Modeling Cancer Metabolism: from the Generic to the Personalized

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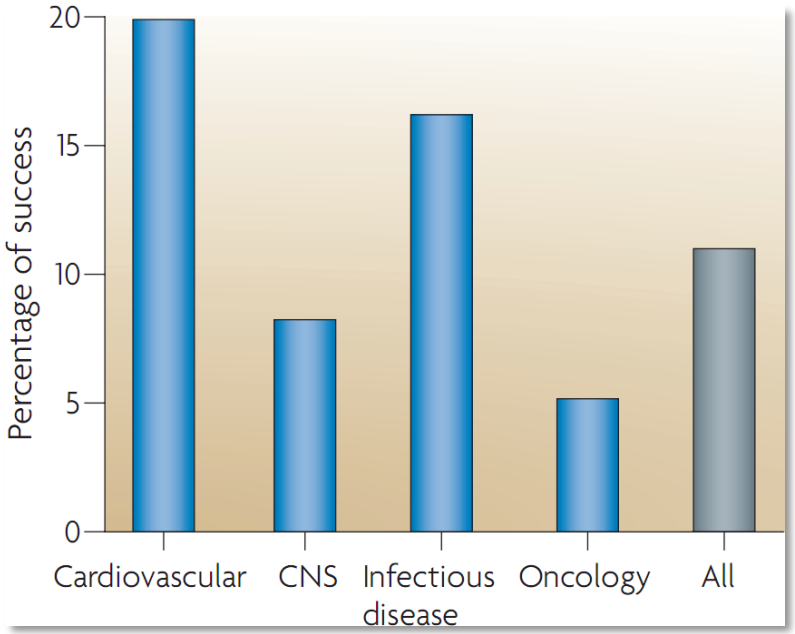
Outline

- Why study the metabolism of cancer?
- How can we study metabolism *in-silico*?
- Three approaches to study cancer metabolism:
  1. **Generic** cancer metabolic model (MSB, Folger. et al 2011)
  2. **Cancer type-specific** metabolic model (Nature, Frezza et al. 2011)
  3. **Personalized** metabolic model

Folger, O., et al., *Predicting selective drug targets in cancer through metabolic networks.* Mol Syst Biol, 2011. **7**: p. 501-501.
Frezza, C., et al., *Haem oxygenase is synthetically lethal with the tumour suppressor fumarate hydratase.* Nature, 2011. **477**(7363): p. 225-228.

Treating Cancer is Challenging

- The improvement in treating cancer is slow
- Cancer metabolism has been neglected
- Interest in cancer metabolism is resurging



Cancer Metabolism is Aberrant

- **Warburg Effect-** anaerobic respiration
- Why should the metabolism of cancer be altered?
  - The tumor microenvironment
  - Oncogene activation
  - Avoiding apoptosis
  - Proliferation

Upper arm metastasis shows high glucose consumption

The constantly beating heart is the only healthy tissue with high glucose consumption

Ovarian cancer shows high glucose consumption

How Can We Model Metabolism?

Kinetic models

Approx. kinetics

Accuracy

Metabolic

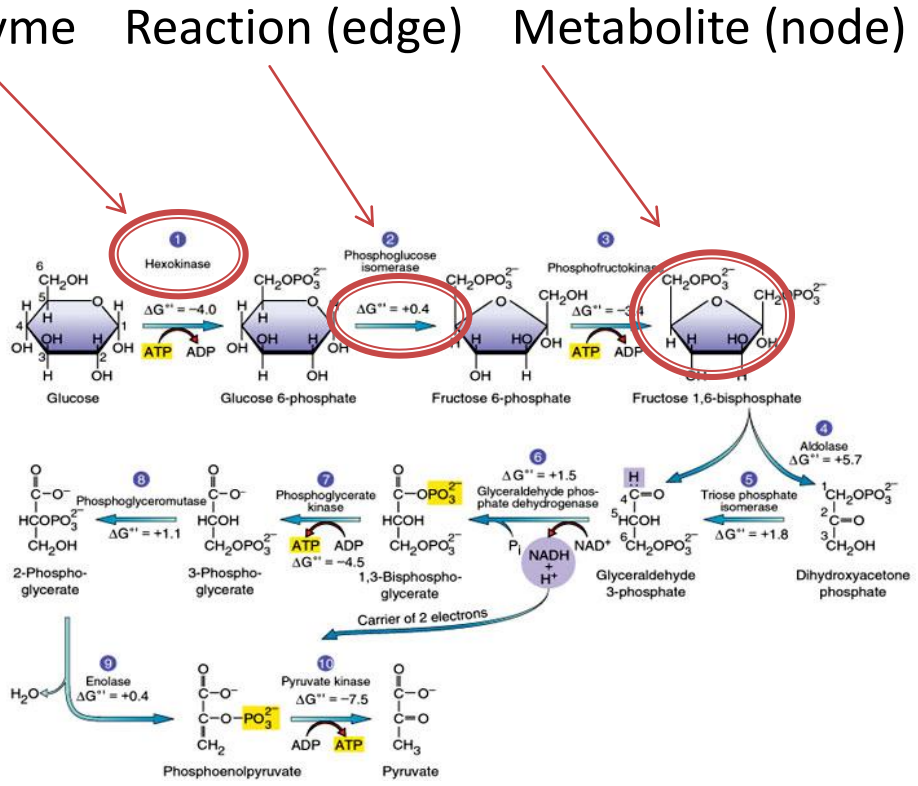
Constraint-based models (CBM)

Scale

Protein-Protein Interaction

Topological analysis

Enzyme Reaction (edge) Metabolite (node)



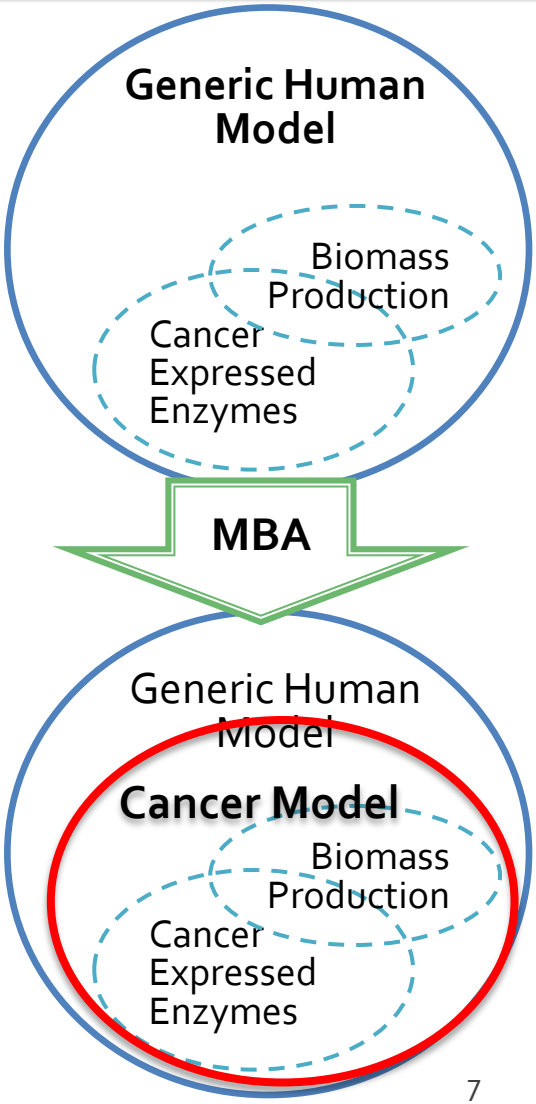
Constraint Based Modeling: the Underlying Framework

- A genome-scale approach to model metabolism
- Predict the flux rate of metabolic reactions
- Allows *in-silico* simulation
- Successfully used in microbiology and biotechnology
- The first human genome-scale metabolic model (Duarte et al. 2007)

Duarte, N.C., et al., *Global reconstruction of the human metabolic network based on genomic and bibliomic data.* Proc Natl Acad Sci U S A, 2007. **104**(6): p. 1777-82.

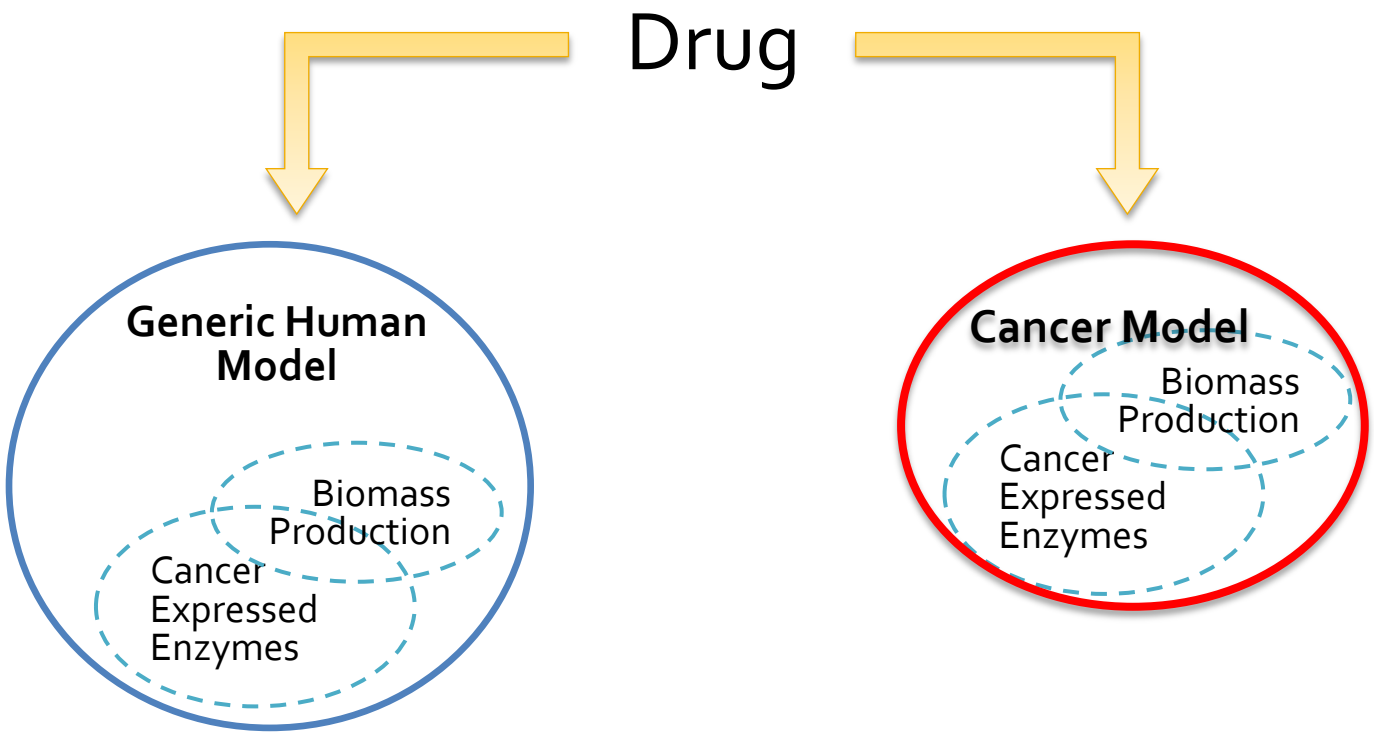
The First Genome-scale Metabolic Model of Cancer

- Human metabolic model
- Add a biomass reaction – simulates growth.
- Identify cancer reactions
- Applied Model Building Algorithm (MBA) (Jerby et al. 2008)
- Approximation of cancer metabolism



Jerby, L., T. Shlomi, and E. Ruppin, *Computational reconstruction of tissue-specific metabolic models: application to human liver metabolism.* Mol Syst Biol, 2010. **6**.

Computationally Identify Selective Drug Targets



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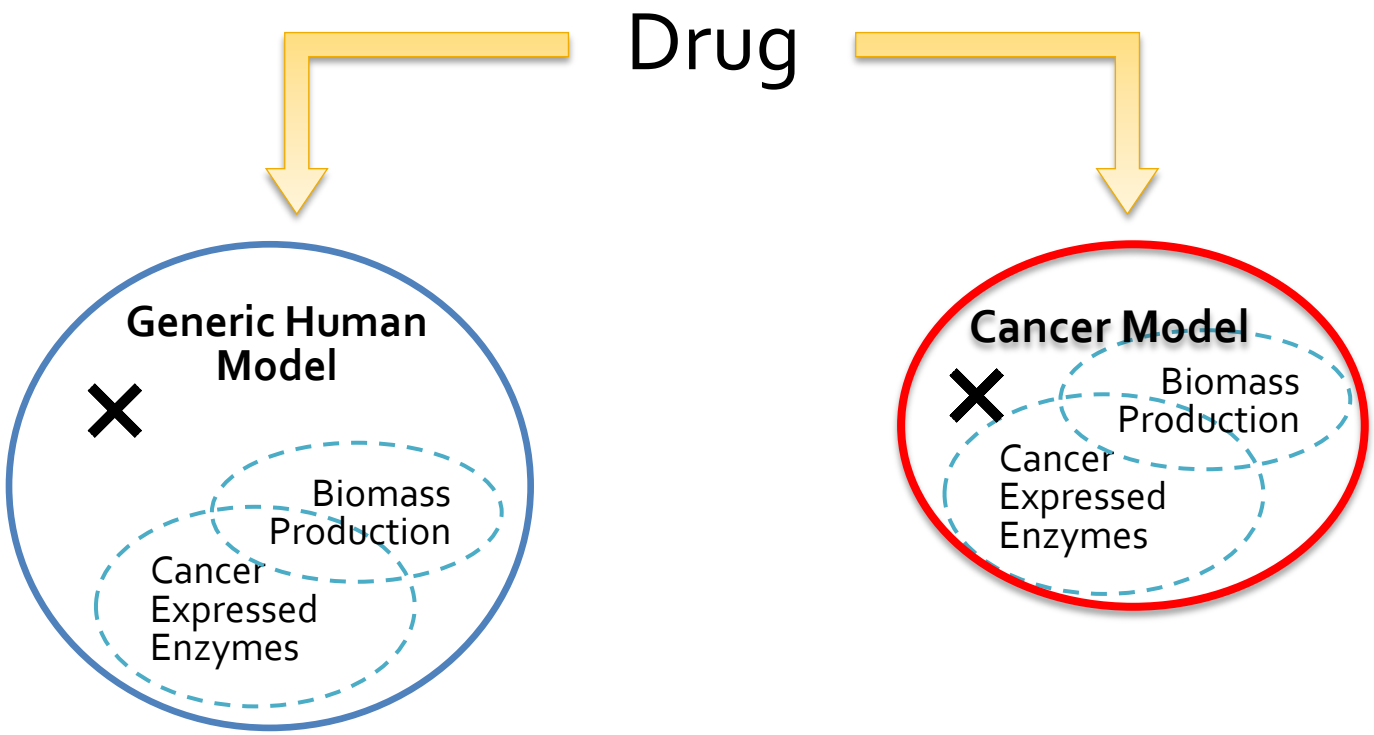

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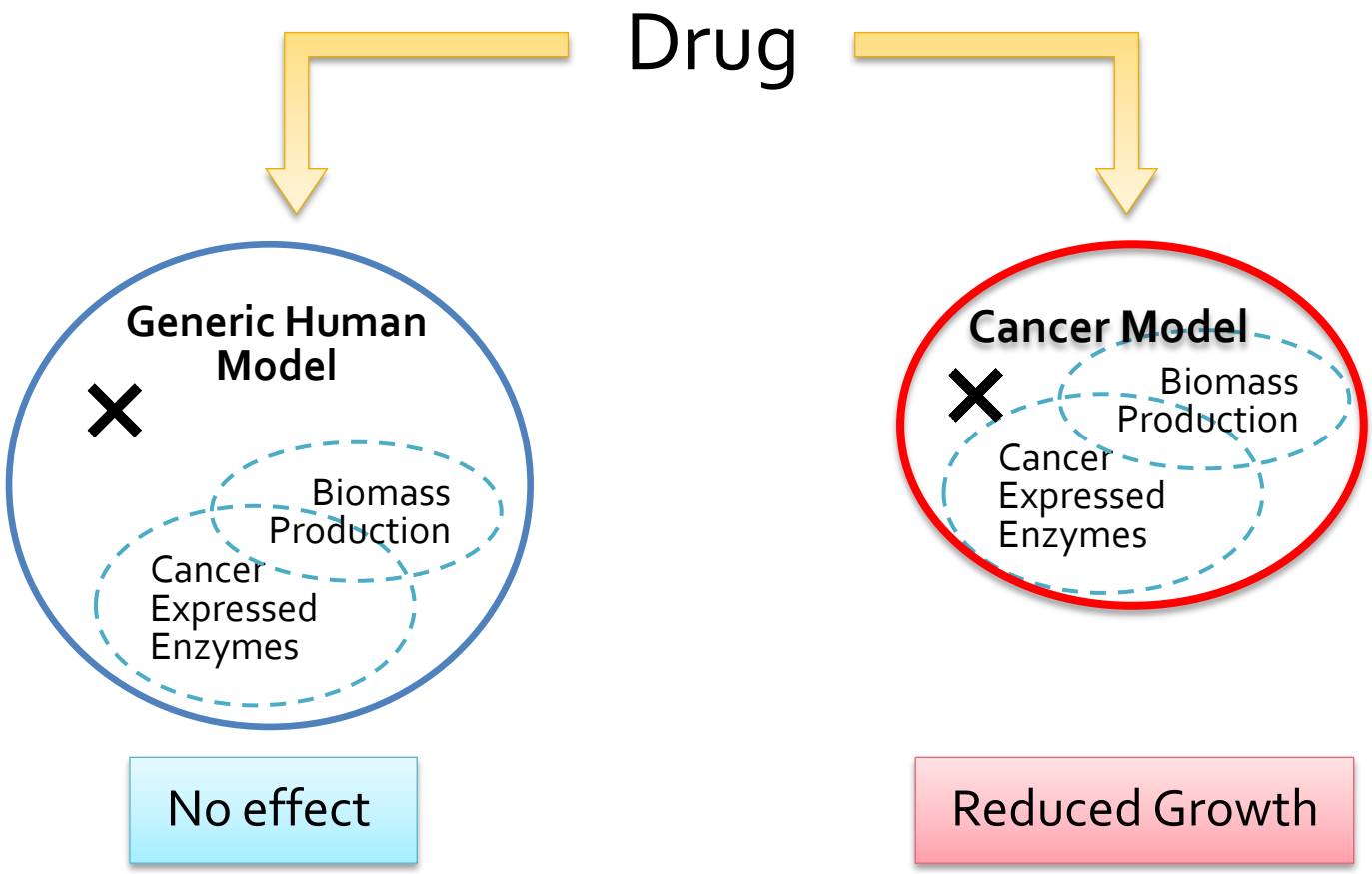
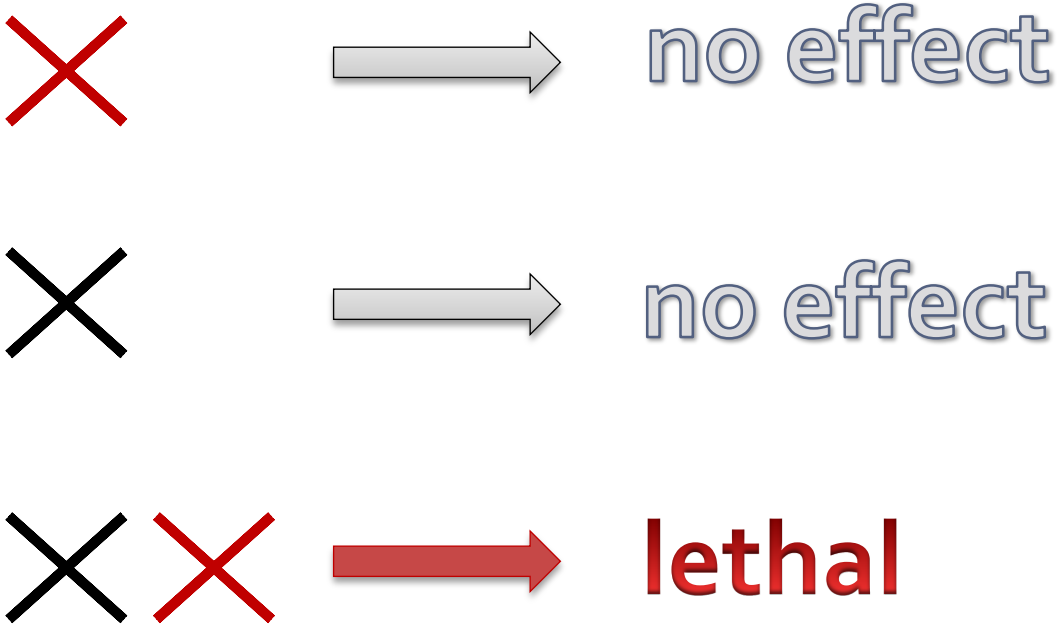


Computationally Identify Synthetic Lethal Pairs



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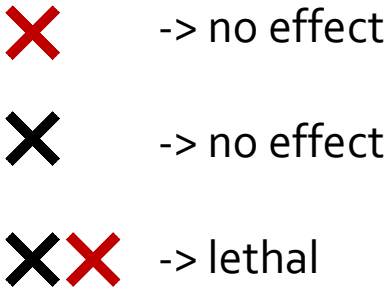
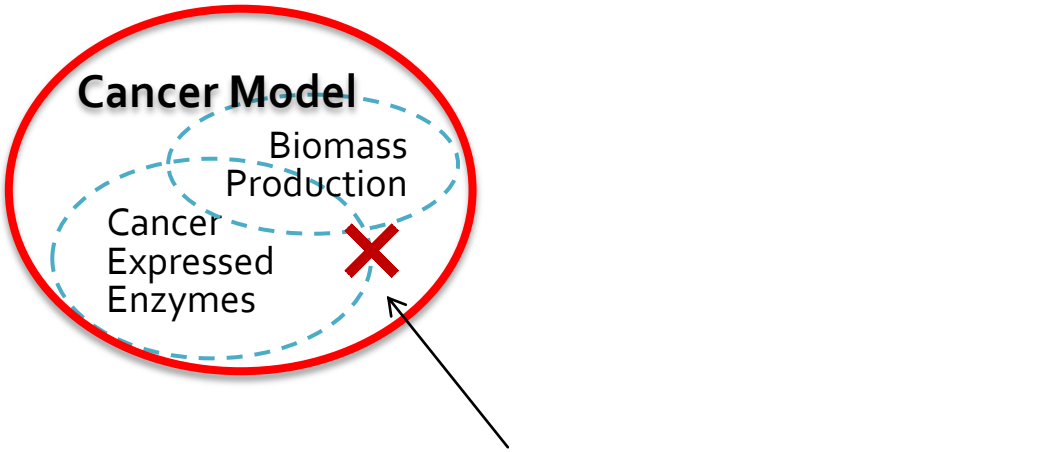


-> no effect

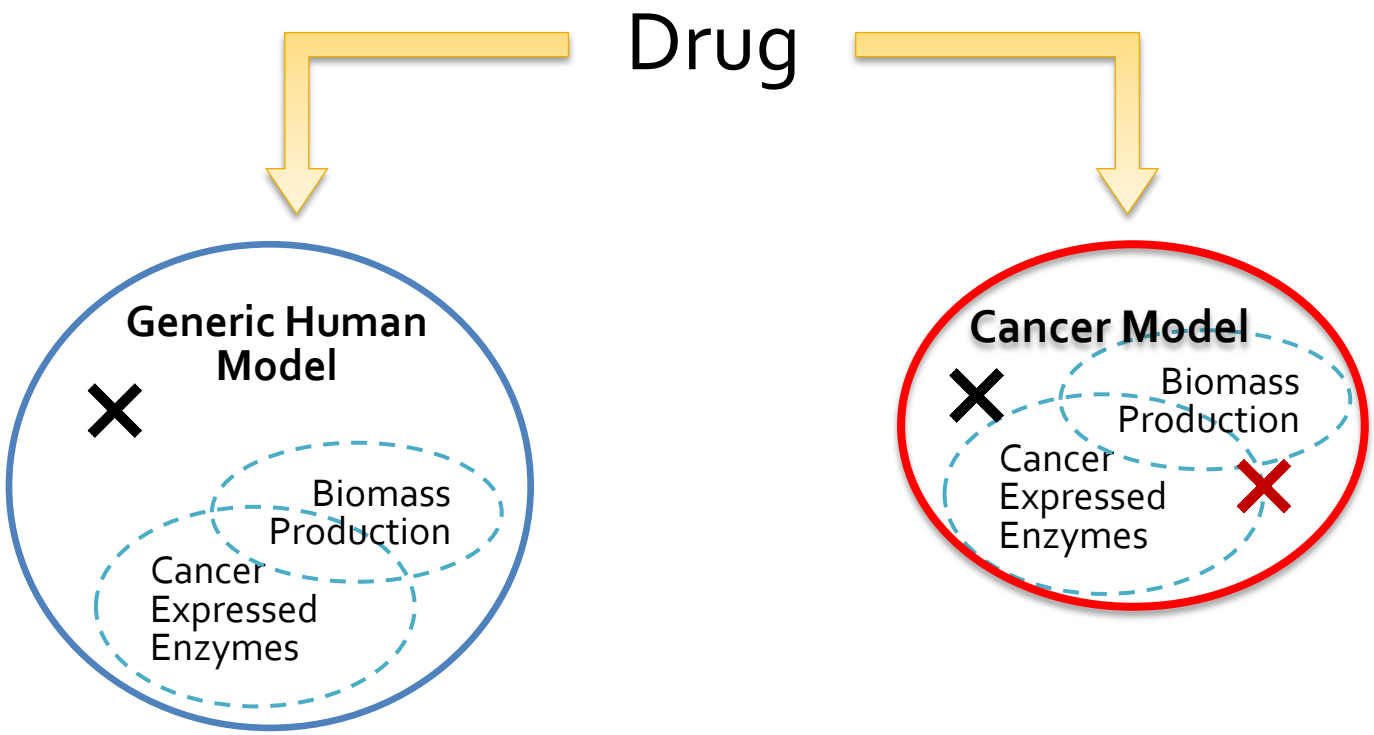
-> no effect

-> lethal



Additional information

Computationally Identify Synthetic Lethal Pairs



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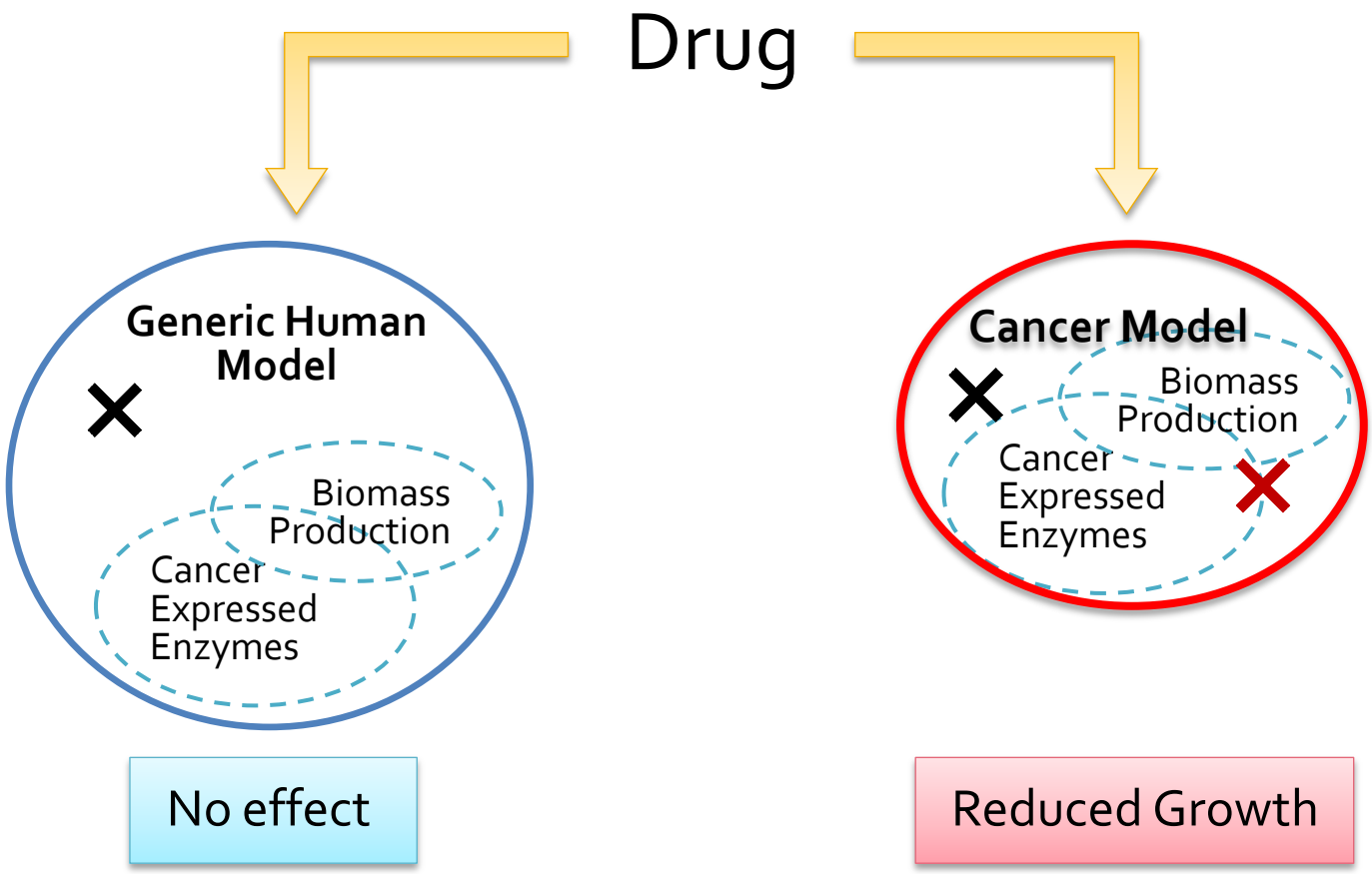
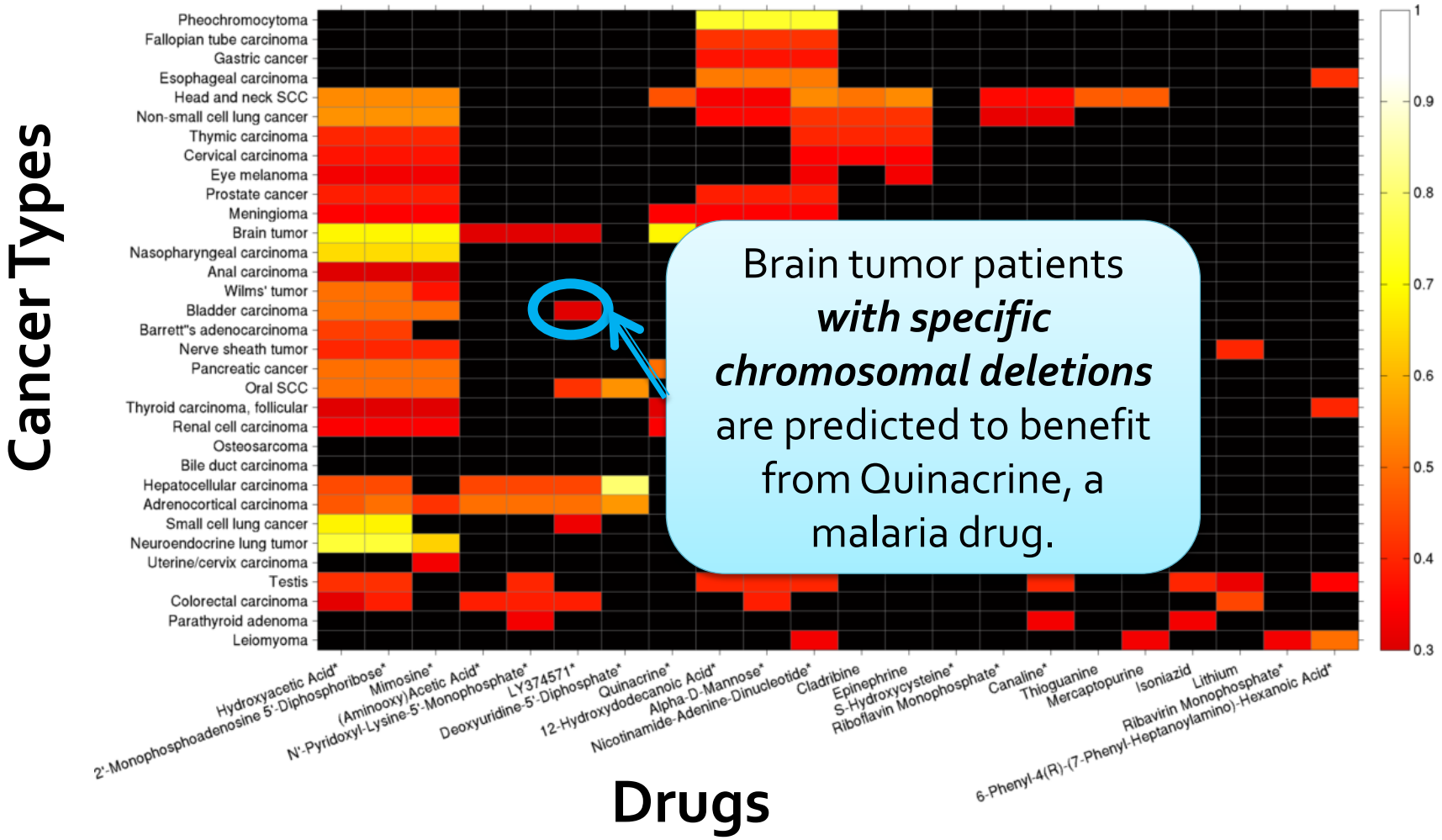
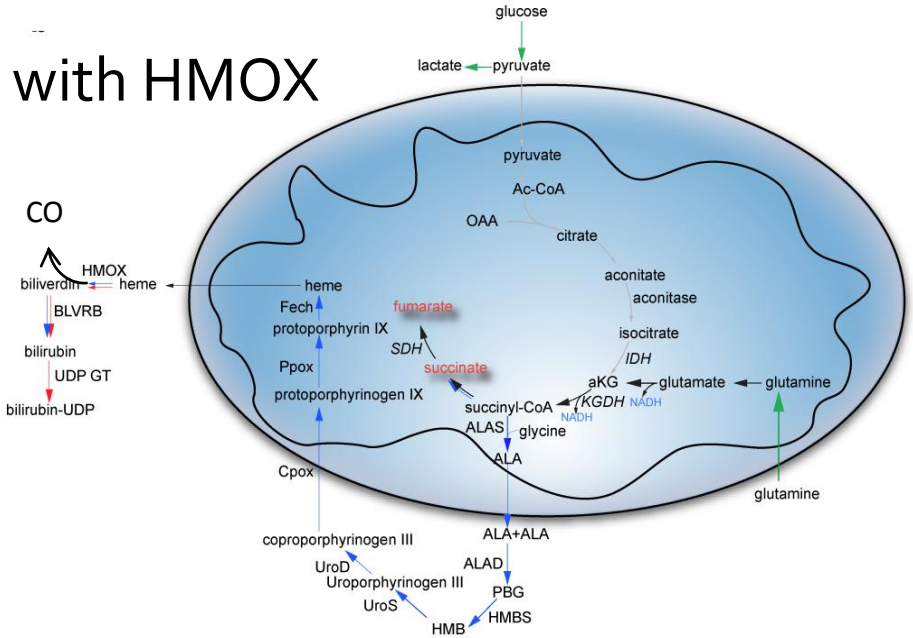


Synthetic Lethal Pairs as Potential Personalized Anticancer Therapy

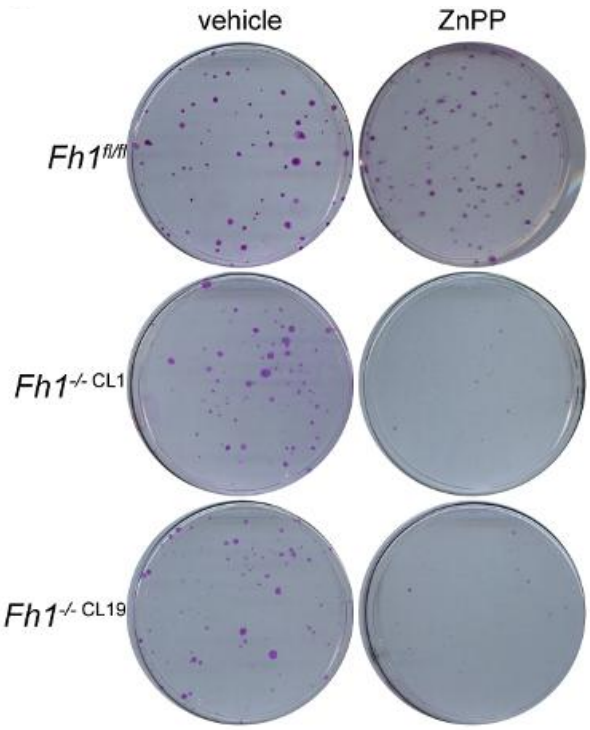


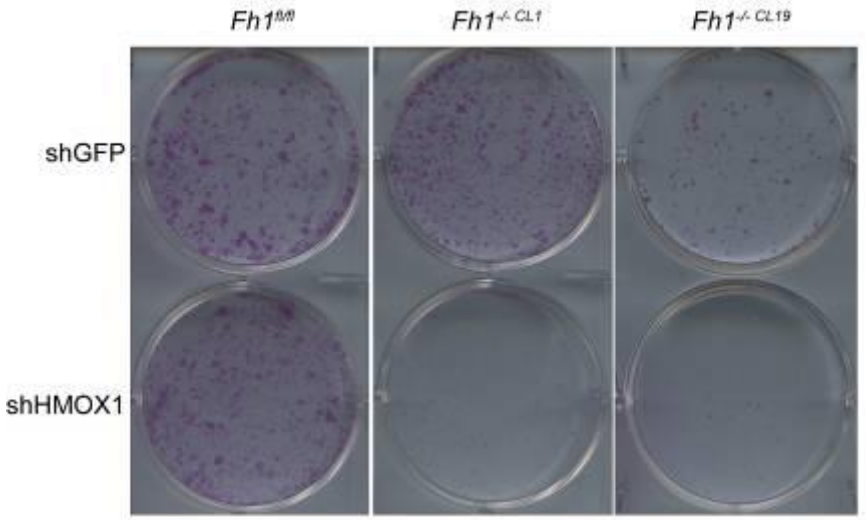
FH-deficient renal cancer

- Mutations in the metabolic gene Fumarate hydratase (FH) cause renal cancer
- Constructed a specific metabolic model of this cancer type
- FH found synthetically lethal with HMOX



HLRCC: Synthetic Lethality Validation





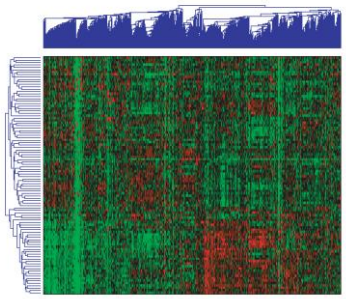
Personalized

"No disease suffered by a live man can be known, for every living person has his own novel, complicated disease, unknown to medicine"

Tolstoy

Method: Metabolic Profiling Analysis (MPA)

Gene expression

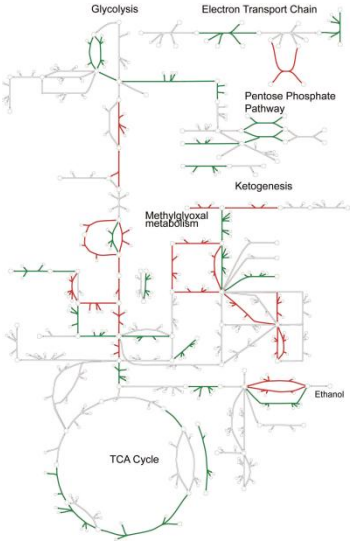


1

GPR

Gene-Protein-Reaction associations

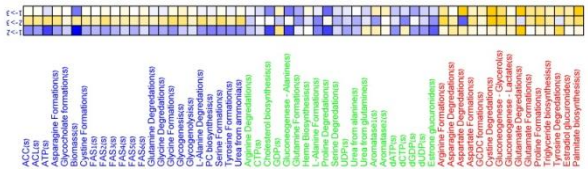
Reactions expression



2

Optimization

Maximize the fit to the expression



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Simulating various metabolic functions

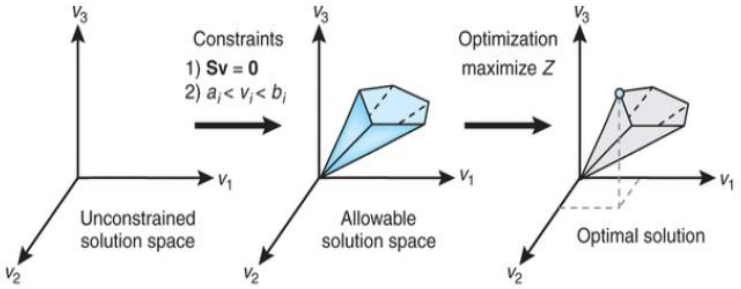
Metabolic Functionality

3

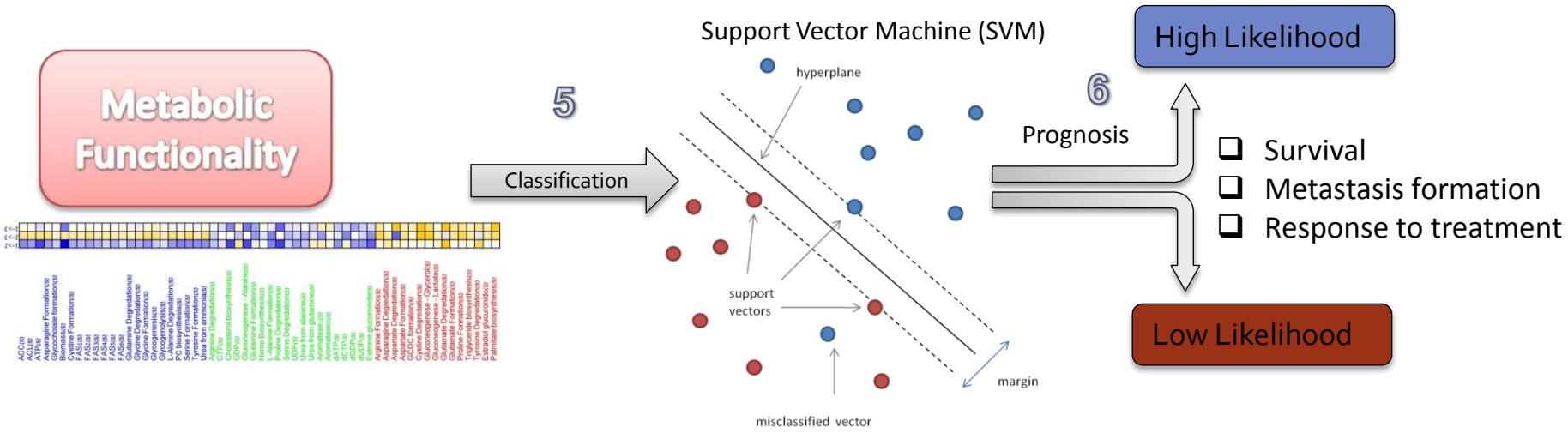
CBM

Constraints

- ❑ Thermodynamic
- ❑ Enzyme capacity
- ❑ Stoichiometric mass-balance



Phenotype Prediction Based on MPA Metabolic Profiles



- Conventional features - gene expression
- MPA replaces those with the metabolic profiles
- Metabolic profile
  - lipid metabolism
  - amino-acids biosynthesis

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THANK YOU

Questions?