A bioengineered microwell-array device to treat type 1 diabetes

Summary

Type 1 diabetes is an autoimmune disease that result in the death of insulin-producing β-cells. These β-cells reside within the pancreatic islets and are often simply referred to as 'islets'. At the moment, clinical islet transplantation is the most promising minimal invasive therapy for the most severe cases of type 1 diabetes. During this therapy, pancreatic islets are harvested from a deceased donor and transplanted in the liver of the recipient, which is a suboptimal implantation site. This thesis therefore describes the design, fabrication and upscaling of a microwell-array islet delivery device aiming to realize extrahepatic islet transplantation.

The device described within this thesis has the unique feature that it contains microwells which prevent aggregation of islets, and thereby the formation of hypoxic and eventually necrotic aggregate cores. Device dimensions were optimized based on computational modeling of the optimal distance between islets, the possibility to overfill microwells and to evaluate stacking of multiple microwell layers. This was subsequently used as input for an in-house built software application that allows extrapolating of current device dimensions towards devices that can hold clinically relevant dosages of islets.

Subsequently, the designed devices were fabricated and extensively tested *in vitro* and *in vivo*. Most importantly, human islets showed to remain functional in upscaled versions of the device over 7 days of *in vitro* culture. Next, empty devices (without islets) showed to be biocompatible and safe in a 3-month rodent model. A first large animal study in mini-pigs also indicated that the pre-peritoneal space and intramuscular space (or supramuscular space) are promising implantation locations for clinical translation. A second large animal study in landrace pigs demonstrated procedural and surgical feasibility of the microwell-array devices. In addition, this study indicated that the exact location of subcutaneous implantation sites highly influences the host tissue response. Implantation sites used during pre-clinical testing should therefore resemble the potential human implantation site as closely as possible.

Besides these practical considerations, the regulatory and legal requirements for medical devices were extensively discussed as well within this thesis. A switch from a university laboratory towards an industrial cleanroom environment is essential to guaranty clean and safe fabrication of islet delivery devices for clinical use. The microwell-array cell delivery device technology is now ready for functional studies in small and large diabetic animals to show efficacy of the treatment, and will be evaluated in the near future. Altogether, the microwell-array islet delivery device is a safe, upscalable and therefore highly promising option for extrahepatic islet transplantation.

As a side project, pancreatic islets were 3D bioprinted within a hydrogel. Previous studies did show islet viability, but not functionality. This was most likely related to the hydrogel properties, as any hydrogel will form a barrier for insulin secretion. A bilateral screening method based on FRAP and rheology was used to select hydrogels for 3D bioprinting. Primary islets cultured within the selected hydrogel were functional as encapsulated islets responded to rises in physiological glucose levels with an increased amount of secreted insulin from the 3D printed constructs. The screening method is therefore suitable for the selection of hydrogels for 3D bioprinting applications.