



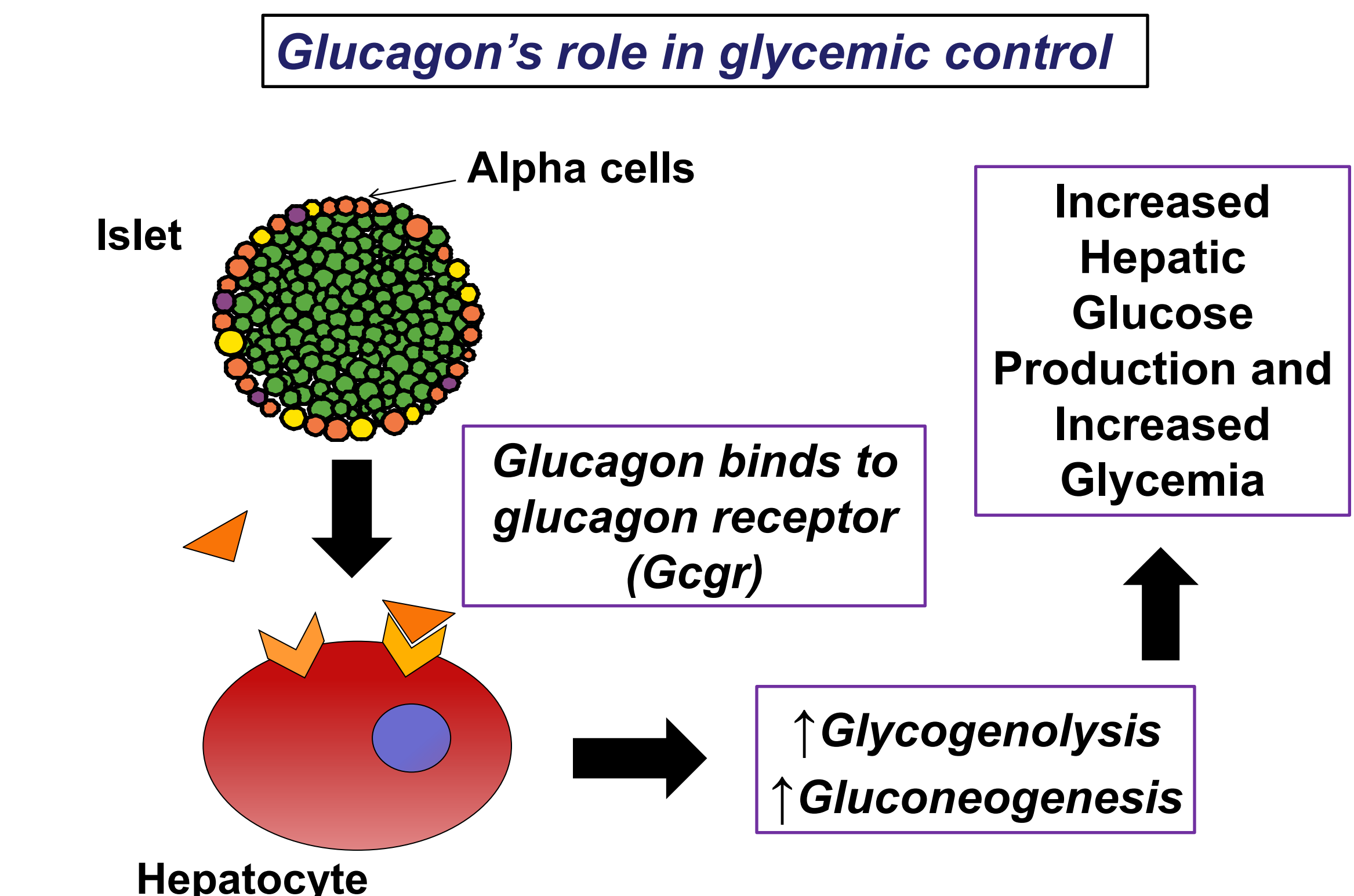
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# Human and Mouse Alpha Cells Proliferate in Response to Glucagon Receptor Blockade



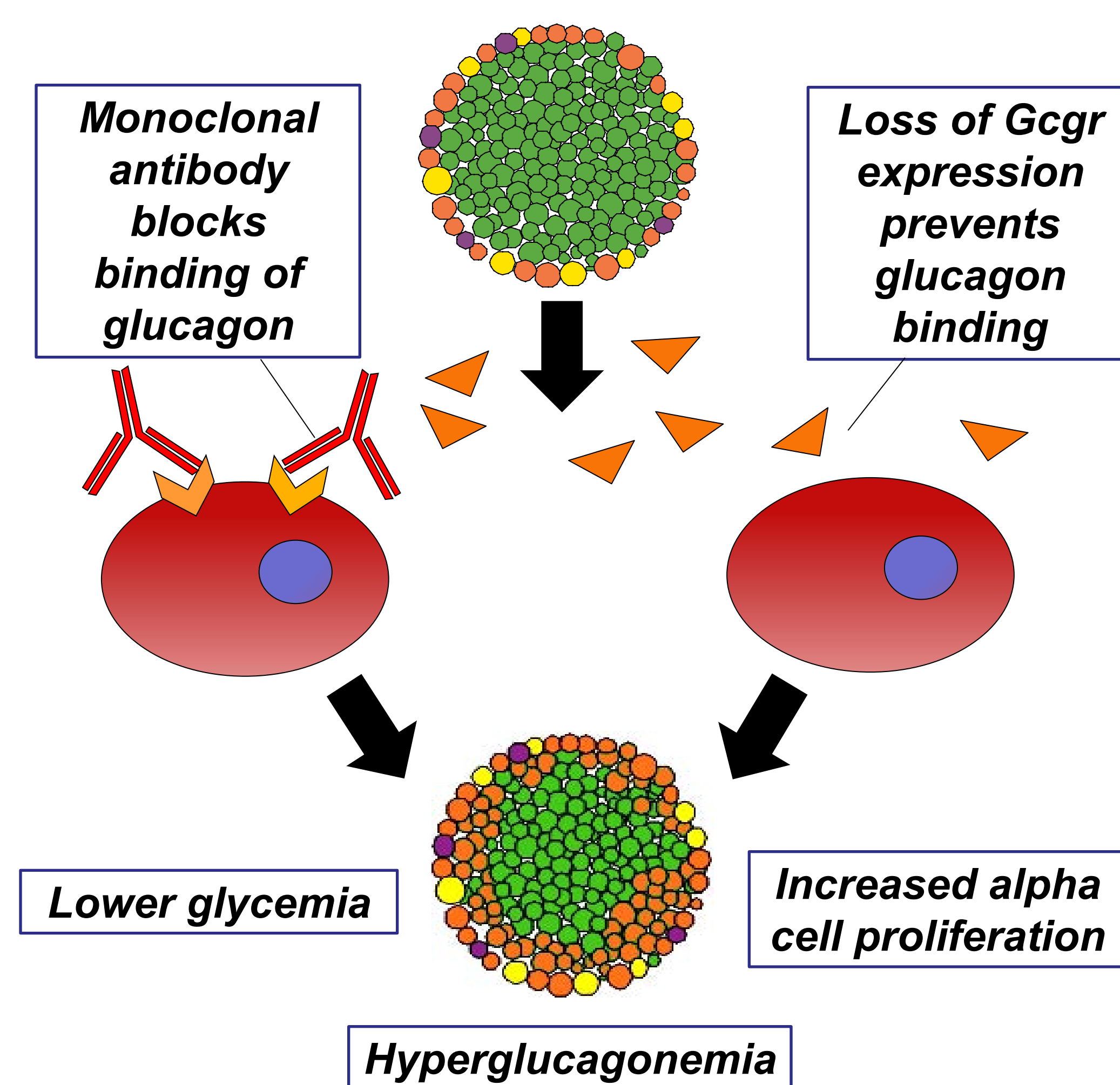
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## Introduction



- 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.*

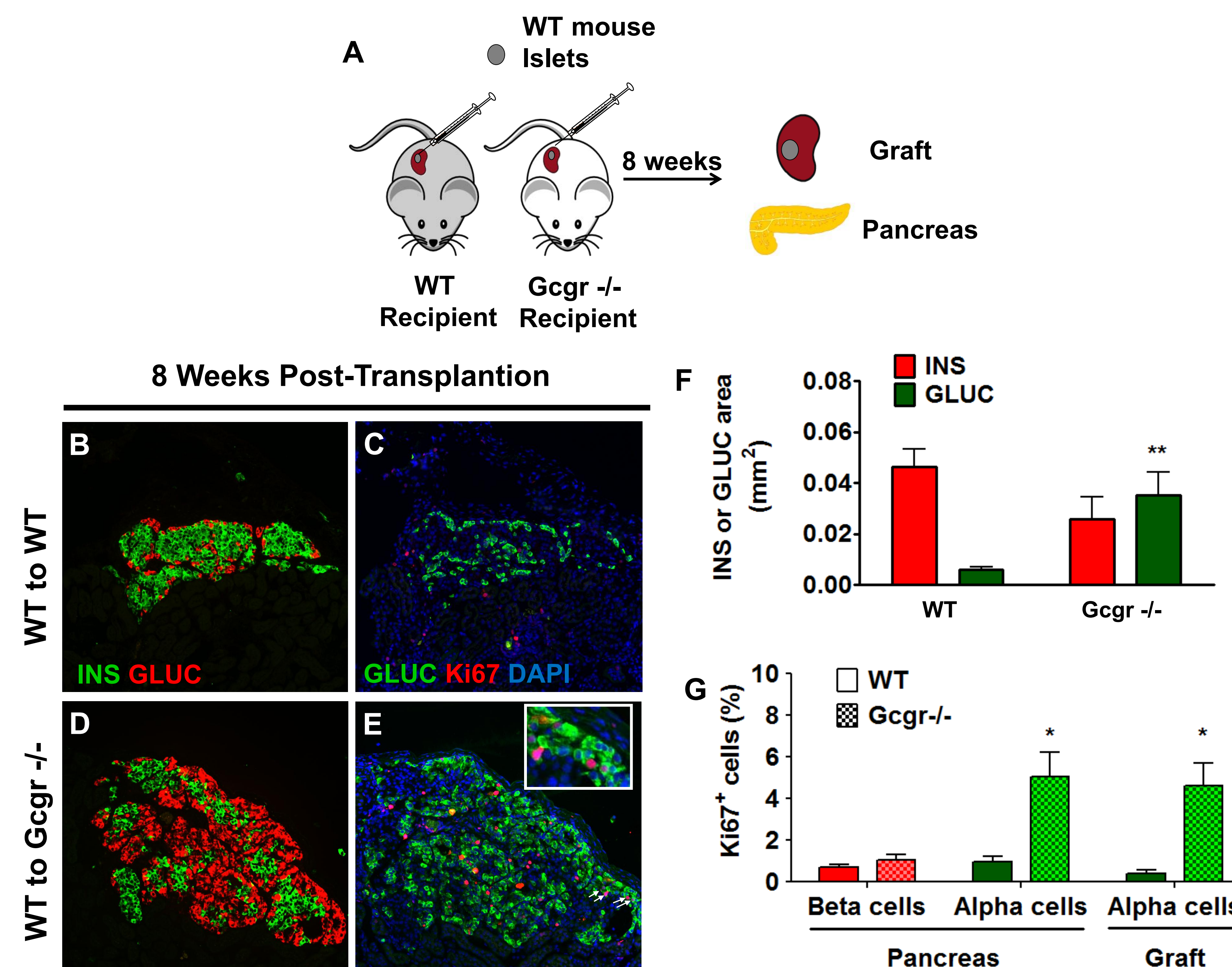


## Hypothesis

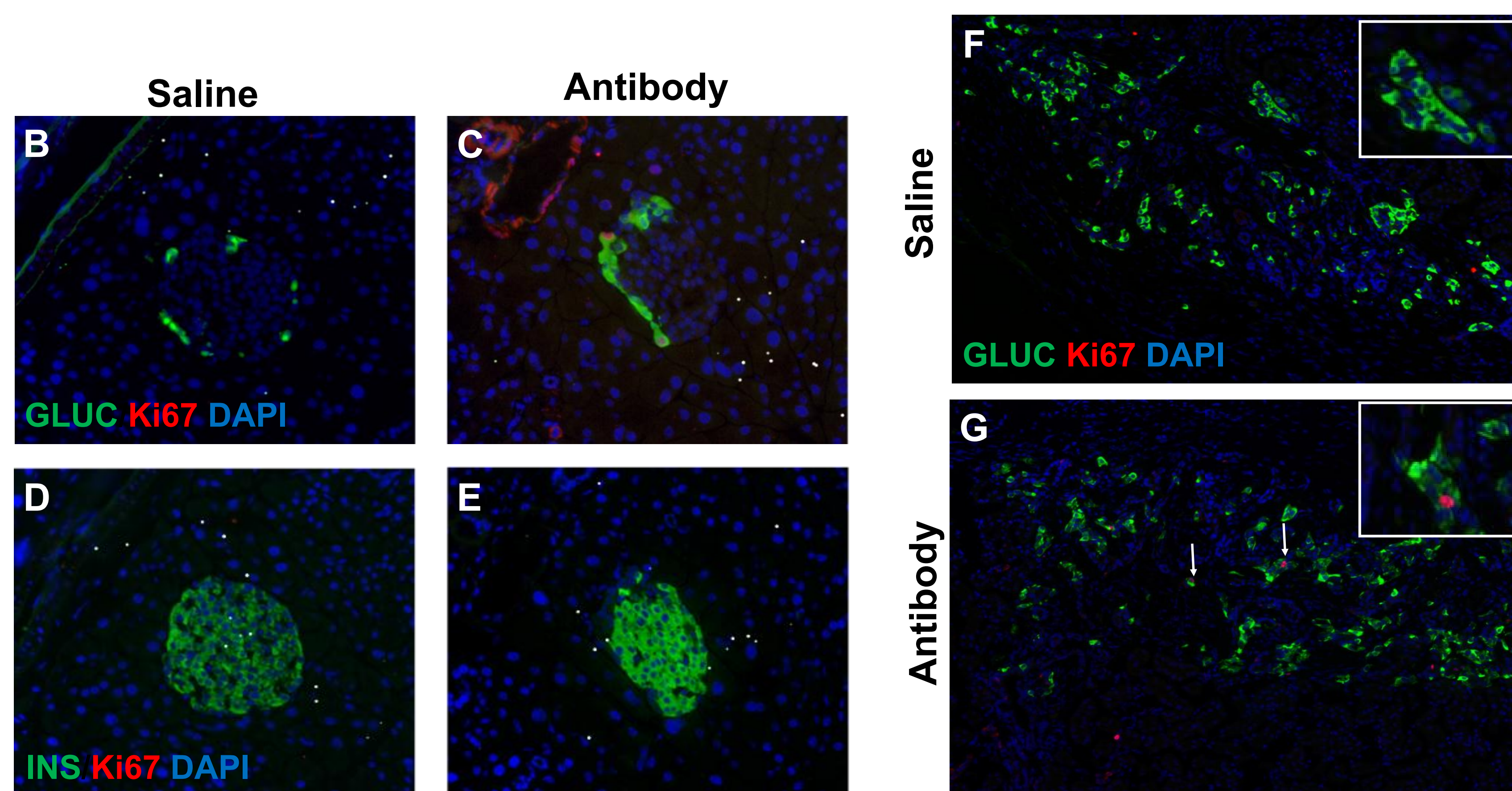
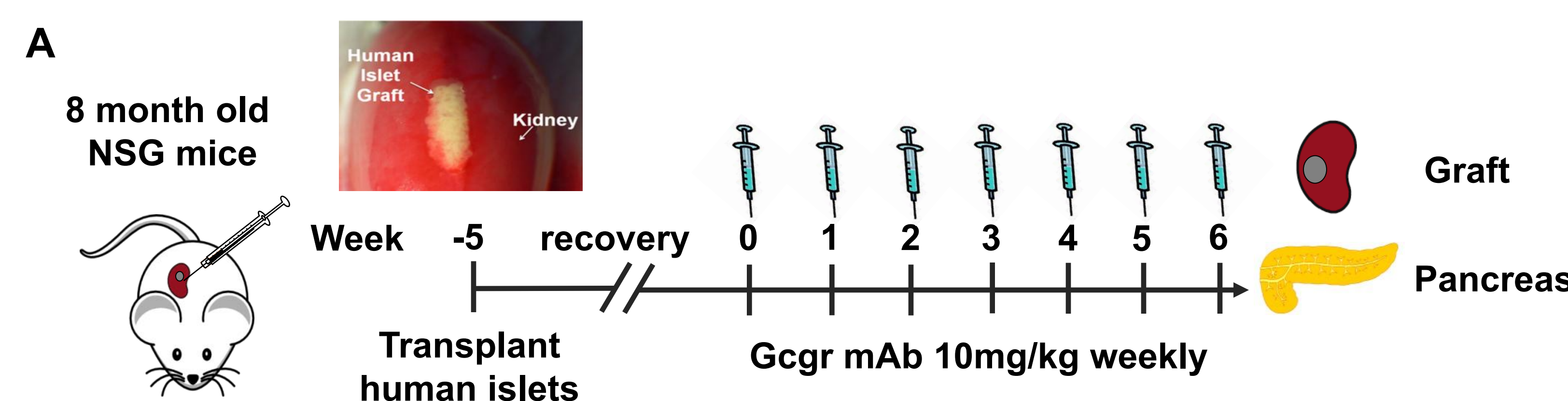
*Loss of Gcgr signaling generates a signal that will stimulate alpha cell proliferation at an extrapancreatic site.*

## Alpha Cells of WT Islets Proliferate Upon Transplantation into Gcgr<sup>-/-</sup> Mice

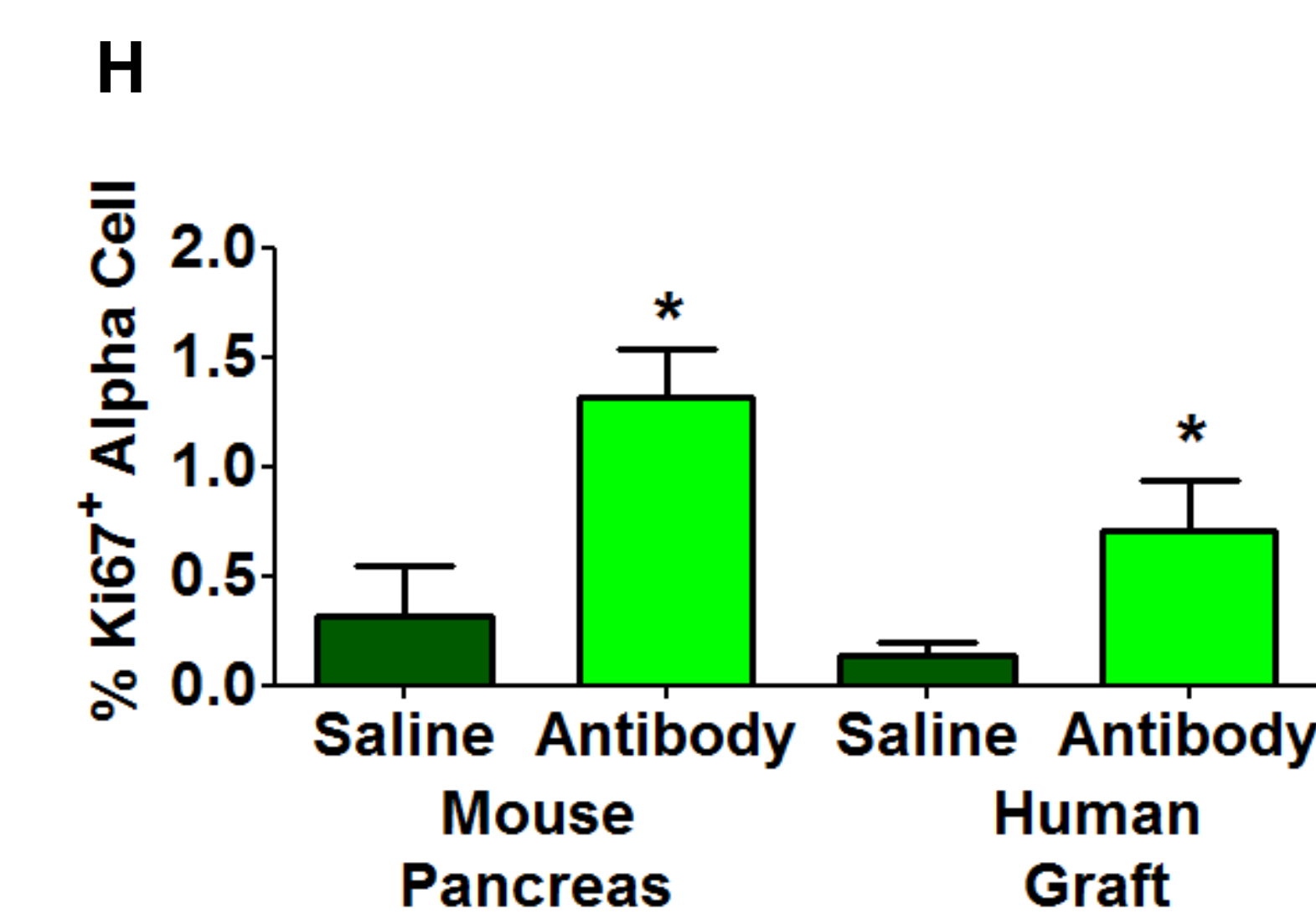
*Alpha cells proliferate in the absence of the pancreatic environment and innervation in Gcgr<sup>-/-</sup> mice. (A) Experimental design for islet transplants into Gcgr<sup>-/-</sup> mice. (B,D) Alpha cell and beta cell area in WT mouse islet grafts transplanted into either WT or Gcgr<sup>-/-</sup>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



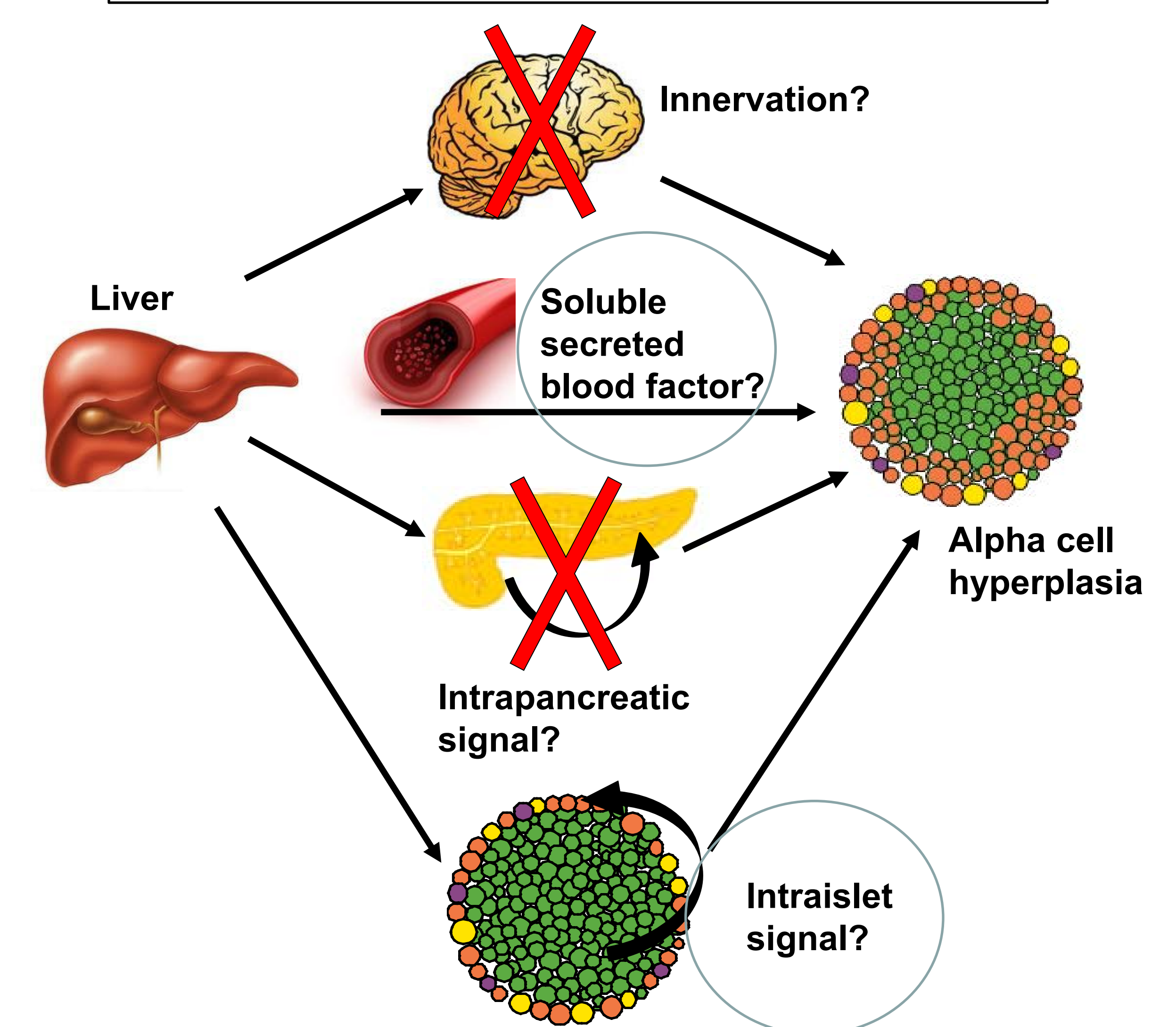
## Summary

- WT mouse islets transplanted into Gcgr<sup>-/-</sup> 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<sup>-/-</sup> mice that promote alpha cell proliferation.

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