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Research Article

Bioartificial Pancreas with Tapered Conduits for Diabetes Management

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ABSTRACT

Diabetes is a disease of failed glucose homeostasis. It requires life-long care. Diabetes was first recorded in a medical text written in english around 1425. Today, the number of patients in the U.S. with diabetes is ~34 million children and adults, and the number is still climbing, with a projected ~300 million worldwide in 2030. Current diabetic care is best described as patients are never truly ride off the disease.

In this paper, we will show the development of a bioartificial pancreas with improved pores for insulin production and tapered pores for better mass transport for diabetes management.

Keywords: Diabetes; Bioartificial pancreas; Encapsulated islet; Mass transplantation; Insulin; Diabetes management

INTRODUCTION

Encapsulation islet

Encapsulated islet was first proposed by T. Chang and later improved by Lim and Sun [1]. A thin semi-permeable membrane with nanopores that could protect cells from immune attack and, at the same time, nanopores allowing nutrients and oxygen to enter, and insulin to exit. It worked well for small animal like rodents, but not well in large animals [2-4].

The repeated hyper and hypo glycaemic episodes, are adversely affect the animals' health, and viability of the transplanted islet (Figure 1).

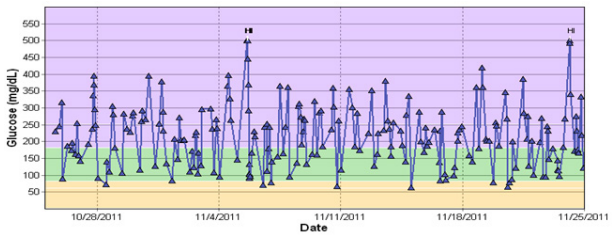

Figure 1: The daily BG line chart of a young diabetic patient on insulin injection. Despite her parent's total dedication, her diabetes was not under good control. Her total daily insulin needs were ~35 units/day with correction boluses from 10 to 20 units/day. Her blood glucose fluctuated widely. There are many others like her suffering from the ravages of the disease where vascular structures throughout the body are being damaged by highly glycosylated blood.

Encapsulated islet longevity study

A total of eight animals received encapsulated islets of different pore sizes. Longevity was determined when encapsulated islets failed to maintain fasting glycemia less than 180 mg/dl for three consecutive days [5,6]. Longevity data below in Figure 2 for 7.6 nm pore radius survived longest. 9.5 nm pore radius data was the average of three transplants, and longevity data for 12 nm pore radius was average of two transplantations. The data suggests encapsulated islets with nanopores could not satisfy both immune-protection and mass transportation requirements simultaneously.

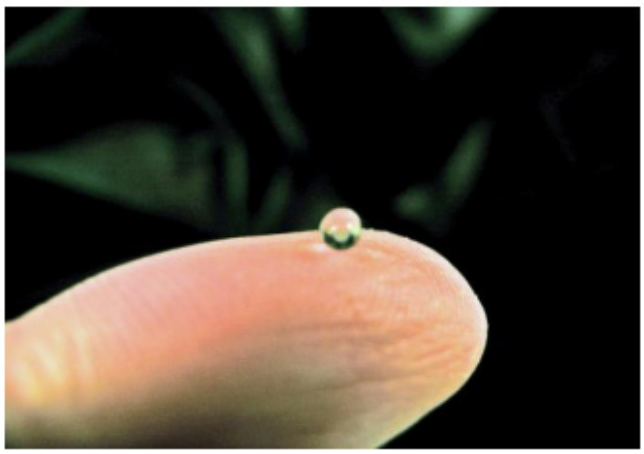

Figure 2: Encapsuled islet retrieved from canine transplantation experiment.

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Encapsulated islet intravenous glucose tolerance test

Slower insulin and blood glucose return to baseline in encapsulated islets (Figure 3).

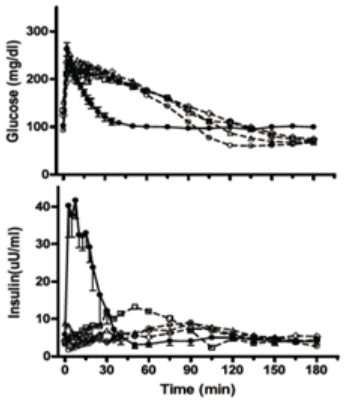

Figure 3: Intravenous Glucose Tolerance Test. Blood glucose collected from the control animals rose rapidly in 5 minutes. It returned to baseline in 30 minutes. On the other hand, glucose collect from experiment animals shot up in 5 minutes and returned to baseline in 90 min. Insulin collected from control animals shot up in 5 minutes and returned to base line in 30 minutes. On the other hand, insulin collected from experiment animals never rose more than 5 μU/ml-10 μU/ml above baseline in 150 minutes-180 minutes.

METHODOLOGY

Electronic artificial pancreas

A computer system was used to assist diabetes management. It can check patient's blood glucose levels remotely and to treat their disease at night without waking them up. It achieved major breakthroughs. It generates a great deal of interest in the diabetic community [7]. Unfortunately, the accomplishment was limited: 76.4% were in range with the AP system versus 67.8% in range without the AP system. If the artificial pancreas was to be offered as a viable treatment for diabetes, it must provide a better management. The artificial pancreas has failed in this challenge (Figure 4).

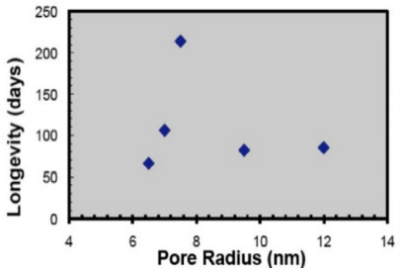

Figure 4: Encapsulated canine Islets Longevity Study.

Search for a better bioartificial pancreas

A Bioartificial Pancreas must be able to function like a healthy pancreas, it must be able to provide immune protection and mass transport simultaneously [8].

Capsules optimization: The capsules must be reproducible. Anion droplets were introduced into a gravity-free reactor at the velocity that matched of the polycation stream. The membrane will have same thickness with uniform pores (Figures 5 and 6).

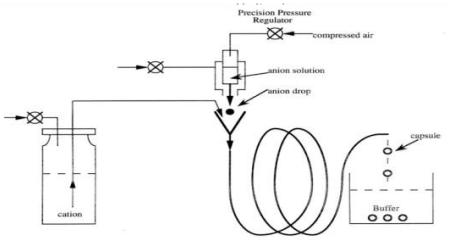

Figure 5: Bioreactor design. The anion droplets were introduced into the microgravity reactor. The polyanion droplets were moving together with polycation stream without any relative motion. The spherical capsules formed with uniform membrane thick less and pores diameter.

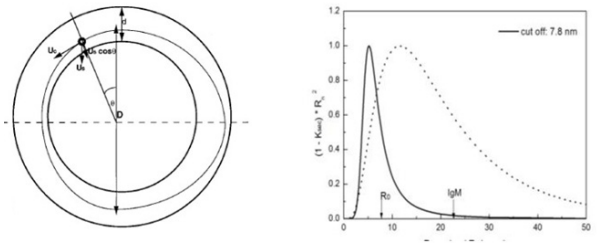

Figure 6: Capsules fabrication in our mutual buoyant reactor. Capsules carried by polycation stream in the reactor. It has little relative motion between capsules and polycation solution. Spherical Capsules have uniform membrane thickness and pore diameters.

Immune protection

NaAlg/NaCS droplets were introduced into the CaCl2 stream forming CaAlg/CaCS droplets. Upon capsule formation, these droplets were reintroduced into PMCG/Poly L- Lysine (PLL) and CaCl2 solution. PMCG bonded with CS forming Ca-Alg/PMCG-CS layer.

Soon after, Poly L-Lysine (PLL) replaced Ca and formed a PLL-Alg/PMCG-CS layer. As the membrane thickens, it formed a PMCG-rich PLL-Alg/PMCG-CS layer at the surface of capsules, and PMCG-deficit PLL-Alg/PMCG-CS layer at the core. It formed tapered conduit [9].

The capsules were ~20 μm in thickness. The pores are gradually decreasing from 25 nm pores at the inner core to 12 nm pores at outer surface. The PMCG-CS/CA-Alg layer connects with CA-CS/CA- Alg at one end and with PLL-Alg/PMCG-CS layer at the other end. Interconnecting these pores together form tapered conduits to enhance the insulin secretion and while keep out immune system.

Mass transportation

There are two mass transport requirements for the Bioartificial Pancreas: 1) Secret insulin out of the capsule. 2) Insulin and blood glucose return to baseline efficiently [10].

Near field mass transplantation improvement

- The capsules are ~200 um in diameter, and ~20 um in membrane thickness. The innermost capsule layer is made of CA-CS/CA-Alginate. The inner pore has ~25 nm pores.
- The middle membrane layer is made of PMCG-CS/CA-Alginate. It connects with CACS/CA-Alg in one end and with PMCG-CS/PLL-Alg layer on the other end. Interconnecting these pores in

succession forms tapered conduits.

• The outer membrane layer is made of PLL-Alg/PMCG-CS. The surface layer has pores ~12 nm to keep immune system out.

• The 12 nm PLL-ALG/P MCG-CS nanopore layer will keep immune system from entering.

• Bioartificial Pancreas design will encapsulated ~4-5 capsules in a ~1 mm-2 mm bead.

• Bioartificial pancreas needs to have approximate ~1,200 beads. It can secrets ~1 unit of insulin when challenged

• Capsules with 25 nm pores at the core, and 12 nm pore at the surface can keep immune system away.

• Nutrient and insulin transport can best be supported by the open spacing between 2mm beads.

• 2 mm vascular bundle will transport insulin efficiently within network.

The uniform capsules beads with ~2 mm in diameter creates enough separation for macro vascular transportation bundle [11-13]. This 2 mm system improve nutrient and insulin transport across the body [14].

Far field mass transplantation improvement

The capsules beads are ~2 mm in diameter create enough separation allowing macro vascular transportation bundle. This 2 mm system improve nutrient and insulin transport across the body by an order of magnitude (Figure 7) [15].

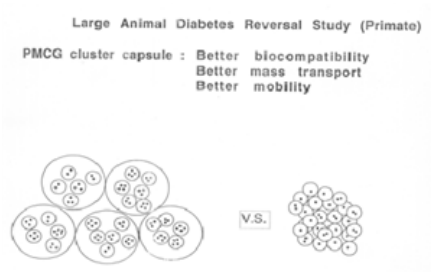

Figure 7: Capsule beads: Capsules with 800 µm in diameter are loosely formed 1-2 mm beads (Figure 9). It allows vascular bundles established in space between beads for macro mass transport for adequate mass transport for insulin, nutrient and oxygen.

Mass transport in vascular bundles

$$Q \sim \frac{R^4 T}{r\eta d} \Delta c N$$

Where 'Q' is mass flux pass through the vascular bundle. R is channel width between capsules or beads. 'C' is the concentration, T is the body temperature, d is the channel length, and N, R and n are characteristics of transfer medium [16-19].

Vascular bundles improve the influx of mass molecules important for islet function/survival and efflux of the desired hormone to rest of body such as insulin to internal organs [20-22].

Mass transport improvement with vascular bundle

Insulin mass transport can best be described as "Two-phase fluid flow with laden particles" [23]. At the beginning of transplantation, the insulin concentration is low. The momentum exchange between insulin and extracellular fluid is negligible. However, as the glucose challenge continues, insulin egress increases. It will accelerate the ingress of extracellular fluid laden with oxygen and nutrients needed for the islet's health. This momentum exchange feeds on each other. These double concentration diffusions driven convective flow [23,24].

Immune protection and mass transplantation

Tapered pores and vascular bundles were able to optimize immune protection and mass transport separately [25-27]. Tapered conduits and vascular bundles can maintain animal health and glucose management for Non-Human-Primate (NHP) diabetes (Figure 8) [28,29].

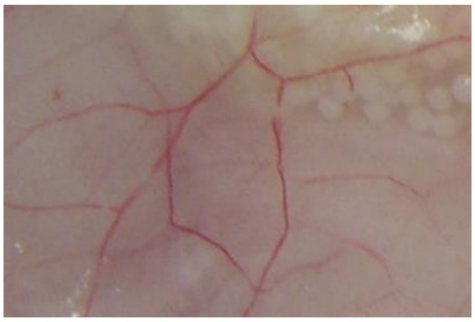

Figure 8: This picture of a bioartificial pancreas. It was taken in a non-human Primate experiment. It has a significant higher flow rate in mass transplant. The capsules were visibly intact and loosely bunded.

Neo-vascularization on the dorsal surface of the embedded encapsulated islets. The encapsulated islets were alive. The vascular network bounded with capsules beads function like a healthy pancreas [30]. The bioartificial pancreas secrets enough insulin when it was challenged and it can transport them throughout the body without delay keeping animal blood glucose normal, and healthy (Figure 9).

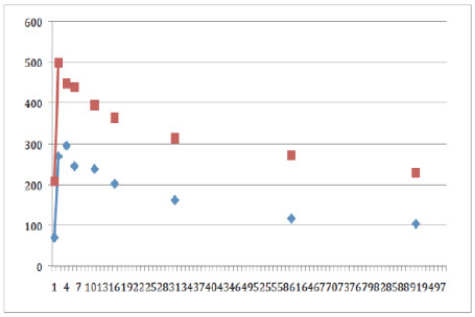

Figure 9: NHP Bioartificial Pancreas Intravenous Glucose Tolerance Test. **Note:** (♦) Rose to 300 mg/dl, (■) Rose to 500 mg/dl

There is No delay in mass transportation measurement between pre and post transplantation. Blood glucose was collected from pre- and post-transplant NHPs. Blood glucose from the pre-transplant healthy animal rose to 300 mg/dl from baseline in 5 minutes and returned to baseline in 45 minutes. On the other hand, blood glucose from the post-transplanted diabetic animal with tapered capsules rose to 500 mg/dl in 5 minutes and returned to baseline in 50 minutes. The two curves tracked each other, this suggested tapered capsules could clear the excess blood glucose as efficiently as a healthy pancreas. This will improve transplantation recipient's health, and extend islet longevity [31].

RESULTS

Large animal transplantation study

Canine allo-transplantation study: Canine 141 received 85,000 Islet Equivalents (IE)/Kg encapsulated islets intraperitoneally and maintained normal glycemia for 214 days (Figure 10).

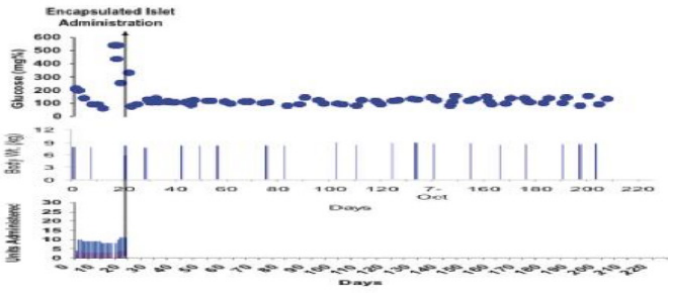

Figure 10: Canine transplantation study no exogenous insulin was administered (lower panel blue bar). Encapsulated islets were not needed until the encapsulated islets failed to maintain fasting glycemia less than 180 mg/dl for three consecutive days.

Non-human-primate diabetes management

A total of ten Non-Human-Primates (NHPs) were used to study the performance of this bioartificial pancreas system. For subcutaneous transplantation, small skin incisions were made on the antero-lateral abdominal wall where small pockets were created in the subcutaneous fat tissue, and capsule patches were placed within. After a five-week incubation period, the encapsulated islets were able to maintain good glycemic concentration shown in results in table (Figure 11 and Table 1) [32].

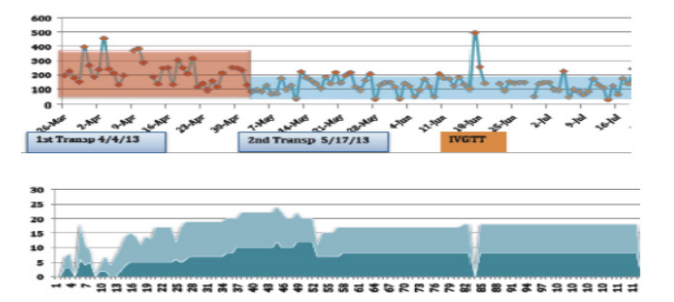

Figure 11: In NHP 3912, we transplanted a total 180,000 encapsulated NHP Islet Equivalents (IE) with tapered capsules. NHP 3912 showed steady diabetic improvement with decreasing supplemental insulin dosage, suggesting encapsulated islets were recovering their normal function.

Table 1: The result panel was the A1C value derived from BG measurement.

	Days (0 to 32)	Days (33 to 65)	Days (66 to 98)	Days (99 to 119)
Plasma glucose	220 ± 74	150 ± 56	127 ± 42	102 ± 37
HbA1c*	9.3	6.85	6.05	5.2

Note: *Converted from average plasma glucose number with A1c calculator for discussion purpose. It demonstrated that the bioartificial pancreas with tapered conduit can clear excess blood glucose as well as a healthy pancreas. The bioartificial Pancreas offered good BG management and functional longevity in NHP.

NHP xeon-transplantation with human donor

NHP model was chosen to study the immune protection efficacy of the encapsulation system with human islets. NHP 4510 (5 Kg in BW) received a total 12 Capsule-Patches containing ~1,350,000 human islets. Soon after the incubation period (~3 weeks), the exogenous insulin requirement for NHP 4510 started to drop. It gradually fell from 25-30 units/day to 7-10 units/day in 90 days, with good glycemic control (Figure 12) [33-35].

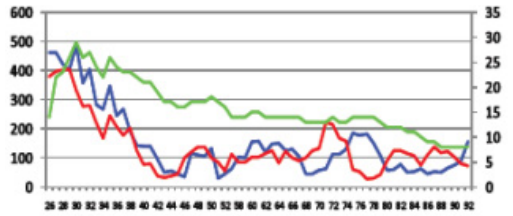

Figure 12: Immunol Protection Study NHP-4510 received two human islet dosages with 900,000 islets IP and 450,000 islets SQ transplantations. Its insulin requirement after two transplants gradually fell from 25-30 units/day to 7-10 units/day, and this had been accompanied by good glycemic control with no immunosuppressive or anti-inflammatory therapy. **Note:** (—) BGAM, (—) BGPM, (—) Insulin

DISCUSSION

We have studied diabetes management in rodents, canines, and NHP as transplant recipients. It all worked well. We have successfully developed a bioartificial pancreas. It functions like a living pancreas. We tested it with rodent islets, canine islets, NHP islets, and human islets, they all functioned well as they should. A Bio-artificial Pancreas with tapered conduits can produce adequate insulin for diabetic patients. Vascular bundle can transport insulin efficiently for patient health. Currently, the only thing we are waiting is human islets supply for diabetes patient care.

CONCLUSION

We have succeeded in developing a bioartificial pancreas for human trial. The larger inner pores of the tapered conduit can accelerate insulin exit. The small pores of the tapered conduit can stop immune attack. The macro vascular bundle can accelerate far field mass transport for patient health. The bioartificial pancreas functions like a healthy human pancreas. We have transplanted rodent islets, canine islets, NHP islets, and human islets in animals, they all functioned well. Bio-artificial Pancreas is ready for human diabetic patient care. Furthermore, Bioartificial Pancreas gives us the clue on the designs of different Bioartificial Organs for different human diseases and illness, such as bioartificial liver and others.

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