Modelling and translating head and neck radiation therapy on all three levels: *in vitro*, *in vivo* and clinical

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PAGE
June 2016
Lisbon,
Portugal

Introduction

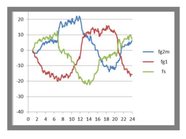
One of the most demanding tasks in pharmaceutical drug development is the capability to predict clinical outcome for a planned study based on preclinical observations. A technique such as *in silico* tumour cell population modelling can help predict the effect of anti-neoplastic agents, and therefore optimise dose and administration scheduling of these agents. Here it is our aim to demonstrate how radiation therapy mechanism of action can be translated from *in vitro* experiments to *in vivo* animal studies and then to the clinic.

Experimental radiation treatment data from *in vitro*[1], *in vivo* xenograft[2,3] and clinical efficacy studies[4] have been extracted from selected literature references. These data included FACS time series analysis of irradiated cultured cells, tumour xenograft growth rate studies and head and neck clinical tumour size from patients during the course of radiation therapy. We used these data to model irradiation mechanism of action in our Virtual Tumour [5] and calibrate the model for the three levels of experimental work.

Using the Virtual Tumour cell population model we were able to translate the efficacy of radiation on three levels: firstly, from *in vitro* to *in vivo* and then from *in vivo* to clinical studies, without changing the underlying mechanism of action of radiation at the cellular level. The only adjustments were values of key parameters of the cell population structure.

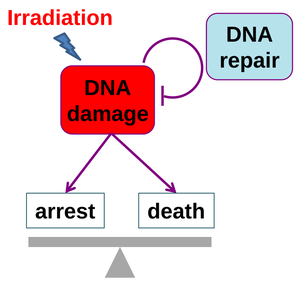
In vitro -> *in vivo* -> clinical translation

Virtual FACS MoA

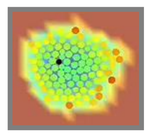


DNA damage/repair model design

Model runs in “FACS” mode. Cells are grown as a 2D layer and sorted according to cell cycle phase



Virtual Tumour Preclinical

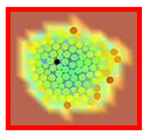


Calibration to preclinical data for each agent

Model runs in “Tumour” mode, adding 3D tumour structure to cell population growth dynamics

Efficacy, PK studies and other key data taken from literature

Virtual Tumour Clinical

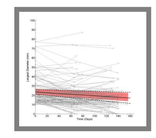


Model conversion to clinical version

Human PK for each agent - usually from a phase I study

Switch preclinical growth settings for clinical growth settings

Clinical predictions



Predict clinical arm efficacy

Model qualification (comparison with actual result)

Optimisation

Provide schedule options to ameliorate efficacies and toxicities

Virtual FACS model for irradiation *in vitro*

The DNA damage and repair rates, as well as the balance between cell cycle arrest and cell death were calibrated in the Virtual Tumour to reflect the effect of irradiation (single dose of 2 Gy at the start of the experiment). The Virtual Tumour is run in “FACS” mode (also called Virtual FACS), simulating a 2D culture of tumour cells (Fig. 1). At the start of the experiment, cells are randomly sampled at various cell-cycle phase time points, hence the cell population is perfectly asynchronous.

Each simulated cell line has its own cell cycle parameters, such as doubling time and cell-cycle phase duration. When irradiation induces DNA damage, cells in G2-M accumulate, due to the activation of the DNA repair checkpoint in G2. Consequently, the pool of cells in G1 decreases. Cells in S phase increase slightly after irradiation, due to a delay in S phase progression under radiation-induced stress. The dynamics of cell accumulation at specific phases is shown to be dependent on the doubling time and sensitive to the individual phase durations.

Simulations show that the Virtual Tumour can accurately reproduce the effect of irradiation on various cell lines in 2D culture.

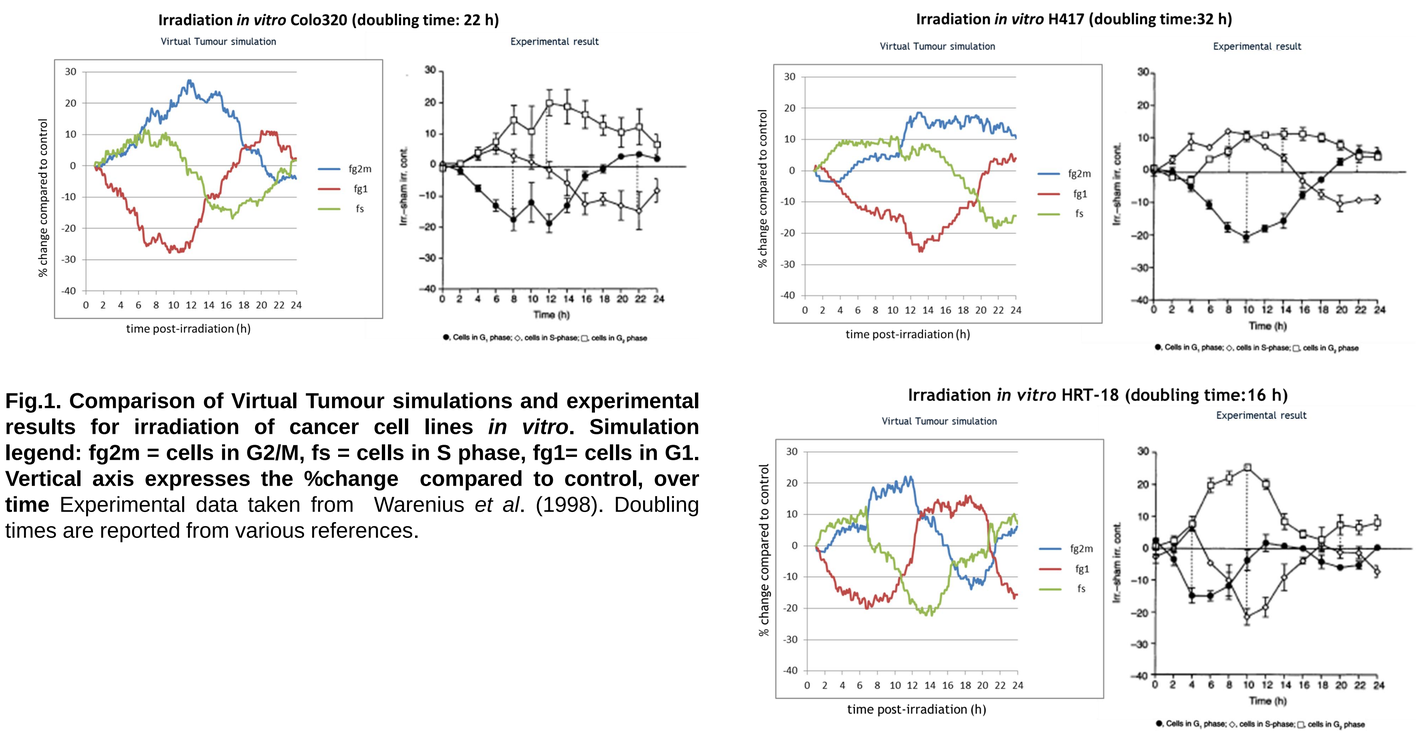


Fig.1. Comparison of Virtual Tumour simulations and experimental results for irradiation of cancer cell lines *in vitro*. Simulation legend: fg2m = cells in G2/M, fs = cells in S phase, fg1= cells in G1. Vertical axis expresses the %change compared to control, over time Experimental data taken from Warenius *et al*. (1998). Doubling times are reported from various references.

Virtual Tumour model for irradiation *in vivo*

The Virtual Tumour uses the same DNA damage and repair model structure than the one built for the Virtual FACS, but extends it to a 3D, spherical tumour cell population, in order to simulate a subcutaneous xenograft tumour in mice. In this architecture, each cell contains an instance of the cell-cycle model, but not all cells are equivalent: some cells are part of an actively growing pool, whereas some cells are part of a necrotic pool, depending on the action of the drugs, as well as the access to nutrients.

The Virtual Tumor was calibrated to reproduce the effect of irradiation on subcutaneous xenograft tumour growth (Fig.2). The model parameter set was unchanged to simulate the various dosing regimens taken from the literature[2,3].

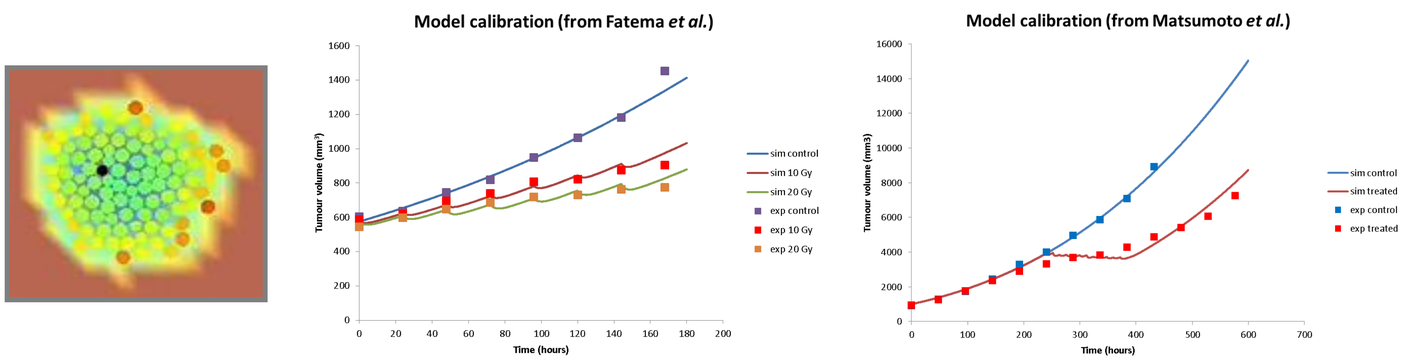


Fig.2. Virtual Tumour model calibration for various dose regimens of irradiation. Head and Neck xenograft tumours. Squares are experimental data, solid lines are simulations. Experimental data taken from Fatema *et al.* (2014) and Matsumoto *et al.* (2012).

Virtual Tumour clinical model for irradiation

The Virtual Tumour used in xenograft tumour growth inhibition studies was converted to the clinic, based on our previous work on translating melanoma from preclinical studies to the clinic[6]. Translating preclinical to clinical uses the following assumptions: DNA damage and repair rates used in preclinical model are unchanged, initial clinical tumour volume at start of treatment corresponds to a tumour with a 10 mm radius, basal cell death rate set to a rate comparable to previous clinical translation.

We extracted from the literature[4] the volume of 47 PET-positive lymph nodes in IR-treated patients over a period of 30 weeks. Using the clinical irradiation regimen in simulations, we show that the Virtual Tumour is able to predict the mean tumour shrinkage of PET-positive lymph nodes over the same period (Fig. 3).

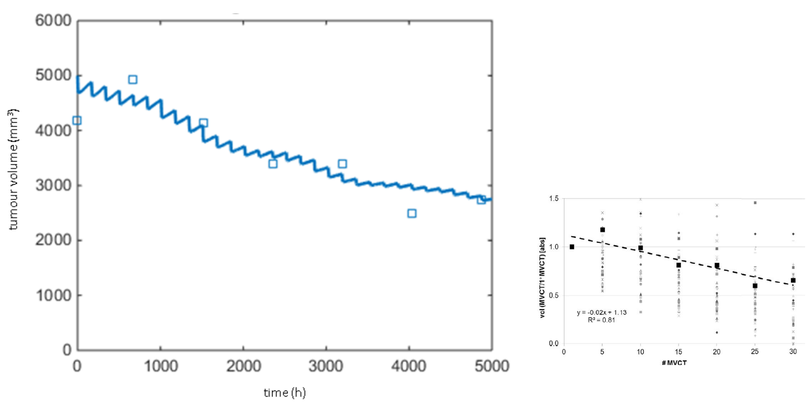


Fig.3. Simulation of the mean volume shrinkage time course of 47 PET-positive lymph nodes over a radiation treatment of 30 weeks. Radiation is administered at a dose of 1.8 to 2.3 Gy every week (MVCT) in 30 fractions and imaging by PET-scan is effected every 5 weeks. Experimental data (shown right) obtained from Belli *et al*. (2015). Squares are experimental data, solid line is the simulation.

Conclusions

We explored how the model could be converted to fit preclinical and then clinical data, using the same mechanism of action from *in vitro* to *in vivo* to clinical. We have shown that cell population structure is key to be able to describe the effect of irradiation at the three levels. This paves the way of using our Virtual Tumour technology to predict clinical outcomes from preclinical studies.

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