Chronic Lymphocytic Leukemia

&

ATM

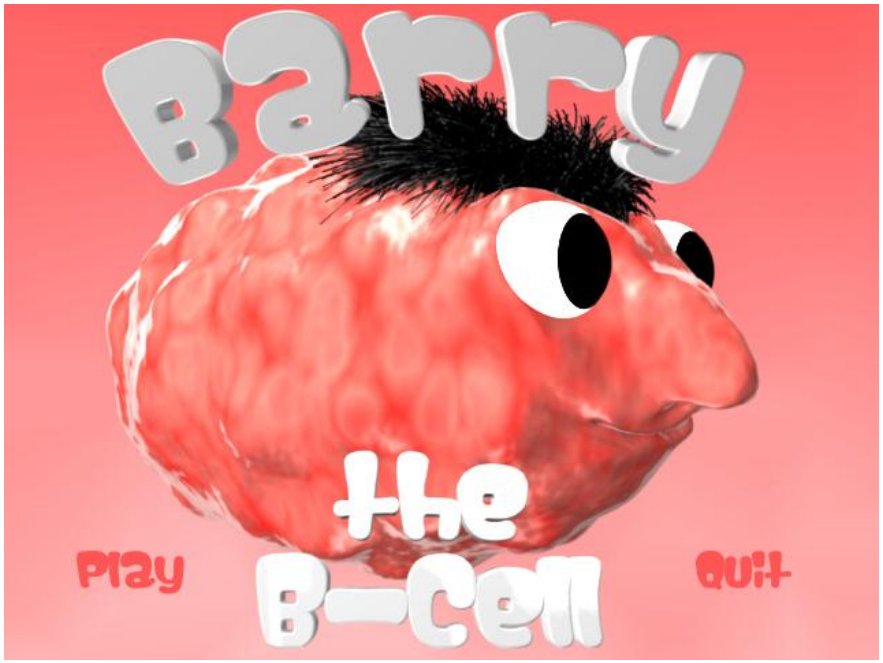
Nick Wleklinski

http://www.inab.org/news/icgc-with-inb-participation-published-in-nature-genetics/

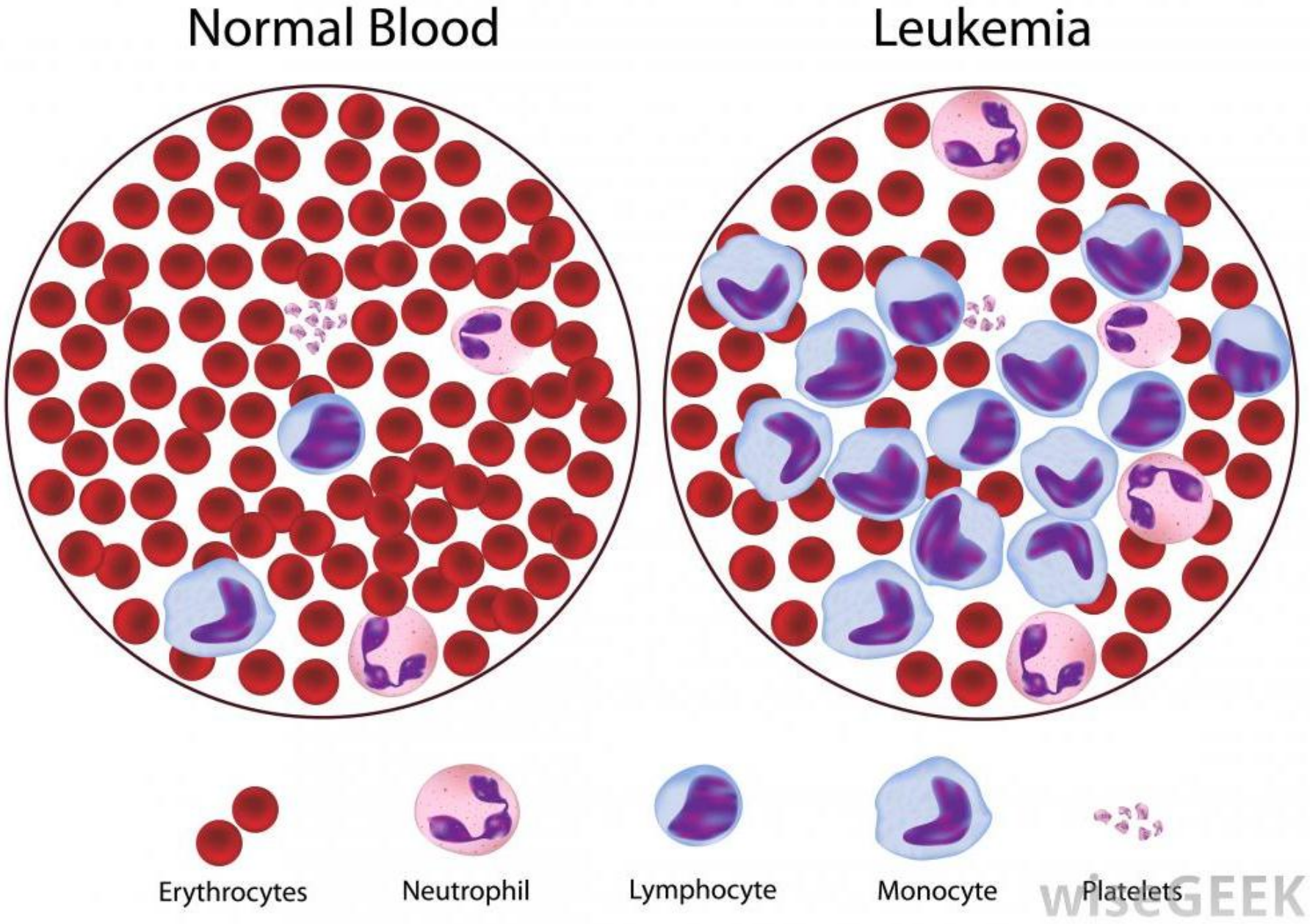
Chronic Lymphocytic Leukemia

Most common leukemia in the Western world

Apoptosis defective B-cells



http://blenderartists.org/forum/showthread.php?99299-Game-Barry-the-B-Cell



http://classconnection.s3.amazonaws.com/739/flashcards/1135739/jpg/9108605-leukemia-versus-normal-blood-eps81328714784885.jpg

Treatment: Chemotherapy

1

2

3

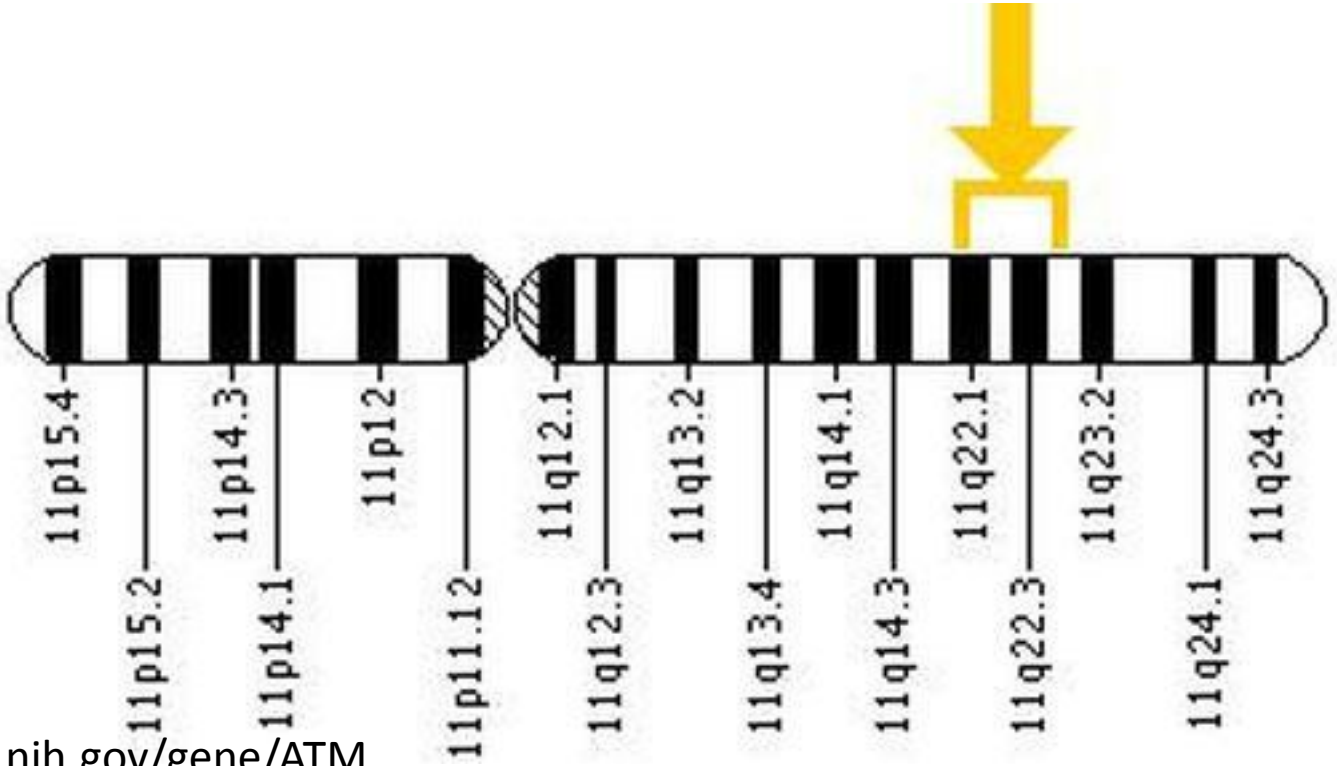
1. http://www.123rf.com/photo_14827589_biohazard-cytotoxic-and-chemotherapy-symbols-icons.html
2. http://badbreeders.net/tag/chemotherapy-drugs/
3. http://www.guardian.co.uk/society/2011/dec/06/cancer-patients-welfare-work-tests

A subset of CLL patients: 11q-

Deletions involving long (q) arm of chromosome 11

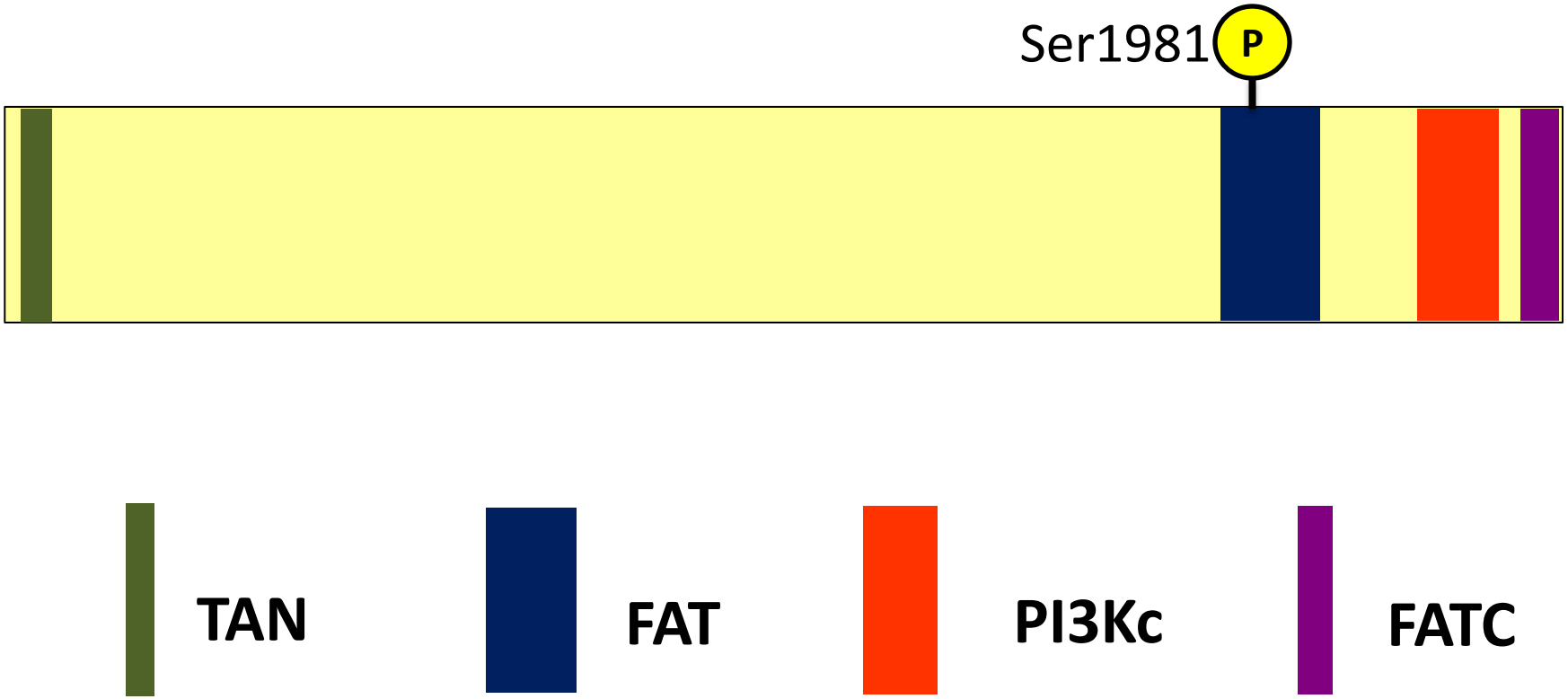
Genes of focus- **Ataxia Telangiectasia Mutated**

More aggressive disease → Chemoresistance

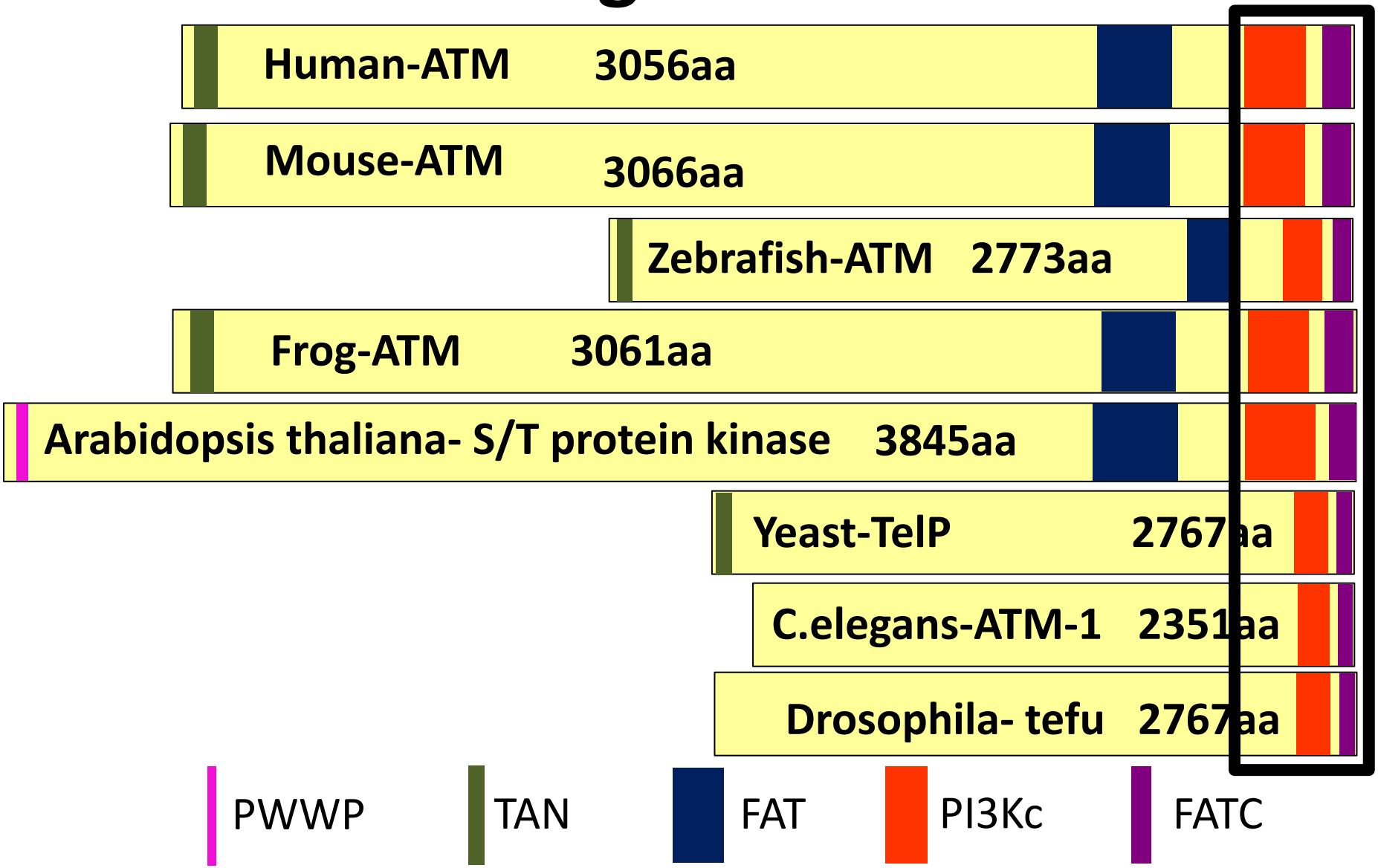


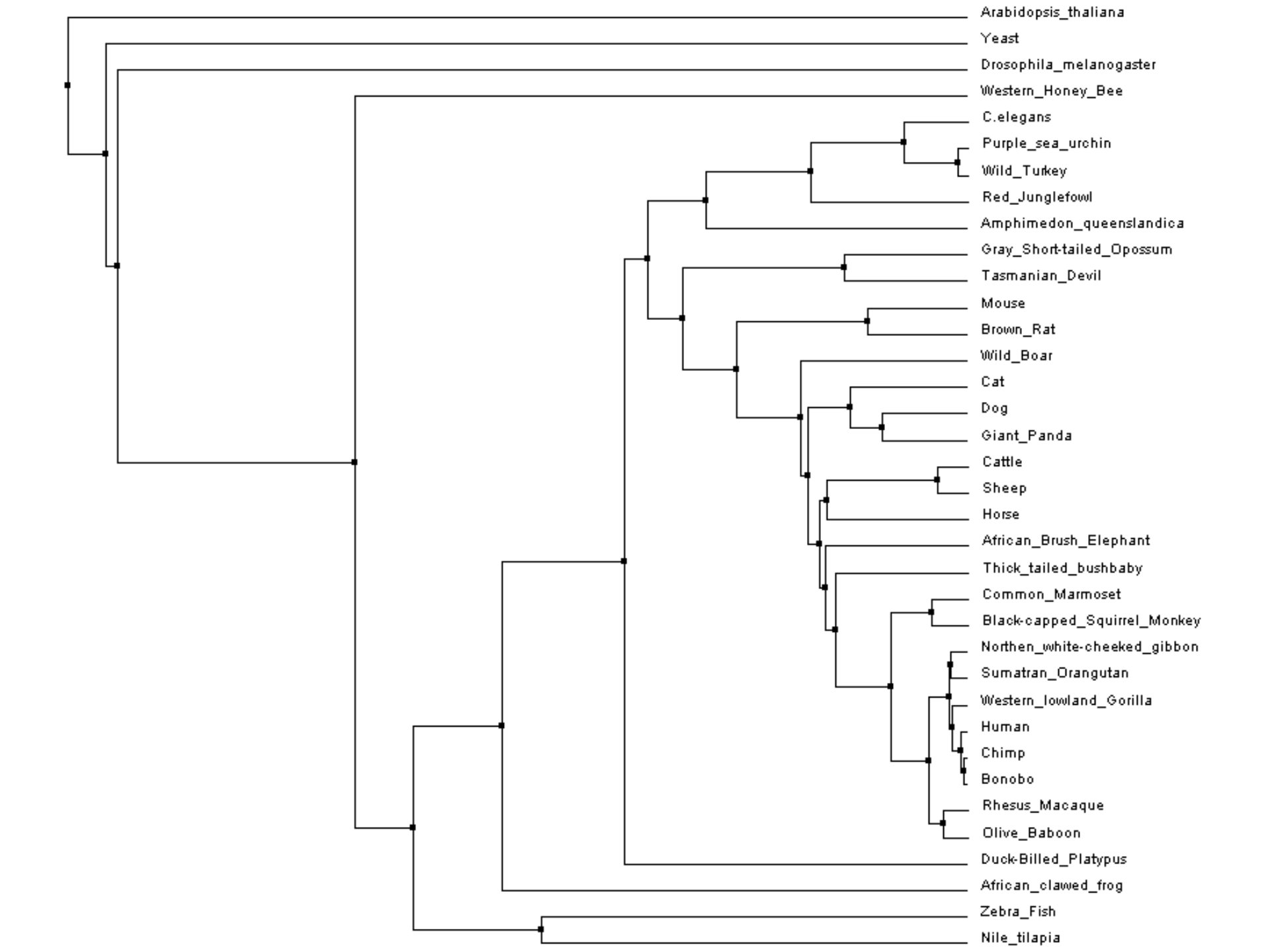
http://ghr.nlm.nih.gov/gene/ATM

ATM is important in DNA repair

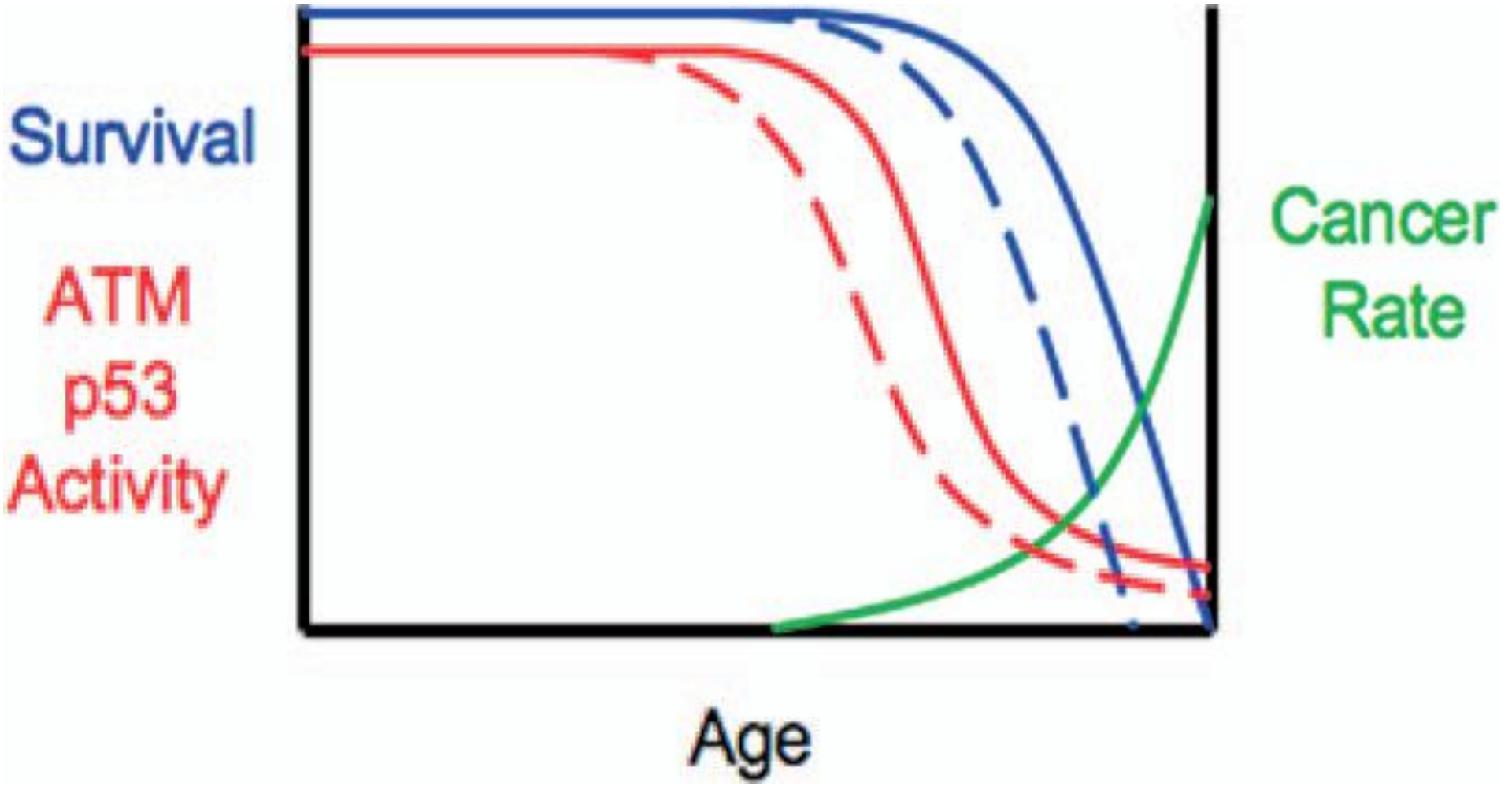


Comparing homologs in model organisms



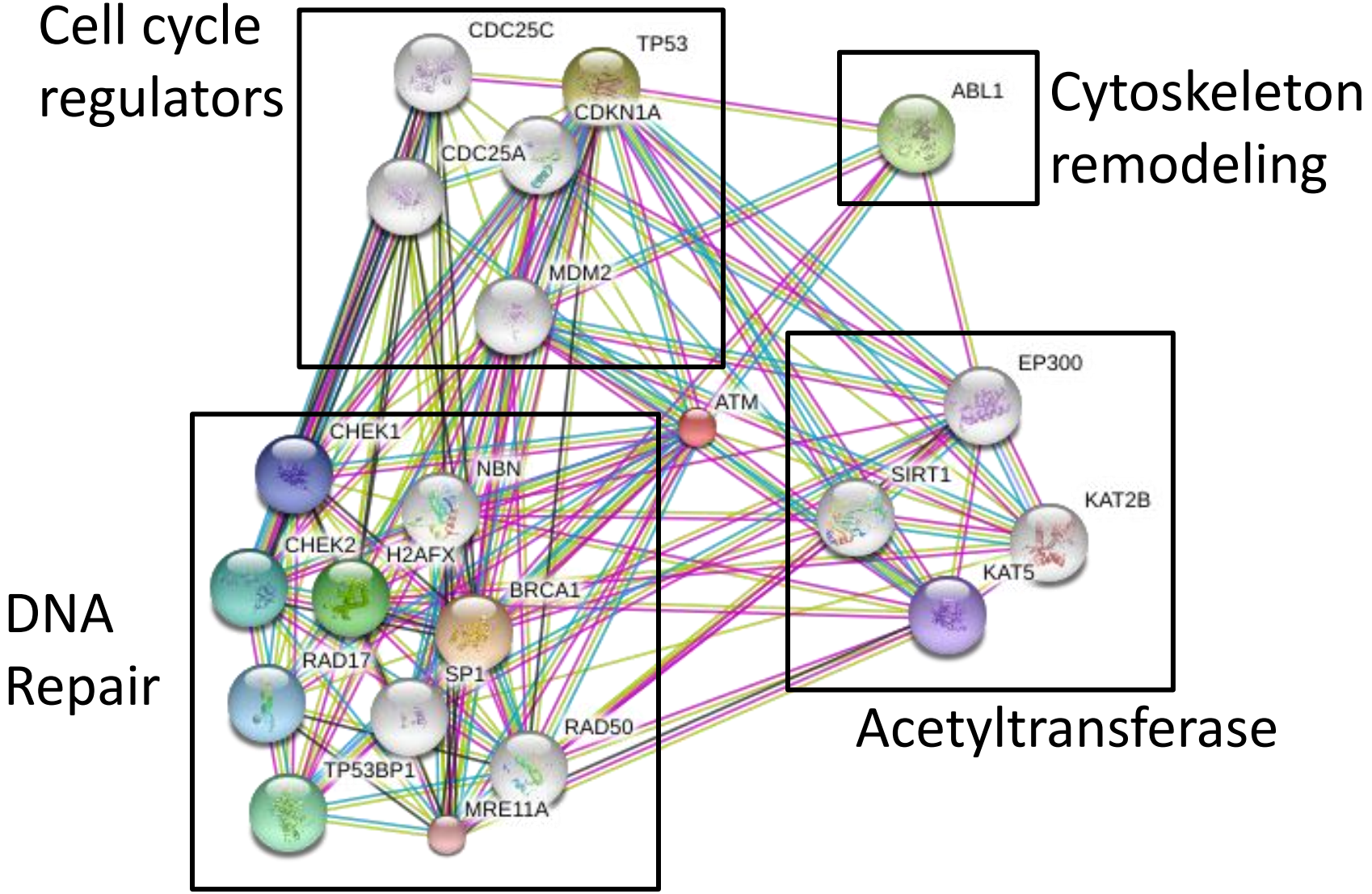

Arabidopsis_thaliana
Yeast
Drosophila_melanogaster
Western_Honey_Bee
C.elegans
Purple_sea_urchin
Wild_Turkey
Red_Junglefowl
Amphimedon_queenslandica
Gray_Short-tailed_Opossum
Tasmanian_Devil
Mouse
Brown_Rat
Wild_Boar
Cat
Dog
Giant_Panda
Cattle
Sheep
Horse
African_Brush_Elephant
Thick_tailed_bushbaby
Common_Marmoset
Black-capped_Squirrel_Monkey
Northen_white-cheeked_gibbon
Sumatran_Orangutan
Western_lowland_Gorilla
Human
Chimp
Bonobo
Rhesus_Macaque
Olive_Baboon
Duck-Billed_Platypus
African_clawed_frog
Zebra_Fish
Nile_tilapia

Decrease in ATM function leads to increased cancer rate

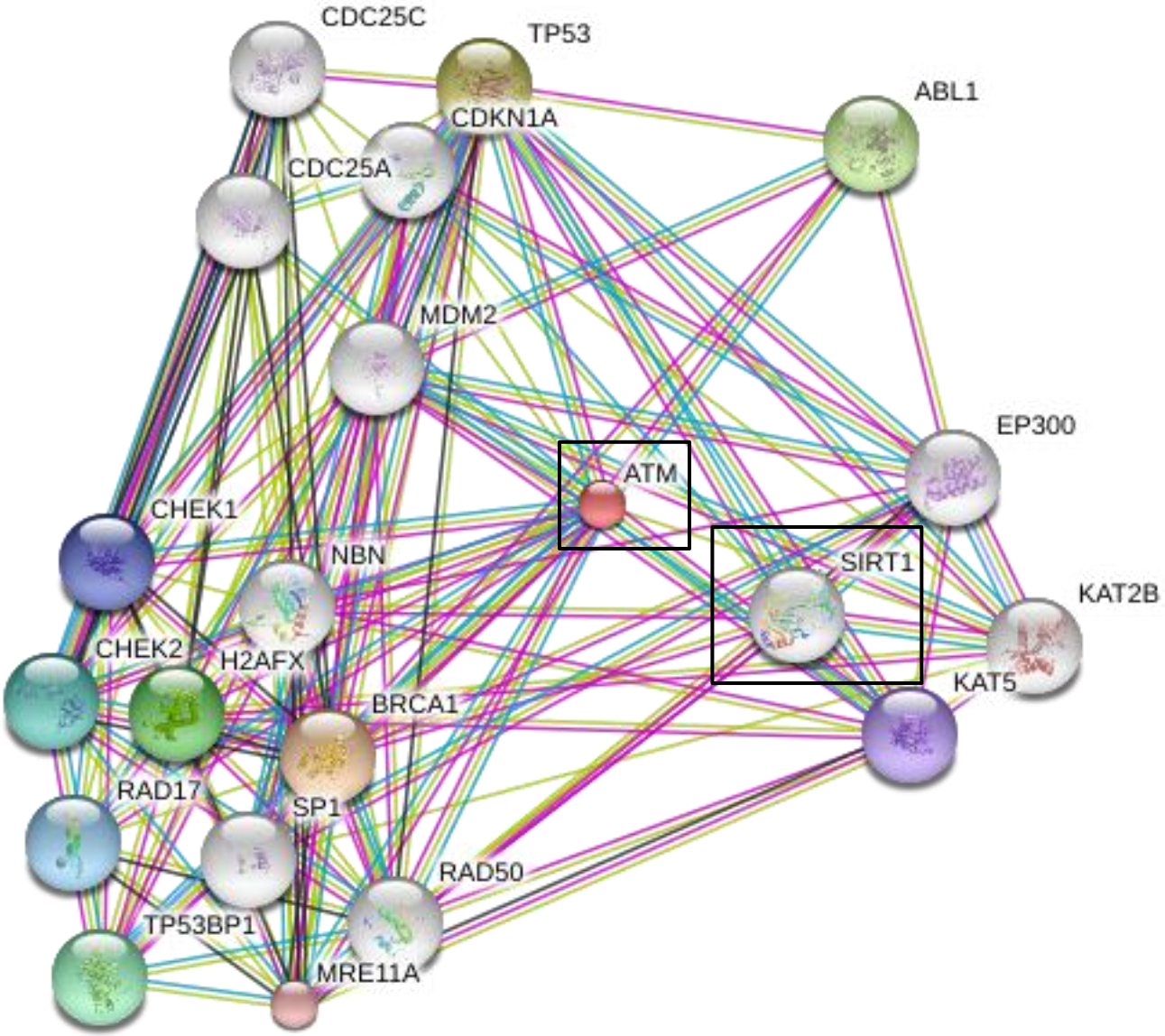


Hinkal, G., & Donehower, L. A. (2007). Decline and fall of the tumor suppressor. *PNAS, 104*(47), 18347-18348. doi:10.1073/pnas.0709330104

ATM interacts with cell maintenance proteins



SIRT1 is known to be involved in cancer



What is Sirtuin 1?

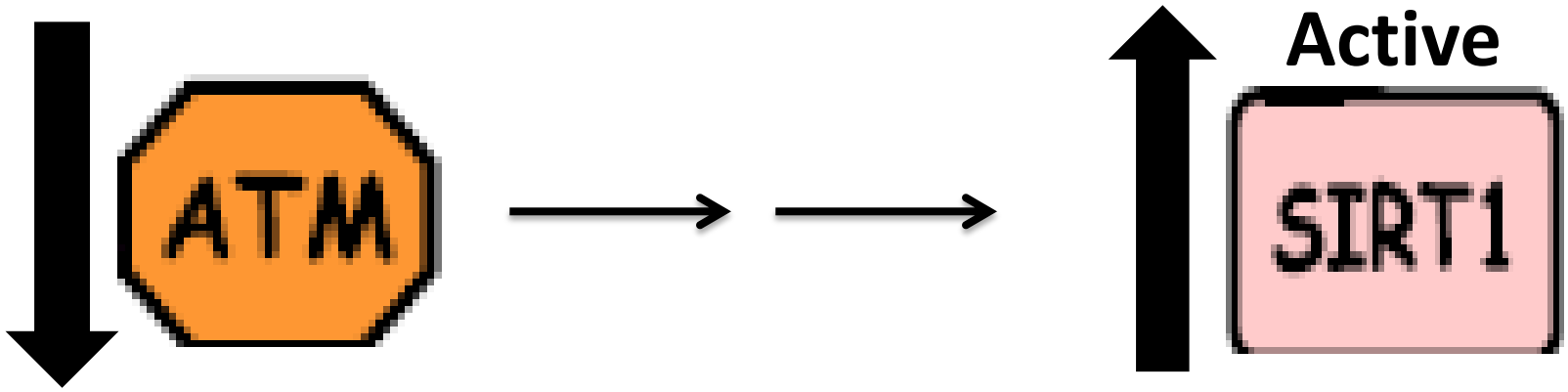
Enzymatic Activities	Primary Localization
Deacetylase	Nucleus

Involved in autophagy and aging of cells

Acts as tumor suppressor and oncogene

Roth, M., & Chen, W. (2013). Sorting out functions of sirtuins in cancer. *Oncogene*, 1-12. doi:10.1038/onc.2013.120

ATM regulates activity of SIRT1 post-translationally

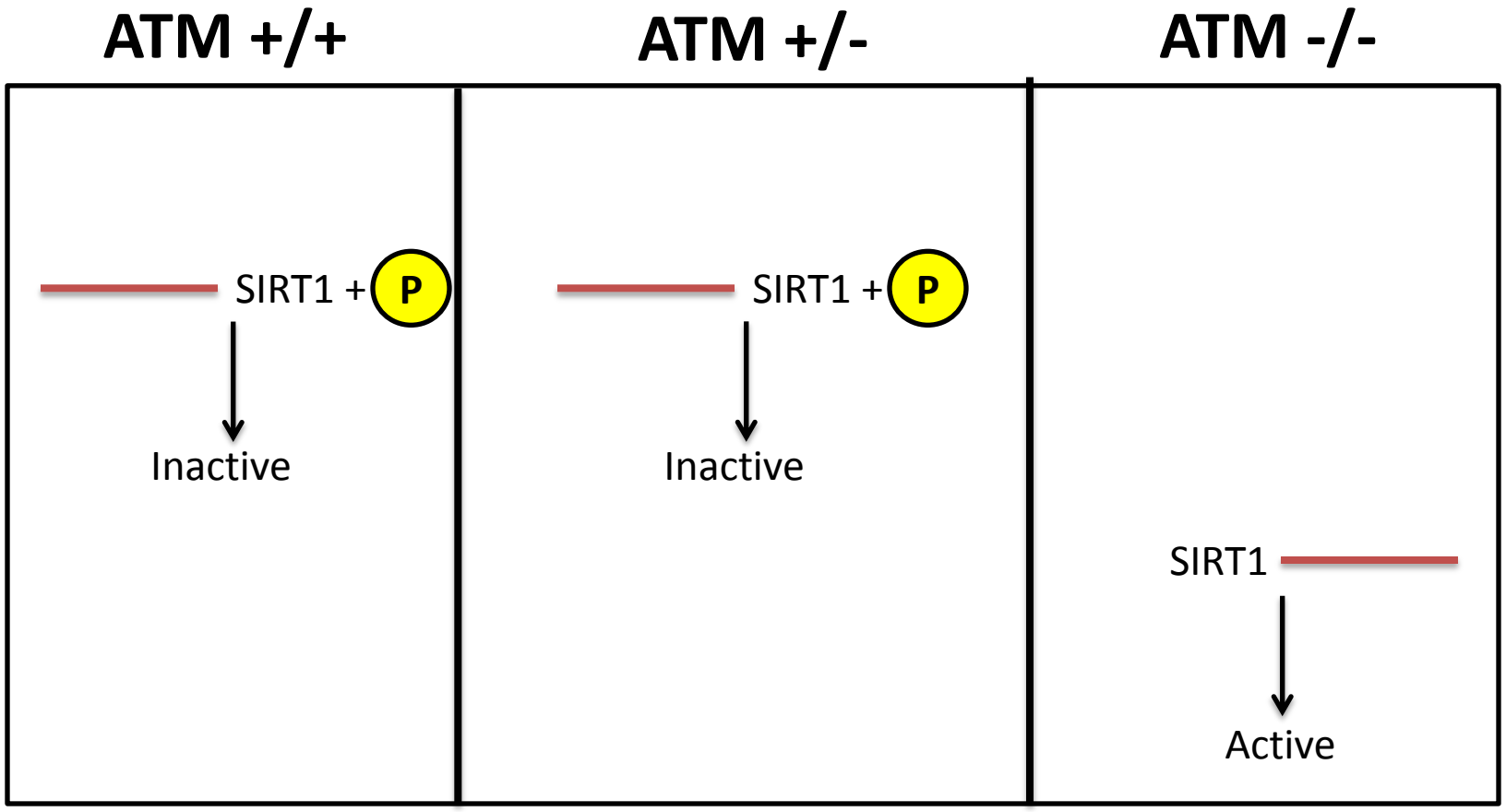


Yuan, J., Luo, K., Liu, T., & Lou, Z. (2012). Regulation of SIRT1 activity by genotoxic stress. *Genes and development, 26*, 791-796. doi:10.1101/gad.188482.112

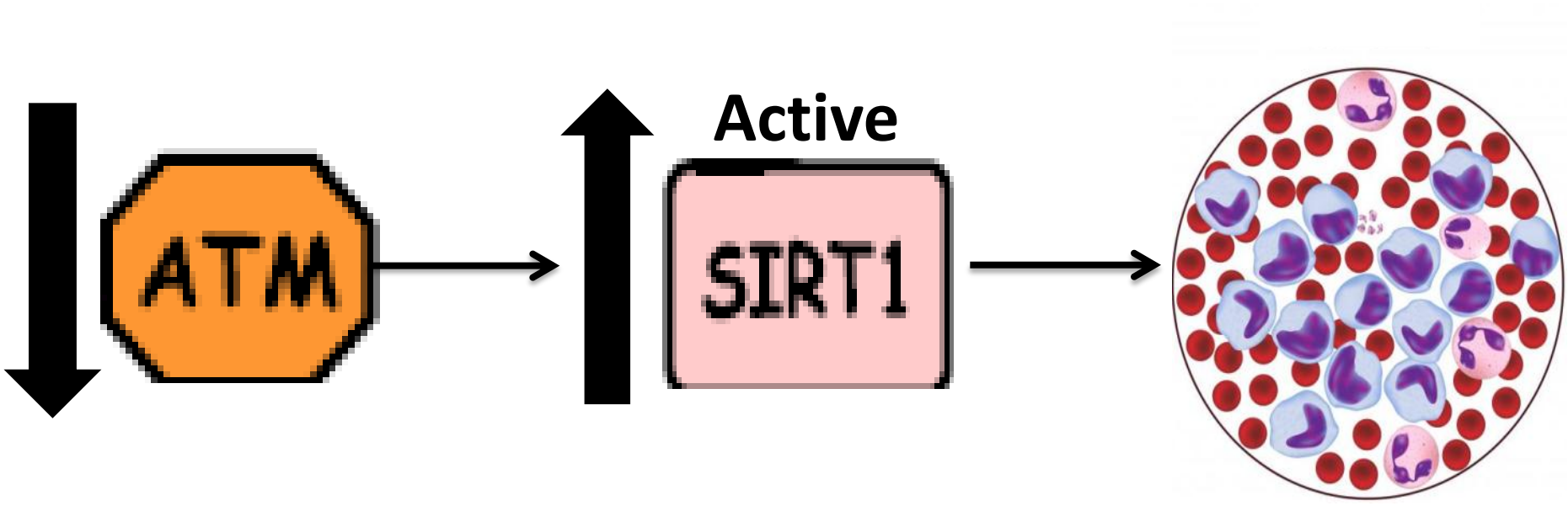
Hypothesis 1: Sirtuin 1 levels are not regulated properly in ATM -/- cells

Are levels of active Sirtuin1 elevated in ATM -/- cells?

Expect results from 2D gel:



Why is this important?



↑ Autophagy → Reduced sensitivity to chemotherapy

Yuan, J., Luo, K., Liu, T., & Lou, Z. (2012). Regulation of SIRT1 activity by genotoxic stress. *Genes and development, 26*, 791-796. doi:10.1101/gad.188482.112

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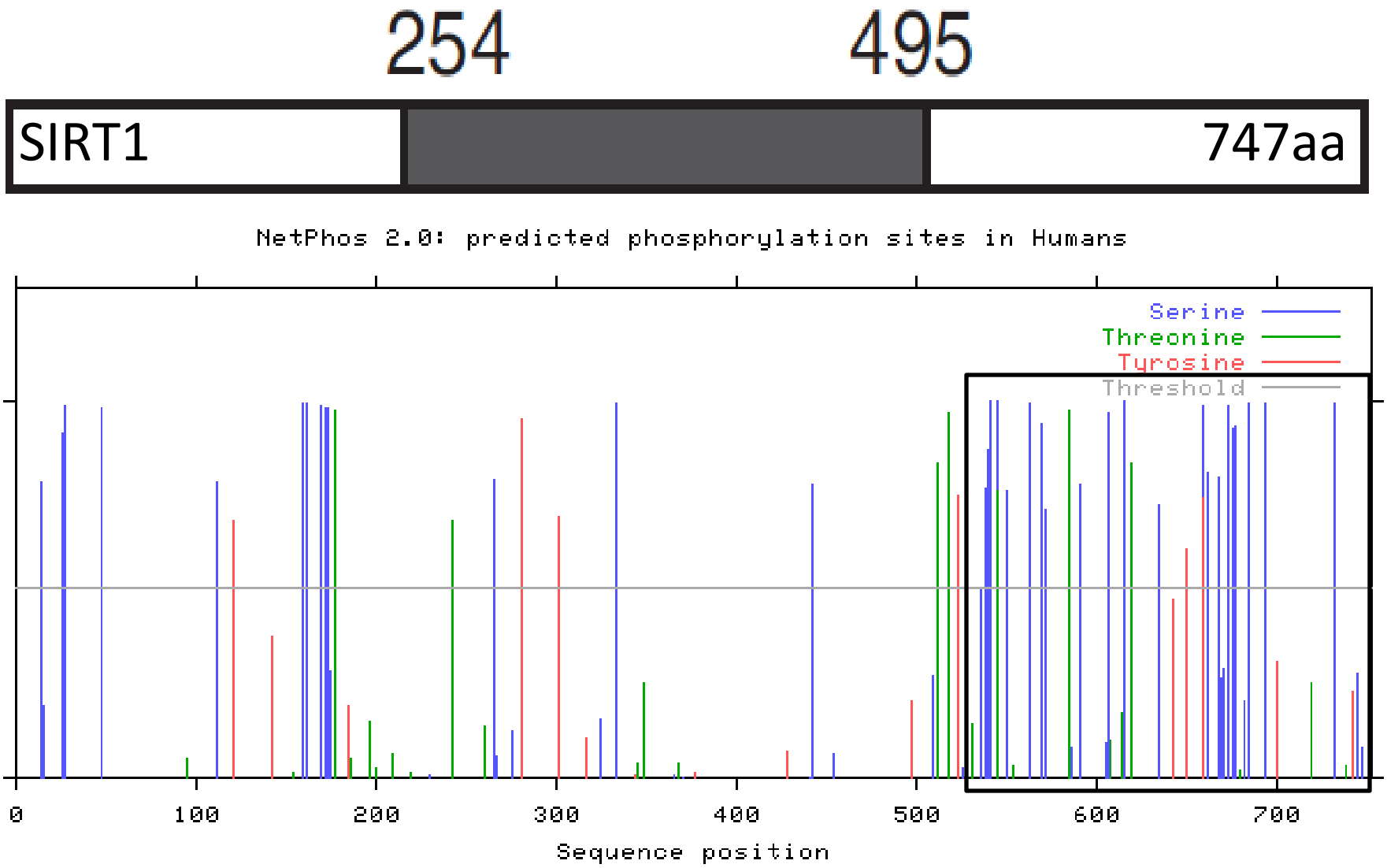
Hypothesis 2: Sirtuin 1 is regulated differently in the blood

Are there phosphorylation sites specific for SIRT1 activation in blood?



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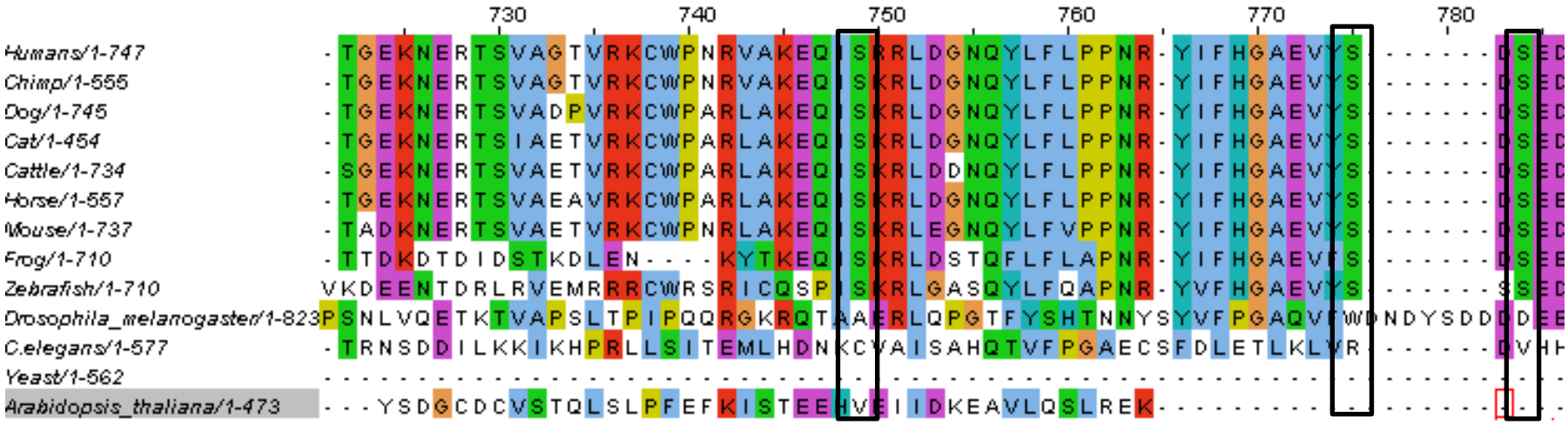
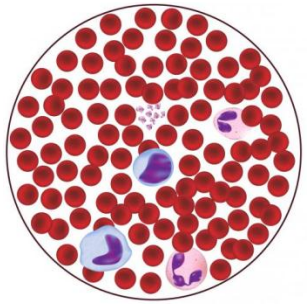


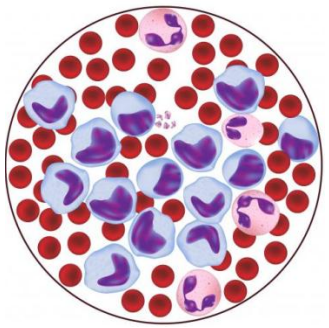
Disrupt these sites and see if they affect SIRT1 function

Inhibiting SIRT1 function in leukemic cells should reduce leukemic cell population

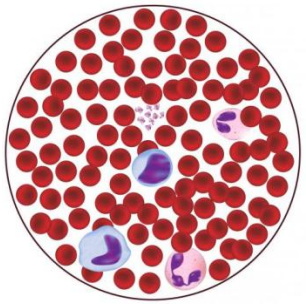
ATM+/+ | SIRT1 +/+ ⟶



ATM-/- | SIRT1 +/+ ⟶

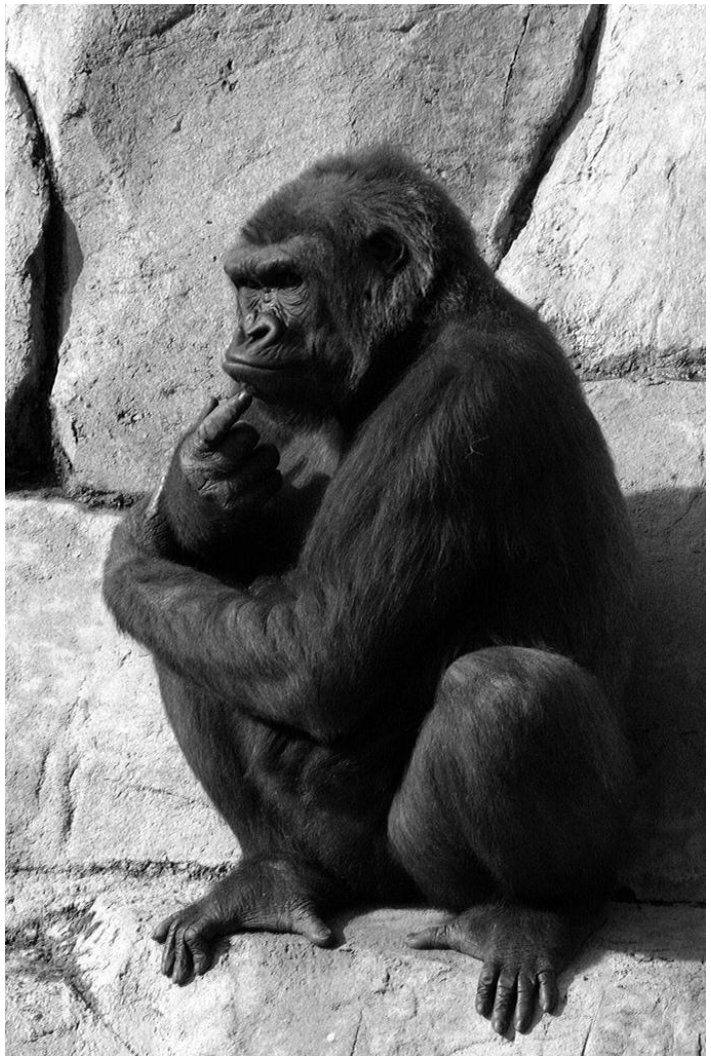


ATM -/- | SIRT1 -/- ⟶



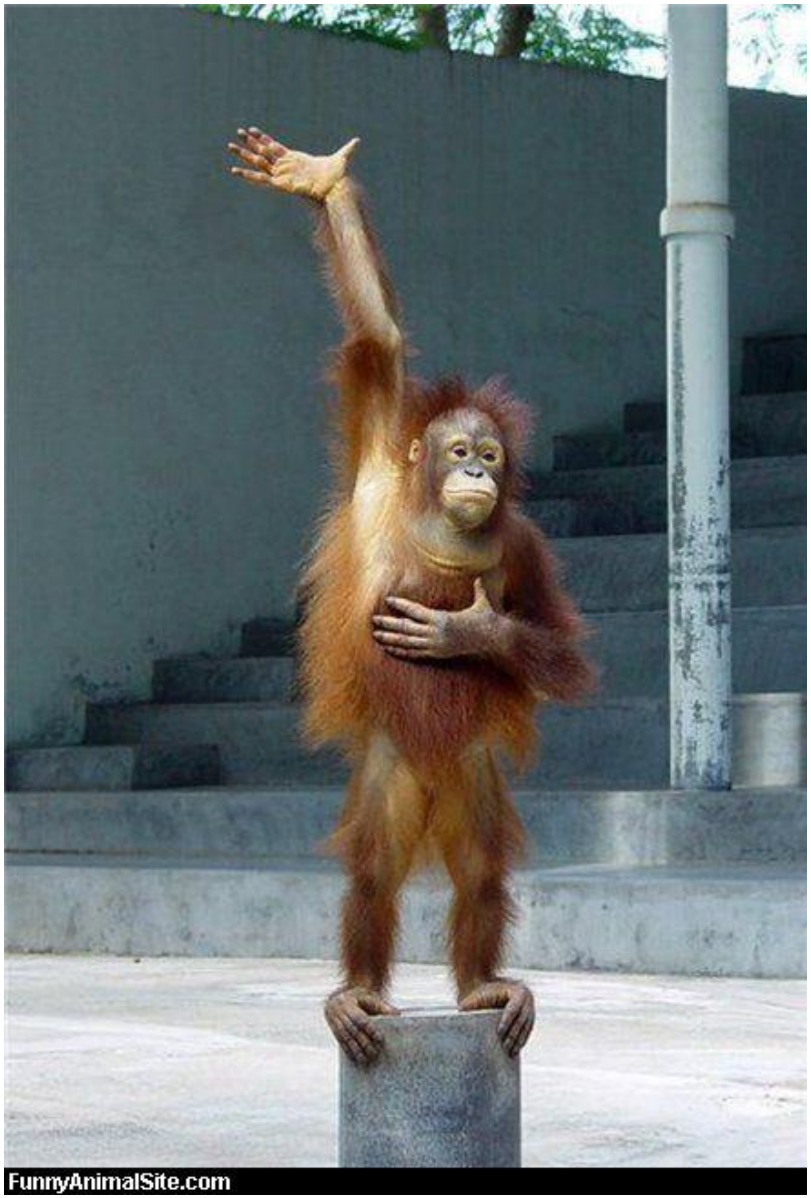
Where do we go from here?

- Do chemical genetic screens to look for drugs that interact with blood specific phosphorylation site on SIRT1
- Look at interaction of ATM with other sirtuins
- Incorporate SIRT1 inhibitors with chemotherapy for CLL patients with an 11q-



http://commons.wikimedia.org/wiki/File:Deep_in_thought.jpg

Questions?



http://reknown.com/2011/08/test-your-social-media-savvy/