

594 Supplemental Figure 1. **Genetic interruption of glucagon signaling stimulates beta cell**
595 **proliferation in pancreatic and transplanted mouse islets.** (A-B) Quantification of pancreatic
596 islet beta cell proliferation in (A) 6 week-old $Gcgr^{+/+}$ (black bar, all males) and $Gcgr^{-/-}$ (red striped
597 bar, all males) and (B) 8 week-old $Gcgr^{+/+}$ (black bar) and $Gcgr^{-/-}$ (red bar) mice (n=2-4 females
598 and 3 males per group, unpaired t test, ***p < 0.001 versus $Gcgr^{+/+}$, *p < 0.05 versus $Gcgr^{+/+}$). (C)
599 Schematic of approach for subcapsular renal transplantation of $Gcgr^{+/+}$ (wild type, WT) donor
600 islets into control ($Gcgr^{Flox}$) or liver-specific $Gcgr$ knockout ($Gcgr^{Hep^{-/-}}$) recipient mice. Created
601 with BioRender.com (D) Representative images of islet grafts from WT to Flox and WT to Hep^{-/-}
602 recipients after four weeks. Grafts are immunostained for insulin (green), Ki67 (red) and DAPI
603 (blue). White arrows indicate Ki67+ insulin+ cells. Dashed yellow lines indicate kidney-graft

604 boundary. **(E)** Quantification of beta cell proliferation in transplanted islets from WT to Flox
605 (black bar) and WT to Hep^{-/-} (red striped bar) groups (n=4 males per group, unpaired t test, **p <
606 0.05 versus WT to Flox).

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608 Supplemental Figure 2. SLC7A2-**dependent stimulated beta cell proliferation is islet**

609 **autonomous.** **(A)** Schematic of approach for subcapsular renal transplantation of *Slc7a2*^{+/+}

610 (wild type, WT) and *Slc7a2*^{-/-} (KO) donor islets into *Slc7a2*^{+/+} (WT) recipient mice followed by

611 control IgG or GCGR-Ab treatment. Created with BioRender.com **(B)** Representative images of

612 *Slc7a2*^{+/+} (upper row) and *Slc7a2*^{-/-} (bottom row) islet grafts from *Slc7a2*^{+/+} kidney capsules after

613 two weeks of IgG or GCGR-Ab treatment. Grafts are immunostained for insulin (green), Ki67

614 (red) and DAPI (blue). White arrows indicate Ki67+ insulin+ cells. Dashed yellow lines indicate

615 kidney-graft boundary. **(C)** Quantification of beta cell proliferation in transplanted islets from

616 *Slc7a2*^{+/+} and *Slc7a2*^{-/-} donors treated with IgG (black circles) or GCGR-Ab (blue circles; n=2

617 females and 2 males per treatment group, two-way ANOVA with Fisher's LSD test, **p < 0.01

618 versus IgG treated). **(D)** Quantification of pancreatic islet beta cell mass in *Slc7a2*^{+/+} (black bars)

619 and *Slc7a2*^{-/-} (blue bars) IgG or GCGR-Ab-treated mice (n=2-5 females and 3-6 males per

620 group).

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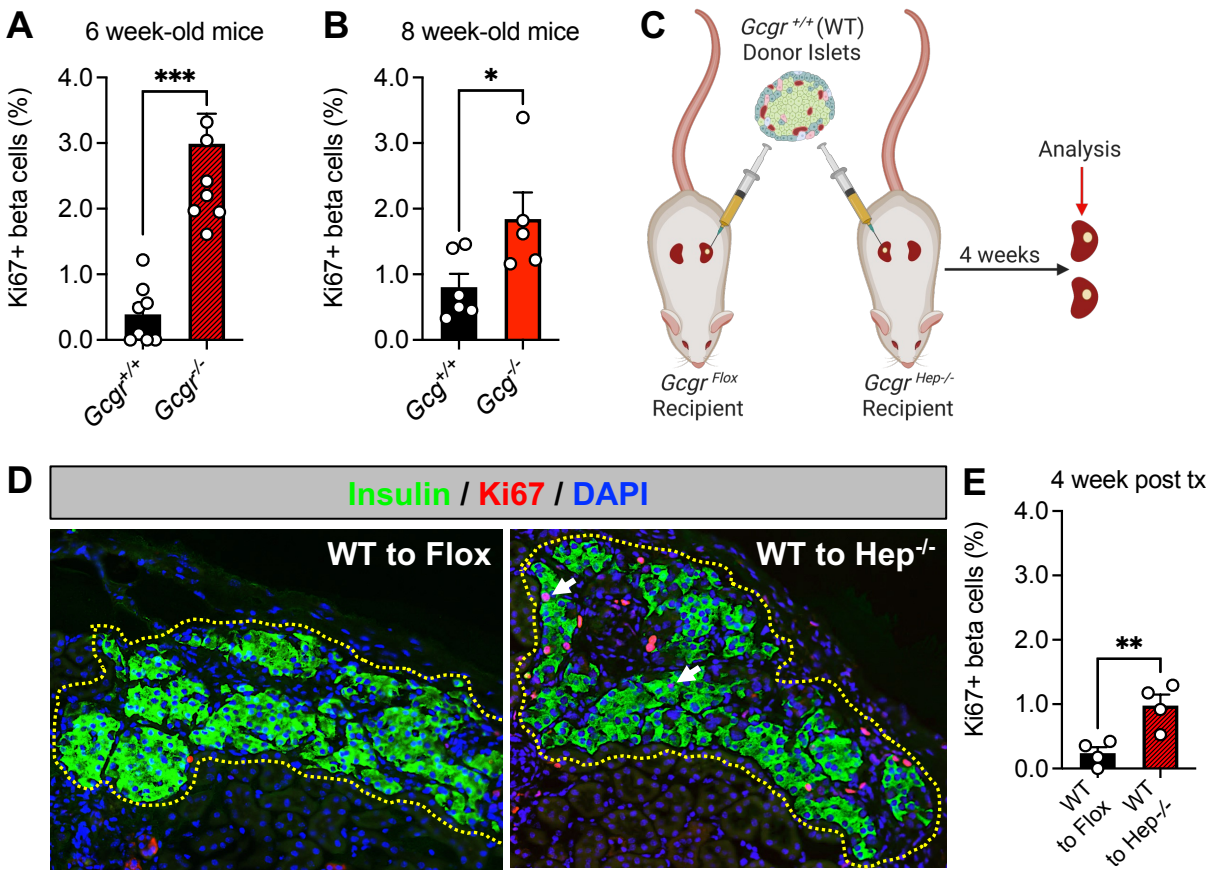
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632 Supplemental Table 1: *Human Islet Donor Information.*
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Donor ID	Age	Ethnicity/Race	Sex	BMI (kg/m ²)	HbA1c (%)	Cause of Death	Islet Source
AELC213	10	Hispanic/Latino	F	25.4	N/A	Head Trauma/Blunt Injury	Other
AFEA331	45	Black	M	29.3	5.0	CVA/ stroke	IIDP
AIFV371	28	Hispanic/Latino	F	24.7	5.0	CVA/ stroke	HPAP
1	32	N/A	M	29.5	N/A	N/A	IIDP
2	47	N/A	M	22.3	N/A	N/A	IIDP
3	55	N/A	M	28.4	N/A	N/A	IIDP
4	43	N/A	M	29.6	N/A	N/A	IIDP
5	46	N/A	M	28.8	N/A	N/A	IIDP
6	41	N/A	F	31.1	N/A	N/A	IIDP
7	47	N/A	F	25.6	N/A	N/A	IIDP
8	52	N/A	M	33.2	N/A	N/A	IIDP

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Supplemental Figure 1



Supp Fig 2: Slc7a2 is required for Gcgr-Ab-induced beta cell proliferation in transplanted mouse islets

