Virtual Tumour Clinical: Literature Example

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Introduction

Combination therapies of targeted agents with generics and/or radiotherapy in oncology are becoming more widespread within the pharmaceutical industry as healthcare providers ask for "game-changing" improvements in response and survival rates at an affordable price. In order to obtain substantial breakthroughs in survival rates, clinical investigators are looking at increasingly complex schedules that are challenging to optimise[1]. Virtual Tumour clinical is being developed to tackle this issue by providing clients with dosing and schedule options that should help improve the success of phase III studies.

Pre-clinical to Clinical Virtual Tumour

Virtual Tumour is a dynamical mathematical model of a growing tumour[2,3]. Our pre-clinical model is able to:

- distinguish between proliferating and necrotic tissue;
- consider cell-cycle heterogeneity.

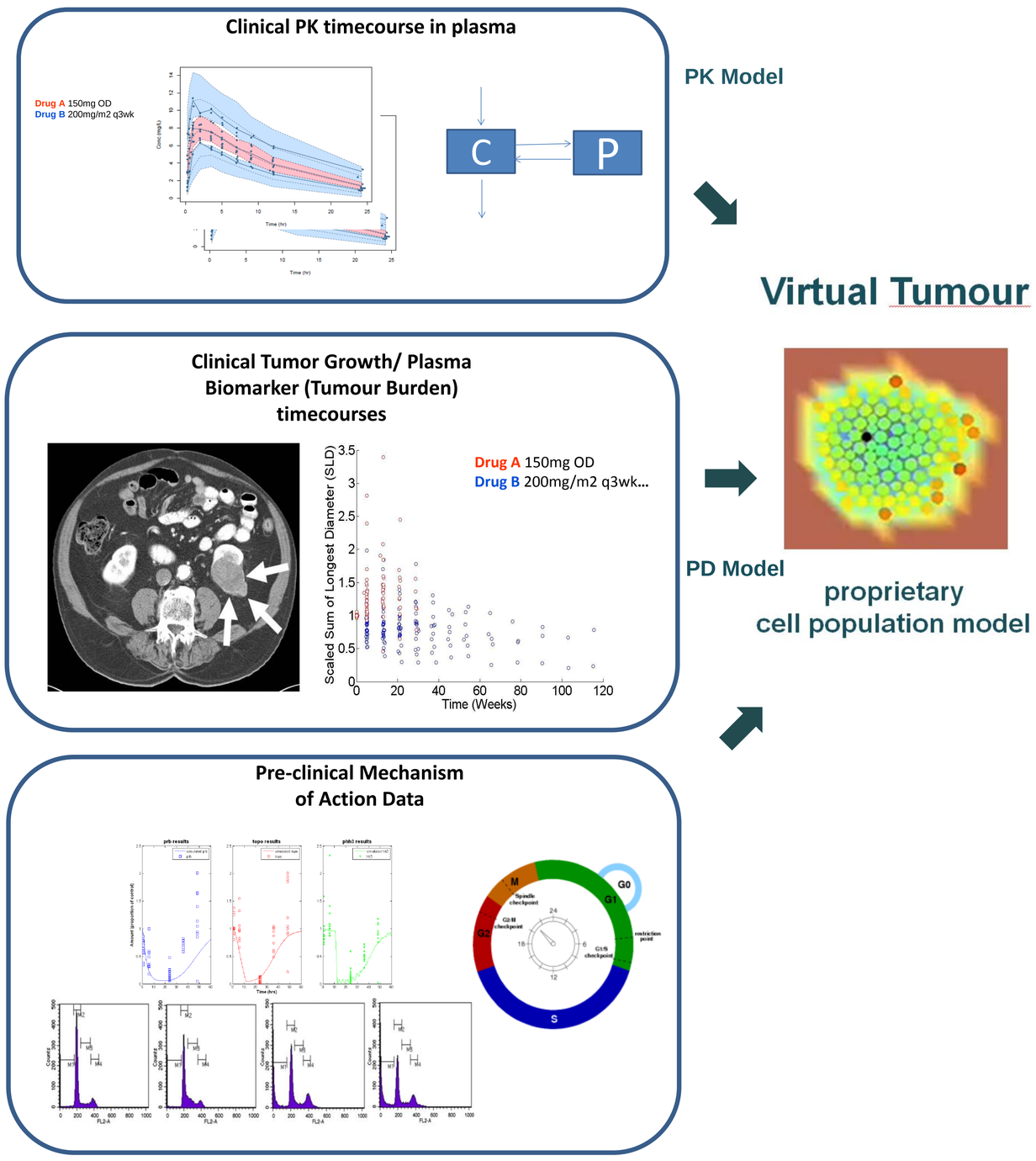
Moving from our successful pre-clinical model to the clinic will most likely require a number of changes as there are a large number of differences between xenografts and human tumours. For Virtual Tumour clinical we are currently considering the following differences:

- doubling times;
- genetic heterogeneity:
  - consider different drug effects on different tumour cells;
  - resistance development;
- structure.

The main output of Virtual Tumour clinical will be parameters related to tumour burden such as the sum of longest diameters (SLD) and plasma biomarkers of tumour burden (e.g. PSA, M65 etc.). The temporal dynamics of these markers have recently been shown to correlate with survival across a number of disease areas[4,5,6].

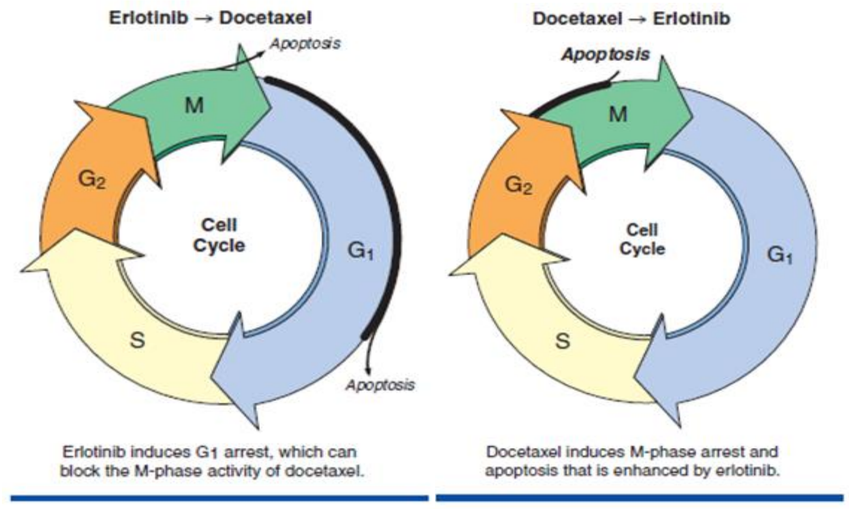
Physiomics' Virtual Tumour technology

The Clinical Virtual Tumour takes as input the following data sets:



Example: Erlotinib + Docetaxel in NSCLC

There are a number of reported phase III failures (no overall survival benefit) involving EGFR tyrosine kinase inhibitors in combination with chemotherapy[7]. An hypothesis as to why the combination worked so well pre-clinically but not clinically has centred around the drugs effects on the cell-cycle[7]:



VT clinical is an ideal technology to explore sequencing/scheduling effects mentioned here. Standard PKPD approaches struggle to account for synchronisation and de-synchronisation effects accurately.

Methods

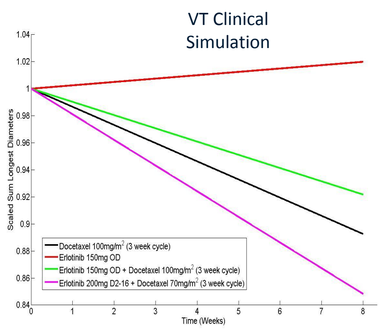
A recent survival model has suggested that changes in tumour size at week 8 may well be predictive of survival in addition to other baseline factors[8]. Therefore we looked at this metric for model calibration and validation.

In order to calibrate Virtual Tumour clinical we extracted the following information from the literature:

- doubling times of NSCLC;
- effect on the cell-cycle for each drug;
- estimate of the amount of tumour shrinkage of each compound in isolation;
- tumour shrinkage effect of the combination was not available but we assumed it to be no better than docetaxel alone since the combination showed no survival advantage over monotherapy.

Results

Once calibrated we simulated/predicted what the effects of tumour shrinkage were likely to be for a novel intercalated schedule which has reported a remarkable survival statistics in a phase II study[9].



Drugs	Schedule	Calibration /Prediction	VT Clinical Ranking	Clinical Ranking Response Rate[9]
Docetaxel + Erlotinib	70mg/m2 Day 1 + 200mg Days 2-16 (3 week cycle)	Prediction	1	1
Docetaxel	100mg/m2 Day 1 (3 week cycle)	Calibration	2	=2
Docetaxel + Erlotinib	100mg/m2 Day 1 + 150mg OD (3 week cycle)	Calibration	3	=2
Erlotinib	150mg OD	Calibration	4	3

Conclusion

Our initial attempt at bridging our Virtual Tumour technology from the pre-clinical to clinical arena appears to be promising. We are able to qualitatively show that certain schedules already explored in the clinic for EGFR inhibitors in combination with chemotherapy can lead to very different outcomes depending on the sequence used. Sequencing effects are likely to play a significant role in improving the use of targeted therapies.

References:

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