Network Synergy Recent Papers

AJ Fagan

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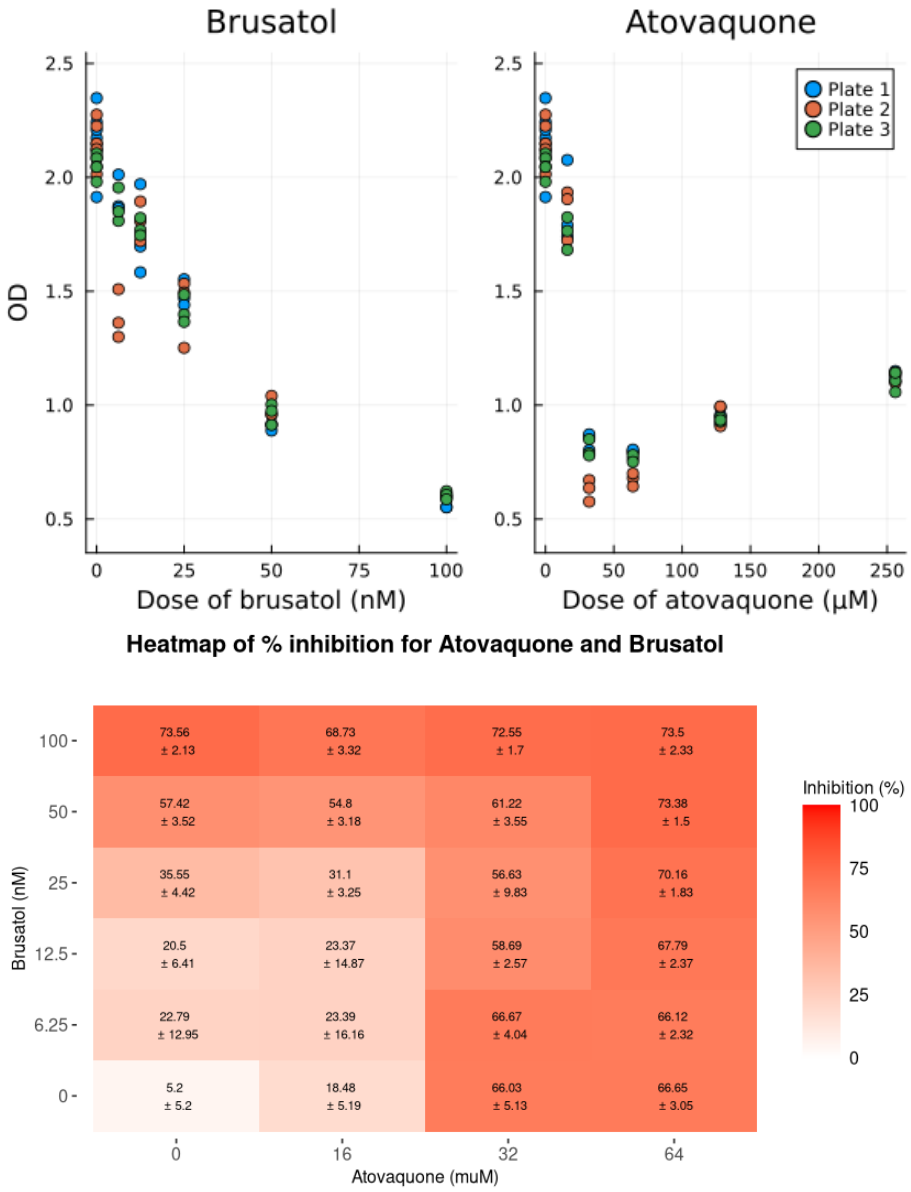
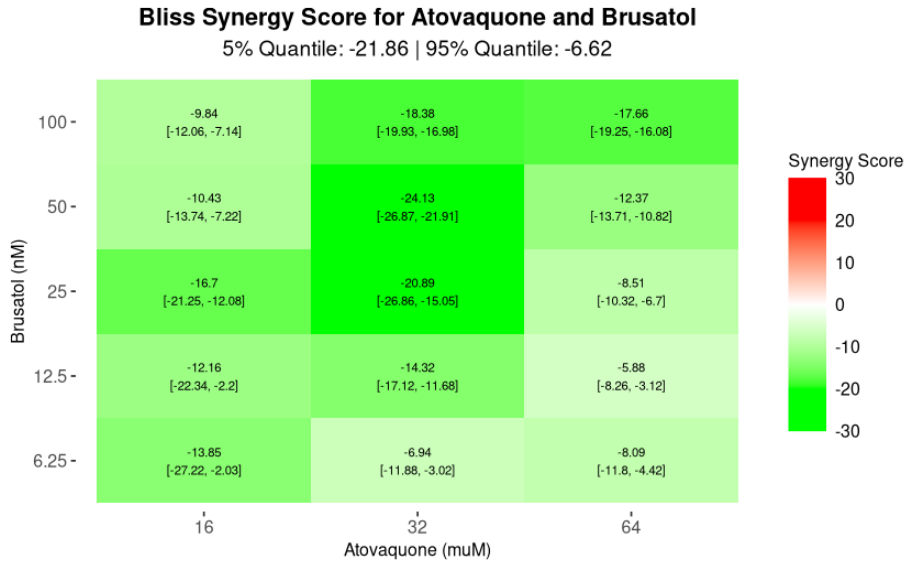
Synergy via Potency





Promises of Synergistic Combinations

The promises associated with synergistic drug combinations are:

- Overcoming chemoresistance
- Repurposing existing drugs
- Increasing efficacy
- Reducing toxicity

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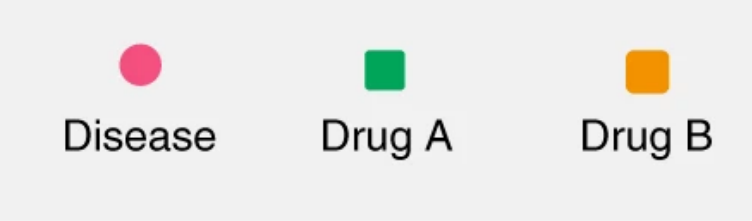
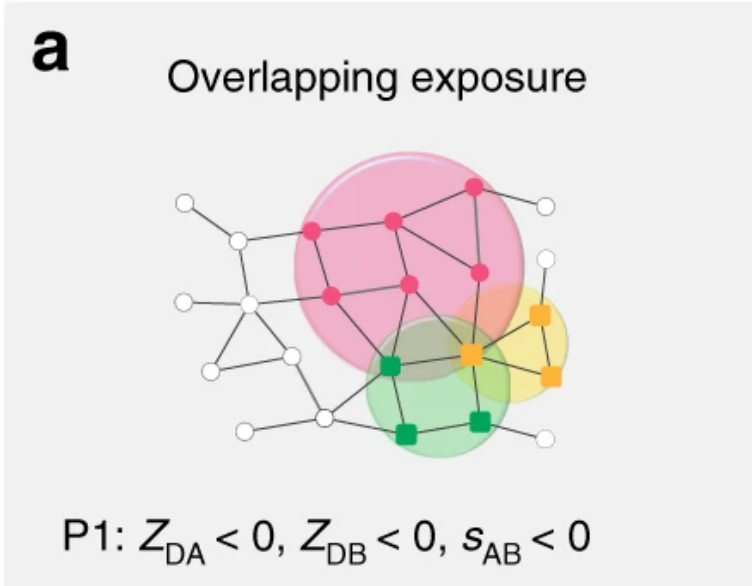
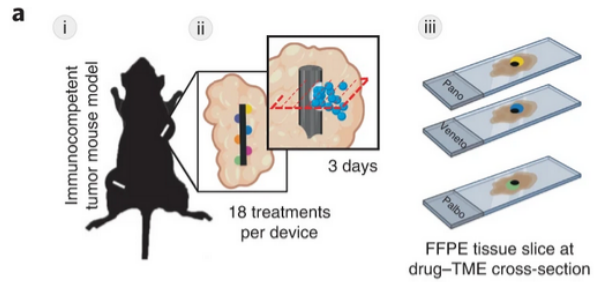
Relevant XKCD

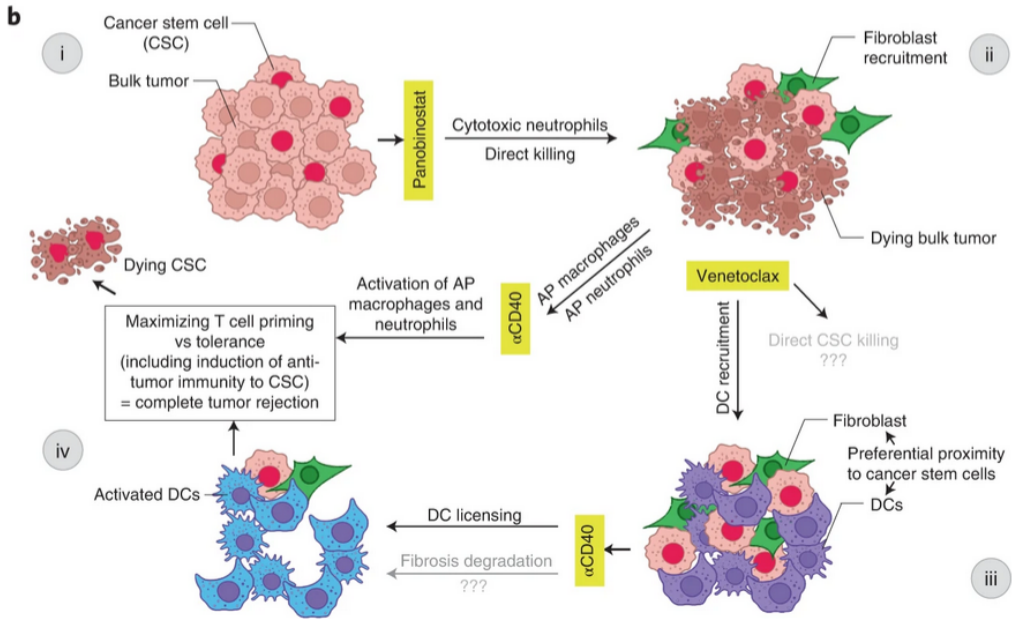
Synergy via Biological Networks

Goal: describe the mechanism, rather than the strength, of interaction between two drugs.









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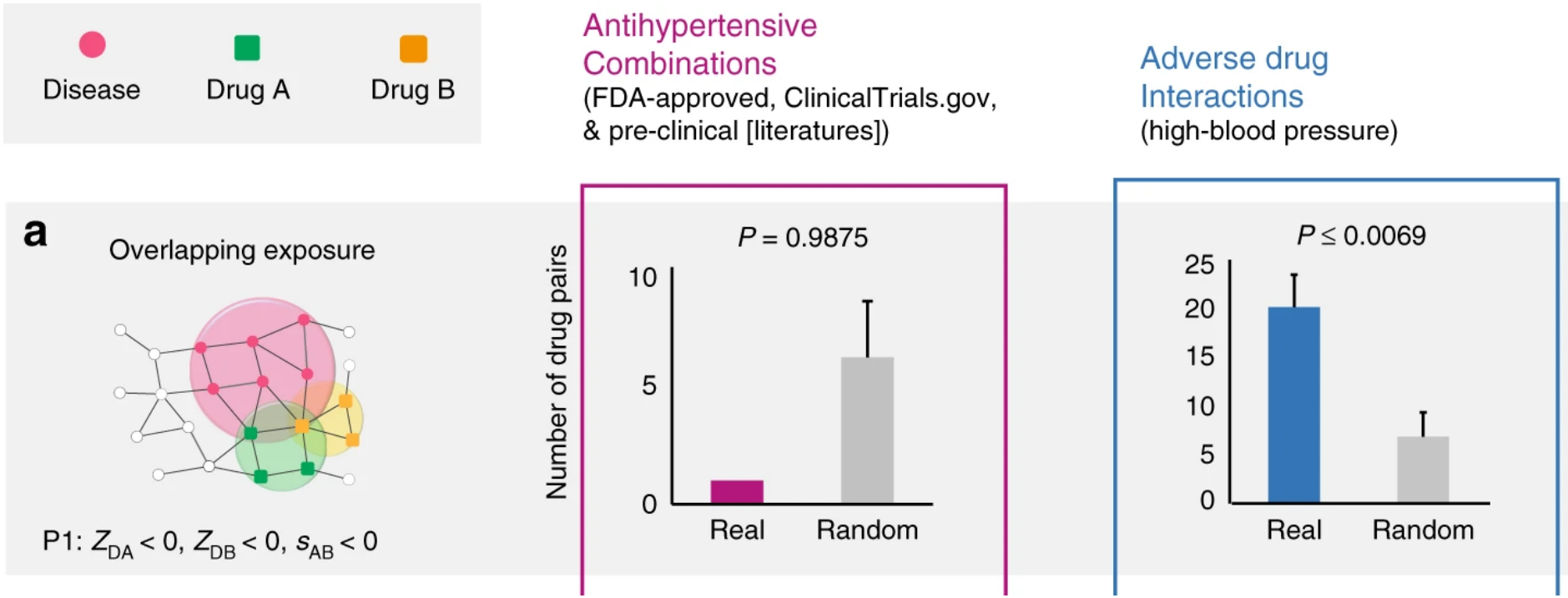
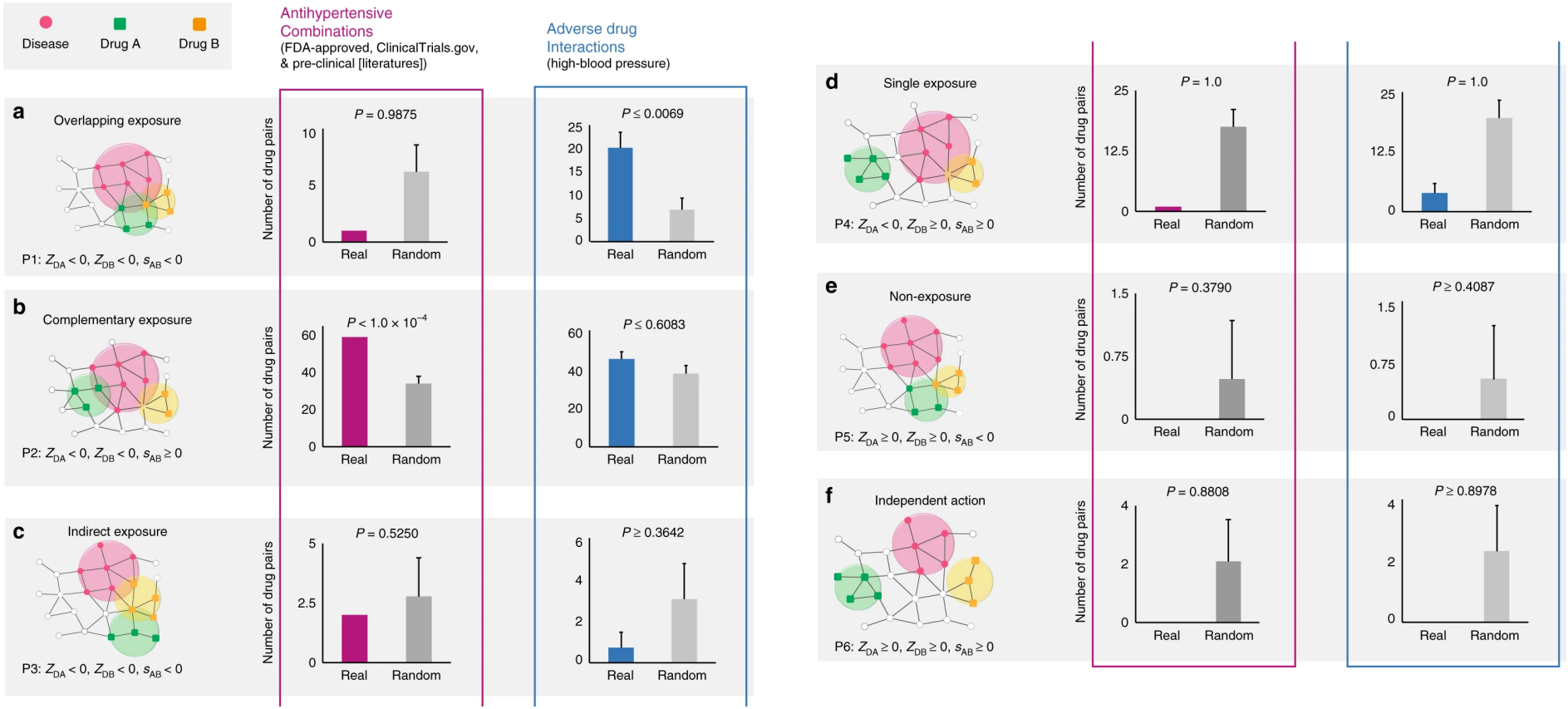
Module Approach



Network-based prediction of drug combinations, Cheng, Kovacs, Barabasi, 2019 [2]

Module Approach



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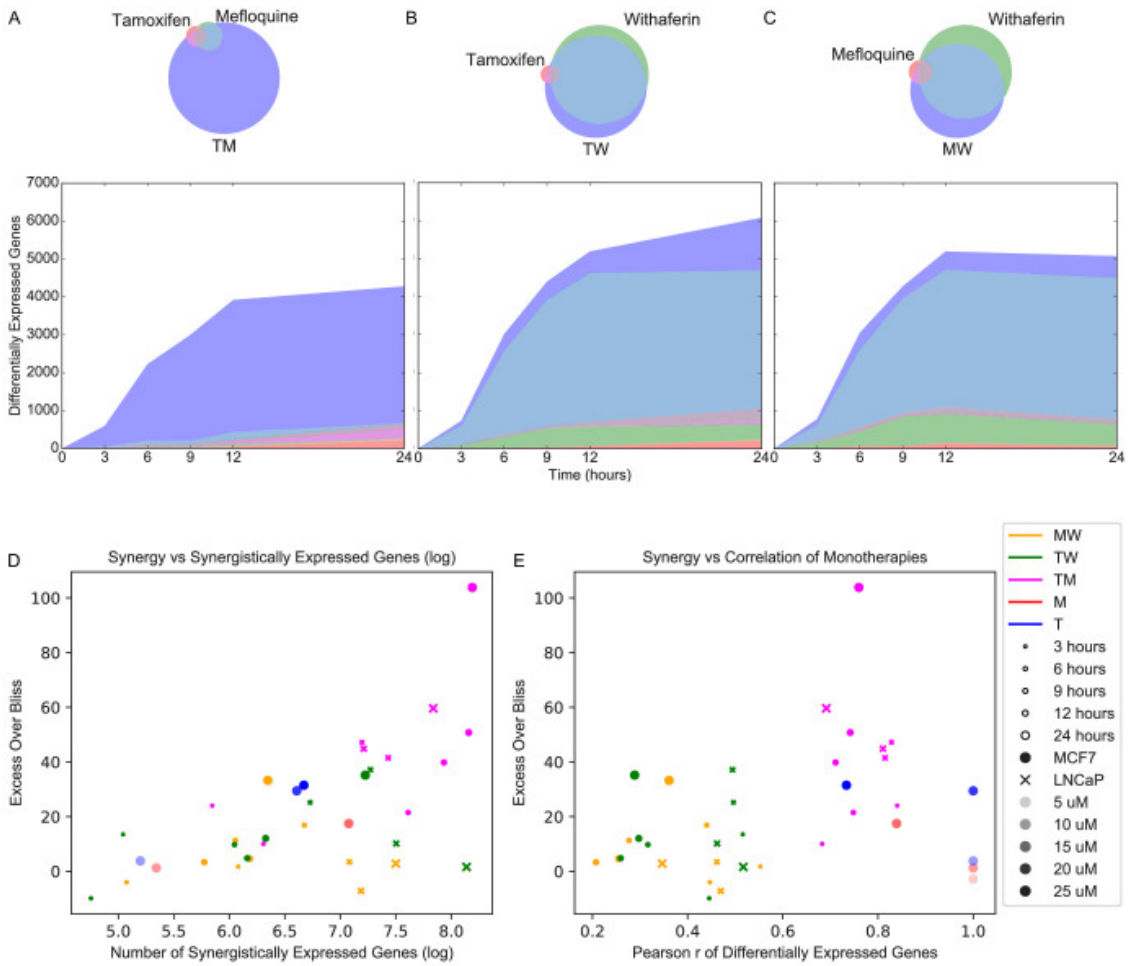
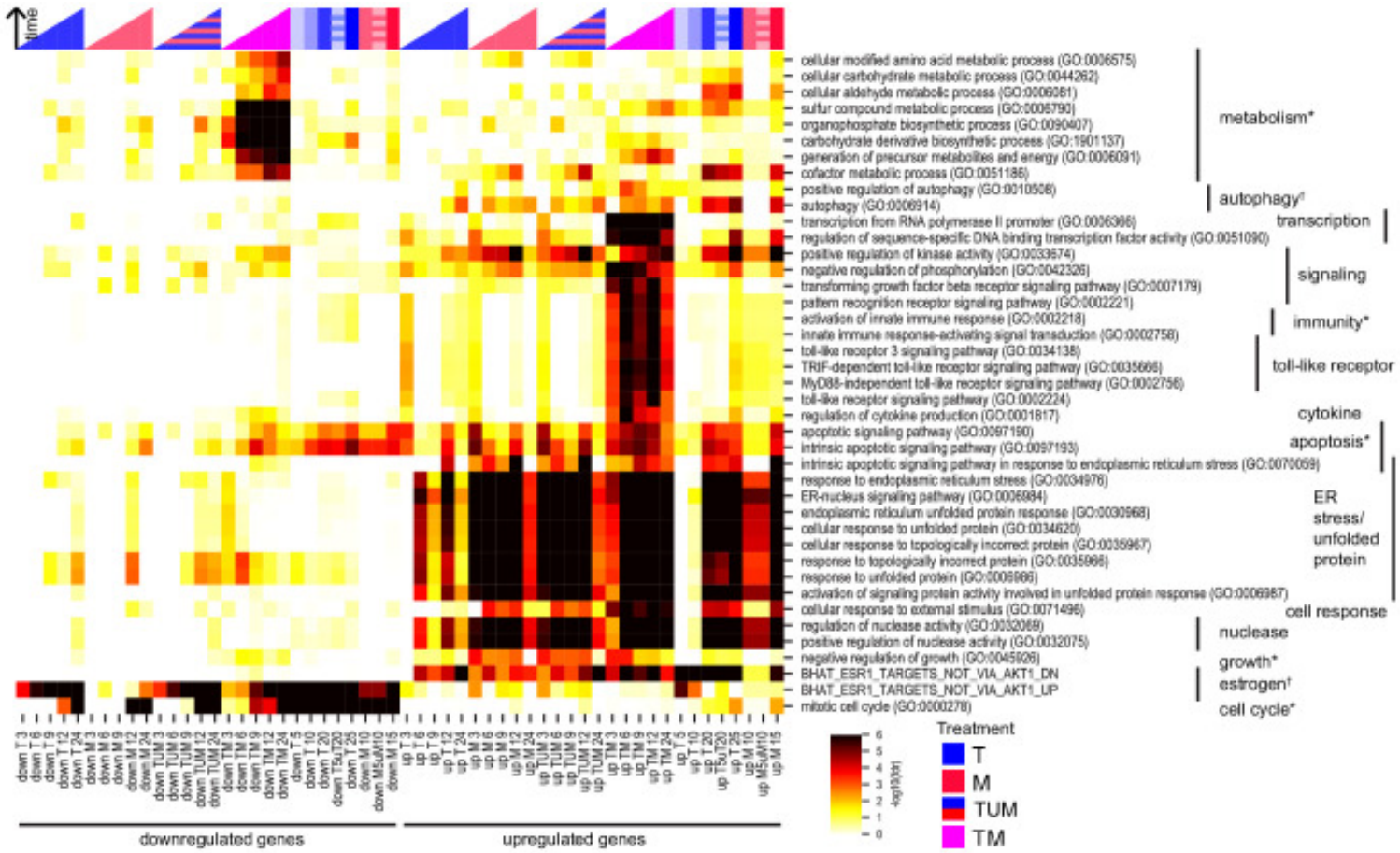
Synergy in Transcriptional Profiles



The transcriptomic response of cells to a drug combination is more than the sum of the responses to the monotherapies, Diaz et. al., 2020 [3]

Synergistically Expressed Genes in GSEA



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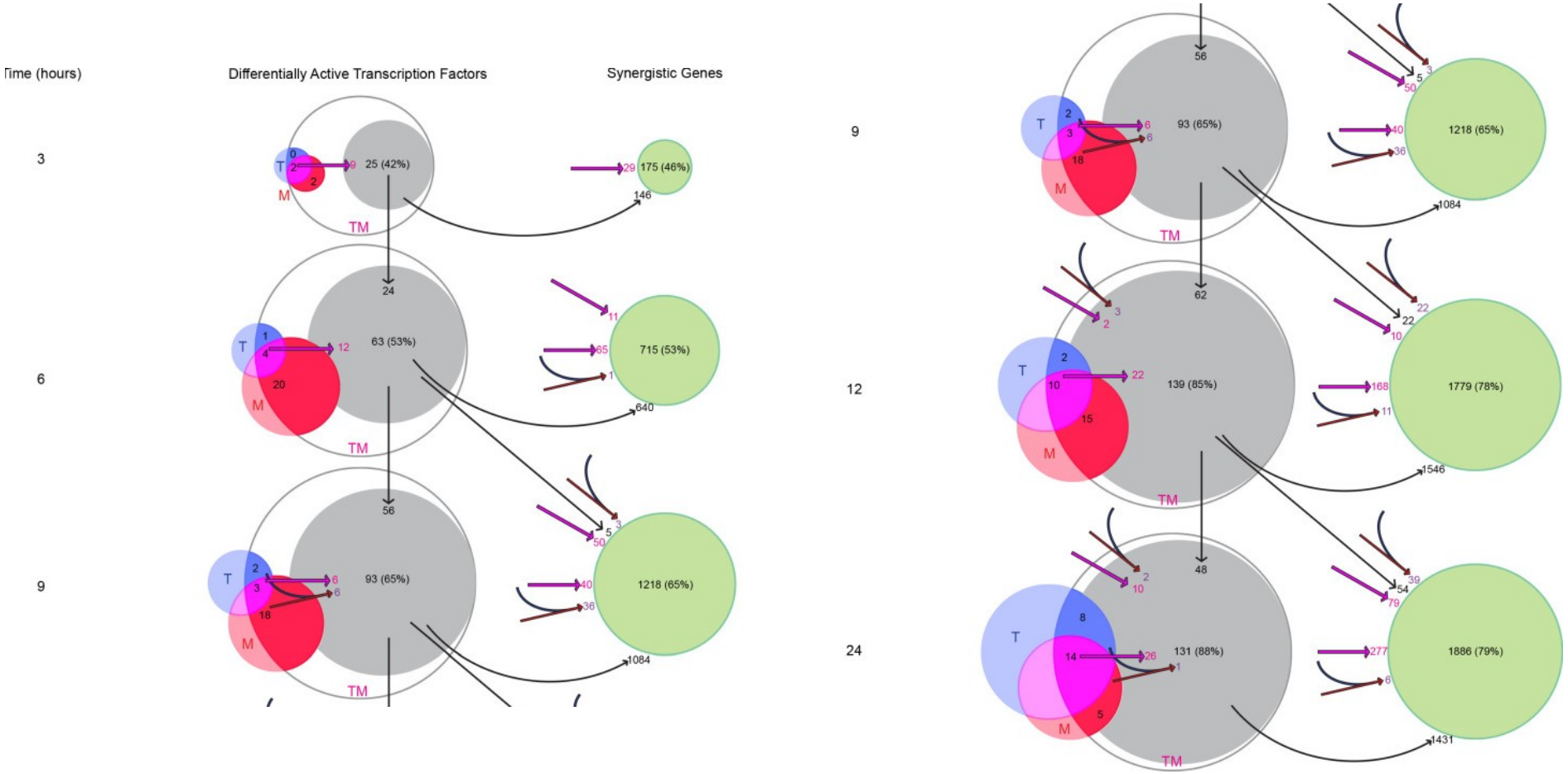
Transcription Cascade of Differentially Active TFs



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The Sham-Combination Principle

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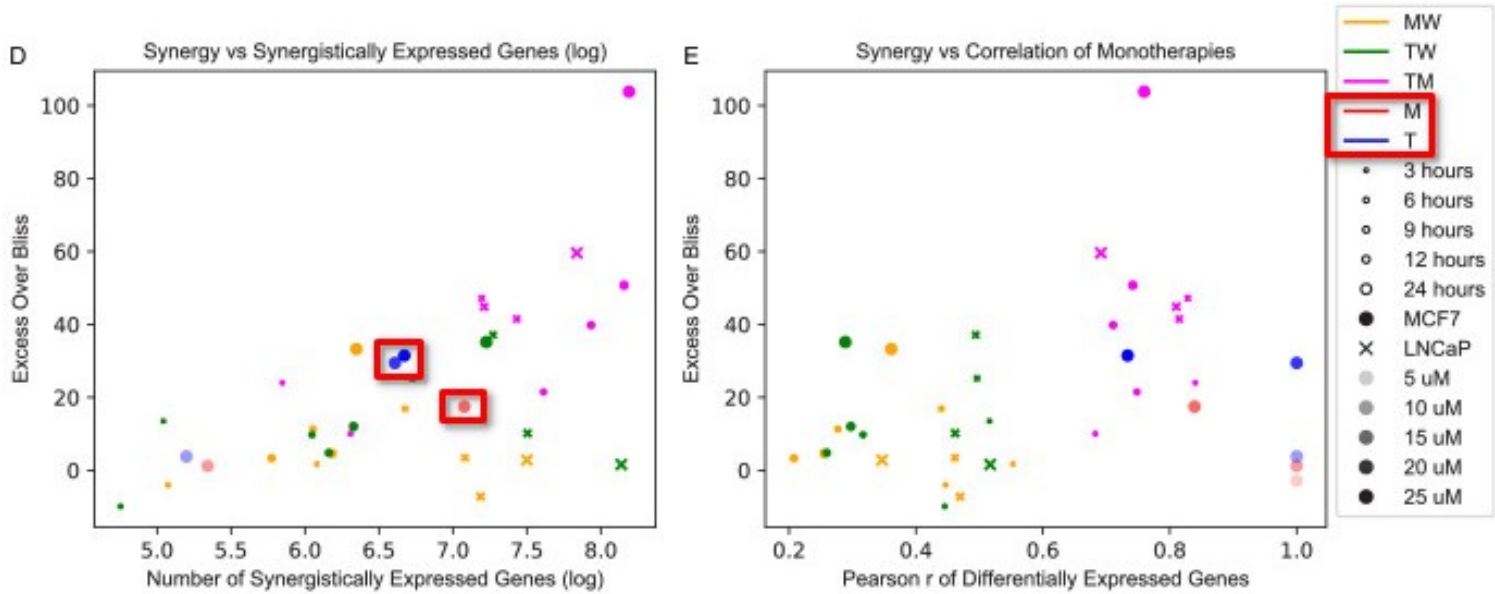
A drug combined with itself should be additive.



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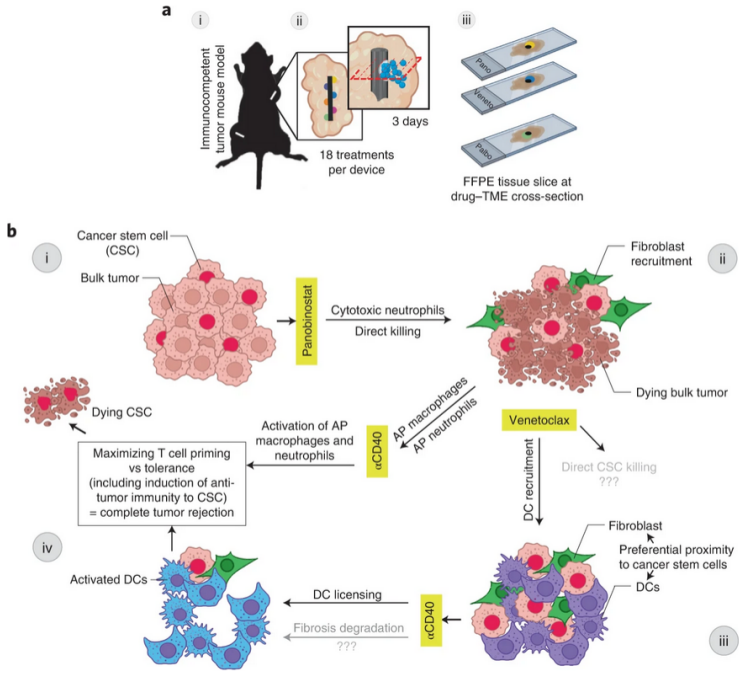
Multiplex Implantable Microdevice Assay



- An Implantable Microdevice (IMD) emits a small amount of several types of drugs into spatially separated regions of the tissue
- Multiplexed Immunohistochemical (mIHC) stainings enable spatial analysis of the TME's response to each treatment
- Synergisic treatment combinations, such as immunotherapies, can be predicted from the results

Identifying drug combinations that enhance treatment responses mediated by the tumor microenvironment, Tatarova, Jonas, and Gray, 2022 [1]

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Available Data

- Time-course bulk RNA-Seq of Tamoxifin, Withaferin, and Mefloquine in different doses, including pairwise combinations
- Drug targets for 42 drugs, and 73 experimentally verified combinations of them
- Various mIHC and/or cycIF imaging from murine breast cancer models
- "Combi-seq" (bulk RNA-seq, but for many drug combinations) data for 420 drug combinations [4]

References I


Identifying drug combinations that enhance treatment responses mediated by the tumor microenvironment.
Nature Biotechnology, 40(12):1770–1771, December 2022.


Feixiong Cheng, Istvan A. Kovacs, and Albert-Laszlo Barabasi.
Network-based prediction of drug combinations.
Nature Communications, 10(1):1197, March 2019.


Jennifer El Diaz, Mehmet Eren Ahsen, Thomas Schaffter, Xintong Chen, Ronald B Realubit, Charles Karan, Andrea Califano, Bojan Losic, and Gustavo Stolovitzky.
The transcriptomic response of cells to a drug combination is more than the sum of the responses to the monotherapies.
Elife, 9, September 2020.

References II


L. Mathur, B. Szalai, N. H. Du, R. Utharala, M. Ballinger, J. J. M. Landry, M. Ryckelynck, V. Benes, J. Saez-Rodriguez, and C. A. Merten.
Combi-seq for multiplexed transcriptome-based profiling of drug combinations using deterministic barcoding in single-cell droplets.
Nature Communications, 13(1):4450, August 2022.