Quantitative systems pharmacology modeling of biotherapeutics in oncology

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Section I.
Introduction to translational modeling in oncology

Chapter 1

Introduction and scope

1.1 Challenges in oncology drug development

Significant advances have been made in the treatment of cancer in the past decades, with a shift away from cytotoxic drugs, towards more targeted therapies, immune-oncology drugs, cancer vaccines and cell-based treatments. Groundbreaking new therapies have been identified, with a myriad of potential combination therapies possible. Some 50 years since 'the war on cancer' was declared, these are enabling a different era in cancer treatment with declines in mortality and morbidity, less side effects and talk of chronic treatments [1]. Despite these advances, the success rate of oncology drug development remains the lowest among all the therapeutic areas [2] with an overall success rate of only 3.4%, mainly driven by failure in Phase 2 [2].

There are multiple reasons why oncology drug discovery and development are so difficult. First, cancer is an exceptionally heterogeneous and adaptable disease, with massive variability between tumors and within a tumor. At the molecular level, it is likely that no two cancers are identical. In treating cancer, we are therefore treating a multitude of different diseases [1]. This is exacerbated by the fact that patients are entering trials heavily pre-treated with high potential for drug resistance. A 'one size fit all' approach will not work in cancer treatment. Secondly, it is difficult to translate from preclinical data to the clinic to predict efficacy and toxicity [3]. Until recently, efficacy was assumed to be dose related and clinicians would push cancer drugs to the maximum tolerated dose (MTD) in clinical development, which was subsequently defined as the efficacious dose [3]. This assumption may have been possible for small molecule drugs but is much less appropriate for biotherapeutics. The trade-off between efficacy and toxicity has almost always been resolved in the clinic and remains a large source of drug failure.

The workhorse preclinical model in oncology is the mouse xenograft model, which comprises subcutaneous implantation of a human cell line or tumor into immune compromised host mice [4]. The xenograft model represents extreme simplification of human cancer, as it does not account for complexities of tumor metastasis, host immunity, tumor heterogeneity, and the development of treatment resistance that is routinely observed in cancer patients [5]. However, the drug exposure response relationship derived from these models is useful for understanding efficacy and if accompanied by rigorous quantitative analysis such as mathematical modeling, can be used to translate from mouse to human to predict clinical anti-tumor response [6, 7]. Clinically translatable biomarkers are another useful tool likely to improve preclinical to clinical translation, and advances in experimental techniques has made these easier to measure. However, often the biomarkers need to be measured kinetically in tumor tissue, necessitating tumor biopsies from patients, which are still not common path. In vitro to in vivo correlation is thought to be poor, which means that in vitro assays are typically only used for drug screening. A rigorous unifying preclinical to clinical translational framework could facilitate oncology clinical development by better identifying translational strategies, patient selection criteria and appropriate biomarkers to measure [3].

1.2 Biotherapeutic modalities used to treat cancer

Large molecule biotherapeutics in oncology are enabling tumor targeting, activation and re-targeting of the immune system to kill cancer cells, and stimulation of separate immunomodulatory pathways from one molecule. However, the versatility of these molecules brings with it an additional level of complexity, with intricate mechanisms of action and concentration response relationships that are non-intuitive and difficult to predict. In this thesis, different types of biotherapeutic drugs are discussed including monoclonal antibodies (mAbs), antibody drug conjugates (ADCs), T-cell engagers (TCEs) and other bispecific antibodies (bsAbs)- see Figure 1. mAbs have formed the backbone of many successful biotherapeutic modalities for the treatment of cancer. Monospecific mAbs have been used to target specific tumor receptors such as HER-2 and CD20 to inhibit signaling and/or trigger antibody dependent cellular toxicity (ADCC) [8]. This has resulted in first generation mAb drugs in oncology such as trastuzumab and rituximab. More recently, mAbs have been used to target immune checkpoint receptors such as CTLA4 and PD1 on T cells, releasing negative immune regulation of the tumor [9]. This has led to revolutionary new immunotherapy treatments including ipilimumab and pembrolizumab. Although undoubtedly a breakthrough in cancer treatment, immunotherapy still only works well in a minority of patients and for certain cancer types [9]. ADCs are a targeted therapy for cancer treatment, combining a specific mAb to a tumor antigen linked to a potent cytotoxic agent [10]. They make use of the specific binding properties of the antibody to deliver a cytotoxic payload to cancer cells for increased efficacy, whilst minimizing exposure of normal tissues. Brentuximab-vedotin and ado-trastuzumab-emtansine are examples of ADCs on the market for oncology indications. T cell retargeting molecules are bispecific antibodies, or antibody fragments, that bind to CD3 on the surface of T cells and to a tumor associated antigen (TAA) on the tumor cell surface [11]. When both CD3 and the TAA are engaged, the proximity of the T cell and tumor cell results in the formation of an immune synapse, stimulation of the T cell and 'redirection' of cytotoxic activity against the tumor cells. Blinatumomab is a CD19 x CD3 bispecific T cell engager that has received regulatory approval. A second wave of bsAbs are emerging, with tumor selective recruitment and activation of T cells, or more powerful immunomodulation by targeting two distinct immunomodulatory pathways [12].

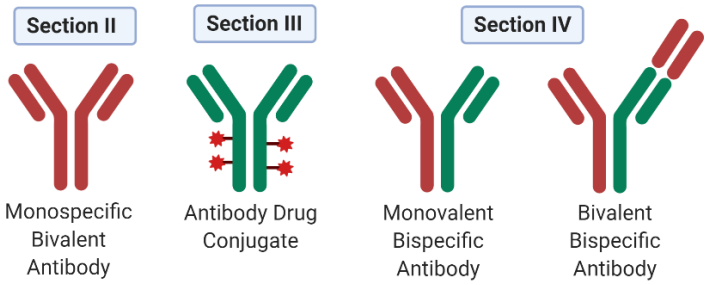

Figure 1: Biotherapeutic drug modalities discussed in different sections of this thesis.

1.3 Mathematical modeling in oncology drug development

To overcome the challenges in oncology drug discovery and development, and to deconvolve the complexities of novel biotherapeutic modalities, innovative approaches are needed. Mathematical modeling is a key tool which has been shown to increase efficiency and effectiveness in drug discovery and development and can be used to facilitate design, selection and preclinical to clinical translation of oncology therapies and to optimize clinical trials [13]. Mathematical modeling can be used to integrate data from disparate sources including literature, preclinical experimental data, and clinical data, to examine the relationships between a drug, the biological system, and the disease process. A quantitative framework is assembled which can provide mechanistic understanding of drug function, enabling optimal experimental design and faster data interpretation. The model framework can be used at early stages to aid in the identification of optimal drug properties for next generation molecules, including optimal target, epitopes, and drug format. Once a lead compound has been selected, the model can be used to translate from preclinical in vitro and in vivo studies to the clinic, to inform clinical study design including prediction of clinical starting dose, efficacious dose, and regimen.

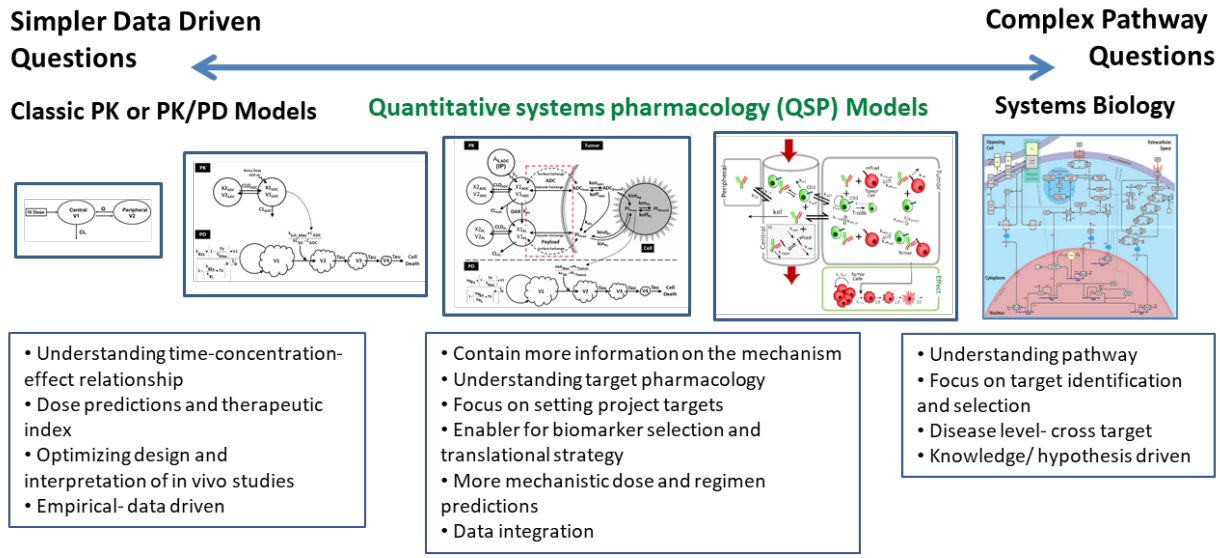

Figure 2: The continuum of mathematical models utilized in drug discovery and development. In this thesis PK, PK/PD and quantitative systems pharmacology models are used, depending on the questions asked and the objective of the modeling. Systems biology modeling was not in the scope of this thesis.

1.4 Scope of this thesis

The aim of this work was to investigate different ways in which mechanistic mathematical modeling and simulation can be used to help with quantitative decision making in oncology drug discovery and development. **Section I** introduces the thesis and its scope. **Section II** focuses on modeling of mAbs, **Section III** on ADCs and **Section IV** on bispecific antibodies. Conclusions and further perspectives are discussed in **Section V**.

Different levels of mathematical modeling were used depending on the questions asked and are introduced in **Chapter 1** (Figure 2). For example, a more statistical population-pharmacokinetic (pop-PK) modeling approach was used for analysis of a large mAb PK dataset with quantitation of variability (**Chapter 2**). Pharmacokinetic/ pharmacodynamic (PK/PD) modeling was used for data driven interpolation of in vitro and in vivo datasets with limited extrapolation (**Chapters 3 & 4**). Quantitative systems pharmacology (QSP) modeling was used to answer more complex mechanistic questions, involving integration of data from disparate sources (literature, in vitro, in vivo and the clinic), linkage of drug pharmacology to biological systems and disease, and multi-scale predictions (**Chapters 4, 5, 6 & 7**).

The scope of this work extends from early drug discovery through to clinical trials, and includes use of modeling and simulation to influence:

- Hypothesis testing
- Interpretation of large datasets to simplify processes, and to avoid unnecessary in vivo studies
- Establishment of in vitro to in vivo correlations
- Preclinical to clinical translational strategies to predict PK and PD
- Competitor differentiation, to ensure that therapeutically beneficial molecules are progressed to clinical studies
- Prediction of optimal clinical doses and regimens
- Precision medicine approaches, including identification of sensitive parameters impacting dose in patients, which could be used as clinical diagnostics and/or to select the optimal patient population.

1.5 Outline of this thesis

In **Chapter 1**, the challenges of oncology drug development are introduced, along with the increasingly diverse array of biotherapeutic modalities being developed to treat cancer. The role of mathematical modeling in the process is discussed.

In **Chapter 2**, pop-PK modeling was used for a meta-analysis of the linear PK of mAbs across different species used in the pharmaceutical industry. This work indicated that linear PK of therapeutic mAbs can be considered a class property, with a typical set of parameters identified across species, with similar values to endogenous IgG. Strategies are presented for predicting linear PK of mAbs with less reliance on cynomolgus monkeys and use of smaller animal or in silico alternatives.

In **Chapter 3**, in vitro to in vivo correlation (IVIVC) was established for ADCs using a PK/PD modeling approach. A comparable efficacy parameter, tumor static concentration (TSC), was derived for in vitro and in vivo experiments and a predictive correlation determined. The methodology established here could potentially be applied to all anti-cancer drugs (large and small molecules). This work has many applications including early triage of ADCs, prevention of unnecessary in vivo studies and saving of resources.

In **Chapter 4,** a PK/PD modeling approach was used for quantitative comparison of a new generation HER2 ADC (PF-06804103) with trastuzumab-DM1 (T-DM1), to ensure efficacy differentiation and as a rationale to pursue clinical development of PF-06804103. This included comparison of TSC values across a range of in vivo tumor models, representing different disease origins (breast, gastric and lung), clinical pathologies such as low-high HER2 expression and resistance to T-DM1. A mechanistic model was developed to describe non-linearity in T-DM1 PK in patients due to binding to shed HER2. A similar model was then used to predict clinical PK for PF-06804103. A translational strategy was proposed to predict clinical efficacy in patients.

In **Chapter 5**, a translational QSP model for ADCs is presented, which was used for preclinical clinical translation of inotuzumab-ozogamicin, a CD22 targeting ADC for the treatment of B cell malignancies. The model predicted progression free survival responses for inotuzumab versus non-Hodgkin's Lymphoma (NHL) that were comparable to observed clinical trial results, demonstrating its utility for predicting efficacy of ADCs. The model was also able to give useful mechanistic insight into optimal dosing regimens and sensitive parameters impacting outcome. This knowledge could be applied to optimize the design of ADCs in the discovery phase of research and/or for selection of predictive diagnostic in the clinic.

In **Chapter 6**, a translational QSP model for T cell retargeting CD3 bsAbs is presented. This model predicts trimolecular complex formation between drug, T cell and tumor cells required to form an immune synapse, which triggers T cell activation and cytotoxicity. The model was used to characterize the PK/PD relationship in mouse tumor models and translated to the clinic to predict clinical efficacious dose. Notably, this model can also be applied at early stages to aid in CD3 bsAb design and candidate selection.

In **Chapter 7**, as a means of a general conclusion to this investigation, mechanistic quantitative pharmacology strategies for the early clinical development of bispecific antibodies (bsAbs) in oncology is presented. This includes use of modeling to understand complexities of bsAbs, impact decision making and aid in clinical translation, trial design, and prediction of regimens and strategies to reduce dose limiting toxicities. BsAbs are an integral component of the current therapeutic research strategy in oncology and explorative preclinical and emerging clinical data indicate potential for enhanced efficacy and reduced systemic toxicity. The strategies discussed could be powerful tools to facilitate clinical success of bsAbs, while decreasing time required for non-clinical development.

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