

Professor Rachel Gibson

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**THE GUT MICROBIOME**  
WHY DOES IT MATTER IN CHEMOTHERAPY-INDUCED GUT  
TOXICITY?

# Conflict of Interest Disclosure

Professor Rachel Gibson, PhD

- Consulting Fees received from Kaleido Biosciences



# History of the gut microbiome in chemotherapy-induced gut toxicity (CIGT)

- Changes in the gut microbiome were first reported in 1965
- Over recent years it has become increasingly recognized as a key player in the development of CIGT

## The Nature and Control of Infections in Patients with Acute Leukemia

EMIL FREI, III,<sup>1</sup> ROBERT H. LEVIN,<sup>2</sup> GERALD P. BODEY,<sup>3</sup> EDWARD E. MORSE,<sup>4</sup>  
AND EMIL J. FREIREICH

*National Cancer Institute, Bethesda, Maryland*

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## Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview

NMA Blijlevens, JP Donnelly and BE De Pauw

*Department of Hematology, University Medical Center St Radboud, Nijmegen, The Netherlands*

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Oral MBI is reported to affect 60% to 100% of transplant recipients<sup>1</sup> and is characterised by pain, oedema, erythema, lesions, pseudomembrane formation, excessive mucous production, reduced saliva and bleeding, all of which reduce the patient's ability to eat and drink. In contrast, there are no reliable data on the incidence of gut MBI although intestinal symptoms affect almost every transplant recipient to some extent and include nausea, vomiting, abdominal cramping and watery diarrhoea occasionally accompanied by macroscopic blood loss. The exact course and severity of bowel symptoms of MBI are also difficult to ascertain because many patients are in such pain due to oral MBI that they only gain relief from narcotic analgesia which induces constipation as a result of reduced gut motility. There are also a number of scoring systems for oral MBI<sup>2</sup> although none is universally accepted and all lack standardisation. As yet, there is no system for registering gut MBI although there are published definitions for grading toxicity of individual signs and symptoms. Consequently, much more is known about the course of oral MBI than its intestinal counterpart. Oral MBI is known to begin around the time conditioning therapy is completed, and has been shown to worsen until a peak is reached after which it declines gradually until resolving completely. The onset and duration of mucositis has also been shown to mirror the course of neutropenia<sup>3</sup> (Figure 1). This phenomenon may not be peculiar to any one specific regimen. It would

Support Care Cancer  
DOI 10.1007/s00520-013-1741-7

ORIGINAL ARTICLE

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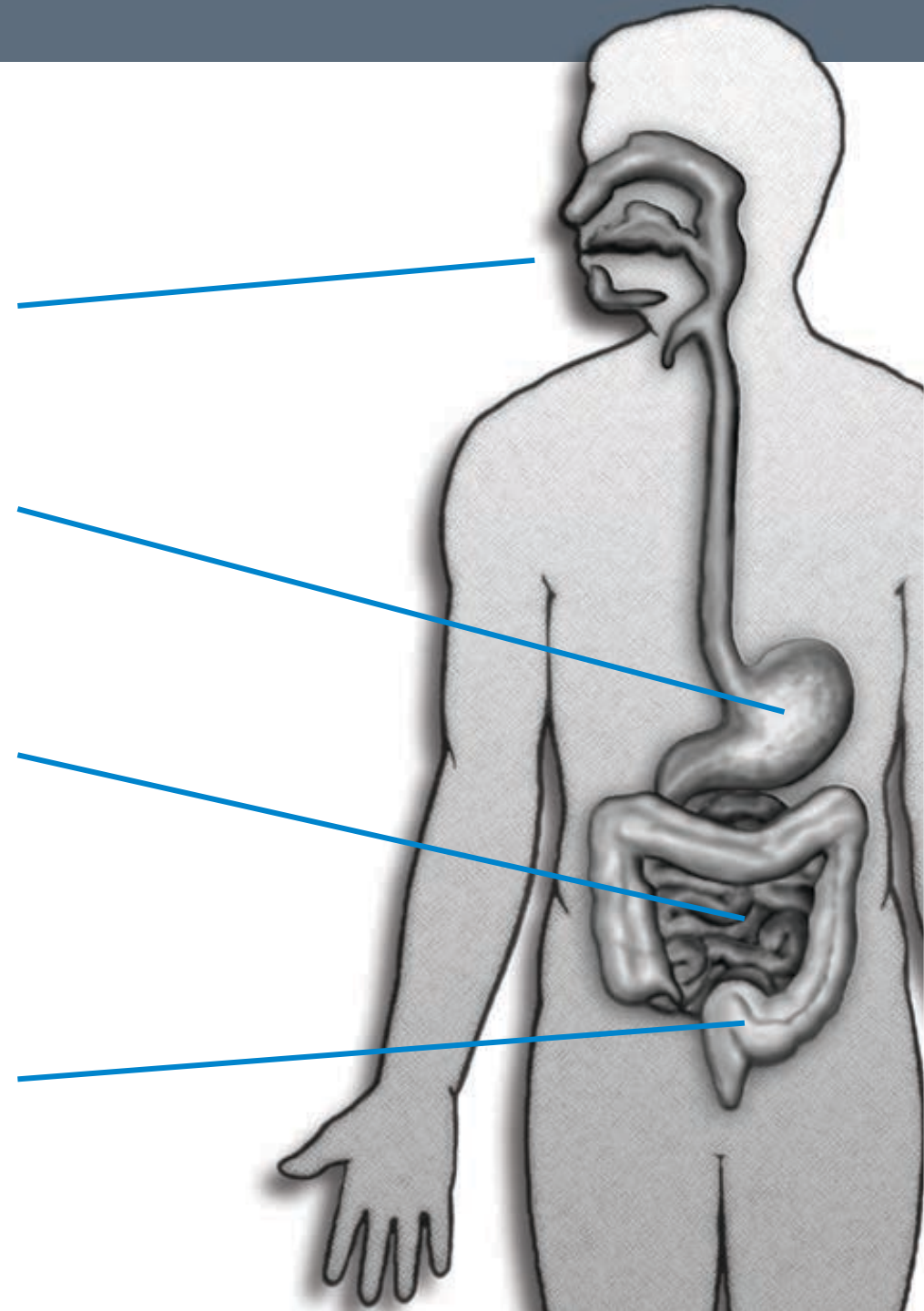
# The microbiome through the gut

**Oral cavity:** Complex ecosystem with moderate numbers of microorganisms. Predominant species; *Streptococcus*; *Actinomyces* & other obligate anaerobes

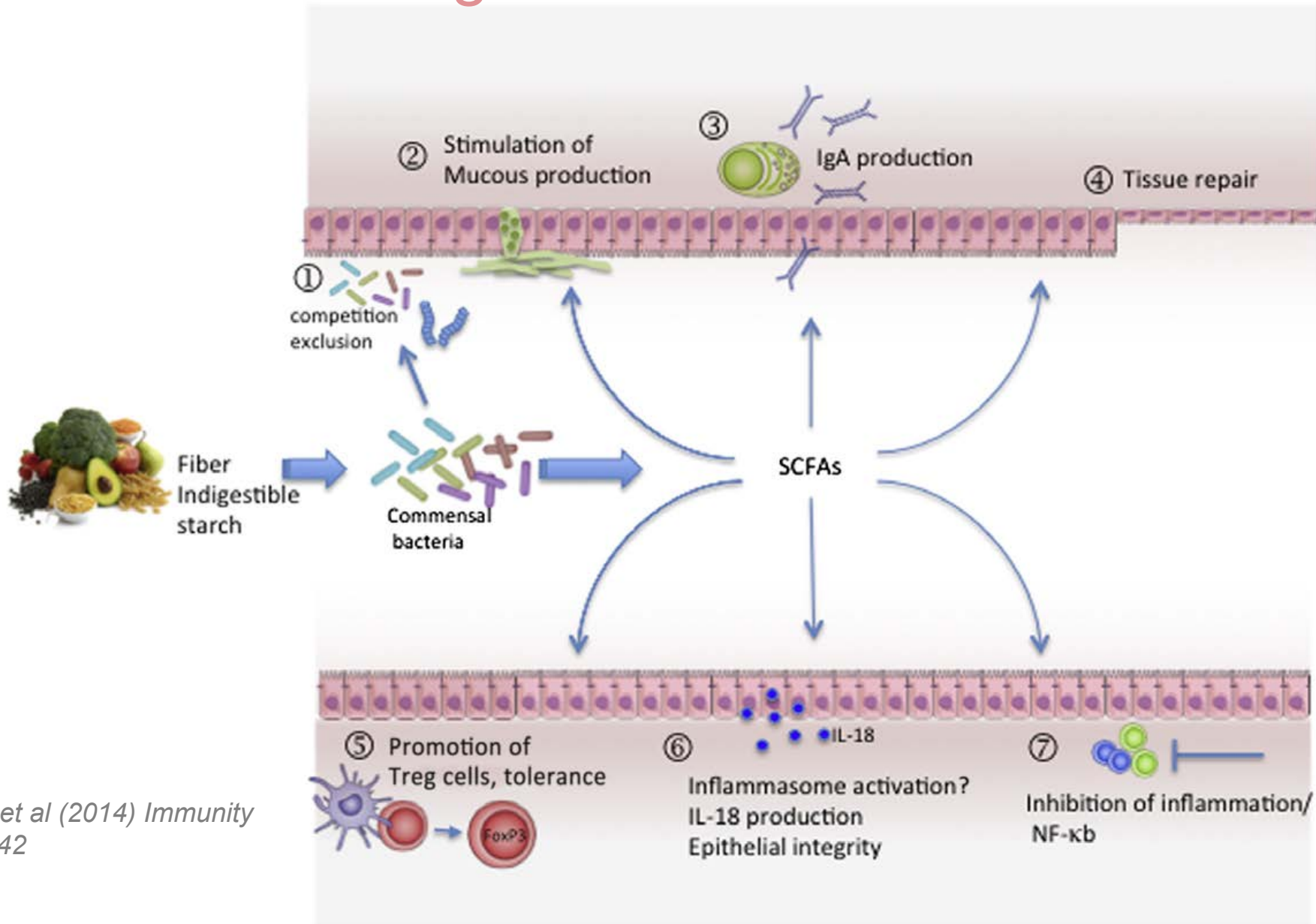
**Stomach:** Relatively low numbers of microorganisms due to highly acidic environment. Most prevalent species is *H. pylori*

**Small intestine:** Relatively low number of microorganisms; due to presence of oxygen, antimicrobials and acidic environment. Those present are predominantly gram-positive bacteria. Most prevalent species *Lactobacillus* & *Enterococcus faecalis*

**Large intestine:** Highest volume of microorganisms, particularly in descending colon. Different populations in the lumen and mucosal regions. Predominant species are the anerobic *Bacteroides* & *Bifidobacterium*

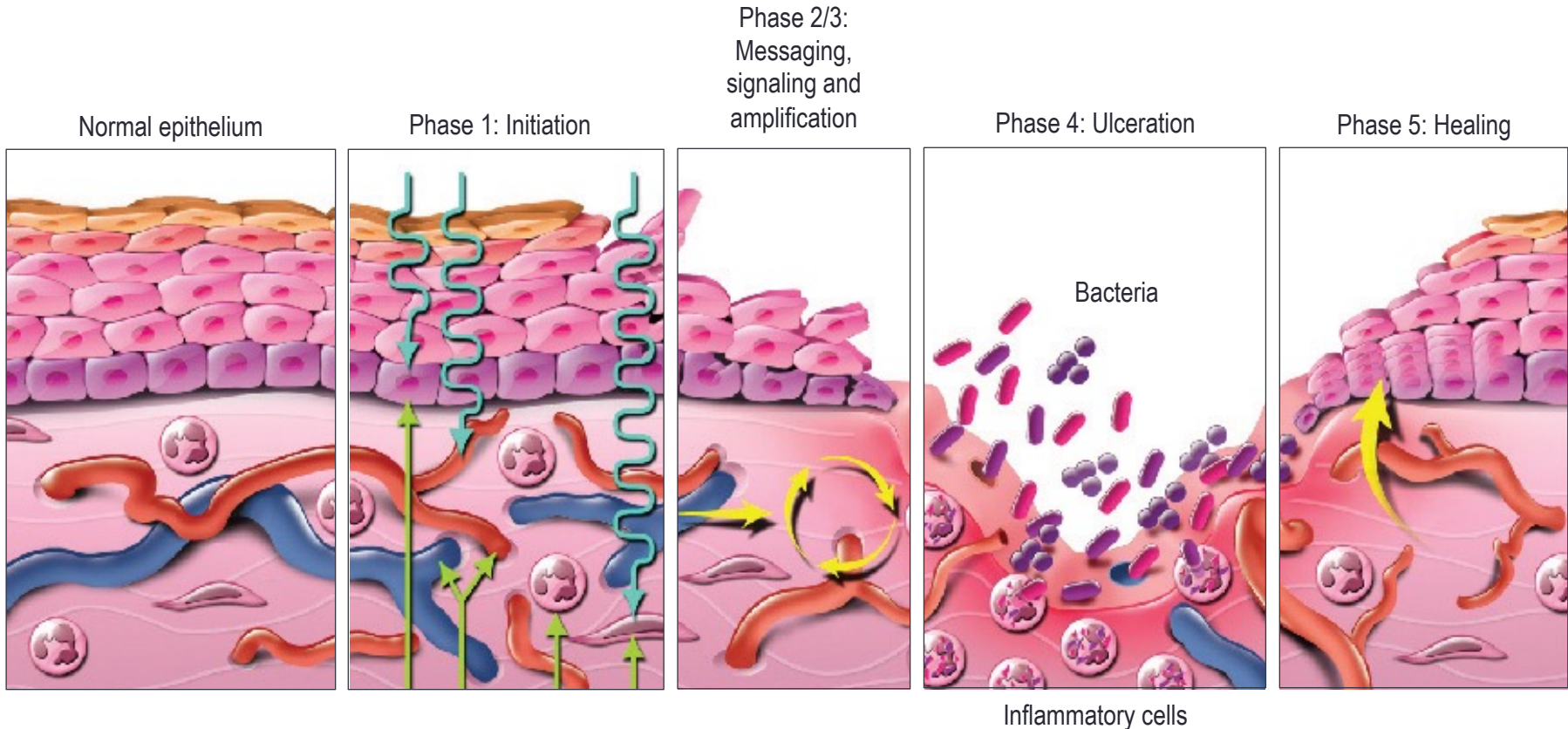


# Functions of the gut microbiome



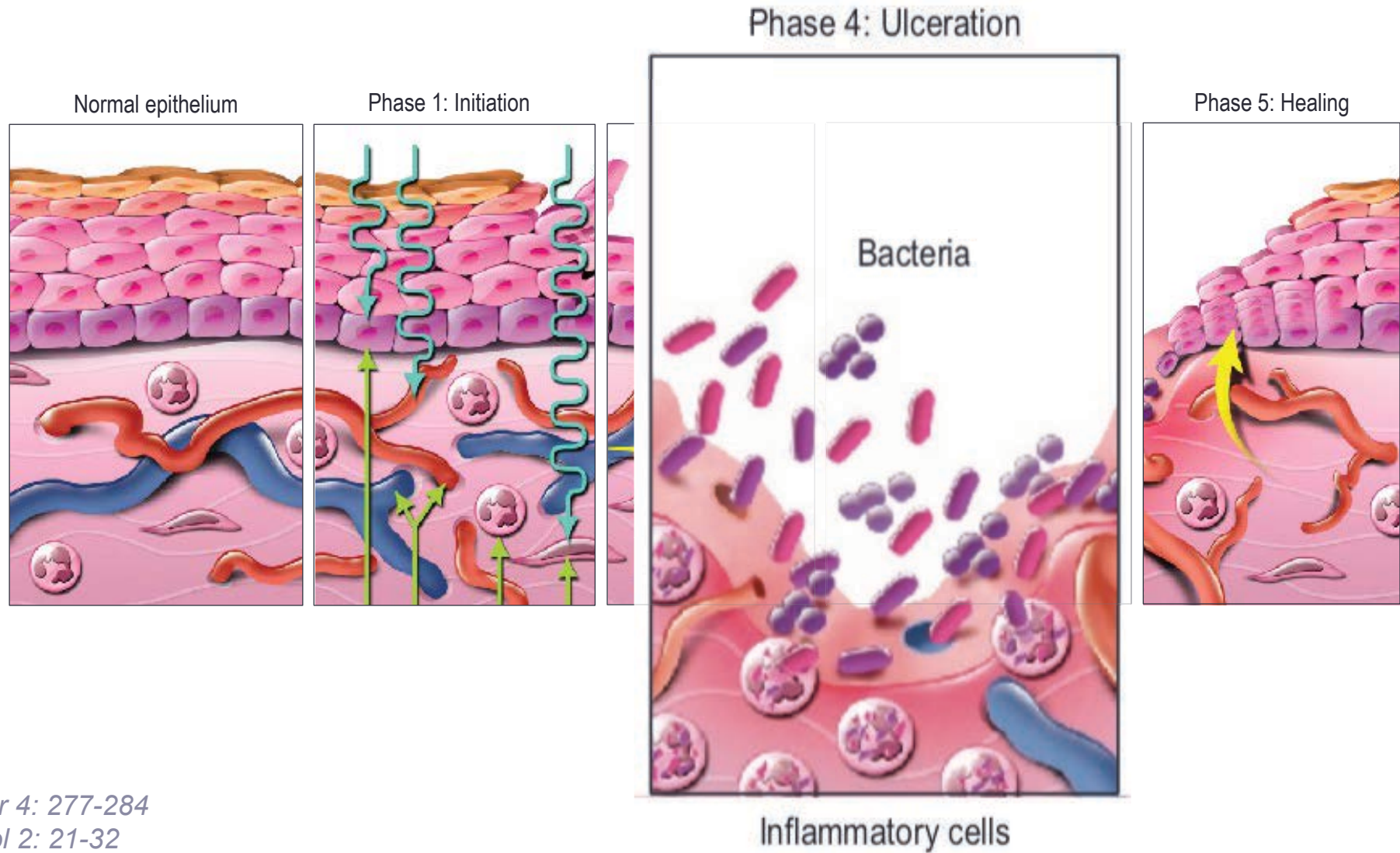


# The current 5-Phase mucositis model



Sonis (2004) *Nat Rev Cancer* 4: 277-284  
Sonis (2004) *J Support Oncol* 2: 21-32

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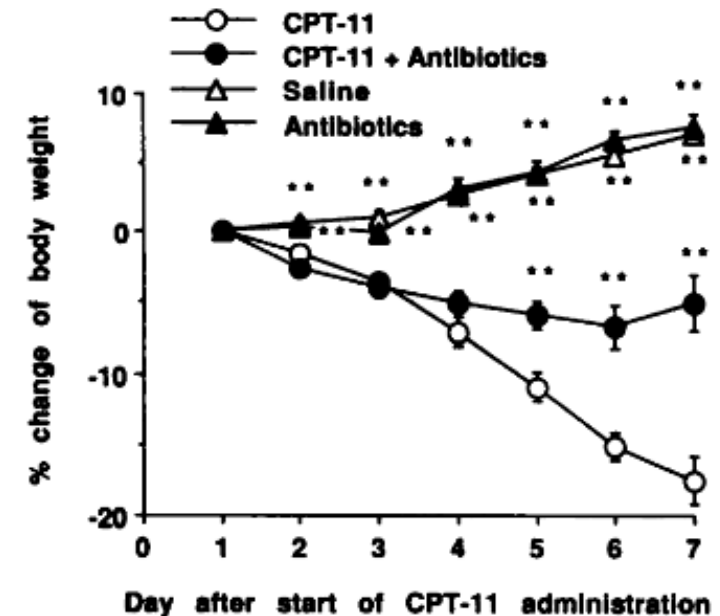
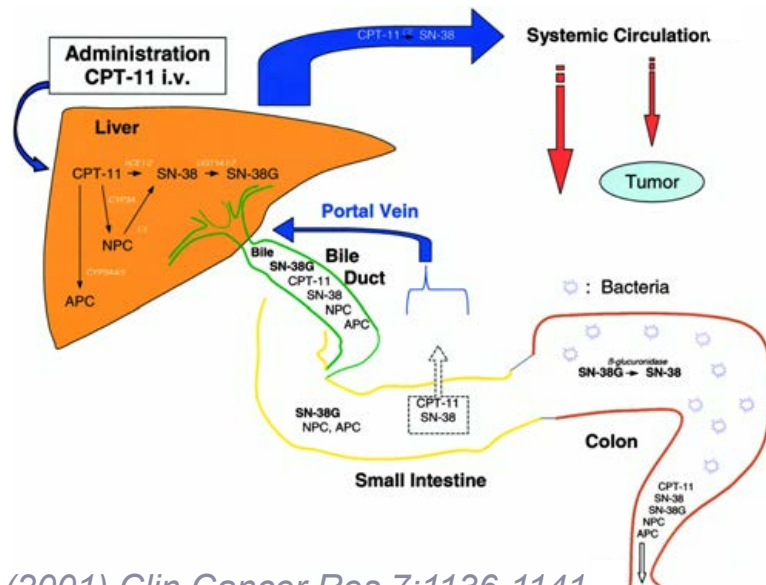
# Early pre-clinical studies of the gut microbiome

[CANCER RESEARCH 56, 3752–3757, August 15, 1996]

## Involvement of $\beta$ -Glucuronidase in Intestinal Microflora in the Intestinal Toxicity of the Antitumor Camptothecin Derivative Irinotecan Hydrochloride (CPT-11) in Rats

Kiyoshi Takasuna,<sup>1</sup> Takehiro Hagiwara, Masaaki Hirohashi, Michiyuki Kato, Mamoru Nomura, Eiichi Nagai, Tsuyoshi Yokoi, and Tetsuya Kamataki

Drug Safety Research Laboratory [K. T., T. H., M. H., M. K., M. N.] and Medical Product Management and Market Planning [E. N.], Daiichi Pharmaceutical Co., Ltd., 16-13 Kitakasai 1-chome, Edogawa-ku, Tokyo 134, and Division of Drug Metabolism, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, [T. Y., T. K.], Japan



# Early clinical studies of the gut microbiome

1136 Vol. 7, 1136–1141, May 2001

Clinical Cancer Research

## *Advances in Brief*

### Modulation of Irinotecan-induced Diarrhea by Cotreatment with Neomycin in Cancer Patients<sup>1</sup>

Diederik F. S. Kehrer,<sup>2</sup> Alex Sparreboom,  
Jaap Verweij, Peter de Bruijn, Corine A. Nierop,  
Jacqueline van de Schraaf, Elisabeth J. Ruijgrok,  
and Maja J. A. de Jonge

Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, 3075 EA Rotterdam [D. F. S. K., A. S., J. V., P. d. B., C. A. N., J. v. d. S., M. J. A. d. J.], and Department of Pharmacy, University Hospital Rotterdam, 3015 GD Rotterdam [E. J. R.], the Netherlands

Neomycin significantly:

- ameliorated diarrhea in 6 out of 7 patients (85%)
- reduced fecal  $\beta$ -glucuronidase activity
- decreased fecal concentrations of pharmacologically active metabolite SN-38

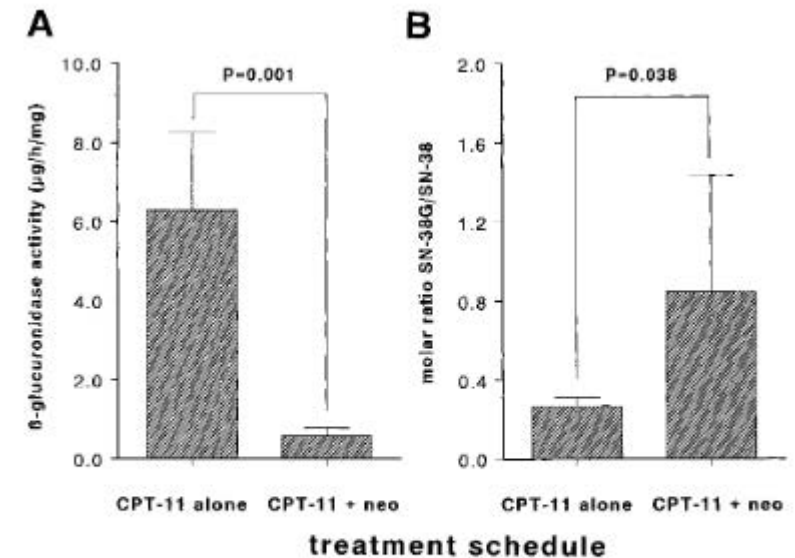
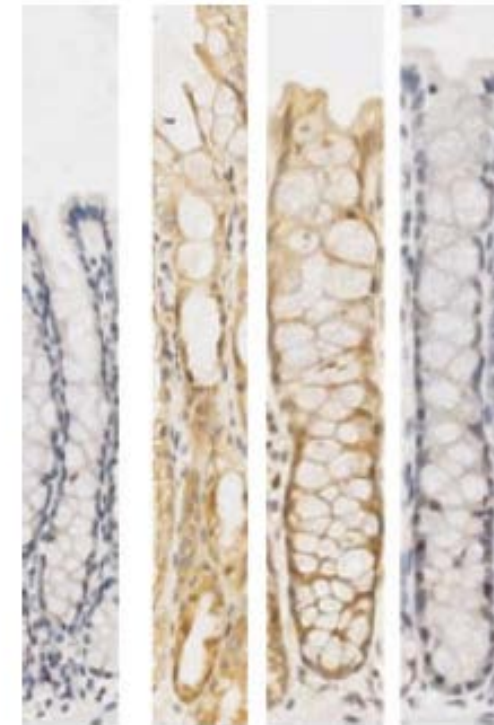
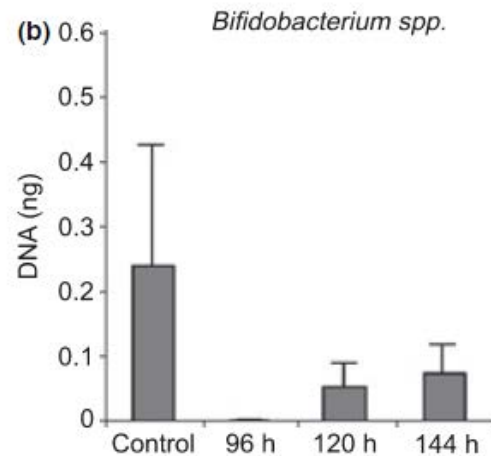
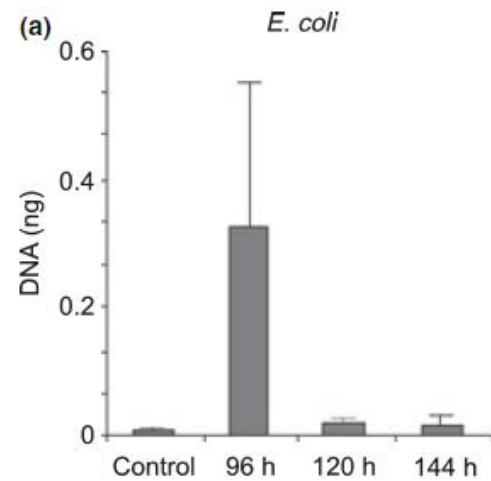


Fig. 3 Fecal  $\beta$ -glucuronidase activity (A) and fecal SN-38G/SN-38 concentration ratios (B) in patients treated with 350 mg/m<sup>2</sup> i.v. CPT-11 in the absence and presence of oral neomycin. Data are displayed as mean values of seven patients; bars, SD.

# Early pre-clinical studies of the gut microbiome

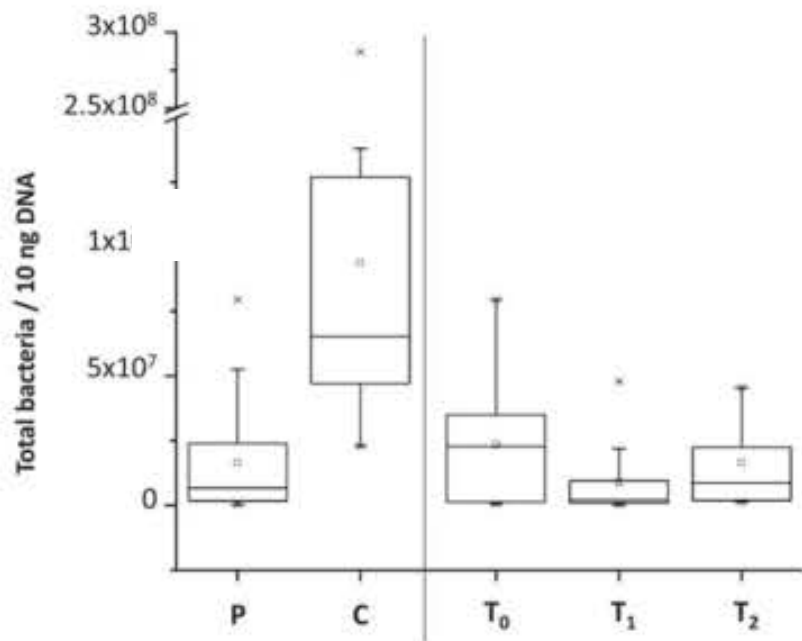
- Stringer and colleagues conducted extensive research on changes between commensal and pathogenic bacteria following chemotherapy



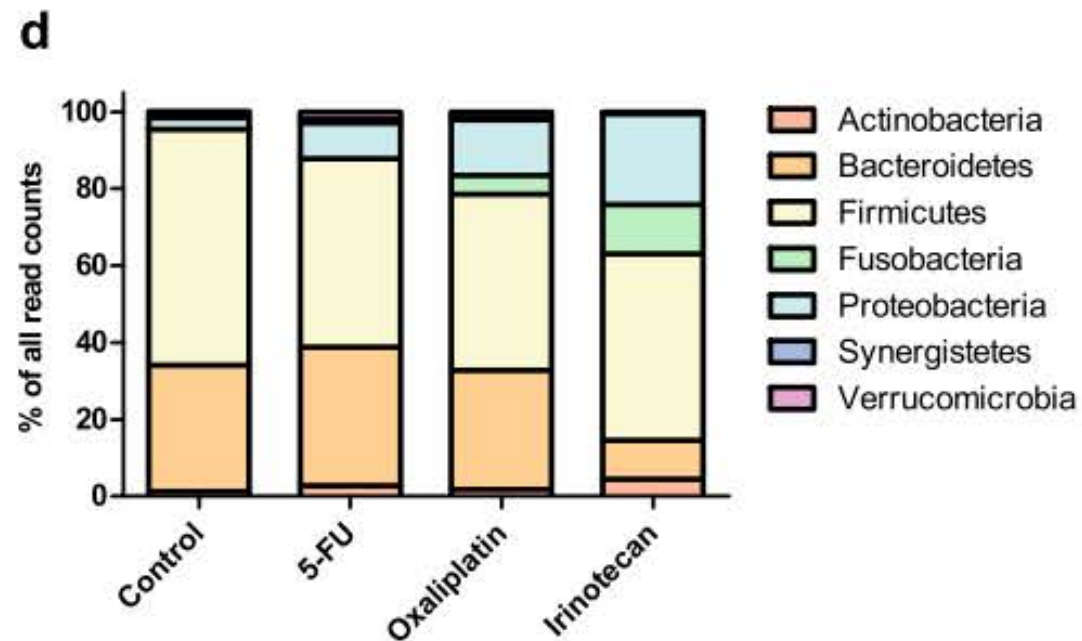
$\beta$ -glucuronidase

Control h    96 h    120 h    144

# Both clinically and pre-clinically, chemotherapy changes the gastrointestinal bacterial profile



**Figure 2. TaqMan qPCR quantification of bacterial 16S rRNA coding regions showing lower abundance in patients undergoing chemotherapy and antibiotic treatment (P) than healthy controls (C). T<sub>0</sub>, samples taken before a single shot of chemotherapy; T<sub>1</sub>, 1–2 days after chemotherapy; T<sub>2</sub>, 5–9 days after chemotherapy; Asterisk indicates a significant difference at p < 0.05.**



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# MODULATION OF THE MICROBIOME FOR EFFECTIVE SUPPORTIVE CANCER CARE

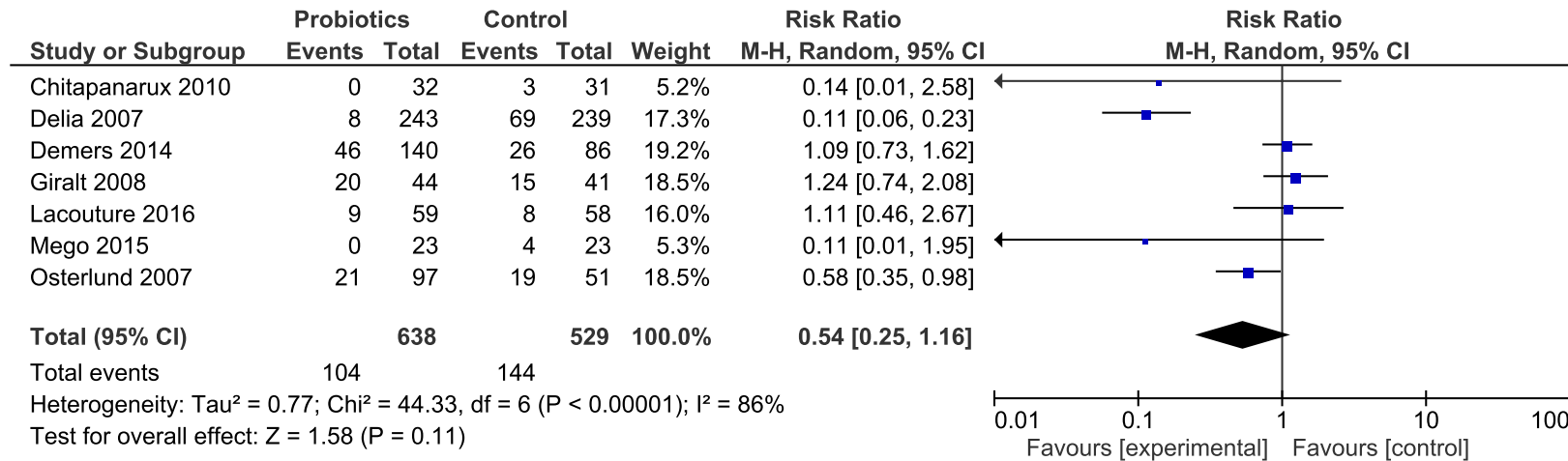
# The use of probiotics in supportive care

- Lactobacillus-containing probiotics are suggested for the prevention of GI toxicity in patients receiving pelvic radiotherapy (MASCC Guidelines, 2014)<sup>1</sup>

- BUT

Very narrow indication

Widespread applicability is unclear<sup>2</sup>



<sup>1</sup>Lalla RV et al (2014) Cancer 120: 1453-1461

<sup>2</sup>Wardill HR et al, (2018) Curr Opin Supp Pall Care 12: 187-197

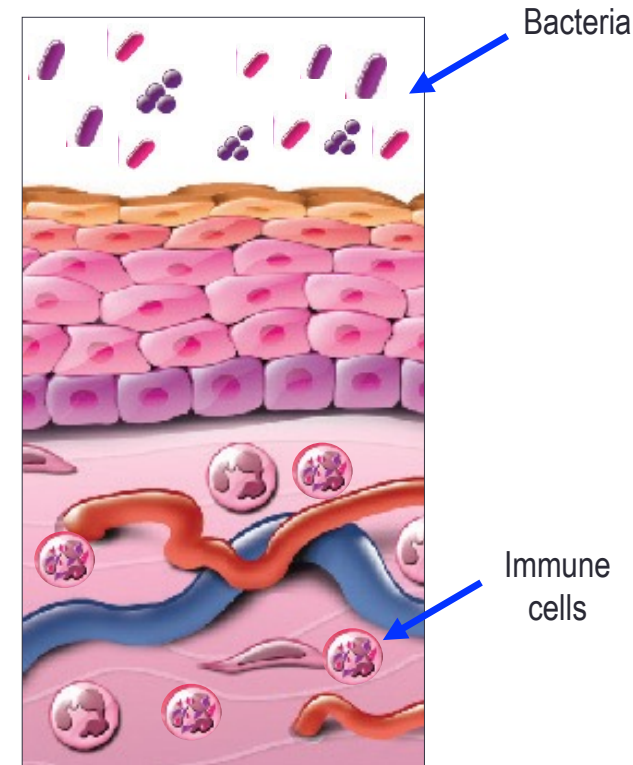


# Time to take a step back?

- Critical that we now work to comprehensively and critically evaluate the role of the microbiome in CIGT to guide intervention design
  - Characterize dynamic shifts in microbiome relative to treatment milestones (diarrhea, barrier dysfunction, infection)
  - Identify unique microbial phenotypes at baseline associated with desired response (both treatment efficacy and toxicity)
    - ✓ Clinical phenomena drive pre-clinical investigation / design

# Can the gut microbiome be used as risk predictor for CIGT?

- Few effective treatments for CIGT
- Risk prediction previously successful
  - 34 patients - 30% with severe CIGT – identified genetic variability in TLR2 & TNFa along with cancer type to be predictive <sup>1</sup>*
  - Specific and sensitive with ROC of 87.3% <sup>1</sup>*
  - Can the gut microbiome also be used as a risk predictor?***



# The gut microbiome as a risk predictor for CIGT

- Well established chemotherapy causes many changes to the gut microbiome
- Microbiome regulates individual's risk of CIGT
- Pre-treatment microbial profiling = novel risk stratification method and possibility of identification of patients at high risk of developing CIGT<sup>1</sup>

## *Aim*

- To examine the relationship between pre-chemotherapy treatment microbial samples and severity of CIGT



<sup>1</sup>Wardill and Tissing, W (2017) *Curr Opin Support Palliat Care* 11: 125-132.

# Pre-treatment *Blautia* abundance regulates CIGT risk



# Recruitment

**Breast and colorectal cancer patients recruited (5-FU-based treatment)<sup>1</sup>**

**Stool samples collected: before treatment and at day 5 (across a range of chemotherapy cycles)**

**Microbiome composition assessed by 16S pyrosequencing** (Australian Genome Research Foundation)

**Clinical case notes to assess diarrhea (NCI CTCAE v5.0<sup>2</sup>)**

<sup>1</sup>Stringer et al (2013) *Supp Care Cancer* 21(7), 1843-52.

<sup>2</sup>Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

# NCI CTCAE v5.0

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change	Increase of <4 stools per day over baseline	+4-6 stools per 24 h over baseline; IV fluids indicated < 24 h; moderate increase in ostomy output compared to baseline; not interfering with daily living	+7 stools per 24 h over baseline; incontinence; IV fluids 24 h; hospitalization; severe increase in ostomy output compared to baseline; interfering with daily living	Life-threatening consequences (e.g. hemodynamic collapse)
<b>“Non-toxic”</b>		Excluded	<b>“Toxic”</b>	

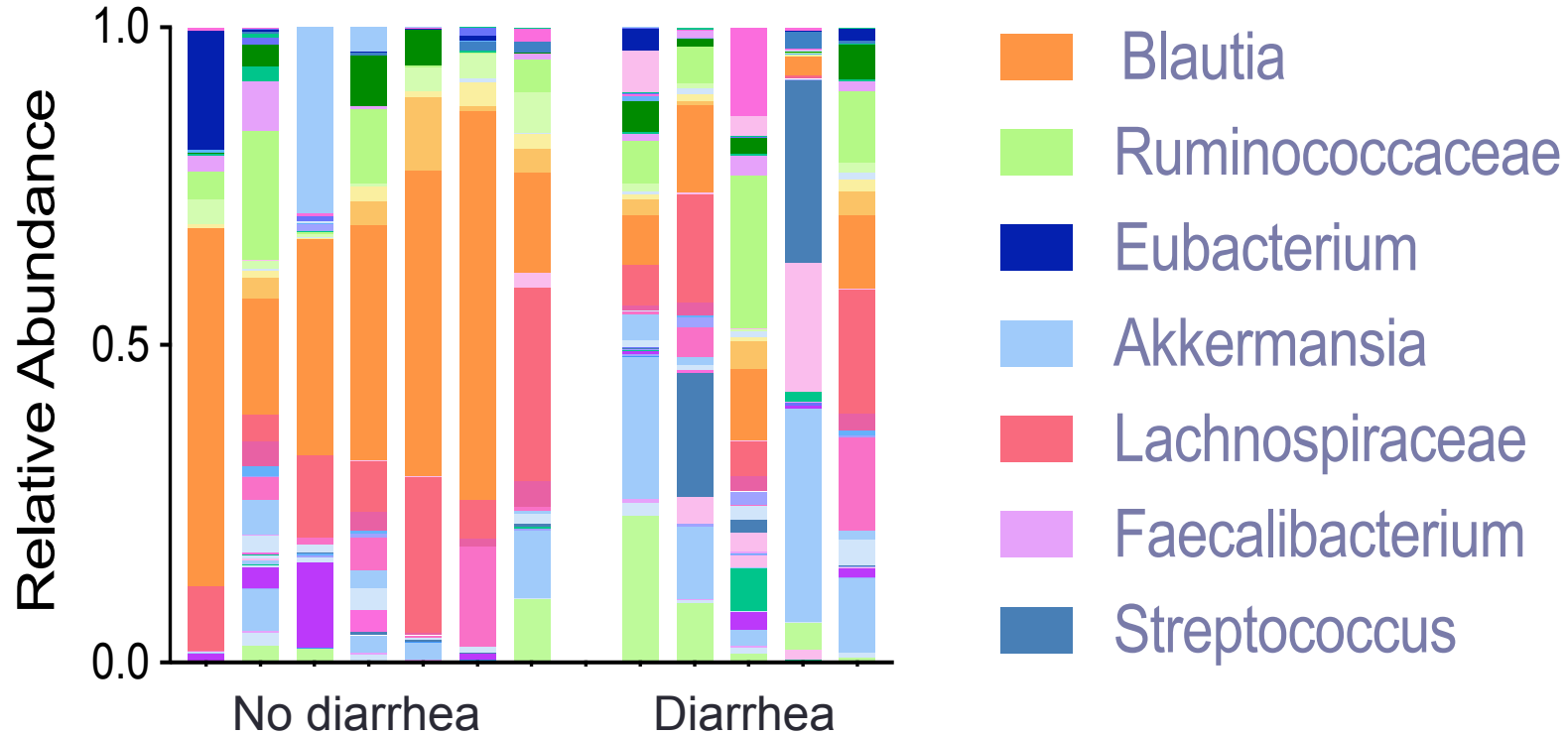
# No demographic differences between non-toxic and toxic patients

	Non-toxic (n=8)	Toxic (n=4)
<b>Age</b>		
Median (range)	54.5 (38-72)	61.5 (56-68)
<b>Sex (n (%))</b>		
Female	4 (50%)	1 (25%)
Male	4 (50%)	3 (75%)
<b>Cancer type (n (%))</b>		
Breast	1 (12.5%)	1 (25%)
Colon	6 (62.5%)	1 (25%)
Rectal	1 (12.5%)	2 (50%)
<b>Treatment protocol (n (%))</b>		
FOLFOX	7 (87.5%)	1 (25%)
FEC	1 (12.5%)	1 (25%)
Radiation + 5-FU	0 (0%)	2 (50%)
<b>Sample treatment cycle</b>		
Median (range)	4 (3-10)	3 (1-4)

All values P=NS

# Baseline microbiome composition drives treatment response

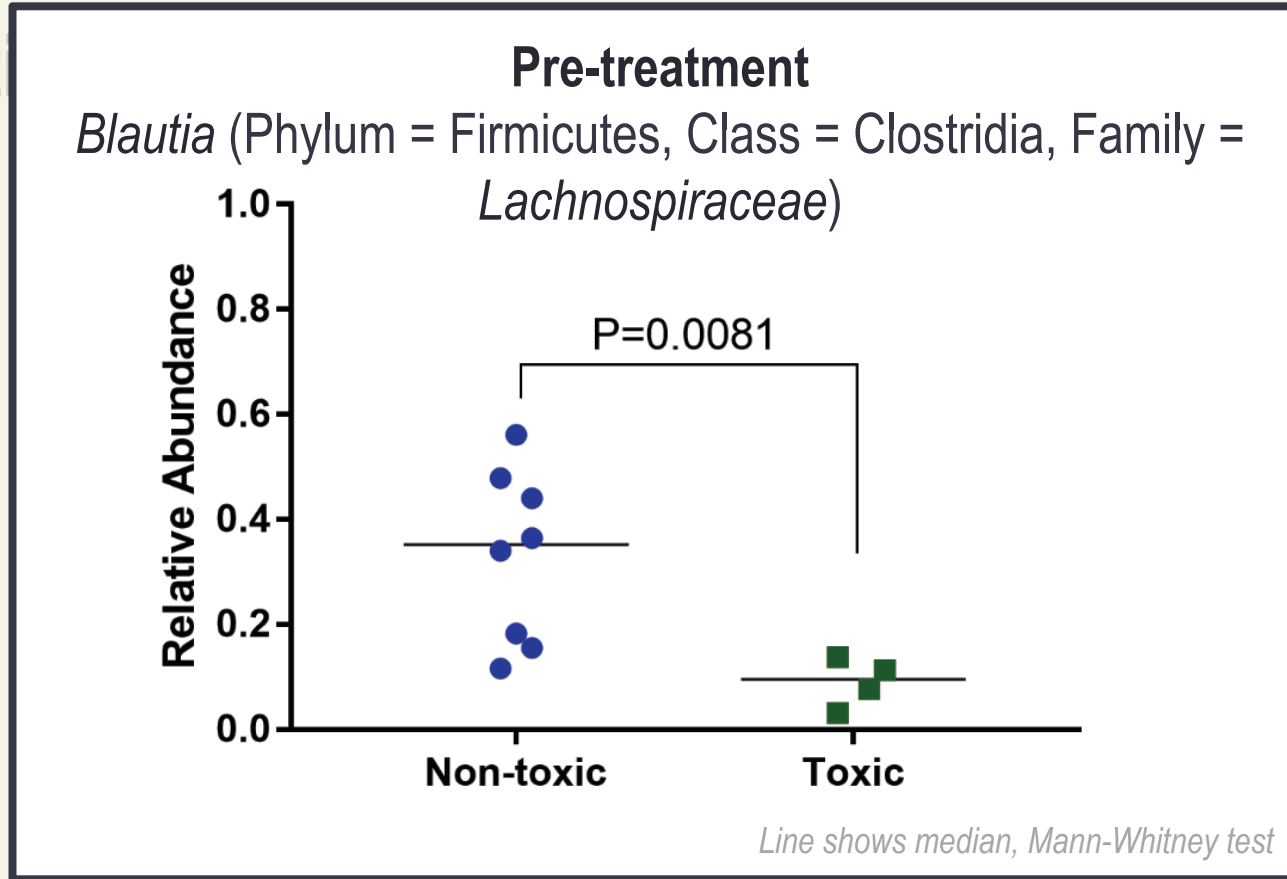
- *Blautia* is critical in determining CIGT in patients receiving 5-FU-based chemotherapy



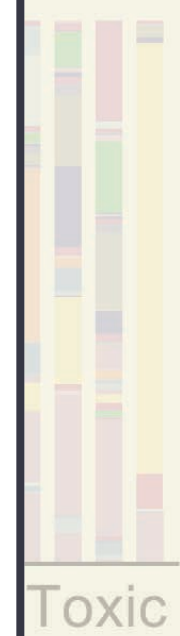


Relative

Relative Abundance



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## Take home message:

- The gut microbiome is critical in shaping individual responses to cancer therapy
- It has potential to be further exploited
  - In-depth, longitudinal analysis is required to understand temporal relationship with treatment milestones and outcomes
  - Baseline microbial profiling is likely to play a role in risk prediction
  - Interventions need to be guided by clinical phenomena

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