

# Widespread genetic epistasis among cancer genes

Audrey Q. Fu<sup>†</sup>

Joint work with Xiaoyue Wang<sup>†</sup>, Megan E. McNerney,  
and Kevin P. White\*

<sup>†</sup>equal contributions; \*corresponding author  
University of Chicago

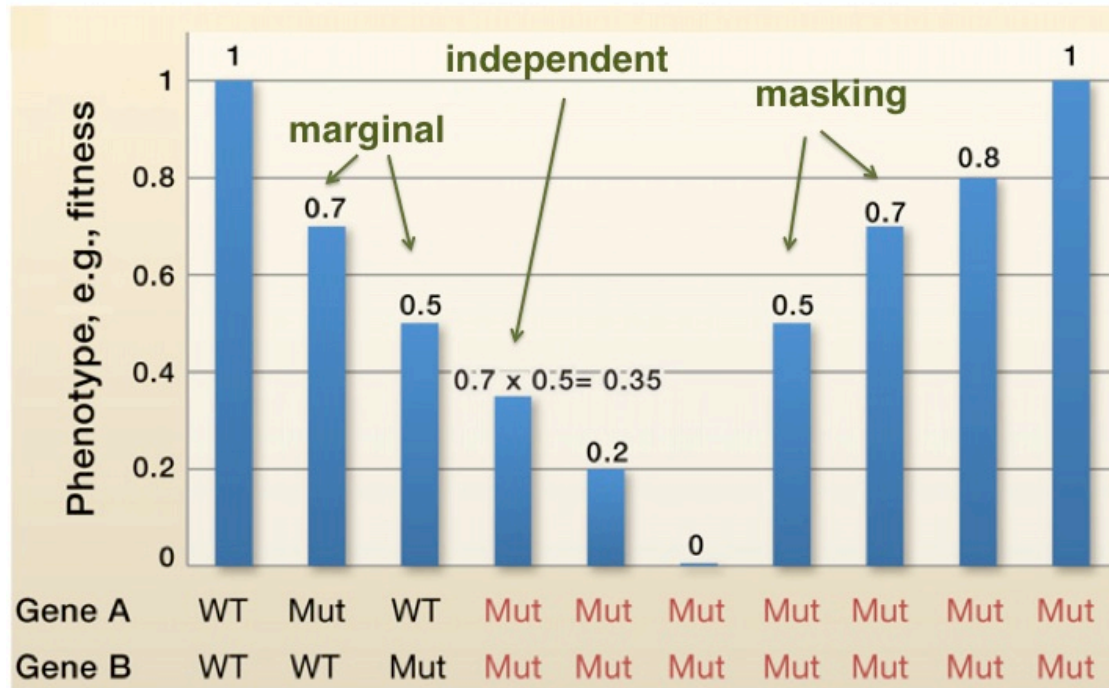
3<sup>rd</sup> TCGA Symposium, NIH

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Poster #76

[audreyqyfu@uchicago.edu](mailto:audreyqyfu@uchicago.edu)

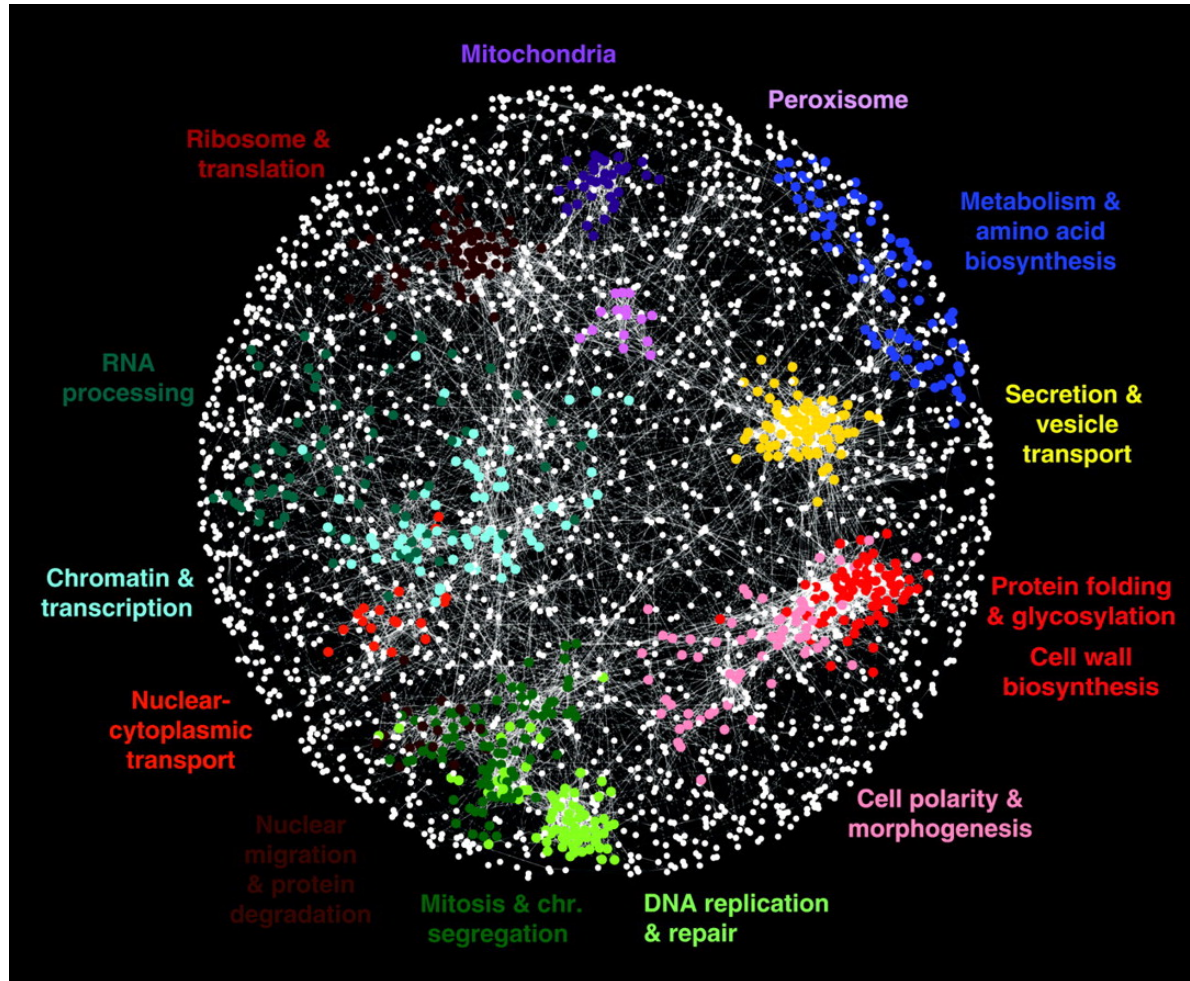
# Genetic epistasis/interaction



adapted from Ashworth et al. (2011), Cell

- Epistasis:
  - Bateson (1907): masking.
  - Fisher (1918): departure from additive model.
  - Departure from additive or multiplicative model.

# Genetic epistasis map in yeast



Costanzo et al. (2010), Science

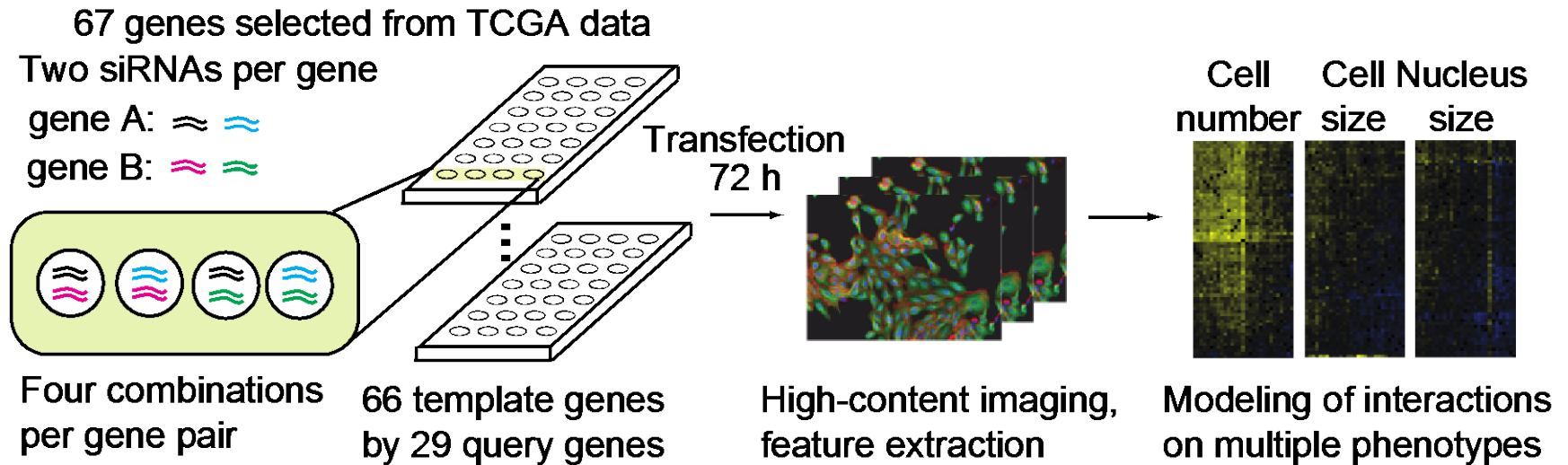
# Identifying interacting gene pairs

- Selecting frequently co-altered cancer genes with statistical significance from TCGA;
- RNAi single and double knockdown experiment;
- Transformation and regression for inference of epistasis.



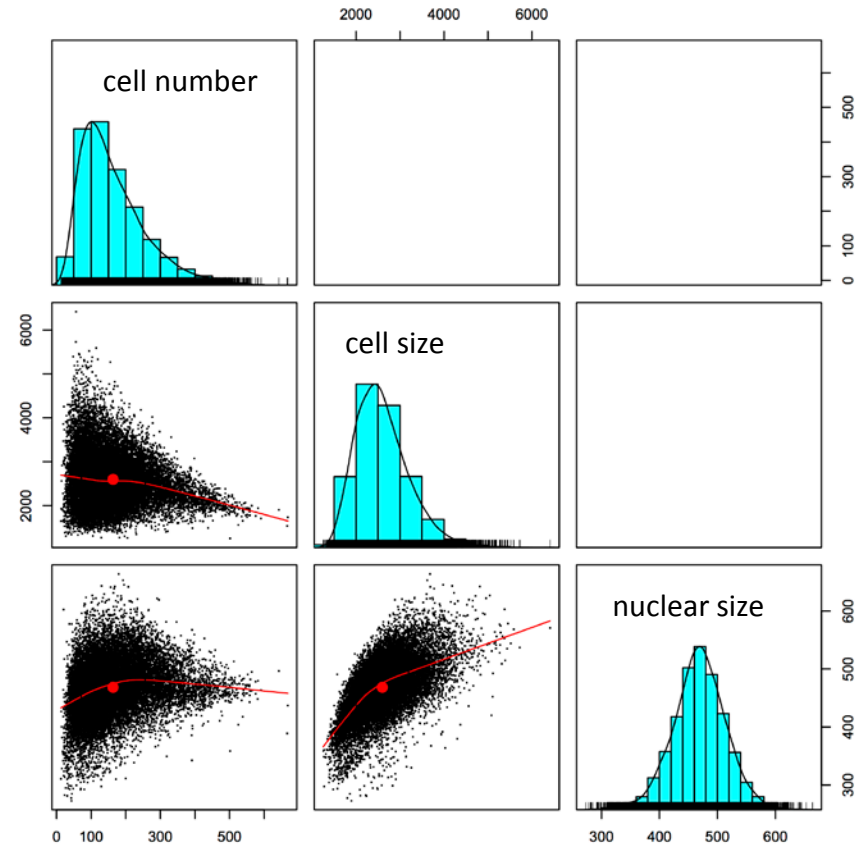
# Identifying interacting gene pairs

- **RNAi knockdown experiment** (MCF10A breast epithelial cell line):



# Identifying interacting gene pairs

- **Analysis of RNAi data:**
- Interaction models:
  - Additive: nuclear size;
  - Multiplicative
    - cell number and cell size;
    - additive after log.
- Seemingly Unrelated Regression (SUR):
  - Account for dependence among phenotypes;
  - Account for batch effect.



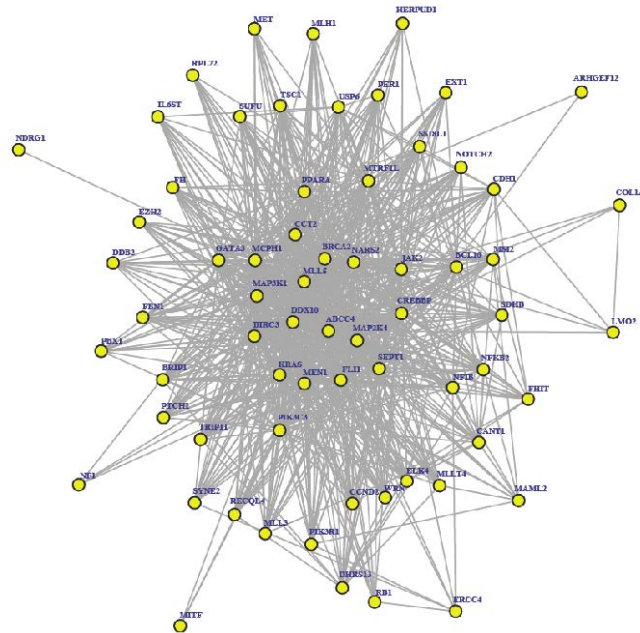
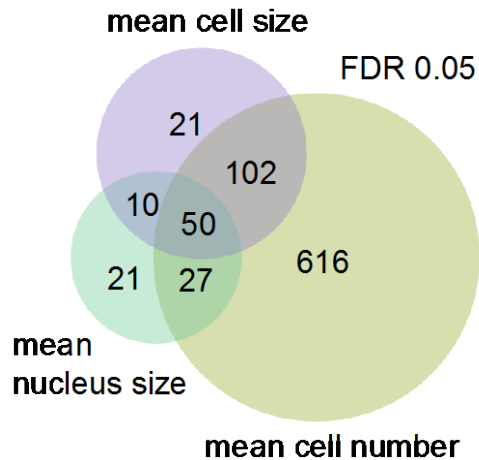
$$y_{pbijr} = \beta_0 + \beta_{1b} + \beta_2 G_i + \beta_3 G_j + \beta_4 (G_i \times G_j) + \varepsilon_{pbijr}$$

$$\varepsilon \sim \text{Normal}(0, \Omega)$$

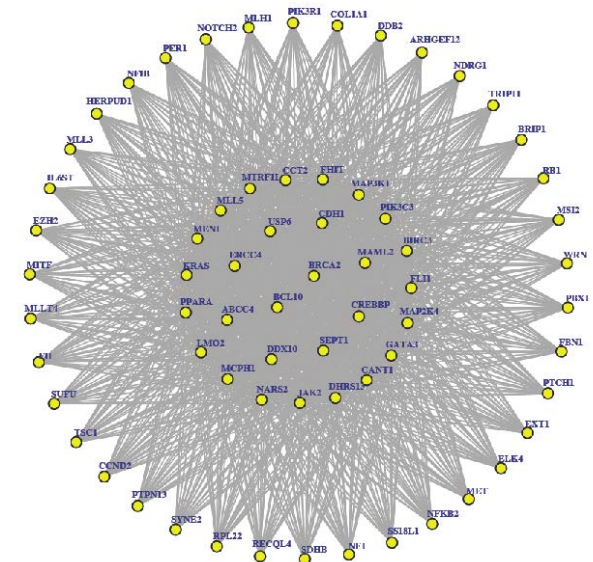
$$\Omega = \Sigma_{3 \times 3} \otimes I_N$$

# An epistasis map

- **Inferred epistasis map (847 significant interactions):**



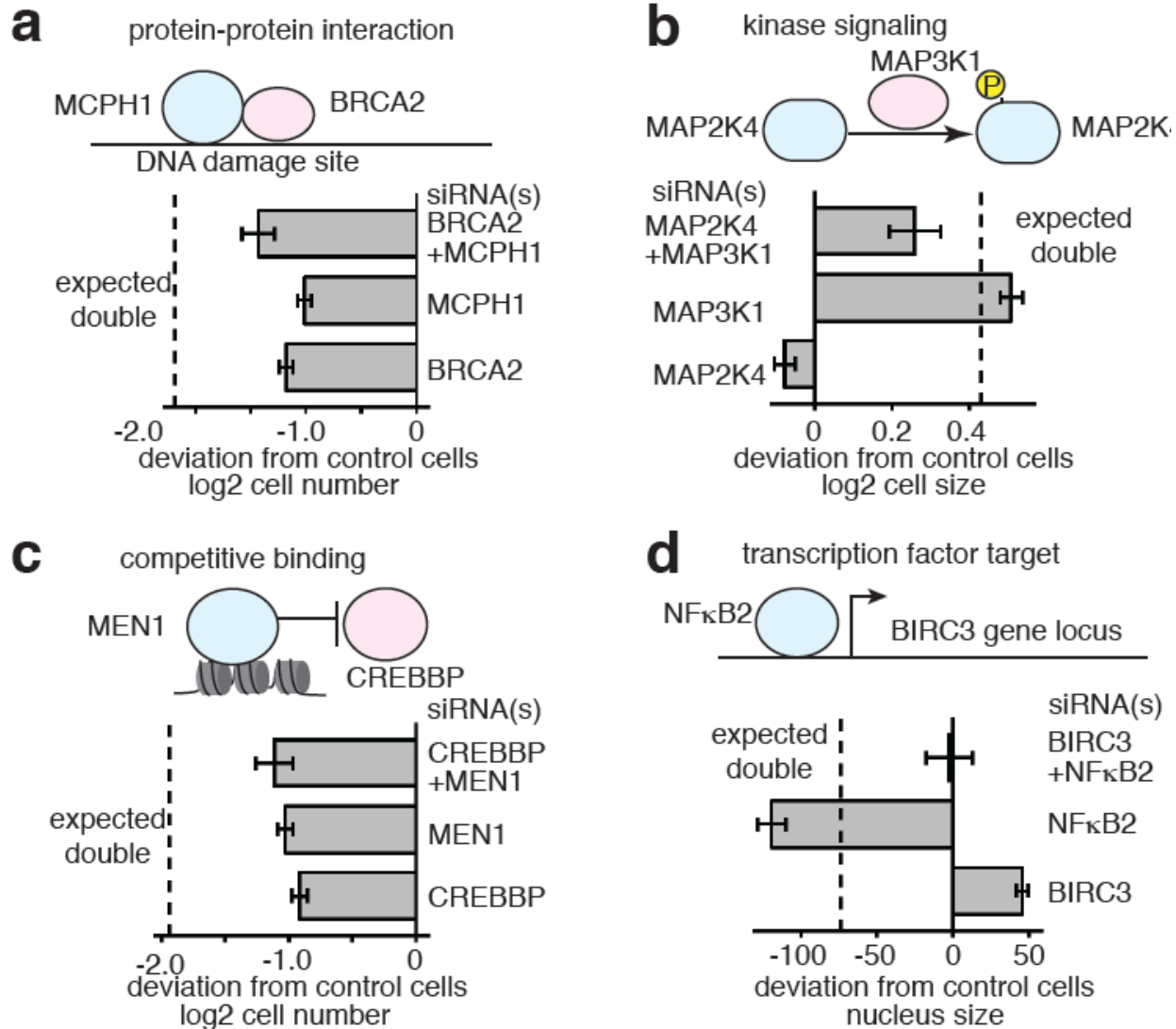
## Experimental Design Map



- **Topology:**
  - (Adjusted) connectivity: median 62%;
  - Small-worldness: 1.5 (1.1 for design map).
- **Genetic interactions:**
  - Majority (82%) are novel;
  - Over half exhibit masking effects.

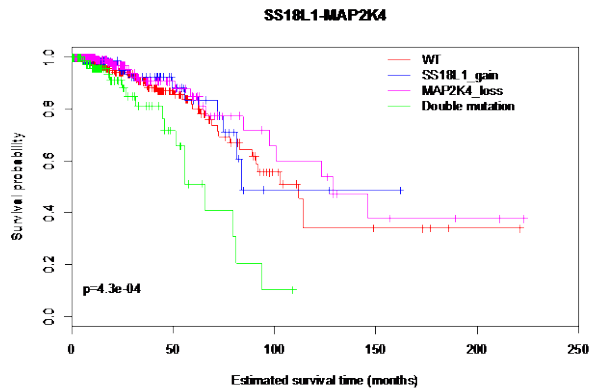


# Genetic interactions and molecular interactions

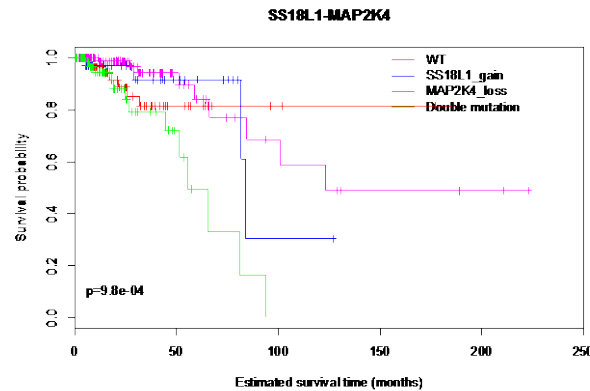


# Genetic interactions and survival

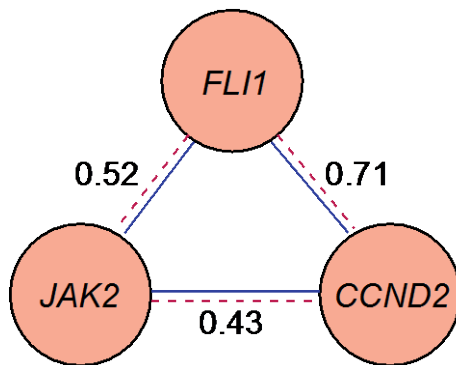
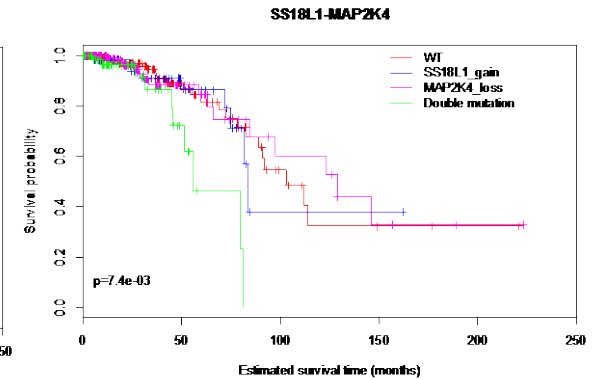
all samples



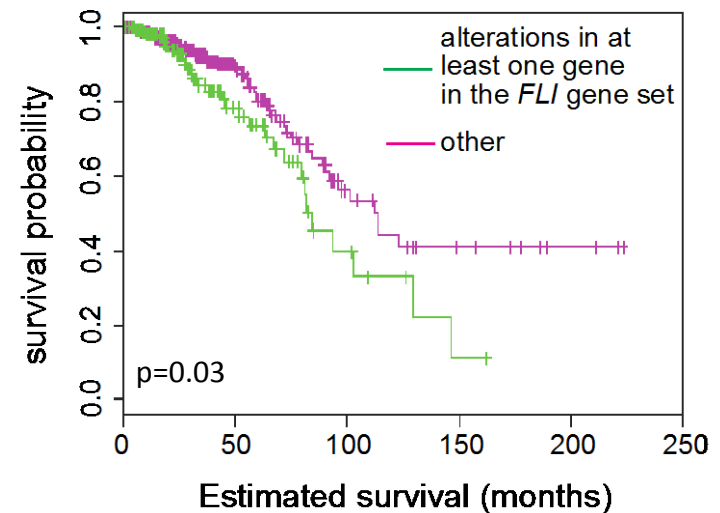
loss of *TP53*



ER positive



— Genetic interaction  
- - - Expression correlation



# Genetic interactions and survival

Gene pairs with different outcome when co-altered

		0	1
Gene pairs with genetic interactions	0	646	15
	1	811	36

Fisher's exact test  
p-value: 0.023

Result: interacting gene pairs are enriched in gene pairs associated with reduced survival time ( $p=0.02$ ; Fisher's exact test).

# Acknowledgements

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- Other members in the White lab.

Poster #76 [audreyqyfu@uchicago.edu](mailto:audreyqyfu@uchicago.edu)