

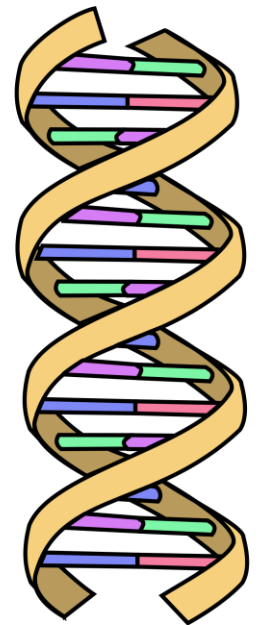
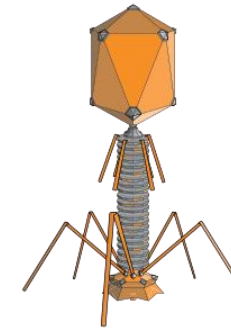
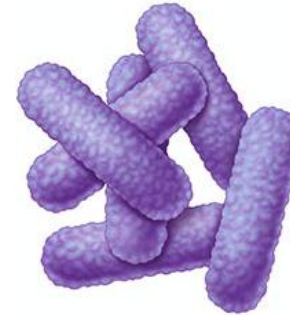
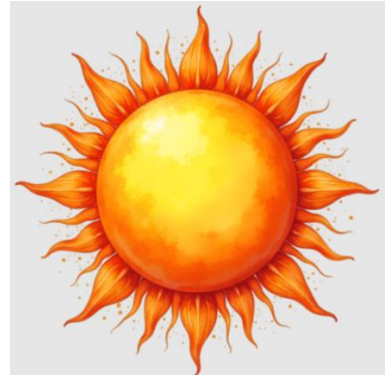


PROBIOTICI U ONKOLOGIJI

dr. sc. Marin Golčić, dr. med.
Specijalist internističke onkologije

KBC Rijeka Klinika za tumore
Medicinski fakultet Sveučilišta u Rijeci

ŠTO JE ZAPRAVO RAK?



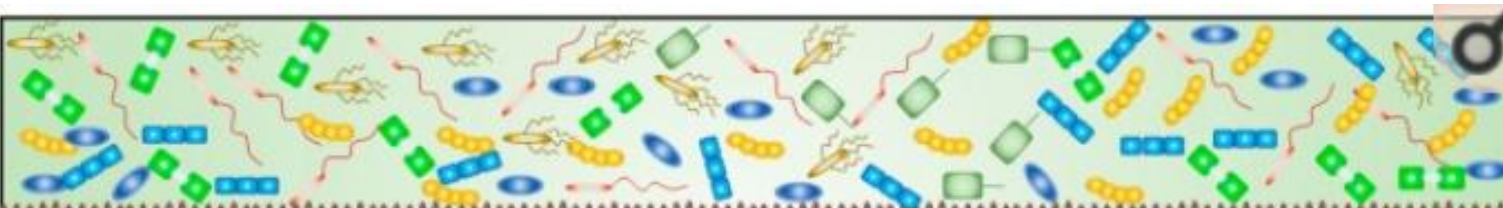
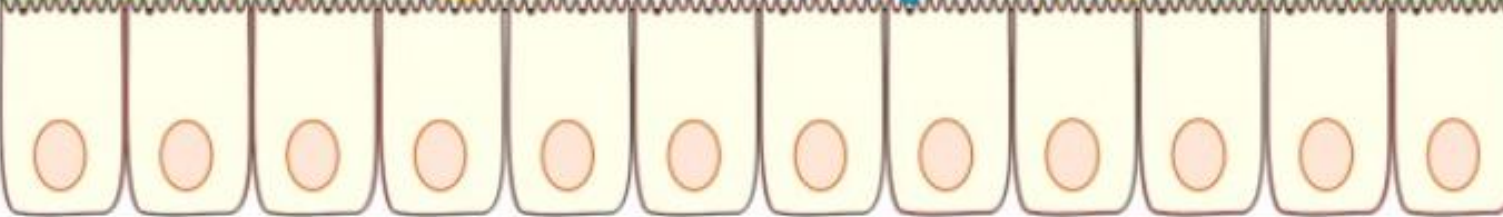
Rak = genetska bolest -
poremećaj gena za kontrolu rasta i
diobe stanica koji dovodi do
nekontroliranog rasta

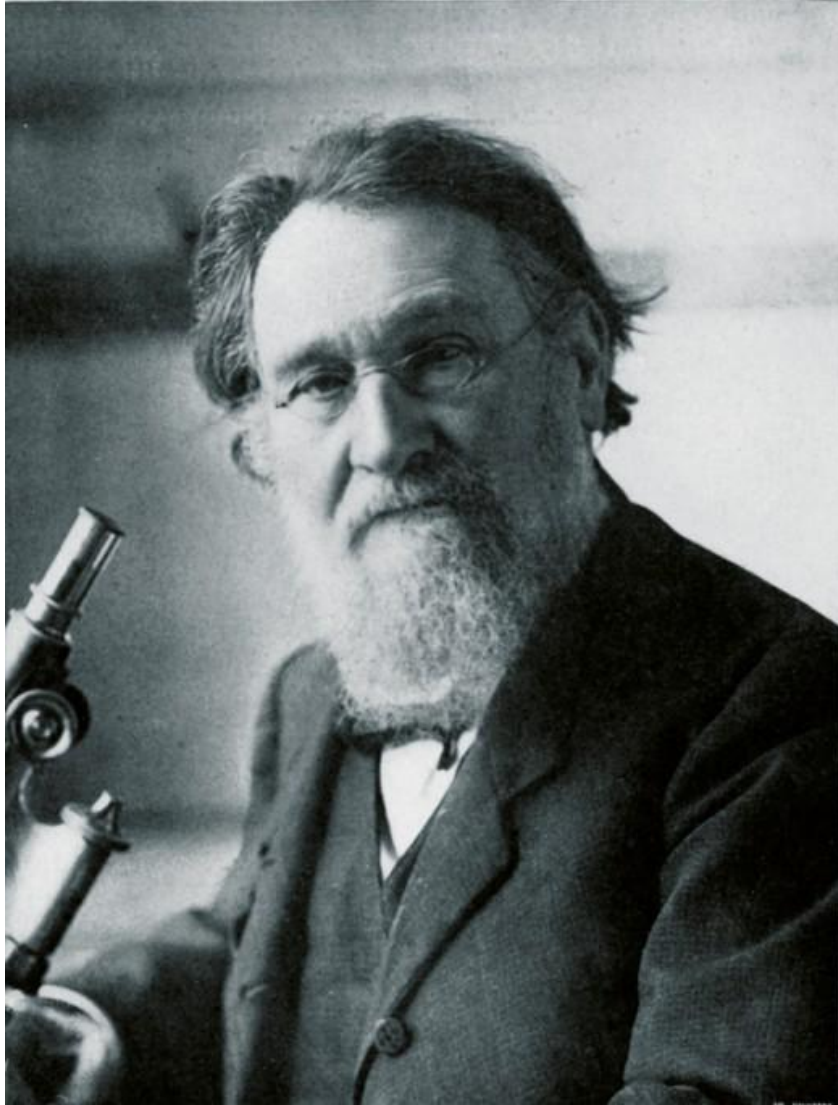
Rak <> kronična upala



BAKTERIJE I RAK?

I) BAKTERIJE ŠTITE OD TUMORA,

Mucus and Microbiota						
Gut Epithelium						
Role in Cancer	Anti-tumoral					
Microorganism	<i>Propionibacteria</i>	<i>S enterica</i>	<i>L casei</i>	<i>Gut bacteria spp</i>	<i>Gram negative bacteria</i>	<i>Lactobacilli spp</i>
Effectors	Butyrate, propionate	MPL	Ferricrome	Pyridoxine	LPS	unknown
Effects	Histone deacetylases inhibition	Used in anticancer vaccines as adjuvant	Apoptosis triggered in cancer cells	Anti-cancer immune response activation		



Recycling Metchnikoff: probiotics, the intestinal microbiome and the quest for long life



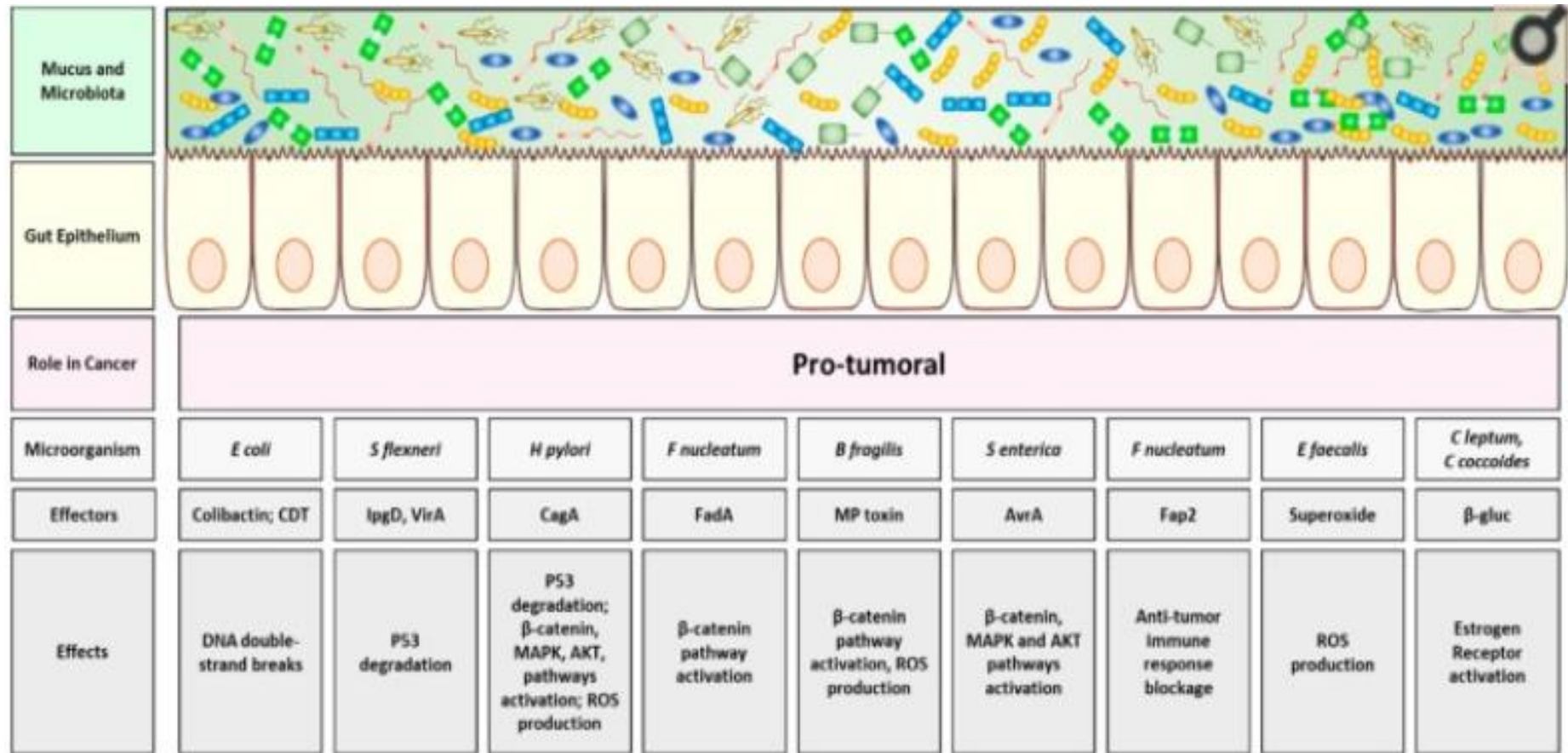
Philip A. Mackowiak^{1,2*}

¹ Medical Care Clinical Center, VA Maryland Health Care System, Baltimore, MD, USA

² Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

Over a century ago, Elie Metchnikoff theorized that health could be enhanced and senility delayed by manipulating the intestinal microbiome with host-friendly bacteria found in yogurt. His theory flourished for a time, then drifted to the fringe of medical practice before re-emerging in the mid-1990s as a concept worthy of mainstream medical attention. Metchnikoff also predicted the

2) BAKTERIJE UZROKUJU TUMORE,



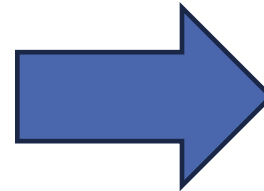
MEET *the* MICROBIOLOGIST

The Self-Experimentation
of Barry Marshall



Nobel Prize in
Physiology or
Medicine 2005

Peptic ulcer – an infectious disease!



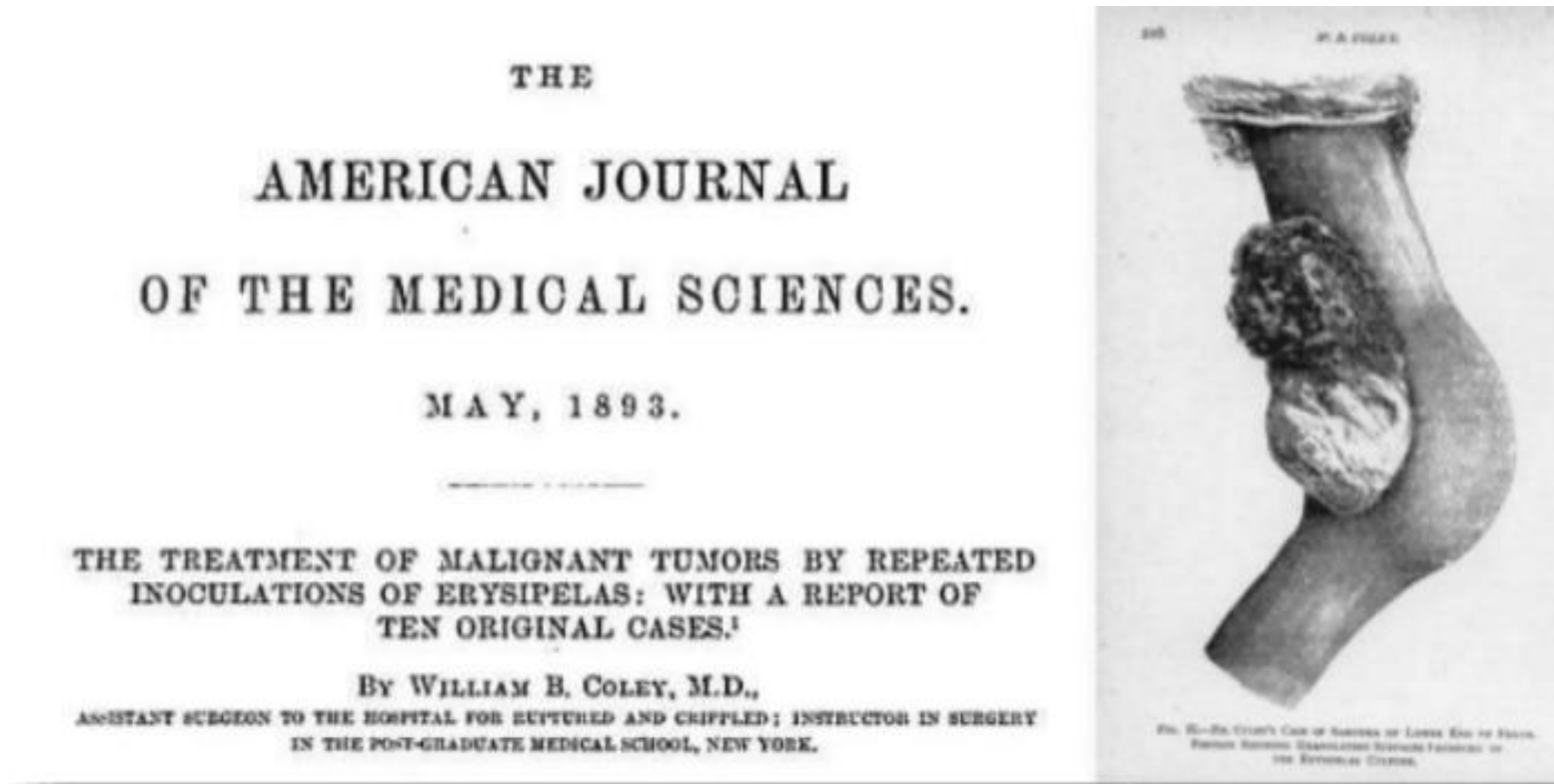
H. pylori infection is a **major risk factor for gastric cancer**, with a reported adjusted hazard ratio (HR) of **3.91**, and even higher for CagA-positive strains (HR of 6.27)

<https://www.gioncologynow.com/post/treatment-for-h-pylori-reduces-gastric-cancer-risk-even-in-those-with-family-history>

<https://www.nobelprize.org/prizes/medicine/2005/press-release/>

3) BAKTERIJE LIJEČE TUMORE

- Dr. William B. Coley je injicirao inaktivirani streptokok i *Serratia* u pacijenta s inoperabilnim sarkomom te je postigao smanjenje tumora, nastavio sa preko 1000 pacijenata u New Yorku...
- **1893.**



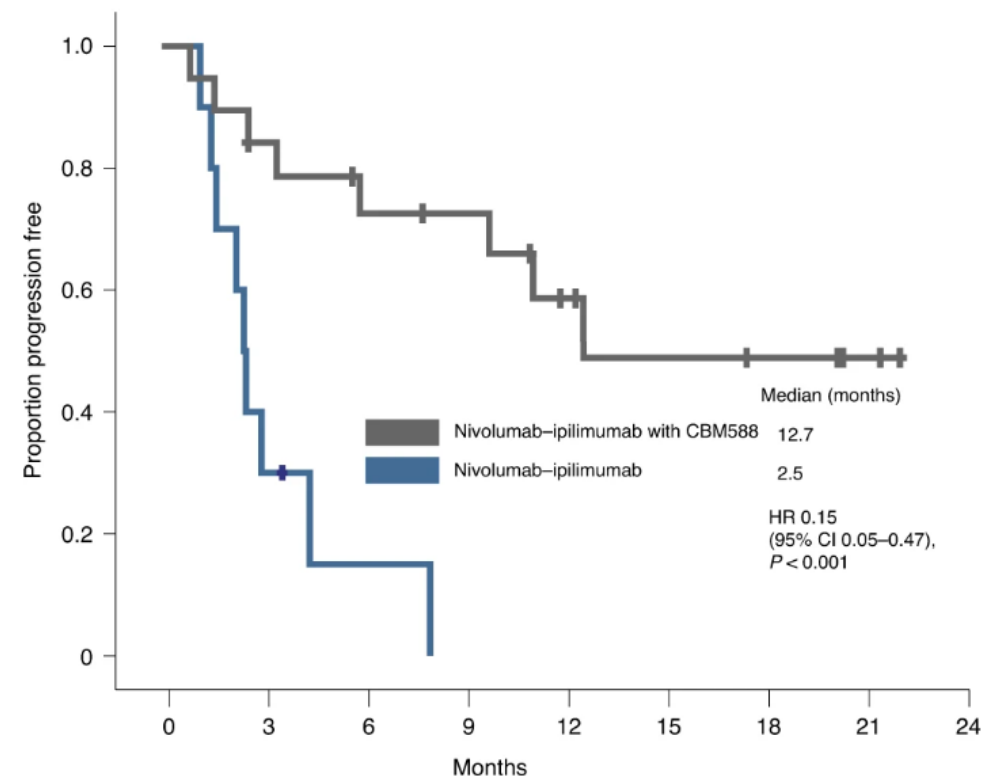
Article | [Open access](#) | Published: 28 February 2022

Nivolumab plus ipilimumab with or without live bacterial supplementation in metastatic renal cell carcinoma: a randomized phase 1 trial

[Nazli Dizman](#), [Luis Meza](#), [Paulo Bergerot](#), [Marice Alcantara](#), [Tanya Dorff](#), [Yung Lyou](#), [Paul Frankel](#), [Yujie Cui](#), [Valerie Mira](#), [Marian Llamas](#), [Joann Hsu](#), [Zeynep Zengin](#), [Nicholas Salgia](#), [Sabrina Salgia](#), [Jasnoor Malhotra](#), [Neal Chawla](#), [Alex Chehrazi-Raffle](#), [Ramya Muddasani](#), [John Gillece](#), [Lauren Reining](#), [Jeff Trent](#), [Motomichi Takahashi](#), [Kentaro Oka](#), [Seiya Higashi](#), ... [Sumanta K. Pal](#)  [+ Show authors](#)

[Nature Medicine](#) **28**, 704–712 (2022) | [Cite this article](#)

65k Accesses | **382** Citations | **531** Altmetric | [Metrics](#)



ZAŠTO SU STALA ISTRAŽIVANJA?

- Problem: metodologija
 - Različiti sastavi bakterijskih toksina, dozaža
 - Različita primjena (i.v./i.m./ direktno u tumor)
- Nekonzistentni rezultati (danas poznato preko 50 tipova sarkoma), i mnoge molekularne alteracije u svakom
- Razvoj radioterapije i kemoterapije
- **Manjak popratne tehnologije (DNA/RNA sekvencioniranje, monoklonalna antitijela)**



MIKROBIOM I RAK?

Microbiome

Microbiota

Bacteria

Archaea

Fungi

Protists

Algae

+ “Theatre of activity”

Microbial structural elements

Proteins/
peptides

Lipids

Poly-
sacharides

Nucleic acids
structural DNA/RNA

mobile genetic elements
incl. viruses/phages relic DNA

Internal/external structural elements

Environmental
conditions

Microbial metabolites

Signalling
molecules

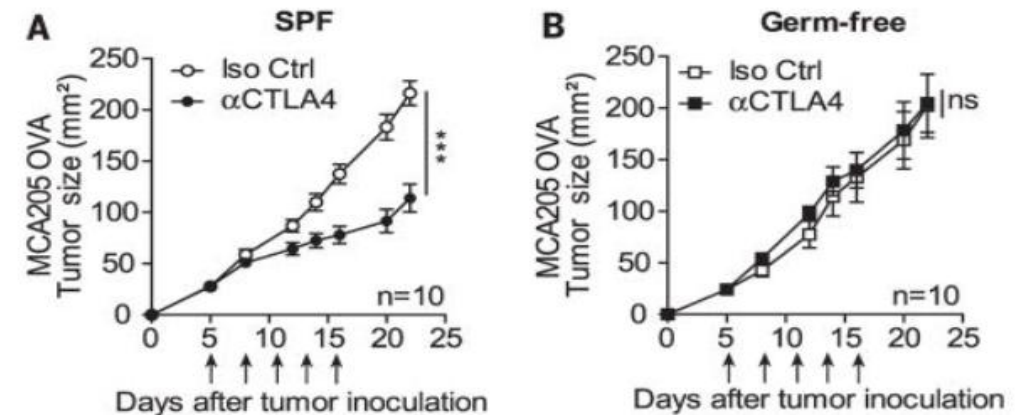
Toxins

(An)organic
molecules

Biome: a reasonably well defined habitat which has distinct bio-physio-chemical properties

VAŽNOST MIKROBIOMA U ONKOLOGIJI

- Glodavci sa 'sterilnim' crijevima ne reagiraju ili slabije reagiraju na **oksaliplatinu** (Iida N, Science 2013.), **cisplatinu** (Gui QF, Genet Mol Res, 2015), i **ciklofosfamid** (Viaud S, Science 2013)
- Imunoterapija ne utječe na tumorski volumen u miševa sa **sterilnim crijevima** - nadoknadom određenih bakterijskih sojeva učinak imunoterapije se vraća
- Ključni lijekovi u onkologiji



MIKROBIOM KAO PROGNOŠTIČKI FAKTOR

Table 1 Studies on gut microbiota target innate and adaptive immune cells to promote ICI efficacy

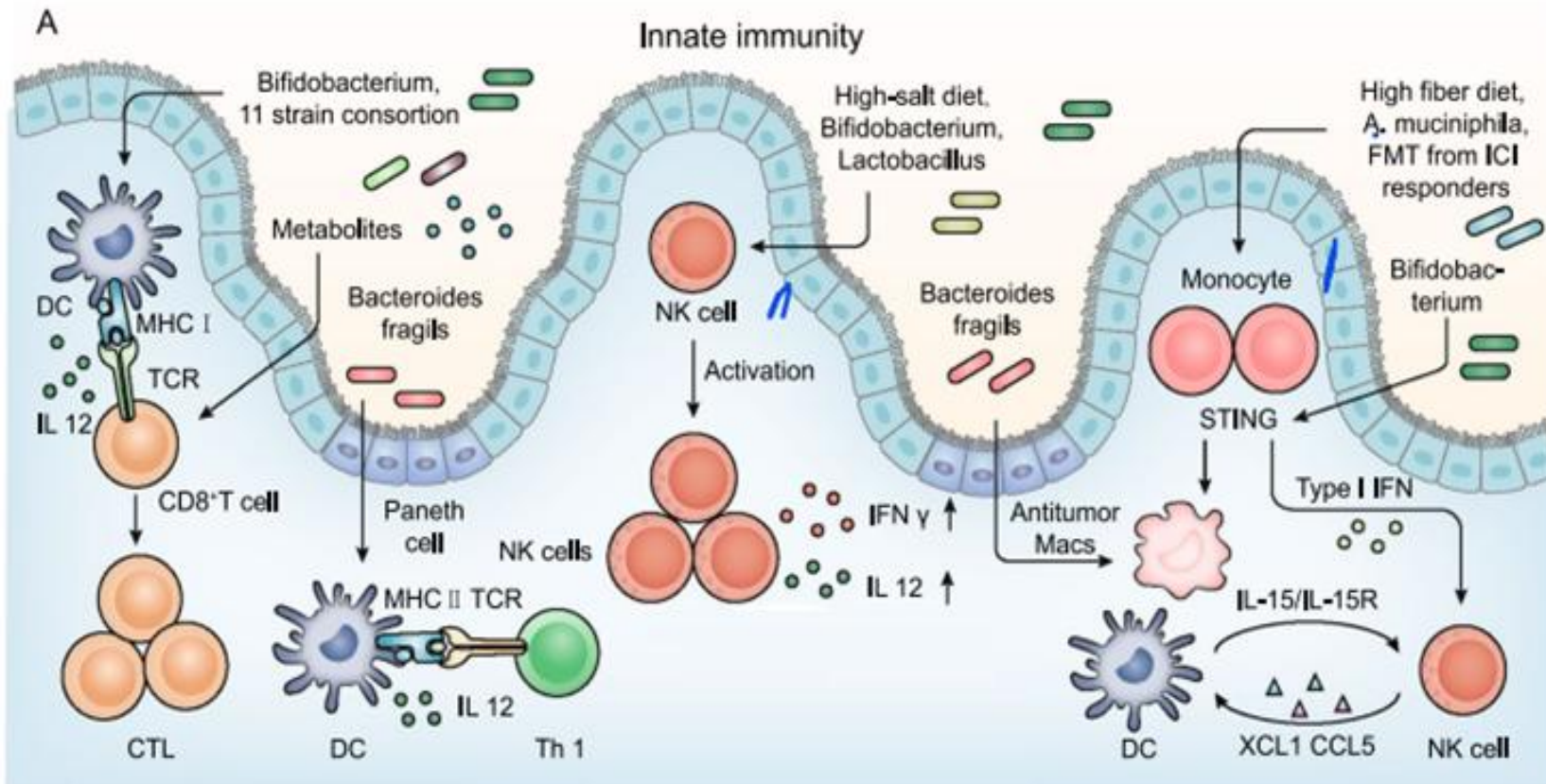
Year	Cancer types	ICI	Beneficial gut microbiota	Interventions factors and/or biological effects	References
2015	Melanoma	PD-L1 inhibitor	<i>Bifidobacterium</i>	DCs and CD8+ T cells	[16]
2015	Melanoma	CTLA4 inhibitor	<i>Bacteroides fragilis</i>	Tumor draining lymph nodes: Th1; TME: DCs	[17]
2018	NSCLC, RCC, Urothelial carcinoma	PD-1 inhibitor, CTLA4 inhibitor	<i>Akkermansia muciniphila</i>	TME: IL-12 and CCR9 + CXCR3 + CD4 + T lymphocytes	[31]
2018	Melanoma	PD-1 inhibitor	<i>Faecalibacterium</i> , <i>Ruminococcaceae</i> , <i>Clostridiales</i>	Mice receiving R-FMT: Increased innate effector cells and decreased suppressive myeloid cells; Mice receiving NR-FMT: Increased RORγt T helper 17 cells	[32]
2018	Melanoma	PD-L1 inhibitor	<i>Bifidobacterium longum</i> , <i>Collinsella aerofaciens</i> , <i>Enterococcus faecium</i>	Mice receiving R-FMT: Augmented T cell responses	[33]
2017	Melanoma	CTLA4 inhibitor	<i>Faecalibacterium</i>	CD4+ T cells and CD25	[49]
2019	Adenocarcinoma, melanoma	PD-1 inhibitor	Eleven strains	IFNγ + CD8 T cell, CD103 + DC, and MHC Ia	[50]
2020	CRC, Intestinal cancer, Bladder cancer, melanoma	PD-L1 inhibitor, CTLA4 inhibitor	<i>Bifidobacterium pseudolongum</i> , <i>Akkermansia muciniphila</i> , <i>Lactobacillus johnsonii</i> , <i>Olsenella species</i>	DCs and Th1; Inosine: A _{2A} R on Th1	[51]
2020	Colon cancer, T cell lymphoma	CD47 inhibitor	<i>Bifidobacterium</i>	STING signaling and DCs	[52]
2021	Melanoma	PD-1 inhibitor	<i>Enterococcaceae</i> , <i>Enterococcus</i> , <i>Streptococcus australis</i>	FMT-R patients: TME: CD8 + T cell; Gut: APC	[15]
2021	Melanoma	PD-1 inhibitor	<i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> families, <i>Bifidobacteriaceae</i> , <i>Coriobacteriaceae</i> families	FMT-R patients: PBMCs: CD8+ T cells and MAIT cells; TME: CD8 + T cells, HLA II, CD74 and GZMK FMT-NR patients: Increased myeloid cells and CD4+ regulatory T cells	[14]
2021	Lymphoma, Colon carcinoma, Melanoma, Breast carcinoma	ICI	A high-fiber diet, <i>Akkermansia</i>	Monocytes, Macrophages	[53]

APC: antigen presenting cell; A_{2A}R: adenosine 2A receptor;

Tek djelomično
preklapanje
„dobrih
bakterija”

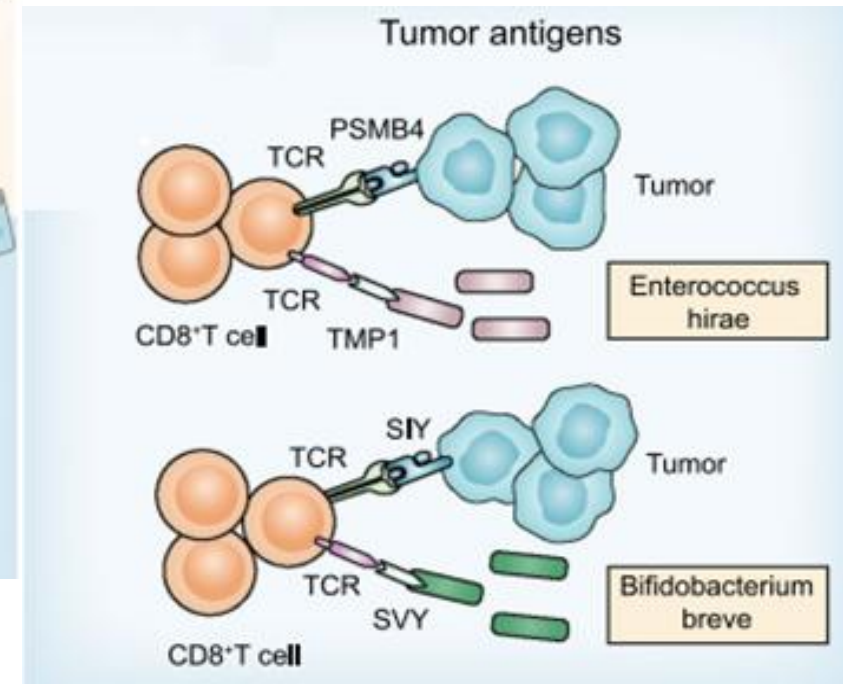
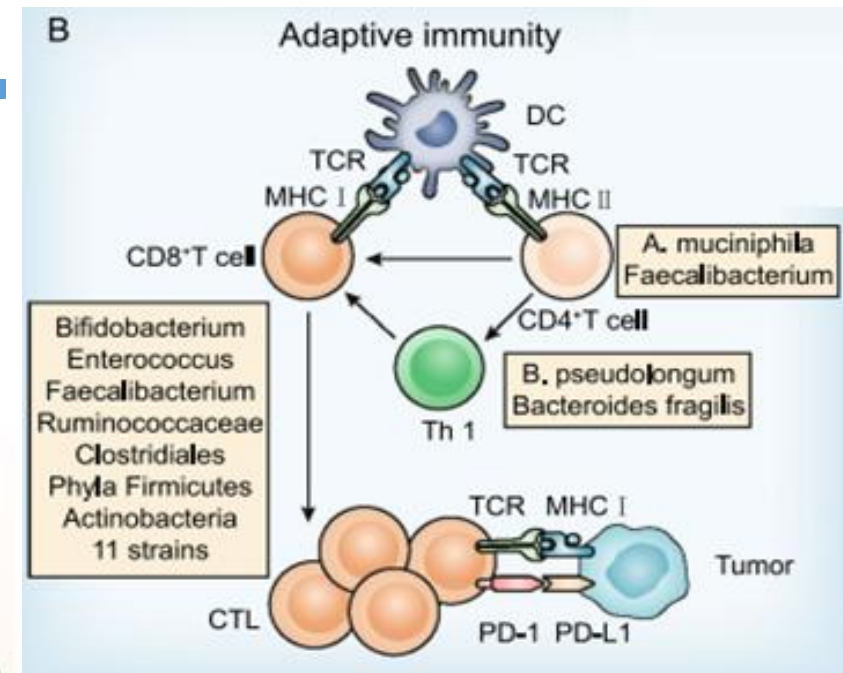
„LOŠE BAKTERIJE” KONZISTENTNIJE

ZAŠTO MIKROBIOM UTJEČE NA RAK?



STING = microbiota-derived stimulator of interferon genes

Lu et al. Journal of Hematology & Oncology (2022) 15:47





PROBIOTICI I RAK?

-
- 1) Učinci na prevenciju malignih oboljenja
 - 2) Učinci povezani sa suportivnom terapijom**
 - 3) Učinci povezani s onkološkom terapijom

PREVENCIJA MALIGNIH OBOLIJEENJA

- 1) *L. Bacillus Shirota* redovno korištenje > 4 puta tjedno od adolescencije s 35% nižim rizikom za karcinom dojke te 40-50% nižim karcinomom mjehura
- 2) *L. Rhamnosus* i *Propionibacterium freudenreichii* može utjecati na razinu aflatoxina (rizik za karcinom jetre).
- 3) Probiotici mogu smanjiti rizik od postoperativnih komplikacija nakon operacije karcinoma debelog crijeva

PROBLEM

- 1) Vrlo mali broj istraživanja
- 2) Izrazito teško dizajnirati kvalitetne studije
 - 1) Faktori koji utječu na rezultate
 - 2) 'Compliance' pacijenata
 - 3) Veliki broj pacijenata potreban
- 3) Dvojbeni rezultati koji su jako teško primjenjivi u svakodnevnom životu
 - 1) Koliko dugo uzimati probiotike?
 - 2) U kojoj dozi?
 - 3) Utjecaj hrane i lijekova?
 - 4) Individualnost mikrobiote

SUPPORTIVNA TERAPIJA

- **Proljev:** s irinotekanom do 50-90% bolesnika
 - Rani: direktni kolinergični učinak na crijeva
 - Kasni: citotoksični učinak na stanice crijeva, gubitak integriteta mukoze i malapsorpcijski efekt
- Trenutne smjernice: loperamid i promjena prehrane

Table 2 Study results.

	Placebo arm		Probiotic arm		p-value
	N	%	N	%	
Primary endpoint					
Diarrhea grade 3 or 4	4	17.4	0	0.0	0.11
Secondary endpoints					
Diarrhea grade 1	8	34.8	5	21.7	0.51
Diarrhea grade 2	2	8.7		17.4	0.67
Diarrhea grade 3	3	13.0	0	0.0	0.23
Diarrhea grade 4	1	4.3	0	0.0	1.00
Diarrhea all grades	14	60.9	9	39.1	0.24
Enterocolitis	2	8.7	0	0.0	0.49
Bloating	4	17.4	2	8.7	0.67
Usage of antidiarrheal drugs					
Loperamid (mean days)	10.4	—	4.5	—	0.45
Loperamid (mean tablets)	37.7	—	5.9	—	0.49
Diphenoxylate (days)	9.1	—	0.3	—	0.08
Diphenoxylate (tablets)	21.3	—	0.3	—	0.08

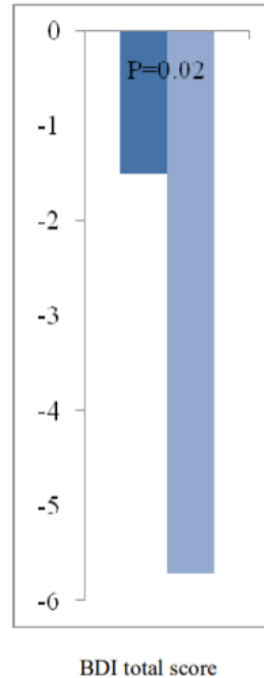
- Mego i suradnici: redukcija gradus III/IV proljeva s **17% na 0%** tijekom davanja irinotekana
 - *Bifidobacteria i Lactobacillus*
 - 6 tjedana
 - Bez dodatnih nuspojava

SUPPORTIVNA TERAPIJA

- **Depresija** je čest problem u onkoloških bolesnika
- Prevalencija kliničke depresije se procjenjuje na oko **25%**
- Moguća povezanost s preživljenjem

U bolesnika s karcinomom pluća i bez znakova depresije preživljenje je bilo **14 mjeseci**, u odnosu na **6,8 mjeseci** u bolesnika s depresijom (HR 1.9)

- Utjecaj probiotika na depresiju u onkoloških bolesnika – ne znamo, ali:
- Više kliničkih studija na ne-onkološkim bolesnicima
 - Bolesnici s velikom depresivnom epizodom > 8 tjedana placebo vs ***L.acidophilus, casei i B. bifidum***
 - Poboljšanje u Beck Depression Index (-5.7 vs -1.5)



Akkasheh G et al: Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition*. **2016** Mar

Kreber et al: Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. *Psychooncology* 2014.

Arrieta et al: Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Ann Surg Oncol* 2013.

Pinto-Sanchez MI et al: Probiotic Bifidobacterium longum NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome. *Gastroenterology* **2017**. Aug

KONTROVERZA S IMUNOTERAPIJOM

Meta-Analysis > [Front Immunol.](#) 2025 Mar 21;16:1538969. doi: 10.3389/fimmu.2025.1538969.
eCollection 2025.

Assessing the impact of probiotics on immunotherapy effectiveness and antibiotic-mediated resistance in cancer: a systematic review and meta-analysis

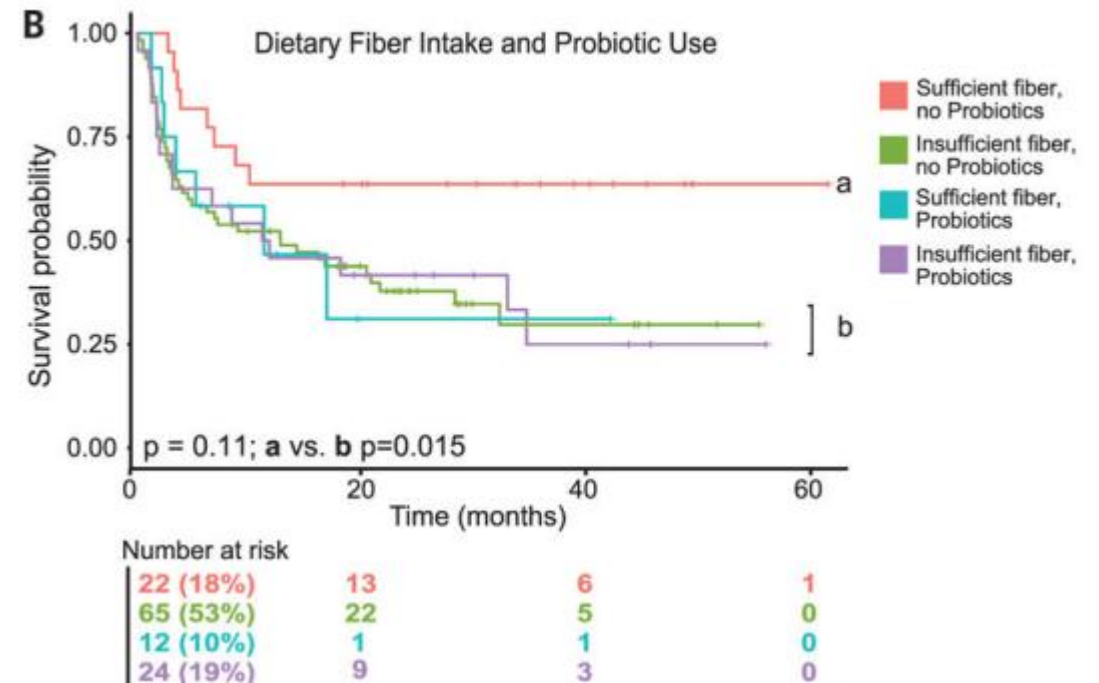
Shuya Zhao ^{1 2}, Zian Lu ¹, Fangmin Zhao ³, Shihuan Tang ⁴, Lishan Zhang ¹, Cuiling Feng ²

= 0.002). For non-small cell lung cancer (NSCLC) patients exposed to antibiotics, the use of probiotics was associated with superior OS ($I^2 = 0.0\%$; HR=0.45, 95% CI: 0.34-0.59, $p < 0.001$) and PFS ($I^2 = 0.0\%$; HR=0.48, 95% CI: 0.38-0.62, $p < 0.001$) when compared to non-users. Subgroup differences were observed

Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

CHRISTINE N. SPENCER ^{ID}, JENNIFER L. MCQUADE ^{ID}, VANCHESWARAN GOPALAKRISHNAN ^{ID}, JOHN A. MCCULLOCH ^{ID}, MARIE VETIZOU ^{ID},
ALEXANDRIA P. COGDILL ^{ID}, MD A. WADUD KHAN ^{ID}, XIAOTAO ZHANG ^{ID}, MICHAEL G. WHITE ^{ID}, [...] JENNIFER A. WARGO ^{ID} +80 authors [Authors Info](#)
[& Affiliations](#)

SCIENCE





LoE	Guideline
III	The panel suggests that <i>probiotics containing Lactobacillus</i> spp. may be beneficial for the prevention of RT-induced or RT-CT–induced diarrhea in patients with pelvic malignancy.

ŠTO JE PROBLEM S PROBIOTICIMA I ONKOLOGIJOM?

PROBLEMI S DIZAJNOM STUDIJA

- ‘Doze?’
 - ✦ Varijabilnost koncentracije od 1×10^8 do 20×10^{10}
 - ✦ Doziranje od 1x1 do 4x1
- Sastav?
 - ✦ Od 1 do 10 sojeva bakterija
 - ✦ Pomoćne tvari
- Trajanje uzimanja?
 - ✦ 4 tjedna do 10 mjeseci pa i nekoliko godina
- Kontroverzni rezultati
 - Metabolički i upalni parametri
 - Jako mali broj studija na ljudima, rijetke potvrdne studije, „more” nekvalitetnih studija
 - Sigurnost – opisani rezultati i sepse u imunokompromitiranih bolesnika



Clinical Gastroenterology and Hepatology

Available online 14 March 2018

In Press, Corrected Proof ?



The Unregulated Probiotic Market

Claudio de Simone  

 [Show more](#)

<https://doi.org/10.1016/j.cgh.2018.01.018>

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the remark "success depends on the preparation..." Dr.
Coley, in London in 1911, following recognition at Guy's

„Isti probiotik” = različit učinak

Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

Niv Zmora ¹¹ • Gili Zilberman-Schapira ¹¹ • Jotham Suez ¹¹ • ... Zamir Halpern ¹² ✉ • Eran Segal ¹² ✉ • Eran Elinav ^{12, 13} ✉ • [Show all authors](#) • [Show footnotes](#)

Published: September 6, 2018 • DOI: <https://doi.org/10.1016/j.cell.2018.08.041>

predictive baseline host and microbiome features, but indistinguishable by probiotics presence in stool. Consequently, probiotics induced a transient, individualized impact on mucosal community structure and gut transcriptome. Collectively, empiric probiotics supplementation may be limited in universally and persistently impacting the gut mucosa, meriting development of new personalized probiotic approaches.

Isti probiotik = različit učinak

„...all the current knowledge
emphasises the **complexity**
nad **bidirectionality**...
between microbiome and
cancer.”

ZAKLJUČAK

- Bakterije mogu uzrokovati, sprječavati i liječiti rak
- Rak može mijenjati sastav mikrobioma
- Studije s probioticima imaju izazove zbog dizajna studija, nereguliranog tržišta, individualnosti ljudi
- Kada koristiti probiotik u onkologiji:
 - **Prevenција proljeva tijekom RT ili KT/RT tumora zdjelice**
 - Liječenje proljeva tijekom kemoterapije
 - Uz antibiotik tijekom onkološkog liječenja
- Koji probiotik koristiti:
 - Onaj koji je baziran na laktobacilima i bifidobacilima, višesojni > monosojni
 - One tvrtke koje ulažu u znanstvena istraživanja



Hvala na pažnji!