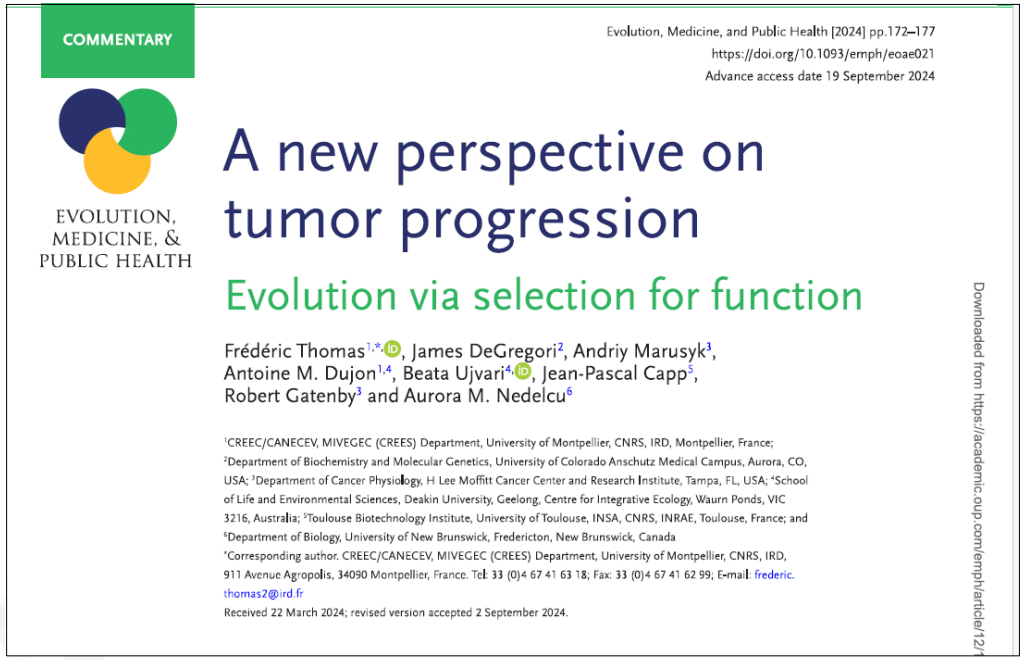
A New Perspective on Tumor progression

Frédéric THOMAS



COMMENTARY

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Evolution, Medicine, and Public Health [2024] pp.172–177
https://doi.org/10.1093/emph/eoae021
Advance access date 19 September 2024

A new perspective on tumor progression

Evolution via selection for function

Frédéric Thomas[1,*], James DeGregori[2], Andriy Marusyk[3], Antoine M. Dujon[1,4], Beata Ujvari[4], Jean-Pascal Capp[5], Robert Gatenby[3] and Aurora M. Nedelcu[6]

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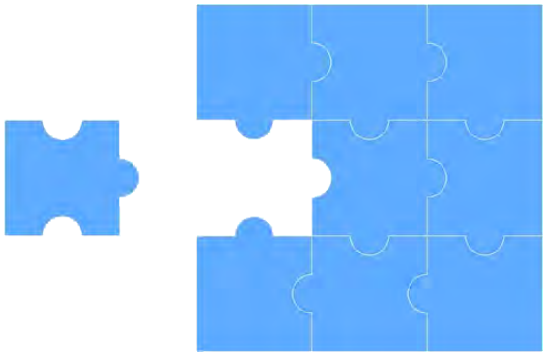
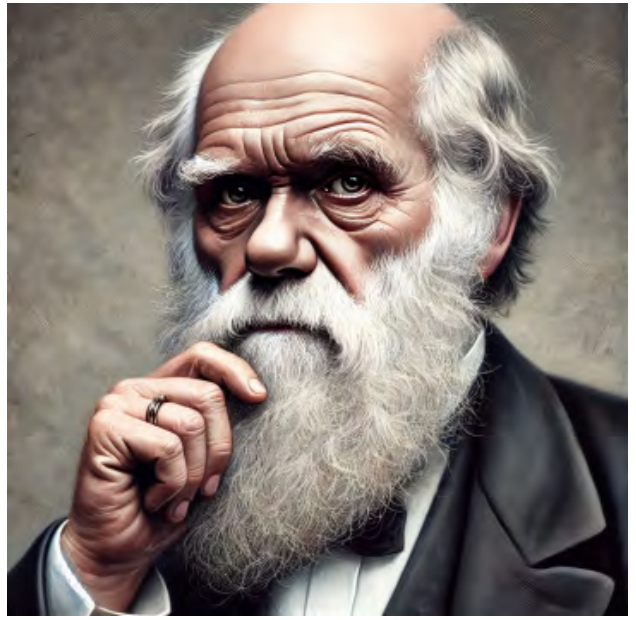
Received 22 March 2024; revised version accepted 2 September 2024.

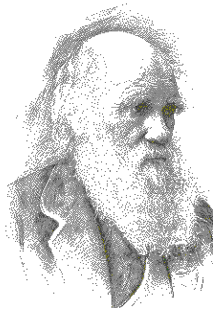




“Nothing in Biology Makes Sense Except in the Light of Evolution”

- Theodosius Dobzhansky (1973)

CANCER



Cancer is a Disease of **Clonal Evolution** Within the Body

Nature 1975

Nature Vol. 255 May 15 1975

review article

Mutation selection and the natural history of cancer

John Cairns*

Survival of the rapidly renewing tissues of long-lived animals lik... against the natural selection of fitter variant cells (that is, th... This article discusses three possible protective mechanisms and s... features of the natural history of certain common cancers of ...

We are accustomed to thinking of the combination of natural variation and natural selection as a force for the good, that creates and maintains the fittest in a species and discards the unfit. This is the fundamental theorem of biology. But when we turn from the competition between the individuals of a species to the competition between the individual cells within a single animal, we see that natural selection has now become a liability. The dangerous mutations are now those that confer on a cell an increased survival advantage. We may therefore expect to find, especially in animals which undergo continual cell multiplication during their adult life, the evolution of mechanisms that protect the animal from being taken over by any "fitter"

tumours of ... cells (the sarcomas and ... dominately a disease of the ... elia (Table 1).

This paper ... programme of cell renewal in ... minise the risk from somatic ... features of natural carcino... ms of such a programme.

1 Between cells

Science 1976

...he Clonal Evolution of ...umor Cell Populations

...ability permits stepwise selection ...and underlies tumor progression.

Peter C. Nowell

...s from one ...nges in the ...a neoplastic ... are related ...practical interest. That neoplasms frequently develop as a clone from a single cell of origin is a concept gaining increased acceptance, and various investigators, beginning with chromosome studies on trans-

Despite this wide recognition that most neoplasms have a unicellular origin and clonal growth pattern, relatively little emphasis has been placed on the developmental evolution of tumor cell populations, and the apparent genetic instability underlying the sequential acquisition of biological characteristics that we associate with tumor progression. This article suggests a model for the evolution of tumor cell populations in terms of stepwise genetic variation, and considers some of the evidence that this model is a valid one for most mammalian neoplasms. Some of the theoretical and practical implications of this concept of

...ariants are eliminated, be... metabolic disadvantage or immunologic destruction (for example, T_s), but occasionally one has an additional selective advantage with respect to the original tumor cells as well as normal cells, and this mutant becomes the precursor of a new predominant subpopulation.

Over time, there is sequential selection by an evolutionary process of sublines which are increasingly abnormal, both genetically and biologically. Because this sequence is not completely random, certain similarities are acquired by different tumors as they progress; but divergence also occurs as local conditions in each neoplasm differently effect the emergence of variant sublines. Ultimately, the fully developed malignancy as it appears ... has a unique, aneuploi... ated with aberrant ... and specific antigenic ... it also has the capabili... ation as long as the tu... relative positions in ... an solid tumors ... as well as certain ... dicated in Fig. 1, along ... ical characteristics ... various stages of neoplastic development.

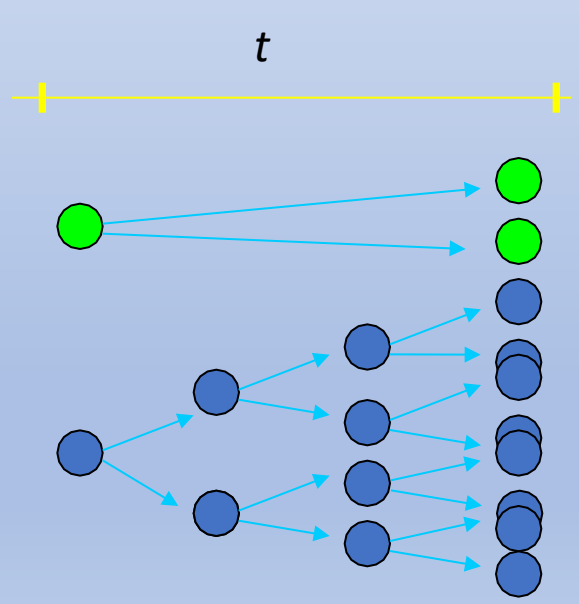
In the following sections, particular aspects of the model are considered in more detail, with major emphasis on evi-

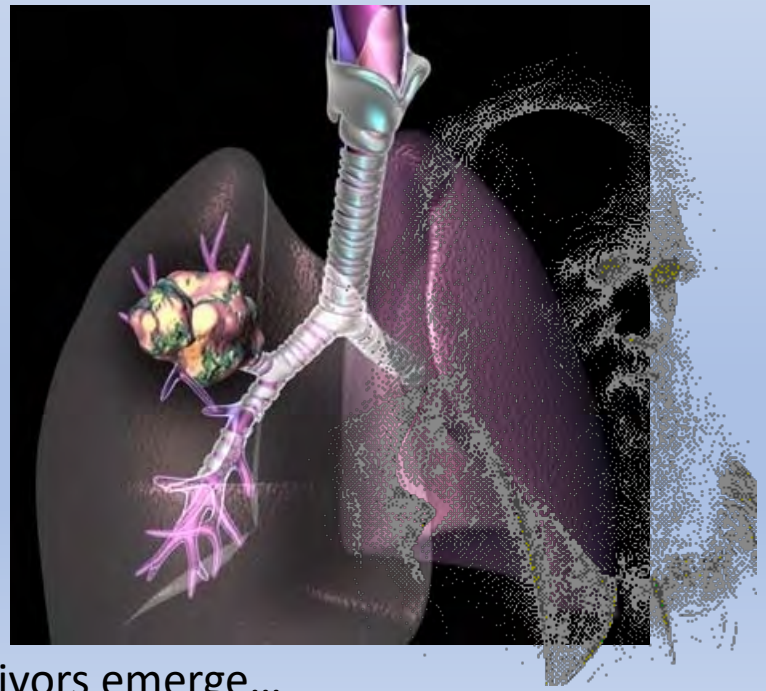
Natural selection

- Natural selection occurs in neoplasms because (epi) genetic mutations generate heritable variation, and some mutations confer a selective advantage or disadvantage on the cell

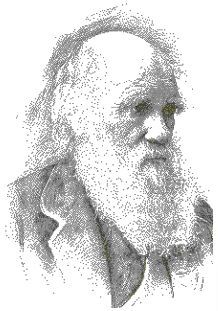
- Resources are limited

Differential reproductive success between clones

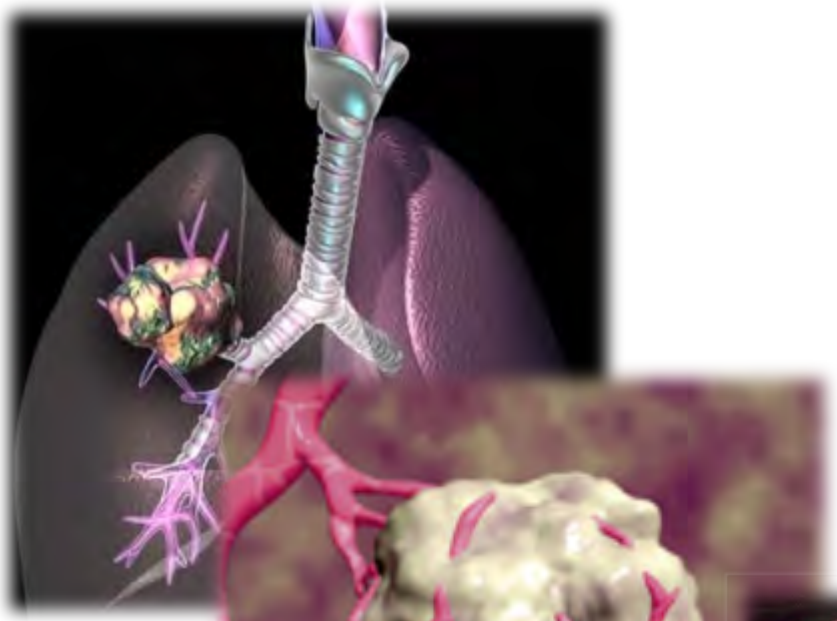


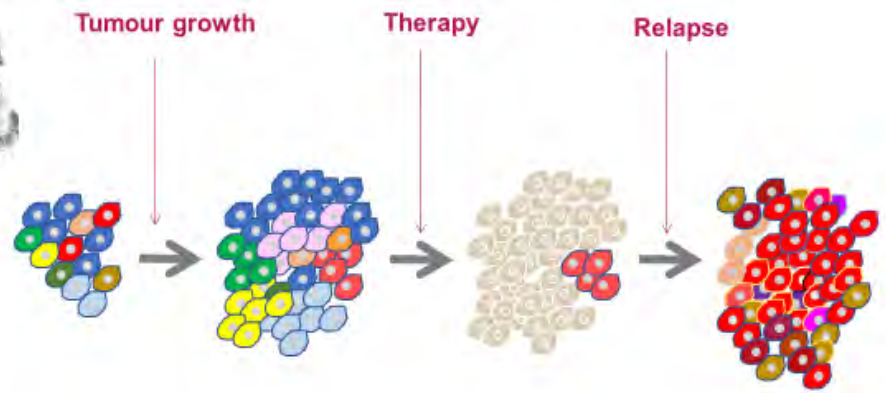


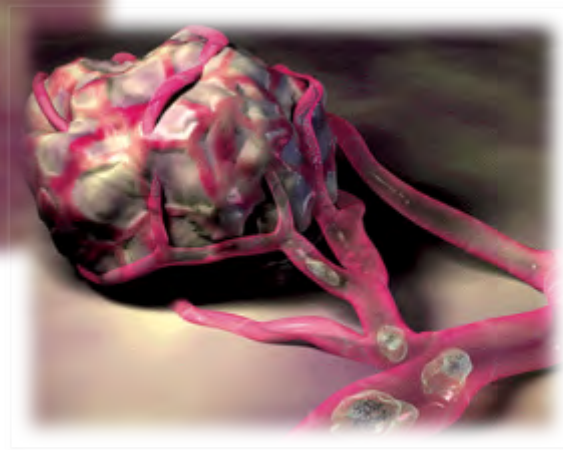
Best adapted survivors emerge…



Natural Selection / Oncogenic Selection







2021

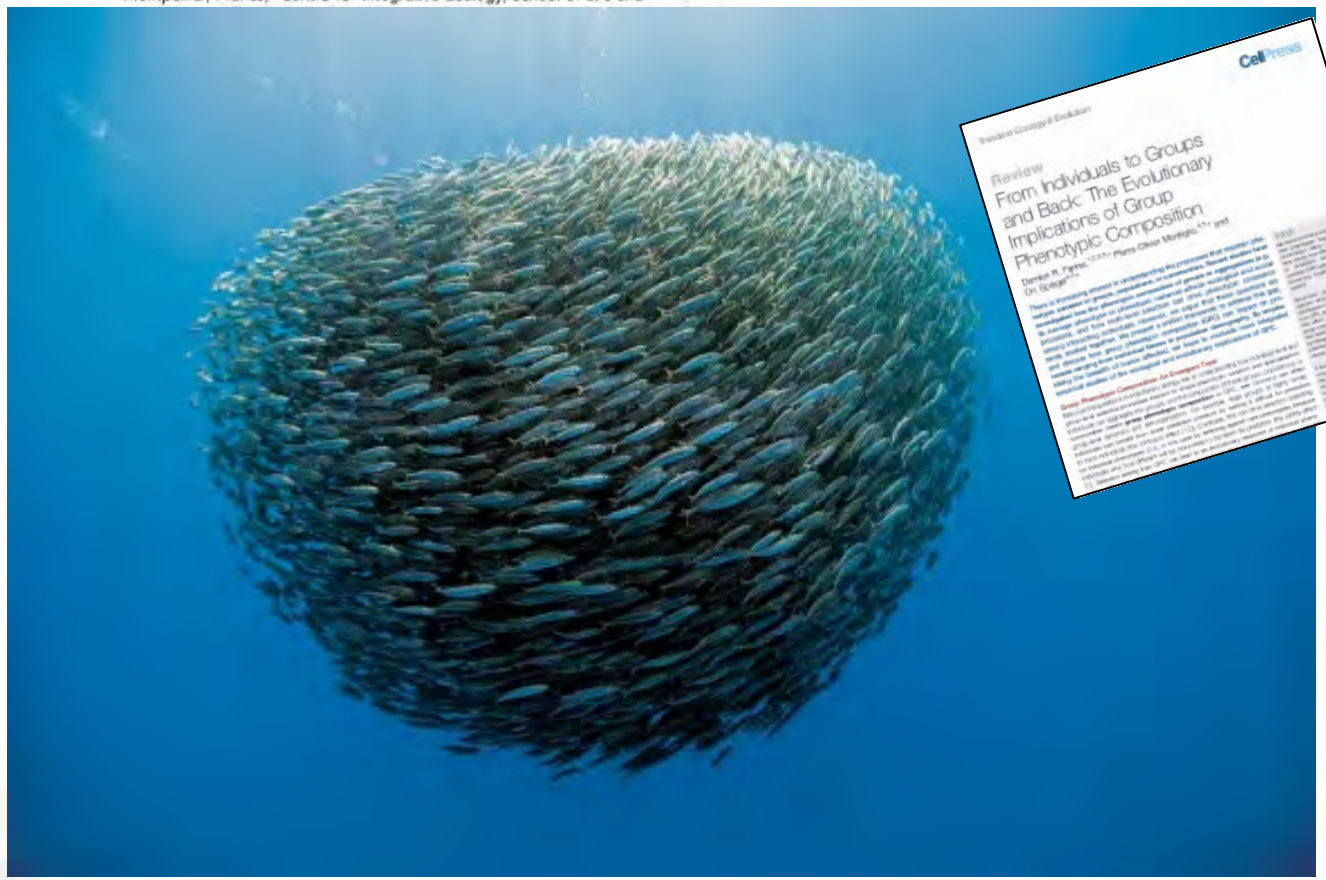
eLife REVIEW ARTICLE

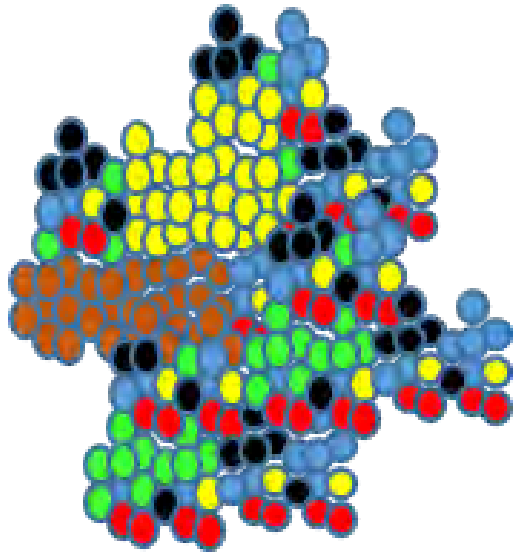
Group phenotypic composition in cancer

Jean-Pascal Capp[1†], James DeGregori[2†], Aurora M Nedelcu[3†], Antoine M Dujon[4,5], Justine Boutry[6], Pascal Pujol[4], Catherine Alix-Panabières[4,6], Rodrigo Hamede[7], Benjamin Roche[4], Beata Ujvari[8,7†], Andriy Marusyk[9†], Robert Gatenby[9†], Frédéric Thomas[4†*]

[1]Toulouse Biotechnology Institute, University of Toulouse, INSA, CNRS, INRAE, Toulouse, France; [2]Department of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus, Aurora, United States; [3]Department of Biology, University of New Brunswick, Fredericton, New Brunswick, Canada; [4]CREEC/CANECEV, MIVEGEC (CREES), University of Montpellier, CNRS, IRD, Montpellier, France; [5]Centre for Integrative Ecology, School of Life and

Cells but clusters of cells too…





Group Phenotypic Composition
GPC

An appropriate spatio-functional distribution of intra-tumoral heterogeneity conducive to tumor progression

Tumors capable of progressing are those that possess a suitable group phenotypic composition (GPC)

eLife

Group phenotypic compos

Jean-Pascal Capp[1†], James DeGregori[2†], Aurora M
Justine Boutry[3], Pascal Pujol[4], Catherine Alix-Panal
Benjamin Roche[4], Beata Ujvari[5,7†], Andriy Marusyk
Frédéric Thomas[4†*]

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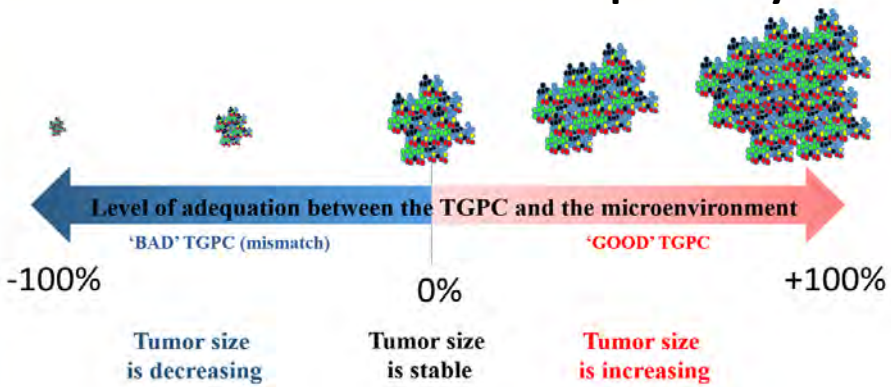
Environmental Sciences, Deakin University, Geelong
Human Circulating Cells (LCCRH), University Medica
Montpellier, France; [7]School of Natural Sciences, Ur
Australia; [8]Department of Cancer Physiology, H Lee Moffitt Cancer Center and
Research Institute, Tampa, United States

Abstract Although individual cancer cells are generally considered the Darwinian units of selection in malignant populations, they frequently act as members of groups where fitness of the group cannot be reduced to the average fitness of individual group members. A growing body of studies reveals limitations of reductionist approaches to explaining biological and clinical

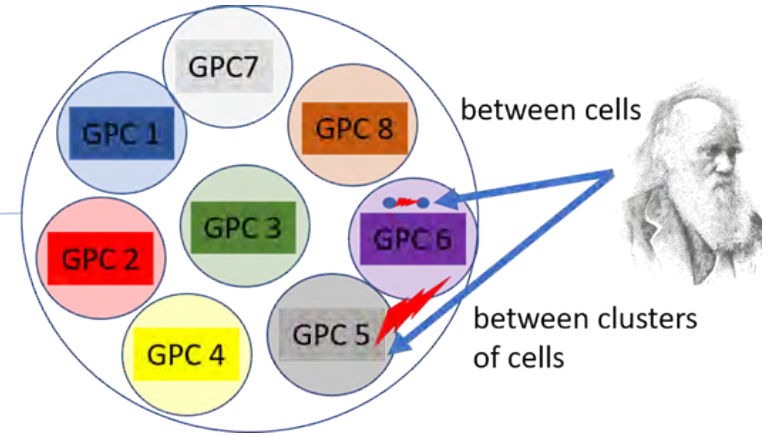
Levels of tumoral GPC optimality

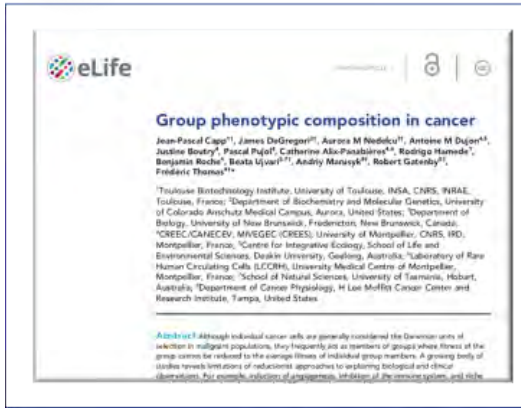


So it is widely accepted that tumorigenesis is a process that can be explained in its entirety by Darwinian processes essentially based on interactions between cells and groups of cells.

1
Between cells

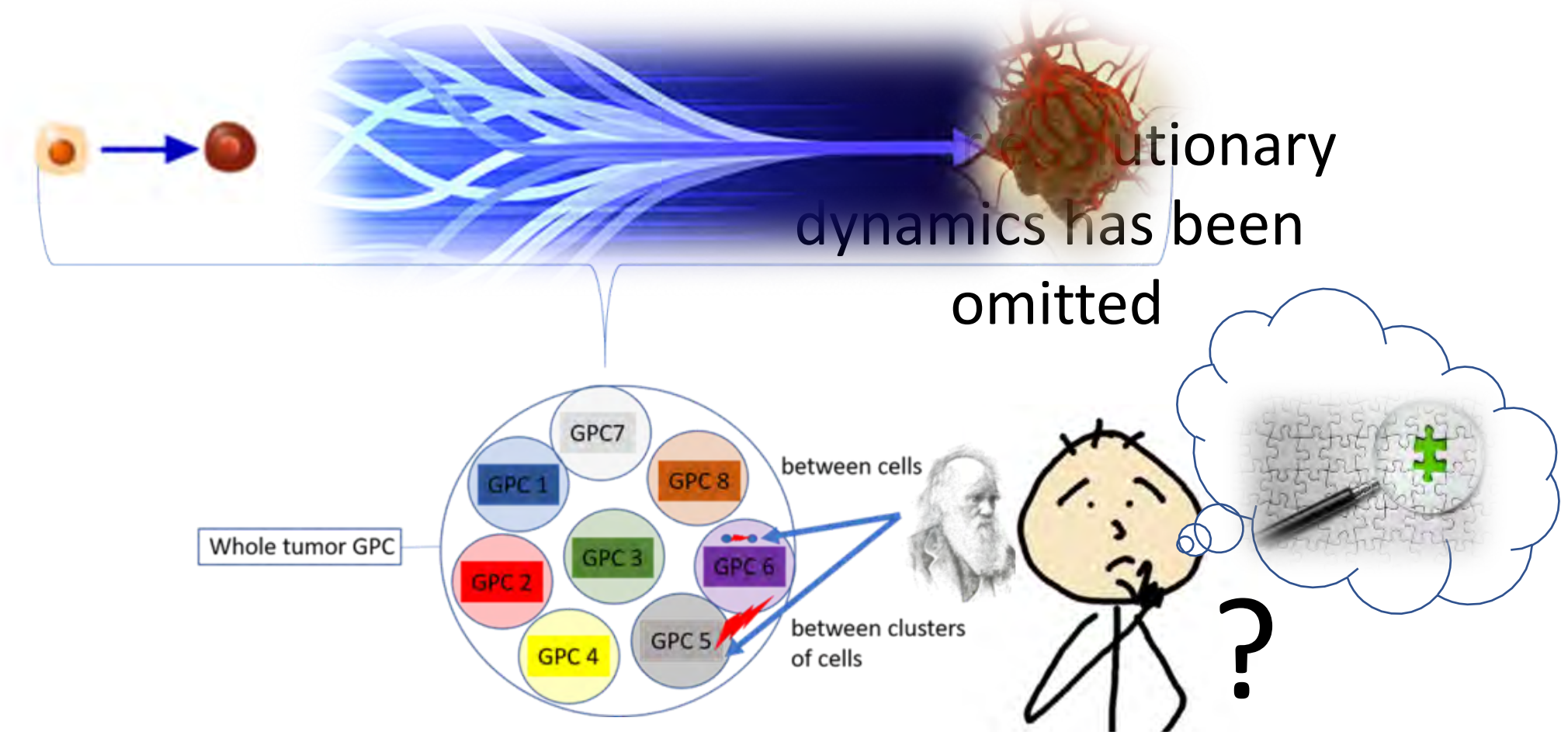
Whole tumor GPC





2
Between cells
+ Clusters of cells

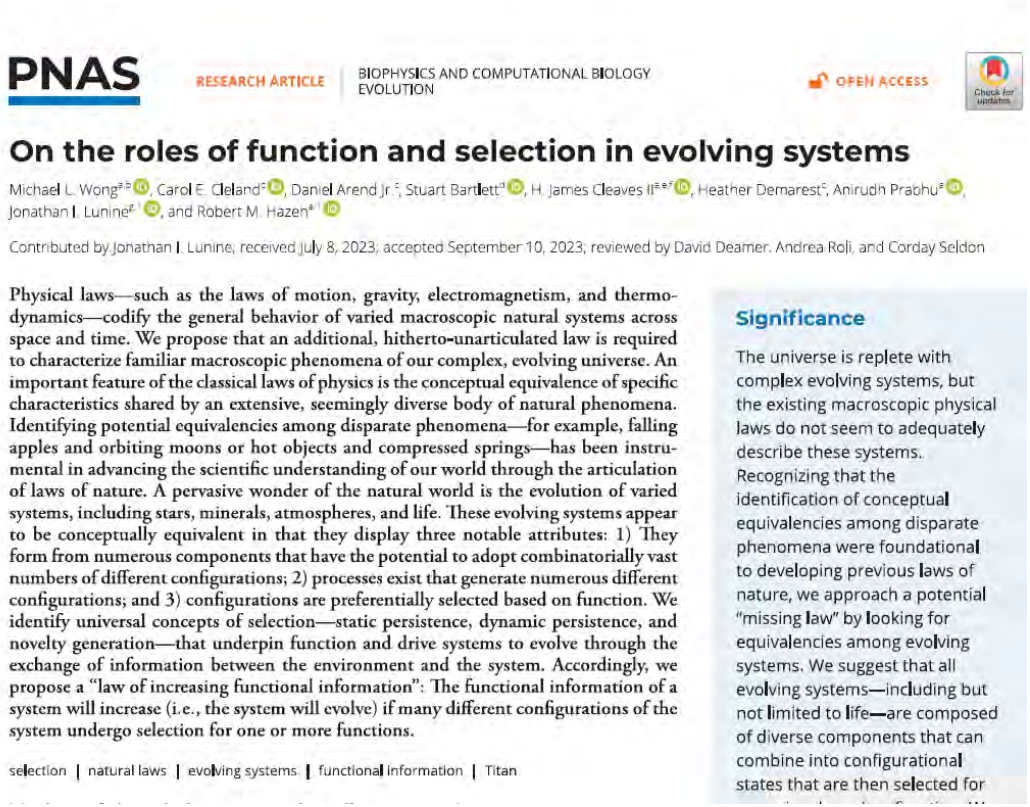
The aim today is to challenge this point of view, by stating that…



…utionary dynamics has been omitted

Law of increasing functional information

La loi de l'augmentation de l'information fonctionnelle



PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY EVOLUTION OPEN ACCESS

On the roles of function and selection in evolving systems

Michael L. Wong[a,b], Carol E. Cleland[c], Daniel Arend Jr.[c], Stuart Bartlett[a], H. James Cleaves II[a,e,f], Heather Demarest[c], Anirudh Prabhu[a], Jonathan I. Lunine[d,1], and Robert M. Hazen[a,1]

Contributed by Jonathan I. Lunine; received July 8, 2023; accepted September 10, 2023; reviewed by David Deamer, Andrea Roli, and Corday Seldon

Physical laws—such as the laws of motion, gravity, electromagnetism, and thermodynamics—codify the general behavior of varied macroscopic natural systems across space and time. We propose that an additional, hitherto-unarticulated law is required to characterize familiar macroscopic phenomena of our complex, evolving universe. An important feature of the classical laws of physics is the conceptual equivalence of specific characteristics shared by an extensive, seemingly diverse body of natural phenomena. Identifying potential equivalencies among disparate phenomena—for example, falling apples and orbiting moons or hot objects and compressed springs—has been instrumental in advancing the scientific understanding of our world through the articulation of laws of nature. A pervasive wonder of the natural world is the evolution of varied systems, including stars, minerals, atmospheres, and life. These evolving systems appear to be conceptually equivalent in that they display three notable attributes: 1) They form from numerous components that have the potential to adopt combinatorially vast numbers of different configurations; 2) processes exist that generate numerous different configurations; and 3) configurations are preferentially selected based on function. We identify universal concepts of selection—static persistence, dynamic persistence, and novelty generation—that underpin function and drive systems to evolve through the exchange of information between the environment and the system. Accordingly, we propose a "law of increasing functional information": The functional information of a system will increase (i.e., the system will evolve) if many different configurations of the system undergo selection for one or more functions.

selection | natural laws | evolving systems | functional information | Titan

Significance

The universe is replete with complex evolving systems, but the existing macroscopic physical laws do not seem to adequately describe these systems. Recognizing that the identification of conceptual equivalencies among disparate phenomena were foundational to developing previous laws of nature, we approach a potential "missing law" by looking for equivalencies among evolving systems. We suggest that all evolving systems—including but not limited to life—are composed of diverse components that can combine into configurational states that are then selected for

Three types of functions according To Wong et al. 2024:

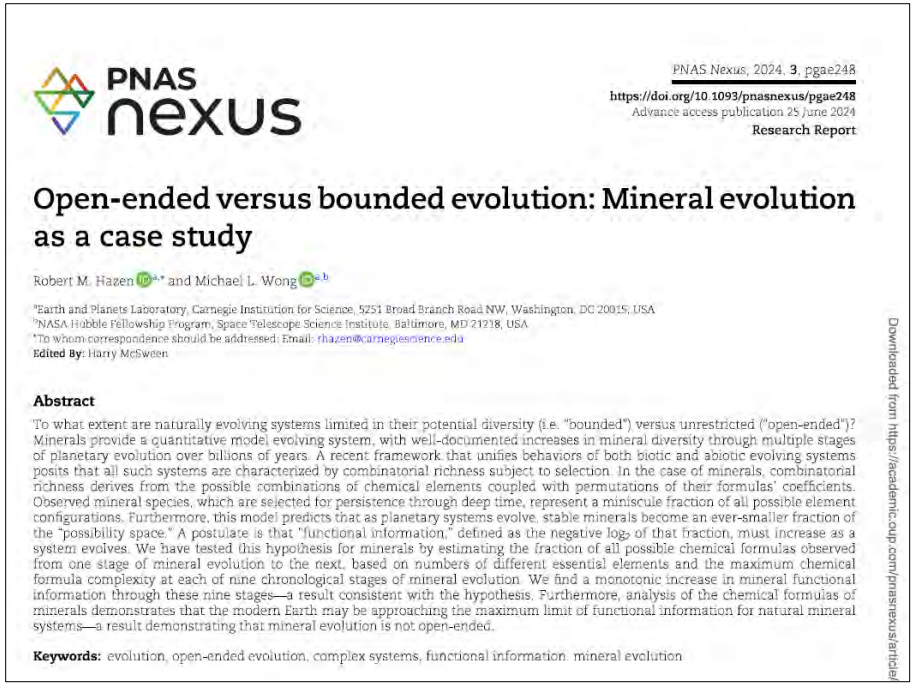
Static persistence

Dynamic persistence

Novelty generation

This law of increasing functional information, expanded Charles Darwin's theory of evolution by natural selection to include non-living systems.

Minerals consistently become more complex over time when subject to selection pressures



PNAS nexus

PNAS Nexus, 2024, 3, pgae248
https://doi.org/10.1093/pnasnexus/pgae248
Advance access publication 25 June 2024
Research Report

Open-ended versus bounded evolution: Mineral evolution as a case study

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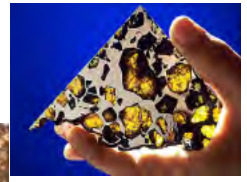
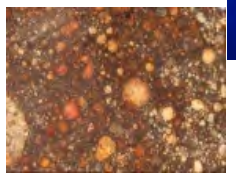
[b]NASA Hubble Fellowship Program, Space Telescope Science Institute, Baltimore, MD 21218, USA
*To whom correspondence should be addressed: Email: rhazen@carnegiescience.edu
Edited By: Harry McSween

Abstract

To what extent are naturally evolving systems limited in their potential diversity (i.e. "bounded") versus unrestricted ("open-ended")? Minerals provide a quantitative model evolving system, with well-documented increases in mineral diversity through multiple stages of planetary evolution over billions of years. A recent framework that unifies behaviors of both biotic and abiotic evolving systems posits that all such systems are characterized by combinatorial richness subject to selection. In the case of minerals, combinatorial richness derives from the possible combinations of chemical elements coupled with permutations of their formulas' coefficients. Observed mineral species, which are selected for persistence through deep time, represent a miniscule fraction of all possible element configurations. Furthermore, this model predicts that as planetary systems evolve, stable minerals become an ever-smaller fraction of the "possibility space." A postulate is that "functional information," defined as the negative $\log_2$ of that fraction, must increase as a system evolves. We have tested this hypothesis for minerals by estimating the fraction of all possible chemical formulas observed from one stage of mineral evolution to the next, based on numbers of different essential elements and the maximum chemical formula complexity at each of nine chronological stages of mineral evolution. We find a monotonic increase in mineral functional information through these nine stages—a result consistent with the hypothesis. Furthermore, analysis of the chemical formulas of minerals demonstrates that the modern Earth may be approaching the maximum limit of functional information for natural mineral systems—a result demonstrating that mineral evolution is not open-ended.

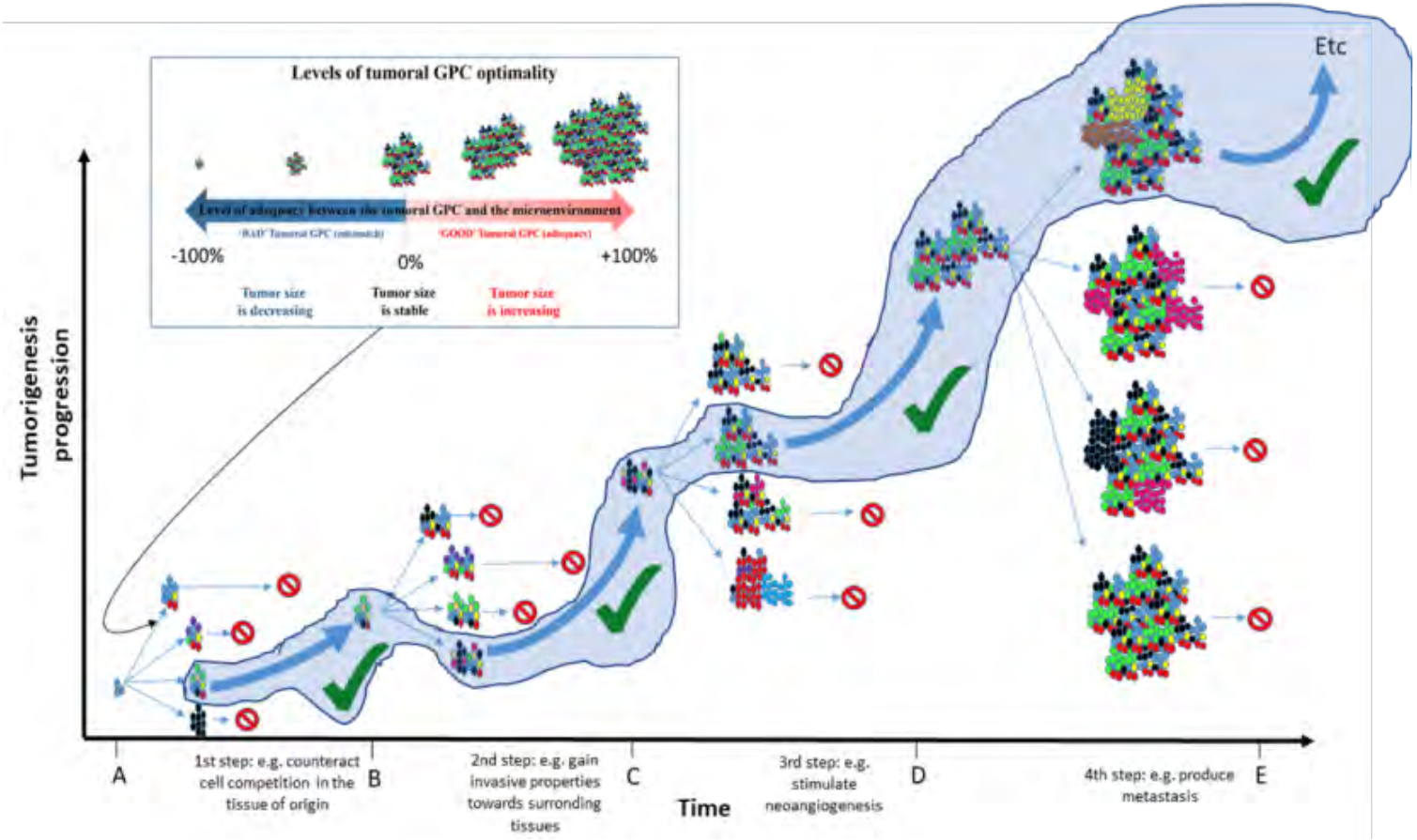
Keywords: evolution, open-ended evolution, complex systems, functional information, mineral evolution





Over a period of more than 4.6 billion years, starting with the earliest known minerals from before Earth formed around 4.54 billion years ago and ending with all of the minerals on our planet today, **the number of mineral types increased from 27 to around 9,000.** This increase in Earth's mineral complexity also occurred at each mineral evolution stage — the first stage being the formation of the earliest minerals and the final stage being modern-day Earth, where mineral creation is facilitated by life.

The ability to develop a favorable GPC is thus subject to selection



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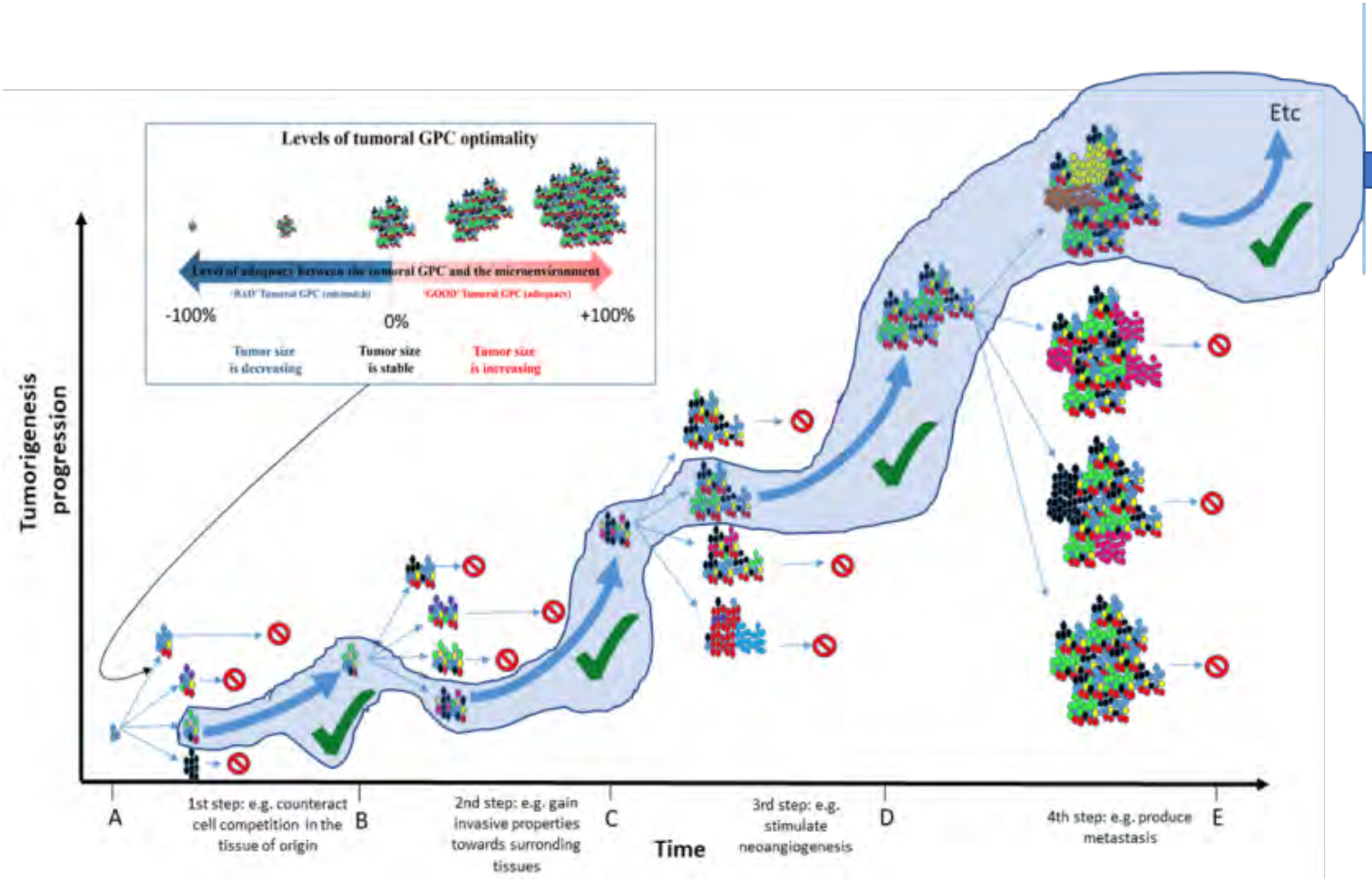
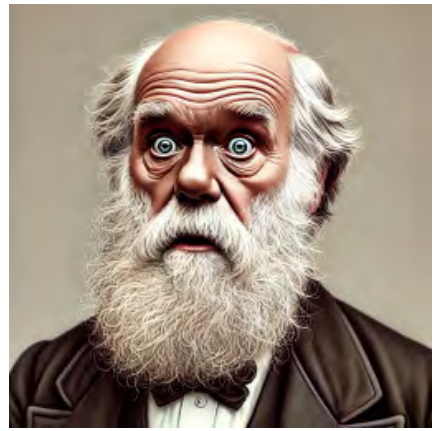
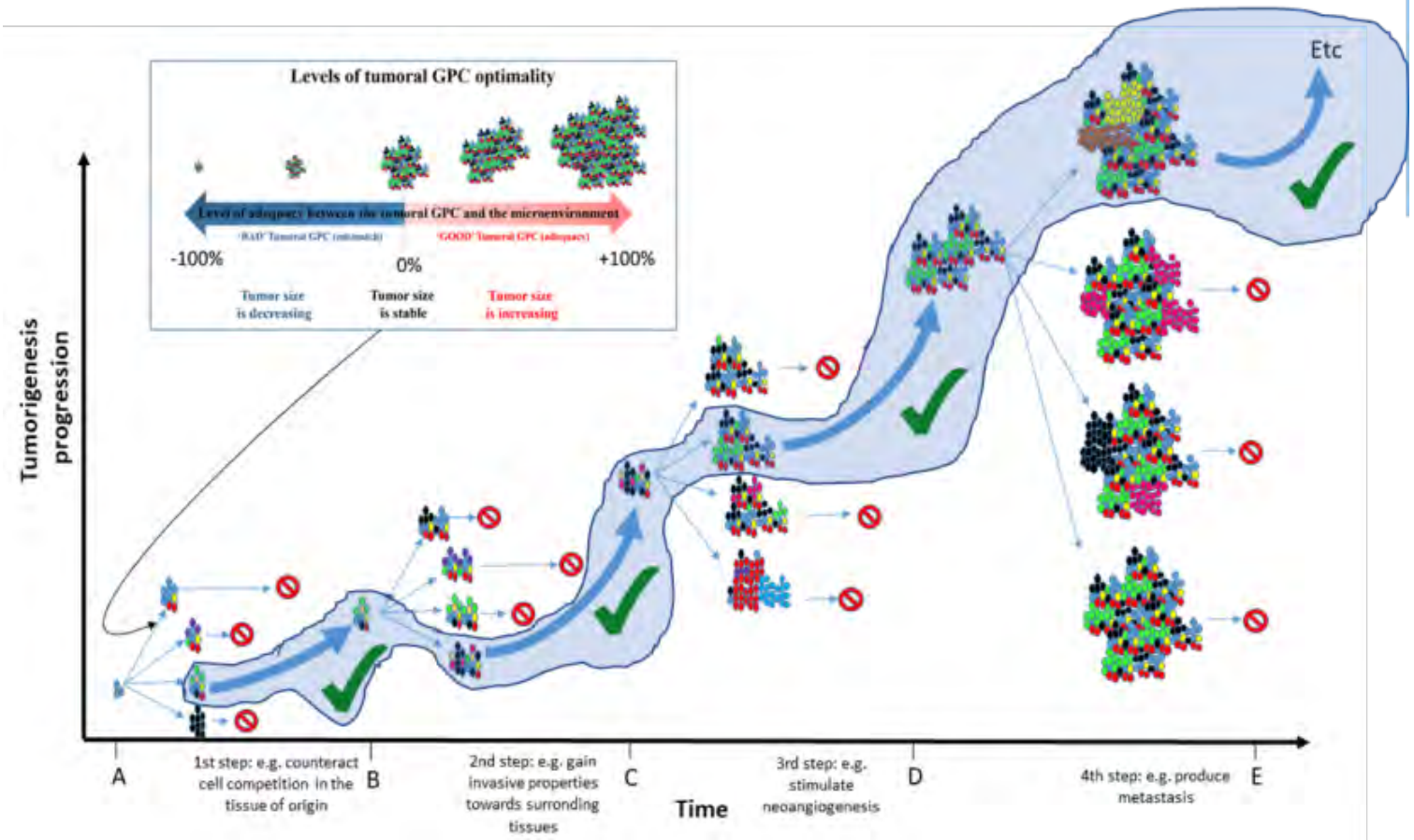


Selective process

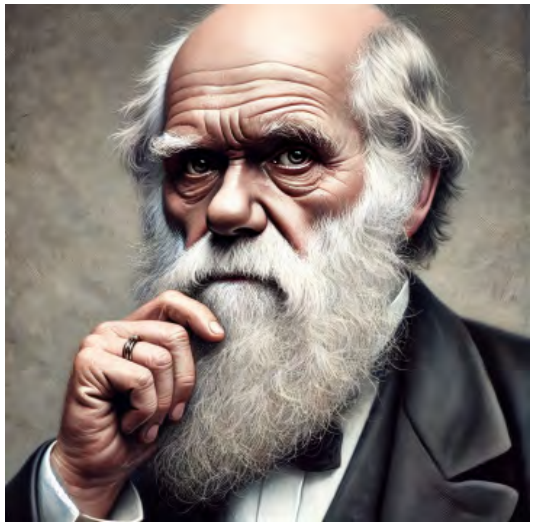
But NOT a classical Darwinian one !



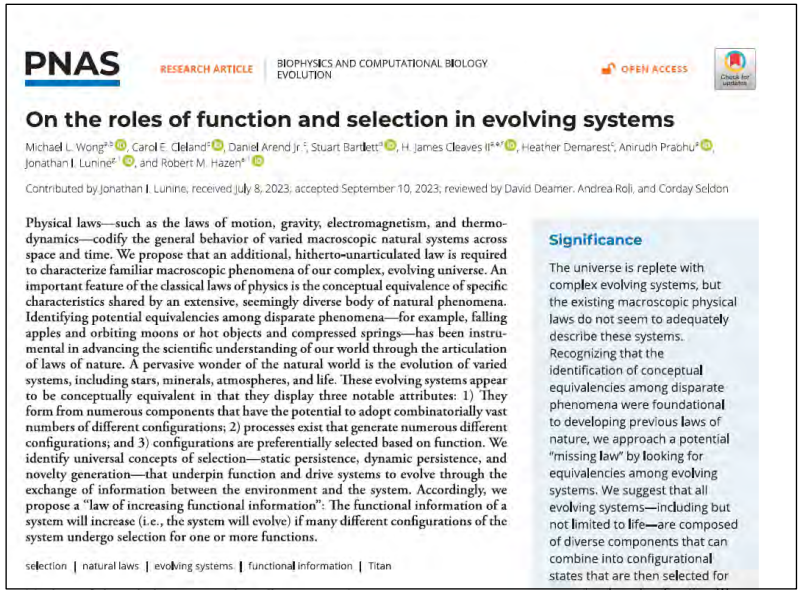
There is no notion of heritability or reproductive success, etc. Tumors are not in competition…



Yet, they evolve…



Tumor functionality can include either of the three types of functions envisioned by Wong et al.: **static persistence**, **dynamic persistence**, and **novelty generation**.



PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY EVOLUTION | OPEN ACCESS

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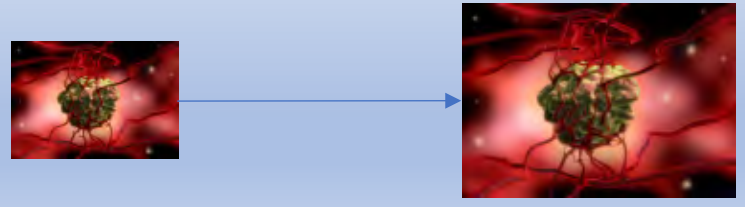
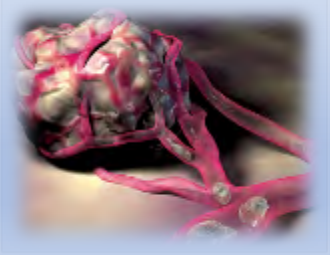
For instance, the ability of a tumor to maintain its size (through adaptively changing its GPC) in response to immune attacks and microenvironmental changes can be viewed as selection for "**static persistence**"

whereas its growth in response to various intra-tumour and microenvironmental changes (e.g., through increased plasticity, inducing angiogenesis) might involve selection for "**dynamic persistence**"



Similarly, the acquisition of the ability to invade and migrate (i.e., a novel capability) can be considered the result of selection for "**novelty generation**".



Tumors progress through selection based on function

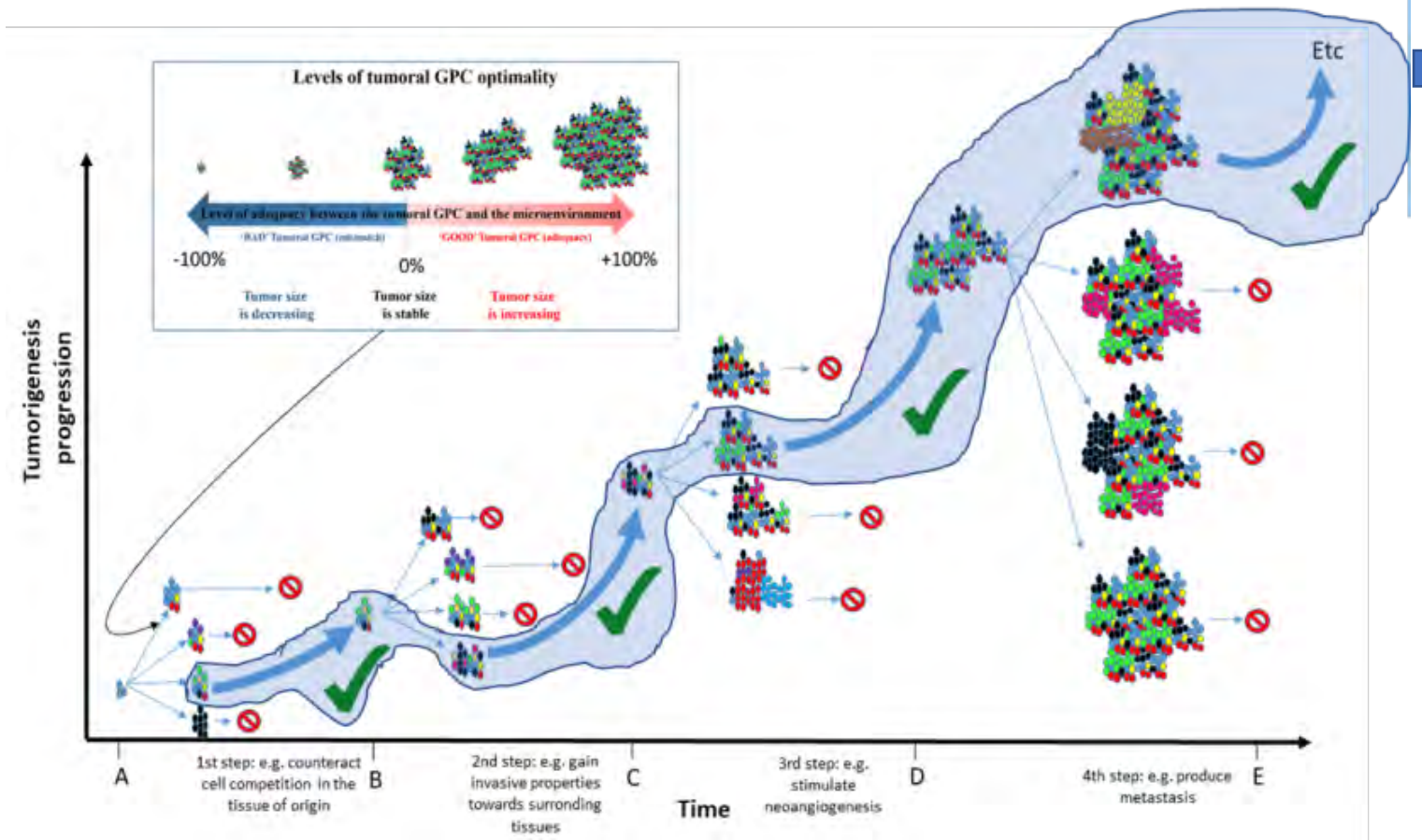

COMMENTARY

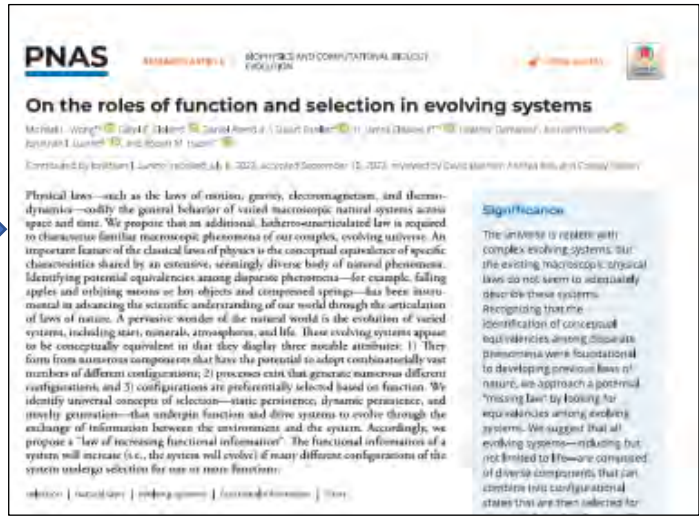
EVOLUTION, MEDICINE, & PUBLIC HEALTH

A new perspective on tumor progression

Evolution via selection for function

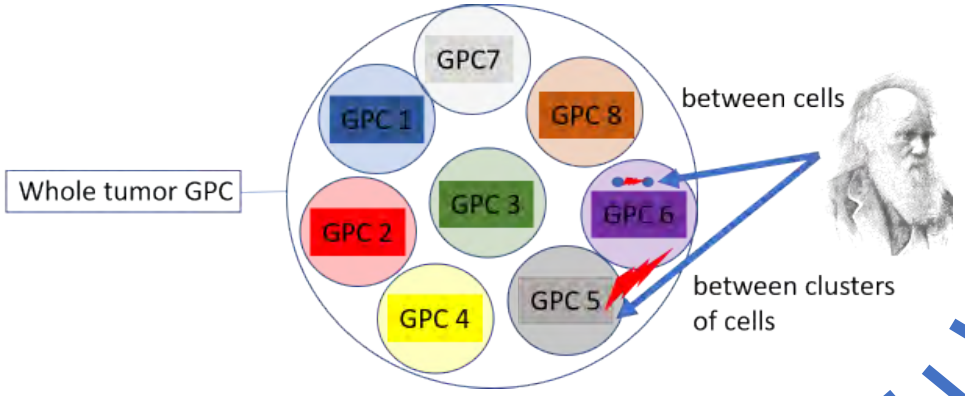
Frédéric Thomas, James DeGregori, Andriy Marusyk, Antoine M. Dujon, Beata Ujvari, Jean-Pascal Capp, Robert Gatenby and Aurora M. Nedelcu

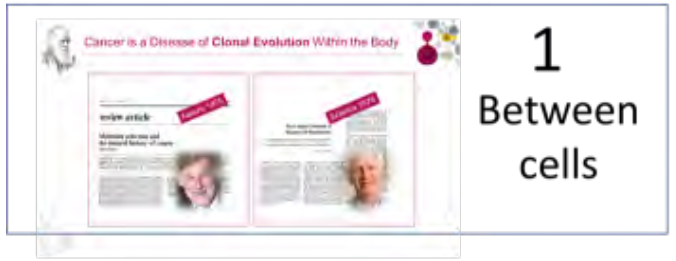



PNAS

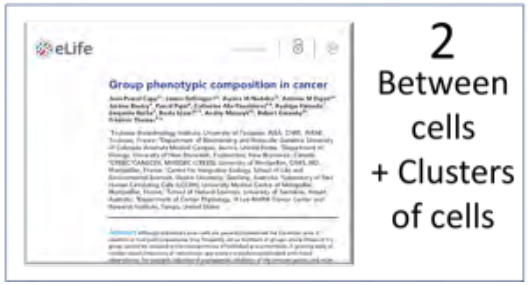
On the roles of function and selection in evolving systems

Significance





1
Between cells

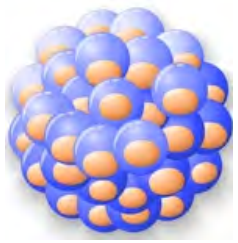


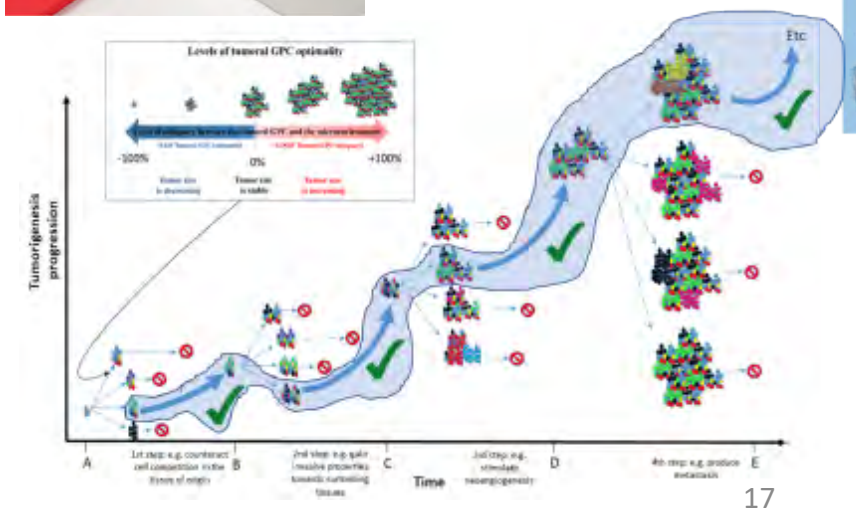
2
Between cells + Clusters of cells

Myriads of GPCs

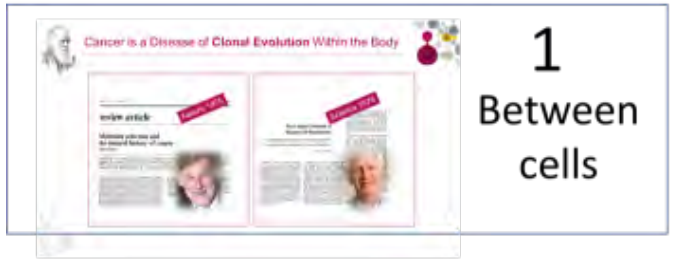
Most of them …

Selection on function



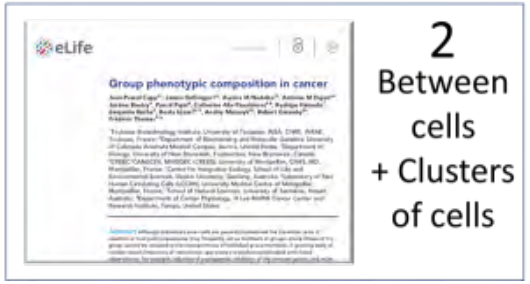


Darwinian processes between cells and groups of cells do not alone explain tumorigenesis; they merely feed into another form of selection, non-Darwinian, at the tumor level (selection based on function).

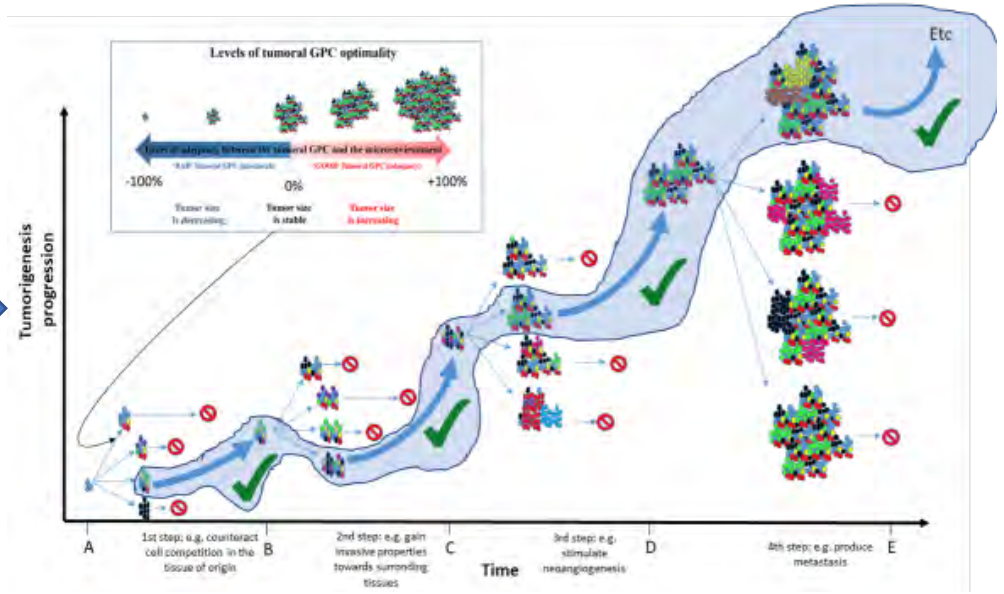


1
Between cells

+

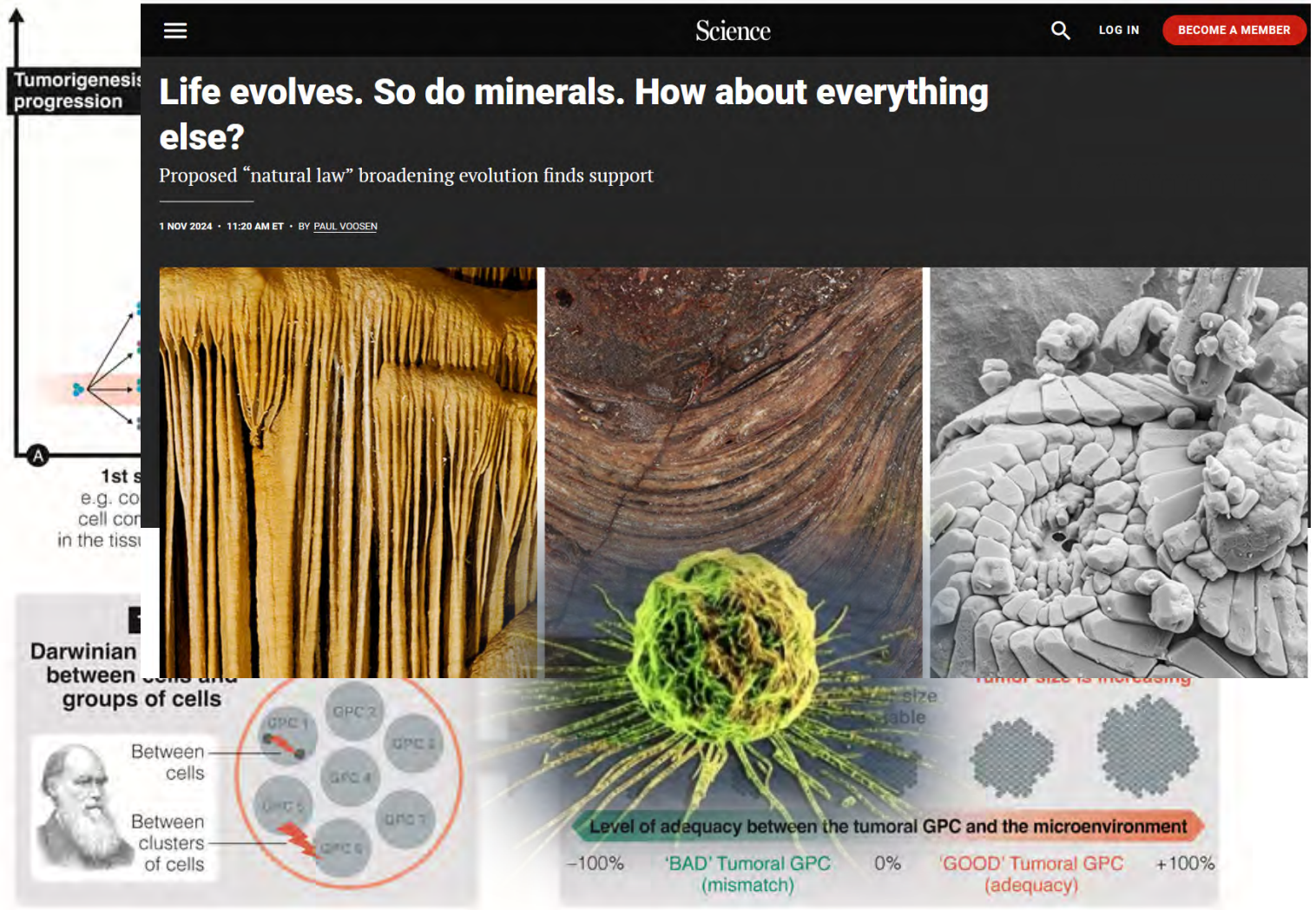


2
Between cells
+ Clusters of cells



Selection on function

In other words, tumorigenesis is the result of three distinct nested selective processes



Exploiting the role of ‘selection for function’ in tumor progression to develop new therapeutic strategies against cancer

Frédéric THOMAS[1]*, Jean-Pascal CAPP[2], Antoine M. DUJON[1,3], Andriy MARUSYK[4], Mario CAMPONE[5], Pascal PUJOL[1,6], Catherine ALIX-PANABIERES[1,7,8], Benjamin ROCHE[1], Beata UJVARI[3], Robert GATENBY[4] & Aurora M. NEDELCU[9]*, ***En preparation***

Targeting functional networks within a tumor’s

Targeting functional networks involves identifying and disrupting specific pathways or cellular interactions that are essential for tumor growth and survival. For example, blocking molecular signals that allow cancer cells to communicate, cooperate with stromal cells, or adapt to environmental changes can inhibit tumor progression.

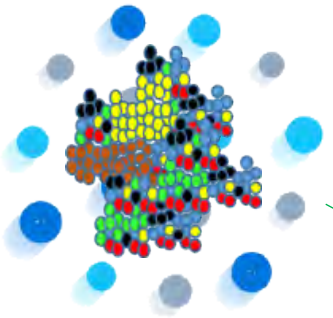
Traditional cancer treatments often aim to eliminate as many tumor cells as possible, focusing on targeting the physical form of individual cells.

GPC-based therapies

Tumor with an oncogenic GPC, including cellular and non-cellular components as well as their interaction network.

Traditional cancer treatments

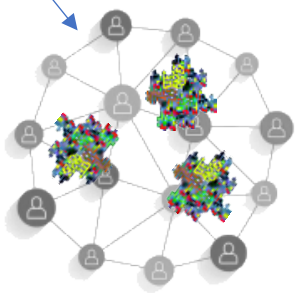
Therapy that does not aim to eradicate the maximum number of cells but rather focuses on destroying the interacting components of the functional network



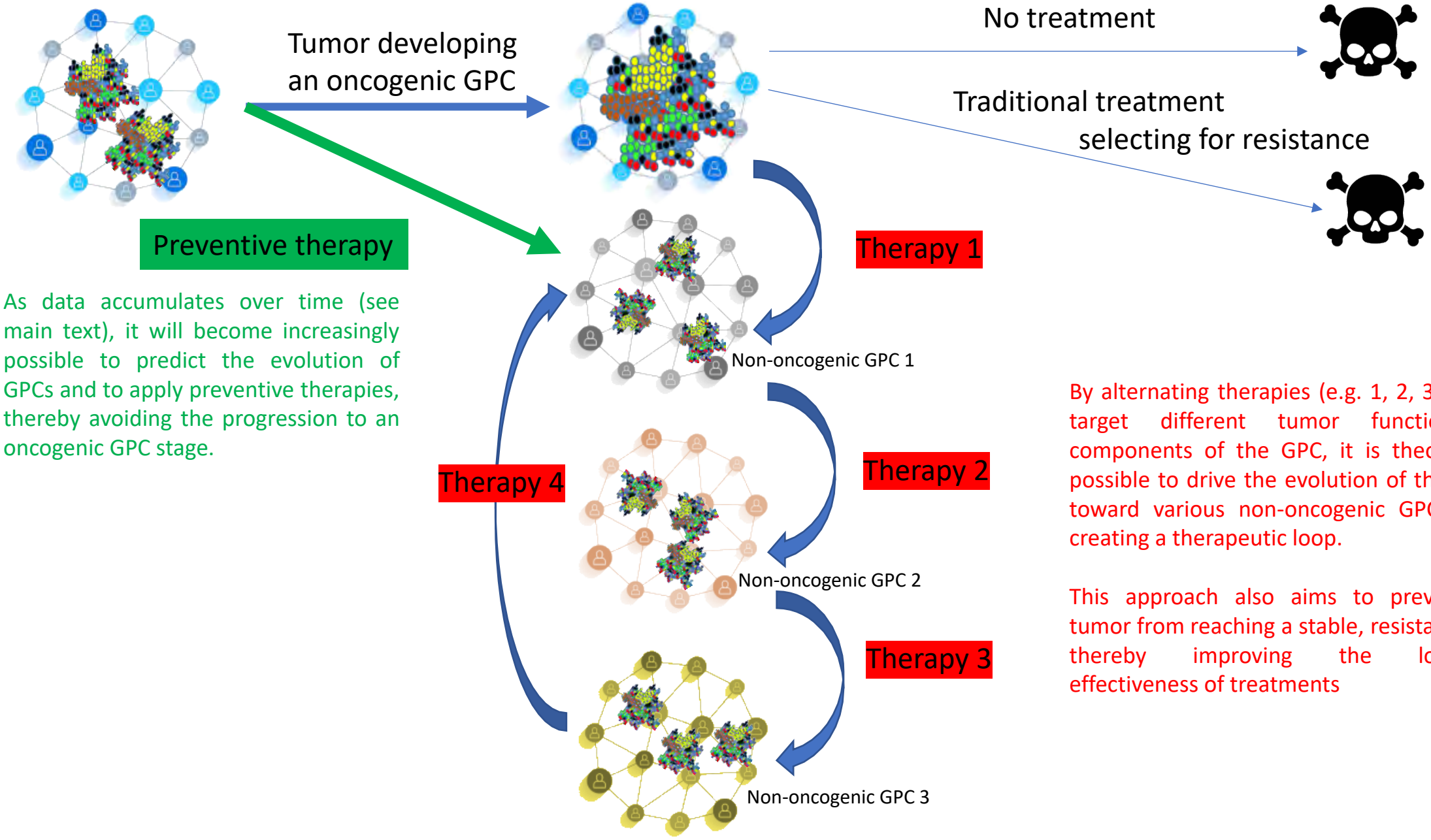
The tumor dies and disappears because the functional network has been too severely altered.

Therapy that kills the maximum number of cells without necessarily targeting the interacting components of the functional network.

The tumor does not disappear, but it takes time to regenerate the interacting components of a functional network, which may (**on the left**) or may not (**on the right**) yield an oncogenic GPC.



The tumor can restore an oncogenic GPC because the previous functional network remains active.

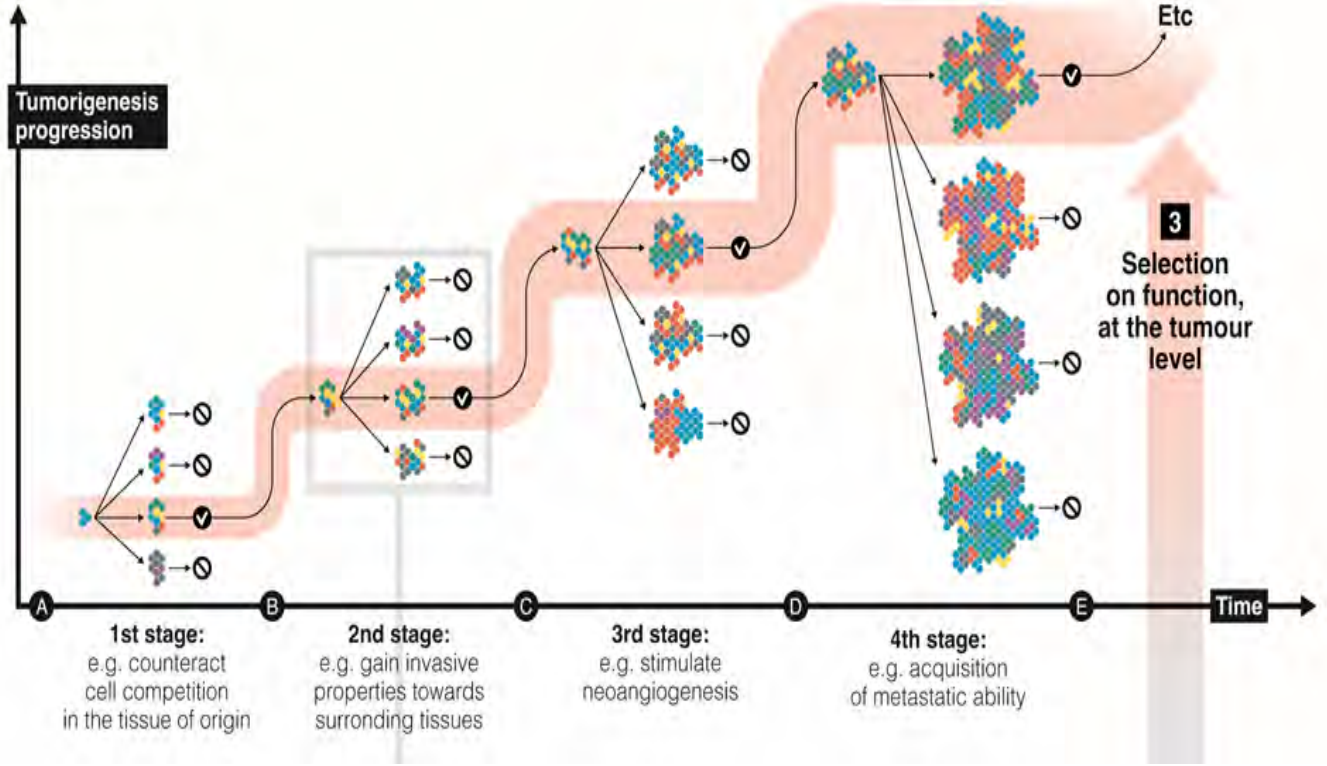


As data accumulates over time (see main text), it will become increasingly possible to predict the evolution of GPCs and to apply preventive therapies, thereby avoiding the progression to an oncogenic GPC stage.

By alternating therapies (e.g. 1, 2, 3, 4) that target different tumor functions or components of the GPC, it is theoretically possible to drive the evolution of the tumor toward various non-oncogenic GPCs, even creating a therapeutic loop.

This approach also aims to prevent the tumor from reaching a stable, resistant state, thereby improving the long-term effectiveness of treatments

Modifying the microenvironment can also destabilize tumors by disrupting the GPC/microenvironment coupling responsible for tumor growth. In other words, therapies can be developed to **create a mismatch between the tumor GPC and its surrounding microenvironment.**



The tumor microenvironment, which includes immune cells, fibroblasts, blood vessels, and the extracellular matrix, plays a crucial role in forming and maintaining a tumor's GPC. Interactions between tumor cells and the microenvironment can either support or hinder tumor progression. Therefore, modifying the tumor microenvironment, such as inhibiting angiogenesis or enhancing the anti-tumor immune response, can potentially disrupt the oncogenic GPC and inhibit tumor growth.

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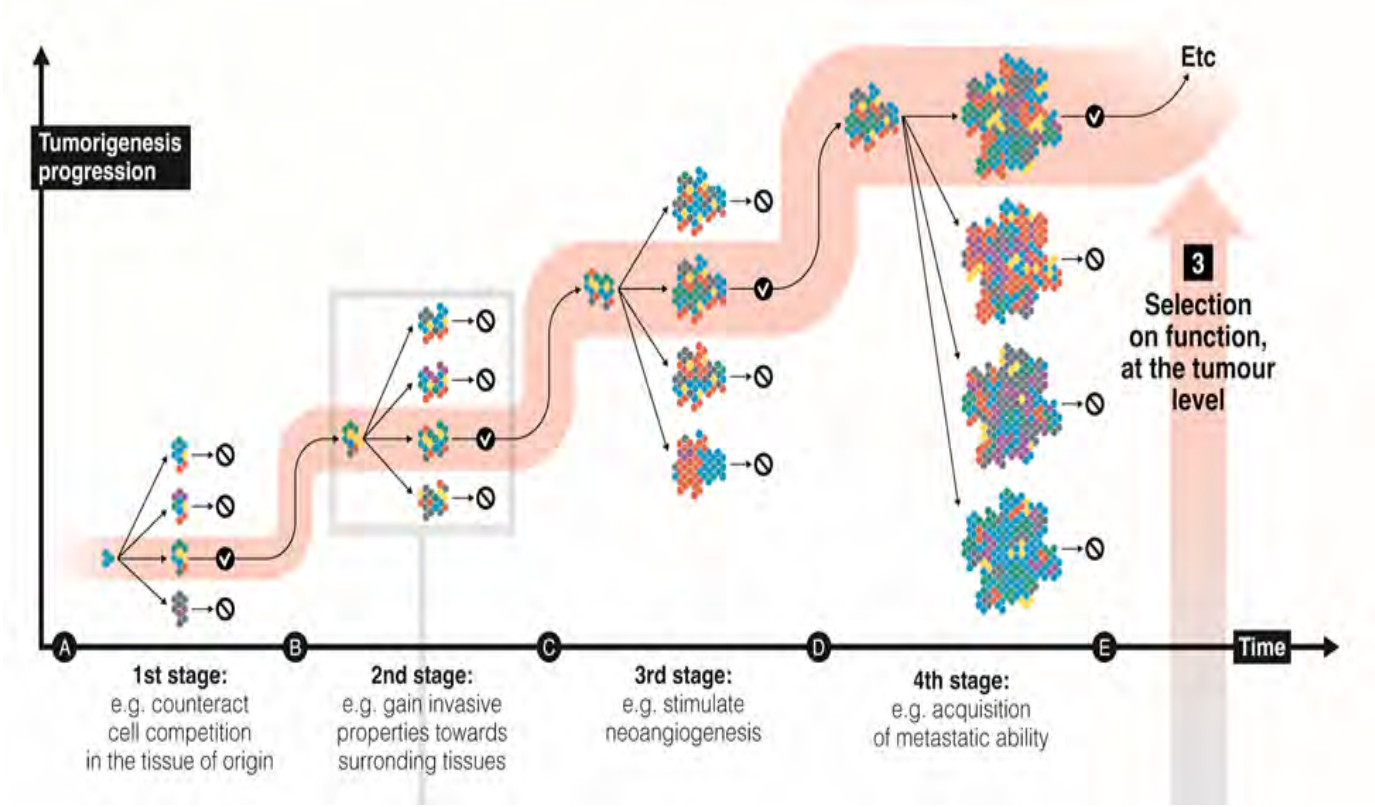

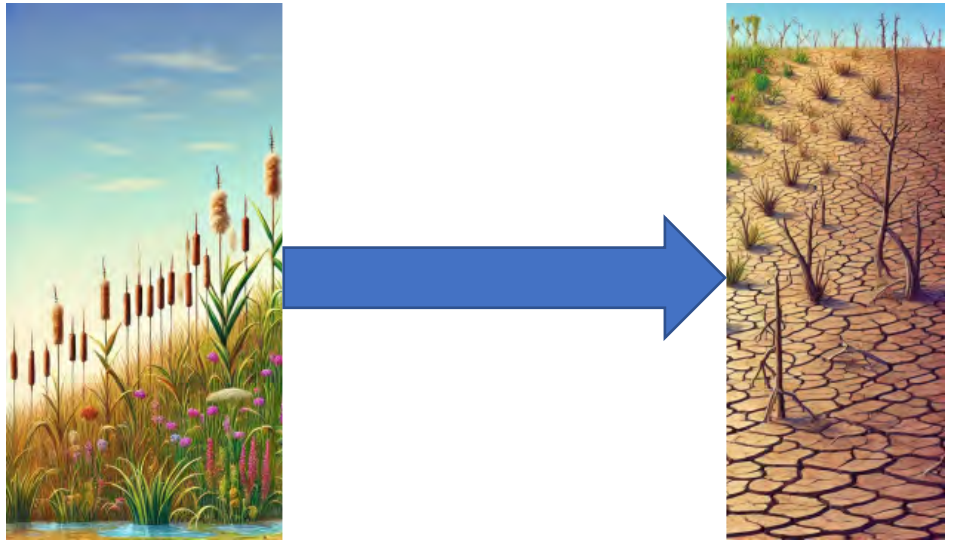

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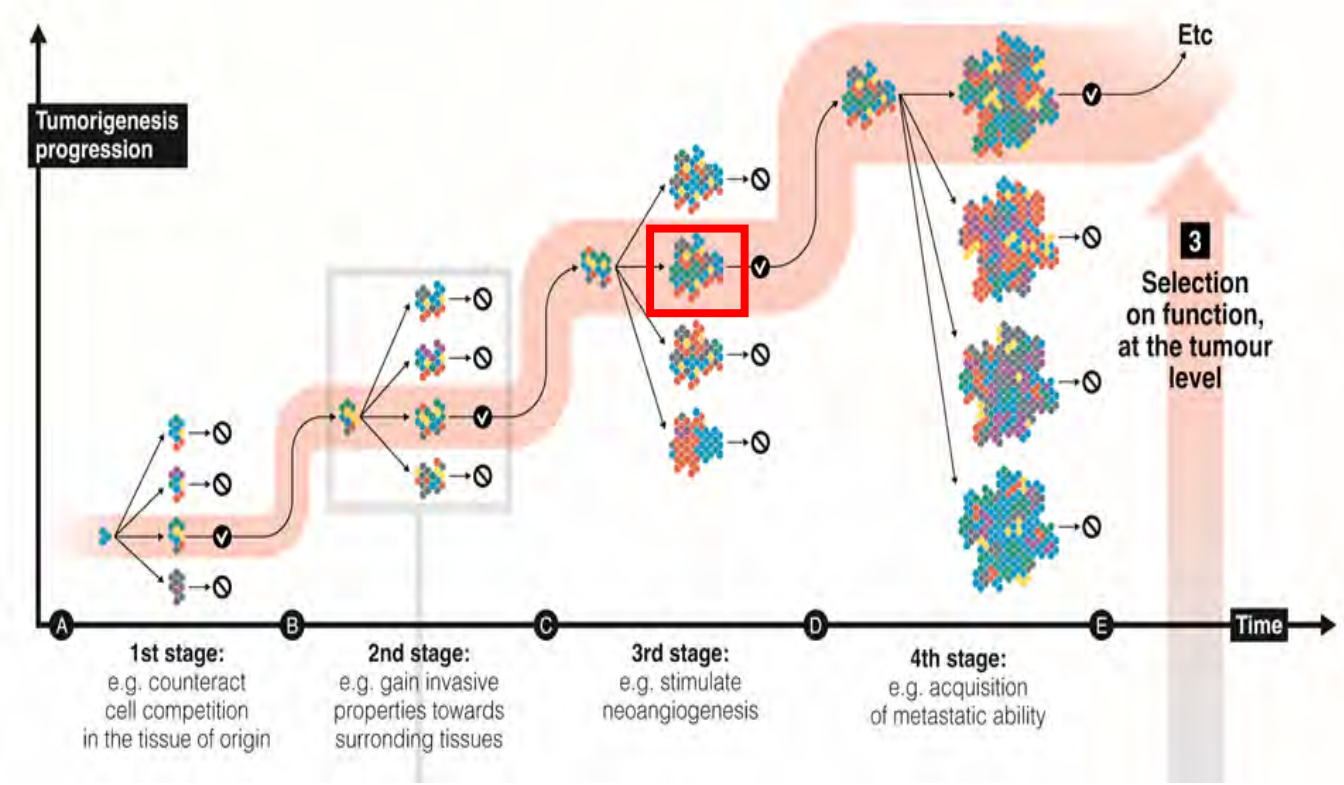

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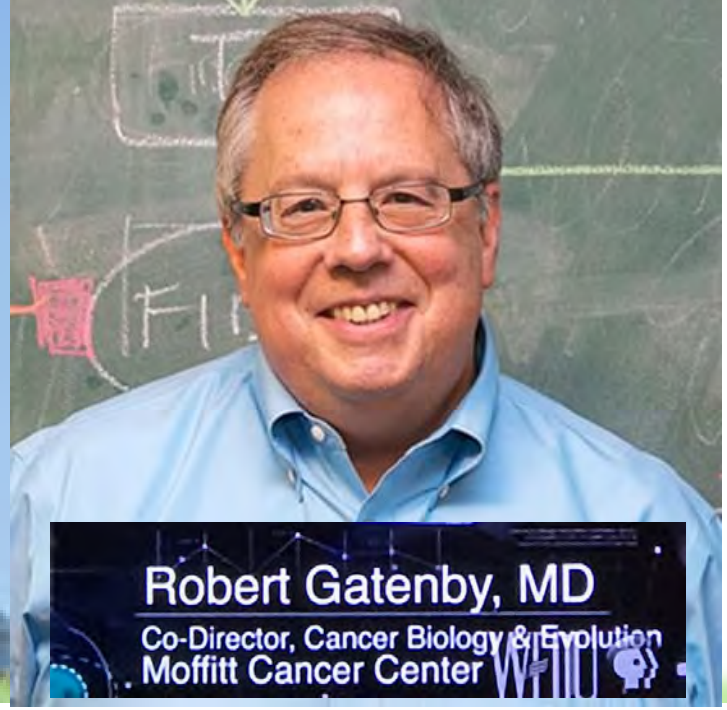
Adaptive Therapy

Modifier la compétition entre cellules malignes aggressives et cellules bénignes



Cancer Res. 2009 June 1; 69(11): 4894–4903. doi:10.1158/0008-5472.CAN-08-3658.

Adaptive Therapy

Robert A. Gatenby[1], **Ariosto S. Silva**[1], **Robert J. Gillies**[1], and **B. Roy Frieden**[2]

[1]Department of Integrative Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida

[2]School of Optical Sciences, University of Arizona, Tucson, Arizona

Abstract

A number of successful systemic therapies are available for treatment of disseminated cancers. However, tumor response is often transient, and therapy frequently fails due to emergence of resistant populations. The latter reflects the temporal and spatial heterogeneity of the tumor microenvironment as well as the evolutionary capacity of cancer phenotypes to adapt to therapeutic perturbations. Although cancers are highly dynamic systems, cancer therapy is typically administered according to a fixed, linear protocol. Here we examine an adaptive

Adaptive Therapy

A change of strategy in the war on cancer

SUSCEPTIBLE

RESISTANT

KILLED

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-01968-5 OPEN

Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer

Jingsong Zhang[1], Jessica J. Cunningham[2], Joel S. Brown[2,3] & Robert A. Gatenby[2,4]

Abiraterone treats metastatic castrate-resistant prostate cancer by inhibiting CYP17A, an enzyme for testosterone auto-production. With standard dosing, evolution of resistance with treatment failure (radiographic progression) occurs at a median of ~16.5 months. We hypothesize time to progression (TTP) could be increased by integrating evolutionary dynamics into therapy. We developed an evolutionary game theory model using

DOUBLE BIND

Owls facilitate the hunting success of snakes and vice versa

Published in final edited form as:
Mol Pharm. 2012 April 2; 9(4): 914–921. doi:10.1021/mp200458e.

Exploiting evolution to treat drug resistance: Combination therapy and the double bind

David Basanta[1], **Robert A. Gatenby**[1], and **Alexander R. A. Anderson**[1]
[1]Integrated Mathematical Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA

Abstract

Although many anticancer therapies are successful in when initially administered, the evolutionary dynamic that often, resistance is an inevitable outcome. Resear evolutionary double bind could be an effective way to bind two therapies are used in combination such that more susceptible to the other. In this paper we presen framework of a double bind to study the effect that su Furthermore we use this mathematical framework to suggest a synergistic effect between a p53 cancer vac recapitulates the latest experimental data and provide on the commensalistic relationship between the tumo

Keywords

Evolutionary Game Theory; Evolutionary Double Bi Immunotherapy; Chemotherapy; Combination therap

1.2 Introduction

Cancer is an evolutionary disease [1]. One

Perspectives In Cancer Research

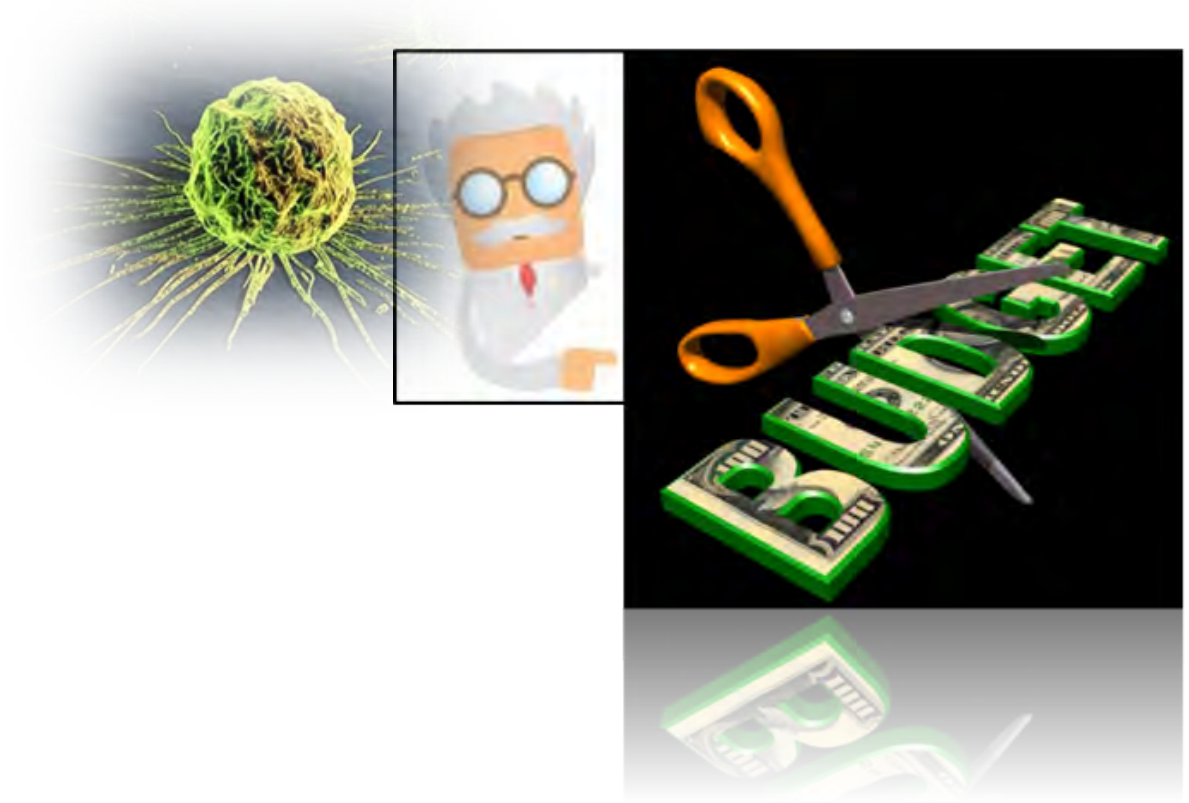
Lessons from Applied Ecology: Cancer Control Using an Evolutionary Double Bind

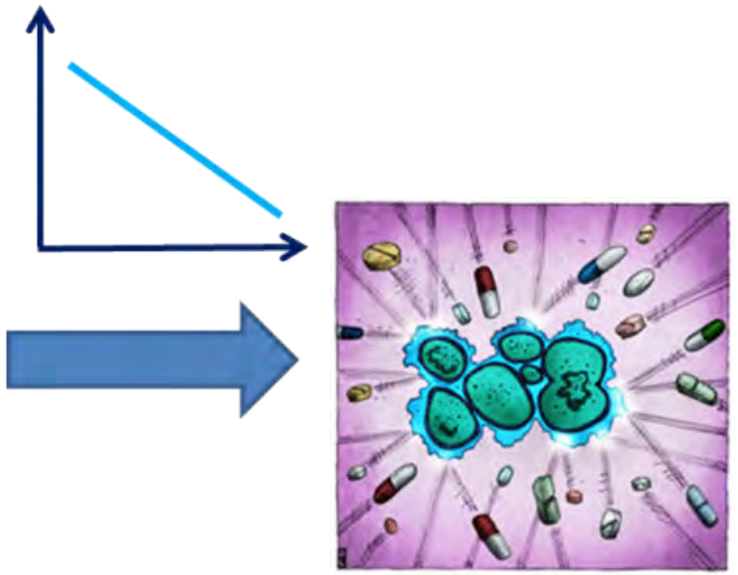
Robert A. Gatenby,[1] Joel Brown,[2] and Thomas Vincent[3]

Abstract

Because the metastatic cascade is largely governed by the ability of malignant cells to adapt and proliferate at the distant tissue site, we propose that disseminated cancers are analogous in many important ways to the evolutionary and ecological dynamics of exotic species. Although pests can be decimated through the application of chemical toxins, this strategy virtually never achieves robust control as evolution of resistant phenotypes typically permits population recovery to pretreatment levels. In general, biological strategies that introduce predators, parasitoids, or pathogens have achieved more durable control of pest populations even after emergence of resistant phenotypes. From this we propose that long term outcome from any treatment strategy for invasive pests, including cancer, is not limited by evolution of resistance, but rather by the phenotypic cost of that resistance. If a cancerous cell's adaptation to therapy is achieved by upregulating xenobiotic metabolism or a redundant signaling pathway, the required investment in resources is small, and the original malignant phenotype remains essentially intact. As a result, the cancer cells' initial high level of fitness is little changed and unconstrained proliferation will resume once resistance evolves. Robust population control is possible if resistance to therapy requires a substantial and costly phenotypic adaptation that also significantly reduces the organism's fitness in its original niche: an evolutionary double bind. [Cancer Res 2009;69(19):7709–7712]

1. Kotler et al. 1992. The combined effect of snakes and owls on the foraging behavior of gerbils. Ann Zool Fenn 29: 199-206





Evolutionary double bind

In an evolutionary double bind two therapies are used in combination such that evolving resistance to one leaves individuals more susceptible to the other.

Cancer Research

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Controversy and Consensus

First Strike–Second Strike Strategies in Metastatic Cancer: Lessons from the Evolutionary Dynamics of Extinction

Robert A. Gatenby, Jingsong Zhang, and Joel S. Brown

DOI: 10.1158/0008-5472.CAN-19-0807 Check for updates

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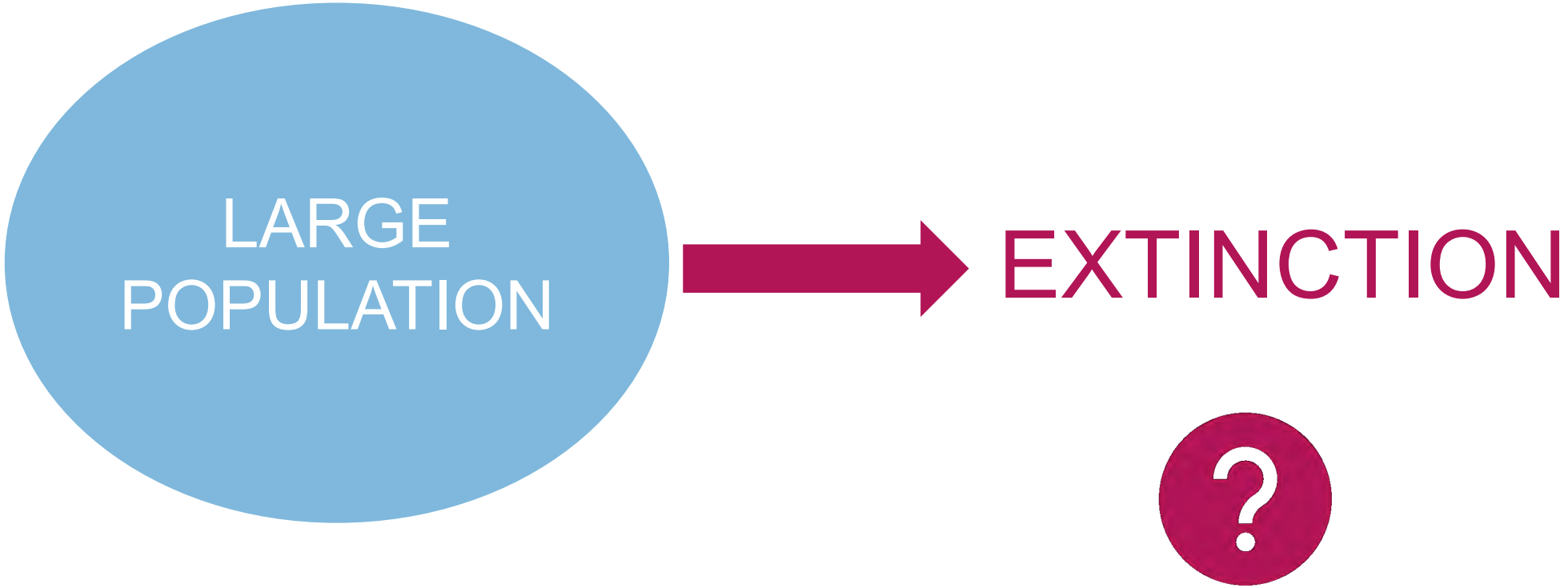
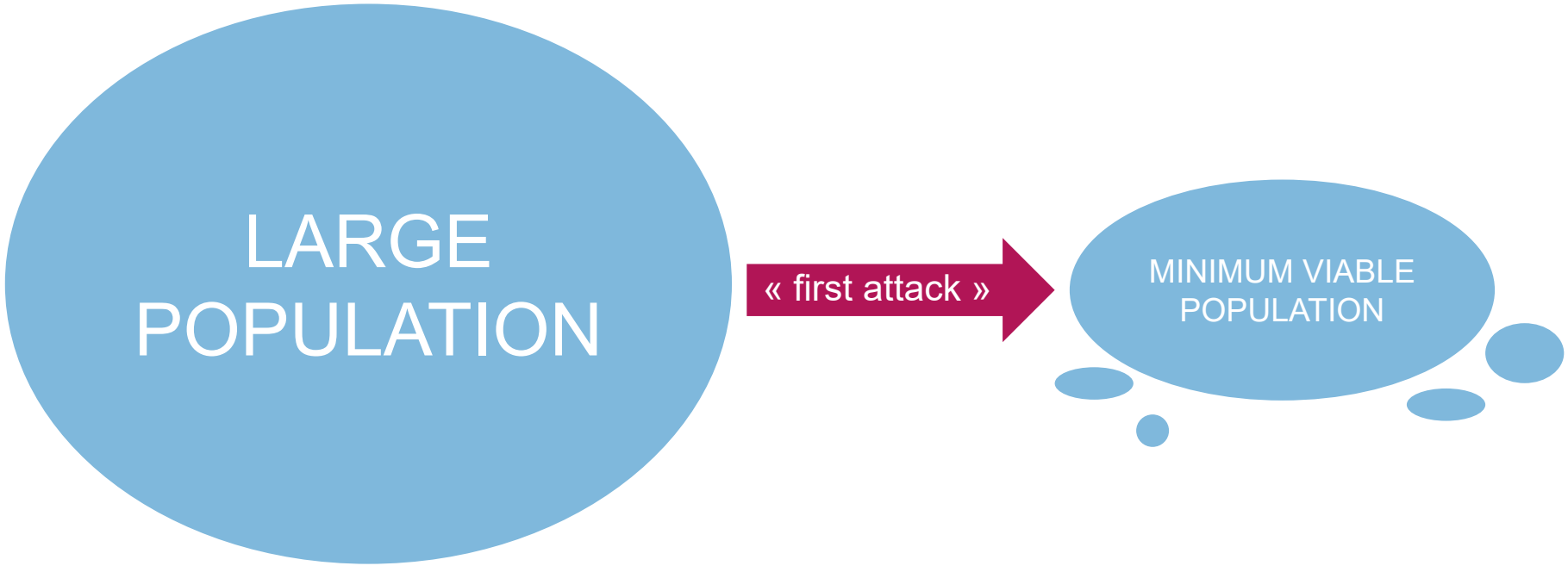
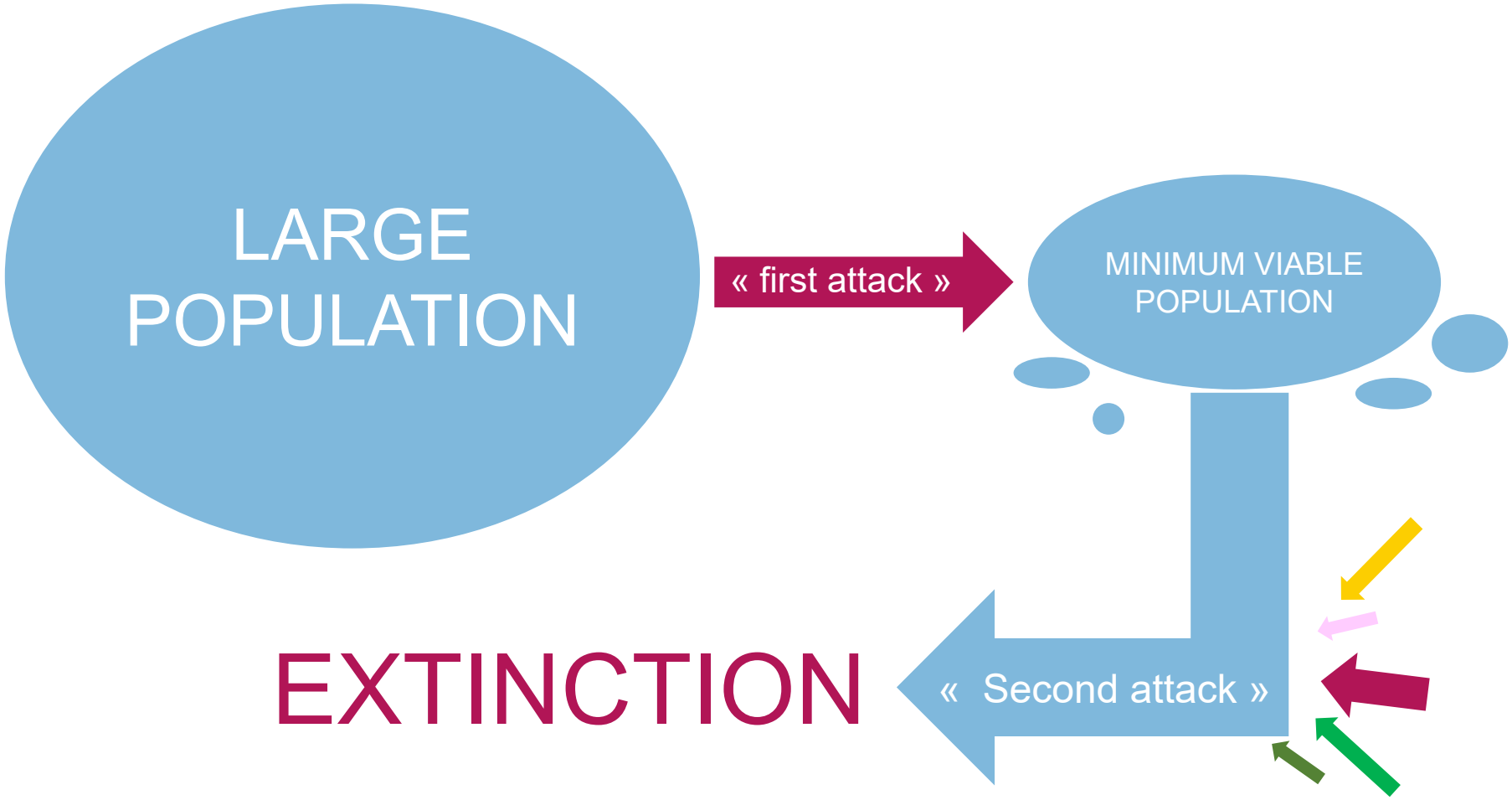
Published OnlineFirst June 20, 2019
doi: 10.1158/0008-5472.CAN-19-0807

Evolutionary dynamics of Extinction

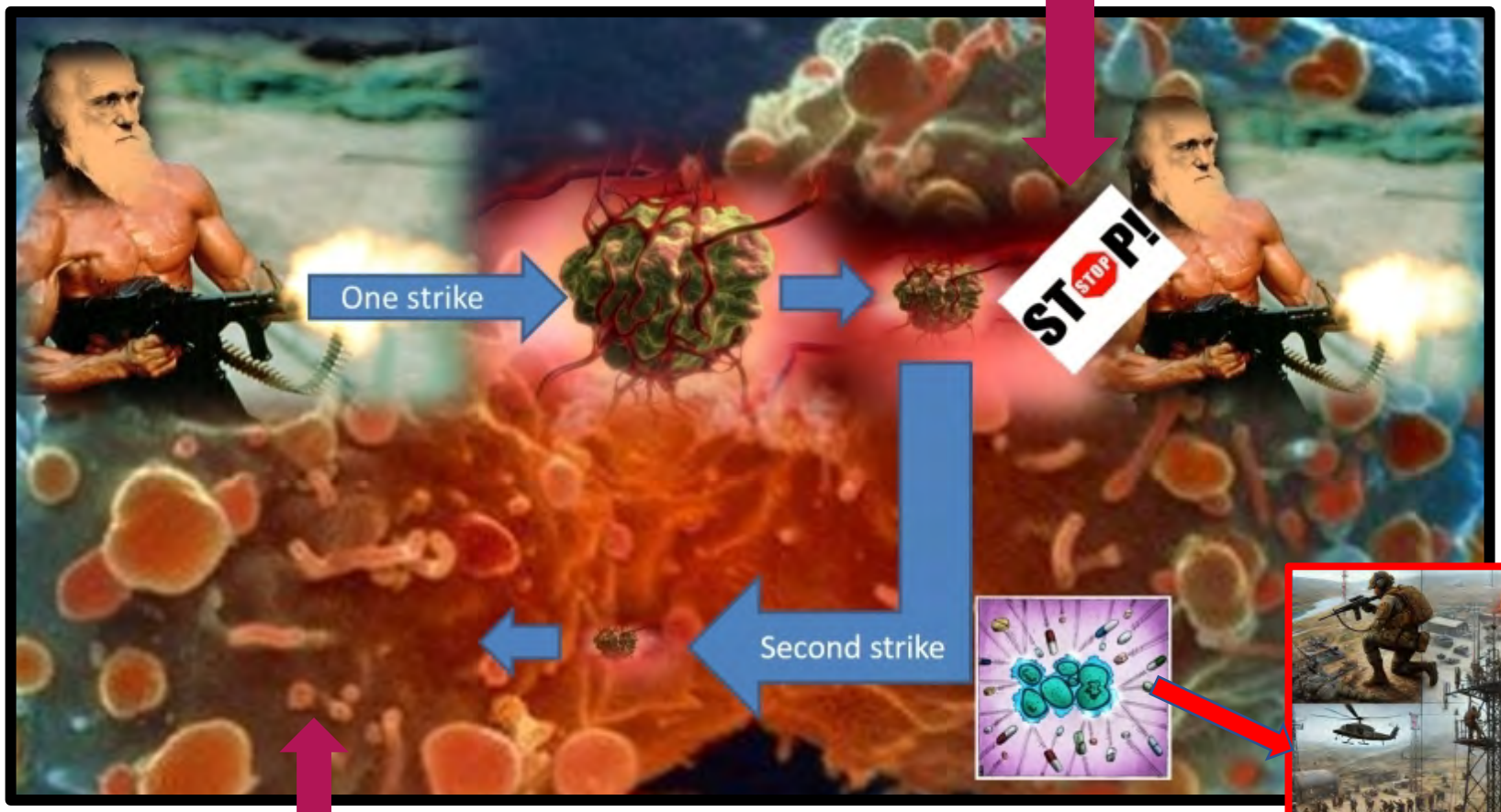

LARGE
POPULATION
EXTINCTION
?


LARGE POPULATION
« first attack »
MINIMUM VIABLE POPULATION


LARGE POPULATION
« first attack »
MINIMUM VIABLE POPULATION
« Second attack »
EXTINCTION

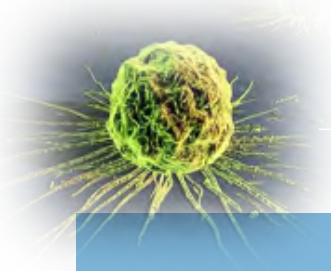
First strike-second strike

Change the therapy even if it works



Continue the therapy

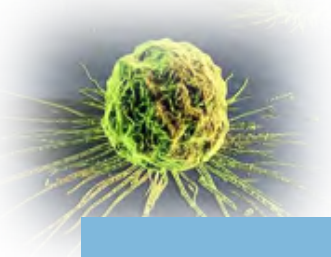
Cancer is problematic for human health mainly because it often evolves so fast that it is able to outrun our defence systems.



Death

LIFE EXPECTANCY

By reducing cancer evolution rate by 2 or 3 fold, most of our tumours would become harmless due to the cancer would appear beyond our present life expectancy.



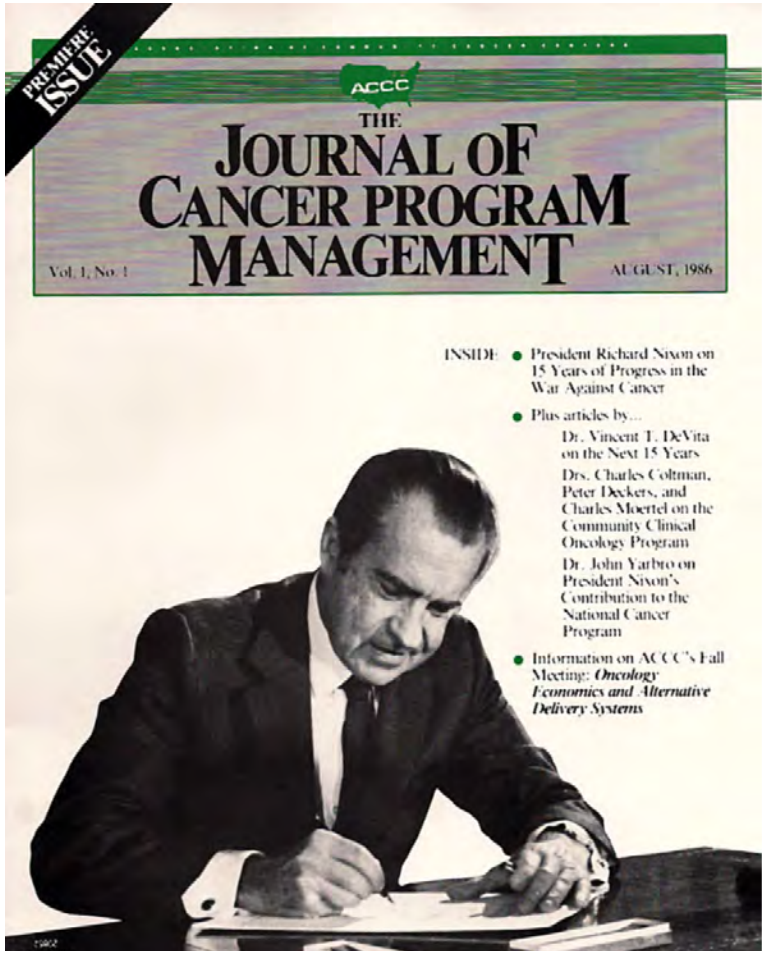
Death

LIFE EXPECTANCY

How Do We Slow Down Evolution?

- Reducing the mutation rate since it reduces the diversity in the population of cells
- Slow down the division rate
- Slow evolution by reducing the population size of the tumor and/or by reducing the fitness differences among cells (since differences in survival and reproduction are what drive evolution)
- Manipulating the environment to encourage cancer cells to evolve in the direction of a slower life history rendering them for instance dormant

More than 50 years after President Richard Nixon declared a war on cancer, victory remains elusive…



President Richard Nixon signs the National Cancer Act, Dec. 23, 1971, launching a $1.6 billion federal crusade to conquer cancer. (AP)


COMMENTARY

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Evolution, Medicine, and Public Health [2024] pp. 172–177

Advance access date 19 September 2024

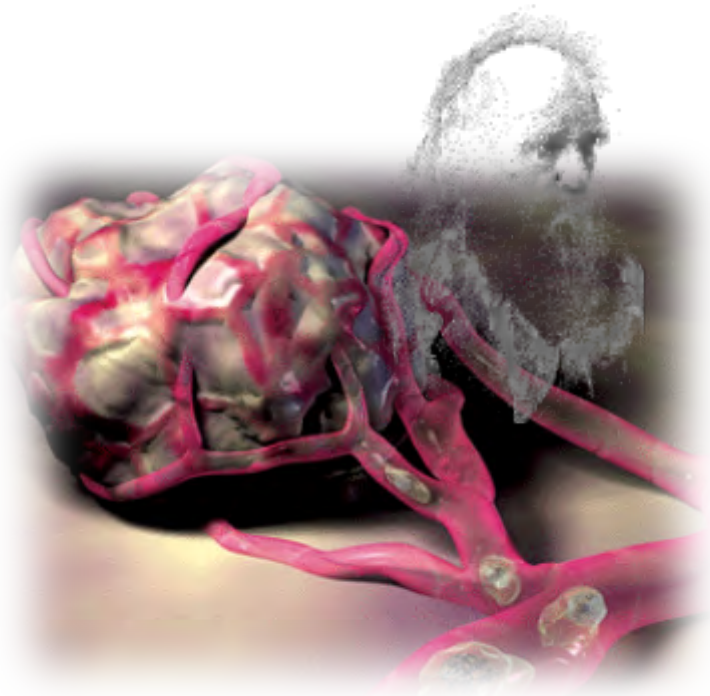
A new perspective on tumor progression

Evolution via selection for function

Frédéric Thomas, James DeGregori, Andriy Marusyk, Antoine M. Dujon, Beata Ujvari, Jean-Pascal Capp, Robert Gatenby and Aurora M. Nedelcu

ABSTRACT

THE PREMISE



Thérapies fondées sur le GPC : pour quels types de tumeurs ?

- Tumeurs dont la complexité structurelle et fonctionnelle limite l'efficacité des approches traditionnelles ciblant les cellules individuelles, e.g. cas de cancers localement avancés mais non métastatiques, où les interactions complexes entre la tumeur et son microenvironnement rendent une résection chirurgicale complète difficile.

- Pour les cancers ayant développé une résistance aux traitements cytotoxiques, la thérapie basée sur le GPC peut cibler les réseaux fonctionnels qui soutiennent la résilience de la tumeur.

- Les tumeurs présentant une forte hétérogénéité intratumorale, contenant de nombreuses sous-populations cellulaires coopératives, pourraient également bénéficier de cette approche, car elle perturbe les interactions qui soutiennent leur adaptabilité.

- cas où les amas de cellules tumorales circulantes (CTC) contribuent à la dissémination métastatique, cibler le GPC de ces amas pourrait limiter leur capacité à échapper au système immunitaire et à coloniser d'autres sites. En revanche, pour les tumeurs plus petites et localisées, les approches traditionnelles (par exemple, la chirurgie suivie de radiothérapie ou de chimiothérapie) peuvent être plus appropriées.

La stratégie thérapeutique que nous proposons cible le GPC de la tumeur, plutôt que de se concentrer uniquement sur les cellules cancéreuses individuelles. Cette approche viserait à déstabiliser les réseaux fonctionnels de la tumeur qui soutiennent sa survie et sa progression.

Voici une stratégie proposée en plusieurs volets :

1.Déstabilisation des réseaux fonctionnels : En ciblant des nœuds clés dans les réseaux fonctionnels de la tumeur (comme ceux impliqués dans l'angiogenèse, l'évasion immunitaire ou le remodelage de la matrice extracellulaire), on pourrait démanteler le système de soutien de la tumeur. Par exemple :

1. Des **agents anti-angiogéniques** (comme le bevacizumab) pourraient priver la tumeur de nutriments essentiels.
2. Les **inhibiteurs des points de contrôle immunitaires** (comme les inhibiteurs de PD-1/PD-L1, tel que le pembrolizumab) pourraient restaurer la surveillance immunitaire, renforçant ainsi la capacité du système immunitaire à attaquer la tumeur.
3. Les **inhibiteurs du remodelage de la matrice** empêcheraient la propagation de la tumeur en maintenant la structure extracellulaire.

2.Thérapie séquentielle et adaptative : La mise en place d'un plan de traitement séquentiel pourrait empêcher la tumeur de stabiliser une GPC résistante. En alternant des thérapies ciblant différentes fonctions (par exemple, le métabolisme, l'évasion immunitaire), cette approche pourrait maintenir la tumeur en perpétuelle adaptation, jusqu'à la piéger dans un état non oncogénique.

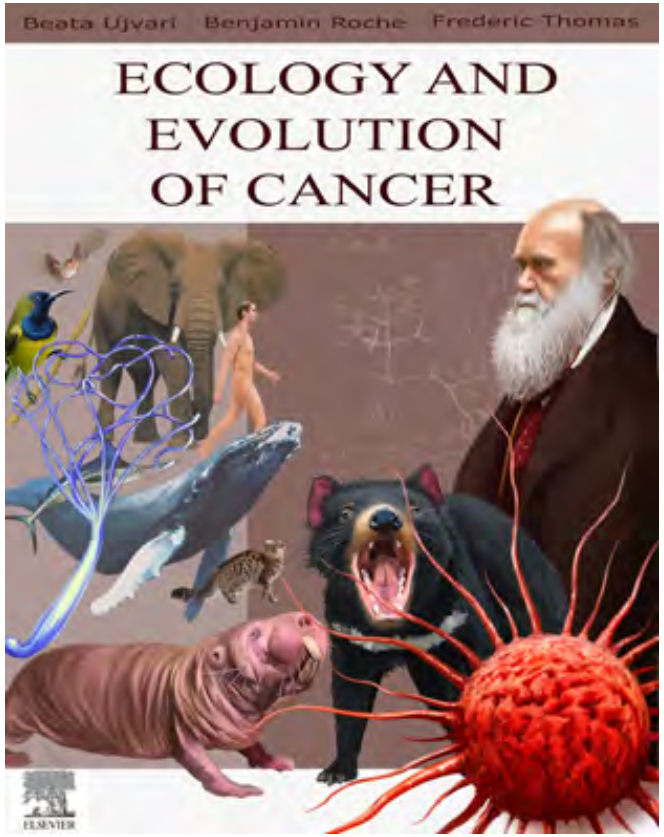
3.Modulation du microenvironnement : Modifier le microenvironnement de la tumeur pour créer des discordances avec son GPC pourrait encore déstabiliser la tumeur. Par exemple, des thérapies qui stabilisent le pH extracellulaire pourraient perturber l'environnement acide souvent exploité par les cellules cancéreuses pour survivre, et le Losartan pourrait être utilisé pour réduire la densité des fibroblastes associés au cancer et améliorer la délivrance des médicaments.

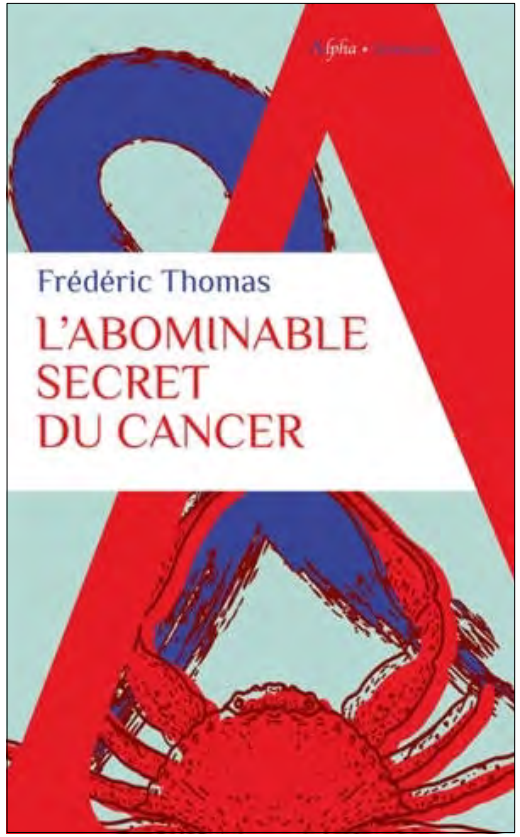
4.Favoriser les clones non-oncogéniques : Introduire des conditions qui privilégient les phénotypes non oncogéniques pourrait orienter l'évolution de la tumeur vers un état moins agressif. Par exemple, altérer les voies métaboliques pour favoriser la phosphorylation oxydative par rapport à la glycolyse pourrait diminuer la capacité d'adaptation et l'agressivité de la tumeur.

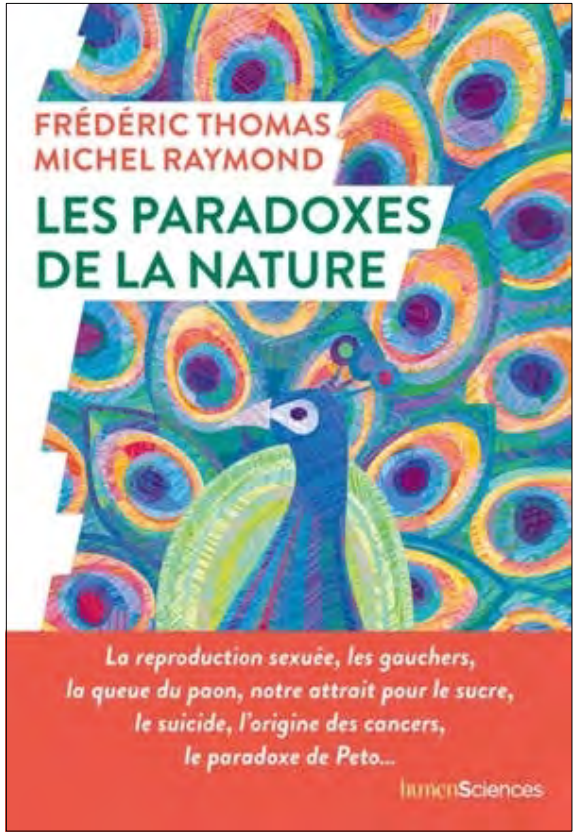
5.Surveillance en temps réel et ajustements : En utilisant des biopsies liquides et la transcriptomique spatiale, il serait possible de suivre l'évolution de la GPC et d'ajuster les traitements en temps réel. Cette approche adaptative permettrait de choisir des combinaisons de traitements et des moments précis pour prendre de vitesse l'évolution de la tumeur.

Cette stratégie s'appuie sur la dynamique évolutive de la tumeur, en visant à la fois à déstabiliser les GPC oncogéniques et à promouvoir l'émergence de phénotypes moins agressifs, avec pour ambition de transformer le cancer en une condition chronique et gérable.

Thank you for your attention…







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