Professional Advancement Virtual Engagement Series

CURE

Coming in December

Seminar 11

Putting the "I" in Science: Leveraging Your Story to Chart Your Career - Dr. Gloria Coronado

December 14, 2021, 3 – 5 p.m. ET

NIH NATIONAL CANCER INSTITUTE

Coming Soon: Early Investigator Advancement Program (EIAP)

Goal: to facilitate the advancement of scientists from diverse backgrounds to independent investigators

Aims

- Enhance professional skills
- Guide preparation of an R01 grant application
- Provide access to a mentoring and peer network
- Grow a community of emerging independent investigators from diverse backgrounds

Participant

Focus on Diversity: Participants must be U.S. citizens, legal permanent residents, or non-citizen nationals

Individuals from groups identified in NIH's Notice of Interest in Diversity (NOT-OD-20-031) as underrepresented in the biomedical, clinical, behavioral, and social sciences are particularly encouraged to apply.

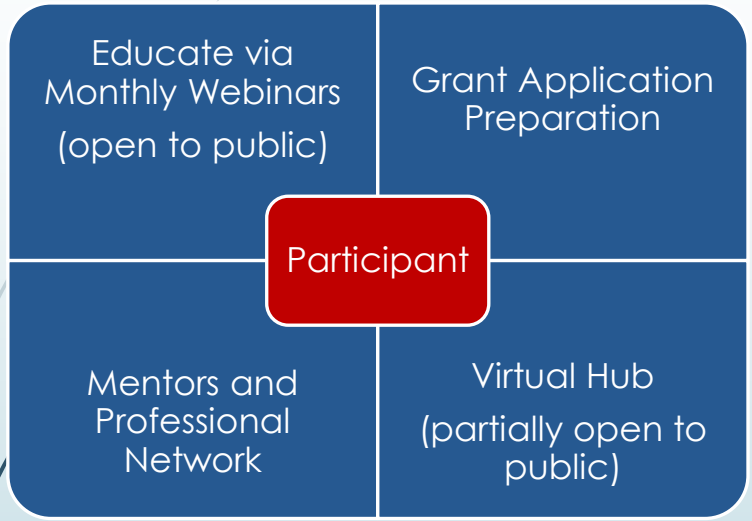
NIH Notice of Interest in Diversity

- Race and ethnicity
- Disability
- Disadvantaged background

EIAP Program Components

Pre-Application Webinar
December 9, 2021, 4-5 pm ET

Program Components



Outcomes for Each Participant

- Complete a R01 grant proposal
- Become part of a group of peers with similar career goals
- Engage with mentors who are established investigators
- Become familiar with job and funding opportunities
- Develop professional and management skills critical to growing a research group

Contact: Alison Lin, PhD
EIAP@nih.gov

NATIONAL CANCER INSTITUTE

@NCICRCHD

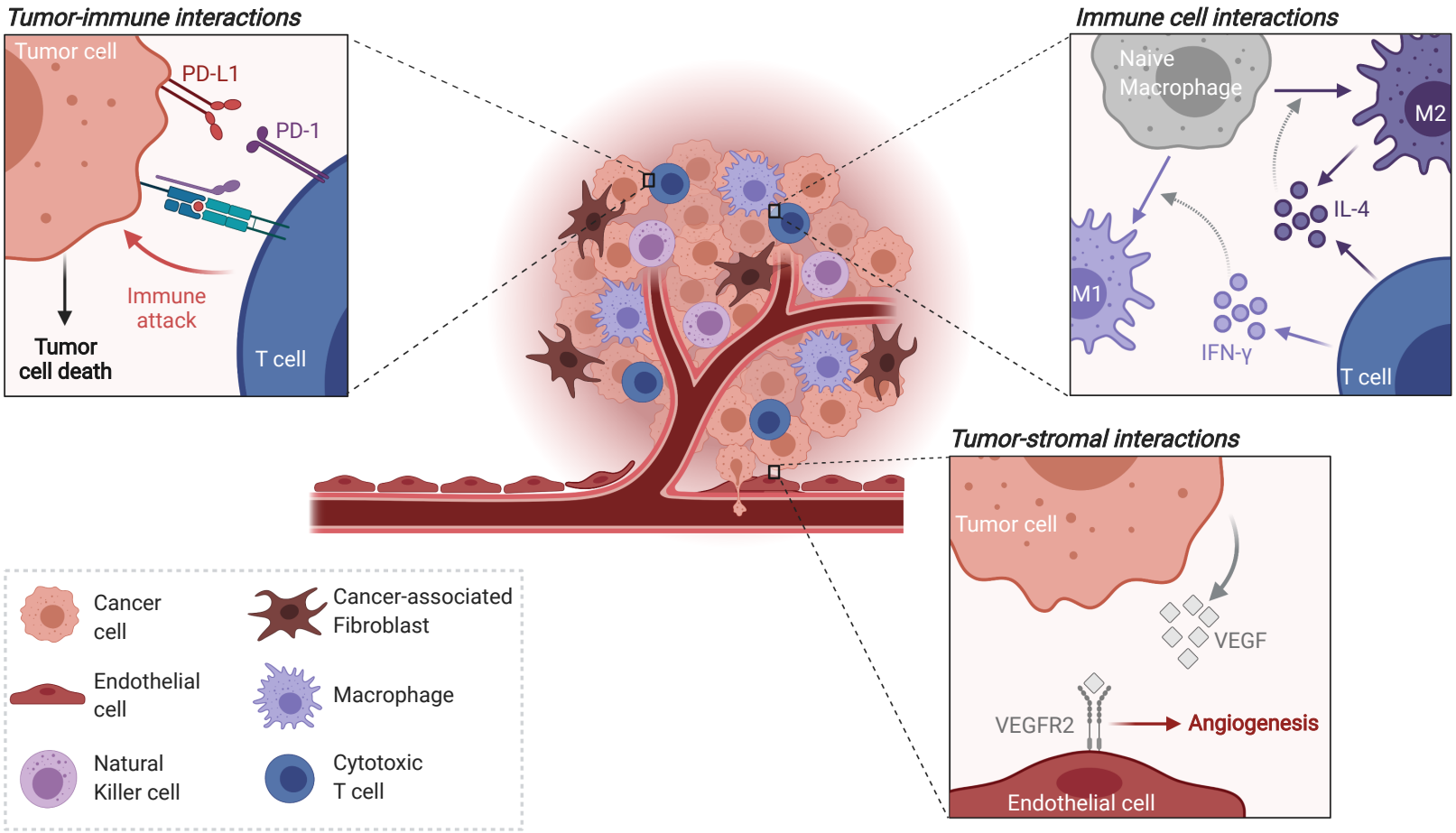
https://www.cancer.gov/about-nci/organization/crchd

www.cancer.gov **www.cancer.gov/espanol**

Cancer systems biology

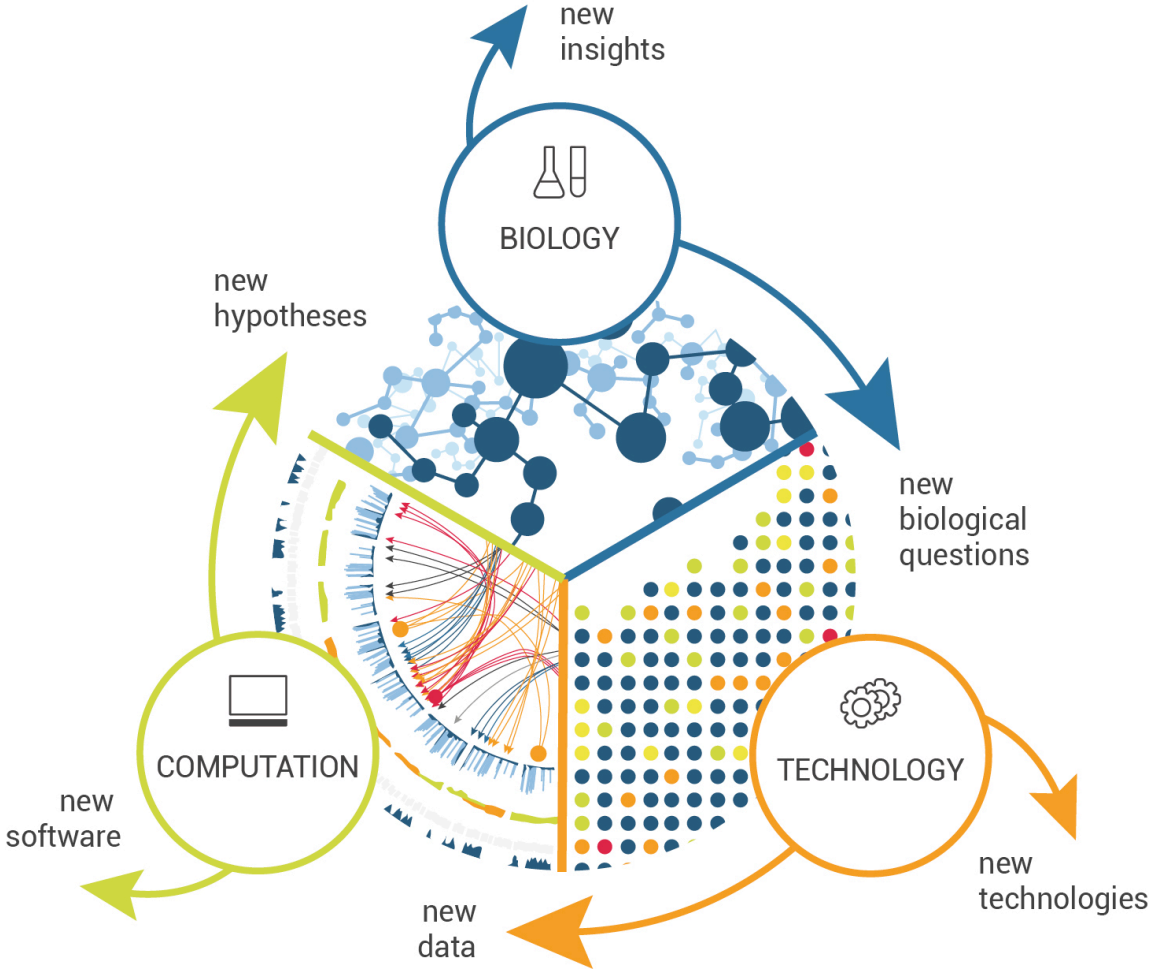
integrating
experimental and **computational**
approaches
to study the complexities of cancer

Cancer systems biology



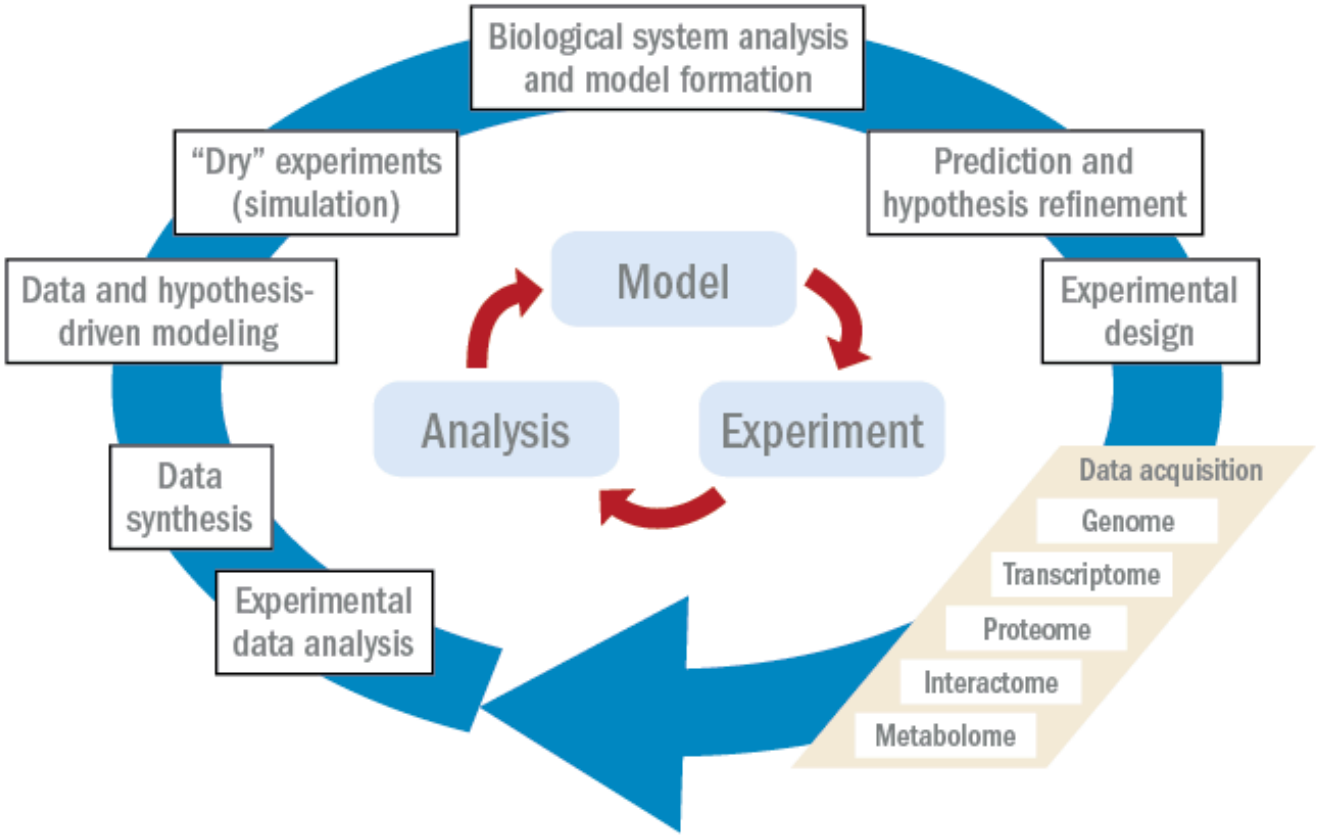
Song, Li, Makaryan and Finley, 2021. *Curr Opin Sys Biol*

Systems biology



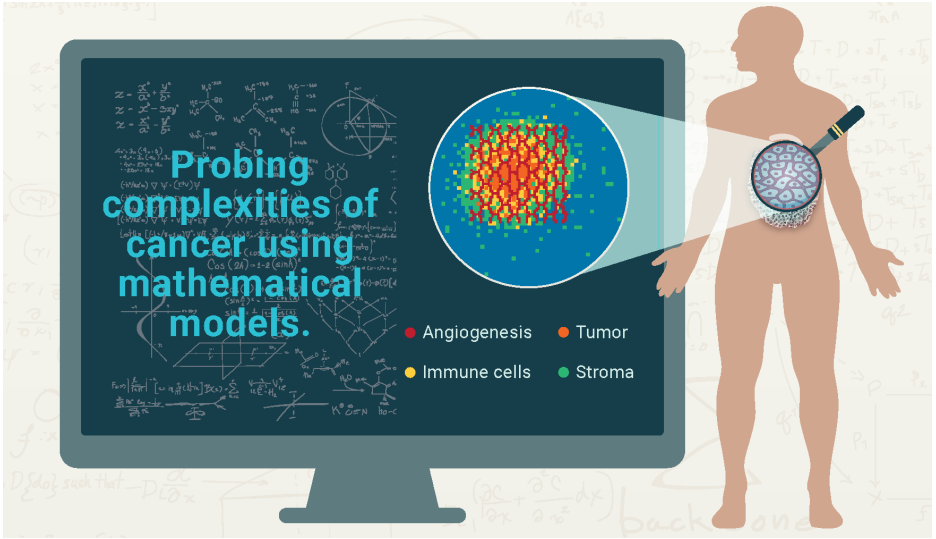
Source: Institute for Systems Biology; OmicScouts

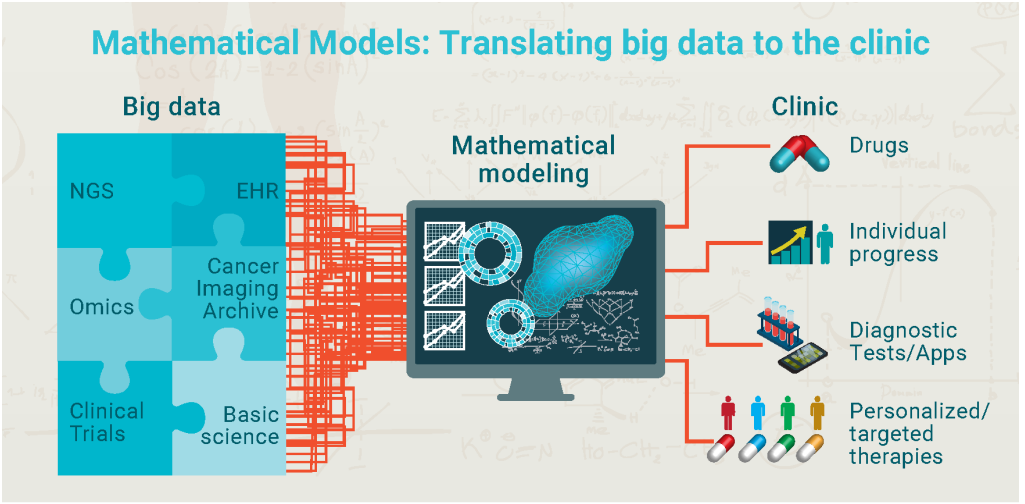
Systems biology



Source: Agilent Technologies

Cancer systems biology: Computational approaches



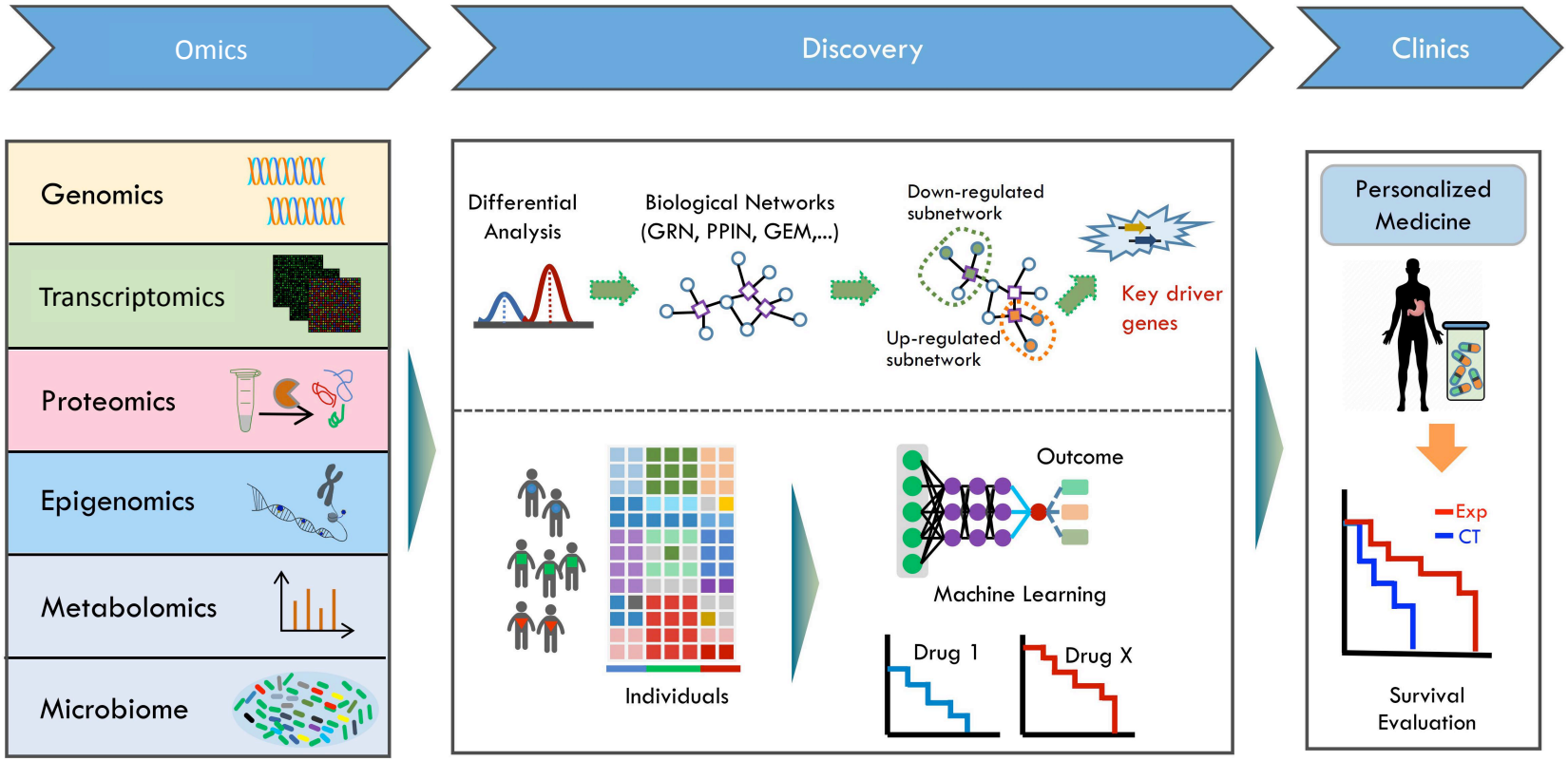


Mathematical Oncology Content Collection
DOI: 10.1200/CCI.19.00017

JCO® Clinical Cancer Informatics
An American Society of Clinical Oncology Journal

Rockne and Scott. 2019. *JCO CCI*

Cancer systems biology: Experimental approaches

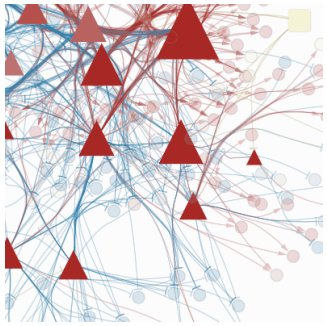


Shi, et al. 2020. *Front. Mol. Biosci*

Cancer systems biology

integrating
experimental and **computational**
approaches
to study the complexities of cancer

Get connected!

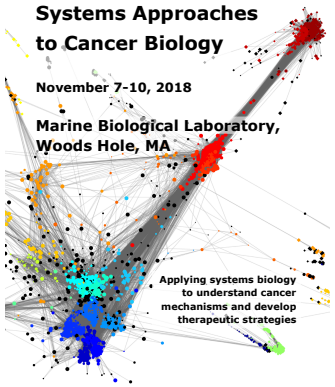


Association for Cancer Systems Biologists **(ACSB)** —

fosters, promotes and advocates for cancer systems biology and the needs of the researchers in the field

NIH Cancer Systems Biology Consortium

- *Division of Cancer Biology Undergraduate Research Program **(DCB-SURP)**: Summer 2022*
- *Junior Investigators Meeting: late summer 2022*

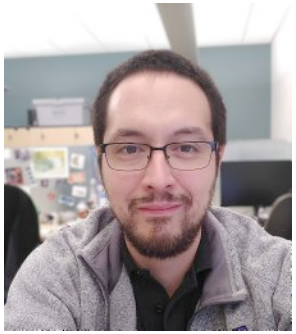


Systems Approaches for Cancer Biology **(SACB)** Conference

- *October 19-22, 2022*
- *Virtual + in-person (Woods Hole, MA)*

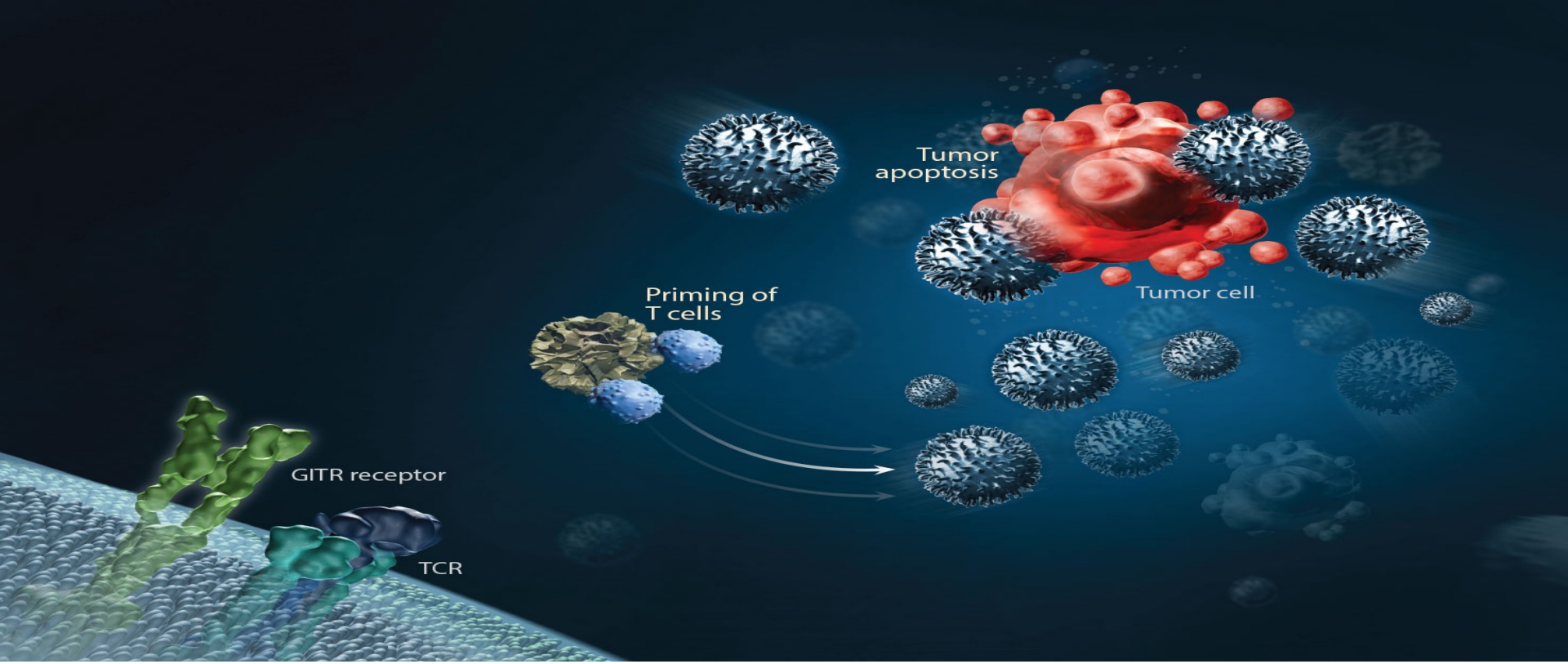
Trachette Jackson, PhD
Professor of Mathematics and
University Diversity and Social
Transformation Professor
University of Michigan

Michael Murrell, PhD
Associate Professor of
Biomedical Engineering
Yale University



Jorge Gómez Tejeda Zañudo, PhD
Postdoctoral Associate
Broad Institute &
Dana-Farber Cancer Institute

Joshua François, Ph.D.
Postdoctoral Research Fellow
Harvard University



Multiscale Models for Predicting Optimum Immune and Targeted Therapy Schedules

Goals

- We are combining multiscale mathematical approaches with novel cellular quantification experimental technologies in order to:
  - To gain a deeper, more robust understanding of tumor-immune dynamics
  - To optimize combination immunotherapy and receptor kinase targeted therapy

Aggressive Bladder Cancer Mutations

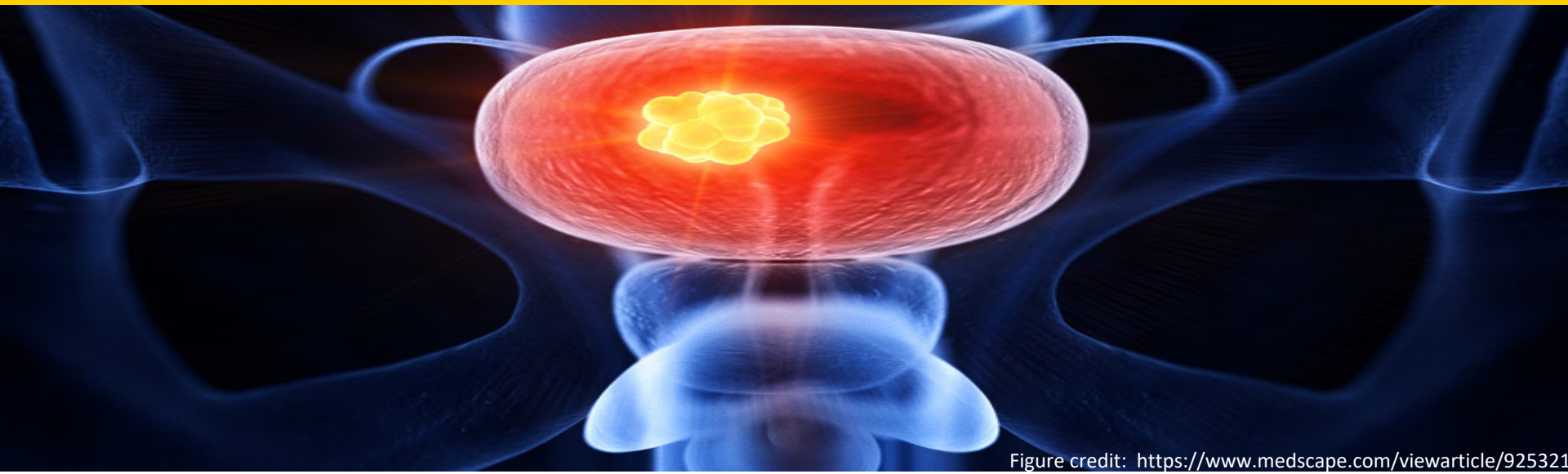


Figure credit: https://www.medscape.com/viewarticle/925321

- Genomic analysis of bladder cancer has identified frequent alterations of FGFRs, including mutations of *FGFR3* that activate the receptor via ligand-independent dimerization → increased cell proliferation and survival.

Targeted Therapy

- Clinical trials using SMIs of FGFR3 are leading to promising clinical responses for patients with FGFR3 mutations.
- Last year, the FDA approved the first FGFR3 targeted therapy for bladder cancer.

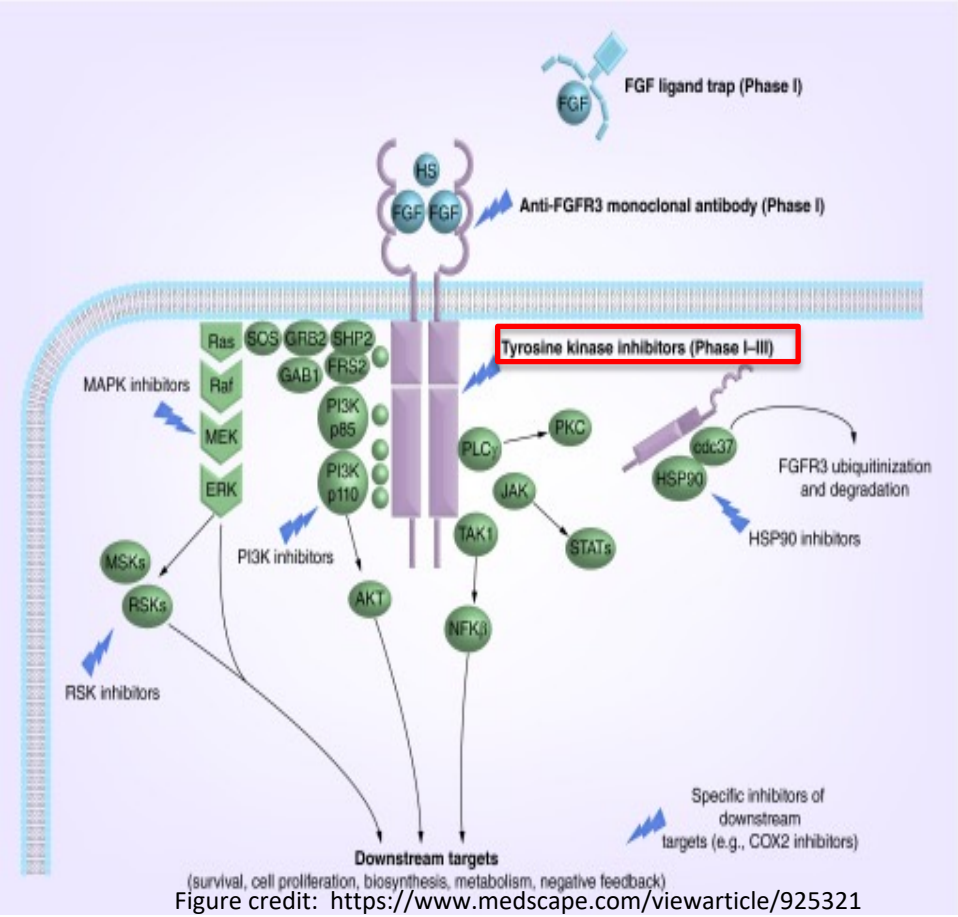
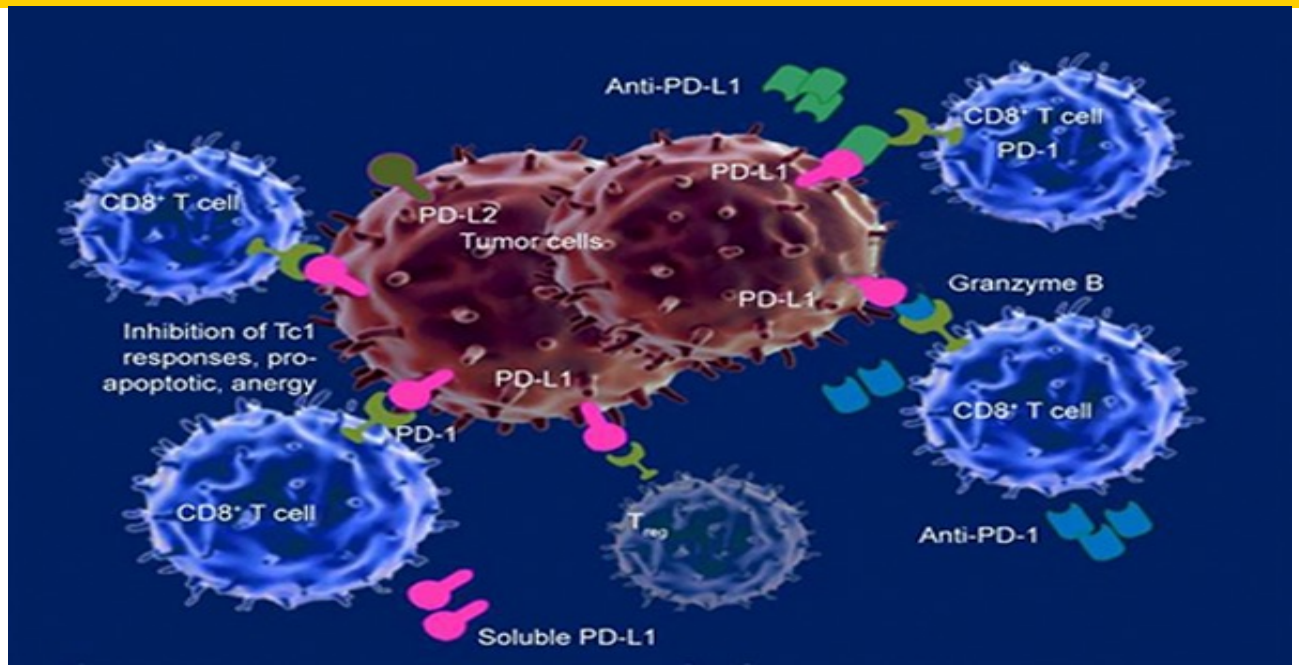


Figure credit: https://www.medscape.com/viewarticle/925321

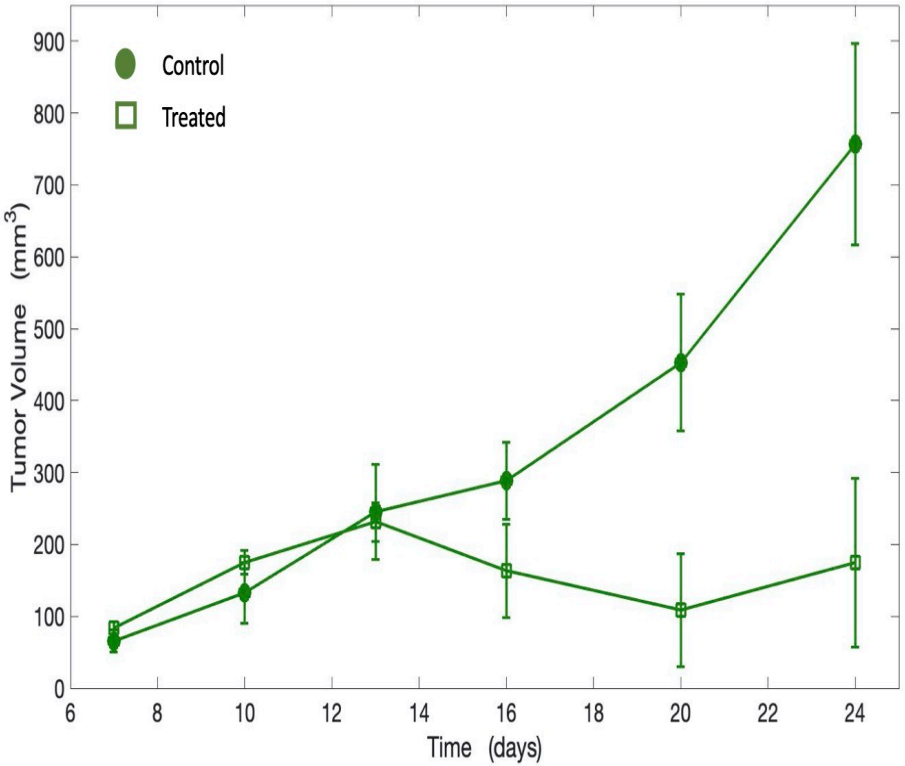
Immunotherapy



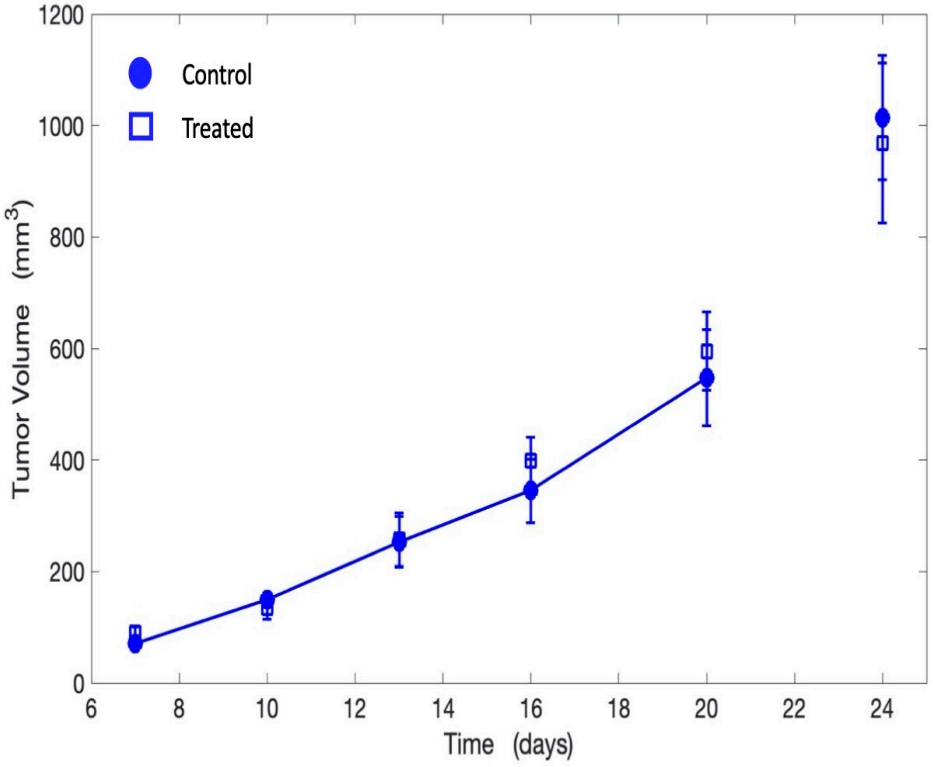
- MAbs targeting the PD-1/PD-L1 pathway have resulted in favorable outcomes in advanced bladder cancer.
- Despite the activity of these drugs in some patients, the objective response rate remains less than 25%.

Mutations Hinder Immunotherapy

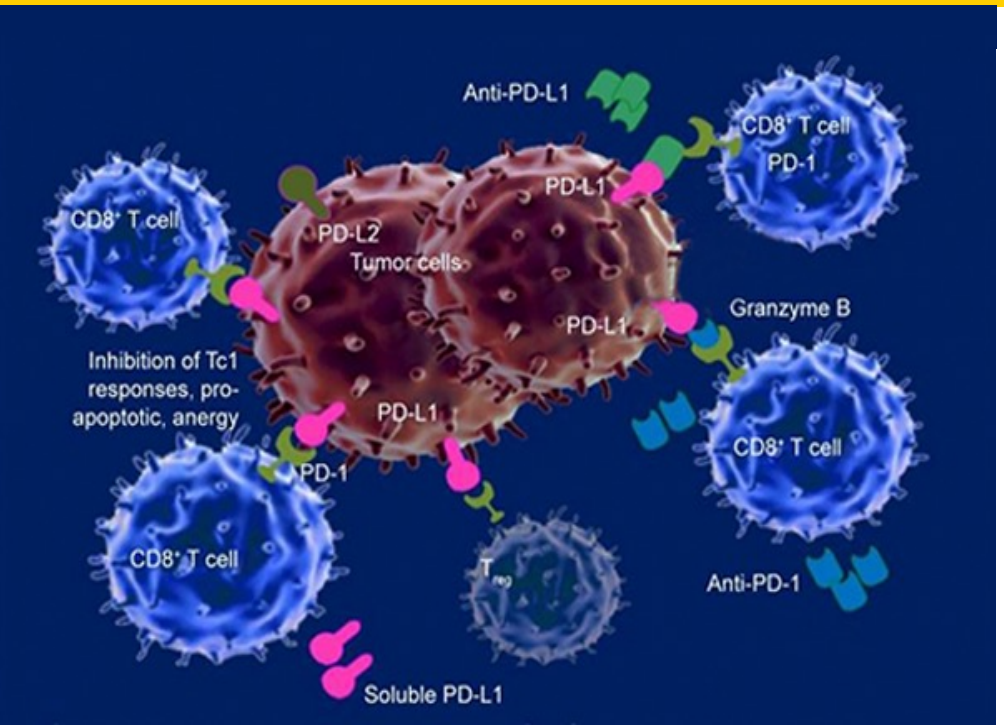
Wild Type Cells

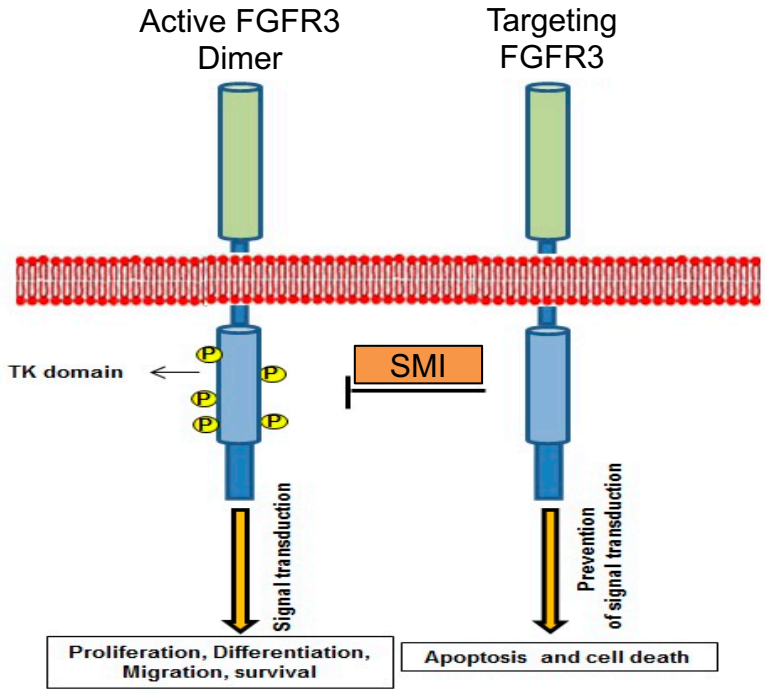


Mutant Cells



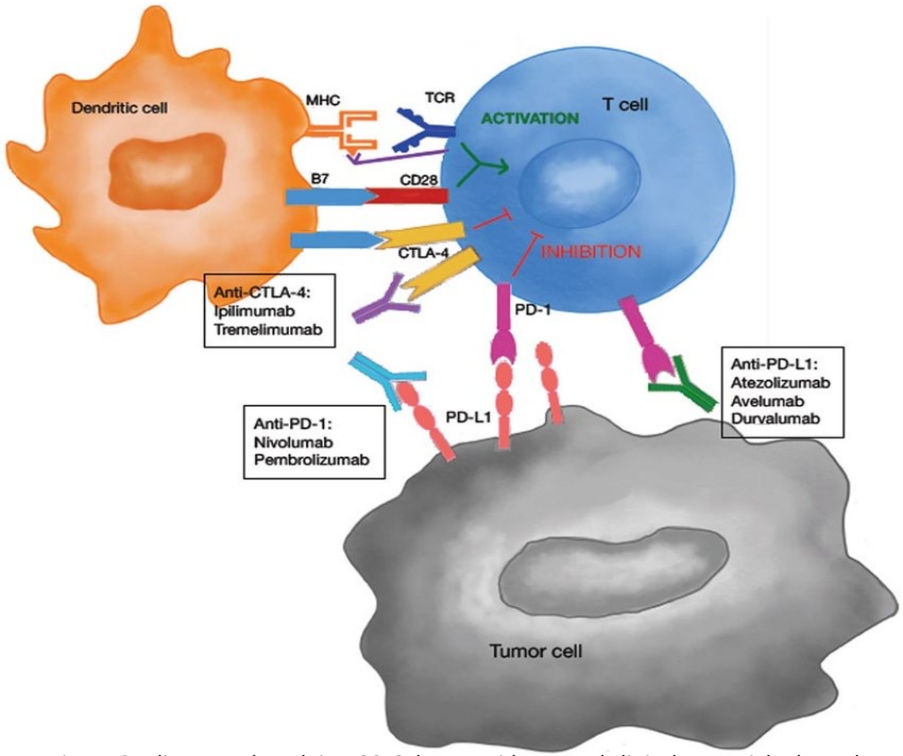
Combination Therapy





Co-acting combination of potent immune checkpoint inhibitors and specific FGFR3 inhibitors potentially offers an advance in targeted therapeutics for cancer.

Optimizing Combination Therapy



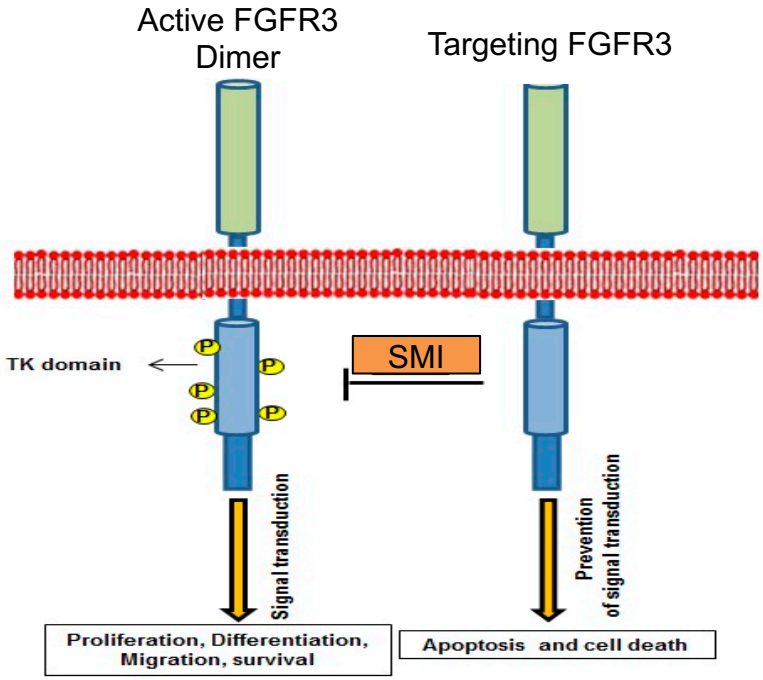
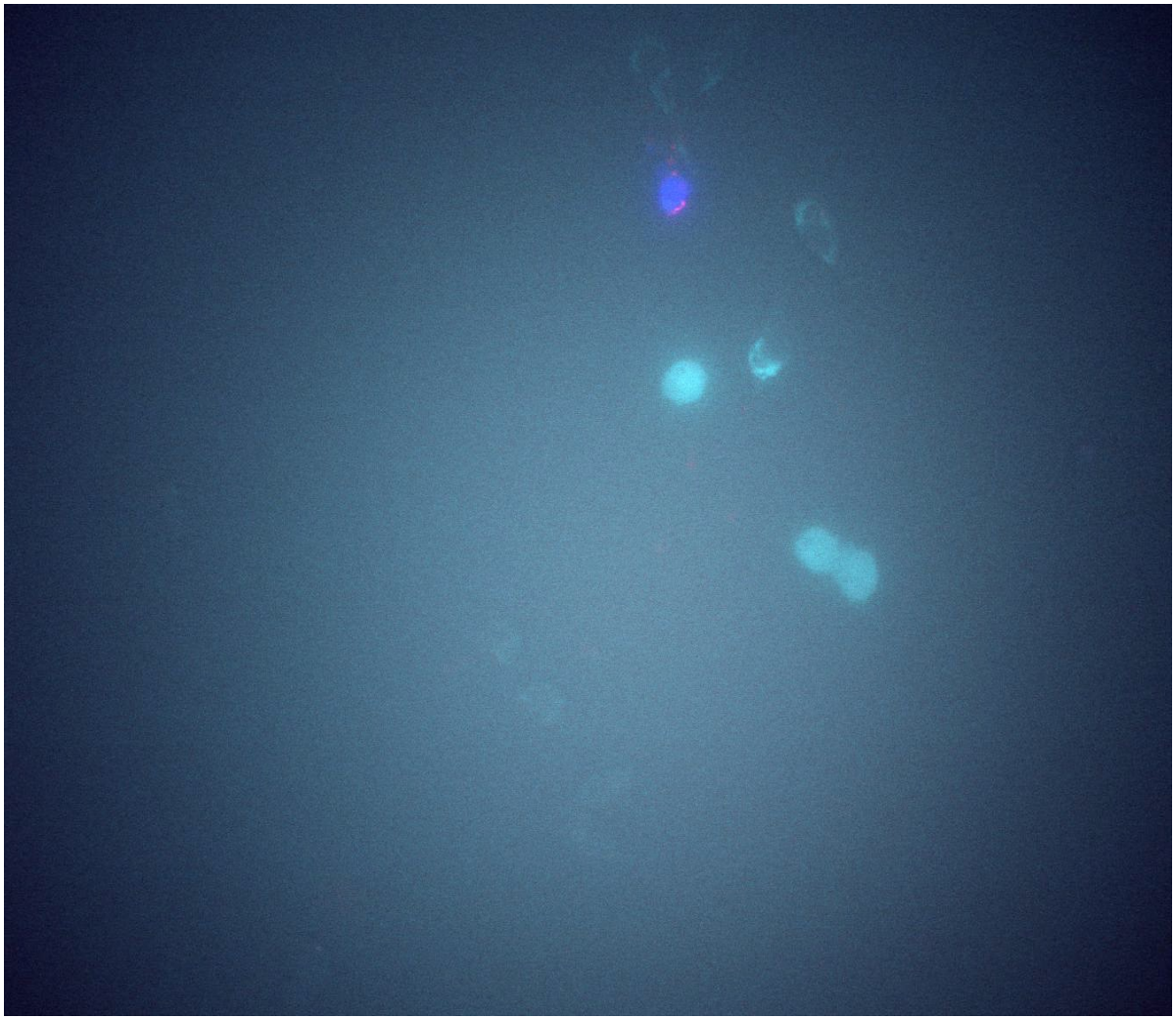


Figure Credit: Durvalumab in NSCLC: latest evidence and clinical potential. *Ther Adv Med Oncol*. 2018

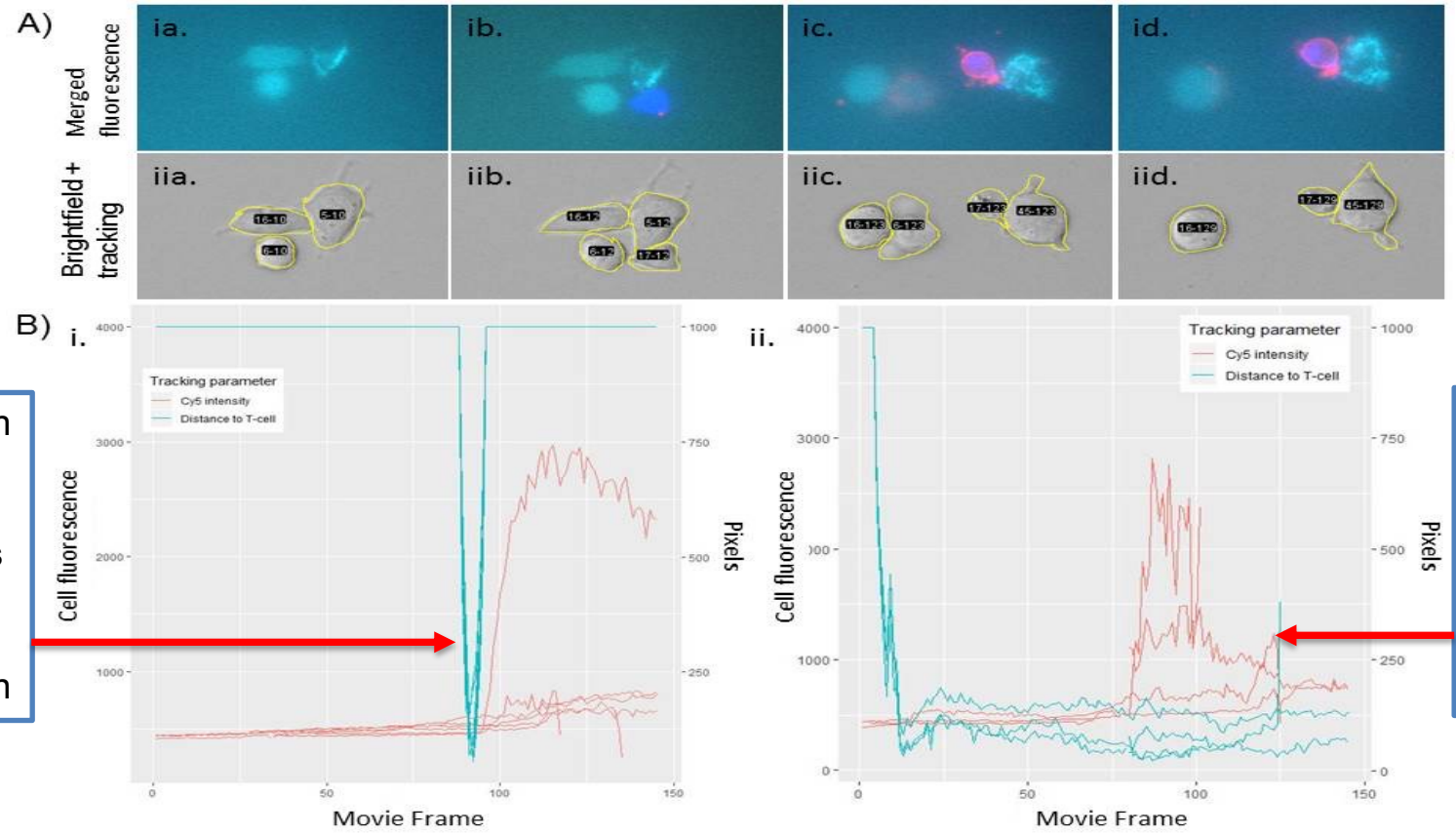
A powerful and practical way to optimize novel drug combinations for clinical cancer treatment is to use data-driven computational models.

Preliminary Data: Live Cell Tracking

- My collaborators developed a novel pipeline to track and quantify the interactions of living tumor cells and immune cells, including cell death.



Preliminary Data: Live Cell Tracking

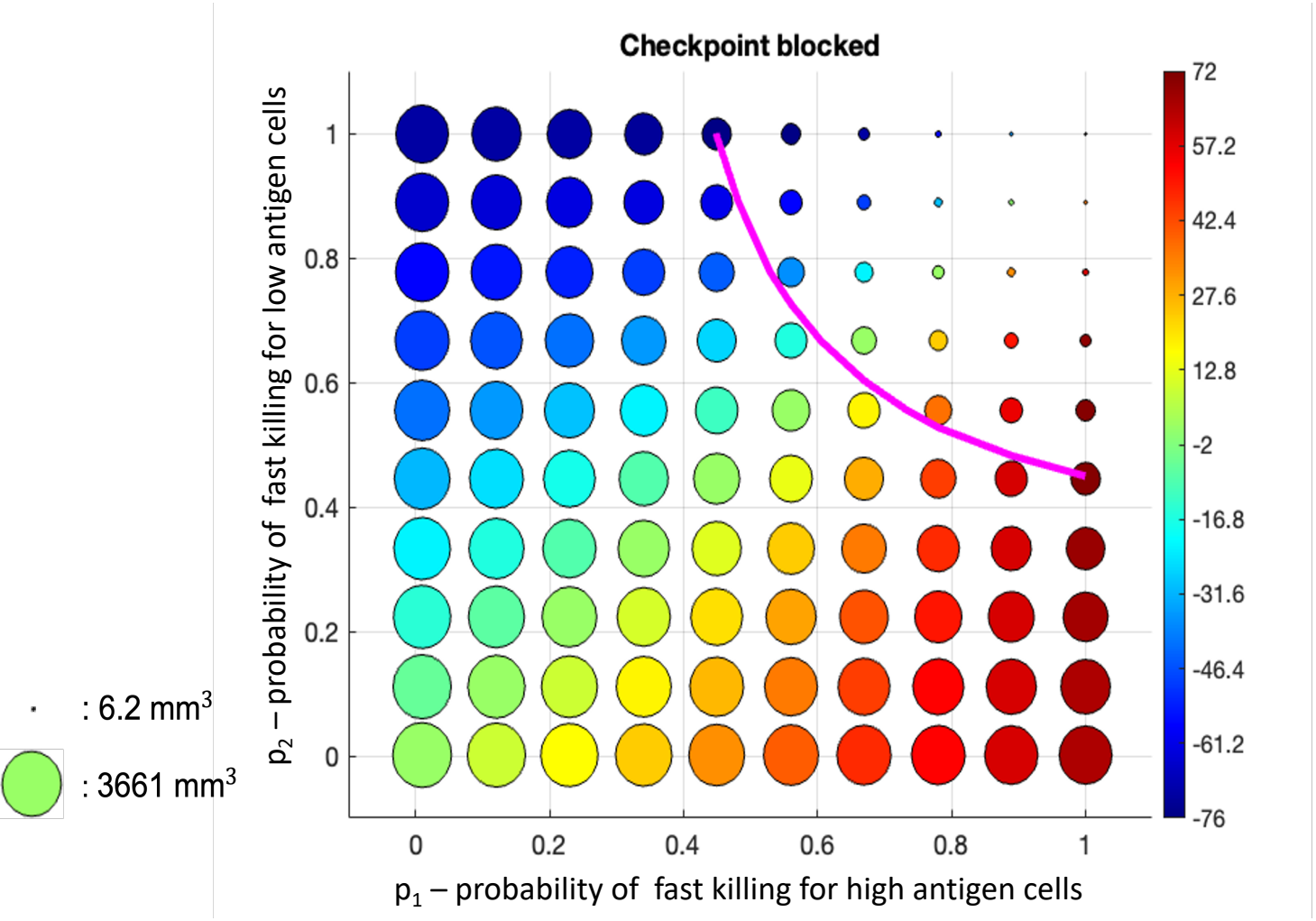


Cell death marker rapidly increases following minimal colocation

Extended cellular colocation of before cell death marker increases

- Evidence of both rapid and slow killing during tumor-immune interactions.
- The proportion of slow and rapid killing within a solid tumor could have significant impact on immune mediated anti-cancer effects.

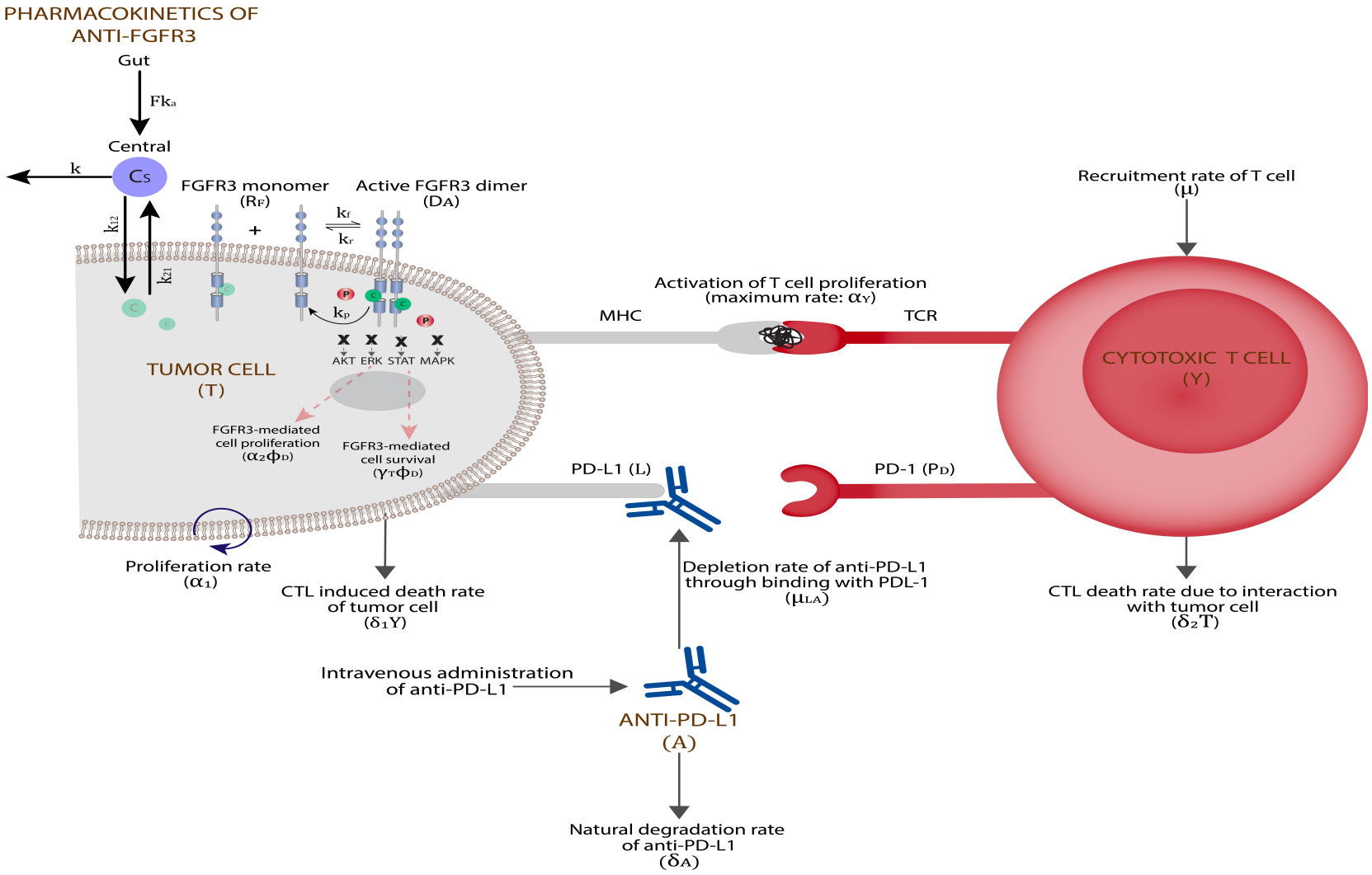
Impact of Fast/Slow Killing Probabilities



Colors represent % change in the proportion of low antigen cells compared to the checkpoint active case.

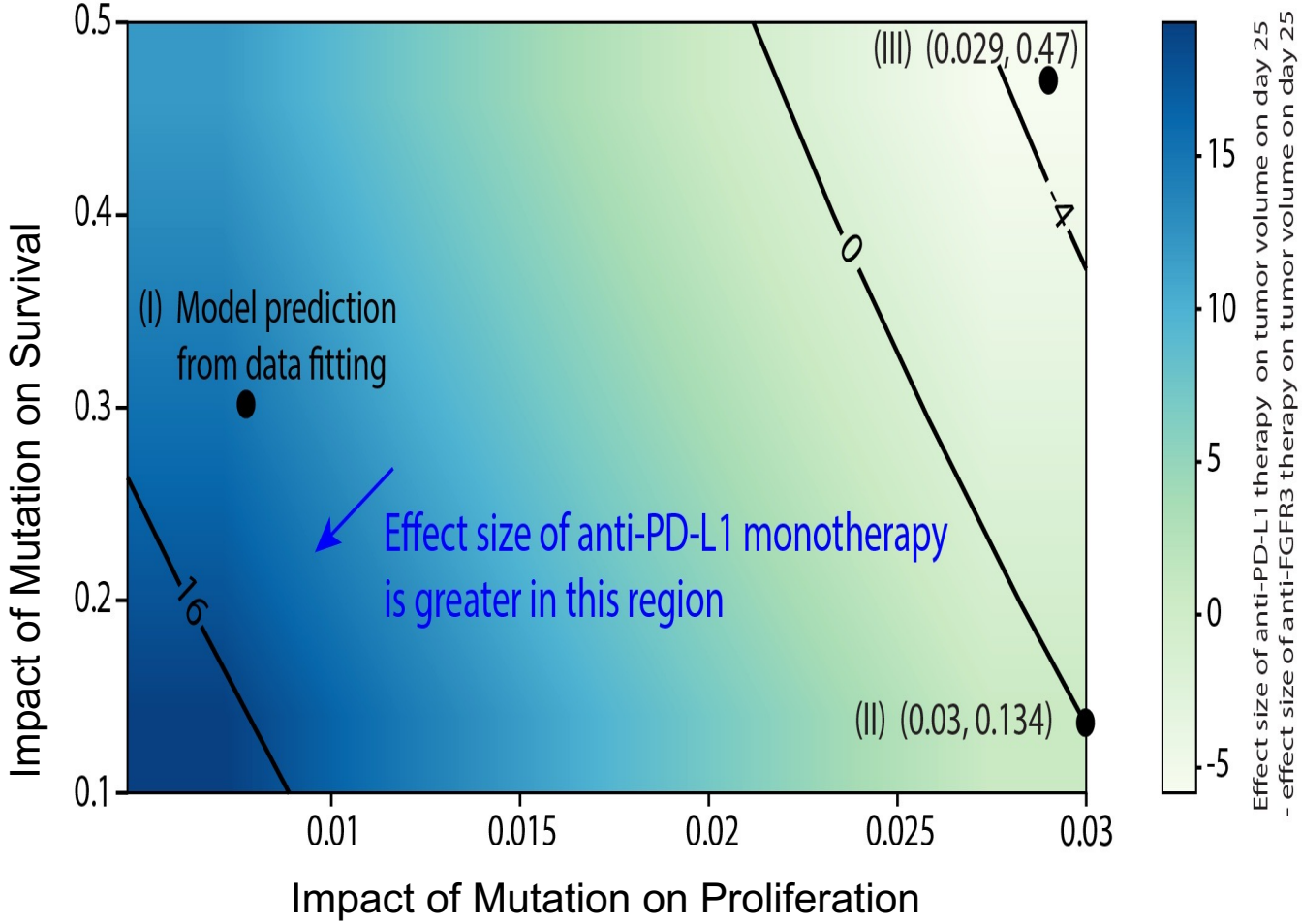
: 75% reduction of total tumor volume after checkpoint blockade

FGFR3 Mutation and Immune Dynamics

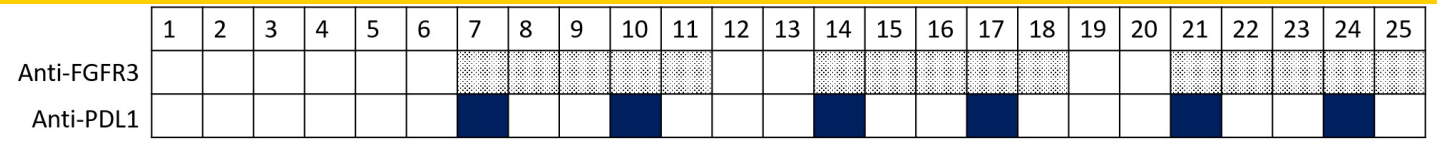


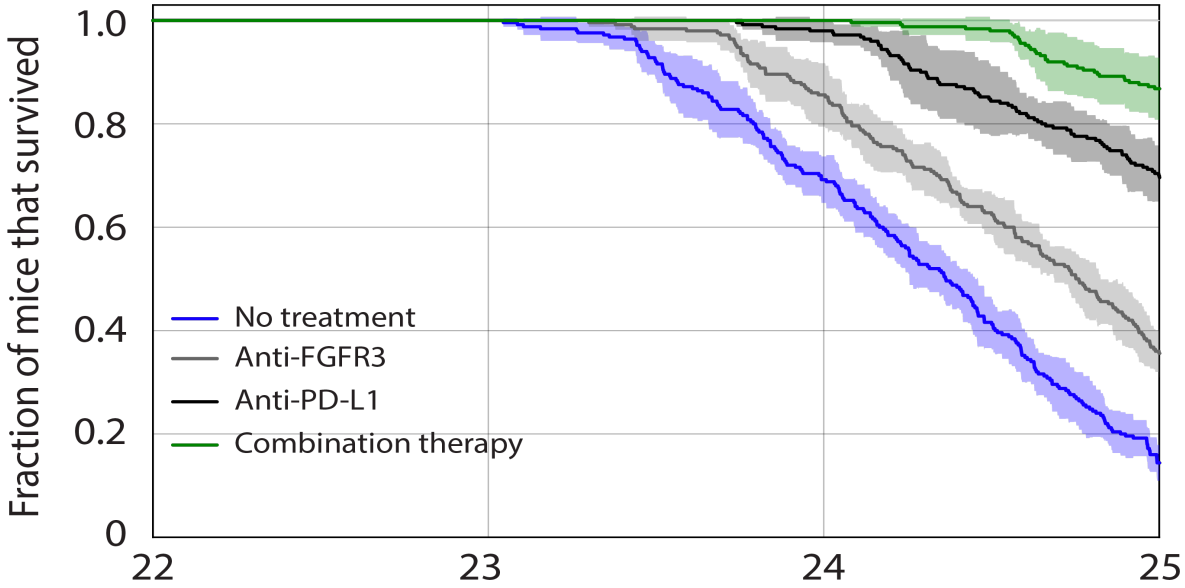
Model Predictions: Monotherapies

- We can predict when targeted therapy outperforms the immune therapy.
- The heatmap shows the difference between the immune and targeted therapies on day 25 as the impact of the mutation on proliferation and survival varies.



Model Predictions - Combo Therapy

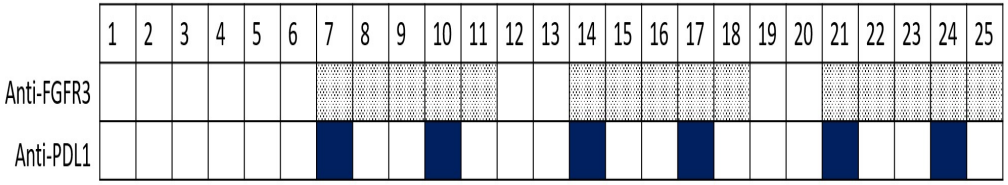




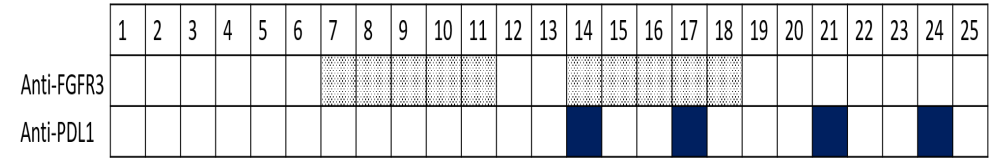
Mean number of mice at risk				Average % of mice that survived
No treatment	50	34	7	(14%)
Anti-FGFR3	50	42	18	(36%)
Anti-PD-L1	50	49	34	(70%)
Combination therapy	50	50	43	(86%)

Comparing Dosing Strategies

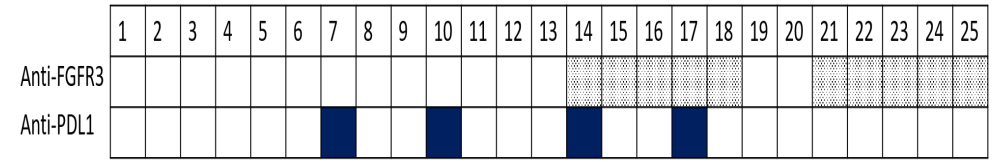
Baseline Schedule: Co-treatment



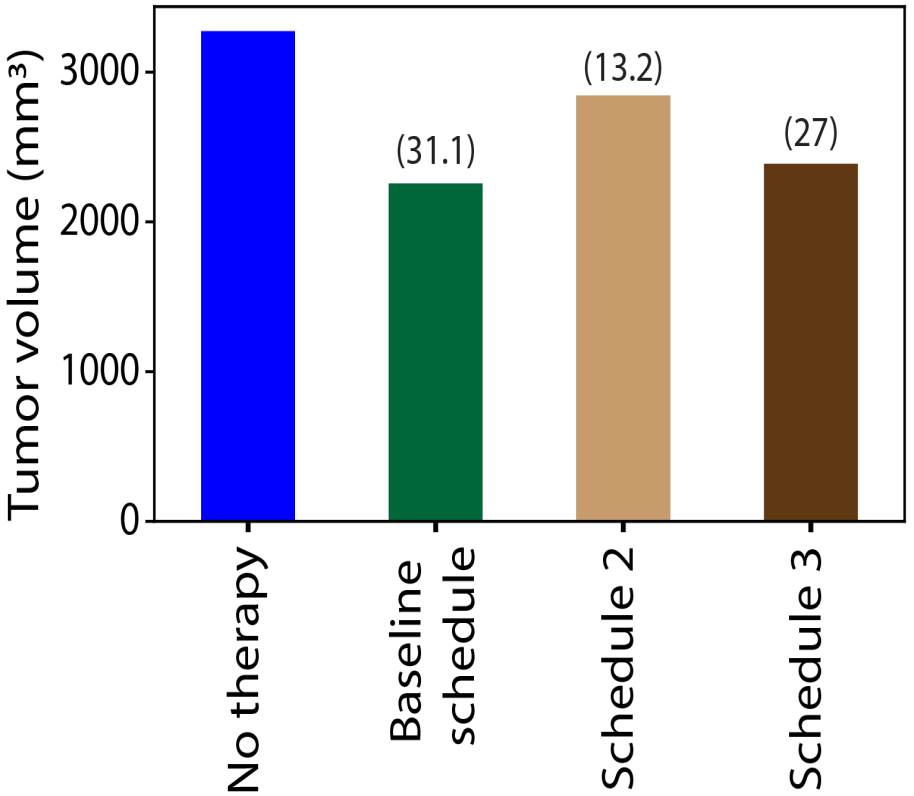
Schedule 2: Pretreatment with RTK Targeted Therapy



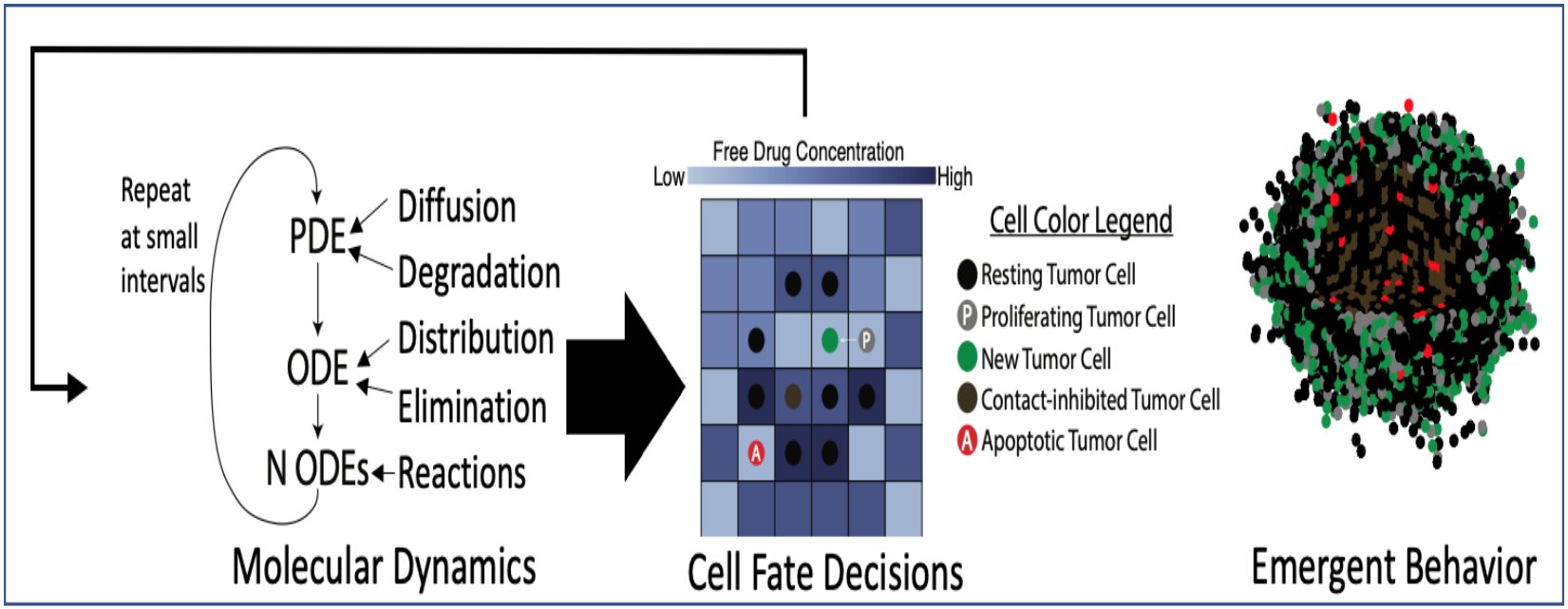
Schedule 3: Pretreatment with Immune Checkpoint Therapy



Model prediction of tumor volume on day 25
(% reduction in tumor volume relative to no treatment)



Next Steps: Agent-based Modeling



Collaborators

Dr. Alexander Pearson, MD PhD
University of Chicago

Dr. Randy Sweis, MD
University of Chicago

Dr. Kamaldeen Okuneye, PhD
Applied Biomath, Boston

Dr. Daniel Bergman
University of Michigan

Shirlyn Wang
University of Michigan

November 30th, 2021
PAVES Seminar 10: Cancer Systems Biology

Mathematical models of biological networks: applications to metastatic reprogramming and cancer drug resistance

Jorge Gómez Tejeda Zañudo
Postdoctoral Associate
Broad Institute of MIT and Harvard
Dana-Farber Cancer Institute
Nikhil Wagle's lab

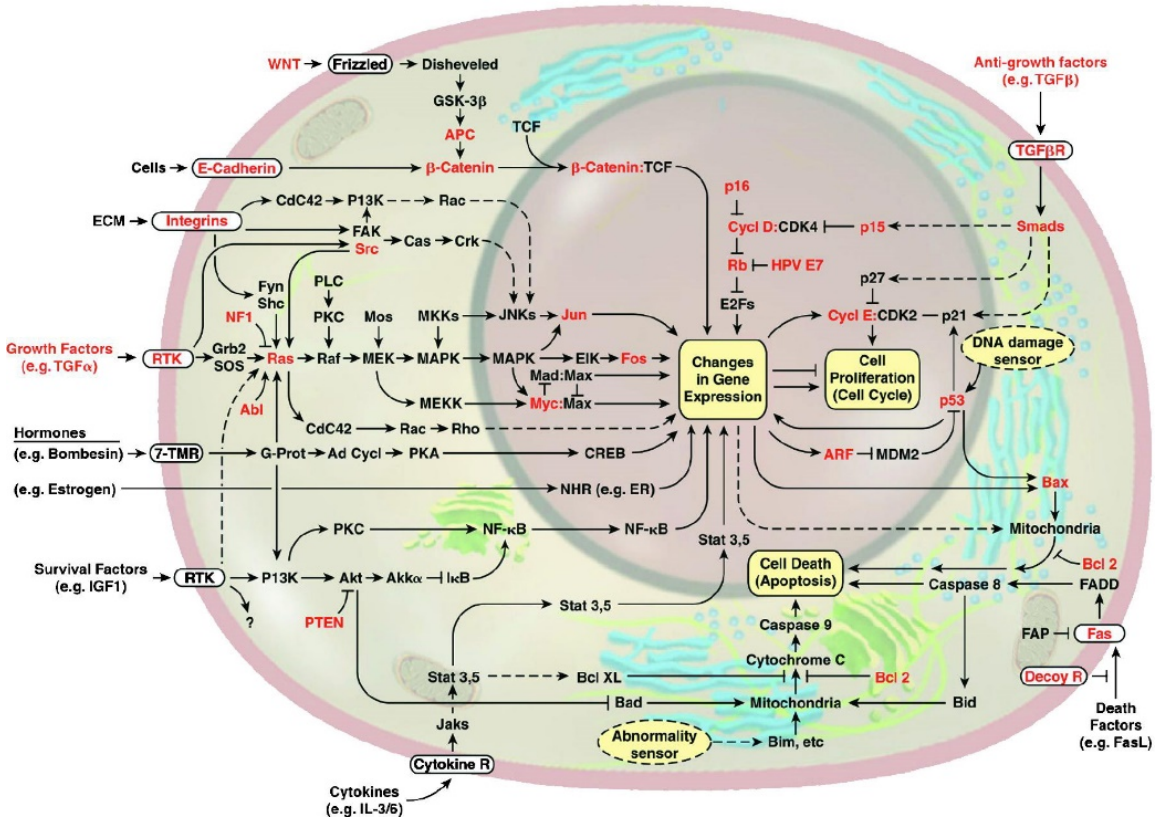
Outline

1) Research program: Modeling decision-making of the biological networks underlying cancer

2) Academic trajectory

3) Resistance mechanisms to targeted therapies in breast cancer

Cellular decision-making emerges from the dynamics of the underlying complex intracellular network



Cellular decision-making

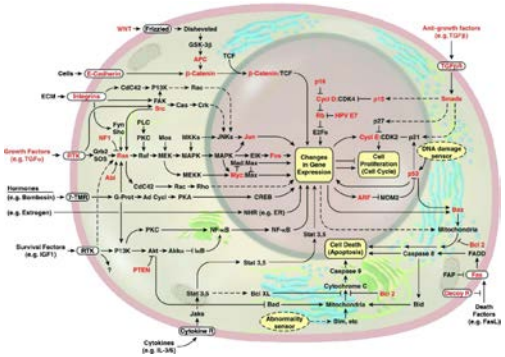
Death vs survival
Proliferation vs arrest
Phenotype switching

Hanahan, Weinberg (2000)

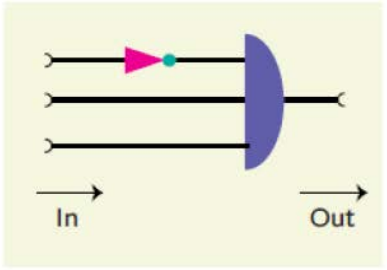
Motivation

Understand and *model* how the dynamics of intracellular networks give rise to decision-making in cancer cells

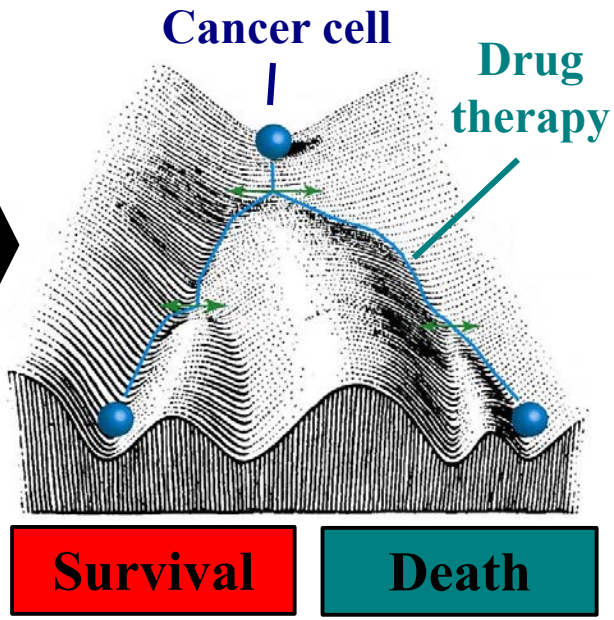
Intracellular network



Mathematical model



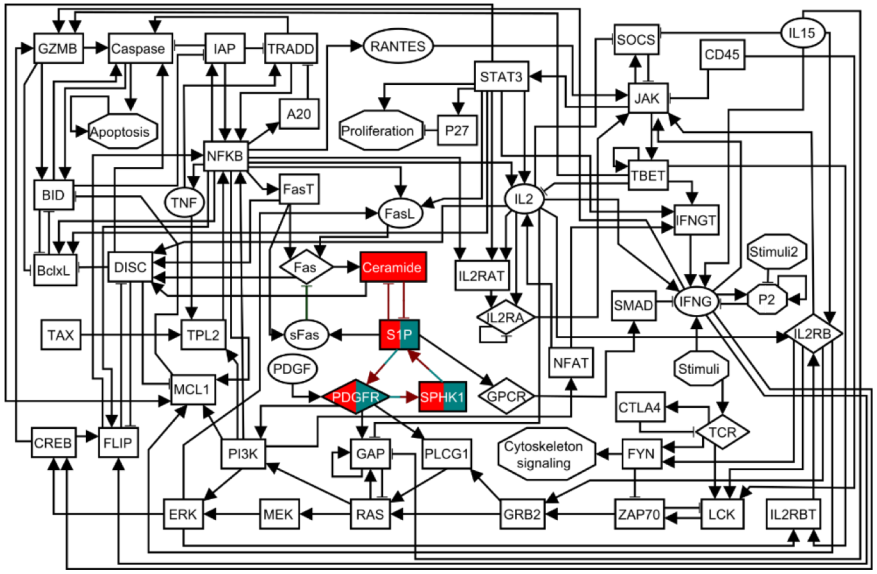
Decision-making dynamics



Network-based modeling

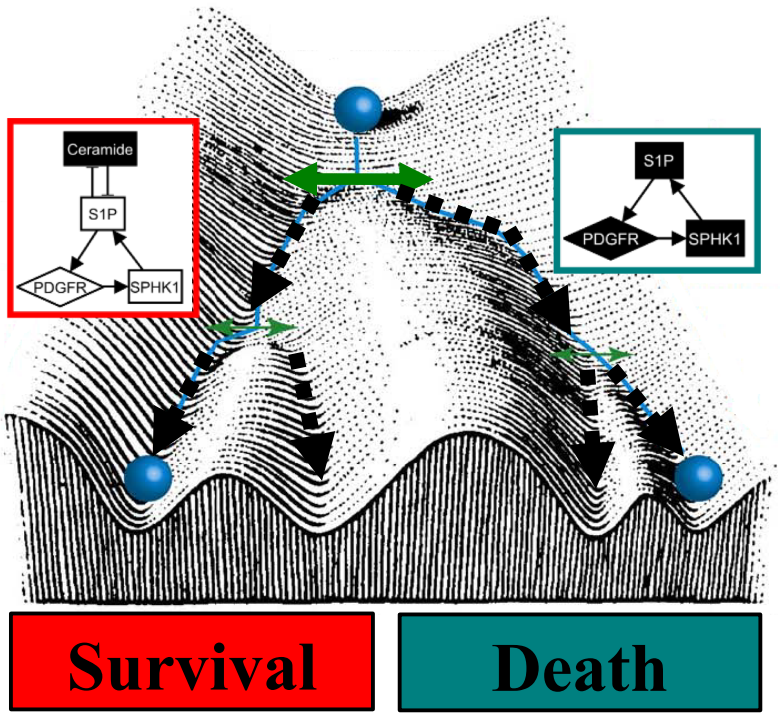
Understand: Connecting the network structure and function to decision-making dynamics

Network structure + mathematical model



J.G.T. Zañudo et. al. PLoS Comp. Bio. 2015
J.G.T. Zañudo et. al. PNAS 2017
J.G.T. Zañudo et. al. Physical Biology 2019
J.C. Rozum, **J.G.T. Zañudo** et. al. Science Advances 2021

Decision-making dynamics + network control theory

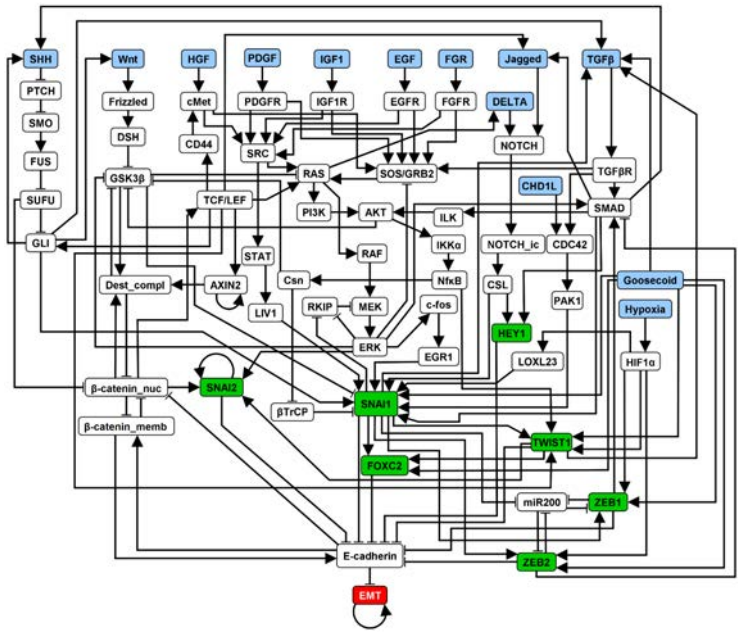


Dynamics of cancer networks

J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

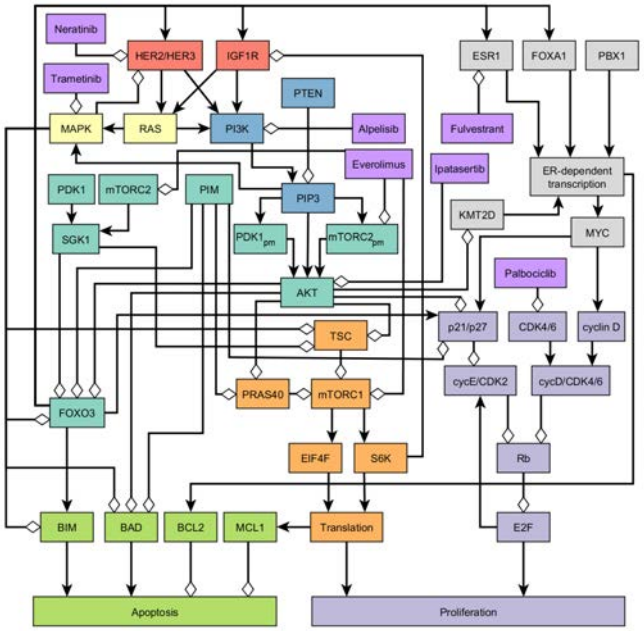
Model: Building models of the dynamics of intracellular networks underlying decision-making processes in cancer, to predict:

Nodes that block metastatic reprogramming
(EMT in liver cancer)



SN Steinway, **JGT Zañudo**, et al. Cancer Res. (2014).
SN Steinway*, **JGT Zañudo***, et al. npj Syst. Biol. & Appl. (2015).

Mechanisms of drug resistance and drug combinations
(targeted therapies in breast cancer)

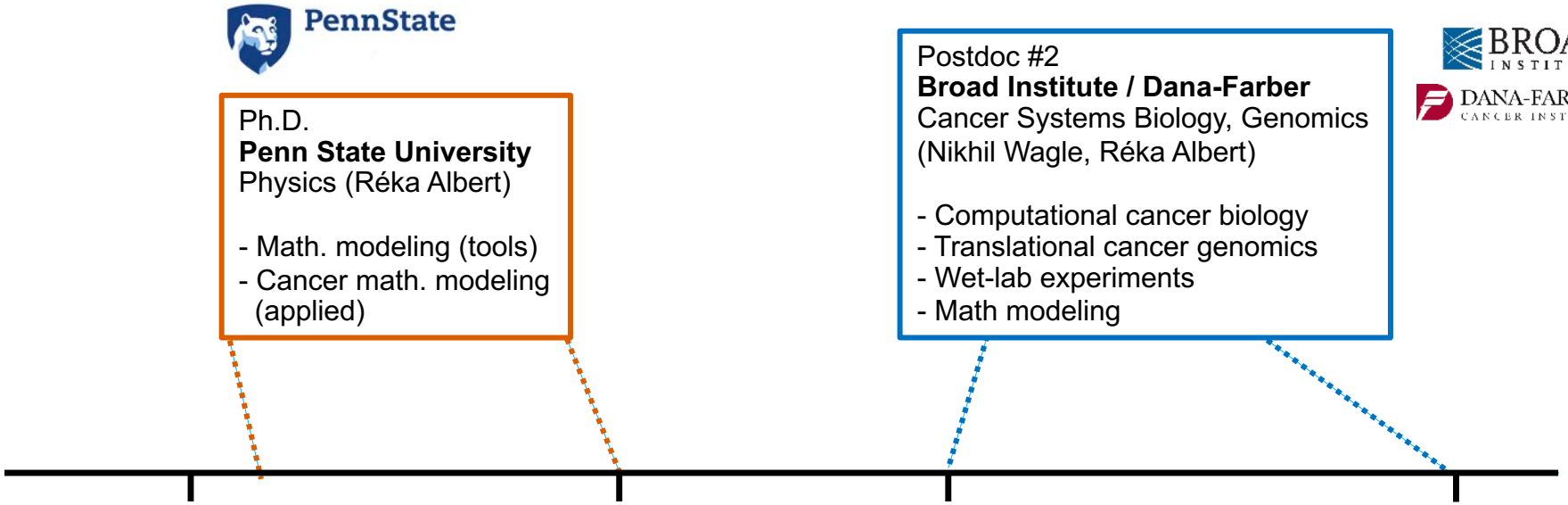


JGT Zañudo, et al. Cancer Convergence. (2017).
JGT Zañudo, et al. Cancer Research. (2021).

Academic trajectory

J.G.T. Zañudo

Math models of biological networks: metastatic reprogramming and cancer drug resistance



College
U. de Guadalajara
(Mexico)

- Physics
- Math. modeling

Ph.D.
Penn State University
Physics (Réka Albert)

- Math. modeling (tools)
- Cancer math. modeling (applied)

Postdoc #1
Penn State University / Broad Institute
Physics / Cancer Systems Biology
(Réka Albert, Nikhil Wagle)

- Math modeling (tools / applied to cancer)
- Wet-lab experiments
- Computational cancer biology
- Translational cancer genomics

Postdoc #2
Broad Institute / Dana-Farber
Cancer Systems Biology, Genomics
(Nikhil Wagle, Réka Albert)

- Computational cancer biology
- Translational cancer genomics
- Wet-lab experiments
- Math modeling

Instructor
Broad Institute / Dana-Farber
Cancer Genomics
(Nikhil Wagle)

- Computational cancer biology
- Translational cancer genomics

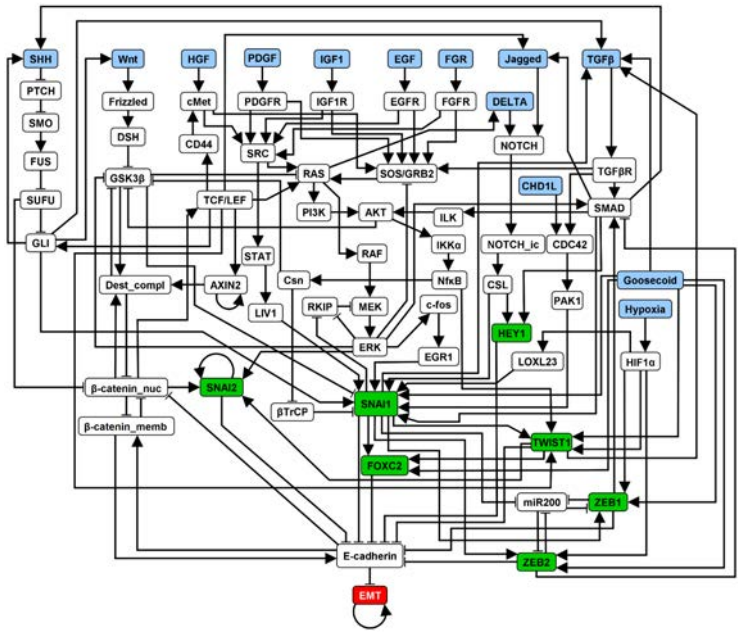
Dynamics of cancer networks

J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

Model: Building models of the dynamics of intracellular networks underlying decision-making processes in cancer, to predict:

Nodes that block metastatic reprogramming

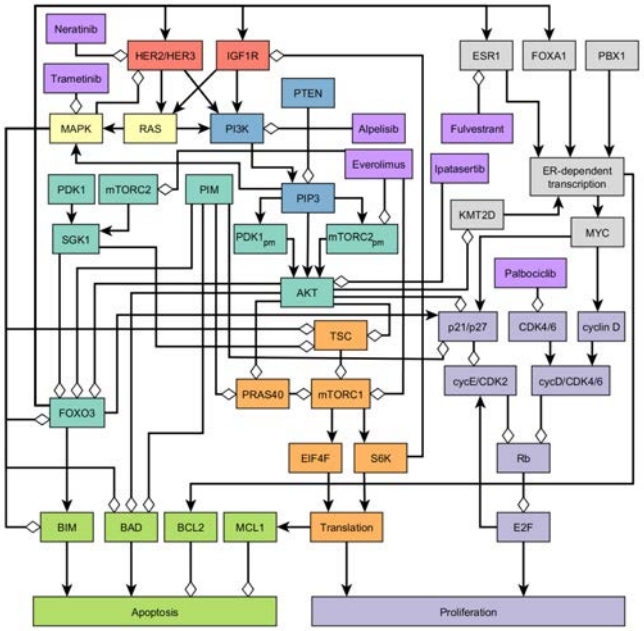
(EMT in liver cancer)



SN Steinway, **JGT Zañudo**, et al. Cancer Res. (2014).
SN Steinway*, **JGT Zañudo***, et al. npj Syst. Biol. & Appl. (2015).

Mechanisms of drug resistance and drug combinations

(targeted therapies in breast cancer)



JGT Zañudo, et al. Cancer Convergence. (2017).
JGT Zañudo, et al. Cancer Research. (2021).

PI3Kα inhibitors in breast cancer

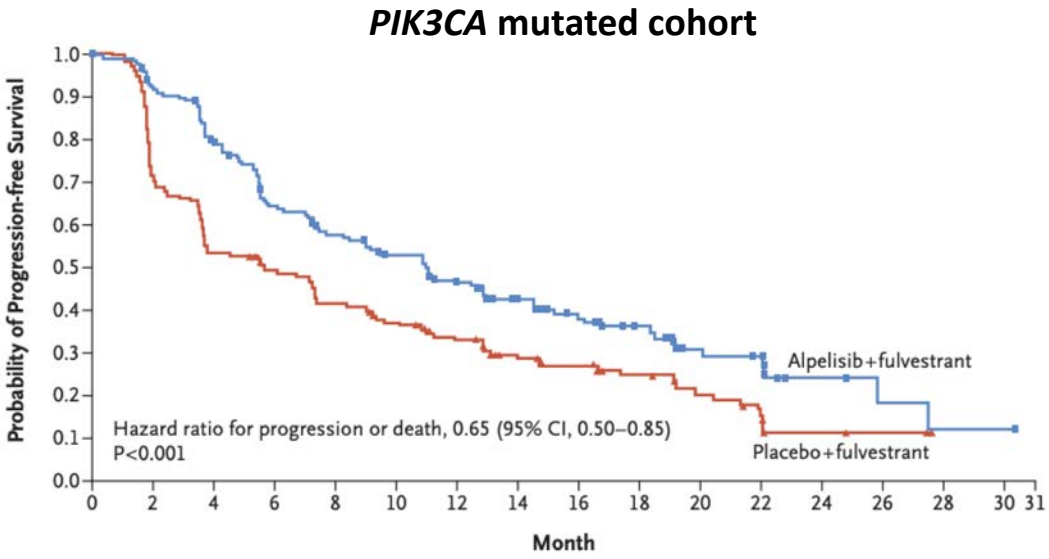
In 2019, alpelisib (PI3Kα inhibitor) became the first approved therapy specifically for metastatic ER-positive breast cancer with *PIK3CA* mutations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

Fabrice, et al. NEJM (2019)



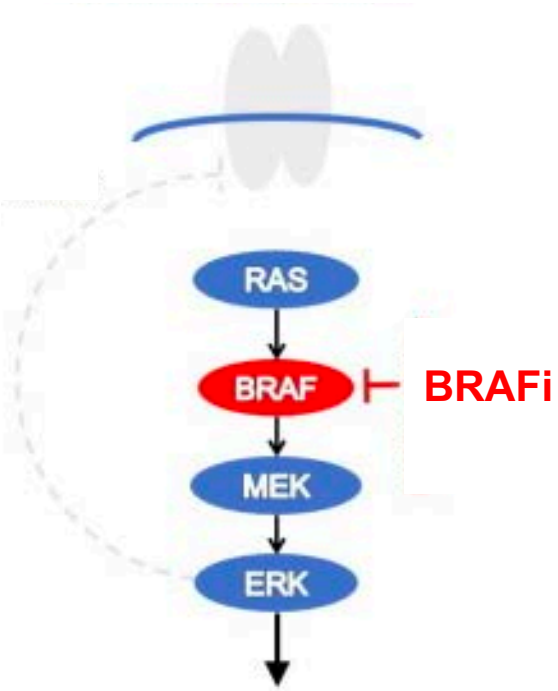
Which of the known resistance mechanisms will be observed clinically?

Are we missing important resistance mechanisms?

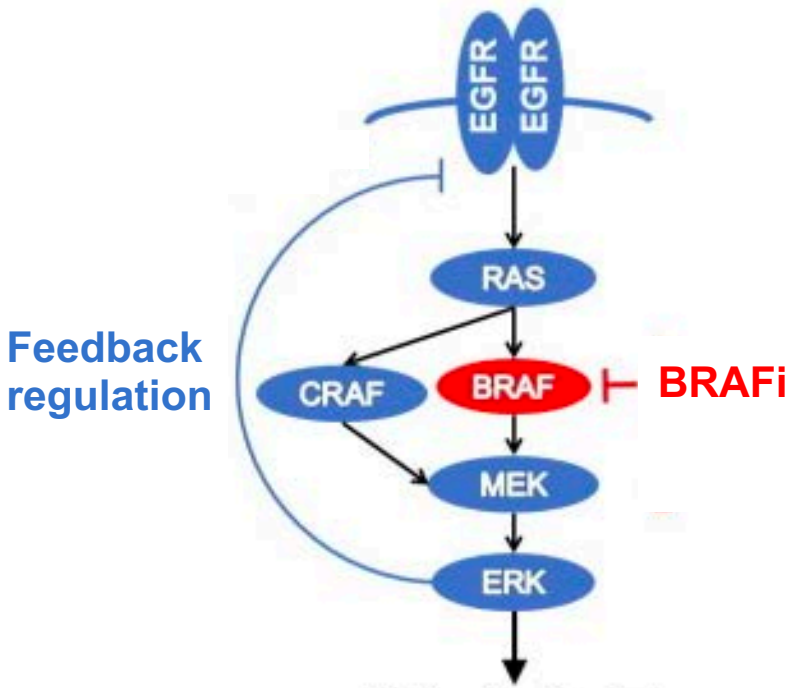
Why do we need math models?

Lessons from drug resistance to BRAFi (and other targeted therapies): signaling pathways are not linear cascades – feedback regulation is important

Melanoma (*BRAF* mutant)
Sensitive to BRAFi



Colorectal cancer (*BRAF* mutant)
Resistant to BRAFi due to EGFR feedback

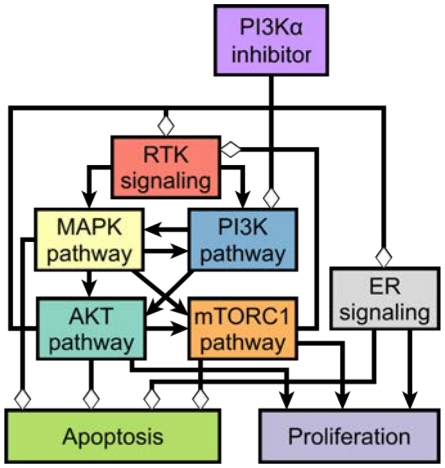


Prahallad et al. Bernards' lab. Nature (2012)

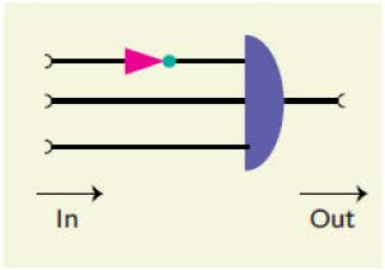
Network models and drug resistance

Our approach: Mathematical model of the network of signaling pathways relevant to PI3K-alpha inhibitors in ER+ *PIK3CA* mutant breast cancer

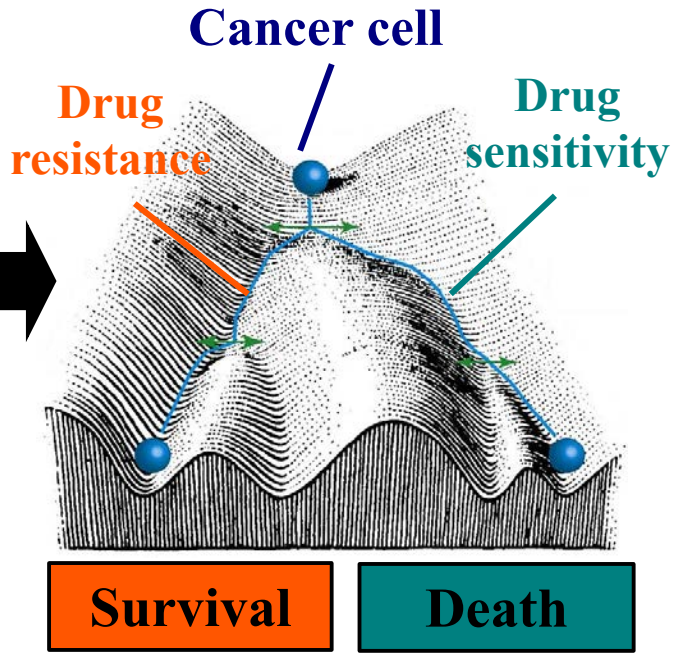
Network of signaling pathways



Mathematical model



Network dynamics and decision-making

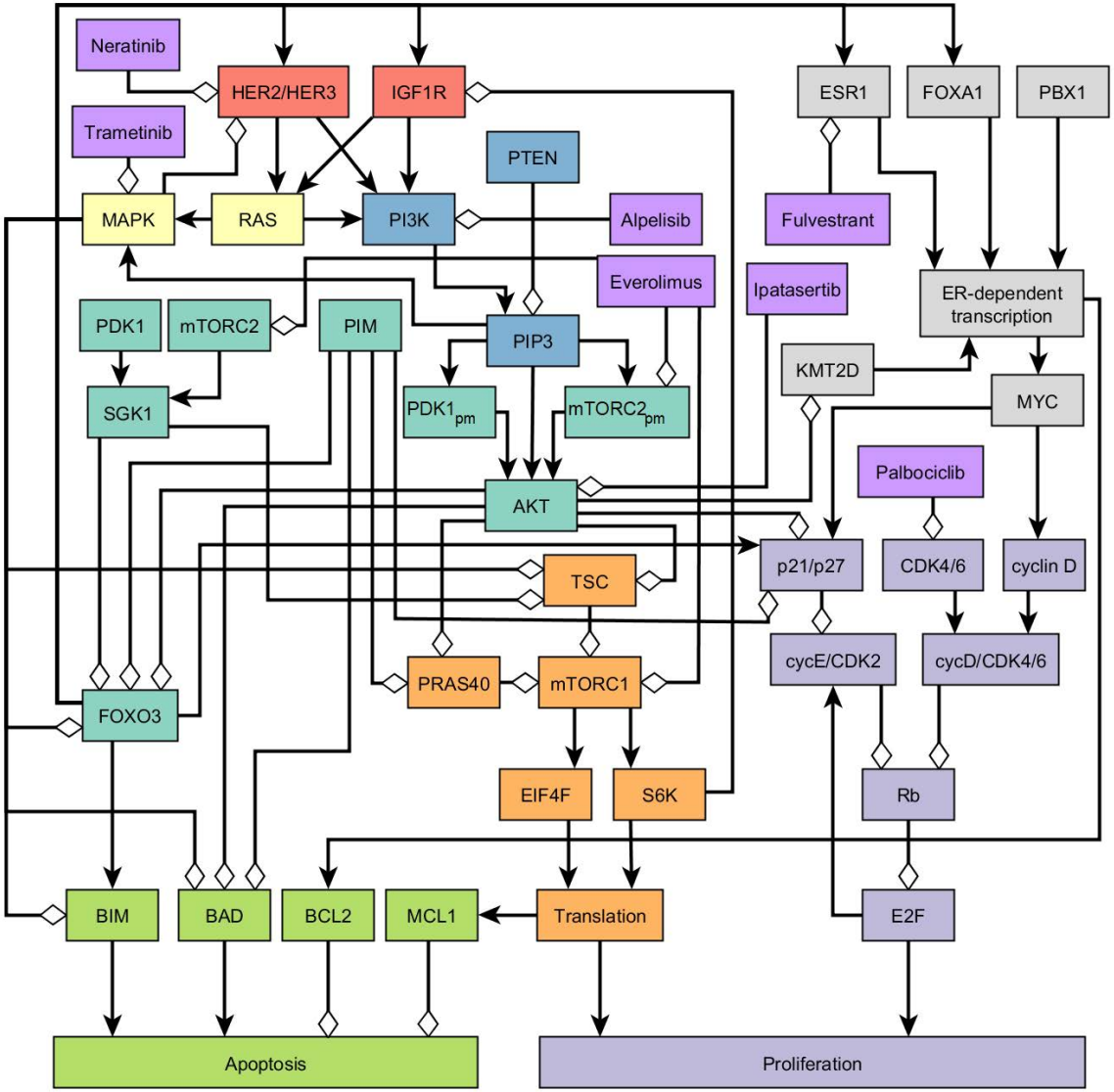


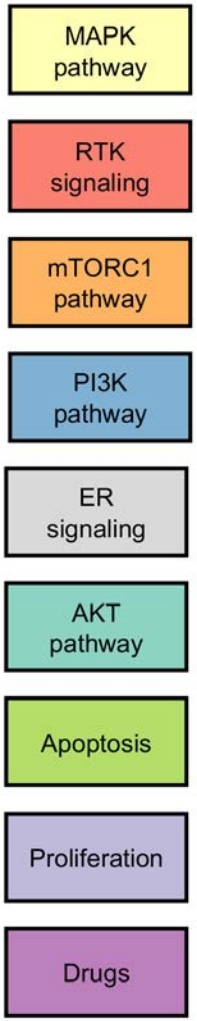
Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol. 9, 1-10.

Breast cancer network model

J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

We built a network that captures the current knowledge of response/resistance to PI3Kα inhibitors in (ER-positive *PIK3CA*-mutant)

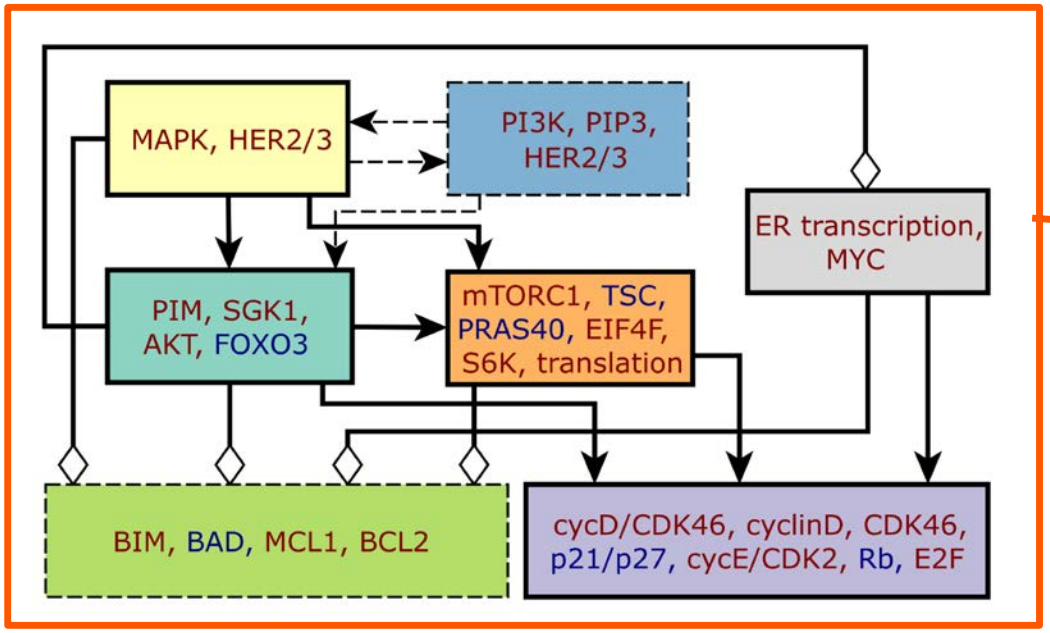


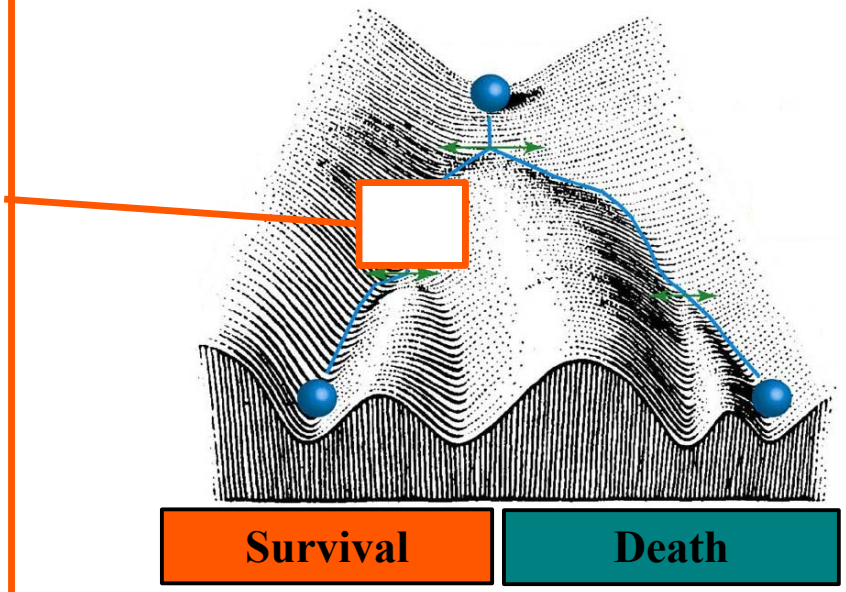


JGT Zañudo et al. (2017) Cancer Convergence 1, 5.

Resistance to PI3K inhibitors

We used the model to systematically search for PI3Ki resistance mechanisms





Red: High activity
Blue: Low activity

PI3K pathway
MAPK pathway
AKT pathway
mTORC1 pathway
ER signaling
Apoptosis
Proliferation

New predictions: **knockdown of FOXO3** reduces sensitivity to PI3K inhibition and is a potential resistance mechanisms.

JGT Zañudo et al. (2017) Cancer Convergence 1, 5.

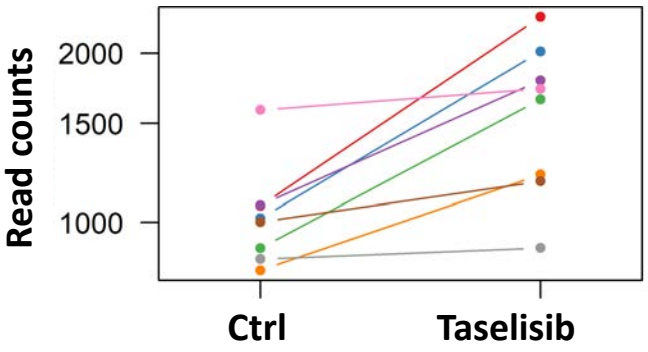
FOXO3 KD and resistance to PI3Ki

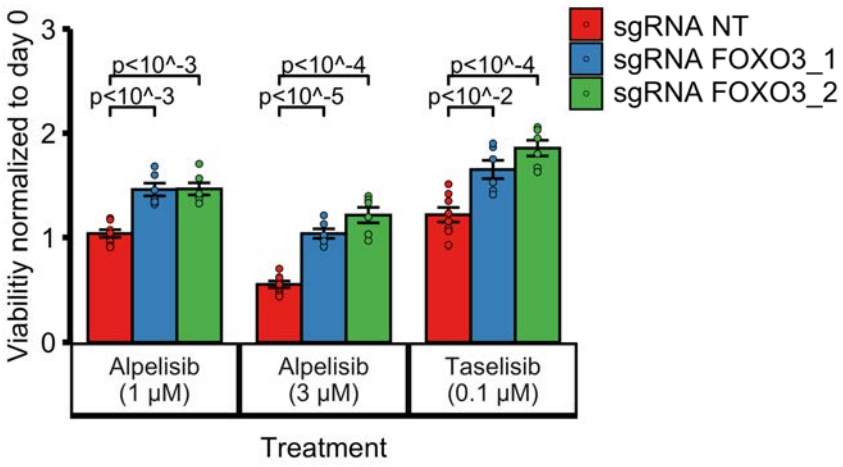
J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

We experimentally confirmed that FOXO3 KD decreases sensitivity to PI3K inhibitors and is a potential resistance mechanism

MCF7

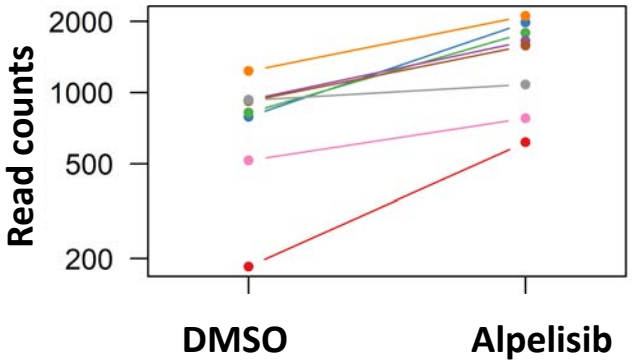
FOXO3 KD (CRISPR screen) $p<2\cdot10^{-3}$ $FDR<10^{-1}$

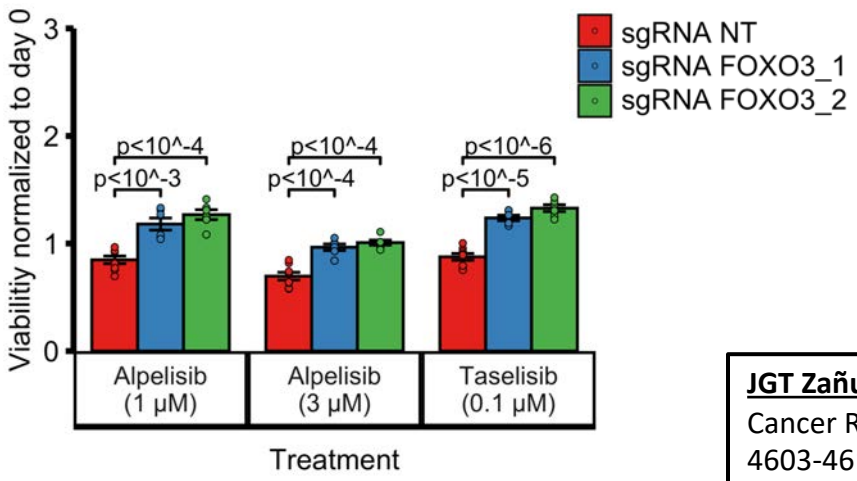




T47D

FOXO3 KD (CRISPR screen) $p<10^{-5}$ $FDR<10^{-3}$





JGT Zañudo et al.
Cancer Research 81, 4603-4617 (2021)

FOXO3 KD and resistance to PI3Ki

J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

FOXO3 knockdown result is surprising given its pro-survival role in feedback regulation

RESEARCH ARTICLE | CANCER

PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor–positive breast cancer

Science Translational Medicine 2015

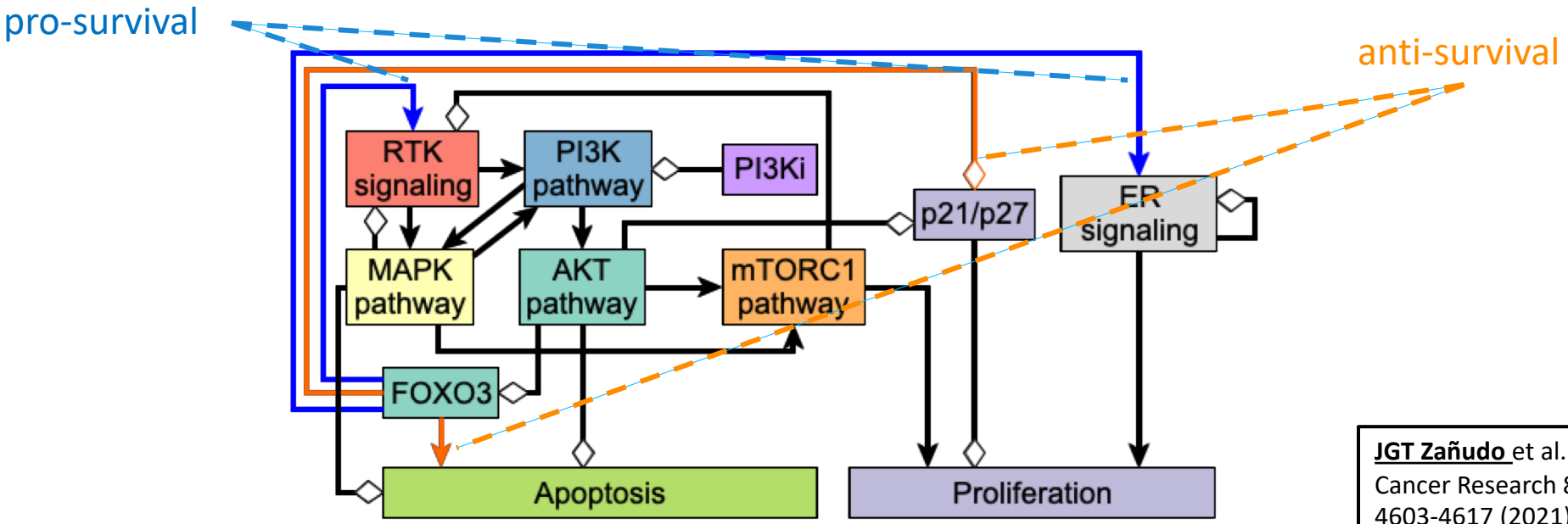
RESEARCH ARTICLE | CANCER

The brain microenvironment mediates resistance in luminal breast cancer to PI3K inhibition through HER3 activation

Science Translational Medicine 2017

FOXO3 has pro-survival (feedbacks) and anti-survival (tumor suppressor) effects

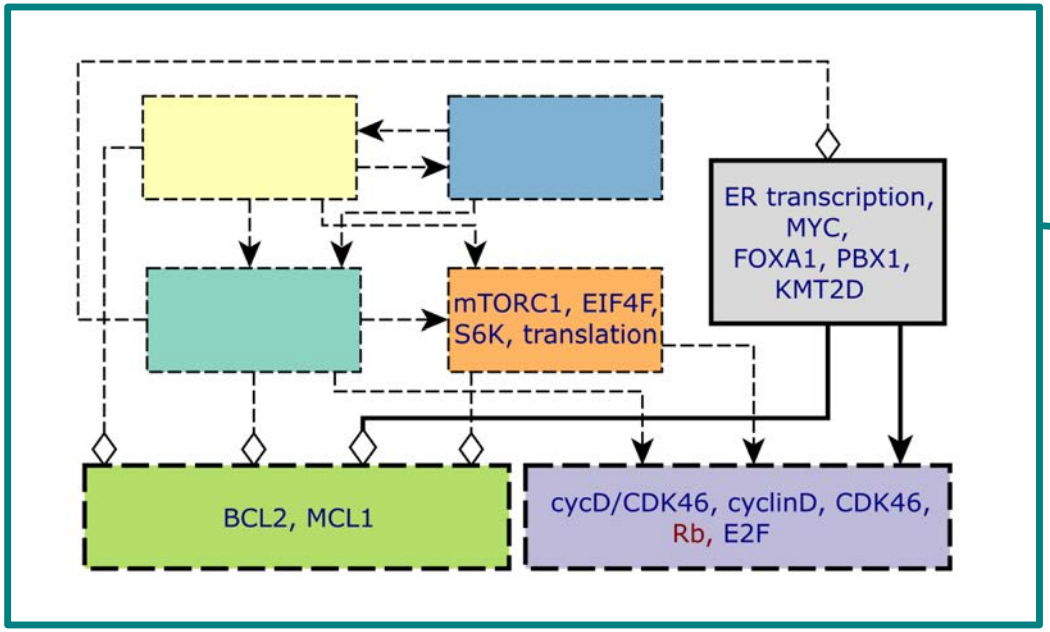
Our model captures that the tumor suppressor effect can dominate

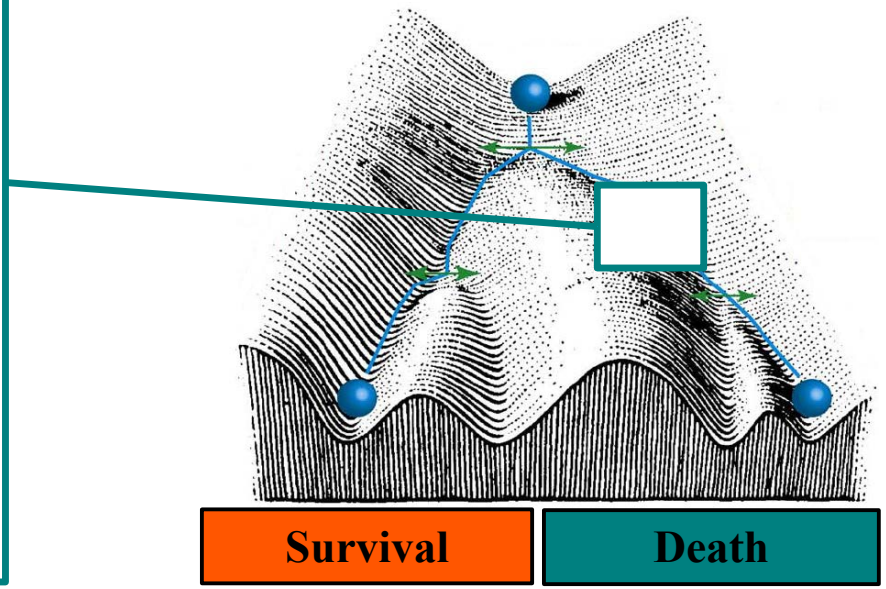


JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

Synergy with PI3Kα inhibitors

We systematically searched for synergistic combinations with PI3Kα inhibitors





Red: High activity
Blue: Low activity

PI3K pathway
MAPK pathway
AKT pathway
mTORC1 pathway
ER signaling
Apoptosis
Proliferation

New predictions: synergy with the inhibition of anti-apoptotic proteins **MCL1 and BCL2 (BH3 mimetics)**.

JGT Zañudo et al. (2017) Cancer Convergence 1, 5.

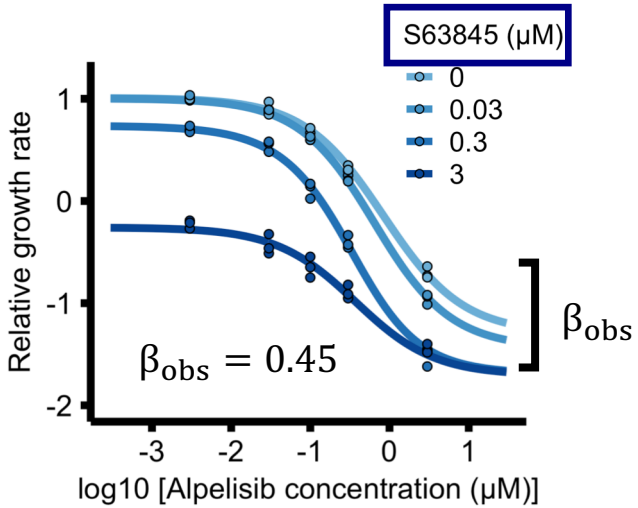
Synergy with PI3Kα inhibitors

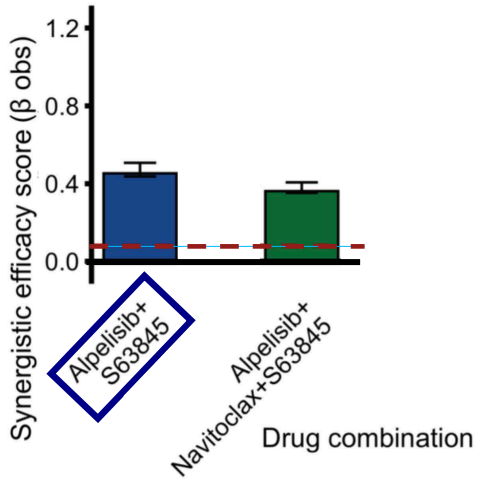
J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

We experimentally showed that BH3 mimetics and PI3Kα inhibitors are synergistically efficacious, and the BH3 mimetic needed is cell-line-specific

MCF7

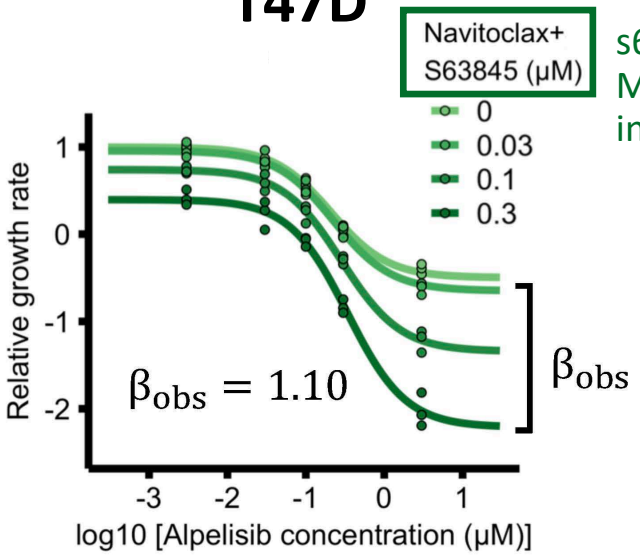
s63845: MCL1 inhibitor

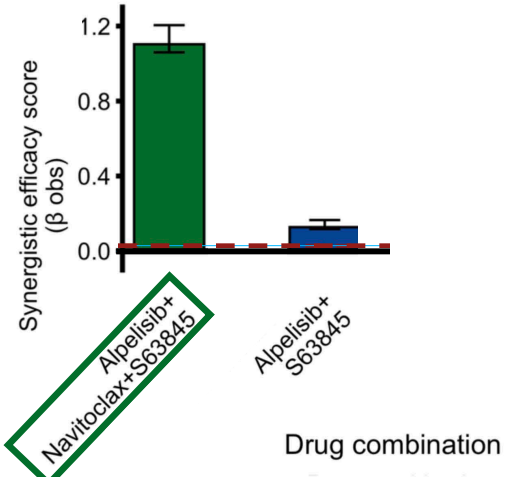




T47D

s63845 + navitoclax: MCL1 + BCLXL/BCL2 inhibitor



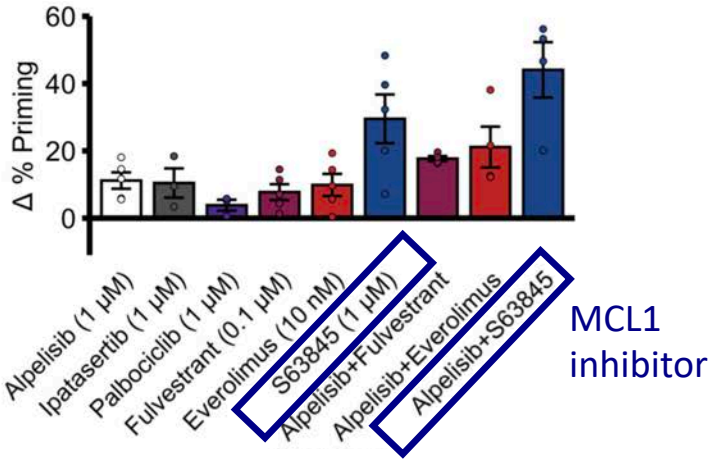


JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

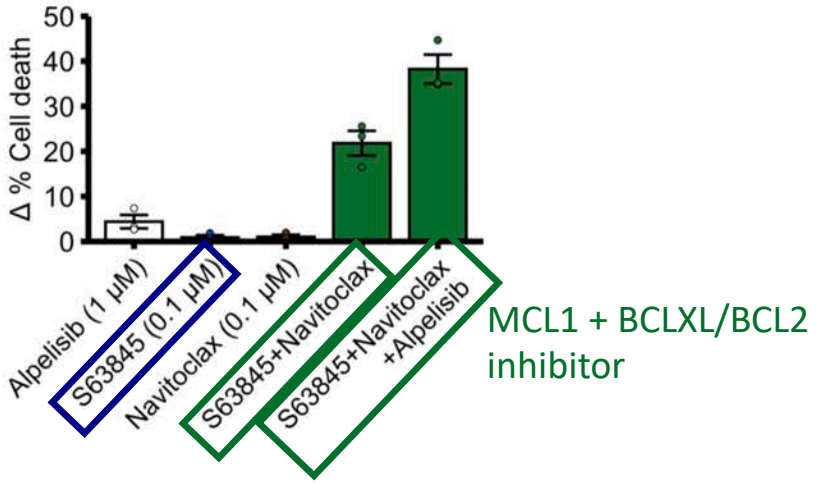
BH3 mimetics as effective drug combos

BCL-XL expression explained the differential sensitivity to BH3 mimetics and updated model reproduced the cell line-specific behavior

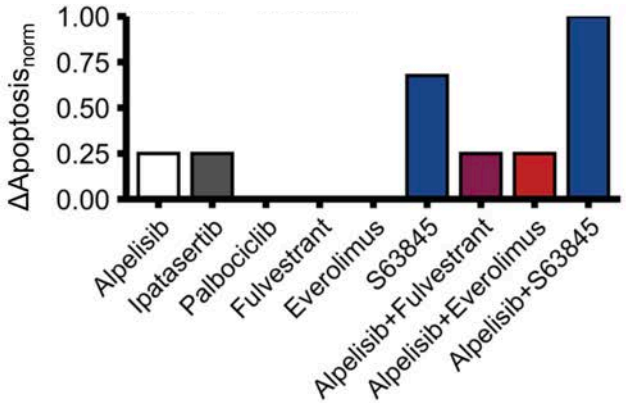
MCF7 - Experiments



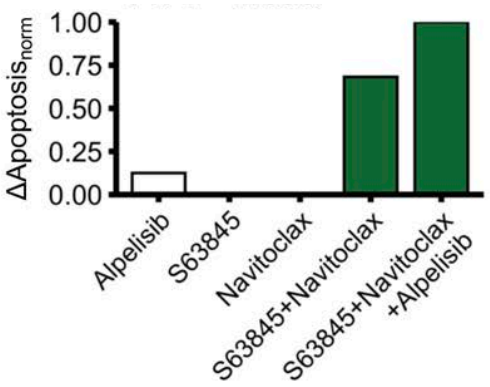
T47D - Experiments



MCF7 - Model



T47D - Model



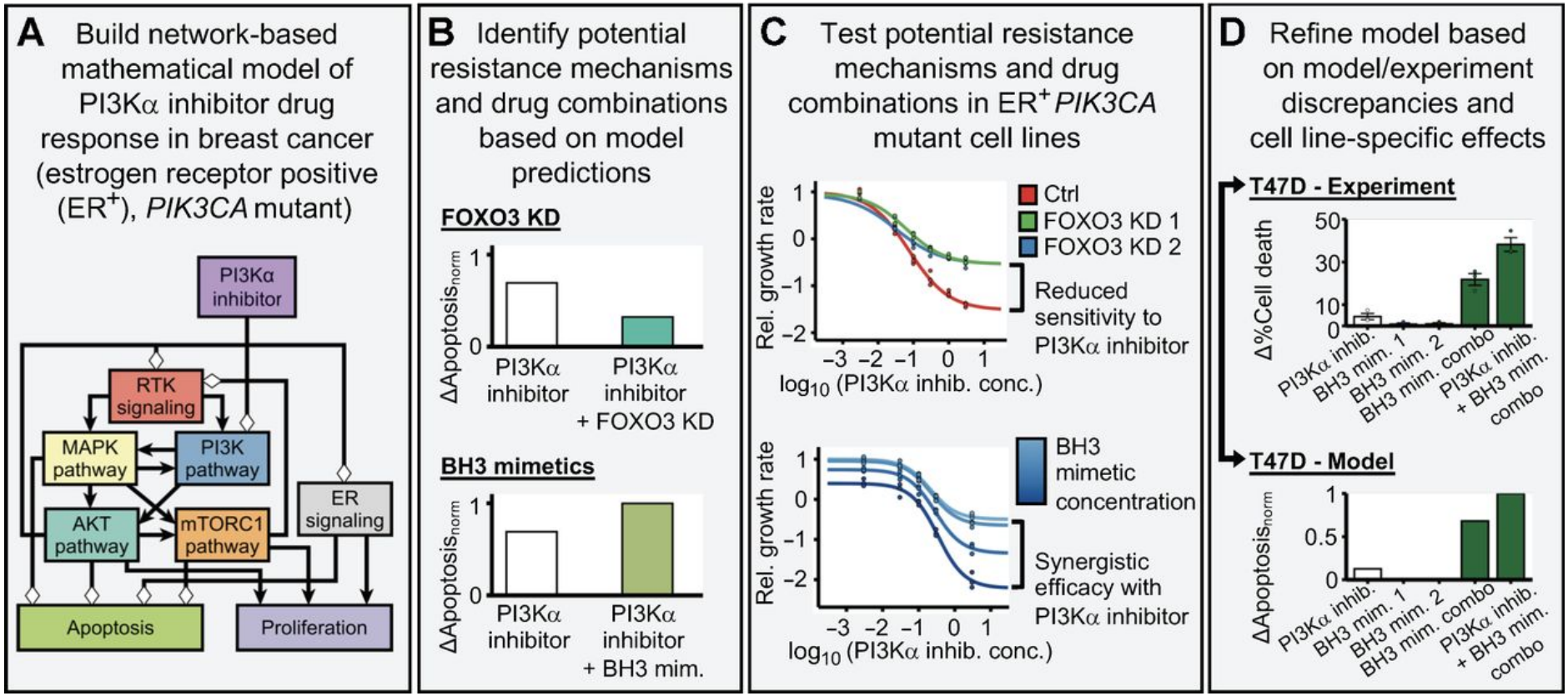
JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

Conclusions

Mathematical models and experimental work to identify potential resistance mechanisms and drug combinations for PI3Kα inhibitors in ER+ *PIK3CA*^{mut} breast cancer

Experimentally confirmed model's predictions: FOXO3 knockdown as a potential resistance mechanism, PI3Kα inhibitors + (tumor-specific) BH3 mimetics as an efficacious drug combination

JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)



Acknowledgements

ALBERT LAB

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Steven Steinway
Gang Yang
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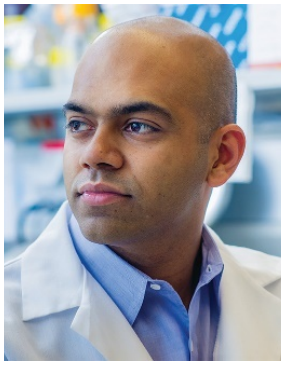
Jordan Rozum
Eli Newby
Xiao Gan
Parul Maheshwari
Fatemeh Nasrollahi

WAGLE LAB



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Utthara Nayar (Johns Hopkins)
Gabi Johnson
Kailey Kowalski
Esha Jain
Jorge Buendía
Dewey Kim

SU2C convergence team

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Tony Letai (Dana Farber)
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José Baselga (Sloan Kettering , AstraZeneca)
Arnold Levine (IAS)
Suzanne P. Christen (IAS)

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Jorge Gómez Tejeda Zañudo
Postdoctoral researcher
Broad Institute of MIT and Harvard
Dana-Farber Cancer Institute

BROAD INSTITUTE

DANA-FARBER CANCER INSTITUTE

Thank you for your time!

Contact: jgtz@broadinstitute.org
@jgtzanudo (Twitter)

EXTRA SLIDES

Synergy with PI3Kα inhibitors

J.G.T. Zañudo
Network models of ER+ breast cancer identify PI3Kα inhibitor sensitivity factors and drug combinations

BROAD INSTITUTE
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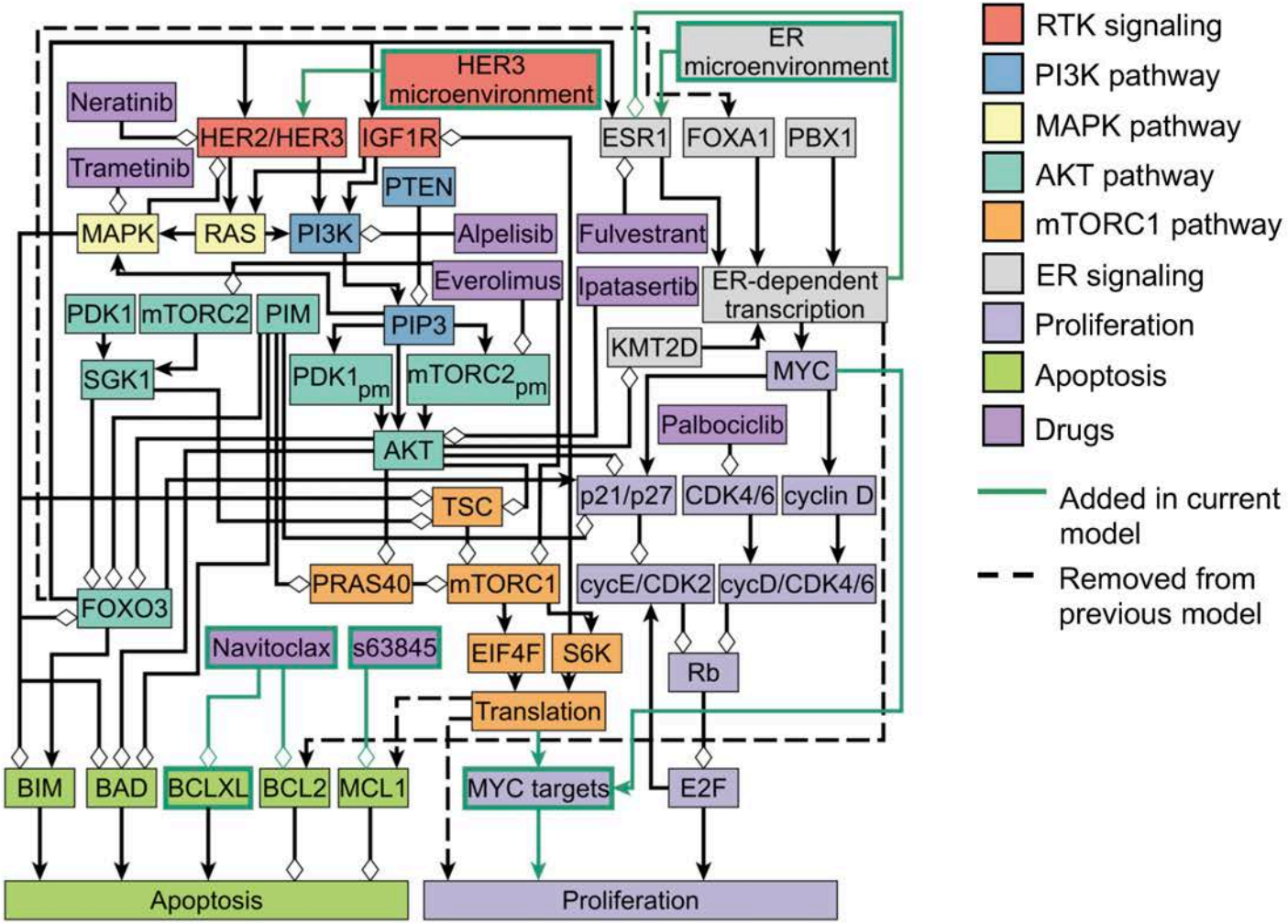
We built an updated version of the model incorporates:

(1) cell-line-specific aspects

(2) discrepancies found by our experiments



JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

Building the ER+ *PIK3CA*^{mut} BC model

BROAD INSTITUTE
DANA-FARBER CANCER INSTITUTE

Steps in constructing a mathematical model of a signaling network

Response to PI3Kα inhib. in ER+ *PIK3CA* mut BC

Phenomenon:
Identify cancer process

Response/resistance to PI3Kα inhib. (*in vitro*, *in vivo*, clinical literature). Tissue-specific interactions (breast cancer)

Identify nodes and edges,, and regulatory functions for each node

Known resist. mechanisms, clinically relevant drugs in BC

Addition of deregulated elements (e.g. mutations) and external stimuli (e.g. drugs)

Proliferation, Apoptosis in response to PI3Kα inhib., resist. mech., other drugs

Simulate information propagation, Determine cellular outcomes

Potential PI3Kα inhib. resist. mechanisms, drug combos

Prediction

PI3Kα inhib. response in cell lines with predicted resist. mechanisms, drug combos

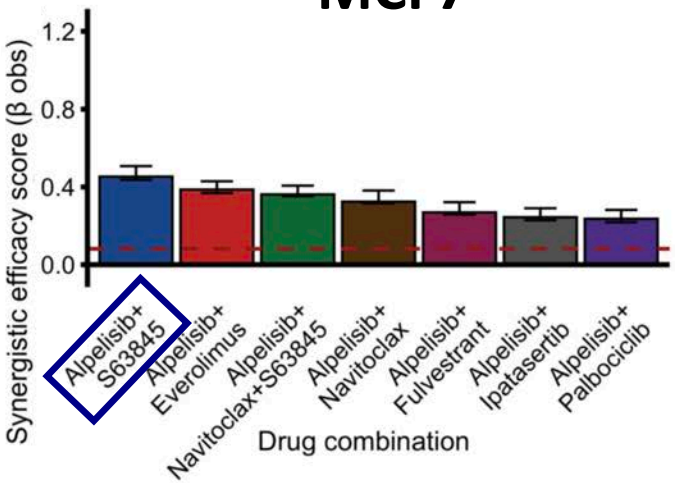
Validation

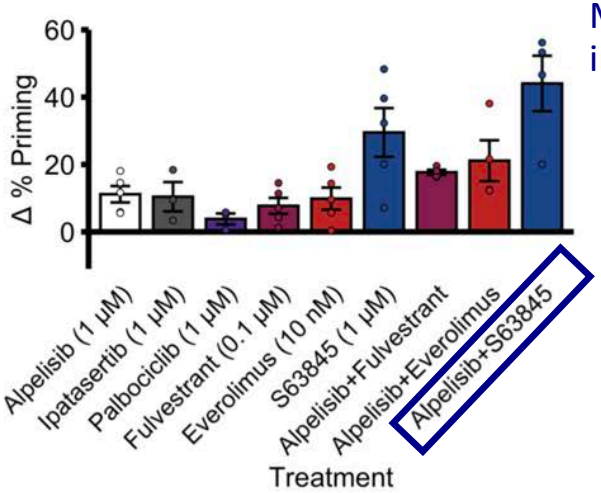
Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol

Synergy with PI3Kα inhibitors

BH3 mimetics and PI3Kα inhibitors are as synergistically efficacious (or more) than other known synergistic combinations, and cause more apoptosis

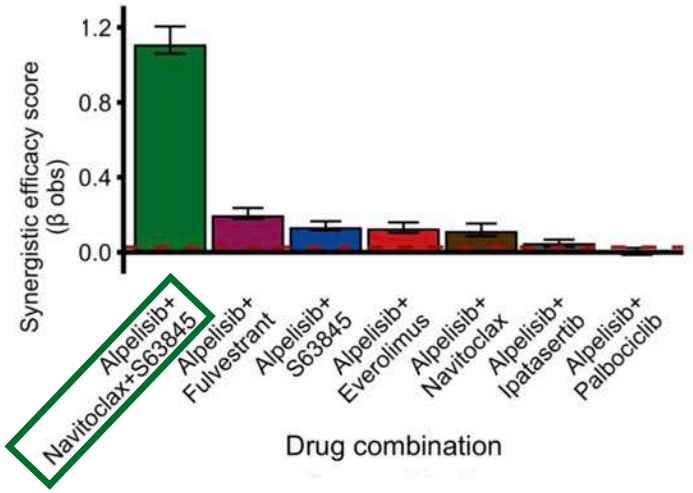
MCF7

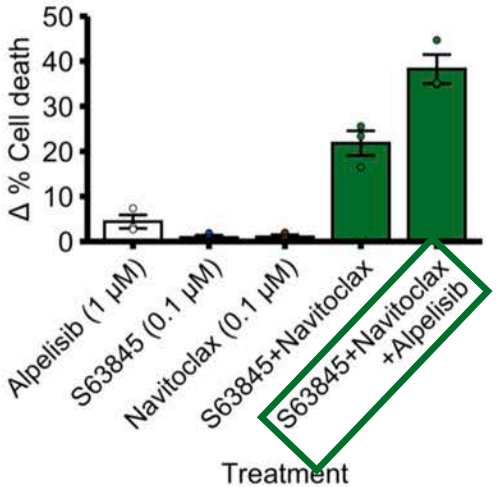




s63845: MCL1 inhibitor

T47D





s63845 + navitoclax: MCL1 + BCLXL/BCL2 inhibitor

JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

HARVARD
MEDICAL SCHOOL

Studying the relationship between DNA damage in cancer cells and immune responses

Joshua François

Postdoctoral Research Fellow, Harvard Medical School

PAVES 2021

My Personal Journey

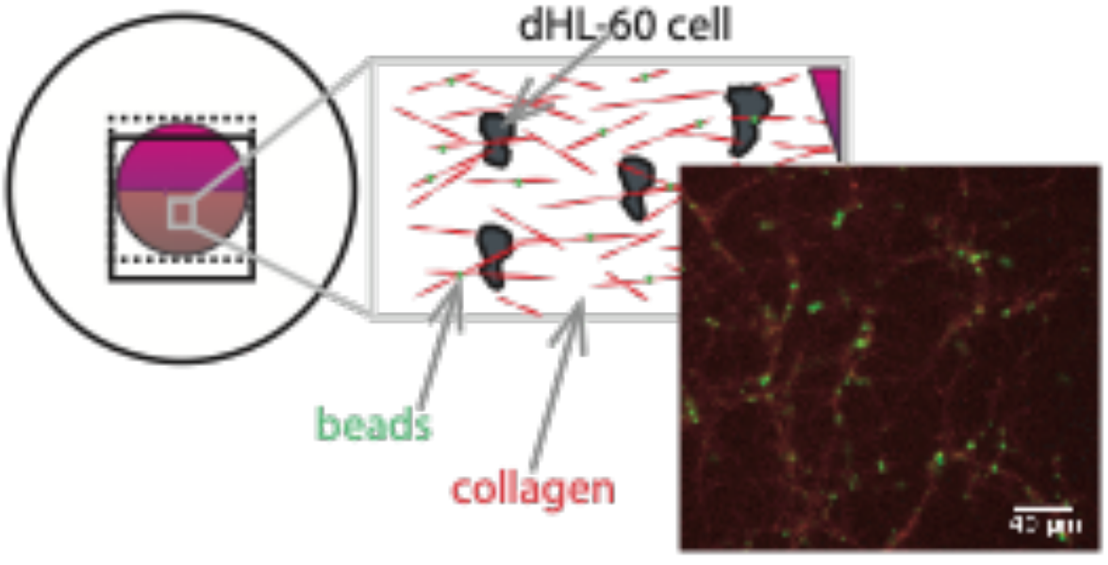
University of Maryland, Baltimore County

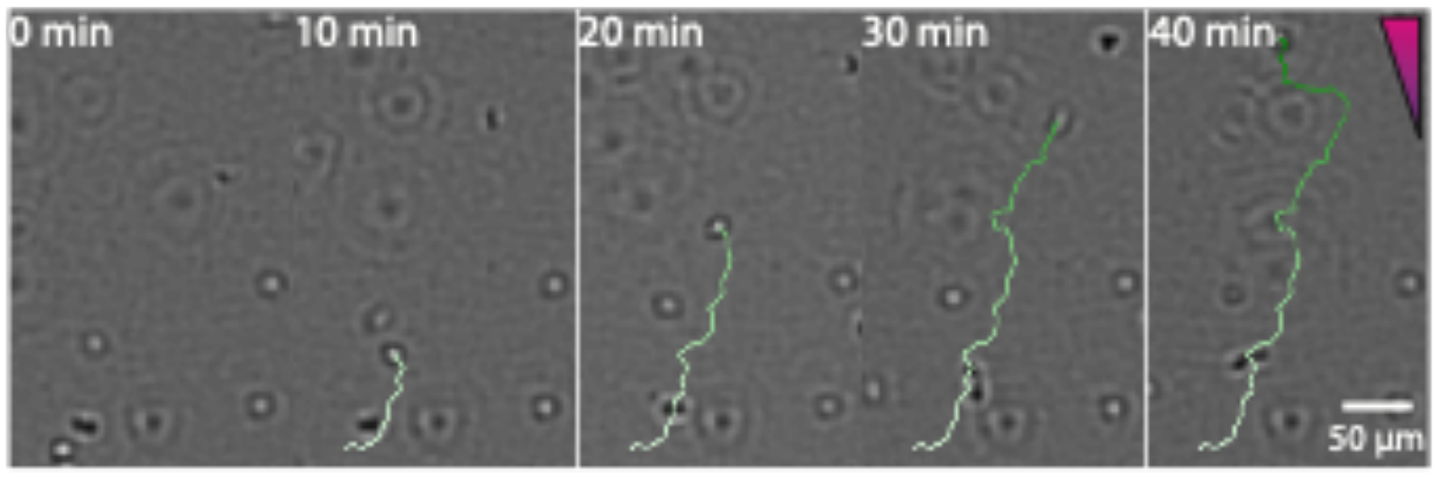
B.S. Mechanical Engineering

University of California, San Diego

Ph.D. Bioengineering

Mechanics of Neutrophil Migration in 3-D environments



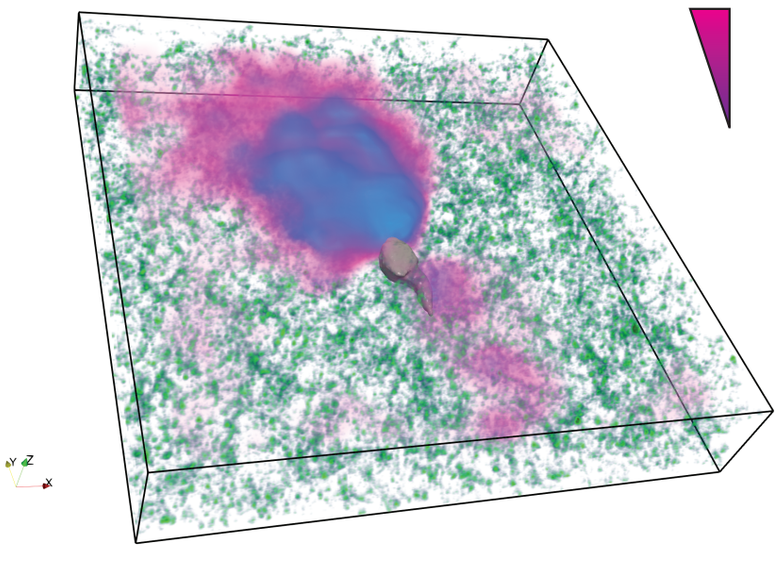


- *Built custom migration chamber for directed 3-D neutrophil migration in collagen gels*
- *Developed automated label and label-free cell tracking methods for tracking > 20,000 cells*

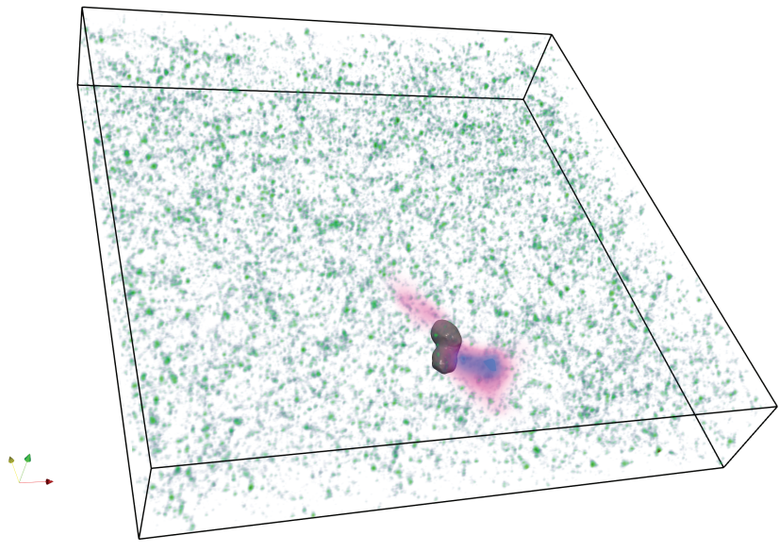
François *et al*. Science Advances. 2021

3-D neutrophil migration is dependent on ability to deform local environment and turn

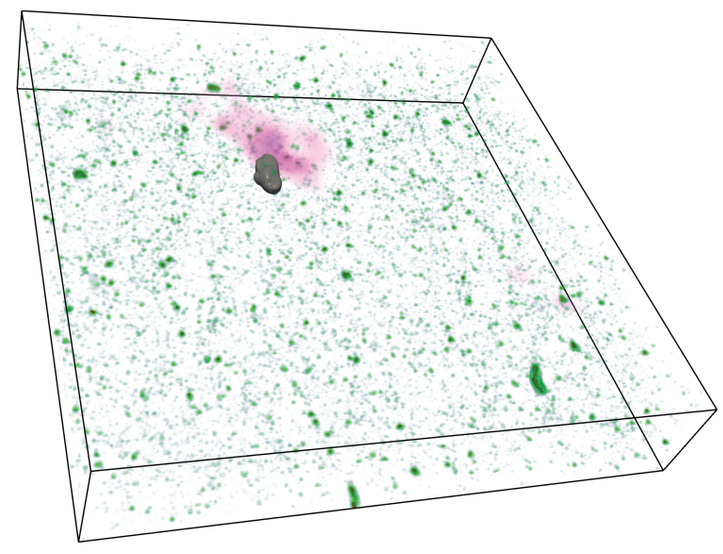
0.25 mg/mL, untreated

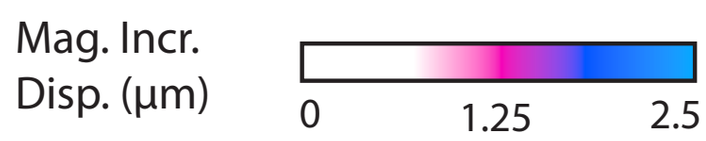


0.25 mg/mL, blebbistatin



0.25 mg/mL, ck666





Findings

Low-Density 3-D Environments: *Neutrophils rely on ability to deform surroundings*

High-Density 3-D Environments: *Neutrophils rely on ability to turn*

Proteins involved in cell contractility, and turning crucial for neutrophil migration in 3-D environments

François *et al*. Science Advances. 2021

My Personal Journey

University of Maryland, Baltimore County

B.S. Mechanical Engineering

University of California, San Diego

Ph.D. Bioengineering

Harvard Medical School

Postdoctoral Research Fellow,
Systems Biology

p53 dynamics can alter cell fates

p53 recognizes cellular stress

- DNA damage
- unusual growth signals
- oncogene activation
- hypoxia
- etc.

Different p53 dynamics linked to fate

- Pulsatile -> DNA damage repair
- Sustained -> Senescence

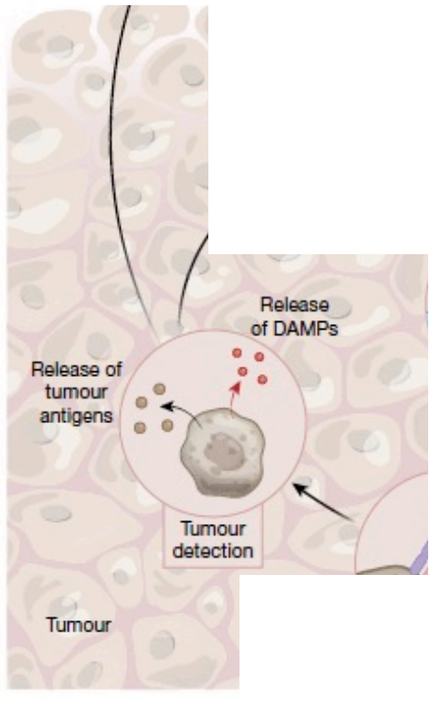
Cellular stress signals in tumors can illicit immune responses

Immune system can respond to tumor cells after cellular stress

Innate and adaptive responses

- Priming of adaptive immune cells
- Amplification of innate immune response
- Innate and adaptive immune cell mediated killing

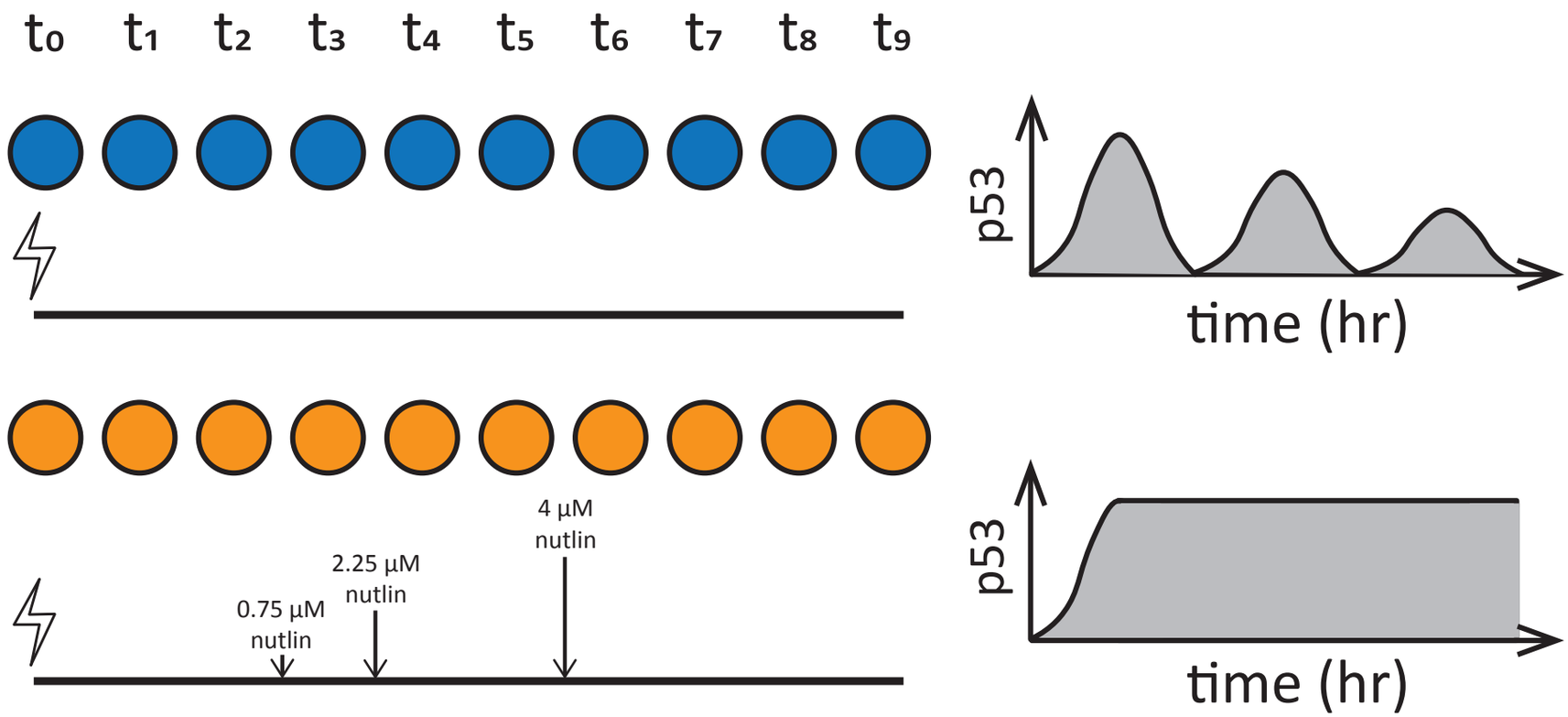
Major cellular stress sensor is p53



Can p53 dynamics in cancer cells alter immune responses?

Demaria *et al*. Nature. 2019

Time course analysis of gene expression in MCF-7 cells after DNA damage

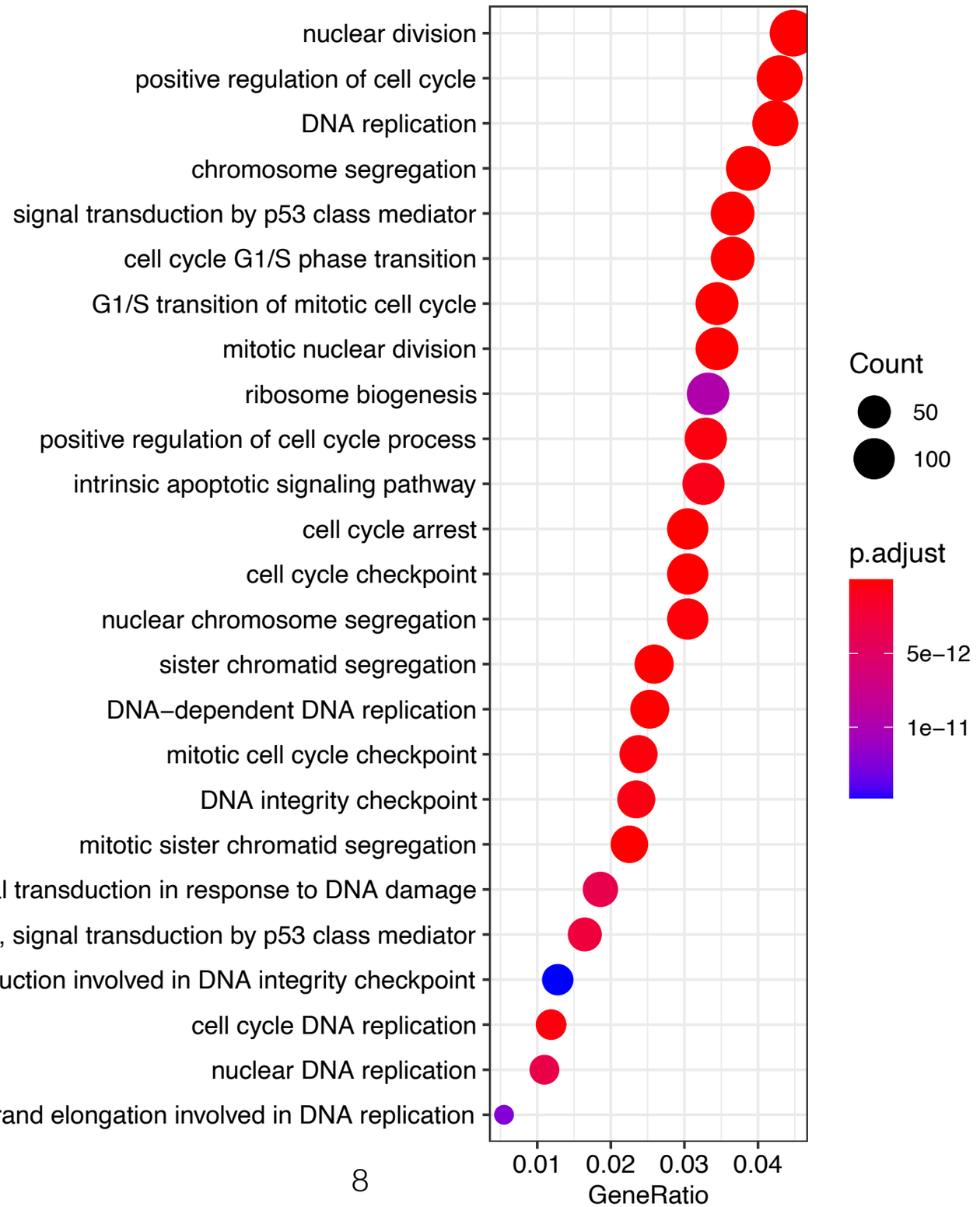


Do p53 dynamics induce the expression of immune response related genes? Yes!

Are some of these immune response genes p53-dependent? Yes!

Do p53-dependent immune response gene expression dynamics differ with pulsatile or sustained p53 expression? Yes!

Over-representation of genes belonging to gene ontologies expected to be involved in DNA damage pathways



Results and Current/Future Work

Preliminary results

- Differential DNA damage responses in cancer cells result in expression of p53-dependent immune response genes

Current/Future work

- Experimentally validate gene expression dynamics of CSF-1, PAI-1, TNFRSF10B, and FAS
- Investigate functionally consequences of differential expression dynamics for immune cells

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