Virtual Tumour Modelling

The Effect of Aurora Kinase Inhibitors on the Cell Cycle

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PHYSIOMICS rational therapeutics

Introduction

Physiomics plc is currently developing sophisticated computational models of biological systems, concentrating primarily on the field of oncology. The aim of the Physiomics approach is to significantly improve drug target identification and validation by the use of *in silico* models, reducing project attrition in the biotechnology and pharmaceutical industries by aiding rational drug design. Moreover, the modular approach combines whole-body (multiple compartment) physiology-based pharmacokinetic modelling with mathematical models of biochemical processes running in a multi-cellular simulation environment. In so doing, our approach is also able to offer predictions and explanations of the clinical effects of NCE's under development with unparalleled scope and detail, thus helping to ensure success through clinical development.

Here we present recent results of the effects of the Aurora kinase inhibitor, VX-680, on our "virtual tumour" simulations. The results parallel experimental observations published for this important new anti-cancer drug thus illustrating the power of the Physiomics approach.

The Physiomics Modular Approach to Biological Modelling

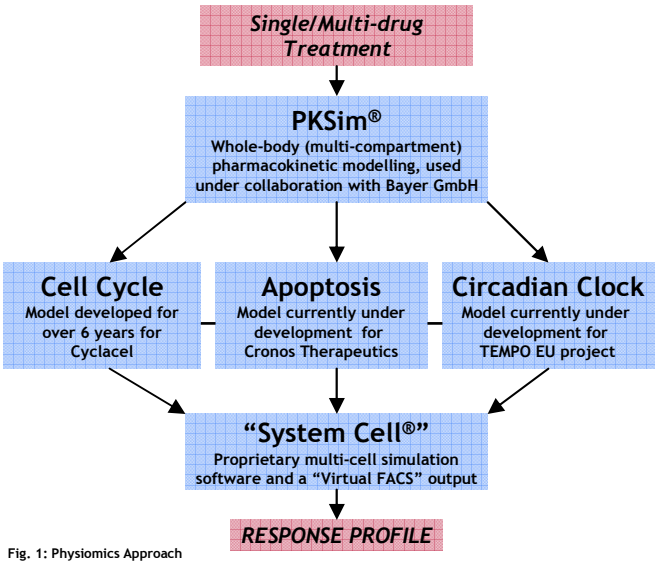

Fig. 1: Physiomics Approach

Our Core Cell Cycle Model

The Physiomics cell cycle model is possibly the largest in the world and is based upon a complex series of mathematical equations surrounding cyclins and CDKs, and their interactions with both regulators and effectors [1].

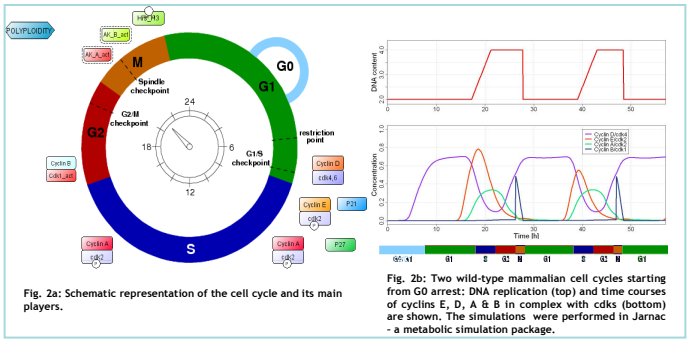

Fig. 2a: Schematic representation of the cell cycle and its main players.

Fig. 2b: Two wild-type mammalian cell cycles starting from G0 arrest: DNA replication (top) and time courses of cyclins E, D, A & B in complex with cdks (bottom) are shown. The simulations were performed in Jarnac - a metabolic simulation package.

The model includes over 100 reactions with over 100 species, and has been created with information carefully curated from the available scientific literature (Physiomics' library contains over 2000 articles).

Modelling a "Virtual Tumour" with "Virtual FACS"

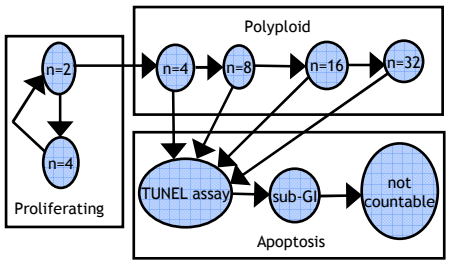

Figure 3: Model State Machine

SystemCell® is a computational environment capable of simulating heterogeneous populations of cells. Moreover, it is able to import the tissue drug concentration profiles predicted by the pharmacokinetic simulations performed by the PK-Sim® software. The "Virtual Tumour" model is composed of a population of SystemCell objects each consisting of a deterministic cell-cycle biochemical reaction network and a discrete event based state machine. The state machine is shown in Figure 3. The states *n=2…32* are non-apoptotic where *n* is the number of DNA copies in the cell. The probability of moving to the apoptotic TUNEL state (as measured by FACS) increases with the number of DNA copies.

The Effects of the Aurora Kinase Inhibitor, VX-680, on the Cell Cycle

Aurora kinases are new key targets for anti-cancer therapy. They are involved in regulation of the cell cycle from G2-phase to cytokinesis. The Phase II compound, VX-680 (Vertex Pharmaceuticals Inc. in clinical development with Merck & Co Inc.) is the subject of extensive published preclinical experimental data. We have used our ODE cell cycle model in combination with the cell population simulator, SystemCell® to model the effects of VX-680 on wild type (A549 cells) and p53-negative (A549-E6) cells. The results accurately reproduce experimental data [2].

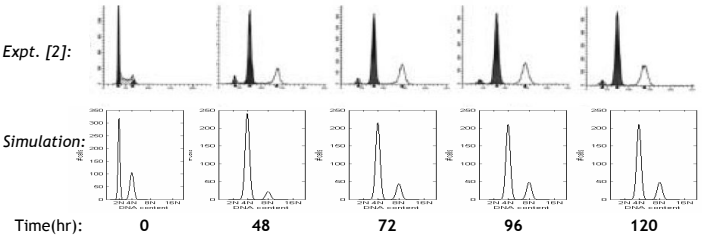

Fig. 4a: A549 (Wild Type) Cells

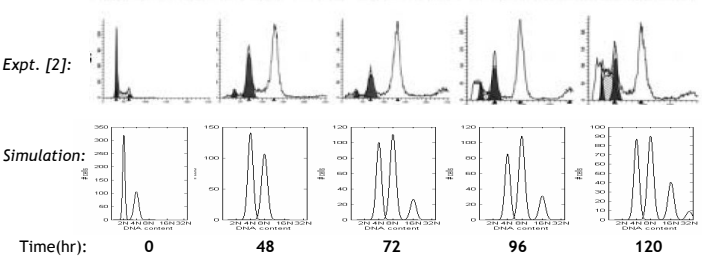

Fig. 4b: A549-E6 (p53 -/- cells)

Conclusions

We present preliminary results illustrating the responses of cancerous cells to treatment with VX-680. Drug treatment leads to different polyploid phenotypes characterized by varying DNA content from 4N to 16N and apoptosis. Moreover, it is shown how our ODE cell cycle model running in combination with our multicellular environment package SystemCell® can simulate the drug effect on populations of cells.

References:

[1] Chassagnole, C. et al. **Using a mammalian cell cycle simulation to interpret differential kinase inhibition in anti-tumour pharmaceutical development** Biosystems 83 (2006) 91-97

[2] Gizatullin, F. et al. **The Aurora Kinase Inhibitor VX-680 Induces Endoreduplication and Apoptosis Preferentially in Cells with Compromised p53-Dependent Postmitotic Checkpoint Function** Cancer Research 66 (2006) 7668-77