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Special Section on Pharmacokinetics and ADME of Biological Therapeutics–Editorial

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Therapeutic biologics (TBs), which represent diverse entities of biologics, including antibodies, antibody-drug conjugates (ADCs), therapeutic replacement enzymes, peptides, small interfering RNAs, and antisense oligonucleotide (ASO) drugs have revolutionized the treatments of a wide range of diseases. TBs are receiving major attention in drug development pipelines. Generally, TBs perform highly specific and complex functions with low off-target toxicity, the features that could be challenging for small molecule drugs. Since the introduction of insulin as the first TB drug, the progression of novel class entities from relatively small and native proteins to the next generation TBs with more and more complex structures, such as conjugated peptides, fusion proteins, and ADCs, has introduced many new challenges related to the characterization of catabolism, biotransformation, distribution, and elimination. In addition, the advancement in protein engineering further diversifies the group of available TB molecules by introducing bispecific antibodies, multifunctional antibody-based biologic therapeutics, and non–antibody-based nanobodies (e.g., caplacizumab, which contains only a single-domain fragment of an antibody).

The distribution and elimination of TBs are determined by target-mediated and/or non–target-mediated processes, as well as physiochemical properties, such as molecule sizes and surface charges. Renal filtration can be dominant for TBs with small molecular weights, e.g., <~50 kDa, and large net positive charges. Antibodies with a molecular weight of greater than 150 kDa are limited to the intravascular space, with little distribution to the interstitial space of extravascular organs and tissues. The elimination of TBs is commonly facilitated by nonspecific proteolytic degradation in lysosomes. Cellular uptake of antibodies can be mediated by either target-mediated internalization or non–target-mediated pinocytosis, followed by intracellular lysosomal degradation to small peptides and amino acids. The rate of target-mediated drug disposition (TMDD) is related to the expression of the target antigen, the affinity of antigen bound, the rate of internalization, and the extent of lysosomal catabolism. TMDD is more efficient than pinocytosis and can be a major elimination process for therapeutical proteins (TPs). In addition, many antibodies and their derivatives can interact with immunoglobulin-specific receptors, such as the neonatal Fc receptor (FcRn) and Fcγ receptor. These receptors can prevent IgG antibodies from proteolytic degradation and reduce the systemic clearance (CL) of the TPs (Ryman and Meibohm, 2017).

The size, charge, and modification of TBs need to be taken into consideration in the prediction of elimination pathways. Since the appropriate tools to characterize absorption, distribution, metabolism, and excretion (ADME) of TBs are still lacking, characterizing the exposure, metabolic or catabolic biotransformation, TMDD, and elimination of TBs in the preclinical phase is more difficult as compared with small molecules. In this special section of Drug Metabolism and Disposition on "Pharmacokinetics and ADME of Biological Therapeutics," a series of review and research articles are presented to highlight the current practice and future perspectives in characterizing ADME of TBs.

Taguchi et al. (2021) investigated whether chronic renal impairment affects nivolumab CL and found that total CL of nivolumab was approximately 1.4 times higher in rats with surgically initiated chronic kidney disease than that in control rats. The data suggest that the renal excretion of nivolumab increases as renal function deteriorates and that the baseline urinary albumin/creatinine ratio can be a potential indicator for the renal CL prior to nivolumab treatment under conditions of renal impairment.

Conjugation with hydrophilic polymers [e.g., polyethylene glycosylated (PEGylated) peptides or proteins] can increase the size of TBs and result in a slower renal CL for polymer conjugated biologics. It is also worth noting that ADME characteristics of PEGylated molecules may differ from native TBs of a similar size. PEGylation is one of the most commonly used synthetic macromolecular polymers to modify small molecule drugs, peptides, and proteins for the improvement of their water solubility, biocompatibility, and stability. PEGylated nanodrug delivery systems, including polymeric nanoparticles, polymeric micelles, solid lipid nanoparticles, and liposomes, have become promising technologies for the improvement of delivery for TBs; unfortunately, due to poor safety and effectiveness, the use of PEGylated nanodrug delivery systems has been associated with a relatively high rate of failures in clinical trials or of withdrawal from clinical use. In this special section, Yin et al. (2022) reviewed the ADME data of block copolymers containing polyethylene glycol, aiming to improve understanding of the in vivo fate of the PEGylated copolymers after they are released from nanocarriers.

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ABBREVIATIONS: ADME, absorption, distribution, metabolism, and excretion; ADR, adverse drug reaction; ASO, antisense oligonucleotide; CL, clearance; FcRn, neonatal Fc receptor; FDA, Food and Drug Administration; IQ, Innovation & Quality Consortium; PEGylated, polyethylene glycosylated; PK, pharmacokinetic; TB, therapeutic biologic; TMDD, target-mediated drug disposition; TP, therapeutical protein.

Accumulation of PEGylated copolymers in organs including the liver, spleen, lung, and kidney can directly cause toxic reactions. Moreover, PEGylated polymers and their degradation products can interact with drug transporters and metabolic enzymes, resulting in drug-nanocarrier interactions and potential adverse reactions. Since most current studies only focus on the in vivo pharmacokinetics (PK) of the free drugs, these authors highlight the need to more deeply understand the polymers' in vivo PK behaviors and urge drug hunters to pay greater attention to the in vivo fate of polymers.

The Innovation & Quality Consortium (IQ) Translational and ADME Sciences Leadership Group (TALG) working group for the ADME of TPs conducted a survey of IQ member companies with an objective to understand current industrial practices of assessing ADME for TPs, to learn the regulatory strategy and experiences in interacting with regulatory agencies, and to provide recommendation on the best practices in conducting ADME studies for TPs. Three articles related to this survey are included in this special section. In "Absorption, Distribution, Metabolism, and Excretion (ADME) of Therapeutic Proteins: Current Industry Practices and Future Perspectives" (Bolleddula et al., 2022), Bolleddula and colleagues evaluated the nature of ADME studies that are used in regulatory biologics license applications (BLA). After comparing the current ADME practices in IQ member companies and those in the regulatory BLA submissions, the authors found that, although most companies are exploring various ADME characteristics of their TPs early to optimize the molecules in the preclinical phases, there are disparities between current activities conducted by companies in TP programs and what were submitted as part of regulatory packages. Based on the findings, the authors made recommendations for conducting TP ADME studies.

In "A Cross Company Perspective on the Assessment of Therapeutic Protein Biotransformation" (Walles et al., 2022), Walles and colleagues noted that a more in-depth understanding of biotransformation is needed for increasingly diverse modalities. The authors, who are participants of the IQ TP-ADME working group, summarized the current practices in studying TP biotransformation and related learnings in the biopharmaceutical industry. In addition, the authors discussed various case studies and recommended a fit-for-purpose approach for conducting TP biotransformation studies to support internal decision making based on the data generated in discovery and development.

Characterization of PK and biodistribution of an ever-increasing catalog of novel modality TPs is a hot topic within the pharmaceutical industry. In "Characterizing the pharmacokinetics and biodistribution of therapeutic proteins: an industry white paper" (Ball et al., 2022), Ball and colleagues reviewed the current industrial practices and the advances and challenges in characterizing PK and biodistribution of TPs during drug development and made recommendations to address the knowledge gaps. The authors also noted that the "traditional in vivo biodistribution study" is becoming insufficient and that it is necessary to have a clear understanding of the advantages and limitations of the ever-expanding range of experimental systems and bioanalytical techniques adapted for different TP types to thoroughly characterize the interactions of TPs with its target(s), target biology, and off-target interactions at a microscopic scale.

Mathematical and mechanistic PK models are pivotal for describing exposure-efficacy and exposure-toxicity relationships for TPs in preclinical species and humans for diverse scenarios, such as TMDD, FcRn-mediated recycling, renal elimination, and tissue distributions. In addition to the IQ efforts on TP ADME characterization, Liu and Shah (2022) further highlighted the importance of PK modeling as a powerful tool to support model-informed drug development of TPs. Understanding PK characteristics of TPs can help with achieving sufficient and prolonged drug exposure at the site of action. The authors discussed state-of-the-art models that can recapitulate critical processes of TP ADME, and they highlighted the emerging needs to integrate physicochemical properties of TPs in PK models, to explain intermolecular PK variability, and to elucidate novel disposition mechanisms of next-generation TPs using mechanistic PK or physiologically based PK (PBPK) models.

ASO drugs are single-stranded nucleic acid polymers. ASO drugs have shown significant potential to provide transformative treatments of a variety of hard-to-treat or rare human diseases, such as Duchenne muscular dystrophy. Although there are currently more than 100 ASO drugs in various phases of clinical trials, with some likely to be approved within a few years (Crooke et al., 2021), adverse drug reactions (ADRs), particularly hepatotoxicity and kidney toxicity, remain a major safety concern for these drugs. In "Adverse Drug Reactions and Toxicity of the FDA approved Antisense Oligonucleotide Drugs" (Alhamadani et al., 2022), Alhamadani et al. reviewed the ADRs and toxicity of ten FDA)-approved ASO drugs, using the information in drug labels and the results from preclinical studies, clinical trials, and postmarketing real-world studies. The authors described that ASO drugs are often associated with hepatotoxicity, nephrotoxicity, and hypersensitivity reactions. The ADRs of ASO drugs share some common mechanisms of toxicity through either hybridization-dependent off-target effects or RNAse-H1–dependent reduction in off-target RNAs (Burel et al., 2016).

ADME properties have direct impacts on efficacy and ADRs of ASO drugs. Thus, in a related article in this special section, Migliorati et al. (2022) reviewed the formulation, dosage, sites of administration, local and systematic distribution, metabolic or catabolic degradation, and excretion of ten ASO drugs that are approved by the US FDA. The authors described unique ADME characteristics of the ASO drugs, which can be distinct from small molecule drugs. They also identified several knowledge gaps in our understanding of these ASO drugs, including endocytosis, endosomal release, intracellular/nuclear trafficking, and cellular extrusion. As well, the authors provided future directions on ADME characterization for ASO drugs.

The increasing complexity of the next generation of TBs demands more mechanistic ADME studies for many unsolved fundamental questions, such as how ADME properties are altered by molecular weight, substitutions of charged amino acids, TMDD, FcRn interaction, molecule shape, PEGylation, and formulation. The field of ADME of TBs requires continuous influx of in vitro and in vivo ADME studies that incorporate new concepts and technologies. When these new concepts and technologies become more readily available in the drug development settings, improved strategies

can be implemented to aim at optimizing the ADME profiles and facilitating intelligent design and development of next-generation TBs. We hope that the articles in this special section will propel the development in this filed by fully acknowledging the current knowledge gaps and describing various technologies and the best practices that may expedite the evaluation of new TBs using more efficient ADME studies and mathematical and mechanistic PK models.

Yurong Lai and Xiao-bo Zhong

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Address correspondence to: Dr. Yurong Lai, Drug Metabolism, Gilead Science Inc., 333 Lakeside Drive, Foster City, CA 94404. E-mail: yurong.lai@gilead.com