Optimal Drug Cocktails for Intervention in Triple-Negative Breast Cancer Cell Motility via Feedback System Control

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Overview

Motivations

- 1/5 of patient deaths caused by breast cancer every year are attributed to triple-negative breast cancer (TNBC).
- TNBC poses a clinical difficulty with few treatment options.
- Extensive time and costs are required to determine effective drug combinations with multiple concentrations.
- Tumors may develop resistance to drugs.
- Drugs at high dosages pose toxic side effects.

Methods

- Select drugs to reduce cell motility and growth, and inhibit subsequent cancer metastasis.
- Feedback System Control (FSC)
  - two-level factorial design
  - response surface methodology

Results

- FSC efficiently identifies optimal drug cocktails with reduced time and resources.
- Optimal drug cocktails effectively treat TNBC at minimal dosages and have immense potential to save the lives of breast cancer patients.

Introduction

Breast Cancer Statistics

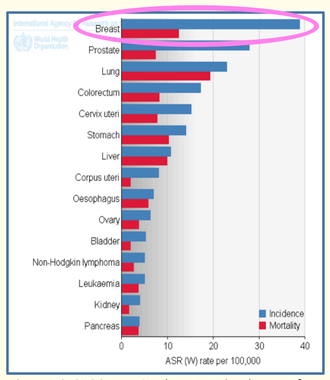
Over 1 million patients diagnosed annually.

More than 450,000 deaths in year 2008.

Globally, in women

- most frequently diagnosed cancer
- most common invasive cancer
- second-most common cause of cancer deaths

Age-Standardized Cancer Incidence and Mortality Rates: Both Genders



Source: GLOBOCAN project by International Agency for Research on Cancer, 2008.

Challenges

Most Types of Breast Cancer

- distinguished by the overexpression of three key membrane proteins/receptors:
  - estrogen receptor
  - progesterone receptor
  - Her2/neu receptor

Triple-Negative Breast Cancer (TNBC) Cells

- do not overexpress these three receptors
- do not respond to traditional receptor-targeted therapies

Solution

Targeted Inhibition by Drugs

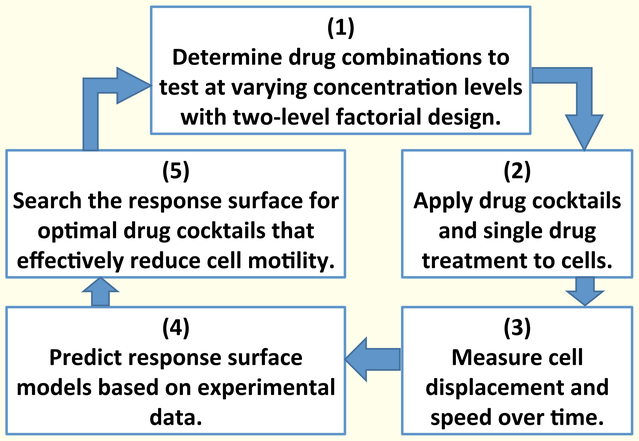
- Docetaxel – prevents microtubule assembly and disassembly
- Sirolimus – impairs a pathway regulating protein synthesis and cell growth
- Maraviroc – impedes virus entry into host cells

Drug Intervention in TNBC Cell Motility

- impede cell proliferation and migration
- prevent subsequent cancer metastasis

Methods

Feedback System Control (FSC)



Drug Treatment

Types of Drug Treatment

- drug cocktails vs. single drug treatment
- variable concentrations tested
  - minimum dosage: 0.01 μM
  - maximum dosage: 10.00 μM

Advantages of Optimal Drug Cocktails

- lowest drug concentration possible – limit potential toxic side effects
- multiple drugs – target several pathways, eliminate resistance that tumors may develop to one drug

FSC – Two-Level Factorial Design

Factorial Experiment

- Test all combinations of drugs, with each drug at varying concentration levels.
- Total number of drug combinations = $(\text{number of concentration levels})^{\text{number of drugs}}$

Two-Level Factorial Design

- Test 3 drugs, each at 2 concentration levels.
- $2^3 = 8$ total drug combinations tested.

FSC – Response Surface Methodology

Purpose

- Predict the response surface in the region of drug treatments studied.
- Search the response surface for the drug treatment that produces the optimal response.

Advantages

- Predict the effects of drug combinations that were not tested.
- Account for drug-drug interactions.
- One drug may promote or suppress the effects of another drug due to signaling by downstream effectors in targeted pathways.

First-Order Model for 3 Drugs

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{23} x_2 x_3 + \beta_{13} x_1 x_3 + \varepsilon$$

Second-Order Model for 3 Drugs

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{33} x_3^2 + \beta_{12} x_1 x_2 + \beta_{23} x_2 x_3 + \beta_{13} x_1 x_3 + \varepsilon$$

General Second-Order Model for *k* Drugs

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i=1}^{k-1} \sum_{j=i+1}^{k} \beta_{ij} x_i x_j + \varepsilon$$

Variables

y = cell displacement or speed

x = drug concentrations

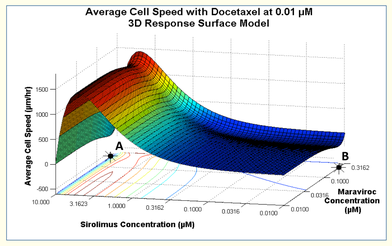
$\beta_{ij} x_i x_j$ = interaction term, effects of one drug on the performance of another drug

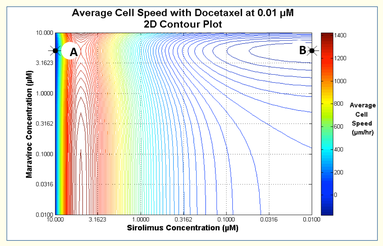
Results

Docetaxel at 0.01 μM

A: Sirolimus 10 μM, Maraviroc 5.01 μM

B: Sirolimus 0.01 μM, Maraviroc 5.01 μM (optimal drug cocktail)

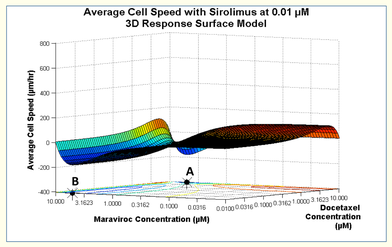


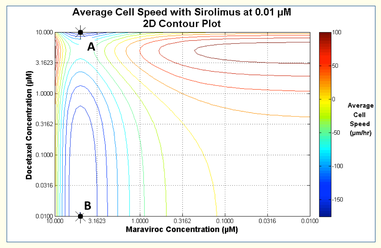


Sirolimus at 0.01 μM

A: Docetaxel 10 μM, Maraviroc 5.01 μM

B: Docetaxel 0.01 μM, Maraviroc 5.01 μM (optimal drug cocktail)

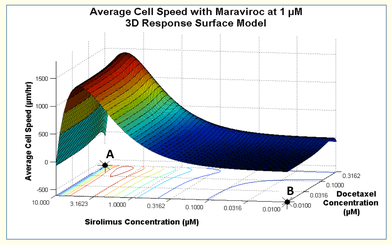


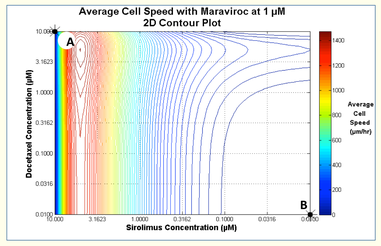


Maraviroc at 1 μM

A: Docetaxel 10 μM, Sirolimus 10 μM

B: Docetaxel 0.01 μM, Sirolimus 0.01 μM





Discussion

Response Surface Models

- Point "A" – drug treatment
  - minimum cell displacement and speed
  - two drugs applied at high concentrations
- Point "B" – optimal drug cocktail
  - next lowest cell displacement and speed
    - predicted cell displacement: -4,378.76 μm
    - predicted cell speed: -175.15 μm/hour
  - the most drugs at low concentrations
    - Docetaxel and Sirolimus at minimum concentration: 0.01 μM
    - Maraviroc at medium concentration: 5.01 μM
  - reduces the potential side effects and toxicity caused by high drug dosages

Drug cocktails with lower concentrations are more effective than single drug treatment at high concentrations.

Conclusions

Cell motility can be more efficiently reduced by an optimal drug cocktail at lower concentration levels, than by a single drug at a high concentration.

- Reduce drug resistance that TNBC tumors may develop to one drug.
- Simultaneously inhibit multiple molecular assemblies that affect TNBC.
- Reduce toxic side effects caused by high dosages.

Drugs were selected to reduce cancer metastasis.

- Target pathways involved in cell motility and proliferation.
- Eliminate the need for receptor-targeted therapies that are ineffective for TNBC tumors.

FSC with response surface methodology rapidly pinpoints optimal drug cocktails.

- Model the predicted response surface based on experimental data.
- Predict the efficacy of un-tested drug treatments.
- Reduce the time and resources needed to test all possible drug combinations.

Future Work

Advanced searches for drug treatment

- Treat cancers and disorders in addition to TNBC.
- Screen large drug libraries.
- Rapidly accelerate patient diagnosis and treatment with efficient searches.

Broader drug search library

- Test additional drugs and dosage levels.
- Enable more accurate predictions by response surface models.

Orthogonal Array Composite Design (OACD)

- OACD comprises two-level factorial design and three-level orthogonal array.
- Among all possible combinations, only combinations selected by OACD are tested.

Improved response surface model

- Power transform with Box-Cox transformation.
- Stabilize variance and tend towards normal distribution of data.

Confocal microscopy

- Analyze drug-induced damage by reconstructing 3D images of cytoskeletons.
- Evaluate structural morphologies over time.

Acknowledgements

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