

## Minireview

# How Current Understanding of Clearance Mechanisms and Pharmacodynamics of Therapeutic Proteins Can Be Applied for Evaluation of Their Drug-Drug Interaction Potential

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### ABSTRACT:

Increasing use of therapeutic proteins (TPs) in polypharmacy settings calls for more in-depth understanding of the biological interactions that can lead to increased toxicity or loss of pharmacological effect. Factors such as patient population, medications that are likely to be coadministered in that population, clearance mechanisms of a TP, and concomitant drugs have to be taken into account to determine the potential for drug-drug interactions (DDIs). The most well documented TP DDI mechanism involves cytokine-mediated changes in drug-metabolizing enzymes. Because of the limitations of the current preclinical models for ad-

ressing this type of DDI, clinical evaluation is currently the most reliable approach. Other DDI mechanisms need to be addressed on a case-by-case basis. These include altered clearance of TPs resulting from the changes in the target protein levels by the concomitant medication, displacement of TPs from binding proteins, modulation of Fc $\gamma$  receptor expression, and others. The purpose of this review is to introduce the approach used by Pfizer scientists for evaluation of the DDI potential of novel TP products during drug discovery and development.

### Introduction

There have been significant advancements in the development of therapeutic proteins (TPs) over the past two decades. As a result, the number and diversity of biotherapeutic modalities on the market and at various stages of preclinical and clinical development have increased dramatically. As TPs are being used more commonly in polypharmacy settings, there has been an increase in the concern for potential TP drug-drug interactions (DDIs), which may cause either a loss of pharmacological effect or an increase in toxicity. Some examples of clinically observed DDIs include a 1.5-fold increase in trastuzumab serum levels by paclitaxel, a 44% reduction of adalimumab clearance after multiple dosing of methotrexate, and decreased exposure of simvastatin and omeprazole by 57 and 28%, respectively, after coadministration with tocilizumab (Zhou and Davis, 2009). Early profiling for cytochrome P450 (P450) and transporter-mediated DDIs,

used preclinically to de-risk small molecule drugs, allowed safer and more successful therapies to be delivered to patients. However, TP DDIs is a new and evolving scientific area with very few specific guidelines or consistent approaches available.

It is important that a systematic, science-driven approach be used (Zhou and Davis, 2009; Huang et al., 2010; Lee et al., 2010). This approach includes understanding the pharmacology and clearance mechanisms of a TP, the patient population, and medications that are likely to be coadministered in that population, as well as potential mechanisms of DDIs. Given the complexity of these factors and the limited knowledge in this area, at present clinical evaluation is the most reliable approach for studying TP DDIs.

The most well documented TP DDI mechanism involves cytokine-mediated changes in drug-metabolizing enzymes. Multiple *in vitro* and a number of *in vivo* human studies have demonstrated the effect of individual cytokines and their modulators on P450s and transporters (Strehlau et al., 2000; Prandota, 2005; Morgan et al., 2008; Morgan, 2009). In these cases, the TP plays the role of DDI perpetrator, whereas the victim is typically a small molecule (SM) drug.

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**ABBREVIATIONS:** TP, therapeutic protein; DDI, drug-drug interaction; P450, cytochrome P450; SM, small molecule; mAb, monoclonal antibody; IFN, interferon; IL, interleukin; PK, pharmacokinetic(s); LBA, ligand-binding assay.

At present, the most accepted preclinical approach for assessment of the effects of specific cytokine(s) and/or cytokine modulators on drug-metabolizing enzymes and transporters uses human hepatocytes treated with physiologically relevant amounts of cytokines and/or cytokine modulators (Huang et al., 2010; Lee et al., 2010). This method allows direct evaluation of the effect of TPs on P450s and transporters; however, it has a number of limitations and requires further optimization. Furthermore, translation of these *in vitro* findings to the *in vivo* setting has not been established at present. Potential *in silico* approaches are being evaluated (e.g., Symcyp); however, these approaches suffer from the same lack of understanding of the basic mechanisms of TP DDIs. Thus, it is likely that all cytokine modulators (cytokines, anti-cytokine mAbs, anti-cytokine receptor mAbs) will need additional scholarship on their DDI potential.

Because the hallmark of inflammation is the up- and down-regulation of cytokines, attenuation of preexisting inflammatory states by cytokine modulators will probably alter systemic exposures of SM drugs toward exposures similar to those observed for populations in noninflammatory states, and, therefore, it may not be necessary to address these types of DDIs early in development when studies are conducted using healthy volunteers. However, this hypothesis will need to be evaluated in the appropriate patient population during drug development. Notwithstanding, there may be situations when drug-metabolizing enzymes are expected to be modified in a manner that might result in abnormal exposure of a SM drug. These situations present a safety concern, especially for SM drugs with narrow therapeutic windows that undergo therapeutic drug monitoring, and this type of interaction should be addressed during early development. This situation is not unique to TPs. Anti-inflammatory SM drugs can have similar effects on P450s, and, therefore, this mechanism of DDI should not be overlooked for SM drugs either.

DDI mechanisms, other than those mediated by cytokines, need to be addressed on a case-by-case basis. These include altered clearance of TPs resulting from the changes in the target protein levels by the concomitant medication, displacement of TPs from binding proteins [heparin effect on palifermin (Amgen, Inc., 2007)], or modulation of Fc $\gamma$  receptor expression, which may result in decreased clearance of TPs [methotrexate effect on adalimumab (Weisman et al., 2003; Bunescu et al., 2004)].

Another type of DDI can occur as a result of an immune response generated against one TP, which cross-reacts with a secondary administered TP. This type of DDI will not be discussed in this review. Nonetheless, with increases in polytherapy, interactions via immunogenic responses may become more common.

The purpose of this review is to introduce the approach used by Pfizer scientists for evaluation of the DDI potential of novel TP products during drug discovery and development.

### Preclinical Considerations for Evaluation of Cytokine-Mediated DDIs

If a TP drug candidate is one of the cytokines for which the effect on P450s and transporters has been previously reported and characterized (IFN $\alpha$ , IFN $\alpha$ -2b, IFN $\beta$ , IL-2, IL-6, human growth hormone, IL-1, tumor necrosis factor- $\alpha$ , or IL-10) or if it is a mAb directed against one of those cytokines or their receptors, no additional preclinical experiments are recommended. Given the inherent variability of *in vitro* systems, this class of biotherapeutic agents would require a clinical DDI evaluation as described below.

If a TP drug candidate is a cytokine for which the effect on P450s and transporters has not been previously characterized or if it is a mAb directed against that type of cytokine or its receptor, it is recommended that the effect of this TP on P450s and transporters be evaluated using a human cultured hepatocyte assay. At a minimum, three different hepatocyte donors should be tested. To determine whether this hepatocyte assay is appropriate, it is important to under-

stand the mechanism via which the TP can modulate cytokines (i.e., direct versus indirect/down stream impact). The outcome from this assay can be used to qualitatively assess the likelihood of a DDI. Regardless of the results from current *in vitro* systems, clinical DDI evaluation may still be needed as discussed later.

Immunomodulatory TPs are typically evaluated for the potential to elicit cytokine release (tumor necrosis factor- $\alpha$ , IL-6, INF $\gamma$ , or IL-8) in the *in vitro* human cytokine release assay as part of a standard safety assessment. However, the current state of the art of this assay is limited to hazard identification using blood from healthy donors. Therefore, interpretations of cytokines generated in the cytokine release assay may not translate to *in vivo* situations, especially in diseased patients or in patients for whom the target does not exist in circulation. Because the effects on P450s for the four cytokines listed above have been reported (Strehlau et al., 2000; Prandota, 2005; Morgan et al., 2008; Morgan, 2009), no additional experiments are recommended at this time.

All of these assays are qualitative in nature and should not be interpreted in a quantitative manner at this time. Further *in vitro-in vivo* characterization is ongoing to improve the future utility of these assays.

### Clinical Considerations for Evaluation of Cytokine-Mediated DDIs

The interaction to be investigated in this case is the effect of a cytokine-modulating TP (perpetrator) on a SM drug (victim).

For TP DDI studies in which the mechanism of DDI is believed to be P450-mediated, it is recommended that clinical studies be conducted in patients rather than healthy volunteers, because P450 levels can be suppressed by inflammatory cytokines in patients. Anti-cytokine therapies can “normalize” P450 levels and, as a result, alter clearance of SM drugs. In healthy volunteers, cytokine levels are not elevated; therefore, cytokine modulators have little impact on P450 levels and would not be expected to alter P450 activity. Other important considerations for using patients instead of healthy volunteers include concerns surrounding the potential toxicity of either the TP or SM drug in healthy subjects and PK differences for TPs between patients and healthy subjects.

Individual substrate(s) for specific P450 enzymes should be considered for clinical evaluations that address the effects of TPs on the PK of SM drugs. A less optimal, but acceptable, approach for assessing the effect of a TP on the PK of a SM drug is the “cocktail approach” (Bjornsson et al., 2003). This type of evaluation can be conducted in phase 1b/2/3 trials as appropriate.

For evaluation of the effect of TPs on SM drugs, study designs including parallel-group, crossover (TPs with short half-lives), or single-sequence crossover designs (TPs with long half-lives) (e.g., SM drug PK defined in patients during a run-in period followed by SM drug PK defined after single- and/or multiple-dose TP administration) are commonly used. In addition, DDI assessments can use cross-study comparisons, which may involve comparison of data from healthy subjects versus patients. The results of such analyses should be evaluated as “hypothesis-generating” and generally need to be confirmed.

### Preclinical and Clinical Considerations for Evaluation of DDI Mechanisms, Other Than Those Mediated by Cytokines

At present, no preclinical studies are required for this type of DDI. DDI evaluation may be conducted on a case-by-case basis using a risk-based strategy. The strategy should evaluate the probability of the TP drug candidate to be a DDI victim or perpetrator based on its clearance mechanisms and biological mechanism of action. These DDI studies can be conducted during the later stages of development.

A population PK approach can be used for initial assessment, followed by a formal study if a DDI has been identified (Duan 2007; Huang et al., 2010). Whereas a population PK approach can be used to evaluate a TP as both a perpetrator and a victim, blood samples collected during late-phase studies are often used for determination of TP concentrations and, thus, only allow for evaluation of a TP as a victim. To evaluate a TP as a perpetrator, concentration data for concomitant medications also need to be collected. It is important to remember that TPs can be involved in DDIs with another TP and not only with SM drugs. The underlying mechanisms for these types of interactions could be more complicated and will require further investigation. Table 1 provides a list of questions and considerations that should help with gathering relevant information for determining whether TP drug candidates are likely to be DDI victims and/or perpetrators. This template (Table 1) can be used as a tool for summarizing information for any type of DDI mechanism.

### Clinical Considerations for TPs Intended for Use in Combination with Other Drugs (SM Drug or Another TP)

When a TP is designed to be coadministered with another drug (either a SM drug or another TP), *in vivo* DDI studies may need to be conducted even when there is no known mechanism of DDI. These types of studies should be considered in phase 1/2 when the combination is first given to evaluate the feasibility of the combination and provide information for safety evaluation. Early evaluation of DDIs with the combination drug can help set a development strategy and guide late-stage study designs.

Interactions to be investigated include both the effect of the TP candidate on the concomitant drug (SM drug or another TP) and the effect of the concomitant drug on the TP candidate. Selection of the interacting drugs for the DDI investigation is based primarily on the potential for concomitant usage, PK and pharmacodynamic properties of the compounds, and the therapeutic windows for selected drugs.

The effect of the TP on the concomitant drug is best evaluated using a within-patient comparison. Crossover designs can be applied for TPs with short half-lives and parallel-group or single-sequence crossover designs (e.g., chemotherapy PK defined in patients during a run-in period followed by chemotherapeutic PK defined after single- and/or multiple-dose administration of the TP) can be used for TPs with long half-lives. The possible effects of antidrug antibodies on the interpretation of crossover DDI studies of two biotherapeutic agents of the same modality will need to be considered.

The evaluation of the effect of a concomitant drug on the TP may be evaluated by cross-study comparison (e.g., TP PK defined in patients after TP treatment in combination with another drug (SM drug or TP), compared with TP PK as defined in a first-in-patient single-agent TP study), especially when the TP has a long half-life.

Early evaluation of DDIs between TPs and SM drugs used for cancer treatment is of particular importance because of the narrow therapeutic index of many anticancer drugs. Although the consideration for general DDI evaluation of oncology TPs is similar to that of other therapeutic areas, challenges exist in conducting formal DDI studies in cancer patients. Unlike evaluations for nononcology TPs, DDI evaluations are not usually conducted as stand-alone studies but rather as substudy evaluations as part of an ongoing study. It is preferable to conduct DDI evaluations (when there is a sound rationale) during early phase 1b/2 because this typically includes relatively small studies, and operational issues can be better managed.

When DDIs are observed, appropriate labeling language will probably be required for the package inserts.

### Bioanalytical Considerations

When *in vivo* DDI studies (either preclinical or clinical) are performed, potential interference of each concomitant drug on the quantification of the other should be investigated. In most cases, TPs are quantified using

TABLE 1  
*Assessment of TPs as potential DDI perpetrators or victims*

Assessment	Questions and Considerations
<b>TP as DDI perpetrator</b>	
1. TP is a cytokine, anti-cytokine, or cytokine modulator or causes release of cytokines <i>in vivo</i> or in a CRA.	Which cytokines are affected? Have effects of those cytokines on P450 and transporters been previously reported? If yes, no <i>in vitro</i> testing is required. If no, additional <i>in vitro</i> testing may be required to determine which P450s are likely to be affected.
2. TP candidate is intended to be used in combination with SM and/or other TP drugs.	Is it known what cytokine levels are typical in the intended patient population? What is the therapeutic index of those SM or TP drugs? What are the clearance mechanisms of the concomitant NTI TP? If the NTI compound is cleared via any of the P450s listed in 1, TP DDI clinical investigation involving intensive PK profiling of the NTI will probably be needed. If it is cleared via other pathways, PK data may be collected but not necessarily via intensive sampling. If any of the NTI clearance mechanisms (other than P450) are expected to be affected by the TP drug candidate, develop a risk-based strategy for addressing DDIs.
3. TP candidate is an immunomodulator.	Potential DDIs if concomitant medication is a mAb and Fc $\gamma$ receptors are involved in its clearance
<b>TP as DDI victim</b>	
1. Therapeutic index of TP drug candidate	If NTI, develop a risk-based strategy for addressing DDIs.
2. Target and target type	What are the biological consequences of inhibiting this target? Soluble/cell surface target and can it be shed? Will blocking this target affect clearance of endogenous proteins, etc.?
3. Clearance mechanisms of TP drug candidate (target-mediated clearance, peptidates, binding proteins, Fc $\gamma$ receptors, etc.)	If contribution of target-mediated clearance is significant at the clinical dose and concomitant drug may affect target expression potential for DDI.
4. TP candidate (through its mechanism of action) modulates expression of downstream receptors involved in elimination of concomitant TP or its own elimination.	Potential for DDIs
5. TP drug candidate interacts with endogenous proteins (other than target).	Potential for DDIs if concomitant medications alter levels of endogenous proteins that are involved in clearance of the TP

CRA, cytokine release assay; NTI, narrow therapeutic index.

analytical platforms different from those for SM drugs. Quantification of SM drugs typically uses liquid chromatography coupled to tandem mass spectrometry assays, whereas analytical methods for detection of TPs are based primarily on ligand-binding assays (LBAs). The specificity and selectivity of LBAs largely rely on the reagents used in the assays and the matrices in which the samples are collected. Because an extraction procedure is not always implemented during LBA analysis, the structurally related endogenous molecules, metabolic species, and other binding proteins or SM drugs could potentially interfere with the quantification of the TP of interest. It is therefore necessary to assess the interference of concomitant TP or SM drugs on the selectivity of the LBA used for quantifying the TP of interest during assay validation.

### Conclusions

The study of TP DDIs is an evolving science, but it clearly can have important clinical implications. It is crucial to interpret data carefully, in particular for cytokines, because several cytokines are typically altered in parallel or sequentially. With that in mind, an effort to understand the potential for DDIs should begin with an understanding of the pharmacology and clearance mechanisms of the TPs and potential coadministered drugs and of the relevant patient population. Although evaluation of TP DDIs is still in its infancy, additional studies in this area will undoubtedly lead to improved preclinical tools to predict clinical outcomes and, ultimately, to better guidelines for drug development.

### Authorship Contributions

Wrote or contributed to the writing of the manuscript: Kraynov, Martin, Hurst, Fahmi, Dowty, Cronenberg, Loi, Kuang, Fields, Fountain, Awwad, and Wang.

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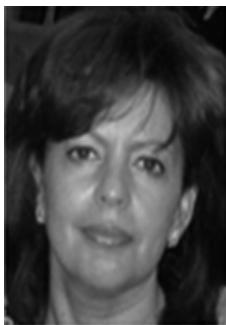


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