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

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

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

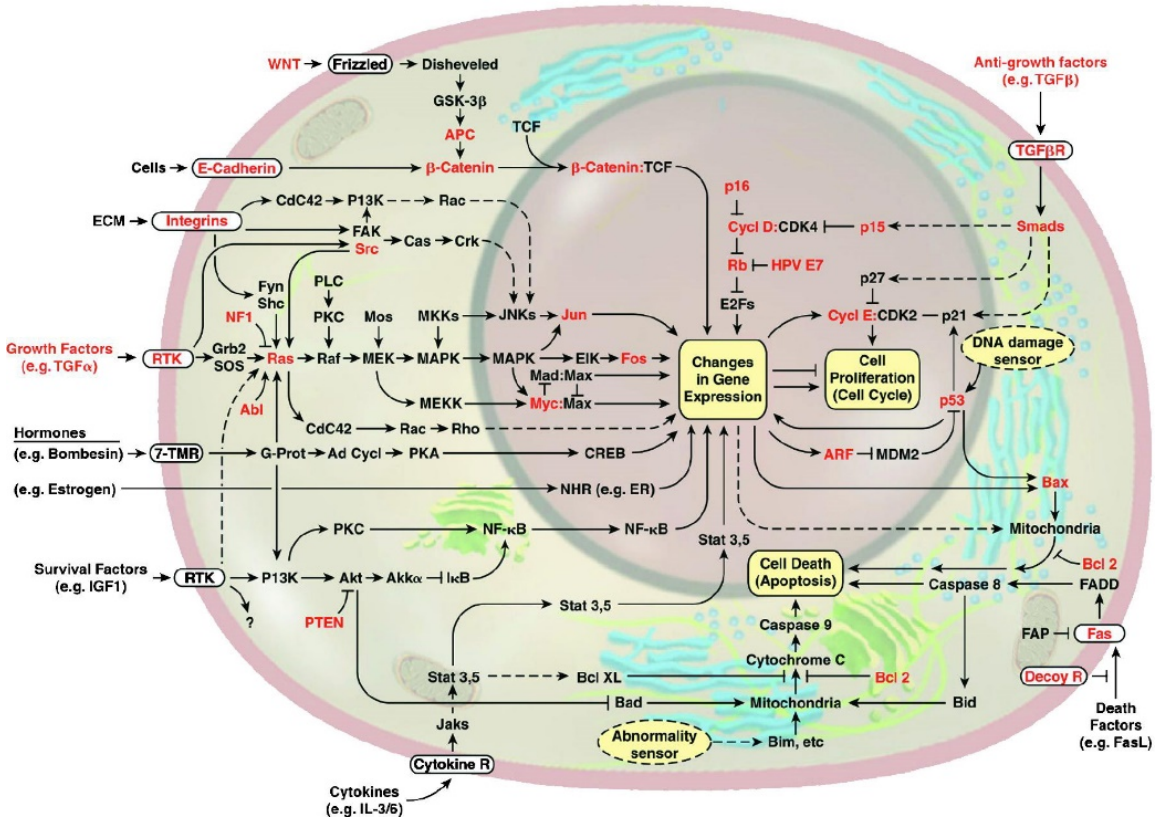
Outline

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

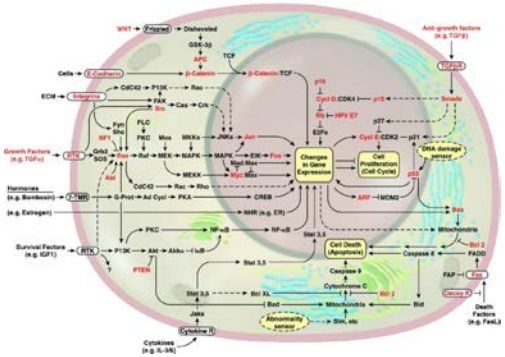
Death vs survival
Proliferation vs arrest
Phenotype switching

Hanahan, Weinberg (2000)

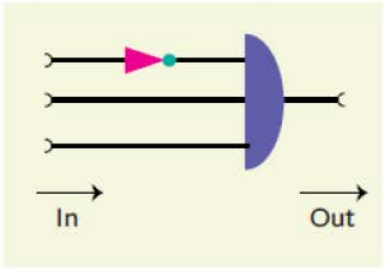
Motivation

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

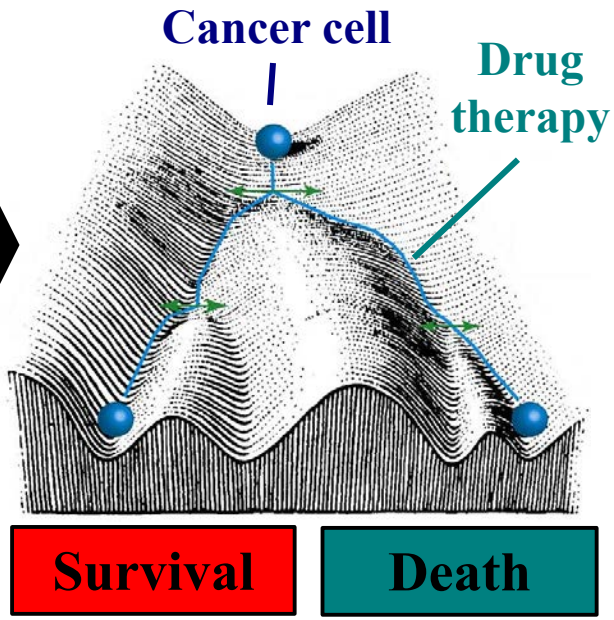
Intracellular network



Mathematical model



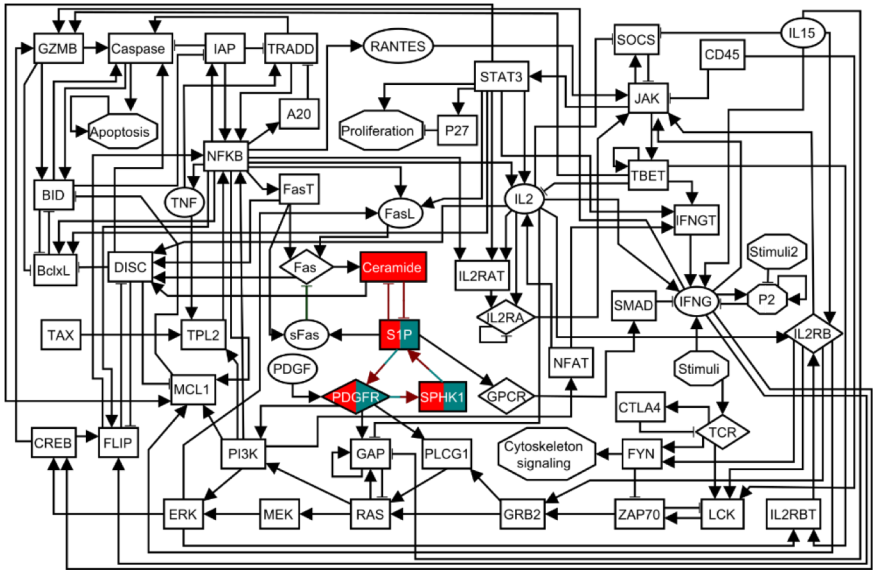
Decision-making dynamics



Network-based modeling

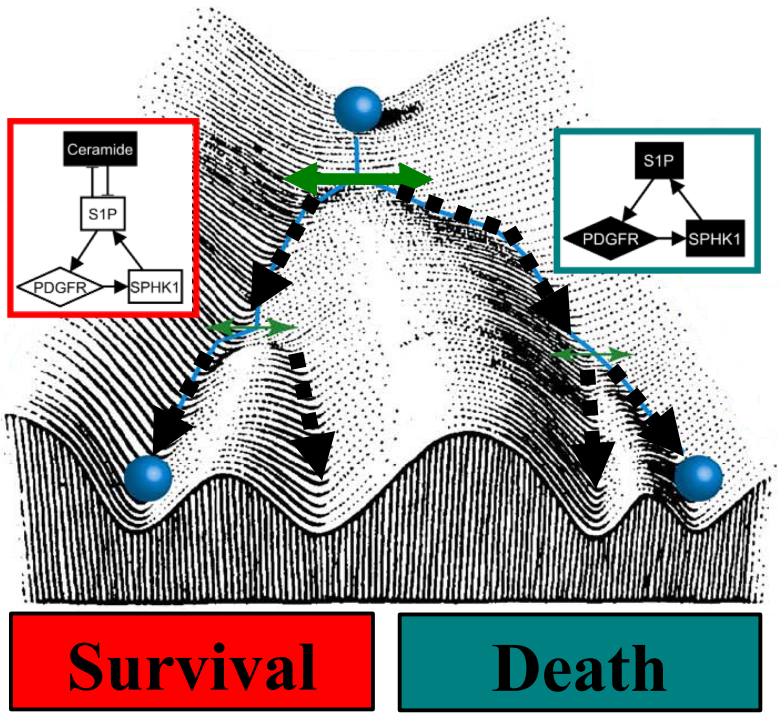
Understand: Connecting the network structure and function to decision-making dynamics

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

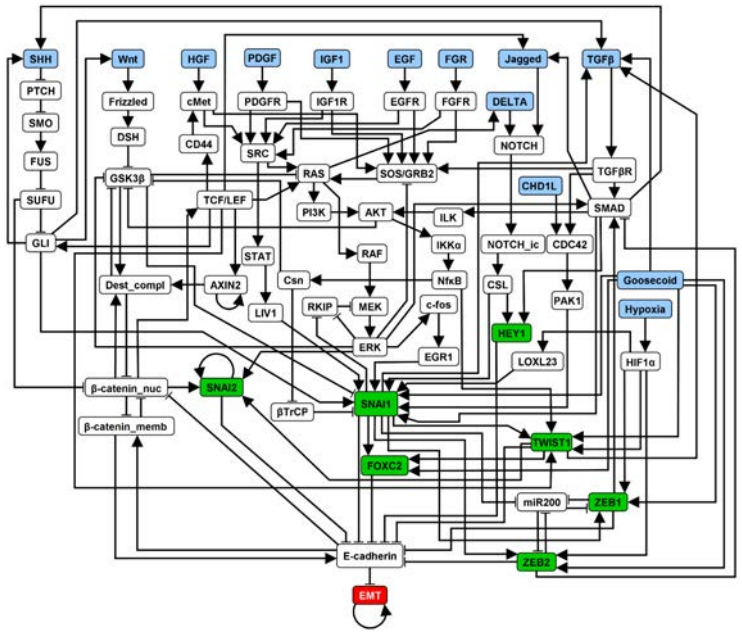


Dynamics of cancer networks

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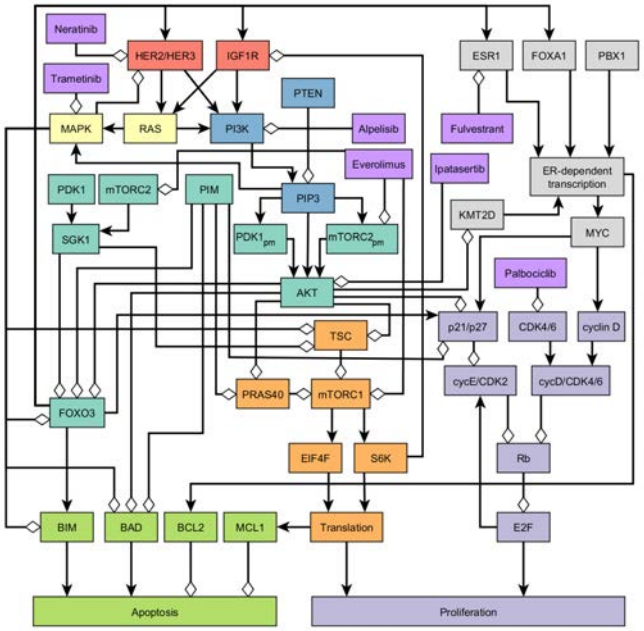
Mechanisms of drug resistance and drug combinations
(targeted therapies in breast cancer)

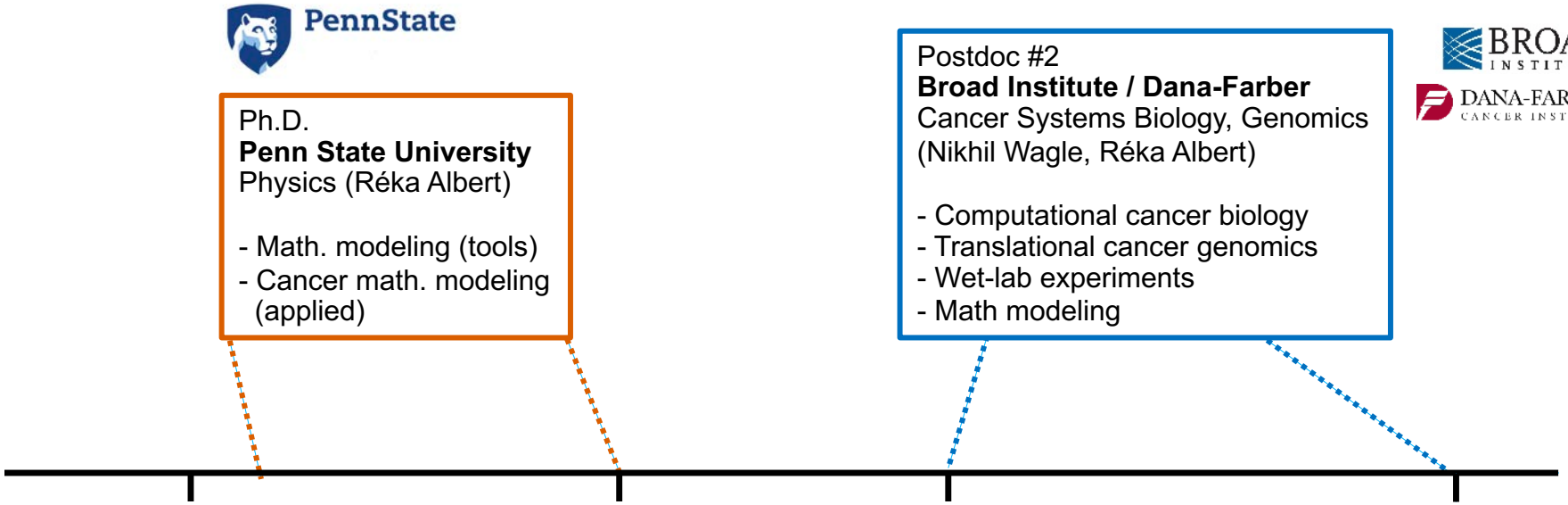


JGT Zañudo, et al. Cancer Convergence. (2017).
JGT Zañudo, et al. Cancer Research. (2021).

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

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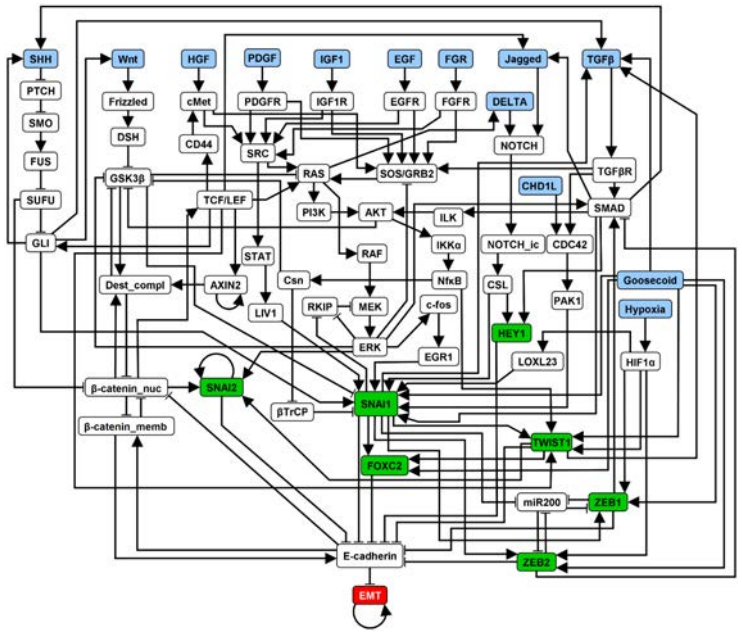

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Mechanisms of drug resistance and drug combinations

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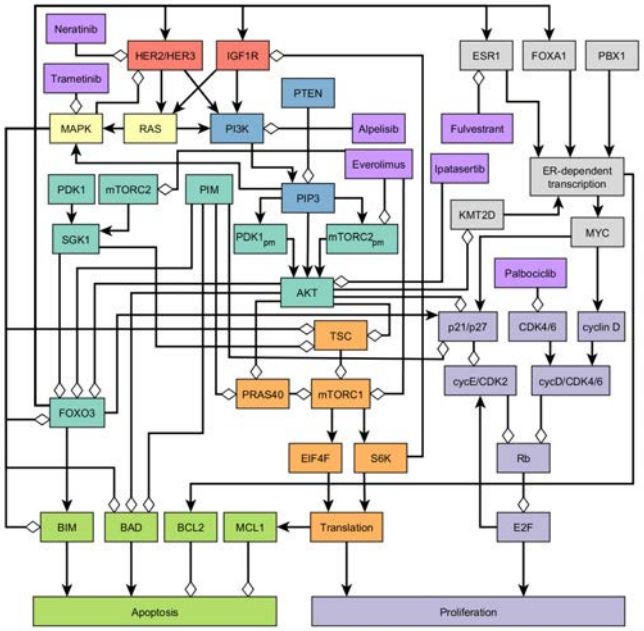

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JGT Zañudo, et al. Cancer Research. (2021).

PI3Kα inhibitors in breast cancer

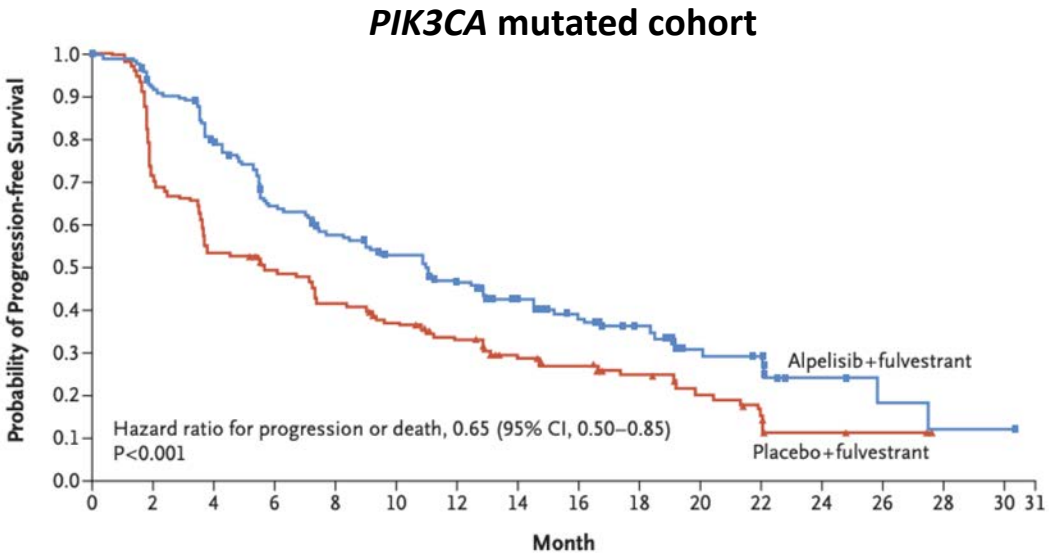
In 2019, alpelisib (PI3Kα inhibitor) became the first approved therapy specifically for metastatic ER-positive breast cancer with *PIK3CA* mutations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Fabrice, et al. NEJM (2019)



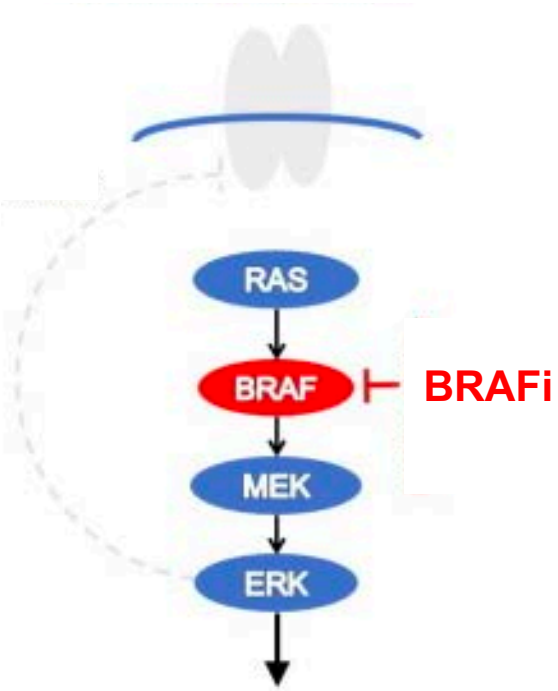
Which of the known resistance mechanisms will be observed clinically?

Are we missing important resistance mechanisms?

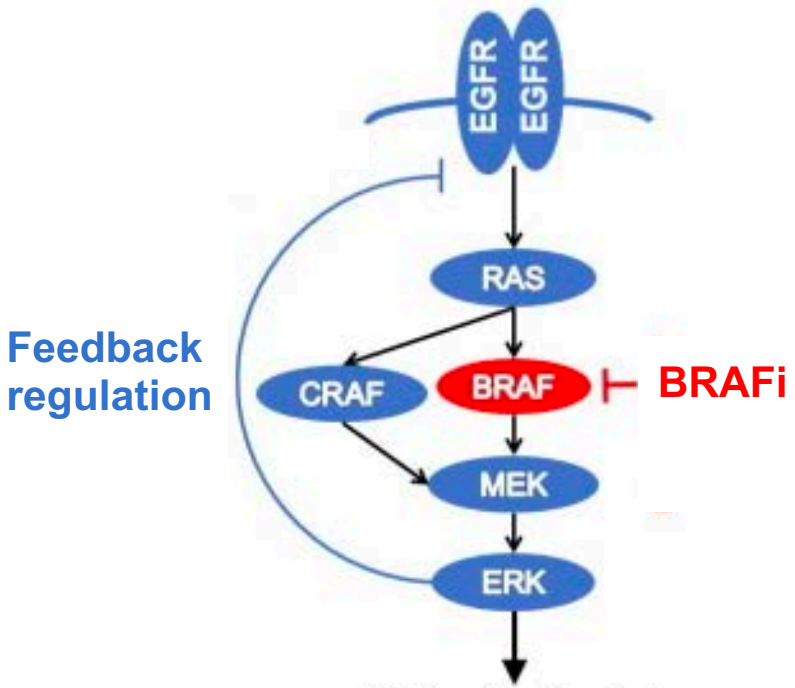
Why do we need math models?

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

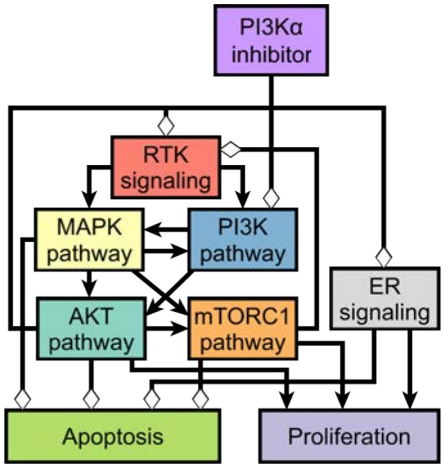


Prahallad et al. Bernards' lab. Nature (2012)

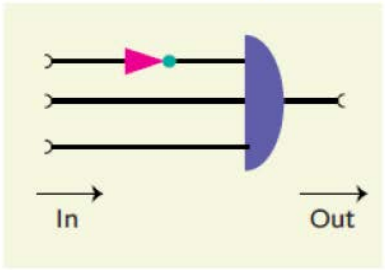
Network models and drug resistance

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

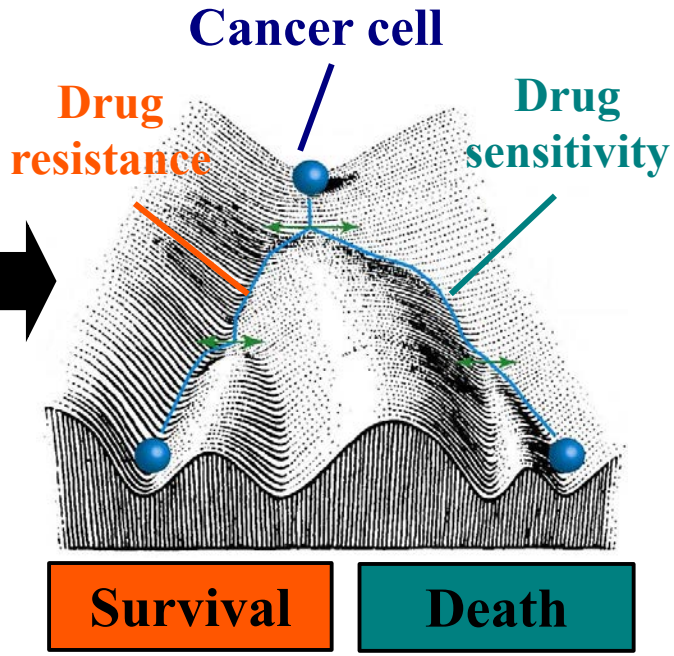
Network of signaling pathways



Mathematical model



Network dynamics and decision-making

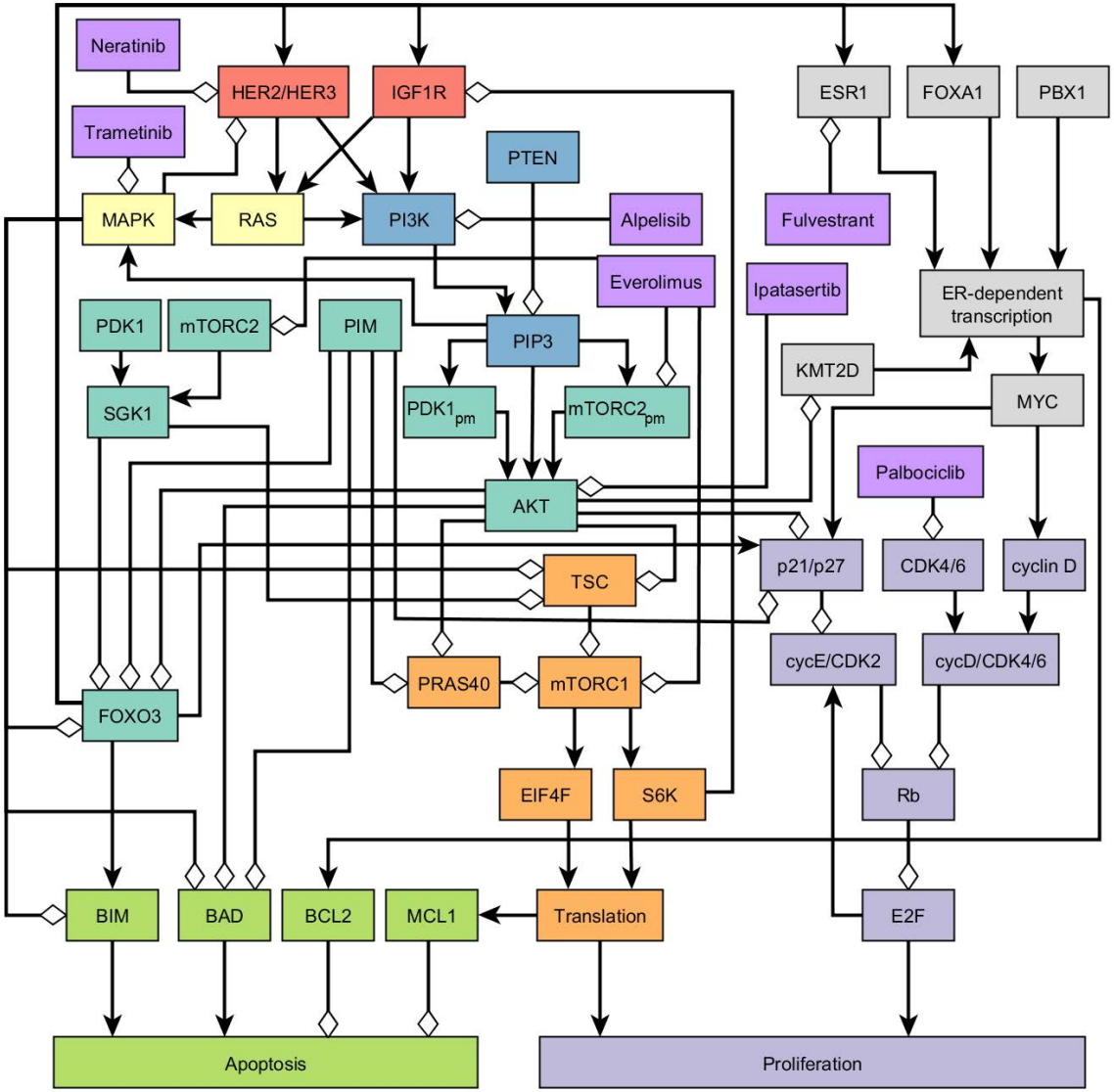


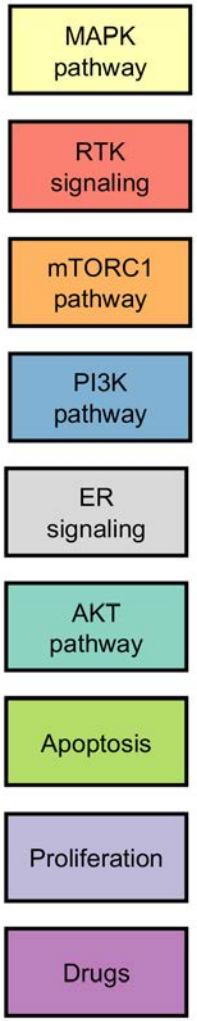
Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol. 9, 1-10.

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)

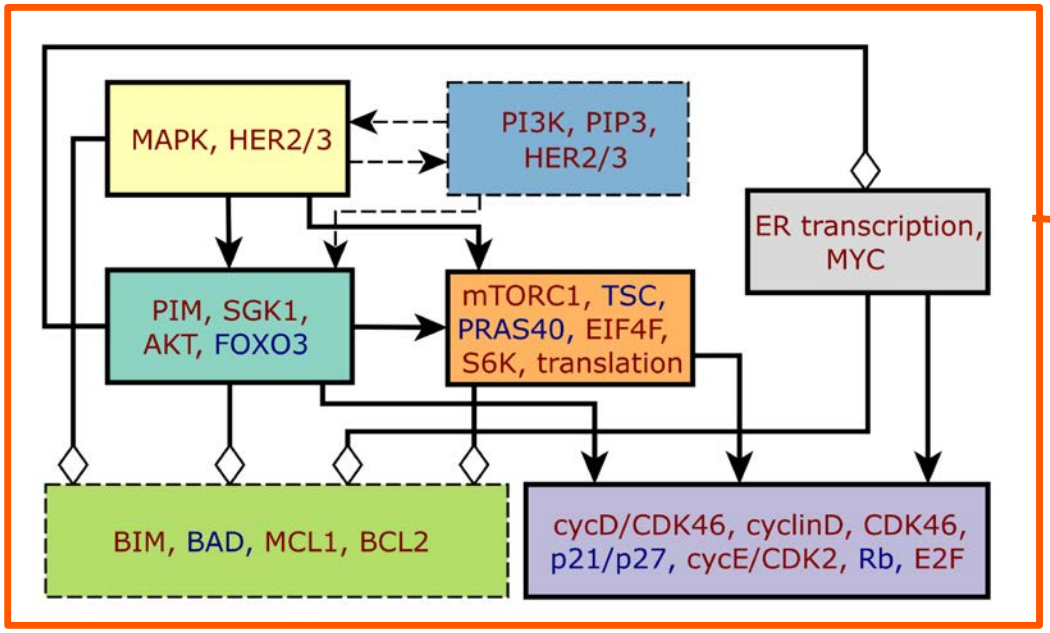


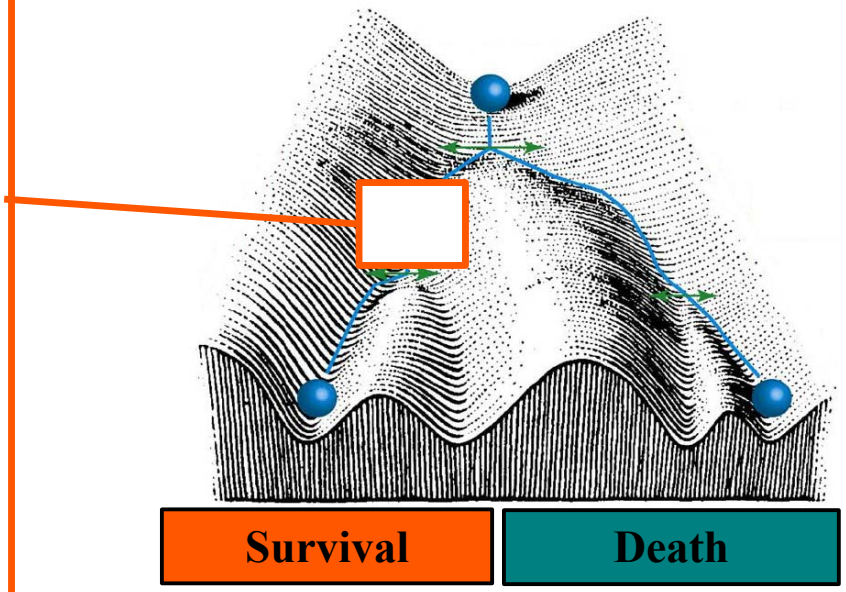


JGT Zañudo et al. (2017) Cancer Convergence 1, 5.

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

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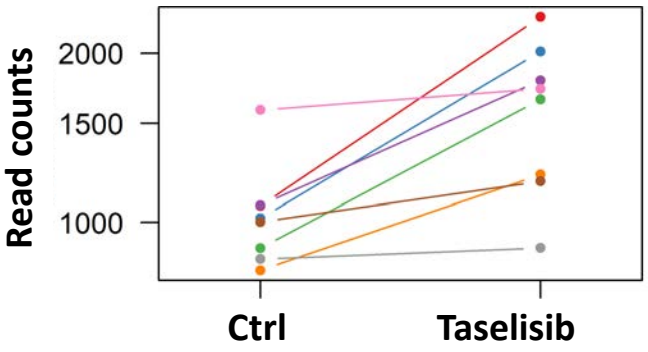
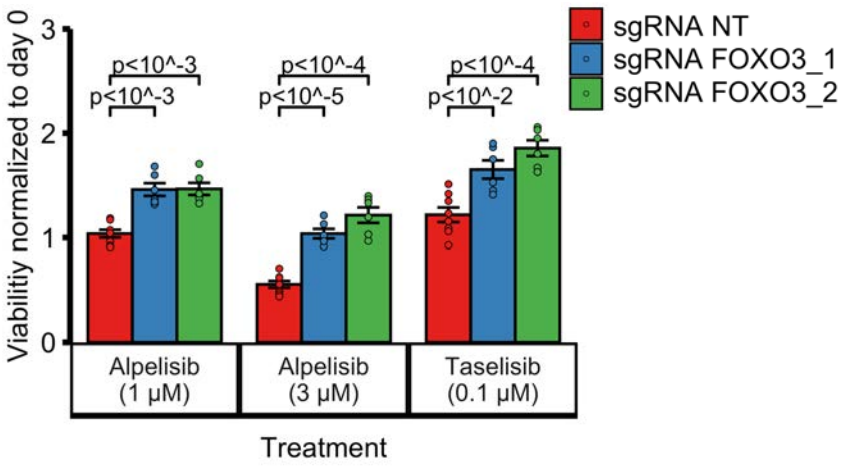
Math models of biological networks: metastatic reprogramming and cancer drug resistance

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

MCF7

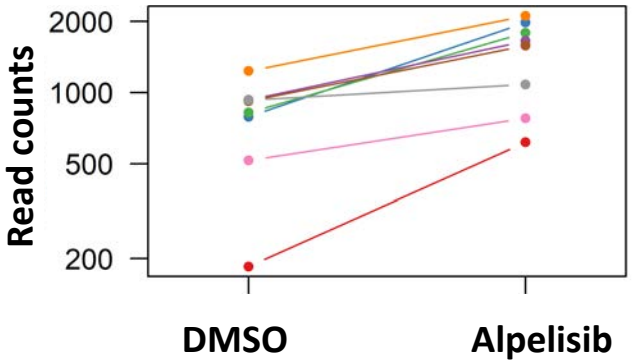
FOXO3 KD (CRISPR screen) $p<2\cdot10^{-3}$ $FDR<10^{-1}$

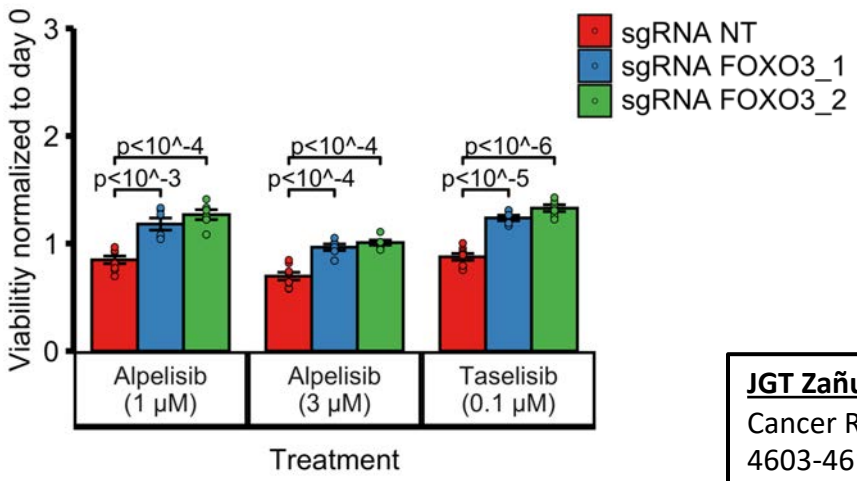




T47D

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

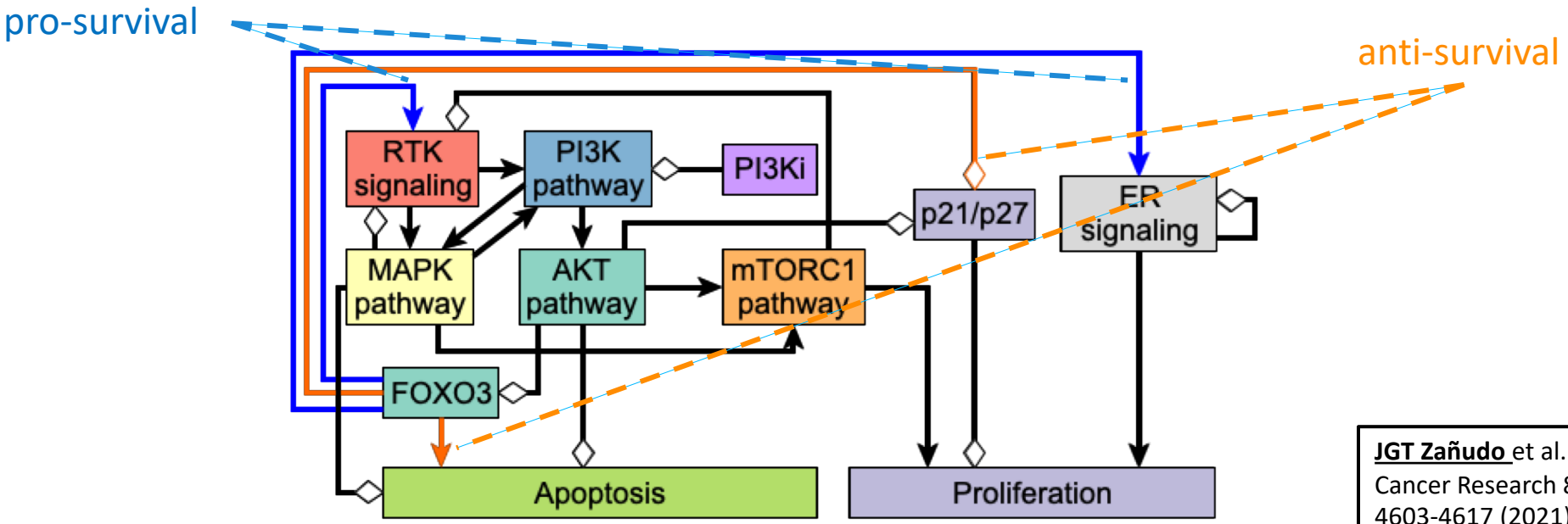
RESEARCH ARTICLE | CANCER

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

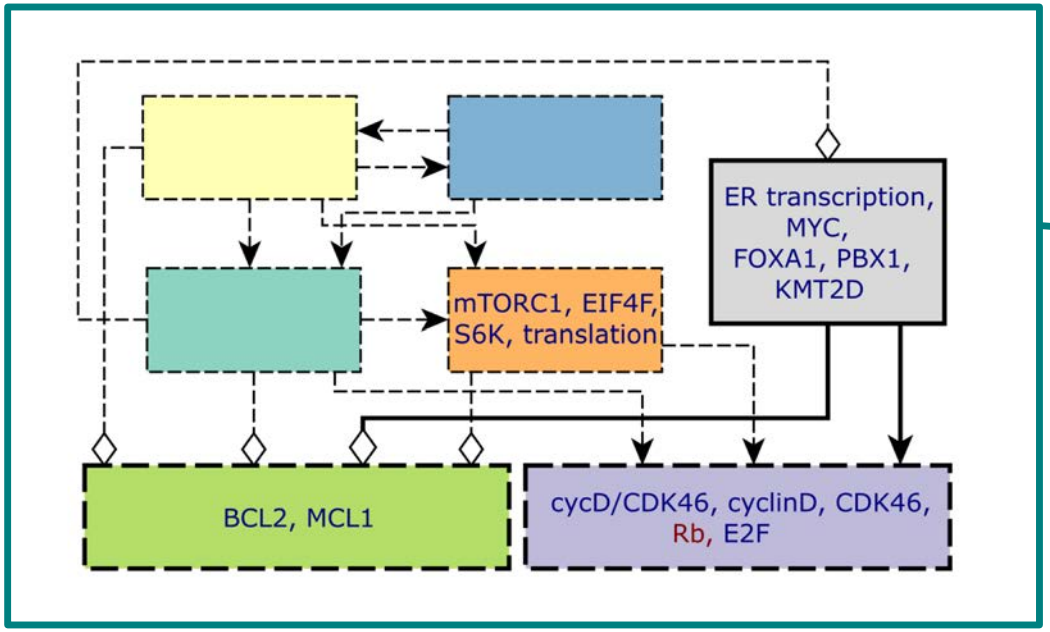
Our model captures that the tumor suppressor effect can dominate

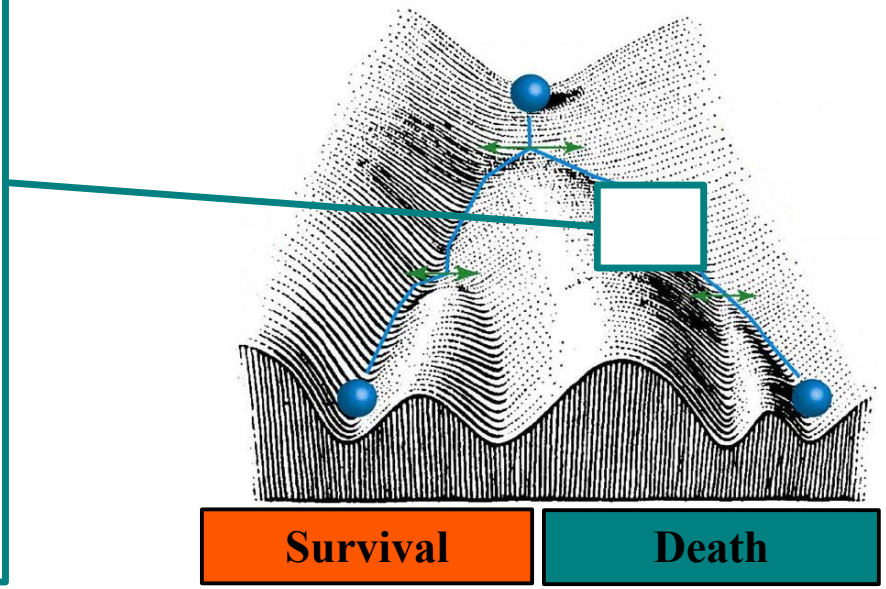


JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

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.

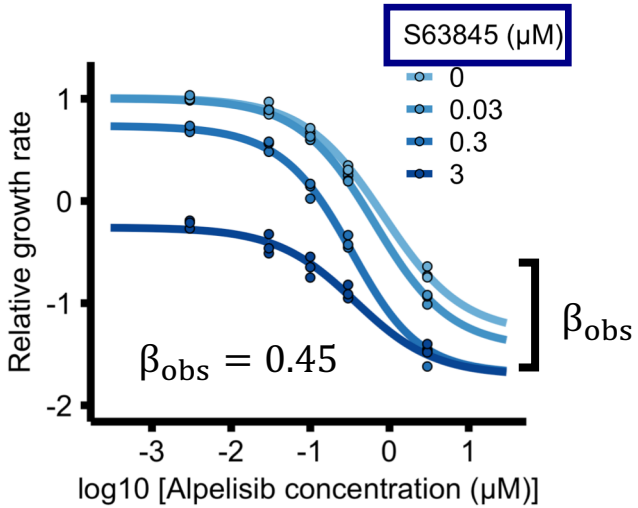
Synergy with PI3Kα inhibitors

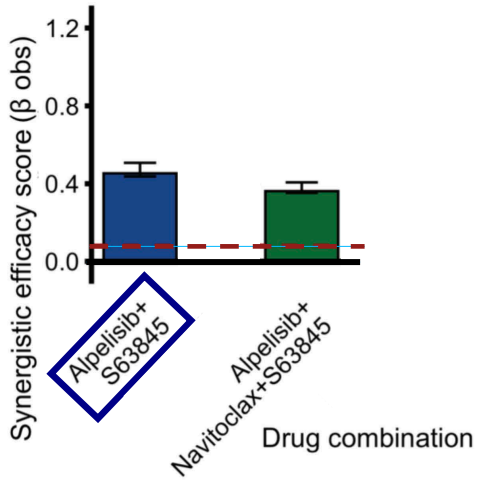
J.G.T. Zañudo
Math models of biological networks: metastatic reprogramming and cancer drug resistance

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

MCF7

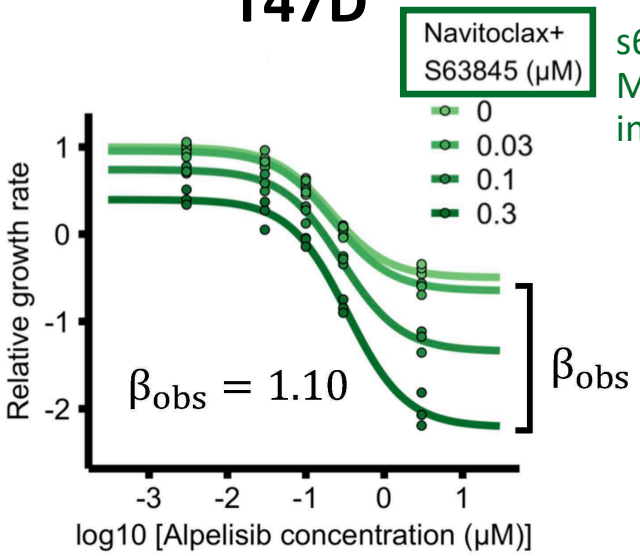
s63845: MCL1 inhibitor

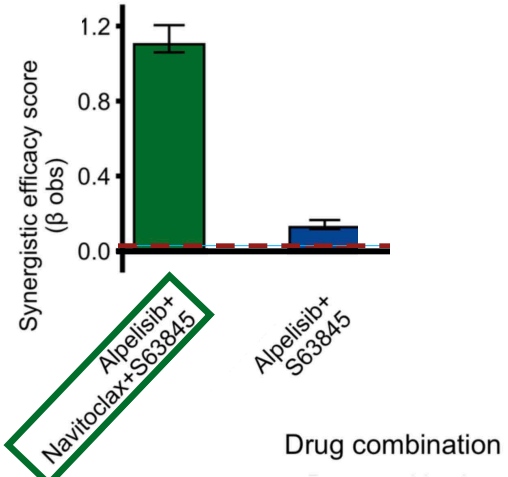




T47D

s63845 + navitoclax: MCL1 + BCLXL/BCL2 inhibitor



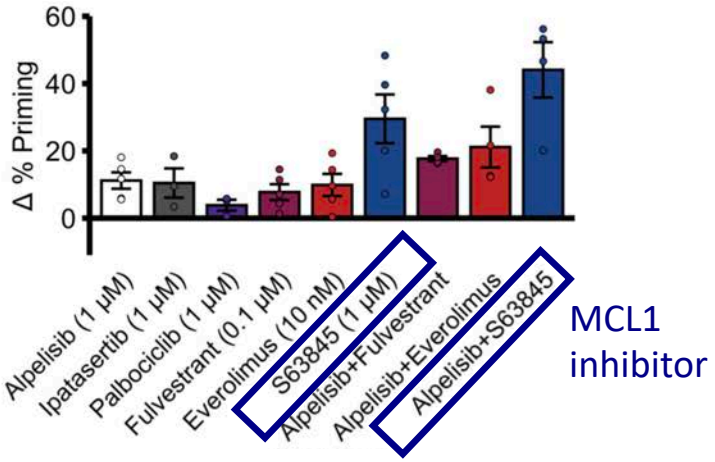


JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

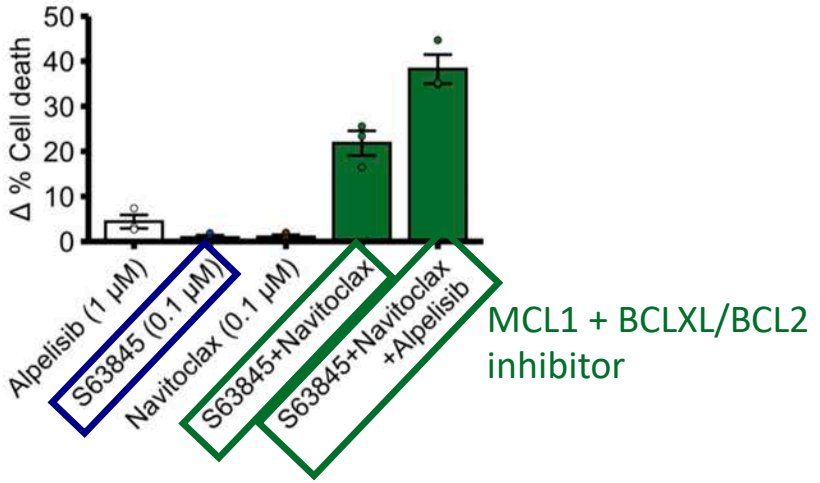
BH3 mimetics as effective drug combos

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

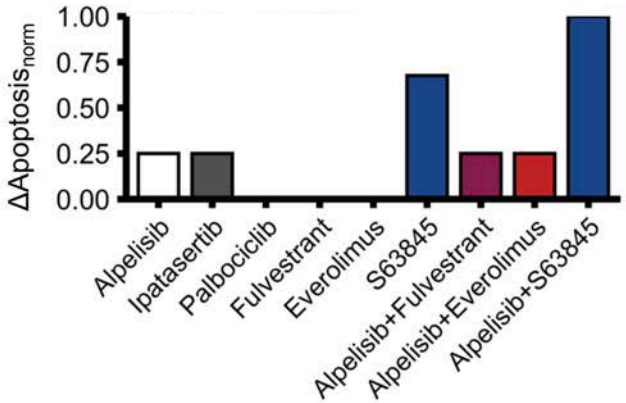
MCF7 - Experiments



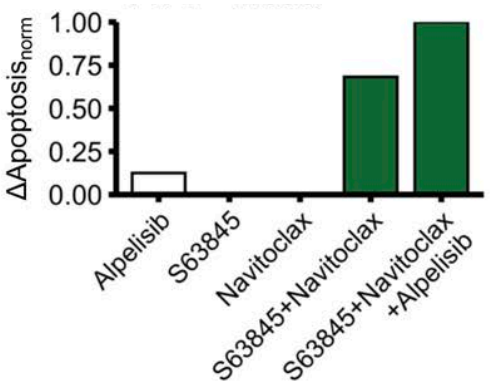
T47D - Experiments



MCF7 - Model



T47D - Model



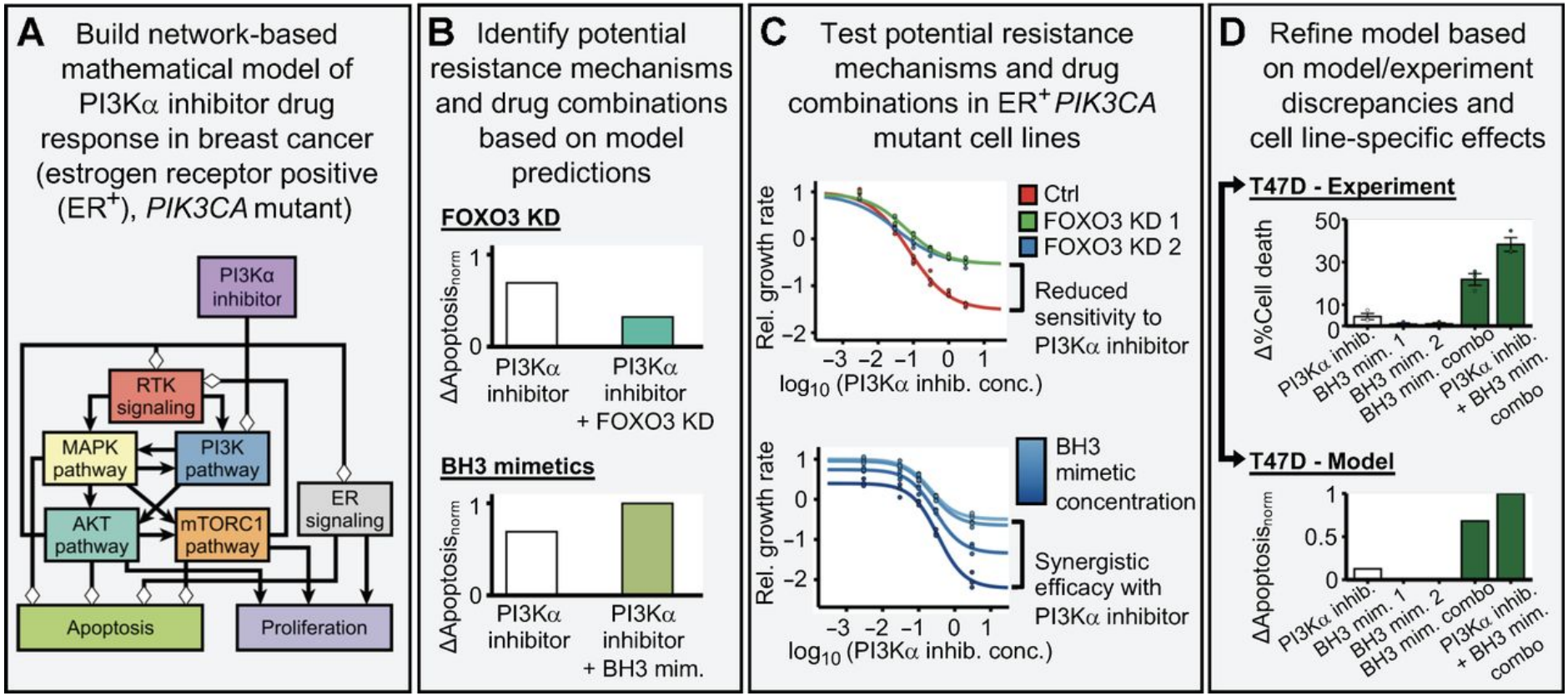
JGT Zañudo et al. Cancer Research 81, 4603-4617 (2021)

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)

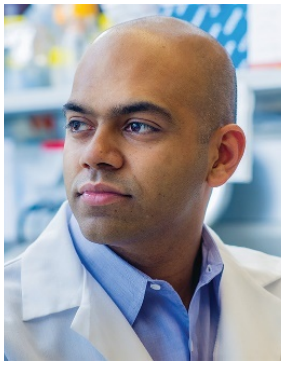


Acknowledgements

ALBERT LAB

Réka Albert
Steven Steinway
Gang Yang
David Wooten
Jordan Rozum
Eli Newby
Xiao Gan
Parul Maheshwari
Fatemeh Nasrollahi

WAGLE LAB



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

SU2C convergence team

Joan Montero (IBEC)
Tony Letai (Dana Farber)
Raul Rabadan (Columbia)
Maurizio Scaltriti (Sloan Kettering, AstraZeneca)
José Baselga (Sloan Kettering , AstraZeneca)
Arnold Levine (IAS)
Suzanne P. Christen (IAS)

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Thank you for your time!

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EXTRA SLIDES

Synergy with PI3Kα inhibitors

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

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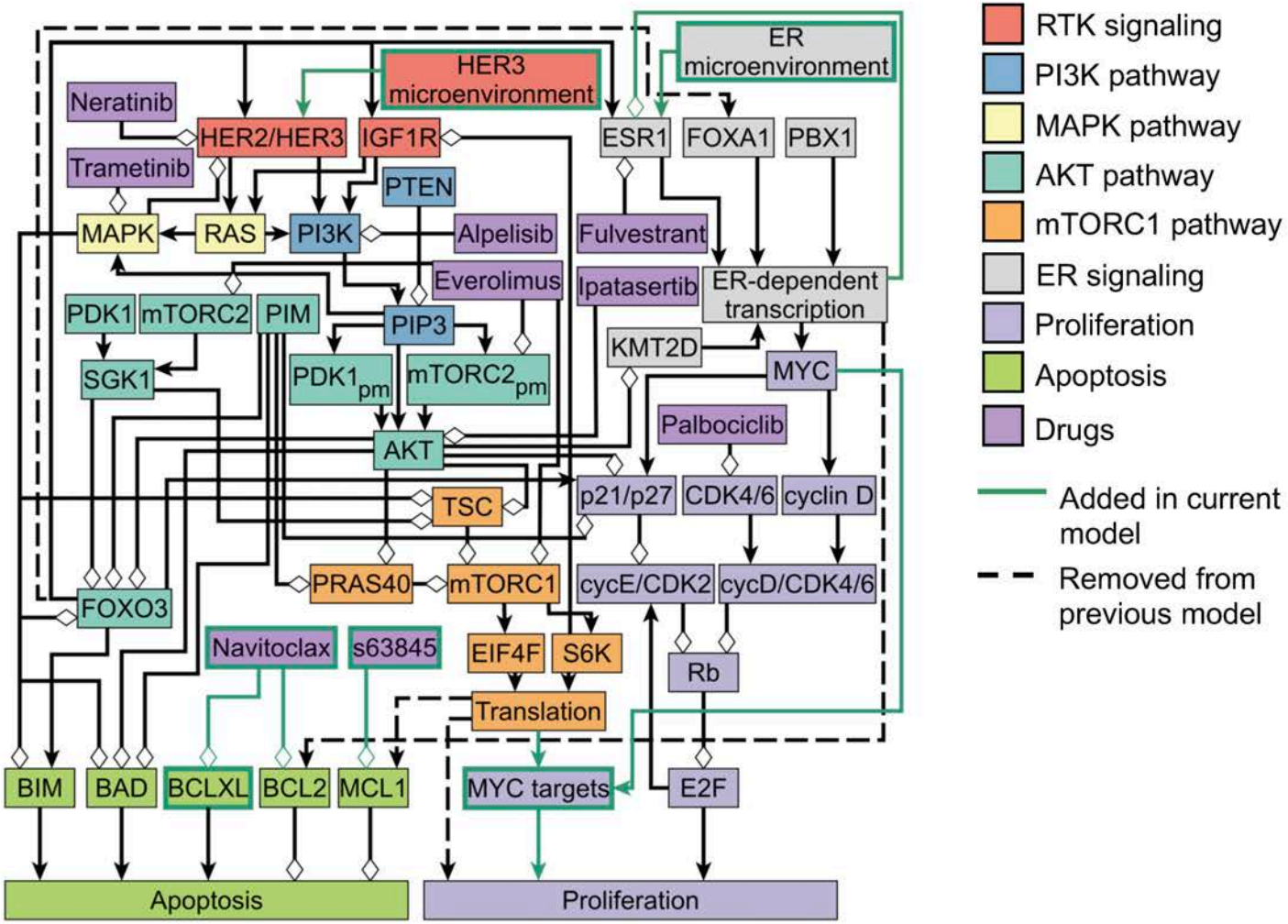
We built an updated version of the model incorporates:

(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

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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

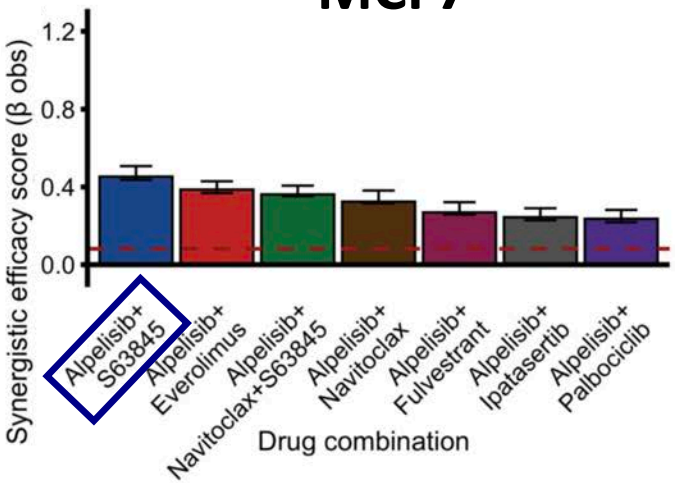
Validation

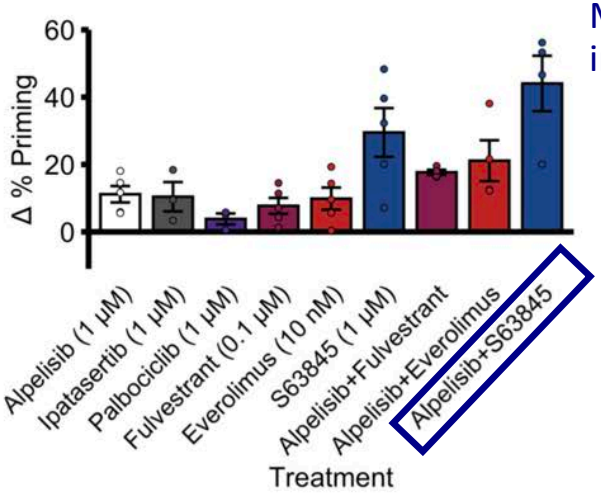
Zañudo, Steinway, & Albert (2018). Curr. Opinion in Syst. Biol

Synergy with PI3Kα inhibitors

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

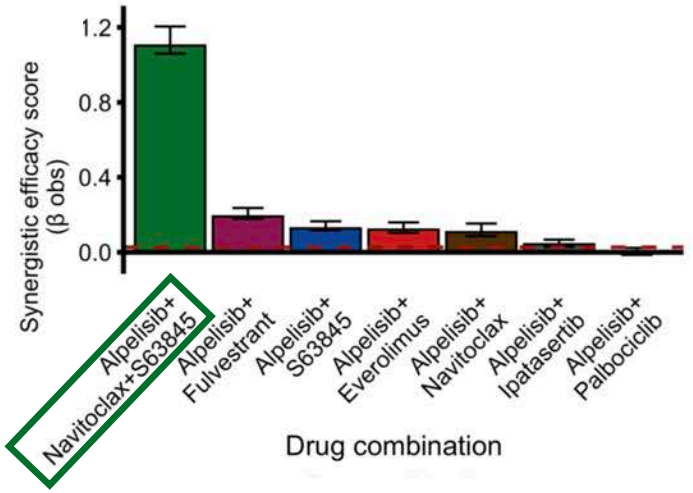
MCF7

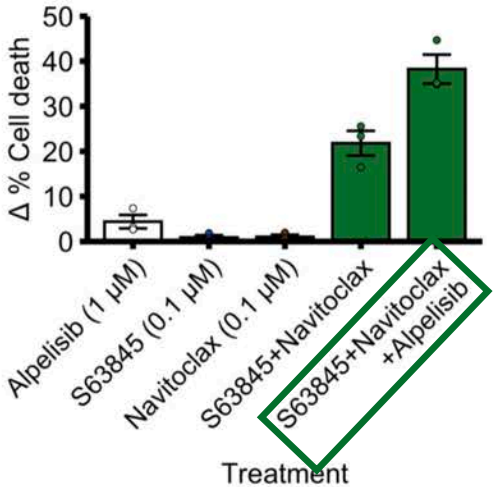




s63845: MCL1 inhibitor

T47D





s63845 + navitoclax: MCL1 + BCLXL/BCL2 inhibitor

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