Physiologically Based Pharmacokinetic Modeling To Predict Drug-Biologic Interactions with Cytokine Modulators: Are These Relevant and Is Interleukin-6 Enough?

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ABSTRACT

Drugs that modulate cytokine levels are often used for the treatment of cancer as well as inflammatory or immunologic disorders. Pharmacokinetic drug-biologic interactions (DBIs) may arise from suppression or elevation of cytochrome P450 (P450) enzymes caused by the increase or decrease in cytokine levels after administration of these therapies. There is in vitro and in vivo evidence that demonstrates a clear link between raised interleukin (IL)-6 levels and P450 suppression, in particular CYP3A4. However, despite this, the changes in IL-6 levels in vivo rarely lead to significant drug interactions (area under the curve and Cmax ratios < 2-fold). The clinical significance of such interactions therefore remains questionable and is dependent on the therapeutic index of the small molecule therapy. Physiologically based pharmacokinetic (PBPK) modeling has been used successfully to predict the impact of raised IL-6 on P450 activities. Beyond IL-6, published data show little evidence that IL-8, IL-10, and IL-17 suppress P450 enzymes. In vitro data suggest that IL-1β, IL-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ can cause suppression of P450 enzymes. Despite in vivo there being a link between IL-6 levels and P450 suppression, the evidence to support a direct effect of IL-2, IL-8, IL-10, IL-17, IFN-γ, TNF-α, or vascular endothelial growth factor on P450 activity is inconclusive. This commentary will discuss the relevance of such drug-biologic interactions and whether current PBPK models considering only IL-6 are sufficient.

SIGNIFICANCE STATEMENT

This commentary summarizes the current in vitro and in vivo literature regarding cytokine-mediated cytochrome P450 suppression and compares the relative suppressive potential of different cytokines in reference to interleukin (IL)-6. It also discusses the relevance of drug-biologic interactions to therapeutic use of small molecule drugs and whether current physiologically based pharmacokinetic models considering only IL-6 are sufficient to predict the extent of drug-biologic interactions.

Introduction

Biologic drugs have been used or tested in combination with small molecule drugs for the treatment of immunologic diseases such as inflammatory bowel disease and rheumatoid arthritis (Paramsothy et al., 2018; Dolinger et al., 2021; nouse et al., 2008) and oncolgic disorders such as leukemia, breast cancer, gastrointestinal stromal tumors, and colorectal cancer (Sharman et al., 2019; Canoi et al., 2019; Vallilas et al., 2021; Poindessous et al., 2011). Many of these biologics modulate cytokine levels. An increase or decrease in cytokines levels has been shown to suppress or elevate cytochrome P450 (P450) enzymes (Abdel-Razzak et al., 1993, 1994; Donato et al., 1993, 1997; Guillaume et al., 1998; Sunman et al., 2004; Aitken and Morgan, 2007; Dallas et al., 2012; Dickmann et al., 2012; Li et al., 2014; Klein et al., 2015; Mimura et al., 2015; Rubin et al., 2015). P450 enzymes are an important class of enzymes responsible for the metabolism of many small molecule drugs (Wienkers and Heath, 2005; Zangr and Schwab, 2013). Thus, pharmacokinetic drug-biologic interactions (DBIs) may arise after coadministration of small molecules and biologics. For therapeutic proteins acting as cytokine modulators, the US Food and Drug Administration (FDA) requires language in the label to indicate whether there is a potential for drug-drug interactions (DDIs) (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-drug-interaction-assessment-therapeutic-proteins-guidance-industry).

Despite the clear in vitro and in vivo links between interleukin (IL)-6 levels and P450 suppression and in particular CYP3A4, the changes in IL-6 levels in vivo rarely lead to significant drug interactions (i.e., <2-fold; Morgan et al., 2008; Harvey and Morgan, 2014; Coutant and Hall, 2018). Physiologically based pharmacokinetic (PBPK) modeling has been used successfully to predict the impact of raised IL-6 on P450 activities (Machavaram et al., 2013, 2019; Xu et al., 2015; Jiang et al., 2016; Lenoir et al., 2021;
Evidences of Cytokine Suppression of P450 Enzymes In Vitro

In Vitro P450 Suppression by IL-6

The majority of the available in vitro data focus on IL-6. Of the cytokines tested in vitro, IL-6 generally causes the greatest P450 suppression, with CYP3A4 being the most sensitive. (Abdel-Razzak et al., 1993, 1994; Donato et al., 1993, 1997; Guillén et al., 1998; Summan et al., 2004; Aitken and Morgan, 2007; Dallas et al., 2012; Dickmann et al., 2012; Li et al., 2014; Klein et al., 2015; Mimura et al., 2015; Rubin et al., 2015). Decreases in CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4 activity/mRNA/protein abundance of up to 36%, 78%, 72%, 54%, 88%, 39%, 50%, and 98% have been reported, although suppression of CYP1A2 often did not reach statistical significance (Abdel-Razzak et al., 1993, 1994; Donato et al., 1993, 1997; Guillén et al., 1998; Summan et al., 2004; Aitken and Morgan, 2007; Dallas et al., 2012). These studies usually measure the effect of cytokines at a single concentration that is far in excess of those seen in diseases or after administration of immunomodulators. For example, IL-6 concentrations of 0.5–200 ng/ml have been used in vitro, whereas mean values in patients with rheumatoid arthritis (RA) and postsurgery are 54 and 229 pg/ml, respectively (Machavaram et al., 2013). Another meta-analysis comprising 11,583 patients with cancer reported a median IL-6 serum level of 6.95 pg/ml (range: 0.23–78.5 pg/ml) compared with the control level of 1.31 pg/ml (range: 0.37 pg/ml) (Lippitz and Harris, 2016). A mean serum peak IL-6 concentration of 4400 pg/ml was observed after initiation of blinatumomab (up to 90% decrease in cytokine levels) in patients with acute lymphoblastic leukemia (Xu et al., 2015), which is still lower than IL-6 concentrations used in most in vitro assays.

In the Dickmann et al. (2011) in vitro study, cryopreserved and fresh human hepatocytes were used to determine the suppression of several P450s by IL-6 over a range of concentrations (0.5–10,000 pg/ml) that are more relevant to those observed in disease states or after administration of immunomodulators. The IL-6 concentration that supports significant P450 suppression is unlikely if IL-6 concentration is below EC50 (4.23 pg/ml in the absence of dexamethasone) is close to the upper limit of the range of values for individual hepatocyte donors reported by Dickmann et al. (2011). Contrarily, the CYP3A4 mRNA EC50 value reported by Dickmann et al. (2011) is about 30-fold lower than the value reported by Evers et al. (2013) (94.7 pg/ml in the absence of dexamethasone).

In Vitro P450 Suppression by Other Cytokines

Suppression of P450s by IL-2 has been measured in vitro in two studies (Summan et al., 2004; Dallas et al., 2012). Dallas et al. (2012) reported that IL-2 did not have a statistically significant effect on CYP1A2, CYP2C9, or CYP3A4 mRNA or activity in cryopreserved hepatocytes incubated with 10 ng/ml IL-2 for 48 hours. Modest but significant suppression (<25%) of CYP2B6 and CYP2C19 (activity only) was observed (Table 1). CYP2D6 mRNA was increased by 50%, whereas CYP2D6 activity was decreased by 22% (Table 1). Comparison with the IL-6 activity and mRNA suppression by IL-6 in the same in vitro assay as represented by the ratios of percent decrease relative to IL-6, shows that IL-2 has less of a suppressive action when compared with IL-6 (Table 1). Summan et al. (2004) reported no suppression of CYP3A3 mRNA activity by IL-2 (2–200 ng/ml) in hepatocyte cultures but a concentration-dependent 50%–70% suppression in hepatocyte/Kupffer cell cocultures. This suggests that IL-2 acts via an indirect mechanism, probably through stimulating Kupffer cells to produce other cytokines such as IL-6.

Suppression of P450s by interferon (IFN)-γ has been measured in vitro in six studies (Abdel-Razzak et al., 1993, 1994; Donato et al., 1993, 1997; Guillén et al., 1998; Aitken and Morgan, 2007). Abdel-Razzak et al. (1993) reported that IFN-γ did not change CYP2C2 or CYP3A mRNA in fresh hepatocytes incubated with 50 U/ml IFN-γ for 72 hours. In contrast, a 21%–55% decrease in nifedipine activity (CYP3A substrate) was found in two donors. A marked reduction in CYP1A2 and CYP2E1 mRNA was observed in two of three donors, and ethoxyresorufin-O-deethylase (EROD) activity was reduced by 29%–53% in six donors (Table 2). Similarly, in a follow-up study, EROD activity was significantly reduced by 22%–42% in four fresh hepatocyte donors incubated with 50 U/ml IFN-γ for 72 hours (Table 2). (Abdel-Razzak et al., 1994). Aitken and Morgan (2007) reported that incubation of fresh hepatocytes with 10 ng/ml IFN-γ for 24 hours led to a statistically significant decrease in CYP2C8, CYP3A4, and CYP2B6 mRNA and protein expression of CYP3A4 and CYP2B6 (Table 2). IFN-γ did not have a statistically significant effect on CYP2C9, CYP2C18, or CYP2C19 mRNA; however, a significant decrease in CYP2C9 protein expression was observed after 24 hours in one donor (Aitken and Morgan, 2007). Guillén et al. (1998) reported that IFN-γ reduced CYP1A2, CYP2B6, CYP2A6, and CYP3A4 activity in fresh hepatocytes incubated with 300 U/ml IFN-γ for 48 hours (Table 2). Comparison of the P450 activity, protein expression, or mRNA

TABLE 1

P450 mRNA or activity percent decrease measured in cryopreserved human hepatocytes incubated with IL-2 or IL-6

Data were extracted from Dallas et al. (2012); n = 3 donors were treated with 10 ng/ml IL-2 or IL-6 for 48 hours.

| CYP2B6 activity | CYP2C19 activity | CYP2D6 activity | CYP2D6 mRNA |
|-----------------|-----------------|-----------------|-------------|
| % Decrease by IL-2 | % Decrease by IL-6 | % Decrease by IL-2 | % Decrease by IL-6* |
| 21 | 30 | 0.70 |
| 22 | 65 | 0.34 |
| 22 | 39 | 0.56 |
| 1.5 | 2.4 | 0.63 |

* The ratios compare the extent of suppression by IL-2 relative to IL-6. Despite high between-laboratory variability, the reported CYP3A4 activity Eₘₐₓ values (0.20–0.38 in the absence of dexamethasone) are consistent with those reported in Dickmann et al. (2011). Similarly, the CYP3A4 activity EC₅₀ value reported by Evers et al. (2013) (217 pg/ml in the absence of dexamethasone) is close to the upper limit of the range of values for individual hepatocyte donors reported by Dickmann et al. (2011). Contrarily, the CYP3A4 mRNA EC₅₀ value reported by Dickmann et al. (2011) is about 30-fold lower than the value reported by Evers et al. (2013) (94.7 pg/ml in the absence of dexamethasone).
suppression caused by IFN-γ to that caused by IL-6 in the corresponding studies shows that IFN-γ generally has a similar or reduced suppressive action when compared with IL-6, with the exception of CYP1A2 activity where IFN-γ is a more potent suppressor (Table 2).

There are no reported E_min and EC_50 values describing the IFN-γ suppression of P450s, and the majority of the in vitro data have been measured at a single IFN-γ concentration. However, concentration-dependent suppression of CYP1A2 activity has been reported, allowing the calculation of E_min and EC_50 values for IFN-γ (Donato et al., 1993, 1997; Guillén et al., 1998). The calculated IFN-γ E_min and EC_50 values are 0.629 and 2460 pg/ml (measured at 500–150,000 pg/ml in Donato et al., 1993), 0.572 and 4400 pg/ml (measured at 1500–50,000 pg/ml in Donato et al., 1997), and 0.601 and 4098 pg/ml (measured at 2500–50,000 pg/ml in Guillén et al., 1998), respectively (Table 4). Comparing these values to those for IL-6 [mean E_min (range) = 0.230 (0.062–0.529) and mean EC_50 (range) = 1251 (142–4070) pg/ml] (Dickmann et al., 2011) (Table 4) suggests that IFN-γ is not as potent a CYP1A2 suppressor as IL-6. It should be noted that the IFN-γ concentrations used in vitro are far in excess of physiologic concentrations in healthy subjects (7.5–21.2 pg/ml or 0.3 ± 0.1 U/ml) and those with RA (17.9–32.6 pg/ml), acute respiratory infections (3.4 ± 1.3 U/ml) (Brockmeyer et al., 1992; Caris et al., 2020), or acute lymphoblastic leukemia after blinatumomab administration (peak ~440 pg/ml) (Xu et al., 2015).

Suppression of P450s by tumor necrosis factor (TNF)-α has been measured in vitro in five studies (Abdel-Razak et al., 1993; Aitken and Morgan, 2007; Dallas et al., 2012; Klein et al., 2015; Mimura et al., 2015). Abdel-Razak et al. (1993) reported that TNF-α decreased CYP1A2, CYP2C, CYP2E1, and CYP3A mRNA levels by 30%–80% in all three donors after 72-hour incubation (Table 3). EROD and nifedipine oxidation activities were also decreased by 32%–85% and 24%–90%, suggesting reduced CYP1A2 and CYP3A4 activities. Similarly, Aitken and Morgan (2007) reported significant reduction in CYP2C8 (but not CYP2C9) and CYP3A4 mRNA levels (n = 9). Additionally, they quantified CYP2B6, CYP2C9, and CYP3A4 protein levels using western blotting and found that TNF-α treatment significantly reduced CYP2B6 and CYP2C9 proteins by 87% and 94%, respectively (Table 3). The CYP3A4 protein level decreased in a similar trend, but statistical significance was not detected. Dallas et al. (2012) measured mRNA levels and enzyme activities for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. After TNF-α treatment, reduction in CYP1A2, CYP2D6, and CYP3A4 mRNA levels were detected (Table 3). TNF-α also reduced CYP3A4 mRNA by 51% in hepatoma cell line FLC-4 over a 24-hour incubation, although TNF-α had no effect on CYP3A4 protein expression or activity (Mimura et al., 2015). Reduction in enzyme activities was significant in all P450 isoforms tested and generally comparable to reduction caused by IL-6 except for CYP1A2, where a greater reduction was observed after TNF-α treatment compared with IL-6 treatment (Table 3).

Klein et al. (2015) proposed HepaRG cells as a surrogate for primary human hepatocytes and, using HepaRG cells, characterized dose-response curves for CYP1A2, CYP2B6, CYP2C9, and CYP3A4 by measuring mRNA levels in a range of TNF-α concentrations (0.1–50,000 pg/ml). Using data from this study, the E_min and EC_50 values of TNF-α for CYP1A2 (0.0337 and 817 pg/ml), CYP2B6 (0.639 and 86.6 pg/ml), CYP2C9 (0.289 and 153 pg/ml), and CYP3A4 (0.107 and 133 pg/ml) were determined (Table 4), suggesting weaker suppression for P450s compared with IL-6 except for CYP1A2. Despite a stronger effect in CYP1A2 suppression compared with IL-6 (Table 4), it should be noted that TNF-α EC_50 values were in excess of concentrations observed in patients with immunologic diseases [e.g., 30.5 pg/ml in RA patients with chronic periodontitis vs. 5.5 pg/ml in control (Thilagar et al., 2018) and 25.7 pg/ml in psoriatic patients vs. 11.2 pg/ml in control (Arcian et al., 2005)] although within the range of TNF-α concentrations observed after administration of cytokine modulators [e.g., peak ~200 pg/ml in patients with acute lymphoblastic leukemia given blinatumomab (Xu et al., 2015)].

In vitro data for other cytokines is limited. Currently, there are no in vitro data available in the public domain regarding P450 suppression by IL-8, IL-17, and vascular endothelial growth factor (VEGF). Xu et al. (2015) indicate that in vitro studies in human hepatocytes revealed no effect of IL-10 on P450 enzymes even at 5000 pg/ml. The studies...
were conducted internally by Amgen Inc.; however, the data were not reported in the publication (Xu et al., 2015).

Although multiple cytokines are raised simultaneously in disease states and after dosing of certain cytokine modulator biologic drugs in vivo, the majority of in vitro studies have assessed the P450 suppression caused by one cytokine alone rather than the effect of a combination of cytokines. Underlying mechanisms of P450 suppression are cytokine specific; hence, synergistic effects on P450 modulation are possible. The pre- and posttranscriptional mechanistic pathways such as transcriptional factor regulation and nitric oxide stimulation were previously discussed (de Jong et al., 2020). However, in vitro data to confirm or refute cytokine synergism are limited. In the Dickmann et al. (2012) in vitro study, cryopreserved and fresh human hepatocytes from one donor were used to determine the suppression of several P450s by IL-1β alone or in combination with IL-6 over a range of physiologically relevant concentrations (10 and 100 pg/ml IL-1β and IL-6). Dickmann et al. (2012) reported IL-1β alone was 6-fold less potent than IL-6 (based upon EC50 values) for suppression of CYP3A4. The combination of IL-1β and IL-6 did not increase the P450 suppression caused by IL-6 alone

### TABLE 3

| Measure | % Decrease by TNF-α | % Decrease by IL-6 | % Decrease by TNF-α / % Decrease by IL-6 | Study |
|---------|---------------------|-------------------|-----------------------------------------|-------|
| CYP1A2 activity | 72 | 23 | 3.13 | Dallas et al., 2012 |
| CYP1A2 activity | 57 | 28 | 2.04 | Abdel-Razzak et al., 1993 |
| CYP1A2 mRNA | 73 | 24 | 3.09 | Abdel-Razzak et al., 1993 |
| CYP1A2 mRNA | 45 | 15 | 3.00 | Dallas et al., 2012 |
| CYP2B6 activity | 35 | 30 | 1.17 | Dallas et al., 2012 |
| CYP2B6 mRNA | NS | 78 | — | Aitken and Morgan, 2007 |
| CYP2B6 mRNA | 63 | 63 | — | Dallas et al., 2012 |
| CYP2B6 protein | 59 | 62 | 0.95 | Aitken and Morgan, 2007 |
| CYP2C8 mRNA | 64 | 54 | 1.17 | Aitken and Morgan, 2007 |
| CYP2C9 activity | 16 | 35 | 0.47 | Dallas et al., 2012 |
| CYP2C9 mRNA | NS | 34 | — | Aitken and Morgan, 2007 |
| CYP2C9 mRNA | 63 | 63 | — | Dallas et al., 2012 |
| CYP2C9 protein | 94 | 88 | 1.07 | Aitken and Morgan, 2007 |
| CYP2C19 activity | 84 | 65 | 1.29 | Dallas et al., 2012 |
| CYP2C19 mRNA | NS | 37 | — | Dallas et al., 2012 |
| CYP2C19 mRNA | 72 | 72 | — | Dallas et al., 2012 |
| CYP2D6 activity | 45 | 39 | 1.15 | Dallas et al., 2012 |
| CYP2D6 mRNA | 46 | 240 | opposite direction | Dallas et al., 2012 |
| CYP2E1 mRNA | 44 | 52 | 0.84 | Abdel-Razzak et al., 1993 |
| CYP3A4 activity | 70 | 76 | 0.92 | Dallas et al., 2012 |
| CYP3A4 activity | 60 | 38 | 1.58 | Abdel-Razzak et al., 1993 |
| CYP3A4 activity | NS | 69 | — | Mimura et al., 2015 |
| CYP3A4 mRNA | 58 | 52 | 1.10 | Abdel-Razzak et al., 1993 |
| CYP3A4 mRNA | 81 | 95 | 0.85 | Aitken and Morgan, 2007 |
| CYP3A4 mRNA | 85 | 95 | 0.87 | Dallas et al., 2012 |
| CYP3A4 mRNA | 61 | 78 | 0.78 | Mimura et al., 2015 |
| CYP3A4 mRNA | NS | 45 | — | Aitken and Morgan, 2007 |

NS, no significant change. “—”, not applicable.

In Dallas et al. (2012), cryopreserved human hepatocytes were treated with 10 ng/ml TNF-α or 10 ng/ml IL-6 for 48 hours. In Abdel-Razzak et al. (1993), primary human hepatocytes were treated with 50 U/ml TNF-α or 50 U/ml IL-6 for 72 hours. In Aitken and Morgan (2007), primary human hepatocytes were treated with 10 ng/ml TNF-α or 10 ng/ml IL-6 for 24 hours. In Mimura et al. (2015), primary human hepatocytes were treated with 10 ng/ml TNF-α or 10 ng/ml IL-6 for 48 hours.

* The ratios compare the extent of suppression by TNF-α relative to IL-6.

### TABLE 4

| Measure | System | Cytokine | Incubation Concentration (pg/ml) | Incubation Time (h) | Emin (fold) | EC50 (pg/ml) | Emax × EC50 | Study |
|---------|--------|----------|----------------------------------|---------------------|-------------|-------------|-------------|-------|
| CYP1A2 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.157 | 271 | 42.5 | Dickmann et al., 2011 |
| CYP1A2 mRNA | HepaRG cells | TNF-α | 0.1–50,000 | 24 | 0.0337 | 817 | 27.5 | Klein et al., 2015 |
| CYP2B6 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.0311 | 70 | 2.18 | Dickmann et al., 2011 |
| CYP2B6 mRNA | HepaRG cells | TNF-α | 0.1–50,000 | 24 | 0.639 | 86.6 | 55.3 | Klein et al., 2015 |
| CYP2C9 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.214 | 71.3 | 15.3 | Dickmann et al., 2011 |
| CYP2C9 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.0386 | 153 | 5.91 | Dickmann et al., 2011 |
| CYP2C9 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.0525 | 121 | 6.35 | Dickmann et al., 2011 |
| CYP2C9 mRNA | HepaRG cells | TNF-α | 0.1–50,000 | 24 | 0.289 | 153 | 44.3 | Klein et al., 2015 |
| CYP2C9 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.302 | 151 | 45.6 | Dickmann et al., 2011 |
| CYP3A4 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.00 | 3.23 | 0.00 | Dickmann et al., 2011 |
| CYP3A4 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.107 | 133 | 14.2 | Klein et al., 2015 |
| CYP3A5 mRNA | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.0343 | 51 | 1.75 | Dickmann et al., 2011 |
| CYP1A2 activity | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.241 | 73.2 | 17.6 | Dickmann et al., 2011 |
| CYP1A2 activity | Human hepatocyte | IFN-γ | 500–150,000 | 24 | 0.629 | 2460 | 1547 | Donato et al., 1997 |
| CYP1A2 activity | Human hepatocyte | IFN-γ | 1500–50,000 | 24 | 0.572 | 4400 | 2517 | Donato et al., 1997 |
| CYP1A2 activity | Human hepatocyte | IFN-γ | 2500–50,000 | 24 | 0.601 | 4098 | 2463 | Guillén et al., 1998 |
| CYP3A4 activity | Human hepatocyte | IL-6 | 5–50,000 | 72 | 0.23 | 1251 | 288 | Dickmann et al., 2011 |

IFN-γ and TNF-α data were digitalized from the figures in the publications; subsequently, Emin and EC50 values were estimated using a 4-parameter fit.
for CYP1A2 and CYP2C9. The combination of 100 pg/ml IL-1β with IL-6 reduced the suppression of CYP2B6 caused by 100 pg/ml IL-6 alone. In contrast, the combination of 100 pg/ml IL-1β and IL-6 had an additive downregulation on CYP3A4 mRNA and activity compared with IL-6 alone, reducing CYP3A4 mRNA/activity to 26% versus 37% of control values, respectively.

Xu et al. (2015) also studied the suppression of multiple P450s in three hepatocyte donors when incubated with a cocktail of cytokines (IL-2, IL-6, IL-10, IFN-γ, and TNF-α). Three concentrations of cytokines were used, based on the low (125 pg/ml for all cytokines), mid (2000 pg/ml IL-6, IL-10, and IFN-γ with 500 pg/ml for IL-2 and TNF-α) and high (20,000 pg/ml IL-6, IL-10, and IFN-γ with 1000 pg/ml for IL-2 and TNF-α) levels of cytokines observed after dosing of blinatumomab (0.5 to 90 μg/m² per day) to patients with non-Hodgkin Lymphoma. Similar P450 suppression was observed with the mid- and high-concentration cytokine cocktails, indicating that the suppression is maximized by the mid-strength cytokine levels (Xu et al., 2015). Limited suppression was observed in most donors for CYP2C19 and CYP2D6 activity, even with high cytokine levels, whereas >50% suppression of CYP1A2, CYP2C9, and CYP3A4 activity was observed in two or three donors with the highest cytokine levels. The level of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 suppression observed with mid- or high-strength cytokine cocktails by Xu et al. (2015) was within the range of values reported by other in vitro studies using IL-6, TNF-α, or IFN-γ alone (Abdel-Razzak et al., 1993, 1994; Donato et al., 1993, 1997; Sunman et al., 2004; Aitken and Morgan, 2007; Dallas et al., 2012; Dickmann et al., 2012). This suggests that suppression by combinations of cytokines is not likely to increase the extent of P450 suppression compared with incubation with a single cytokine.

Evidence of Cytokine Suppression of P450 Enzymes In Vivo

Changes in circulating cytokine levels have been linked to alterations in drug metabolism in vivo (Morgan et al., 2008; Harvey and Morgan, 2014). There are several reports of alteration of P450 substrate pharmacokinetics (PK) in disease/infection after vaccination where there is an inflammatory response and hence increase in circulating cytokine levels. In addition, DDIs between P450 substrates and biologic drugs that are themselves cytokines or cytokine modulators have been reported (Huang et al., 2010; Lee et al., 2010; Evers et al., 2013).

In Vivo P450 Suppression by IL-6. The correlations between raised IL-6 concentrations and P450 activity have been reviewed previously (Morgan et al., 2008; Harvey and Morgan, 2014; Coutant and Hall, 2018). A few examples are detailed here. Raised IL-6 concentrations have been significantly correlated with decreased CYP1A2, CYP2C9, CYP2C19, and CYP3A4 activity in congestive heart failure, cancer, bone marrow transplant, coronavirus disease 2019 (COVID-19) infection, and surgery patients (Chen et al., 1994; Frye et al., 2002; Sato et al., 2016; Trouil et al., 2019; Lenoir et al., 2021a,b). In contrast, raised IL-6 concentrations were associated with increased CYP2E1 activity in patients with ovarian cancer and CYP2C9 activity in hip surgery patients (Trouil et al., 2019; Lenoir et al., 2021ab). However, CYP2D6 activity did not change in hip surgery patients within 3 days of surgery or in patients infected with COVID-19 (Lenoir et al., 2021ab).

Several therapeutic protein-drug interactions relating to IL-6 have also been reported. Administration of sarilumab or tocilizumab to patients with RA led to a decrease in simvastatin, midazolam, omeprazole, and S-warfarin area under the curve (AUC), a slight increase in CYP1A2 AUC, and no effect on CYP2D6 activity (Zhang et al., 2009; Schmitt et al., 2011; Zhuang et al., 2015; Lee et al., 2017). Similarly, patients infected with COVID-19 who received tocilizumab >12 hours prior to lopinavir administration had significantly lower lopinavir (CYP3A4 substrate) exposure (Marzolini et al., 2020). Sarilumab and tocilizumab are monoclonal antibodies (mAbs) that block IL-6 from binding to its receptor and hence remove the suppressive effect of raised IL-6 on P450s in RA and COVID-19 patients, leading to increased P450 activity and coadministered drug clearance.

In Vivo P450 Suppression by Other Cytokines. CYP1A2, CYP2C2, CYP2E1, and CYP3A protein expression was reduced to 37%, 45%, 60%, and 39% of control values in hepatic microsomes isolated from surgical samples from hepatectomy patients receiving high doses of IL-2 (9 or 12 × 10^6 U/m²) prior to surgery (Elkahwaji et al., 1999). Similarly, methoxyresorufin and erythromycin activity was significantly reduced after IL-2 administration (Elkahwaji et al., 1999). Indinavir trough concentrations and AUC significantly increased with a corresponding significant decrease in oral clearance (Cl/F) after administration of IL-2 (aldesleukin) in patients with human immunodeficiency virus (HIV) (Piscitelli et al., 1998). However, significant increases in IL-6 reduced the suppression of CYP2B6 caused by 100 pg/ml IL-6 alone. In contrast, the combination of 100 pg/ml IL-6 and IL-2 reduced the suppression of CYP2B6 caused by 100 pg/ml IL-6 significantly. IL-6 concentrations and P450 activity have been reviewed previously (Morgan et al., 2008; Harvey and Morgan, 2014; Coutant and Hall, 2018). A few examples are detailed here. Raised IL-6 concentrations have been significantly correlated with decreased CYP1A2, CYP2C9, CYP2C19, and CYP3A4 activity in congestive heart failure, cancer, bone marrow transplant, coronavirus disease 2019 (COVID-19) infection, and surgery patients (Chen et al., 1994; Frye et al., 2002; Sato et al., 2016; Trouil et al., 2019; Lenoir et al., 2021ab). In contrast, raised IL-6 concentrations were associated with increased CYP2E1 activity in patients with ovarian cancer and CYP2C9 activity in hip surgery patients (Trouil et al., 2019; Lenoir et al., 2021ab). However, CYP2D6 activity did not change in hip surgery patients within 3 days of surgery or in patients infected with COVID-19 (Lenoir et al., 2021ab).

Basiliximab and daclizumab are monoclonal antibodies (mAbs) that act as IL-2 receptor α (IL-2Rα) antagonists. After administration of IL-2Rα antagonists (mainly basiliximab) to renal transplant patients, tacrolimus trough concentrations significantly increased (Sifontis et al., 2002; Lin et al., 2015). Similarly, significantly increased cyclosporine trough concentrations, early cyclosporine toxicity, and a lower dose requirement were found in pediatric renal transplant patients after dosing with basiliximab when compared with controls (Strehlau et al., 2000). The reduction in tacrolimus and cyclosporine clearance is thought to be due to basiliximab blocking the binding of circulating IL-2 to IL-2Rα on T cells, and instead IL-2 binds to the IL-2R on hepatic and intestinal cells leading to suppression of CYP3A4 (Sifontis et al., 2002). In contrast, administration of daclizumab to patients with multiple sclerosis had no effect on the exposure of midazolam, S-warfarin, omeprazole, caffeine, or dextromethorphan (Tran et al., 2016). IL-6 concentrations in AUC of CYP3A4 substrates simvastatin and midazolam (Schmitt et al., 2016). In contrast, raised IL-8 levels in patients with ovarian cancer were compared to those in patients with RA who received sarilumab or tocilizumab treatment (Zhuang et al., 2015). Since IL-8, TNF-α, and IL-6 could all contribute to effects in CYP2E1 and CYP3A4 activity, a direct role of IL-8 in a CYP2E1 or CYP3A4-mediated DDIs is inconclusive.
A double-blind crossover study where 8 μg/kg of IL-10 and placebo were administered to healthy volunteers once daily for 6 days has been published (Gorski et al., 2000). On days 4 and 5, tolbutamide (CYP2C9), caffeine (CYP1A2), dextromethorphan (CYP2D6), and midazolam (CYP3A4) were coadministered. The study showed that administration of IL-10 did not alter CYP1A2, CYP2C9, and CYP2D6 activities and that the CYP3A activity was reduced by only 12% ± 17%. The IL-10 concentrations after dosing of 8 μg/kg are likely to be much higher than those observed in patients with immune disorders (89.5 pg/ml in psoriasis, 58.7 pg/ml in RA, and 12.6 pg/ml in systemic lupus erythematosus) (Lacki et al., 1995; Godsell et al., 2016; Sobhan et al., 2016).

There are few reports linking IFN-γ to suppression of P450 metabolism in vivo, and there are no data after direct dosing of IFN-γ or IFN-γ antagonists. In healthy subjects suffering with an acute viral respiratory infection, IFN-α and IFN-γ concentrations were significantly increased (2.7- and 11.3-fold, respectively) and antipyrine clearance was significantly decreased (1.3-fold) compared with controls (Brockmeyer et al., 1992). IFN-α and IFN-γ concentrations are also markedly higher in HIV patients with severe disease. When these patients were treated with zidovudine, the IFN-α and IFN-γ concentrations significantly decreased (60% and 59%, respectively) and antipyrine clearance significantly increased (1.2-fold) (Brockmeyer et al., 1992, 1998). Decreases in theophylline, antipyrine, caffeine, mephenytoin, debrisoquine, chlorozoxazone, and erythromycin metabolism have been reported after direct administration of INF-α to hepatitis and melanoma patients, as reviewed by Lee et al. (2010). Therefore, the P450 suppression observed in respiratory infection and HIV patients may be due to increased IFN-α rather than IFN-γ. Other cytokines such as IL-6 may also be increased in these diseases. Changes in antipyrine clearance in subjects with respiratory infection or in HIV patients treated with zidovudine are generally more limited than the changes in P450 substrate clearance reported upon administration of IL-6R antagonists to patients with RA (Schmitt et al., 2011; Zhuang et al., 2015).

There have been several reports of vaccine-drug interactions, which have been attributed to increases in IFN-γ concentrations after vaccination (Pellegrino et al., 2015). The data for warfarin (CYP2C9) are conflicting between studies, which may reflect the limited effect of IFN-γ on CYP2C9 in vitro (Aitken and Morgan, 2007). Reports for theophylline (CYP1A2) are also conflicting (Jonkman and Upton, 1984; Pellegrino et al., 2015), potentially due to inappropriate timing of some studies, whereby the maximum P450 suppression and effect on theophylline PK were missed due to the sparse sampling used. There are limited reports of vaccine interactions with anticonvulsants (e.g., carbamazepine, phenytoin, and phenobarbital) showing an increase in anticonvulsant exposure after vaccination, although the extent and duration of the drug-vaccine interaction differs widely between reports (Pellegrino et al., 2015). Vaccination also causes a significant transient increase in IL-6 and other cytokine concentrations (Tsai et al., 2005; Wright et al., 2005; Brydon et al., 2008; Harrison et al., 2009; Herrin et al., 2014; Sharpley et al., 2016; Kuhlman et al., 2018). Therefore, the role of IFN-γ in drug-vaccine interactions is not clear.

Frye et al. (2002) reported that in congestive heart failure patients given a metabolic probe cocktail consisting of caffeine (CYP1A2), mephentoin (CYP2C19), dextromethorphan (CYP2D6), and chlorozoxazone (CYP2E1), a significant inverse relationship was found between both TNF-α and IL-6 plasma concentrations and the activity of CYP2C19. Since both TNF-α and IL-6 could contribute to suppression of CYP2C19 activity, the role of TNF-α in a CYP2C19-mediated DDI is inconclusive. In another study, patients with HIV had lower CYP3A4 and CYP2D6 activity when compared with age- and sex-matched healthy volunteers (18% and 90%, respectively) but no significant difference for CYP1A2 (Jones et al., 2010). Higher TNF-α concentrations in patients with HIV were significantly correlated with the reduced CYP3A4 activity but not CYP2D6 activity (Jones et al., 2010). Raised TNF-α levels in patients with ovarian cancer (45.4 pg/ml) were significantly associated with increased CYP2E1 activity (3-fold) and reduced CYP3A4 activity (42%) when compared with healthy volunteers (Trousil et al., 2019). However, the changes in enzyme activity were also significantly associated with IL-6 and IL-8 levels. Since IL-8, TNF-α, and IL-6 could all contribute to effects on CYP2E1 and CYP3A4 activity, the role of TNF-α in a CYP2E1- or CYP3A4-mediated DDI is inconclusive. In patients with psoriasis, TNF-α concentrations were also significantly increased (~12 pg/ml) when compared with healthy subjects; however, no correlation was found between raised TNF-α levels and venlafaxine (CYP2D6 and P-gp substrate) metabolic ratios (Godoy et al., 2016). Similarly, TNF-α levels in patients infected with COVID-19 or after hip surgery did not correlate with the decreased CYP1A2, CYP2C19, or CYP3A4 activity observed in these patients, which is likely due to the increased IL-6 levels (Lenoir et al., 2021a,b).

A few therapeutic protein-drug interactions relating to TNF-α have also been reported. Etanercept is a fusion protein that blocks TNF-α from binding to its receptor and hence would remove any suppressive effect of raised TNF-α on P450s in patients. Administration of etanercept to healthy volunteers had no effect on digoxin (P-gp substrate) or warfarin (CYP2C9 substrate) exposure (Zhou et al., 2004a,b); however, healthy volunteers would be expected to have low circulating TNF-α levels, and hence any potential P450 suppression prior to etanercept administration would be minimal. Wen et al. (2020) reported a case study of a patient with ankylosing spondylitis, hypertension, diabetes mellitus, and IgA nephropathy who was receiving etanercept and cyclosporine. Use of etanercept was correlated with increased cyclosporine (CYP3A4 substrate) clearance; however, the authors suggest that this was due to the large decrease in circulating IL-2 concentrations after administration of etanercept rather than a direct effect of TNF-α on CYP3A4 (Wen et al., 2020).

In vivo data regarding P450 suppression by VEGF and IL-17 are extremely limited. In one phase I/I clinical trial, bevacizumab (anti-VEGF mAb) was administered to non–small-cell lung cancer patients with erlotinib (CYP3A4 substrate) and exposure of both drugs was compared with that in patients receiving each drug alone (Herbst et al., 2005). No differences in erlotinib PK were found upon coadministration of bevacizumab, suggesting that VEGF does not have a suppressive effect on CYP3A4. In patients with psoriasis, IL-17 concentrations were significantly increased (~4 pg/ml) when compared with healthy subjects; however, no correlation was found between raised IL-17 levels and venlafaxine (CYP2D6 substrate and P-gp) metabolic ratios (Godoy et al., 2016).

Finally, it is worth noting the cytokine modulatory effects of some small molecule drugs such as toll-like receptor (TLR)-7 agonists. Jones et al. (2012) hypothesized that the time-dependent PK observed for PF-04878691 was a result of P450 suppression caused by TLR-7 agonism causing elevation of cytokine levels. This example illustrates that cytokine-mediated DDIs are not limited to biologies only, as small molecules that alter cytokine levels can also lead to modulation of P450 expression.

**PBPK Modeling of Cytokine Suppression of P450 Enzymes**

Data for the in vitro suppression of P450 activity or mRNA from Dickmann et al. (2011) have been used to successfully describe the clinical consequences of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 suppression by IL-6 in PBPK models (Machavaram et al., 2013, 2019; Xu et al., 2015; Jiang et al., 2016; Lenoir et al., 2021c; Stader et al., 2022). The former three models are designed...
to capture the therapeutic protein-drug interactions in patients who have chronically raised IL-6 levels (Machavaram et al., 2013, 2019; Jiang et al., 2016). Even at the highest IL-6 concentration tested (100 pg/ml) by Machavaram et al. (2019), only small suppression of CYP2C9 and CYP2D6 (37.7% and 26.8% reduction in enzyme levels, respectively) and weak DDIs with S-warfarin and dextromethorphan (AUC ratios = 1.33 and 1.36, respectively) were predicted. No interaction was predicted for the CYP1A2 substrate caffeine. Suppression of CYP2C19 and CYP3A4 was moderate (46% and 43% reduction in enzyme levels, respectively) and moderate DDIs were predicted with CYP3A4 substrates (AUC ratios = 2.30 and 2.07 for simvastatin and midazolam, respectively). The predicted and observed AUC and peak concentration (Cmax) ratios in the presence and absence of chronically elevated IL-6 are summarized in Fig. 1.

In contrast, the models published in Xu et al. (2015), Lenoir et al. (2021), and Stader et al. (2022) focus on transiently raised IL-6 levels. IL-6 levels increased rapidly to a mean peak of ~1600 pg/ml (60,000 pg/ml in the subject with the highest levels) at 6 hours after blinatumomab administration and then decreased to baseline by 48 hours (Xu et al., 2015). The maximum predicted suppression of CYP3A4, CYP1A2, and CYP2C9 was 28%, 9%, and 17%, occurring at 48, 48, and 70 hours after blinatumomab administration, respectively (Xu et al., 2015). Predicted CYP3A4 and CYP1A2 levels had returned to baseline by 1 week and CYP2C9 by 9 days after blinatumomab administration (Xu et al., 2015). Weak interactions were predicted for CYP3A4 substrates simvastatin and midazolam (AUC ratios = 1.9 and 1.7, respectively), whereas no interaction (AUC ratio < 1.25-fold) was predicted for CYP1A2 substrates theophylline and caffeine or CYP2C9 substrate S-warfarin when dosed 48 hours after blinatumomab (Xu et al., 2015). IL-2, IL-10, IFN-γ, and TNF-α were also significantly raised after blinatumomab dosing (peak ~170, 2400, 440, and 200 pg/ml, respectively, at the highest blinatumomab dose level). However, these cytokines were not included within the PBPK model due to the lack of in vivo data showing a meaningful effect of IL-10 or a direct effect of IL-2, IFN-γ, and TNF-α on P450 activity. The predicted AUC and Cmax ratios in the presence and absence of transiently elevated IL-6 are also summarized in Fig. 1.

Similarly, Stader et al. (2022) considered the effects of higher IL-6 concentrations (1–50,000 pg/ml) observed in patients with COVID-19; however, only a weak interaction with CYP3A4 substrate midazolam (AUC ratio = 1.33) was predicted even at the highest IL-6 concentration. Lenoir et al. (2022) recovered the concentrations of omeprazole and 5-OH-omeprazole in subjects before and after hip surgery by incorporating the combinatorial effects of elevated IL-6 (peak ~50 pg/ml at 24 hours after surgery) and coadministration of esomeprazole (a mechanism-based

**Fig. 1.** Summary of observed and simulated effects of chronic and transient IL-6 elevation using PBPK modeling. Data extracted from Machavaram et al. (2019) (steady-state IL-6 = 50 or 100 pg/ml), Jiang et al. (2016) (steady-state IL-6 = 50 pg/ml), Xu et al. (2015) (peak IL-6 = 1600 pg/ml) and Stader et al. (2022) (peak IL-6 = 50,000 pg/ml). Black and blue bars represent predicted and observed data, respectively. White, yellow, pink, and red areas represent insignificant, weak, moderate, and strong interactions, respectively. The observed data included in the Machavaram and Jiang papers were from the same sources (Zhang et al., 2009; Schmitt et al., 2011; Zhuang et al., 2015).
inhibitor for CYP2C19). It is likely that reduction in CYP2C19 activity was due mostly to inhibition by esomeprazole and minimally to suppression by IL-6, but this was not confirmed using the model in the paper.

In comparison with the PBPK models described above, a recent publication has used a top-down fitting approach with a PBPK model to predict the effect of inflammation on CYP2C19 and CYP3A4 suppression (Simon et al., 2021). Instead of modeling IL-6, C-reactive protein (CRP) concentrations were related to CYP2C19 and CYP3A4 activity using an empirical model fitted to clinical data, and the resultant in vivo parameters for downregulation of P450 activities were integrated into a PBPK model (Simon et al., 2021). The recovery of midazolam, voriconazole, and omeprazole concentrations in patients with a mean CRP of 25.3 mg/l versus 0.5 mg/l suggest that the activity of CYP2C19 and CYP3A4 can be predicted using CRP concentration. The production of CRP is stimulated by IL-6; thus, they are highly correlated in diseases (Del Giudice and Gangestad, 2018).

**Conclusions and Current Knowledge Gap**

Raised cytokine levels have been linked to suppression of P450 enzymes both in vitro and in vivo (Gorski et al., 2000; Aitken and Morgan, 2007; Morgan et al., 2008; Huang et al., 2010; Lee et al., 2010; Dallas et al., 2012; Evers et al., 2013; Harvey and Morgan, 2014; Klein et al., 2015). In vitro data suggest that IL-6 is the most potent suppressor of the majority of P450s and that CYP3A4 is the most sensitive P450 enzyme (Tables 1–3). Compared with IL-6, IFN-γ and TNF-α appear to have a reduced or similar suppressive effect, although they may cause greater suppression of CYP1A2. IL-2 and IL-1β P450 suppression is minor, and IL-10 does not cause P450 suppression even at high concentrations. Incubation data are lacking for other cytokines. The limited data for incubation of cytokine cocktails with hepatocytes suggest similar extents of P450 suppression for combined cytokines compared with IL-6 alone. In vivo data supporting a direct effect of IL-2, IL-8, IL-10, IL-17, IFN-γ, TNF-α, or VEGF on P450 activity are inconclusive, and the reported interactions could be driven by increases in a range of cytokines, including IL-6. Although raised levels of IL-6, IFN-γ and/or TNF-α could lead to P450 suppression, the cytokine levels observed in common immune disorders are generally lower than the in vitro EC50 values (Table 4), suggesting minimal P450 suppression in most patients. However, transiently elevated concentrations after dosing of cytokine modulators (e.g., blinatumomab) may be close to or above EC50 values.

By incorporating in vitro P450 mRNA Emax and EC50 values of IL-6 (Dickmann et al., 2011), current PBPK models are able to predict concentrations of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 substrates in the presence of chronically raised IL-6 (Machavaram et al., 2013, 2019; Jiang et al., 2016) and concentrations of CYP2C19 and CYP3A4 substrates in the presence of transiently raised IL-6 (Xu et al., 2013, 2019; Jiang et al., 2016) and concentrations of CYP2C19 and CYP3A4 mRNA levels in human hepatocytes.

When evaluating DBI liability, one should consider two opposite directions for the interaction. Cytokine levels can decrease due to downregulation of the activity of proinflammatory cytokines (e.g., RA treatment), or conversely, they can transiently increase due to rapid release of cytokines into the blood from immune cells (e.g., cytokine release syndrome). The former case is similar to PBPK simulation scenarios used in Machavaram et al. (2013), (2019) and Jiang et al. (2016), whereas the latter case would be analogous to PBPK simulation scenarios in Xu et al. (2015) and Stader et al. (2022). In both cases, the risk of DBIs is generally reported to be moderate or weak in most patients (Coutant and Hall 2018) and can likely be predicted with PBPK models considering IL-6 alone, given that other cytokines are less potent P450 suppressors and circulating at concentrations much lower in diseases than those used in most in vitro incubations. Although cytokines can markedly increase after cytokine modulator dosing, significant DBI is still unlikely as the elevation is transient and enzyme levels return to baseline quickly, as demonstrated in the PBPK simulations. Despite the low risks, caution needs to be taken in DBI assessment for drugs with narrow therapeutic index/low safety margins.

In conclusion, after dosing of cytokine-modulating drugs, the levels of multiple cytokines are likely to be increased or decreased simultaneously. The in vitro and in vivo data suggest that IL-6 is the most important cytokine when considering the effect of cytokine modulators on small molecule drug PK, although the available data are very limited in some cases. Published PBPK models assessing the effect of IL-6 on small molecule PK can adequately predict DBIs in a range of disease states. Hence, it is likely that inclusion of other cytokines into such PBPK models is not warranted and that any DBI interactions will generally be weak.

**Authorship Contributions**

Conducted experiments: Chen, Gill.

Provided new reagents or analytic tools: Chen, Gill.

Conducted research design: Chen, Jones, Gill.

Participated in manuscript: Chen, Gill.

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