Model-based analysis of patient-derived organoids for evaluating anticancer drug: a step towards improving translational cancer research

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BACKGROUND

3Rs (Replacing Reducing and Refining):

The 3Rs principle, endorsed by regulatory agencies, is a guiding framework for ethical and responsible use of animals in research [1].

- Replacement: Researchers must explore alternative methods to replace animal use in research.
- Reduction: Researchers are encouraged to minimize the number of animals used by considering alternative preclinical models.
- Refinement: Researchers should implement measures to enhance animal welfare and minimize pain, such as less invasive techniques and optimized protocols.

Cancer organoids:

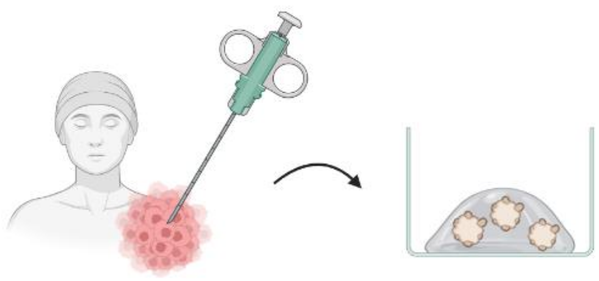
Cancer organoids are 3D structures that are grown in the lab from a patient's tumour cells, designed to mimic the characteristics of the tumour from which they are originated [2]

- Organoids occupy a middle ground between 2D cell cultures and in vivo models, attracting scientific attention for their potential [3].
- Their usage in translational cancer research still faces obstacles, including the need to investigate their ability to predict therapeutic dosage or concentration levels and support the drug development process.

OBJECTIVE: Conducting a model-based analysis of cholangiocarcinoma patient-derived organoids (PDOs) [4] while integrating mathematical modelling and simulation. This integration has the potential to improve the use of the organoids for evaluating the efficacy of the anticancer drugs in translational cancer research

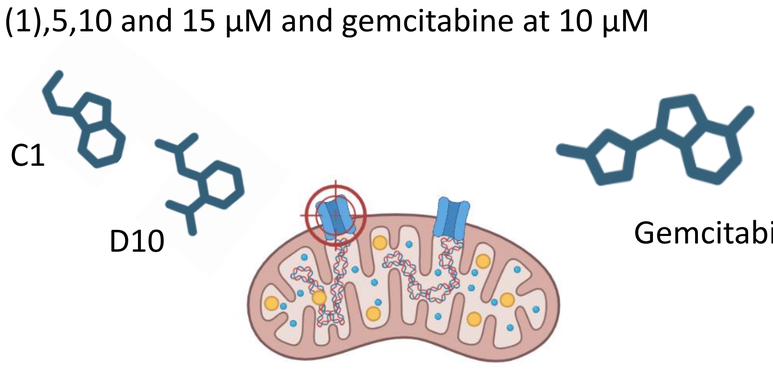
METHODS

Step 1: From patient to PDO



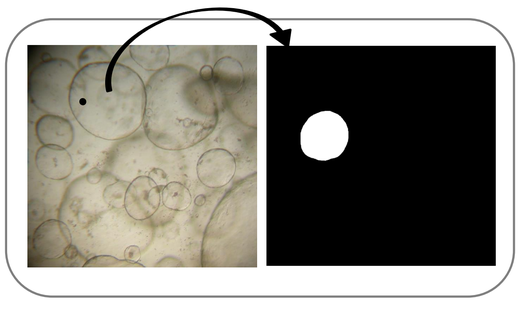
Step 2: Treatment

Two experimental small molecules targeting Voltage Dependence Anion Selective Channel isoform 1 were tested at (1),5,10 and 15 µM and gemcitabine at 10 µM

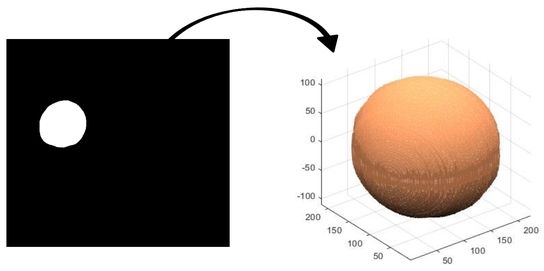


Step 3: From PDO to PDO data

1) Semi-automated segmentation of the single organoid

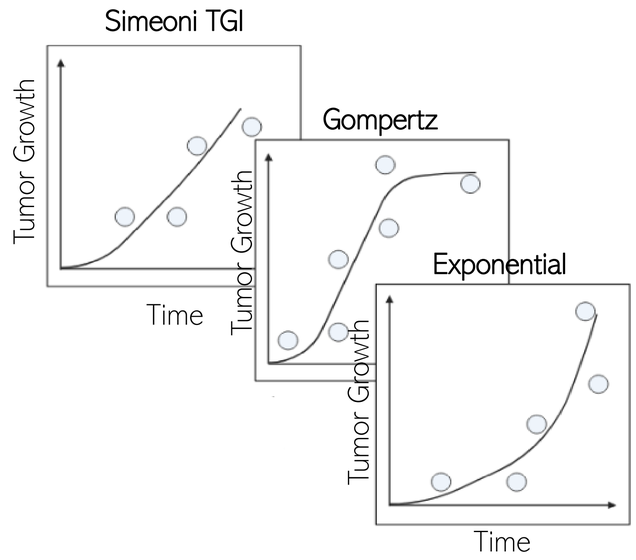


2) Calculate organoid morphometric parameters



(i.e.) Area, Surface Area, Volume, Sphericity

Step 4: From PDO data to PDO TGI model



RESULTS

The Simeoni model with saturation phase turns out to be the best model to describe unperturbed growth and TGI time profile of patient-derived cholangiocarcinoma organoids.

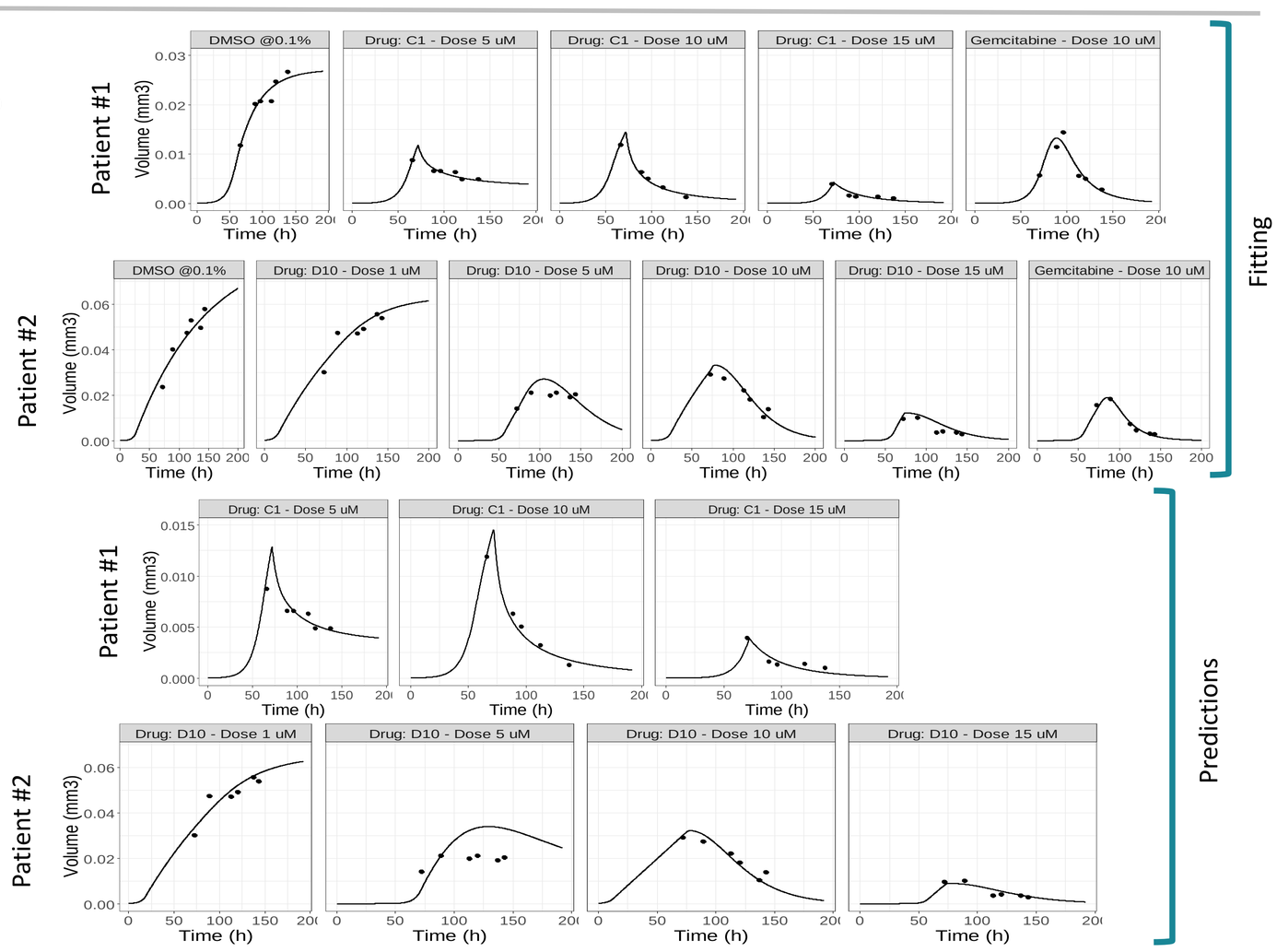
The study also found that the effect of small molecules on tumor growth was non-linear, suggesting that there may be complex, dynamic interactions between the molecules and the cancer cells

- C1 effect – Emax model
- D10 effect – Hill model (alpha = 2)

A compartment effect had to be introduced to model the delay in the inhibition of organoid growth for Gemcitabine treatment

The model has been also used to predict "unseen" dosages

	MPE	MAPE
C1 – Dose 5uM	2.24%	7.87%
C1 – Dose 10uM	-3.26%	18.1%
C1 – Dose 15uM	-3.19%	28.7%
D10 – Dose 1uM	0.47%	5.59%
D10 – Dose 5uM	19.14%	37.78%
D10 – Dose 10uM	-6.1%	11.11%
D10 – Dose 15uM	13.0%	23.8%



CONCLUSIONS:

The use of modelling and simulation (M&S) techniques has the potential to substantially improve the accuracy of 3D in vitro cancer models, thereby increasing their usefulness for subsequent in vivo experiments while adhering to the principles of the 3R framework (Replace, Reduce, Refine).

REFERENCES

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