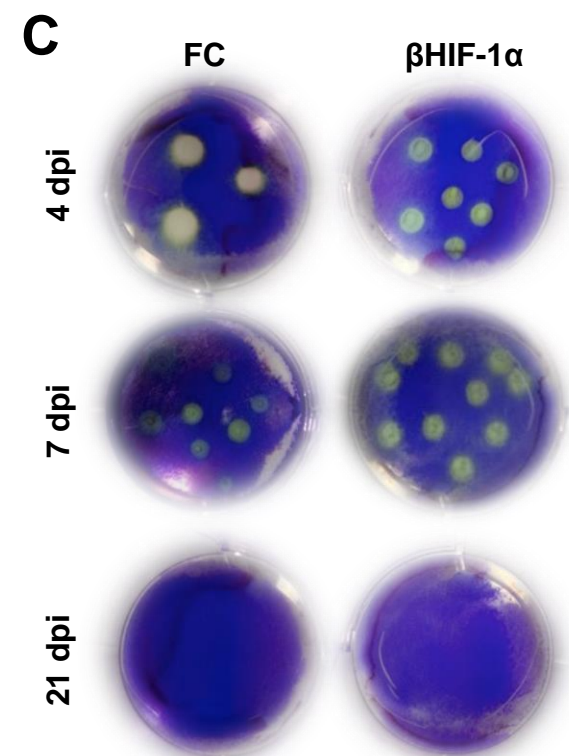
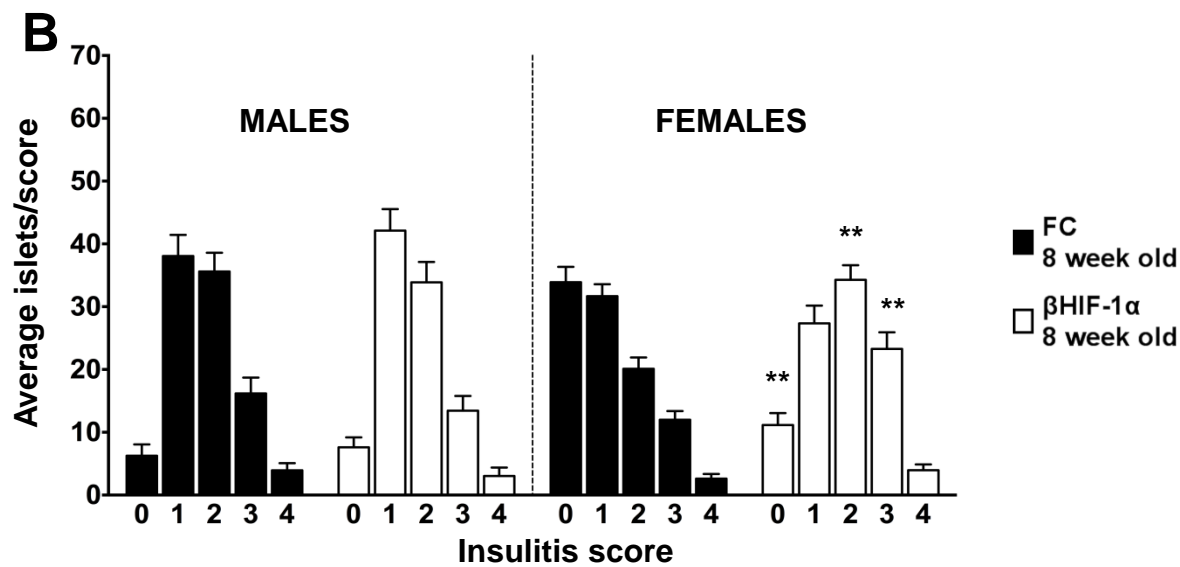
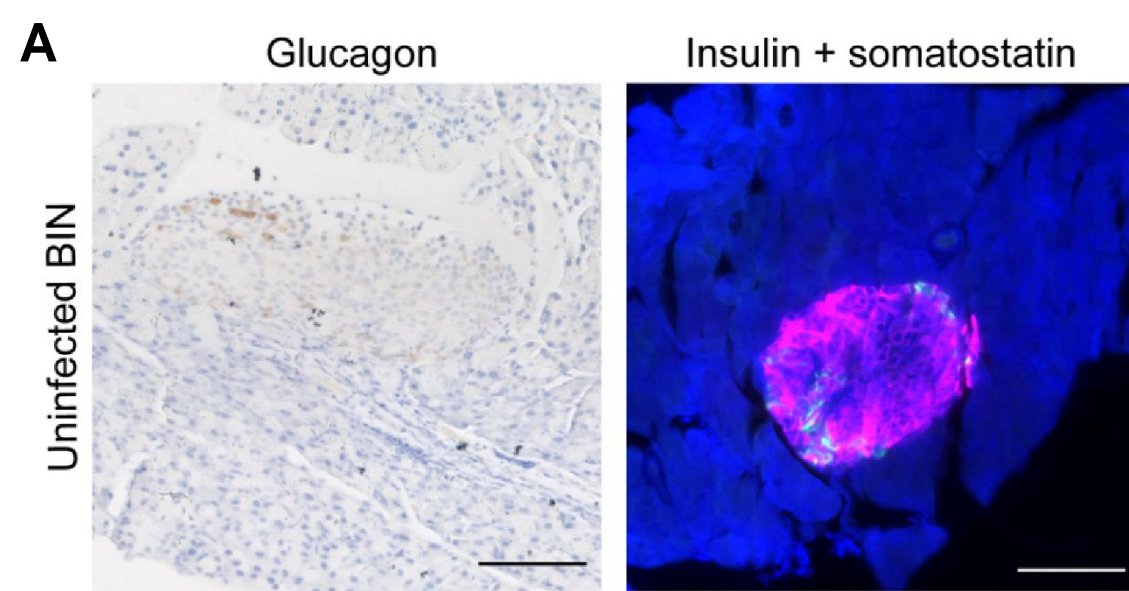


Cell Reports, Volume 27

Supplemental Information

β Cell Hypoxia-Inducible Factor-1 α Is Required for the Prevention of Type 1 Diabetes

Amit Lalwani, Joanna Warren, David Liuwantara, Wayne J. Hawthorne, Philip J. O'Connell, Frank J. Gonzalez, Rebecca A. Stokes, Jennifer Chen, D. Ross Laybutt, Maria E. Craig, Michael M. Swarbrick, Cecile King, and Jenny E. Gunton

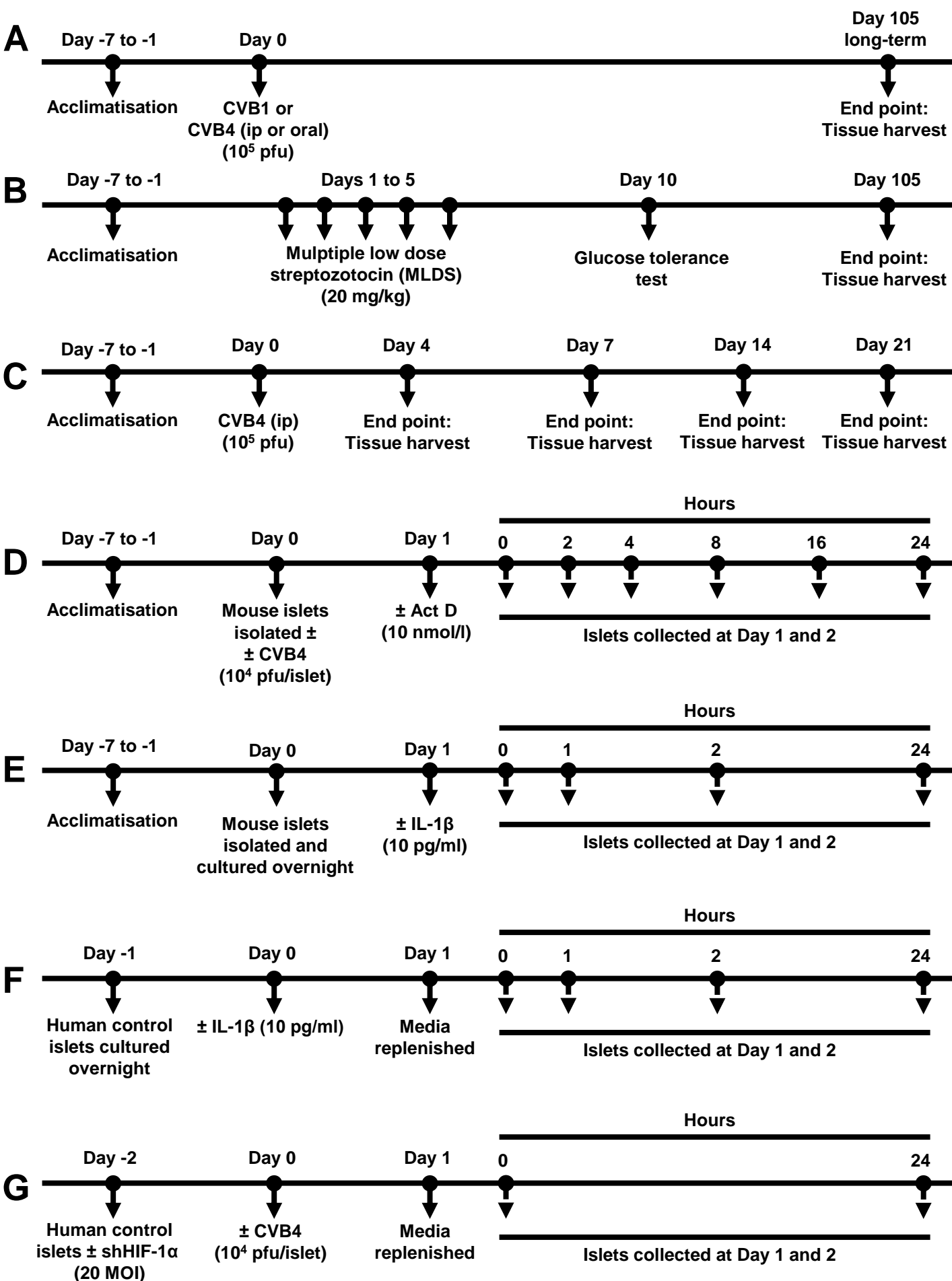


Supplementary Figure 1. Related to Figure 1, Star Methods Experimental Model and Subject Details.

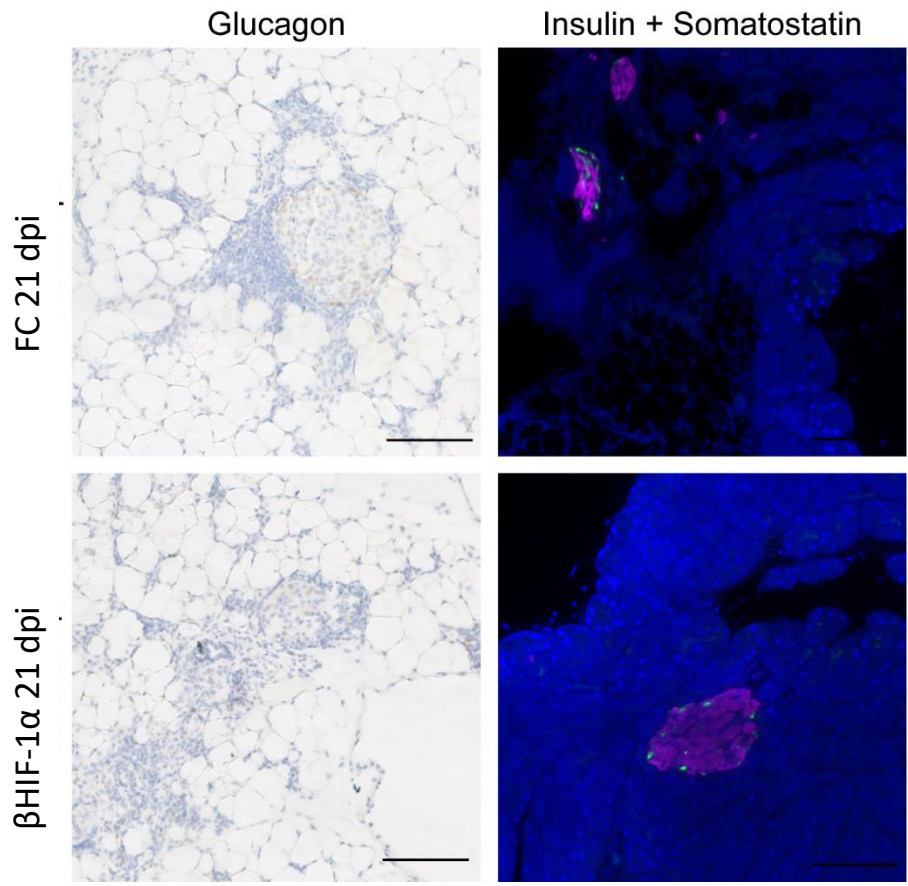
A) Baseline islet architecture appears normal in β HIF-1 α mice. Scale bar indicates 100 μ m. Glucagon positive cells are stained brown. Somatostatin positive cells are green, and insulin positive cells are pink.

B) Baseline insulinitis scores at 8 weeks of age in 8-week old floxed control (FC) and β HIF-1 α mice. **= $p < 0.01$ versus FC.

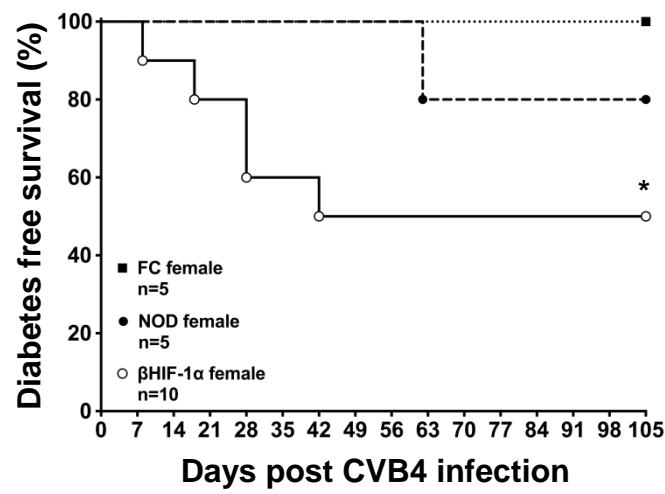
C) Images of plaque assays of pancreatic tissue from FC and β HIF-1 α mice. No plaques were detected at day 21.



Supplementary Figure 2. Experimental timelines. Relates to Figures 1, 2 and 6. Pfu= particle forming units. Act D = actinomycin D. MOI = multiplicity of infection.

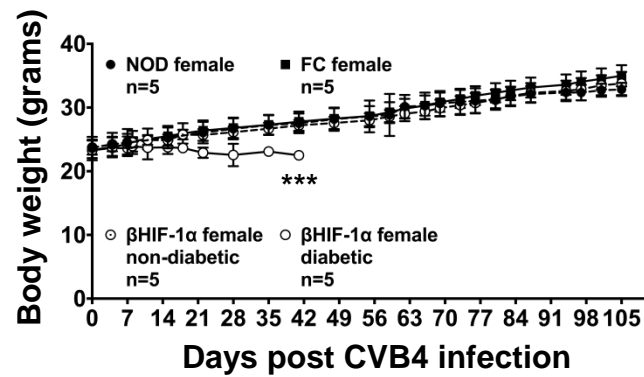


Supplementary Figure 3. Relates to Figure 3. Islet histology at 21 days after CVB4 infection. The scale bars indicate 100 μ m. Glucagon is shown in brown in the left panels. In the right panels insulin is in pink and somatostatin positive cells are in green.

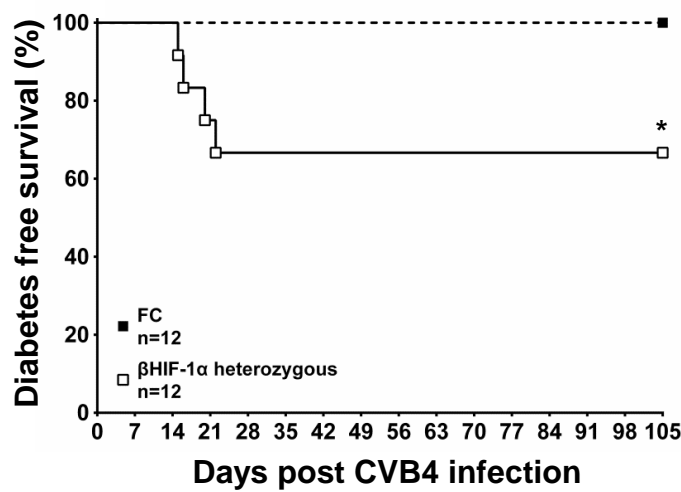
A**Supplementary Figure 4. Relates to Figure 1.**

A) Diabetes-free survival in female mice which were infected with CVB4 at 8 weeks of age.

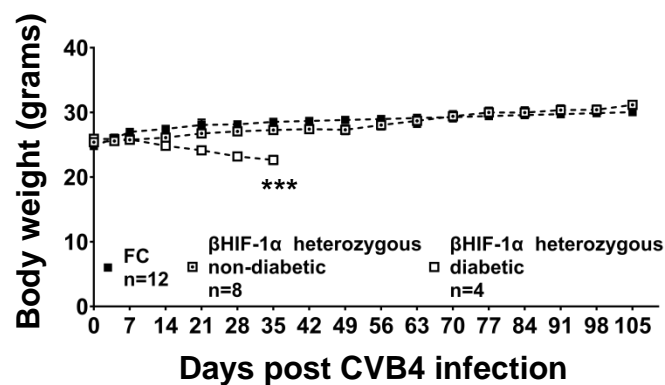
*=p<0.05 compared to controls.

B

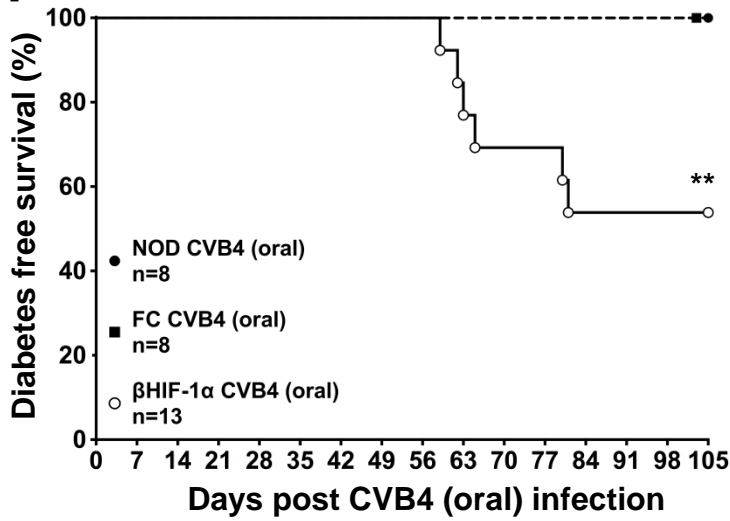
B) Body weight in the same female mice shown in part A). ***=p<0.001 versus controls.

C

C) Diabetes free survival in male heterozygous βHIF-1α mice compared to floxed controls (FC) infected with CVB4 at 8 weeks of age. *=p<0.05 compared to floxed controls.

D

D) Body weight in the same male mice shown in part C). ***=p<0.001 versus controls.

A

Supplementary Figure 5. Relates to STAR METHODS – METHODS.

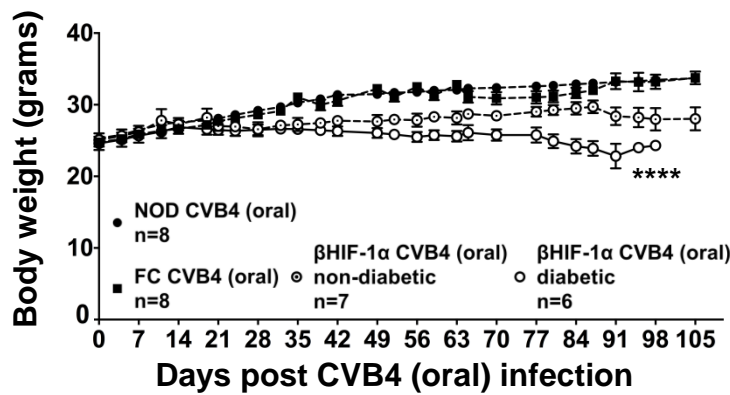
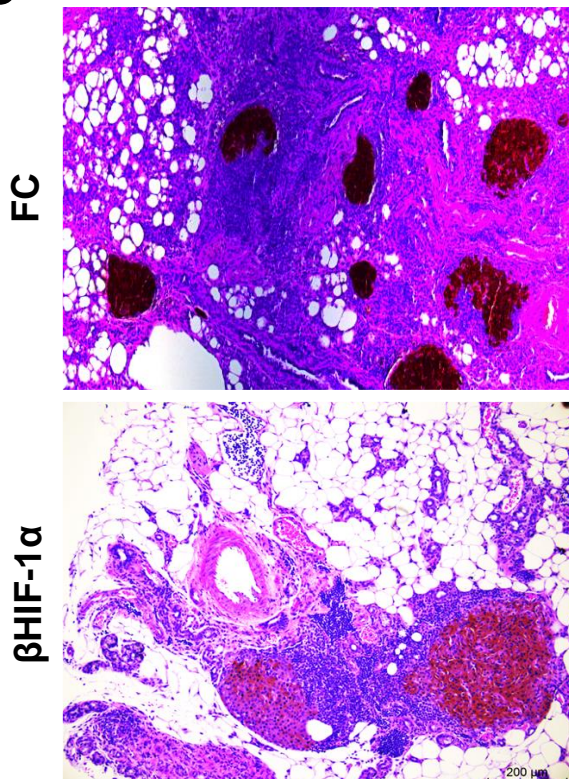
A) Diabetes-free survival after oral gavage with CVB4. **= $p < 0.01$ versus controls.

B) Body weight curves in mice from A).

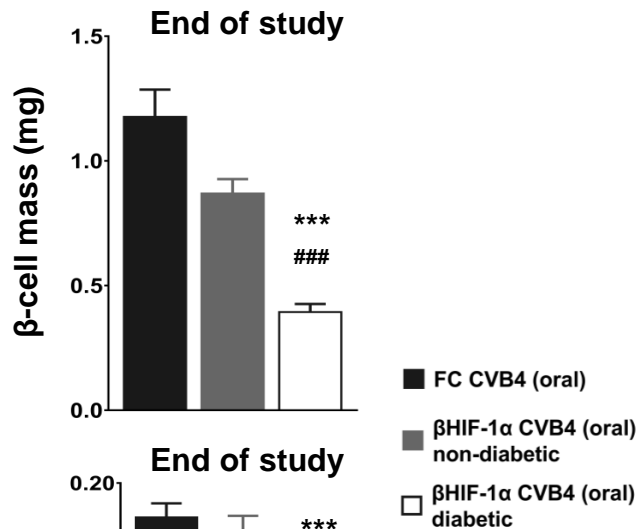
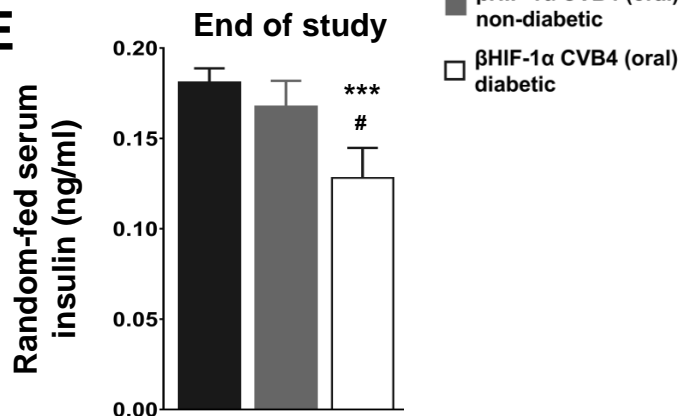
C) Insulin immunohistochemistry with H&E counterstain at end of study in orally gavaged mice.

D) β -cell mass at the end of study. *** $p < 0.001$ vs FC. ### $p < 0.001$ vs non-diabetic β HIF-1 α mice.

E) Random-fed serum insulin at the end of study. *** $p < 0.001$ vs FC. # $p < 0.05$ vs non-diabetic β HIF-1 α mice.

B**C**

Insulin and H&E (end of study)

D**E**

Supplementary Table 1: Flow cytometry antibodies (arranged alphabetically). Relates to Star Methods; Methods – isolation of infiltrates.

Antibody	Fluorochrome	Clone	Catalog number	Supplier
CD11b	AF488	M1/70	557672	BD Biosciences
CD11c	APC	HC3	550261	BD Biosciences
CD19	PE-CY7	1D3	552854	BD Biosciences
CD25	APC	PC61	557192	BD Biosciences
CD27	BV421	1G.3A10	740028	BD Biosciences
CD3	BUV737	17A2	564380	BD Biosciences
CD4	FITC	GK1.5	553729	BD Biosciences
CD4	PE	IT3T4	12-0041-82	eBioscience
CD45	BUV395	30-F11	564279	BD Biosciences
CD8	BV650	53-6.7	563234	BD Biosciences
F4-80	BV421	T45-2342	565411	BD Biosciences
Granzyme B	PE	NGZB	12-8898-80	eBioscience

Supplementary Table 2: Mouse real-time PCR primers (arranged alphabetically). Relates to Figures 5 and 6

GENE	SPECIES	PRIMER	SEQUENCE
<i>18s</i>	Mouse	Forward	atggccgttcttagttggtg
		Reverse	cgctgagccagtcagtgtag
<i>A20</i>	Mouse	Forward	tggaaagaagggtgatcagg
		Reverse	accccaccgatacagagatg
<i>Atf3</i>	Mouse	Forward	gctgccaagtgtcgaacaag
		Reverse	cagtttccaatggcttcagg
<i>Bak1</i>	Mouse	Forward	cgctacgacacagagtcca
		Reverse	ggtagacgtacagggccaga
<i>Bax</i>	Mouse	Forward	tgcagaggatgattgctgac
		Reverse	gatcagctcgggcactttag
<i>Bcl2</i>	Mouse	Forward	tctgaaggattgatggcaga
		Reverse	catcagccacgcctaaaagt
<i>Bclxl</i>	Mouse	Forward	ccattgctaccaggagaacc
		Reverse	aggagctggtttaggggaaa
<i>Bik1</i>	Mouse	Forward	ggcctgctgctgttatcttt
		Reverse	taaccggtgacaattgcaga
<i>Bip</i>	Mouse	Forward	aggacaagaaggaggatgtggg
		Reverse	accgaagggtcattccaagtg
<i>Catalase</i>	Mouse	Forward	atgaagcagtggaggagcagc
		Reverse	ctgtcaaagtgtgccatctcgtc
<i>Chop</i>	Mouse	Forward	ttcactactcttgaccctgcgtc
		Reverse	cactgaccactctgttccgtttc
<i>Cxadr (CAR)</i>	Mouse	Forward	ccctgggggtgcaaataag
		Reverse	gatccatccacgaagcatct
EV RNA	Mouse	Ev1	caagcacttctgtttccccgg
		Ev2	tctccggcccctgaatgcg
		Ev3	attgtcaccataagcagcca
		Ev4	cacygcatggccaatccaa
<i>Gpx</i>	Mouse	Forward	acagtccaccgtgatgccttc
		Reverse	ctcttcattcttccattctctg
<i>Grp94</i>	Mouse	Forward	aaacggcaacacttcggtcag
		Reverse	gcatccatctcttccctcatc
<i>Hif-1α</i>	Mouse	Forward	tcaagtcagcaactggaag
		Reverse	tatcgaggctgtgcgactg
<i>Igp2</i>	Mouse	Forward	agccagagcacacacatgac
		Reverse	atccctgaactcctggatca
<i>Mda5</i>	Mouse	Forward	cttgtcacgaacgagatagcc
		Reverse	ccaggacatacgtgctttca
<i>NfκB</i>	Mouse	Forward	gttccagtacttgccagacacaga
		Reverse	gaagttgagttcgggtaggca
<i>Nod2</i>	Mouse	Forward	gccagtacgagtgtgaggatca
		Reverse	cagctccaagatgttctccgtgta
<i>Rig-</i>	Mouse	Forward	acaaccacaacctgttctgaca
		Reverse	tggcgagaatatctttgctttct
<i>Sod1</i>	Mouse	Forward	atggggacaatacacaaggctg
		Reverse	caatgatggaatgctctctgag
<i>Tbp</i>	Mouse	Forward	tatcactctgccacaccag
		Reverse	atgatgactgcagcaaatcg
<i>Trib3</i>	Mouse	Forward	tcttcagcaactgtgagaggacg
		Reverse	tccagacatcagccgctttg

**Supplementary Table 3: Human real-time PCR primers (arranged alphabetically).
Relates to Figure 6**

GENE	SPECIES	PRIMER	SEQUENCE
<i>BAK1</i>	Human	Forward	ctcctgcccagactacagg
		Reverse	accctggattacactgtgc
<i>BAX</i>	Human	Forward	ttcatccaggatcgagca
		Reverse	atcctctgcagctccatgt
<i>BCI2</i>	Human	Forward	aggctcgctcaatcaagaaa
		Reverse	cttcccaaaaagaaatgcaa
<i>BCIXL</i>	Human	Forward	gtaaactggggtcgattgt
		Reverse	tgctgcattgttccataga
<i>CXARD (CAR)</i>	Human	Forward	gttgagttgcagggtgtgg
		Reverse	ctcaaaccaactgtcaacagc
<i>EV RNA</i>	EV	EV1	caagcacttctgttccccgg
		EV2	tcctccggcccctgaatgcg
		EV3	attgtcaccataagcagcca
		EV4	cacygcatggccaatccaa
<i>HIF-1α</i>	Human	Forward	gaaagcgcaagtctctcaaag
		Reverse	tgggtaggagatggagatgc
<i>IGP2</i>	Human	Forward	ggcagttggcgatgactt
		Reverse	ccagggcagtcccactta
<i>MDA-5</i>	Human	Forward	tggacaagcttctagttagagacg
		Reverse	cctgattcatttccattgtttc
<i>NOD2</i>	Human	Forward	caacacctccttgcagtcc
		Reverse	ccacctcaagctctggtgat
<i>RIG-I</i>	Human	Forward	cacctggtttgcctaattcgt
		Reverse	tcagcctgaatatactgcacctc
<i>TBP</i>	Human	Forward	tggatatctttgccaattcatct
		Reverse	atcttccaattgcgtgaaaac
<i>TLR3</i>	Human	Forward	tggatatctttgccaattcatct
		Reverse	atcttccaattgcgtgaaaac