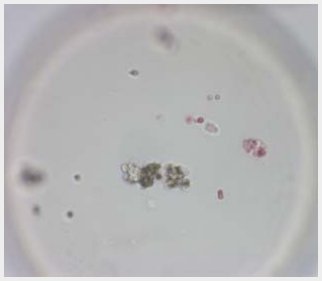
Diabetes: Cell-in-a-Box® for insulin producing cells

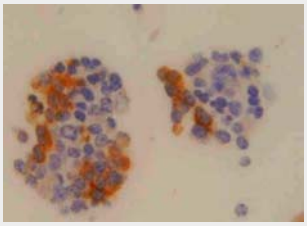
Diabetes could be treated not only by implanting islet cells but also using embryonic stem cells or cells genetically modified to express insulin. The cells are encapsulated to protect them from the immune system. The feasibility of using Cell-in-a-Box® for the successful encapsulation of islet cells and the production of insulin in response to glucose has already been shown and published.



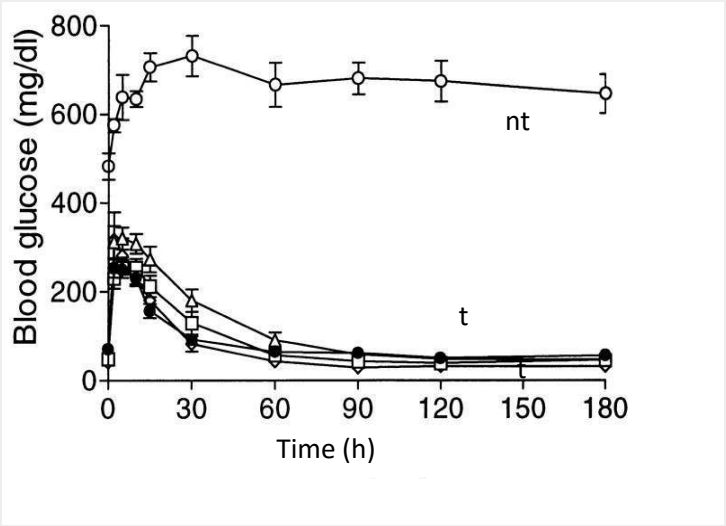
Encapsulated, insulin producing cells (DTZ detection assay)

SAFETY OF ENCAPSULATED CELLS IN CLINICAL TRIALS

- Demonstrated safety in clinical trials for up to two years
- Additional favourable toxicological data in various animal models
- Capsules can be removed and/or replaced
- "Off-the-shelf", one product for all patients
- Product can be stored for periods in excess of 1 year, delivered and used in a simple way: important factors for handling and trading
- Innovative cell therapy based approach for the effective treatment not only of diabetes but also of many other conditions and diseases



Encapsulated cells are alive and producing insulin after 6 months in vivo.



Rescue of diabetic rats with porcine islets and Cell-in-a-Box® technology:
Blood sugar levels of diabetic rats treated (t) with encapsulated porcine islet cells and non-treated control (nt)

DIABETES

Diabetes mellitus is characterized by hyperglycemia (high blood sugar) and other signs. There are three main forms of diabetes: type 1, type 2, and gestational diabetes (occurring during pregnancy), which have similar signs, symptoms, and consequences, but different causes and population distributions.

Type 1 is usually caused by the destruction of beta cells as a result of an autoimmune reaction. Type 2 is caused by a resistance to the effects of insulin, sometimes progressing to loss of beta cell function. Gestational diabetes is similar to type 2 diabetes. The hormones of pregnancy cause insulin resistance in women.

Although type 1 and 2 are currently incurable they are manageable with diet and external insulin.

Complications of diabetes include cardiovascular disease, retinal blindness, chronic renal failure, poor wound healing leading to amputation, nerve damage and erectile disorders.

TREATING TYPE 1 DIABETES

Since type 1 diabetes arises from the failure of pancreatic beta cells, a number of studies have been undertaken to replace the pancreas or beta cells (Vinik et al.,2004).

Microscopic or nanotechnological approaches are under investigation for the treatment of type I diabetes. In one proposed case, implanted stores of insulin are released by a rapid response valve sensitive to blood glucose levels. At least two approaches have been demonstrated *in vitro*. These closed-loop insulin pumps are naturally not as precise in controlling blood sugar levels as functioning beta cells.

Type 1 diabetics who have received a kidney-pancreas transplant (when they have developed diabetic nephropathy) and become insulin-independent may be "cured" from their diabetes, but generally they have to remain on long-term immunosuppressive drugs and there is a possibility that autoimmune disease will develop in the transplanted organ (Vinik et al., 2004).

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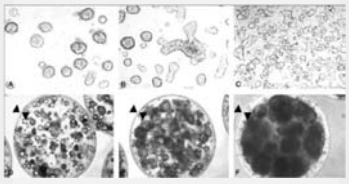
ADVANTAGES OF Cell-in-a-Box® FOR DIABETES

- Encapsulated cells respond to physiological stimuli (e.g. produce insulin in response to blood glucose levels)
- No adverse immune reactions
- Capsules could be placed sub-cutaneously so they can be easily removed

"Off-the-shelf" one product for all patients

TYPES OF ENCAPSULATED CELLS THAT COULD BE USED FOR DIABETES

- Islets
  - * Human origin
  - * Porcine origin
- Stem cells (human) Differentiation to beta cells
- Genetically modified cells



Encapsulated islet cells grow to fill out the available space

FUTURE TREATMENTS

Islets: transplants of exogenous beta cells have been performed in both mice and humans in experimental settings, but this has not yet become regular clinical practice. Thus far, such transplants, as expected, provoke an immune reaction so that long-term immuno-suppressive drugs are needed to protect the transplanted cells (Shapiro et al., 2006).

Stem cell research has also been suggested as a potential cure since it may permit regrowth of islet cells which are genetically part of the treated individual, thus perhaps eliminating the need for immuno-suppressants. However, the same mechanism which originally led to islet destruction may also destroy stem-cell regenerated islets (Vinik et al., 2004).

A recent trial of 15 patients with type 1 diabetes that were treated with stem cells raised from their own bone marrow after immune suppression showed that the majority of patients did not require any insulin treatment for prolonged time periods (Voltarelli et al., 2007).

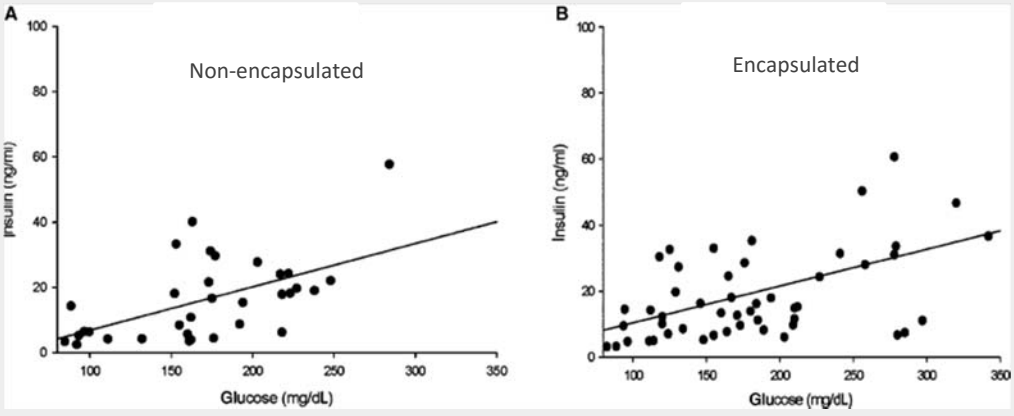
Cell-in-a-Box®

Diabetes was originally one of the reasons why encapsulation technologies were developed, since it was thought that it should be possible to transplant islet cells in some sort of protective capsule and thus restore glucose regulated insulin production to type 1 diabetics.

FEASIBILITY DEMONSTRATED

We have previously demonstrated the feasibility of Cell-in-a-Box® with primary hamster beta (HIT-15) cells (Stiegler et al., 2006) as well as primary porcine islet cells (Schaffellner et al., 2005). As well as showing good viabilities upon encapsulation, both cell types respond to sugar with production of insulin *in vitro*. Diabetic rats remained normoglycemic for more than 6 months after treatment with Cell-in-a-Box® porcine islets (see page 1).

Further reading:
Vinik et al. (2004) Med Gen Med 6:12
Schaffellner et al. (2005) Transplant Proc.37:248-52
Shapiro et al. (2006) N Engl J Med 355:1318-30.
Steigler et al. (2006) Xenotransplantation 3:337-44
Voltarelli et al. (2007) JAMA 297:1568-76
Salmons et al. (2014) Diabetes Research & Treatment 1:1-7



Encapsulation of a pancreatic beta cell line does not affect their ability to respond to glucose by producing insulin in a dose responsive manner.

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