# Reverting to Single Cell Biology in Cancer

PAUL DAVIES AND KIM BUSSEY

BEYOND CENTER FOR FUNDAMENTAL CONCEPTS IN SCIENCE
ARIZONA STATE UNIVERSITY

PRECISION MEDICINE PROGRAM
MIDWESTERN UNIVERSITY

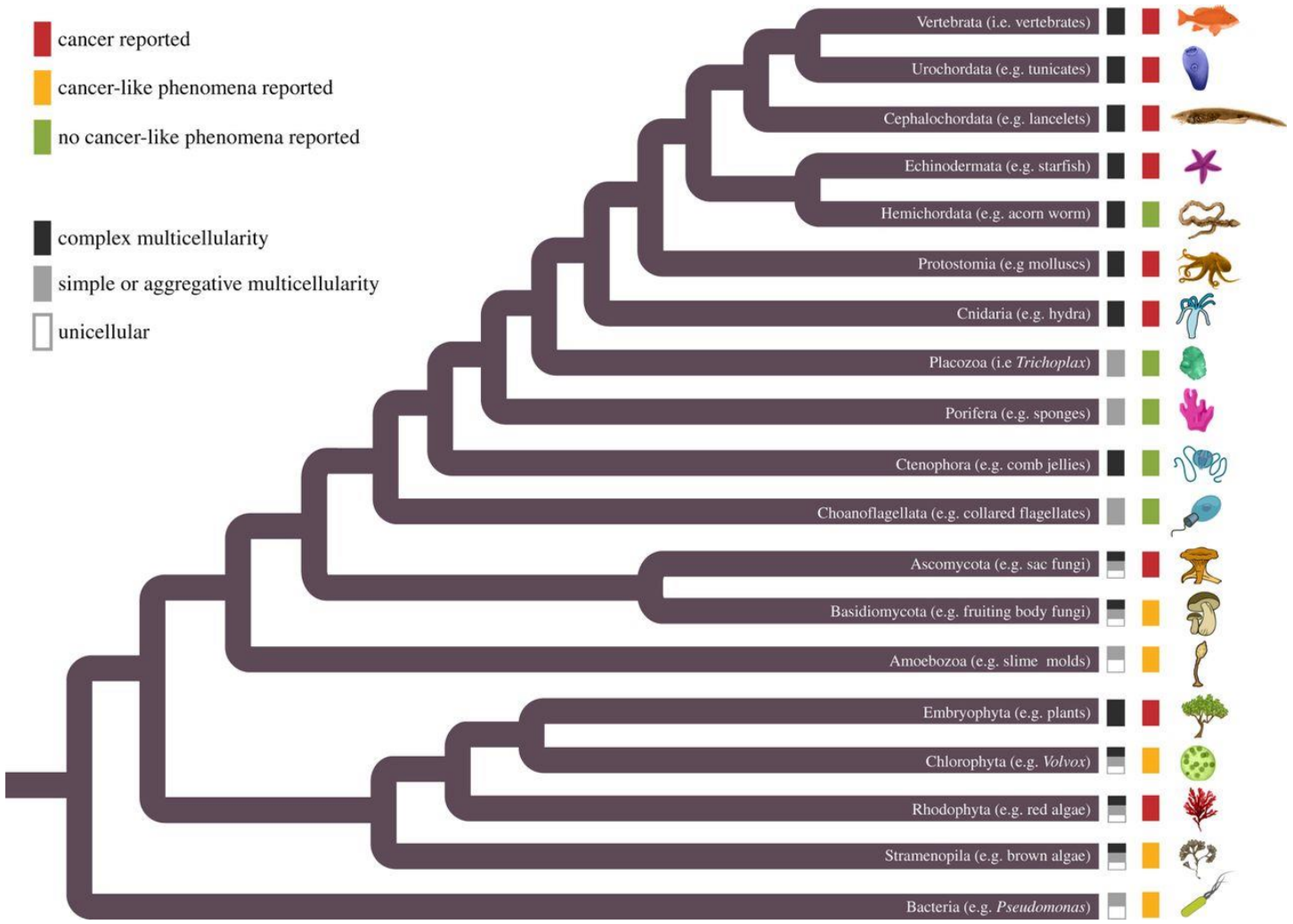
What is cancer as
*a biological phenomenon*?

Why does it exist?

What is its place in the great story of life on Earth?


Cancer is a window on the past

# Cancer across the tree of life

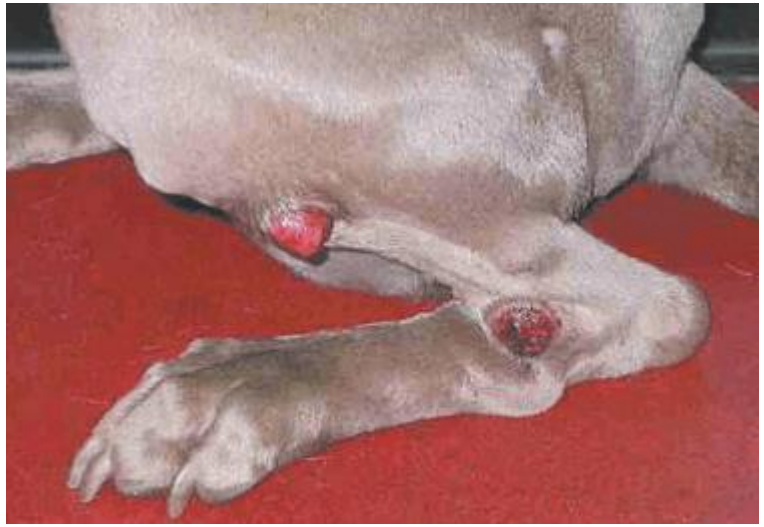


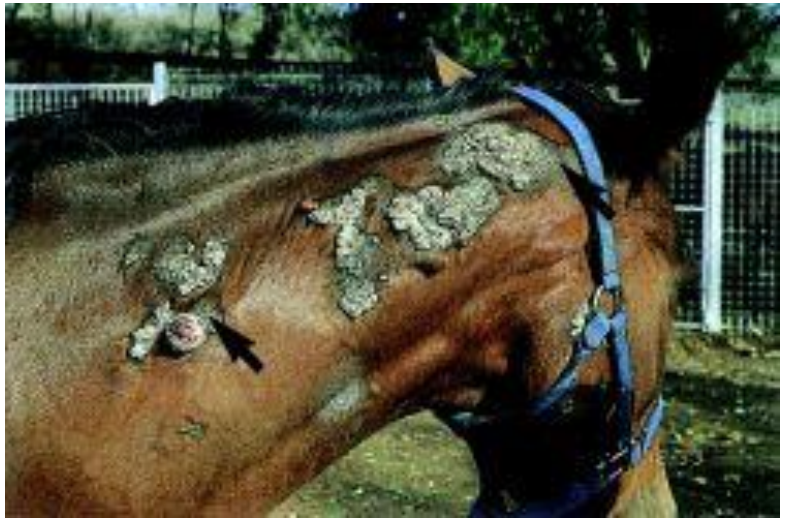

C. Athena Aktipis et al. Phil. Trans. R. Soc. B 2015;370:20140219

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

***Key fact: cancer pervades multicellular life***

Cancer is not “life gone wrong” but  a deep-rooted and therefore ancient property of life itself. To understand cancer we need to know its place in the overall story of life



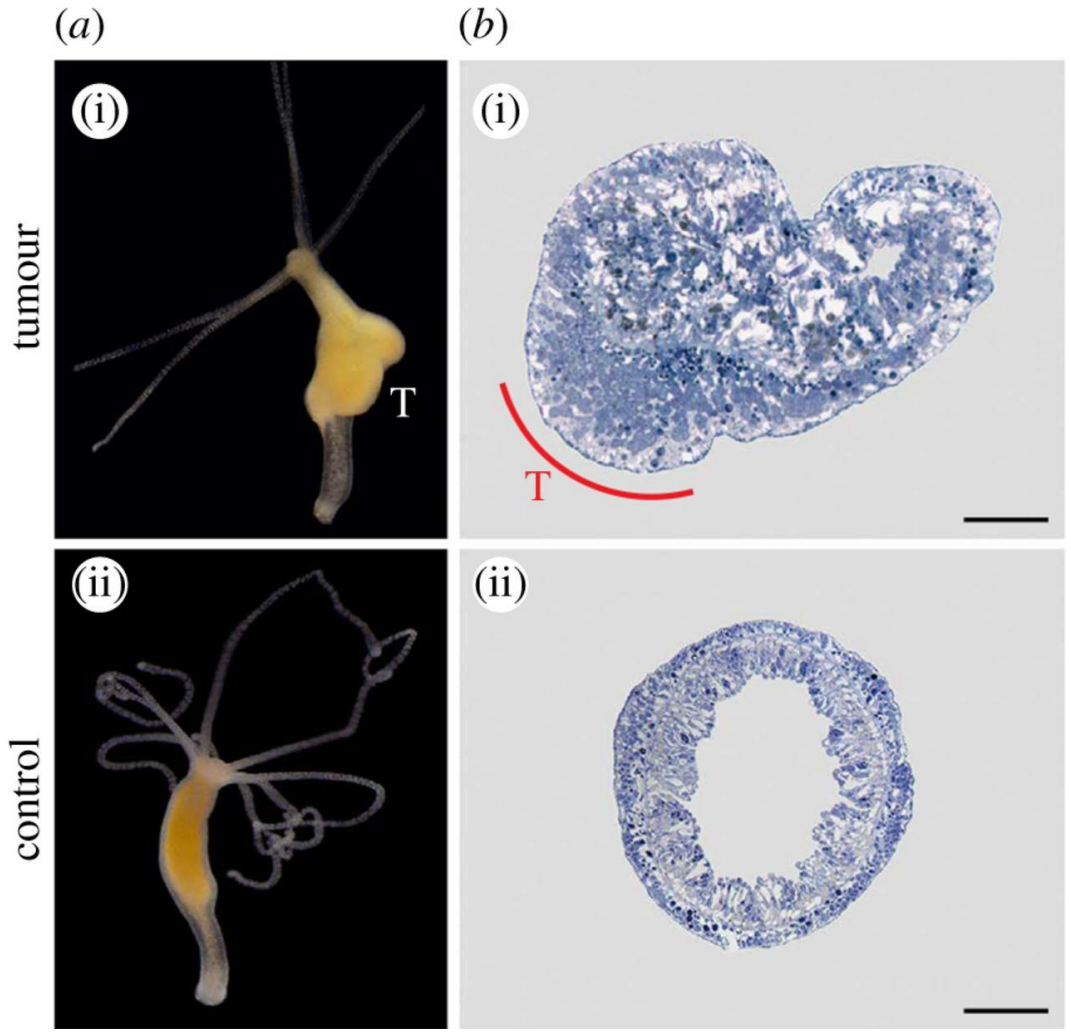


# Fasciations in plants

C. Athena Aktipis et al. Phil. Trans. R. Soc. B 2015;370:20140219

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

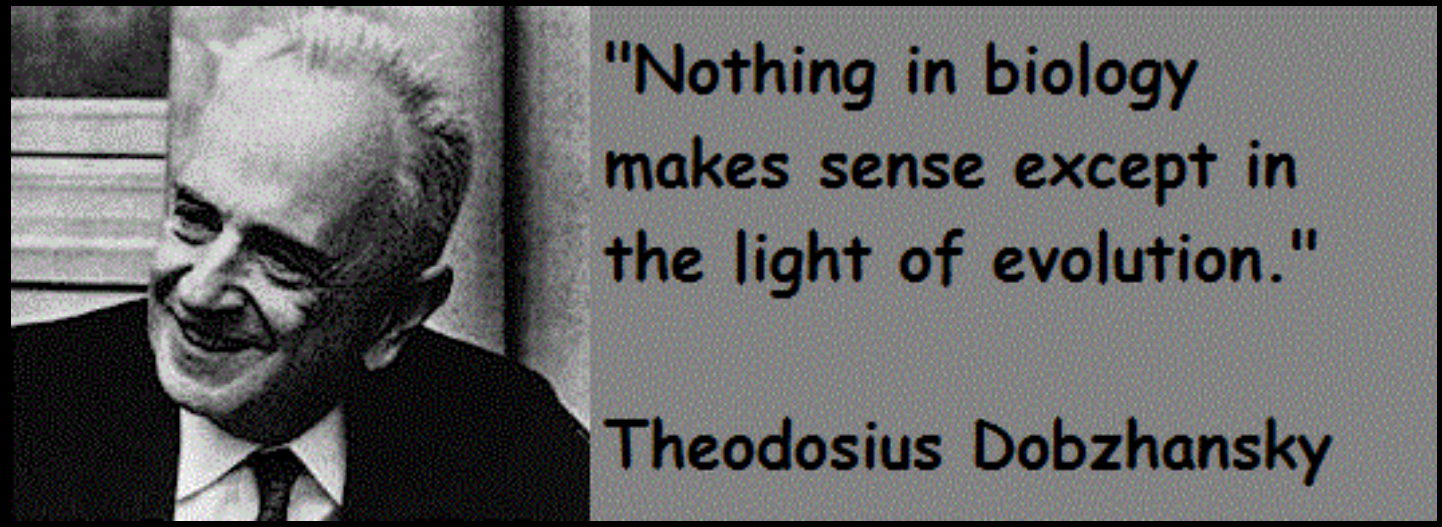
# Cancer in hydra




C. Athena Aktipis et al. Phil. Trans. R. Soc. B 2015;370:20140219

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

# Origin of cancer:
# tracing its deep evolutionary roots




Cancer is the re-expression of an  ancestral phenotype
(atavism)

# Basic hypothesis

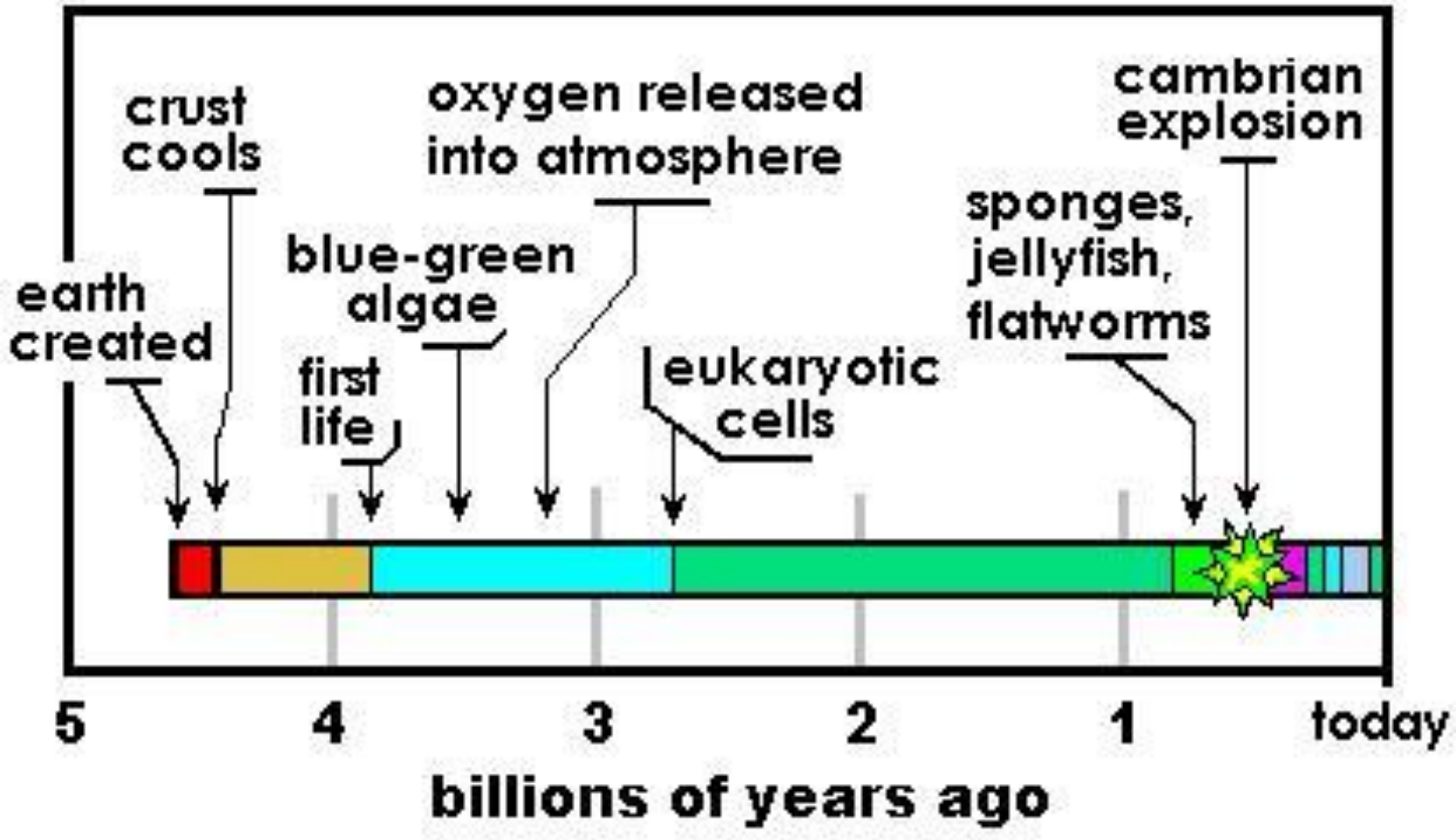
In cancer, cells re-wire information flows to default back to ancestral unicellular pathways and ancestral phenotypes

# Theodor Boveri (1914)

"I regard it as beyond doubt that the tendency to multiply indefinitely is a primaeval property of cells."

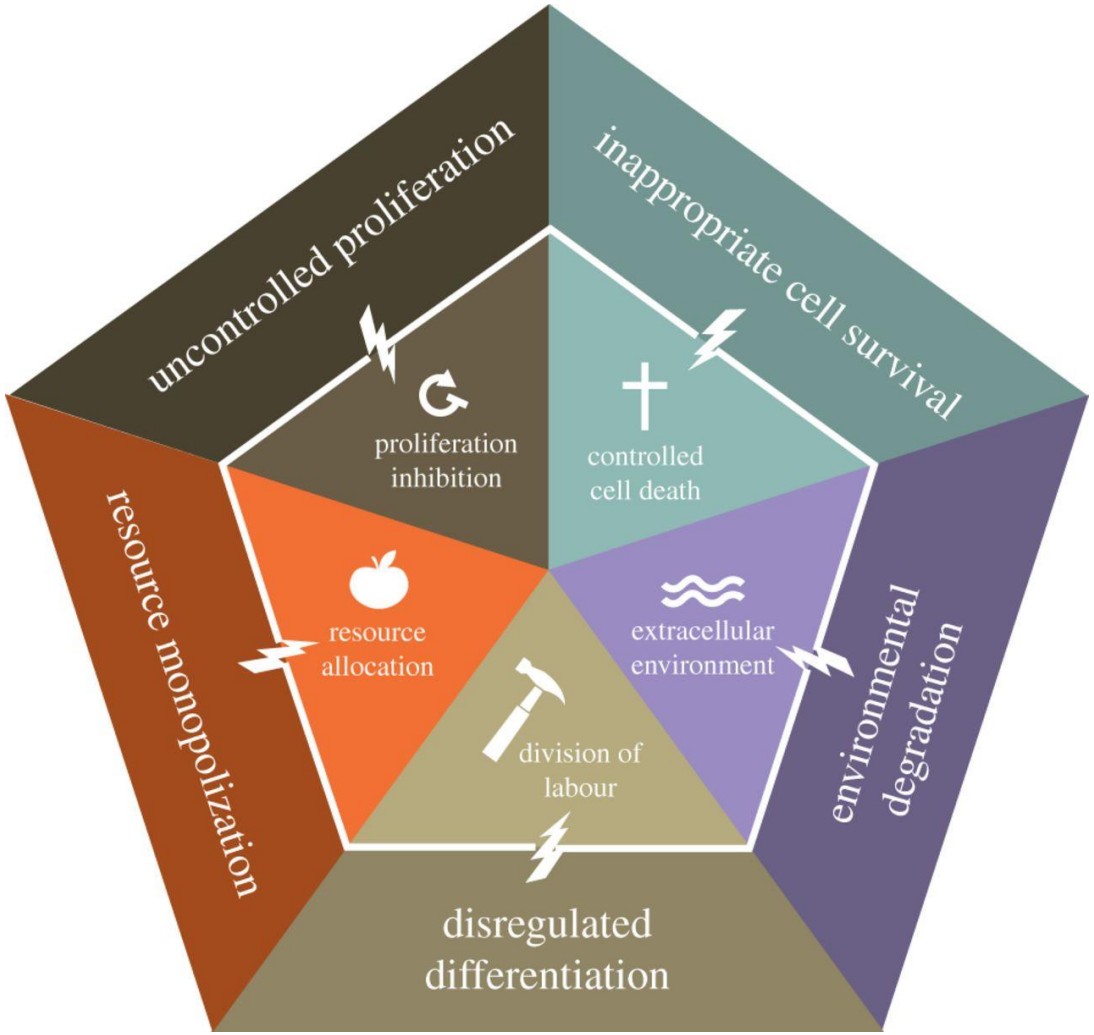
If regulatory mechanisms are disrupted:

"…this change may well be enough to induce an altruistic cell to revert to its egoistical mode and thus release its multiplication from restraint."




***Cancer is a breakdown of the ancient cooperative contract between cells and organism***

# The five foundations of multicellularity




Cancer: the “cheating phenotype”

C. Athena Aktipis et al. Phil. Trans. R. Soc. B 2015;370:20140219

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

# Some predictions

- Gene *ages* will be a key factor in cancer incidence and progression.
- Cancer should show a transcriptional shift toward unicellularity..
- The cancer phenotype should be suppressed when a tumor is placed in a physiologically normal multicellular environment. The immediate microenvironment of a malignant tumor is not actually physiologically normal.

# Addressing Evolutionary Ages of Genes



## A phylostratigraphy approach to uncover the genomic history of major adaptations in metazoan lineages

**Tomislav Domazet-Lošo[1], Josip Brajković[1] and Diethard Tautz[2]**

[1] Division of Molecular Biology, Ruđer Bošković Institute, Bijenička cesta 54, P.P. 180, 10002 Zagreb, Croatia
[2] Institute for Genetics, Zülpicher Straße 47, D-50674 Cologne, Germany

**Macroevolutionary trends traditionally are studied by fossil analysis, comparative morphology or evo-devo approaches. With the availability of genome sequences and associated data from an increasing diversity of taxa, it is now possible to add an additional level of analysis: genomic phylostratigraphy. As an example of this approach, we use a phylogenetic framework and embryo expression data from *Drosophila* to show that grouping genes by their phylogenetic origin can uncover footprints of important adaptive events in evolution.**

### Introduction

Comparison of metazoan genome sequences has shown that a significant fraction of genes occurs only in defined lineages [1–8]. This implies that these genes have arisen during the evolution of the respective lineages, probably in the context of lineage specific adaptations (see Glossary). The origin of such new genes seems to occur in a punctuated manner, that is, new genes initially evolve very quickly until they become locked into a pathway [2–4]. If these genes would then retain an association with a particular pathway, one could infer their evolutionary origin on the basis of the function of the genes in extant organisms and of an assessment of their phylogenetic emergence (see Introduction in Online Supplementary Material). This is the principle of 'phylostratigraphy', which we present here as a general approach to trace evolutionary innovations using data from genome projects.

The best data for a pan-metazoan statistical evaluation of gene evolution are currently available from *Drosophila* and we have focused our analysis on this dataset. However,

*Corresponding author:* Domazet-Lošo, T. (tdomazet@irb.hr).
Available online 29 October 2007.

www.sciencedirect.com

How old is that oncogene?

Domazet-Lošo and Tautz *BMC Biology* 2010, **8**:66
http://www.biomedcentral.com/1741-7007/8/66


RESEARCH ARTICLE Open Access

# Phylostratigraphic tracking of cancer genes suggests a link to the emergence of multicellularity in metazoa

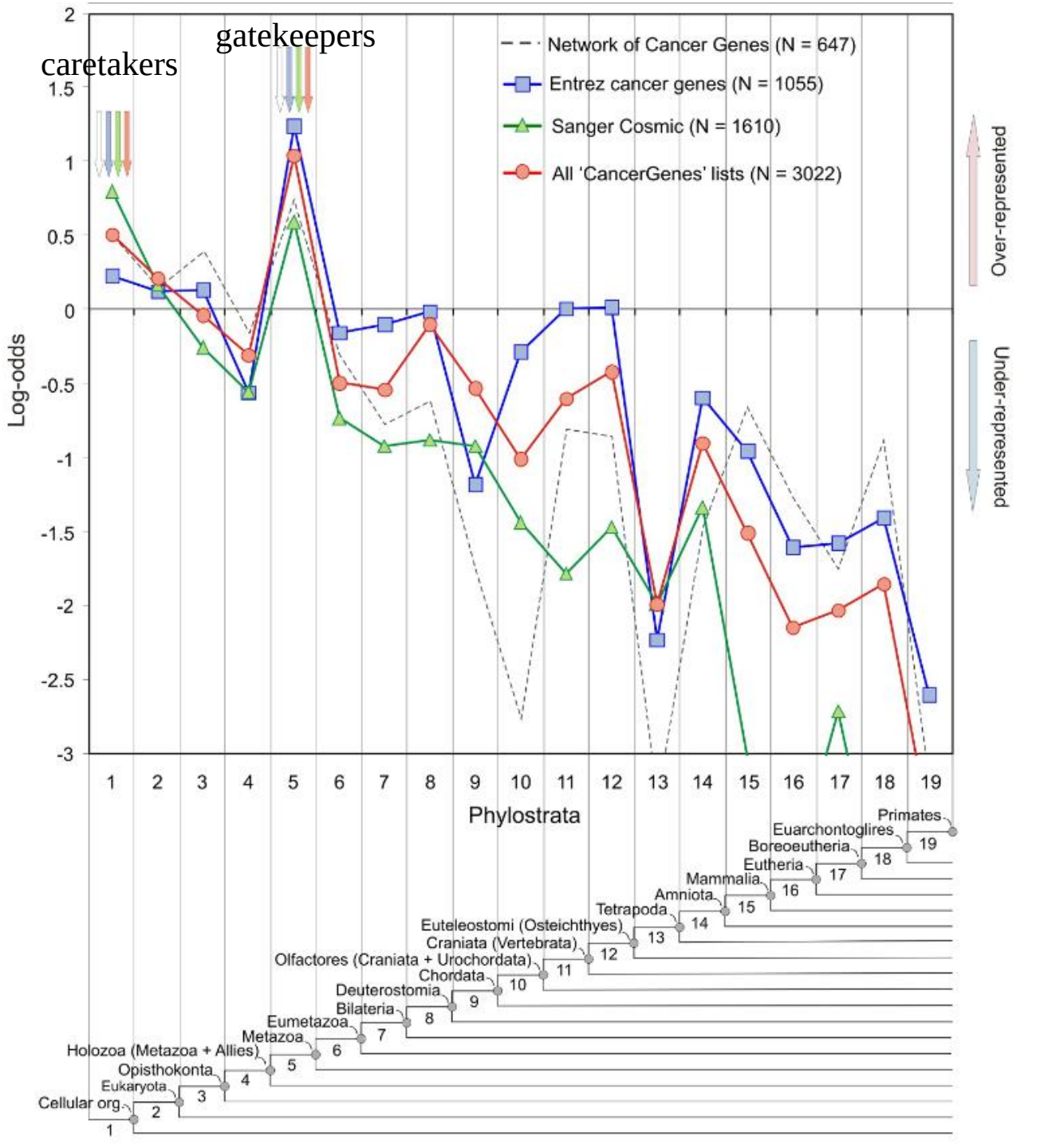
Tomislav Domazet-Lošo[1,2] and Diethard Tautz*[1]

**Abstract**

**Background:** Phylostratigraphy is a method used to correlate the evolutionary origin of founder genes (that is, functional founder protein domains) of gene families with particular macroevolutionary transitions. It is based on a model of genome evolution that suggests that the origin of complex phenotypic innovations will be accompanied by the emergence of such founder genes, the descendants of which can still be traced in extant organisms. The origin of multicellularity can be considered to be a macroevolutionary transition, for which new gene functions would have been required. Cancer should be tightly connected to multicellular life since it can be viewed as a malfunction of interaction between cells in a multicellular organism. A phylostratigraphic tracking of the origin of cancer genes should, therefore, also provide insights into the origin of multicellularity.

‘We find two strong peaks of the emergence of cancer related protein domains, one at the time of the origin of
the first cell and the other around the time of the evolution of the multicellular metazoan organisms.’

Domazet-Lošo and Tautz *BMC Biology* 2010, **8**:66
http://www.biomedcentral.com/1741-7007/8/66



PNAS

# Altered interactions between unicellular and multicellular genes drive hallmarks of transformation in a diverse range of solid tumors

Anna S. Trigos[a,b], Richard B. Pearson[b,c,d], Anthony T. Papenfuss[a,b,e], and David L. Goode[a,b,1]

[a]Computational Cancer Biology Program, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia; [b]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, VIC 3010, Australia; [c]Department of Biochemistry and Molecular Biology, The University of Melbourne, Parkville, VIC 3010, Australia; [d]Department of Biochemistry and Molecular Biology, Monash University, Clayton, VIC 3168, Australia; and [e]Bioinformatics Division, The Walter & Eliza Hall Institute of Medical Research, Parkville, VIC 3052, Australia

Edited by Robert H. Austin, Princeton University, Princeton, NJ, and approved April 17, 2017 (received for review November 18, 2016)

**Tumors of distinct tissues of origin and genet**
**common hallmark cellular phenotypes, includi**

REVIEW

BJC

British Journal of Cancer (2018) 118, 145–152 | doi: 10.1038/bjc.2017.398

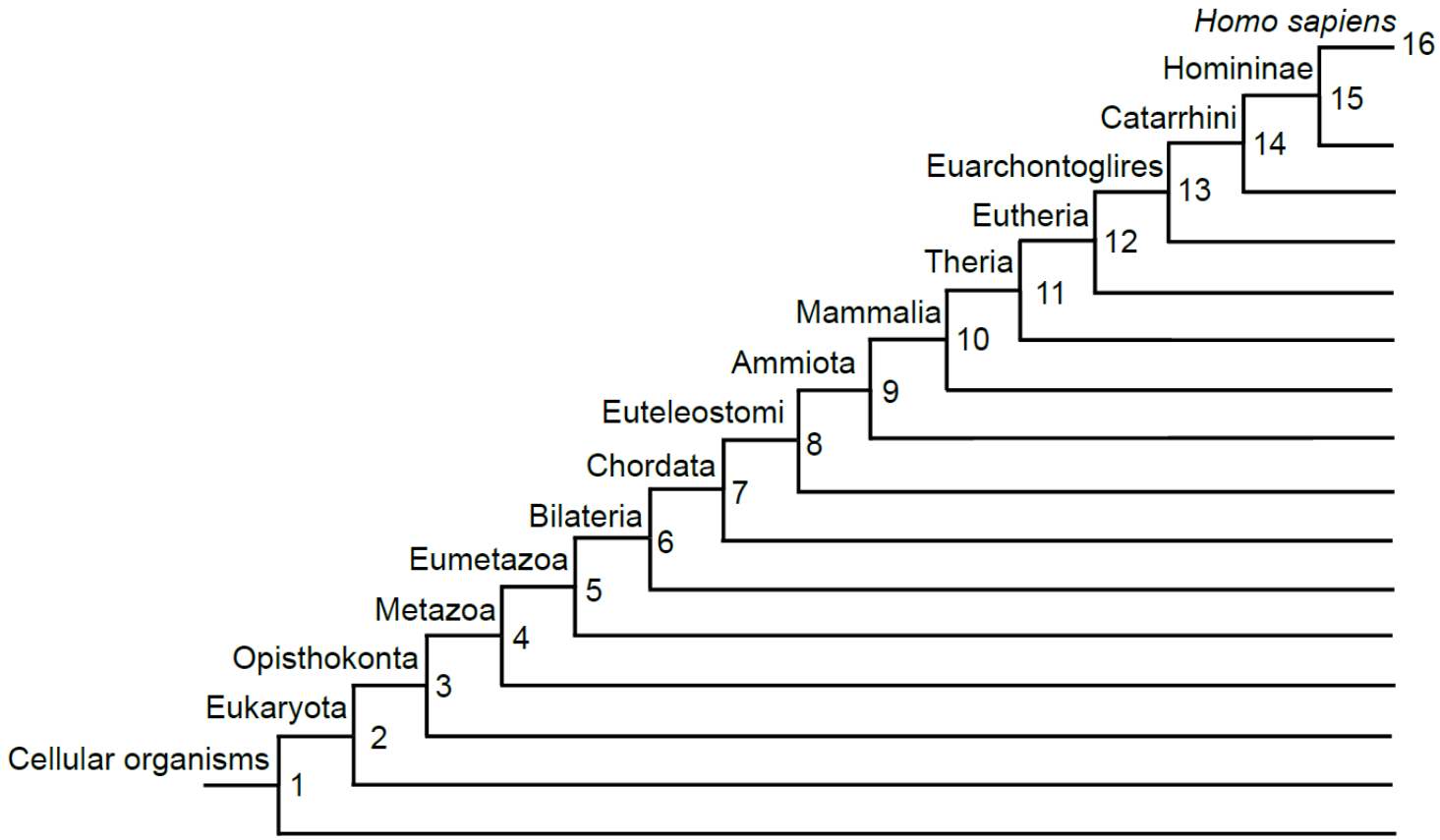
BJC OPEN

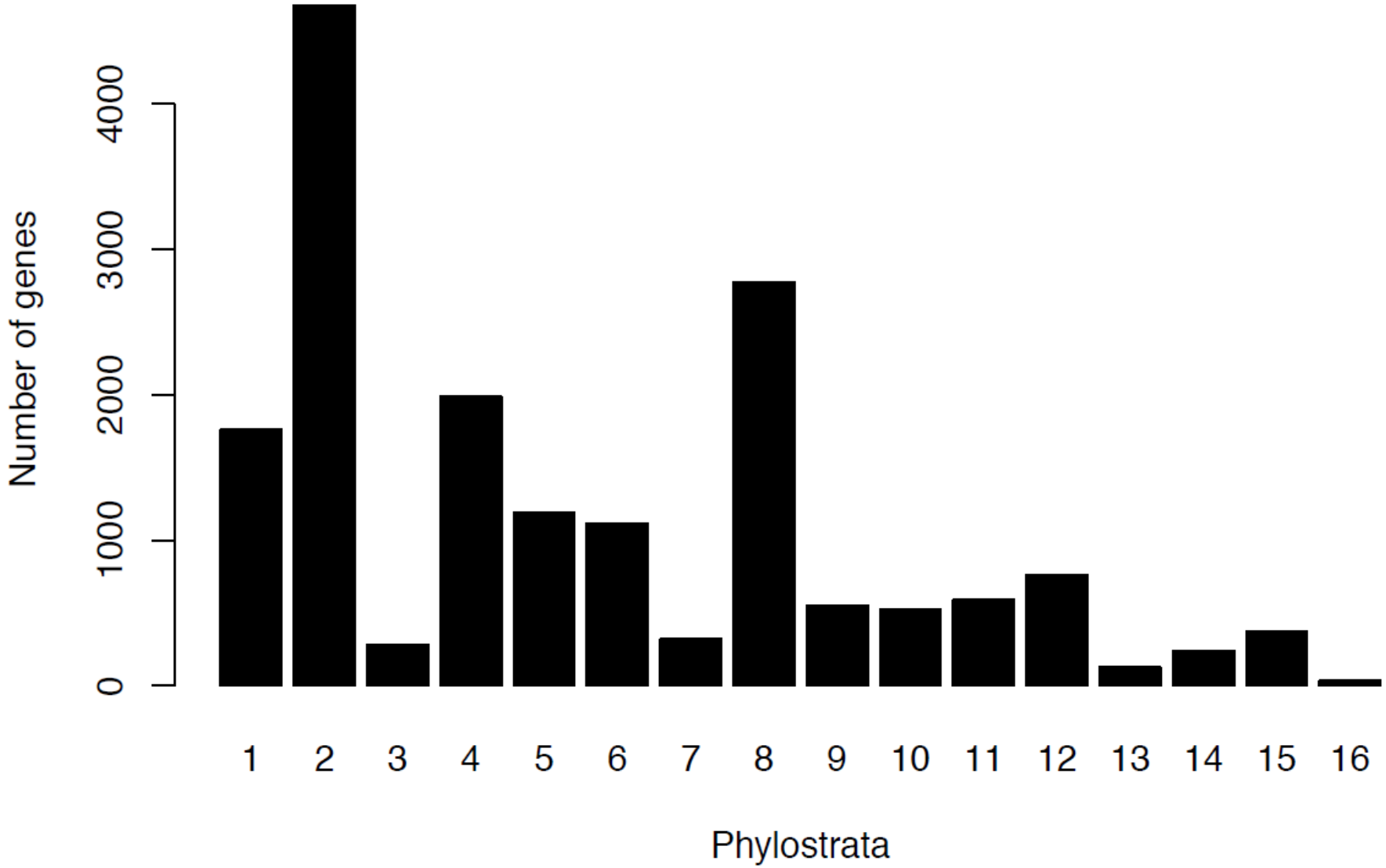
Keywords: evolution; systems biology; networks; atavism; multicellularity; network medicine

# How the evolution of multicellularity set the stage for cancer

Anna S Trigos[1,2], Richard B Pearson[2,3,4], Anthony T Papenfuss[1,2,5] and David L Goode[*,1,2]

*[1]Computational Cancer Biology Program, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia; [2]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, VIC 3010, Australia; [3]Department of Biochemistry and Molecular Biology, The University of Melbourne, Parkville, VIC 3010, Australia; [4]Department of Biochemistry and Molecular Biology, Monash*

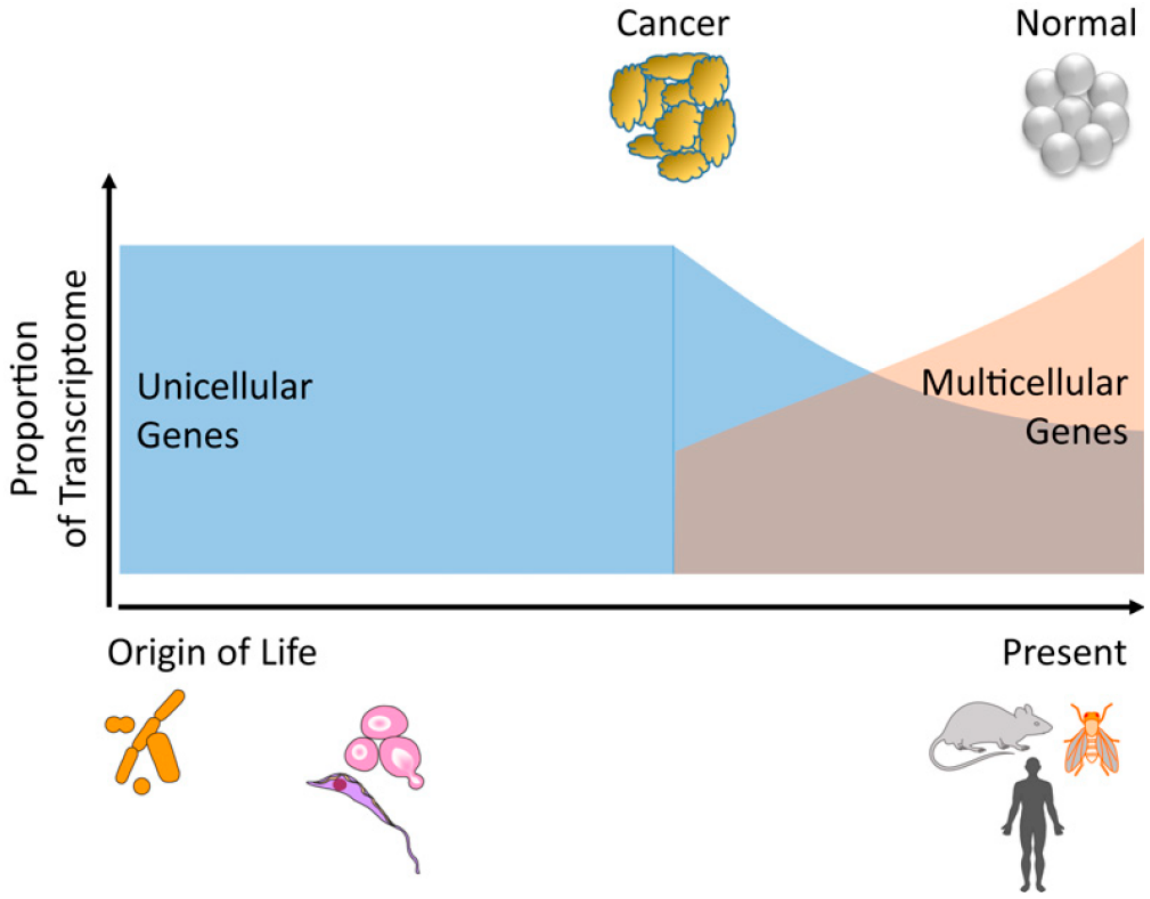

Homo sapiens
16
Homininae
15
Catarrhini
14
Euarchontoglires
13
Eutheria
12
Theria
11
Mammalia
10
Ammiota
9
Euteleostomi
8
Chordata
7
Bilateria
6
Eumetazoa
5
Metazoa
4
Opisthokonta
3
Eukaryota
2
Cellular organisms
1



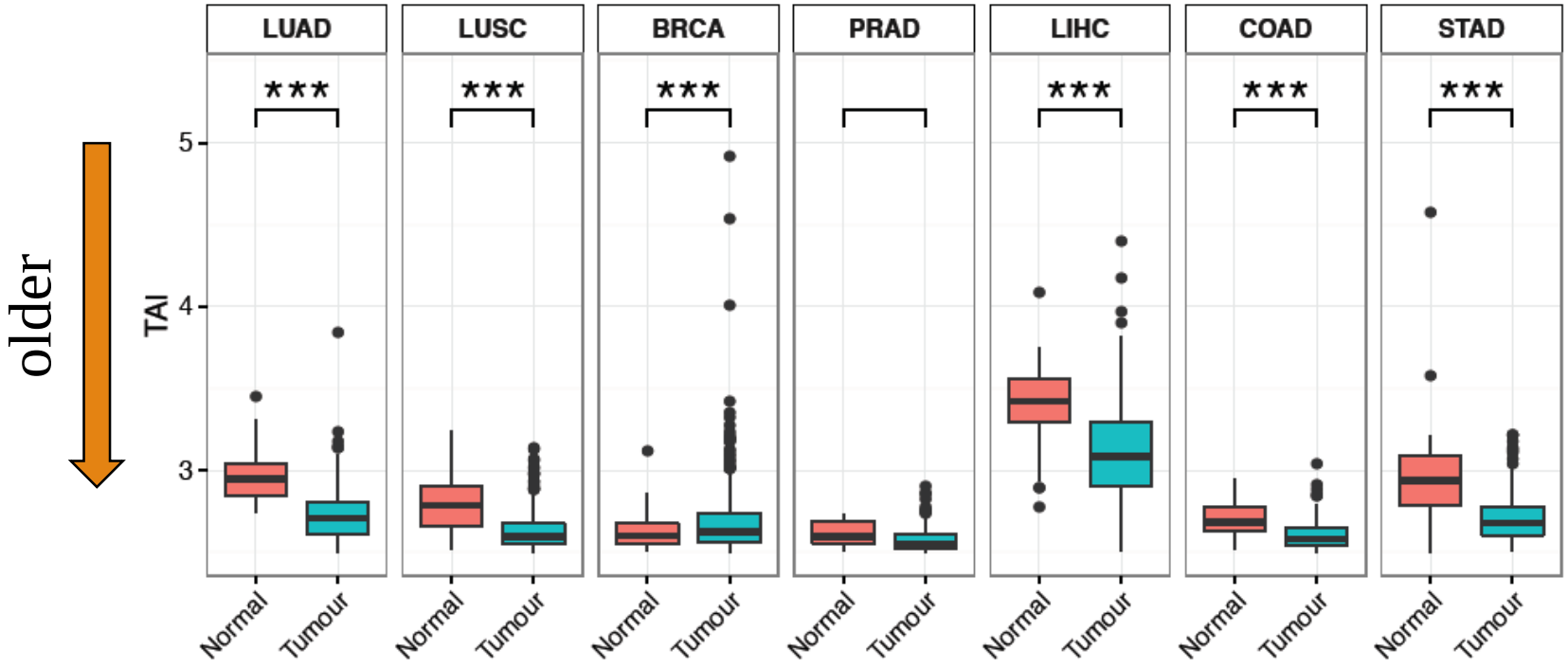

Altogether 40% of human genes are assigned to unicellular ancestors (phylostrata1-3), and 60% were assigned to multicellular ancestors (phylostrata 4-16).

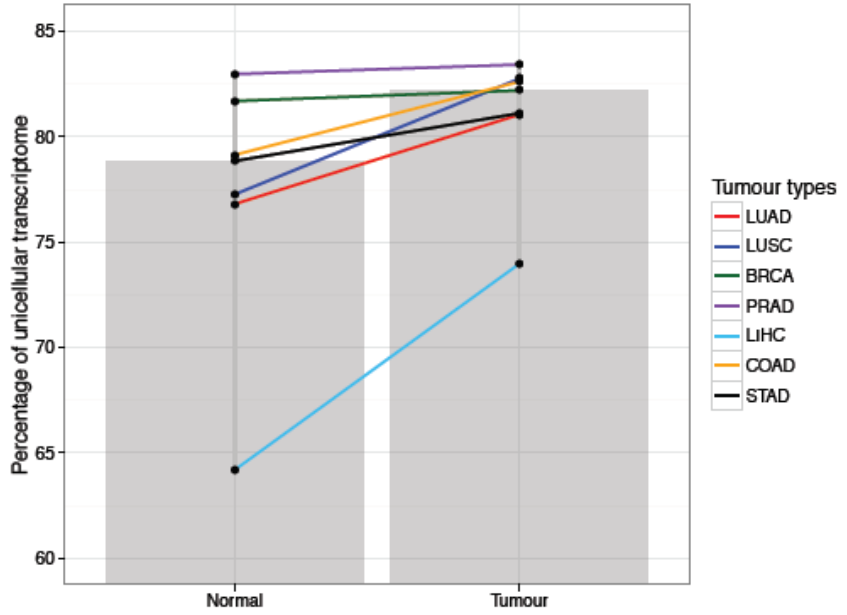
# Ancestral gene regulatory networks drive cancer

Kimberly J. Bussey[a,b], Luis H. Cisneros[a,c], Charles H. Lineweaver[d], and Paul C. W. Davies[c,1]

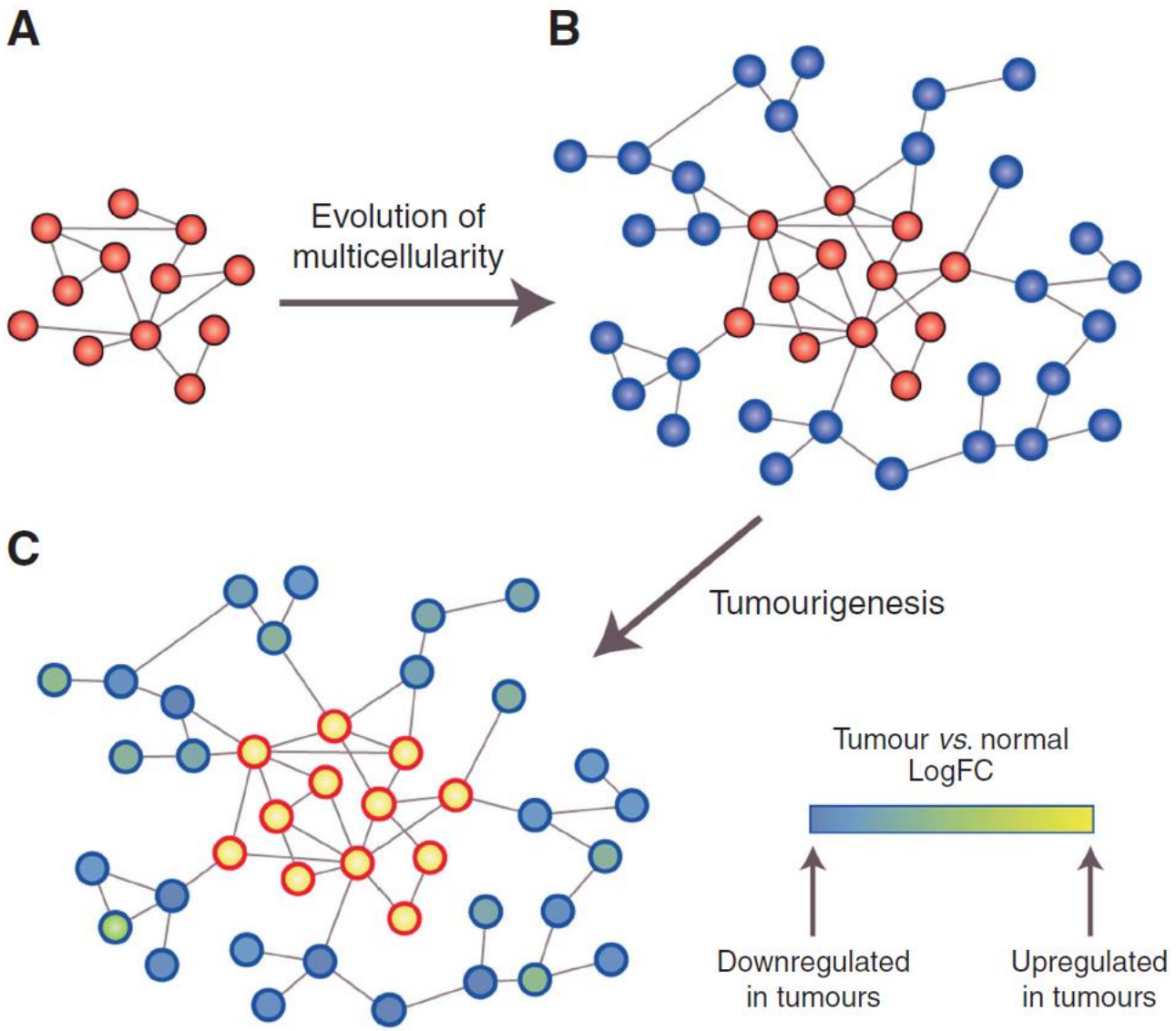



Compared to normal, cancer increases the proportion of its transcriptome coming from unicellular genes.

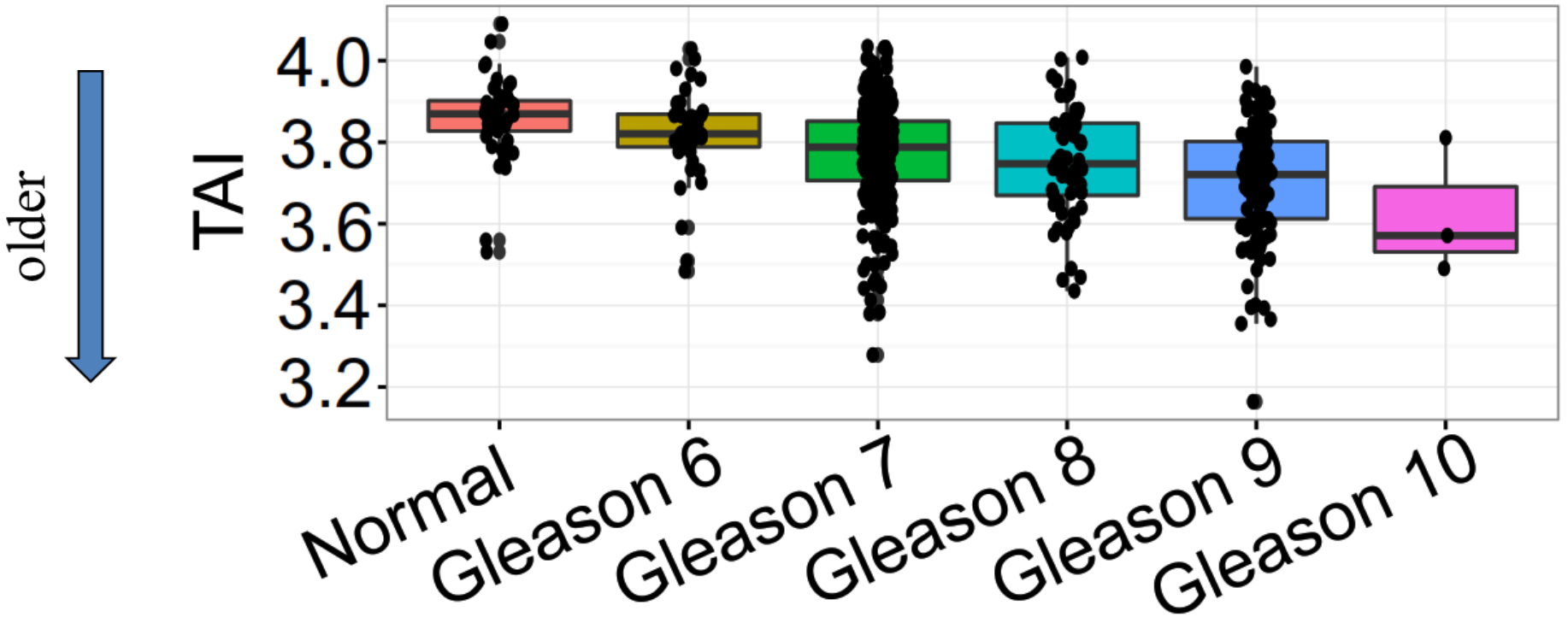



Trigos et al, PNAS 2017


A
B
Evolution of
multicellularity
C
Tumourigenesis
Tumour *vs.* normal
LogFC
Downregulated
in tumours
Upregulated
in tumours

# Less differentiated tissues have older transcriptomes




Trigos et al, PNAS 2017

# Further predictions

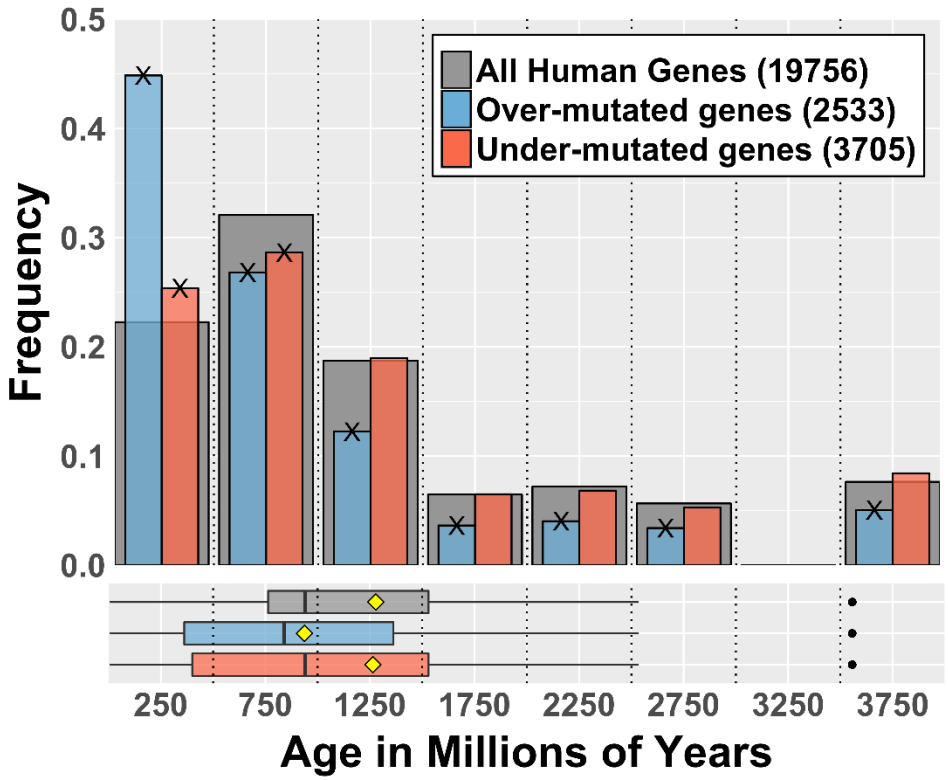
- Younger genes should be enriched in mutations in cancer
- Genes that are causally involved in cancer should be older than the emergence of complex multicellularity 600 million years ago.
- Cancer should employ unicellular responses to cellular and environmental stresses..

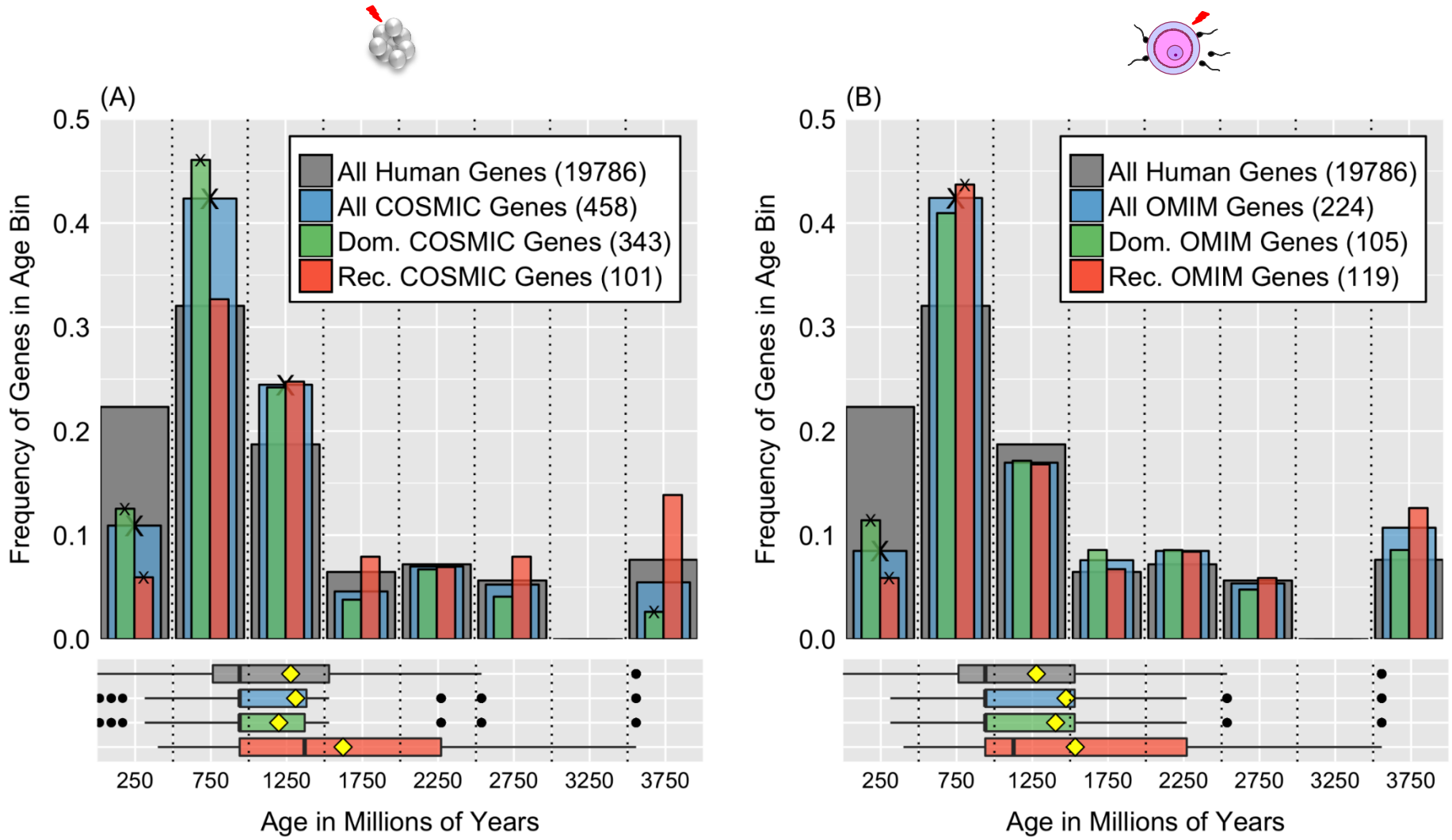
PLOS ONE | https://doi.org/10.1371/journal.pone.0176258 April 25, 2017

RESEARCH ARTICLE

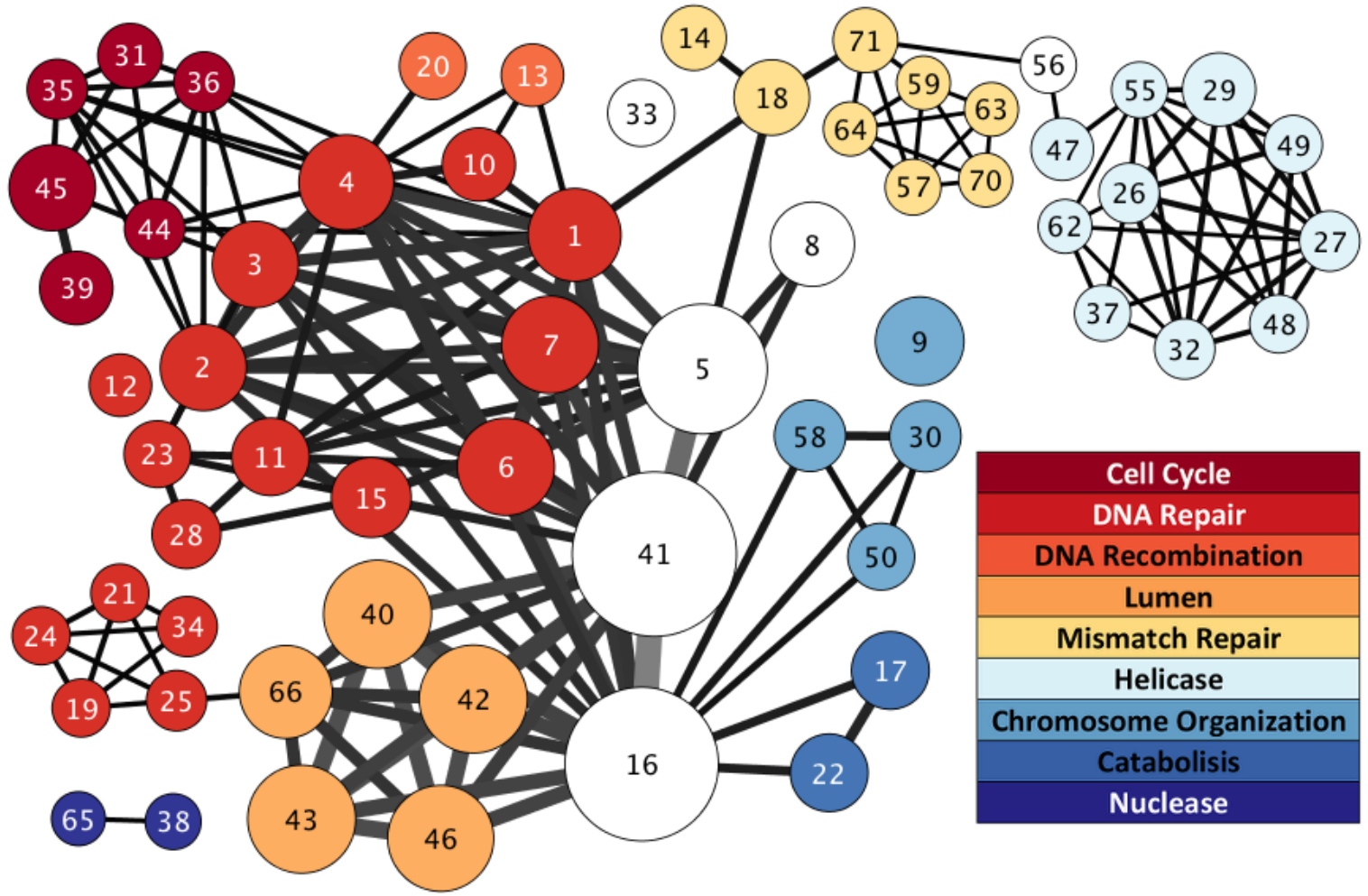
# Ancient genes establish stress-induced mutation as a hallmark of cancer

Luis Cisneros[1,2☯], Kimberly J. Bussey[1,3☯*], Adam J. Orr[4], Milica Miočević[5], Charles H. Lineweaver[6], Paul Davies[2]





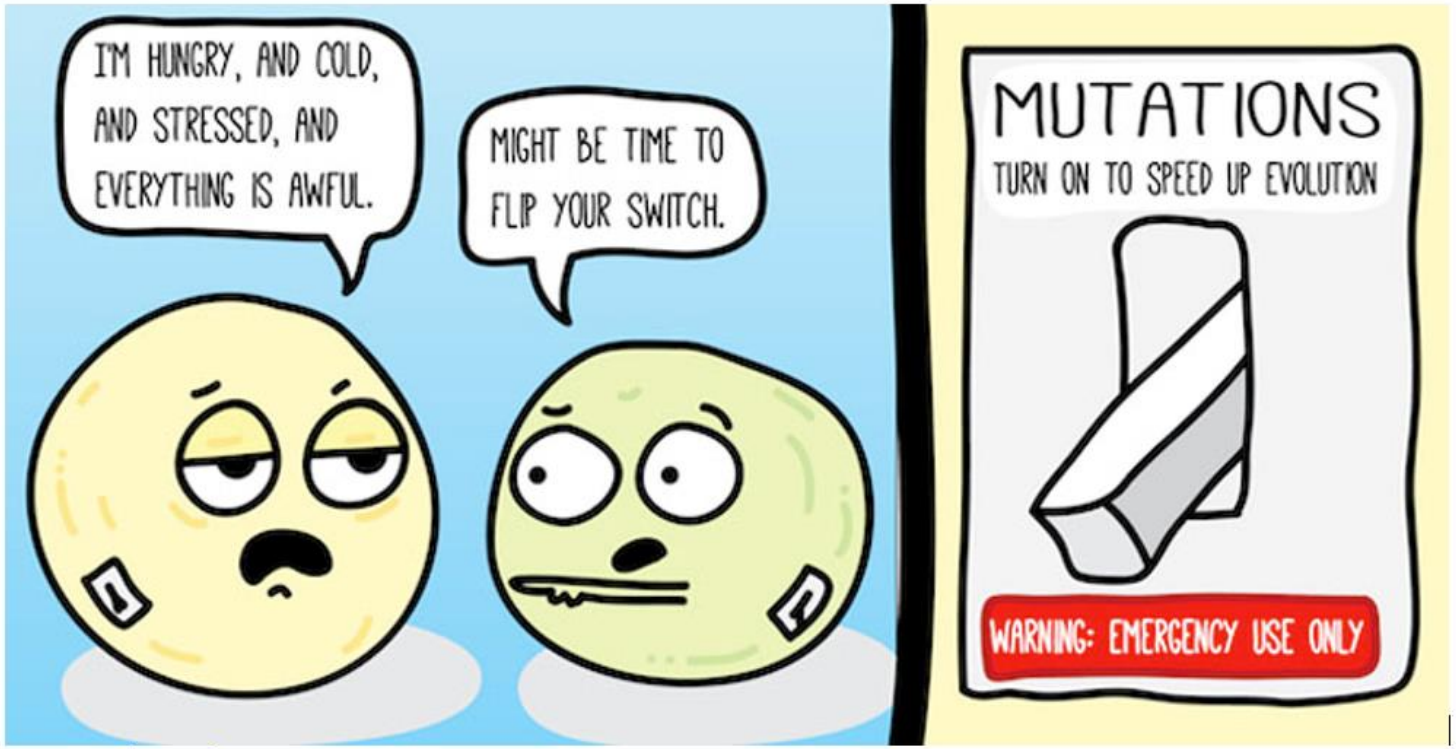

- Genes causally implicated in cancer are under-represented among young (<500 MY) genes.
- Dominant COMSIC genes are younger than recessive COSMIC genes




Functional enrichment network of recessive COSMIC cancer genes highlights DNA repair and cell cycle control.

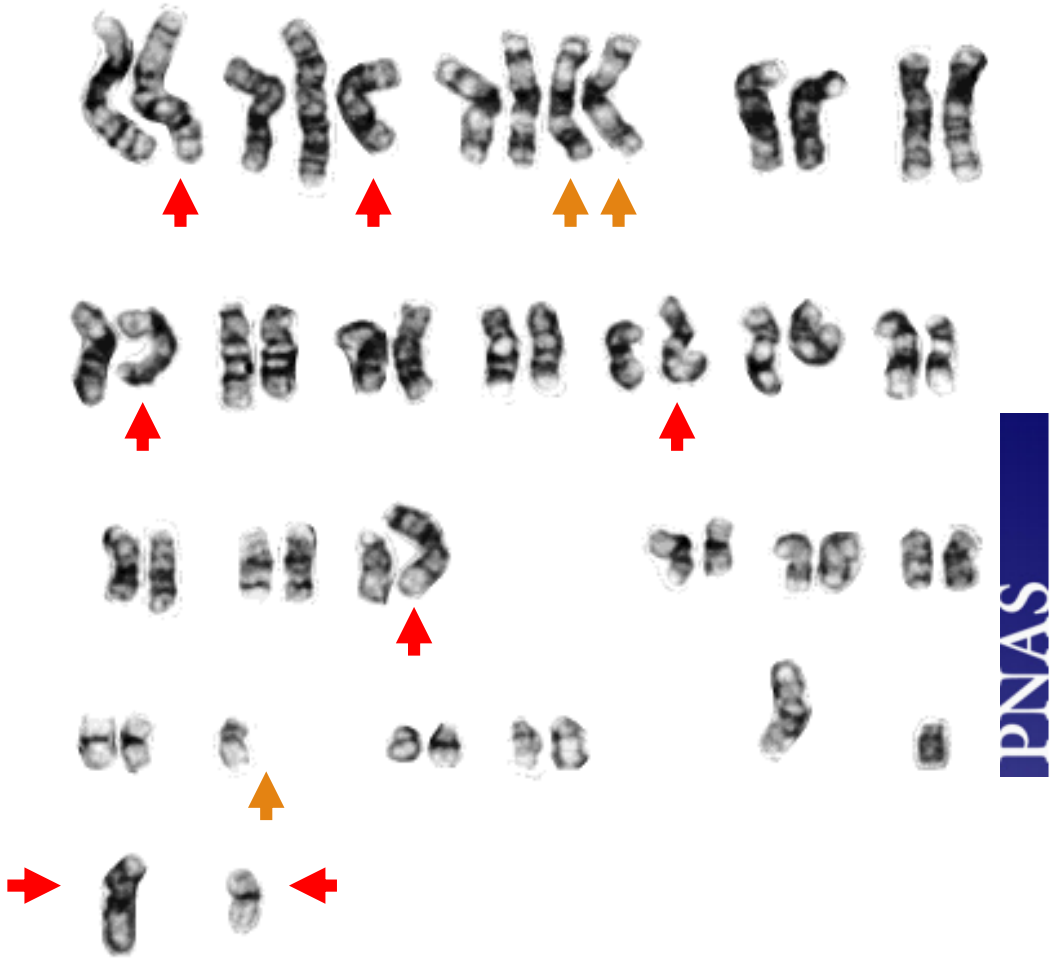
# DOES EVOLUTION EVOLVE UNDER PRESSURE?

Galhardo RS, Hastings PJ, Rosenberg SM. Mutation as a Stress Response and the Regulation of Evolvability. Crit Rev Biochem Mol Biol. 2007;42: 399-435. pmid:17917874




*Beatrice the Biologist*

# Stage III Sacrococcoygeal endodermal sinus tumor



48-51,XY,add(1)(p36),+add(2)(q31),
+3,+3,add(6)(q2?7), add(10)(q26),
add(15)(p11),+mar1,+mar2[cp7]/
46, XY[13]

PNAS

## Karyotypic "state" as a potential determinant for anticancer drug discovery

Anna V. Roschke*†, Samir Lababidi†‡, Giovanni Tonon*†, Kristen S. Gehlhaus*, Kimberly Bussey‡, John N. Weinstein‡, and Ilan R. Kirsch*§

*Genetics Branch and ‡Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

Edited by Albert de la Chapelle, Ohio State University, Columbus, OH, and approved January 7, 2005 (received for review July 30, 2004)

**Cancer is a genetic disease caused by genomic instability. In many** We looked for relations between these markers of chromo-

Adapted from Figure 2, Bussey et al, Cancer Genet Cytogenet 25:134-46, 1999

RESEARCH ARTICLE | DRUG RESISTANCE

# Regulation of the error-prone DNA polymerase Polκ by oncogenic signaling and its contribution to drug resistance

Kelsey Temprine[1,2,*], Nathaniel R. Campbell[1,3], Richard Huang[1], Erin M. Langdon[4,†], Theresa Simon-Vermot[1]...
+ See all authors and affiliations

*Science Signaling* 28 Apr 2020:
Vol. 13, Issue 629, eaau1453
DOI: 10.1126/scisignal.aau1453

RESEARCH ARTICLE

# Adaptive mutability of colorectal cancers in response to targeted therapies

Mariangela Russo[1,2,*], Giovanni Crisafulli[1,2], Alberto Sogari[1,2], Nicole M. Reilly[3], Sabrina Arena[1,2], Simona Lam...
+ See all authors and affiliations

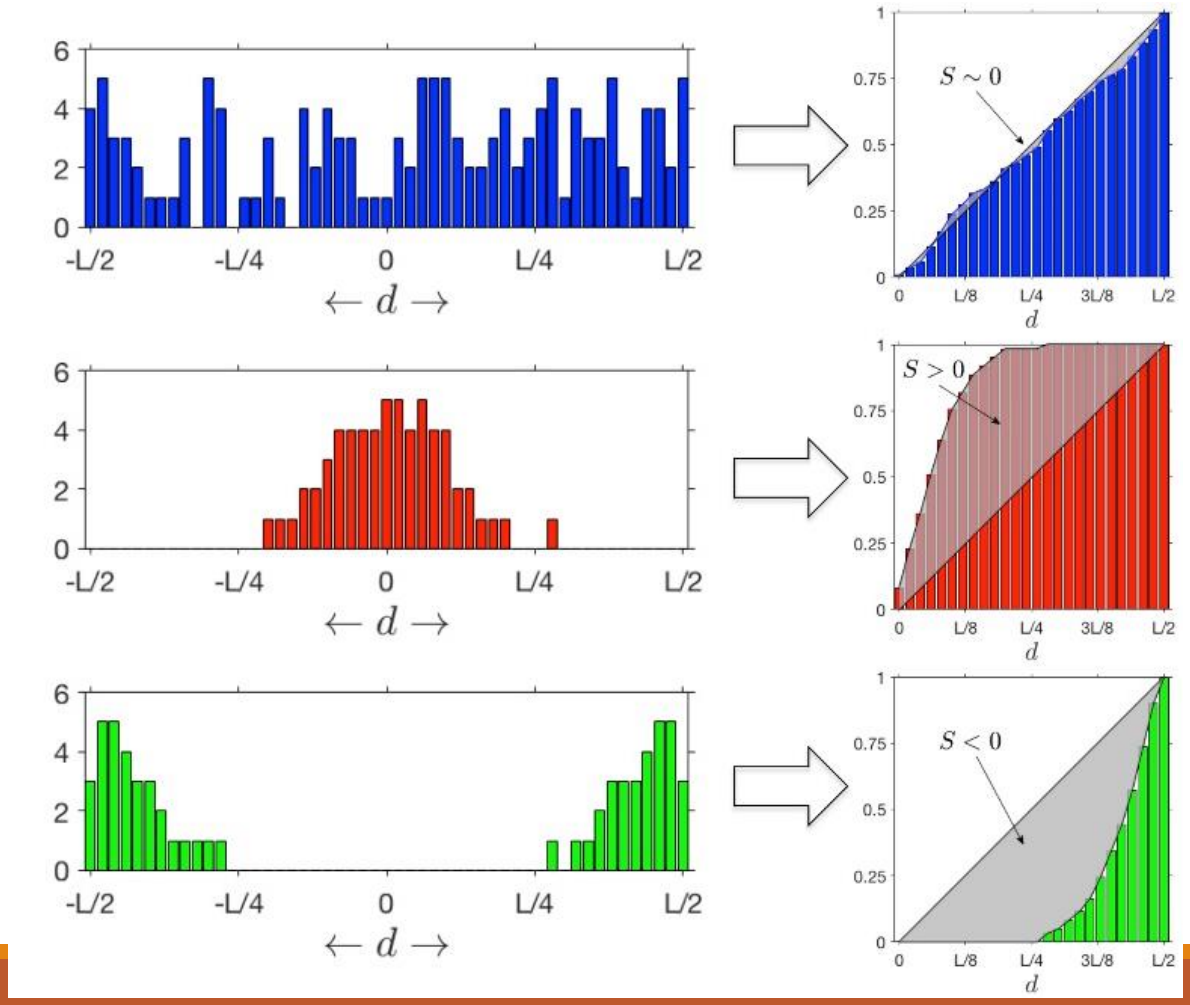
*Science* 20 Dec 2019:
Vol. 366, Issue 6472, pp. 1473-1480
DOI: 10.1126/science.aav4474

CANCER

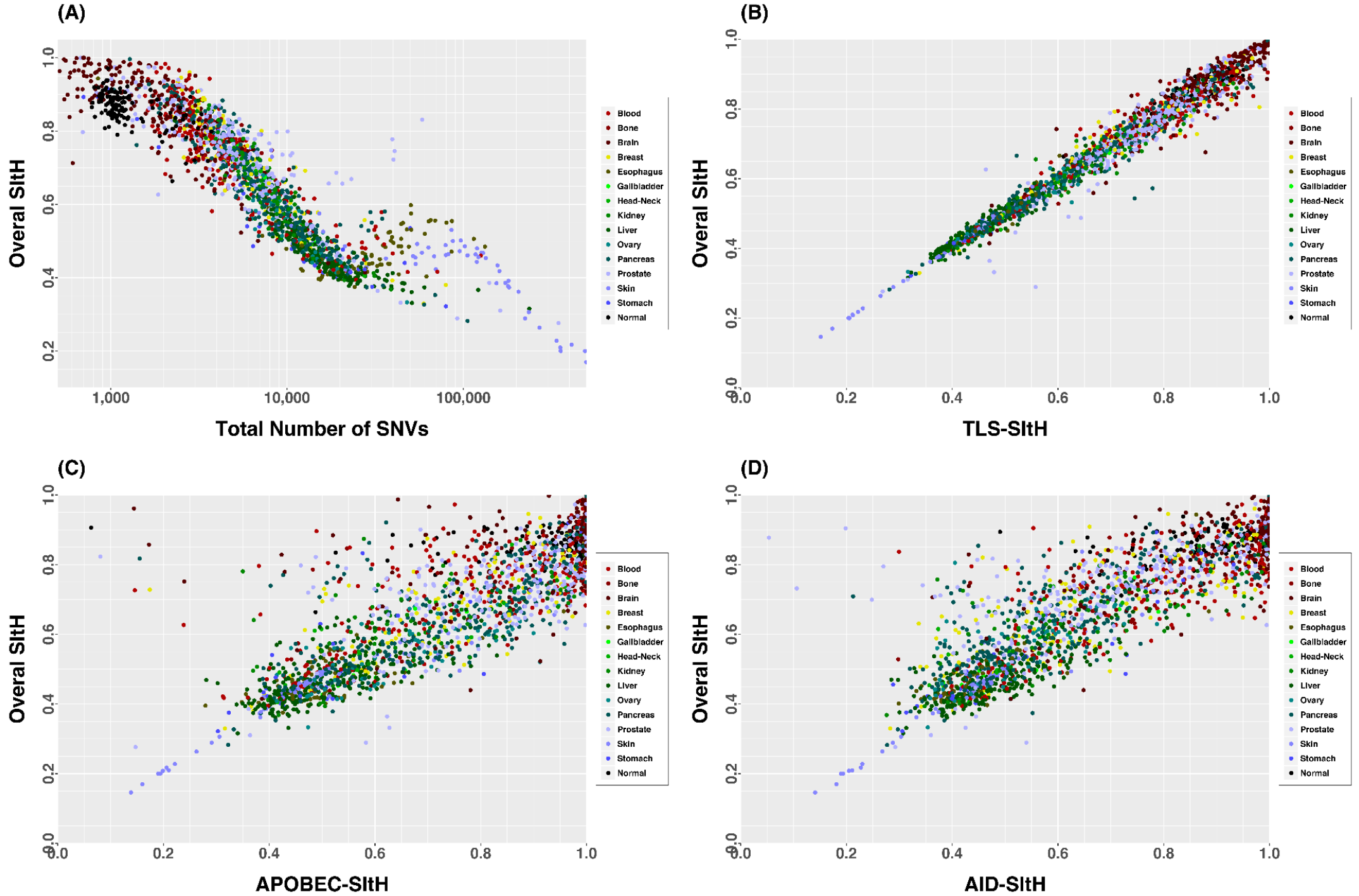
# MTOR signaling orchestrates stress-induced mutagenesis, facilitating adaptive evolution in cancer

Arcadi Cipponi[1,2]*, David L. Goode[3,4], Justin Bedo[5,6,7], Mark J. McCabe[2,8], Marina Pajic[1,2], David R. Croucher[1,2], Alvaro Gonzalez Rajal[1], Simon R. Junankar[1,2], Darren N. Saunders[9], Pavel Lobachevsky[3], Anthony T. Papenfuss[5,6,7,10], Danielle Nessem[1], Max Nobis[1,2], Sean C. Warren[1,2], Paul Timpson[1,2], Mark Cowley[2,8], Ana C. Vargas[11], Min R. Qiu[2,12], Daniele G. Generali[13,14], Shivakumar Keerthikumar[3,4], Uyen Nguyen[1], Niall M. Corcoran[15,16,17], Georgina V. Long[18,19,20,21], Jean-Yves Blay[22,23], David M. Thomas[1,2]*

# SItH (Stress Introduced Heterogeneity) Score




The SItH Score is a way of quantifying how mutations are distributed in a cluster


(A)
Overal SItH
1.0
0.8
0.6
0.4
0.2
1,000
10,000
100,000
Total Number of SNVs
(B)
Overal SItH
0.0
0.2
0.4
0.6
0.8
1.0
TLS-SItH
(C)
Overal SItH
APOBEC-SItH
(D)
Overal SItH
AID-SItH
Blood
Bone
Brain
Breast
Esophagus
Gallbladder
Head-Neck
Kidney
Liver
Ovary
Pancreas
Prostate
Skin
Stomach
Normal

| | Grouping | Cox Proportional Hazard Regression | | | Observation |
|---|---|---|---|---|---|
| | | HR | CI | p-value | |
| **Overall SItH** | Primary Tumors | 0.4184 | 0.1983 - 0.8829 | 0.0222 | Large SItH predicts increased patient survival |
| | Recurrent and Metastatic Tumors | 7.987 | 1.241 - 51.41 | 0.0295 | Large SItH predicts decreased patient survival |
| **Cluster SItH IQR** | N/A | 5.045 | 1.399 – 18.19 | 0.0134 | Large IQR predicts decreased patient survival |
| | IQR above or below median | 1.37 | 1.1011 - 1.705 | 0.00475 | Cut-Off predicts poor prognosis |

# Therapeutic Implications

- Single cells EVOLVE to survive. If cancer is single cell behavior, then adaptability is a selectable trait.
- “Take no prisoners” will apply a strong selective pressure that will select for adaptability and thus resistance
- To take advantage of adaptability, we  should think about what multicellularity “buys” a cell and create therapies that select for those behaviors rather than selecting against unicellular behavior
- Need a way to characterize tumors that takes into account both adaptive potential of the tumor and the host’s available cancer defenses

# Acknowledgments


Luis Cisneros

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Milica Miočević

Susan Rosenberg

Bob Austin

Athena Aktipis

Carlo Maley

Charlie Vaske

David Thomas

Arcadi Cipponi

David Goode

Anna Trigos

International Genomics Consortium

Pan-Cancer Analysis Working Group (PCAWG)

1000 Genomes Project



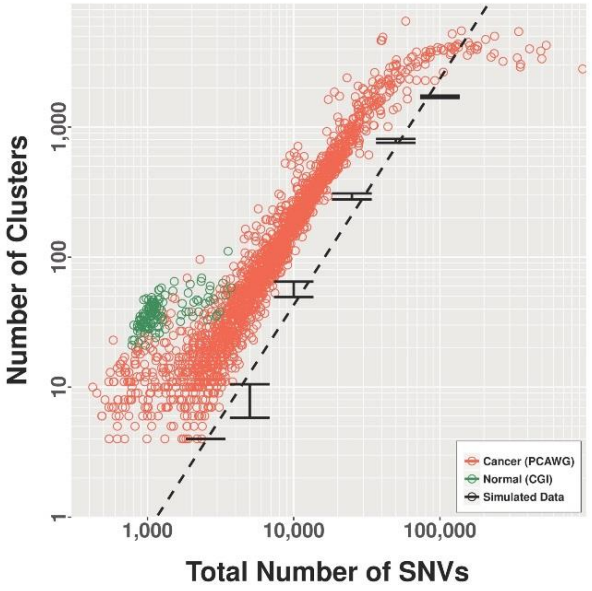


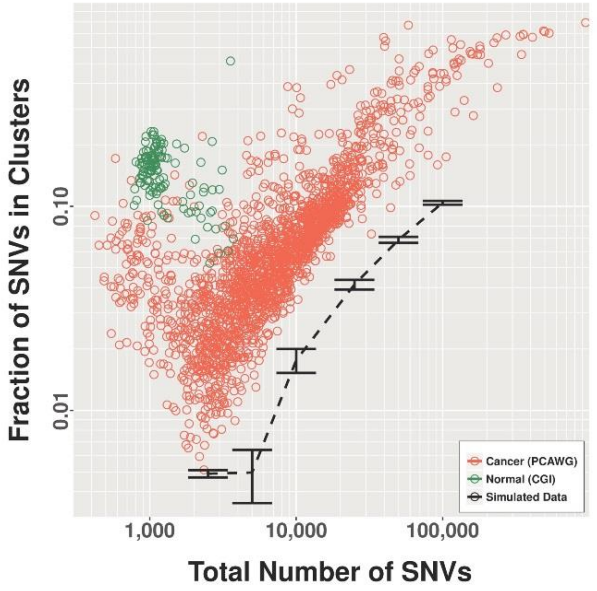


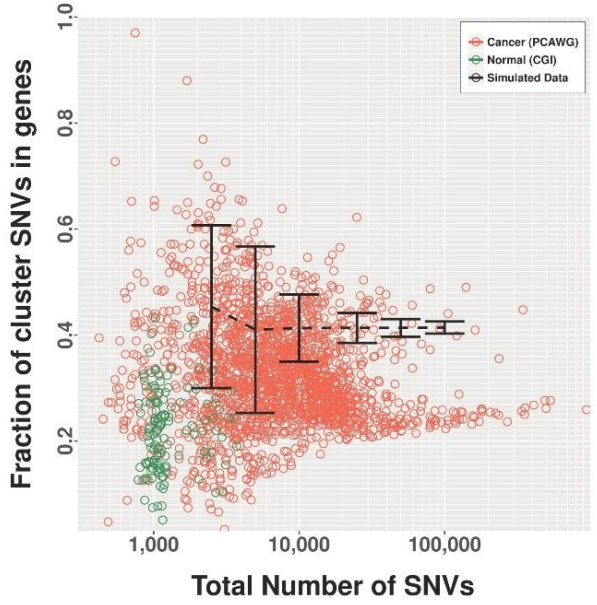




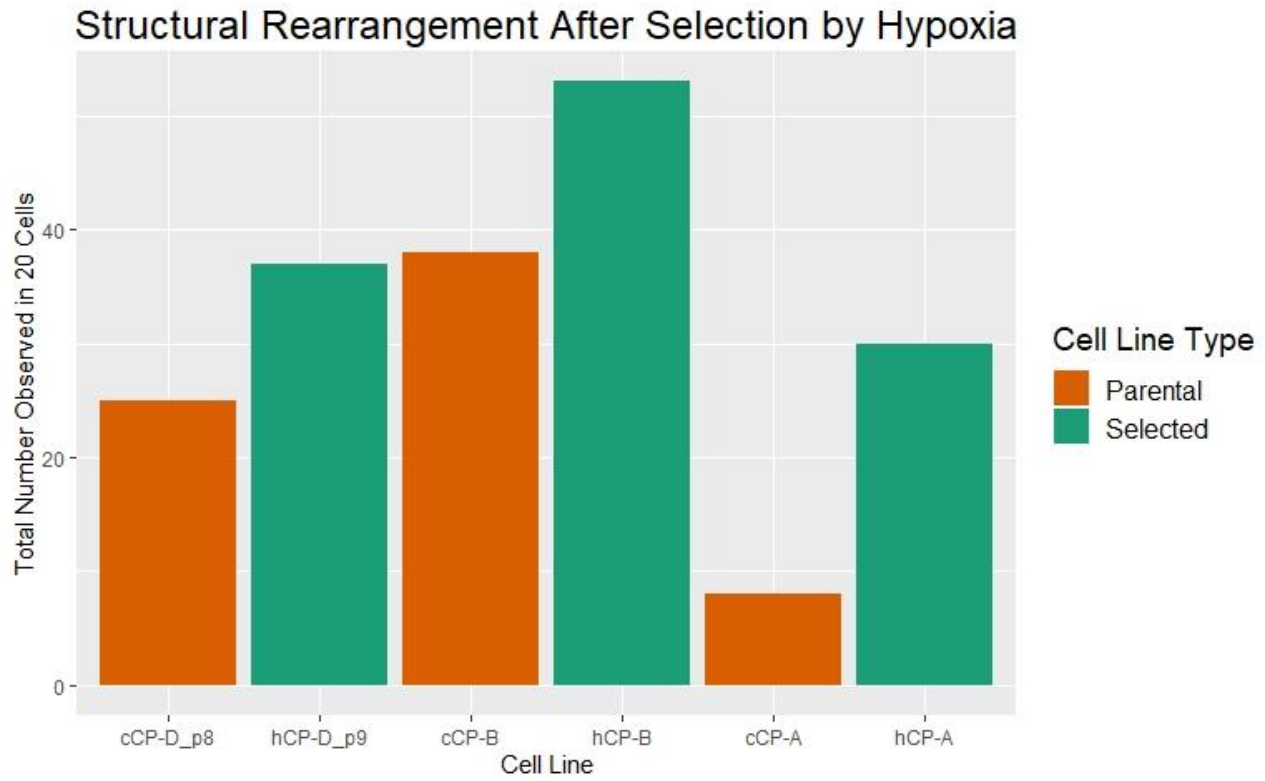
# Clustering versus mutational load

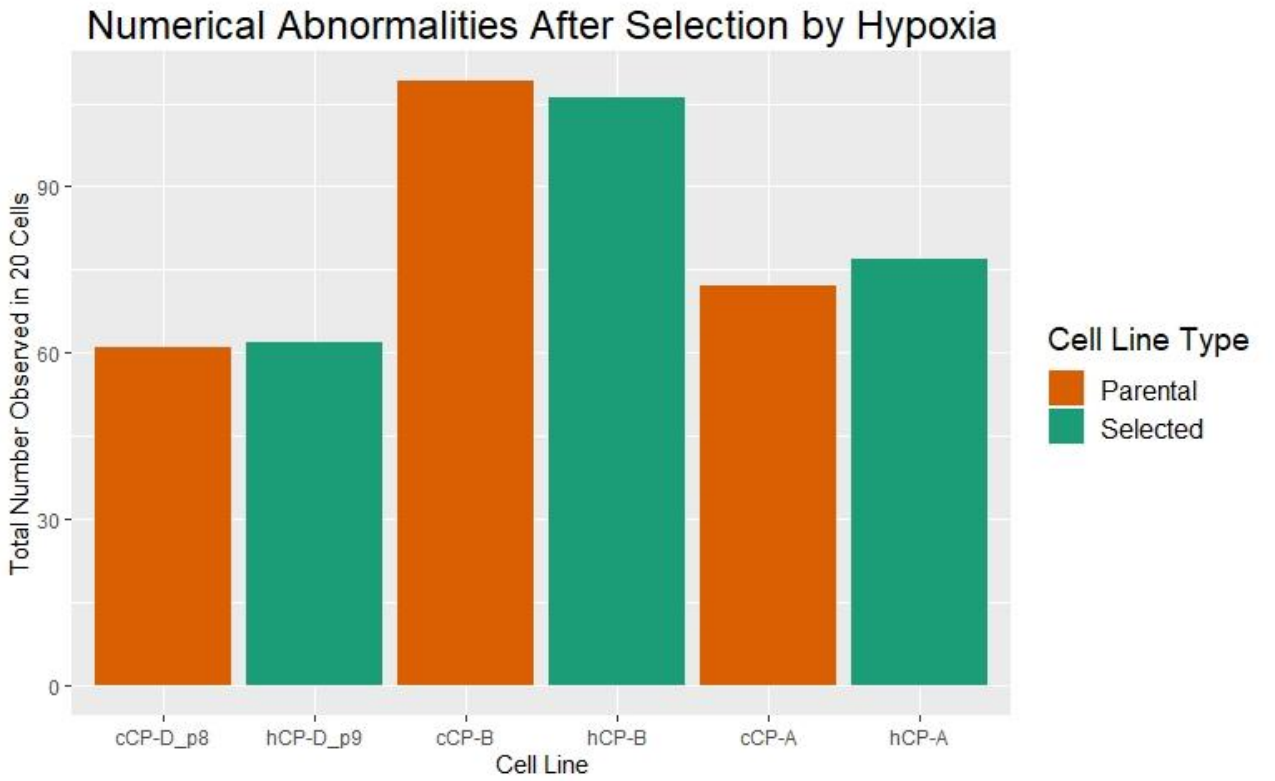


# Selection increases structural but not numerical abnormalities



# Reversion of the Malignant Phenotype of Human Breast Cells in Three-Dimensional Culture and In Vivo by Integrin Blocking Antibodies

**V.M. Weaver,* O.W. Petersen,‡ F. Wang,* C.A. Larabell,* P. Briand,§ C. Damsky,‖ and M.J. Bissell***

*Ernest Orlando Lawrence Berkeley National Laboratory, Berkeley, California 94720; ‡Structural Cell Biology Unit, Institute of Medical Anatomy, The Panum Institute, DK-2200 Copenhagen N, Denmark; §Department of Tumor Endocrinology, Division of Cancer Biology, Danish Cancer Society, DK-2100, Copenhagen O, Denmark; and ‖Departments of Stomatology and Anatomy, University of California, San Francisco, California 94143



# The stroma as a crucial target in rat mammary gland carcinogenesis

**Maricel V. Maffini[1], Ana M. Soto[1,*], Janine M. Calabro[1], Angelo A. Ucci[2] and Carlos Sonnenschein[1]**

[1]Department of Anatomy and Cellular Biology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA
[2]Department of Pathology, Tufts-New England Medical Center, 750 Washington Street, Boston, MA 02111, USA
*Author for correspondence (e-mail: ana.soto@tufts.edu)

*Accepted 20 November 2003*
*Journal of Cell Science 117, 1495-1502 Published by The Company of Biologists*
*doi:10.1242/jcs.01000*

## Stromal Regulation of Neoplastic Development

## *Age-Dependent Normalization of Neoplastic Mammary Cells by Mammary Stroma*

Maricel V. Maffini, Janine M. Calabro,
Ana M. Soto, and Carlos Sonnenschein

*From the Department of Anatomy and Cellular Biology, Tufts University School of Medicine, Boston, Massachusetts*

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**RESEARCH ARTICLE**

# Transmembrane potential of GlyCl-expressing instructor cells induces a neoplastic-like conversion of melanocytes via a serotonergic pathway

Douglas Blackiston[1,2], Dany S. Adams[1], Joan M. Lemire[1], Maria Lobikin[1] and Michael Levin[1,*]