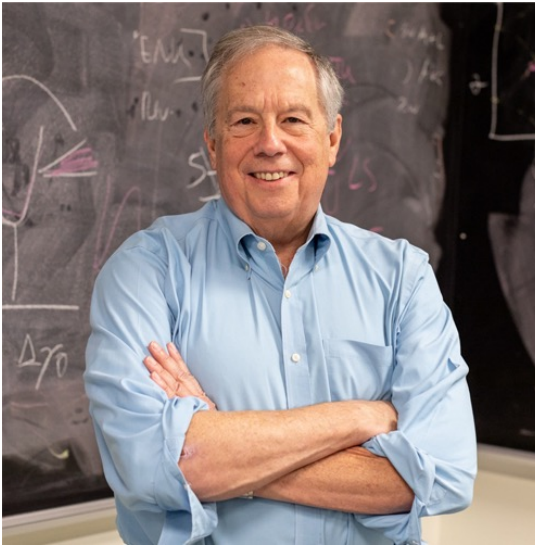


Evolutionary Game Theory, a biologist's perspective
Evolution of Cancer Therapy Resistance as a Multifactorial Dynamic Process

Andriy Marusyk, PhD

Department of Tumor Microenvironment and Metastasis, Moffitt Cancer Center





[CANCER RESEARCH 63, 6212–6220, October 1, 2003]

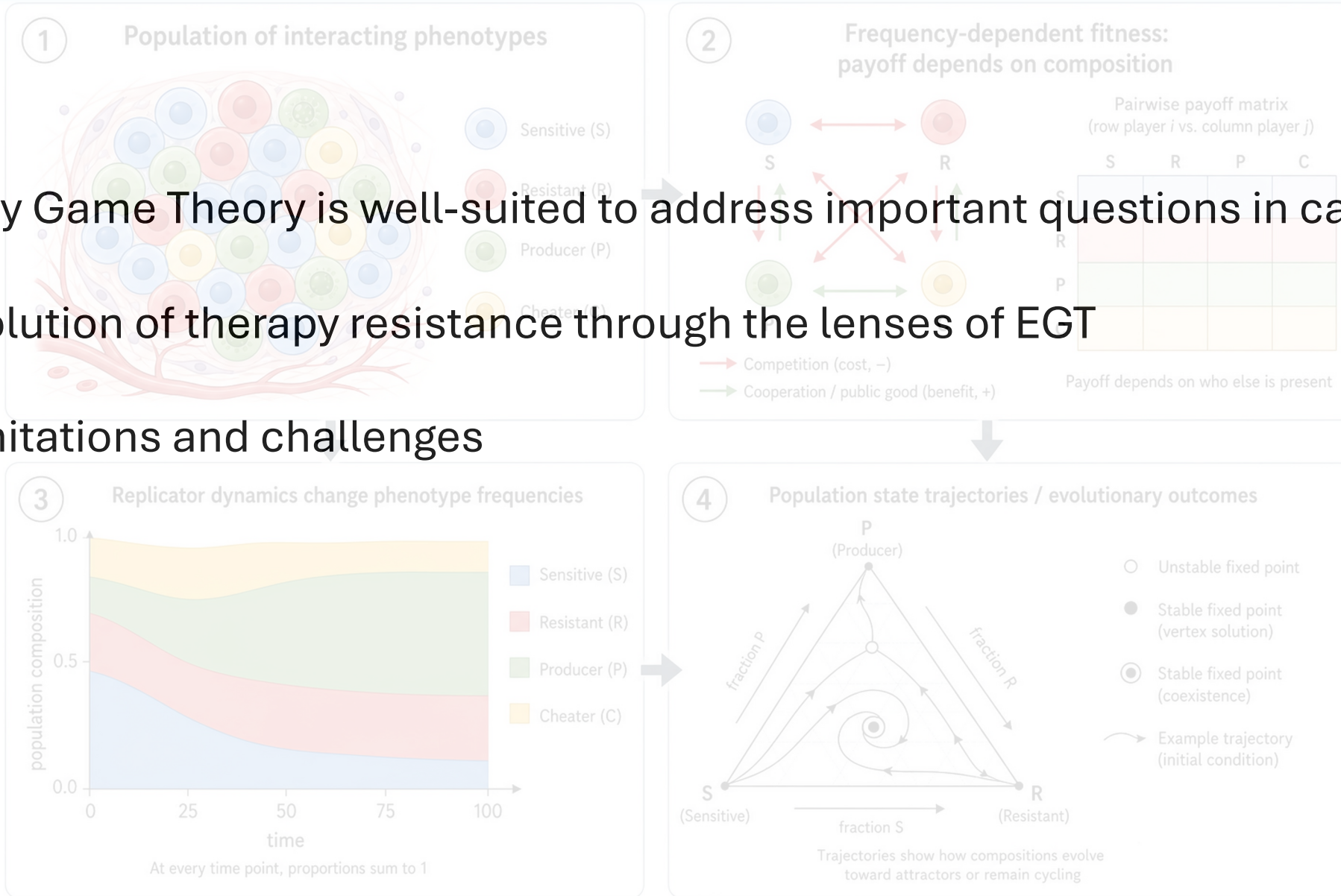
An Evolutionary Model Of Carcinogenesis

Robert A. Gatenby¹ and Thomas L. Vincent

Departments of Radiology [R. A. G.], Applied Mathematics, and Aerospace and Mechanical Engineering [T. L. V.], University of Arizona, Tucson, Arizona 85724

Outline

1. Why Game Theory is well-suited to address important questions in cancer biology
2. Evolution of therapy resistance through the lenses of EGT
3. Limitations and challenges

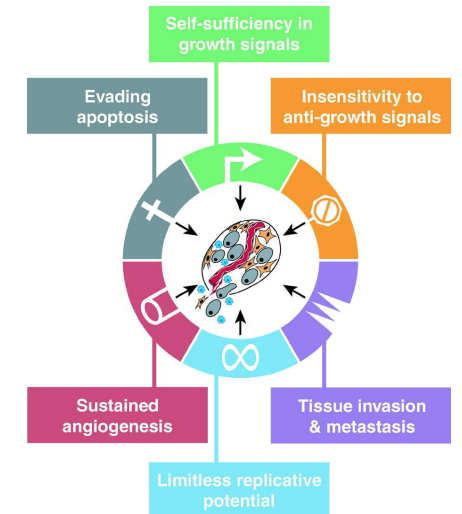
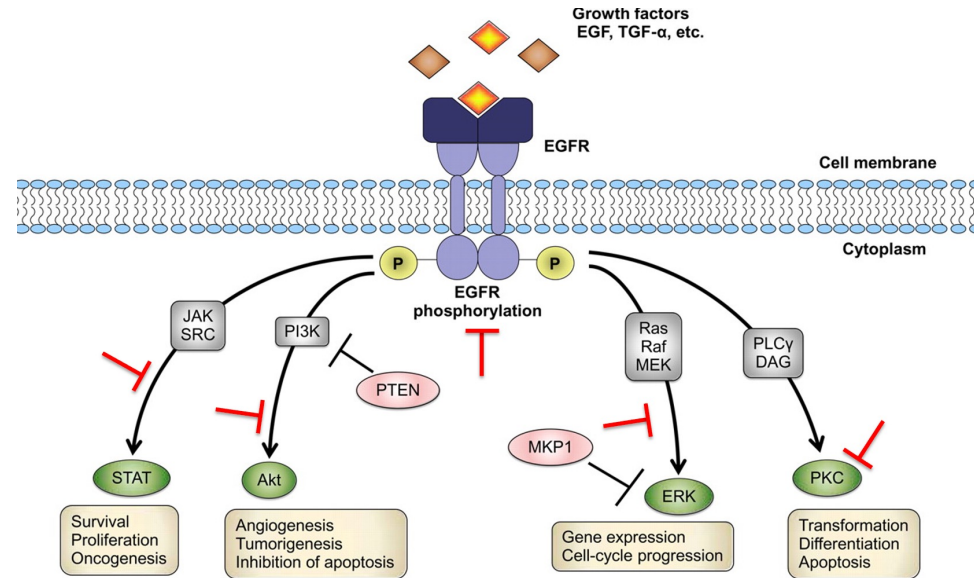
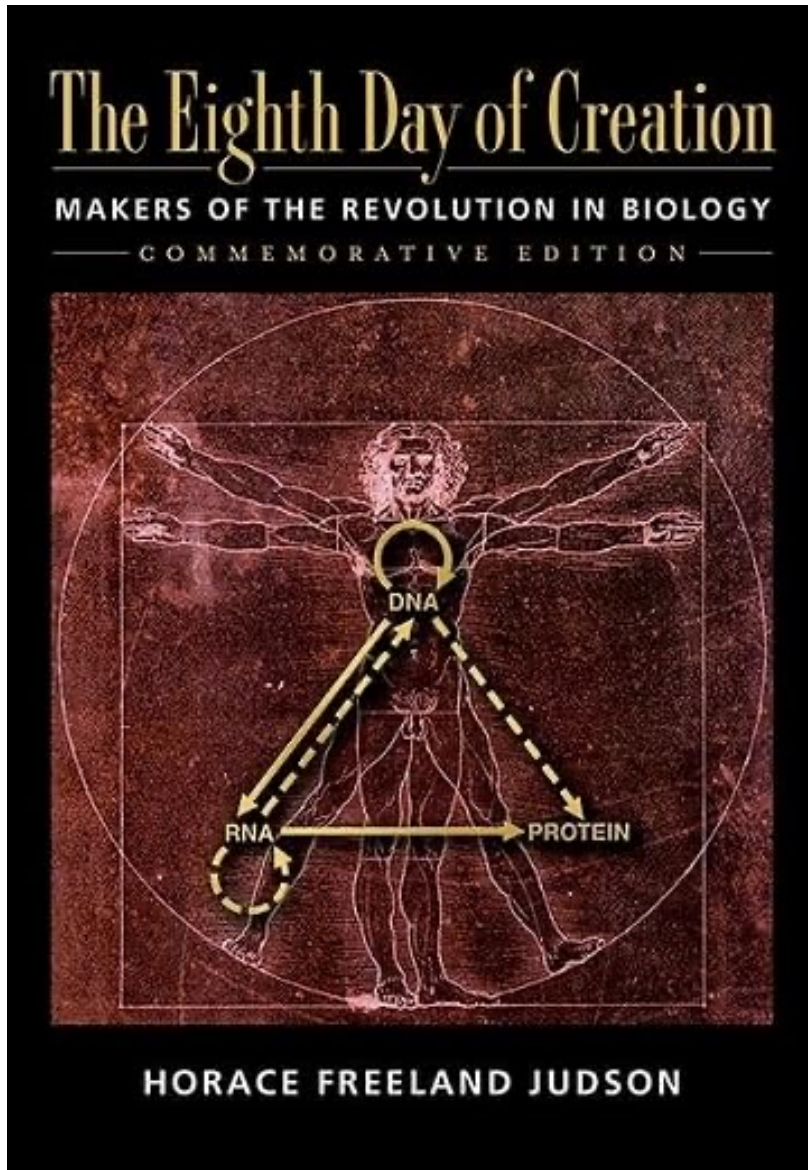


Cancer: a multifaceted phenomenon

Cancer is a *group of diseases* in which abnormal cells grow beyond normal tissue boundaries, invade nearby tissue, and can spread to distant organs



Cancer through the lenses of molecular oncology



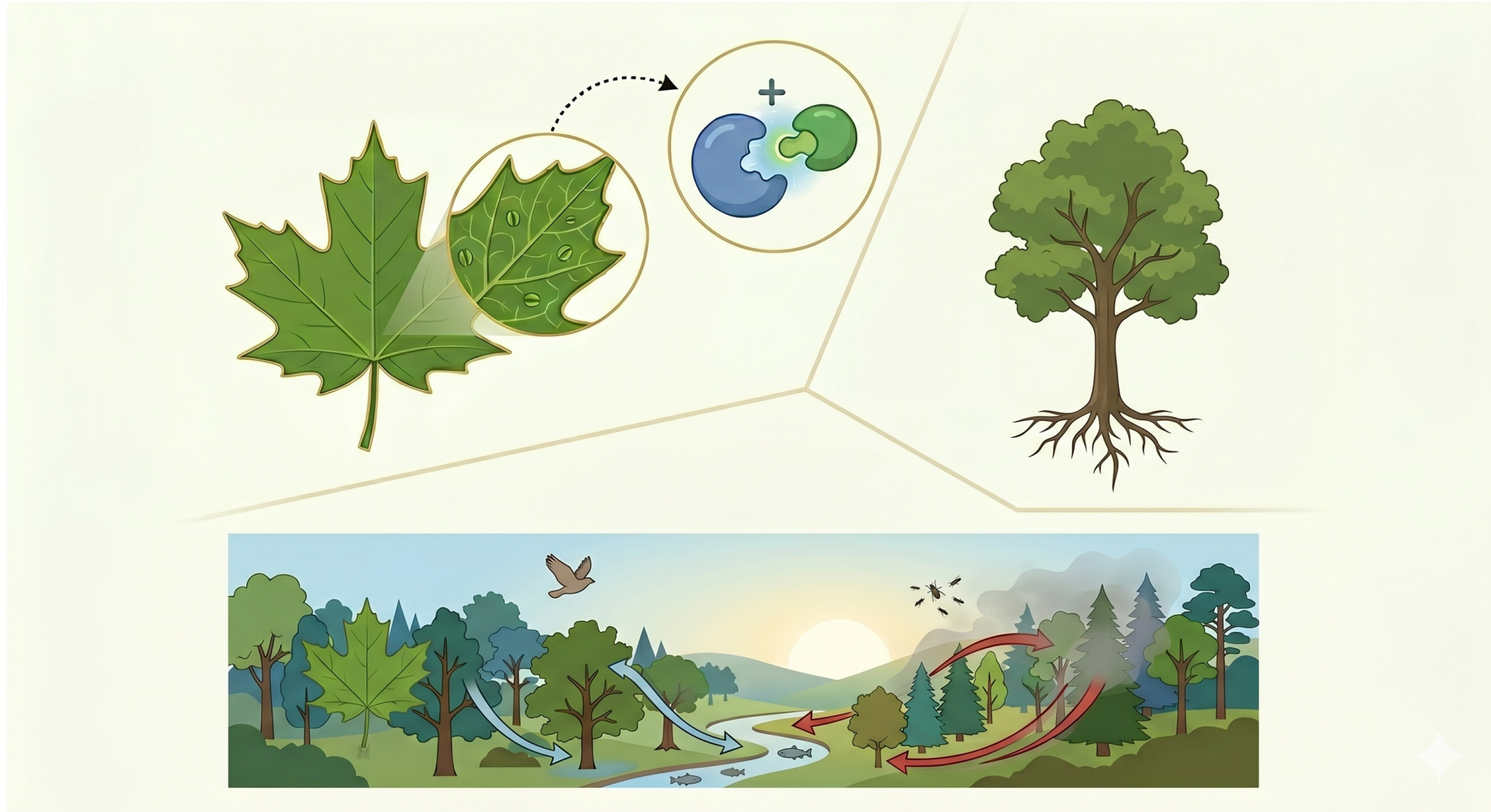
Hanahan and Weinberg, Cell 2020

Identify “driver”
genes/pathways



Develop therapies
targeting the
drivers

Molecular oncology perspective is blind to some of the essentials



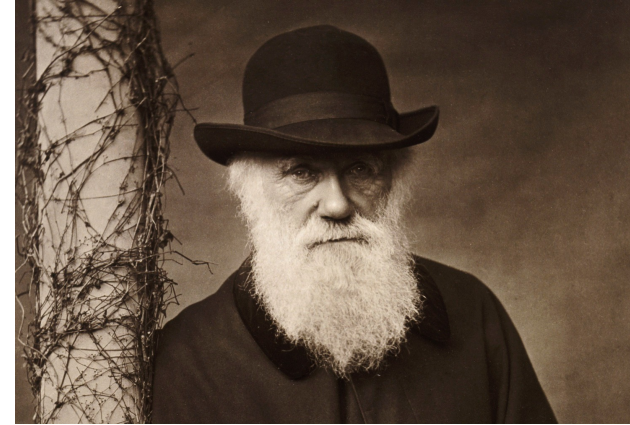
Darwin's big idea: Evolution by Natural Selection



Nothing in Biology Makes Sense Except in the Light of Evolution

BY THEODOSIUS DOBZHANSKY

THE AMERICAN BIOLOGY TEACHER, MARCH 1973



Game Theory in Cancer

PROCEEDINGS B

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Darwin review



Cite this article: Brown JS. 2016 Why Darwin would have loved evolutionary game theory. *Proc. R. Soc. B* **283**: 20160847. <http://dx.doi.org/10.1098/rspb.2016.0847>

Received: 20 April 2016
Accepted: 16 August 2016

Subject Areas:
behaviour, ecology, evolution

Keywords:
evolutionary game theory, adaptation, fitness, natural selection, evolutionarily stable strategy, cancer

Author for correspondence:

Joel S. Brown
e-mail: squirrel@uic.edu

Why Darwin would have loved evolutionary game theory

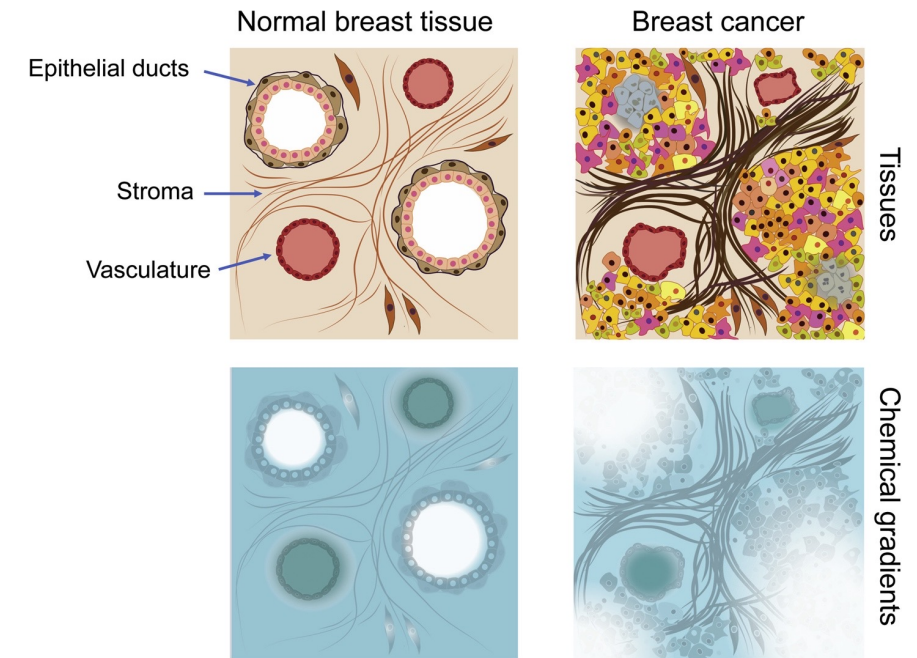
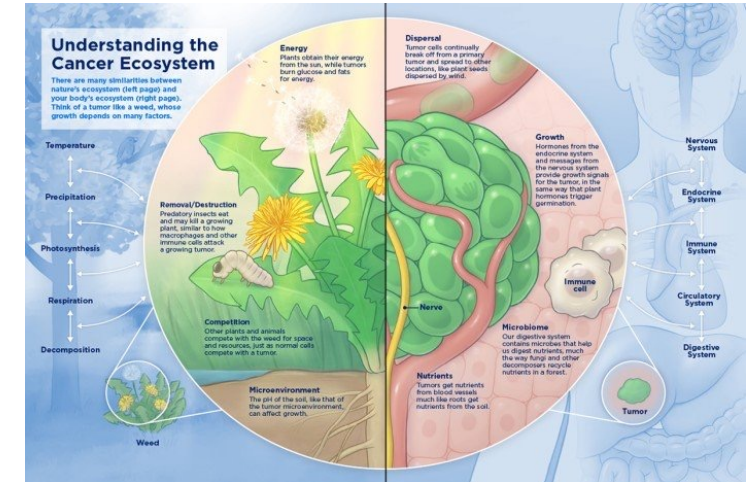
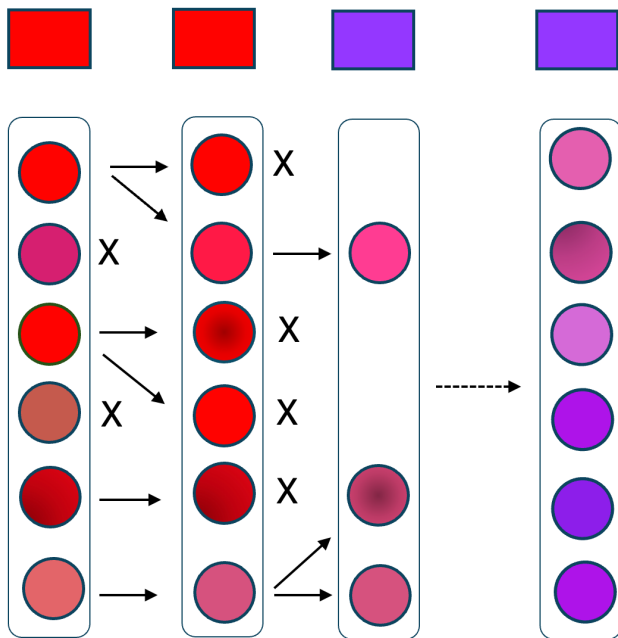
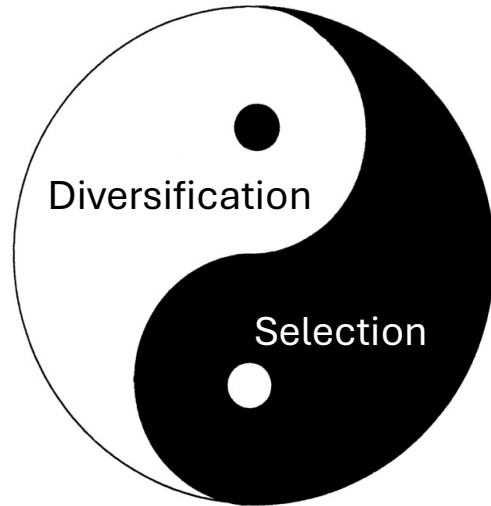
Joel S. Brown

Department of Biological Sciences, University of Illinois at Chicago, Chicago, IL 60607, USA

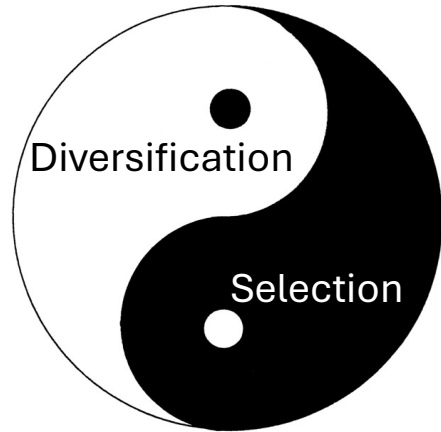
JSB, 0000-0001-9255-3355

Humans have marvelled at the fit of form and function, the way organisms' traits seem remarkably suited to their lifestyles and ecologies. While natural selection provides the scientific basis for the fit of form and function, Darwin found certain adaptations vexing or particularly intriguing: sex ratios, sexual selection and altruism. The logic behind these adaptations resides in frequency-dependent selection where the value of a given heritable phenotype (i.e. strategy) to an individual depends upon the strategies of others. Game theory is a branch of mathematics that is uniquely suited to solving such puzzles. While game theoretic thinking enters into Darwin's arguments and those of evolutionists through much of the twentieth century, the tools of evolutionary game theory were not available to Darwin or most evolutionists until the 1970s, and its full scope has only unfolded in the last three decades. As a consequence, game theory is applied and appreciated rather spottily. Game theory not only applies to matrix games and social games, it also applies to speciation, macroevolution and perhaps even to cancer. I assert that life and natural selection are a game, and that game theory is the appropriate logic for framing and understanding adaptations. Its scope can include behaviours within species, state-dependent strategies (such as male, female and so much more), speciation and coevolution, and expands beyond microevolution to macroevolution. Game theory clarifies aspects of ecological and evolutionary stability in ways useful to understanding eco-evolutionary dynamics, niche construction and ecosystem engineering. In short, I would like to think that Darwin would have found game theory uniquely useful for his theory of natural selection. Let us see why this is so.

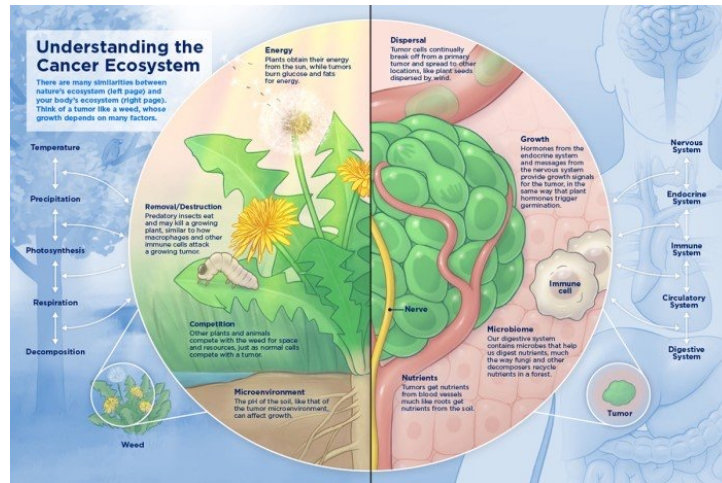
Cancer as an eco-evolutionary process



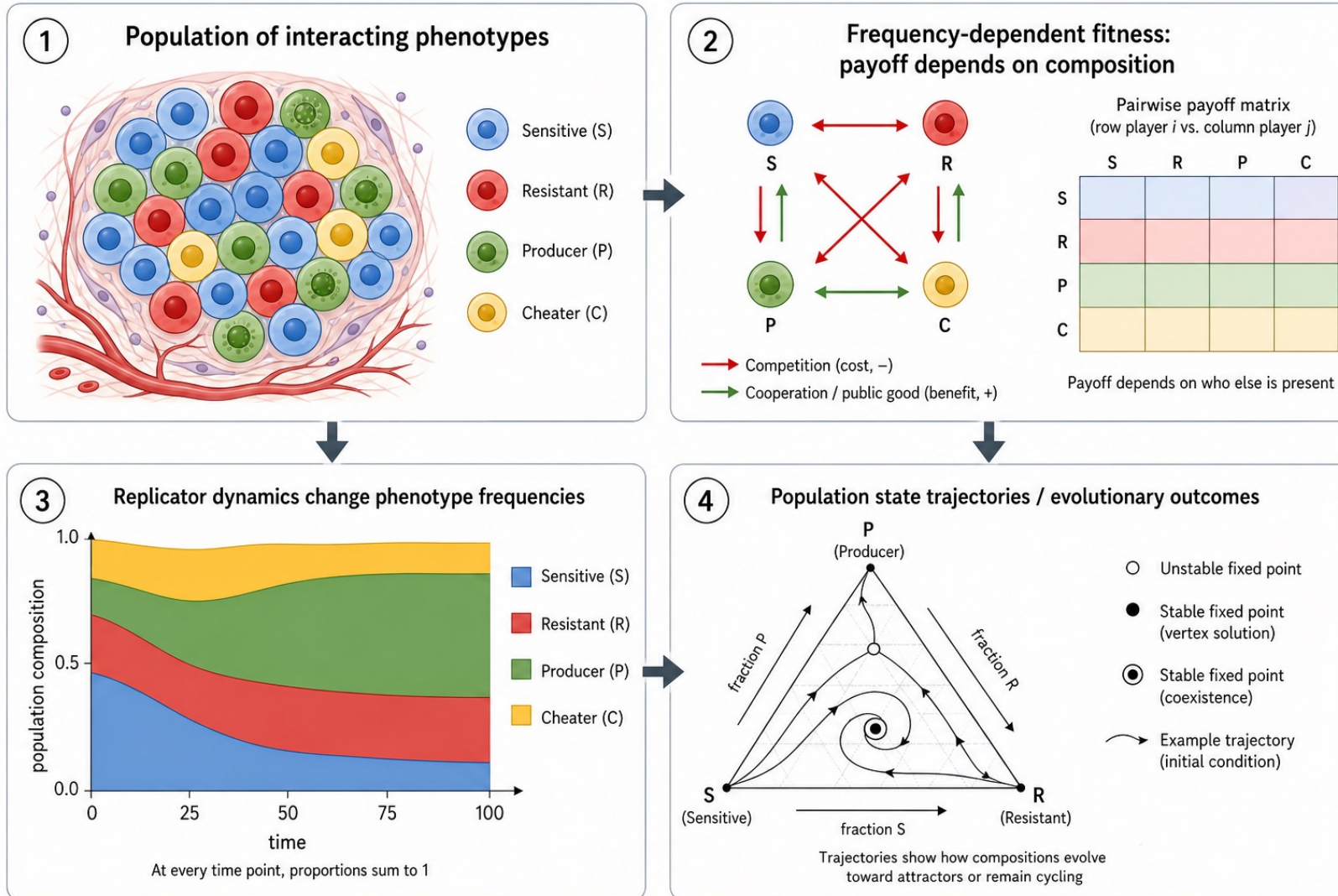
What makes cancer suitable for game theory analyses



- **Heterogeneous replicating populations**
- **Spatial/environmental heterogeneity**
- **Competition for limiting resources**
 - Nutrients (building blocks and energy sources)
 - Oxygen and redox
 - Growth factors
 - Space
- **Interactions**
 - Immune system components
 - Other non-malignant cell types
 - Other tumor cell types



Game Theory in Cancer



- (1) Tumors as replicating populations
- (2) Subpopulations defined by distinct frequency-dependent payoffs
- (3) Dynamics driven by replication and fitness
- (4) ESS

Game Theory in Cancer

Dynamic Games and Applications (2022) 12:313–342
<https://doi.org/10.1007/s13235-021-00397-w>

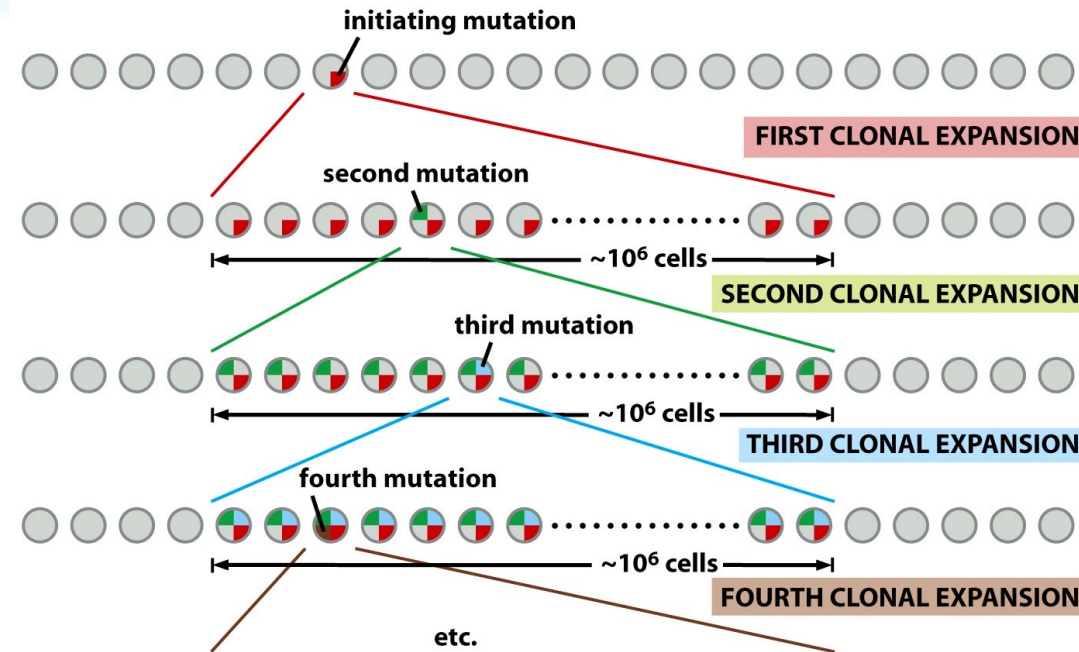


The Contribution of Evolutionary Game Theory to Understanding and Treating Cancer

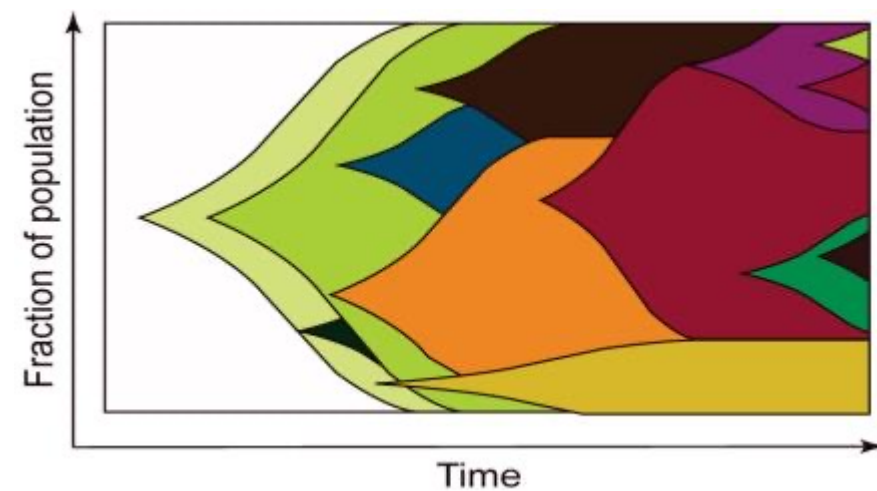
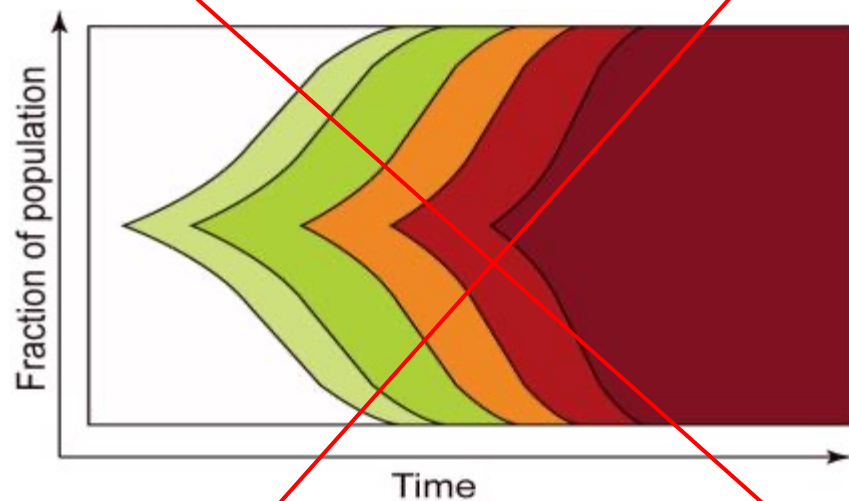
Benjamin Wöfl^{1,2} · Hedy te Rietmole³ · Monica Salvioli^{4,5} ·
Artem Kaznatcheev^{6,7} · Frank Thuijsman⁵ · Joel S. Brown^{8,9} ·
Boudewijn Burgering^{3,10} · Kateřina Staňková^{5,11}

Accepted: 5 July 2021 / Published online: 30 August 2021
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Case in point: causes and consequences of intratumor heterogeneity



The Biology of Cancer (© Garland Science 2007), Robert Weinberg



Marusyk & Polyak **BBA 2010**

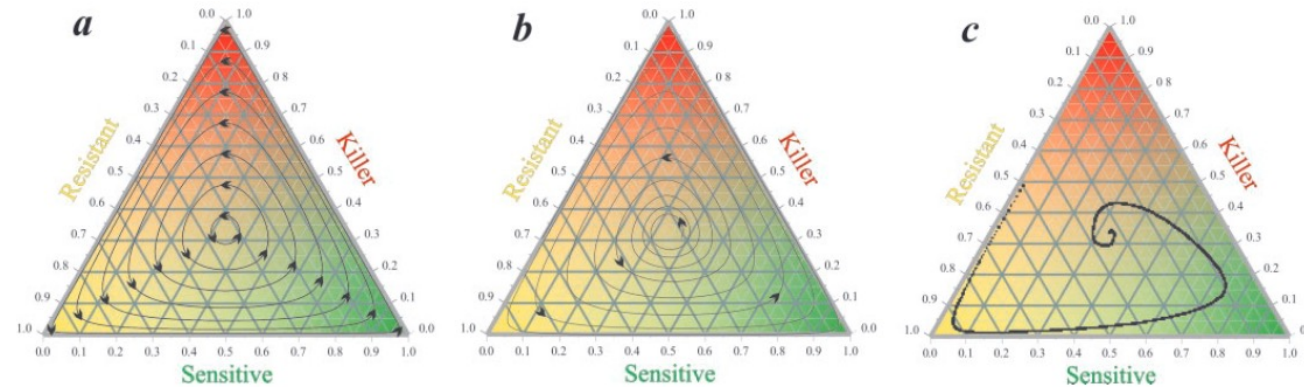
Game Theory in biodiversity

Chemical warfare between microbes promotes biodiversity

Tamás L. Czárán^{*†}, Rolf F. Hoekstra^{*§}, and Ludo Pagie^{*||}

PNAS 2002

^{*}Theoretical Biology and Ecology Research Group of the Hungarian Academy of Sciences and Eötvös University, H-1117 Budapest, Pázmány Péter sétány 1/C, Hungary; [†]Laboratory of Genetics, Department of Plant Sciences, Wageningen University, Dreijenlaan 2, 6703 HA, Wageningen, The Netherlands; [‡]Department of Bioinformatics, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands; and [§]Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501



➤ [Proc Natl Acad Sci U S A. 2007 Jan 16;104\(3\):876-81. doi: 10.1073/pnas.0607651104.](#)
Epub 2007 Jan 8.

Cooperation and conflict in microbial biofilms

Joao B Xavier¹, Kevin R Foster

Game Theory in Cancer



European Journal of Cancer
Volume 33, Issue 9, August 1997, Pages 1495-1500



Original paper

Game-theory models of interactions between tumour cells

I.P.M. Tomlinson^{1 2}

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Evolution of cooperation among tumor cells

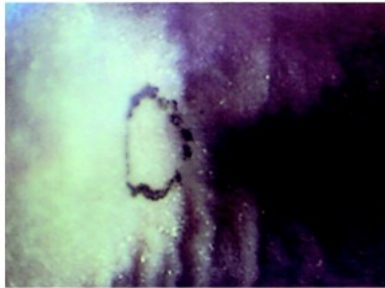
Robert Axelrod^{*†}, David E. Axelrod[‡], and Kenneth J. Pienta[§]

^{*}Gerald R. Ford School of Public Policy and Department of Political Science, University of Michigan, Ann Arbor, MI 48109; [†]Department of Genetics and Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, Piscataway, NJ 08854; and [§]Departments of Internal Medicine and Urology, University of Michigan Medical School, Ann Arbor, MI 48109

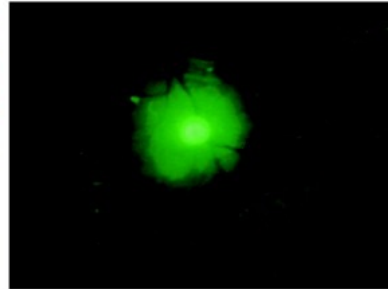
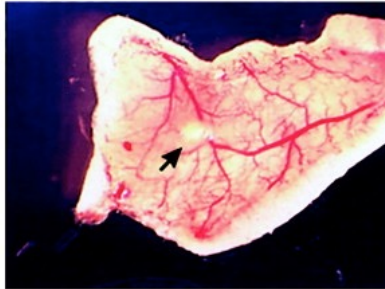
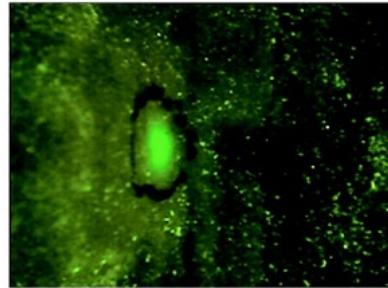
Contributed by Robert Axelrod, July 19, 2006

Tumor growth requires navigating environmental bottlenecks

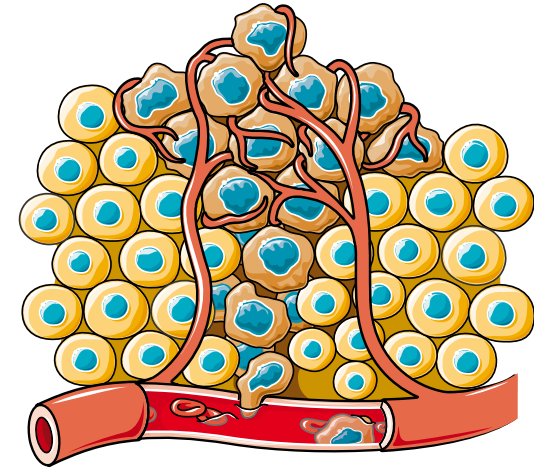
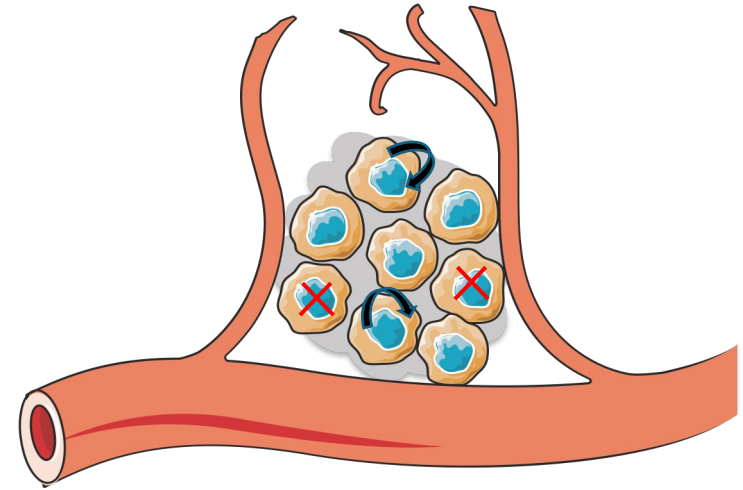
bright field



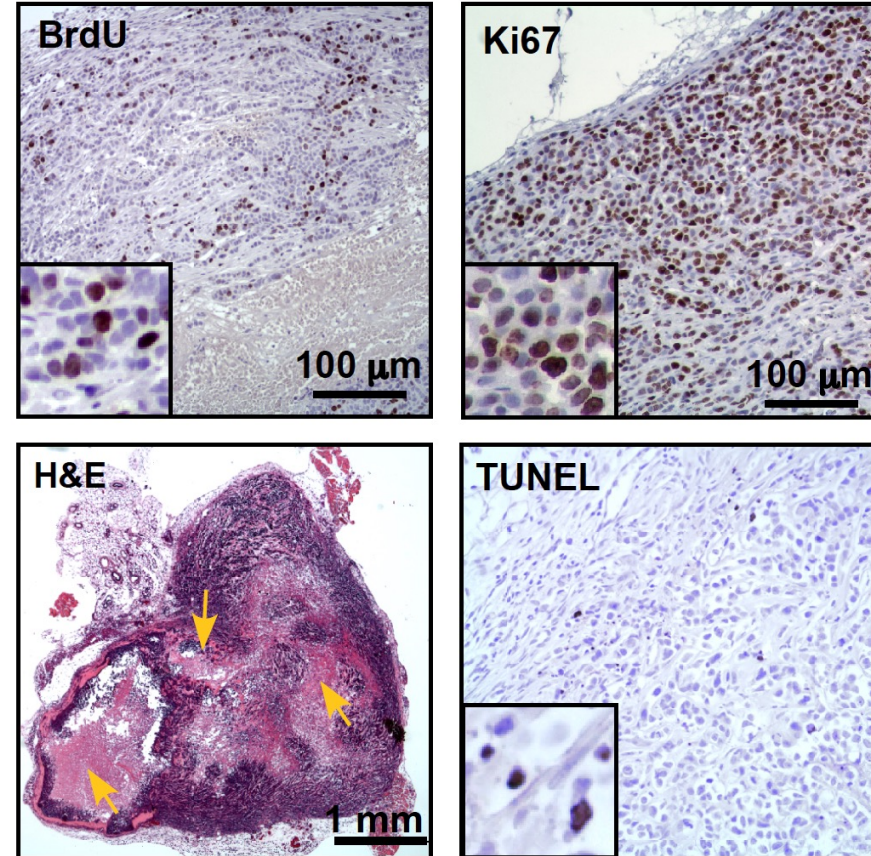
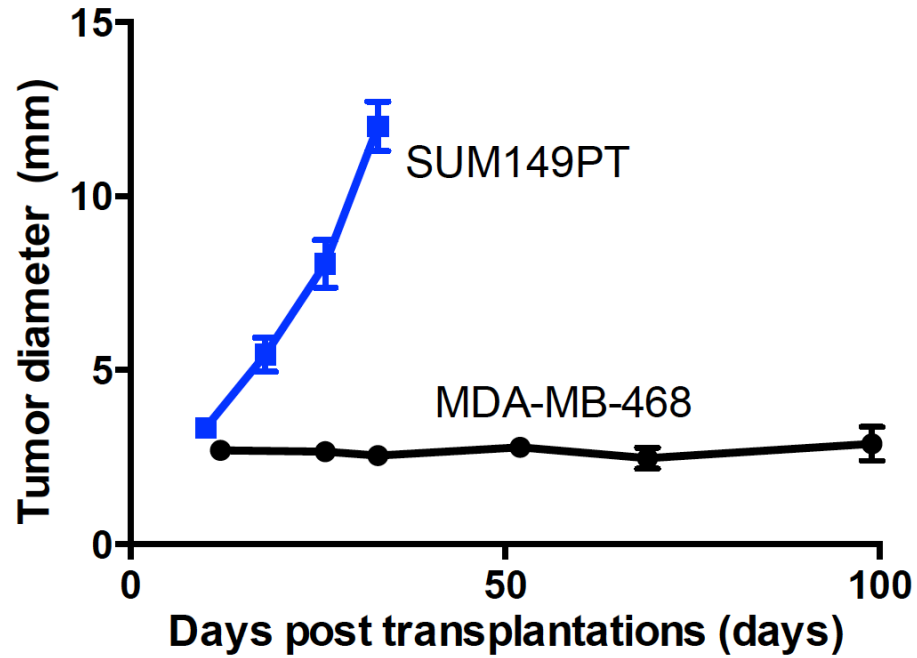
fluorescence



Udagawa et al FASEBJ 2002

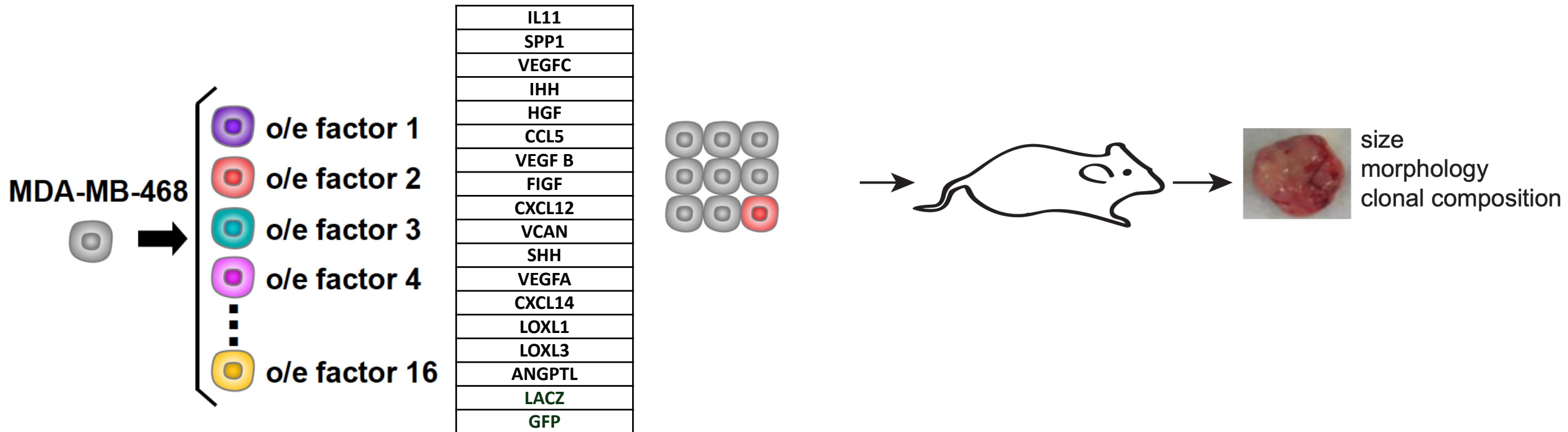


Model system of a tumor growth bottleneck

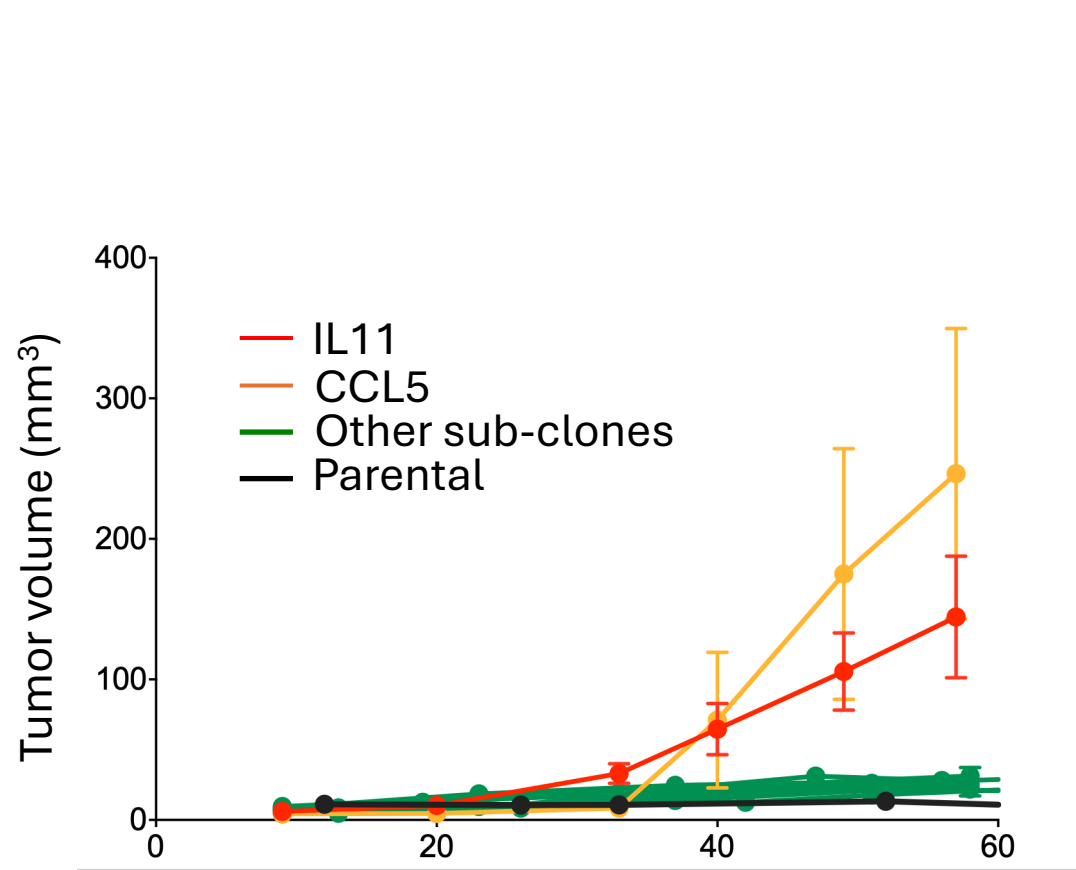


Experimental idea:

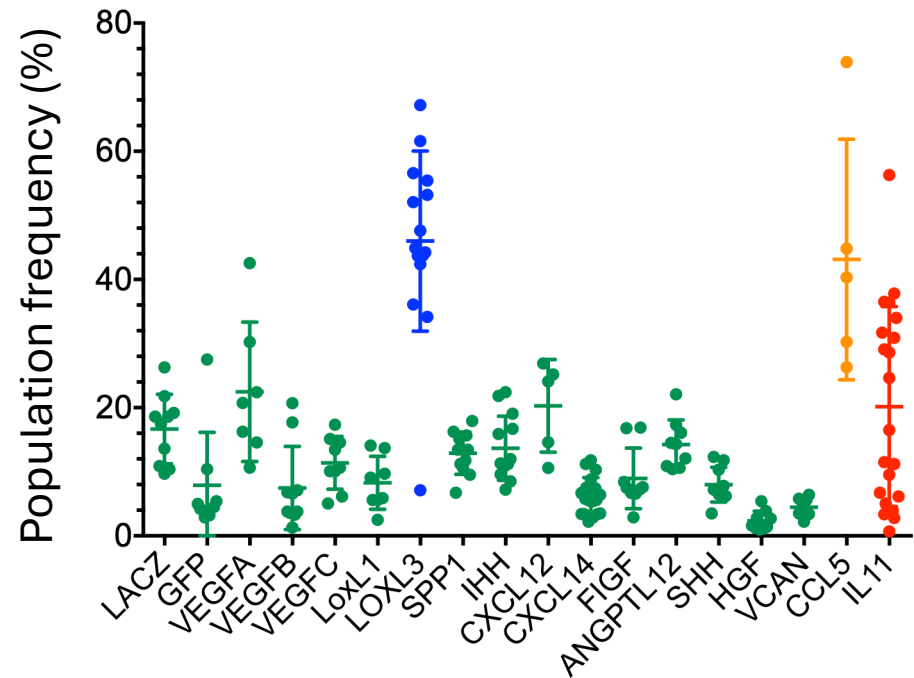
- Find secreted factors capable of overcoming the bottleneck
- Interrogate fitness consequences



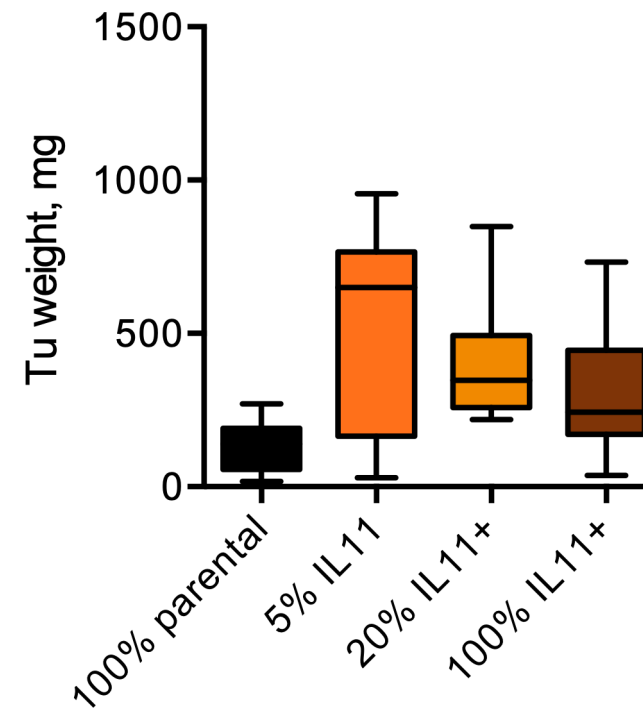
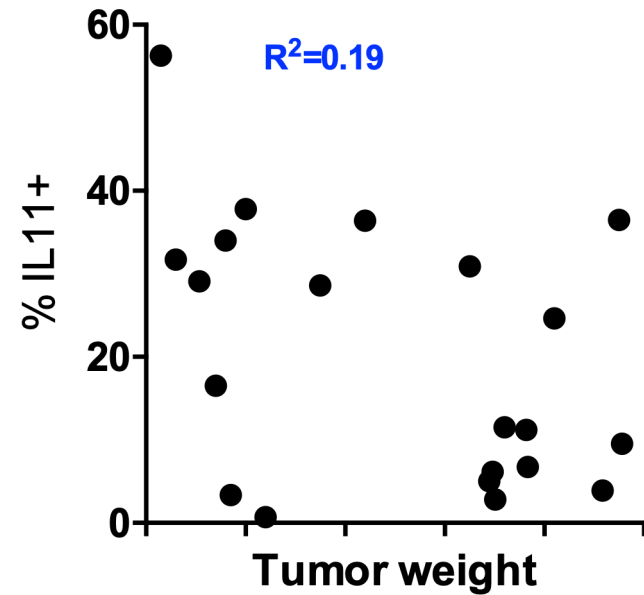
The ability to drive population growth is not strictly linked with higher fitness



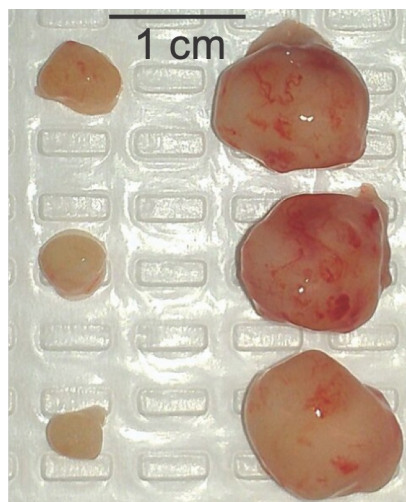
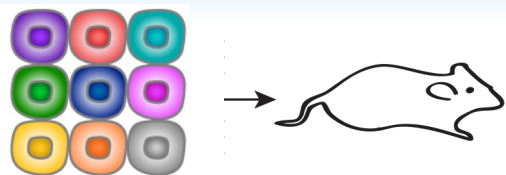
IL11
CCL5
VEGFC
IHH
HGF
SPP1
VEGF B
FIGF
CXCL12
VCAN
SHH
VEGFA
CXCL14
LOXL1
LOXL3
ANGPTL
LACZ
GFP



The ability to drive population growth is not strictly linked with higher fitness

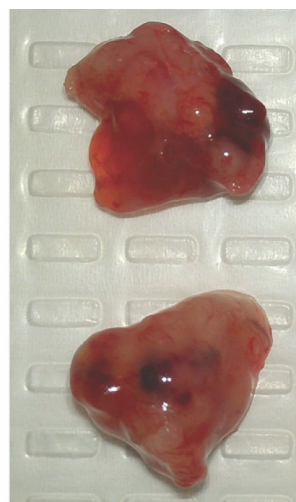


Clonal interactions lead to emergence of new important phenotypes



Parental

IL11



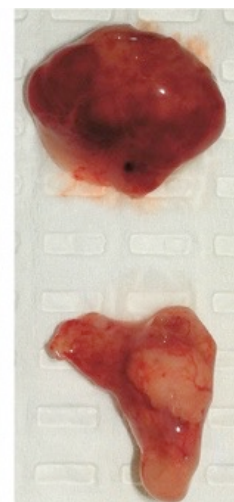
Polyclonal



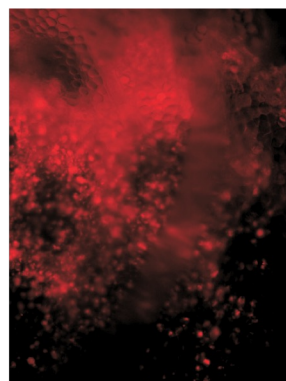
Polyclonal
w/o IL11



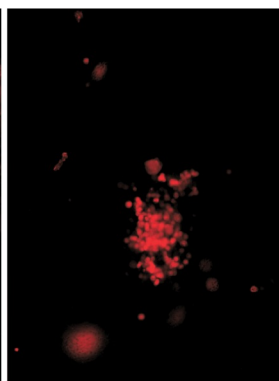
FIGF



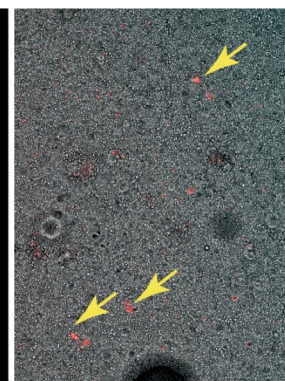
FIGF+IL11



Lymph node

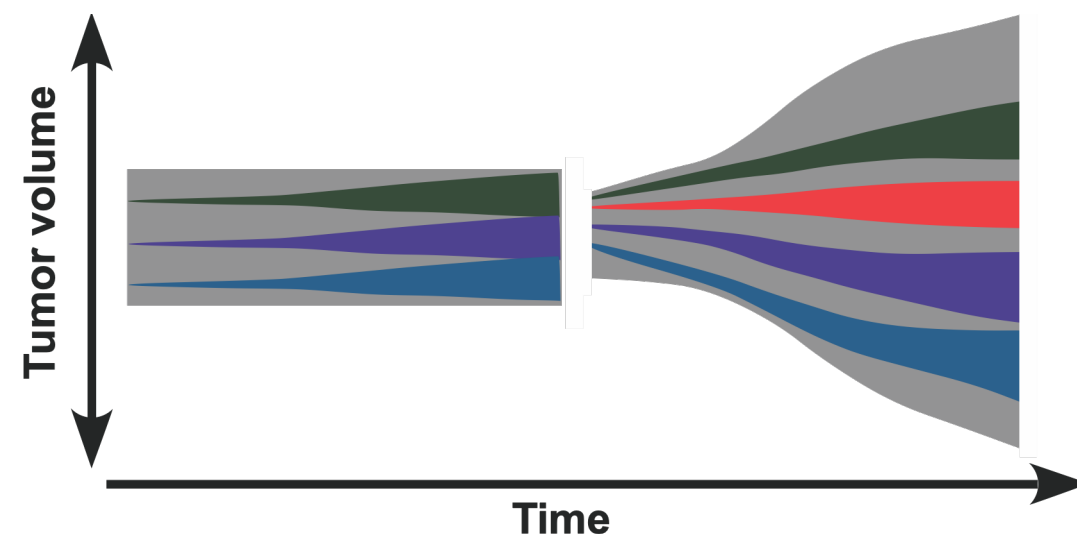
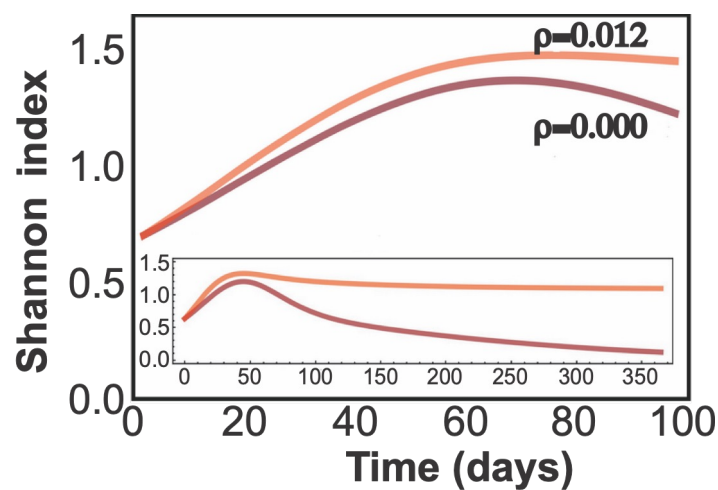
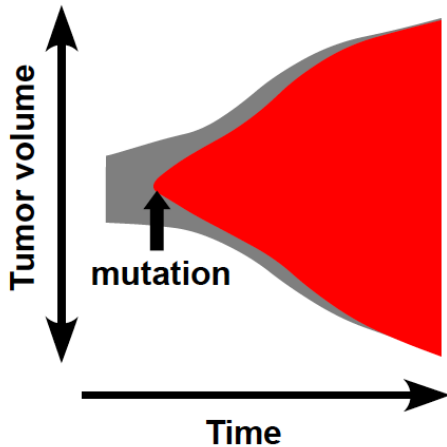
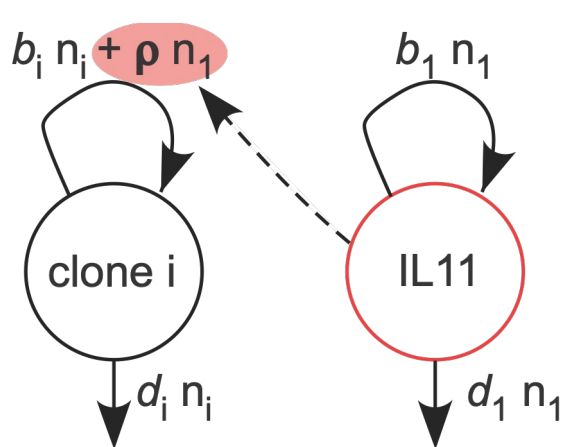


Peritoneal wall



Bone marrow

Clonal interactions stabilize clonal heterogeneity



Outline

1. Why Game Theory is well-suited to address important questions in cancer biology
2. Evolution of therapy resistance through the lenses of EGT
3. Limitations and challenges

Despite remarkable responses, therapies eventually fail

Baseline



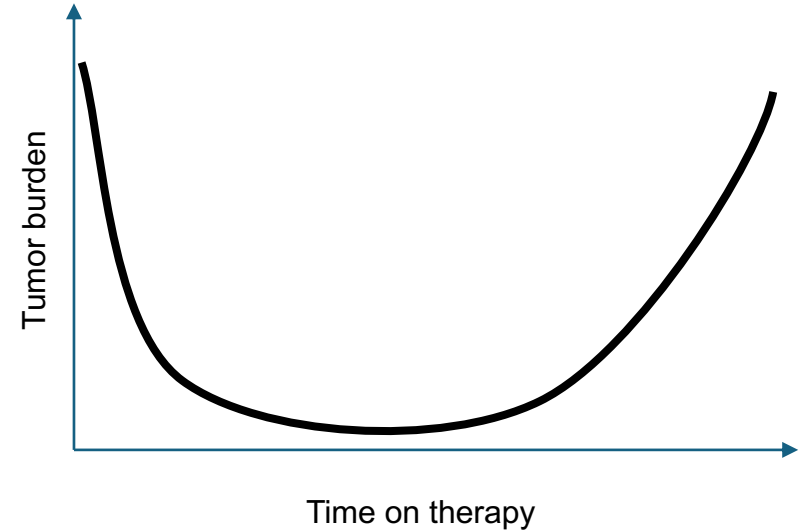
Remission



Relapse

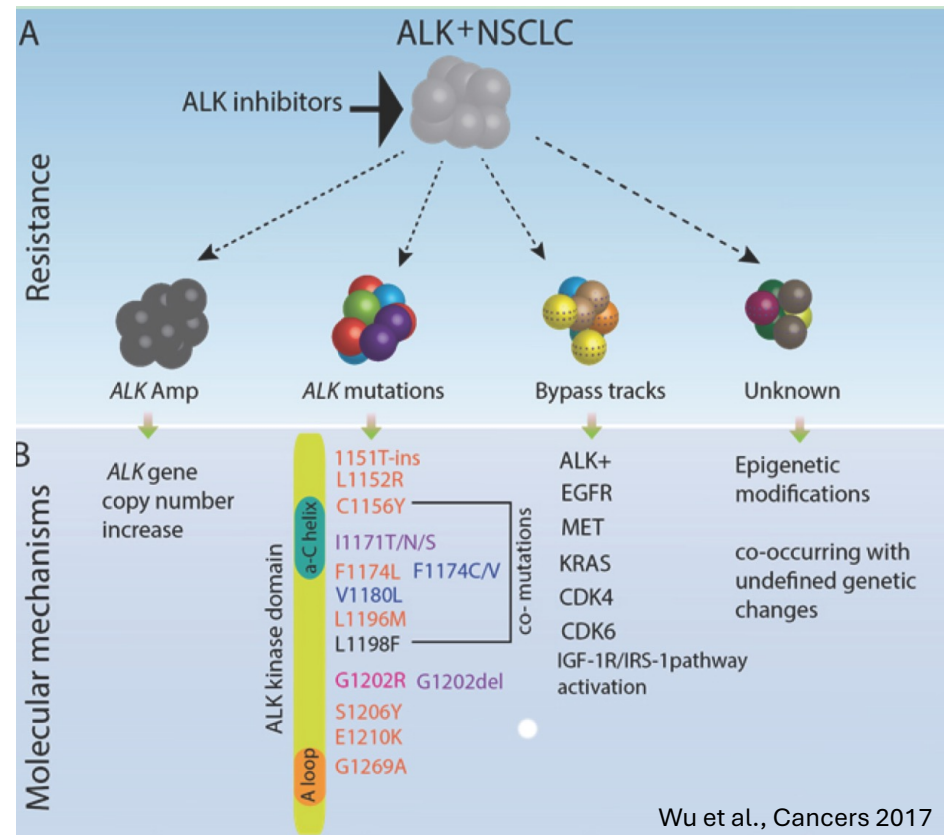


Wagle et al JCO 2011

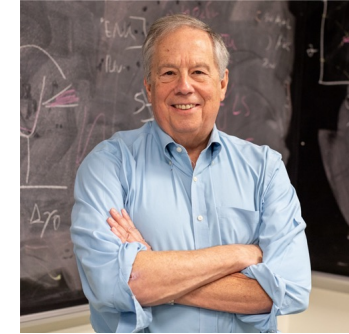
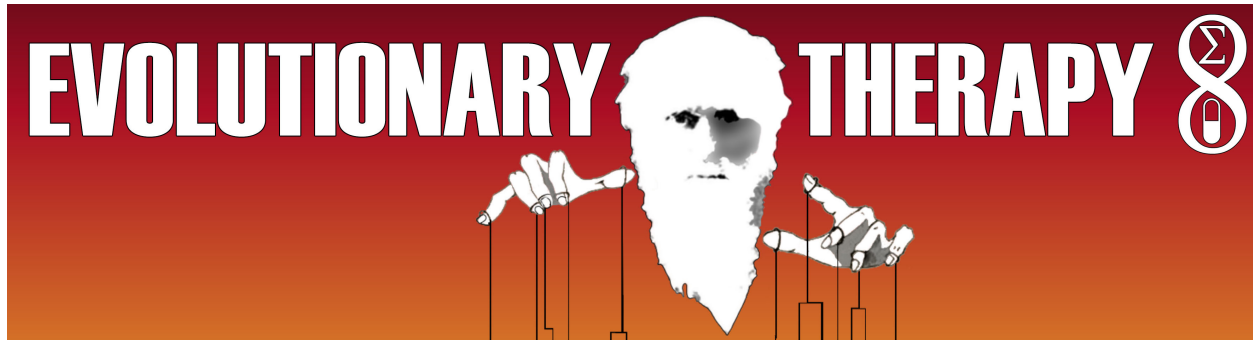


- A subset of tumor cells survives therapy
- **Residual populations evolve**

Major efforts are directed to discovery/targeting resistance mechanisms



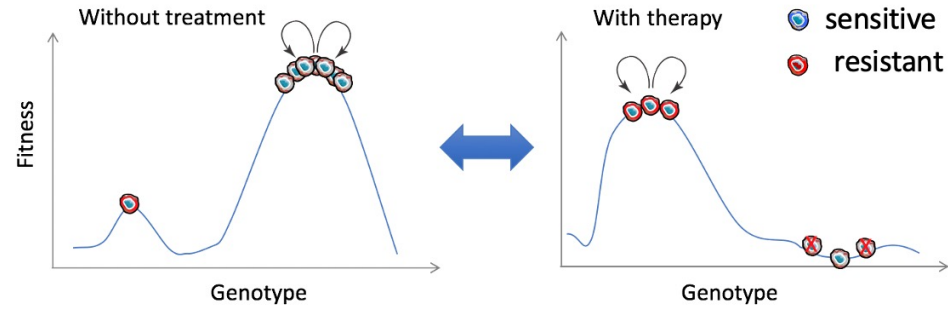
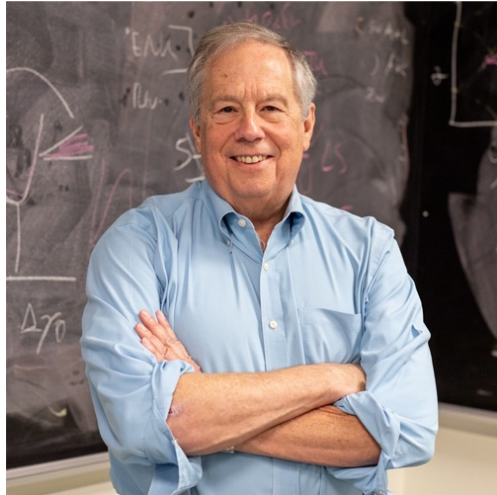
Harnessing understanding of cancer evolution to improve responses



- Predict how cancer responds to treatment
- Develop therapeutic strategies that anticipate these changes
 - Extinction
 - Steer to indolence
 - Extension of remissions



Adaptive Therapy Concept

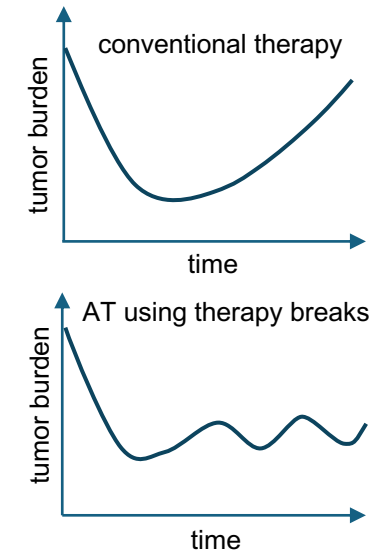
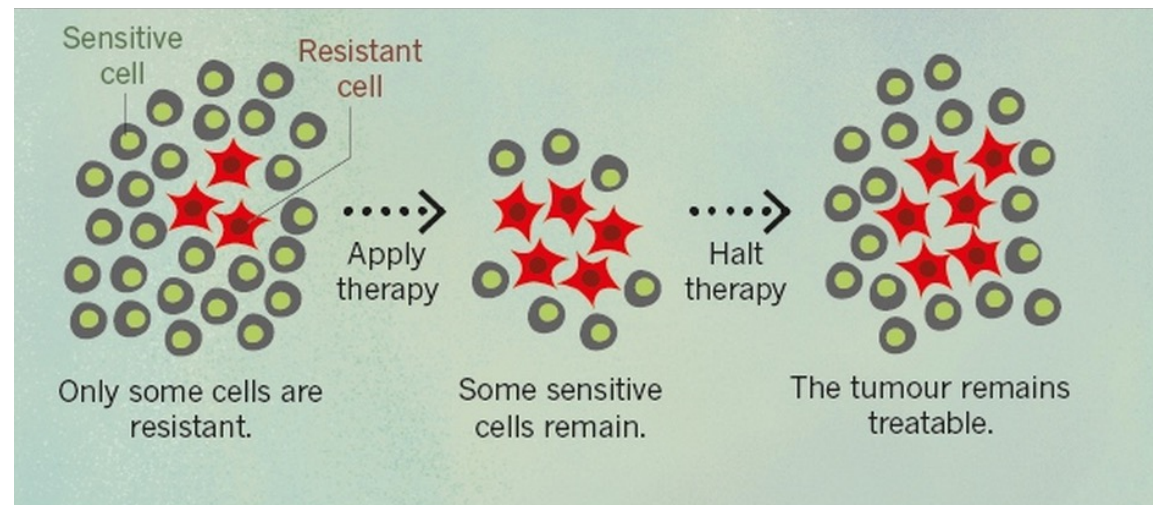
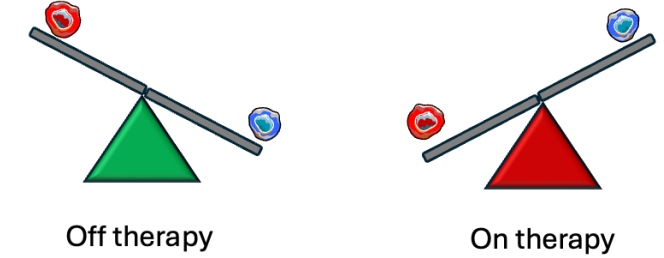


Cancer Res. 2012 Dec 15;72(24):6362-70. doi: 10.1158/0008-5472.CAN-12-2235. Epub 2012 Oct 12.

Evolutionary approaches to prolong progression-free survival in breast cancer.

Silva AS¹, Kam Y, Khin ZP, Minton SE, Gillies RJ, Gatenby RA.

⊕ Author information



Evolutionary Therapy through the lenses of EGT

Published in final edited form as:

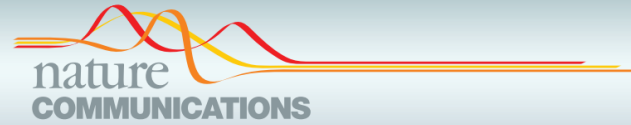
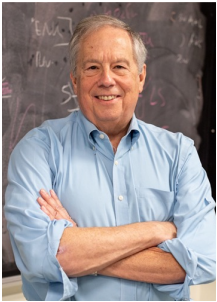
Phys Biol. 2012 December ; 9(6): . doi:10.1088/1478-3975/9/6/065007.

Cancer treatment as a game: integrating evolutionary game theory into the optimal control of chemotherapy

Paul A. Orlando¹, Robert A. Gatenby², and Joel S. Brown³

“Here, we view **cancer treatment as a game** in which the **oncologists choose a therapy** and **tumors ‘choose’ an adaptive strategy**. We propose the oncologist can gain an upper hand in the game by choosing treatment strategies that anticipate the adaptations of the tumor. ... The tumor ‘chooses’ its strategy by natural selection and the oncologist chooses her strategy by solving a control problem.”

Applying game theory towards adaptive therapies



ARTICLE

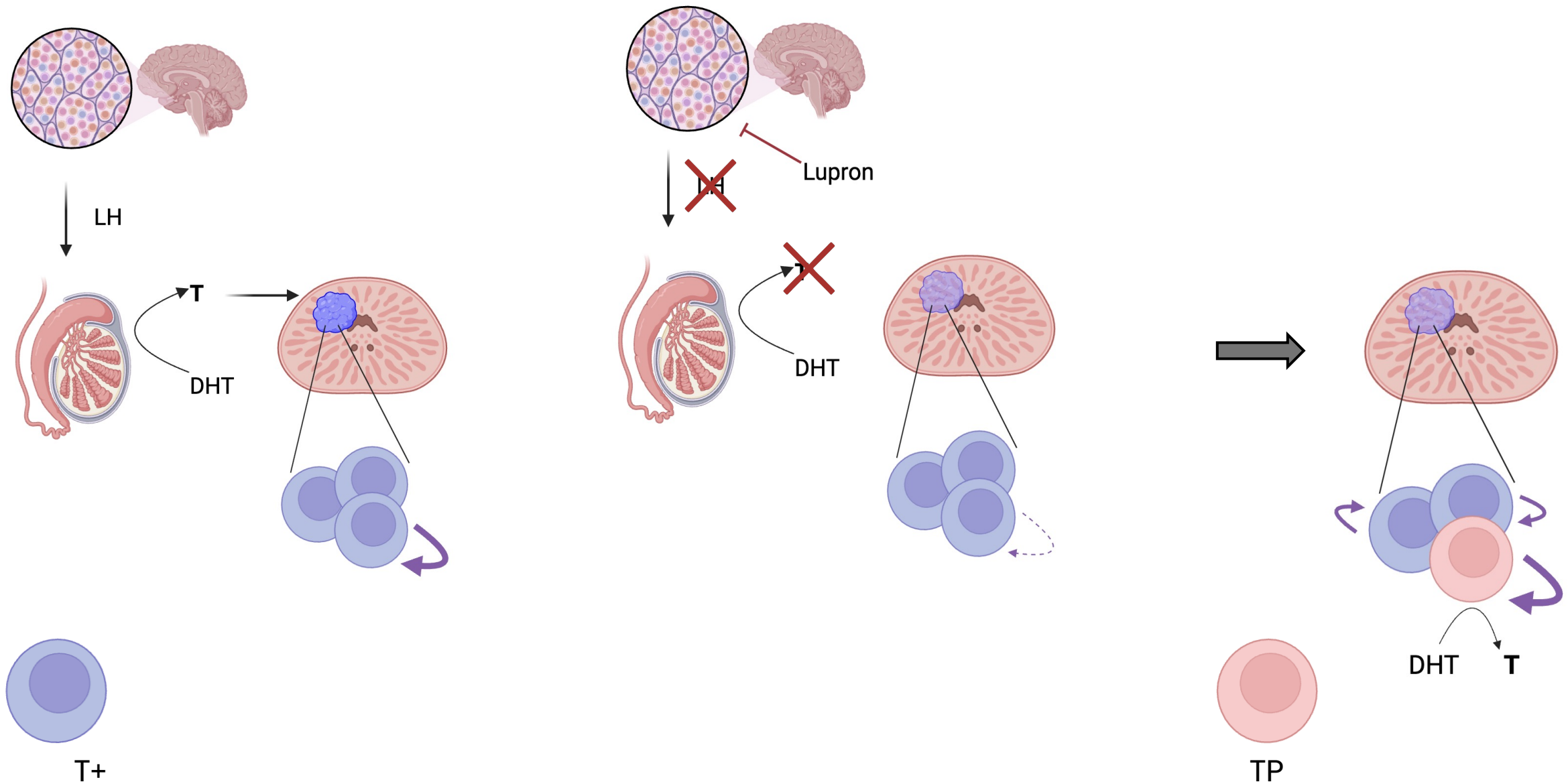
DOI: [10.1038/s41467-017-01968-5](https://doi.org/10.1038/s41467-017-01968-5)

OPEN

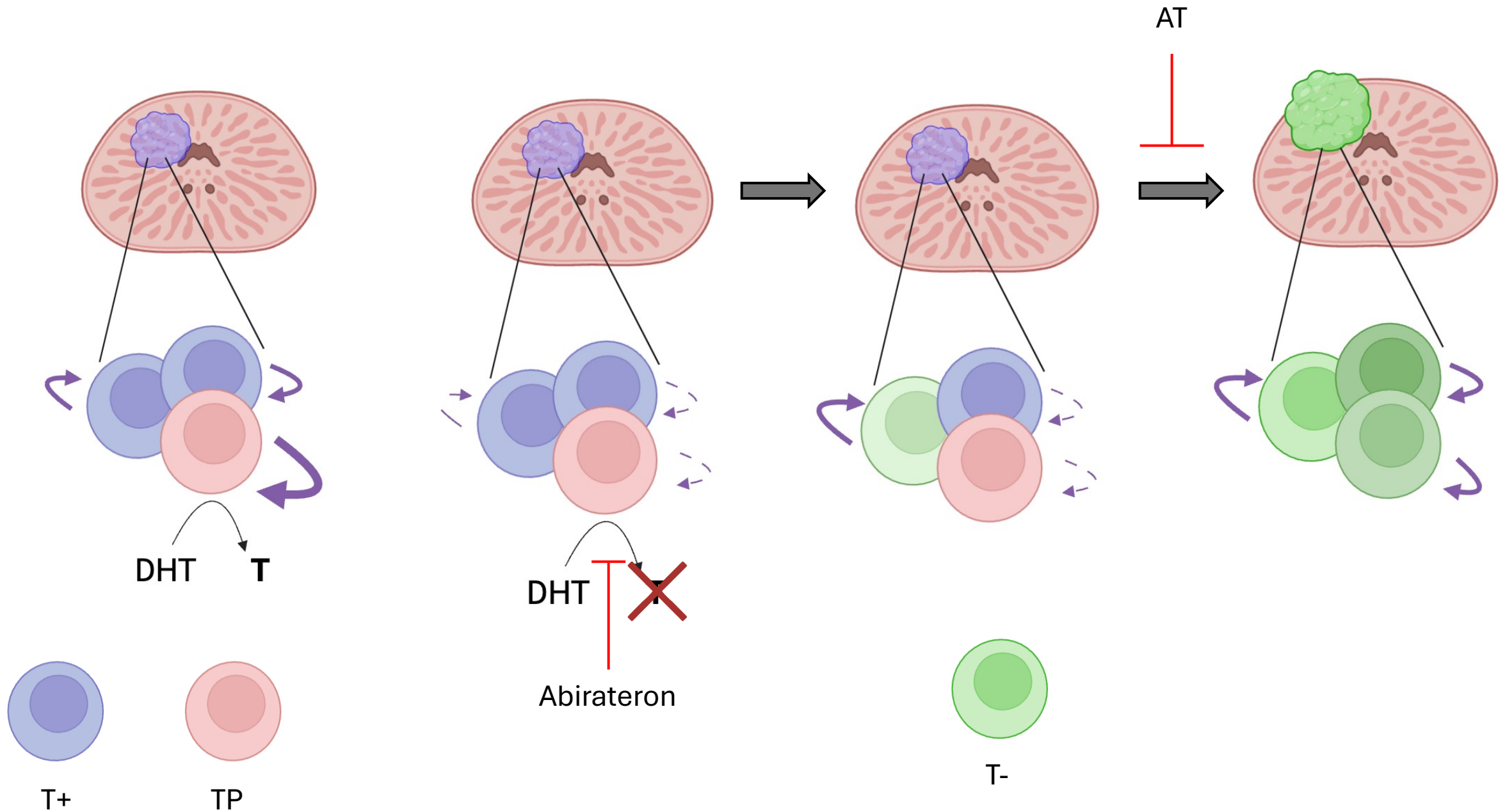
Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer

Jingsong Zhang¹, Jessica J. Cunningham², Joel S. Brown^{2,3} & Robert A. Gatenby^{2,4}

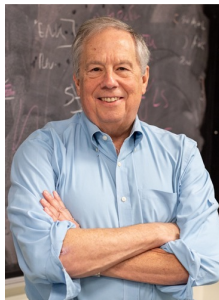
Context: testosterone dependent prostate cancers



Context: evolution of testosterone - independence

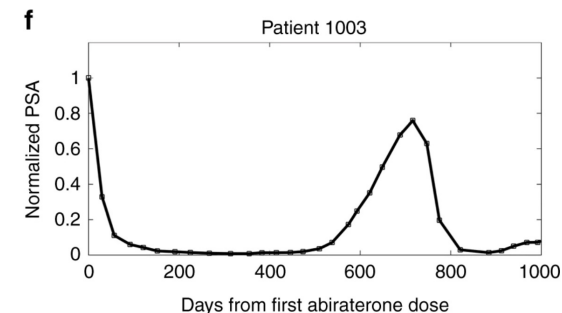
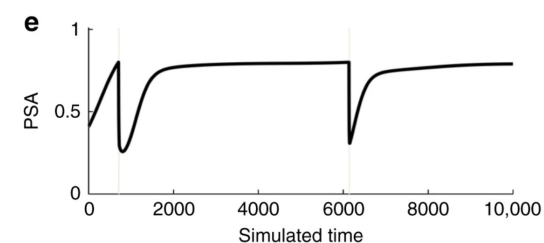
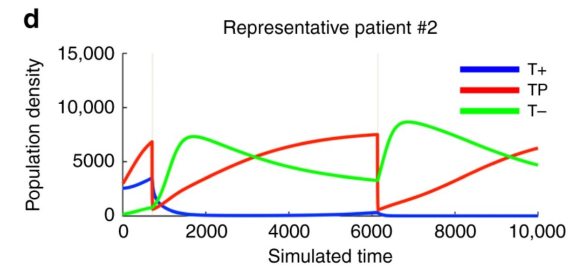
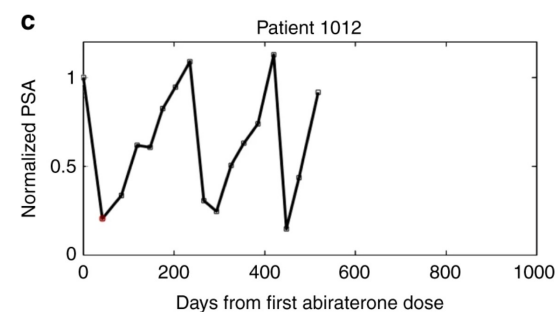
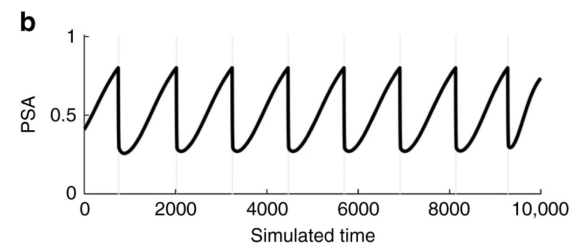
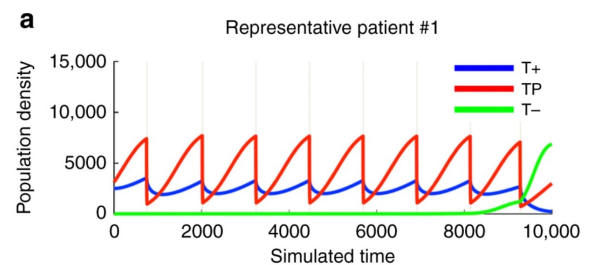


EGT provides conceptual framework to structure AT

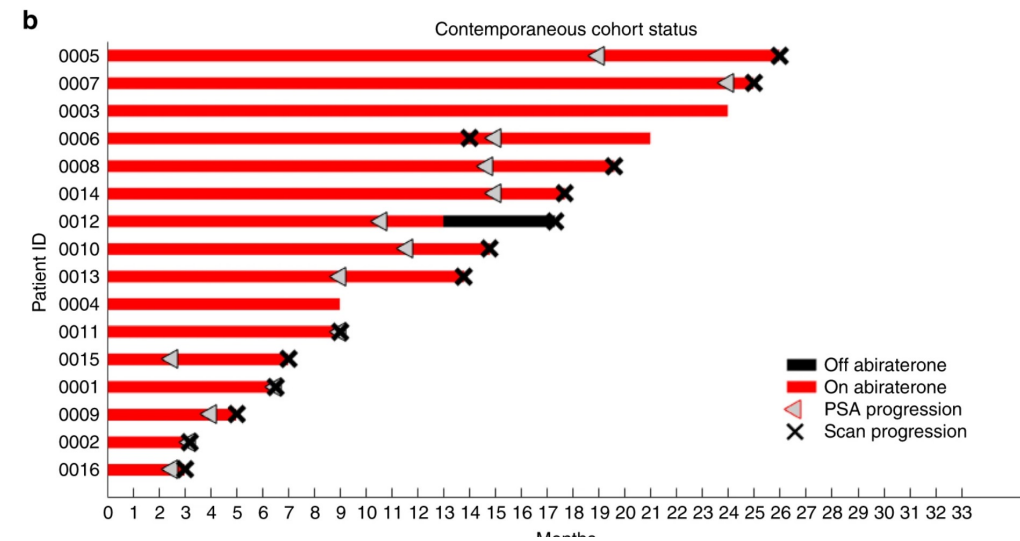
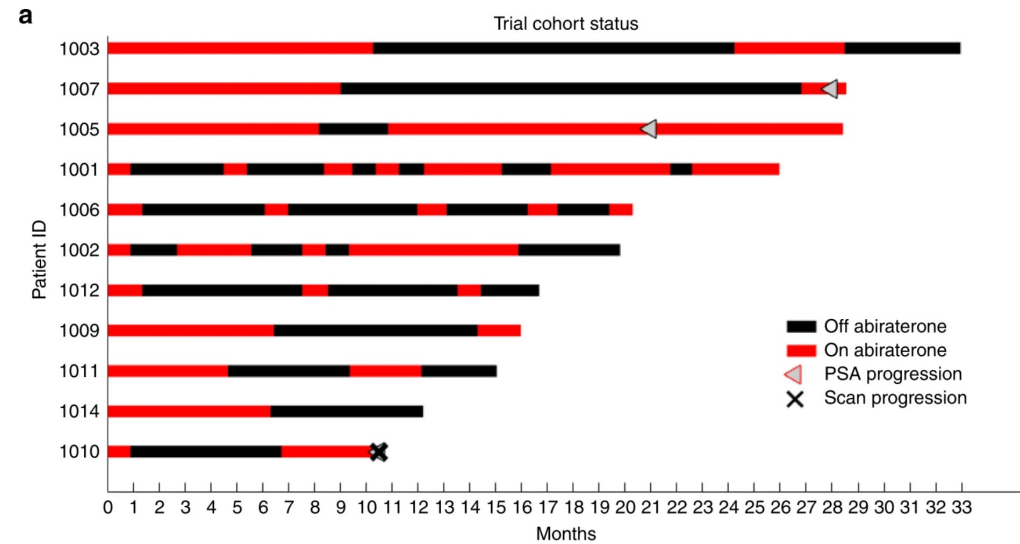
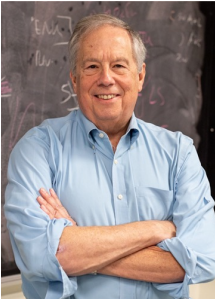


$a_{ij} =$

	T+	TP	T-
T+	α_{11}	α_{12}	α_{13}
TP	α_{21}	α_{22}	α_{23}
T-	α_{31}	α_{32}	α_{33}



Superiority of AT in a clinical trial



Review

Optimizing Cancer Treatment Using Game Theory A Review

Kateřina Stařková, PhD^{1,2}; Joel S. Brown, PhD³; William S. Dalton, MD, PhD^{3,4};
Robert A. Gatenby, MD³

» [Author Affiliations](#)

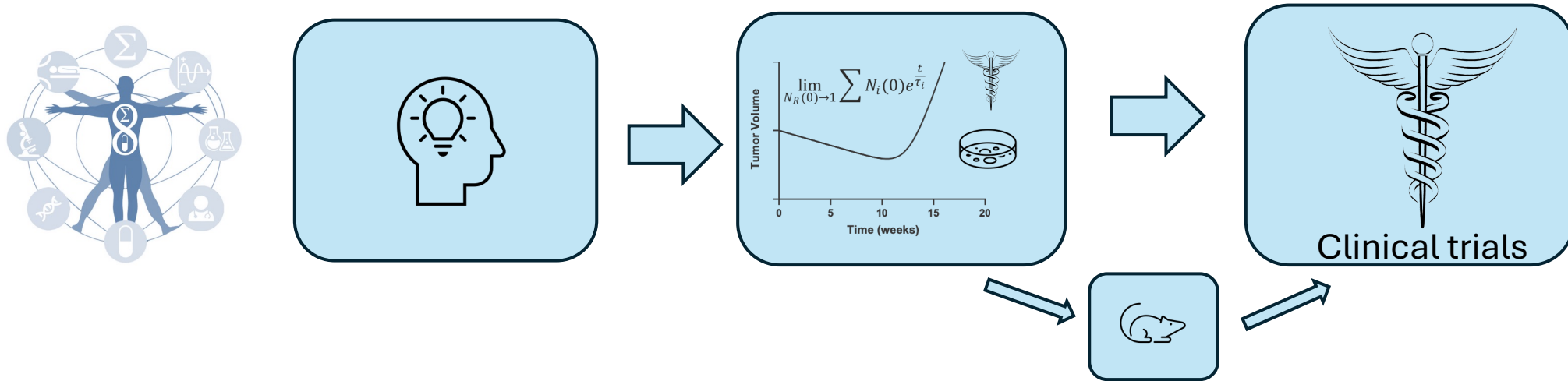
Outline

1. Why Game Theory is well-suited to address important questions in cancer biology
2. Evolution of therapy resistance through the lenses of EGT
3. **Challenges and limitations**

Understanding the game



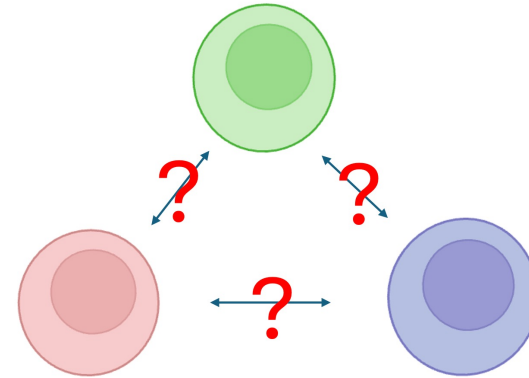
Evolutionary therapy pipeline



How do we identify the game?

$a_{ij} =$

	T+	TP	T-
T+	α_{11}	α_{12}	α_{13}
TP	α_{21}	α_{22}	α_{23}
T-	α_{31}	α_{32}	α_{33}



Inferring games from experimental data



“**Effective game**” as an assayable hidden variable

nature
ecology & evolution

Article | Published: 18 February 2019

Fibroblasts and alectinib switch the evolutionary games played by non-small cell lung cancer

Artem Kaznatcheev✉, Jeffrey Peacock, David Basanta, Andriy Marusyk✉ & Jacob G. Scott✉

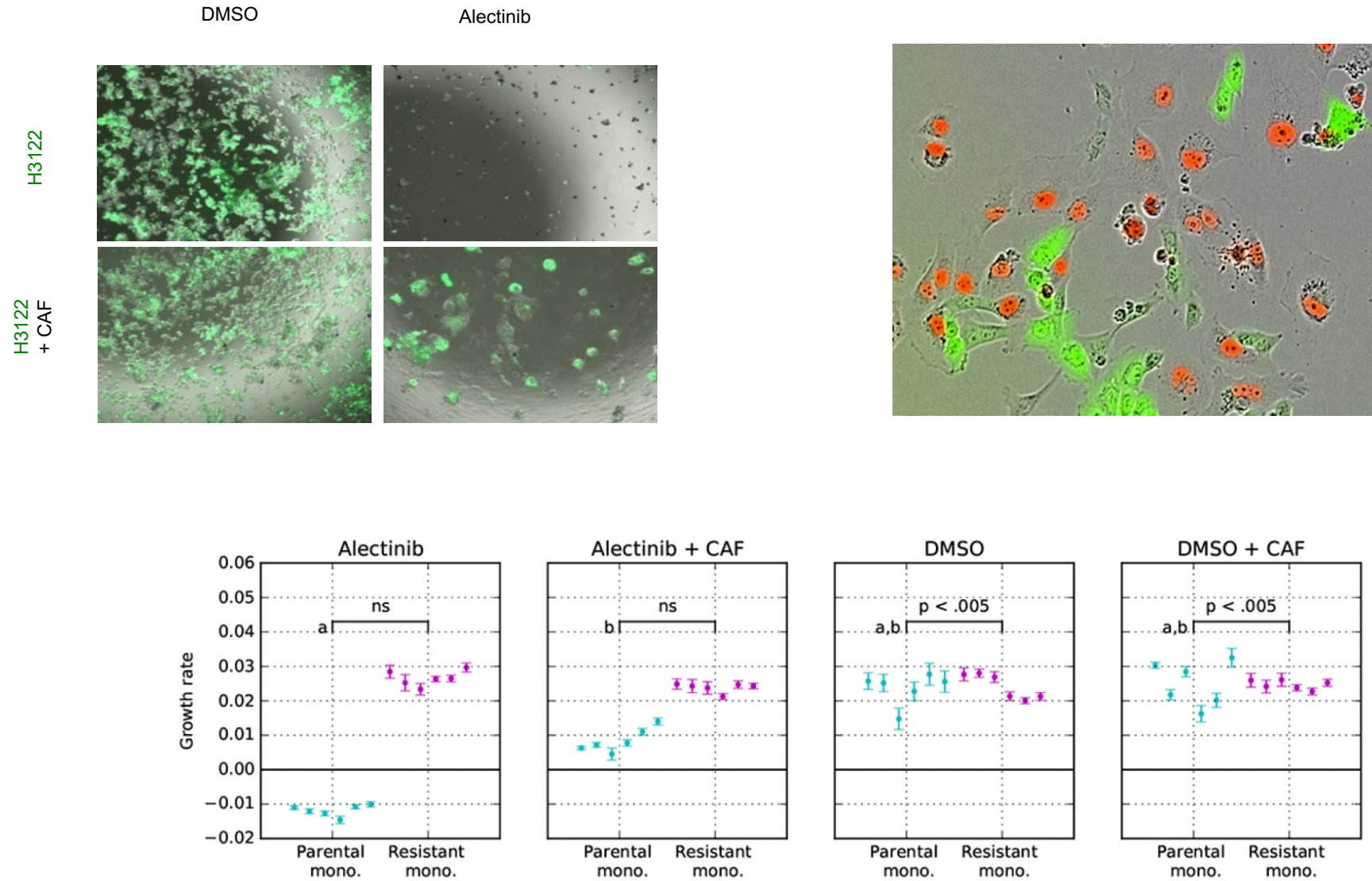
Nature Ecology & Evolution 3, 450–456 (2019) | Download Citation ↓

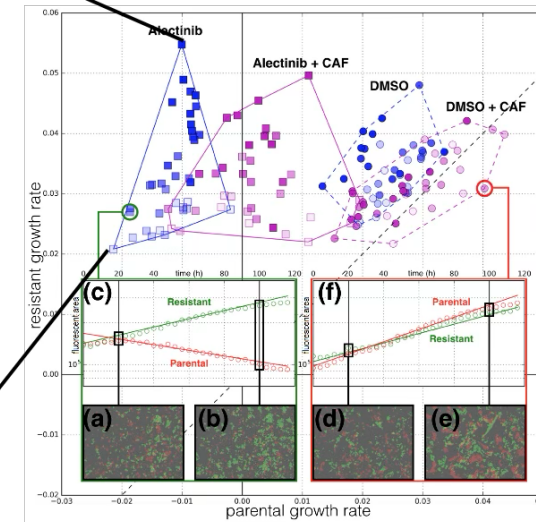
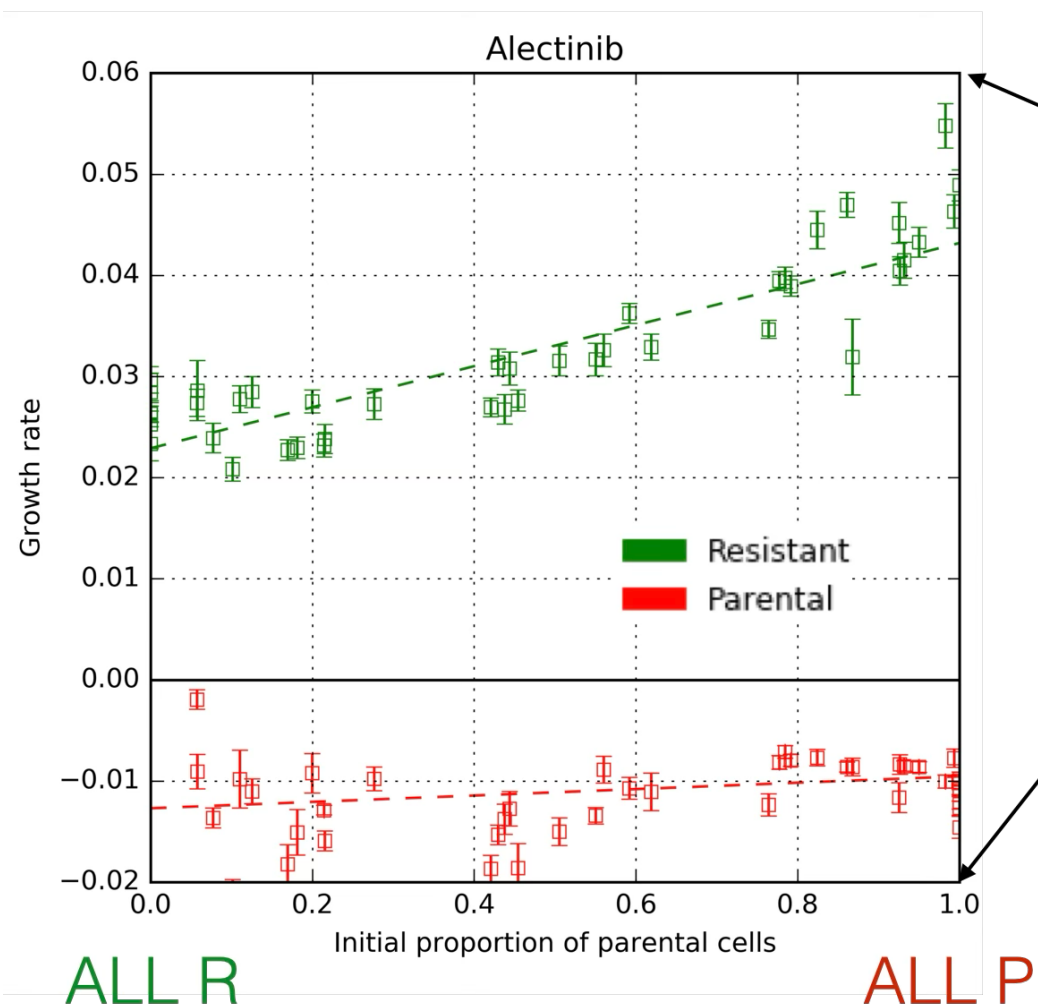
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T+	α_{11}	α_{12}	α_{13}
TP	α_{21}	α_{22}	α_{23}
T-	α_{31}	α_{32}	α_{33}

Frequency-dependent growth can be approximated by an “**effective game**” (*population-level rule* that maps the current mix of strategies in the population to the fitness of each strategy)

Inferring games from experimental data





- The absolute and relative fitness of sensitive and resistant cells are frequency-dependent

Next step: from growth rates to payoff matrix

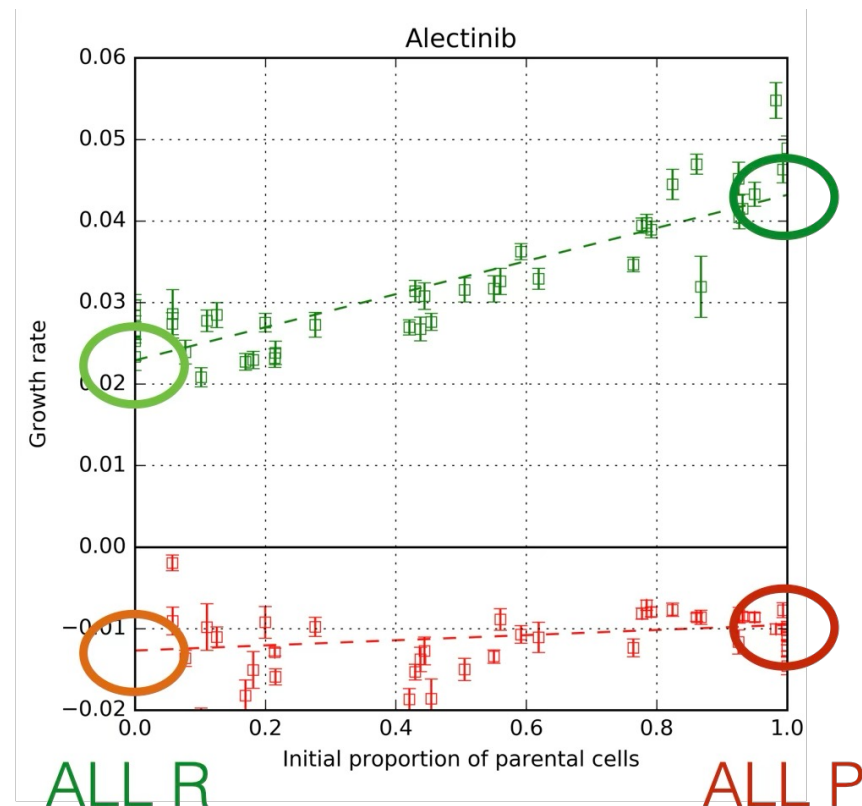
$$\begin{matrix} P & R \\ P & \begin{pmatrix} A & B \\ C & D \end{pmatrix} \\ R & \end{matrix} \Rightarrow \begin{cases} \frac{d}{dt} N_P = N_P \left(A \frac{N_P}{N_T} + B \frac{N_R}{N_T} \right) \\ \frac{d}{dt} N_R = N_R \left(C \frac{N_P}{N_T} + D \frac{N_R}{N_T} \right) \end{cases}$$

$\hat{w}_P$: parental growth rate
 $\hat{w}_R$: resistant growth rate

$$\begin{aligned} A &= -0.01 \\ B &= -0.013 \\ C &= 0.043 \\ D &= 0.023 \end{aligned}$$

Alectinib

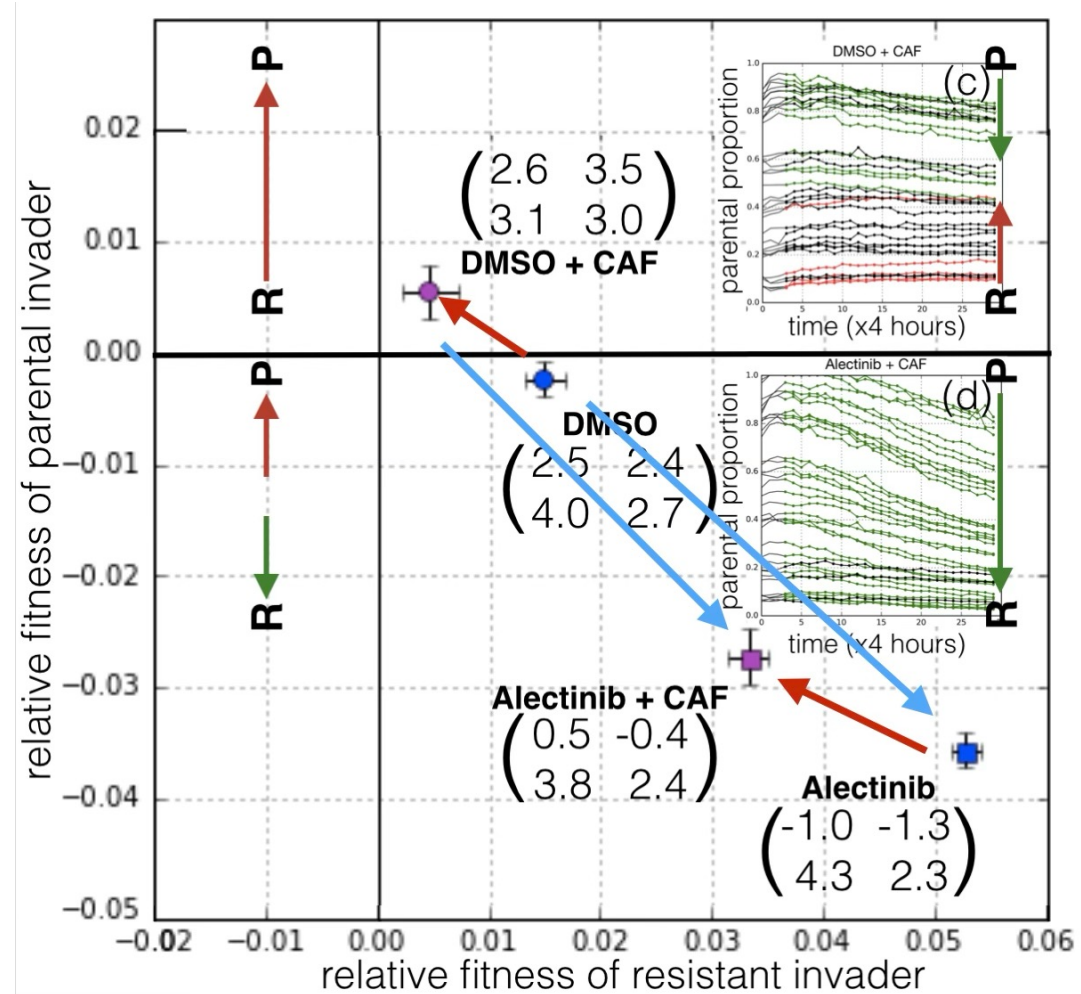
$$\begin{pmatrix} -1.0 & -1.3 \\ 4.3 & 2.3 \end{pmatrix}$$



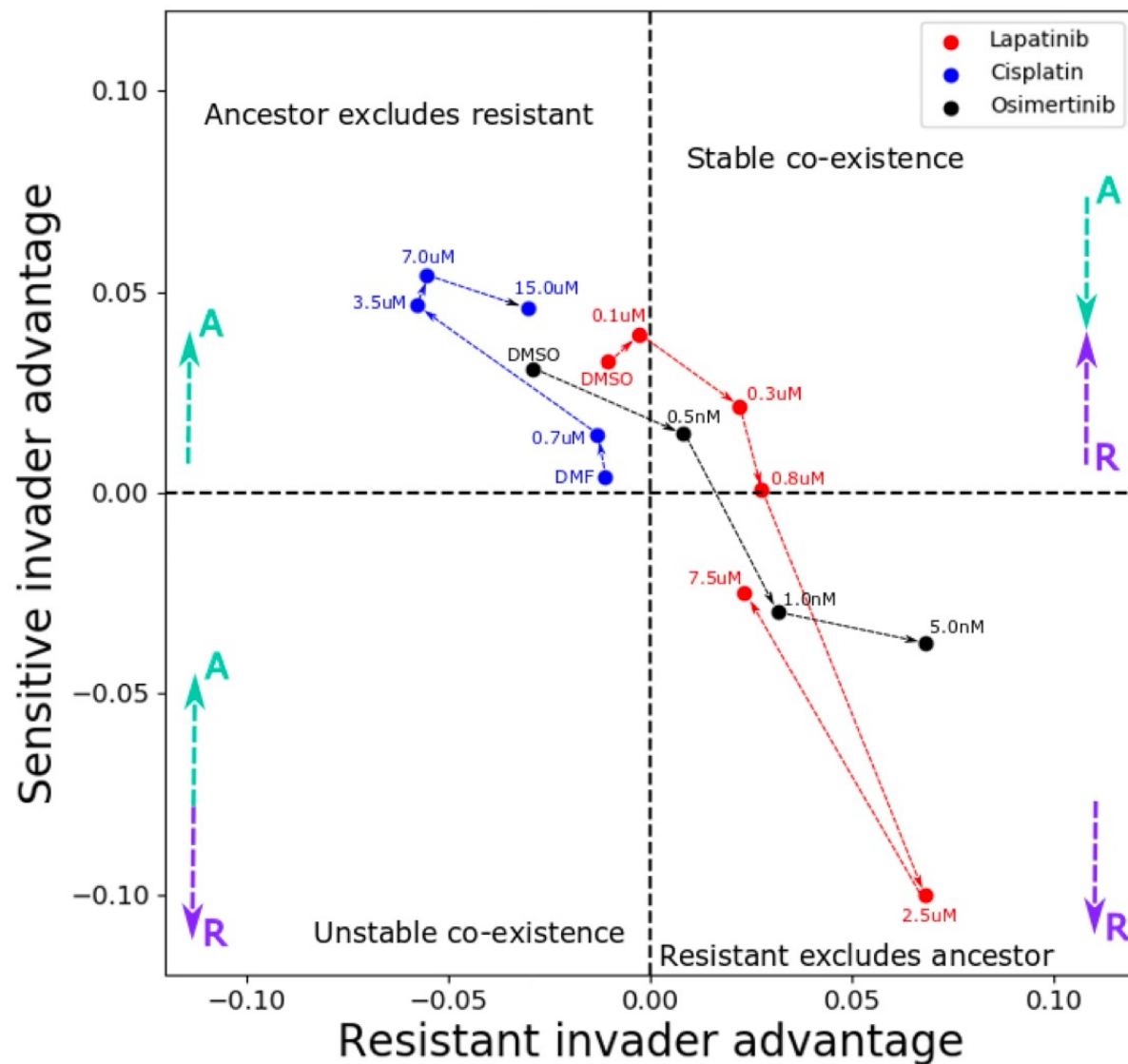
Alectinib and CAF shift the game

Adding CAFs shifts the game up/left

Adding alectinib shifts the game down/right



This could be done with different therapeutic contexts



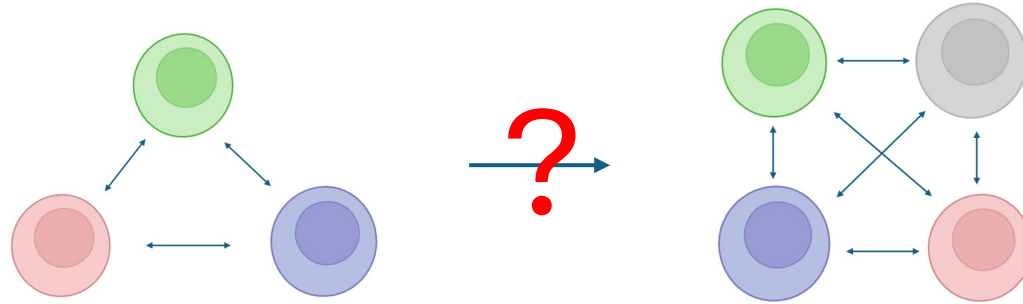
SCIENCE ADVANCES | RESEARCH ARTICLE

CANCER

Measuring competitive exclusion in non-small cell lung cancer

Nathan Farrokhian^{1†}, Jeff Maltas^{2†}, Mina Dinh², Arda Durmaz¹, Patrick Ellsworth¹, Masahiro Hitomi², Erin McClure², Andriy Marusyk³, Artem Kaznatcheev^{4*}, Jacob G. Scott^{1,2,5*}

Game stability?

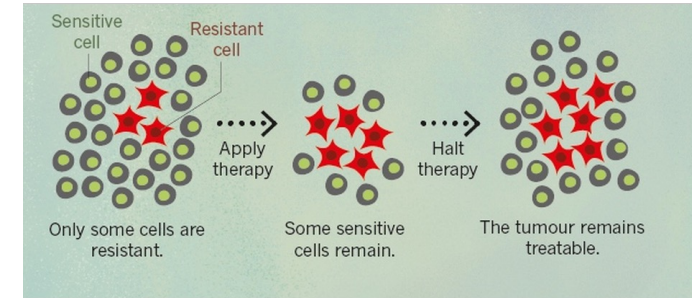
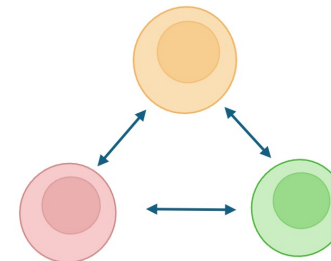
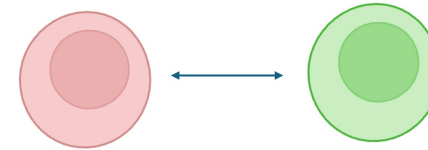
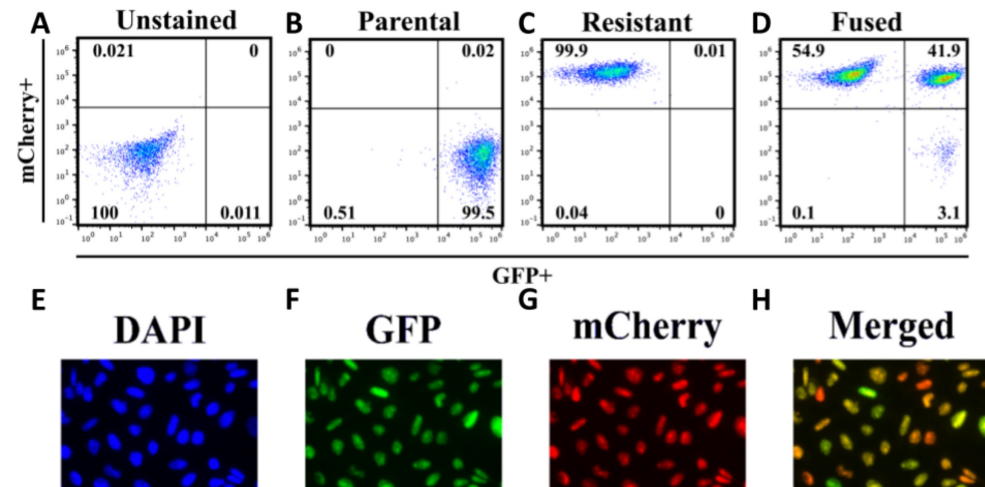


Cancers can create new games

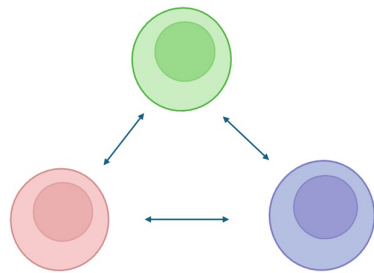
bioRxiv preprint doi: <https://doi.org/10.1101/2024.12.02.626399>; this version posted October 24, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Cell-Cell Fusion in NSCLC Promotes Evolution of Therapeutic Resistance

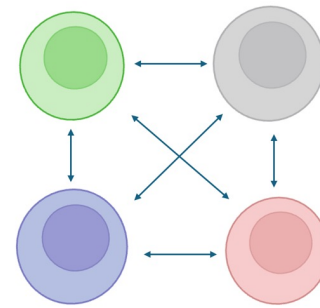
Paulameena V. Shultes^{1, 3, +}, Dagim S. Tadele^{3, 5, +}, Arda Durmaz³, Davis T. Weaver^{1, 3}, Rowan Barker-Clarke³, Mina N. Dinh^{1, 3}, Siqing Liu⁶, Endalkachew A. Alemu⁶, Simon Rayner⁶, Andriy Marusyk⁷, and Jacob G. Scott^{1, 2, 3, 4, *}



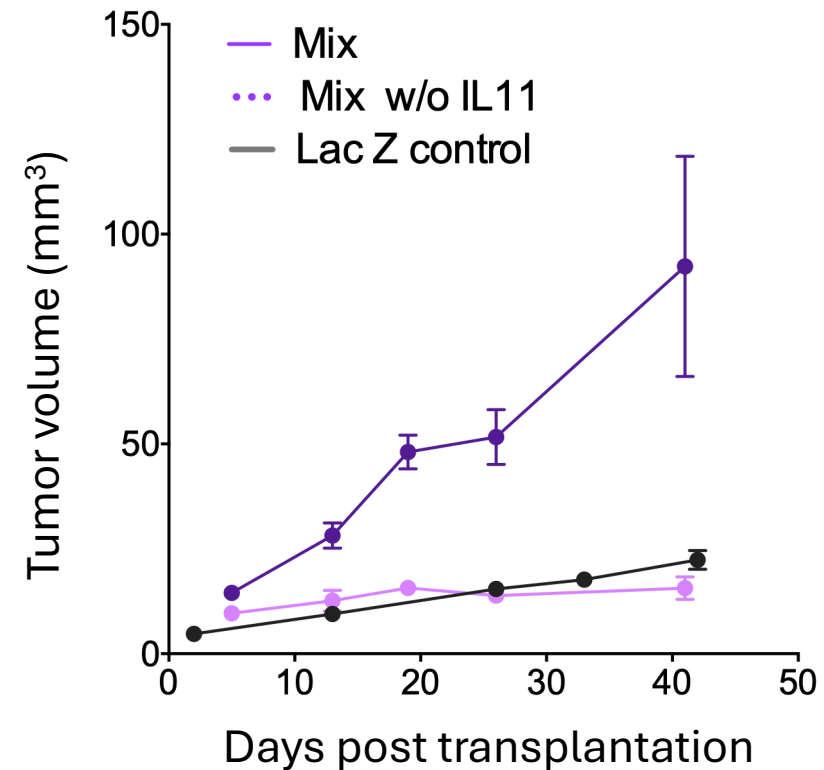
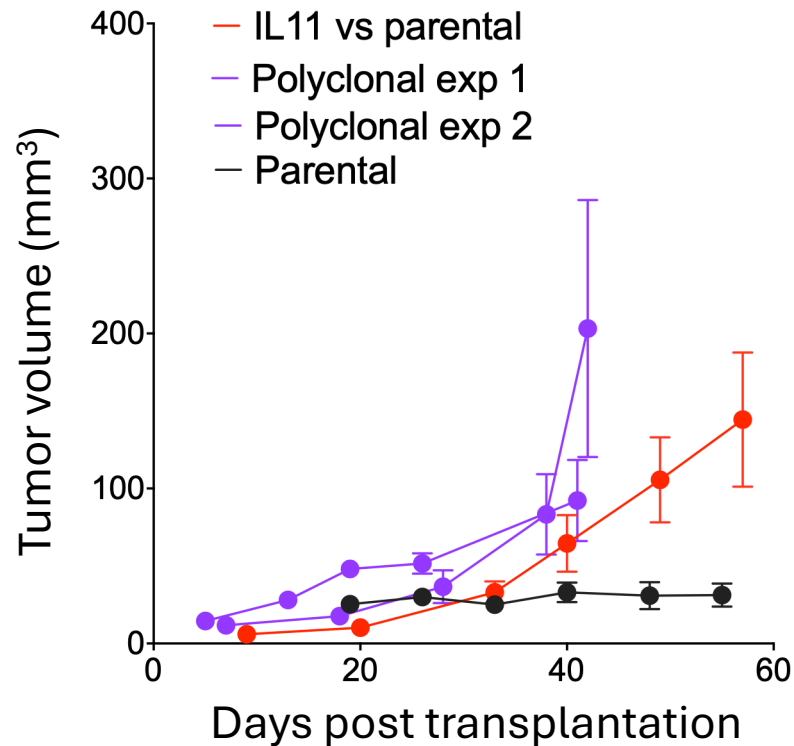
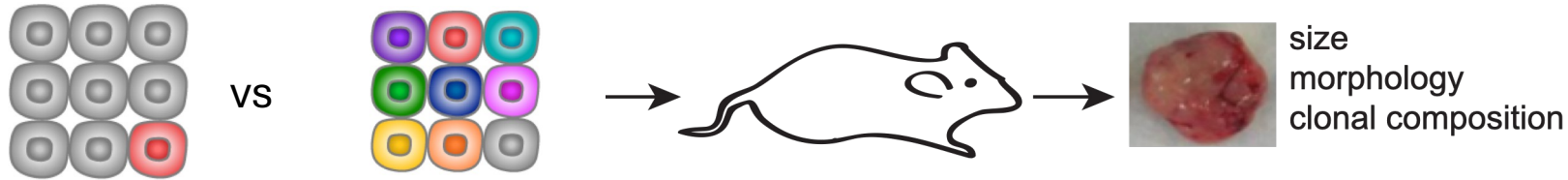
Are the games analyzable?



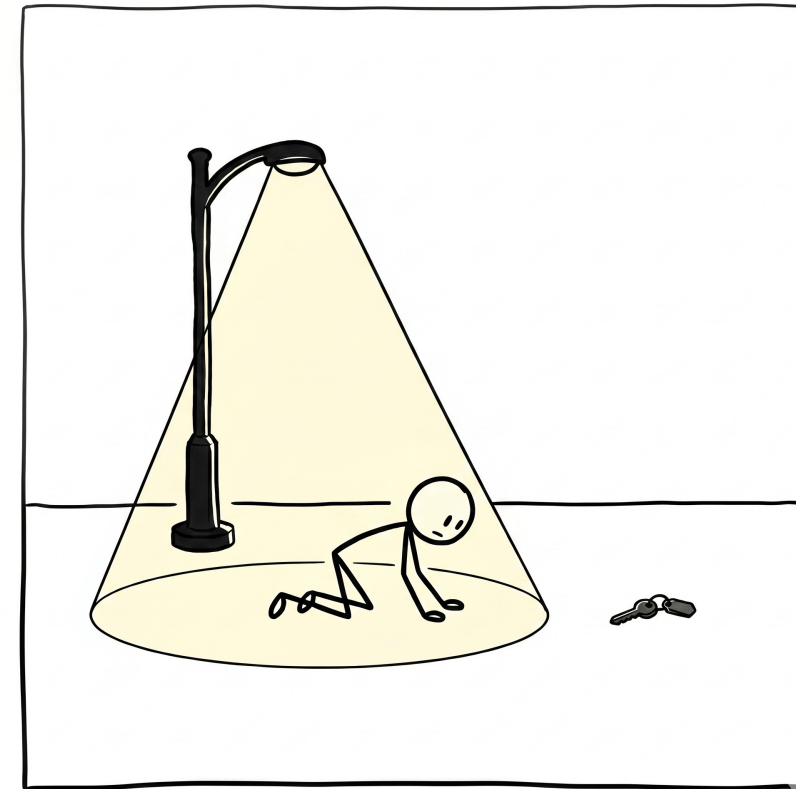
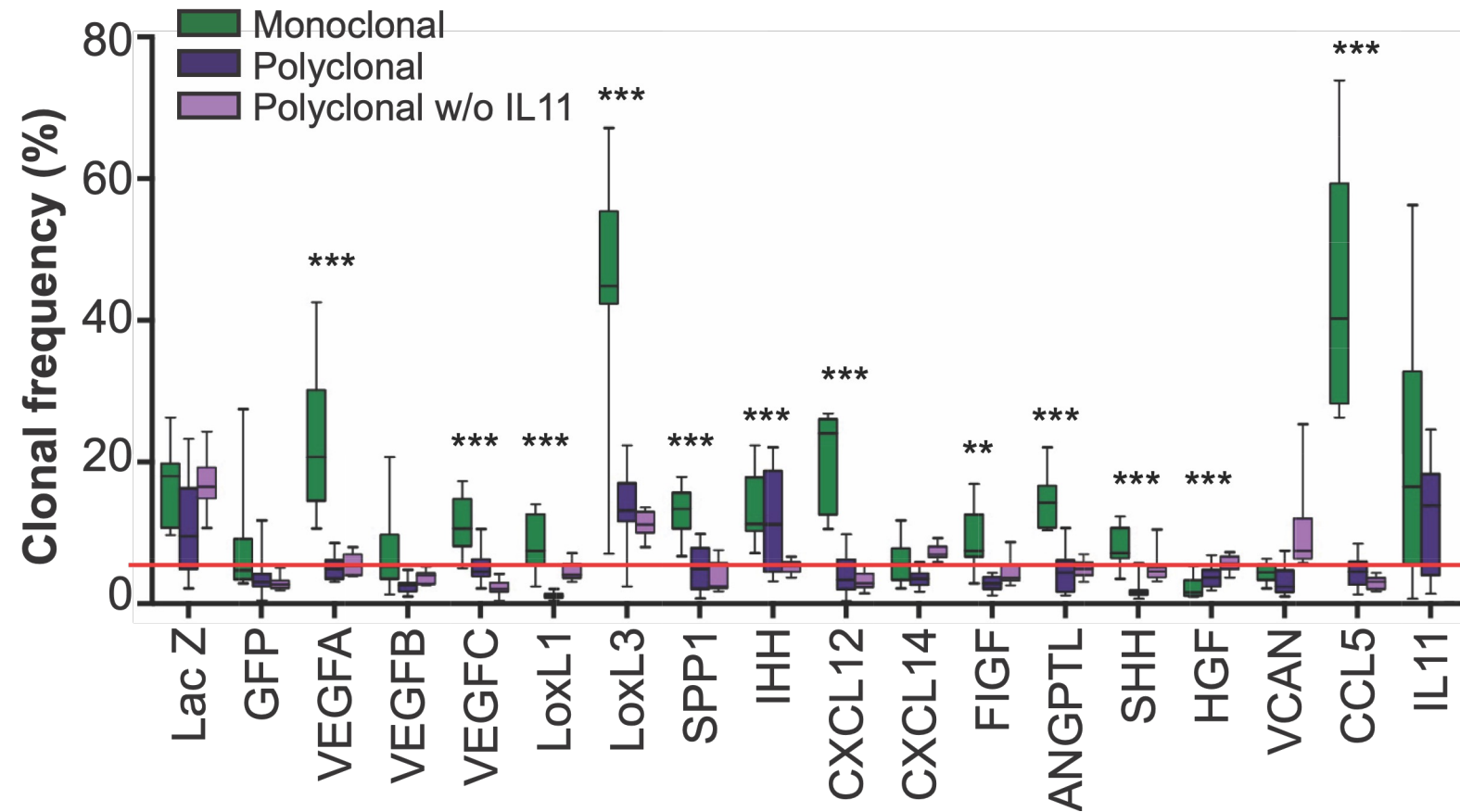
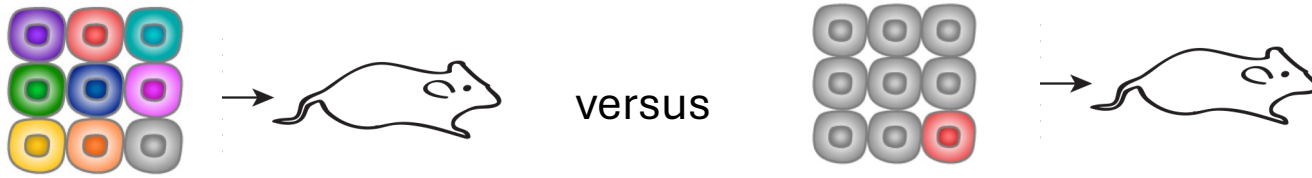
vs



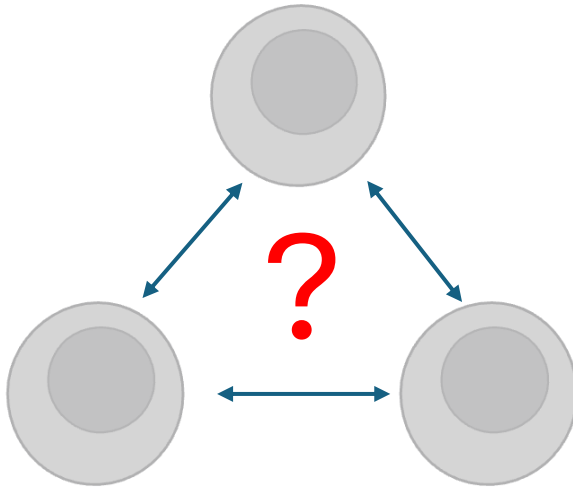
Presence of other populations impact population growth and fitness



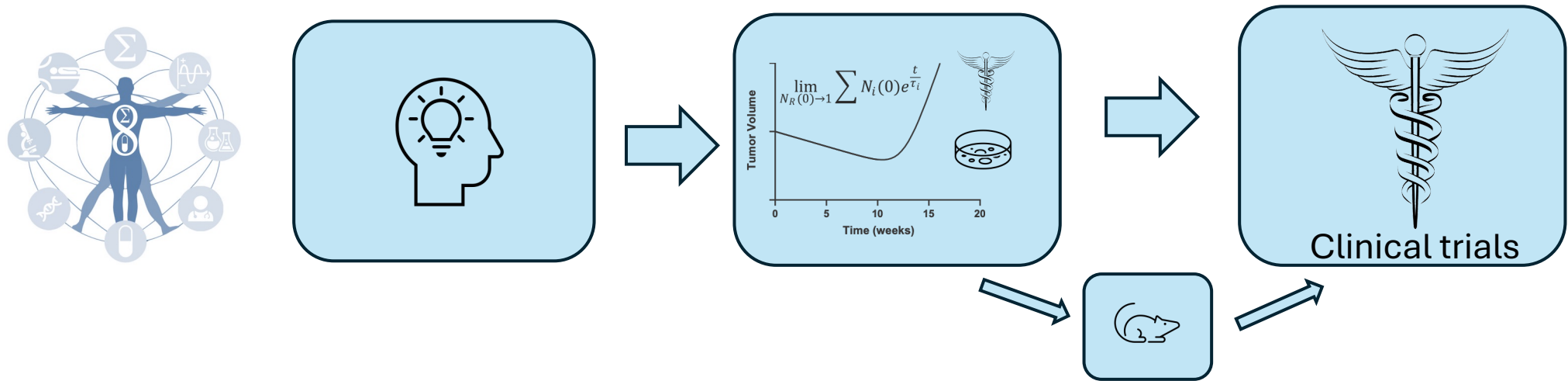
Multiclonality can drastically complicate fitness of individual subpopulations



Is there a game to be analyzed?

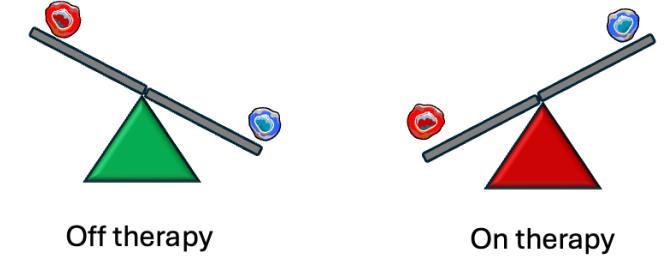
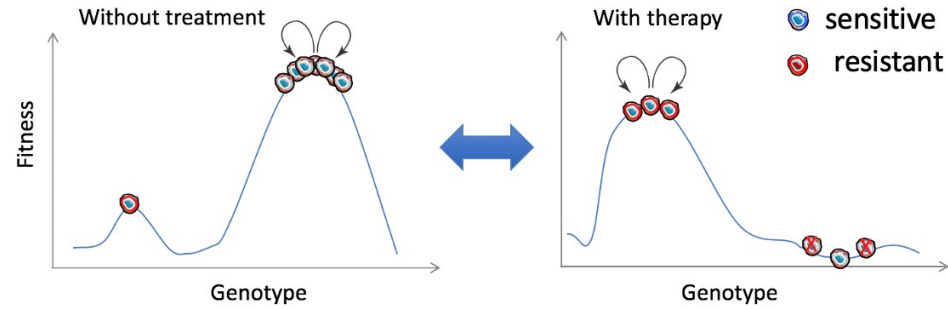


Evolutionary therapy pipeline



Case in point:
AT assumptions

Adaptive Therapy Concept

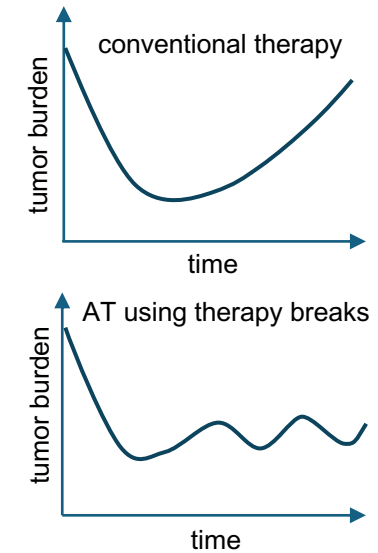
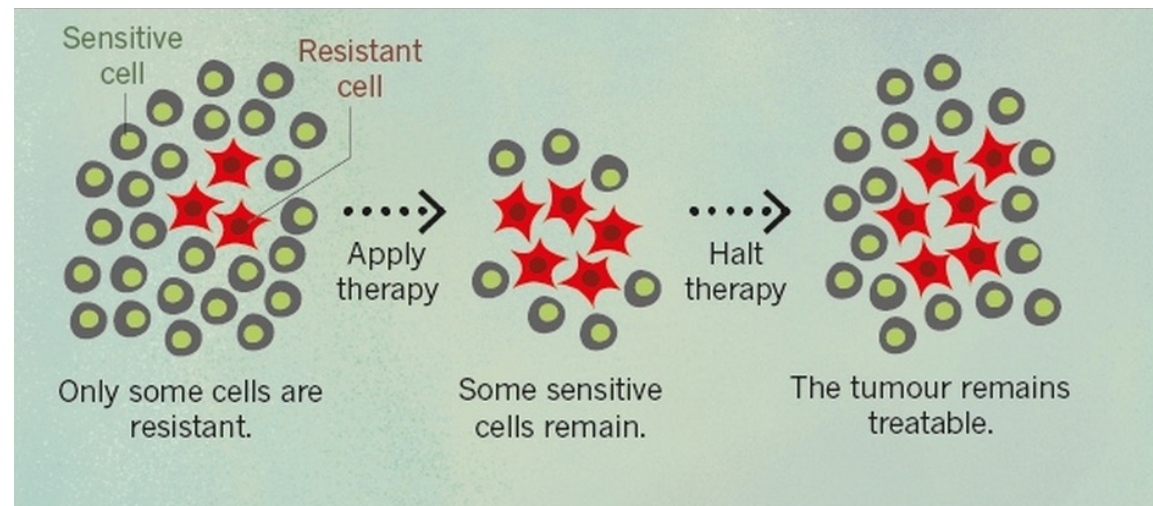


[Cancer Res.](#) 2012 Dec 15;72(24):6362-70. doi: 10.1158/0008-5472.CAN-12-2235. Epub 2012 Oct 12.

Evolutionary approaches to prolong progression-free survival in breast cancer.

[Silva AS¹](#), [Kam Y](#), [Khin ZP](#), [Minton SE](#), [Gillies RJ](#), [Gatenby RA](#).

[+ Author information](#)



Pre-existent resistance is not a given

ARTICLE

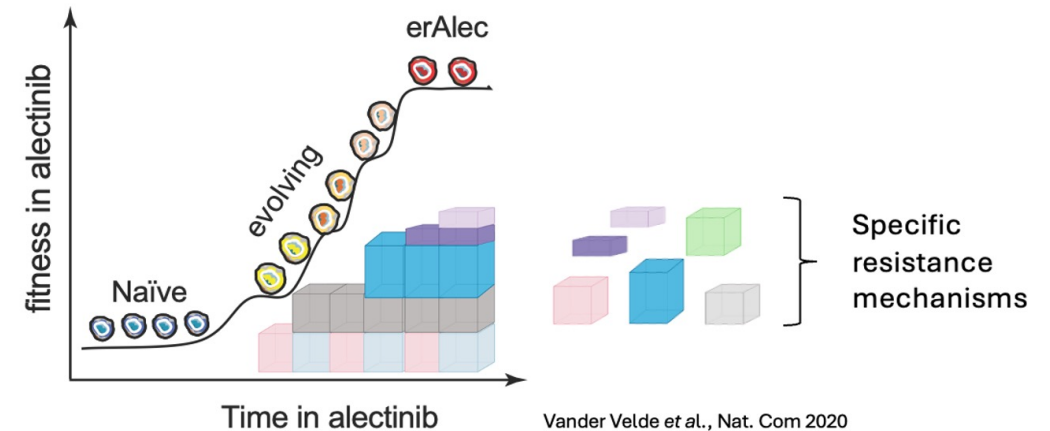
<https://doi.org/10.1038/s41467-020-16212-w>

OPEN



Resistance to targeted therapies as a multifactorial, gradual adaptation to inhibitor specific selective pressures

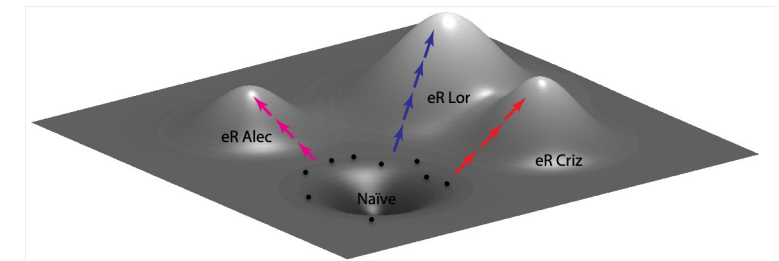
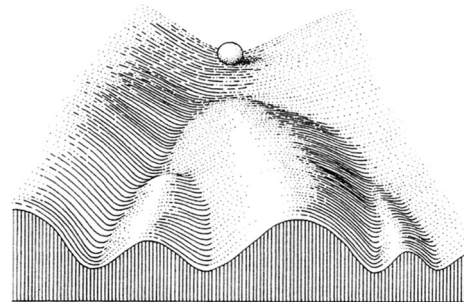
Robert Vander Velde^{1,2}, Nara Yoon³, Viktoriya Marusyk¹, Arda Durmaz^{3,4}, Andrew Dhawan³, Daria Miroshnychenko¹, Diego Lozano-Peral^{1,5}, Bina Desai^{1,6}, Olena Balyńska¹, Jan Poleszhuk⁷, Liu Kenian⁸, Mingxiang Teng⁹, Mohamed Abazeed³, Omar Mian³, Aik Choon Tan⁹, Eric Haura¹⁰, Jacob Scott^{3,4,5,6} & Andriy Marusyk^{1,2,5,6}



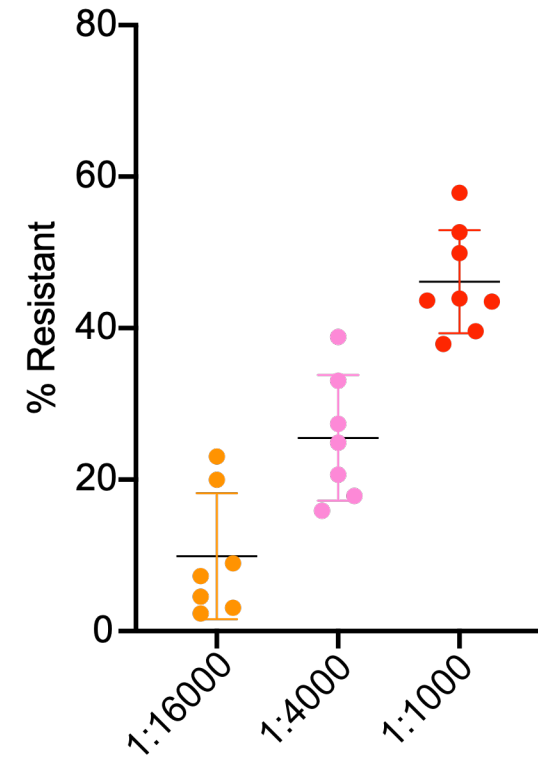
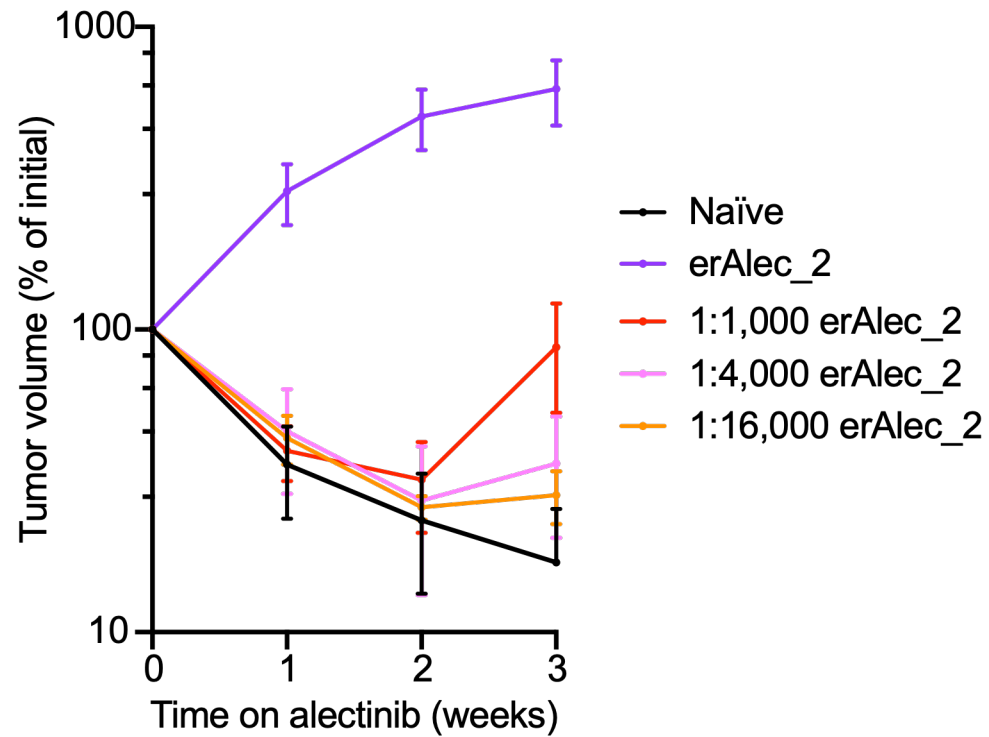
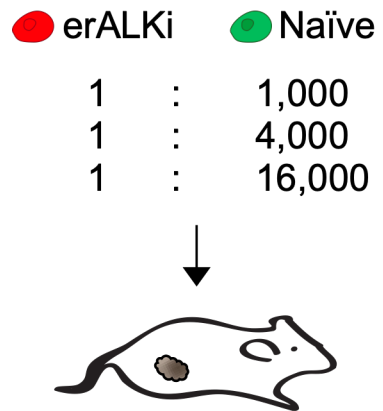
Cellular adaptation to cancer therapy occurs by progressive state transitions along a resistance continuum

Gustavo S. França^{1,2}, Maayan Baron^{1,3}, Benjamin R. King^{2,3,4}, Jozef P. Bossowski^{4,5}, Alicia Bjornberg^{5,6}, Maayan Pour^{1,2,3}, Anjali Rao^{1,3}, Ayushi S. Patel^{1,2,3}, Selim Misirlioglu⁶, Dalia Barkley¹, Kwan Ho-Tang^{6,8}, Igor Dolgalev⁷, Deborah A. Liberman^{1,2}, Gal Avital¹, Felicia Kuperwaser^{1,2}, Douglas A. Levine^{6,9}, Thales Papagiannakopoulos^{3,6}, Andriy Marusyk⁵, Timothee Lionnet^{2,10,11}, Itai Yanai^{1,2,11,12}

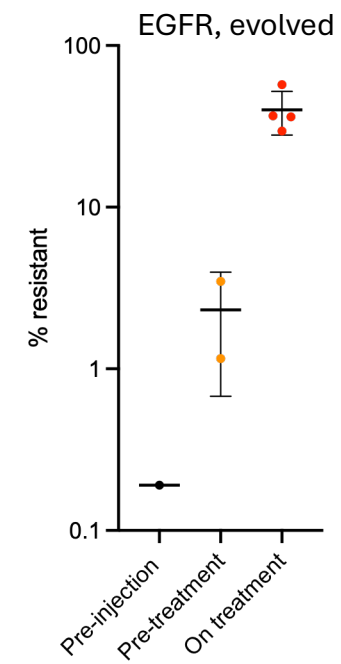
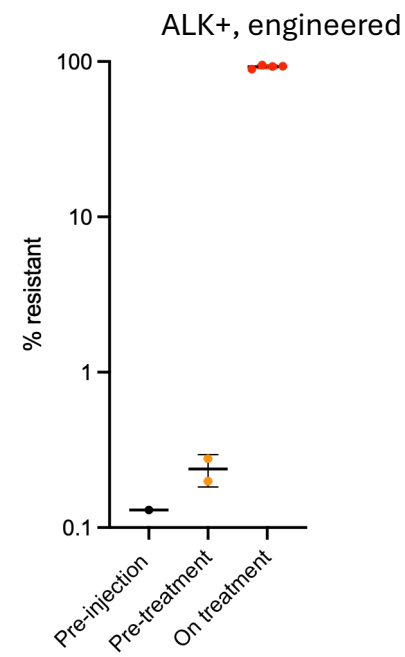
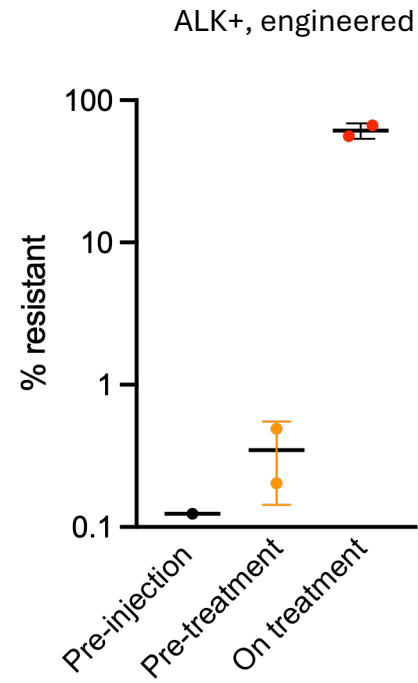
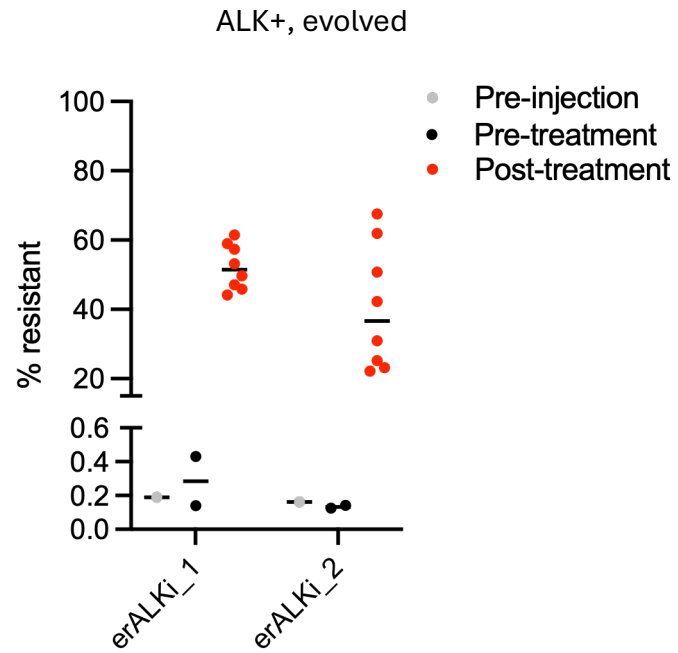
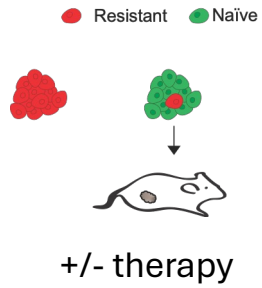
Nature, 2024



Pre-existent resistance can lead to rapid relapse

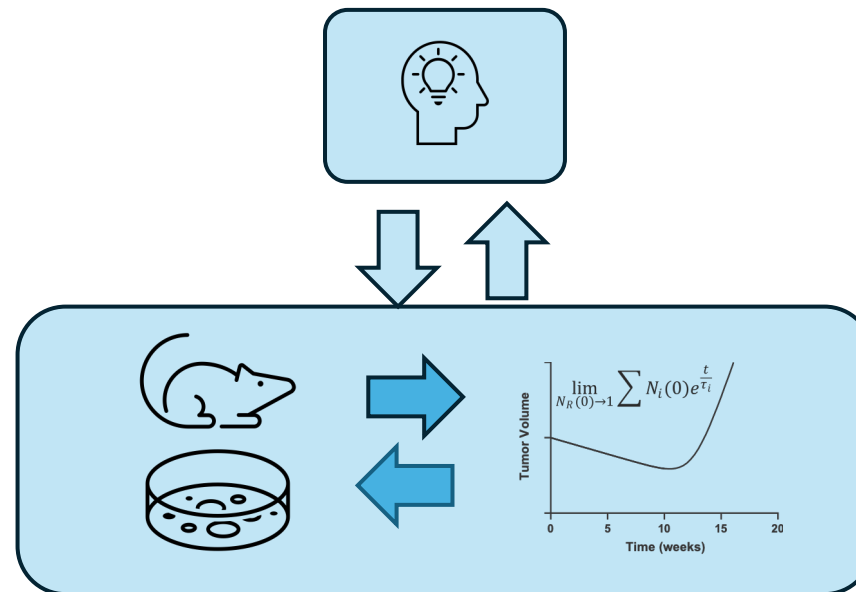


Resistance does not necessarily have a fitness cost

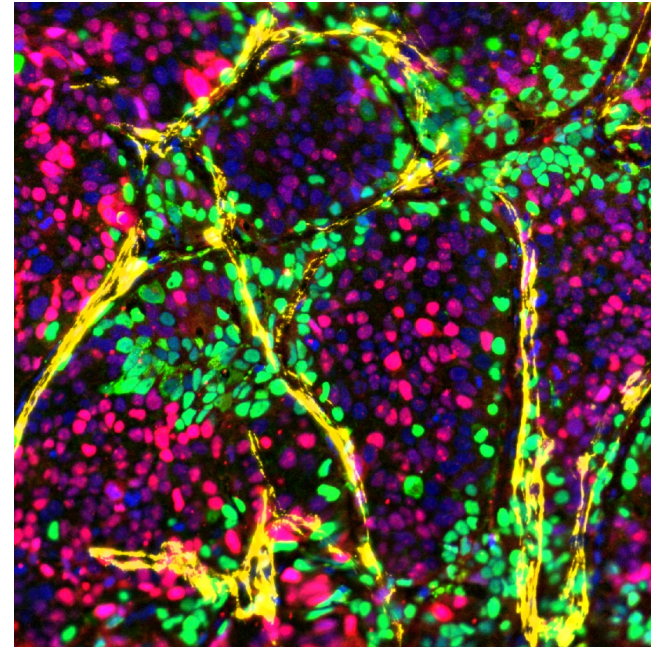
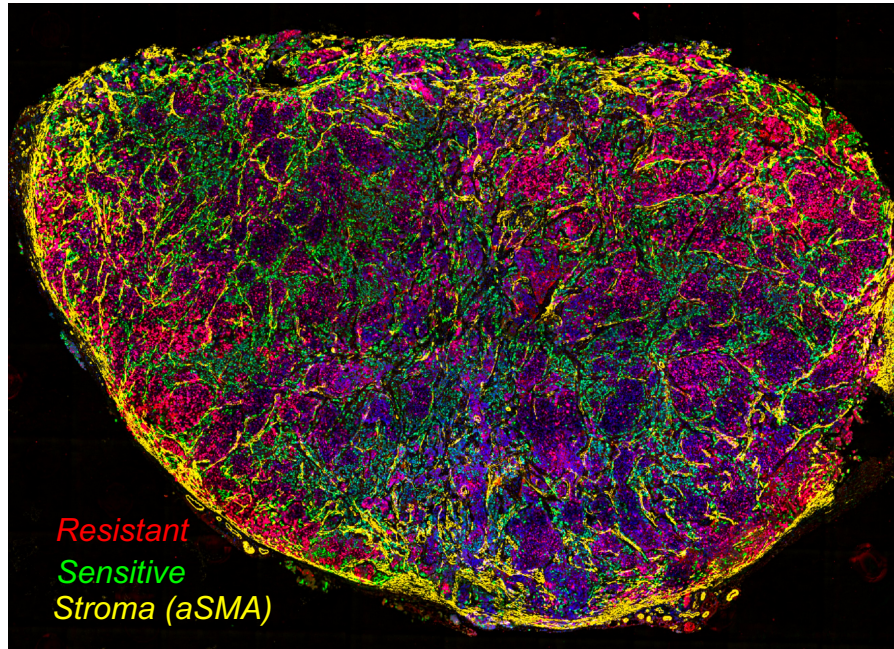


What have we learned?

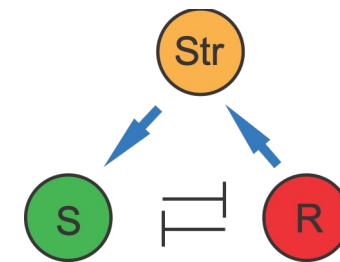
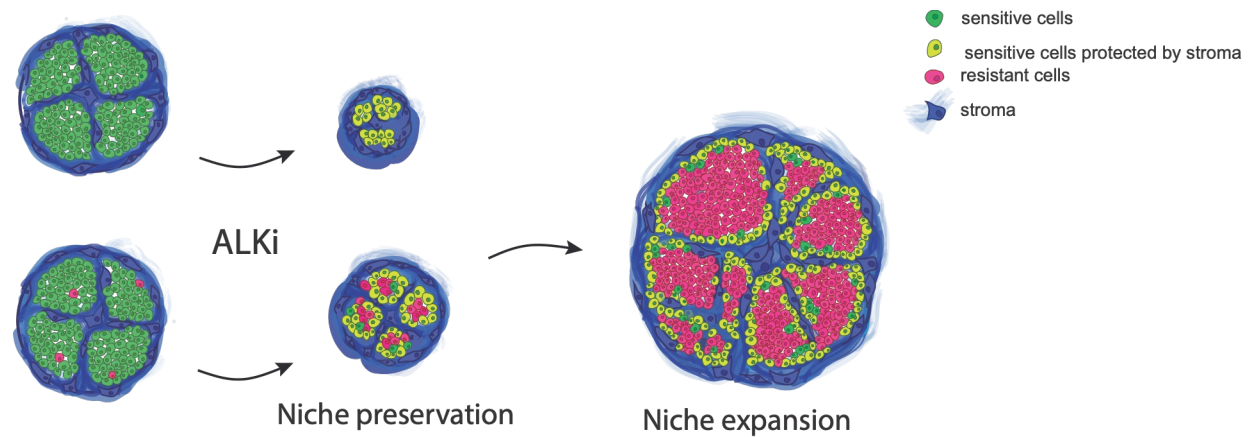
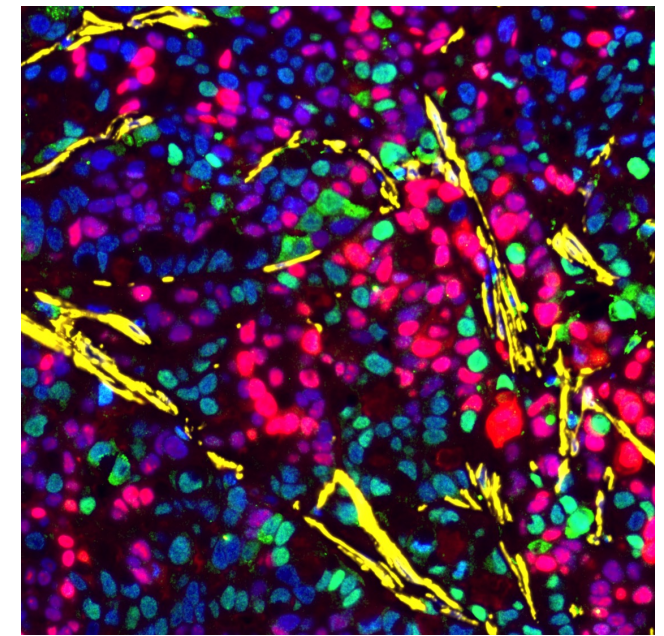
- AT assumptions might be wrong
- “Listening” to biology opens new ideas



Mixed tumors ALKi



Vehicle control



Take-home messages

- Eco-evolutionary underpinning of cancer lands to wide EGT applicability
- EGT is indispensable for addressing some of the biological and therapeutic challenges
- EGT success in cancer biology hinges on
 - Identifying the right problems
 - Deciphering the underlying biology
 - Addressing some major technical challenges



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Marusyk lab

Current:

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Virgile Camont

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Olena Balynska
Diego Peral
Matthew Froid
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Mark Robertson-Tessi
Joel Brown
Jeff West
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Moffitt other:

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