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A Genetically-Engineered Probiotic Designed to Consume Methionine for the Treatment of Homocystinuria

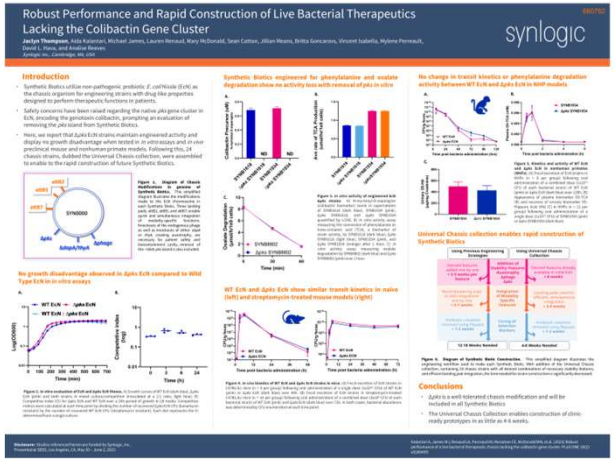
Analise Reeves, PhD

June 1, 2023

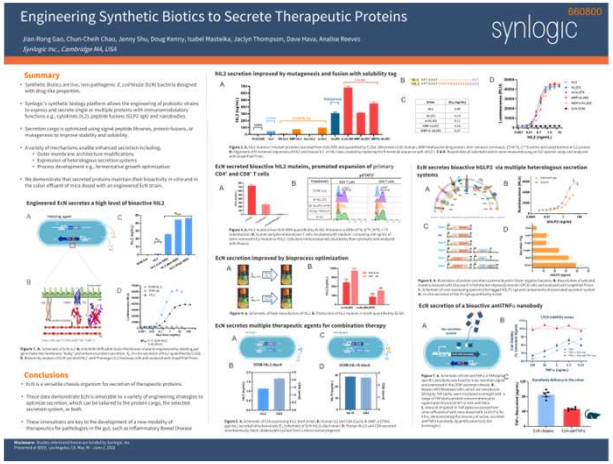
SEED

2023 SYNTHETIC BIOLOGY:
Engineering, Evolution & Design

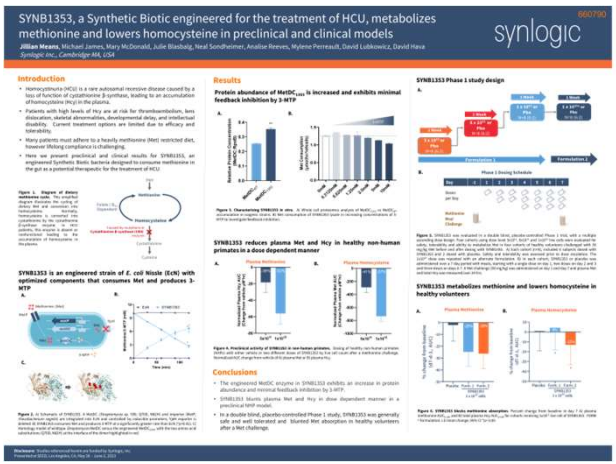
Synlogic Posters at SEED



Jackie Thompson
Tuesday May 30
Poster 38A



JR Gao
Wednesday May 31
Poster 51B



Jill Means
Thursday June 1
Poster 51C

Synthetic Biotics: Precise Engineering to Address Specific Biology

FMT

Consortia

Single strain

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Engineered Synthetic Biotic

Microbiome focused

Colonizing

Broad biological effects

Complex drug products

Microbiome independent

Non-colonizing

Engineering principles

Validated biology

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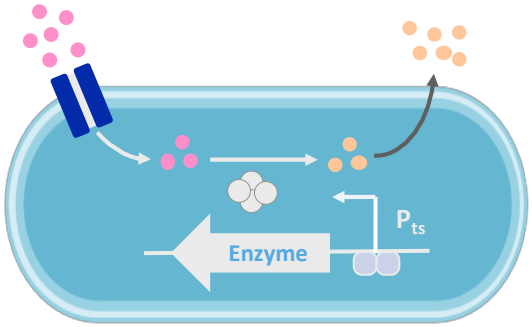
Advancing a New Paradigm of Biotherapeutics

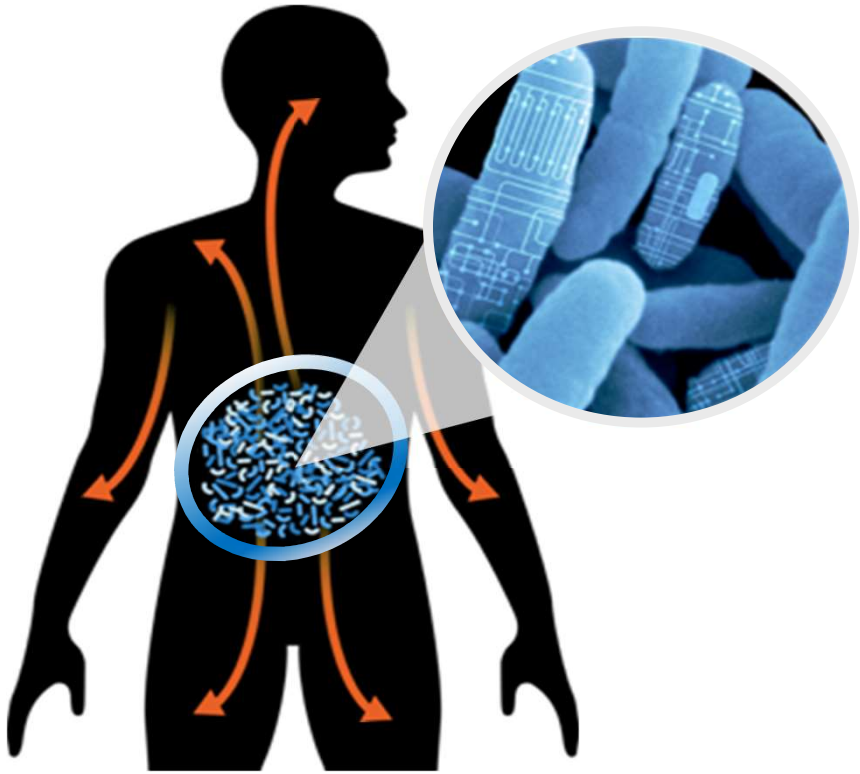
Goal: To use engineered probiotic bacteria to deliver therapeutic function from within the GI tract

Synthetic Biotics

Well-characterized **probiotic chassis** + Programmable **genetic engineering**



Convert disease-causing targets to harmless metabolites



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GI = gastrointestinal

Probiotics as a Delivery Vehicle for Therapies

Application of synthetic biology to probiotic “chassis”

100 years of *E. coli* strain Nissle 1917

Ulrich Sonnenborn, 2017

Why *E. coli* Nissle?

- Available over the counter in many countries
- Leverage >100 year safety profile
- Amenable to genetic manipulation
- Easy to manufacture

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Engineering a probiotic to metabolize methionine

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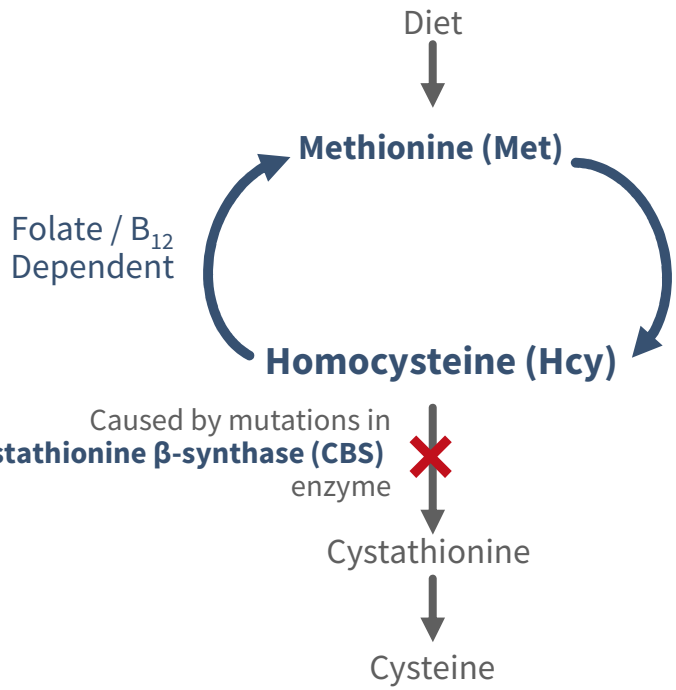
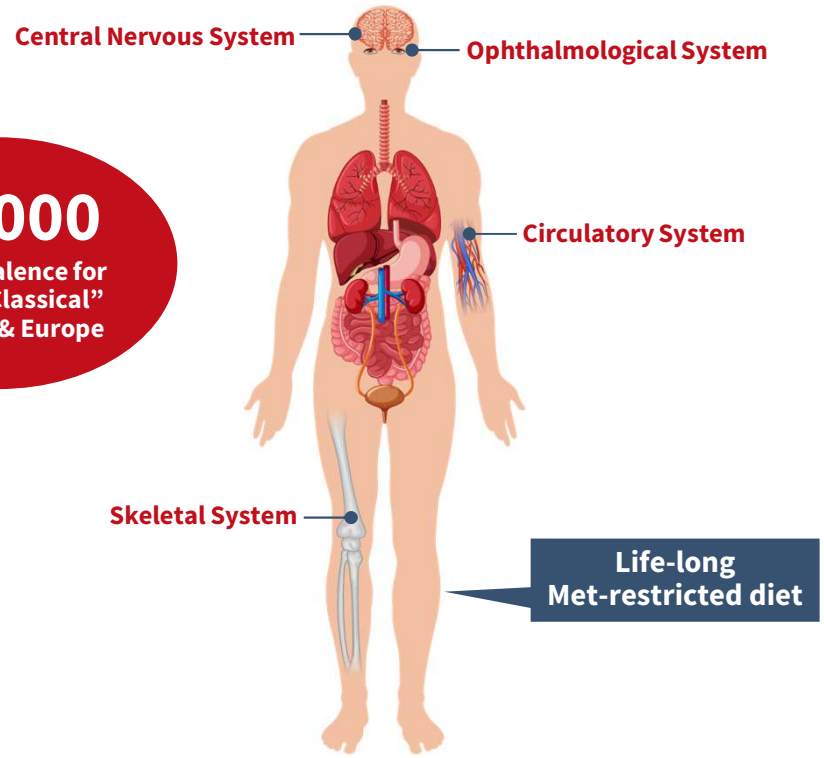
Homocystinuria, a rare metabolic disease with unmet need

Homocystinuria Etiology



~5,000
Est. prevalence for CBS or "Classical" HCU, US & Europe

Multi-system complications



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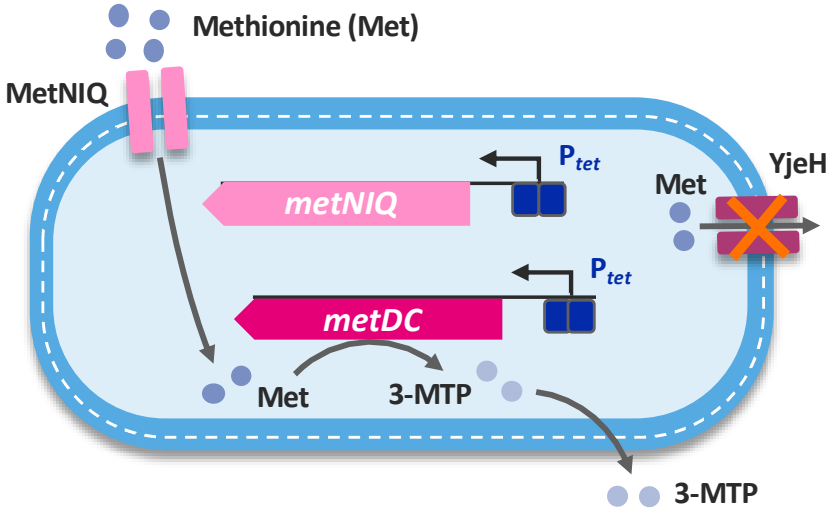
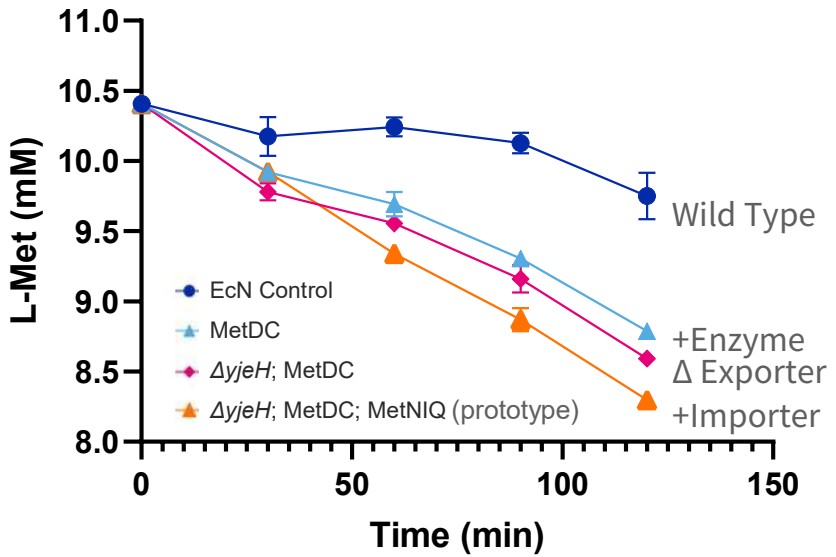
Engineered prototypes consume methionine in vitro

Met consuming prototype design



Additive parts increase activity



Key design elements:

1. Methionine decarboxylase enzyme, MetDC, *Streptomyces*
2. Methionine Importer: MetNIQ, *E. coli*
3. Methionine Exporter: YjeH, *E. coli*

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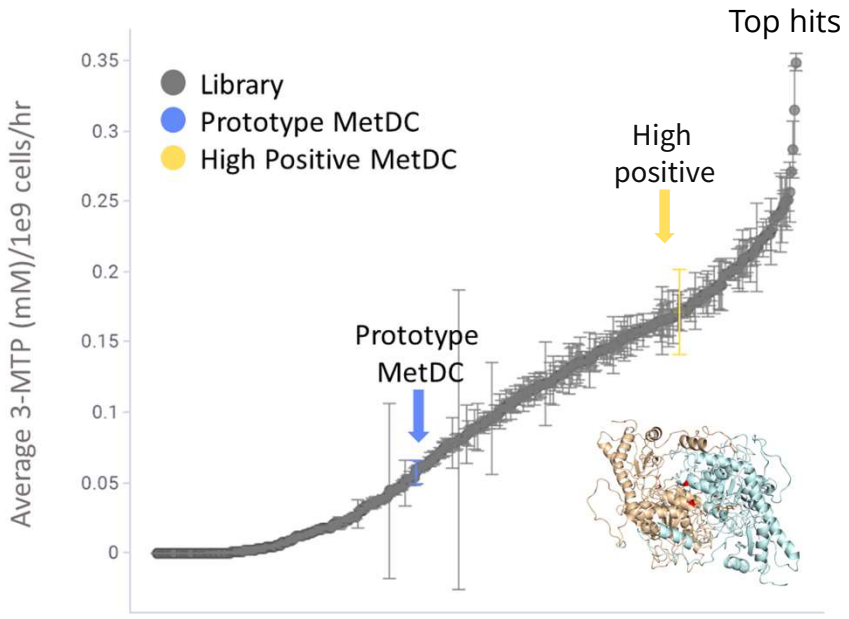
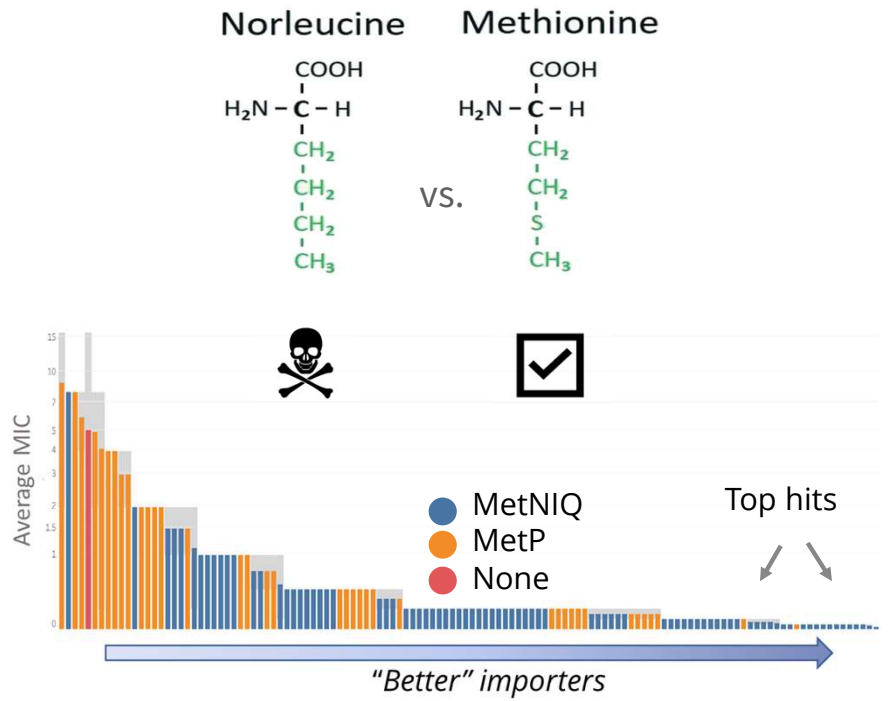
High Throughput screening identifies top performing proteins

MetDC protein engineering library



- Metagenomic library was also screened, but yielded few hits

Anti-metabolite selection of importer metagenomic library



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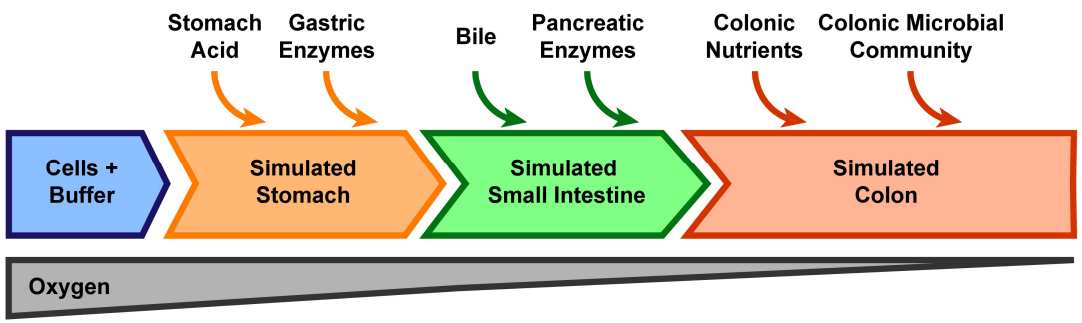
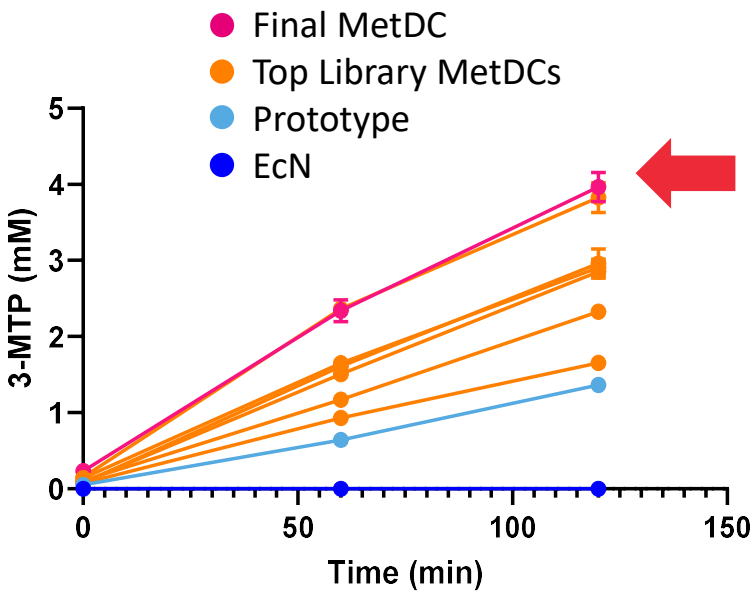
Secondary screen identifies lead MetDC with improved activity

In vitro simulation (IVS) assay



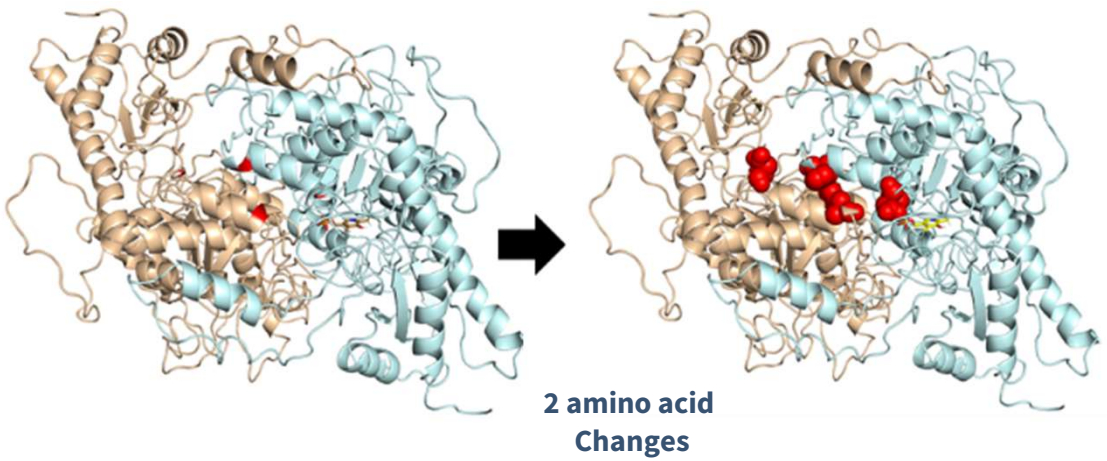
Models transit through the gut

Lead 3MTP Production



Secondary screen identifies lead MetDC with improved activity

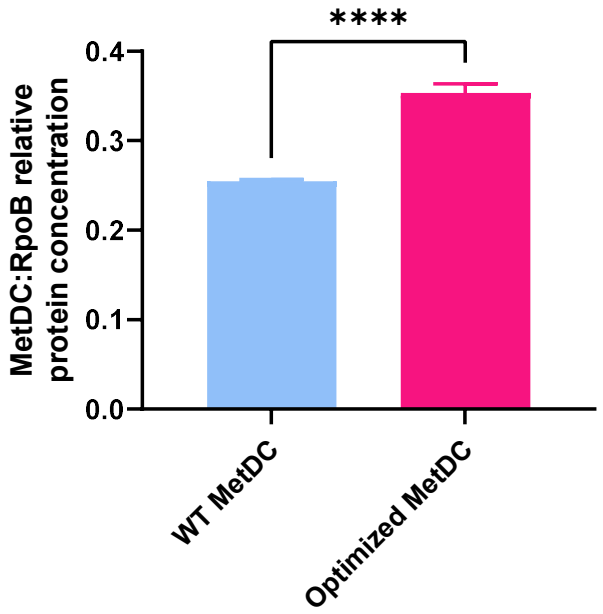
Optimized MetDC



Prototype MetDC

Optimized MetDC (Q70D, N82H)

Increased protein stability



Possible contributing mechanism

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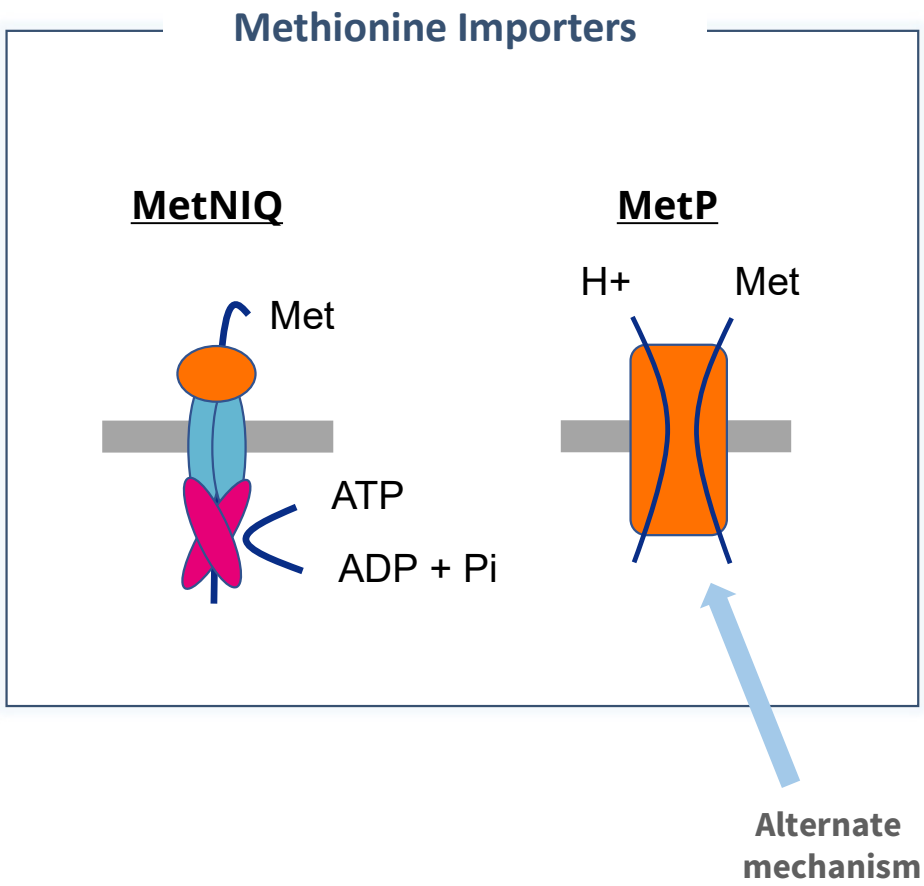
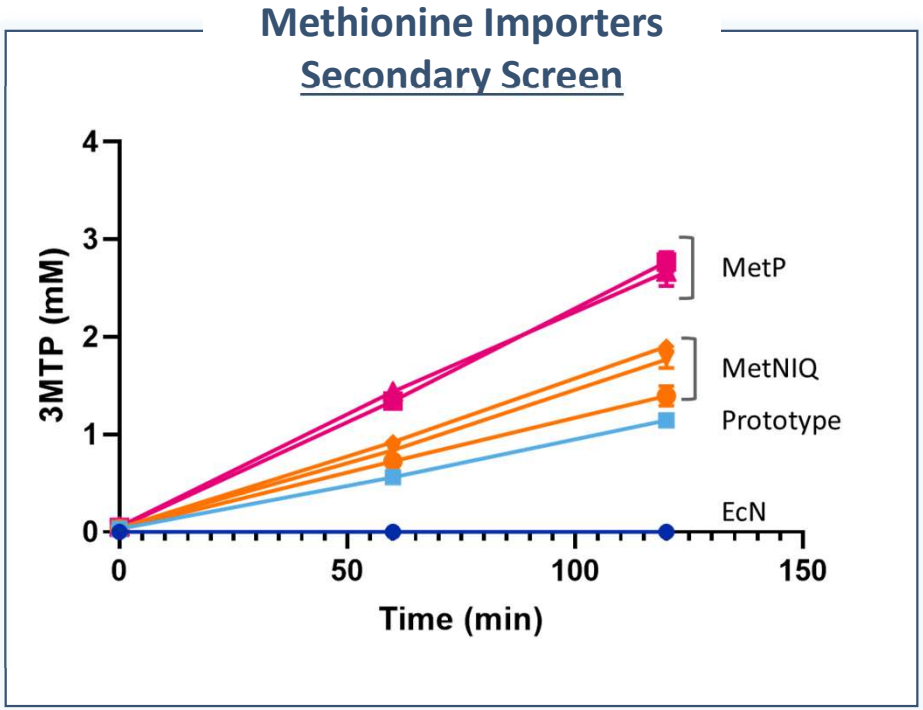
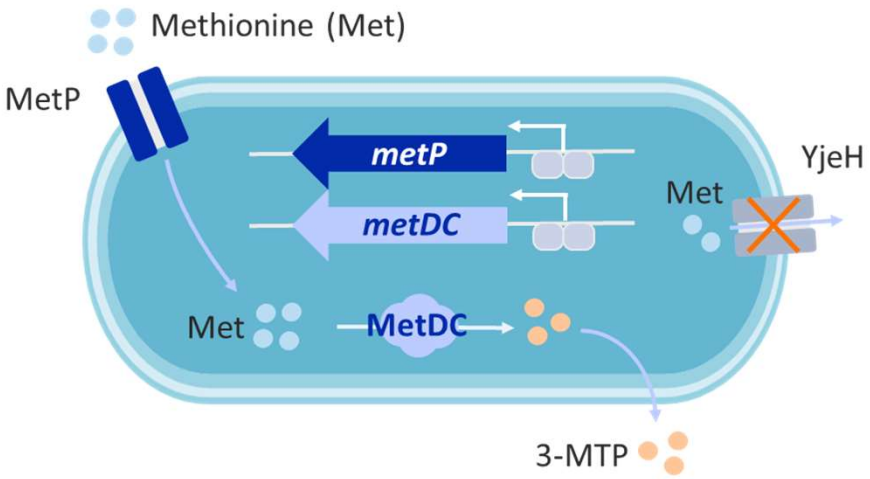
Identification of more active Met importers



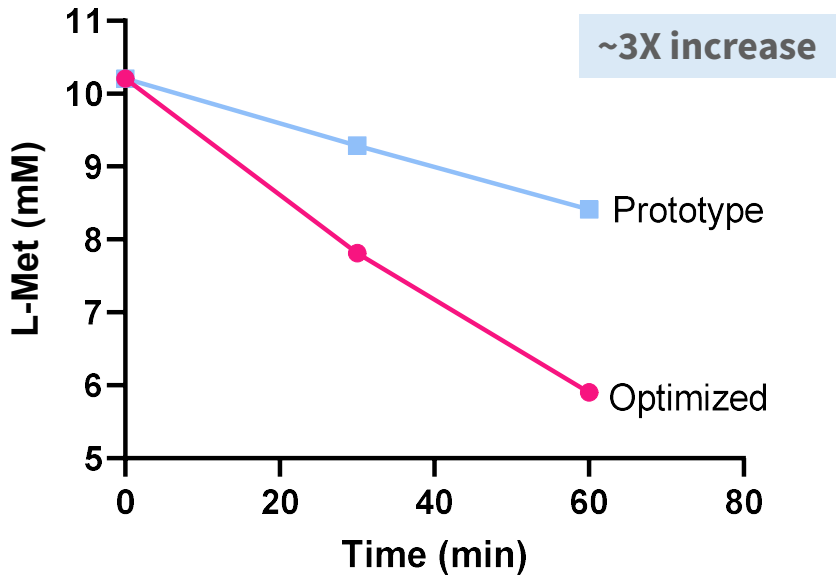


Combining optimized components improves activity

Optimized components



Combined Met degrading activity



Improved Parts:

1. Methionine decarboxylase enzyme, **MetDC (Q70D, N82H)** *Streptomyces*
2. Methionine Importer: **MetP, *Flavobacterium segetis***
3. Methionine Exporter: YjeH, *E. coli*

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SYNB1353, a methionine metabolizing Synthetic Biotic

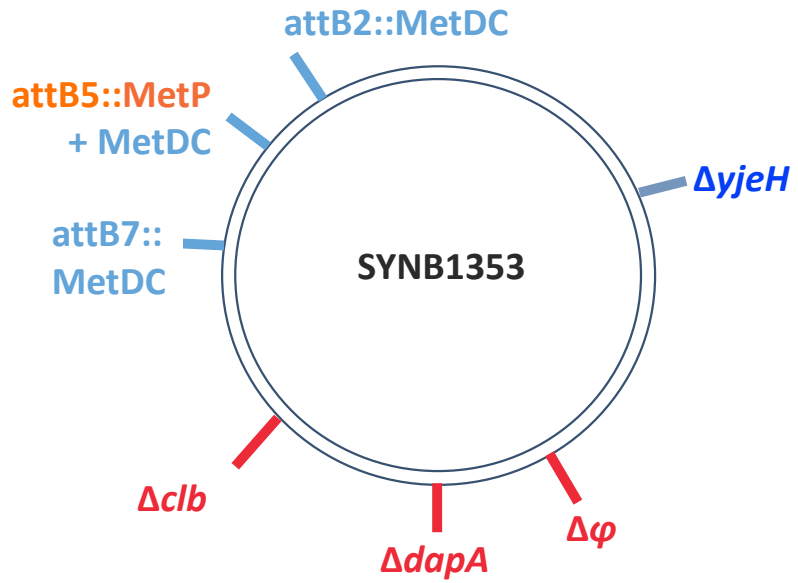
Naming SYNB1353

Akhenaten was an ancient Egyptian pharaoh

Speculated that he suffered from **HCU**

His ruling started in **1353** b.c.

Chromosomal Map



Clinic ready features:

- Δ*dapA* – containment
- Δ*φ* – manufacturing
- Δ*clb* – safety

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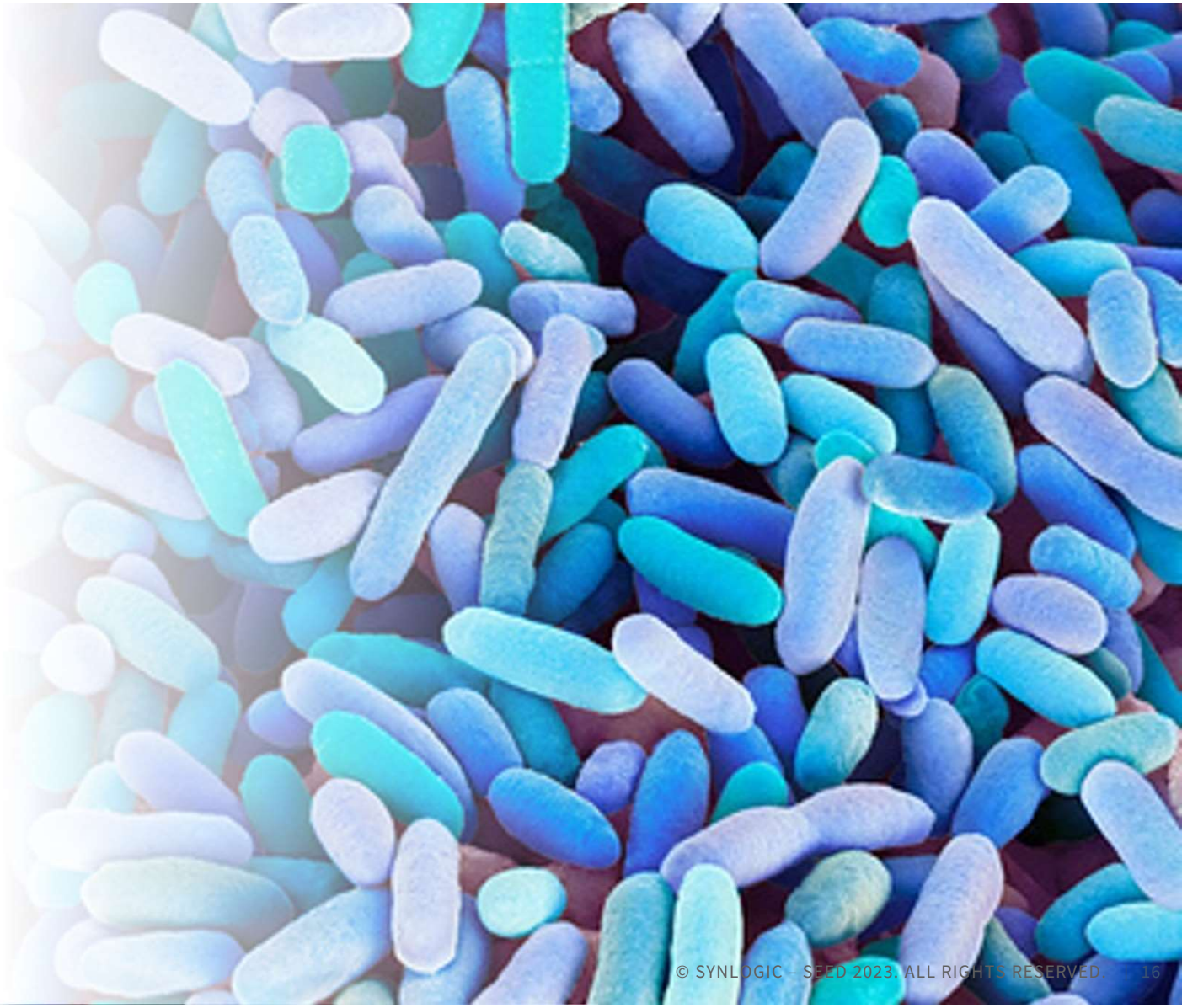
In vivo testing of SYNB1353



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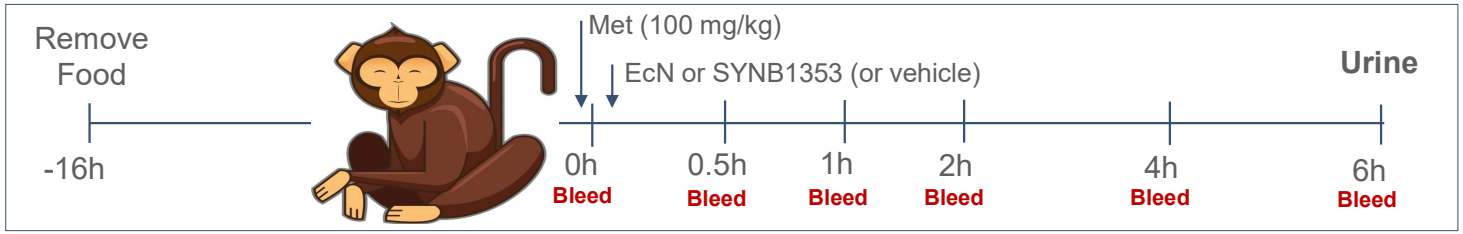
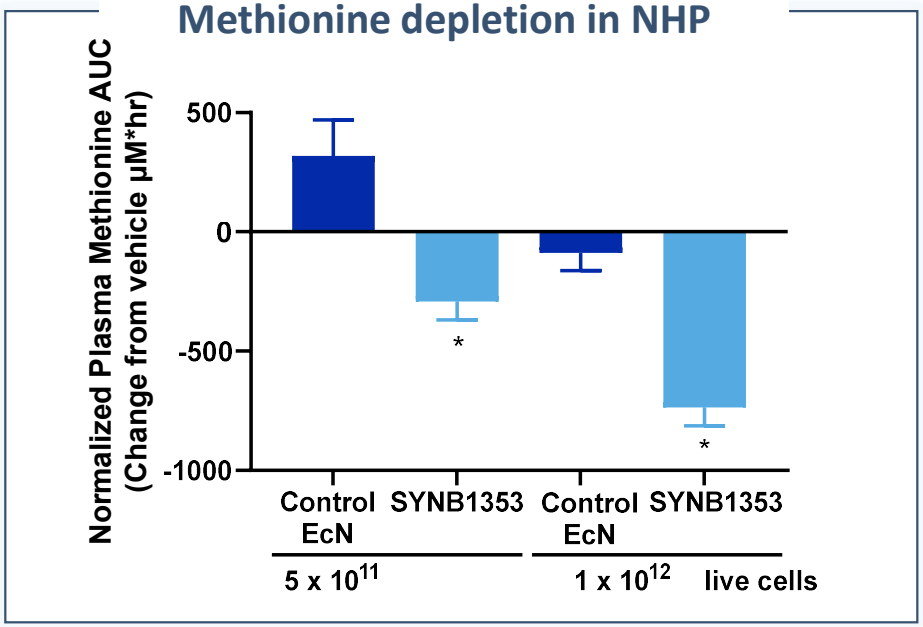
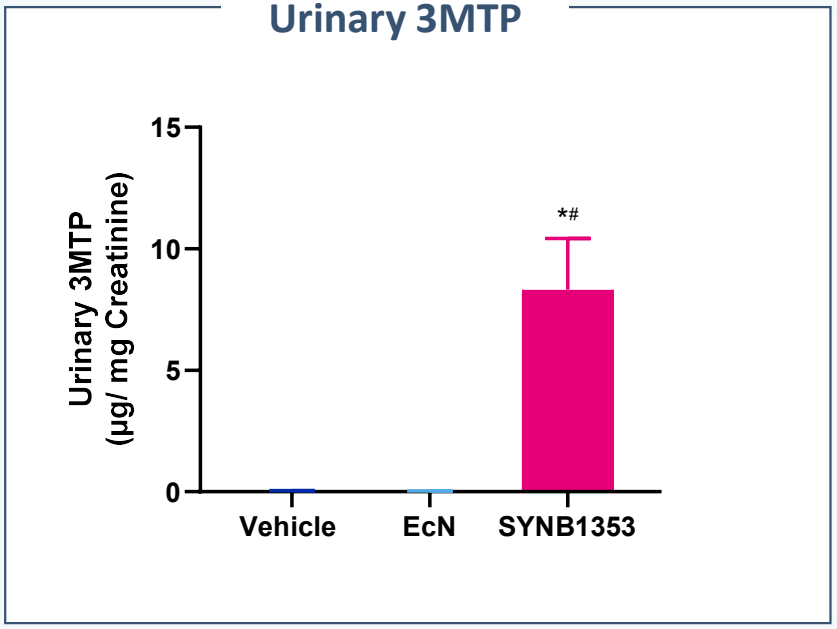
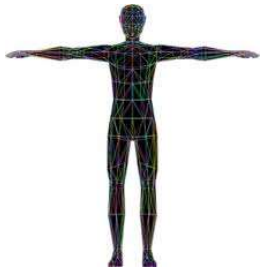
In vivo efficacy of SYNB1353 in healthy NHPs

SYNB1353 results in significant blunting in serum Met and Hcy following challenge



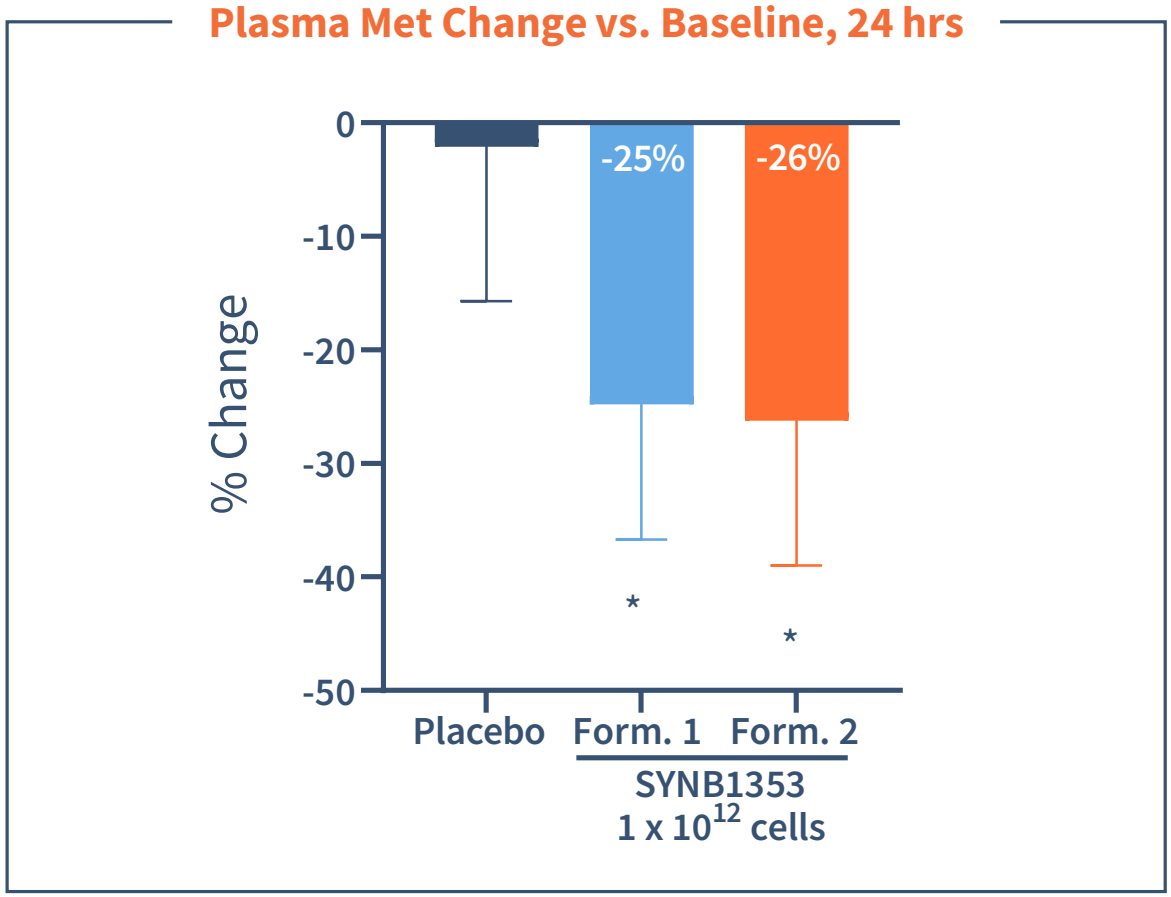






Phase 1

SYNB1353: Proof-of-Mechanism Achieved



Advancing to Phase 2

LS mean change, 95% CI
*$p < 0.05$

Form = formulation; placebo n=8, 1x10^{12} form 1 n=6, 1x10^{12} form 2 n=5

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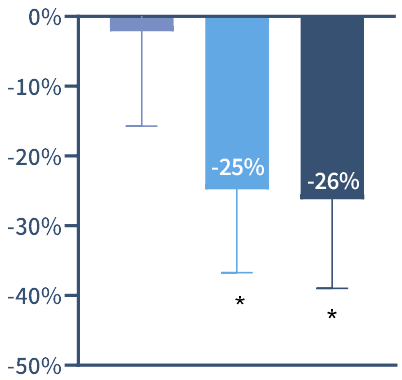
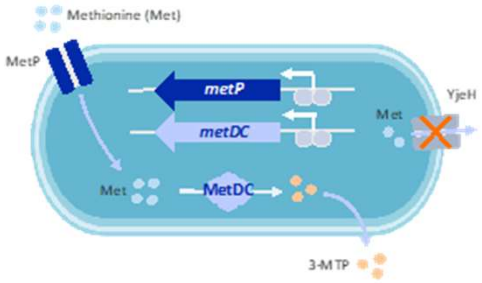
A synthetic biology platform with multiple hits

MET

-26%

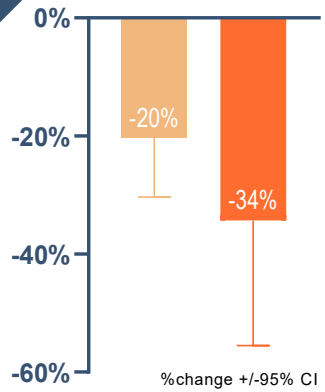


SYNB1353

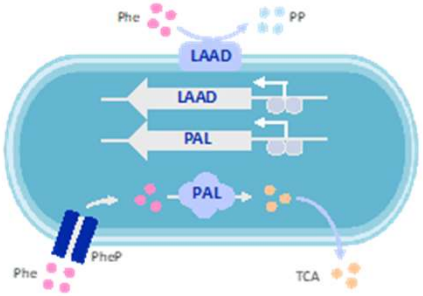


PHE

-34%

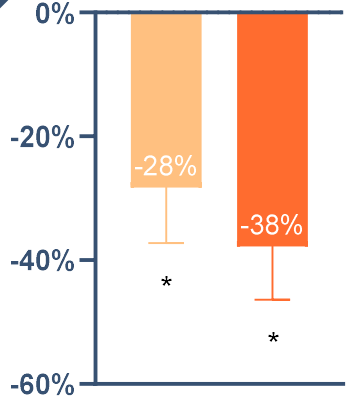


SYNB1934

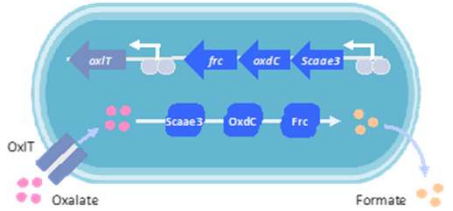


UOX

-38%



SYNB8802



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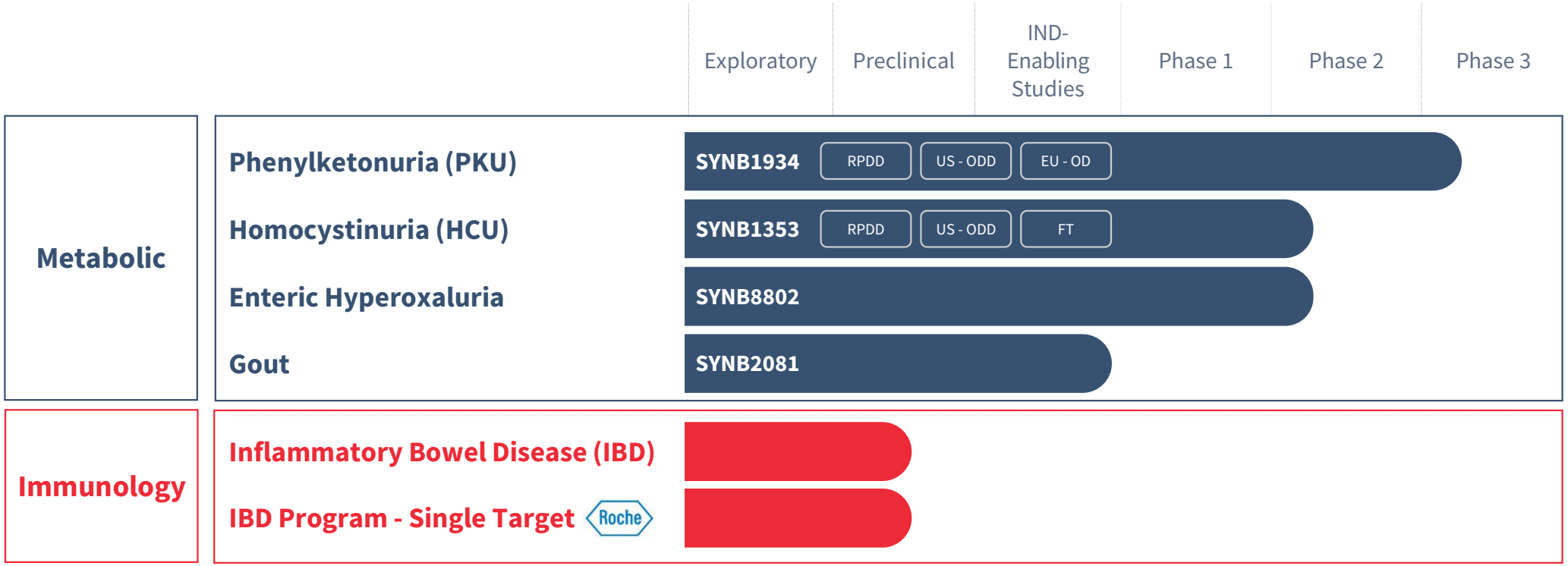
Advancing a New Class of Biotherapeutics



RPDD = Rare Pediatric Disease Designation granted by FDA
EU - OD = Orphan Designation granted by EMA
US - ODD = Orphan Drug Designation granted by FDA
FT = Fast Track granted by FDA

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Acknowledgements

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- Chris Bergeron

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