

Weill Cornell Medical College in Qatar



# Islet Cell Transplantation

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# Pancreas/Islet Transplantation

- 1966: Whole Pancreas Transplant: (Minnesota).
- 30,000 (90% 1 yr graft survival). Manchester: 1848 to 2014.
- 1894: Dr Watson-Williams and Mr Harshant transplanted minced sheep pancreas (xenotransplant) into the thigh of a 15 year old boy with diabetic ketoacidosis. Although the boy's glycosuria improved for 24 h, the procedure failed

# No. of Adult Islet Allografts in Patients with Diabetes by Year from 1974 through 2003



**James Shapiro  
(2000)  
Edmonton protocol**



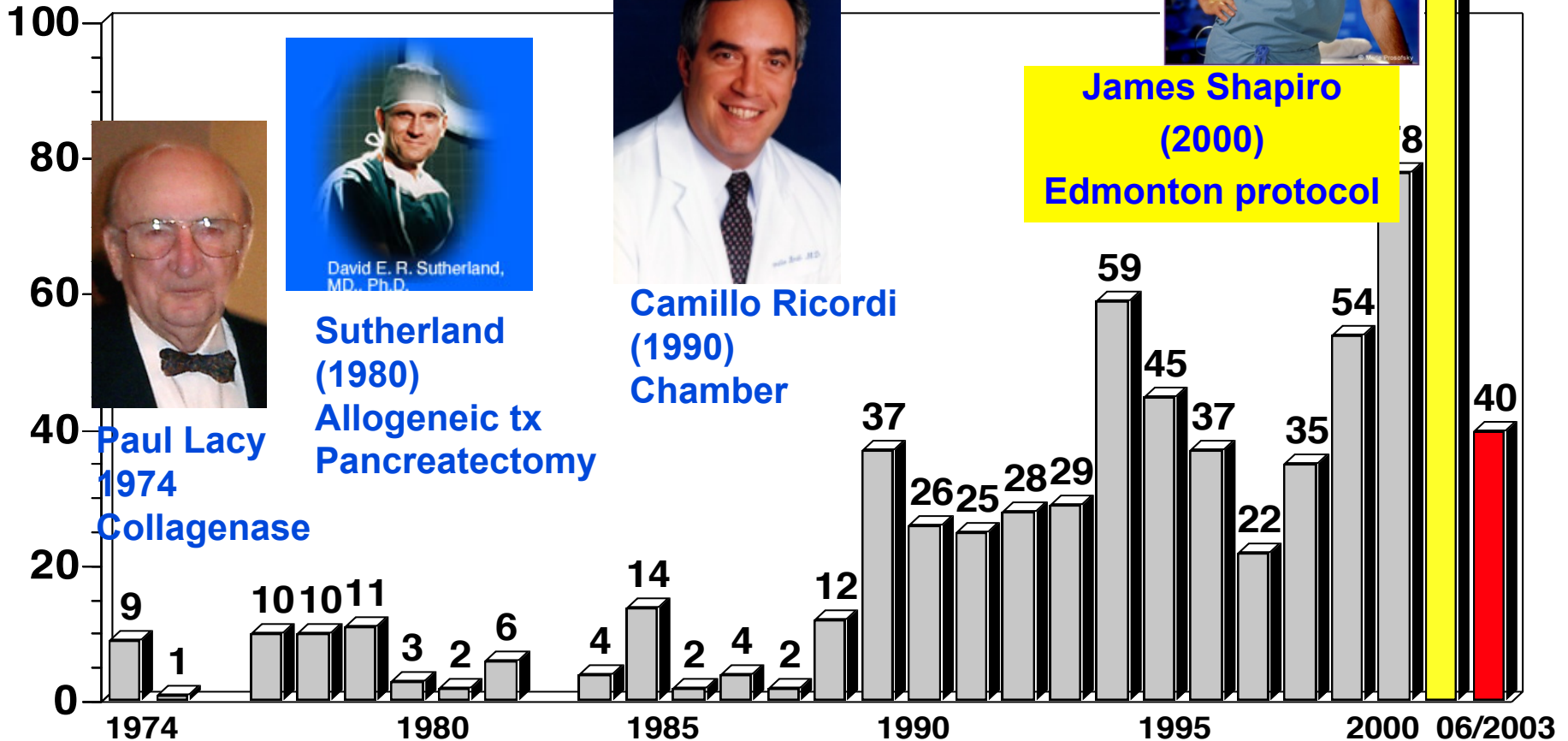
**Camillo Ricordi  
(1990)  
Chamber**



**David E. R. Sutherland,  
MD, Ph.D.  
Sutherland  
(1980)  
Allogeneic tx  
Pancreatectomy**



**Paul Lacy  
1974  
Collagenase**



**No. of Adult Islet Allografts by Year**

Issue date: April 2008



*National Institute for  
Health and Clinical Excellence*

# Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

This guidance updates and partially replaces interventional procedure guidance 13 issued in October 2003.

## 1 Guidance

1.1 The evidence on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus shows short-term efficacy with some evidence of long-term efficacy. The evidence on safety shows that serious complications may occur as a result of

warning ('hypoglycaemia unawareness'), with life-threatening consequences.

## 2.2 Outline of the procedure

2.2.1 Islet cells are obtained from pancreata of

National commissioning group: funding for highly specialised services

# UK Islet Transplant Consortium (UKITC)



Oxford

Kings

Newcastle

Bristol

Manchester

Royal Free

Edinburgh

# Islet Transplantation UK

- 1st Transplant in UK: 2005
- Total performed to 2014: 129
- Assessment: £3,395
- Islet isolation: £4,460
- Islet transplantation alone (ITA) x2: £69,231

# Who is suitable?

- Type 1 diabetes, duration >5 years
- Age 18–65 years
- C-peptide negative, <0.16 nmol/l.
- GFR within normal range for age
- **First priority: Recurrent severe hypoglycaemia (SH) of at least one year's duration, with at least 2 episodes of SH (coma, seizure, hospitalisation (blood glucose concentration <2 mmol/l)).**
- **Second priority:**  
ETDRS 3 step progression to pre-proliferative or proliferative retinopathy;  
macular oedema; worsening microalbuminuria (>50ug/min/3 months);  
painful neuropathy of increasing severity.

# Who is not suitable

- Insulin **>0.7** units/kg/day
  - ~50 units/day for a 70 kg patient
- Overweight
  - BMI **>28** kg/m<sup>2</sup>
- Poor kidney function
  - GFR **<60** ml/min



# Manchester Pathway

Review of insulin treatment or a trial of insulin pump therapy if suitable

Works well?

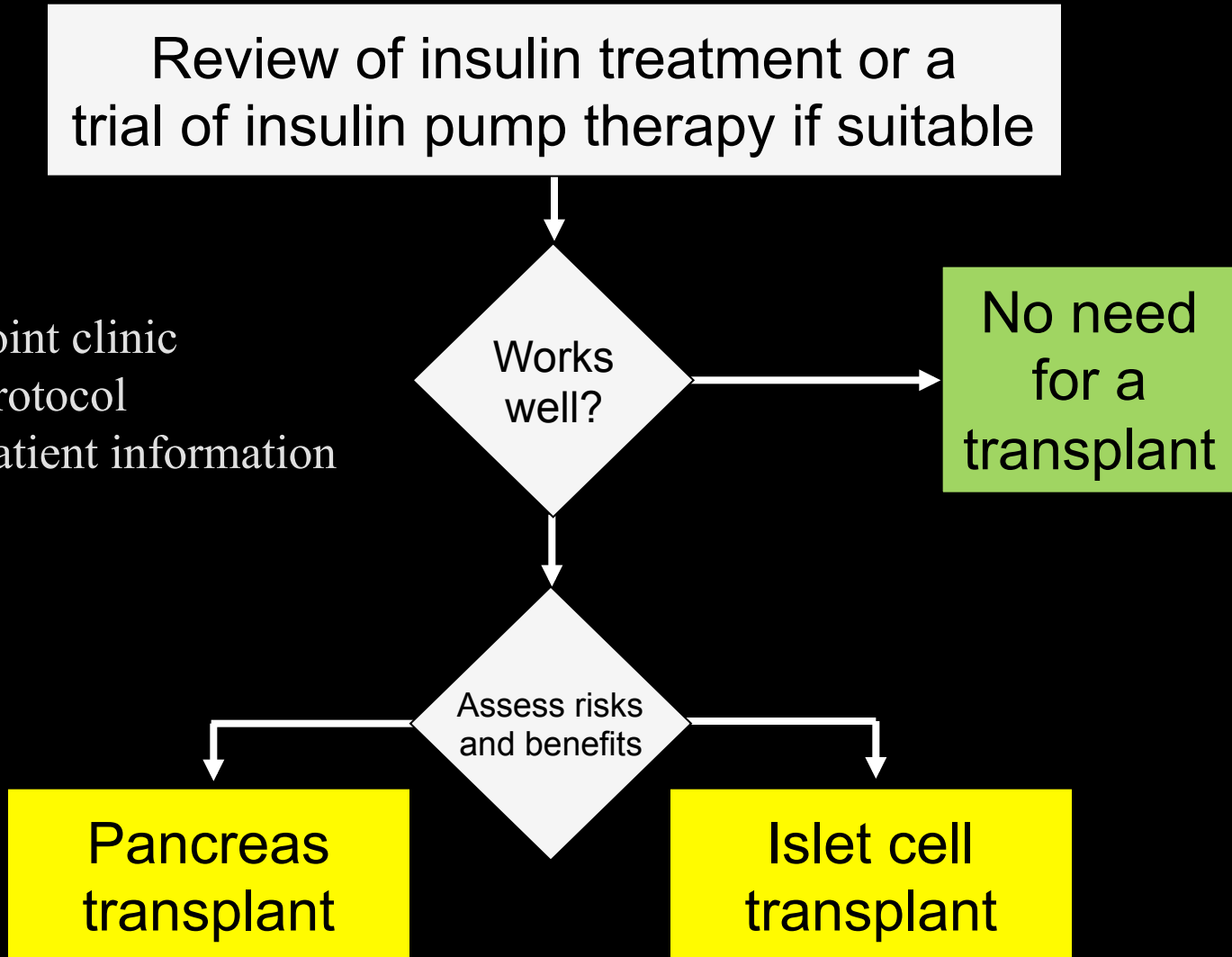
No need for a transplant

Assess risks and benefits

Pancreas transplant

Islet cell transplant

- Assess in Joint clinic
- Common protocol
- Common patient information



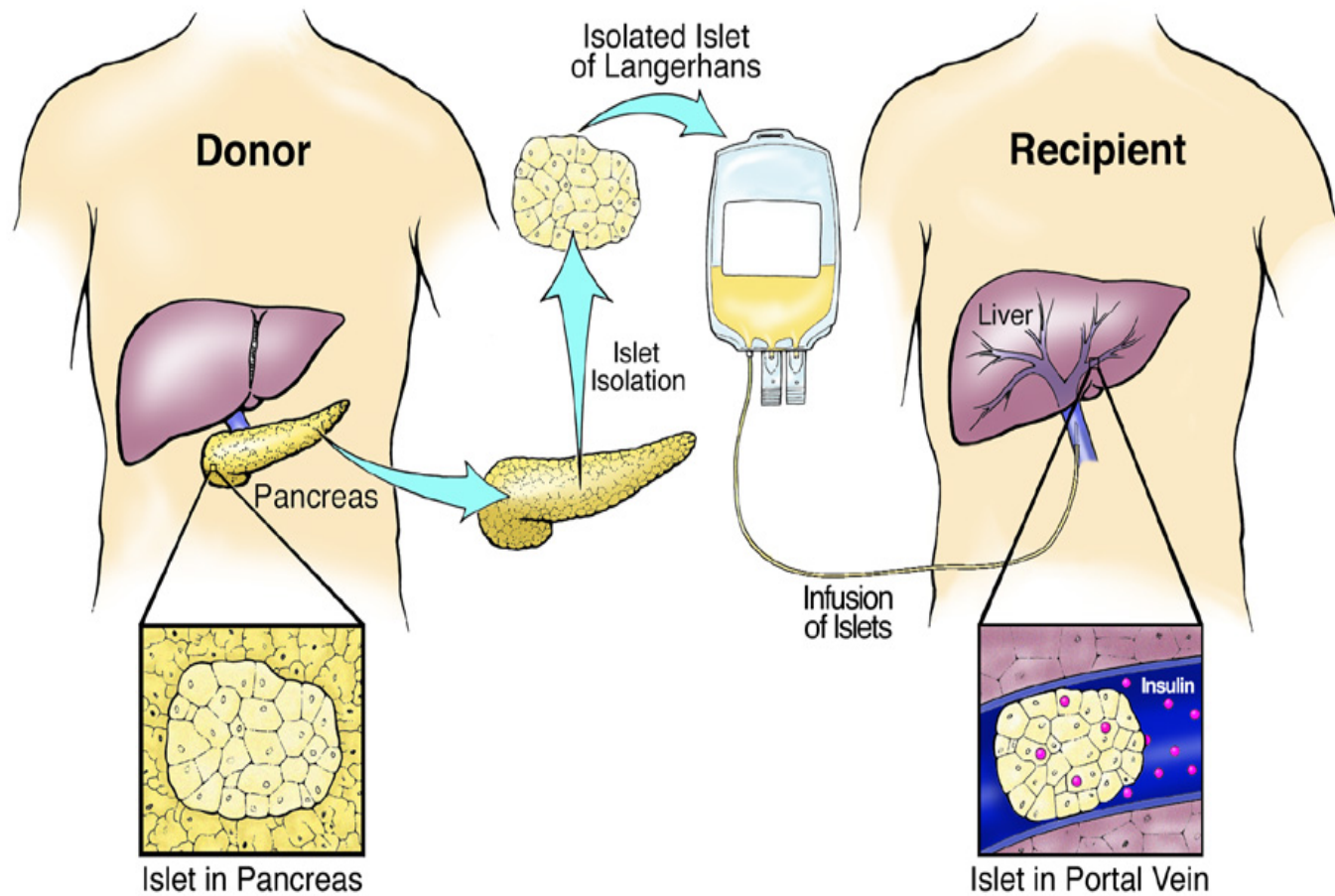
# Pre-transplant work-up

- Clinic visits++
- Continuous glucose monitoring
- Kidney, heart and liver scans
- Blood tests++
- Psychological, eye and teeth checks
  
- Waiting time ~6-18 months

# Before the islets are given ...

- Admitted to ward
- Nil by mouth, IV fluids
- Insulin, IV infusion
- Anticoagulation
- Anti-rejection, Alemtuzumab (Campath)
- Sedation with local anaesthetic
  - or short general anaesthetic

# Basics of IT



# Catheter in the portal vein



- Distal end of the 4f sheath into the main portal vein
  - Check portal pressure  $<14$  mmHg (20 cm H<sub>2</sub>O)
  - Portogram to assess anatomy

# Islet Transplantation

4FR catheter for  
portal vein cannulation



Islets infused  
via blood bag





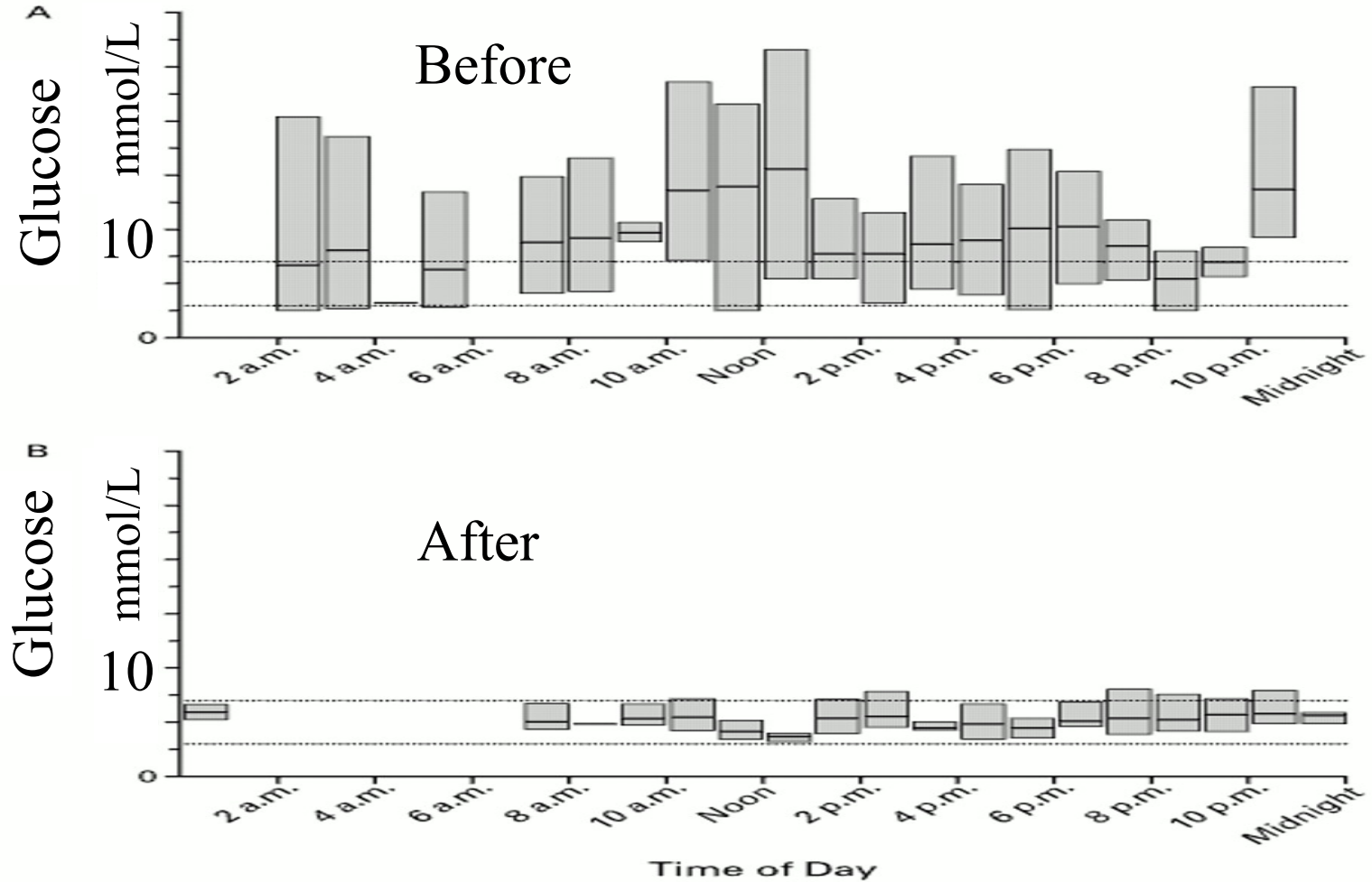
# Islet Transplantation



**What are the main benefits?**



# Glucose control

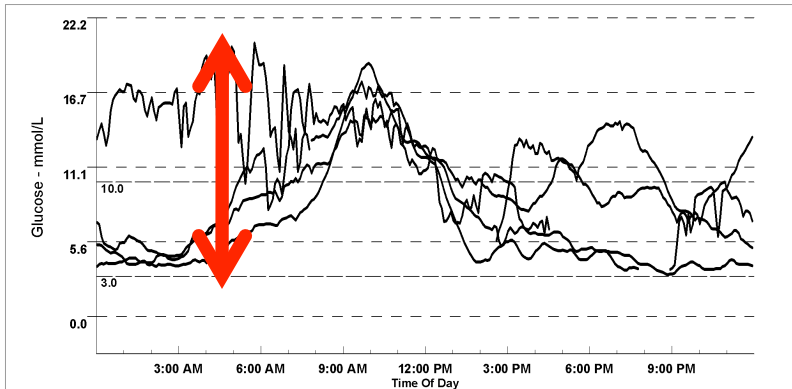


# 24-hour glucose profile

Sensor Modal Day

Patient: Leslie Jones  
ID: M0714535

Medtronic Solutions: CGMS iPro  
CGMS iPro 2.2A



Legend	Sunday	Tuesday	Thursday	Saturday
	Monday	Wednesday	Friday	

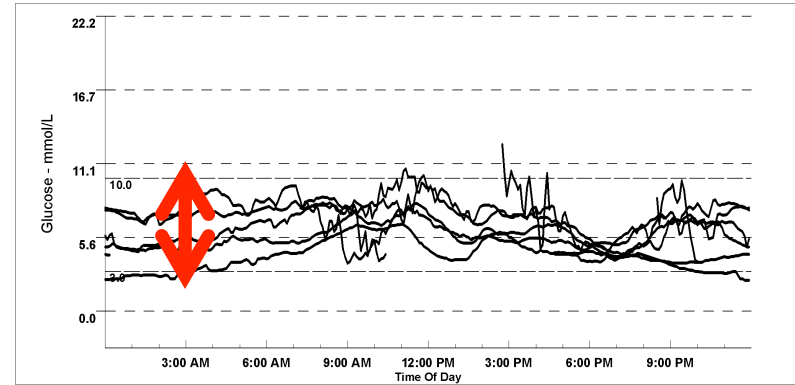
Dr Martin Rutter

Report Printed: 23-Jan-11 2:15 PM

Sensor Modal Day

Patient:  
ID: LPJ\_6month\_sept10

Medtronic Solutions: CGMS iPro  
CGMS iPro 2.2A

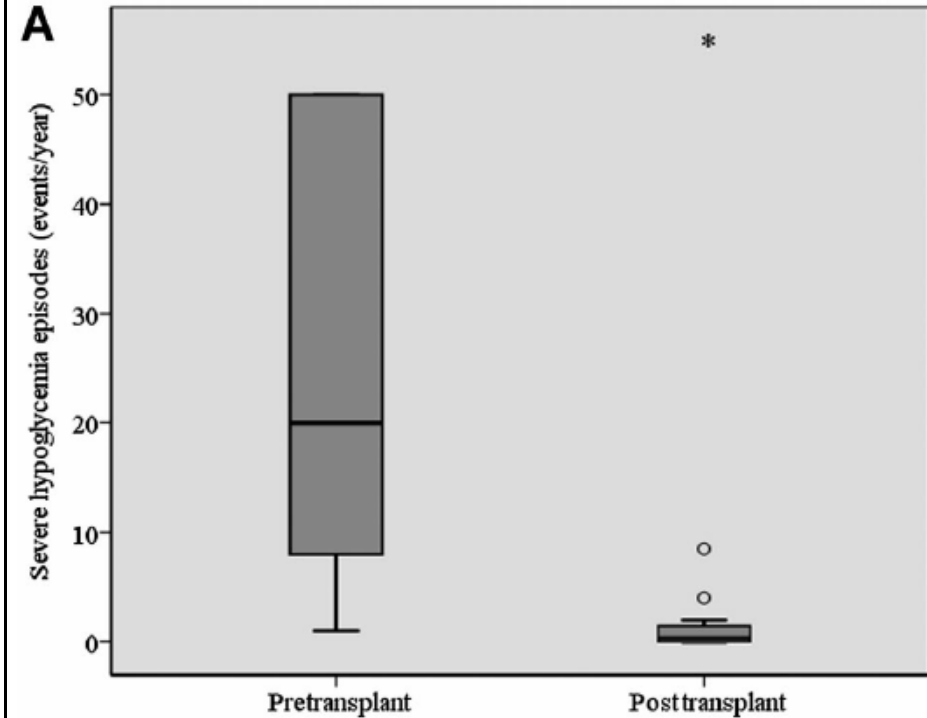
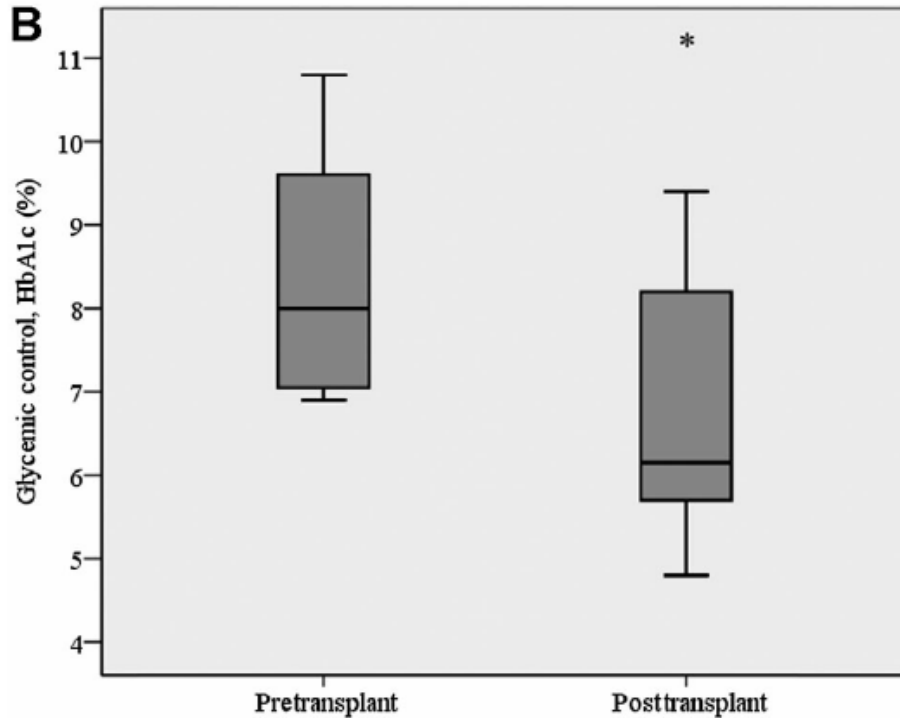


Legend	Sunday	Tuesday	Thursday	Saturday
	Monday	Wednesday	Friday	

Report Printed: 23-Jan-11 2:19 PM

# Attainment of Metabolic Goals in the Integrated UK Islet Transplant Program With Locally Isolated and Transported Preparations

UK 1 yr graft survival 87%



Brooks et al. AJ Transplantation 2013; 13: 3236-3243

# Weight Loss

↓ 9kg

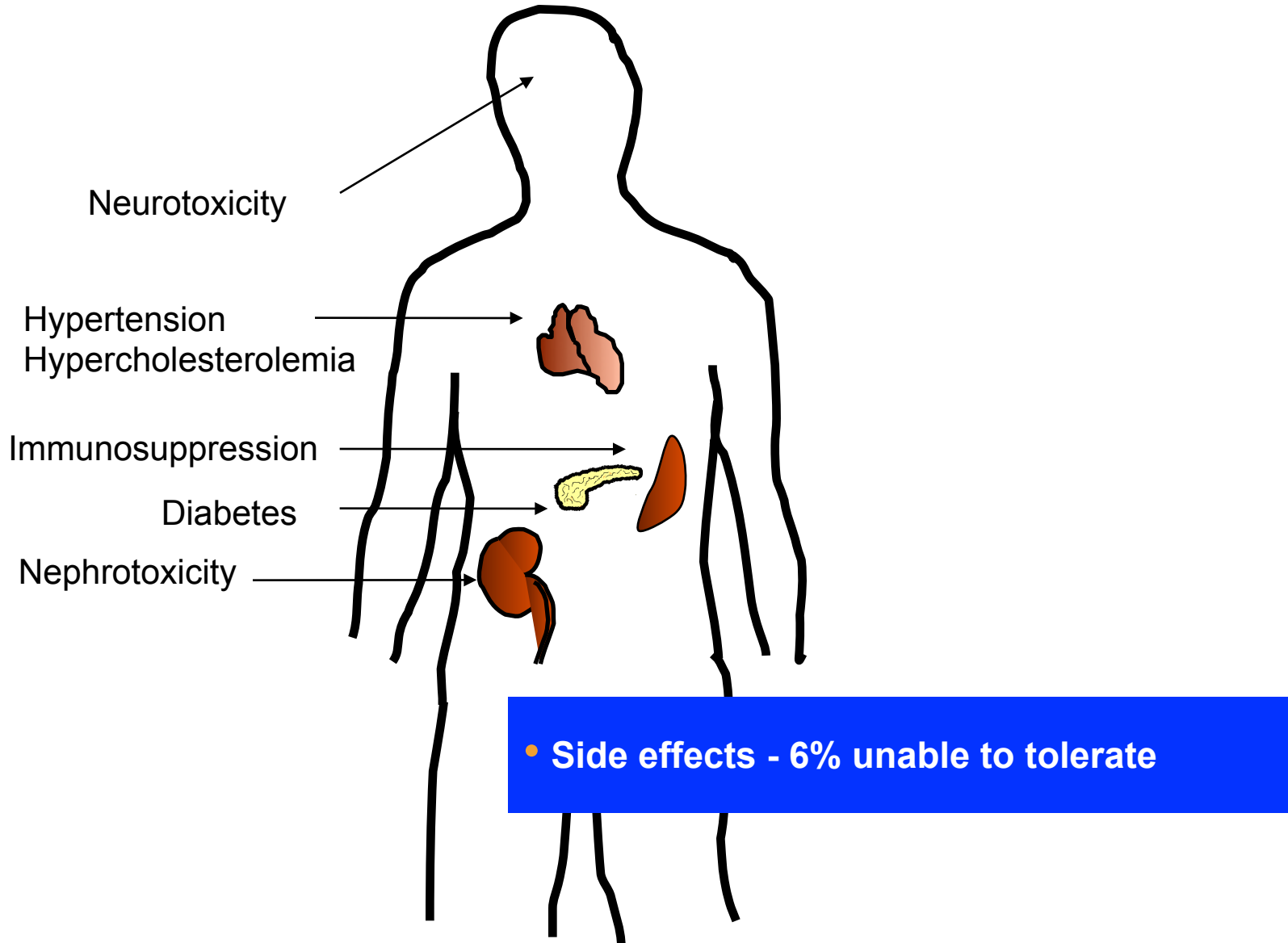


**"This treatment has been fantastic!  
Before my transplant, I was always eating to avoid "hypos", and now, it's like the clock  
has been turned back to when my diabetes was easy"**

# Short term risks

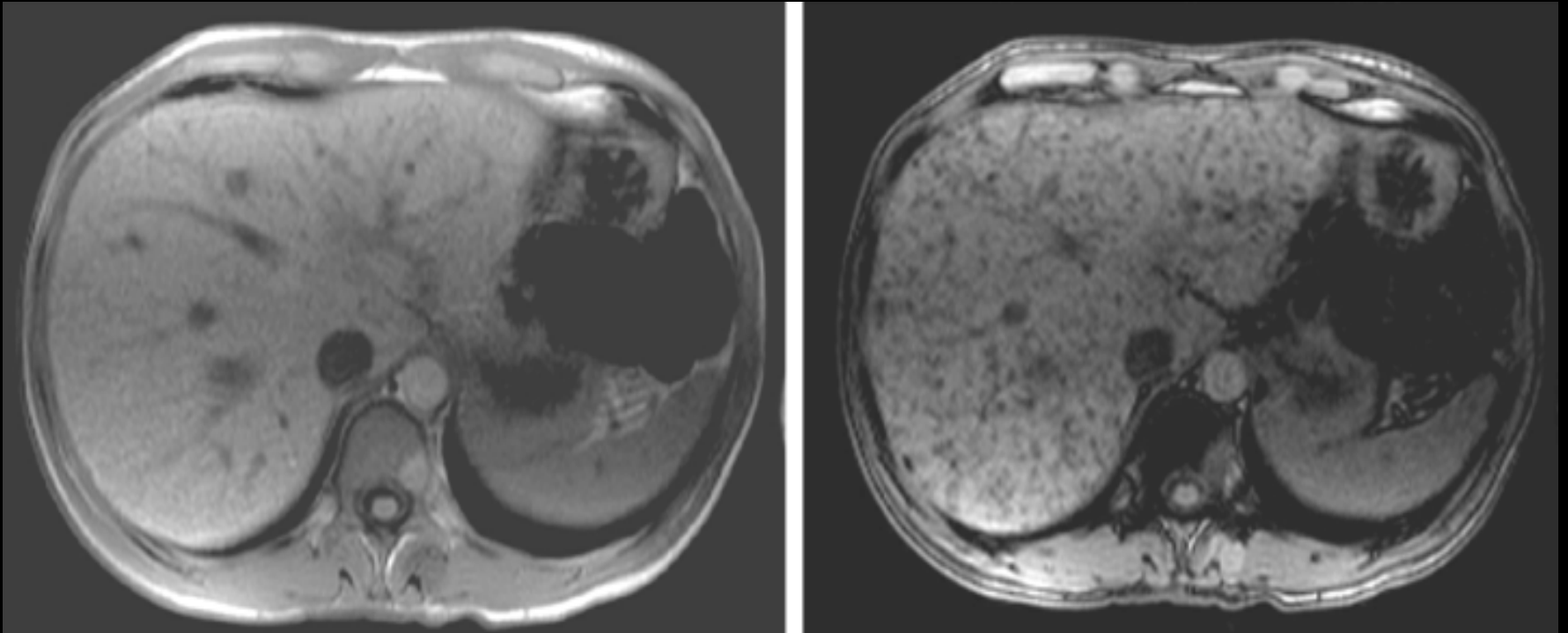
- Bleeding or haematoma, 10% usually mild
- Portal vein thrombosis, 5%
  - major cause for failure in early transplants
- Sepsis
- Gall bladder puncture

# Sirolimus and Tacrolimus - Drug Side Effects



# Hepatic Steatosis

T1 weighted MRI: Periportal loss of signal intensity which is diagnostic for geographic steatosis



Markmann et al. Diabetes 2003, 52: 1591-1594

# Long term risks



# Cancer

3-year risk of cancer and relative risk in CRF patients receiving kidney transplants or usual care

	Transplant	No transplant	RR	XS cases/1000
Any cancer (not skin)	8%	6%	1.2	11
Melanoma	0.30%	0.15%	2.2	1.5
Any skin cancer	7%	3%	2.6	43

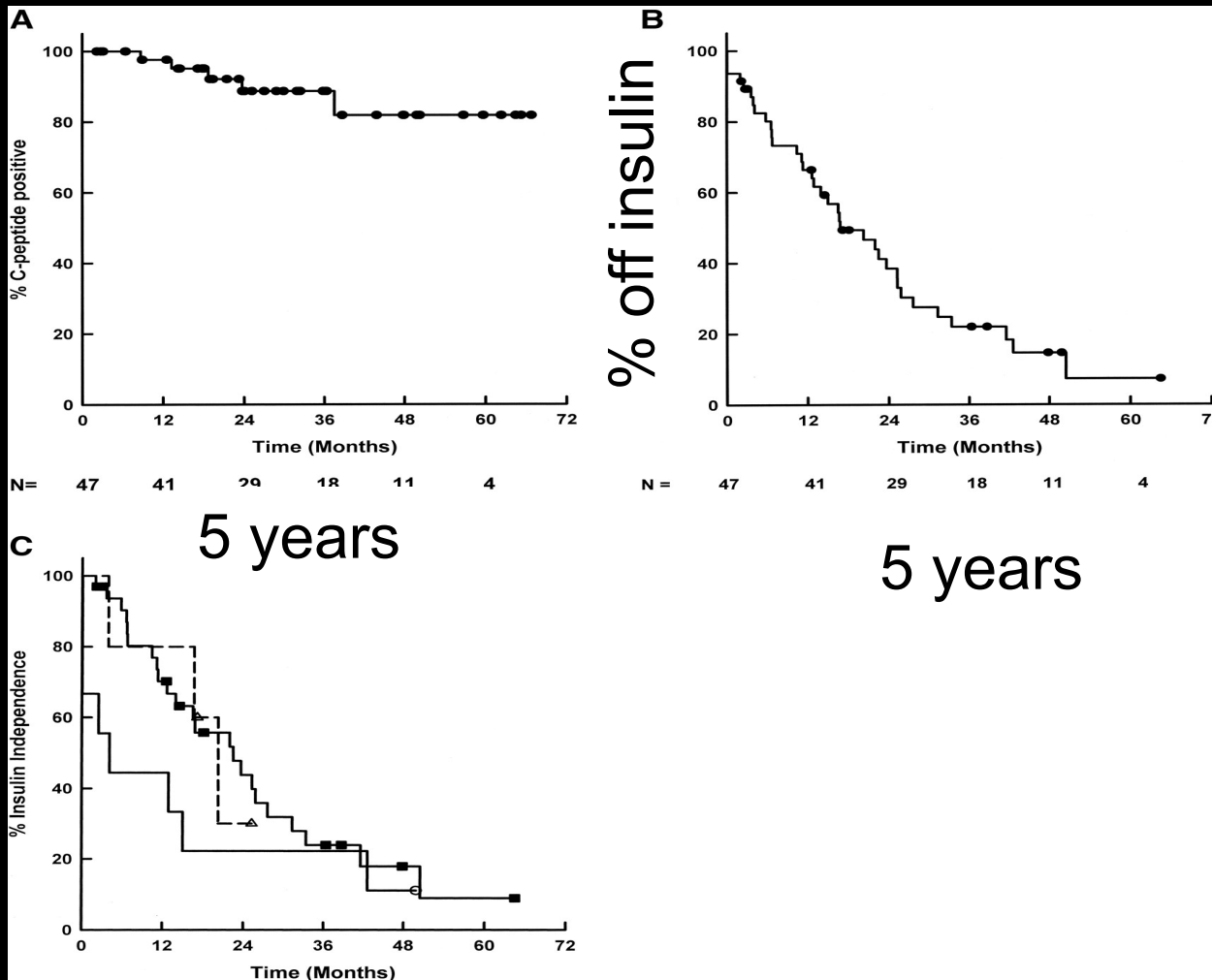
**Kasiske BL et al. Am J Transplant. 2004; 4:905-913**

# Infection

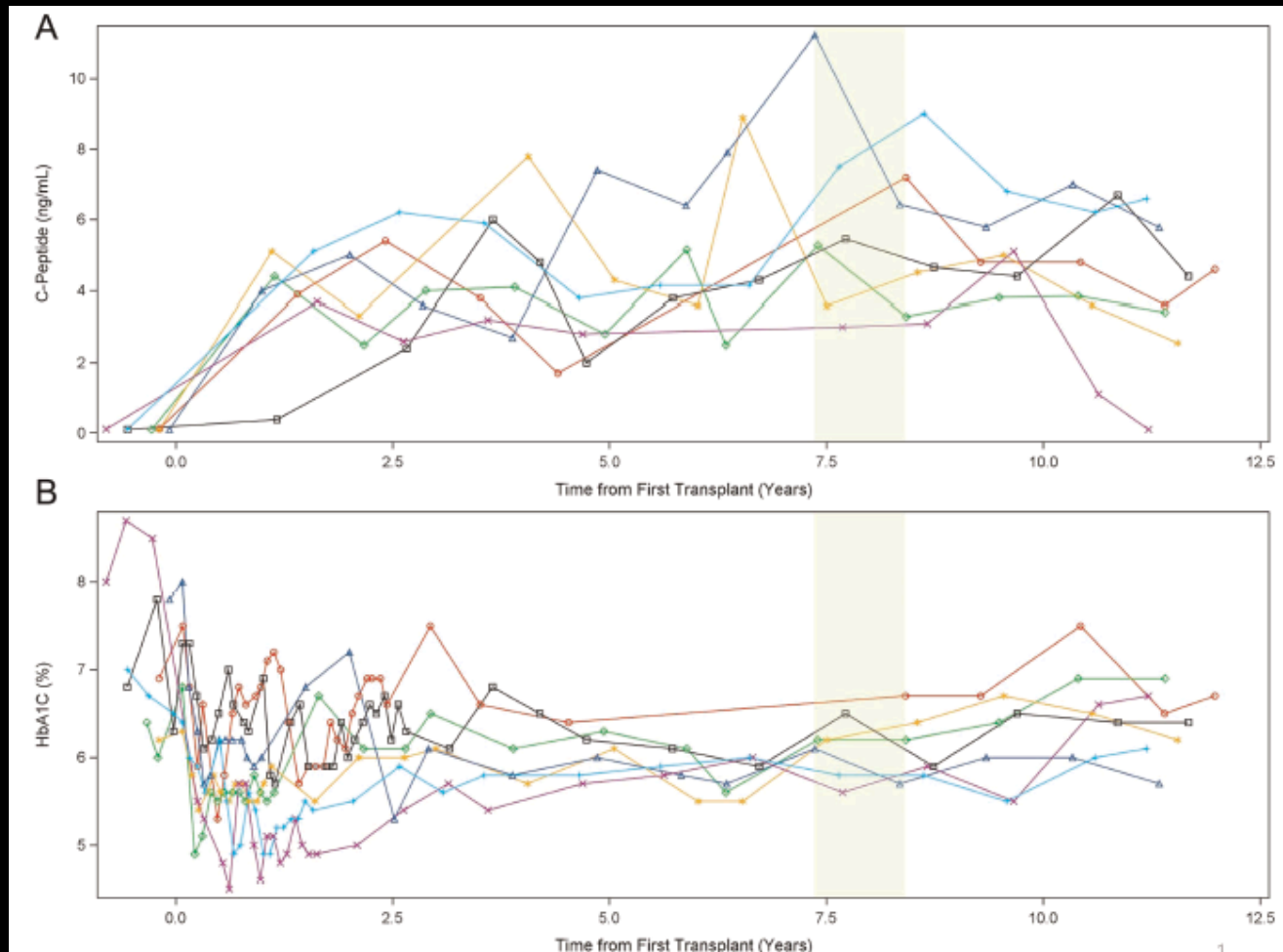
- International registry
- 500+ patients
  - 2% risk of life-threatening infection over 6 years
  - 0.3% risk of death due to infection

# Edmonton 5-years: 11% Insulin-free

% making insulin



# Long-Term Follow-Up of the Edmonton Protocol of Islet Transplantation in the United States



**5/7 needed Insulin: 25-50% of pre-transplant dose**

Brennan et al A J Transplantation 2016; 16: 509-517

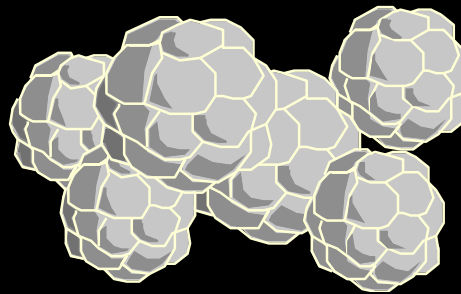
# 60% of Islets fail immediately!

**Insufficient islet mass**

**IBMIR**

Instant blood mediated inflammatory reaction

**Failure to engraft**



**Toxicity of anti-rejection drugs**

Tacrolimus levels  
x3 in portal vein

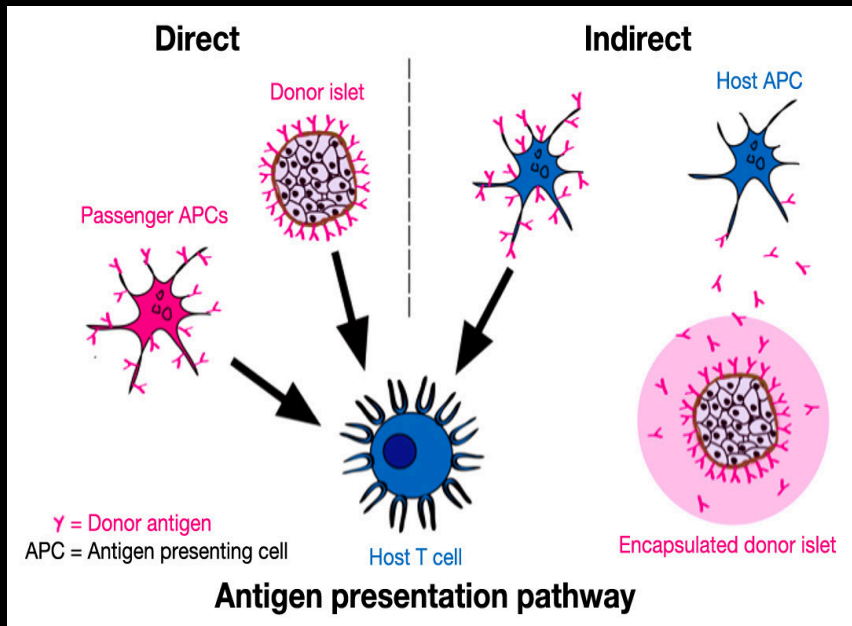
**Islets**

**Inadequate blood supply**

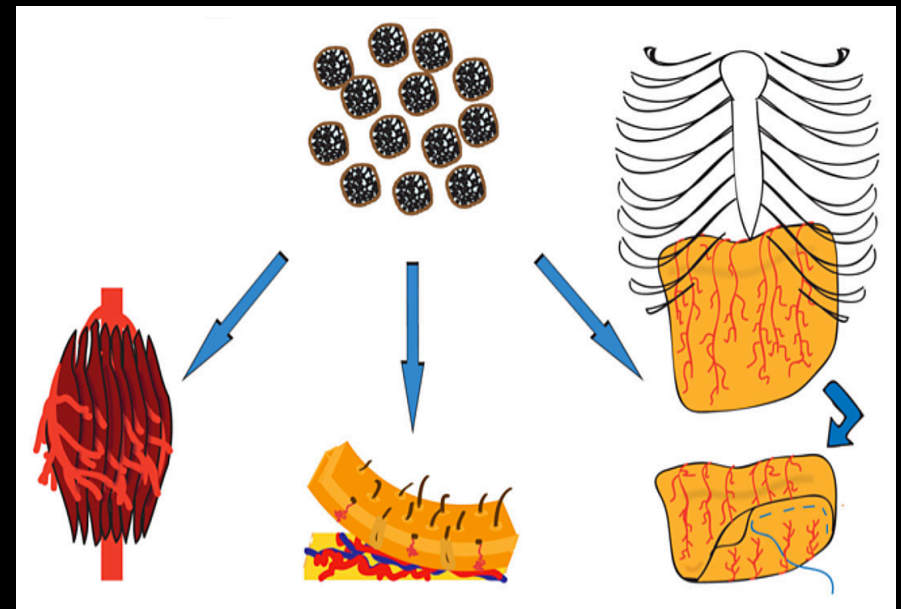
**Allograft rejection**

# Enhancing Clinical Islet Transplantation through Tissue Engineering Strategies

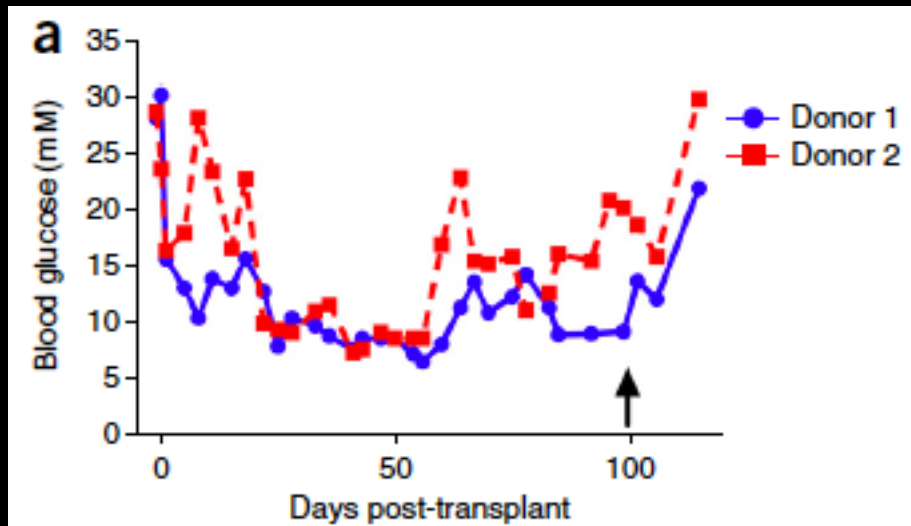
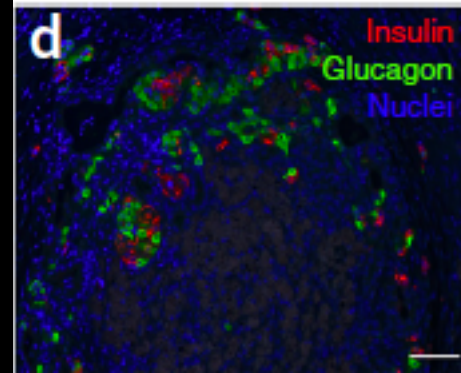
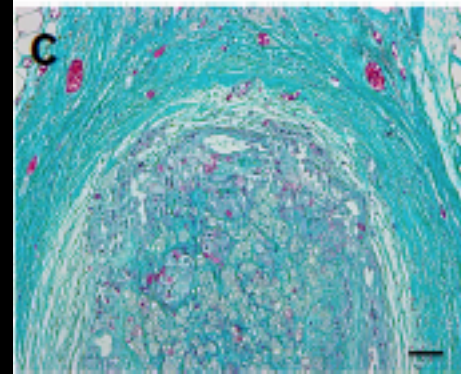
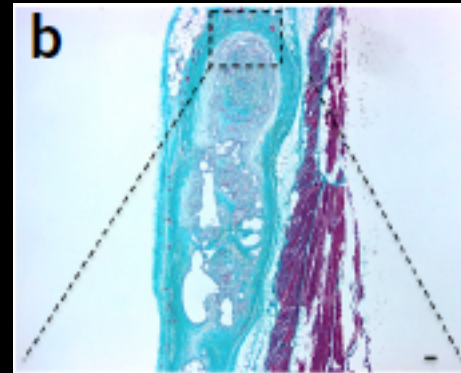
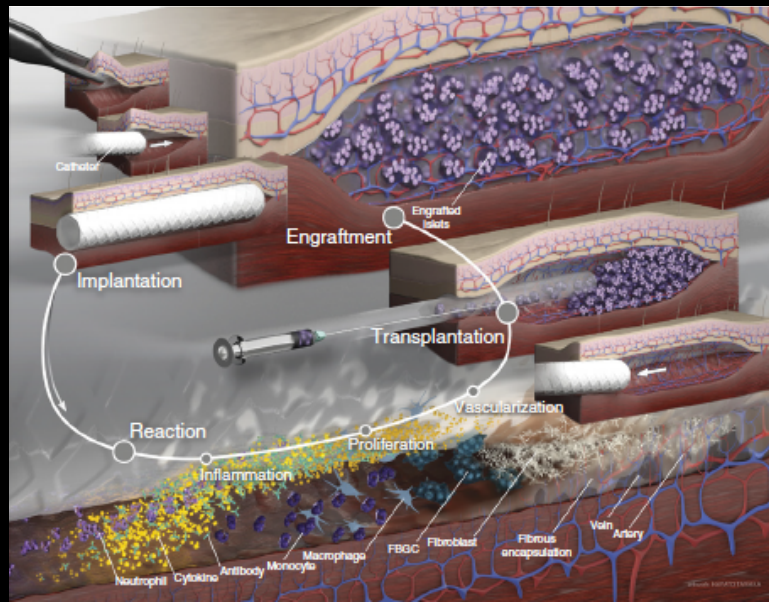
## Immune/inflammation



## Vascularity



# A prevascularized subcutaneous device-less site for islet and cellular transplantation



# Future Avenues

- In vitro expansion of human islets (fetal pancreata)
- Genetically engineered non-islet or human cell lines
- Stem cells (mutagenesis/teratoma)
- Xenotransplantation (other species)
- Encapsulation of Islets
- Biodegradable scaffold to protect B-cells placed in omentum (Miami-Feb 2014)



**Thank you**