Summary

- Synthetic Biotics are live, non-pathogenic E. coli Nissle (EcN) bacteria designed with drug-like properties.
- Our synthetic biology platform allows the engineering of probiotic strains with versatile and disparate modalities that can influence inflammatory pathways in vivo, including:
  - Short chain fatty acid and lactate production that can alter inflammatory signaling
  - Aryl hydrocarbon receptor (AHR) metabolites to reduce inflammation and enhance mucosal healing in preclinical IBD models
  - Production and secretion of human proteins, including cytokines
- These innovations are key to the development of gut-targeted therapeutics for inflammatory-based pathologies such as Inflammatory Bowel Disease (IBD).

Engineering EcN to produce Short Chain Fatty Acids and Lactate

A. Glucose
B. Engineering Metabolic Pathway Flux in EcN
C. Increase over wild type
D. Anti-CD3
E. FoxP3
F. IL-10
G. Glucose
H. Pyruvate
I. Acetate
J. Lactate
K. Propionate
L. Succinate
M. Phosphorpyruvate
N. Lactate
O. Ethanol
P. Acetate
Q. Arabinobiose
R. Colonic
S. Bacterial

Schematic of SFCA metabolic pathways that can be altered for SCFA production. Red Xs denote possible genes modified for a butyrate producing strain. C. In vitro measurement of excess SCFA produced from engineered EcN strains as compared to wild type EcN. Dark blue var denotes EcN-Lac.

Mouse study design. 1e10 CFU EcN-Lac were gavaged into wild type mice daily for 3 days prior to anti-CD3 treatment. After 24 hrs, mice were sacrificed and colons were harvested.

hIL22 secretion by EcN induces IL22 dependent gene expression in vivo

A. WT EcN
B. EcN
C. EcN-IL-22

Development and characterization of EcN-IL-22, an integrated hIL22 Secreting Strain

A. EcN-IL-22
B. hIL-22 Secretion
C. hIL-22 Secretion

Fig. 1. A. Schematic of EcN-Lac. The lactate producing strain was engineered by removing the ptp gene from the EcN lac gene under the control of an inducible promoter. B. Schematic of SFCA metabolic pathways that can be altered for SCFA production. Red Xs denote possible genes modified for a butyrate producing strain. C. In vitro measurement of excess SCFA produced from engineered EcN strains as compared to wild type EcN. Dark blue var denotes EcN-Lac.

D. Mouse study design. 1e10 CFU EcN-Lac were gavaged into wild type mice daily for 3 days prior to anti-CD3 treatment. After 24 hrs, mice were sacrificed and colons were harvested.

E. % of FoxP3+ Tregs present in the colon.
F. Gene expression in the colon measured by qPCR and normalized to Gapdh.

Presented at the Precision Medicine in IBD meeting, Boston, MA, Jan 30 – Feb 1, 2023

SYNTHETIC BIOTICS AS A VERSATILE PLATFORM TO TREAT INFLAMMATORY BOWEL DISEASE

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DISCLOSURES: This study was funded by Synlogic Inc.