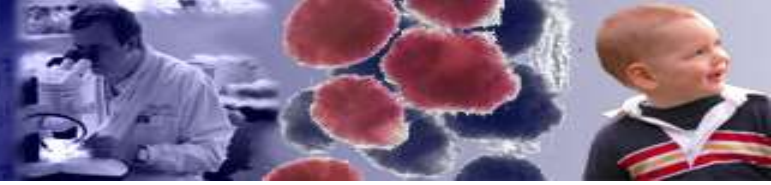

‘Islet Transplantation: From Research to Reality’

Paul R V Johnson

Director of Oxford Islet Transplant Programme

,

NUFFIELD DEPARTMENT OF SURGICAL SCIENCES

Oxford Centre for Diabetes Endocrinology & Metabolism

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UK ANNOUNCES NEW 50P COIN TO COMMEMORATE BREXIT

Outline

- Rationale for Islet Transplantation
- Methods
- Current Results
- Ongoing Challenges / Future Opportunities

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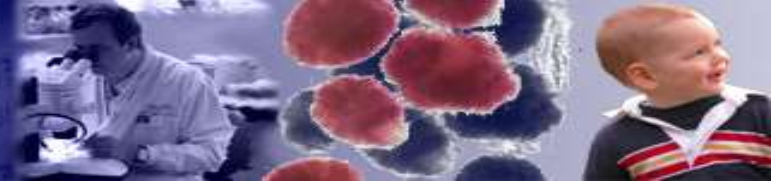
Rationale

Ideal Treatment for T1DM
(once it has developed)



1) Restore true normal glucose homeostasis by coordinated islet hormone release (rather than just manage glycaemic excursions)

2) ‘Switch off’ ongoing autoimmune destruction

3) Replace islet-cells that have been destroyed

4) Prevent any secondary complications or reverse them if they have already developed

5) Treatment well-tolerated + appropriate for children

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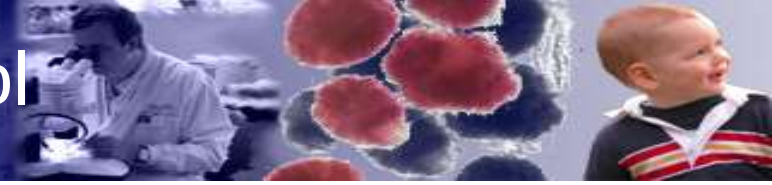
Benefits of Tight Glycaemic Control



Intensive glucose control versus conventional glucose control for type I diabetes mellitus (Review)

Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A

THE COCHRANE COLLABORATION®

Tight blood sugar control reduces the risk of developing microvascular diabetes complications. The evidence of benefit is mainly from studies in younger patients at early stages of the disease. Benefits need to be weighed against risks including severe hypoglycaemia, and patient training is an important aspect in practice. The effects of tight blood sugar control seem to become weaker once complications have been manifested. However, further research is needed on this issue. Furthermore, there is a lack of evidence from RCTs on the effects of tight blood sugar control in older patient populations or patients with macrovascular disease. There is no firm evidence for specific blood glucose targets and treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities.

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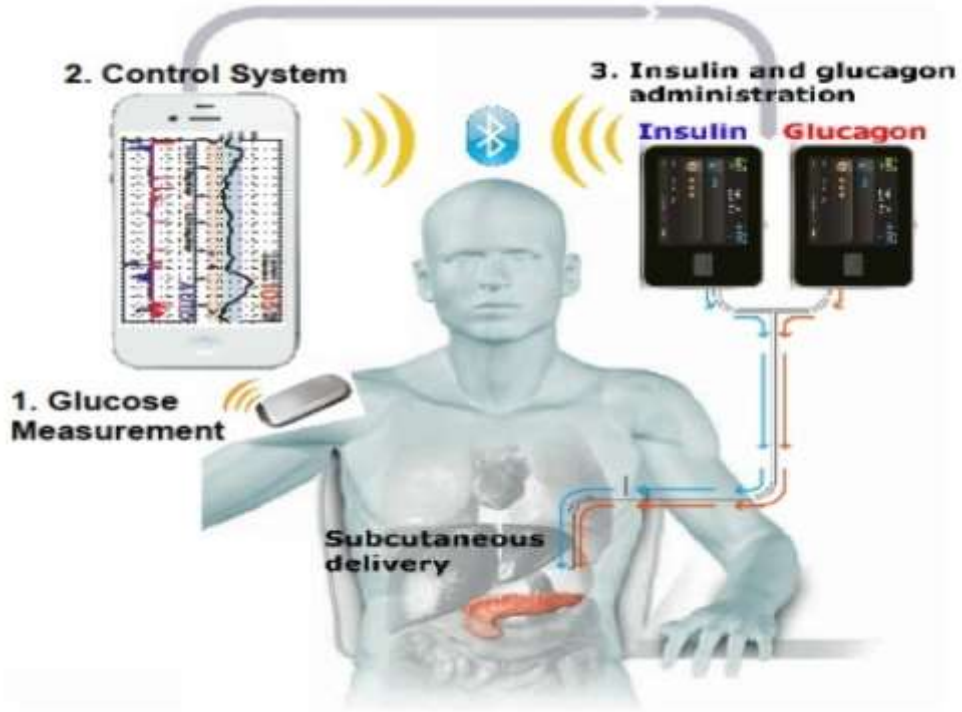
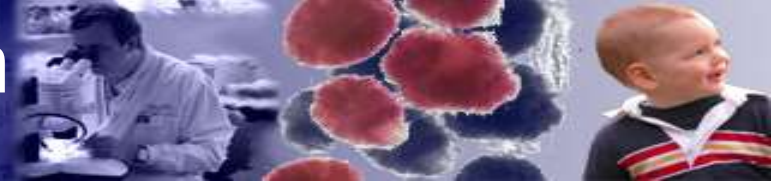
Advancing Technology

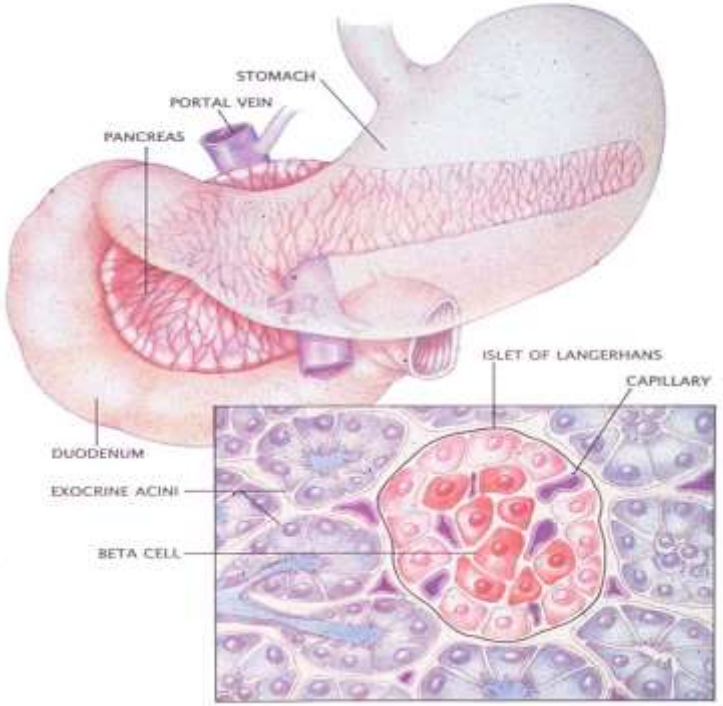


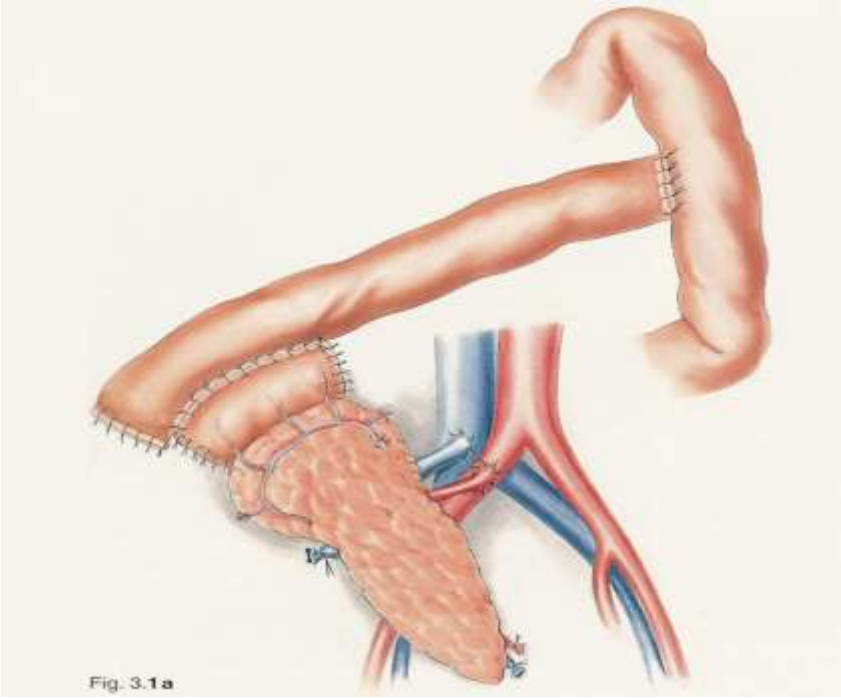
Technology vs Transplantation



Treatment Aim	Technology	Transplantation
1) Potential to restore normal glucose homeostasis	(✔)	✔
2) Prevent /Reverse secondary complications	✔	✔
3) Replace lost beta-cells	X	✔
4) Switch off autoimmunity	X	✔

Whole Pancreas Transplantation





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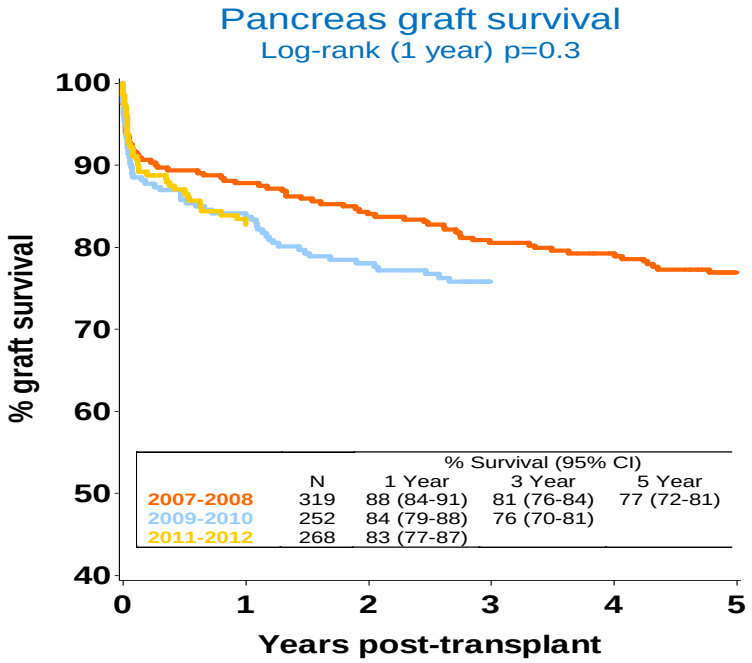
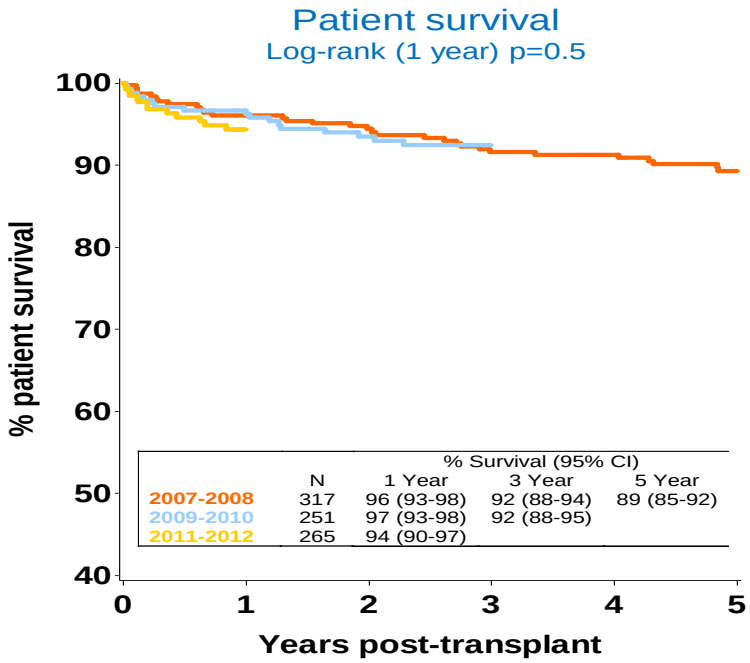
UK SPK Results





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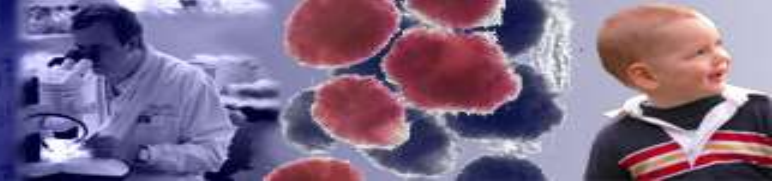
Patient Survival



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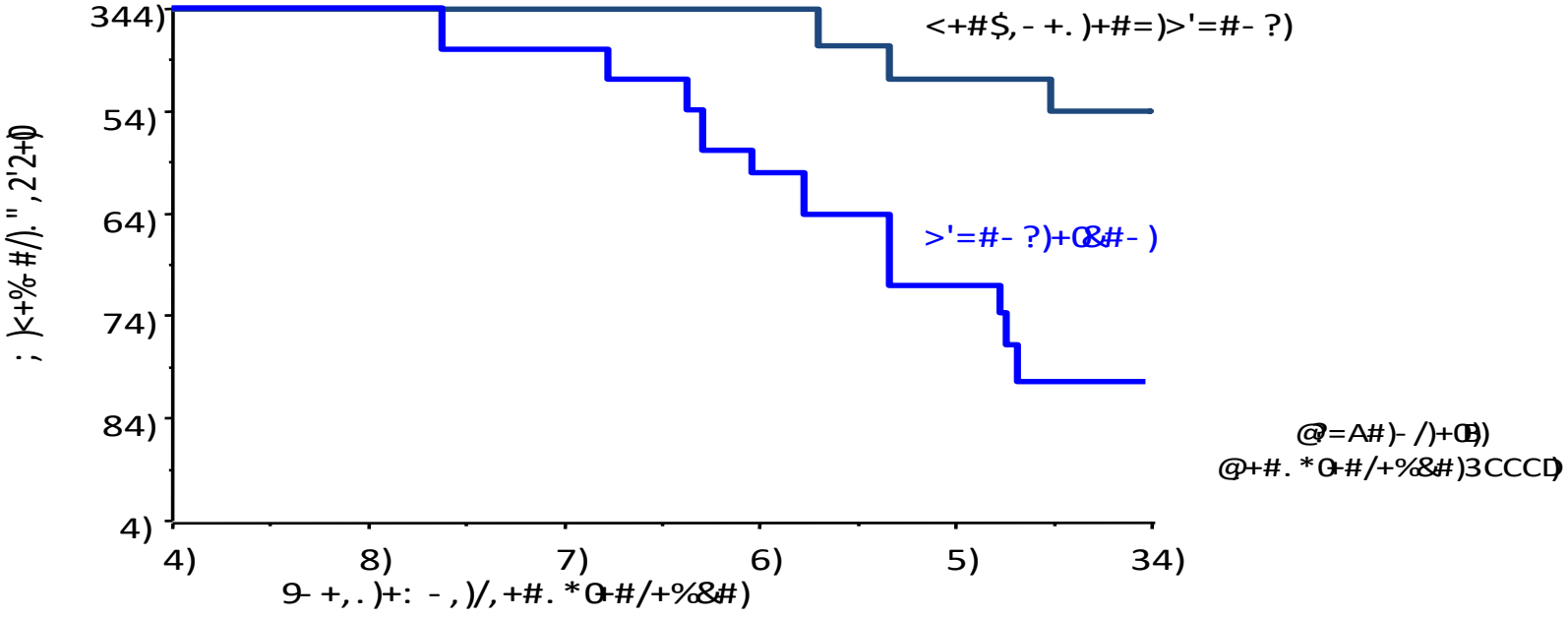

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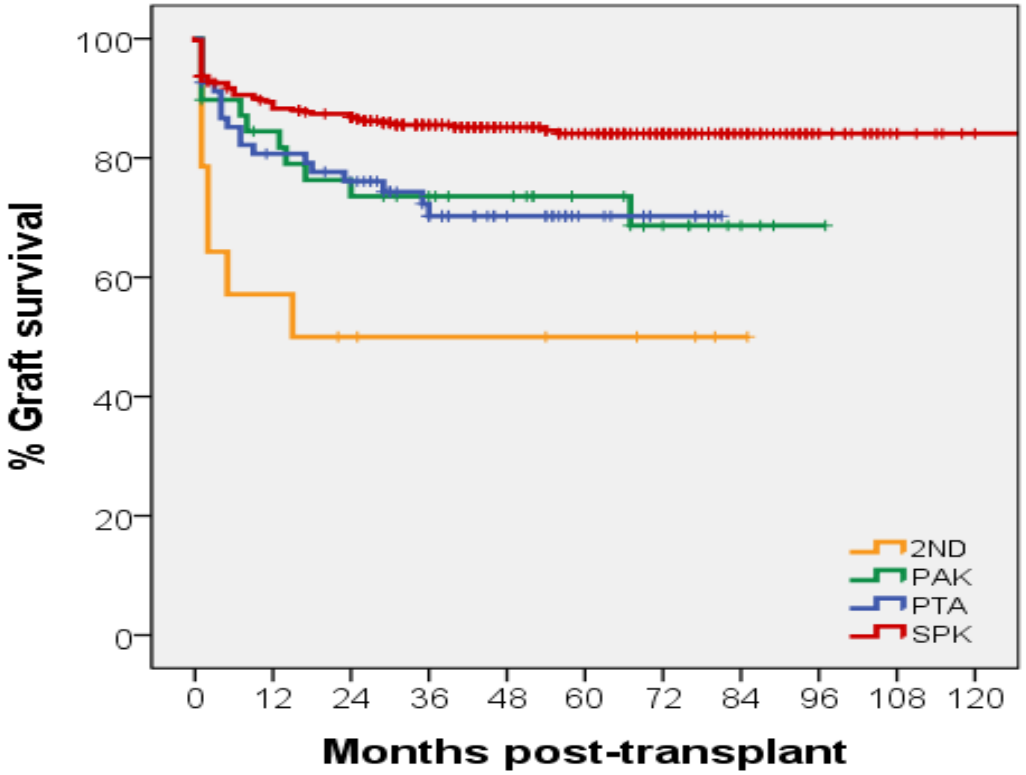
SPK vs PTA



	1 year	3 year	5 year
SPK	88%	86%	84%
PTA	79%	70%	70%
PAK	76%	74%	74%
2nd Tx	57%	50%	50%

Cold Spring Harb Perspect Med 2014;4:a015610

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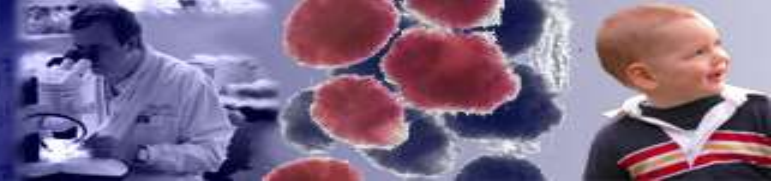
Whole Pancreas Tx



- Very good results when combined with renal graft with high levels of insulin independence and stabilisation / reversal of secondary complications
- Still major procedure, with significant morbidity and mortality
- Unlikely to ever be applicable to children without 2^{o} complications
- Is Risk / Benefit of PTA justifiable for treating hypoglycaemic unawareness alone?

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Whole Pancreas vs Islets

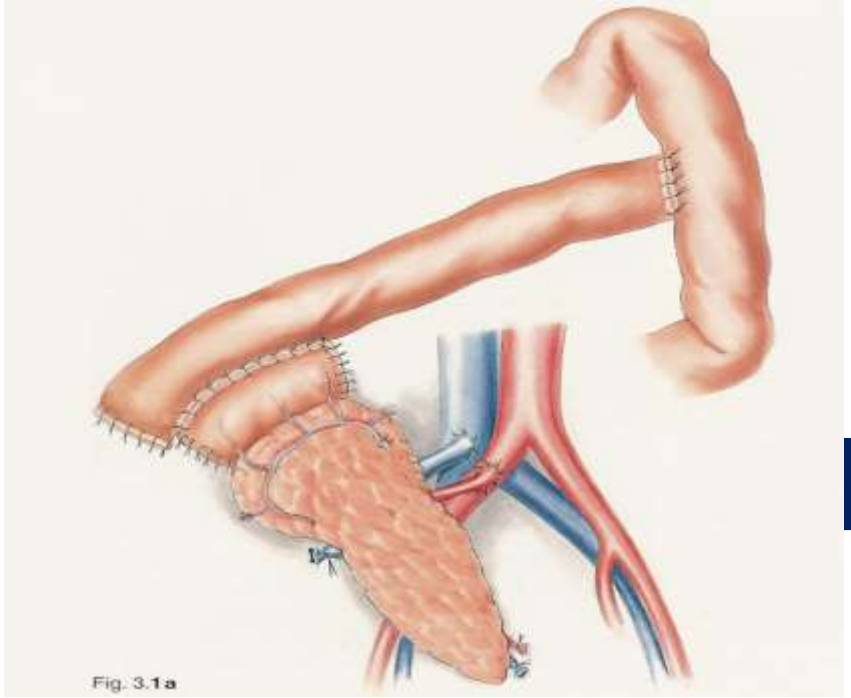
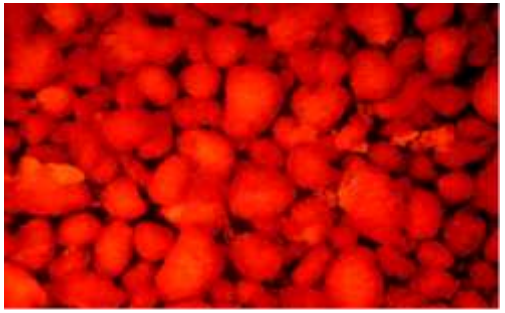


Fig. 3.1a



< 5 ml

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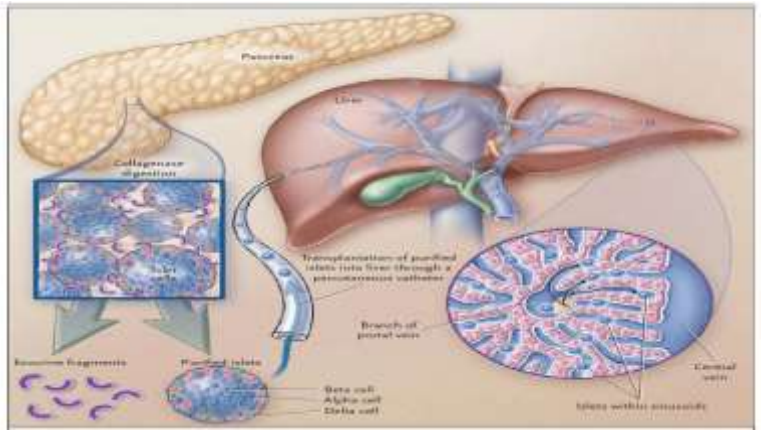
Islet Transplantation



- Endocrine pancreas only
- Minimally invasive with minimal morbidity or mortality
- Can restore normal glucose homeostasis with coordinated secretion of all islet hormones
- Potential to immunomodulate islet graft or promote strategies for immune tolerance
- Techniques all potentially applicable to children

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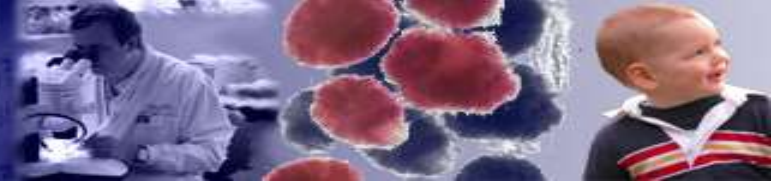
Islet Transplant Options



- **Diabetes with hypoglycaemia-unawareness**
  - Islet transplant alone (ITA)

- **Diabetes with renal failure**
  - Simultaneous islet + kidney (SIK)
  - Islet after kidney (IAK)

- **Surgically-induced diabetes**
  - Islet Auto-transplantation

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Islet Transplant Options

- **Diabetes with hypoglycaemia-unawareness**
  - Islet transplant alone (ITA)

- **Diabetes with renal failure**
  - Simultaneous islet + kidney (SIK)
  - Islet after kidney (IAK)

- **Surgically-induced diabetes**
  - Islet Auto-transplantation

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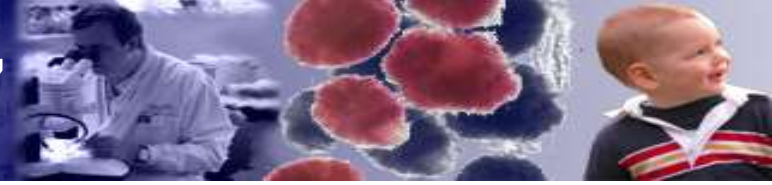
Whole Pancreas vs Islets!

‘Beta Cell Replacement’



Whole Pancreas Transplantation,
Nephrology
Islet Transplantation,
Diabetology,
Stem-Cell Biology,
Bioengineering,
Nanotechnology

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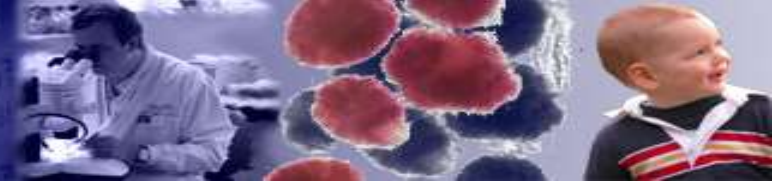
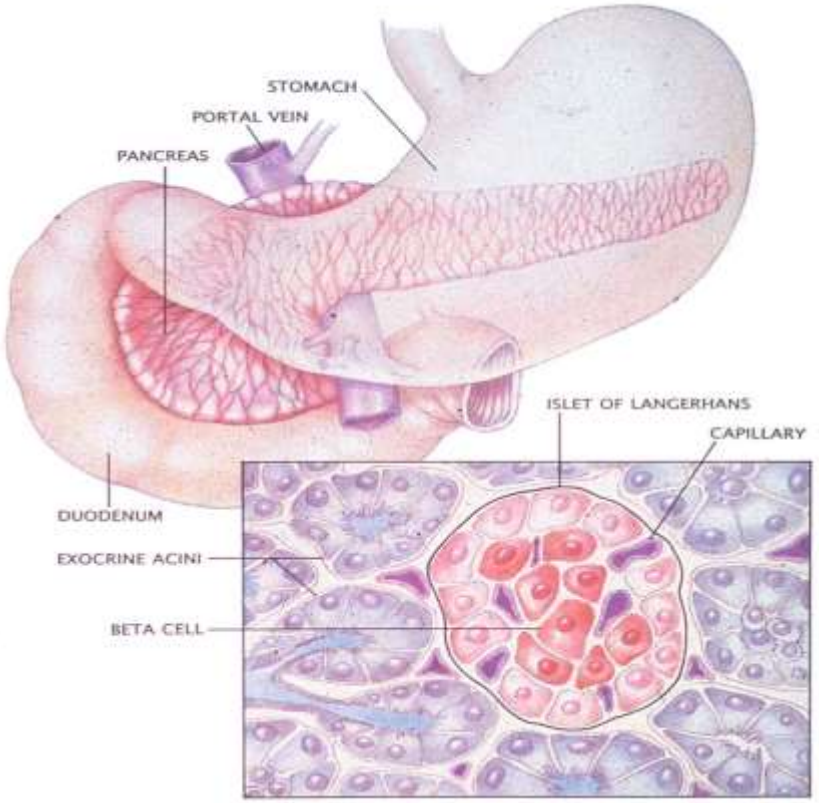
Methods

Human Islet Isolation





2 stages:

- Collagenase Digestion (releasing islets)
- Density-Gradient Purification (separating islets)

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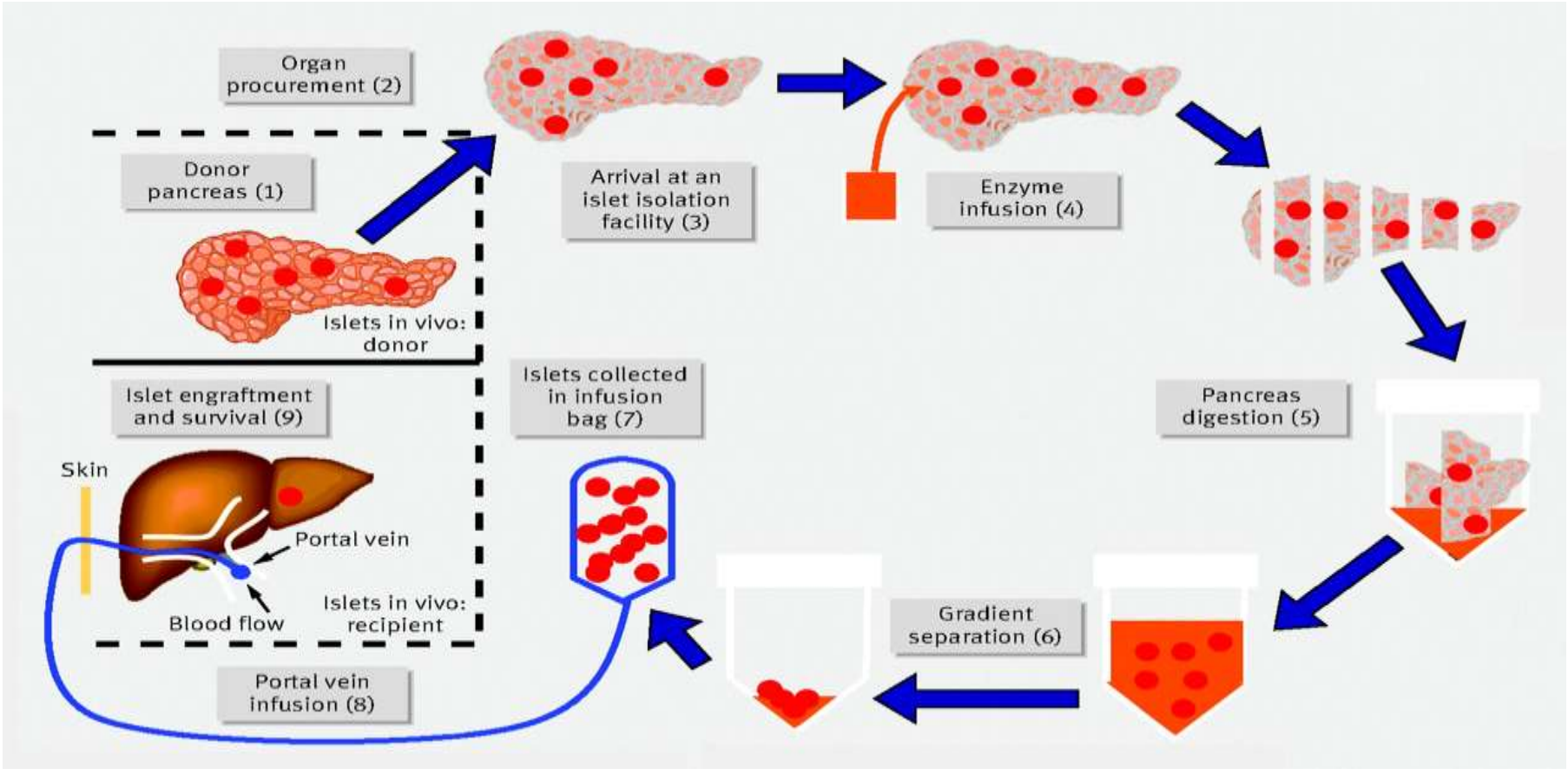
Islet Isolation and Islet Transplantation



Islet Isolation Facility

DIABETES RESEARCH & WELLNESS FOUNDATION™

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30/11/2012

Dissection and Perfusion

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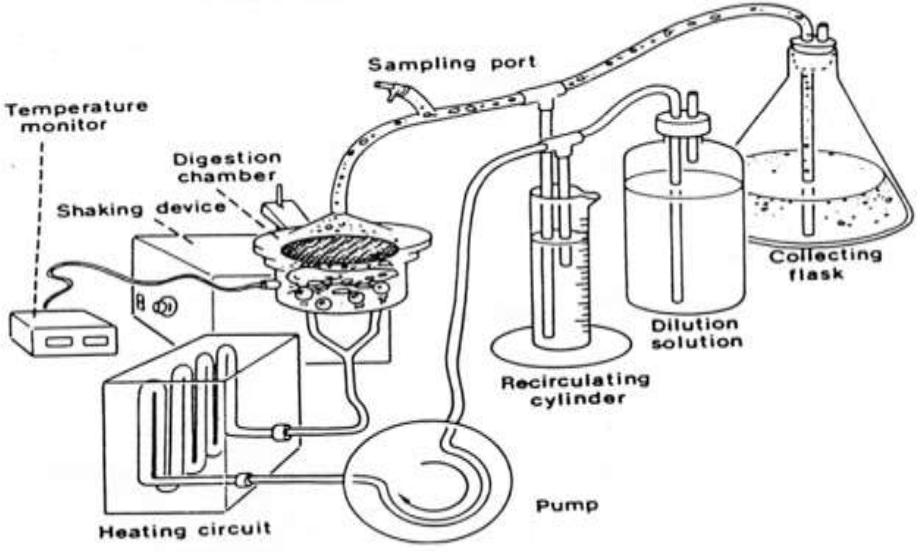
Pancreas Digestion



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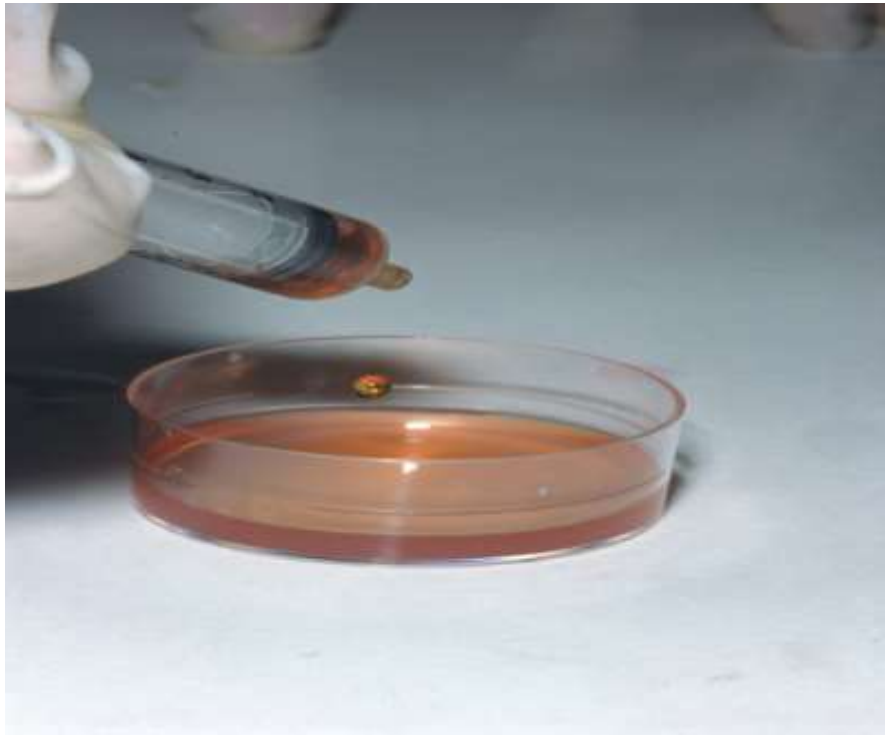
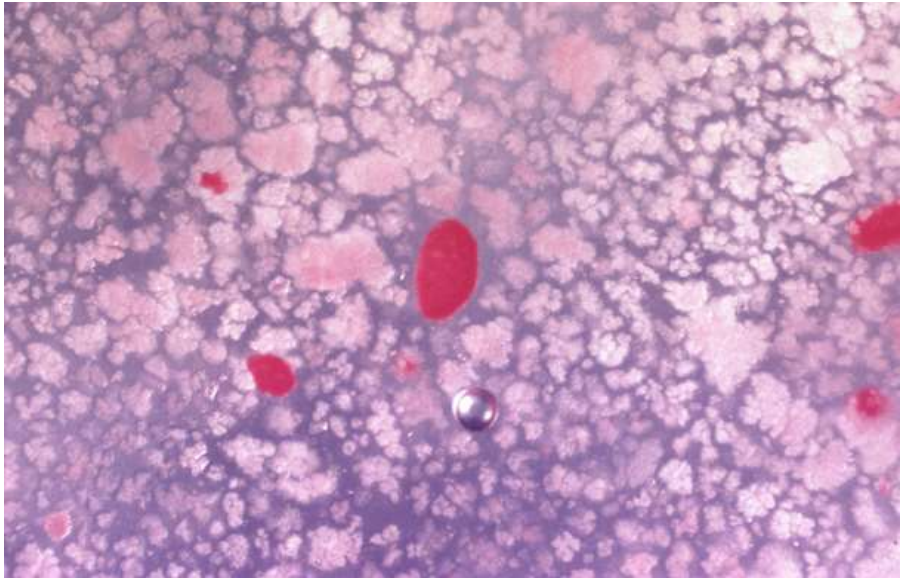
Monitoring Digestion





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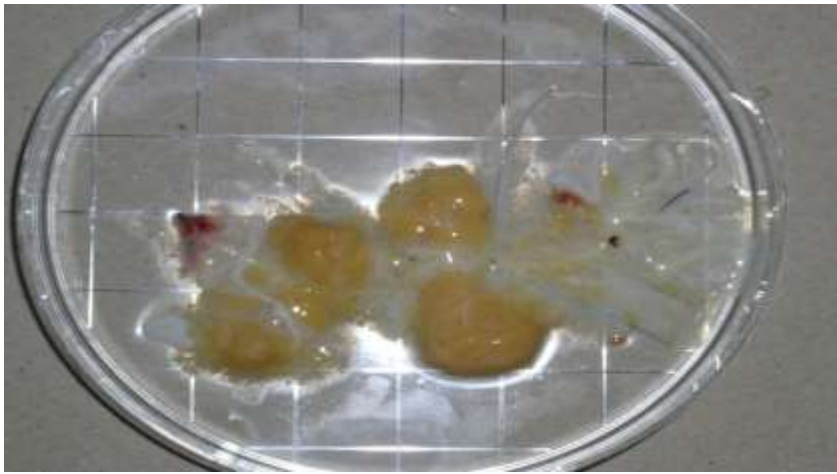
Optimal Digestion



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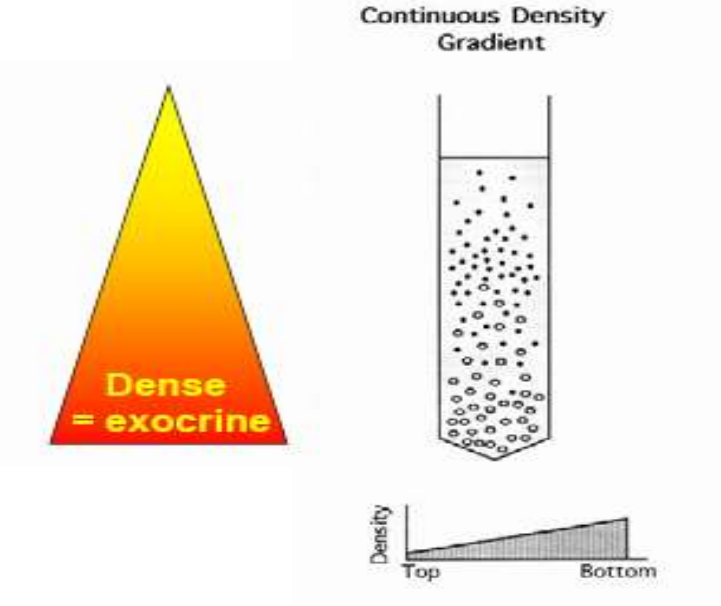
Density-Gradient Purification



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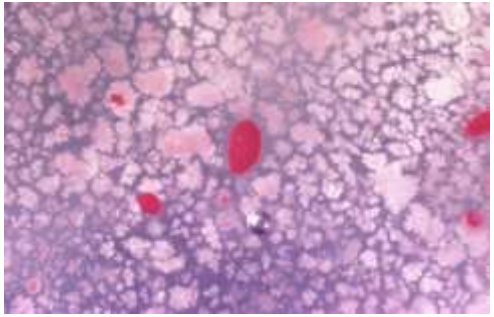
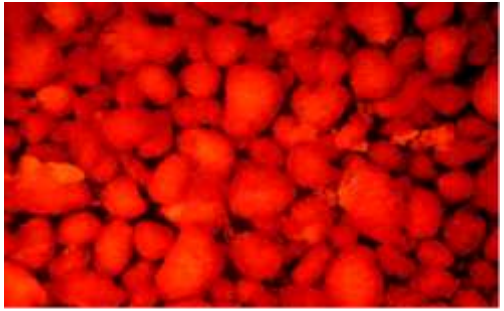
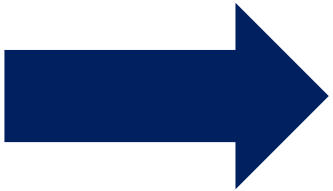
Why purify?







20 – 50 ml

< 5 ml

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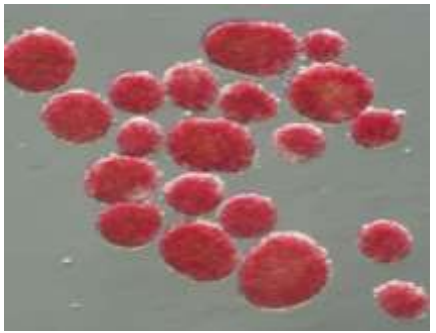
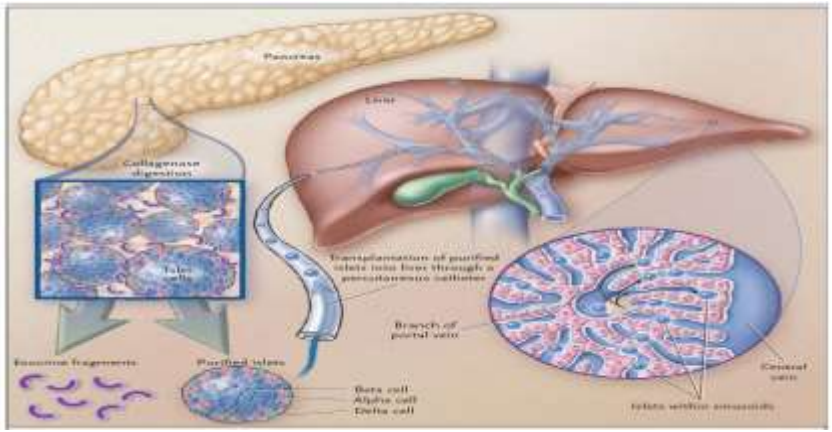
Culture



- Logistics
- Quality testing
- Patient pre-treatment

Islet Transplant (1)



- Percutaneous transhepatic approach via portal vein (or laparoscopic / mini-lap.)
- Antibiotic and Heparin cover
- Infuse over 20-30 minutes
- Monitor portal pressure throughout

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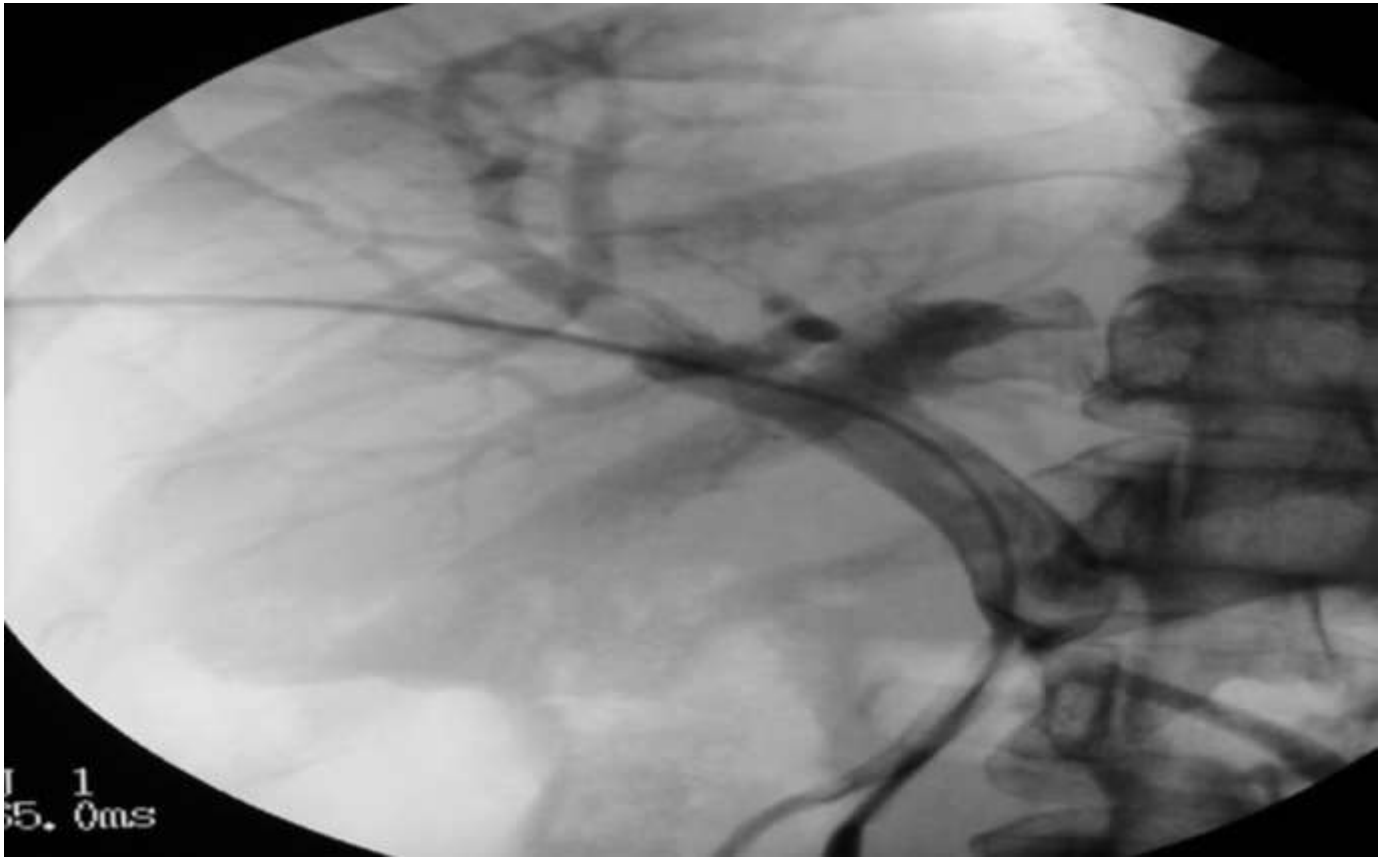
Islet Transplant (2)



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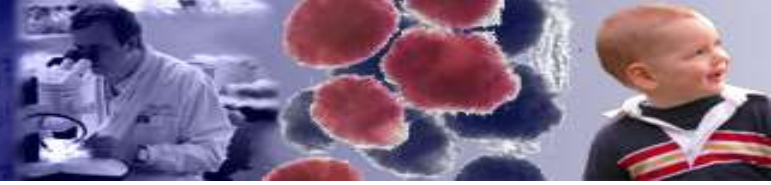
Alternative Transplant Sites



- Spleen
- Omentum
- Forearm
- Kidney subcapsule
- Testis / Ovary / Eye

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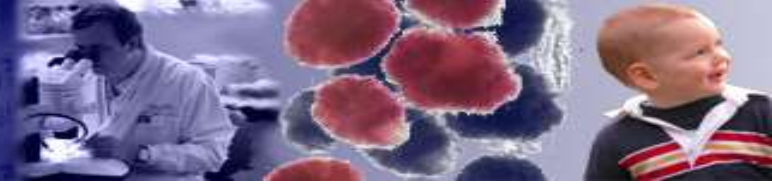
Current Results

History of Islet Tx



1980s

•Routine reversal of diabetes in animal models

1990s

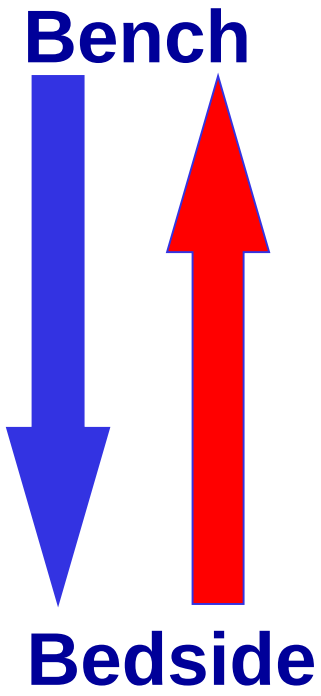
•Translation to human studies with 493 transplants in 40 institutions

2000 - 2008

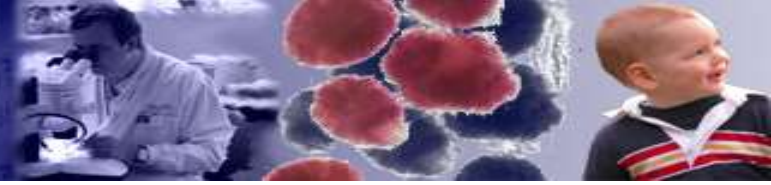
•Edmonton Protocol enables good outcomes of clinical islet transplantation for at least 1 year post transplantation

2008 - present

•More consistent outcomes with improved graft longevity



Edmonton Protocol



The New England Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

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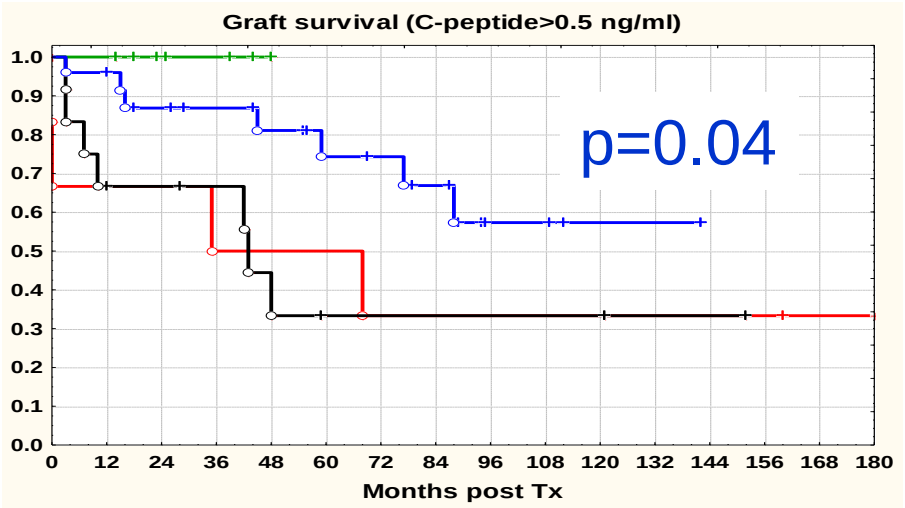
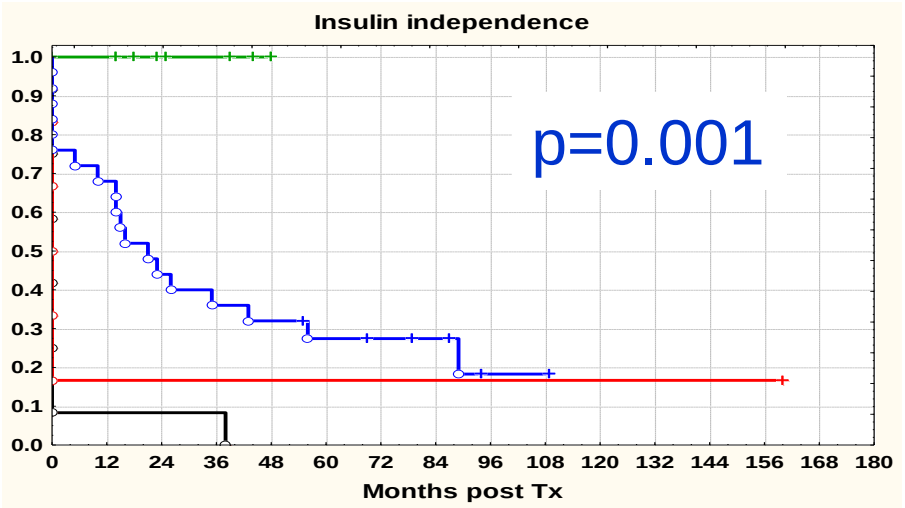
Geneva Results





- **Era 1: 1992-1996, N=6** (ATG - CsA - Aza - Steroids)
- **Era 2: 1997-2000, N=12** (anti-IL2R - FK -MMF -Steroids)
- **Era 3: 2001-2007, N=25** (anti-IL2R - Rapa - FK - Steroid-free)
- **Era 4: 2008-2012, N=11** (ATG - anti-TNF - FK - MMF - Steroid-free)

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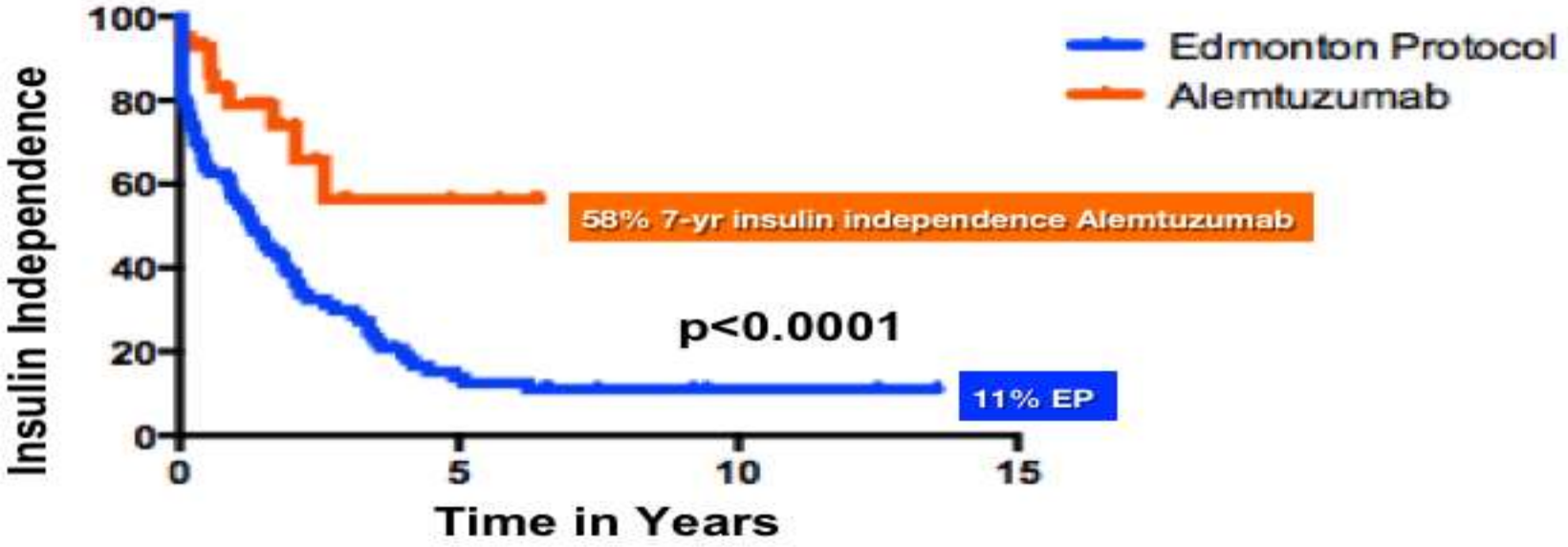
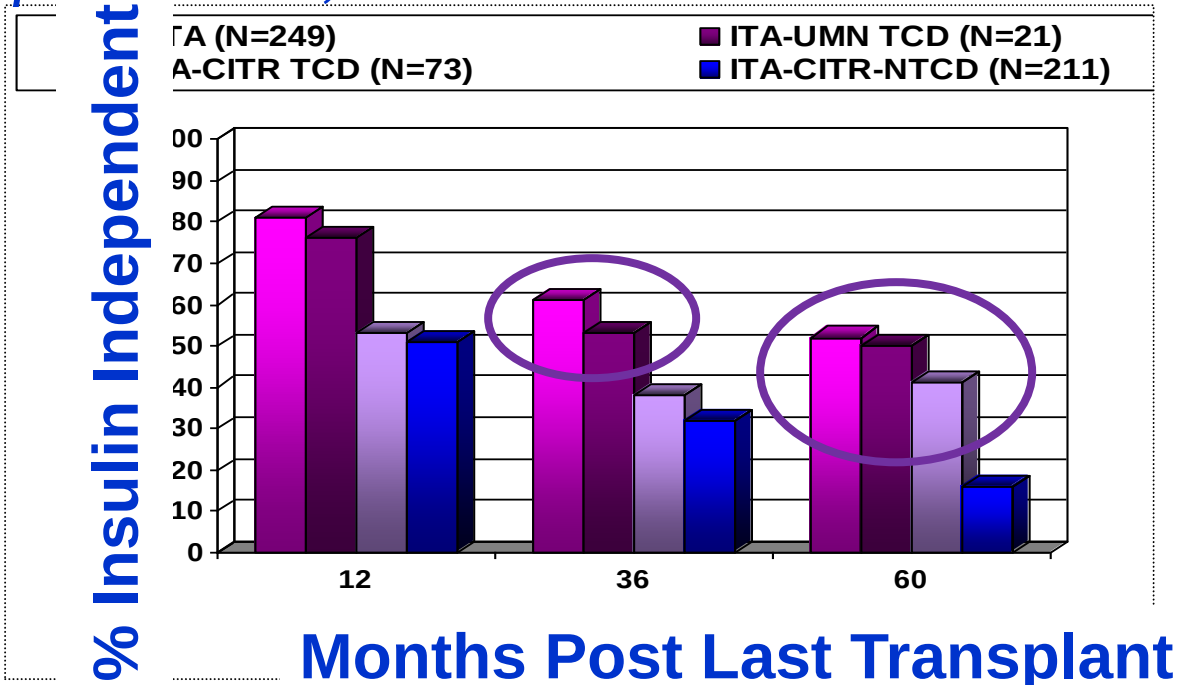
Edmonton Results 2015



5 Year II Rates

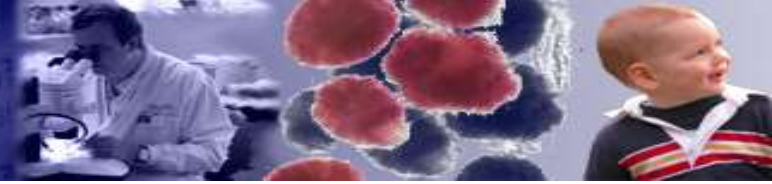
Bellin et al. Am J Transplant 2012; 12:1576

	3y II (%)	5yr II (%)
PTA	60%	52%
UMN-TCD	53%	50%
CITR-TCD	38%	41%
CITR-NTCD	33%	16%



No statistical difference

UK Islet Tx Programme



Oxford

Kings

Edinburgh

Bristol

Manchester

Newcastle

Royal Free

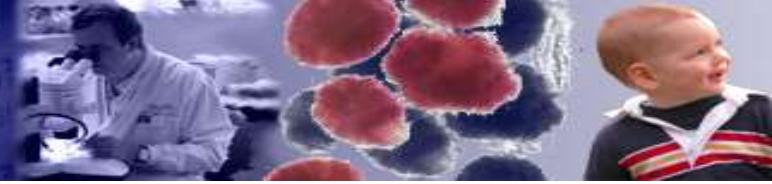
Isolation and Transplant

Transplant Only

UKITC

UK Islet Transplant Consortium

Selection Criteria



- **Established Type 1 diabetes for more than 5 years**
  - **>18 years old**
  - normal renal function or microalbuminuria
  - NOT if insulin dose more than 0.7U/kg

1) Recurrent severe hypoglycaemia >1 year

- documented evidence of glucose <2mmol/L
- despite compliance with intensified insulin regimen
- normal renal function or microalbuminuria

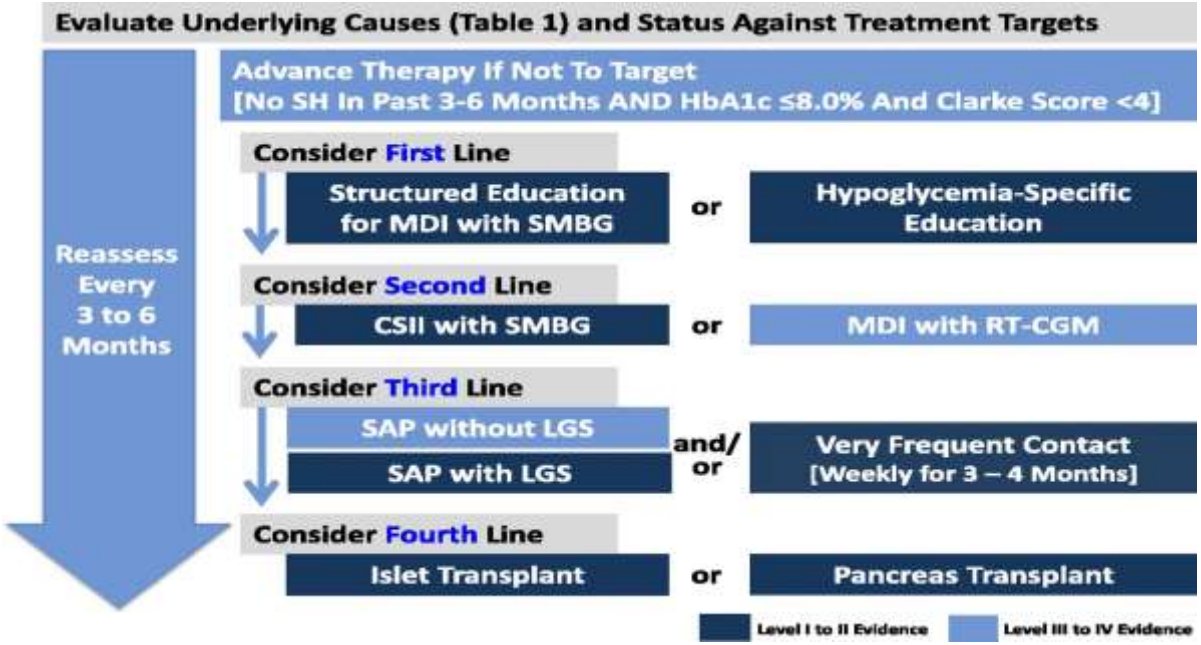
2) Sub-optimal control despite functioning renal graft

- severe hypoglycaemia; unstable diabetes
- HbA1c >7%

UKITC
UK Islet Transplant Consortium

Treatment of Hypoglycaemia

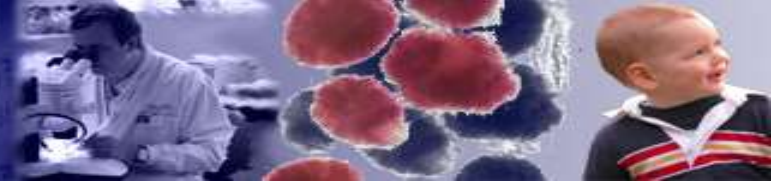
Proposed treatment algorithm for patients with T1D and problematic hypoglycemia.



Pratik Choudhary et al. Dia Care 2015;38:1016-1029

American Diabetes Association.

UNIVERSITY OF OXFORD



Primary Outcome Measures for Islet Tx

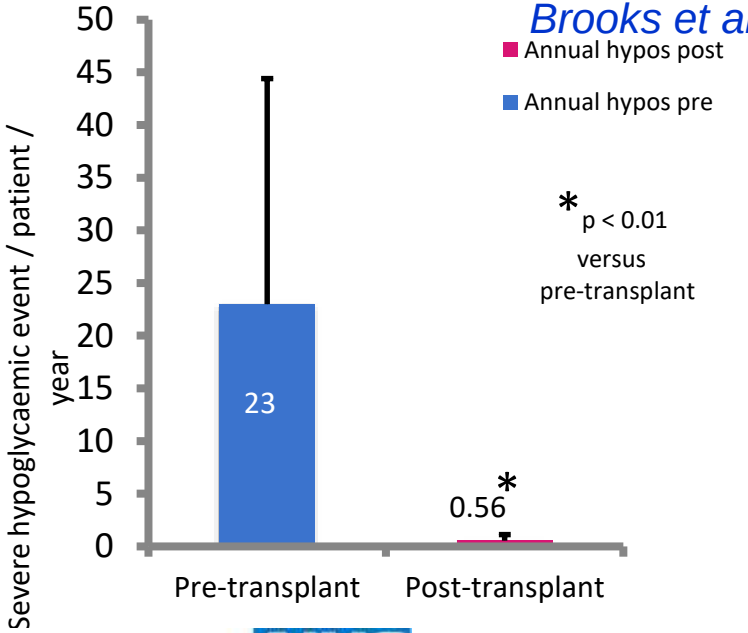
- Resolution of life-threatening hypoglycaemic unawareness
- Stabilisation of glycaemic control (HbA1C)
- NOT primarily insulin independence

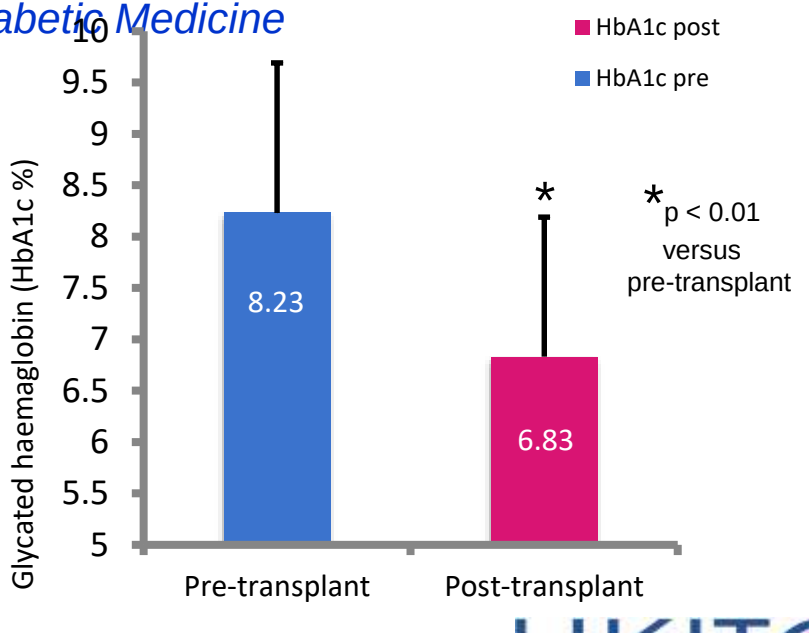
UKITC
UK Islet Transplant Consortium

Outcomes

Outcomes in 24 UK patients in first 3 years of NHS funded programme (April 2008 to March 2011)

Brooks et al., Diabetic Medicine

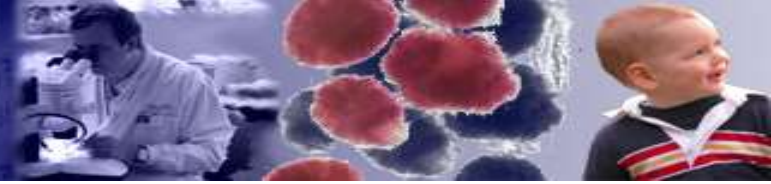




NHS Blood and Transplant

UKITC UK Islet Transplant Consortium

CITC Phase 3 Trial



American Diabetes Association. Diabetes Care

Diabetes Care 2016 Jul; 39(7): 1230-1240.

Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

Bernhard J. Hering[1], William R. Clarke[2]✉, Nancy D. Bridges[3], Thomas L. Eggerman[4], Rodolfo Alejandro[5], Melena D. Bellin[6], Kathryn Chaloner[2,†], Christine W. Czarniecki[3], Julia S. Goldstein[3], Lawrence G. Hunsicker[2], Dixon B. Kaufman[7], Olle Korsgren[8], Christian P. Larsen[9], Xunrong Luo[10], James F. Markmann[11], Ali Naji[12], Jose Oberholzer[13], Andrew M. Posselt[14], Michael R. Rickels[12], Camillo Ricordi[5], Mark A. Robien[3], Peter A. Senior[15], A.M. James Shapiro[15], Peter G. Stock[14] **and** Nicole A. Turgeon[9] **for the Clinical Islet Transplantation Consortium***

- Primary end-points were freedom from severe hypoglycaemic events Day 28-365 and an HbA1C of <7% at Day 365

- Achieved in 87.5% at 1 year; 71% at 2 years

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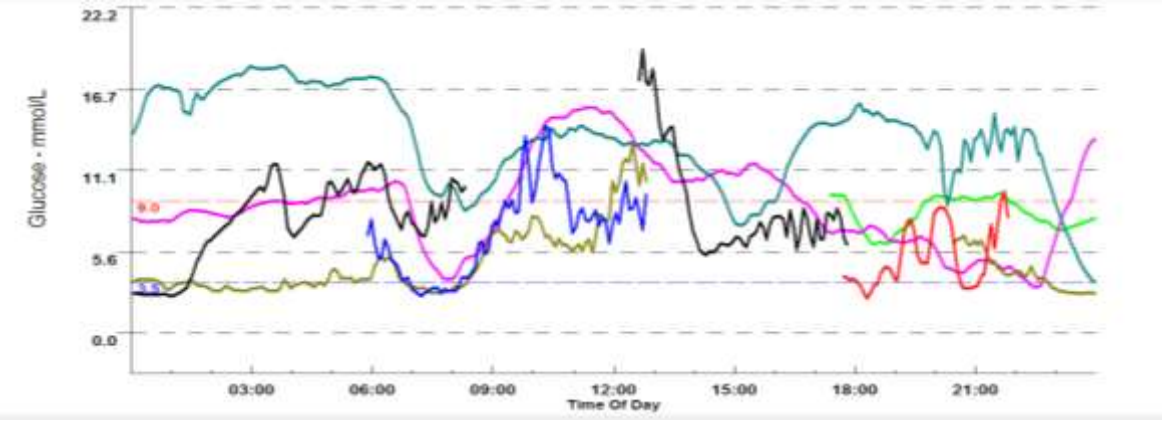
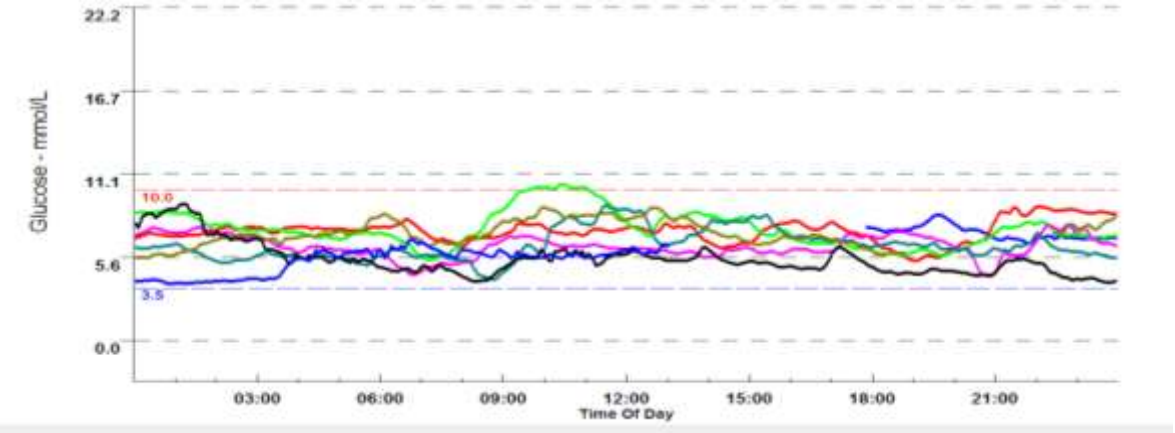
Patient RML after 12 months



HbA1c 7.0%



HbA1c 5.1%

100% Insulin Reduction

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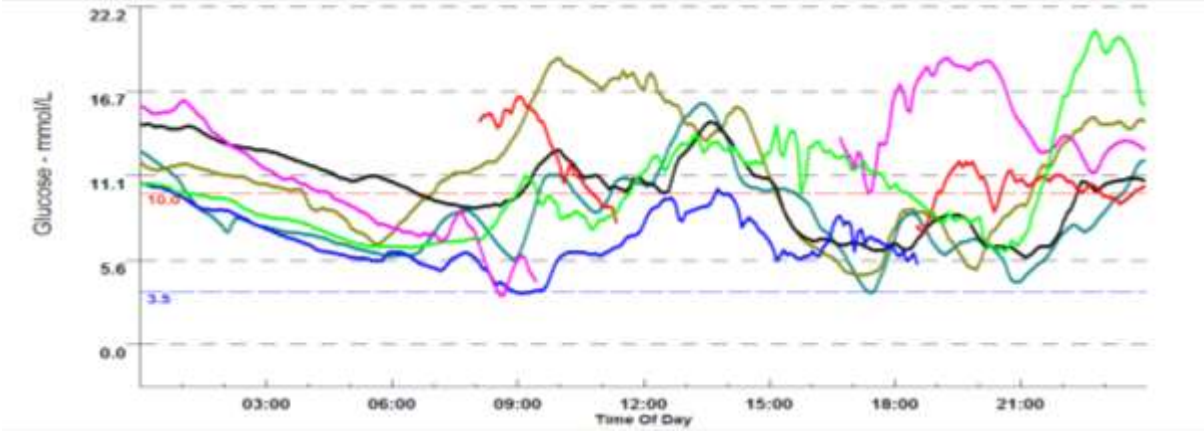
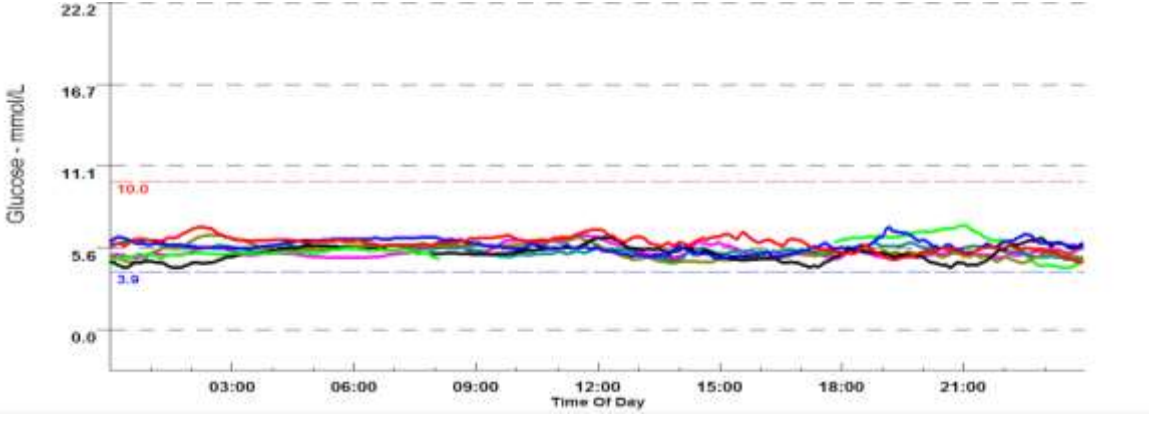
Patient CH after 11 months



HbA1c 7.7%



HbA1c 5.3%

Insulin Reduction 85%

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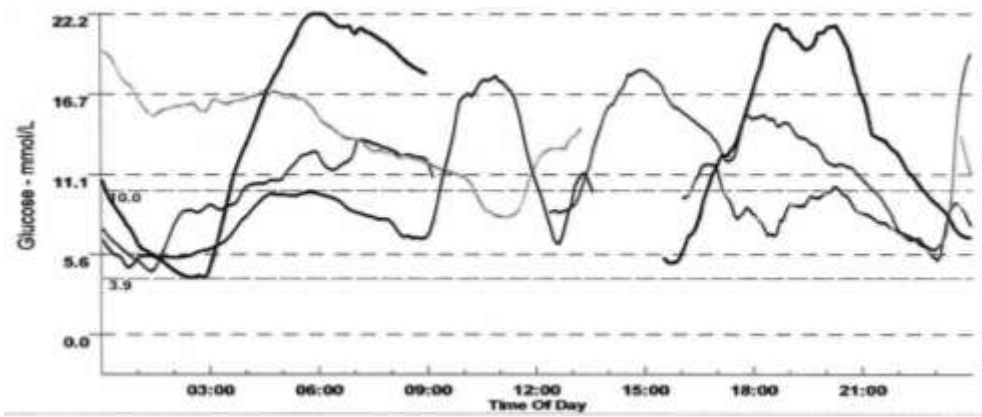
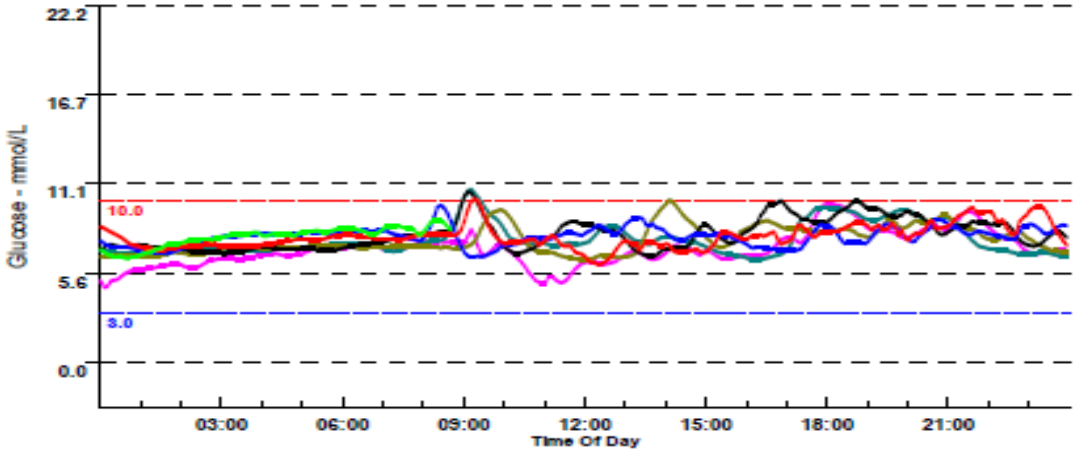
Distributed Islets to Newcastle 1yr



HbA1c 9.6%



HbA1c 6.3%

Insulin Reduction 100%

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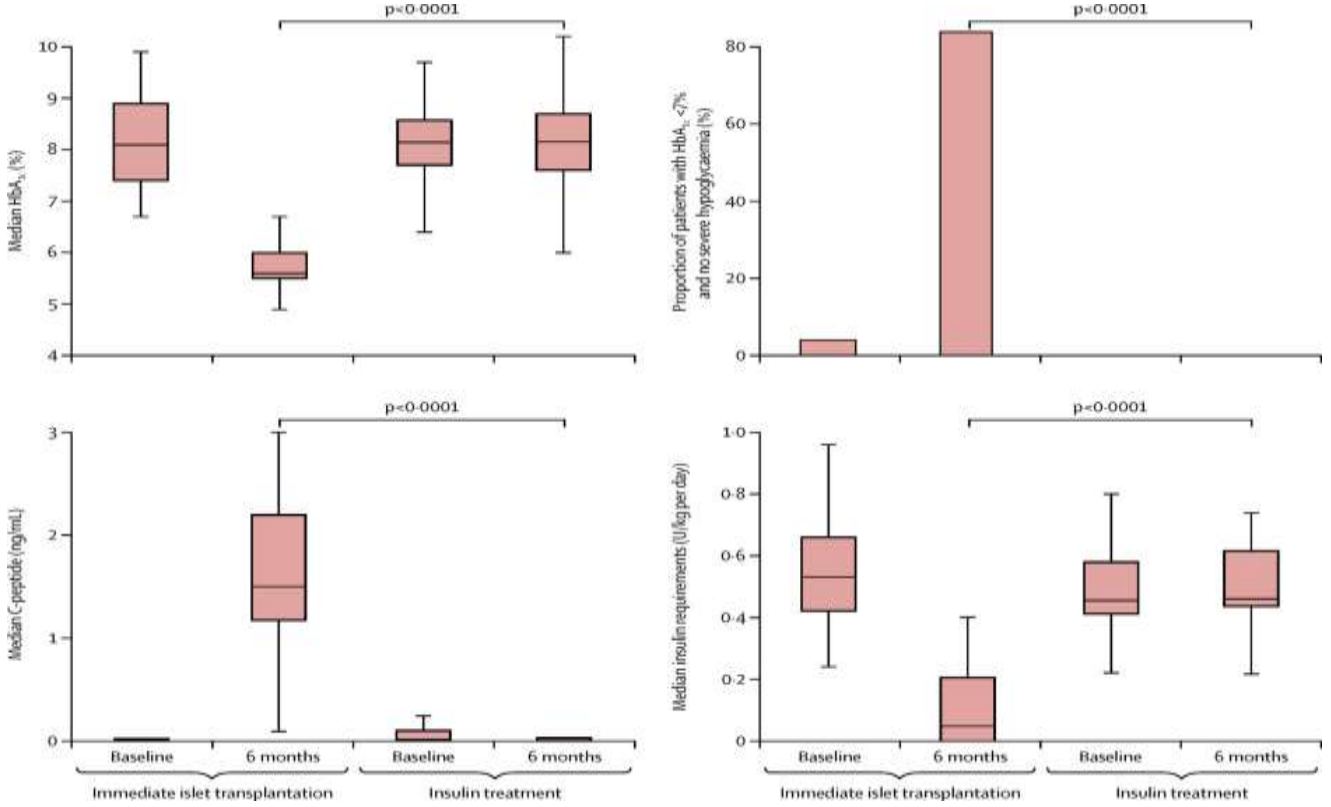
TRIMECO Trial



Lablanche et al. Lancet Diab. And Endocrinol.2018; (6):7

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Benefits of Graft Function (C-peptide +ve)

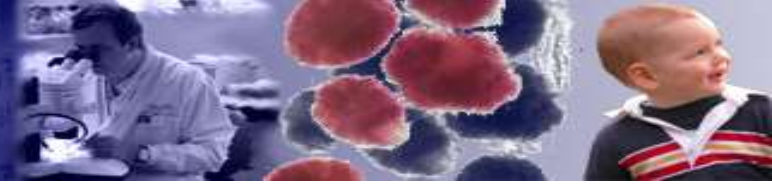

TABLE 2. Annual rate of change in GFR by ^{99m}Tc-DTPA and MDRD in the medical and post-ICT groups

Δ GFR (mL/min/1.73 m²/yr)	Medical (95% CI)	ICT (95% CI)	*P*
^{99m}Tc-DTPA all subjects	−2.98 (−1.81 to −4.15)	−1.27 (−0.50 to −2.04)	≤0.0001
≥2-yr follow-up	−4.79 (−2.44 to −7.14)	−1.42 (−0.44 to −2.40)	≤0.0001
≥3-yr follow-up	−3.55 (−1.53 to −5.57)	−1.40 (−0.32 to −2.48)	≤0.0001
MDRD all subjects	−3.53 (−2.49 to −4.57)	−1.49 (−1.06 to −1.92)	≤0.0001

GFR, glomerular filtration rate; ICT, islet cell transplantation; DTPA, ^{99m}Tc-diethylenetriaminepentaacetate; MDRD, modification of diet in renal disease; CI, confidence interval.

Improved microangiopathy

Vancouver, ITA

TABLE 3. Progression of diabetic retinopathy in the medical and post-ICT groups

	Medical		ICT	
	No. eyes	No. progressed	No. eyes	No. progressed
Mild NPDR	16	0	8	0
Moderate NPDR	19	1	12	0
Severe NPDR	6	2	2	0
PDR	41	7	29	0
Total	82	10[a]	51	0[a]

[a] The progression is significantly more in the medical than the post-ICT group ($P<0.01$).

ICT, islet cell transplantation; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Thompson et al. Transplantation 2011; 91: 373.

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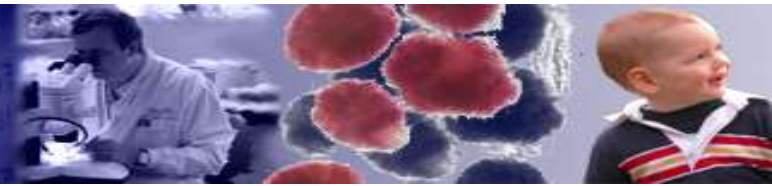
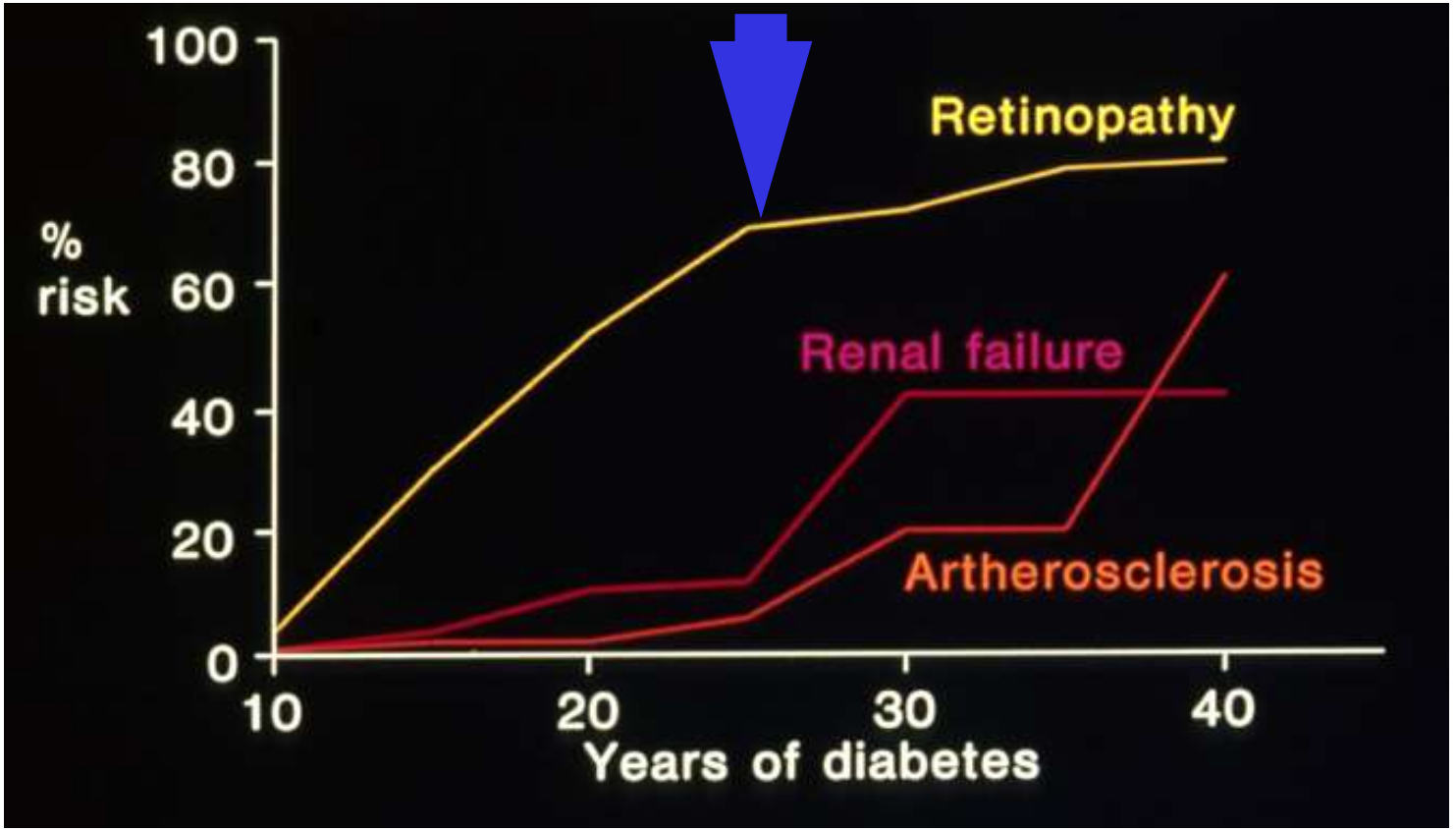
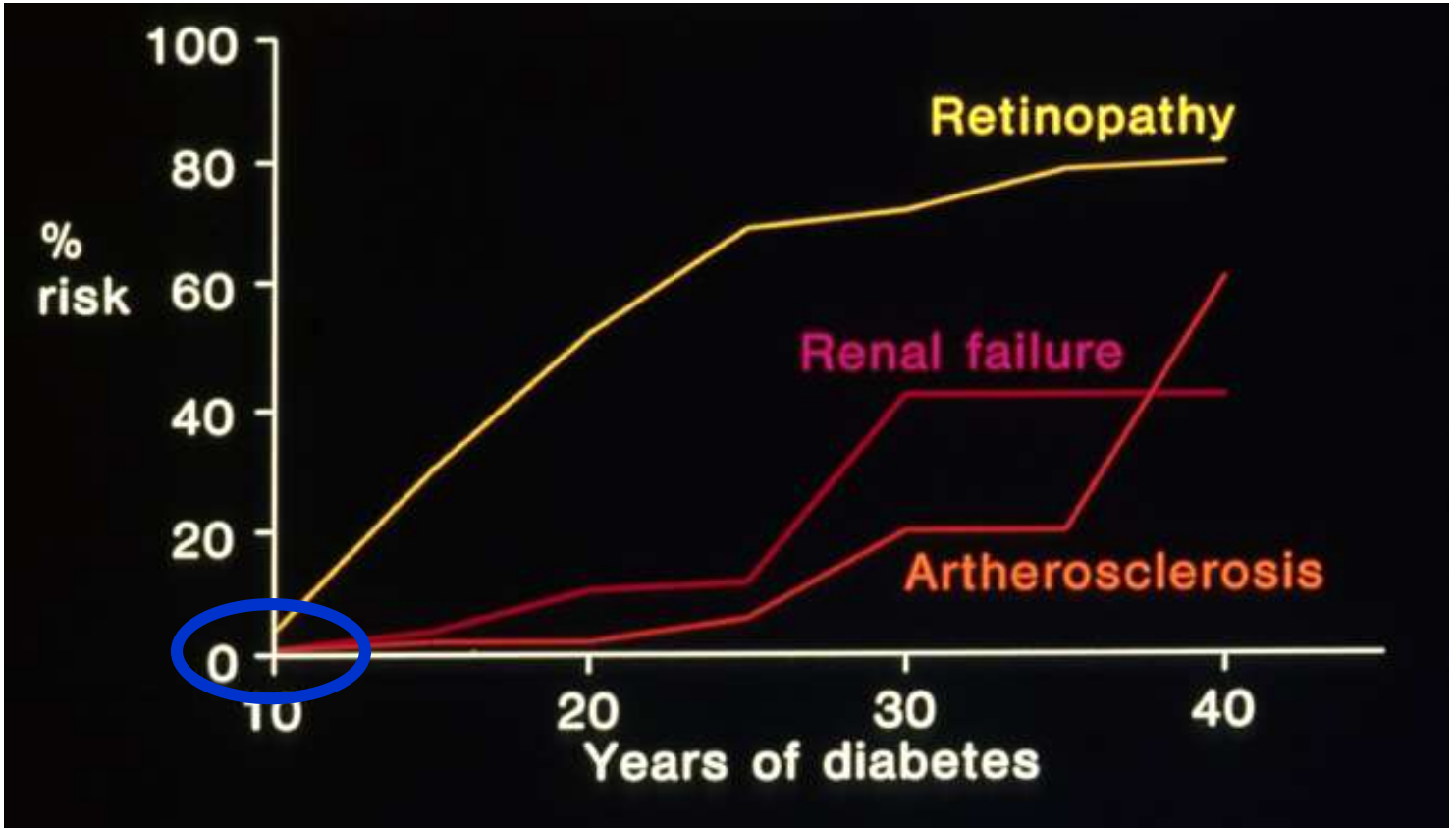
Ongoing Challenges and Future Opportunities



Current Era


100
80
%
risk
60
40
20
0
Retinopathy
Renal failure
Artherosclerosis
10
20
30
40
Years of diabetes

Next Era


100
80
% risk
60
40
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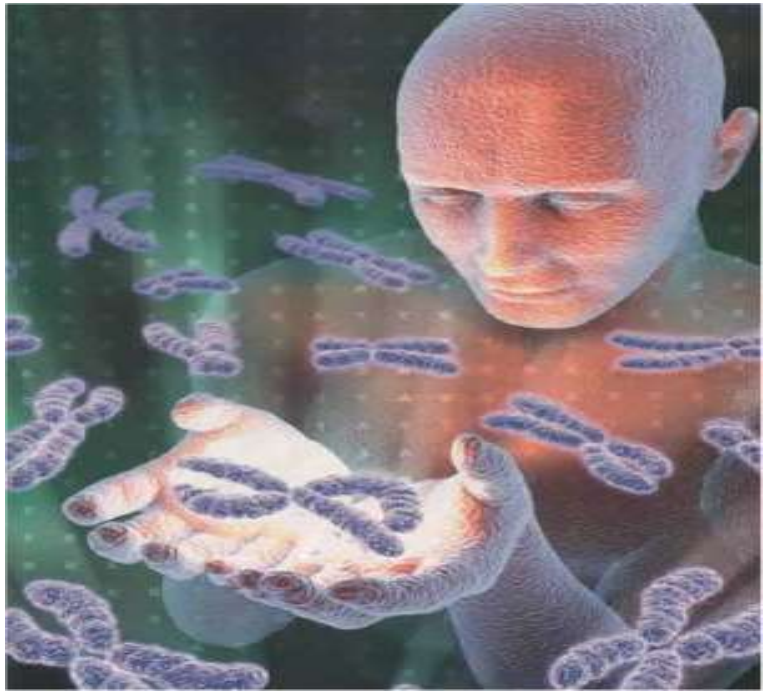
0
Retinopathy
Renal failure
Artherosclerosis
10
20
30
40
Years of diabetes

Moving Islet Tx to Children



1. **Optimise Islet Isolation**
   (from pancreas procurement to targeted donor-specific pancreas digestion)

2. **Improve Islet Graft Survival**
   (novel strategies of pre-transplant islet conditioning / islet modification)

3. **Availability of Non-Cadaveric Renewable Islet Source**
   (xenogeneic or islet stem cells)

4. **Development of immunosuppressive-free immune strategies**
   (tolerance or immuno-isolation)

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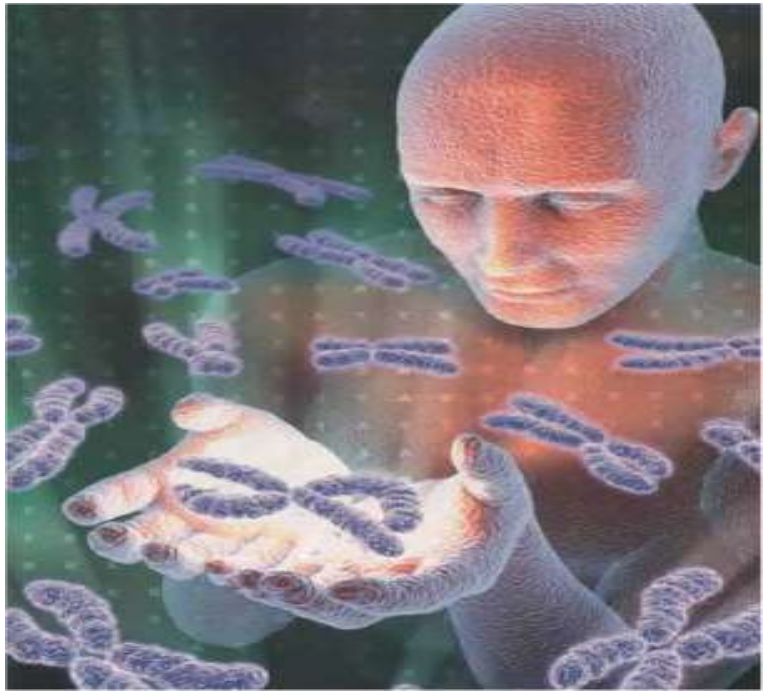
Moving Islet Tx to Children



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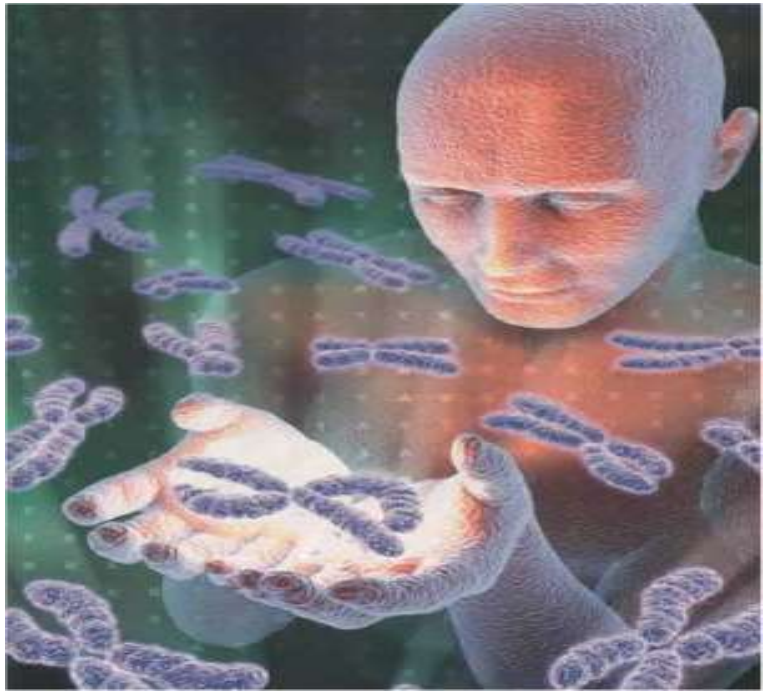

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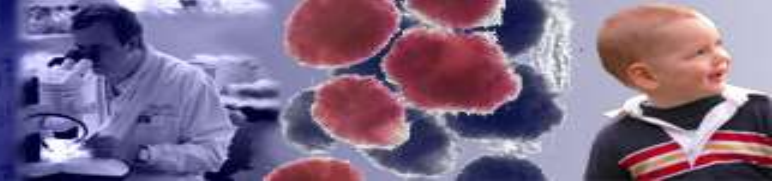
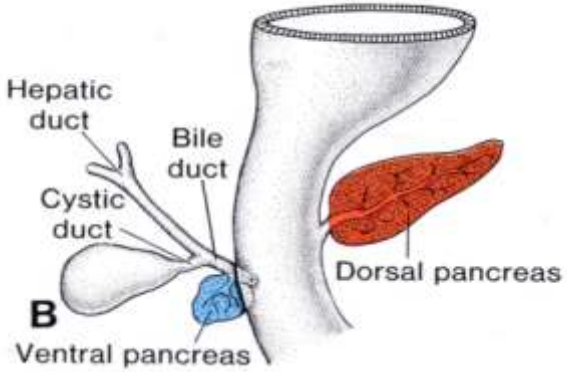
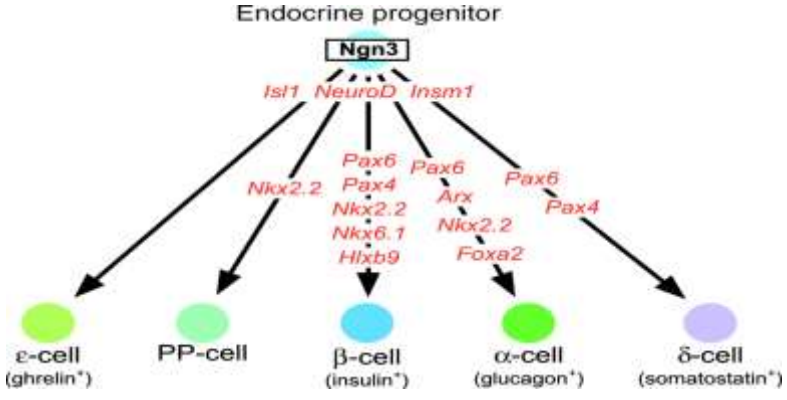
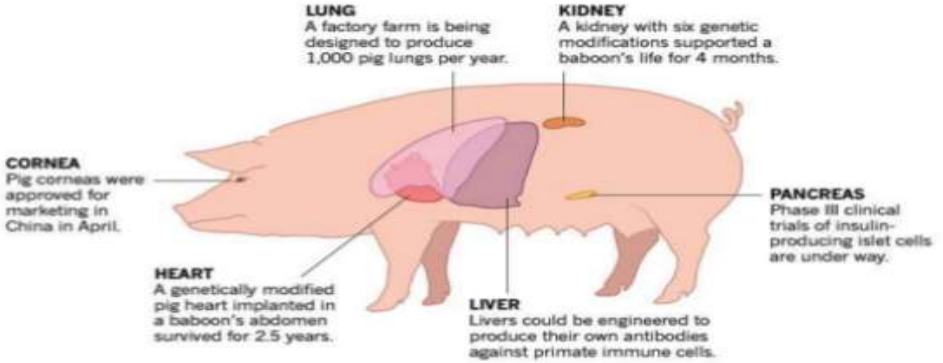
Alternative Islet Sources







CRISPR/Cas9 gene editing leads to a strong revival of xenotransplantation



Reardon, Nature 2015
Yang et al Science 2015

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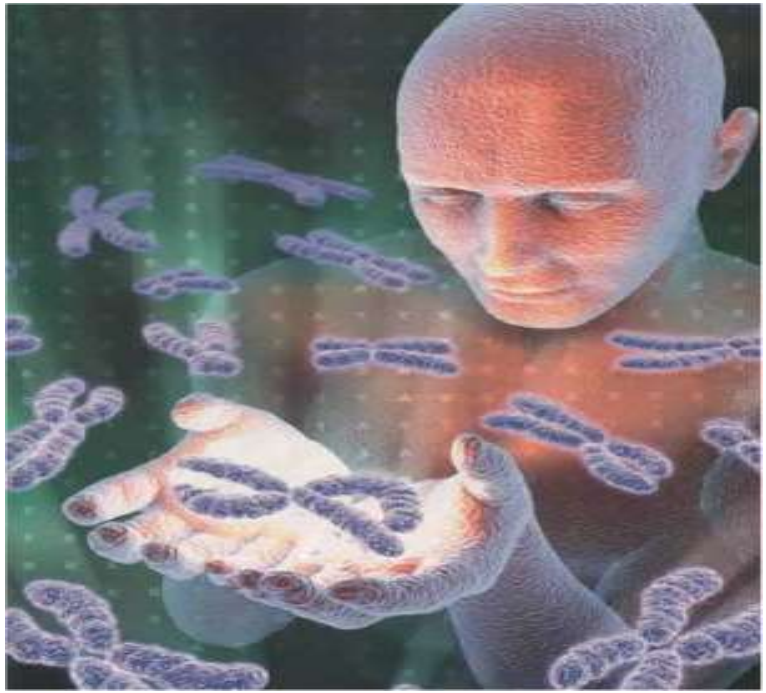
Moving Islet Tx to Children



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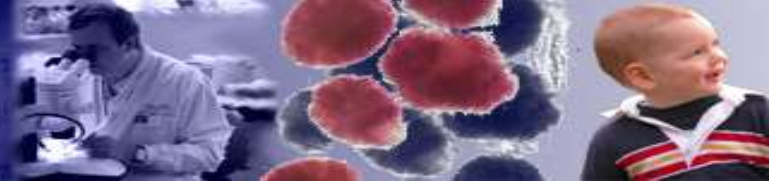
Immune Strategies



- Imunoalteration (Immune Tolerance)

- Immunoisolation (Micro- and Macro-Encapsulation)

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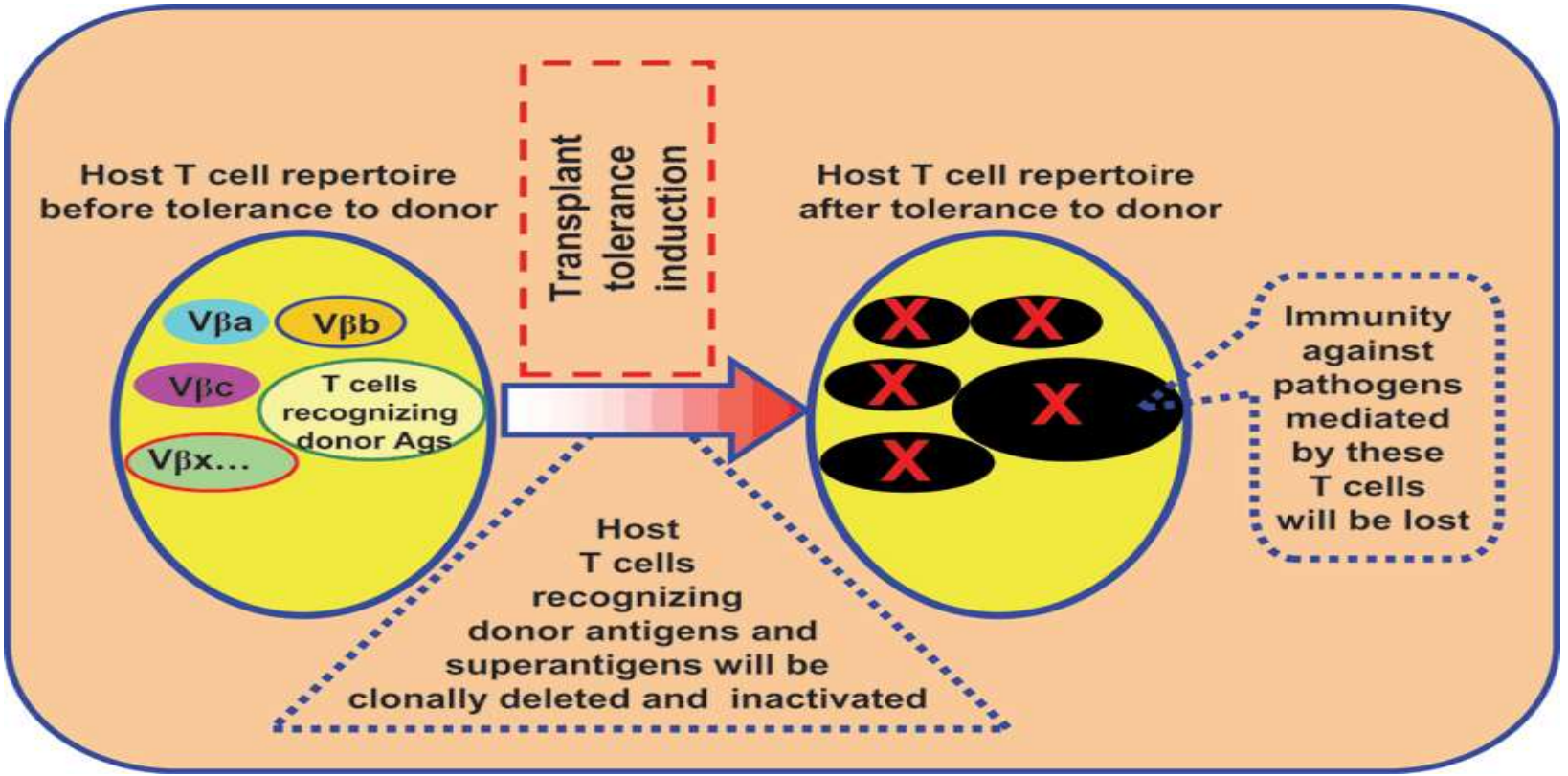
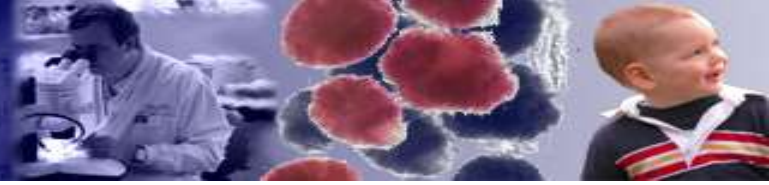
Immune Tolerance



Immune Strategies



- Imunoalteration (Immune Tolerance)

- Immunoisolation (Micro- and Macro-Encapsulation)

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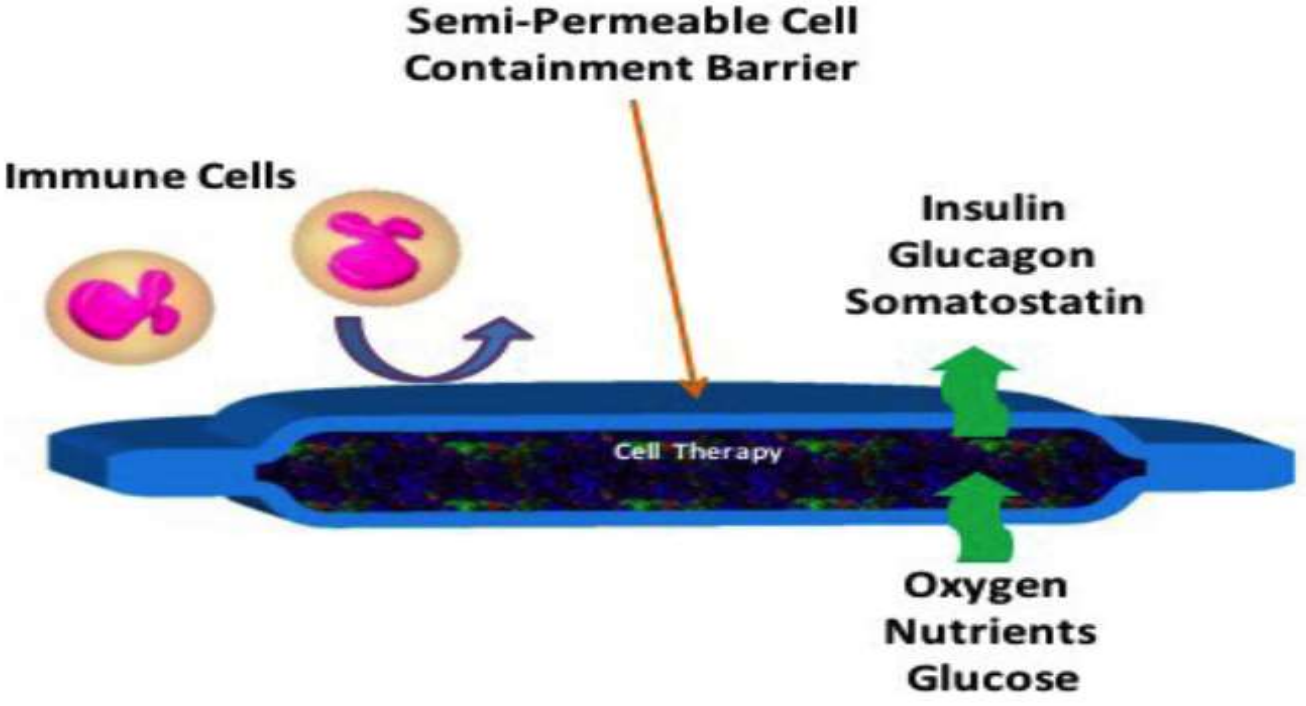
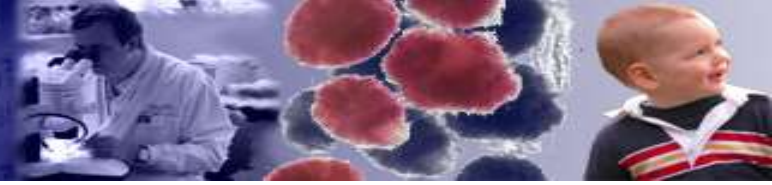
Micro-encapsulation

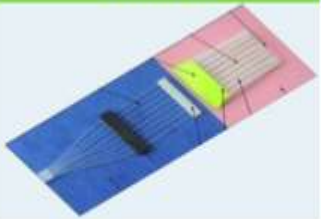
Macro-encapsulation



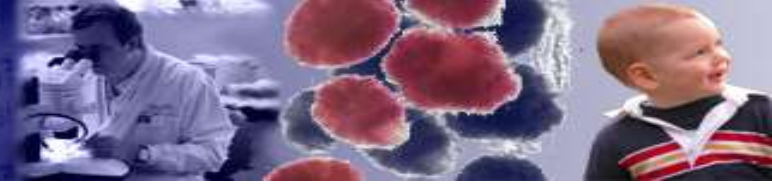
Macro-encapsulation



1st intention →

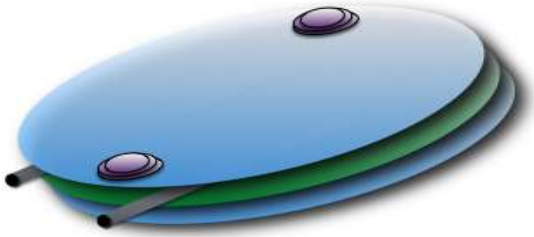
	SERNOVA CORP	Beta-O2	VIACYTE	DEFYMED
Implantation site	Sub-cutaneous	Extra-peritoneal	Sub-cutaneous	Extra-peritoneal
Filling/Emptying of cells	Yes *But Invasiveness to be assessed*	No	Yes (Unique Entry/Exit)	Yes (Separate Entry/Exit)
Cell type for clinical trials	Human islets	Human islets	Stem cells	Human islets
Cell number	Sufficient	Sufficient	Non-sufficient	Sufficient
Stage of development	Phase I/II-a clinical	Phase I/II-a clinical	Phase I/II-a clinical	Preclinical
How does it look like?				

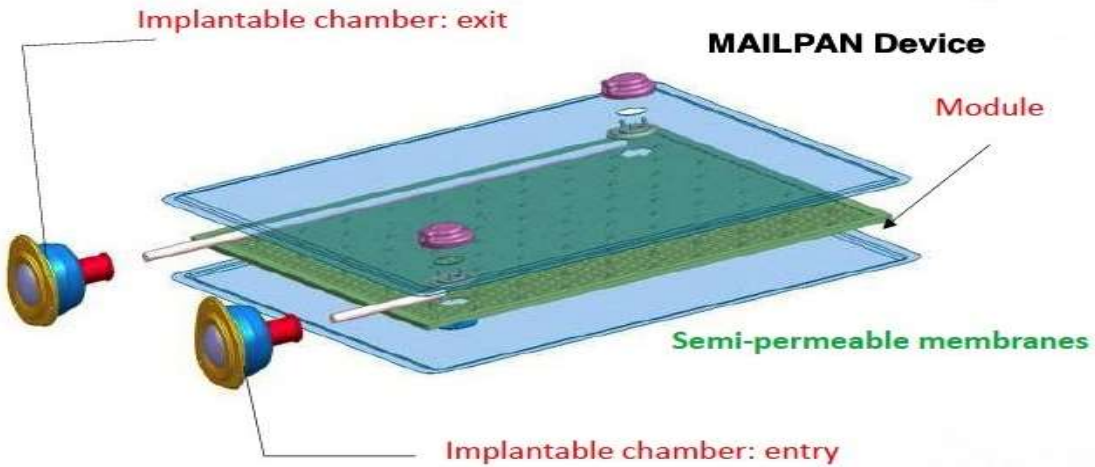
MAILPAN Device



Islet Encapsulation:

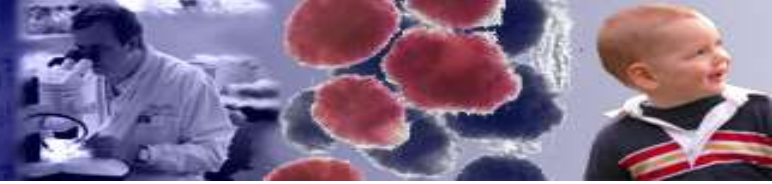
- immunoprotection
- biocompatibility
- stability
- selective permeability
- capacity





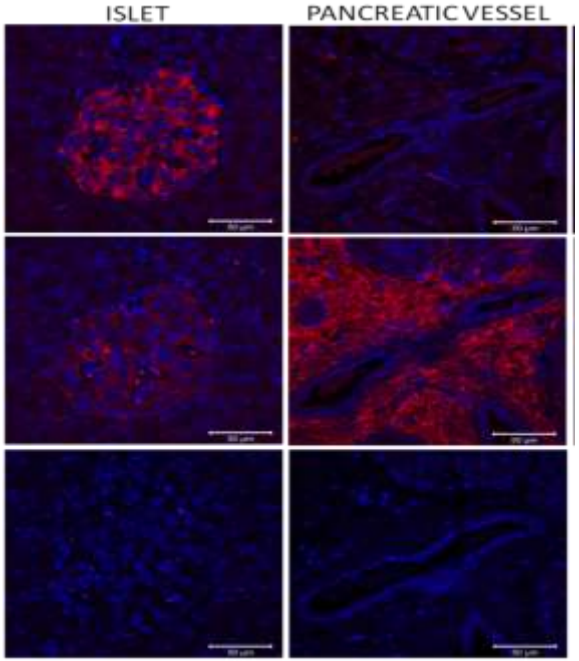
Defymed

β-Gel

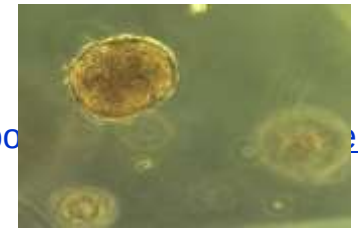


Mimics the pancreas extracellular matrix (ECM)

- Composed of native ECM molecules pancreatic proteins (to support and support islets
- Oxygen producing particles
- Provides structure and spacing to islets



β-Gel will l suppo e the ver



DRIVE
DIABETES REVERSING IMPLANTS

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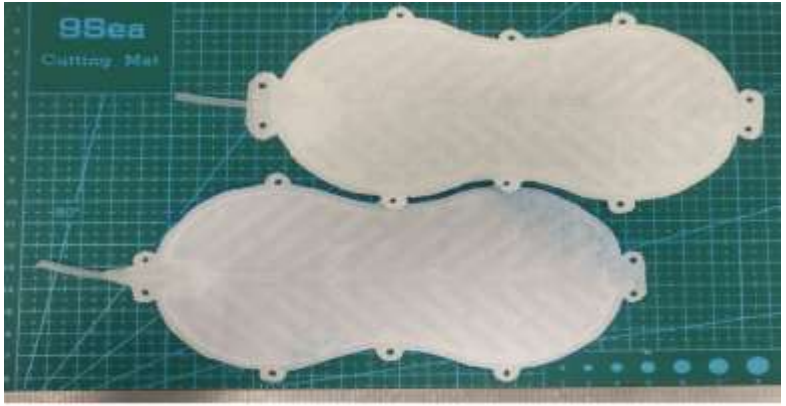
β-Shell

A smart biocompatible implant for delivery of β-Gel to an extra-vascular site



- Drug eluting shell for enhanced bio-integration
- Engineered to selectively isolate immune system cells while allowing insulin and glucose transport.
- / via minimally invasive
  ure

DRIVE
DIABETES REVERSING IMPLANTS

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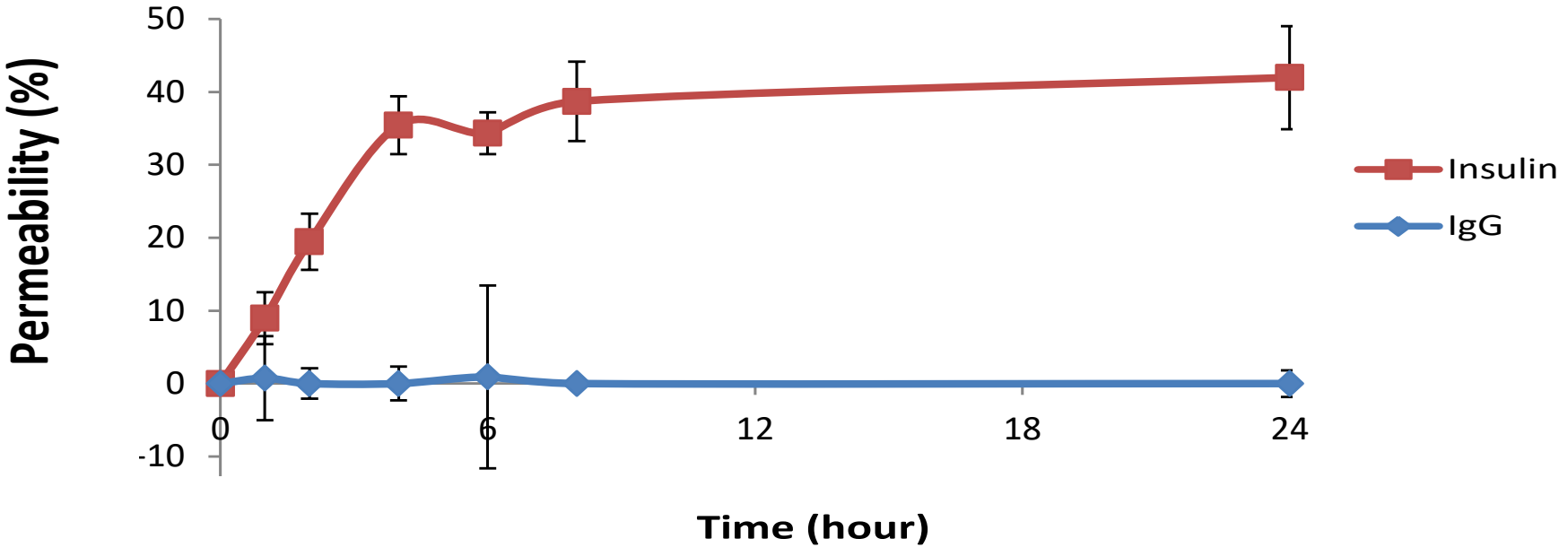
Biofunctionality (1)



Defymed

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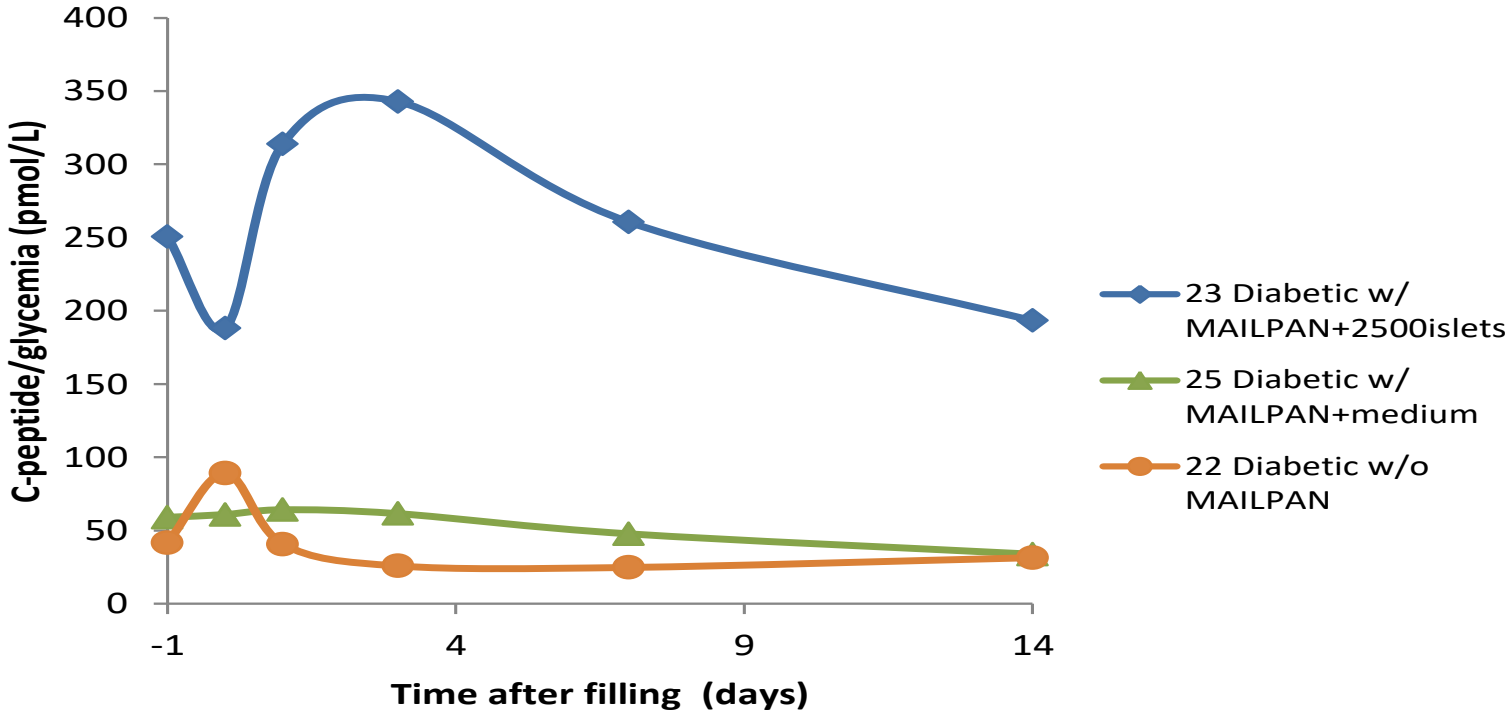
Biofunctionality (2)



Defymed

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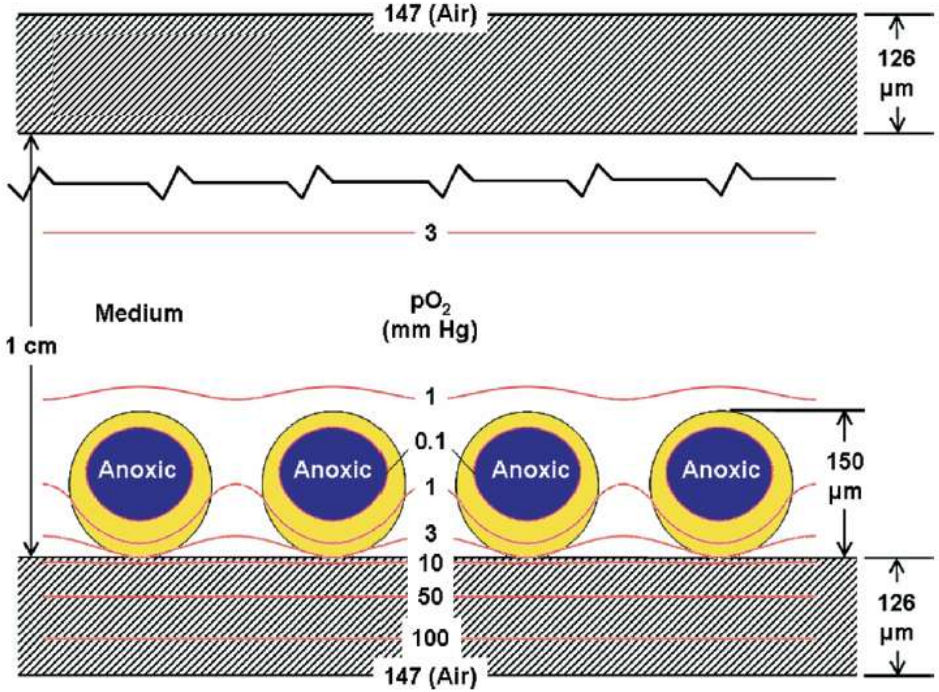
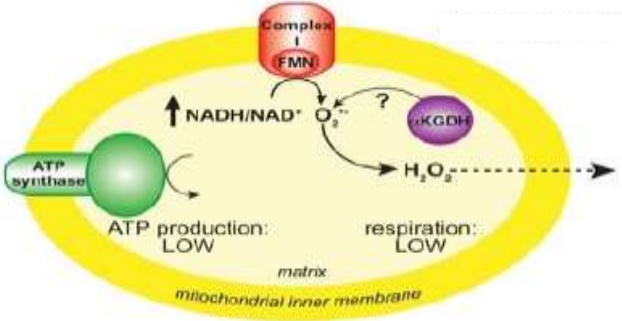
Islet Hypoxia



Hypoxia

Dysfunction
(Murphy, 2009)



ROS high

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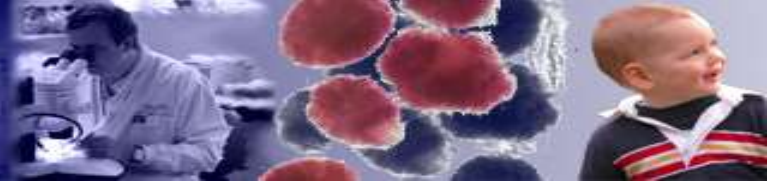
Exciting Times!



"The future ain't what it used to be!"

Yogi Bera 1998

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Conclusions

- Islet transplantation works well in selected patients
- Number of ongoing challenges before it can be applied more widely
- Development of immune tolerance or encapsulation protocols required before implementing treatment in children
- Cell isolation / cell transplant techniques applicable for potentially treating many other surgical conditions in children eg liver, myocytes, engineering etc

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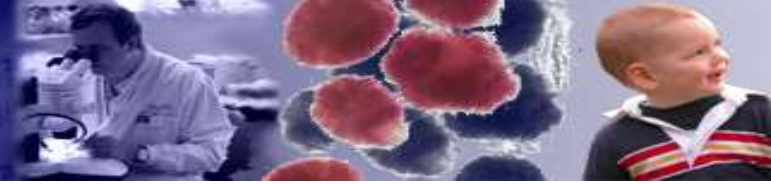
Oxford Islet Tx Group



Paul Johnson
Alistair Lumb
Steve Hughes
Sarah Cross
Jennifer Fox
Paul Bateman
Daniel Brandhorst
Heide Brandhorst
Anju Abraham
Lia Anguelova

Chitra Ballav
Samuel Acreman
Rebecca Vaughan
Rebecca Spiers
Rebecca Miller
Elisa Maillard
Ionnanis Spiliotis
Di Shen
Phoebe Tsou
Yukari Kimura

UKITC
UK Islet Transplant Consortium

Diabetes UK

European Commission

JDRF
Juvenile Diabetes Research Foundation International
dedicated to finding a cure

NIHR

MRC

NCG

wellcome trust

DRIVE
DIABETES-REVERSING IMPLANTS
FOR ENHANCED VIABILITY AND LONG-TERM EFFICACY

DIABETES RESEARCH & WELLNESS FOUNDATION