Islet Transplantation:
Triumphs and Barriers

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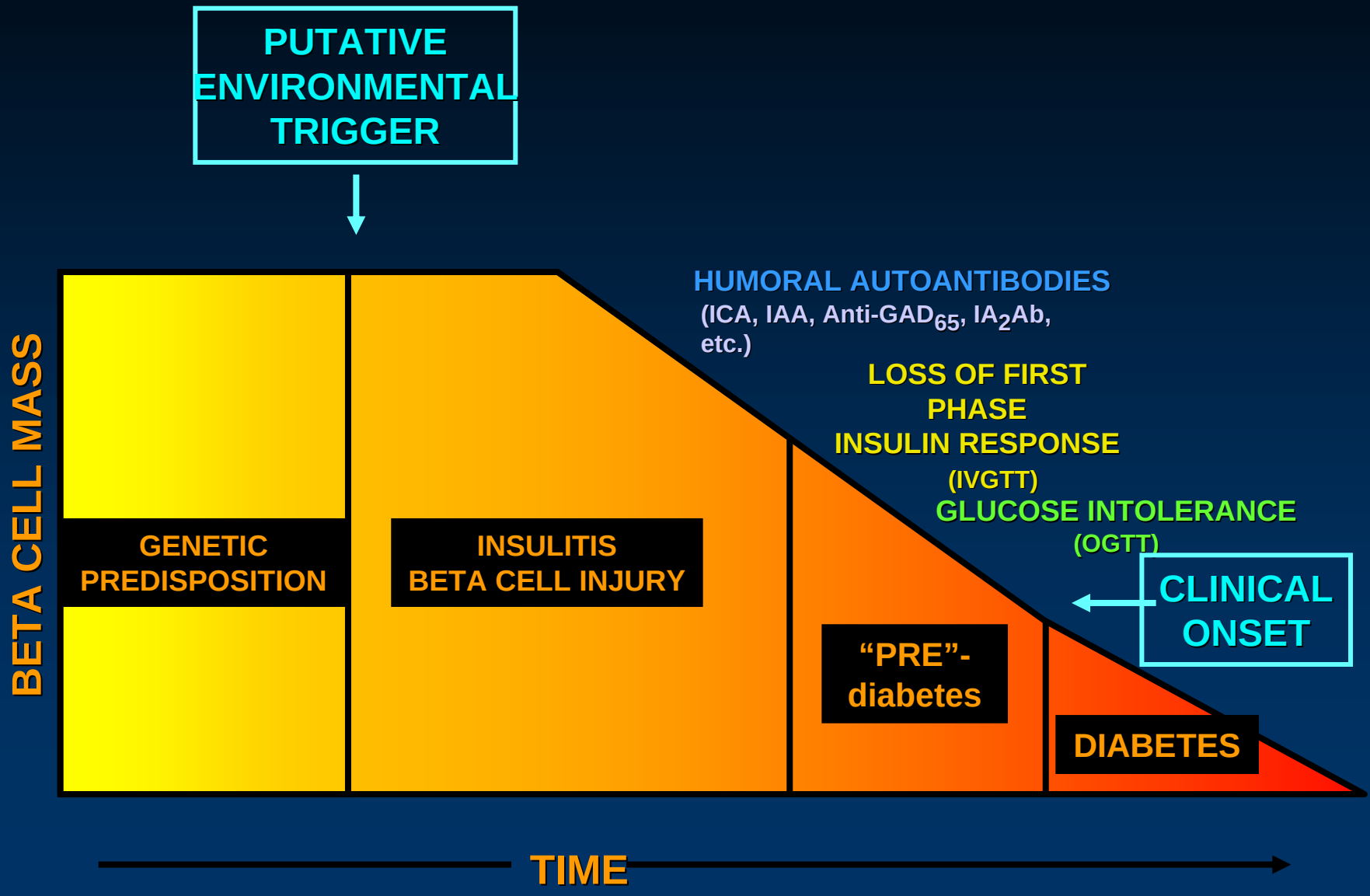
Objectives

- Brief overview of Type 1 diabetes
- Progress in islet transplantation
  - past, present and future
- Potential application in type 2 diabetes

Natural History of Type 1 Diabetes

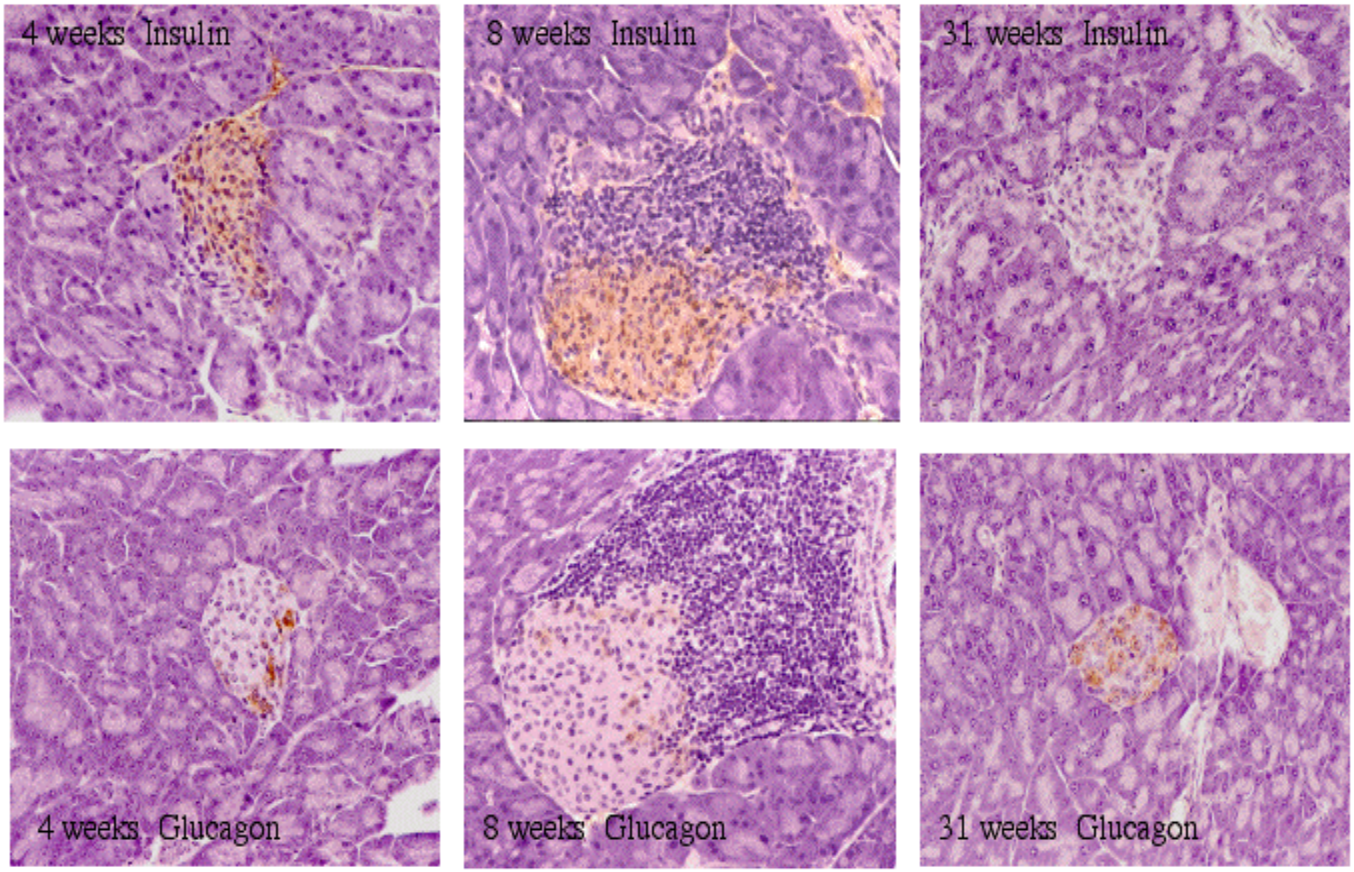


Progression of Autoimmune Diabetes

Phase 1: insulitis

Phase 2: Destructive

Figure 1. Progression of diabetes in the NOD mouse

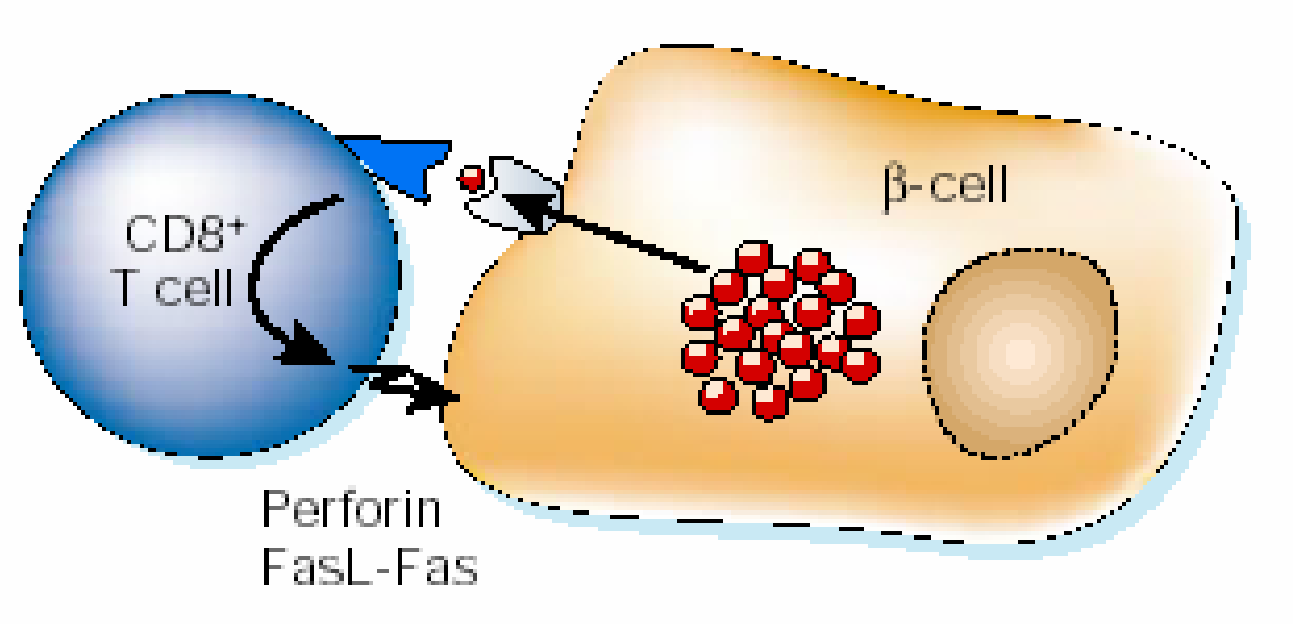


insulin

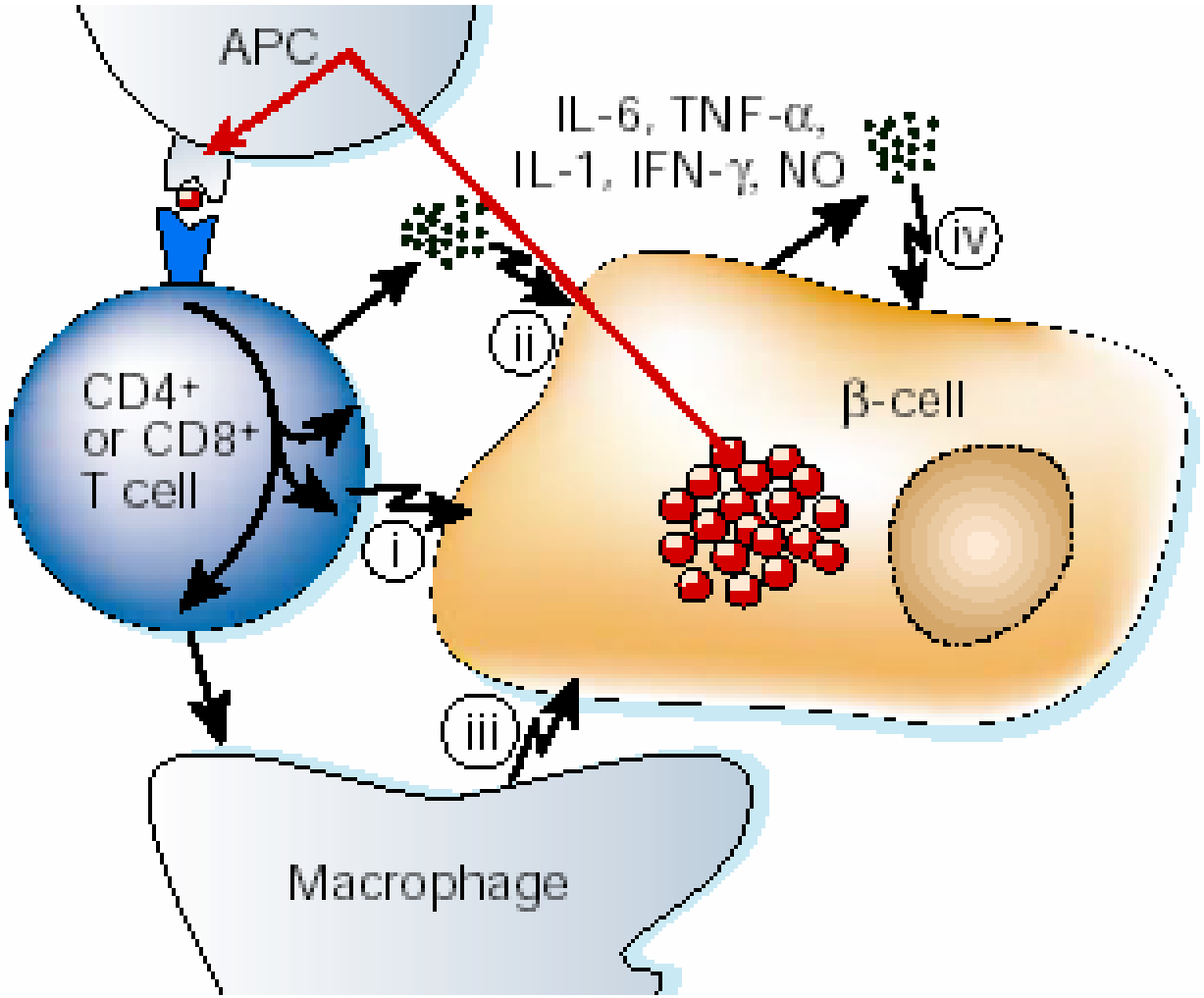
glucagon

4 weeks **8 weeks** **31 weeks**

Contact dependent β cell death

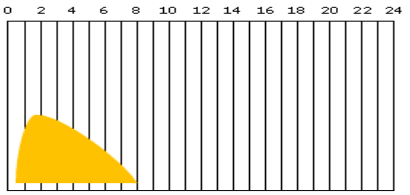


β cell destruction: End Stage




N
R


DISETRONIC
H-TRONplus V100
U/h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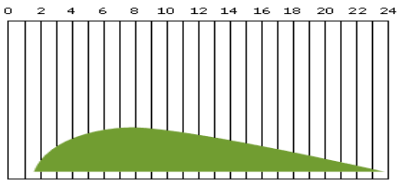
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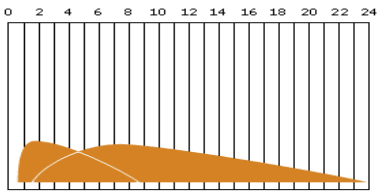
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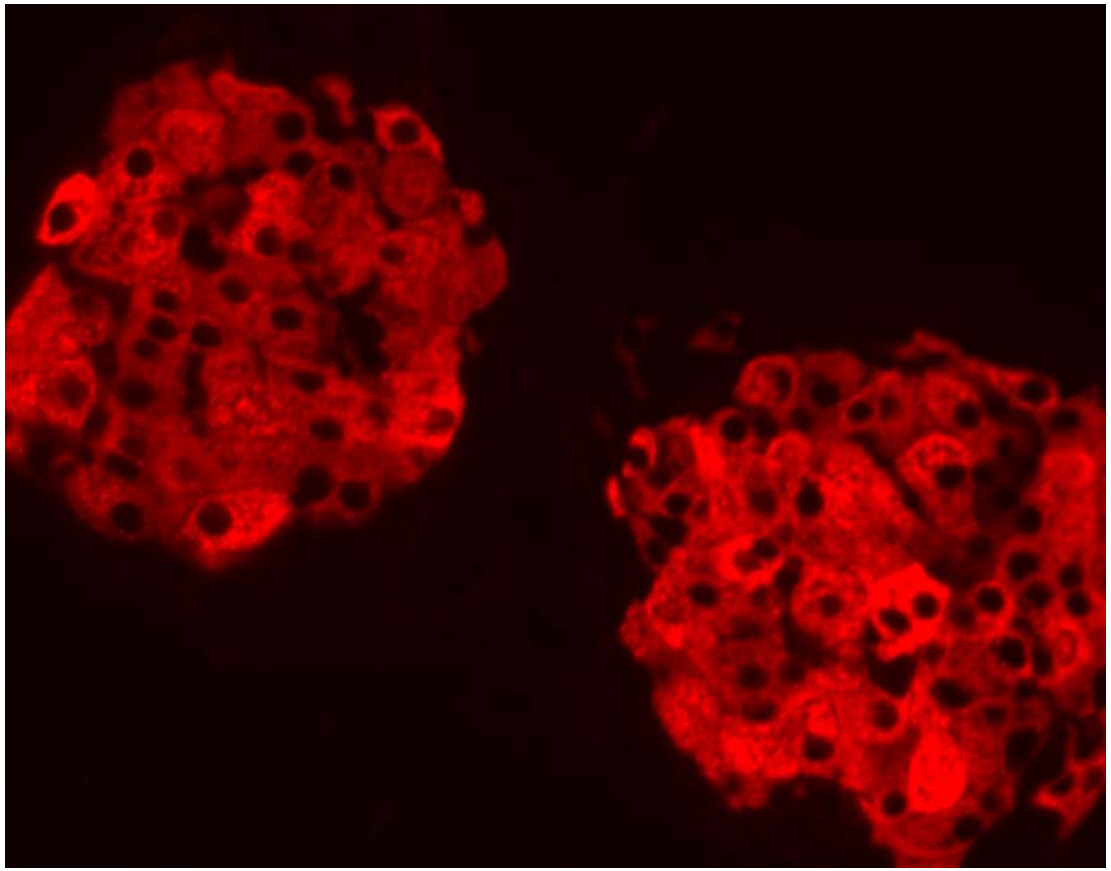
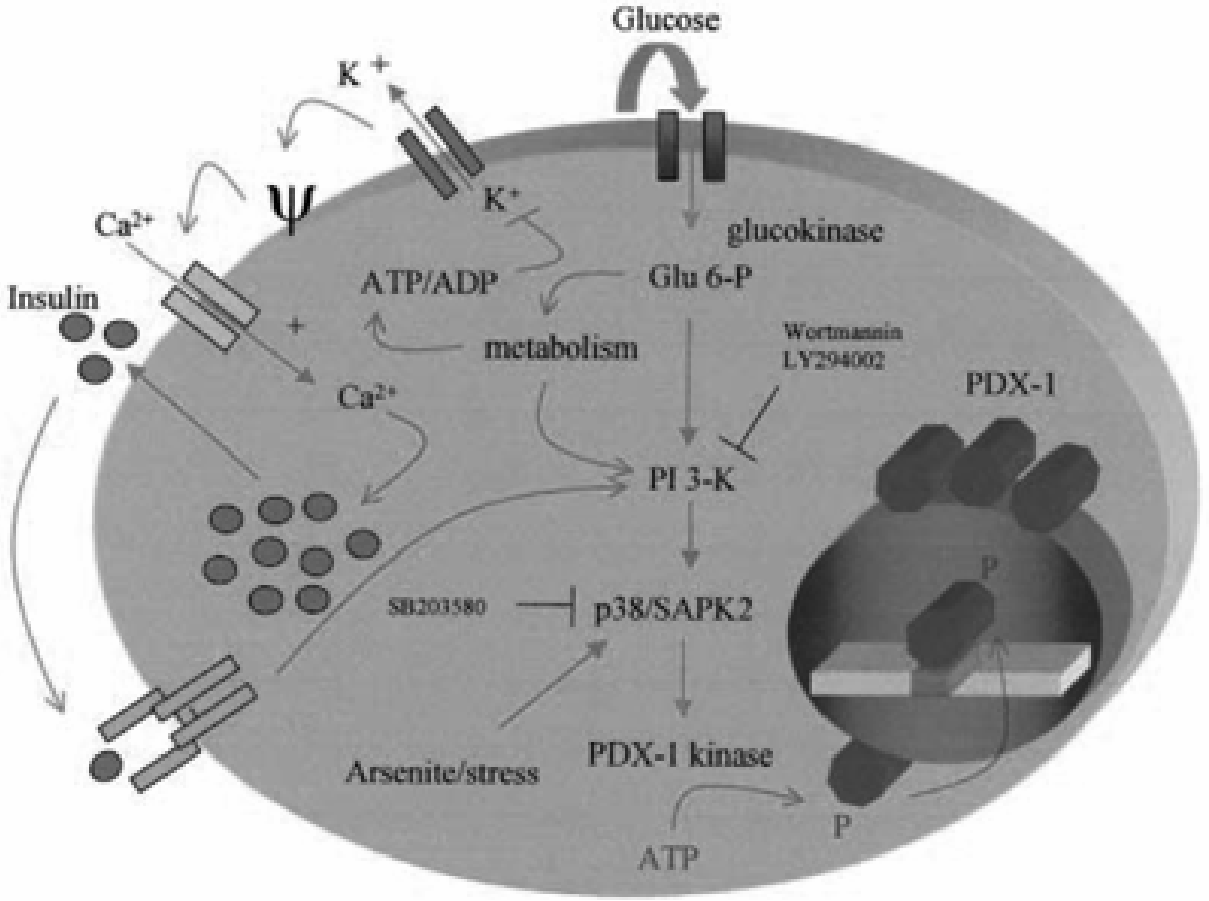
DCCT

- intensive insulin therapy
  - frequent injections
  - pumps
- significant protection against
  - nephropathy, neuropathy and retinopathy
- three fold increase in serious hypoglycemic events
  - seizure
  - coma




Glucose
K +
K+
Ca2+
Ψ
glucokinase
ATP/ADP
Glu 6-P
Insulin
+
metabolism
Wortmannin
LY294002
PDX-1
Ca2+
PI 3-K
P
SB203580
p38/SAPK2
PDX-1 kinase
Arsenite/stress
P
ATP

Whole Pancreas Transplantation

- prolong life
- reverse established nephropathy
- improve quality of life

- too morbid to advocate for most patients with Type 1 diabetes

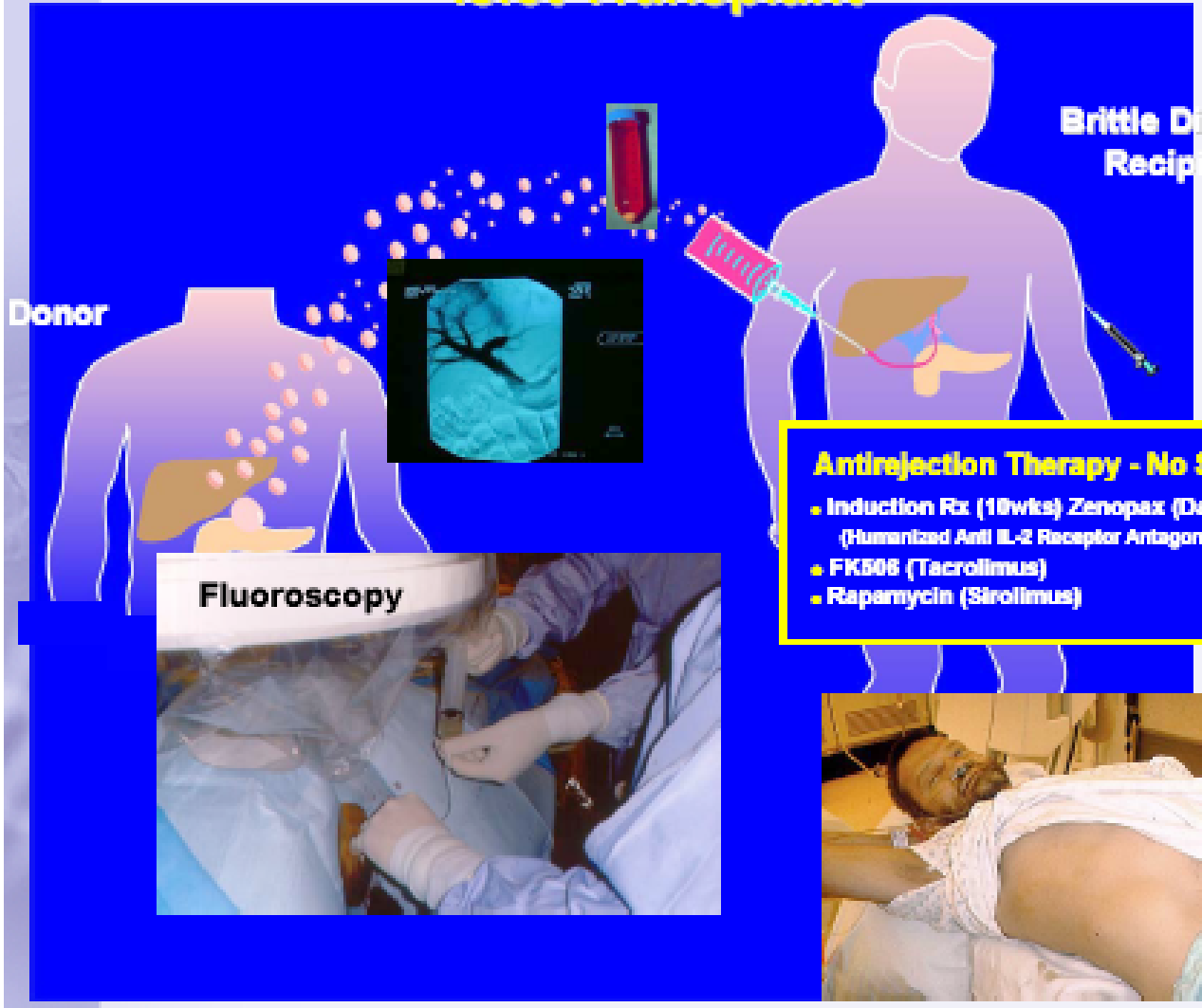
Whole Pancreas Transplantation (cont'ed)

- freedom from insulin, glucose monitoring and dietary restriction
- improved overall quality of life
- particulaly for patients with hypoglycemic unawareness, brittle diabetes or gastroparesis

Islet transplantation

- avoids surgical risk of the exocrine component
- 1967-Paul Lacy successfully isolated islets from pancreas
- 1970’s-trials and tribulations of human islet transplantations

Islet Transplant



Antirejection Therapy - No Steroids

- Induction Rx (10wks) Zenopax (Daclizumab)
  (Humanized Anti IL-2 Receptor Antagonist)
- FK506 (Tacrolimus)
- Rapamycin (Sirolimus)

Limitations in islet transplantation

- inadequate transplant mass
- inadequate islet potency
- inadequate prophylaxis allograft rejection or autoimmunity
- routine use of toxic and diabetogenic immunosuppression after transplantation

Glucocorticoid free immunosuppressive protocol

- sirolimus
- tacrolimus
- anti IL2 R monoclonal ab (daclizumab)

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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.

continued improvements

- islet isolation techniques
- immunosuppressives

- Despite these advances:
- islet tansplantation only approved for:
  - unstable forms of type 1 diabetes
  - recipients of other solid organ allografts

Follow-up Edmonton data

- Over 50 patients
- One year insulin independence rate of 80%
- Three year islet graft function ~90%
- 2 patients remaining insulin free beyond 4 years

Significant advances

- reliable single donor islet transplantation protocols
- refinement of islet culture protocols
- better pancreas transport system
- improved recovery of trapped islets
- furthur immunomodulation therapy
  - anti-TNFα
  - calcineurin inhibitor-sparing strategies
  - tolerogenic T cell depletion antibodies

Limitations

- Islet transplantation is much less effective in patients with high autoantibodies (GAD, ICA)
- post-infusion bleeding (10%)
- Portal vein thrombosis (<0.5%)
- malignancy, post transplant lymphoma, sepsis (rare but feared complications)
- poor engraftment (25-50%)
- islet apoptosis (anoikis, ischemia)

Islet composition

- lower beta cell content than was previously thought
- grafts contained substantial population of exocrine and ductal tissue
- donor age affects islet yield and purity
- positive corelation between islet progenitor cells (ductal-epithelial cells) and long term metabolic success

In vitro islet graft manipulation strategies

- Expand islet mass using potent islet growth factors
  - Hepatocyte growth factor
  - Islet neogenesis-associated peptide (INGAP)
  - Epidermal growth factor and gastrin
- depletion of dendritic cells
- high oxygen exposure
- UV irradiation

Tolerance induction

- Myelodepletion, Immunomodulation with regulatory T cells
- Immune Protection of the islets
  - immunoprevileged sites
  - Encapsulation of the islets
- Costimulation blockade
  - CTLA4 Ig, anti-CD40L, Inducible co-stimulator (ICOS)

Further experimental strategies to facilitate better engraftment

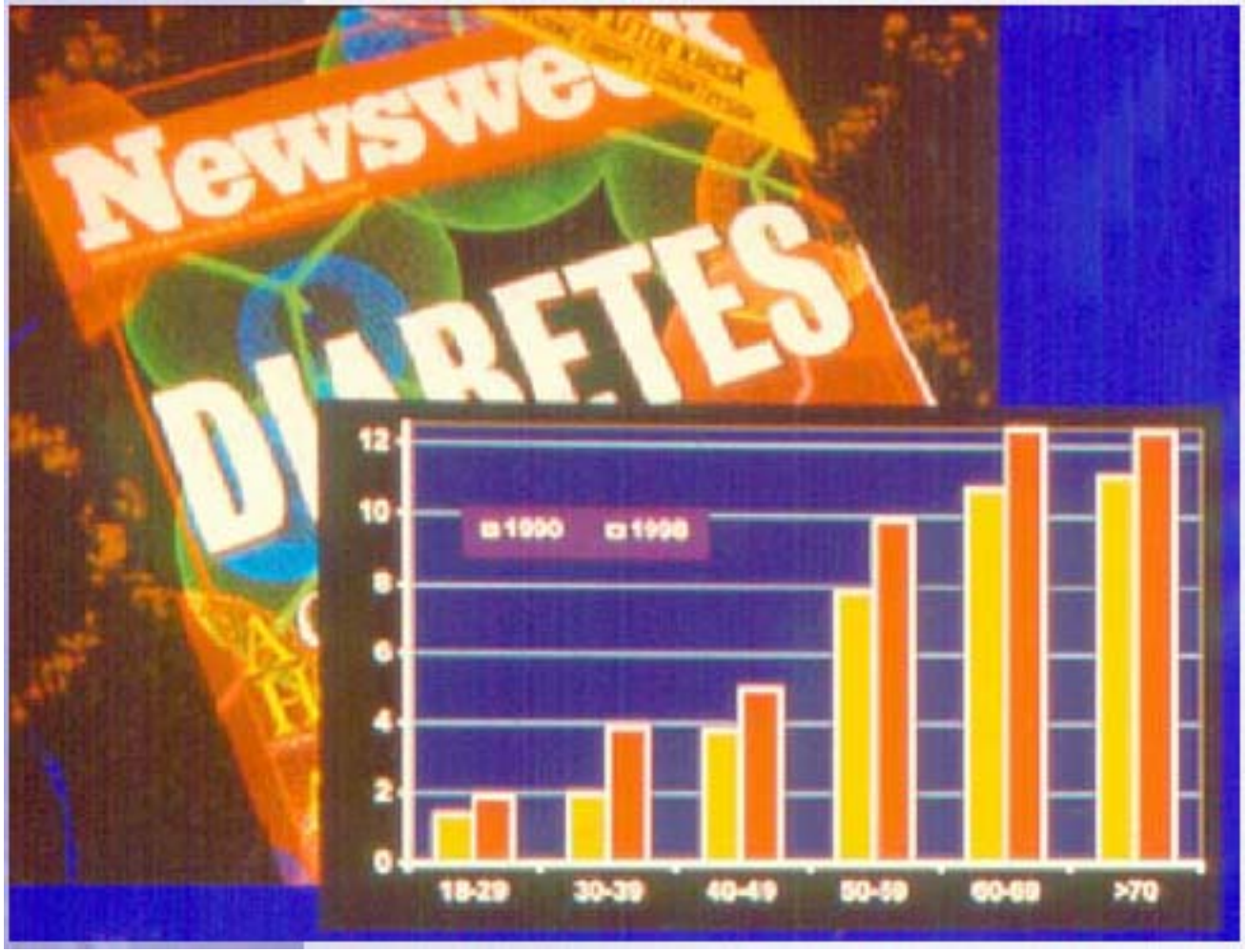
- gene therapy -vascular endothelial growth factor to promote islet neovascularization
- anti-macrophage therapy
- anti-inflammatory therapy (anti-TNFa)
- anti-oxidant therapy
  - nicotinamide, Vit D3
  - statins

Alternative islet sources

- Genetic engineering
  - hepatocytes to secrete single chain insulin analog
  - intestinal mucosal K cells to secrete insulin
  - NeuroD-betacellulin
  - c-kit
- transplantation of embryonic stem cells
- Xenotransplantation

Ultimate goal:

- Evasion of immune destruction
- unlimited source of beta cells
  - survival/replication of exixting beta cells
  - pancreatic stem cells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