Predicting the effect of combination schedules on xenograft tumor using the Virtual Tumor

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Addressing the problem of drug combination optimization

We have developed a "Virtual Tumor" model to aid with the design of optimal combination chemotherapy regimens. When multiple drugs, combination schedules, sequences and doses are considered, the number of possibilities increases combinatorially, and can not be realistically tested either clinically or in animal models. The model combines disparate data, at the cell and tumor level, into a consistent picture, and leverages them to make testable predictions about tumor response. Thousands of simulations can be performed if necessary to find the best treatment regime.

We present here a validation study of our Virtual Tumor, made in collaboration with our partner, Lilly. We predicted xenograft growth of two anti-cancer drug combinations using experimental data collected from single drug exposure uniquely. We accurately predicted the xenograft course for two different regimens – one simultaneous and one sequential – of the two drugs, which were compared with experimental results in a single-blind test. We show how a computational approach helps explain how multiple drug exposure and correct sequence leads to synergy, and how it can be used to subsequently design optimal schedule and combination treatments.

Physiomics Virtual Tumor technology

The 'Virtual Tumor' is a sophisticated computer model that simulates tumor cell division and the effect of antineoplastic drugs, taking into consideration the differences between proliferative cells and those that are part of the necrotic core. The complexity of the model is deliberately constrained so that it can be parameterized with data that is usually produced during drug development. This data includes pharmacokinetic (PK) data for the drug, biomarkers showing the cell population response, and xenograft growth measurements showing how tumor growth is affected. This technology provides a rationale for designing an appropriate schedule, and allows our partners to prioritize the most effective drug combinations.

Here to calibrate the Virtual Tumor we integrated pharmacokinetic models of the drugs of interest (Figure 1). The pharmacodynamic effect for each drug was calibrated by using various data sources: *in vivo* target inhibition (*IVTI*, figure 2), xenograft growth time courses (Figure 3). We also used flow cytometry and public literature data. The table below summarizes the data that was used for Virtual Tumor calibration.

PK profile	Plasma and tumor PK profile for each compound near the planned concentration range	Figure 1
Biomarker data	Cell cycle phase biomarkers *(in vivo* target inhibition): TopoII and pHH3 Cytometry data, literature information	Figure 2
Xenograft tumor growth time courses	Control tumor growth rate Treated tumor growth with each drug in isolation	Figure 3

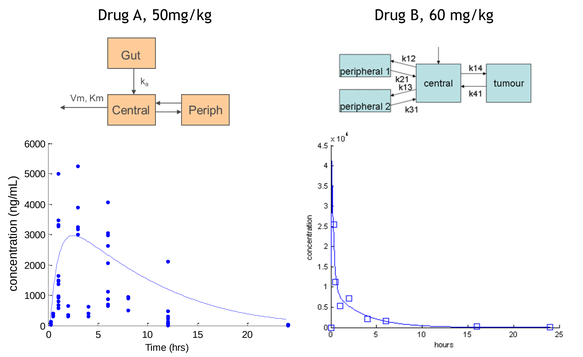


Figure 1. Tumor PK profiles for each drug used in combination. Solid lines: simulation, dots/squares: experimental values. On top of each PK profile the compartmental model used is shown.

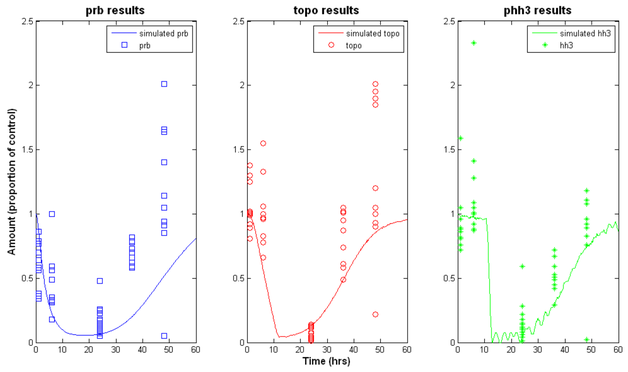
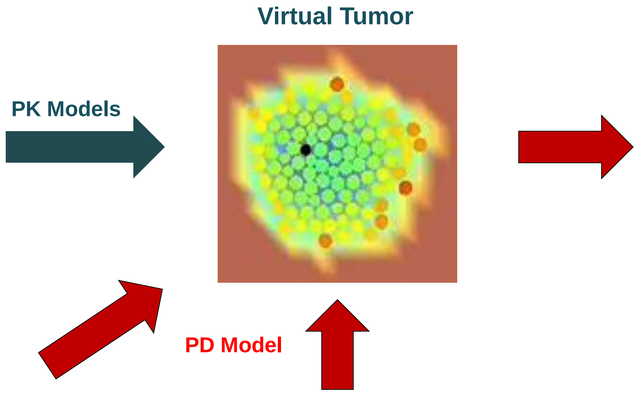


Figure 2. *In vivo* target inhibition biomarker data for drug A. Experimental measurements, measured on tumor sections using immunohistochemistry (dots) are overlaid with simulated time courses (solid lines). The same parameter set is used in the Pharmacodynamic model for all three biomarkers.



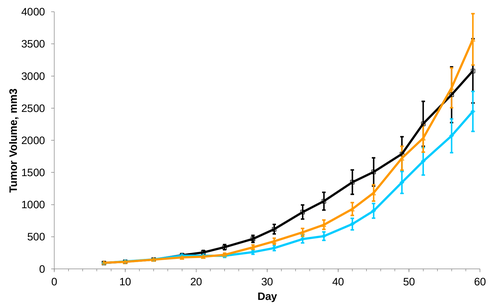


Figure 3. Xenograft tumor growth profiles for control (black), drug A 50 mg/kg qdx21 (blue), drug B 60mg/kg q3dx7 (orange). Tumor cell is Calu-6.

Predicting xenograft tumor growth

Once calibrated, the Virtual Tumor was used to generate tumor growth for two administration schedules: one schedule where both drugs are given concomitantly and one schedule were they are given sequentially (Figure 4). A predicted mean and interval of confidence were calculated over a period of 60 days.

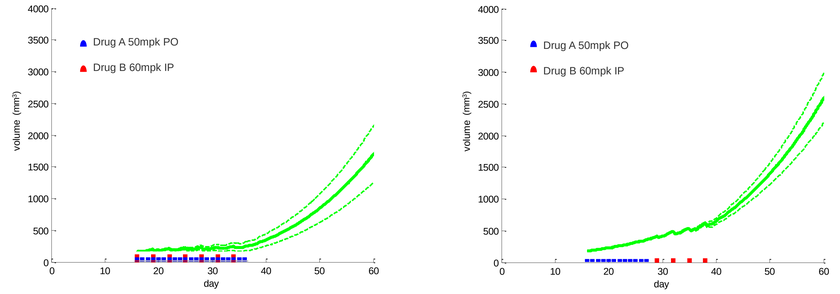


Figure 4. Predicted growth of xenograft tumor treated with two proprietary drugs combined in different ways. The green lines show our prediction, along with estimated upper and lower bounds. Schedules for the two drugs are indicated in red and blue on the bottom axis. Left: both drug schedules overlap, right: drugs are taken sequentially

Our predictions were then compared against experimental data, in a single-blind test (Figure 5). The predictions are in good agreement with the experimental data, and again accurately capture the schedule dependency.

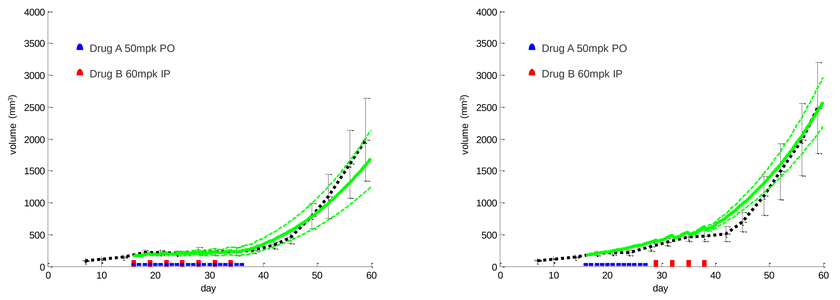


Figure 5. Virtual Tumor predictions and experimental results overlay. The prediction time courses are superimposed with the experimental average xenograft growth (black lines, along with 5 and 95 percentile error bounds.)

The Virtual Tumor is able to integrate the combined effects of two chemotherapeutic agents using calibration data from single-drug experiments. This technology is now used to help optimize regimens and predict the best combinations using a library of standard of care agent models.

Conclusion

Since the early 1960s, drug combination therapy has been used to treat cancer, because of the limited number of malignancies that could respond to single-agent chemotherapy. Combination chemotherapy regimens have been designed on the basis of mechanism of action of the drugs, tumor cell specificity, balance between effectiveness and toxicity, and synergy between drugs.

With the Virtual Tumor, simulations of different drug administrations can be quickly made and the best schedule regimen chosen for verification *in vivo*. The Virtual Tumor can be used for predicting and optimizing schedules and combinations for a wide range of molecules, including small molecules and biotherapy.

Simulations such as those shown here allow our partners to avoid costly trial-and-error approaches to determining the best administration schedules. Furthermore, it can be used to simulate thousands of possible schedules for combinations of different drugs that would be effectively impossible to investigate experimentally, and allow prioritization of the most effective drug combinations.

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