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Bioartificial Pancreas with Tapered Conduits for Diabetes Management

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Abstract

Diabetes is a life-long illness, it requires life-long solution. Today's treatment is trading one type of pain with another, never truly ride off the illness. When Artificial Pancreas (AP) offered a possibility of cure, it stirred up a great deal of interest in the diabetic community [(1)]. The system was based on artificial intelligence. It can automate the dosing of insulin to reduce high blood sugar levels overnight. The most dangerous time for diabetes. Artificial Pancreas may be able to allow diabetic patients to sleep through the night without waking up to check and manage their blood glucose levels. It was a significant advancement. However, the achievement was limited: 76.4% in range with the system vs. 67.8% without the system. This accomplishment was creditable, but not optimal. If Artificial Pancreas was to be offered as a viable treatment for diabetes, it must be a life-long solution and must be a total solution. Artificial Pancreas has failed in this challenge. We decided to pursue an alternative approach, a self-regulated system: bioartificial pancreas. It has the potential became a complete cure.

Key Words; Diabetes, Islets, Encapsulation, Bioartificial Pancreas, tapered conduit

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Introduction

Bioartificial Pancreas is a system based on encapsulation of living cells. It was proposed by T. Chang [(2)] and later adapted by Lim and Sun for diabetes management. [(3)] Its design was based on a thin semi-permeable membrane that could protect cells from immune attack while allowing nutrient and oxygen to enter, and insulin to exit. It worked well in rodents, but not well enough in large animals. Despite the dedication of many, improvement was limited. We decided to screen a new polymer system (Table 1) for diabetes management.

Table 1

Polymer Match Screening Matrix	
Polycation Group	**Polyanion Group**
chitosan	sodium alginate
glycol chitosan	PG alginate
DEAE-dextran	CM-cellulose
quarternized hydroxymethyl cellulose, JR-125	cellulose sulfate
poly (dimethylamino-co-epichlorhydrin), quarternized	gellan gum
polyethyleneimine	gum arabic
polyethyleneimine/hydroxyethylated	maleic anhydride
gelatin A, pH 4	pacrylamide carboxyl-mod
quarternized polyamine, B50	pAA/MPSA
poly L-lysine	pmaleic acid
polyallylamine	tripoly phosphate
polydiallyl dimethylammonium chloride	'polyvinyl sulfone
DADMAC-acrylamide, C3204/C505	polyvinyl sulfonic acid
cationic polyacrylamide, Jayfloc 3468	polystyrene sulfate
poly (2-DMAE-methacrylate)	polyvinyl phosphonic acid
poly (acrylamide-methacryloxyethyl-trimethyl-ammonium bromide)	polyvinyl phosphate
poly (methacryloxyethyl-trimethyl-ammonium bromide)	polyacrylic acid
poly (2-hydroxy-3-methacryloxypropyl-trimethyl-ammonium chloride)	pmethacrylic acid
poly (3-chloro-2-hydroxypropyl-methacryloxyethyl-dimethyl ammonium chloride)	pacrylamide/acrylic acid
poly (butylacrylate-methacryloxyethyl-trimethyl-ammonium bromide)	anionic acrylamide
copolymer DMAE-methacrylate-acrylamide (Betz #1158)	gelatin A pH9
copolymer DMAE-acrylate-acrylamide (Betz #1-#5)	gelatin B pH 6.5
copolymer dimethylaminoethyl-acrylate-acrylamide (Hunk #5)	pglutamic acid
copolymer MDEAE-acrylate-acrylamide (Betz #1160P)	pgalacturonic acid
poly (methylene-co-guanidine), plus 0.2 g/l CaCl2)	CM-dextran
cationic polyacrylamide proprietary (496C/492C)	CM-amylose
poly (vinly pyrrolidone-DMAE-methacrylate-quarternized)	dextran sulfate
polyethyleneimine, epichlorhydrin modified	heparin
poly (1-methyl-2-vinylpyridinium bromide)	chondroitin 4-sulfate
poly (1-methyl-4-vinylpyridinium bromide)	chondroitin 6-sulfate
polyamine 4030	hyaluronic acid
polyamide 5087/792a	xanthan
poly DADMAC/N-isopropyl-acrylamide (pDADMAC/NIPAAM)	carrageenan lambda
polymidazoline, quarternized	methylvinyl-ether/maleic acid
polyvinylamine	methylvinylether/maleic anhydride

Table 1 Polymer Screening *More than 100 polyanion and polycation pairs have been screened [(4, 5)] for capsule formation, stability and functions. The most promising system was Alginate, CS, CA, PMCG, and Poly L-Lysine.*

Theory

Immuno-protection [(6)] Using the random walk model, the immuno-protection is proportional to D^2/ R^2, where R is average pore size and D is the membrane thickness.

Mass Transport [(7)] Using the interwoven pipes model, the mass transport is proportional to R^4/D, where R is average pore size, and D is the membrane thickness.

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Mechanical Strength Mechanical strength of capsules was measured by placing an increasing uniaxial load on the capsule until the capsule burst. The capsule mechanical strength—a function of chemical bonds and membrane thicknesses— can be adjusted anywhere from a fraction of a gram load to many tens of grams load to meet transplantation requirements. On average, ~ 20 grams load works well for our experiment.

Porous Distribution Apparent pore size of the capsular membrane is measured by size exclusion chromatography (SEC), that determines exclusion of dextran solutes from the column packed with microcapsules. Using neutral polysaccharide molecular weight standards makes it possible to evaluate the membrane porosity under the conditions when solute diffusion is controlled only by its molecular dimension. From the measured values of solute size exclusion coefficients (K_{SEC}) and known size of solute molecules, one could approximate the pore size distribution (PSD) and the required modifications.

Background

Biocompatibility Capsules made of five components has transplanted in large animals such as canines and non-human-primates (NHP). It worked well for months and showed no sign of complication. Omental surface was mildly vascularized, and capsules were minimally attached. The surface of the vast majority of the retrieved capsules was clean and could easily be washed off of the omental surface. Capsule integrity had been excellent with minimal capsule "breakage." The retrieved encapsulated islets were alive (figure 1). Evidence of tissue reactivity had been minimal in animals. The new polymer system was biocompatible and functional well in large animals.

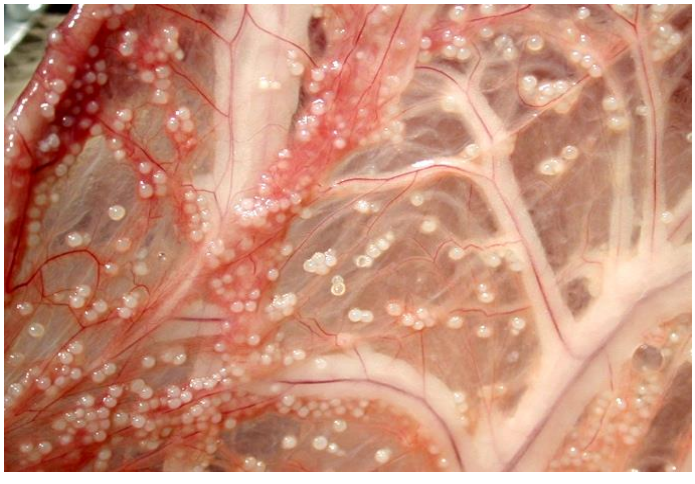

Figure 1. Biocompatibility *Study* *Normal dog received encapsulated islets on 2/14/01. No complications with this animal prior to sacrifice on 8/28/01. No abnormalities*

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for the organs. Omental surface mildly vascularized and capsules were very minimally attached and could be washed off of the omental surface. All islets were alive, and underneath each capsule was evidence of neo-vascularization.

Canine Diabetes Reversal

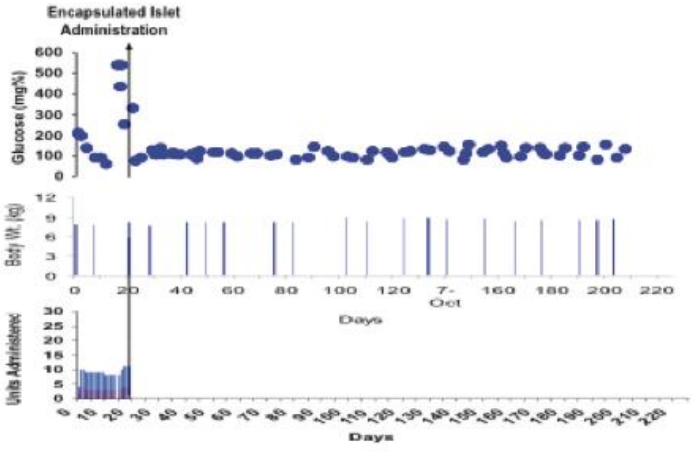

Figure 2 Canine transplantation study [8] *Canine 141 received 85,000 Islet equivalent (IE)/Kg encapsulated islets intraperitoneally and maintained normal glycemia for 214 days. Exogenous insulin was administered (blue bar) prior to transplantation and did not return until after the encapsulated islets failed to maintain fasting glycemia less than 180 mg/dl for three consecutive days.*

Encapsulated Islets Retrieval

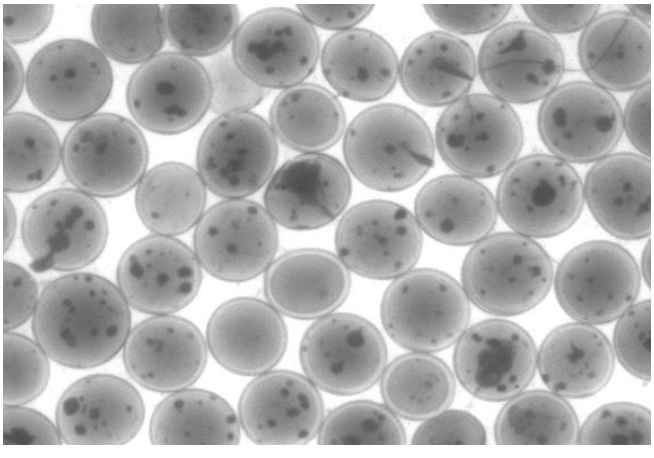

Figure 3. Encapsulated islets retrieved *from total pancreatectomized animal-canine # 141, were healthy and biocompatible after 214 days. Capsule surfaces were clean with no sign of breaching. Increased vascularized areas were present in conjunction with gently adhered capsules. Approximately 50% of the encapsulated islets were gently*

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adhered to the omental surface. The enclosed pancreatic cells were alive and well. Except, islets have lost ~50% of mass in the main time, which led to early transplant failure.

Longevity Study A total of eight animal-canines received encapsulated islets of different pore sizes. The longevity vs. pore sizes was determined when encapsulated islets failed to maintain fasting glycemia less than 180 mg/dl for three consecutive days.

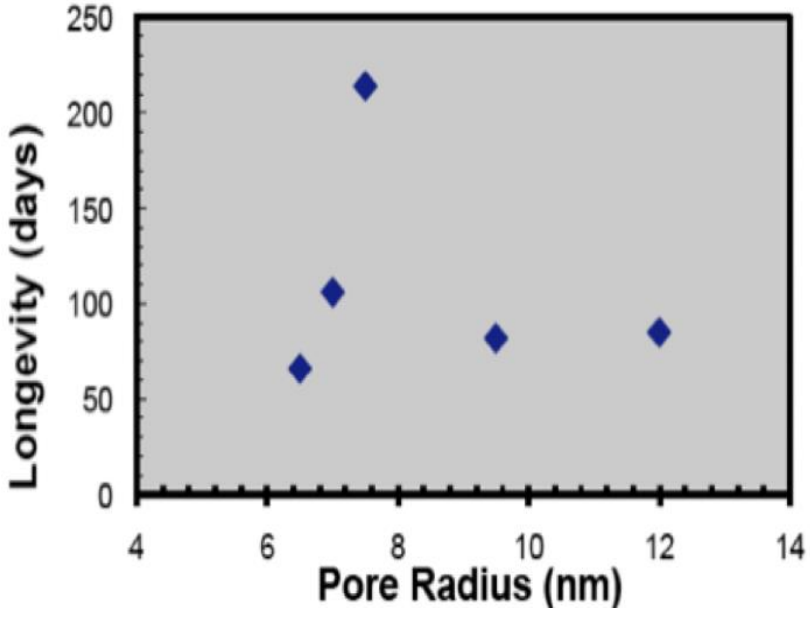

Figure 4. Transplant Longevity *A total of eight canines received encapsulated islets of different membrane pore sizes. It was transplanted intraperitoneally and maintained exogenous insulin independence with a single transplantation. Fifteen (15) nm pore size longevity measurements were the average of three animals.*

Intravenous Glucose Tolerance Test (IVGTTs) (9)

Glucose and insulin were collected from five controlled animal-canines, and four experiment animal-canines for IVGTT measurements

Blood glucose collected from controlled animals shot up in 5 min. and returned to baseline in 30 min. On other hand, glucose collect from experiment animals shot up in 5 min. and returned to baseline in 90 min.

Insulin collected from controlled animals shot up in 5 min. and returned to base line in 30 min. similar to excess blood glucose measurements. On the other hand, insulin collected from experiment animals never rose more than 5-10 µU/ml above baseline in 150-180 min. (Figure 5). The animal suffered repeated hyper and hypo glycemic episodes. Those episodes adversely affect the animals' health and transplanted islets longevity.

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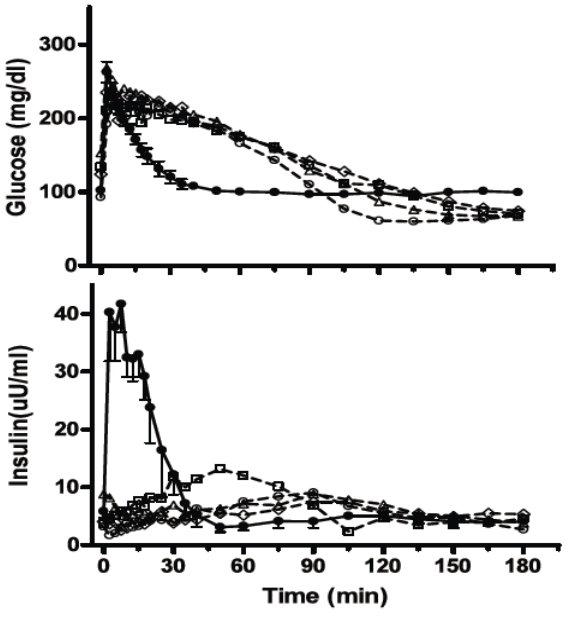

Figure 5 *Glucose and insulin were collected from five controlled animal-canines and four experiment animal-canines for IVGTT measurements. Experiment animals with capsules did not return to baseline as controlled animals. The experimental animals suffered repeated hypo and hyper glycemic episodes. Those episodes adversely affect the animals' health and transplanted islets longevity.*

Tapered Conduit - Materials

The pore size compromise has limited its longevity. To improve this, we decided to incorporate tapered conduit into the capsule design.

We enlarged the inner pores of this capsule for mass transport, and we reduced the outer pores for immuno-protection. Tapered conduit construction has reported before. Only a brief description will be presented here. [(10-12)]

Tapered conduit capsules were formed simultaneously and diffusely. Polyanion droplets [NA/Alginate (1-3%) and NA/CS (0.5-3%)] were introduced into a running polycation stream [(13-14)] of [PMCG (0.5-2.5%), Poly L-Lysine (PLL) (0. 025 -0.1%), and $CaCl_2$ (0.5-3%)]. Ca- Alg. /Ca-CS. was formed first. Trailing behind, PMCG bonded with CS preferentially forming Ca-Alg./PMCG-CS layer. PMCG continued its migration inward, as the capsule membrane thickened

Poly L-Lysine (PLL) trailed further behind, formed a thin PLL-Alg./PMCG-CS layer slowly to cover the outer surface. PLL-Alg. layer had the smallest pores. It restricted PMCG penetration. It created a PMCG rich PLL-Alg./PMCG-CS layer at the outer surface and PMCG deficit PMCG-CS./CA-Alg. layer at the core. It formed tapered conduits.

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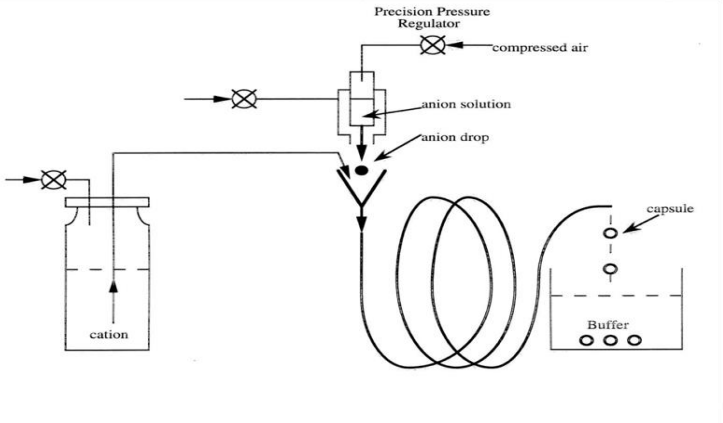
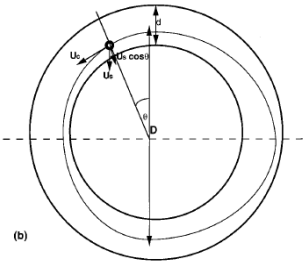
Bioreactor A microgravity reactor system was developed for tapered capsules production.

(A) System Design [15]



(B) Capsule Flow path



(C) Pore Size Distribution

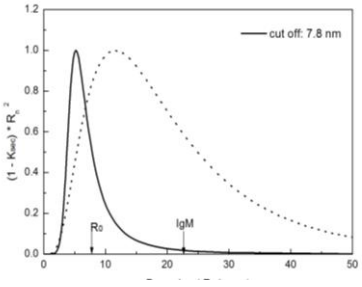


Figure 6 Bioreactor design and pore size distribution *(A) is a simplified drawing of capsule formation reactor. (B) is the capsule flow path carried by polycation steam in the reactor with min. relative motion between capsules and polycation. (C) is capsules pore size distribution processed in bioreactor.*

Tapered Conduit Design

The bioartificial pancreas with tapered Conduit improves mass transport without compromising the immuno-protection.

A) Innermost membrane layer is made of CA-CS/ CA-Alginate. It is a biocompatible layer. Approximate ~ 7-8 Islet equivalent (IE) were encapsulated in capsule. It has pore size ~ 35 nm in diameter. Its primary function is to start the insulin going.

B) Outer membrane layer is made of PMCG-CS /PLL-Alg. It has pores size ~14 nm in diameter. Its primary function is to keep immune system out.

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C) Middle membrane layer is made of PMCG-CS/ CA-Alginate. It is a tapered layer. The PMCG-CS/ CA-Alg. layer connects with CA-CS / CA-Alg. in one end and with PMCG-CS/ PLL-Alg. layer on the other end. Interconnecting these pores together form tapered conduits.

D) Approximate ~ 7- 8 islet equivalent (IE) in a capsule, and ~ 4- 5 capsules in an alginate bead, and ~ 1,200 beads, in one capsule patch. It secreted ~ 1 unit of insulin when challenged

E) The alginate beads open up inner spacing to vascular network for influx of molecules important for islet function/survival, and efflux of the desired hormone, like insulin.

This is a cartoon drawing of a fragment of the capsular membrane with tapered conduits. It is a 20-µm membrane.

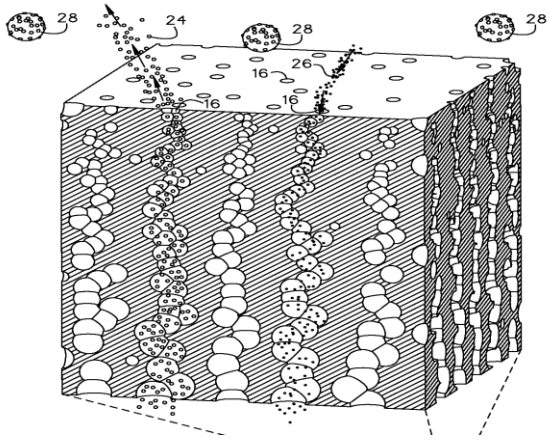

Figure 7 Tapered Capsule: *The capsule is 800 µm in diameter, with ~20 µm in thickness. The pores are gradually decreasing from 35 nm to 14 nm outwardly (Drawing not to scale). The PMCG-CS/ CA-Alg. layer connects with CA-CS / CA-Alg. in one end and with PLL-Alg./PMCG-CS layer on the other end. Interconnecting these pores together form tapered conduits. The small circles (24) are the outflow of insulin (~4nm), and the black dots (26) are the inflow of extracellular fluid laden with glucose molecules and oxygen. The large spheres (28), outside of the membrane, are the immune system.*

Tapered Conduit Mass transport

Insulin transport in tapered conduit can best be described as "**particle laden two-phase fluid flow**.[(16)] 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. This "**Double Concentration Gradient Diffusion Driven Convective Flow.**"[(17)] will increase the mass transport in both directions.

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Diabetes Study

Non-Human-Primate (NHP) Non-Human-Primate (NHP) was chosen to study the bioartificial pancreas with tapered conduit. NHP has a similar DNA structure as human. [19] NHP is temperamental and fragile and does not endure stress or treatment well. NHP makes a challenging model for islet transplantation. If bioartificial pancreas system with tapered conduits functions well in NHP model, it will likely function well in humans. This makes NHPs very valuable trial subjects for the new bioartificial pancreas system.

IVGTT With Tapered Conduit Blood glucose was collected from pre and post transplanted NHPs. Blood glucose from the pre-transplanted healthy animal (▲) shot up to 300 mg/dl from baseline in 5 min. and returned to baseline in 45 min. On the other hand, blood glucose from the post-transplanted diabetic animal with tapered capsules (■) shot to 500 mg/dl in 5 min. and returned to baseline in 50 min. The two curves tracked each other, this suggested tapered capsules could clear the excess blood glucose as efficiently as a healthy pancreas. This will extend islet longevity and improve transplantation recipient's health.

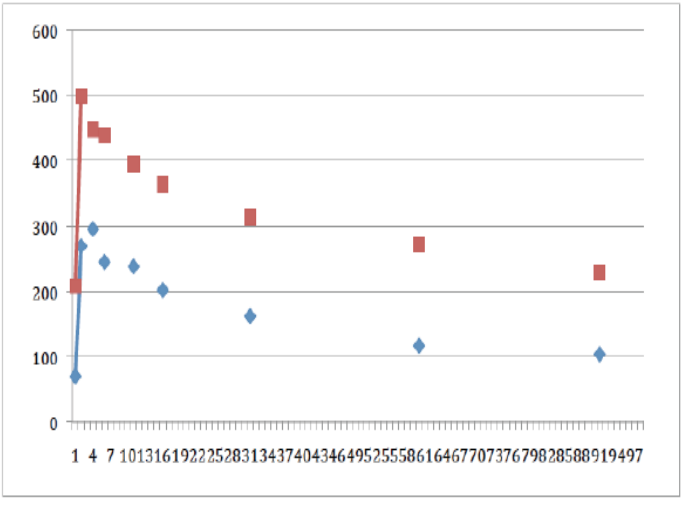

Figure 8 IVGTT measurements from transplanted NHP *Glucose concentration collected from the pre-transplanted healthy Non-Human-Primate (▲), its glucose rose from baseline 100 mg/dl to 300 mg/dl in 5 min. and returned to its baseline in 45 min. Glucose concentration collected from post transplanted diabetic Non-Human-Primate (■) rose from baseline 200 mg/dl to 500 mg/dl in 5 min. and returned to baseline in 50 min. Those two curves are tracking each other. This suggest islets in tapered capsules can clear the excess glucose nearly as efficiently as a healthy pancreas, and it will likely lengthen islet longevity and restore patient's health.* [18]

Vascular Bundling Collection of encapsulated islets developed a vascular network intradermal to improve the influx of molecules important for islet function/survival and efflux of the desired hormone, such as insulin.

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Bio-Artificial Pancreas

Bioartificial pancreas is a collection of encapsulation capsules. Our capsule is ~ 800 µm in diameter and 20 µm in thickness. For type I patient, we need transplant encapsulated islets from two or more human donor pancreases. On the other hand, for type II patient, we need encapsulated islets from part of human pancreas

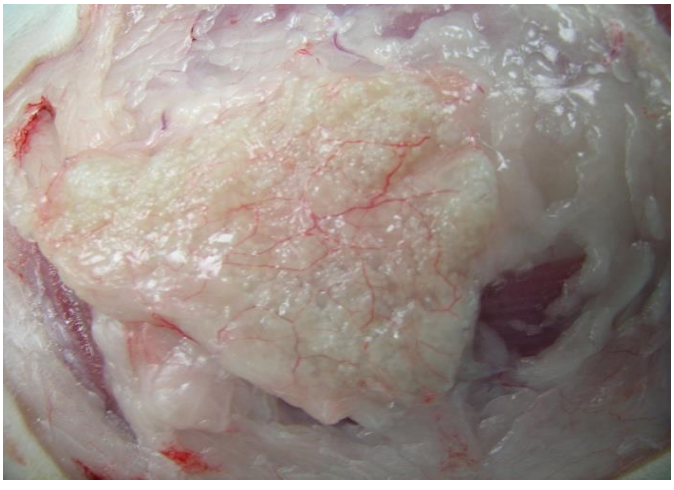

Figure 9 Neo-Vascularization I *This picture was taken immediately after the Capsule-Patch was exposed by peeling back the skin. The Capsule-Patch was transplanted on subcutaneous fat tissue five months ago. The capsules were visibly intact with some neo-vascularization on the dorsal surface of the embedded encapsulated islets.*

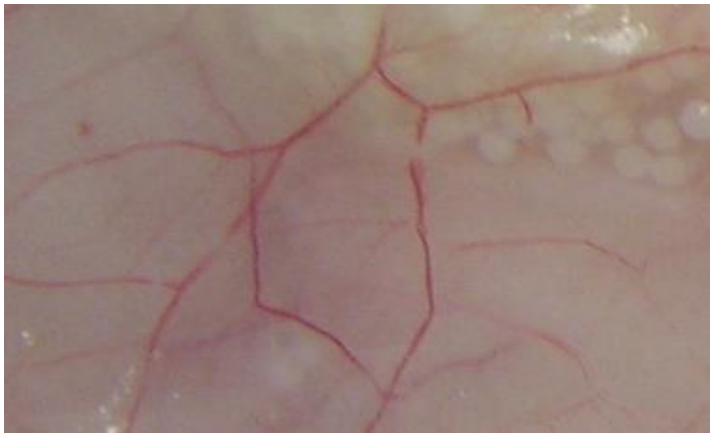

Figure 10 Neo-Vascularization II *Upon closer examination. The capsules were visibly intact with neo-vascularization on the dorsal surface of the embedded encapsulated islets. The encapsulated islets were alive. The vascular network allows encapsulated islets to function as a healthy organ.*

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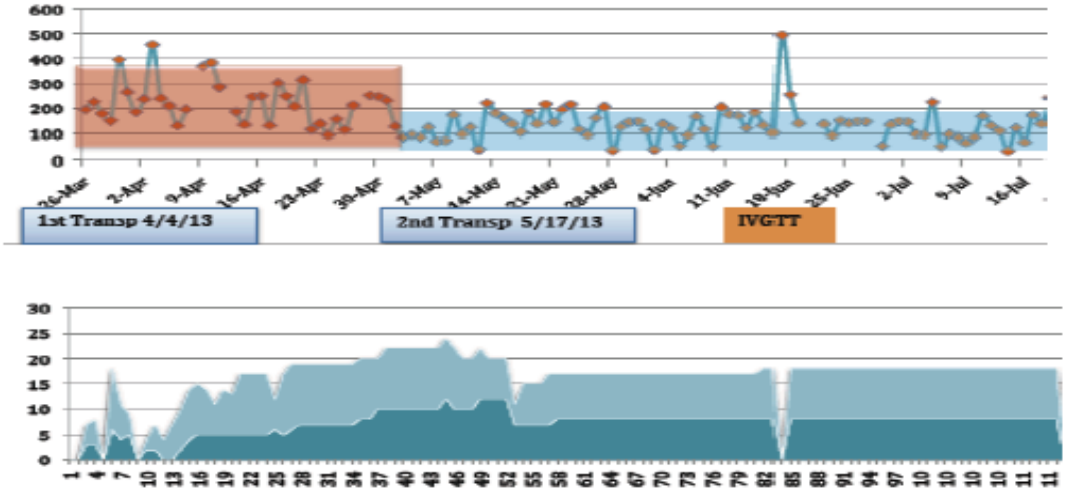
Experimental Results

Non-Human-Primate Trial

A total of ten (10) non-human-primates (NHP) 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 three to four weeks incubation period, encapsulated islets were able to maintain good glycemic control.

In NHP 3912, [20] we transplanted a total 180,000 encapsulated NHP islet equivalent with tapered capsules. It has shown steady diabetic improvement with decreasing supplemental insulin dosage, suggesting encapsulated islets were recovering their normal function.



	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

* Converted from average plasma glucose number with A1c calculator for discussion purpose

Table 2 Bioartificial pancreas transplantation *Glucose collected from NHP 3912 pre and post-transplantation. The top panel was the unedited data. Middle panel was the exogenous insulin, and the lower panel was the A1c value. It demonstrated that the bioartificial pancreas with tapered conduit can clear excess blood glucose as well as a healthy pancreas, Bioartificial Pancreas offered good BG management and functional longevity.*

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Conclusion

In this paper, we present a Bio-Artificial Pancreas with built-in tapered conduits for diabetic management. Transplantation results in canine and NHP were successful. Bioartificial pancreas kept the blood glucose at normal levels. Transplantations demonstrated improvements in Basal Insulin therapy, and Blood Glucose Control. Bio-artificial pancreas transplantation was well tolerated and biocompatible. The nanotechnology provided design modifications, increased the mass transport, enhanced immuno-protection. The most important contribution of all, improved health of the patient.

Potential Benefits for type I diabetic patients;

Therapeutic Transplantation: Bioartificial Pancreas with tapered conduit can provide increasing insulin output to diabetic patients in real time, maintaining normal blood glucose, while keeping the immune system at bay. It can offer Type I diabetic patients a healthy and worry-free life.

Sub-therapeutic Transplantation: Frequent glucose monitoring and multiple insulin injections have driven many Type II diabetic patients into depression. Self-regulating corrective insulin bolus from bioartificial pancreas can calm down blood glucose fluctuation in real time. and offer recipient better health.

Xenotransplantation experiments. 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 (data not shown). Recently, we have secured the approval of a human clinical trial application abroad.

Potential Benefits for type II diabetic patients;

There are 330 million children and adults in the United States, ~ 10% of the population with diabetes, and 90% of them are type II diabetes. Most patients with type II diabetes experience progressive loss of islet function. Their overworked islets seem to burn out, and these patients will eventually need insulin injections or islet transplantation to manage their diabetes. [(21)] Many Type II diabetes patients will benefit from sub-therapeutic bioartificial pancreas transplantations. It can replace their damaged islets and keep their diabetes disease in check. This transplantation protocol can arrest the progression of their diabetes before it starts to ravage their bodies and rob them of their quality of life (Table 2).

In summary, bioartificial pancreas with tapered conduit can provide long term diabetes management without immunosuppressive drug.

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