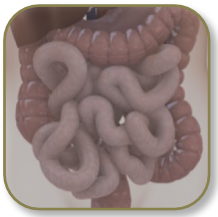
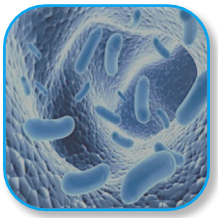
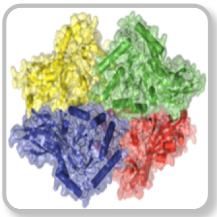
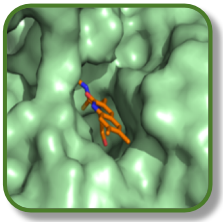
SYMBERIX

THERAPEUTIC TARGETING OF THE GUT MICROBIOME WITH SYMBIOTIC DRUGS

Ward Peterson Ph.D.

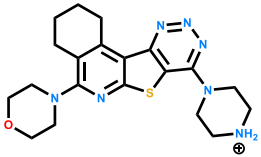





Global Engage

6TH MICROBIOME R&D & BUSINESS COLLABORATION FORUM

VISION

Pharmaceutical Control of the Microbiome



Health & Symbiosis

Pharmaceutics

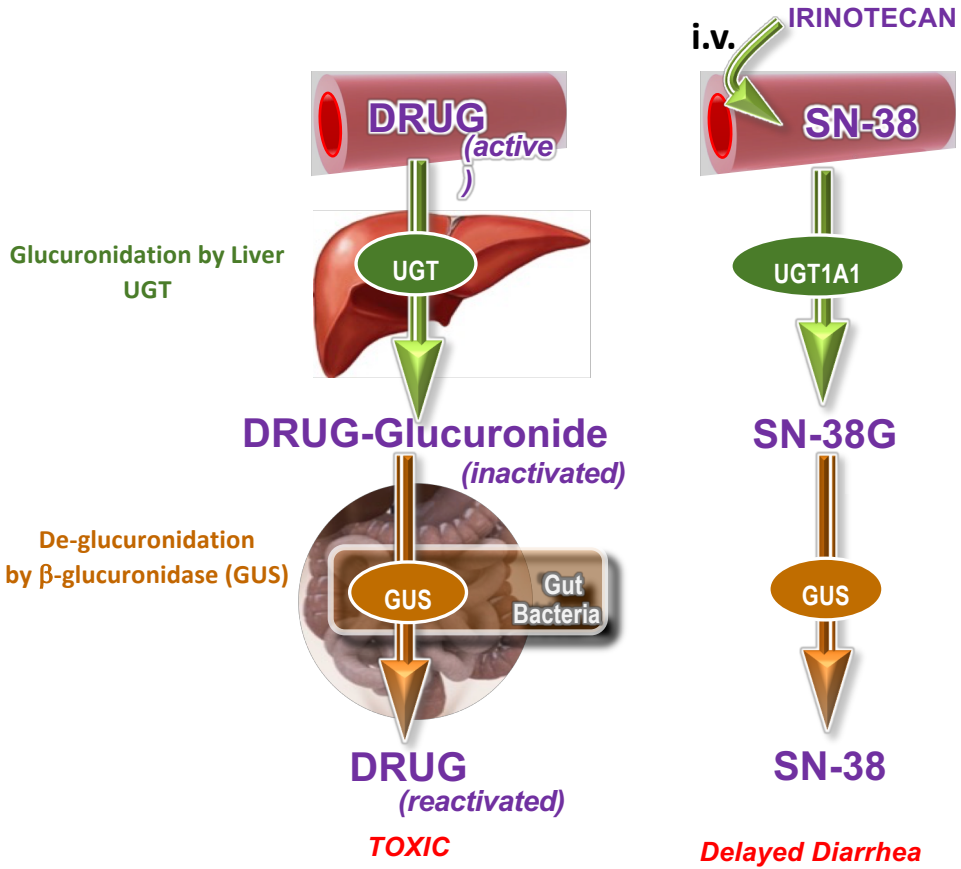
Illness & Dysbiosis

"Symbiotic Drugs"

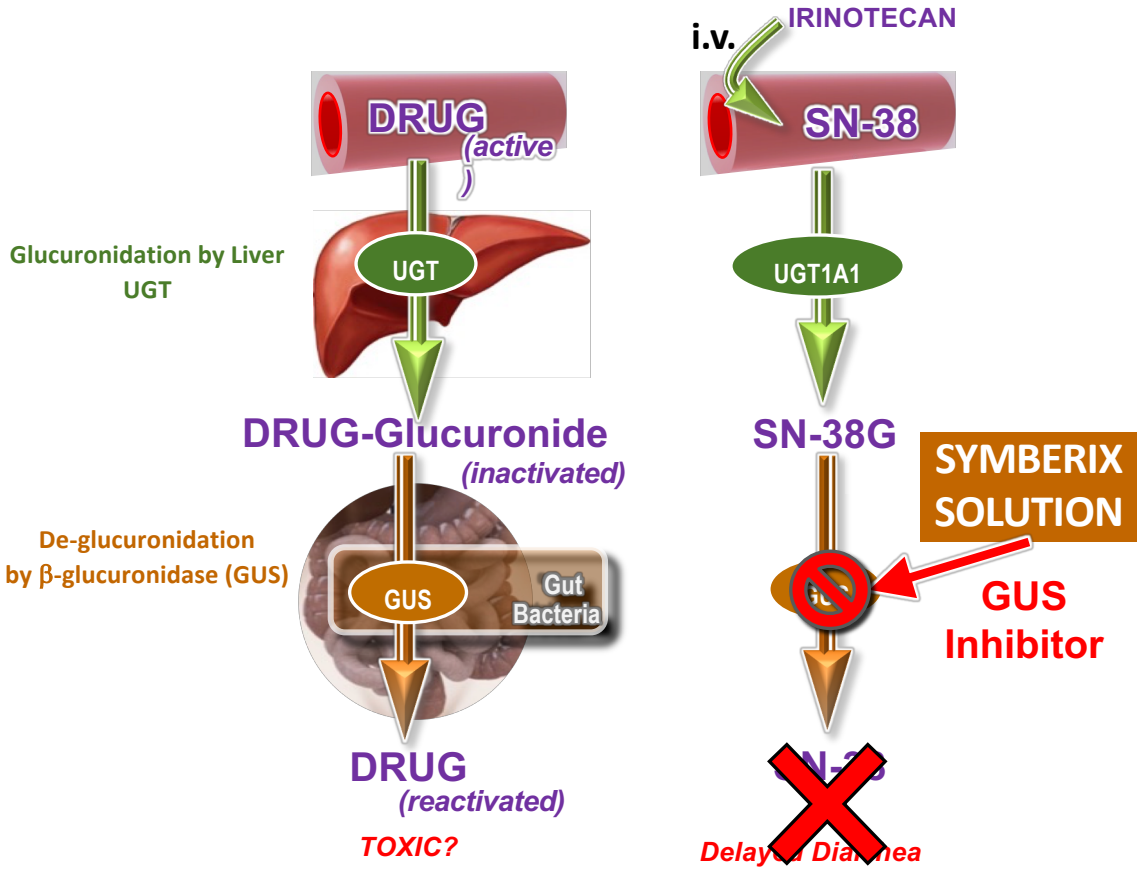
MISSION

Discover and Develop *Symbiotic Drugs* to Improve Human Health Through the Microbiome

How the Gut Microbiome Contributes to Drug-Induced Intestinal Toxicities



Symberix's Solution



Chemotherapy-Induced Diarrhea (CID): An Unmet Medical Need

88% of glucuronidated anti-cancer drugs are associated with diarrhea as a common side effect

Drug-Class	GI Toxicity
Tyrosine Kinase Inhibitors (TKI)	~30-95%
Histone Deacetylase Inhibitors (HDAC)	~11-69%
Camptothecin	~90%
Taxanes	~37-40%

All CID

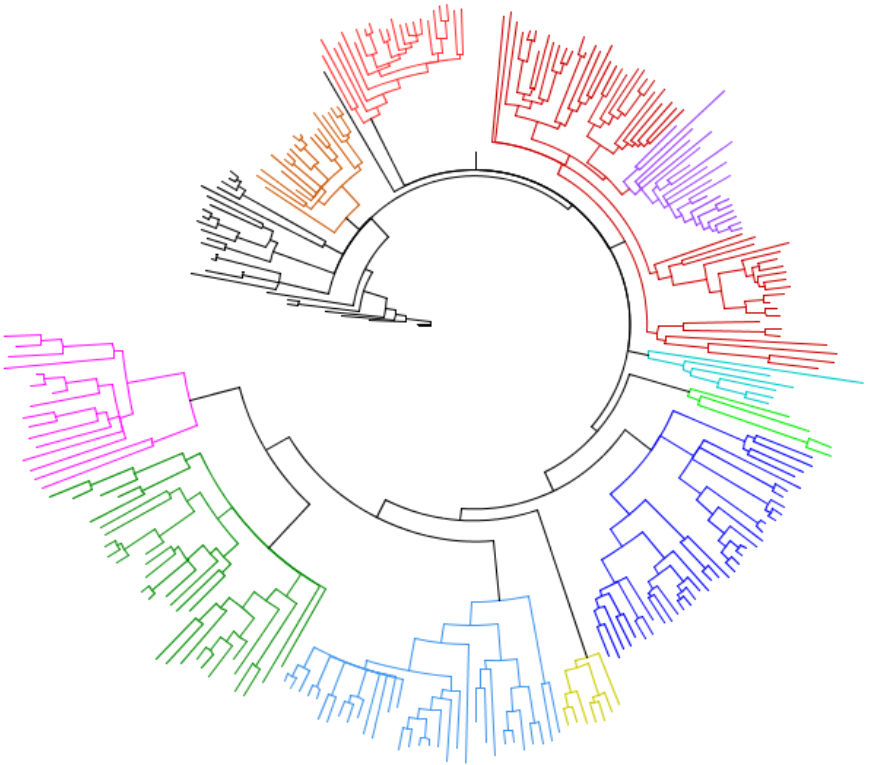
- **>300,000 patients/year in US (all CID)**
- **Hospitalization alone: $1B/year**
- **No FDA-approved products**

Consequences of CID	Frequency
Delay chemotherapy	70%
Decrease dose strength	45%
IV fluid and electrolytes	35%
Hospitalization	10%
Death	3%

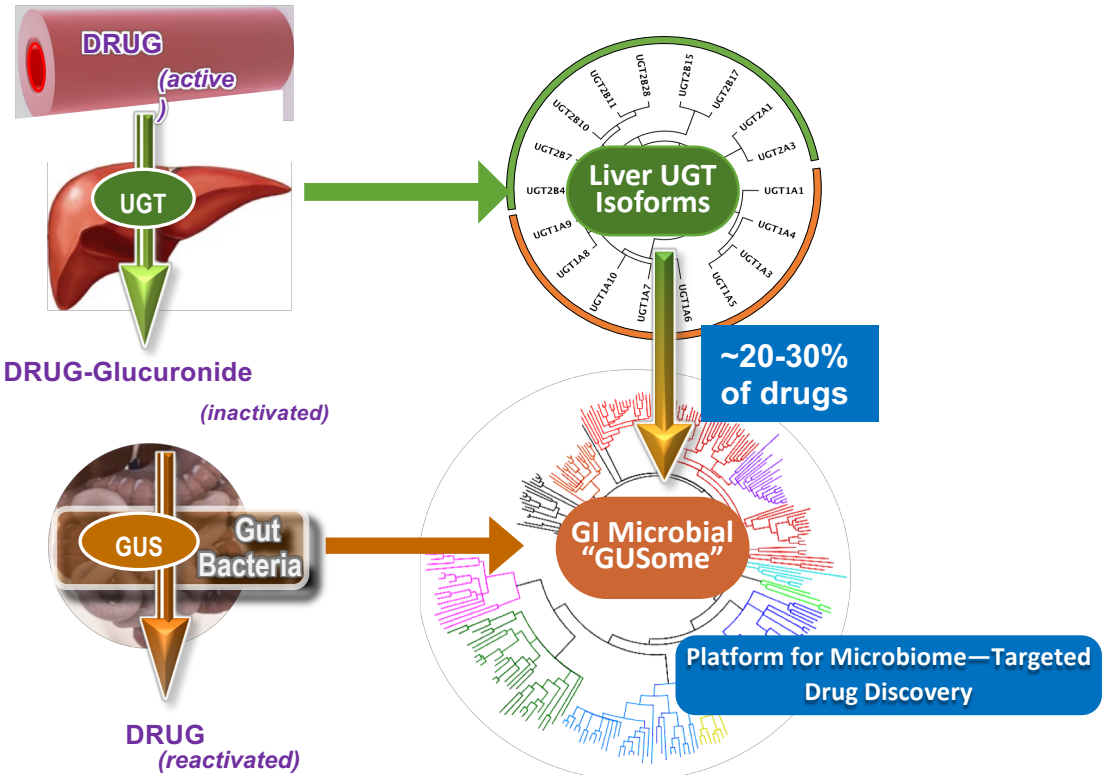
ALL CID:
US Market ~$2B
Global Market ~$5B

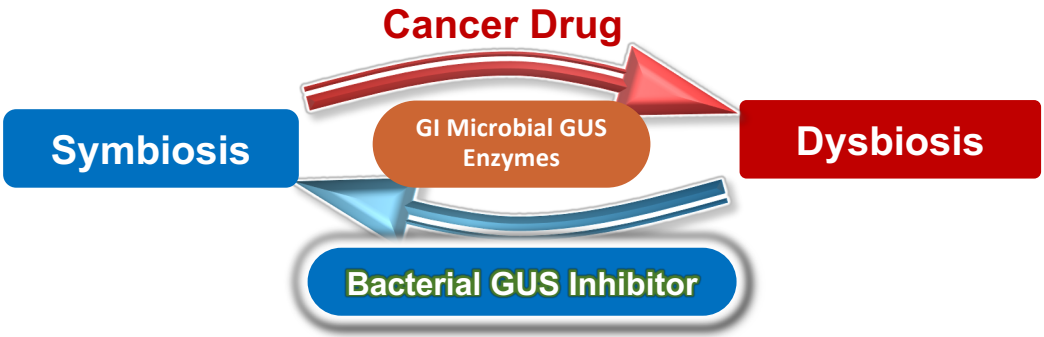
GUSome Diversity

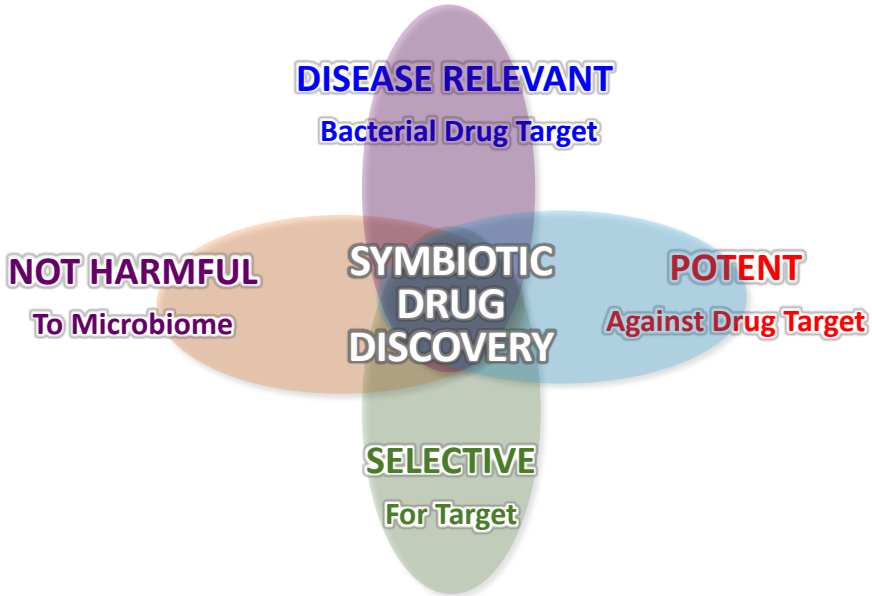
GUSome = 279 unique microbial GUS orthologs + 1 human GUS ortholog



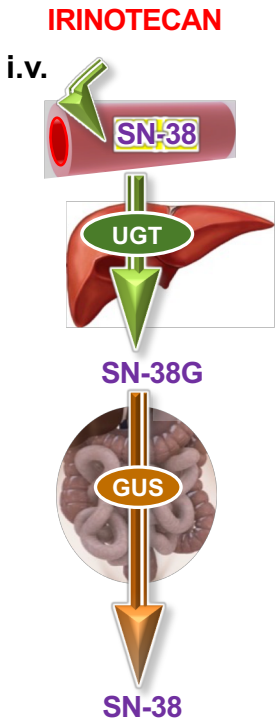
UGT-GUS Axis of Metabolism

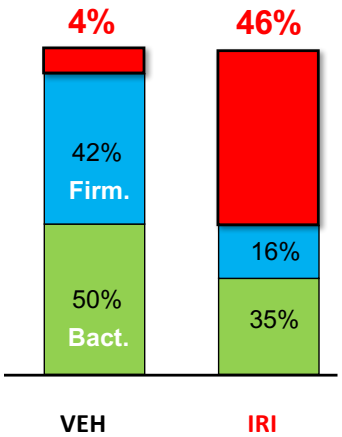



Cancer Drug
Symbiosis
GI Microbial GUS Enzymes
Dysbiosis
Bacterial GUS Inhibitor


DISEASE RELEVANT
Bacterial Drug Target
NOT HARMFUL
To Microbiome
SYMBIOTIC DRUG DISCOVERY
POTENT
Against Drug Target
SELECTIVE
For Target

Irinotecan Induces Gut Dysbiosis

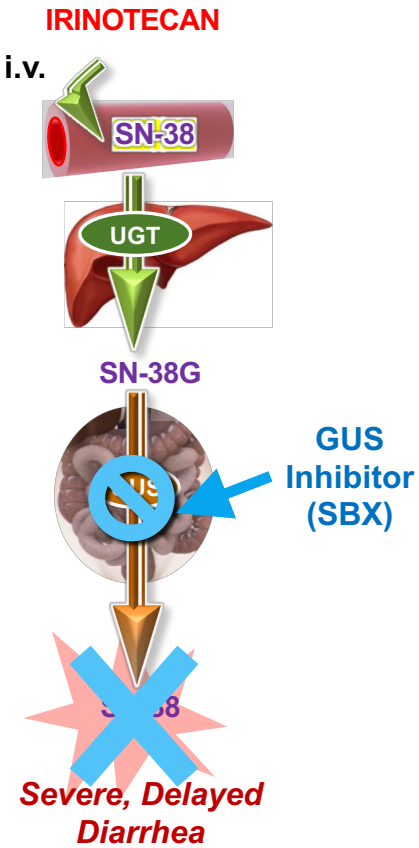


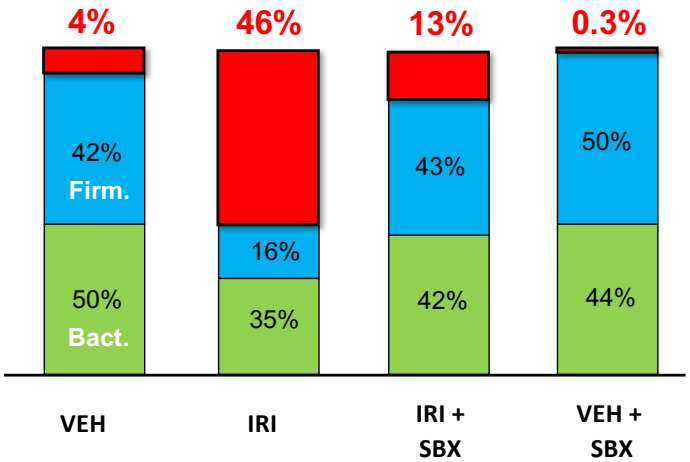


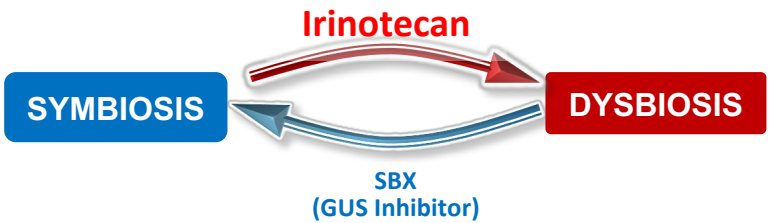
Irinotecan

SYMBIOSIS → DYSBIOSIS

Restoring Symbiosis with Symbiotic Drugs



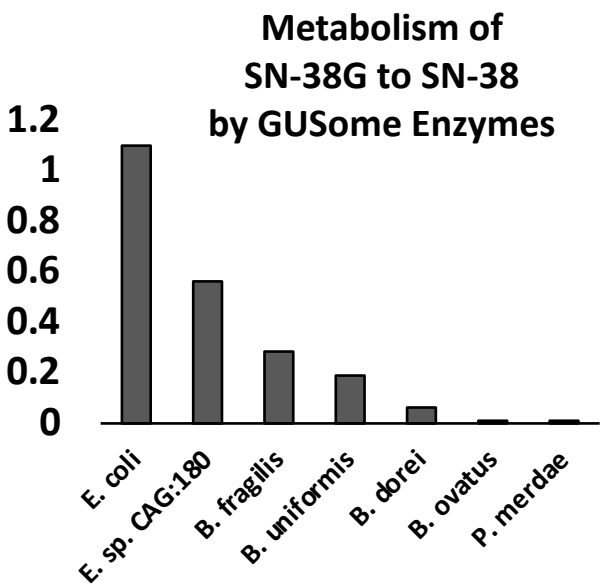




Disease Relevant Bacterial Drug Target

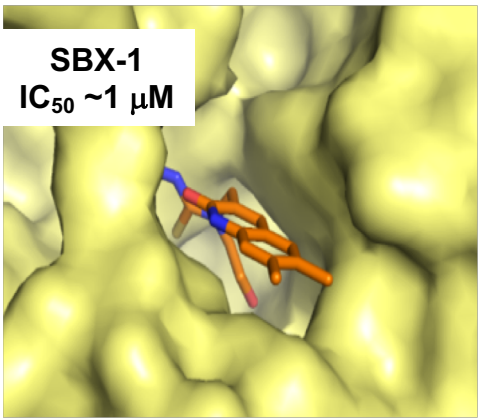
Proteobacteria phylum, *Enterobacteriaceae* family, and/or *Escherichia* genus		
	Colorectal Cancer	IRI Treatment
Swidsinski, 1998	↑	-
Stringer, 2008	-	↑
Shen, 2010	↑	-
Arthur, 2012	↑	-
Lin, 2012	-	↑
Wang, 2012	↑	-
Wu., 2013	↑	-
Lin, 2014	-	↑
Redinbo (unpublished)	-	↑

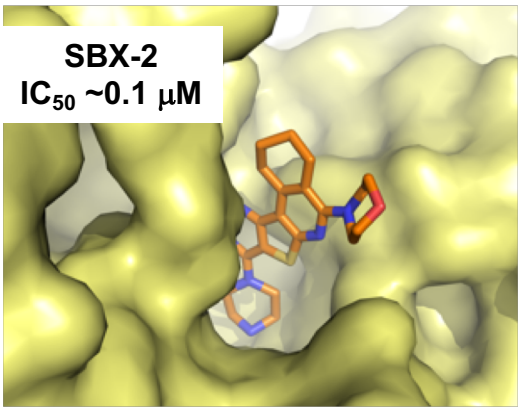
↑ = Species bloom



E. coli GUS is a relevant target

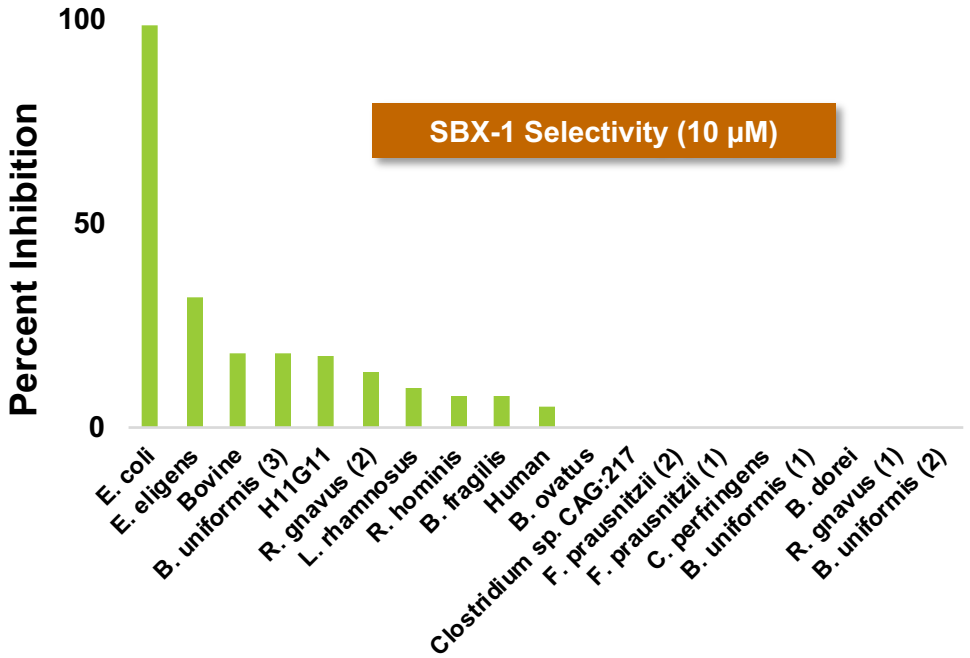
SBX-1 (Scaffold-1) and SBX-2 (Scaffold-2) Analogs



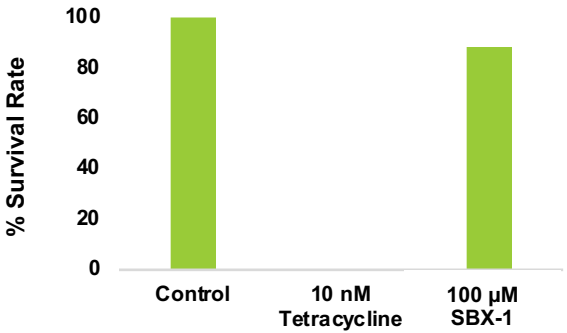


Crystal structure, SBX-1 and SBX-2 bound to *E. coli* GUS

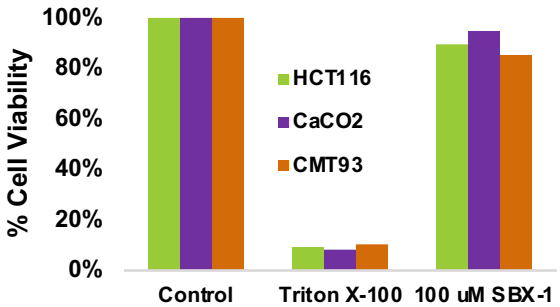
Drugging the Relevant *E. coli* GUS Target



Non-Antibiotic Activity

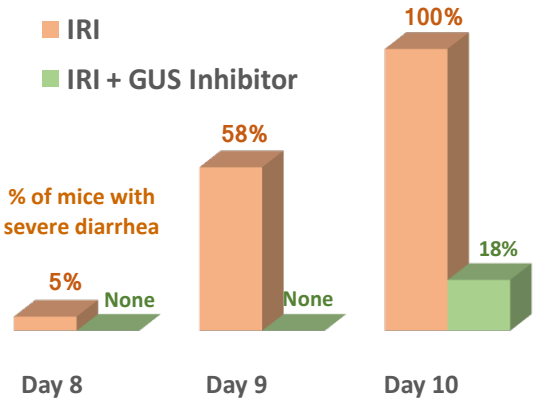


Non-Cytotoxic Activity

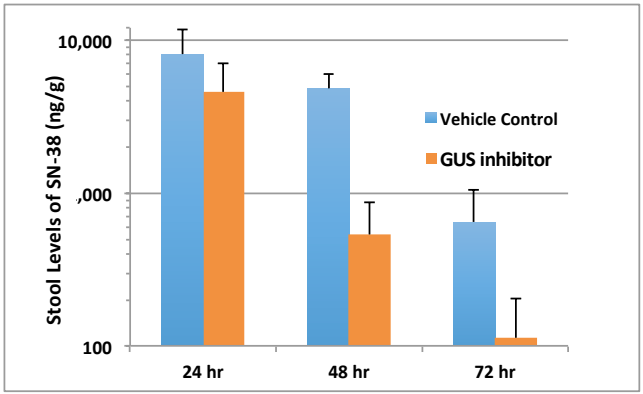


Efficacy of GUS Inhibitor

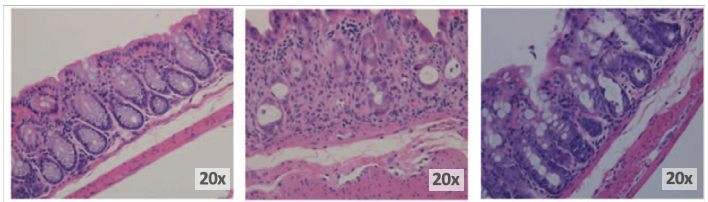
Protection from IRI-induced diarrhea



GUS inhibitor reduced SN-38 levels in stool



Histologic preservation of intestinal cells



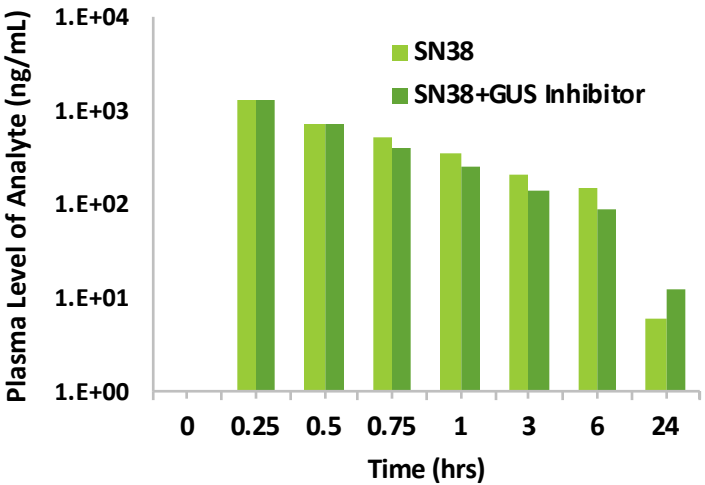
THERAPEUTIC GOAL

Prevent IRI-induced diarrhea without compromising survival outcomes

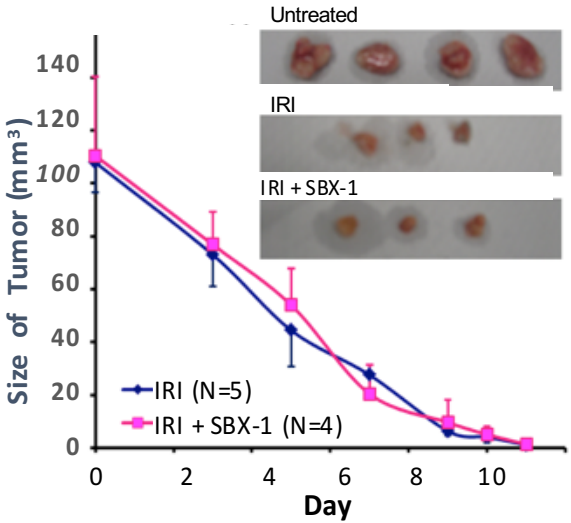
Wallace BD, et al., Science **330**:831-835 (2010)

SBX Treatment: Does Not Compromise IRI Anti-Tumor Efficacy

GUS inhibitor does not alter SN38 levels in plasma



GUS inhibitor does not reduce IRI anti-tumor efficacy



SBX Treatment: More Frequent IRI Dosing & Improved IRI Efficacy

C3-Tag Triple Negative Breast Cancer GEMM Mice

IRI Dosing Scheme

Week 1: Two treatments/week

Week 2 & 3: Three treatments/week

Week 4+: Five treatments/week

Doses (Weekdays Only)

GUS Inhibitor: 0.5 mg/kg, oral, twice-daily

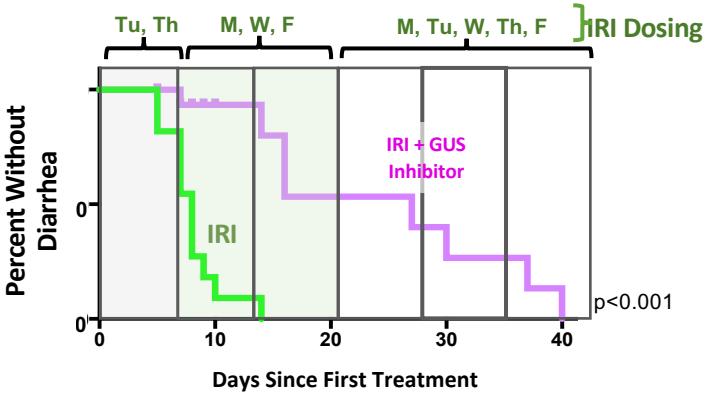
IRI: 50 mg/kg, intraperitoneal injection, once-daily

Vehicle: Saline (no GUS inhibitor)

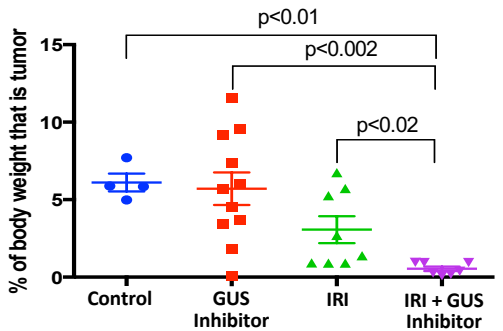
POTENTIAL UPSIDE

Improve chemotherapy survival outcomes

Protection from diarrhea

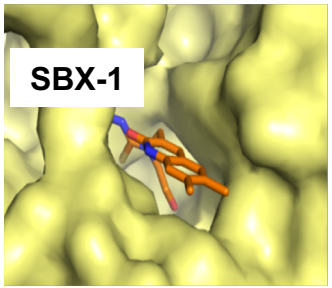


Improved IRI efficacy

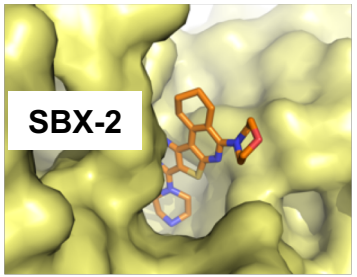


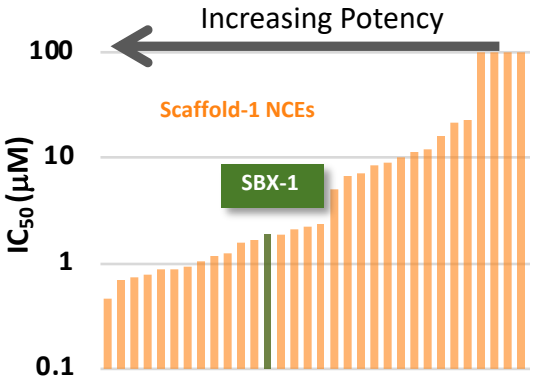
Unpublished Data

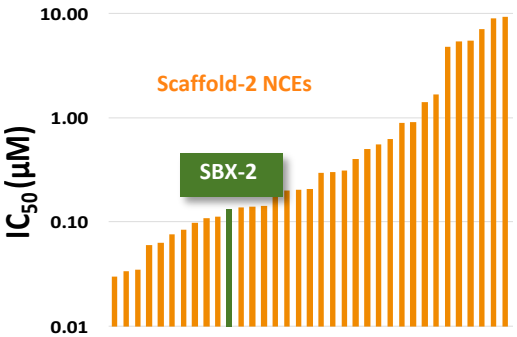
GUS Inhibitors: SBX-1 (Scaffold-1) and SBX-2 (Scaffold-2) Analogs



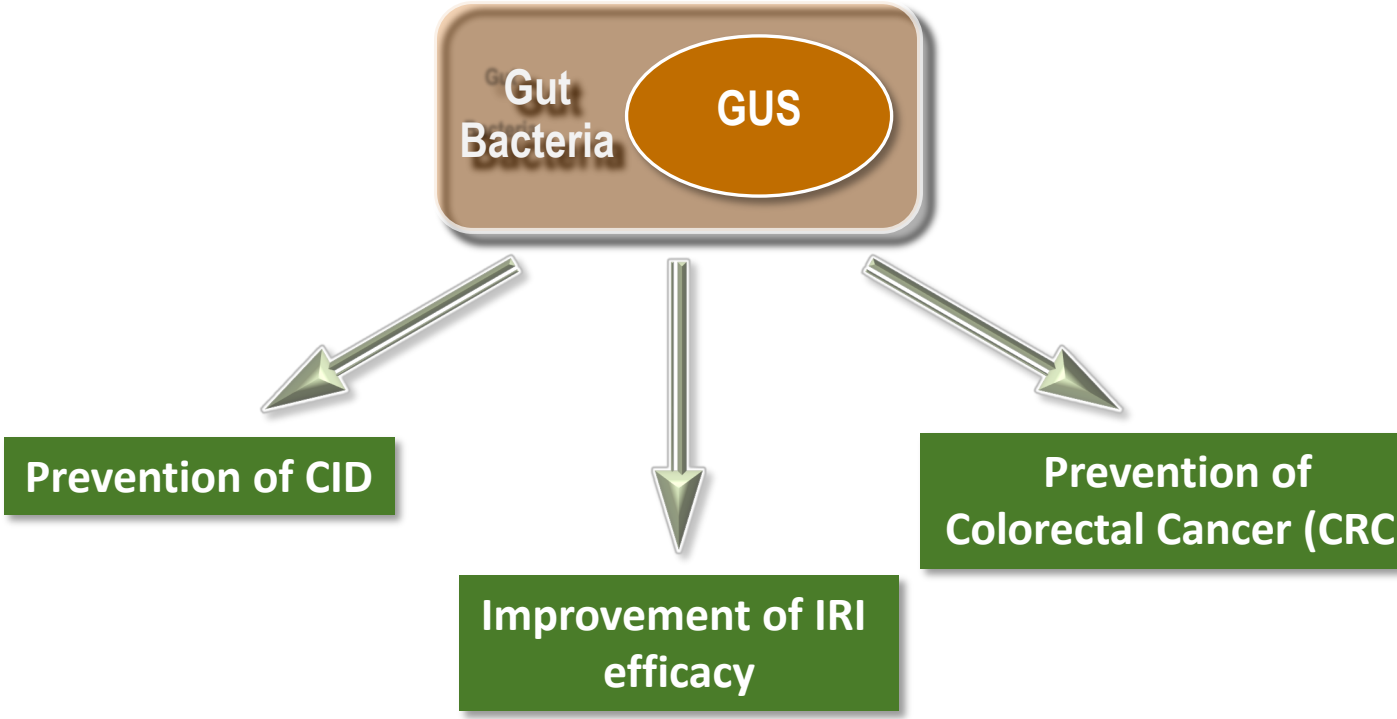
Crystal structure, SBX-1 and SBX-2 bound to *E. coli* GUS







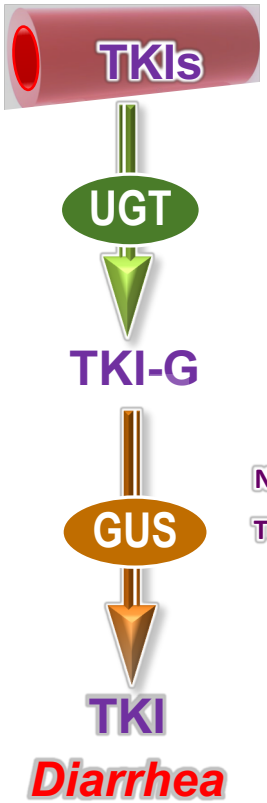
One Target – Multiple Therapeutic Applications



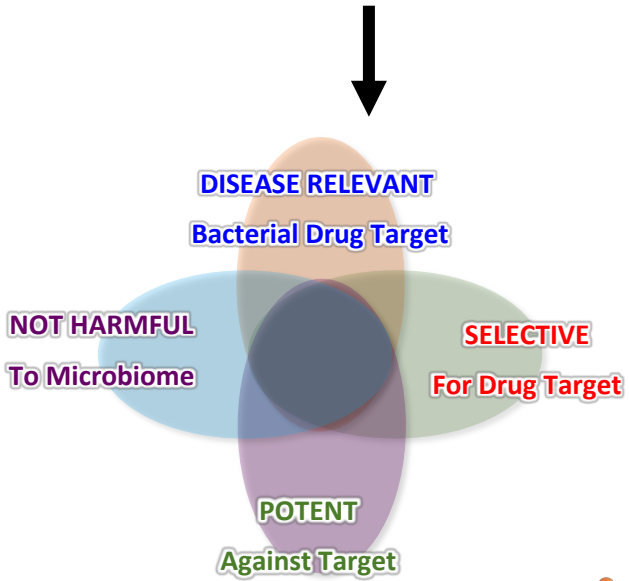
Can this be applied to other Chemotherapeutic drug classes?

Tyrosine Kinase Inhibitors - GI toxicity

Targeted Cancer Therapy	% of Patients with Diarrhea
Sorafenib	55%
Regorafenib	40%
Erlotinib	54%
Gefitinib	54%
Bortezomib	51%
Imatinib	49%
Sunitinib	66%
Afatinib	95%
Vandetanib	79%
Dasatinib	31%
Bosutinib	84%

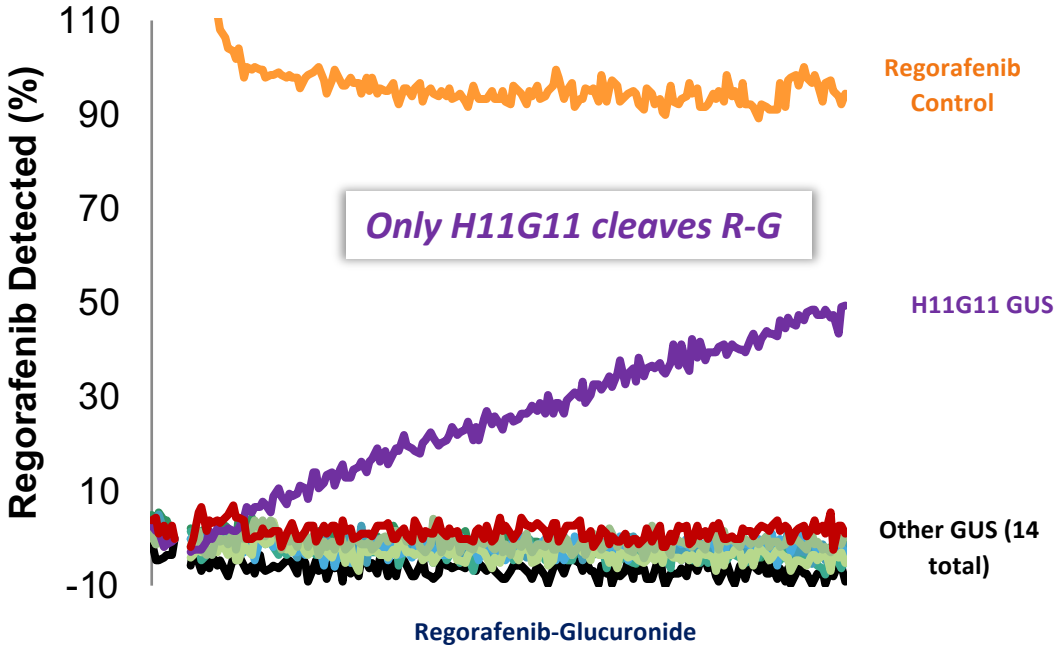


Two TKIs:
Sorafenib and Regorafenib

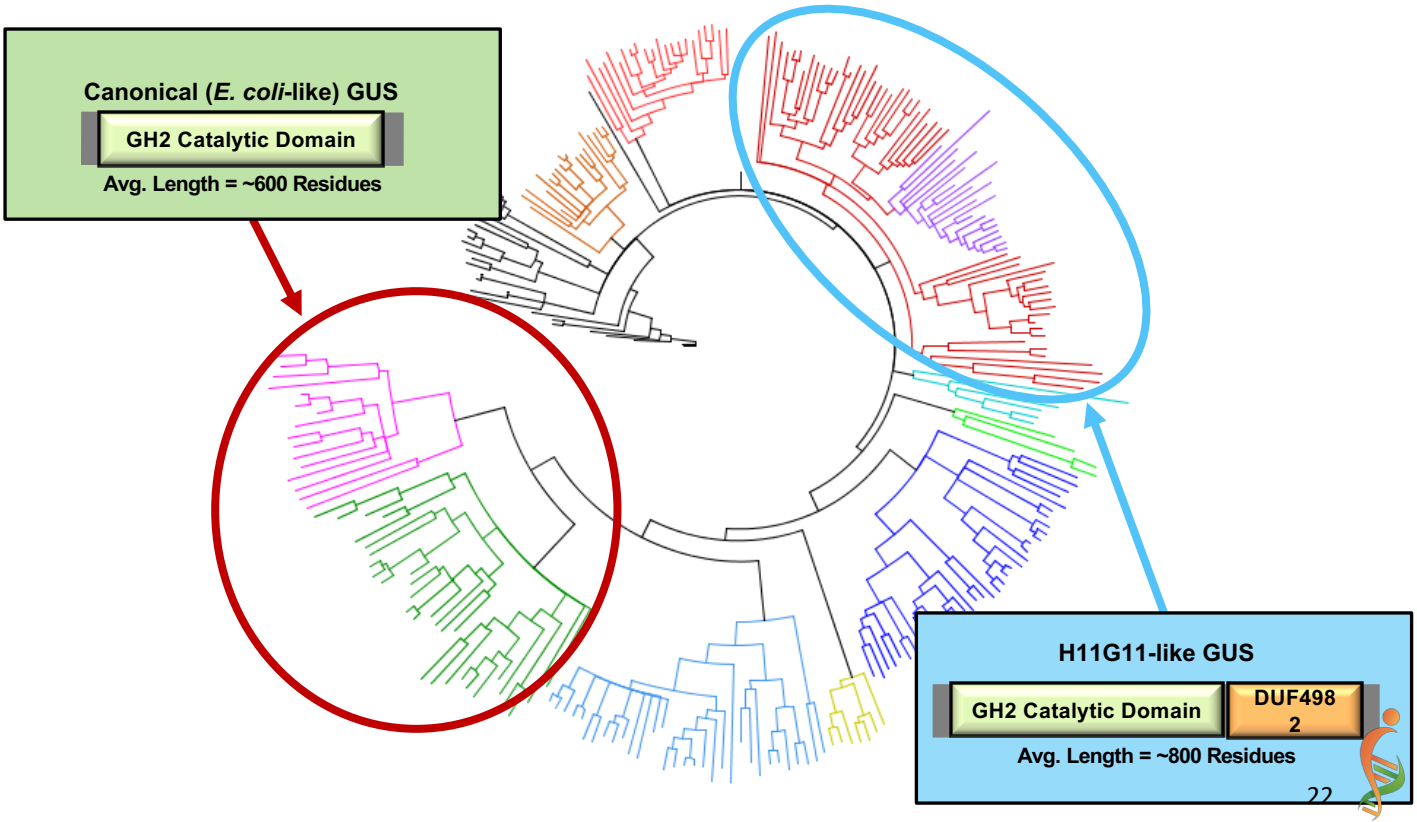


Mining the GUSome for TKI-G Cleavage

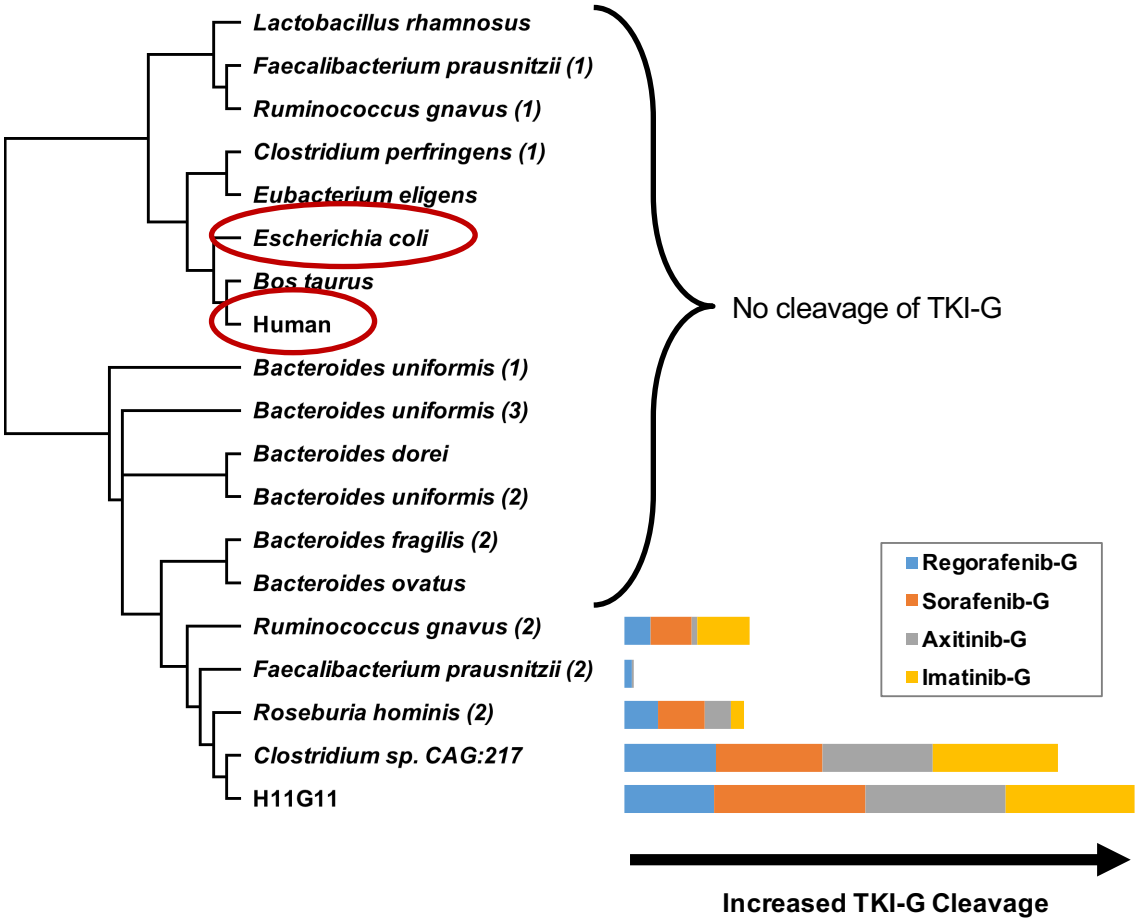
GOAL: Identify GUS orthologs that cleave regorafenib-glucuronide (R-G)



GUSome Diversity

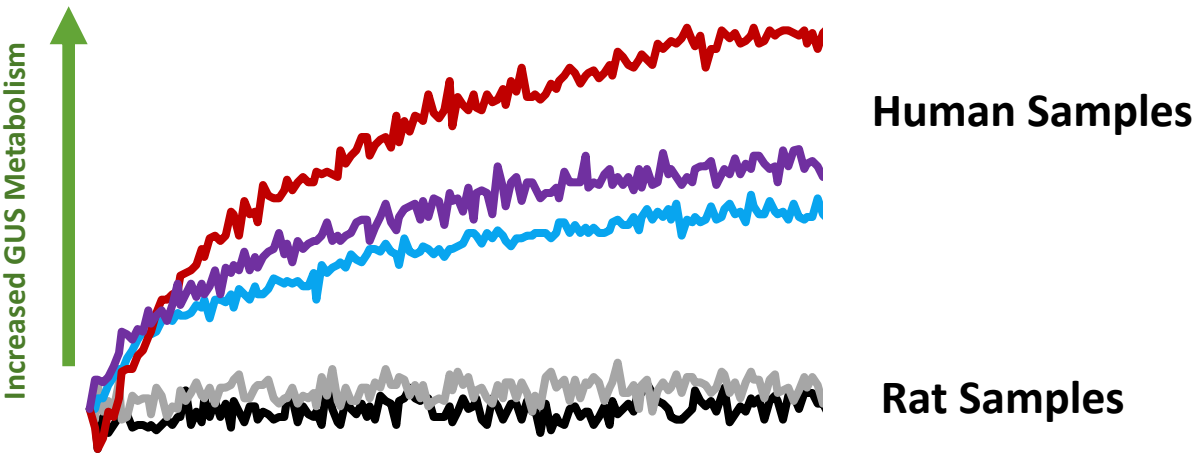


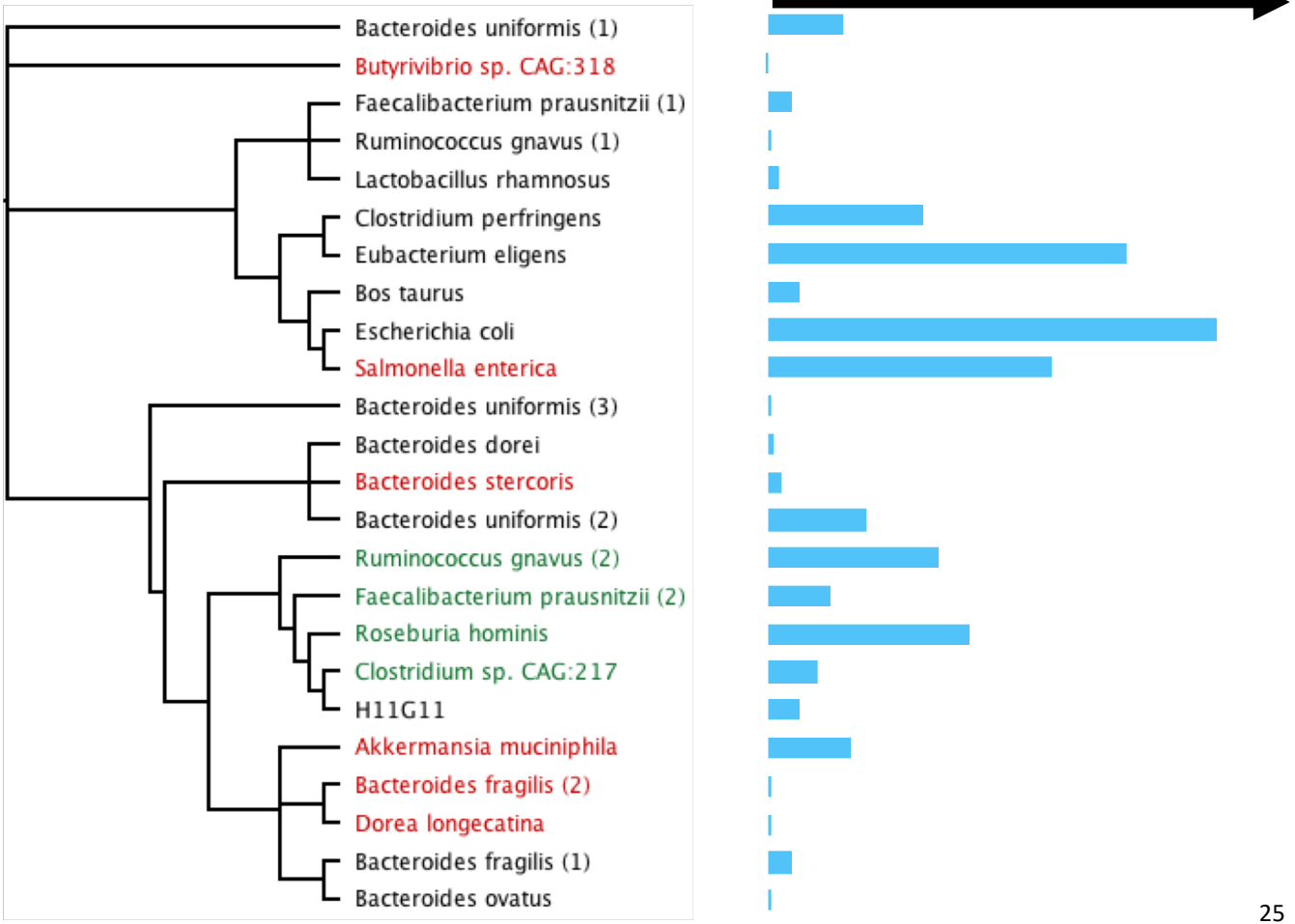
H11G11-like Enzymes Cleave Multiple TKI-Gs



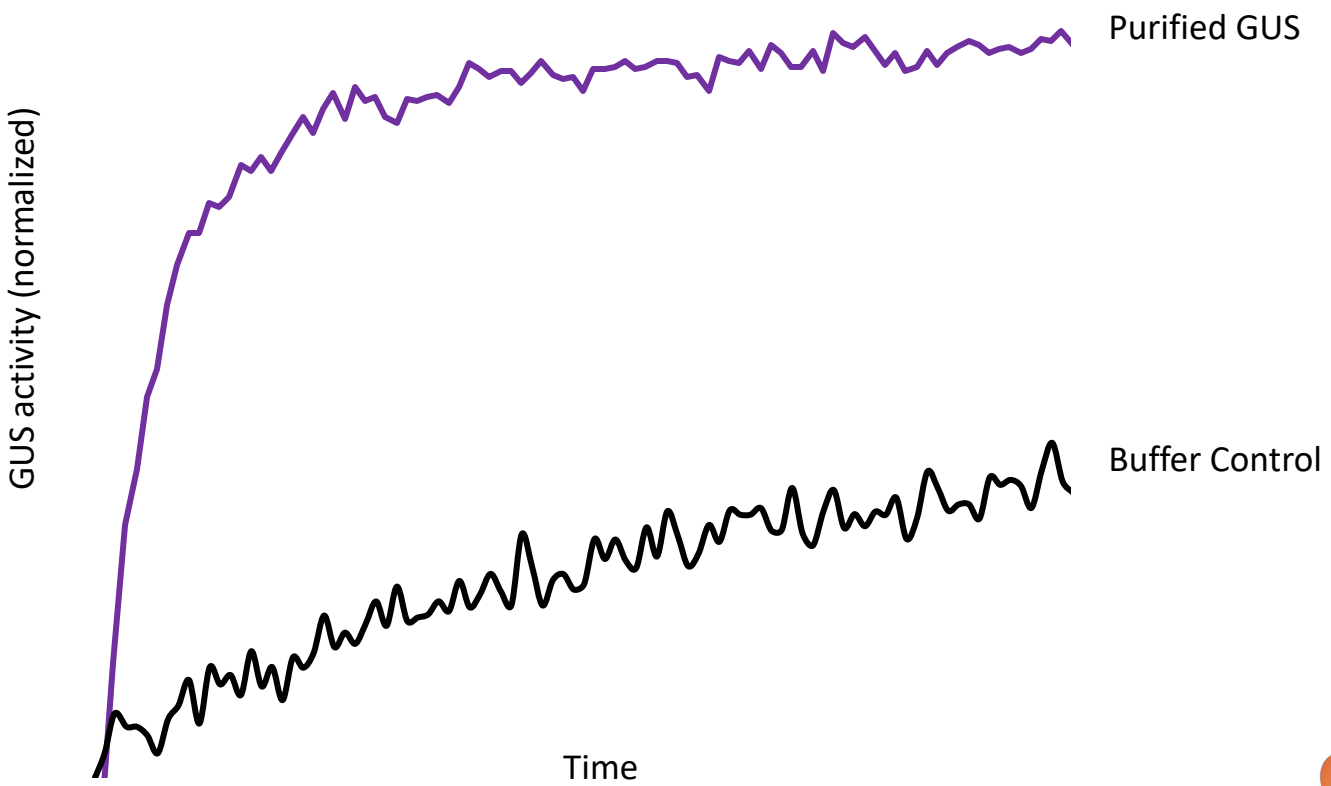
Is the Identified GUS Target Relevant to Human Health?

Ex vivo fecal protein extracts tested for activity against regorafenib-G

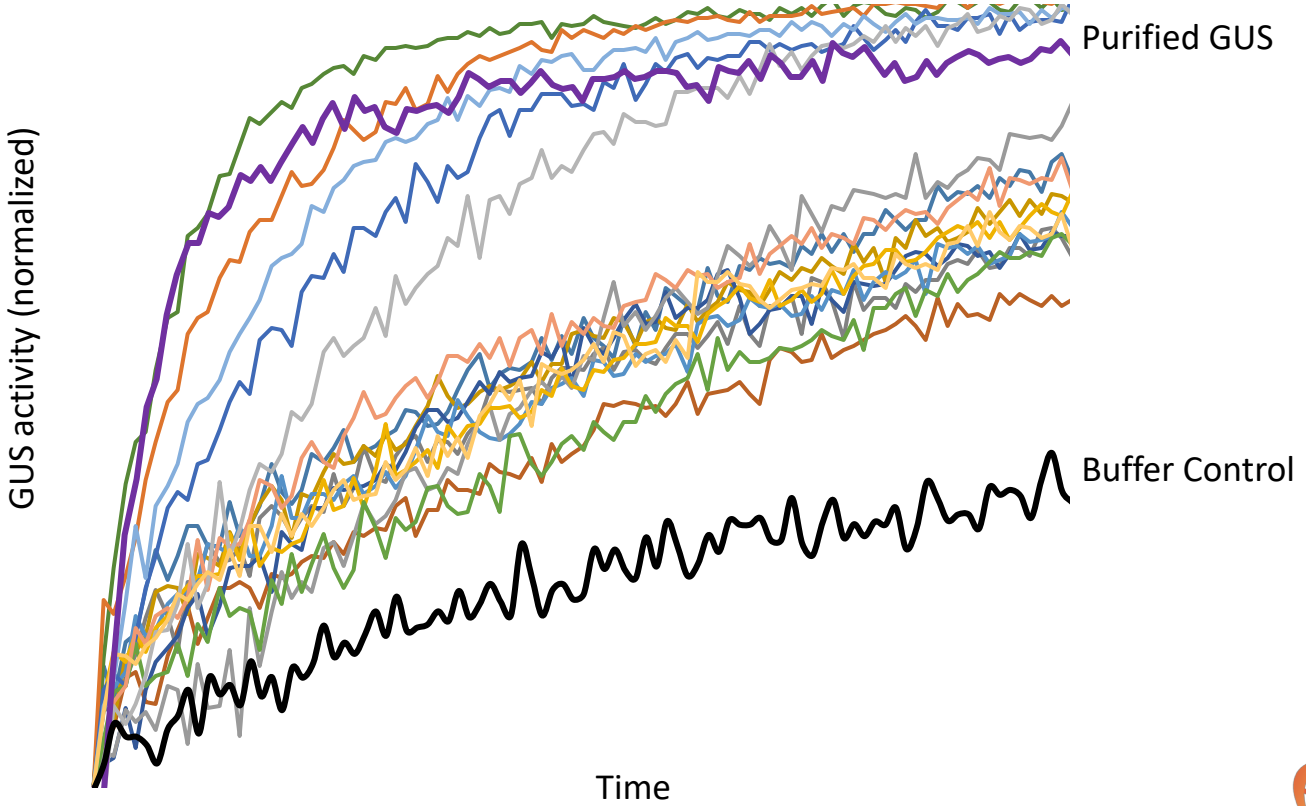



Increasing GUS Activity of Drug - Glucuronide
Bacteroides uniformis (1)
Butyrivibrio sp. CAG:318
Faecalibacterium prausnitzii (1)
Ruminococcus gnavus (1)
Lactobacillus rhamnosus
Clostridium perfringens
Eubacterium eligens
Bos taurus
Escherichia coli
Salmonella enterica
Bacteroides uniformis (3)
Bacteroides dorei
Bacteroides stercoris
Bacteroides uniformis (2)
Ruminococcus gnavus (2)
Faecalibacterium prausnitzii (2)
Roseburia hominis
Clostridium sp. CAG:217
H11G11
Akkermansia muciniphila
Bacteroides fragilis (2)
Dorea longecatina
Bacteroides fragilis (1)
Bacteroides ovatus

Profiling GUS Activity from Human Stool

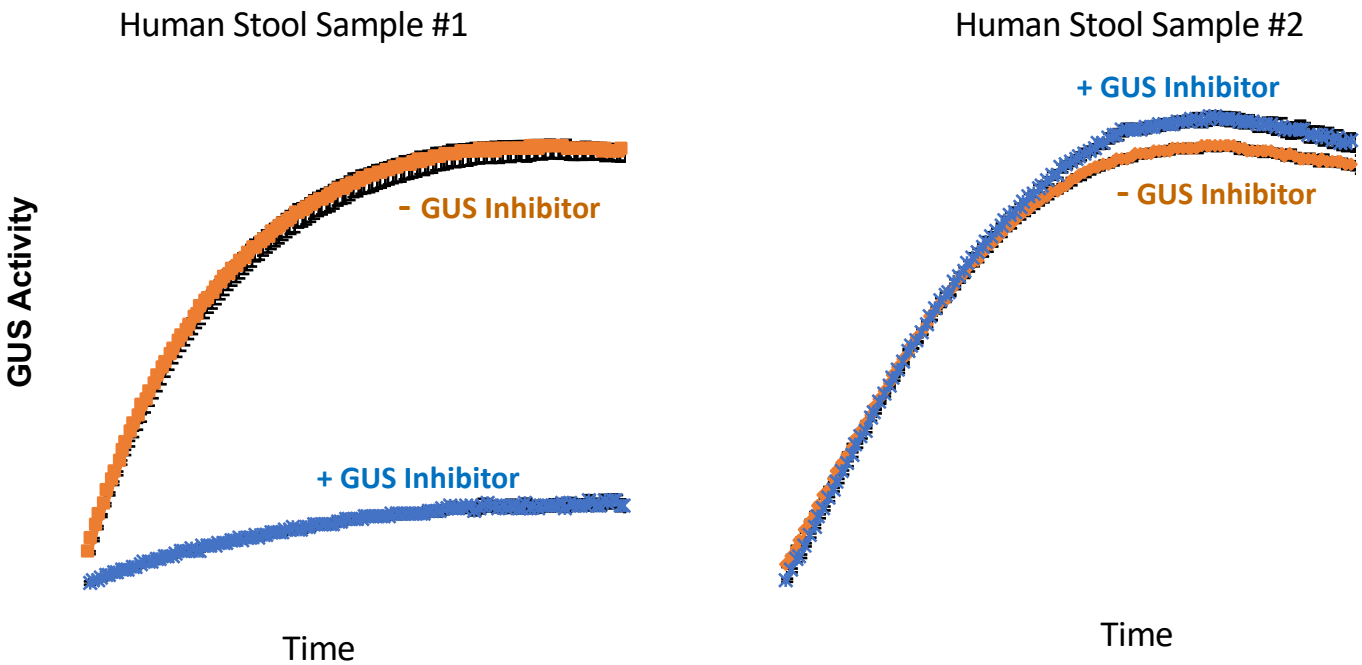


Profiling GUS Activity from Human Stool



Data from Human Stool-Derived Microbiota

Total GUS activity against an enterotoxic drug-glucuronide



Companion Diagnostic / Personalized Medicine

Clinical Relevance of GUSome

Current Focus

- Prevention of chemotherapy-induced diarrhea
  - Irinotecan/camptothecins
  - TKI's
  - Other target anti-cancer drugs
- Improve cancer drug efficacy
  - Irinotecan and beyond

Platform Expansion

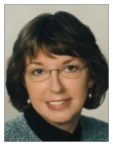
- Other drug-induced toxicities
  - NSAIDs
  - Immunosuppressant toxicity post-organ transplant
- IBD (Ulcerative colitis, Crohn's)
- Intestinal bacterial pathogenesis
  - Salmonella, Shigella, Klebsiella
- Chemoprevention of colorectal cancer

Acknowledgement

Management and BOD

Matthew Redinbo, Ph.D.
Co-Founder & BOD Member

Ward Peterson, Ph.D.
Co-Founder, President & BOD Member



P. Kay Wagoner, Ph.D.
BOD Member

Greg Mossinghoff, MBA
Chief Business Officer

NIH

National Cancer Institute

National Center for Advancing Translational Science

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of General Medicine Sciences

Scientific and Medical Advisors

Bert O'Neil, M.D. GI oncologist
20+ years, clinician and clinical researcher

Sridhar Mani, M.D. Oncologist & geneticist
20+ years oncology clinical and basic research

Urs Boelsterli, Ph.D. Basic & translational research
30+ years, mechanisms of NSAID toxicity

Martin Blaser, M.D. Internist & microbiologist
25+ years, microbial symbiosis & infectious disease