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

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ABSTRACT

Background Registry data on patients with type 1 diabetes mellitus who undergo pancreatic islet trans-

ISLET transplantation has been investigated as a treatment for type 1 diabetes mellitus in selected patients with inadequate glucose control

diabetes

Five-Year Follow-Up After Clinical Islet Transplantation

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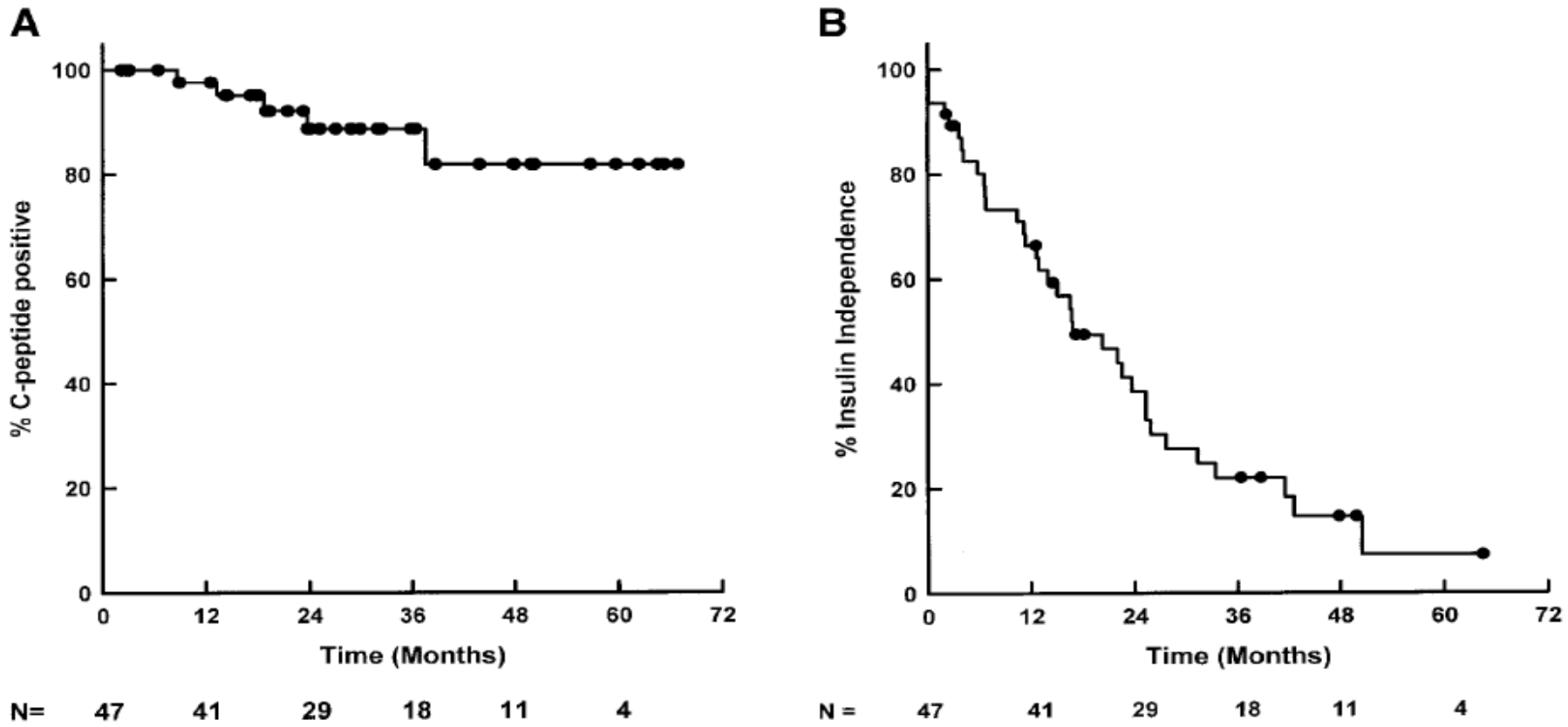

Ryan EA *Diabetes* 54:2060-2069, 2005

The Islet Transplant Experiment: Time for a Reassessment

J. S. Bromberg, B. Kaplan, P. F. Halloran and R. P. Robertson

American Journal of Transplantation 2007; 7: 2217–2218
Blackwell Munksgaard

Publication of the initial results of the Edmonton protocol in 2000 (1) raised hopes that many of the technical and immunologic hurdles of islet transplantation had finally been solved and that a new era for the treatment and cure of type 1 diabetes had arrived. Unfortunately, while shortterm results utilizing this specific protocol were repeatedby other groups around the globe, long-term follow-up revealed that islet transplantation with this particular protocol is far less successful than originally hoped (2,3). Thus, although 5 years after transplantation 85% of recipients had measurable plasma C-peptide, well-controlled HbA1c levels, significant diminution in amount of daily insulin required, and virtually no clinical hypoglycemia (3), only 10% of patients experienced freedom from exogenous insulin use. While this still may represent partial success in alleviating the debilitating symptoms that brought them to islet transplant in the first place, such a claim needs to ultimately be established in a controlled trial, like other medical advances. Moreover, toxicities from the calcineurin inhibitors combined with sirolimus used for immunosuppression produced worrisome trends in renal function (4). Given continued insulin dependence, the shortage of donor organs, the complications of immunosuppression, and the great expense of this procedure, sober reassessment of the clinical applicability of this protocol and particular experiment is needed.

Decay in Islet Function

- Rejection?
- Autoimmunity?
- Drug toxicity?
- No precursor cells?

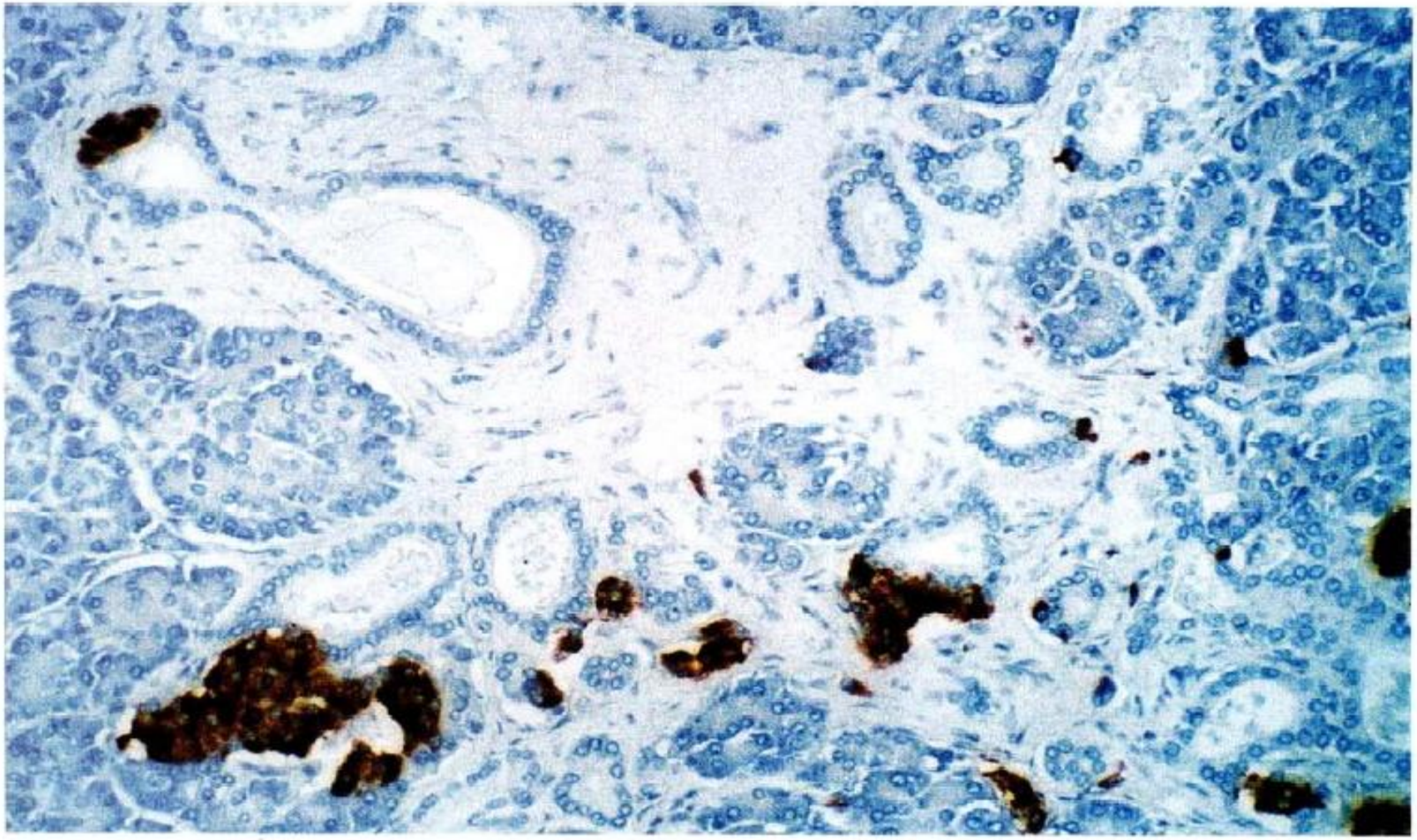

FIG. 5. Section of pancreas (×20 magnification) stained for insulin. Numerous pancreatic ducts are shown, with insulin-positive cells present in the duct walls demonstrating new islet formation from exocrine ducts.

PRELIMINARY COMMUNICATION

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Single-Donor, Marginal-Dose Islet Transplantation in Patients With Type 1 Diabetes

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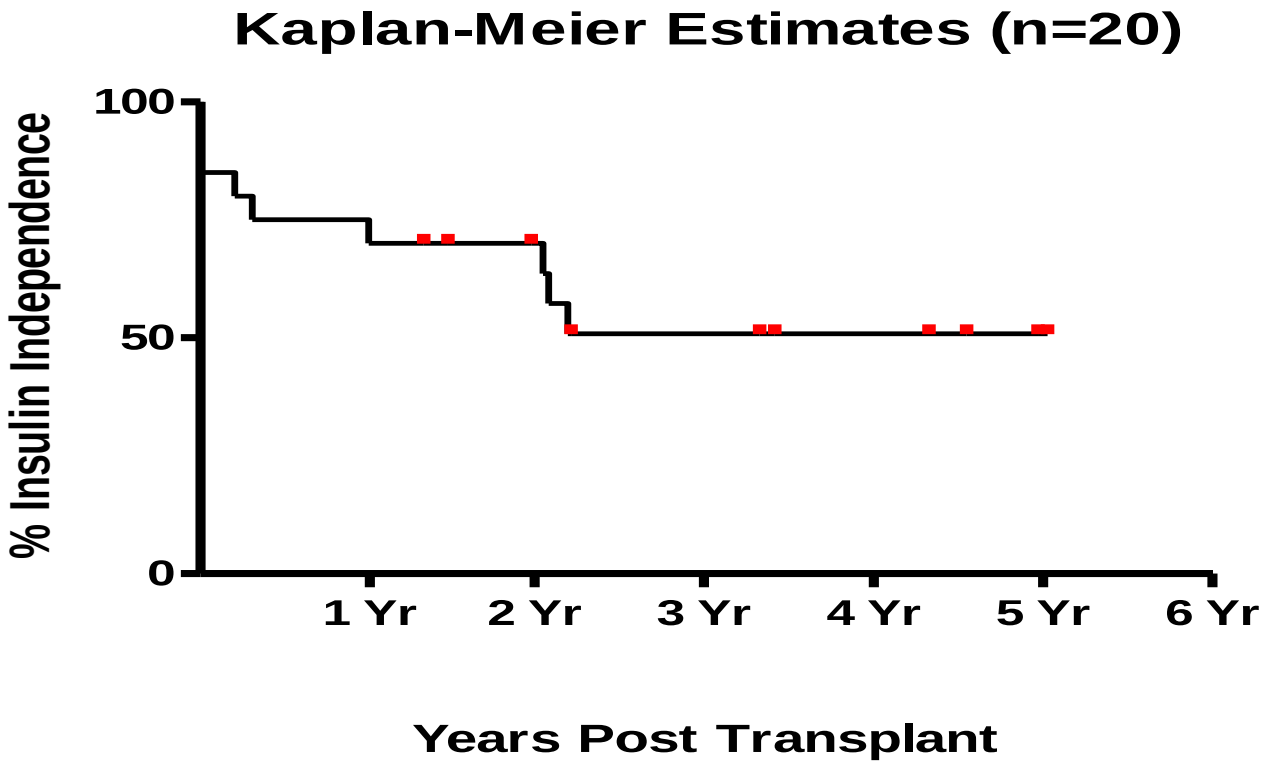
Context Islet allografts from 2 to 4 donors can reverse type 1 diabetes. However, for islet transplants to become a widespread clinical reality, diabetes reversal must be achieved with a single donor to reduce risks and costs and increase the availability of transplantation.

Objective To assess the safety of a single-donor, marginal-dose islet transplant protocol using potent induction immunotherapy and less diabetogenic maintenance immunosuppression in recipients with type 1 diabetes. A secondary objective was to assess the proportion of islet transplant recipients who achieve insulin independence in the first year after single-donor islet transplantation.

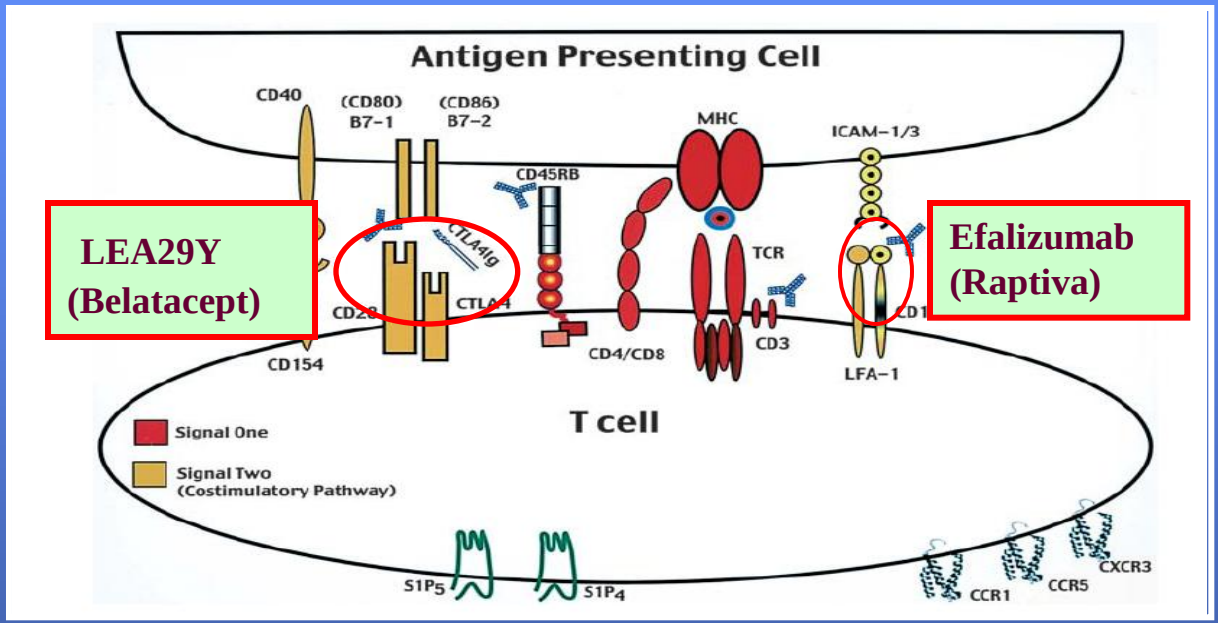
Design, Setting, and Participants Prospective, 1-year follow-up trial conducted July 2001 to August 2003 at a single US center and enrolling 8 women with type 1 diabetes accompanied by recurrent hypoglycemia unawareness or advanced secondary complications.

Interventions Study participants underwent a primary islet allotransplant with 7271 (SD, 1035) islet equivalents/kg prepared from a single cadaver donor pancreas. Induction immunosuppression was with antithymocyte globulin, daclizumab, and etaner-

Insulin Independent Graft Survival Rate
All Subjects



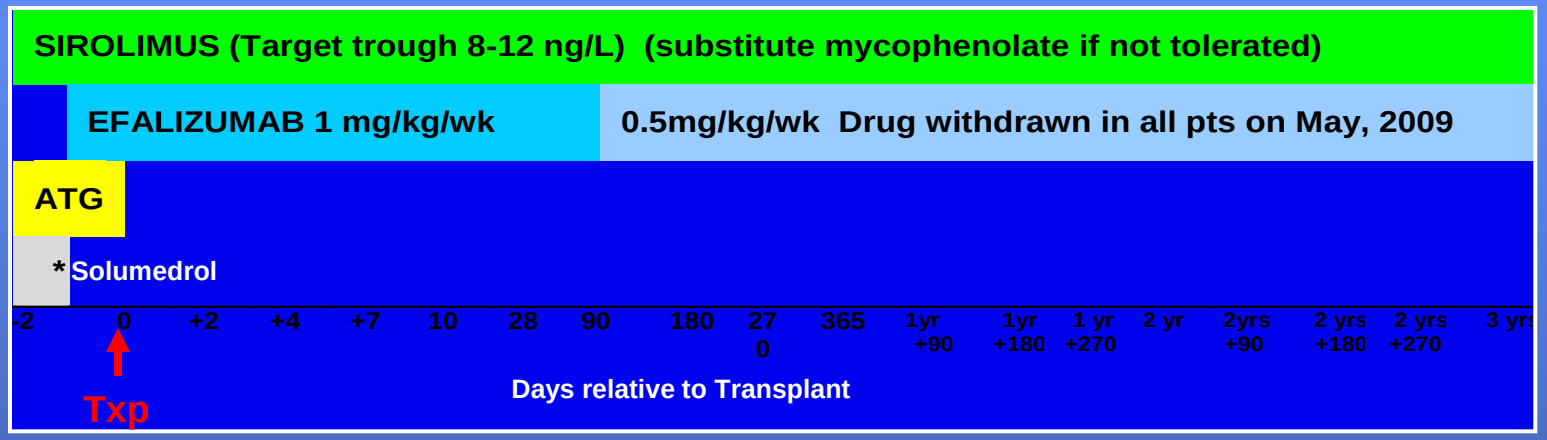
Costimulation/Adhesion Blockade



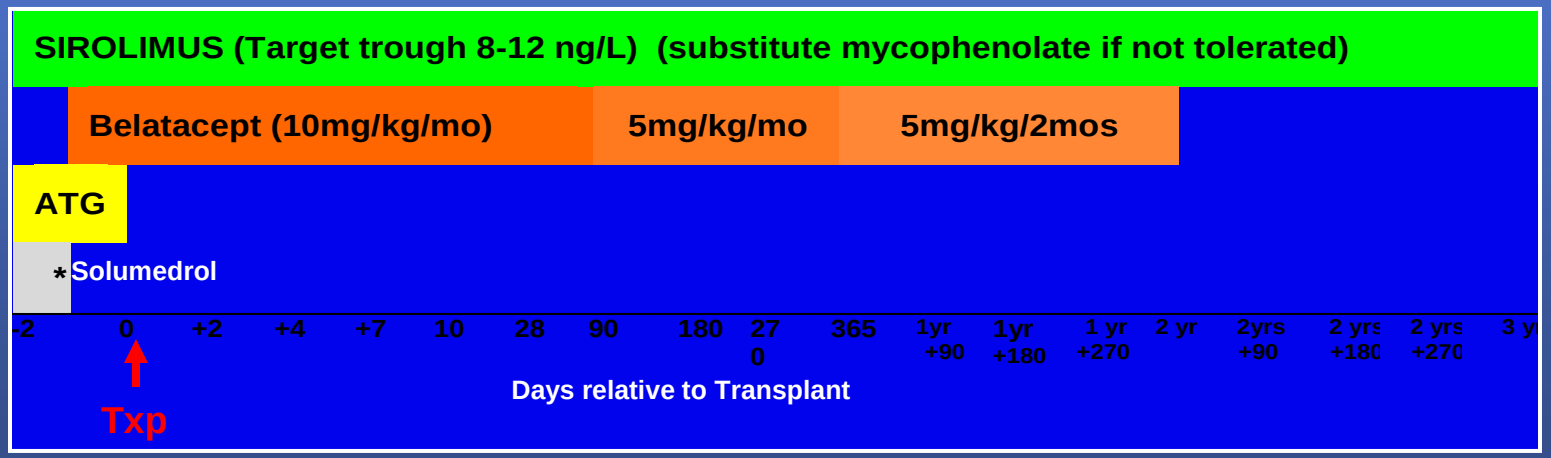
- Used successfully in kidney (both) and liver transplantation (belatacept)
- Allow reduction of CNI's w/o increased rejection

Adverse Effects
- Both increase risk of PTLD if used at high doses
- Both increase risk of PML (fatal)
- Raptiva taken off market 5/09 (4 cases PML/40,000pts)

Immunosuppressive Protocols

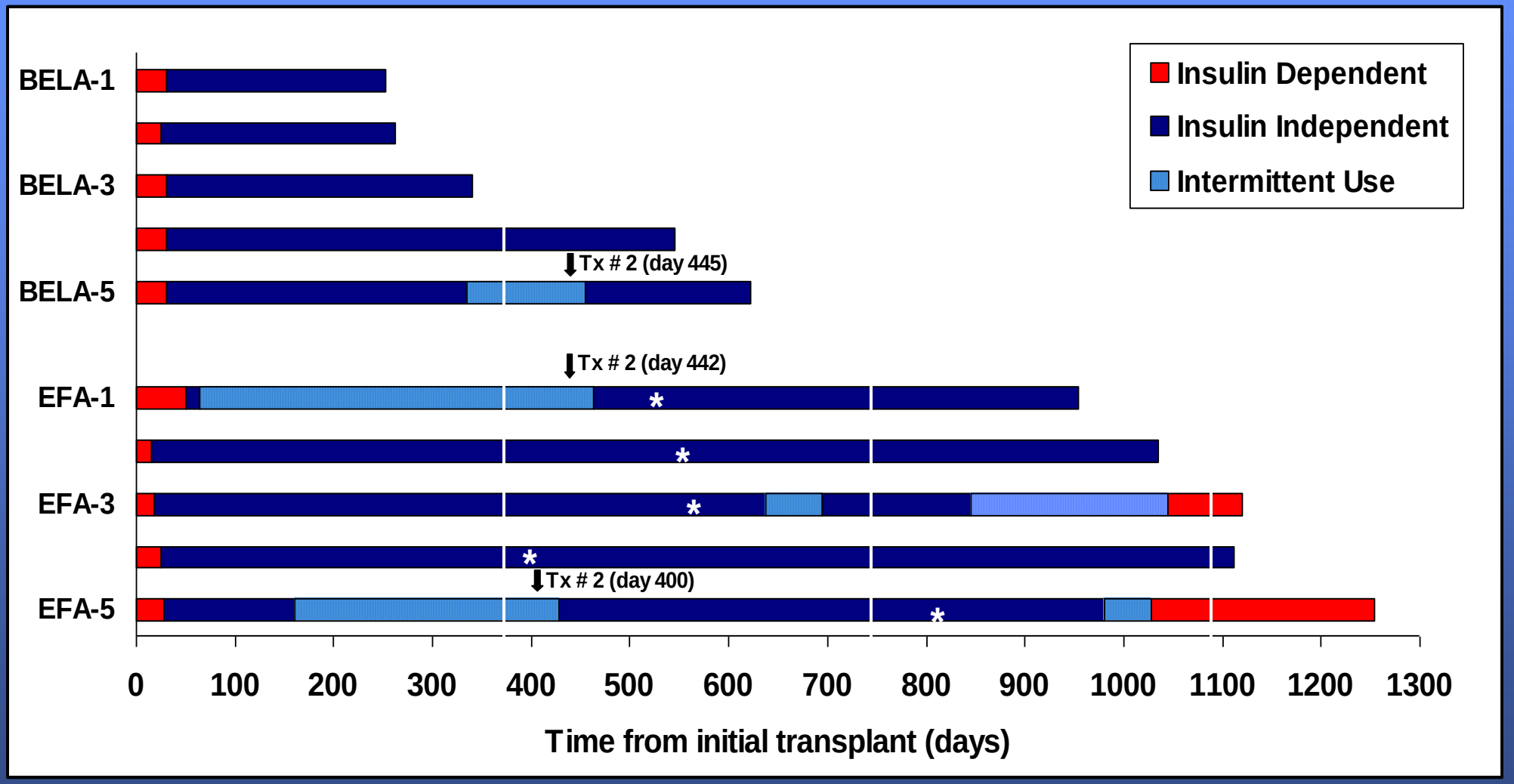


Efalizumab



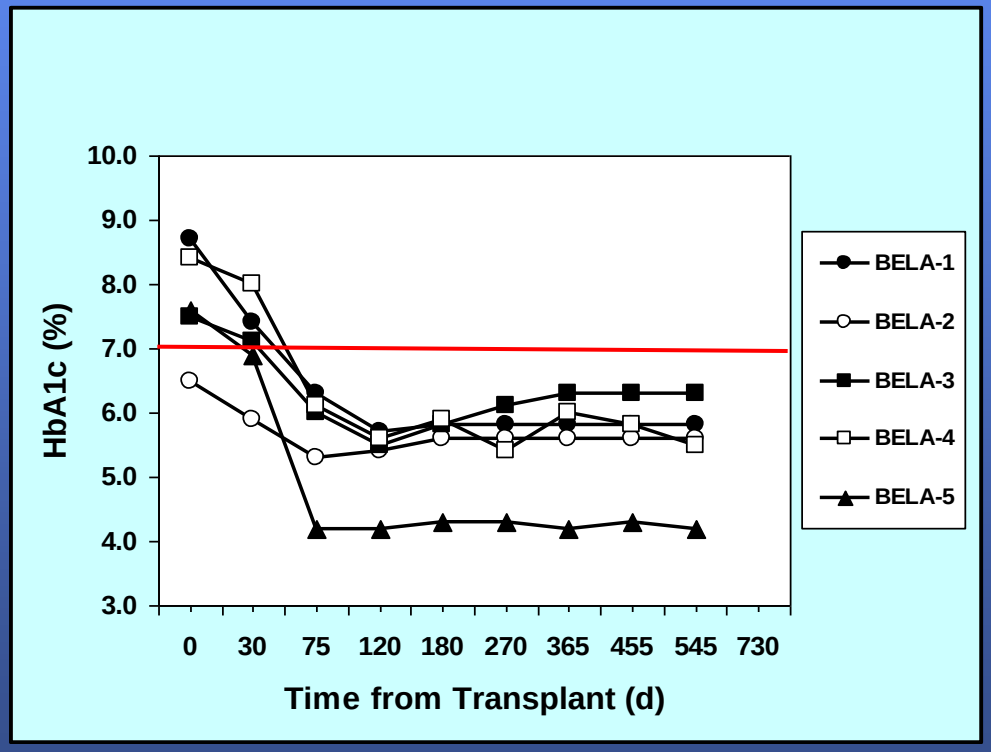
Belatacept

Graft Function



HbA1c Levels after Islet Transplantation

Belatacept



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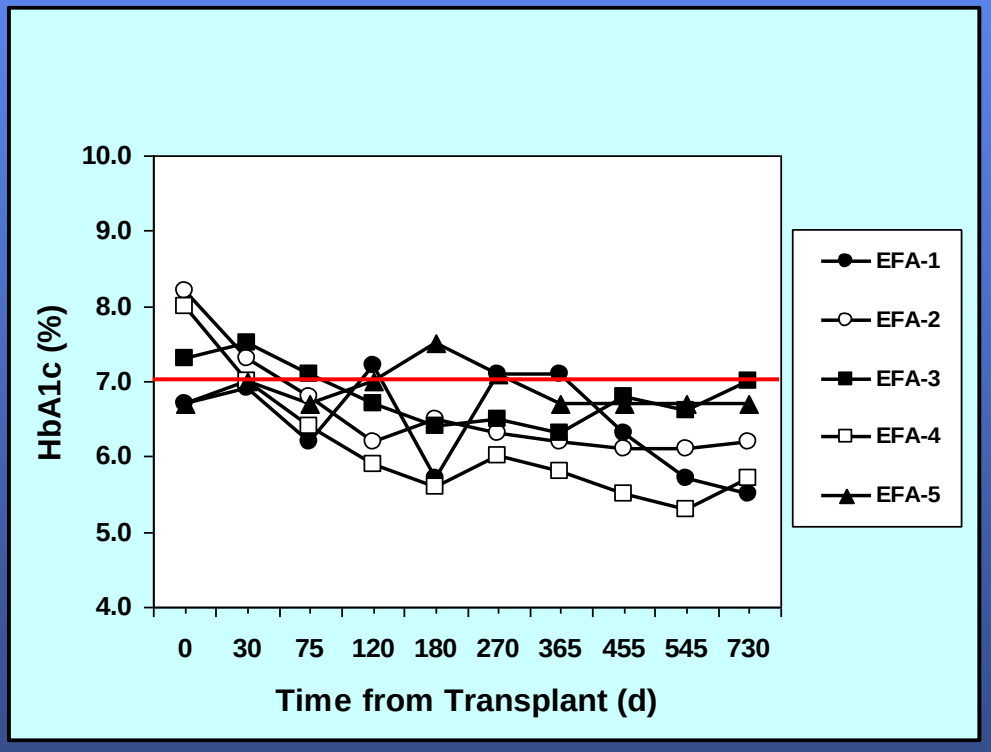
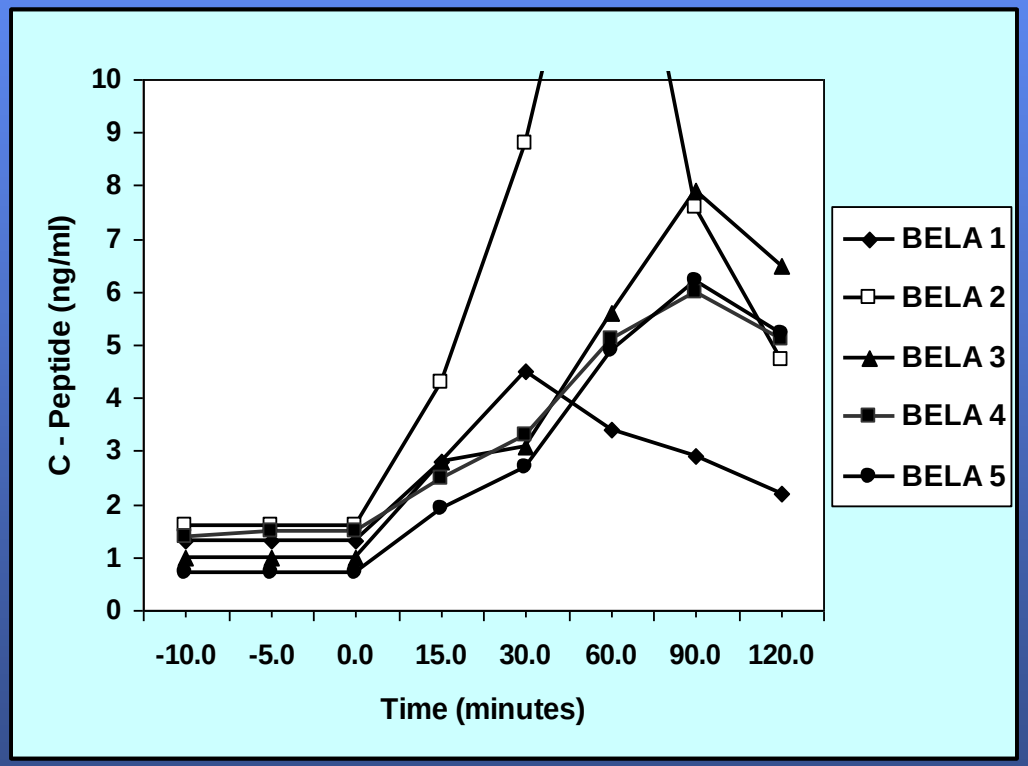


C-peptide Responses to a Mixed Meal Tolerance Test



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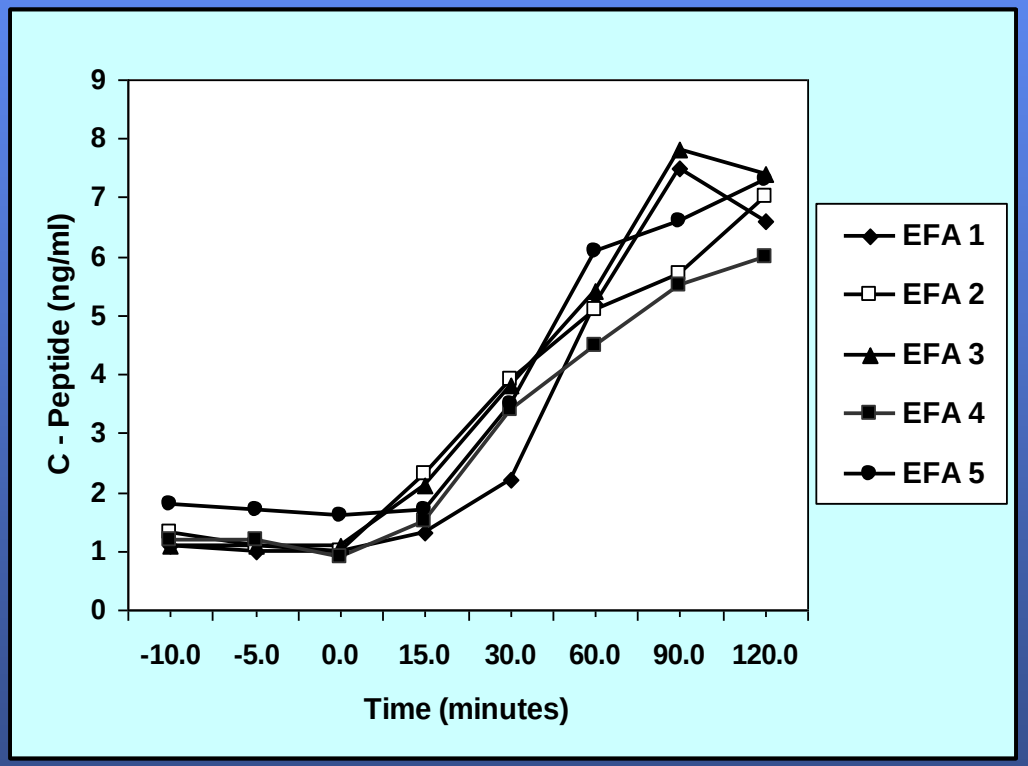
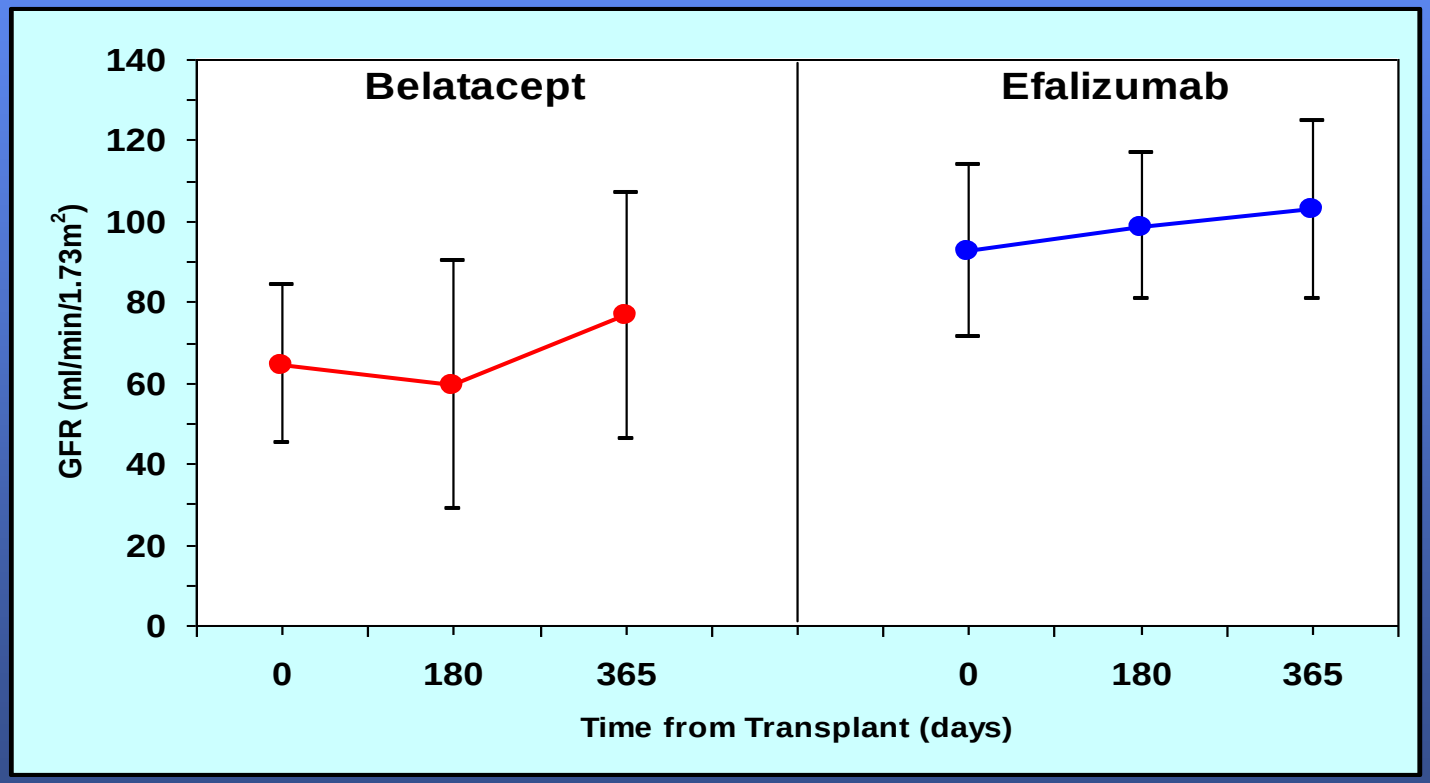


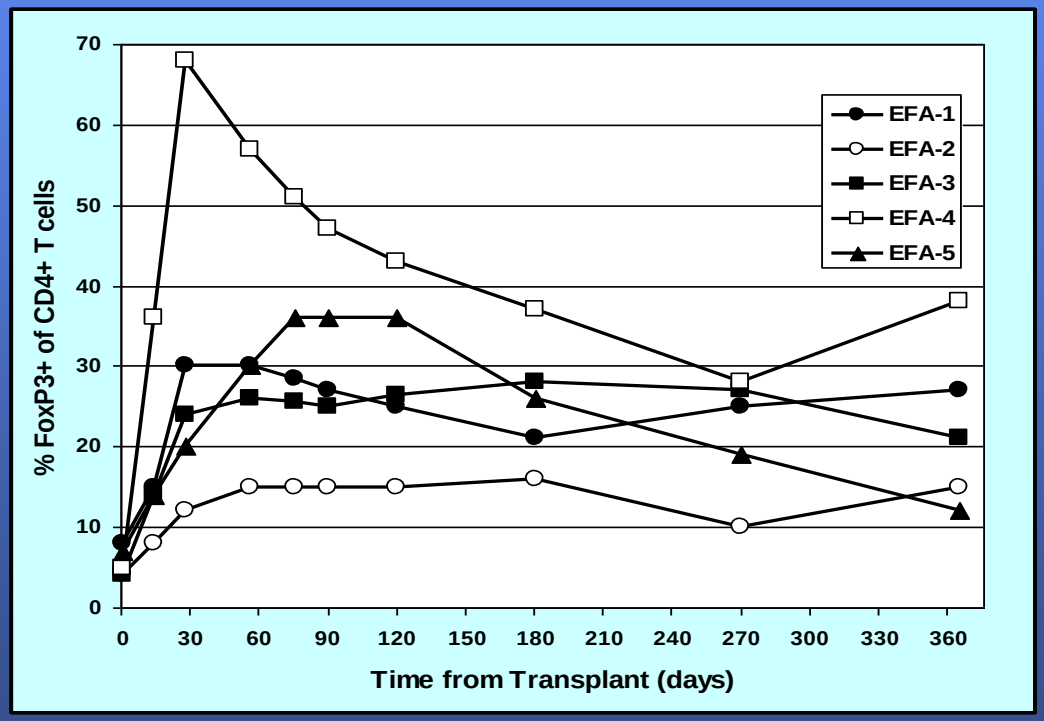
Efalizumab

Glomerular Filtration Rates after Islet Transplantation



T Reg Kinetics in Islet Recipients

Efalizumab



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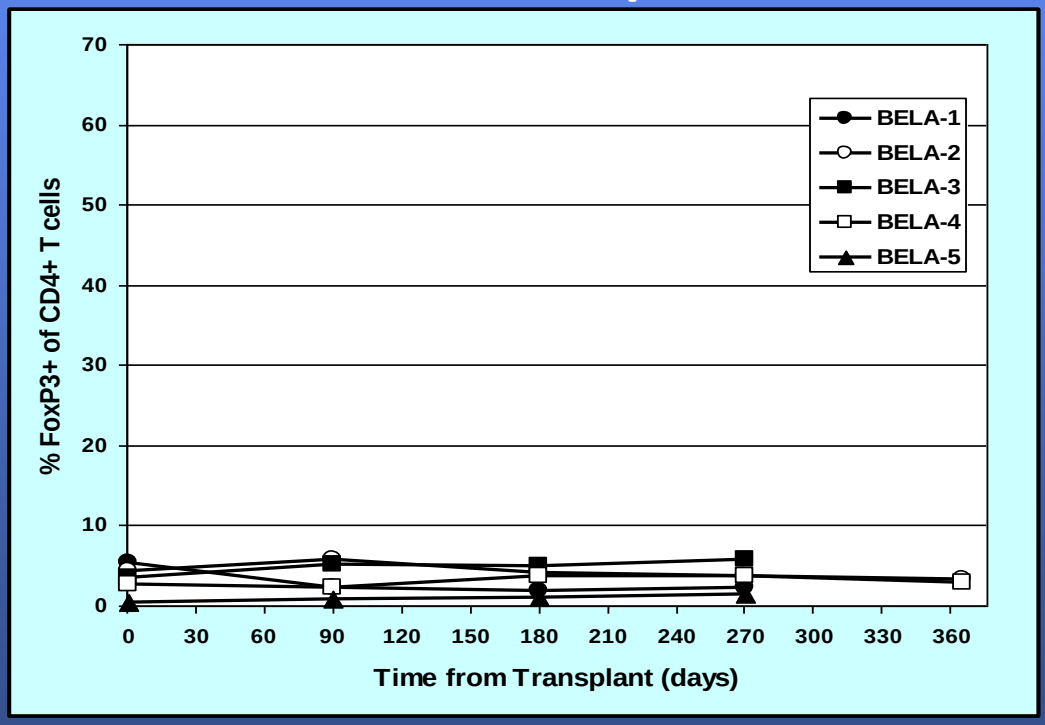
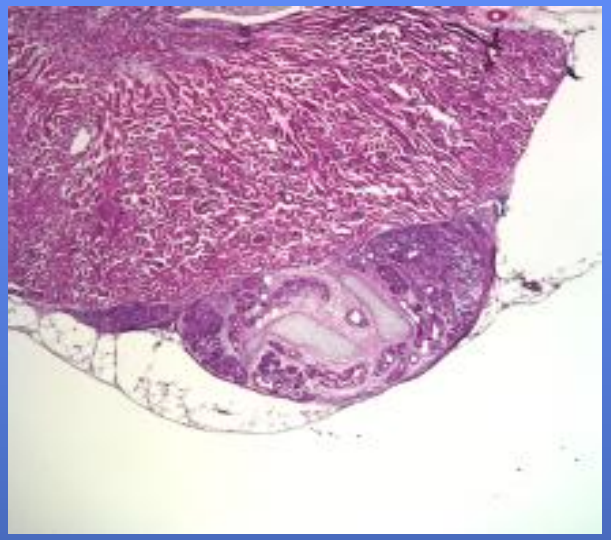
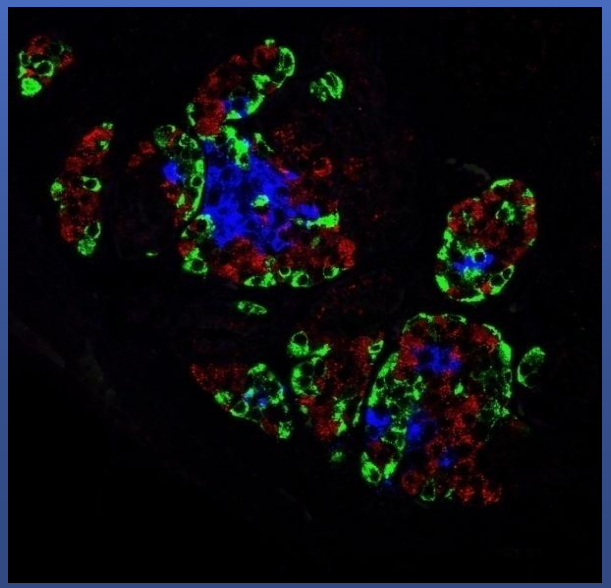


Day 109 Post Transplant: Pro-Islets Functional Endocrine Staining

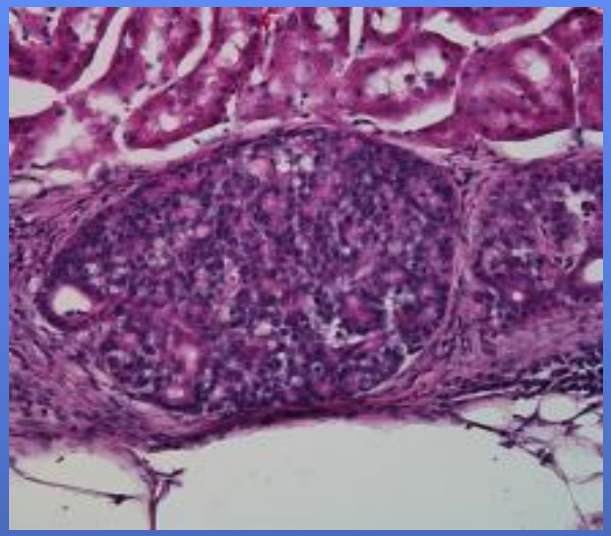
Glucagon, Somatostatin, Insulin

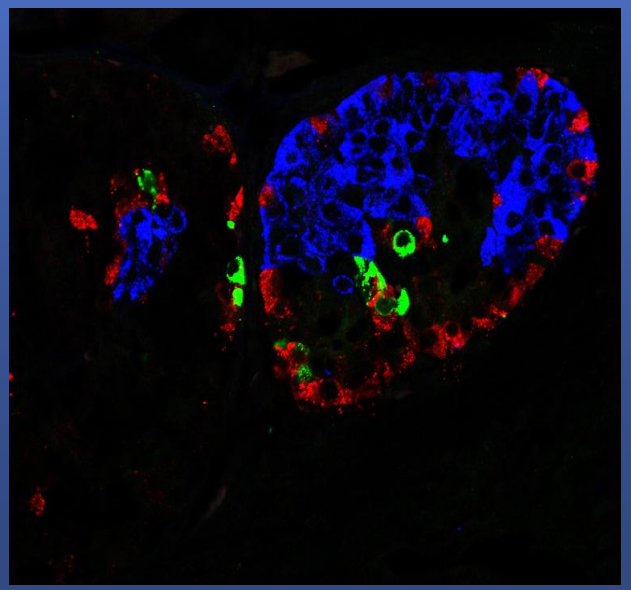
#5464 CTLA4Ig+MR1





#5466 CTLA4Ig+MR1





Summary – Effective immunosuppression for adult alloislet transplantation and Pro-Islet transplantation

1. Aggressive immunosuppression necessary to achieve success with adult islet allotransplantation.
2. Long term insulin independence achieved with non-nephrotoxic regimens following adult islet allotransplantation using co-stimulation blockade.
3. Pro-Islets function in immunocompetent mice when transplanted beneath kidney capsule when using similar immunosuppressive regimens (co-stimulation blockade).
4. Will similar immunosuppression be necessary and/or effective with immunoisolation device?

Pro-Islets and Viacyte Immune Isolation Device Observations (E Kroon)

1. Pro-Islets are immunogenic.

2.Immune Response to Pro-Islets can be controlled with conventional Immunosuppression.

3.Pro-Islets function in ViaCyte Immune Isolation Device (Immunodeficient mice).

4.Pro-Islets do not function in ViaCyte Immune Isolation Device (immunocompetent mice).