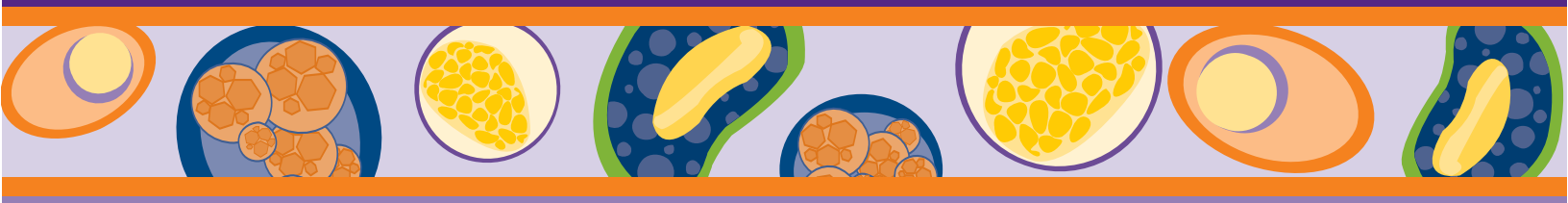
Immunobarriers for Pancreatic Islet Transplantation

March 29 - 30, 2004

The Embassy Suites Hotel
at the Chevy Chase Pavilion
Washington, D.C.



U. S. Department of Health and Human Services

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Table of Contents

Table of Contents

Agenda

Chair: Michael J. Lysaght, PhD, Brown University

Day 1 – Monday, March 29, 2004

8:00am	**Registration and Continental Breakfast**
9:00am	**Welcome** *Dr. Maren R. Laughlin, NIDDK* *Dr. Belinda Seto, Deputy Director, NIBIB*
9:05am	**Immunobarriers for Islet Transplantation: Overview and Workshop Goals** *Michael J. Lysaght, Brown University*
	Session I: Requirements for Successful Immunoisolation *Co-chairs: Gordon C. Weir & Arne Andersson*
9:30am	**Failure Mechanisms in Islet Encapsulation: What Are They and What Can We Do About Them?** *Clark K. Colton, Massachusetts Institute of Technology*
10:00am	**The Encapsulated Islet in the Immune Environment** *Ronald G. Gill, University of Colorado Health Sciences Center*
10:30am	**The Challenge of Species Scaling** *David W. Scharp, Novocell, Inc.*
11:00am	**Discussion**
12:00pm	**Lunch**

Agenda

Session II: Issues with Current Approaches to Encapsulation
Co-chairs: Michael V. Sefton and Olle Korsgren

1:30pm **Alginate Microcapsules – How Can They be Improved?**
Gudmund Skjak-Braek, Norwegian University of Science and Technology, NTNU

2:00pm **Macroencapsulation**
Thomas Loudovaris, Theracyte, Inc.

2:30pm **Nanoperforated Materials**
Tejal Desai, Boston University

3:00pm **Break**

3:30pm **Discussion**

5:00pm **Adjourn**

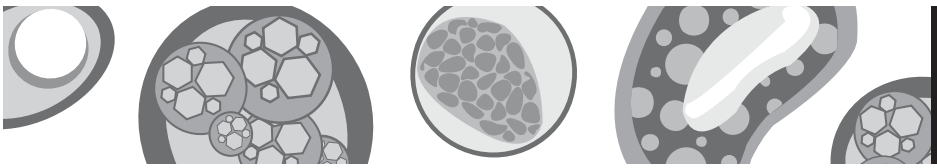
6:30pm **Dinner and Poster Session** *(Maggiano's Restaurant)*

9:30pm **Adjourn**

Agenda

Day 2 – Tuesday, March 30, 2004

8:00am	**Continental Breakfast**
	Session III: New Directions *Co-chairs: Ray Rajotte and Alvin C. Powers*
8:30am	**What Can We Learn from Encapsulating Cells that Do Not Secrete Insulin for the Potential Treatment of Diabetes?** *Patrick Aebischer, Swiss Federal Institute of Technology EPFL*
9:00am	**Assessment of Industry-wide Encapsulation Approaches** *Scott R. King, Islet Sheet Medical, LLC.*
9:20am	**Co-transplantation of Porcine Islets with Sertoli Cells in Type 1 Diabetic Patients Produces Atypical Humoral Immune Responses as Assessed by Elicited Anti-pig Antibodies** *David White, University of Western Ontario*
9:40am	**Drug Incorporated Islet Capsules** *You Han Bae, University of Utah*
10:00am	**Break**
10:30am	**Conformal Coating** *Elliot L. Chaikof, Emory University School of Medicine*
11:10am	**3-D Fabrication Techniques** *Mehmet Toner, Harvard Medical School*
11:30am	**Discussion/Recommendations**
12:30pm	**Adjourn**



Speaker Abstracts

Immunobarriers for Islet Transplantation: Overview and Workshop Goals

Michael J. Lysaght, PhD

Center for Biomedical Engineering
Brown University
Providence, RI

The use of semi-permeable membrane barriers to enable the transplantation of islets to an immunocompetent host was originally proposed in the nineteen sixties and first demonstrated in rodent models in the late nineteen seventies by two separate investigative groups, each employing different immunoisolation technologies. These early successes spawned a succession of research and development programs, supported by aggregate funds in the hundreds of millions of dollars, which nevertheless which have failed to result in routine success in large animal models, let alone in a clinically viable therapy. The question is "why" ….and providing the best possible answer is a primary goal of this conference. This issue is raised in the context of congressionally-mandated funding in the area of diabetes with the specific objective of asking whether renewed research into immunobarriers should be supported and, if so, with what priorities.

Among the Important Questions to address are:

1. What is currently known about the required transport properties of semipermeable biomaterials materials for islet isolation. What do such barriers have to pass, what to they have to exclude; and at what rates. Can appropriate transport parameters be defined and measured. If the answers to these basic questions are not currently available, what would it take to get them?

2. What are the technical barriers to species scaling: why does islet isolation appear to work so splendidly in rodent models but consistently fail in canine and non-human primate models?

3. What is the "state of the art" in currently available barrier biomaterial technology?

4 What is the potential role in islet transplantation for emerging technologies such as nanofabrication and islets derived from cloned animals of reduce immunogenicity?

5. What of relevance to the "bio-artificial pancreas" can be learned from parallel activities with immunoisolation in other areas of tissue engineering

It is hoped that the conference will reach a consensus on whether significant funding of immunobarriers is warranted by the likelihood of clinically applicable results. And, if so, how should the research be organized and structured?

Immunobarriers are, of course, only one part of the much bigger quest for improved therapies for diabetes. Aspects such as stem cells, islet sourcing, the "Edmonton protocol", closed loop insulin delivery systems, are all important. However, these additional topics are beyond the reach of this conference which will focus exclusively on basic and applied issues in immunobarriers.

Failure Mechanisms in Islet Encapsulation: What Are They and What Can We Do About Them?

Clark K. Colton, BChE, PhD

Massachusetts Institute of Technology
Cambridge, MA

Although most publications in this field focus only on the partial success achieved, it is only by focusing on the failures that we can learn what went wrong and how to fix it. A wide variety of failure mechanisms can be inferred from the available literature: (1) the simplest problem is capsule breakage, which leads to loss of tissue and enhanced immune stimulation. The solution to this problem must be found in improved materials and and polymer engineering. (2) Because encapsulated islets are removed from their blood supply, substantial diffusion gradients exist for oxygen, nutrients, secreted insulin, and waste products. Of these, oxygen supply limitations are most serious, leading to reduction of insulin secretory capacity, loss of beta cells by central necrosis, and release of immunogenic degradation products. Approaches to reduce the magnitude of these problems by increasing oxygen concentration in the islet microenvironment include enhancement of (a) the local pO2 external to the capsule and (b) the oxygen permeability of the encapsulating material. (3) All other failure modes stem from immune responses. (a) Recognition of the capsule material as a foreign material leads to macrophage activation, fusion into giant cells on the surface, and formation of a fibrotic layer, further exacerbating transport limitations. This is a problem of materials bioincompatibility. (b) The autoimmune response, which leads to type 1 diabetes in the first place, remains a problem. (c) Allogeneic and xenogeneic tissue elicit a response to foreign tissue by the indirect pathway that responds to soluble antigens released by the encapsulated islet. The allogeneic response is much weaker, and some data suggest that a physical barrier alone is sufficient to protect allogeneic tissue. Xenogeneic tissue can produce a humoral response and a florid external cellular response around the capsule. Activated immune cells release free radicals and nitric oxide that can attack the islets within the capsule, in addition to nitric oxide release by the islets themselves in response to hypoxia. Use of scavengers within the capsule may ameliorate this problem. In addition, the immune cells cells utilize nutrients and consume oxygen. The only way to eliminate this problem is to prevent activation from occurring by local immunosuppression resulting from release of agents within the capsule. Other failure mechanisms likely exist. Only by careful research can they be identified and means for dealing with them be developed.

The Encapsulated Islet in the Immune Environment

Ronald G. Gill, PhD

Barbara Davis Center for Childhood Diabetes
University of Colorado Health Sciences Center
Denver, CO

While an important endeavor in cell/tissue transplantation is developing immunoisolation technologies for attenuating anti-donor immunity, there are few experimental results that clearly indicate the nature and extent of host immunity to encapsulated transplants. In particular, the nature of adaptive (antigen-specific) cellular and humoral responses to encapsulated islet allografts and xenografts remains unclear. Importantly, two types of immune responses to transplants occur: (1) 'Direct' (or donor MHC-restricted) antigen presentation in which T cells engage native donor MHC-peptide complexes expressed on the surface of graft-derived antigen-presenting cells (APC); and (2) 'Indirect' (or host MHC-restricted) antigen presentation in which donor-derived antigens are captured by recipient APCs, degraded, and re-presented in association with recipient MHC molecules. A key tenet of this discussion is that immunoisolation is not actually antigen isolation, *per se*, but rather is *cell* isolation. That is, while synthetic membrane barriers are designed to prevent cell-cell contact between host and donor cells (the 'direct' pathway), we and others have long postulated that soluble antigens derived from the transplant are likely to gain access to the host immune system (the 'indirect' pathway). That is, despite the encapsulation barrier, there is still the potential for graft-derived peptide antigens to traverse the isolating membrane and be presented by host-type APCs. This pathway appears to be most pronounced in response to xenogeneic, rather than allogeneic islets.

Importantly, exogenous antigens are generally processed and presented by class II MHC molecules and so invoke a predominantly CD4 T cell response. Data presented illustrate the importance of this presentation pathway, especially for islet xenograft rejection. A long-standing assumption is that this CD4 T cell-dependent pathway triggers an inflammatory response resulting in non-specific 'bystander' killing of the target graft, generally by soluble mediators/cytokines. However, while the injury/killing of islet cell initiated by a variety of inflammatory mediators/cytokines is well documented in vitro, the degree of non-specific inflammatory killing in vivo is less clear. Data presented indicate that CD4 T cell-dependent 'inflammatory' responses demonstrate surprising specificity in vivo. For example, acute rejection of islet xenografts can occur in vivo without

apparent injury to admixed islet isografts in the same microenvironment. This has two important implications regarding encapsulated islet transplants: (1) It is possible that inflammatory mediators produced by an indirect 'bystander' response do *not* contribute demonstrably to the damage of encapsulated islet transplants that are spatially sequestered from the actual site of antigen recognition, and (2) Constricting an encapsulation membrane to exclude inflammatory mediators may not be necessary in vivo and may result in an unnecessary reduction in graft viability.

Alginate Microcapsules – How Can They be Improved?

Berit Strand[1], Yrr Mørch and Gudmund Skjåk-Bræk, PhD

1 Institute of Biotechnology, NTNU Trondheim N-7034 Norway

Due to the very gentle, simple and rapid immobilisation procedure alginate gel- or alginate polycation entrapment is still the most promising method for islets encapsulation. Long-time *in vivo* applications have, however, been hampered by early graft rejection due to overgrowth by fibroblasts, as well as by mechanical and chemical instability.

For improving the functionality of the alginate capsules it is essential to recognise that alginate is a family of poly-mers with a wide range in chemical composition, molecular size and, hence, in their functional properties. Selection and characterisation of the materials is therefore crucial. We will discuss how the functional properties of the capsules can be correlated with the composition, molecular size and purity of the capsule polymers as well as with the encapsulation techniques.

Some of the problems listed above could be overcome by having materials more homogeneous from the chemical and the macromolecular standpoints and displaying a wider range of compositions than those it is currently possible to extract from seaweed. A way to achieve this is by the molecular engineering of alginates using a family of recently discovered C-5 epimerases. These enzyme converts in-chain M into G residues and have the unique capacity to alter the entire polysaccharide backbone without breaking the macromolecular chain. By treating alginate with the enzyme mannuronan-C-5 epimer-ase, it is possible to increase the content and sequential arrangements of GulA, and hence, to alter both the flexibility of the chains and to introduce or enhance the co-operative ion-binding of the polymers. For the first time it is feasible to produce compositionally homogeneous alginates either as mannuronan, polymers with ManA-GulA as repeating structure, or alginates with extreme composition and sequential structure not found in Nature. Some functional properties of enzyme modified alginates, which are of significance for their use as immunobarrier will be discussed.

Macroencapsulation

Thomas Loudovaris, PhD

Theracyte, Inc.
Irvine, CA

If islet transplantation is the cure for insulin dependant diabetes (IDD) then a means of protecting them from the destructive immune system must be found. Immune suppression with drugs has demonstrated that islet transplantation can cure IDD, but at the expense of continuous treatment with drugs that have their own adverse effects. Encapsulation can provide a physical immune barrier that should eliminate the need for these drugs. Encapsulation comes in several forms, microencapsulation and macroencapsulation. This presentation will discuss macroencapsulation, its advantages, disadvantages and the different forms. The advantage of macrocapsules is that of safety. Every device can be tested and inspected for leaks or defects during manufacture and as well as after implantation, every device can be quantitatively removed. Also macrocapsules are usually made of are of durable materials such medical grade polymers.

Macroencapsulation comes in different forms, in the form of vascular implants, islets are enclosed around a permeable membrane tube implanted as a shunt in the vascular system. Blood flowing through the tube would provide glucose and nutrients to the islets, the islets would detect the level of glucose and release insulin appropriately. However, biocompatibility can be a serious issue with vascular devices as they can suffer clotting which can be life threatening.

Diffusion chambers have been around since at least the 1950's and were even used as means to interpret mechanisms of graft rejection as reviewed by Bernard Amos in 1962. Diffusion chambers are typically planar or tubular in design. Because of intimate contact between macrocapsules and the hosts tissues, biocompatibility is an issue that needs addressing. Biocompatibility has been approached either by adjusting the outer chemistry of the device membranes or adjusting the outer physical structure of the implant.

Once biocompatibility has been resolved, devices can be tested for the immune protective capabilities. Highly permeable membranes have been found to be protective of allografts but not xenografts. Membrane permeability can be

altered to be restrictive of immune molecules but this also restricts nutrient flow into the device, meaning less islets can be supported and making the device less practical in size. Alternatively, xenogeneic islets can be co-transplanted in devices with protective cells such as Sertoli cells or cells engineered to release immune suppressive factors in the vicinity of the device.

Also discussed will be the possibility that empty macrocapsules can be implanted and the islets loaded later after the device wound has healed.

Nanoperforated Materials

Tejal Desai, PhD

Boston University
Boston, MA

Type 1 diabetes is caused by the autoimmune destruction of pancreatic islet [beta]-cells. Destruction of [beta]-cells appears to result from direct contact with infiltrating T-cells and macrophages as well as from exposure to inflammatory cytokines and reactive oxygen/nitrogen species. Techniques for immunoisolation and immobilization of viable cells within semipermeable microcapsules have been developed using highly sophisticated polymeric and inorganic membrane based systems. However, most of these immunoisolation barriers will not protect cells from the damage caused by soluble inflammatory mediators and are difficult to control in terms of membrane pore size, path length, and density. An alternative approach is the use of nanoperforated materials as a platform for the delivery of cells, using techniques such as anodization, photolithography, or e-beam lithography. This talk will discuss various approaches to achieve nanoscale pores and their ability to allow sufficient diffusion of nutrients and oxygen and screen out immune molecules of interest.

What Can We Learn from Encapsulating Cells that Do Not Secrete Insulin for the Potential Treatment of Diabetes?

P. Aebischer, MD and W. Pralong, MD

Institute of Neuroscience
Swiss Federal Institute of
Technology Lausanne, EPFL
Lausanne, Switzerland

The encapsulation technology consists in surrounding cells by a semipermeable synthetic membrane allowing cells from either allogeneic or xenogeneic sources to be transplanted in the absence of pharmacological immunosuppression. This technique has been initially developed for the transplantation of insulin secreting cells in the context of diabetes. More recently, encapsulation has been applied for a variety of conditions including anemia, hemophilia, human growth hormone deficit and neurodegenerative diseases. The fact that these applications 1) do not rely on a tight feed-back controls and 2) require less cells has allowed various groups to develop the technology up to clinical trials. The following information was gained from this work. Contact inhibited cell lines are the preferred cell sourcing. Cell lines offer several advantages including unlimited availability, the possibility of rapid *in vitro* screening for the presence of pathogens from which cell banks are established, and the suitability for stable gene transfer using non-viral based recombinant DNA techniques. Initially, cell lines from xenogeneic origin were the preferred source as they provide an additional advantage since the transplanted cells will be rejected by the host immune system in the event of device breakage. The biosafety issues related to the presence of xenogeneic viruses preclude today the use of xenogeneic cells in humans. Human cell lines had to be developed while minimizing the oncogenic risk. To increase the safety level, the engineered cells typically express a suicide genes allowing their elimination in case of capsule breakage. An essential observation is the need to select clonal cell lineage for optimal adaptation to the harsh capsule environment. Cell lines can be pre-selected for low oxygen consumption. From the capsule point of view, open membranes lead to the best long-term survival as antibodies and complement are relatively inefficient in allogeneic conditions. Parameters such as the use of an appropriate capsule luminal matrix and the use of an initial low cell loading density do also significantly affect the long-term viability of encapsulated cells. All these observations should hopefully help to improve the outcome of transplanting encapsulated insulin secreting cells.

Assessment of Industry-wide Encapsulation Approaches

Scott R. King

Islet Sheet Medical, LLC.
San Francisco, CA

Islet cell encapsulation has long promised much but delivered little. Fulfillment of certain design criteria, e.g., control of permeability, is within the reach of several technologies; however, *a successful bioartificial pancreas must simultaneously fulfill several disparate yet stringent design criteria*. Most researchers have focused on a single facet of the problem and therefore have produced a bioartificial pancreas that fails to fulfill other essential criteria.

Certain design criteria are absolute: if not fulfilled the device will unavoidably fail, usually for reasons that follow from immutable laws of physics in relation to mammalian cell physiology. For instance, the existence of an unstirred hydrogel barrier greater than 200 micrometers thick between the islet and the surrounding blood-perfused tissue effectively renders the islet useless because of insufficient oxygen flux for islet function. Similarly, a device that provokes a fibrotic inflammatory response dooms the islets inside. Fulfillment of all such essential design criteria does not guarantee success. But *failure to fulfill a single essential criterion leads inevitably to failure*.

The presentation will describe the known essential criteria (listed below) and related physics including key concepts of oxygen diffusion. I will then selectively review historical and ongoing work on the bioartificial pancreas to identify designs that cannot work. It is hoped that work on designs that cannot work will be abandoned to make resources available for designs that can work in the expectation that such a reallocation of resources will speed progress.

These essential design criteria have been published by King *et al.* (Graft 4:491 (2001)):

We believe that any bioartificial pancreas intended to function for an extended time in a large animal must achieve, at a minimum, the following criteria:

- The process for making the device does no damage to islets as assessed by viability staining and glucose-stimulated insulin secretion.

- Minimal fibrotic reaction to a cell-free device is seen at 2 weeks and 8 weeks. The integrity of the device must be undiminished.

- Permeability of the membrane barrier minimally reduces diffusivity of insulin, significantly impedes diffusion of IgG, and substantially impedes diffusion of complement.

- Host immune cell contact with the encapsulated tissue is absolutely excluded.

- The center of every islet is less than 200 μm from the outer surface of the capsule.

- At least 20% of the total capsule volume is comprised of islets.

These criteria must be met or there can be no possibility of clinical success.

Co-transplantation of Porcine Islets with Sertoli Cells in Type 1 Diabetic Patients Produces Atypical Humoral Immune Responses as Assessed by Elicited Anti-pig Antibodies

D.J.G. White[2], FRC Path PhD, R.A. Valdes-Gonzalez[1], L.M. Dorantes[1], G.N. Garibay[1], E. Bracho[1], L. Teran[1], L. Silva[1], P. Valencia[1], L. Copeman[2],

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2 Robarts Research Institute University of Western Ontario Ontario, Canada

Protocol: 12 patients with type 1 diabetes were transplanted with neonatal pig islets and sertoli cells (35-100/islet) derived from a SPF herd of large white pigs. The cells were inserted into neovascularised collagen tubes created by implanting a closed stainless steel mesh containing an inner Teflon stent subcutaneously 8 weeks prior to transplantation. No immunosuppression was given. 11 patients received a second transplant 6 months after the first procedure. 6 of these recipients have a significant reduction in the requirement for exogenous insulin at more than 2 years post transplant with one patient being insulin independent for more than one year. Patients were monitored for lytic antibodies to porcine RBC and anti-GAL IgM and IgG antibodies. IgG isotypes were measured by FACS analysis using a pig kidney cell line as targets.

Results: All patients demonstrated an increase in anti-pig antibodies in response to the first transplant. Mean GAL IgM responses rose from a pre-transplant value of 1:90 to 1:180 (1 $\log_2$). This declined to pretransplant levels (1:90) by 6 months. These anti-GAL IgM responses were significantly ($P<0.01$) less than those previously reported for islet transplants alone (in immunosuppressed patients) where the titre increased at one month from 1: 85 to 1: 980. Anti-GAL IgG responses in the two patient populations were comparable at one month. In our study mean titres increased from 1:150 to 1:3200. By 6 months post transplant these had declined to a mean titre of 1:750. IgM Responses at one month to a second transplant were similar to those seen after the first transplant. Thus anti-GAL IgM mean titres increased from 1:90 to 1:190 (1.1$\log_2$). In contrast IgG titres increased from a pre-transplant level of 1:750 to 1:2500. Thus these anti-GAL IgG responses to a second transplant (1.7 $\log_2$) were significantly less than those induced by the first transplant (4.4 log2 $P=0.03$). Anti-pig haemolytic antibodies mimicked the results seen with anti-GAL IgM.

Conclusion: Patients transplanted with a combination of porcine islets and Sertoli cells produce atypical humoral immune responses to their graft. Anti GAL IgM responses are significantly reduced, as is the secondary response by Anti-GAL IgG.

Drug Incorporated Islet Capsules

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University of Utah
Salt Lake City, UT

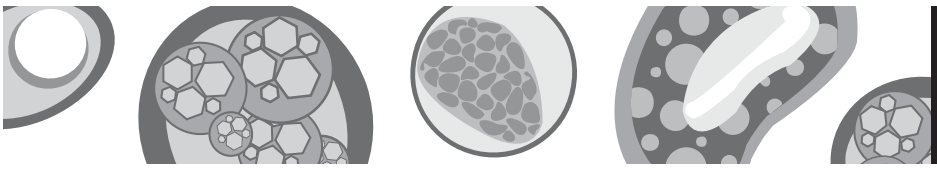
Biohybrid artificial organs, encapsulated foreign cells in immunoisolating polymeric capsules assume that physical isolation of transplanted cells from humoral and cellular immune responses reduces the use of immunosupressing agents. When the cells or tissues are subject to autoimmune reactions, as it happens in insulin dependent diabetes, the physical immunoisolation becomes important for cell transplantation. Unsolved problems associated with this approach include cell sources, biocompatibility issue of the encapsulating materials, incomplete immunoisolation, large volume, hypoxia induced cell necrosis, shedding of cell protein fragments from lysed cells, and the replacement of dead or exhausted cells. As a partial effort to overcome some of these difficulties, drug conjugated polymers for co-encapsulation with pancreatic islets have been employed.

Crosslinked hemoglobin (Hb-C): To enhance the viability and insulin-secretory response of islets by facilitated oxygen supply, an oxygen carrier, hemoglobin cross-linked (Hb–C) via a bifunctional poly(ethylene glycol) (PEG) was synthesized, resulting in Hb–C of 102,000 Da. The coencapsulation of Hb–C (0.25 mM) and islets in alginate–PLL–alginate capsules improved insulin secretion from the islets. At the end of *in vitro* long-term culture (8 weeks) of the microcapsules at 300 mg/dL (G) glucose stimulation and pO_2=40 mmHg, the islet viability and insulin secretion were compared with control islet microcapsules (without Hb–C) and the results show islet viability of about 380 percent and the rise in insulin secretion of 55 percent over control after 8 weeks. Introducing the Hb–C into islet microcapsules also showed a better insulin secretion pattern and a faster response to glucose stimulation than the control microcapsules. In addition, islet viability and insulin secretion in the microcapsules with Hb–C was not prone to the attack of nitric oxide (NO) generated by adding S–nitroso–N–acetylpenicillamine (SNAP: a NO donor) in the culture medium. To briefly examine the efficiency of Hb–C, 500 microencapsuled islets (25–30 percent of islets required for normoglycemia reported in most articles) were intraperitonially transplanted in mice. After transplantation of islet microcapsules, blood glucose levels and body weight of the recipients were monitored. The blood glucose levels were sharply increased after streptozotocin injection (200 mg/kg). While, in the case of diabetic mice, hyperglycemia (over 500 G) persisted throughout the experimental period, diabetic mice receiving islet microcapsules with Hb–C showed a rapid decrease in the blood glucose level and gained normoglycemia within 1 week, which was maintained for up to

8 weeks. However, islet microcapsules without Hb–C recovered only partially from the high blood glucose levels, followed by gradual increase in the glucose levels from week 3 after transplantation.

Sulfonylurea/polymer conjugate (SUP): The SUPs are expected to increase the insulin secretion activity of islets, especially at low glucose concentration. SUP1 increased the insulin secretion preferentially at low glucose concentration. The amount of secreted insulin by SUP1 (10 nM SU equivalent) showed no significant difference from that of glibenclamide at both low (50 G) and high (200 G) glucose concentrations although more insulin was secreted by SUP1 than by glibenclamide at low glucose concentrations. Islet microcapsules with or without SUP2 (a more water soluble conjugate) were cultured with RPMI 1640 medium (200 G glucose) for 4 weeks to investigate the long-term effect of SUP2 on insulin secretion. Islet microcapsules with SUP presented higher insulin secretion over 2 weeks than those without SUP. At weeks 2 and 4, islet microcapsules with or without SUP were stimulated by low (50 G) and high (300 G) glucose. As a result, the basal level for both islet microcapsules gradually decreased over time. Interestingly, at 300 G glucose concentration, the islet microcapsules with SUP2 maintained their insulin-secretory ability till week 4, while those without SUP2 gradually decreased the insulin secretion.

Glucagon-like peptide-1 (GLP-1)/polymer conjugate (VAPG): GLP-1/polymer conjugate (VAPG) was designed to enhance the functionality of islets at high glucose concentration because GLP-1 increases the insulin secretion in a glucose-dependent manner. The pancreatic ß-cells contain specific receptors for GLP-1 that induce cAMP formation, insulin biosynthesis and insulin secretion. The VAPG was synthesized by conjugation of GLP-1(7-37) to a water-soluble polymer, poly(N-vinyl pyrrolidone-co-acrylic acid) (VAP)-graft-PEG (3.4 KDa). In the study of the glucose-dependent insulinotropic activity of VAPG, it was clear that, while both GLP-1 and VAPG had no effect on islet stimulation at low glucose concentration, high glucose levels stimulated insulin secretion from islets assisted by GLP-1 or VAPG. The insulin secretion, stimulated by VAPG, was enhanced up to 184 percent compared with the control (neither GLP-1 nor VAPG) at high glucose concentration (300 G). However, the bioactivity of VAPG was much less than that of GLP-1 because the random chemical conjugation to GLP-1 possibly leads to the deformation of a structure specific toward the GLP-1 receptors, which could weaken the binding affinity of GLP-1 to its receptors. A dose-response experiment with various concentrations of VAPG (0.1, 1, 10, 100, 1000 nM; GLP-1 equivalents) revealed that the concentration of GLP-1 in VAPG required to induce the insulin secretion was at least 100 nM. The ED_{50} of VAPG was about 54.8 nM and the insulin secretion with over 1000 nM GLP-1 concentration showed saturation.



Poster Abstracts

Biocapsule for Immunoisolation of Islet Cells Using Silicon Nanopore Membranes

Francis J. Martin, PhD

iMEDD Inc.
Columbus, OH

Several investigators have pursued the feasibility of using a macro-sized capsule containing pancreatic endocrine cells encapsulated within a diffusion membrane barrier to protect the cells from immunological rejection. The goal is to achieve euglycemia in a transplant recipient without the use of immunosuppression. We describe a unique type of macro-encapsulation device called a Biocapsule that uses a microfabricated silicon membrane with pores that are truly nanoscale. An implantable device suitable for rodents and a second device for use in small dogs were constructed using 5 µm thick membranes with 18 nm-sized pores. The diffusion properties of the membrane were determined for glucose, insulin, IgG and Complement species, and these diffusion data were compared to other membranes previously used for macro-encapsulation of cells. The silicon nanopore membrane was found to be superior to other membranes tested. Cell viability data in a Biocapsule were also obtained for rat islets and insulinoma cells (ßTC3). These early *in vitro* viability results were promising, indicating that long-term cell survival could potentially be achieved. Using a standard perifusion system, we obtained excellent dynamic insulin output profile data for a Biocapsule containing rat islets in response to a glucose challenge. These dynamic data were obtained after the Biocapsule was held two weeks in culture. Finally, we demonstrated initial short-term euglycemia in a diabetic rodent model using the Biocapsule implant.

Development of Encapsulated Human Islets: Effect of Material Selection on Product Performance

W.G. Tsang,PhD, C.C. Huntenburg, T. Zheng, A. Schaeffer, Y.P. Wang, K. Lim, E. Leoncio and P. Tram

AmCyte, Inc.
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Successful islet encapsulation requires proper selection of alginate and its polyelectrolyte counterpart such as PLL or PLO among others. Efforts have been made to address manufacturing and characterization as well as to investigate the effect of material characteristics on capsule performance. The manufacturing and characterization of PLL and PLO has been reported[1] and the effects of their characteristics on capsule properties have been investigated. In general, the length of pendent primary amine side chain affects the density of the membrane-forming polyelectrolyte complex and therefore the pore size of the capsule membrane.[2] The size (MW) of PLL and PLO determine the thickness of the capsule membrane and therefore the strength and diffusion characteristics of the membrane . Alginate, however, is a complex natural product with limited availability of well-characterized material. Despite recent progress made on alginate characterization[3], the effect of alginate characteristics on capsule properties remains unclear.

In a recent study we investigated the effect of two blends of alginate on capsule performance. Alginates were purified and lyophilized from commercially available starting materials. They were characterized by GPC for MW and polydispersity.[4] Isomeric composition, viscosity, concentration and purity (protein and endotoxin) were determined. Two formulations of microencapsulated human islets (A1 and A2) were made from two distinct alginate mixtures. They were blended from high G and high M alginate to achieve required viscosity. Islets were from the same batch of isolated human islets. PLL was kept constant for both formulations. *In vitro* and *in vivo* performance of A1 and A2 encapsulated islets were investigated. They were maintained in culture for 3 months and subjected to *in vitro* perifusion analysis to determine insulin and c-peptide release profiles. They were then transplanted into non immune suppressed STZ induced diabetic C57B mice.

For *in vitro* perifusion analysis, A1 has an insulin release profile closer to that of non-encapsulated islets, while A2 has a much-delayed (flattened) release profile. Also, A1 has a c-peptide release profile similar to its insulin release profile, while A2 has a more rapid c-peptide release profile than its insulin release profile. The above differences suggest that A2 has more restricted diffusion characteristics than A1. While the release kinetics of insulin and c-peptide of A1 and A2 were obviously different, the integration of overall c-peptide release suggests similar amounts of c-peptide/insulin were secreted from intra-

capsular islets in A1 and A2 at the time of analysis. For the *in vivo* analysis, A1 and A2 significantly lowered the BG level of transplanted diabetic mice to normal level while empty capsules did not. Analysis of retrieved capsule showed higher insulin release and more surviving endocrine cells in A1 than A2. Some cellular attachment was observed on retrieved grafts. There were slightly more cell deposition on A2 than A1.

We have demonstrated that the properties of alginate affect the performance of encapsulated islets both *in vitro* and *in vivo*. Alginate manufacturing, characterization as well as the correlation of specific alginate characteristics with capsule performance should be an integral part of investigations in the development of encapsulated human islets.

[1] "The Synthesis of Poly(L-Ornithine Hydrogenbromide)" Pease et al., Macromolecular Synthesis, Volume 11, 63-68 (1990)

[2] "Encapsulation of Materials" W.G. Tsang and A.W. Shyr U.S. Patent 4,663,286 (1987)

[3] ASTM Designation: F 2064-00; "Standard Guide for Characterization and Testing of Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Products Application"

[4] "Molecular Mass Distribution of Sodium Alginate by High-Performance Size-Exclusion Chromatography" Ci et al., J. of Chromatography A. 864 (1999)

ASTM Standards and Guidelines for Encapsulation Using Alginate

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The American Society for Testing and Materials International (ASTMi, www.astm.org) through Committee F04 Tissue Engineered Medical Products (TEMPs) is making a concerted effort to establish standards and guidelines for the entire field of tissue engineered medical products. Biocompatibility and standard chemical properties of biomaterials used as matrices, scaffolds and immobilizing agents in TEMPS are a concern. Therefore, the ASTMi has established a number of task groups to produce standards and guidelines for such biomaterials. Alginate is a naturally occurring biomaterial that may be used for encapsulation of living cells to form an artificial organ TEMP, such as encapsulated pancreatic islets. In order to aid in successful clinical applications and to help expedite regulatory approval of the devices, the alginate used must be fully characterized and documented. Critical parameters such as guluronic/mannuronic content, molecular weight, polydispersity and viscosity in addition to more general parameters such as dry matter content, heavy metal content, bioburden and endotoxin content are described in ASTM documents, as well as a general guideline on the encapsulation process.

The ASTMi Standard Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications (F2064) provides guidance on selection of testing methodologies and safety criteria. This guide has been recognized by the FDA, Center for Devices and Radiological health (CDRH). Important parameters such as monomer composition, sequential structure, molecular weight and molecular weight distribution are treated in several Standard Test Methods: F2259: Standard Test Method for the Determination of Monomer Sequence and Composition of Alginate by ^{1}H NMR, and WK964: Standard Test Method for the Determination of the Molecular Weight of Sodium Alginate by Size Exclusion Chromatography with Multi-angle Light Scattering Detection (SEC-MALS).

Finally, several methodologies describing how to gel alginate are outlined in F2315: Standard Guide for the Immobilization or Encapsulation of Living Cells or Tissue in Alginate Gels. Here, parameters that can influence the performance of the final application, such as viscosity, molecular weight, monomer sequence, gelling ion, gel strength, etc., are described.

In summary, the innate characteristics as well as the functional properties of the biopolymer will influence the performance of the final product and its use. These Standards and Guidelines represent a part of the effort on behalf of the ASTM and other interested parties to ensure quality and standardization in TEMPs. The process of manufacturing, characterization and regulatory issues of relevance will determine the successful acceptance for use of these biopolymers in artificial organ and tissue engineering applications.

Cell Encapsulation in Alginate Using an Electrostatic Bead Generator

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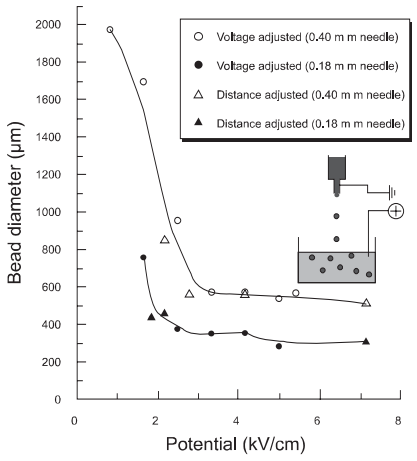
One application utilizing the gelling properties of alginate is the immobilization or encapsulation of living cells to form artificial organs and cell therapy constructs. Here, cells in an alginate solution can be entrapped inside an alginate gel bead by dripped into a bath of calcium chloride where gelling occurs instantaneously. This alginate gel "biofactory" can then be implanted into an animal or man and act as a continuous production system for, for example, insulin. Such beads have been implanted into animals and diabetic patients. The biofactories have been seen to function *in vivo* for at least one year.

For most uses, and in particular those involving immobilization of living cells, the size of the droplets needs to be controlled in some manner. Smaller beads or capsules have the advantage of a higher surface to volume ratio allowing good transport of essential nutrients and are also less fragile. Diffusion limitations within larger beads may limit cellular metabolism as the lack of essential substances like oxygen supply to the interior of the beads may lead to cell death as a result of consumption from the surrounding cells. Therefore a good control of bead size and shape is crucial and should be carefully controlled. The electrostatic bead generator is one alternative in the production of small spherical alginate beads containing biological materials.

The bead generator consists of a power unit of 0-10 kV, a potentiometer for fine-tuning of the voltage, an autoclavable needle holder, and a safety enclosure with an electrical safety switch. The alginate solution is fed into the instrument in a controlled manner using a syringe pump. A magnet stirrer underneath the gelling bath to keep the beads separated during gelling. The basic principle of the instrument is the use of an electrostatic potential to pull the droplets from a nozzle tip. An electrostatic voltage of a few kV is set between the nozzle feeding the alginate solution and the gelling bath. The droplet size is also largely determined by selecting an appropriate nozzle size. Using this type of instrument, beads below 200 µm and with



a small size distribution may be generated. The desired bead size is obtained simply by adjusting the voltage (electrostatic potential) of the instrument. Bead size will be dependent of the following parameters: voltage and distance between the needle tip and the gelling bath, solution viscosity, flow rate of the solution as well as needle diameter. A suitable distance between the needle tip and the gelling bath for this instrument is around 10 mm. The appropriate bead size is selected by voltage adjustment. In the figure, the effect on the average bead diameter as a function of voltage is shown. As can be seen bead diameter decreases with smaller needle diameters and increasing voltage. The bead generator has been used successfully in several studies involving immobilization of living cells.

Efficacy Study for Microencapsulated Adult Porcine Islets Using Microislet's Proprietary Formulation MPF2 in Mice

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Transplantation of encapsulated porcine islets is a potential treatment for individuals with type 1 diabetes. MicroIslet Inc. has developed a new proprietary alginate based encapsulation formulation with improved efficacy and biocompatibility in small animals. The encapsulation development activities included formulation refinement, islet loading studies, and bead structure optimization. This enhanced formulation was tested *in vitro* and using *in vivo* animal models.

Islets were purified from pig pancreata and encapsulated using MicroIslet's proprietary encapsulation technology. The encapsulation process has a very high degree of reproducibility resulting in microcapsules with a mean diameter of 630 micron, and a mean islet loading of 1.5 islet equivalents (IE). The encapsulated islets are consistently greater than 90–98% viable for 5 days after isolation. Longterm *in vitro* viability was maintained at a minimum of 80% for 4 weeks in culture.

Over 100 diabetic (STZ induced) C57BL/6 mice were successfully transplanted with encapsulated porcine islets. The encapsulated islets were transplanted intraperitoneally with islet doses ranging between 1,000 and 10,000 IE/mouse. At doses of 2,500 IE/mouse and above, a 100% success rate was achieved for the first two weeks after transplantation. Graft function was sustained for 100 days in 80% of the animals. These graft survival data suggest that a dose of 2,500 IE/mouse is effective to achieve extended normoglycemia in mice. Glucose tolerance tests conducted by administering glucose into the peritoneum demonstrated rapid and unhindered secretion of insulin into the blood stream. Efficacy has been observed for longer than 6 months in this animal model, illustrating the exceptional quality and biocompatibility of this encapsulation system.

Adult porcine islets encapsulated in MicroIslet's proprietary formulation (MPF2) are a viable means for transplantation of xenogeneic tissue.

Naked and Encapsulated Adult Porcine Islets Render Nod/Scid Mice Normoglycemic

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The concept of islet allotransplantation as a treatment for Type I Diabetes has been demonstrated as feasible by the pioneering work done at various sites in the US and Canada during the last five years. However, there still exists a considerable shortage of tissue for transplantation. The focus of MicroIslet, Inc. is to meet the increased demand for endocrine tissue by providing immune-isolated adult porcine islet xenografts. To date, using our semi-automated isolation system, we have obtained yields of 370,006 ± 162,628 IE with approximately 90% purity in 31 consecutive isolations (>90% successful islet isolation rate). Encapsulation of porcine islets in 2 types of Ca^{2+} -alginate microcapsules were tested for function in streptozotocin-induced diabetic mouse models. Initial studies were performed with immune deficient NOD/SCID mice to test the hypothesis that the naked islets were of high quality and that the encapsulated islets would survive and function *in vivo*. In 4 experiments, naked and encapsulated porcine islets were transplanted into the peritoneal cavities of 47 immunodeficient, diabetic mice (NOD/SCID). Animals received varying amounts of graft tissue ranging from 500 to 10^4 IE per animal, with a return to normoglycemia occurring in 100% of the animals within 2 days of transplantation. These animals maintained graft function for more than 6 months post-transplantation. Animals were transplanted with islets encapsulated in two proprietary microcapsule formulations MPF 1 (PLO coated Ca^{2+} -alginate bead) and MPF 2 (Ca^{2+} -alginate bead). After 185 days, the grafts were explanted and upon examination of the beads, only about 5-10% of the explanted material exhibited any loss of structural integrity. The return of diabetes was observed when the grafts were explanted. Using animals without an intact immune system, we have validated the quality and integrity of the pig islets and encapsulation. These studies also demonstrate excellent islet compatibility with 2 microcapsule formulations. We have obtained an initial estimation of dose required to treat the diabetic mouse and have validated the sterility and quality of the product for successful transplantation in the NOD-SCID mouse model. This animal model is an ideal system to test any future refinements in the isolation and encapsulation procedures.

Islet Microencapsulation by Inverted Selective Withdrawal

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Although increasingly successful, islet transplantation continues to be hampered by inadequate donor material and continued immunosuppressive requirements. Immunoisolation by microencapsulation has met with experimental success, which has been limited by factors such as incomplete encapsulation and fibrotic response to capsules. We have been studying microencapsulation by modification of the recently described technique, "selective withdrawal." Selective withdrawal occurs when aspiration force is applied to a liquid interface, resulting in a thin spout of liquid in the phase (layer) opposite the aspirator. When the spouting phase contains particles, physical instability occurs in the spout, resulting in beads of liquid conformally surrounding the particles. Photocrosslinking of biocompatible liquid polymer (polyethylene glycol) droplets allows generation of stable microcapsules. Therefore, we propose to determine the ability of a modification of the selective withdrawal method to coat pancreatic islets, and to test these pancreatic islets for *in vitro* and *in vivo* function vs. non-encapsulated islets. Technical factors thus far considered in encapsulating islets as distinct from non-biological particles as originally described have included 1) alternative geometries, including inverted selective withdrawal, to coax islets to the liquid interface, 2) variable phase viscosities affecting spout characteristics including thickness, flow rate and particle entrainment within the spout (a highly viscous oil lower phase has worked best in our hands), 3) variable effluent collection geometries to allow in-line photocrosslinking of microcapsules, and 4) identification and optimization of phase variables including flow rates and interface height to achieve optimal coat thickness. After multiple design iterations and optimization of these modifications, we have been able to reproducibly encapsulate islets via selective withdrawal. Microcapsule assessments, including completeness of encapsulation, coat thickness, pore size, and *in vitro* and *in vivo* islet function (compared with non-encapsulated islets) are currently in progress.

Tissue Engineering a Pancreatic Substitute: Cell Sources and Enabling Technologies

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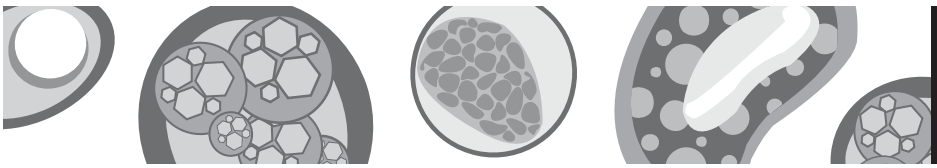
A pancreatic tissue substitute for treatment of insulin-dependent diabetes has significant potential in providing a less invasive, more physiologic regulation of blood glucose levels than insulin injections. The core, enabling technologies needed for developing such a substitute depend strongly on the type of cells used. With allo- or xenogeneic cells, encapsulation in permselective barriers improves immune acceptance, as it inhibits passage of antibodies and precludes passage of cytotoxic cells. However, immune protection is not complete, and some immune suppression may still be needed to prolong survival of the implant. Potentially autologous non-beta cells targeted by gene transfer vectors or retrieved as a biopsy from the patient and genetically engineered *ex vivo* relax the immune acceptance problems but pose challenges regarding the secretion of insulin in response to physiologic stimuli. Stem cells constitute another possible cell source, however, their differentiation into beta-like cells remains a significant challenge.

Our group focuses on developing a system of recombinant, potentially autologous non-beta cells exhibiting both acute and sustained insulin secretion dynamics; and on developing methods to non-invasively monitor pancreatic tissue implants. Non-beta cells engineered for insulin secretion include hepatic cells and intestinal endocrine L cells. To improve the secretion dynamics of hepatic cells, we have pursued the manipulation of preproinsulin mRNA stability and the encapsulation of cells in bioactive materials, which serve as glucose-responsive barriers to insulin release. With enteroendocrine L cells, we have demonstrated their ability to secrete recombinant insulin with similar kinetics as endogenous glucagon-like peptide-1 in response to post-prandial signals. Non-invasive monitoring of pancreatic substitutes by NMR imaging and spectroscopy has proven valuable in assessing construct function *in vitro* and, more importantly, post-implantation *in vivo*. The importance of pursuing these research directions in parallel and in an integrated systems fashion is discussed.



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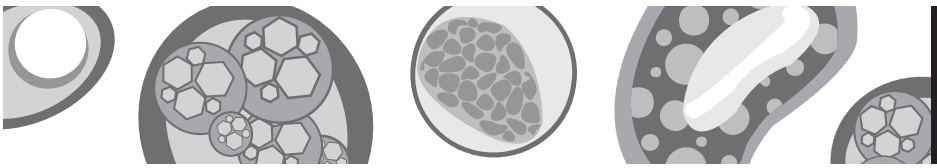

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