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## **Cell-laden alginate hydrogels for the treatment of diabetes**

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## **Abstract**

**Introduction:** Diabetes mellitus is an ever-increasing medical condition that currently affects 1 of 11 adults who may have lifelong commitment with insulin injections. Cell-laden hydrogels releasing insulin may provide the ultimate means of correcting diabetes. Here, we provide insights of this cell-based approach including latest preclinical and clinical progress both from academia and industry.

**Area covered:** The present article focuses on reviewing latest advances in cell-laden hydrogels both from the technological and biological perspective. The most relevant clinical results including clinical trials are also discussed.

**Expert opinion:** Current progress in technological issues (stem cells, devices, biomaterials) have contributed cell encapsulation science to have a very relevant progress in the field of diabetes treatment.

**Keywords:** Diabetes mellitus, cell encapsulation, cell-laden hydrogels, alginate, drug delivery

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## Article highlights

- Cell-laden hydrogels enable long-term release of biological active agents such as insulin.
- Biological, material and technological aspects are key to success.
- Some approaches are being evaluated in clinical trials (Phase 1-2)
- Adequate source of insulin producing cells remains a critical issue.
- Stem-cell technologies have raised optimism about the scalable generation of insulin producing cell sources

## 1. Introduction

Diabetes mellitus is a serious worldwide medical condition impacting quality of life and the health care system. According to the International Diabetes Federation, 463 million adults (1 of 11) were affected in 2019 and that number is expected to increase to 700 million by 2045. Furthermore, the incidence of type 1 diabetes (T1D) has increased 3-4% over the last 30 years which support the influence of environmental factors (1). Current total annual medical costs are enormous and may be as high as 760 billion dollars (2). In the case of type 1 diabetes (T1D), the National Diabetes Statistics Report has shown that it is increasing among people under 20 (3). In this type of diabetes, pancreatic  $\beta$ -cells are progressively lost, daily injections of insulin are associated with frequent hypoglycemia and threat for disabling hypoglycemic unawareness. Recent progress in the field has shown that a number of factors including  $\beta$ -cell gene expression, islet morphology and endoplasmic reticulum stress signaling have a critical role in  $\beta$ -cell failure in T1D (mostly IRE1 driven) and T2D (mostly PERK–eIF2 $\alpha$  dependent) (4).

From a therapeutic perspective, automated insulin pumps equipped with sensors to monitor blood glucose and mimic the natural insulin release could address the current challenges in the field. However, accurate monitoring of glycemia during

physical activity or at night can be difficult to achieve, which has prompted engineers to look for more accurate and more responsive systems (5).

Implantation of insulin-producing islet cells may provide the ultimate means of correcting T1D. The technology of cell-laden hydrogels is fairly simple, it consists on enclosing insulin-secreting within semipermeable hydrogels, usually implantable, and coated with a polymeric thin cover, which permits nutrient exchange and exchange of cell-produced biologically active agents in the absence of immunological rejection. This approach is now being explored in a wide range of human diseases including blood disorders, acute liver failure, spinal cord injury, and diabetes(5).

The technology, however, is not new. The leading concept dates to 1960, when T.M.S. Chang first proposed the idea of the “artificial cell” (6). Shortly thereafter, the therapeutic benefits of encapsulated pancreatic islets were demonstrated by Lim and Sun in diabetic rats and by Soon-Shiong in a diabetic patient (7). With those results, a few companies started developing devices for encapsulating pancreatic cells.

Today, several industrial efforts remain underway including efforts by Seraxis, Pharmacyte, Semma Therapeutics, Sernova, and ViaCyte.

Currently, some of these approaches are being evaluated in clinical trials (Phase 1-2) (5), though none of them has moved forward into the clinics. “Good things take time” is apt proverb for this field but it is what has occurred during that time that leads many to the conclusion that we are on the brink of being able to at least finally test optimal (and hopefully prove) encapsulated islet-containing devices. This optimism is based largely on significant progress in the interface of biomaterials and cellular engineering. Many first encapsulation attempts were done without a global technological/biological evaluation, optimized cell dose or non-suitable cell selection. Below we discuss, some of the pivotal advances and how they contribute to this optimism.

## **2. Technological issues**

Several decades of research and clinical evaluations have uncovered the complexity of merging scientific fields as diverse as cell biology, engineering, biomaterials, and immunology to develop a therapeutic. The potential of cell encapsulation requires a partnership that takes advantage of the ingenuity of academia and the development experience of large pharma (8). As discussed in detail below, the manufacture of high-quality biocompatible material is available on reasonably large scales and in

combination with equally scalable human stem cell-derived beta cells are significant advancements if not true breakthroughs (9).

From an industrial perspective, we are now more able to address 2 overarching obstacles that have plagued the field of cell encapsulation; identifying a potentially therapeutic factor and being able to deliver it in a pharmacokinetically appropriate manner (5). For diabetes, the first issue is straightforward as insulin is a known commodity. Insulin replacement works and pancreatic transplants can cure the disease. This stands in contrast to other indications where delivering potentially efficacious molecules such as trophic factors or antibodies (often using genetically modified cells that are unrelated to the disease itself) requires a different starting point with unknown variables centered around dosing, efficacy, and toxicity (10). With increasingly large-scale human stem cell-derived beta cell production it should be possible to focus increasingly on the second issue. Without reliable, consistent, and readily available cells it has not possible to establish manufacturing and quality controls that enable the evaluation of chemical and structural changes in the configuration of cell containing devices (5). Insulin administration has known pharmacokinetic and glucose responsiveness requirements. But in the past, limited supplies of cell preparations, and lab to lab variability has made animal to human translations difficult (8). Of course, further refinements in differentiation protocols will optimize cell identify/composition (beta and other islet cell types) purity (removing unwanted cells), and potency (insulin control and responsiveness) (11). Moreover, other technologies including cellular engineering approaches such as CRISPR may allow future cellular tweaking to minimize host responses to grafting or facilitate the response of the encapsulated cells to environmental cues (12).

### **3. Device considerations**

The 3 major encapsulation approaches for islet are intravascular macrocapsules, extravascular macrocapsules and extravascular microcapsules (13-15) (Figure 1). Intravascular devices are connected to the vascular system of the patient allowing rapid exchange of glucose, insulin and nutrients (16) (Figure 1.c). Although potentially efficacious, clinical application is compromised by high risk of thrombosis and infection. Although some new approaches for intravascular devices are under investigation (17) most current efforts are focused on extravascular devices. Extravascular devices can be safely implanted in readily accessible implantation

sites and can be retrieved/replaced if replenishable cell sources (stem or progenitor cells) are considered or if functional limitations such as poly-hormonal secretion, or excessive hormone secretion necessitate refilling (18, 19).

Extravascular devices are available in macro- and microcapsules. Within macrodevices groups of islets are encapsulated and implanted into surgically accessible sites such as under the skin or intraperitoneally. A challenge in the field of macrocapsules has been a non-ideal surface to volume ratio (8). As a consequence, diffusion of oxygen can be slow and islet-cells compete for these nutrients, limiting seeding density to 5–10% of the volume of the device (13). Novel developments to overcome these issues include oxygen generators such as the so-called Beta-O2 device which is a macrodevice connected to an oxygen port (20-22) (Figure 1.b). Another design are lipid membranes based on the cornea that facilitate diffusion of oxygen towards the islets (23). This same innovative device is supplied by atmospheric air and allows for easy retrieval and replacement of islets. The device has a port that is fixed on the skin through which the islets are loaded (23). Long term efficacy studies are required but this device configuration could be ideal for testing first generation insulin-producing cells obtained from stem cells. The other approach is encapsulation of islets in their own individual microcapsule.

Microcapsules are spherical and suffer less from diffusion issues due to more optimal volume to surface ratios (24) (Figure 1.c). Furthermore, microcapsules display sufficient structural integrity and cell incorporation is possible via nontoxic molecules and reagents. The majority of the approaches in this direction rely on polysaccharides such as alginate as the primary material coupled with a thin poly-amin coating to provide immunoprotection or to enhance mechanical stability even more (25). Biocompatibility can be enhanced by identification of alginate analogs that do not provoke strong inflammatory responses, application of anti-biofouling molecules such as polymer brushes, immunomodulating biomaterials such as zwitterions (26-28) as well as by intracapsular modifications to lower the susceptibility of cells to inflammatory stress (29). A challenge however is finding and documenting a proper relationship between surface properties and biological response in the body to better understand the impact of surface topographies (8). Overall, there is optimism about testing different device approaches in humans, but lack of an adequate source of insulin producing cells has hampered these tests. While a significant gap exist between availability and demand for cadaveric

pancreata (30) stem cell-derived insulin-producing cells or animal derived islets could eventually bridge this gap (31).

#### **4. Clinical proof-of-concept**

Clinical proof of concept for the therapeutic use of encapsulated islets has been obtained. Several groups have demonstrated long-term (ranging from 70 days to 6 months) survival of micro-and macroencapsulated porcine islet transplants in non-human primates (32, 33). Moreover, some success has been reported in humans transplanted with microencapsulated porcine islets (34). Improved HbA1c levels and reduced hypoglycemic episodes were noted in these patients for more than 600 days (34). Others reported that alginate encapsulated porcine islets reduced exogenous insulin requirements using a commercial product named Diabecell® (35). Most recently, stem-cell-derived  $\beta$  cells were transplanted into non-immunosuppressed T1D mouse models and reportedly induced normoglycemia for up to 174 days (27,36). These developments have led to the point where several companies are vigorously developing encapsulated islet products and evaluating them in clinical trials (see Table 1).

#### **5. Expert opinion**

The science of cell encapsulation for diabetes has progressed from basic research to a point of clinically evaluating therapeutically meaningful products on a potentially wide-scale basis. Current progress in device development has created biocompatible, long-term functioning, and retrievable cellular devices for replenishable insulin-producing cell sources. Oxygen and other essential nutrient supplying technologies have been developed that can contribute to long-term function of an efficacious glucose regulating concept. Also, current developments in stem-cell technologies have raised optimism about the scalable generation of insulin producing cell sources; although some issues still remain. These include production scale up, perfecting the interface between biomaterials, immunology, and cell function, and widening the availability of the few current stem-cell sources. Last but not least, this technology allows retrieval of implanted cell-loaded devices which represents a critical safety aspect and a unique advantage of encapsulation devices. This may especially relevant when living medicines are implanted into accessible sites such as the omental pouch. Progress on some of the key parameters described

herein may help to accelerate the translation of insuling releasing cell-laden hydrogels into medical reality.

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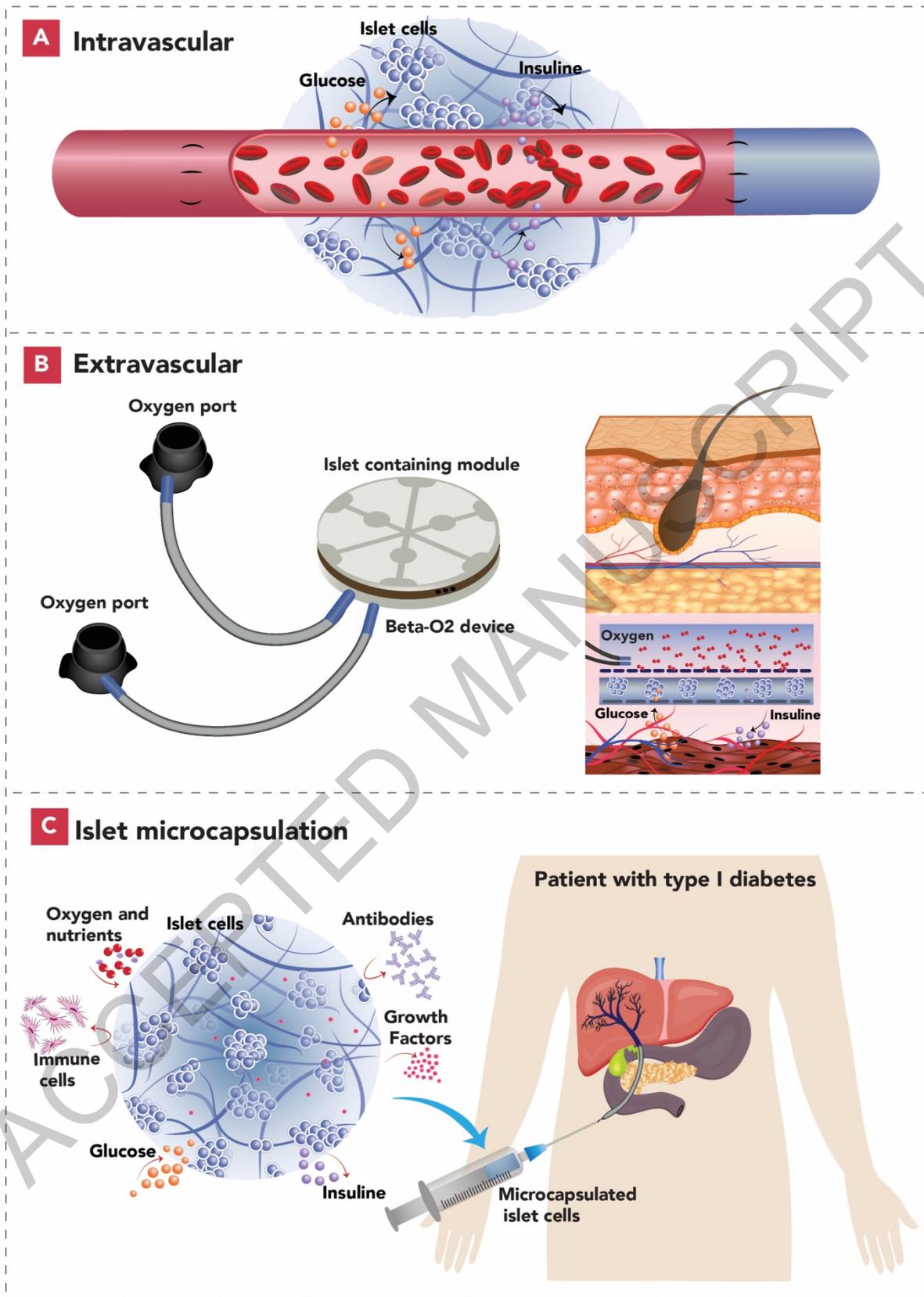
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## Figures

**Figure 1:** Schematic illustration of the various islet delivery schemes on the market today. (A) Islet cells are implanted within a biomaterial device in the vicinity of a vascular network. (B) Other schemes capitalize upon more ingenious devices that can deliver oxygen to the entrapped cells from outside the body. (C) Hydrogel microencapsulation provide a more biomimetic approach, wherein islet cells are injected into the patient within a native-like matrix that protects them from harm, while providing them with optimal growth and functioning conditions.

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**Table 1.** Current clinical trials summary. Developed devices for diabetes application.

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PRODUCT	DEVICE DESCRIPTION	CLINICAL TRIALS (clinicaltrials.gov)	STUDY	ESTIMATED DATES	CURRENT STATUS
VC-01	Encaptra® drug delivery system allows pancreatic precursor cells to deliver, differentiate and mature after surgical implantation	One-Year Follow-up Safety Study in Subjects Previously Implanted With VC-01™.NCT02939118	-Cohort study -200 participants	2016-2021	Enrolled
		A Safety, Tolerability, and Efficacy Study of VC-01™ Combination Product in Subjects With Type I Diabetes Mellitus.NCT02239354	-Phase 1/2 -69 participants	2014-2021	Active
VC-02	A system designed to allow blood vessels to enter the device and directly interact with the implanted pancreatic precursor cells.	A Safety, Tolerability, and Efficacy Study of VC-02™ Combination Product in Subjects With Type 1 Diabetes Mellitus and Hypoglycemia Unawareness. NCT03163511	-Cohort study -75 participants	2017-2022	Recruiting
		A Safety and Tolerability Study of VC-02™ Combination Product in Subjects With Type 1 Diabetes Mellitus. NCT03162926	-Phase 1/2 -3 participants	2017-2018	Completed
PEG-Encapsulated Islet Allografts	Encapsulated islets	Safety and Efficacy of PEG-Encapsulated Islet Allografts Implanted in Type I Diabetic Recipients. NCT00260234	-Phase 1/ 2 -12 participants	2005-2014	Terminated
DIABECCELL®	Encapsulated pig beta cells	Open-label Investigation of the Safety and Effectiveness of DIABECCELL® in Patients With Type 1 Diabetes Mellitus.NCT01739829	-Phase 2 - 8 participants	2011-2014	Completed
Cell Pouch™	An implantable medical device which provides a vascularized environment for therapeutic cells	A Safety, Tolerability and Efficacy Study of Sernova's Cell Pouch™ for Clinical Islet Transplantation.NCT03513939	-Phase 1/2 -7 participants (July 2019)	2019-2022	Recruiting
Beta-Air®	A device that allows encapsulated cells to be properly oxygenated.	An Open Label, Pilot Investigation, to Assess the Safety and Efficacy of Transplantation of Macro-encapsulated Human Islets Within the Bioartificial Pancreas Beta-Air in Patients With Type 1 Diabetes Mellitus.NCT02064309	-Phase 1/2 -4 participants	2014-2019	Active