Engineered Pancreatic Tissue for the treatment of Diabetes (Yissum)

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Categories	Diabetes, Cell, therapy, Tissue Engineering
Development Stage	Secretion and regulation of in-vivo-like quantities of insulin for at least three months by engineered micro pancreas (EMPs). Restoring normoglycemia with less than human 500 leq/mouse. Scaling up completed and preparing for phase-I clinical trials
Patent Status	PCT publication number: WO2010/086856. Patent is under examination in US and Europe.

The Challenge:

The current state of the art involves isolating islets from a cadaveric donor pancreas. Each recipient receives islets from one to as many as three donors. The islets are infused into the patient's portal vein, and are kept from being destroyed by the recipient's immune system through the use immunosuppressants.

The field presents three main challenges:

- Limited beta-cell availability is one obstacle to the widespread use of islet transplantation in type-1 diabetic patients.
- Yet another major problem is the lack of proper function of the islets after transplantation. Since the year 2000, several hundred people have received islet transplants but by five years after the procedure, few than 10% of total patients are free of daily insulin supplementation. Thus there is an urgent need to improve on current islet transplantation procedures.
- A third major drawback is immune rejection either of implanted heterologous cells or of the patients autologous insulin-producing beta cells.

Strategy:

- Aleph beta claims it has solutions already to overcome points 2 and 3 and plans to have fully overcome point 1 within five years. The company strategy thus plans to capitalize on points 2 and 3 in the short term by going straight to the clinic whilst its R&D will concentrate on point 1.

Technology:

- Our technology is based on the premise that in order to have proper function of beta cells it is necessary to provide an appropriate stromal micro-environment. We have developed a method to prepare organ-specific micro-scaffolds which preserve the architecture and the basic composition of the organ stroma and ensure that no seeded cell will be more than 150 microns from a source of nutrients and gases. A patent on this subject, US 7,297,540 issued November 2007. Using this technology we were first able to re-differentiate and organize lung seeded precursor cells into surfactant secreting alveoli (Tissue Eng Part C Methods. 2011 Aug;17(8):861-70). For the last three years we have been exclusively working in beta cell function and expansion using engineered micro pancreas (EMPs) composed of islets and/or beta

cells and micro-scaffolds.
- We have spent great care in optimizing the system in vitro prior to performing in vivo experiments. As a result we believe we have a breakthrough in the field by succeeding in creating engineered endocrine micro pancreata (EMPs) that survive for at least 90 days in vitro.
- During that period EMPs express high levels of key beta-cell specific genes and secrete quantities of insulin per cell similar to freshly isolated human islets for more than three months in vitro in a glucose-regulated manner.
- When implanted subcutaneously into Streptozotocin-treated hyperglycemic NOD-SCID mice, Io-EMPs become vascularized and rescue the mice in a dose response manner, with 440 human IEqs/mouse being sufficient for obtaining normoglycemia.
- We have also developed a proprietary capsule which allows us to encapsulate human EMPs and implant them in xenogeneic hosts. We have shown that EMPs in such implants produce angiogenic factors which induce the formation of a vascular network around the capsule but do not penetrate it. EMPs then receive nutrients and gases by diffusion from the membrane capsule and continue to secrete insulin in a regulated manner in vivo without immune rejection for long periods.

Product marketing strategy:

Betalin's strategy is to approach the market with three sequential products:

Our first product: engineered pancreatic organ Io (EMP-Io) will be based on normal human islets derived from donors.

- EMP-Ios enough to treat one patient will be sold at 100k US.
- We estimate to prepare and treat around 200 patients during the first year.
- This number is expected to rise by 35% per year for the next three years.

Our second product: engineered pancreatic organs beta (EMP-B) will be based on expanded human cells.

- EMP-Bs enough to treat one patient will be sold at 150k US.
- We estimate to prepare and treat around 2000 patients during the first year on launching this product.
- This number is expected to rise by 100% per year for the next five years.
- Based on data we have available already (see appendix) additional research that will be performed in Betalin it is feasible that within 3 years the company will be ready to implement this product.

Our third product: engineered pancreatic organs beta (EMP-stemB) will be made not from expanded beta cells but from stem cells differentiated into the beta cell pathway (EMP-stemB).

- EMP-stemBs enough to treat one patient will be sold at 150k US.
- We estimate to prepare and treat around 20000 patients during the first year on launching this product.
- This number is expected to rise by 100% per year for the next five years.
- Based on progress on the stem research field and research that will be performed in betalin it is feasible that within 5-8 years the company will be ready to market this product

Clinical Trials:

Clinical trials will be done in collaboration with Prof. James Shapiro in Edmonton Canada.

Researcher Information www.bio.huji.ac.il/eng/staff_in.asp?staff_id=79

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