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

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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
- PCT Filed

## Publications:

## Biz Dev Contact:
- Louise Sarup
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## Cornell Reference:
- D-9894
## 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\textsuperscript{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\textsuperscript{cKO} mice. F: Immunofluorescence demonstrated changes in cell types consistent with conversion of colonic tissue to ileum-like tissue.
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Supporting Data / Figures

Figure 3: Generation of bona fide nutrient-absorbing enterocytes in Satb2<sup>KO</sup> colon. A: The scRNA profiles of Satb2<sup>KO</sup> colonic enterocytes closely resemble ileal enterocytes. B: The microvilli of Satb2<sup>KO</sup> 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<sup>KO</sup> colon compared to control colon and approaches that of a healthy ileum.

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**Supporting Data / Figures**

**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-D:** 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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