

A Probiotic Gene Cassette for Ulcerative Colitis Treatment

Jason M. Crawford, Ph.D. (Emilee Shine)

&

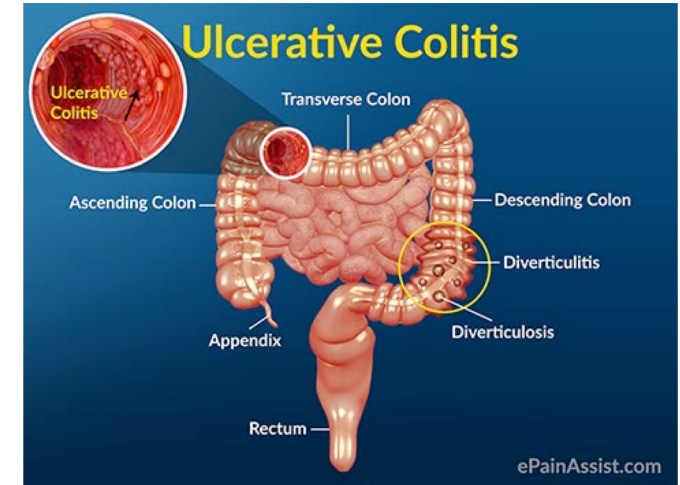
Richard A. Flavell, Ph.D., F.R.S. (Abigail Jarret)

GutReactions

Develop a probiotic for ulcerative colitis (UC)

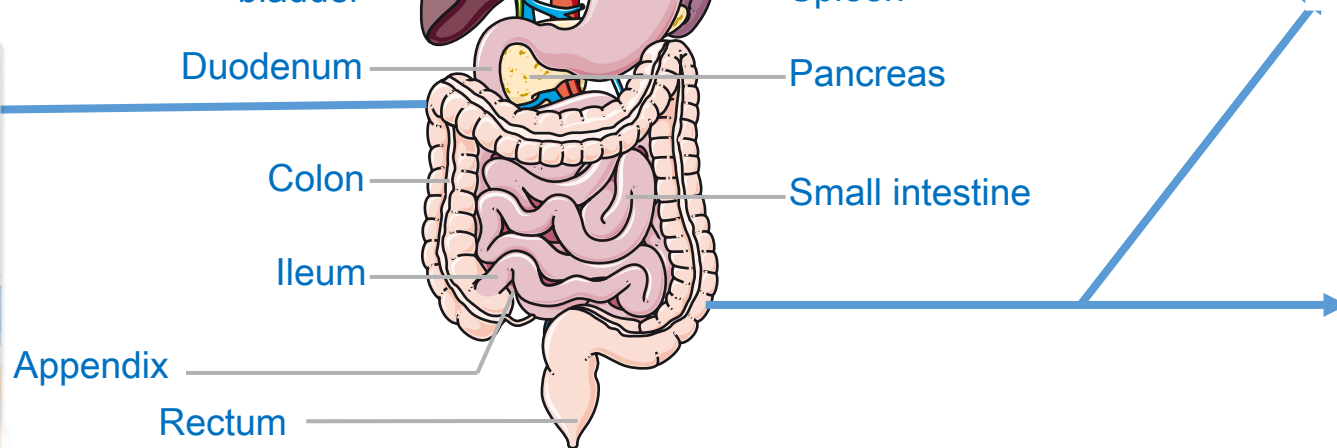
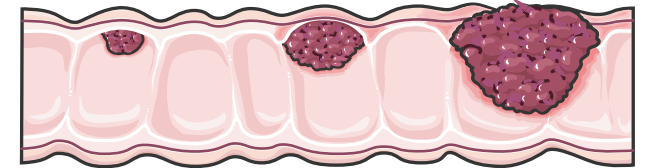
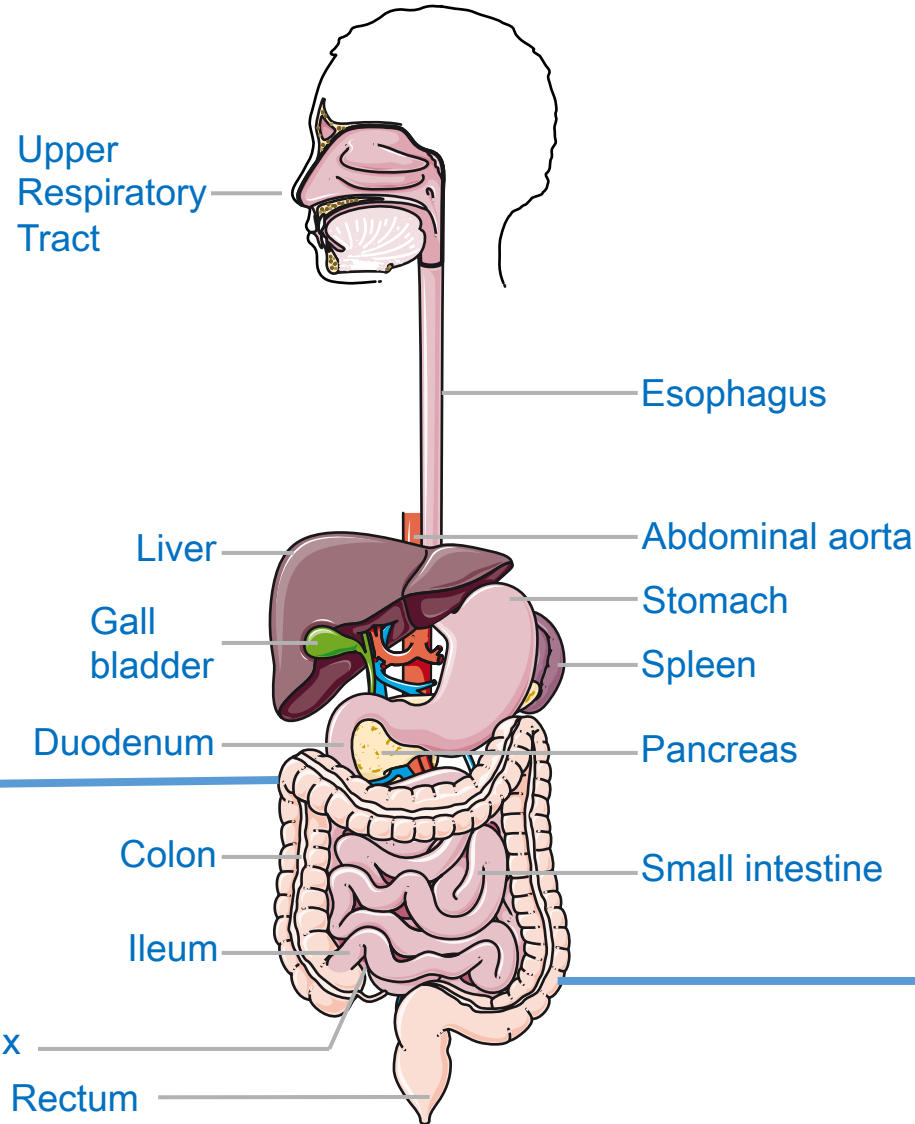
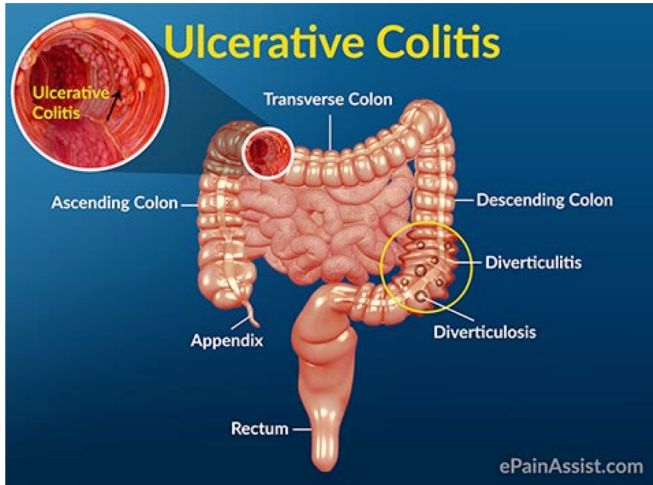
Goal: Bugs as Drugs

Develop probiotic for UC with higher efficacy and lower toxicity



- > 1.4 million Americans and rising are afflicted with IBD
- Patients are generally treated with mesalamine/sulfasalazine
- Estimated \$10 billion in world drug revenue for IBD in 2017
- **35% of patients report no improvement and nearly 20% experience adverse events**
- **2/3 of patients eventually have surgical resection of the bowel**

Products for ulcerative colitis (UC) and colorectal cancer



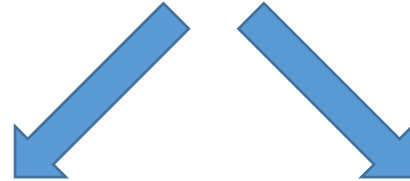
Bugs as Drugs: Establish commercial viability of products for UC

“Mutualist”



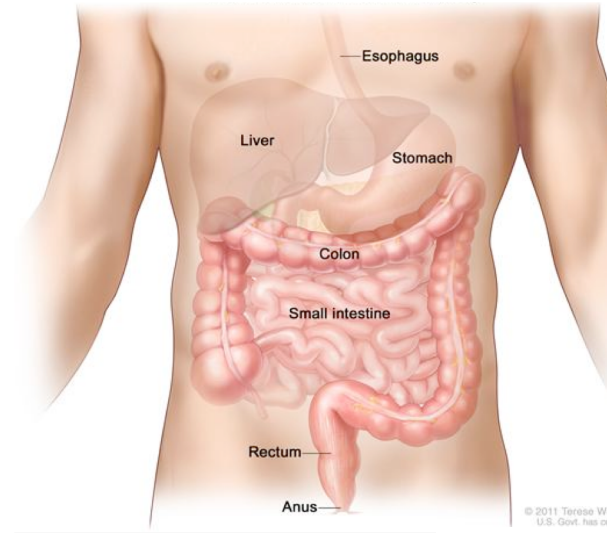
mutaflor.ru

Inflammatory bowel diseases



vs.

“Pathogen”



cancer.gov

Cancer

Known to be efficacious in clinical trials
Pathway is found in a variety of *E. coli* (99% identical)
We have identified pathway products with probiotic activities
These products represent commercially-relevant deliverables

Genes in colibactin pathway are required for probiotic efficacy
E. coli probiotics contribute to deleterious Enterobacteriaceae load

Mature colibactin causes colorectal cancer

Establish commercial viability of novel products for UC

“Mutualist”

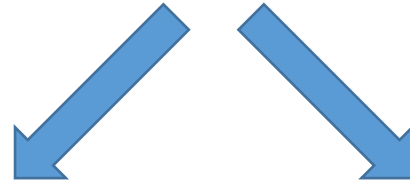


mutaflor.ru

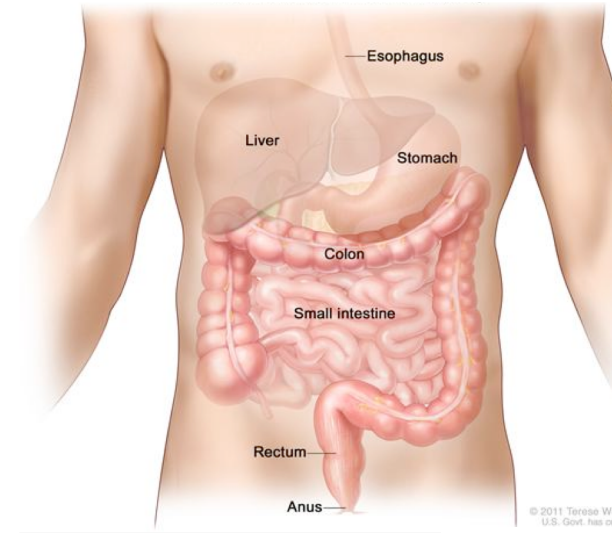
Inflammatory bowel diseases

- Known to be efficacious in clinical trials
- Pathway is found in a variety of *E. coli* (99% identical)
- We have identified pathway products with probiotic activities
- These products represent commercially-relevant deliverables

Genes in colibactin pathway are required for probiotic efficacy
E. coli probiotics contribute to deleterious Enterobacteriaceae load

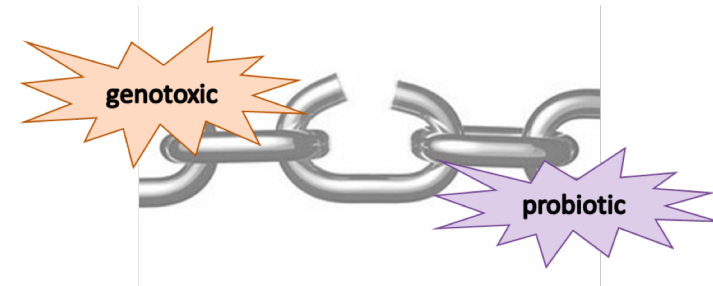


“Pathogen”



cancer.gov

Cancer



Mature colibactin causes colorectal cancer

Establish commercial viability of novel products for UC

“Mutualist”

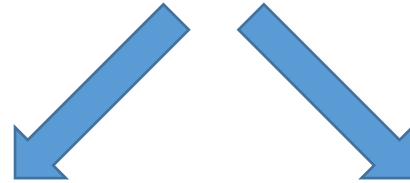


mutaflo.ru

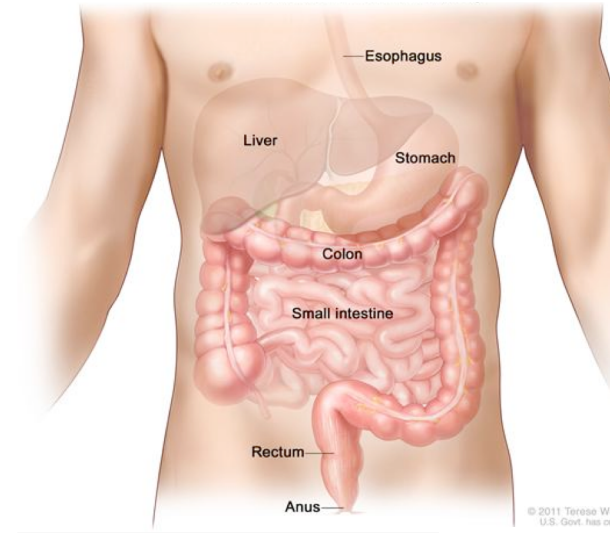
Inflammatory bowel diseases

- Known to be efficacious in clinical trials
- Pathway is found in a variety of *E. coli* (99% identical)
- We have identified pathway products with probiotic activities
- These products represent commercially-relevant deliverables

Genes in colibactin pathway are required for probiotic efficacy
~~*E. coli* probiotics contribute to deleterious Enterobacteriaceae load~~

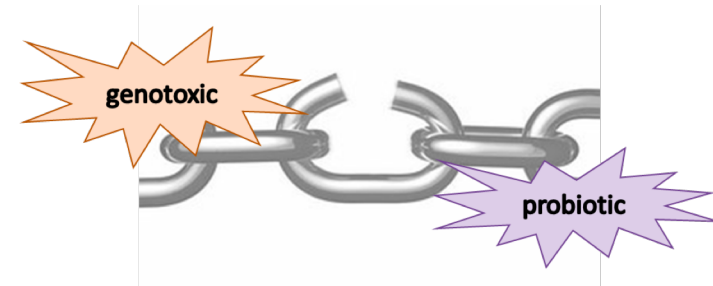


“Pathogen”



cancer.gov

Cancer

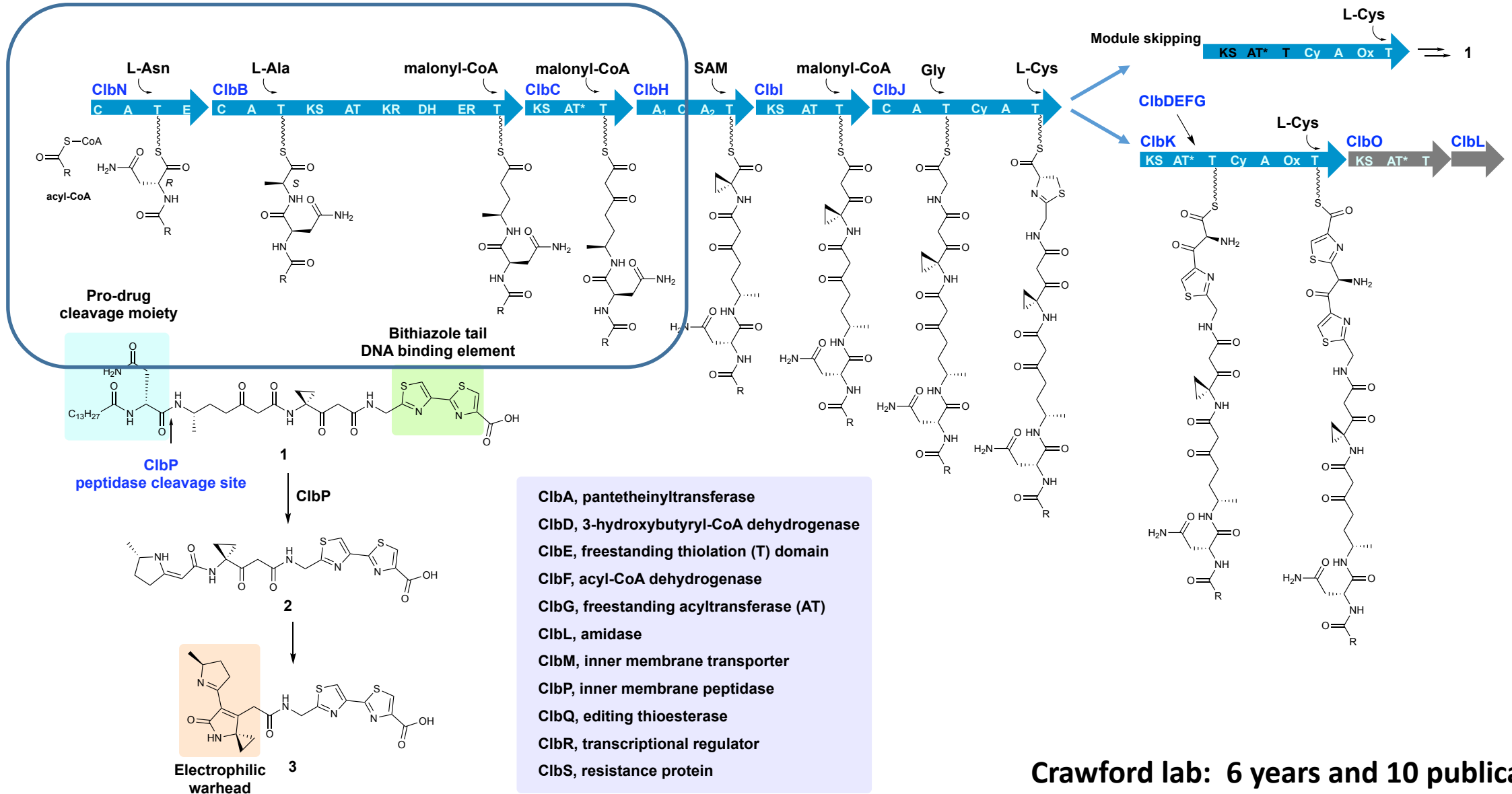


Mature colibactin causes colorectal cancer

Colibactin polypharmacology regulates probiotic activity

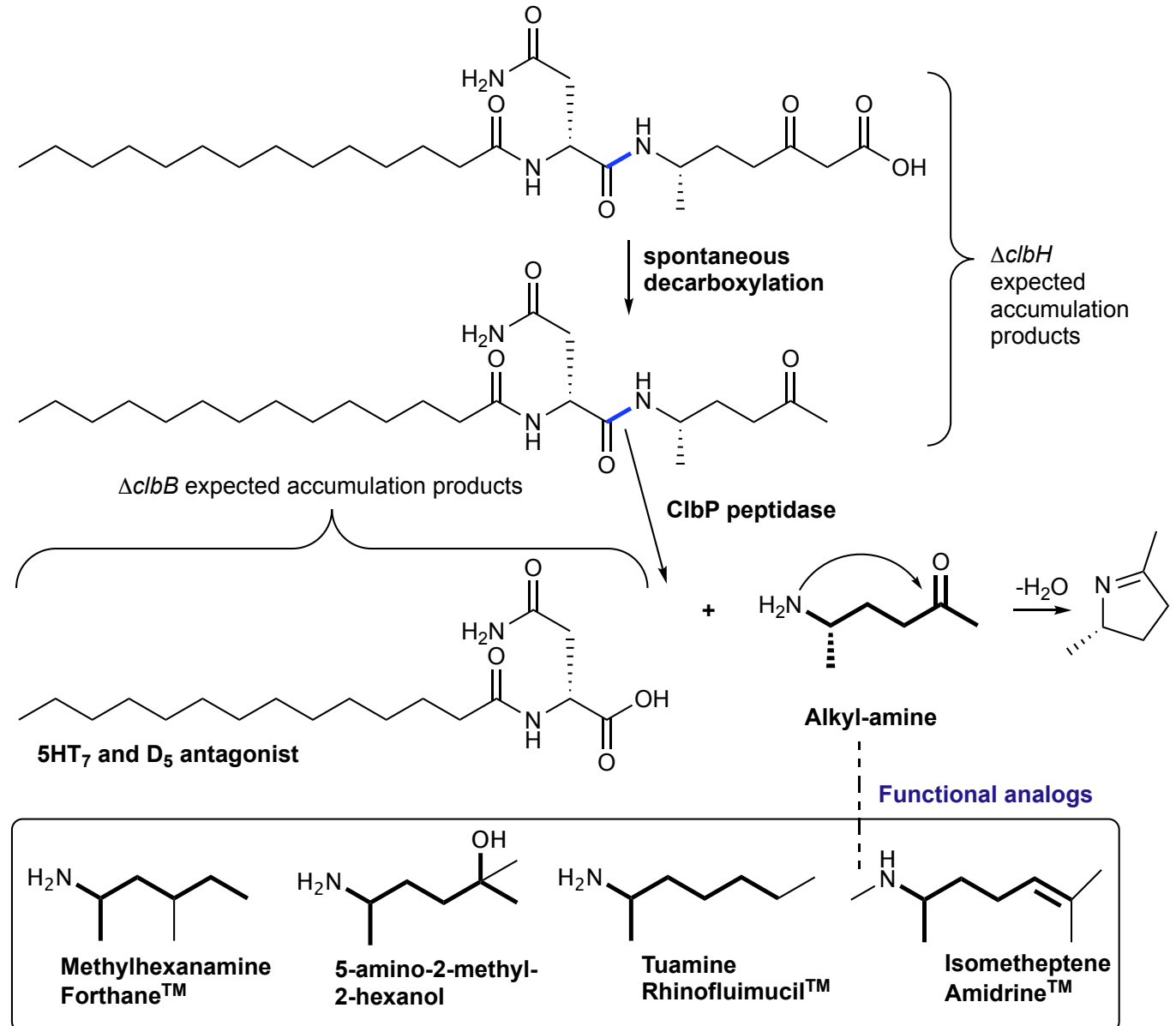
Probiotic

Carcinogenic



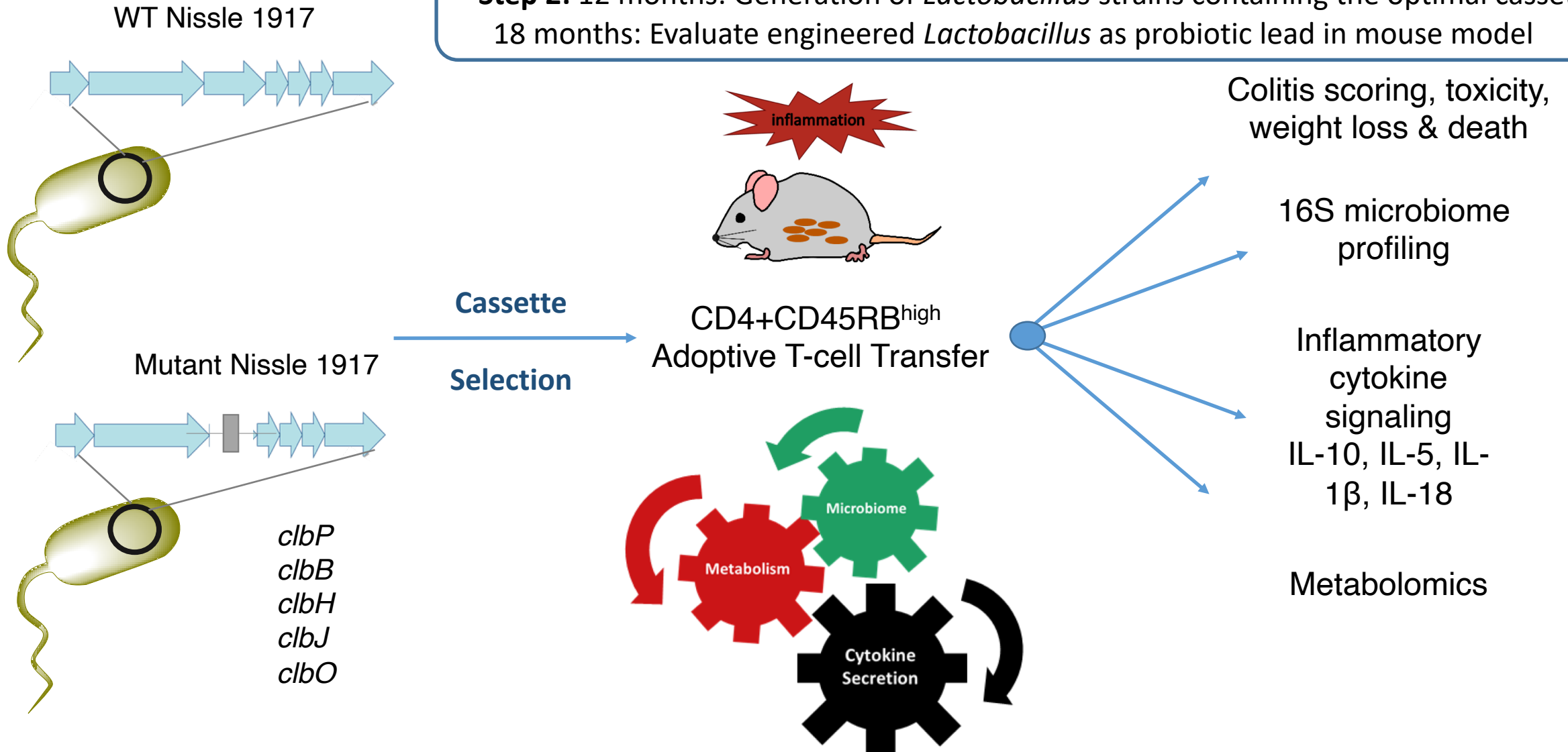
Cassette products 1 & 2 regulate catecholamine pathways

- Cassette 1 produces a 5-HT₇ GPCR antagonist, a phenotype that ameliorates colitis in mice
- Cassette 2 produces a 5-HT₇ GPCR antagonist and functional alkyl amine analogs
- Cassettes lack genotoxicity
- Probiotics have been engineered in our lab



Programmed probiotics

Step 1: 6 months: Engineered Nissle evaluation and optimal cassette selection
Step 2: 12 months: Generation of *Lactobacillus* strains containing the optimal cassette
18 months: Evaluate engineered *Lactobacillus* as probiotic lead in mouse model



Blavatnik Funds

Step 1: 6 months: Engineered Nissle evaluation and optimal cassette selection

Step 2: 12 months: Generation of *Lactobacillus* strains containing the optimal cassette

18 months: Evaluate engineered *Lactobacillus* as probiotic lead in mouse model

○ **Step 1: Evaluate efficacy of engineered probiotics in hand versus Mutaflor**

Genesis Biotech Group: \$235,000 0-6 month period; **Go, No Go**

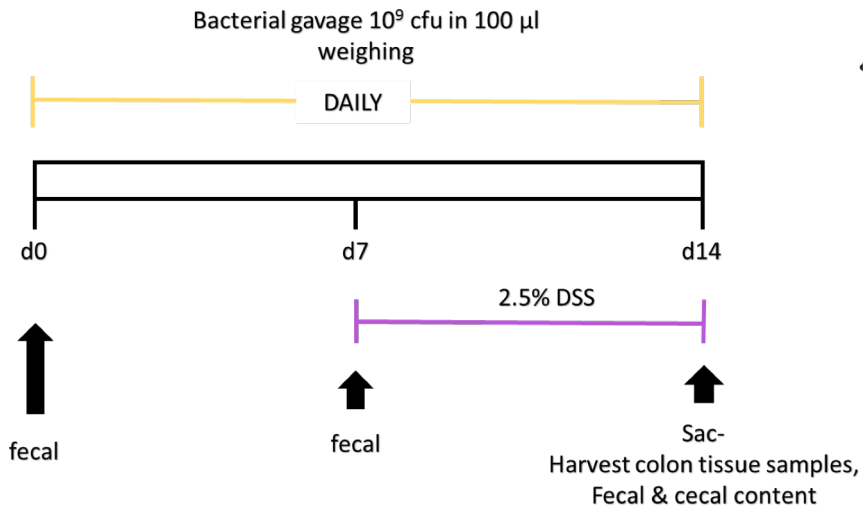
○ **Step 2: Transfer optimal cassette into *Lactobacillus acidophilus***




Compare *L. acidophilus* deliverable to Mutaflor, mesalamine, and Humira

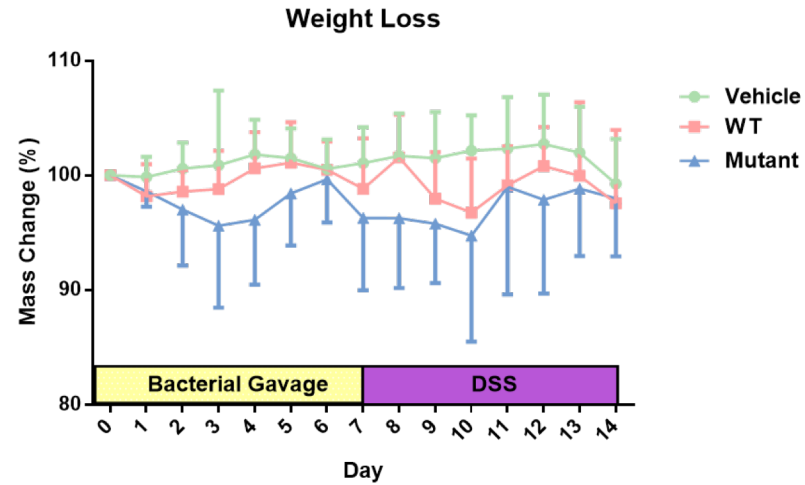
Genesis Biotech Group: \$157,100 6-15 month period; **Go, No Go**

○ **Aim for human studies within 2 years**

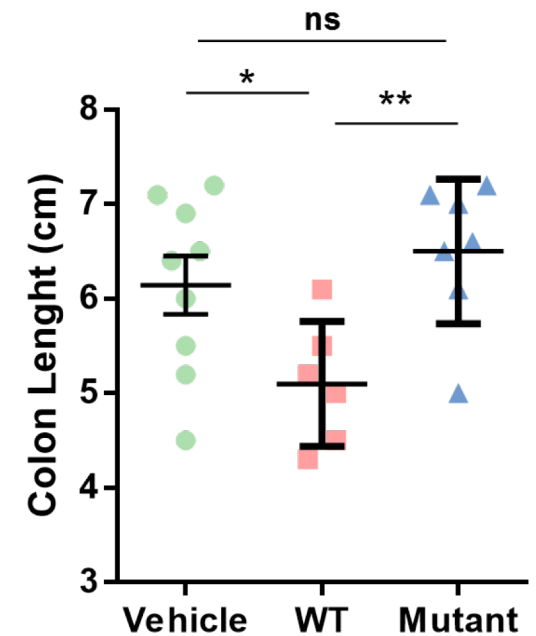
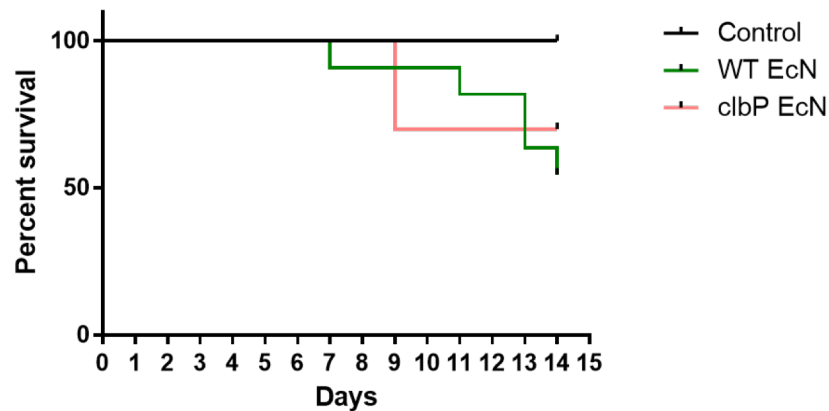
Wildtype colibactin pathway in Mutaflor is toxic to mice



-  N = 10
Vehicle control
-  N = 10
WT EcN
-  N = 10
EcN *clbP*



Survival proportions: Survival of Three groups



Genesis Notes: Quote will be in 3 parts

1. "Protocol Transfer"
2. Step 1
3. Step 2