Virtual Tumour Clinical development: translational modelling of vemurafenib, selumetinib and docetaxel in metastatic melanoma

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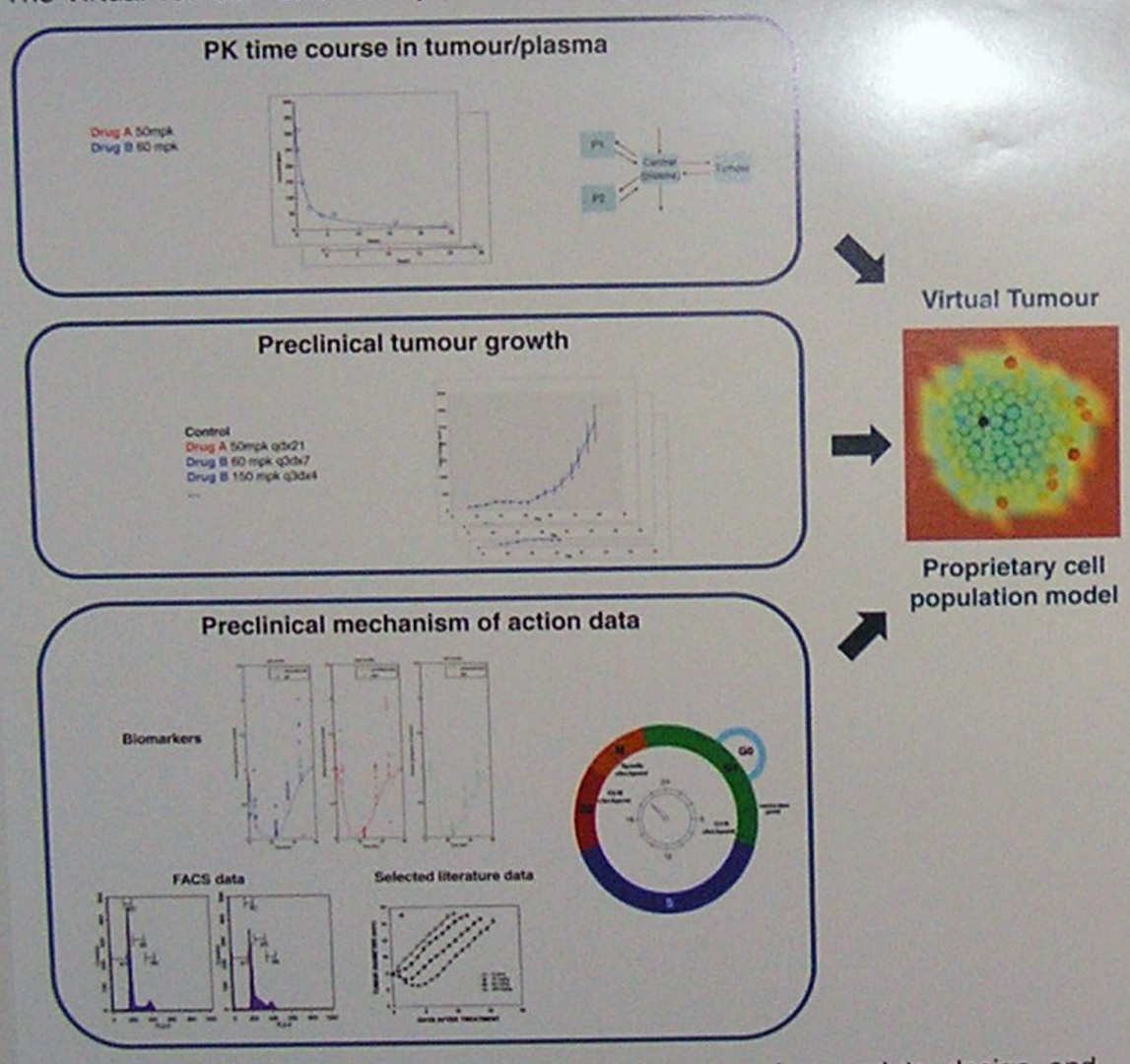
Introduction

The translation of results from animal to man is a key phase in oncology drug development. Being able to determine the doses at which to start taking key biopsy measurements and when we expect to start seeing efficacy are important for a successful evaluation of a new drug within early clinical development. Furthermore, being able to accurately translate combination schedules from mouse to man would provide significant cost savings and speed up clinical development times.

Here we show two sets of results highlighting the translational predictivity of Virtual Tumour[1] Clinical. The first example highlights the back-translational capabilities of the model for vemurafenib, where we train the model to clinical data[2] and determine whether we can predict the outcome in xenografts studies[3]. The second example looks at using the model for forward translation: we train the model to preclinical monotherapy data[4] only for docetaxel and selumetinib, and assess whether we can predict the efficacy of both arms of a recent phase II trial[5] assessing the combination versus docetaxel monotherapy.

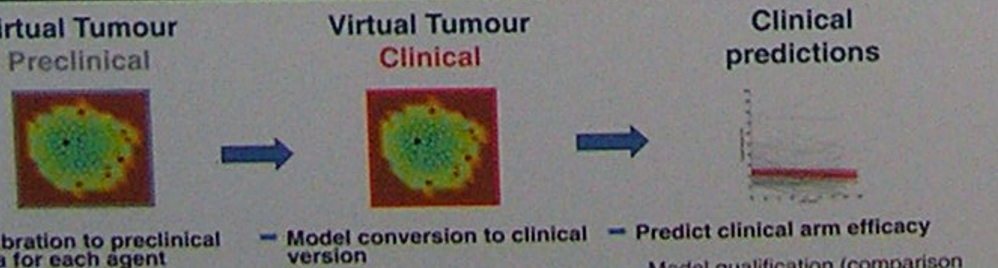
The Physiomics Virtual Tumour Technology

The Virtual Tumour[1] takes as input the following data sets:



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



- **Calibration to preclinical data for each agent**
  - Efficacy and PK studies
  - Key data taken from partner's experimental data sets or from literature
- **Model conversion to clinical version**
  - Human PK for each agent - usually from a phase I study
  - Switch preclinical growth settings for clinical growth settings
- **Predict clinical arm efficacy**
  - Model qualification (comparison with actual result)
- **Optimisation**
  - Provided schedule options to ameliorate efficacies and toxicities

Clinical Data

1. Vemurafenib[2]: 20 patients with a total of 69 lesions
2. Phase II docetaxel/selumentinib *vs* docetaxel/placebo[5]: ~ 40 patients with a total of ~100 lesions in each arm

References

1. D. Orrell and E. Fernandez, Using Predictive Mathematical Models to Optimise the Scheduling of Anti-Cancer Drugs, *Innovations in Pharmaceutical Technology* (2010).
2. I. Bollag et al. Evolutionary dynamics of cancer in response to targeted combination therapy. eLife (2013).
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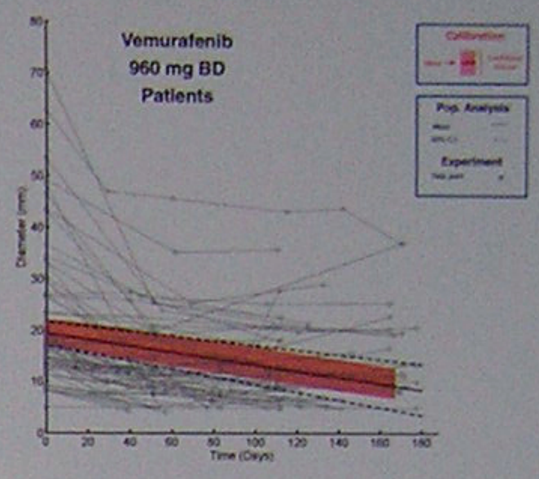
5. A. Gupta et al. DOC-MEK: A double blind randomized phase 2 trial of docetaxel with or without selumetinib in wild-type BRAF advanced melanoma. *Ann. Oncol* (2014).
6. D. Banerji et al. The first in human study of the hydrogen sulfate (Hyd-Sulfate) capsule of the MEK 1/2 inhibitor AZD6244 (ARRY-142886): A phase I open-label multicenter trial in patients with advanced cancer. Clin. Cancer Res. (2010).

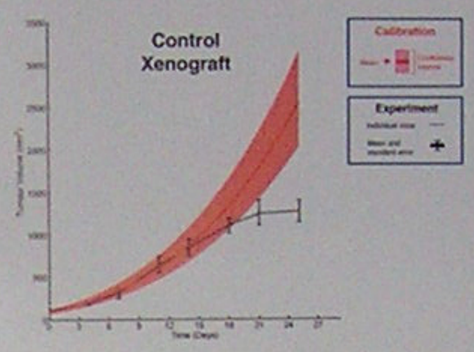
Example I – Back Translation of Vemurafenib

Step 1 – **Analyse** clinical data using population analysis approach (using a linear model) – see right panel (FDA sourced PK model used)

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

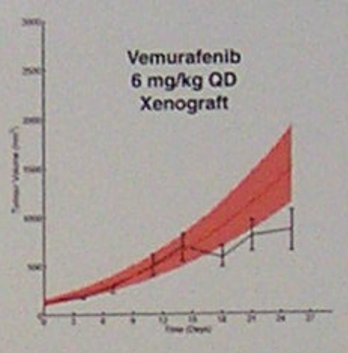
Step 3 – **Switch** clinical growth settings for preclinical growth settings and calibrate preclinical model to control growth – see panel below

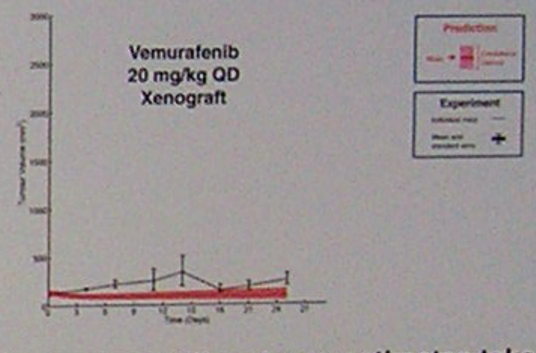




Step 4 – **Swap** clinical PK for preclinical PK and generate **predictions** of preclinical monotherapy effects

Step 5 – **Compare** prediction with actual result – see panel below





Results: model correctly predicts the xenograft response with potency estimates taken from the clinic.

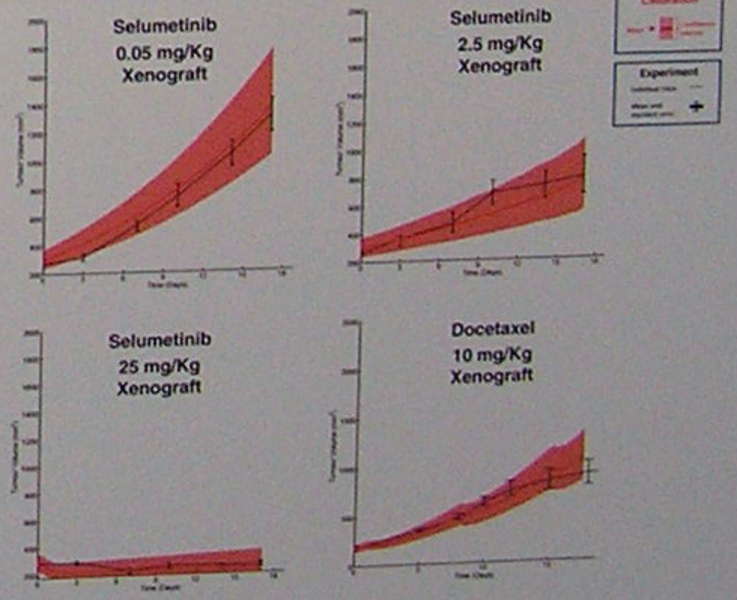
Example II – Forward Translation of Docetaxel/Selumetinib

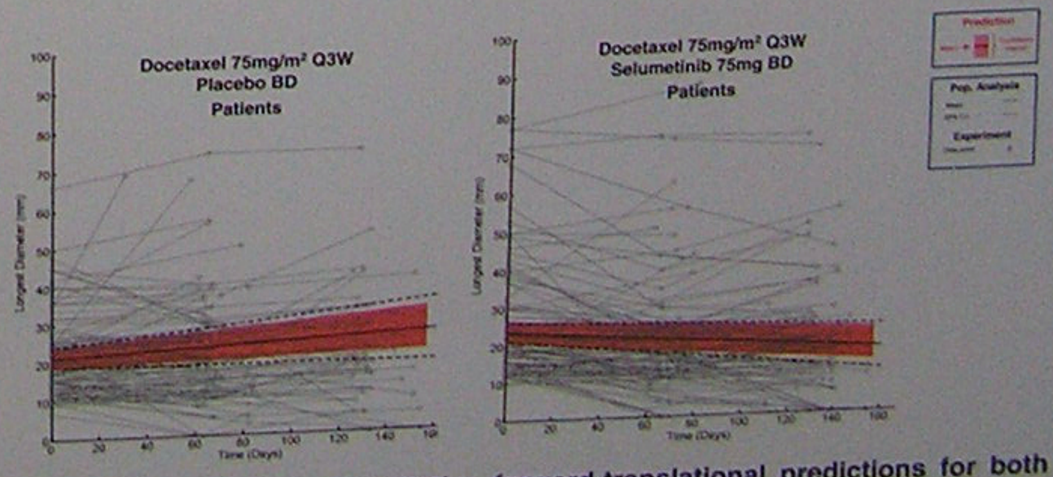
Step 1 – **Calibrate** Virtual Tumor to both monotherapy and combination mean clinical signal – see right panel

Step 2 – **Switch** preclinical growth settings and PK for clinical growth settings and PK[6]

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

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





Results: model makes accurate quantitative forward-translational predictions for both arms of the study.

Clinical study result[5]: ORR 32% docetaxel/selumetinib v 14% docetaxel (p = 0.059).

Conclusions

We demonstrated that Virtual Tumour Clinical can make accurate predictions of the mean change in lesion size over time for a phase II clinical study using preclinical PK/PD and clinical PK data. Furthermore, it should be noted that primary xenografts were not required for this study, highlighting the model's potential to result in significant cost savings. The accurate predictions of the model demonstrate its capability for assisting drug development within the arena of translational science.