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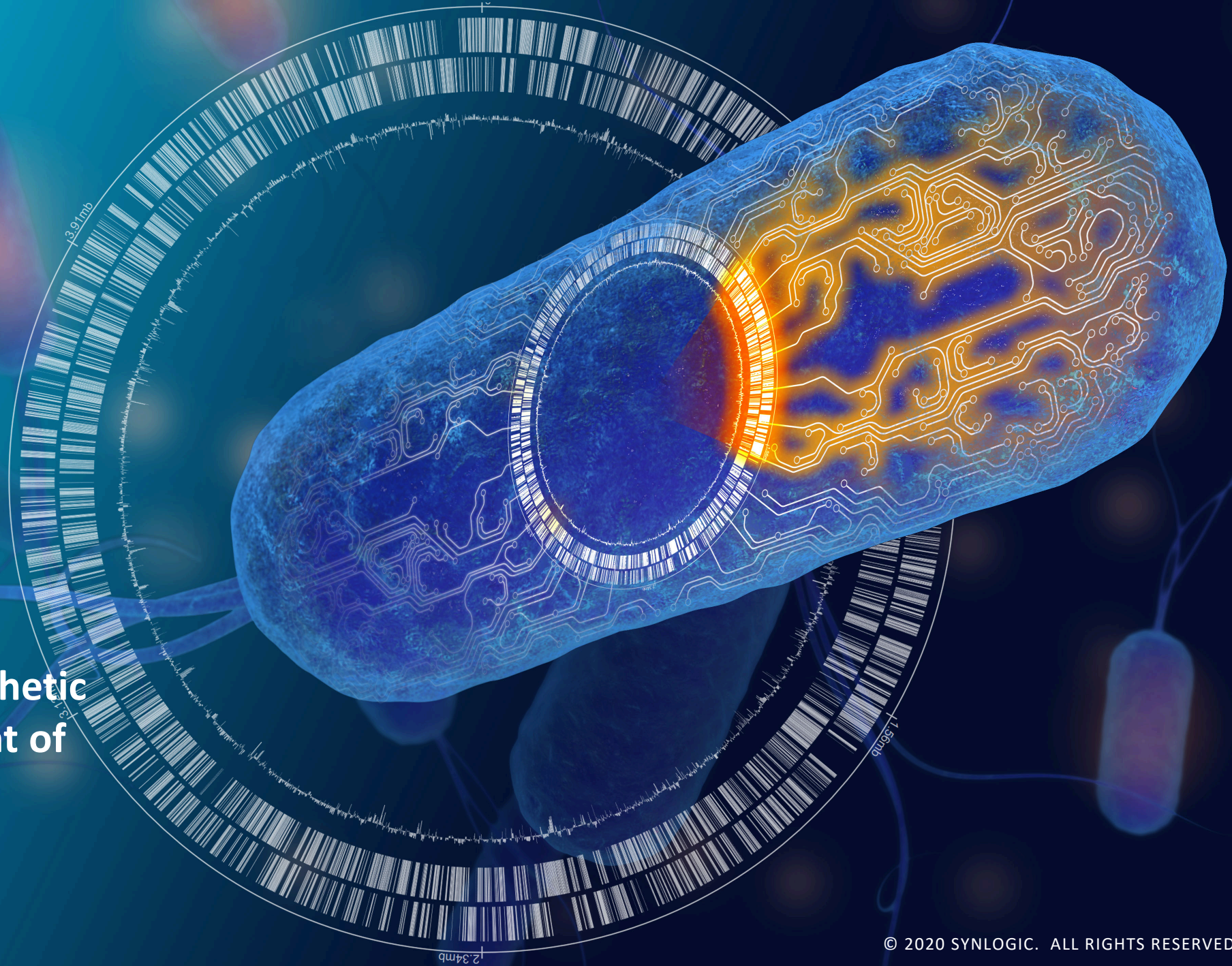
DESIGNED FOR LIFE



Development of a Synthetic Biotic for the Treatment of Enteric Hyperoxaluria

Mark Charbonneau
Synlogic, Inc.

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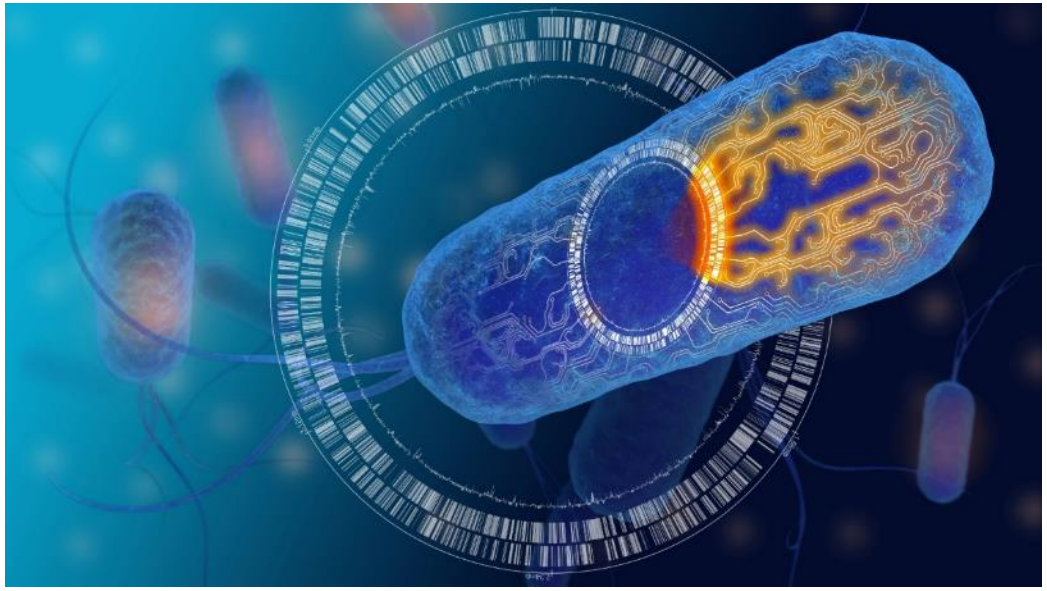
Synthetic Biotic Therapeutics: A New Class of Medicines

Bacteria and Humans Co-Evolved and Co-Exist

We Rationally Design Bacteria to Provide Clinical Benefit

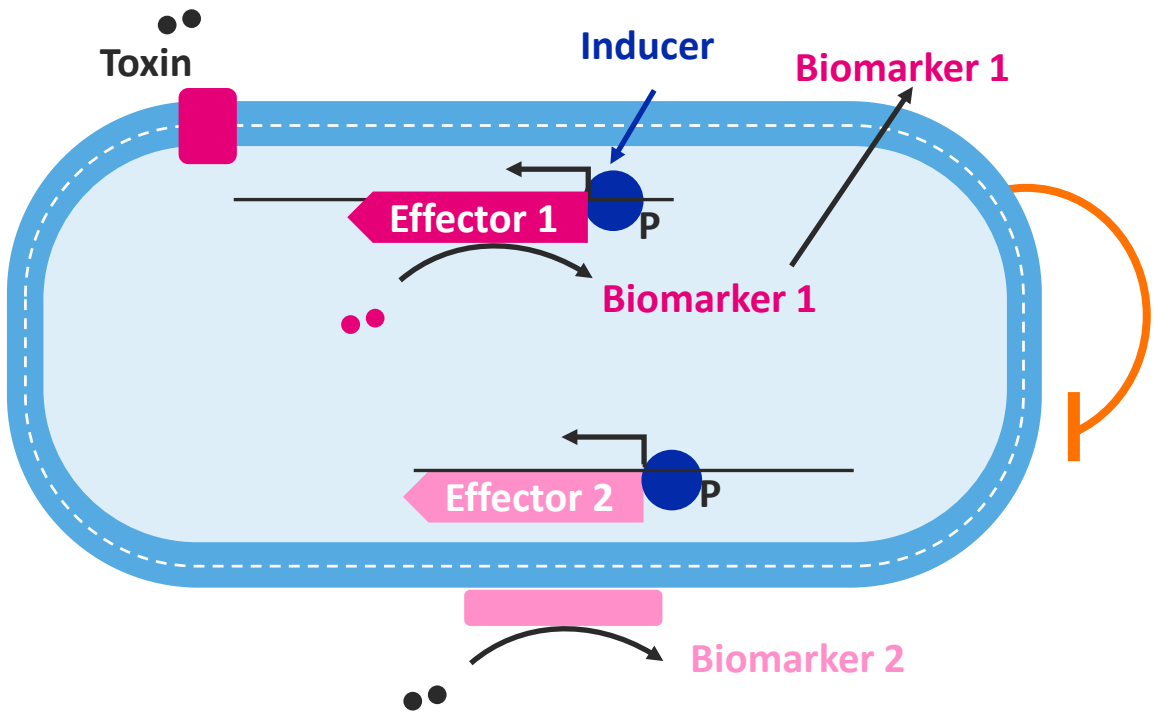


The Result Is Therapeutic Bacteria With Programmable Therapeutic Mechanisms

Library of Parts To Generate Prototypes

Synthetic Biology Library Rapidly Generates Drug Candidates

Component	*Benefit*
Bacterial Chassis	Probiotic *E. coli* Nissle 1917: Decades of human use & safety data
Effectors	Produce therapeutic benefit and generate biomarkers
Switch	Inducer-promoter pair: Controls gene expression *in vivo*
Biocontainment	Auxotrophies: Prevent growth within or external to the body



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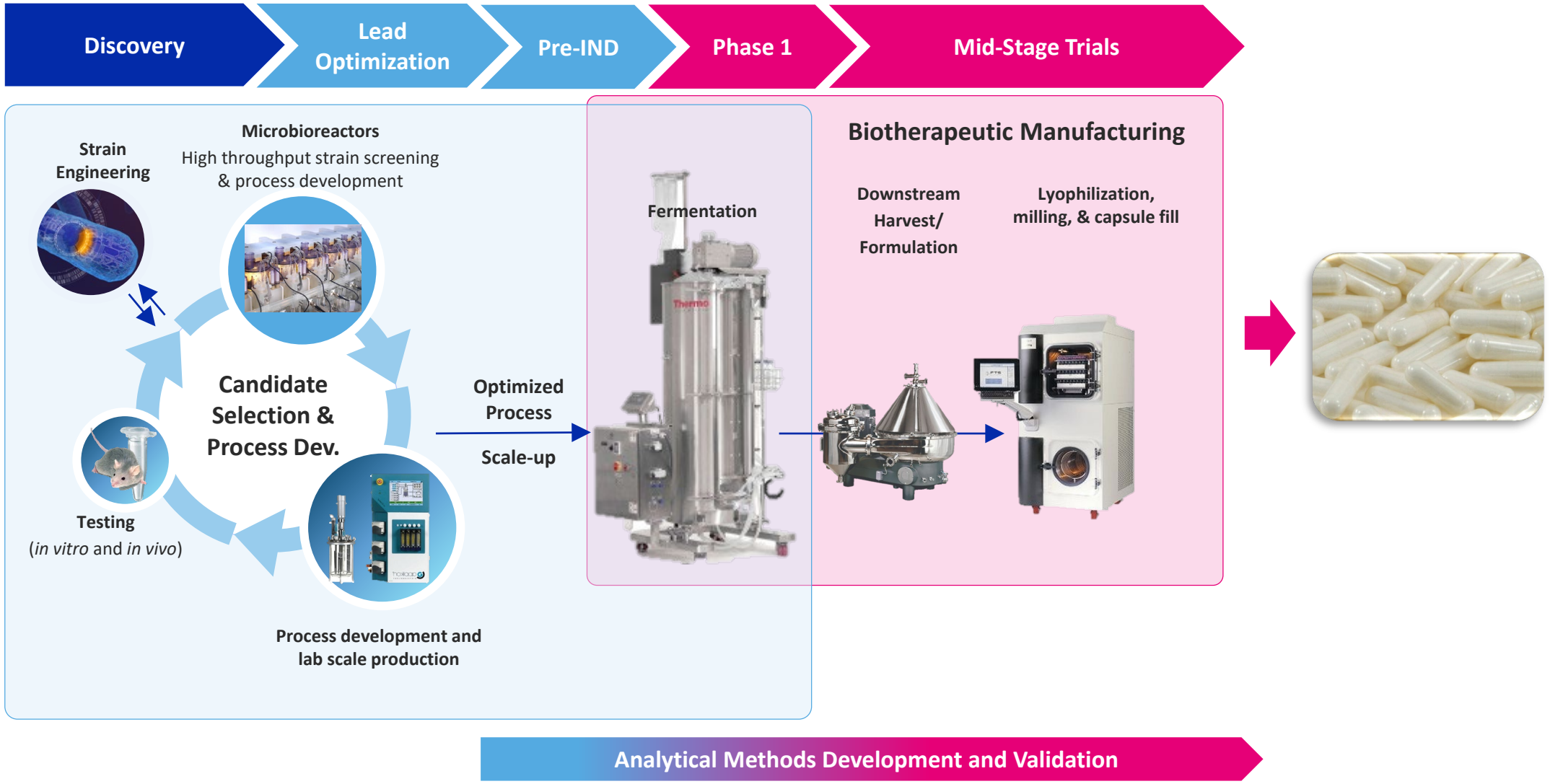
Synlogic Internal GMP Manufacturing Capabilities

In-house Process Development and Clinical Manufacturing for Early & Mid-Stage Trials



Building a Diverse Portfolio of Synthetic Biotic Medicines

Platform for Clinical Benefit Across Multiple Disease States

Internal Focus:

Metabolic Diseases

Consumption of toxic metabolites from the GI tract

External & Collaboration Focus:

Immunomodulation

Immunology and oncology: Leveraging the ability of bacteria to **interact** with the immune system

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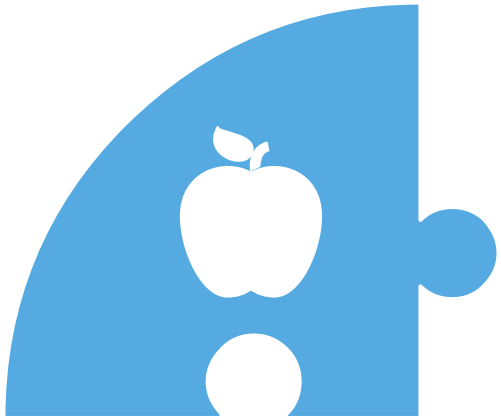
Why **Metabolic Diseases** For Synthetic Biotic Medicines?

Validated Biology

Diseases with known pathophysiology. Dietary intervention provides support for GI-based approach



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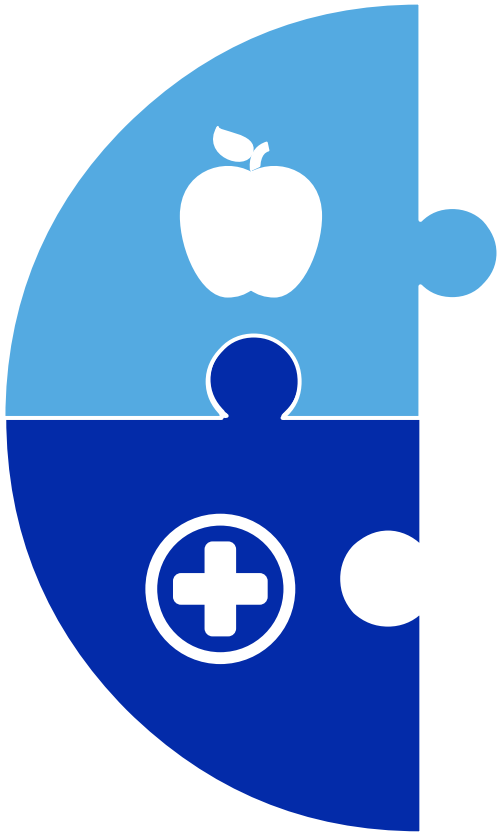

Unmet Medical Need

Across both inherited and acquired metabolic diseases

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Unique Advantage of SYNB

Bacteria act catalytically, can contain multiple enzyme pathways and are protected from digestion within the GI tract.

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Why **Metabolic Diseases** For Synthetic Biotic Medicines?

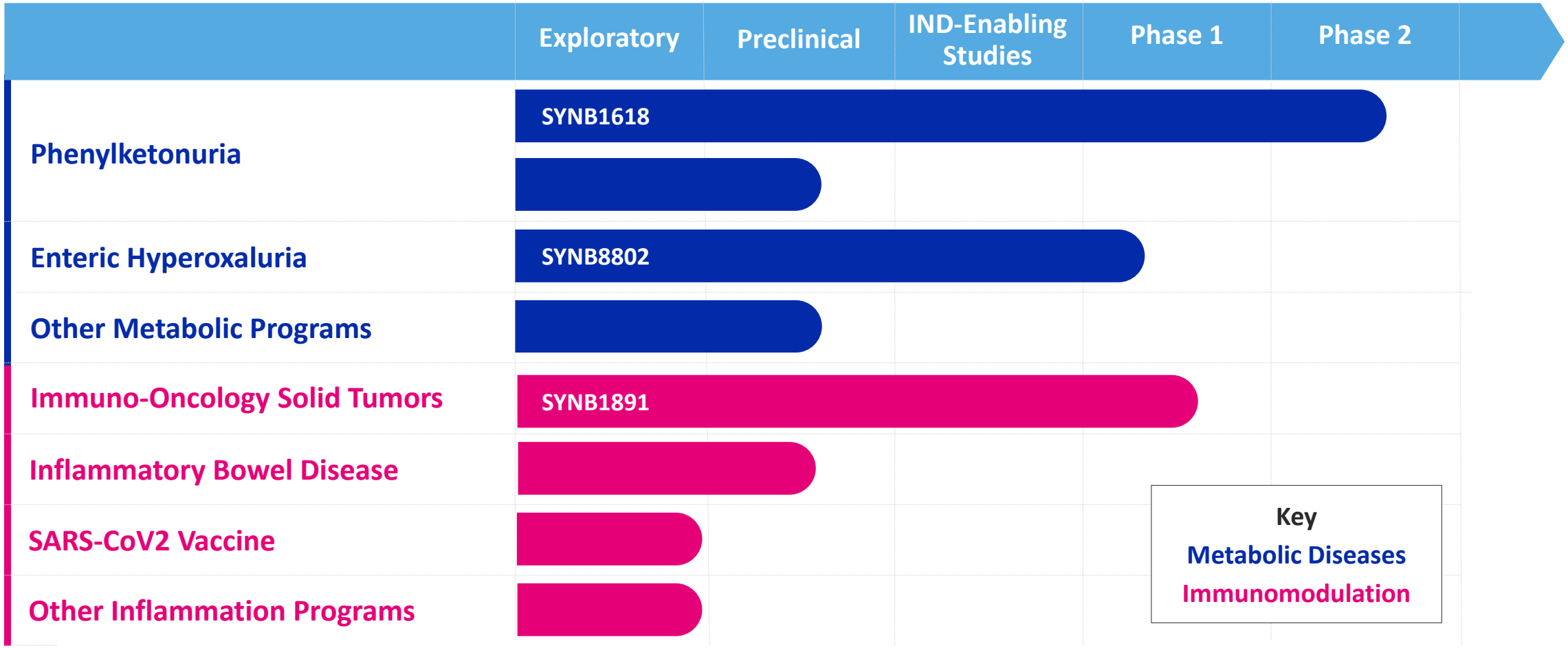
Validated Biology
Diseases with known pathophysiology. Dietary intervention provides support for GI-based approach

Unmet Medical Need
Across both inherited and acquired metabolic diseases

Platform Proof of Mechanism
PKU program demonstrated we can consume toxic metabolites in the GI tract. Subsequent programs build on experience.

Unique Advantage of SYNB
Bacteria act catalytically, can contain multiple enzyme pathways and are protected from digestion within the GI tract.

Robust Pipeline



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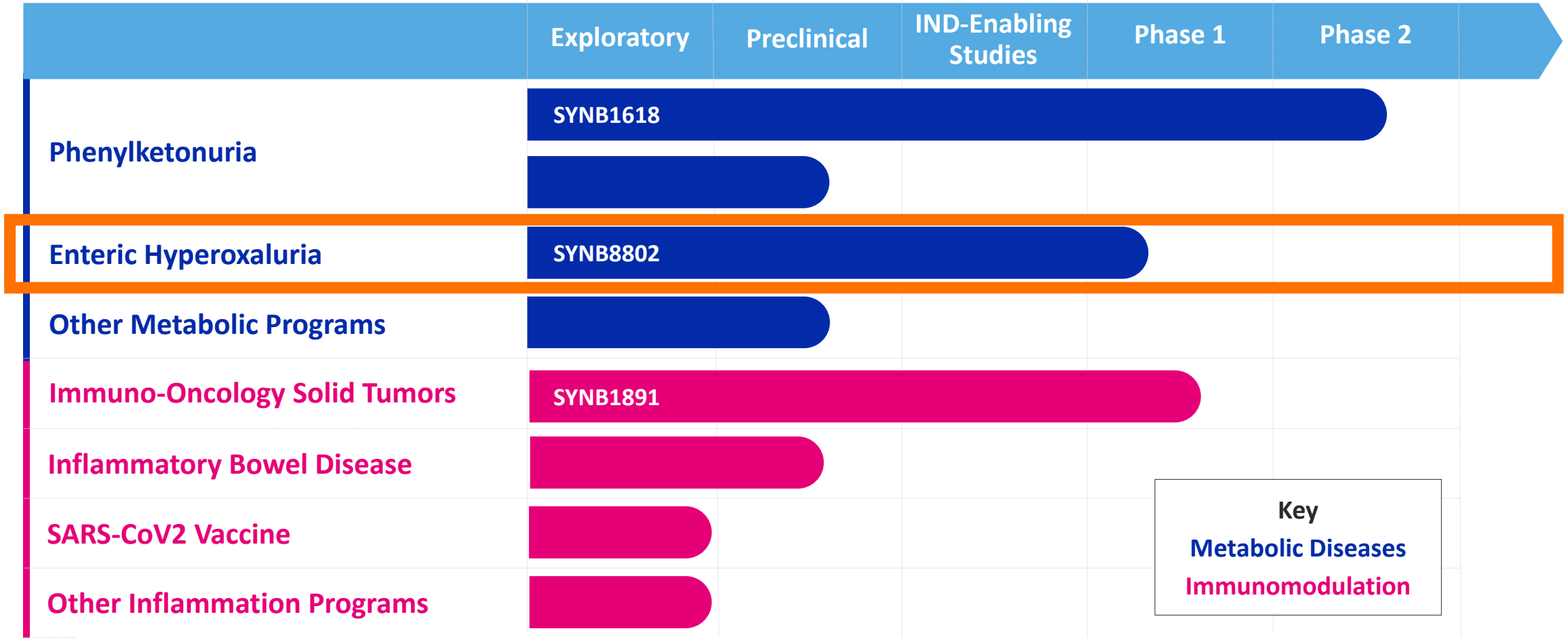
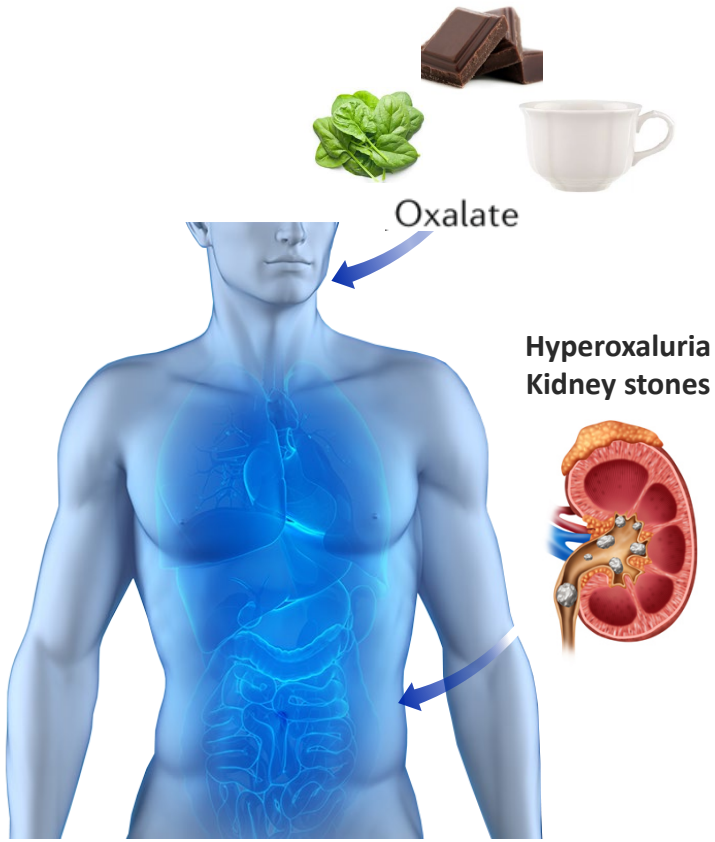


Enteric Hyperoxaluria

Dietary Sources of Oxalate



	Enteric Hyperoxaluria
Pathology	Pathogenic hyperabsorption of dietary oxalate, often accompanies bowel disease or bariatric surgery
Urinary Oxalate Levels	45 – 130 mg / 24 hrs (up to 3x normal)
Onset	Adult
Clinical Mgmt	Limited nutrition options; treatment of kidney stones as they occur; nephrocalcinosis; dialysis
U.S. Epidemiology	200,000 – 250,000

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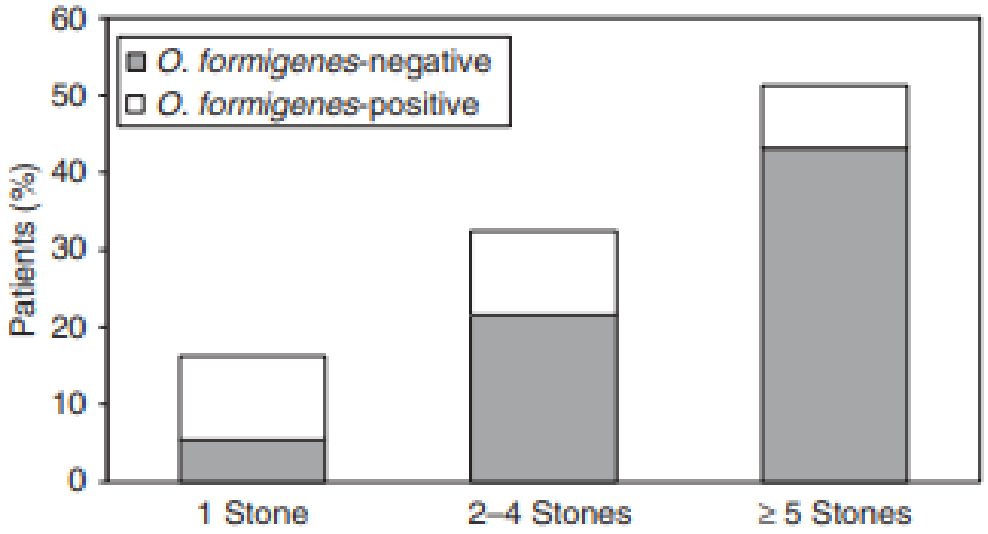
Kidney Stone Disease and Gut Microbiota

Importance of GI Tract Microbiota in Oxalate Degradation

Oxalobacter formigenes, a gut commensal bacterium

- Gram negative rod bacterium
- Obligate anaerobe
- Colonizes 38-77% of healthy human gut
- Dependent on oxalate for growth and survival
- **Degrades oxalate to produce formate and CO_2**

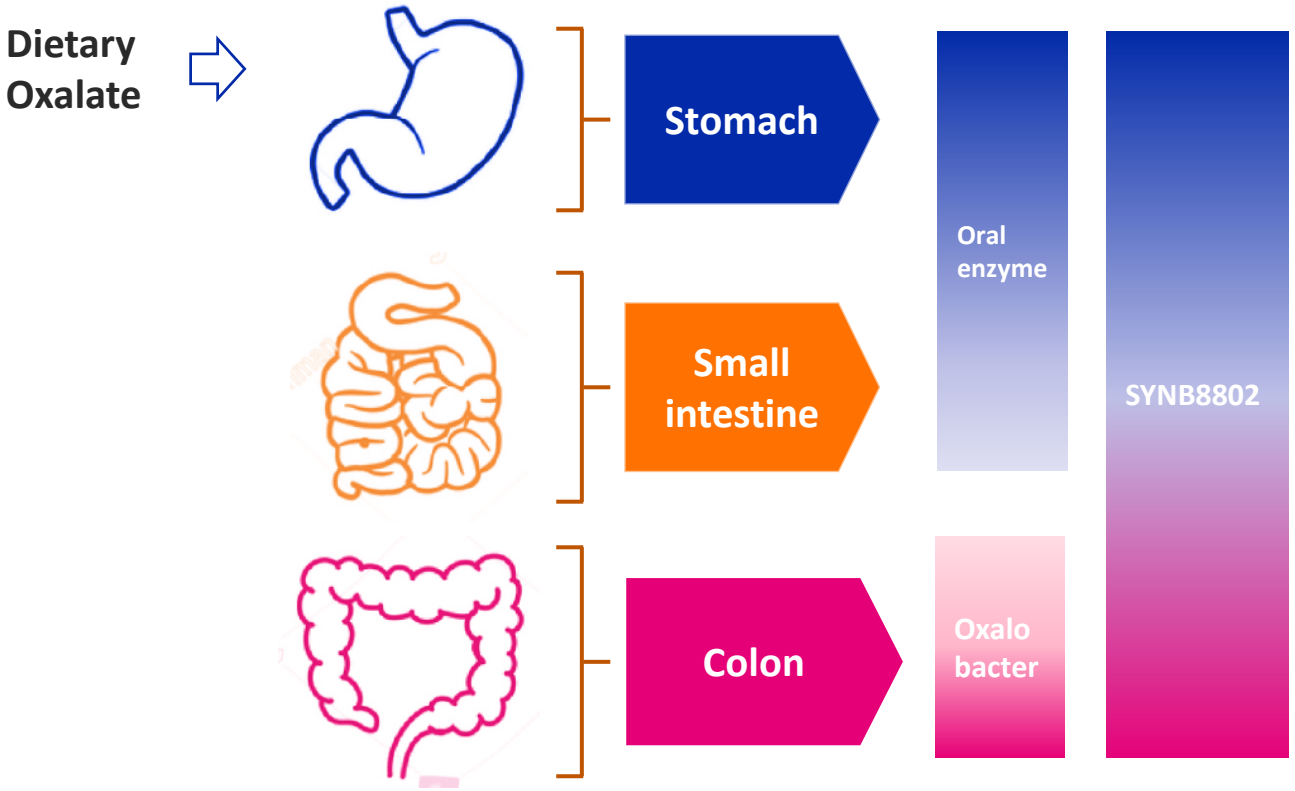
Oxalobacter colonization associated with reduced stone formation[2]



[2] Siener et al. Kidney International (2013) 83, 1144–1149; doi:10.1038/ki.2013.104; published online 27 March 2013

***Oxalobacter formigenes* provides a pathway to degrade dietary oxalate**

Considerations for GI based therapies for EH



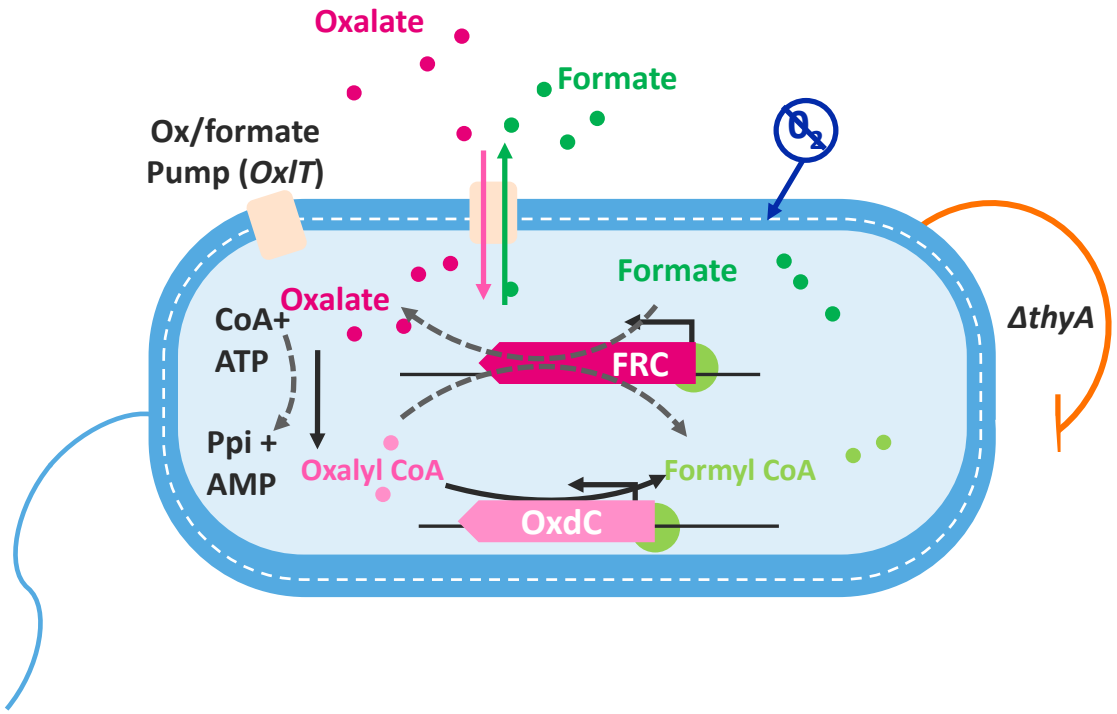
- Pathogenic hyperabsorption of dietary oxalate
- Dietary oxalate absorbed throughout GI tract
- Opportunity to degrade oxalate throughout GI tract, esp. in colon

Intestinal Degradation of Oxalate Throughout GI Tract Could Enhance Oxalate Lowering

Hyperoxaluria strain SYNB8802

Engineered to convert oxalate to formate

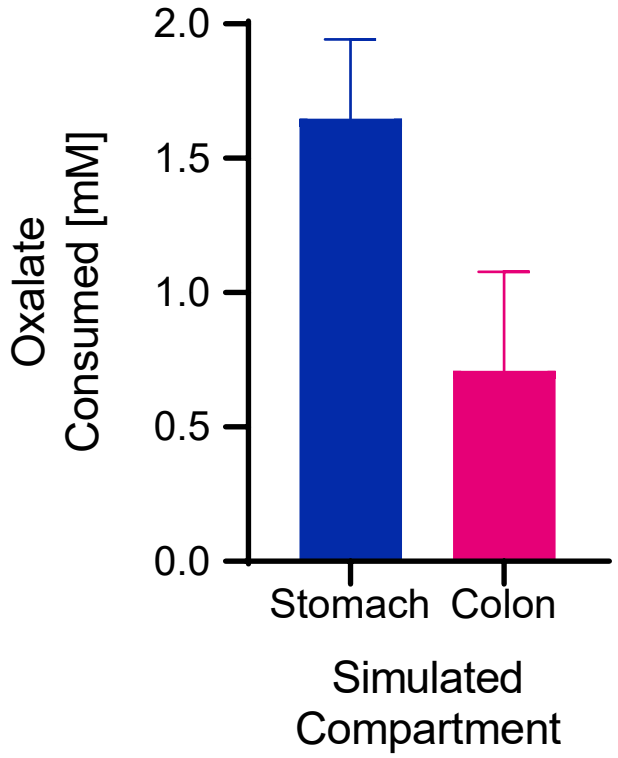
Component	Approach	Benefit
Bacterial Chassis	*E. coli* Nissle	Decades of human use
Switch	FNR promoter	Gene expression in low oxygen environment of gut
Pump	*OxlT*	Pumps oxalate in & formate out
Effectors	*OxdC, ScaaE3, Frc*	Catalyze conversion of oxalate to formate
Safety Features	*Δ thyA*	Controls growth



SYN-HOX Designed with pathways to degrade oxalate in the GI tract

SYNB8802 Activity *in vitro* and Bioavailability

In vitro activity of SYNB8802 in Simulated Intestinal Fluids



SYNB8802 Has Potential To Operate Throughout The GI Tract To Lower Absorption Of Oxalate Into The Blood

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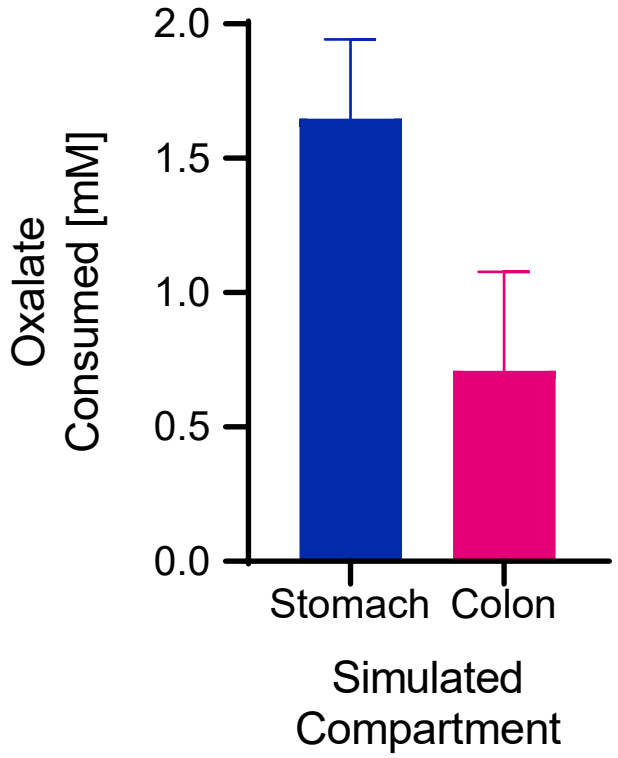
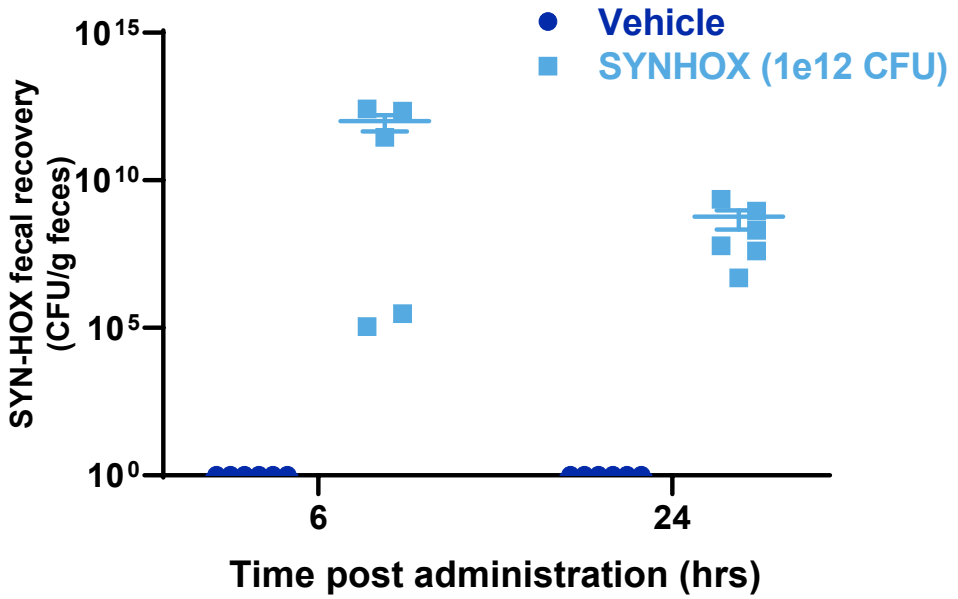


Viable SYNB8802 Recovered in Feces after Oral Dose (NHP)

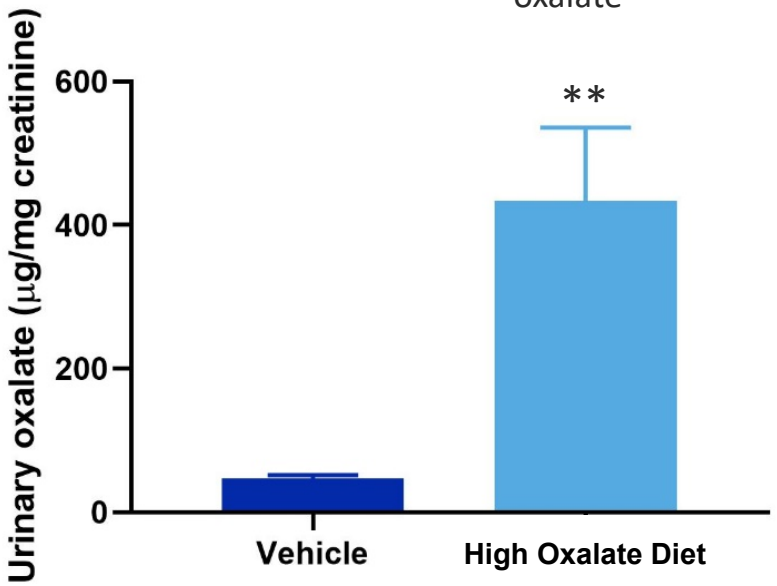


SYNB8802 Has Potential To Operate Throughout The GI Tract To Lower Absorption Of Oxalate Into The Blood

SYNB8802 Attenuates Urinary Oxalate Increase in Healthy Non-Human Primates

Dietary Intervention Increases Urinary Oxalate

400 mg oxalate elevates urinary oxalate



SYN-HOX Consumes Oral Load of Oxalate in Non-Human Primates

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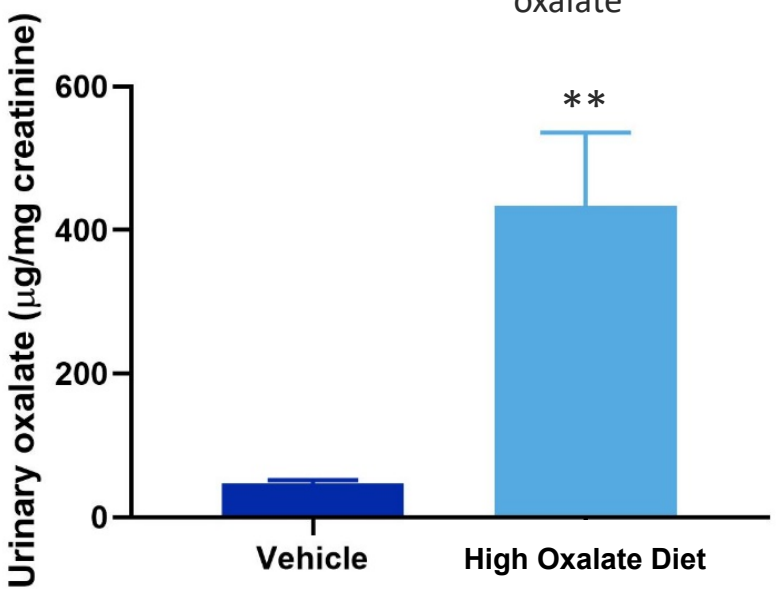

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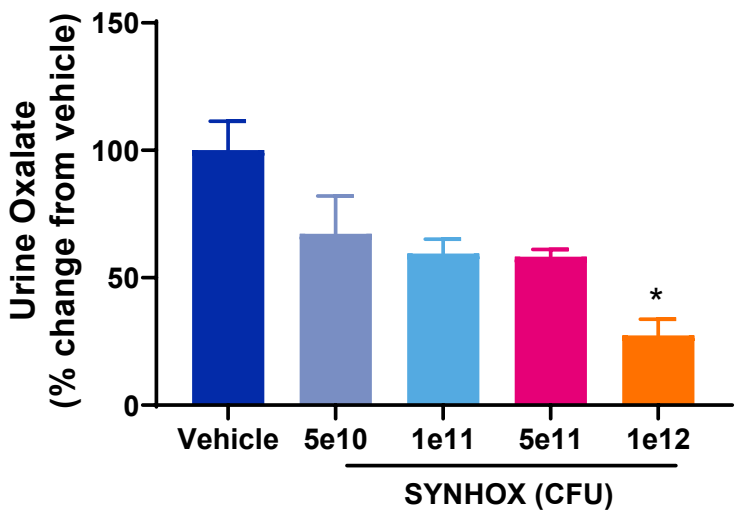

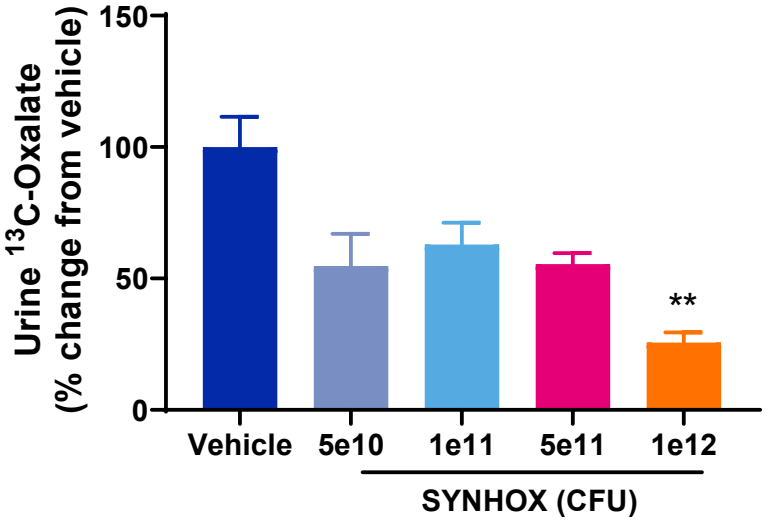

* $p < 0.05$, **$p < 0.01$ versus vehicle

SYN-HOX Consumes Oral Load of Oxalate in Non-Human Primates

In Silico Simulations (ISS) of SYNB8802 Activity in Humans

How do we build confidence that a candidate strain is ready for clinical studies?

Key Question

Is SYNB8802 activity **sufficient** to deliver a clinical benefit to enteric hyperoxaluria patients?

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Strain function *in vivo* is complex and dynamic

- Strain activity is **not** constant
- Gut conditions are **not** constant
- Strain **competes** with host for metabolites

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Our Approach

Leverage *in vitro* data and knowledge of disease biology to perform ***In Silico* Simulations (ISS)** of strain activity in human GI tract

ISS Models of Strain Activity in Humans

Strain Function *in vivo* is Complex and Dynamic

Our Approach

Leverage *in vitro* data and knowledge of disease biology to perform ***In Silico* Simulations (ISS)** of strain activity in human GI tract

Inputs

In vitro Assay Data

Literature Evidence

ISS Model

Ordinary Differential Equations

Parameter Estimates

Outputs

Biomarker Production

Serum/Urine Metabolite Concentrations

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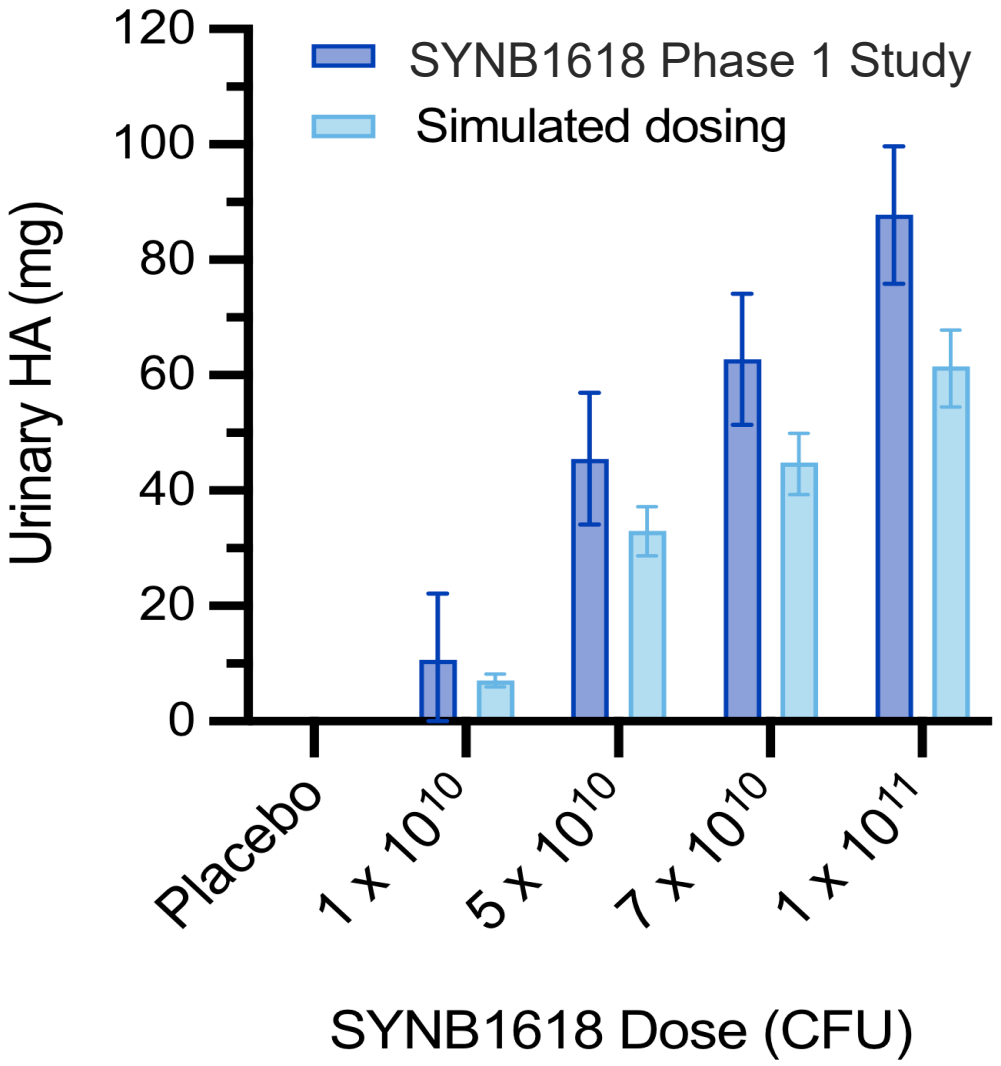
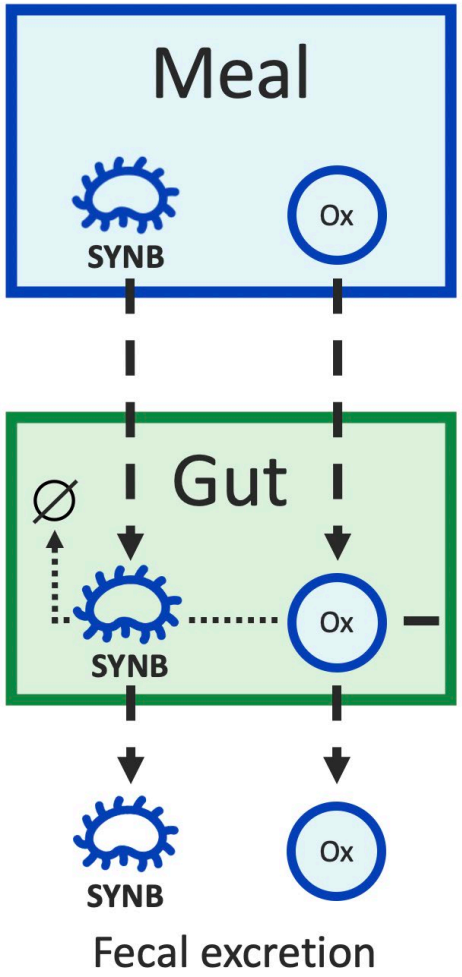
Validated predictions of strain activity in humans

Example: ISS Model for PKU Program (SYNB1618)



SYNB8802 ISS Model

Simulated Strain Activity in GI impacts Urinary Oxalate



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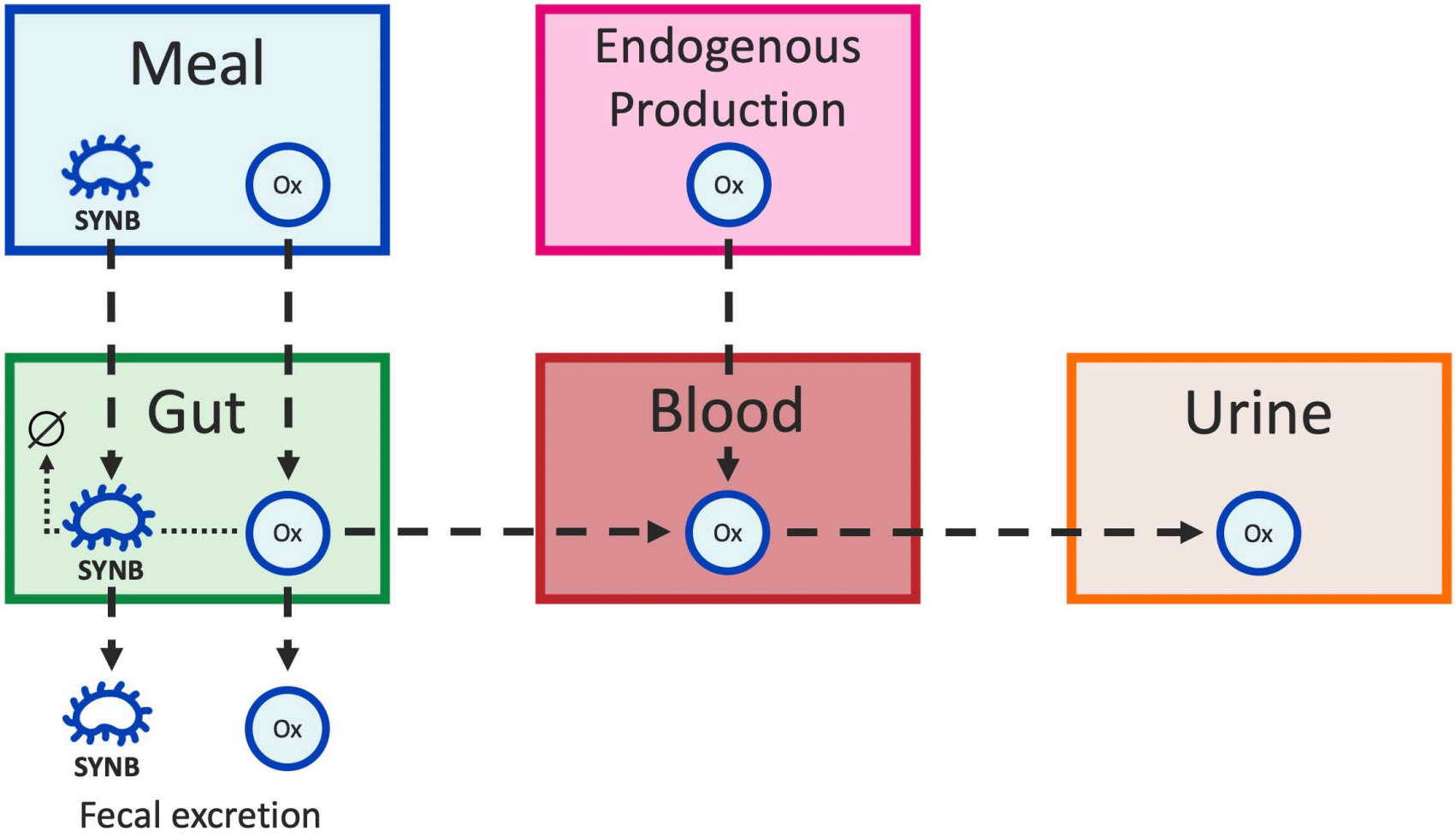

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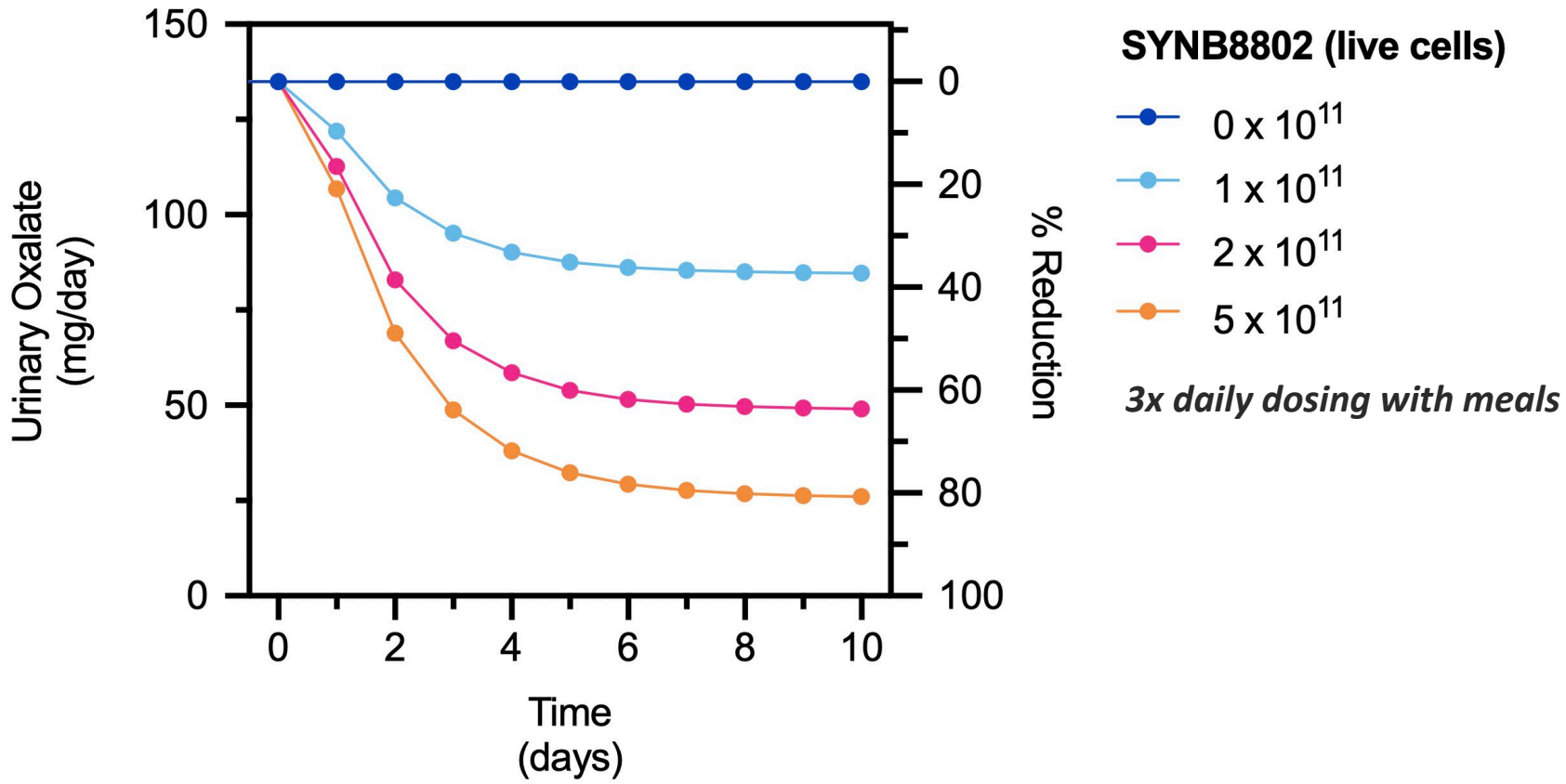

Modeling Suggests SYNB8802 may Achieve >20% Urinary Oxalate Lowering at Target Dose Range

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Enteric Hyperoxaluria: Phase 1 Design Provides PoC Opportunity

Phase 1a
Healthy Volunteers

Multiple Ascending Dose

- High oxalate & low calcium diet run-in
- *Primary:* Safety & tolerability
- *Secondary:* Microbial kinetics of strain
- *Exploratory:* Change in plasma and urine biomarkers

Phase 1b
Enteric Hyperoxaluria Patients

Cross-over

- 3x daily dosing
- N = 20 patients (Roux-en Y gastric bypass)
- UOx >70 mg/day

Roux-en-Y Gastric Bypass Population Provides Opportunity to Demonstrate Urinary Oxalate Lowering in Disease State

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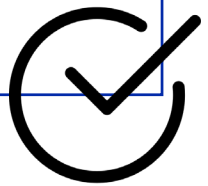
SYNB8802 Conclusions

Enteric Hyperoxaluria results in significant kidney damage with limited treatment options

SYNB8802 has the potential to meaningfully lower urinary oxalate levels

SYNB8802 Phase 1 clinical study initiated ahead of schedule



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