Development of a Synthetic Biotic, SYNB8802, for the treatment of Enteric Hyperoxaluria

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Background

Oxalate arises from a variety of dietary and endogenous sources and is an end-product of human metabolism. Enteric Hyperoxaluria (EH) is caused by excessive absorption of dietary oxalate due to an underlying malabsorptive GI disease. Such as one of the most popular weight-loss surgeries in the United State, Roux-en-Y gastric bypass, as well as short bowel syndrome. Oxalate is associated with recurrent kidney stones, nephrolithiasis, and progressive renal damage. In severe cases untreated EH can progress to systemic oxalosis, a condition in which oxalate accumulates in joints, bones, eyes, heart, and other organs.

There are currently no approved treatments for EH. Disease management aims to decrease the risk of recurrent kidney stones and progressive disease by limiting the intake of dietary oxalate and fat, increasing dietary calcium intake, and maintaining adequate fluid intake. However, the efficacy of dietary treatments alone is limited and there is an unmet medical need for novel therapies. We describe here the development of SYNB8802, a Synthetic Biotic medicine engineered to consume oxalate within the GI tract and convert it to nontoxic metabolites as a novel treatment approach to EH.

Methods & Results

Strain Design

SYNB8802 is a genetically engineered, non-colonizing strain of Escherichia coli Nissle 1917 (EcN). It was developed by engineering a pathway for oxalate degradation derived from the human commensal microorganism Oxalobacter formigenes including one gene from Saccharomyces cerevisiae to form a probiotic strain EcN. (Figure 1) SYNB8802 activity was assessed in media containing 13C2-oxalate. While no oxalate consumption or fermentation production was observed for control EcN, SYNB8802 degraded 13C2-oxalate in a linear fashion over the course of 60 min and concurrently produced 13C-labeled formate. (Figure 2)

In vitro simulation (IVS)

To estimate SYNB8802 activity under conditions representing the GI lumen, an in vitro simulation (IVS) system was developed, comprising a series of incubations in media representing human stomach, small intestine, and colon compartments by simulating luminal pH and oxygen, gastric and pancreatic enzymes, and GI transit times. The rate of oxalate degradation was estimated in each simulated compartment (Figure 3). Oxalate consumption was highest in simulated gastric fluid (SGF) (1.35±0.04 and 1.52±0.08 µmol oxalate/1011 cells) at one and two hours post incubation, respectively and remained at similar levels after 1h incubation in simulated small intestinal fluid (SIF). Oxalate consumption decreased to 0.88±0.04 µmol oxalate/1011 cells after 2h incubation in SIF. SYNB8802 activity further diminished to 0.2±0.14 µmol oxalate/1011 cells in the completely anaerobic conditions of simulated colonic fluid (SCF), where it remained relatively stable over the 48h incubation period. These data suggest that SYNB8802 has the potential to metabolize oxalate throughout the human GI tract.

Conclusions

• SYNB8802 is engineered to metabolize oxalate to formate and CO2.
• Development of IVS shows differential activity of SYNB8802 based on GI compartment.
• Urinary oxalate could be elevated in NHPs using a dietary model.
• SYNB8802 leads to a decrease in UOx in dietary induced Hyperoxaluria in NHPs in a dose-dependent manner.
• Preclinical data support full clinical development.
• Safety and tolerability of SYNB8802 is being explored in a Phase 1/2a study (NCT04629170).
• Part B seeking proof-of-concept in Roux-en-Y patients is open for enrollment.

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