Mechanistic Quantitative Pharmacology Strategies for the Early Clinical Development of Bispecific Antibodies in Oncology

Alison Betts[1,2,*] (iD) and Piet H. van der Graaf[2,3] (iD)

Bispecific antibodies (bsAbs) have become an integral component of the therapeutic research strategy to treat cancer. In addition to clinically validated immune cell re-targeting, bsAbs are being designed for tumor targeting and as dual immune modulators. Explorative preclinical and emerging clinical data indicate potential for enhanced efficacy and reduced systemic toxicity. However, bsAbs are a complex modality with challenges to overcome in early clinical trials, including selection of relevant starting doses using a minimal anticipated biological effect level approach, and predicting efficacious dose despite nonintuitive dose response relationships. Multiple factors can contribute to variability in the clinic, including differences in functional affinity due to avidity, receptor expression, effector to target cell ratio, and presence of soluble target. Mechanistic modeling approaches are a powerful integrative tool to understand the complexities and aid in clinical translation, trial design, and prediction of regimens and strategies to reduce dose limiting toxicities of bsAbs. In this tutorial, the use of mechanistic modeling to impact decision making for bsAbs is presented and illustrated using case study examples.

Cancer is a complex, multifactorial disease. Crosstalk between signaling cascades and multiple mediators of tumor survival and immune evasion exist. Genetic alterations lead to heterogeneity in tumor cell antigen expression within and between patients. Acquisition of resistance to therapy is associated with upregulation of alternative receptors as well as pathway switching between receptors. Overall, this means that specific targeting of a single receptor is often insufficient for efficacy and standard of care consists of combinations of therapies to kill tumor cells.[1] However, development of individual drugs for a combination therapy can be a costly and time-consuming process requiring separate manufacturing processes and filing the safety of each antibody component separately.[2,3]

During the past decade, advances in protein engineering have resulted in the ability to robustly and cost-effectively synthesize bispecific antibodies (bsAbs) as an alternative to combination therapy or use of mixtures.[4] This has led to an explosion of bsAbs in drug development–currently there are 57 bsAbs in clinical trials in patients with cancer,[5] with a large diversity in formats.[6] Thus far, blinatumomab (Blincyto; Amgen) is the only bsAb approved in oncology.[7] Blinatumomab is a CD19/CD3 bispecific T-cell engager (BiTE), which was initially approved in 2014 for Philadelphia chromosome-negative relapsed or refractory (r/r) B-cell precursor acute lymphoblastic leukemia (ALL) in adults.[8] Since then, it has gained approval for treatment in pediatric patients with ALL and for minimal residual disease-positive B-cell precursor ALL, where it is the first US Food and Drug Administration (FDA) approved treatment for this specific patient population. Despite the success of blinatumomab, there remains many opportunities to improve this

modality in new generation bsAbs. For example, blinatumomab has a boxed warning due to cytokine release syndrome (CRS) and neurological toxicities experienced by patients.[8] In addition, the small structure of blinatumomab and lack of an Fc domain leads to accelerated clearance and short half-life in patients, such that a continuous infusion regimen is required.[9] This has opened the door to an evolution of ~ 100 different bispecific formats varying in size, arrangement, valency, flexibility, and geometry of their binding modules, as well as in their distribution and pharmacokinetic (PK) properties.[6] In addition to immune cell re-targeting, bsAbs have the capacity to simultaneously target multiple disease pathways, releasing the potential for attractive new therapies with enhanced efficacy and tumor selectivity leading to reduced systemic toxicity and improved therapeutic index (TI). To this end, bsAbs are being utilized for several different applications in oncology, which are summarized below and illustrated in **Figure 1**.

Although bsAbs have great potential, their clinical development is complex with many inherent challenges. To start with, it is difficult to translate from preclinical efficacy studies, which may be conducted in immunodeficient mice engrafted with human cancer cells and immune cells, or with immune competent syngeneic mice engrafted with human cancer cells using surrogate murine antibodies, or in transgenic mice to predict clinical efficacy. Many bsAbs in oncology have immune agonistic properties and a minimal anticipated biological effect level (MABEL) approach is required for selection of clinical starting doses. Selection of clinical starting dose is highly dependent upon the type of *in vitro* assay chosen to determine MABEL and can result in selection of overly conservative doses and many
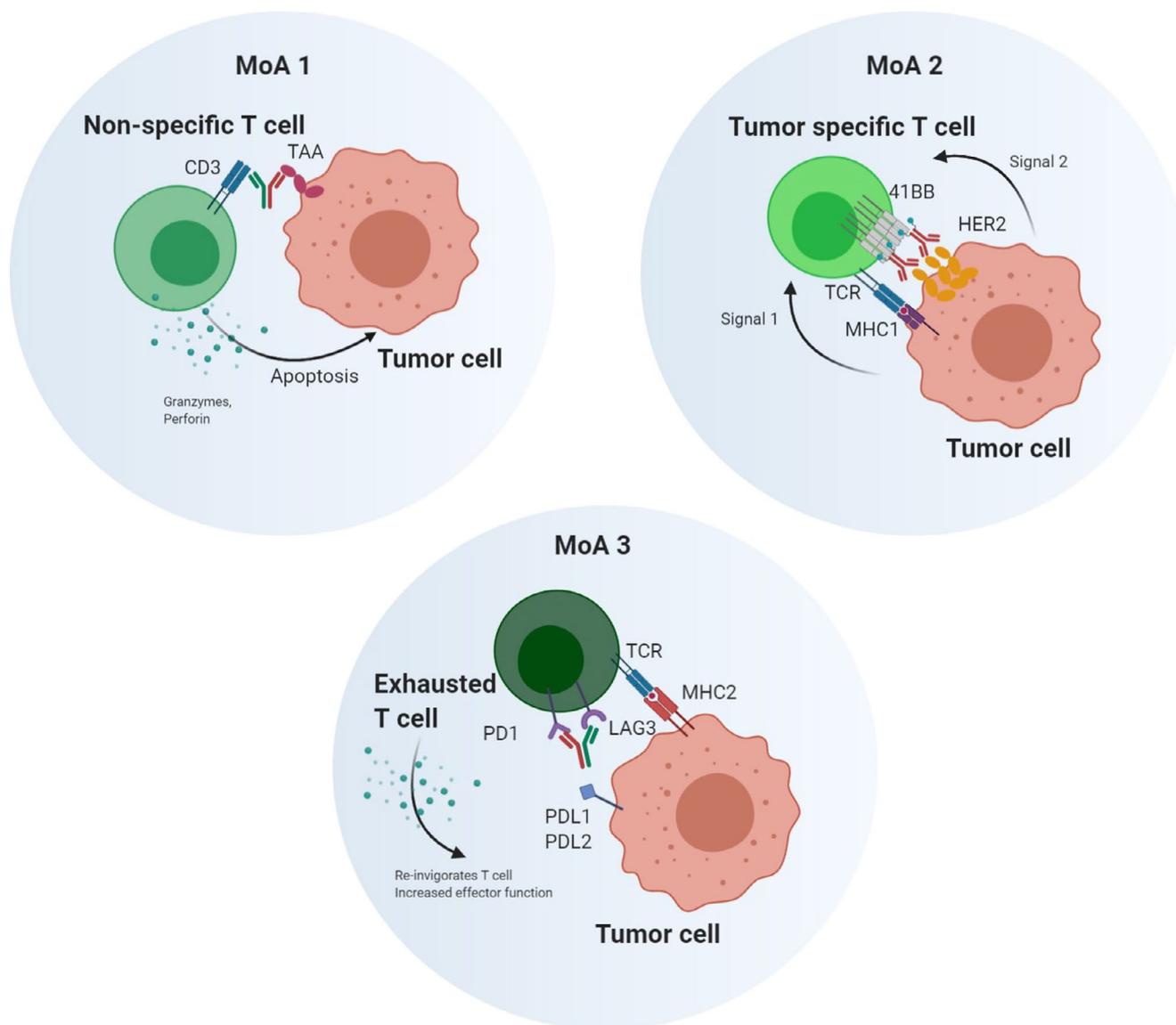
Figure 1 Mechanism of action (MoA) of bispecific antibodies (bsAbs). MoA 1—CD3 T cell engagers. These bsAbs bind to CD3 expressed by the T cell and a specific antigen expressed by the tumor cell, resulting in the formation of an immune synapse. This stimulates the T cell and "re-directs" cytotoxicity against the tumor cell. MoA 2—Tumor targeting. These bsAbs direct binding toward the tumor by binding to a specific antigen on the tumor cell and to an immune receptor expressed on tumor infiltrating T cells (or other immune cells). For example, a bsAb binding to HER2 on tumor cells and 4-1BB on T cells is shown, which can result in a potent antitumor immune response. MoA 3—Targeting multiple immune modulatory receptors. These bsAbs can bind to different targets modulating immune responses, thus allowing combined biological effects and synergies. For example, a bsAb targeting PD-1 and LAG-3 expressed on exhausted T cells and/or TILs is shown, which inhibits the immunosuppressive mechanisms associated with these targets.

rounds of dose escalation before reaching efficacious doses in the clinic. In addition, the efficacious dosing regimen of the two targets cannot be independently controlled for a bsAb, as it would for a combination therapy of two monospecific antibodies. As a result, it may be challenging to optimize target engagement for two targets. For example, combination of a binding domain for an immune agonist with an immune antagonist would require different levels of target engagement necessitating different PK profiles from pulsatile to complete exposure. There are many factors impacting variability in the clinic, including affinity of the individual arms, potential for avidity, target expression, presence of soluble target, and PK, to name a few (**Table 1**). In addition,

key safety concerns, such as CRS, require to be minimized and managed in the clinical setting.

The inherent complexity of bsAbs lends itself well to the use of mathematical modeling and simulation, in order to map out the mechanistic pathways and consider the impact of multiple variables. Mechanistic approaches, such as quantitative systems pharmacology (QSP) models, combine computational modeling and experimental data to examine the relationships between a drug, the biological system, and the disease process.[10,11] These models describe the biophysics of binding of bsAbs to their membrane receptors and soluble target in different compartments (e.g., blood, periphery, tumor, and immune tissues) using a system of ordinary

Table 1 Variables impacting efficacy and toxicity of bsAbs

Variable (unit)	Quantitative method of analysis	Potential range	Examples	Considerations
Drug properties of bsAbs				
Affinity for each target (Kd; nM)	Surface plasmon resonance (e.g., Biacore, Kinexa)	pM–nM	Blinatumomab: CD19 1.49 nM/CD3 260 nM[9]; Solitomab: Epcam 16 nM/CD3 77 nM[74]; AMG330: CD33 8.0 nM/CD3 5.1 nM[75]; PCad-LP-DART: Pcad 0.47 nM/CD3 11.4 nM[13]; PRS-343: HER-2 0.3 nM/41BB 5 nM[19]; MGD-013: PD1 1.0/LAG3 0.1 nM[76]	For CD3 bsAbs, a relatively higher affinity for the TAA compared to CD3 may improve tumor localized T-cell activation and reduce systemic CD3 targeting and toxicity.
Avidity (cross linking chi-factor)	On cell binding by ELISA and/or flow cytometry + QSP model	1e2–1e6[46]		May be a requirement for tumor targeting to prevent on target/off tumor toxicity.
PK: elimination half-life (hours–days)	Ligand binding assay Occasional mass spectrometry.	hours–days	Typical mAb: 16–21 days[77]; Blinatumomab (BiTE): 2 hours[9]; Pcad-LP-DART: 1 day[13]; Solitomab (BiTE): 4.5 hours[70]; AFM-13: 8.7–19.2 hours[15]; PRS-343: 5 days[20]	Dictated by presence of an Fc domain. Soluble target may act as a peripheral sink. Potential for target mediated drug disposition.
System properties of bsAb targets				
Receptor expression (receptors/cell)	Flow cytometry: Phycoerythrin conjugated antibodies (1:1) and calibration beads (QuantiBRITE or Bangs) to determine antigen binding capacity	100: limit of detection; 1e3: low; 1e4: medium; 1e5–1e6: high	**Tumor cells[a]**: PDL1: 1e4[78]; HER2 (different cancers): 2e4–1e6[79,80]; BCMA (multiple myeloma): 1,479 (42–1.4e4)[81]; Pcad: 2.8e4[13]; Epcam: 1.1e5[74]; CD19 (B cell leukemias): 1–3.8e4 — **Immune cells[b]**: CD3 (T cells): 5e4–1e5[82]; CD16 (NK cells): 7.9e4 ± 3.0[82] 3.64e5 (median)[83]; 41BB (monocytes and other immune cell types) ~1e3[84]; PD1 (TILs): 5e4 (1e4–1e5)[78]	Is the receptor constitutively expressed or inducible? What % of cells express the receptor (heterogeneity of expression)? Quantify across tissues, species and in disease.
Soluble target in the central compartment (nM)	Mass spectrometry or ELISA	<1–100 nM	HER2: 0.15 nM (upper limit of normal)–22 μM (MW = 100 kDa)[49]; BCMA: 16 nM–94 nM (MW = 5.3 kDa)[53]; Pcad: 1.1 nM (0.4–4.1)[13]; PDL1: 0.05–0.139 nM (MW = 25 kDa) (Durvalumab BLA); PD1 (pancreatic and NSCLC patients): 0.00143–1.85 nM (MW = 14kDa)[85,86]	Variable across species. May be higher in patients expressing high levels of target. For HER2 and BCMA correlates with efficacy.
Internalization/turnover rate	Amnis FACs	minutes–hours	Pcad: 0.1728 1/day[13]	

bsAbs, bispecific antibodies; ELISA, enzyme-linked immunosorbent assay; PK, pharmacokinetic; QSP, quantitative systems pharmacology; TAA, tumor associated antigen; TIL, tumor infiltrating lymphocyte.
[a]Expression on human tumor cells (where possible). [b]Expression on human whole blood lymphocytes.

differential equations. The receptor binding interactions can then be linked to downstream pharmacodynamic (PD) response and efficacy or toxicity. To do this, QSP models integrate data from diverse sources and assays, including drug assays (e.g., K_ds or half-maximal effective concentration), system parameters (receptor expression and internalization rates), *in vitro* experimental data, preclinical *in vivo* studies, and clinical data. A quantitative framework is assembled that can provide mechanistic understanding of bsAb 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 QSP 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.

In this tutorial, the mechanism of action (MoA) of bsAbs in oncology drug development will be discussed, and specific clinical pharmacology challenges in early-stage clinical development will be considered and reviewed. The use of mechanistic modeling and simulation strategies to address these challenges will be presented, supported by case studies that exemplify the application and impact of mechanistic modeling in the drug development process. Note that challenges and modeling strategies for bsAbs in later-stage clinical development are out of the scope of this tutorial and will not be discussed.

MECHANISM OF ACTION OF BISPECIFIC ANTIBODIES IN ONCOLOGY

Engagement of immune cells (adaptive immune response)

The majority of bsAbs in clinical trials are CD3 T cell engager (TCE) molecules. These bsAbs bind to CD3 in the T cell receptor/CD3 protein complex expressed on the surface of T cells and to a tumor associated antigen (TAA) on the tumor cell surface. When both CD3 and TAA are engaged, the proximity of the T cell and the tumor cell result in the formation of an immune synapse, stimulation of the T cell, and "re-direction" of cytotoxicity against the tumor cell (**Figure 1**). CD3 bsAbs have minimal tumor cell killing on their own,[12] and efficacy and on-target toxicity are driven by the formation of a trimolecular complex (hereafter trimer) between the bsAb, T cell, and tumor cell.[13]

CD3 bsAbs have exhibited clinical validation for hematological malignancies through blinatumomab, and several other TCEs in clinical trials. These include BiTEs, half-life extended diabodies/antibody fragments and full length heterodimeric IgGs targeting TAAs, including CD20, BCMA, CD33, CD19, CD123, and others. There are a smaller number of CD3 bsAbs in clinical development for solid tumors, targeting, for example, HER2, DLL3, gpA33, and CEA for metastatic breast cancer, small-cell lung cancer, colorectal cancer, and other solid tumor indications, respectively. Blinatumomab and other CD3 bsAbs are reviewed extensively in the work by Yuraszeck *et al.*[14]

Engagement of immune cells (innate immune response)

In addition to T cells, other effector cells or immune cell subsets can also be recruited to tumor cells. For example, bsAbs have been developed to target natural killer (NK) cells, which are potent cytotoxic lymphocytes of the innate immune system. An example of an NK cell redirector is AFM-13, a tandem diabody construct targeting CD16 on NK cells and CD30 on tumor cells.[15] In a phase I trial in patients with r/r Hodgkin's lymphoma, treatment with AFM-13 resulted in activation of NK cells and a decrease in soluble CD30 in peripheral blood, and 3 of 26 patients had a partial response.[15] AFM-13 is now in a phase II trial for patients with Hodgkin's lymphoma.

Tumor targeting

These bsAbs focus their immune-activating pharmacologic effects to the tumor environment, thereby achieving improved efficacy as well as reduced systemic immune-related adverse effects (**Figure 1**). They are an emerging class of bsAbs, which are mainly in the preclinical phase. However, explorative preclinical and emerging clinical data suggest great potential.[16]

4-1BB is a potent co-stimulatory receptor, which is upregulated on effector T cells, and upon stimulation promotes cytotoxic function as well as induction of immunological memory.[17] It is a good candidate for tumor targeting as systemic activation can result in severe toxicity. For example, the initial clinical development of the agonistic 4-1BB monospecific antibody urelumab was terminated due to fatal hepatotoxicity, with a maximum tolerated dose of 0.1 mg/kg q3w.[18] A 4-1BB/HER2 bispecific molecule PRS-343 is designed to facilitate T-cell co-stimulation by tumor-localized, HER2-dependent 4-1BB clustering, and activation (**Figure 1**).[19] In a phase I study in patients with HER2-positive cancer, PRS-343 demonstrated single-agent antitumor activity, including partial responses, and was well-tolerated at doses up to 8 mg/kg q2w.[20]

Another popular target for tumor-focused bsAbs is CD47, an innate checkpoint receptor, which is widely expressed on many tumor types. Interaction with its receptor SIRPα on macrophages and dendritic cells acts as a "don't eat me signal" enabling tumor cells to evade phagocytosis and clearance. Blockade of CD47 in preclinical studies using monospecific antibodies has resulted in encouraging efficacy. However, CD47 is expressed on the membranes of all cells in mice and humans, including red blood cells, which can act as a substantial "antigen sink," resulting in limited systemic use of CD47 inhibitors due to side effects. BsAbs, which target tumor-specific receptors with high binding affinity on one arm and CD47 with weaker affinity on the other arm, are a popular strategy for increasing tumor cell targeting and enhancing TI. A bispecific antibody targeting PD-L1 and CD47,[21] showed significantly enhanced tumor targeting and therapeutic efficacy vs. monotherapy. In addition, as critical innate and adaptive checkpoints on tumor cells, CD47 and PD-L1 coordinate to suppress immune sensing.

Combining check-point inhibition and immune modulating receptors

BsAbs are also being used to combine checkpoint inhibitors or for dual targeting of checkpoint inhibitors and co-stimulators of the immune response, or inhibitors of exhaustion markers (**Figure 1**). These compounds may combine the activity of the original drugs, but also allow for additional synergies and unexpected novel

biological effects that could not be achieved by combining the corresponding monospecific antibodies. A potential disadvantage of such compounds may be the risk of toxicity due to strong immune activation. Most of these bsAbs block two inhibitory checkpoint pathways, such as PD-1 or PD-L1 combined with other immunosuppressive targets, such as TGF-β, LAG-3, and TIM-3. For example, MGD-013 is a bsAb based on the dual affinity re-targeting (DART) platform that targets PD-1 and LAG-3, which are both expressed on exhausted T cells and tumor infiltrating lymphocytes (**Figure 1**). Inhibition of these targets has been shown to exert a synergistic effect on tumor immunity in mice.[22] MGD-013 is currently in phase I clinical trials. There are many other dual immunomodulator bsAbs in preclinical development, including MCLA-134, which targets PD-1/TIM-3 and XmAb-20717, which targets CTLA-4/PD-1.[16]

The MoA of T cell engagers, tumor targeting bsAbs, and bsAbs targeting multiple immune modulating receptors are shown pictorially in **Figure 1**.

EARLY CLINICAL PHARMACOLOGY CHALLENGES FOR BISPECIFIC ANTIBODIES
Selection of clinical starting dose: How to define MABEL

To ensure maximum clinical benefit of phase I dose escalation clinical trials, particularly for patients in early dose cohorts, it is important to select a safe starting dose and then rapidly escalate to the efficacious dose. To select a starting dose of bsAbs, including CD3 bsAbs, a MABEL approach is recommended due to their immune agonistic properties.[14] The principal of MABEL is that it is better to start with the lowest dose believed to be active, rather than the highest dose thought to be safe. However, MABEL can be difficult to interpret, and this can result in selection of a starting dose that is far below doses required for efficacy in patients and consequently dose escalation trials can take several years.[23] For example, Amgen's BCMA BiTE (AMG-420) entered clinical trials in 2015 with a starting dose of 0.2 µg/day. The first positive clinical results were reported 3 years later in patient cohorts that were dosed several logs higher than the initial cohort, with a dose of 400 µg/day finally selected as the efficacious dose for further investigations.[24] Another example is Roche's cibisatamab (CEA-TCB), a novel T-cell-bispecific (TCB) antibody targeting CEA, which started phase I clinical trials in 2014, at a starting dose of 52 µg.[25] In the dose expansion cohort, doses up to 600 mg have been evaluated over a period of 5 years.[26]

An important issue is the approach used for determining MABEL of CD3 bsAbs. Traditionally, MABEL is based upon doses that achieve receptor occupancy (RO) of ~ 10–20%, however, this approach is not recommended for CD3 bsAbs as they are immune agonists with low and variable RO required for efficacy.[27] The most popular method is to use a PK driven approach, where the recommended clinical starting dose is calculated by setting the predicted drug exposure below 20% of the maximal effective concentration (EC_{20}), which is selected as a threshold from *in vitro* assays.[27,28] This method is easy to accomplish, and regulatory agencies typically accept proposed starting doses corresponding to 10–30%, or even in some cases 50% pharmacological activity,[27] depending on the target biology and other factors, including

the proposed application, available data, and impact of the model-based decision. However, this approach can be misleading as it is calculated using bsAb concentration rather than trimer concentration, which is required to drive efficacy and toxicity.[13] It is highly dependent upon the experimental conditions of the *in vitro* assay used to determine EC_{20}, which can result in substantially different MABEL doses. These assays include cytokine release, cytotoxicity, and T-cell activation/proliferation assays, which are commonly used to determine bsAb activity. In order to observe activity *in vitro* in short time frames, the assays are generally completed under nonphysiological conditions, including effector:target (E:T) cell ratios of > 5:1, which are significantly higher than those observed in patient tumors and use cell lines that overexpress target. In addition, often the most sensitive assay is selected for MABEL determination. Depending on the *in vitro* experimental conditions, an overly conservative *in vitro* threshold can be selected, which may result in a starting dose that results in many rounds of subefficacious dose escalation, or a starting dose could be selected that is too close to the efficacious dose such that it gives safety concerns. A better method is to use a mathematical modeling approach for selection of clinical starting doses for bsAbs, which can integrate *in vitro* data generated under different experimental conditions to estimate a single EC_{20} based on trimer concentrations, rather than bsAb concentrations. The mathematical model can be translated to the clinic and the *in vitro* trimer EC_{20} can be used as a threshold to predict a relevant clinical starting dose, which is independent of experimental conditions. A QSP modeling approach to MABEL is discussed in detail below.

Determining clinical efficacious dose: Nonintuitive dose-response relationships of bsAbs in early clinical trials

Historically, in oncology drug development, efficacy has been assumed to be dose related and cancer drugs are escalated to the maximum tolerated dose in phase I clinical trials, which is subsequently defined as the efficacious dose.[29] However, bsAbs have a complex MoA, which can make dose response relationships nonintuitive and difficult to rationalize. For example, a specific complexity of CD3 bsAbs is efficacy and on-target toxicity are driven by trimer formation between the bsAb, T cell, and tumor cell.[13] A bell-shaped concentration vs. response relationship can be observed, which is a well-described phenomenon for ternary complexes.[30–32] When bsAb concentrations are low, conditions favor bivalent binding and the formation of trimers. As bsAb concentration is increased, an optimal concentration is reached for trimer formation. If additional bsAb is added, it will be in excess and favor monovalent binding to form dimers between bsAb and T cells or bsAb and tumor cells. This results in decrease in response as dimers cannot trigger cytotoxicity (**Figure 2**). The width of the bell shape, or efficacy window of the bsAb (**Figure 2**), will depend upon variables impacting trimer formation, such as receptor expression, E:T ratio and the binding affinity of the bsAb for CD3 and its specific tumor antigen.[33] As a result, the bell-shaped relationship will be different for every bsAb and could be different for every patient treated with a given bsAb. This could potentially impede interpretation of phase Ia dose escalation trials and impact selection of doses for phase Ib expansion cohorts, or even
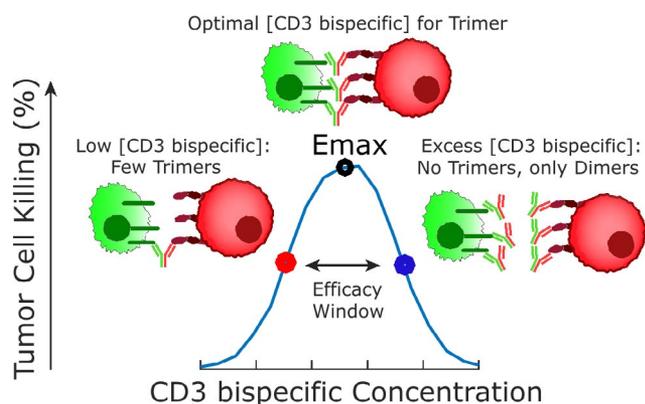
Figure 2 Bell-shaped concentration response relationship observed for CD3 bispecific antibodies. E_{max}, maximum effect.

recommended phase II doses. For example, it may be difficult to determine whether a dose close to the projected efficacious dose is ineffective due to being on the right-hand side of the bell-shaped response and when to stop dose escalation. The bell-shaped relationship has been confirmed preclinically for CD3 bsAbs[34,35] and mechanistic modeling can be used to predict it and to optimize variables to minimize its impact on efficacy and toxicity. For example, Schropp *et al*. developed an equilibrium binding model for bsAbs and investigated how changes in receptor and bsAb concentration impacted the formation of the trimolecular complex and the efficacy window of the bell-shaped curve.[33]

In addition to CD3 bsAbs, the bell-shape relationship could affect other bsAbs that form ternary complexes by binding *in trans* to link effector and target cells, including NK cell engagers, tumor targeting agents, and dual immunomodulators. To optimize drug dosing and scheduling in the clinic, a rational dose selection approach using mathematical modeling is recommended, which will account for the variables discussed above. This mathematical framework could be updated with emerging clinical data (such as PK or receptor expression data) to refine dosing protocols in real time and to help in the interpretation of complex data.

Specific features of bsAbs impacting variability in clinical response

A major challenge in oncology drug development is interindividual variability in drug response, which affects both efficacy and toxicity. BsAbs are a complex drug modality, binding to two distinct targets, often with two separate mechanisms of action. As a result, many different variables can impact the concentration vs. response and toxicity relationship for bsAbs in individual patients. These variables can be categorized as "drug specific" and "system specific" parameters.[36] Drug-specific parameters typically include pharmacologic parameters, such as affinity and avidity, and PK parameters, including clearance, volume of distribution, and elimination half-life. System-specific parameters include receptor expression, concentrations of soluble target, receptor internalization/turnover rates, and E:T ratio. In **Table 1**, some of these variables are listed along with quantitative methods of analysis and ranges of values possible for bsAbs and their targets. The PK of bsAbs has already been reviewed and will not be covered here.[37]

In addition, variability due to comorbidities, comedications, and disease severity are other important factors influencing variability in clinical responses, especially at later stages of clinical development, which are out of scope in this tutorial. Further discussion on some of the unique features of bsAbs, which may impact response across patients are reviewed below.

Impact of avidity. A key variable of bsAbs, especially those with multi-valency, is their ability to have enhanced functional affinity due to avidity.[16,38] Affinity is defined as the strength, expressed in thermodynamic terms, of the binding interaction between a single antigen and a single region of the mAb.[38] Avidity, however, is the accumulated strength of multiple affinities summed up from multiple binding interactions and is commonly referred to as a functional affinity.[38] The strength of avidity is likely a function of tethering producing an increased local concentration of the antibody due to restriction of diffusion to the cell membrane, and epitope and format-specific steric variability.[39]

Avidity arising from binding of a bsAb to two receptors on a target cell may lead to greater efficacy than a combination with two antibody molecules, each binding only a single receptor.[40] Avidity often correlates with receptor expression,[39–41] and it is therefore believed that the avidity effect could, in some circumstances, be exploited to reduce systemic toxicity, due to the higher density of receptors on tumor cells leading to enhanced avidity of bsAbs compared with normal cells expressing a lower concentration of receptors.[42] To benefit from the potential advantages of avidity, protein engineers are modulating bsAbs to have weaker affinity for their receptors in order to minimize normal tissue binding, without impairing the potency for target cells.[43] This is seen in nature, where T cells can distinguish between high and low antigen expressing cells by means of relatively low affinity T cell receptors that can still achieve high affinity binding to target cells expressing high levels of target antigen.[44] However, these are complex interactions and the interplay of factors, such as affinity, avidity, and format valence, in relation to the ability of a bsAb to promote target selectivity is not yet well understood.[42] Because avidity can vary with receptor expression, it is likely to result in different observed functional affinities/potencies of bsAbs across patients. To understand avidity and predict its variability and impact on tumor targeting, efficacy, and potential to reduce systemic toxicity, it is important that it can be quantified. First of all, the intrinsic affinity of the monovalent interaction in equilibrium binding experiments should be determined.[41] The avidity could then be predicted using a mathematical model of the bivalent interaction and related to receptor expression, ratios of targets, and affinity under different conditions relevant to the clinic.[39–41,45,46]

Impact of soluble target. Another factor that can impact the PK/PD of bsAbs and lead to patient variability in the clinic is the presence of soluble target, or the shed ectodomain (ECD) of a membrane bound target, which can act as a significant sink for bsAbs restricting the amount of drug free to distribute to the tumor[47] and potentially impacting efficacy.[48] This is especially prevalent for bsAbs in immune oncology, which are often potent activators of the immune system requiring low doses for efficacy.[27]

As a result, circulating concentrations of soluble target/ECD are not saturated at dose levels administered in clinical trials. Levels of soluble target/ECD can also vary significantly across species, complicating preclinical to clinical translation. They are often higher in patients who overexpress tumor target and are variable across patients, impacting doses driving efficacy and toxicity. For example, high levels of shed HER2 ECD have been detected in patients with cancer (2.21 μg/mL) compared with those in healthy subjects (< 15 ng/mL).[49] For the anti-HER2 antibody trastuzumab, high levels of serum HER2 ECD are associated with rapid clearance and decreased benefit from trastuzumab therapy.[49–51] BCMA was bound to be shed and is elevated in patients with multiple myeloma (MM), correlating with disease status and survival.[52] Ghermezi *et al*. showed that serum BCMA (sBCMA) was significantly lower in 43 aged-matched healthy donors (median 36.8 ng/mL), than 46 patients with smoldering MM (median 88.9 ng/mL) and 44 patients with active MM prior to treatment (median 505.9 ng/mL).[53] There was significant variability in each group; for example, the active untreated group had sBCMA levels ranging from undetectable to ~ 5,500 ng/mL.[53] The sBCMA levels were found to directly correlate with response to treatment and clinical status. Specifically, patients with complete response had significantly lower sBCMA levels (median 38.6 ng/mL) than those with partial response (median 99.7 ng/mL) or nonresponsive disease (median 195.3 ng/mL).[53] There are several bsAbs targeting HER2 and BCMA in clinical development and levels of shed target are likely to impact patient variability to drug treatment and resulting efficacy. For targets less well understood, measurement of soluble target levels is also recommended to de-risk impact on efficacy and toxicity. For the CD3 bsAbs, binding to circulating T cells expressing CD3 can also act as significant sink for the drug. Leong *et al*. showed that high affinity CLL1/CD3 TCEs were more potent *in vitro* but had comparable potency to lower affinity variants *in vivo*.[54] This was due to differences in PK, with higher affinity variants showing higher clearance *in vivo* due to binding to CD3 on circulating T cells. Given the ability to impact the therapeutic efficacy of bsAbs, binding to soluble target needs to be accounted for in all experimental systems and species in order to provide meaningful PK and dose predictions. QSP modeling is an ideal way to do this and will be discussed later in this tutorial.

Impact of target burden. Target burden is an important factor, which can vary substantially across patients and correlate with doses driving efficacy/toxicity and the likelihood of clinical success of bsAbs. Target burden is a function of the number of receptors expressed per cell and the number of cells. For bsAbs, targets can be expressed on both tumor cells and immune cells, and can vary substantially depending on tumor burden, E:T ratio, disease status, and patient-specific factors, such as prior treatment. Immune targets can also be inducible with potential to vary during treatment in response to therapy. In addition, tumor targets can display significant intratumoral heterogeneity resulting in bsAbs only targeting a subpopulation of cells where receptor is expressed.[55] An analysis of the CEA/CD3 TCB cibisatamab showed that activity strongly correlated with CEA expression, with higher potency observed in high CEA-expressing tumor cells with a threshold of ~ 10,000 CEA binding sites per cell required for efficient tumor cell killing.[44] In line with this, cibisatamab was unable to induce T-cell mediated killing of primary epithelial cells expressing < 2,000 CEA binding sites per cell *in vitro*.[44] The measurement of target burden is therefore recommended as an important factor impacting the success of bsAb clinical trials and may require adaptation of clinical trial design to include comprehensive longitudinal tissue collection protocols. Incorporation of target burden into predictions of efficacious doses using QSP modeling are exemplified in the case studies presented below.

USE OF MODELING AND SIMULATION IN DECISION MAKING FOR BISPECIFIC ANTIBODIES

Model-based approaches are increasingly being used to support decisions spanning the entire drug development process, from preclinical development through to postmarketing.[56] In early clinical trials, mechanistic modeling can be used to select a clinical starting dose so that patients in early cohorts can benefit from clinical trials. Modeling approaches can also be used to select optimal regimens and step-dosing protocols to avoid cytokine release syndrome, and other toxicities. Mechanistic modeling can be used to predict efficacious dose so that phase I first-in-human trials can be designed to escalate efficiently to doses where most benefit to patients is predicted.[57] Quantitative modeling approaches can be used to determine which biomarkers are predicted to best correlate with efficacy or toxicity.[10] In the face of significant variability, modeling can be used to deconvolve efficacy from variability to predict a robust dose and regimen for phase Ib expansion trials, or recommended phase II dose. Mechanistic modeling can be used to optimize predictions in specific patient populations or for different indications and for defining patient selection criteria so that the trials have greater chance of success. Simulation based on mechanistic models could be used as a basis for selecting combination therapies, which is generally more empirically derived, and unfeasible to determine experimentally via a "trial and error" process.[10,58]

In this section, the utility of mechanistic models to drive decision making and enable success for bsAbs in early clinical trials will be discussed, including preclinical to clinical translation, determining clinical starting and efficacious doses, considerations for early clinical trial design, and predicting toxicities. In addition, consideration of good QSP practice, including model verification, validation, and uncertainty quantification will be reviewed.

Translational strategies

Preclinical to clinical translation of bsAbs is required to predict efficacious doses in patients and is a key determinant of clinical success.[23] It is particularly challenging for bsAbs, as they have (at least) two targets and mechanisms of action to translate, with multiple inter-related factors impacting efficacy. In oncology, mouse xenograft models have become the mainstay of clinical translation, as efficacy (tumor growth inhibition) in response to drug can be measured dynamically over time.[59] However, for bsAbs in immune oncology, *in vivo* models are not ideal and often

contrived, with very different conditions to those observed in patients. Two classes of *in vivo* models are currently most widely used: (i) immunocompromised mice with engraftment of human cancer cells and immune cells (ii) immunocompetent syngeneic mice engrafted with human cancer cells.[59] The latter are perhaps more translationally relevant as they possess fully intact immune systems, however, they require mouse surrogate bsAbs to be used instead of human bsAbs to avoid immunogenicity.[60] Non-human primates serve as good toxicology species; however, they lack tumor tissue and are therefore not relevant for understanding efficacy. The complex MoA of bsAbs and the distinct conditions of preclinical *in vivo* models demands an integrated analysis to translate to the clinic. QSP modeling and simulation approaches can incorporate and systematically analyze *in vitro*, preclinical, and clinical data to simultaneously assess the individual effect of, as well as the dynamic interactions among, various factors.[34] Some examples of the use of QSP models to translate preclinical data to the clinic are emerging in the literature for the CD3 bsAbs. For example, Campagne *et al*.[61] developed a PK/PD model for a bispecific CD123/CD3 DART molecule in non-human primates. The model describes DART molecule binding to peripheral CD3 expressing cells and CD123-positive cells, T-cell trafficking, activation, and expansion, and resulting peripheral depletion of CD123 cells. By integrating primary PK and pharmacology, the model represents an efficient translational framework to provide quantitative predictions of drug disposition and potency in humans, and to predict dosing strategies to inform ongoing clinical trials. A translational QSP model is presented for CD3 bispecific molecules by Betts *et al*.,[13] which integrates *in silico*, *in vitro*, and *in vivo* data in a mechanistic framework, to quantify and predict efficacy across species. This is discussed in more detail in case study 1.

Jiang *et al*.[34] proposed a mechanism-based PK/PD model based on target cell-biologic effector cell complex formation and used it to describe and predict *in vitro* cytotoxicity. The model was also used to translate from *in vitro* data to the clinic, validated using blinatumomab data. The model reasonably projected the exposure-response relationship of blinatumomab in patients with ALL by incorporating drug-specific parameters identified from *in vitro* cytotoxicity data and system-specific parameters based on human physiology and pathology data for multiple T-cell redirecting bsAbs under different experimental conditions. A similar approach was taken by Hua *et al*.[62] who developed *in vitro* and human QSP models for an Epcam/CD3 bsAb, solitomab, and used the model to show that number of trimers/T cell required to drive cytotoxicity *in vitro* could be used as a target engagement metric to translate to human and predict clinical efficacious dose. The inherent complexities of bsAbs mean that clinical translation will be challenging to determine empirically, but may be aided by mechanistic models that capture the pathophysiology of the disease and the mechanisms of action of each agent.[14]

Optimizing design of clinical trials

A holistic, mechanistic methodology to select MABEL-based clinical starting doses of bsAbs is to use a QSP modeling approach.[28] For CD3 bsAbs, an *in vitro* QSP model can be used to estimate the trimer concentration that results in 20% tumor cell killing (trimer EC_{20}). The model describes bsAb binding to CD3 on T cells and TAA on tumor cells to form dimers and then trimers, which are linked to cytotoxicity and/or T cell proliferation. The model accounts for the specific conditions of the *in vitro* assay, including the number of cells, E:T ratio, and receptor expression on tumor cell lines used in the experiment. It can then be translated to human by incorporation of a PK model, and updating parameters (including E:T ratio and receptor expression) to reflect patient tumors, in order to determine the dose required to achieve trimer concentrations approximating trimer EC_{20} in the clinic. This approach accounts for tumor trimer concentrations driving efficacy/toxicity and normalizes for differences between *in vitro* experimental conditions and the clinic. This method was used to predict clinical starting dose of a P-cadherin/CD3 bsAb using the MABEL approach and is described in case study 2. Another advantage of using a QSP model is that it provides a translational framework where the same model can be used for determining the starting and efficacious doses. Clinical trials can subsequently be designed for rapid escalation from the predicted starting dose to the efficacious dose, to reduce patients receiving subtherapeutic doses, and reducing overall time in phase I.[63] The QSP approach to MABEL can be integrated with other clinical trial design strategies, such as use of single patient cohorts early in the early stages of dose escalation and even intrapatient dose escalation. The model can also be used for a sensitivity analysis to determine key parameters driving efficacy and toxicity. Such a QSP modeling approach was described in case study 1. The mathematical model can be updated with emerging clinical data and used to refine drug dosing and scheduling as well as guiding go/no-go decisions.

Predicting toxicities associated with bsAbs

The key safety concerns with bsAbs, mainly from clinical data on CD3 bsAbs, are excessive release of cytokines, which may translate to potentially life-threatening CRS and target organ toxicity due to redirection of T cells to normal tissues expressing the TAA (off-tumor/on-target cytotoxicity).[63] These toxicities can prevent efficacious doses of bsAbs being reached in the clinic before the onset of adverse events (AEs) and consequently limit the clinical utility of bsAbs.

Since the development of the first CD3 bsAb, clinical trials have shown that they can cause rapid and uncontrolled T cell mediated CRS, even at very low doses.[64,65] Mechanisms for mitigating CRS in the clinic have been implemented, including a "priming" dose strategy (i.e., a lower initial dose followed by a higher maintenance dose), timely supportive care, corticosteroids administered prophylactically or upon onset of symptoms, and IL6/IL6R mAbs (e.g., tocilizumab) upon onset of CRS.[66,67] New generation CD3 bsAbs are being designed with reduced CD3 affinity, or with novel CD3 epitopes that limit cytokine release but maintain cytotoxic activity, or with different mAb formats to reduce potential for CRS.[68] However, predicting the incidence and severity of CRS from preclinical experiments remains a challenge and selection of dose priming regimens in the clinic is mostly based on an empirical trial and error approach. These challenges could be addressed through mathematical modeling, and an example of a "fit-for-purpose" PK/PD approach is discussed in case study 3.

Due to the small number of TAA required on target cells, off-tumor/on-target toxicities can become an issue with CD3 bsAbs[69] and result in dose-limiting toxicities, limiting TI in some cases.[70] For example, in a phase I clinical study with solitomab, an EpCAM/CD3 BiTE construct, treatment of r/r EpCAM + solid tumors was associated with AEs, including severe diarrhea and increase in liver enzymes, which precluded dose escalation to potential therapeutic levels.[70] EpCAM was subsequently shown to be expressed in the gastrointestinal tract epithelia and liver bile duct of patients.[70] The AEs associated with solitomab treatment, therefore, likely represent off-tumor/on-target toxicity due to T cell activation and killing of nonmalignant cells. A QSP model developed for solitomab demonstrated that trimers/T cell required for *in vitro* cell killing (~ 200–400) were similar to the number predicted at the maximum tolerated dose observed in the clinical study. The TI for solitomab was predicted to be close to 1 based on the trimers/T cell formed in tumor and in normal tissue. Multiple ways to mitigate potential off-tumor/on-target toxicities are currently being investigated in preclinical development. If the TAA is overexpressed in tumors, relying on avidity is one potential way to selectively target the tumor.[43] An alternative mechanism, shown in non-human primate studies, is the use of masked antibodies, where the mask is only cleaved in the tumor microenvironment.[71]

Good QSP practice

QSP models are complex, with a variety of data used in model development, often from disparate sources. Many calculations require propagation between models. In addition, models often span multiple time scales from binding to disease modification. As such, QSP models need to be rigorously evaluated and conform to a set of best practices before enabling clinical decisions. A process of good QSP practice is recommended based on model verification, validation, and uncertainty quantification paradigm. A white paper has been published that presents a minimum set of recommendations to guide QSP practitioners.[72] Some critical considerations are also discussed below.

First, a "right sized" model should be used that is suitable for the question asked and has reasonable assumptions. A model verification step should be included to determine that the computational model and analysis accurately represent the underlying mathematical model and its solution. The model should be validated to determine if it is an accurate representation of the real world from the perspective of intended use. Finally, to quantify the accuracy of the prediction and the data, an uncertainty quantification step should be undertaken. These steps are a requirement to evaluate QSP models, to increase understandability to enable model reuse, and to enable routine and unbiased calculation of prediction uncertainty to better understand the consequence of parameter error and patient variability.

CASE STUDIES

The following case studies were selected as useful representative examples where QSP or other mechanistic modeling approaches have impacted early clinical development strategies for particular bsAbs, with the ability to be repurposed for other bsAbs. Case

Study 1 exemplifies the impact of a QSP modeling approach to translate from preclinical *in vivo* studies to the clinic to predict efficacious dose of a CD3 bsAb.[13] Case study 2 uses the same modeling framework to predict clinical starting dose and demonstrates *in vitro* to clinical translation.[28] Case study 3 demonstrates a QSP approach to predict and therefore minimize CRS toxicities upon bsAb dosing.[73] In each case, the focus is on the strategic applications of the mechanistic modeling and its impact. Technical details, including specific models structures, equations, and parameter values, are not included, and can be found in the published manuscripts.[13,28,73] The case studies all describe a generalized CD3 bsAb model based on CD3 engaged through trimer formation, as the important variable driving efficacy and on-target/off-tumor toxicity. As such, this model is a useful platform for all CD3 bsAbs and bsAbs, which bind *in trans* configuration (described as MoA 1 and 2 in **Figure 1**). The CRS model has further applicability to immune modulators resulting in cytokine release. These models could play an important role in design and interpretation of early clinical trials.

Case study 1: Preclinical to clinical translation of a P-cadherin/CD3 DART bsAb using QSP modeling

A QSP model was developed for a P-cadherin/CD3 DART bsAb (Pcad-LP-DART), capable of predicting trimer formation and linking it to tumor cell killing.[13] The model was used to quantify the PK/PD relationship of Pcad-LP-DART in mouse xenograft models. The model, which had the general structure presented in **Figure 3**, integrated the PK of Pcad-LP-DART, its binding to soluble P-cadherin and circulating T cells in the systemic circulation, its biodisposition in the tumor and the formation of a trimolecular complex with T cells, and P-cadherin expressing tumor cells in the tumor microenvironment. The model incorporated T cell kinetics in the tumor, including T cell proliferation and contraction. The concentration of the trimer in the tumor was used to drive efficacy in the mouse using a model of tumor cell growth and killing. A hybrid approach was used in the modeling where known parameters were fixed in the model up-front (binding kinetics, receptor expression, number of T cells, and tumor cells) and unknown parameters were estimated using the model to fit the data (tumor cell growth and killing parameters). A tumor static concentration was calculated and used as an estimate of minimum efficacious trimer concentration across mouse tumor models. The tumor static concentration values were in the picomolar range, demonstrating the inherent potency of this mechanism.

The model was translated to the clinic by incorporating predicted human PK and clinically relevant measures, such as T cell concentration (circulating and tumor), tumor volumes, soluble P-cadherin levels, CD3, and P-cadherin expression. The model was subsequently applied to predict clinical PK, including impact of binding to soluble P-cadherin and prediction of clinical efficacious dose. The model was also used for sensitivity analysis and showed that P-cadherin expression and number of T cells in the tumor were sensitive parameters impacting clinical efficacy. The resulting QSP model and strategy offer a translational framework for CD3 bsAbs, which could be used for decision making at different stages
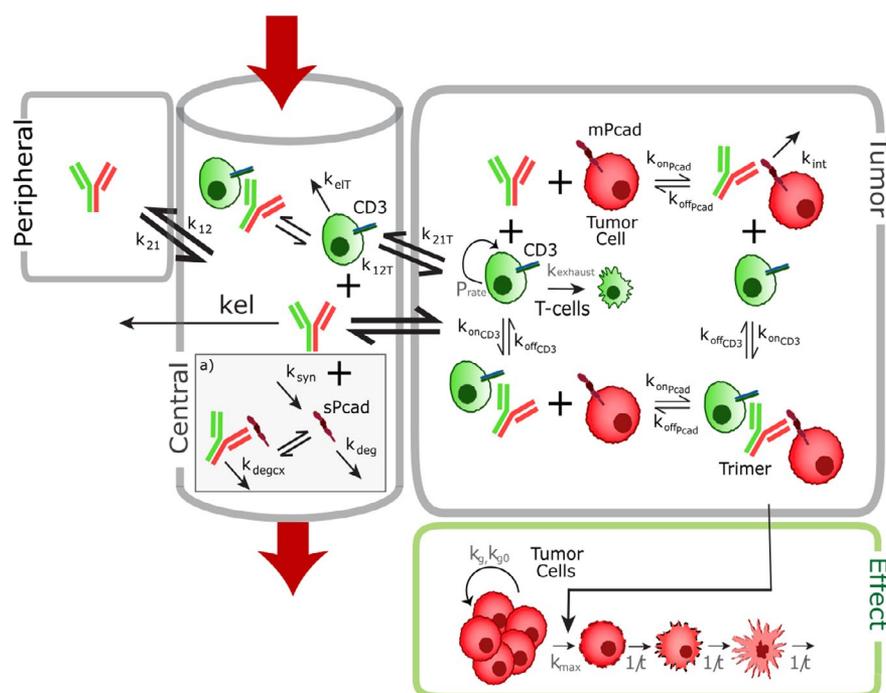
Figure 3 Model framework for trimer formation and tumor growth inhibition of CD3 bispecific antibodies (bsAbs). Formation of trimers among drugs, T cells, and tumor cells, is required for efficacy. The quantitative systems pharmacology model predicts trimer concentration and links it to tumor cell killing. The model shown here is for P-cadherin-LP-DART, which is a bsAb molecule that binds to P-cadherin (Pcad) on tumor cells and CD3 on T cells. Drug can also bind to soluble P-cadherin (sPcad) in the central compartment.

of the drug discovery and development process from drug design through to candidate selection and clinical dose predictions.[13]

Case study 2: Predicting clinical starting dose of a P-cadherin/CD3 DART bsAb using a QSP model/MABEL based approach

A QSP modeling approach was used to project clinical starting dose based on MABEL principles for a P-cadherin/CD3 DART bsAb (Pcad-LP-DART; described in case study 1).[28] The QSP approach was based on the principle that trimer formation among drug, T cell, and tumor cell is driving efficacy and not drug concentration alone. Orthogonal approaches, including PK based methods and receptor occupancy, were also investigated. In the QSP modeling approach, a mechanistic *in vitro* model was constructed describing binding of P-cad-LP-DART to T cells and tumor cells in a dish, to form inactive dimers and the active trimer species. Predicted trimer concentration was linked to *in vitro* T cell kinetic and cytotoxicity experiments to determine EC_{20} of trimer driving T cell proliferation and tumor cell killing. The model was able to capture *in vitro* data at various E:T ratios using the same EC_{20} value, which was considered to be the *in vitro* MABEL. The *in vitro* MABEL was then translated to the *in vivo* MABEL in order to predict human MABEL dose, by incorporation of predicted human PK (which included binding to soluble P-cadherin) and physiological parameters (described previously in case study 1). The MABEL human dose was determined as the predicted average tumor trimer concentration at steady-state equal to the *in vitro* MABEL (EC_{20}, trimer). The predicted clinical MABEL dose using the QSP approach was 1.9 ng/kg/dose.

To build confidence in projecting the MABEL dose, additional approaches were explored, including a PK driven and receptor occupancy approach (**Table 2**). For the PK driven approach, MABEL was defined as the lowest EC_{20} (based on drug concentration) across a panel of *in vitro* assays, including cytotoxicity and cytokine release. The MABEL-based human starting dose was calculated by simulating the predicted human PK and identifying the dose to keep drug concentrations below the EC_{20} values defined from cytotoxicity and cytokine release assays. The resulting MABEL was 1.5 ng/kg dose, which was similar to the PK/PD approach. Finally, MABEL was estimated by determining drug concentration required for 10% RO, using equilibrium drug-receptor interaction theory and predicted human PK. This method resulted in MABEL doses of 360 and 8,300 ng/kg/week for 10% P-cadherin and 10% CD3 occupancy, respectively, which were much higher than the QSP model or PK driven approaches. The RO-based approach is not considered to be appropriate for immune agonists.[27] The MABEL doses using the PK, QSP, and RO approaches are summarized in **Table 2**. Collectively, a dose of 1.5 ng/kg/week was suggested as the first-in-human trial starting dose consistently supported by the QSP-driven and PK-driven approaches.[28] In this example, the QSP-based and PK-based approaches gave similar starting dose predictions, which increased confidence in the suitability of the proposed starting dose to ensure the safety of patients given the potency of Pcad-LP-DART. The same model was used to predict efficacious dose (case study 1) and, therefore, the clinical trial could be designed to escalate efficiently to the projected efficacious dose. The prediction using

Table 2 Projection of minimal anticipated biological effect level for P-cadherin LP-DART, reviewed in case study 2

	In vitro assay	Efficacy variable	MABEL	Starting dose[a] (ng/kg/week)
PK/PD-driven approach	*In vitro* kinetic cytotoxicity assay	Cytotoxicity EC_{20}, syn = 1.2×10^{-6} nM	Maximum tumor synapse conc. < EC_{20}, syn	1.9
PK-driven approach	*In vitro* cytokine release assay	Cytokine release EC_{20}, CRA = 0.025 ng/mL	C_{max} < EC_{20}, CRA	1.5
	In vitro cytotoxicity assay	Cytotoxicity EC_{20}, CTL = 0.01 ng/mL	C_{ave} < EC_{20}, CTL	
RO	*In vitro* binding	RO EC_{10}, RO = 6 (P-cad) and 134 (CD3) ng/mL	C_{max} < EC_{10}, RO	360 (P-cad) 8,300 (CD3)

C_{ave}, average concentration; C_{max}, maximum concentration; EC_{10}, effective concentration 10%; EC_{20}, effective concentration 20%; MABEL, minimal anticipated biological effect level; PD, pharmacodynamic; PK, pharmacokinetic; RO, receptor occupancy.
Reproduced with permissions from ref. 28
[a]One hour infusion.

the PK method, assumes drug concentration alone is driving efficacy and is very sensitive to conditions used in the *in vitro* assay (including E:T ratio, incubation times, and cell lines). For example, the predicted PK driven MABEL dose ranged from 1.5 ng/kg/week to 79.5 ng/kg with only a small difference in E:T ratios (5:1 and 3:1) and incubation times (24, 48, or 72 hours). If this *in vitro* experiment had been used to inform MABEL using the PK-driven approach, the clinical starting dose would have been much closer to the projected efficacious dose and potentially an inappropriate choice. The advantage of the QSP method is that it uses trimer concentration for driving efficacy and the predicted dose is independent of experimental conditions.

Case study 3: A model framework to characterize cytokine release upon CD3 bsAb therapy

In the work by Chen *et al.*, 2019,[73] a quantitative modeling framework was developed for characterizing cytokine profiles upon CD3 bsAb treatment, with the goal to facilitate the design of priming dose strategies to minimize CRS toxicities (**Figure 4**). The model describes cytokine release stimulated by CD3 bsAbs forming trimers by binding to CD3 on T cells and TAA on tumor cells. Tumor kinetics are accounted for in the model to determine the impact of tumor burden on the active trimer concentration. The release of cytokines is controlled by a time variant negative feedback loop, which prevents over activation of the immune system and accounts for the priming effect,
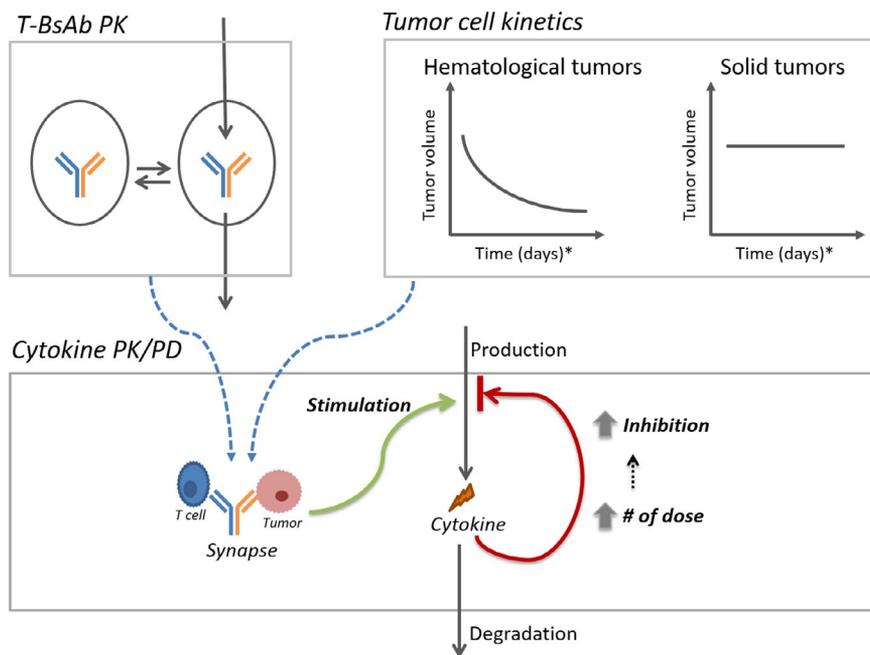

Figure 4 Cytokine release pharmacokinetic/pharmacodynamic (PK/PD) model for CD3 bispecific antibodies, reviewed in case study 3. Reproduced with permissions from ref. 73. Briefly, an appropriate PK model accounts for the drug exposure. Depending on the tumor type (hematological or solid), the tumor kinetics are accounted for in the model to account for the impact of tumor burden on the active synapse concentration. For the cytokine PD model, the synapse exposure then stimulates cytokine release. A time-variant negative feedback loop accounts for the priming effect, where the negative inhibition increases with the increasing number of doses. T-bsAb, T-cell–engaging bispecific antibody.

where negative inhibition increases with increasing number of doses. The model was able to describe cytokine release data for blinatumomab in patients and for P-cadherin LP DART in cynomolgus monkeys, across a wide range of dose levels and regimens. The model could be used to design optimal dosing regimens to be tested in clinical trials, and with more development could be used to translate from cynomolgus monkeys to humans. In addition, based on similarities in underlying mechanisms, the current model could be used for other immune agonistic bsAb therapeutics.

CONCLUSIONS

In conclusion, bsAbs are an exciting immunotherapeutic modality with potential to further improve clinical efficacy and safety in the treatment of cancer. Their inherent complexity leads to significant clinical pharmacology challenges, in a disease area that is already difficult to treat and characterized by heterogeneity and development of resistance. Mathematical modeling and simulation are powerful tools, which can be used to integrate diverse knowledge and data to predict/refine clinical dosing regimens and design trials to optimize efficacy and TI. Modeling can be used to guide rational decision making, to inform precision medicine strategies, and to increase overall efficiency and effectiveness of the oncology clinical development process. In the future, combination of QSP modeling with data science methods, including machine learning, will further strengthen the role of modeling as an essential quantitative tool in oncology.

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