Genomic Parasites Nibbling Away at Us: Why I Should Win the Nobel Prize

Science Circle
May 16th 2020

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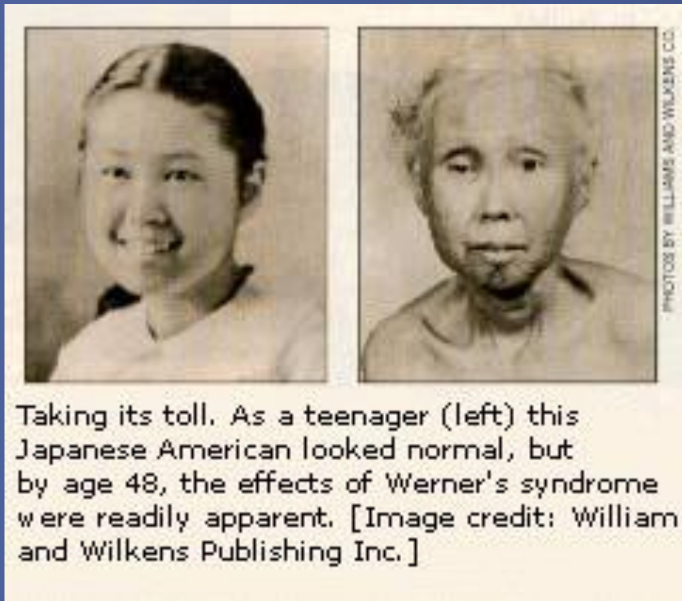
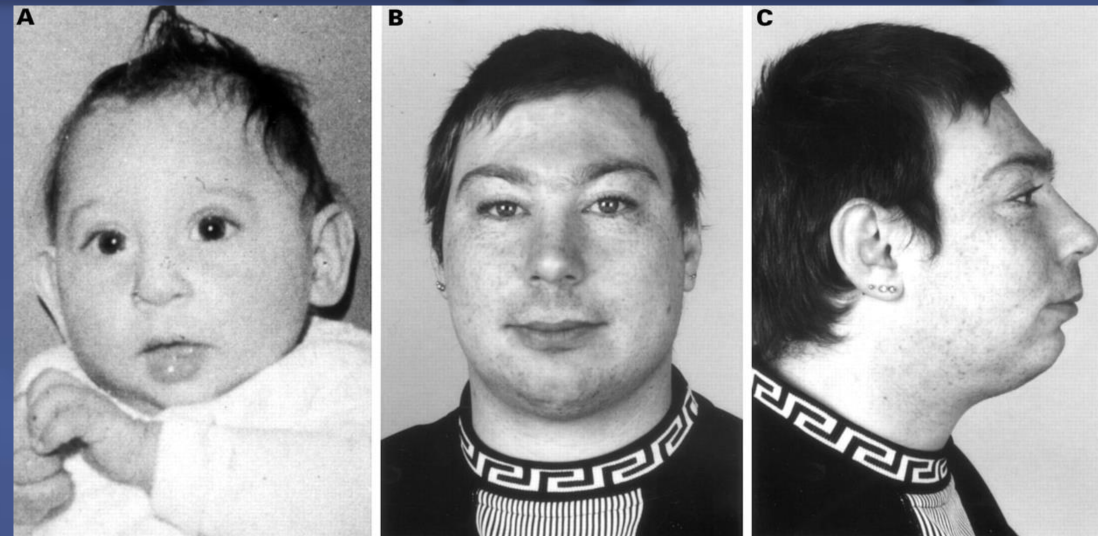
Progeria (Segmental)



Werner Syndrome
1904

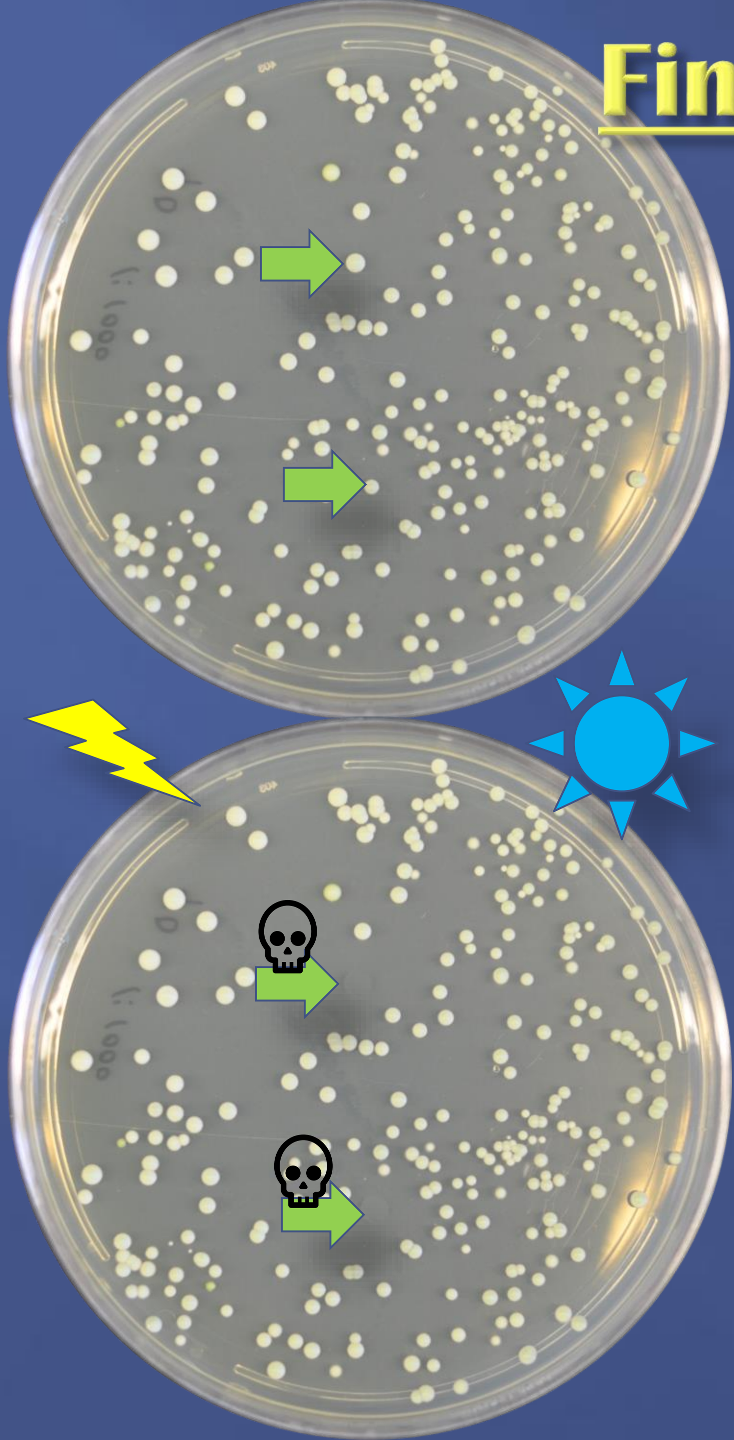


Nijmegen breakage Syndrome
1981

Seckel Syndrome
1960

Finding Yeast Repair Genes

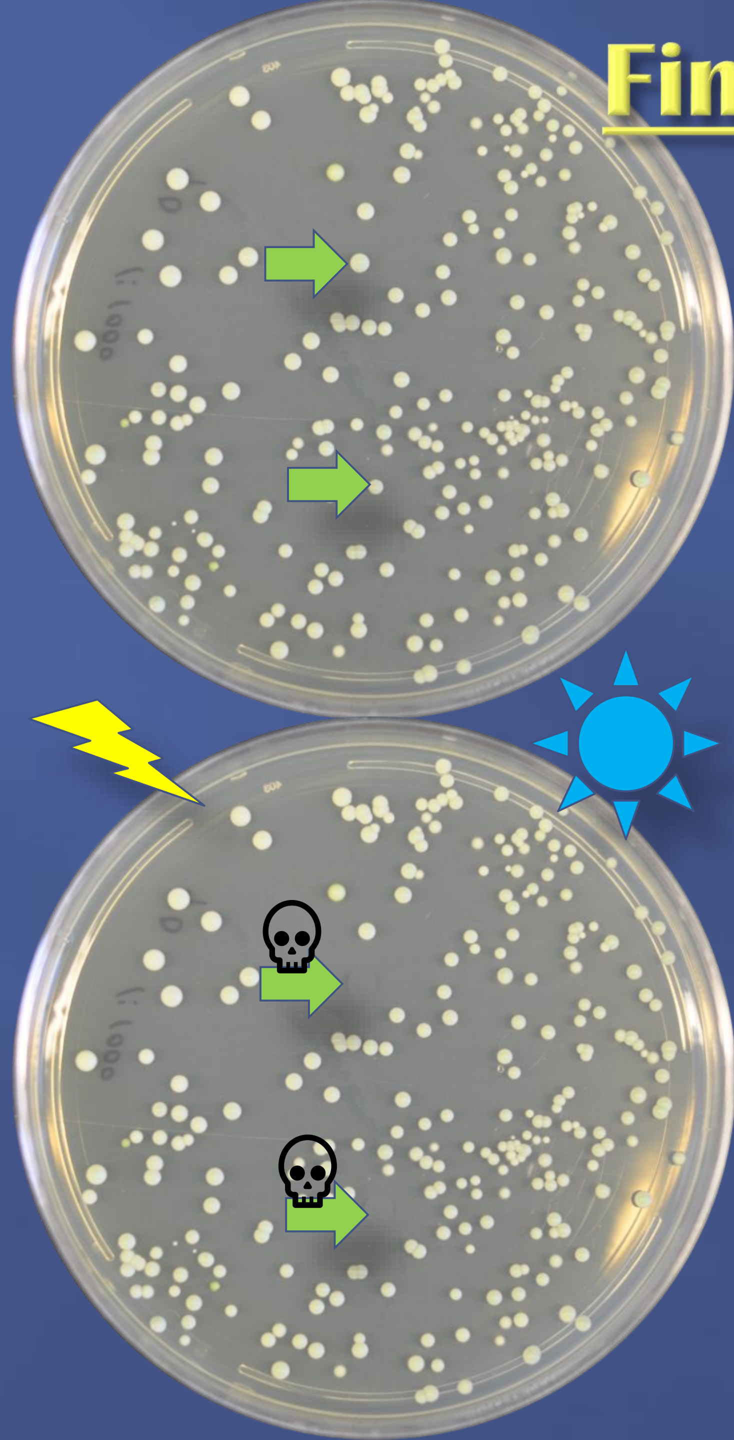
Genes: RAD(X) XRS(X)

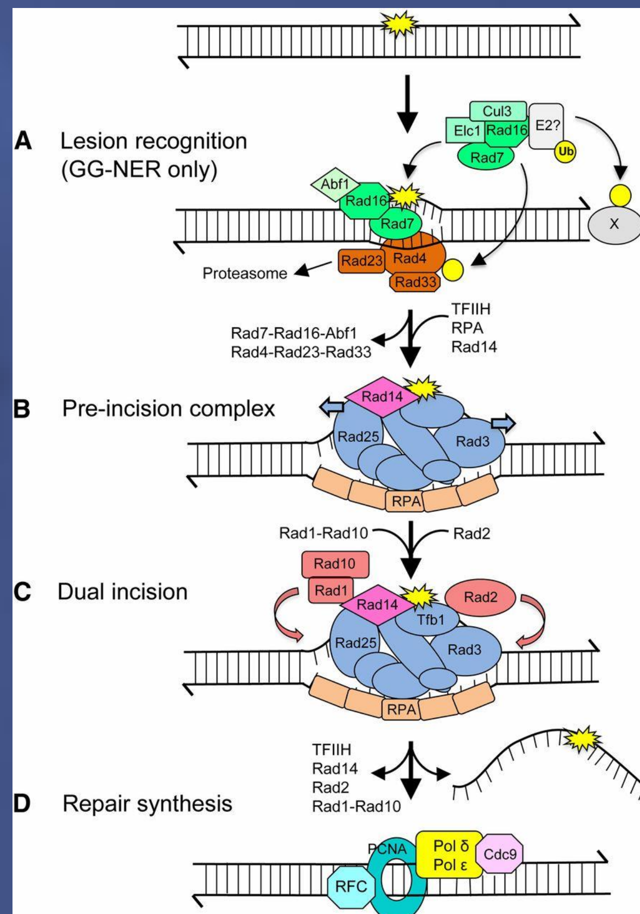


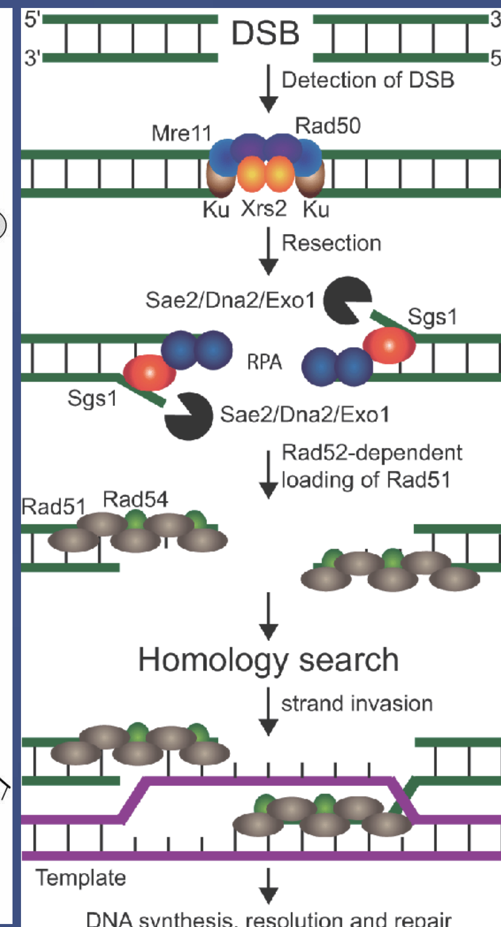
Finding Yeast Repair Genes

Genes: RAD(X) XRS(X)

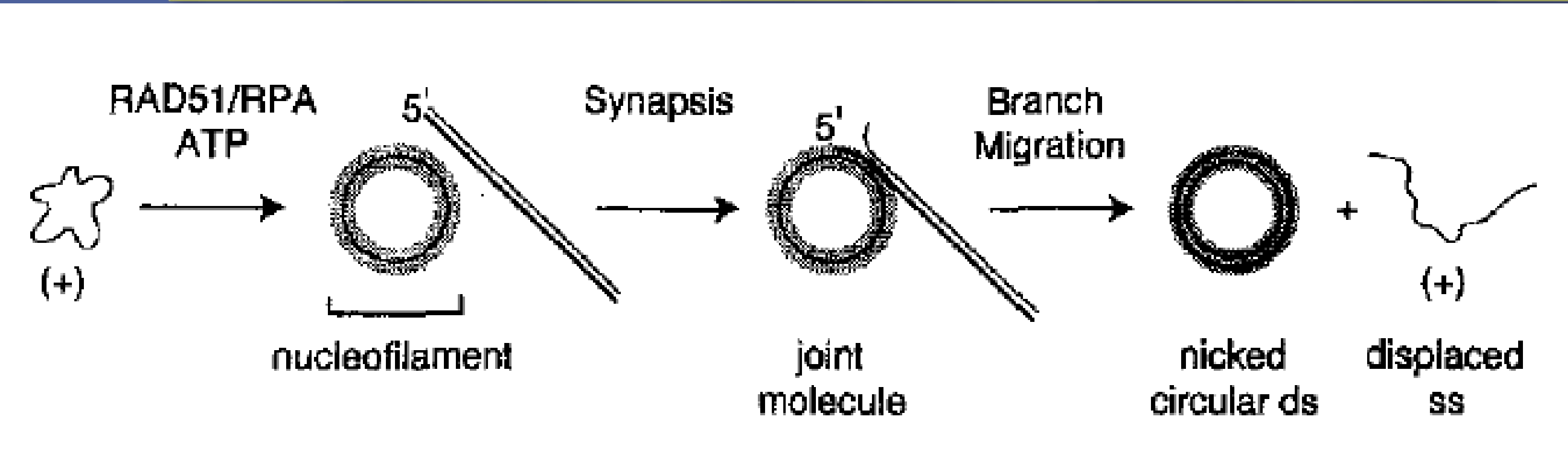
NER HR



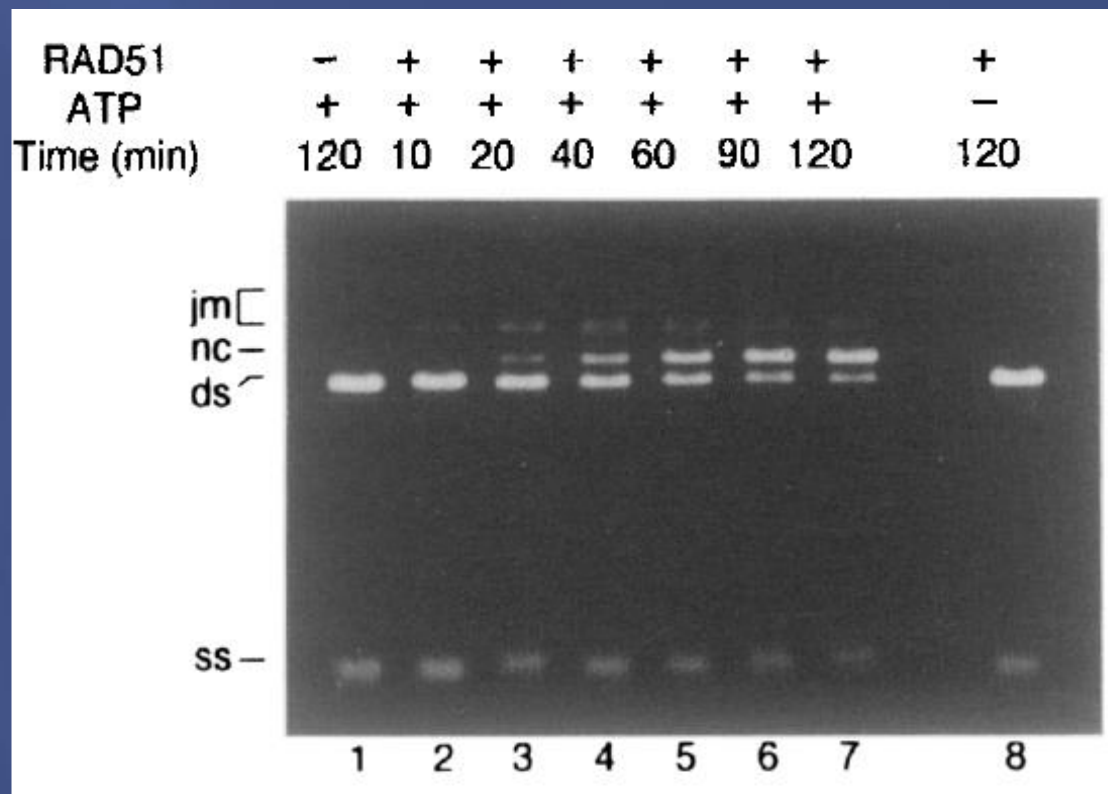




What a Rad Protein Does—Rad51

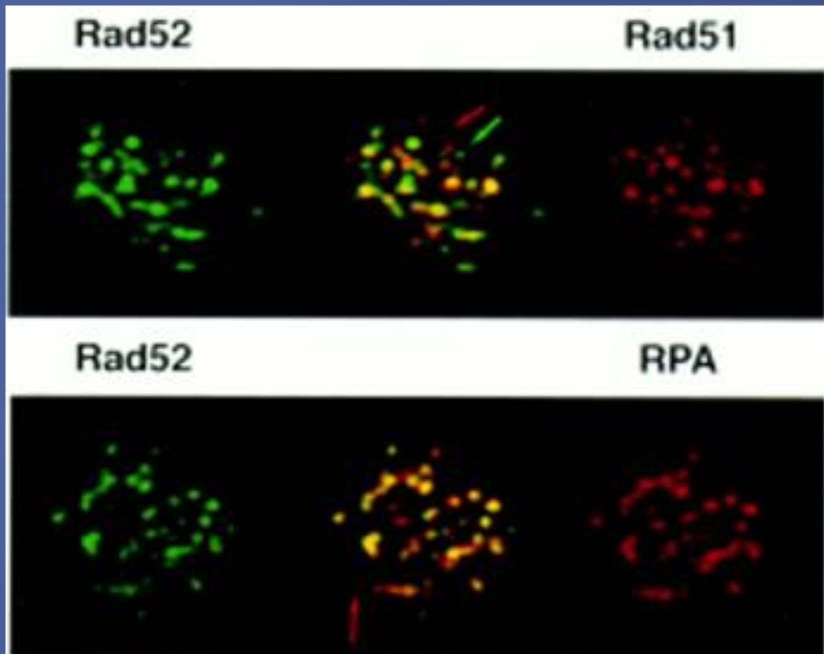


Strand Invasion—a way to repair DSBs by copying from a similar sequence

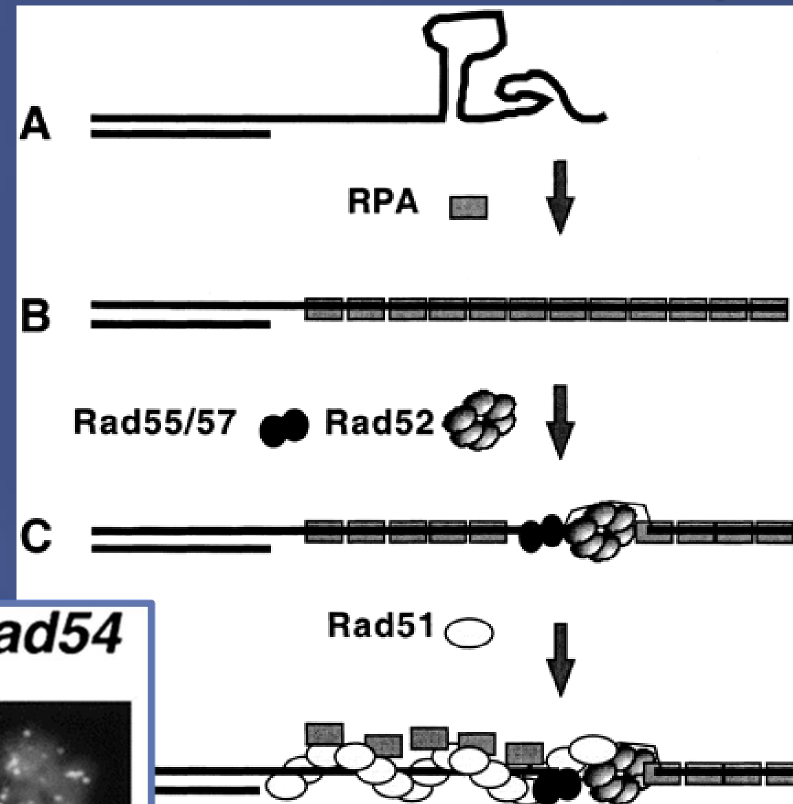


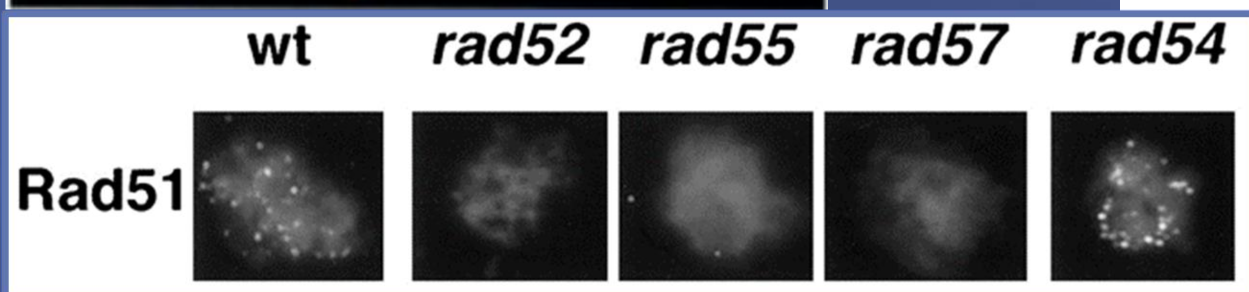
Sung, P., & Robberson, D. L. (1995). DNA strand exchange mediated by a RAD51-ssDNA nucleoprotein filament with polarity opposite to that of RecA. *Cell*, 82(3), 453-461.

I believe this is about me



Strand Invasion—Rad51 has help



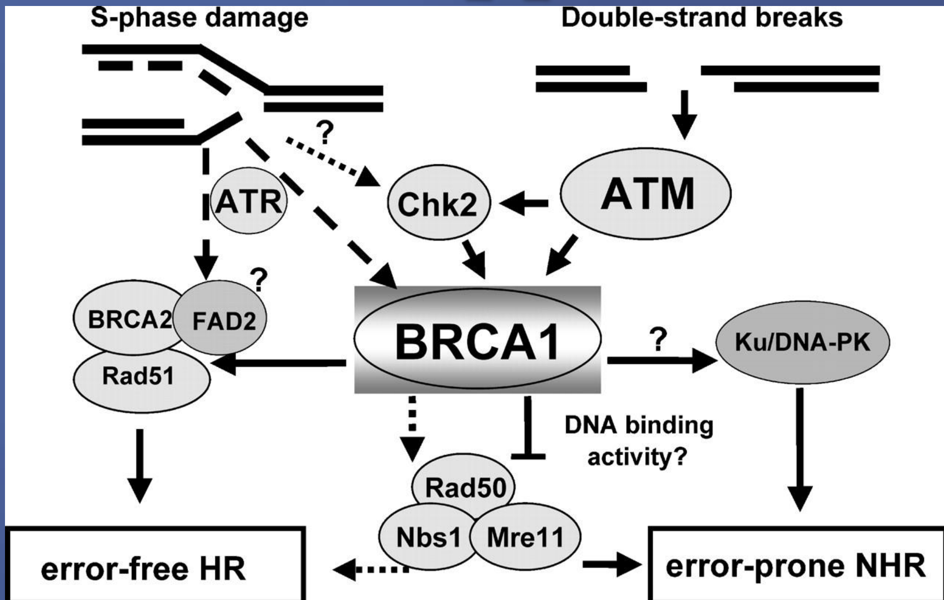


Gasior, S. L., Wong, A. K., Kora, Y., Shinohara, A., & Bishop, D. K. (1998). Rad52 associates with RPA and functions with Rad55 and Rad57 to assemble meiotic recombination complexes. *Genes & development*, 12(14), 2208-2221.

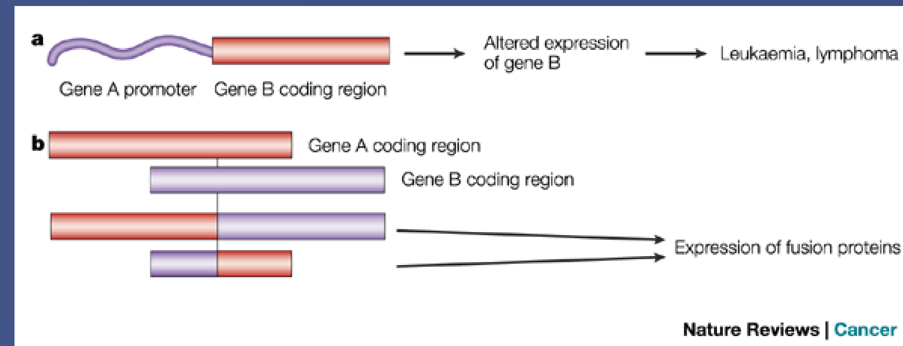
Shinohara, A., & Ogawa, T. (1998). Stimulation by Rad52 of yeast Rad51-mediated recombination. *Nature*, 391(6665), 404-407.

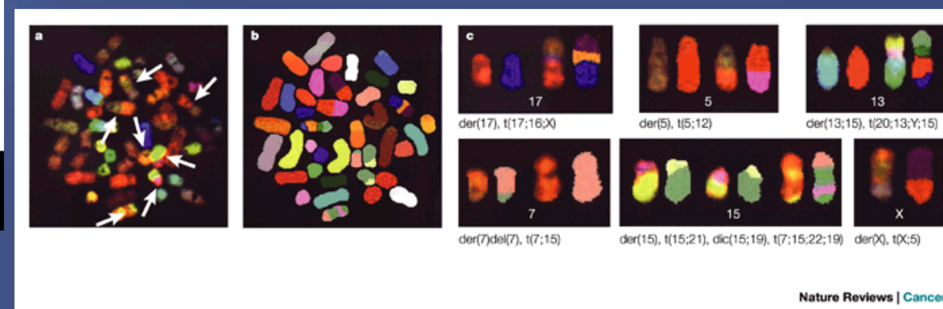
Cancer and DSB Repair

Tumor suppressors & translocations



Zhang, J., & Powell, S. N. (2005). The role of the BRCA1 tumor suppressor in DNA double-strand break repair. *Molecular Cancer Research*, 3(10), 531-539.





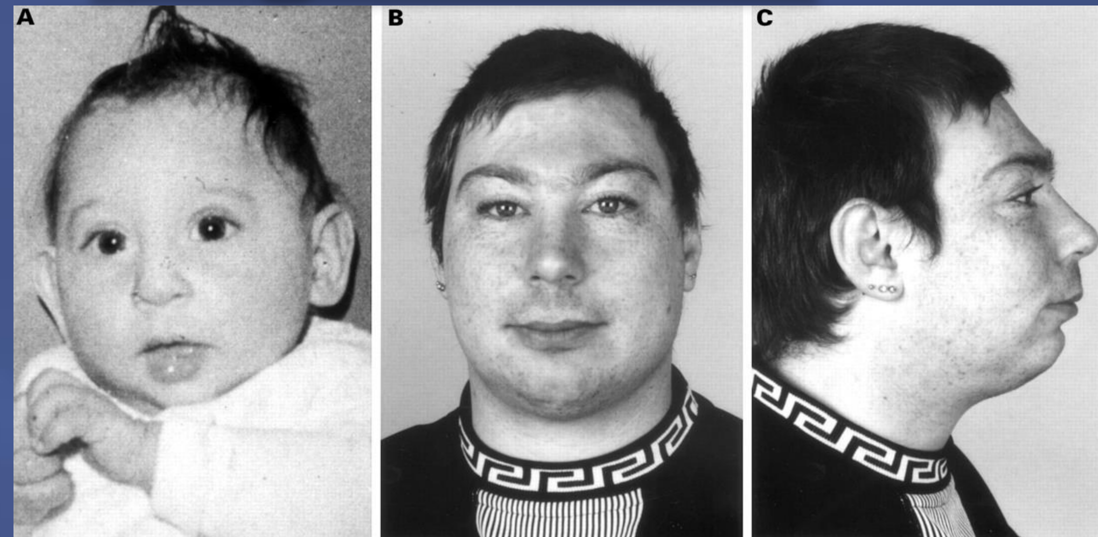
Rowley, J. D. (2001). Chromosome translocations: dangerous liaisons revisited. *Nature Reviews Cancer*, 1(3), 245-250.

Cancer is a result of repair (mostly of DSBs?) going awry.
Repair genes are important for preventing cancer.

Progeria Genes

Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image credit: William and Wilkens Publishing Inc.]

Werner Syndrome
1904
RECQL2/SGS1

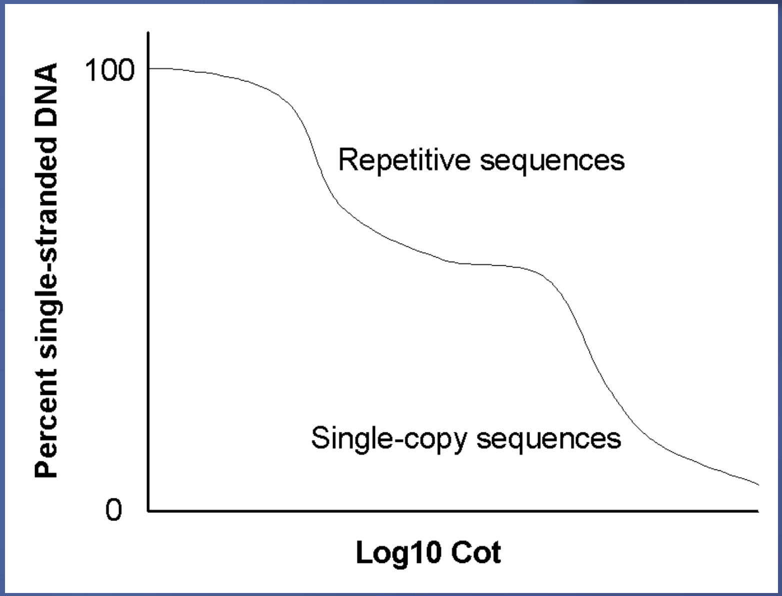


Nijmegen breakage Syndrome
1981
NBS1/XRS2

Seckel Syndrome
1960
ATR/MEC1(RAD3)

Understanding what genes/proteins do even in primitive organisms helps us understand their roles in humans

Cot DNA and Alu



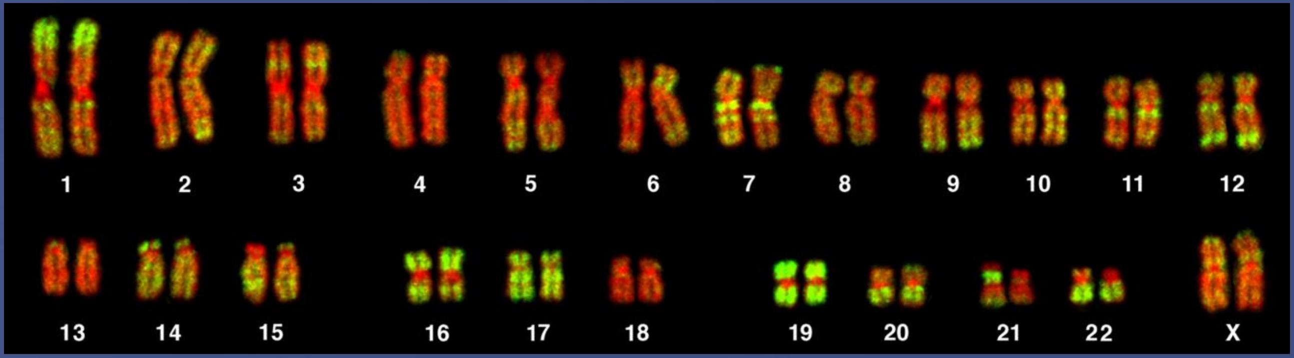
7SL RNA head

Deininger, P. L., Jolly, D. J., Rubin, C. M., Friedmann, T., & Schmid, C. W. (1981). Base sequence studies of 300 nucleotide renatured repeated human DNA clones. *Journal of molecular biology*, 151(1), 17-33.

https://en.wikipedia.org/wiki/Cot_analysis

Alu

DNA



https://en.wikipedia.org/wiki/Alu_element

Alu elements are small RNA only encoding species abundant in the human genome

LINE-1 in Human Disease

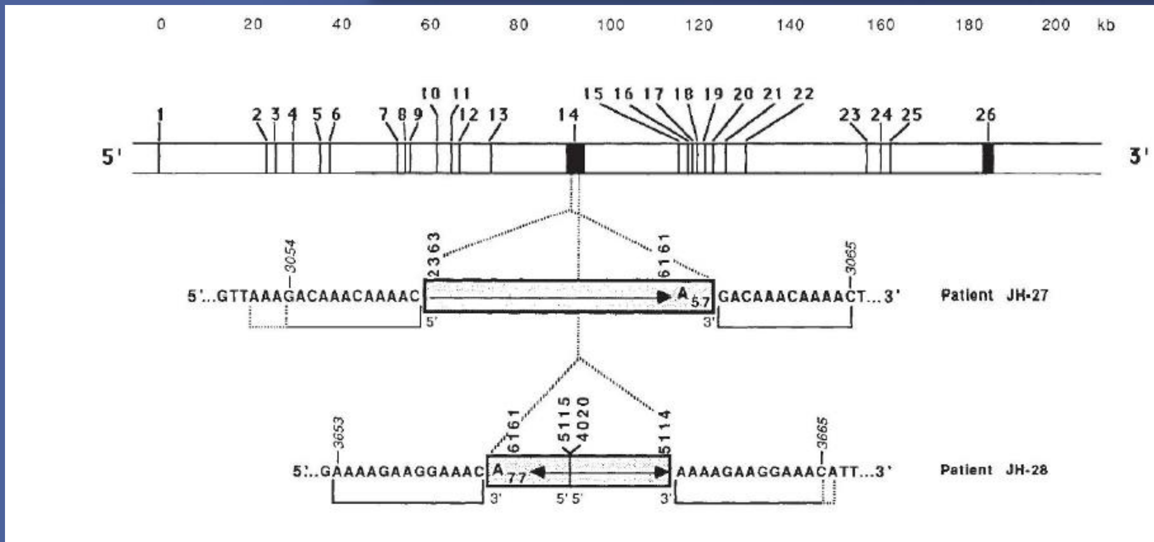
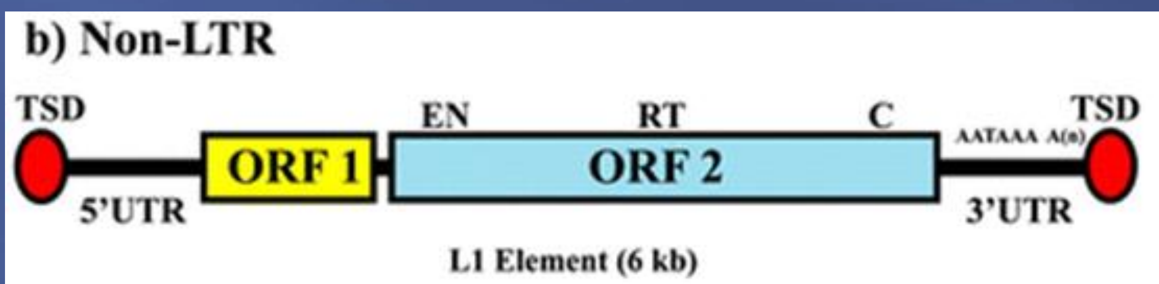
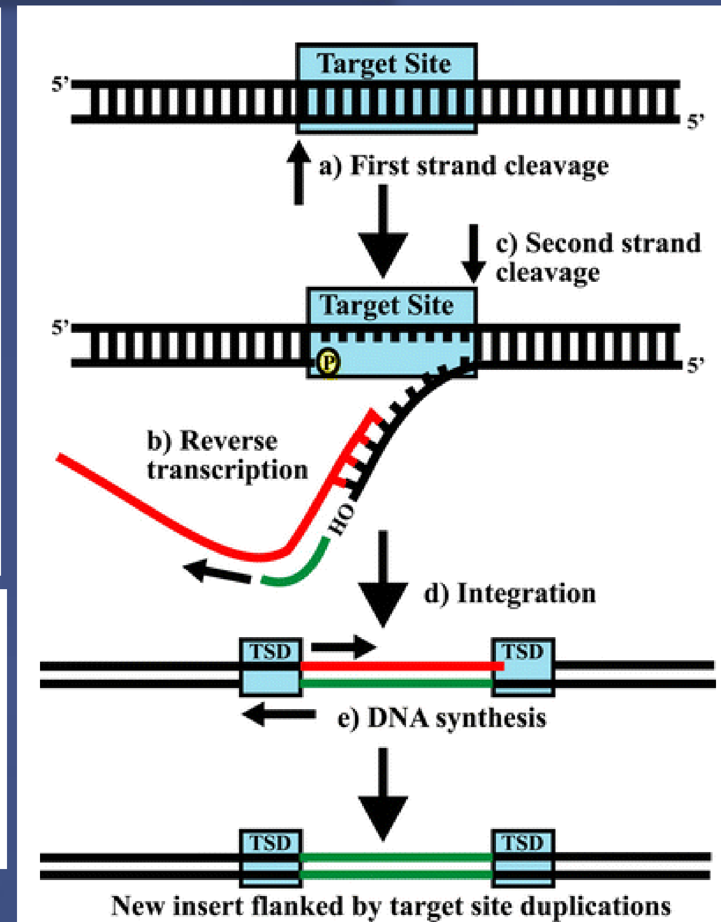


Fig. 2 Diagram of L1 insertions in exon 14 of the factor VIII gene. The factor VIII gene spans 186 kb and contains 26 exons .



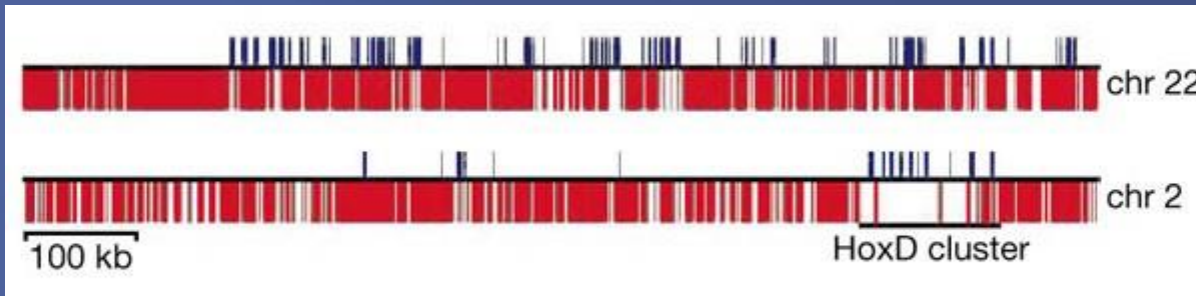


Hancks, D. C., & Kazazian, H. H. (2016). Roles for retrotransposon insertions in human disease. *Mobile DNA*, 7(1), 9.

Ostertag, E. M., & Kazazian Jr, H. H. (2001). Biology of mammalian L1 retrotransposons. *Annual review of genetics*, 35(1), 501-538.

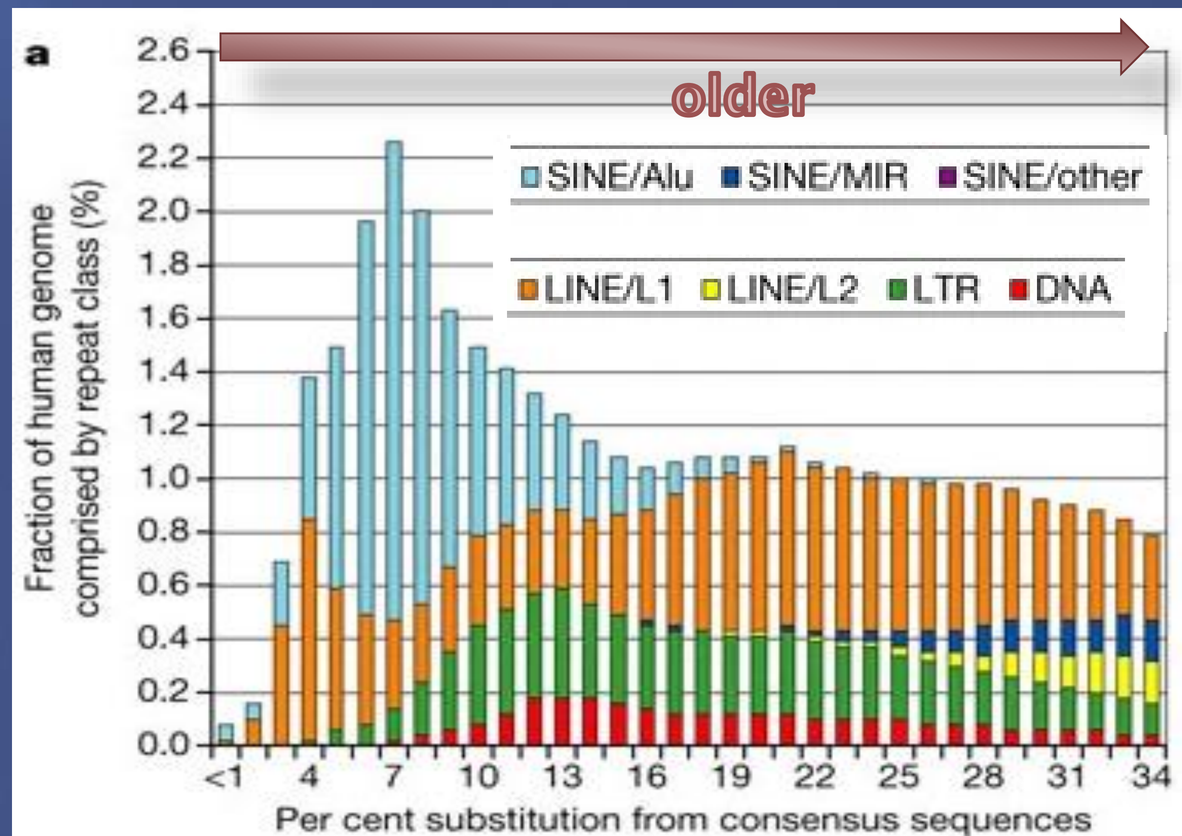
Kazazian, H. H., Wong, C., Youssoufian, H., Scott, A. F., Phillips, D. G., & Antonarakis, S. E. (1988). Haemophilia A resulting from de novo insertion of L1 sequences represents a novel mechanism for mutation in man. *Nature*, 332(6160), 164-166.

Alu and LINE-1 in Human Genome



Repeats
Exons

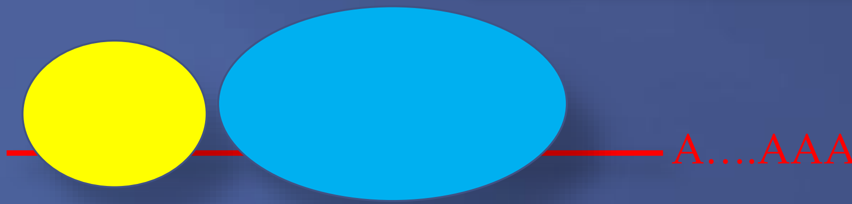
Alu 11%
LINE-1 17%

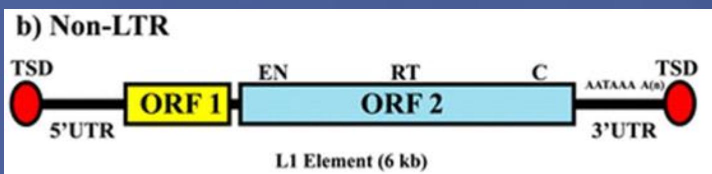


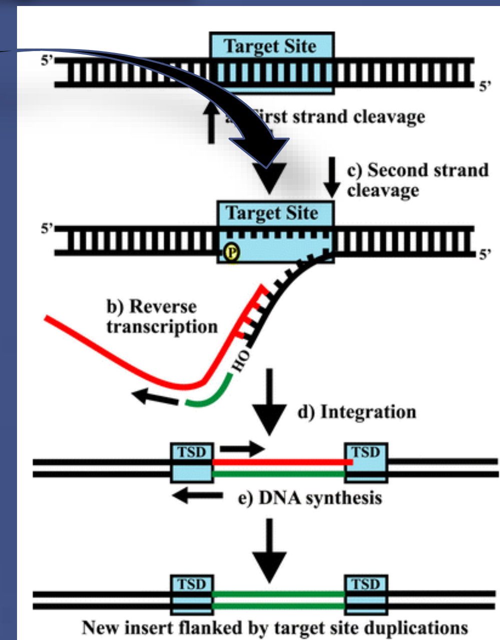
Still several active full length elements

International Human Genome Sequencing Consortium. (2001). Initial sequencing and analysis of the human genome. *Nature*, 409, 860-921.

LINE-1 Life Cycle





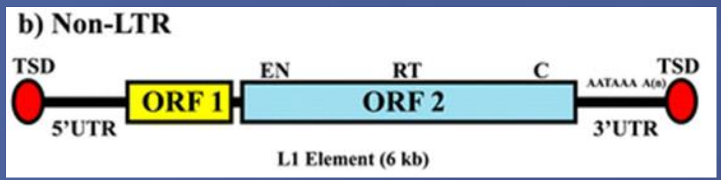


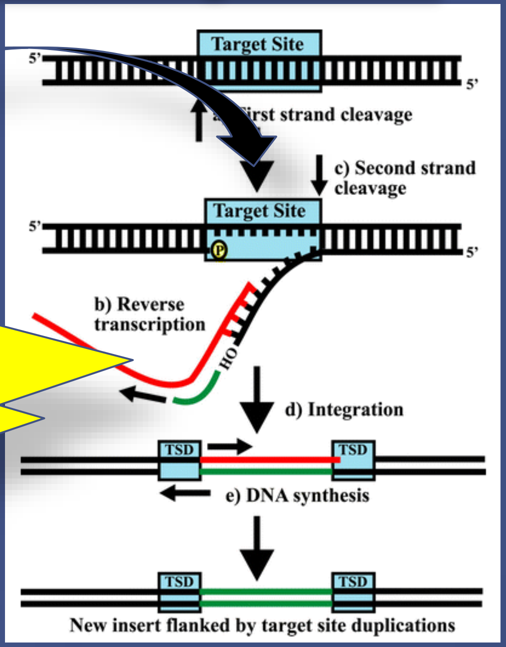
Cut

Copy

Integrate

LINE-1? DSBs? DNA Repair?

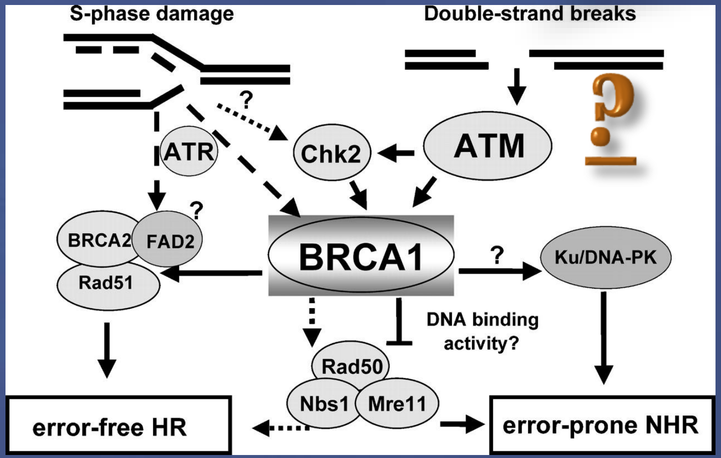




Cut

Copy

Integrate



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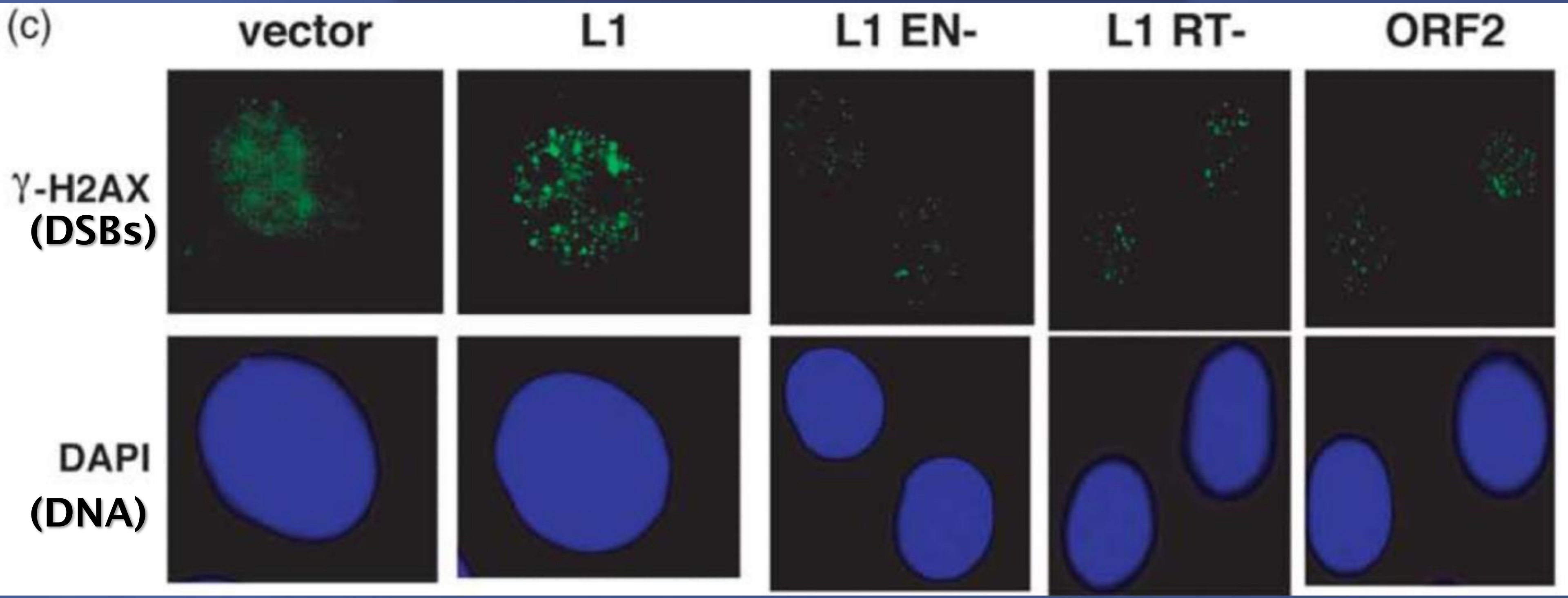
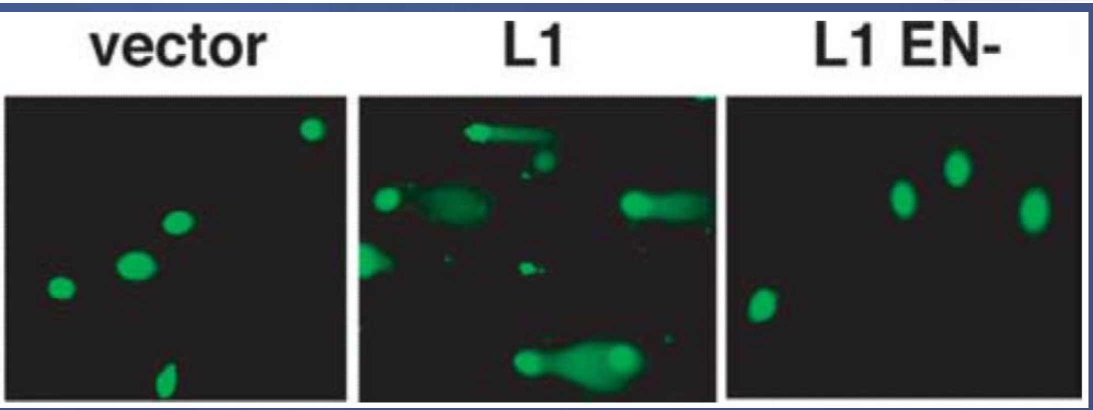
LINE-1 Creates DSBs

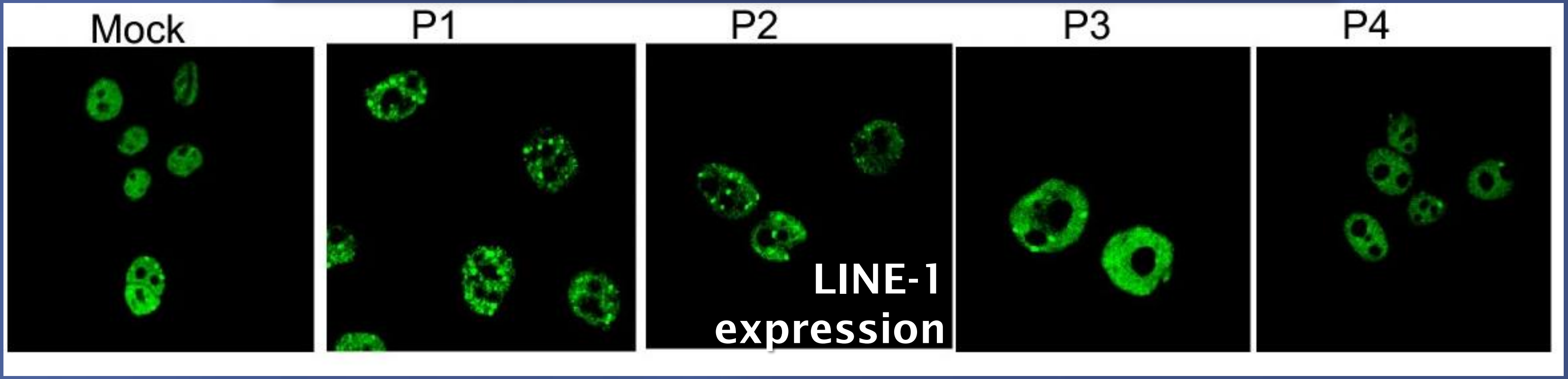




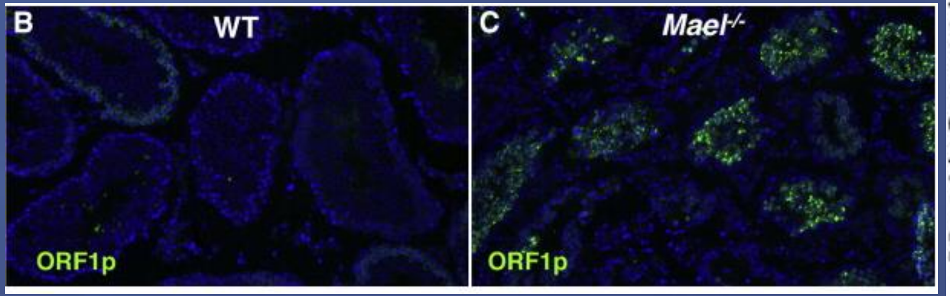
L1 makes DSBs >1000 fold than it makes insertions (a very rough estimate)

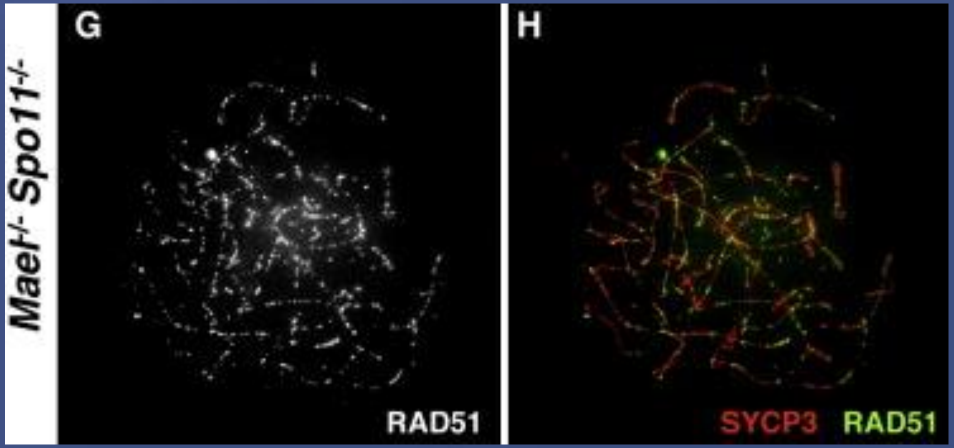
Gasior, S. L., Wakeman, T. P., Xu, B., & Deininger, P. L. (2006). The human LINE-1 retrotransposon creates DNA double-strand breaks. *Journal of molecular biology*, 357(5), 1383-1393.

LINE-1 Creates DSBs cont.



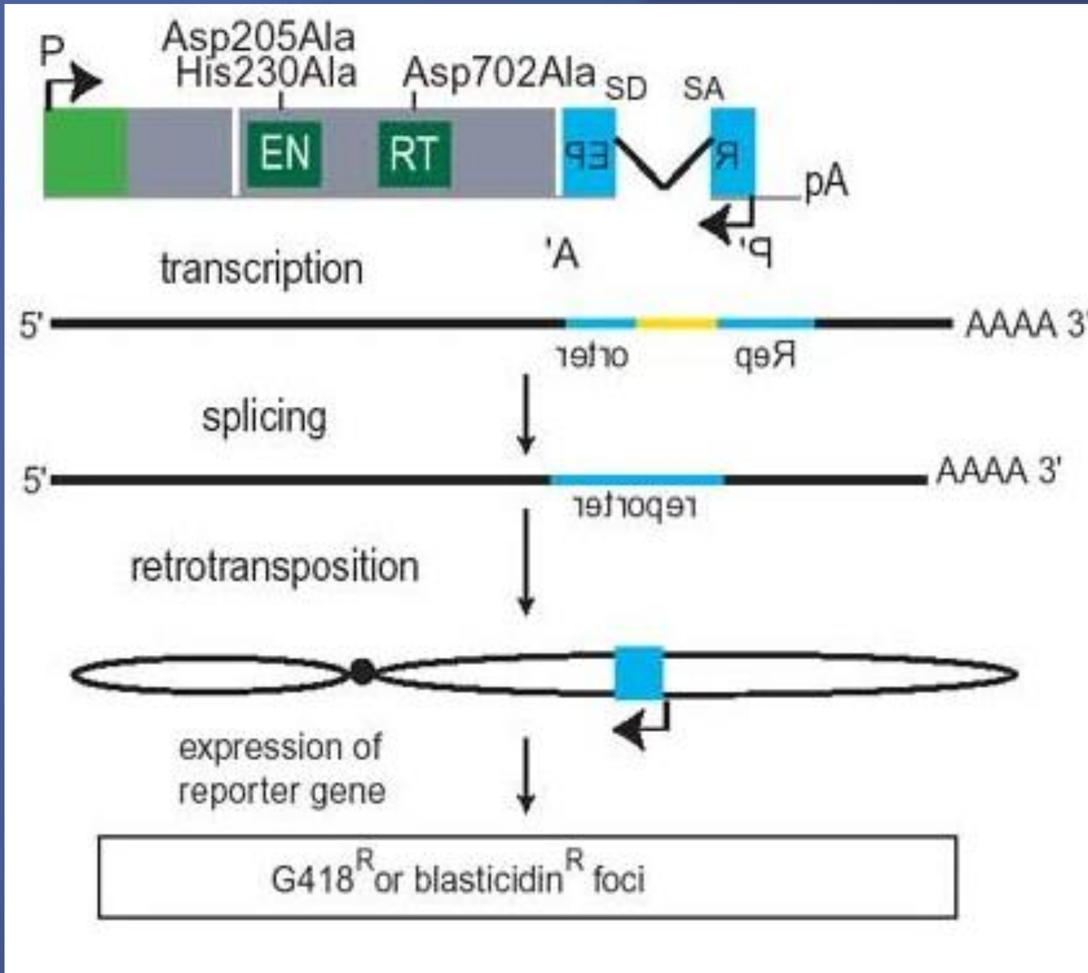
Belgnaoui, S. M., Gosden, R. G., Semmes, O. J., & Haoudi, A. (2006). Human LINE-1 retrotransposon induces DNA damage and apoptosis in cancer cells. *Cancer cell international*, 6(1), 13.

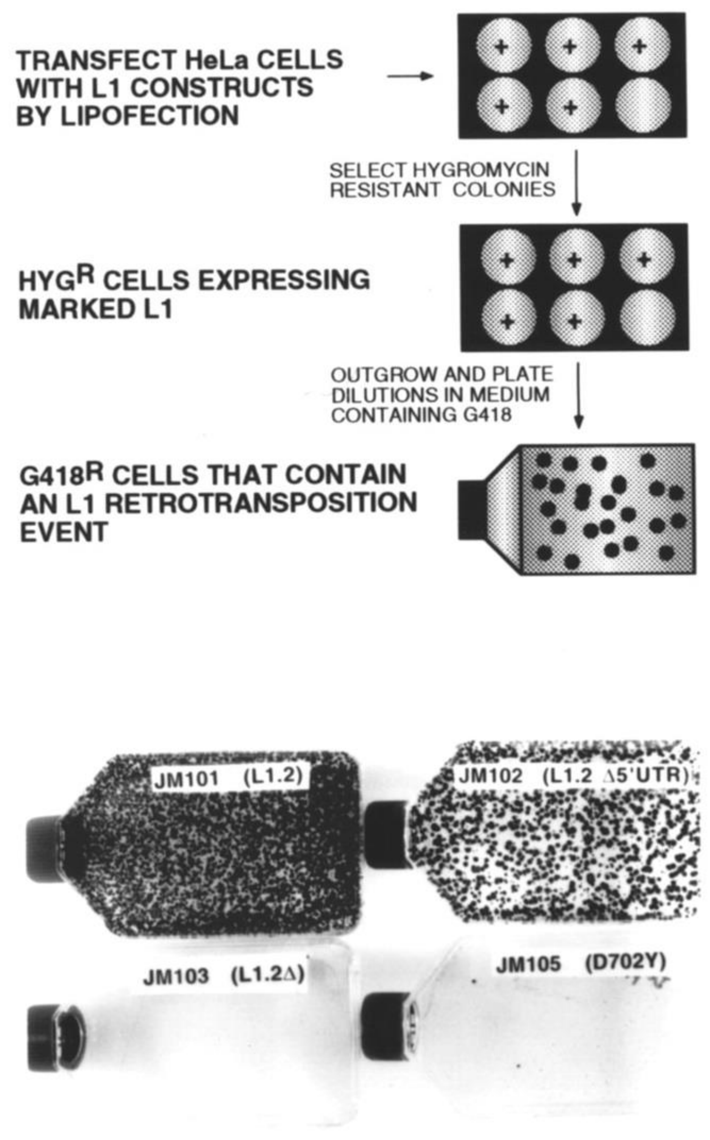




Soper, S. F., van der Heijden, G. W., Hardiman, T. C., Goodheart, M., Martin, S. L., de Boer, P., & Bortvin, A. (2008). Mouse maelstrom, a component of nuage, is essential for spermatogenesis and transposon repression in meiosis. *Developmental cell*, 15(2), 285-297.

LINE-1 Assay

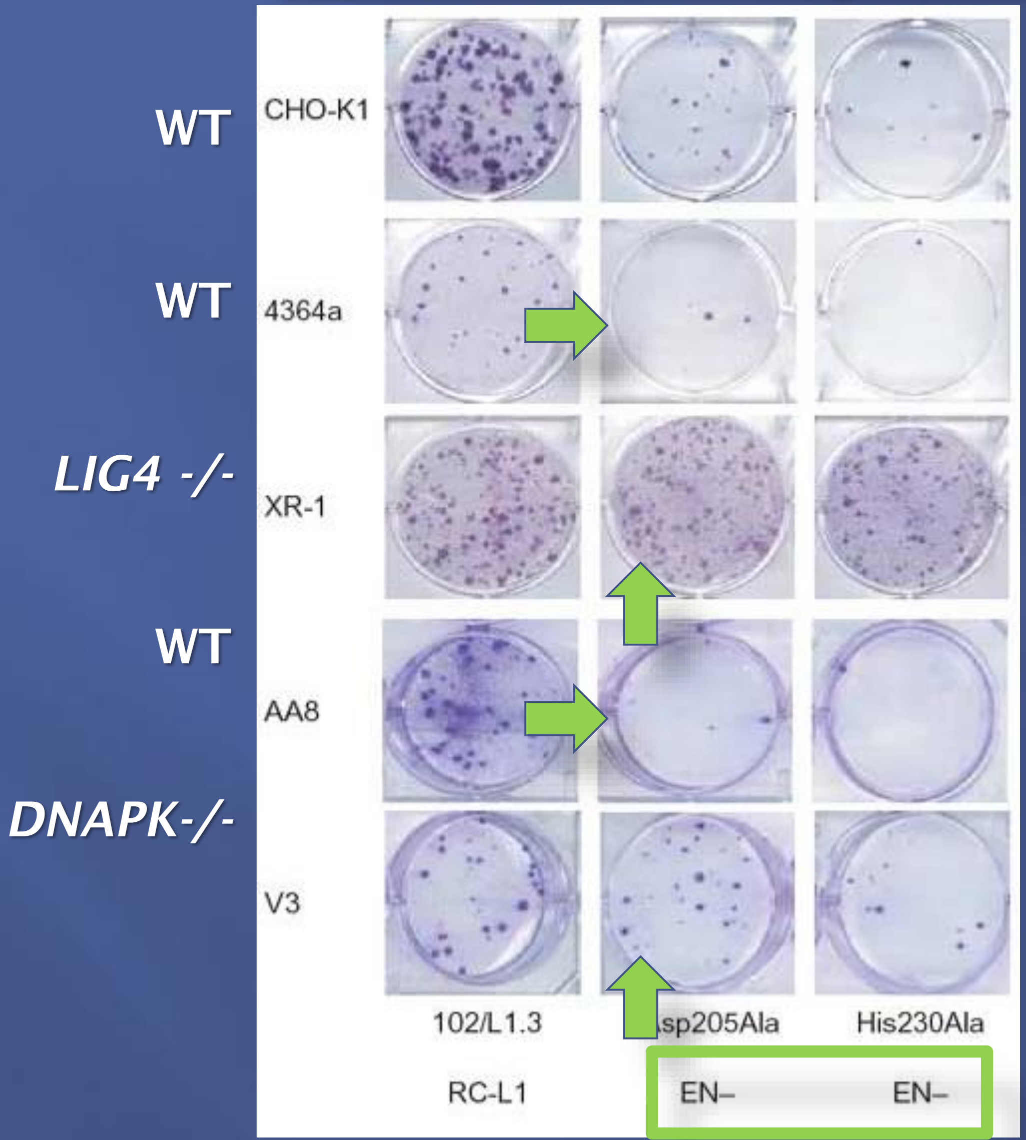




A way to experimentally measure retrotransposition

Moran, J. V., Holmes, S. E., Naas, T. P., DeBerardinis, R. J., Boeke, J. D., & Kazazian Jr, H. H. (1996). High frequency retrotransposition in cultured mammalian cells. *Cell*, 87(5), 917-927.

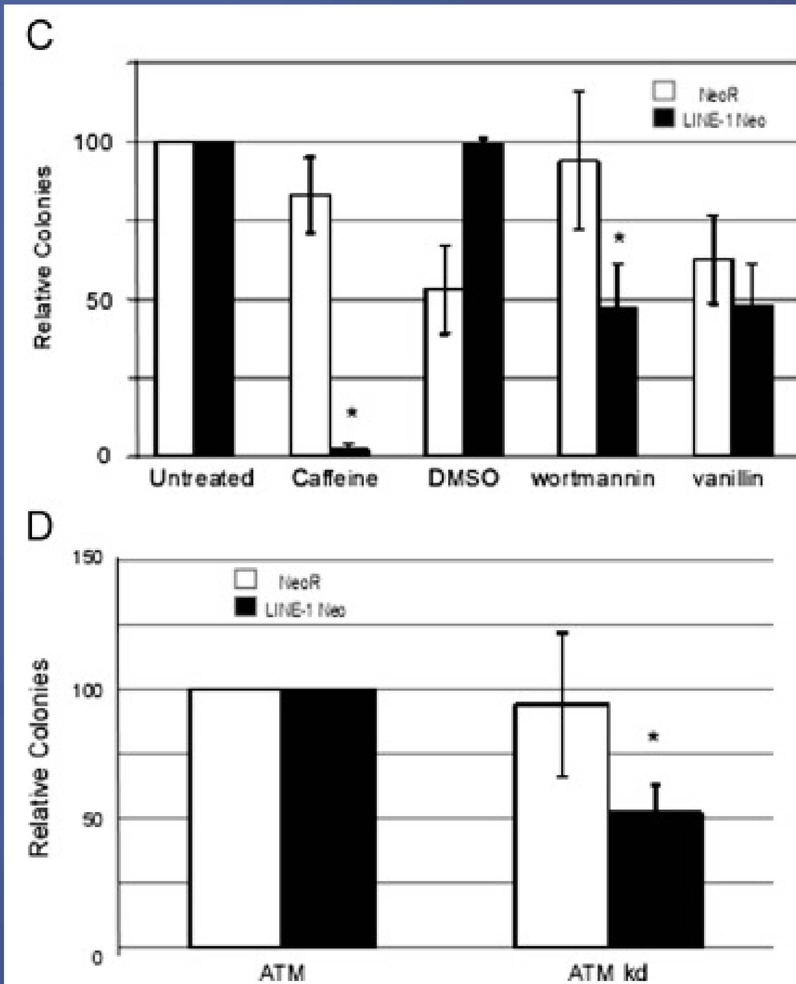
LINE-1 Assay and DNA Repair

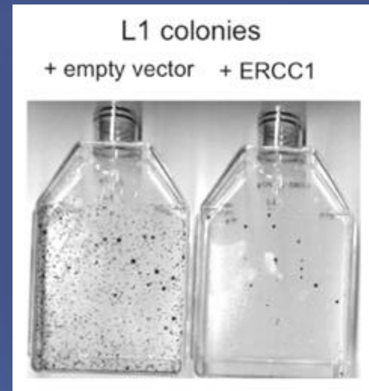


Defective DNA repair lets defective L1 work

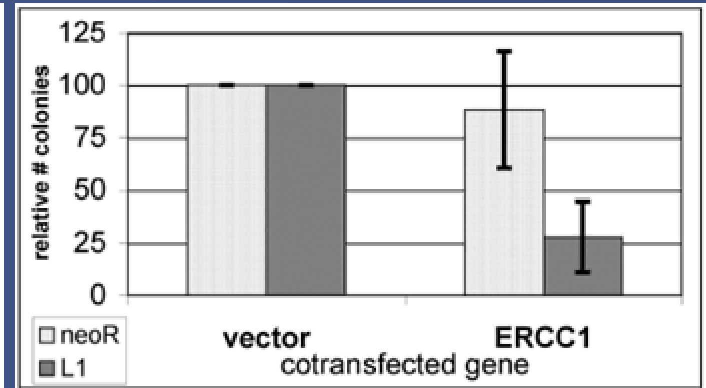
Morrish, T. A., Gilbert, N., Myers, J. S., Vincent, B. J., Stamato, T. D., Taccioli, G. E., ... & Moran, J. V. (2002). DNA repair mediated by endonuclease-independent LINE-1 retrotransposition. *Nature genetics*, 31(2), 159-165.

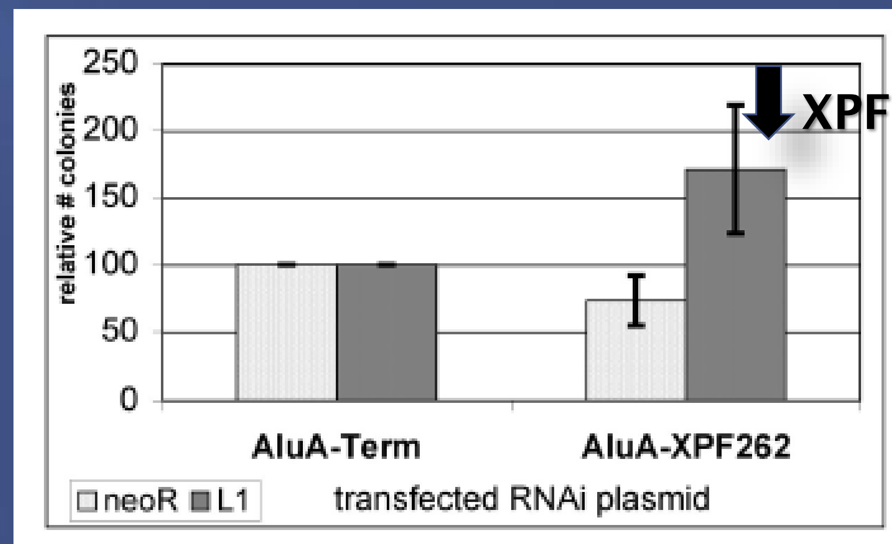
LINE-1 Depends on ATM Limited by XPF





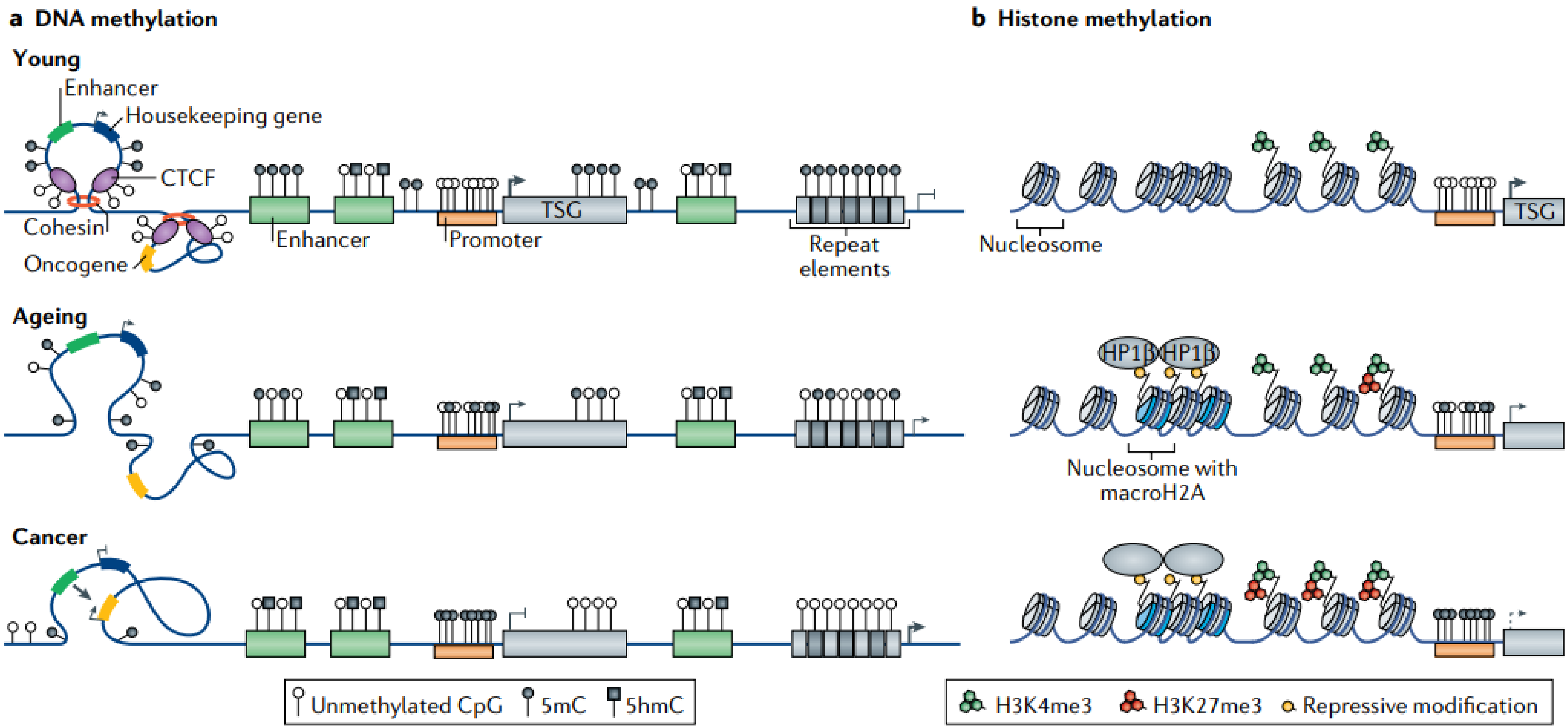
no ERCC1 +ERCC1





Wallace, N. A., Gasior, S. L., Faber, Z. J., Howie, H. L., Deininger, P. L., & Galloway, D. A. (2013). HPV 5 and 8 E6 expression reduces ATM protein levels and attenuates LINE-1 retrotransposition. *Virology*, 443(1), 69-79.
Gasior, S. L., Roy-Engel, A. M., & Deininger, P. L. (2008). ERCC1/XPF limits L1 retrotransposition. *DNA repair*, 7(6), 983-989.

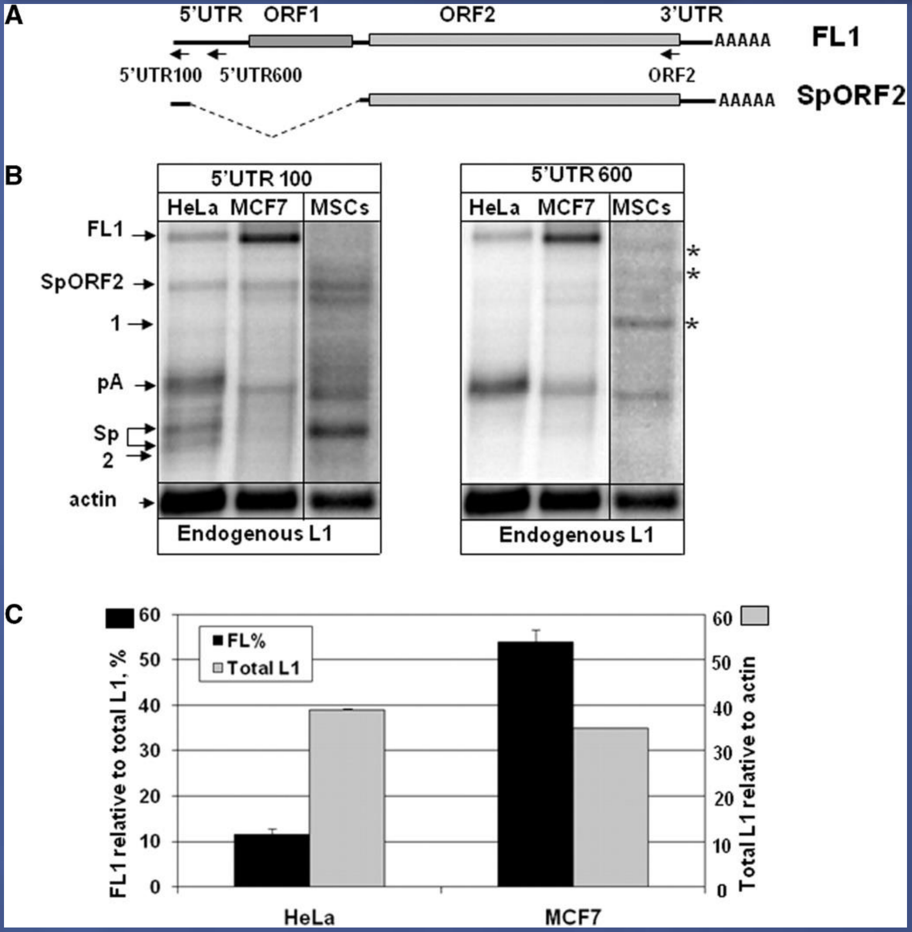
A moment for methylation

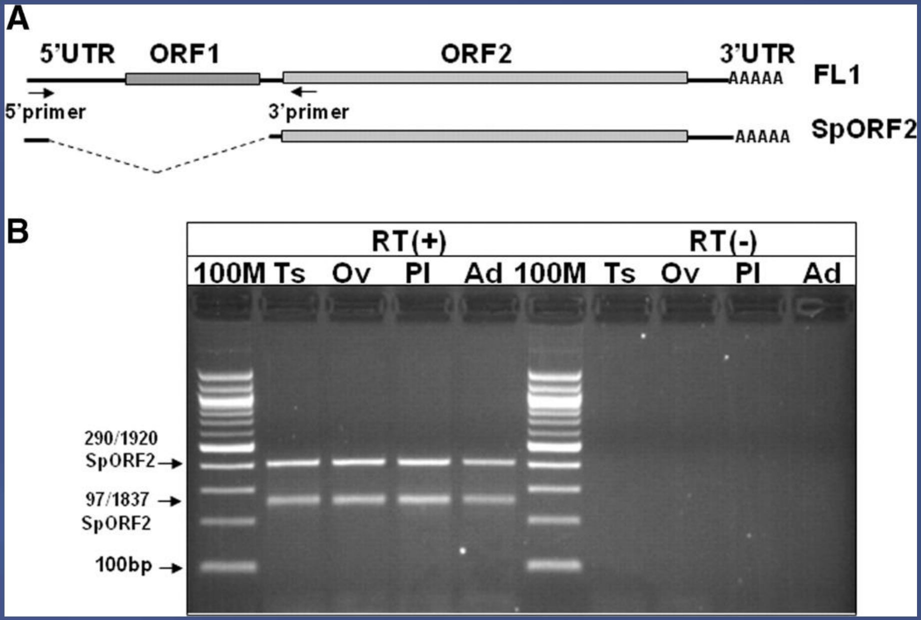


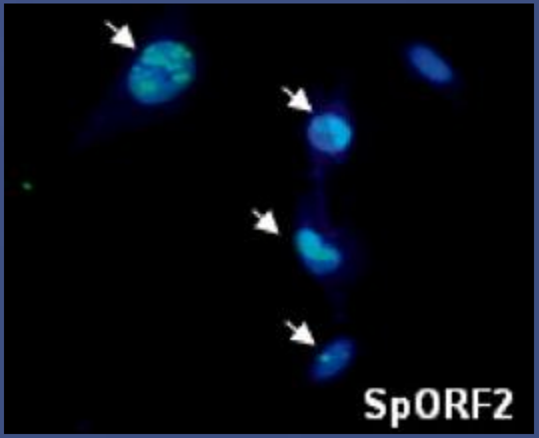
Expression controls are modified in cancer and aging. In particular, repeats become unrepressed

Michalak, E. M., Burr, M. L., Bannister, A. J., & Dawson, M. A. (2019). The roles of DNA, RNA and histone methylation in ageing and cancer. *Nature Reviews Molecular Cell Biology*, 1.

LINE-1 Full-length and ORF2 Expression



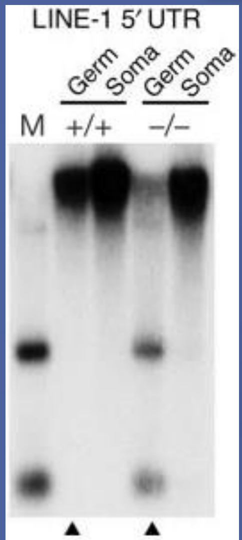




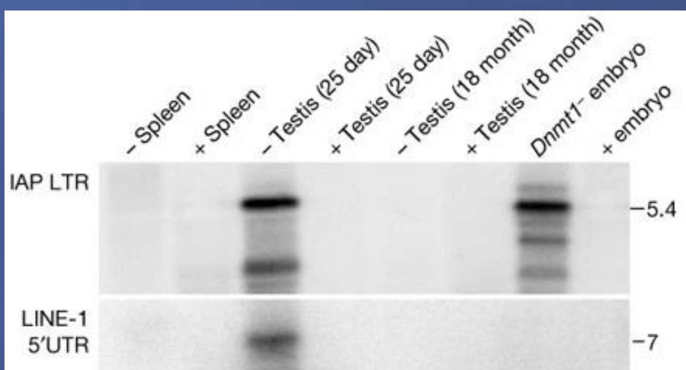
DSB potential exists in normal cells and higher levels seen in cancer cell lines

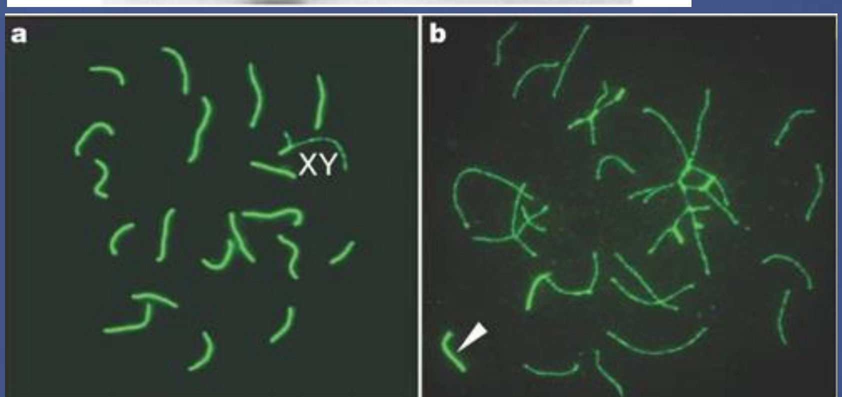
Belancio, V. P., Roy-Engel, A. M., Pochampally, R. R., & Deininger, P. (2010). Somatic expression of LINE-1 elements in human tissues. *Nucleic acids research*, 38(12), 3909-3922.

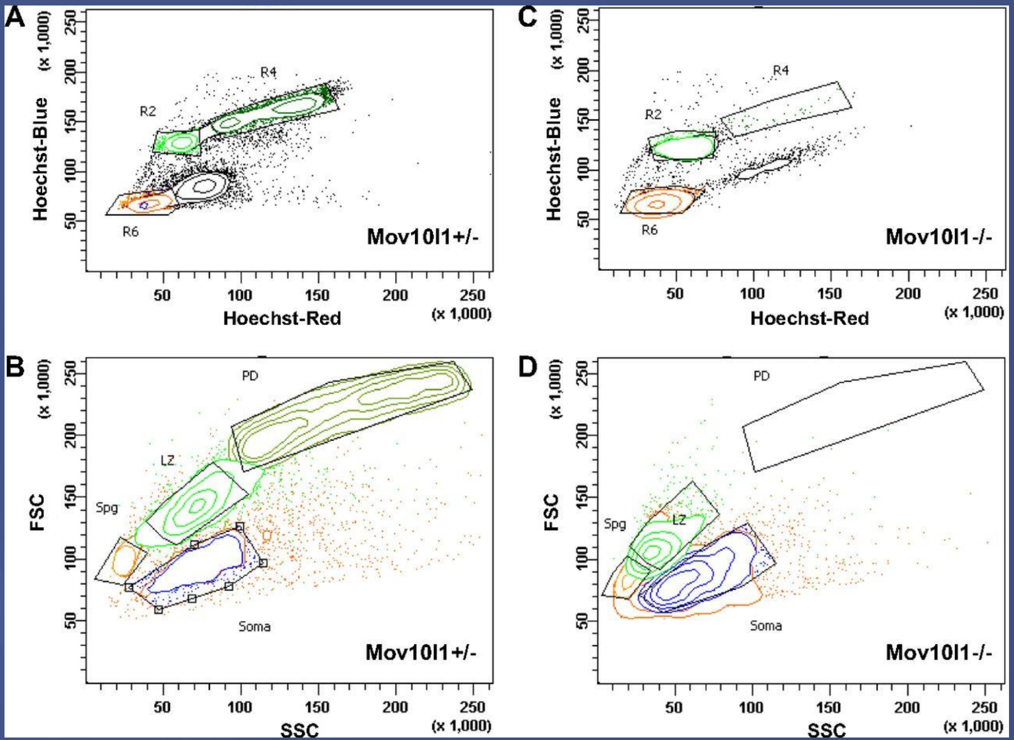
LINE-1 and Sterility

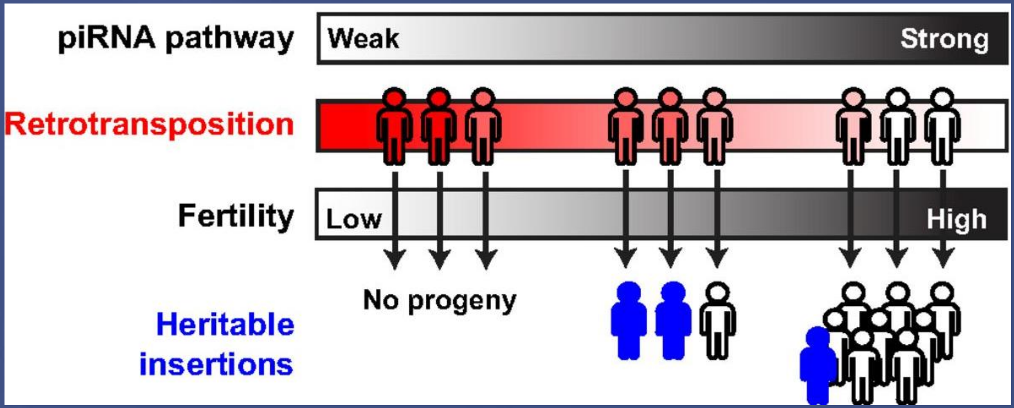


Bourc'his, D., & Bestor, T. H. (2004). Meiotic catastrophe and retrotransposon reactivation in male germ cells lacking Dnmt3L. *Nature*, 431(7004), 96-99.



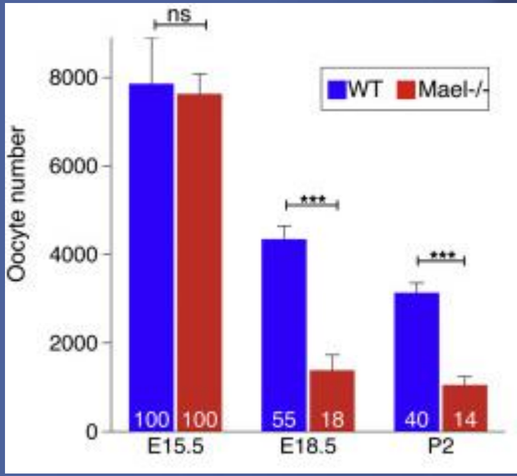


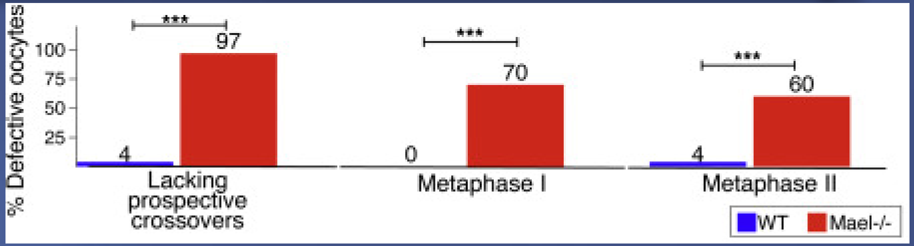


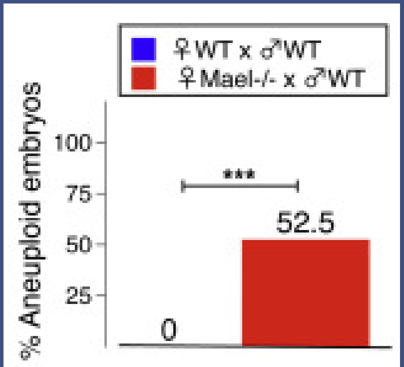


Newkirk, S. J., Lee, S., Grandi, F. C., Gaysinskaya, V., Rosser, J. M., Berg, N. V., ... & Ye, P. (2017). Intact piRNA pathway prevents L1 mobilization in male meiosis. *Proceedings of the National Academy of Sciences*, 114(28), E5635-E5644.

LINE-1 and Sterility

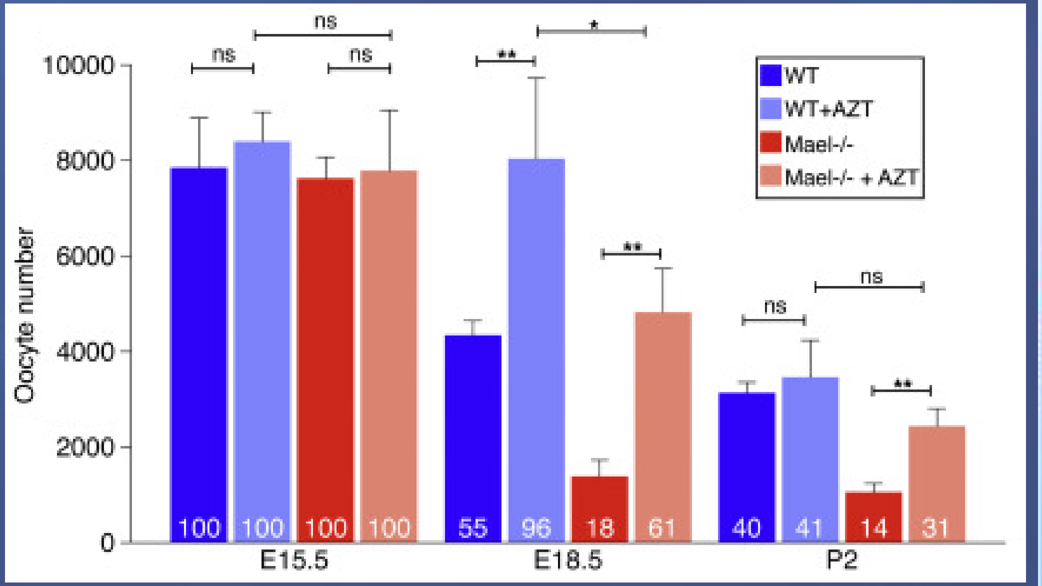


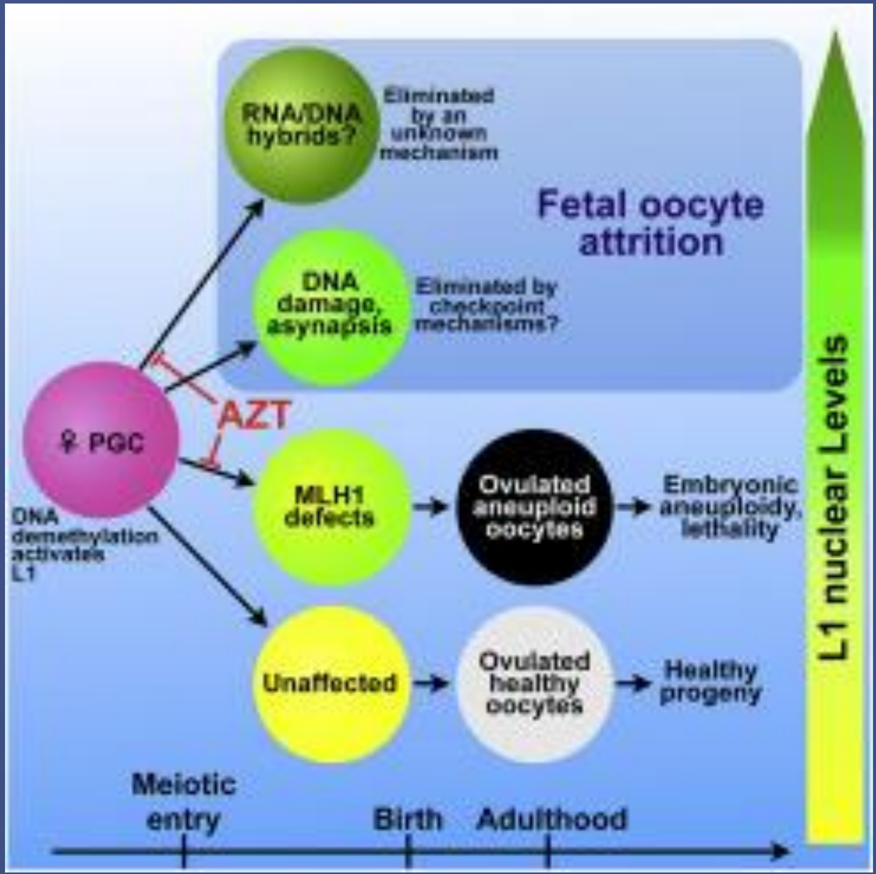




L1 expression

L1 + RT inhibitor

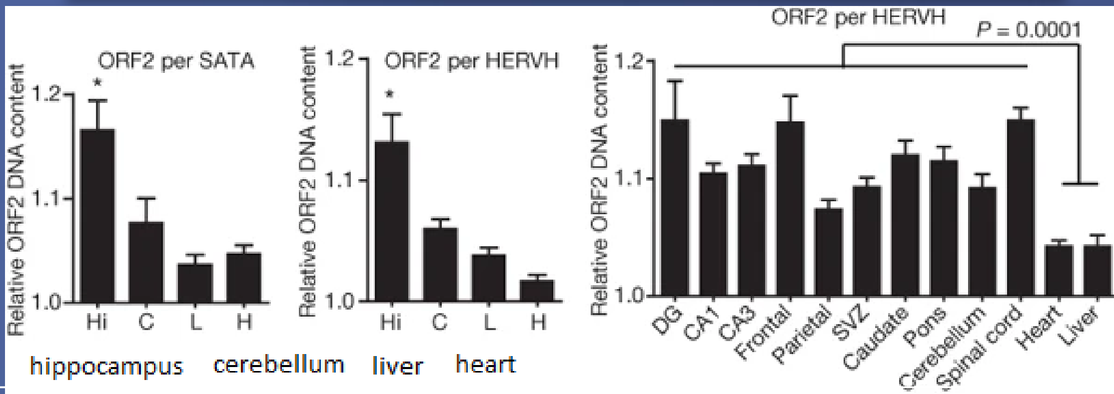


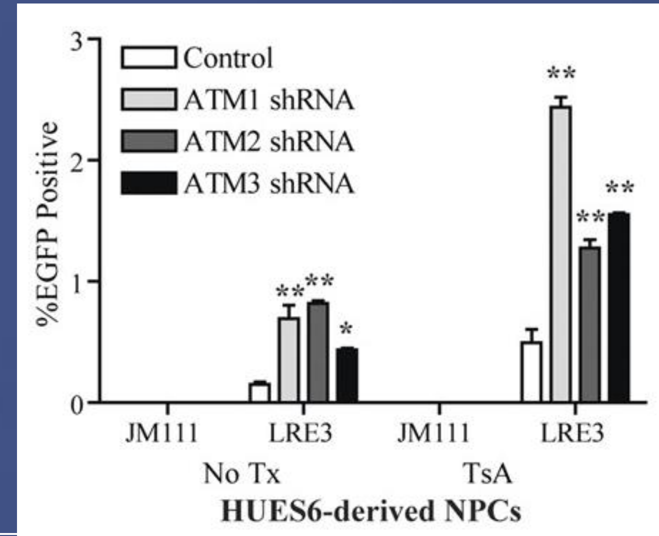


RT inhibitor alleviates L1 damage

Malki, S., van der Heijden, G. W., O'Donnell, K. A., Martin, S. L., & Bortvin, A. (2014). A role for retrotransposon LINE-1 in fetal oocyte attrition in mice. *Developmental cell*, 29(5), 521-533.

LINE-1 and The Brain





Coufal, N. G., Garcia-Perez, J. L., Peng, G. E., Yeo, G. W., Mu, Y., Lovci, M. T., ... & Gage, F. H. (2009). L1 retrotransposition in human neural progenitor cells. *Nature*, 460(7259), 1127-1131.

Coufal, N. G., Garcia-Perez, J. L., Peng, G. E., Marchetto, M. C., Muotri, A. R., Mu, Y., ... & Gage, F. H. (2011). Ataxia telangiectasia mutated (ATM) modulates long interspersed element-1 (L1) retrotransposition in human neural stem cells. *Proceedings of the National Academy of Sciences*, 108(51), 20382-20387.

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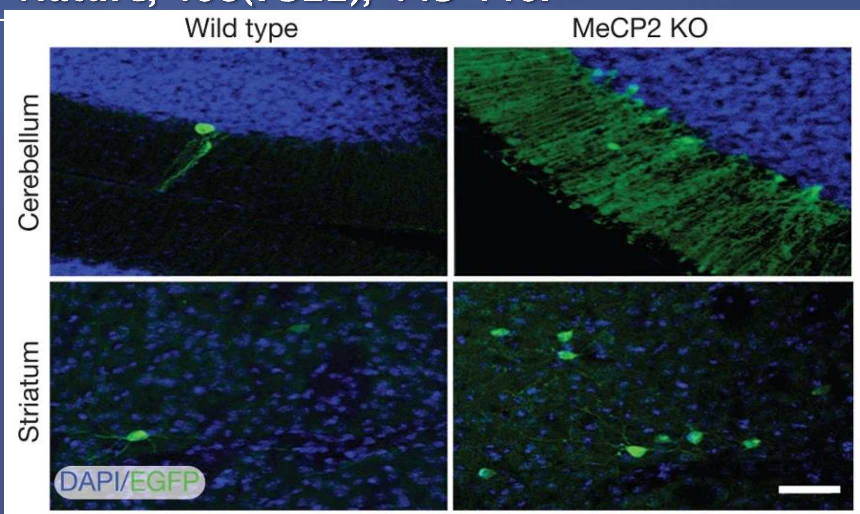
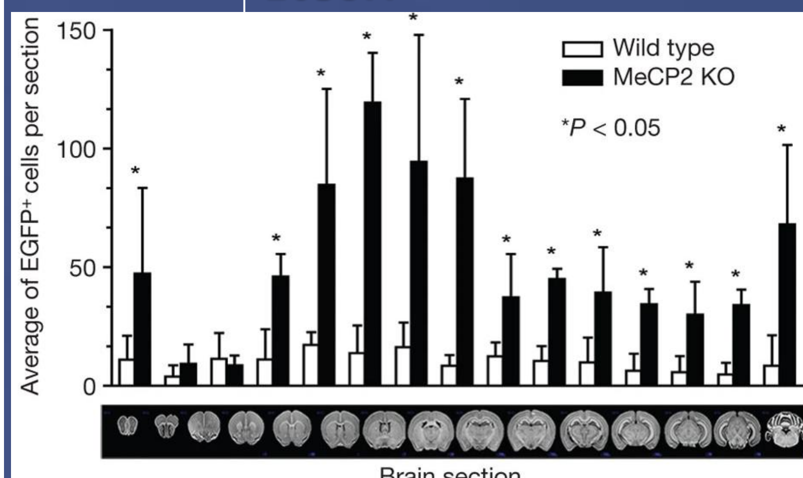
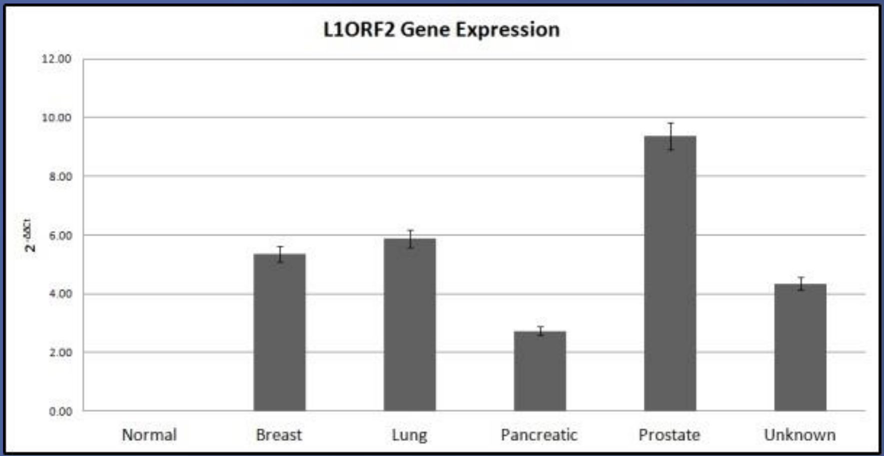




LINE-1 and Cancer



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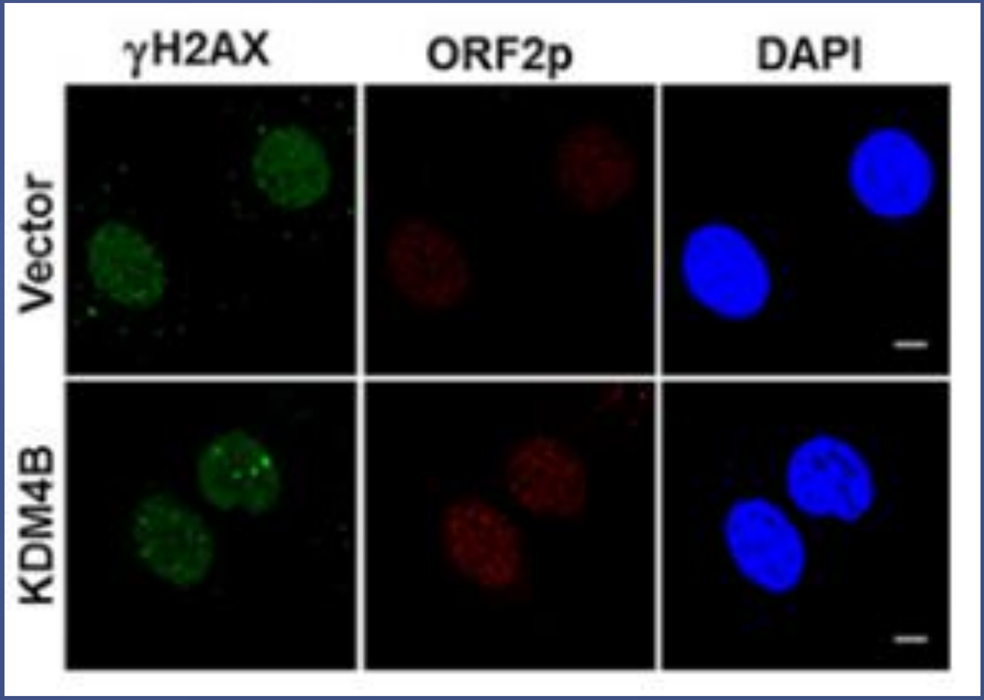

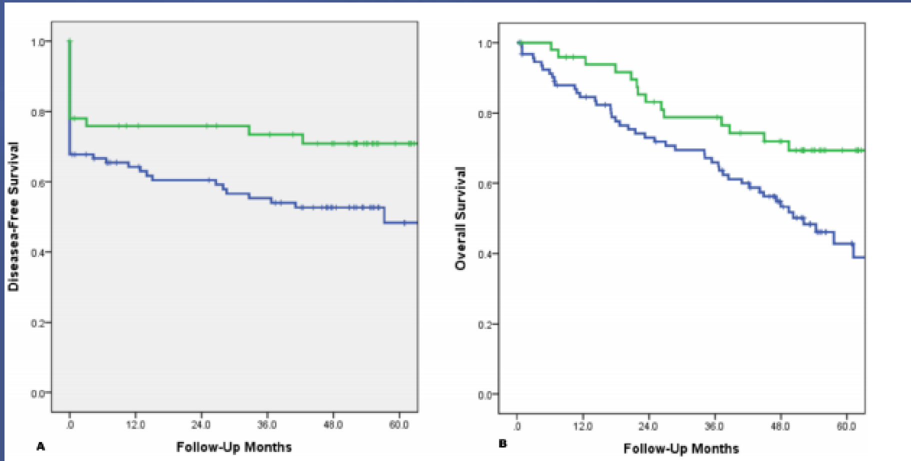

Fig 2. A) Green Line: 5-year disease-free survival of patients with normal LINE-1 methylation(76%) Blue Line: 5-year disease-free of patients with LINE-1 hypomethylation(41%, p = 0.001). B) Green Line: 5-year overall survival of patients with normal LINE-1 methylation(76%) Blue Line: 5-year overall survival of patients with LINE-1 hypomethylation(41%, p = 0.001).

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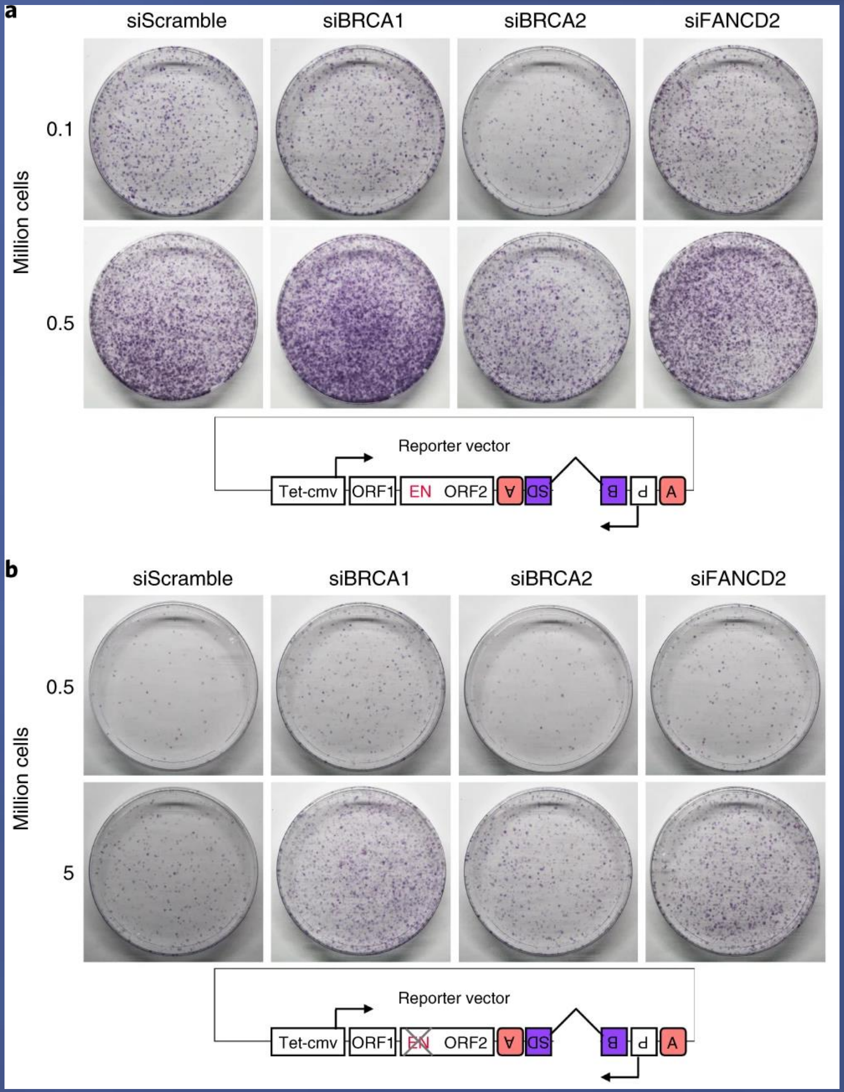
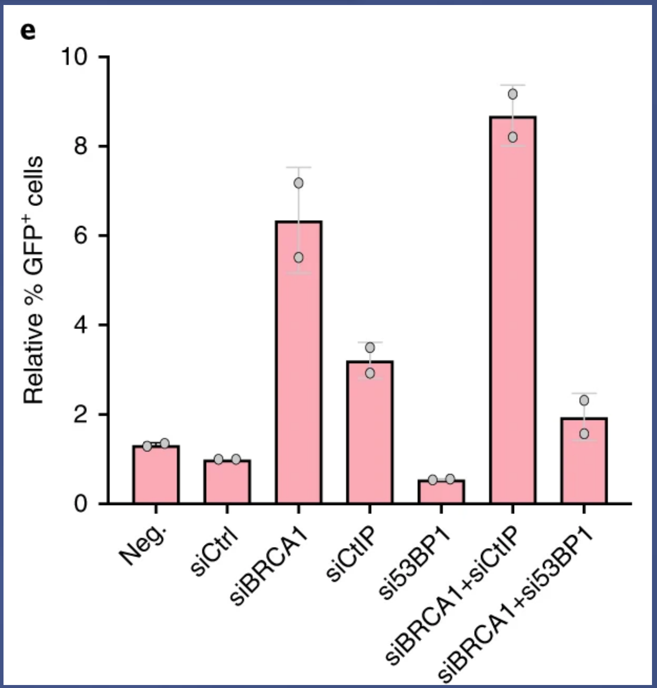
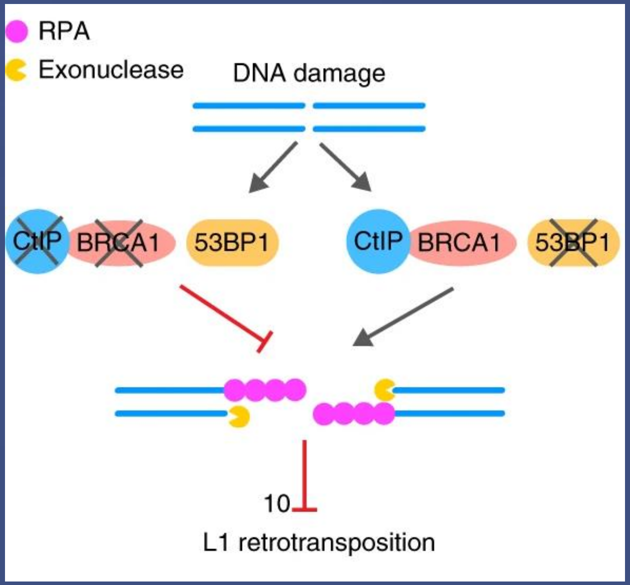
LINE-1 and Cancer







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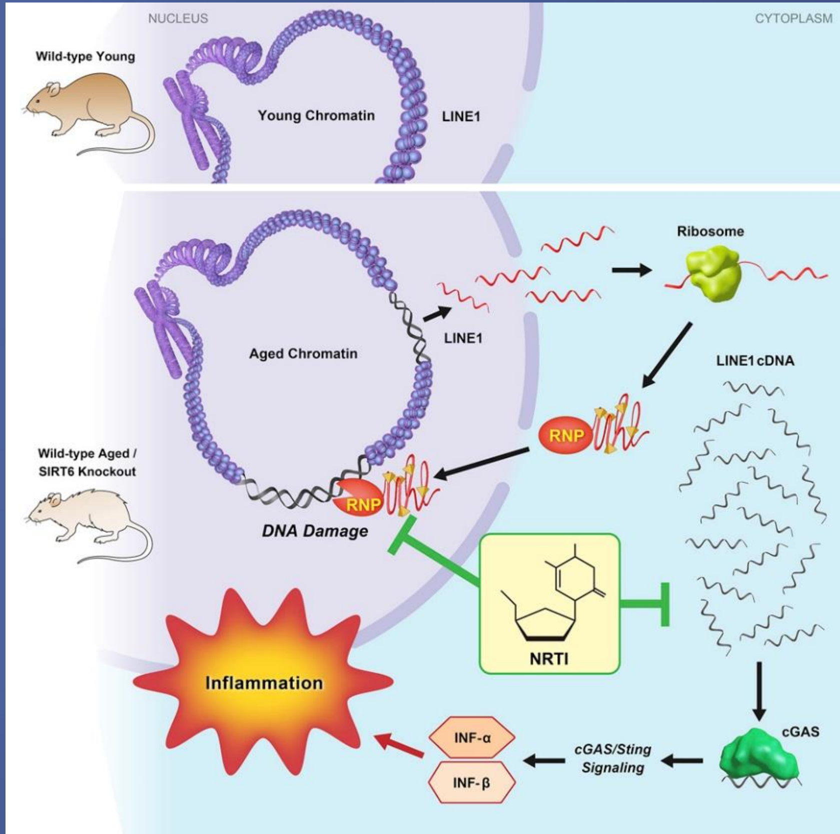
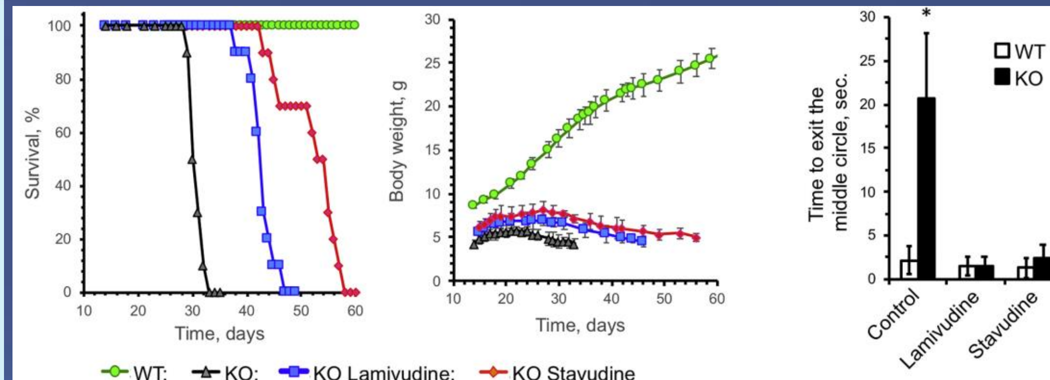
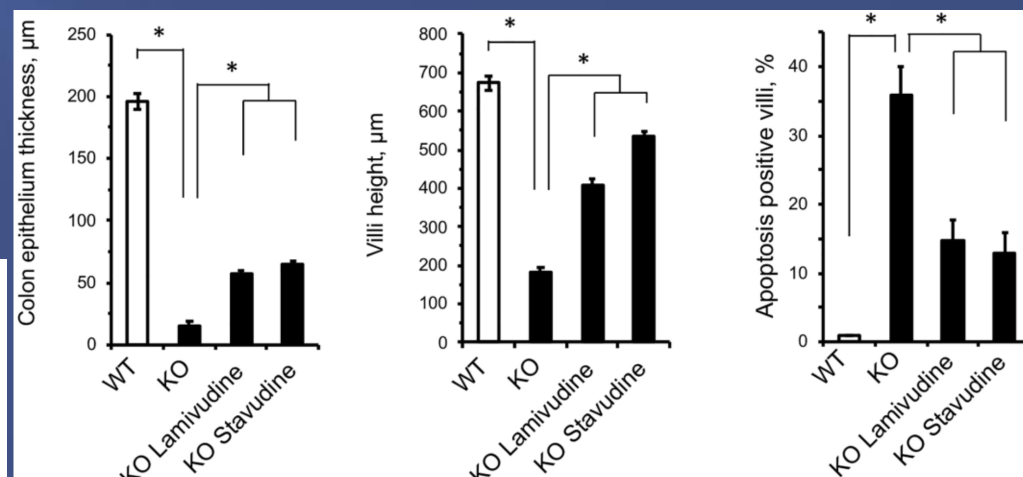
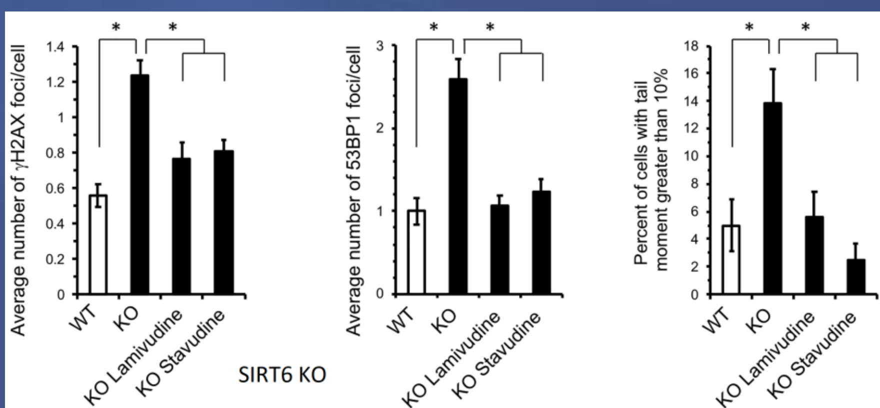
LINE-1 and Aging









Whole organism health in a mouse aging model improved by limiting L1 RT activity

Simon, M., Van Meter, M., Ablaeva, J., Ke, Z., Gonzalez, R. S., Taguchi, T., ... & Neretti, N. (2019). LINE1 derepression in aged wild-type and SIRT6-deficient mice drives inflammation. *Cell metabolism*, 29(4), 871-885.

LINE-1 Impact on Human Health

- Source of DSBs and rearrangements and inserted DNA and cDNA
  - Expression is designed to be limited by host chemistry
  - Effects of intermediates are also recognized and limited
- Expression can be unsuppressed
  - Maybe causative of initiation of cancer
  - Ongoing activity in cancer progression
  - With aging, expression and increases
  - Interesting expression patterns and effects in gametogenesis
  - Neuronal activity
- Dramatic effect in those deficient in repair or repression

What makes a Nobel Prize?

- Technical Achievement with huge impact
  - Watson Crick DNA Structure 1962
  - Kary Mullis 1993 PCR
  - Capecchi, Evans and Smithies ESC KO 2007
  - Shimomura, Chalfie and Tsien GFP 2008
  - Fire and Mello RNA interference 2006
- Discovery with major human health impact
  - Fleming, Chain and Florey penicillin 1945
  - Furchgott, Ignarro and Murad nitric oxide as vasodilator 1998
- Those the turned science on its head
  - McClintock Transposons 1983
  - Stanley B. Prusiner Prions 1997
  - Marshall and Warren *Helicobactor pylori* causes ulcers 2005
  - Fire and Mello RNA interference 2006

As to whom…

- Haig Kazazian-LINE-1 in genes
  - John Moran-LINE-1 assay
  - JL Goodier-mouse LINE-1, transduction, AML
- Prescott Deininger
  - Myself, Victoria Belancio
  - Astrid Engel, Mark Batzer-Alu Biology
- Jef Boeke – meth. DNA repair and L1 (also sirtuins, yeast Ty)
  - Scott Devine-genome variation
- Methylation Folk [Tim Bestor]

Dedication

Jerzy Jurka – 1950–2014

Mercury News Obit

Mobile DNA

Google Scholar Profile

pioneer in the field of mobile DNA, founder, president and director of research at Genetic Information Research Institute from 1994 to 2014

first publication related to Mobile DNA was the discovery of an Alu element in an alpha globin gene in the late 1980s while working with Temple Smith

"A fundamental division in the Alu family of repeated sequences." He named AluJ after himself.

built and maintained the most fundamental database of mobile DNA elements, Repbase

Further Reading

Background
https://en.wikipedia.org/wiki/DNA_damage_theory_of_aging

https://www.fasebj.org/doi/full/10.1096/fj.201700502rr Kazazian's Retrospective

https://en.wikipedia.org/wiki/LINE1