New System – lower incidence of liver injury

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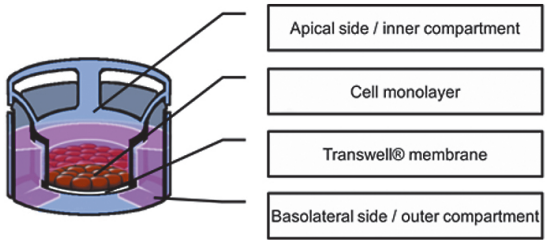
Despite the continuous implementation of safety screenings and biomarker panel evaluation, a number of compounds reaches drug approval and then be found to induce liver toxicity. Improving the currently available safety tests would have several economic and ethical benefits. The goal of this project was to develop a novel cell-based system that may improve the accuracy of the current pre-clinical prediction of drugs inducing liver injury.

Our liver is the main site of accumulation and detoxification of drugs, hence its being continuously exposed to serious toxic effects. Drug-induced liver injury is one of the most common reasons for severe liver damage and one of the leading causes for acute liver failure and death.

Whilst the development and increased use of liver transplantation as a decisive treatment option for patients with severe liver damage, the invasive surgery and a lifelong immunosuppressive therapy that continuously exposes the body to infections, inevitably reduce the life quality and expectancy of these patients. Besides the heavy burden for the patient, costs for the healthcare arise depending on the patients' health status and circumstances. The estimated costs for a liver transplantation and standard immunosuppressive therapy over ten years lie within 300,000 – 400,000 CHF per patient.



Scheme of the 3D cell system, simulating the liver, blood (basolateral), and bile (apical) compartments.

From the pharmaceutical industry perspective, drug-induced liver injury has become a leading cause of attrition of compounds during drug development and it is one of the most frequent causes for drug withdrawals, restrictions, and project terminations. In the last 40 years, twelve compounds have been withdrawn from the market due to severe, unexpected liver damage. Drug development programs from preclinical to market approval for a single compound can generate up to 10 billion CHF in costs. Thus, drug withdrawal or project termination in late development represents a substantial financial loss. On the other hand, unnecessary attritions might deprive the community of new treatment options as well as the pharmaceutical companies of substantial profit margins.

This thesis has focused on the development of a simple, fast and inexpensive 3D cell system to improve the accuracy of the prediction of drugs inducing liver injury in the early development phase. We envisage the platform to complement the current preclinical tests, particularly to abate the rate of drug attrition.

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