Liquid Biopsy Approaches to Support Clinical Drug Interaction Assessment & Subject Phenotyping

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David has been in the pharmaceutical industry for 31 years and currently holds the title of Senior Scientific Director as head of the Transporter Sciences Group at Pfizer (Groton, CT). Before joining Pfizer in 2014, he spent productive periods at Searle, Abbott Labs, Merck, and Bristol-Myers Squibb. During that time, he served on both scientific (Associate Research Fellow, Senior Research Fellow) and managerial (Director, Senior Director, Executive Director) ladders.

He has authored over a dozen book chapters, 170 peer-reviewed manuscripts, has presented at >80 venues (scientific symposia/meetings/webinars), and served on the editorial boards of various DMPK-related journals (e.g., *Current Drug Metabolism*, *Drug Metabolism Letters*, *Xenobiotica*, *Drug Metabolism & Disposition*). In addition, he has edited/co-edited three text books related to drug interactions and one on the topic of drug metabolism. Presently, he is a member of the International Transporter Consortium (ITC) and also serves as adjunct professor at the College of Pharmacy, University of Rhode

Island. In 2009, David was inducted as Fellow of The American Association of Pharmaceutical Scientists (AAPS).

Over the last 5 yrs, David has worked extensively with colleagues in Japan (Pfizer Tokyo, Prof. H. Kusuhara at University of Tokyo, Prof Y. Sugiyama at The Riken Institute, and Dr. K. Furihata at the P-One Clinic) to advance transporter biomarker research. More recently, such transporter biomarker efforts have included the laboratory of Prof. M. Niemi (University of Helsinki, Finland). Presently, his research has also extended to Flinders University (A. Rowland lab, Adelaide, Australia), which has involved the exploration of serum- and plasma-derived EV as liquid biopsy.

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Various clinical tools have been developed to support the study of genotype-phenotype associations and drug-drug interactions (DDI) involving drug-metabolizing enzymes (e.g., cytochromes P450, CYP) and drug transporters. These have included probe drugs, probe drug cocktails, micro-dosing, tissue imaging reagents, and endogenous compounds in plasma and urine that present as biomarkers. More recently, attention has turned to "liquid biopsy" methods, which involve the profiling (proteomics and CYP activity) of immunocaptured cargo-laden and tissue-specific extracellular vesicles (EV) present in human blood. The presentation will describe the isolation, characterization, and profiling of serum EV (mixtures of exosomes and small microvesicles) in support of CYP and organic anion transporting polypeptide (OATP) profiling. Examples include CYP2D6 genotype-phenotype associations, CYP3A5 genotype-liver protein expression profiling, differentiation of gut CYP1A2 versus CYP3A4 activity, induction profiling (liver CYP3A4, CYP2D6, OATP1B1, and OATP1B3) following an inducer (rifampicin), and expression profiling of serum-derived liver EV from pregnant versus non-pregnant females. With further validation and wider use, it is envisioned that the EV-based liquid biopsy approach will be deployed alongside established drug probe-based methods and emergent drug transporter biomarkers. Such advancements are warranted because of the absence of CYP biomarkers (beyond CYP3A4/5), increasingly complex DDI involving gut and/or liver CYP3A4/5, and questions regarding transporter induction.

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