SACB Meeting. MBL.
Nov 9th 2018.

Drug resistance mechanisms and combinatorial drug treatments in breast cancer: a network modeling approach

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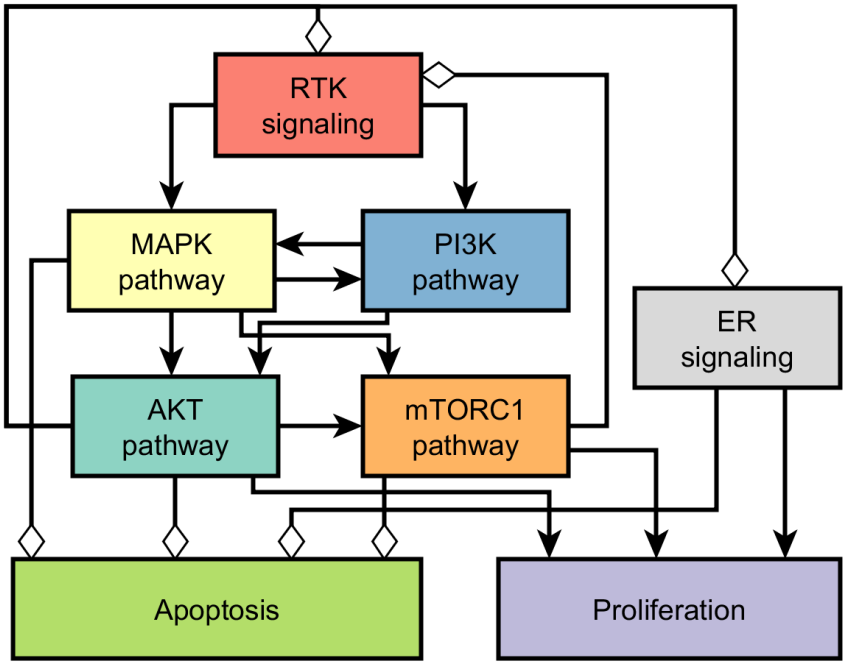
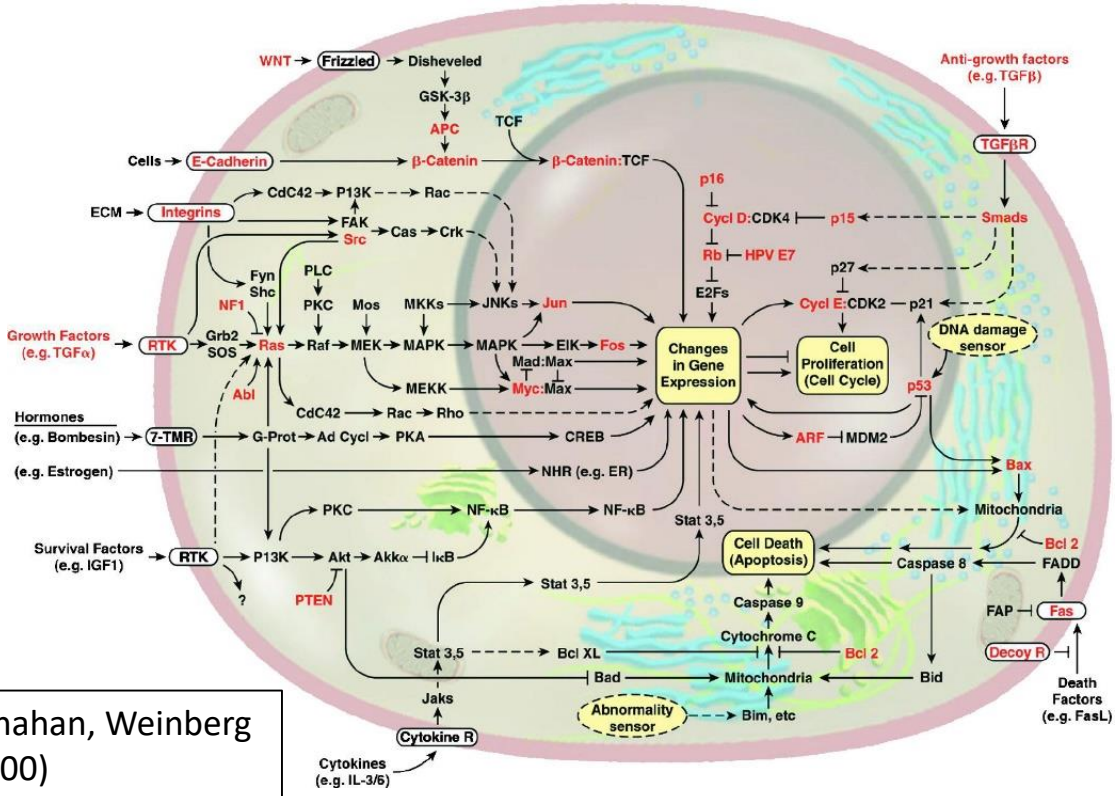


Cellular phenotypes arise from the interactions of molecular components

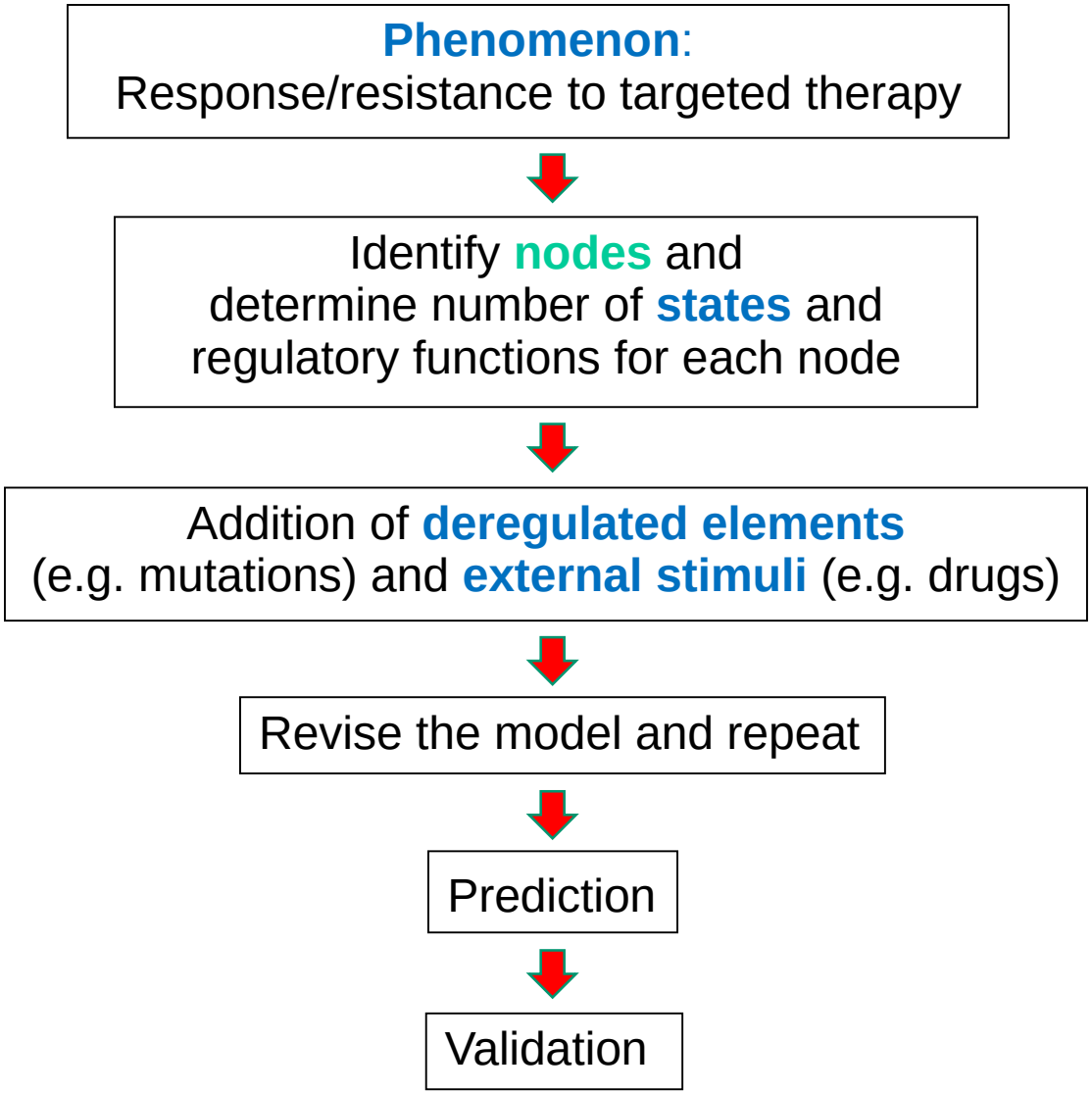
Interconnection of breast cancer signaling pathways → network model

Network model: *Dynamics of information propagation through these pathways and their connection to cellular behaviors*



Hanahan, Weinberg (2000)

Steps in constructing a Boolean model of a signaling network



Breast cancer network model

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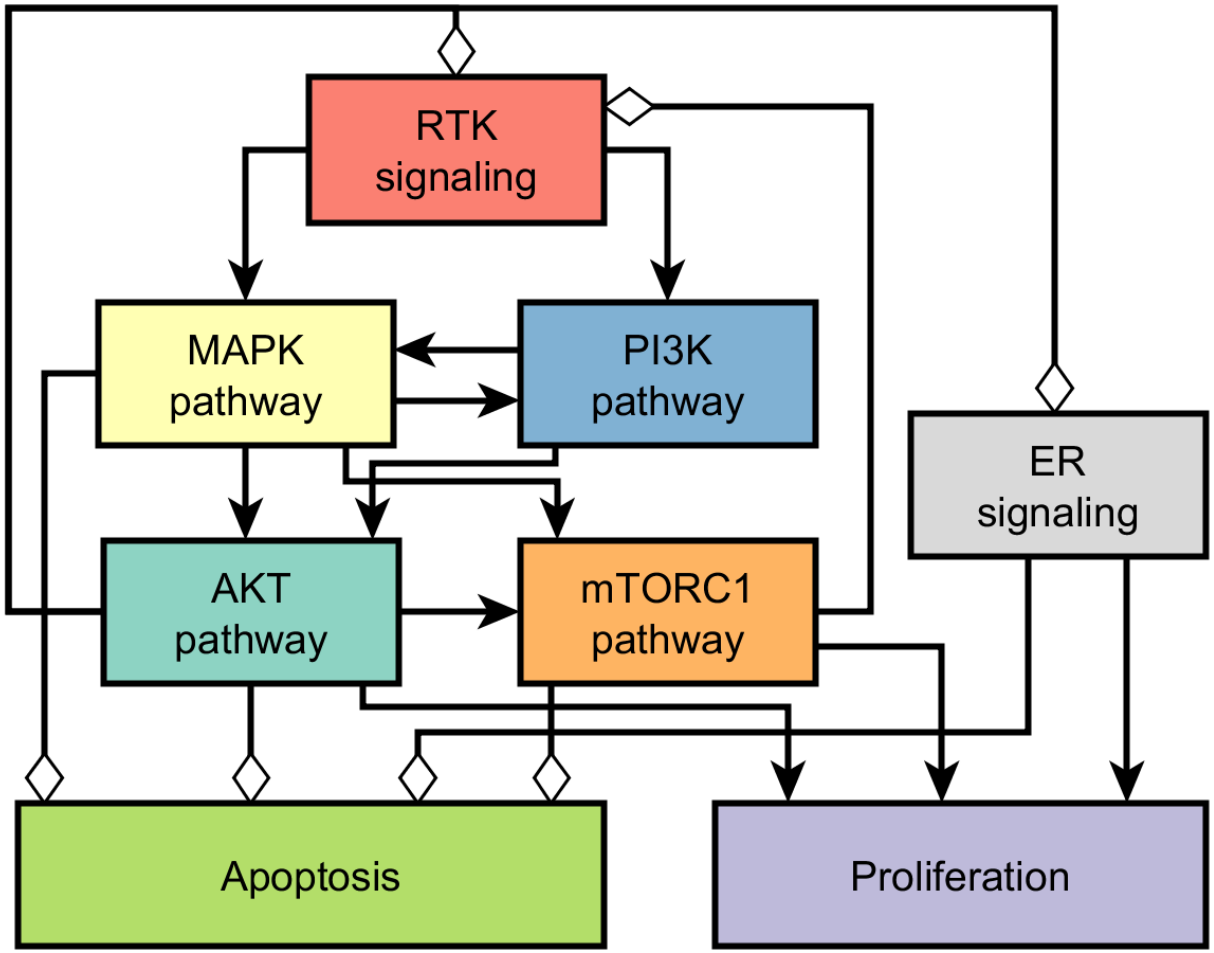
Network modeling of breast cancer to predict drug resistance mechanisms & combinatorial drug treatments

The general structure of the network model (based on what we know)
ER-positive PIK3CA-mutant breast cancer



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Breast cancer network model

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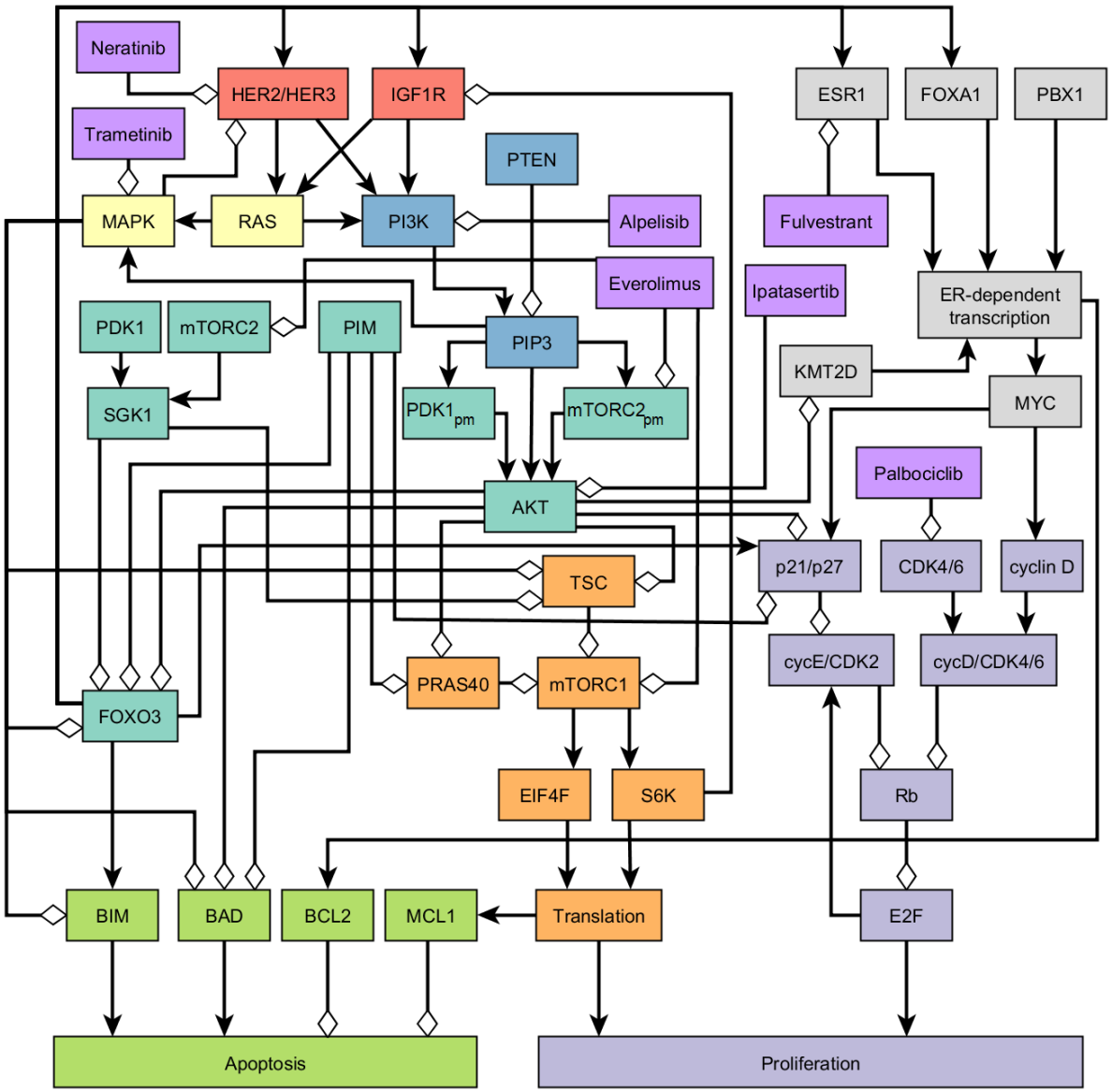
The signaling network: response to pharmacological perturbation



MAPK pathway

RTK signaling

mTORC1 pathway

PI3K pathway

ER signaling

AKT pathway

Apoptosis

Proliferation

Drugs

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Response to PI3K inhibitors

Model recapitulates several known experimental and clinical outcomes

Table 4 Illustration of experimental and clinical outcomes in ER+ and HER2+ breast cancer reproduced by the model

Experimental or clinical outcome	References
Drug inhibition of MEK in HER2+ breast cancer cells leads to increased HER2/HER3 heterodimer formation and higher PI3K activation	(Turke et al., 2012)
High HER3 expression induces resistance to PI3K inhibitors, which is overcome by HER3 blockade, in HER2-amplified and/or PIK3CA-mutant breast cancer cell lines and brain metastases of mouse xenografts.	((Kodack et al., 2017); (Chakrabarty et al., 2012))
High PIM expression is a resistance mechanism to PI3K inhibitors in ER+ (PIM1/2/3) and HER2+ (PIM2) breast cancer cell lines. High PIM1/3 expression is observed in biopsies of ER+ human tumors treated with PI3K inhibitors.	((Le et al., 2016); (Zwang et al., 2017))
High PDK1/SGK1 expression is a resistance mechanism to PI3K inhibitors in HER2+ breast cancer cell lines and mouse xenografts tumors. High SGK1 expression and activity in breast cancer tumor samples causes intrinsic resistance to PI3K inhibitors.	(Castel et al., 2016)
High PDK1 and AKT2 expression are putative resistance mechanisms to PI3K inhibitors; they are observed in biopsies of ER+ human tumors treated with PI3K inhibitors.	(Le et al., 2016)
Inhibition of PI3K induces a rapid downregulation of MAPK signaling and induction of apoptosis in ER+ and HER2+ breast cancer cell lines and mouse xenograft tumors. In HER2+ breast cancer cell lines, MAPK activity is reactivated following the induction of RTKs.	((Costa et al., 2015); (Will et al., 2014); (Ebi et al., 2013))
Inhibition of AKT (directly by AKT inhibitors or indirectly by mTOR or PI3K inhibitors) induces the activity of the transcription factor FOXO3, which upregulates a shared set of RTKs, including HER3, IGF1R, in HER2+ breast cancer cell lines and mouse xenografts tumors.	((Chandarlapaty et al., 2011); (Rodrik-Outmezguine et al., 2011); (Chakrabarty et al., 2012))
Inhibition of PI3K in ER+ breast cancer cell lines induces the transcription factor activity of FOXO3, which binds the promoters of ESR1 and HER3, and upregulates their expression. The upregulation of ESR1 expression in response to PI3K inhibitors has also been observed in ER+ mouse xenograft tumors and ER+ human breast cancer tumor biopsies.	((Bosch et al., 2015); (Kodack et al., 2017))

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Resistance to PI3K inhibitors

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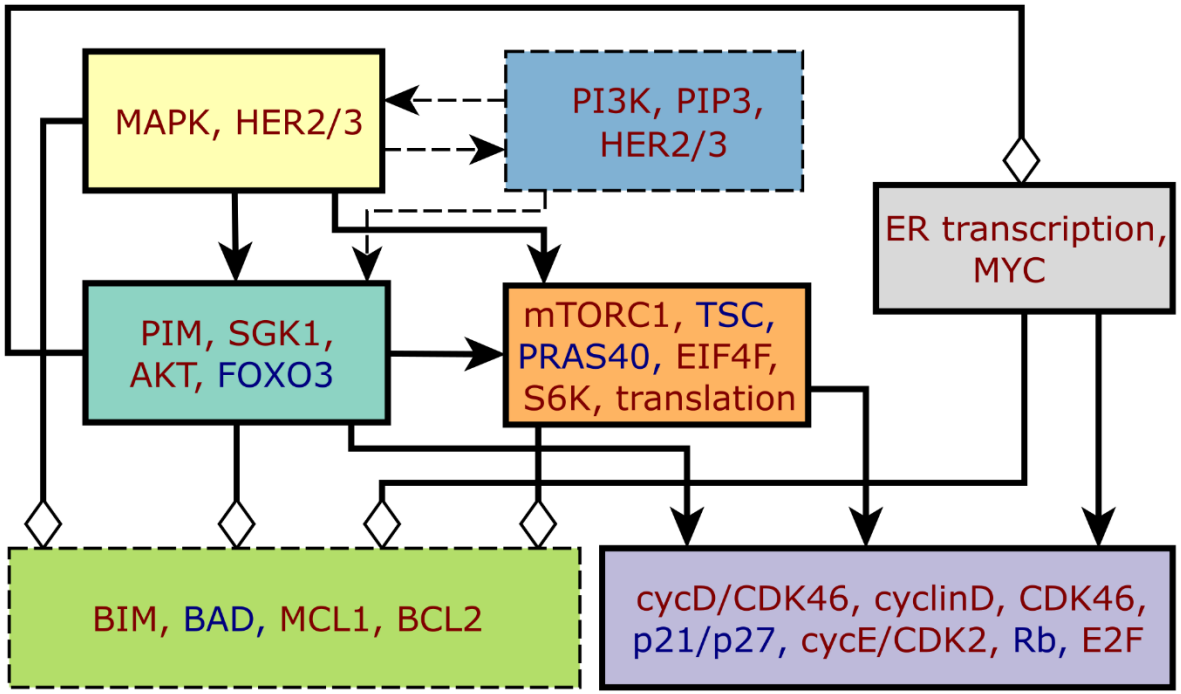
Systematic search for PI3Ki resistance mechanisms



Red: Increased activity
Blue: Decreased activity

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

Predicts loss of FOXO3, TSC, RB, P27, or PRAS40, increased MAPK signaling, MYC overexpression (among others) as resistance mechanisms

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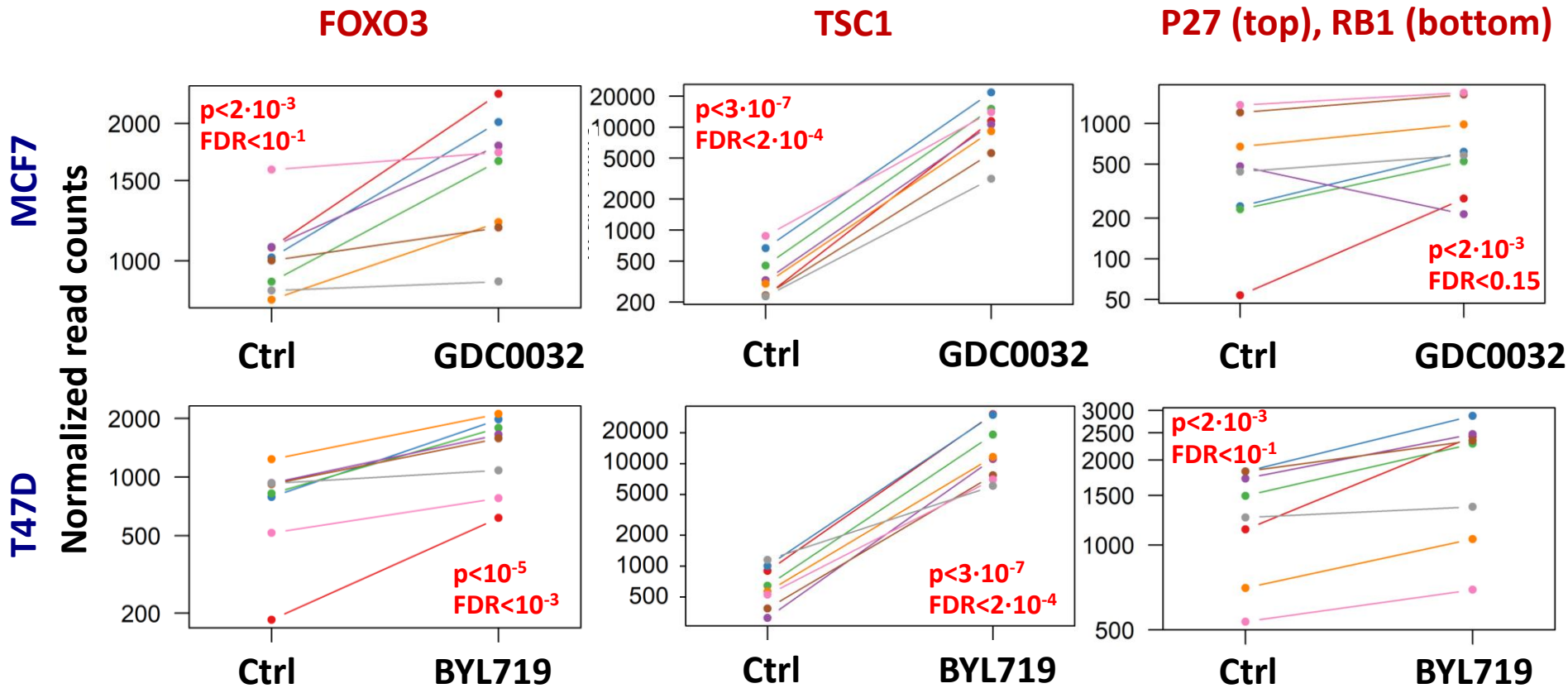
Resistance to PI3K inhibitors

J.G.T. Zañudo

Network modeling of breast cancer to predict drug resistance mechanisms & combinatorial drug treatments

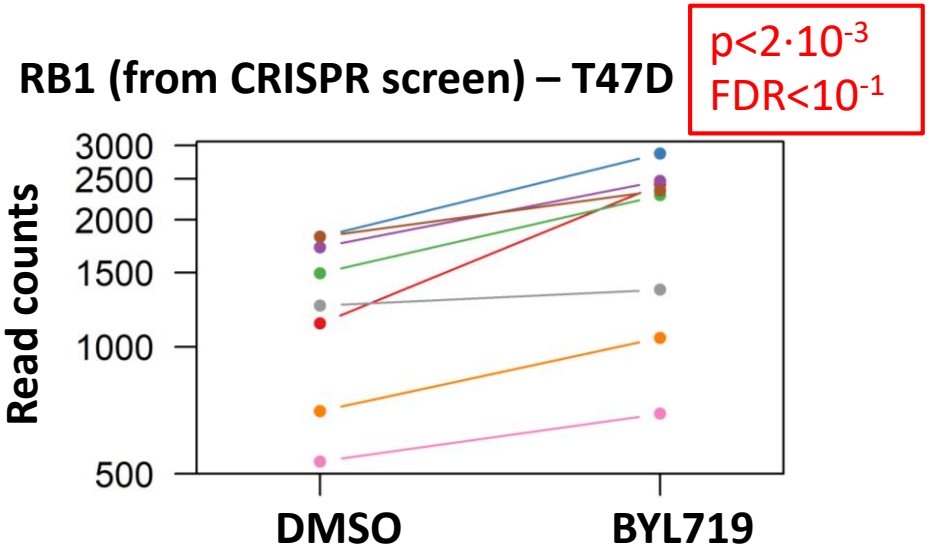
CRISPR screens backup FOXO3, TSC1/2, RB1, P27, PRAS40 as putative resistance mechanisms

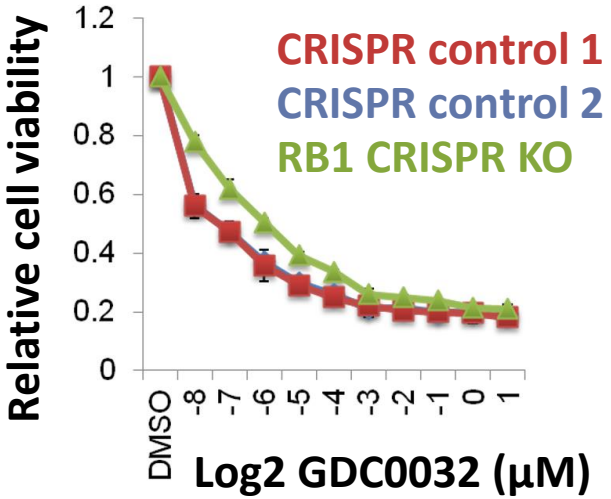


Unpublished:
From Guotai Xu
(Scaltriti, Baselga labs)

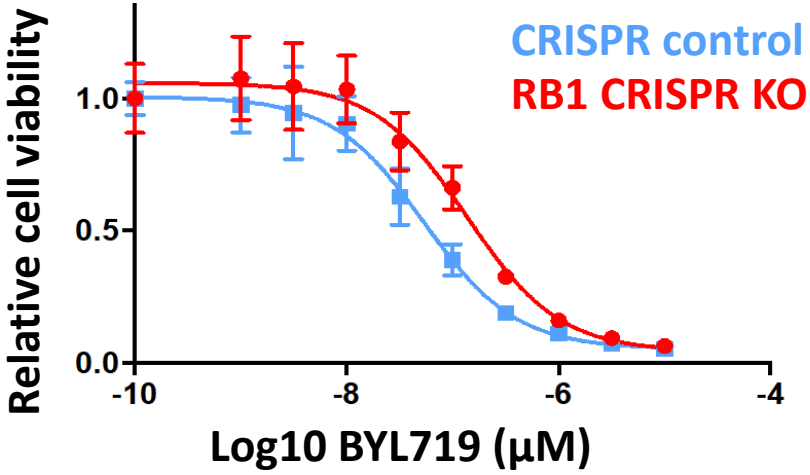
Resistance to PI3K inhibitors

Drug response experiments confirm loss of RB1 decreases sensitivity of T47D cells to PI3K inhibitors





Guotai Xu (Scaltriti, Baselga labs)

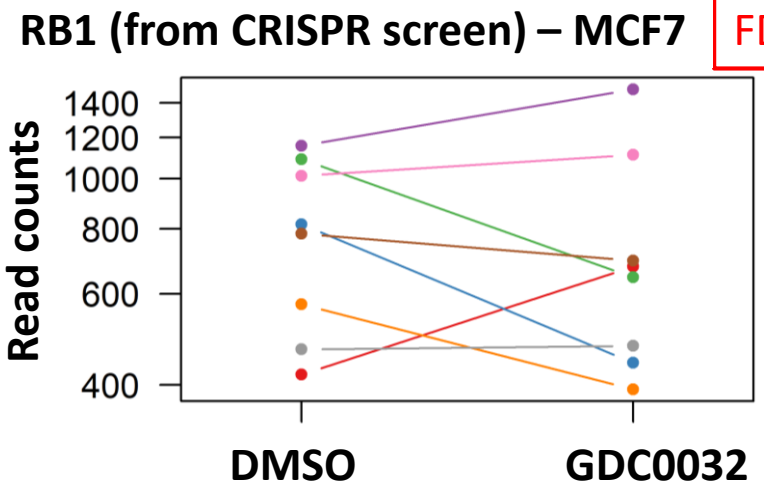


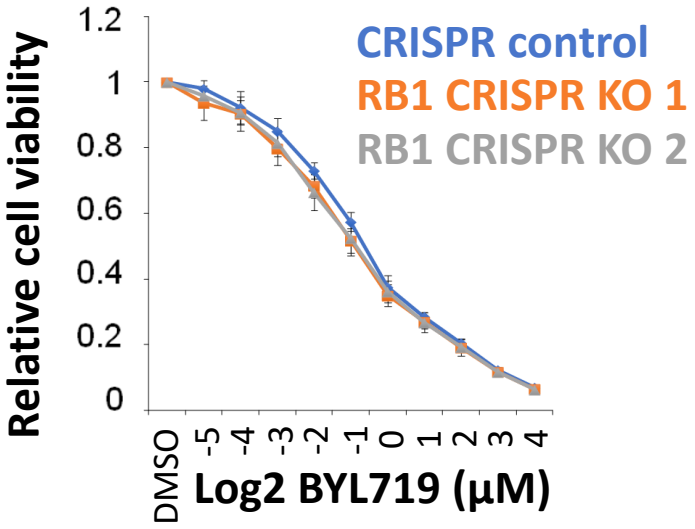
Seth Wanders, Gaby Johnson (Wagle lab)
Flora Luo (Garraway lab)

Resistance to PI3K inhibitors

Drug response experiments confirm loss of RB1 has no effect in sensitivity of MCF7 cells to PI3K inhibitors

$p<2\cdot10^{-1}$
FDR<0.92





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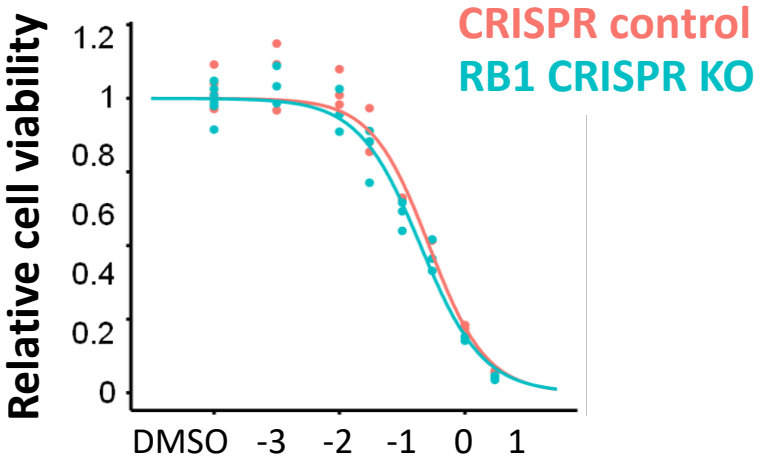
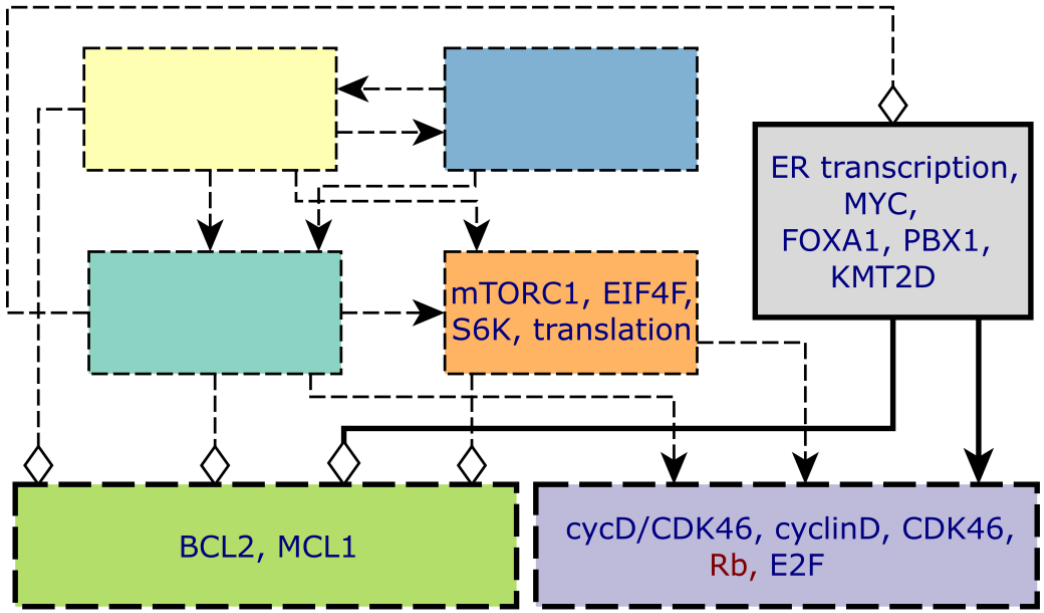


Seth Wanders, Gaby Johnson (Wagle lab)
Flora Luo (Garraway lab)

Synergy with PI3K inhibitors

Systematic search for synergistic combinations with PI3K inhibitors



Red: Increased activity
Blue: Decreased activity

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

Model predicts synergy with the inhibition of anti-apoptotic proteins MCL1 and BCL2

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Synergy with PI3K inhibitors

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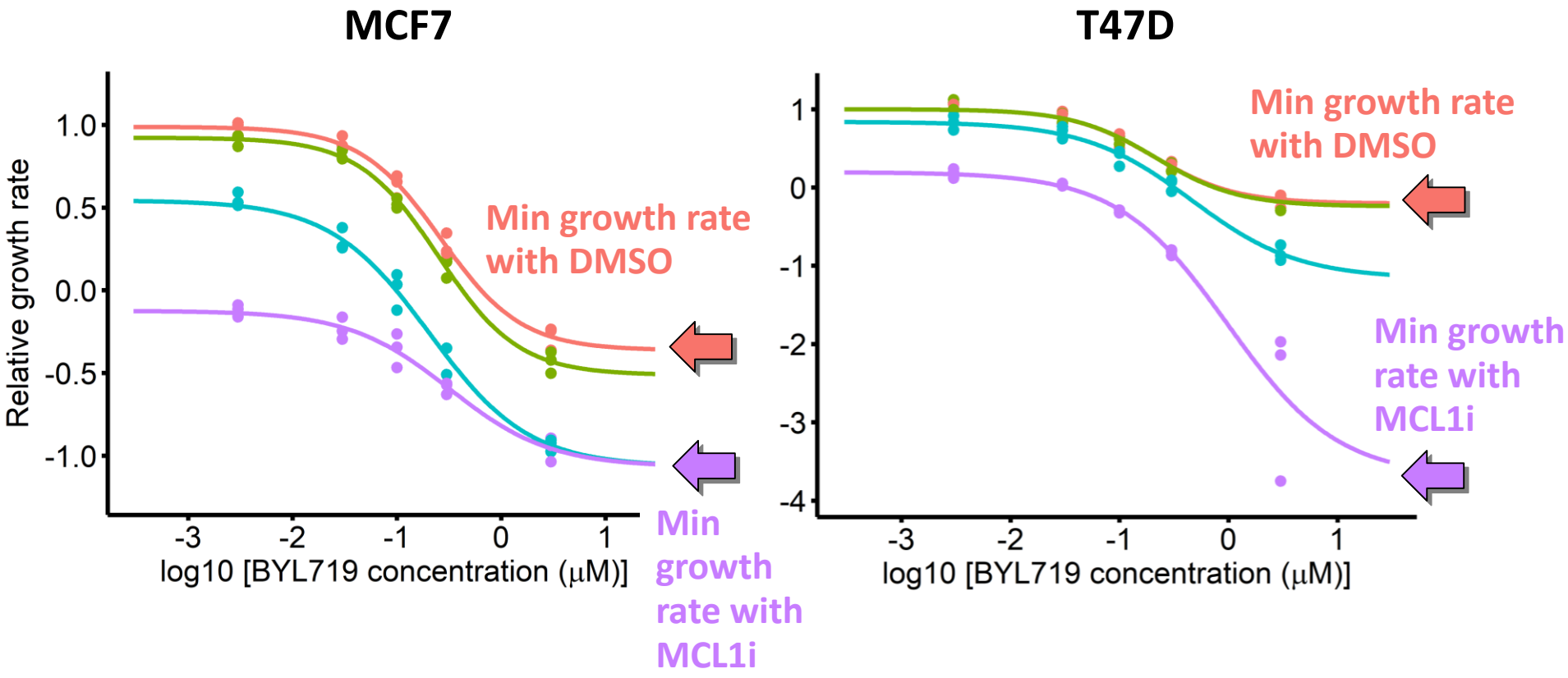
Network modeling of breast cancer to predict drug resistance mechanisms & combinatorial drug treatments

MCL1 inhibitor (S63845) is synergistic with PI3K inhibitor (BYL719)



MCF7	T47D
DMSO	DMSO
MCL1i (0.03 μM)	MCL1i (0.03 μM)
MCL1i (0.3 μM)	MCL1i (0.3 μM)
MCL1i (3 μM)	MCL1i (3 μM)

+ BCLXL/BCL2i (0.3 μM)

In collaboration with Pingping Mao, Kailey Kowalski (Wagle lab)

Synergy with PI3K inhibitors

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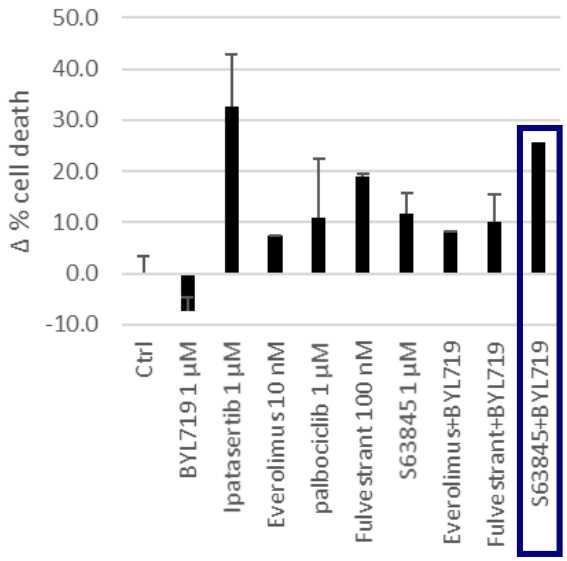
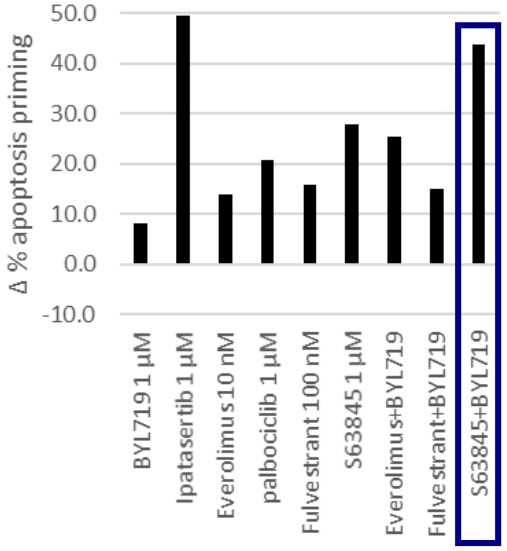
Network modeling of breast cancer to predict drug resistance mechanisms & combinatorial drug treatments

MDAMB415

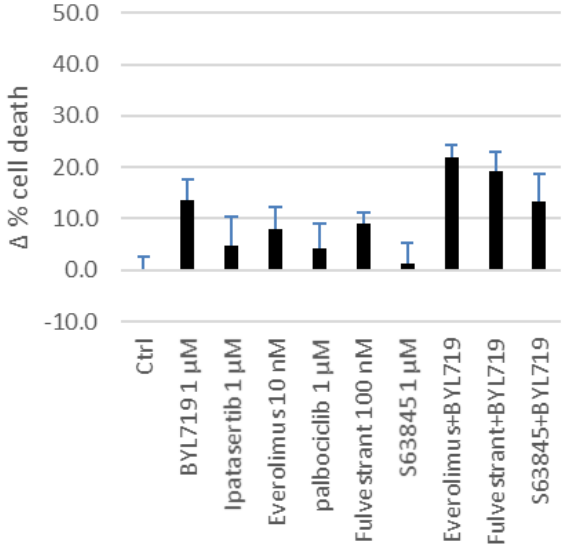


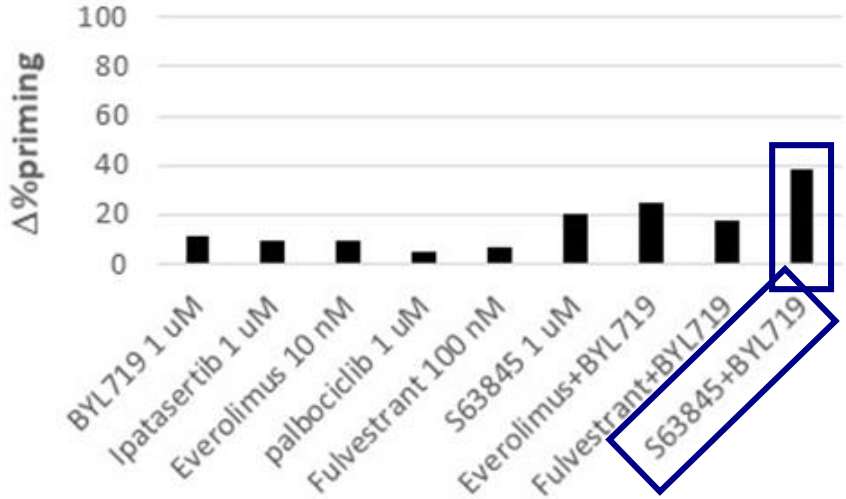


MCL1 inhibitor (S63845) and PI3K inhibitors (BYL719) induce cell death in MDAMB415 and MCF7 cells

In collaboration with Joan Montero and the Letai lab

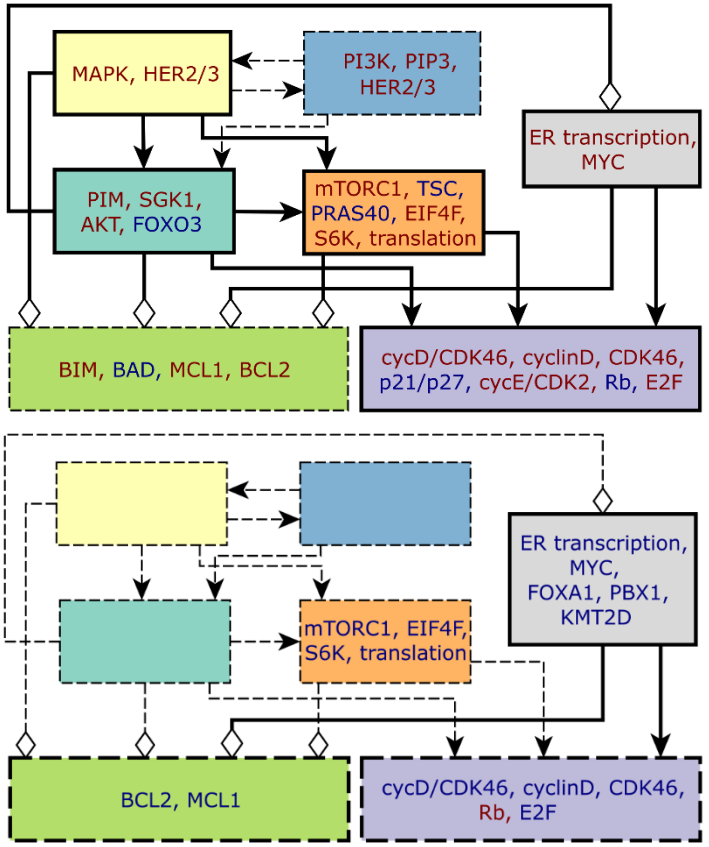
MCF7





Conclusions

- Constructed breast cancer network model, integrates known pathways and deregulations
- Identifies PI3Ki resistance mechanisms (**RB1, PRAS40, FOXO3**, **P27**), and predicts combinatorial drug interventions (**PI3Ki + MCL1i**)
- Several predicted resistance mechanisms were confirmed in CRISPR screens and drug-response experiments



Outlook

- Verify resistance mechanisms and combinations:

- BH3 profiling, cell viability (Montero lab, Letai lab, Wagle lab)
- CRISPR KOs (Wagle lab, Scaltriti lab, Baselga lab)

Acknowledgements

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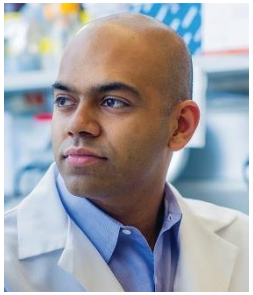
Network modeling of breast cancer to predict drug resistance mechanisms & combinatorial drug treatments

ALBERT LAB

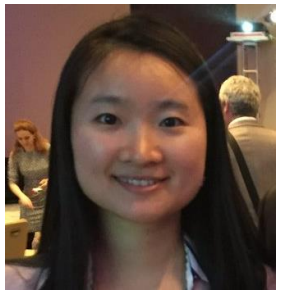
Réka Albert

PENNSTATE 1855

WAGLE LAB



Nick Wagle



Pingping Mao

Kailey Kowalski

Seth Wander
Gabi Johnson

BROAD INSTITUTE

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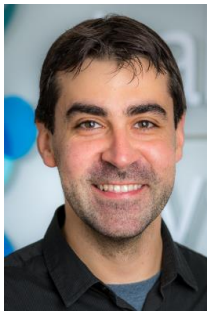
LETAI LAB

Tony Letai



Joan Montero

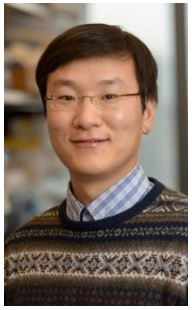
SCALTRITI LAB

1884
Memorial Sloan Kettering Cancer Center

Maurizio Scaltriti

BASELGA LAB

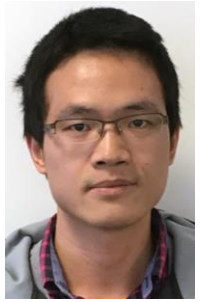
Jose Baselga



Guotai Xu

RABADAN LAB

Raul Rabadan



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COLUMBIA UNIVERSITY

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NSF

STAND UP TO CANCER

THE V FOUNDATION for Cancer Research

Thank you for your time!

Questions, comments, suggestions?

Complaints???

Contact: **jgtz@broadinstitute.org**
jgtz@phys.psu.edu
@jgtzanudo (Twitter)

Read more: SpringerOpen blog post
Using physics, math and models to fight cancer drug resistance
http://blogs.springeropen.com/springeropen/2018/01/04/physics-math-to-fight-cancer-drug-resistance/