Reducing animal experiments with the Virtual Tumour

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Introduction

Preclinical testing of novel cancer treatments are enormously time and animal consuming, due to the large number of anti-cancer agents and the variety of tumour types. Typically, drugs are tested on human tumour tissue, which has been transplanted on mice, called a *xenograft*. When multiple drugs, combination schedules, sequences and doses are considered, the number of possibilities increases combinatorially. Usual laboratory methods will involve trial and error, requiring a large amount of animal testing.

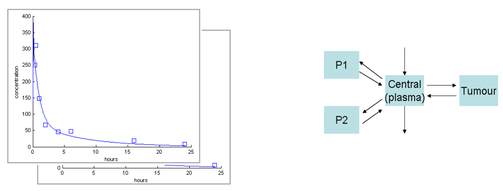
We have developed an *in silico* model of a xenograft called "Virtual Tumour" to aid and accelerate the design of optimal drug schedules. This allows experimentalists to prioritise the most effective drug combinations and dramatically reduce the number of animal experiments performed for validation *in vivo*.

Physiomics' Virtual Tumour technology

The Virtual Tumour takes as input the following data sets:

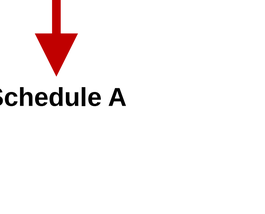
PK time course in tumour/plasma

Drug A 50mpk
Drug B 60 mpk



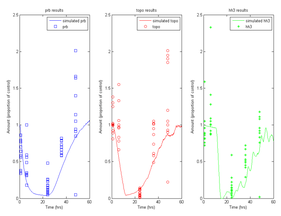
Pre-clinical Tumour Growth

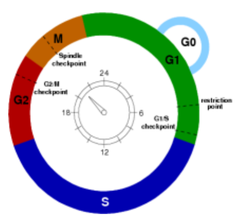
Control
Drug A 50mpk qdx21
Drug B 60 mpk q3dx7
Drug B 150 mpk q3dx4
…



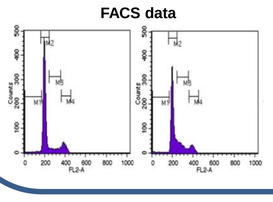
Pre-clinical Mechanism of Action Data

Biomarkers

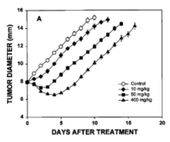




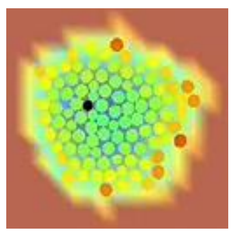
FACS data



Selected literature data



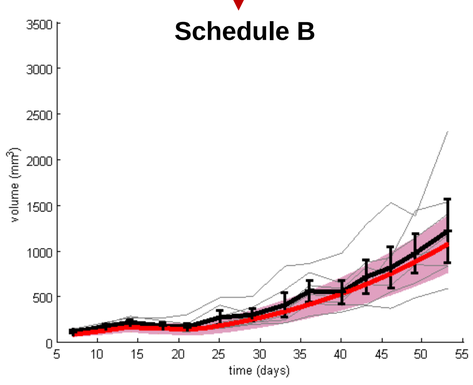
Virtual Tumour



growing tumour computer model

Schedule A

Schedule B



Predicted

Mean → Confidence interval

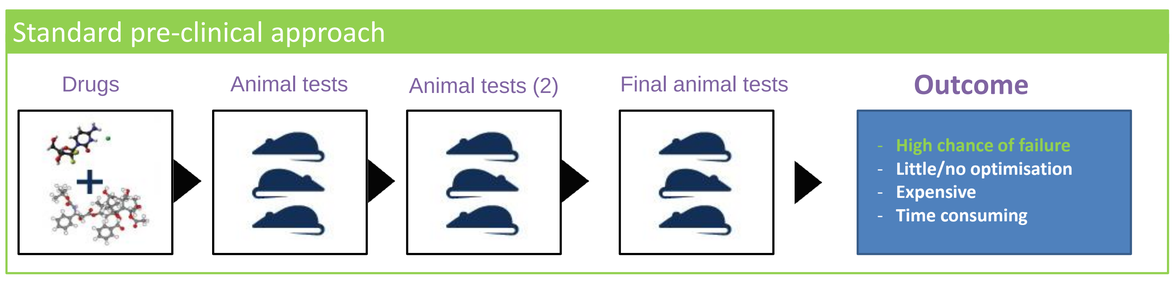
Experiment

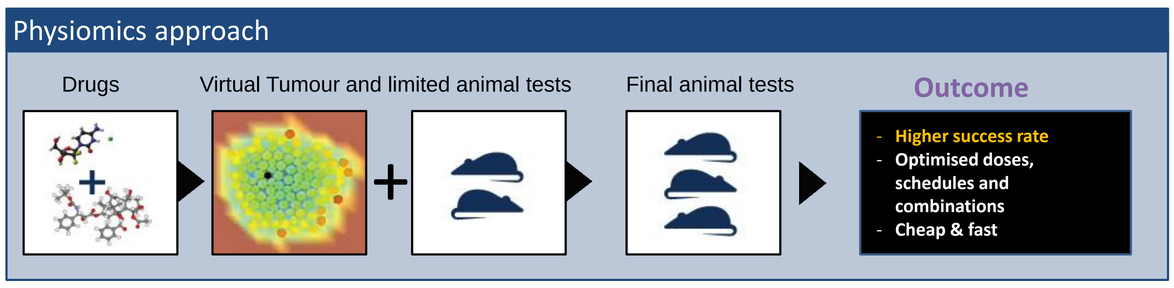
Individual mice

Mean and standard error

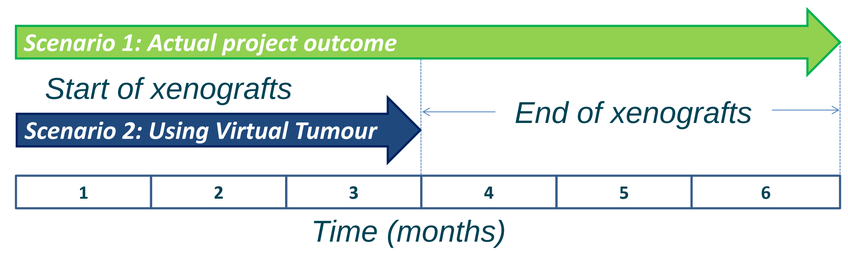
The Virtual Tumour simulations and predictions can be used to design and simulate new, rational experiments by ranking combinations and dosing schedules in specific tumour cell lines. This allows researchers to eliminate unnecessary and redundant experiments, thus reducing the amount of animals consumed in xenograft studies.

Eliminating Unnecessary Dosing Studies with Virtual Tumour



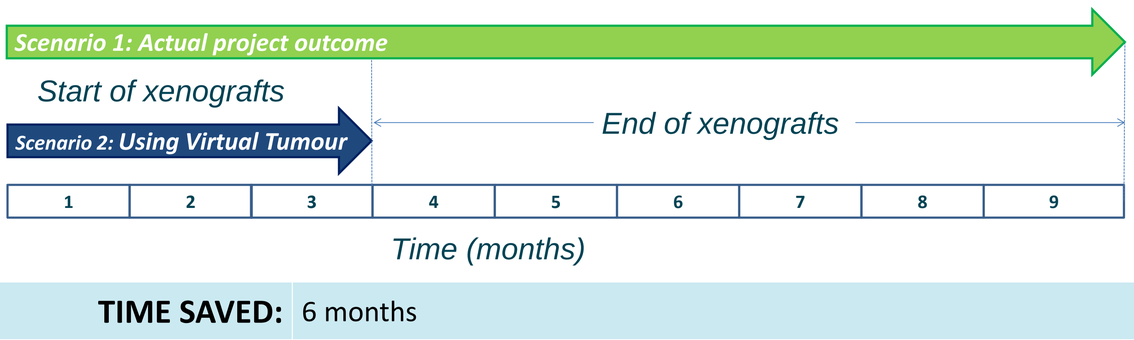


CASE STUDY 1:	Improved the efficacy of a combination
PROJECT:	Study to determine the optimal regimen for a DNA repair inhibitor combined with irradiation
DURATION:	6 months
OUTCOMES:	An improved regimen (complete growth inhibition with negligible toxicity), which was better than expert opinion predicted and needed less experimentation



TIME SAVED:	3 months
ANIMALS SAVED:	8 groups of 8 mice
OTHER BENEFITS:	Cost savings associated with 3-month study Increased the chance of their candidate making it to market. (1% reduced attrition estimated $17m)

CASE STUDY 2:	Determined that the customer already had an optimal regimen
PROJECT:	Optimise dosing and scheduling for a targeted agent combined with a DNA repair inhibitor (retrospective study)
DURATION:	Original project took 9 months to complete
OUTCOMES:	Demonstrated that use of Virtual Tumour provided the same answer with less animals, overall cost and much less elapsed time



TIME SAVED:	6 months
ANIMALS SAVED:	18 groups of 8 mice
OTHER BENEFITS:	Cost savings associated with 6-month study Opportunity cost saving of deploying scientists on other projects

Conclusion

We demonstrated that the Virtual Tumour can reduce the number of animal experiments. In one of the case studies, this number could have been reduced by half. Furthermore, it can accelerate the discovery of optimal drug regimens. Since the Virtual Tumour simulates and predicts the outcomes of many classes of anti-cancer agents, this technology paves the way to dramatically replace and reduce animal studies in xenograft studies routinely done to demonstrate and optimise drug combinations.

References:
D. Orrell and E. Fernandez (2010), Using Predictive Mathematical Models to Optimise the Scheduling of Anti-Cancer Drugs, *Innovations in Pharmaceutical Technology*, p59-62.