COLLOQUIA IN MEMBRANE TRANSPORT

Venue: Medical University Vienna, Center for Physiology and Pharmacology,

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Friday 15.03.2013   14:00 s.t.   **Matthias Schwab** (host: Michael Trauner)
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"Pharmacogenomics of transporter proteins:

clinical implications"

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Abstract:
Variation in drug disposition and response is a major concern associated with many drugs used in all medical disciplines. The clinical relevance of variability is most evident with drugs with a narrow therapeutic window. Pharmacogenomics aims to elucidate the genomic determinants of drug efficacy and toxicity. Variants in genes that are relevant for ADME processes such as drug transporters have been identified as important confounders affecting therapy and patient outcome. In addition non-genetic, gene regulatory as well as epigenetic factors contribute significantly to the expression and function of human membrane transporters. For instance hepatic drug metabolism and elimination requires drug uptake that is determined by transporters in the sinusoidal membrane of hepatocytes. Organic Anion Transporting Polypeptides (OATP) and Organic Cation Transporters (OCTs) are expressed in human liver (OATP1B1, OATP1B3, OATP2B1, OCT1, OCT3), but also in kidney (OCT2) and other tissues, mediating the uptake of endogenous compounds (e.g. bile acid by OATPs) and of several drugs (e.g. statins, anti-diabetic and anticancer drugs). Numerous clinical studies support the relevance of common/rare variants in the respective genes (*SLCO1B1, SLC22A1, SLC22A2*) altering either pharmacokinetics and/or drug response of substrates. The common *SLCO1B1* variant c.521T>C is highlighted by its association to an increased risk for simvastatin-induced myopathy. *SLC22A1* variants have been considered to contribute to the anti-hyperglycemic effect of metformin. Recently in addition to genetic variation of transporter genes a more comprehensive approach including several *-omics* approaches (e.g. genomics, epigenomics, transcriptomics, proteomics, metabonomics) has been considered for the identification of further putative targets for better prediction of drug response. For example, next generation sequencing and metabonomics are promising for redefining disease diagnosis and predicting therapy response. The system's pharmacology approach will support the integration process of the systems-level understanding of drug response and therefore promotes also the drug discovery process for personalized medicine.