ASX:LCT – OTC:LVCLY

Global Regulatory Challenges and Opportunities

October 2009

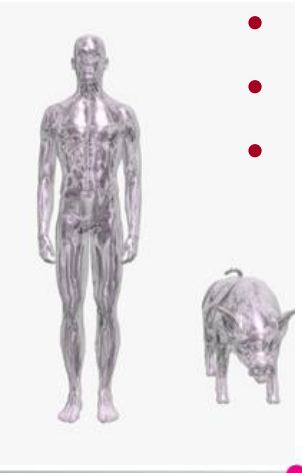
Melbourne

Paul LJ Tan , CEO

Cell Therapeutics with Encapsulation

- LCT is a cell-based therapeutics company
- Cells from high health status pigs
- Functional cells are encapsulated in alginate microcapsules
- Microencapsulated cells may be implanted without immunosuppressive drugs

- GMP Manufacturing Unit in Auckland, New Zealand
- Head office in Sydney, Australia
- Laboratories in Perugia, Italy and Rhode Island, USA
- Listed on ASX and OTCQX



Replacing Lost Cells

LCT Products in Development and Clinical Trial

DIABECELL®

- Porcine islet cells within micro-capsules injected into abdomen to form artificial insulin producing tissue
- In Phase II Clinical Trial

NeurotrophinCell®

- Porcine choroid plexus cells producing neurotrophins implanted to repair endogenous brain and nerve tissue
- Pre-Clinical Development and Research

Encapsulation services

- R&D collaboration with third parties

Program for a GMP Certified Product

Regulatory Guidelines

US FDA Guidance for Industry on the Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans 2003

US Department of Health & Human Services Secretary's Advisory Committee on Xenotransplantation (SACX) Recommendations, 2004

US Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation 2001

WHO Guidance on Xenogeneic Infection/Disease Surveillance and Response: A Strategy for International Cooperation

The European Agency for the Evaluation of Medicinal Products, Points to Consider on Xenogeneic Cell Therapy Medicinal Products

New Zealand Government Gene Technology Advisory Committee Xenotransplantation Checklist – Addendum to Guidelines for Application to GTAC

Draft Guidelines for Preparation of Applicants Involving Clinical Trials of Xenotransplantation in New Zealand

Regulatory Approvals for Porcine Cell Therapeutics

NEW ZEALAND

Medsafe Good Manufacturing Practice (GMP) certification for manufacture of DiabeCell® for use in humans:

IANZ, International Accreditation New Zealand: accreditation for Molecular Diagnostic Laboratory to carry out diagnostics tests relevant to xenotransplantation

GTAC, Gene Technology Advisory Committee through Medsafe:

- Ethics and cultural consideration
- Safety: pig herd, porcine endogenous retrovirus and diagnostic assays
- Public Health, long term monitoring
- Pre-clinical Data/Efficacy

Regional Ethics Committee including Maori Review Research Committee

Approval 2007

National Health Committee

- Reviews safety of xenotransplantation and safety of risk management procedures

Minister for Health

- International peer Review
- Final approval for clinical trial to proceed

Source of Tissue and Cells

Required description of porcine herd

Herd	source herd breed or strain age endogenous retrovirus
Facilities	breeding facilities environment
Operations	husbandry feed exogenous infectious screen endogenous retroviruses screening : standardized assays: PCR, antibody assays, Infectivity tests

High Health Status Closed Pig Herd

High health status pigs: US FDA Guidelines 2003

- **Source Herd:** Absence of xeno-relevant viruses, bacteria and parasites. Does not secrete pig endogenous retroviruses. A closed herd bred in isolation (across 2 facilities): 3 yr health records and regular monitoring . Three generations without mammalian content in feed. NULL pigs
- **Pig Breeding Facilities and Operations:** Two herds in North & Southland, Concession to remaining pigs on Auckland Island
- **Health Monitoring** of pig herd. Panel of tests by accredited laboratory. Donor database.
- **Xenotransplantation Risk Assessment and Risk Management Strategy** Report by Morris, Jackson, Stevenson, Pearce: Professor Roger Morris, Massey University

BioCertified Pig Herd

LCT Designated-Pathogen-Free Pig Breeding Facility

Accredited Diagnostic Labotatory

Virus	Prevalence in general pig Population (PCR)		Prevalence in BioCert herd (PCR)	
	> 20 weeks	7 days	>20 weeks	7 days
PCMV	70%	Not detected	Not detected	Not detected
PLHV	95%	Not detected	Not detected	Not detected
PCV1	Not detected	Not detected	Not detected	Not detected
PCV2	96%	10%	Not detected	Not detected
HepEV	90% (14 weeks)	Not detected	Not detected	Not detected
EMCV	Not detected	Not detected	Not detected	Not detected
Conventional pathogens				
AuJD				
BVD	Not detected	Not detected	Not detected	Not detected
PPV	Not detected	Not detected	Not detected	Not detected
Toxoplasma gondii	Present	Not detected	Not detected	Not detected
Leptospiroses	Present	Not detected	Not detected	Not detected
Mycoplasma hyopneumoniae	Present	Not detected	Not detected	Not detected
	Present		Not detected	Not detected

PERV

Porcine endogenous retroviruses

Low proviral copy number

- Tested herds: 40-50
- Auckland Island pigs: 3 - 30

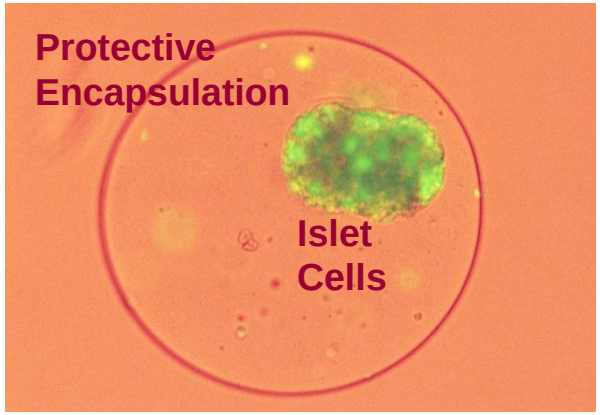
No detectable secreted virus

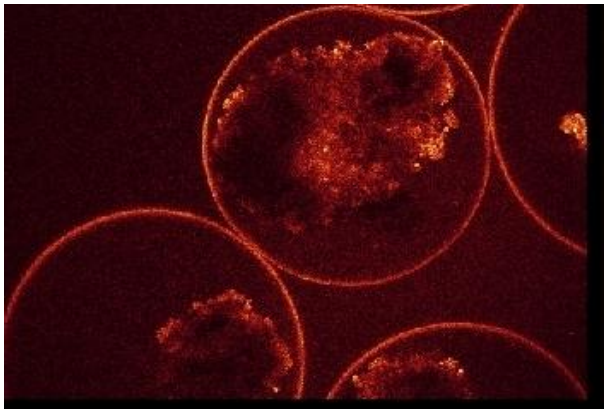
- No PERV RNA in blood
- No c-type reverse transcriptase in culture supernatants or proliferating cells
- Gold standard infectivity tests negative with porcine and human target cells

Null pigs without the PERV C recombination locus

- PERV C 2213 locus negative

DIABECELL® for Insulin Dependent Diabetes



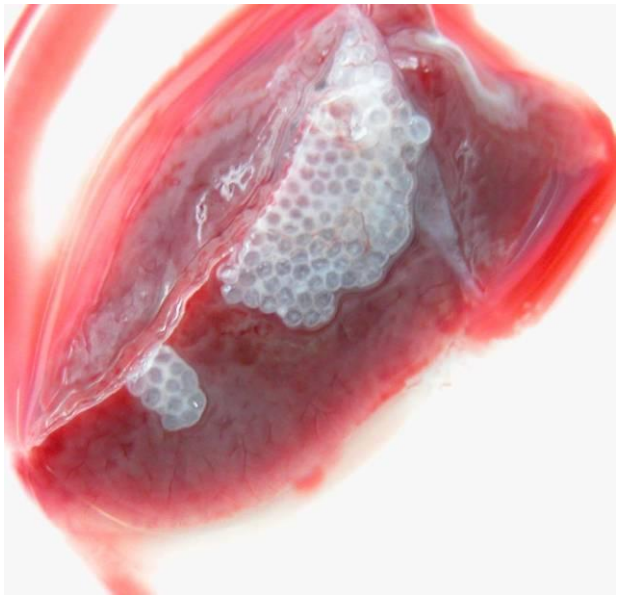


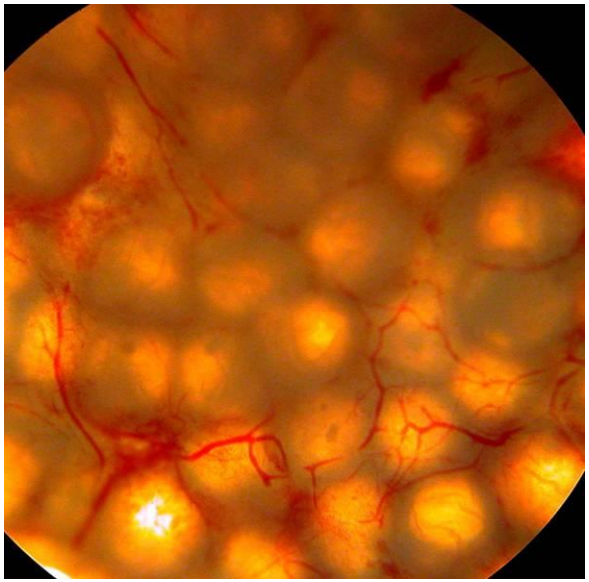
- Cells excised from piglets and coated in patented alginate-based gel to form microspheres
- Microspheres injected into patient using a laparoscope incorporating endoscopic placement
- Engineered structure of microspheres enables nutrients to reach cells but prevents immunological rejection of cells
- Immunosuppressants **not** required
- Cells function naturally in body

DIABECELL® Pre-Clinical Studies

Activity *In Vivo*

Injected Islet Cells Attach to Tissue and Receive a Blood Supply that Maintains Function and Long Term Survival

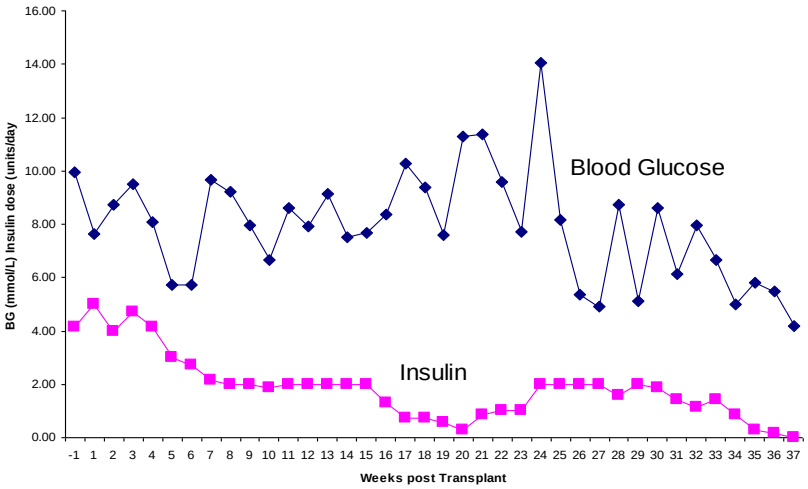




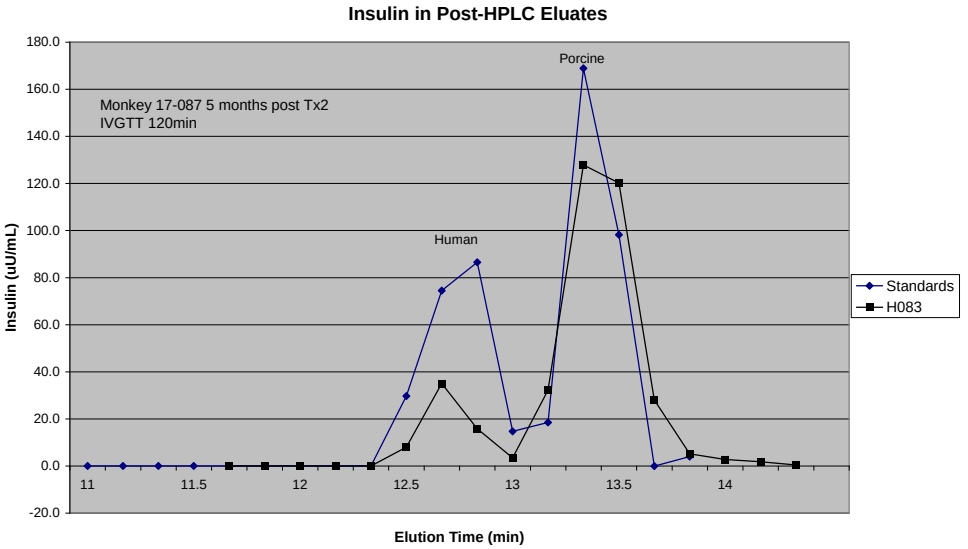
Figures show DiabeCell microcapsules on the surface of the rat liver. Blood vessels grow into the cluster of encapsulated islets which function as an insulin-producing artificial tissue

DIABECELL® in Animals

Dose Response in Streptozotocin-Induced Diabetic Animals



Diabetic cynomolgous monkey
insulin independent after implants



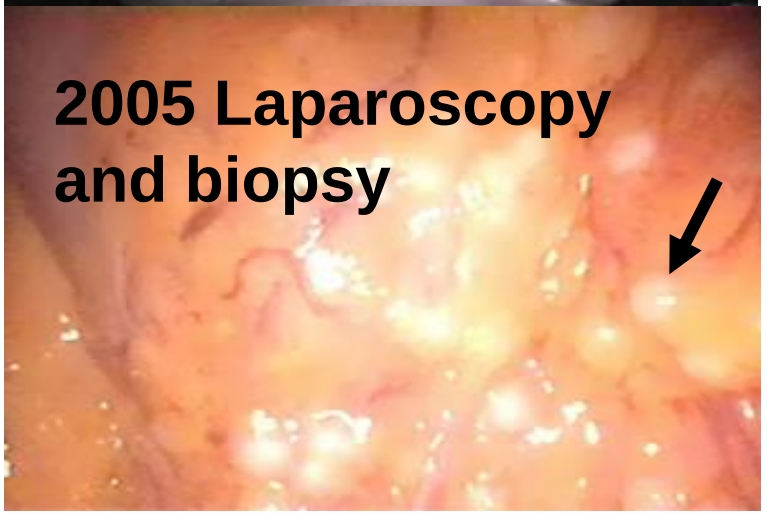
Demonstration of porcine insulin in blood sample
taken at 120 min after oral GTT

Non-human primate studies are not permitted in New Zealand
and were conducted with Maccine Ltd, Singapore

DIABECELL® Prototype Implanted in Human

Case Study published in *Xenotransplantation*, March 2007

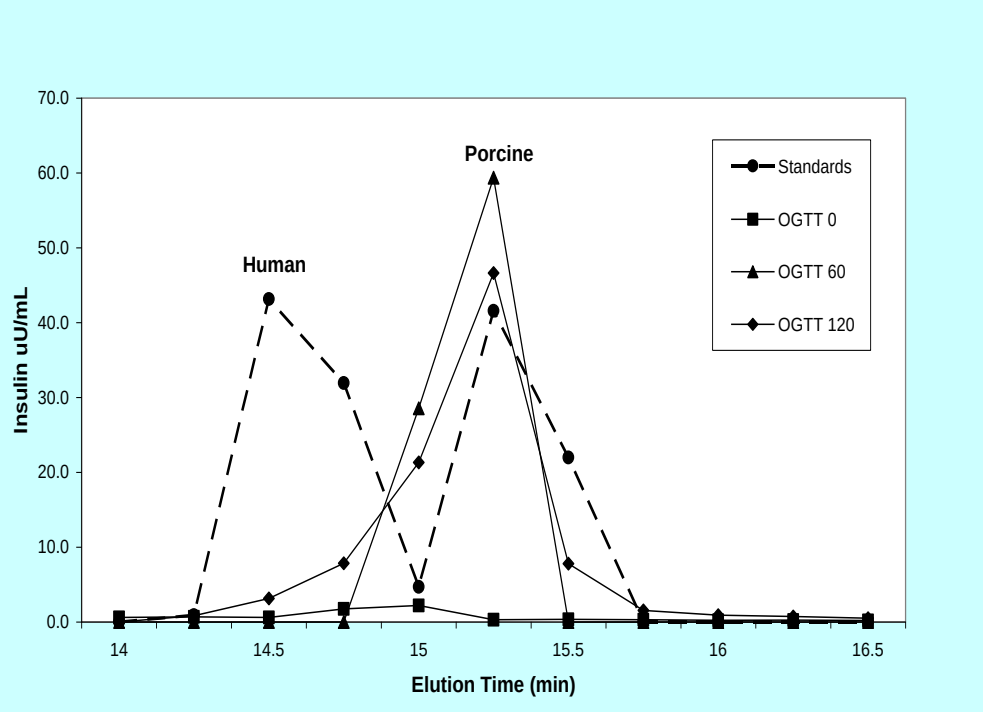
- 1996 implant of prototype product in abdomen of type 1 diabetes patient with poor glucose control
- Patient showed long-term clinical improvement
- In 2005, biopsy showed live islet cells and pig insulin was detected in blood
- Longest reported survival and function of cell implant without immunosuppression drugs

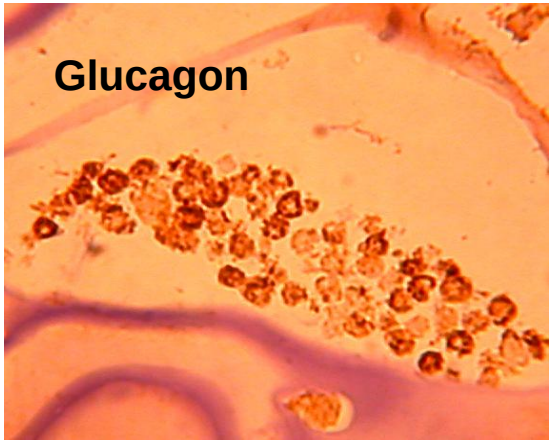


DIABECELL® Prototype Functional after 10 yr

Case Study published in *Xenotransplantation*, March 2007

Retrieval of viable cells producing insulin





Manufacturing Accreditation

GMP certification annual recertification and audit as required in specific jurisdiction

- **FACILITIES: Manufacturing and cell processing**
animal preparation, surgical theatre, clean room design, validation laboratory, diagnostic laboratory, stores, designated areas for cleaning ands sterilization, floor plans, flow of staff and goods

- **MATERIALS: Information on safety and toxicity**
Biocompatibility of materials cells and alginate capsule

- **OPERATIONS**: **Manufacturing** procedures for maintaining clean room status, harvesting, isolation, culture, encapsulation, standard operating procedures. Staff training.

- **SPECIFICATIONS**: **Cell isolation and quality control**: processing of raw materials, enzymes used, islet yield, purity, viability, insulin secretion, QC release criteria, for final encapsulated product, product transport

Cell Processing of Encapsulated Cell Product

Process Flow Diagram

Equipment

Materials

Reagents

Transport of donor

transportation times
conditions

Preparation of donors

medications

Surgical

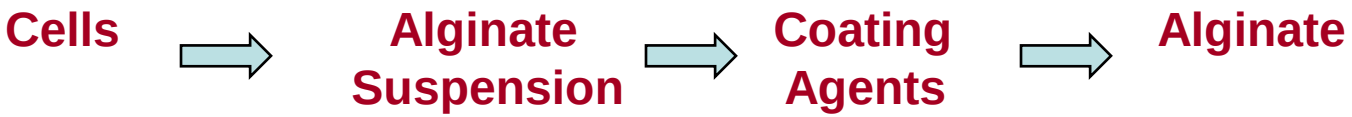
anaesthetics
exsanguination
surgical procedure
warm/cold ischaemia time

Cell processing

enzyme digestion

QC of cells
pre-encapsulation

Cell Encapsulation



Equipment

Pump, air/gas supply/monitors/encapsulation device
Device material and needles

Materials

Alginate, Polyornithine
Biocompatibility studies

Methods

Layer by layer nanoporous membrane
validating assays

Quality Control

Validation assays and Final Specifications

Morphology, capsule strength, porosity (insulin release), cell viability and function

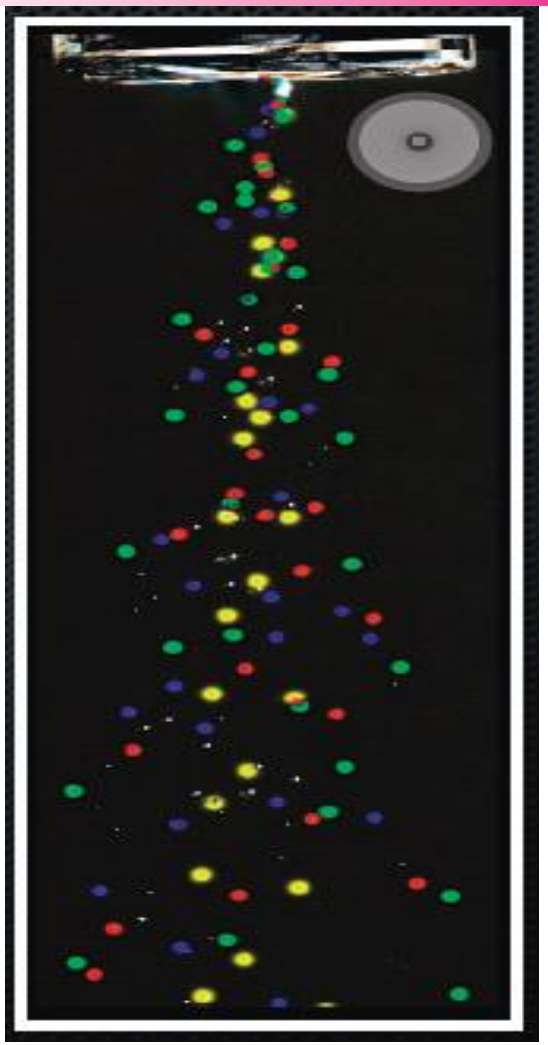
Encapsulation

Materials: Alginate and Polyornithine

- Physical and Chemical properties
- Grade, purity
- Method of purification
- Manufacturer

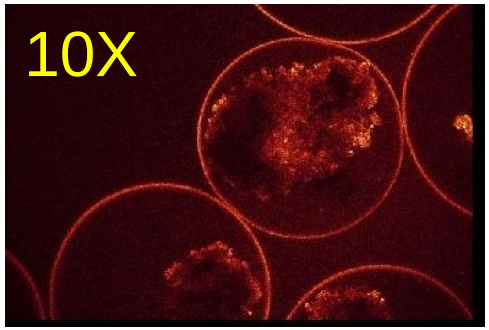
Encapsulation

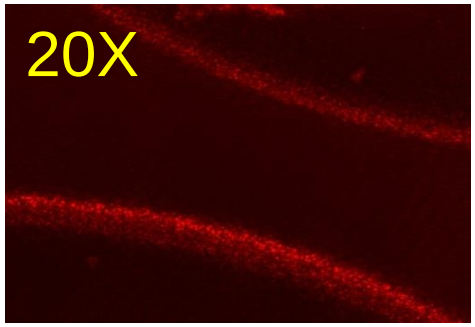
- Process description
- Critical factors for crosslinking
- Stability: capsule wall thickness, strength
- Biocompatibility
- Sterility

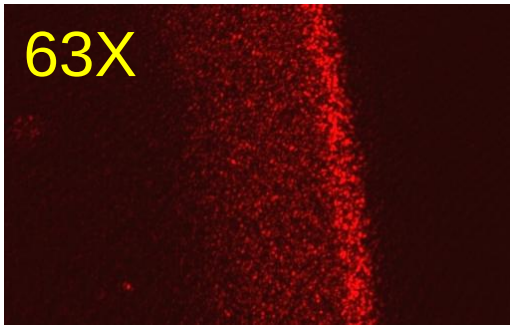


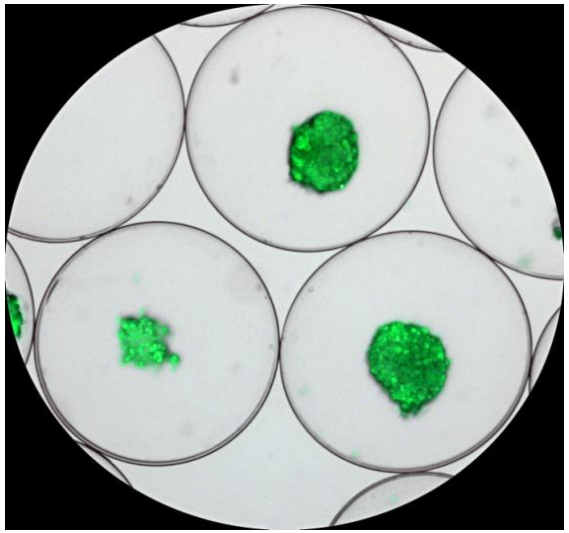
Encapsulated Cell Droplets

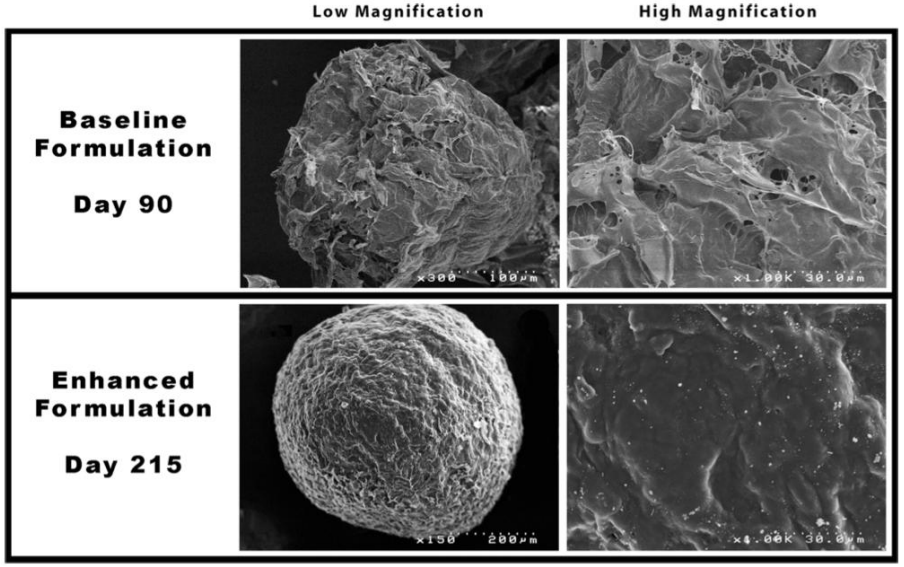
DIABECELL® Porcine Islets in Nanoporous Capsule



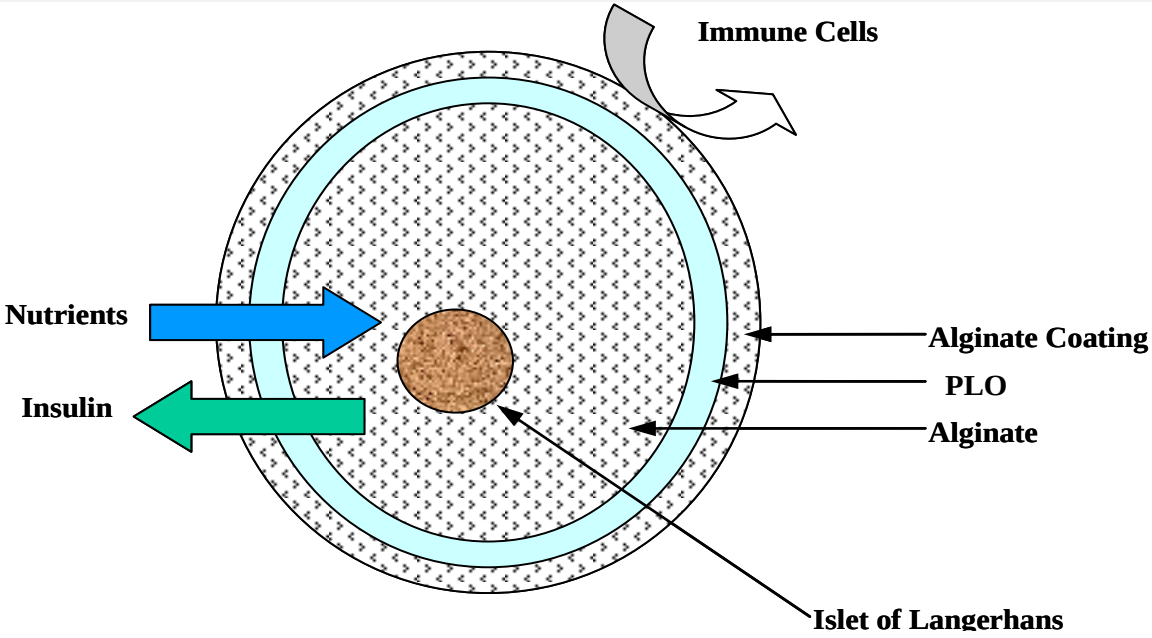


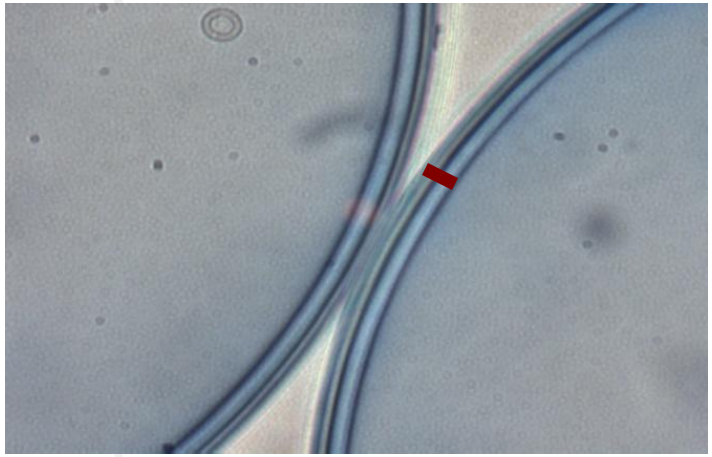






Capsule Characteristics



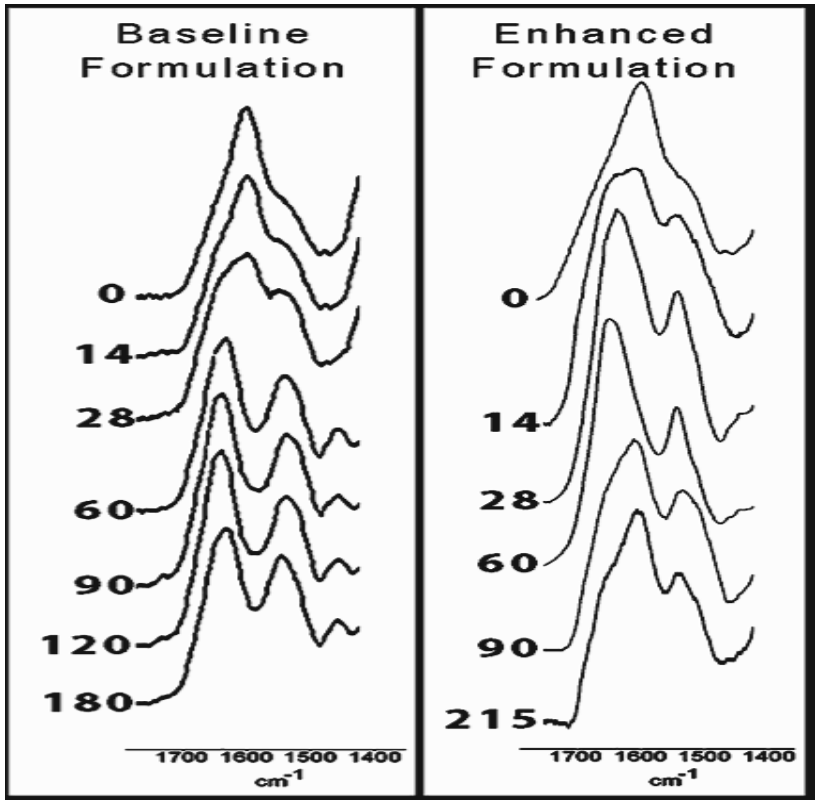


Wall thickness: 14-18 um

Stability of APA capsules: *In vivo*

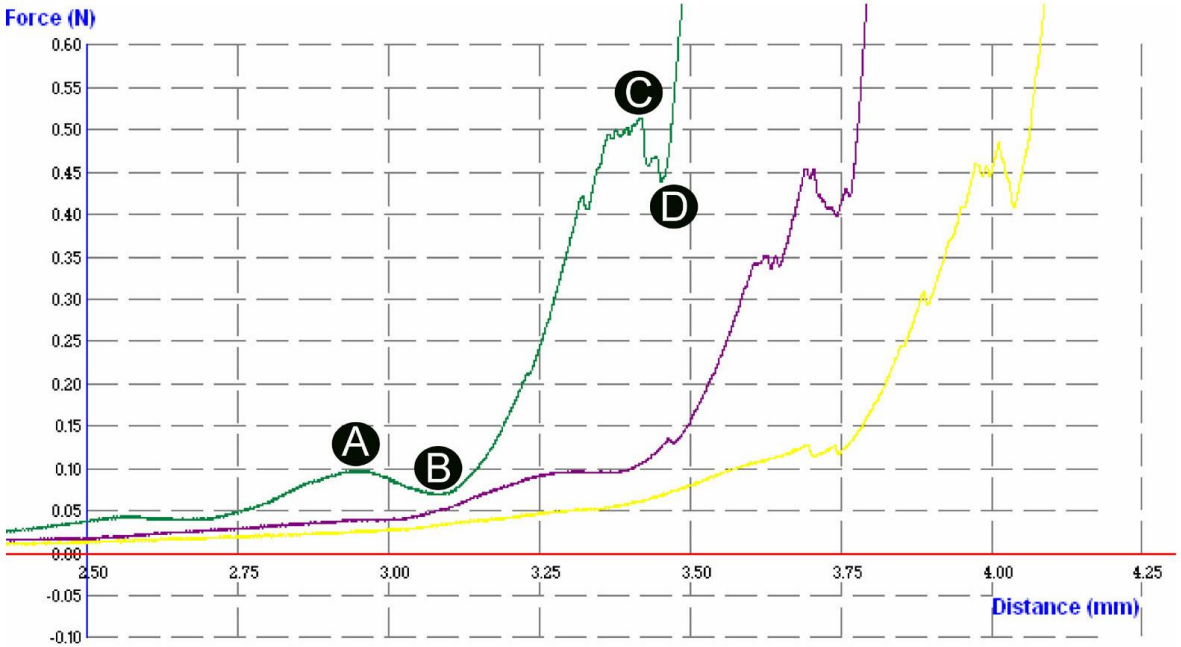
APA capsules remained stable for more than nine months

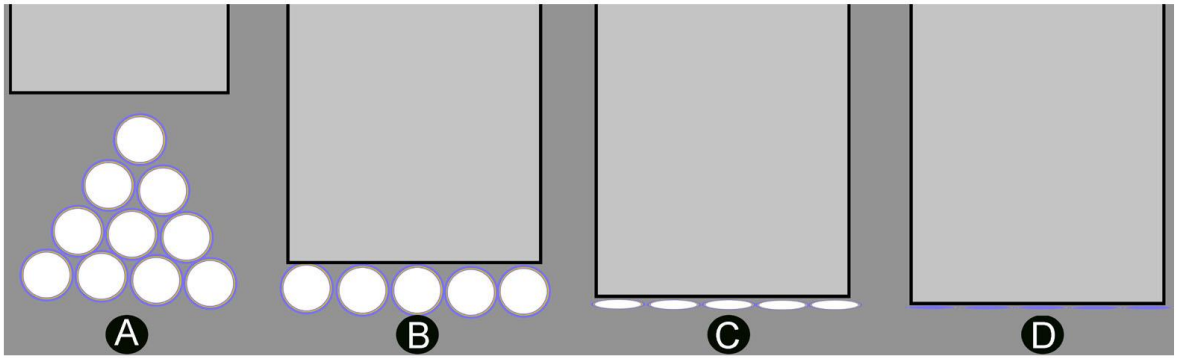
- **Enhanced Formulation**: Shoulder at 1550 cm^{-1} associated with the amide bond of PLO layer remained a small amplitude peak, and the carboxyl peak of the alginate component at 1590 cm^{-1} maintain uniformity.
- **Baseline Formulation**: Transition from day 28 to day 60, where the amount of surface pitting reaches a level to completely shift the spectrum to that of PLO.



Fournier transformed infra-red spectroscopy

Capsule Strength





Product Manufacture
Cellular and Capsule Specifications

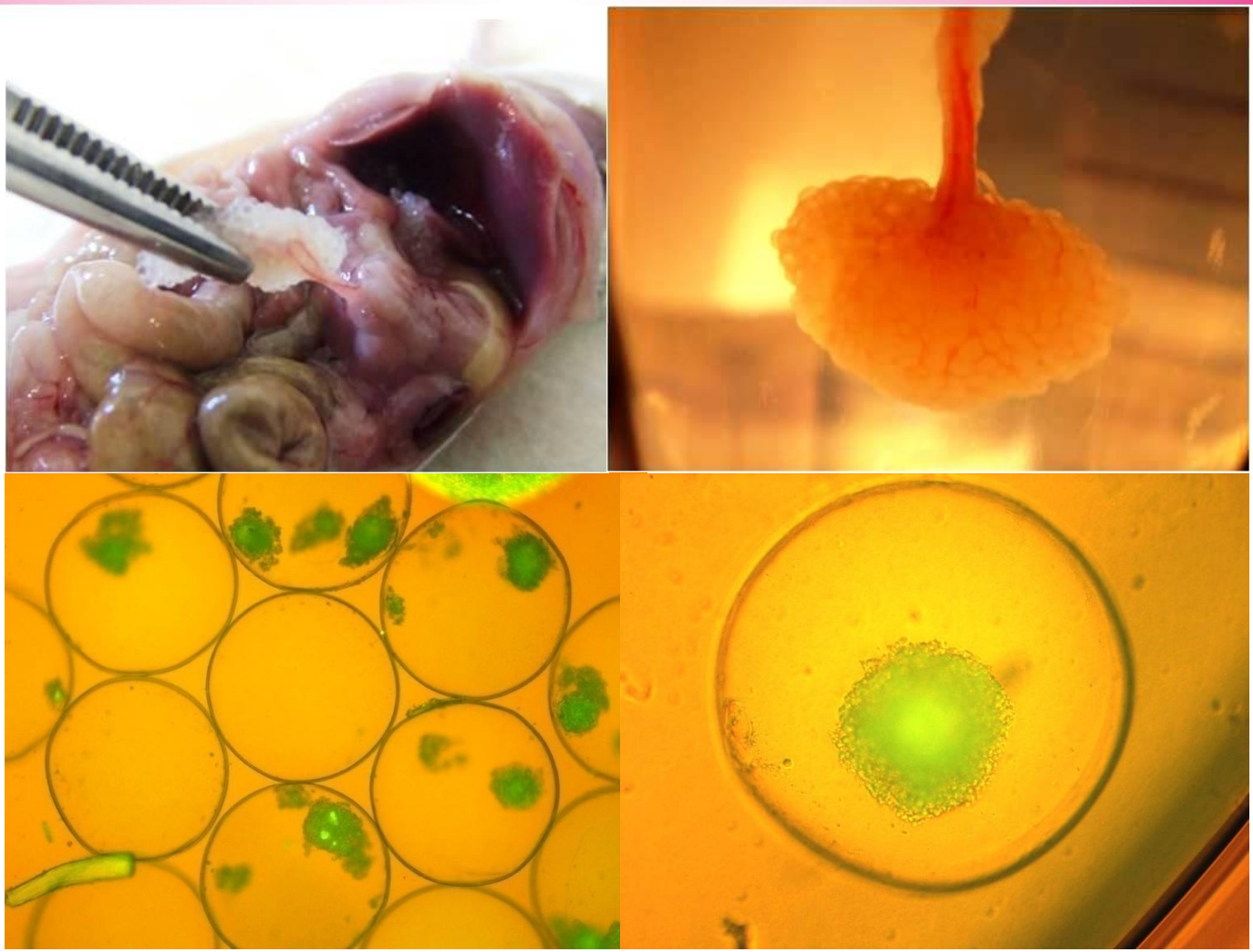
CELL	Purity Viability Max insulin release Insulin stimulation index
CAPSULE	Integrity Size Capsule wall thickness Occupancy Stability Biocompatibility
FINAL PRODUCT	Sterility Transport

Biocompatibility studies: APA capsules

In vivo studies: Cluster of APA capsules in peritoneal cavity with high vascularization.

Capsules remain clear.

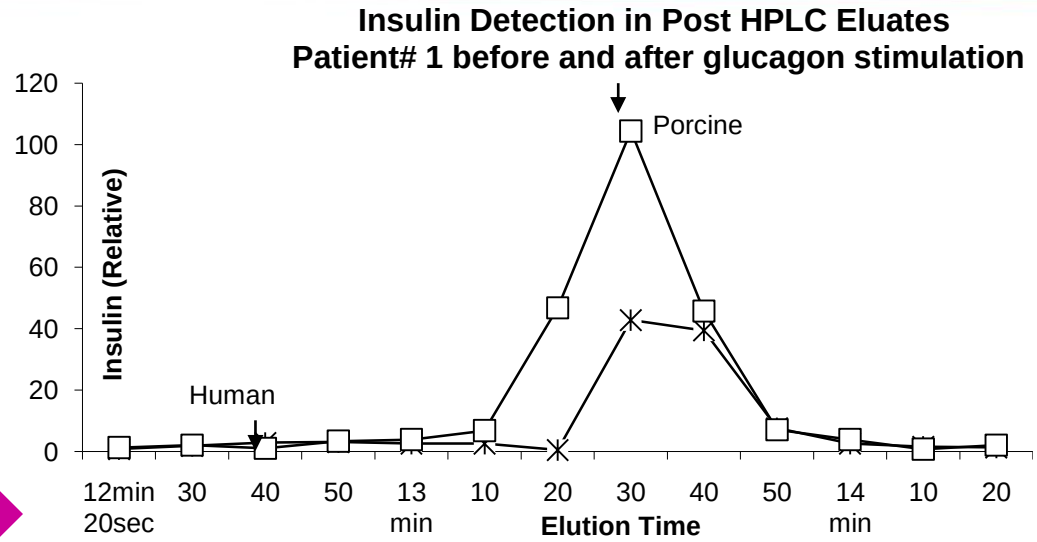
Viability of cells: >90%

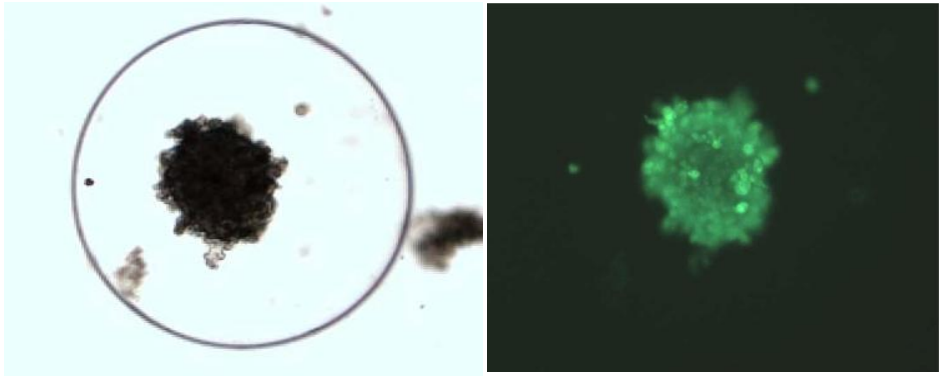


DIABECELL® Phase I/IIa Clinical Trials

Patient R001 preliminary data:

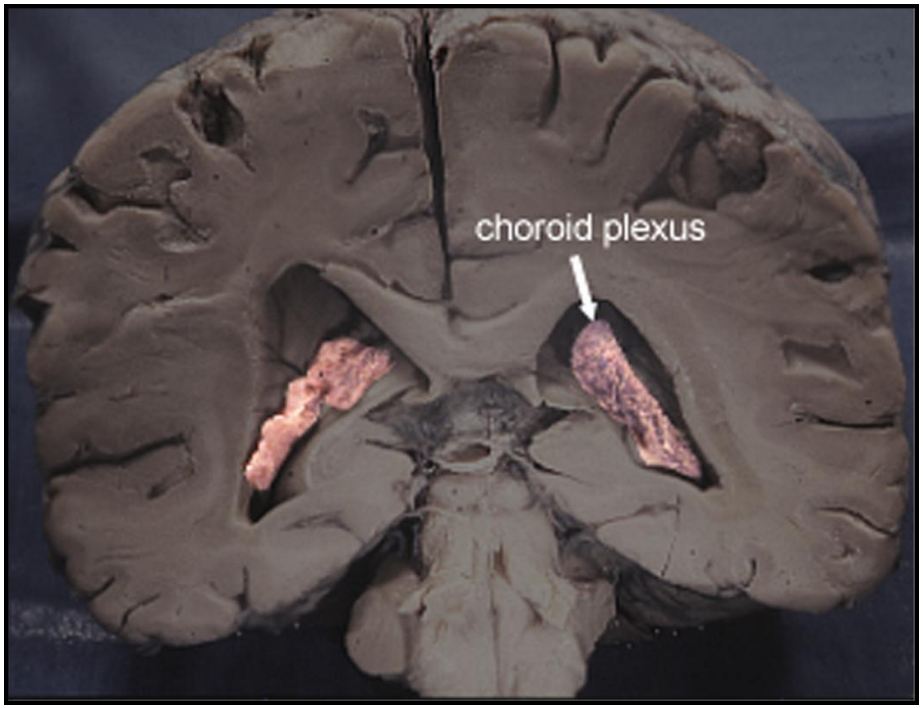
Implant Jun 2007

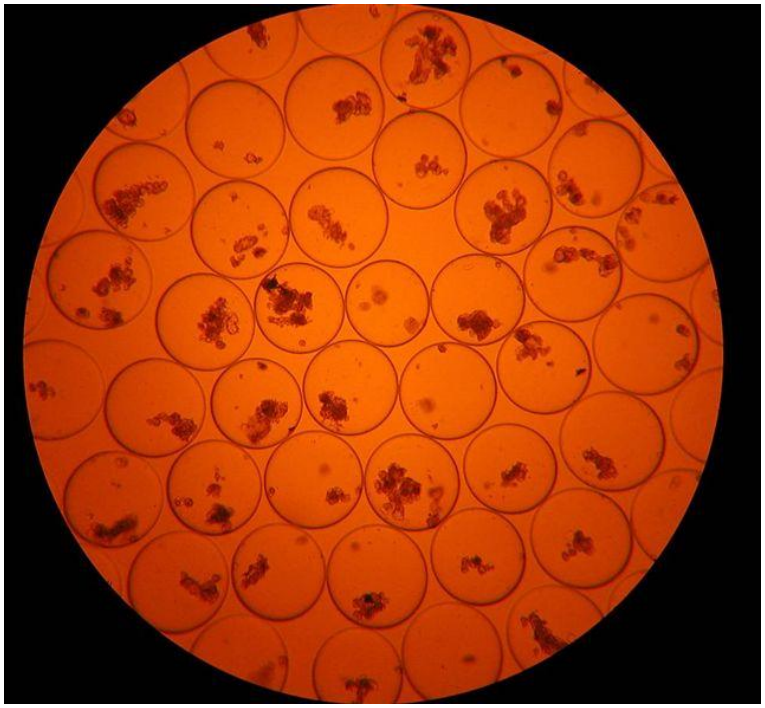




Retrieved Capsule Dec 2007

NeurotrophinCell

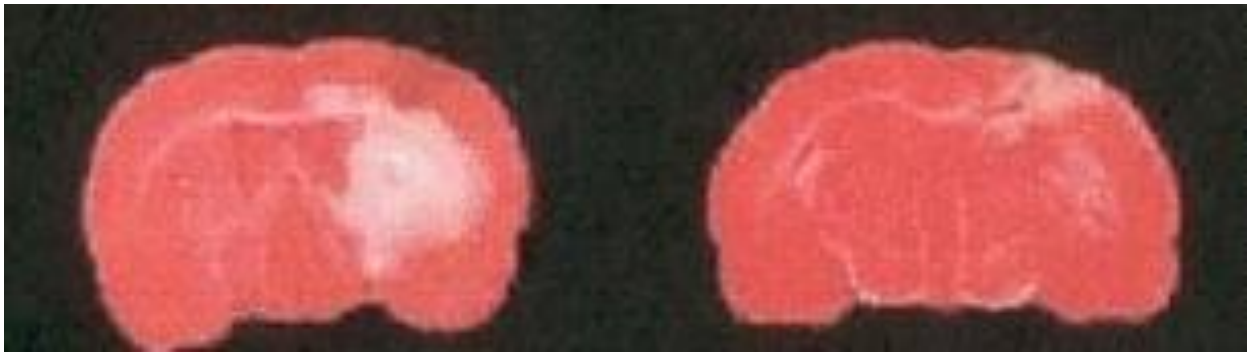




Alginate encapsulated porcine choroid plexus cells

NeurotrophinCell

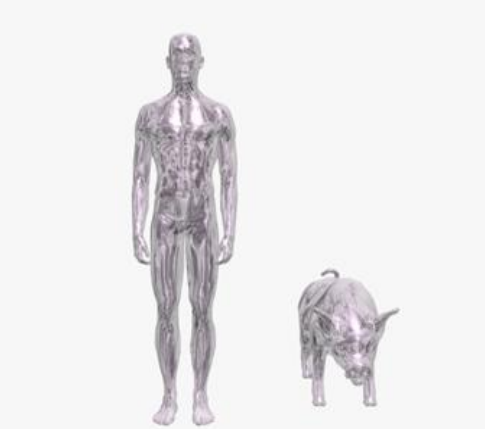
- Choroid Plexus cells
- Naturally produce reparative brain hormones
- Encapsulated in immunoprotective coating for treating
- Huntington's, Parkinson's, stroke, brain injury



Untreated Treated

Rat brain sections from stroke model
White areas indicate damaged brain tissue

Encapsulated Porcine Live Cell Products



Definition of Porcine Herd

- Closed herd
- Free of Infectious Agents

Combination Product

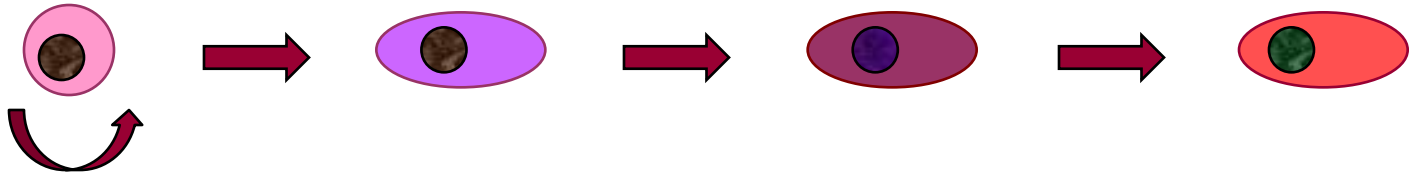
- Cell specifications
- Capsule specification
- Sterility
- Transport

Post Implant

- Safety Monitoring

Cell Therapeutics Regulatory Considerations

Self-Renewal **Commitment** **Differentiation** **Terminal Differentiation**



Cell Characterization & Manufacturing

Gene expression
In vitro differentiation
Cell Banks
Feeder Layers
Growth Factors
Donors
Viruses
Genetic defects

Lot Release
- Identity
- Potency
- Safety
- Viability
- Purity

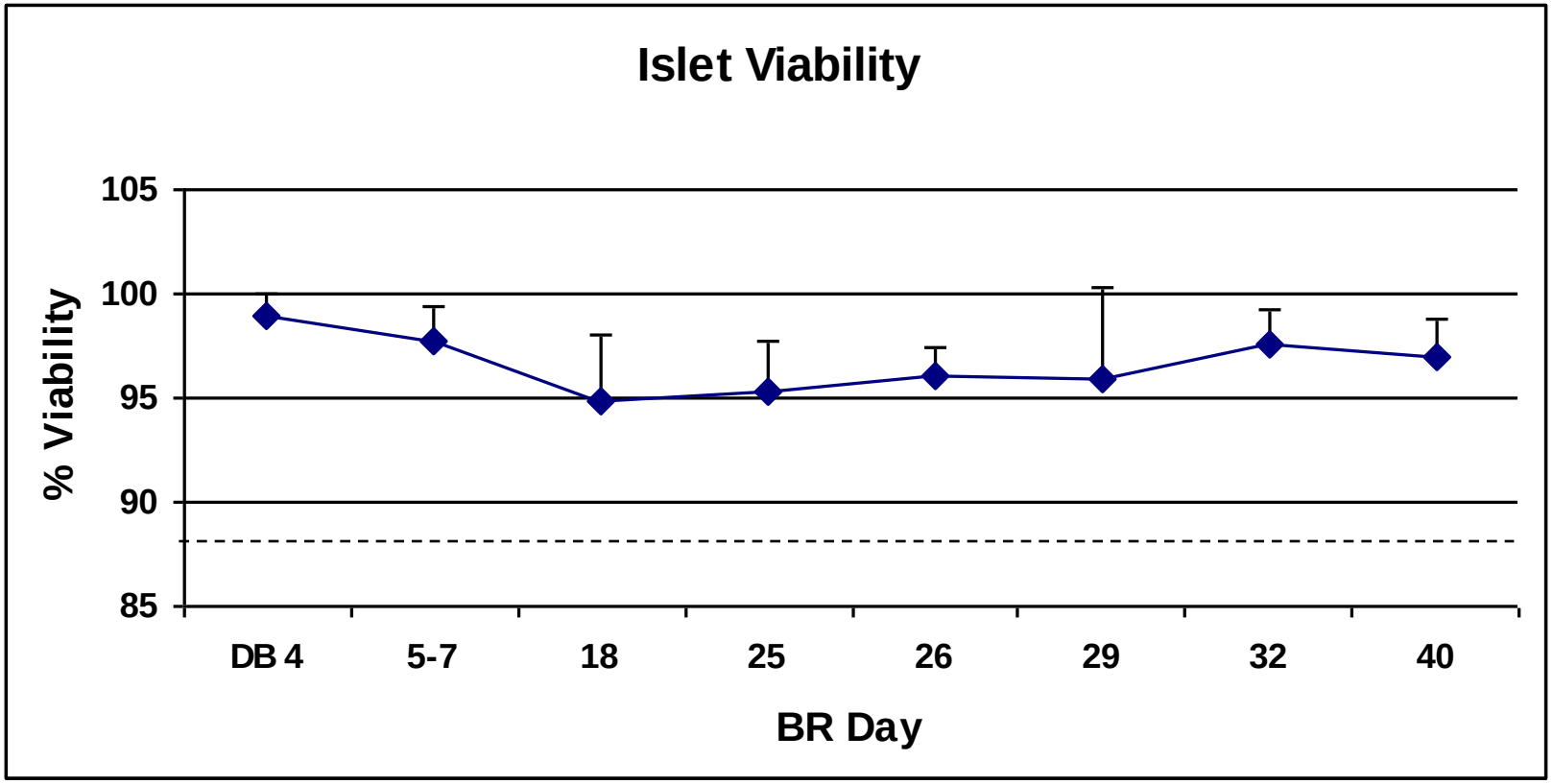
Mutation
Tumourigenesis
Apoptosis

Xenotransplantation
- Mouse feeder cells
- Animal serum - FBS

Exogenous Factors
- Cell-cell interaction
- Growth Factors

Useful Information: Donald W Fink, Jr., PhD at www.fda.gov/cber/tissue

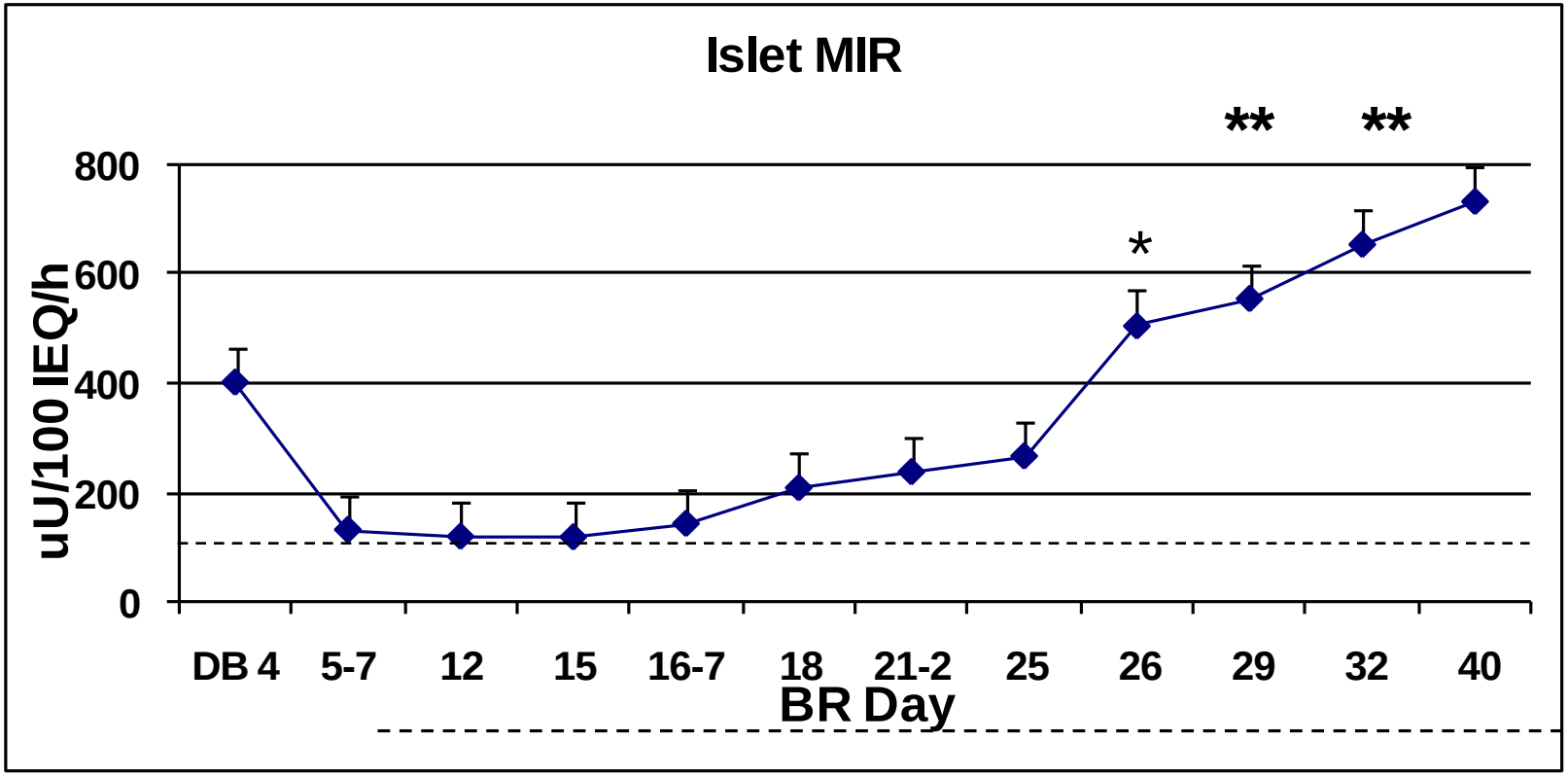
Shelf Life Stability (BR103-109)



Data are mean + SD

Shelf Life Functional Stability

Maximum Insulin Release



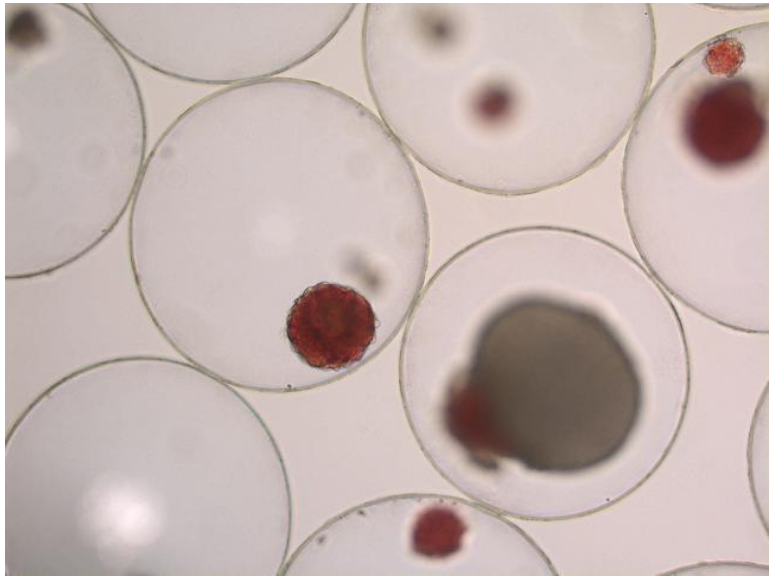
Human Embryonic Stem Cells

FDA Regulation of Stem Cell-Based Products

Selected issues:

- Malignant transformation
  spontaneous
  protracted ex-vivo culture
- Migration of Cells
  movement away from site of implant
- Immunogenicity
  eventual MHC expression
- Impact of non-target cell
  implant of undesired target cell

Donald W Fink ,Jr., PhD
Science - 26 June 2009



hES cell line
with low frequency undetermined
non-target cell cluster

living cell technologies

ASX:LCT – OTC:LVCLY
Auckland, New Zealand
Sydney, NSW, Australia