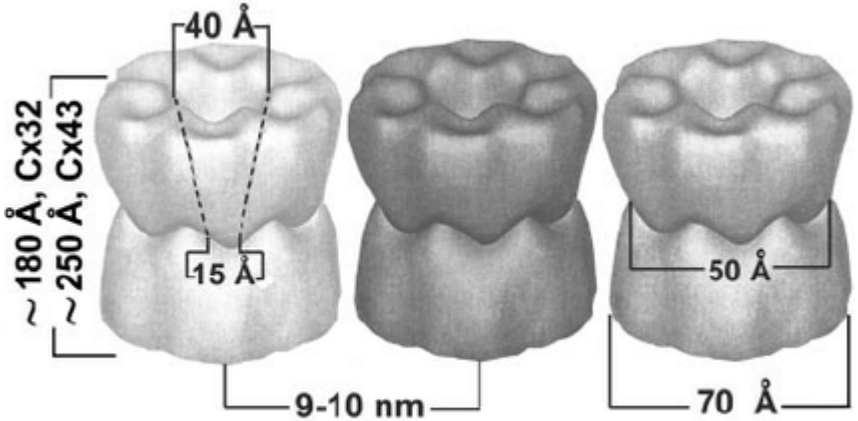
A physics perspective on cancer



João Carvalho
CFisUC : Physics Department : University of Coimbra
15 February 2023

CFisUC

1 2 9 0 UNIVERSIDADE D COIMBRA

Saez JC, Berthoud VM, Branes MC, Martinez AD, Beyer EC. Plasma membrane channels formed by connexins: their regulation and functions. Physiol Rev. 2003 Oct;83(4):1359-400. doi: 10.1152/physrev.00007.2003.

"There's a belief in underlying simplicity that has guided physics since forever. Where we see complication, that's where we don't understand the **principles** yet." Andrew Ewald

in **Cancer and the artillery of physics** Gabriel Popkin, Johns Hopkins Magazine, 2018

Disclaimer (personal view)

The opinions expressed in this presentation are those of the **author**. They do not purport to reflect the opinions or views of the CFisUC, UC or its members.

The presented views result mainly from conceptual work, bibliographic research, discussions with collaborators, thought experiments and theoretical reasoning (only the researcher ego was hurt in this work)

Every week media present good news about cancer advancements

But people are still dying from **cancer**, and every diagnosis is a Damocles sword in the person (& family) life

Sword of Damocles, Richard Westall, 1812

https://www.icr.ac.uk/blogs/science-talk/page-details/asco-2019-icr-research-makes-waves-at-world-s-largest-cancer-conference,
https://www.pancreaticcancer.org.uk/news-and-blogs/deadliest-cancers-have-received-just-7-of-research-funding-over-10-years/

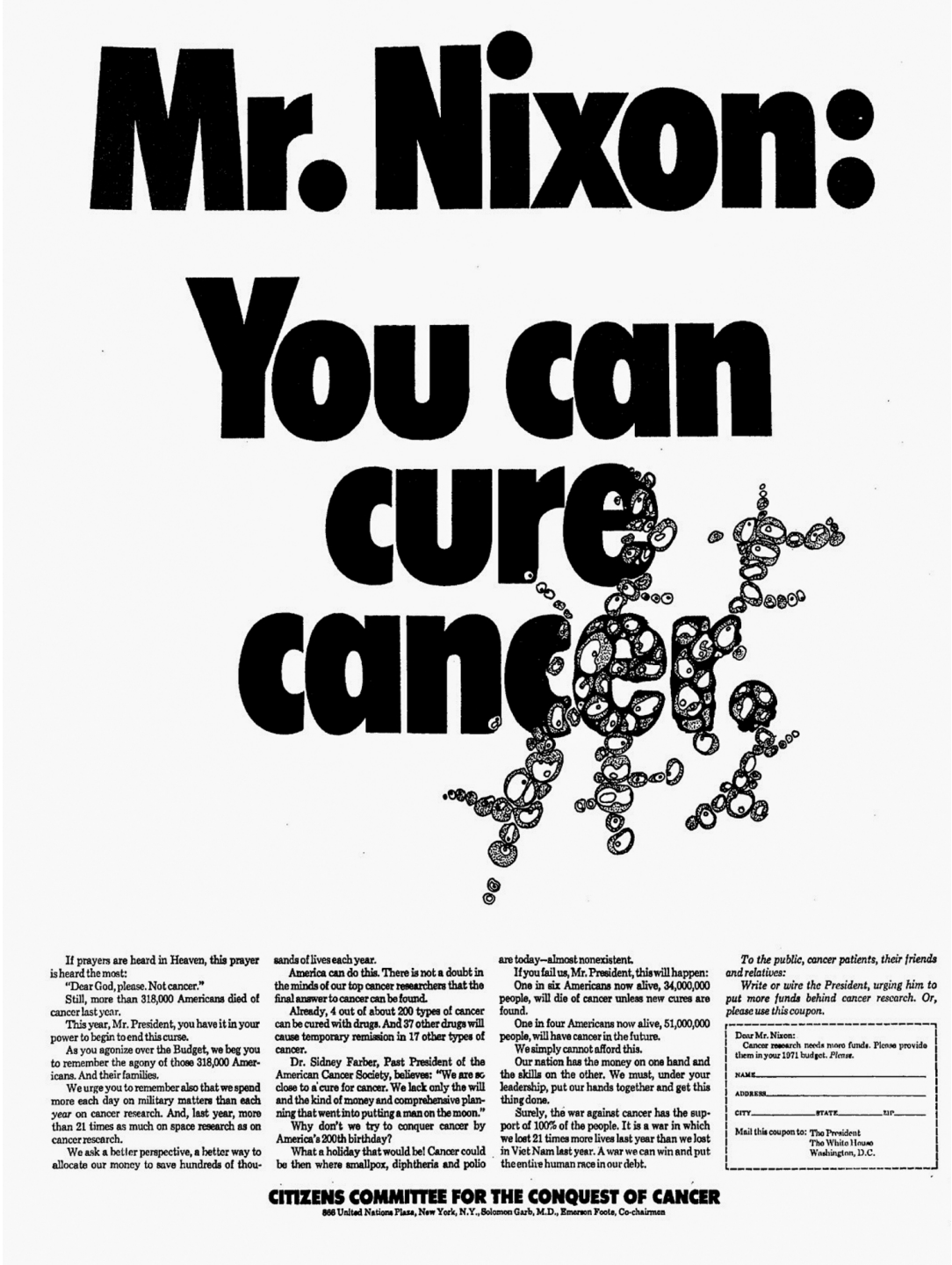
NOTE

The medical condition usually designated by cancer is not a single disease

Cancer is a group of diseases (actually more than 100) characterized by the uncontrolled proliferation of cells

A full-blown **war on cancer** started 50 years ago

What have we advanced?



Mr. Nixon:

You can cure cancer.

If prayers are heard in Heaven, this prayer is heard the most:

"Dear God, please. Not cancer."

Still, more than 318,000 Americans died of cancer last year.

This year, Mr. President, you have it in your power to begin to end this curse.

As you agonize over the Budget, we beg you to remember the agony of those 318,000 Americans. And their families.

We urge you to remember also that we spend more each day on military matters than each *year* on cancer research. And, last year, more than 21 times as much on space research as on cancer research.

We ask a better perspective, a better way to allocate our money to save hundreds of thousands of lives each year.

America can do this. There is not a doubt in the minds of our top cancer researchers that the final answer to cancer can be found.

Already, 4 out of about 200 types of cancer can be cured with drugs. And 37 other drugs will cause temporary remission in 17 other types of cancer.

Dr. Sidney Farber, Past President of the American Cancer Society, believes: "We are so close to a cure for cancer. We lack only the will and the kind of money and comprehensive planning that went into putting a man on the moon."

Why don't we try to conquer cancer by America's 200th birthday?

What a holiday that would be! Cancer could be then where smallpox, diphtheria and polio are today—almost nonexistent.

If you fail us, Mr. President, this will happen:

One in six Americans now alive, 34,000,000 people, will die of cancer unless new cures are found.

One in four Americans now alive, 51,000,000 people, will have cancer in the future.

We simply cannot afford this.

Our nation has the money on one hand and the skills on the other. We must, under your leadership, put our hands together and get this thing done.

Surely, the war against cancer has the support of 100% of the people. It is a war in which we lost 21 times more lives last year than we lost in Viet Nam last year. A war we can win and put the entire human race in our debt.

To the public, cancer patients, their friends and relatives:

Write or wire the President, urging him to put more funds behind cancer research. Or, please use this coupon.

Dear Mr. Nixon:
Cancer research needs more funds. Please provide them in your 1971 budget. *Please.*

NAME_____

ADDRESS_____

CITY_____ STATE_____ ZIP_____

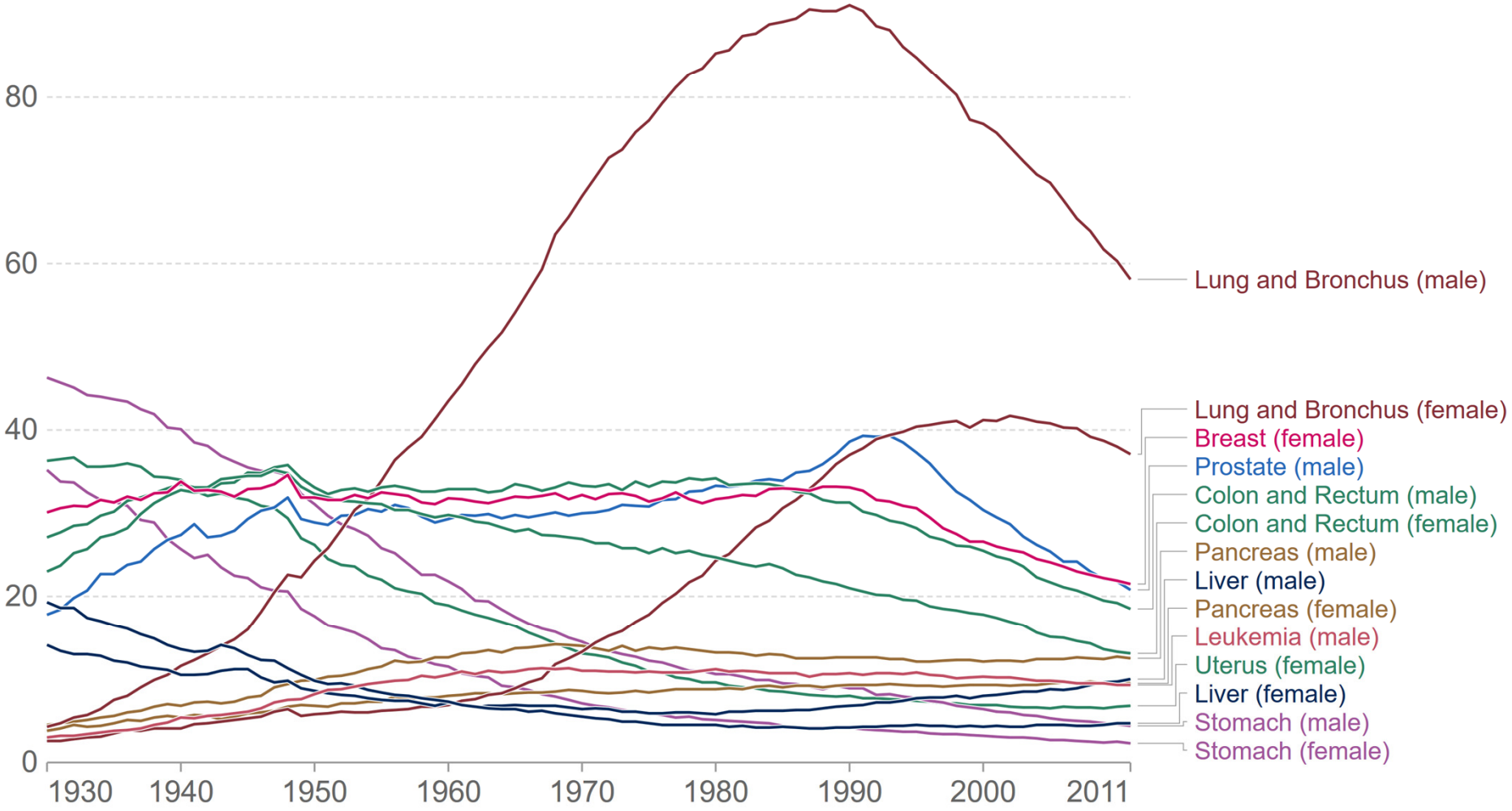
Mail this coupon to: The President
The White House
Washington, D.C.

CITIZENS COMMITTEE FOR THE CONQUEST OF CANCER

866 United Nations Plaza, New York, N.Y., Solomon Garb, M.D., Emerson Foote, Co-chairmen

Cancer death rates in the United States over the long-run

Age-standardized death rates from various forms of cancer in males and females, measured as the number of deaths per 100,000 individuals. Age-standardization is based on normalisation to the standard US population structure in the year 2000.



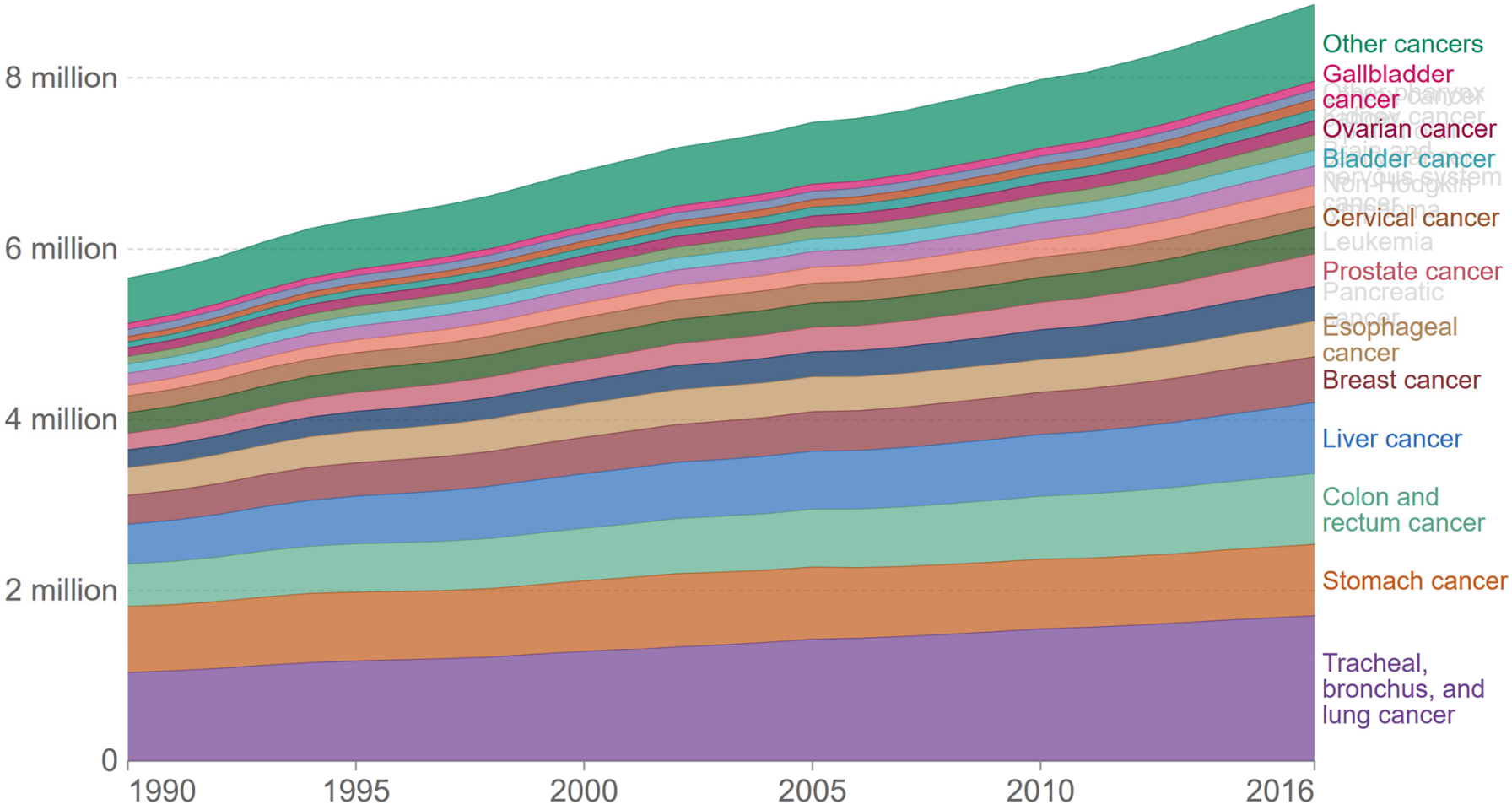
Source: American Cancer Society

OurWorldInData.org/cancer • CC BY

Cancer deaths by type, World, 1990 to 2016

Our World in Data

Annual cancer deaths by cancer type, measured as the total number of deaths across all age categories and both sexes. Smaller categories of cancer types with global deaths <100,000 in 2016 have been grouped into a collective category 'Other cancers'. See sources for list of grouped cancers.



Source: IHME, Global Burden of Disease (GBD)

OurWorldInData.org/cancer • CC BY

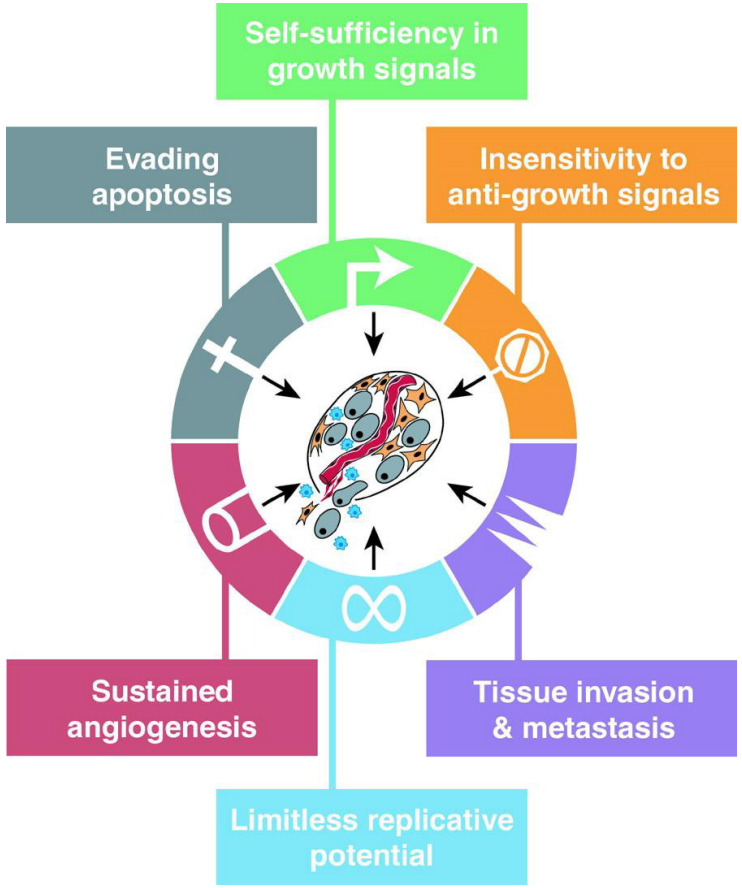
Note: All cancer types with less than 100,000 global deaths in 2016 into a collective category 'Other cancers'.

World population: 1990=5.3G, 2016=7.5G

Very Influential Publication (VIP)

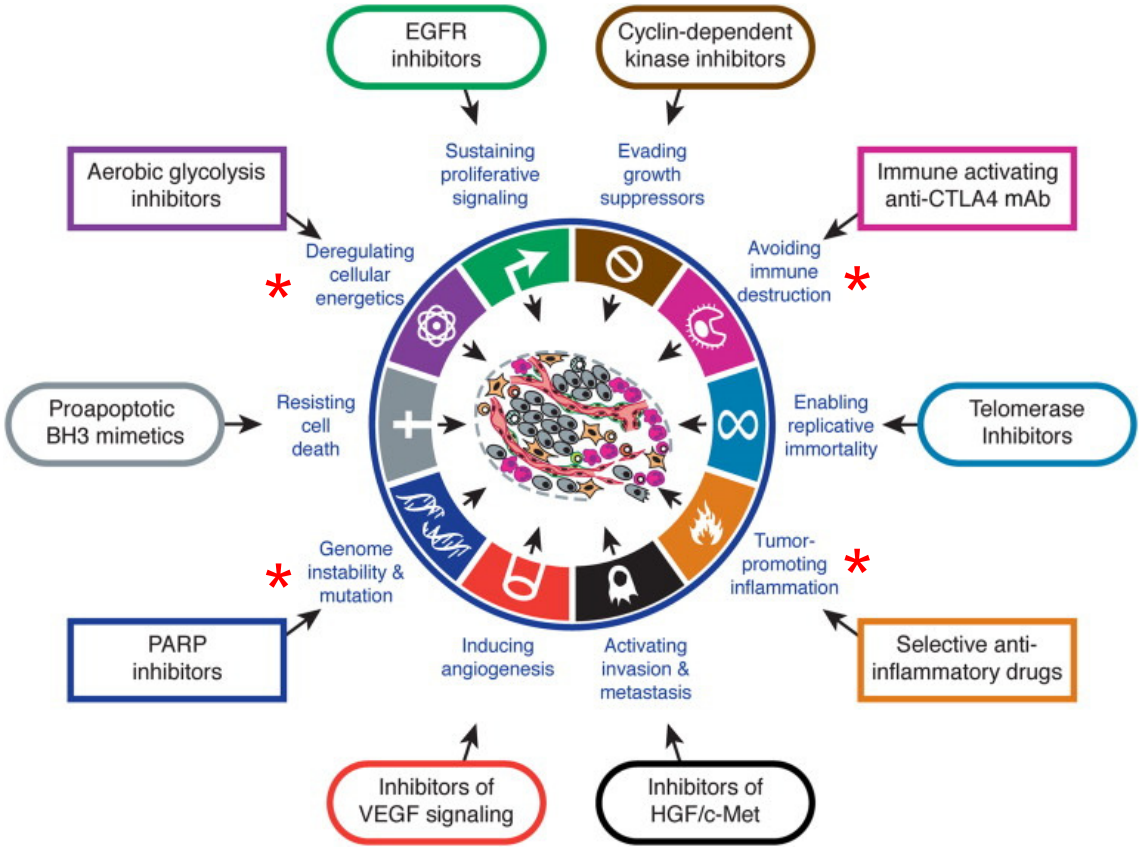
Douglas Hanahan and Robert A. Weinberg "**The hallmarks of cancer**", Cell, 2000 (~40k citations)

Six characteristics of cancer cells acquired through successive **genetic mutations** at the disease origin and progress: the **cancer cell** paradigm

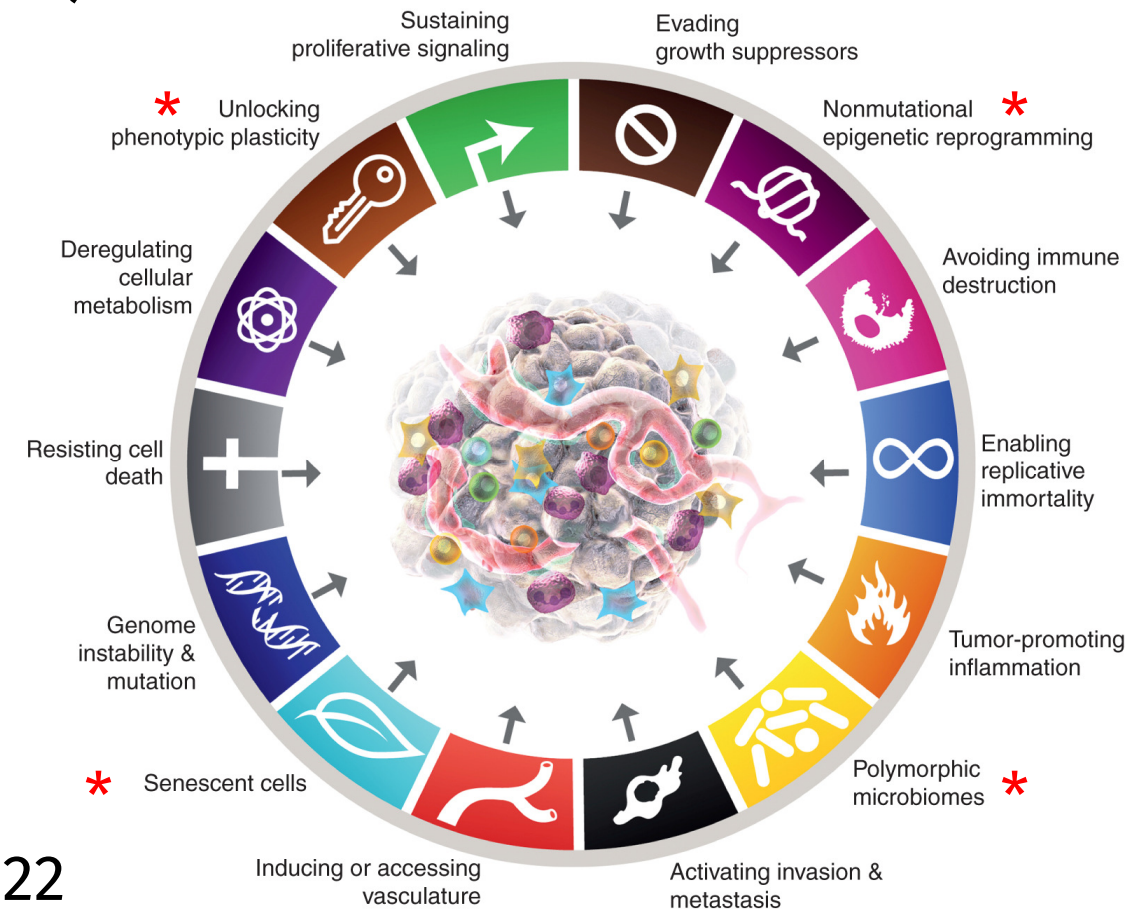


Later updated with further 4 hallmarks:

Douglas Hanahan and Robert A. Weinberg
“**Hallmarks of Cancer: The Next Generation**”,
Cell, 2011 (~67k citations)



And it was further updated with extra 4 properties (growing into irrelevance, almost everything fits in!)

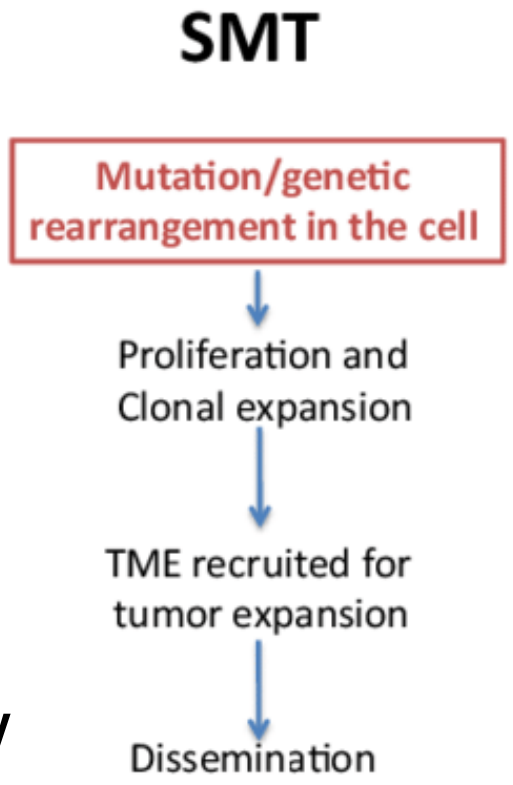


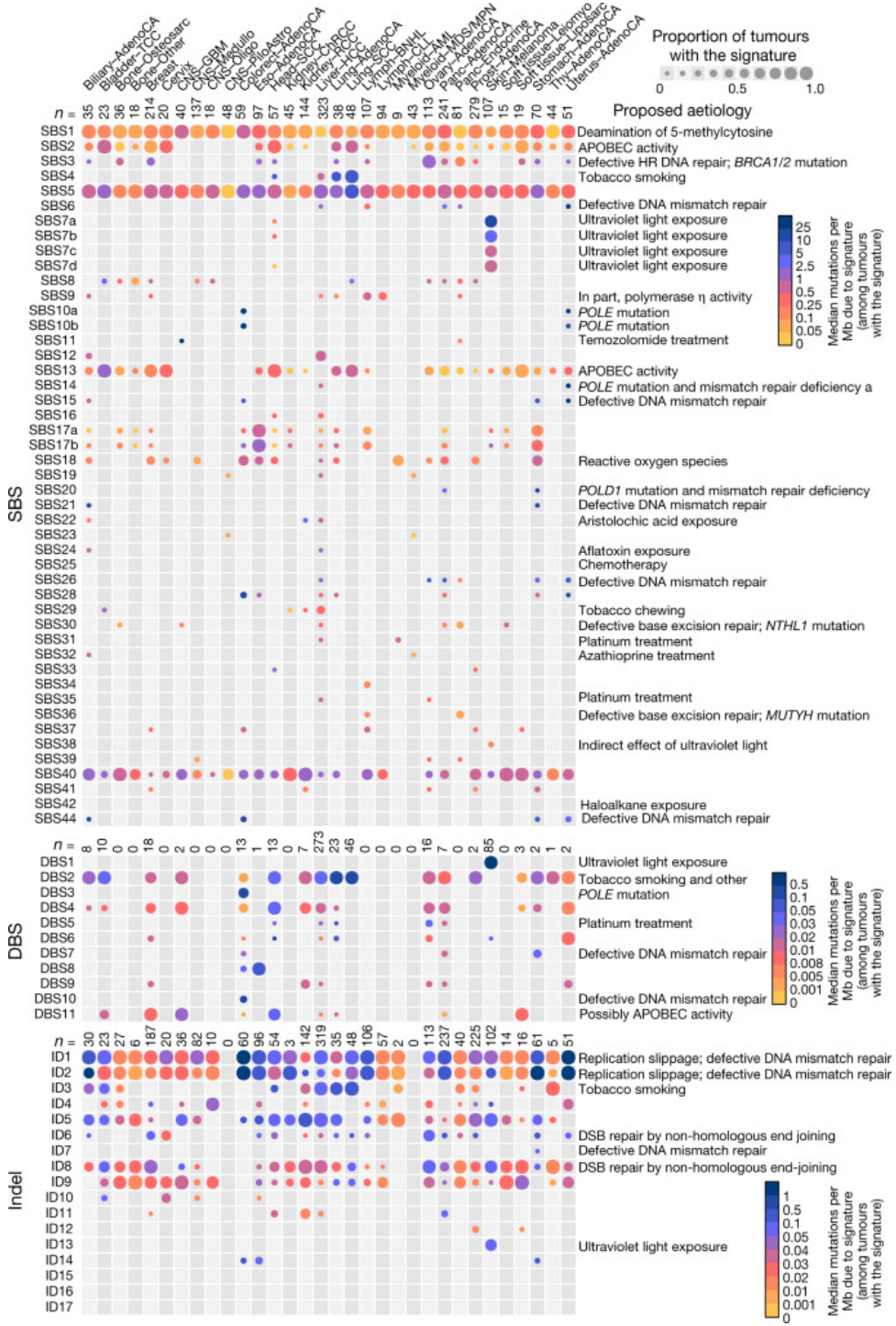
Douglas Hanahan
“**Hallmarks of Cancer: New Dimensions**”,
Cancer Discov., 2022

The standard model of cancer origin: the somatic mutation theory

Some **successes** (like hereditary susceptibility, or the prevention of mutagenic chemicals or radiation, genetic therapies, etc.)

Many **contradictions** under the proverbial carpet (cancers without mutations, cancers originated by foreign objects or by no mutagenic chemicals, normal tissues with many mutations, cancer reversal, ...)





No relevant genetic signatures for mutations in different cancer types (even after huge investment)

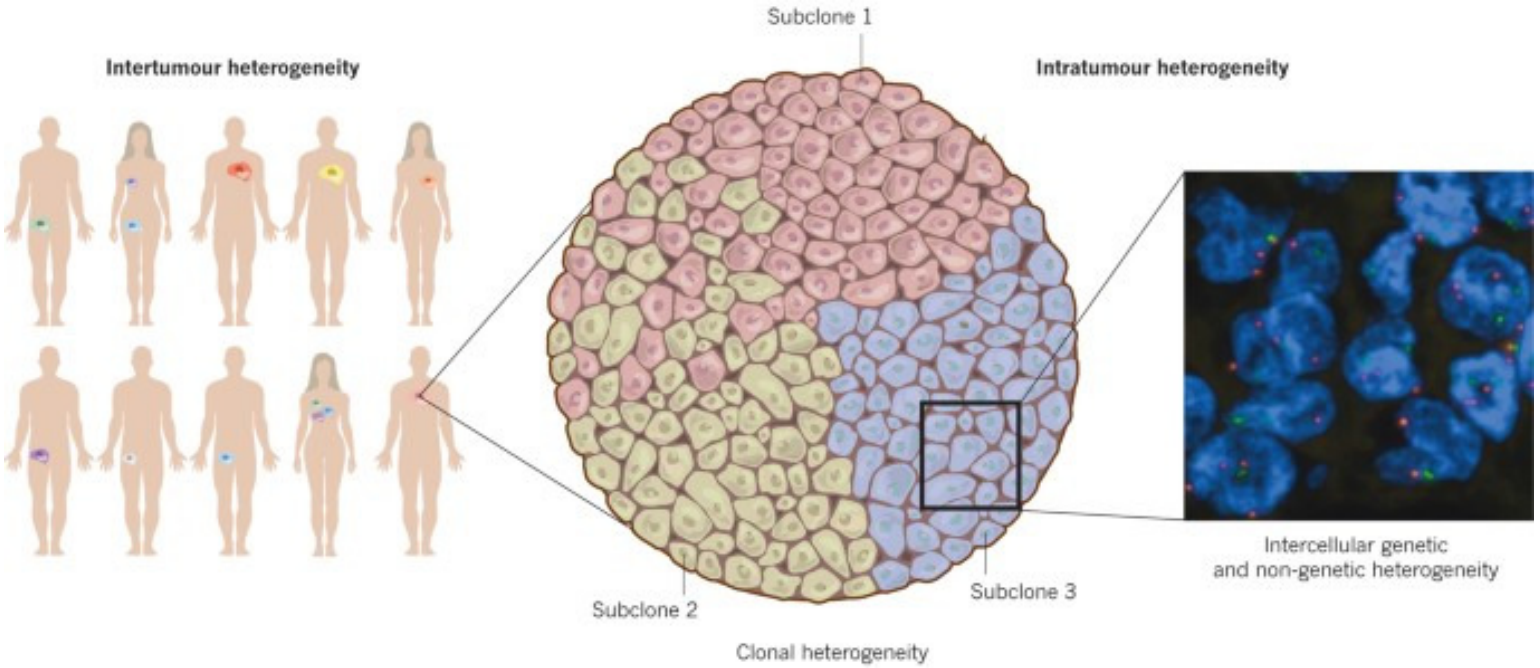
Very **heterogeneous**, even in a single tumor in a particular patient

Alexandrov, L.B., Kim, J., Haradhvala, N.J. *et al.* The repertoire of mutational signatures in human cancer. *Nature* **578**, 94–101 (2020). https://doi.org/10.1038/s41586-020-1943-3

No two tumors are genetically equal

Huge genetic **heterogeneity**, even in the same tumor tissue

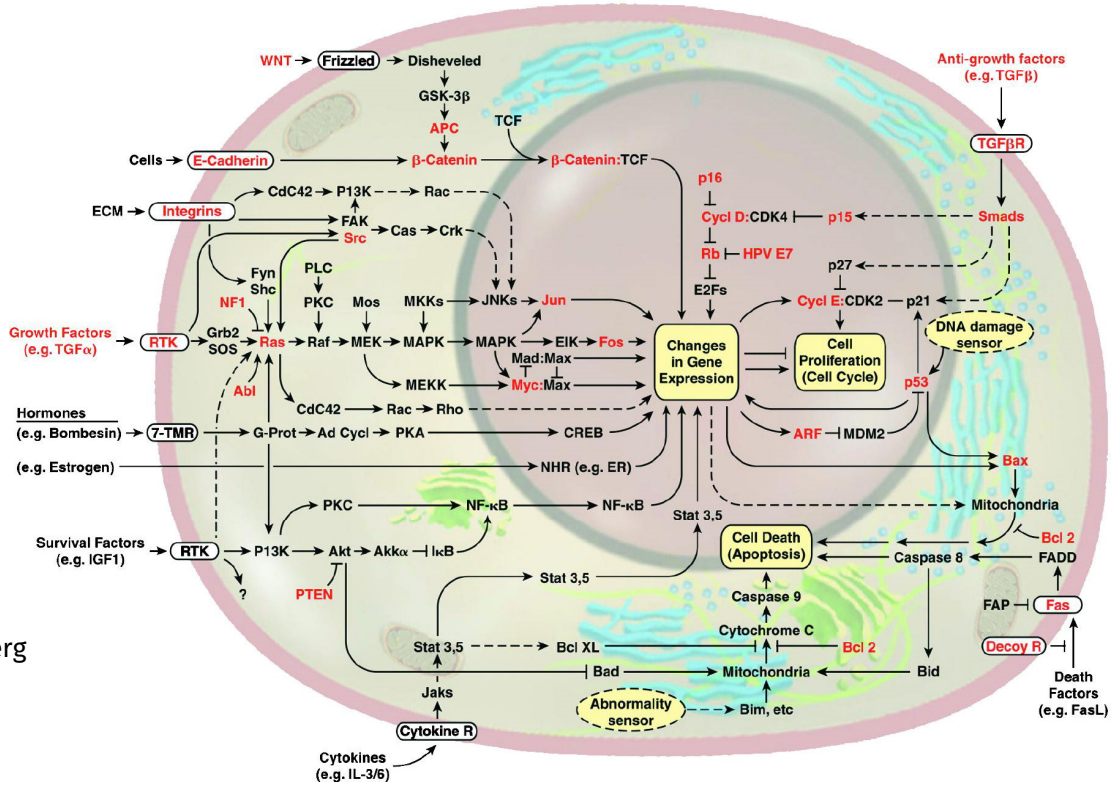
No coherent theory guides the results interpretation



Burrell, R., McGranahan, N., Bartek, J. *et al.* The causes and consequences of genetic heterogeneity in cancer evolution. *Nature* **501**, 338–345 (2013). https://doi.org/10.1038/nature12625

Huge **complexity** of genetic interactions

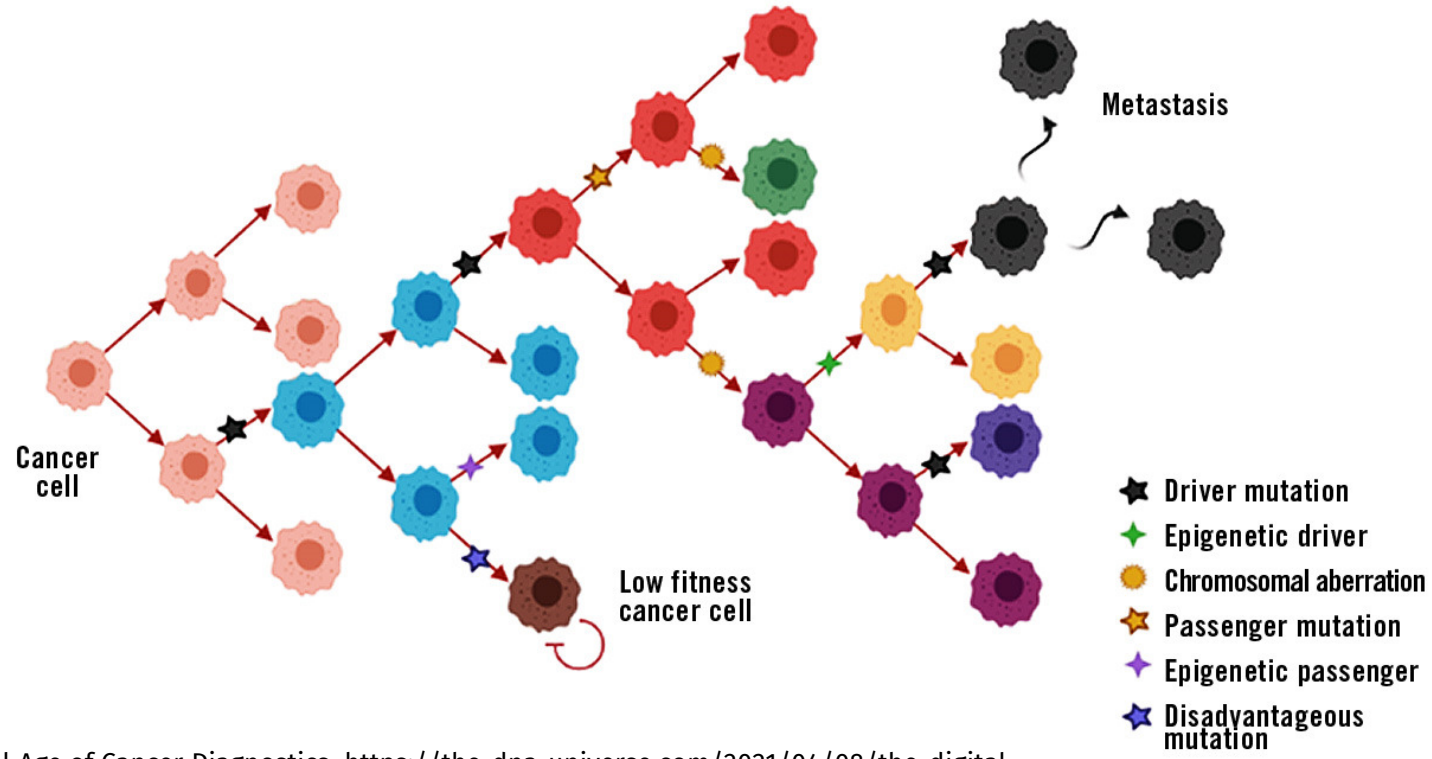
In the absence of a reliable **theory**, and when (almost) all results are possible, publish the ones that better fit your (and the editor) prejudices...



Douglas Hanahan and Robert A Weinberg
"The hallmarks of cancer", Cell, 2000

Houdini-like escapes, as driver and passenger mutations (Ugh!)

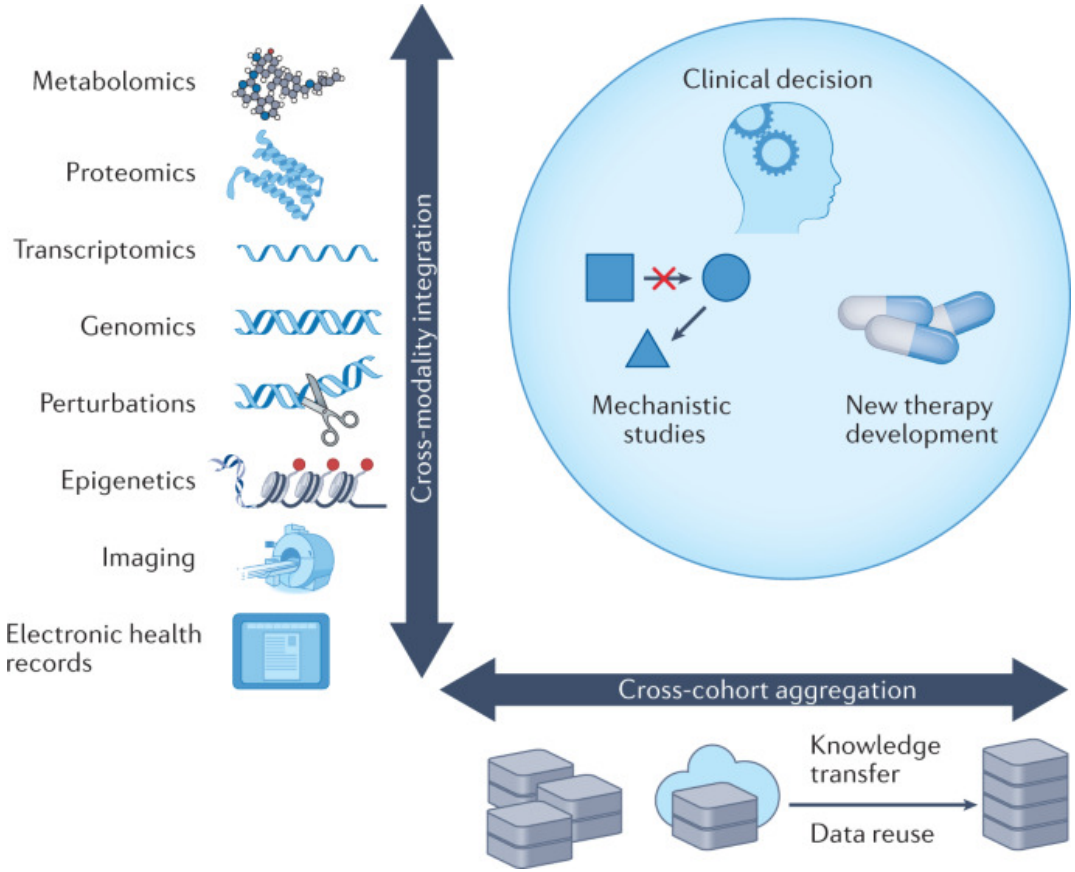
Every justification for each contradiction found in data is reasonable per se (but all together are a mess!)



The Digital Age of Cancer Diagnostics, https://the-dna-universe.com/2021/04/08/the-digital-age-of-cancer-diagnostics/

What to do about the (unexplained) problems?

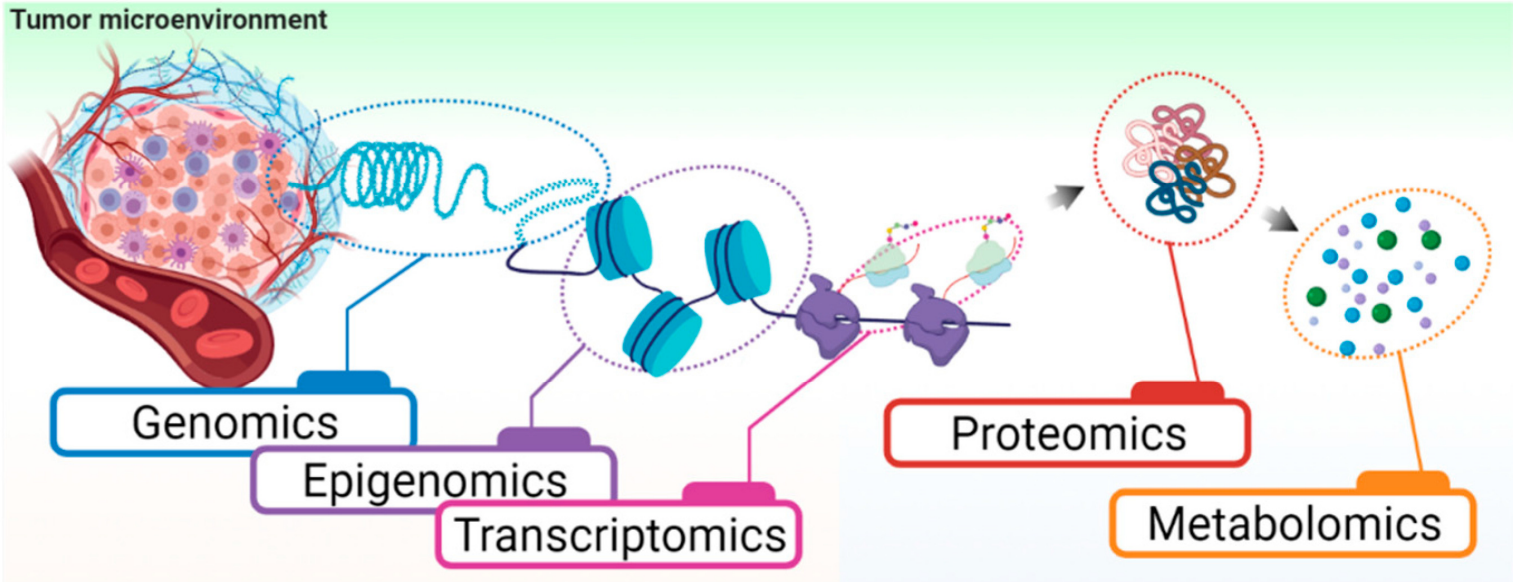
If something doesn't work, put (much) more **resources** on it... (actually almost all resources!)



Jiang, P., Sinha, S., Aldape, K. *et al.* Big data in basic and translational cancer research. *Nat Rev Cancer* **22**, 625–639 (2022). https://doi.org/10.1038/s41568-022-00502-0

A fantastic technology was developed for genomic sequencing and it is the prime tool to acquire (huge amounts of) data on cancer (**omics** revolution)

Problem: more exception cases than real (or useful and usable) predictions



Yoon SJ, Lee CB, Chae SU, Jo SJ, Bae SK. The Comprehensive "Omics" Approach from Metabolomics to Advanced Omics for Development of Immune Checkpoint Inhibitors: Potential Strategies for Next Generation of Cancer Immunotherapy. Int J Mol Sci. 2021;22(13):6932. doi: 10.3390/ijms22136932.

This is a huge and long **mutational** bet (all eggs in a very fragile basket)

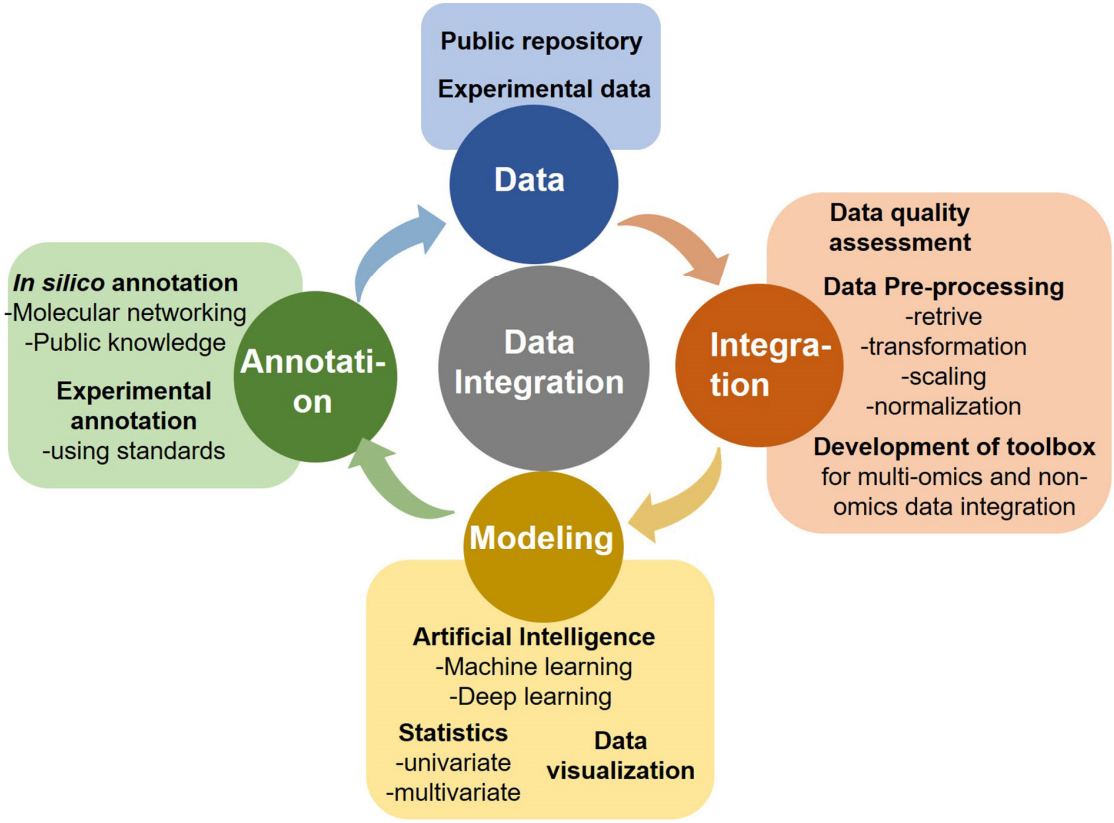
(Important) **biases** in experiments design, results interpretation and accepted publications

Photo collage by Robert Hood / Fred Hutch News Service, https://www.fredhutch.org/en/news/center-news/2020/02/spinning-science-overhyped-headlines-snarled-statistics-lead-readers-astray.html

Great AI life sciences challenge

What can be learned from so many millions of experiments and publications?

Put together all the in vitro, in vivo and clinical trials and try to extract useful information and patterns



Patel SK, George B and Rai V (2020) Artificial Intelligence to Decode Cancer Mechanism: Beyond Patient Stratification for Precision Oncology. *Front. Pharmacol.* 11:1177. doi: 10.3389/fphar.2020.01177

However, important negative or contradictory results don't see the daylight (or are overlooked)

Problem if the published information is limited by **biases**...

Groupthink 	**Belief Bias** 	**Courtesy Bias** 	**Anchoring Effect** 	**Availability Heuristic** 
Bandwagon Effect 	**Status Quo Bias** 	**Gambler's Fallacy** 	**Ostrich Effect** 	**Illusion Of Validity** 
Reactive Devaluation 	**Demotivating Effect** 	**Pygmalion Effect** 	**Bystanders Uncertainty** 	**Confirmation Bias** 

www.TeacherToolkit.co.uk/Bias-Thinking

But, are there alternatives?

Promotional still from "Crossroads“, in https://owlcation.com/humanities/The-Crossroads-a-liminal-setting-for-occult-and-supernatural-activities

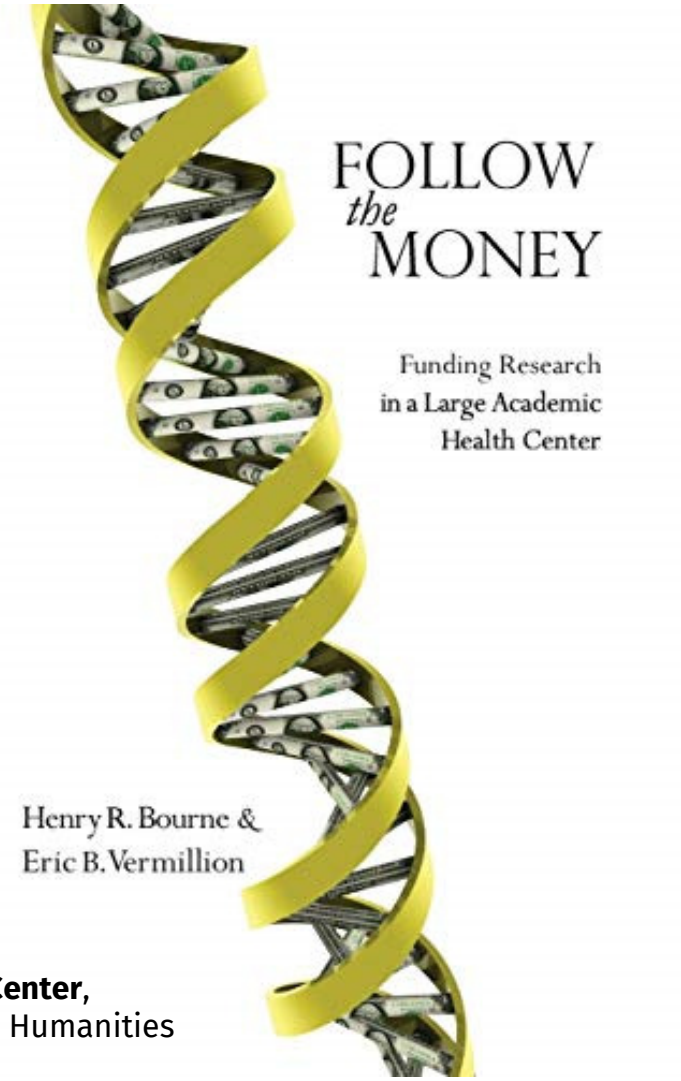
And if genetic mutations found in cancer tissues are not a cause but a consequence of the cancer progress?

Beware: controversial views

Health and wealth (there are HUGE commercial interests involved)!

Follow the (research and clinical) **money**

Please do not rock the very influential health research boat…



Follow the Money : Funding Research in a Large Academic Health Center, Bourne, Henry R., Vermillion, Eric B., University of California Health Humanities Press, 2016 ISBN 10: 0996324216

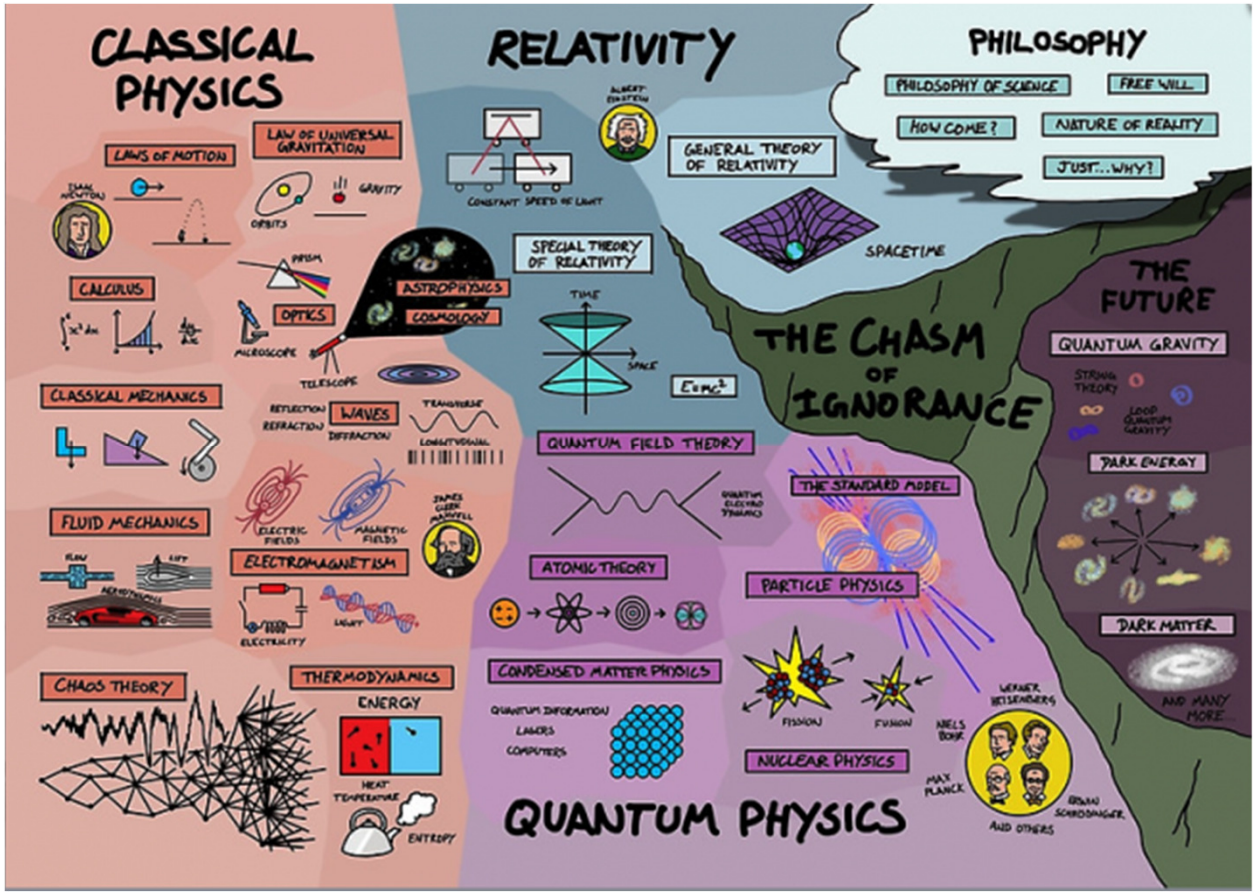
Funding constraints and career advancement obstacles (if not following the herd thinking!)

Please keep (your research) inside the box!

https://www.gsb.stanford.edu/insights/thinking-inside-box-why-virtual-meetings-generate-fewer-ideas

Conservation laws in medicine (but not what you are thinking about)

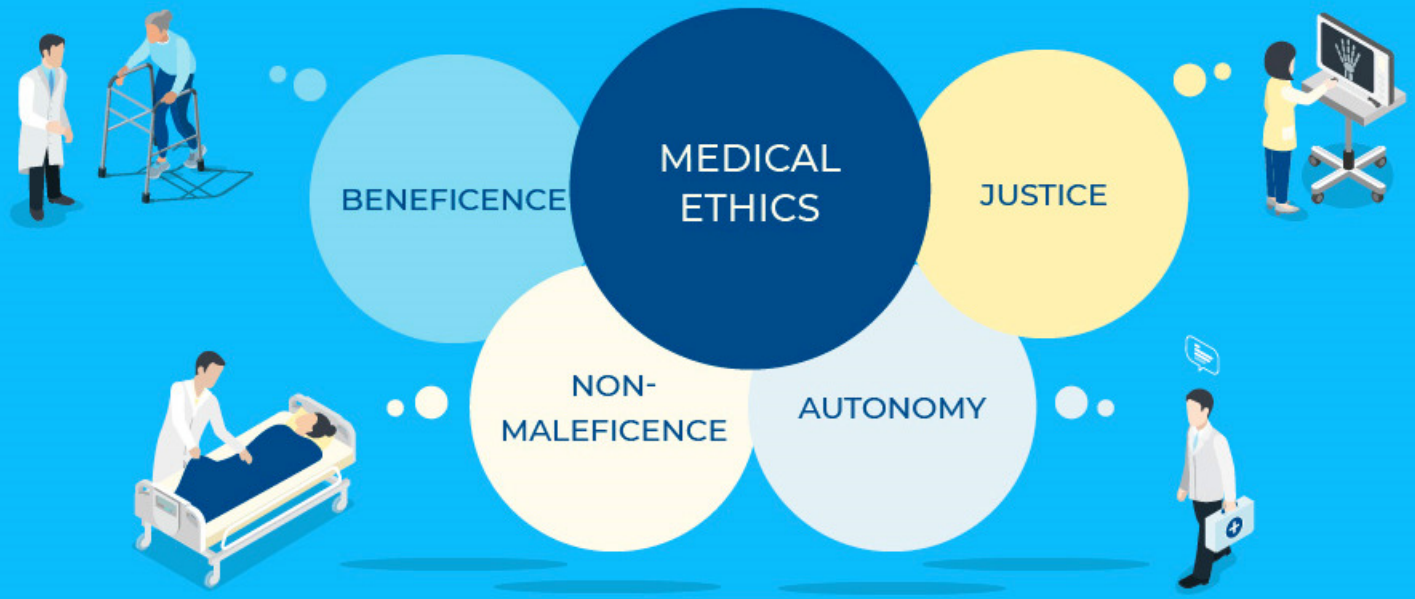
Why not support more broad views and speculative ideas, as in Physics?



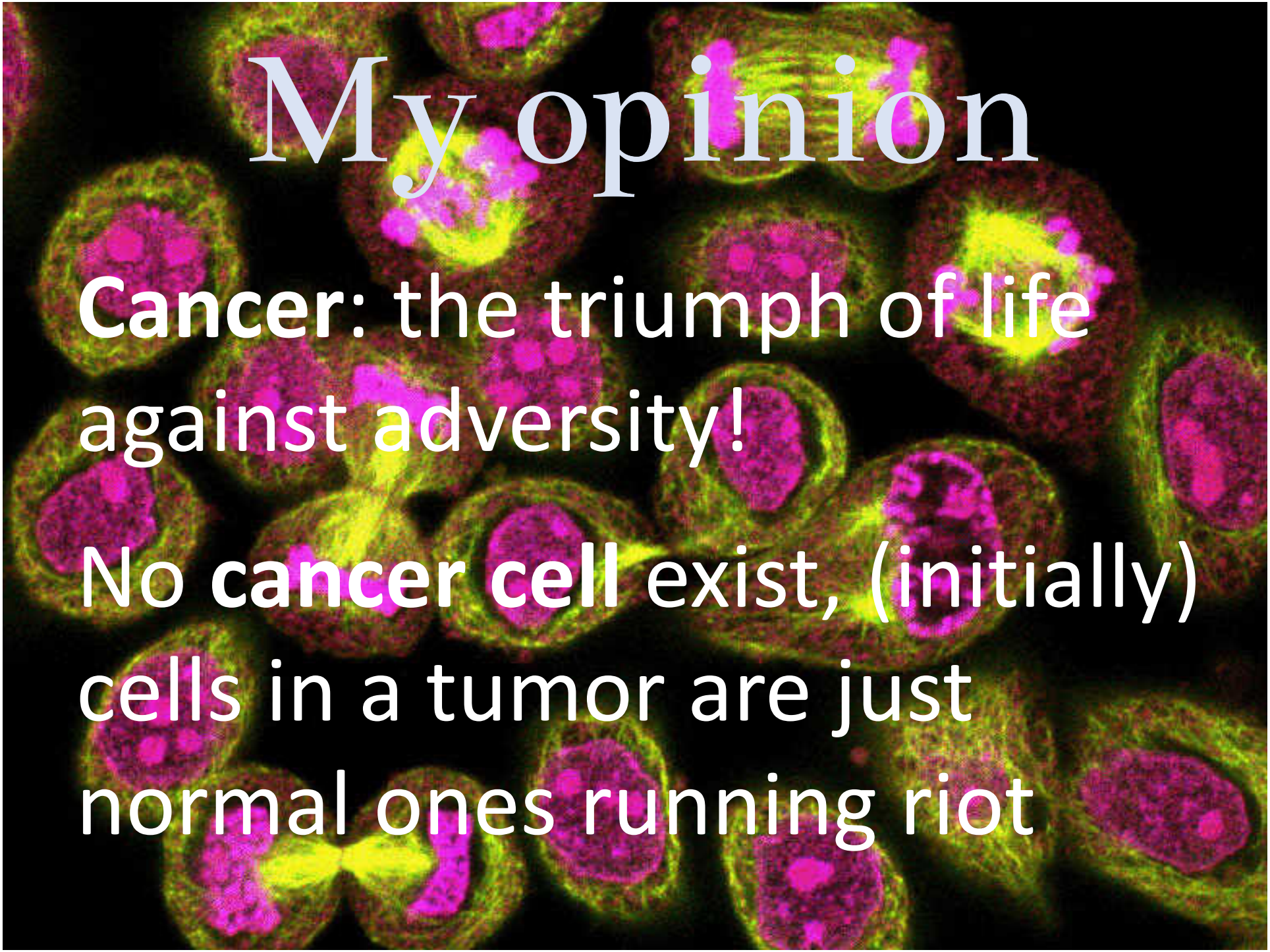
https://www.openculture.com/2016/12/the-map-of-physics.html

There are very important (and required) ETHICS barriers in medical research (to avoid unreasonable risks)

But, what about the fundamental importance of contrary thinking for scientific development?



https://www.frasersinterview.com.au/free-resources/medical-school-interview-ethical-scenarios/?degree=Postgraduate



My opinion

Cancer: the triumph of life against adversity!

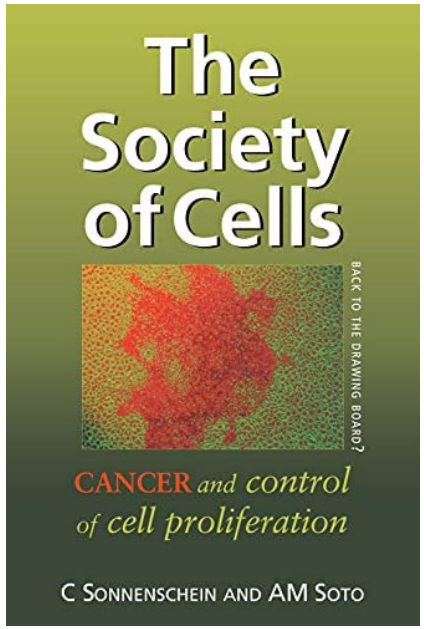
No **cancer cell** exist, (initially) cells in a tumor are just normal ones running riot

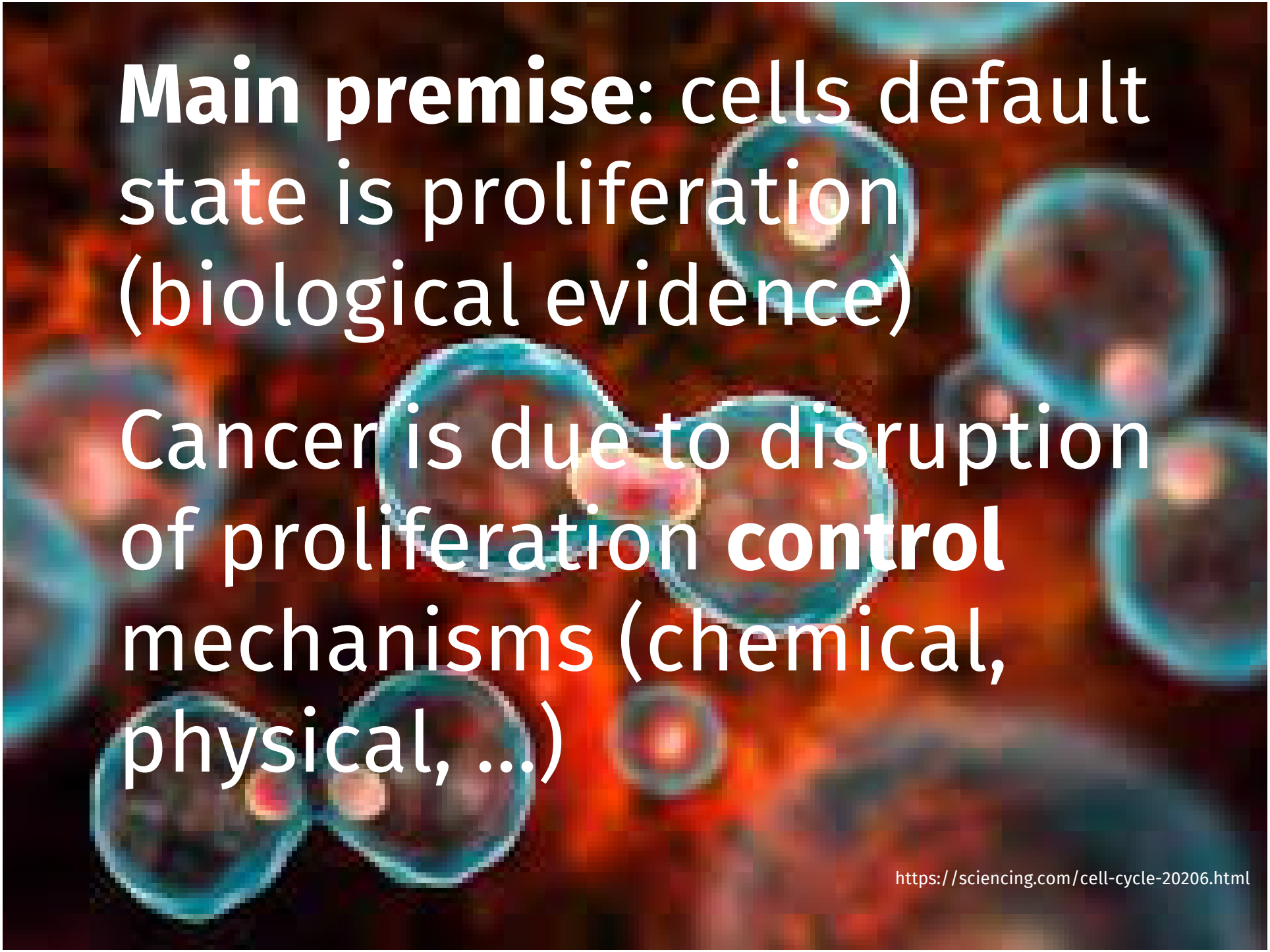
Tissue Organization Field Theory

(TOFT) by Carlos Sonnenschein and Ana M Soto

Cancer as a tissue **organization** problem, not a cell-centered issue (you'll never solve a traffic jam by knowing everything about a car...)

Endorse a theory-guided research




Main premise: cells default state is proliferation (biological evidence)
Cancer is due to disruption of proliferation **control** mechanisms (chemical, physical, ...)
https://sciencing.com/cell-cycle-20206.html

RESEARCH ARTICLE | 15 MARCH 2004

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

Maricel V. Maffini, Ana M. Soto, Janine M. Calabro, Angelo A. Ucci, Carlos Sonnenschein

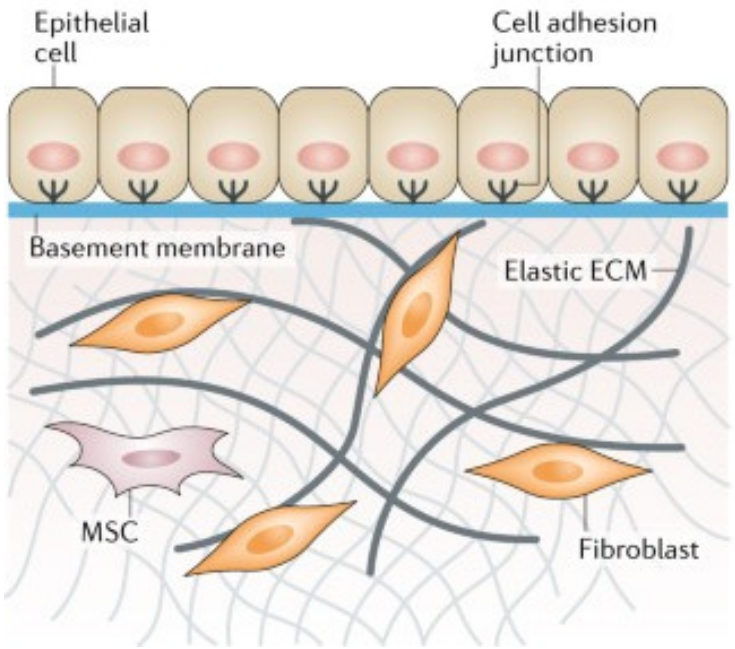
+ Author and article information

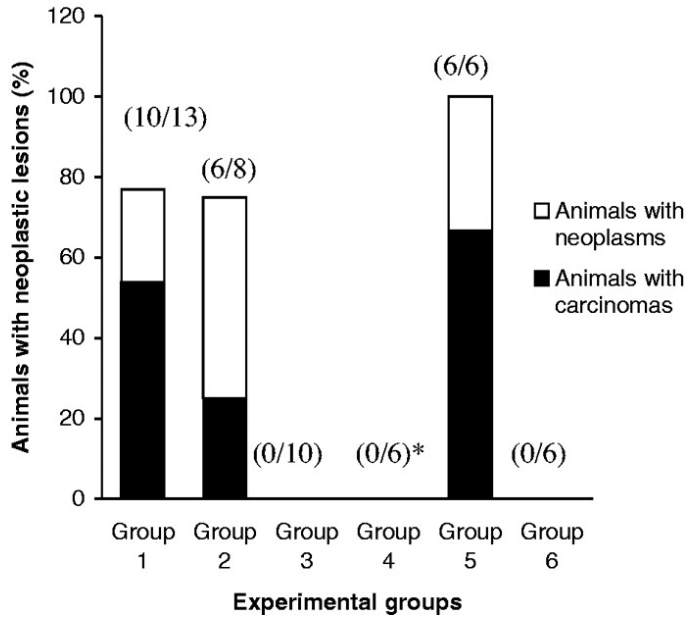
J Cell Sci (2004) 117 (8): 1495–1502.

https://doi.org/10.1242/jcs.01000 **Article history**

Simple **experiment**: rat mammary tissue recombination model (with the chemical carcinogen N-nitrosomethylurea (NMU)) to determine whether the primary target of the carcinogen is the epithelium, the stroma or both tissue compartments

Valkenburg, K.C., de Groot, A.E. & Pienta, K.J. Targeting the tumour stroma to improve cancer therapy. *Nat Rev Clin Oncol* **15**, 366–381 (2018). https://doi.org/10.1038/s41571-018-0007-1





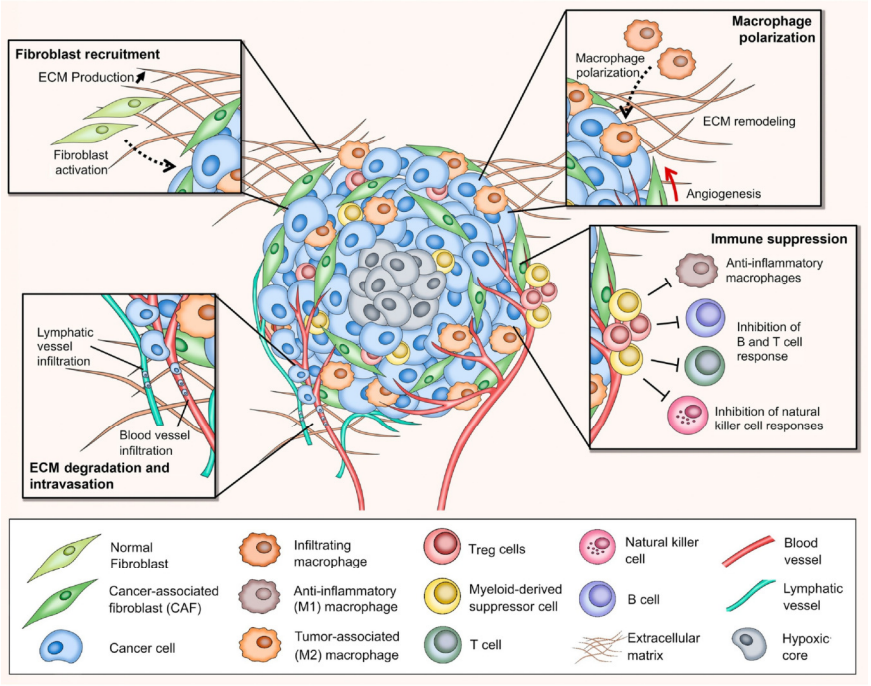
Group	Epithelial	Stroma
1	Vehicle	NMU
2	NMU	NMU
3	NMU	Vehicle
4	Vehicle	Vehicle
5	NMU	
6	Vehicle	

Conclusion: the carcinogen in the environment (stroma fat pad) is at the cancer origin, independent of epithelial cells exposure

Consequences

Move from a cell-centered research to a more holistic approach

Discover the **tissue organization** mechanisms (fundamental for cancer prevention and therapy)

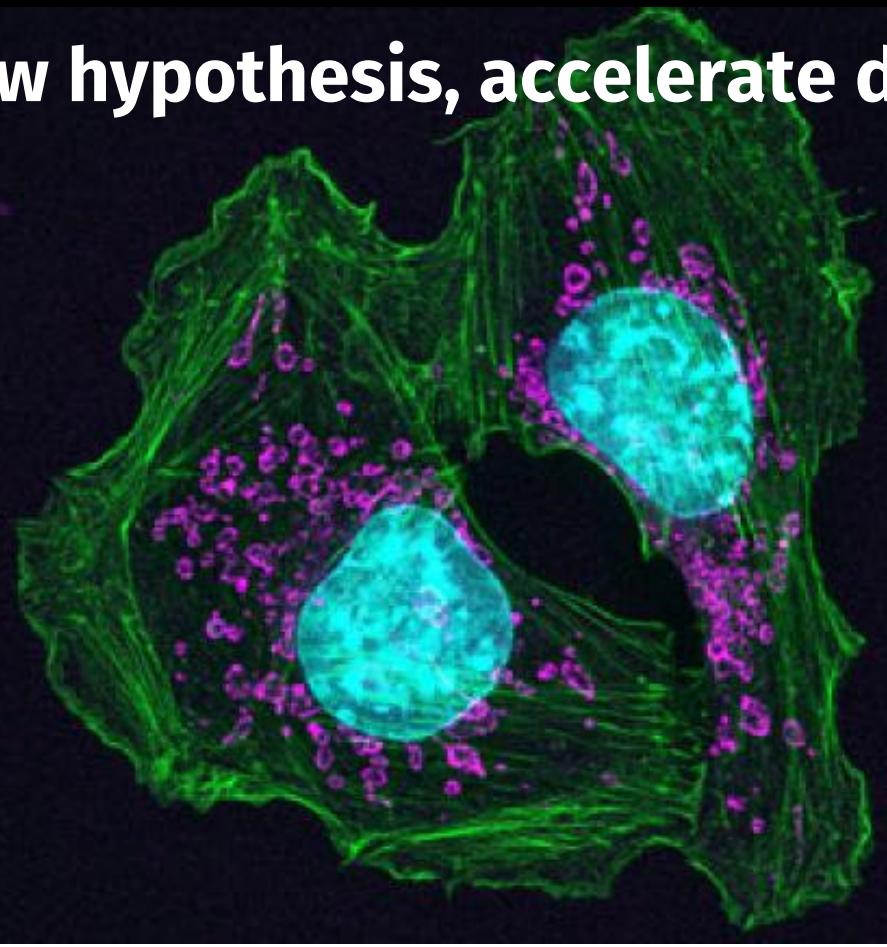


Rodrigues J, Heinrich MA, Teixeira LM, Prakash J. 3D In Vitro Model (R)evolution: Unveiling Tumor-Stroma Interactions. Trends Cancer. 2021;7(3):249-264. doi: 10.1016/j.trecan.2020.10.009.

A theory-guided research allows for its proof or disproof (scientific method)

Avoid the tunnel vision and ad-hoc explanations...

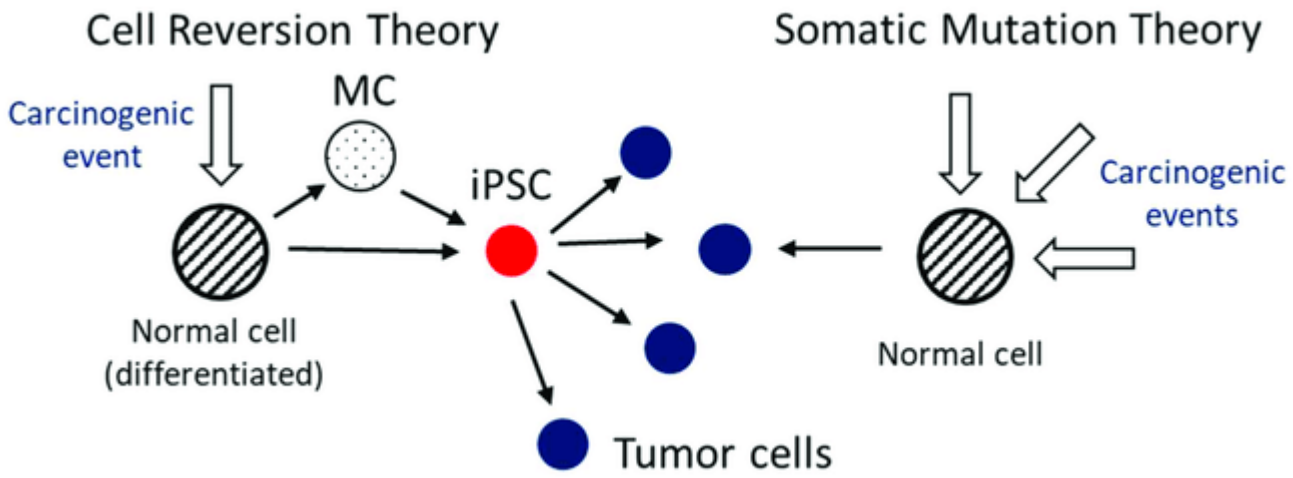
Try new hypothesis, accelerate discoveries



https://www.cam.ac.uk/research/news/ai-system-may-accelerate-search-for-cancer-discoveries

There are other **alternative** theories of cancer initiation, but none of them is mainstream or being actively and intensively tested, as

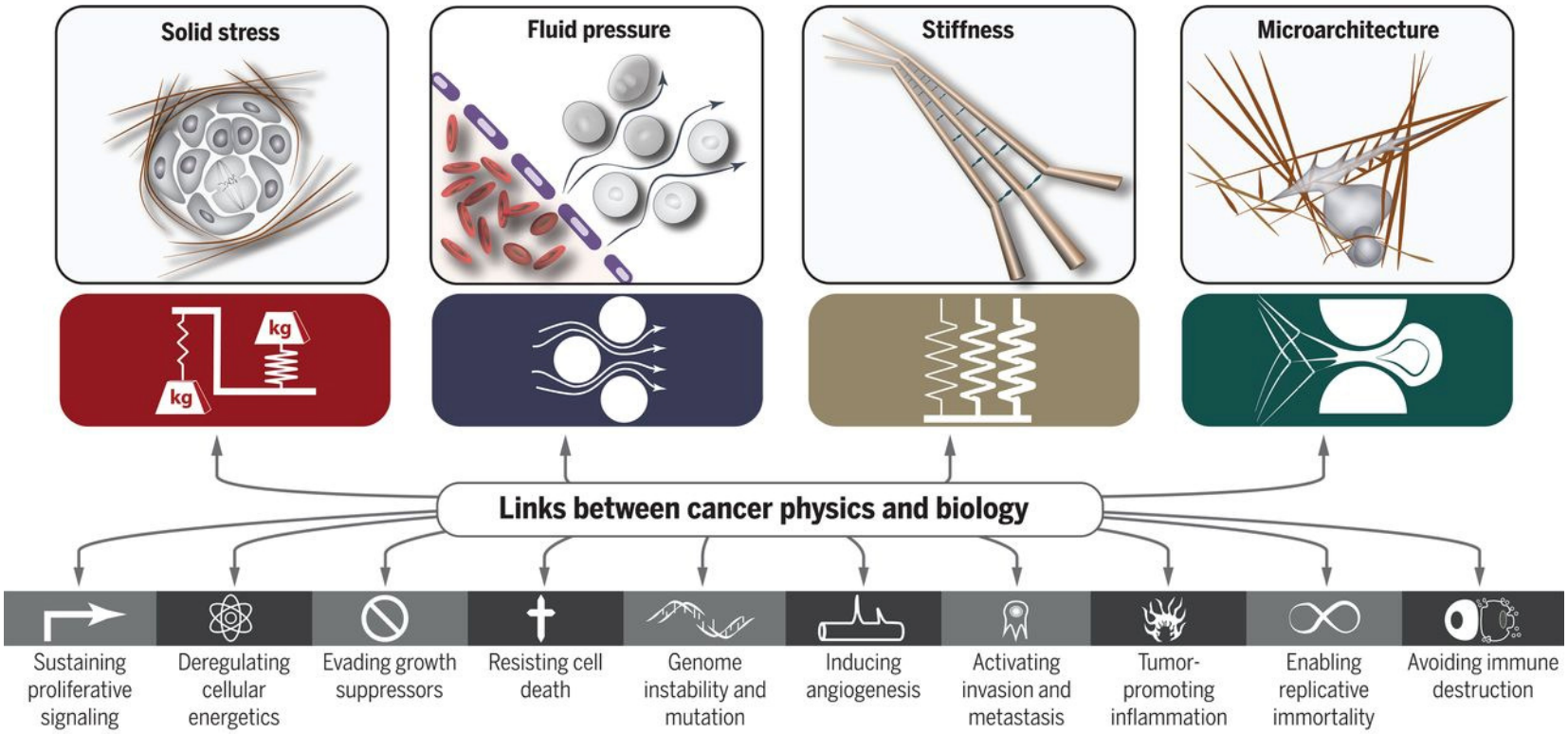
- Detached pericyte hypothesis
- Brücher–Jamall paradigm (chronic inflammation)
- Cell reversal theory



Carvalho J. Cell Reversal From a Differentiated to a Stem-Like State at Cancer Initiation. Front Oncol. 2020;10:541. doi: 10.3389/fonc.2020.00541.

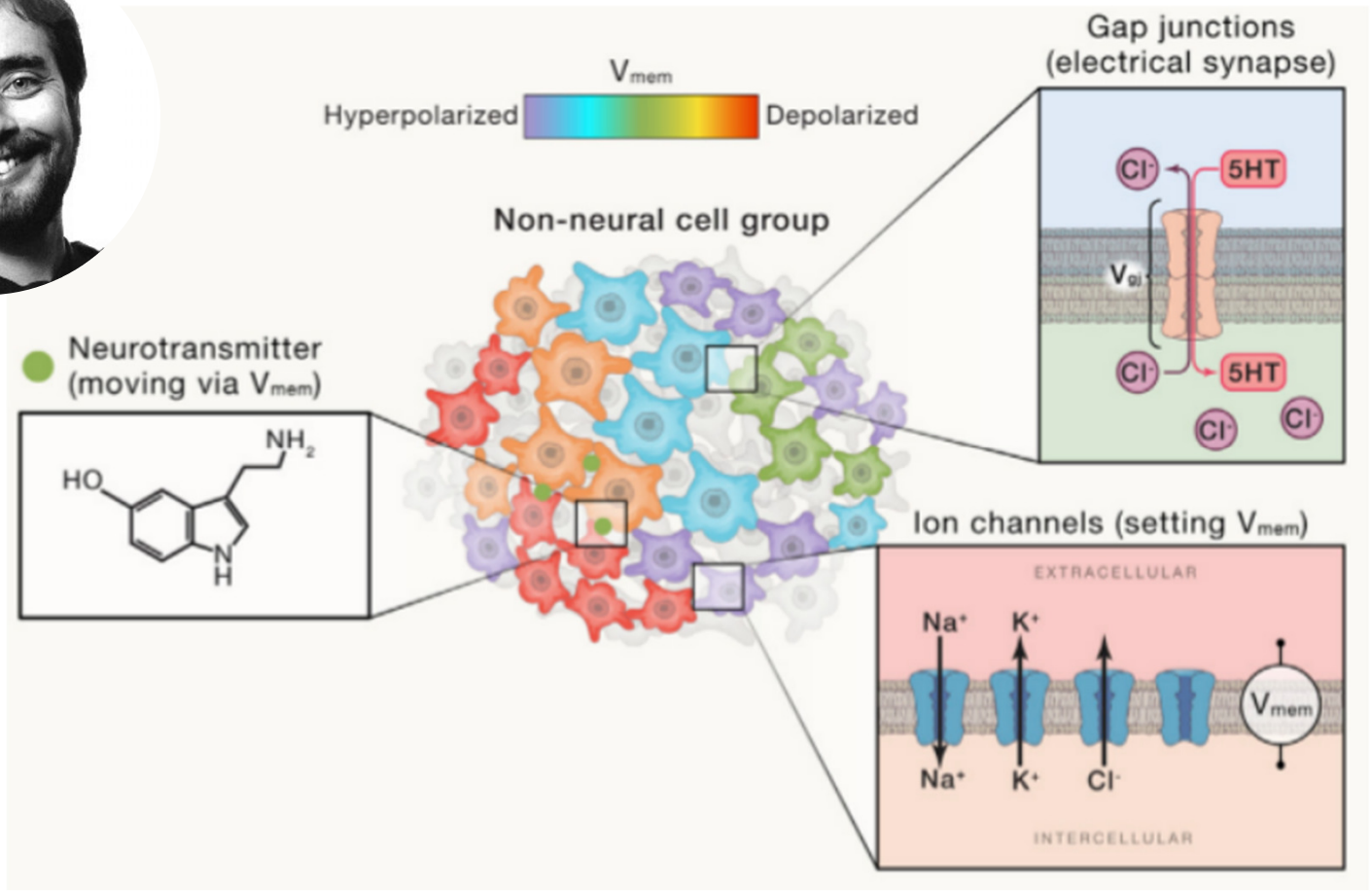
What are the consequences for (our) research at the CFisUC's Soft and Biological Matter group?

Where can **Physics** contribute?



Nia HT, Munn LL, Jain RK. Physical traits of cancer. Science. 2020;370(6516):eaaz0868. doi: 10.1126/science.aaz0868.

Michael Levin et al. Bioelectricity Lab at the Tufts University (regeneration and cancer)



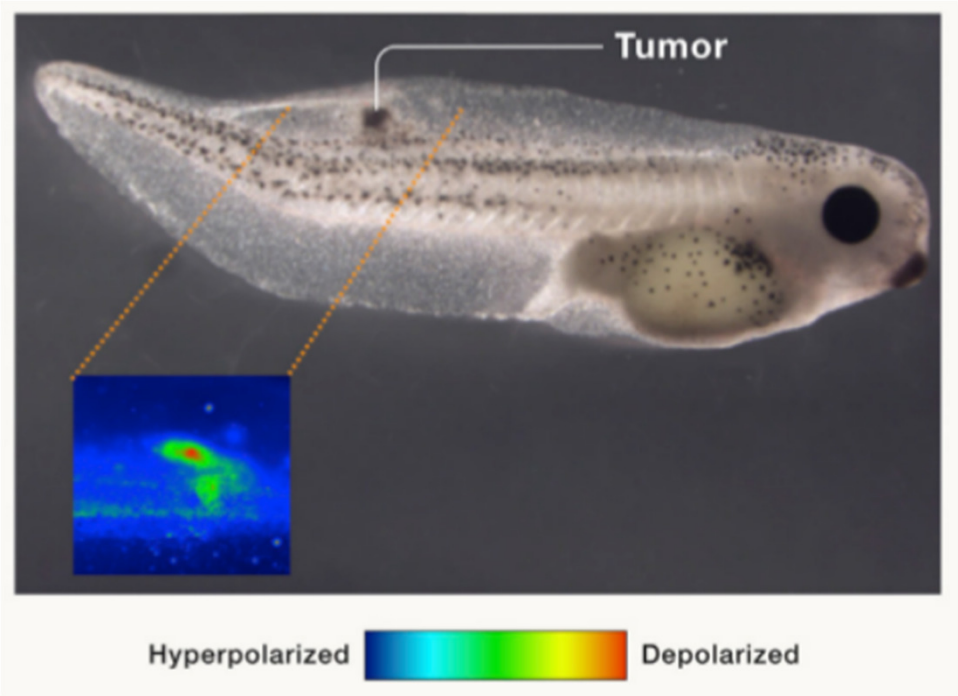
Levin M. Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer. Cell. 2021;184(8):1971-1989. doi: 10.1016/j.cell.2021.02.034.

The bioelectric hypothesis

(a clear bias, because we are physicists...)

The **Tissue organizing field** is the cells bioelectric communication and electric environment

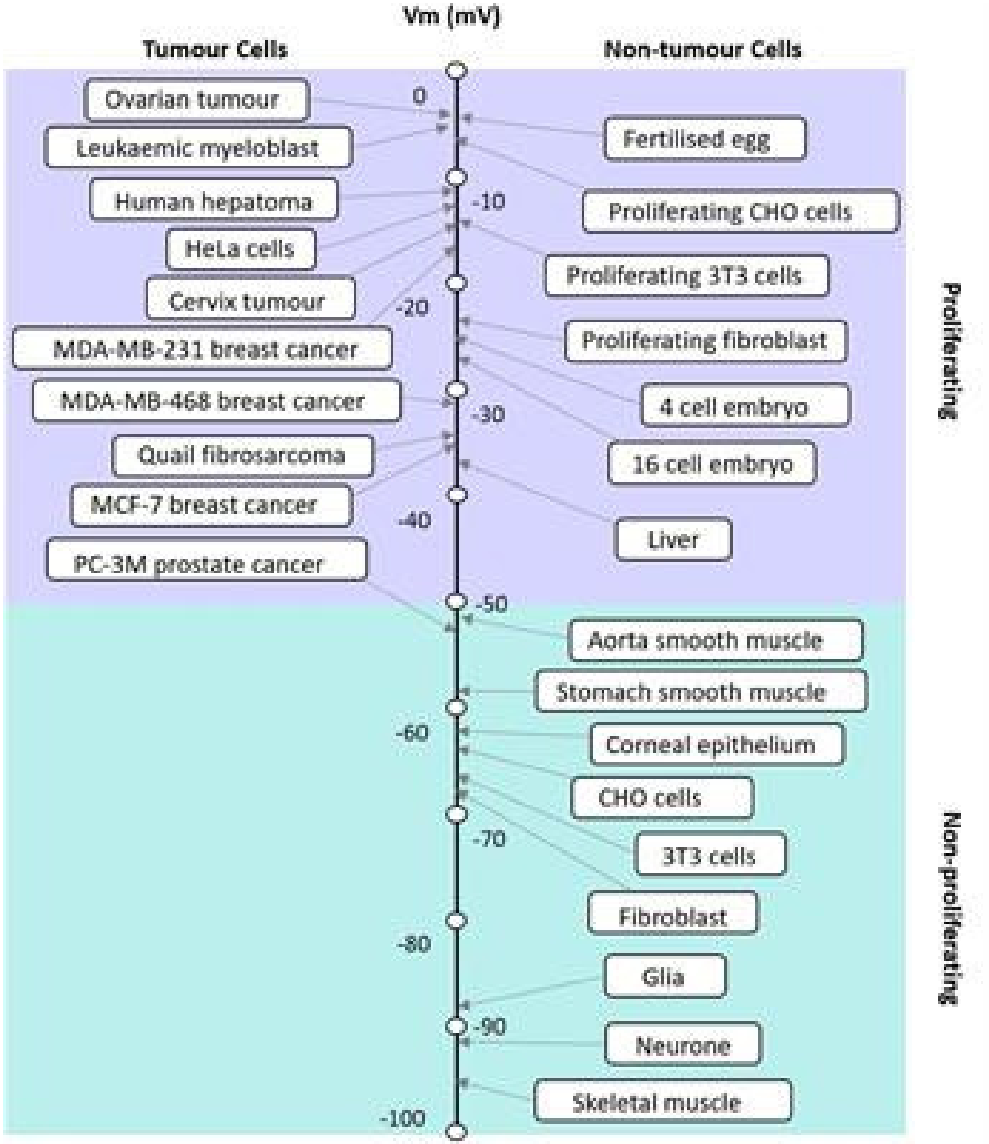
Involved in genomic regulation, as cell proliferation



Levin M. Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer. Cell. 2021;184(8):1971-1989. doi: 10.1016/j.cell.2021.02.034.

(Hyper)polarized cells are quiescent and depolarized cells are proliferative

Hypothesis: cancer initiation by cell membrane depolarization, which propagates in the tissue?

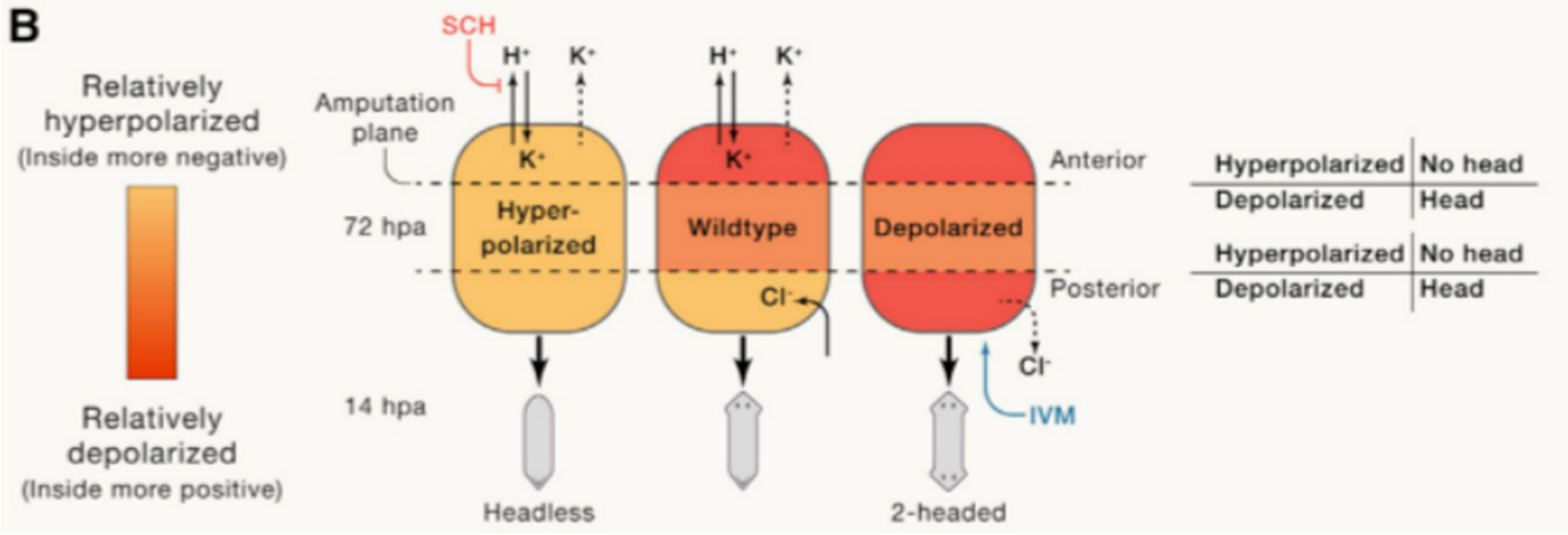


Abdul Kadir L, Stacey M, Barrett-Jolley R. Emerging Roles of the Membrane Potential: Action Beyond the Action Potential. Front Physiol. 2018;9:1661. doi: 10.3389/fphys.2018.01661

Performed fundamental regeneration experiments with planarian worm

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

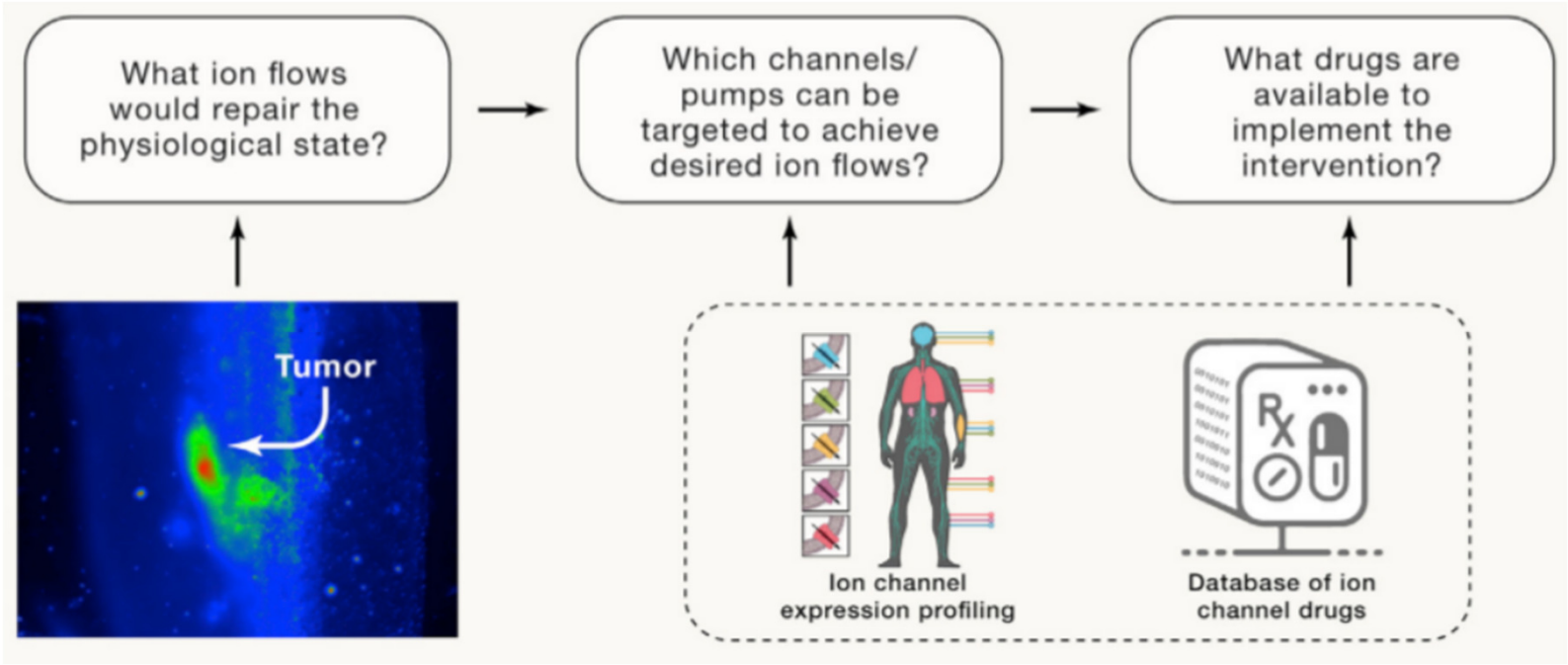
Change of tissue bioelectric **polarization** state by ionic channels manipulation drives the organism development



Levin M. Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer. Cell. 2021;184(8):1971-1989. doi: 10.1016/j.cell.2021.02.034.

The good news: the manipulation of ionic channels, pumps and gap junctions can change the cells/tissue polarization state

If bioelectricity is at the origin of cancer, its state is **reversible** (at least initially, electroceuticals)



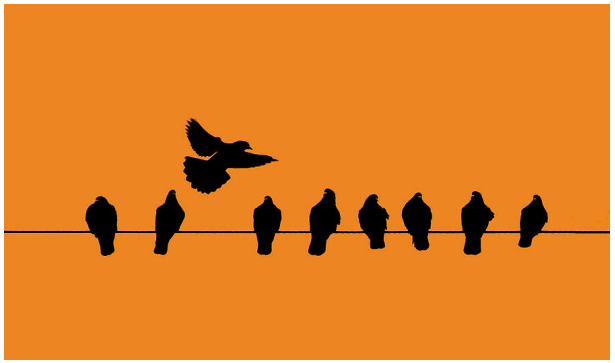
Levin M. Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer. Cell. 2021;184(8):1971-1989. doi: 10.1016/j.cell.2021.02.034.

Bioelectric research in CFisUC

Successive submission of exploratory projects on this area to Portuguese FCT (need a multidisciplinary evaluation)

The challenge of not fitting in the box (or in the right panel)

FCT
Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR



The Non Conformist is a photograph by Thomas Shanahan which was uploaded on August 15th, 2019. https://fineartamerica.com/featured/the-non-conformist-thomas-shanahan.html

Developing collaboration with FMUC (Filomena Botelho's Biophysics Lab), DCV (Paulo Rocha's Bioelectric Lab) and CNC (João Peça's Neuronal Circuits and Behavior Lab)



Some publications in cancer and bioelectric models and simulations in different settings

HYPOTHESIS AND THEORY article

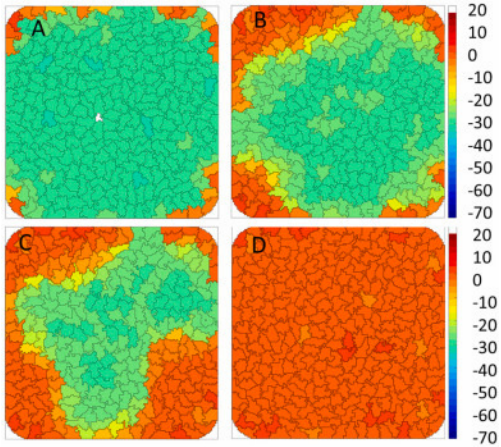
Front. Oncol., 15 April 2020
Sec. Molecular and Cellular Oncology
https://doi.org/10.3389/fonc.2020.00541

This article is part of the Research Topic
The Role of Epigenetic Modifications in Cancer Progression
View all 18 Articles >

Cell Reversal From a Differentiated to a Stem-Like State at Cancer Initiation

João Carvalho*

CFisUC, Department of Physics, University of Coimbra, Coimbra, Portugal



Article | Open Access | Published: 30 June 2021

A bioelectric model of carcinogenesis, including propagation of cell membrane depolarization and reversal therapies

Joao Carvalho

Scientific Reports **11**, Article number: 13607 (2021) | Cite this article

Article | Open Access | Published: 02 June 2022

A computational model of organism development and carcinogenesis resulting from cells' bioelectric properties and communication

Joao Carvalho

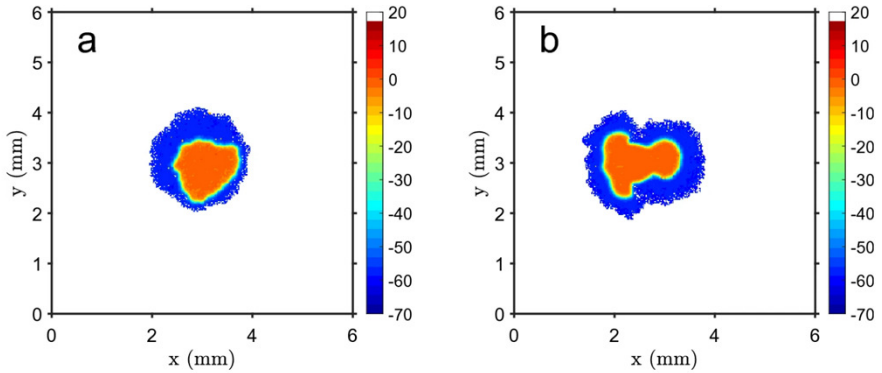
Scientific Reports **12**, Article number: 9206 (2022) | Cite this article

ELSEVIER

Journal of Theoretical Biology
Volume 557, 21 January 2023, 111338

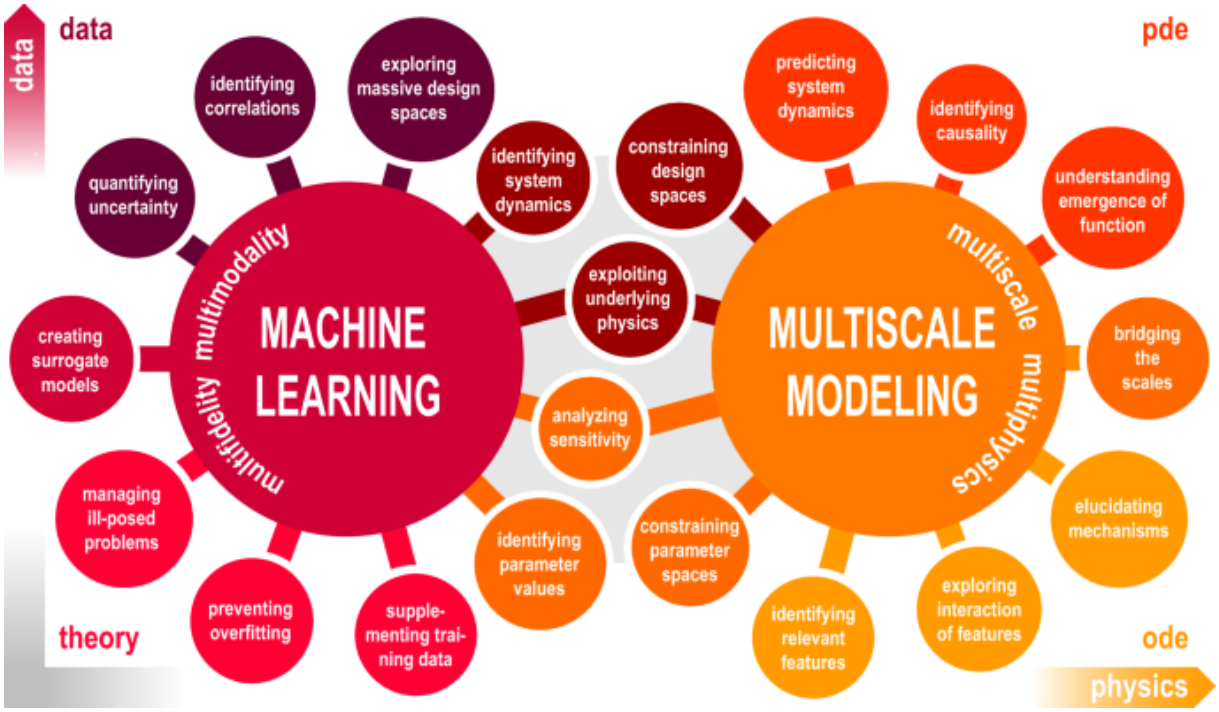
A computational model of cell membrane bioelectric polarization and depolarization, connected with cell proliferation, in different tissue geometries

Joao Carvalho



A brave new world of **cancer research** is ahead of us: how and when to move from the current (stagnant) paradigm?

Many obstacles to overcome to **open** cancer research landscape to new visitors and visions



Alber M, Buganza Tepole A, Cannon WR, De S, Dura-Bernal S, Garikipati K, Karniadakis G, Lytton WW, Perdikaris P, Petzold L, Kuhl E. Integrating machine learning and multiscale modeling-perspectives, challenges, and opportunities in the biological, biomedical, and behavioral sciences. NPJ Digit Med. 2019;2:115. doi: 10.1038/s41746-019-0193-y.

(Near) future cancer therapies for **precision oncology**: immunotherapy, genetic vectors… (with help from Artificial Intelligence tools)

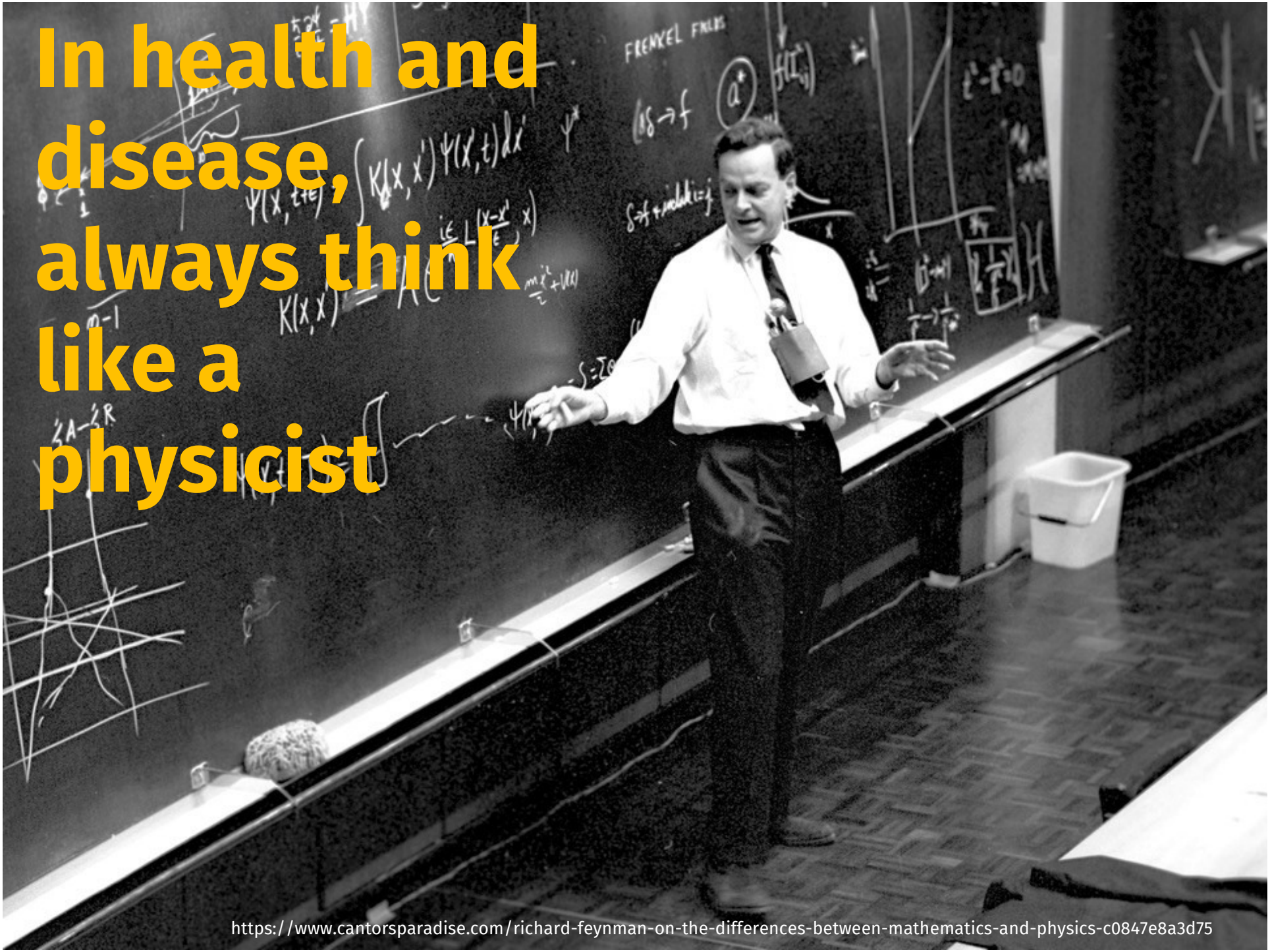
But at what cost and with which effectivity? (need to consider its accessibility, secondary effects…)

Take home messages

Cancer research needs a robust and (very) wide **multidisciplinary** approach

Not all hope is lost

In health and disease, always think like a physicist



https://www.cantorsparadise.com/richard-feynman-on-the-differences-between-mathematics-and-physics-c0847e8a3d75

‘There is nothing more practical than a good theory’ Kurt Lewin

(actually a psychologist!)

Lewin, K. (1952). Field theory in social science: Selected theoretical papers by Kurt Lewin. London: Tavistock.

Kurt Lewin - 1936, Iowa City, from the collection of Tomasz Kardaś, *in* https://history.easp.eu/people/lewin-kurt

Collaborators

CFisUC Rui Travasso, Marcos Gouveia, António Cardoso



Bioelectricity Lab Paulo Rocha

Biophysics Lab Filomena Botelho, Margarida Abrantes, Salomé Pires



Neuronal Circuits and Behavior Lab João Peça, Ana Maria Cardoso


Tufts University Michael Levin, Carlos Sonnenschein, Ana Soto



MD Anderson Cancer Center Jinsong Liu, **National Cancer Institute** Stuart Baker



Thank you for your time and patience!
All questions welcome
https://openai.com/dall-e-2/

https://www.mdanderson.org/cancerwise.html