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Quantitative systems pharmacology modeling of biotherapeutics in oncology

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Quantitative systems pharmacology modeling of biotherapeutics in oncology

Alison M. Betts

1. Mathematical modeling is a key tool which has been shown to increase efficiency and effectiveness in drug discovery and development. It can be used to facilitate molecule design, selection, preclinical to clinical translation, and to optimize clinical trials of oncology therapies.
   This thesis

2. Modeling can be a useful tool to reduce, refine and replace animal experimentation, by enabling *in vitro* to *in vivo* correlations and use of simulation of virtual experiments.
   This thesis

3. The size of a model in translational drug research should be mainly determined by the question asked. *This thesis*

4. Mechanistic Quantitative Systems Pharmacology (QSP) models require an investment in data and development time; however, they offer a high return with respect to the granularity of the answers they provide. *This thesis.*

5. Platform QSP models are amenable to reuse and repurposing to support diverse decisions from early drug discovery through to clinical studies. *This thesis.*

6. Modeling can help to understand variability in the clinic and to identify factors impacting drug response in individual patients, paving the way for precision medicine strategies, informing clinical diagnostics, biomarkers, and doses for different oncology indications. *This thesis.*

7. Considering the demonstrable impact of mathematical models on the rational design of treatment regimens, we should no longer rely on empirical approaches in cancer drug development. *This thesis and Barbolosi et al., Nature Reviews 2016.*

8. The most widely accepted definition of QSP modeling is “the quantitative analysis of the dynamic interactions between drug(s) and a biological system that aims to understand the behavior of the system as a whole...” *van der Graaf & Benson, Pharm Res 2011.*

9. A superior understanding of inherent immune biology is required to design effective and safe strategies to utilize the human response against cancer, to achieve durable responses and/ or complete tumor eradication in patients. *Based on Chen & Mellman, Immunity, 2013*

10. A rigorous preclinical to clinical translational framework using the same underlying mathematical model could facilitate oncology clinical development by better identifying translational strategies, patient selection criteria, and appropriate biomarkers to measure.
    Based on Zhu, Future Science, 2018

11. The significance of QSP modeling depends upon the clarity of the question, the rigor of our answers and an openness to challenge our preconceived thinking*. Inspired by Carl Sagan, and his encouragement to ask courageous questions to interrogate the ambiguities of the universe.*

12. As scientists, we must forge new paths, and do things differently to change the status quo. *Inspired by Ralph Waldo Emerson and his philosophy encouraging American authors to find their own style instead of emulating foreign predecessors.*