UTILITY OF *IN VITRO* METHODS IN DRUG–DRUG INTERACTION ASSESSMENT AND PREDICTION FOR THERAPEUTIC BIOLOGICS

THERESA NGUYEN, NARENDRA KISHNANI, and RAYMOND EVERS

5.1 INTRODUCTION

Therapeutic proteins (TPs) are increasingly being coadministered with small molecule (SM) drugs and/or other biologics such as monoclonal antibodies (mAbs). Historically, interactions between TPs and SMs have not been considered very likely because mechanisms involved in the disposition of both modalities are fundamentally different. In the case of SMs, various drug-metabolizing enzymes and transporters expressed primarily in the intestine, liver, and kidney are involved in absorption, distribution, and elimination. For mAb, non-ligand and ligand-mediated clearance pathways are involved. In addition, binding to the neonatal Fc receptor (FcRn) functions as a salvage pathway that protects IgG molecules from lysosome-mediated degradation. In general, these differences will make it less likely that drug–drug interactions (DDIs) will occur between TPs and SMs. However, the situation may be different for TPs involved in pathways that modulate the immune system because it has been demonstrated that increased cytokine exposure can result in reduced levels of cytochrome P450 (CYP) enzymes and drug transporters.

Theoretically, the effects of cytokines on CYPs can therefore mediate DDIs between TPs and SMs when immunomodulating biologics (e.g., cytokines and cytokine modulators) are used in the treatment of cancer, infections, or inflammation. The scenarios that could lead to suppression or desuppression of enzymes have been outlined by Morgan[1] (Figure 5-1): When an individual, previously stabilized on a SM drug regimen becomes afflicted with an infection or inflammatory

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing,
Edited by Shayne C. Gad