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Quantitative proteomics and pharmacokinetic modeling in the optimization of drug dosing

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Personalized medicine is crucially dependent on an understanding of the concentrations of drug-metabolizing enzymes and transporters in human tissue. We used proteomic measurements to quantify enzymes and transporters in liver, intestine, brain and skin and the data was analyzed to inform pharmacokinetic models of drug metabolism. Such models allow more accurate estimates of effective, minimally toxic doses of drugs for adults, children and the elderly. We have developed QconCAT-based LC-MS/MS methodology for quantifying the cytochrome P450 and UGT enzymes and the drug transporters in human tissue. The QconCATs (artificial proteins consisting of labeled standard peptides, released by proteolysis) initially did not express in *E. coli* and fusion methods for expressing recalcitrant QconCATs were developed as a part of the project. Our results show wide variation in a population between the levels of the different enzymes, for example CYP3A4, which metabolizes many important drugs, present with a range 10.4–262.1 pmol mg⁻¹ protein in the liver. We determined several correlations between enzymes in about 50 human livers, including a positive correlation between levels of CYP3A4 and CYP2B6. Our studies now extend to brain, intestine and to pediatric livers. Most recently, label-free quantification has been shown to give broadly comparable results and in addition, shown to give quantification data on other proteins in the samples.

Biography

Jill Barber completed her PhD at the University of Cambridge in the UK and then carried out Post-doctoral Research in the Universities of Karlsruhe, Heidelberg and Oxford. She settled at the University of Manchester and worked on NMR spectroscopy until 2005 when she began collaboration with Professor Simon Gaskell on Proteomics. Her current work on proteomics in drug metabolism is a result of collaboration with Professor Amin Rostami. She has published about 100 research papers and is also a National Teaching Fellow of the Higher Education Academy in recognition of her teaching.

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