Targeting epigenetic readers preserves β-cells by modulating inflammatory pathways in diabetes

Vinny Negi, PhD

Yechoor lab

Division of Endocrinology and Metabolism

University of
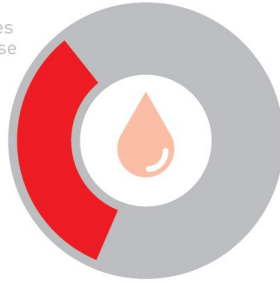**Pittsburgh**

Introduction
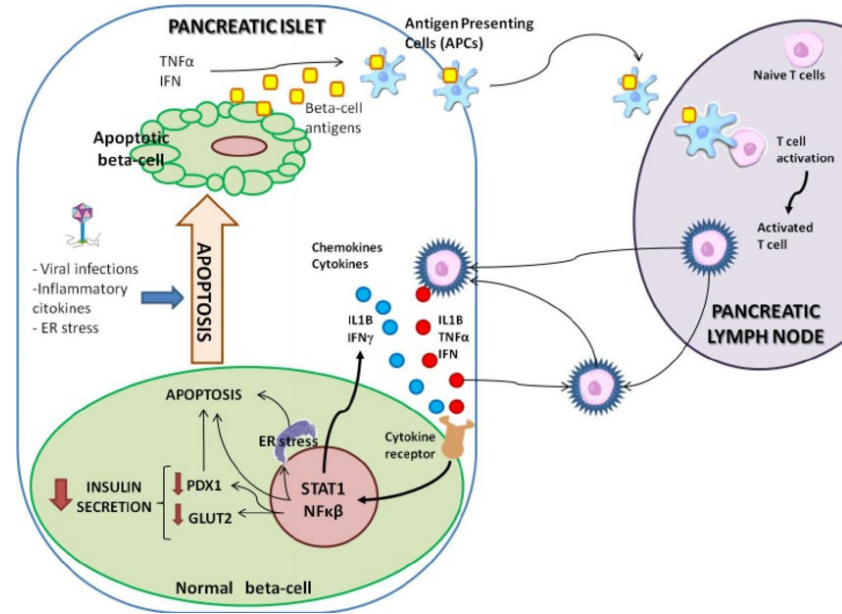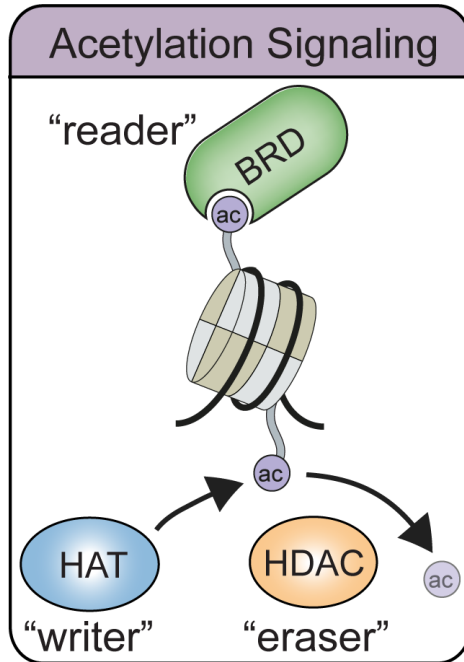

Source: World Health Organization, 2020

Beta-cell apoptosis - key cause of reduced beta-cell mass in diabetes

Type 1 Diabetes - Pathogenesis, Genetics and Immunotherapy. DOI: 10.5772/22089

University of Pittsburgh

I-BET: epigenetic inhibitors

Acetylation Signaling

"reader" BRD
ac

HAT "writer"
HDAC "eraser"
ac

- Can increase or decrease gene expression depending on interacting partners
- Anti-proliferative and -inflammatory drug
- Used in cancer and auto-immune diseases

University of Pittsburgh

I-BET increases β-cell proliferation

Epigenetic modulation of type-1 diabetes via a dual effect on pancreatic macrophages and β cells

RESEARCH ARTICLE

BET Bromodomain Proteins Brd2, Brd3 and Brd4 Selectively Regulate Metabolic Pathways in the Pancreatic β-Cell

Jude T. Deeney[1], Anna C. Belkina[2], Orian S. Shirihai[1], Barbara E. Corkey[1], Gerald V. Denis[3]*

Original Research

Bromodomain and Extra Terminal Proteins Inhibitors Promote Pancreatic Endocrine Cell Fate

Lukas Huijbregts, Maja Borup Kjær Petersen, Claire Berthault, Mattias Hansson, Virginie Aiello, Latif Rachdi, Anne Grapin-Botton, Christian Honore and Raphael Scharfmann

- In diabetes, I-BET has shown to improve pancreatic beta-cell proliferation in NOD mice model
- Stimulate anti-inflammatory phenotype of macrophage

Aim

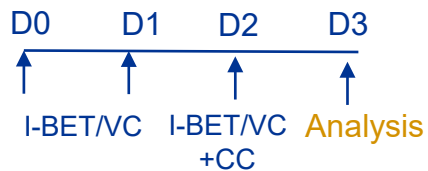- Determine the role of Bromodomain proteins in the pathogenesis of β-cell failure in diabetes

Objectives

- Test whether antagonizing Brd proteins with I-BET can protect β-cells from cytokine induced cell death and dysfunction
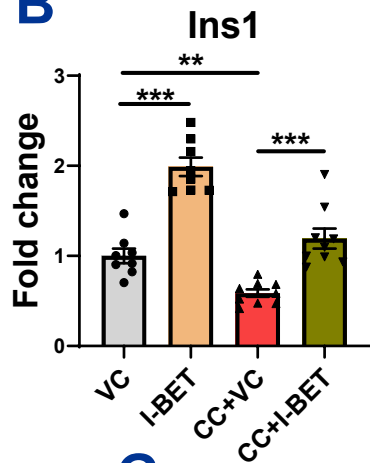- Determine its mechanism of action

University of Pittsburgh

I-BET protects against β-cell dysfunction

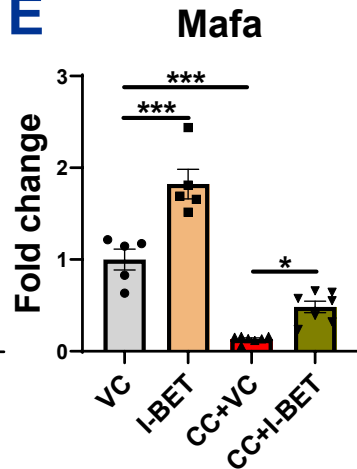**A** Timeline: D0 — I-BET/VC, D1, D2 — I-BET/VC +CC, D3 — Analysis

B Ins1 — Fold change, groups: VC, I-BET, CC+VC, CC+I-BET

C Ins2 — Fold change, groups: VC, I-BET, CC+VC, CC+I-BET

D Pdx1 — Fold change, groups: VC, I-BET, CC+VC, CC+I-BET

E Mafa — Fold change, groups: VC, I-BET, CC+VC, CC+I-BET

F Western blot: VC, I-BET, CC-8h (VC, I-BET); Pdx1 (37kda), α-Tub (50kda), Mafa (37kda), α-Tub (50kda)

G Pdx1 — Densitometry, groups: VC, I-BET, CC+VC, CC+I-BET

H Mafa — Densitometry, groups: VC, I-BET, CC+VC, CC+I-BET

University of Pittsburgh
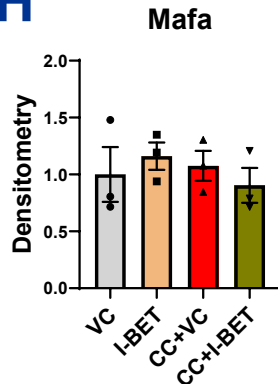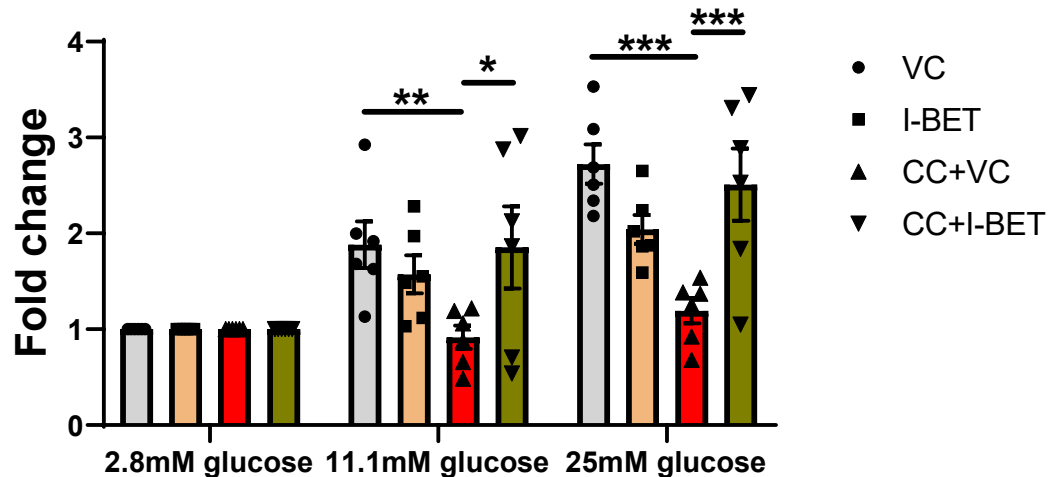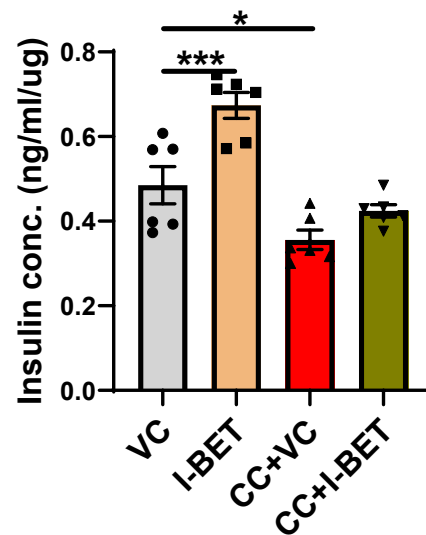
I-BET restores glucose-stimulated insulin secretion

A Glucose stimulated insulin secretion index

B Insulin content

# I-BET reverses secretion and metabolism related genes

A

CC+I-BET CC+VC I-BET VC
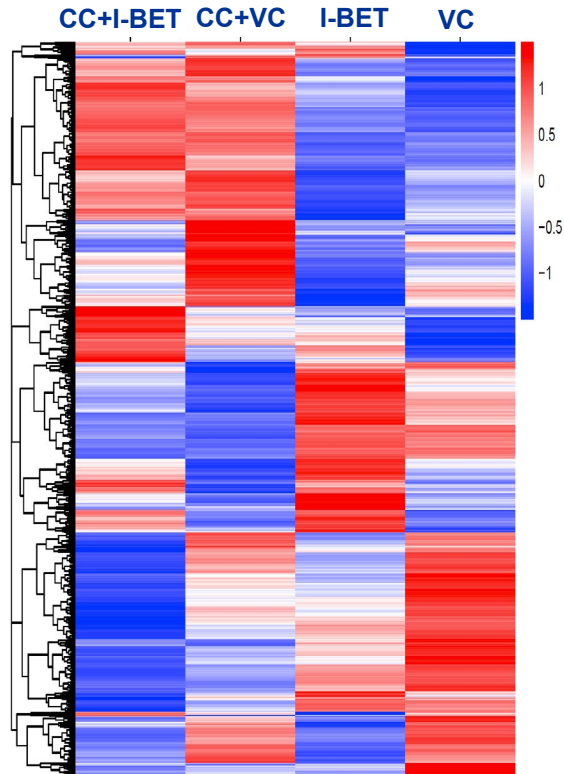
B

Pathway enrichment of differentially expressed genes among CCVC and CCIB by IPA

| Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score
Synaptogenesis Signaling Pathway	11.1	0.308	1.054
Reelin Signaling in Neurons	10.4	0.402	1.732
CXCR4 Signaling	9.63	0.353	1.54
Unfolded protein response	9.52	0.518	1.46
Type II Diabetes Mellitus Signaling	9.21	0.366	1.372
Pancreatic Adenocarcinoma Signaling	8.89	0.394	1.567
Insulin Secretion Signaling Pathway	8.8	0.307	2.194
Glioma Signaling	8.74	0.391	1.095
STAT3 Pathway	8.57	0.363	-1.151
Thrombin Signaling	8.45	0.317	2.335

I-BET decreases NF-kB pathway activation
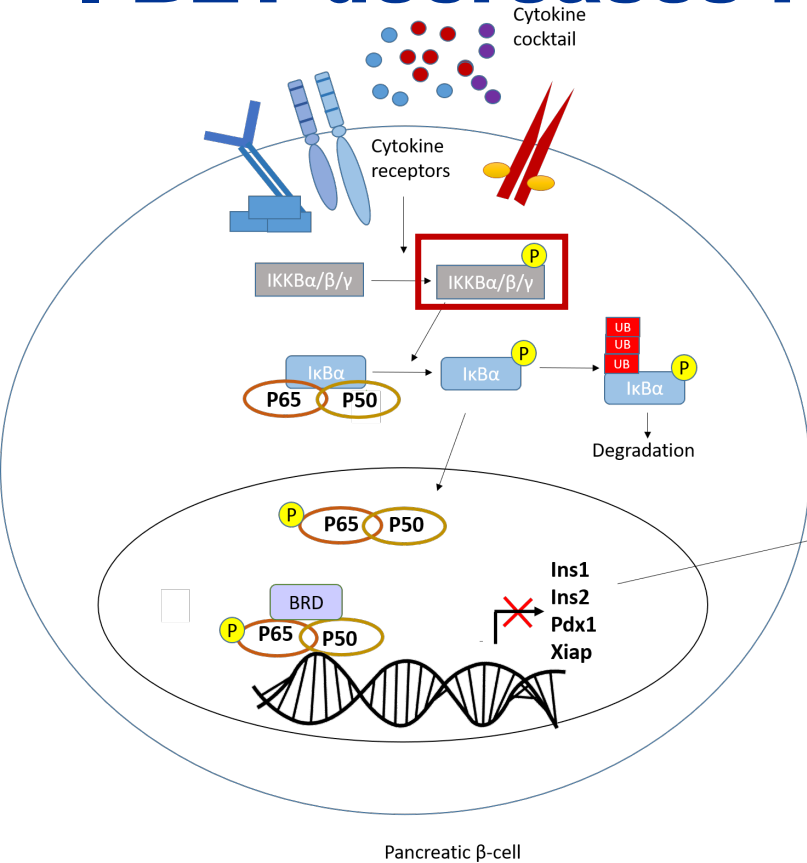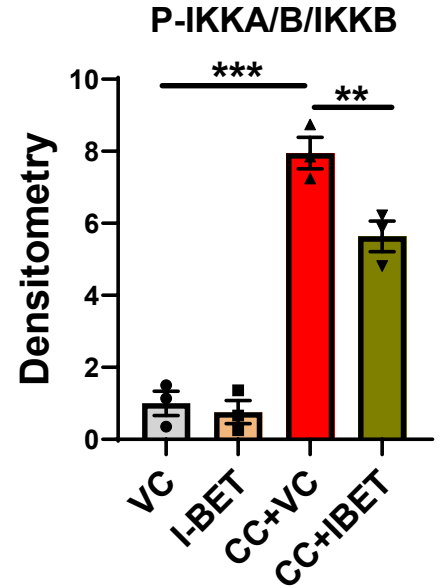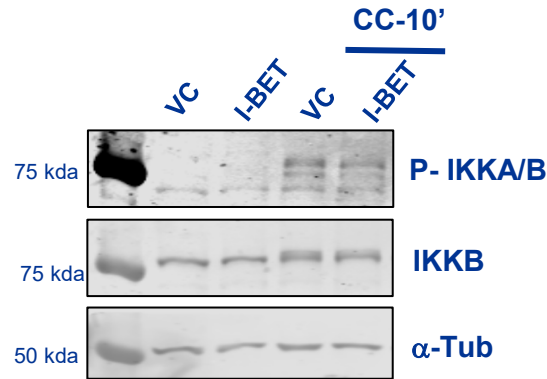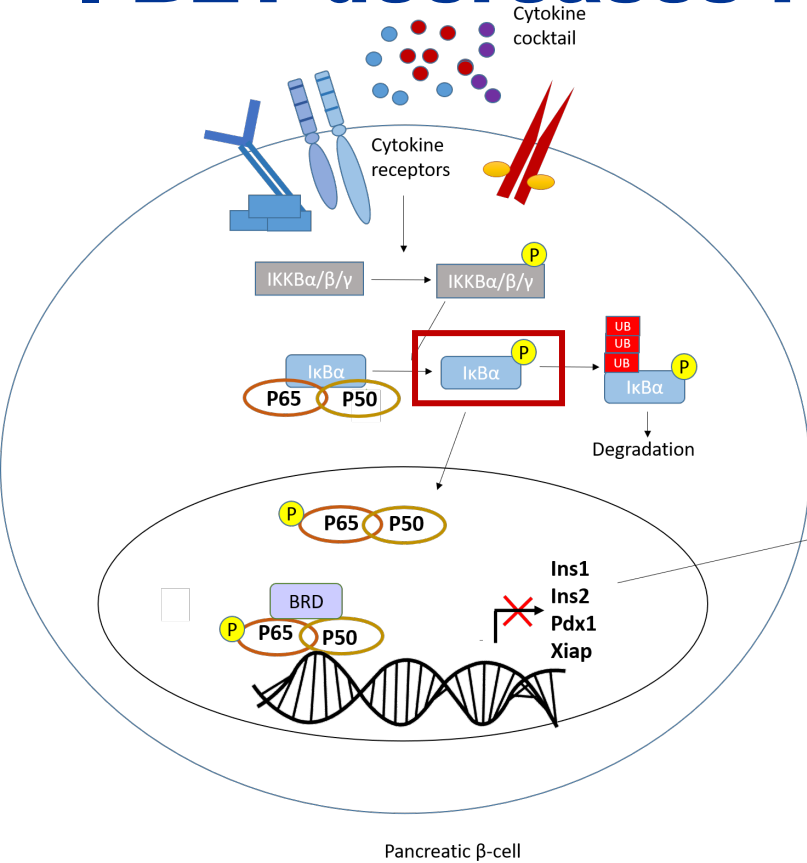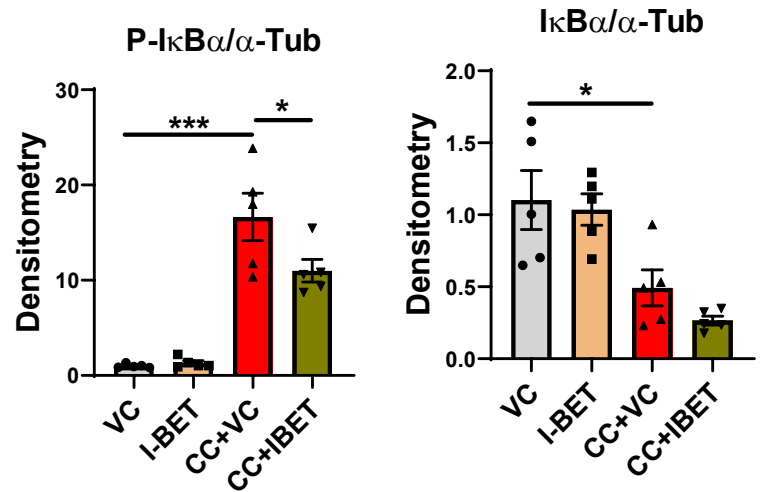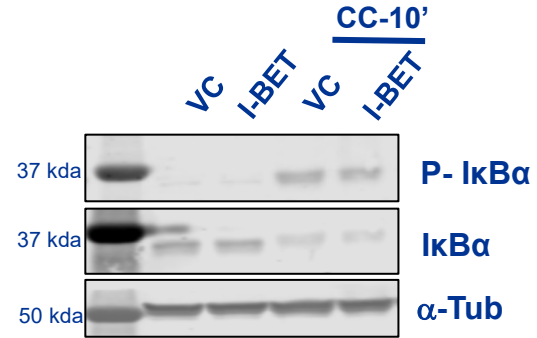
I-BET decreases NF-kB pathway activation

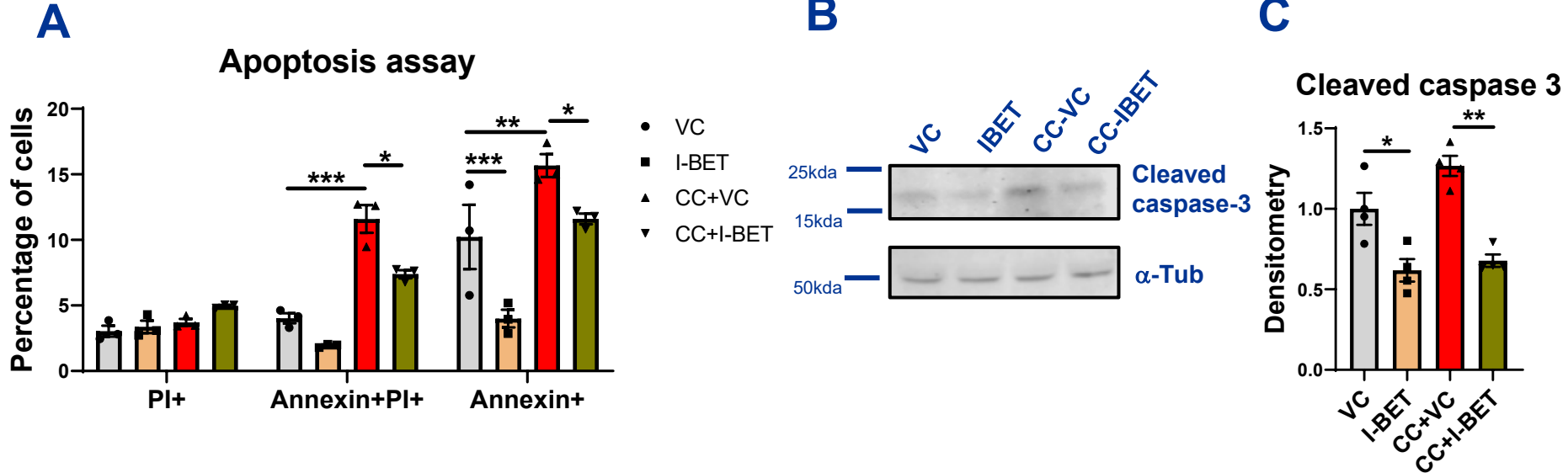# I-BET decreases NF-kB pathway activation
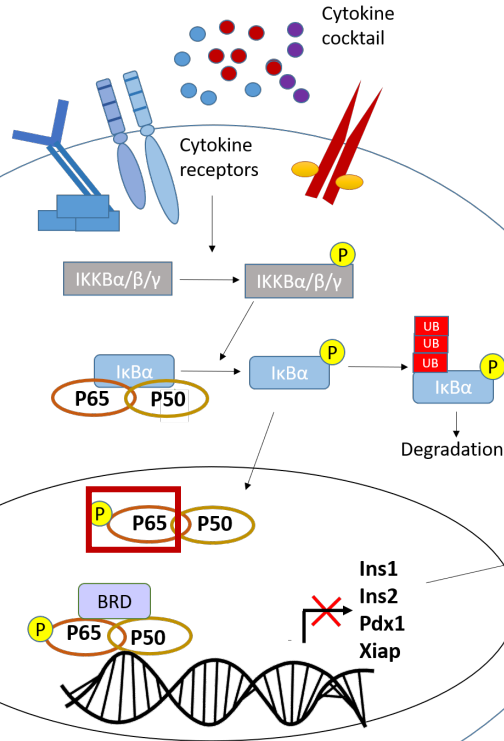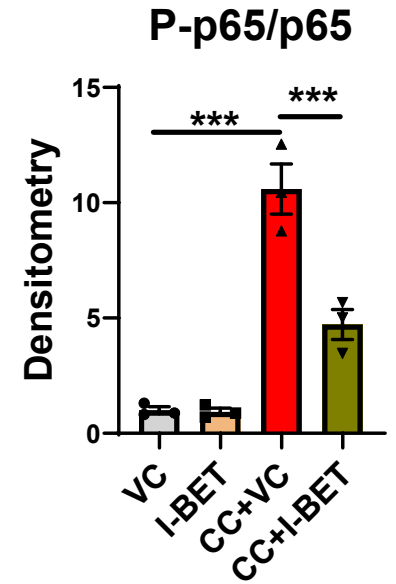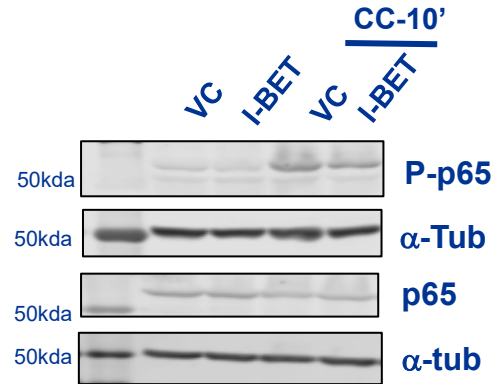
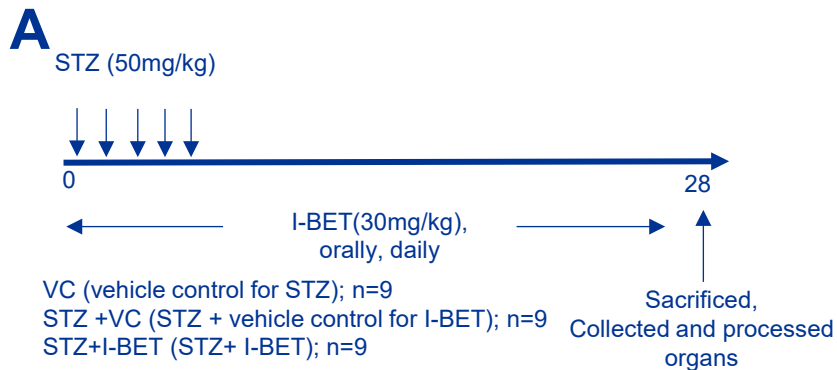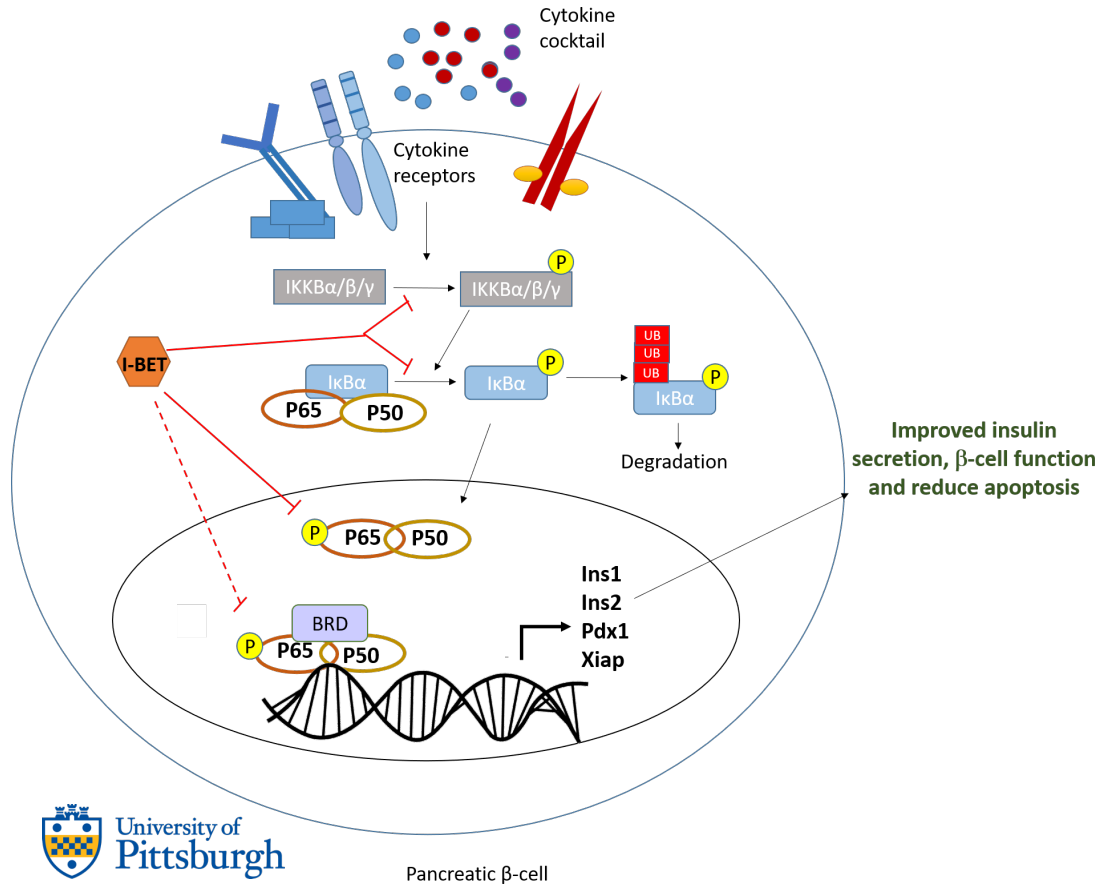# I-BET decreases cytokine induced apoptosis

I-BET protects against STZ mediated reduction in β-cell mass
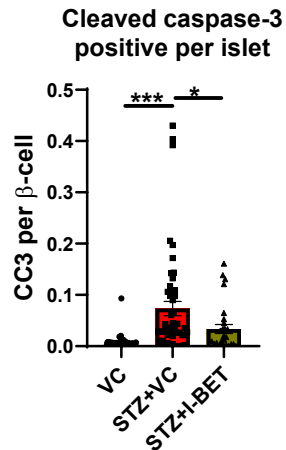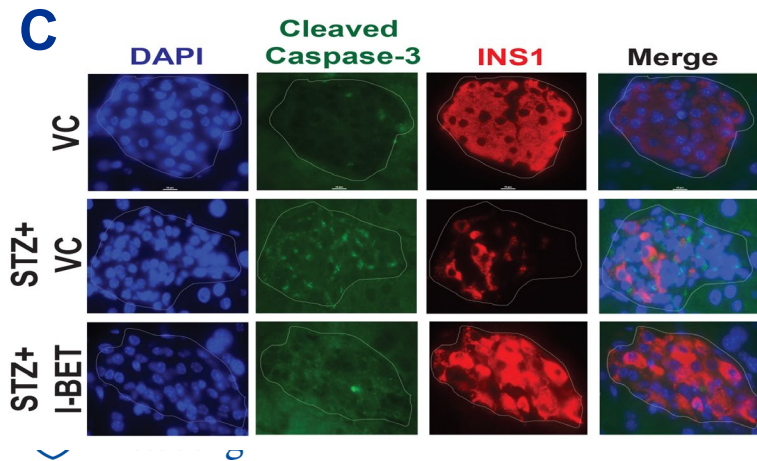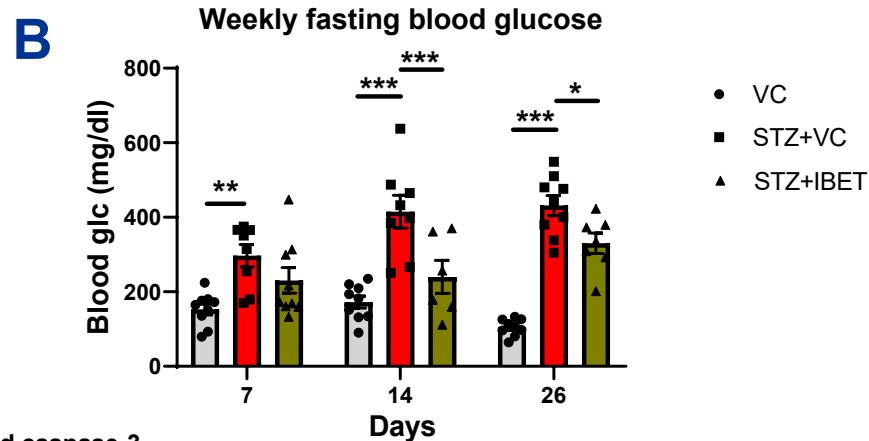
Conclusion

- I-BET protects against cytokine induced beta-cell apoptosis in vitro and STZ- in vivo model by targeting NF-kB pathway.

Acknowledgement

Yechoor Lab

Vijay Yechoor, MD

Jeong Kyung Lee, PhD

Ruya Liu, MD, PhD

Feng Li, MD, PhD

Melissa Perez-Garcia, MD

Ping Yang, MD

Moulik Lab

Mousmi Moulik, MD

Rajaganapati Jagannathan, PhD

University of Pittsburgh

Thank you