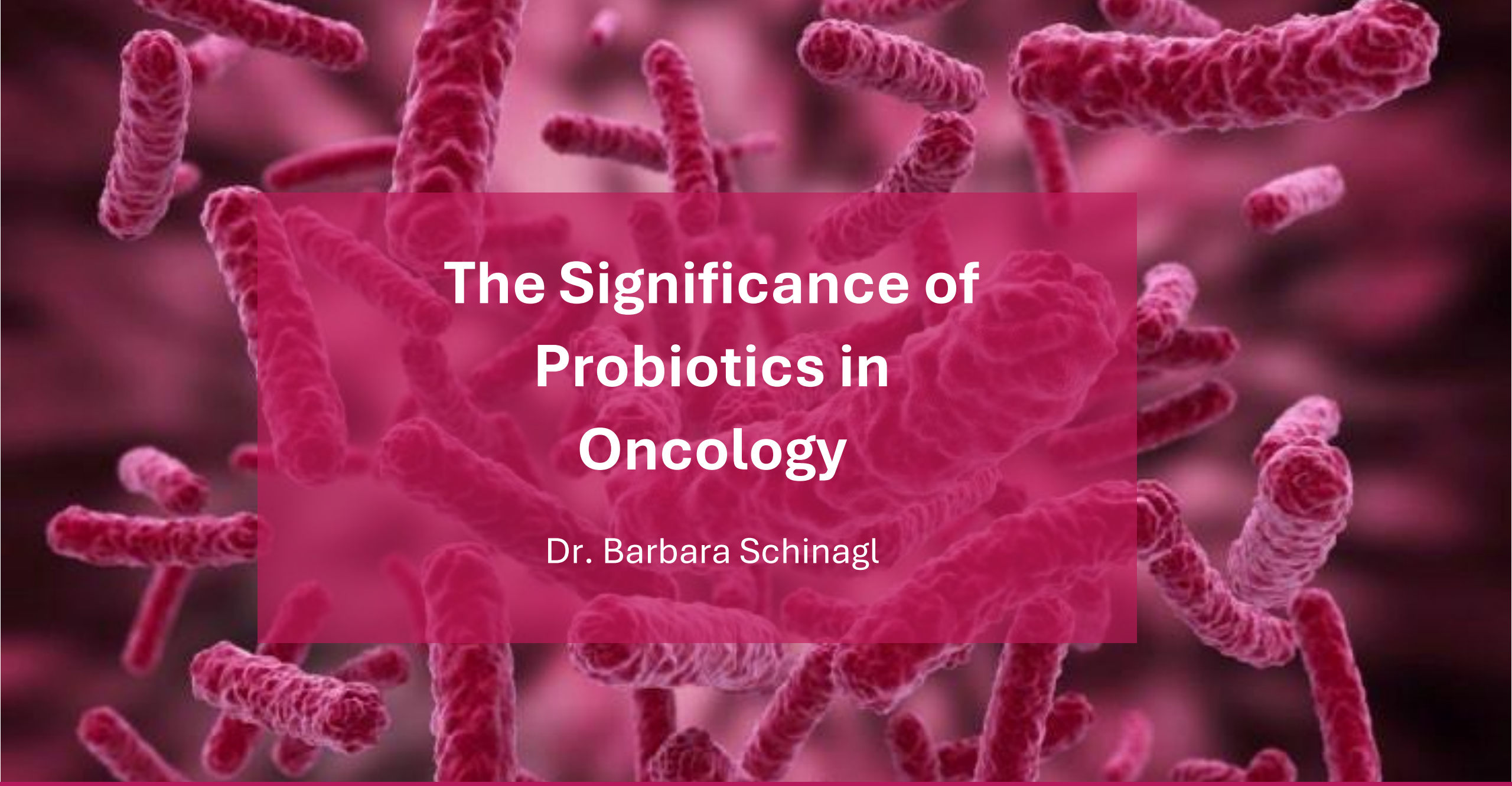
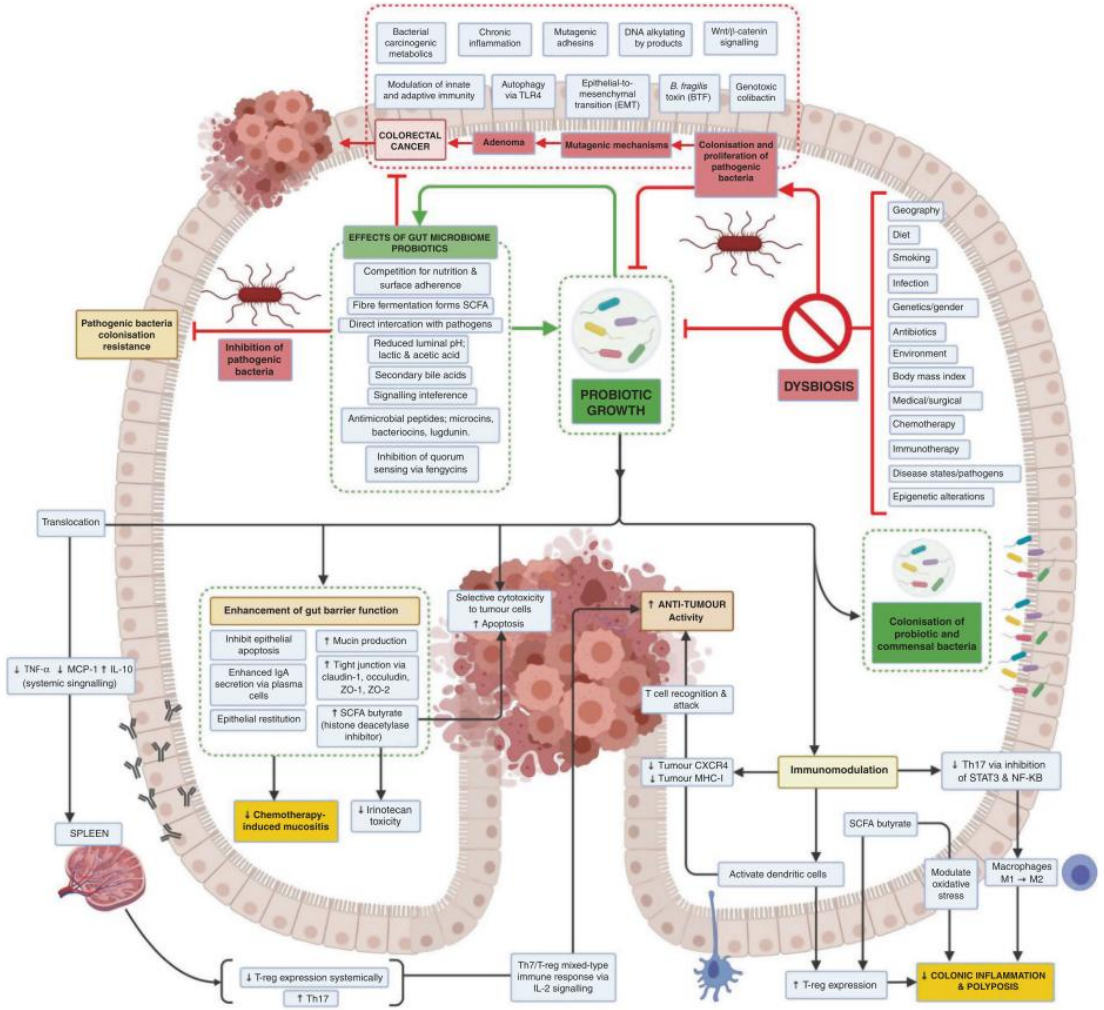


The Significance of Probiotics in Oncology

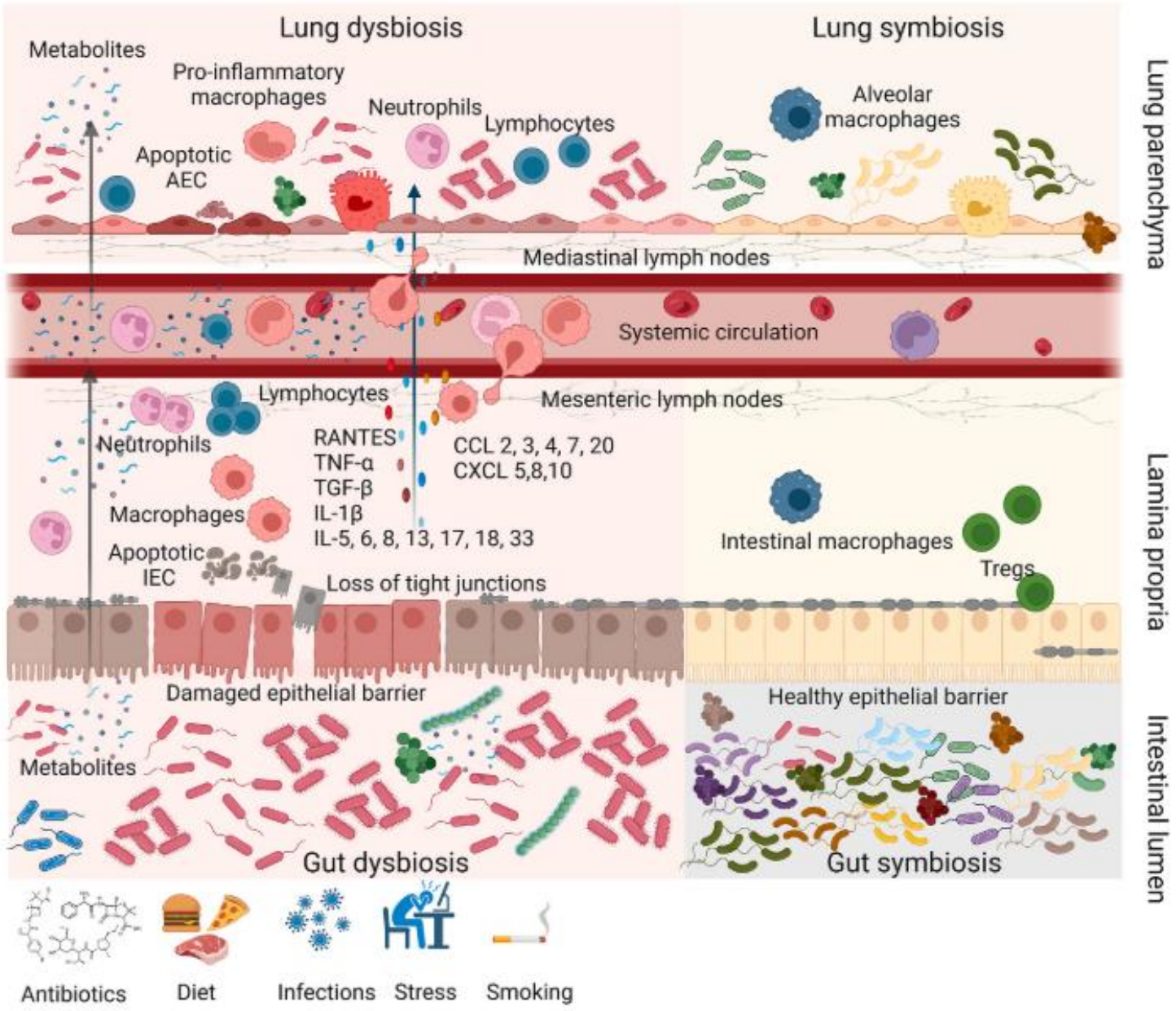
Dr. Barbara Schinagl

The gut microbiome: what the oncologist ought to know



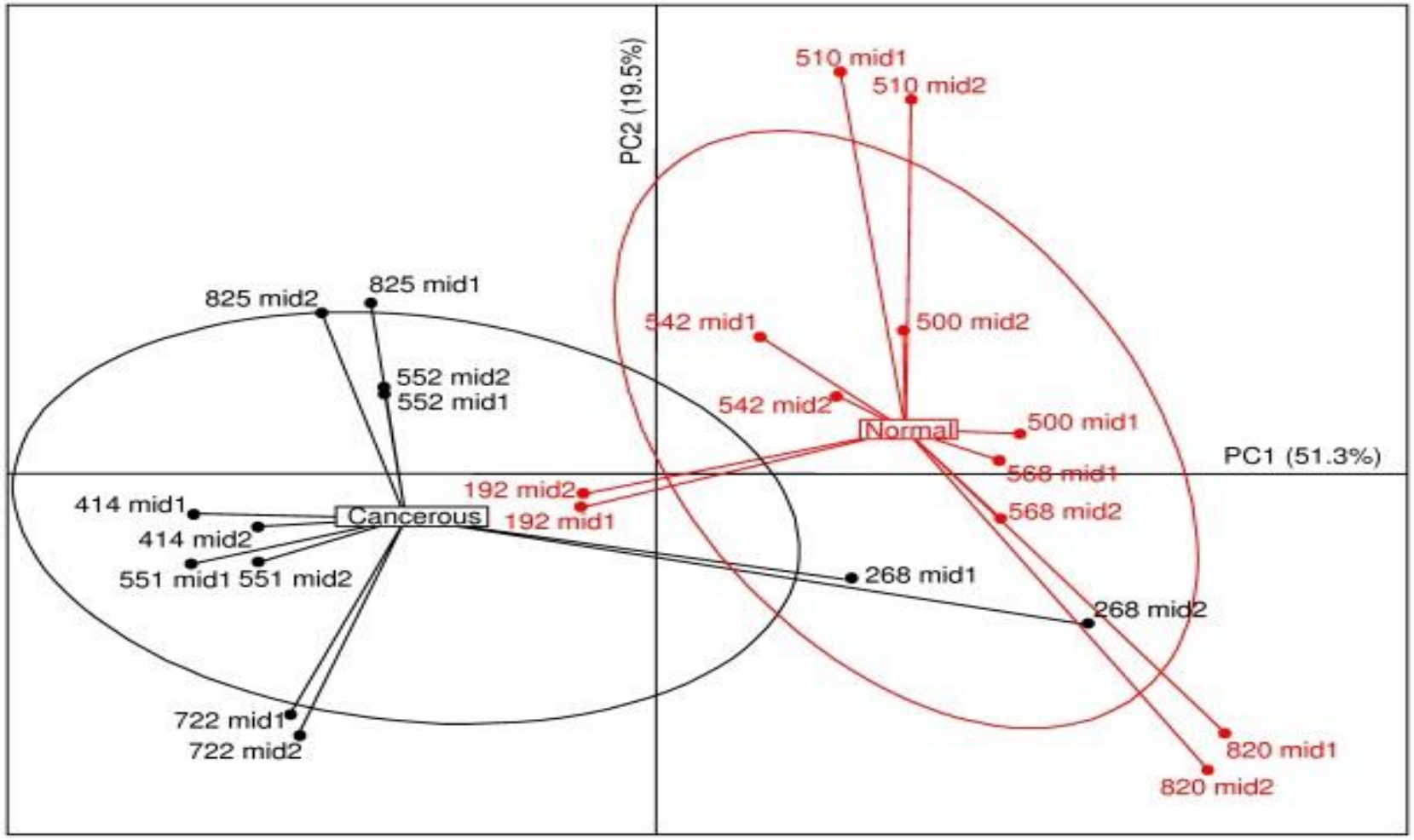
Lee, K. A., Luong, M. K., Shaw, H., Nathan, P., Bataille, V., & Spector, T. D. (2021). The gut microbiome: what the oncologist ought to know. In British Journal of Cancer (Vol. 125, Issue 9, pp. 1197–1209). Springer Nature. https://doi.org/10.1038/s41416-021-01467-x

Gut microbiota dysbiosis is a major trigger for dysbiosis in the whole body and vice versa



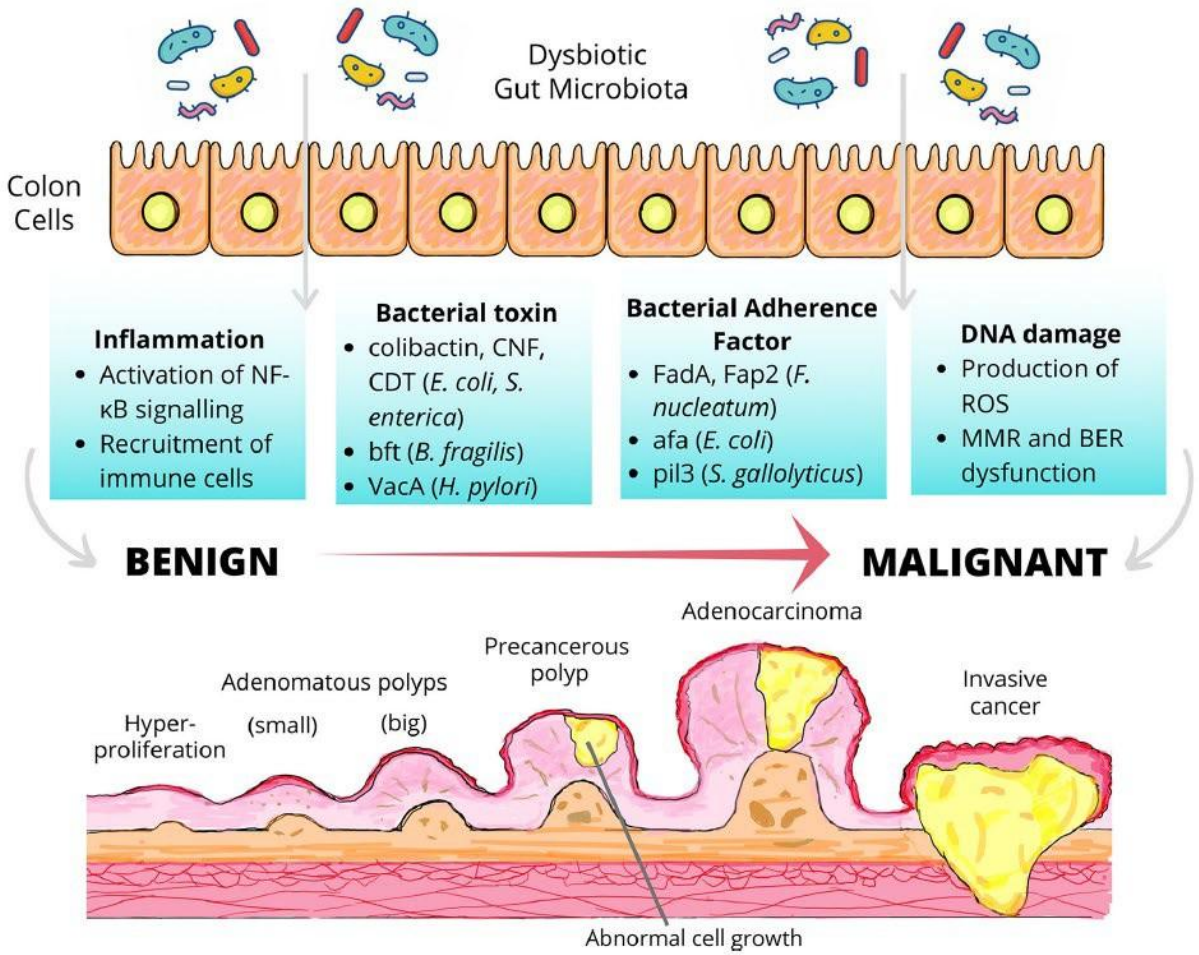
Eladham, M. W., Selvakumar, B., Saheb Sharif-Askari, N., Saheb Sharif-Askari, F., Ibrahim, S. M., & Halwani, R. (2024). Unraveling the gut-Lung axis: Exploring complex mechanisms in disease interplay. In Heliyon (Vol. 10, Issue 1). Elsevier Ltd.

Clear difference in the microbiota between healthy and cancer patients



Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, et al. (2011) Microbial Dysbiosis in Colorectal Cancer (CRC) Patients. PLoS ONE 6(1): e16393.

Carcinogenesis: Correlation between diet and microbiome



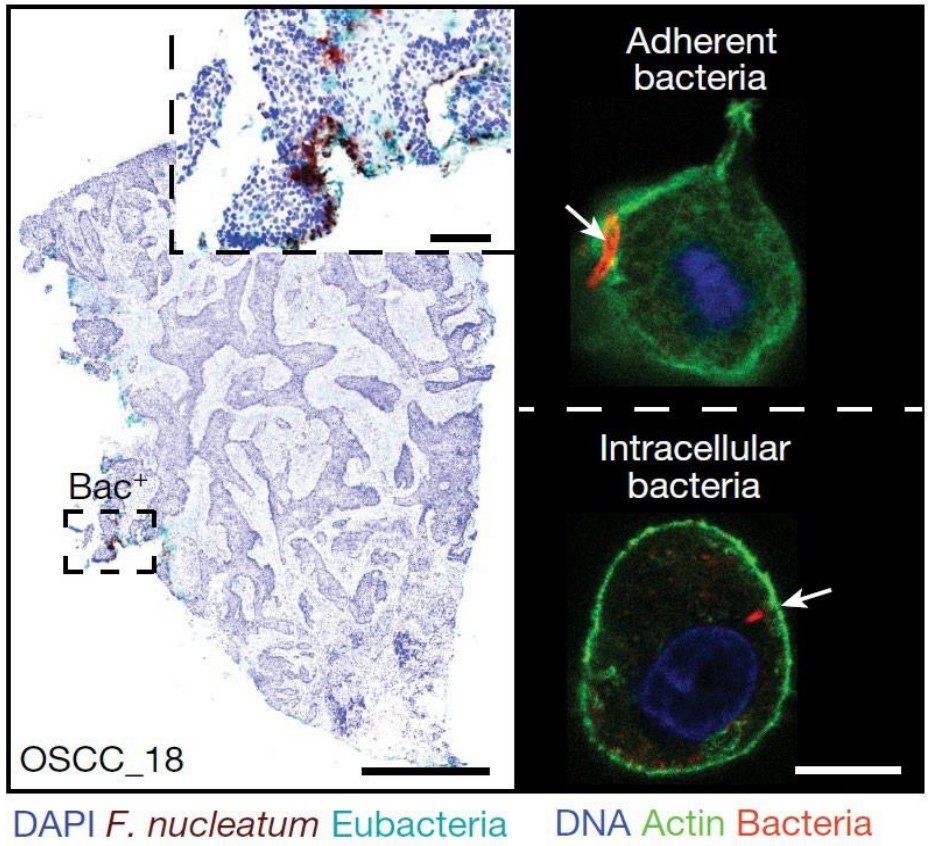
Dysbiotic gut microbiota causes **abnormal cell growth and mutations** due to:

- inflammation
- bacterial toxins
- activation of fibroblasts
- ROS production
- DNA damage

Loke YL et al. Colon carcinogenesis: the interplay between diet and gut microbiota. Frontiers in Cellular and Infection Microbiology. 2020, 10:603086. doi: 10.3389/fcimb.2020.60308612

Fusobacterium nucleatum

F. nucleatum (red) infected primary tumor



- Is found in oral and intestinal microbiome
- Can enter human cells and disrupt erythrocytes
- Associated with colon cancer (abundance of *F. nucleatum* in cancer patients is 1000 times higher!)

1. Wu Y, Guo S, Chen F, et al. Fn-Dps, a novel virulence factor of Fusobacterium nucleatum, disrupts erythrocytes and promotes metastasis in colorectal cancer. PLoS Pathog 2023;19:e1011096.
2. Galeano Nino JL, Wu H, LaCourse KD, et al. Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer. Nature 2022;611:810-817.

Probiotics –
a new approach to support
cancer therapy

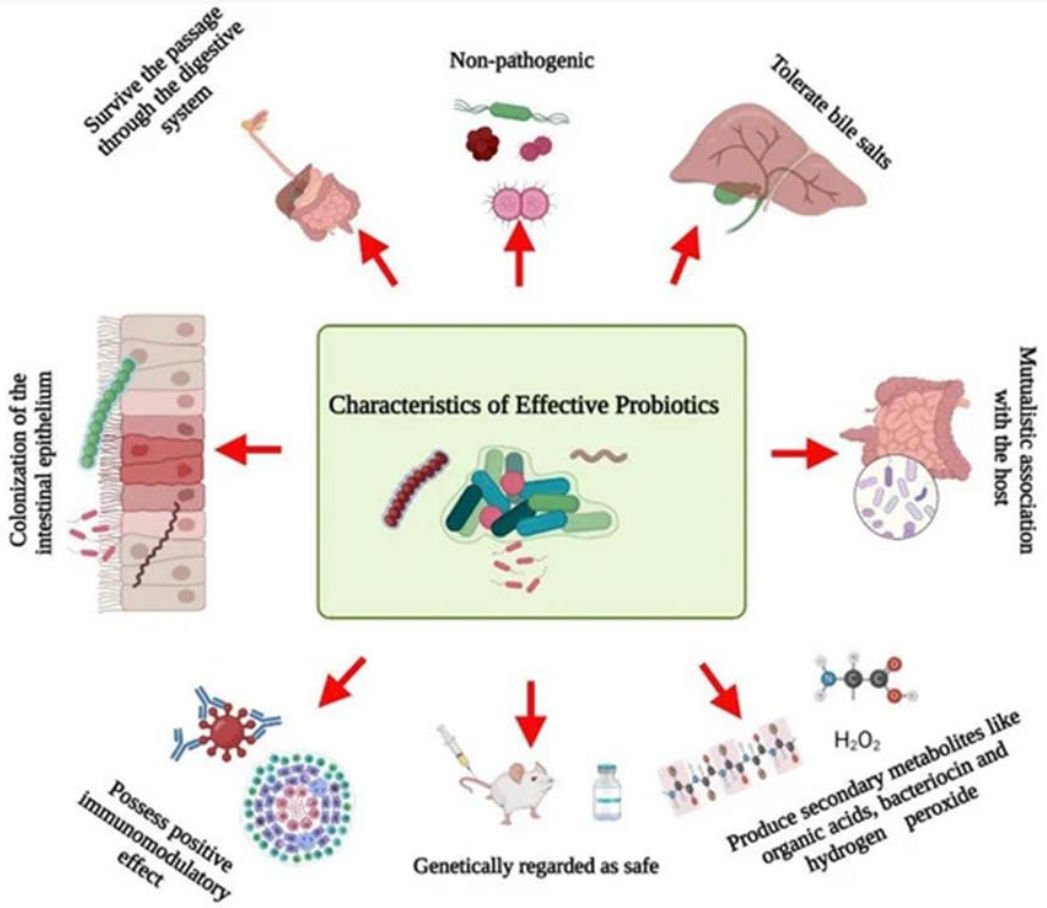
Where do probiotics act?

Cancer prevention or treatment

- ✓ Colorectal cancer
- ✓ Liver cancer
- ✓ Pancreatic cancer
- ✓ breast, cancer
- ✓ lung cancer

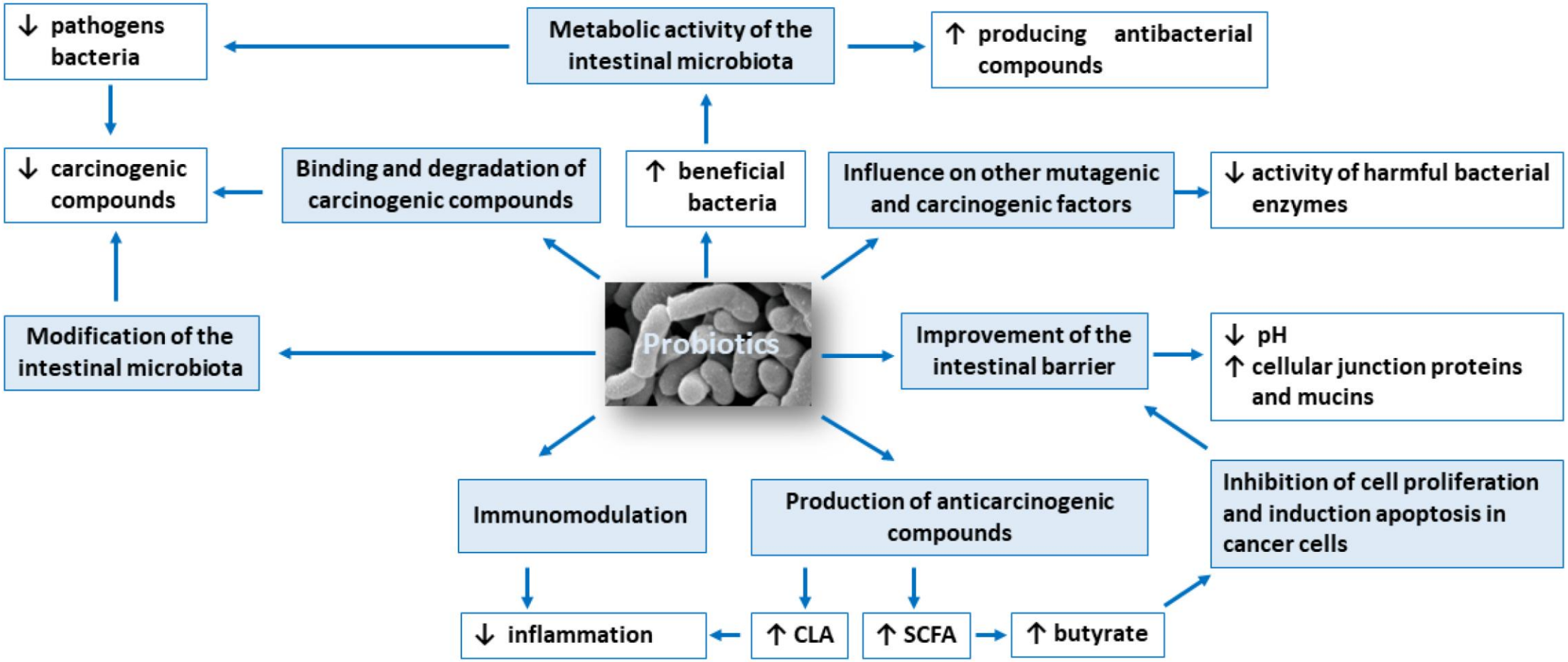
Improvement of side effects of anti-tumor treatment

- Diarrhea
- Mucositis
- Graft-versus-host disease
- Other inflamation reaction



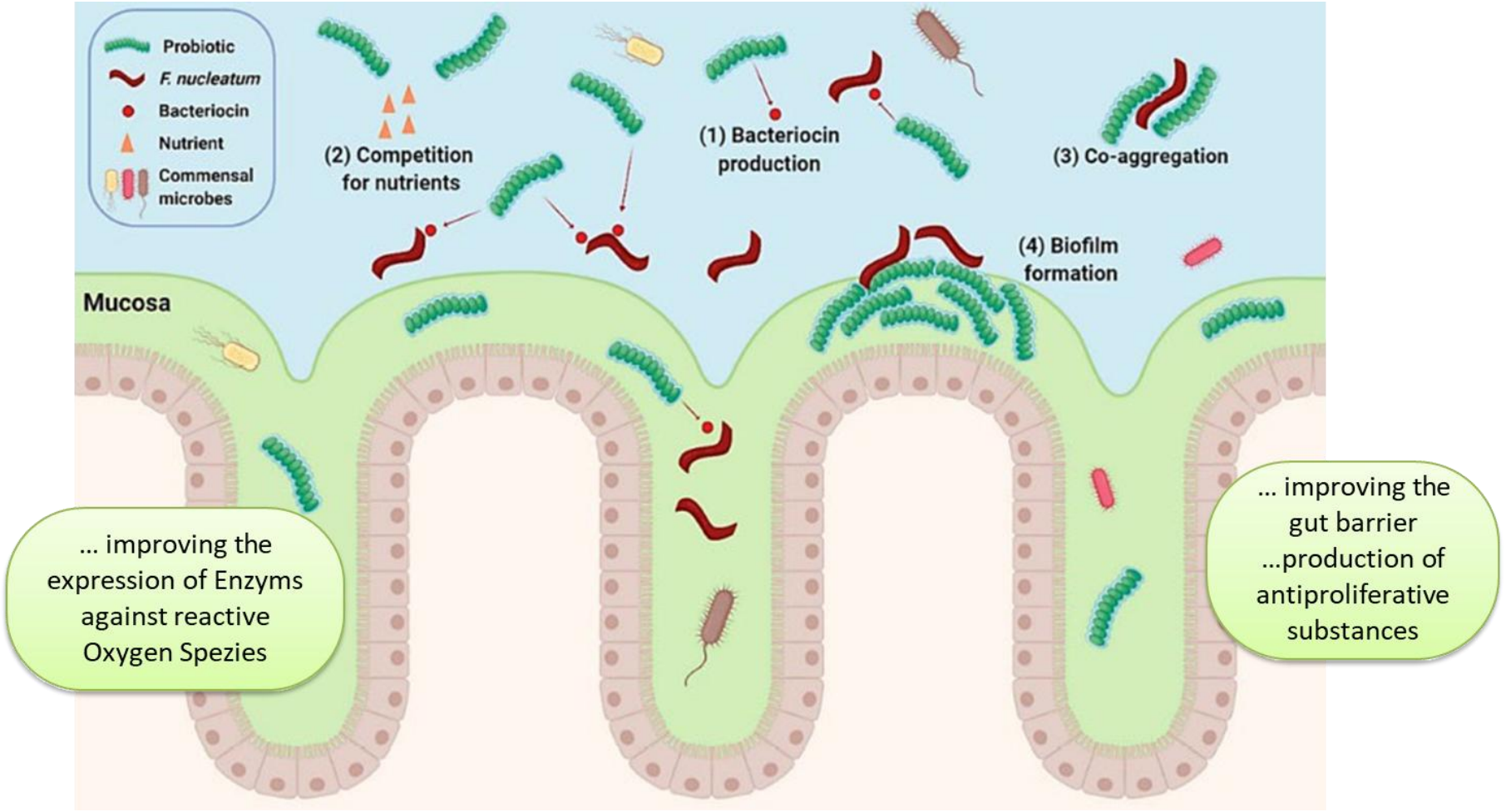
Lu, K., Dong, S., Wu, X., Jin, R., & Chen, H. (2021). Probiotics in Cancer. In Frontiers in Oncology (Vol. 11). Frontiers Media S.A.
Sankarapandian V, Venmathi Maran BA, Rajendran RL, Jogalekar MP, Gurunagarajan S, Krishnamoorthy R, Gangadaran P, Ahn B-C. An Update on the Effectiveness of Probiotics in the Prevention and Treatment of Cancer. Life. 2022; 12(1):59.

Probiotics in cancer prevention



Śliżewska K, Markowiak-Kopeć P, Śliżewska W. The Role of Probiotics in Cancer Prevention. Cancers (Basel). 2020 Dec 23;13(1):20. doi: 10.3390/cancers13010020. PMID: 33374549; PMCID: PMC7793079.

Probiotic mechanisms for the elimination of pathogens as *F. nucleatum* from our intestine



Lawrence GW, Begley M, Cotter PD, et al. Potential Use of Biotherapeutic Bacteria to Target Colorectal Cancer-Associated Taxa. Int J Mol Sci 2020;21.

How can we alleviate the negative side effects of cancer treatment?

Chemotherapy and radiation cause:

- Reduction of microbiome diversity
- Exacerbation of inflammation in the gut
- Destruction of intestinal barrier function
- Malnutrition & cachexia

80% of all patients in cancer therapy suffer from severe intestinal problems

- Diarrhea
- High risk for infections with pathogens (*F. nucleatum*, *C. difficile*)
- Delays/enforced stop in cancer therapies because of health status

Significant alleviation of mucositis symptoms during radiotherapy through the oral commensal bacterium *Streptococcus salivarius K12*

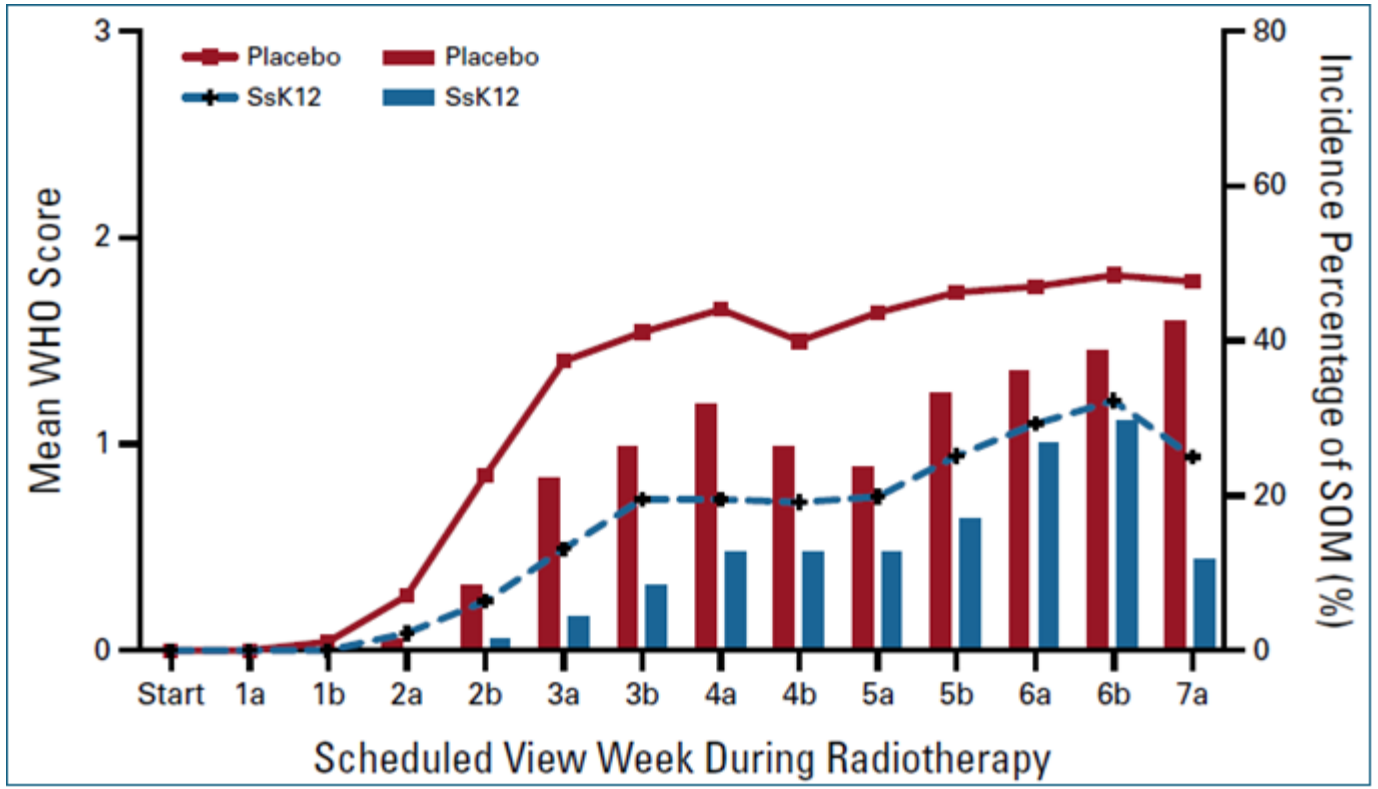
Original Reports | Head and Neck Cancer

Streptococcus salivarius K12 Alleviates Oral Mucositis in Patients Undergoing Radiotherapy for Malignant Head and Neck Tumors: A Randomized Controlled Trial

Xingchen Peng, MD[1]; Zixia Li, MDS[2]; Yiyan Pei, MM[1]; Shuhao Zheng, DDS[2]; Jinchi Liu, MDS[2]; Jingjing Wang, MD[1]; Ruidan Li, MD[1]; and Xin Xu, DDS[2]

DOI https://doi.org/10.1200/JCO.23.00837

Streptococcus salivarius K12 reduces oral mucositis in radiotherapy patients



Signifikant reduction of oral mucositis during the radiotherapy of malignant head- and neck tumors through oral ***Streptococcus salivarius K12*** supplementation.

Peng X, Li Z, Pei Y, Zheng S, Liu J, Wang J, Li R, Xu X. Streptococcus salivarius K12 Alleviates Oral Mucositis in Patients Undergoing Radiotherapy for Malignant Head and Neck Tumors: A Randomized Controlled Trial. J Clin Oncol. 2024 Apr 20;42(12):1426-1435.

Successful application of probiotics in oncology

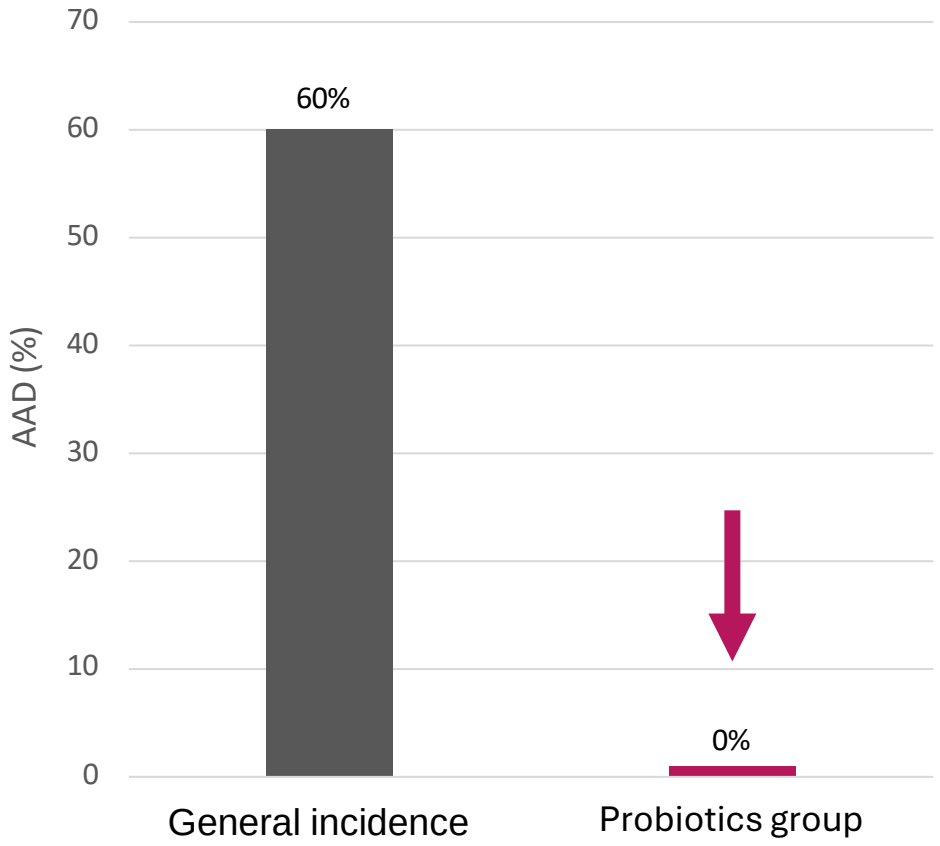
- Application of an specifically developed multispecies probiotic during chemotherapy leads to a reduction in nausea and diarrhea, thereby improving the feasibility of the planned therapy and reducing the frequency of therapy discontinuations.

OA Markus Hell, SALK,
2011

- Not one single case of a *Clostridium difficile*-associated infection within 3 years by using indication-specific multispecies probiotics in all patients in the intensive care unit of the University clinic in Graz.

Univ. Prof. Dr. Voith Augustin
Univ Clinic Graz
2023

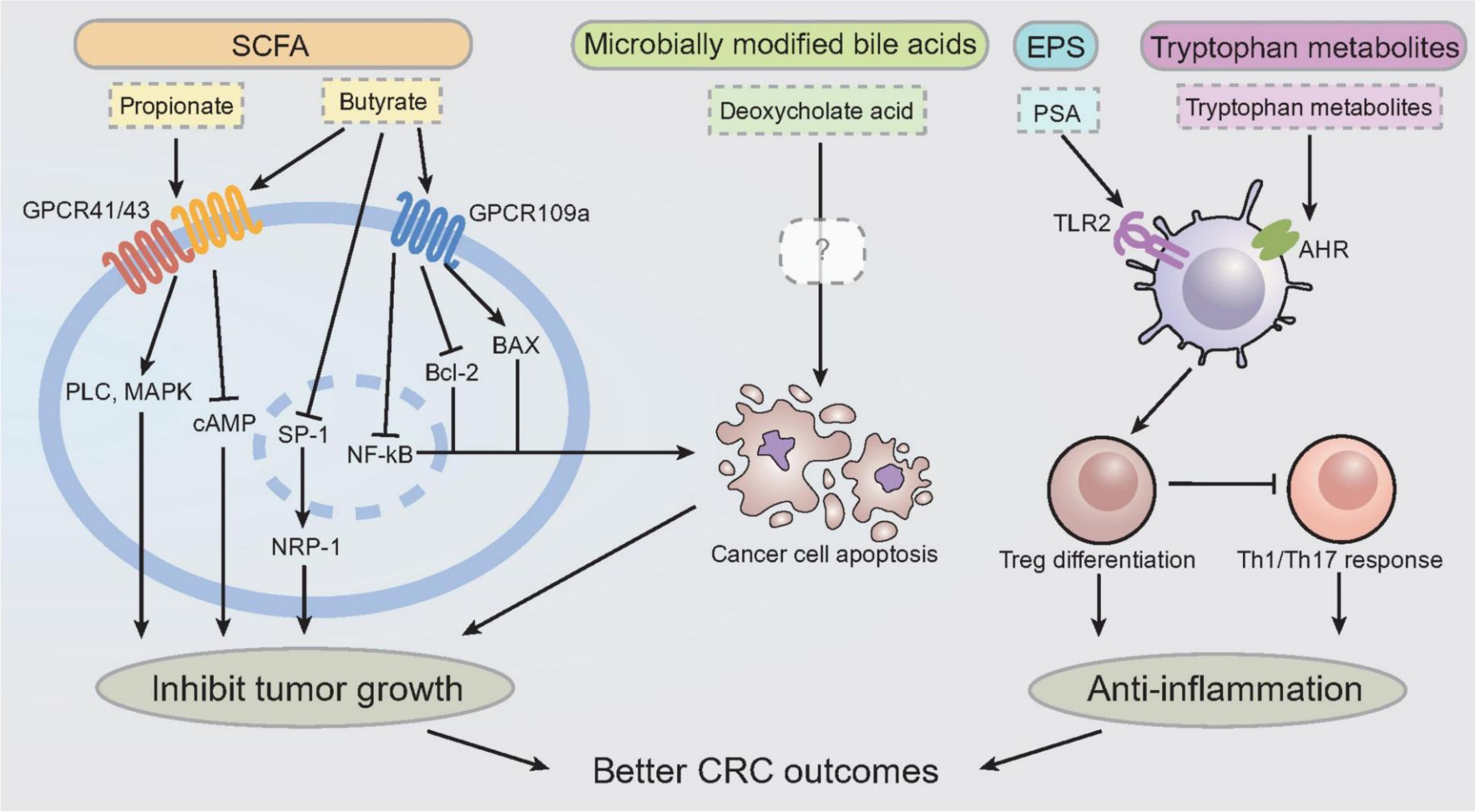
Reduction of diarrhea in patients during chemotherapy



Successful reduction of diarrhea to **0%!** during chemotherapy using a specific multispecies probiotic.

Rabl H., Der positive Effekt eines Multispezies-Probiotikums bei chirurgischen Patienten mit Antibiose. CHAZ 2021.

Beneficial insights into postbiotics against colorectal cancer



Song, D., Wang, X., Ma, Y., Liu, N. N., & Wang, H. (2023). Beneficial insights into postbiotics against colorectal cancer. In Frontiers in Nutrition (Vol. 10). Frontiers Media S.A. https://doi.org/10.3389/fnut.2023.1111872

Metabolites of a medically relevant multispecies probiotic are highly effective against pathogens and have positive effects on the microbiome

nutrients

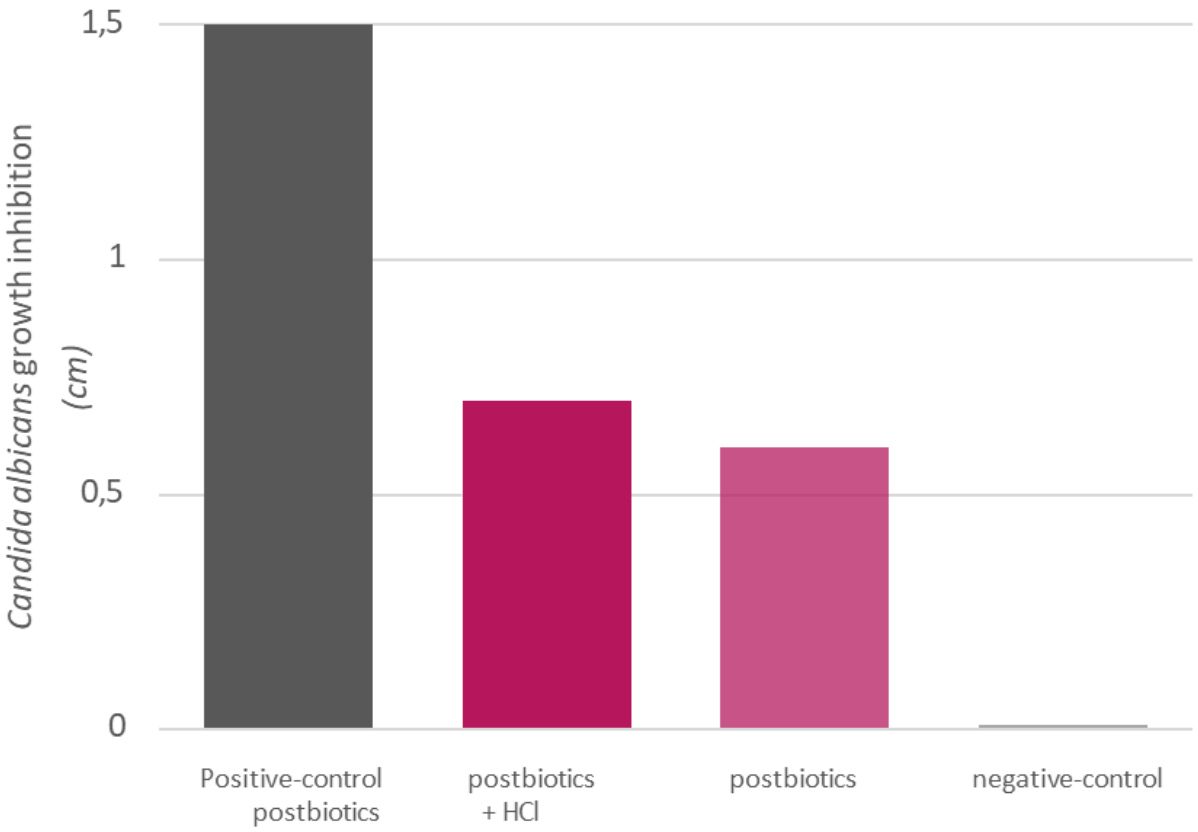
MDPI

Article

Insights into the Composition of a Co-Culture of 10 Probiotic Strains (OMNi BiOTiC® AAD10) and Effects of Its Postbiotic Culture Supernatant

Bernhard Kienesberger [1], Beate Obermüller [1,*], Georg Singer [1], Christoph Arneitz [1], Paolo Gasparella [1], Ingeborg Klymiuk [2], Angela Horvath [3,4], Vanessa Stadlbauer [3,4], Christoph Magnes [5], Elmar Zügner [5], Pablo López-García [4], Slave Trajanoski [6], Wolfram Miekisch [7], Patricia Fuchs [7], Holger Till [1] and Christoph Castellani [1]

The growth of pathogens is significantly reduced through the postbiotic



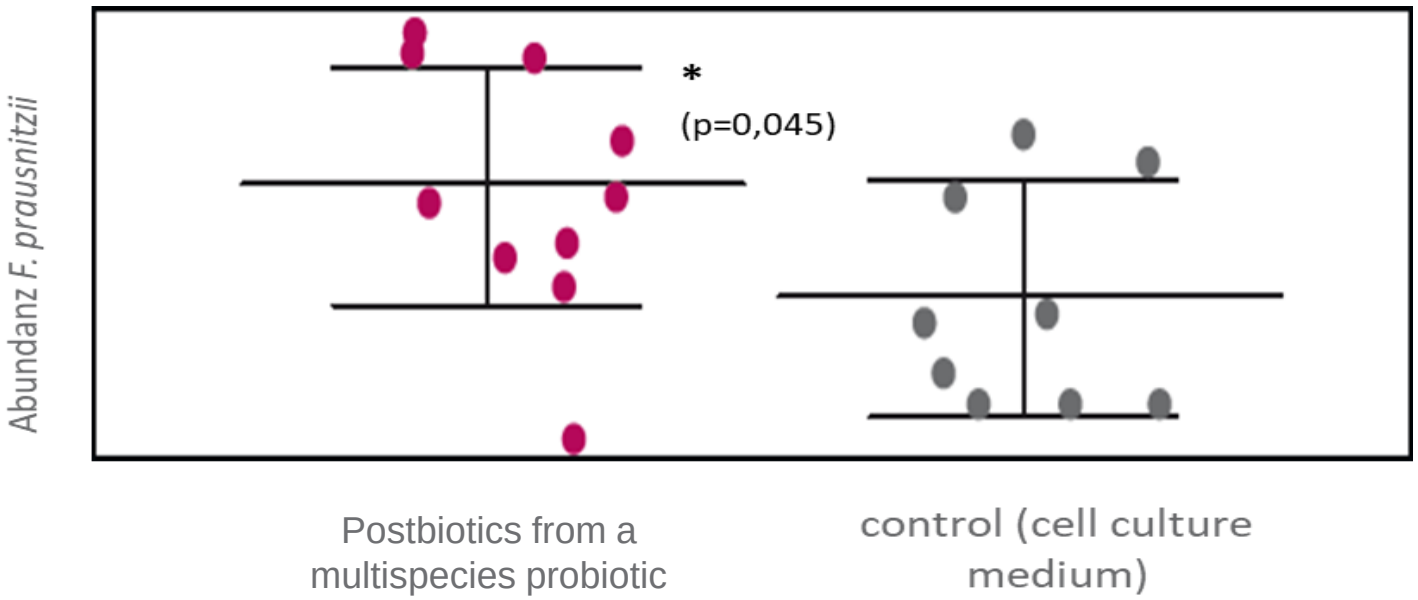
122 different metabolites in the postbiotic

48 hours after application of probiotic:

- Growth of *C. albicans* significantly reduced!
  → antifungal effect
- Growth of *listeria* significantly reduced
  → antibacterial effect

Kienesberger B. et al. *Insights into the Composition of a Co-Culture of 10 Probiotic Strains (OMNi BiOTiC® AAD10) and Effects of Ist Postbiotic Culture Supernatant*. Nutrients 14(6):1194 (2022)

Administration of postbiotic increases the abundance of *Faecalibacterium prausnitzii*



Administration of postbiotic after 196h

- Increased abundance of *F. prausnitzii*
- Supports growth of important symbionts

Kienesberger B. et al. Insights into the Composition of a Co-Culture of 10 Probiotic Strains (OMNi BiOTiC® AAD10) and Effects of Its Postbiotic Culture Supernatant. Nutrients 14(6):1194 (2022)

A high diversity of the microbiome increases the effectiveness of immunotherapy

Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment
Noriho Iida *et al.*
Science **342**, 967 (2013);
DOI: 10.1126/science.1240527

The immune system is triggered by the existing microbiota,thus the milieu around the tumor is changed. The commensal bacteria provoke reactions against cancer cells regardless of the location of the tumor in the body.

Psychological support of cancer patients using probiotics

Univ. Prof. Dr.med. J. Sehouli, Charité Berlin, Mayo Conference 2019

Probiotic support for 500 cancer patients before surgery:

for an average **5 days** treatment with a multispecies probiotic (2x per day) in more than 50% of patients:

- Improvement of quality of sleep
- Improvement of resiliance
- Improvement of general psychological conditions

The positive effect of multispecies probiotic on chemotherapy-associated side effects - especially on cachexia

Assoz. Prof. Priv.-Doz. Dr.med.univ.

nutrients

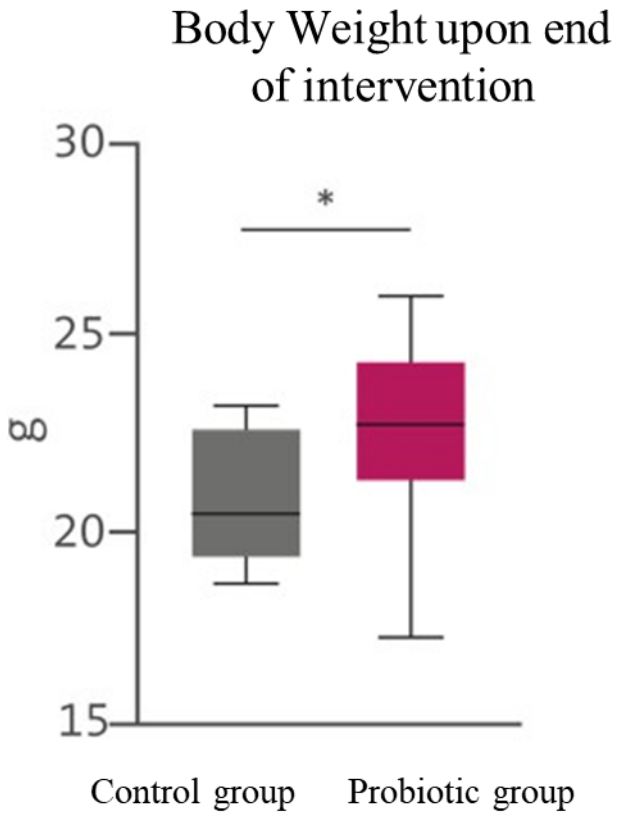
MDPI

Article

Probiotic OMNi-BiOTiC® 10 AAD Reduces Cyclophosphamide-Induced Inflammation and Adipose Tissue Wasting in Mice

Beate Obermüller [1], Georg Singer [1,*], Bernhard Kienesberger [1,2], Barbara Mittl [1], Vanessa Stadlbauer [3,4], Angela Horvath [4], Wolfram Miekisch [5], Patricia Fuchs [5], Martina Schweiger [6], Laura Pajed [6], Holger Till [1] and Christoph Castellani [1,7]

A multispecies probiotic leads to a significantly lower loss of body weight during chemotherapy



Starting point

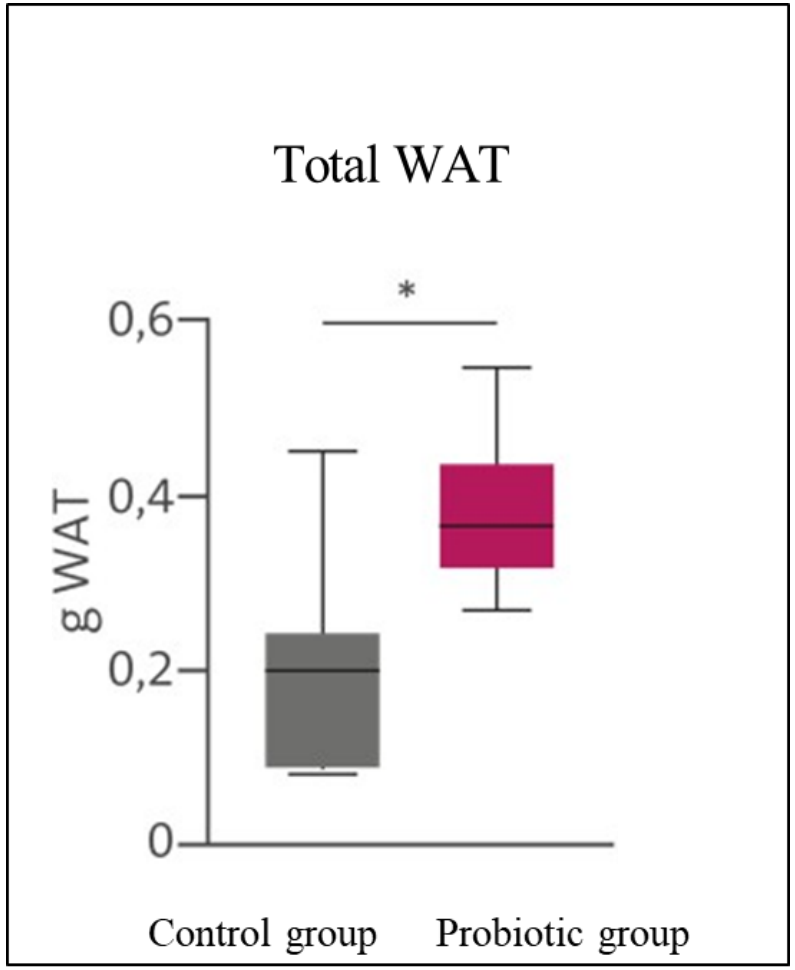
- NO significant difference in body weight between the probiotic and control group
- Identical calorie intake throughout the trial

➢ **The loss of body weight in the probiotic group was significantly lower compared to the control group**

Anti-“chemotherapy-induced cachexia“-effect

Obermüller B. et al. Probiotic OMNi BiOTiC® 10 AAD Reduces Cyclophosphamide-Induced Inflammation and Adipose Tissue Wasting in Mice. Nutrients 15:3655 (2023)

… also, a reduced loss of white adipose tissue (WAT) during chemotherapy was found in the probiotic group

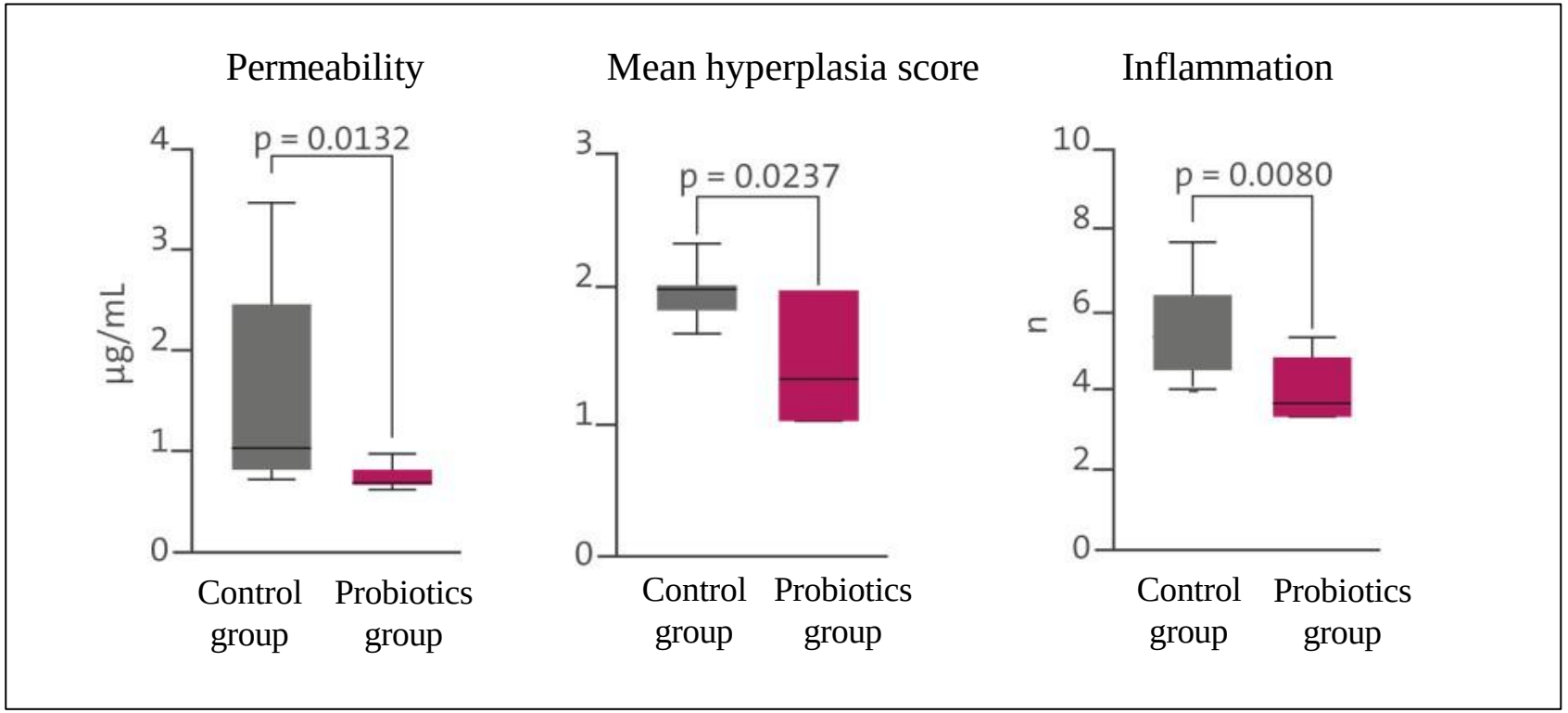


- The loss of **WAT** of the mice in the multispecies probiotic group was **significantly lower** compared to the mice in the control group

Anti-“chemotherapy-induced cachexia“-effect

Obermüller B. et al. Probiotic OMNi BiOTiC® 10 AAD Reduces Cyclophosphamide-Induced Inflammation and Adipose Tissue Wasting inMice. Nutrients 15:3655 (2023)

Multispecies probiotic strengthens the intestinal barrier and significantly reduces inflammation



- **significant reduction of gut permeability**
- **the control group displayed a significantly increased incidence of lesions and intestinal wall inflammation**

And even systemic inflammation was reduced through this multispecies probiotic

Param.	Unit	Aqua		10 AAD		
		Median	25–75 Perc.	Median	25–75 Perc.	*p*-Value
INF-γ	pg/mL	13.1	3.0–60.3	3.0	3.0–11.2	0.160
IL-1α	pg/mL	18.1	6.3–813.8	1.0	1.0–8.0	**0.022**
IL-1β	pg/mL	7.2	0.4–765.9	0.4	0.4–1.7	**0.021**
IL-6	pg/mL	862.1	263.8–121,076	27.5	27.5–307.9	**0.011**
IL-10	pg/mL	7.9	1.9–236.3	0.1	0.1–1.6	**0.018**
IL-15	pg/mL	8.1	2.6–30.9	0.3	0.3–2.7	**0.018**
IL-17	pg/mL	17.0	1.6–38.6	1.6	1.6–4.7	0.056
MIP-1α	pg/mL	2.2	0.1–167.5	0.1	0.1–0.1	0.076
MIP-1β	pg/mL	1.4	0.9–119.1	0.7	0.6–3.8	**0.042**
MIP-2	pg/mL	99.2	32.9–19,710	26.0	26.0–50.7	**0.024**
MCP-1	pg/mL	552.6	49.6–21,255	51.8	28.3–1161	0.385
TNF-α	pg/mL	59.9	10.9–276.5	1.7	1.7–20.8	**0.024**
G-CSF	pg/mL	3121	1421–4864	510	51.1–1636	**0.021**
GM-CSF	pg/mL	5.1	3.4–48.7	3.4	3.4–3.4	**0.029**
M-CSF	pg/mL	1.4	0.4–3.8	0.3	0.2–0.4	**0.046**
MPO	ng/mL	118.4	60.6–283.9	48.9	29.6–68.7	**0.040**
NE	ng/mL	30.9	6.9–30.9	4.3	2.2–11.6	0.061
LBP	ng/mL	271.1	74.3–2764	125.2	56.5–344.4	0.291
VEGF	ng/mL	16.2	2.2–32.5	0.6	0.1–4.1	**0.047**
TGF-β1	pg/mL	26,143	17,586–31,665	34,677	29,160–44,524	**0.019**
TGF-β2	pg/mL	986.4	696.2–1232	1141	911.6–1330	0.436

Bold: statistically significant values.

Multispecies probiotic :

- significant reduction of pro-inflammatory cytokines in the serum
- significant increase of anti-inflammatory cytokines

→ **The multispecies probiotic induces a significant anti-inflammatory effect**

Obermüller B. et al. Probiotic OMNi BiOTiC® 10 AAD Reduces Cyclophosphamide-Induced Inflammation and Adipose Tissue Wasting in Mice. Nutrients 15:3655 (2023)

Probiotic Influence on ICI therapy in breast cancer and its metastasis

Randomized, placebo-controlled, double-blinded

Patients suffering from breast cancer; Immune Checkpoint Inhibitor (ICI) therapy planned:

placebo 1	placebo 2	probiotic 1	probiotic 2
placebo	mediterranean diet	Multispecies probiotic	Multispecies probiotic + mediterranean diet

Examination parameters

- microbiome analysis
- therapeutic effect of ICI-therapy
- side effects
- tumor growth

(Prof. Marion Kiechle, TU München)