Influența microbiomului intestinal asupra efectelor adverse ale chimioterapiei în patologia oncologică

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The influence of the gut microbiome on the adverse effects of chemotherapy in oncological pathology

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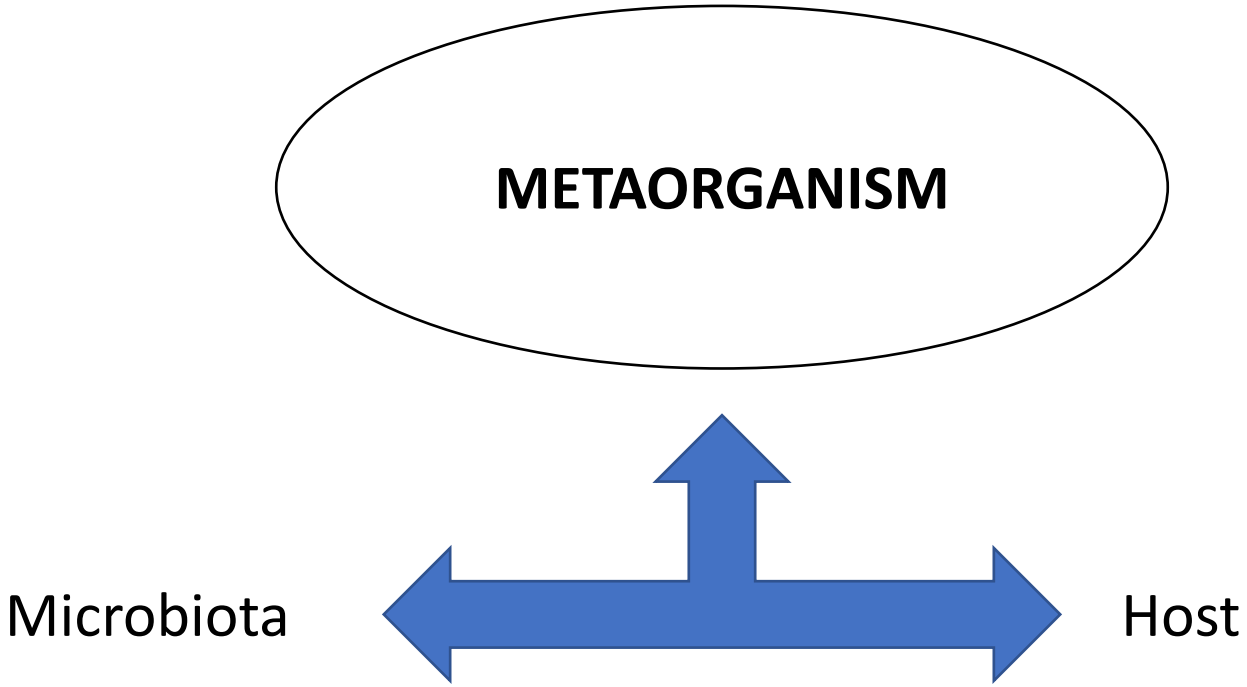
Chemotherapy adverse events (AE)

- AEs → main drawback of chemotherapy
- Up to 87% of people experienced at least one AE during and after chemo
- Common AEs: nausea and vomiting, diarrhea, constipation, mucositis, CTX induced peripheral neuropathy (CIPN), fatigue etc.
- Challenges:
  - implementation of effective strategies for preventing and managing AE's;
  - minimising health service costs and the financial burden for patients and their families;
  - developing of effective biomarkers that have been developed to predict and/or proactively manage CTX-induced AEs

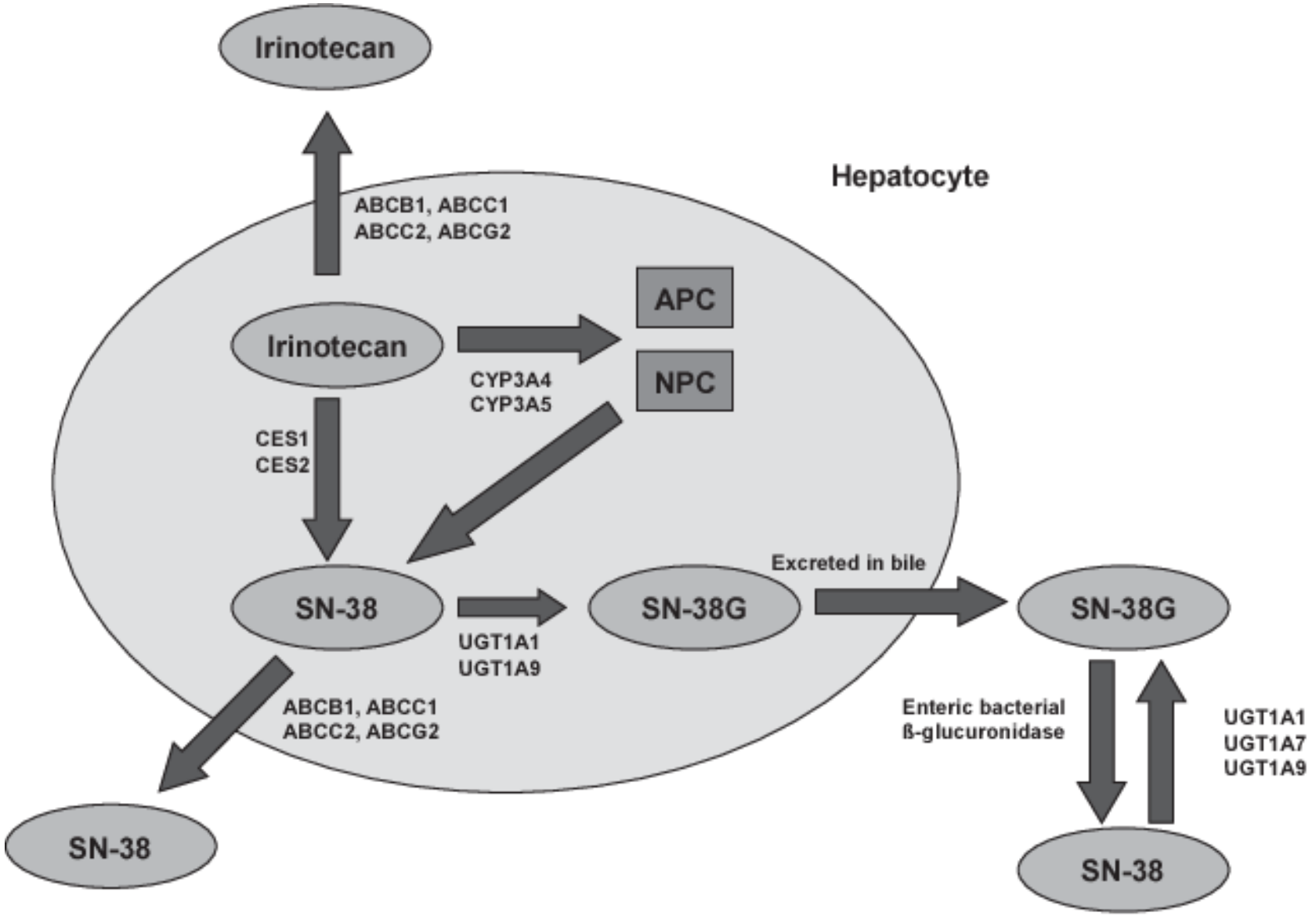
Oh B, Boyle F, Pavlakis N, *et al*. Emerging Evidence of the Gut Microbiome in Chemotherapy: A Clinical Review. Front Oncol. 2021 Sep 16;11:706331.



- facilitation of drug efficacy;
- abrogation and compromise of anticancer effects;
- mediation of toxicity;

DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 11th ed. ISSN/ISBN: 9781496394637. Wolters Kluwer Health | Lippincott Williams & Wilkins

Irinotecan



Paulík A, Grim J, Filip S. Predictors of irinotecan toxicity and efficacy in treatment of metastatic colorectal cancer. Acta Medica (Hradec Kralove). 2012;55(4):153-9. doi: 10.14712/18059694.2015.39

The Four-Herb Chinese Medicine PHY906 Reduces Chemotherapy-Induced Gastrointestinal Toxicity

Wing Lam[1], Scott Bussom[1], Fulan Guan[1], Zaoli Jiang[1,2], Wei Zhang[1], Elizabeth A. Gullen[1], Shwu-Huey Liu[2] and Yung-Chi Ch...
+ See all authors and affiliations

Science Translational Medicine 18 Aug 2010:
Vol. 2, Issue 45, pp. 45ra59
DOI: 10.1126/scitranslmed.3001270

PHY906

- *Glycyrrhiza uralensis*
- *Paeonia lactiflora*
- *Scutelleria baicalensis*
- *Ziziphus jujuba*

biotransformation via bacterial β-glucuronidase

Restorative effect on the intestinal epithelium

Reduced irinotecan gastro-intestinal toxicity

Lam W, *et al*. The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity. Sci Transl Med. 2010 Aug 18;2(45):45ra59.

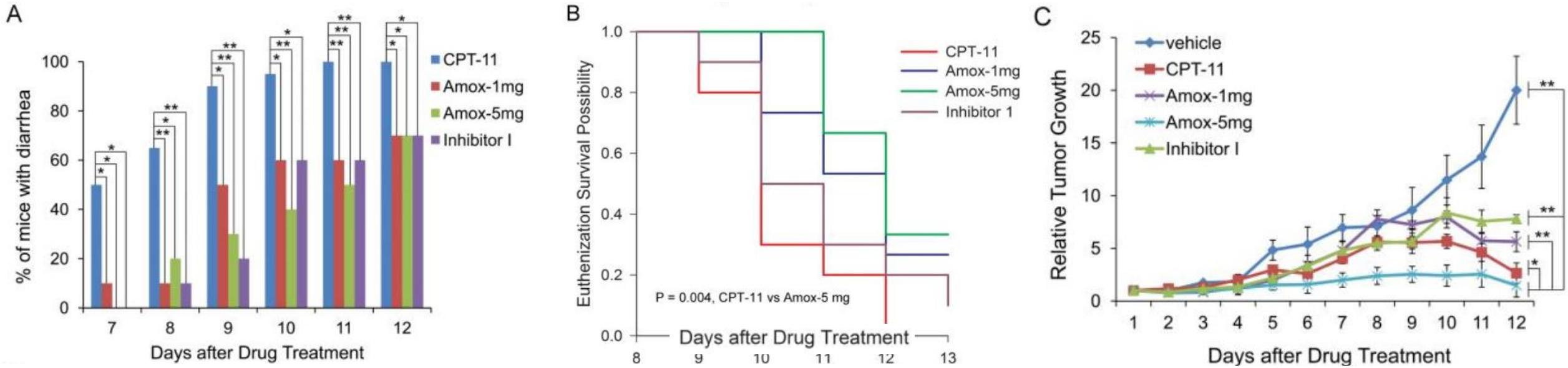
Published OnlineFirst April 29, 2014; DOI: 10.1158/1078-0432.CCR-14-0395

Clinical Cancer Research

Cancer Therapy: Preclinical

Old Drug New Use—Amoxapine and Its Metabolites as Potent Bacterial β-Glucuronidase Inhibitors for Alleviating Cancer Drug Toxicity

Ren Kong[1], Timothy Liu[1], Xiaoping Zhu[1], Syed Ahmad[3], Alfred L. Williams[3], Alexandria T. Phan[2], Hong Zhao[1], John E. Scott[3], Li-An Yeh[3], and Stephen T.C. Wong[1,2]



Effects of Amoxapine on CPT-11-induced diarrhea, survival and tumor growth in tumor-bearing mice

Kong R *et al*. Old drug new use--amoxapine and its metabolites as potent bacterial β-glucuronidase inhibitors for alleviating cancer drug toxicity. Clin Cancer Res. 2014 Jul 1;20(13):3521-30.

BCPT Basic & Clinical Pharmacology & Toxicology

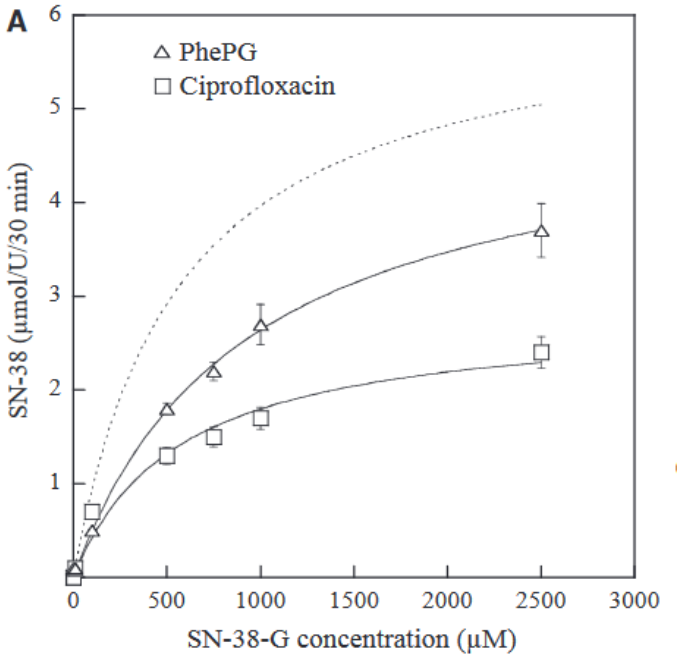
Basic & Clinical Pharmacology & Toxicology, 2016, **118**, 333–337 Doi: 10.1111/bcpt.12511

The Inhibitory Effect of Ciprofloxacin on the β-Glucuronidase-mediated Deconjugation of the Irinotecan Metabolite SN-38-G

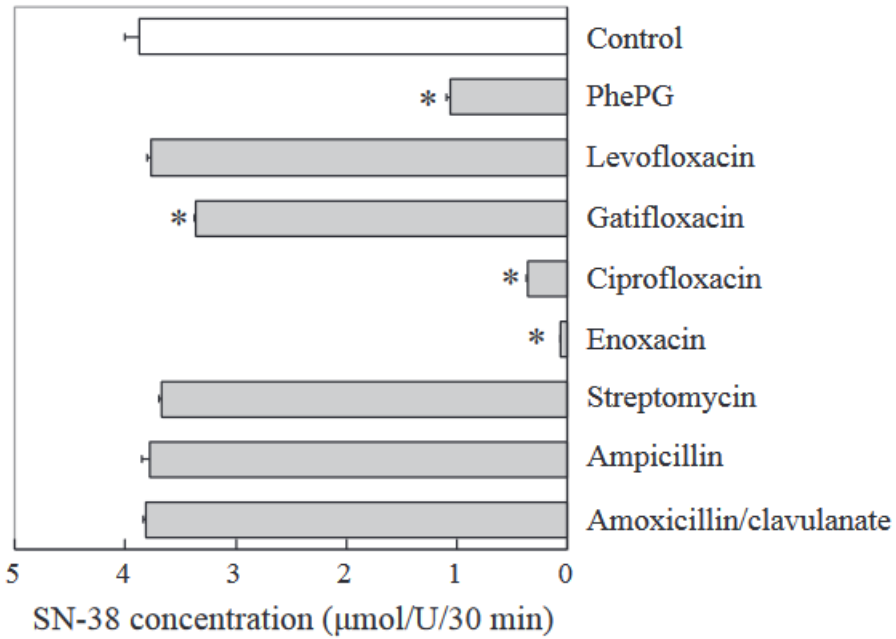
Takaaki Kodawara[1], Takashi Higashi[1], Yutaka Negoro[1], Yukio Kamitani[1], Toshiaki Igarashi[1], Kyohei Watanabe[1], Hitoshi Tsukamoto[1,2], Ryoichi Yano[1], Mikio Masada[3], Hiromichi Iwasaki[1,2] and Toshiaki Nakamura[1]

[1]Department of Pharmacy, University of Fukui Hospital, Eiheiji-cho, Yoshida-gun, Fukui-ken, Japan, [2]Infection Control and Prevention, University of Fukui Hospital, Eiheiji-cho, Yoshida-gun, Fukui-ken, Japan and [3]Osaka University of Pharmaceutical Sciences, Takatsuki-shi, Osaka-fu, Japan

(Received 11 September 2015; Accepted 20 October 2015)



The analysis of the kinetics of the b-glucuronidase-mediated deconjugation of SN-38-G to SN-38 in the presence of inhibitors.



The effects of various antibacterial drugs on the deconjugation of SN-38-G to SN-38.

Kodawara T, *et al*. The Inhibitory Effect of Ciprofloxacin on the β-Glucuronidase-mediated Deconjugation of the Irinotecan Metabolite SN-38-G. *Basic Clin Pharmacol Toxicol*. 2016 May;118(5):333-7

Methotrexate

RESEARCH ARTICLE | FEBRUARY 15 2015

TLR Signaling Modulates Side Effects of Anticancer Therapy in the Small Intestine

Magdalena Frank; Eva Maria Hennenberg; Annette Eyking; Michael Rünzi; Guido Gerken; Paul Scott; Julian Parkhill; Alan W. Walker; Elke Cario

+ Author & Article Information

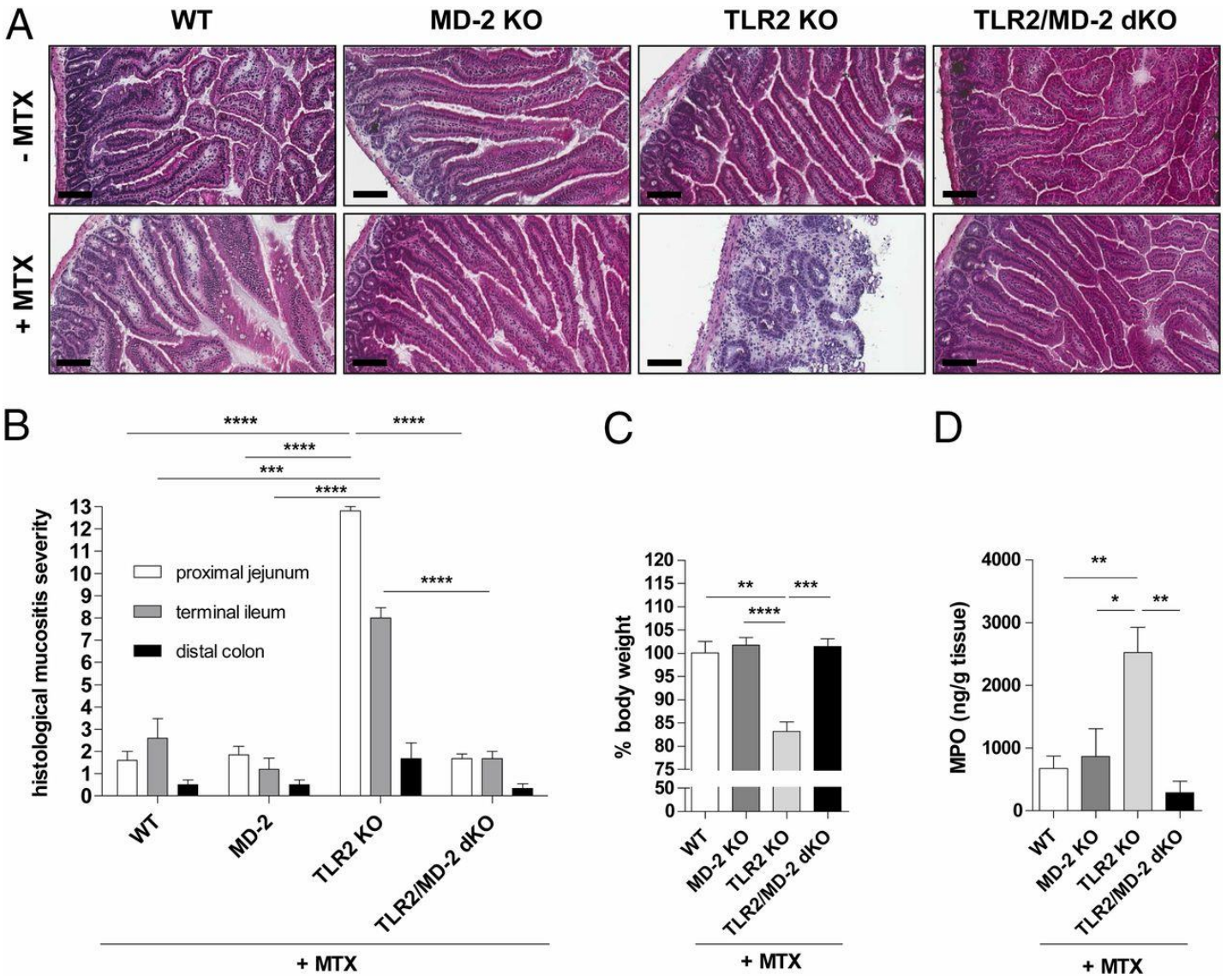
J Immunol (2015) 194 (4): 1983–1995.

https://doi.org/10.4049/jimmunol.1402481 **Article history**

- WT, TLR2 KO, MD-2 KO and TLR2/MD-2 dKO murines
- Cultures of human duodenal pinch biopsies ex vivo

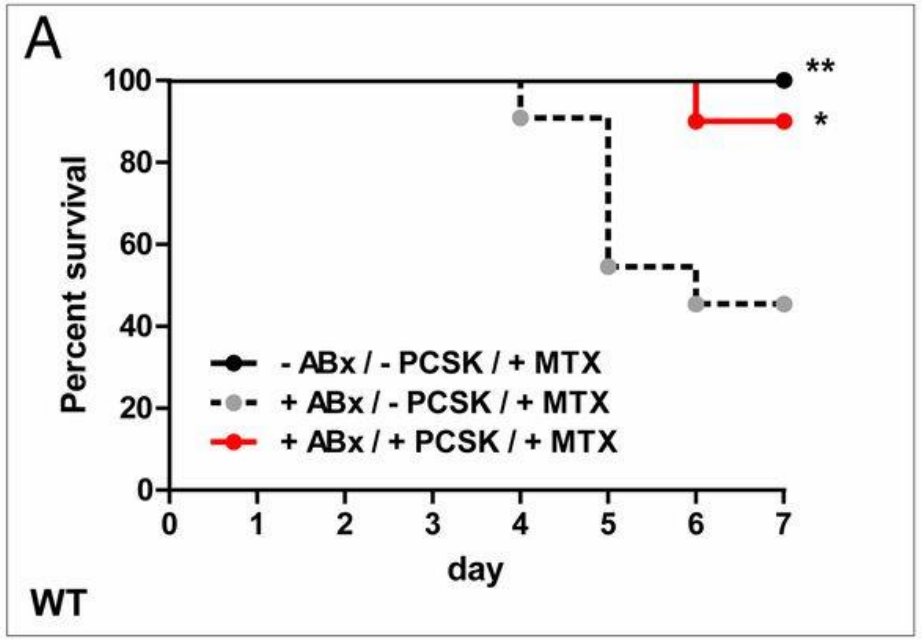
Frank M, *et al*. TLR signaling modulates side effects of anticancer therapy in the small intestine. J Immunol. 2015 Feb 15;194(4):1983-95..

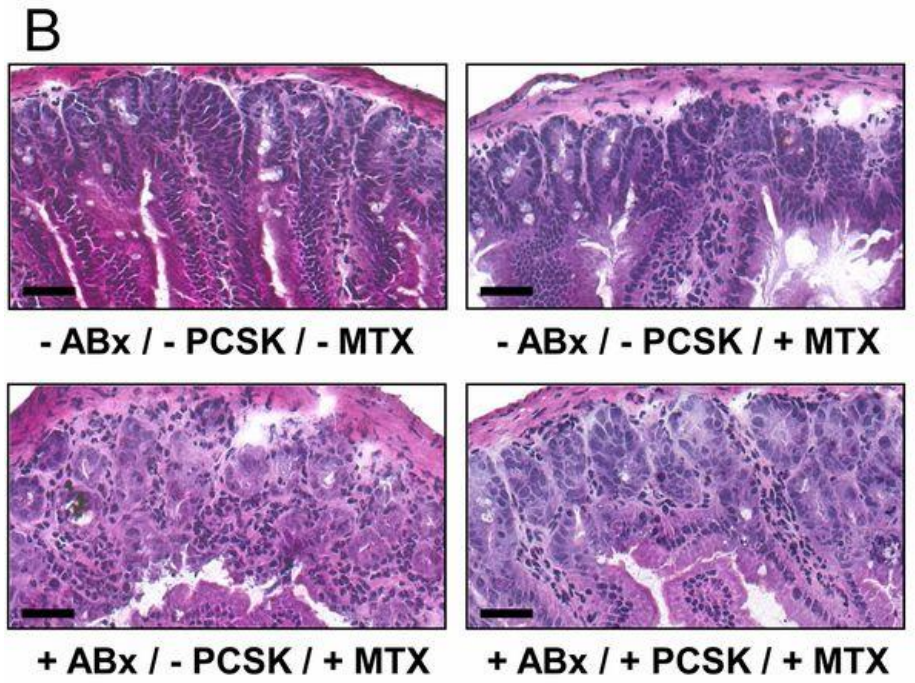
Genetic deletion of TLR2, but not MD-2, in mice results in severe chemotherapy-induced intestinal mucositis



Frank M, *et al*. TLR signaling modulates side effects of anticancer therapy in the small intestine. J Immunol. 2015 Feb 15;194(4):1983-95..

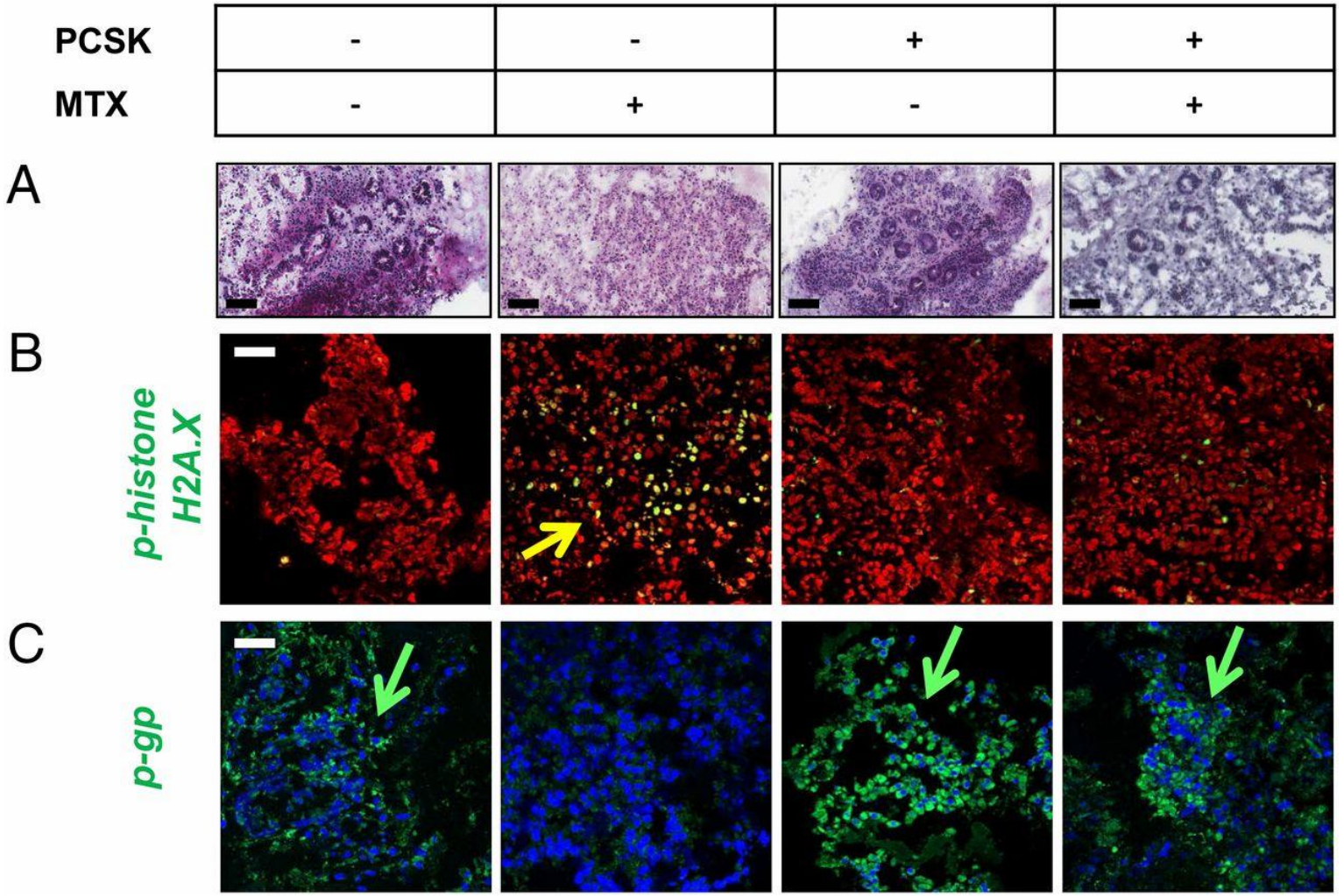
Gut microbiota depletion results in increased small intestinal chemotoxicity in WT mice, which is alleviated by TLR2 ligand supplementation





Frank M, *et al*. TLR signaling modulates side effects of anticancer therapy in the small intestine. J Immunol. 2015 Feb 15;194(4):1983-95..

Treatment with the TLR2 agonist PCSK prevents chemotherapy-induced cytotoxic damage in human duodenal lamina propria mononuclear cells of patients



Frank M, *et al*. TLR signaling modulates side effects of anticancer therapy in the small intestine. J Immunol. 2015 Feb 15;194(4):1983-95..

Oxaliplatin

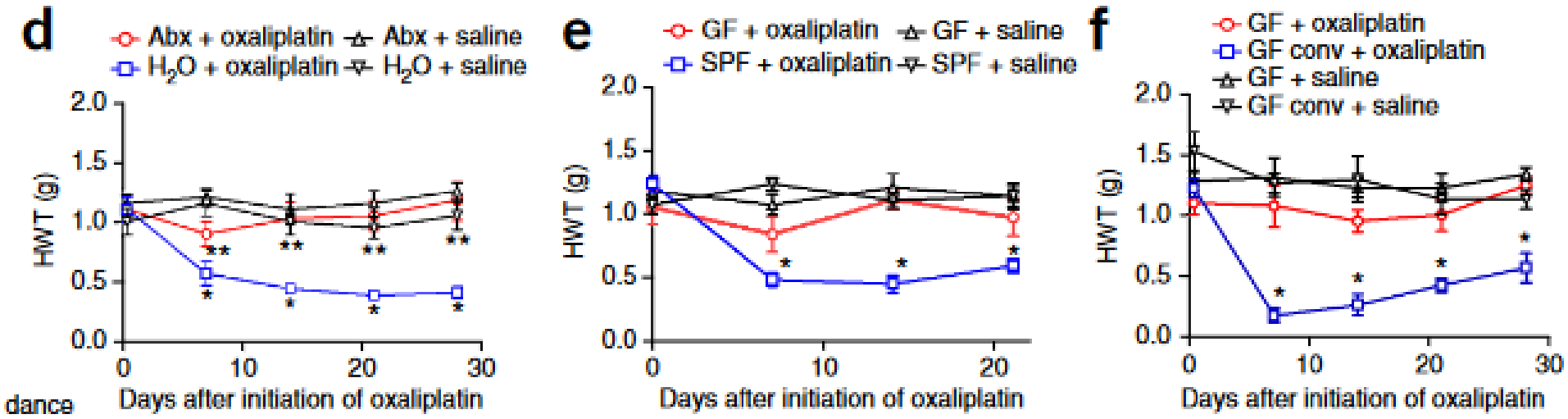
Lim, G., You, Z. et al. Gut

→abx mice (fed water containing antibiotics), H2O mice (fed regular water),

SPF (specific pathogen-free) and GF (germ-free) mice

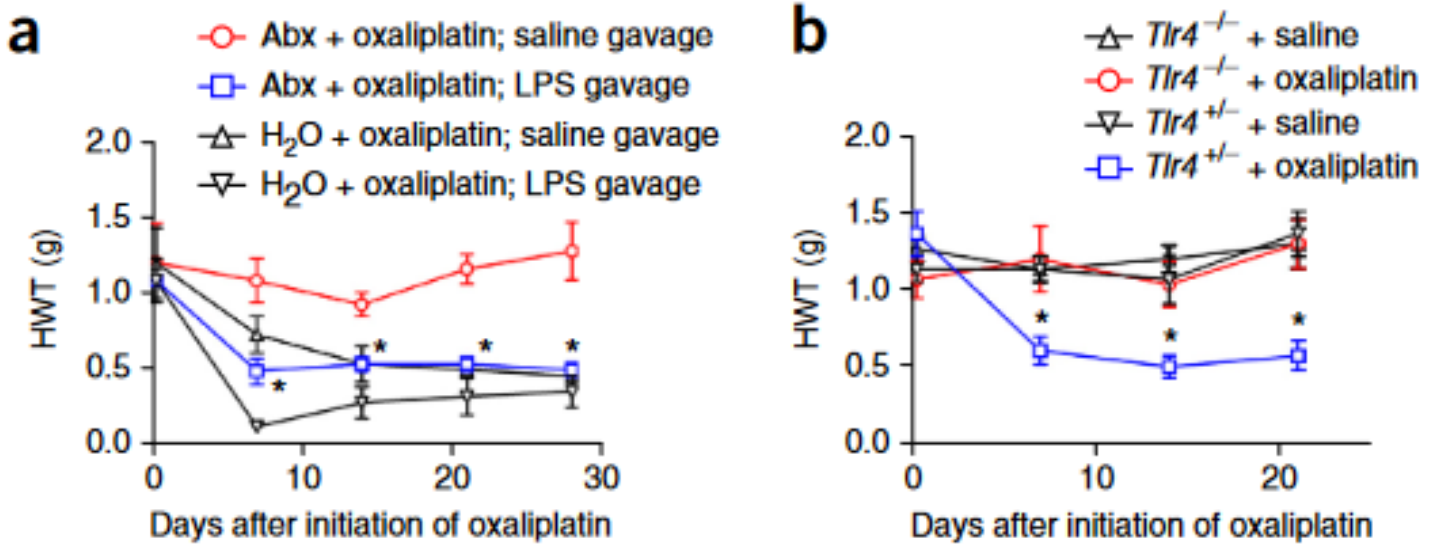
Shen, S., Lim, G., You, Z. *et al*. Gut microbiota is critical for the induction of chemotherapy-induced pain. Nat Neurosci 20, 1213–1216 (2017).

The gut microbiota promotes the development of oxaliplatin-induced mechanical hyperalgesia



Shen, S., Lim, G., You, Z. *et al*. Gut microbiota is critical for the induction of chemotherapy-induced pain. Nat Neurosci 20, 1213–1216 (2017).

- Lipopolysaccharides → bacterial wall component
- LPS is a ligand of Toll-like receptor 4 (Tlr4)



- These results suggest that gut microbiota influenced the development of mechanical hyperalgesia following oxaliplatin therapy through an LPS–TLR4 pathway – hematopoietic cells

Shen, S., Lim, G., You, Z. *et al*. Gut microbiota is critical for the induction of chemotherapy-induced pain. Nat Neurosci 20, 1213–1216 (2017).

Published: 06 May 2021

Probiotic Therapy (BIO-THREE) Mitigates Intestinal Microbial Imbalance and Intestinal Damage Caused by Oxaliplatin

Wenzhen Yuan, Xingpeng Xiao, Xuan Yu ✉, Fuquan Xie, Pengya Feng, Kamran Malik, Jingyuan Wu, Ze Ye, Peng Zhang & Xiangkai Li ✉

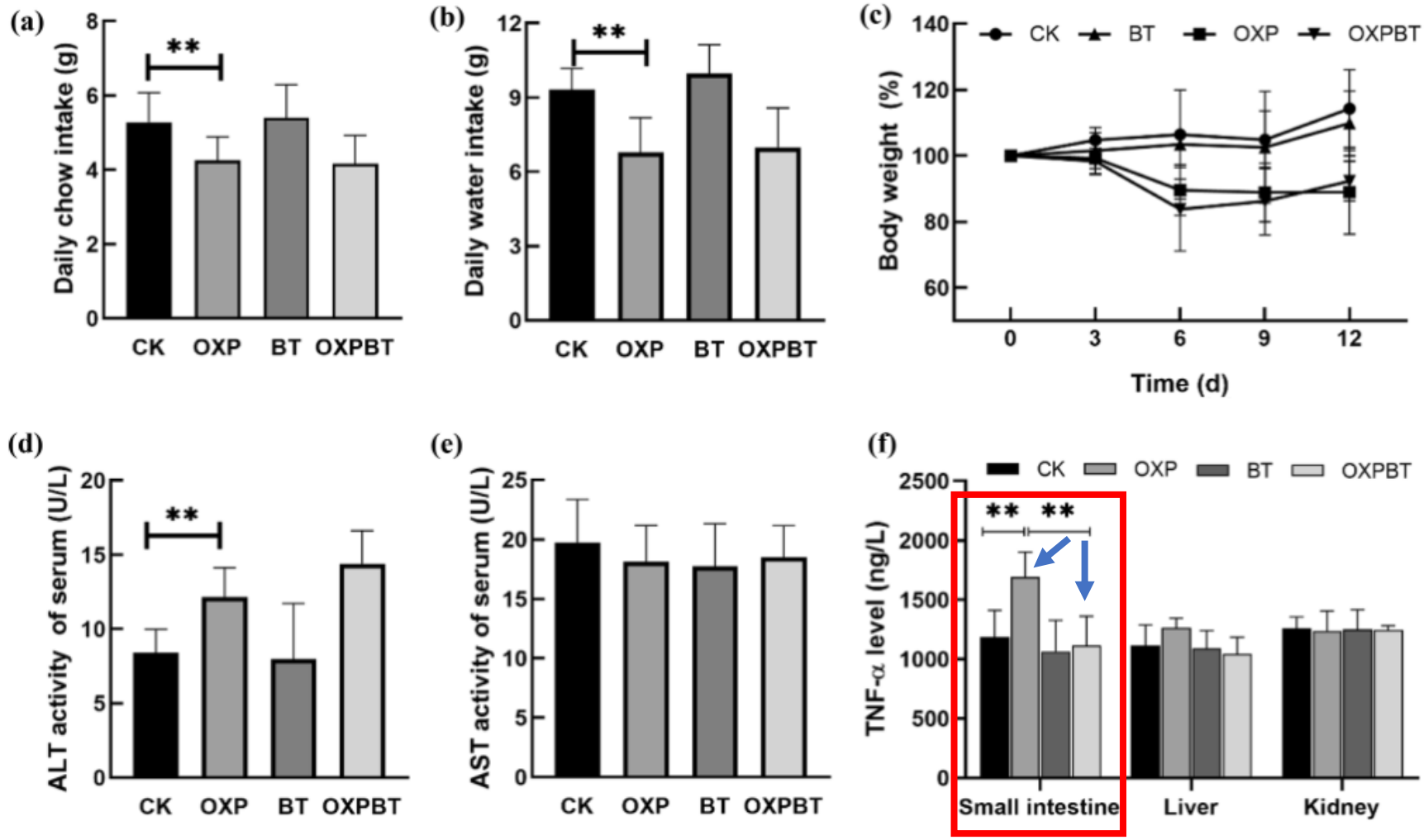
Probiotics and Antimicrobial Proteins **14**, 60–71 (2022) | Cite this article

- Two probiotic strains, *B. mesentericus* TO-A and *S. faecalis* T-110, were selected from the composition of the BIO-THREE tablets

- It has been reported that the use of BIO-THREE is safe and effective for the treatment of ulcerative colitis

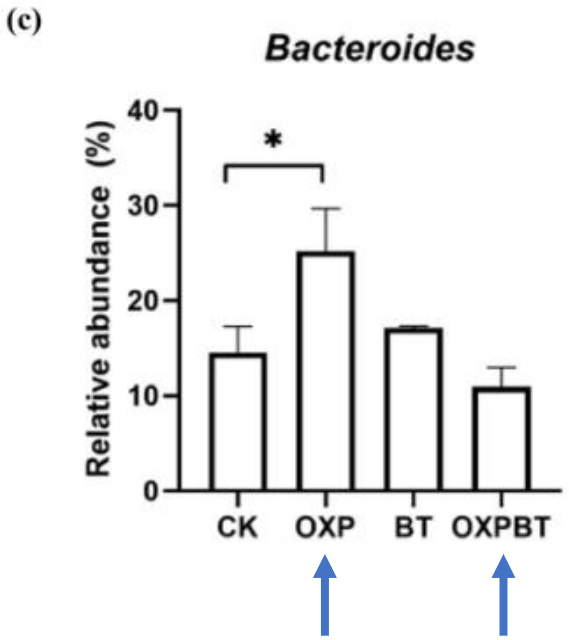
Yuan W, *et al*. Probiotic Therapy (BIO-THREE) Mitigates Intestinal Microbial Imbalance and Intestinal Damage Caused by Oxaliplatin. Probiotics Antimicrob Proteins. 2022 Feb;14(1):60-71.

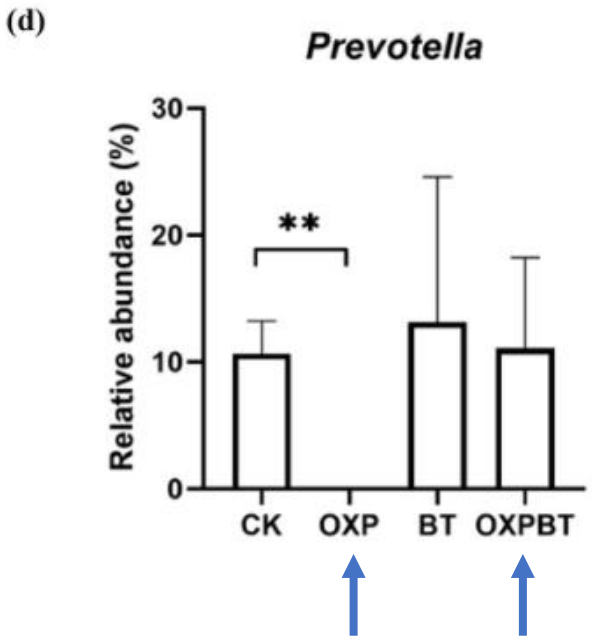
Oxaliplatin had a negative effect on the small intestine, which was counteracted by the probiotics (CK levels of TNF-α)

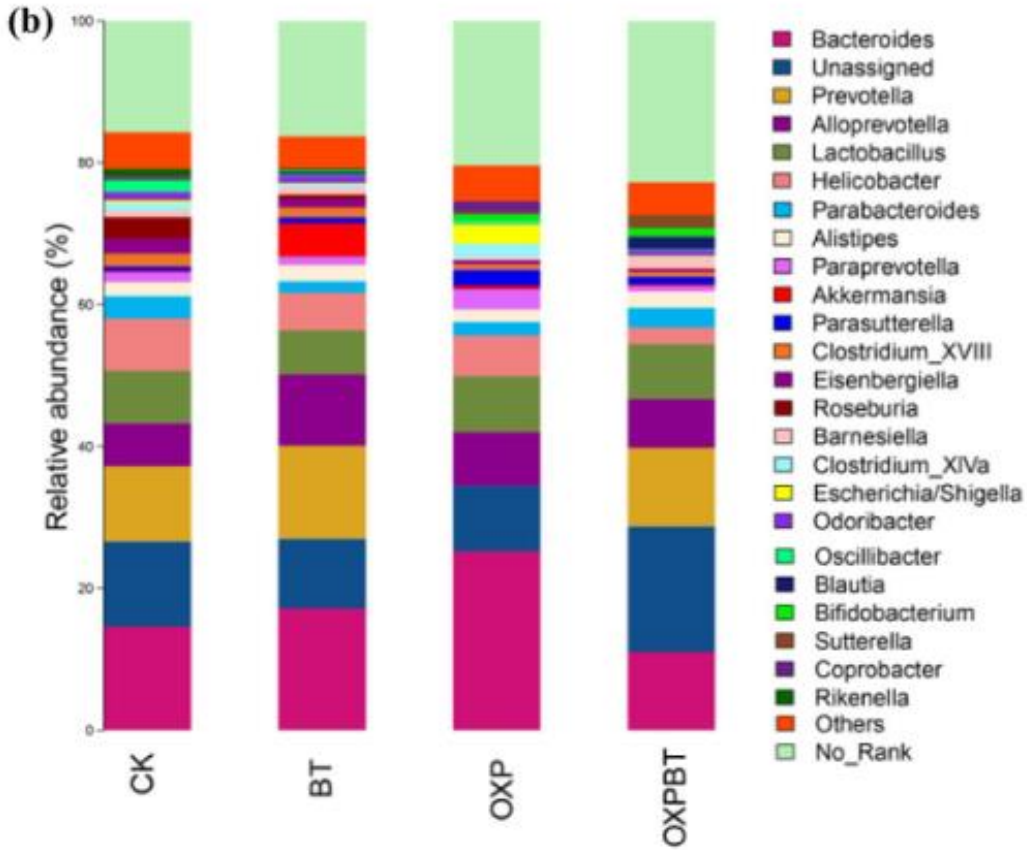


Yuan W, *et al*. Probiotic Therapy (BIO-THREE) Mitigates Intestinal Microbial Imbalance and Intestinal Damage Caused by Oxaliplatin. Probiotics Antimicrob Proteins. 2022 Feb;14(1):60-71.

The abundance of *Prevotella* and *Bacteroides* was significantly changed by treatment with oxaliplatin

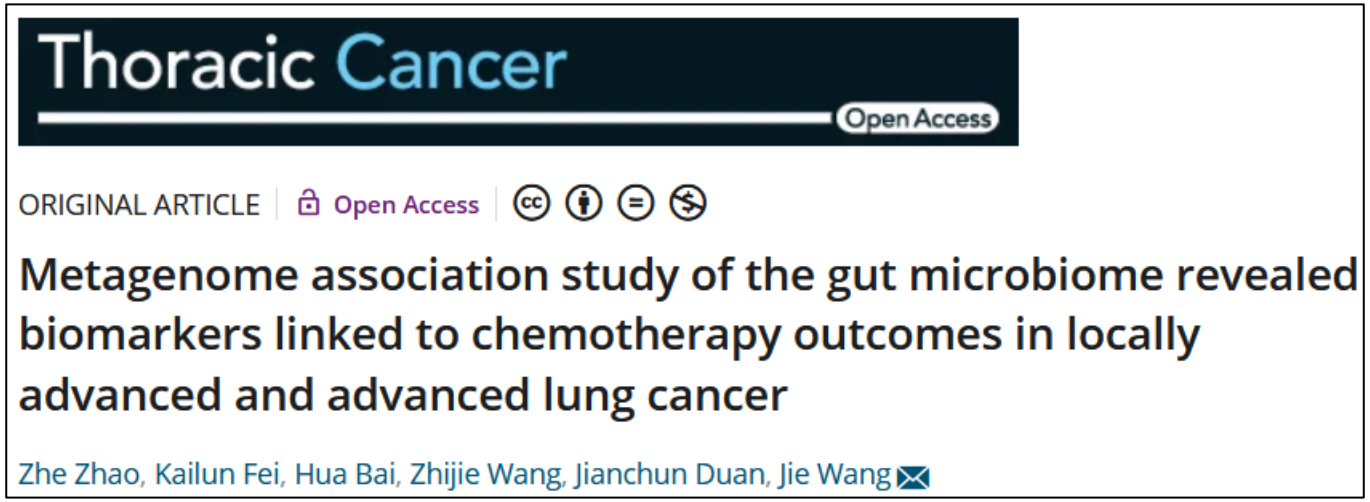






Yuan W, *et al*. Probiotic Therapy (BIO-THREE) Mitigates Intestinal Microbial Imbalance and Intestinal Damage Caused by Oxaliplatin. Probiotics Antimicrob Proteins. 2022 Feb;14(1):60-71.

Human clinical trials



- 64 patients with locally advanced and advanced lung cancer
- 1st line chemotherapy:
  - PEM combined with CDDP or CBP ± bevacizumab for patients with lung ADK
  - PTX or GEM in combination with CDDP or CBP for lung SCC
  - ETO in combination with CDDP or CBP for SCLC
  - PTX combined with CDDP or CBP for lung adenosquamous carcinoma
- Analysis of baseline stool samples before chemotherapy treatment, through metagenomics of the gut microbiota

Zhao Z, *et al*. Metagenome association study of the gut microbiome revealed biomarkers linked to chemotherapy outcomes in locally advanced and advanced lung cancer. Thorac Cancer. 2021 Jan;12(1):66-78.

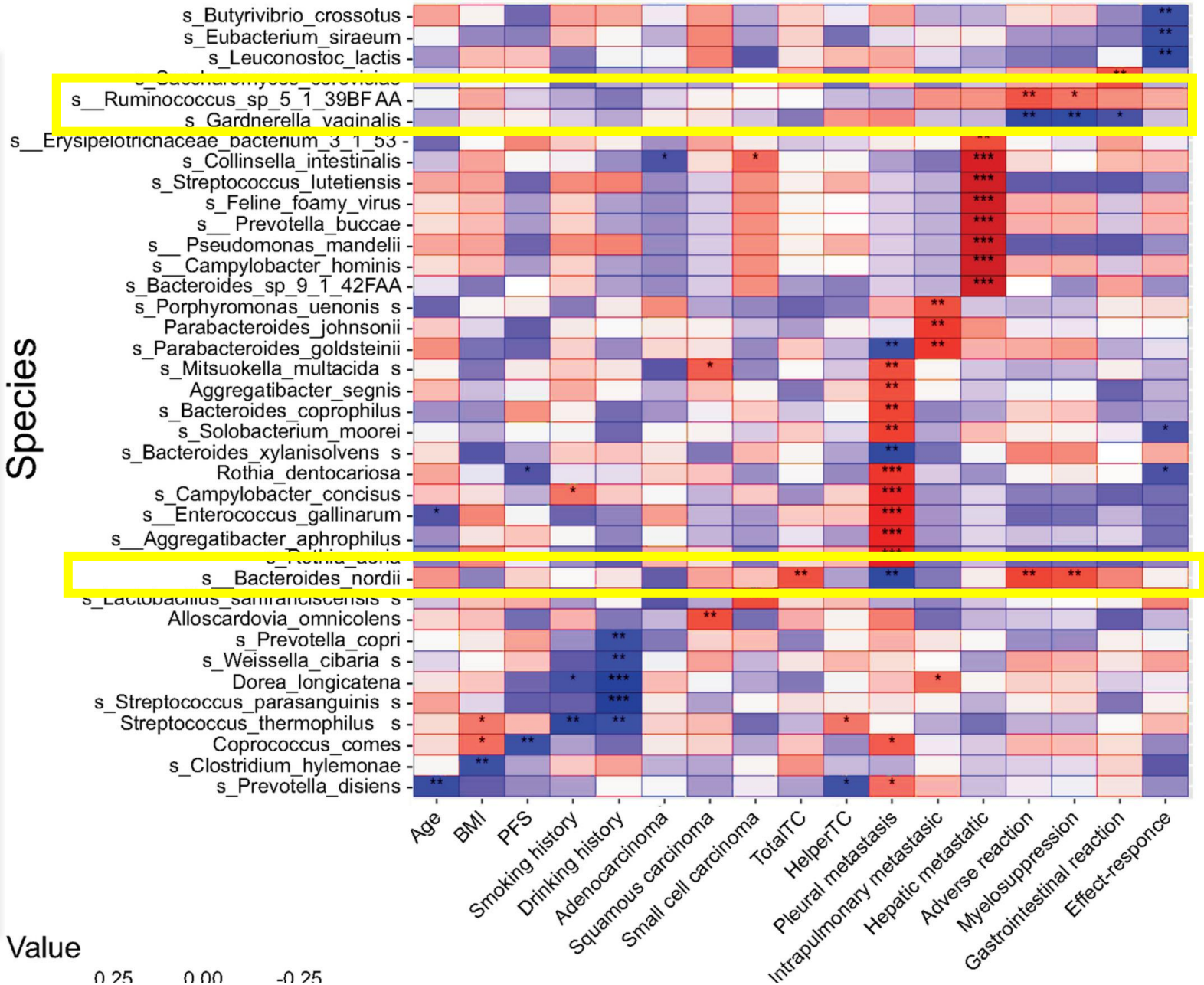
AEs recorded

Characteristics	No. of patients (*N* = 64)	%
Myelosuppression	64	
0	4	6.25%
I	21	32.81%
II	18	28.125%
III	14	21.875%
IV	7	10.94%
Gastrointestinal reaction	64	
0	6	9.375%
I	40	62.5%
II	14	21.875%
III	4	6.25%
IV	0	0

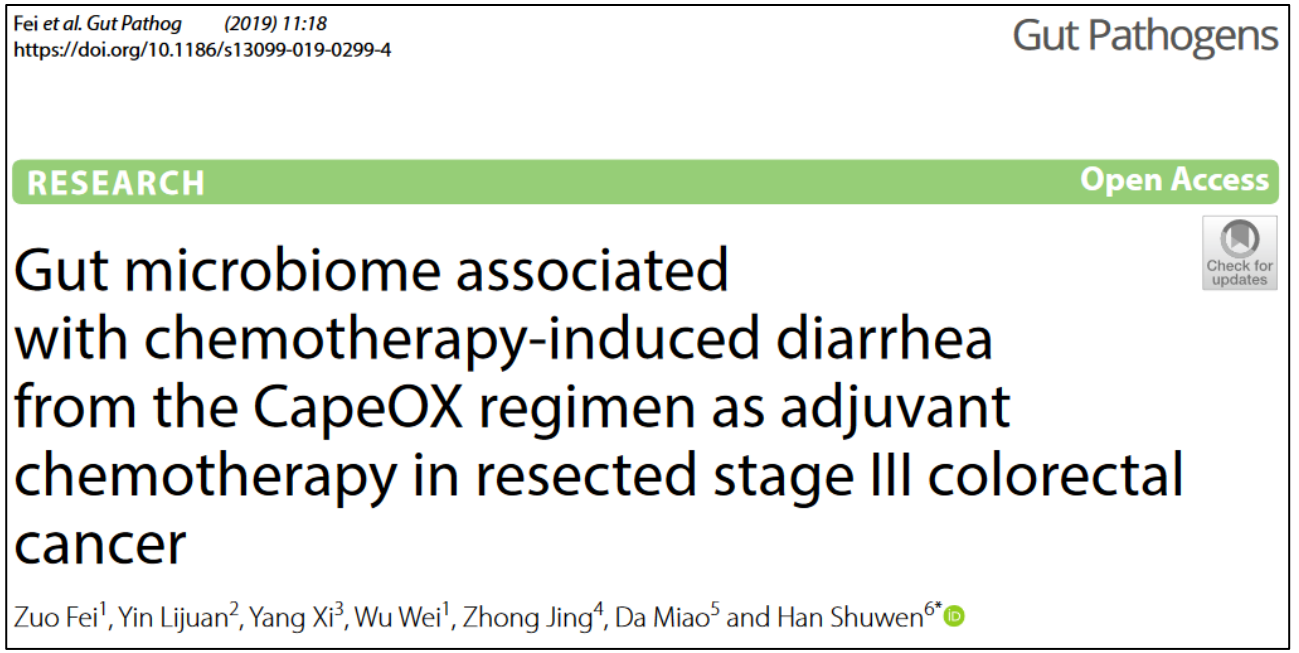
Zhao Z, *et al*. Metagenome association study of the gut microbiome revealed biomarkers linked to chemotherapy outcomes in locally advanced and advanced lung cancer. Thorac Cancer. 2021 Jan;12(1):66-78.

AEs after chemo

- ↑ *Bacteroides nordii*
- ↑ *Ruminococcus sp_5_1_39BFAA*
- ↓ *Gardnerella vaginalis*



Zhao Z, *et al*. Metagenome association study of the gut microbiome revealed biomarkers linked to chemotherapy outcomes in locally advanced and advanced lung cancer. Thorac Cancer. 2021 Jan;12(1):66-78.



Fei *et al. Gut Pathog* (2019) 11:18
https://doi.org/10.1186/s13099-019-0299-4

Gut Pathogens

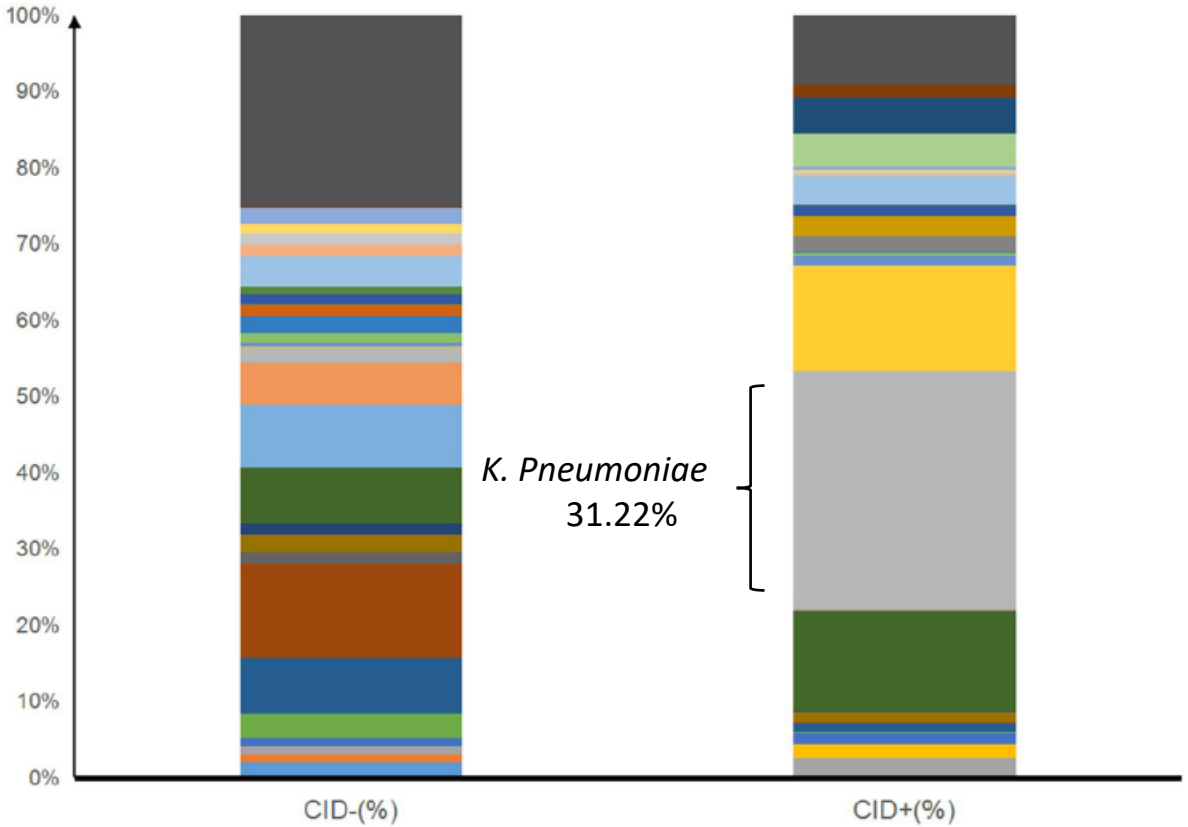
RESEARCH Open Access

Gut microbiome associated with chemotherapy-induced diarrhea from the CapeOX regimen as adjuvant chemotherapy in resected stage III colorectal cancer

Zuo Fei[1], Yin Lijuan[2], Yang Xi[3], Wu Wei[1], Zhong Jing[4], Da Miao[5] and Han Shuwen[6*]

- 17 patients were finally included in the study
  - CID+ = 4 (CID grade 2)
  - CID- = 13
- Stool samples of the patients were collected in the 2 weeks after the 8 cycles of chemotherapy

Fei Z, *et al*. Gut microbiome associated with chemotherapy-induced diarrhea from the CapeOX regimen as adjuvant chemotherapy in resected stage III colorectal cancer. Gut Pathog. 2019 Apr 30;11:18.



- **CID**
  - ↓ a-diversity
  - ↑ Proteobacteria
  - ↑ Enterobacteriales
  - ↑ Gammaproteobacteria
  - ↑ Enterobacteriaceae
    - ↑ Klebsiella
  - ***Klebsiella pneumoniae was the most predominant species (31.22%) among the gut microbiome***

- **NO CID**
  - ↑ Clostridiales,
  - ↑ Clostridia
  - ↑ Ruminococcaceae
  - ↑ Bacteroidetes
  - ↑ Bacteroidia
    - ↑ Bacteroidales
    - ↑ Bacteroides
    - ↑ Bacteroidaceae

Fei Z, *et al*. Gut microbiome associated with chemotherapy-induced diarrhea from the CapeOX regimen as adjuvant chemotherapy in resected stage III colorectal cancer. Gut Pathog. 2019 Apr 30;11:18.

Perspectives

- Pharmacomicrobiomics?
- Gut microbiota as a biomarker for outcomes?
- FMT?
- Dietary interventions?
- Probiotics, prebiotics and synbiotics?
- Antibiotics, ecology and synthetic engineering?

Thank you!