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Chronotherapy: Seliciclib dosing schedules determined using a detailed computational cancer model

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TEMPO SIXTH FRAMEWORK PROGRAMME

PHYSIOMICS rational therapeutics

Introduction

- **Chronotherapy [1]:**
  - Scheduling drug administration according to the time of day
  - In rodents, tolerability varies up to 10-fold for more than 30 anti-cancer drugs
  - Clinically validated for Oxaliplatin, 5-FU and doxorubicin
- **TEMPO [2]:**
  - EU-funded, multi-disciplinary project
  - Objective is to define optimal chronotherapeutic schedules for Seliciclib and Irinotecan
  - Experimental data passed to modellers who predict schedules that are then validated by experimentalists
- **Physiomics:**
  - Specialises in mechanistic pharmacodynamic modelling of anti-cancer drugs
  - Designing optimal chronotherapeutic schedules for Seliciclib as part of TEMPO
  - Progress is presented here

Methods

The modelling strategy adopted by Physiomics follows the process shown in Figure 1.

MODEL CONTSTRUCTION:

- Based on ODEs and stochastic equations
- Structure determined from critical evaluation of the literature (5000 articles in Physiomics' library)
- Includes processes shown in Figure 2
- Includes 276 reactions
- Parameterised by qualitative fitting to data, continuously being improved

MULTI-CELL MODELLING:

- Physiomics' proprietary software, "SystemCell®", allows multiple copies of the model to be run simultaneously
- Runs on high performance computer at Institute of Life Science, University of Wales Swansea [3]
- Allows higher levels of abstraction to be simulated such as variability in drug response and cell synchronisation

PK-MODELLING:

- We use commercially-available PBPK modelling software, "PK-Sim®" [4]
- Software enables simulation of concentration-time profiles in different organs
- Model used here has not been fitted to experimental data, but specific parameters such as LogP have been used

SIMULATION OF SELICICLIB:

- Currently accepted MOA is used:
  - Inhibition of CDKs 1,2,7,9
  - Inhibition of expression of mdm2, XIAP, survivin and mcl-1

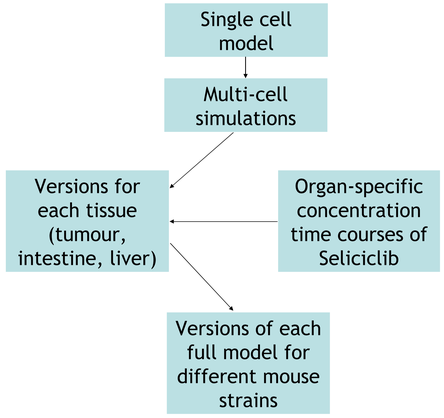


Figure 1: Modelling strategy used by Physiomics for TEMPO project

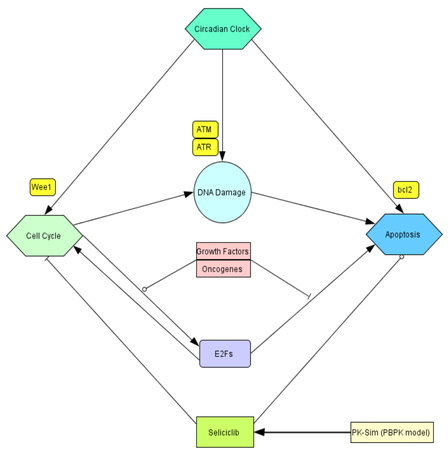


Figure 2: Conceptual model adopted by Physiomics for Seliciclib chronotherapy modelling

Results

Figure 3: Simulated concentration-time courses for Seliciclib in different mouse organs after a 50mg/kg oral administration. Although the model has been calibrated only with physicochemical data for Seliciclib, the plasma profile agrees with experimental data for oral dosing [5]. Interestingly, the concentrations reached in the intestine and liver are greater than the plasma, although this is not unexpected for an orally-administered drug. The PK-Sim model still requires calibration of active processes using experimental data to be provided by the consortium so the time courses used in subsequent simulations should be considered to be theoretical.

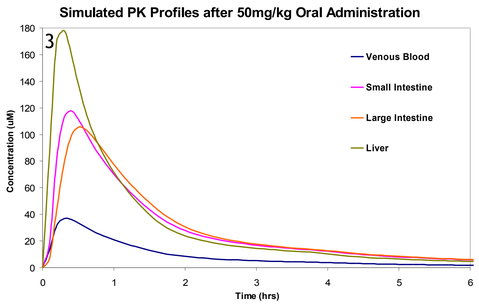
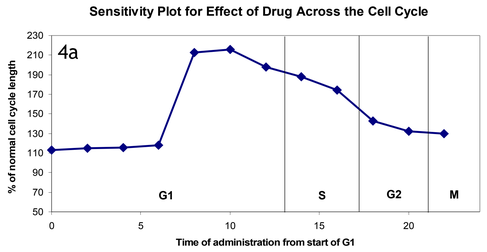
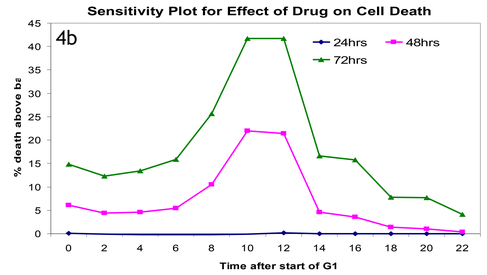
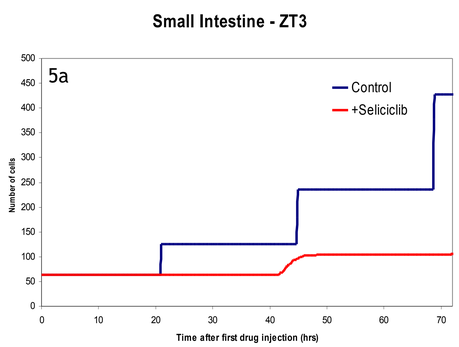


Figure 4a and b: "Sensitivity Zone" analysis of the cell cycle and cell death to Seliciclib. The graphs show how the response of the cell cycle (a) and apoptosis (b) vary according to the dosing time of Seliciclib, as determined using the plasma PK profile of Seliciclib from Figure 3 administered to a single cell. The dosing time was advanced by 2 hrs for each simulation experiment. The results suggest that single cells and synchronised cell populations will be most sensitive around 10hrs after the start of G1 (ZT12). The variation in sensitivity to cell cycle arrest is in accordance with inhibition of CDK1 and CDK2 [6].





Figures 5a and 5b: Simulated growth of a synchronised cell population using the concentration-time courses for small intestine after repeated 50mg/kg oral administration at different ZT times. The figures show that in agreement with Figures 4a and 4b, dosing the drug at ZT19 has a much greater effect than at ZT3. As the cells are synchronised, they divide simultaneously giving the step-like growth kinetics. The steps are smoothed upon drug treatment due to increased cell death, which is stochastic, and the variability in drug response between the cells. The effect on the small intestine, as opposed to other "healthy" tissues, was delineated by using the concentration-time courses simulated by PK-Sim for this organ. Simulations of small intestine were chosen because Seliciclib causes nausea and vomiting in high doses suggesting that there may be an effect on the rapidly dividing cells in the gut [7]. The simulations suggest that the toxicity of Seliciclib due to its action on the intestine will be worse with dosing at ZT19.



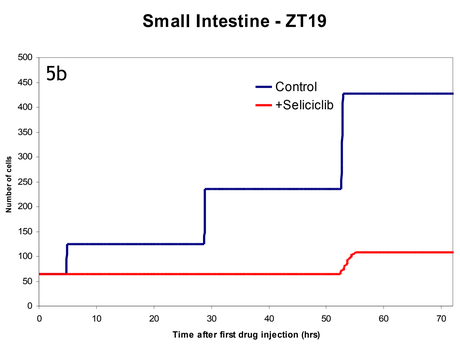


Figure 7: Tumour cell population growth following repeated administration at different circadian times using plasma PK profile. Perhaps unsurprisingly, the model shows no difference in efficacy between different dosing times. This suggests that the differences in efficacy observed experimentally [8] are due to either partial cell synchronisation in the tumour and/or differences in PK between circadian dosing times.
Interestingly, the simulations show that the drug causes partial cell synchro-nisation in line with experimental data [8]. This suggests that alternating schedules may have the greatest effect on tumour tissue.

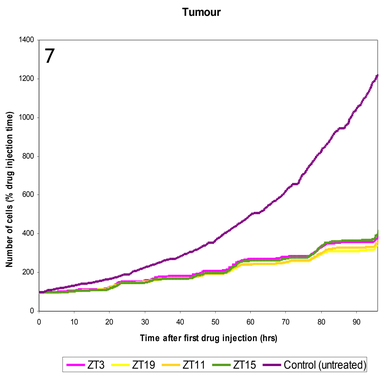
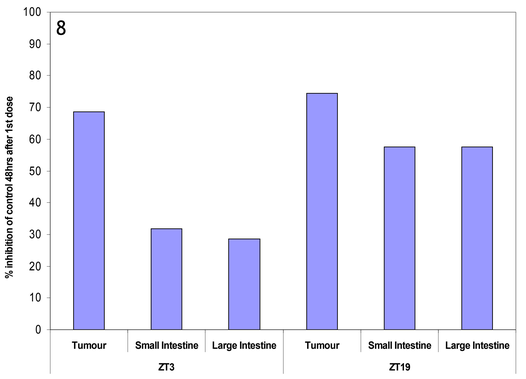


Figure 8: Comparison of ZT3 and ZT19 on cell population growth at 48hrs. The figure shows that the effect of Seliciclib on healthy tissues may be higher at ZT19 (i.e. more toxicity at ZT19) in line with experimental data [8].



Future Perspectives

Model is not yet calibrated with experimental data but shows some characteristics in line with existing data:

- Similar plasma profile following oral dosing (not shown)
- Greater toxicity at ZT19 than ZT3
- Resynchronisation of tissues following treatment with Seliciclib

Future work in the TEMPO project will include the following:

- Calibration of single-cell model with experimental data
- Develop different versions for different "chronotoxicity classes" (strains)
- More accurately simulate tumour growth using our "Virtual Tumour" technology
- Validation of model predictions by experimentalists

Beyond the end of TEMPO we aim to do the following:

- Extend the chronotherapy aspect of the model to humans
- Launch the chronotherapy model as a service

Ultimately our model will eliminate the need for a "trial and error" approach to determining optimal chronotherapeutic dosing schedules.

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