Special Section on Pharmacokinetic and Drug Metabolism Properties of Novel Therapeutic Modalities—Commentary

Pharmacokinetic and Drug Metabolism Properties of Novel Therapeutic Modalities

Brooke M. Rock and Robert S. Foti

Pharmacokinetics and Drug Metabolism, Amgen Research, South San Francisco, California (B.M.R.) and Pharmacokinetics and Drug Metabolism, Amgen Research, Cambridge, Massachusetts (R.S.F.)

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ABSTRACT

The discovery and development of novel pharmaceutical therapies is rapidly transitioning from a small molecule–dominated focus to a more balanced portfolio consisting of small molecules, monoclonal antibodies, engineered proteins (modified endogenous proteins, bispecific antibodies, and gene-based therapies). This commentary, and the special issue as a whole, aims to highlight these emerging modalities and the efforts underway to better understand their unique pharmacokinetic and absorption, disposition, metabolism, and excretion (ADME) properties. The articles highlighted herein can be broadly grouped into those focusing on the ADME properties of novel therapeutics, those exploring targeted-delivery strategies, and finally, those discussing oligonucleotide therapies. It is also evident that whereas those exploring targeted-delivery strategies, and finally, those focusing on the ADME properties of novel therapeutics. The articles highlighted herein can be broadly grouped into those focusing on the ADME properties of novel therapeutics, those exploring targeted-delivery strategies, and finally, those discussing oligonucleotide therapies. It is also evident that whereas the field in general continues to progress toward new and more complex molecules, a significant amount of effort is still being placed on antibody-drug conjugates. As therapeutic molecules become increasingly complex, a parallel demand for advancements in experimental and analytical tools will become increasingly evident, both to increase the speed and efficiency of identifying safe and efficacious molecules and simultaneously decreasing our dependence on in vivo studies in preclinical species. The research and commentary included in this special issue will provide researchers, clinicians, and the patients we serve more options in the ongoing fight against grievous illnesses and unmet medical needs.

SIGNIFICANCE STATEMENT

Recent trends in drug discovery and development suggest a shift away from a small molecule–dominated approach to a more balanced portfolio that includes small molecules, monoclonal antibodies, engineered proteins, and gene therapies. The research presented in this special issue of Drug Metabolism and Disposition will serve to highlight advancements in the understanding of the mechanisms that govern the pharmacokinetic and drug metabolism properties of the novel therapeutic modalities.

Introduction

The speed at which science is evolving has unveiled new biologic pathways and novel drug targets (Santos et al., 2017). In many cases, modulating new targets can require exploring their pharmacology beyond classic small molecule-target interactions, leading to an influx of new therapeutic modalities. A look at the new drugs approved by the U.S. Food and Drug Administration since 1980 illustrates a rapidly emerging change from approvals dominated by small molecules (prior to 2000) to a more balanced portfolio of small molecules and “non–small molecule” drugs such as monoclonal antibodies, engineered proteins, oligonucleotides, and vaccines (Fig. 1A) (Reichert, 2003; Mullard, 2018; Morrison, 2019). Likewise, in the last 10 years, the list of top-selling drugs in North America has swung from being dominated by small molecules to now including eight protein therapeutics among the ten top-selling drugs in the United States (Quan et al., 2018; Wineinger et al., 2019). Indeed, an analysis of the total sales of the top ten drugs in each year from 2010 to present shows a decreasing dependence on small-molecule revenue and a rapid shift toward sales of monoclonal antibodies and engineered proteins (Fig. 1B) (https://www.pharmacytimes.com; https://www.drugs.com/top200; Philippidis, 2019).

As molecular biology and genetic techniques continue to evolve, modalities beyond typical small and large molecules are rapidly finding their way into the drug discovery pipeline. This evolution is requiring drug metabolism and pharmacokinetic researchers to develop new tools to understand the absorption, disposition, metabolism, and excretion (ADME) of these new chemical entities, as described in the review by (Datta-Mannan, 2019) included in this issue. The fact that many of these analytical and experimental tools were developed to characterize monoclonal antibodies is a particular challenge, as emerging research suggests that many of the newer, highly-engineered therapeutic proteins may not be subject to the same disposition mechanisms as unmodified antibodies (Vugmeyster et al., 2012; Ueda, 2014). In this issue of Drug Metabolism and Disposition a series of primary research articles and review articles are presented to highlight the importance of understanding new modalities from an

ABBREVIATIONS: ADME, absorption, disposition, metabolism, and excretion; ASO, antisense oligonucleotide; ON, oligonucleotide; PK-PD, pharmacokinetic-pharmacodynamic.
monoclonal antibodies (mAb) and engineered proteins (B). In addition, this issue contains a review article with perspectives on the following:

1. biodistribution and pharmacokinetic considerations of new modalities,
2. targeted drug delivery, and
3. oligonucleotide therapies. In this issue, we will focus on the following:

### Biodistribution and Pharmacokinetic Considerations of New Modalities

Establishing a pharmacokinetic-pharmacodynamic (PK-PD) relationship with small and large molecules has traditionally been performed by measuring drug concentration from the blood compartment and linking that concentration to a response (Bueters et al., 2013; Singh et al., 2015; Glassman and Balthasar, 2016). However, new technologies in targeted delivery have required ADME scientists to think beyond the blood compartment for drug and pharmacodynamic measurements to aid in the development of translational models, especially for pharmacological targets expressed outside of the vasculature (Shah, 2015; Glassman and Balthasar, 2016; Tibbitts et al., 2016). For many new modalities, understanding the biodistribution and exposure to the active form of the molecule at the therapeutic site of action is critical to establishing a PK-PD relationship (Lin, 2009; Shah and Betts, 2013; Conner et al., 2014; Glassman et al., 2015). In vitro assays that can provide information on biodistribution and pharmacokinetic behavior of a molecule prior to conducting in vivo studies are crucial to informing the design of new modalities and can increase the speed at which new modalities reach clinical trials (Xu and Yugmeyer, 2012; Pearson and Rock, 2015). One such assay described in this issue is a novel in vitro assay by Foti et al. that informs biodistribution and exposure to the active form of the molecule at the therapeutic site of action while reducing exposure to other regions of the body (Humphreys et al., 2017; Srinivasasaro and Low, 2017). The hallmark examples of targeted drug delivery are antibody-drug conjugates (ADCs), in which a cytotoxin (e.g., small molecule) is covalently attached to a monoclonal antibody targeting the tissue of interest and ultimately increasing the efficacy and therapeutic index of the cytotoxin. There are numerous publications on the ADME properties of ADCs that affect both biodistribution and efficacy (Bomstein, 2015; Hamblett et al., 2016; Kraynov et al., 2016). For therapies that are designed to directly deliver to the site of action it is also important to understand the blood stability as well as the rate of delivery, as many such molecules use linker strategies that may be susceptible to degradation by proteases found in circulation (Tsukikawa and An, 2018). Two articles by Zhang et al. (2019a,b) define different linkages to either peptides or antibodies that enable the effective delivery of the warhead. These authors also point out elements to consider when measuring drug stability either in vitro or in vivo. Directed drug delivery has also enabled the success of oligonucleotides as therapeutics (Zimmermann et al., 2017).

### Oligonucleotide Therapeutics

Oligonucleotide (ON) therapeutics use a biologic process known as RNA interference (RNAi), in which short interfering RNA molecules (siRNAs) or antisense oligonucleotides (ASOs) neutralize a target mRNA sequence to prevent subsequent protein translation (Nair et al., 2017; Andersson et al., 2018). Although the potential applications of ASOs and siRNAs to the field of therapeutics is vast, understanding the underlying delivery efficiency and relative tissue distribution remain significant challenges. It is well established in the ON field that sensitive bioanalytical assays are required to study the ADME properties of ONs (Humphreys et al., 2019a; Thayer et al., 2019). Presented herein is an overview by Post et al. (2019) of ADME properties of an ASO from preclinical species to clinical outcomes. In addition to the need to understand the translation of ON therapeutics, there remains only limited information on the potential for drug-drug interactions, or the potential effects of protein binding, topics addressed herein by Ramsden et al. (2019b) and Humphreys et al. (2019b), respectively. The therapeutic potential of ON therapeutics is rapidly increasing with the development of new delivery techniques, as evidenced by the multitude of ongoing clinical trials (Titze-de-Almeida et al., 2017; Zimmermann et al., 2017; Saw and Song, 2019). As the field continues to evolve, ADME scientists will have the opportunity to inform the design of newer-generation molecules, specifically for the kinetics of drug delivery and impact of comedications on therapeutic treatments.

### Conclusion

In the past decade the expansion of biology and genetics has increased the need for ADME scientists to expand the tools available...
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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Rock, Foti.

Datta-Mannan A (2019) Mechanisms influencing the disposition of monoclonal antibodies and


Morrison C (2019) Clinical proof of concept for a novel hepatocyte-targeting


Address correspondence to: Dr. Brooke M. Rock, Pharmacokinetics and Drug Metabolism Amgen, Inc., 1120 Veterans Boulevard, South San Francisco, CA 94080. E-mail: brookef@amgen.com; or Dr. Robert S. Foti, Pharmacokinetics and Drug Metabolism Amgen, Inc., 360 Binney Street, Cambridge, MA 02142. E-mail: rfoti@amgen.com


Perhaps one of the greatest challenges in drug discovery is the generation

 novice opportunities required to design and develop new modalities and the novel

 experiments approaches needed to characterize such modalities. ADME

 scientists across industry and academia are now faced with a unique

 opportunity and responsibility to continue exploring and discovering new

 approaches to keep up with and advance the ever-changing face of

 therapeutic modalities. This special issue of Drug Metabolism and Disposition on the Pharmacokinetic and Drug Metabolism Properties of Novel Therapeutic Modalities will serve to highlight some of these emerging tools that will be critical in transforming today’s experimental molecules into tomorrow’s successful therapeutics.

Authorship Contributions

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References


Disposition

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