Islet transplantation for the treatment of diabetes: Progress and Challenges

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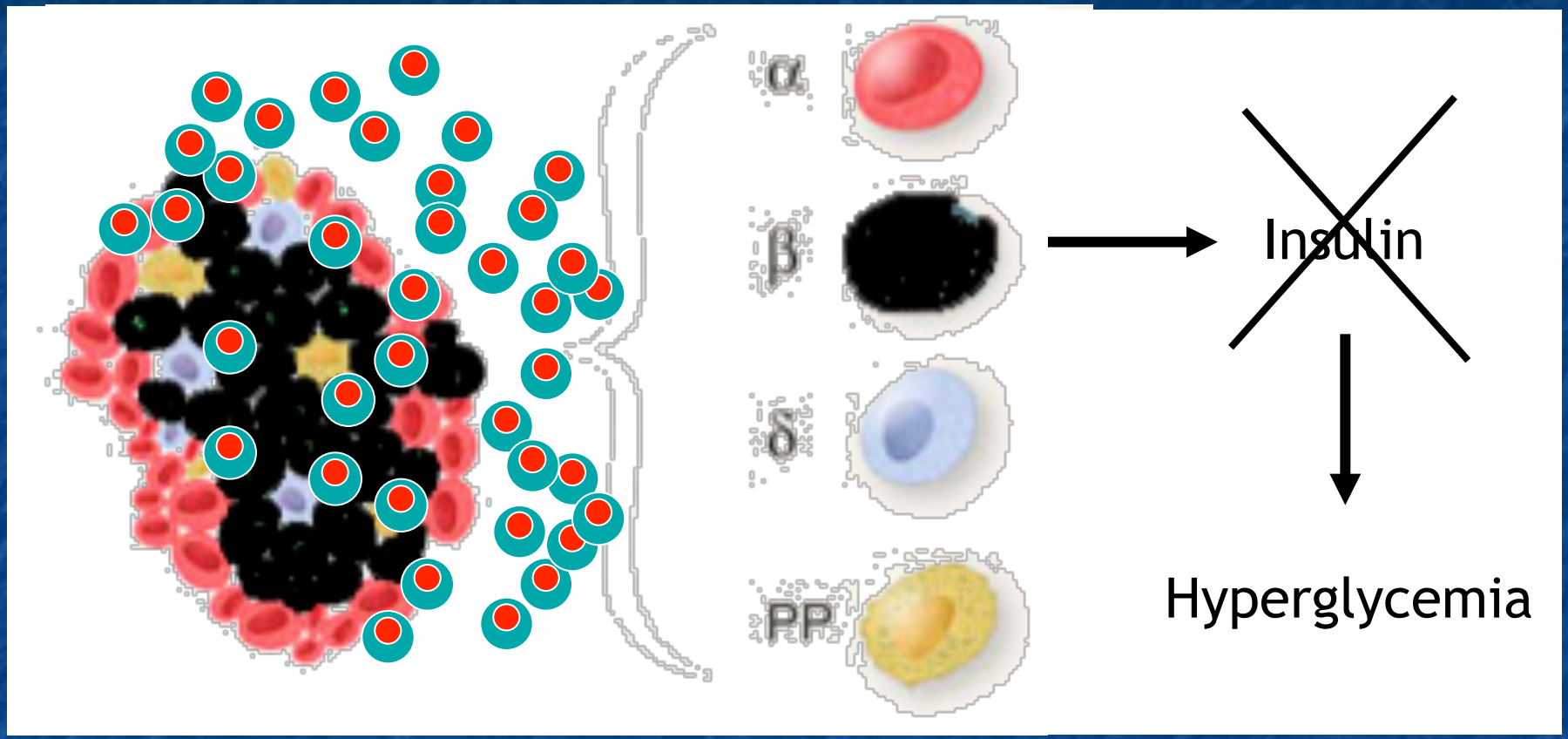
October 6, 2012
Batumi, Georgia

Type 1 diabetes



Autoimmune destruction of beta cells

Type 1 diabetes

The number of adults with diabetes has doubled world-wide over the last three decades to nearly 350 million

5-15 % of cases of diabetes worldwide

0.24% of W. European pop

Incidence/100,000 pop:

9.2 new cases in Switzerland

57.6 new cases in Finland

4.6 new cases in Georgia

Selective autoimmune destruction of b-cells

↳ b-cell replacement

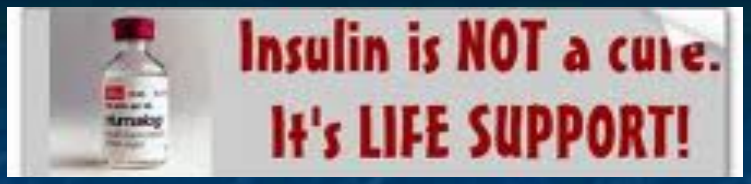
Insulin

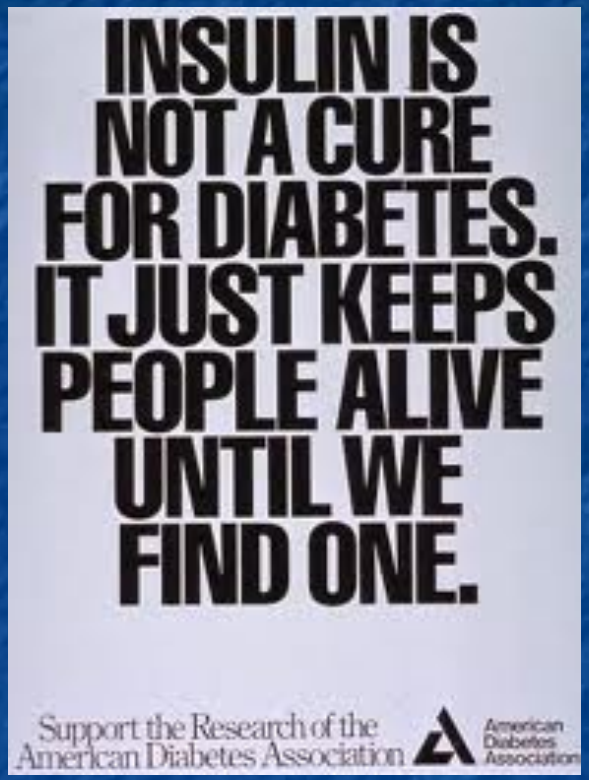
Banting & Best

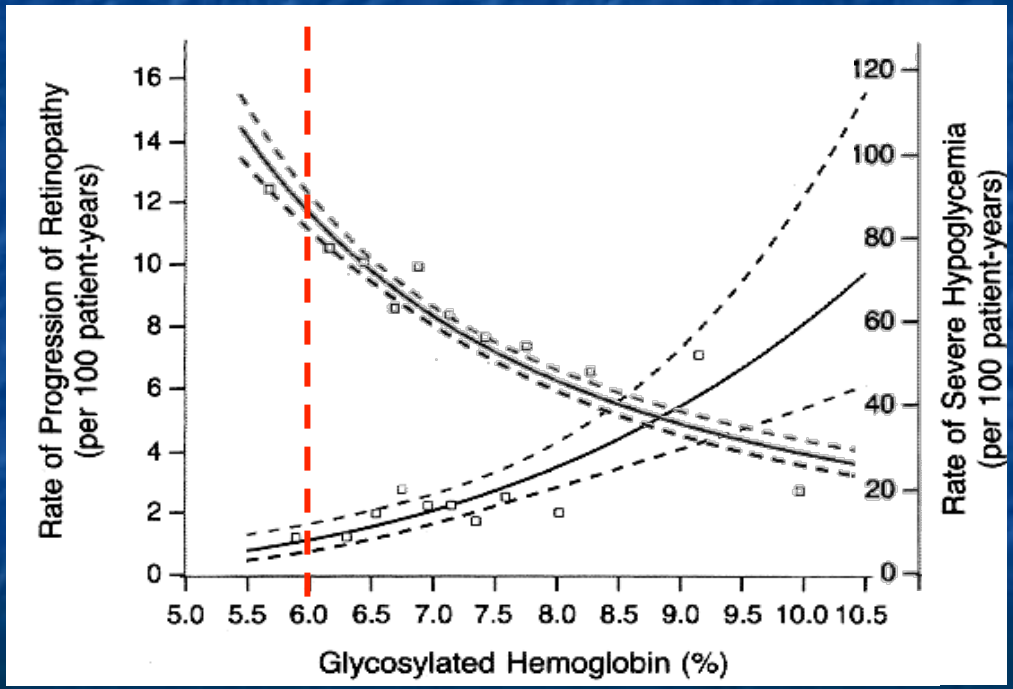
1921- isolation of insulin

1922 - first patient treated

1923 : Nobel Prize

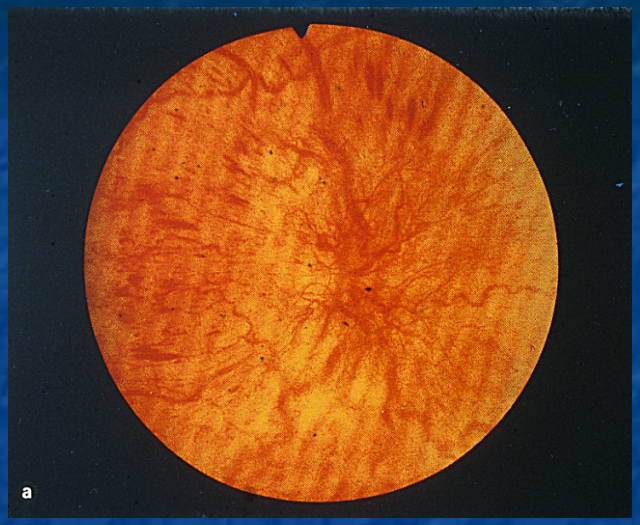






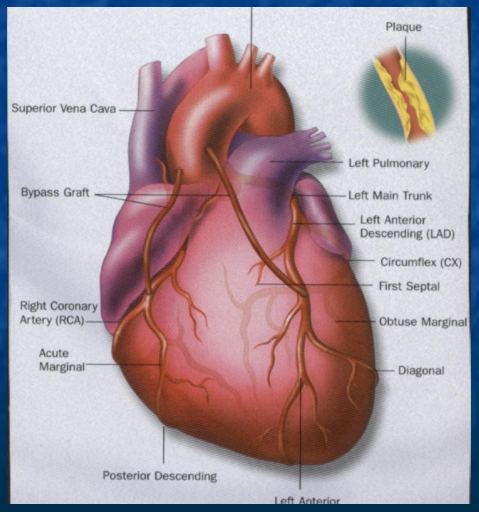
DCCT. N Engl J Med 1993; 329: 977.

Progression of diabetic disease

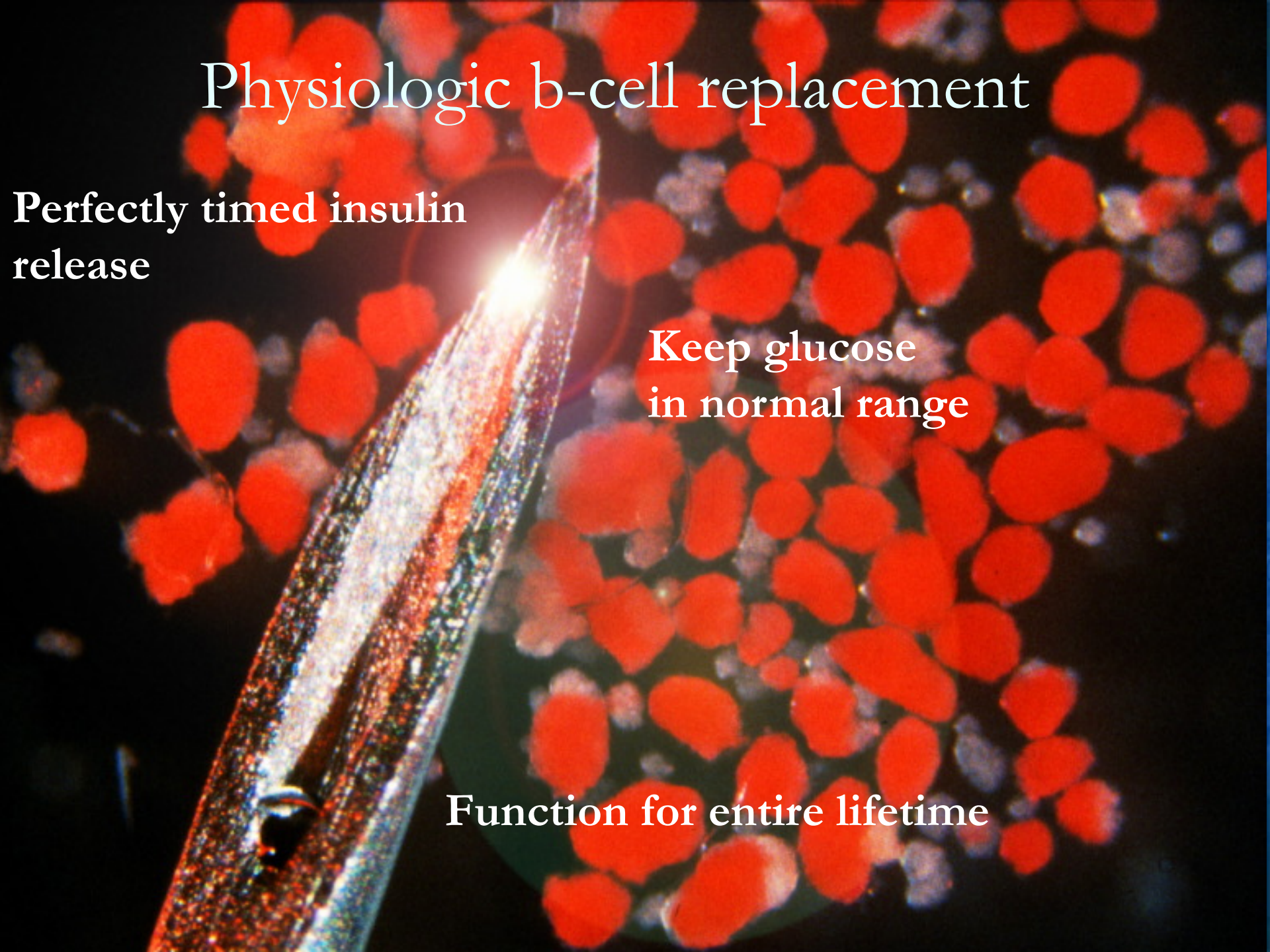


retinopathy → blindness

nephropathy → dialysis



macroangiopathy → amputation, myocardial infarction


Physiologic b-cell replacement
Perfectly timed insulin release
Keep glucose in normal range
Function for entire lifetime

Main Contributors

Paul Lacy
Colin Weber
Ray Rajotte
David Scharp
… many others

John Najarian
David Sutherland
(1977)

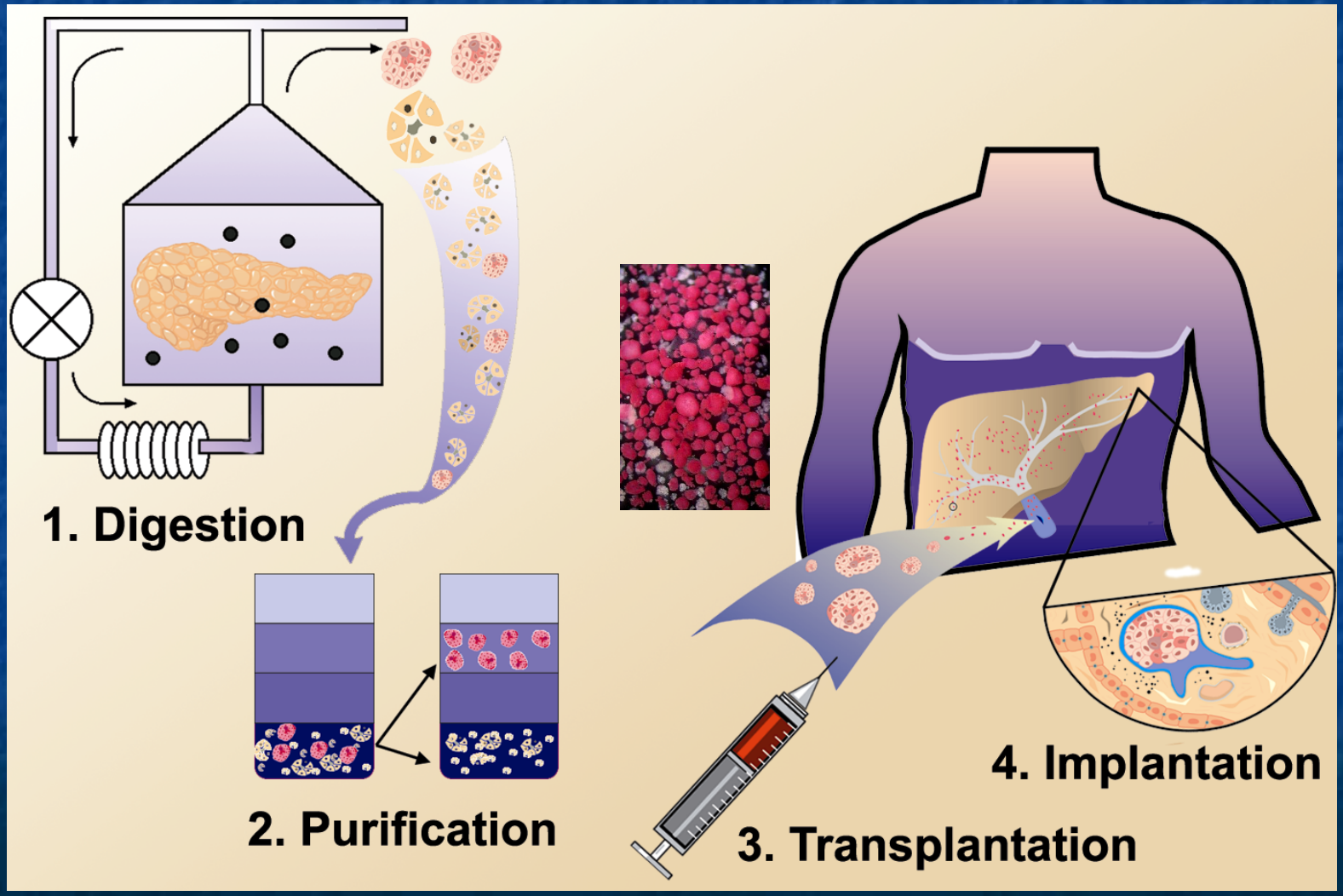
Camillo Ricordi
Automated method
(1989)

Bernhard Hering
Giessen/Minnesota
Geneva, Milan

James Shapiro
(2000)

Automated method for human islet isolation

Ricordi C, Lacy PE et alt; Diabetes. 1988 Apr;37(4):413-20.



"Insulin independence after solitary islet transplantation in type 1 diabetic patients using steroid-free immunosuppression"

Shapiro AMJ et al, NEJM 2000; 343:230

- **7 consecutive patients achieved euglycemia during a mean follow-up of 11 months, with normal HgbA1c and GTT**
- 6/7 patients required >1 donor (>1 transplant) a median of 29 days from the first procedure
- Mean islet equivalents =11,400/kg required to achieve euglycemia
- Cadaveric pancreata from older donors >45 yo (70% would have been discarded)

Clinical Islet Transplantation Consortium

Islet Transplant Activity

(1999-2011)

Edmonton (65)

Miami (28)

Minneapolis (22)

NIH (6)

Northwestern (7)

U Penn (12)

Harvard (11)

Houston (7)

UC San Francisco (2)

St Louis (8)

Cincinnati (6)

U. Maryla

Seattle (6

U Mass (2

Memphis (3)

Emory (6)

Vancouver (7)

Columbia NY (2)

City of Hope CA (1)

Brazil (3)

Geneva/GRAGIL (19)

Milan (35)

Zurich (10)

Giessen (27)

Kings (UK) (1)

Sydney (3)

Innsbruck (11)

Kyoto (Japan) (1)

Shanghai (China) (1)

Estimated 400 patients at 35 institutions- 80% success

SIK/IAK

Black – SIK/IAK

Indications for Tx

- Type 1 DM + end-stage kidney failure:
  Simultaneous islet-kidney Tx (SIK)

- Type 1 DM in kidney graft recipient:
  Islet after kidney Tx (IAK)

- Treatment of chronic complications of diabetes

Indications for Tx

- Brittle type 1 diabetes, severe hypoglycemia

  Islet Tx alone (ITA)

- Treatment of acute complications of diabetes/ insulin therapy

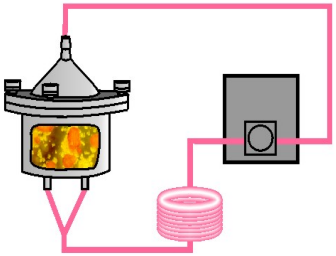
Challenges for Islet Transplantation

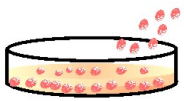
Procurement and cold ischemic damage to donor pancreas

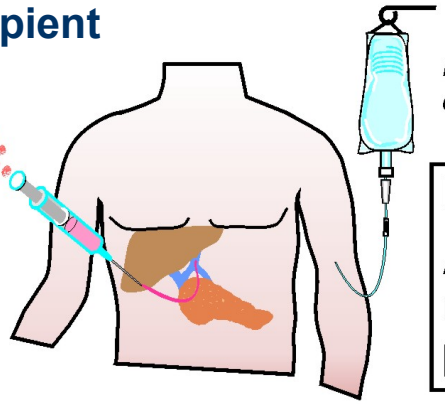
6,182 available organs (US)
Only 23.8% procured/used
~ 400 organs for islets

Side effects of anti-rejection, anti-autoimmunity immunosuppressive drugs

2-3 donor organ islets/recipient







Diabetogenic drugs

Ectopic intravascular site

Activation of damaging non-immune inflammatory pathways

Labour intensive and relatively inconsistent islet isolation

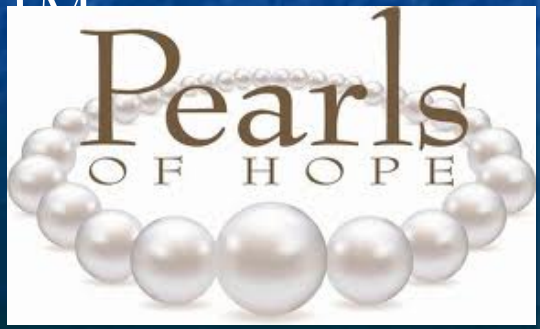
Isolation fails 50% of time

Recipient autoimmunity and alloimmunity

Long-term "success"
80% at I yr →
~ 20% at 5 yrs

Future of Cell Therapy for Diabetes

- Perform islet transplantation without chronic immunosuppression
- Create a "universal donor" source of insulin-secreting cells for transplantation
- Stem Cells, Tissue reprograming, regeneration of beta cells
- Immune Tolerance
- Tissue Engeenering
- Hybrid Devices and Local Delivery of IS/IM
- Find alternative implantation site

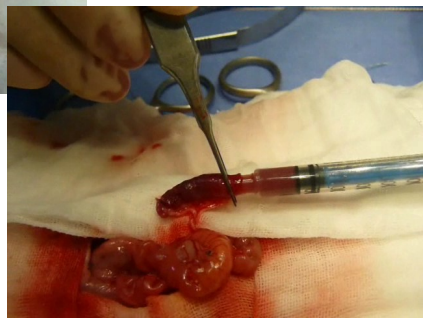


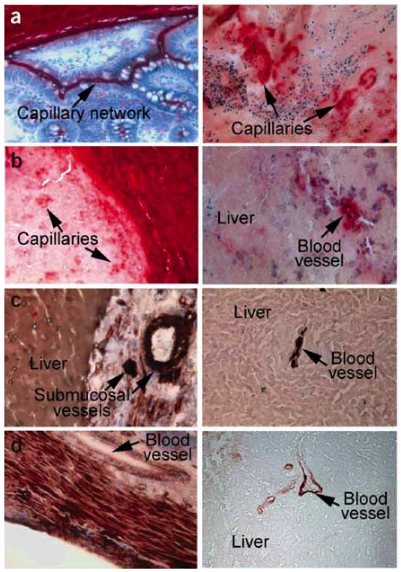
nature medicine

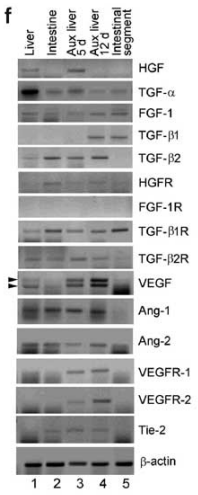
TECHNICAL REPORTS

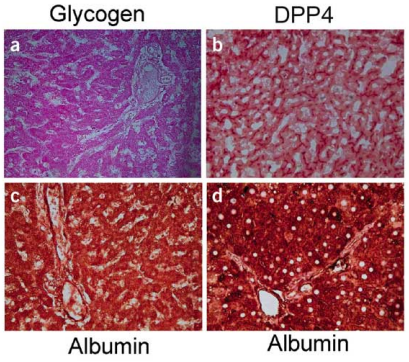
Isolated small intestinal segments support auxiliary livers with maintenance of hepatic functions

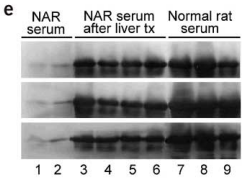
Brigid Joseph[1,2,6], Ekaterine Berishvili[3,6], Daniel Benten[1,2], Vinay Kumaran[1,2], Ekaterine Liponava[3], Kuldeep Bhargava[5], Christopher Palestro[5], Zurab Kakabadze[3] & Sanjeev Gupta[1,2,4]

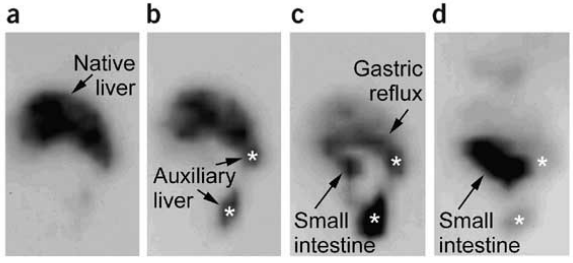


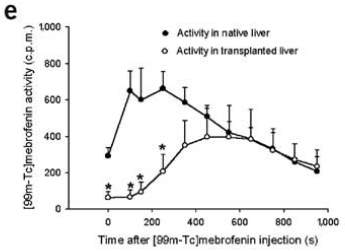












Joseph B et alt. Nat Med. 2004 Jul;10(7):749-53

Hypothesis

Small intestinal submucosa would serve as a suitable place for pancreatic islet transplantaton

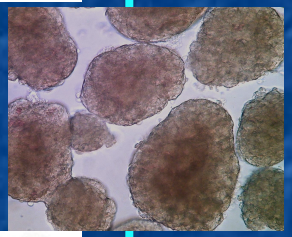
Priorities of IS Site

- Extravascular site
- Portal drainage
- Well vascularized environment
- Naturally enriched in collagen types I, III and VI, glycosaminoglycans (hyaluronic acid, chondroitin sulfate A and B, heparin, heparan sulfate), proteoglycans, fibronectin
- Several growth factors required for angiogenesis and cell growth are expressed in the intestinal submucosa (**VEGF, FGF, HGF, and TGF-b**)

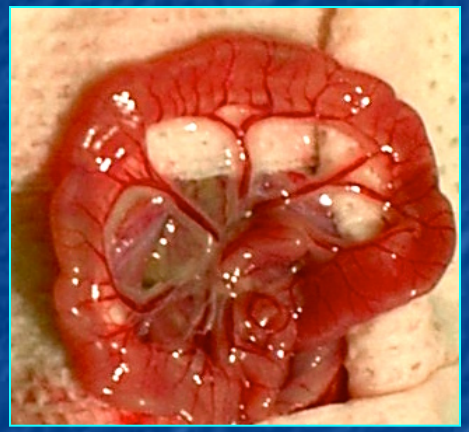
Materials and Methods

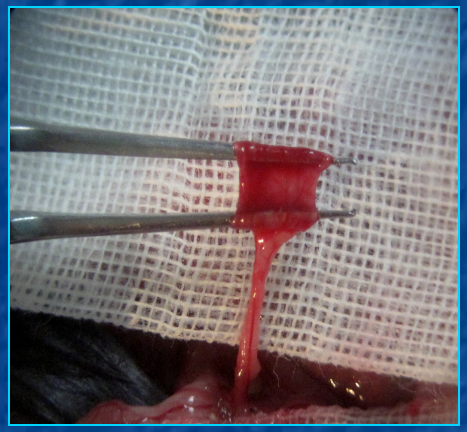
Fabrication of intestinal segments and islet transplantation

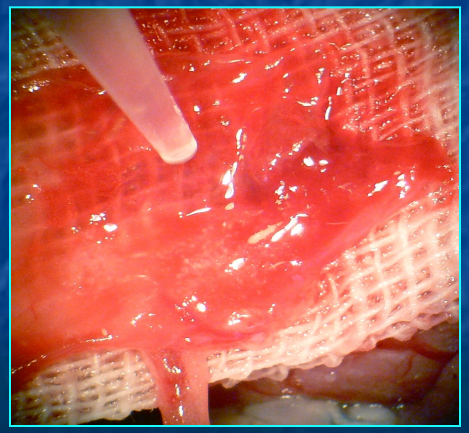
Lewis Rats

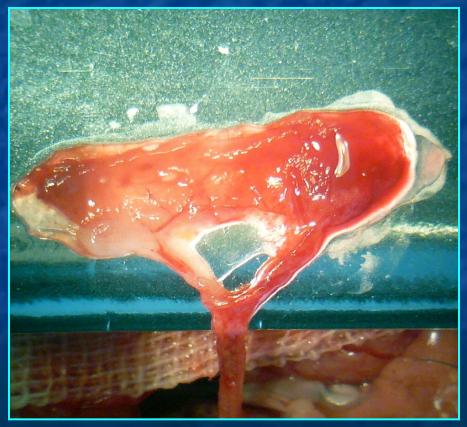


STZ diabetic
Lewis Rats

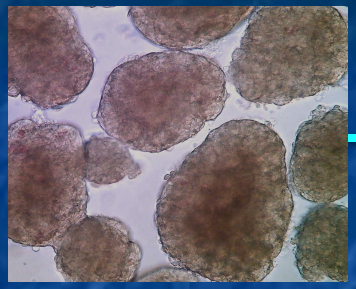








Pancreatic Islet Tx into the intestinal submucosa induces euglicemia

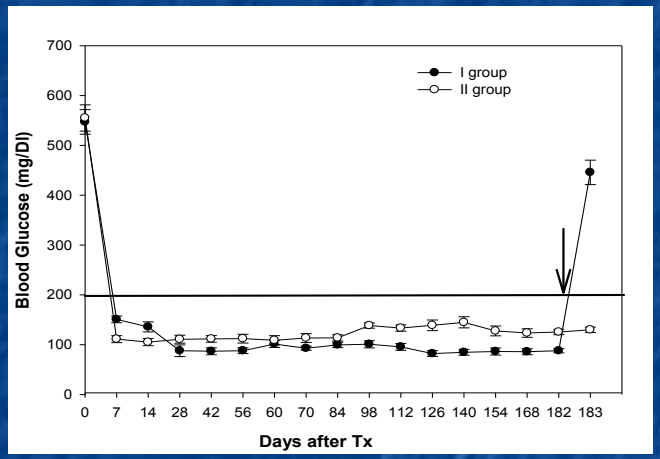


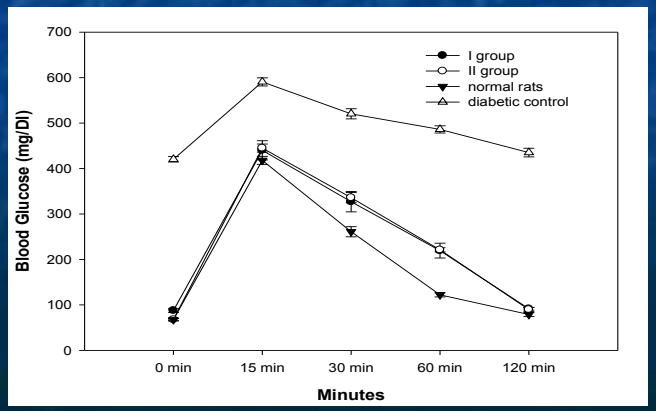
IS Tx & IP Tx

500 IEQ

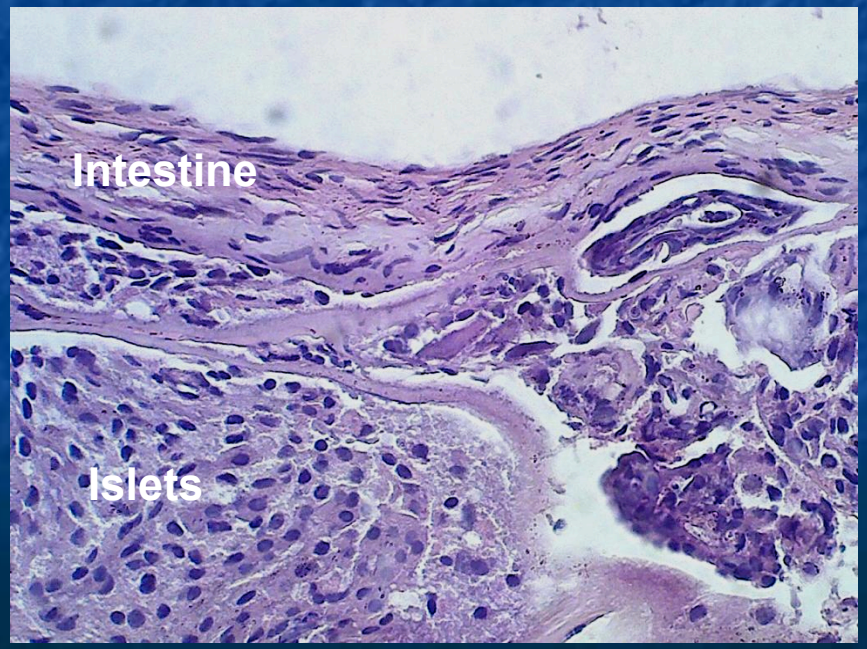
Stz diabetic Lewis Rats
(n=20)

IS graft removal:
1 w, 2 w, 1.5 m, 3 m, 6 m





POD 7



Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Long-term engraftment and function of transplanted pancreatic islets in vascularized segments of small intestine

Zurab Kakabadze,[1] Sanjeev Gupta,[2] Daniel Brandhorst,[3] Olle Korsgren,[3] and Ekaterine Berishvili[1]

1 Department of Clinical Anatomy, Tbilisi State Medical University, and Division of Cell Transplantation, Georgian National Institute of Medical Research, Tbilisi, Georgia
2 Departments of Medicine and Pathology, Diabetes Center, Marion Bessin Liver Research Center, Cancer Center, Gottesman Institute for Stem Cell Research and Regenerative Medicine, and Institute for Clinical and Translational Research, Albert Einstein College of Medicine, Bronx, NY, USA
3 Department of Oncology, Radiology & Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden

Keywords
islets, pancreas, portal vein, small intestine, transplantation.

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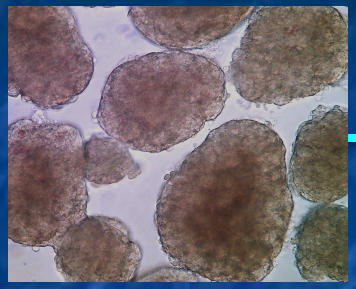
Received: 5 July 2010
Accepted: 7 August 2010
Published online: 6 September 2010

doi:10.1111/j.1432-2277.2010.01160.x

Summary

This study evaluated the potential of vascularized small intestinal segments for pancreatic islet transplantation. Islets isolated from Lewis rats were transplanted into diabetic syngeneic recipients. Segments of small intestine were prepared by denudation of the mucosal layer prior to implantation of pancreatic islets into the segments. Animal groups were established to determine engraftment, survival and function of islets transplanted into either intestinal segments or portal vein over up to 60 days. We found transplantation of functionally intact pancreatic islets into small intestinal segments was well tolerated. Transplanted islets were rapidly engrafted in intestinal segments as demonstrated vascularization and expression of insulin and glucagon throughout the 60-day duration of the studies. Transplantation of islets restored euglycemia in diabetic rats, which was similar to animals receiving islets intraportally. Moreover, animals treated with islet transplants showed normal responses to glucose challenges. Removal of graft-bearing intestinal segments led to recurrence of hyperglycemia indicating that transplanted islets were responsible for improved outcomes. Therefore, we concluded that vascularized intestinal segments supported reorganization, survival and function of transplanted islets with therapeutic efficacy in streptozotocin-treated diabetic rats. The approach described here will be appropriate for studying islet biogenesis, reorganization and function, including for cell therapy applications.

Intestinal Submucosal Site vs Liver

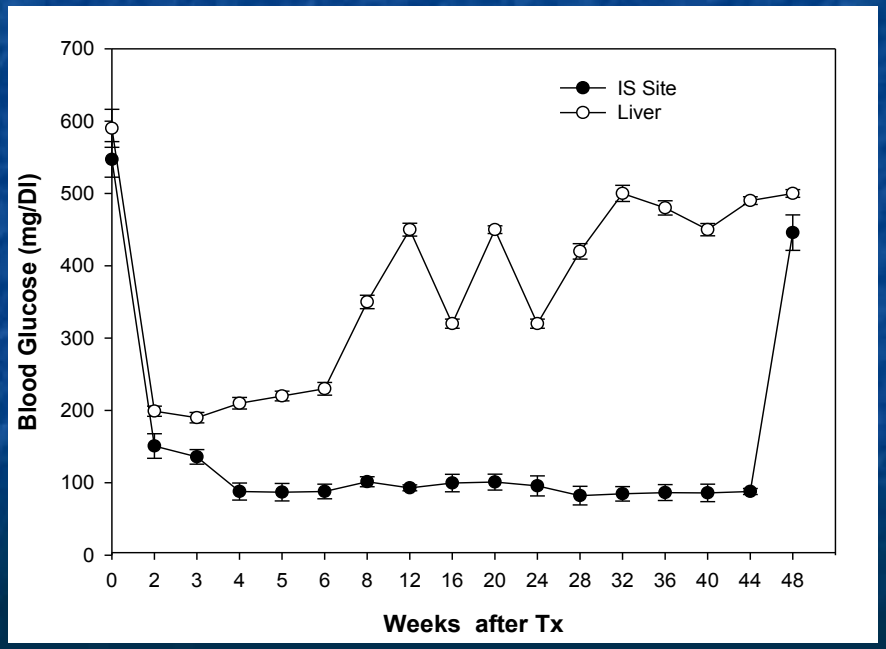


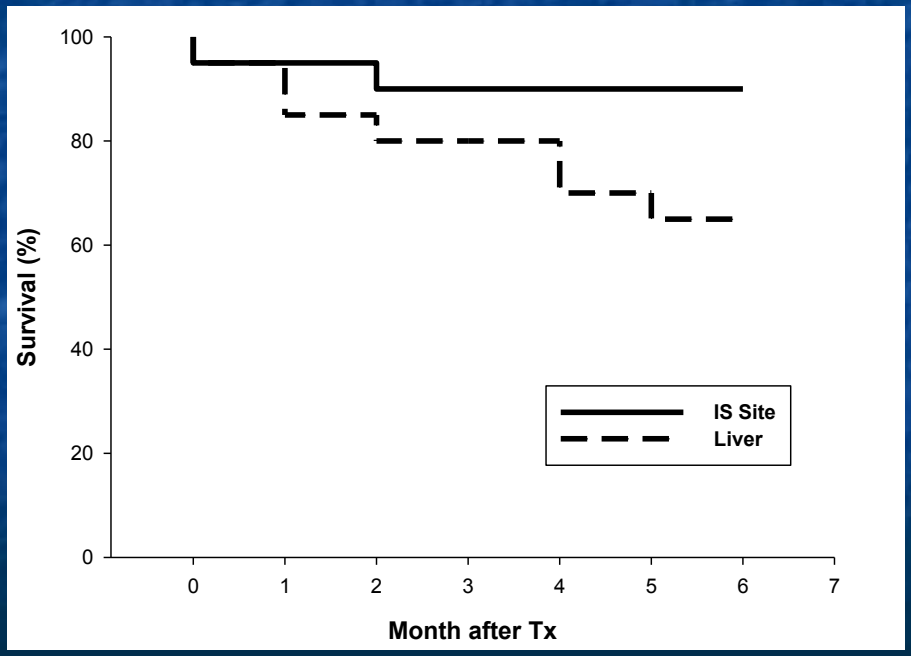
IS Tx vs IP Tx

350 IEQ

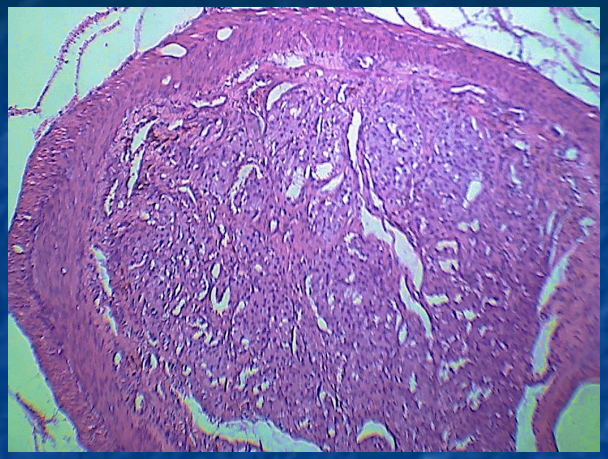
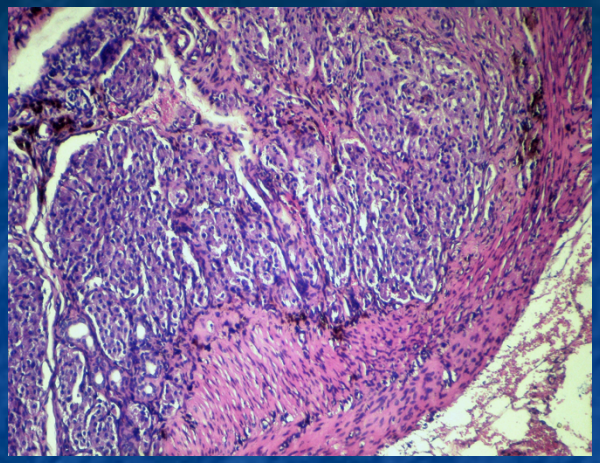
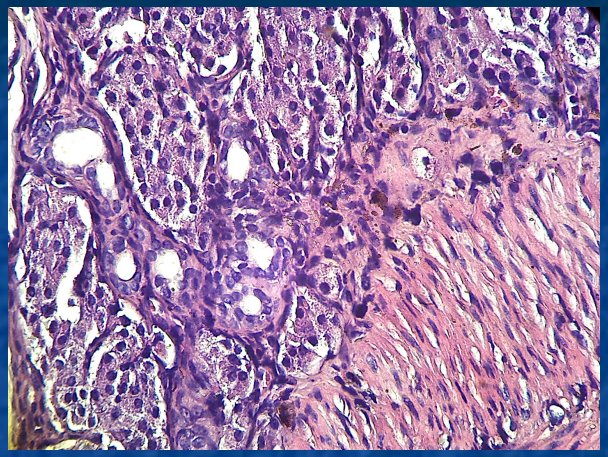
Stz diabetic Lewis Rats
(n=20)

IS graft removal: 1 w, 2 w,
1.5 m, 3 m, 6 m, 9m, 12 m

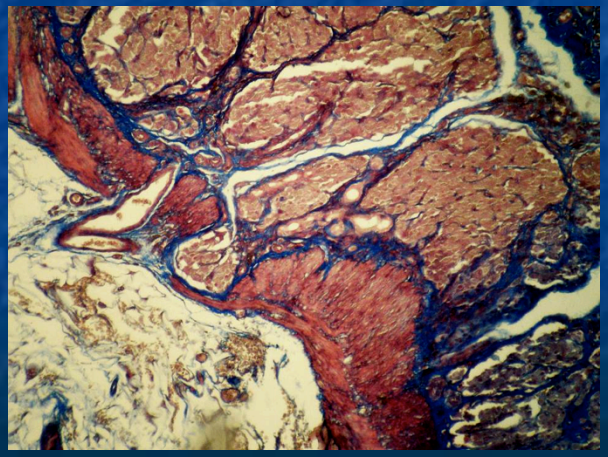
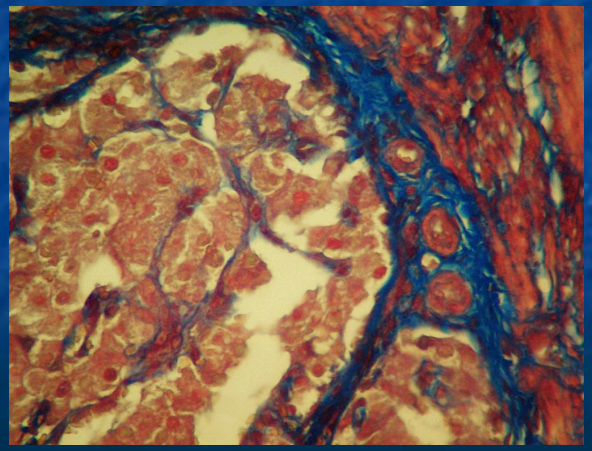
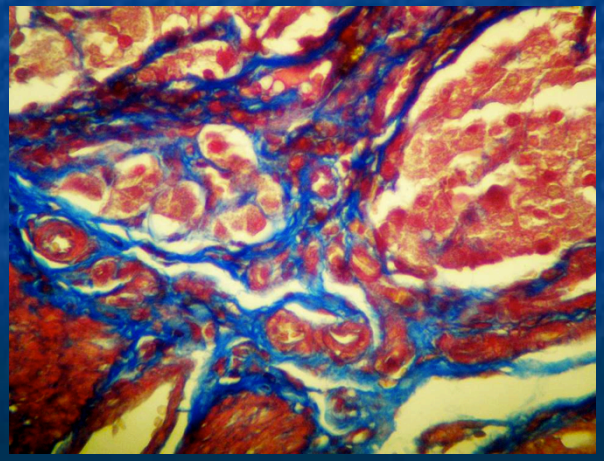




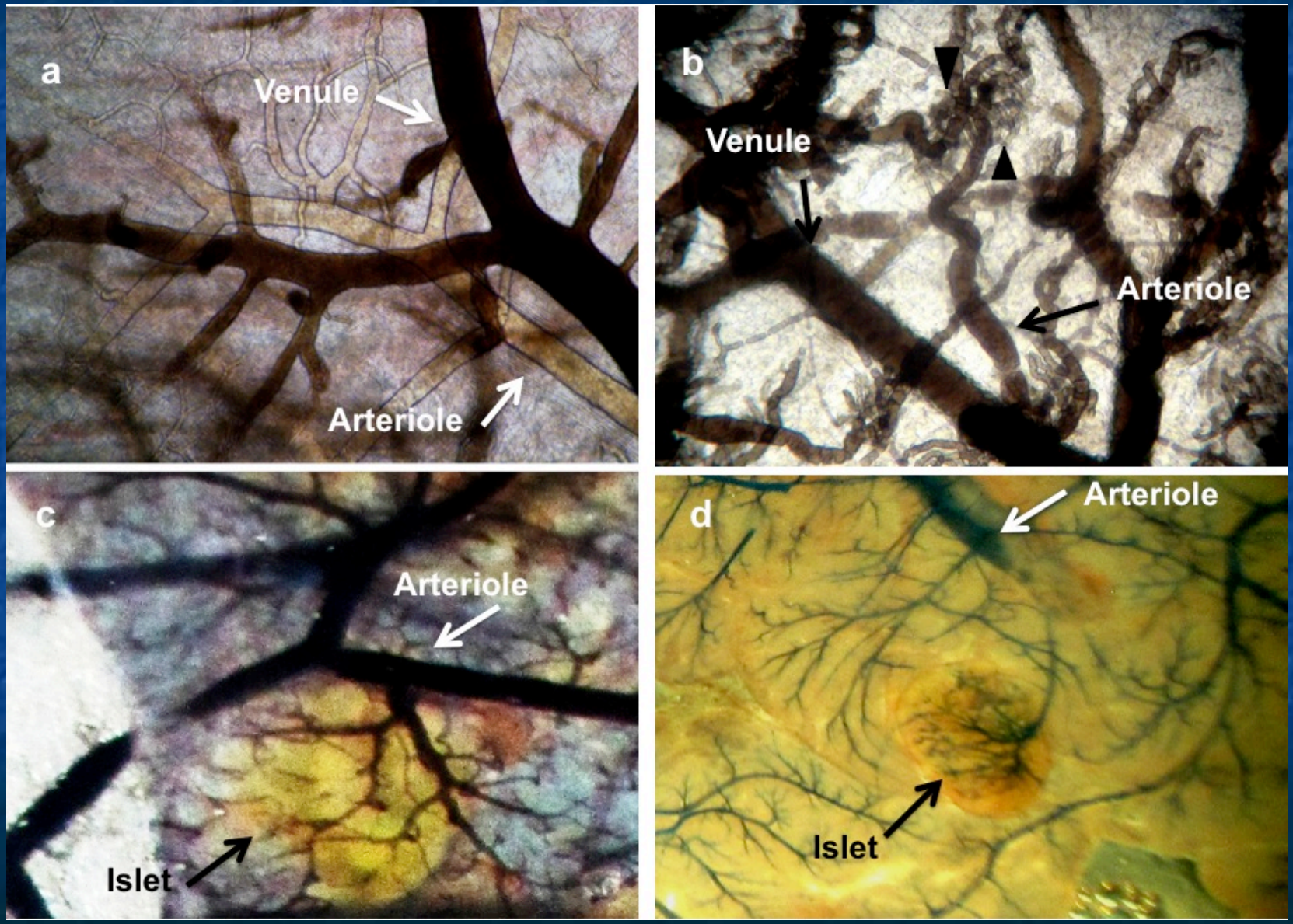
H&E

Masson's Trichrome

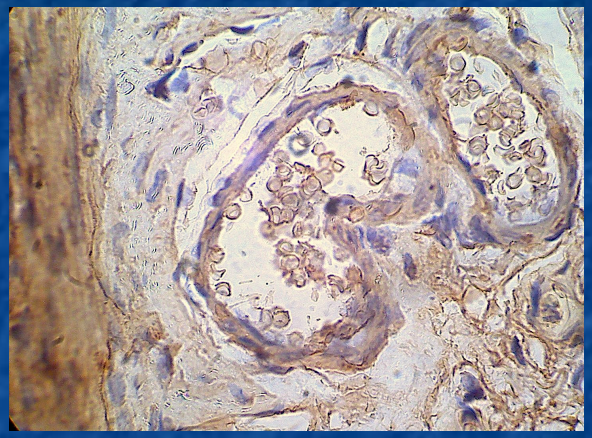




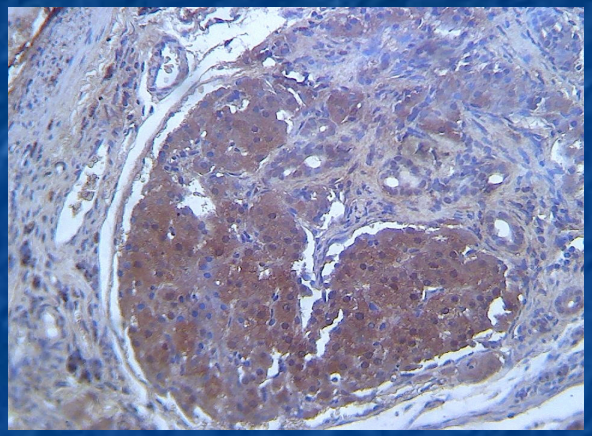
Vascular casting of graft bearing intestinal segment

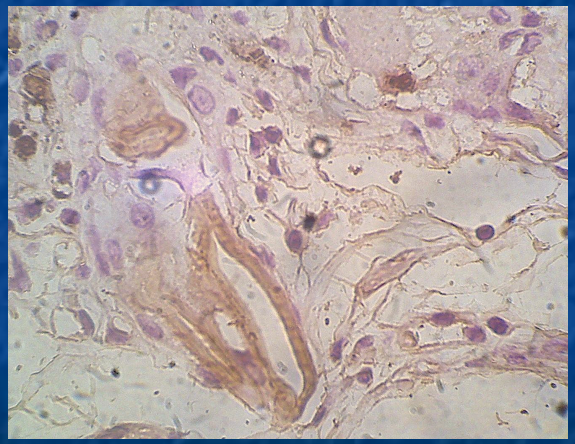


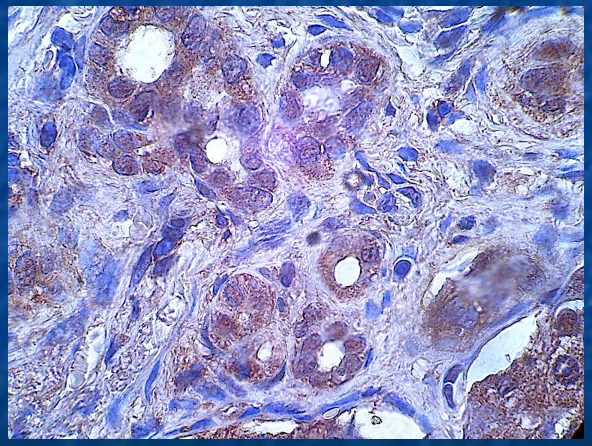
α-SMA

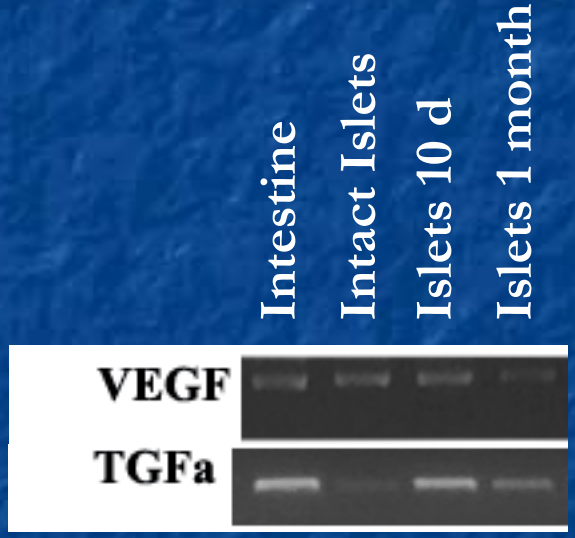
VEGF





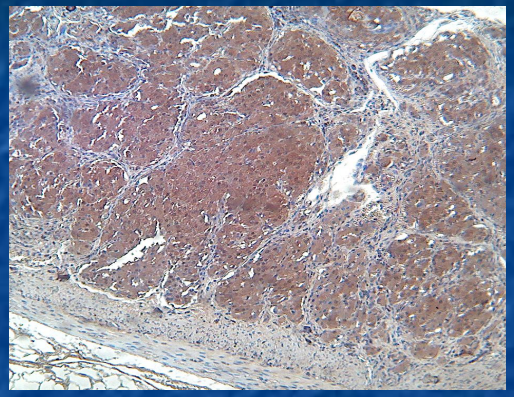


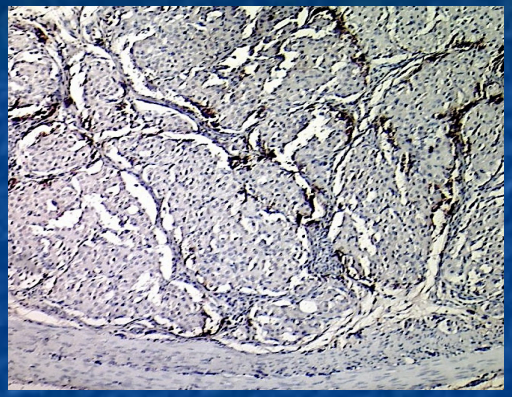


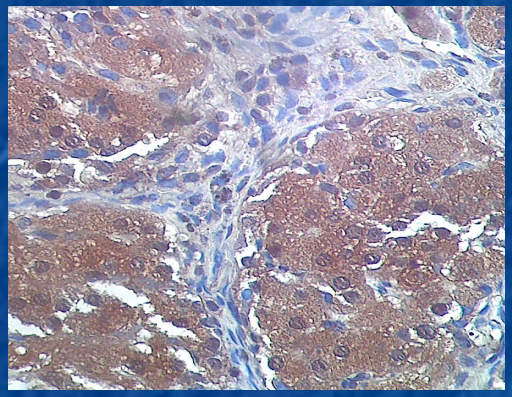

Intestine
Intact Islets
Islets 10 d
Islets 1 month
VEGF
TGFa

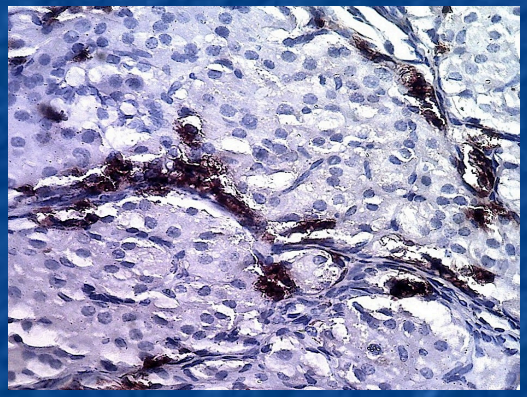
Insulin

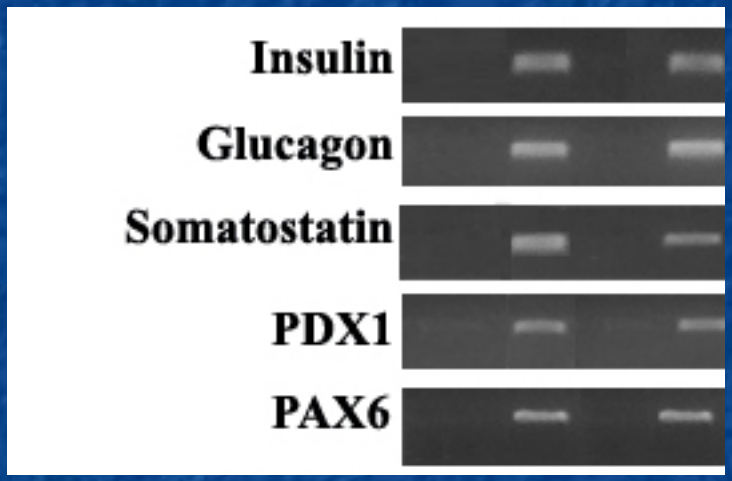
Glucagon











Conclusions

- Our studies demonstrate that pancreatic islets can be successfully transplanted into vascularized small intestinal segments with the potential to correct hyperglycemia in diabetic rats
- Islets transplanted in intestinal segments had normal morphology, and maintained expression of insulin as well as glucagon.
- These encouraging features of the isolated intestinal segment open new research avenues for addressing biological mechanisms and clinical applications.
- This tissue-engineering approach could eventually be considered for cell therapy in diabetes mellitus.

An Isolated Venous Sac as a Novel Site for Cell Therapy in Diabetes Mellitus

Zurab Kakabadze,[1] Koba Shanava,[1] Camillo Ricordi,[2] A.M. James Shapiro,[3] Sanjeev Gupta,[4] and Ekaterine Berishvili[1,5]

Background. Transplanting pancreatic islets is of significant interest for type 1 diabetes mellitus. After intraportal injection of islets, inferior engraftment and eventual loss of transplanted islets constitute major limitations. Therefore, alternative approaches will be helpful. Here, we evaluated in animals whether an isolated venous sac would support survival of transplanted islets, along with correction of hyperglycemia.

Methods. Pancreatic islets isolated from adult Lewis rats were transplanted either into an isolated venous sac made from lumbar vein or into the portal vein of syngeneic rats. The integrity and vascular organization of the venous sac was determined by studies of the local microcirculation. The engraftment, survival, and function of transplanted islets were analyzed by histology, including endocrine function in situ and by glycemic control in rats with streptozotocin-induced diabetes.

Results. Transplanted islets showed normal morphology with insulin expression in isolated venous sac during the long term. Transplanted islets received blood supply from vasa vasorum and had access to drainage through venous tributaries in the venous sac. This resulted in restoration of euglycemia in diabetic rats. Removal of islet graft-bearing venous sac in diabetic rats led to recurrence of hyperglycemia. By contrast, euglycemia was not restored in rats treated by intraportal transplantation of islets.

Conclusions. We demonstrated that pancreatic islets successfully engrafted and functioned in the isolated venous sac with ability to restore euglycemia in diabetic rats. Therefore, the isolated venous sac offers a new site for transplantation of pancreatic islets. This would be clinically beneficial as an alternative to intrahepatic islet transplantation.

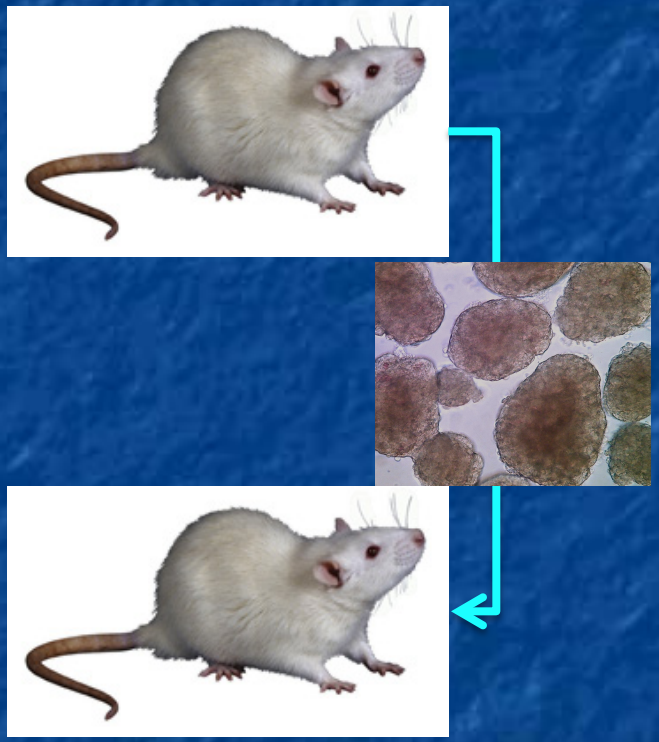
Keywords: Islets, Pancreas, Intravascular transplantation.

(*Transplantation* 2012;94: 319–324)

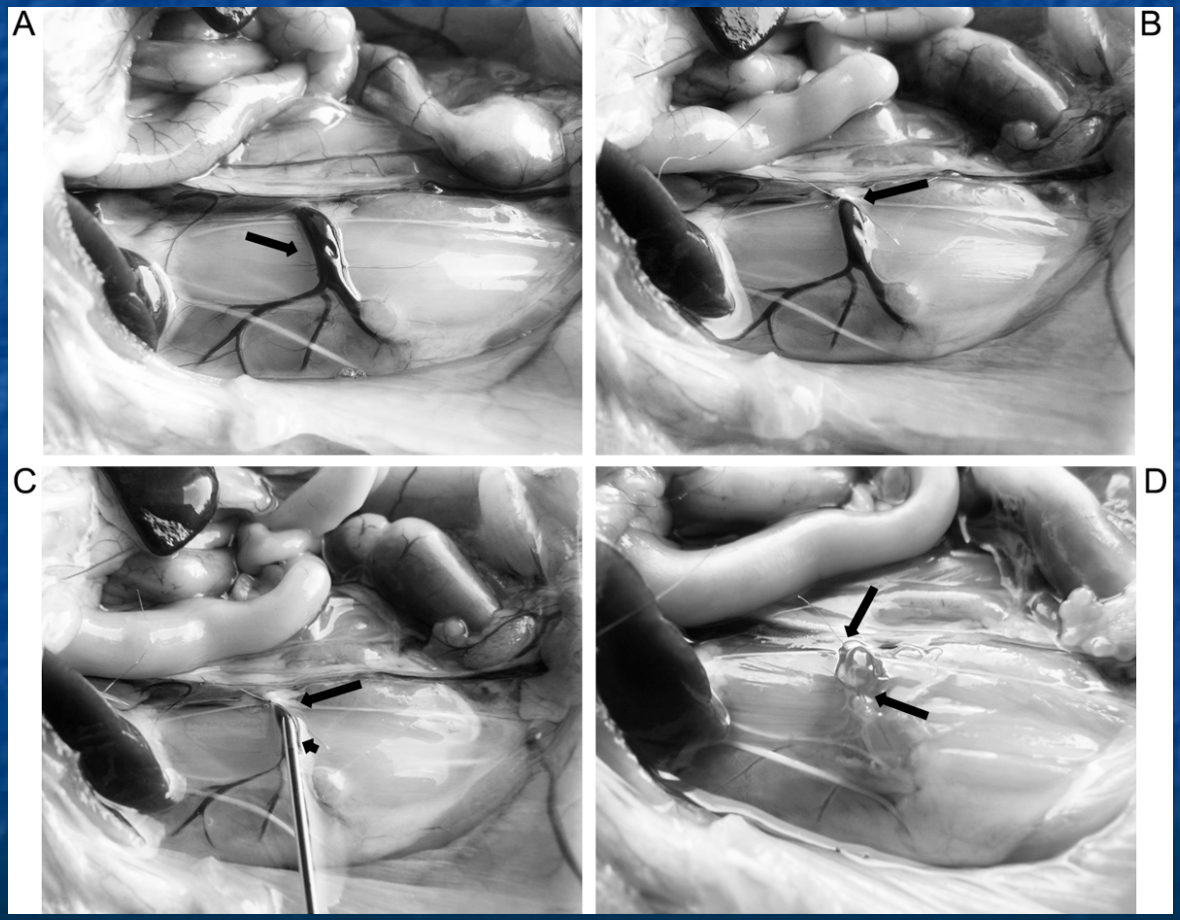
Materials and Methods

Fabrication of venous sac and islet transplantation

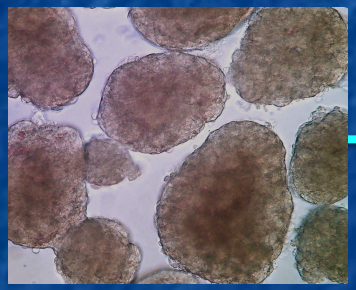
Lewis Rats



STZ diabetic
Lewis Rats



Pancreatic Islet Tx into the venous sac induces euglicemia



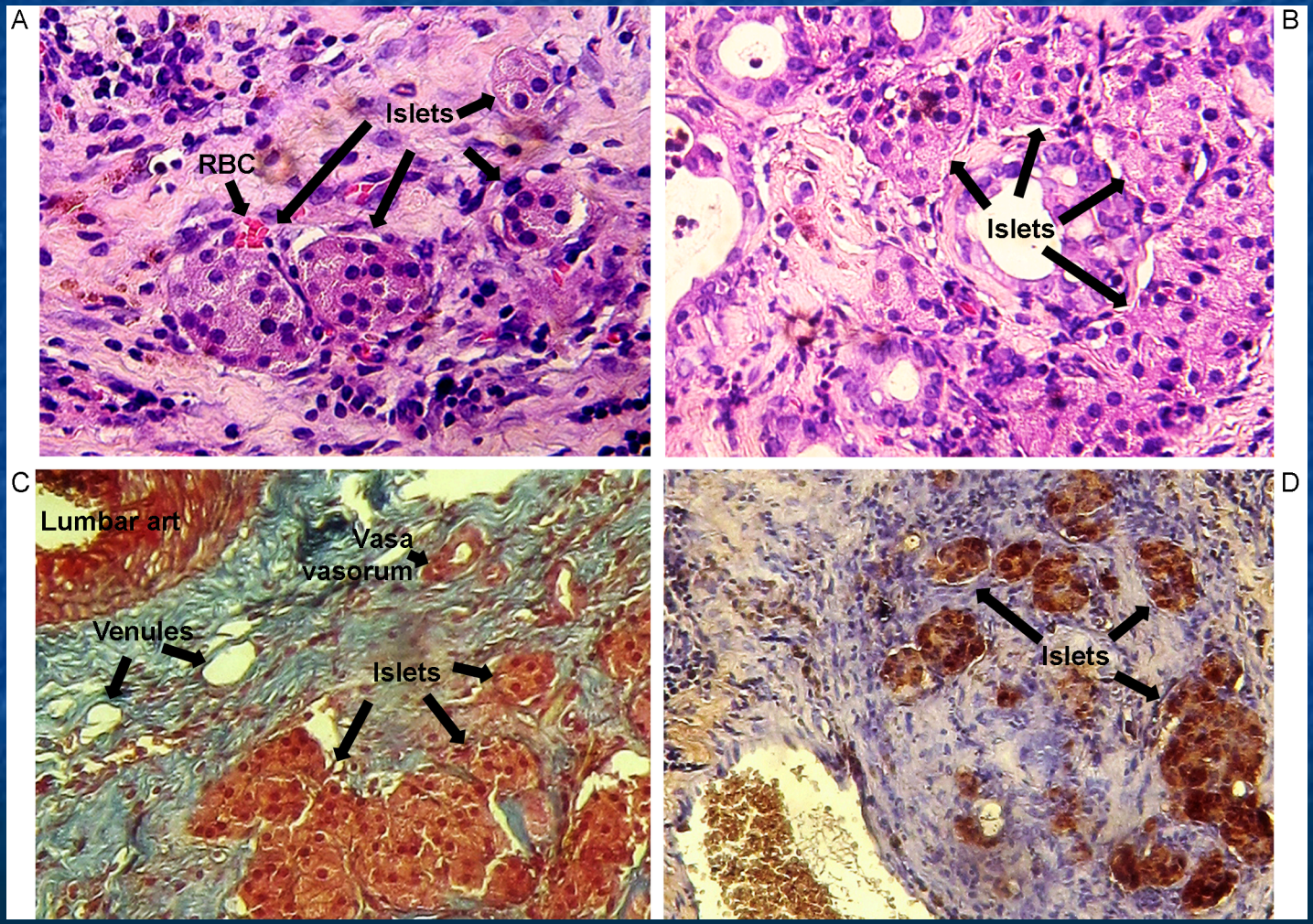
IV Tx & IP Tx

350 IEQ

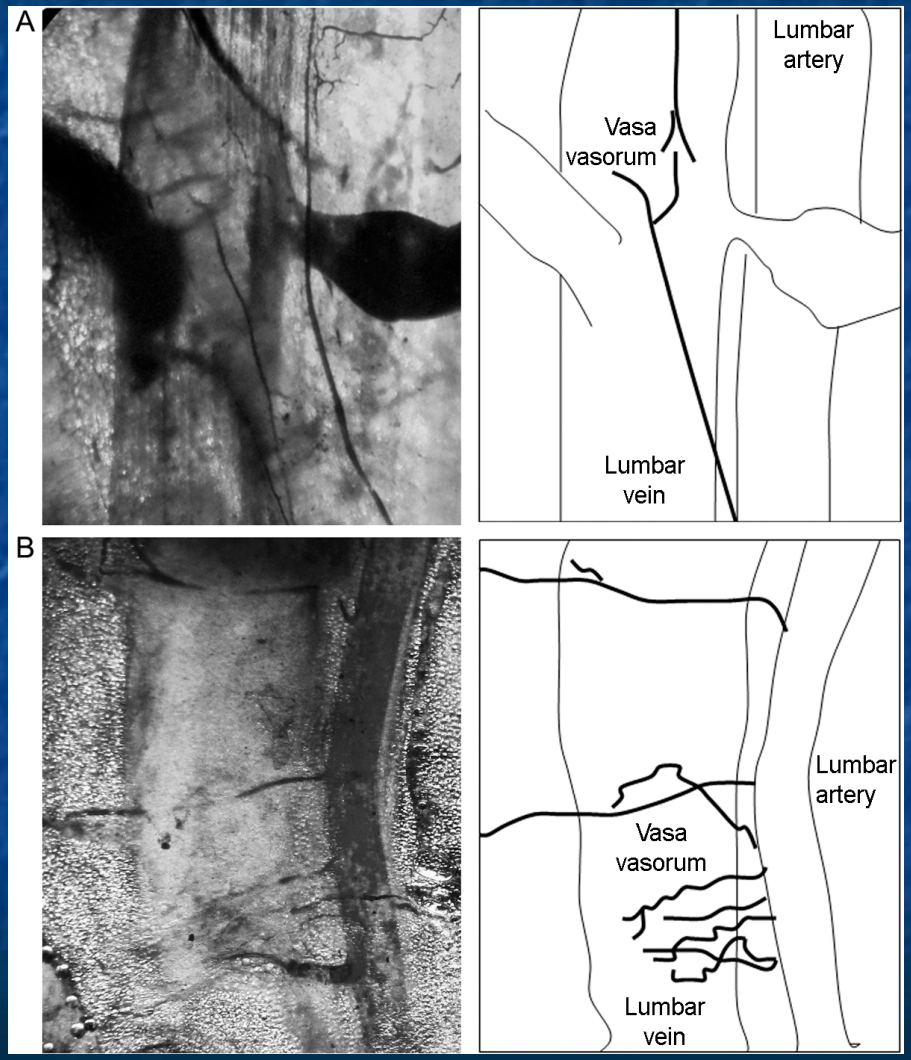
Stz diabetic Lewis Rats
(n=20)

IV graft removal:
3 d, 7 d, 14 d,
60d

Histopathological evaluation of explanted islet-containing venous sacs



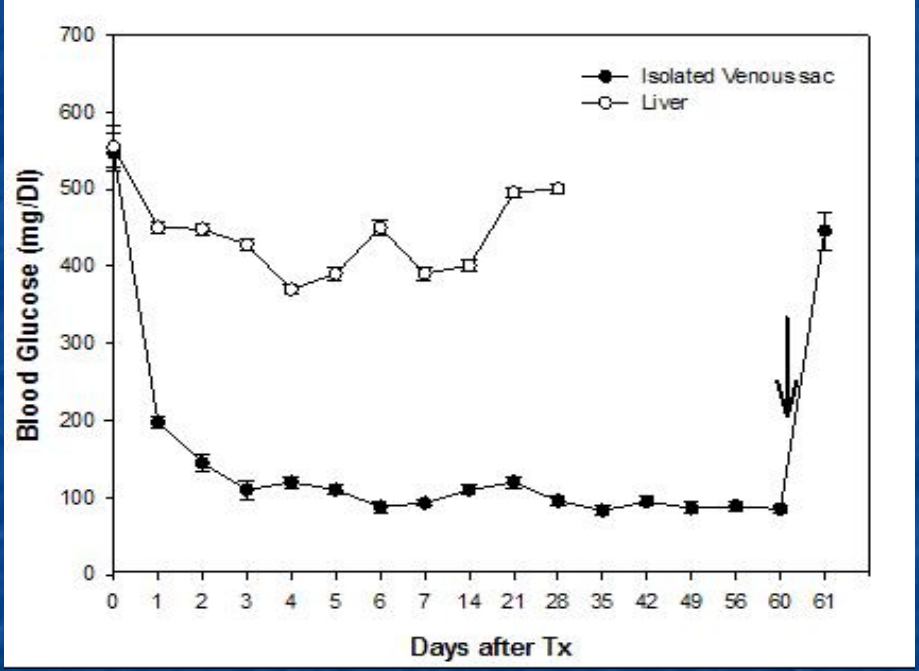
Integrity and vascular supply of venous sacs

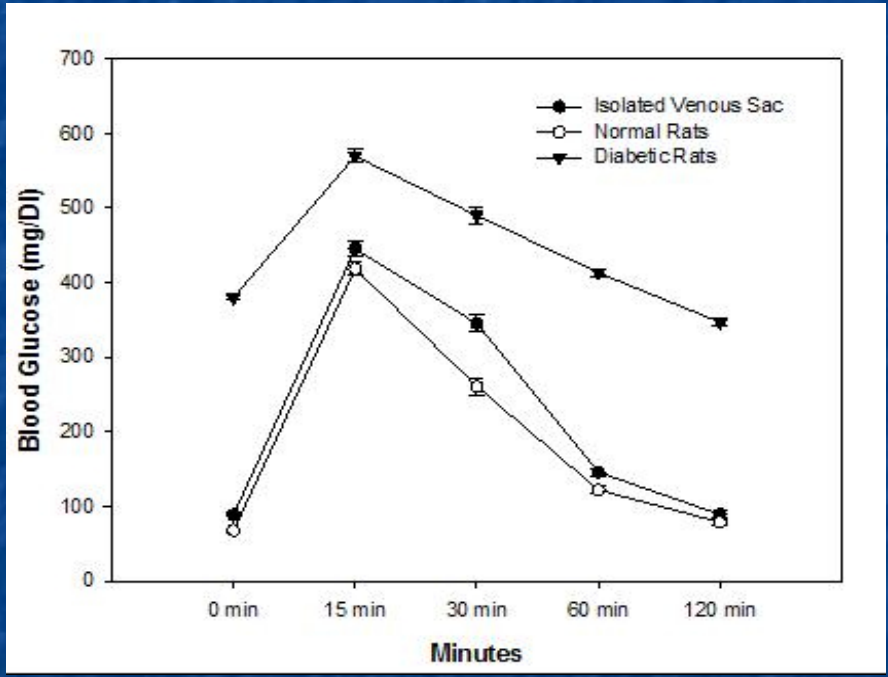


(A) Vascular casts obtained with latex dye of lumbar vessels showing vasa vasorum in healthy rat.

(B) Vascular casts in rat 3 d after islet transplantation showing patent vessels and vasa vasorum

Regulation of blood glucose levels in diabetic rats after islet transplantation





Conclusions

- Our studies demonstrate that venous sac permitted engraftment, survival and function of transplanted pancreatic islets over the long-term
- Even a minimal mass of pancreatic islets in isolated venous sacs was successful in restoring euglycemia in STZ-treated diabetic rats .
- the venous sac should be useful for testing the fate and function of stem cell-derived pancreatic beta cells or islets in the future
- The simplicity of transplanting islets in venous sac should advance studies for clinical development.

Acknowledgments

EFSD/ New Horizons Initiative

Tbilisi State Medical University:

Head of the Department of Clinical Anatomy

Dr. Zurab Kakabadze MD, PhD

Dr. Koba Shanava MD

Diabetes Research Institute, Miami, FL

Dr. Camillo Ricordi

Dr. A. Pillegi

Dr. D. Molano

Clinical Islet Transplant Program and Department of Surgery, University of Alberta

Dr. AM James Shapiro MD, PhD

Departments of Medicine and Pathology, Diabetes Center, Marion Bessin Liver Research Center, Gottesman Institute for StemCell Research and Regenerative Medicine, and Institute for Clinical and Translational Research, Albert Einstein College of Medicine, Bronx, NY:

Professor Sanjeev Gupta MD, PhD

Thank You!

Mesenchymal stem cells forming a beautiful heart shape.
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