

# **Transplantation of Microencapsulated Neonatal Porcine Islets in Patients with Type 1 Diabetes: Safety and Efficacy**

**R.B Elliott, O Garkavenko, P Tan,  
N.N Skaletsky, A Guliev, B Draznin**

**Auckland, New Zealand;  
Moscow, Russia; Denver, CO, USA**

# Presenter Disclosure

**Boris Draznin, MD, PhD**

**Board Member/Advisory Panel: none**

**Consultant: none**

**Employee: none**

**Research Support: Amylin; Sanofi-Aventis;  
Novo-Nordisk**

**Speaker's Bureau: none**

**Stock/Shareholder: none**

**Other: none**

- **Destruction or severe malfunction of pancreatic islets is the core pathogenetic feature of diabetes**
- **Cure of diabetes is impossible without restoration of pancreatic islet –  $\beta$ -cell – function**
- **Pancreatic  $\beta$  – cells are the only cells capable of sensing ambient blood glucose and converting this information into regulated insulin secretion**

# Strategies to Restore $\beta$ -cell Function

- Islet transplantation
- Stem cell derived insulin producing cells
- Non-islet cells genetically modified
- Islet cell regeneration

- **T1DM - > 2,000,000 patients**
- **T2DM - >20,000,000 patients in the U.S. alone**
- **Only around 1,000 cases of allogenic islet transplantation**

# Islet Transplantation

**Intrahepatic allotransplantation with immune suppression is not the answer to treatment of Type 1 diabetes**

# Porcine Islets

## Pro:

- Porcine insulin
- Essentially unlimited supply of cells for transplantation
- Islets respond to the same physiological range of glucose as human islets
- Potential to do implants without immunosuppression
- Ethical considerations

## Con:

- Humans express high titers of antibodies against Galactose (1,3)  $\alpha$ -galactose residue present in most pig cells
- Retroviruses

# Pig Viruses

- Pig Hep E
- Pig circovirus type 2
- Cytomegalovirus
- Pig lymphotropic herpesvirus
- Others



# Pig Endogenous Retrovirus (PERV)

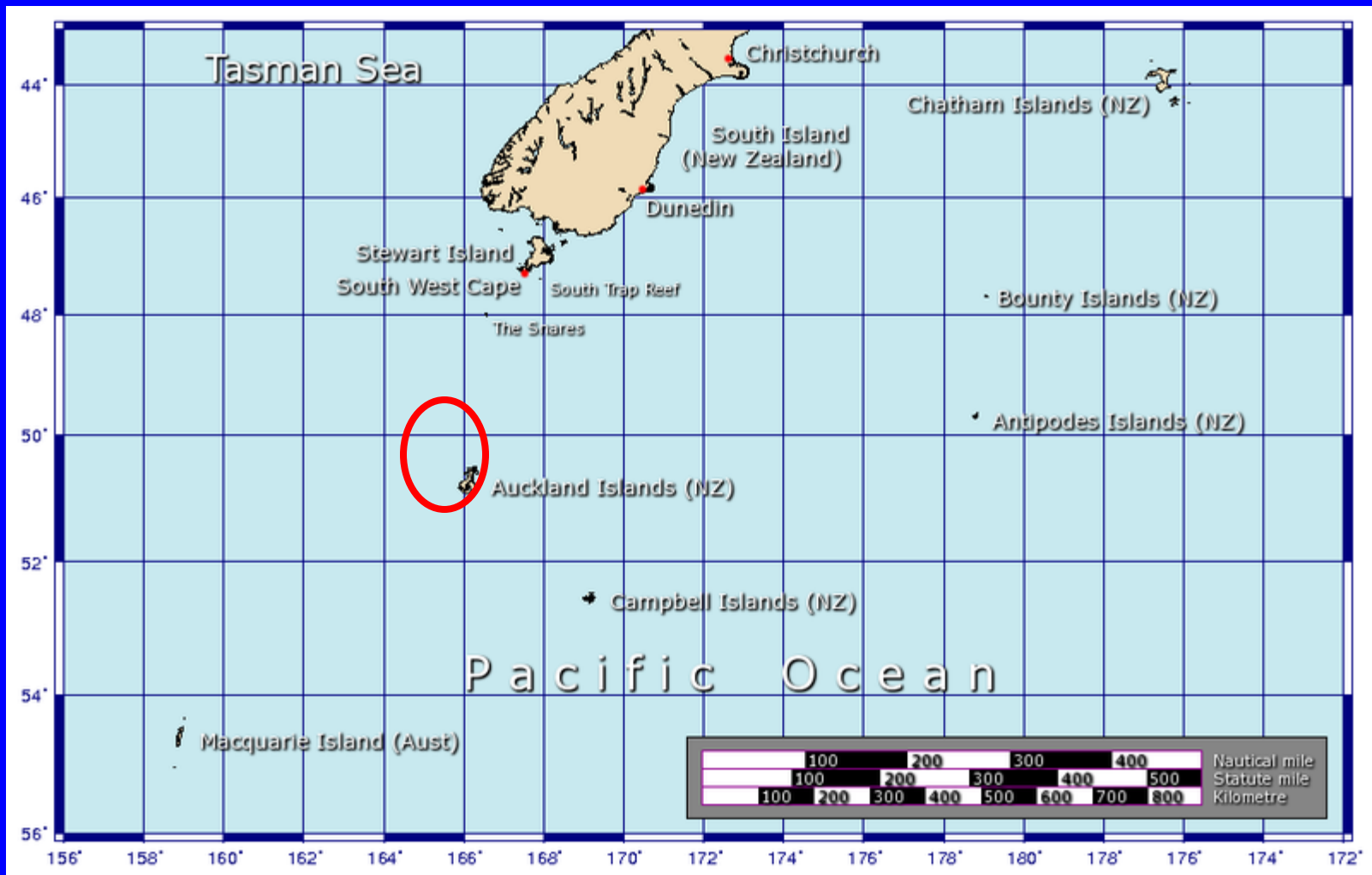
- Part of the pig genome (with more than 100 of per-viruses)
- PERV- A and PERV- B are infections to human cells in vitro

# Prerequisites for Xenotransplantation

- **Cells must be free from any xenotic agent**
- **Islets must be uncontaminated, undamaged, free of exocrine tissue**
- **Anti-rejection strategy should not be based on immunosuppression**

# Cells Free From any Xenotic Agent

- **Source herd must be free of infections capable of being transmitted to man  
Specific Pathogen Free animals (SPF)**
- **Must be housed in the Designated Pathogen Free (DPF) facilities**
- **Must be checked for infection status frequently**



**Discovered in 1806; Area 220 sq miles; Temp 35-65° F; humid, cloudy and very windy.**



# Viruses in New Zealand and Auckland Islands Herd

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	Not detected	Not detected	Not detected	Not detected
BVD	Not detected	Not detected	Not detected	Not detected
PPV	Present	Not detected	Not detected	Not detected
<i>Toxoplasma gondii</i>	Present	Not detected	Not detected	Not detected
Leptospiroses	Present	Not detected	Not detected	Not detected
<i>Mycoplasma hyopneumoniae</i>	Present		Not detected	Not detected

# Islet Isolation

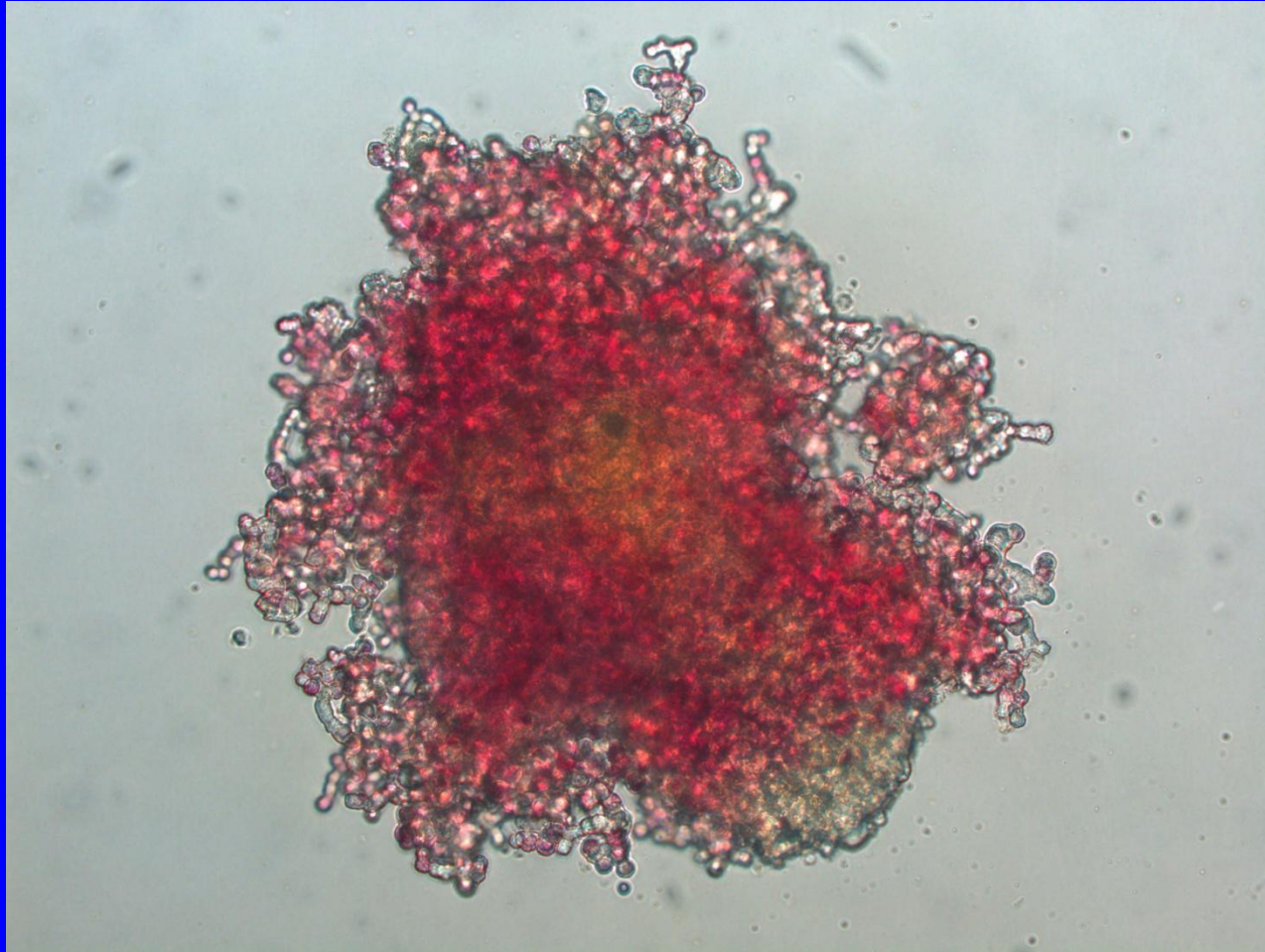
- **Stress to the tissue**
- **Harsh enzymatic digestion**
- **Encapsulation**
- **Storage**
- **Transport**
- **Viability at the time of transplantation**

# Uncontaminated



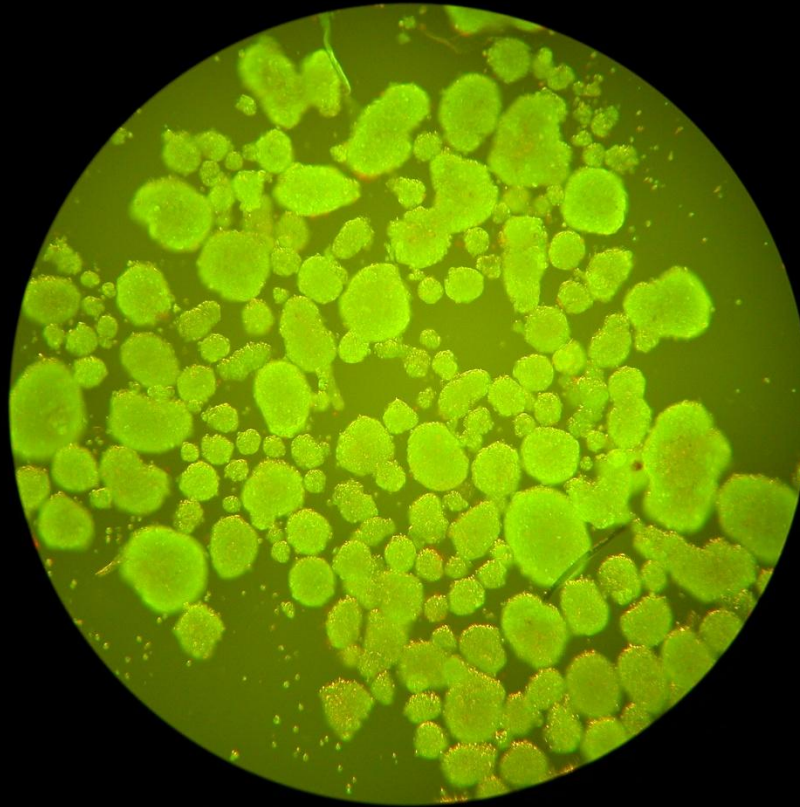


# Undamaged



Free floating  
islet day 15  
culture.  
Insulin  
producing  
cells red Zinc  
staining DTZ.

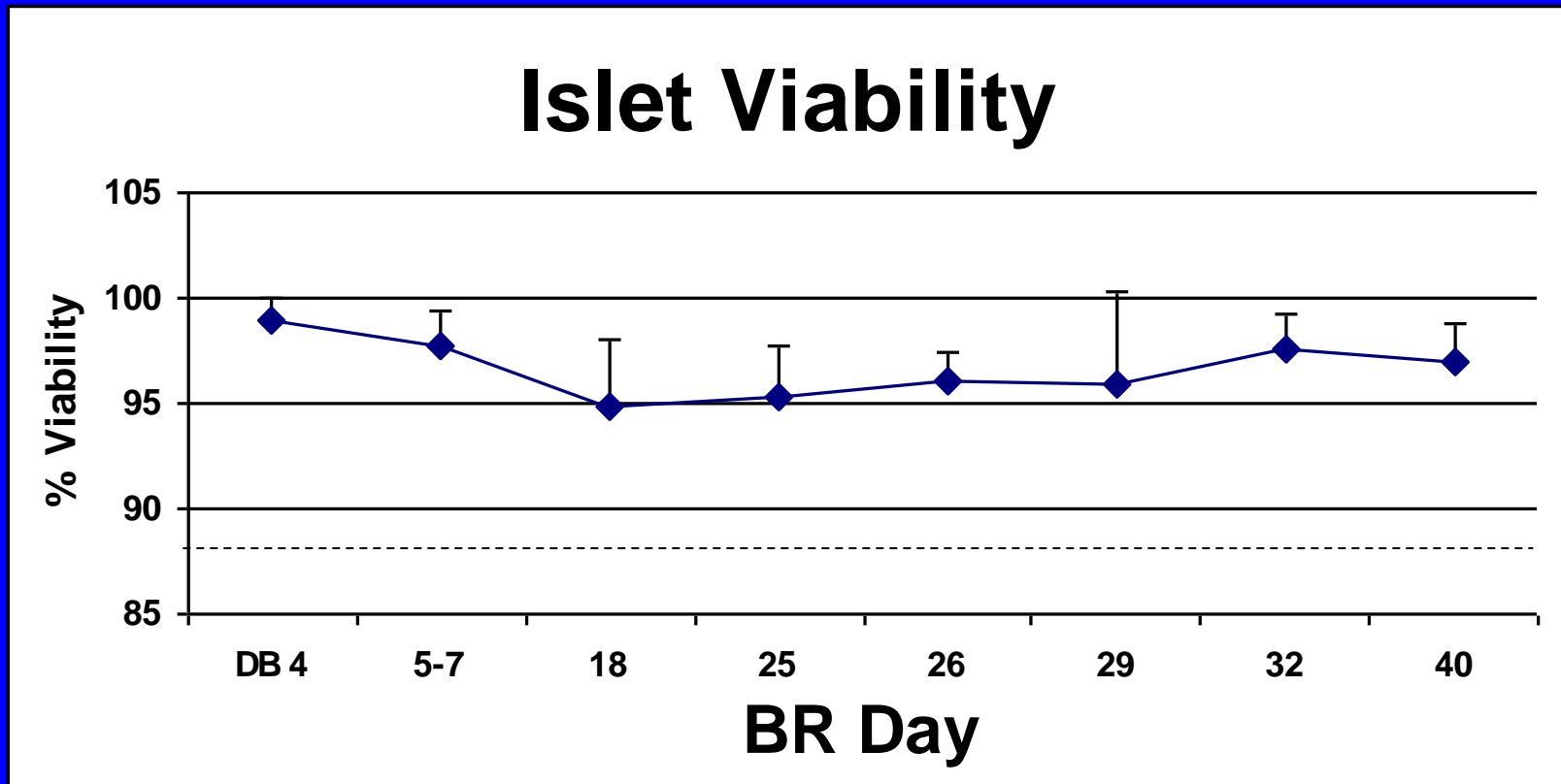
# Viable



**Porcine Free  
Islets AOPI  
staining**

**Viability > 95%**

# Shelf Life Stability (BR103-109)



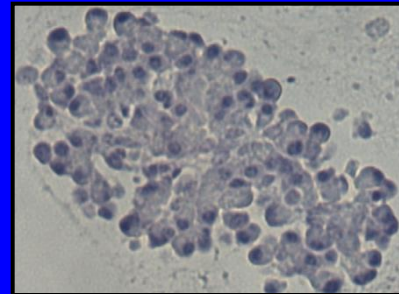
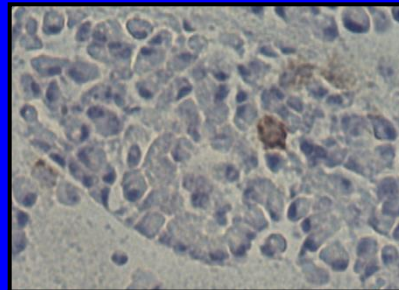
Data are mean + SD

# Differentiation in Neonatal Islets

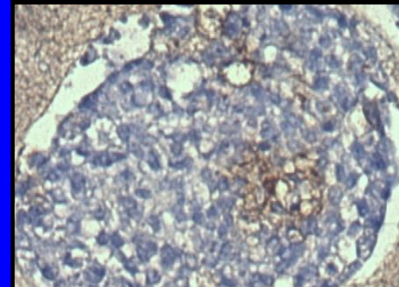
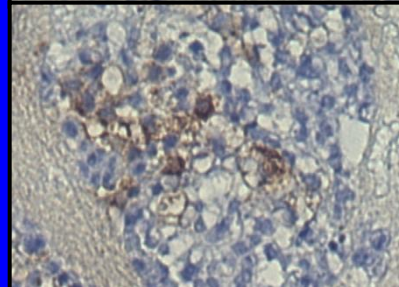
**Insulin**

**Glucagon**

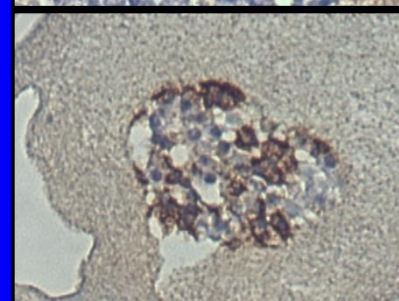
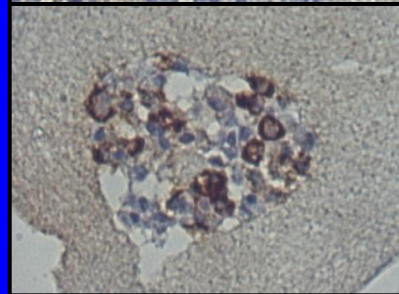
**day 1**  
(free islets)



**day 4**  
(free islets)

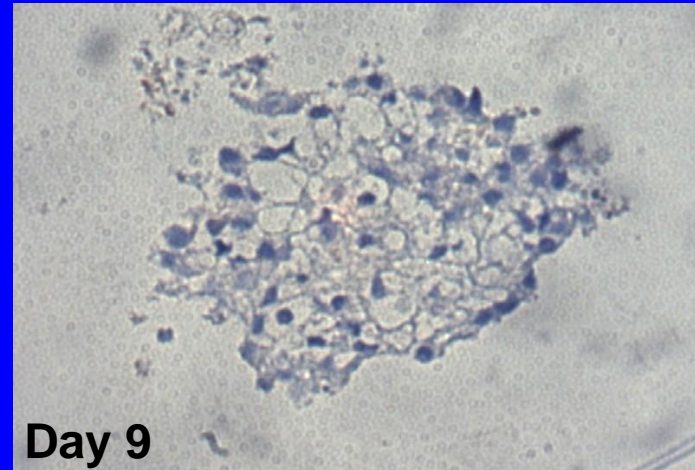
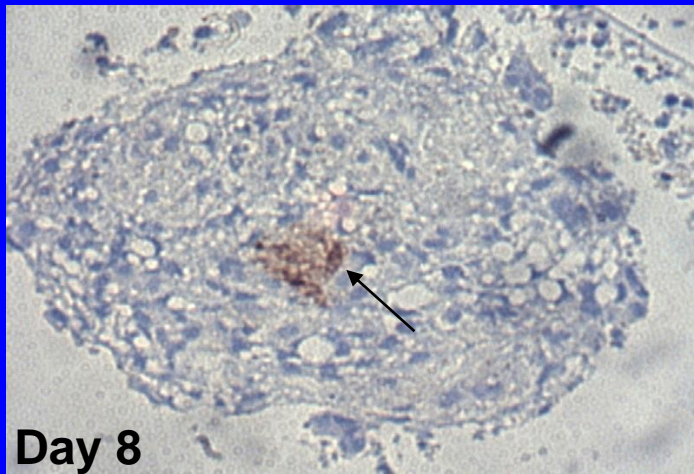
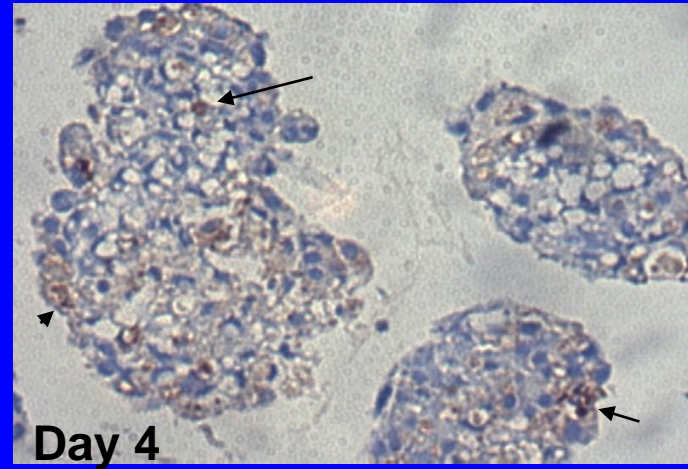
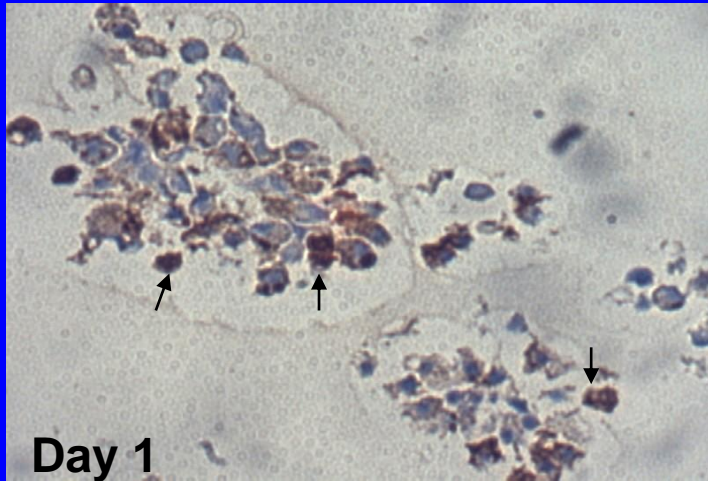


**day 35**  
(encapsulated islets)





# Exocrine Free (amylase)



# Microencapsulation

- **Surrounding of islet cells with a highly biocompatible biopolymer called alginate which reduces the host's immune response to the implanted islets**
- **Alginate coat allows insulin, glucose, oxygen and other nutrients to diffuse freely, while blocking antibodies and T-cells**

# NanoBioCapsule Attributes

**Strong, Elastic Physical Barrier**

**Unrestricted Cell Viability**

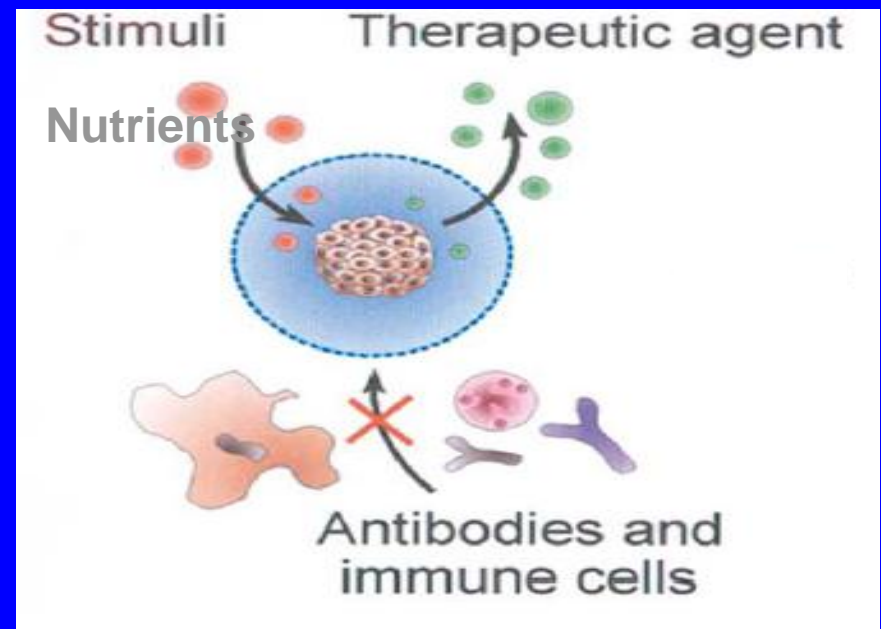
**Allow Inward Nutrient Diffusion**

**Outward Protein and Metabolite Release**

**Immunoisolation**

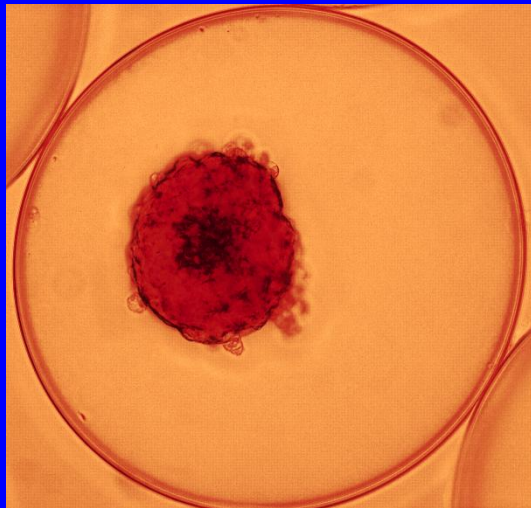
**Control Internal Cell Attachment**

**Biocompatible**

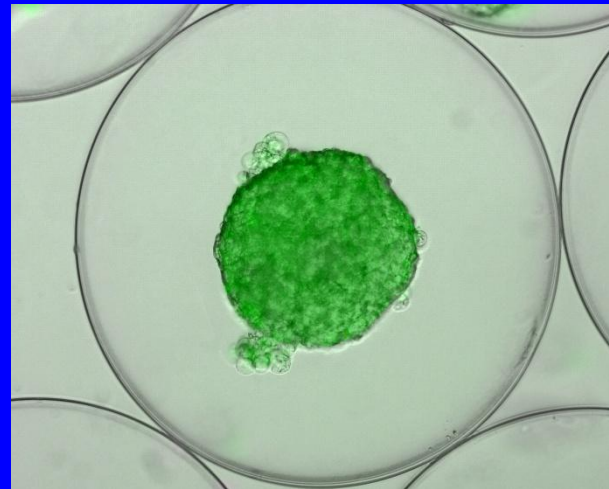


# DIABECELL<sup>®</sup> Encapsulated Neonatal Porcine Islets

DTZ 10x

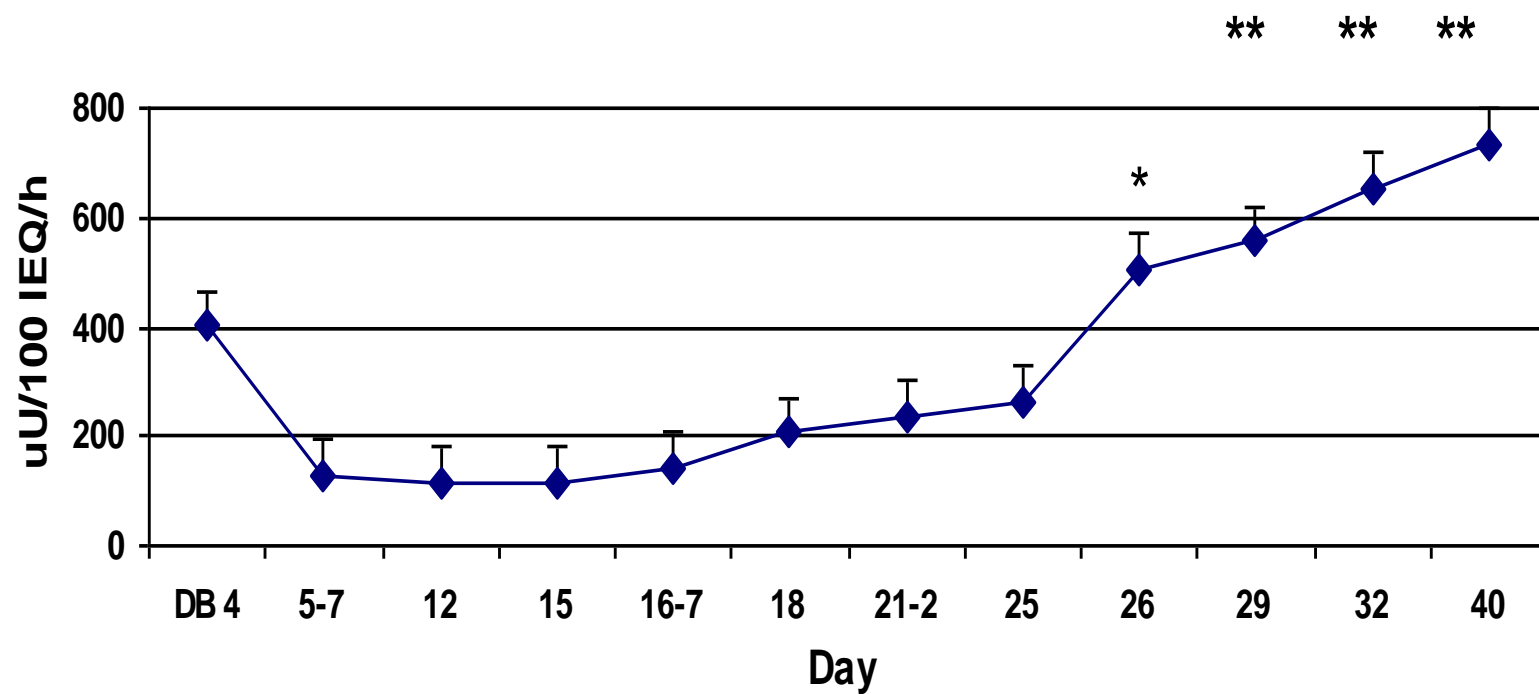


AOPI 10x



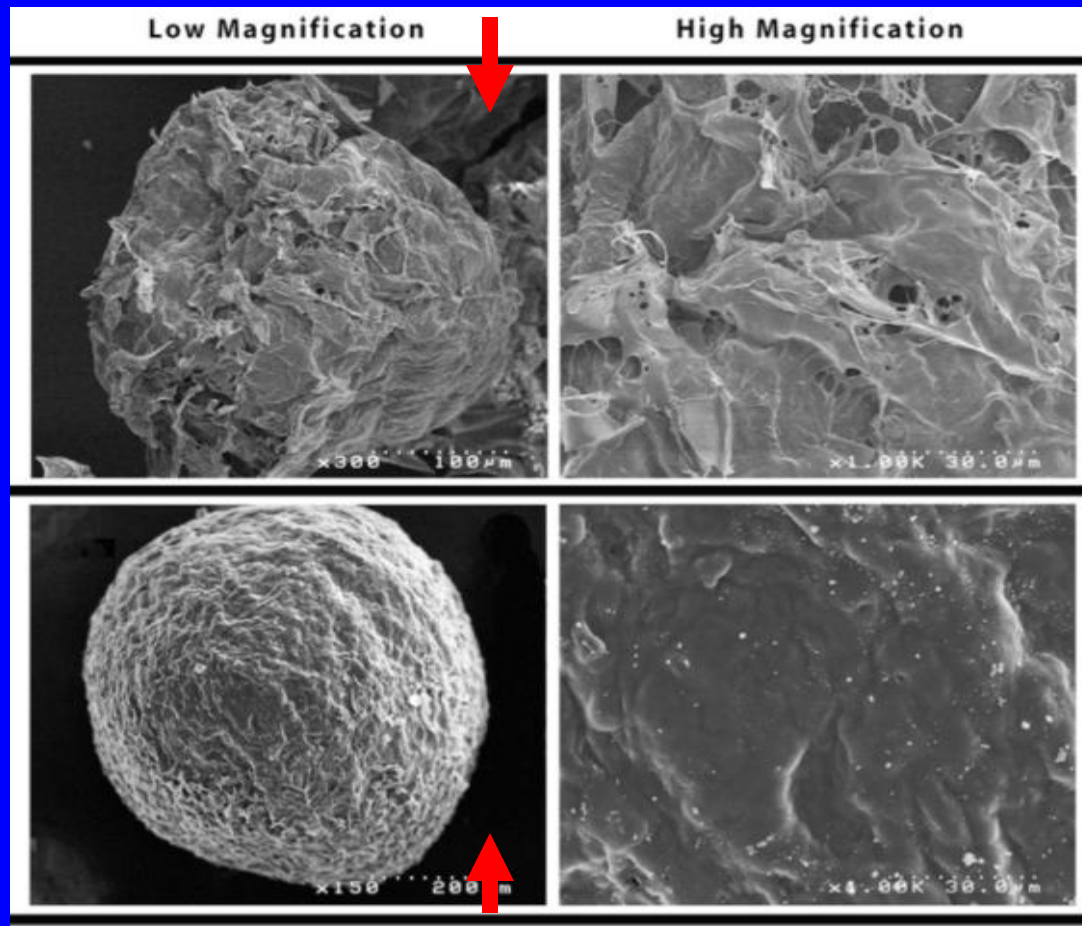


## Islet Maximum Insulin Release



# LCT's Encapsulation

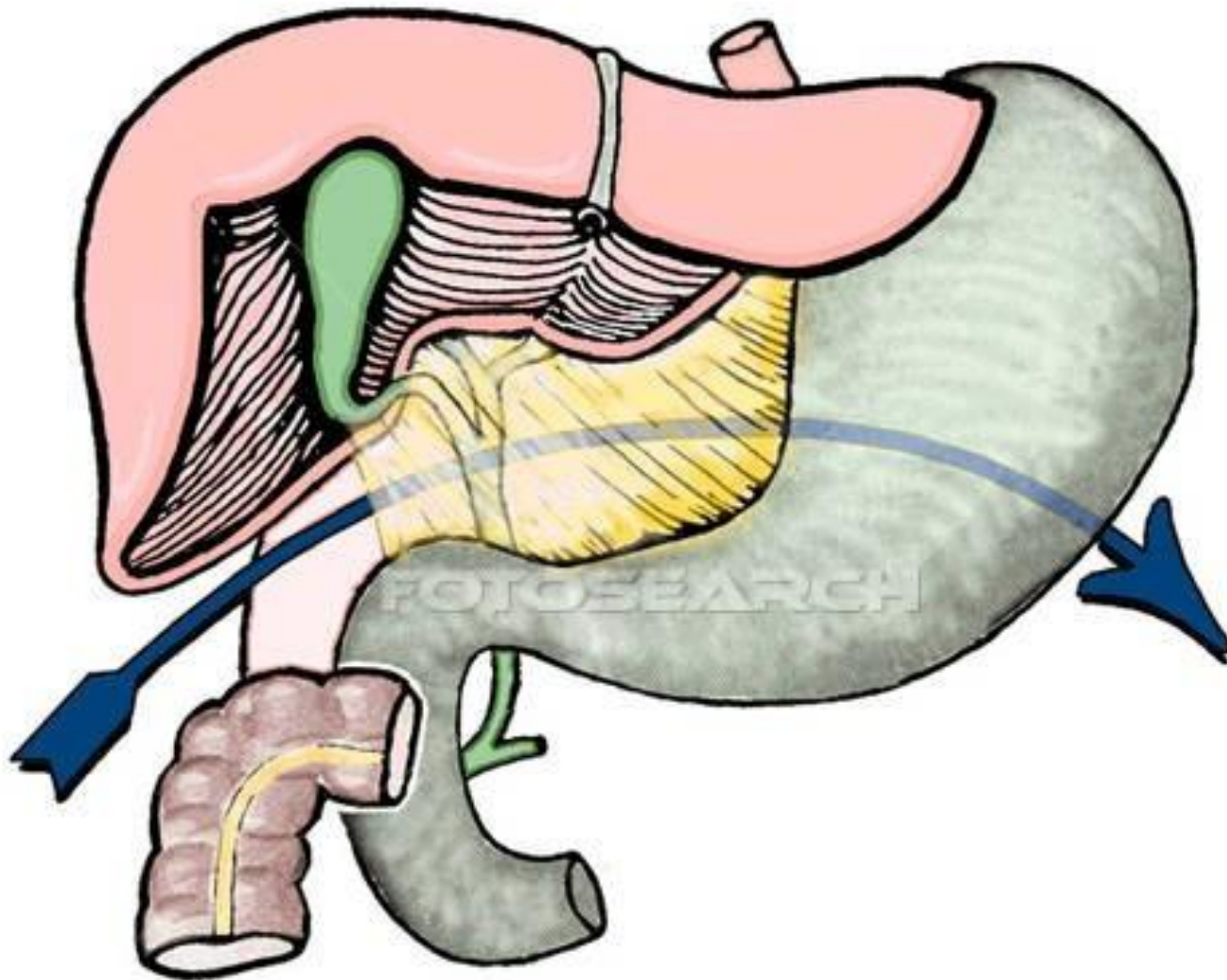
Other alginate capsule [90days]

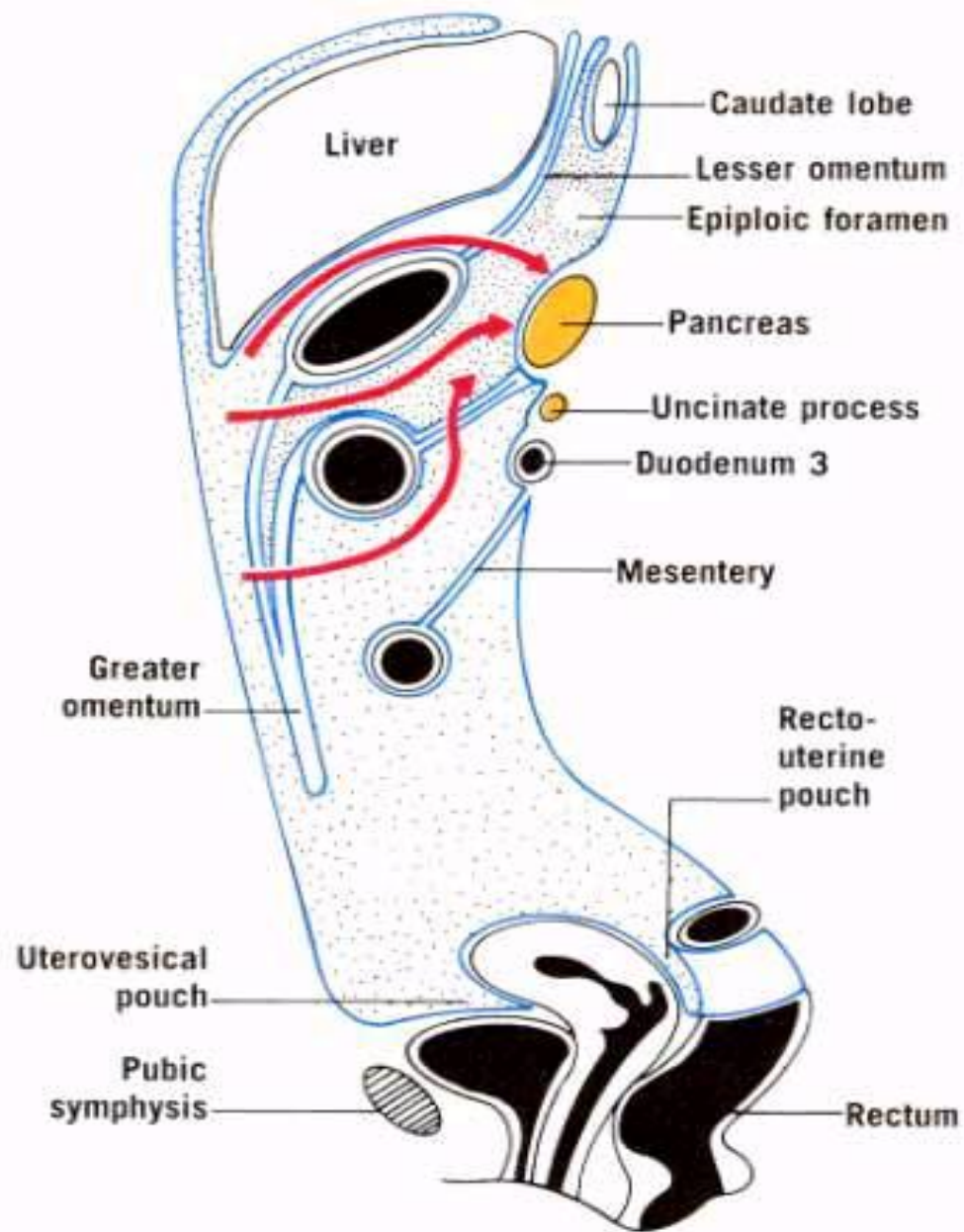


LCT capsule [215 days]

# Patients and Methods

- **8 Patients with T1 DM**
- **Age 23 – 63**
- **Duration of diabetes 5 to 15 years**
- **Dose of neonatal islets between 5,000 and 10,000 Islet Equivalents per Kg body weight**
- **Delivered laparoscopically into the lesser sac of omentum**





# Clinical Data



**Phase I/IIa 2007 – 2010**

**Sklifasovsky Institute, Moscow, Russia**

## **Subjects**

- **8 adult Type 1 diabetes patients**
- **Insulin dependent > 5 years**

## **Dose**

- **5,000 – 10,000 islet equivalents/kg**
- **Up to 3 repeat implants**

# Results of the First Human Trial

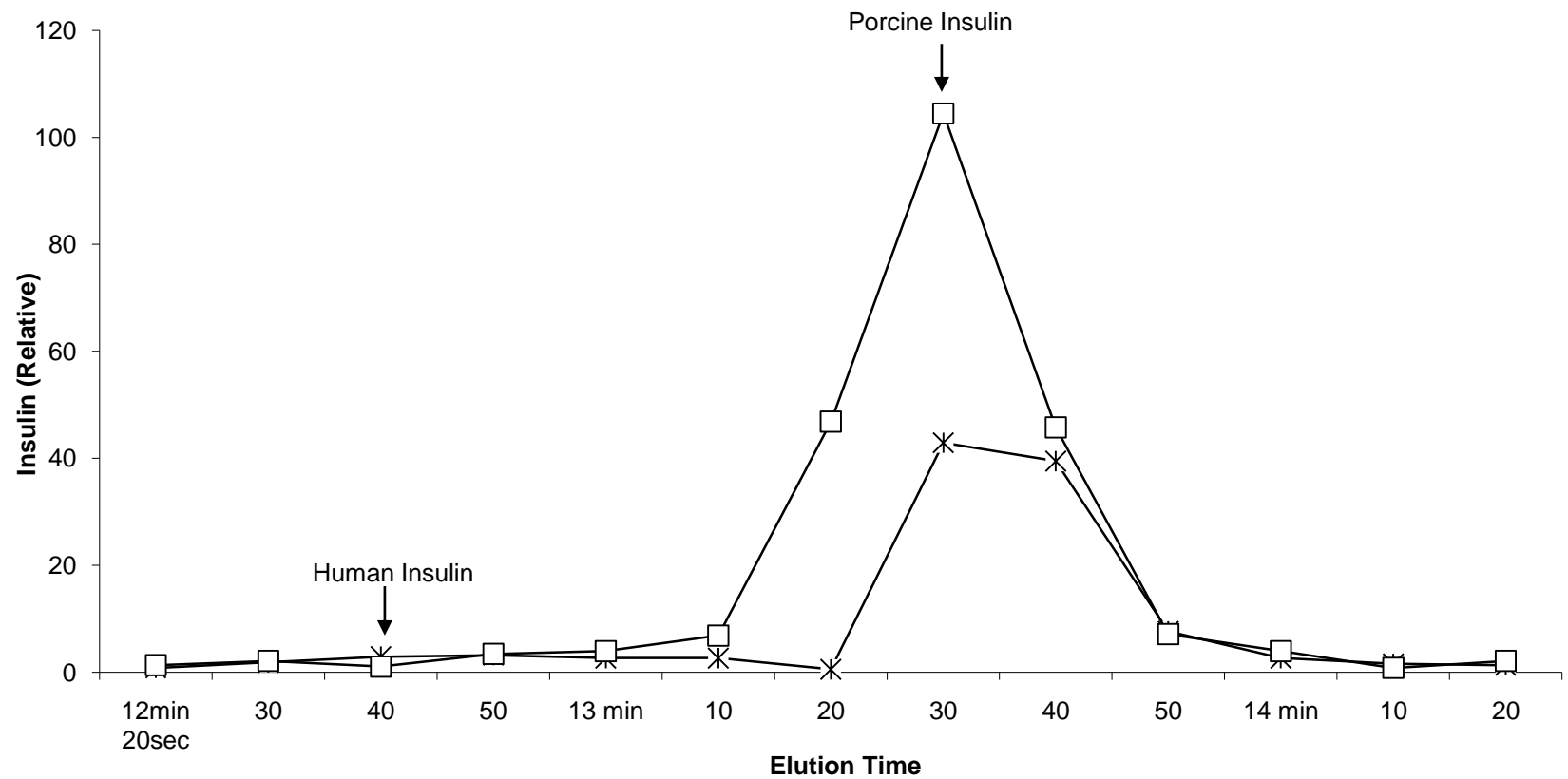
Patient No.	No. of Implants	Follow-up (Weeks)	Insulin Dose (Units/day)		% Dose Reduction	HbA1c (%)		↓
			Pre-Implant	3-6mo after		Pre-Implant	3-6 mo after	
1	3	96	113	76	33	7.1	6.3	0.8
2	3	84	22	0	100	8.2	7.3	0.9
3	3	72	66	53	14	10.1	7.4	2.7
4	3	60	30	27	10	7.6	6.5	1.1
5	2	30	68	58	15	9.8	6.2	3.6
6	1	20	41	51	-	8.5	8.5	0
7	2	18	37	0	100	8.3	4.9	3.4
8	1	18	83	83	0	11.3	8.2	3.1



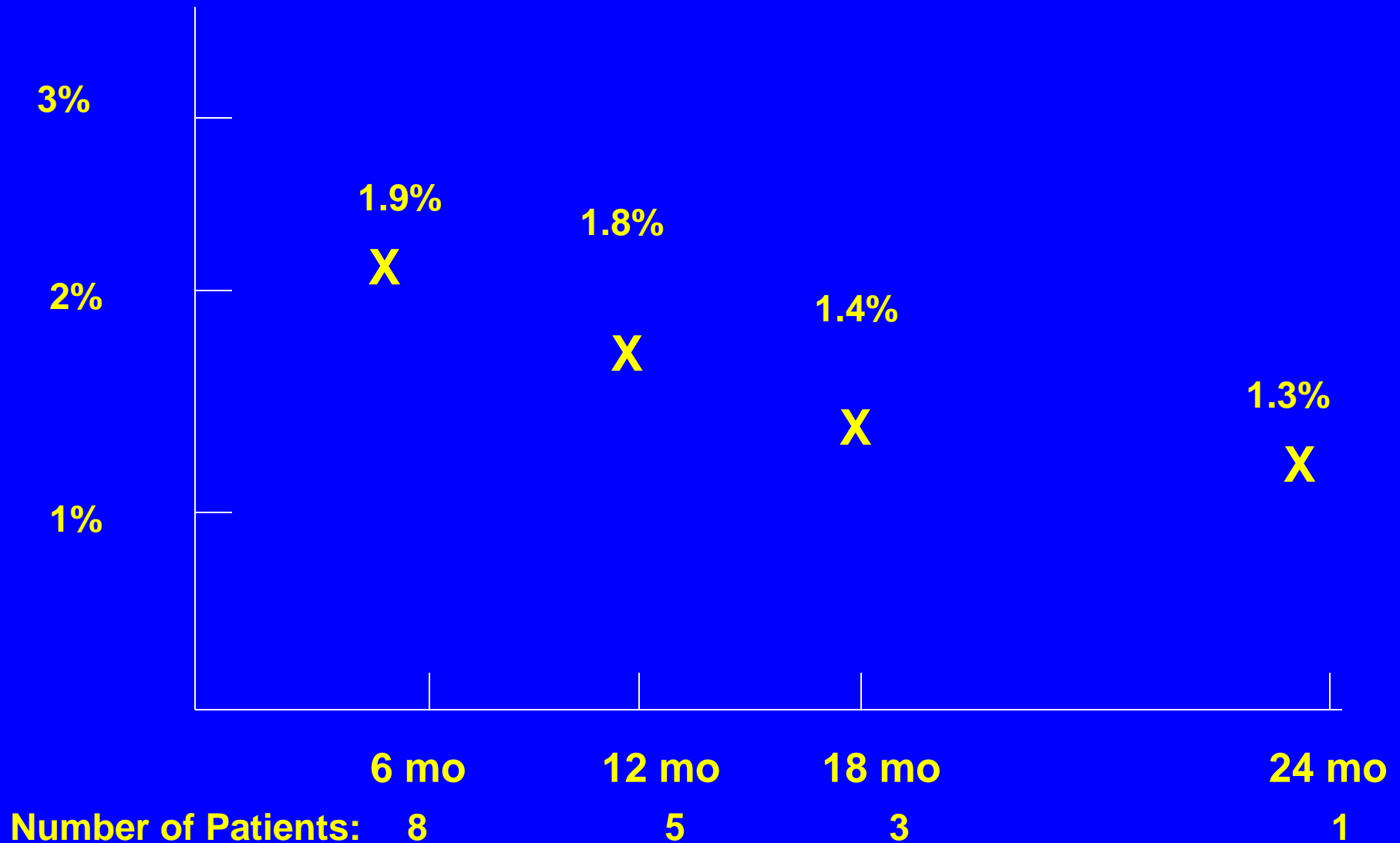
# Results

- Two out of 8 patients became insulin independent
- Insulin dose was reduced by 34%
- HbA1c was reduced from 8.86% to 6.91%
- Viable islets were recovered from 5 patients
- Porcine insulin was detected
- No side effects and no xenosis

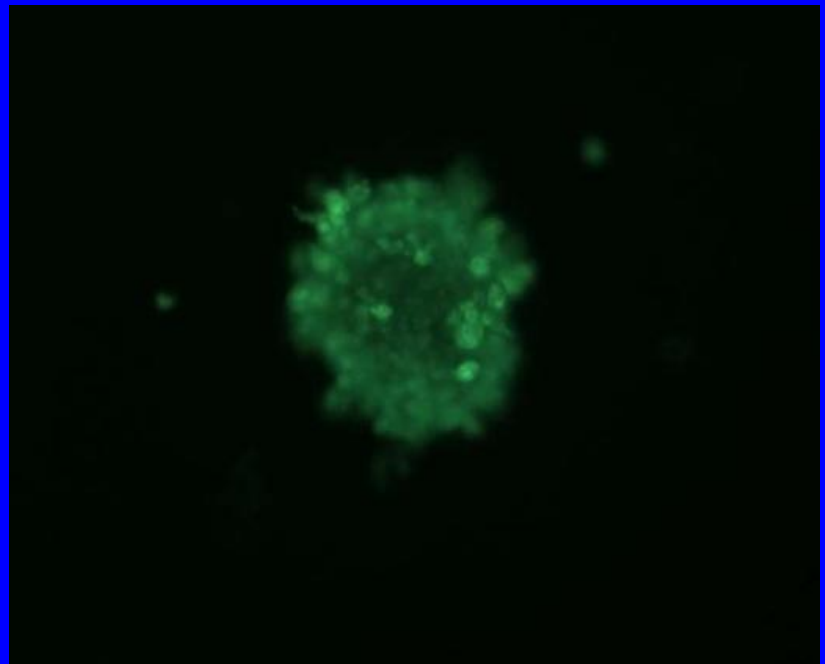
**Insulin Detection in Post HPLC Eluates**  
**Patient# 1 before and after glucagon stimulation**



# Efficacy – Reduction in HbA1c (mean)



# Patient Implant – Recovered Cells



# **Safety Within a Week of Transplant**

**Significant adverse events - NONE**

**2 pts – abdominal discomfort – resolved in 5 days**

**2 pts – creatinine elevations to 1.5 for 3 days**

**2 pts – low grade fever for 3 days**

## **Safety at 24 Months**

- **No significant adverse events to date**
- **PERV RNA - negative**
- **PERV DNA - negative**

## **Preliminary Efficacy**

- **Improved blood glucose control with reduced HbA1c**
- **Reduced daily dose of insulin injections**
- **Two patients off insulin up to 32 weeks**
- **Intact capsules retrieved after 6 months**
- **Pig insulin detected in patient blood**

# Candidates for Xenotransplantation

- **“Brittle diabetes” with or without other complications**
- **Severe hypoglycemia with attempts to optimize care**
- **Hypoglycemic unawareness**

➡ **7 patients in New Zealand have received transplants in the past 6 months.**

# Summary

- **Safety objectives have been met**
- **Proof of concept in humans – possible to achieve therapeutic success without immunosuppression**
- **Future questions – the effect of the appropriate dose of islets on magnitude and duration of response**



# Conclusions

- Careful manufacturing of encapsulated islets from neonatal pigs yields a product that shows significant promise as a treatment of T1DM without immunosuppression
- Regulatory concerns around PERV appear to be a non-issue. Other xenoses can be avoided

**Thanks for your kind  
attention...**

