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Translational pharmacology

Translational pharmacokinetics and pharmacodynamics of monoclonal antibodies

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Monoclonal antibodies (mAbs) are an important therapeutic class with complex pharmacology and interdependent pharmacokinetic (PK) and pharmacodynamics (PD) properties. Understanding the PK and PD of mAbs and their biological and mechanistic underpinnings are crucial in enabling their design and selection, designing appropriate efficacy and toxicity studies, translating PK/PD parameters to humans, and optimizing dose and regimen to maximize success in the clinic. Significant progress has been made in this field however many critical questions still remain. This article gives a brief overview of the PK and PD of mAbs, factors that influence them, and areas of ongoing inquiry. Current tools and translational approaches to predict the PK/PD of mAbs in humans are also discussed.

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Introduction

Monoclonal antibody (mAb) therapeutics are an important and rapidly growing class of therapeutic agents with over 470 molecules in the clinical pipeline and many more in earlier stages of drug development [1]. Selecting the right mAb is a key determinant of its clinical success and depends on early understanding of its PK/PD and successfully translating it to humans. Compared to small molecules, biologics such as mAbs have unique characteristics that make their pharmacokinetics (PK) and pharmacodynamics (PD) quite complex [2,3]. An integrated understanding of its PK/PD characteristics including exposure at the site of action, target occupancy and expression of functional pharmacological activity are important in improving its clinical success [4]. The utility of translational PK/PD spans different phases of drug development and can contribute to target evaluation, design and selection of candidate molecule with optimal properties, and dose and regimen selection in preclinical and clinical studies [5]. Understanding PK/PD of mAbs and factors that impact them, are essential to achieve these translational goals. This review describes the PK and PD characteristics of mAbs, and translational PK/PD approaches to predict human PK/PD.

Pharmacokinetics and pharmacodynamics of mAbs

The mAb therapeutics currently on the market are from the immunoglobulin G (IgG) isotype such as IgG1, IgG2, and IgG4, which in general have PK characteristics such as slow clearance, long half-life, and limited tissue distribution. This long half-life offers the advantage of less frequent dosing in patients as compared to small molecules. After intravenous (IV) administration, typical mAb serum PK profiles are

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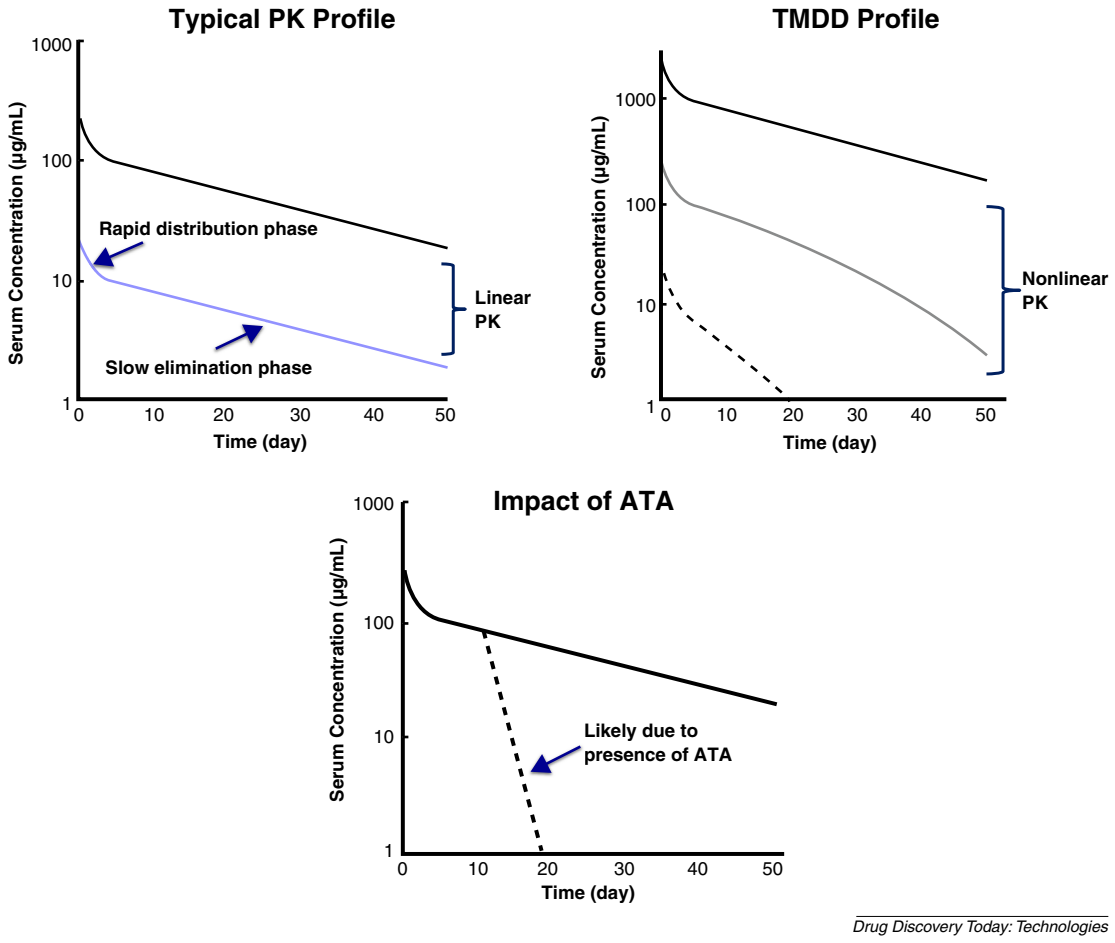

Figure 1. Representative PK profiles for mAbs.

biphasic with a rapid distribution phase and a slower elimination phase as shown in Fig. 1. PK properties of mAbs are unique in that they are dependent on their structure as well as can be markedly influenced by the biology of their target antigen, a concept termed as target-mediated drug disposition or TMDD [6]. Table 1 summarizes the PK characteristics of mAbs and their absorption, distribution, and clearance processes are briefly described below.

Absorption

Oral administration for mAbs is precluded mainly due to their instability in the gastrointestinal tract (denaturation by acidic pH or proteolytic degradation), as well as their limited intestinal permeability due to their poor lipophility and large molecular size [2,3]. mAbs are usually administered parenterally, either by IV, subcutaneous (SC), or intramuscular (IM) injections. Bioavailability after SC administration is quite variable and can range from 20–95%, and absorption is likely facilitated via the lymphatic system, however the exact mechanisms are poorly understood and preclinical models to predict human bioavailability are not well established [7,8]. The rate of absorption is slow with maximal plasma concentrations observed ~1–8 days following SC or IM injection.

Distribution

The distribution of mAbs is generally limited to the vascular and interstitial spaces due to its large size and hydrophilicity [2,9]. Following IV administration, distribution from vascular space into tissue interstitial space is mainly by convection (fluid flow from blood to interstitial spaces). Other factors that influence mAb distribution include diffusion, pinocytosis, receptor-mediated endocytosis, elimination from the tissue, as well as biophysical characteristics of the mAb such as charge and hydrophobicity [3]. In cases of specific binding to the antigen, aspects such binding affinity, receptor expression, and kinetics of receptor turnover and antigen-mAb binding can impact distribution. The extent of mAb partitioning from circulation into most tissues generally ranges from ~5–15%, except for brain where it is much lower [10]. Compared to normal tissues, distribution in tumors could be different due to differences in tumor physiology and dependent on target expression and tumor characteristics [11].

Table 1. PK characteristics of mAbs

Attributes	mAb characteristics
Binding	• Binding very specific for target antigen • Binding to FcRn and recycling contributes to long half-life • Binding to Fcγ receptors can result in effector functions
PK/PD	• PK usually dependent on biology of target antigen and PD • Typically biphasic PK profiles with relatively fast distribution phase and slower elimination phase; long half-life
Dose proportionality	• Non-linear PK at low doses • Linear PK at high doses after saturation of target • mAbs against soluble antigens with low endogenous levels typically exhibit linear PK
Distribution	• Distribution usually limited to blood and interstitial spaces • Partitioning from blood to tissues is typically ~5–15%, except for brain where it is much lower
Metabolism	• Catabolism by proteolytic degradation into amino acids
Excretion	• No renal CL of intact antibody. May be cleared by damaged kidneys. Uncommon if MW >20 kDa
Immunogenicity	• Formation of ATAs against mAb could occur • ATAs could impact PK, PD, efficacy, safety • Immunogenicity in animals not predictive of humans

Clearance

Since mAbs are large molecules that are above the glomerular filtration cut-off threshold, they are primarily eliminated by proteolytic catabolism that results in smaller peptides and amino acids that can be reused for new protein synthesis. Other pathways involved in removal of mAbs are target mediated clearance, non-specific pinocytosis, and Fc gamma receptor (FcγR) mediated clearance [2,3]. These complex clearance pathways of mAbs can be categorized as specific and non-specific clearance.

Specific or target mediated clearance of mAbs is mediated by the interaction of the mAb with its target antigen. This pathway includes binding of mAb to its target antigen leading to internalization of the antibody-receptor complex in case of a membrane bound target, and subsequent intracellular protein catabolism. Aspects of target antigen biology such as whether it is soluble vs. membrane bound, its distribution, expression level, and turnover rate, and whether it can be down-modulated or upregulated can impact the specific clearance pathway of mAbs. At low doses, target-mediated clearance pathways can lead to non-linear PK of mAbs, until the target is saturated at higher doses, after which the PK becomes linear as shown in Fig. 1. For soluble antigens with low endogenous levels, typically linear PK has been observed across species (e.g., adalimumab against TNF-α, bevacizumab against VEGF-A), whereas when endogenous levels are high, non-linear PK has been observed (e.g., omalizumab against IgE) [12–14]. For membrane bound antigens, typically non-linear PK has been observed until a higher dose where target is saturated (e.g., cetuximab and panitumumab against EGFR) [15]. In addition, when target antigen can be down-modulated or up-regulated by the mAb, it can result in time dependent PK of the mAb as is seen with rituximab (anti-CD20 mAb) which causes B-cell depletion and hence down-modulation of target that results in reduced clearance upon repeat dosing [15].

Non-specific clearance includes non-specific uptake by the cell via pinocytosis and subsequent protein catabolism. Clearance by the non-specific pathway is low and due to its large capacity is not saturated at typical concentrations seen with therapeutic mAbs, thereby resulting in linear PK. Clearance via the non-specific pathway is influenced by interaction of the Fc region on the mAb with the neonatal Fc receptor (FcRn), which plays a role in recycling the mAb back to the cell surface and releasing it into the extracelluar fluid [16]. Binding of an IgG1 mAb to FcRn is a pH-dependent process and modulation of this binding has been shown to impact the clearance of mAbs in both animals and humans [17–19].

Fc-mediated effector functions such as complement-dependent cytotoxicity (CDC, caused by binding to complement C1q) or antibody-dependent cell-mediated cytotoxicity (ADCC, caused by binding to FcγR) can contribute to the mechanism of action of the therapeutic mAb [20], however their impact on mAb clearance is not as straight forward. For both soluble antigens (which form immune complexes with mAbs that could promote FcγR binding) or membrane bound antigens (where mAb binding to target antigen could result in ADCC via FcγR binding), effect of FcγR binding on mAb disposition may come into play depending on target levels and relative contribution of FcγR-mediated clearance to total clearance at the administered dose. For example, Leabman *et al.*, showed that altered FcγRIIIA binding affinity did not affect PK for a set of IgG1 mAbs in cynomolgus monkeys in the linear dose range of those mAbs where target-independent mechanisms (i.e., FcRn) dominate clearance [21]. However, in studies of mAbs against certain target antigens (e.g., CD20 or IgE), where mAb binding to FcγR receptors either

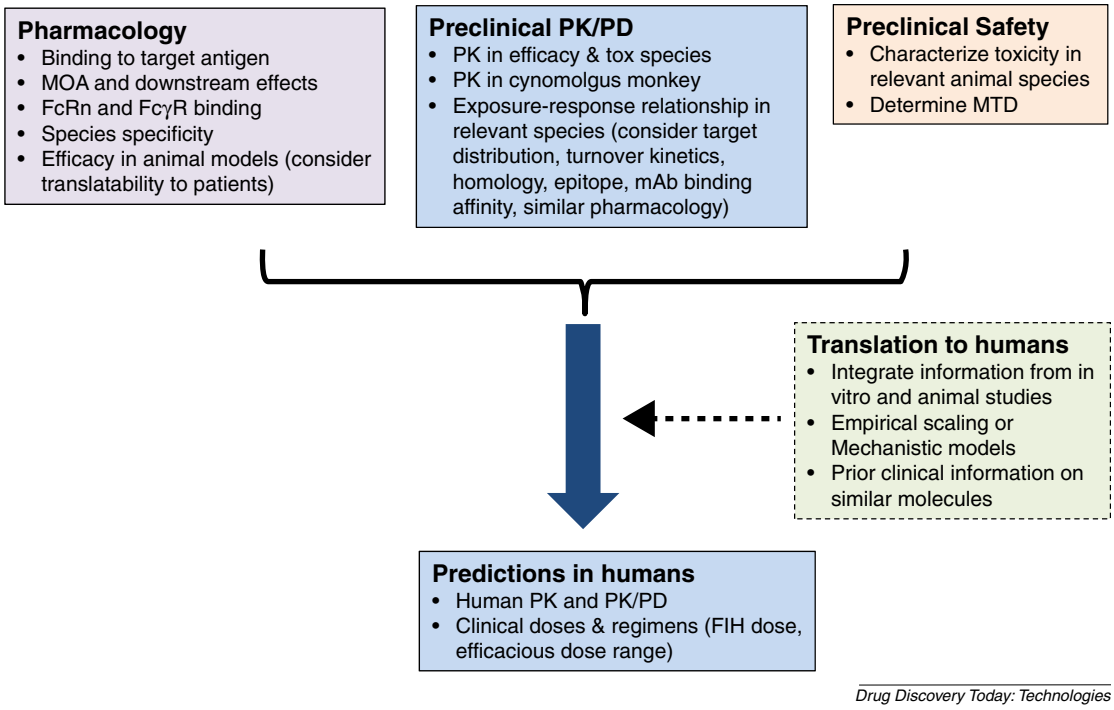

Figure 2. Framework for translation of PK/PD of mAbs from *in vitro* and animal data to humans.

caused depletion of target cells (e.g., anti-CD20) or clearance of immune complexes (e.g., anti-IgE), FcγR binding was shown to impact mAb disposition in the non-linear dose range [22–24].

Other factors that could impact mAb disposition include immunogenicity to therapeutic mAbs resulting in development of anti-therapeutic antibodies (ATAs), and antibody properties such as charge, hydrophobicity, glycosylation, and off-target binding. Isoelectric point and local charge patches have been shown to influence mAb disposition, where increase in positive charge of antibodies likely increases clearance and distribution due to interactions with negatively charged components on the tissue [25]. Lastly, patient characteristics such as disease status, demographic factors, or concomitant medications could also impact mAb PK/PD [3].

Pharmacodynamics

PD refers to the pharmacological effects elicited in the body by a drug. For small molecules, PK is usually independent of PD. However, PK/PD relationships of mAbs are unique due to the TMDD phenomenon and often lead to mAb PK being dependent on PD. As discussed above, mAbs can target soluble or membrane bound antigens and their PD responses could be driven through binding of the target antigen and the corresponding downstream effects and/or by effector functions such as ADCC and CDC. Depending on the mechanism of action of the therapeutic mAb, types of PD responses include inhibition of ligand-receptor interactions by binding of mAbs to soluble targets, down-modulation of target antigen by elimination of target cells, or impact on cell signaling by blocking receptors [2]. In animal or human studies, PD measurements could be directly or indirectly linked to a clinical endpoint.

Translational PK/PD approaches for mAbs

Determining PK/PD relationships across species can help understand how exposure drives response and then use that to predict PK/PD in humans and determine optimal doses and regimens for maximal clinical benefit. A basic framework for translation of PK/PD of mAbs from *in vitro* and animal data to humans is shown in Fig. 2. This includes getting appropriate efficacy, safety, PK and PD data from *in vitro* and *in vivo* studies, understanding exposure-response (PK/PD) relationships, predicting human PK, and finally integrating the PK data with efficacy and safety data to predict PK/PD in humans to estimate first in human (FIH) and efficacious dose ranges in patients. Some of the considerations for types of studies, species selection, available tools, and modeling approaches are discussed below.

Target biology and mAb molecular properties

Understanding the biology of target antigen, mechanism of action of the mAb, and mAb-antigen interactions are impor-

tant assessments early on in the drug development process [2,3,8]. Types of information about target antigen that could impact PK and PD include (i) expression levels, (ii) tissue distribution patterns and which organs and tissues express it, (iii) turnover kinetics in both plasma and various tissues, (iv) whether it can be down-modulated or upregulated, (v) in case of membrane bound targets, whether they can be shed, and (vi) downstream signaling of the target. Aspects of the mAb that are important to characterize are (i) binding affinity to the target antigen, (ii) binding to Fc receptors such as FcRn and FcγR, (iii) assessment of effector functions such ADCC and CDC, (v) molecule characteristics such as charge, pI, hydrophobicity, glycosylation, and (vi) preliminary assessments of off-target binding using *in-silico* or *in vitro* methods such as BV ELISA tools [26,27]. Binding affinity to target antigen can greatly influence PK of mAbs and it is important to obtain measurements of affinity or equilibrium dissociation constant (K_d), association rate constant (k_{on}), and dissociation rate constant (k_{off}). The relationship between antibody-antigen binding kinetics and antigen turnover kinetics is complex and there appears to be an optimal binding affinity beyond which distribution of the mAb to target tissue may be impaired [28,29]. Characterization of binding to FcRn is also essential and as this is a pH dependent interaction, binding affinity should be measured at both pH 6.0 (where FcRn binds mAb in the acidic pH of the endosome) and pH 7.4 (physiological pH where FcRn releases mAb at the cell surface). High binding to FcRn at pH 6.0 along with low binding at pH 7.4 is essential for low clearance of mAbs [17,18]. Several studies have investigated the correlation between FcRn binding affinity and half-life of mAbs, and the contribution of FcRn to prolonging the half-lives of mAbs is well recognized, though this should be put in context of the relative contribution of the FcRn pathway to total clearance [17–19].

Species selection for PK, efficacy and safety studies

Studies to characterize the PK, PD, efficacy, and safety in appropriate animal models are essential in understanding the PK/PD characteristics of the molecule and then translating to humans should be based on similarity of target antigen properties, appropriate binding of mAb to target antigen (i.e., binding species vs. non-binding species) and similar pharmacology upon target binding [3,30]. However, PK/PD of mAbs can be different in animals and human due to differences in either target antigen such as target homology, distribution, expression levels and turnover, or mAb properties such as differences in mAb-antigen binding or binding to FcRn across species. For example, murine FcRn appears to have a much higher affinity to human IgG than human FcRn, while cynomolgus monkey FcRn has similar binding affinity to human IgG as human FcRn [31,32]. Hence, cynomolgus monkeys is typically the preferred species to evaluate PK of mAbs for prediction of human PK. Recently, use of transgenic mice that express human FcRn have been evaluated to assess PK of mAbs and found to be promising [33,34]. In cases, where mAbs do not bind to their target antigen in efficacy or safety species, one approach could be using a surrogate antibody with suitable target-binding properties in the efficacy and safety models. In addition to target antigen or FcRn binding disparities, differences in off-target binding across species resulting in different PK profiles have also been shown for various mAbs. Examples include anti-FGFR (off-target binding to mouse complement component 3), anti-Abeta (off-target binding to fibrinogen in cynomolgus monkey), and anti-NRP1 (possible off-target binding in mouse, rat, human, but not cynomolgus monkey) [35–37]. Off-target binding resulting in safety differences across species has been reported, but is relatively rare [38,39]. For preclinical efficacy studies, selection of appropriate animal models is dependent on the ability to accurately recapitulate conditions of human disease and ability to elicit similar mechanism of action of the mAbs including target engagement, downstream pharmacology and effector functions, which can be very challenging. For example, human tumor xenografts implanted in mice are the primary models used to evaluate anti-tumor efficacy, but could have several differences from human tumors such as faster growth rates, different vasculature, etc.

Immunogenicity

Administration of a therapeutic mAb into animals or humans could result in the formation of anti-therapeutic antibodies (ATA) that can bind to the mAb and form immune complexes that could potentially impact the PK, safety, and efficacy of mAbs. ATAs can be neutralizing (bind to epitopes on mAb needed for biological activity) or non-neutralizing (bind to epitopes not needed for activity) and can confound interpretation of mAb characteristics [2,3,40]. Immunogenicity of mAb varies across species due to the different human fraction based on the type of therapeutic mAb (murine, chimeric, humanized or fully human), and hence animals are not predictive of human immunogenicity. PK profiles can be altered by the presence of ATAs where serum concentrations can suddenly drop due to increased clearance of the immune complexes, as shown in Fig. 1. Approaches to handle this data for PK analysis include excluding ATA-positive animals or using data only until ATA develops and impacts the PK profile [40]. Several groups have also evaluated mechanistic PK/PD models that account for ATA impact on PK and PD [41–43].

Bioanalytical tools

There have been great advances in bioanalytical analytical methods to measure concentrations of mAbs and their target antigen in various matrices such as plasma, bile, tissues from *in vitro* or *in vivo* studies. Multiple forms of the mAb and target antigen can exist in various biological samples, such as free

mAb, free antigen or complexes of the mAb and antigen. Analytes that can be measured include free or bound forms of mAb and target antigen and choice of analyte depends on stage of drug development and type of information desired [44]. As described in detail by Lee *et al.* [44], assessment of free mAb can provide information on availability of mAb for free target and its binding capacity, while total mAb (i.e., free plus bound) can inform interactions between mAb and target. The specificity of the bioanalytical assay is influenced by the ratio of mAb to target and their dynamic equilibrium [44]. Commonly used methods are enzyme linked immunosorbent assays (ELISAs) and more recently liquid chromatography-mass spectrometry assays (LC-MS) [45,46]. Insights into specific and non-specific distribution of mAbs can be obtained from radiolabeled biodistribution studies using tissue cut and count techniques where the tissues are harvested at various timepoints and radioactivity is measured [47,48]. Radioactive probes commonly used include ^{125}I-labeled antibody which reflects tissue uptake kinetics, and ^{111}In-DOTA labeled antibody, a residualizing probe that is charged and highly polar, causing it to accumulate in cells if the labeled mAb is internalized. Other imaging technologies that can be used for investigating *in vivo* biodistribution include single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging [48].

Prediction of human PK/PD

Since PK of mAbs is dependent on PD, prediction of mAb PK in humans needs to take into account both specific and non-specific pathways of disposition. Several modeling approaches are available to translate PK/PD of mAbs from animals to humans and have been discussed in several reviews and summarized below [5,49–52]. These can be broadly categorized as (i) empirical approaches such allometry and species-invariant time methods, and (ii) mechanistic approaches such as TMDD or physiologically based PK (PBPK) models. More recently, advances are being made in new approaches such as systems modeling that integrate systems biology approaches with traditional PK/PD approaches to attempt to understand the whole system in its entirety and improve predictions [54–56].

Empirical approaches for prediction of human PK/PD

Several empirical approaches have been investigated for scaling preclinical PK data of mAbs to humans [49,51]. These approaches are largely based on allometric principles and scaling uses a power model relating body weight and physiological parameters of interest and can be expressed as $Y = a\mathrm{BW}^b$, where Y is the parameter of interest, BW is the body weight, a is the allometric coefficient, and b is the allometric exponent. Important assumptions underlying allometric scaling include linear PK and physiological, anatomic, and biochemical similarity across species. There are several allometric methods including simple allometry (using multiple species), simplified allometry (using only one species) and allometric scaling with correction factors such as maximum life span potential or brain weight [49]. Of all these methods, simplified allometry using only cynomolgus monkeys to scale to humans is the one that appears to provide the best predictions and is recommended by most groups [49,51,52]. This is largely due to the similarity between cynomolgus monkey and humans in terms of both antigen sequence homology (target-mediated pathways) and FcRn binding affinity (non-specific pathways). In addition, as discussed previously, there are differences in mAb-FcRn binding affinities across species that do not comply with the assumptions of allometry and hence using multiple species may not be appropriate.

For mAbs with linear PK, the two key PK parameters of interest, clearance (CL) and volume of distribution (V), can be reasonable scaled from cynomolgus monkeys to humans using a fixed scaling exponent in the following equation: $Y_{human} = Y_{cyno} \times (BW_{human}/BW_{cyno})^b$, where Y is either CL or V, BW is body weight, and b is the fixed scaling exponent [49]. For V, there is general agreement of using an exponent of 1, based on the similarities across species of limited distribution of mAbs to blood and extravascular spaces. For clearance estimation, scaling exponents of 0.85 or 0.8 were proposed by Deng *et al.* and Wang *et al.*, respectively [51,56]. Two other groups proposed an exponent of 0.85 for mAbs with soluble antigens and 0.9 for mAbs with membrane bound antigens [57,58]. All these scaling exponents provided reasonably good clearance predictions from moneys to humans for the set of mAbs evaluated by these groups. Additional PK parameters of interest after SC or IM dosing are rate and extent of absorption and bioavailability. However, these processes are likely influenced by multiple factors such FcRn binding, presystemic catabolism, and injection site. Our understanding of how to predict bioavailability from animals to humans after SC administration is still lacking due to species differences in physiology of hypodermis, lymphatic system and FcRn binding [3,7,49].

For mAbs with non-linear PK, the scaling of PK to humans is not as straightforward due to considerations of target antigen biology differences between animals and humans such as target density, expression profiles, target turnover kinetics, and affinity to the target. Human PK estimates have been made in these cases by using a two-compartment PK model with parallel linear and nonlinear elimination described by the Michaelis–Menten equation to estimate monkey PK parameters followed by allometric scaling to estimate human parameters [49,52]. An analysis on 6 mAbs with nonlinear PK was conducted by Dong *et al.* that showed good prediction of area under the curve (AUC) but overestimation of maximum concentration (Cmax) after SC administration [52]. They concluded that the best predictive performance

was obtained after doses had achieved target-saturating concentrations and PK was in the linear range.

In addition to simplified allometric scaling methods as discussed above, another empirical approach commonly used is the elementary species-invariant time method (or commonly known as elementary Dederick plots) which can predict human PK profiles from monkey PK profiles and is useful for simulating different dosing regimens [49,51]. This method assumes that the dose-normalized drug concentration in animals is equivalent to human and scales the PK time to humans using the CL exponent obtained from simplified allometry [51,59,60]. Similar to simplified allometry, this method works well under conditions of mAb PK linearity and should be used cautiously when mAb doses are in the non-linear range.

To determine concentration-response relationships, traditionally empirical approaches such as the classic Hill equation have been used to obtain parameters such as Emax (maximum effect), EC_{50} (drug concentration that produces 50% of Emax), and Hill coefficient (slope that reflects the steepness of the concentration-response curve) [5]. Translating these parameters to humans is challenging and typically they are assumed to be the same as in animals or scaled across species using *in vitro* assays [50].

Mechanistic approaches for prediction of human PK/PD

Due to limitations of empirical methods for mAbs with nonlinear PK, more mechanistic methods such as TMDD and PKPD models have been explored that take into account physiological turnover and homeostasis of biological components of the system [49]. As discussed previously, TMDD describes drug whose disposition is influenced by binding to the target and this is usually exhibited as a nonlinear dependence on dose [6]. However, some challenges with using these TMDD models are a lack of key data on the target and/or mAb-target antigen complex levels that are needed for appropriate parameter identifiability. In addition, PK data must be available across a wide concentration range at different levels of target saturation to allow discernment of the nonlinearity. Scaling of these model parameters to humans is more complicated and human PK parameters are typically scaled by simplified allometry, while human PD parameters are either experimentally determined, scaled allometrically from monkey parameters or assumed to be the same as monkeys [49,61,62].

Another mechanistic approach is PBPK modeling which integrates physiological and anatomical information with drug specific information from *in vitro* and *in vivo* ADME data, and can allow evaluation of system-specific and drug-specific factors and facilitate translation from *in vitro* to *in vivo* as well as across species [63]. While this has been used extensively for small molecule, its utilization for large molecules is still at an early stage. Due to its complexity compared with traditional PK/PD models, its use has been limited in the development of mAbs. Simplified approaches have been proposed like minimal PBPK models that reduce the dimensions in the model and make it easier to apply [49,63].

More recently, novel approaches such as systems pharmacology models are being investigated which incorporate systems biology concepts with those of PK/PD to aim to understand the behavior of the whole system rather than its individual components. This new systems pharmacology approach has been reviewed in several recent publications [53–55]. Briefly, PK/PD models are usually based on the pharmacology of a single pathway whereas systems pharmacology models are much broader and can incorporate multiple functional interactions within a biological network. This offers the advantage of being able to describe complex patterns of drug action and disease progression, scale across species, and translate PK/PD behavior to humans.

Conclusions

Great strides have been made in improving our understanding of the PK and PD of mAbs and factors that impact them. However, many unresolved questions remain such as factors influencing SC bioavailability, clear role of Fc receptors in efficacy and biodistribution, prediction of immunogenicity, influence on PK/PD of molecular properties such as charge, hydrophobicity, glycosylation, and their interdependencies, and scaling of PD parameters across species. While empirical approaches for translational PK/PD are still commonly used for mAbs with varying degrees of success, mechanistic approaches are increasingly being used as more sophisticated tools become available to generate relevant data. In addition, exciting research is emerging in the nascent systems pharmacology area. Advances in increasingly sophisticated bioanalytical tools coupled with novel efficacy and safety models as well as PK/PD and systems modeling approaches will serve to increase the mechanistic understanding of PK/PD of mAbs and have the potential to improve translatability, refine choice of dose and regimens, inform suitable drug delivery approaches and rationale drug combinations, and enable greater probability of clinical success for novel therapeutic mAbs.

Conflict of interest

The author is an employee of Genentech, a member of the Roche Group, and holds financial interest in Hoffman-La Roche.

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