Characterization and Interspecies Scaling of rhTNF-α Pharmacokinetics with mPBPK Models
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Purpose
TNF-α is a soluble cytokine and target of biologics for treatment of inflammatory diseases. These biologics exert pharmacological effects through binding and neutralizing TNF-α, and preventing TNF-α from interacting with its cell surface receptors. The magnitude of the pharmacological effects is then governed by not only the pharmacokinetics of mAbs, but also the turnover of TNF-α. The pharmacokinetics of TNF-α were extensively examined in some animal species as an anti-cancer agent at relatively high therapeutic doses, but no quantitative characterization of its PK has been established. Therefore, we sought to assess the pharmacokinetics of TNF-α at lower doses and consolidate its PK properties with minimal physiologically-based pharmacokinetic (mPBPK) models. In addition, a semi-mechanistic model was attempted to unravel the absorption kinetics of TNF-α following SC and other routes of administration.

Methods
The pharmacokinetics of rhTNF-α was examined in rats with an ELISA assay following different routes of administration (IV bolus 5 μg/kg, SC bolus 16 μg/kg, low dose SC infusion 11.74 μg/kg/day for 8 h, and high dose SC infusion 117.4 μg/kg/day for 48 h). Other sets of rhTNF-α PK data were digitalized from literature. PK profiles of rhTNF-α following IV doses in rats were fitted with the first-generation mPBPK model. Interspecies scale-up was performed to predict rhTNF-α PK in monkeys by integrating the mPBPK model with simple allometry. A semi-mechanistic model was proposed for characterization of the rhTNF-α absorption kinetics following SC and other routes of administration. All modeling and simulations were performed with the ADAPT 5 program.

Results
The assigned mPBPK model quantitatively delineates the elimination and tissue distribution properties of rhTNF-α. This cytokine exhibits permeability-limited tissue distribution and is systemically cleared via 1) a saturable pathway mediated by TNFR binding and disposition, and 2) linear clearance by renal filtration. Integration of the mPBPK model with simple allometry resulted in predictions of rhTNF-α pharmacokinetics that agreed well with experimental measurements in monkeys. Absorption related parameters obtained from the semi-mechanistic model reflect substantial pre-systemic degradation of rhTNF-α for SC and IM routes and greater contributions of lymph uptake to the systemic absorption through stomach (SW) and intestinal wall (GW) administration.

Conclusion
The pharmacokinetics of rhTNF-α for a diverse array of data in rats were quantitatively characterized with mPBPK models. The knowledge helps to better understand the fate of TNF-α in vivo, allows interspecies scale-up of rhTNF-α PK from rats to monkeys and, importantly, may enable improved projections of the magnitude of pharmacological effects of biologics targeting TNF-α. Also, the absorption kinetics of rhTNF-α following SC and other routes of administration were assessed with a semi-mechanistic model. Despite the limitations, simplifications, and diversity of data sources, model includes all major components of protein PK absorption kinetics and thus offers a reasonable attempt to quantitatively understand and improve the scale-up of protein absorption processes.