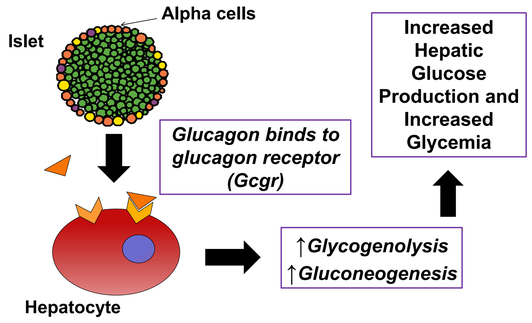
Human and Mouse Alpha Cells Proliferate in Response to Glucagon Receptor Blockade

E. Danielle Dean, PhD; Ana Robledo Reyes, MD; Derek Yee, BS; Kayla McLeod; Gerald Wakefield; Ian McGuinness, BS; Courtney Thompson, BS; Greg Poffenberger, MS; Chunhua Dai, MD; Alvin C. Powers, MD.

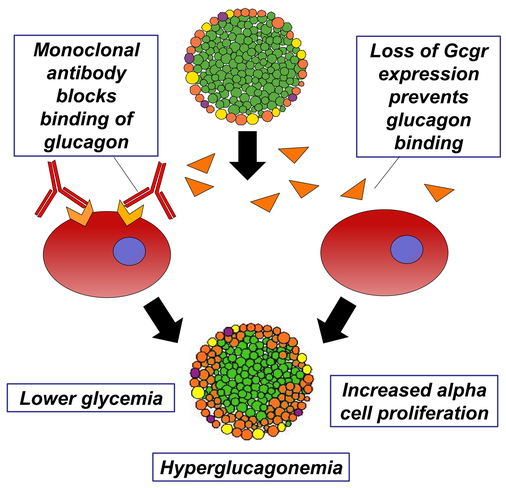
Introduction

Glucagon's role in glycemic control



- Gcgr antagonists are under development as a treatment for type 2 diabetes.
- Gcgrs are expressed in multiple tissues (liver, kidney, brain, adipose, heart, and pancreas).
- Multiple models of glucagon loss of function result in increased alpha cell mass.

Gcgr loss of function promotes improved glycemic control, but also increased alpha cell mass.

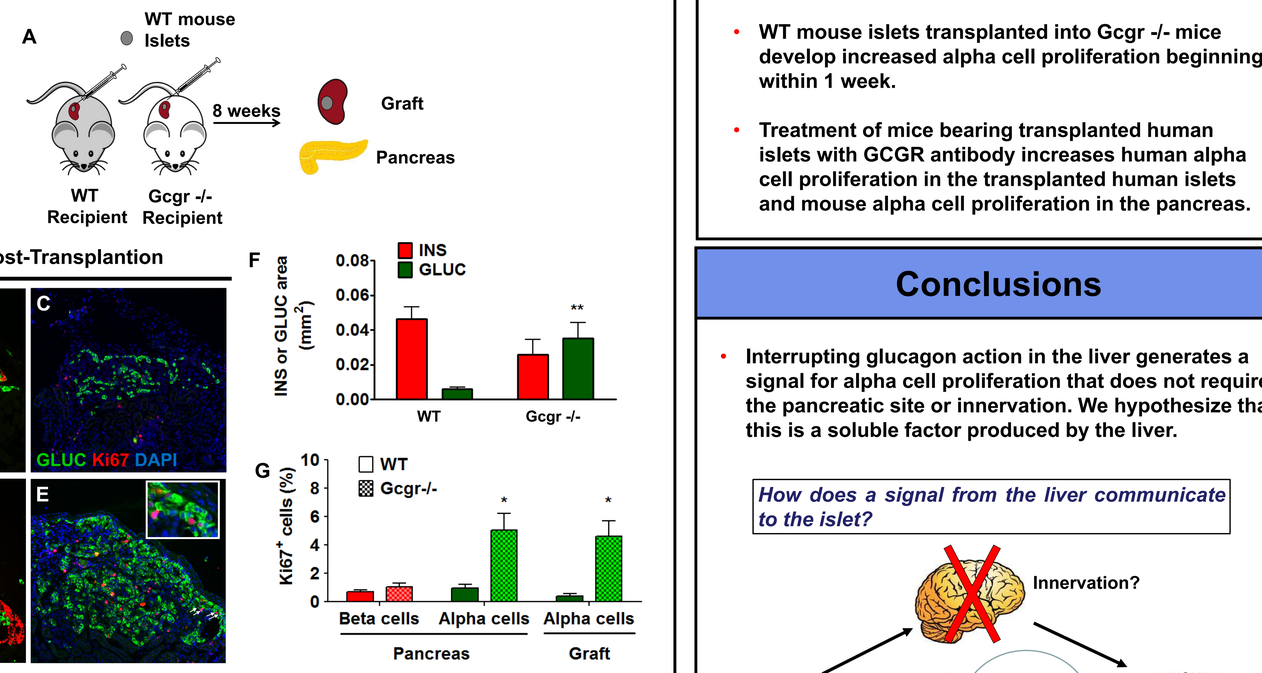


Hypothesis

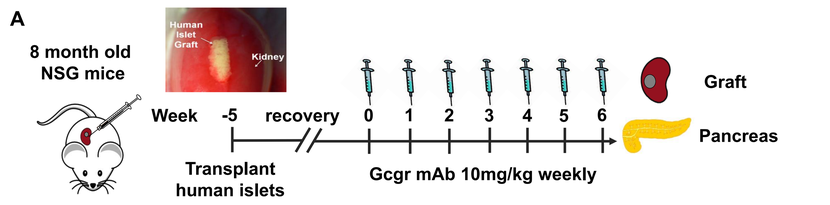
Loss of Gcgr signaling generates a signal that will stimulate alpha cell proliferation at an extrapancreatic site.

Alpha Cells of WT Islets Proliferate Upon Transplantation into Gcgr-/- Mice

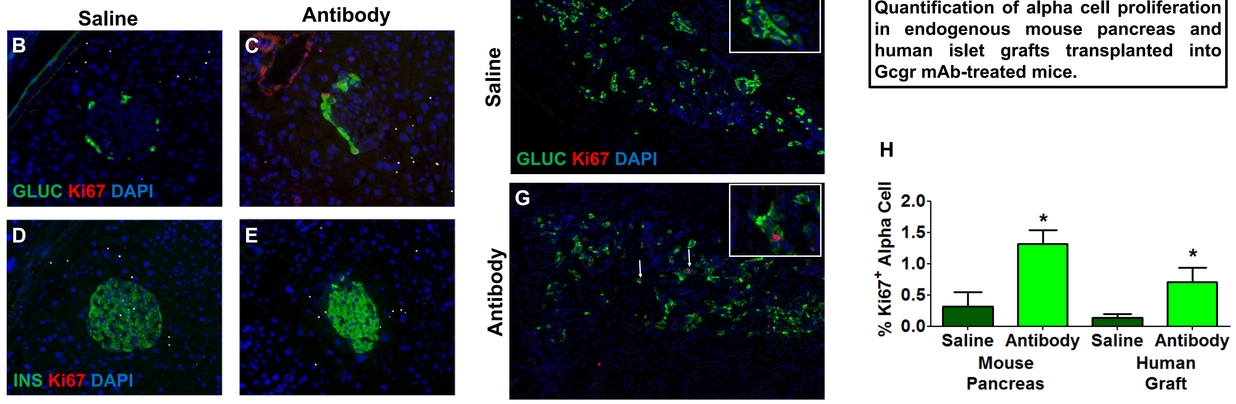
Alpha cell proliferate in the absence of the pancreatic environment and innervation in Gcgr-/- mice. *(A)* Experimental design for islet transplants into Gcgr-/- Mice. *(B,D)* Alpha cell and beta cell area in WT mouse islet grafts transplanted into either WT or Gcgr-/- recipient mice for 8 weeks. *(C,E)* Alpha cell proliferation in WT mouse islet grafts transplanted into either WT or Gcgr-/- recipient mice for 8 weeks. *(F)* Quantification of changes in insulin and glucagon area in WT mouse islet grafts transplanted into either WT or Gcgr-/- recipient mice for 8 weeks. *(G)* Quantification of beta cell (left) and alpha cell (middle) proliferation in the pancreas of WT and Gcgr -/- recipient mice. Quantification of alpha cell proliferation in WT mouse islet grafts transplanted into either WT or Gcgr-/- recipient mice for 8 weeks (right).



Human Alpha Cells Proliferate in Gcgr Antibody-Treated Mice



Human alpha cells proliferate when Gcgr signaling is lost. *(A)* Experimental design for islet transplants into NOD-SCID-γ (NSG) mice. *(B-E)* (F-G) Alpha cell proliferation and mass in human islet grafts transplanted into mice treated with Gcgr mAb for 6 weeks. *(F-G)* Alpha cell proliferation in WT islet grafts transplanted into either WT or Gcgr-/- recipient mice for 1 week. *(H)* Quantification of alpha cell proliferation in endogenous mouse pancreas and human islet grafts transplanted into Gcgr mAb-treated mice.



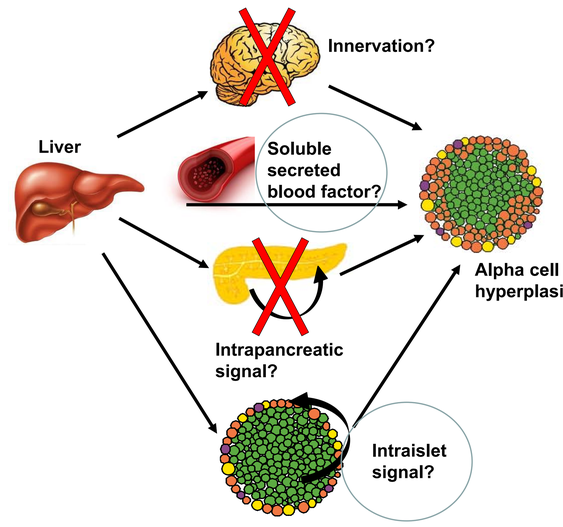
Summary

- WT mouse islets transplanted into Gcgr -/- mice develop increased alpha cell proliferation beginning within 1 week.
- Treatment of mice bearing transplanted human islets with GCGR antibody increases human alpha cell proliferation in the transplanted human islets and mouse alpha cell proliferation in the pancreas.

Conclusions

- Interrupting glucagon action in the liver generates a signal for alpha cell proliferation that does not require the pancreatic site or innervation. We hypothesize that this is a soluble factor produced by the liver.

How does a signal from the liver communicate to the islet?



Future Directions

- Repeating human donor islet transplants into younger NSG mice because alpha cell proliferation is higher in younger mice with shorter mAb treatment (data not shown).
- Perform *in vitro* islet culture experiments to determine if islets respond to factors within the serum of Gcgr -/- mice that promote alpha cell proliferation.

Contact: e.d.dean@vanderbilt.edu