Speaker: A. David Rodrigues, Pfizer

Title: *"Endogenous Probes for Drug-Metabolizing Enzymes and Transporters: Where are we now?"*

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Abstract:

Pharmacokinetics, Dynamics & Metabolism (PDM), Pfizer, Groton CT PK-ADME-DDI (pharmacokinetics-absorption-distribution-metabolism-excretion-drug-drug interaction) science has evolved rapidly. In the early 1990s, the pharmaceutical industry expanded the use of in vitro methods and attention quickly turned to high-throughput screening ("ADME-HTS"). Similar progress supported greater use of computer-assisted databases, data visualization tools, building of structure-activity relationships ("ADME SAR"), modeling and simulation (M&S)-based in vitro-in vivo extrapolations (IVIVEs), and human PK-ADME-DDI projections. In response, a wide array of clinical tools were developed to support phenotyping and DDI assessment (e.g., drug probes specific for individual drug-metabolizing enzymes "DMEs" and some transporters, drug probe cocktails, microdosing, imaging agents). More recently, PK-ADME-DDI science has been influenced by "translational science" (medicine, pharmacology, etc.), pharmacometrics, "omics" (pharmacogenomics, metabolomics, etc), and systems biology. From an industrial standpoint, the goal has always been to support the clinical advancement of novel chemical entities (NCEs) with the desired "target" PK-ADME-DDI profile (e.g., optimal PK properties, lower dose, minimal impact of genotype, and reduced DDI potential as perpetrator and victim). It is not surprising, therefore, that numerous researchers have sought to identify endogenous probes ("markers") for various DMEs (e.g., CYP3A4, CYP2D6, UGT1A1) and transporters (e.g., OCT2, MATE1, OAT3, OATP1B1).

The availability of such probes would facilitate routine (normal healthy volunteer) and specialized (e.g., pediatric, elderly, patients) phenotyping and DDI assessment in a clinical setting, enable early calibration of M&S-based IVIVEs, compliment agency decision tree-based approaches, support earlier risk assessment, and possibly delay and even obviate the need for more formal studies employing drug probes. The presentation will summarize currently available endogenous probes for different DMEs and transporters; the pros and cons, challenges, opportunities, considerations (e.g., kinetics, dynamic range, specificity), and performance versus drug probes. It is concluded that further effort is needed to expand the existing menu of available tools, existing probes need further characterization and validation, and that widely used commercial M&S packages need to be expanded to support modeling of endogenous marker PK-ADME-DDI profiles. Although the potential utility of endogenous probes is great, it is worth noting that vastly improved analytical methods do enable some well-characterized drug probes (individually or as cocktails) to be administered at "sub-therapeutic" ("GRAS") doses (not necessarily "nano" or "micro" doses). In the future, it is likely that clinical phenotyping and DDI assessment will leverage various combinations of probes (drug and endogenous). For a given NCE, it is envisioned that the choice of the most appropriate probe combination will be informed by fully integrated (DME-transporter) in vitro data packages.