Consumption of Uric Acid in the Gastrointestinal Tract with Engineered E. coli Nissle as a Potential Treatment for Gout
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INTRODUCTION
Elevated circulating levels of uric acid (UA) are associated with an increased risk of developing gout and other chronic diseases such as chronic kidney disease (CKD), type 2 diabetes (T2D), and cardiovascular disease (CVD). Despite advancements in treatment options, gout is often poorly managed. In healthy individuals, about 70% of circulating UA is metabolized and excreted by the kidneys, while the remaining 30% is mainly excreted with the feces or further metabolized by the gut microbiota. Not surprisingly, circulating UA is commonly elevated in subjects with impaired kidney function. Furthermore, studies have found that gut microbiota dysbiosis can contribute to the reduced capacity for host UA degradation in gout patients. In light of these findings, we engineered a therapeutic probiotic, SYN-GOUT, to degrade UA within the GI tract for the treatment of gout.

We have successfully demonstrated the utility of using engineered probiotics for metabolic diseases. For example, probiotic bacterium E. coli Nissle (EcN) 1917 was engineered to treat phenylketonuria (PKU)1. The PKU strain is currently being evaluated in clinical trials.

METHODS
- SYN-GOUT is a prototype strain with engineered UA degradation components that are plasmid-based.
- SYN-B2081 is a clinic-ready strain with engineered pathways integrated into the chromosome of E. coli Nissle and all FDA-required biocontainment pieces in place.
- SYN-GOUT in vitro activity was assessed in minimal culture media.
- Male C57/B6 mice were used for the enterocirculation experiments.
- The in vivo activity of the candidate strain SYN-B2081 was determined in non-human primates (Charles River Laboratories, Shrewsbury, MA).

RESULTS
SYN-GOUT consumes UA in vitro, and its activity remains high under low O2 conditions.

CONCLUSIONS
- SYN-GOUT consumed UA in vitro, and was active under hypoxic conditions.
- SYN-B2081 was safe and well-tolerated in NHPs; furthermore, it significantly lowered plasma and urinary levels of UA, indicative of its robust activity in vivo.
- SYN-B2081 could be an effective alternative for the treatment of gout, especially in individuals with compromised kidney function.

REFERENCES

Disclosures
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