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On the use of micro-physiological systems to improve pharmacologically relevant transcellular transport in the liver-kidney axis

In the frameworks of personalized medicine, deciphering the sources of variability in patient drug responses requires the understanding of underlying processes modulating drug pharmacokinetics (PK). This is particularly true to bridge the gap between systemic and local PK, i.e., drug concentration close to its target. In this context,
drugs membrane transporters play a central role particularly those in the liver and kidney, as these organs are involved in ca. 95% of xenobiotic metabolism and elimination. Furthermore, these transporter functions were proposed to be correlated within an inter-organ communication network in which transporters from a distant tissue may compensate for the defective membrane transport of another organ [1].
To study these events, advanced cell culture systems modelling the liver-kidney axis has been developed for which the micro-dynamic environment was implemented. Focus was paid to membrane transporter expression and function as well as metabolism activities.
Our results indicated the central role of flow conditions leading to an increase in drug transporter mRNA expression (e.g., ABCC2, ABCC4, ABCB1, OATP1B1 and OATP1B3) in liver-on-chip as well as in a renal proximal tubule-on-chip devices line (ABCB1, ABCC2, ABCC4, OAT1, OCT2, MATE1). Furthermore, flow conditions favored cells polarization as pictured by Na+/K+ ATPase and P-gp/ABCB1 expressions at the basolateral and apical membranes, respectively. To ensure the relevance of our system, membrane transporter functions was assessed by monitoring metformin transcellular transport, showing an an increased efflux ratio in presence of cells exposed to the shear stress from the microfluidics environment, as compared to static and conventional cell culture.

Key words:
Multi-organ chip; Systems pharmacology; Membrane transporters, Liver kidney axis

Reference

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