Somatic mutations, genome mosaicism, aging and disease

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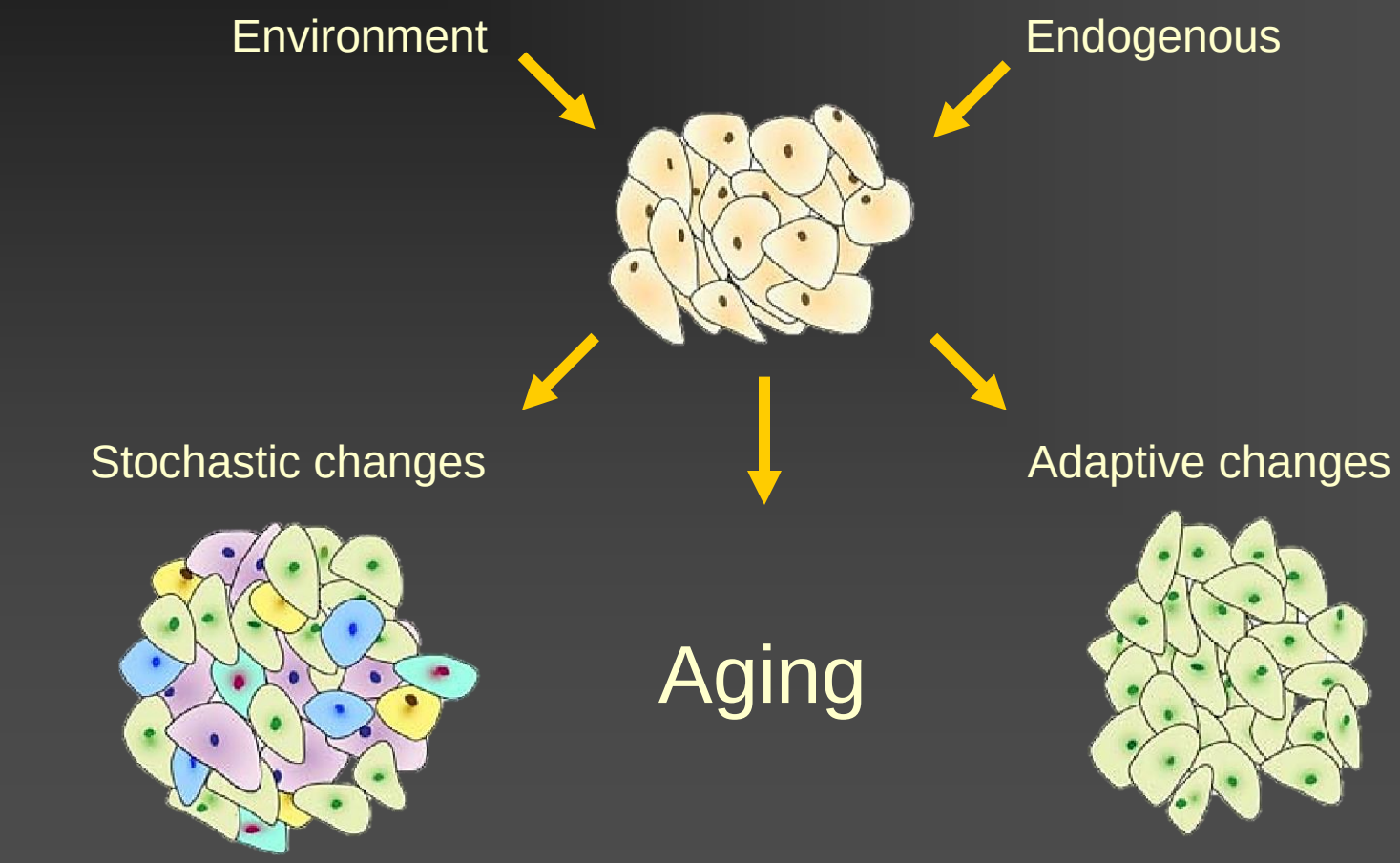
Disclosure:

www.singulomics.com

Stochastic and adaptive changes in aging



Biol. Rev. (1990), **65**, *pp.* 375–398
Printed in Great Britain

AN ATTEMPT AT A RATIONAL CLASSIFICATION OF THEORIES OF AGEING

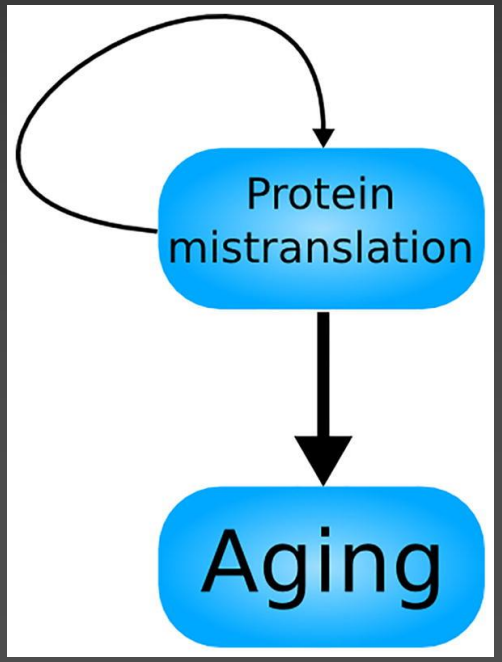
ZHORES A. MEDVEDEV

Genetics Division, National Institute for Medical Research, Mill Hill, London NW7 1AA, U.K.

Proc Natl Acad Sci U S A. 1963 Apr; 49(4): 517–521.
doi: 10.1073/pnas.49.4.517
PMCID: PMC299893
PMID: 13940312

THE MAINTENANCE OF THE ACCURACY OF PROTEIN SYNTHESIS AND ITS RELEVANCE TO AGEING

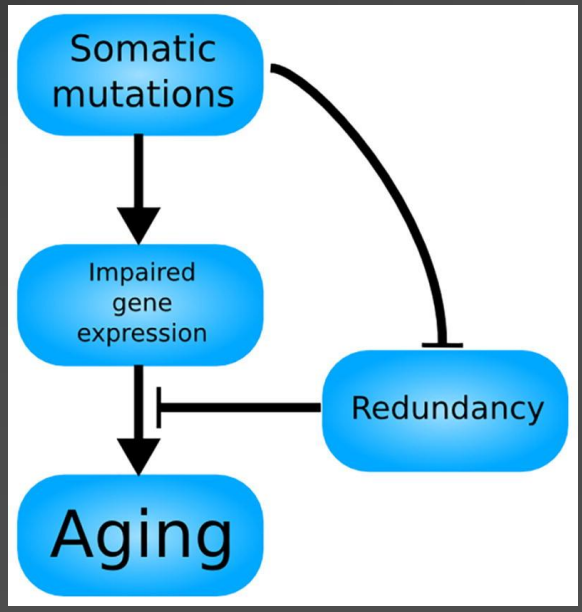
L. E. Orgel



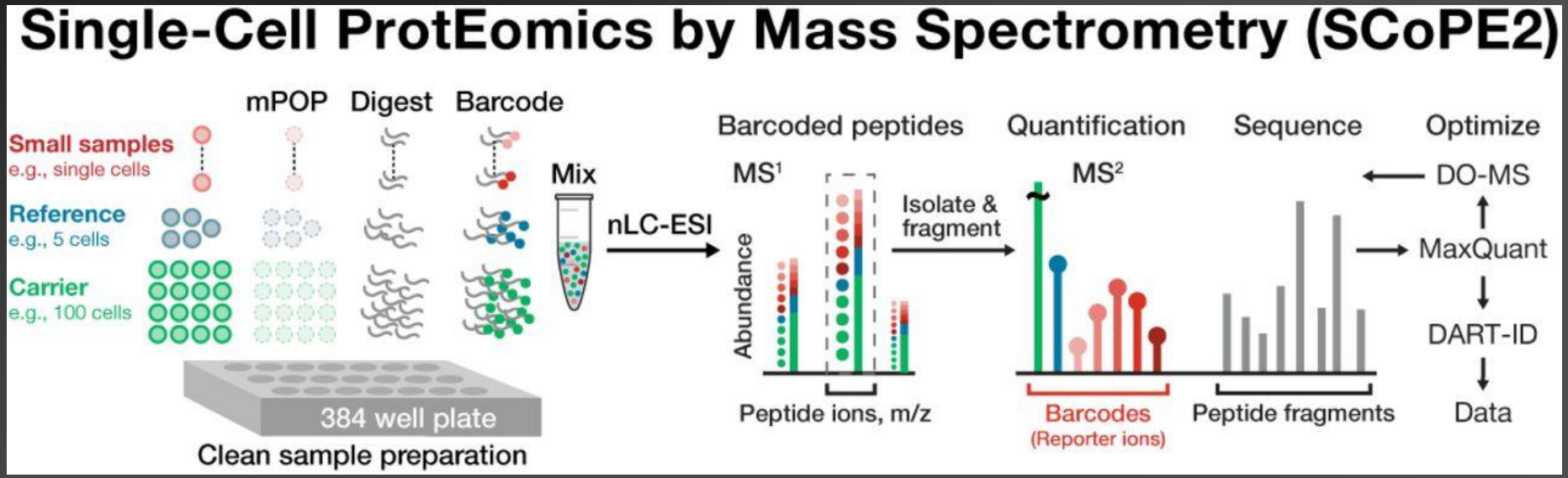
Proc Natl Acad Sci U S A. 1959 Jan; 45(1): 30–45.
doi: 10.1073/pnas.45.1.30
PMCID: PMC222509
PMID: 16590351

ON THE NATURE OF THE AGING PROCESS

Leo Szilard*

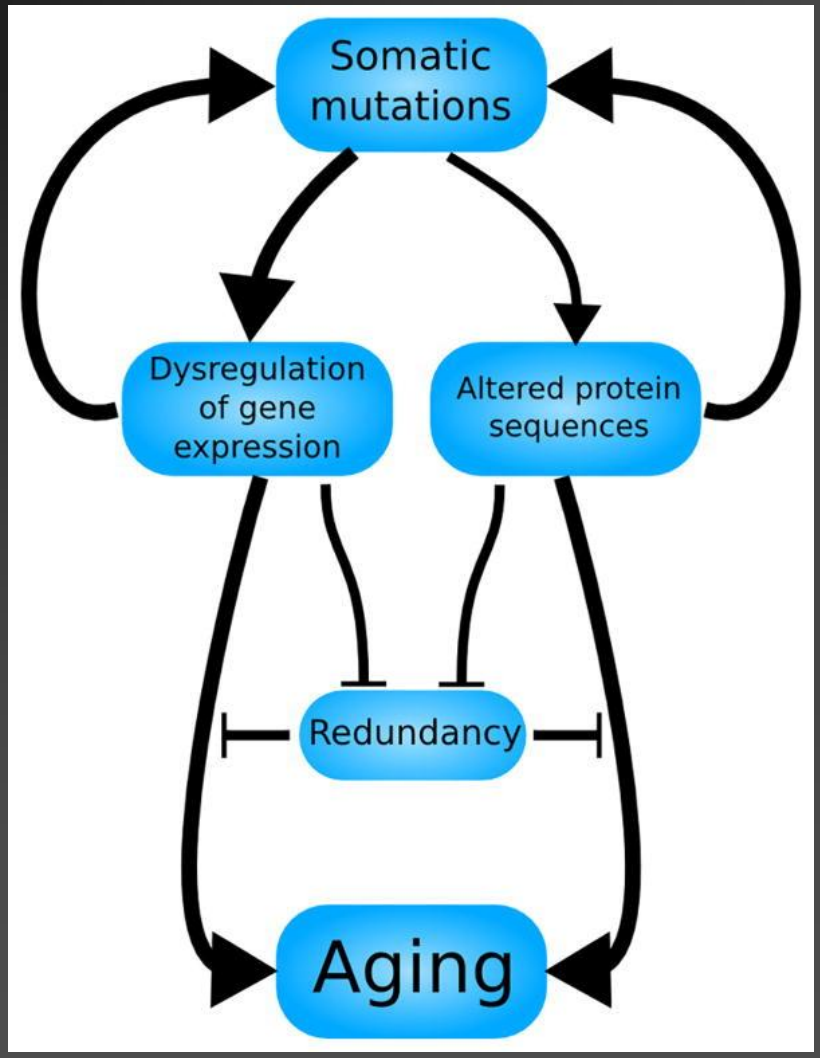


Progress in single-cell proteomics



Slavov, N., Curr Opin Chem Biol 2021

Random mutations affect predominantly gene regulatory sequences



Milholland, Suh, Vijg, Exp. Gerontol. 2017

Somatic DNA mutations: causes and consequences

DNA damage

Errors during repair or replication

DNA mutations

Original allele

A-C-A-G-T-A-G-A-C-C-T-A-A-G-T-A-C-G-T
T-G-T-C-A-T-C-T-G-G-A-T-T-C-A-T-G-C-A

Base substitution | **Single base deletion** | **Inversion** | **… etc.**

Mutated allele

A-C-A-T-T-A-G-C-C-T-A-T-A-C-T-C-G-T
T-G-T-A-A-T-C-G-G-A-T-A-T-G-A-G-C-A

Germline

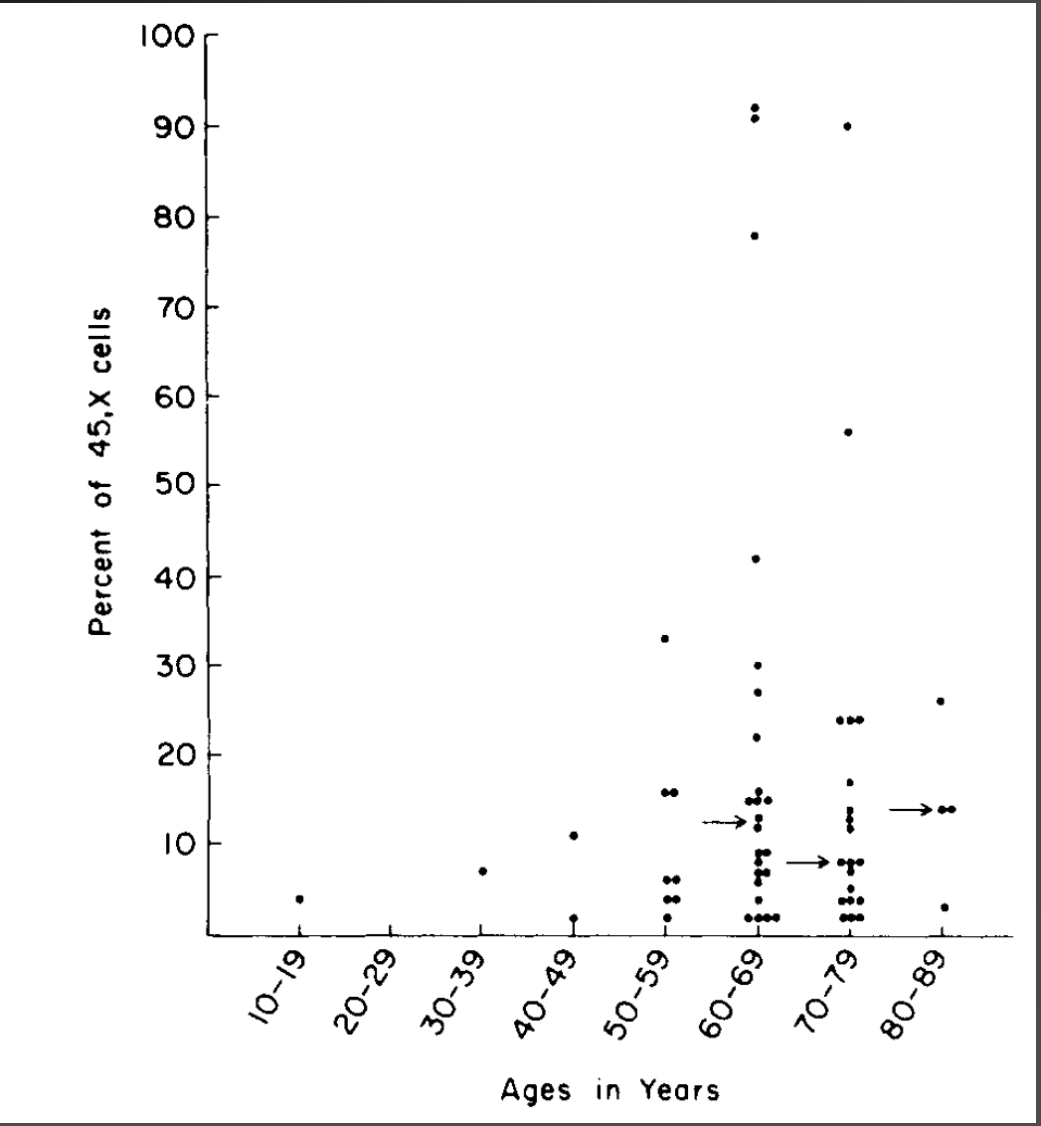
Soma

Diversity and perpetuation of life

Aging?

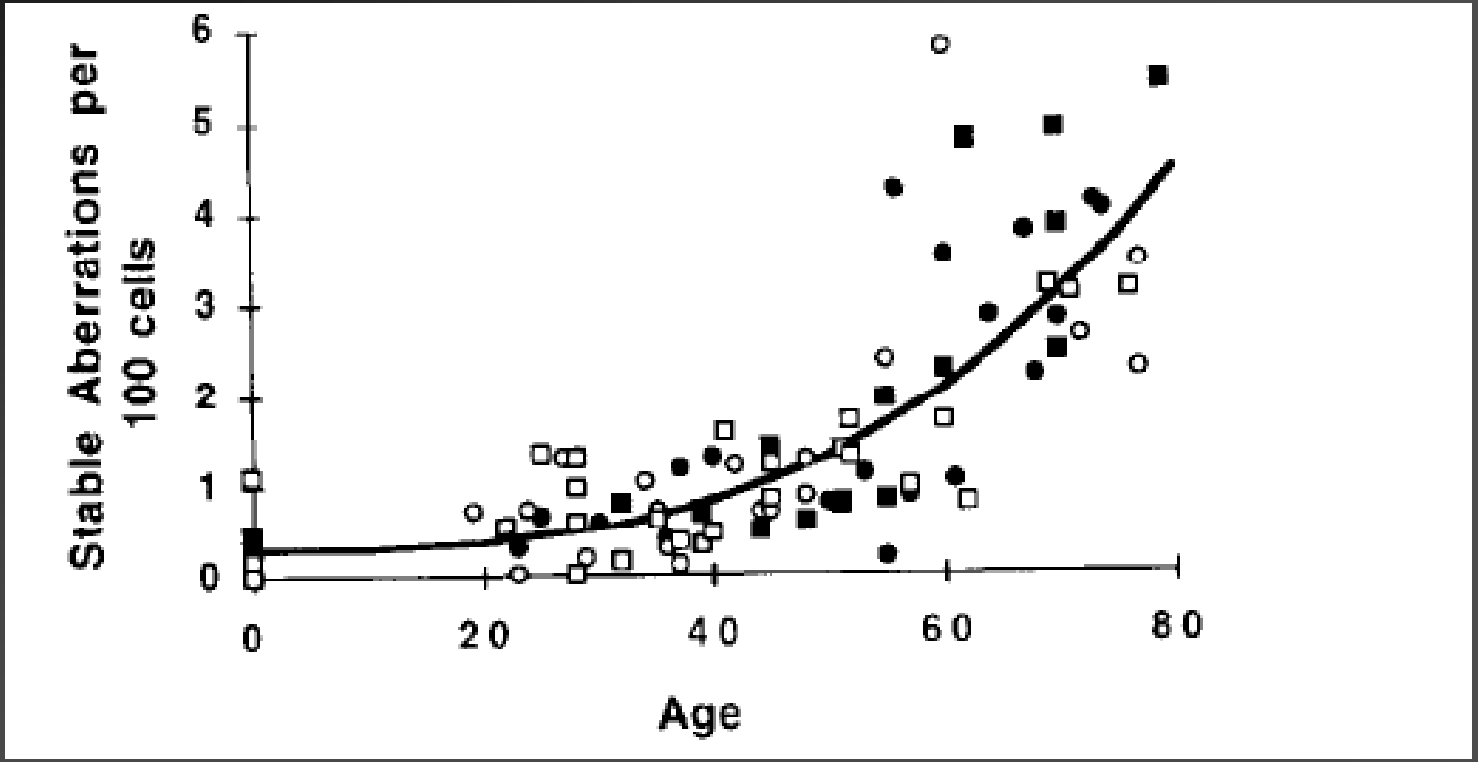
How to measure somatic mutations?

Missing Y metaphases in bone marrow of males



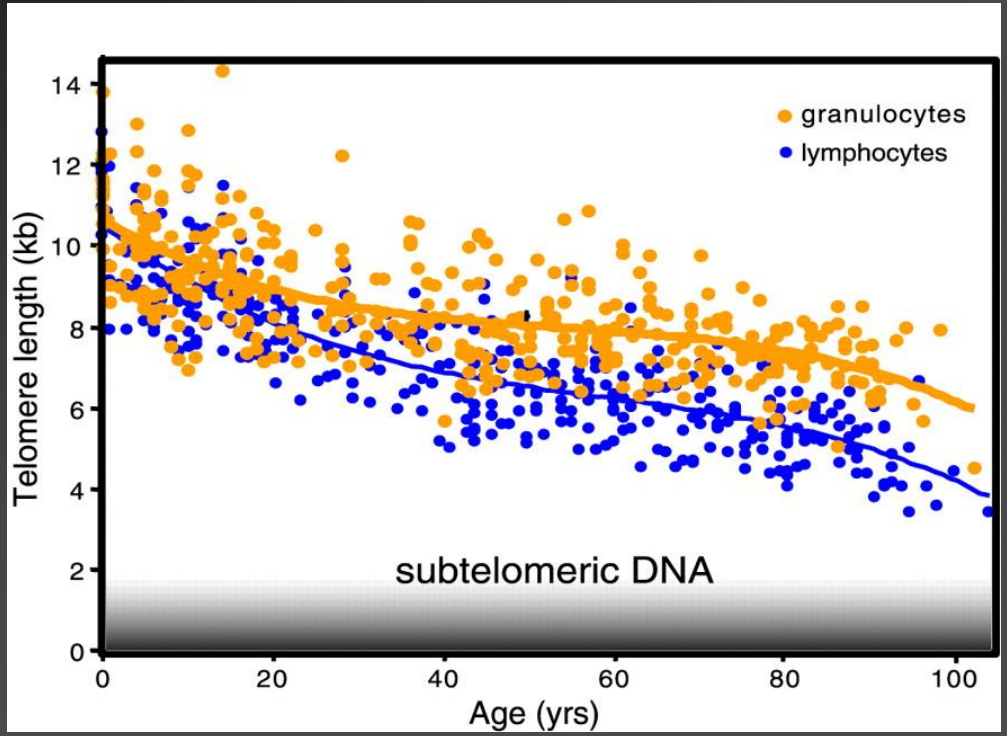
Sakurai and Sandberg, Cancer, 1976

Chromosomal abnormalities and aging



Ramsey et al., Mut Res 1995

Telomere length declines with age



Aubert and Lansdorp, *Phys Rev*, **88**, 2008

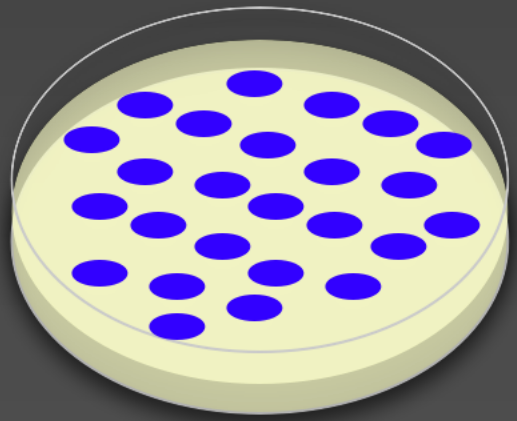
LacZ mutation reporter gene

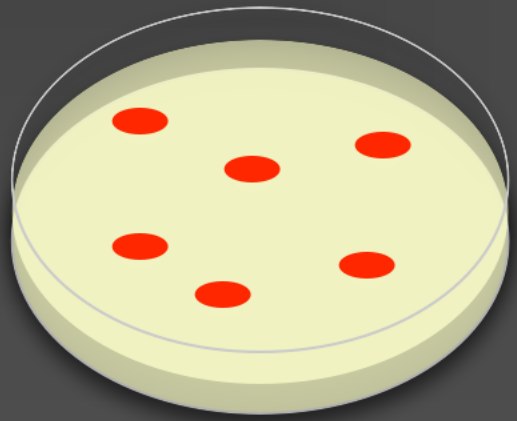
Excision
and ligation

Garcia, et al.,
Nat. Methods 4, 2007

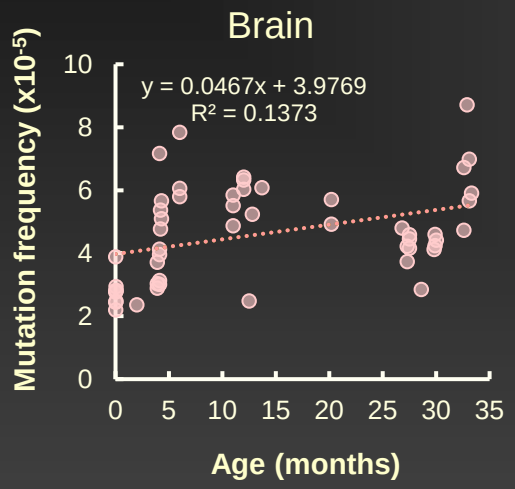
E. coli
transformation

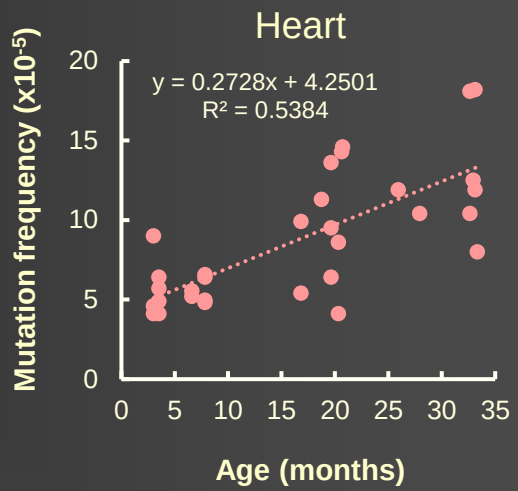
Boerrigter, et al.,
Nature 377, 1995

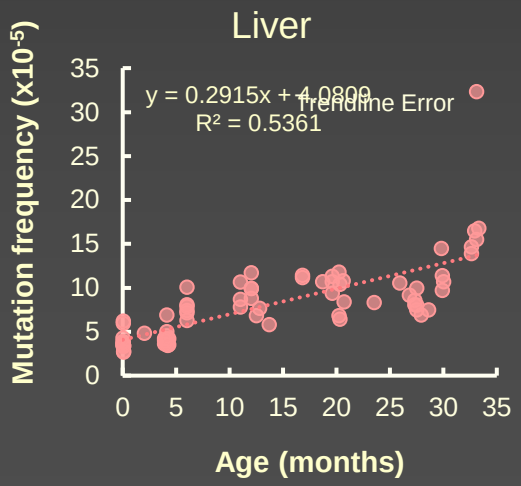


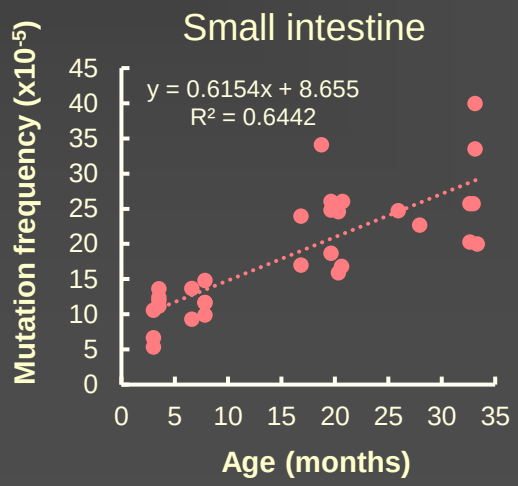


Age-related tissue-specific mutation accumulation in lacZ reporter mice





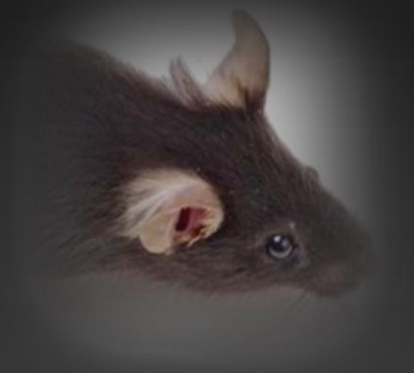


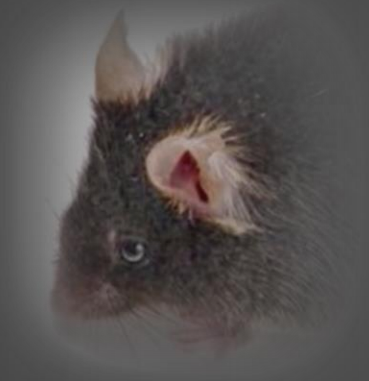


Dollé et al., Nat Genet 1997

Dollé et al., PNAS 2000

Aging-associated accumulation of point mutations and genome rearrangements in organs of mice



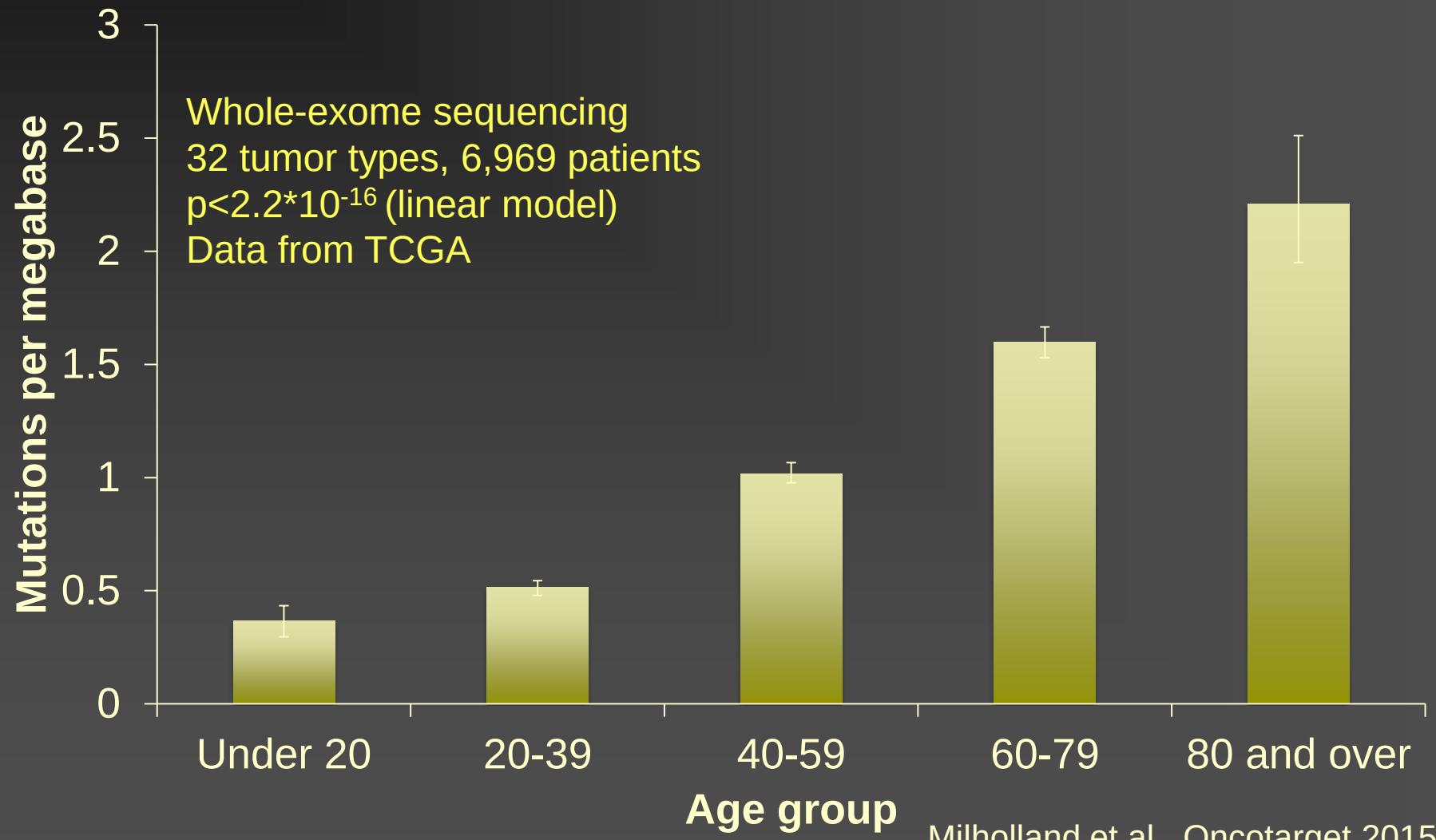


Estimated number of mutational events per cell

	Point mutations		Genome rearrangements	
	Young	Old	Young	Old
Brain	50	74	5	6
Liver	39	113	9	27
Heart	37	103	19	37
Small intestine	89	332	15	24

Dollé et al., Genome Res. 2002

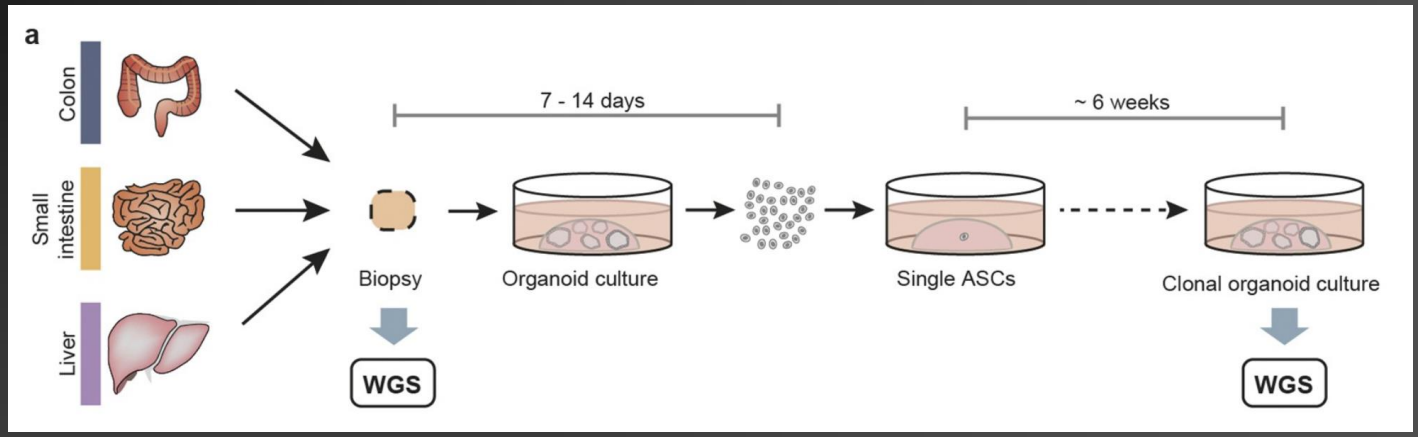
Exponential increase of the number of exome mutations in tumors with age of the patients



Milholland et al., Oncotarget 2015

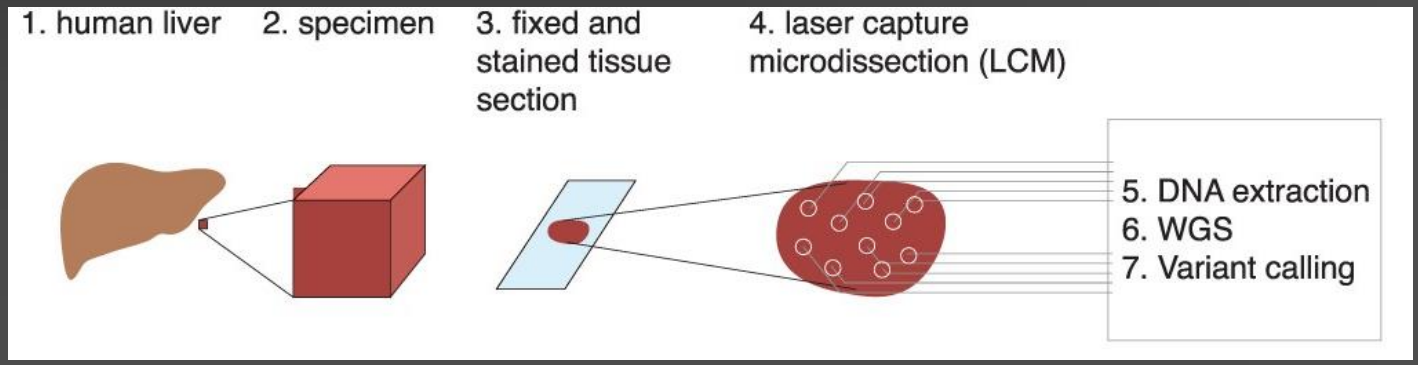
Single cell clonal expansions can be sequenced but only for those cells that are mitotically active

Expand stem cells *in vitro*



Blokzijl F, et al. *Nature*, 2016.

Deep sequencing of natural single cell expansions from micro-biopsies

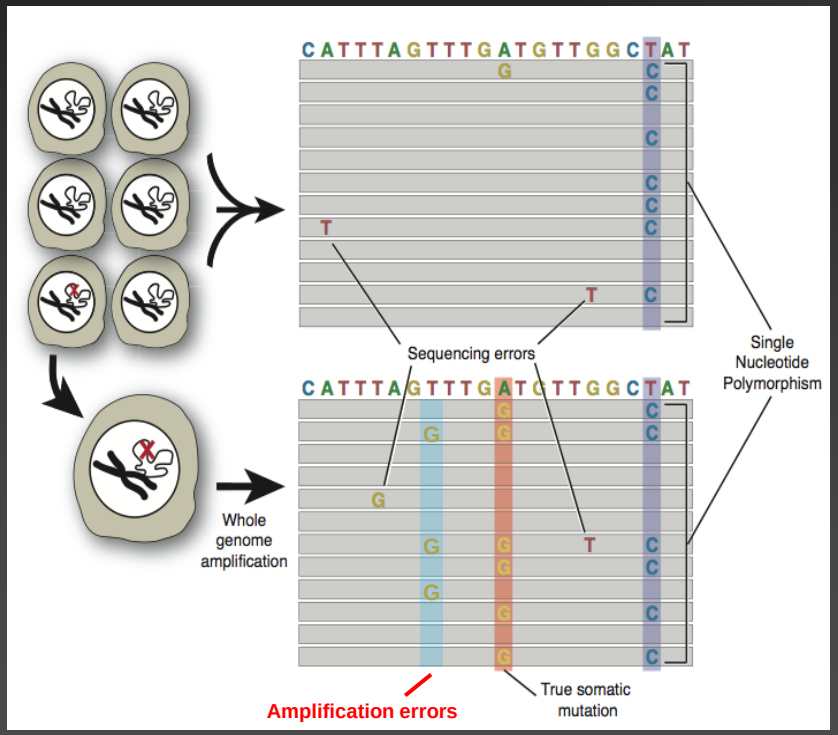


Brunner SF, et al. *Nature*, 2019.

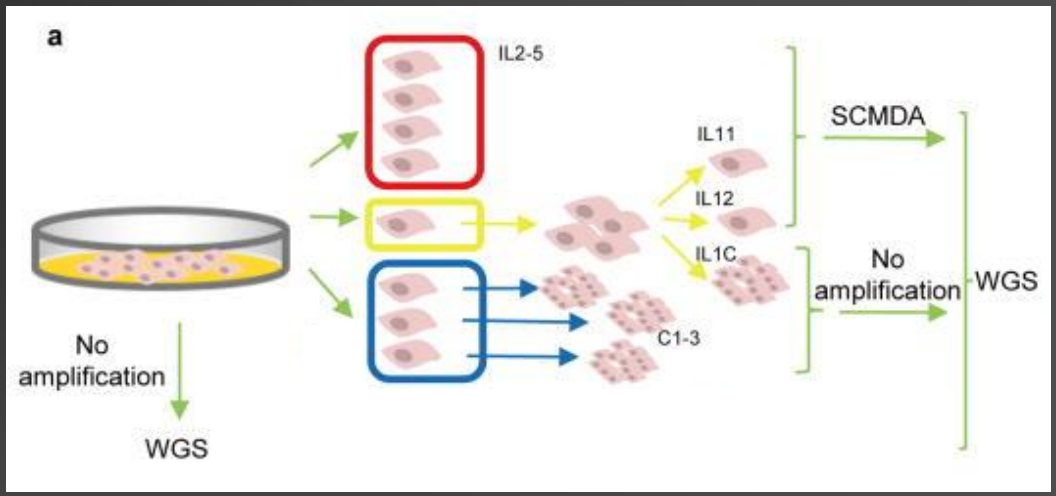
WGS: whole genome sequencing

Gold standard: whole genome sequencing of single cells after amplification

Optimization of variant calling



Single-cell multiple displacement amplification (SCMDA): validation

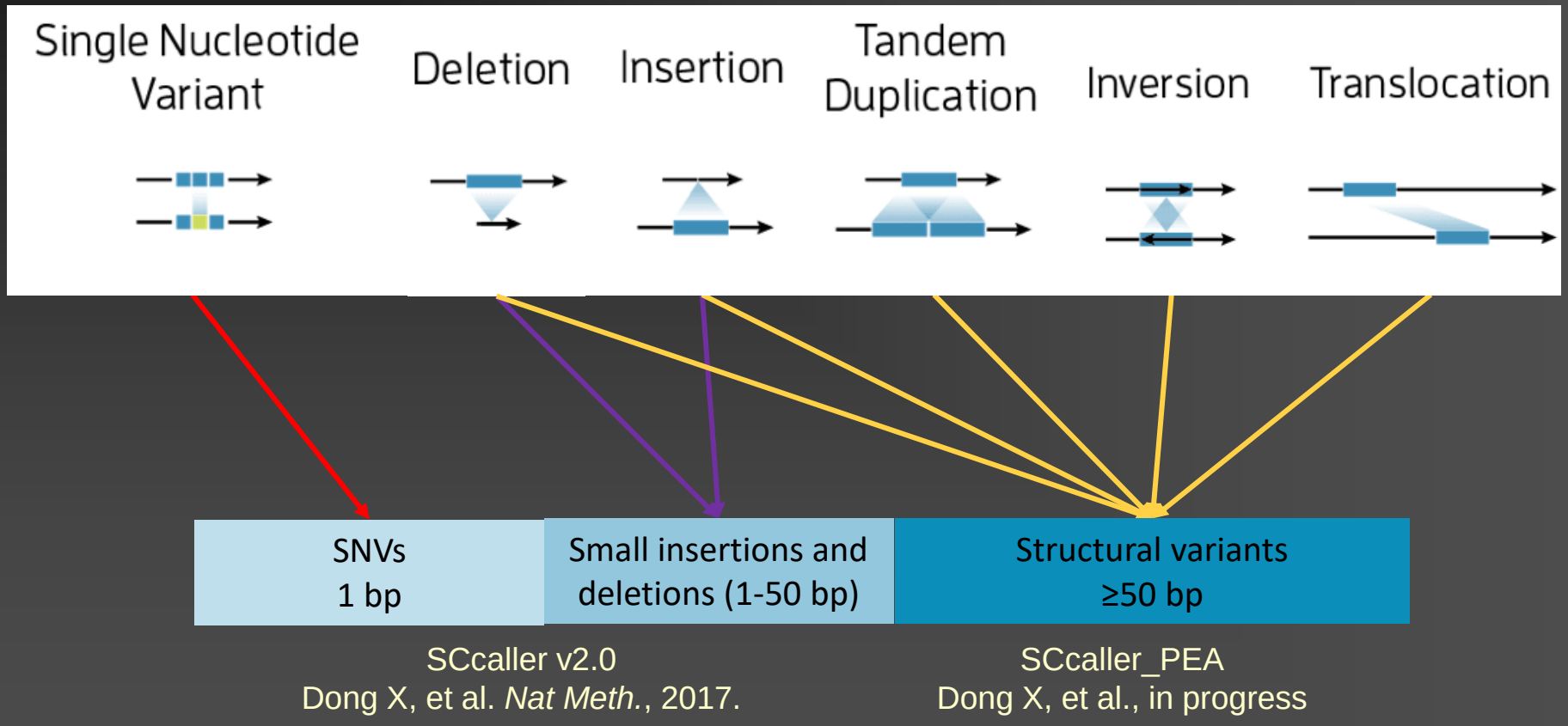


Xiao Dong

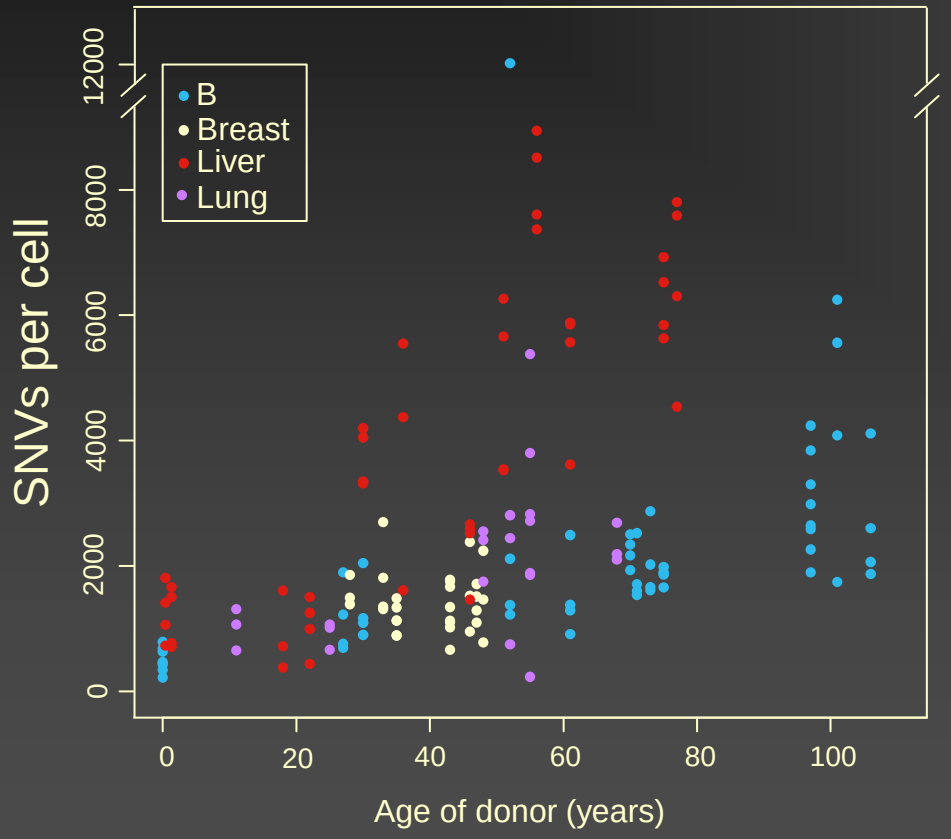
Lei Zhang

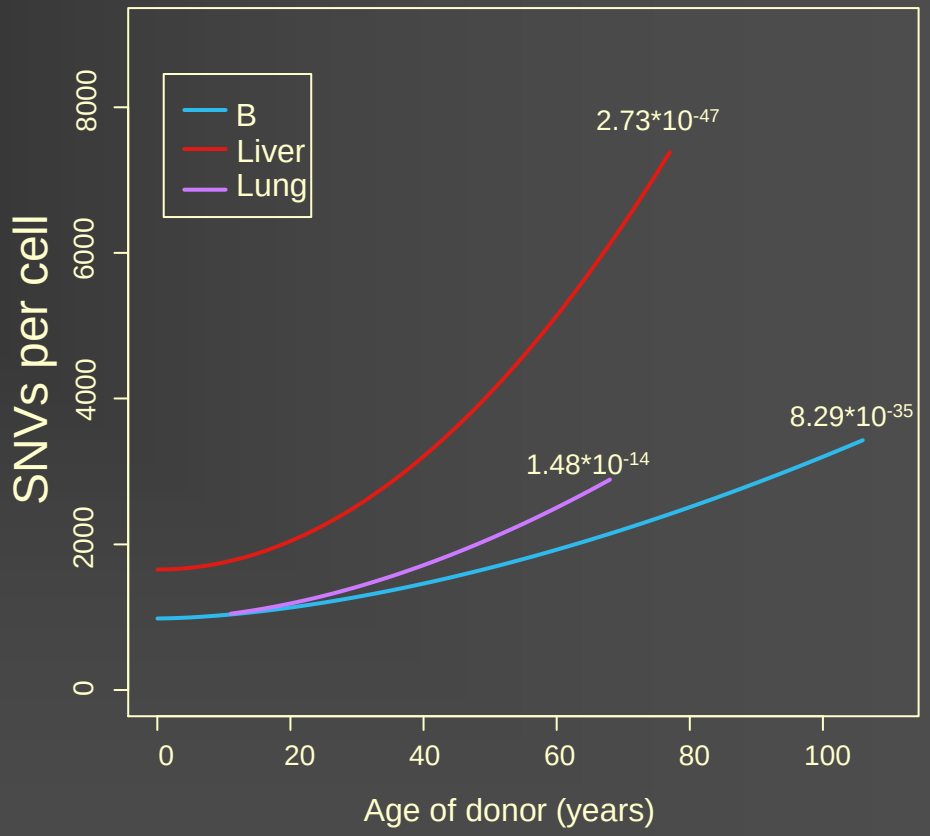
Dong X, Zhang L et al. *Nat. Meth.*, 2017

A genome-wide index for somatic mutations



Single nucleotide variants (SNVs) accumulate at different rates in different tissues during aging



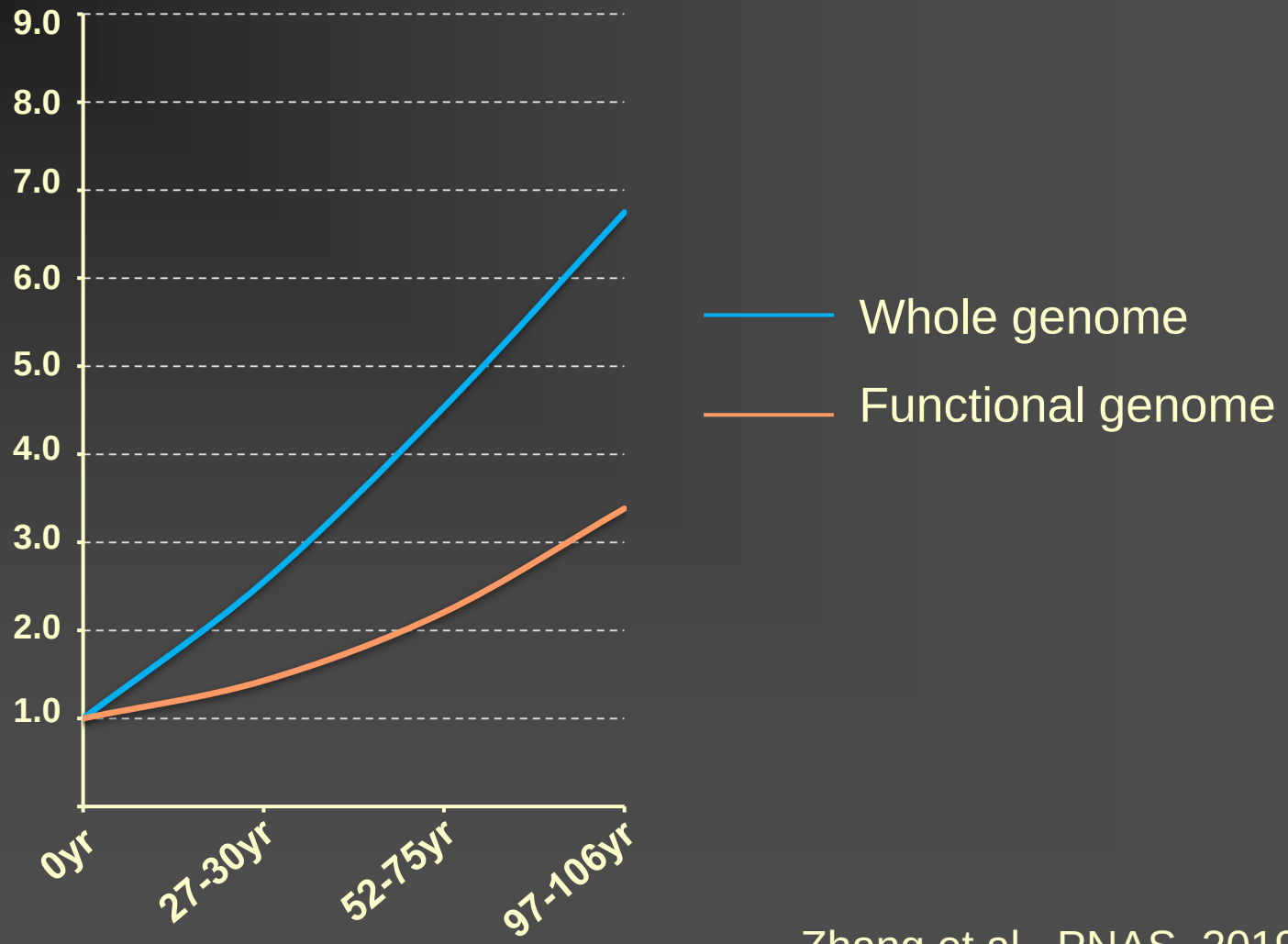


Zhang et al., PNAS 2019; Brazhnik, Sun et al., Sc. Adv. 2020
Huang, unpublished; Sun, unpublished

Fitted model: $SNV = a + Age^{b}$

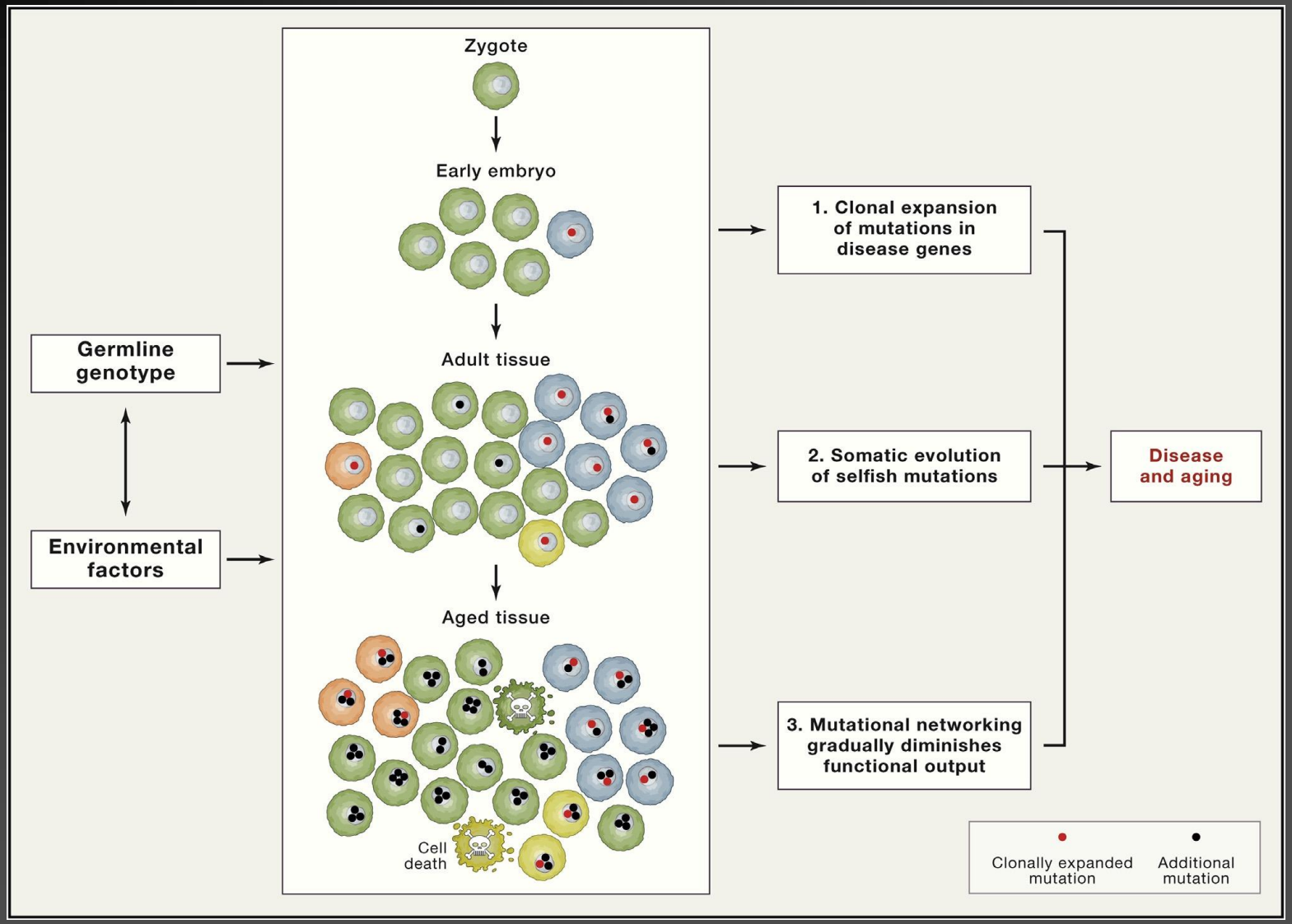
Is there a functional impact of somatic mutations?

Negative selection indicates a damaging effect of somatic mutations in aging



Zhang et al., PNAS, 2019

Pathogenic mechanisms of somatic mutations in aging



Vijg, Dong, CELL 2020

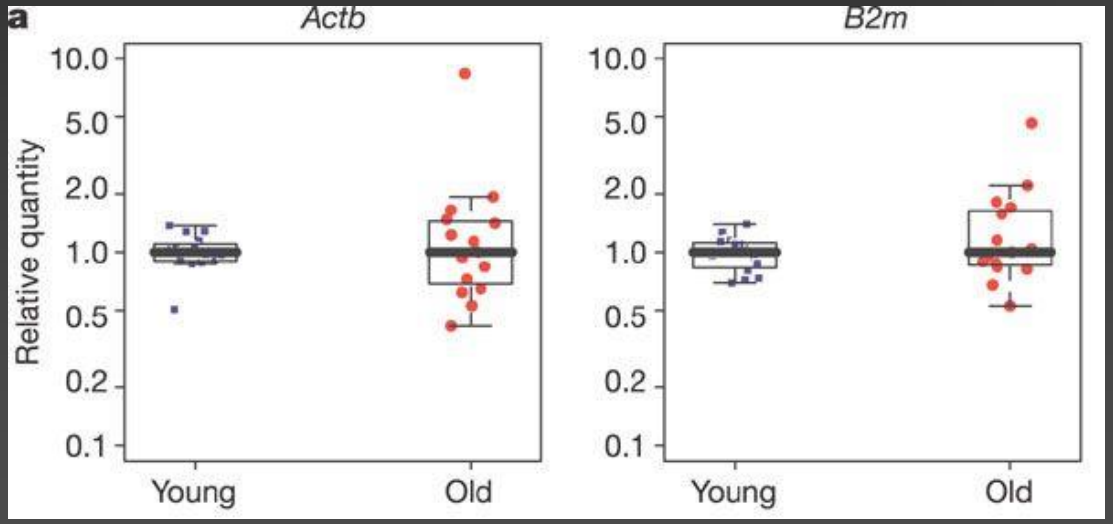
Vol 441|22 June 2006|doi:10.1038/nature04844 nature

LETTERS

Increased cell-to-cell variation in gene expression in ageing mouse heart

Rumana Bahar[1], Claudia H. Hartmann[2], Karl A. Rodriguez[3], Ashley D. Denny[3], Rita A. Busuttil[1], Martijn E. T. Dollé[4], R. Brent Calder[1], Gary B. Chisholm[3], Brad H. Pollock[3], Christoph A. Klein[2] & Jan Vijg[1]

Bahar R et al., Nature 2006

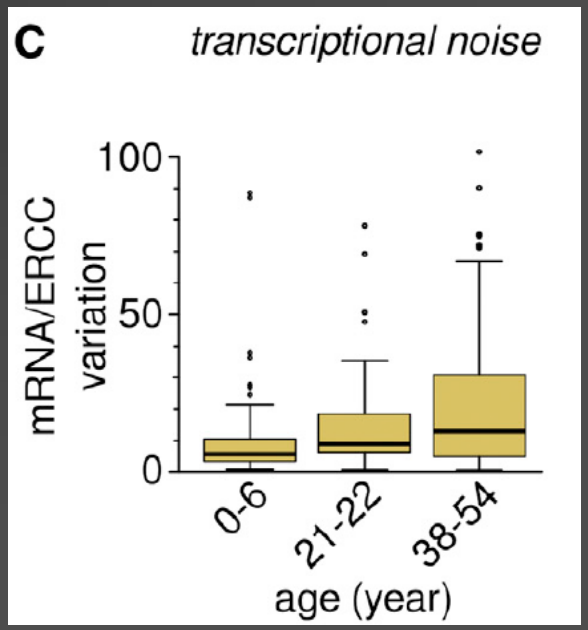


Article Cell

Single-Cell Analysis of Human Pancreas Reveals Transcriptional Signatures of Aging and Somatic Mutation Patterns

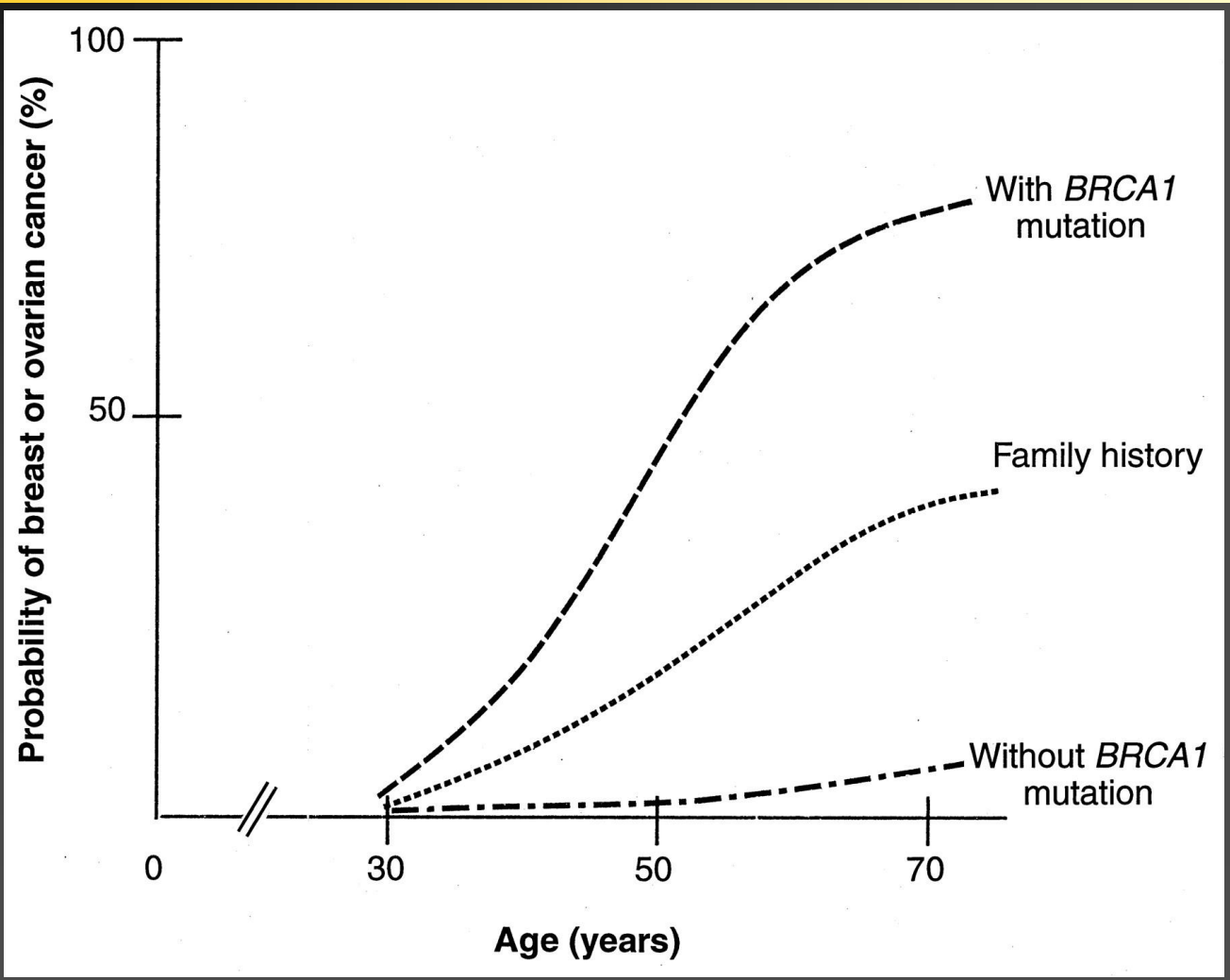
Martin Enge,[1,6] H. Efsun Arda,[2] Marco Mignardi,[1,5] John Beausang,[1] Rita Bottino,[4] Seung K. Kim,[2] and Stephen R. Quake[1,3,4,7,*]

Enge et al., CELL 2017



Somatic mutations and disease risk

Age-related risk of breast and ovarian cancer in BRCA mutation carriers



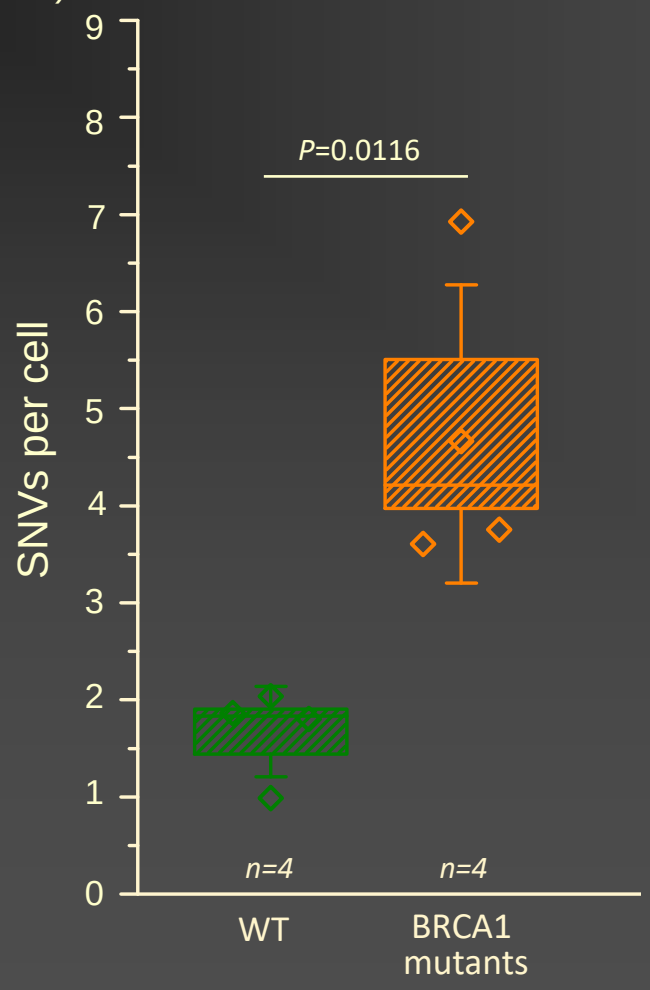
Ponder, *Science*, 1997

Somatic mutation levels in human mammary epithelial cell lines

Cristina Montagna

Ben Ho Park

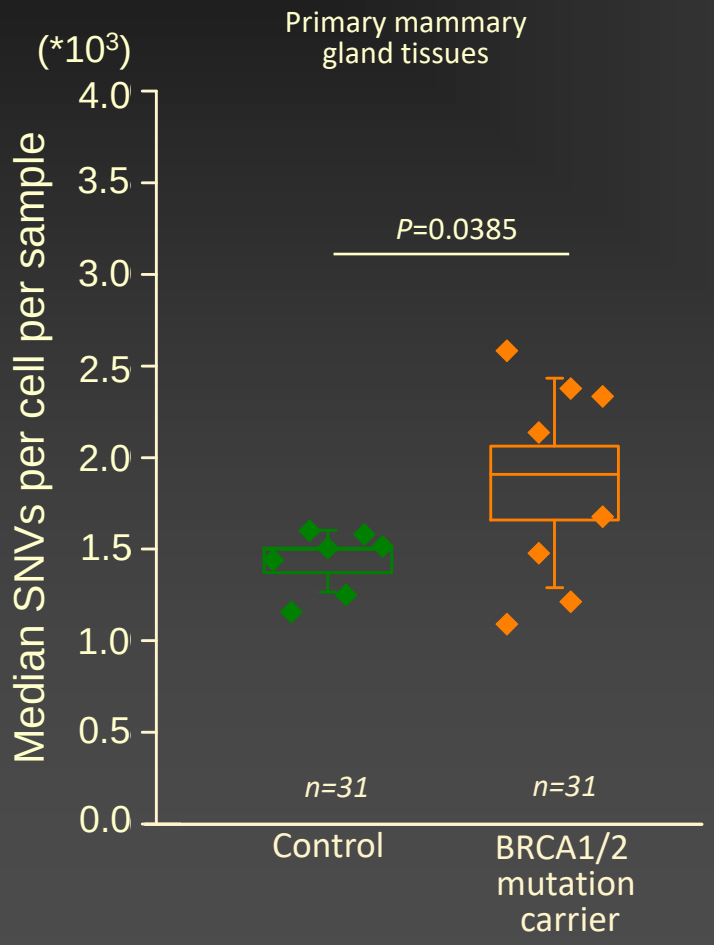
hTERT-IMEC, BRCA1 heterozygote isogenic cell line

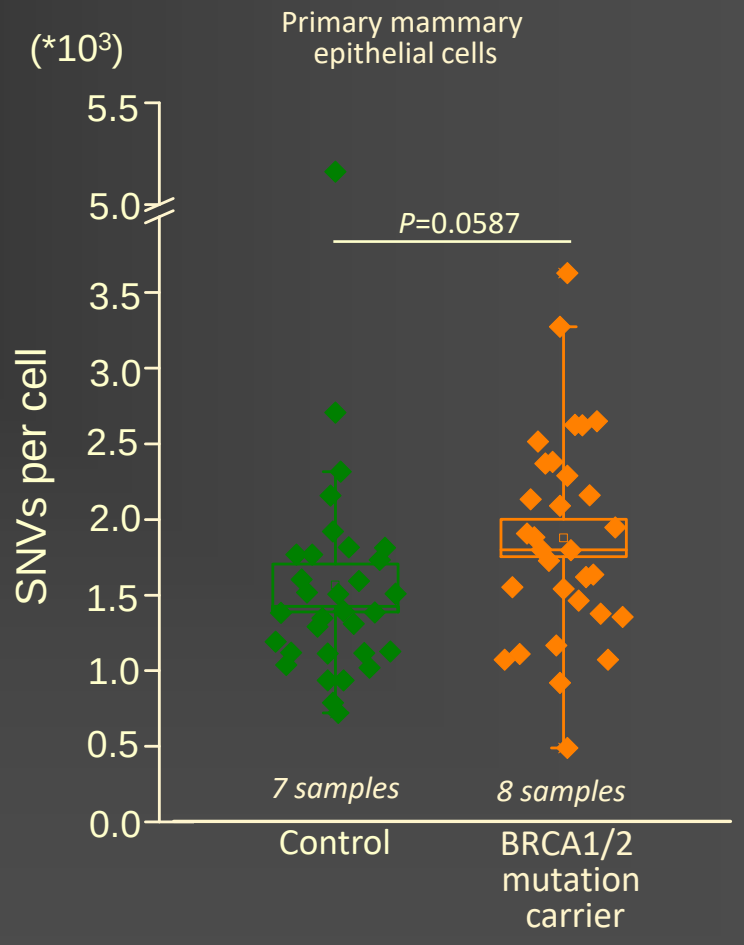


Shixiang Sun

Sun, unpublished

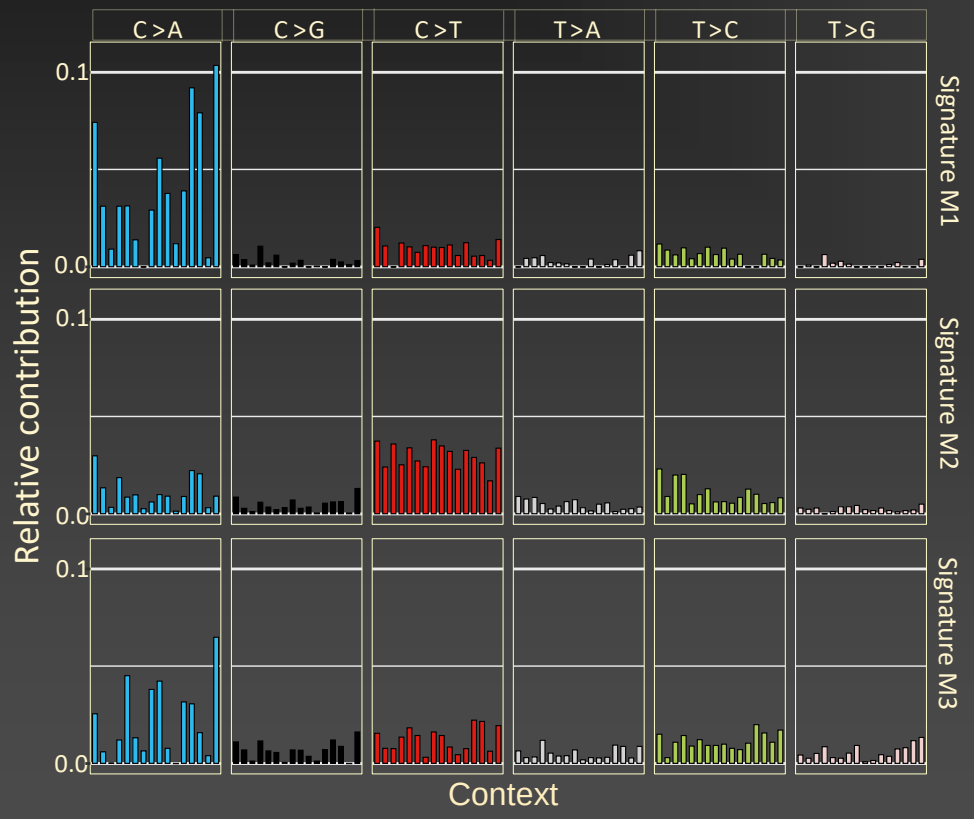
Somatic mutation frequencies in primary human mammary gland cells from BRCA1/2 carriers



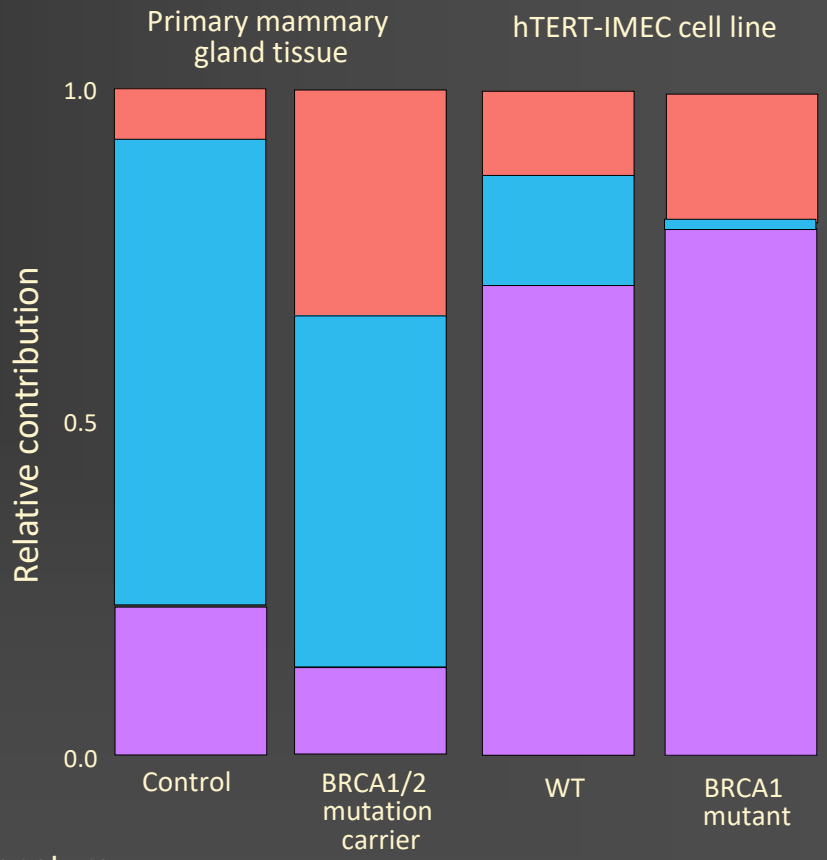


Sun, unpublished

Somatic mutation signatures in BRCA1/2 carriers and controls



Signatures are interpreted according to COSMIC database and Alexandrov *et.al.*, 2020, *Nature* doi.org/10.1038/s41586-020-1943-3.



Sun, unpublished

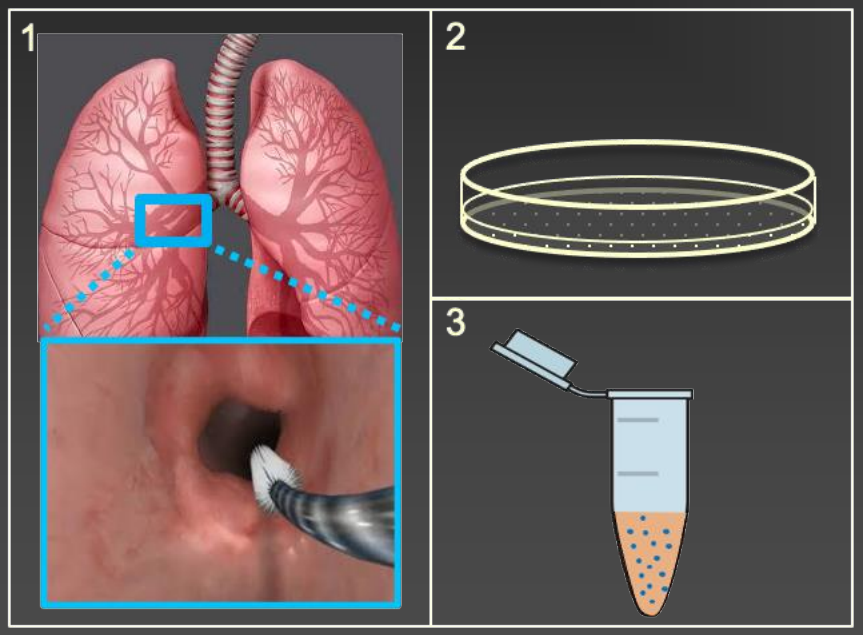
Processing of normal lung cells for somatic mutation analysis


Simon Spivack

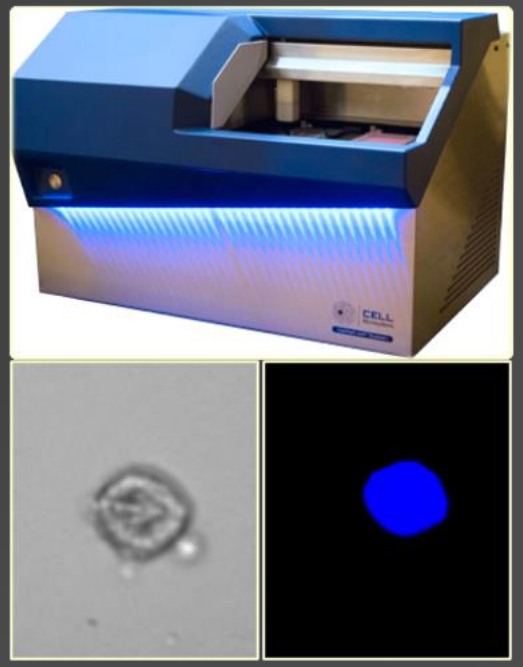

Alex Maslov


Zhenqiu Huang

Bronchial brush, culture and nuclei isolation



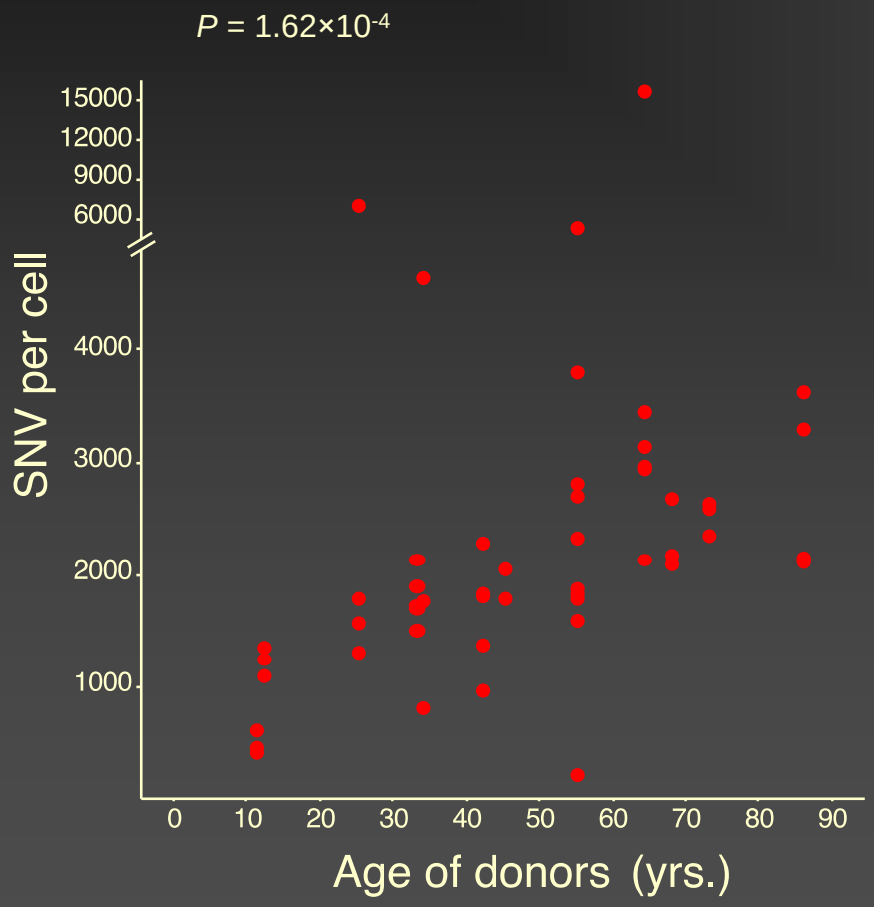
Single nuclei collection

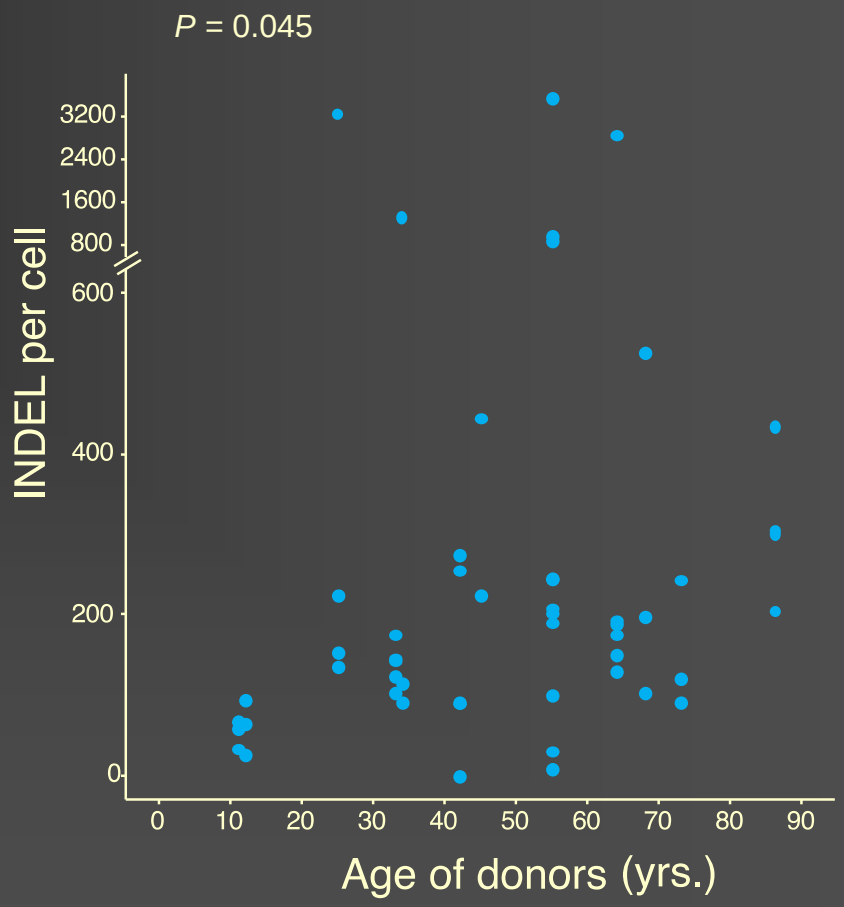


Bright field Hoechst

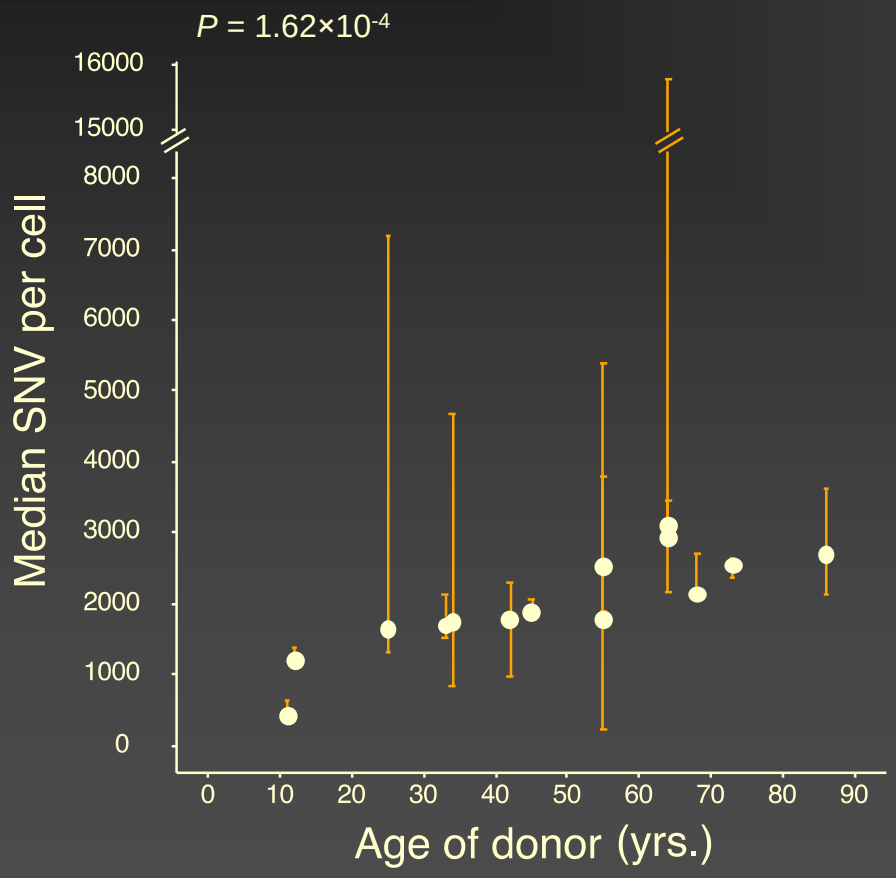
U01 ES029519 (Vijg/Spivack; method)
U01HL145560 (Spivack/Vijg; aging)

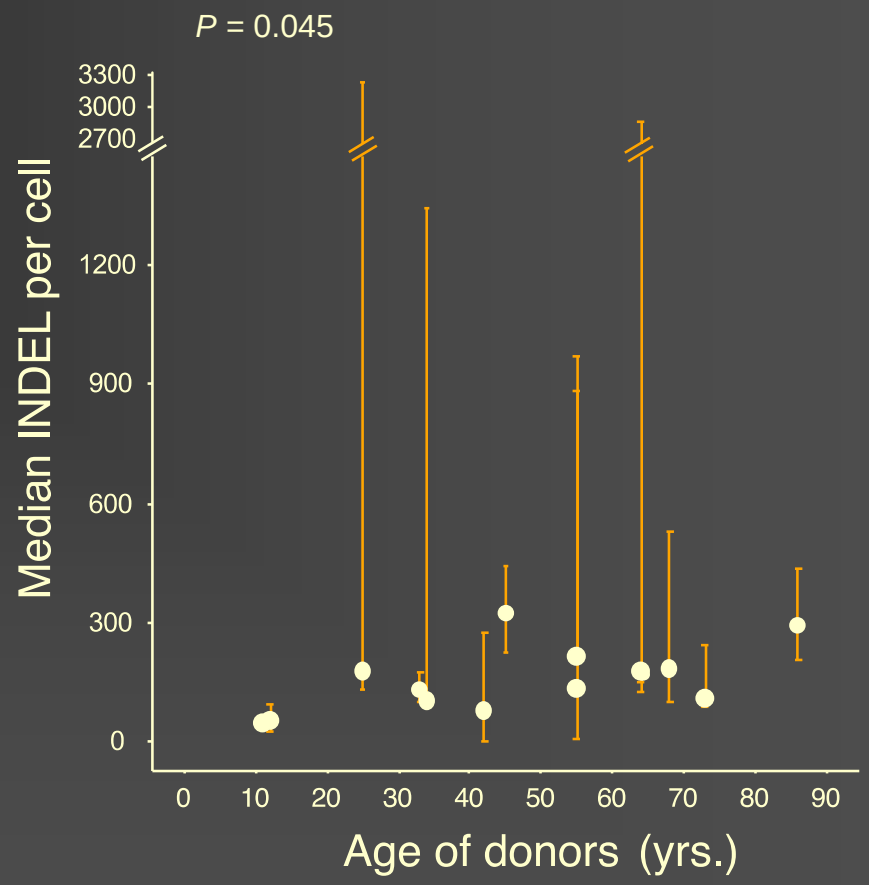
Mutation frequencies in single, bronchial cells of non-smokers as a function of age



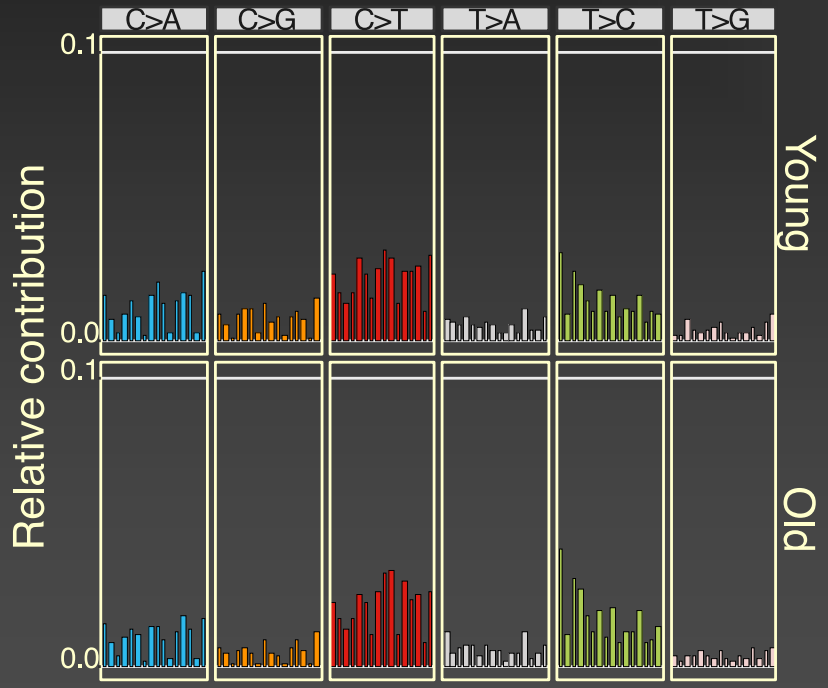


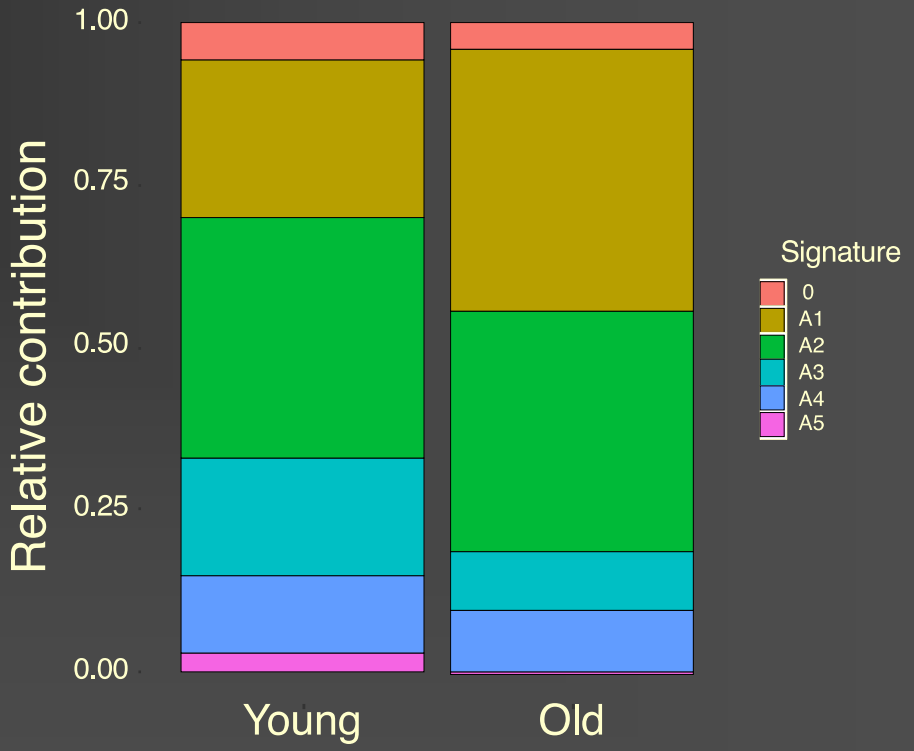
Median single cell mutation frequencies in bronchial cells of non-smokers as a function of age





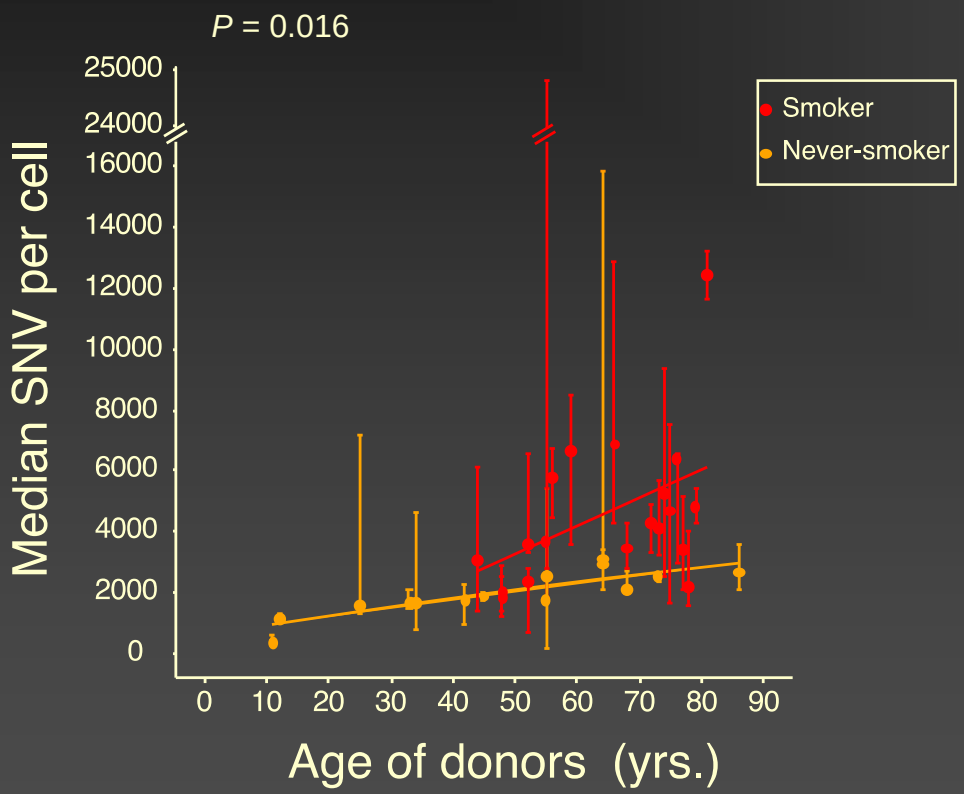
Mutation signatures in human bronchial cells as a function of age

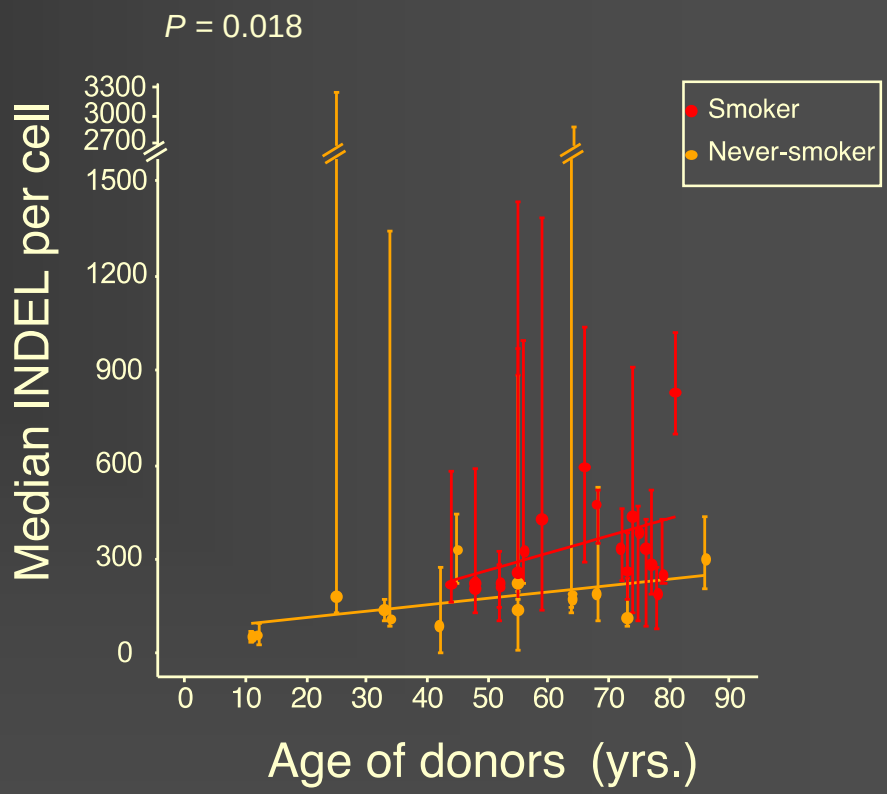




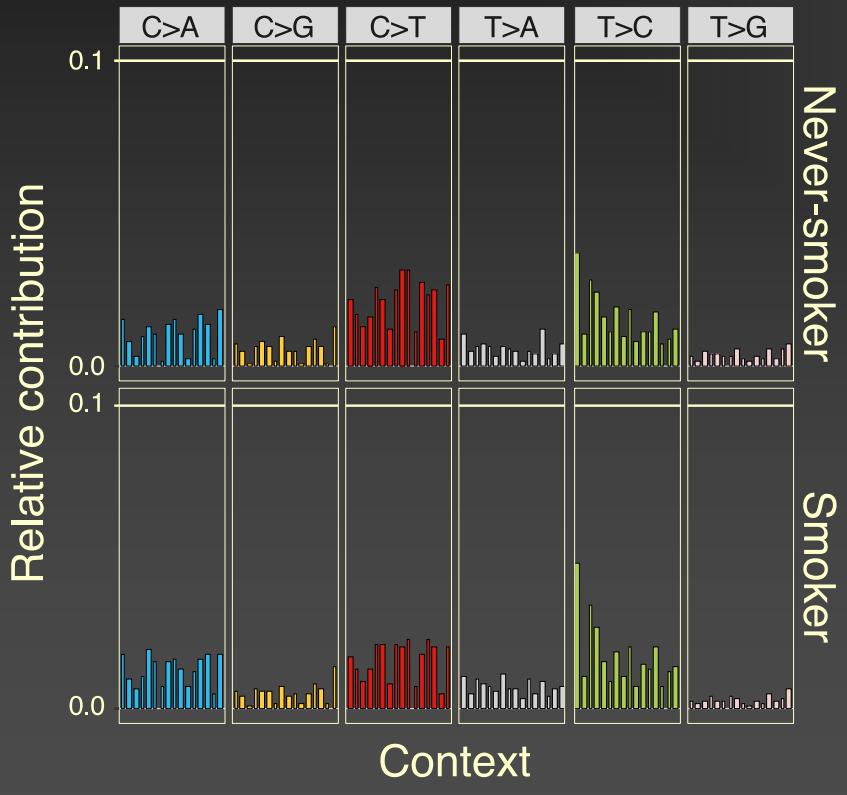
Signature A1 correlates significantly with the COSMIC aging signature SBS5 (https://cancer.sanger.ac.uk/cosmic/signatures; Cosine similarity 0.871)

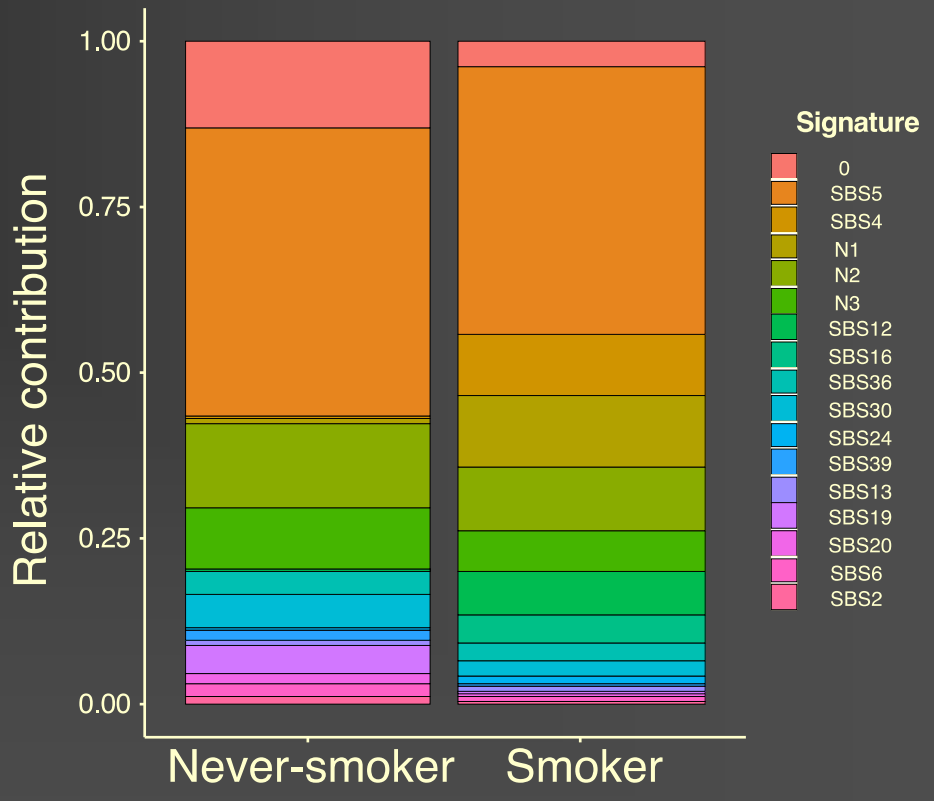
Median mutation frequency in bronchial cells of smokers versus non-smokers across age



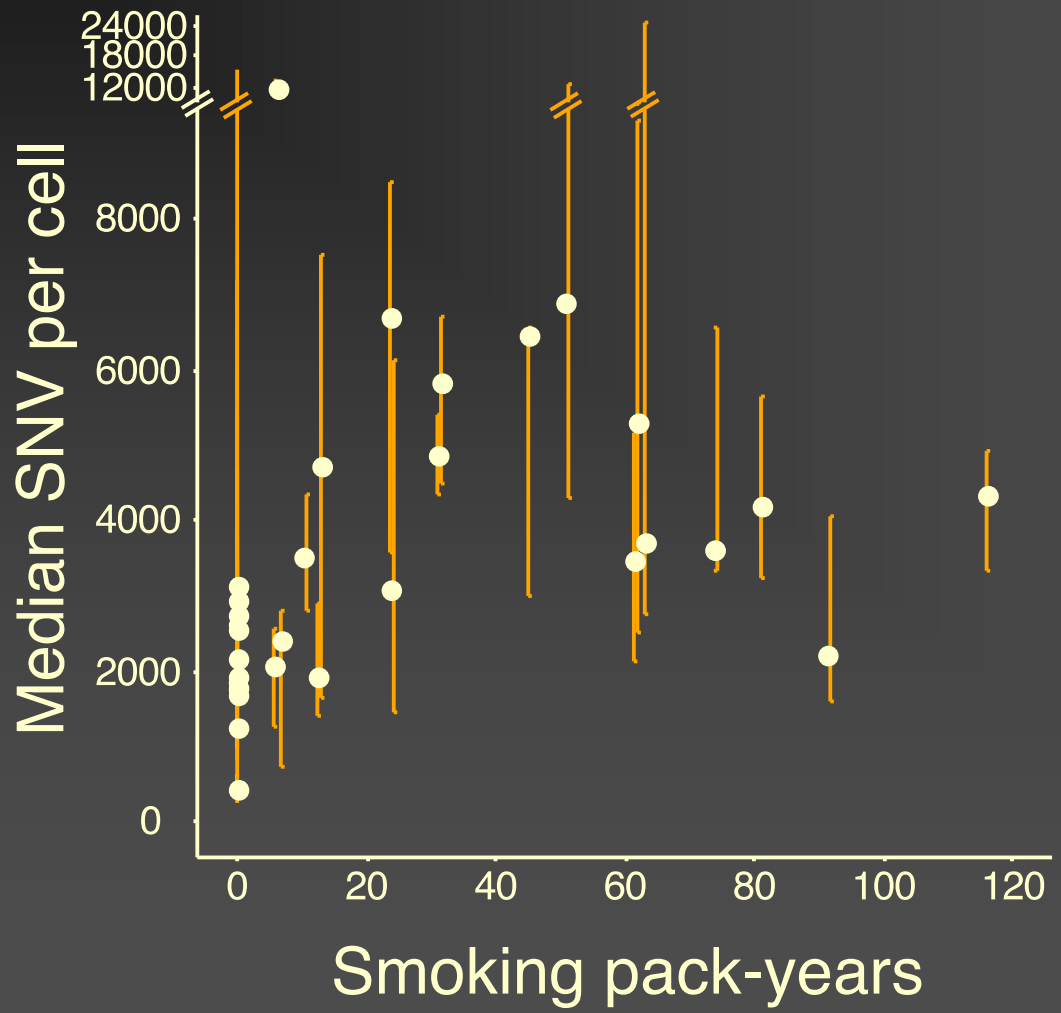


COSMIC mutation signatures in normal bronchial cells from smokers versus never-smokers





Median SNV mutation frequencies in bronchial cells from human subjects as a function of smoking pack years



Interventions for limiting loss of genome sequence integrity

- Preventative measures, such as dietary and life style changes, e.g., UV, tobacco smoke, polycyclic aromatic hydrocarbons
- Dietary antimutagens, e.g., various flavonoids, selenium, plant polyphenols
- Metabolic interventions, e.g., dietary restriction, FOXO
- Direct upregulation of DNA repair pathways
- Elimination of mutant cells

Thank you!

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