

Enhancing Islet Engraftment and Function Using Microporous Scaffolds

William L. Lowe, Jr.

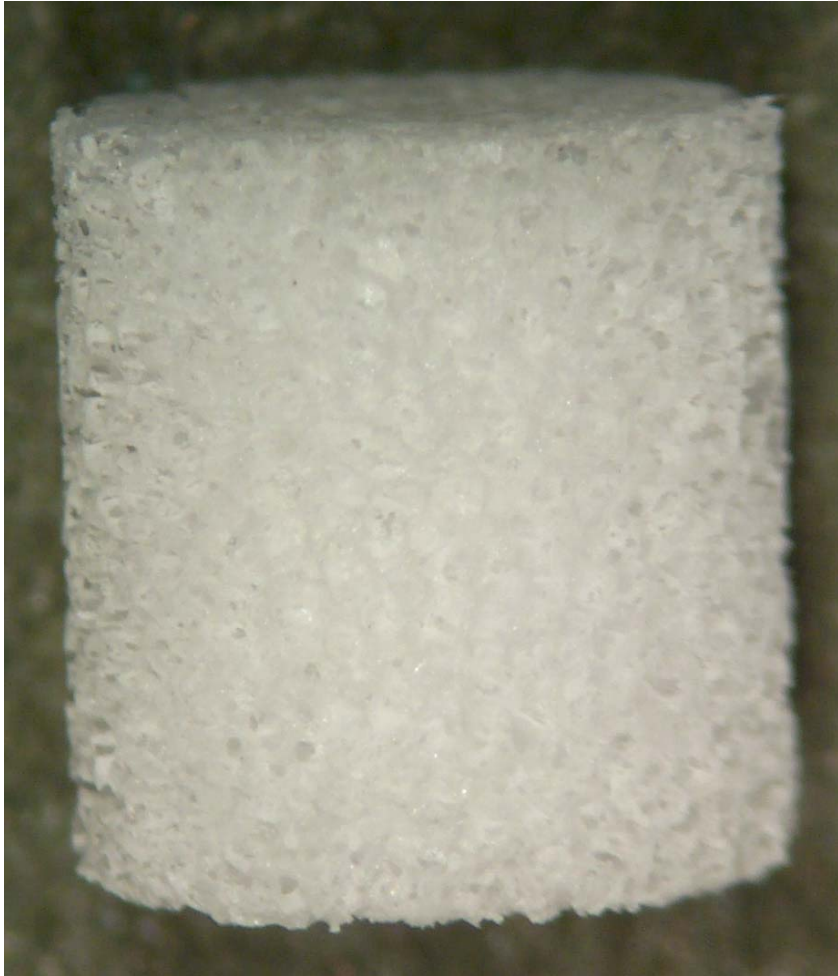
Lonnie Shea

Dixon Kaufman

Goals

- To accelerate progress in cell replacement therapy for diabetes by:
 - Developing an extrahepatic site for cell replacement therapy for diabetes
 - Creating a microenvironment that will optimize survival and function of transplanted islets or cells

Tissue Engineering Approach



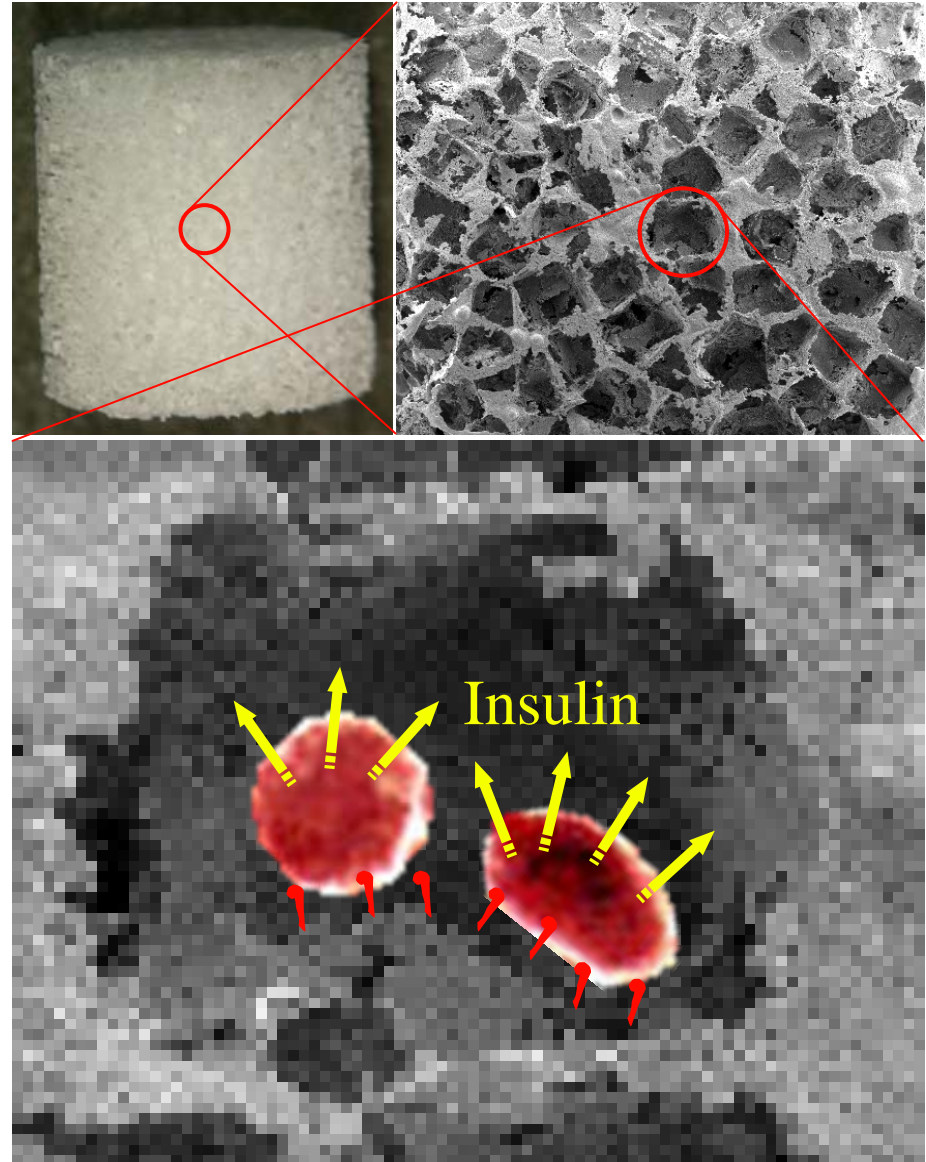
Microporous PLG Scaffold

Advantages

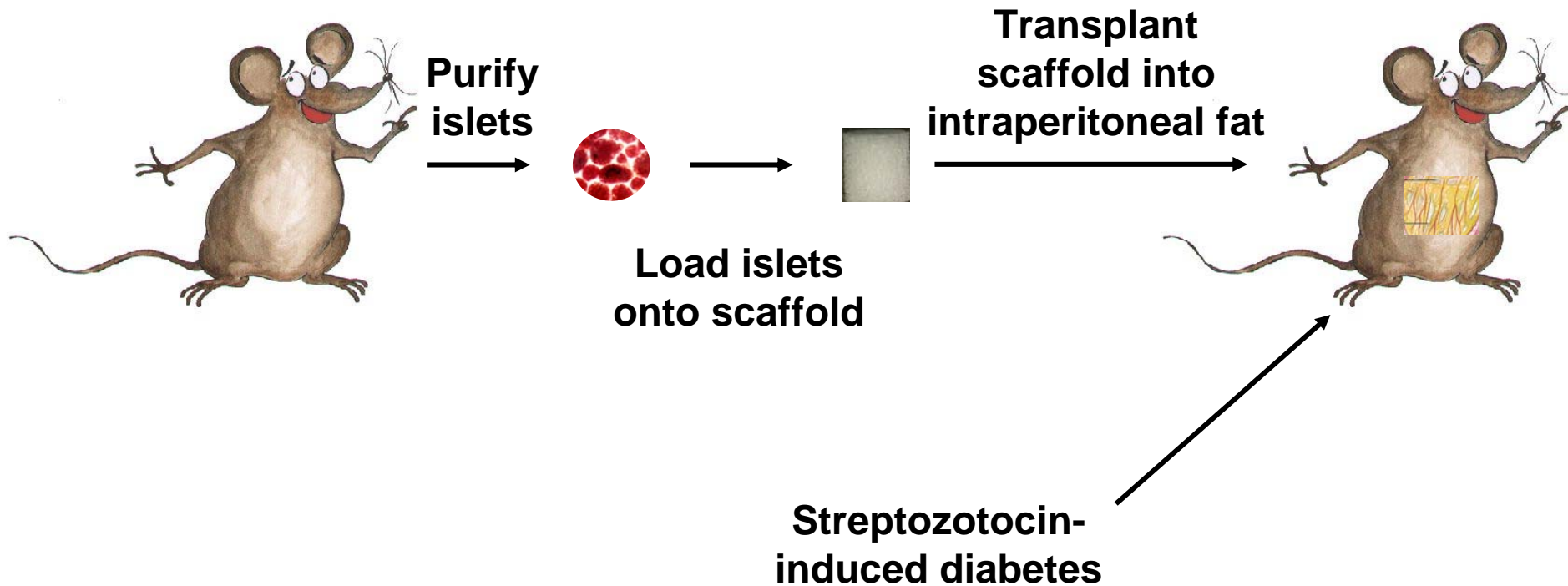
- High porosity
 - Promotes nutrient & waste transport
- Biodegradable/Biocompatible
 - Degrades harmlessly over time
- High surface area / volume
 - Protein adsorption to promote cell attachment
- Sufficient mechanical rigidity
 - Maintains space for tissue formation
- Interconnected pore structure
 - Allows for cell & vessel infiltration for host integration
- Delivery vehicle
 - Controlled release of proteins or DNA

Islet Transplantation on Microporous Scaffolds

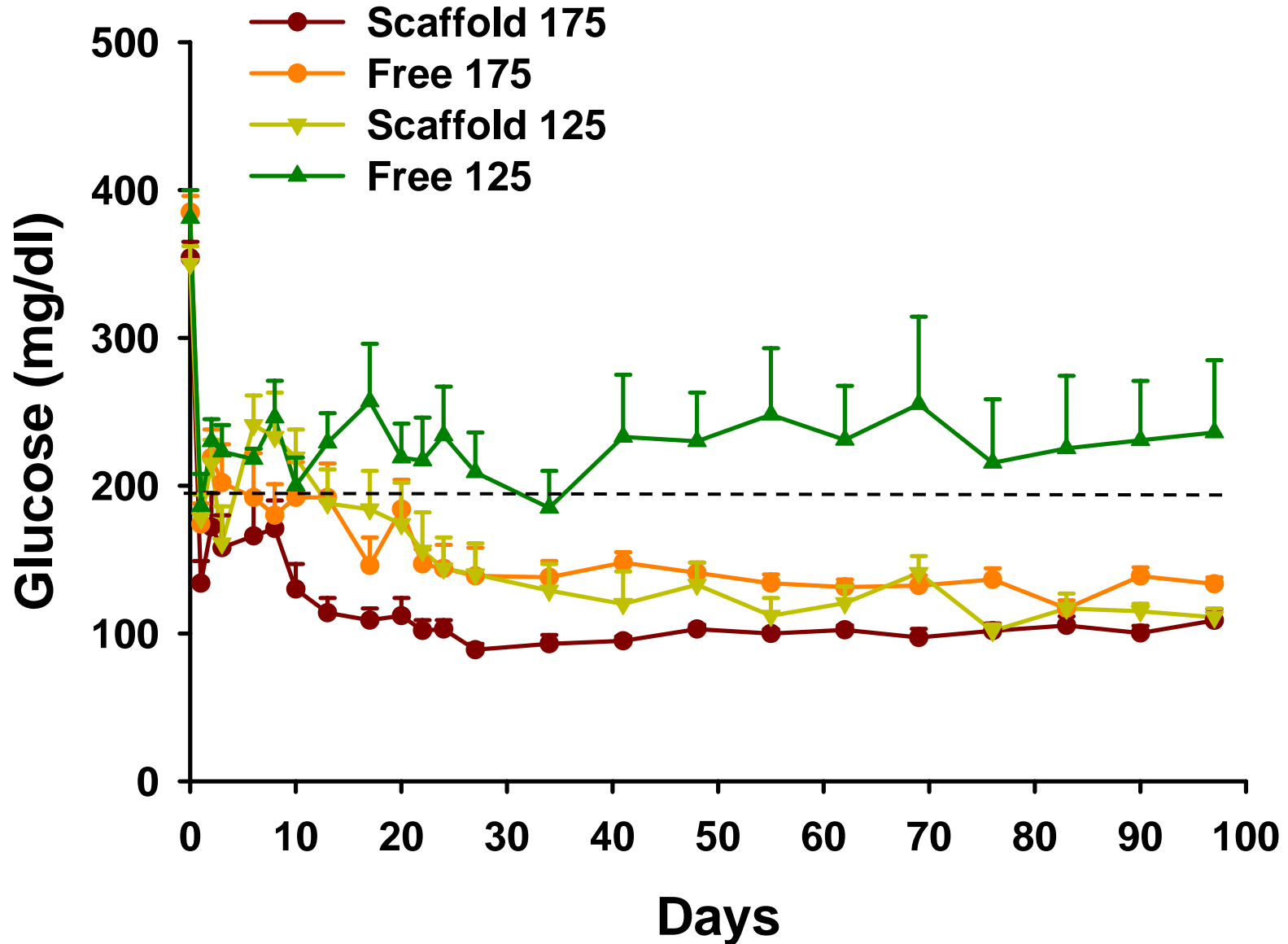
- Islet engraftment may be improved by using the scaffold as a platform for islet transplantation to sites outside the liver



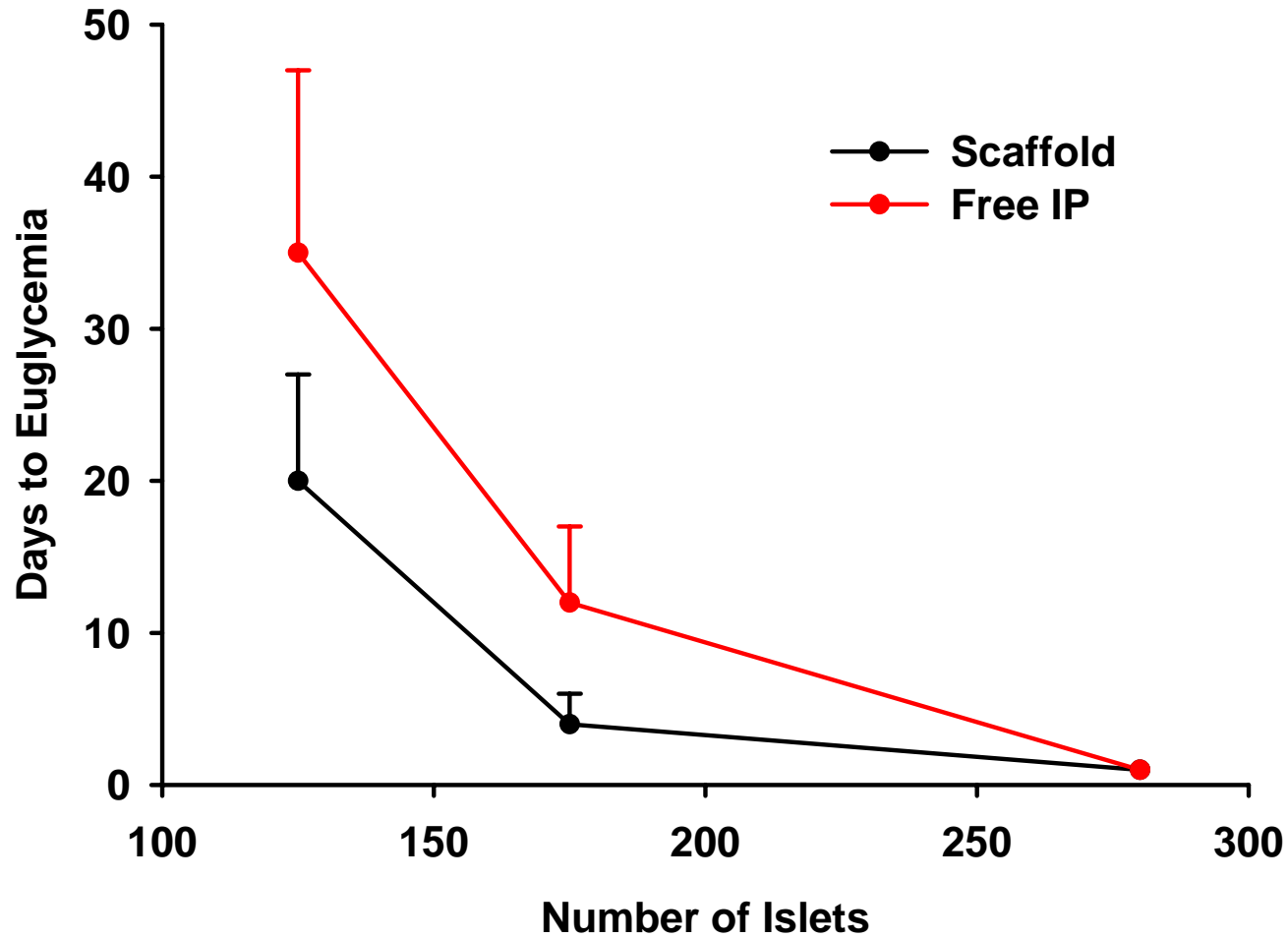
Mouse Model of Islet Transplantation



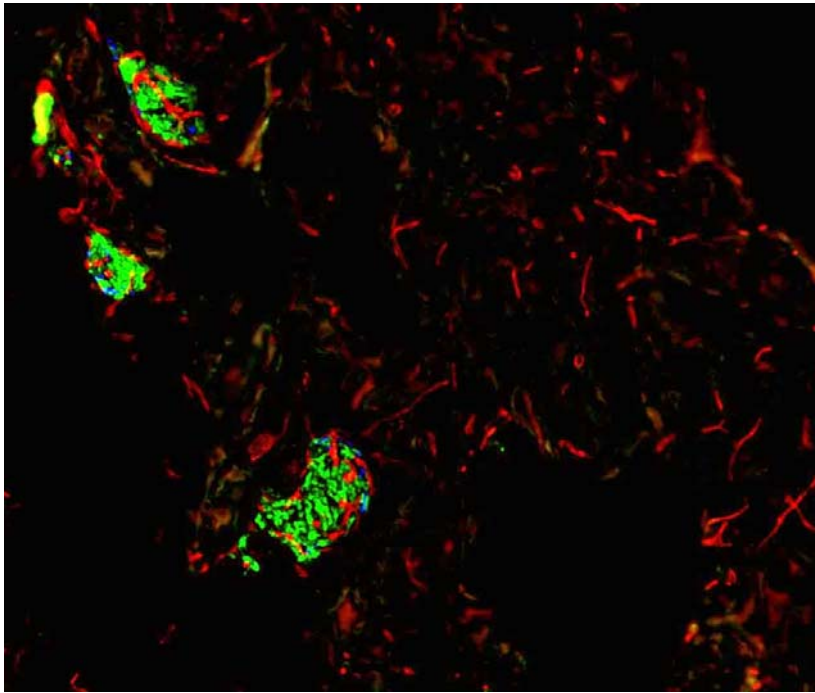
Comparison of Blood Glucose Levels Following Transplantation of Islets Seeded on Scaffolds or Free into the Omentum



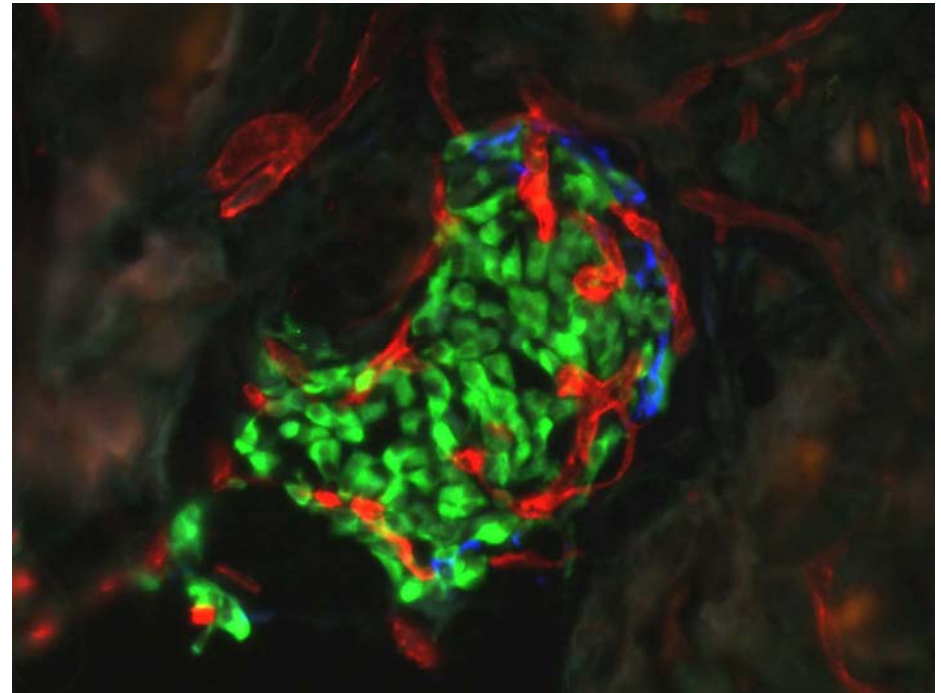
Mean Days to Euglycemia Following Islet Transplantation



Confocal Imaging of Transplanted Islets



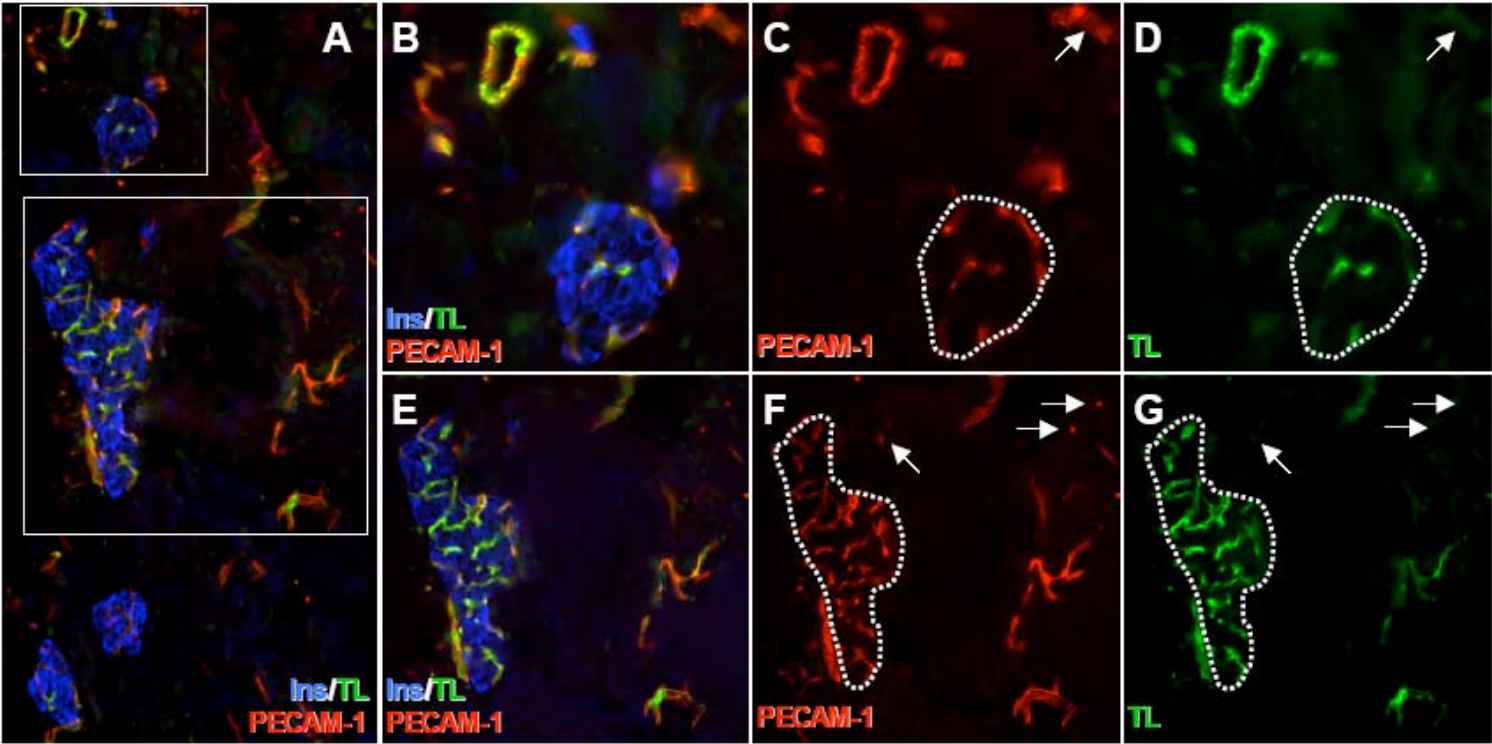
10x



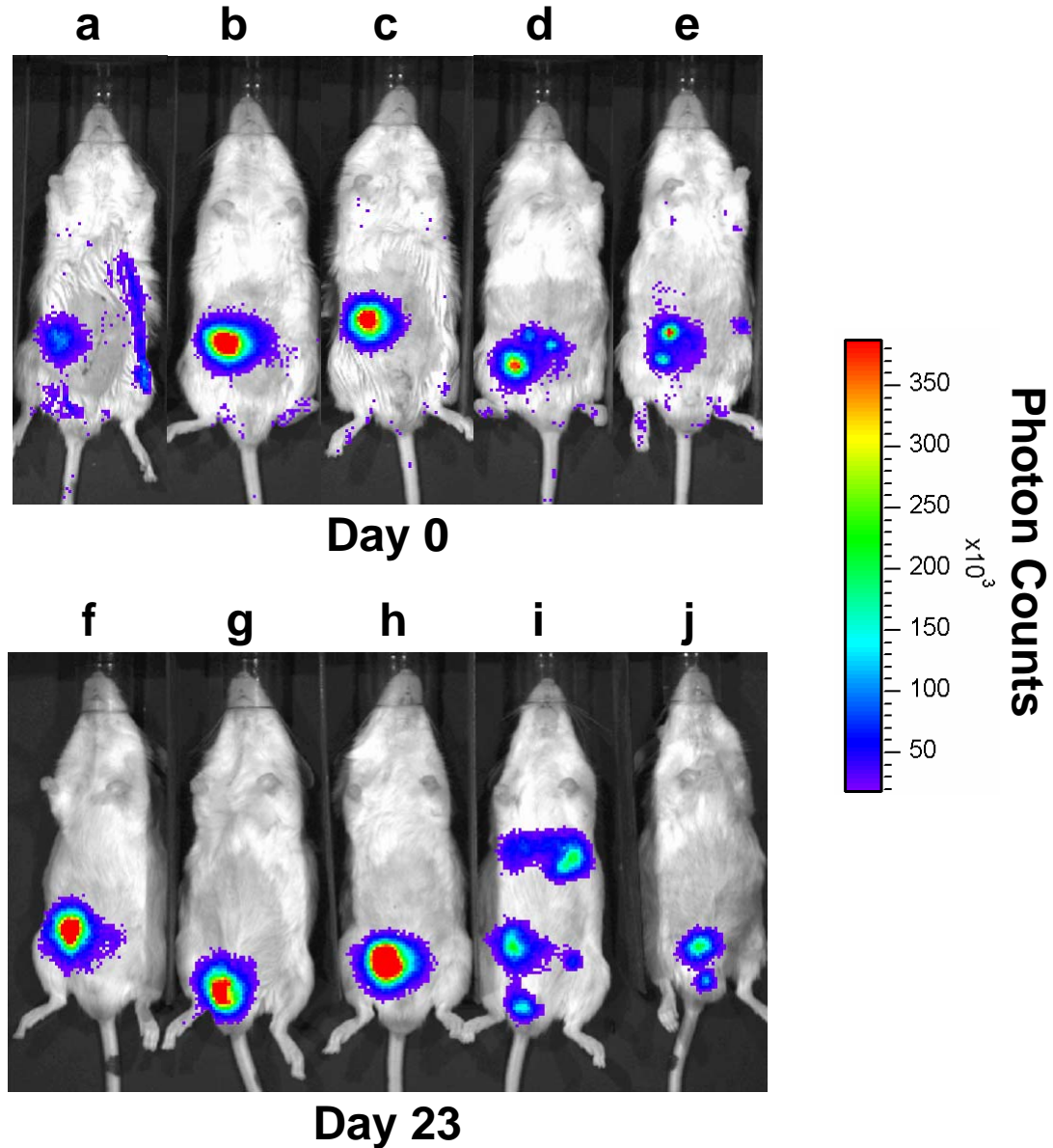
40x

Insulin
Somatostatin
VEGF receptor-2

Functional Vasculature in Transplanted Islets

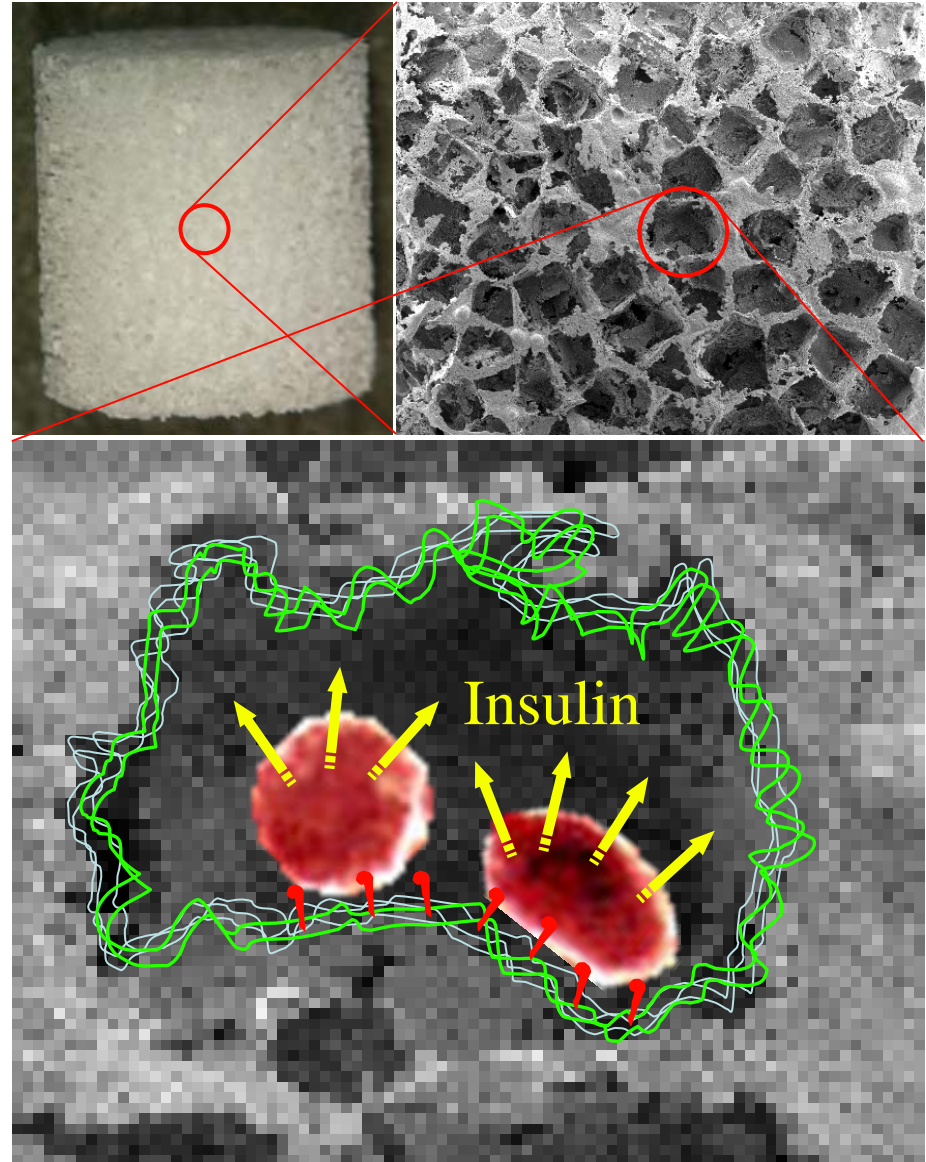


Bioluminescence Imaging of Islets Transplanted on a Microporous Scaffold

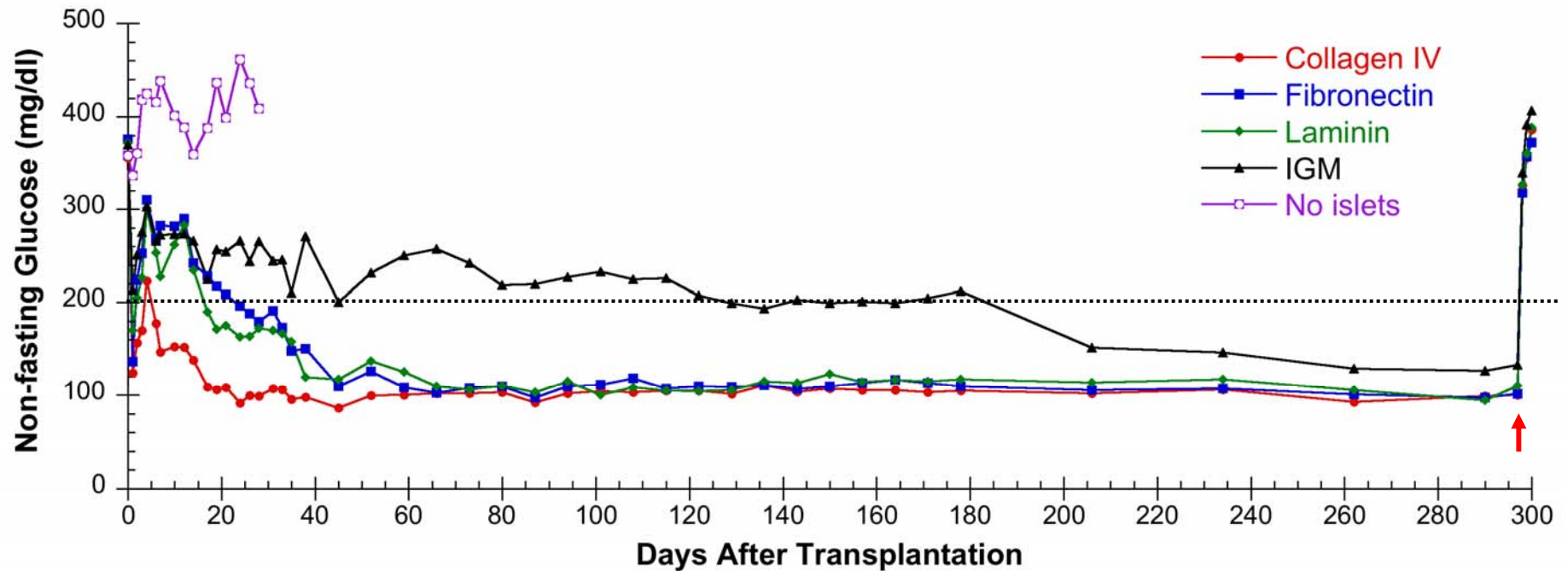


Application of ECM to Scaffolds

- Islet engraftment may be improved by modifying the scaffold to contain components of ECM-creating a more natural “home” for the islets
- Tested the impact of coating the scaffold with collagen IV, laminin-5 or fibronectin

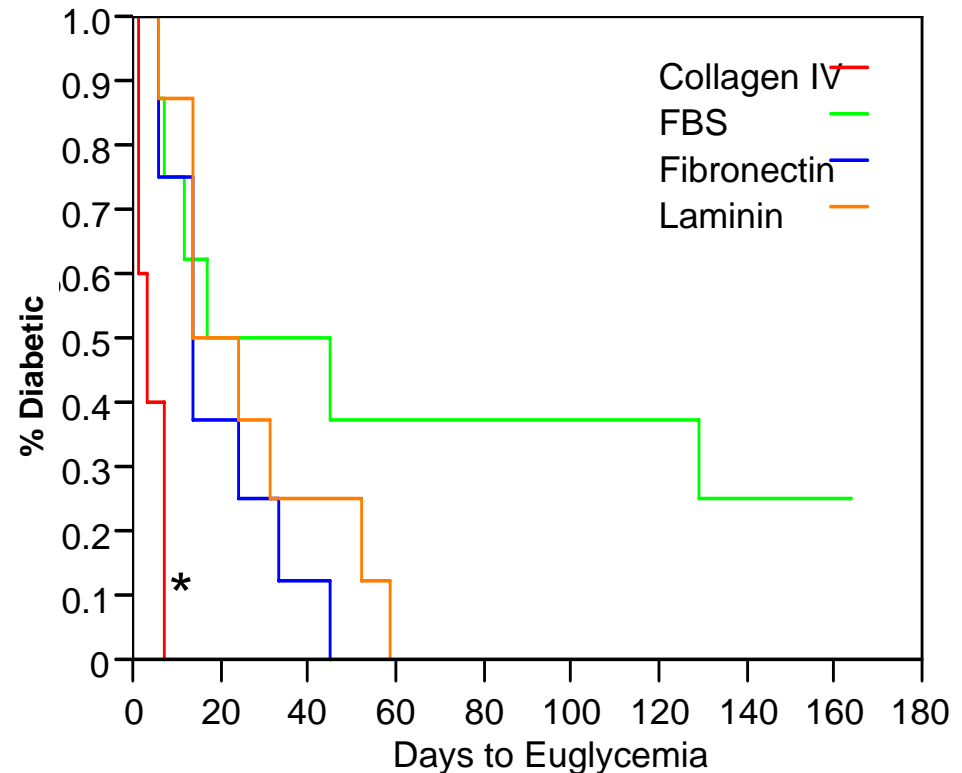


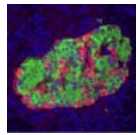
Impact of ECM Components on Islet Function



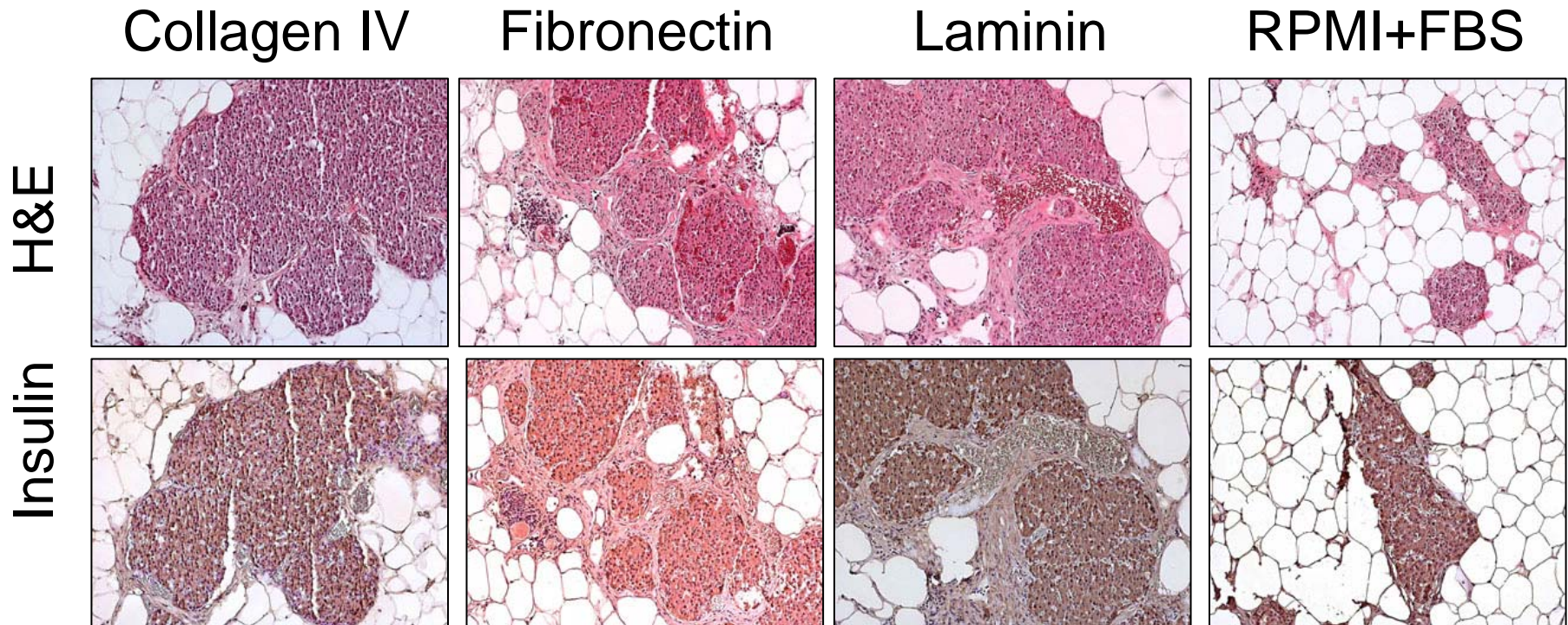
Impact of ECM Components on Islet Function

- Scaffolds pre-coated with collagen IV, laminin-5, fibronectin or FBS
- 125 islets transplanted into intra-peritoneal fat on the scaffold
- Number of mice that converted euglycemia was determined





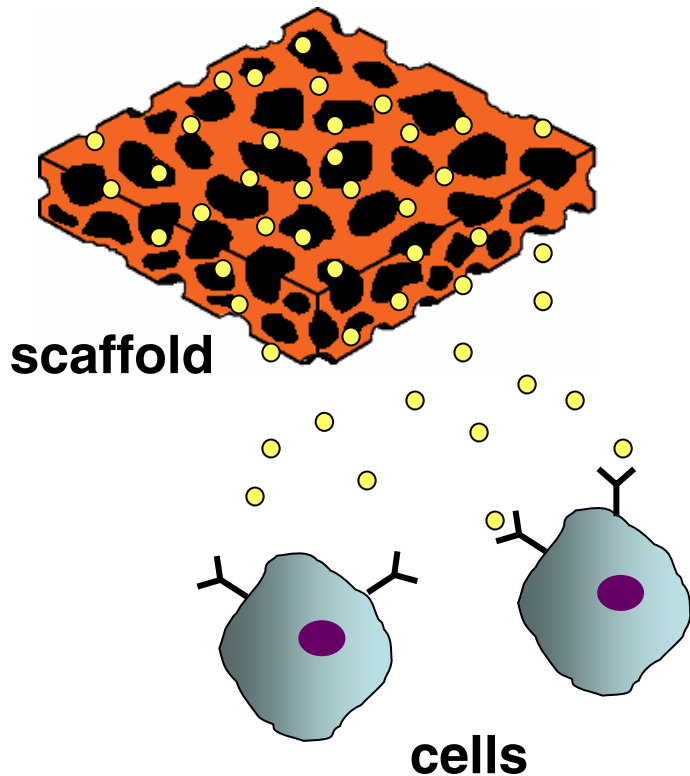
Graft Histology 300 Days Post-Transplant



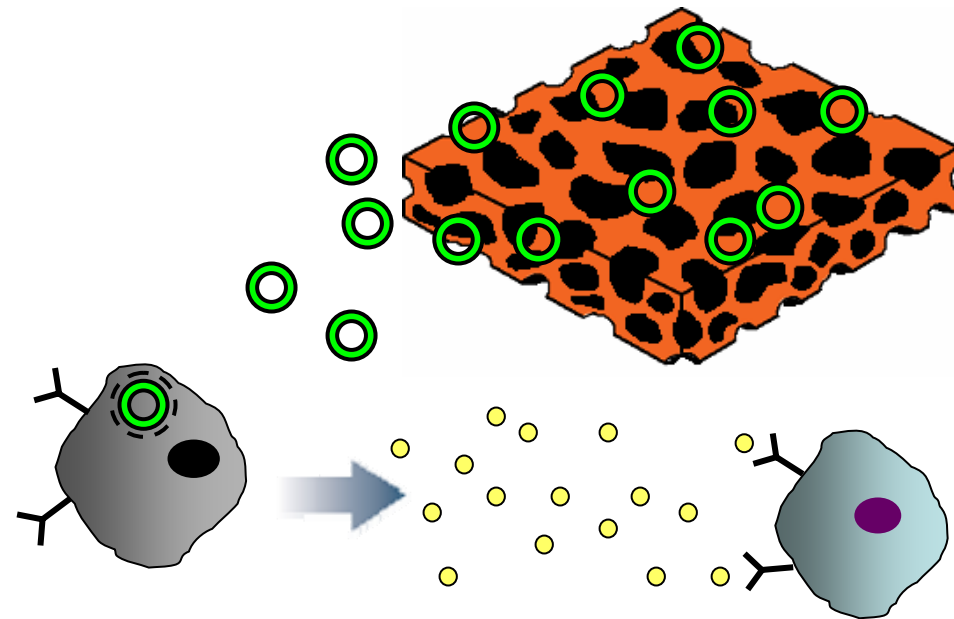
At 300 days post-implant, functional islet grafts were present with a suggestion of improved islet morphology following transplantation on ECM protein-coated scaffolds

Protein and DNA delivery from Scaffolds

Protein Delivery



DNA Delivery



Advantages of DNA Delivery

- Extended protein production
- Stability
- Versatility

Lowe Lab

Amy Aronovitz
Herman Blomeier
Fei Chen
Elizabeth Hughes
Jami Josefson
Marsha Newman

Kaufman Lab

Marshall Baker
Jan Chen
Herman Kissler
Courtney Larsen
Xiaomin Zhang

Shea Lab

Chris Rives
David Salvay
Rob Rayson

Vanderbilt University

Al Powers
Marcela Brissova

ECM of the Islet

- Composed of an islet capsule and basement membrane surrounding intra-islet capillaries
- Capsule contains laminin and collagen IV
- Intra-islet basement membrane consists of collagen IV, fibronectin, and laminin-8 and -10
- Islets express β 1-integrin subunit and several different α -integrin subunits

