THE SYNTHETIC GLYCAN KB295 OPTIMIZES MICROBIOME COMPOSITION AND FUNCTION IN ULCERATIVE COLITIS: RESULTS FROM A PROOF OF PRINCIPLE HUMAN STUDY

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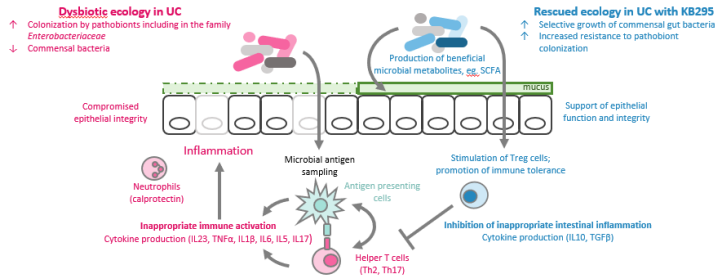
I. PREMISE

- The pathogenesis of ulcerative colitis (UC) involves genetic susceptibility, immune-mediated tissue injury, and environmental factors including disturbances of the gut microbiota, which reinforce the cycle of inflammation (Fig 1).
- Nearly all current approved therapies modify host immunity, rather than directly targeting the microbiota. Fecal microbiota transplantation provides encouraging evidence for the therapeutic potential of gut microbiome modulation.
- Gastrointestinal tract bacteria are ecologically differentiated by their ability to use specific glycans as growth substrates, making glycans a promising and safe alternative to target the microbiome.
- To explore this, we used an *ex vivo* fecal microbiota culture system to identify a synthetic glycan (KB295) with desirable microbiome-modulating activity (Fig 1).
- We also conducted a proof of principle study (NCT04508413) of safety and tolerability of KB295 in patients with UC.

FIGURE 1. TARGETING THE GUT MICROBIOTA WITH SYNTHETIC GLYCAN KB295 INHIBITS INFLAMMATION IN UC



II. METHODS

***Ex Vivo* Experiments**

- Fecal samples from 10 healthy subjects (Fig 2) were incubated anaerobically with KB295 and without (control)
- Assessed microbial metabolite production (eg, SCFA), bacterial growth (eg, culture density, gDNA-extraction yield, 16S rRNA gene copy number), and changes in taxonomic and functional metagenomic composition of fecal microbiomes

Proof of Principle Clinical Study of Patients with Mild to Moderate UC

- Open-label, single-arm study of patients with mild to moderate UC (Fig 3)
- Primary objective: assess safety and tolerability
- Secondary objectives: evaluate changes in disease-associated biomarkers of intestinal inflammation (proof of principle) and change in composition of the gut microbiome (microbial drug target engagement)
- Eligibility criteria:
  - 18-75 years of age with confirmed UC diagnosis (within 6 months)
  - Mild-to-moderate UC symptoms with 3-7 bowel movements per day within 1 week of screening and at least 4-week history of UC symptomatology before screening
  - On stable regimen of UC medication for 2 weeks before randomization, if receiving UC medication

FIGURE 2. *EX VIVO* CULTURE SYSTEM TO ASSESS BIOLOGICAL ACTIVITIES OF SYNTHETIC GLYCANS

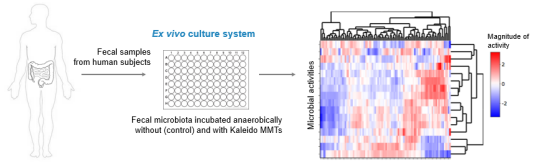
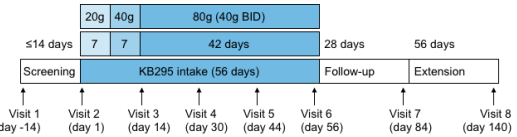
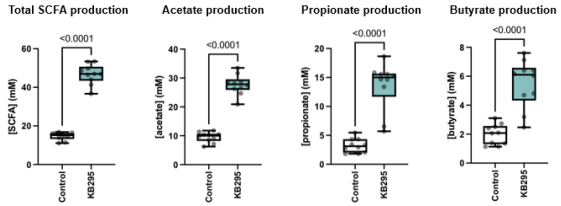


FIGURE 3. K030 STUDY DESIGN



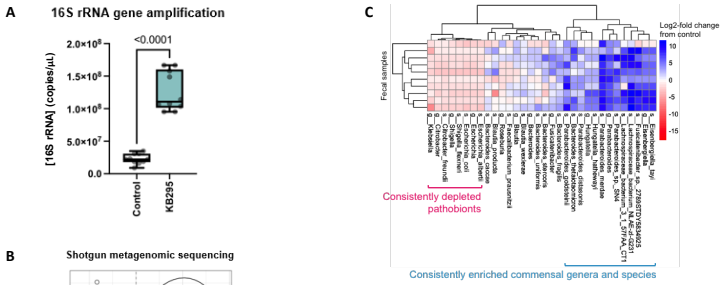
III. *EX VIVO* PRECLINICAL RESULTS

FIGURE 4. INCREASED PRODUCTION OF SCFA IN FECAL SAMPLES FROM HEALTHY SUBJECTS INCUBATED WITH KB295 IN AN *EX VIVO* CULTURE SYSTEM



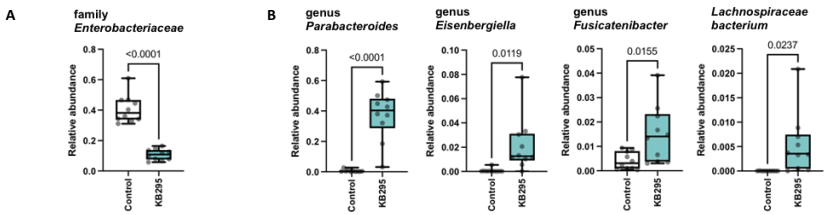
- KB295 was consistently fermented by fecal microbiota from different subjects
- This fermentation yielded a balanced SCFA production profile, suggesting KB295 supports the growth and metabolism of a diverse set of commensal bacteria (Fig 4)

FIGURE 5. *EX VIVO* GROWTH AND CHANGE IN TAXONOMIC COMPOSITION OF FECAL MICROBIOTA WITH KB295



- KB295 supported consistent and robust growth of fecal microbiota in samples from healthy subjects (Fig 5A)
- Metagenomic sequencing revealed that KB295 shifted the taxonomic composition of fecal microbiomes. Ellipse represents 95% CI (Fig 5B)
- KB295 consistently enriched a phylogenetically diverse set of commensal taxa (eg, the genera *Parabacteroides* and *Eisenbergiella*) and depleted pathobiont genera (eg, *Escherichia*, *Klebsiella, Shigella, Citrobacter*) belonging to the family *Enterobacteriaceae* (Fig 5C)

FIGURE 6. *EX VIVO* DEPLETION OF PATHOBIONTS AND ENRICHMENT OF DIVERSE COMMENSAL BACTERIA WITH KB295



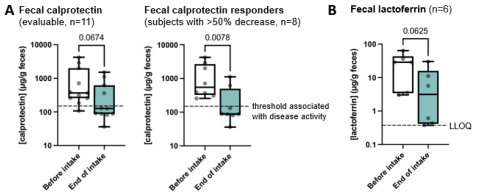
- KB295 decreased the relative abundance of the pathobiont family *Enterobacteriaceae* (Fig 6A)
- KB295 increased the relative abundance of the genus *Parabacteroides*, a group of propionate-producing bacteria. KB295 also enriched butyrate-producing bacteria or close relatives of butyrate-producing bacteria in the family *Lachnospiraceae* (Fig 6B)

IV. PROOF OF PRINCIPLE CLINICAL STUDY RESULTS

Safety and Tolerability

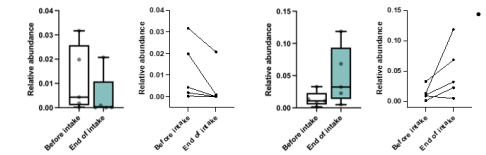
- No patient reported study product-emergent serious adverse events
- Two patients discontinued the study (1 UC exacerbation, 1 family reasons)
- Four patients reduced KB295 dose during the study; 3 patients completed the study
- The most frequently occurring adverse events were expected and consistent with UC disease or study product characteristics (eg, change in bowel habits, flatulence, headache)

FIGURE 7. REDUCTION IN 2 BIOMARKERS OF INTESTINAL INFLAMMATION AFTER KB295 INTAKE



- Median decrease of fecal calprotectin (FCP) of 69.0% across 11 evaluable patients. FCP decreased by >50% in 8/11 patients. The median FCP decrease was 74.1% in responders (Fig 7A)
- Median decrease of fecal lactoferrin of 86.0% across 6 patients with data available (Fig 7B)

FIGURE 8. DEPLETION OF ENTEROBACTERIACEAE PATHOBIONTS AND ENRICHMENT OF COMMENSAL *PARABACTEROIDES*



- Median relative abundance of the pathobiont family *Enterobacteriaceae* decreased across 5 patients with data available (Fig 8A)
- Median relative abundance of the commensal genus *Parabacteroides* increased across 5 patients, with relative abundance increasing in 4 of 5 patients (Fig 8B)

V. CONCLUSIONS

- The gut microbiome is an attractive treatment target for the underlying cause of UC. It may be possible to treat UC by rescuing the dysbiotic intestinal ecology and breaking the cycle of inflammation
- Synthetic glycan KB295 enriches diverse beneficial commensal microbiota and depletes harmful pathobionts thought to propagate the cycle of inflammation. Metabolic stimulation of commensal microbiota restores balanced SCFA production, which is expected to promote intestinal homeostasis
- Decreases in disease-associated biomarkers of intestinal inflammation in our clinical study establish a proof of principle for synthetic glycan modulation of gut microbiome
- These results, along with the proven safety and tolerability of KB295, provide insight into the potential of this strategy in patients with UC

VI. DISCLOSURES & ACKNOWLEDGMENTS

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