# Virtual Tumour Clinical development, part I: translational modelling of docetaxel-thalidomide combination treatment in metastatic, castrate-resistant prostate cancer

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## Introduction

A major cause of drug failure in the clinic is that preclinical studies do not predict with sufficient certainty what will happen in human. Accurately translating information from animal studies to the clinic would have a major impact on attrition rate.

We have developed a mathematical model of a tumour cell population called Virtual Tumour, which has been extensively used to predict the efficacy of single drug or drug combination treatment in preclinical studies. We have now extended and adapted our model to apply to the clinic. Here we report the early stages in creating this 'Virtual Tumour Clinical'. The development history is continued in the companion poster (I-32).

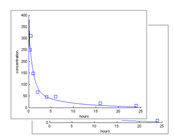
We show the translational capability of the model within the prostate cancer setting by looking at two monotherapies and their combination[1,2,3]. We attempt to relate clinical changes in PSA to preclinical changes in tumour volume. Preclinically it has been shown that changes in PSA do relate to changes in tumour volume in both the docetaxel naïve and resistant setting[4]; however, this has not been shown within the clinic.

## The Physiomics Virtual Tumour Technology

The Virtual Tumour[5] takes as input the following data sets:

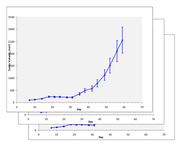
**PK time course in tumour/plasma**

Drug A 50mpk
Drug B 60 mpk



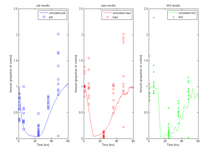

**Preclinical tumour growth**

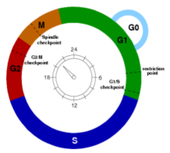
Control
Drug A 50mpk qdx21
Drug B 60 mpk q3dx7
Drug B 150 mpk q3dx4
…



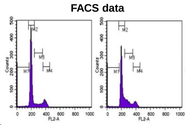
**Preclinical mechanism of action data**

Biomarkers

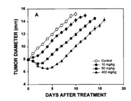




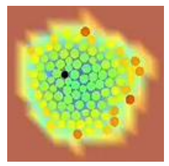

FACS data



Selected literature data




Virtual Tumour

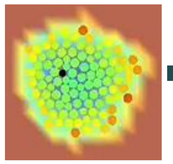


Proprietary cell population model

The Virtual Tumour simulations and predictions can be used to design and simulate new, rational experiments by ranking combinations and dosing schedules in specific tumours. This allows researchers to eliminate unnecessary and redundant experiments/clinical studies, thus reducing the amount of animal and human studies.

## Virtual Tumour Clinical Model Development

Preclinical Virtual Tumour

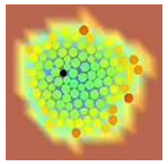


Proprietary cell population model

➡ **Literature data across numerous tumour types:**

- Size of viable cell pool
- Ki67: % proliferating
- Cleaved caspase 3: % apoptotic
- Growth and decay rates of clinical tumours
- Variability in durations of cell-cycle phases

Clinical Virtual Tumour



Proprietary cell population model

## Clinical & Preclinical Data

Clinical data: PSA time-series for docetaxel[2] (n = 25, 30 mg/m2 weekly), thalidomide[1] (n = 53, 200 mg once daily), docetaxel/thalidomide (n = 50)

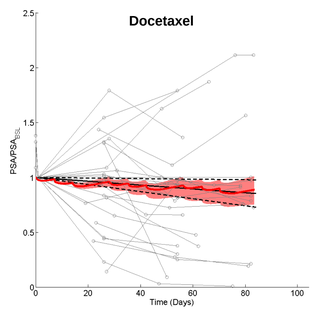
Preclinical data: PC-3 xenograft data for docetaxel[3] (10 mg/kg), thalidomide[3] (100 mg/kg), docetaxel/thalidomide[3].

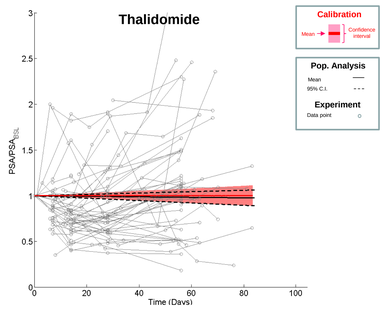
## Stage 1 – Clinical Prediction

**Step 1** – Analyse clinical data using population analysis approach (monotherapy)

Literature-sourced PK models used

**Step 2** – **Calibrate** Virtual Tumour to the mean clinical signal (monotherapy)



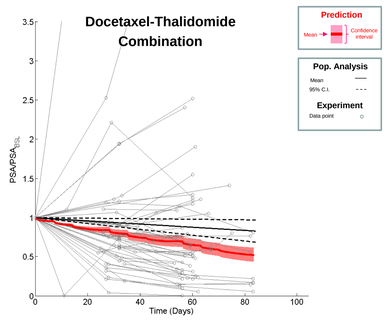




**Step 3** – **Predict** combination behaviour (right panel)

**Step 4** – Analyse clinical data using population analysis approach (combination)

**Step 5** – Compare prediction with actual result







**Results: model correctly predicts the qualitative result observed in the clinic; i.e. response rates for combination better than for monotherapy.**

## Stage 2 – Clinical-Preclinical Translation

**Step 1** – **Calibrate** Virtual Tumour to both monotherapy and combination mean clinical signal:

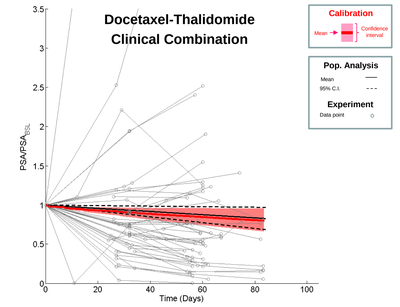
Preclinical PK model sourced from literature

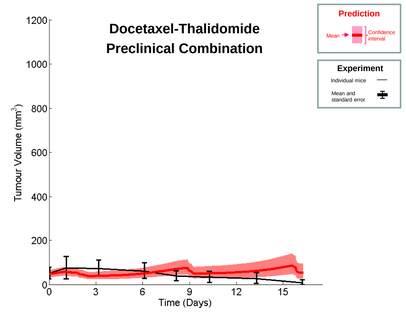
To capture the combination effect better we adjust the growth rate and how quickly the Virtual Tumour can shrink when under treatment

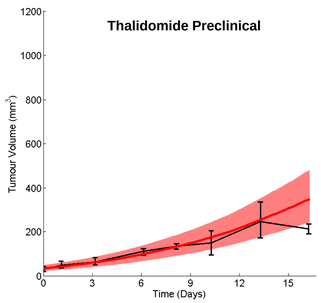
**Step 2** – Switch clinical growth settings for preclinical growth settings

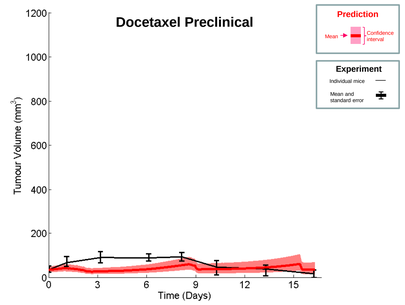
**Step 3** – **Predict** preclinical monotherapy and combination effects

**Step 4** – Compare prediction with actual result




**Results: model makes accurate quantitative back-translational predictions for both the monotherapy and combination studies.**

## Conclusions

We have demonstrated that even in the early stages of Virtual Tumour Clinical development, the model had the ability to relate preclinical tumour size changes to clinical PSA changes within the castrate-resistant prostate cancer setting. However, while successful qualitative predictions of clinical response rates were made from clinical monotherapy data, these predictions were not quantitatively accurate. Thus we embarked on a further phase of development, as documented in our companion poster (III-24), culminating in the successful translation of clinical response in metastatic melanoma from preclinical monotherapy data.

**References**

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4. E.S. de Morree *et al.* (2013), Cabazitaxel antitumour activity in docetaxel-resistant patient-derived prostate cancer xenograft models. *AACR 104th Annual Meeting* , Abstract 316.
5. D. Orrell and E. Fernandez (2010), Using Predictive Mathematical Models to Optimise the Scheduling of Anti-Cancer Drugs, *Innovations in Pharmaceutical Technology*, p59-62.