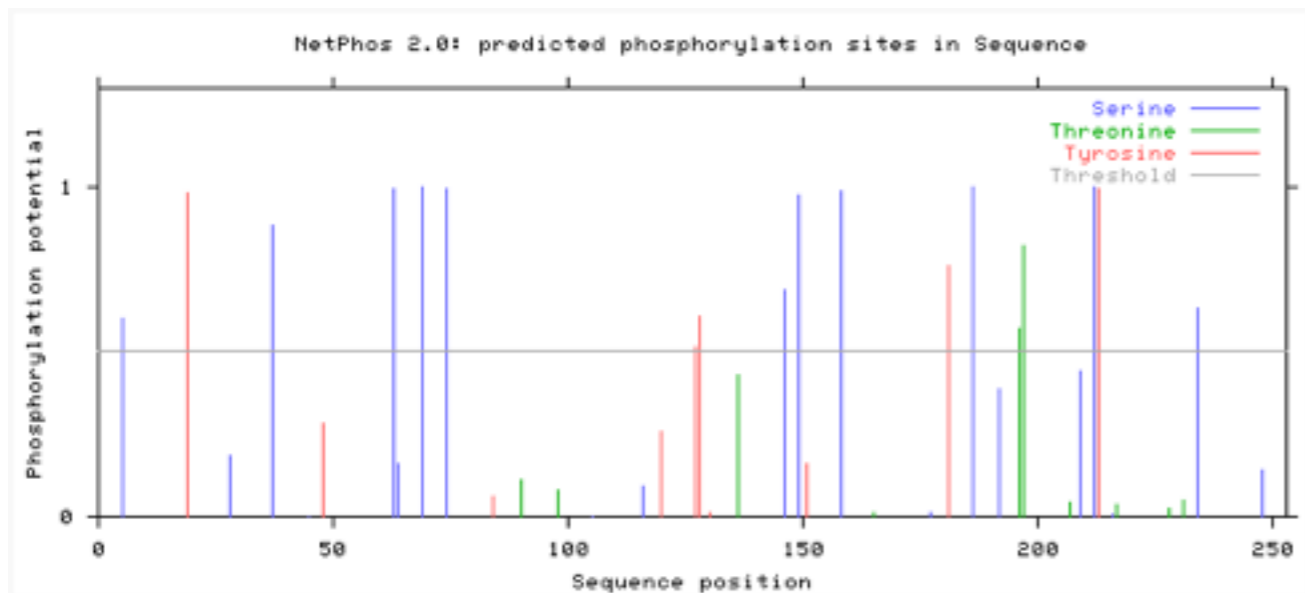


Human

Mouse



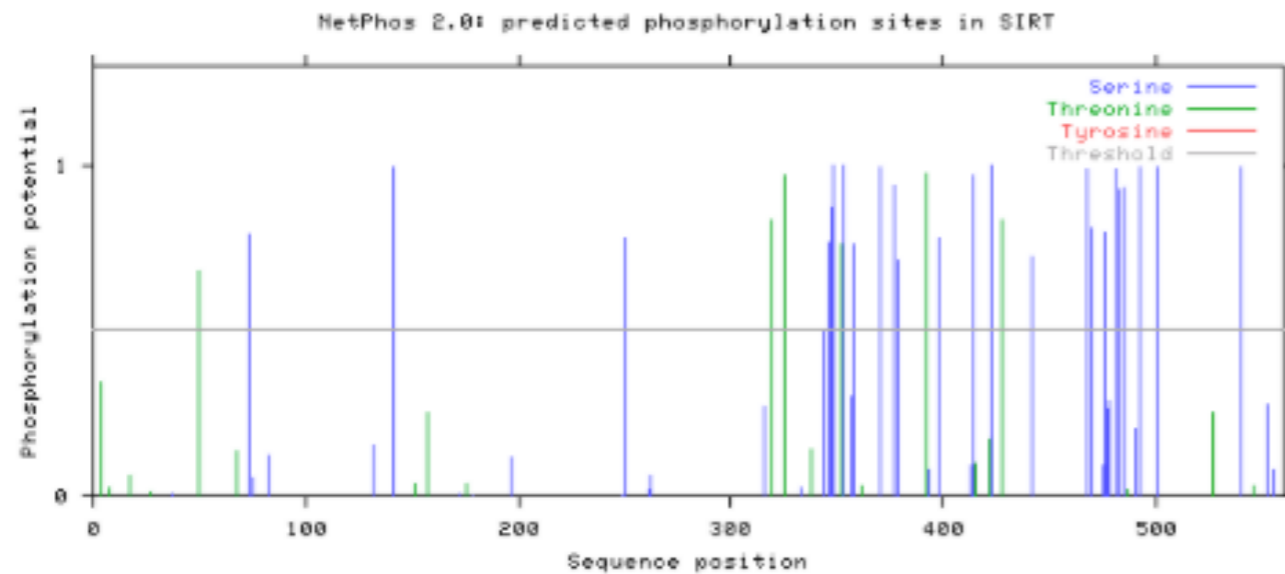
Rhesus Monkey



PTM sites are well-conserved across multiple proteins

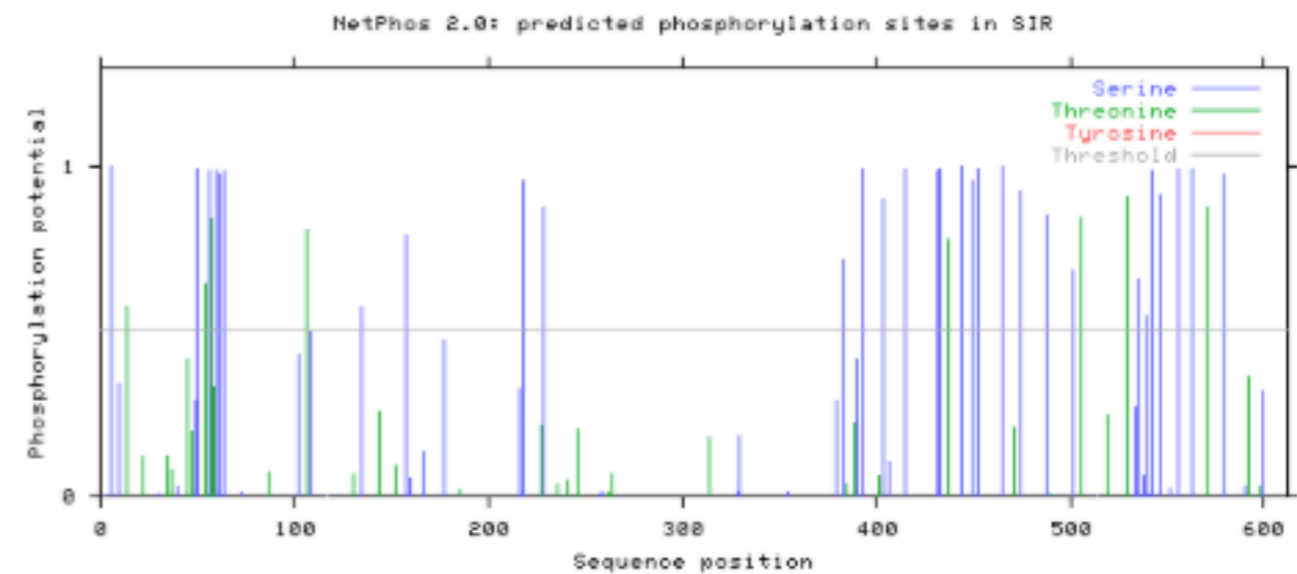
HUMAN

PHOSPHORYLATION SITES: SIRT1

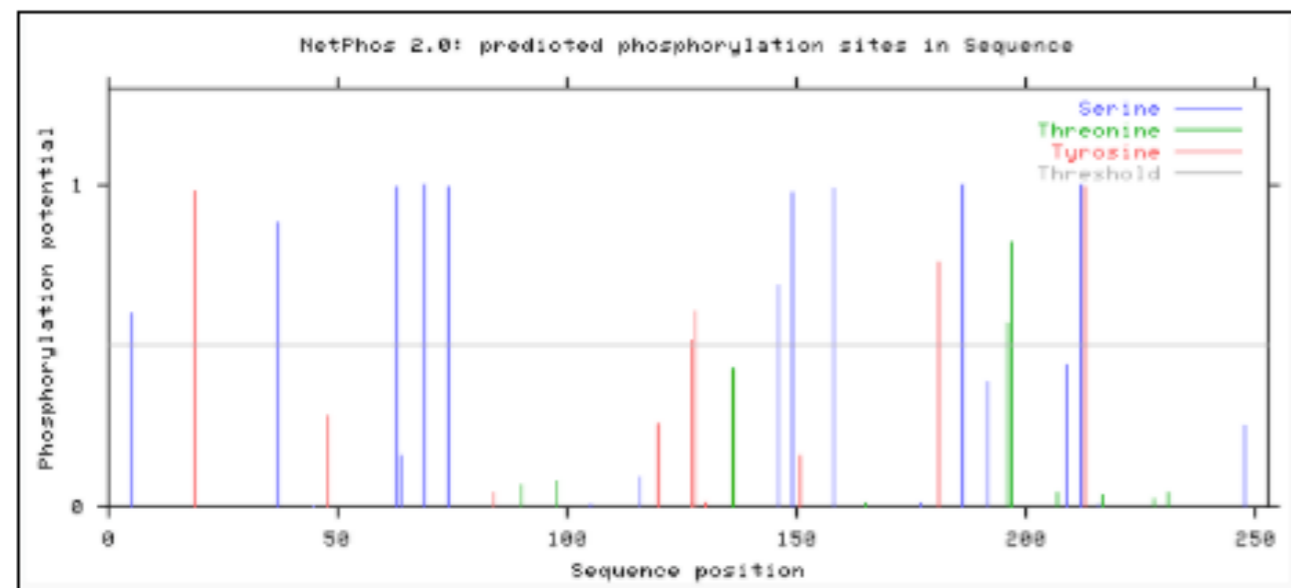


C. ELEGANS

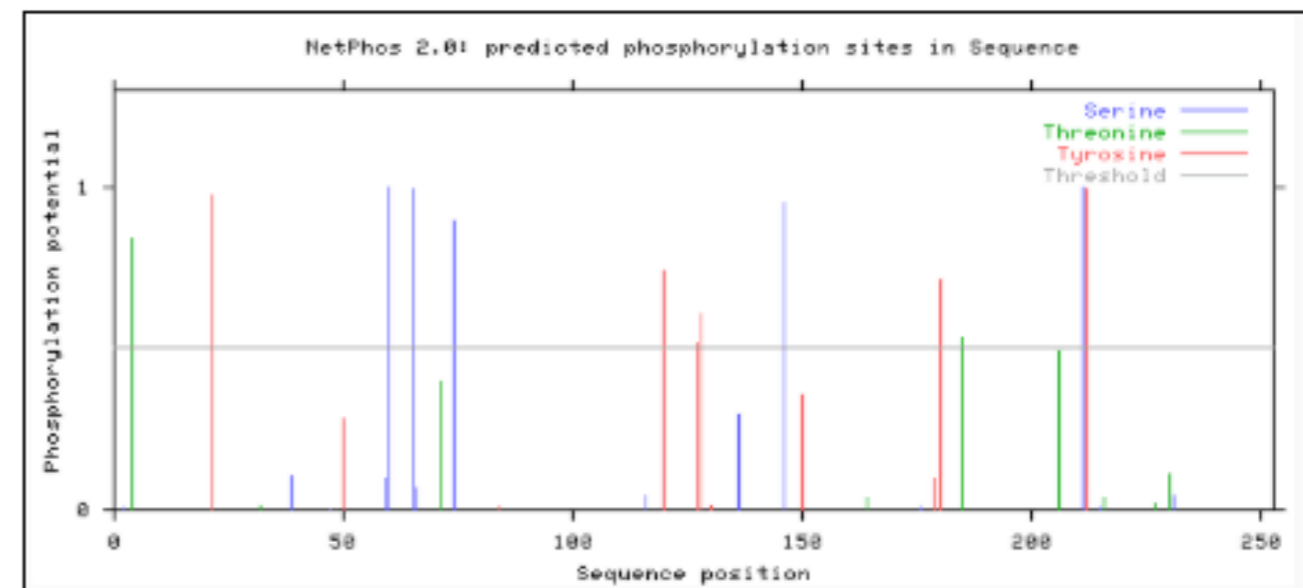
PHOSPHORYLATION SITES: SIR-2.1



PHOSPHORYLATION SITES: STRATIFIN



PHOSPHORYLATION SITES: PAR-5



Meme Motifs

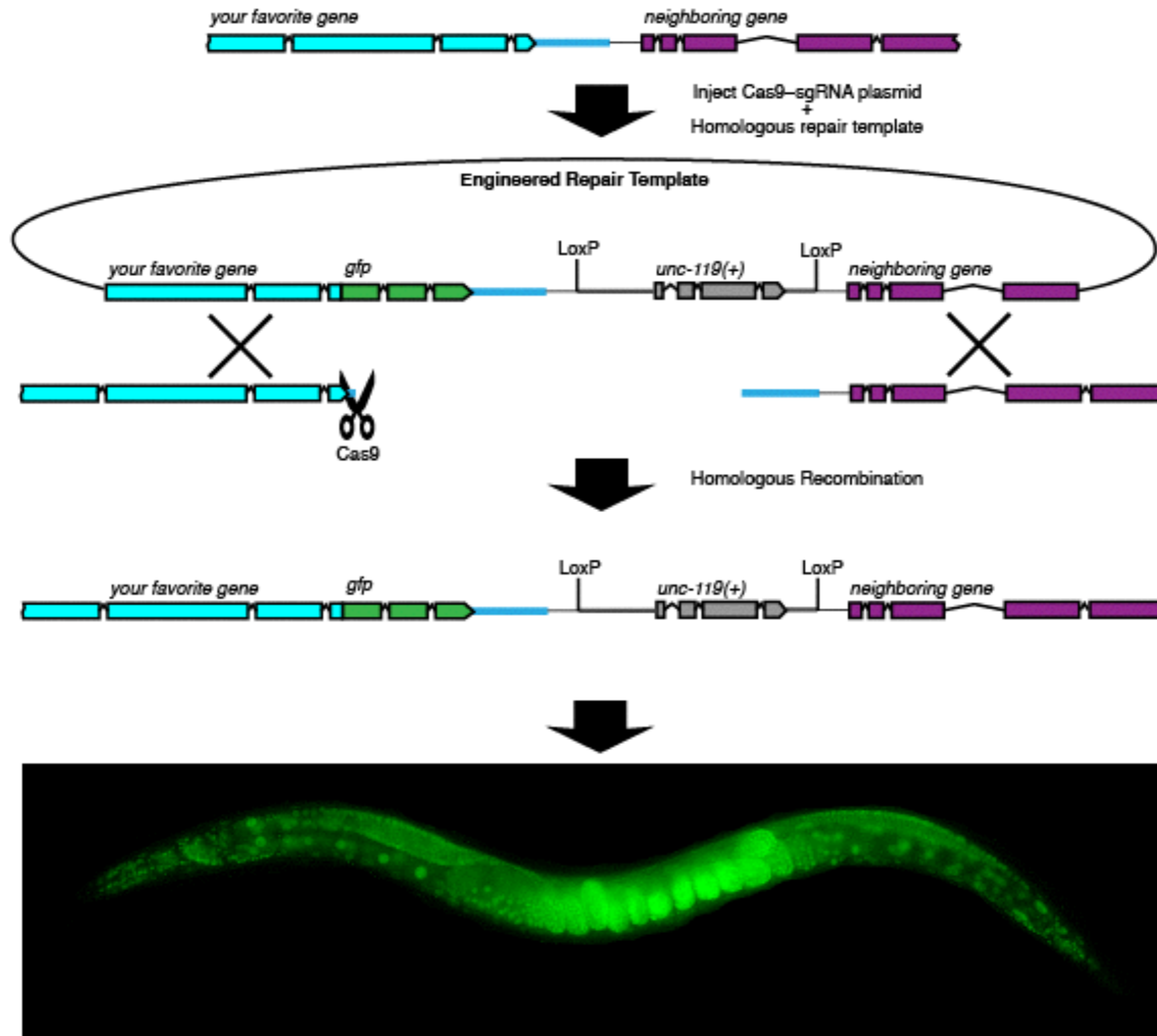
SIRT1 AND STRATIFIN MEME MOTIFS:



SIR-2.1 AND PAR-5 MEME MOTIFS:



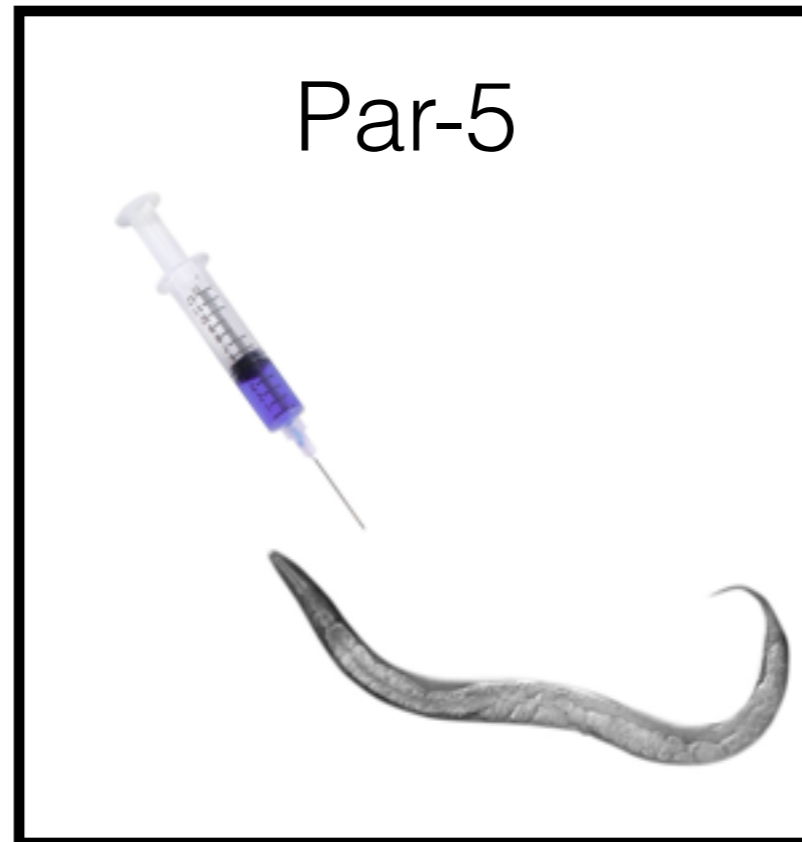
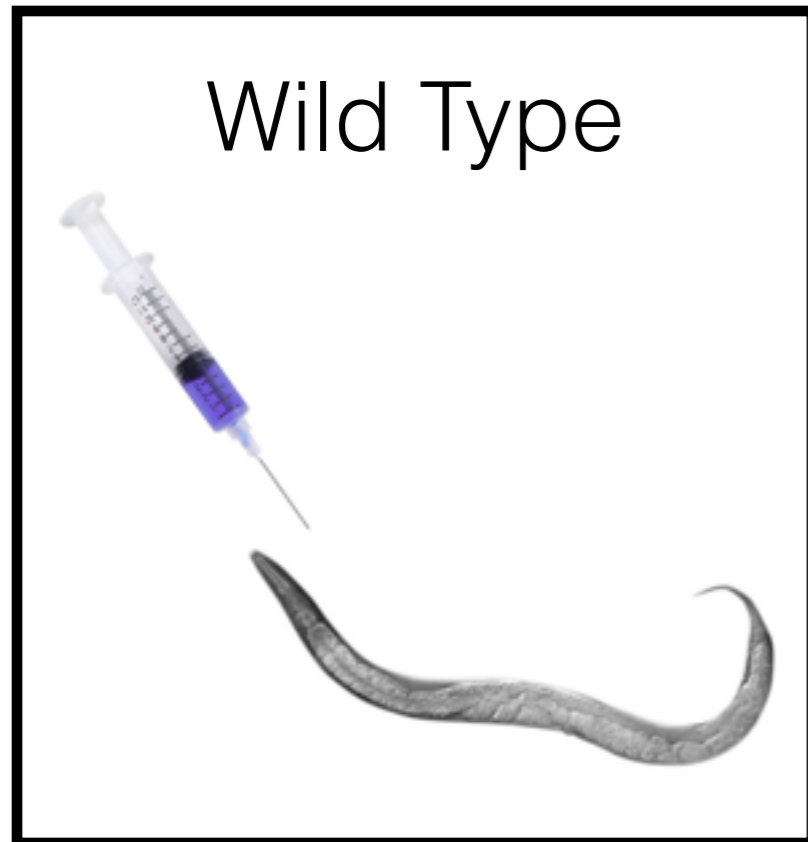
Aim 3: Determine which PAR-5 interacting proteins functions in cell division.



Rationale: Based on Aim 1 and 2, I can determine which proteins could be binding with PAR-5 at the phosphorylation sites to see how it affects development through CRISPR-Cas9.

Aim 3: Determine which PAR-5 interacting proteins functions in cell division.

Experiment:



Rationale: Using CRISPR-Cas9 with swapped amino acids at S/T binding sites observe the affect on development.

Possible Outcomes

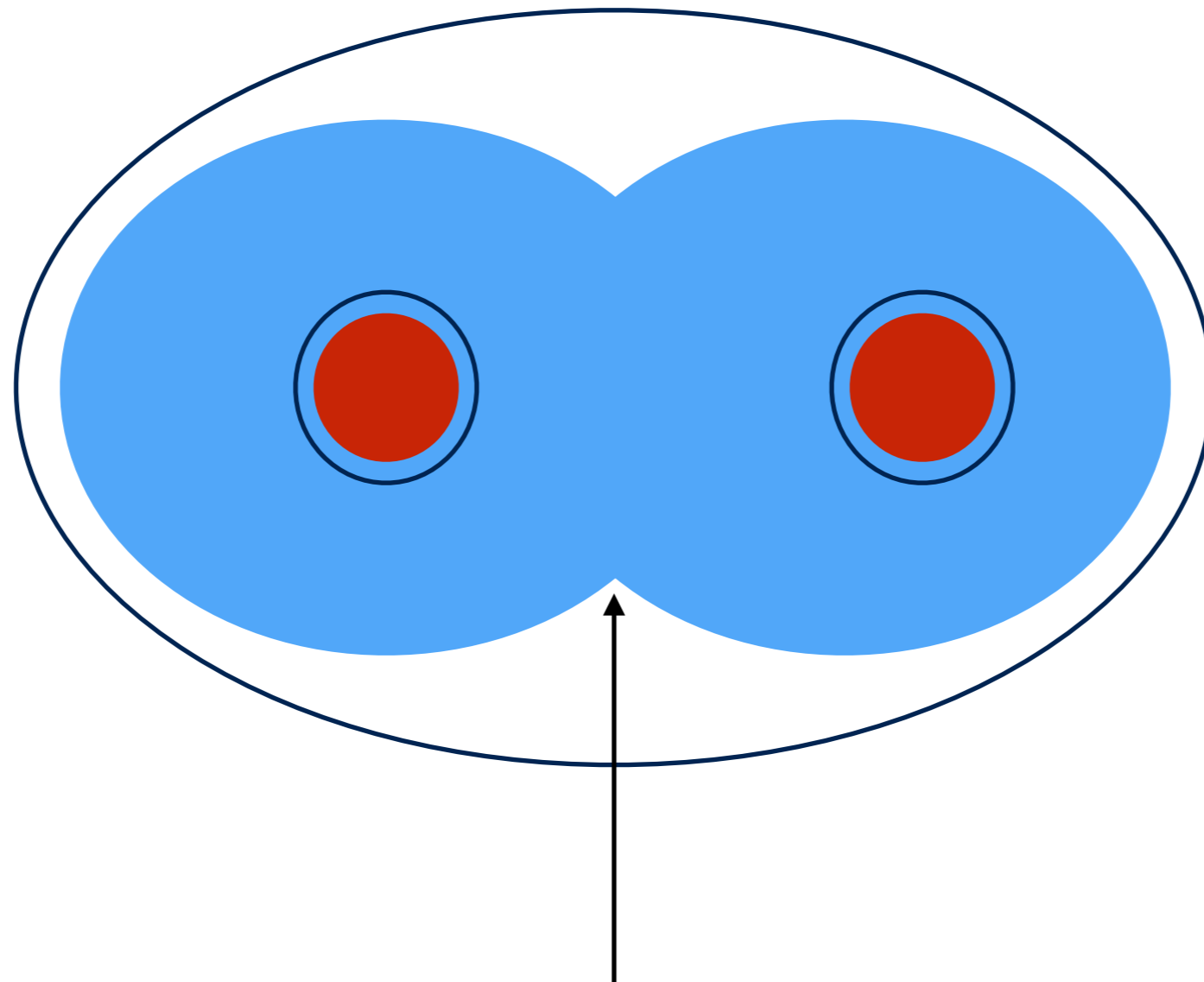


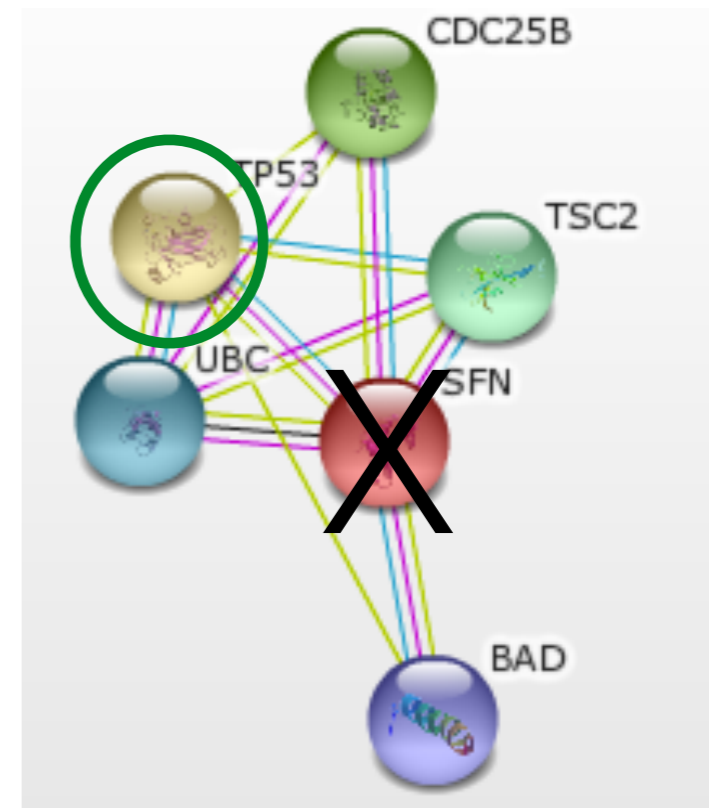
Figure out how to stop this from happening in cancer cells.

Future Directions

14-3-3sigma regulates cell division with the shared help of various binding partners and similar PTM'S

True

False



References

Aristizabal-Corrales, D., L. Fontrodona, M. Porta-de-la-Riva, A. Guerra-Moreno, J. Ceron *et al.*, 2012 The 14-3-3 gene *par-5* is required for germline development and DNA damage response in *Caenorhabditis elegans*. *Journal of Cell Science* 125: 1716-1726.

Aristizabal-Corrales, D., S. Schwartz, Jr. and J. Ceron, 2013 PAR-5 is a PARty hub in the germline: Multitask proteins in development and disease. *Worm* 2: e21834-e21834.

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