Microbiome and GI Cancers

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Disclosure

- Consulting – Immuron, Niche, ProbioTech, Seres, Takeda
- Research Support – Finch, Pfizer, Rebioitx, Ferring, Vedanta

Outline

- Introduction to the microbiome
- Microbial alterations in GI malignancies
- Clinical implications

What's This Microbiome That Everyone's Talking About?

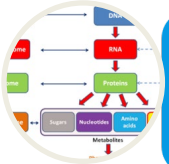
- >10x microbial cells (~100 trillion) than human
- Microbes: 1 – 3% of body's mass
  - 99% of all bacteria are commensal
- Humans possess 23,000 genes
  - Microbes contribute ~3,300,000 genes
- Phyla present
  - Firmicutes and Bacteroidetes: >90%
- Functions such as colonization resistance
- Alterations associated with disease states

Gilbert et al. *Nature Medicine.* 24, 392–400; Scott et al. *Gut*. 68(9): 1624–32.

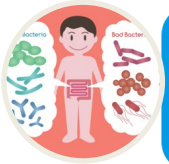
Let’s Get the Terminology in Order

Microbiota: The microorganisms that live in an established environment

Microbiome: The combined genetic material of the microorganisms in a particular niche

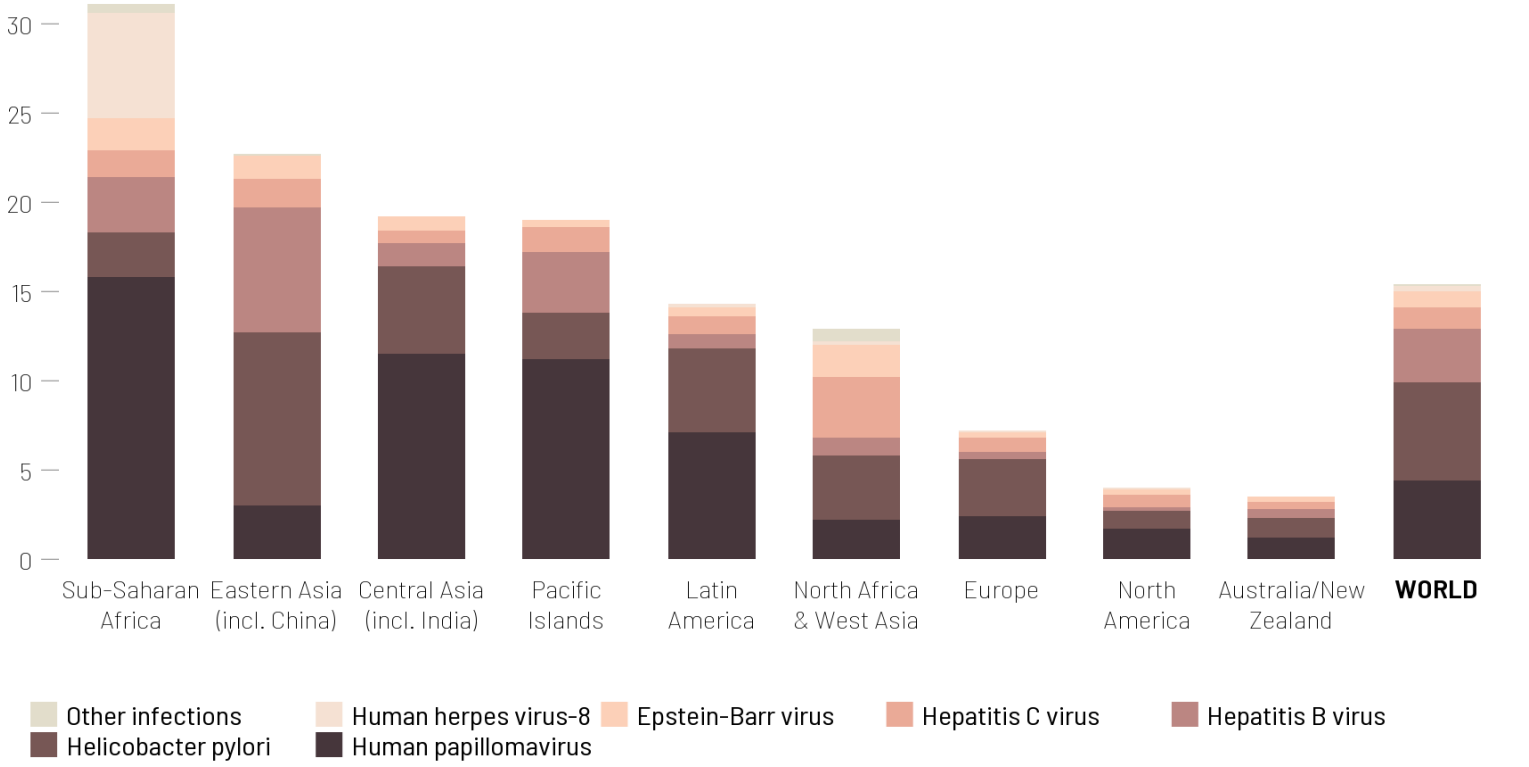


Metabolome: Functional properties of the gut microbiota

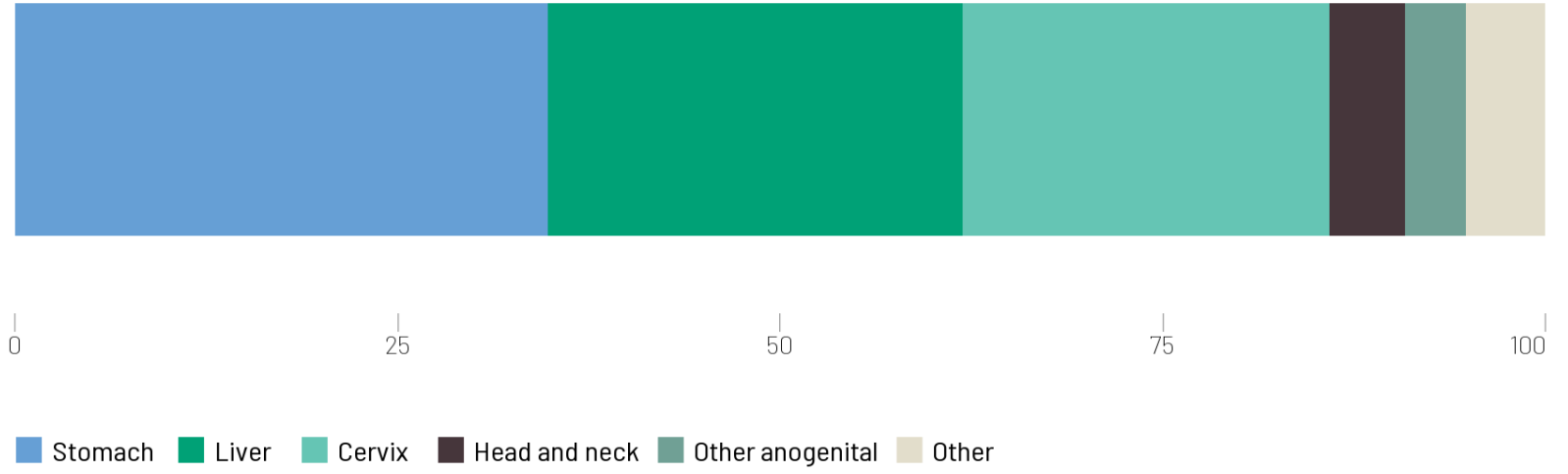


Dysbiosis: A derangement in the microbiota

Proportion of Cancers Attributable to Infections

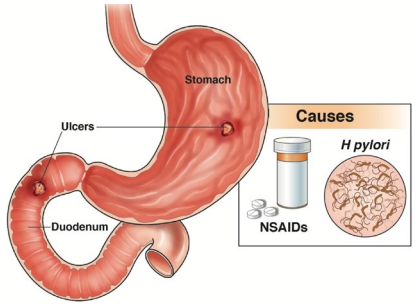


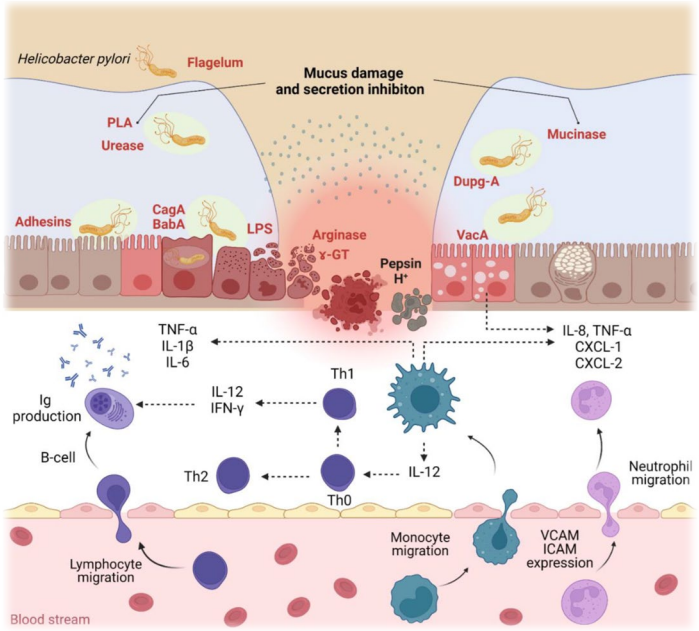
Most Common Infection-Attributable Cancers



Is it just single organisms that are associated?

Microbes and GI Cancers: An Age-Old Tale





Normal mucosa

↓

Chronic active gastritis

↓

Gastric atrophy

↓

Intestinal metaplasia

↓

Dysplasia

↓

Gastric cancer

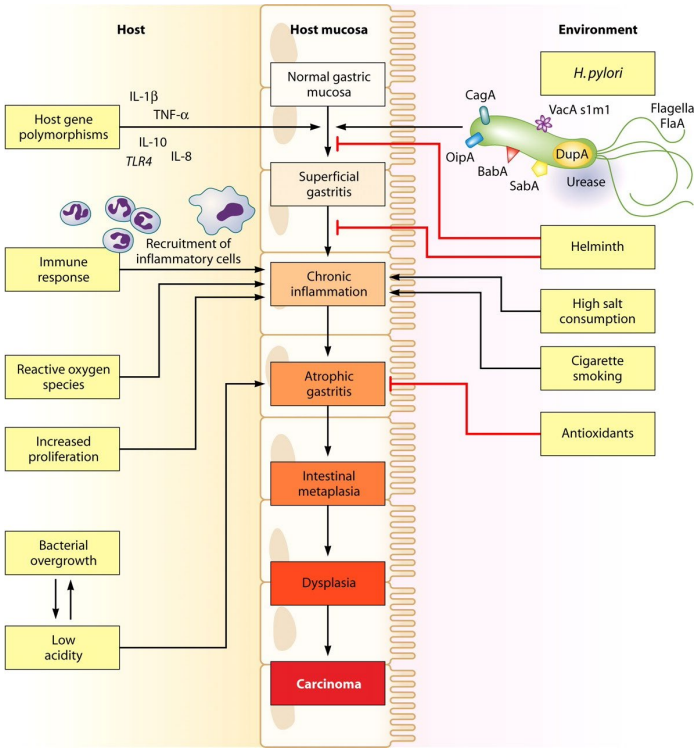
H. pylori

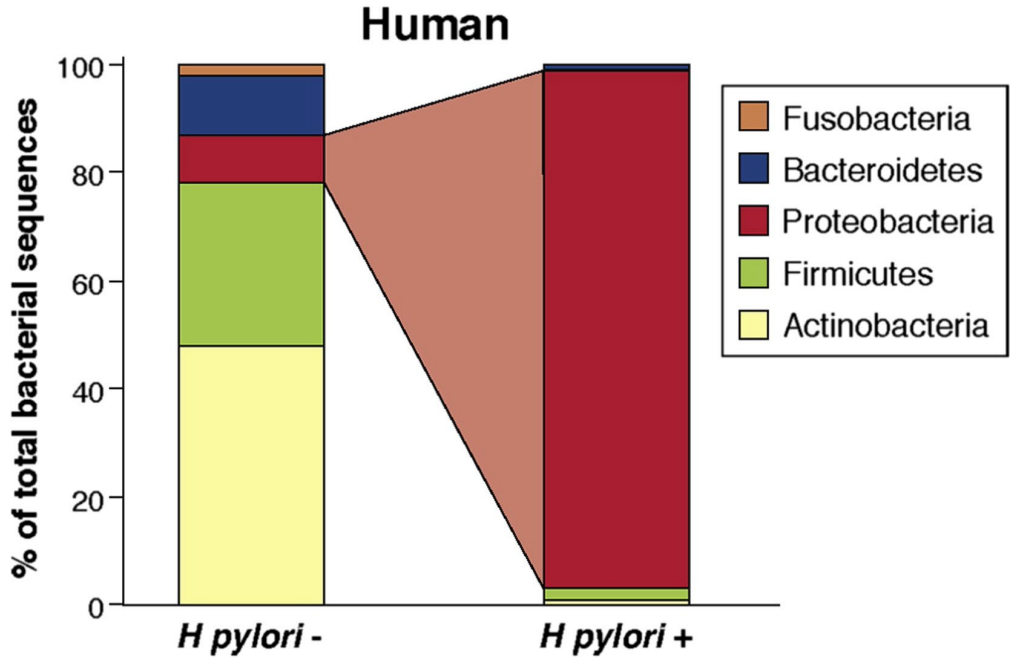
Immune response, diet, gastrin, genetics

Achlorhydria, Carcinogens

Pop et al. *Pharmaceutics*. 2022, 14(7), 1463, https://patient.gastro.org/tag/h-pylori/.

Is *H pylori* a Single Organism Pathogenesis?





Wroblewski et al. *Clin Microbiol Rev*. 2010 Oct;23(4):713-39. Abreu et al. *Gastroenterology*. 2014;146:1534–1546.

Microbiome and CRC in 1969…

Bacteria and the aetiology of cancer of the large bowel

VIVIENNE ARIES, J. S. CROWTHER, B. S. DRASAR, M. J. HILL, AND R. E. O. WILLIAMS

From the Bacteriology Department, Wright-Fleming Institute, St Mary's Hospital Medical School, London

Cancer of the large bowel shows marked variations in geographical distribution (Doll, 1967; Doll, Payne, and Waterhouse, 1966; Davis, Knowelden, and Wilson, 1965) and, with the exception of Japan, the disease is more prevalent in developed than in underdeveloped countries. The reason for this variation is not known but epidemiological evidence suggests that environmental factors may be involved. It is claimed that immigrants from areas with a low incidence of cancer of the large bowel tend to show the same high incidence of this cancer as the local population (Haenszel and Dawson, 1965; Buell and Dunn, 1965). Changes in dietary habit may be especially important (Wynder and Shigematsu, 1967; Buell and Dunn, 1965) and diet is known to affect the nature and distribution of bacteria in the faeces (Hoffmann, 1964; Dubos, 1965).

Among the important metabolic activities of intestinal bacteria is the degradation of bile salts (Hill and Drasar, 1968). It seems possible that some of the bacteria in the bowel could convert bile salts, or steroids in the diet, into carcinogens; Haddow (1958) has reviewed the ways in which it is possible, in the laboratory, to convert deoxycholate into 20-methylcholanthrene, a potent carcinogen.

We have, therefore, compared the bacterial flora of the faeces from people in England, an area with a high incidence of cancer of the large bowel, with that from people in Uganda, where the incidence is low. We have also compared the abilities of English and Ugandan strains of faecal bacteria to degrade bile salts and have examined the products of bile degradation in English and Ugandan faeces.

MATERIALS AND METHODS

Samples of freshly voided faeces from 48 healthy Ugandan adults living in and around Kampala and from 40 healthy English adults living in London were examined. Specimens were preserved for transport and storage as a 10% suspension in meat infusion broth containing 10% glycerol frozen on solid carbon dioxide (Drasar, Shiner, and McLeod, 1969); the bacteria have been found to survive well under these conditions. Specimens were cultivated by the methods described previously (Drasar, 1967) with minor modifications. Approximately equal numbers of English and Ugandan specimens were examined on each day of testing in order to compensate for minor fluctuations in culture media, incubation temperatures, and operational techniques.

Methods for investigating the degradation of bile salts are described elsewhere (Hill and Drasar, 1968; Aries, Crowther, Drasar, and Hill, 1969).

RESULTS AND DISCUSSION

Our findings are summarized in the Table. The same groups of bacteria occurred in both populations but there were significant quantitative differences. Although the dominant bacteria in both populations were non-sporing anaerobes (bacteroides and bifidobacteria), the English specimens contained 30 times more bacteroides than did the Ugandan. Streptococci, enterococci, lactobacilli, and yeasts occurred in significantly greater numbers in the Ugandan specimens. No significant differences were

TABLE

BACTERIAL COUNTS OF FAECES FROM 40 ENGLISH AND 48 UGANDAN ADULTS[1]

Organism	*English*	*Ugandan*	*P*[2]
Bacteroides	9·7 ± 0·6	8·2 ± 1·1	<0·001
Bifidobacteria	9·9 ± 0·3	9·3 ± 0·6	<0·001
Aerobic streptococci	7·0 ± 0·8	7·8 ± 0·9	0·01
Enterococci	5·7 ± 1·3	7·0 ± 1·2	0·01
Lactobacilli	6·0 ± 1·6	7·2 ± 1·1	0·01
Yeasts	1·3 ± 1·8	3·1 ± 2·0	0·01
Enterobacteria	7·5 ± 1·2	8·0 ± 0·8	>0·05
Clostridia	4·4 ± 1·8	4·0 ± 1·9	>0·05
Veillonellae	4·4 ± 2·1	5·3 ± 1·4	>0·05
Filamentous fungi	1·4 ± 1·2	2·2 ± 1·2	>0·05[3]

[1]Arithmetic mean of $\log_{10}$ organisms per g wet weight ± standard error.
[2]Agreed values obtained from both the student *t* test and the χ^2 test.
[3]Agreed value obtained from both a rank test and the χ^2 test.

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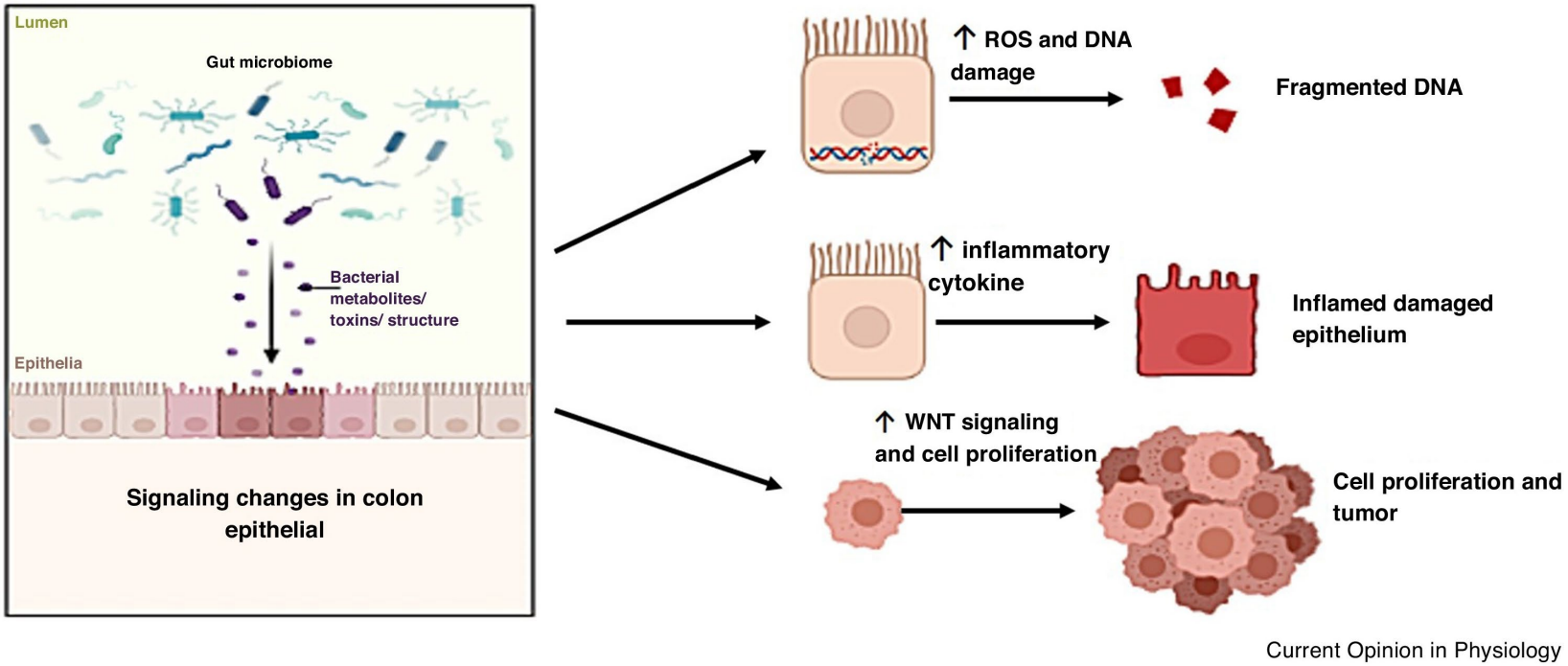
Aries et al. *Gut*. 1969, 10, 334-335.

Microbial Alterations in Colo-Rectal Cancer



Sayed et al. *Curr Opin Physiol*. 2021, 22:100451.

Fusobacterium Nucleatum and CRC

Enriched in tumor compared to normal tissue

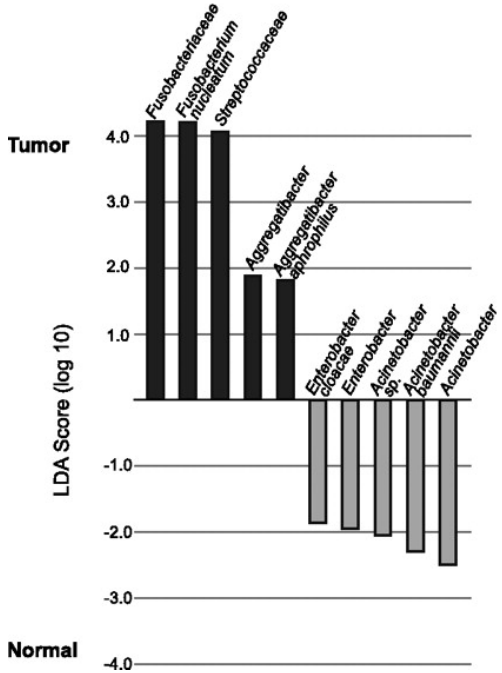
DNA isolated from colon tissues
(9 tumor-normal sample pairs)

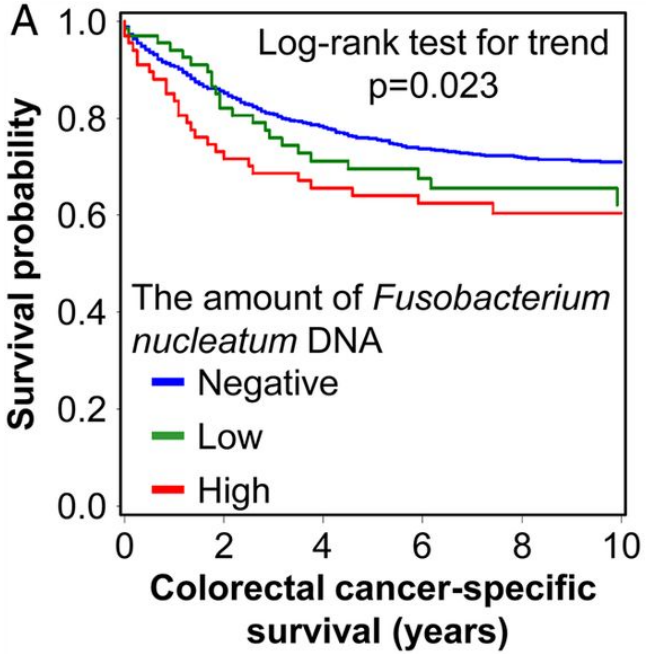
↓ Illumina sequencing

Human whole-genome sequencing data
(1.51 billion reads; median per sample)

↓ PathSeq analysis

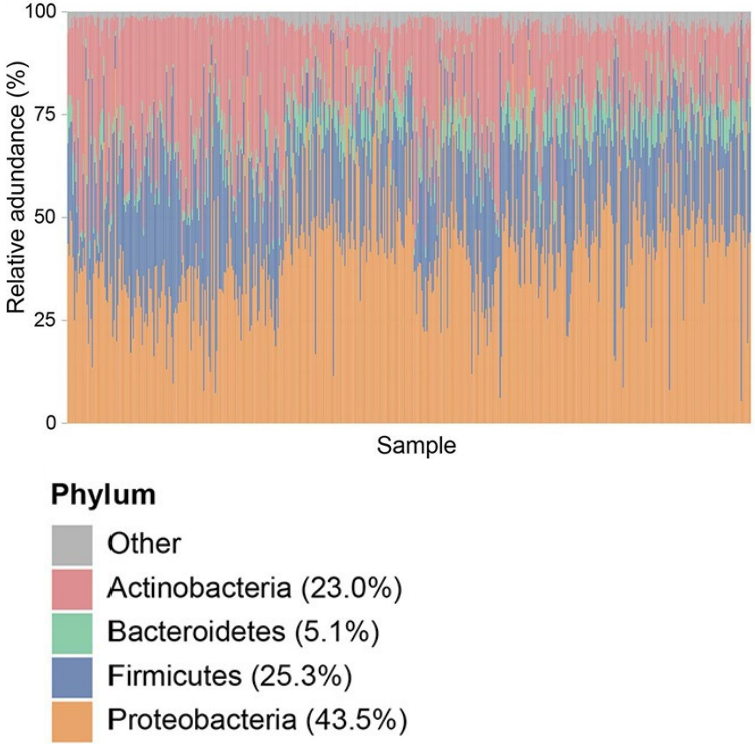
Microbial sequences
(101,000 reads; median per sample)

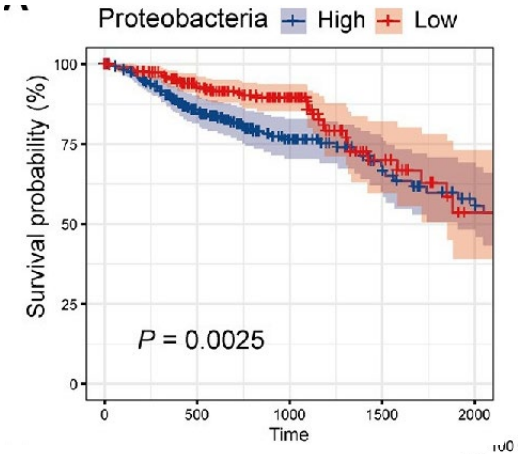


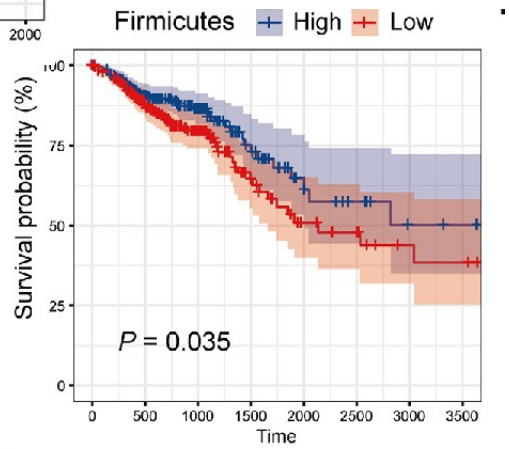


Kostic et al. *Genome Res*. (2012) 22:292-298; Mima et al. *Gut*. 2016 65:1973–1980.

Is *F nucleatum* a Single Organism Pathogenesis?







Xu et al. *Front Microbiol*. 2023 Mar 21;14:1100873.

Is *F nucleatum* Ready for Practice?

- Metronidazole improved survival in mice with CRC with *F nucleatum*
- ? Targeted antibiotics
- ? Targeted microbiome therapeutics

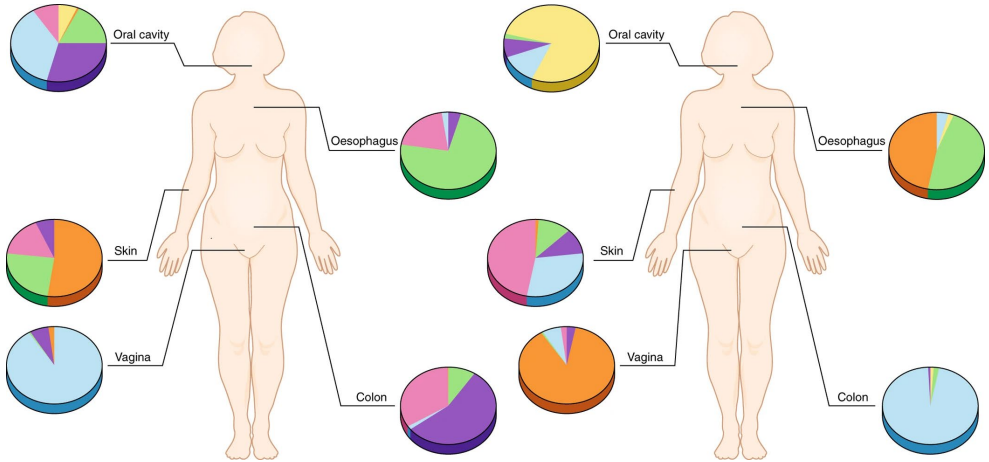
Diets that may promote intestinal inflammation, based on EDIP score

Higher risk of *F nucleatum* – positive CRC but not CRC that do not contain these bacteria

Bullman S et al. *Science*. 358(6369): 1443–1448; Liu et al. *Clin Gastroenterol Hepatol*. 2018 Oct;16(10):1622-1631.e3.

How Does Dysbiosis Relate to Carcinogenesis?

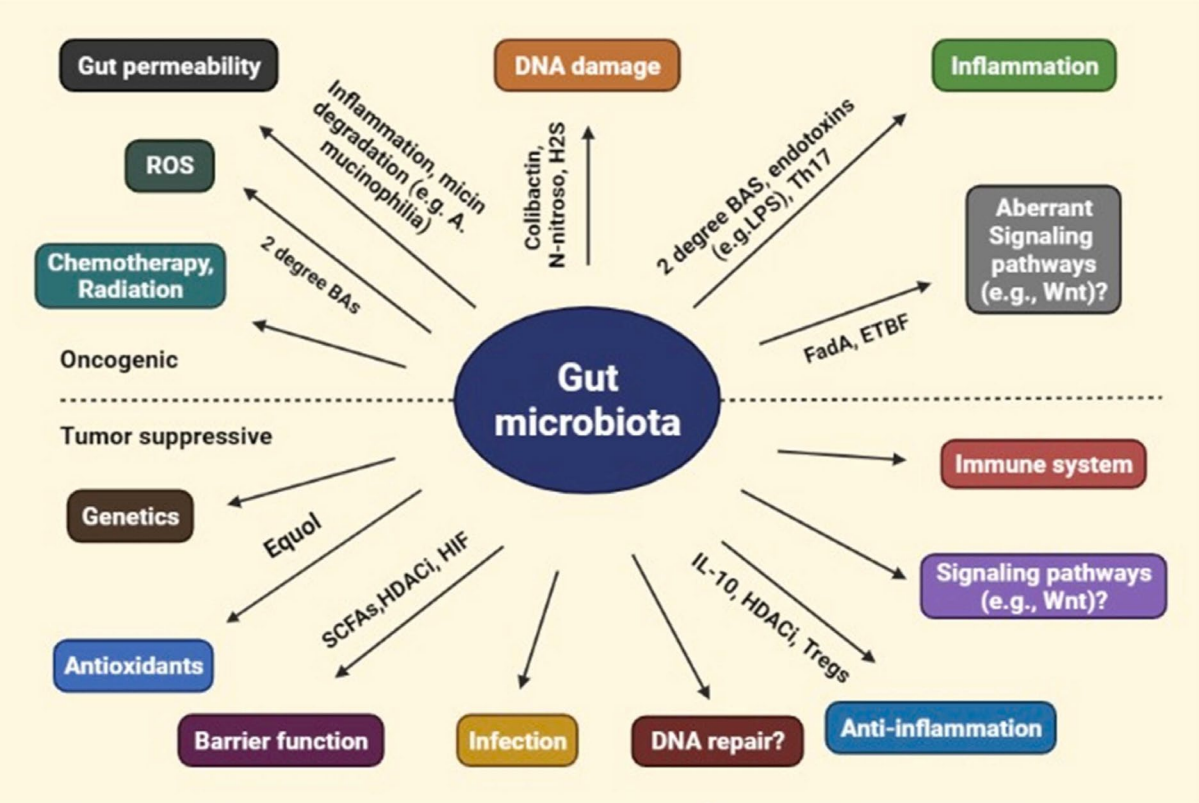
- No accepted quantitative definition of a ‘normal’ microbiome
- Persistent departure from a homeostatic state, towards a cancer promoting and/or sustaining phenotype



Dysbiosis is specific to an individual, the disease and the ecological niche

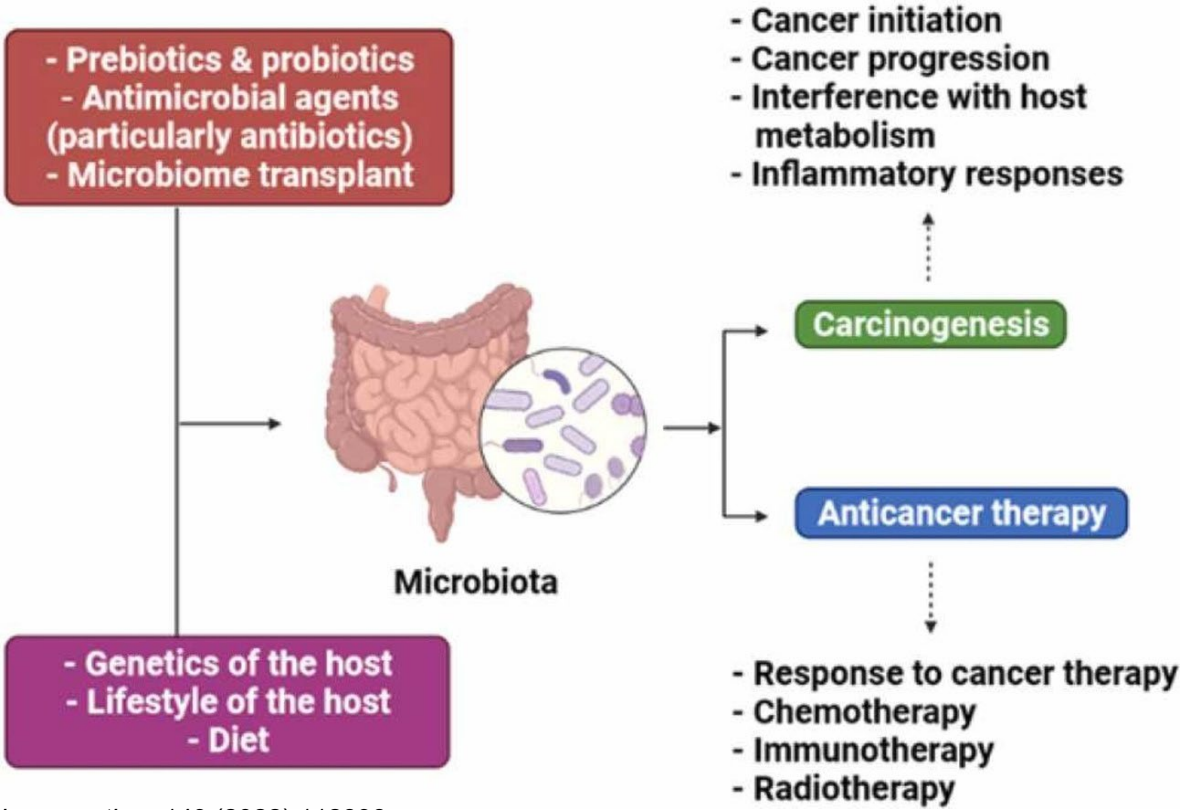
Gilbert et al. *Nature Medicine*. 24, 392–400; Scott et al. *Gut*. 68(9): 1624–32.

Microbiome Interactions with Carcinogenesis



Rahman et al. *Biomed & Pharmacother*. 149 (2022) 112898.

Microbiome and Cancer Biology



Rahman et al. *Biomed & Pharmacother*. 149 (2022) 112898.

What's Happening in Therapeutics?

No FDA approved options

37 Studies: **FMT | Interventional | Cancer**

- 81.1%: Enhance treatment efficacy
  - Immunotherary: Check point inhibitors, PD-1 therapy
- 18.8%: Manage treatment complications
  - Colitis, diarrhea, GVHD, etc

VE800: Oral, defined consortium, 11 strains

- Ability to induce CD8+ T cells
- Enhance checkpoint inhibitor efficacy
- Phase I trial

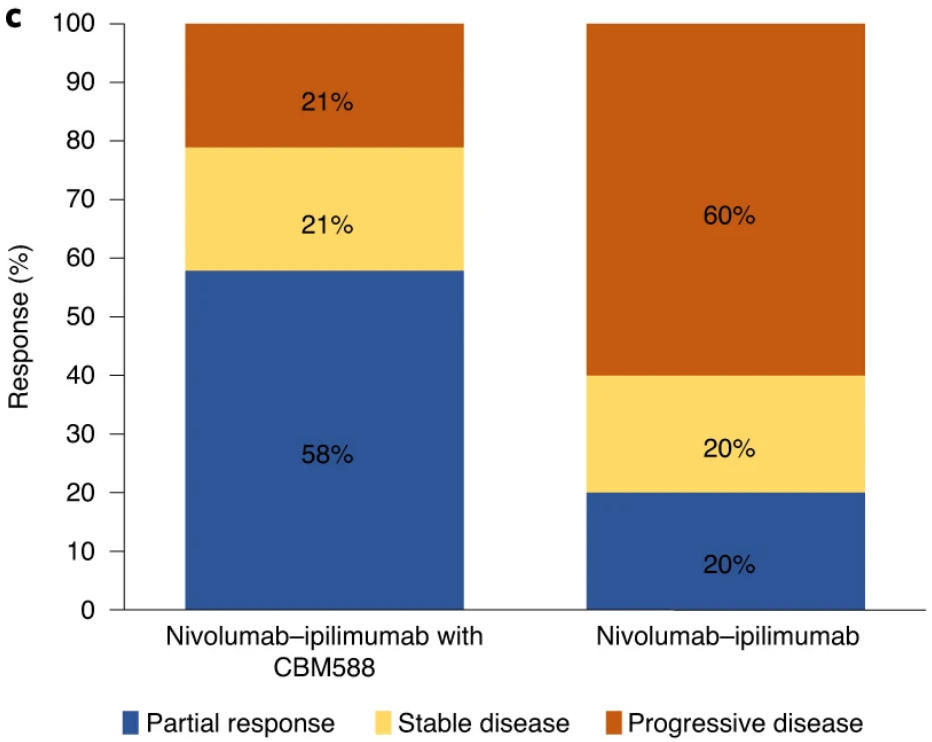
SER-401: Firmicutes spores

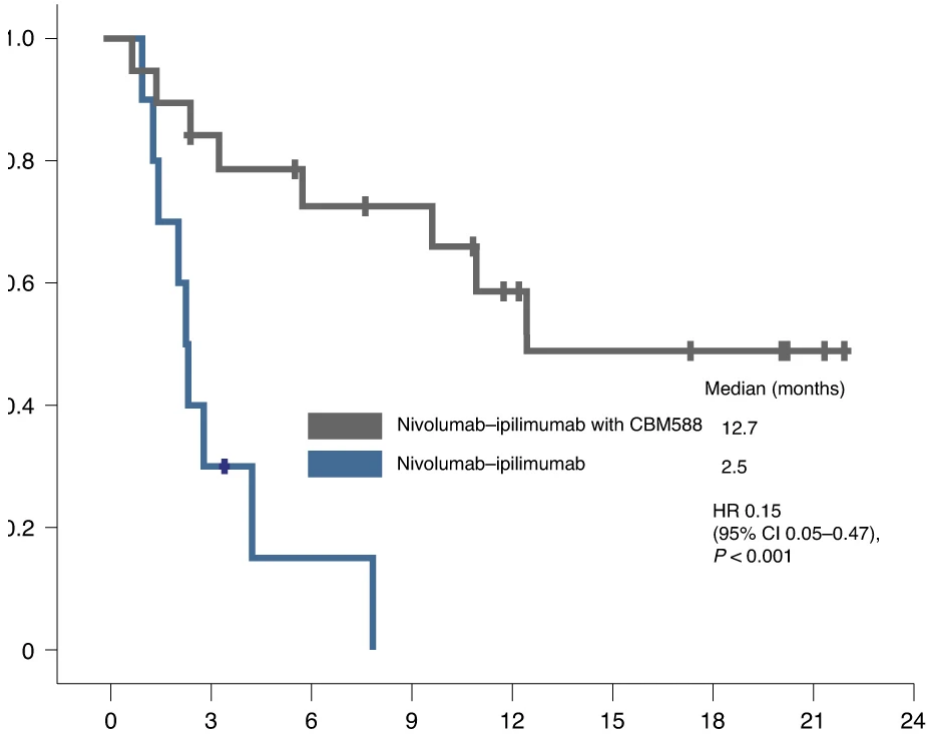
- Enhance anti-PD-1 checkpoint inhibitor efficacy
- Phase I trial

Search conducted on April 10, 2023. *Cancer Res*. 2019;79(13 Suppl):Abstract nr 2839; VedantaBiosciences.com.

ClinicalTrials.gov

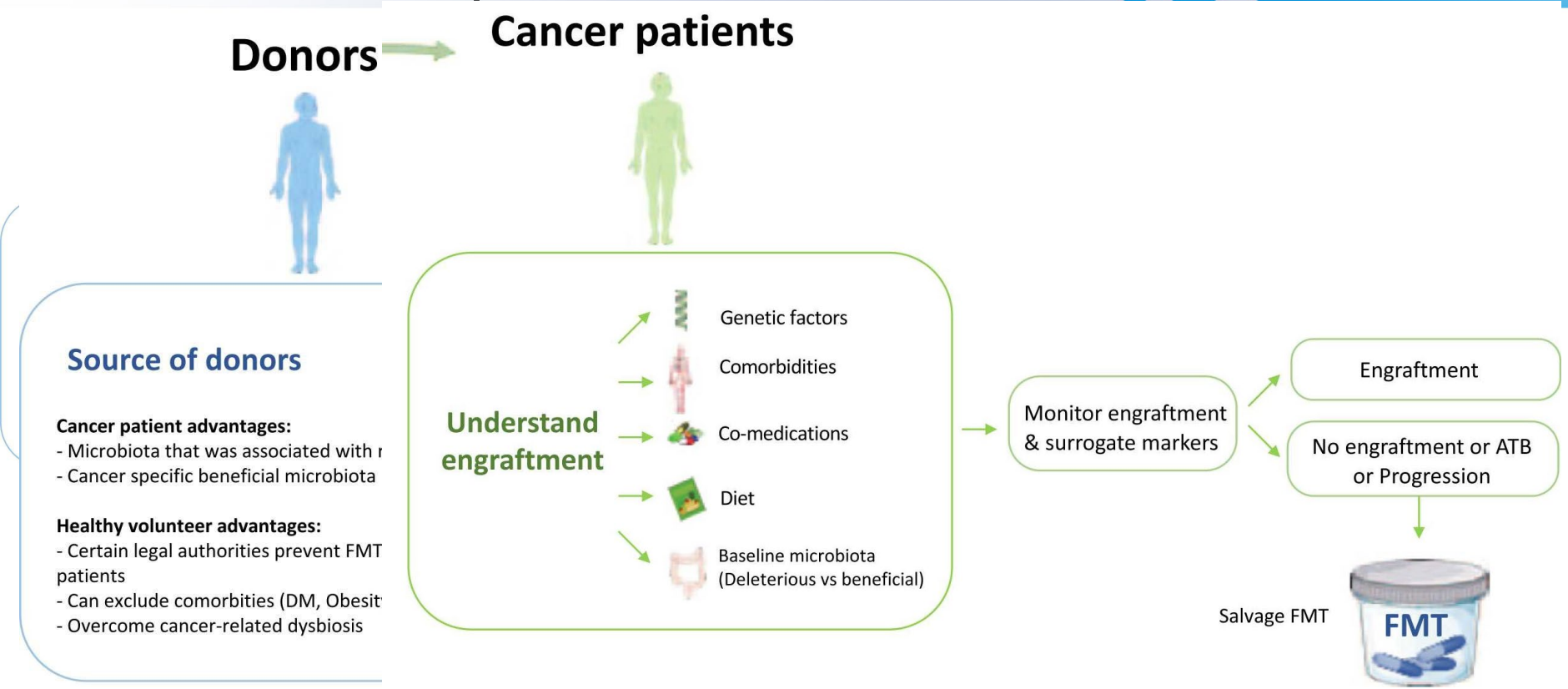
Microbiome therapeutic in metastatic RCC





Dizman et al Nature Medicine **28**, pages 704–712 (2022)

Framework for FMT in Cancer therapeutics



Jamal et al Seminars in Immunology (67), May 2023, 101754

Future Directions for Research

- Large, international cohort studies
- Prospective longitudinal sampling
- More focus on interventional, rather than purely observational studies
- Integration of microbiome analysis with other oncological research projects
- Standardization and transparency in reporting microbiome research

Where Are We at in 2023?

- True associations with *H pylori* and viral Hepatitis
- Interactome: A tripartite, multi-directional framework of environment, epigenetic/genetics and the microbiome
- No direct evidence: commensal microbiome causes cancer
- Plausible mechanisms by which the human microbiome may cause cancer
- 2023: No microbiome therapeutics available for cancers