A bioengineered microwell-array device to treat type 1 diabetes

Scientific and social impact

The value of the current thesis can be described by evaluating its scientific and social implications. The main goal was to develop a cell delivery device that can improve the transplantation of human islets and thereby improve the treatment of the most severe cases of type 1 diabetes. This thesis is therefore relevant for healthcare experts (mainly internists or endocrinologists), type 1 diabetic patients, and peers within the scientific biomaterial and medical device community. Patients were also updated yearly on the developments of the cell delivery device via the annual meeting of the RegMed XB consortium. During this public meeting, a special patient session for type 1 diabetics is organized to obtain feedback from patients and consider their preferences on the design of the device. For instance, the size, shape and number of devices that patients desire or permit are important considerations when designing islet delivery strategies.

A previous version of a polymer-based cell delivery device was already successful to reverse type 1 diabetes in mice. However, this device was made from materials that cannot be used in the clinic. Therefore, a next generation of the device was made from a material that is actually used in the clinics. In addition, the design of the device was upscaled from mouse- towards rat-, pig- and human-sized devices. A computer model was used to optimize the number of cells that can be packed in such cell delivery devices, aiming to minimize the dimensions of the device without harming the cells loaded inside the device. Human islets showed to remain viable and functional within the device when cultured in the lab. The potential of the devices was also evaluated with animal testing. A rat study with empty devices (so without any cells) indicated that the materials were safe and initiated a tolerable healing response in the rats. Next, a mini-pig study indicated that some sites in the body may be more suitable for the placement of the cell delivery devices than others, and two sites were selected for future testing. In addition, surgeons that are planned to perform the first-in-man studies with the cell delivery device were trained by implantation of the devices under the skin in pigs. Seeding cells in the device in a laboratory, transportation of the device from the laboratory towards the operating room and the actual surgery were practiced and showed good clinical potential. Moreover, the skin healed well after removal of the devices, which is important to gain approval for first-in-man testing. In addition, the road towards

the clinics for cell delivery devices were extensively discussed. This includes questions like: What does it mean now that a promising cell delivery device has been developed, what are the next steps to be taken before it can be used in the clinics? Taken together, the developed cell delivery device has a clear clinical potential and will be evaluated in diabetic animal studies in the near future.

Scientifically, one of the key lessons learnt from the studies described in this thesis are the importance of oxygenation for cell delivery devices. Too much competition for oxygen between cells will lead to cell death, and finally a non-functional cell transplantation. It is therefore critical to evaluate oxygen levels in a device where many cells are packed together. The computer model described in this thesis could be adapted to predict oxygen levels for a variety of cell delivery devices and implantation sites.

Another key lesson is the importance of reporting the exact implantation location in animal studies. Two different implantation sites under the skin were evaluated in the pig study: one site where the was a lot of mobility while the other site hardly displayed any mobility. There was a clean difference in the healing of the wounds after surgery, with complications at sites with high mobility. Within scientific literature, the kind of implantation site is often described (for instance under the skin or within the muscle), but the exact locations (for instance in the lower abdominal region or in the neck) are not always described. This also hinders translation of animal studies towards human applications, as it is difficult to interpret data without knowing whether the exact same site was used in animal studies as is intended for human studies.

Besides that the majority of the work in this thesis entails a polymer-based cell delivery device, one chapter of the thesis also focused on hydrogels as cell delivery carriers. Currently, others have only shown that islets can remain alive, but nobody has shown that islets can still secrete insulin while incorporated in such a 3D printed hydrogel. Therefore, a screening method was described to select potentially interesting hydrogels for 3D printing of islets. Based on this screening, a hydrogel formulation was selected, and human islets showed to be able to secrete insulin while incorporated in the hydrogel. However, the selected hydrogel has a few downsides that prevents it from being used in the clinic. Nevertheless,

the screening method was highly successful and has great potential to be included in future evaluations of hydrogel formulations for cell delivery carriers.

Next to scientific impact, this thesis also has social impact. An islet delivery device that can support islets has the potential to reduce the costs for treatment of type 1 diabetes. Currently, patients require an average of 2-3 donors to become free from self-monitoring and regular insulin injections. An effective islet delivery device may ensure that a single donor may suffice for a patient, allowing more patients to be treated with the same donor pool. Moreover, important to realize is that even though some patients may still require insulin injections to manage their glucose levels, these patients will have a significant improvement in their quality of life. Currently, type 1 diabetic patients only become eligible for islet transplantation after suffering from the most severe degree of type 1 diabetes for a long period (~ 20 years). These patients therefore require multiple insulin injections a day to try to manage their insulin levels, and often still cannot manage to remain within the recommended range of glucose levels. Islet transplantation would still significantly improve the quality of life when patients would require only a minimal number of insulin injections per day or have a significantly improved glucose time in range. These improvements could already reduce the long-term costs associated with treatment of type 1 diabetes.

Besides human donor islets, the field of islet transplantation has recently managed to create insulin-producing cells from stem cells that could be used to manage glucose levels of type 1 diabetics. This means that insulin-producing cells can be grown in a laboratory and offer an unlimited supply of insulin. This could mean that transplantation of insulin-producing cells would become available for type 1 diabetic patients that are not categorized within the most severe cases of the disease. Although highly promising, there is still a risk that these stem cells form tumors. It is therefore highly wanted to be able to remove these cells if any cancerous cells are detected. Using an islet delivery device would therefore be ideal, as removal of the device would also mean that all stem cells are removed from the body. Also, important to notice is that recent first-in-human tests with insulin-producing stem cells have shown no signs of tumor formation. The use of insulin-producing stem cells for islet transplantation may therefore become the gold standard for treatment of type 1 diabetes in the future. Next to type 1

diabetes, the cell delivery device can also be used to transplant other types of cell clusters to treat other diseases (as extensively discussed in the chapter 9 – Discussion). Given that insulin is a hormone, the cell delivery device can be used to treat other diseases that are related to loss of hormone production. In addition, cells within cell clusters could be engineered to secrete other factors to treat a wide variety of different diseases. Having a cell delivery device that supports the survival of incorporated cells could therefore treat numerous diseases.

Finally, the data described in this thesis also has commercial value. A patent application was written describing the invention of the cell delivery device and a spin-off company called *Lighthouse Biomedical* was founded. The goal of *Lighthouse Biomedical* is to industrialize the production of the devices, and to get the devices officially certified and ready for distribution. The aim is therefore to actually bring the devices towards type 1 diabetic patients and in a later stage also potentially to patients suffering from other diseases. Taken together, this thesis has scientific, social and commercial value and the first steps have been taken to ensure that the obtained value is going to be translated to the clinic.