Mechanisms of Monoclonal Antibody–Drug Interactions

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Abstract

The concept of monoclonal antibodies (mAbs) as pharmacotherapeutics was validated in the mid-1980s with the successful clinical development of the fully murine mAb muromonab-CD3 for prevention of acute organ rejection. However, clinical applications of fully murine mAbs are restricted, owing to the high incidence of serious immune-mediated side effects, particularly upon repeated exposure. The rate and severity of immune-mediated toxicities of these agents were significantly attenuated by the development of mouse/human chimeric, fully human, and humanized mAbs. These refinements in molecular structure allowed repeated, long-term administration, where therapeutically warranted, which, in turn, broadened the scope of indications for this class of therapy. Presently, numerous mAbs are approved or are undergoing clinical evaluation for treatment of oncologic and chronic inflammatory diseases. The current experimental development landscape spans respiratory, metabolic, and central nervous system disorders as well as infectious disease. A consequence of the expanding numbers of mAb indications is concomitant administration of these agents with established small molecule pharmacotherapies, which necessitates a comprehensive understanding of mAb–small molecule drug interactions as well as mAb-mAb interactions. Current knowledge indicates that mAbs do not elicit a direct effect on the metabolic/clearance pathways for small molecular therapeutics. However, the immunomodulatory properties of mAbs can indirectly alter clearance of certain small molecule entities through the attenuation of noncatabolic enzymatic pathways.

INTRODUCTION

Paul Ehrlich (1) initially described the concept of antibodies as therapeutic agents in his seminal 1891 manuscript "Experimental Studies on Autoimmunity," in which he introduced the term "*antikörper*," German for antibody (2). He also introduced the concept of *Zaberkugel* (magic bullet) therapeutics. He reasoned that if a compound could be engineered to selectively target a disease-causing organism, then a toxin for that organism could be delivered to the organism by the selective compound. Functional and structural characterization of antibodies began in earnest in the late nineteenth century and culminated in several seminal findings on the generation and maturation of the humoral immune response, many of which received recognition by the Nobel Prize Committee (3; **Figure 1**). However, the key scientific breakthrough that advanced the evaluation of antibodies as therapeutic modalities was the development of hybridoma technology by Niels K. Jerne, Georges J.F. Köhler, and César Milstein, which allowed reliable production of quantities of monospecific or identical antibody moieties—i.e., monoclonal antibodies (mAbs)—sufficient for research or therapy.

The first successful clinical development of a mAb was the fully murine muromonab-CD3 for treatment of acute organ rejection in 1986. However, frequent and significant immune-mediated toxicities were associated with administration of fully murine mAbs, particularly upon repeated administration of the compound. Advancements in genetic engineering resulted in the development of chimeric (mouse/human), humanized, and fully human therapeutic mAbs. The reduction and/or elimination of nonhuman amino acid sequences resulted in a significant decrease in immune-mediated associated toxicities, which, in turn, broadened the therapeutic landscape for these mAbs. Over the past 30 years, therapeutic mAbs have become an increasingly important component of pharmacotherapy and have made a significant impact on the drug discovery and development process. It is estimated that more than 500 mAbs are presently in development (4), and approximately 30 mAbs currently are approved by the U.S. Food and Drug Administration (FDA) under Biologic License Applications (5; **Table 1**). The majority of approved and experimental mAbs in the clinic are for oncologic indications, but the therapeutic landscape for mAbs is

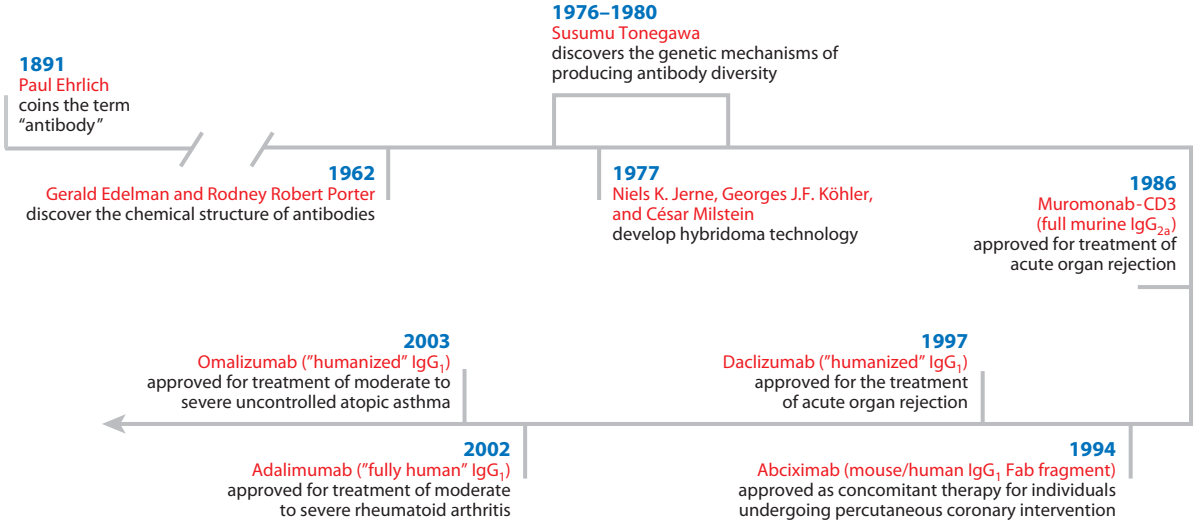

Figure 1

Major milestones in humoral immune response and therapeutic monoclonal antibody (mAb) development. IgG, immunoglobulin G.

Table 1 Therapeutic monoclonal antibodies (mAbs) approved by the Food and Drug Administration

Generic name	Antibody target	Antibody type	Therapeutic area	Company	FDA approval
Muromonab-CD3	CD3	Murine, IgG_{2a}	Immunology	Janssen-Cilag	June 19, 1986
Abciximab	GP IIb/IIIa	Chimeric, IgG_1	Cardiovascular	Centocor	Dec. 22, 1994
Capromab pendetide	PSMA	Murine, IgG_1	Imaging	Cytogen	Oct. 28, 1996
Nofetumomab	Carcinoma-associated antigen	Murine, IgG_2	Imaging	Boehringer Ingelheim	Aug. 20, 1996
Rituximab	CD20	Chimeric, IgG_1	Oncology	Genentech	Nov. 26, 1997
Daclizumab	IL-2Rα	Humanized, IgG_1	Immunology	Roche	Dec. 10, 1997
Basiliximab	IL-2Rα	Chimeric, IgG_1	Immunology	Novartis	May 12, 1998
Palivizumab	RSV	Humanized, IgG_1	Anti-infection	AZ	June 19, 1998
Infliximab	TNF-α	Chimeric, IgG_1	Immunology	Centocor	Aug. 24, 1998
Trastuzumab	HER2	Humanized, IgG_1	Oncology	Genentech	Sept. 25, 1998
Alemtuzumab	CD52	Humanized, IgG_1	Oncology	Ilex	May. 7, 2001
Ibritumomab tiuxetan	CD20	Murine, IgG_1	Oncology	Spectrum	Feb. 19, 2002
Adalimumab	TNF-α	Human, IgG_1	Immunology	Abbott	Dec. 31, 2002
Omalizumab	IgE	Humanized, IgG_1	Pulmonary	Genentech	June 20, 2003
Tositumomab; I131	CD20	Murine, IgG_{2a}	Oncology	GSK	June 27, 2003
Efalizumab	CD11a	Humanized, IgG_1	Immunology	Genentech	Oct. 27, 2003
Cetuximab	EGFR	Chimeric, IgG_1	Oncology	ImClone	Feb. 12, 2004
Bevacizumab	VEGF	Humanized, IgG_1	Oncology	Genentech	Feb. 26, 2004
Technetium fanolesomab	CD15	Murine, IgM	Imaging	Palatin	July 2, 2004
Natalizumab	α4-integrin	Humanized, IgG_4	Immunology	Biogen Idec	Nov. 23, 2004
Ranibizumab	VEGF-A	Humanized, IgG_1	Ophthalmology	Genentech	June 30, 2006
Panitumumab	EGFR	Human, IgG_2	Oncology	Amgen	Sept. 27, 2006
Eculizumab	CP C5	Humanized, $IgG_{2/4}$	Hematology	Alexion	Mar. 16, 2007
Certolizumab pegol	TNF-α	Humanized	Immunology	UCB	Apr. 22, 2008
Golimumab	TNF-α	Human, IgG_1	Immunology	Centocor	Apr. 25, 2009
Canakinumab	IL-1β	Human, IgG_1	Immunology	Novartis	June 17, 2009
Ustekinumab	IL-12/IL-23	Human, IgG_1	Immunology	Centocor	Sept. 25, 2009
Ofatumumab	CD20	Human, IgG_1	Oncology	GSK	Oct. 26, 2009
Tocilizumab	IL-6r	Humanized, IgG_1	Immunology	Roche	Jan. 8, 2010
Denosumab	RANKL	Human, IgG_2	Women's Health	Amgen	June 1, 2010

Abbreviations: Ig, immunoglobulin; CD, cluster of differentiation; GP, glycoprotein; PSMA, prostate-specific membrane antigen; IL, interleukin; RSV, respiratory syncytial virus; TNF, tumor necrosis factor; HER, human epidermal growth factor receptor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; CP, complement; RANKL, receptor activator for nuclear factor κB ligand.

broadening into chronic autoimmune, respiratory, metabolic, and central nervous system (CNS) disorders. A significant consequence of the expansion of mAb therapy is the coadministration of these agents with established pharmacotherapy regimens. This polypharmacy situation becomes even more complex in elderly patients; approximately 30% of patients aged 57 years and older use at least five prescription medications (6).

Based on the scientific literature, small molecule medications that frequently cause drug-drug interactions (DDIs) when coadministered with other small molecular therapeutics generally have

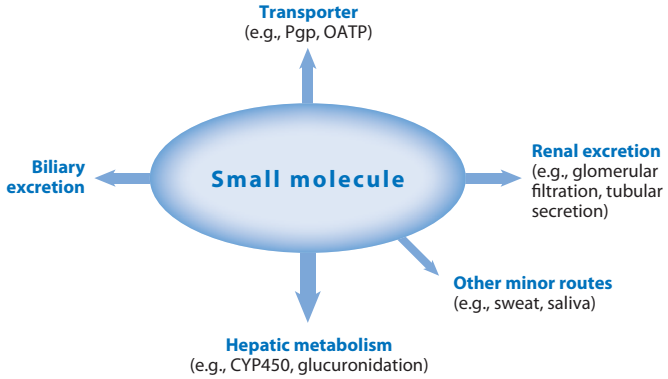

Figure 2

Diagram of elimination pathways for small molecule pharmacotherapies. Abbreviations: CYP, cytochrome P; OATP, organic anion-transporting polypeptide; Pgp, p-glycoprotein. Adapted with permission from Reference 11.

a lower propensity for DDIs when coadministered with mAbs (5, 7–10). The distinguishing factors are the differences in the disposition mechanisms of chemically derived moieties and mAbs.

DISPOSITION MECHANISMS OF SMALL MOLECULES AND MONOCLONAL ANTIBODIES

Small molecules are usually eliminated by noncatabolic pathways such as hepatic metabolism, renal excretion, and biliary excretion, as illustrated in **Figure 2**. In contrast, mAbs are eliminated via catabolic processes (**Figure 3**). Broadly speaking, mAbs are eliminated via two major routes: a nonspecific pathway and a target-mediated pathway.

The vast majority of approved and experimental therapeutic mAbs is of the immunoglobulin G_1 (IgG_1) isotype. In general, endogenous IgG or IgG-based mAb agents have relatively long half-lives (approximately 14 to 28 days), owing primarily to the salvage mechanism of the neonatal Fc receptor (FcRn; also called the Brambell Receptor). Brambell and colleagues (12, 13) first postulated the regulation of IgG homeostasis by FcRn, and it was confirmed several decades later (14–17; illustrated in **Figure 4**). The FcRn receptor binds IgGs and IgG-based mAbs with high affinity in the acidic environment (approximately pH 6) of the endosome, prevents their release into the lysosome, and eventually returns them to systemic circulation, which is at physiological

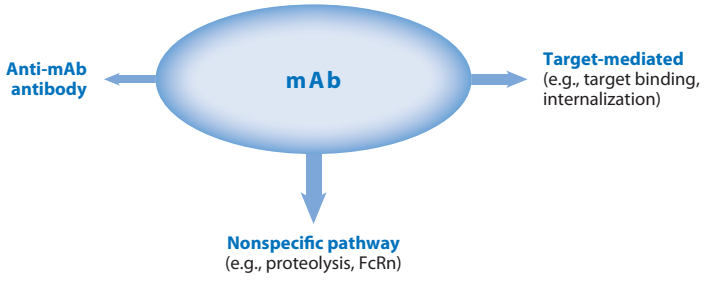

Figure 3

Diagram of elimination pathways for monoclonal antibody (mAb) therapies. FcRn, neonatal Fc receptor. Adapted with permission from Reference 11.

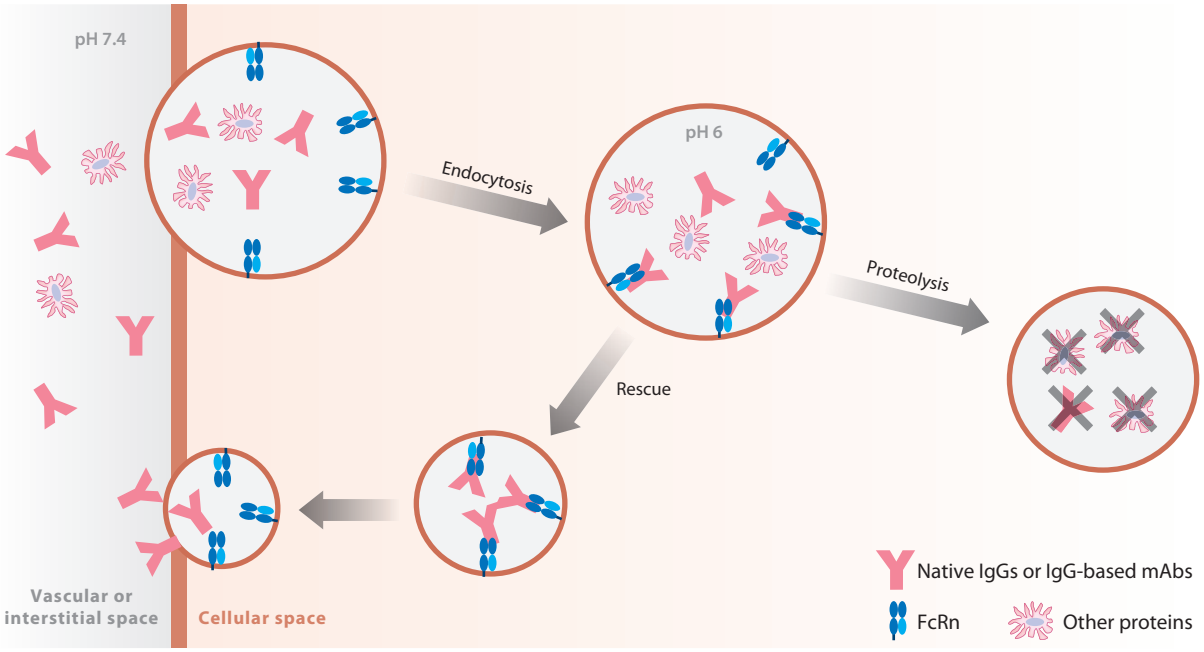

Figure 4

Schematic of neonatal Fc receptor (FcRn)-mediated salvage for immunoglobulin G (IgG) and IgG-based monoclonal antibodies (mAbs).

pH (7.4). Without the salvage function of the FcRn, IgGs or IgG-based mAbs, like other proteins, are taken into cells by pinocytosis and catabolized rapidly upon fusion of the endosome with the lysosome. Thus, the protective function of the FcRn significantly extends the circulating half-lives of endogenous IgGs and IgG-based mAb therapeutics, compared with the half-lives of other systemic native or therapeutic proteins.

Because the disposition of mAbs does not occur through noncatabolic pathways such as hepatic metabolism or transporters, they do not compete directly with chemically derived entities for these pathways. Thus, from a mechanistic perspective, the likelihood of direct DDI (mAb as a victim) occurring during coadministration of other concomitant medications is unlikely to be high.

CHARACTERISTICS OF MONOCLONAL ANTIBODY–DRUG INTERACTIONS

Generally, mAb-drug interactions can be classified into three categories: mAbs as perpetrators of mAb–small molecule DDIs, mAbs as victims of mAb–small molecule DDIs, and mAb-mAb DDIs.

Monoclonal Antibodies as the Perpetrators of Drug-Drug Interactions

When a therapeutic mAb is coadministered with a small molecule, theoretically, any effect of the mAb on the elimination pathways of that small molecule may impact its pharmacokinetics. However, as depicted in **Figures 2** and **3**, mAbs and small molecules do not share common or overlapping clearance mechanisms. Thus, mAbs are not predicted to affect directly the hepatic, renal, or biliary elimination of small molecules. However, certain therapeutic mAbs may exert

an indirect effect on hepatic clearance pathways through the pharmacological properties of these agents. For example, certain cytokines significantly affect the expression of cytochrome P450 (CYP450) enzymes (18–20) and can regulate drug transporter expression (21, 22). Thus, mAbs that target cytokines that modulate certain CYP450 isozymes or drug transporters have the potential to indirectly alter the clearance rate of small molecule entities that are metabolized or transported through these pathways.

As known for decades, infection and inflammation can reduce the body's capacity to eliminate drugs from the circulation, primarily through modulation of CYP450 isozymes. Processes that may alter hepatic CYP450 expression include oxidative stress, transcriptional regulation, post-transcriptional regulation, and phosphorylation (23). Kato and colleagues (24) were the first to establish that viral infection modulates small molecule drug metabolism by reporting changes in hexobarbital and strychnine metabolism in mice with virus-induced hepatitis. It was subsequently documented that influenza virus infection impaired clearance of theophylline, a CYP450 1A2 substrate (25, 26), which resulted in hospitalization with mild to severe CNS-associated toxicities of theophylline, ranging from headache to seizures. The hypothesis for the altered theophylline clearance is that the body releases endogenous interferons in response to influenza infection that, in turn, modulate the activities of certain CYP450 isozymes (27–33). Williams et al. (34) confirmed the above hypothesis in a clinical study by demonstrating that interferon (IFN)-α administration decreased the theophylline clearance rate in subjects with chronic hepatitis. The effects of infections on CYP450-catalyzed reactions were also reported during infection with Newcastle disease (35), encephalomyocarditis (36), influenza vaccine (37), murine leukemia (38), and HIV (39) viruses in vivo.

The first scientific report documenting that a systemic inflammatory condition altered drug metabolism was the finding of Samaras & Dietz (40) that trypan blue caused a prolonged pentobarbital sleeping time in rats. Attenuation of drug metabolism by systemic inflammation was reported in both experimental and disease-induced inflammatory conditions. An experimental septic condition was mimicked in healthy subjects by intravenous administration of purified endotoxin (bacterial lipopolysaccharide). The generation of a systemic inflammatory response resulted in the modulation of hepatic CYP450 activity (41). In patients undergoing allogeneic bone marrow transplantation, inflammatory cytokine production correlated with a significant increase in cyclosporine systemic exposure, or area under the drug concentration–time curve (AUC) (42). It is well established that certain surgical procedures can result in increased production of certain proinflammatory cytokines (43). Gidal and colleagues (44) reported altered clearance of carbamazepine that correlated with increased interleukin (IL)-6 concentrations following epilepsy surgery.

In vitro investigations. Numerous studies document the effect of cytokines on CYP450 enzymes in vitro. Aitken & Morgan (45) studied the effect of several inflammatory agents on CYP450 mRNAs. In addition, Huang and colleagues (10) recently documented a list of CYP450 isozymes that are altered in the presence of specific cytokines and cytokine modulators (such as some anticytokine mAbs). For example, based on in vitro studies on human tissues and/or on clinical studies, IL-1, IL-2, IL-6, IL-10, basiliximab (a mouse/human chimeric mAb to the IL-2 receptor), muromonab-CD3, and tocilizumab (a humanized mAb to the IL-6 receptor) all can alter CYP450 3A activity (10). However, in vitro studies have limited value in the qualitative and quantitative prediction of clinical interactions involving cytokines or cytokine modulators because of inconsistent practices in using in vitro approaches and techniques to assess the DDI propensity of therapeutic proteins, including mAbs. The lack of general guidance or an evaluation framework in in vitro systems hinders robust examination of the value and the utility of this approach. In

addition, the lack of effective data sharing across pharmaceutical companies and research institutes also hampers a better understanding of the in vitro–in vivo predictability of this approach.

Preclinical investigations. In the well-established adjuvant-induced arthritis (AIA) model of chronic inflammation in rats, elevated levels of proinflammatory mediators occur within a few days of adjuvant injection. Because proinflammatory cytokines suppress CYP450 enzyme expression and activity (18), the AIA animal model is used to assess the impact of disease on CYP450 enzyme activity. Ling & Jamali (46) found that the rise in proinflammatory mediators in the AIA model was responsible for the observed reductions in CYP450 content and verapamil clearance (up to a 55% reduction). This finding is consistent with the prolonged sleep time after administration of pentobarbital (47) and hexobarbital (48) to AIA rats. Guirguis & Jamali (49) also observed a significantly diminished propranolol oral clearance in AIA rats, which was also believed to be due to the substantial suppression of CYP450 by inflammatory cytokines. Infliximab, a chimeric anti–tumor necrosis factor α (TNF-α) mAb approved for the treatment of moderate to severe rheumatoid arthritis (50), partially restores the diminished CYP450 levels in the AIA model. In contrast, administration of infliximab did not significantly reverse the suppression of verapamil clearance. In general, currently available data indicate that translation of results in animals to humans is inconsistent, and conducting in vivo risk-based DDI studies in humans is a more informative, reliable and sensible path forward for therapeutic proteins, including mAbs (10).

Clinical investigations. The observation in rats of diminished clearance of small molecules owing to the suppression of CYP450 by proinflammatory mediators translates to humans, as evidenced by similar findings in subjects with active rheumatoid arthritis, celiac disease, and Crohn's disease (51). Mayo and coworkers (52) observed that oral clearance of both *S*- and *R*-verapamil was significantly decreased in patients with rheumatoid arthritis. Ling and coworkers (53) found that verapamil pharmacokinetics were relatively normal in subjects with rheumatoid arthritis whose active disease was in remission. On the basis of in vitro findings, the first dedicated clinical drug-disease-drug interaction study explored the effect of tocilizumab in modulating the pharmacokinetics of CYP450 substrate drugs in patients with active rheumatoid arthritis (54). One week following a single intravenous administration of 10 mg kg^{-1} tocilizumab, systemic exposures to omeprazole (a CYP450 2C19 substrate) and simvastatin (a CYP450 3A4 substrate) were reduced by 28% and 57%, respectively.

Mechanisms. Although the mechanism by which inflammatory diseases and individual proinflammatory cytokines suppress the CYP450 isozyme is not well understood, formation of NO, which inhibits CYP450, is a plausible explanation (55). It is logical to postulate that cytokine-induced overproduction of NO could be responsible for the attenuation of activity and for the transcription of CYP450 by a diverse array of immunostimulants. In addition, Aitken and colleagues (23) suggested that other factors such as inflammatory cytokines, oxidative stress, transcriptional regulation, posttranscriptional regulation, and phosphorylation might also play roles in the alteration of hepatic CYP450 expression in inflammation and infection. Morgan and colleagues (21) proposed pathways for diminished metabolism during inflammation and infection, as illustrated in **Figure 5**. Several cytokines, such as TNF-α, IL-6, and IL-1β, are capable of downregulating the expression of multiple CYP450 isozymes in primary human hepatocytes (45). Morgan (20) also demonstrated the effect of onset or amelioration of inflammation on CYP450 expression or activity and the effect of anticytokine drugs (including anticytokine mAbs), as shown in **Figure 6**.

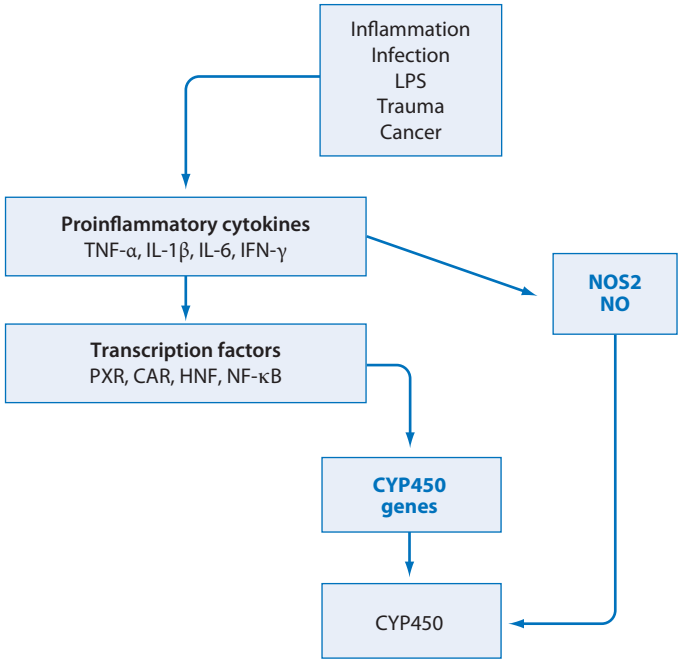

Figure 5

Schematic of diminished drug metabolism during inflammation and infection. Abbreviations: CAR, constitutive androstane receptor; CYP450, cytochrome P450; HNF, hepatocyte nuclear factor; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; NO, nitric oxide; NOS2, nitric oxide synthase 2; PXR, pregnane X receptor; TNF, tumor necrosis factor. Adapted with permission from figure 1, Reference 21.

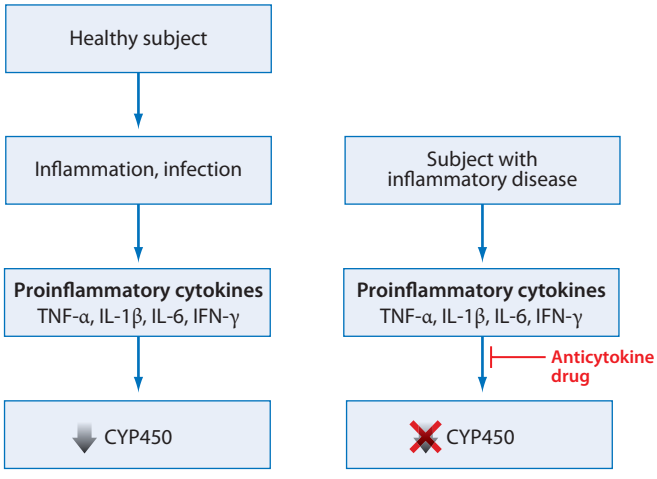

Figure 6.

Schematic of the effects of inflammation and anticytokine treatment on cytochrome P450 (CYP450). Abbreviations: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor. Adapted with permission from Reference 20.

Monoclonal Antibodies as Victims of Drug-Drug Interactions

DDIs are unlikely to alter large-capacity processes, such as fluid-phase endocytosis, phagocytosis, and catabolism. However, small-capacity processes that are drug- or component-specific, such as anti-drug antibody development, target-mediated disposition, and interactions between IgG and FcRn, may have a higher propensity for causing DDIs (56). For example, the coadministration of methotrexate significantly decreases the clearance of infliximab, a mouse-human chimeric anti-TNF-α mAb, and the decrease in clearance rate directly correlates with the decrease in the immunogenicity rate (57). When infliximab was administered without methotrexate, the immunogenicity rates were 53%, 21%, and 7% in patients who were receiving repeated treatment of infliximab at 1, 3, and 10 mg kg^{-1}, respectively. In contrast, the immunogenicity rates were greatly decreased (15%, 7%, and 0%, respectively), when infliximab was administered with methotrexate; this is largely, if not completely, attributed to the immunosuppressive effect of methotrexate. In addition, other immunosuppressive agents such as azathioprine or mercaptopurine were found to prevent the formation of antibodies against infliximab, thus reducing the incidence of infusion reactions and increasing the duration of response (58). Similar methotrexate effects also are observed for two other human anti-TNF-α mAbs, adalimumab (59) and golimumab (60). It is believed that concomitant use of immunosuppressive drugs can induce immunological tolerance to infliximab and adalimumab (61). Another plausible hypothesis is that methotrexate alters the disposition of anti-TNF-α mAbs by suppressing CD64 expression on monocytes (62). Interestingly, methotrexate does not appreciably affect the clearance of etanercept (63), a human anti-TNF-α fusion protein; this is not well understood. One plausible explanation is the low incidence of etanercept immunogenicity in the absence of methotrexate (64).

Kovarik and colleagues (65) reported that azathioprine and mycophenolate mofetil reduced basiliximab clearance in renal transplant patients by 22% and 51%, respectively, a result not anticipated from the perspective of conventional DDI mechanisms. Although the mechanism leading to this diminished clearance remains speculative, the known ability of both concomitant medications to suppress anti-drug antibody formation may play an important role (66, 67). One study also suggested that azathioprine could decrease IgG synthesis (68); however, whether this mechanism is relevant to the reduced basiliximab clearance or is interconnected with azathioprine's primary function of suppressing immune response is unclear.

Another striking example of a DDI not anticipated from a conventional perspective is the effect of paclitaxel, a small molecule antimicrotubule agent, on trastuzumab, a humanized IgG_1 mAb directed against the extracellular domain (ECD) of the human epidermal growth factor 2 (HER2) receptor. In a nonhuman primate study, paclitaxel in combination with trastuzumab resulted in a twofold decrease in trastuzumab clearance and in a 1.5-fold increase in trastuzumab serum concentrations (69). However, significant effects of paclitaxel on trastuzumab clearance were not observed in either a population pharmacokinetic study (70) or a phase 2 study in subjects with metastatic breast cancer (71). Because the reported incidence of immunogenicity to trastuzumab was very low, 1 out of 903 (69), suppression of the immune response by paclitaxel does not seem a plausible mechanism, even though paclitaxel, an antineoplastic drug, also has immunosuppressive properties (72). Nonclinical studies indicate that the complex formed between trastuzumab and the ECD of HER2 has a faster clearance rate than free trastuzumab (69). A population pharmacokinetic study of trastuzumab in patients with HER2 metastatic breast cancers confirmed this result (70). The clearance of trastuzumab increased with baseline ECD level. Circulating ECD is only a small fraction of the total load of HER2 receptor antigen. It is a reasonable presumption that high circulating ECD levels are correlated with high tumor burdens. Oude Munnink and colleagues (73) recently reported that an extensive HER2+ tumor load can significantly affect trastuzumab pharmacokinetics and organ distribution. Even though limited evidence exists,

perhaps the paclitaxel-induced reduced clearance of trastuzumab is due to the perturbation by paclitaxel of the formation of the trastuzumab-ECD complex.

Monoclonal Antibody–Monoclonal Antibody Interactions

FcRn plays a vital role in maintaining the relatively long half-lives of IgG and IgG-based mAbs. The IgG clearance rate increases with increasing IgG plasma concentration, and this phenomenon is believed to be due to the saturation of FcRn (74). Although FcRn-mediated recycling is capacity limited, given the total amount of endogenous IgG of 50–100 g, the usual dose of most mAbs of <10 mg kg^{-1} increases the total IgG body load by only <1–2% (4). Thus, theoretically, when two different mAbs are coadministered, no discernible DDI is anticipated, and the limited clinical observations, to date, echo this prediction. When bevacizumab, a humanized IgG_1 mAb directed against vascular endothelial growth factor A (VEGF-A), was administered at a dose of 15 mg kg^{-1} and intravenously followed by rituximab, a chimeric mAb that targets CD20, at a dose of 375 mg m^{-2}, no mutual DDI (or mAb-mAb interaction) was observed (75). Results of a phase 1 trial in patients who had undergone previous treatment for metastatic breast cancer indicated that the combination of trastuzumab (doses of 3, 5, or 10 mg kg^{-1} every two weeks intravenously), and bevacizumab (dose regimen of 4 mg kg^{-1} intravenous loading and 2 mg kg^{-1} intravenous maintenance weekly), had an enhanced antitumor effect but no detectable influence on the pharmacokinetics of either mAb (76). However, as predicted, intravenous administration of a large dose of IgG (2 g kg^{-1}) increased the clearance of two mAb-based systemic therapies: 7E3, a mouse-human chimeric fragment antigen binding (Fab) of a mAb directed against human glycoprotein IIb/IIIa (dose of 8 mg kg^{-1}), and a murine antimethotrexate IgG_1 mAb (dose of 8 mg kg^{-1}), by 2.37-fold and 2.66-fold, respectively (77).

FINAL REMARKS

Therapeutic protein–small molecule drug interactions are an emerging and increasingly relevant area of pharmacology research. Unlike the conventional DDIs between small molecules, their mechanisms are quite complex and, at present, not well understood and elucidated. Many of those interactions are the result of interplay among the disease nature and severity, the victim, and the perpetrator. Drug-disease interactions or DDIs involving mAbs, to date, have not revealed changes in systemic exposure [area under the drug concentration–time curve (AUC), C_{max}] equivalent to those observed with small molecule drugs (10), and very few mAb–small molecule interactions mandate specific dose adjustment (5, 7, 10). Nevertheless, more extensive and inquisitive research is needed to help us better understand the underlying mechanisms of direct and indirect DDIs involving mAbs from pharmacokinetic, pharmacodynamic, toxicological, and clinical response perspectives. The diversity of targets and disease indications for therapeutic mAbs currently under evaluation in the clinic provides hope and promise for many significant unmet medical needs. However, it also imposes an imminent urgency to drug development scientists in academia, industry, and regulatory agencies to better understand the science of concomitant mAb-mAb and mAb–small molecule drug interactions. The projected need will be more apparent as new delivery methodologies for mAbs (i.e., inhaled and intranasal) and mAb-derivative therapies are developed, thus further broadening the therapeutic landscape and mAb-drug interactions.

DISCLOSURE STATEMENT

H.Z. is an employee of Centocor Research & Development, Inc., a subsidiary of Johnson & Johnson. M.A.M. is a paid consultant for Centocor Ortho Biotech Services.

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