A Synthetic Biotic, SYNB8802, Lowers Urinary Oxalate in Preclinical Models and Healthy Volunteers with Induced Dietary Hyperoxaluria

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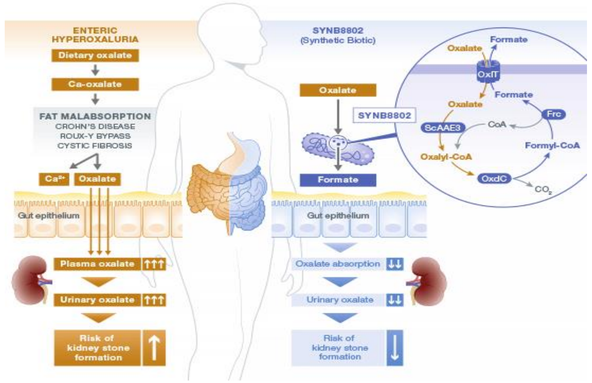
Introduction

- Oxalate is an end-product of human metabolism and is present in a variety of common foods, including green vegetables, nuts, grains, fruits and chocolate.
- Enteric hyperoxaluria (EH) is a metabolic disorder commonly observed in patients with underlying GI disease related to fat malabsorption, such as IBD, or surgical interventions such as Roux-en-Y.
- Chronic EH is associated with recurrent kidney stones, nephrocalcinosis, and chronic kidney disease, which can lead to kidney failure and the need for kidney transplantation.
- Untreated EH can progress to systemic oxalosis, a condition in which oxalate accumulates in joints, bones, eyes, heart, and other organs.
- SYNB8802 is an engineered probiotic, derived from *Escherichia coli* Nissle and designed to degrade oxalate.

Synopsis



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Conclusion

- SYNB8802 is an engineered bacterial therapeutic capable of consuming oxalate in the gut and lowering urinary oxalate and may be as a potential treatment for EH.
- Oral administration of SYNB8802 leads to significantly decreased UOx excretion in non-human primates.
- Mathematical modeling using *in vitro* and *in vivo* preclinical data predicts clinically meaningful lowering of UOx excretion in EH patients.
- SYNB8802, was safe and well-tolerated in a Ph I study in healthy volunteers (HV).
- SYNB8802 led to a consistent and significant dose-related reduction of UOx and fecal oxalate in HVs on a high oxalate diet, confirming strain ability to access dietary oxalate from within the gut.

Results

SYNB8802 degrades oxalate *in vitro*

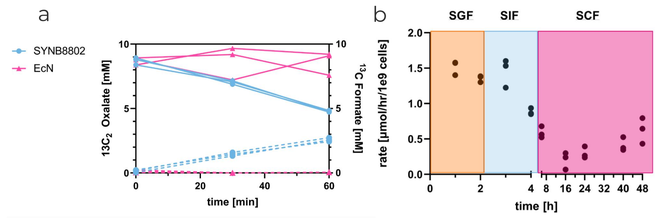


Fig. 1a. SYNB8802 (blue) metabolizes oxalate (solid lines) and produces formate (dotted lines).. Wild type Nissle (pink) is unable to consume oxalate. **b**. In vitro simulation (IVS) of SYNB8802 transitioning through simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid (SCF). Three biological replicates were run and plotted separately.

In silico simulation model schematic and simulated UOx lowering subsequent dietary oxalate removal by SYNB8802

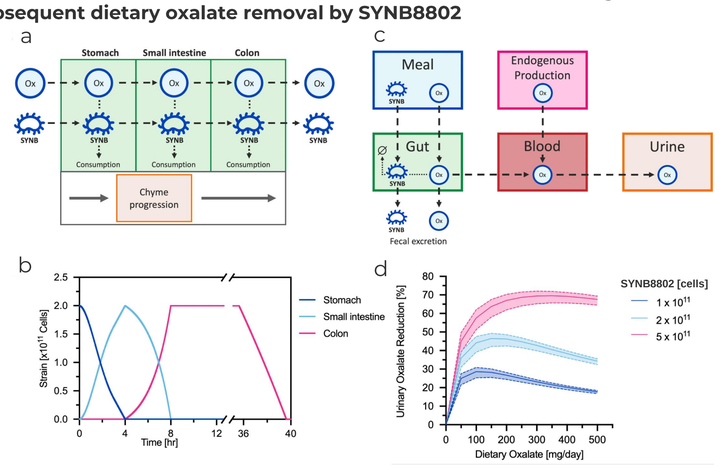
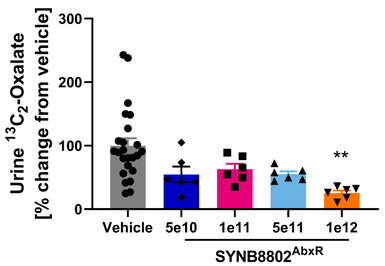


Fig. 2a. Oxalate and SYNB8802 transit through the stomach, small intestine, and colon are modeled according to a physiological function of chyme progression. **b**. SYNB8802 begins in the stomach and empties into the small intestine during the first 4 h post-meal. From 4 to 8 h post-meal, SYNB8802 empties from the small intestine into the colon. **c**. ISS connects invitro strain activity knowledge to host and disease biology. **d**. Simulated UOx reduction for EH patients after 5 days dosing with 1×10^{11}, 2×10^{11}, and 5×10^{11} SYNB8802 cells TID as a function of dietary intake of oxalate. Solid curves represent simulations under a baseline assumption of increased dietary oxalate absorption in EH patients (4× healthy absorption). Shaded regions represent a simulated range of increased dietary oxalate absorption (two simulations: 3× healthy absorption and 5× healthy absorption).

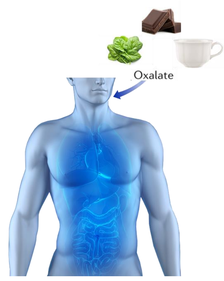
SYNB8802 lowers UOx *in vivo* in preclinical models of acute Hyperoxaluria

Fig. 3a. Non-human primate (NHP) model development study design. **b**. The y-axis shows UOx normalized to creatine. X-axis shows baseline UOx levels after overnight fast, and UOx measured 6 h post-administration of either a spinach preparation (triangle, pink) or water (circle, blue) (n = 6 for each group).

Fig. 3c. Urinary recovery of oxalate in NHPs. The y-axis shows change in UOx from vehicle control. The x-axis shows vehicle (control, grey) and increasing doses of SYNB8802^{AbxR} (n = 24 for vehicle, n = 6 for treatment groups). **d**. Urinary recovery of $^{13}C_2$ oxalate in NHPs. The y-axis shows change in urinary $^{13}C_2$-oxalate from vehicle control. The x-axis shows vehicle (control, grey) and increasing doses of SYNB8802^{AbxR} (n = 24 for vehicle, n = 6 for treatment groups).



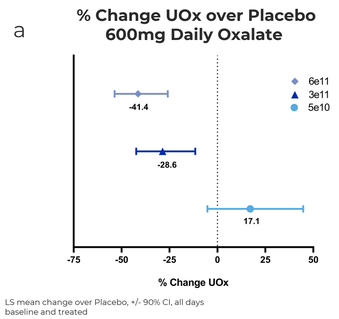
SYNB8802 was safe and well-tolerated in healthy volunteers



	Randomized to SYNB8802 (N=6) or placebo (N=3)	
Diet Run-in 4 days	Optional Dose-ramp Up to 4 days	TID Treatment Period 5 days
Controlled diet and daily 24-hr UOx collection		

Fig. 4. Study design. 4-day high oxalate diet run in, followed by dose ramp and a three times daily (TID) treatment period.

Dose-related reduction of urinary and fecal oxalate at well-tolerated doses



LS mean change over Placebo, +/- 90% CI, all days baseline and treated

Fig. 5a. SYNB8802 showed dose-related reduction of UOx and was generally well tolerated in healthy volunteers. No serious or systemic adverse events were observed. Most frequent AEs mild or moderate, transient, and GI-related. A dose-ramp improved tolerability.

Fig. 5b. SYNB8802 led to dose-related reduction of fecal oxalate confirming that changes in UOx were related to consumption of oxalate by SYNB8802 in the GI tract. Total fecal oxalate was quantified using a high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) method