Hepatic Uptake of the Tyrosine Kinase Inhibitors: Focus on OATP-1B1 and -1B3
V. Khurana, M. Minocha, D. Pal, A. K. Mitra
University of Missouri, Kansas City

Purpose
Metabolism of tyrosine kinase inhibitors (TKIs) is mainly mediated via hepatic route, but the contrivance responsible for their hepatocellular accumulation is still unknown. This study was designed to understand the contribution of hepatic transporter proteins in the hepatic uptake of 5 TKIs- pazopanib, canertinib, erlotinib, vandetanib and nilotinib.

Methods
In vitro cellular accumulation studies of pazopanib, erlotinib, canertinib, nilotinib and vandetanib was conducted using CHO cells - wild type as well as stably transfected with humanized OATP-1B1 and OATP-1B3 transporter proteins. Michaelis-Menten kinetic parameters including maximum transport rate (Vmax) and Michaelis-Menten constant (Km) were calculated using KaliedaGraph 3.5.

Results
Out of the 5 TKIs tested, 2 TKIs namely nilotinib and vandetanib showed their affinity towards OATP-1B1 and OATP-1B3 transporter whereas canertinib showed its affinity only towards OATP-1B3 transporter. The Km values of OATP-1B1 for nilotinib and vandetanib were 10.14 ± 1.91 and 2.72 ± 0.25µM respectively and Vmax values of OATP-1B1 for nilotinib and vandetanib were 6.95 ± 0.47 and 75.95 ± 1.99 nmoles/mg protein/min respectively. Likewise, Km values of OATP-1B3 for canertinib, nilotinib and vandetanib were 12.18 ± 3.32, 7.84 ± 1.43 and 4.37 ± 0.79µM respectively and Vmax values of OATP-1B3 for canertinib, nilotinib and vandetanib were 15.34 ± 1.59, 6.75 ± 0.42 and 194.64 ± 10.58 nmoles/mg protein/min respectively. These findings suggest that hepatic uptake of nilotinib and vandetanib occurs via both OATP-1B1 and -1B3 but only OATP-1B3 is responsible for uptake of canertinib in hepatic tissue.

Conclusion
These findings indicate towards the involvement of OATP-1B1 and/or OATP-1B3 transporter proteins in the hepatic disposition of TKIs and confirms the affinity of these hepatic uptake transporters as a determinant of the pharmacokinetic profile of TKIs. These uptake transporters will indirectly regulates elimination pathways and may play a role in the variable response to the treatment with TKIs. The uptake of TKIs into the hepatocytes may represent a previously unrecognized source of inter-individual variability in response to TKIs therapy.