Use of the Virtual Patient Technology to Improve Drug Safety: A Personalized Medicine Test Case

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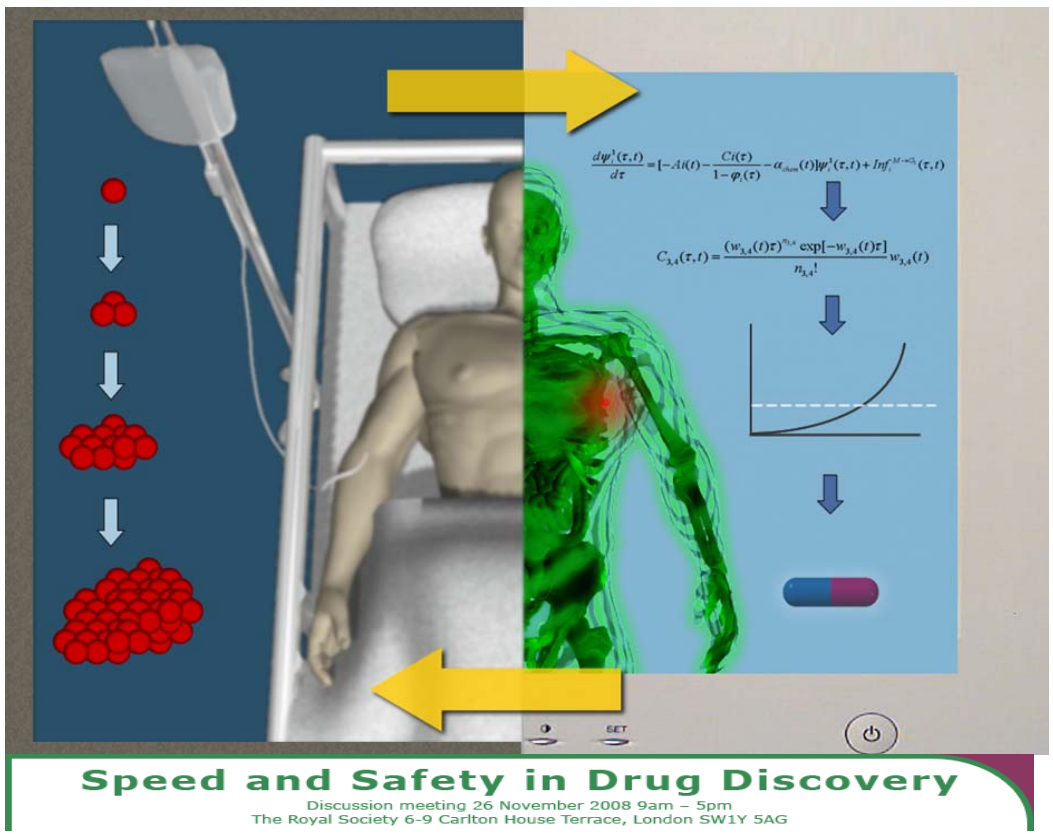
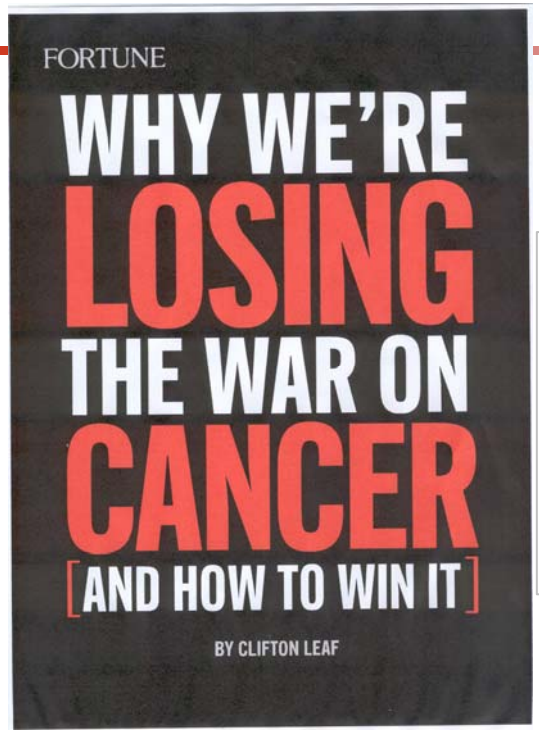


Agenda

- Problem: Research on intracellular interactions does not suffice for forecasting patient response
- Solution: BioMathematics relates molecular changes to their effects on the patient
- Method: Use Biomaths to construct Virtual Patient(s)
- Clinical validation:
  - Efficacy
  - safety
- Use:
  - i) drug development,
  - ii) treatment personalization,
  - iii) new response biomarkers

Need To Predict Effects Of Intra-cellular Interactions On The Whole Organism



WHY THE NEW DRUGS DISAPPOINT

FLAWED MODELS FOR DRUG development. Obsession with tumor shrinkage. Focus on individual cellular mechanisms to the near exclusion of what's happening in the organism as a whole. All

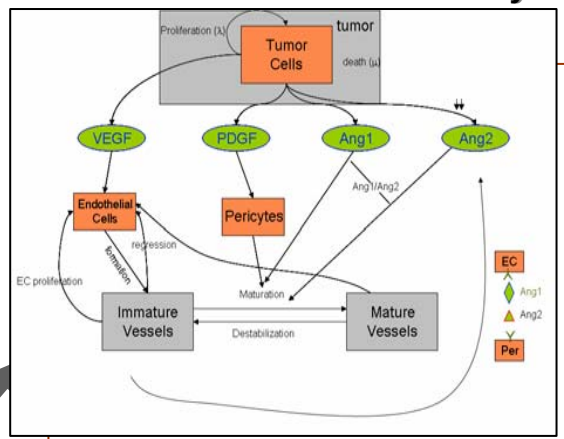
March 22, 2004

Predicting drug safety is enabled by predicting the effects of short-range interactions on the safety of the whole organism in the long-range

Optimata's Virtual Patient® Technology (OVP)

- *Preclinical (in vitro, xenograft, biomarkers)*
- *Clinical data of patient examinations (biochemical, immunological, genetics profile, tumor dynamics).*

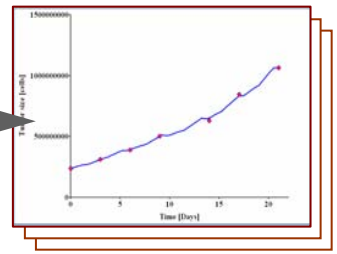
Efficacy modules



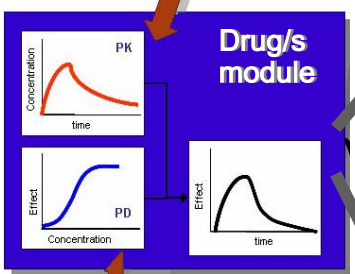
RCC module

NSCLC module

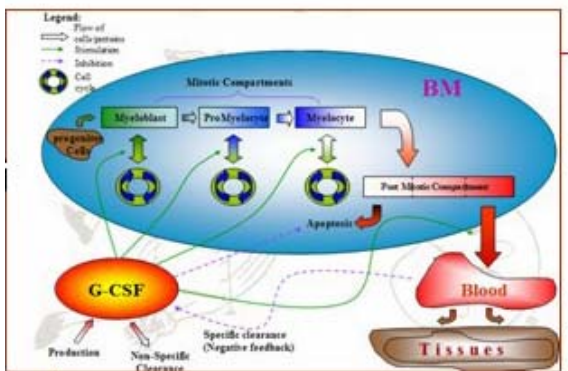
Predict efficacy



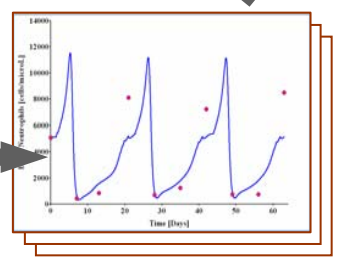
Preclinical and clinical PK data



Preclinical (in vitro, xenograft, biomarkers) and clinical PD data

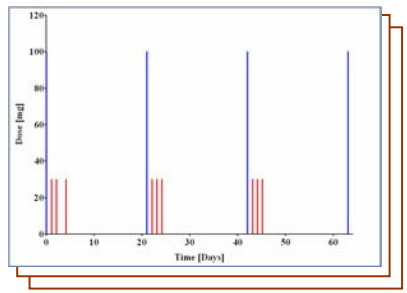


Predict toxicity & adverse effects



Safety modules

Optimize schedule



Preclinical biomarkers
Clinical trials patients individual biomarkers (biochemistry, hematology, immunology, genetics profile).

OVP Efficacy Validation in Metastatic Breast Cancer (MBC)

PRESS RELEASE
Tuesday 10 October, 2006

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"VIRTUAL CANCER PATIENT" PREDICTS HOW BREAST CANCER PATIENTS RESPOND TO TREATMENT

A computer generated "virtual cancer patient" can predict how patients with advanced breast cancer respond to treatment with 70 per cent accuracy, scientists reveal at the NCRI Cancer Conference in Birmingham today.

The team from Nottingham City Hospital, in collaboration with researchers at the Institute for Medical Biomathematics in Israel, undertook a pilot study on 33 patients with advanced breast cancer that had spread to the liver, lymph nodes or lungs. They used the cyber-patient, based on advanced mathematical models, to find out which drug out of two would work best in each patient, based on certain characteristics of their cancer, such as the size of their tumours and how fast they were growing.

In this retrospective study, part funded by Cancer Research UK, the Optimata "virtual cancer patient" (OVP) model accurately predicted how around 70 per cent of the patients responded to their treatment. In the future, technology like this could help doctors tailor treatment more accurately to ensure every patient receives the most appropriate therapy to treat their particular disease.

Accuracy of clinical response prediction was improved to r=0.79 (p<0.001);

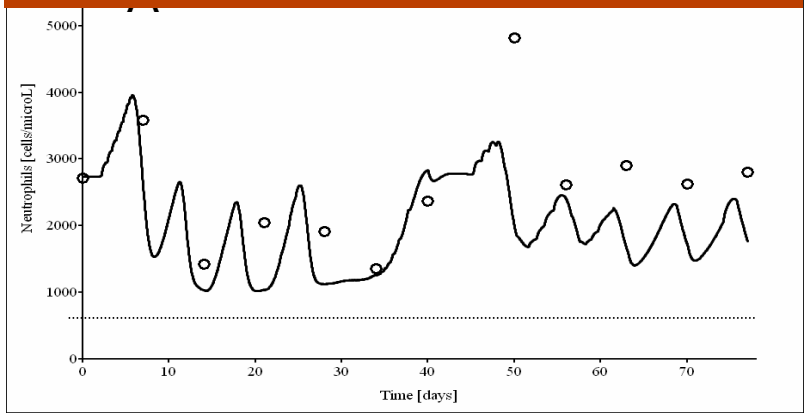
Clinical Validation Example in MBC: Toxicity

Method:

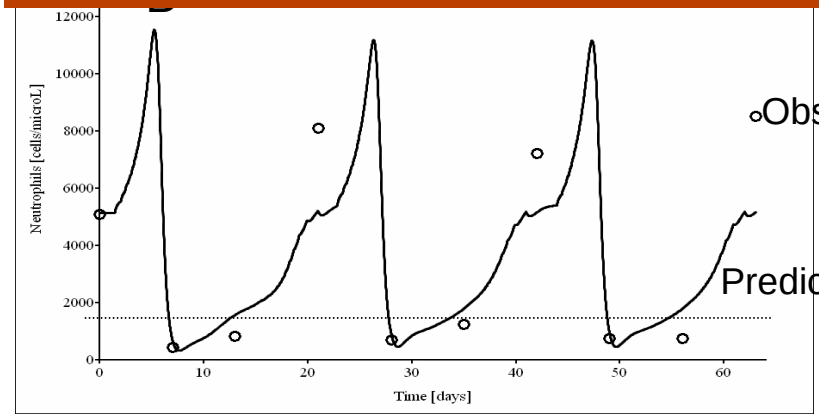
- Weekly blood counts were collected from 38 MBC patients from Nottingham City Hospital (NCH) UK, treated by DOC, 67-100 mg/m2, Q21D, N=18, and 23-35 mg/m2 , Q7D, N=20
- These were randomly divided into a training (N=12), and a validation set (N=26)
- Validation set included patients from NCH and Soroka University Medical Center, Israel
- Initial patient's data and treatment plan were input into the OVP and simulated to predict neutrophil profile for each patient in the validation set
- Neutrophil counts and neutropenia grade were predicted by the model and compared to the patients' counts at the corresponding time-points.

Clinical Validation Example in MBC
Toxicity Results

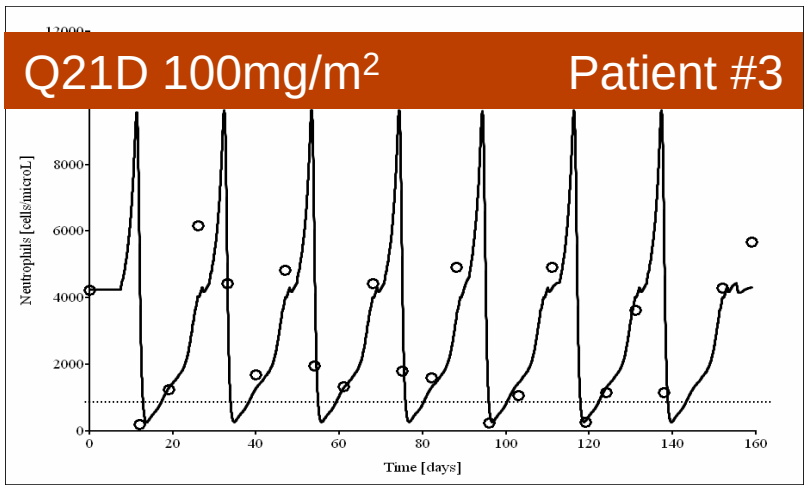
Q7D 25-35mg/m² Patient #1



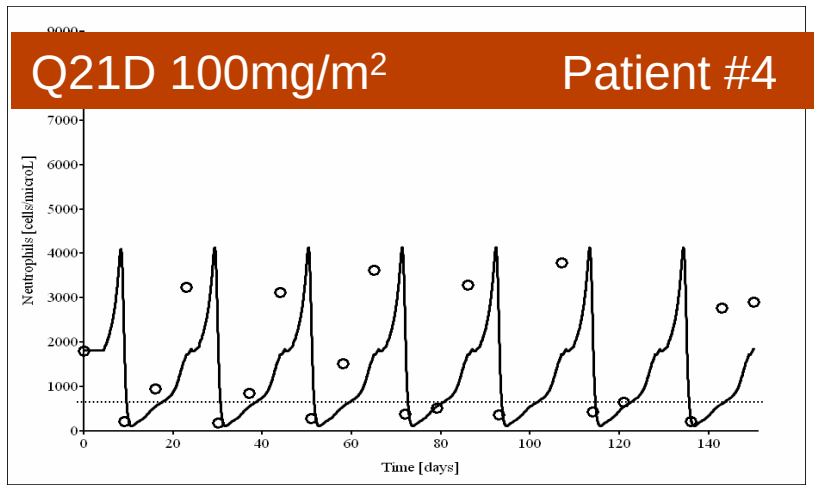
Q21D 100mg/m² Patient #2



Q21D 100mg/m² Patient #3

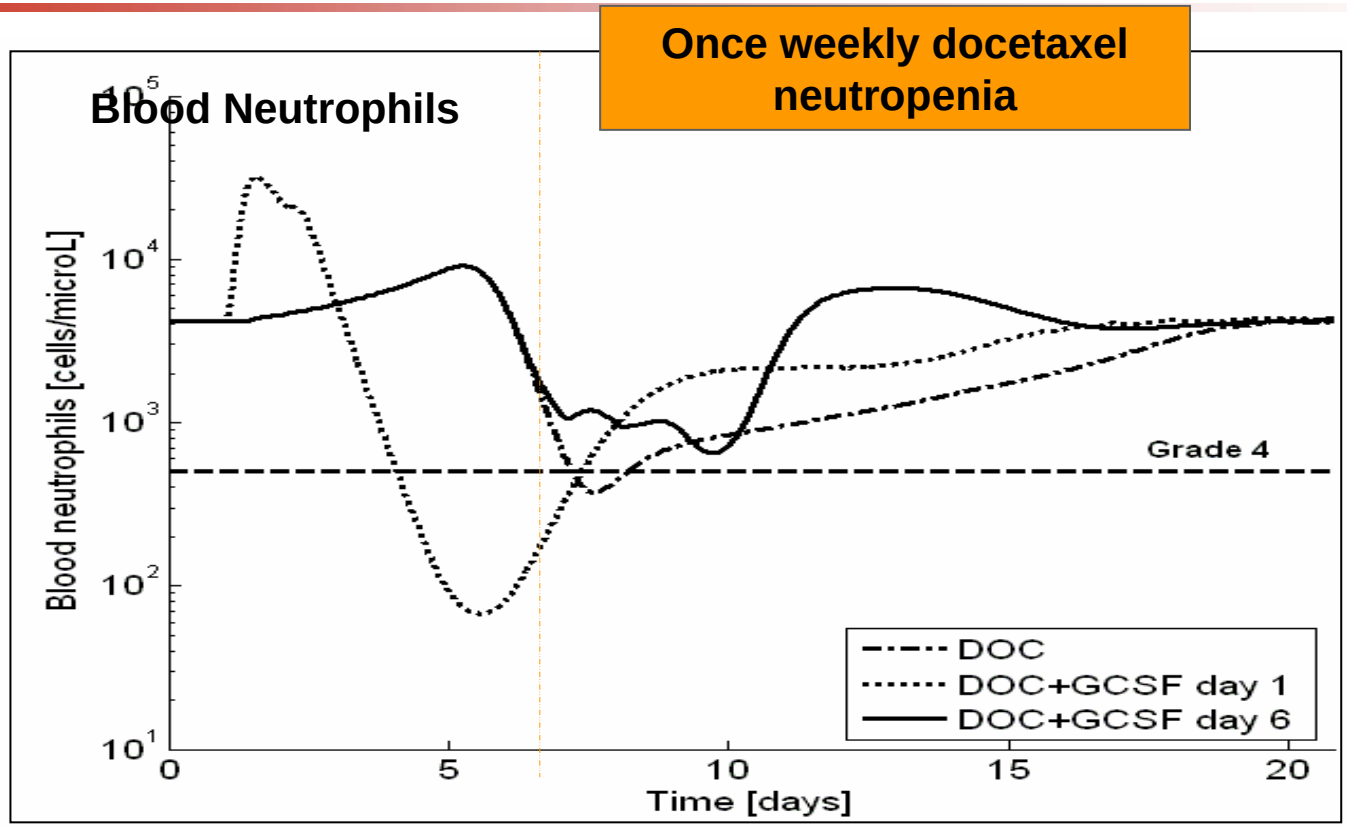


Q21D 100mg/m² Patient #4



Prediction of neutrophil profiles (solid lines) vs. observed neutrophil profiles (circles); results show highly significant precision in nadir time predictions **(r = 0.99);** grade 4 neutropenia was **correctly predicted in 81%** of the patients (21/26).

Timing of G-CSF support significantly affects the grade of DOC-induced neutropenia



•G-CSF applied **1** day post-DOC, before BM can recover, cannot compensate the post mitotic cell loss; next dosing is prevented

•G-CSF application **6** days post DOC causes only mild neutropenic response

Docetaxel and GCSF Regimens Calculator

Neutrophils Baseline (mean)	3050	Neutrophils/µl
Overall Treatment Duration	12 Weeks	

optimata
Navigating Drug Development

Docetaxel Dose (mg/m2)*

	Tri-weekly	Bi-weekly	Weekly
○	60	40	20
○	75	50	25
◉	100	67	33
○	125	83	42
○	150	100	50

* Each of the lines has the same dose intensity. In red, regimens that are not in clinical practice.

☑ GCSF Administration

	Tri-Weekly Docetaxel	Bi-weekly Docetaxel	Weekly Docetaxel
GCSF Onset (days) following Docetaxel	6	1	2
GCSF Dose (µg/day)	60	300	60
GCSF Duration (days)	3	5	2

Get Predictions

Expected Neutropenia

Docetaxel Dosing Interval	Per the Overall Treatment: Duration at Grade 3/4	Max Grade	Total GCSF (µg)	Per a Typical Docetaxel Cycle: Duration at Grade 3/4	Time of Nadir	Grade Before Next Administration
Tri-Weekly	18	4	720	5	10	0
Bi-weekly	18	4	9000	3	5	0
Weekly	18	3	1440	2	6	2

Virtual Patient for Treatment Personalization

Cancer Res 2008; 68: (21). November, 1 2008

A new treatment personalization method by combining:

- tumor xenografts
- OVP models

was use to suggest an improved treatment schedule for a Mesenchyma Chondro Sarcoma (MCS) patient

Mesenchymal Chondrosarcoma (MCS)

- MCS accounts for about 1% of all chondrosarcomas.
- Overall 5-year survival is 55%
- This disease usually follows an aggressive course with a high rate of distant metastases

The patient

- VN – a 45-year old white male in excellent health
- Growing mediastinal mass was found in 2004
- Primary tumor was resected
- Multiple new bilateral pulmonary nodules thirty days after the operation.
- Aggressive chemotherapy with Ifosphamide, cisplatin and etopisde for 6 cycles, VACA (vincristine, doxorubicin, cyclophosphamide, and dactinomycin) for 2 cycles, and sunitinib orally for 8 weeks
- Additional liver and bone metastases
- Severe myelosuppression with pancytopenia

Method

- Lung netastasis was biopsied
- Xenografted to mice
- Treated by many mono & combo regimens
- OVP prospectively predicted tumor growth inhibition (TGI) in xenografts
- Model upscaled to the patient
- Best treatment was predicted

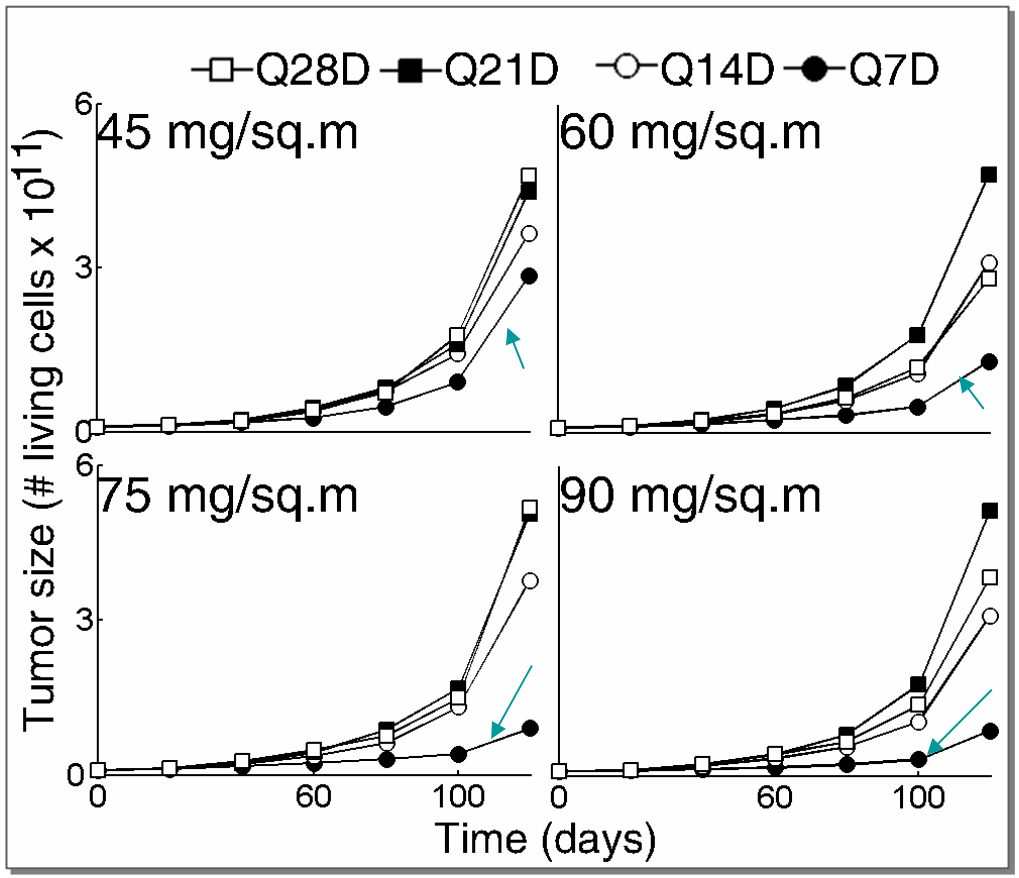
OVP predictions of treatment efficacy and prospective validation in xenograft experiments

	Regimen				Predicted Results (TGI[1])	Observed Results (TGI[1])	Accuracy
	Drug	Dose (mg/kg)	Route	Schedule			
1	Control				2.01	2.11	**94.8 %**
2	CPT-11	100	IP	Q7Dx3	57.2%	59.4 %	**96.2 %**
	Bevacizumab	10	IP	Q3Dx10			
3	Gemcitabine	40	IP	Q3Dx4	76.36%	109.3 %	**70.1 %**
	Docetaxel	6.3	IV	Q2Dx3			
	Bevacizumab	10	IP	Q3Dx10			
4	Doxorubicin	2	IV	QDx5	65.3%	56.4%	**84.2 %**
	Bevacizumab	10	IP	Q3Dx10			
5	Sorafenib	60	PO	QDx10	40.4%	38.9%	**96.1 %**
6	Sorafenib	60	PO	QDx10	71.0 %	87.2 %	**81.4 %**
	Bevacizumab	10	IP	Q3Dx10			

[1]Tumor Growth Inhibition

Average prediction accuracy: 87.2 %

Treatment Personalization – Predictions of improved schedule in the MCS patient



Regimens containing Bevacizumab applied intravenously in combination with once-weekly Docetaxel are predicted more efficacious in the MCS patient than all other simulated Docetaxel schedules.

Gorelik et al, 2008

Treatment Personalization – Predictions

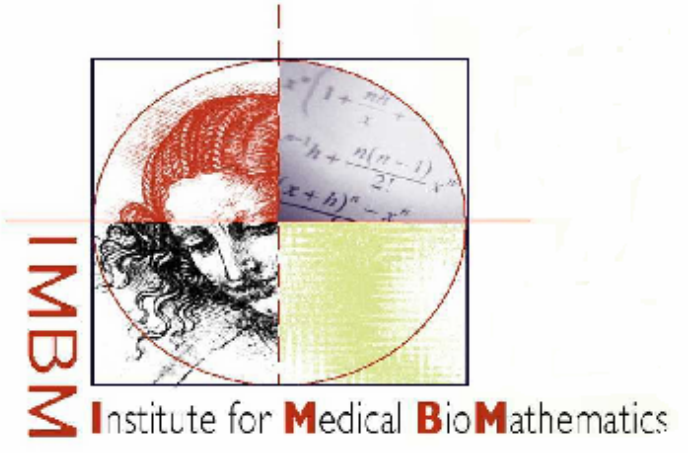
Weekly Docetaxel in the patient resulted in stable metastatic disease and relief of pancytopenia, due to tumor infiltration.

The advantage of weekly Docetaxel on the tri-weekly regimen is directly related to the tumor's angiogenesis rate.

Gorelik et al, 2008

Summary

- ✓ Virtual Patient technology formalizes complex drug-patient interactions
- ✓ Successful validation enables technology to be employed for identifying improved regimens & indication
- ✓ A successful treatment personalization endeavor improves patient's survival and quality of life
- ✓ Once weekly Docetaxel inflicts significantly lower neutropenia; G-CSF should be applied 6D post chemo
- ✓ Once weekly Docetaxel is more efficacious for patients with intense angiogenesis



Thank You

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