Harnessing meta-analysis to develop an oncology patient population for physiologically based pharmacokinetic (PBPK) modelling with application to AstraZeneca oncology projects

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Objectives: There is an underlying assumption that pharmacokinetic differences between healthy volunteers (HV) and cancer patients (CPs) are typically not clinically relevant; hence, oncology studies are conducted in HV whenever feasible. However, certain compounds exhibit fundamental pharmacokinetic disparities between HV and patients [1]. Given the effects of tumor-associated inflammation on enzyme and transporter expression, we performed a meta-analysis of clinical pharmacokinetics of CYP-sensitive substrates to quantitatively compare enzyme expression differences between HV and cancer patients.

Methods: 19 cancer patient studies/123 HV studies (conducted between 1983 and 2016) were used in this analysis. These studies provided data on a total of 316 cancer patients and 2056 HV across all substrates of interest. The automated sensitivity analysis function within a PBPK toolbox (Simcyp®) was subsequently harnessed to adjust hepatic/intestinal enzyme abundances in order to account for observed discrepancies between HV and CPs.

Results: Of the 11 probe substrates investigated, seven displayed marked exposure differences >1.25-fold between CPs and HV. For caffeine, theophylline, midazolam, simvastatin, omeprazole, and a subset of oncology compounds, reducing CYP1A2, CYP2C19, and CYP3A4 abundances by 20, 33, and 30%, respectively, in a virtual CP effectively captures CP pharmacokinetic profiles. Further investigation in six AZ internal compounds showed an ~30% exposure difference between HV and CP which was reasonably captured by this CYP-modified population.

Conclusion: Our CYP-modified virtual cancer population appears to be a promising addition to the AstraZeneca scientific toolbox for PBPK modelling of oncology compounds, and has the potential to improve pharmacokinetic predictions towards more patient-centric precision medicine.