Development of a kidney-on-a-chip model for compound screening and transport studies

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Stellingen behorende bij het proefschrift

Development of a Kidney-on-a-Chip model for compound screening and transport studies

1. To reduce animal testing with *in vitro* models, a platform is needed which is efficacious in identifying nephrotoxicants and provides insights into their mode of toxicity. (This thesis)
2. Features like correct polarization, leak tightness, and drug-transporter expression of *in vitro* grown proximal tubule cell layers are essential properties when studying the active elimination of drugs and metabolites from the body. (Chapter 2, This thesis)
3. Flow is essential for the tube formation of proximal tubule cells in a microfluidic system. (Chapter 2, This thesis)
4. Time-lapse imaging can be a powerful tool to detect nephrotoxic events by monitoring the cell morphology and cellular response to the exposure in real time. (Chapter 5, This thesis)
5. "*Besides the major concern of ethics, a few more disadvantages of animal experimentation are the requirement of skilled/trained manpower and time consuming protocols.*" (Doke, Saudi Pharm., 2015). It should not be overlooked that on long term *in vitro* models will not only reduce and replace animal testing, but they will most probably make clinical tests and drug use safer since the research focus lies on the human organism.
6. *"Transporters should be considered in the development of in vitro cell models for nephrotoxicity prediction"* (Lin, Curr. Chem. Genomics Transl. Med., 2017). During the development of new cell-based models for nephrotoxicity prediction, this consideration should always be included. However, maintaining the correct phenotype of the renal cells is as important since this is essential for the formation of leak tight epithelial barriers.
7. *"[...] using AU [artificial urine] in the upper chamber of the Transwell could improve polarization of renal tubular epithelial cells by simulating or mimicking the microenvironment that usually exposes to renal tubular cells in vivo.*" (Vinaiphat, Cell Death Discov., 2018). This approach can be improved by exposing the cells to perfusion flow at the apical side of the cell membrane.
8. "*TEER [transepithelial electrical resistance] is more sensitive than a fluorescent reporter leakage assay and capable of time-lapse monitoring under flow conditions*." (Nicolas, Lab Chip, 2021). Combining TEER with the assays developed during this thesis will lead to a better understanding of the cellular response after an AKI event and during disease modeling of the proximal tubules.
9. "*The ability to induce substantial vascularization and morphological maturation of kidney organoids in vitro under flow opens new avenues for studies of kidney development, disease, and regeneration*." (Homan, Nat. Methods, 2019). However, renal organoid models are still very limited when the aim is to study renal clearance and tubular–vascular exchange since controlled access to the lumina of the tubes and vessels is highly desirable, and can be achieved for example by using the OrganoPlate.
10. The best artificial membrane for cells to grow on is no membrane.
11. *"I have frequently been questioned, especially by women, of how I could reconcile family life with a scientific career. Well, it has not been easy.*" (Marie Curie) Nowadays the situation of working women has significantly improved. However, it is still not easy to satisfy family life and a scientific career for both genders - men and women.