Impact of Infection and Inflammation on Hematopoietic Stem Cells

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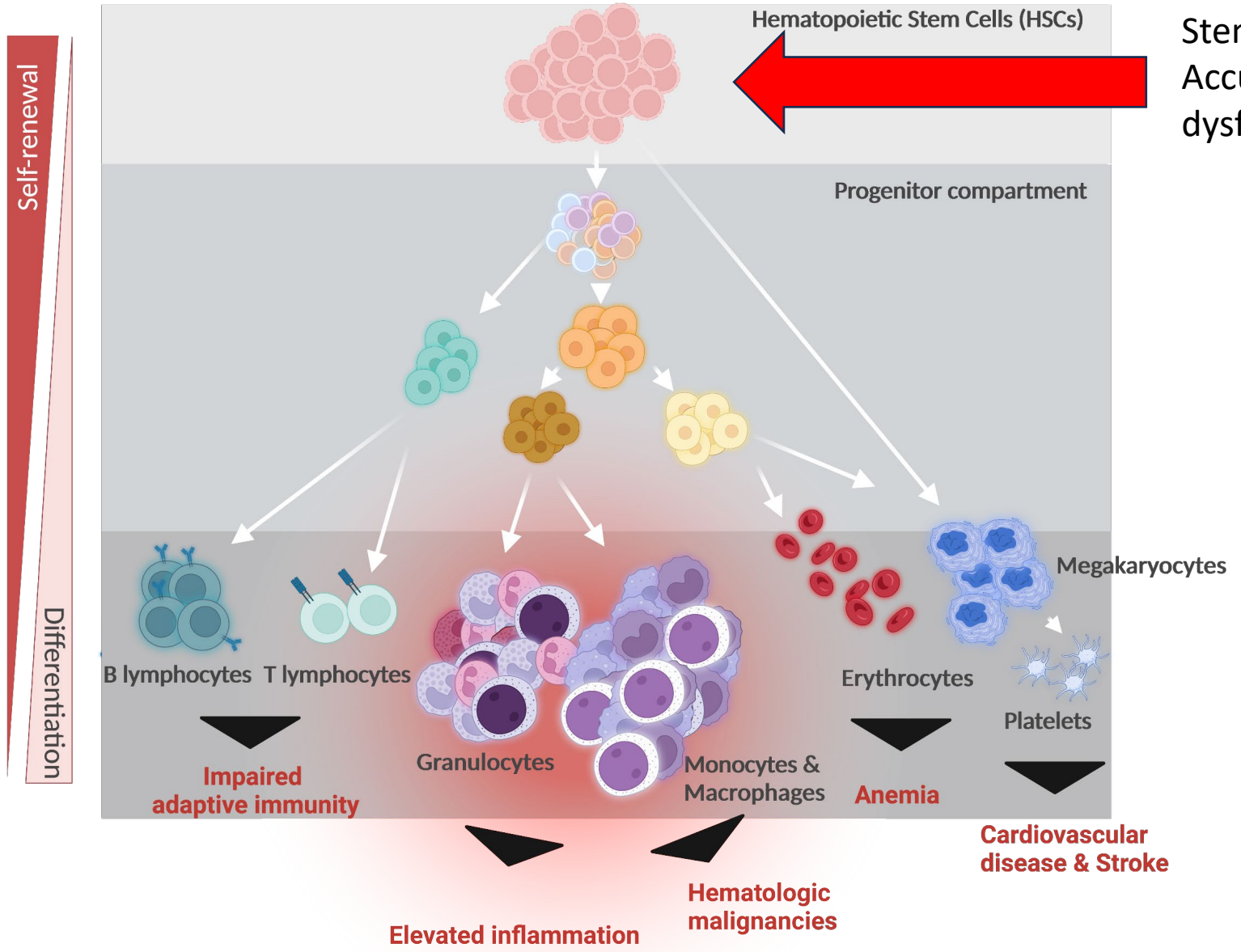
Disclosure of conflicts of interest

None

JAHRESTAGUNG 2024 BASEL 11.–14. Oktober

Age-associated dysfunction of the hematopoietic system



Stem cell exhaustion?
Accumulation of dysfunctional HSCs?

Aging is driven by the interplay of multiple complex factors over time

Genotype

+

Environment

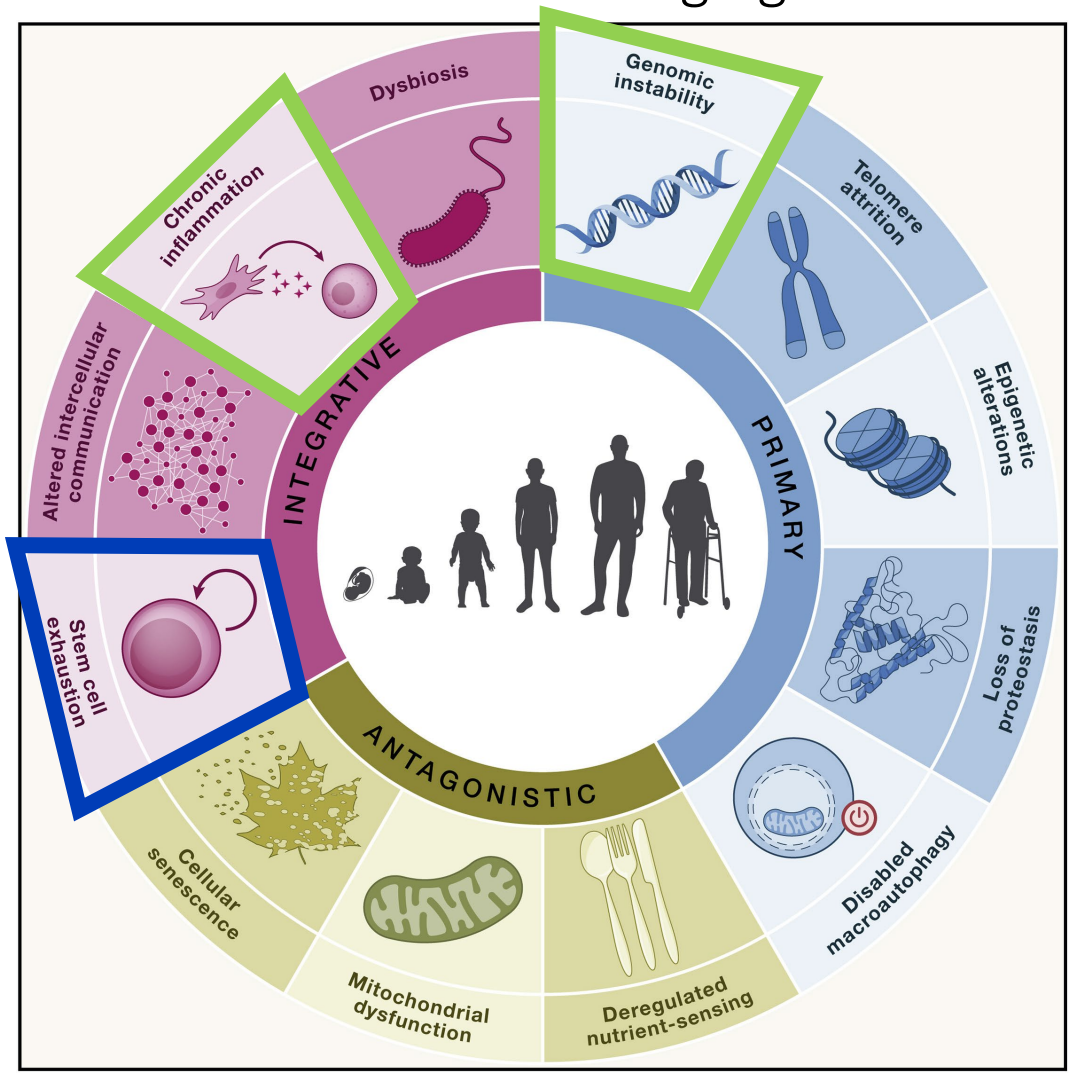
x

Time

=

Phenotype

Hallmarks of Aging



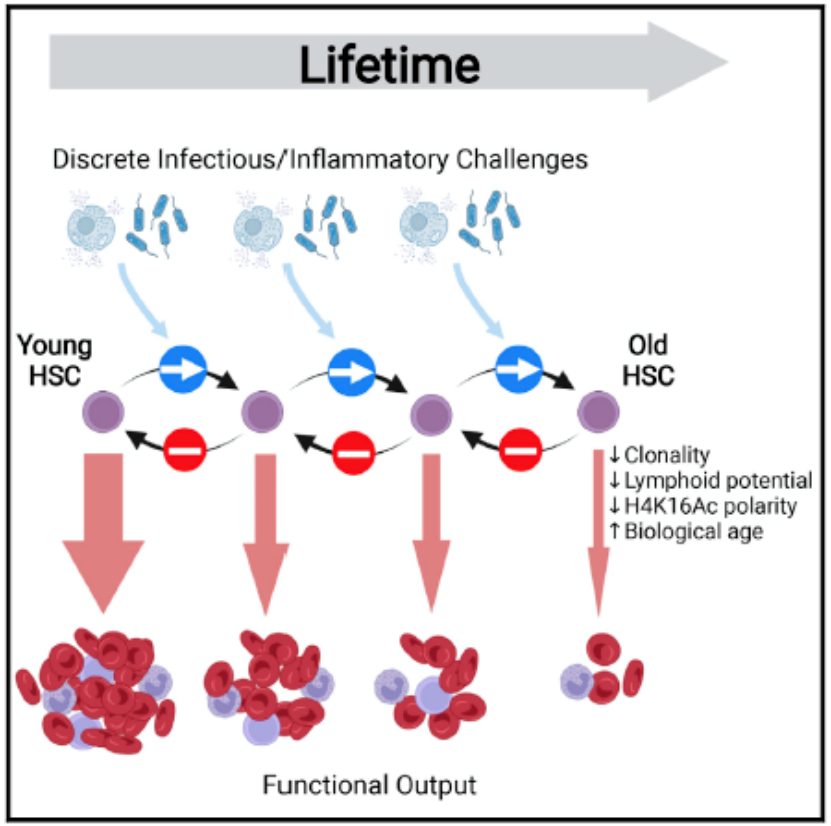
López-Otín et al Cell, 2023

Cell Stem Cell

Short article

Inflammatory exposure drives long-lived impairment of hematopoietic stem cell self-renewal activity and accelerated aging

Graphical abstract



Authors

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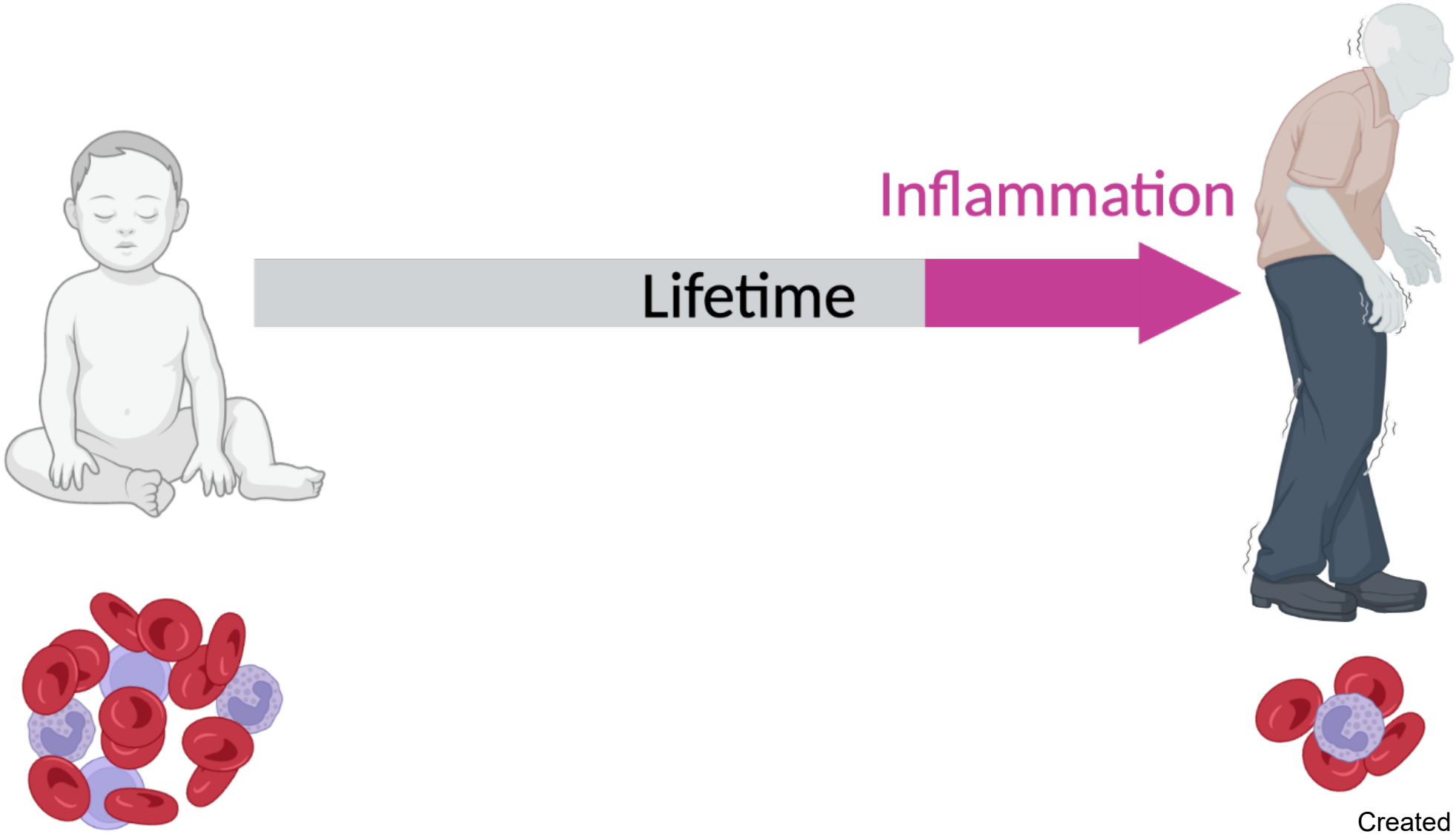
In brief

Inflammation and infection acutely suppress HSC function. However, the long-term ramifications of such challenges are unclear. This study demonstrates that murine HSCs fail to recover functional potency up to 1 year post-inflammatory/infection challenge, meaning that such events can have accumulative effects over a lifetime; this promotes acquisition of the aged state.

Chronic low grade inflammation (inflammaging) suppresses HSC function?



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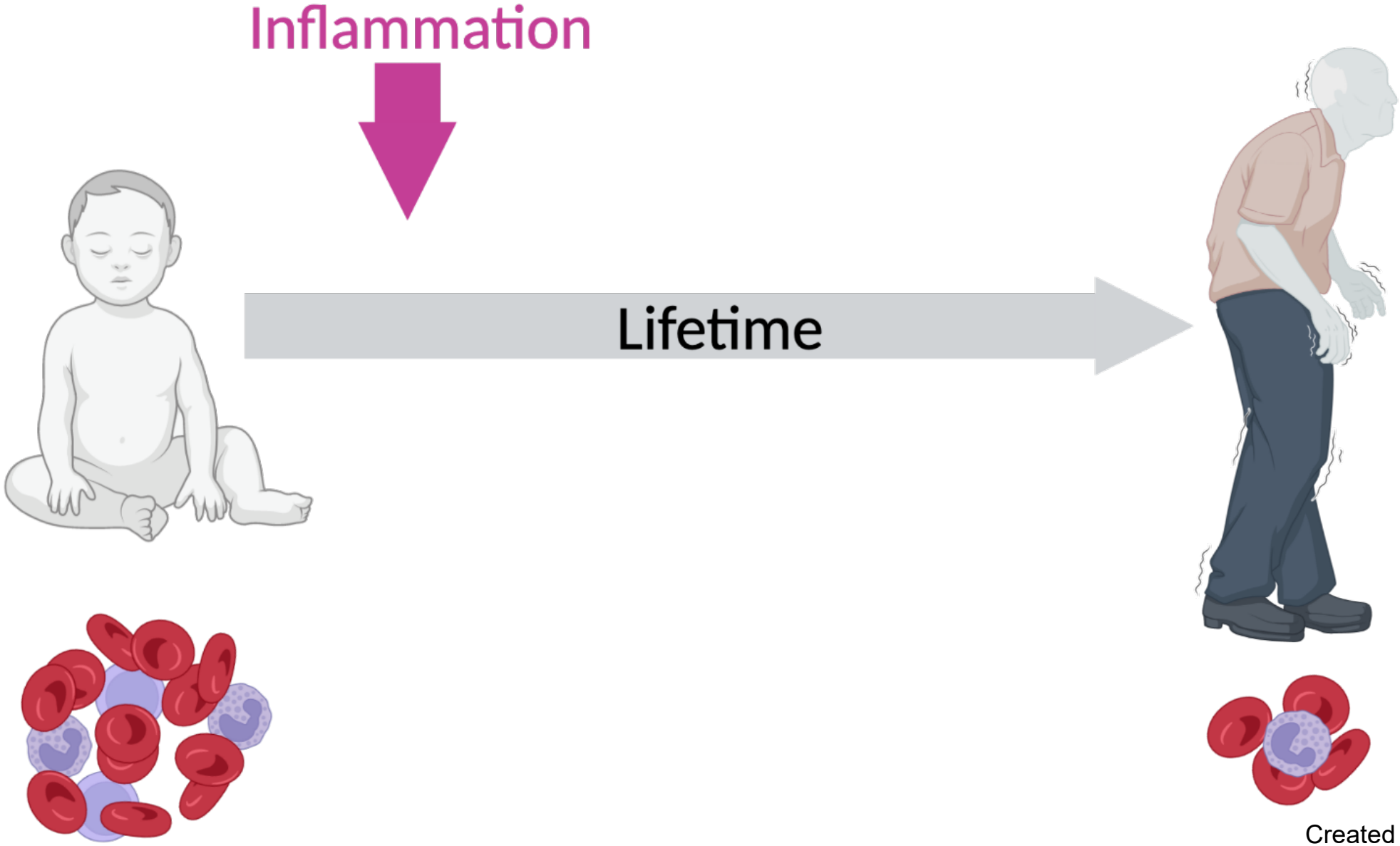
Does inflammatory exposure in early life mediate long-term inhibitory effects?



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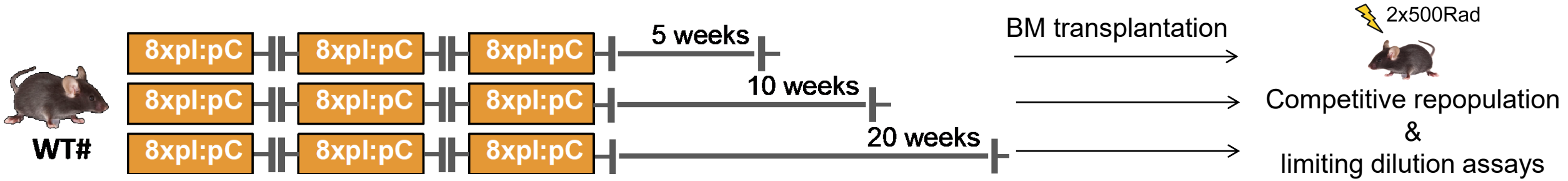
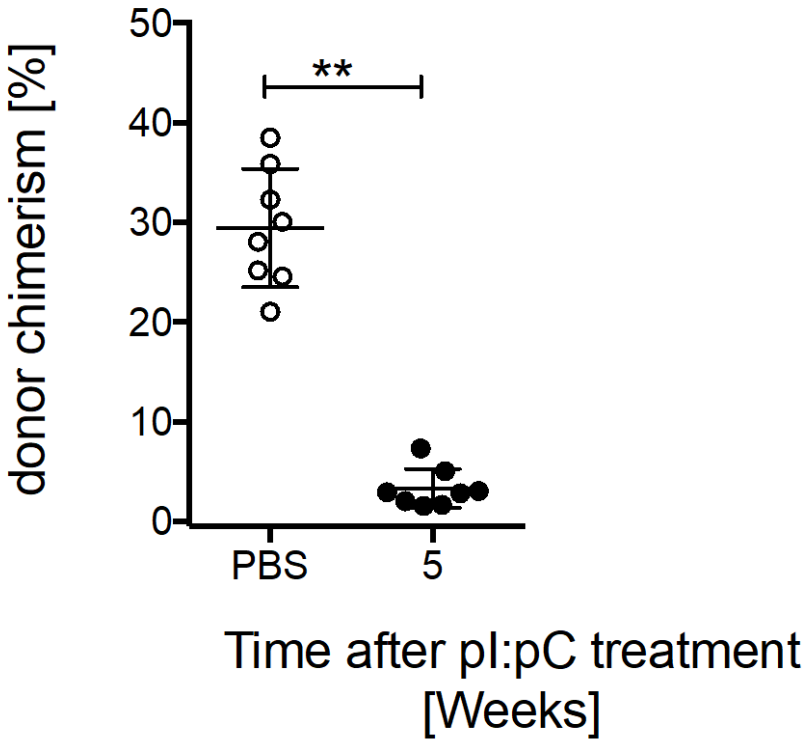
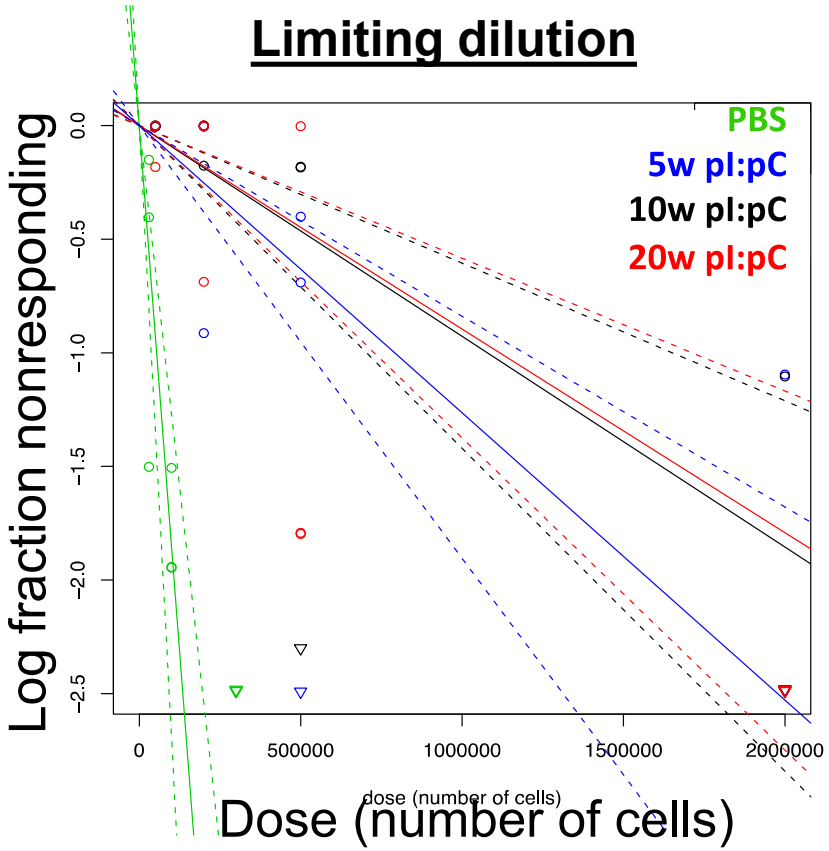
Irreversible depletion of HSCs following inflammatory stress



Competitive repopulation

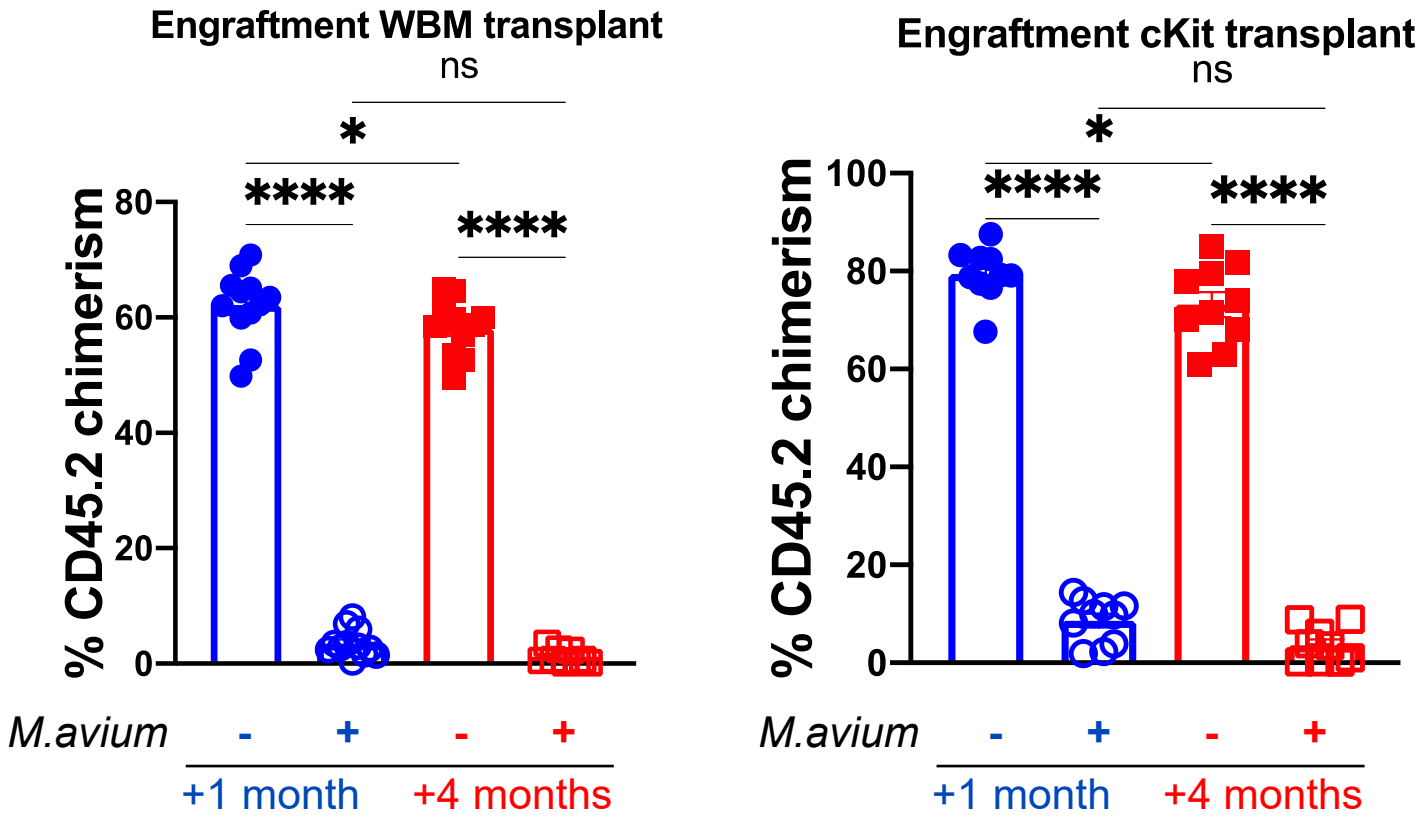


Limiting dilution



Group	Estimate of HSC frequency
PBS	1 in 54 042
5 weeks pI:pC	1 in 791 051
10 weeks pI:pC	1 in 1 078 255
20 weeks pI:pC	1 in 1 116 341

HSCs do not recover after inflammatory challenge with Mycobacterium avium



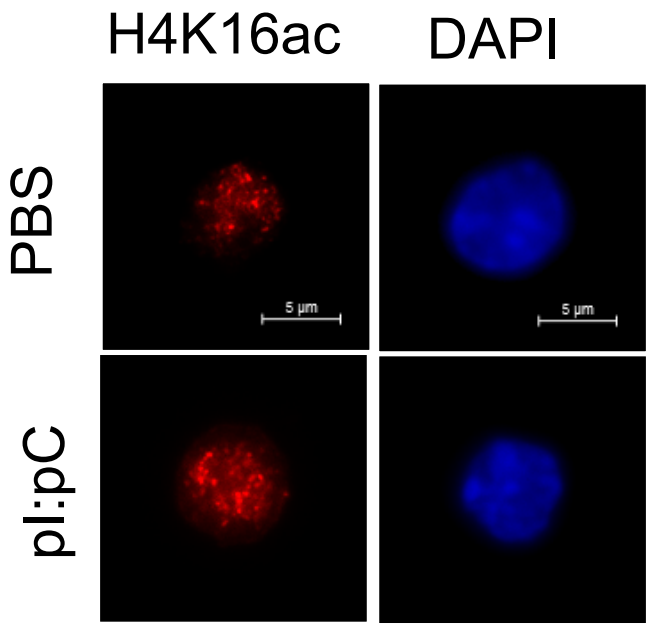
Katherine King
Baylor College of Medicine

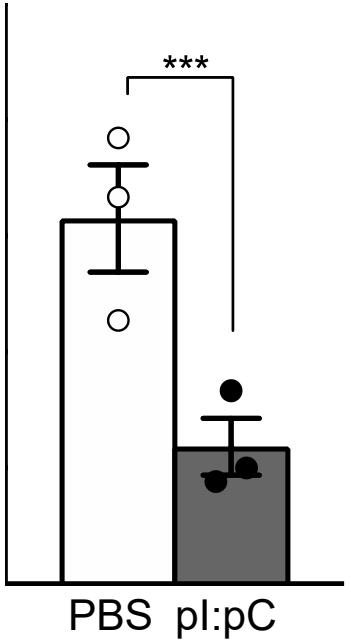
Inflammation in early life drives accelerated aging

WT#

8xpI:pC 8xpI:pC 8xpI:pC 4 weeks Sacrifice and analyze

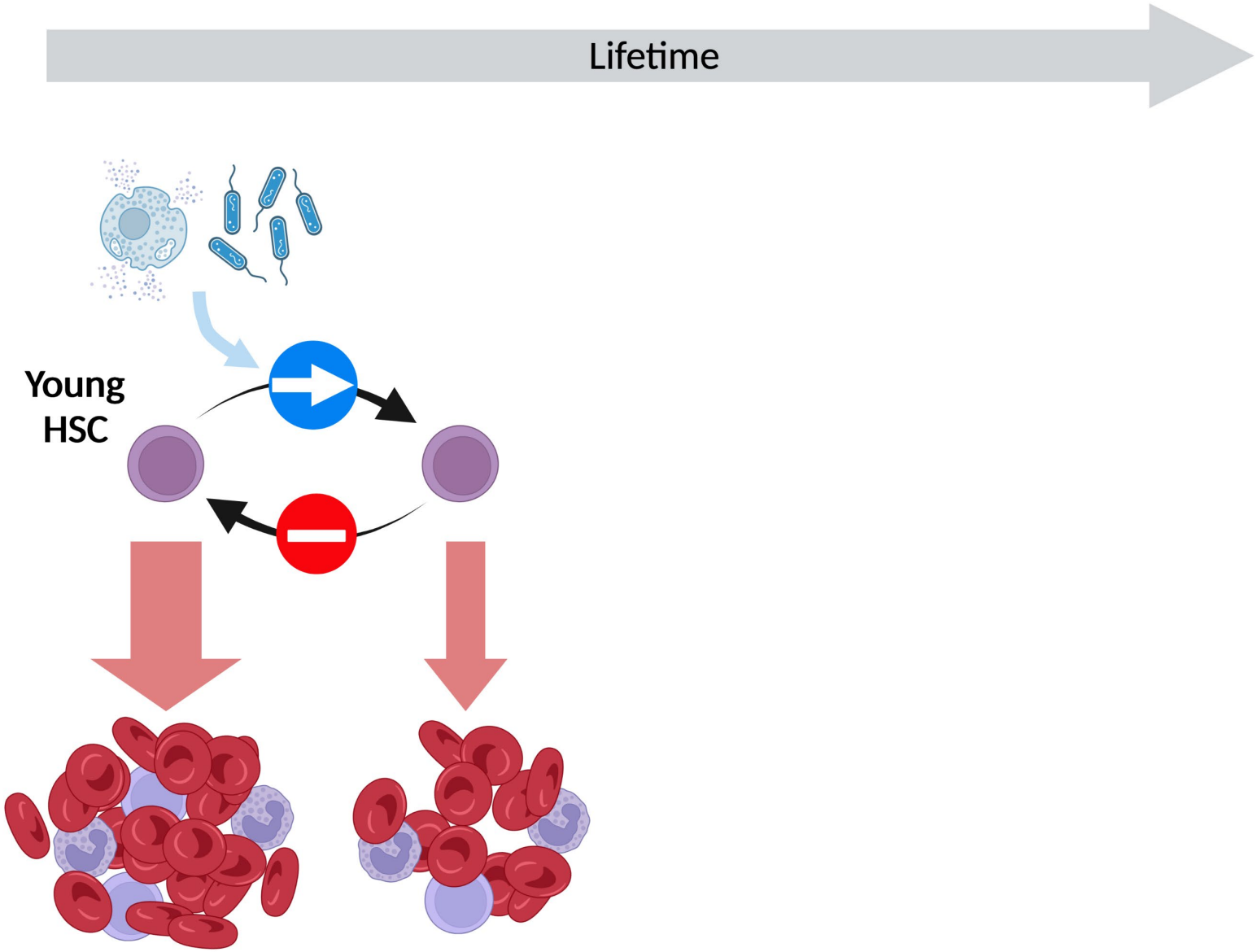
Pronounced loss in LT-HSC polarity





Carolina Florian

Summary



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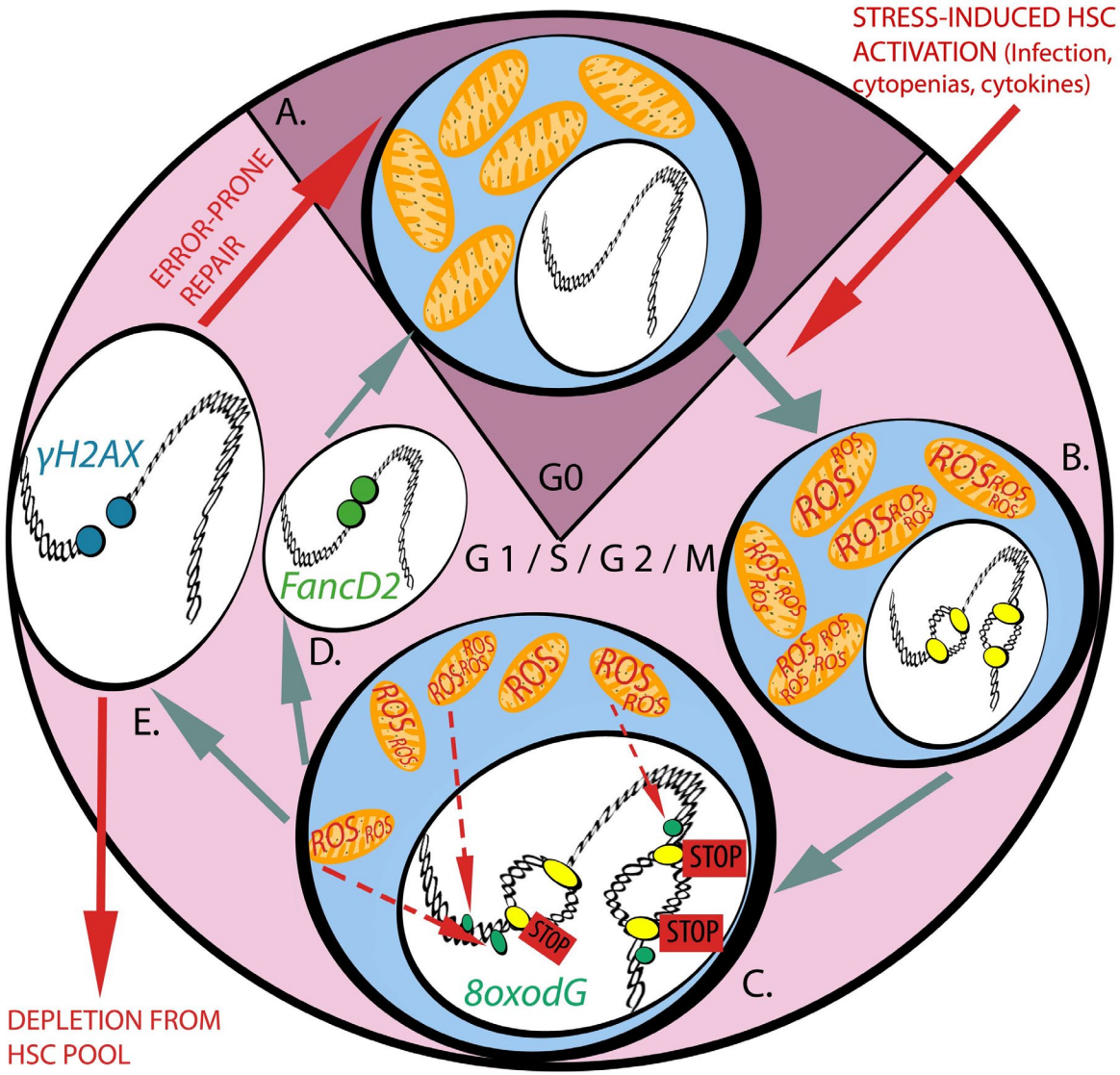
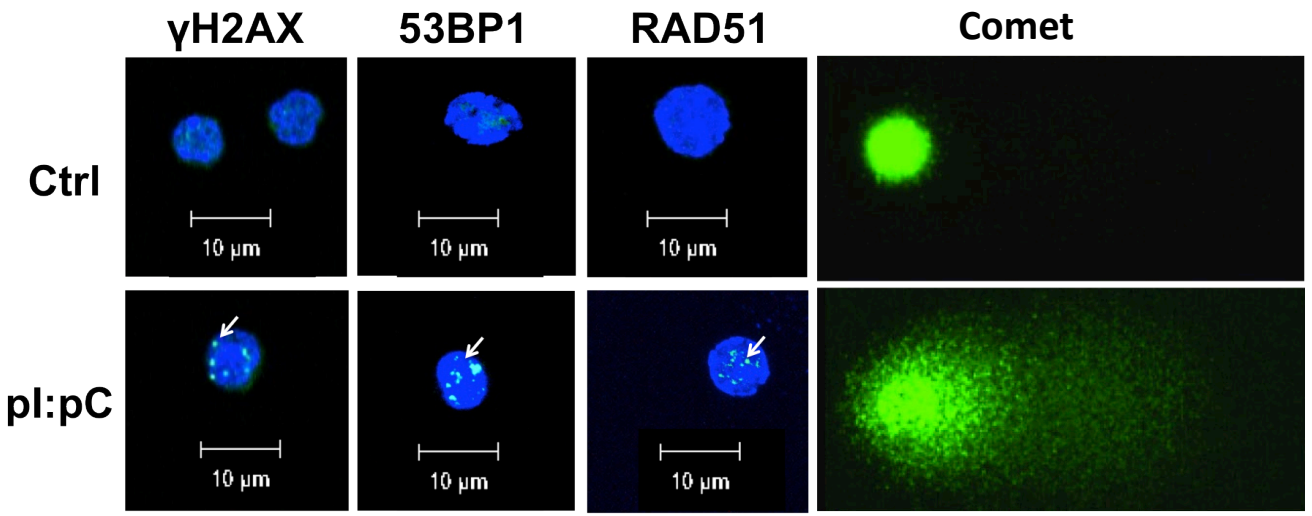
Bogeska et al., Cell Stem Cell, 2022

Exit from dormancy drives DNA damage in HSCs

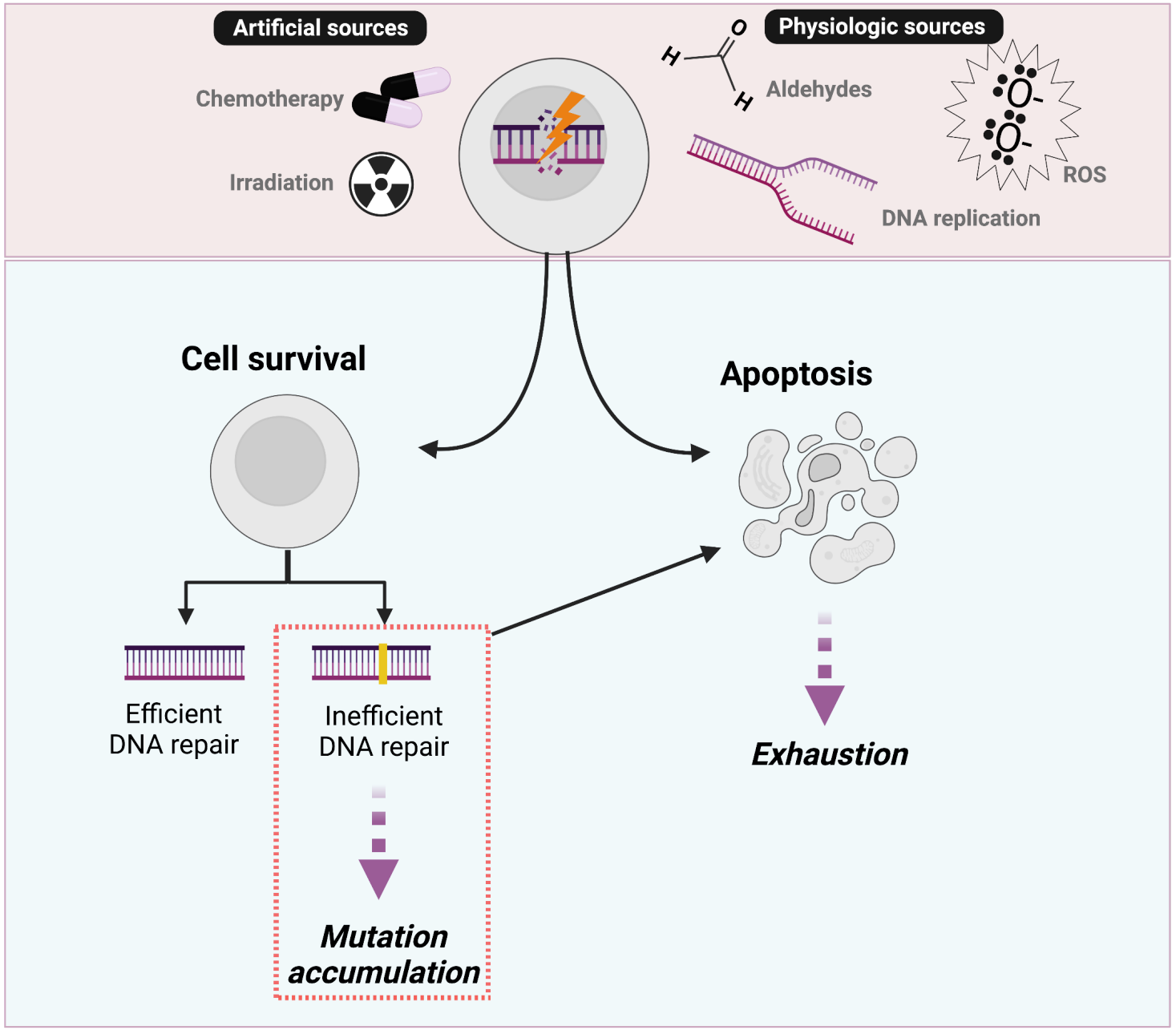




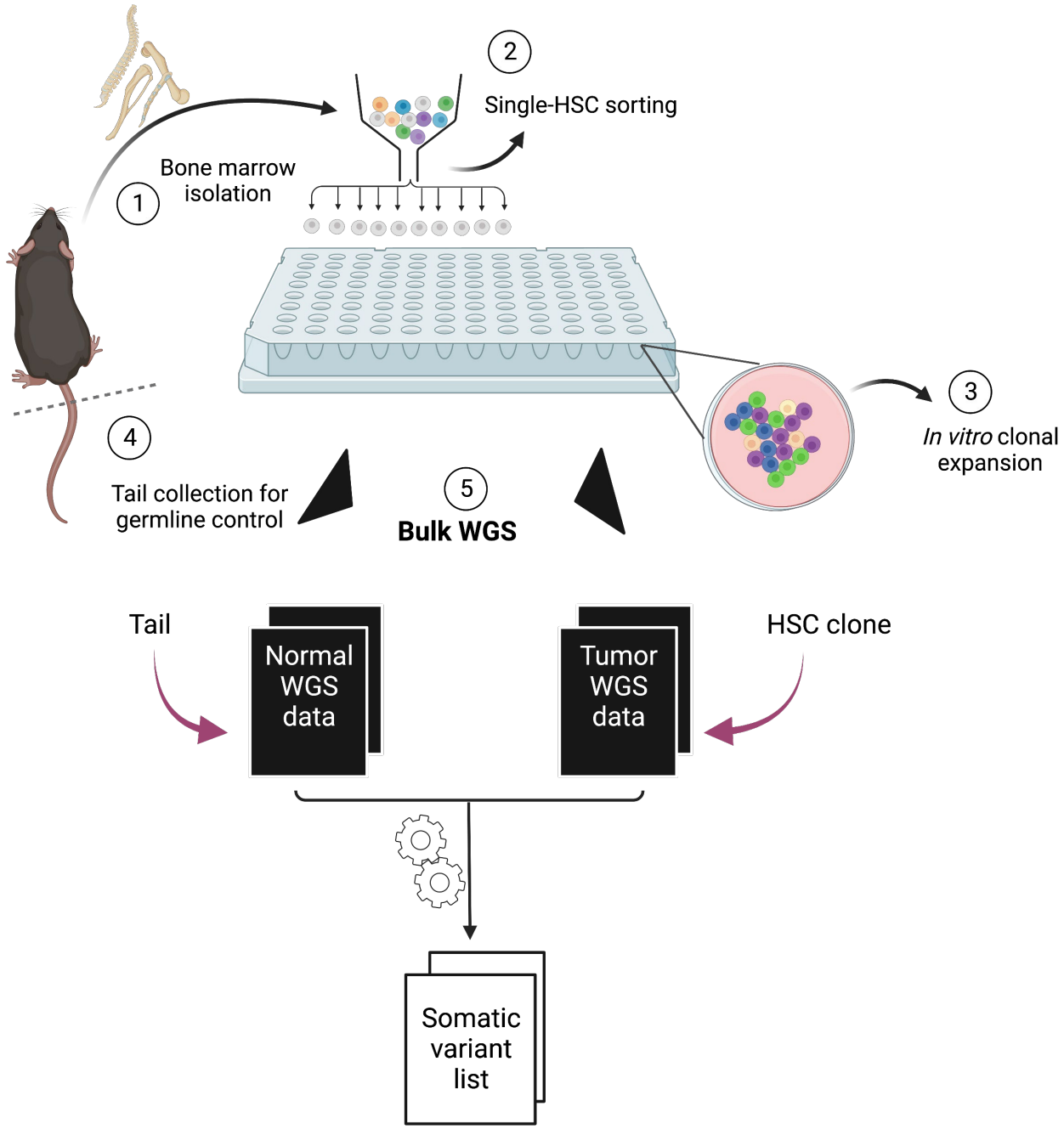
Walter *et al.*, Nature, 2015

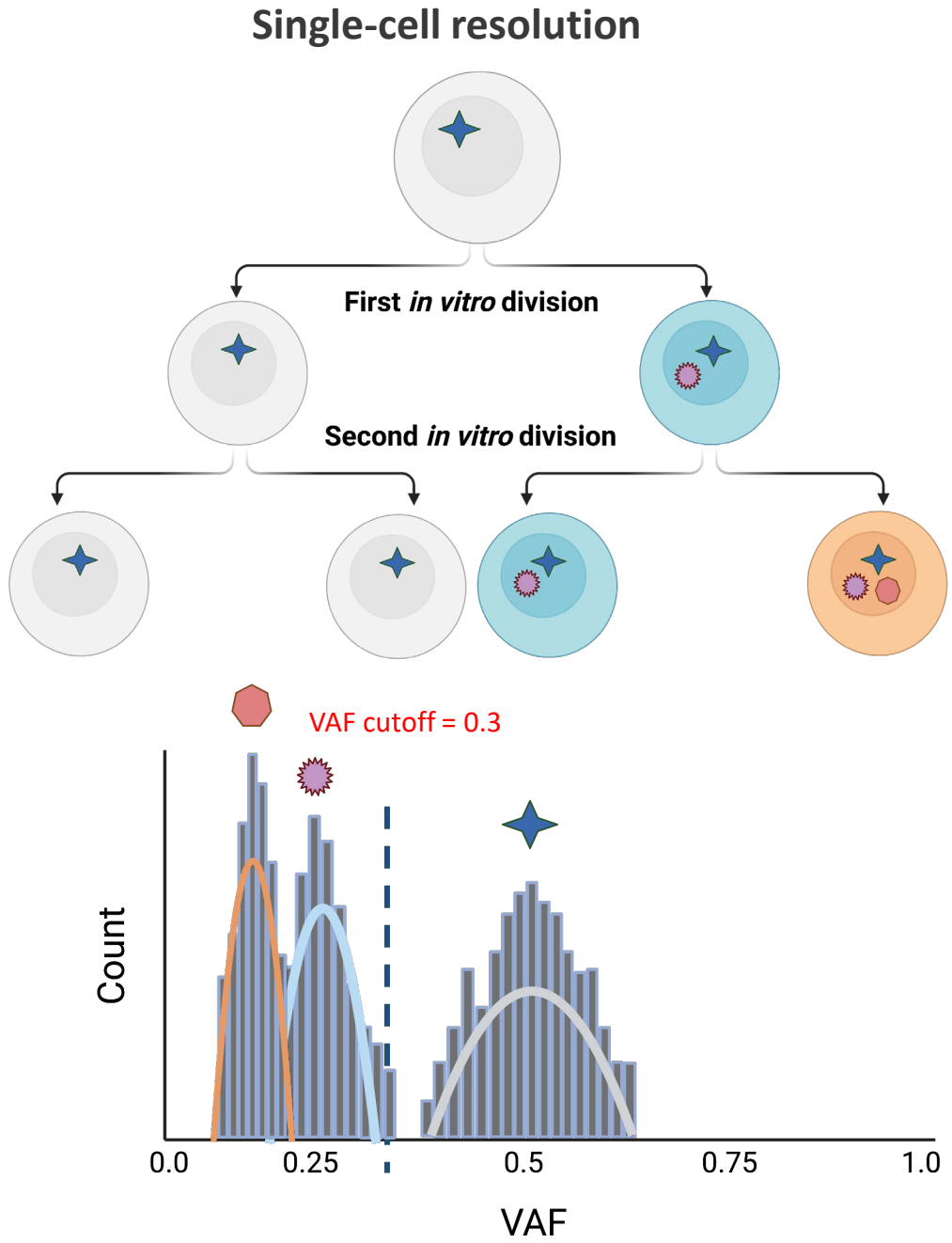
Mechanisms of mutation acquisition during ageing

Foteini (Fenia) Fotopoulou

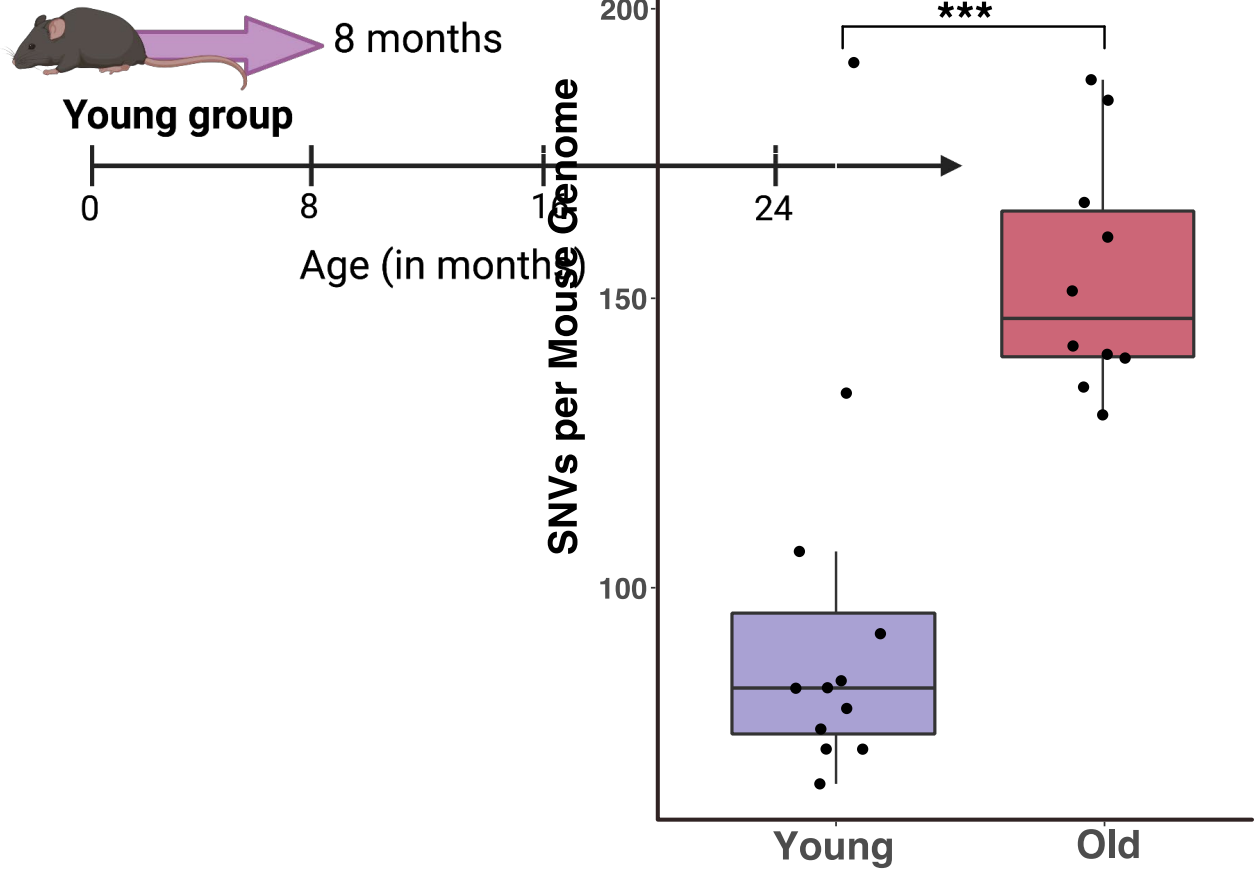


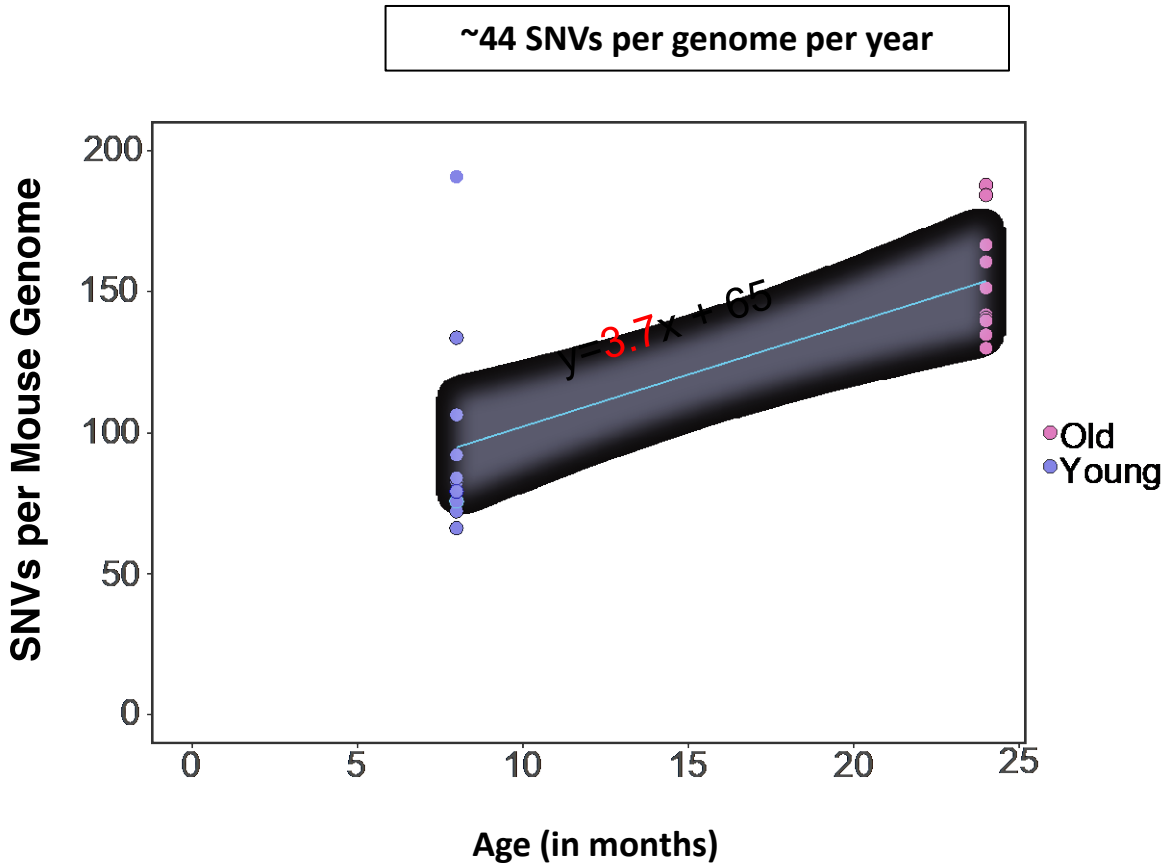
Mutation burden assessment in single HSC genomes



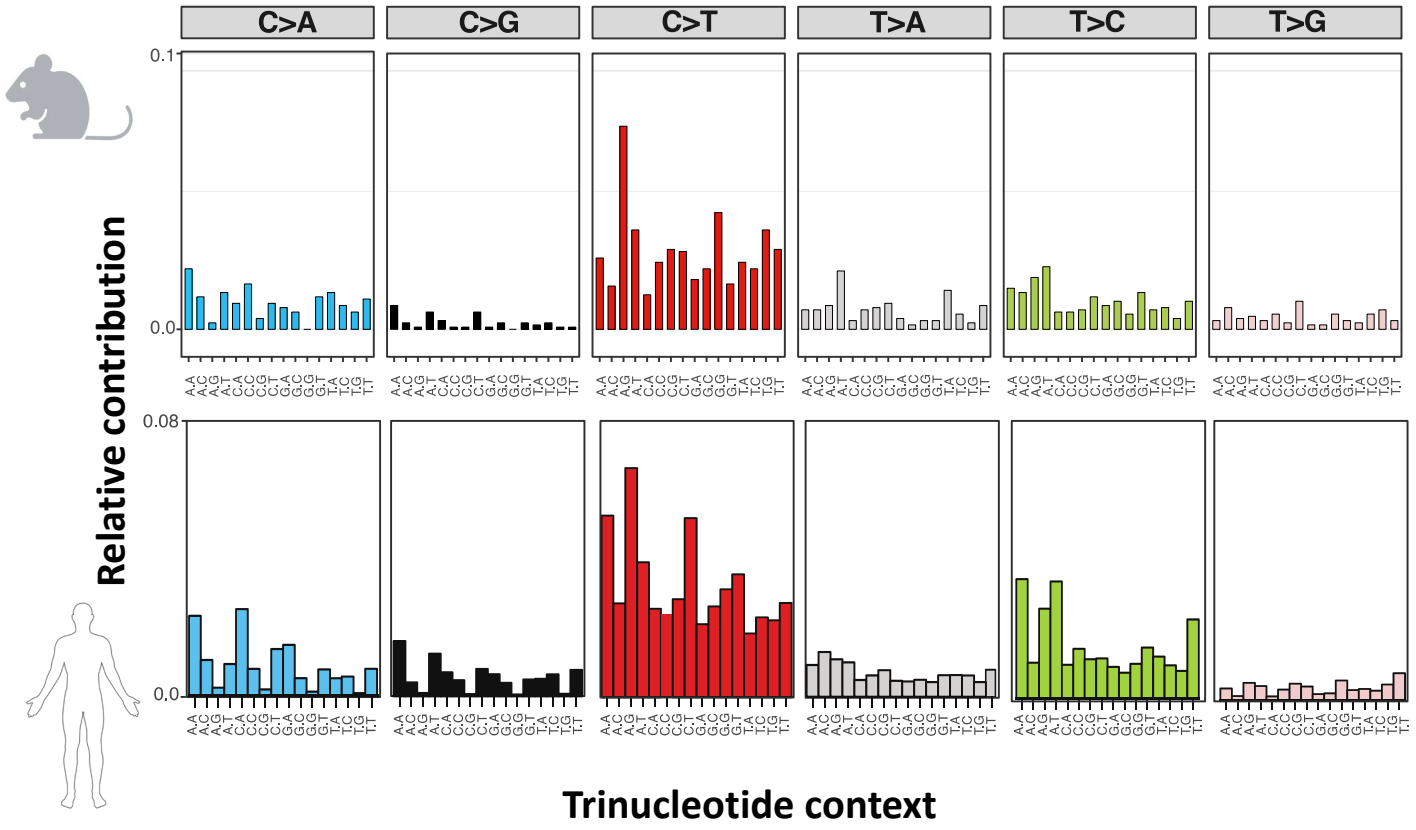


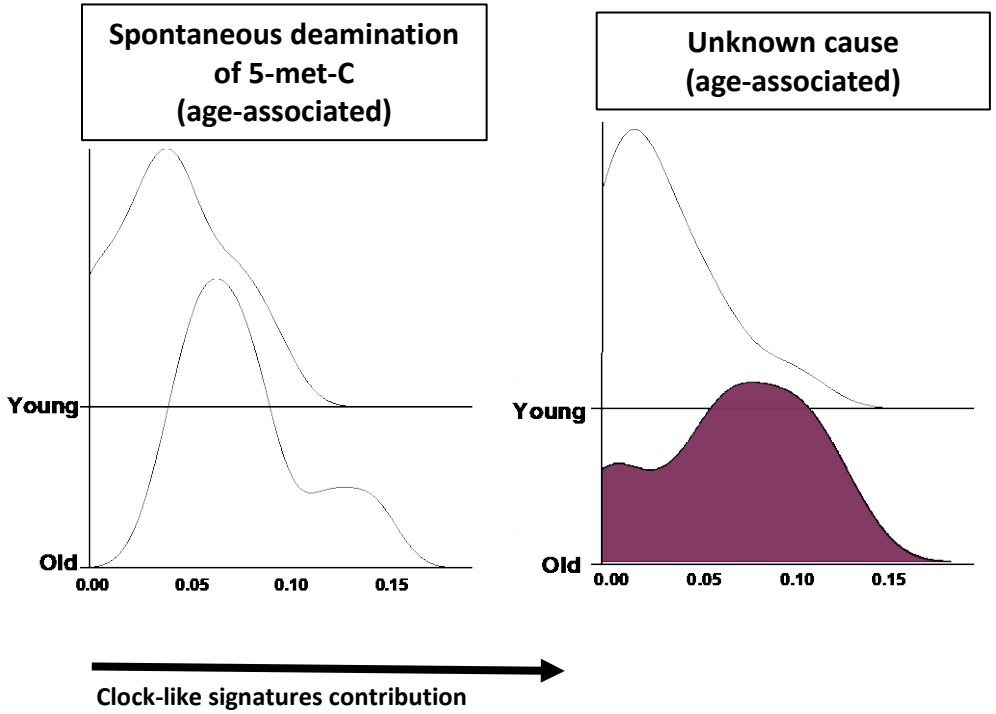
The SNV burden increases with age in murine HSCs





Analogous mutagenic processes between mouse and human HSCs

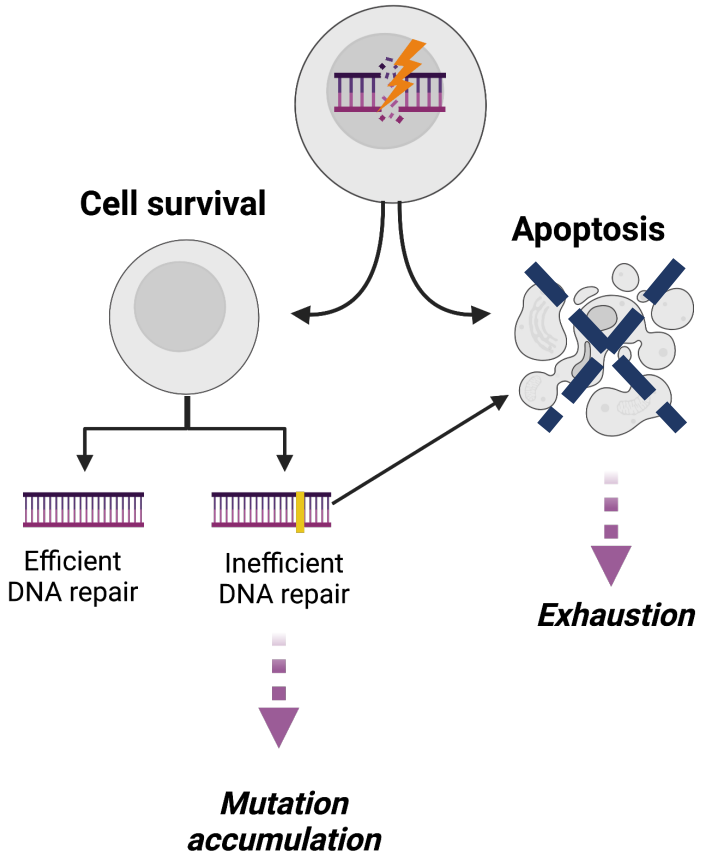


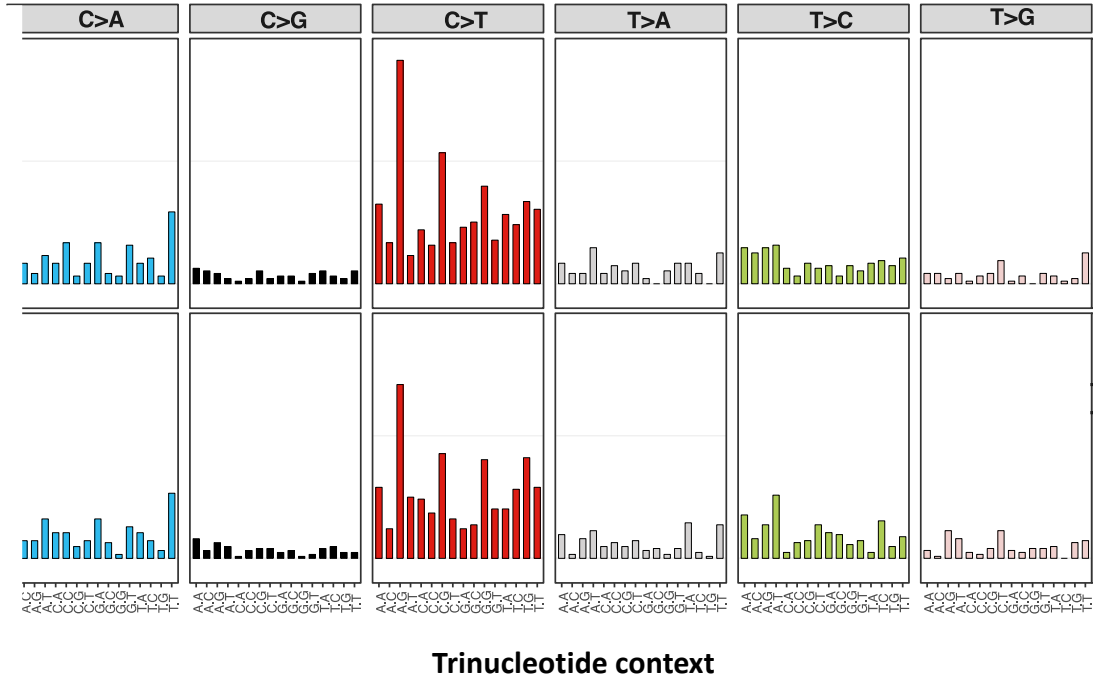


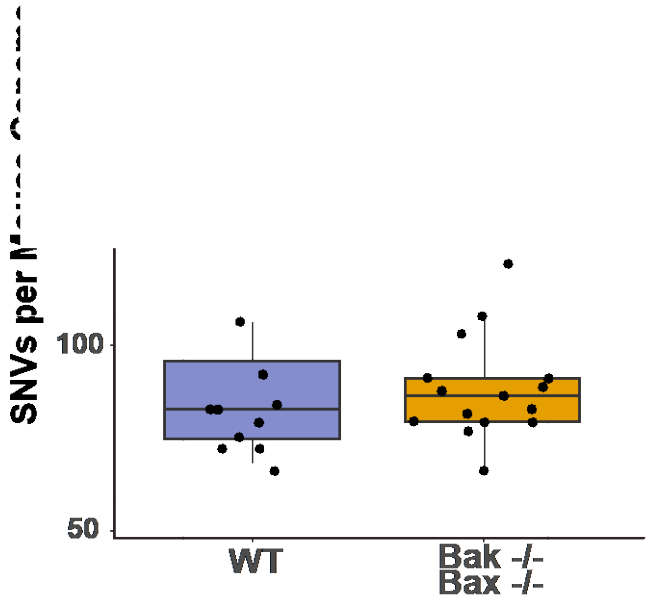
human pattern from Osorio et al. Cell Reports, 2018

Cell-intrinsic apoptosis does not maintain genomic integrity in HSCs

Do HSCs present low apoptotic thresholds?

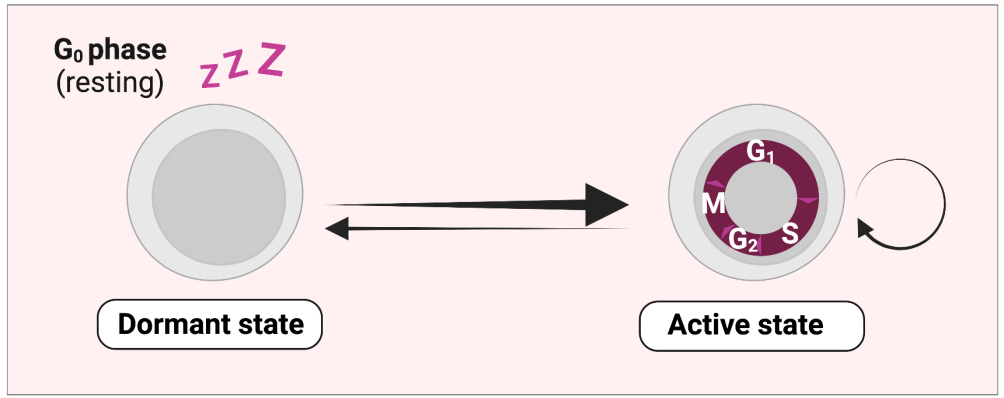




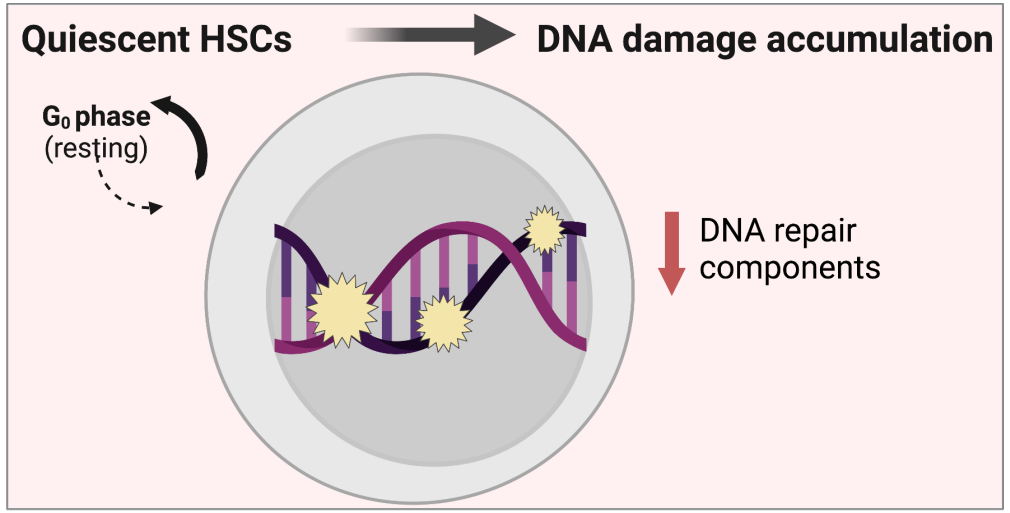


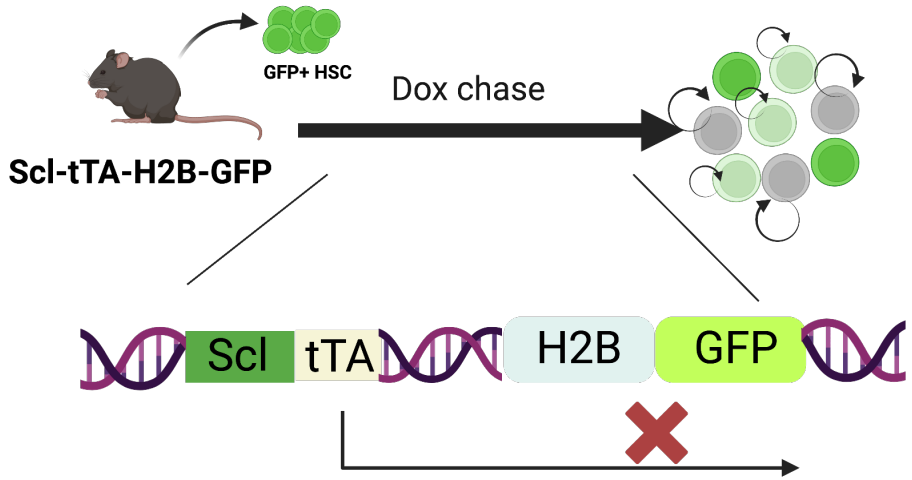
Apoptosis is dispensable under physiologic conditions

Dormant HSCs consist 2-5% of the aged HSC population



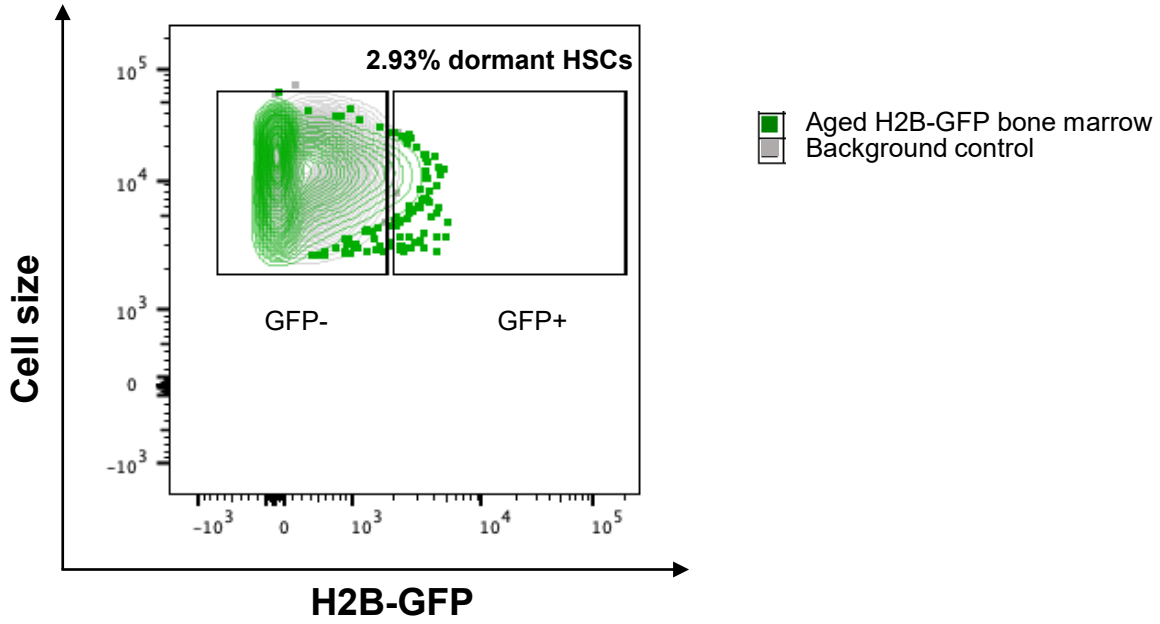
Dormant HSCs preserve a **younger-like fitness** compared to their active counterparts *(Sacma et al., Nature Cell Biology, 2019).*



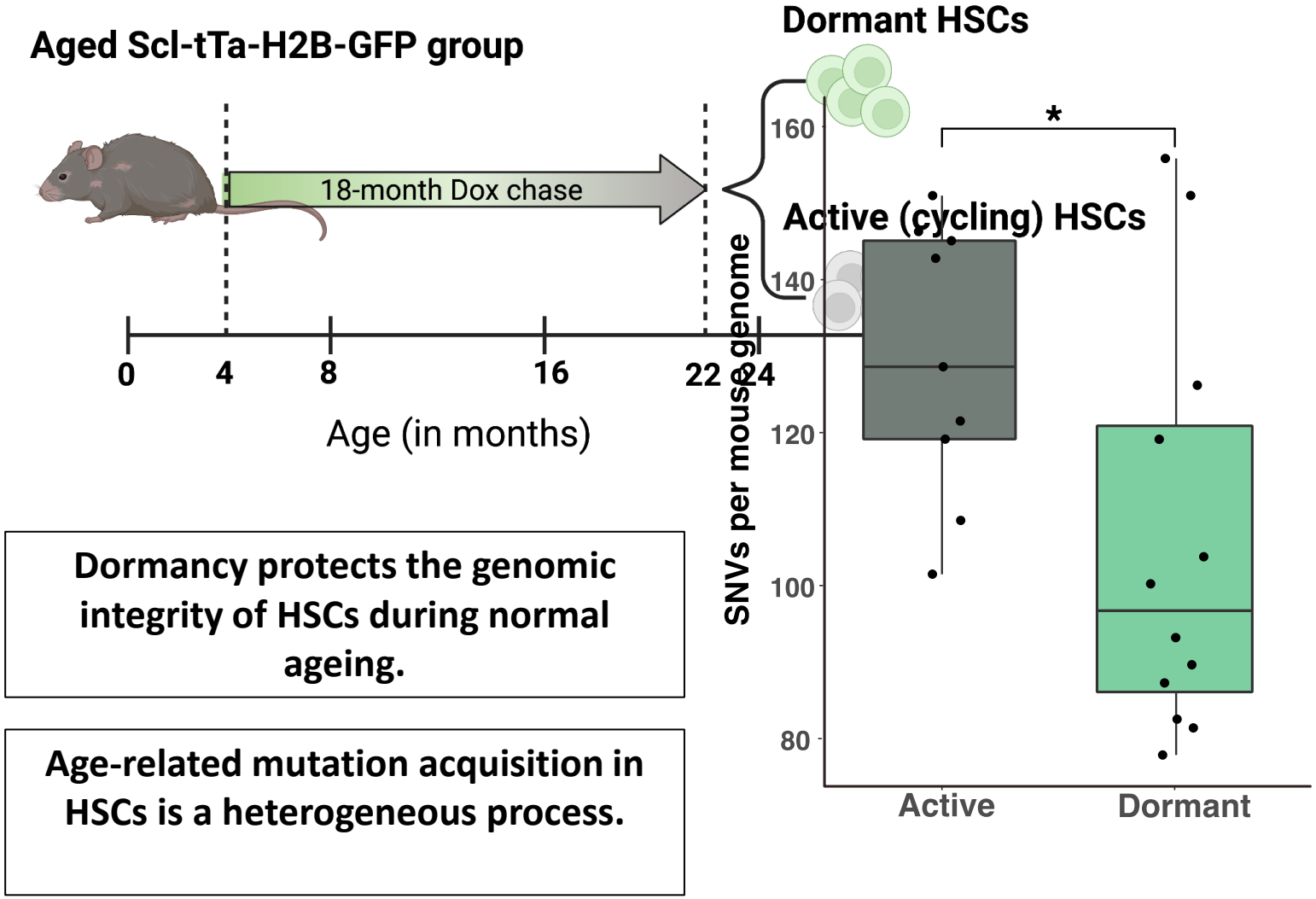


Wilson et al., Cell, 2008

Frequency of dormant HSCs

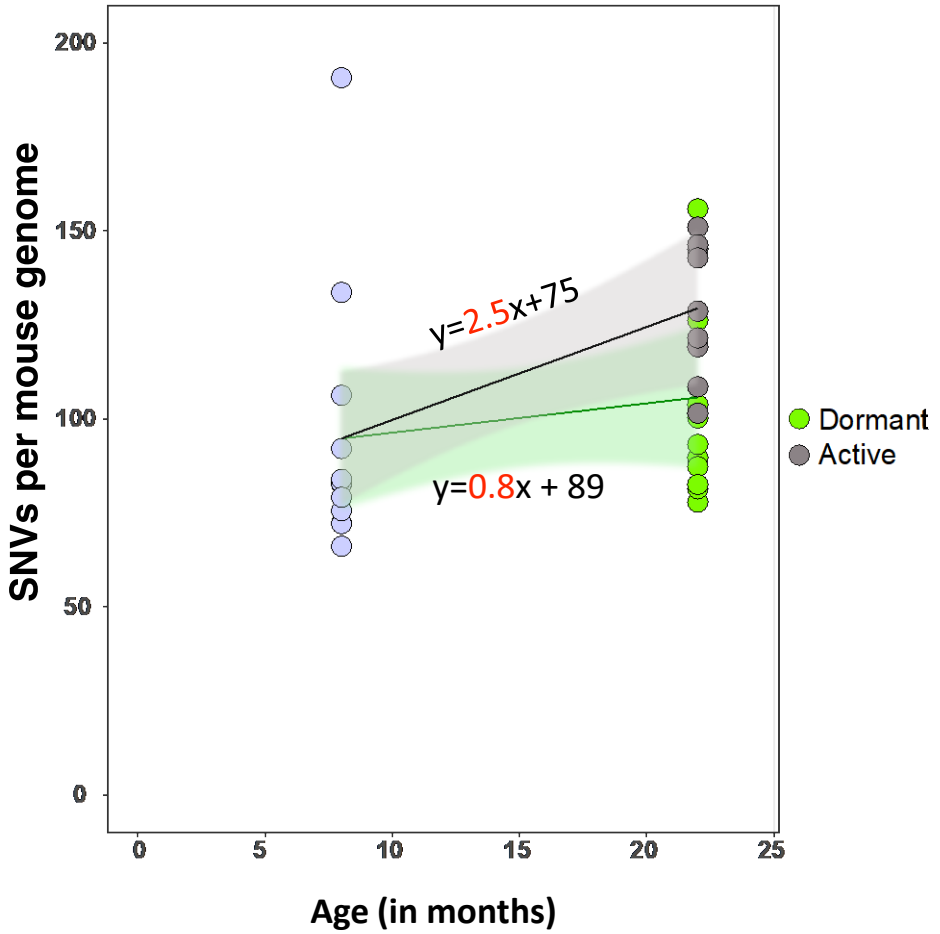


Dormancy restricts the age-associated mutagenesis in HSCs

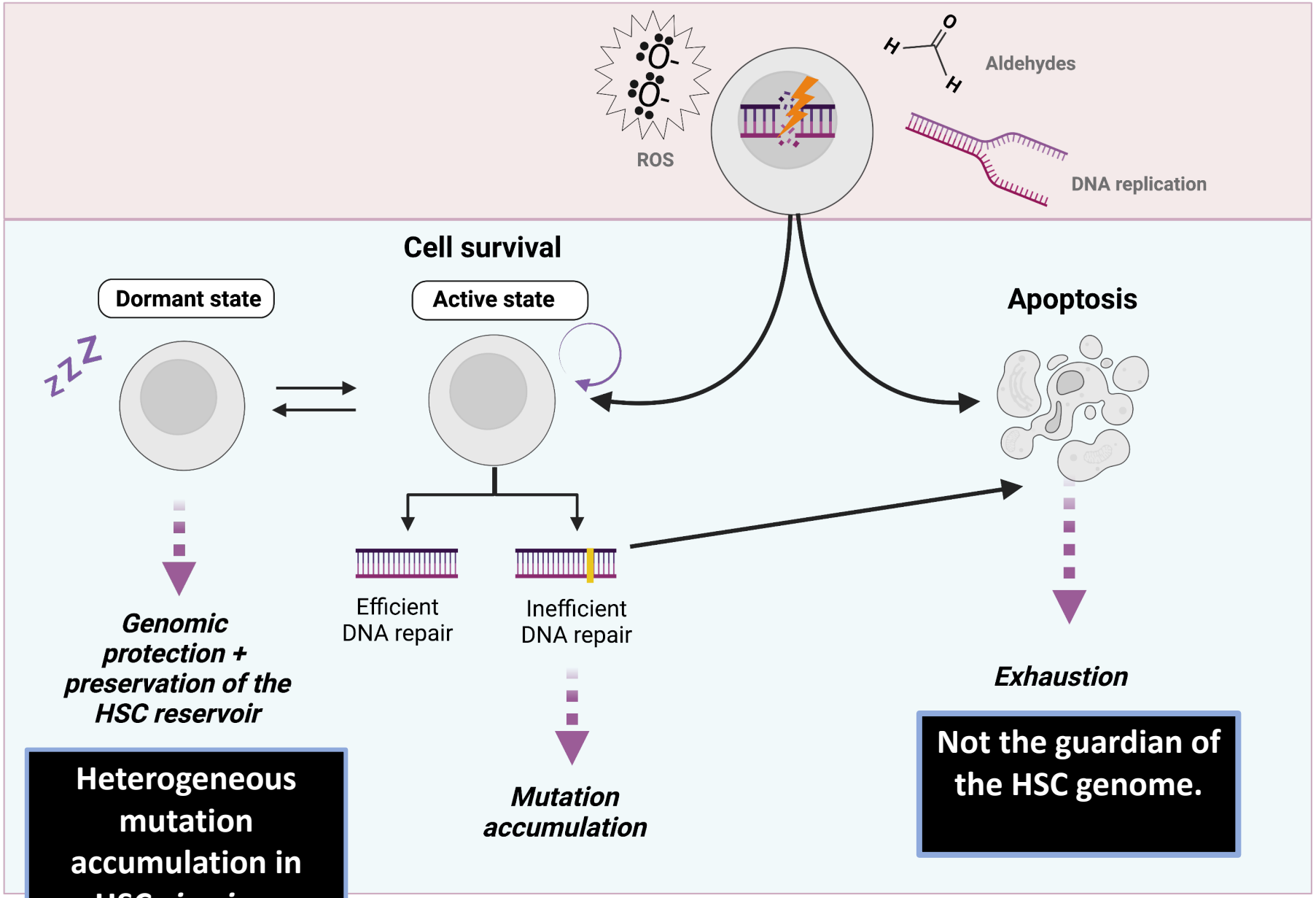


Dormancy protects the genomic integrity of HSCs during normal ageing.

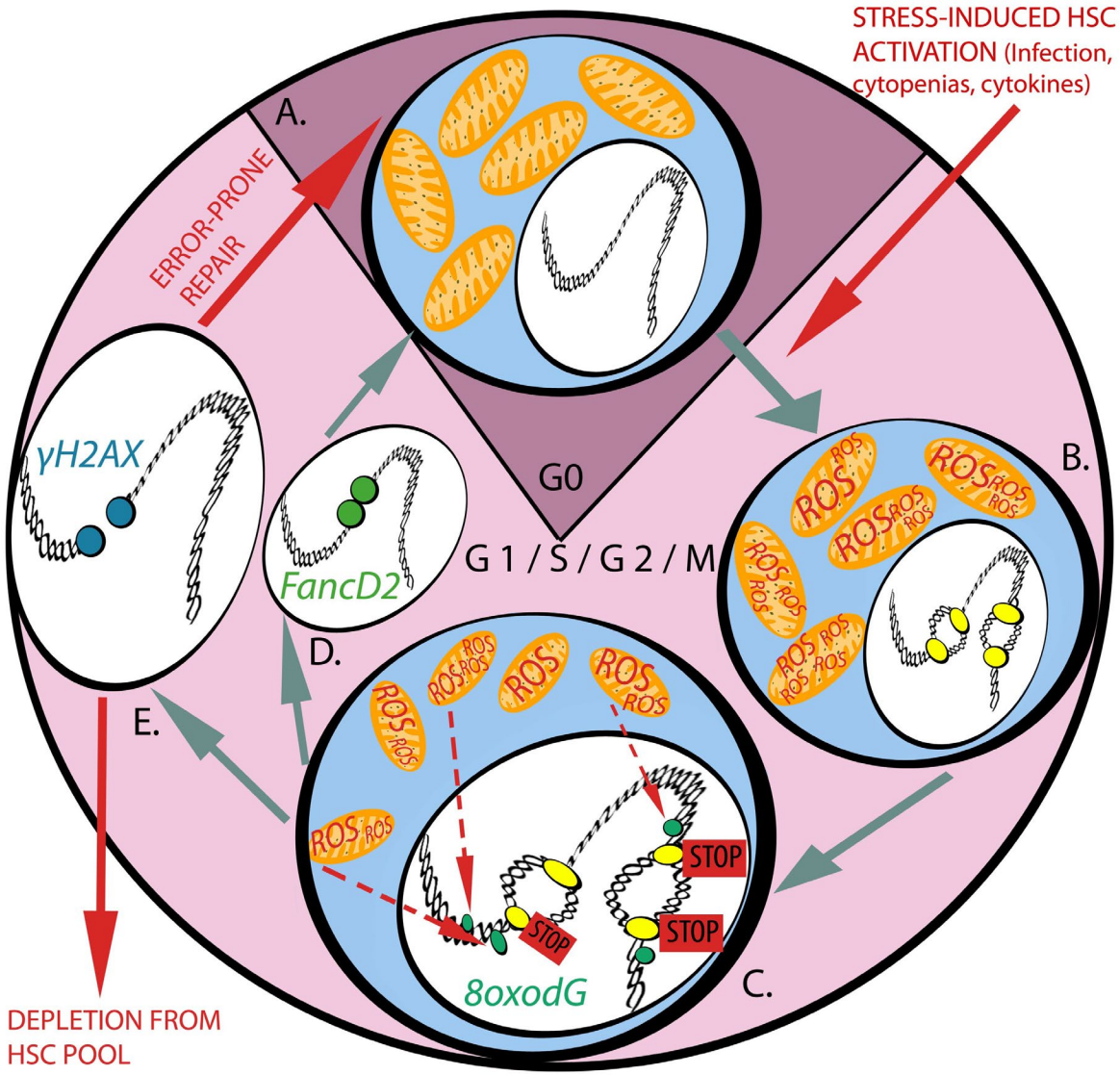
Age-related mutation acquisition in HSCs is a heterogeneous process.

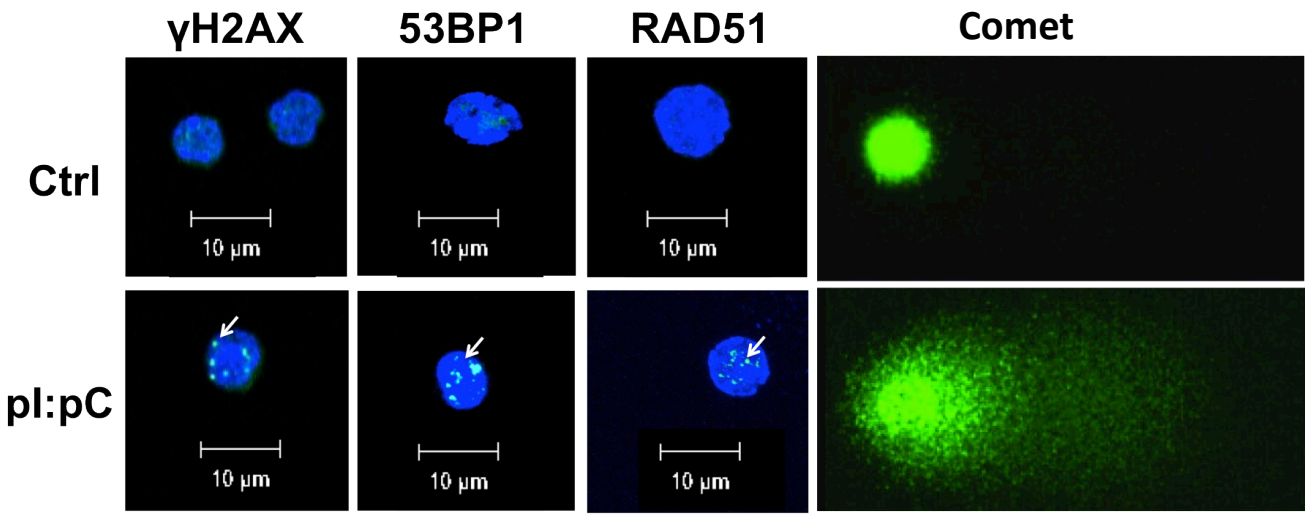


Summary


ROS
Aldehydes
DNA replication
Cell survival
Dormant state
Active state
Apoptosis
zzz
Genomic protection + preservation of the HSC reservoir
Efficient DNA repair
Inefficient DNA repair
Mutation accumulation
Exhaustion
Heterogeneous mutation accumulation in HSCs in vivo.
Not the guardian of the HSC genome.

Does inflammation/emergency hematopoiesis accelerate mutation acquisition rate in the HSC compartment?





Walter *et al.*, Nature, 2015

Acknowledgments

Acknowledgments

Division of Experimental Hematology

- **Foteini Fotopoulou**
- Megan Druce
- Viktoria Flore
- Ruzhica Bogeska

Wellcome Sanger Centre

- Inigo Martincorena
- Alex Cagan

German Cancer Research Center

- Benedikt Brors

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

HI-STEM HEIDELBERG INSTITUTE FOR STEM CELL TECHNOLOGY AND EXPERIMENTAL MEDICINE