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Pharmacological and Pharmacokinetic Properties Play an Important Role in Determining its Effectiveness

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DESCRIPTION

There are several variables that can impact the Pharmacokinetics (PK) of a monoclonal Antibody (mAb) or Fc-fusion molecule, with FcRn-mediated recycling being the most important. IgG-FcRn interaction may be exploited to develop a range of therapeutic antibodies with dramatically increased half-life or capacity to remove undesired antigen from circulation *via* Fab or Fc engineering. Glycosylation of a mAb or Fc-fusion protein can have a major influence on its PK. Variants with pI values of 1-2 unit difference are expected to alter PK, with lower pI values being advantageous for a longer half-life. The majority of mAbs display Target-Mediated Drug Disposition (TMDD), which has significant implications for preclinical and clinical trial designs. Anti-Drug Antibody (ADA) response and off-target binding can also alter mAb PK, which must be carefully considered throughout the discovery stage. Monoclonal Antibodies are predominantly absorbed by convection through the lymphatics and may be readily supplied in high doses/volumes *via* the subcutaneous route with co-formulation of hyaluronidase.

Using cynomolgus monkey data and allometric scaling techniques, the human PK of a mAb may be adequately predicted. The original barriers to human immunogenicity of murine mAbs were removed by the 1980s molecular biology revolution, which permitted humanization of murine antibodies and, finally, the successful production of completely humanized antibodies. Humanization significantly decreases a therapeutic antibodies immunogenicity in humans, allowing for continuous administration. Throughout the last decade, such advancements in antibody technology have resulted in an explosion in the creation of therapeutic mAbs. More than 47 mAbs and derivative medications have been licensed for human use as of today, with several of them becoming blockbusters. Five of the top ten selling medications in 2014 were monoclonal antibodies, and one was an Fc fusion molecule, with annual revenues above 6.5 billion US dollars. Antibodies or antibody derivatives are expected to account for around 30% of novel medications in the near future.

Fc-fusion proteins, Antibody-Drug Conjugates (ADCs), immunocytokines (antibody-cytokine fusions), and antibody-enzyme fusions are examples of antibody derivatives. The pharmacological and pharmacokinetic characteristics of a mAb have a significant role in determining its efficacy. A mAb binds to a target (such as receptors, soluble antigens, etc.) and produces antagonistic (i.e., blocking or neutralizing) or agonistic (i.e., activating) effects, which in turn cause downstream pharmacological effects that result in efficacy and/or undesirable side effects. This is best described as "what a drug does to the body." The easiest way to sum up a mAb's Pharmacokinetics (PK) is to ask "what the body does to the medication." How a mAb is processed by the body under healthy or pathological circumstances will define how it behaves *in vivo*. The clearance or half-life of a mAb determines the body's "exposure," which determines the extent of pharmacodynamics (PD) effects. The exposure-response (PK-PD) relationship governs how a drug affects the body. Understanding this relationship is critical to drug discovery and development. Because mAbs are large proteins of 150 kDa, they have some unique PK properties, making the discovery and development pathway of mAbs significantly different from that of small molecule drugs.

CONCLUSION

Many factors related to an antibody's structure and functions, such as FcRn mediated recycling, glycosylation patterns, overall charge and pI, target-mediated clearance, anti-drug antibody response, and off-target binding, determine its unique PK properties