Modelling the Emergence of Resistance to Chemotherapeutics with Virtual Tumour

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Introduction

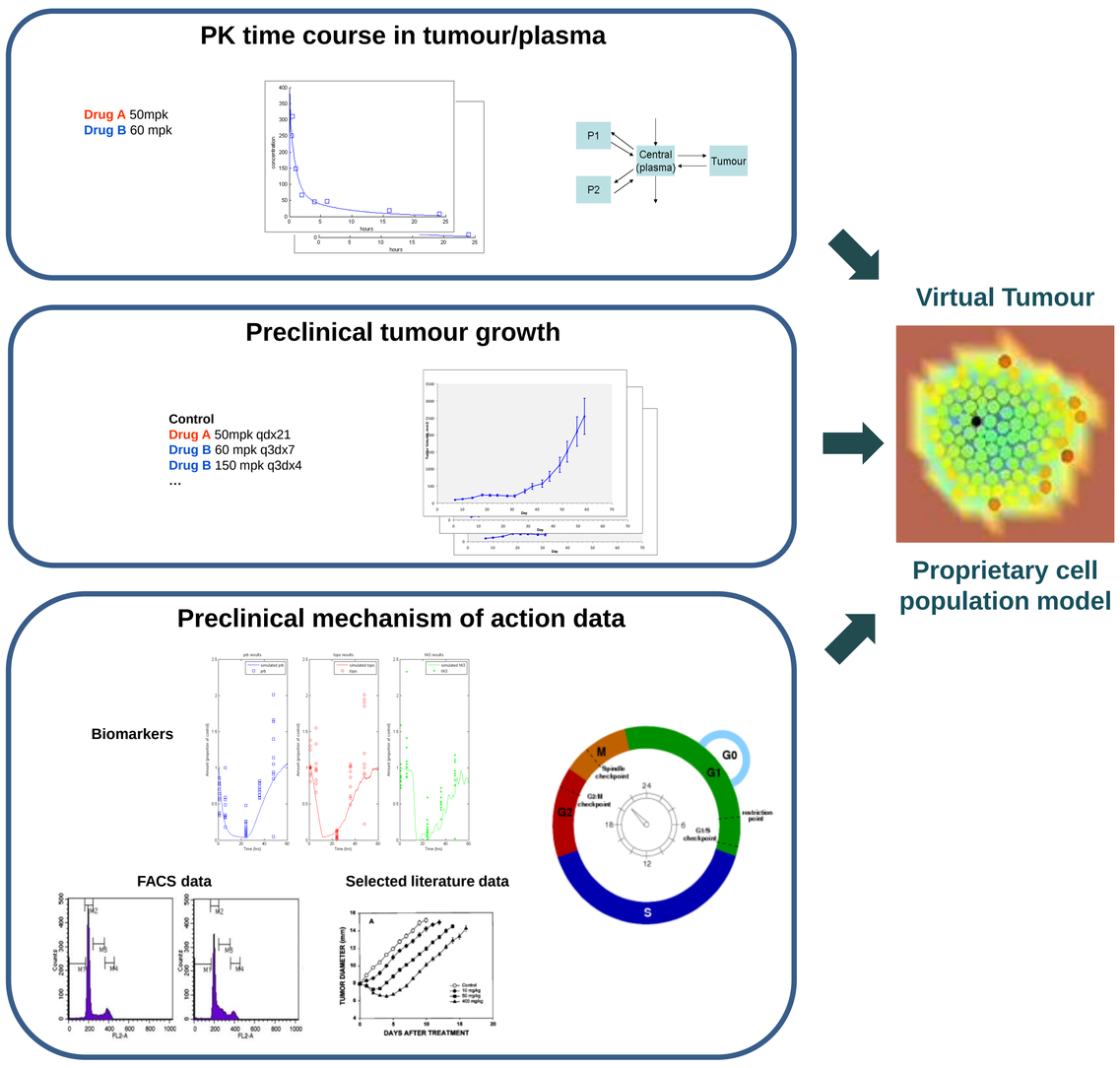
Drug resistance is a major cause of treatment failure in cancer, and understanding and overcoming mechanisms of resistance is a key challenge in advancing cancer therapy[1]. Although the progression from cytotoxic chemotherapy to drugs aimed at specific molecular targets has improved response rates and reduced adverse effects, in most cases there is still no effective treatment for metastatic disease[2].

Resistance arises from mutations in the genome of cancer cells and/or epigenetic changes[3]. The problem is compounded by considerable intra- and inter-tumour genetic heterogeneity, dictated by the genetic background and history of each cancer cell[2,3]. It is therefore becoming increasingly clear that cancer should be managed through personalized medicine[4], although this is unlikely to be widespread in clinical practice in the immediate future. In the interim, recent studies have shown that the emergence of drug-resistant disease can at least be delayed through treatment with novel dosing regimens[5,6].

Physiomics has developed a 'Virtual Tumour' (VT) technology that can predict how a tumour will respond to drug exposure. The VT platform integrates pharmacokinetic and pharmacodynamic effects, and models the way individual cells behave within a tumour population. These agent-based methods are particularly suitable for modelling multiple cell populations, and representing the heterogeneity of a clinical tumour. Given the significance of cancer drug resistance, and the form that future cancer therapy is likely to take, Physiomics is actively engaged in developing personalized medicine solutions. As a first step, we have incorporated chemotherapeutic resistance into our VT platform.

The Physiomics Virtual Tumour Technology

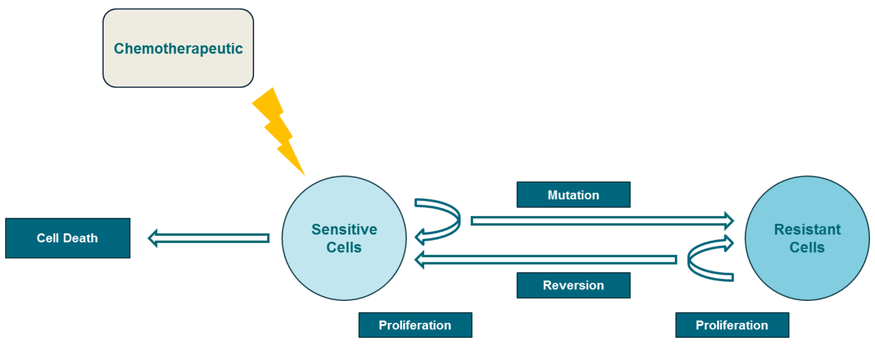
The Virtual Tumour takes as input the following data sets:



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

The Resistance Module

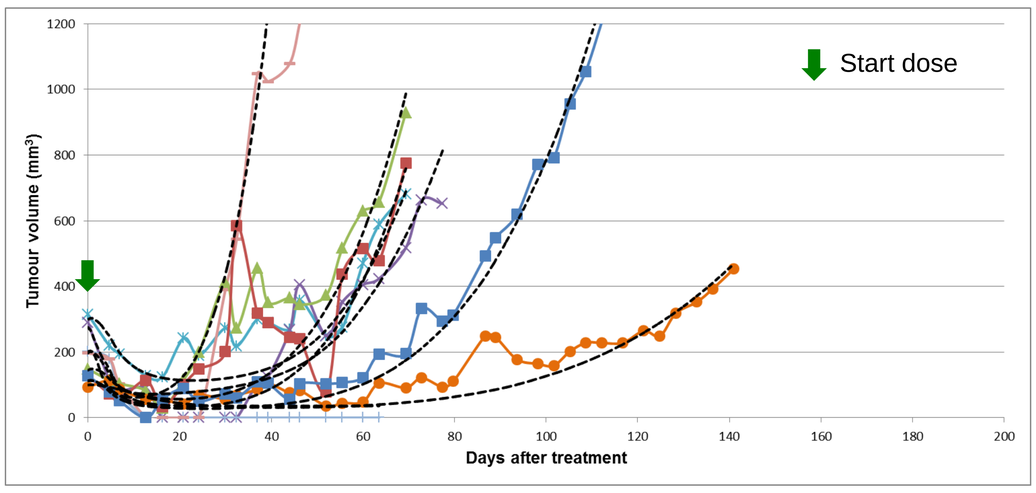
A provisional model for chemotherapeutic resistance has been developed as an add-on module for the Virtual Tumour platform.



This fundamental model has been customized to represent resistance to vemurafenib in *BRAF*-mutated melanoma, where resistant cells have a fitness disadvantage in the absence of drug[6].

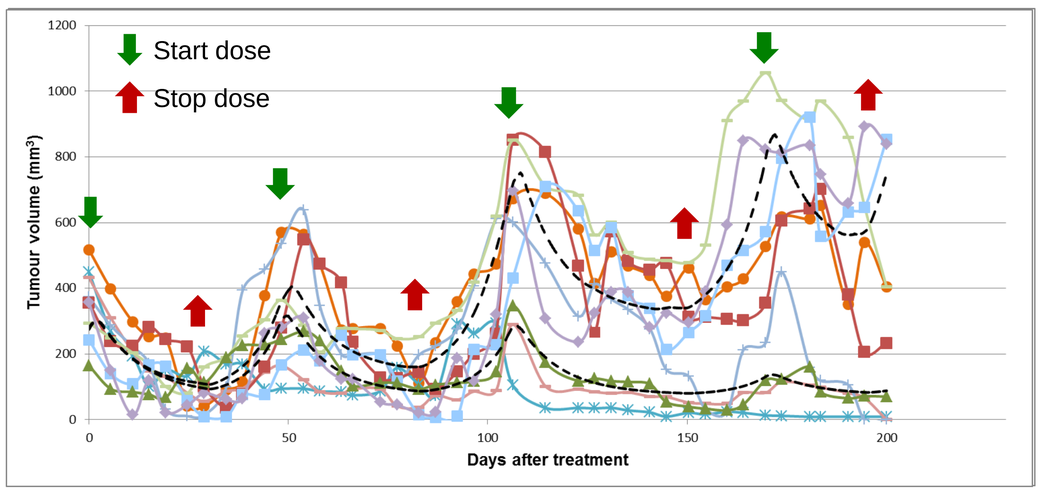
Model Comparison with Experimental Data

Continuous dosing of HMEX1906 xenografts with vemurafenib results in rapid emergence of resistance[6]. This effect can be simulated using the model. The pre-existing population of resistant cells was fixed, while the growth kinetics and vemurafenib efficacy were calibrated individually for each xenograft.



Tumour growth kinetics of naïve HMEX1906 xenografts dosed continuously with vemurafenib (15 mg/kg twice daily). Experimental data (coloured lines and symbols) from [6], overlaid by simulation results (dashed black line).

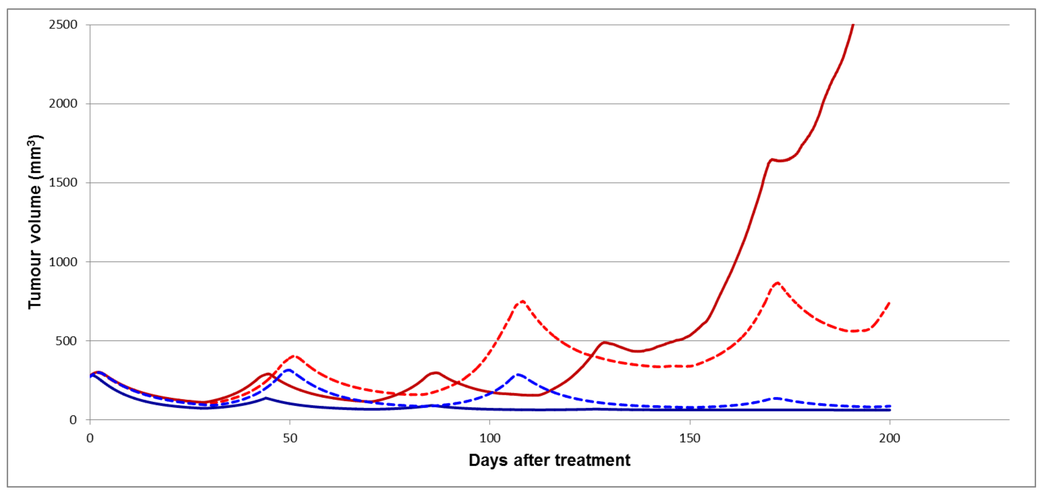
However, intermittent dosing of HMEX1906 xenografts with vemurafenib delays the emergence of resistance[6], and the model also reflects this behaviour. The model was calibrated separately for two groups of xenografts, sensitive (no resistant cells) and resistant (pre-existing resistant cells).



Tumour growth kinetics of naïve HMEX1906 tumours dosed intermittently with vemurafenib (15 mg/kg twice daily, adaptive schedule). Experimental data (coloured lines and symbols – green arrow: drug on, red arrow: drug off) from [6], overlaid by simulation results (dashed black line).

Optimal Dosing Schedules to Delay Resistant Disease

The model also confirms that the 'adaptive' dosing regimen employed in the experimental study (15 mg/kg twice daily on an approximate four-week on two-week off schedule) provides optimal efficacy in tumours with pre-existing resistant cells. However, a strict four-week on two-week off schedule (15 mg/kg twice daily) fails to delay the emergence of resistant disease. In sensitive tumours with no pre-existing resistant cells, the strict schedule is more effective in yielding early tumour regression. Clinical translation of this model, in combination with patient stratification, could be used to personalize treatment of tumours that carry mutations leading to drug resistance.



Simulated tumour growth kinetics of naïve HMEX1906 tumours dosed intermittently with vemurafenib. Original adaptive schedule (15 mg/kg twice daily) in resistant tumours, dashed red line; strict four-week on two-week off schedule (15 mg/kg twice daily) in resistant tumours, solid red line; adaptive schedule in sensitive tumours, dashed blue line; strict schedule in sensitive tumours, solid blue line.

Conclusions

We have successfully validated the resistance module of our Virtual Tumour technology, which can now be used to design preclinical schedules that delay the emergence of resistant disease. The next step is to integrate this module into our clinical platform, via our existing validated translational Virtual Tumour for metastatic melanoma, enabling prediction of time to relapse and regimen optimization for stratified patient groups.

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