

Physiologically-based pharmacokinetic (PBPK) modelling for predicting drug-disease interactions: Suppression of CYP3A4 by interleukin-6 in cancer populations

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Background

Interleukin-6 (IL-6) has been reported to suppress CYP3A4 activity with the half maximal inhibition concentration (EC₅₀) estimated at 61.0 pg/mL and a minimum activity level (E_{min}) of 23.3% (Fig. 1) [1-3]

IL-6 is a major inflammatory cytokine that is upregulated in cancer patients

Cancer patients may be prescribed tyrosine kinase inhibitors (TKIs) for anti-cancer therapy, which are primarily metabolized by CYP3A4 enzymes

Current gaps

Existing PBPK models for TKIs do not account for the IL-6 suppressive effect on CYP3A4 which can lead to variability in drug efficacy for cancer patients due to differences in IL-6 levels

Objective

To quantify the IL-6 suppressive effect on CYP3A4 activity and predict its effect on the PK for midazolam and TKIs in cancer patients using PBPK modelling.

Method

Model construction

- Whole-body PBPK models were developed in MATLAB (R2024a) using the Simbiology module for CYP3A4 substrates midazolam, acalabrutinib and erlotinib (Fig. 2)
- CYP3A4 *in vitro* metabolic clearances from human liver microsomes and rhCYP enzymes were scaled to *in vivo* liver clearance using CYP3A4 abundance and liver weight
- Cancer-specific physiological differences include distribution of body and organ weights, protein binding and IL-6 concentrations
- Variability in IL-6 in different cancer types were presented in Table 1 [4-6]

Study populations

- 17 *in vivo* clinical studies for healthy and cancer populations were used
- Midazolam:** 1 healthy, 1 non-small cell lung cancer (NSCLC) and 2 general cancer study populations [7-10]
- Acalabrutinib:** 6 healthy and 3 chronic lymphocytic leukemia (CLL) study populations [11-16]
- Erlotinib:** 2 healthy and 2 NSCLC study populations [17-20]

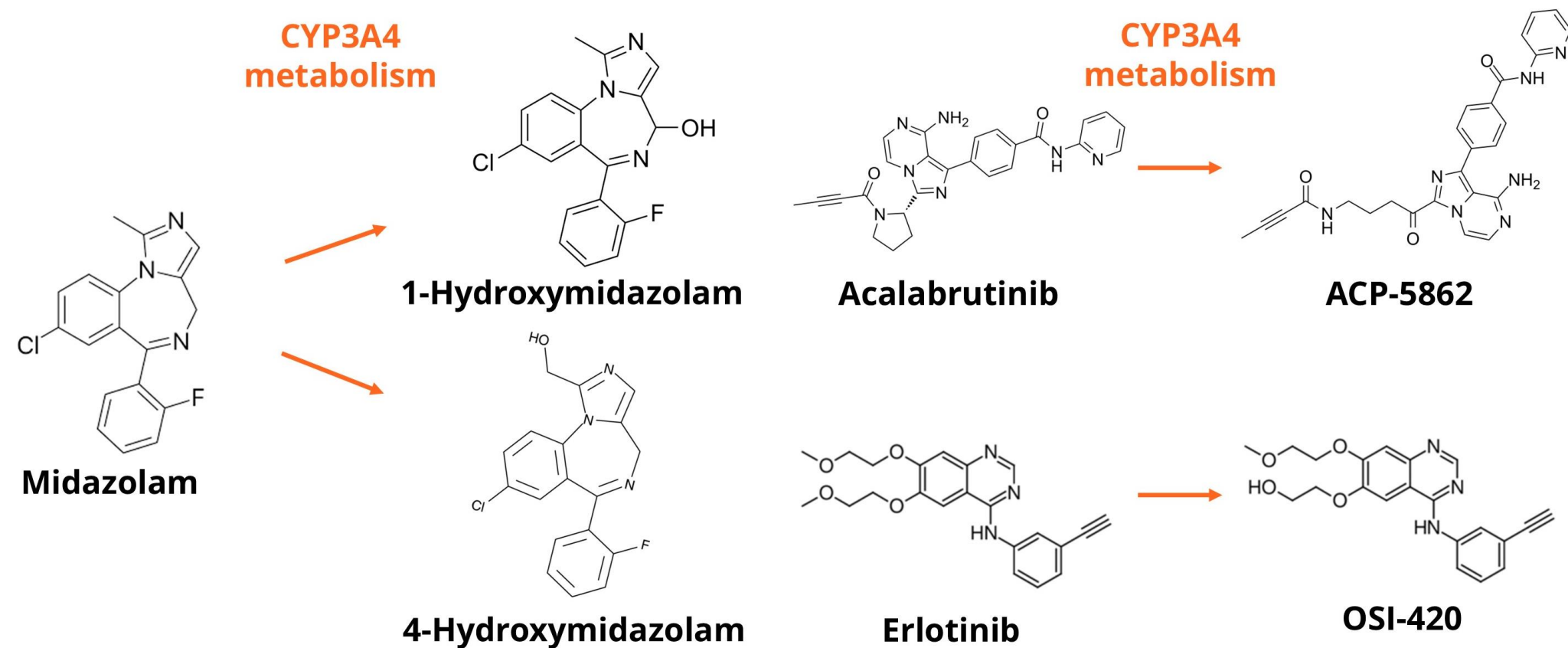


Figure 2. PBPK models were developed for midazolam, acalabrutinib and erlotinib which were all primarily metabolized by CYP3A4 in the liver.

Table 1. Mean and variability of IL-6 levels implemented in the PBPK model in different cancer populations.

Cancer	Mean (pg/mL)	SD (pg/mL)	Reference
General	14.3	12.20	Inagaki <i>et al.</i> 2008 [4]
CLL	60.3	12.94	Hassan <i>et al.</i> 2021 [5]
NSCLC	36.5	10.89	Yanagawa <i>et al.</i> 1994 [6]

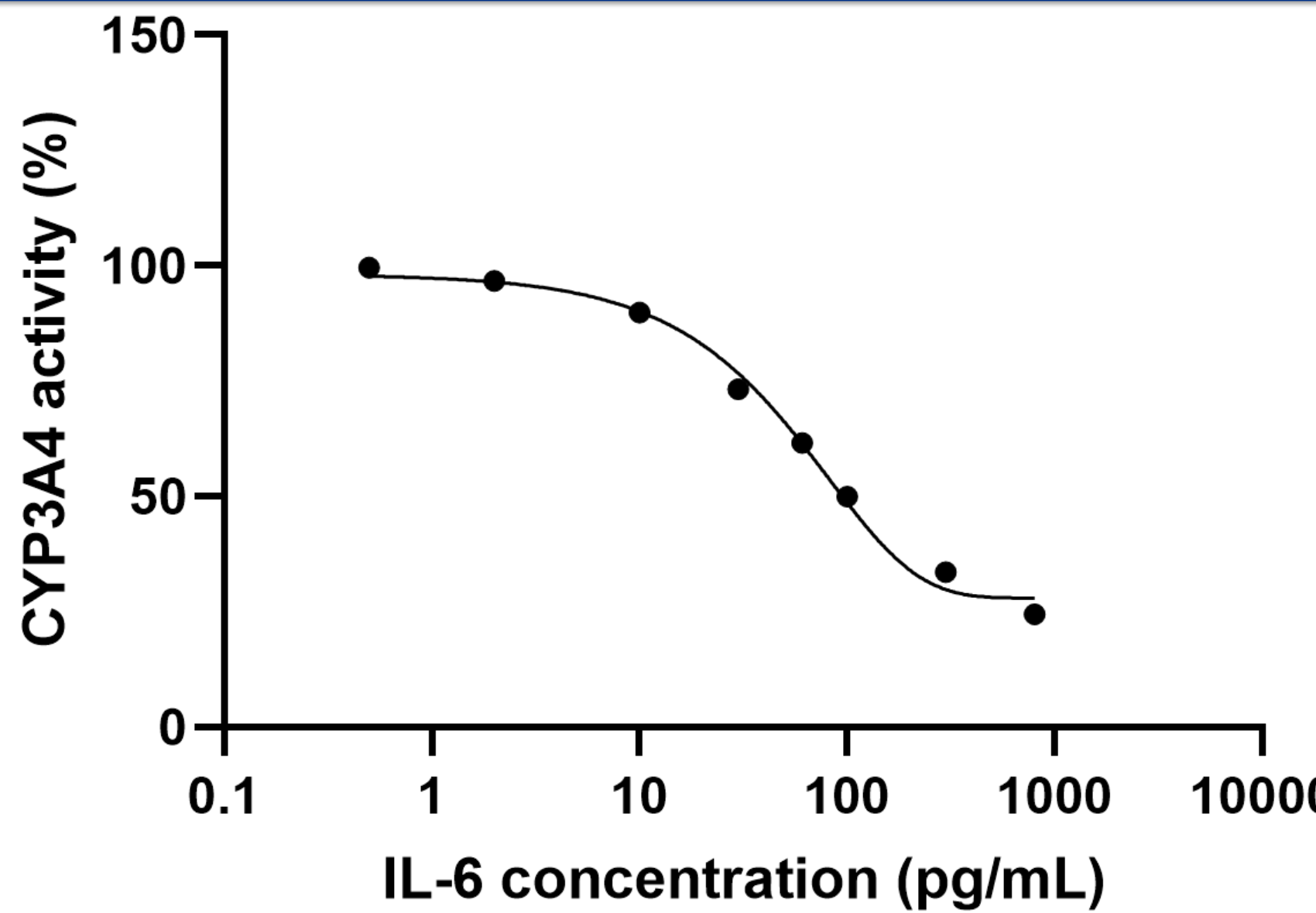


Figure 1. Suppression of CYP3A4 activity at different IL-6 concentrations. EC₅₀ was estimated at 61.0 pg/mL and E_{min} was 23.3% averaged across multiple studies [1-3].

Results

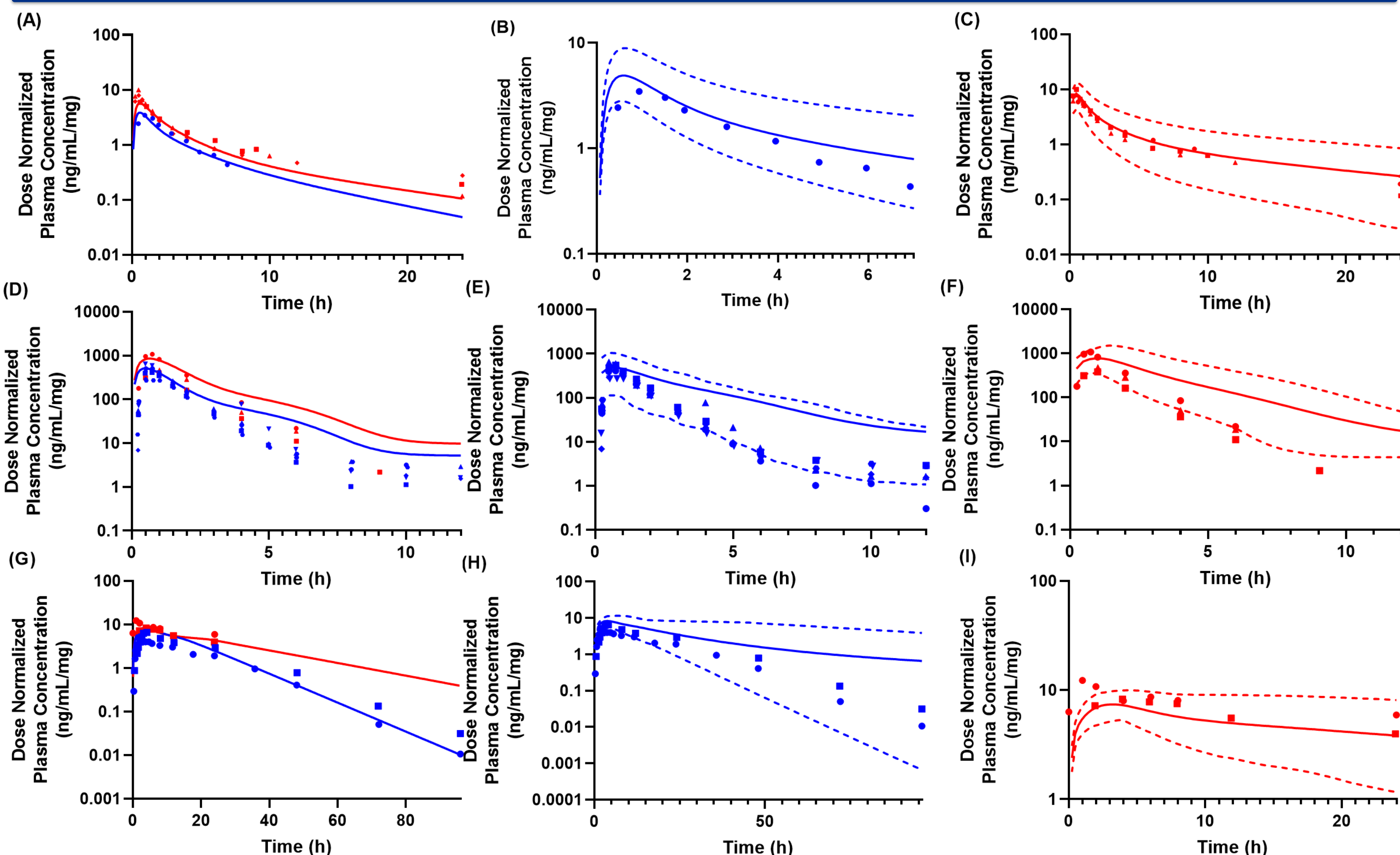


Figure 3. Simulated plasma concentrations overlaid with observed clinical data for midazolam (A-C), acalabrutinib (D-F) and erlotinib (G-I) in both healthy (blue) and cancer (red) populations. Three types of graphs were presented per drug: 1) a population representative simulation for a healthy and cancer individual respectively (A, D, G), a healthy (B, E, H), and a cancer population simulation (C, F, I). Solid colored lines (—) represent the mean simulated concentration while the dashed colored lines (---) represent the simulated 5th and 95th percentiles. Colored symbols represent observed clinical data from a clinical study. All plasma concentrations were normalized by dose amount in ng per mL per mg dose.

Table 2. Comparison of PK parameters between observed clinical data (one representative study selected per population/drug) and population representative simulation data in both healthy and cancer populations for midazolam, acalabrutinib and erlotinib.

Drug	PK parameters	Healthy			Cancer		
		Clinical data	Simulated data	Fold-change	Clinical data	Simulated data	Fold-change
Midazolam	C _{max} (ng/mL)*	3.47	3.85	1.11	9.92	7.23	0.73
	AUC _{0-t} (ng/mL.h)*	10.41	10.17	0.98	25.60	22.95	0.90
	t _{max} (h)	0.94	0.60	0.64	0.49	0.50	1.03
	t _{1/2} (h)	1.99	3.40	1.71	6.84	7.90	1.16
	CL (L/h)	85.78	79.85	0.93	38.22	42.40	1.11
Acalabrutinib	C _{max} (ng/mL)*	4.31	5.26	1.22	10.75	8.50	0.79
	AUC _{0-t} (ng/mL.h)*	6.11	10.31	1.69	17.94	19.05	1.06
	t _{max} (h)	0.74	0.50	0.68	0.75	0.70	0.93
	t _{1/2} (h)	5.70	1.21	0.21	0.99	1.90	1.92
	CL (L/h)	160.34	97.00	0.60	54.80	47.85	0.87
Erlotinib	C _{max} (ng/mL)*	6.59	8.36	1.27	8.28	8.35	1.01
	AUC _{0-t} (ng/mL.h)*^	38.41	41.75	1.09	136.89	137.96	1.01
	t _{max} (h)	4.13	4.00	0.97	3.94	3.70	0.94
	t _{1/2} (h)	10.80	8.44	0.78	18.22	23.05	1.27
	CL (L/h)	6.49	5.98	0.92	4.14	3.55	0.86

*Normalized by dose amount
^Normalized to 24 h

From observed clinical studies (Table 2 & Fig. 3A, 3D, 3G)

Healthy
Lower AUC_{0-t}
(when dose normalized)
Higher CL

Cancer
Higher AUC_{0-t}
(when dose normalized)
Lower CL

INTER-VARIABILITY IN IL-6 LEVELS FROM 1.5-80.2 pg/mL

From simulation results (Table 2 & Fig. 3C, 3F, 3I)

Implementing IL-6 suppression on CYP3A4 led to accurate prediction in cancer populations with good fitting of simulated plasma concentrations and PK parameters to observed data

CYP3A4 SUPPRESSION OF 1.9-43.6% IN CANCER POPULATIONS



Limitations & Assumptions

- Assumes IL-6 accounts for majority of CYP3A4 suppression effect
- Other cytokines such as IL-8, IFN-γ and CCL-5 are elevated in cancer patients, but their suppression effects on CYP3A4 remained unknown [21]
- Concentrations of cytokines known to suppress CYP3A4 such as IL-1β and TNF-α are not high enough to elicit significant suppression response in CYP3A4 despite being elevated in cancer patients [2-3]



Conclusion

- ✓ Elevated IL-6 can **significantly increase exposure of drugs metabolized by CYP3A4** in cancer populations
- ✓ Our work provides an extension to PBPK cancer models for use in **improving dosing regimens of anticancer drugs** reliant on **CYP3A4 metabolism**
- ✓ Recommendations for future works looking at **other prominent cytokines on CYP3A4 suppression**



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