**Paper Outline**

**Multi-pathway modeling of response to AKT inhibitors in breast cancer**

**Modeling AKT inhibitor response in breast cancer using multi-pathway signatures**

Predicting drug response to AKT inhibitors at the multi-pathway level in breast cancer

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Introduction

* Breast cancer statistics
* History of personalized medicine in breast cancer and why it’s inefficient
  + - (HER2 story)
* The need for personalized drug response predictions
* Why the pathway-based approach is better
* AKT/BAD/IGF1R/HER/ERK in breast cancer
* Goal: Modeling and validating drug response predictions using a pathway based approach to provide individualized treatments.

Methods

1) Overexpression of pathway elements using adenovirus in HMEC cells

- Virus we used, infection time, MOI, all the specifics

*-* Western blot figures for each signatures (supplements)

- Just the phosphorylated proteins and the B-action

2) Data processing and normalization

Sequencing methods, processing (Rsubread), normalization, batch adjusting

- Signatures

- ICBP

- CCLE

- TCGA

3) Generation and validation of genomic signatures that represent pathway activity

- ASSIGN parameters, test data tests, correlation parameters, boot strap method

4) Validating finding in cell lines and patient cells

-Reagents, protocols

Results

*1) Validation of the genomic signatures (in methods, one Figure)*

* AKT, HER2, IGF1R, BAD, ERK predictions correlate with ICBP drug response data (more interesting)
* Show all correlation one heat map
* Boxplot for sensitive and resistance for each signature(mClust)
* Should we add TCGA validation?

*3) BAD/ERK pathway activity correlates with chemotherapy response (tie in with 2)*

* ICBP boxplots of pathway activation in BAD/ERK for multiple chemo drugs
* TCGA hopefully, survival curves from patients that got chemo and had high bad activity vs. those that don’t.

\*\*Balko et al. DUSP4, a negative regulator of ERK1 & 2

DUSP4 loss after chemo correlates with poor patient outcome by activating RAS-ERK pathway

*6) Predictive models for Sigma AKT using gene expression signature’s*

*-*Building the model (method)

- Testing the model

1) Publically available data

- GDSC or CCLE

- Probably can’t do with TCGA

2) Breast cancer cell lines in the lab

3)Patient cells pleural effusions

- Test the EC50 for sigmaAKT

7) *Predictive models for Sigma AKT using multi-omic data*

*-*Building the model (method)

- Testing the model

1) Publically available data

- GDSC or CCLE

- Probably can’t do with TCGA

2) Breast cancer cell lines in the lab

3)Patient cells pleural effusions

- Test the EC50 for sigmaAKT

4) Contribution of adding multi-omic data

*2) Are multi-pathway prediction better predict than single pathway ?*

- Describe which pathways work best together for predictions

- Table with prediction/drug response correlations and p-values.

4) *Other ideas*

*- IGF1R pathway activation and response to AKT inhibitiors*

***- AKT pathway response to AKT inhibitors, Pi3k inhibitors.***

***- HER2 response to AKT and PI3K drugs***

*- ERK pathway response to PI3K, mTOR, and AKT drugs*

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*5) Subtypes specific pathway deregulation in breast cancer cell lines and TCGA data*

What pathways are important in each subtype in breast cancer cell lines.

-ICBP correlation matrix between subtypes and drug predictions

-Validate in CCLE (need to do this)

-TCGA maybe (need to comment on why it is not as good)