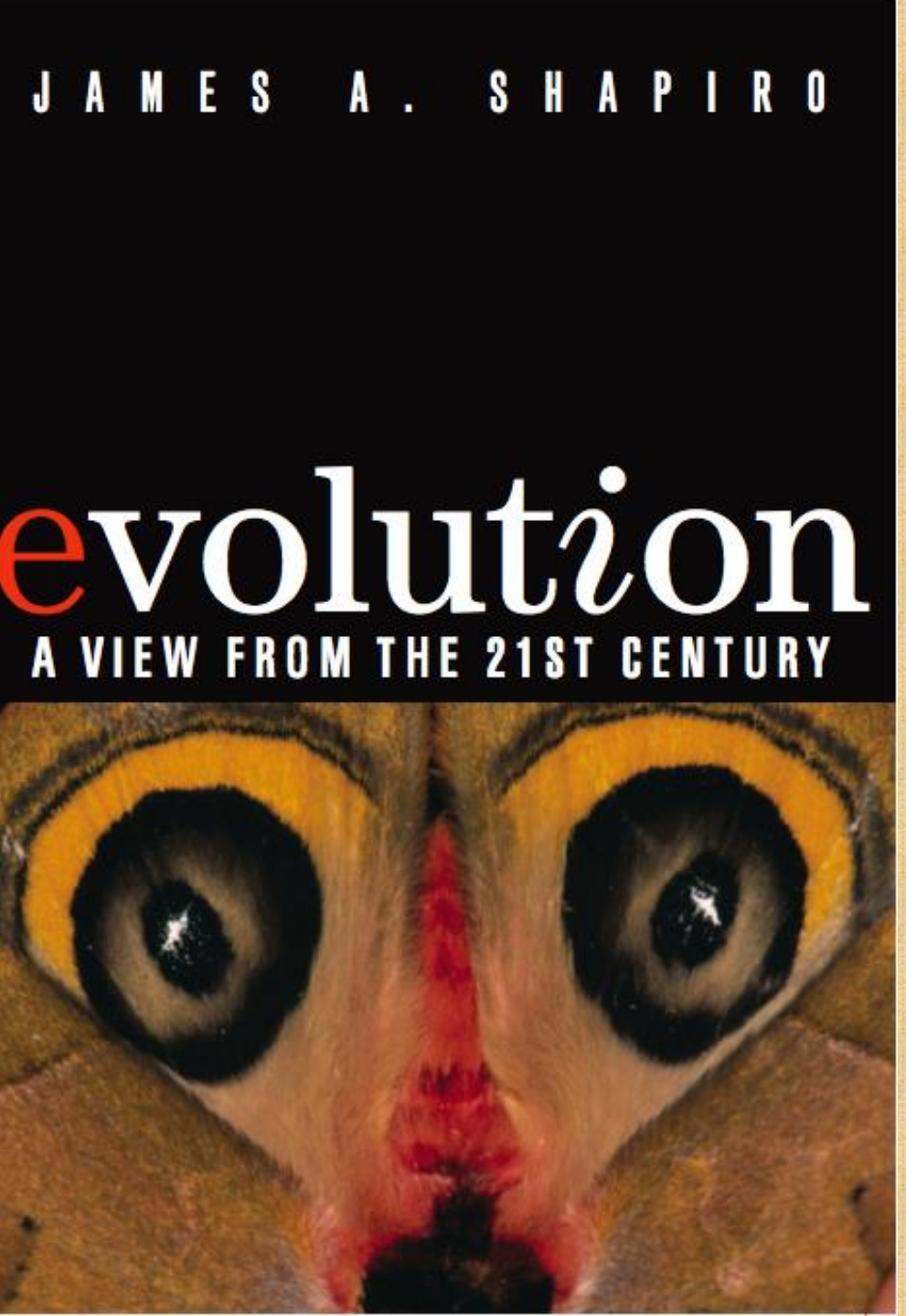


What Can Evolutionary Biology Learn from Cancer Biology?

- James A. Shapiro
- University of Chicago
- jsha@uchicago.edu; http://shapiro.bsd.uchicago.edu

- Cancer and Evolution Symposium 2020
- October 14-16, 2020

"The failure of current cancer treatments to successfully eradicate metastatic disease, likely results from a misunderstanding of the *natural history* of cancer. Rather than seeing malignancy as a consequence of Darwinian microevolution driven by stochastic mutations, it can be considered as the result of a programmed response illicitly accessed by a few key mutations …This programme appears to have been imprinted through evolution to cope with DNA damage and stored in the evolutionary memory of the genome." (italics added)

Erenpreisa, J. and M. S. Cragg (2013). "Three steps to the immortality of cancer cells: senescence, polyploidy and self-renewal." Cancer Cell Int **13**(1): 92.

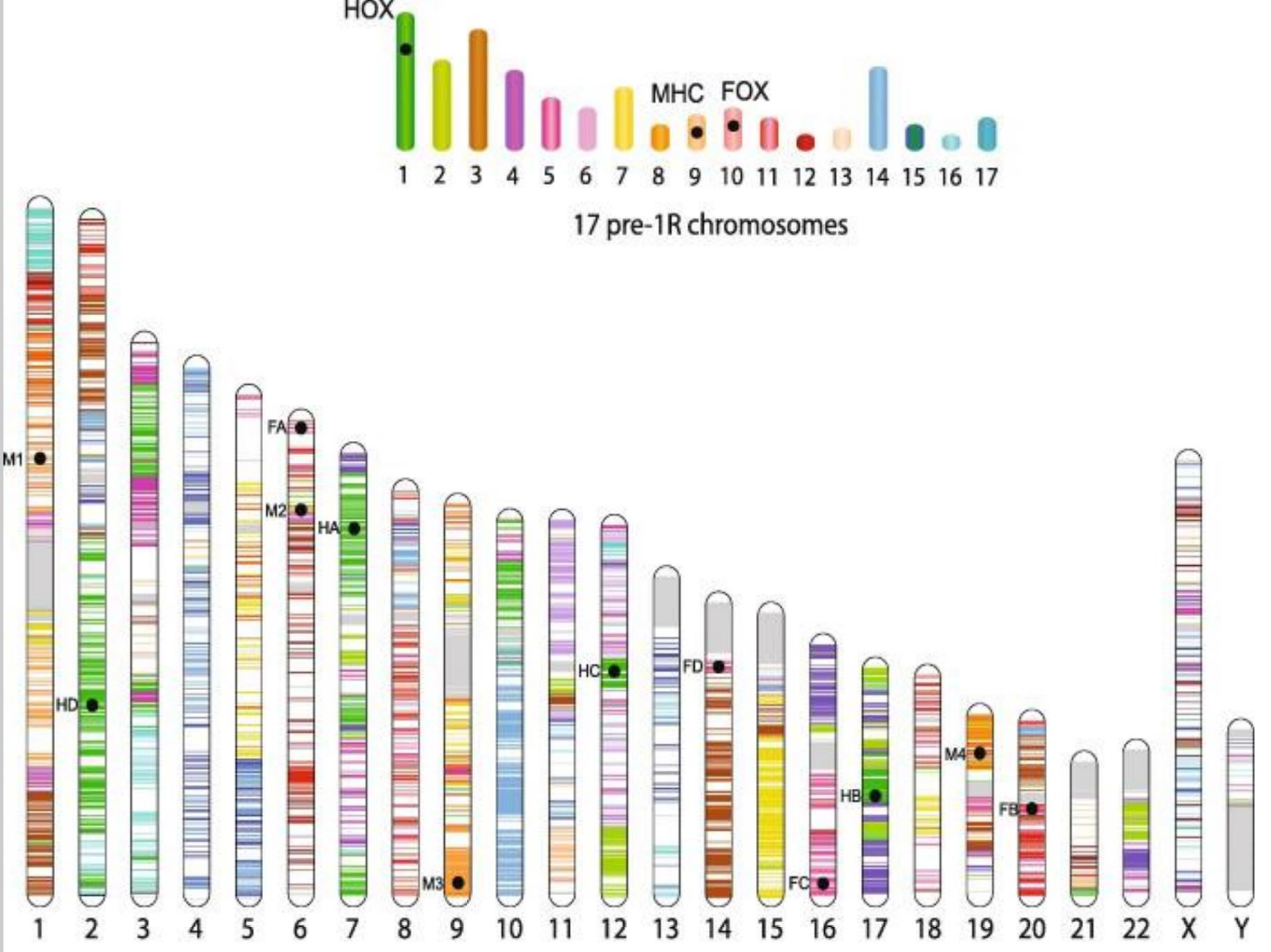
Macroevolution is not the same as Microevolution

Cancer is a Disease of Macroevolution

- Microevolution = gradual evolution by accumulation of independent localized mutations optimizing individual adaptations, as Darwin described in 1859.

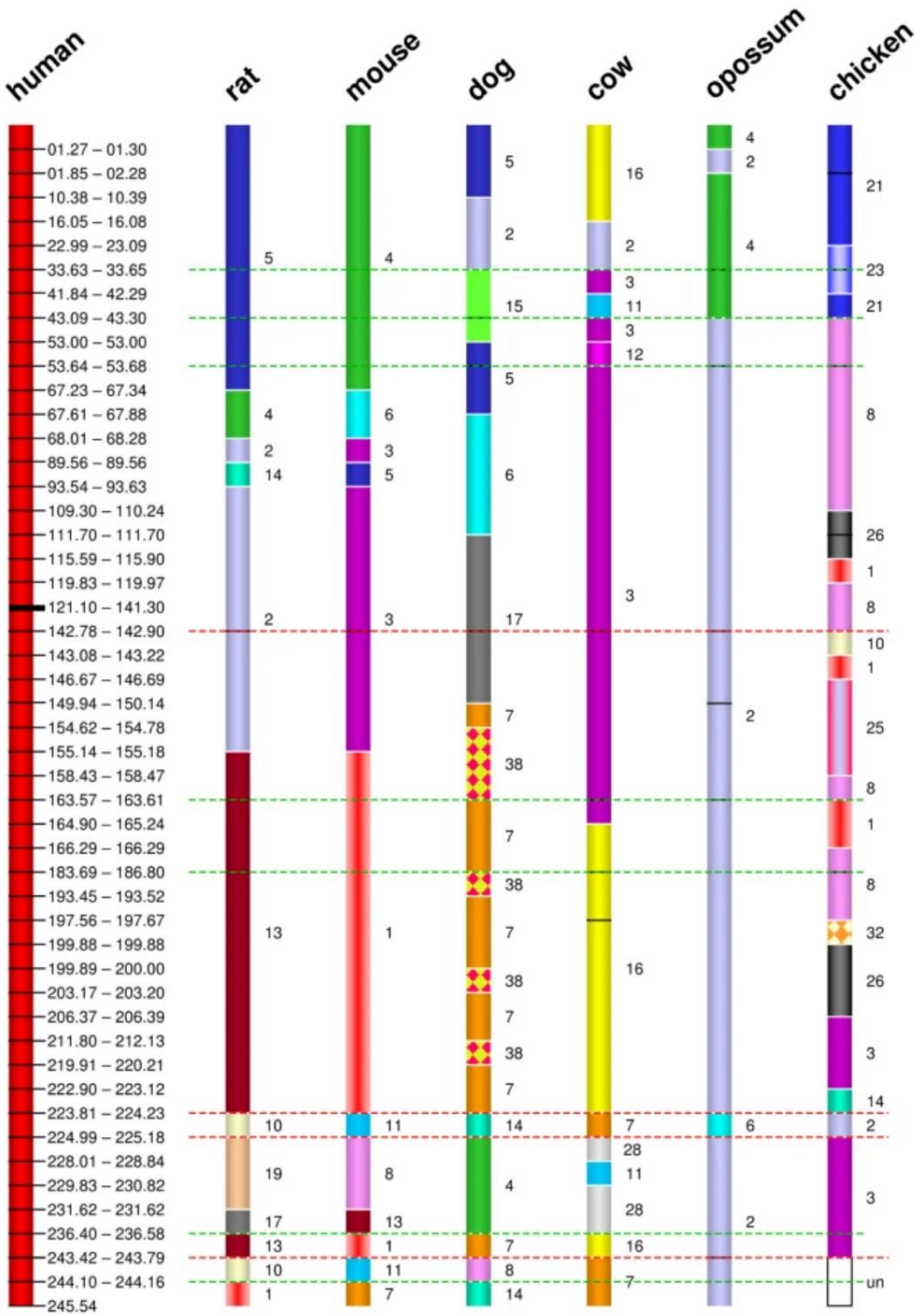
- Macroevolution = punctuated evolution generating new species and new taxa involving chromosome or karyotype restructuring

- Goldschmidt, R. (1940). The Material Basis of Evolution (The Silliman Memorial Lectures Series), (Reissued 1982) New Haven CT, Yale Univ.Press
- White, M. J. D. (1945). Animal cytology and evolution, Cambridge University Press. (3rd Edition, 1973)
- Stebbins, J., G.L. (1951). "Cataclysmic Evolution." Scientific American **184**(4): 54 –59.
- Heng, H. H. (2019). Genome Chaos: Rethinking Genetics, Evolution, and Molecular Medicine, Academic Press.



Chromosome Changes in Human Evolution

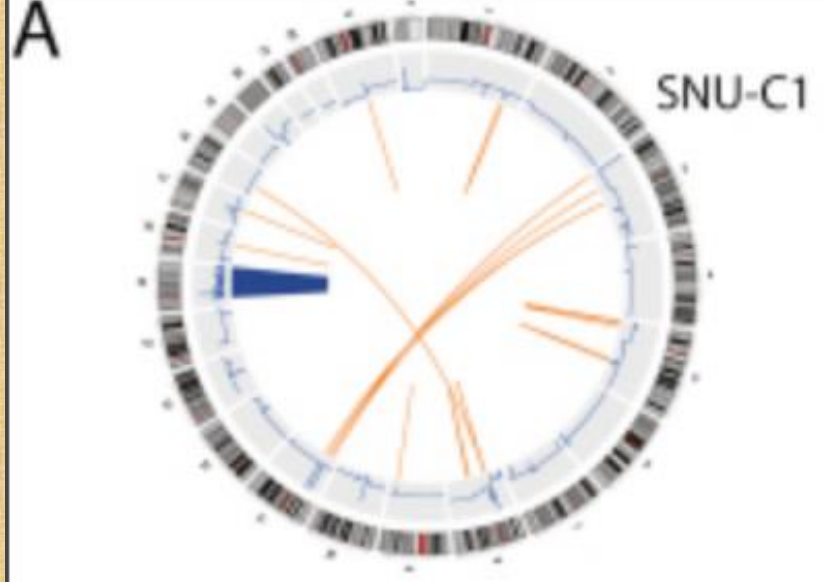
Sacerdot, C., A. Louis, et al. (2018). "Chromosome evolution at the origin of the ancestral vertebrate genome." Genome Biol **19**(1): 166.



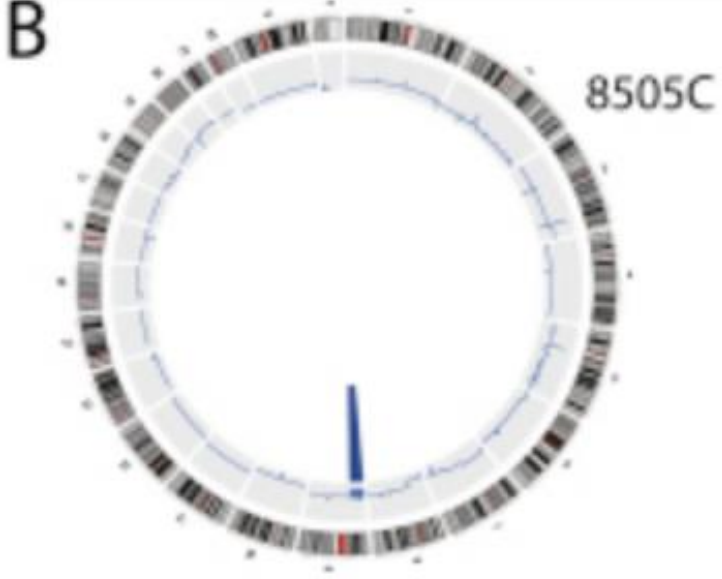
Where Is Human Chromosome 1 in Other Mammals?

"The chromosome number of the orthologous segments in the analyzed species is indicated to the right of each conserved segment. Chromosomal breakpoints have been evenly spaced in order to optimize visualization of the conserved syntenic segments. The resulting ideograms of the chromosomes and conserved segments are therefore not drawn to scale. The centromeric region is indicated by a black horizontal bar on the human ideogram. The stippled red lines indicate breaks present in all analyzed non-human genomes and which may thus be attributable to rearrangements specific to the primate lineage…Stippled green lines indicate the positions of 'reused breakpoints', defined as locations in which breakpoints were found to map to the same genomic intervals in at least three species from two different clades.

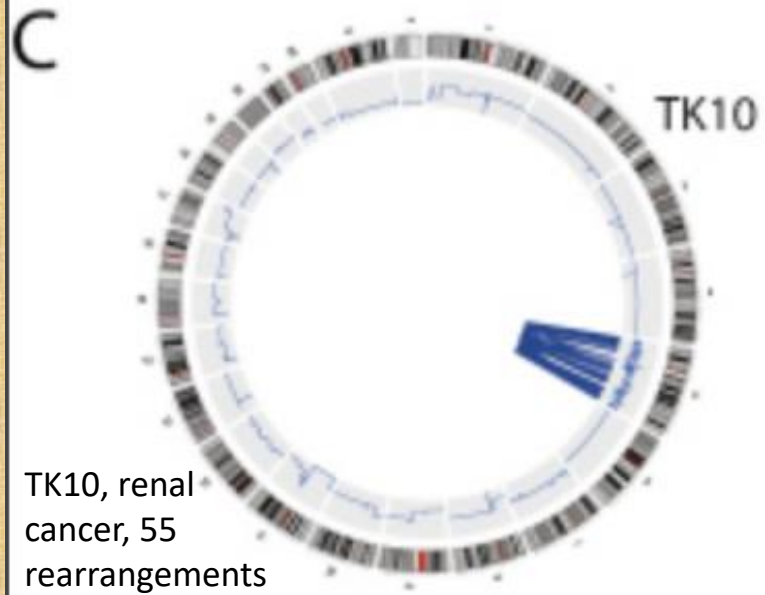
Kemkemer, C., M. Kohn, et al. (2009). "Gene synteny comparisons between different vertebrates provide new insights into breakage and fusion events during mammalian karyotype evolution." BMC Evol Biol **9**: 84



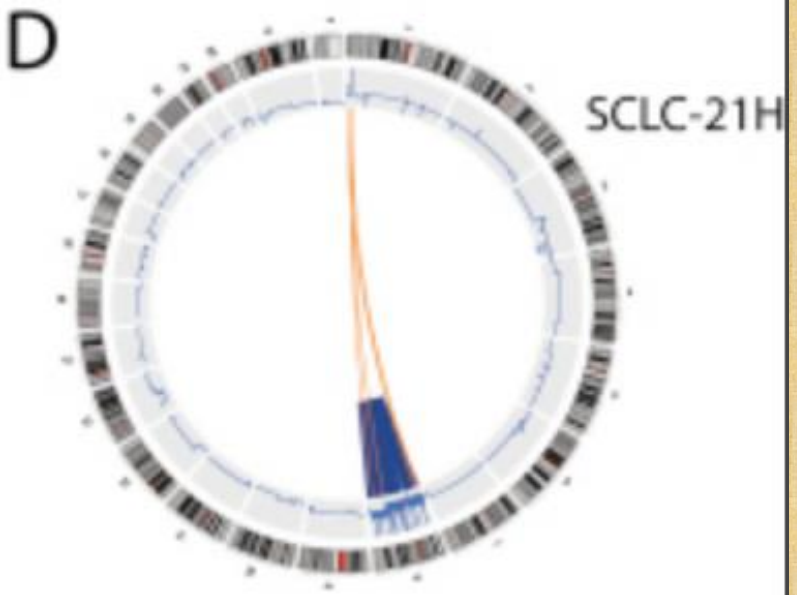
SNU-C1, colorectal cancer, 239 rearrangements of chromosome 15



8505C, thyroid cancer, 77 rearrangements on short arm of chromosome 9



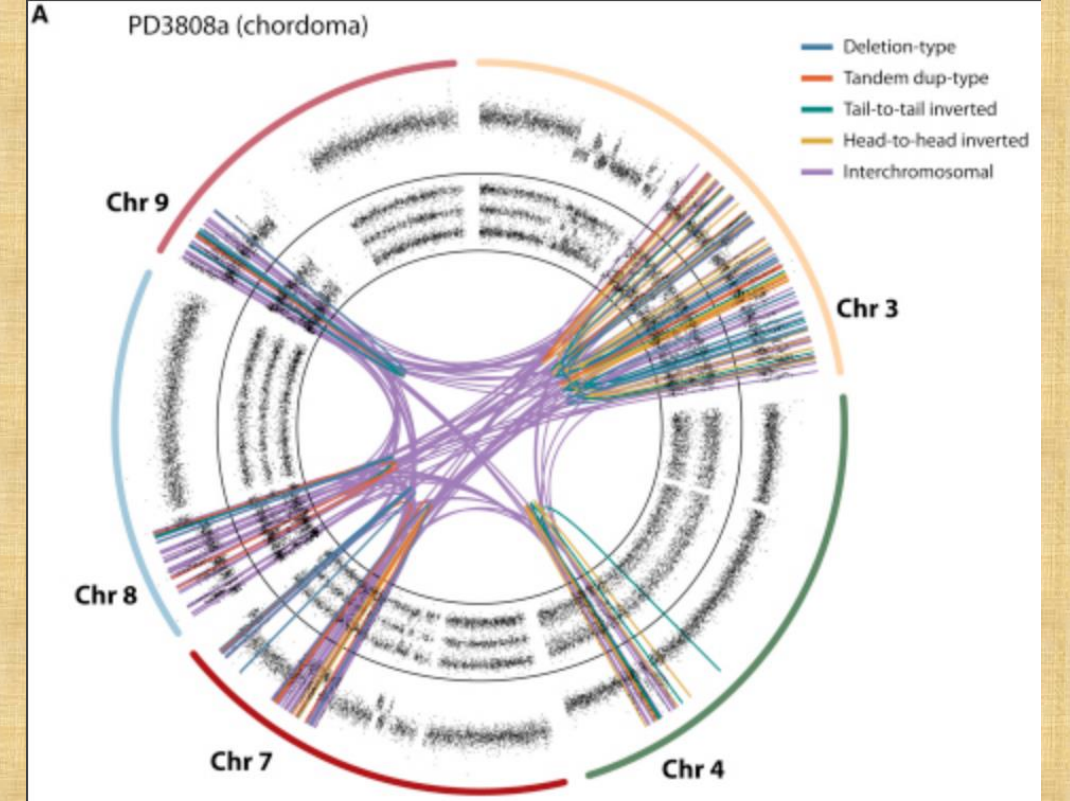
TK10, renal cancer, 55 rearrangements of chromosome 5



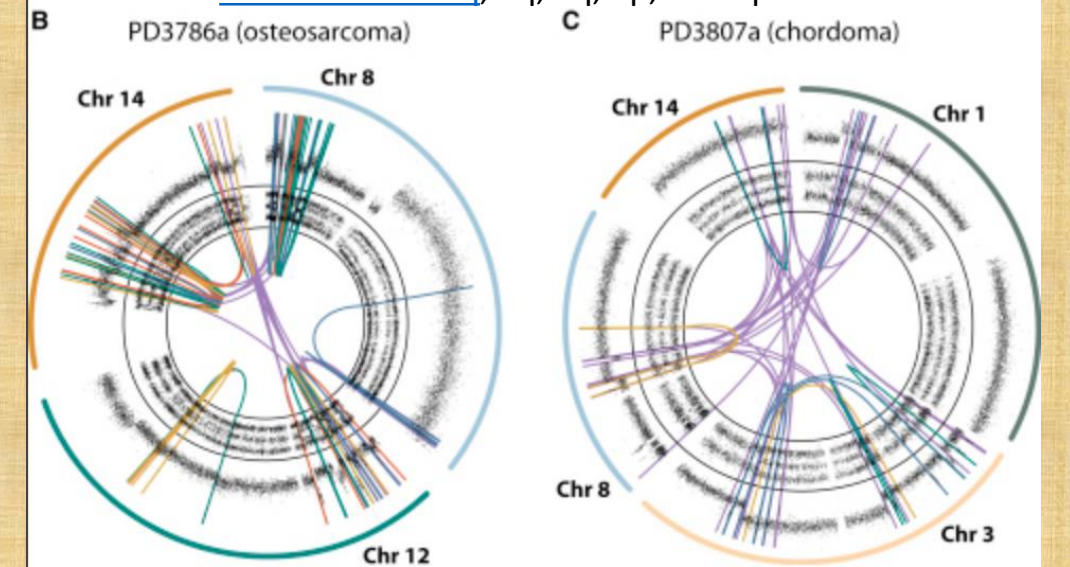
SCLC-21H, lung cancer cell line, 85 CNVs on chromosome 8

Stephens, P. J., C. D. Greenman, et al. (2011). "Massive genomic rearrangement acquired in a single catastrophic event during cancer development." Cell 144(1): 27-40.

“Complex rearrangement of single chromosomes Is seen in at least 2%–3% of all cancers.”



PD3808a, 147 rearrangements interlinking chromosomes 3q, 4q, 7q, 8p, and 9p



Stephens, P. J., C. D. Greenman, et al. (2011). "Massive genomic rearrangement acquired in a single catastrophic event during cancer development." Cell 144(1): 27-40.

Baca, S. C., D. Prandi, et al. (2013). "Punctuated evolution of prostate cancer genomes." Cell 153(3): 666-677

Shen, M. M. (2013). "Chromoplexy: a new category of complex rearrangements in the cancer genome." Cancer Cell 23(5): 567-569.

What Does the Difference Between Chromothripsis and Chromoplexy Mean?

- We have just seen two distinct signature patterns for dozens to hundreds of multisite chromosome rearrangements in cancer that involve only a small subset (1-5) of the 23 human chromosomes. Why is that significant?

- The involvement of only a small part of the karyotype in these multiple exchanges tell us they are highly **non-random** in the genome. Hence, they are the products of organized cell biological activity and not due to multiple accidents.

- The fact that there are at least two different signature patterns (and there are several more) is evidence for the existence of more than one *evolved* complex (4D) cellular repair system capable of generating such clustered, distinctive, and highly nonrandom rearrangements.

First Cancer Biology Lesson for Evolutionary Biology:

Cancer cells Restructure their Genomes at Key Stages in Evolution

to Acquire New Traits (Malignancy, Metastasis, Chemotherapy Resistance).

The Necessary Massive Genome Restructuring can Happen Suddenly,

Executed by Cellular Routines Acting Abruptly at Many Genome Sites

(as in Chromothripsis & Chromoplexy). What do we currently know about

cell processes that trigger karyotype restructuring?

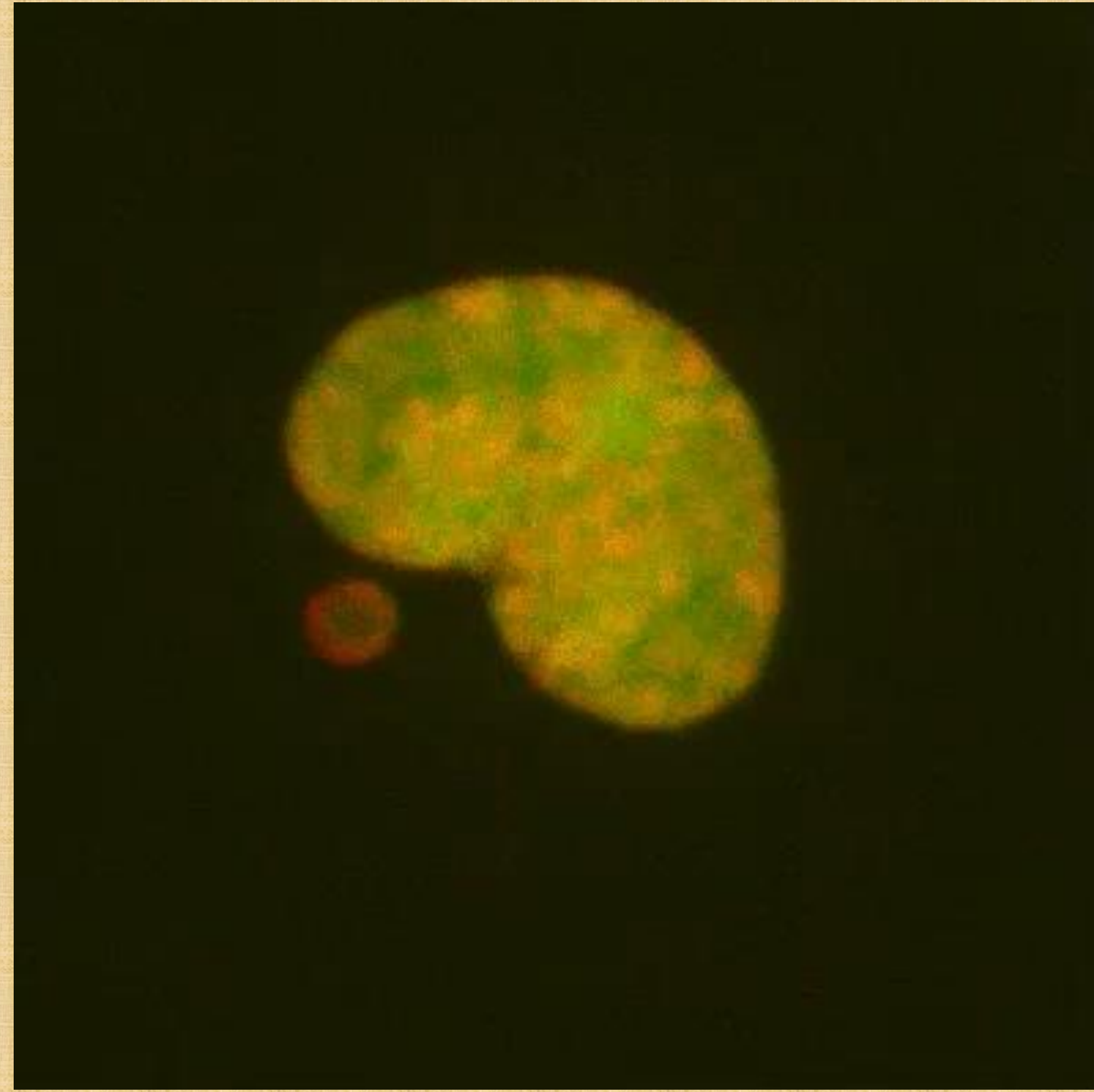
Gerlinger, M., N. McGranahan, et al. (2014). "Cancer: evolution within a lifetime." Annu Rev Genet 48: 215-236.

A Lagging Chromosome in a *Micronucleus* Leads to Chromothripsis:

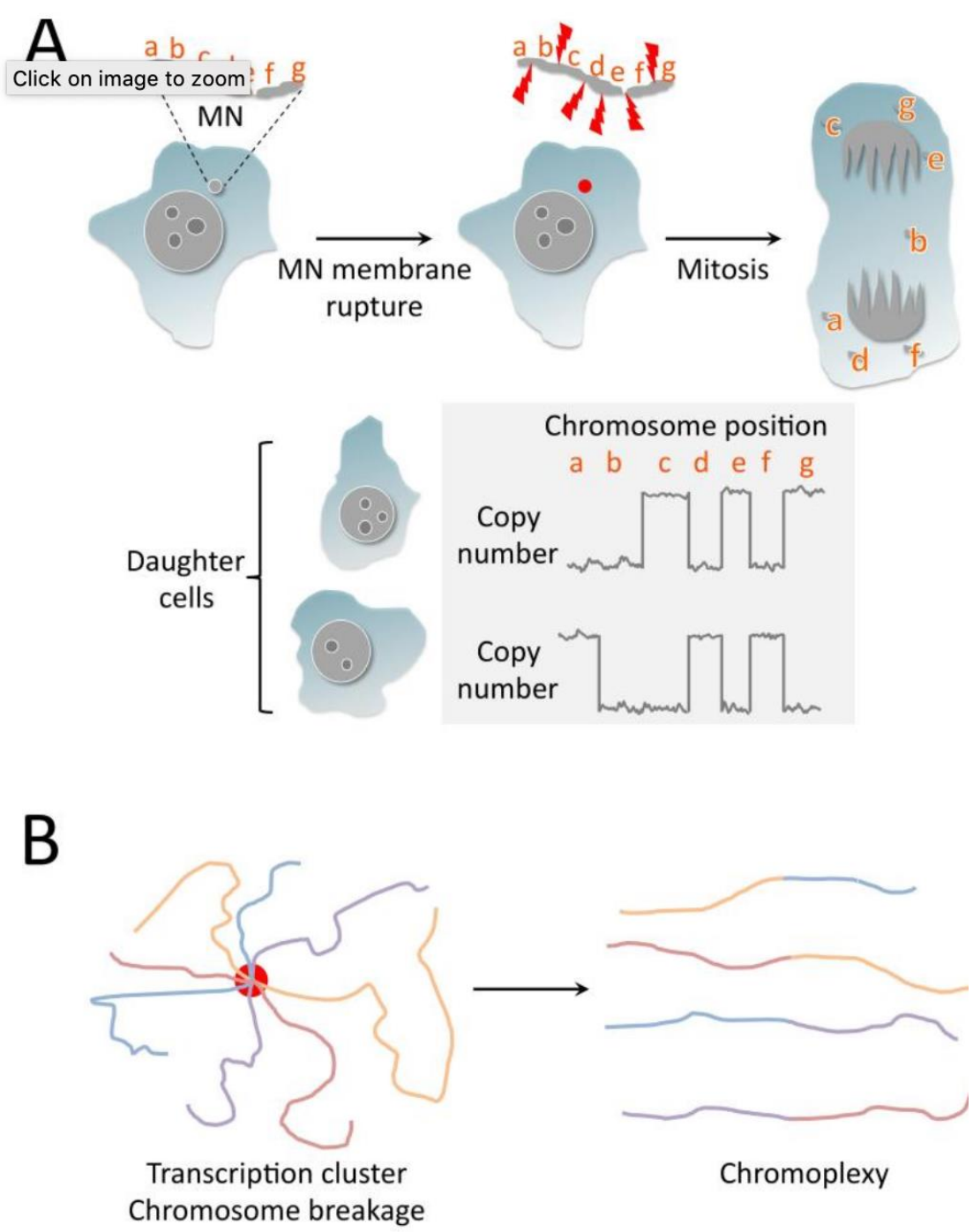
Onset of DNA replication (green) and chromosome shattering in a *micronucleus* (red)

Zhang, C. Z., A. Spektor, et al. (2015). "Chromothripsis from DNA damage in micronuclei." Nature **522**(7555): 179-184

Umbreit, N. T., C. Z. Zhang, et al. (2020). "Mechanisms generating cancer genome complexity from a single cell division error." Science **368**(6488).



Chromothripsis and chromoplexy mediate catastrophic genome rearrangements *via* distinct mechanisms at different times in the cell cycle.

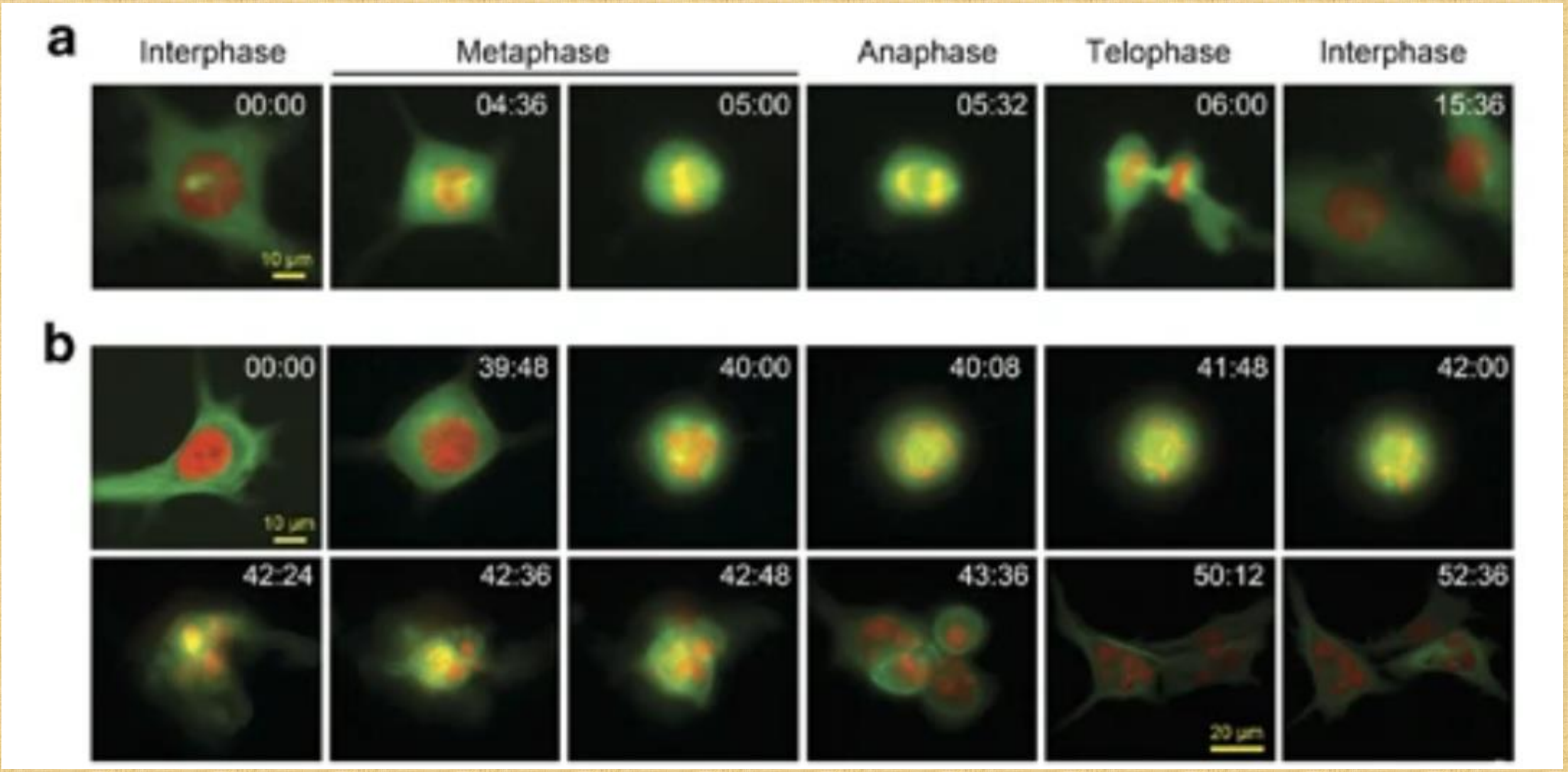


"**A.** Chromothripsis can arise following mitotic damage to micronucleated chromosome(s)…the chromothriptic fragments segregate randomly into the two daughter cells, or are lost (e.g., fragment b shown here). The daughter cell genomes reveal constrained copy number oscillations characteristic of chromothripsis. **B.** A model of chromoplexy in prostate cancer. Clustering of transcriptional elements (red circle), for example, at androgen receptor (AR) responsive loci, coupled with AR-associated chromosome breakage, leads to rejoining of broken chromosoms with the production of linked translocations characteristic of chromoplexy."

• Willis, N. A., E. Rass, et al. (2015). "Deciphering the Code of the Cancer Genome: Mechanisms of Chromosome Rearrangement." Trends Cancer **1**(4): 217-230.

Polyploid Giant Cancer Cell (PGCC) Division ≠ Mitosis

Red = chromatin, green = microtubules



Niu, N., J. Zhang, et al. (2016). "Linking genomic reorganization to tumor initiation via the giant cell cycle." Oncogenesis **5**(12): e281.

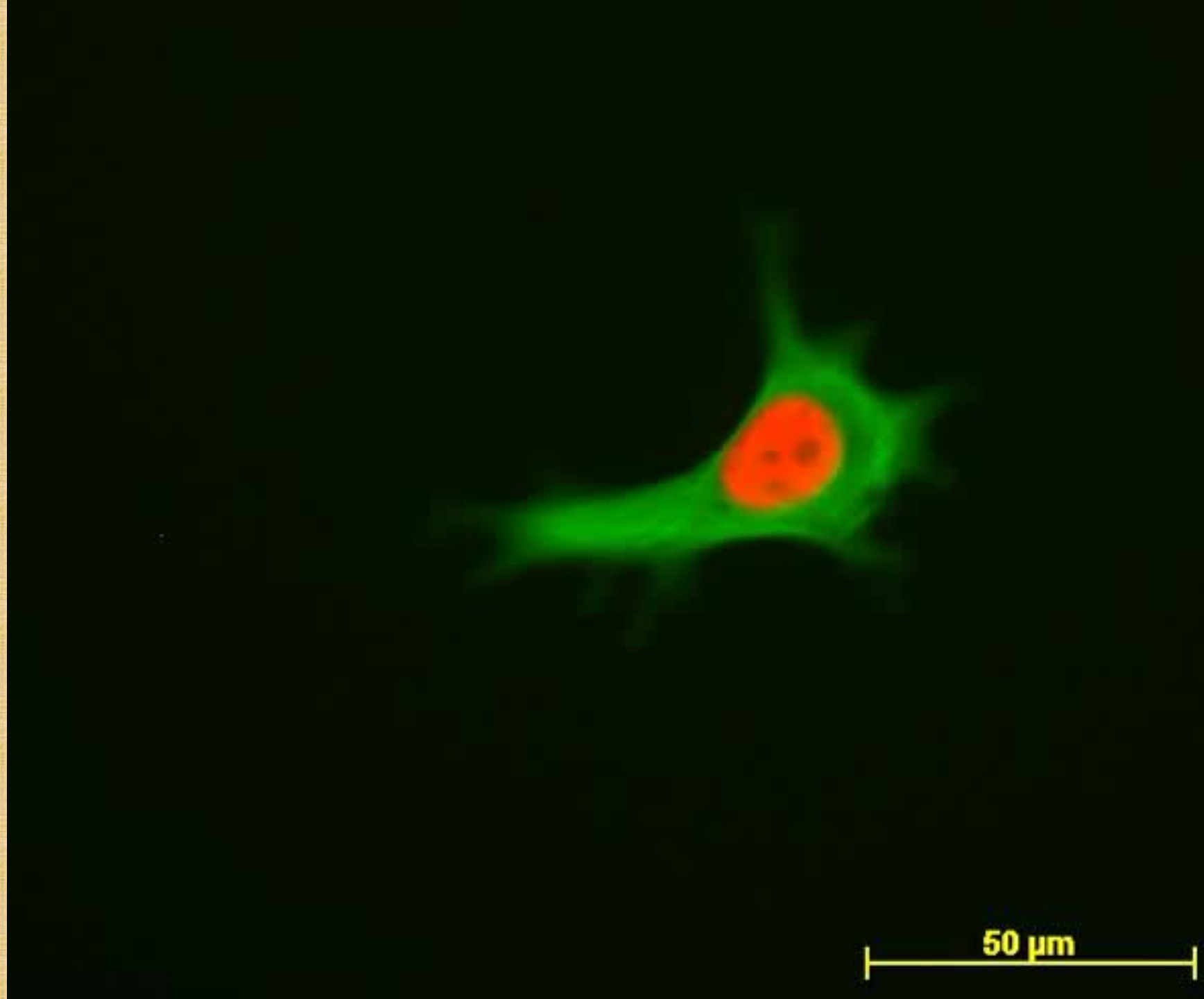
PGCC Amitotic Multipolar Cell Division

(DNA labelled with H2B-mCherry and tubulin labelled with Alpha-Tubulin-EGFP)

Niu, N., J. Zhang, et al. (2016). "Linking genomic reorganization to tumor initiation via the giant cell cycle." Oncogenesis 5(12): e281.

Shabo, I., J. Svanvik, et al. (2020). "Roles of cell fusion, hybridization and polyploid cell formation in cancer metastasis." World J Clin Oncol 11(3): 121-135.

Erenpreisa, J., K. Salmina, et al. (2011). "Polyploid tumour cells elicit paradiploid progeny through depolyploidizing divisions and regulated autophagic degradation." Cell Biol Int 35(7): 687-695.



Polyploidy/Endoreplication – an Ancient Eukaryotic Cell Stress Response

- Lazzerini Denchi, E., G. Celli, et al. (2006). "Hepatocytes with **extensive telomere deprotection and fusion** remain viable and regenerate liver mass through endoreduplication." Genes Dev **20**(19): 2648-2653.
- Erenpreisa, J. and M. S. Cragg (2013). "Three steps to the immortality of cancer cells: **senescence**, polyploidy and self-renewal." Cancer Cell Int **13**(1): 92.
- Schwarz-Finsterle, J., H. Scherthan, et al. (2013). "Volume increase and spatial shifts of chromosome territories in nuclei of **radiation-induced** polyploidizing tumour cells." Mutat Res **756**(1-2): 56-65.
- Losick, V. P., A. S. Jun, et al. (2016). "**Wound-Induced Polyploidization**: Regulation by Hippo and JNK Signaling and **Conservation in Mammals**." PLoS One **11**(3): e0151251
- Scholes, D. R. and K. N. Paige (2015). "Plasticity in ploidy: **a generalized response to stress**." Trends Plant Sci **20**(3): 165-175. (Plants)

Clinical Significance of the Polyploid Response in Healing Recognized by Theodor Boveri in 1914

“One would therefore have to assume that the generation of a malignant tumour as a result of injury takes place in two stages that may be separated from each other by a lengthy interval. The first stage would be the inhibition of cytoplasmic partitioning due to an insult that occurs when the cell is in the process of dividing. This produces the tetraploidy. The second step, however, would be a stimulus that induces the tetraploid cell to divide by multipolar mitosis.

This idea might perhaps provide an explanation for certain specific observations that have been made in the field of tumour research. It has frequently been noted that carcinomas of the skin arise in scars, especially scars resulting from burns, that the scars are often present long before the carcinoma develops and that injury to the scar strongly favours the emergence of the tumour.”

Boveri, T. (2008). "Concerning the origin of malignant tumours by Theodor Boveri (**1914**). Translated and annotated by Henry Harris." J Cell Sci **121 Suppl 1**: 1-84.

Potential Clinical Significance of PGCCs Today

"In summary, we have provided strong evidence for the existence of a giant cell cycle that may constitute a generalized mechanism for survival and generation of genomically altered tumor-initiating cells that contribute to the disease relapse. Defining the molecular mechanisms that regulate **the giant cell cycle should offer novel opportunities for therapeutic intervention** for this devastating disease."

Niu, N., J. Zhang, et al. (2016). "Linking genomic reorganization to tumor initiation via the giant cell cycle." Oncogenesis **5**(12): e281.

Second Cancer Biology Lesson for Evolution Biology:

- Somatic eukaryotic cells have evolved responses to mitotic failure and stress, like micronuclei and polyploidy, that induce major genome reorganizations.

- Activating similar genome-wide responses could help explain rapid evolutionary radiations found after catastrophic events, such as mass extinctions. If correct, the “genome cataclysms” must occur in the germline.

- How Likely is Germline Mitotic Failure & Genome Restructuring?

Chromothripsis Found in the Human Germline

• Kloosterman, W. P., V. Guryev, et al. (2011). "Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline." Hum Mol Genet **20**(10): 1916-1924.

• de Pagter, M. S., M. J. van Roosmalen, et al. (2015). "Chromothripsis in Healthy Individuals Affects Multiple Protein-Coding Genes and Can Result in Severe Congenital Abnormalities in Offspring." Am J Hum Genet **96**(4): 651-656

• Anderson, S. E., A. Kamath, et al. (2016). "A rare example of germ-line chromothripsis resulting in large genomic imbalance." Clin Dysmorphol **25**(2): 58-62.

• Bertelsen, B., L. Nazaryan-Petersen, et al. (2016). "A germline chromothripsis event stably segregating in 11 individuals through three generations." Genet Med **18**(5): 494-500.

Research Starting on **Germline** Chromothripsis – What Will That Mean for Evolutionary Theory?

- Nazaryan-Petersen, L., B. Bertelsen, et al. (2016). "Germline Chromothripsis Driven by L1 Mediated Retrotransposition and Alu/Alu Homologous Recombination." Hum Mutat **37**(4): 385-395.

- Middelkamp, S., S. van Heesch, et al. (2017). "Molecular dissection of germline chromothripsis in a developmental context using patient-derived iPS cells." Genome Med **9**(1): 9.

- Slamova, Z., L. Nazaryan-Petersen, et al. (2018). "Very short DNA segments can be detected and handled by the repair machinery during germline chromothriptic chromosome reassembly." Hum Mutat **39**(5): 709-716.