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Pharmacokinetics of Monoclonal Antibodies and Early Development Issues

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DESCRIPTION

An overview of antibody development, Pharmacokinetics (PK) characteristics, and the application of antibody PK/Pharmacodynamics (PD) in R&D decision making. We also discuss the fundamentals of building a nonclinical PK programme and the many types of PK research that should be conducted during the early phases of monoclonal antibody development.

Endogenous antibodies are largely produced by differentiated plasma B-cells. Therapeutic antibodies, the most prevalent form of biopharmaceutical, have been developed to treat a variety of illnesses, including cancer, immunological disorders, and infectious diseases. Almost 60 antibodies have been commercialized in the United States, while 350 new antibody entities are in active clinical development. IgG antibodies are the most common and well-studied of the five antibody Immunoglobulin (Ig) subtypes (IgA, IgD, IgE, IgG, and IgM).

The development of monoclonal Antibodies (mAbs) as therapeutics began 40 years ago with the introduction of mouse hybridoma technology. Yet, the use of mice mAbs as treatments has been limited by their high Antidrug Antibody (ADA) production, short half-life, and lack of an effector activity. Efforts to reduce immunogenicity led in the development of chimeric and humanized antibodies, which currently make up the vast bulk of commercialized antibodies. Moreover, phage display technology, which employs bacteriophages that produce recombinant human antigen binding fragments to select high affinity binders, led in the manufacture of 100% human antibodies with enhanced diversity and potency. Human antibodies can also be produced using transgenic mice engineered with human immunoglobulin genes, human hybridomas, and patient-derived lymphocytes. IgGs are 150 kDa Y-shaped immunoglobulins composed of two identical heavy and light chains linked by disulphide bonds. The variable domains from both the heavy and light chains constitute the antigen binding region namely “Fab”, which is formed by the two arms of the Y.

Antibody specific binding to antigen *via* variable domains results in major pharmacological effects such as cytokine and growth factor blocking (e.g., infliximab) and receptor blockage and/or receptor modification (e.g., antibodies against Programmed Death 1 (PD1) receptor (e.g., pembrolizumab).

The Y's stem section is known as the fragment crystallizable region called “Fc” and is composed entirely of heavy chains. This section is responsible for mAb binding to Fc receptors for IgG and Complement system proteins such as Fc gamma receptors (FcRs), Complement (C1q) protein, and neonatal FcR. IgG interacts with a number of binding partners, including antigen, complement, Fc receptors for IgG (FcRs), and the neonatal FcR, define the principal therapeutic effects of IgG.

Among them, antibody specific binding to antigen *via* variable domains plays important pharmacological effects such as cytokine and growth factor blocking (e.g., infliximab) and receptor blockage and/or receptor modification (e.g., antibodies against Programmed Death 1 (PD1) receptor (e.g., pembrolizumab). The interaction of the Fc region with other proteins is required for further IgG actions.

CONCLUSION

As demonstrated by antiCD20 antibodies, binding of mAb Fc to FcRs and complement protein causes cellular depletion *via* both Fc mediated Antibody Dependent Cytotoxicity (ADCC) and C1q mediated Complement protein Dependent Cytotoxicity (CDC), and binding to FcRn causes mAb to have a longer half-life in circulation. Antibody Pharmacokinetic (PK) characteristics, like their biological activity, are determined by interactions with their binding partners (antigen, FcRs, and FcRn).