Abstract

Validation of Safety and Function of a new macroencapsulation device in small and large animal models

Jordan Magisson[1], Aladin Sassi[1], Aram Kobalyan[1], Charles-Thibault Burcez[1], Kfir Molakandov[3], Alon M. Levy[3], Pierre Gianello[2], Richard Bouaoun[1], Séverine Sigrist[1].

[1]Defymed, Strasbourg, France; [2]Laboratory of Experimental Surgery, Université Catholique de Louvain, CHEX 5570, Brussels, Belgium; [3]Kadimastem Ltd, Ness-Zionna, Israel

The number of donors required per recipient and the associated immunosuppressive regimen are the major limitations, of human pancreatic islet transplantation. Therefore, an alternative inexhaustible source of insulin-secreting cells is required, in order to allow this therapeutic approach for a large number of patients. Among others, pig islets and human stem cells (hSC) are being currently investigated. Regarding the immunosuppressive regimen, parallel efforts are put together on the development of a bioartificial pancreas that can encapsulate such cells. The concept of this medical device is to immune-isolate the encapsulated cells, whilst protecting the host from these cells. MailPan® is a bioartificial pancreas developed to treat type-1 diabetic patients. This macro-encapsulation device is designed to contain insulin-secreting cells of different origins (animal or human), based on two main features: (i) the use of semi-permeable membranes allowing the passage of glucose and insulin, but impermeable to the components of the immune system; (ii) “In” and “Out” implantable ports in order to allow prevacularization of the MailPan®, and its filling or emptying whenever the cells become exhausted.

To validate the immune-protection of the MailPan® and its biofunctionality, several animal models were used: (i) allogenic models where rat insulin secreting cells were injected in rats within the MailPan® and (ii) a xenogeneic model where human beta cells differentiated from human embryonic stem cells were injected in rats in a MailPan®. Moreover, biointegration of the MailPan® was assessed in pigs and primates, for up to 4 and 8 months of implantation, respectively.

Injection of allogeneic rat islets in the MailPan® did not result in a significant increase of a global inflammatory marker (plasmatic α2-Macroglobulin), and no antibody formation against encapsulated islets was detected after 1 month in the serum of recipients. In diabetic rats, MailPan® device filled with rat beta cells was able to normalize fasting glycaemia, and restore body weight gain. Moreover, MailPan® devices explanted from pigs and primates showed a very satisfying biointegration, as reflected by low or no fibrosis and cell infiltration, with an optimal vascularization of surrounding tissues. Finally, human embryonic stem cells differentiated into insulin secreting cells rapidly displayed functionality, starting 6 days following injection in MailPan® implanted in rats, with a stimulation index ≥ 2, for more than 8 weeks without any sign of rejection.

This study demonstrated the compatibility of the MailPan® with several cell types in allogenic and xenogenic models with a prolonged survival and function of the cells. Further studies are currently ongoing to test the long-term efficacy of the combination.

This work was co-funded by the JDRF and the Eurostars Program (ENCAPSULIN. n°E!13318)