



## Patch Grafting of Biliary Tree Stem/Progenitor Organoids directly into the Pancreas of NRG/Akita Mice corrects Type I Diabetes

### AUTHORS

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### PURPOSE

The pancreas is connected to the duodenum by the hepato-pancreatic common duct, the largest reservoir in the biliary tree of determined endodermal stem/progenitors, precursors to both liver and pancreas<sup>1</sup>. Methods for their isolation and management and extensive characterization of them have been described previously<sup>1</sup>. We focused here on developing novel methods of transplantation of these organoids directly into the pancreas using grafting strategies that we call **“patch grafting”**.

### METHODS

Organoids of biliary tree stem/progenitors were prepared in serum-free, wholly defined medium, Kubota's Medium, designed for determined endodermal stem/progenitors. Organoids were transplanted by patch grafting into the pancreas of pigs and mice. Grafts consisted of organoids embedded into soft (~100 Pa) hyaluronan (HA) hydrogels; placed onto silk backings embedded with more rigid HA hydrogels (~700 Pa); and tethered surgically to the duodenum adjacent to the pancreas and with surgical glue to mesentery superficial to the pancreatic capsule. A coating of HA of intermediate viscoelasticity properties (200-300 Pa) was added at the time of surgery and served to minimize adhesions of the graft to neighboring organs and tissues.

### SUMMARY OF RESULTS

Patch grafts caused transient remodeling of the pancreatic capsule and tissue subjacent to the graft, facilitating engraftment into the pancreas of essentially all donor organoids within a few days and without evidence of ectopic cell distribution. Donor cells migrated and integrated throughout the host pancreas within a week. By 2-3 weeks, the pancreatic capsule and normal histology were restored. Donor cells matured in pigs to functional adult pancreatic cells comprising acinar cells (amylase) and islets (insulin, glucagon). Quantitative functional effects of patch grafts were assessed in mice at 4 weeks and indicated that allografts of murine stem/progenitor organoids patch grafted onto the pancreases of NRG/Akita mice were able to rescue them stably from type I diabetes with restoration of insulin production and of normo-glycemic functions. The engraftment/migration/integration processes were mediated by multiple matrix-metallo-proteinases (MMPs), especially secreted MMPs

## CONCLUSIONS

Organoids of the stem/progenitors from the biliary tree can be transplanted directly and rapidly into the pancreas using patch grafting strategies. The donor cells are able to mature into functional adult pancreatic cells including islets that can correct disease states such as type I diabetes.

<sup>1</sup>Zhang, W. *et al.* Stem Cell-Fueled Maturation Lineages in Hepatic and Pancreatic Organogenesis.

***The Liver: Biology and Pathobiology***, 6th edition, Win Arias, MD, Gillian Whitley, and Allan W.

Wolkoff, MD, editors, Wiley Publishers, Hoboken, New Jersey and NYC, NY (2019). In Press