# Integrated genomic and pathway analysis reveals key pathways across breast subtypes

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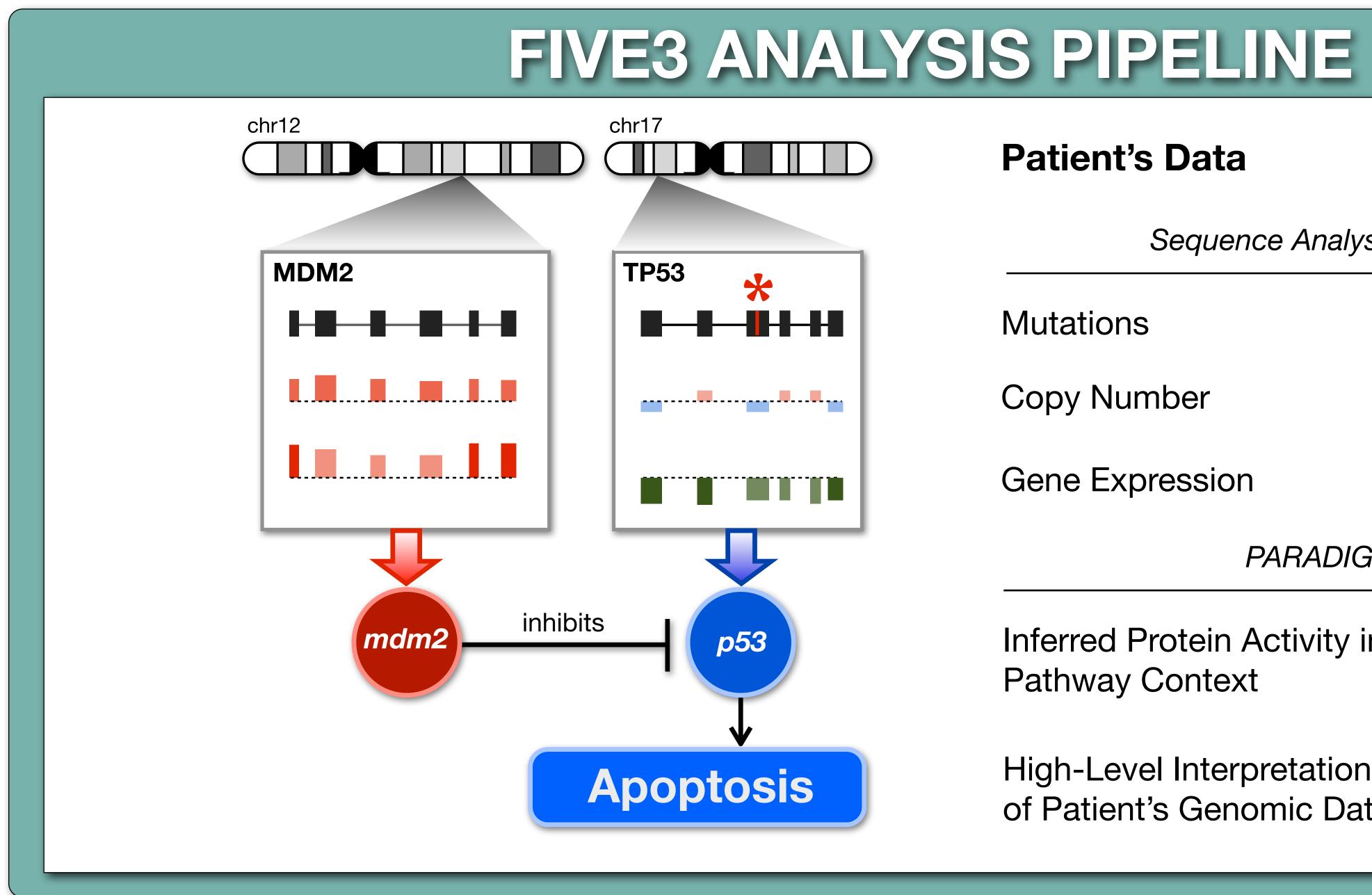**Abstract #P3-06-07**

THE CANCER GENOME ATLAS

## INTRODUCTION

We have created the Five3 Analysis Pipeline to streamline discovery of individual samples' mutations, small indels, copy number alterations, genome rearrangements, expression changes, and resulting pathway activities. By applying this pipeline to the TCGA breast cancer datasets, we recapitulate established breast subtypes at a pathway-dependent level. For example, basal tumors appear enriched for proliferation pathways compared to luminal samples within this cohort. Expanding the pathway analysis to include TCGA lung cancer samples, we find similar subnetworks activated between basal and squamous lung and between luminal and lung adenocarcinomas. This hints at similar genomic mechanisms for these subtypes independent of tissue of origin. Finally, by analyzing genomic alterations across all breast cancers we see mutational clusters in PIK3CA that correspond with publicly-available hotspots [1]. Interestingly, we find that samples with mutations clustered in exon 21 (kinase domain) are upregulated in proliferation-related pathways relative to other domains, independent of subtype and TP53 mutation status.
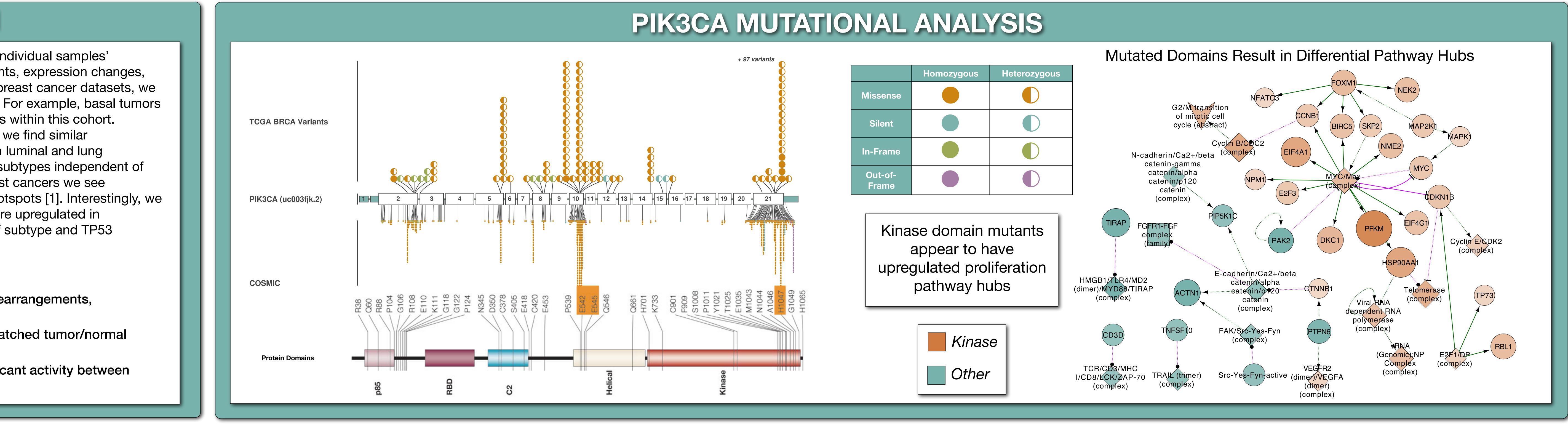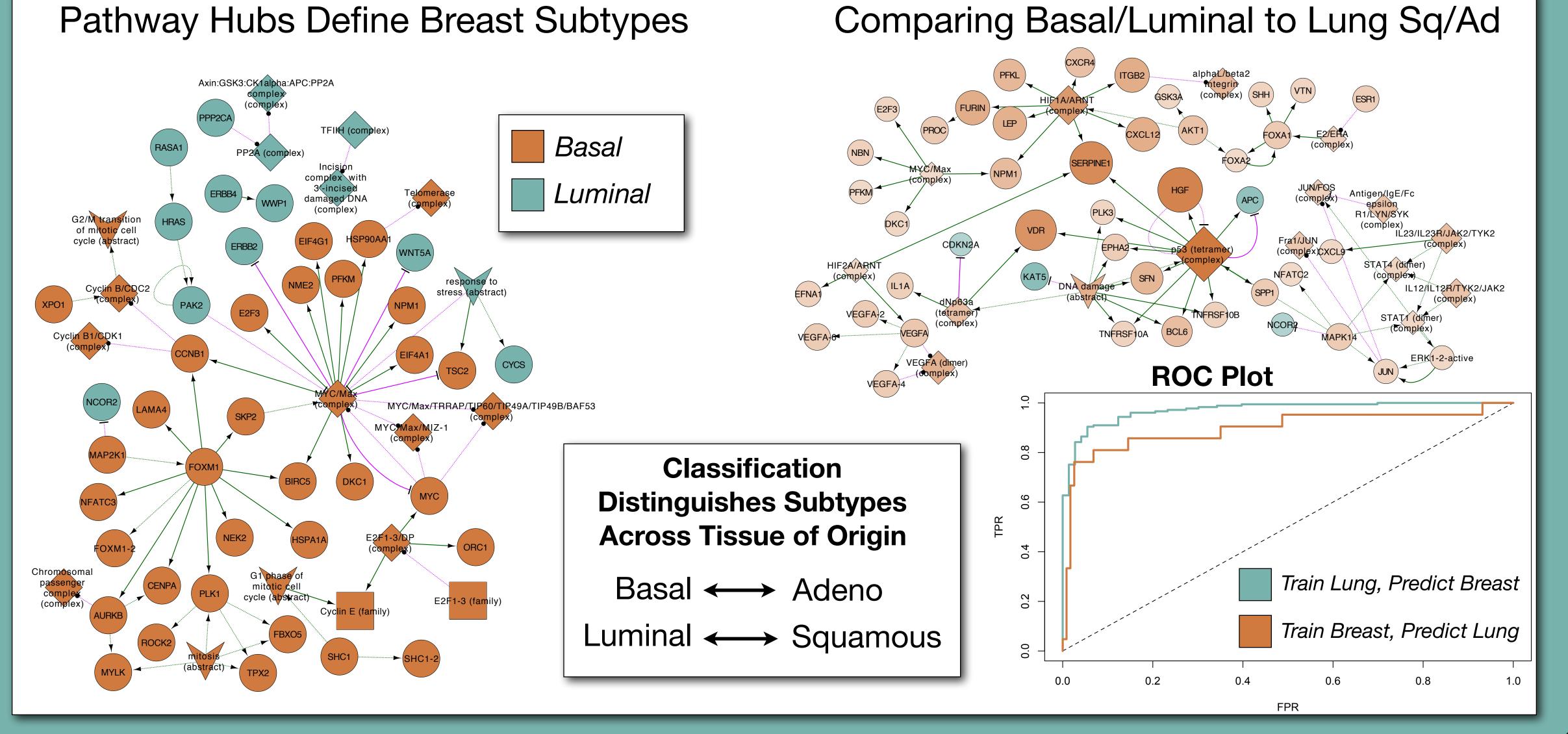
### Key Points

- Automated Analysis Pipeline to discover mutations, indels, CNVs, rearrangements, expression changes and pathway activities
- Powerful sequence analysis designed specifically for processing matched tumor/normal samples
- Integrated PARADIGM Pathway analysis find subnetworks of significant activity between subtypes or phenotypes of interest

## PIK3CA MUTATIONAL ANALYSIS



| | Homozygous | Heterozygous |
|---|---|---|
| Missense | | |
| Silent | | |
| In-Frame | | |
| Out-of-Frame | | |

Kinase domain mutants appear to have upregulated proliferation pathway hubs

Mutated Domains Result in Differential Pathway Hubs

- Kinase
- Other

## FIVE3 ANALYSIS PIPELINE



**Patient's Data**

*Sequence Analysis*

Mutations

Copy Number

Gene Expression

*PARADIGM*

Inferred Protein Activity in Pathway Context

High-Level Interpretation of Patient's Genomic Data

## LUNG SUBTYPE CORRESPONDENCE

Pathway Hubs Define Breast Subtypes

Comparing Basal/Luminal to Lung Sq/Ad

- Basal
- Luminal



**Classification Distinguishes Subtypes Across Tissue of Origin**

Basal ⟷ Adeno

Luminal ⟷ Squamous

**ROC Plot**

- Train Lung, Predict Breast
- Train Breast, Predict Lung

## SUMMARY

- Cancer web analysis pipeline capable of taking raw sequencing data to interpreted pathway activities
- Powerful suite of tools to allow visualization and analysis of mutations, copy-number, expression and pathway activities in an integrated fashion
- Pathway analysis reveals critical hubs that may provide opportunities for additional targeted therapies

## ACKNOWLEDGEMENTS

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2. Andreas G. Bader, Sohye Kang, Li Zhao & Peter K. Vogt. Oncogenic PI3K deregulates transcription and translation. Nature Reviews Cancer 5, 921-929 (December 2005).

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