Weill Cornell Medicine

CRISPR-Mediated SATB2 Inhibition for the Treatment of Short Bowel Syndrome

Lead Investigator:

Steve (Xiaofeng) Huang, Ph.D.

Assistant Professor of Molecular Biology Research in Medicine, Medicine , Weill Cornell Medical College

Business Development Contact:

Louise Sarup

Associate Director, Business Development and Licensing

(646) 962-3523

lss248@cornell.edu

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Background & Unmet Need

- Short bowel syndrome (SBS) results from surgical resection or congenital disease of the small intestine, and leads to an inability to absorb sufficient nutrients
- Over time, the remaining small bowel and colon undergo structural and functional changes to increase nutrient absorption, but ~50% of patients will require long-term total parenteral nutrition (TPN)
- Teduglutide (GLP-2 agonist) is the only FDA-approved therapy for SBS patients who are dependent on TPN
- While teduglutide led to a significant reduction in TPN frequency, only 11% of patients were completely weaned from TPN
- **Unmet Need:** Novel treatments for SBS patients that reduce the need for TPN and improve the ability of the remaining small bowel / colon to absorb nutrients

Technology Overview

- **The Technology:** Inhibition of SATB2 as a therapeutic strategy for the treatment of SBS, exemplified using CRISPR gene therapy
- **The Discovery:** Loss of the transcription factor SATB2 transforms colonic epithelium into ileum-like tissue in mice and human colonic organoids
- Intestinal deletion of SATB2 in mice led to significant remodeling of colonic tissue, with marked changes in tissue morphology, gene expression, and cell type composition
- **PoC Data:** Of note, SATB2 inhibition led to the generation of bona fide nutrient-absorbing enterocytes, with significantly enhanced nutrient absorption in Satb2^{cKO} mice colon compared to negative control
- CRISPR-mediated deletion of SATB2 using an optimized guide RNA (gRNA) replicated the findings observed in mice, suggesting a potential therapeutic strategy for SBS patients

Inventors:
Joe Zhou

Patents:
US Application Filed

Publications:
Gu et al. *Cell Stem Cell*. 2022.
Gu et al. *Nat Commun*. 2024.

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Technology Applications

- SATB2-targeting CRISPR gene therapy using unique gRNA to restore small bowel function in SBS patients
- Cell therapy in which colonic stem cells are harvested from the patient, modified to disrupt the SATB2 gene, and then reimplanted into patients
- Gut-targeting siRNA therapy that reduces SATB2 expression

Technology Advantages

- Inhibition of SATB2 leads to durable gut remodeling that may reduce or eliminate the need for TPN
- SATB2 inhibition may be achieved through a variety of therapeutic approaches
- A single course of treatment may be sufficient to achieve lasting results

Supporting Data / Figures

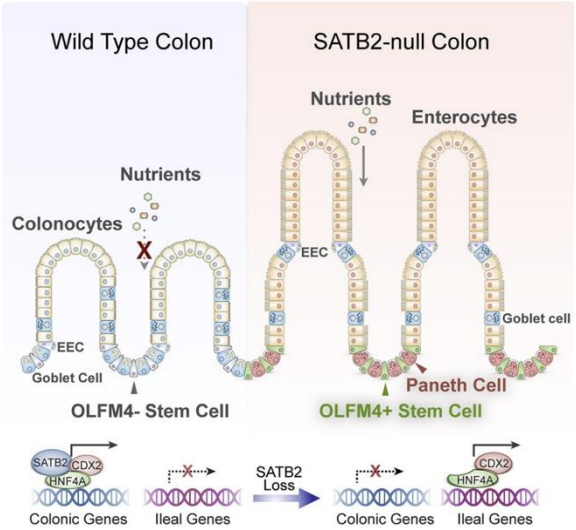

Figure 1: Loss of the transcription factor SATB2 leads to the downregulation of colonic genes and the upregulation of ileal, genes, transforming colonic tissue into ileum-like tissue that absorbs key nutrients.

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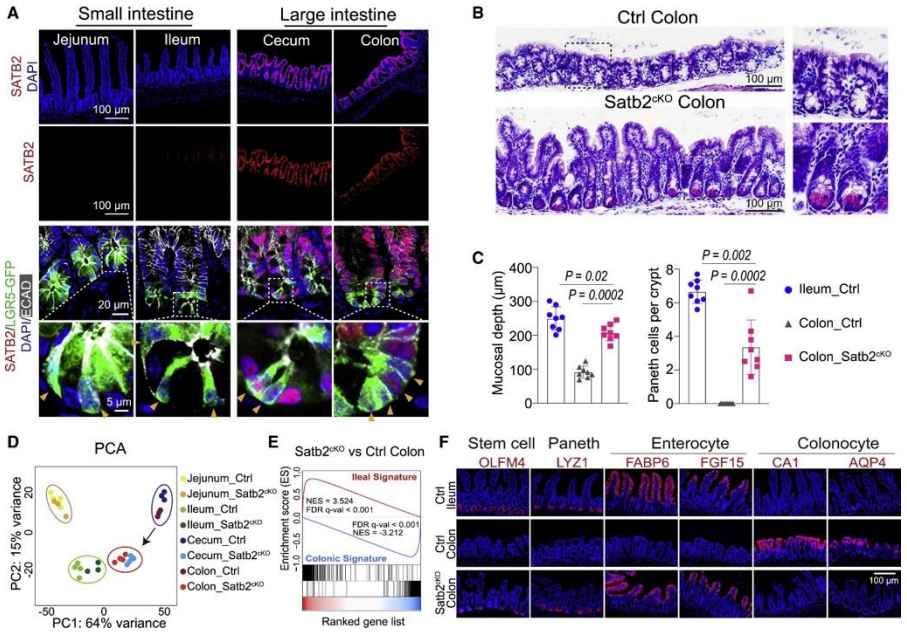

Figure 2: Conversion of large intestine mucosa to one that resembles ileal small intestine in Satb2^{cKO} mice. **A:** SATB2 is expressed in adult murine large intestinal epithelial cells but is absent in the small intestine. **B-C:** Intestinal deletion of *Satb2* in mice leads to morphological changes from colonic to ileum-like tissue. **D-E:** RNA-seq revealed a shift towards small intestine transcriptomes in colonic tissue of Satb2^{cKO} mice. **F:** Immunofluorescence demonstrated changes in cell types consistent with conversion of colonic tissue to ileum-like tissue.

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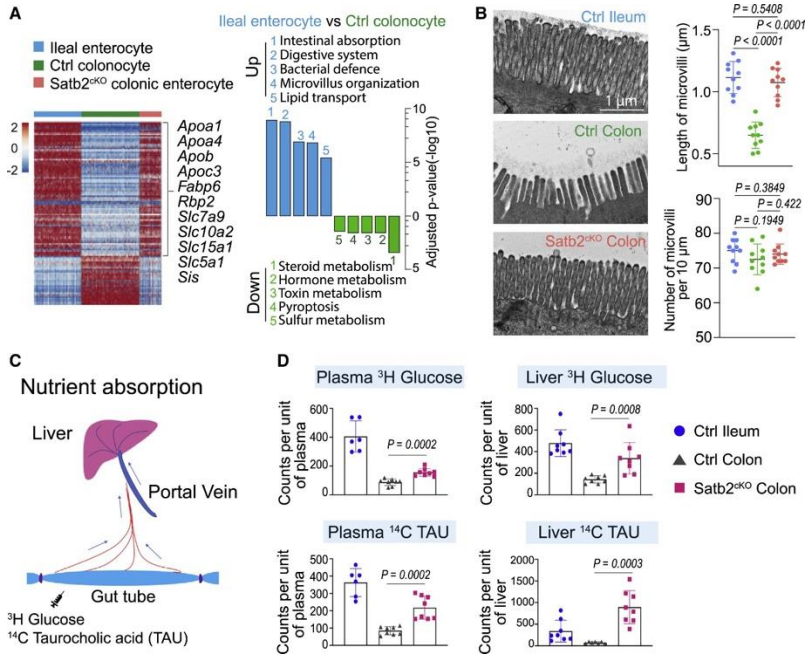

Figure 3: Generation of bona fide nutrient-absorbing enterocytes in Satb2^{cKO} colon. **A:** The scRNA profiles of Satb2^{cKO} colonic enterocytes closely resemble ileal enterocytes. **B:** The microvilli of Satb2^{cKO} enterocytes were significantly longer than those of control colon. **C:** Assay used to measure nutrient absorption. **D:** The amount of glucose and taurocholic acid absorbed is significantly higher in the Satb2^{cKO} colon compared to control colon and approaches that of a healthy ileum.

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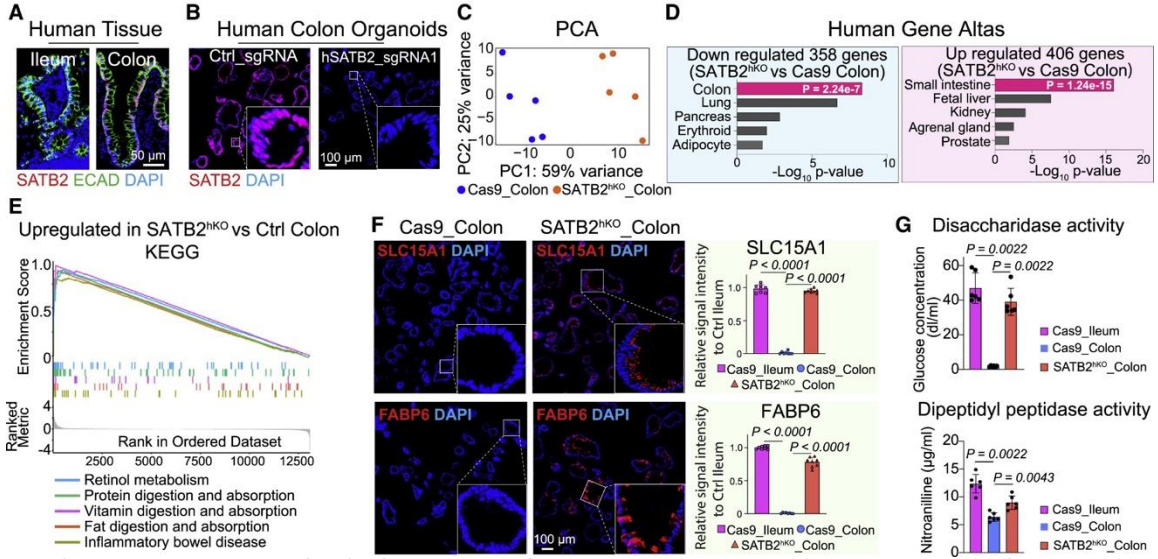

Figure 4: Colonic-to-ileal plasticity after CRISPR-mediated SATB2 deletion in human colonic organoids. **A-B:** SATB2 expression in normal tissue and human colon organoids. **C-E:** Transcriptomes of SATB2-deleted colonic organoids shifted towards the ileum. **F:** The ileal markers SLC15A1 and FABP6 were activated in colonic organoids after SATB2 loss. **G:** Significant activities of key enzymes were detected in SATB2-deleted colonic organoids.

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