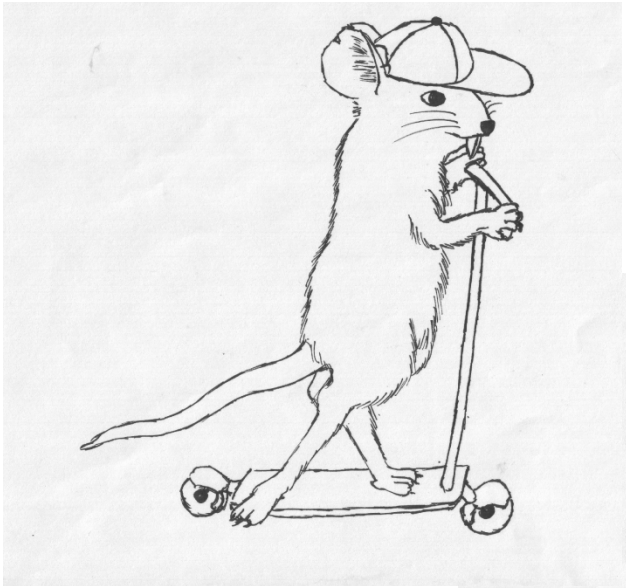
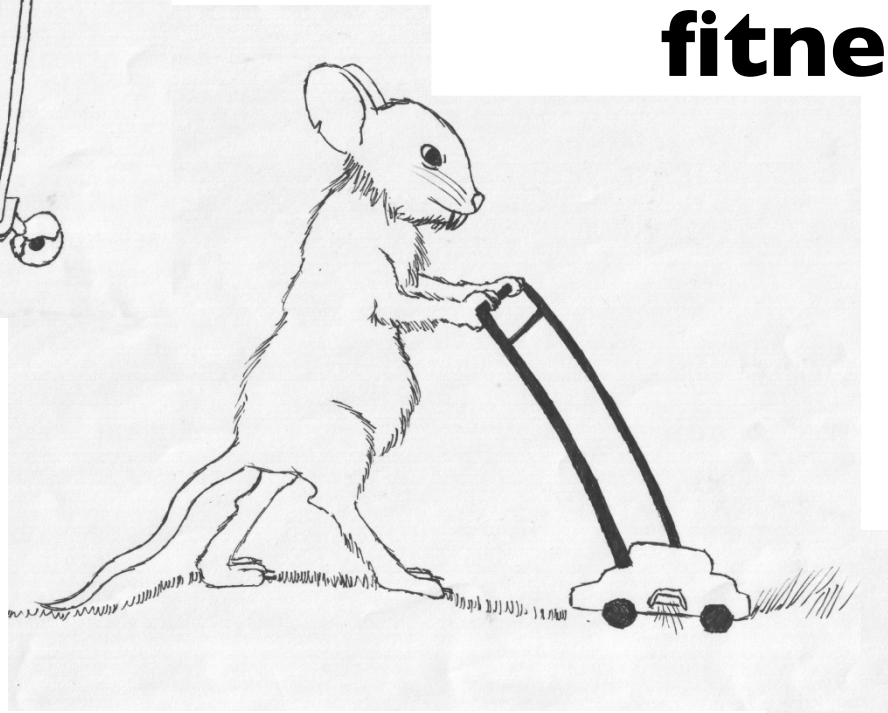
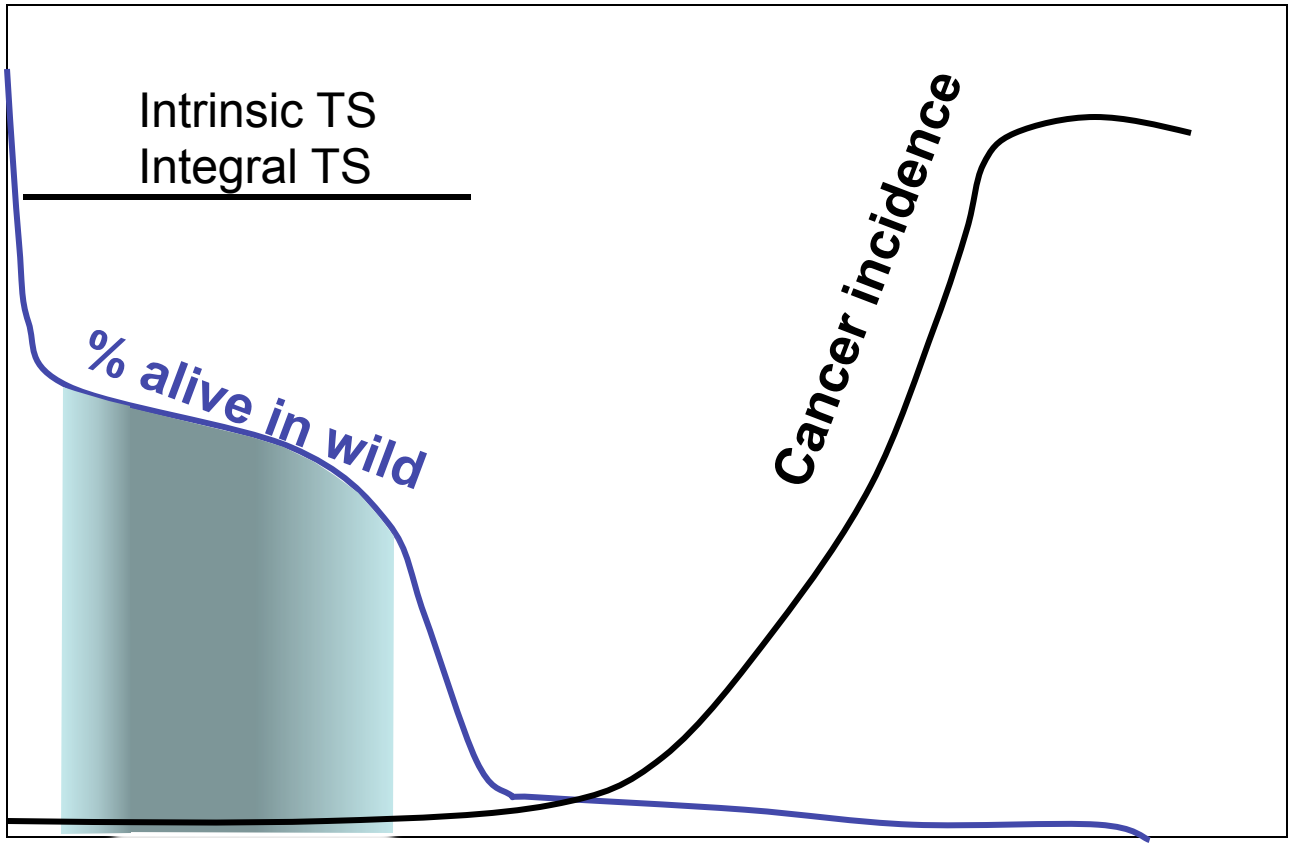


Tumor suppression by modulating stem cell fitness



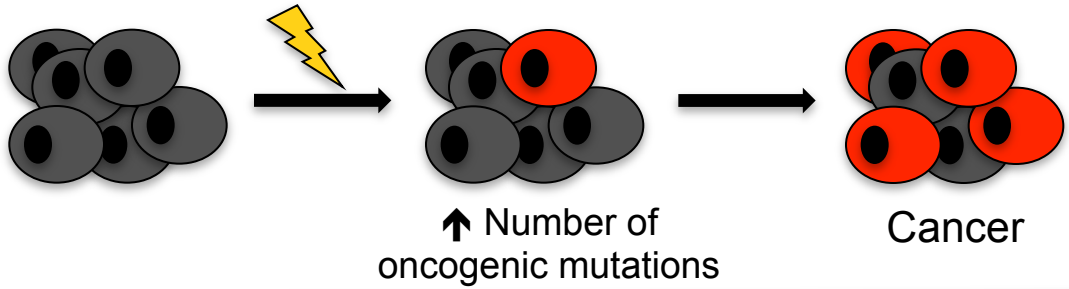
James DeGregori
University of Colorado Denver
School of Medicine

Natural Selection can explain cancer incidence at the species level

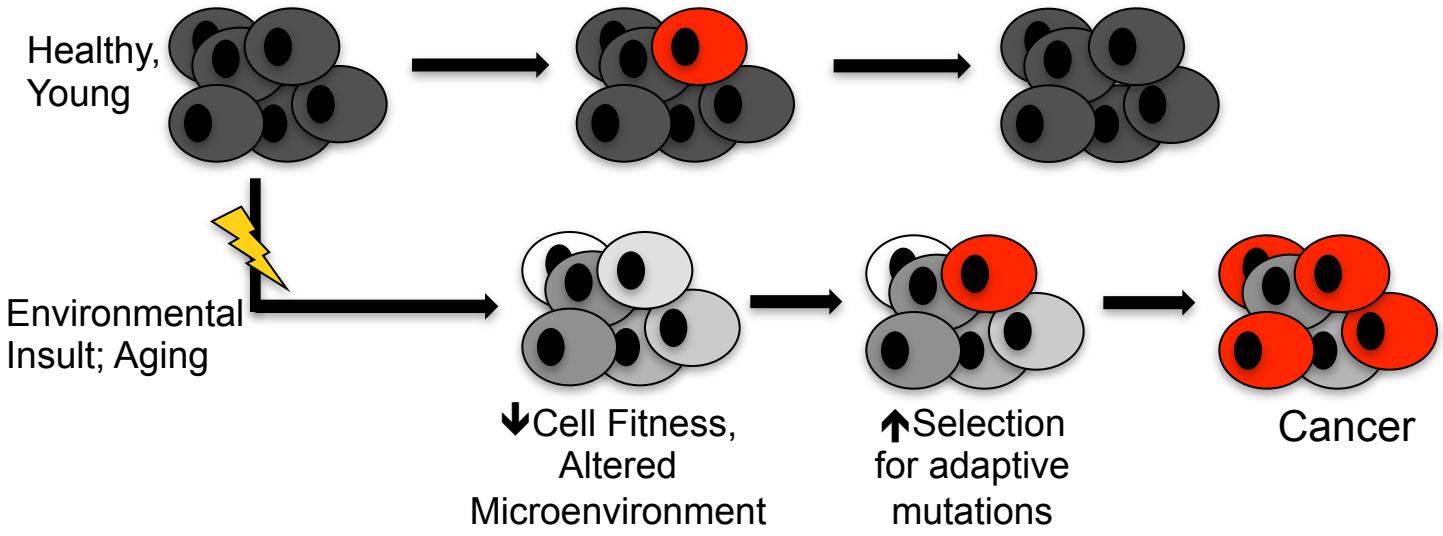


- The evolution of long-lived multicellular animals required the selection for potent tumor suppressive mechanisms.
- There is minimal selection against cancer beyond the age where most animals would already be dead by other causes.
- Better tumor suppression would require additional energy in early life, which would come with a cost.

Conventional View



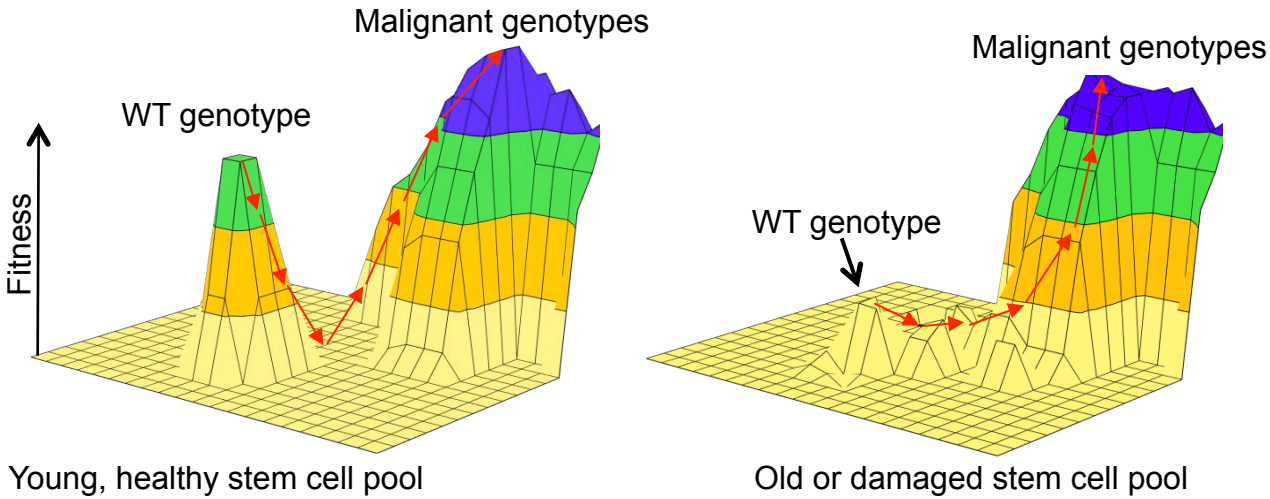
Adaptive Oncogenesis Model



Fitness

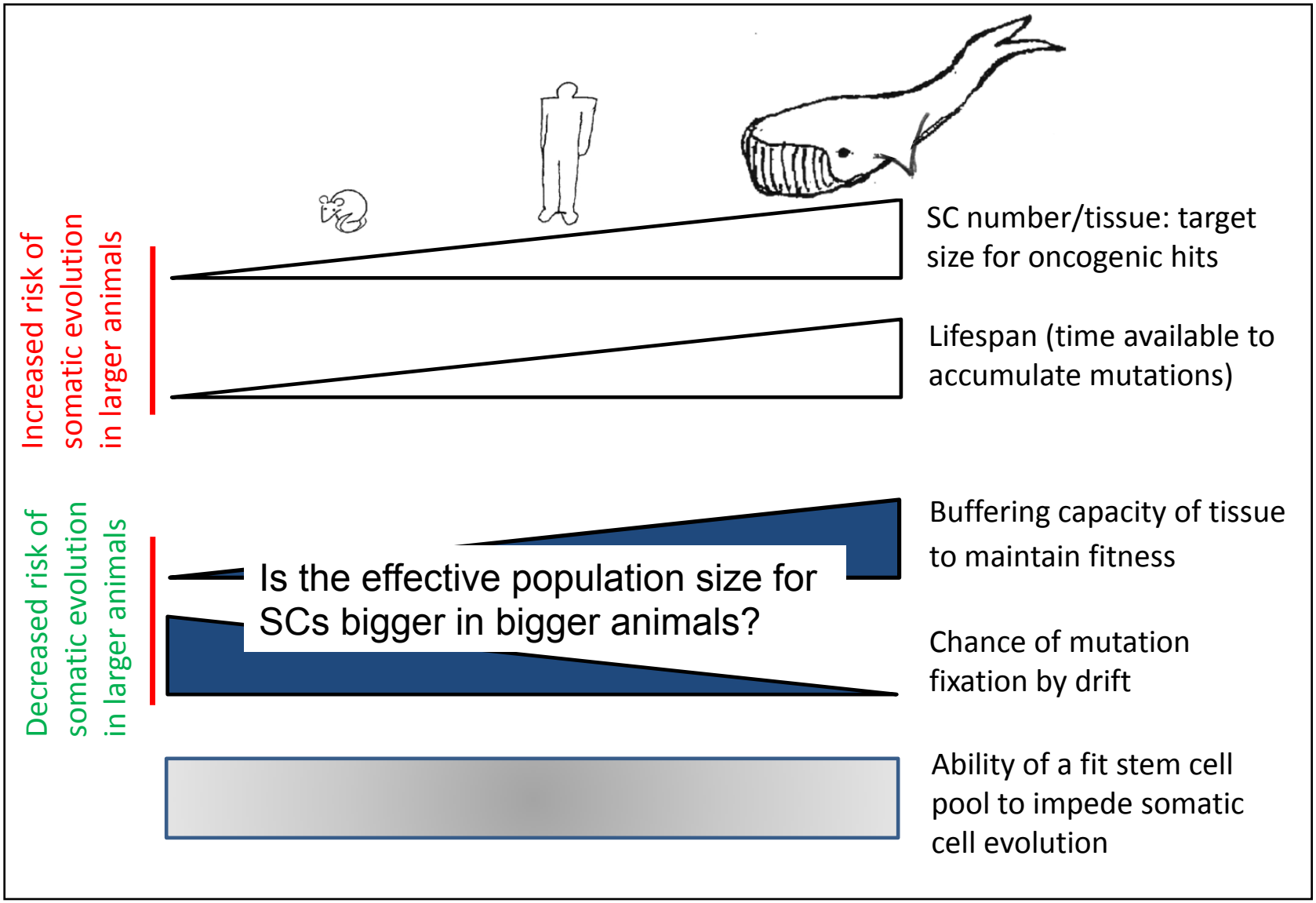
Low High

High stem cell pool fitness is tumor suppressive



DeGregori, J. (2011). Evolved tumor suppression: why are we so good at not getting cancer? Cancer Research, 71: 3739-3744.

Model for how vertebrates with large differences in somatic cell numbers and lifespans similarly avoid cancer through reproductive years.



Why does cancer increase with age?

Accumulation of oncogenic mutations.

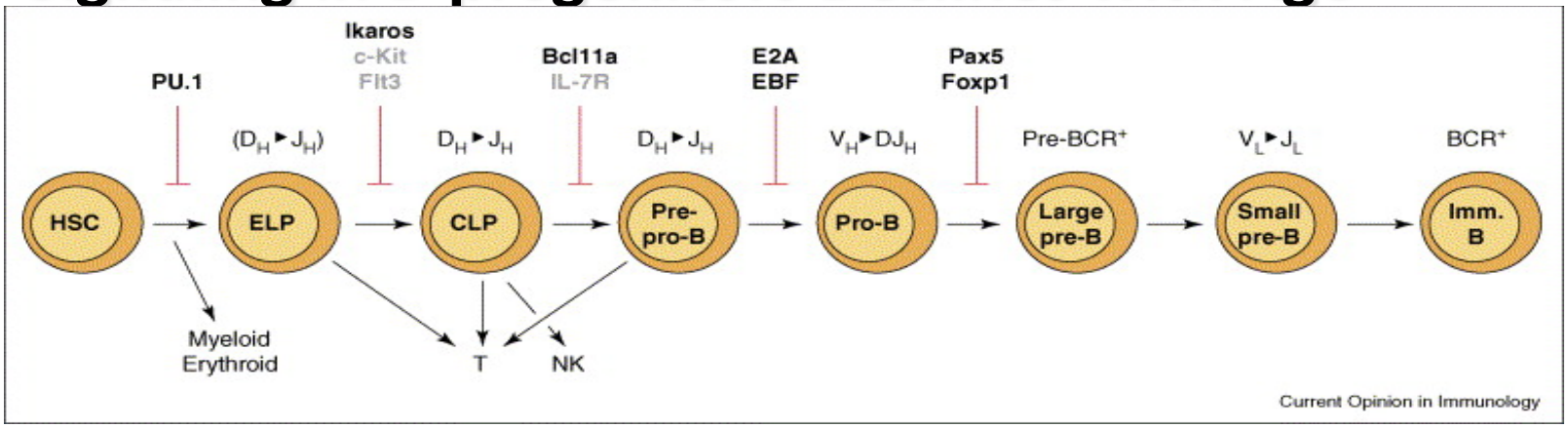
Changes in cellular microenvironment.

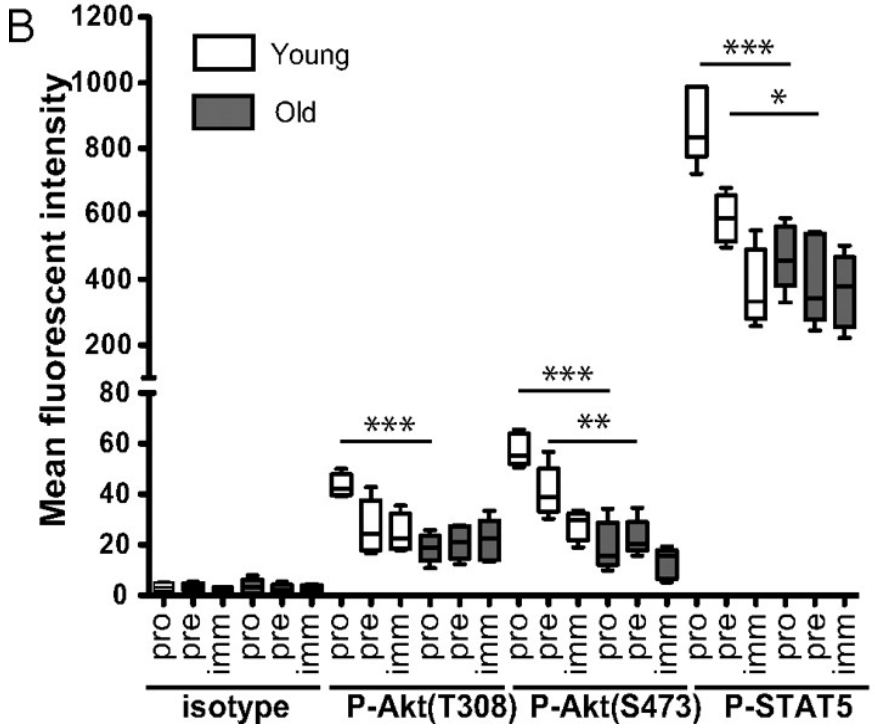
Chronic inflammation.

Decreased immune surveillance.

Does reduction of cellular fitness lead to selection for specific adaptive oncogenic mutations?

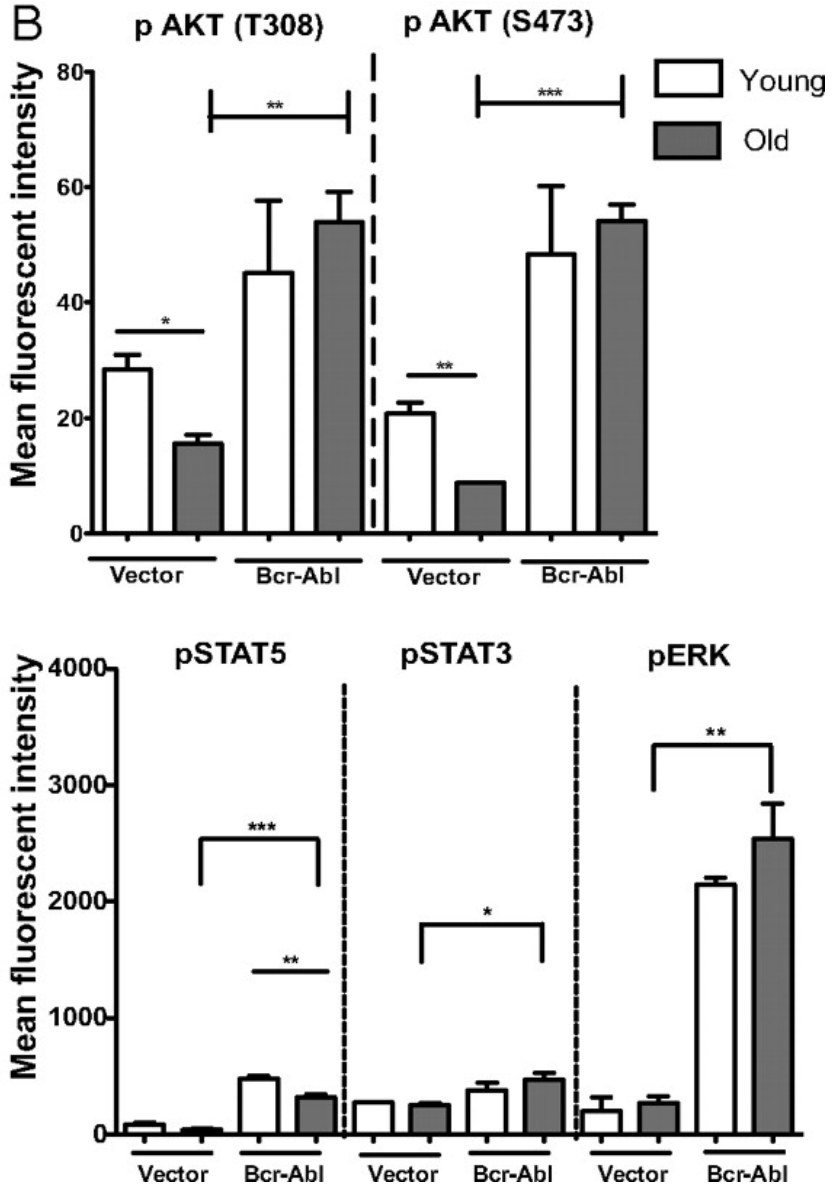
Signaling in B-progenitors Declines with Age





Henry et. al; PNAS; December 14, 2010 vol. 107 no. 50 21713-21718

Bcr-Abl Becomes Adaptive in Aged Backgrounds by Alleviating Aging-Associated Signaling Defects



Henry et. al; PNAS; December 14, 2010 vol. 107 no. 50 21713-21718

- Signaling defects in old B-progenitors contribute to reduced fitness (as determined using competitive transplantation assays.

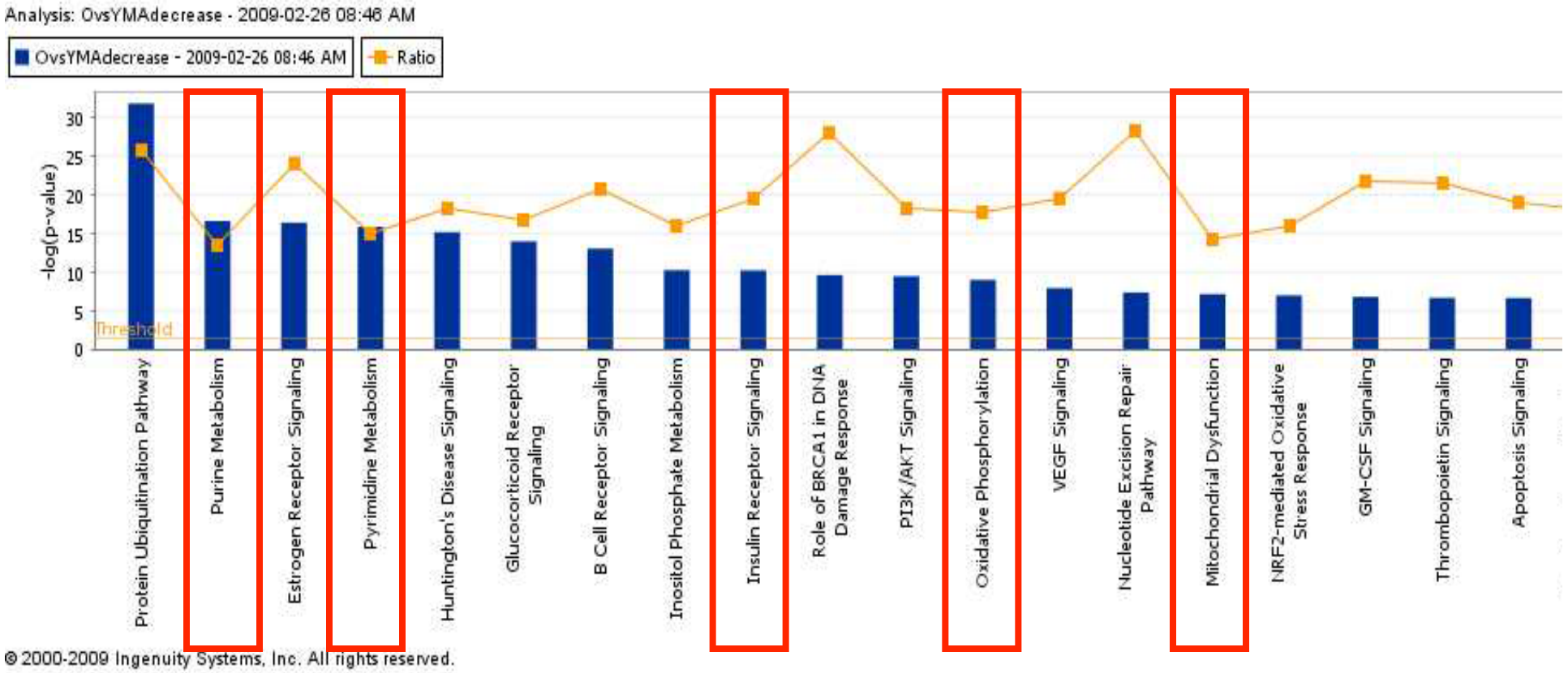
- Bcr-Abl restores signaling, promoting selection for Bcr-Abl expression.

- Selection for Bcr-Abl within old B-progenitor pools leads to increased leukemogenesis.

Henry et. al; PNAS; December 14, 2010 vol. 107 no. 50 21713-21718

What else underlies fitness defects in old B-progenitors?

Anabolic and catabolic pathways decrease in old B-progenitors

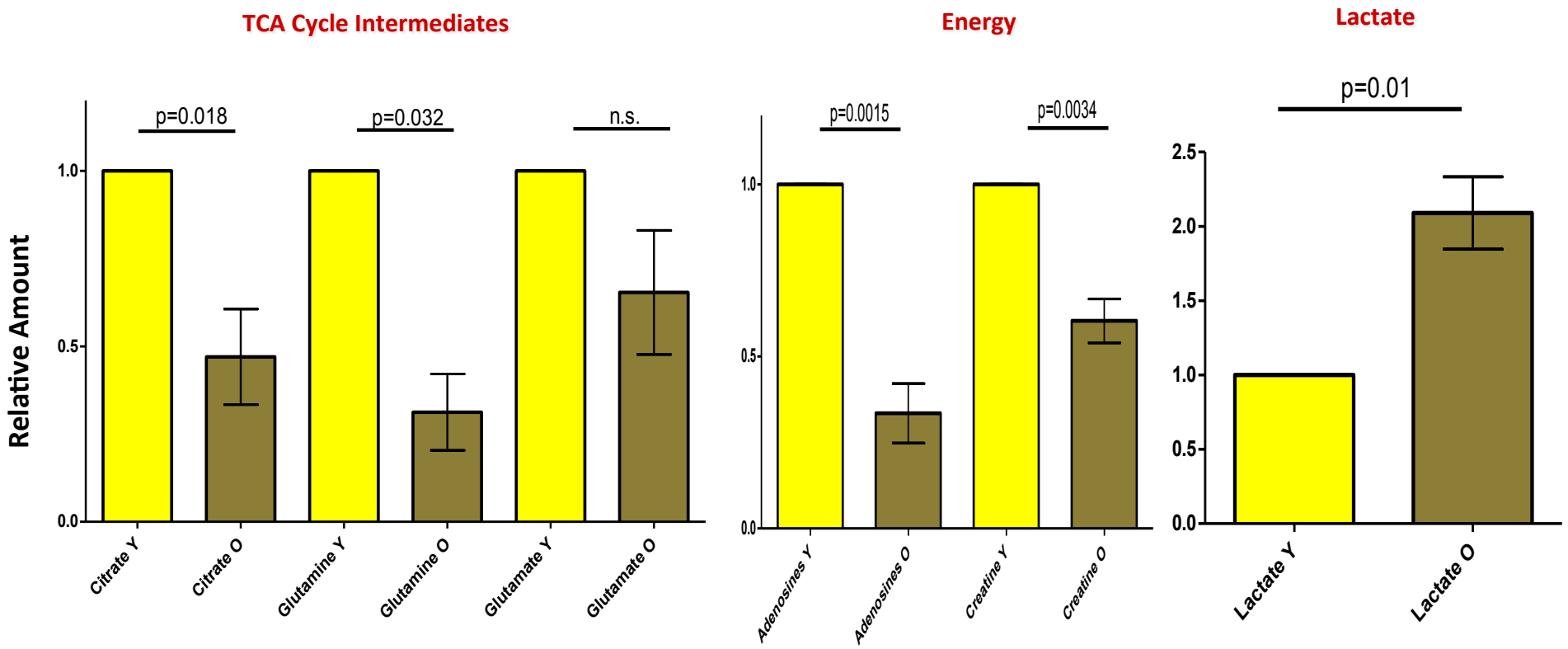


Aging is not a program

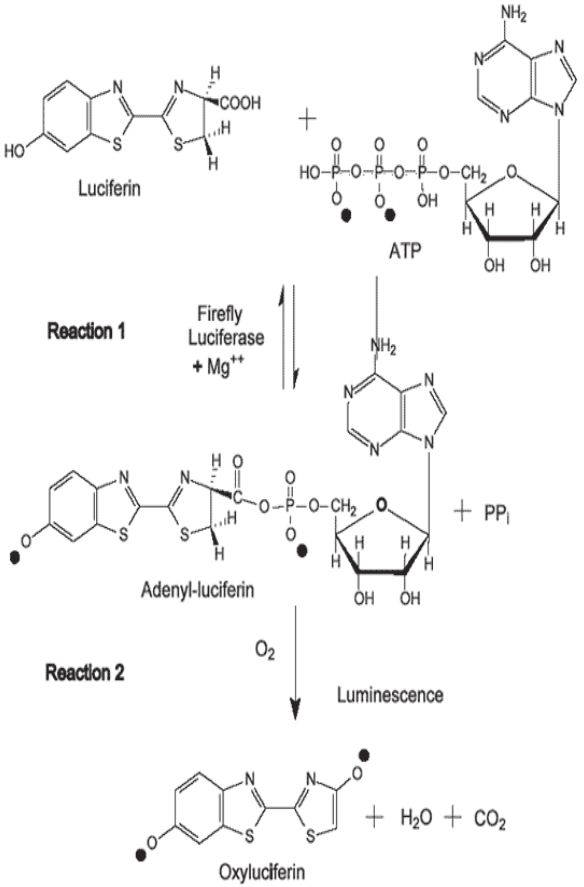
but programs can mediate aging

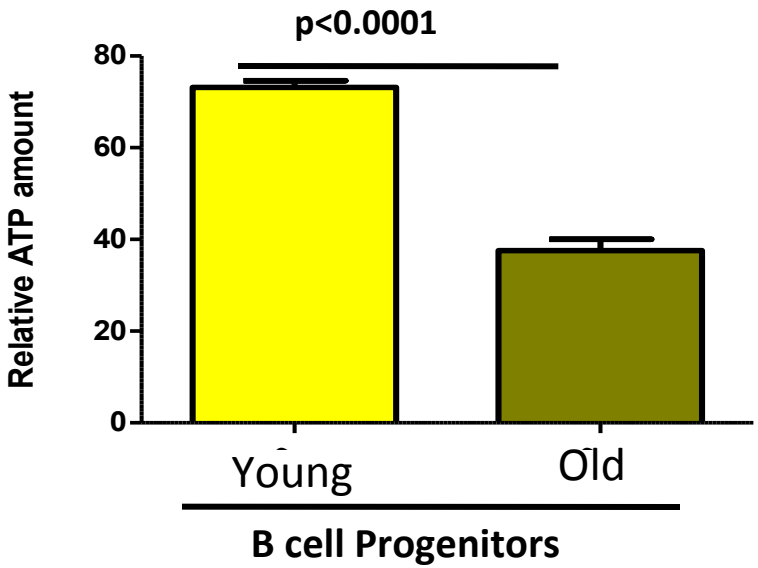
and aging can be deprogrammed.

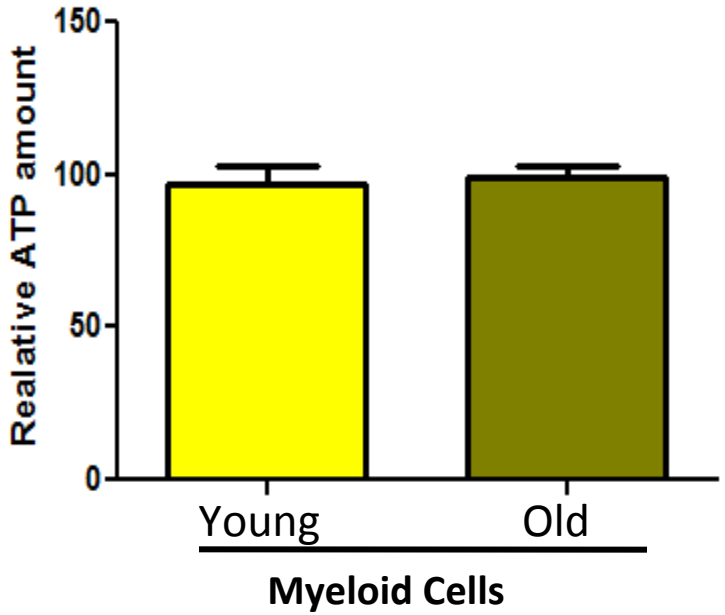
Old B Cell Progenitors Exhibit Metabolic Defects



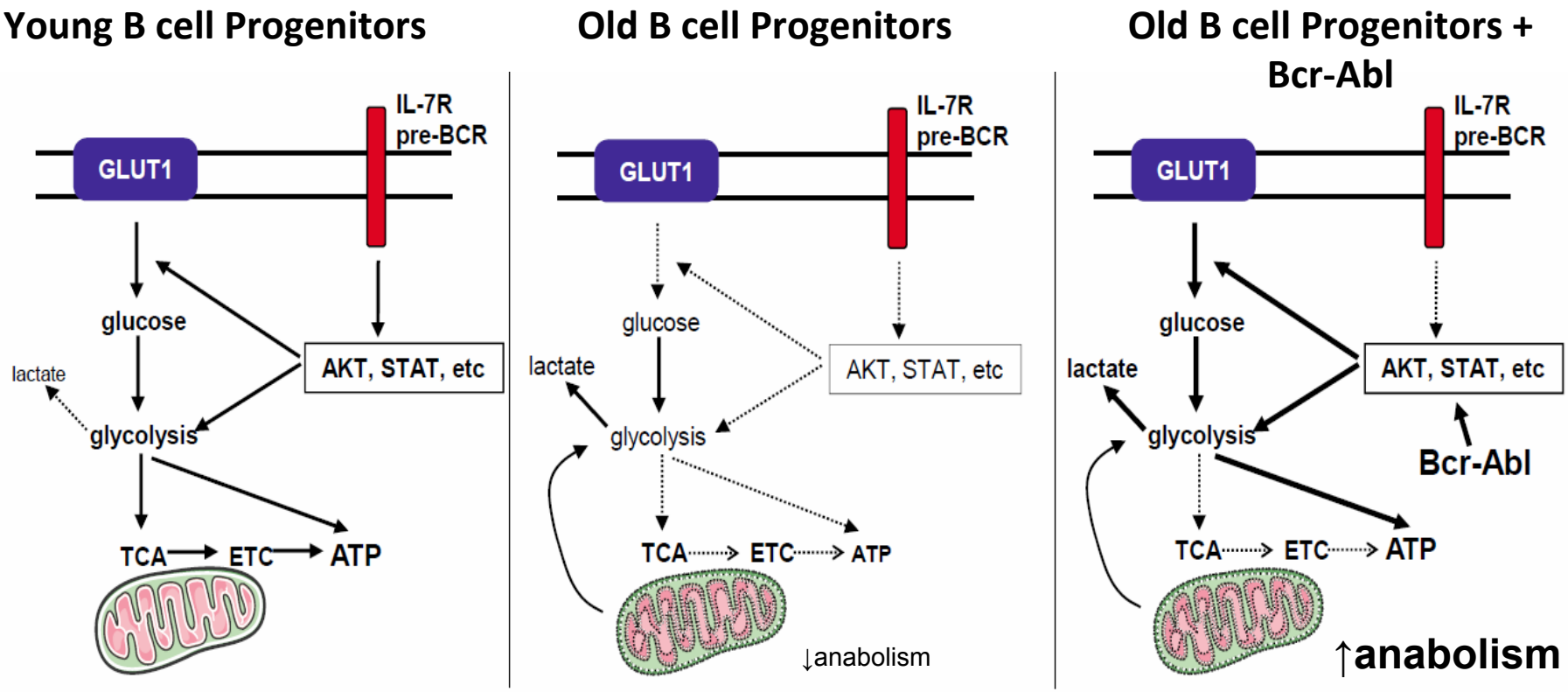
ATP Levels are Decreased in Old B cell Progenitors Relative to Young Ones



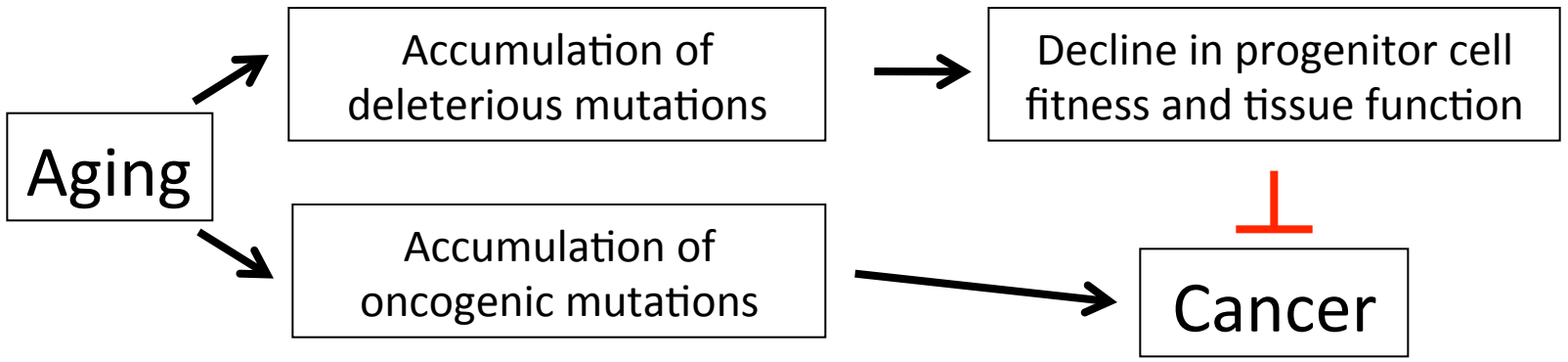




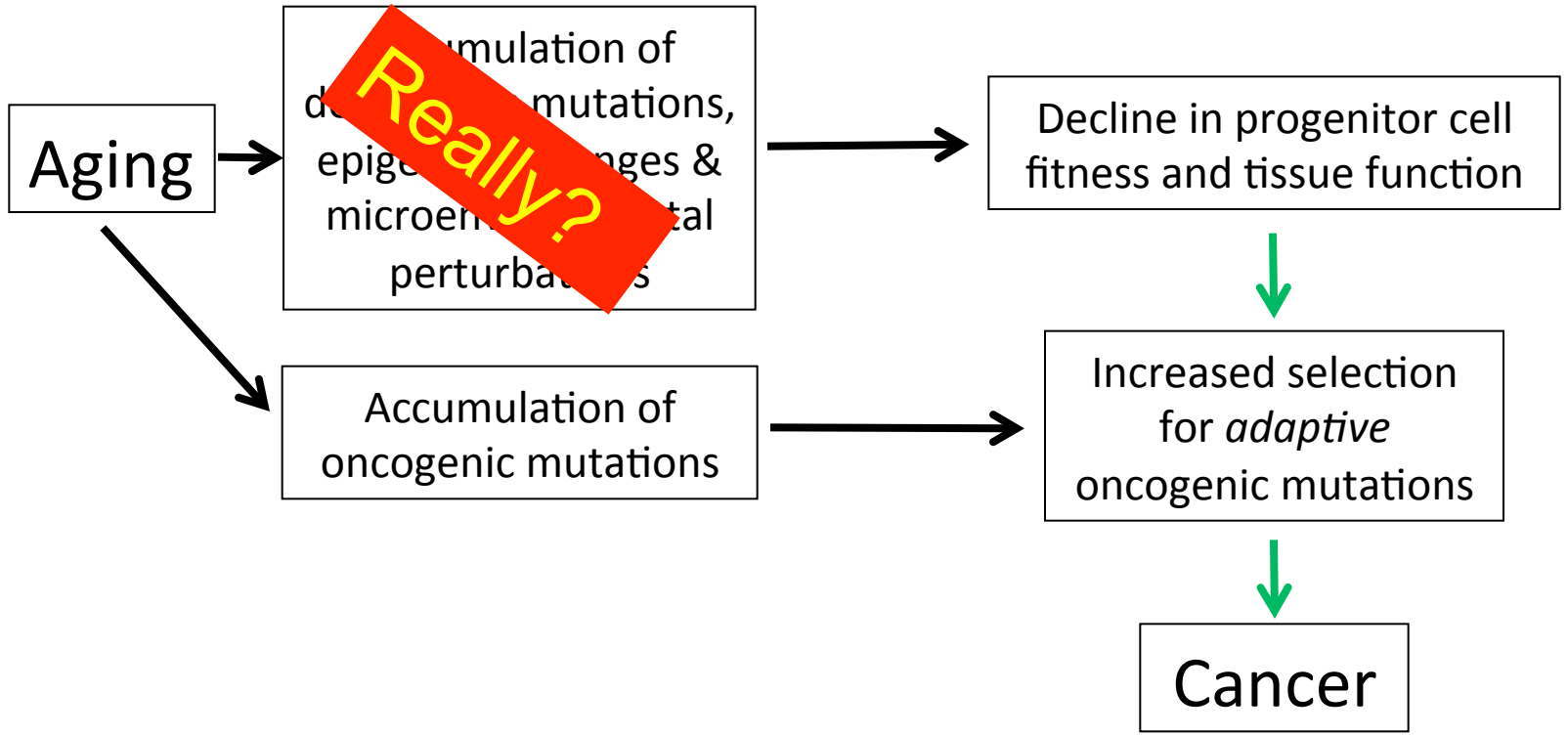
Model for Bcr-Abl Adaptation in an Aged Background



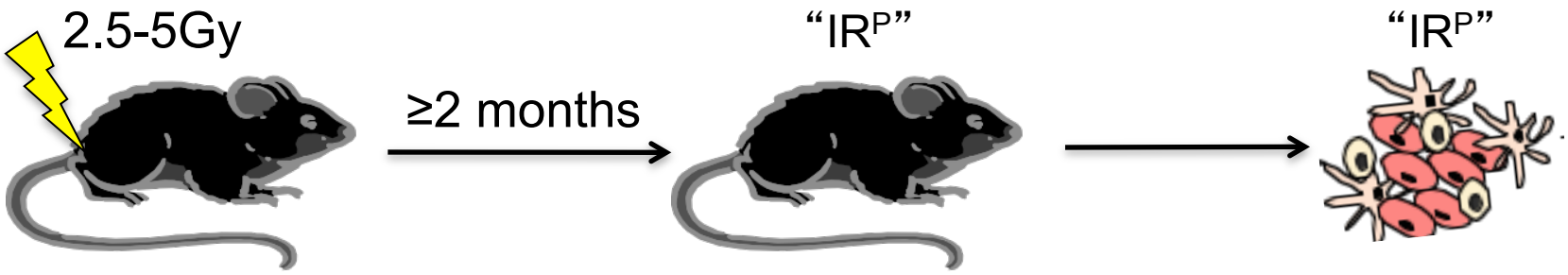
A. Predominant Model



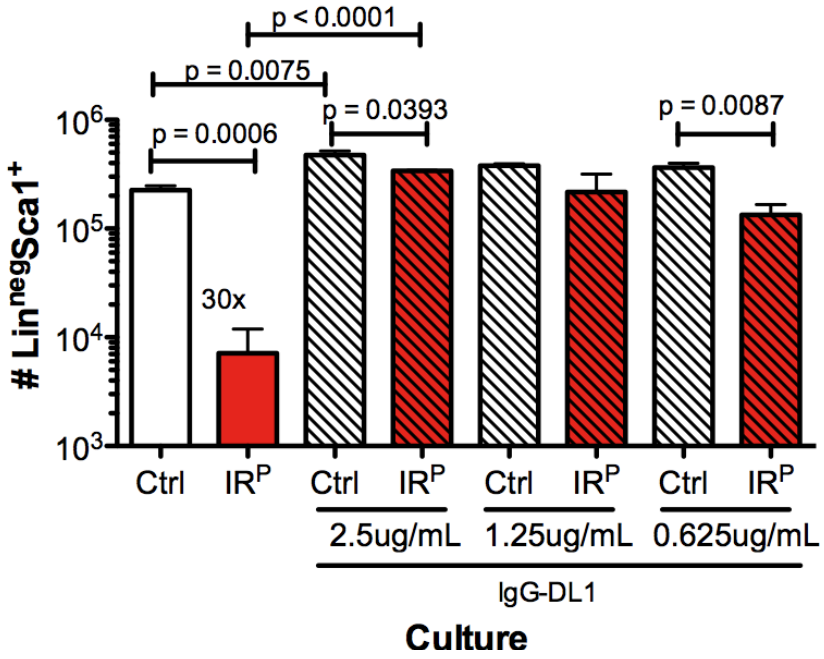
B. Adaptive Oncogenesis Model



Previous Irradiation (IR^P)

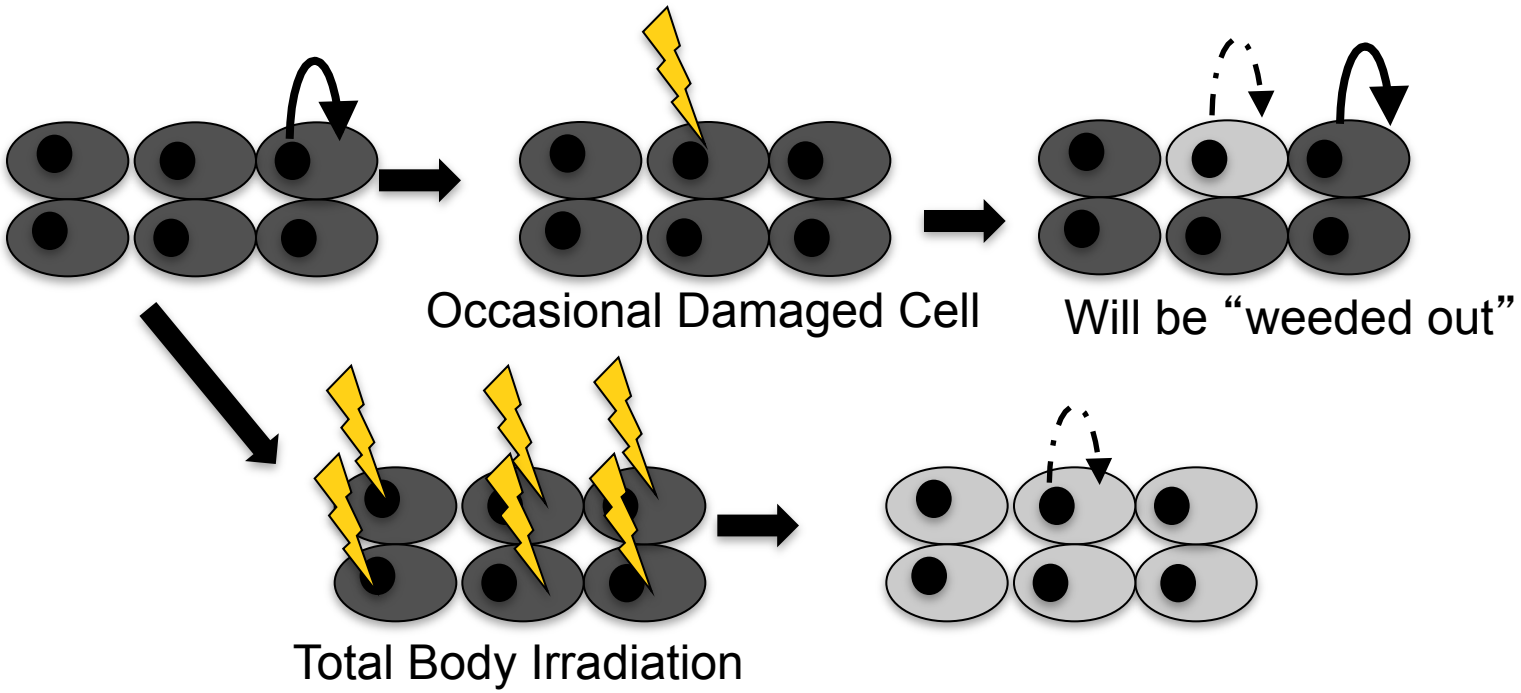


Number of $Lin^{neg}Sca1^+$ Cells Day7



Prior irradiation and HSC fitness

- Previously irradiated HSC exhibit maintenance defects that are *specific, reproducible, somatically heritable, and reversible*.
- Evolved to deal with the occasionally damaged cell?
- "Programmed Mediocrity"?



Hmmm….

- Could “programmed mediocrity” be a mechanism to maintain tissue fitness in youth, but which contributes to tissue decline in old age?


THE LAB
Francesca Alvarez-Calderon
Mark Gregory
*Courtney Fleenor
*Curtis Henry
Vadym Zaberezhnyy
*Matias Casas Selves
Rodrigo Maegawa
*Biniam Adane
Former: *Andriy Marusyk
THE $$$
NCI/NIA
Flow Cytometry
Karen Helm
Christine Childs
Other
Natalie Serkova
Andrea Mertz
Art work: Michael and Gayle DeGregori

So why do kids get cancer?

1) Given expansion of progenitor populations, a mutation can more easily become fixed even if not advantageous.

2) More recent evolution has substantially altered the human brain and immune systems, and a low risk of childhood leukemias affecting these tissues has been a tradeoff (although advantages of a more developed brain and better immune system outweighed the low leukemia risk).

3) There are dietary and genetic factors which correlate with reduced folate and/or reduced dNTP synthesis, which may reduce progenitor fitness, and thus may contribute to childhood cancers.

4) Our immune systems did not evolve to deal with modern conditions, but to conditions with more antigen and pathogen exposures early in life. Thus, our hematopoietic systems are not truly adapted to modern life.

5) Translocations common to childhood leukemias are more likely to occur in fetal or childhood development.