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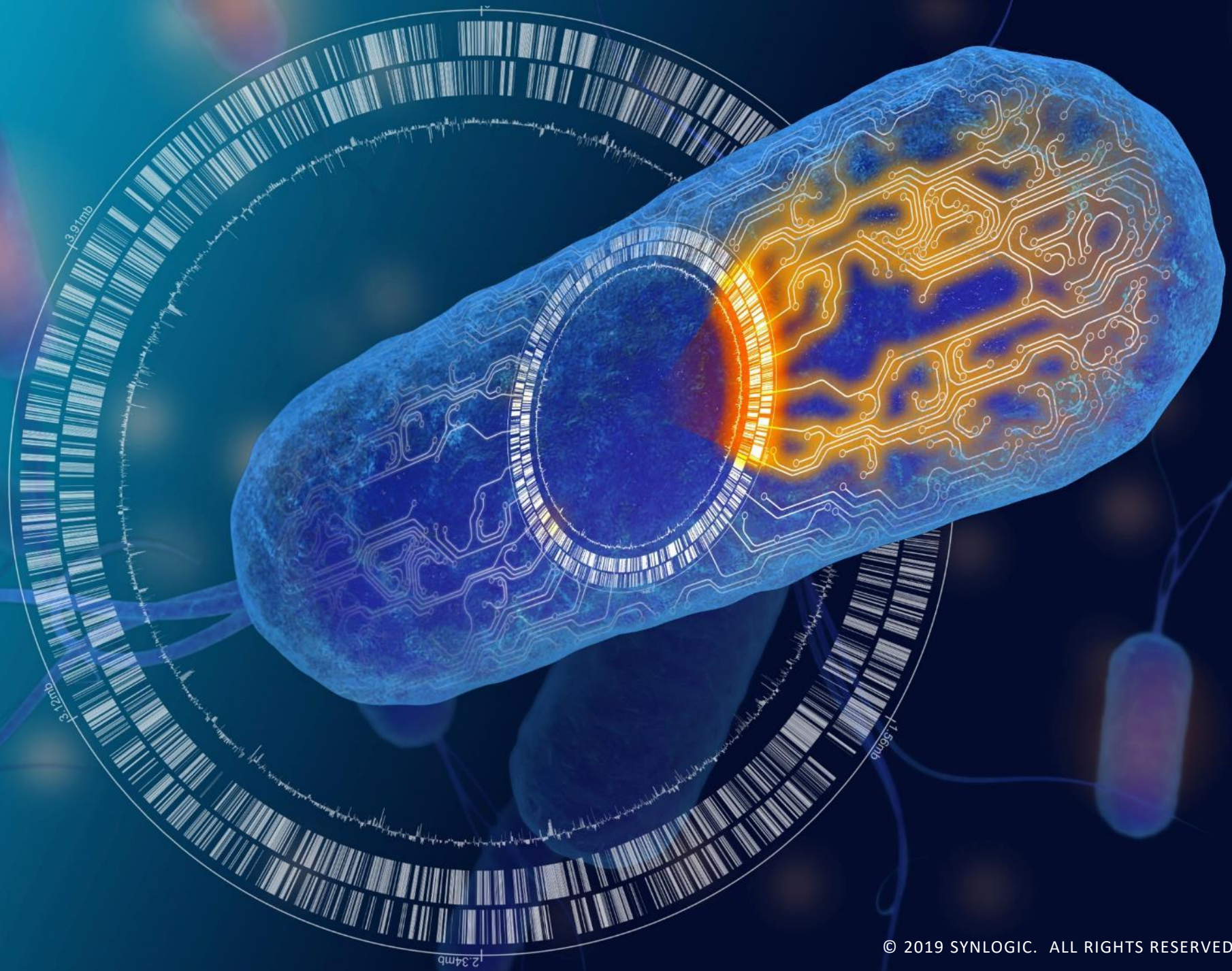
Developing a new class of living medicines

R&D Event
May 27, 2020



R&D Event Kick Off

Dr. Elizabeth Wolffe, PhD

Head of Investor and Corporate Communications

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Synlogic Leadership
Experienced Management + Top-Flight Investors

Aoife Brennan, MB ChB
President & CEO

Biogen | Tolerx

Richard Riese, MD PhD
CMO

Alynlam | Alexion | Pfizer

Gregg Beloff, JD
Interim CFO

Danforth Advisors

Antoine Awad
Head of Tech Ops

Abpro | LEAF | Merrimack

Amanda Kay, PhD
Head of BD & Strategy

Pfizer | L.E.K Consulting
Genzyme

Caroline Kurtz, PhD
Head of Product Development

Ironwood | Genzyme

Board

Peter Barrett, Chair
Atlas Venture

Mike Burgess
Turnstone Biologics

Chau Khuong
Orbimed Advisors

Nick Leschly
Bluebird Bio

Ed Mathers
NEA

Michael Powell
Sofinnova

Richard Shea
Syndax Pharmaceuticals

Patricia Hurter
Lyndra Therapeutics

Collaborators

GINKGO BIOWORKS
THE ORGANISM COMPANY

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Our Agenda Today

Introduction & Welcome	Dr. Aoife Brennan, President & CEO
Synlogic's Product Engine	Dr. Amanda Kay, Head of Strategy & Business Development Tony Awad, Head of Technical Operations
Metabolic Programs	Dr. Caroline Kurtz, Head of Product Development
Metabolic Programs: **Focus on Enteric Hyperoxaluria**	Dr. Richard Riese, Chief Medical Officer *Special Guest: Dr. David Goldfarb, New York University*
Immuno-Modulation: **Upregulation & Downregulation**	Dr. Amanda Kay Dr. Caroline Kurtz
Q & A	Synlogic Leadership Team & Dr. David Goldfarb
Concluding Remarks	Dr. Aoife Brennan

Forward Looking Statements

This presentation contains “forward-looking statements” that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this presentation regarding strategy, future operations, future financial position, future revenue, projected expenses, prospects, plans and objectives of management are forward-looking statements. In addition, when or if used in this presentation, the words “may,” “could,” “should,” “anticipate,” “believe,” “estimate,” “expect,” “intend,” “plan,” “predict” and similar expressions and their variants may identify forward-looking statements. Examples of forward-looking statements include, but are not limited to, the approach we are taking to discover and develop novel therapeutics using synthetic biology; statements regarding the potential of our platform to develop therapeutics to address a wide range of diseases, including: metabolic diseases, inflammatory and immune disorders, and cancer; the future clinical development of Synthetic Biotic medicines; the potential of our technology to treat phenylketonuria and cancer; the expected timing of our anticipated clinical trial initiations and availability of clinical data; the benefit of orphan drug and fast track status; the adequacy of our capital to support our future operations and our ability to successfully initiate and complete clinical trials; the results of our collaborations; and the difficulty in predicting the time and cost of development of our product candidates. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including, without limitation: the uncertainties inherent in the preclinical development process; our ability to protect our intellectual property rights; and legislative, regulatory, political and economic developments, as well as those risks identified under the heading “Risk Factors” in our filings with the SEC. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors included in our quarterly report on Form 10-Q filed with the SEC on May 8, 2020, and in any subsequent filings we make with the SEC. The forward-looking statements contained in this presentation reflect our current views with respect to future events. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our view as of any date subsequent to the date hereof.

Opening Remarks

Dr. Aoife Brennan
MB CHB

President & CEO

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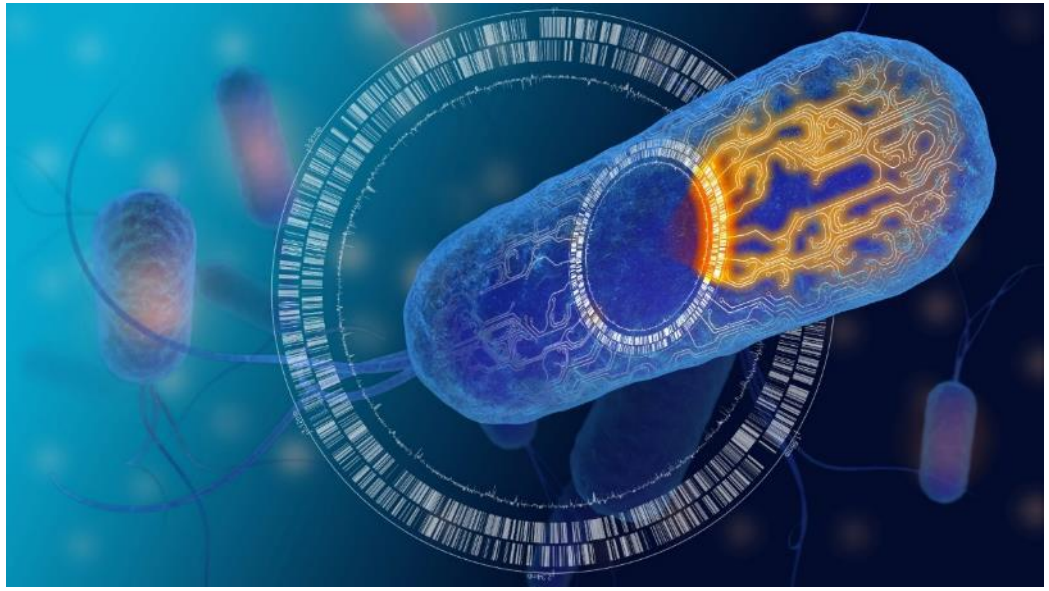
Synthetic Biotic™ Medicines Designed For Life

Synlogic's mission is to
address patients' dynamic therapeutic needs
by developing living medicines
that sense and respond to disease

Synthetic Biotic Medicines: A New Class of Potent Living Medicines

Bacteria & Humans Co-Evolved & Co-Exist

What If We Could Rationally Design Bacteria To Provide Clinical Benefit?



The Result Is Therapeutic Bacteria With Potent And Programmable Therapeutic Effects

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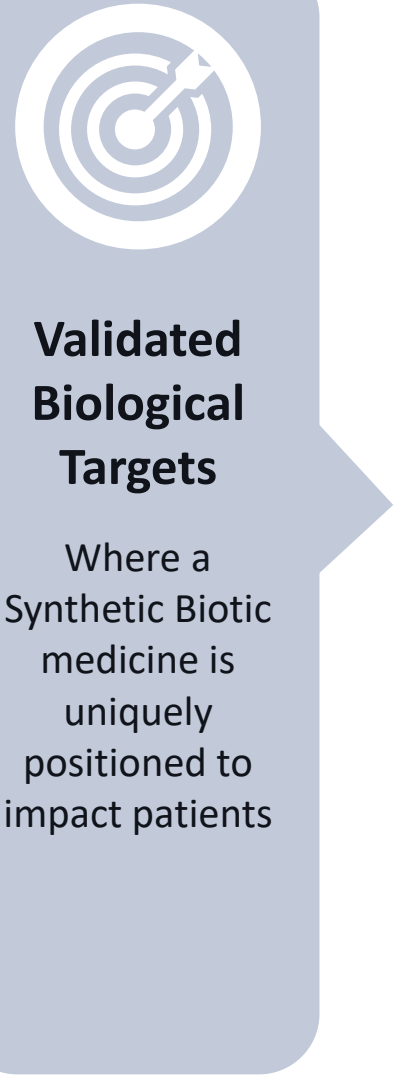
Building a Diverse Portfolio of Synthetic Biotic Medicines

Platform For Clinical Benefit Across Multiple Disease States



Validated Biological Targets

Where a Synthetic Biotic medicine is uniquely positioned to impact patients

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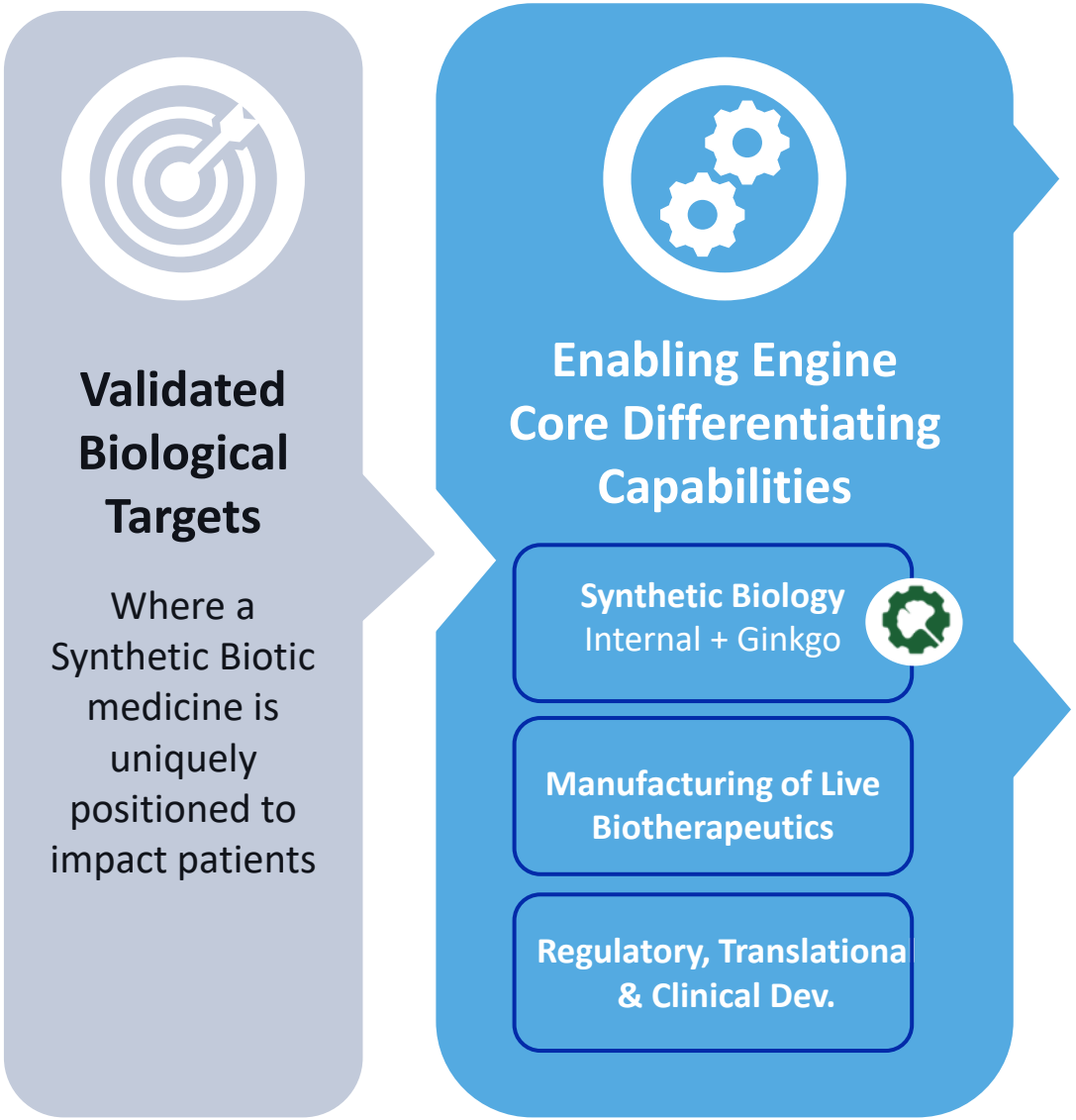

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Building a Diverse Portfolio of Synthetic Biotic Medicines

Platform For Clinical Benefit Across Multiple Disease States

Validated Biological Targets

Where a Synthetic Biotic medicine is uniquely positioned to impact patients

Enabling Engine Core Differentiating Capabilities

- **Synthetic Biology** Internal + Ginkgo
- **Manufacturing of Live Biotherapeutics**
- **Regulatory, Translational & Clinical Dev.**

Internal Pipeline:

Metabolic Programs

Consumption of toxic metabolites from the GI tract

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Platform For Clinical Benefit Across Multiple Disease States

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Internal Pipeline: Metabolic Programs

Consumption of toxic metabolites from the GI tract

External & Partnered Pipeline: Immunomodulation

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

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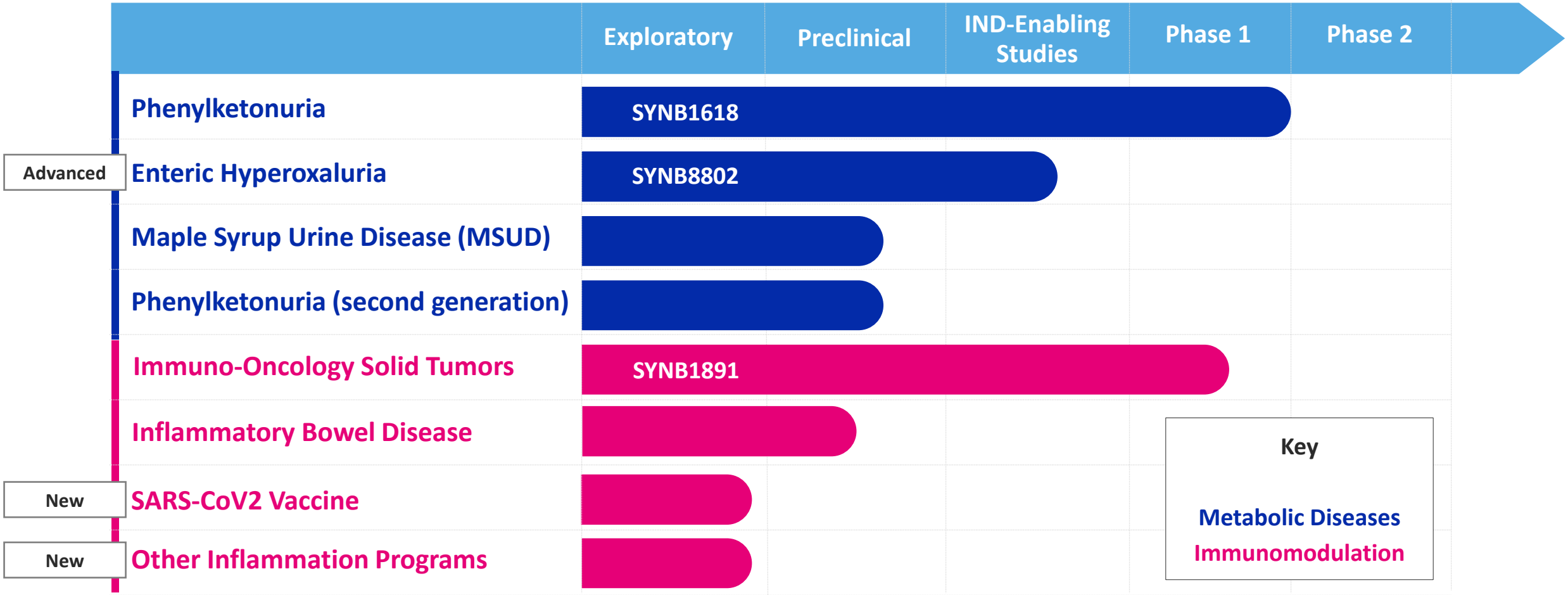
Advancing Synthetic Biotic Medicines Rapidly Into & Through The Clinic



Multiple Expected Upcoming Milestones

Synlogic Entering Data Rich Period In The Clinic

	Expected Milestone	2020 early	2020 mid	2020 late	2021 early	2021 mid	2021 late
SYNB1618 PKU	Initiate Ph.2 study in PKU patients						
	Ph.2 Phe-lowering read-out						
SYNB8802 HOX	Initiate IND-enabling studies	initiated					
	Initiate Ph.1 study in HV and Patients						
	Ph.1 Patient Read-out						
SYNB1891 I/O	Ph.1 Monotherapy read-out						
	Initiate Ph.1 combination study arm						
	Ph.1 Combination therapy read-out						

Significant Clinical Readouts Within Our Current Cash Window

Executive Summary

- We are building a therapeutic platform with potential to **benefit patients in new ways**
- We have the **team**, technology and portfolio to succeed
- Rapidly progressing **internal metabolic programs** through POC
  - SYNB1618 (PKU) demonstrates activity in vivo and moving to Phase 2
  - Accelerated plan for SYNB8802 in enteric hyperoxaluria
- Building portfolio of **partner-able assets** in immunology and oncology
- Funded through multiple upcoming milestones across clinical portfolio

Synlogic's Product Engine

Dr. Amanda Kay, PhD
Head of Strategy & Business Development

Tony Awad, Head of Technical Operations

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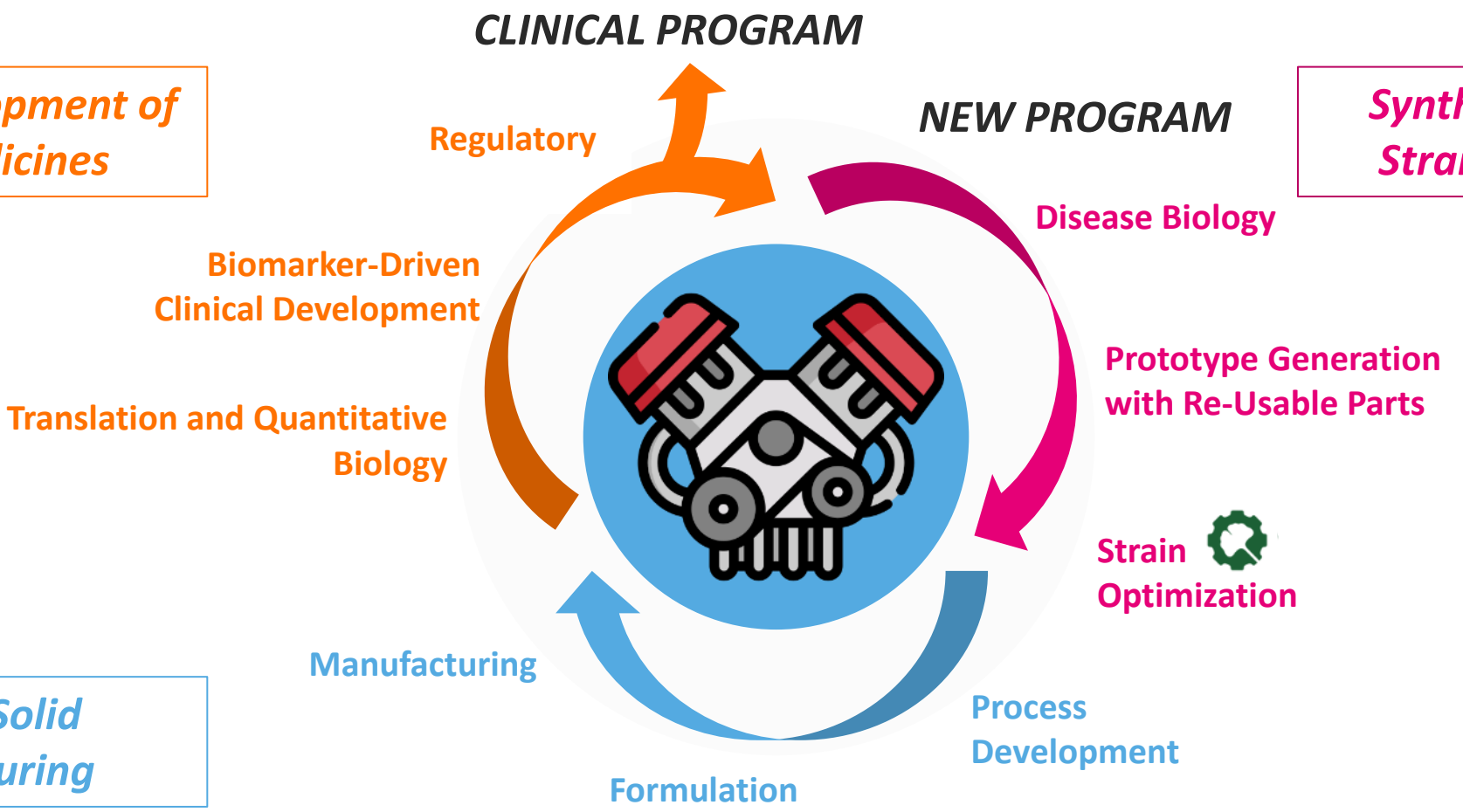
We Have Built the Engineered Living Medicine Engine

Clinical Synthetic Biotic Program Experience Informs the Next Wave of Programs

Clinical Development of Living Medicines

Synthetic Biology & Strain Engineering

Liquid & Solid Manufacturing



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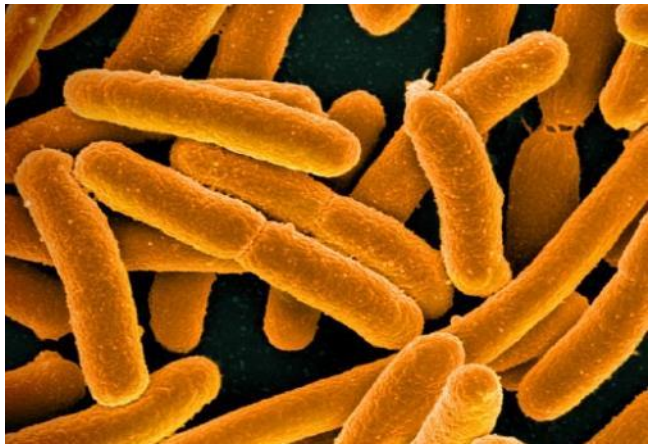
Synthetic Biotic Medicines: A New Class of Dynamic Living Medicines

Cellular + **Programmable** = **Synthetic Biotic Medicine**

Bacterial Chassis
Non-pathogenic



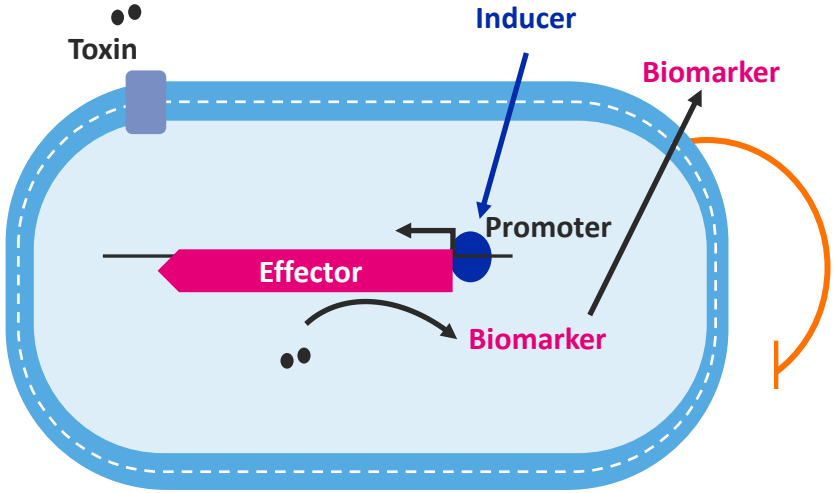
Synthetic Biology
Reusable Parts

Bacterial Chassis

Inducer-Promoter Switch

Effector Design

Safety Features



Reusable Parts Enable Rapid Iteration Of Rationally Designed Prototypes

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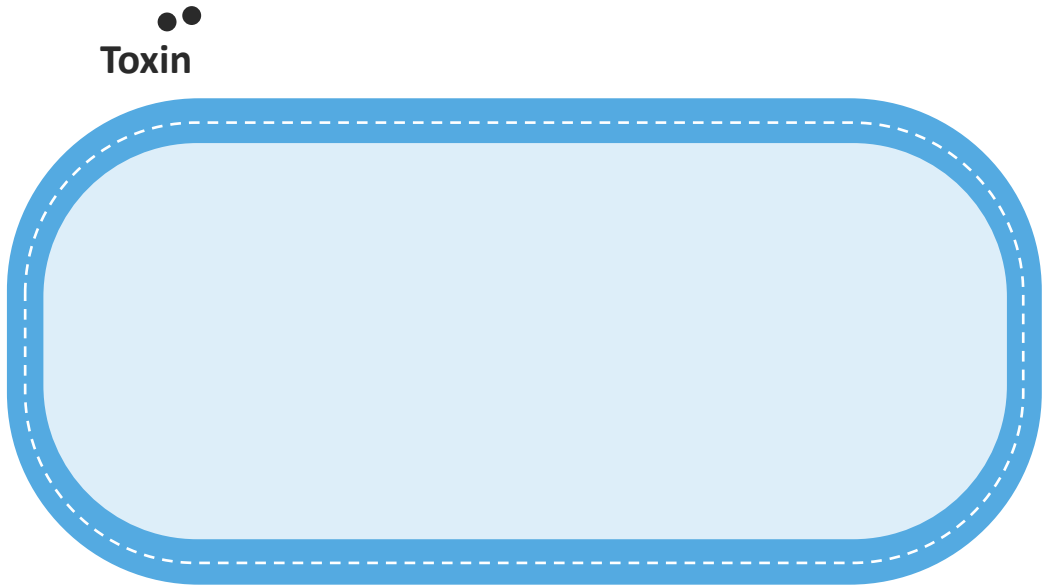
Photo credit: NIH Image Gallery

Library of Parts To Generate Prototypes

Synthetic Biology Library Rapidly Generates Drug Candidates

Component	*Benefit*
Bacterial Chassis	Probiotic: Decades of human use & safety data



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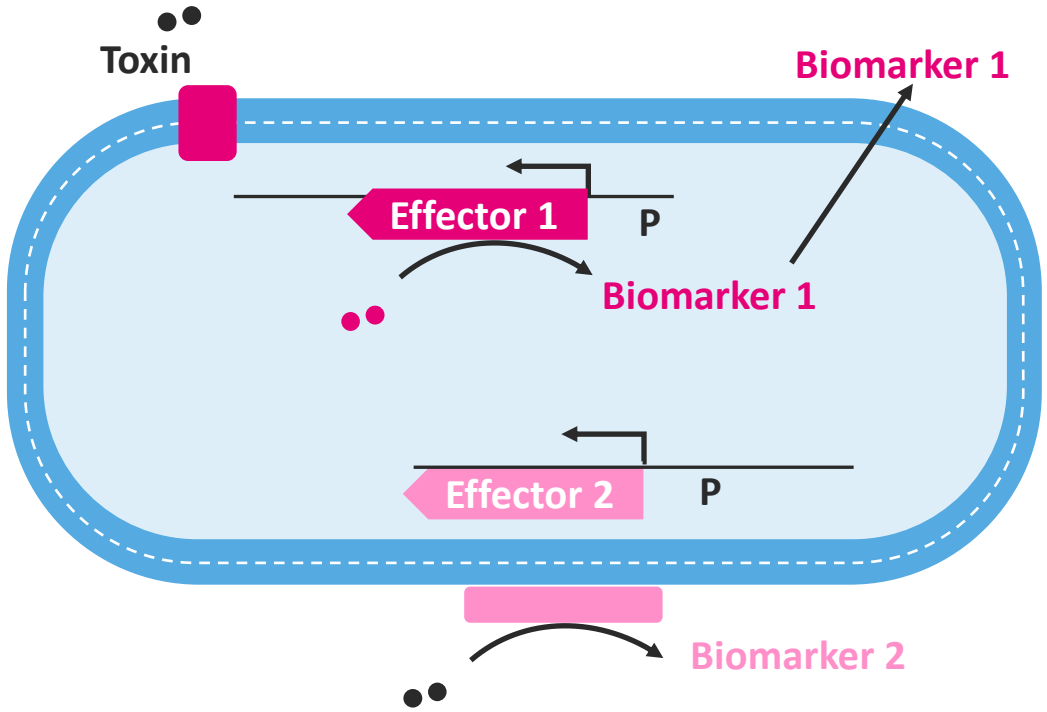
Effector 1 **Effector 2** **….**	Proteins for activity: Can generate biomarkers



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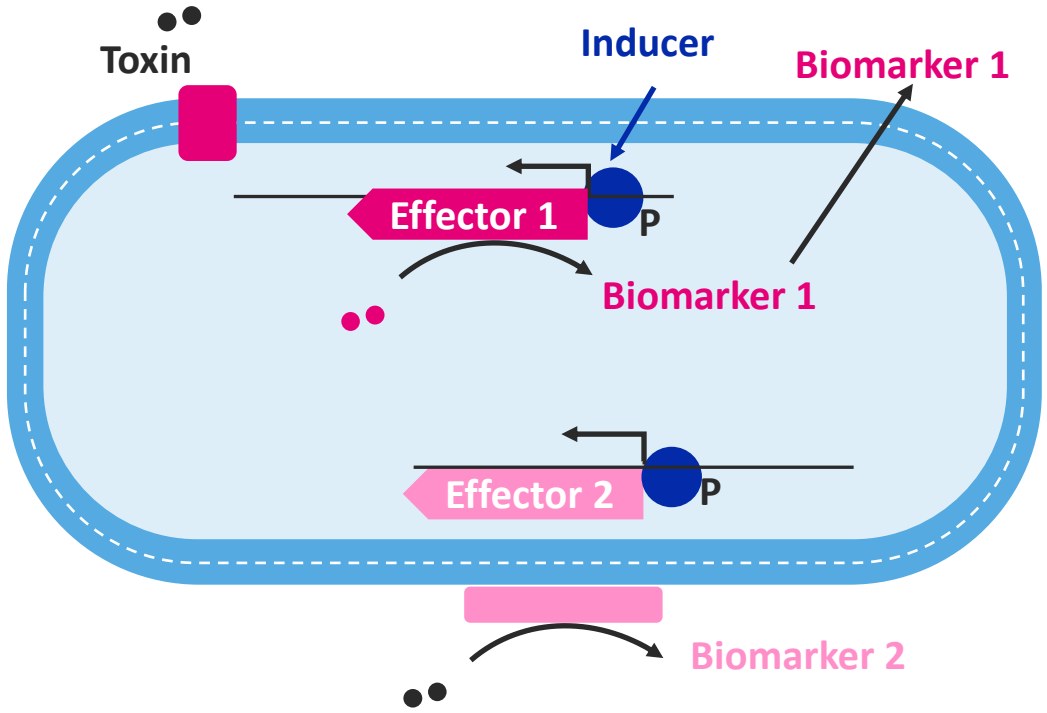

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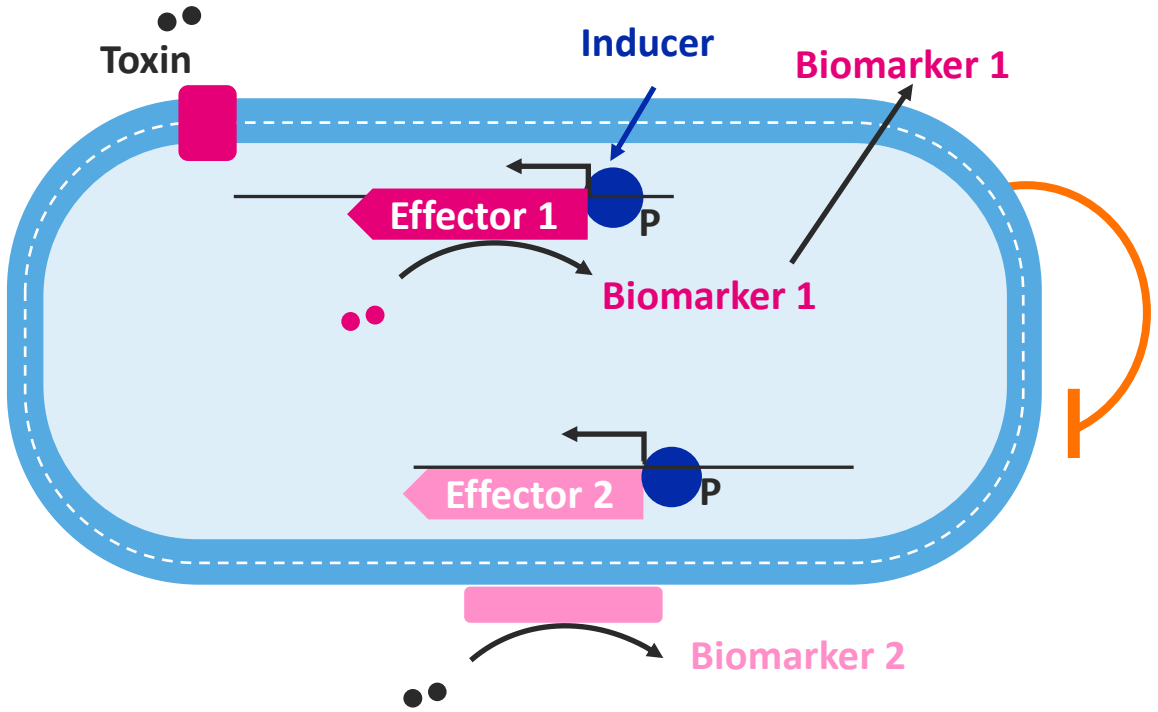
Library of Parts To Generate Prototypes

Synthetic Biology Library Rapidly Generates Drug Candidates

Component	*Benefit*
Bacterial Chassis	Probiotic: Decades of human use & safety data
Effector 1 **Effector 2** **….**	Proteins for activity: Can generate biomarkers
Switch	Inducer-promoter pair: Controls gene expression
Safety Features	Auxotrophies: Prevents growth within or external to the body



Re-Usable Parts Enable Rational Design to Perform Specific Therapeutic Functions

Consume Toxin

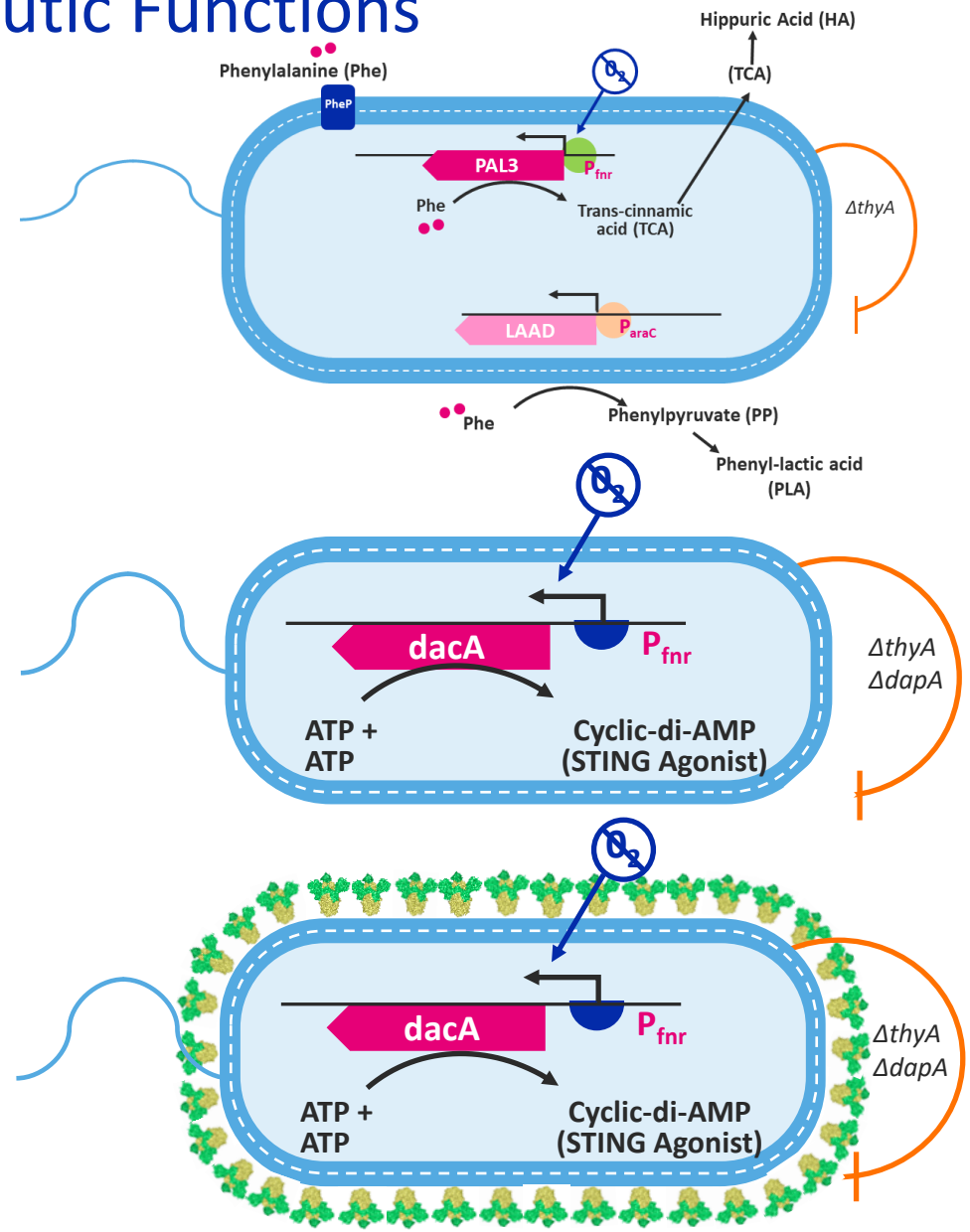
(Metabolic Programs)

Produce/secrete Tx

(Immunomodulation)

Display Tx

(Vaccine)



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Engineered Strain Development Approach

Deliver Candidate Quality Strains in a Timely and Resource Efficient Manner

Therapeutic Idea

Prototype Generation

Rational Pathway Design
Prototype Strain Construction
Potency Benchmarking

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Strain Optimization

CodeBase
High Throughput Enzyme Screening
Expression Optimization
Potency Troubleshooting ('Omics)

Lead Selection

Potency Testing
Quantitative Modeling
Manufacturability Assessment

Iterative Optimization

To improve probability of success in the clinic

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Deliver Candidate Quality Strains in a Timely and Resource Efficient Manner

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Candidate Selection

Animal Disease Models
Process Scale-up
IND Enabling Studies

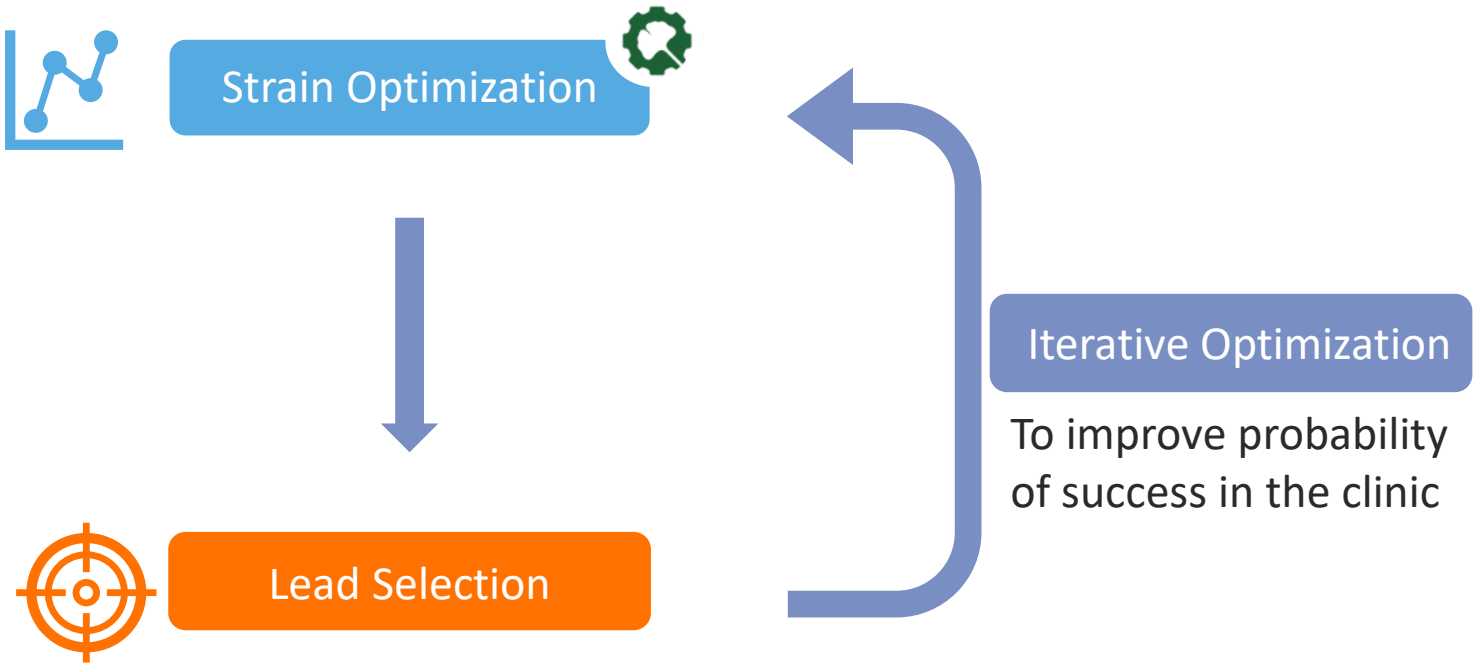
Iterative Optimization

To improve probability of success in the clinic

Rapid Cycle Times: Enteric Hyperoxaluria Prototype to Candidate In <10 Months

Access to Cutting Edge Technology via Ginkgo Collaboration

Optimization of activity and manufacturability improves clinical probability of success



Case-study:

Optimization of MSUD Prototype Strain

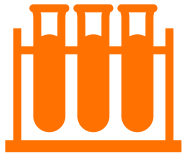
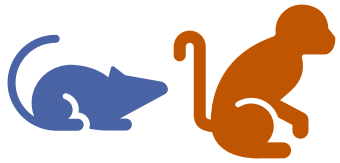
Approach to 3-enzyme pathway

- **Identified >3,800** enzymes
- **Designed 462** combinations
- **Synthesized 383** combinations
- **Screened 254** to identify optimal pathway

Ginkgo & Synlogic Collaboration Resulted In *10-fold Improvement* Over Prototype *In Vitro* Demonstrated Statistically Significant Activity In Non-Human Primates

Multiple Assay Systems Aid Efficacy Modeling for Metabolic Programs

Ability To Prospectively Identify Metabolite Consumption Performance

System	Provides functional data	Advantages
Proprietary *in vitro* simulated gut system (IVS) 	Viability Closed and full system activity	• Inexpensive • High throughput • Strong correlation with activity in human GI tract
Animal models (Rodents and NHPs) 	Activity *in vivo* in health and disease	• Rapid evaluation of disease biology • NHP GI physiology closer to humans • Ability to measure metabolite consumption via feeding experiments
Healthy volunteers 	Safety and tolerability Activity based on biomarkers	• Effective for tolerability • Effective for evaluation of drug presentation • Rapid enrollment

Translational & Quantitative Biology: Predicting Strain Activity in Humans

Inputs

Strain Activity

Metabolite Consumption

Biomarker Read-outs

In Silico Model

Proprietary Synlogic Simulation Models

Outputs

Required Metabolite Consumption For Clinical Benefit

Model Systems Allow **For Rapid Path To Clinic** With **Confidence In Metabolite Consumption** Performance

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Synlogic's Manufacturing Capabilities

Tony Awad, Head of
Technical Operations

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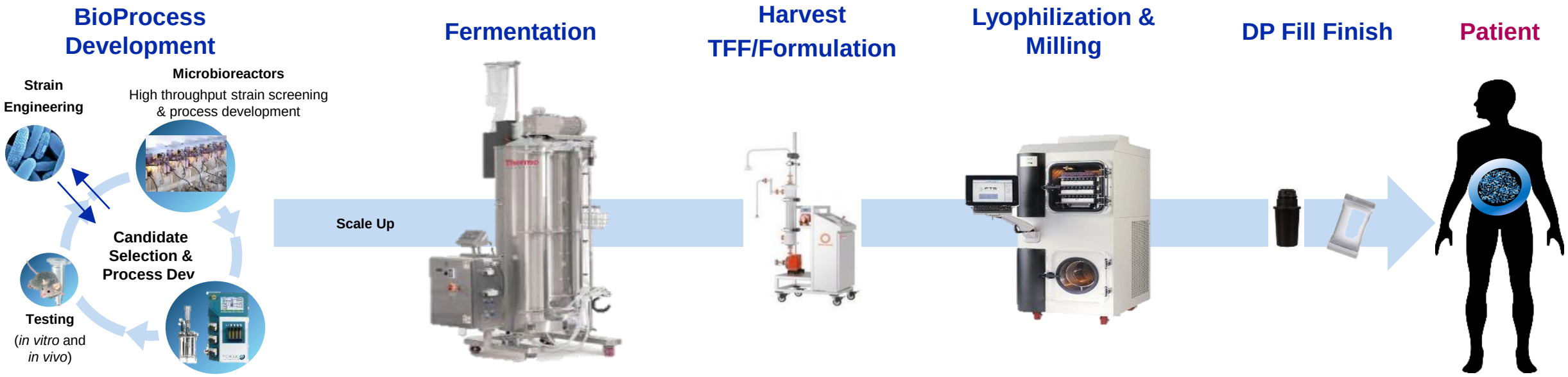
Internalizing Manufacturing Enables Control, Quality, & Speed

MFG Capabilities	Prior Operating Model: Externally Sourced CMO	Key Attributes of Internal Manufacturing	Capabilities Today Synlogic as Primary
Bioprocess Development	Synlogic / External	Speed Flexibility Customizable Cost Effective Efficiency	Synlogic
Analytical Development	External		Synlogic
Formulation Development	Synlogic / External		Synlogic
cGMP Manufacturing (Drug Substance)	External		Synlogic
cGMP Manufacturing (Drug Product)	External		Synlogic
Quality Control	External		Synlogic / CRO

Fully Integrated Process Development and Manufacturing Organization

Deep Investment in Development & Manufacturing Capabilities



Integration: rapid progression through the developmental stages into cGMP manufacturing

Maintains **expert quality oversight**: De-risks tech transfer and development/manufacturing challenges

Synlogic **solid oral capabilities** enable patient friendly bottle/sachet/capsule presentations with good shelf life & stability

From Lab to Patient Faster, With Less Risk and Higher Quality,
Due To Synlogic's Unique Fully Integrated Bacterial Manufacturing Capabilities

Experienced Clinical Development Team Adapting Studies to Post-COVID Era

Direct Engagement With Patients Drives Our Capabilities To Conduct Research post-COVID

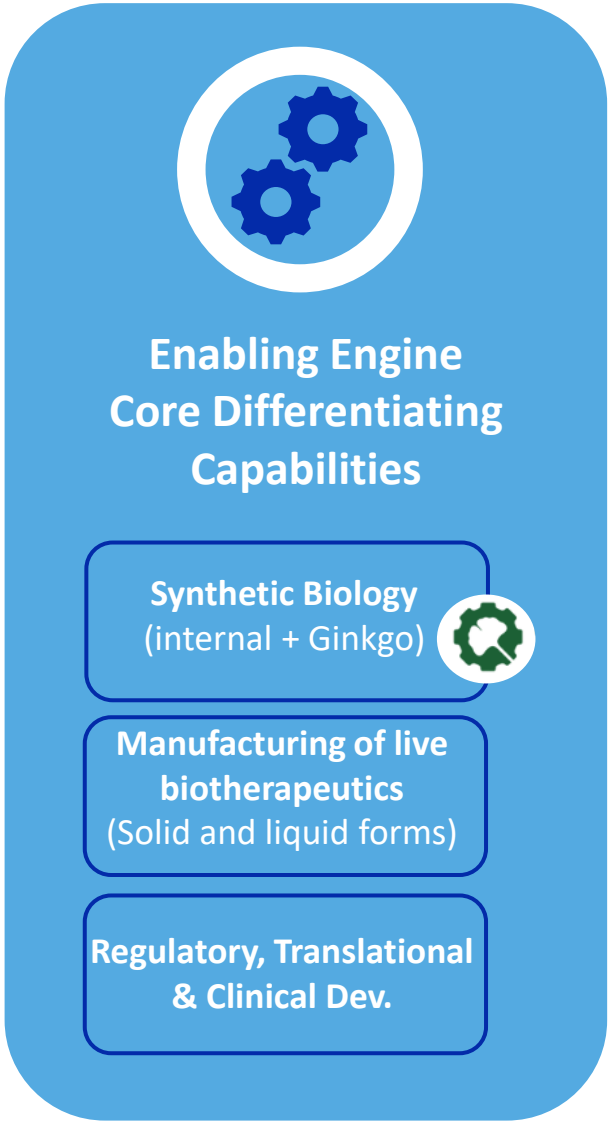
Driven by Experienced Team

- ✓ Deep internal capabilities in safety, regulatory, and clinical (former Alnylam, Alexion)
- ✓ New appointment: Andrew Marsh, Head of Clinical Operations (former Ra, Moderna)

Adapt in Response to COVID-19

- ✓ Study protocols adapted to decentralized clinical process
  - Example: Use of central hub site allows for remote visits in SYNB1618 Ph.2 study
- ✓ Depending on study, some or all study-related activities can be performed at home via home research nurses
- ✓ Investigational product delivered flexibly to site, patient, or home research nurse
- ✓ Substantial clinical work done in Phase 1 units, less impacted by COVID health care facility disruptions

Building the Engine to Develop Synthetic Biotic Medicines



- **200 humans dosed** with Synthetic Biotic medicines
- **3 INDs opened** with the U.S. FDA
- **Supportive regulatory feedback** from global regulatory agencies
- **Internal process development and GMP manufacturing** capabilities established
- **Expanded synthetic biology expertise** with Ginkgo Bioworks collaboration
- **Reusable synthetic biology components** enable platform learning and efficiency

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Metabolic Programs: *Focus on PKU*

Dr. Caroline Kurtz, PhD
Head of Portfolio and
Product Development

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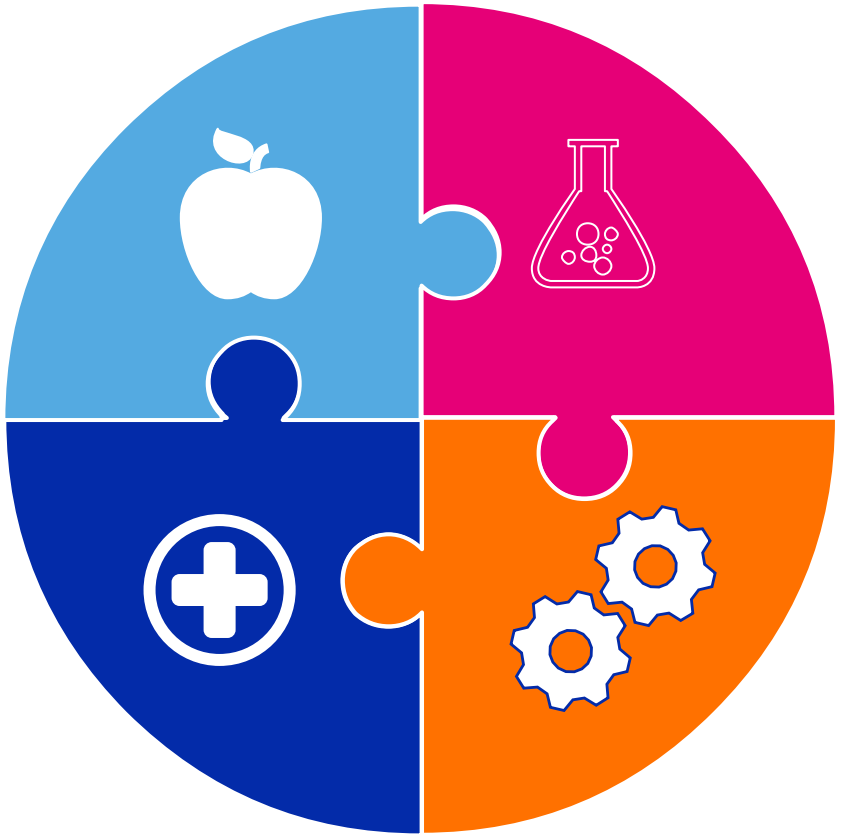
Why Metabolic Diseases For Synthetic Biotic Medicines?

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.

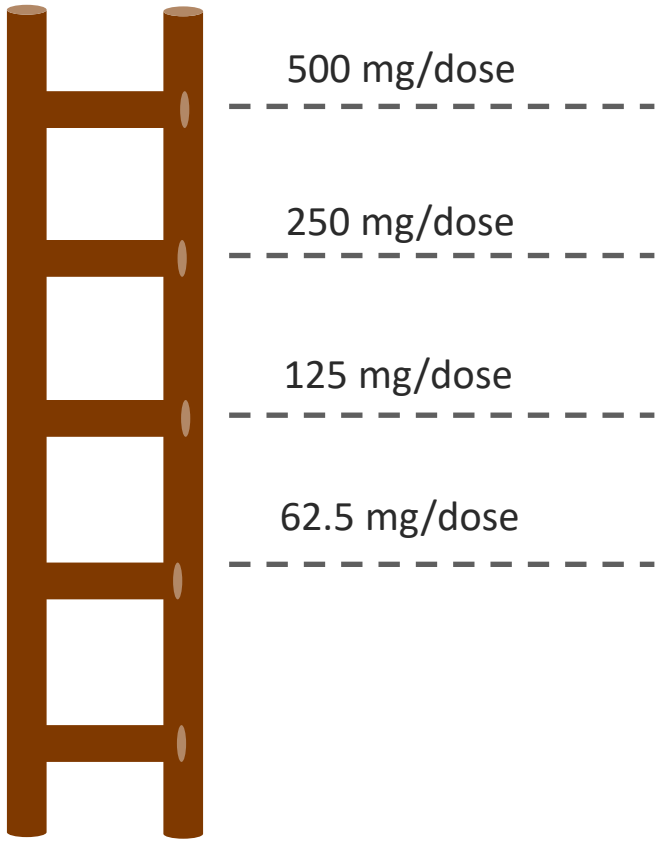
Unique Advantage of SYNB

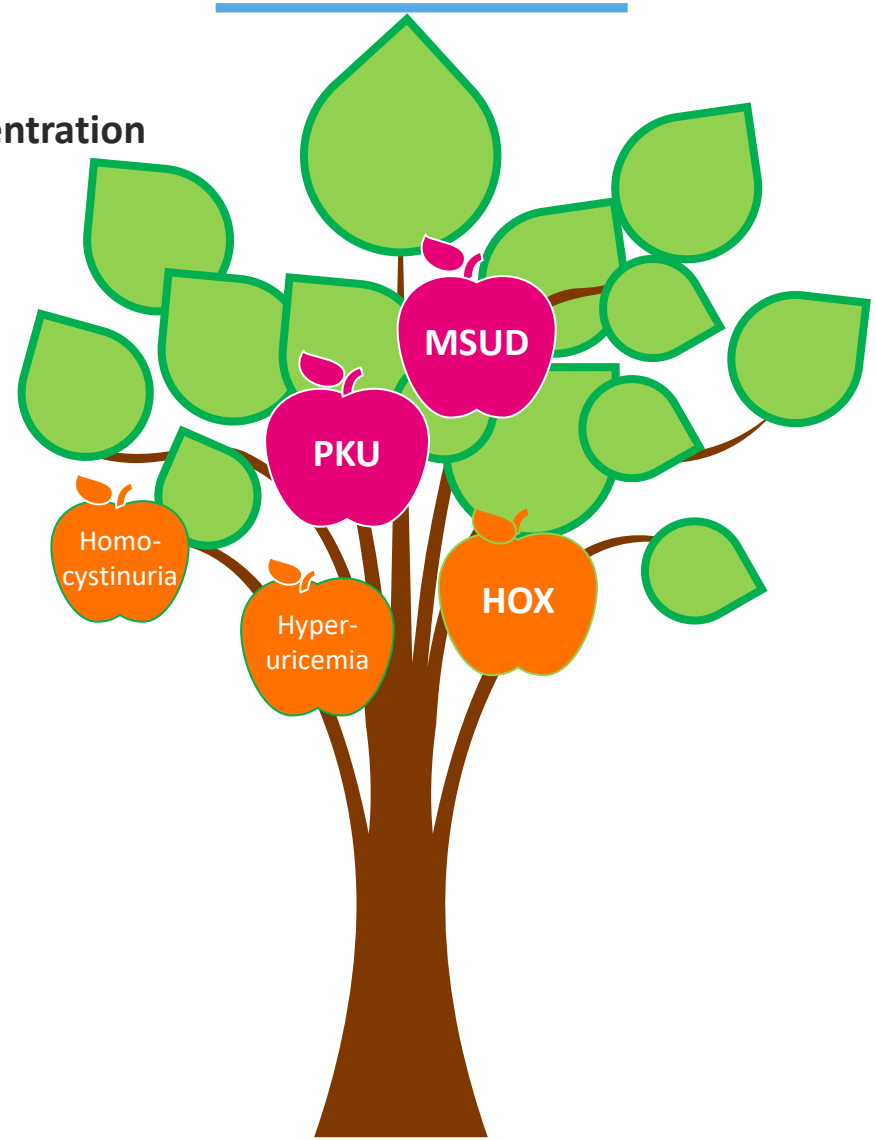
Bacteria act catalytically, can contain multiple enzyme pathways and are protected from digestion within the GI tract.

Focus in Rare Metabolic Disease: Consuming Toxins

"Low Hanging Fruit" as Targets for Expanding our Internal Portfolio

Dose determined by substrate concentration and target levels





Target Substrate Levels >200 mg/dose

Target Substrate Levels <200 mg/dose

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Phenylketonuria (PKU)

Meaningful Opportunity To Improve Patient Lives

Emerging treatment options will continue to leave many patients behind

SYNB1618 demonstrates potential to lower Phe in PKU patients

Phase 2 Phe-lowering trial starting in 2H 2020

Next generation strain in development

Phenylketonuria (PKU)


Julia, living with PKU

Why PKU?

Biology well-understood: Inability to break down phenylalanine (Phe) results in toxic levels in the brain leading to cognitive impairment, convulsions and behavioral problems

⬇ Phe in GI tract = ⬇ blood Phe = clinical benefit for patient

High unmet need particularly for pediatric patients

~ 34,000 patients US + EU

Status

Solid oral formulation of SYNB1618 demonstrated good tolerability and activity in healthy volunteers

Preparing for Phase 2 study in PKU patients

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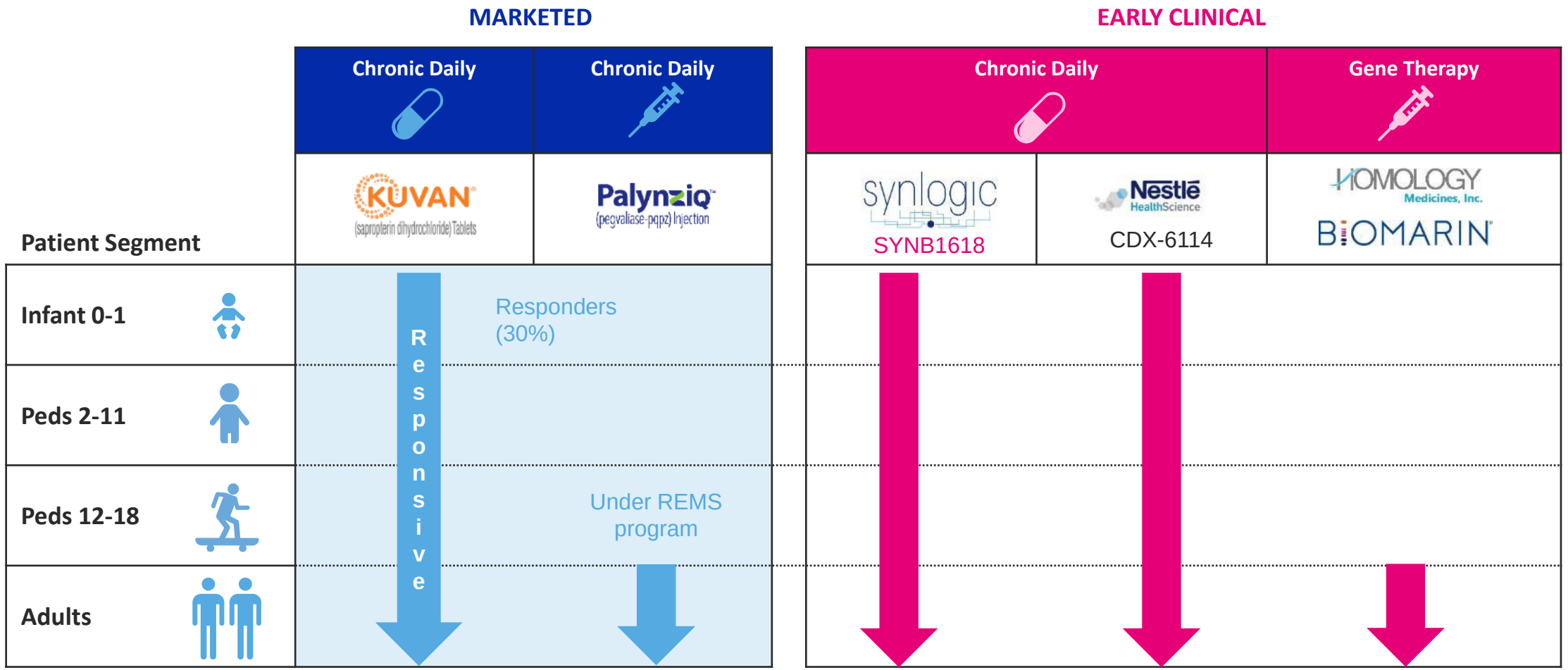
PKU Patients Require Therapeutic Options

SYNB1618 Is Well-Positioned to Address the Needs of All PKU Patients

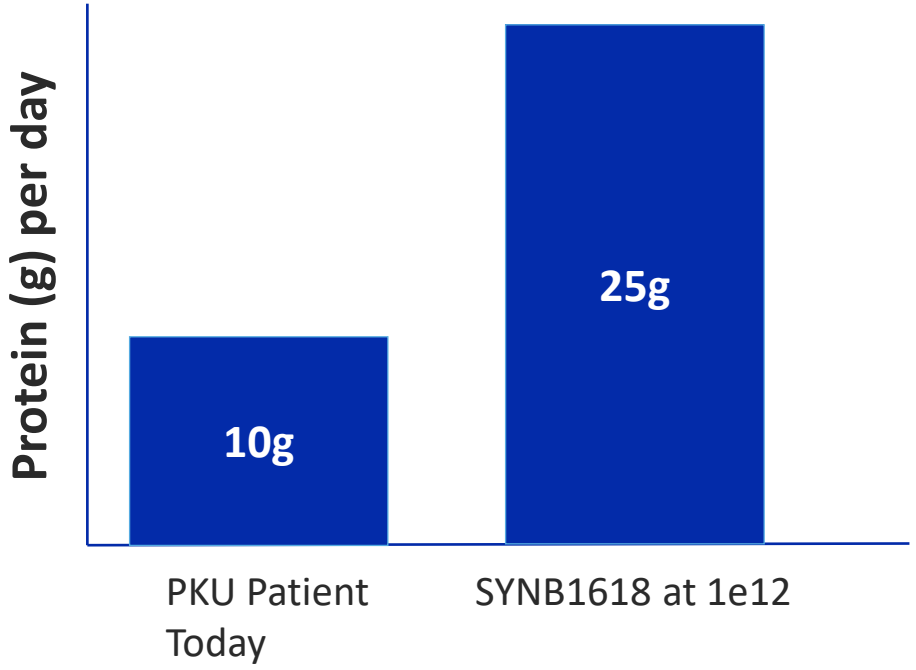


Target Product Profile for PKU

Indication	Reduction of blood phenylalanine in patients with phenylketonuria (PKU) Increase natural protein intake in PKU patients with controlled blood Phe
Target Patient Population	Adults and pediatrics ≥ 12 years of age with phenylketonuria and uncontrolled blood Phe Adults and pediatrics with phenylketonuria and controlled blood Phe on a restricted diet
Efficacy	Primary: Reduction in blood Phe levels by >30% in patients with elevated blood Phe Long term: Increase in natural protein intake by ≥ 15g in PKU patients with controlled blood Phe on a restricted diet
Safety	Tolerability consistent with oral probiotic • Mild GI disturbance
Dosage	Sachet or capsule, dose ≤ 5e11 live cells with meals up to 3X per day

Potential of SYNB1618 to Enable Increased Protein Intake

Possible Protein Consumption



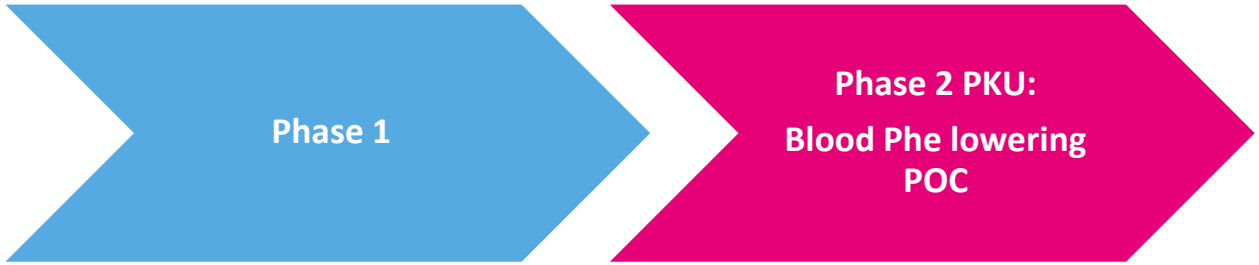
Assumptions

- Strain consumption of 250mg Phe/dose, 3x/day
- Adult patients well controlled on restricted diet and pediatrics

SYNB1618 May Enable Meaningful Increases In Daily Protein Intake For Patients

Phenylketonuria: Clinical Development Strategy

Current Stage



- **Safety, tolerability**

- **Subjects:**
  - healthy adult volunteers >18
  - PKU adult >18 and blood Phe >600 µM

- **Outcomes:**
  - Safety tolerability
  - Pharmacodynamics

- Liquid and Solid formulation

- **Blood Phe lowering**

- **Patients:**
  - Adults with PKU and blood Phe >600 µM

- **Outcomes:**
  - D5 Phe AUC
  - %CFB Fasting Phe

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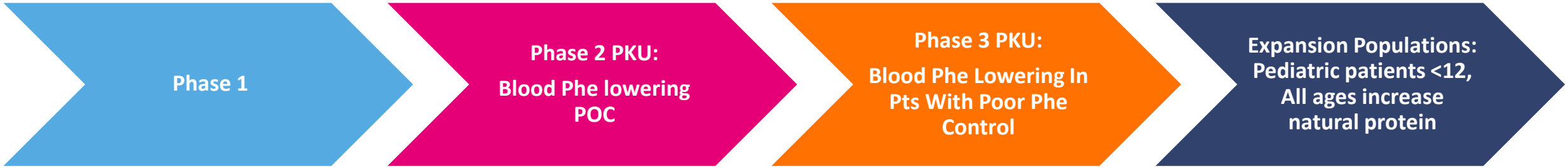
Phenylketonuria: Clinical Development Strategy

Current Stage



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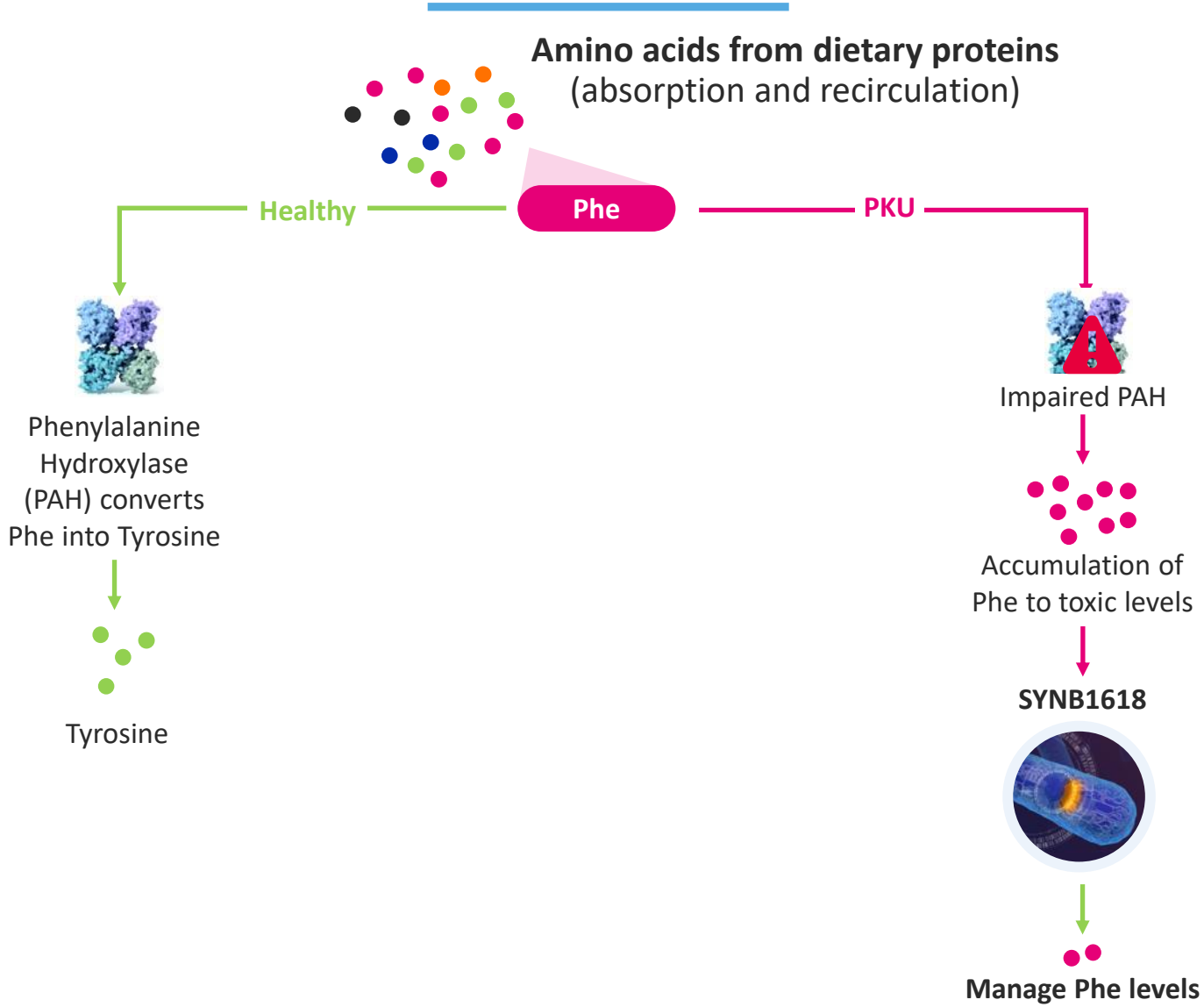
- **Patients:**
  - Adults with PKU and blood Phe >600 µM
- **Outcomes:**
  - D5 Phe AUC
  - %CFB Fasting Phe

- **Blood Phe lowering**
- **Patients:**
  - Adults and pediatrics ≥12 years with blood Phe >600 µM
- **Outcomes:**
  - Change from baseline in blood Phe
  - Percent lowering of blood Phe

- **Protein tolerance while maintaining blood Phe**
- **Patients:**
  - PKU with Blood Phe <600 µM and restricted diet, age ≥12
  - age <12
- **Outcomes:**
  - Change from baseline in blood Phe
  - g/kg natural protein increase while maintain blood Phe <360 µM

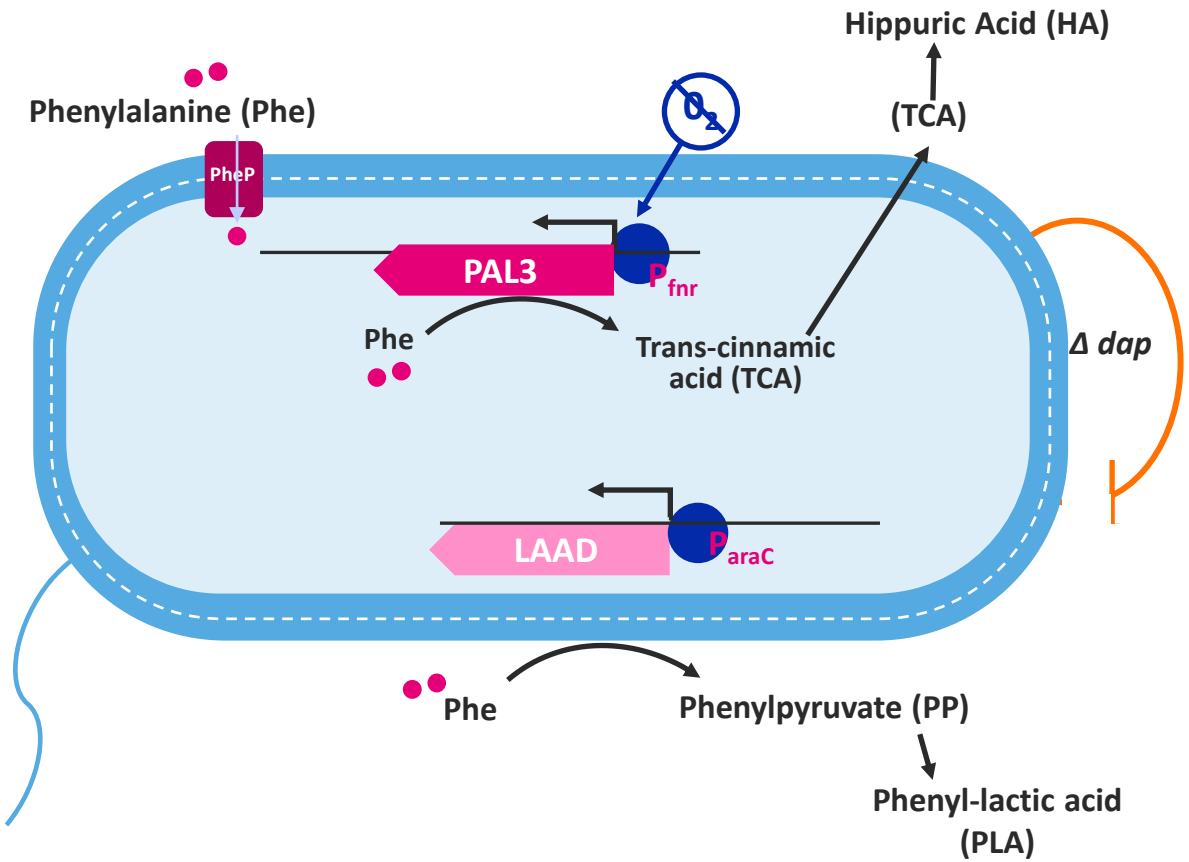
synlogic

Phenylketonuria (PKU) Pathogenesis



SYNB1618 Built From Synthetic Library Specifically To Consume Phe

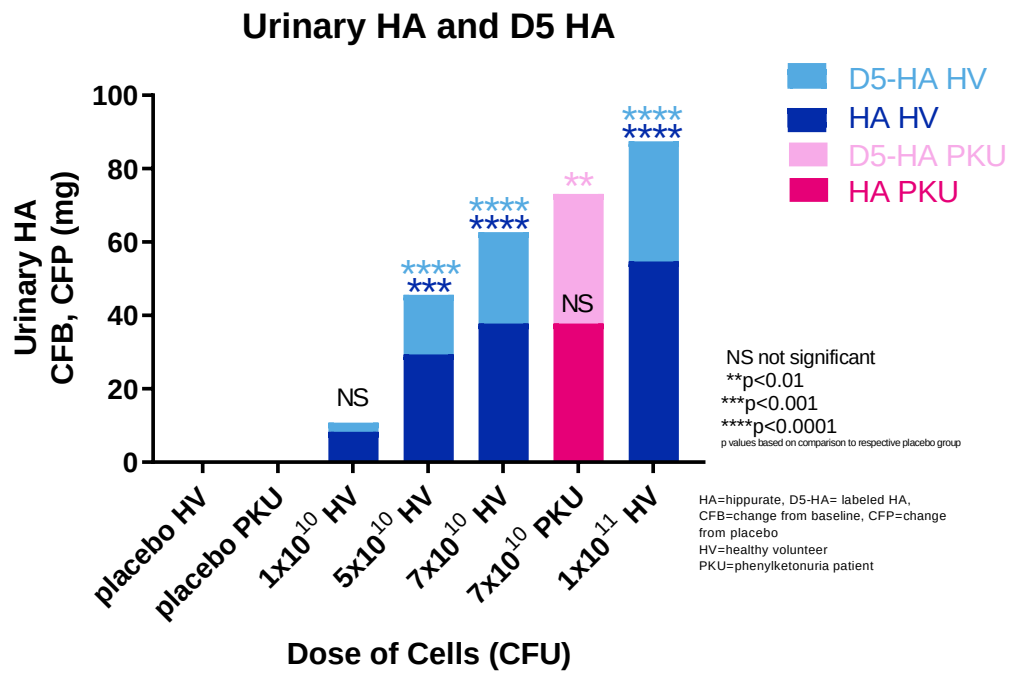
Component	Approach	Benefit
Bacterial Chassis	*E. coli* Nissle	Probiotic - decades of human use & safety data
Switches	FNR & AraC promoter	Promoters control expression during manufacturing and at site of action
Pump	*PheP*	Pumps Phe into cell
Effector 1	*PAL3* Enzyme	Degrades Phe to TCA (measurable biomarker of activity)
Effector 2	*LAAD* Enzyme	Alt. Phe-consuming pathway
Safety Features	*Δ dap*	Auxotrophy – requires diaminopimelic acid (DAP) to grow



synlogic

SYNB1618 in the Clinic: Liquid Formulation in Healthy Volunteers & Patients

URINARY HA AND D5-HA



CONCLUSIONS

- Across 56 healthy volunteers & 14 PKU patients given liquid formulation of SYNB1618:
  - ✓ SYNB1618 consumes Phe in the GI tract based on HA biomarker in a dose dependent manner
  - ✓ No SAEs, no systemic toxicity or infections
  - ✓ AEs mild or moderate in severity, and reversible. Most GI-related
  - ✓ All subjects cleared SYNB1618

Statistically Significant and Equivalent Activity of Liquid Formulation in Healthy Volunteers (HV) and Patients

Development of Solid Oral Formulation of SYNB1618

Liquid
Stable at -80 °C
Early Process
Suitable for dosing in clinic

Phase 1 demonstrated activity in the human GI tract

Lyophilized Powder in Sachet
Stable at 4-8 °C
Optimized Process
Suitable for outpatient studies

Bridging Study in healthy volunteers demonstrated activity and tolerability

To be used in upcoming Ph.2

Lyophilized Powder in Tablets or Other Forms
Scale up to larger fermenter
Suitable for commercialization

Will be developed in parallel with Phase 2

Patient-Friendly Presentations Will Be Developed For Pivotal Studies Based On Stable, Optimized Solid Oral Form

HV Solid Oral Bridging Study Sets Up Phase 2

Bridging Study Questions	
1 What is the MTD of the solid formulation?`	**$2e^{12}$ live cells**
2 Does dose-ramping improve tolerability?	**Yes**
3 Does stomach acid -buffering improve activity?	**Yes**

HV Solid Oral Bridging Study Sets Up Phase 2

Bridging Study Questions	
1 What is the MTD of the solid formulation?`	**$2e^{12}$ live cells**
2 Does dose-ramping improve tolerability?	**Yes**
3 Does stomach acid -buffering improve activity?	**Yes**
4 Does SYNB1618 solid oral demonstrate sufficient **activity** to warrant study in PKU patients?	**Yes**

- D5 **Phe tracer** data: Quantifies strain activity labeled and dietary Phe
- Plasma TCA and **Phe under fasted conditions**: Quantifies strain activity on non-dietary Phe
- **Phe Modeling**: Estimates Potential Phe Lowering in Phase 2 Study

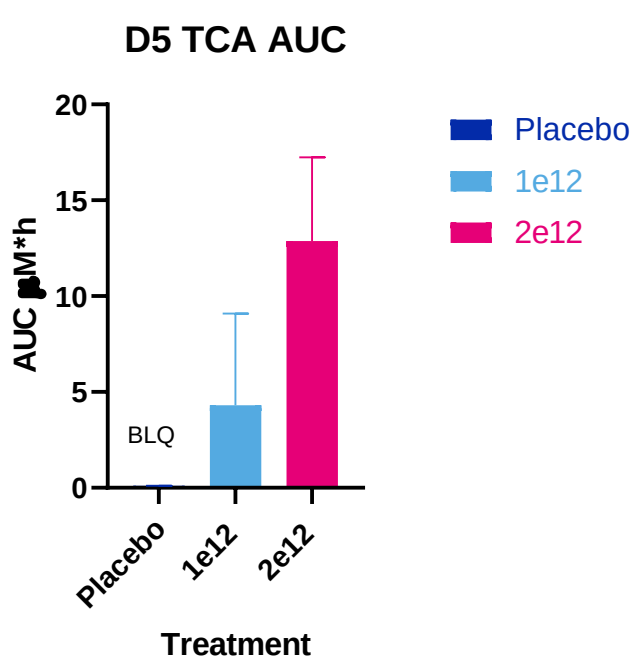
Bridging Study Provides Evidence Solid Oral SYNB1618 Consumes Phe

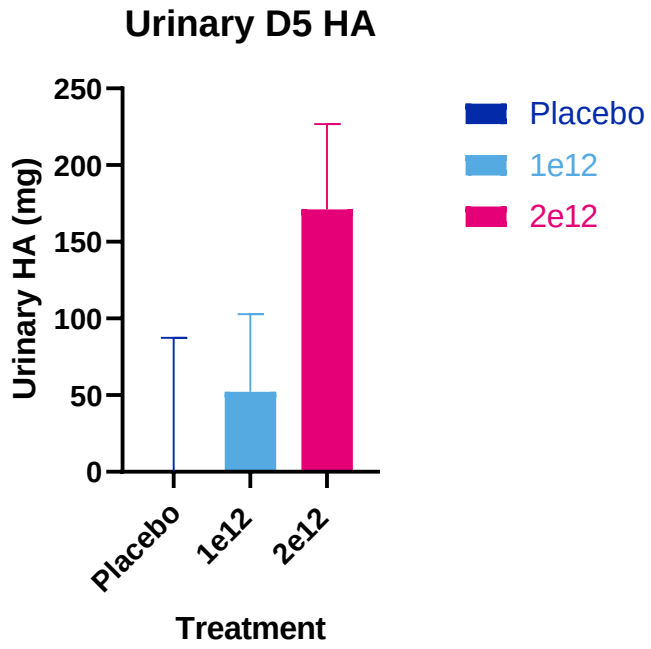
D5 Tracer Data in Healthy Volunteers

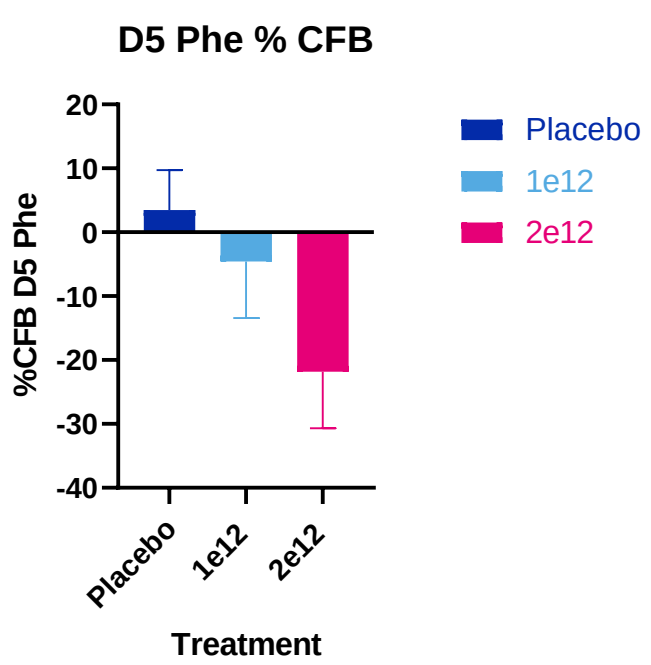
D5 Phe Converted to D5 TCA

D5 TCA Converted to D5 HA

Plasma D5 Phe Blunted







Data are means and 90% CI

SYNB1618 Mechanism Confirmed: Accessed D5 Phe Tracer in Gut & Lowered Plasma D5 Phe

SYNB1618 Has Ability to Access Non-Dietary Phe

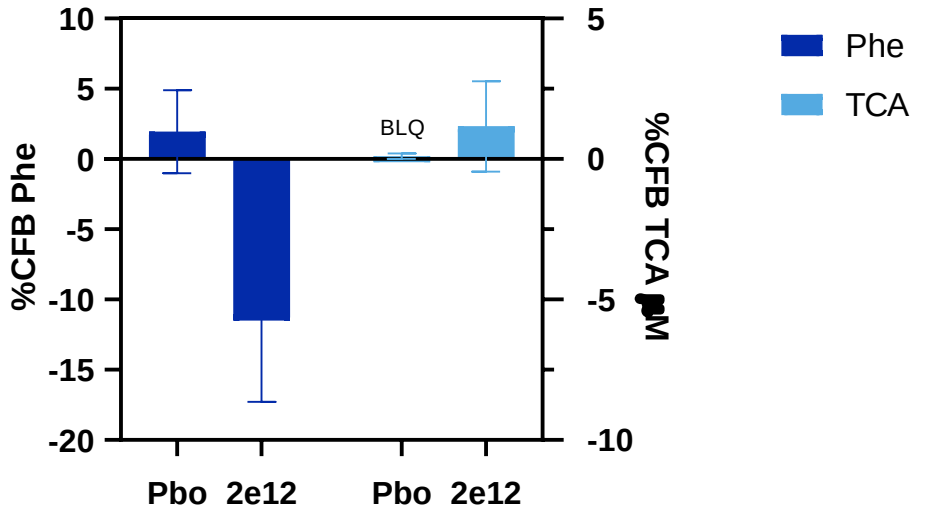
Healthy Volunteers Fasted Overnight

Given a dose of 2e12 SYNB1618

Subjects continued to fast

Plasma TCA and Phe Performed 2 hours later

Plasma Phe and TCA Under Fasted Conditions



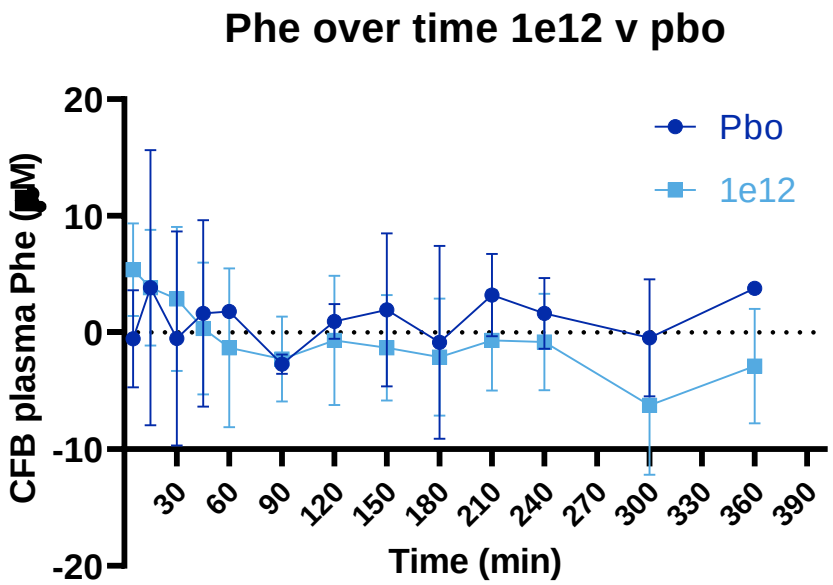
Ability To Access Non-Dietary Phe Supports Potential Combinations With Phe Restricted Diet (e.g. Pediatrics)

Key: HA: Hippurate, D5-HA: labeled HA, CFB: change from baseline, CFP: change from placebo, BLQ, below limit of quantitation

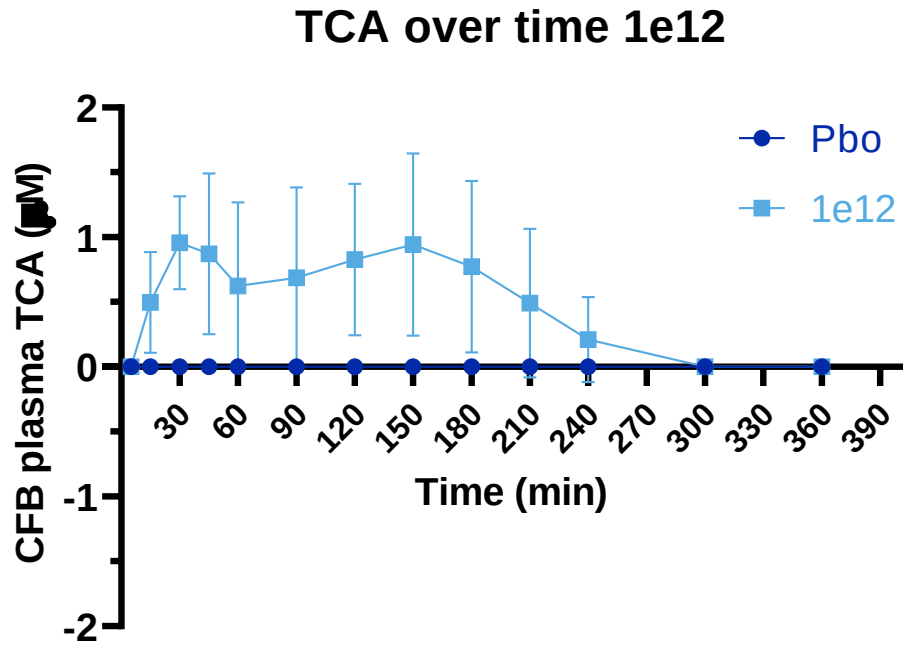
SYNB1618 Has Ability to Access Non-Dietary Phe

Phe Lowering and TCA Production Over Time Under fasted conditions in HV

Plasma Phe Under Fasted Conditions



TCA Under Fasted Conditions



Ability To Access Non Dietary Phe Confirmed In Time Course Studies

Key: HA: Hippurate, D5-HA: labeled HA, CFB: change from baseline, CFP: change from placebo

Translational & Quantitative Biology: Predicting Strain Activity in Humans

Modeling to Build Understanding of Complex Interactions Between Synthetic Biotic, GI Transit, and Substrate Availability

Inputs

Strain Activity

Metabolite Consumption

Biomarker Read-outs

In Silico Model

Proprietary Synlogic Simulation Models

Outputs

Required Metabolite Consumption For Clinical Benefit

Inputs across model systems allows for predictive modeling of clinical activity to enhance confidence in metabolite consumption performance of strain

Phe Modeling From Bridging Study Urinary HA Levels in Healthy Volunteers

Inputs

Strain Activity

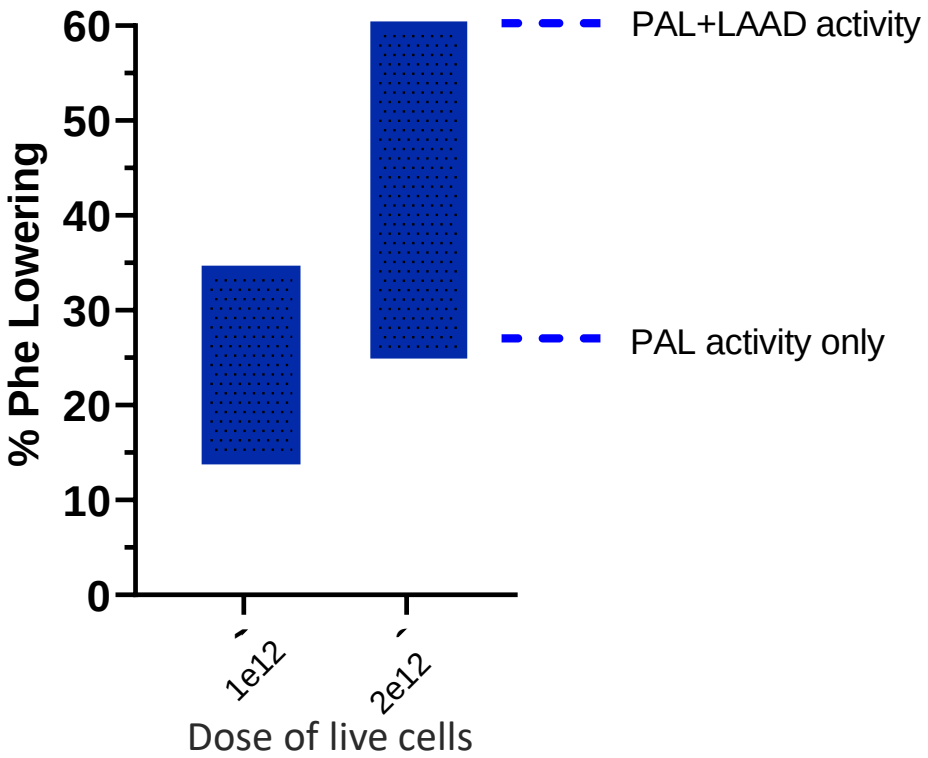
Metabolite Consumption Requirements[1]

Bridging Study Biomarker Read-outs[2]

In Silico Model

Proprietary Synlogic Simulation Models

Outputs: Phe Lowering Potential



Modeling Predicts SYNB1618 Activity In Target Range

1. Kaufman S. 1999 PNAS V96:3160-3164
2. Denny W et al 2019, SSIEM conference

SYNB1618 Phase 2 Study Goals

Study data will inform validity of modeling which has implications for other metabolic programs

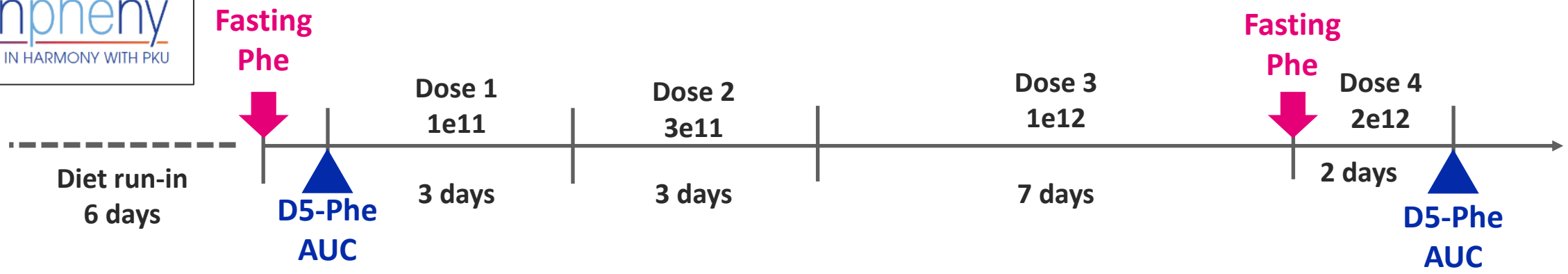
Demonstrate Phe Lowering in PKU Patients

- Plasma Phe lowering in fasted state at 1 x 10^{12} live cells over 7 days
- Post meal D5-Phe AUC lowering at 2 x 10^{12} live cells (**not impacted** by diet)

Validate PD Model

- Understand relationship of strain specific biomarkers with plasma Phe lowering

SYNPHENY Phase 2 Study in PKU



Endpoints

- **Phe Lowering**
  - Change from Baseline in D5 Phe AUC at 2e12 dose
  - Change in Fasting Phe after 7 days at 1e12 dose
- **Safety and Tolerability**

Execution

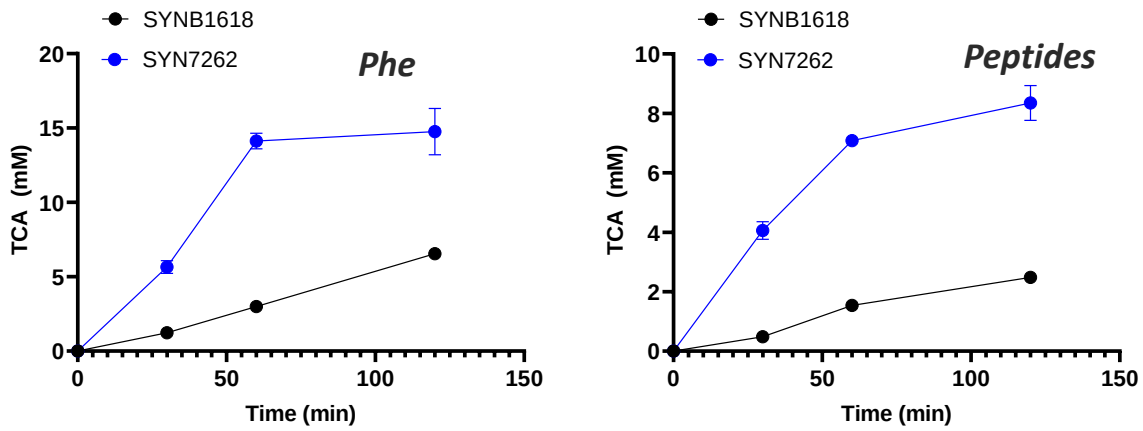
- Flexible design allowing home-based or office-based visits
- Informed by direct patient feedback on executing trials in the COVID era
- Dose ramp to improve tolerability
- Strict diet control to ensure consistent Phe intake, including 6-day run-in

Next Generation PKU Strain In Development

Target *in vivo* activity:
3-4X from SYNB1618

- Initial encouraging *in vitro* hits from collaborator EnEvolv
- Parallel work ongoing at Gingko: Synlogic will select **best-of-breed** from across both
- Clinical development path with **rapid move to pivotal** possible based on SYNB1618 data

PAL variant activity: Peptides and free Phe

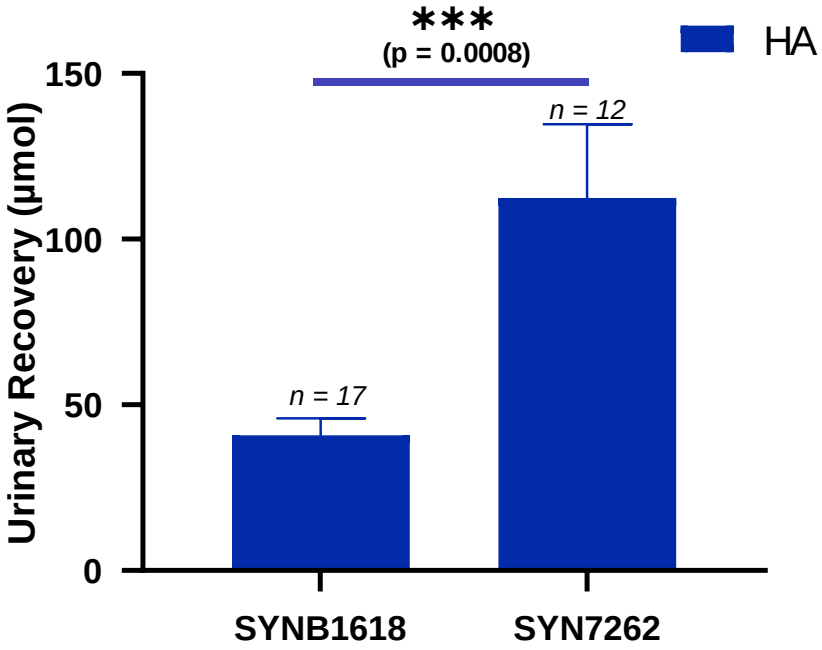


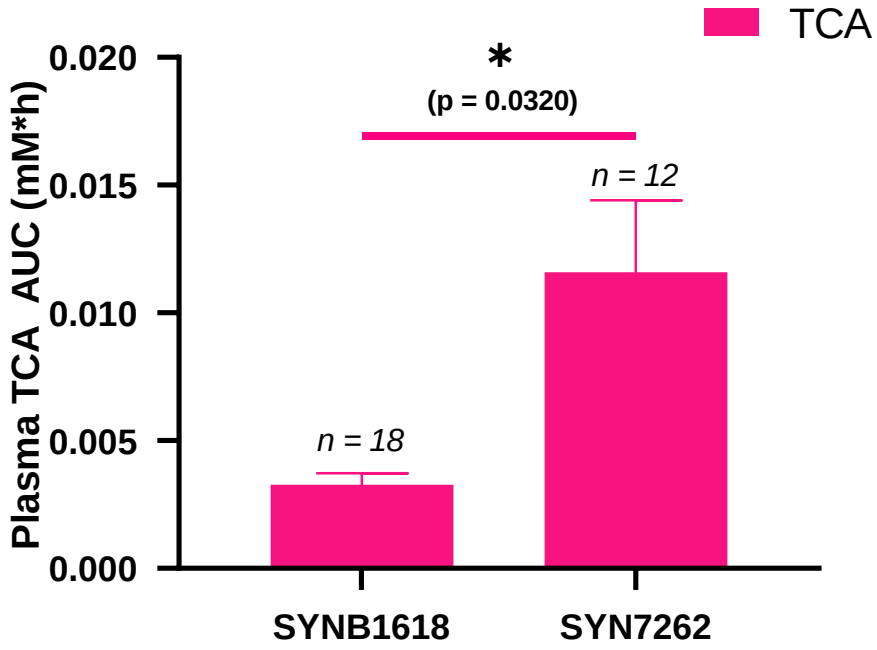
Next Generation Strain Demonstrates 3-4x Activity *In Vitro* Against Free Phe and Peptides

Next Generation PKU Strain In Development

Goal to Improve Potency, Lower Dose

Target *in vivo* activity:
3-4X from SYNB1618





Next Generation Strain Activity Improvements Confirmed In Non-Human Primates

Phenylketonuria (PKU)

Meaningful Opportunity To Improve Patient Lives

Emerging treatment options will continue to leave many patients behind

SYNB1618 demonstrates potential to lower Phe in PKU patients

Phase 2 Phe-lowering trial starting in 2H 2020

Next generation strain in development

Internal Metabolic Pipeline: Enteric Hyperoxaluria

Dr. Richard Riese, MD, PhD
Chief Medical Officer

Enteric Hyperoxaluria

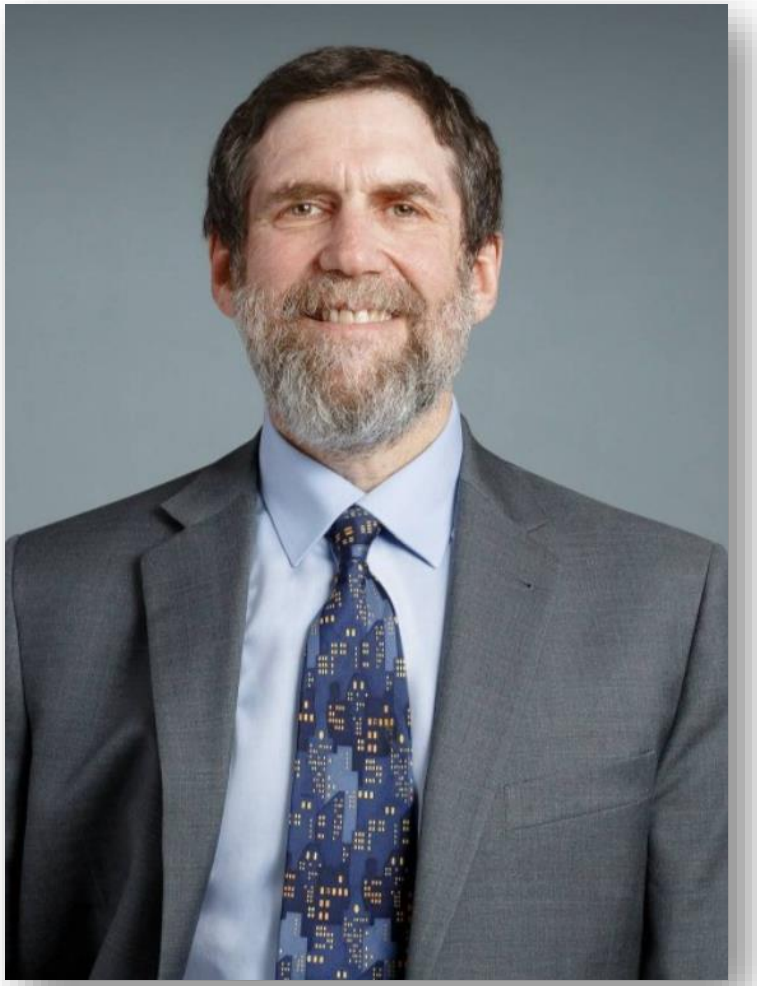
Our Next Step To Synthetic Biotic Medicines

High unmet medical need with no available therapeutic options

Efficient clinical development: PoC achievable in Phase 1b

SYNB8802 has potential to meaningfully reduce urinary oxalate levels

Welcome Dr. David Goldfarb, M.D.



David S. Goldfarb, M.D.

Professor of Medicine and Physiology, NYU School of Medicine
Clinical Chief, Nephrology Division, NYU Langone Health, Chief, Nephrology Section, New York VA Medical Center

Dr. Goldfarb is an internationally-renowned expert in kidney stone prevention. His clinical research has involved many aspects of the care of patients with chronic kidney disease (CKD) and renal failure, including the management of anemia and secondary hyperparathyroidism, hypertension, CKD-MBD, hyperphosphatemia and gout.

His work in stone disease has focused on cystinuria, hyperoxaluria, osteoporosis in stone formers, renal tubular acidosis, metabolic acidosis, role of bacteria in stone disease, uric acid, genetics of stone disease, and the role of diet in stone formation. He is a co-inventor of Moonstone, the first high citrate beverage designed for kidney health. He has had three calcium oxalate stones.

Dr. Goldfarb graduated from the Yale School of Medicine and trained in Internal Medicine at New York VA and NYU, and Nephrology at New York University; he is board-certified in both specialties. He also is certified by the American Society of Hypertension as a specialist in hypertension.

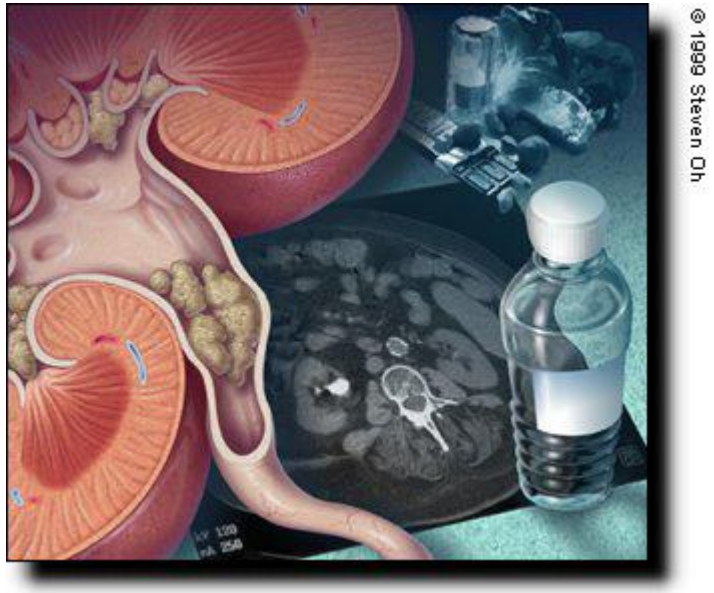
Enteric Hyperoxaluria

David S. Goldfarb, M.D.

Director, Kidney Stone Prevention and Treatment Programs,

New York VAMC and NYU Langone Health

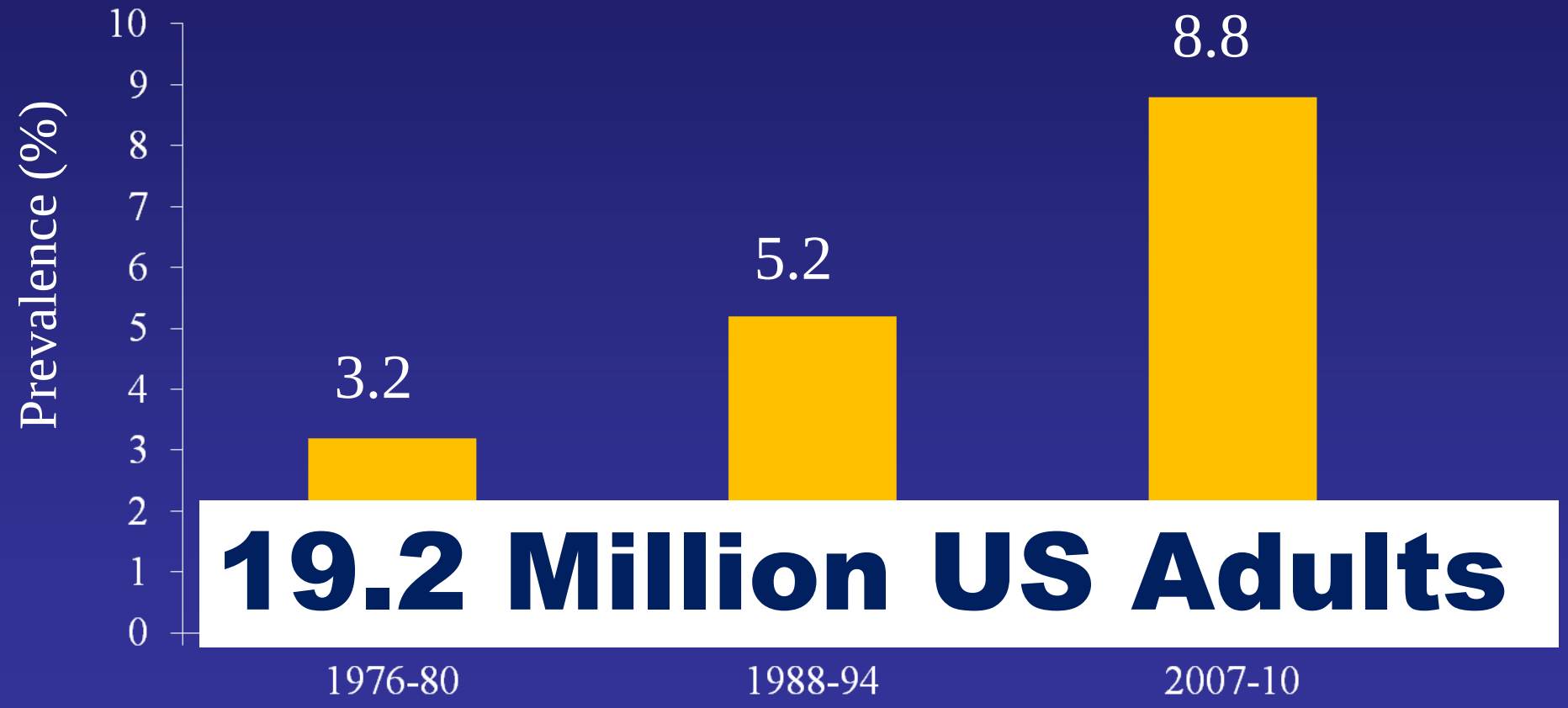
Professor of Medicine & Physiology, NYU School of Medicine



Disclosure

- Consultant:
  - AstraZeneca, Retrophin, Alnylam, Synlogic
  - Owner, Patent Holder: Dr. Arnies, Inc.
  - PMHx: CaOx Stones

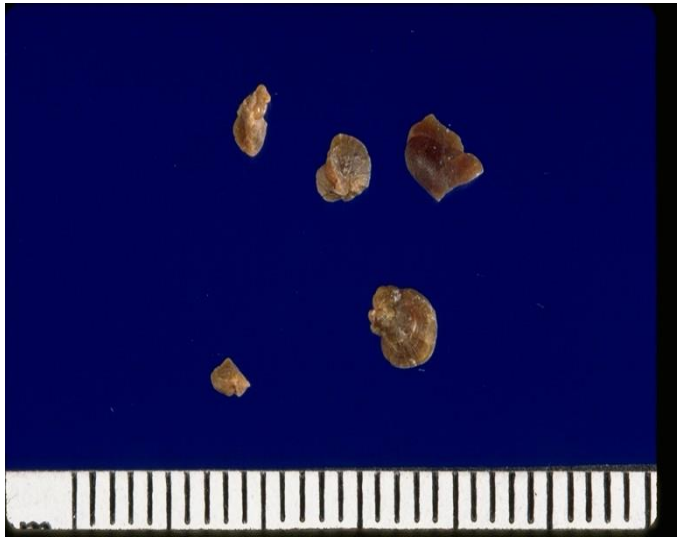
US Population Prevalence of Nephrolithiasis (NHANES 1976-2010)



Stamatelou, KI, 2003; Scales, Eur Urol, 2012

Bowel disease increases stone prevalence

- Estimates are variable and often lacking control groups
- Bowel disease increases risk of stones at least 2 fold
- Surgery for bowel disease increases risk about 3 fold compared to no surgery
- Prevalence of stones:
  - Crohn disease: 6.3%
  - UC: 4.4%
  - IBD with small bowel involved: 8.9%
  - IBD with colon only: 5.3%



Stone composition: general population

	Prevalence
Calcium	80%
Oxalate	80%
Phosphate	20%
Uric acid	10-15%
Struvite	5-10%
Cystine	1%

Stone composition: bowel disease

- Calcium oxalate
- Uric acid

Commonly Measured Risk Factors for Stone Disease

Common Causes of Stones in Bowel Disease

CALCIUM

Hypercalciuria

Low urine volume

Hyperoxaluria: IBD, short bowel, steatorrhea

Hypocitraturia: all bowel diseases, ileostomy

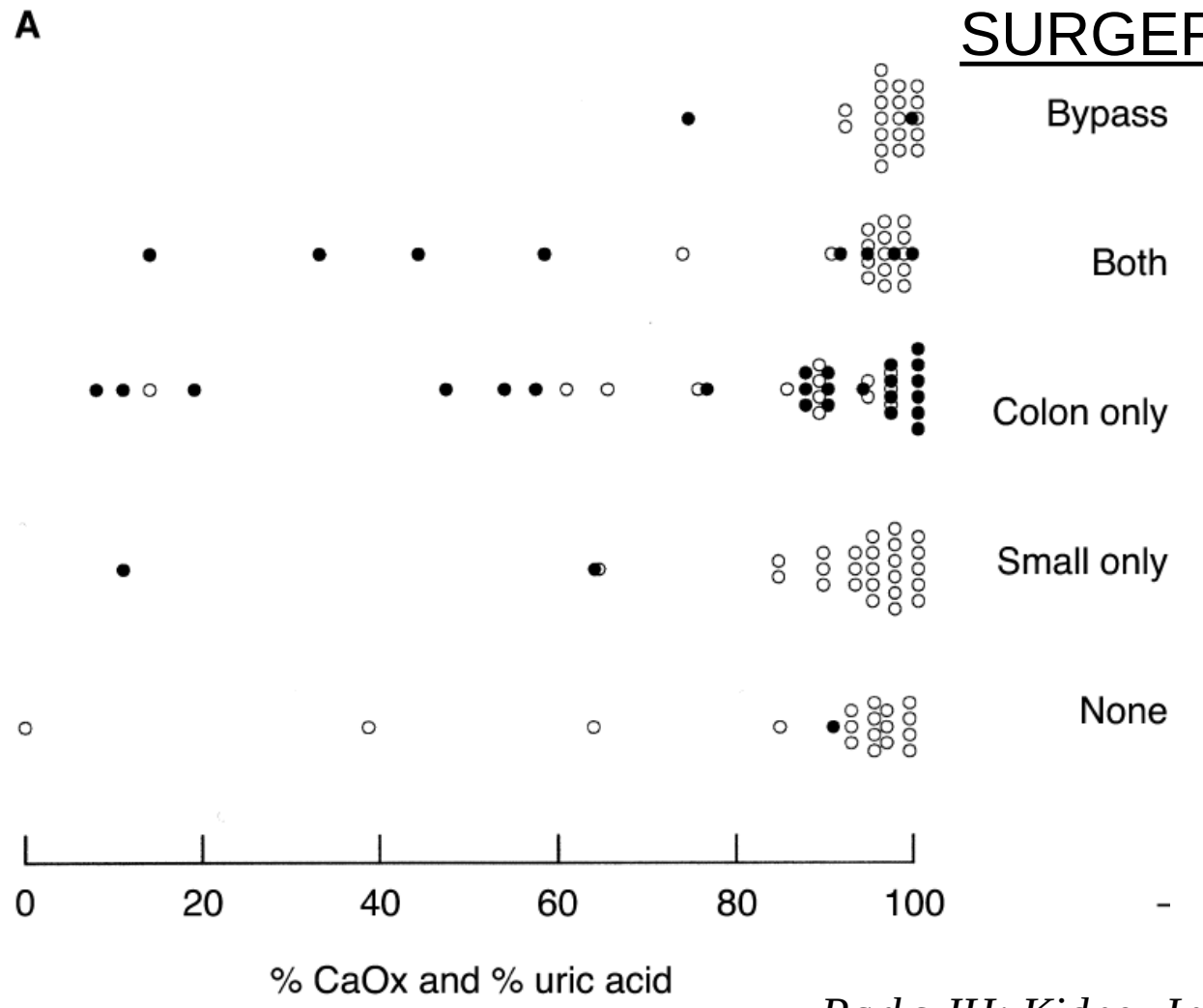
Hyperuricosuria

URIC ACID

Low urine volume: all bowel diseases with diarrhea

Low urine pH: all bowel diseases with diarrhea

Stone composition and bowel surgery



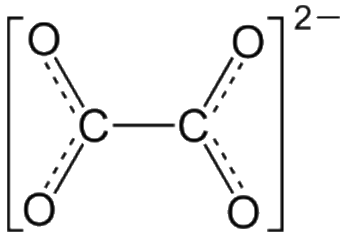
● = most UA

○ = CaOx

180 patients
at U. Chicago

Parks JH; Kidney Int 63: 255, 2003

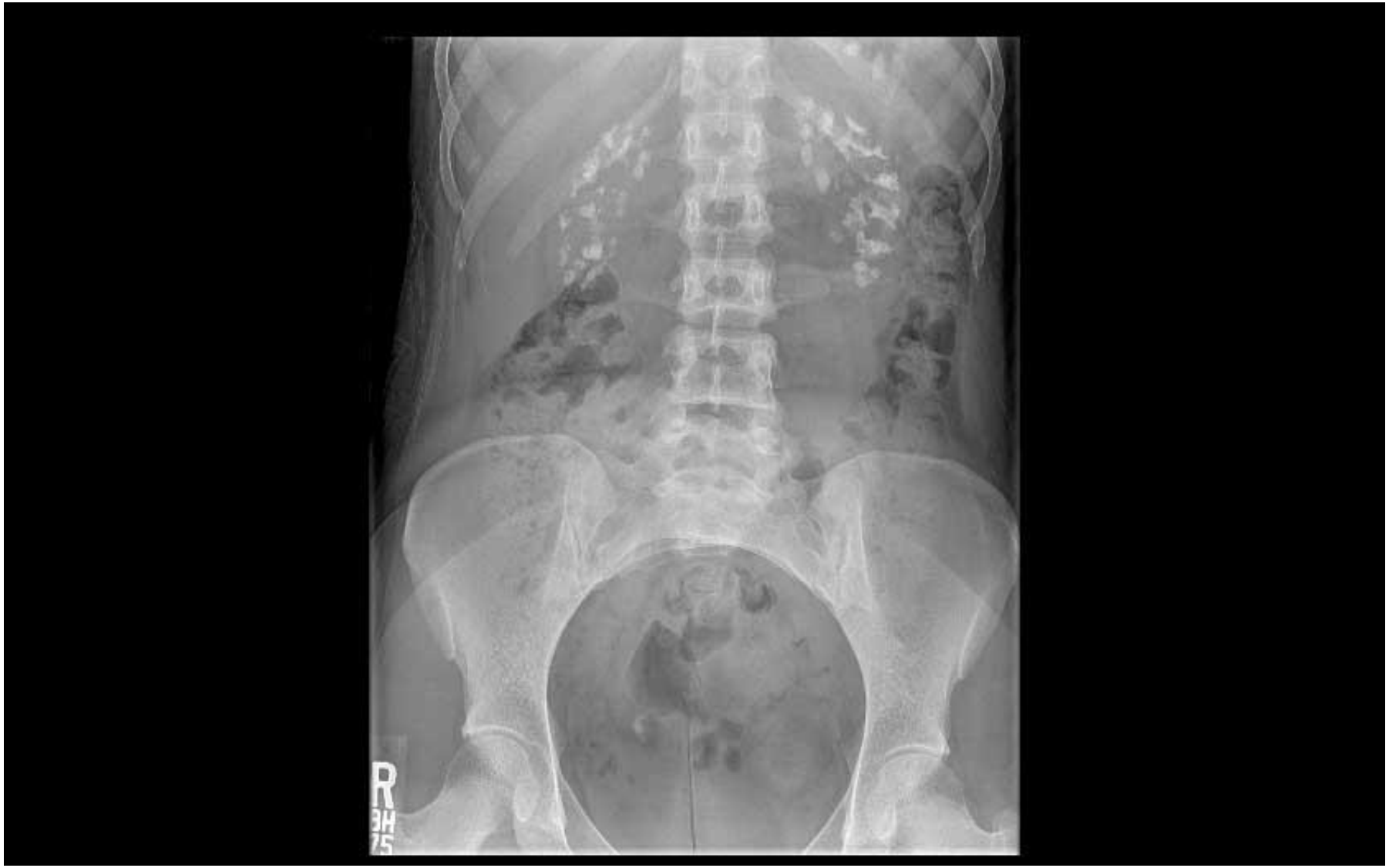
Dietary sources of oxalate



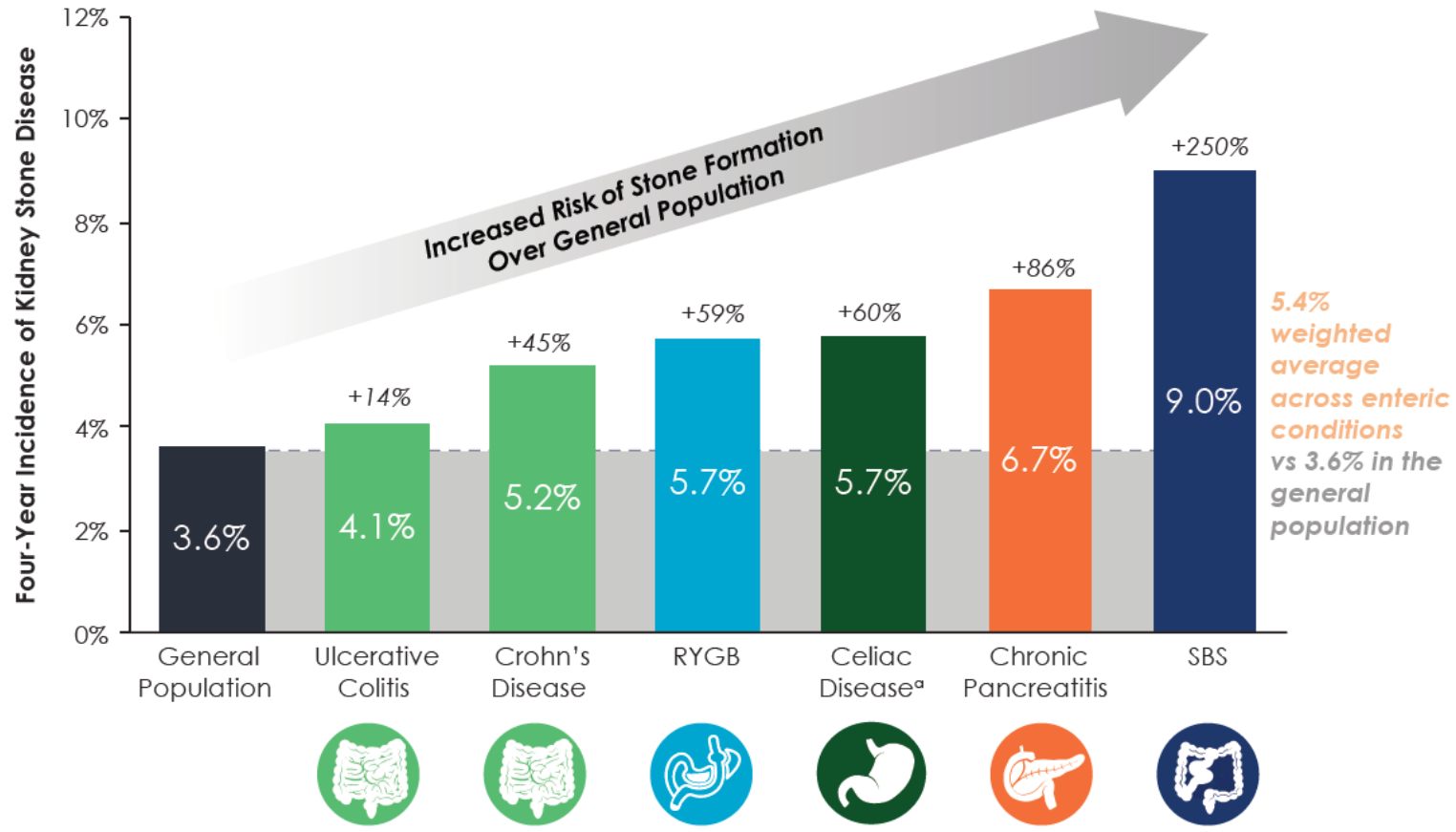
https://regepi.bwh.harvard.edu/health/Oxalate/files/

NYU Langone Health

Nephrocalcinosis: a cause of kidney failure



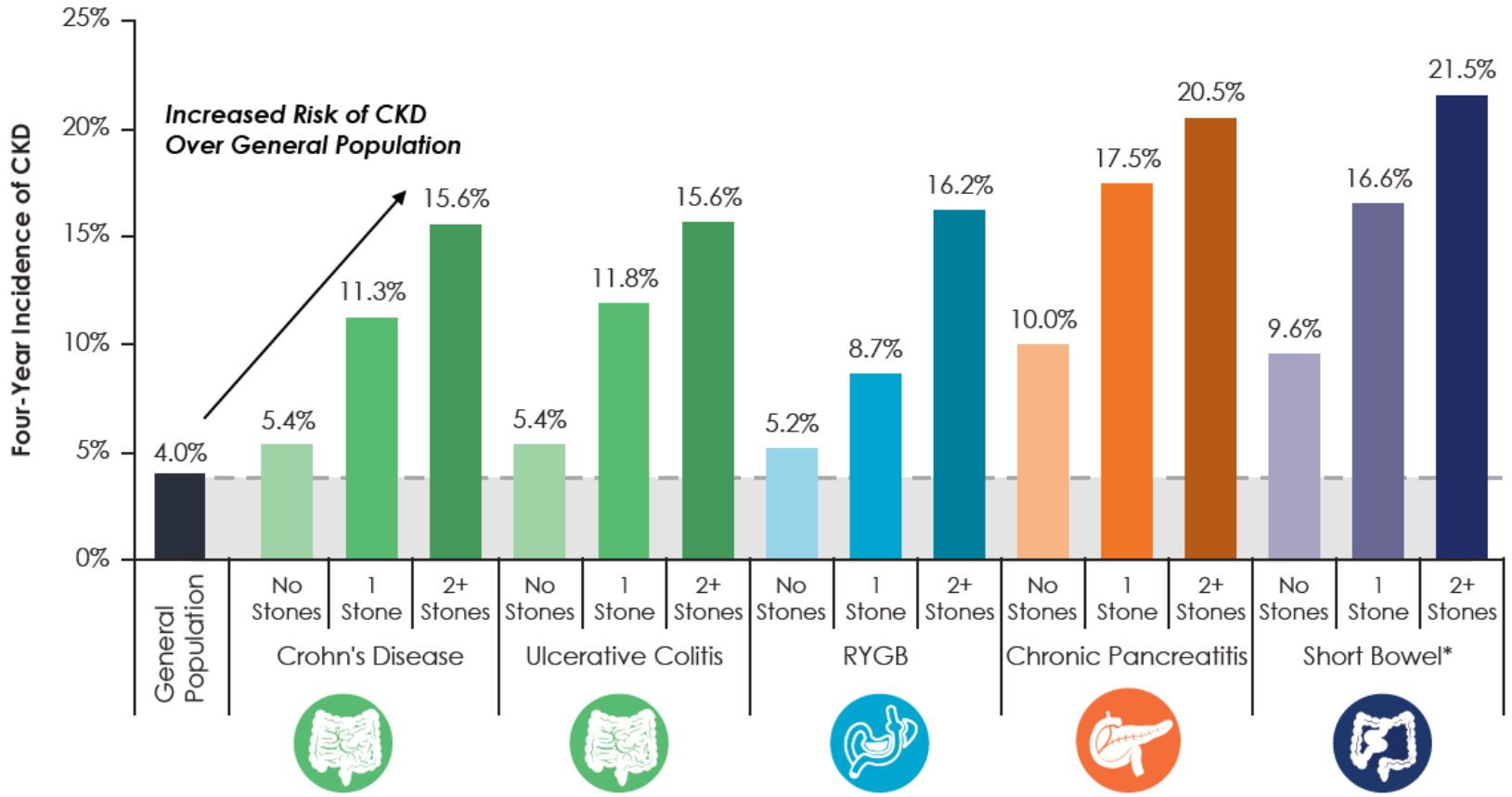
Risk of Kidney Stones in Bowel Disease



[a]Untreated celiac disease.

Tasian GE Poster SA-PO276; Kidney Week 2019

Risk of Developing CKD with Bowel Disease



*Small bowel resection or gastrectomy with Roux-en-Y.

Tasian GE Poster SA-PO276; Kidney Week 2019

ndt
Nephrology Dialysis Transplantation

Full Review

Enteric hyperoxaluria: an important cause of end-stage kidney disease

Table 1. Summary of the cases

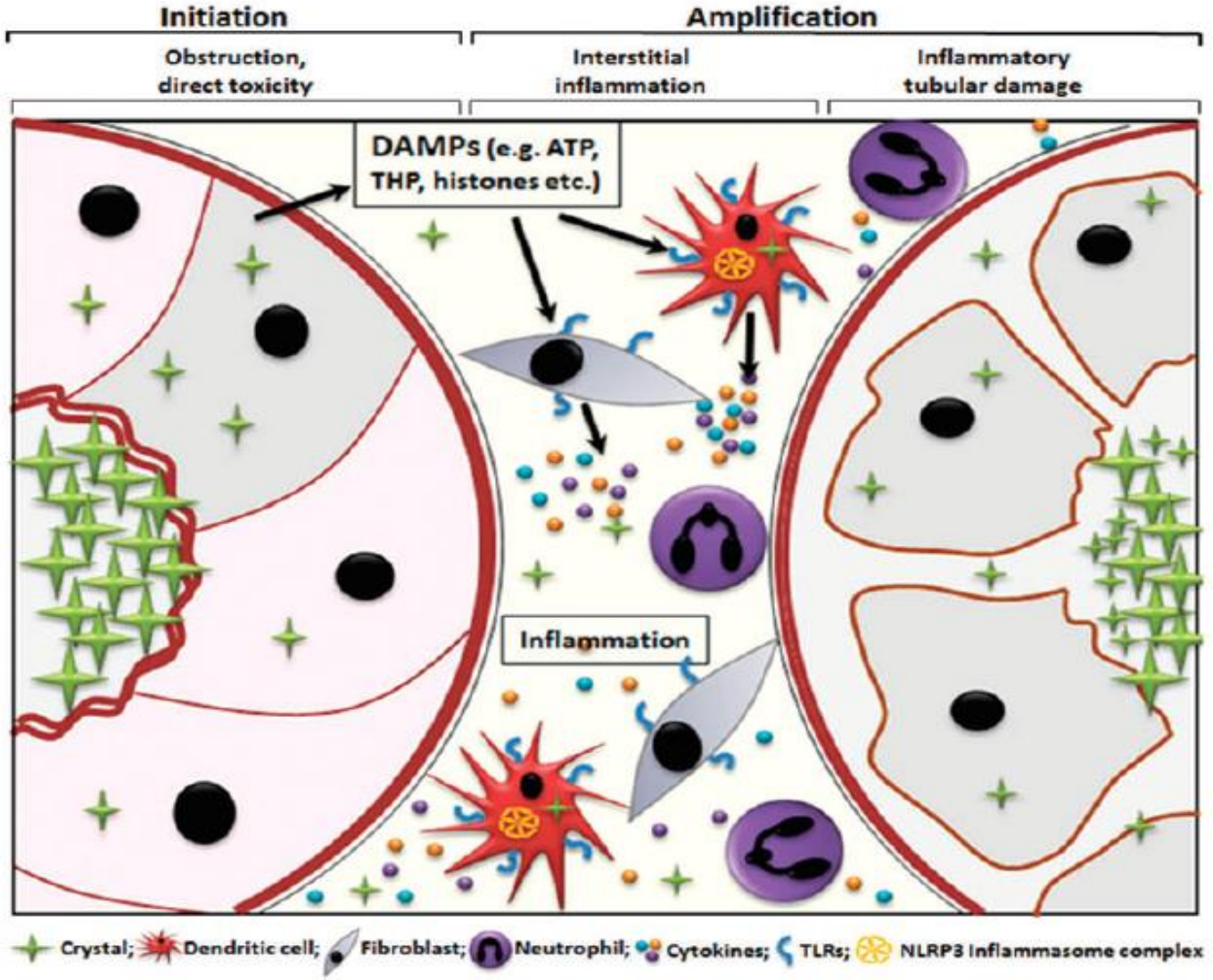
Patient	Primary pathology	Yrs to ESRD	Initial Uox (mg/day)	Post-transplant Uox (mg/day)	Initial CaOx SS	Post-transplant CaOx SS
1	Crohn's disease	20	135	86	12.7	3.6
2	Crohn's disease	29	110	64	5.8	14.5
3	Crohn's disease	NA	114	135	4.8	6.5

Yrs, years; ESRD, end stage renal disease; SS, supersaturation; UOx, urinary oxalate excretion; NA, not available.

- In this review, we highlight three cases of ESKD due to enteric hyperoxaluria following small bowel resections.
- We review current information on the pathophysiology, complications and treatment of this complex disease.

Nazzal L, Puri S, Goldfarb DS NDT 31:375-382, 2016

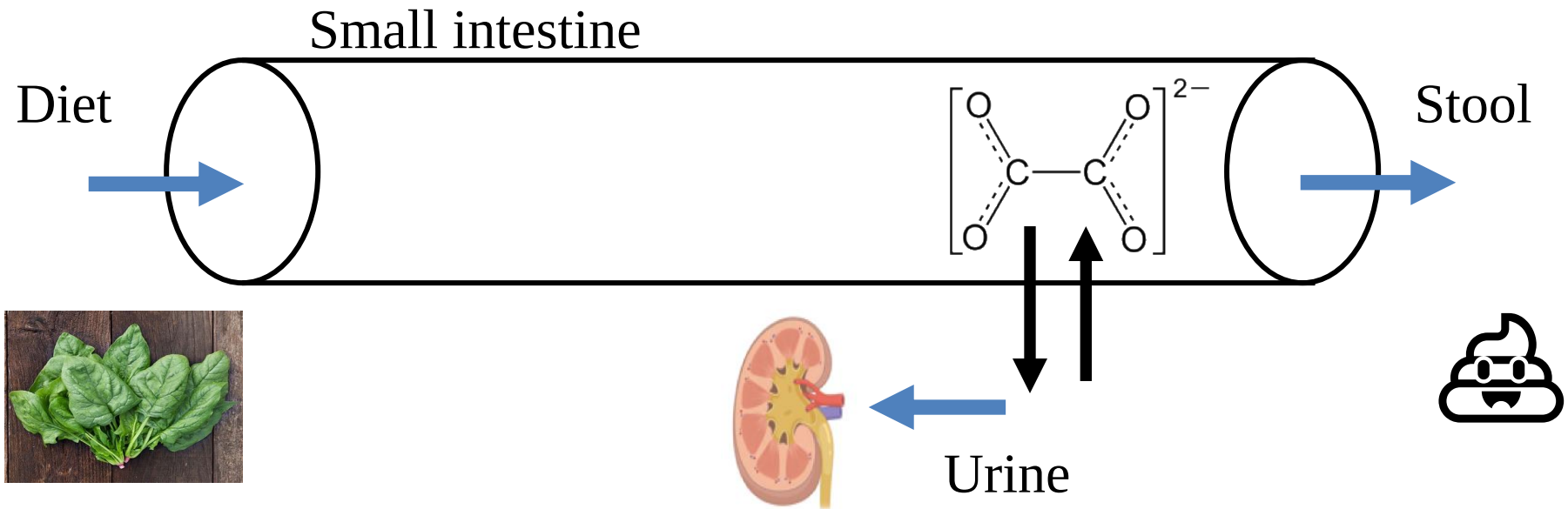
Crystallopathy: crystal-induced inflammation



Mulay SR, NDT 29:507-14, 2014

Oxalate Homeostasis in Health

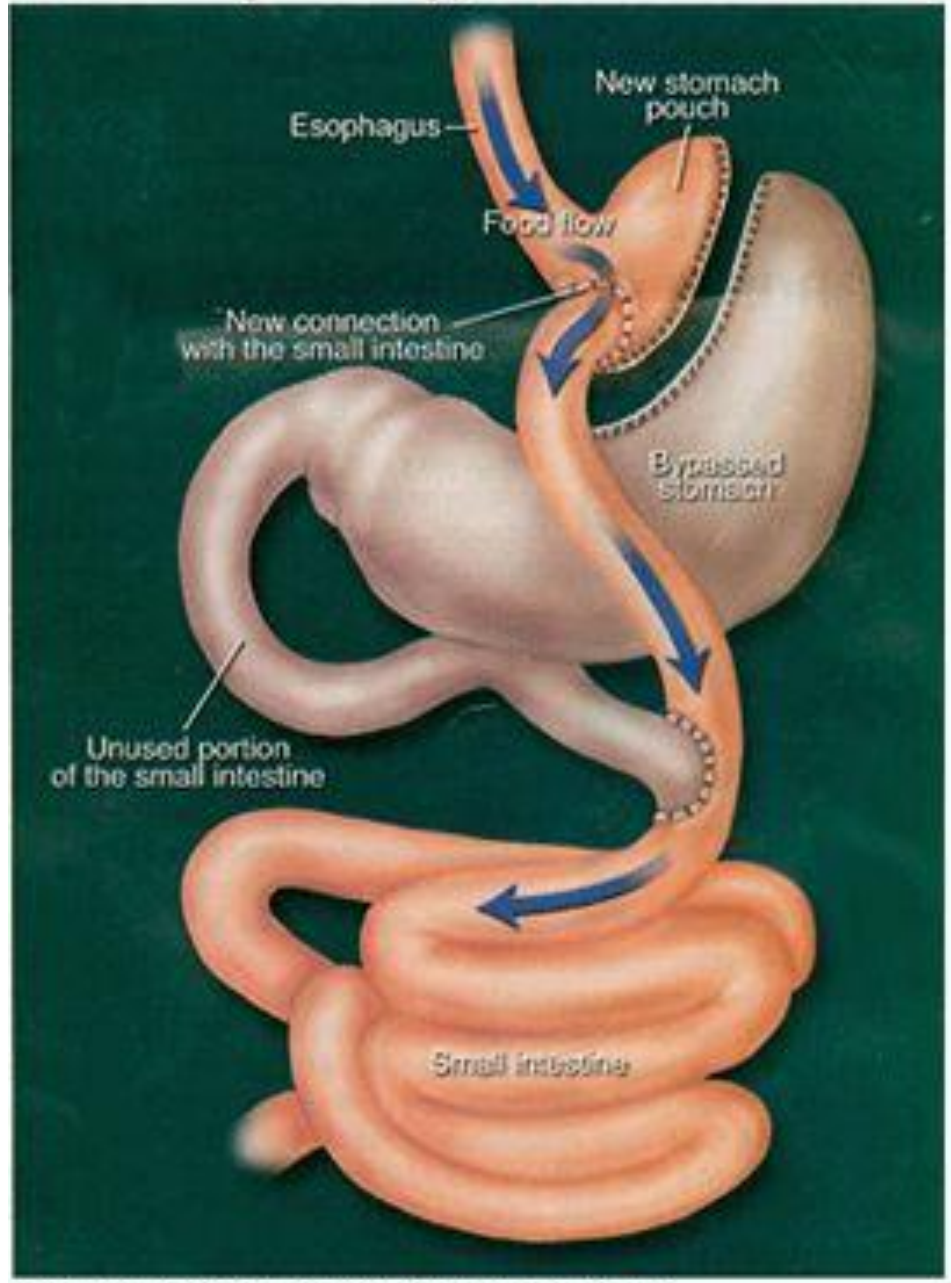
- Oxalate
  - absorbed from the diet
  - produced by hepatic metabolism of glyoxylate
- Intestine modulates
  - passive and active absorption
  - secretion of oxalate.
- Oxalate is excreted in the feces, or urine



Causes of Hyperoxaluria

- Enteric hyperoxaluria
- Dietary hyperoxaluria
  - Includes “idiopathic” hyperoxaluria?
  - Increased oxalate absorption?
- Primary hyperoxaluria
  - Mutations in hepatic enzymes
  - PH1, PH2, PH3

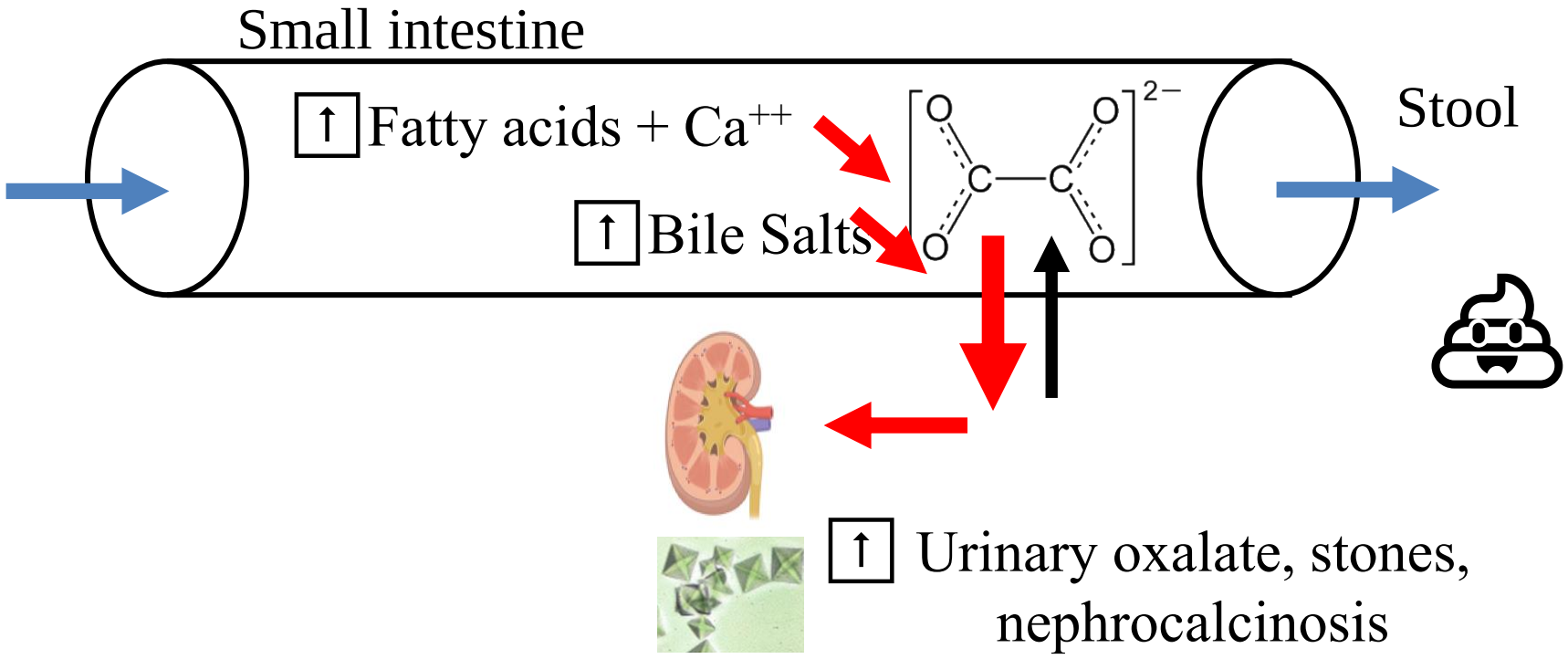
Roux-en-Y gastric bypass



Reproduced from Advance for Nurses 2002

Enteric hyperoxaluria

- Small bowel disease/resection causes steatorrhea: fat in stool
- Bile salt malabsorption and fatty acid malabsorption
  - Colonic fats bind calcium, leaves oxalate uncomplexed
  - Free, unbound oxalate crosses colonic mucosa
- Increased colonic permeability:
  - caused by malabsorbed fatty acids and bile acids
  - perhaps induced by changes in epithelial tight junctions.

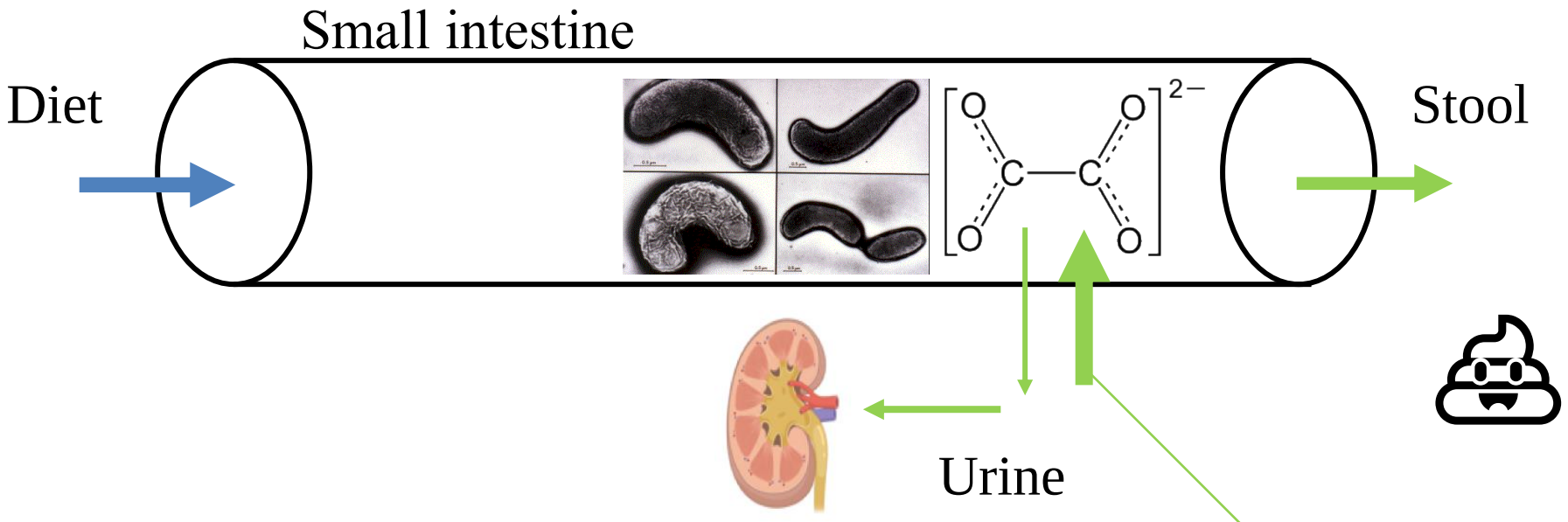


Enteric Hyperoxaluria: Treatment

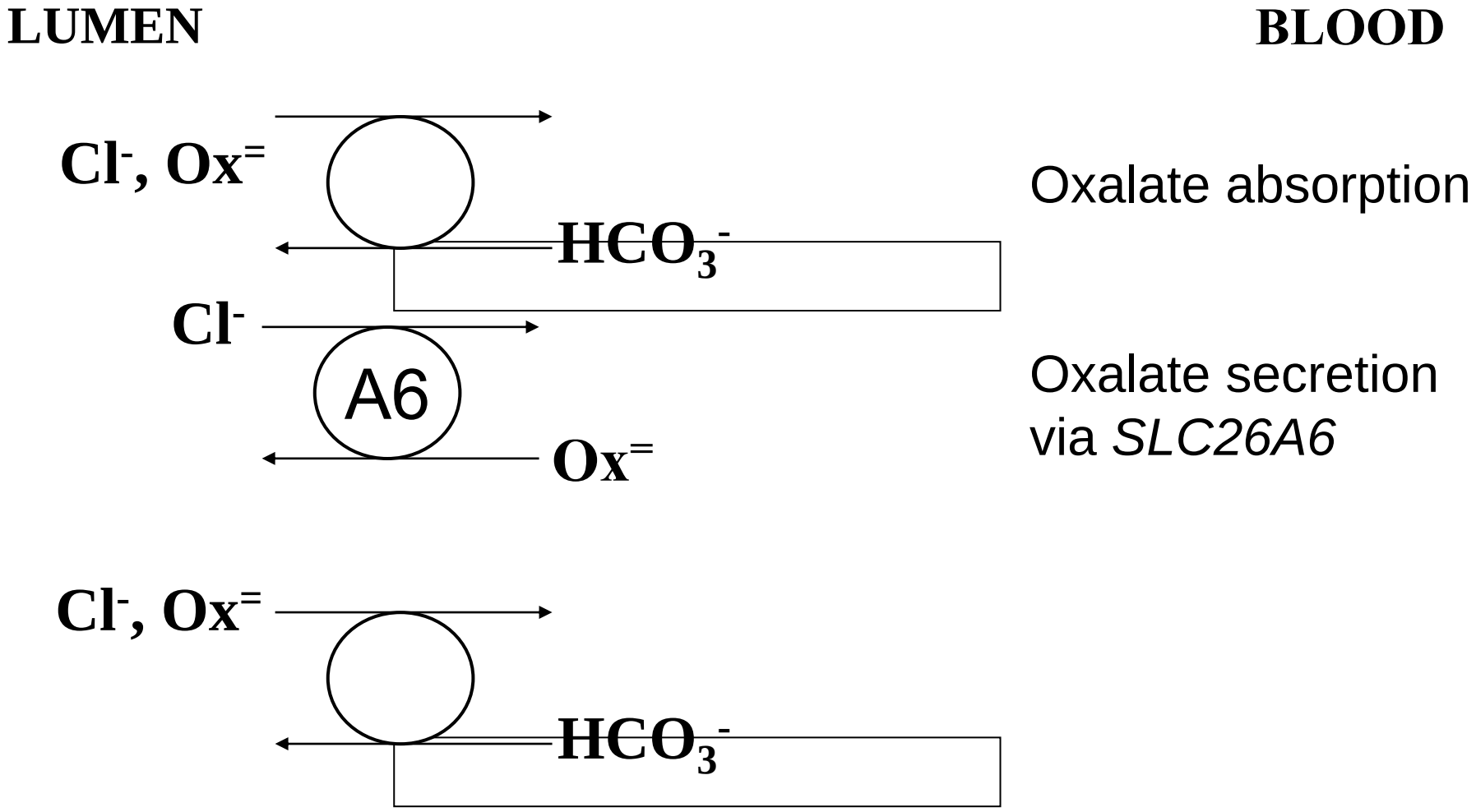
- High fluid intake: dilute all salts
- Reduce dietary oxalate
- Reduce dietary fat intake
- Calcium supplements (500–1,000 mg) with meals
  - Calcium citrate preferred
- Cholestyramine (2–4 g with each meal) suggested
  - binds oxalate and fatty acids
  - data mixed; my experience poor
- Potassium citrate
- No RCTs!

The Oxalobiome

- Intestinal bacteria
  - Degrade oxalate
  - Stimulate oxalate secretion
  - Typified and exemplified by *Oxalobacter formigenes*



Colonic oxalate transport

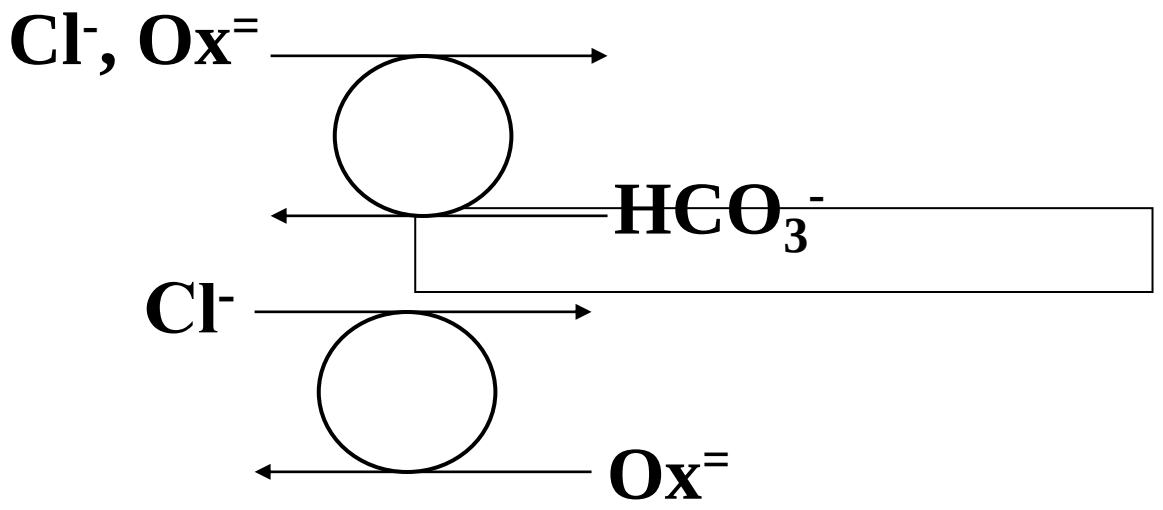


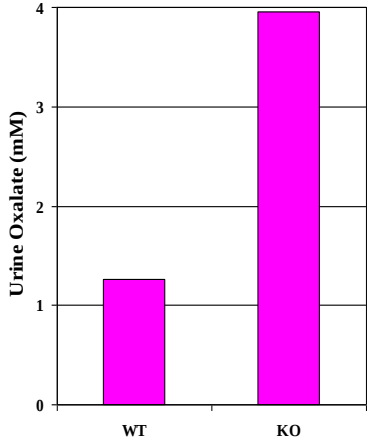
Oxalate absorption

Oxalate secretion via *SLC26A6*

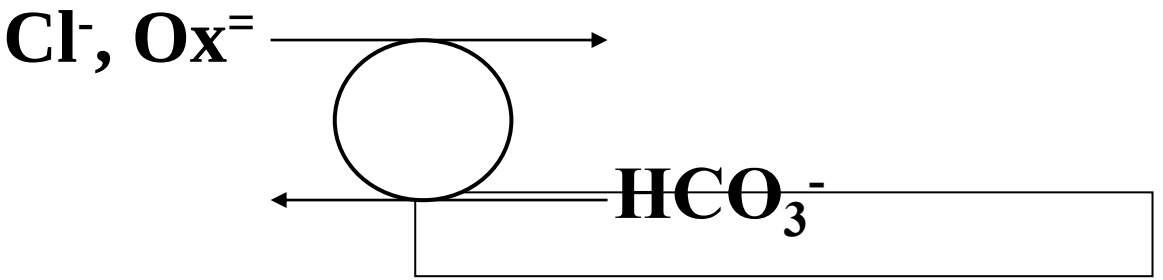
SLC26A6 Knockout

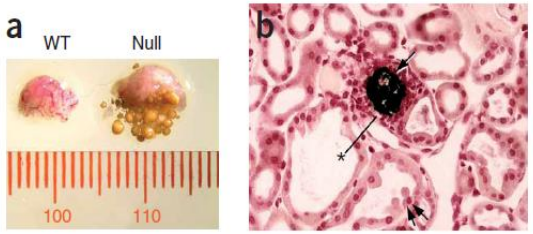
Effect of *SLC26A6* Knockout on Oxalate





Freel Am J Physiol 290:719, 2005



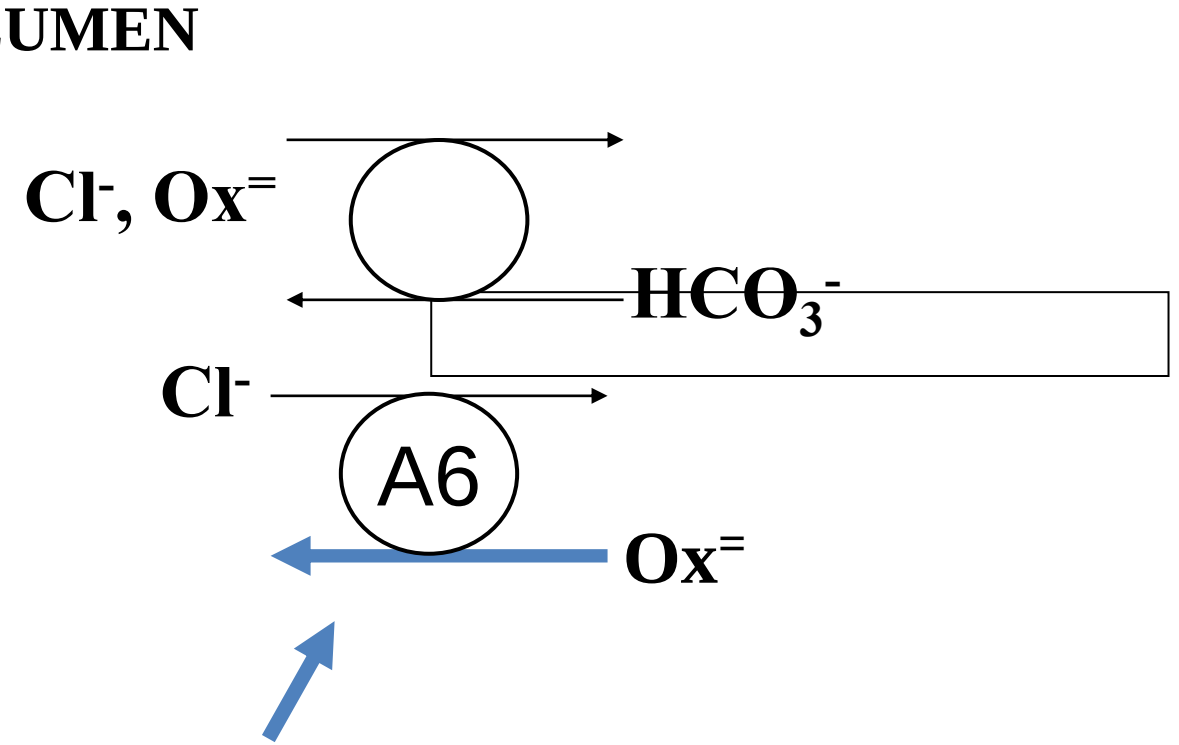


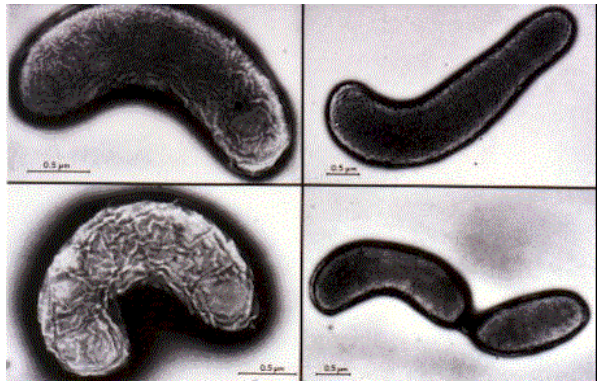
Bladder stones Nephrocalcinosis
Kidney biopsy

SLC26A6 Knockout

Ziang Nat Gen 38:474, 2006

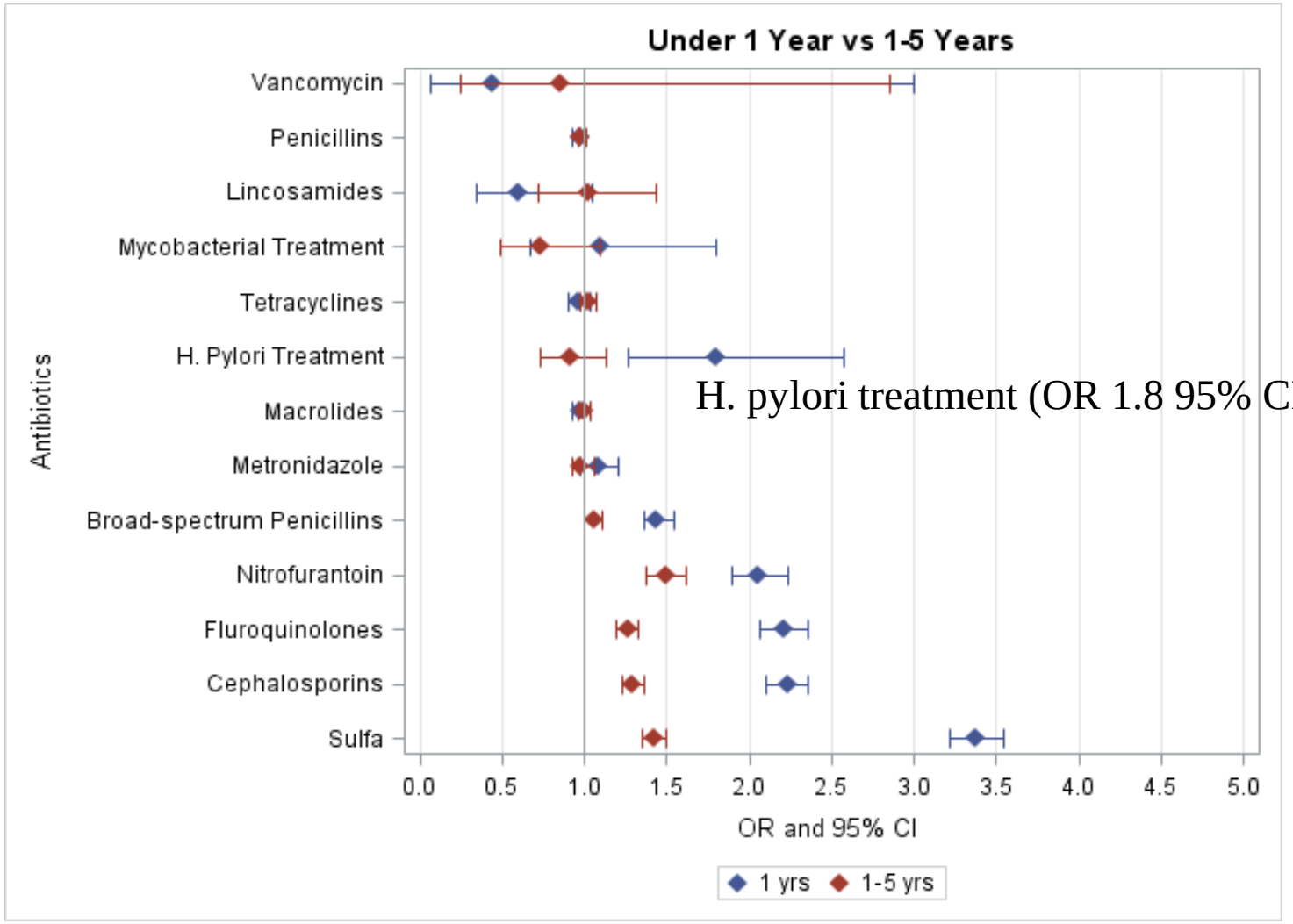
Oxalobacter stimulates oxalate secretion





Arvans D, J Am Soc Nephrol 28:876-887, 2017

Risk of stones with antibiotics



H. pylori treatment (OR 1.8 95% CI 1.3-2.6)

The Health Improvement Network (THIN) database
N = 26,466 patients with stones and 264,647 matched controls

Tasian G et al. JASN 29:1731-1740 2018

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Oxalate and kidney toxicity

Case Report

Accelerated Oxalosis Contributing to Delayed Graft Function after Renal Transplantation

Yvelynne P. Kelly,[1] Astrid Weins,[2] and Melissa Y. Yeung[1]

RESEARCH ARTICLE

Oxalate deposition in renal allograft biopsies within 3 months after transplantation is associated with allograft dysfunction

Malou L. H. Snijders[1,2*], Dennis A. Hesselink[2,3], Marian C. Clahsen-van Groningen[1,2☯], Joke I. Roodnat[2,3☯]

1 Department of Pathology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, 2 Rotterdam Transplant Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, 3 Department of Internal Medicine, Division of Nephrology and Transplantation, University Medical Center Rotterdam, Rotterdam, The Netherlands

Teaching Case

"Green Smoothie Cleanse" Causing Acute Oxalate Nephropathy

Swetha Makkapati, Vivette D. D'Agati, and Leah Balsam

Research

JAMA Internal Medicine | Original Investigation

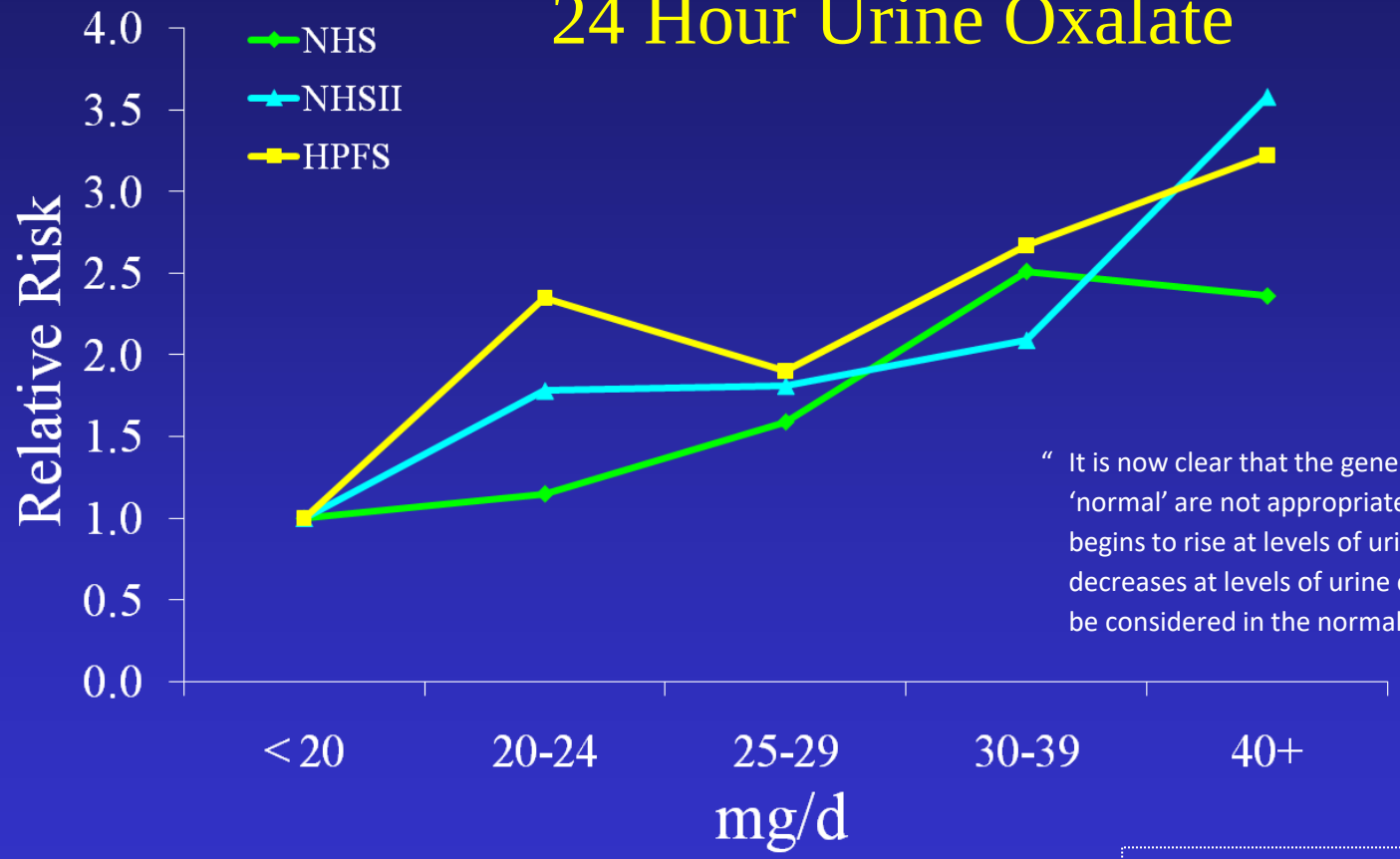
Association of Urinary Oxalate Excretion With the Risk of Chronic Kidney Disease Progression

Sushrut S. Waikar, MD, MPH; Anand Srivastava, MD, MPH; Ragnar Palsson, MD; Tariq Shafi, MBBS, MHS; Chi-yuan Hsu, MD, MSc; Kumar Sharma, MD; James P. Lash, MD; Jing Chen, MD, MMSc, MSc; Jiang He, MD, PhD; John Lieske, MD; Dawei Xie, PhD; Xiaoming Zhang, MS; Harold I. Feldman, MD, MSCE; Gary C. Curhan, MD, ScD; for the Chronic Renal Insufficiency Cohort study investigators

NYU Langone Health

Potential Outcomes of a Study of Enteric Hyperoxaluria:

24 Hour Urine Oxalate



" It is now clear that the generally accepted definitions of 'normal' are not appropriate....The risk of stone formation begins to rise at levels of urine calcium and oxalate and decreases at levels of urine citrate, that traditionally would be considered in the normal range"

Cases: 2237; Controls: 1113

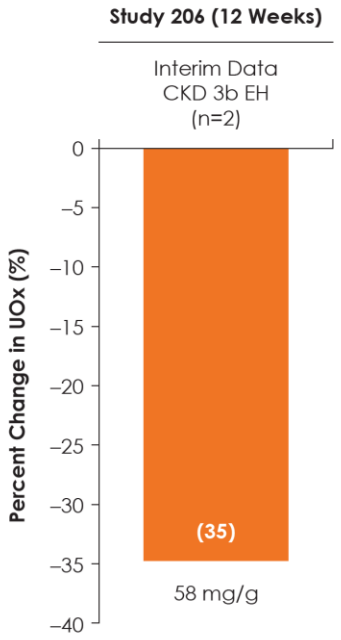
Curhan, Kidney Int 2008

OHF-Sponsored White Paper

- Academics + Industry:
  - Consensus: 20% reduction of UOx would be considered likely to be clinically meaningful
- Reduction of UOx to values of PH3 patients might suffice
- INSTEAD of near normalization
  - Might be achieved by Alnylam & Retrophin in treatment of PH with siRNA

Reloxaliase formerly ALLN-177

- Oxalate-degrading enzyme
- Works in the intestinal lumen



Langman CB; Poster SA-PO815 • Poster
Presented at Kidney Week 2019

Summary

- Urine oxalate is an important risk for kidney stones, nephrocalcinosis, chronic kidney disease and end stage kidney disease
- The intestinal microbiome is clearly a variable that influences urinary oxalate excretion
- There is an unmet need for better, targeted therapies to reduce urinary oxalate excretion

Internal Metabolic Pipeline: Enteric Hyperoxaluria

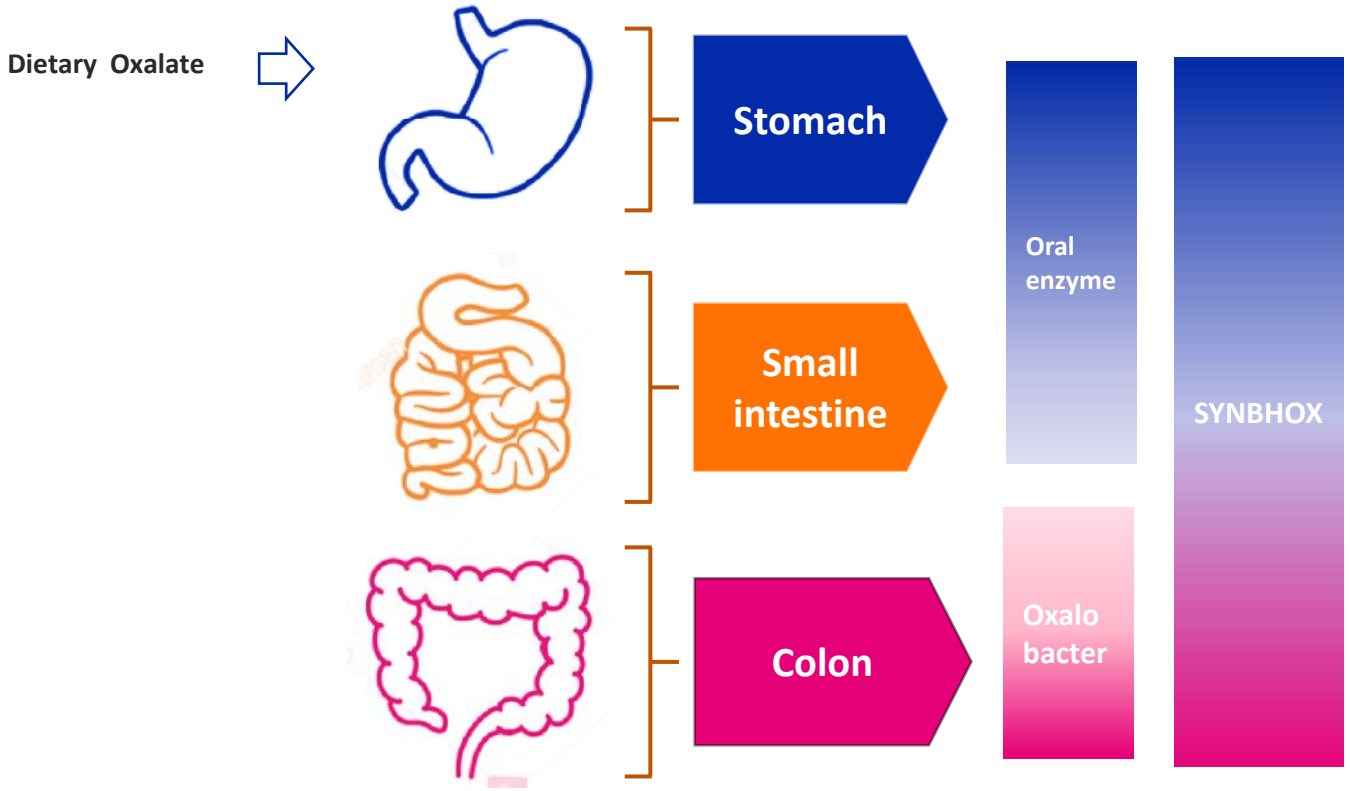
Dr. Richard Riese, MD, PhD
Chief Medical Officer

Target Product Profile for Enteric Hyperoxaluria

Indication	Treatment of enteric hyperoxaluria in patients with recurrent kidney stones
Target Patient Population	Initial: Adults with hyperoxaluria and recurrent kidney stones secondary to GI disorders with relatively preserved renal function Additional: Adults with hyperoxaluria and recurrent kidney stones secondary to GI disorders with severe renal dysfunction, including patients on hemodialysis
Efficacy	Primary: Reduction in urinary oxalate levels by 20-50% Long term: Reductions in kidney stone formation
Safety	Tolerability consistent with oral probiotic • Mild GI disturbance
Dosage	Sachet or capsule, dose <5e11 live cells with meals up to 3X per day

Disease Pathogenesis and Opportunity for SYN-HOX

GI Based Therapies Have Demonstrated Lowering of Systemic Oxalate



Oxalate intake from diet can be absorbed into the body throughout GI tract

Ideal treatment:

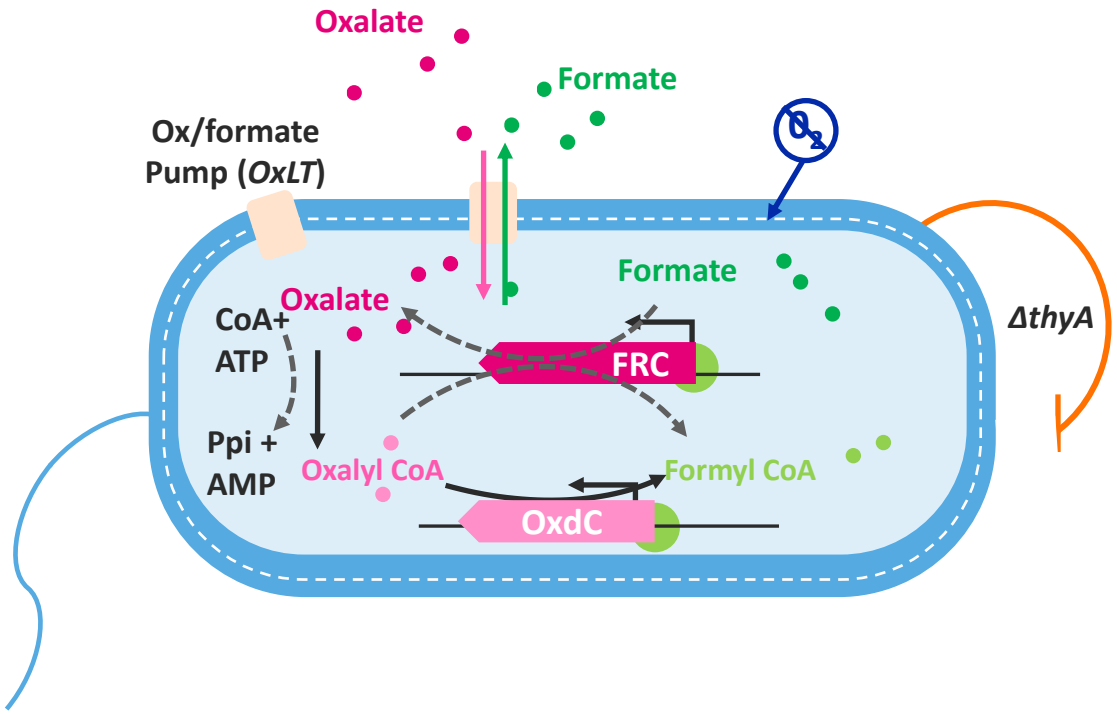
Degrade oxalate across GI compartments

Intestinal Degradation of Oxalate Throughout GI Tract Could Enhance Oxalate Lowering

Hyperoxaluria strain SYNB8802

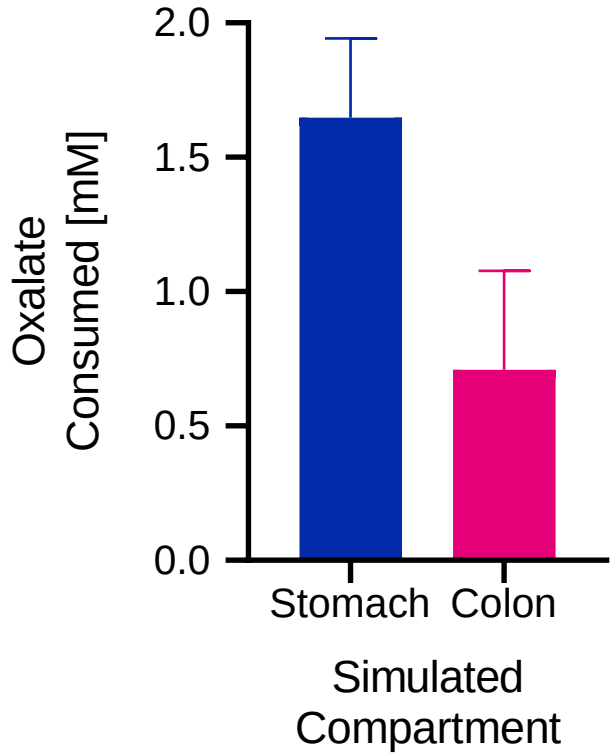
Engineered to convert oxalate to formate

Component	Approach	Benefit
Bacterial Chassis	*E. coli* Nissle	Decades of human use
Switch	FNR promoter	Inducer-promoter pair
Pump	*OxLT*	Pumps oxalate in & formate out
Effector 1	*OxdC and associated components*	Catalyzes conversion of oxalate to formate
Safety Features	*Δ thyA*	Controls growth

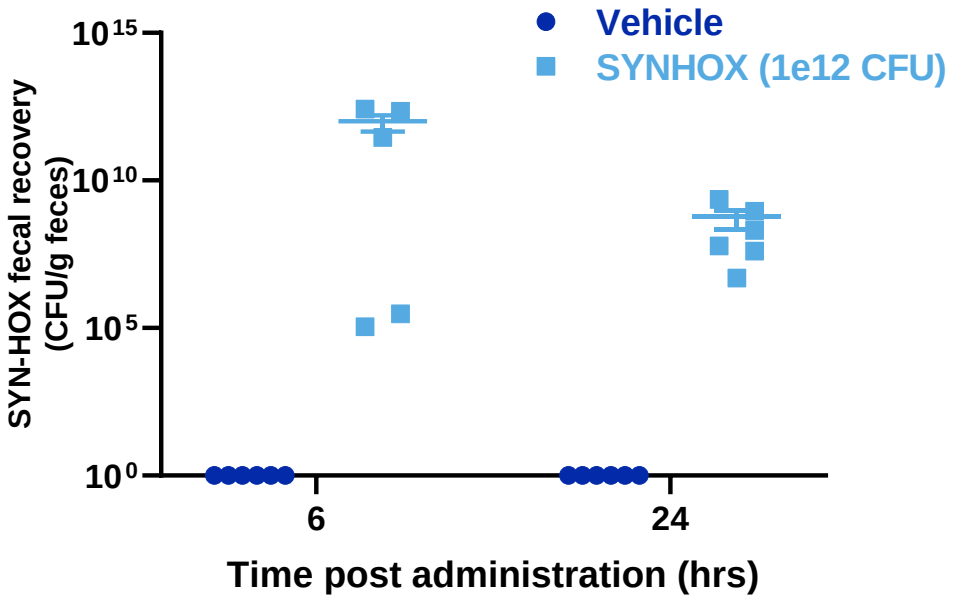


SYN-HOX Activity in Upper and Lower GI

In Vitro Activity of SYN-HOX in Simulated Gut Fluid



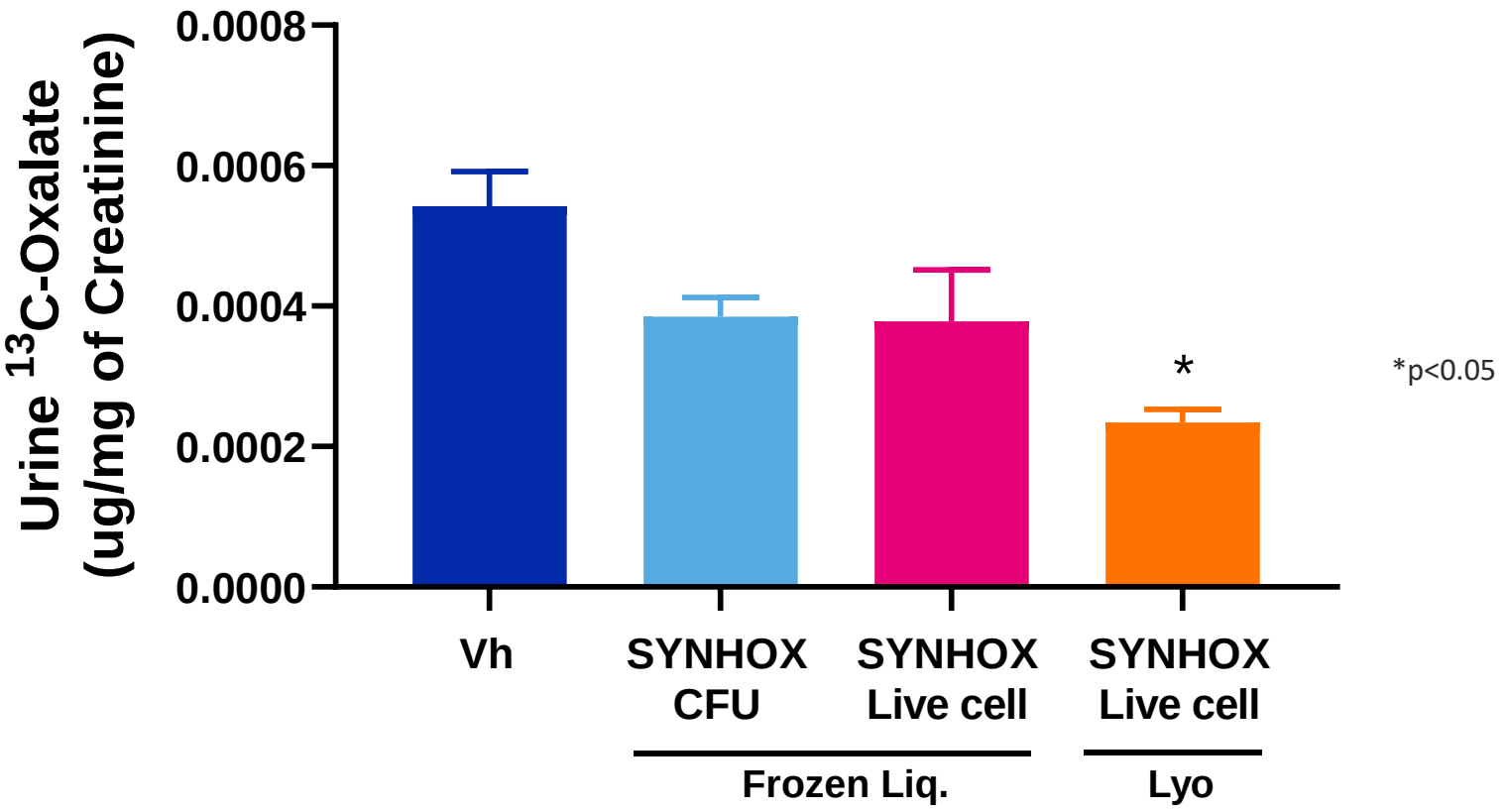
Viable SYN-HOX Cells Recovered in Feces after Oral Dose (NHP)



SYN-HOX Has Potential To Operate Throughout The GI Tract To Lower Absorption Of Oxalate Into The Blood

SYN-HOX Consumes ^{13}C-Oxalate in Mice

Isotope Model Demonstrates Urinary Oxalate Consumption in Gut



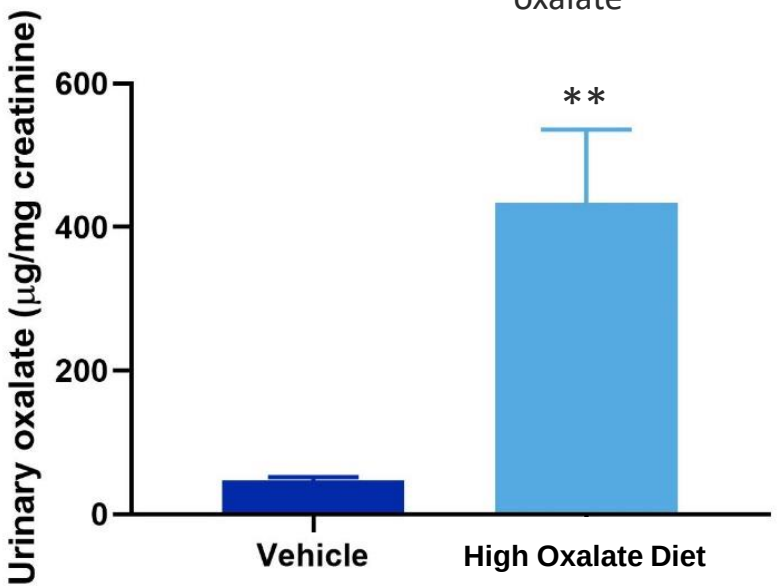
*p<0.05

SYN-HOX Consumes Oral Load of Oxalate in Acute Mouse Model

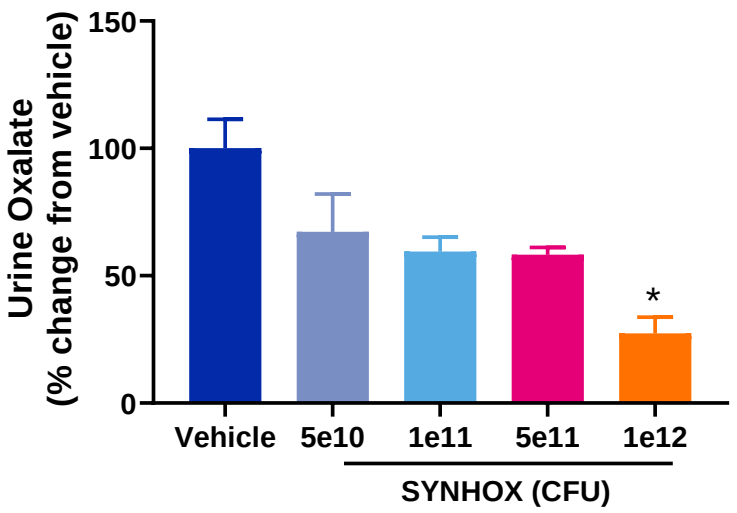
SYN-HOX Attenuates Urinary Oxalate Increase in Healthy Non-Human Primates

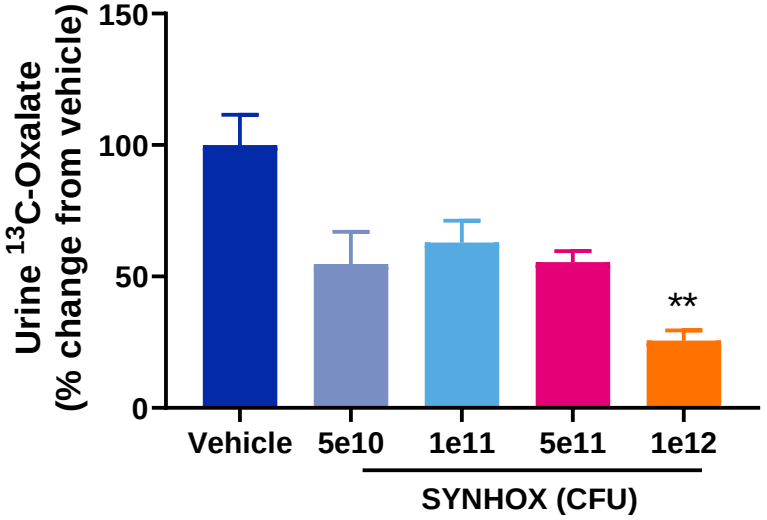
Dietary Intervention Increases Urinary Oxalate

400 mg oxalate elevates urinary oxalate



SYN-HOX Attenuates Urinary Oxalate Increase





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

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

Model Development for Hyperoxaluria

Modeling Activity of SYN-HOX Incorporating GI Site, Transit Time, Substrate Availability

Inputs

- Strain Activity in IVS:
  - Effect of pH
  - Simulated gut compartments
- Human oxalate dietary consumption
- Oxalate absorption
- Urinary oxalate excretion

In Silico Model

Proprietary Synlogic Simulation Models

Outputs

Required Metabolite Consumption For Clinical Benefit

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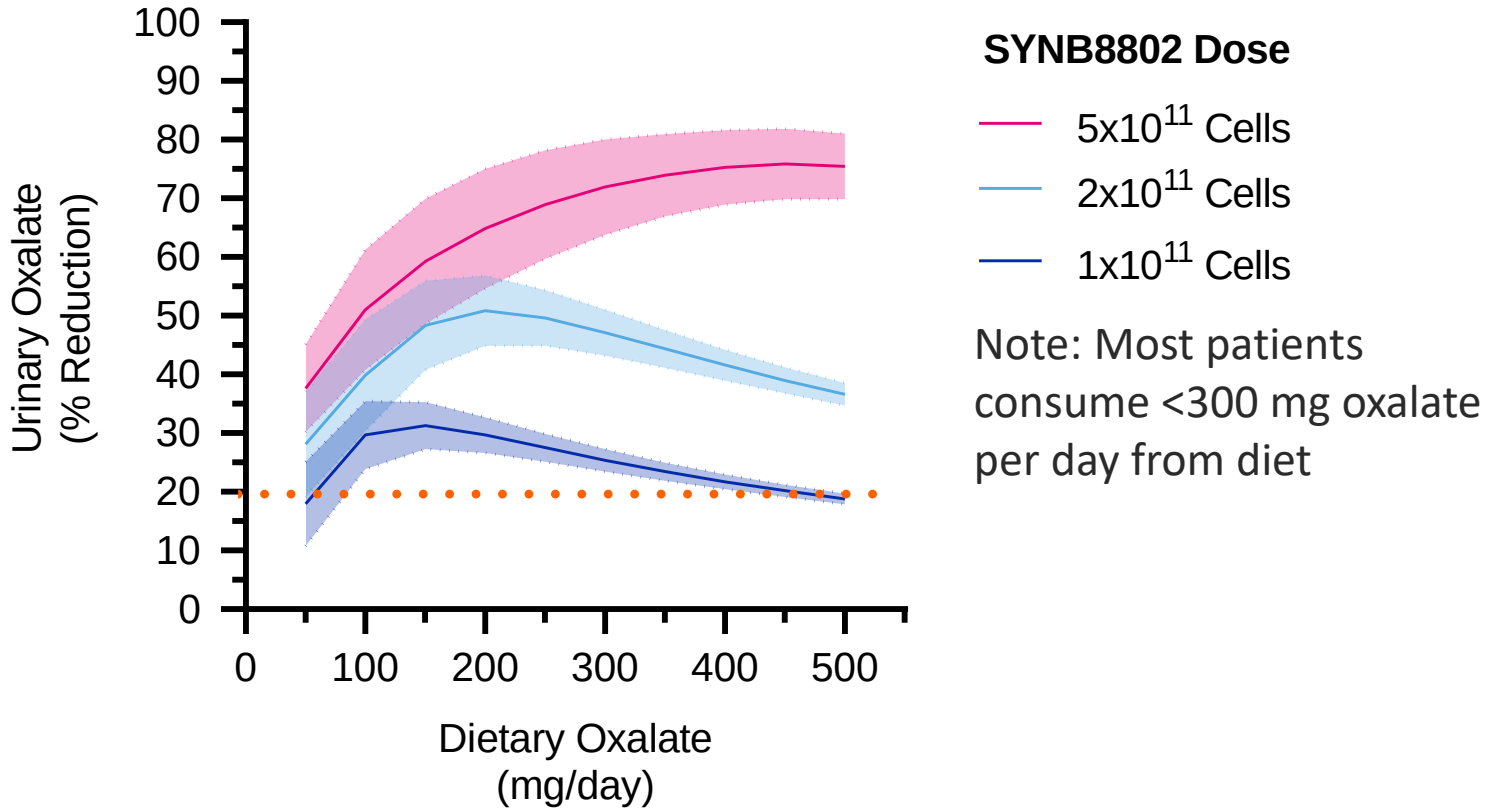
Modeling Of Oxalate Lowering by SYN-HOX

Potential Urinary Oxalate Reduction



Note: Most patients consume <300 mg oxalate per day from diet

Modeling Predicts SYN-HOX Has Potential to Achieve 20%-50% Urinary Oxalate Lowering at Target Dose Range

Enteric Hyperoxaluria: Clinical Development Strategy

Conventional MAD design

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

Cross-over design to enable rapid POC

- TID dosing
- Approx. 20 hyperoxaluria patients (Roux-en Y gastric bypass)
- Uox >70 mg/day

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Patients with EH, preserved renal function & stones as a result of:

- Gastric Bypass
- Inflammatory bowel disease
- Cystic Fibrosis
- Short bowel syndrome
- Chronic biliary or pancreatic diseases

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- Gastric Bypass
- Inflammatory bowel disease
- Cystic Fibrosis
- Short bowel syndrome
- Chronic biliary or pancreatic diseases

"Enteral dialysis" approach

- Patients with:
  - eGFR < 30 mL/min/1.73 m^2, or
  - Requiring hemodialysis, or
  - Systemic oxalosis (blood, bones, heart, skin, retina)

Note: Plasma Ox may be a better endpoint in pts with severe kidney disease or systemic oxalosis

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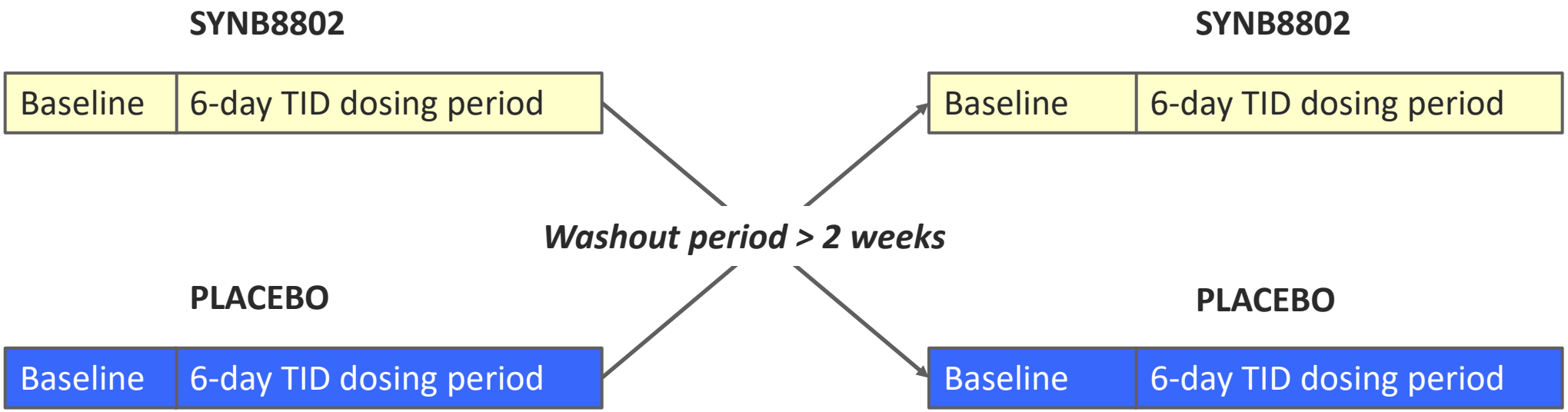
Proof of Concept Phase 1b Study in Enteric Hyperoxaluria

Placebo-controlled crossover study; outpatient on their regular diet



Efficacy Outcomes

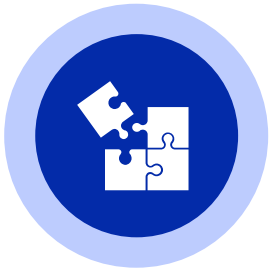
- ***Primary***: Change in 24 h U-Ox vs placebo
- ***Secondary***: Change in U-Ox to creatinine ratio; microbial kinetics
- ***Exploratory***: change in plasma U-Ox, fecal Ox, plasma phosphate, urine biomarkers

N up to 20
Gastric bypass patients (Roux-en-Y)
U-Ox >70 mg/day
Conserved renal function (eGFR > 45)

Evidence Of Urinary Oxalate Lowering Could Be Demonstrated In The First In Patient Study In A Defined Population

Enteric Hyperoxaluria: Moving Forward

Preparing IND Package



Fit within Synlogic Strategy

- ✓ Well understood biology
- ✓ Metabolic disease with high unmet need
- ✓ Metabolite consumption leads directly to lower urine oxalate levels

Program Successes

- ✓ Prototype demonstrates oxalate lowering in preclinical studies
- ✓ Rapid development: program initiation to candidate selection in 10 months
- ✓ In Silico modeling predicts that consumption of >200 mg oxalate in gut will result in >20% oxalate lowering in urine

Next Milestone & Learnings

- Plan to file IND
- Assess safety in Ph.1a
- Evaluate urine oxalate lowering in patients

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Enteric Hyperoxaluria

Our Next Step To Synthetic Biotic Medicines

High unmet medical need with no available therapeutic options

Efficient clinical development: PoC achievable in Phase 1b

SYNB8802 has potential to meaningfully reduce urinary oxalate levels

A Virtual Cup of Coffee with Drs. Goldfarb & Riese

Immunomodulation

Dr. Amanda Kay, Head of Strategy & Business Development

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Immunomodulation

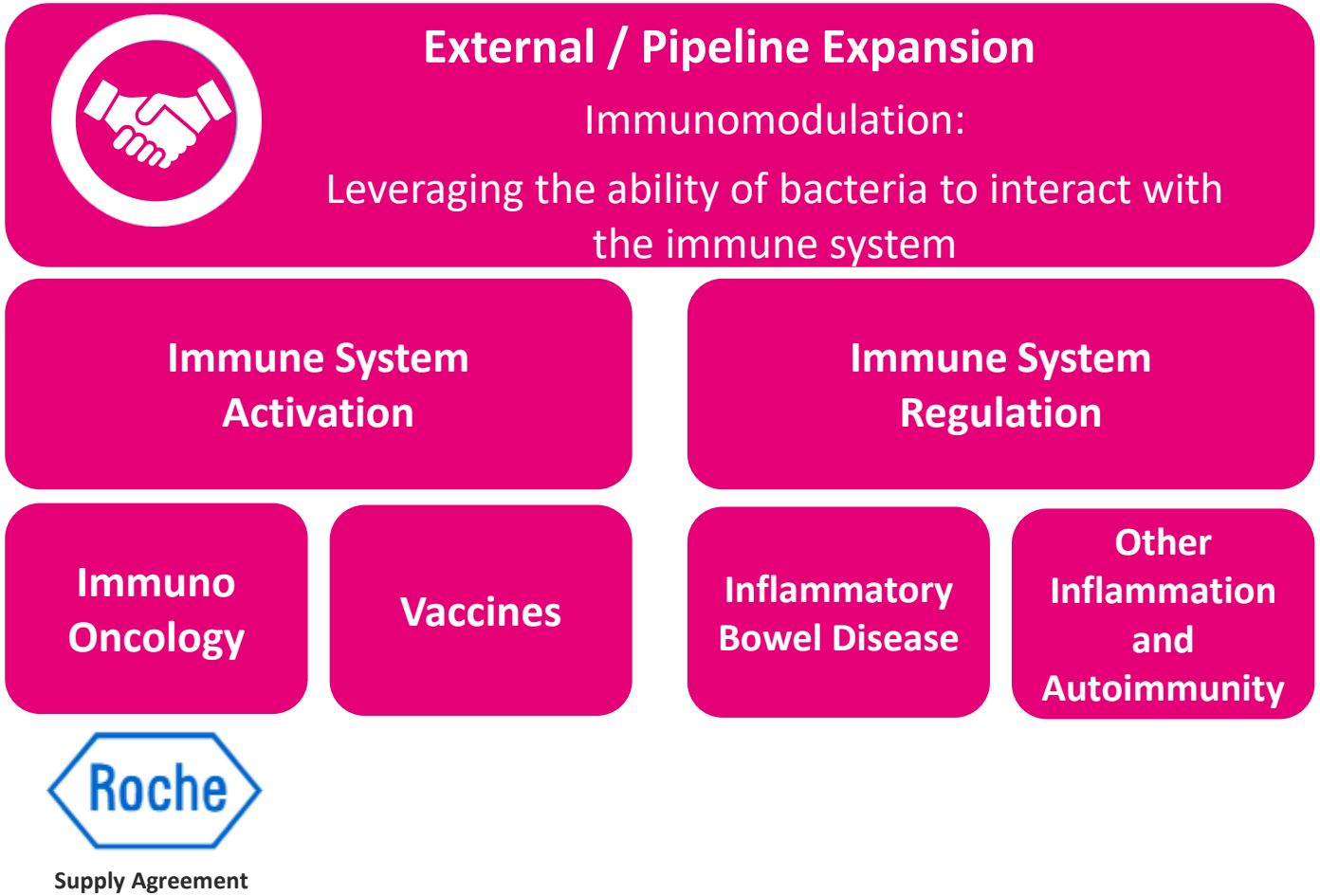
Synthetic Biotics can be engineered for immune activation or regulation

SYNB1891 will provide clinical data in 2020 from a monotherapy cohort

SYNB1618 has potential for improved efficacy relative to other STING approaches

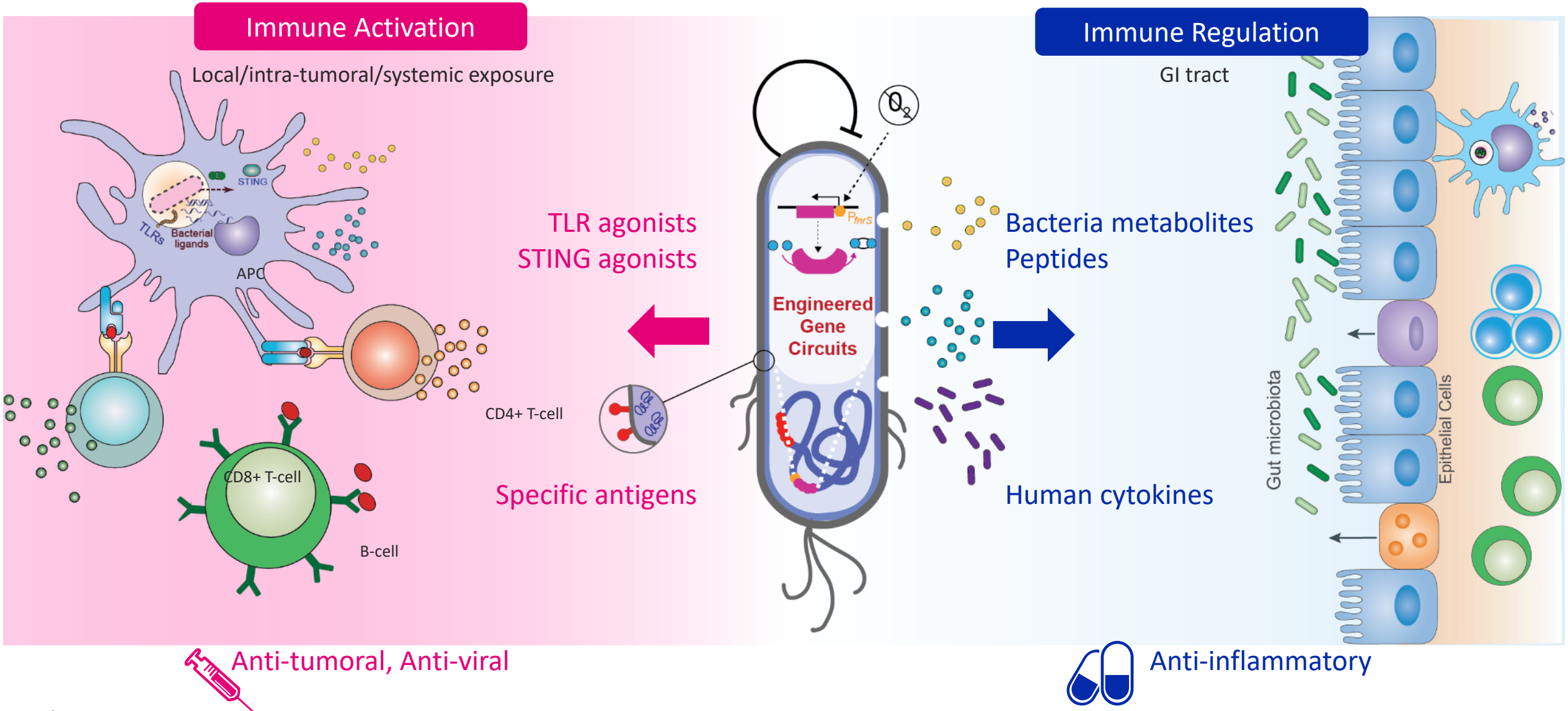
Immunomodulation Focus: Exploit Interaction of Bacteria and Immune System

Initial Exploration Through Partnership



EcN Can Be Engineered for Immune Activation or Immune Regulation

External Pipeline Built on Exploiting the Interaction Between Bacteria and the Immune System



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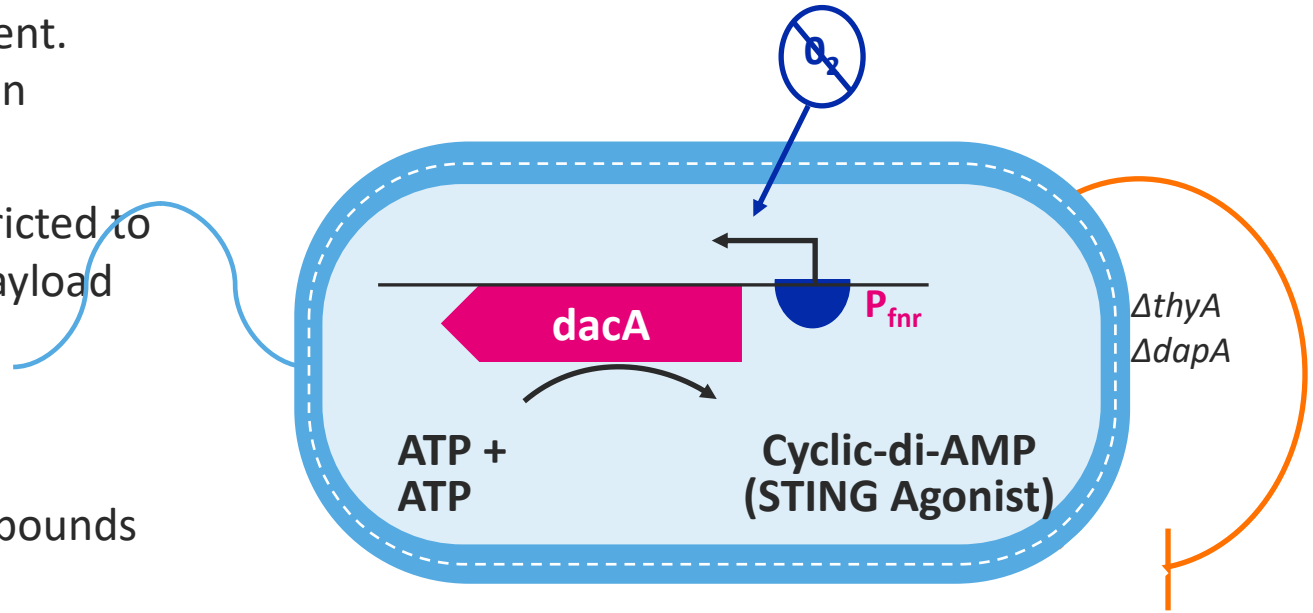
SYNB1891 Design

Leveraging the ability of bacteria to interact with the immune system to turn a cold tumor hot

Component	*Benefit*
Bacterial Chassis	Targeting to antigen presenting cells in the tumor microenvironment. Innate immune activation
Switch	STING-agonist production restricted to hypoxic TME for sustained payload delivery
Effector: STING Agonist	Innate immune activator compounds with chassis effect
Safety Features	Dual auxotrophies inhibit bacterial proliferation outside of tumor



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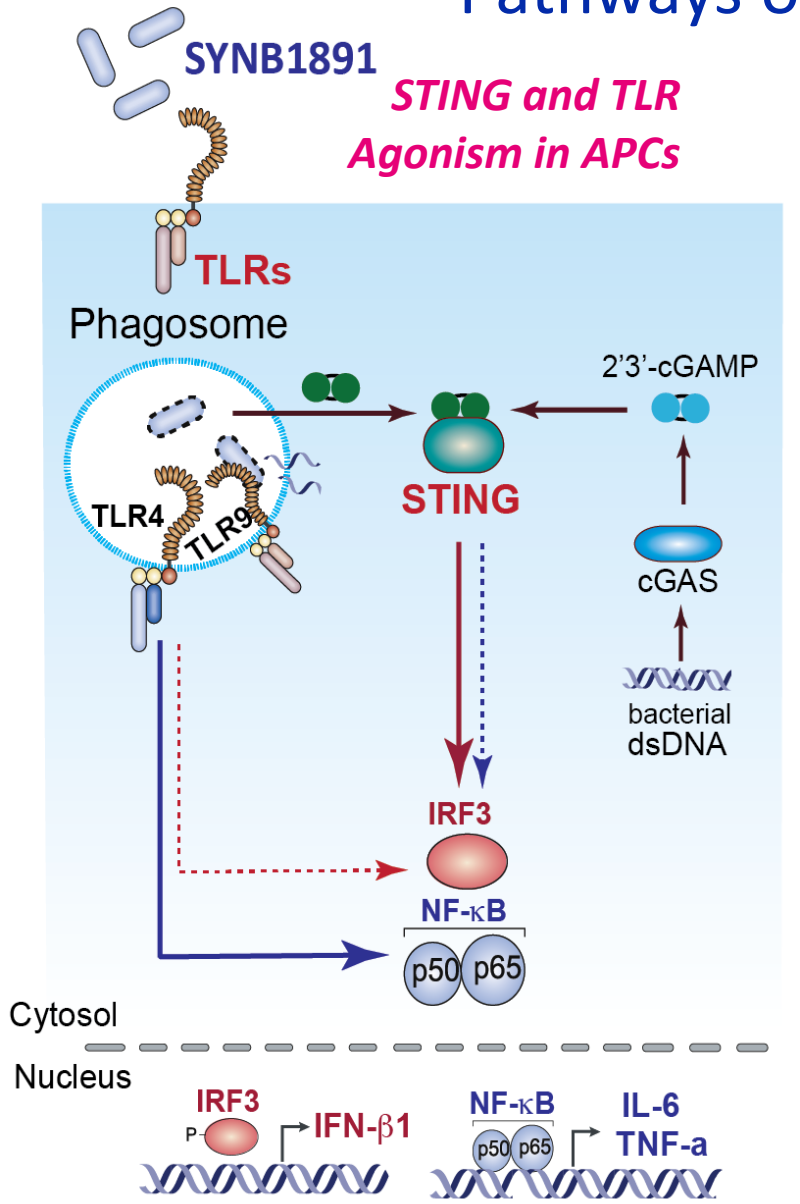
SYNB1891 Combines Signaling Pathways of Other Innate Agonists



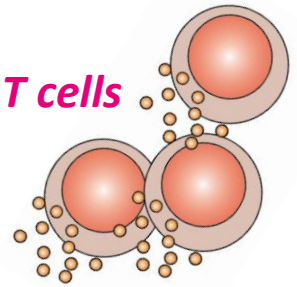
DUAL INNATE IMMUNE AGONIST
Lead to Expression of:

Type I Interferons

Inflammatory Cytokines

Tumor Antigens and …

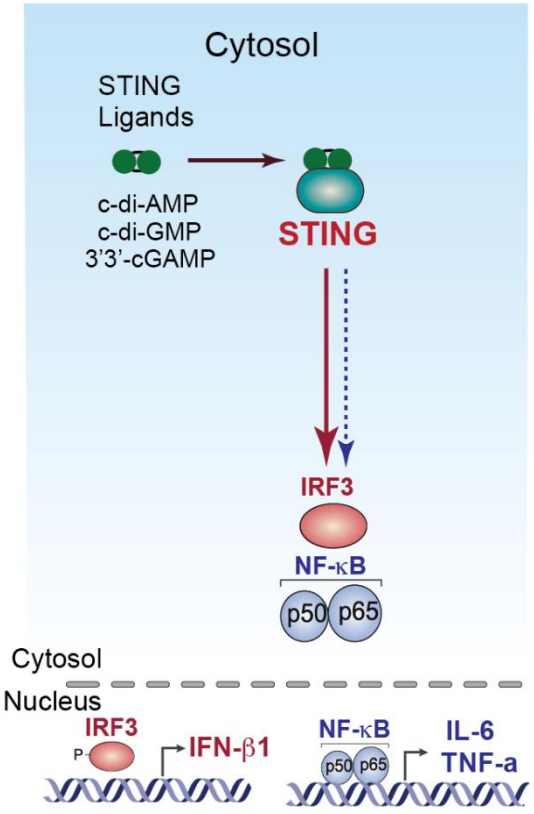
Anti-Tumor T cells



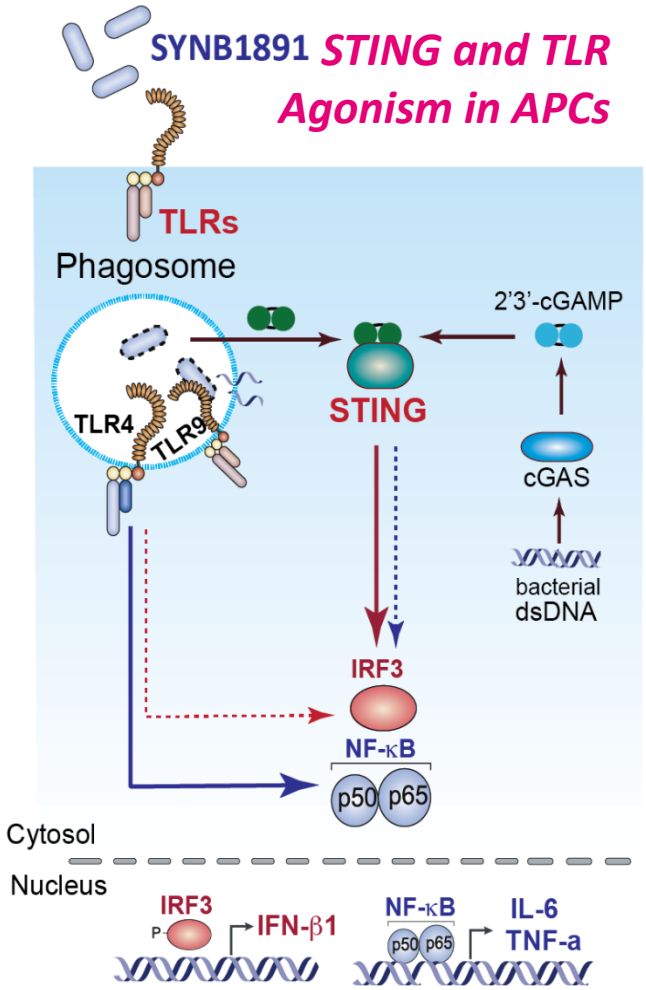
SYNB1891 Combines Signaling Pathways of Other Innate Agonists

STING Agonists

Mainly through IFNb1

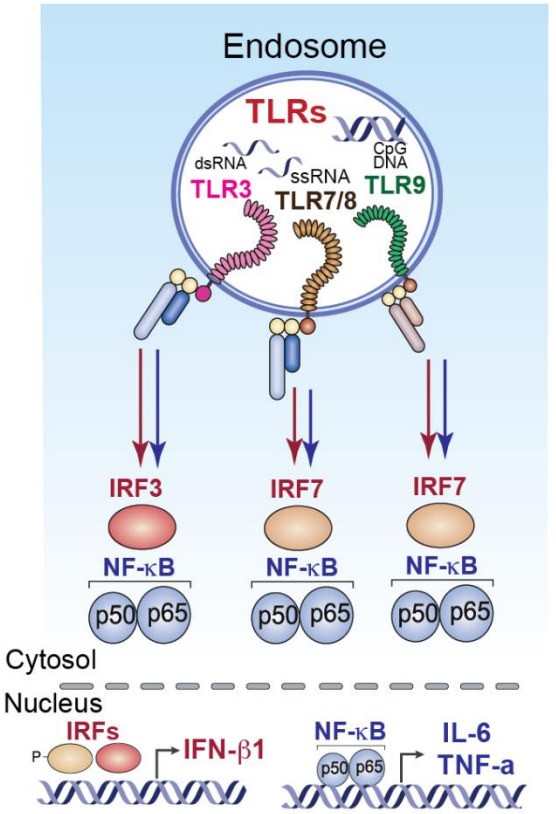


SYNB1891 *STING and TLR Agonism in APCs*

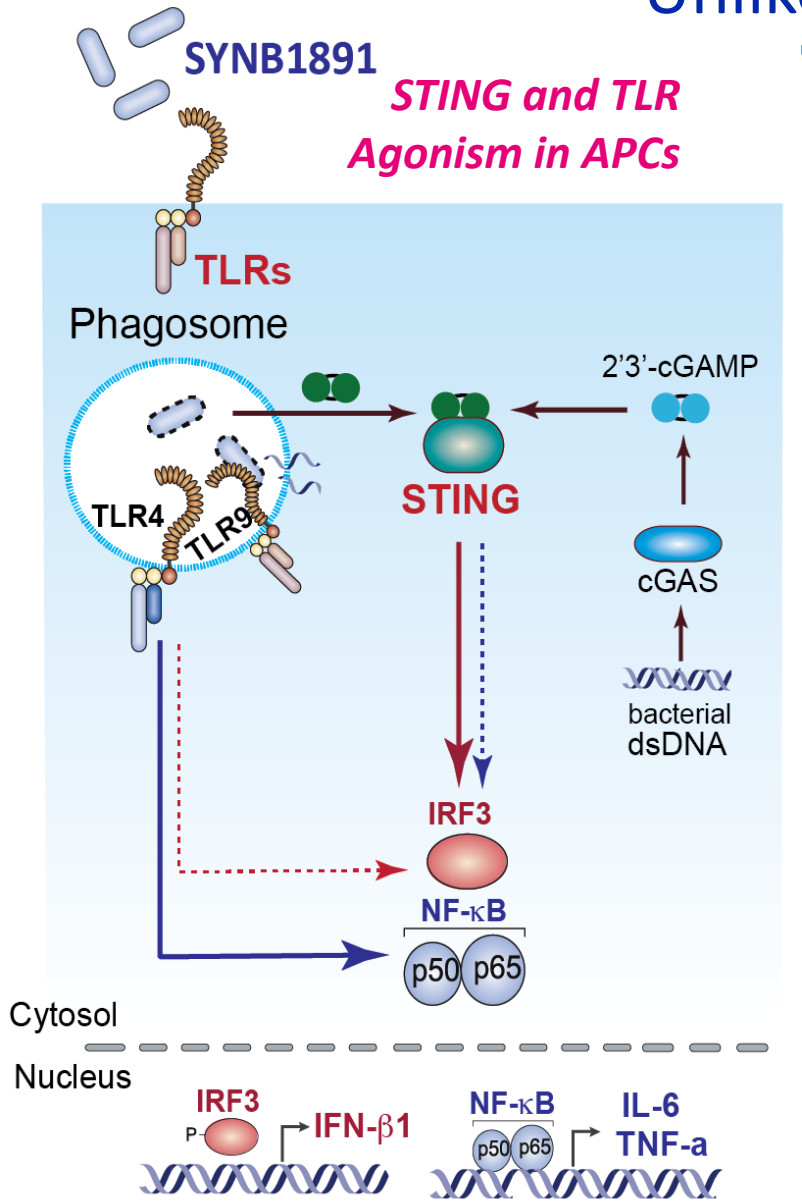


TLR Agonists

Through IFNb1 & Cytokines



SYNB1891 Locally Signals Through Inflammatory Cytokines, Unlike Naked Agonists



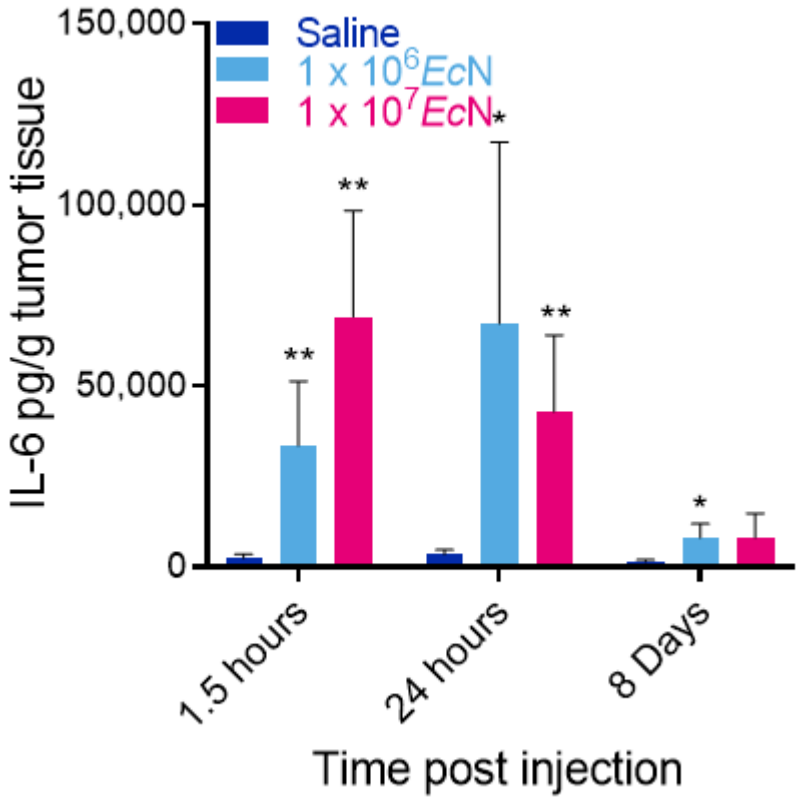
Differentiation of SYNB1891:

1. Chassis as strong stimulator of inflammatory cytokines
2. Two agonists of STING for enhanced IFNβ1
3. Efficacy advantage vs. naked STING agonists as targeted to APCs and tumor

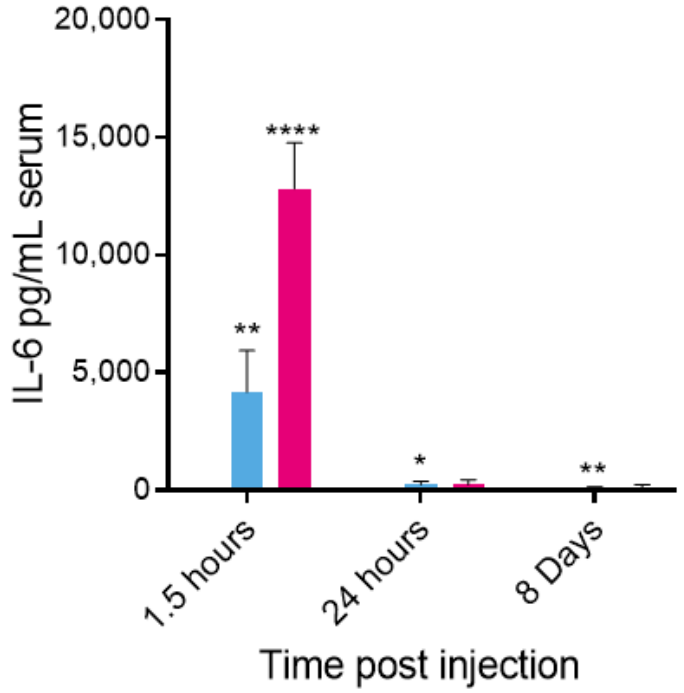
CHASSIS Activates the Innate Immune System and Attenuates Tumor Progression

CT-26 Tumor Bearing Balb/c Mice Treated with *EcN i.t.*

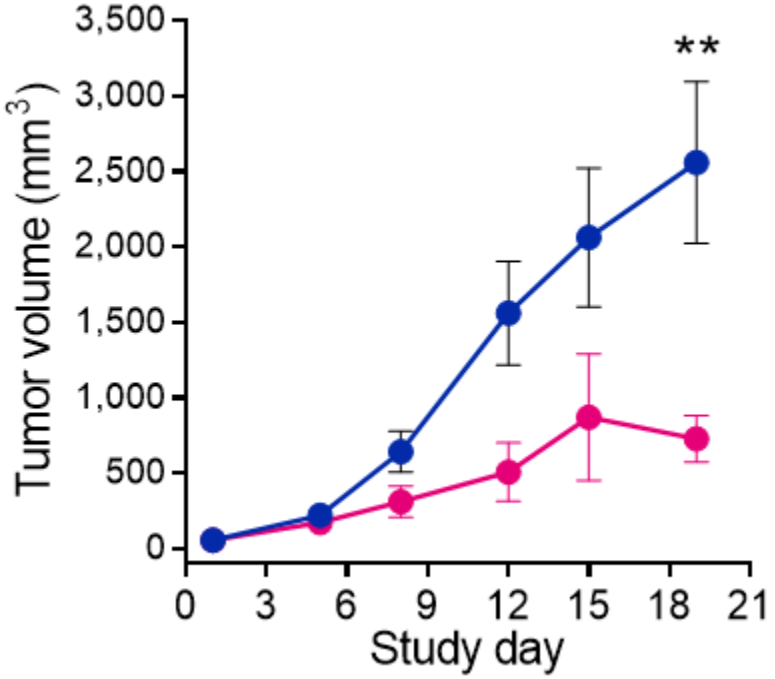
Tumor IL-6 Levels^



Blood IL-6 Levels^



Tumor Volume

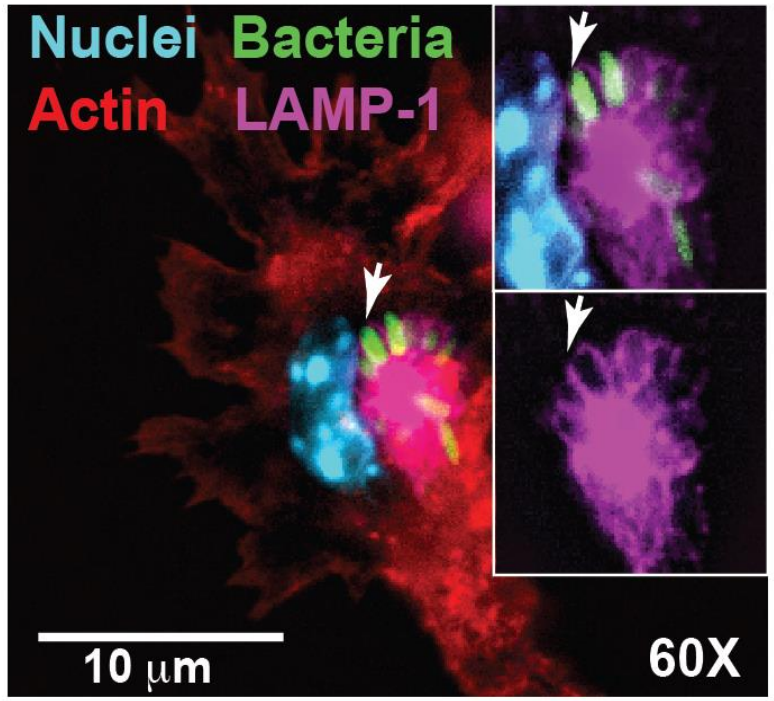


Immune-Stimulating Properties of Chassis Can be Combined with Effector Therapeutic Mechanism

^Similar pattern observed for TNFα

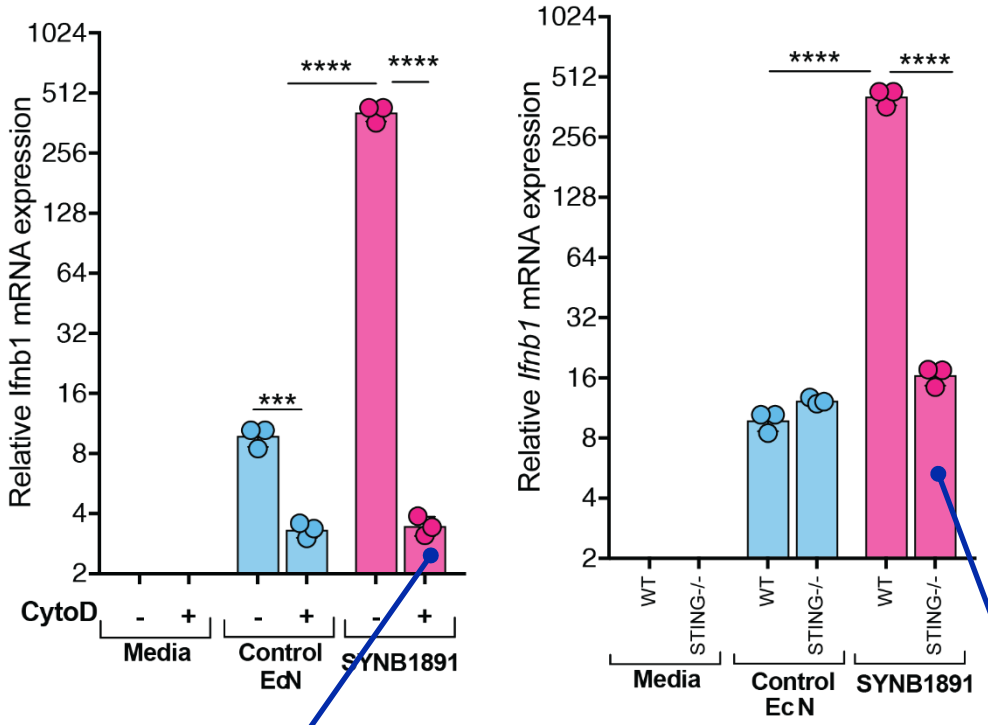
SYNB1891 Induces IFNβ1 in a Phagocytosis- and STING-dependent Manner

SYNB1891 Resides Within Mature LAMP-1-positive Phagosomes



SYNB1891 Targeted to Phagosomes of Antigen Presenting Cells Unlike Naked STING Agonists

Role of Phagocytosis and STING on IFNβ mRNA Expression



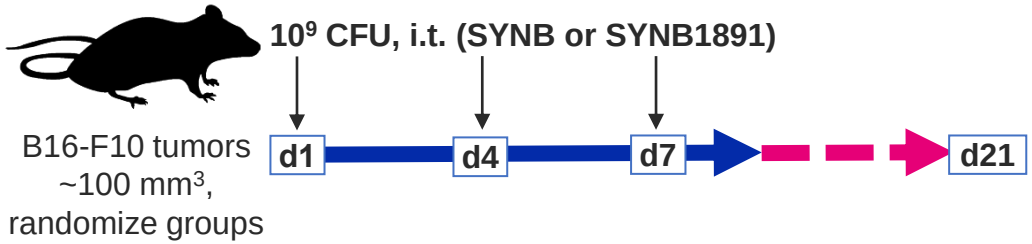
Wild-type or Knockout Mouse Dendritic Cells by Treatment

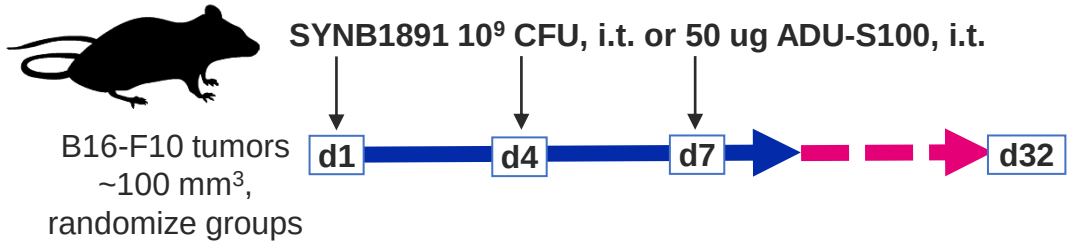
Bacterial internalization is required to induce IFNβ1

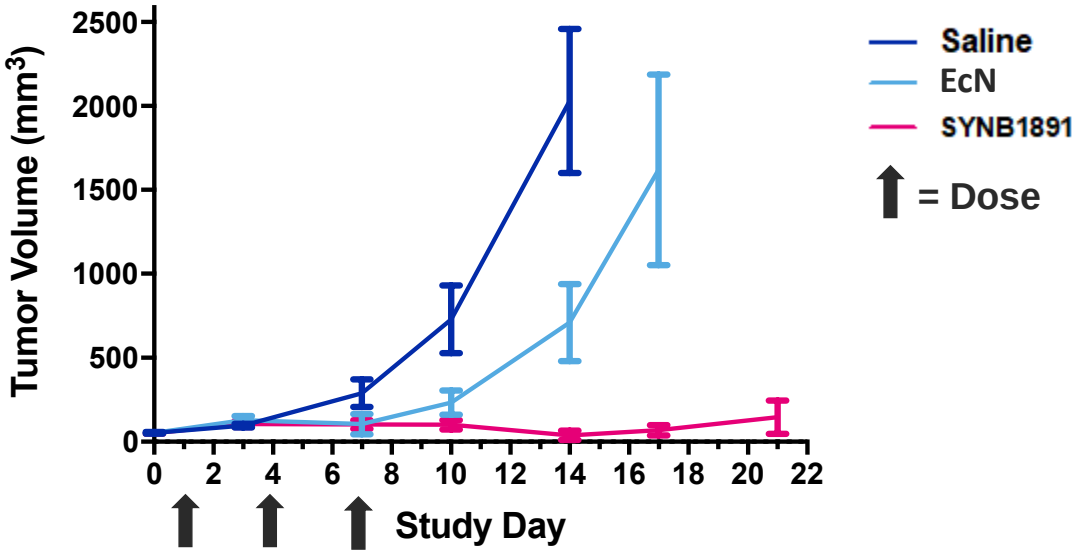
Effector Induces IFNβ1 in a STING-dependent Manner

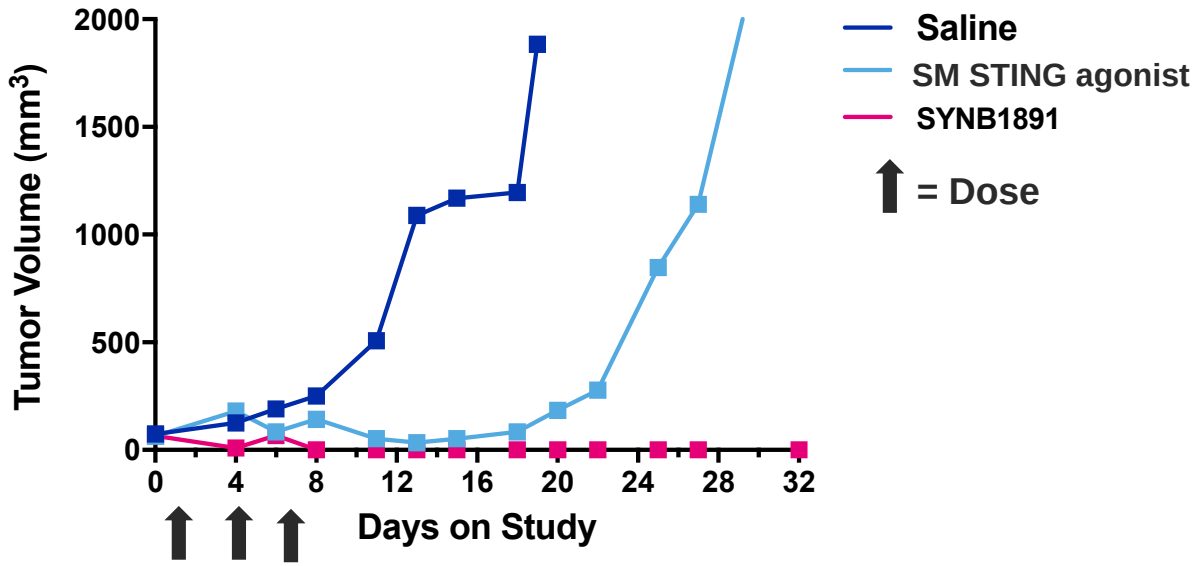
SYNB1891 Induces Potent Anti-tumoral Effects

Effects Superior to 'Naked' STING Agonist in Animal Model of Cold Tumor





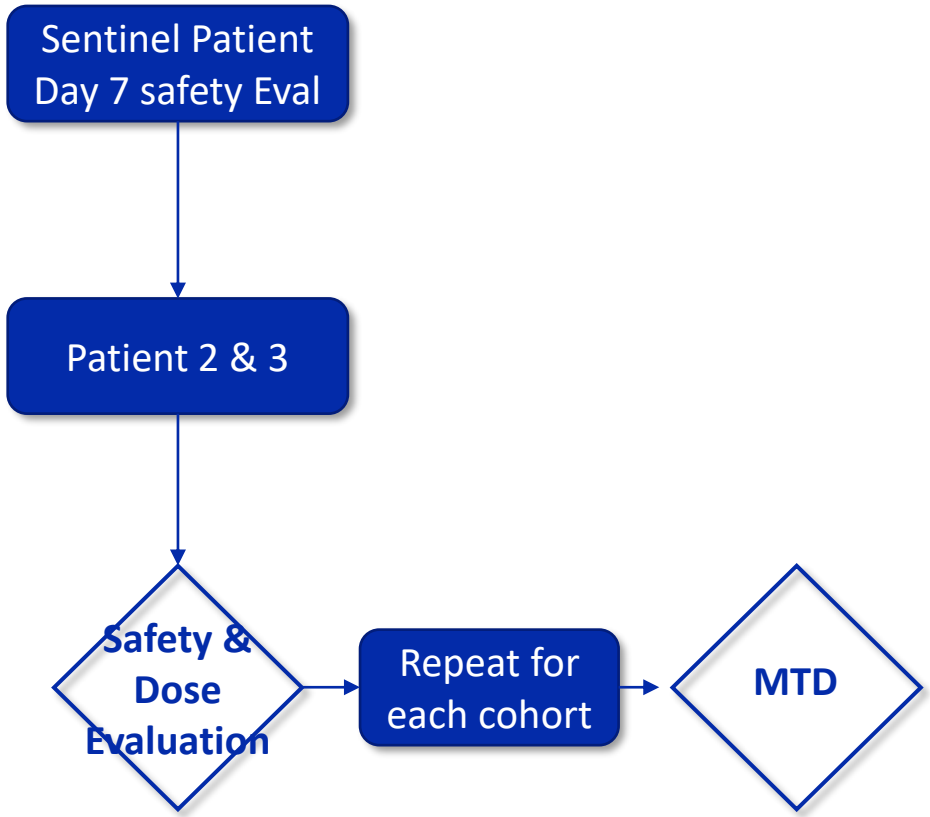




SYNB1891-CP-001 Study Design: Multidose Tolerability, IT Mono and Combo

Proof of Mechanism: Exploratory Biomarkers in Advanced Solid Tumors or Lymphomas

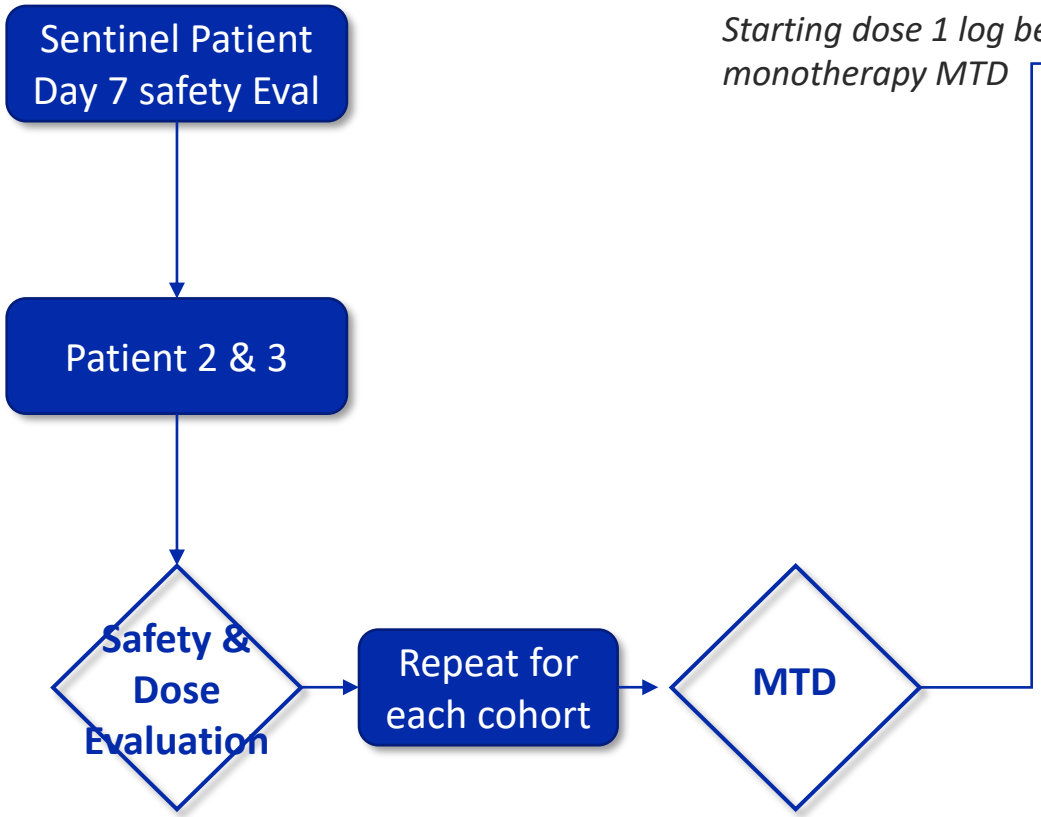
Arm 1: Monotherapy Cohorts



SYNB1891-CP-001 Study Design: Multidose Tolerability, IT Mono and Combo

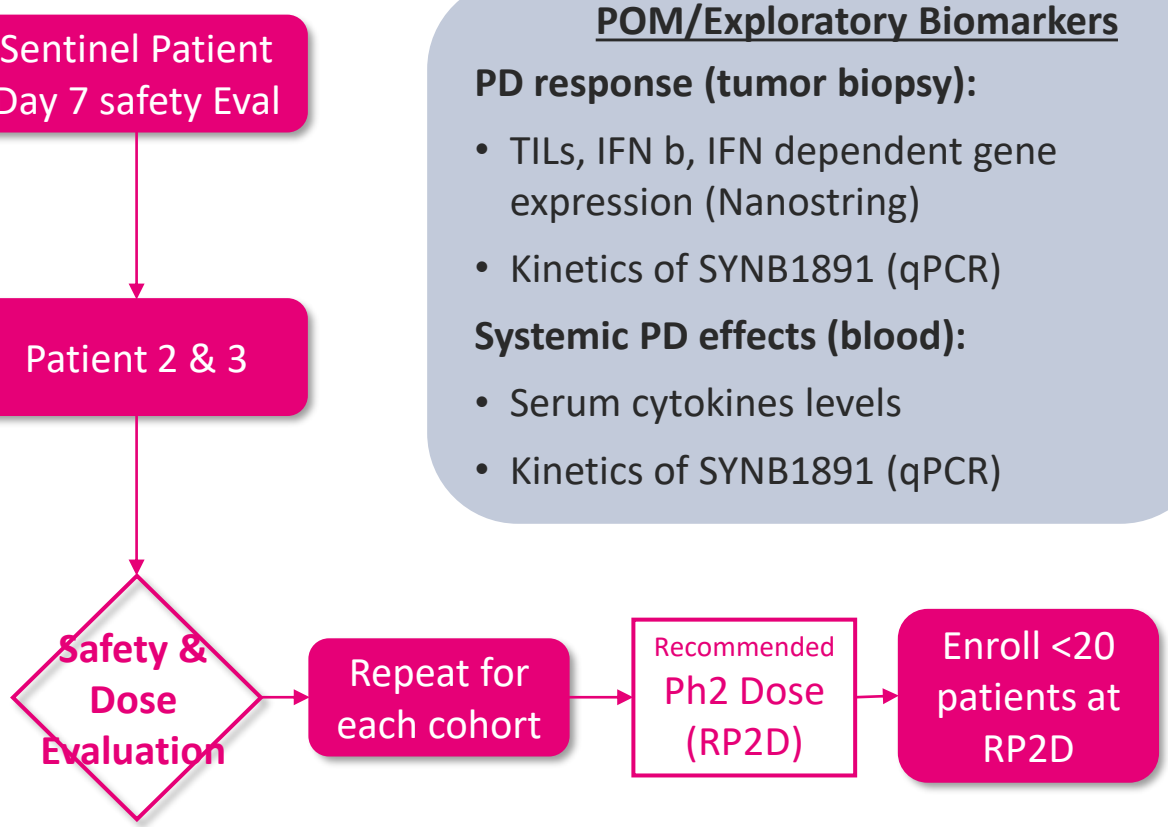
Proof of Mechanism: Exploratory Biomarkers in Advanced Solid Tumors or Lymphomas

Arm 1: Monotherapy Cohorts



Starting dose 1 log below monotherapy MTD

Arm 2: Combination Cohorts - Atezolizumab



POM/Exploratory Biomarkers

PD response (tumor biopsy):

- TILs, IFN b, IFN dependent gene expression (Nanostring)
- Kinetics of SYNB1891 (qPCR)

Systemic PD effects (blood):

- Serum cytokines levels
- Kinetics of SYNB1891 (qPCR)

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Initiated Monotherapy Arm in Q4 2019

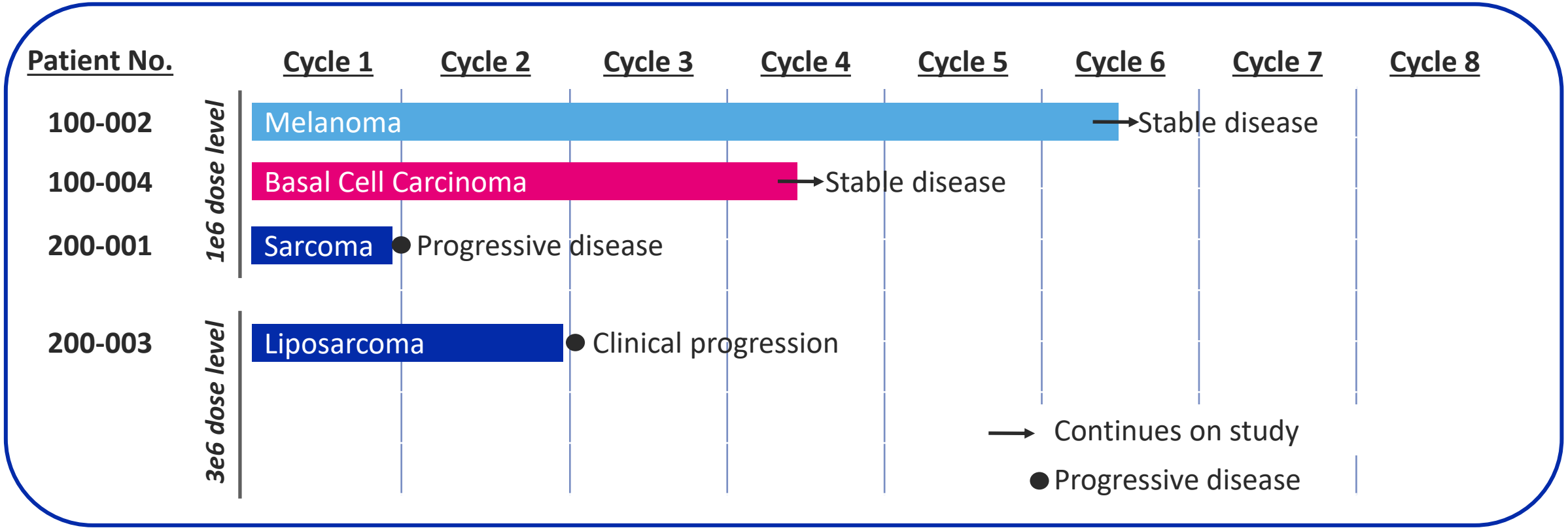
Top National Cancer Investigators: Accrual Continuing Despite COVID-19 Impacts

Dr. Janku	THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®	**Open to enrollment** Site allowing enrollment on a case by case basis due to COVID
Dr. Strauss	MARY CROWLEY CANCER RESEARCH HOPE LIVES HERE™	**Open to enrollment**
Dr. Gutierrez	Hackensack Meridian John Theurer Cancer Center	**Open to enrollment**
Dr. Luke	UPMC | HILLMAN CANCER CENTER	**Open to enrollment**
Dr. Lewis	University of Colorado	**Open to enrollment**

- Five sites activated
- COVID-19 Mitigation:
  - Additional sites
  - Amendment to reduce overnight stay requirement
- Patients in first 2 cohorts dosed
- Clinical Trial Number: NCT04167137

Clinical Trial Status Update: Safety and Tolerability

SYNB1891 Generally Well Tolerated. No DLTs or Infections



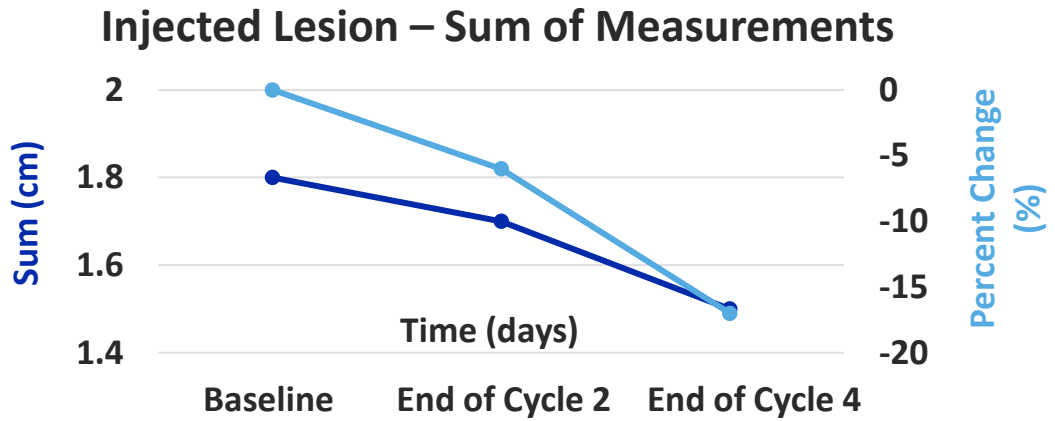
Safety and Tolerability

Injections feasible and generally well tolerated
No DLTs
No infections with SYNB1891

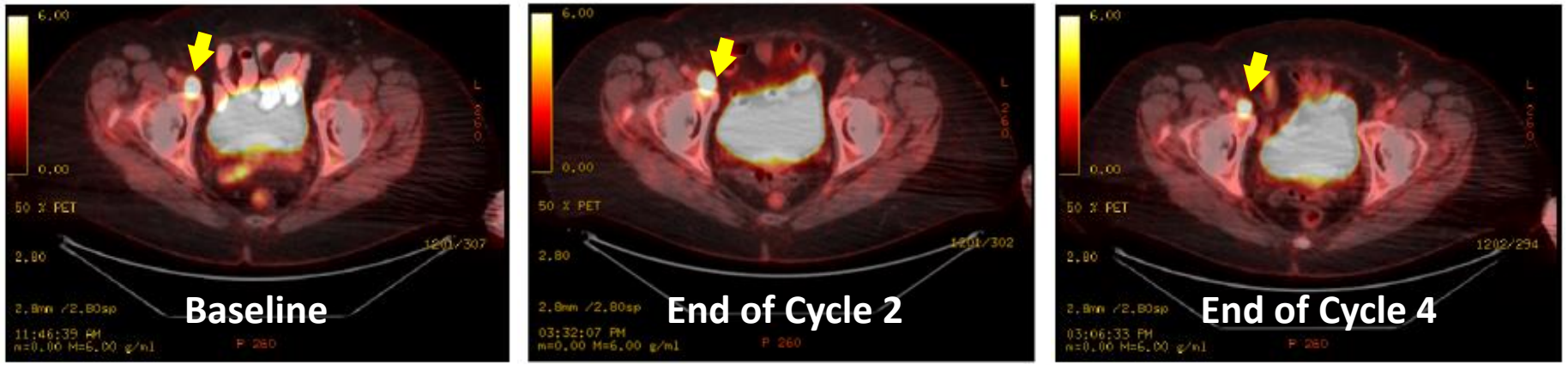
Patient 100-002: Metastatic Melanoma Previously Treated with Nivolumab

None to Mild Treatment-related Adverse Events

63-yo Female	*Adverse Events*
KIT/PDGFRA/KDR Amplification;	Hypoglycemia, anxiety – mild, not related
ATM Deletion	Itching – mild, possibly related
Previous: Local resection, nivolumab	Atrial fibrillation – severe, not related



Injected Lesion – Metabolic Activity



Imaging Results Indicate Stable Disease at 3 mos in Injected Lesion (17% decrease)

SYNB1891: Moving Forward

Continuing Enrollment, Targeting Completion of Monotherapy End of 2020

Fit within Synlogic Strategy

- ✓ Potential-best-in-class STING agonist as activity potentiated by chassis effect
- ✓ Targeted to APCs in the tumor with potential safety benefits
- ✓ Establishes path for future oncology effectors

Program Successes

- ✓ Five sites activated. Will add back-up sites due to Covid-19 slowdown
- ✓ Safe and well-tolerated among first four patients

Next Milestone & Learnings

- Data from monotherapy arm expected late 2020
- Plan to initiate combination with atezolizumab arm early 2021
- Evaluate target engagement at a well-tolerated dose

Immunomodulation: Vaccines

Dr. Caroline Kurtz, PhD
Head of Product Development

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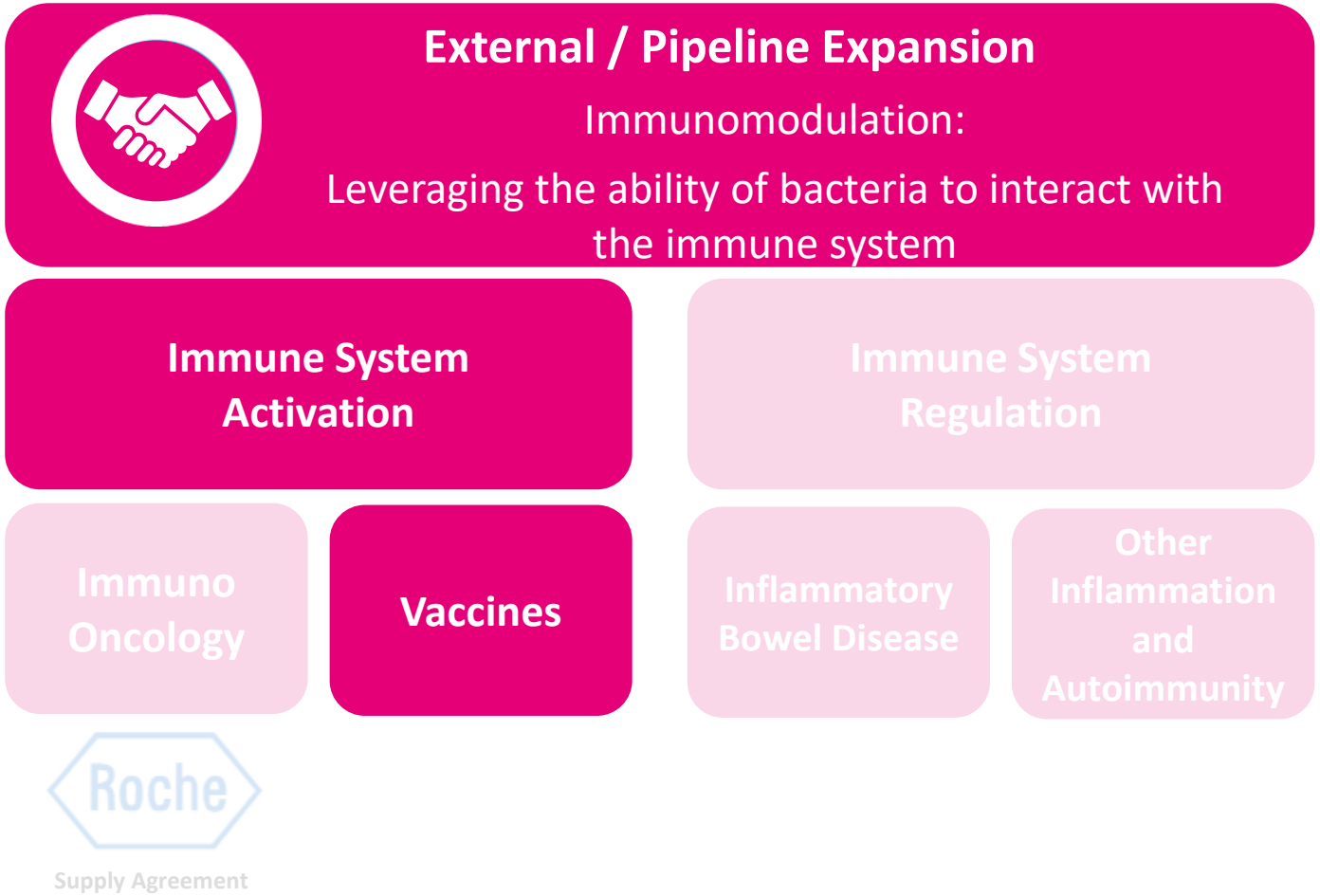
Immunomodulation Focus: Exploit Interaction of Bacteria and Immune System

Initial Exploration Through Partnership

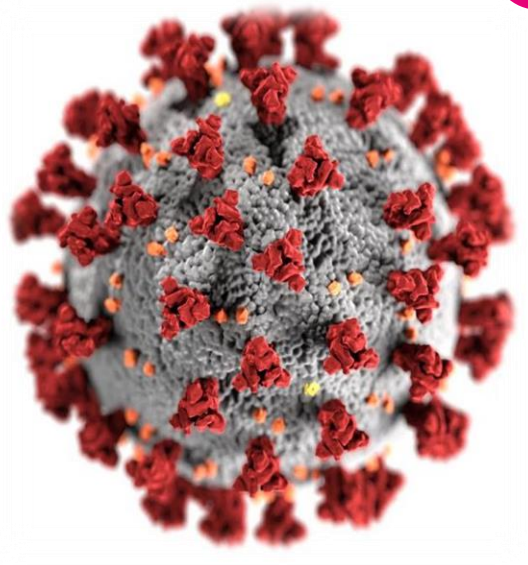


Vaccine Development: Opportunity

Synthetic Biotics Potential For Prevention of SARS-CoV2 and other viruses

Why SARS-CoV2?

- Likely multiple vaccine approaches will be needed globally
- Rapidly developing understanding of host infiltration mechanism
- Excellent first candidate to evaluate potential for vaccine application of orally available, temperature stable Synthetic Biotic products



Synlogic Approach

- STING agonist to induce Th1 / CD8+ T cell response
- Spike protein or receptor binding domain expression on E. Coli Nissle surface
- Potential to result in long lasting immunity with local mucosal delivery

Synlogic and Gingko are collaborating to develop candidate strains

Next Step: Selection of lead candidate

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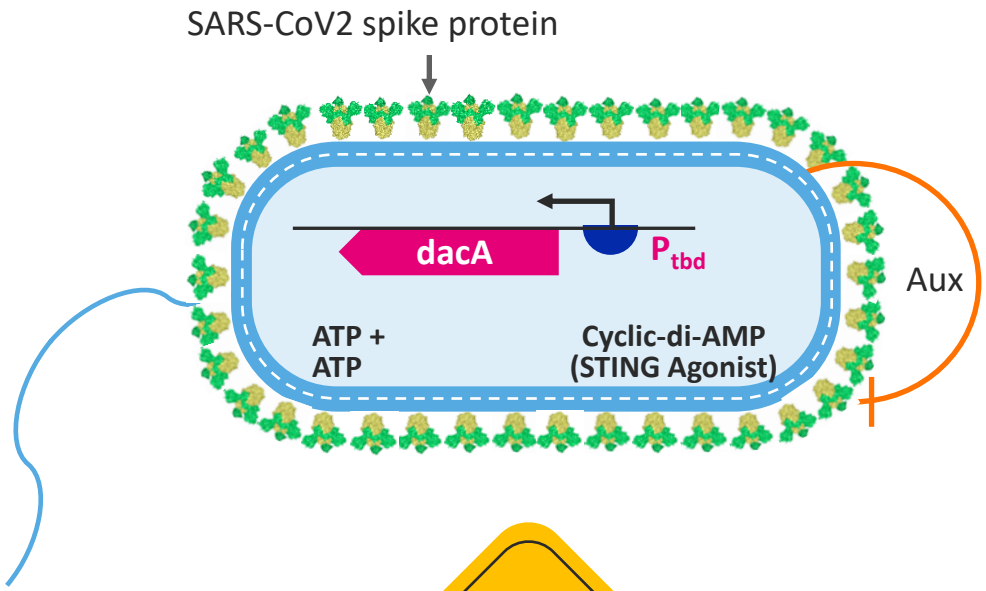
SYNCoV2 Build From Synthetic Library

Component	*Benefit*
Bacterial Chassis	Targeting to antigen presenting cells in the nasal mucosa Innate immune activation Specific immune induction
Switch	STING Agonist: tbd SARS-CoV2 Spike: tbd
Effector 1: STING Agonist	Innate immune activator compounds with chassis effect
Effector 2: SARS-CoV2 Spike	SARS-CoV2 proteins
Safety Features	Auxotrophy to inhibit bacterial proliferation in mucosal epithelium



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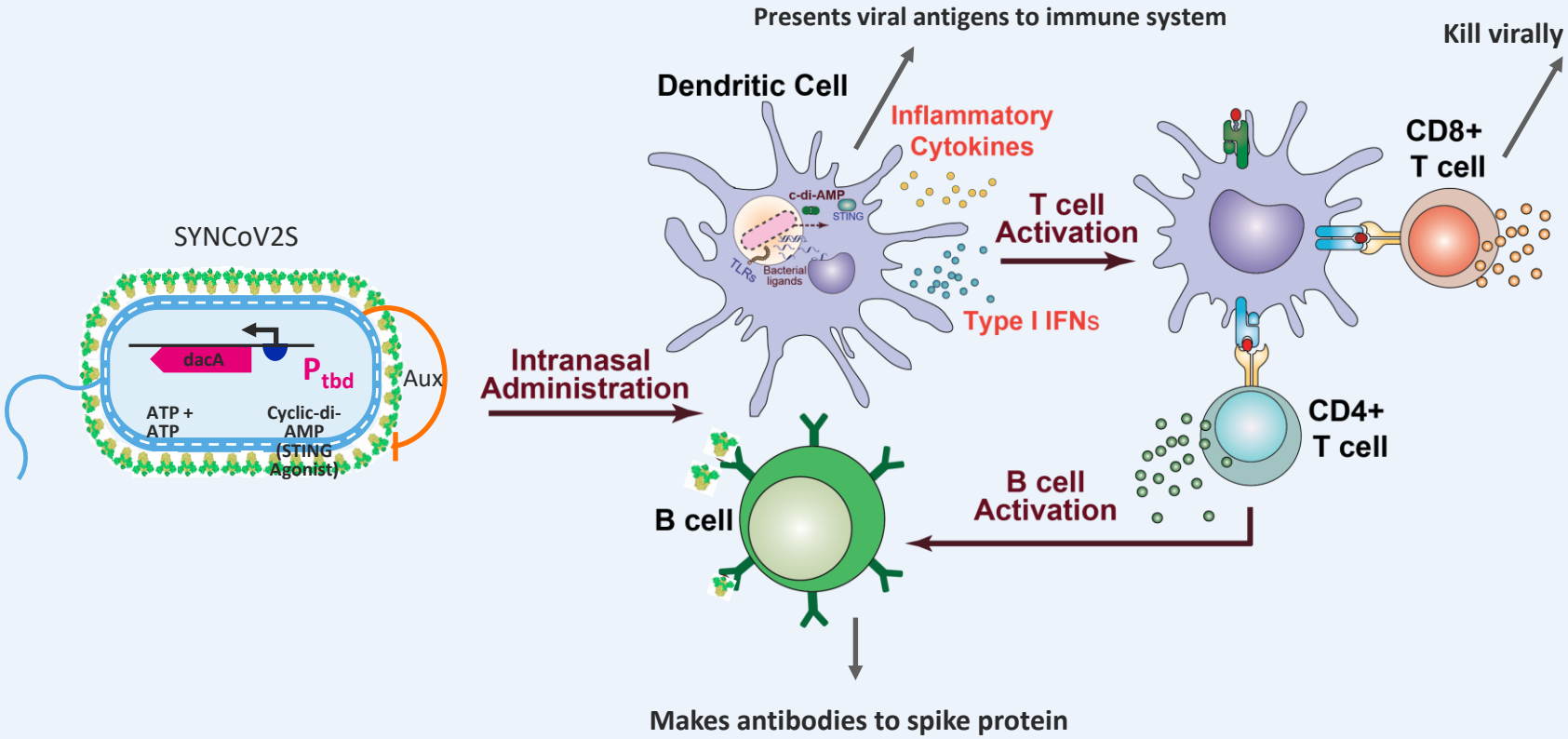
Synlogic SARS-CoV2 Vaccine

Unique Approach To Induce Protective Immunity for COVID-19

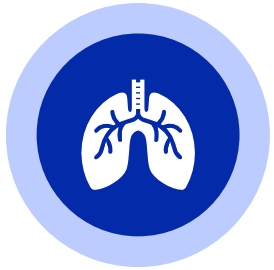


Anti-Viral Immune Response:

- Induction of anti-viral neutralizing antibodies at mucosal surface and systemic
- Induction of anti-viral cytotoxic T cell response

Strain Designed to Induce Both Humoral and Cellular Immunity Protective Immunity to SARS-CoV2

Advantages of Synlogic Approach



Efficacy:

- Rationally designed, specific viral antigens and immune activators engineered into a single Synthetic Biotic
- Induces an antigen specific mucosal and systemic immune response
- Can be adapted if viral sequence changes over time

Safety: EcN chassis used orally in human populations for over 100 years

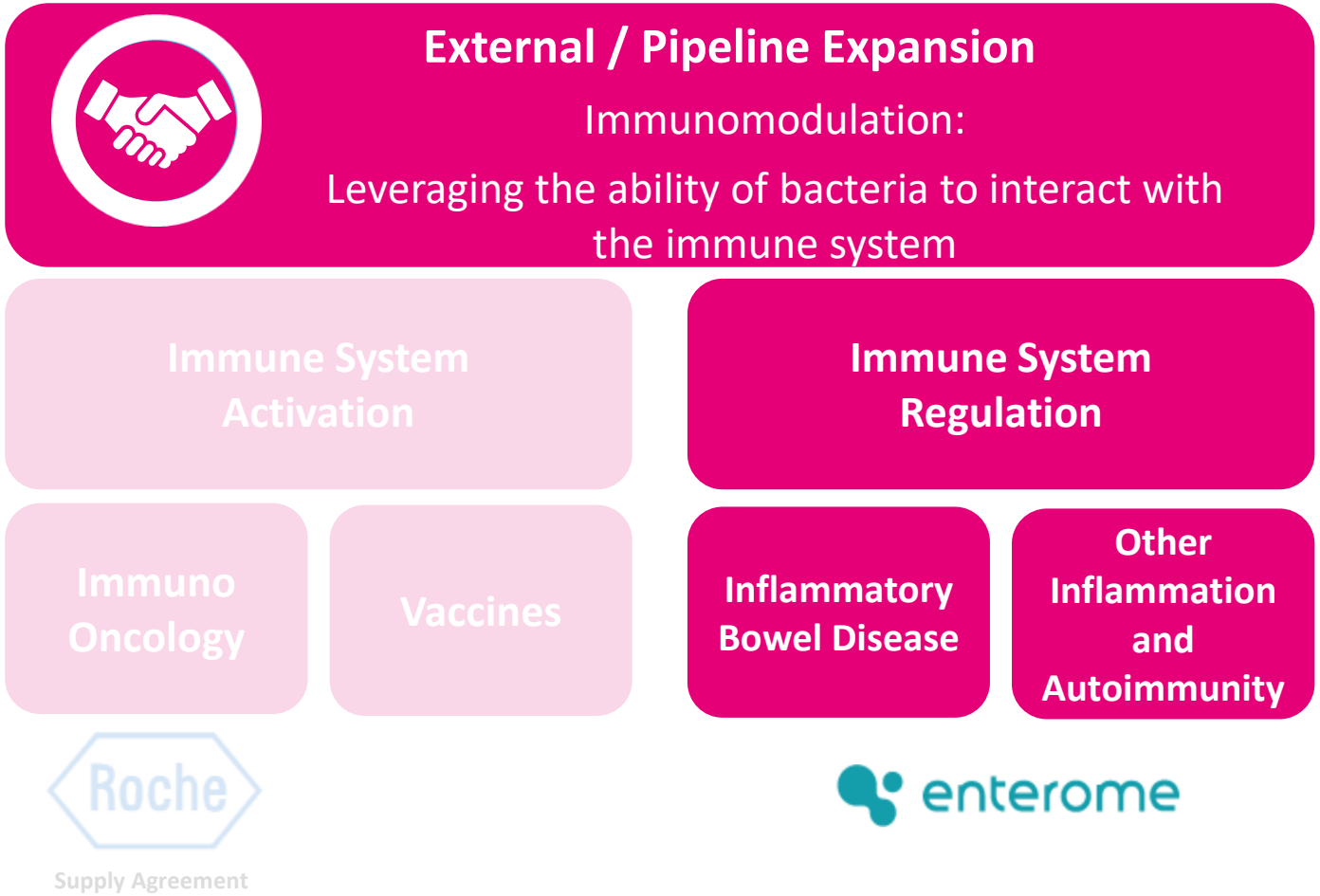
- No live virus
- Local delivery
- Auxotrophy engineered into strain to control growth

Manufacturability & Stability:

- Capability to produce **6 million doses of vaccine** in a single batch (at $1x10^9$ live cells/dose)
- Lyophilized cells with room temperature stability, potential for global distribution

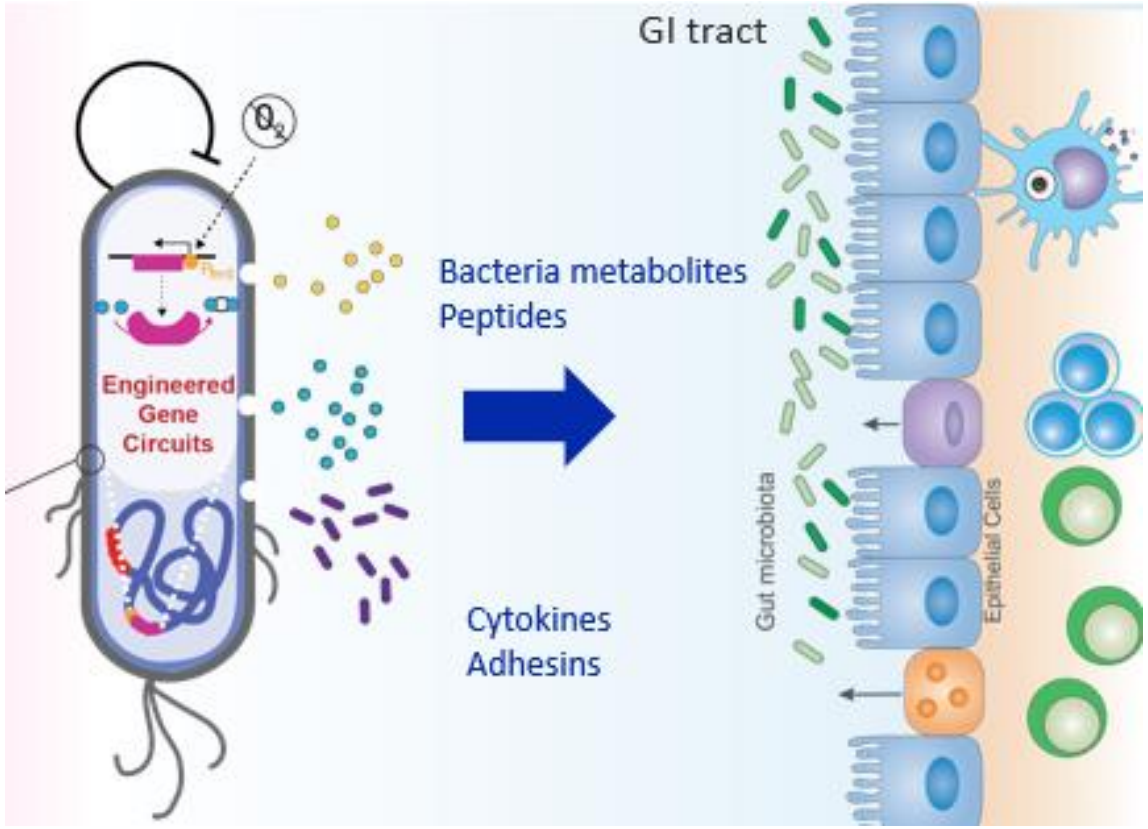
Immunomodulation Focus: Exploit Interaction of Bacteria and Immune System

Initial Exploration Through Partnership



Bacterially-Mediated Immune Regulation

Rationally Designed Synthetic Biotics Have Wide Application Across Range of Disease States



Anti-inflammatory

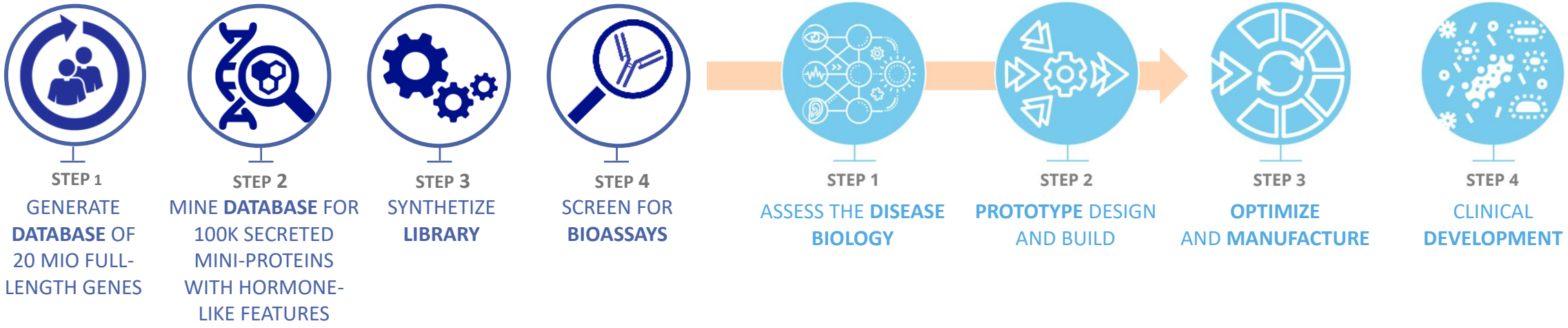
Mammalian Effectors

Produce and secrete mammalian proteins

Bacterial Effectors

Produce and secrete microbiome-derived metabolites, peptides, and proteins

Enterome and Synlogic: Highly Complementary Platforms



enterome

- DNA inserts coding for **highly active (nM range) bacterial effectors** with a known function
- Secreted molecules involved in key functions of human physiology are targeting the **GI tract**
- New libraries dedicated to screen **an untapped reservoir of overlooked bacterial peptides**

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- EcN chassis for production and delivery of microbiome bioactives to the **GI tract**
- Ability to secrete biologically active human peptides and cytokines from EcN in vivo
- **Disruptive cycle time**

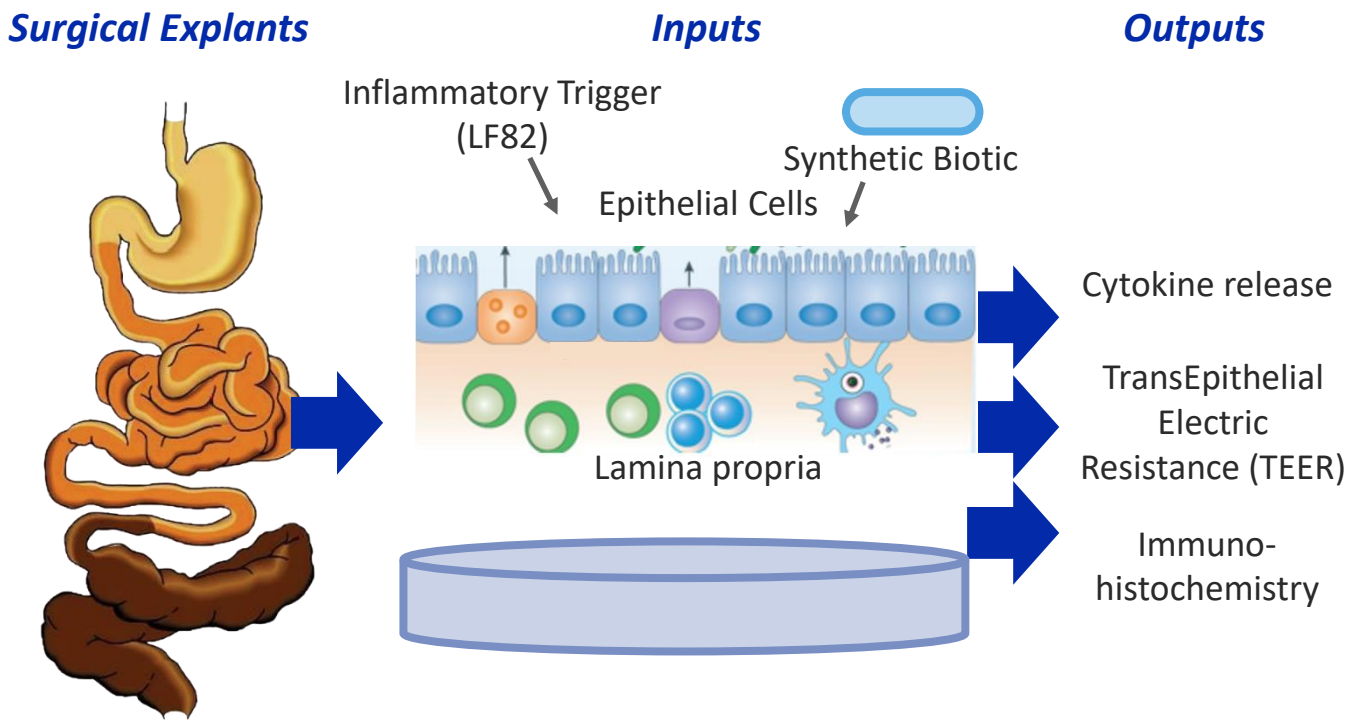
Pilot: Synthetic Biotic Effectors Secreting, Novel Bacterial-Produced Molecules

Secretion of Microbiome-derived Peptides to Down-regulate the Immune Response and Inflammation

Pilot Collaboration

- **Enterome** identified **bacterial peptides**
- **Synlogic** cloned into **bacterial chassis**
- **Testing** ability to induce secretion of anti-inflammatory cytokines
- Validating in **human gut explants system**

Human Gut Explant System



Demonstrates the Opportunity to Expand to Broader Set of Novel Bacterially-produced Effectors

Building a Diverse Portfolio of Synthetic Biotic Medicines

Portfolio Growth Built on Foundational Platform Capabilities

Validated Biological Targets

Where a Synthetic Biotic medicine is uniquely positioned to impact patients

Enabling Engine Core Differentiating Capabilities

- **Synthetic Biology** Internal + Ginkgo
- **Manufacturing of Live Biotherapeutics**
- **Regulatory, Translational & Clinical Dev.**

Internal Pipeline: Metabolic Programs

Consumption of toxic metabolites from the GI tract

External & Partnered Pipeline: Immunomodulation

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

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Our Agenda Today

Introduction & Welcome	Dr. Aoife Brennan, President & CEO
Synlogic's Product Engine	Dr. Amanda Kay, Head of Strategy & Business Development Tony Awad, Head of Technical Operations
Metabolic Programs	Dr. Caroline Kurtz, Head of Translational Sciences & Product Development
Metabolic Programs: Focus on Enteric Hyperoxaluria	Dr. Richard Riese, Chief Medical Officer *Special Guest: Dr. David Goldfarb, New York University*
Immuno-Modulation: Upregulation & Downregulation	Dr. Amanda Kay Dr. Caroline Kurtz
Q & A	Synlogic Leadership Team & Dr. David Goldfarb
Concluding Remarks	Dr. Aoife Brennan

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Available For Questions

Aoife Brennan, MD CHB
President & CEO

Richard Riese, MD PhD
CMO

Gregg Beloff, JD MBA
Interim CFO

Antoine Awad
Head of Tech Ops

Amanda Kay, PhD
Head of BD & Strategy

Caroline Kurtz, PhD
Head of Product Development

David Goldfarb, MD PhD
NYU Langone Center

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Concluding Remarks

Dr. Aoife Brennan
MD CHB

President & CEO

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Executive Summary

- We are building a therapeutic platform with potential to **benefit patients in new ways**
- We have the **team**, technology and portfolio to succeed
- Rapidly progressing **internal metabolic programs** through POC
  - SYNB1618 (PKU) demonstrates activity in vivo and moving to Phase 2
  - Accelerated plan for SYNB8802 in enteric hyperoxaluria
- Building portfolio of **partner-able assets** in immunology and oncology
- Funded through multiple upcoming milestones across clinical portfolio

Multiple Expected Upcoming Milestones

Synlogic Entering Data Rich Period In The Clinic

	Expected Milestone	2020 early	2020 mid	2020 late	2021 early	2021 mid	2021 late
SYNB1618 PKU	Initiate Ph.2 study in PKU patients						
	Ph.2 Phe-lowering read-out						
SYNB8802 HOX	Initiate IND-enabling studies	initiated					
	Initiate Ph.1 study in HV and Patients						
	Ph.1 Patient Read-out						
SYNB1891 I/O	Ph.1 Monotherapy read-out						
	Initiate Ph.1 combination study arm						
	Ph.1 Combination therapy read-out						

Significant Clinical Readouts Within Our Current Cash Window

Synthetic Biotic™ Medicines Designed For Life

Synlogic's mission is to
address patients' dynamic therapeutic needs
by developing living medicines
that sense and respond to disease

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