nPOD
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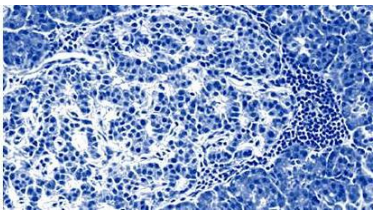

# Subacute and Chronic In Vivo Administration of a Harmine-Exenatide Combination Enhances Glycemic Control and Markedly Expands Human Beta Cell Mass In Vivo


## AUTHORS

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## PURPOSE

Administration of any member of the harmine family of DYRK1A inhibitors in combination with GLP1 family members increases markers of human beta cell proliferation and beta cell numbers in vitro. Here, we assessed the ability of the harmine-exenatide combination to expand beta cell mass in vivo in euglycemic and streptozotocin-diabetic mice over periods of one week to three months. Beta cell mass was measured by iDISCO tissue clearing followed by insulin immunolabeling, visualization by light sheet microscopy and volumetric quantification by Imaris.

## METHODS

In sub-acute studies, daily intraperitoneal injections of low dose harmine (1mg/kg) and/or exenatide (0.5 µg/kg), or control vehicle, were administered to NOD-SCID mice transplanted with a marginal mass (500 IEQ) of human cadaveric islets for 7-14 days. Outcome measures were proliferation (Ki67+/Ins+ cells); glycemic control, IP-GTT, and circulating human insulin concentrations. In chronic studies, mice were infused continuously for three months via subcutaneous implanted Alzet minipumps infusing vehicle, harmine, exenatide, or a harmine-exenatide combination.

## SUMMARY OF RESULTS

Subacute administration of the harmine-exenatide combination, but not harmine or exenatide alone, reversed diabetes, improved IP-GTT and increased human insulin secretion in the marginal mass streptozotocin model of diabetes. Removal of the human islet grafts resulted in prompt return of severe hyperglycemia. The harmine-exenatide combination was also effective in inducing human beta cell proliferation in vivo. In the chronic, three-month harmine-exenatide infusion model, exenatide alone had no effect on human beta cell mass; harmine treatment alone resulted in a 3x increase in beta cell mass. Most importantly, the harmine-exenatide combination resulted in a striking 10-fold increase in human beta cell mass.

| CONCLUSIONS |
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| Subacute and chronic administration of harmine plus exenatide enhances human insulin secretion and beta cell proliferation, markedly improves glycemic control, and results in remarkable increases in human beta cell mass, all in vivo. |