XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

Microbiota e Radioterapia nelle Neoplasie Ginecologiche

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Associazione Italiana
Radioterapia e Oncologia clinica

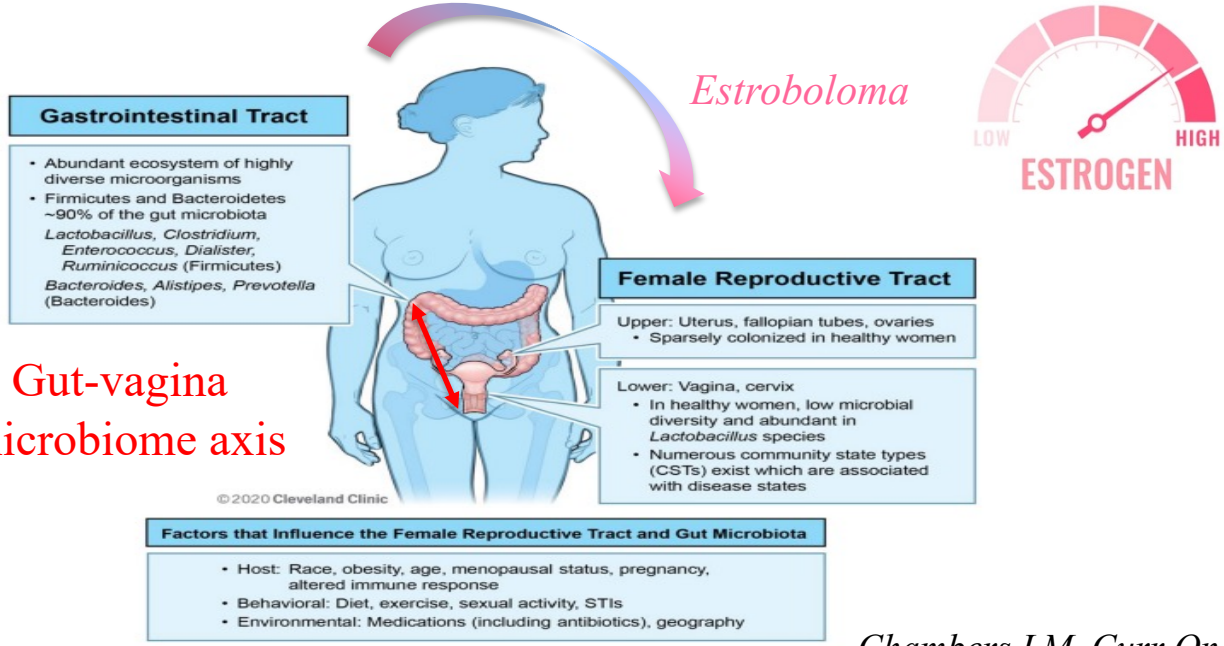
DICHIARAZIONE

Relatore: Ippolito Edy

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

The unique case of gynecological cancers



Chambers LM, Curr Oncol Rep 2021

Microbioma of female reproductive tract

Vagino-cervical M

CST-I
L.Crispatus

CST-II
L.Gasseri

CST-III
L.Iners

CST-IV
No
Lactobacillus

CST-V
L. Jansenii

Lactobacillus spp. → Low pH
> Lactic Acid
< Pathogens

Gardnerella
Atopobium
Prevotella
Megashera
Snethia
→ Bacterial Vaginosis

Uterine

✓ Not sterile

✓ Limited in healthy women

✓ Colonization through vaginal ascension and/orvhematogenous spread

✓ Acinetobacter, Pseudomonas, Cloacibacterium more frequent

Chambers LM, Curr Oncol Rep 2021

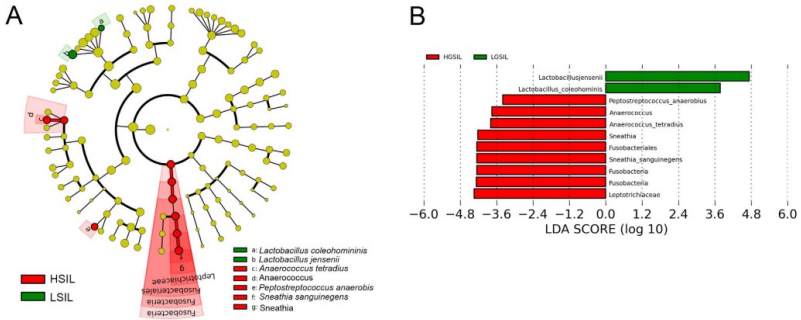
AIRO2023

Radioterapia Oncologica:
l'evoluzione al servizio dei pazienti

«Onco»bioma: microbiota and carcinogenesis Mechanisms

Pro-carcinogenic state through:
- altered host immune response
- changes in hormone metabolism
-modulation of the cell cycle and apoptosis (elicit DNA damage directly and not)
- upregulation of oncogenic pathways

Intraepitelial cervical neoplasia and Vaginal Microbioma

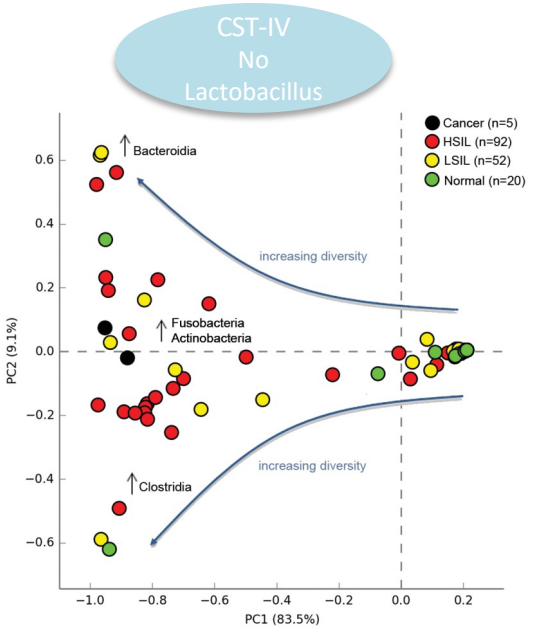


Lowest Lactobacillus

21% LSIL — 27% HSIL — 40% Inv Cancer

Highest Lactobacillus

90% LSIL — 79% HSIL — 60% Inv Cancer



Mitra A, Scient Rep 2015

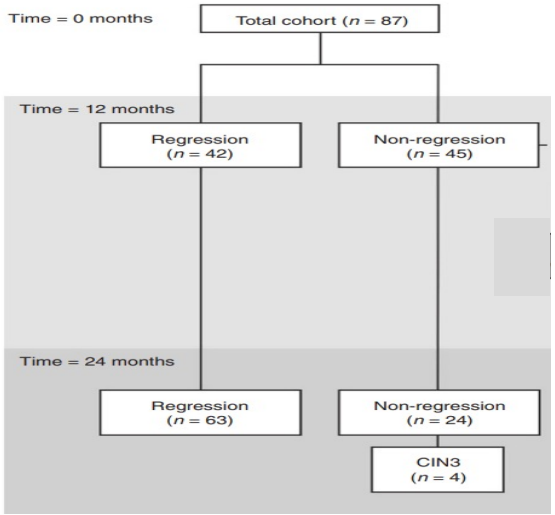
ARTICLE

https://doi.org/10.1038/s41467-020-15856-y OPEN

Check for updates

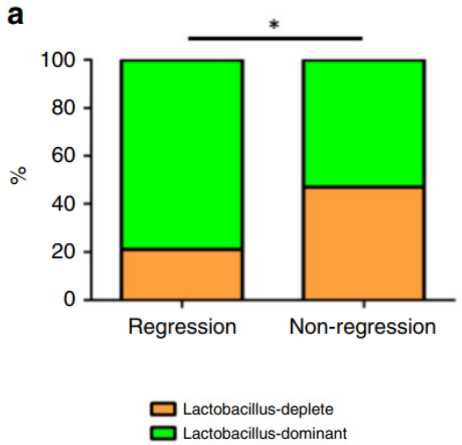
The vaginal microbiota associates with the regression of untreated cervical intraepithelial neoplasia 2 lesions

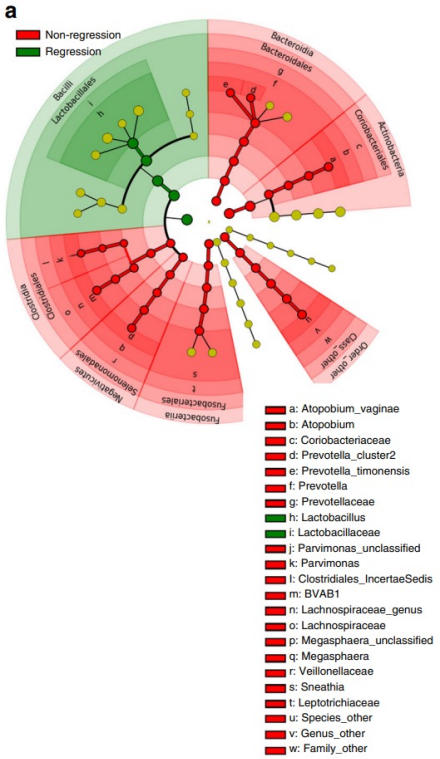
Anita Mitra[1,2], David A. MacIntyre[1,3], George Ntritsos[4], Ann Smith[5], Konstantinos K. Tsilidis[4,6], Julian R. Marchesi[3,7,8], Phillip R. Bennett[1,2,3], Anna-Barbara Moscicki[9,10] & Maria Kyrgiou[1,2,10]✉



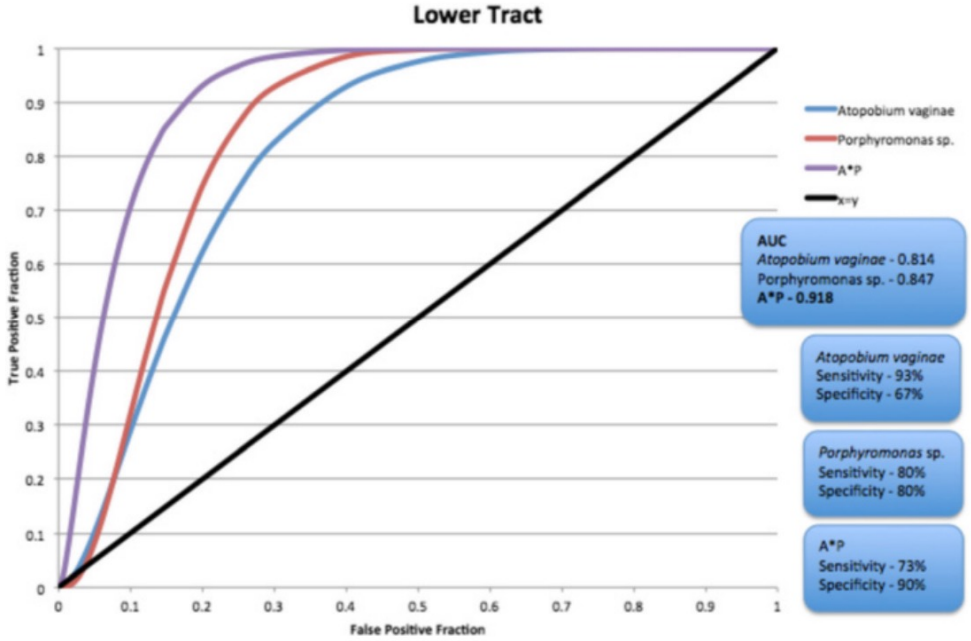
CIN2

CIN3





Endometrial Cancer and GU Microbioma

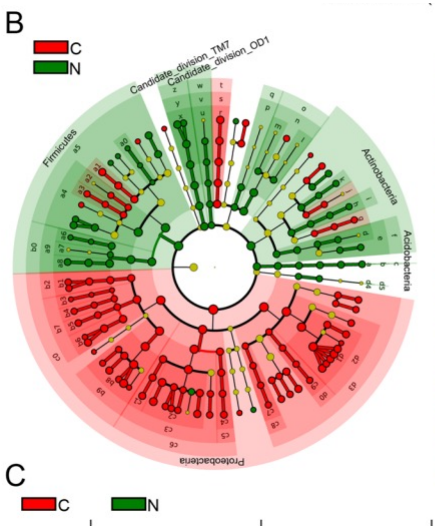


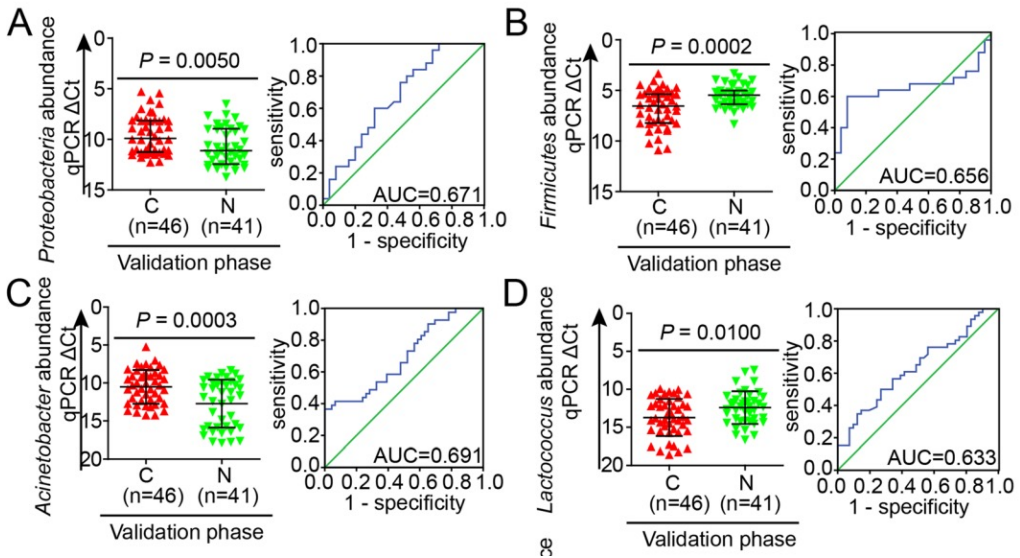
Risk of endometrial cancer > 4.5, especially if associated with low vagina PH

Hokenstad A, Genom Med 2016

Ovarian Cancer and Upper GU Microbioma

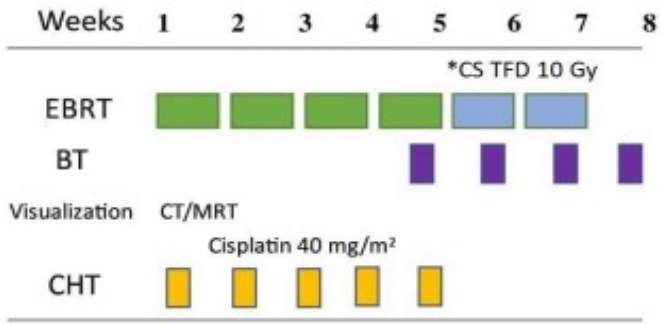
Increased proteobacteria and firmicutes phyla





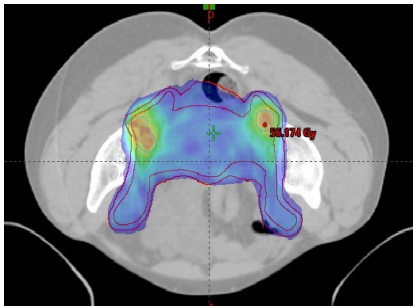
Zhou B, Sci Rep 2019

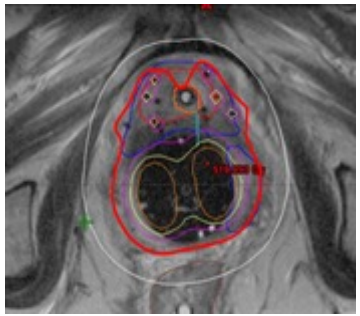
LA cervical cancer standard treatment



ESGO
European Society of Gynaecological Oncology

ASTRO
TARGETING CANCER CARE





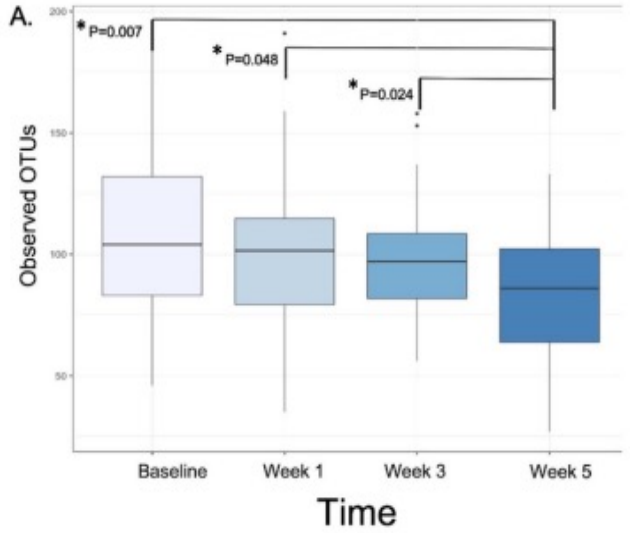
ASCO
American Society of Clinical Oncology

ESTRO
European Society for RADIOTHERAPY & ONCOLOGY

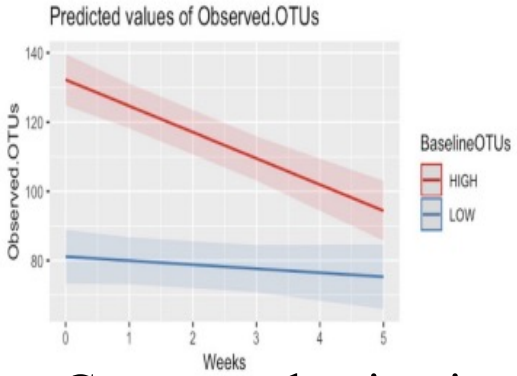
Chemoradiation changes individual microbioma

DURING RT-CT

Gut microbioma



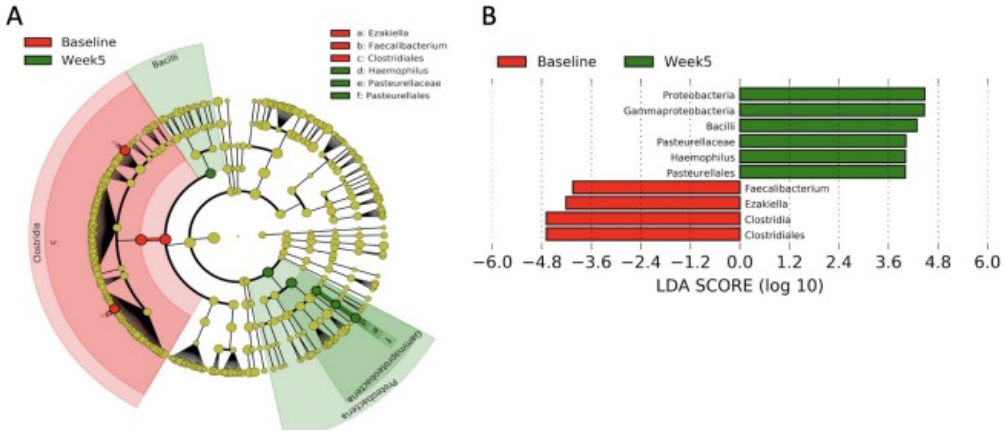
<< Diversity

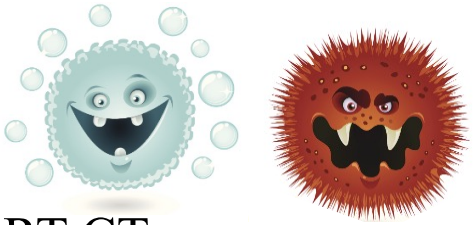


Greater reduction in patients with higher baseline diversity

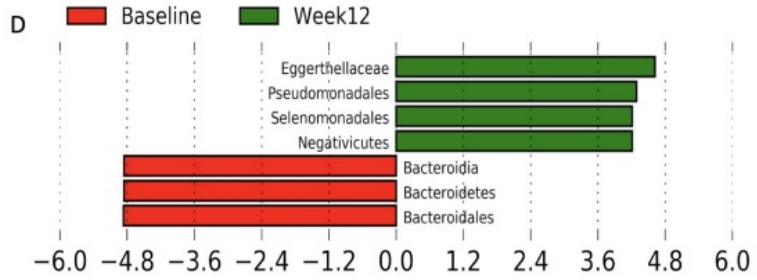
El Alam M, Plos One 2021

Chemoradiation changes individual microbioma





DURING RT-CT
>> Proteobacteria
<< Clostridiales



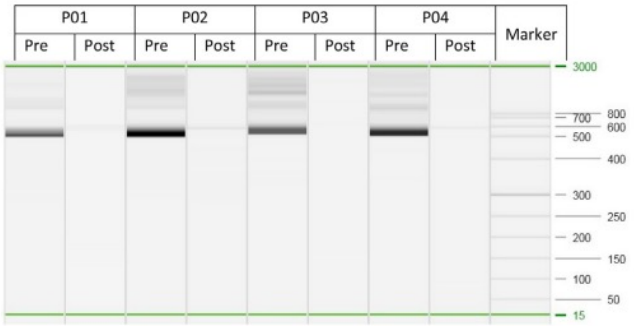
AFTER RT-CT
✓ Clostridiales and Bacteroides returned normal
✓ Bacteroides increased

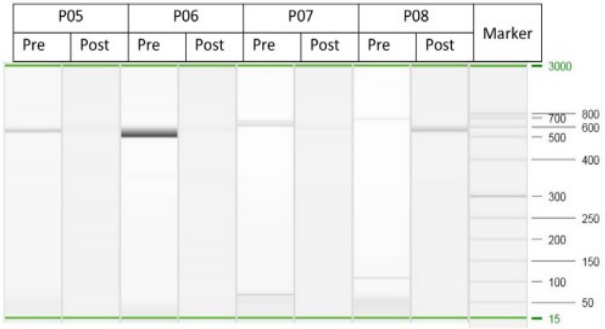
El Alam M, Plos One 2021

Chemoradiation changes individual microbioma

DURING RT-CT

Cervical microbioma



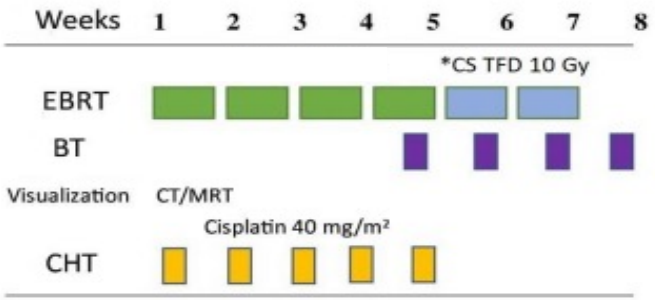


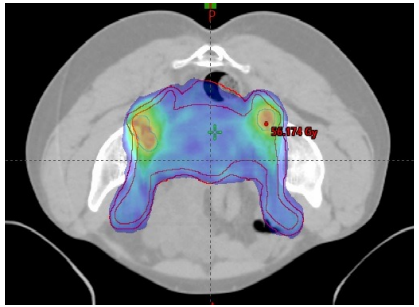
<< Bacterial load

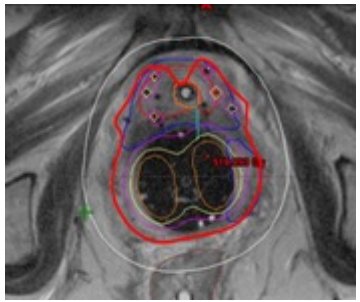
No changes in diversity (alpha and beta)

Tsakmaklis A, Int J Gynecol Cancer 2019

LA cervical cancer standard treatment



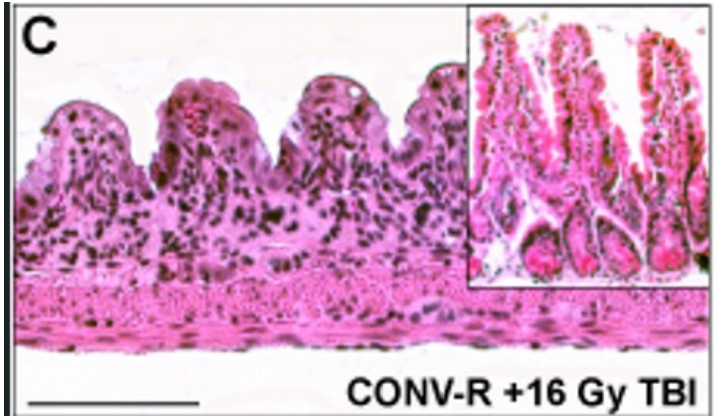




Toxicity

Outcome

Microbiota associated endothelial radiosensitivity

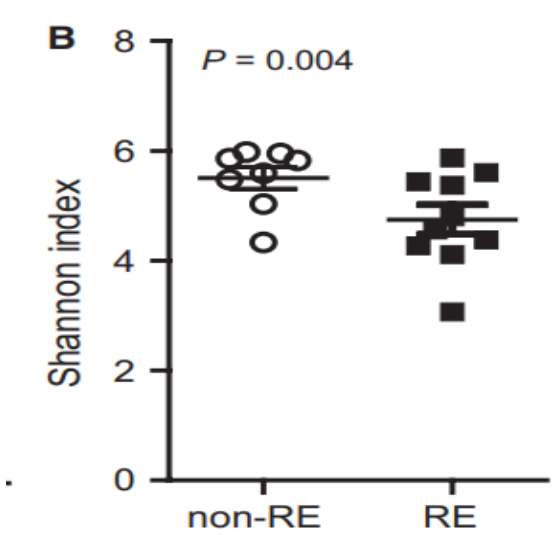


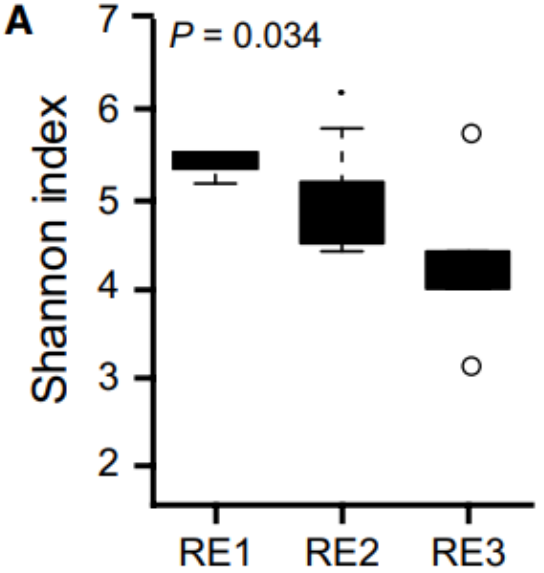
Crawford PA, 2005

Microbioma and toxicity

Radiation Enteritis (RE)

Lower alpha-diversity

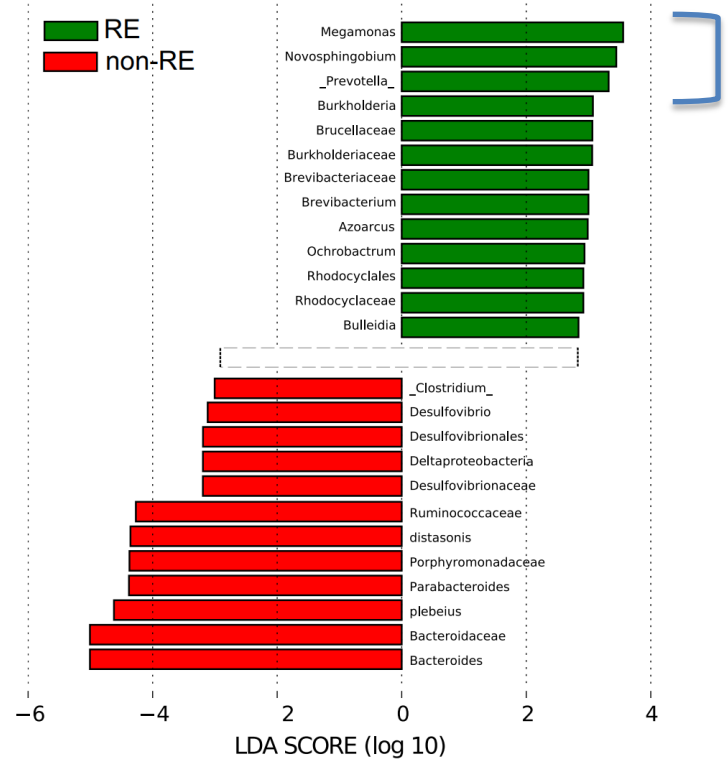




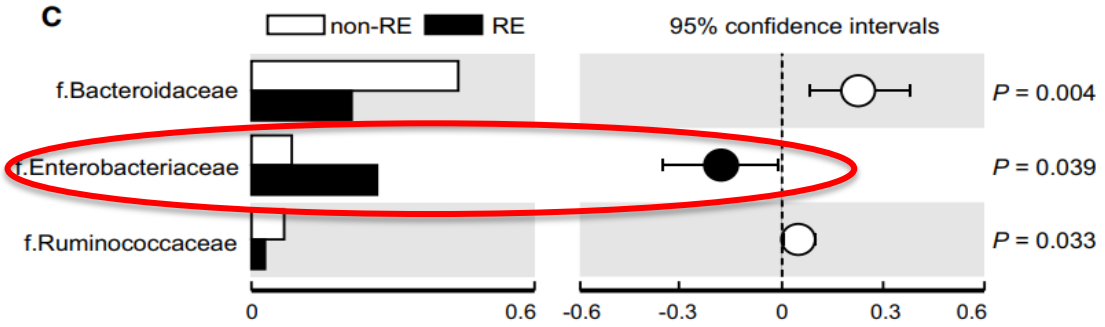
Wang J Cell Mol Med 2019

Microbioma and toxicity

Radiation Enteritis (RE)

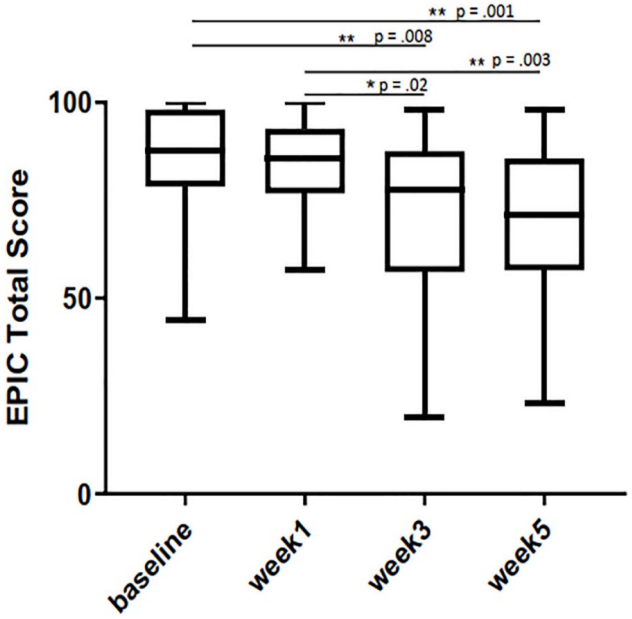


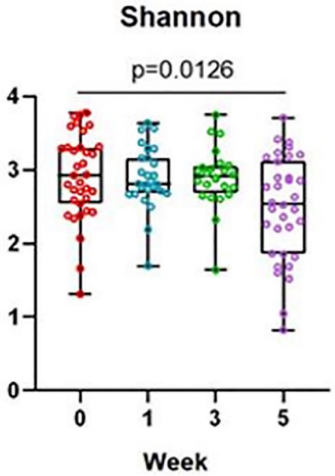
More at risk of developing RE

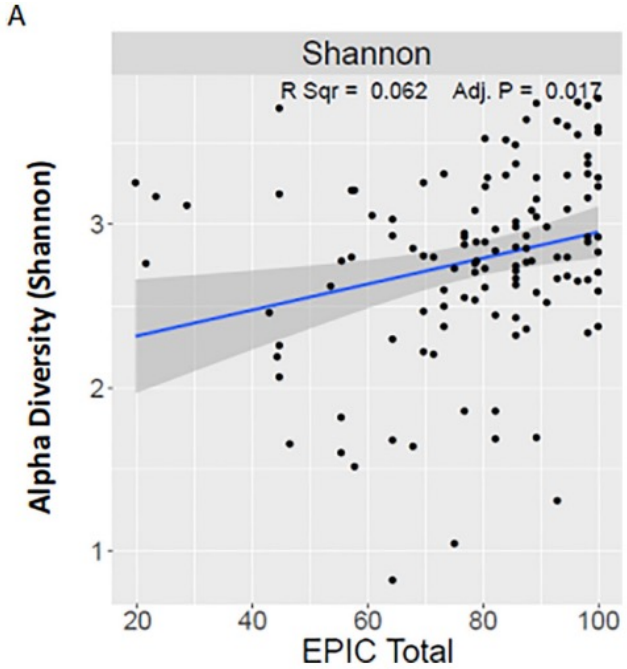


Wang J Cell Mol Med 2019

Microbioma and toxicity

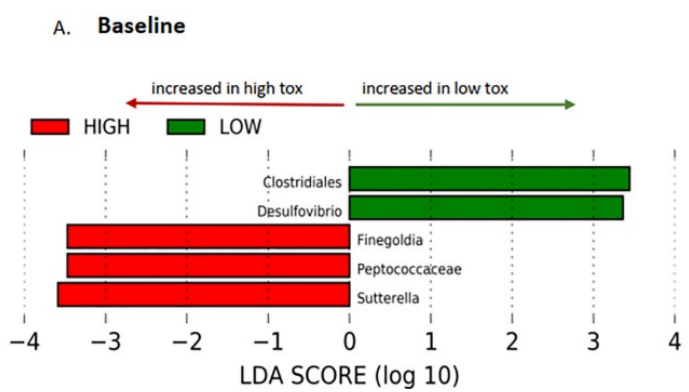


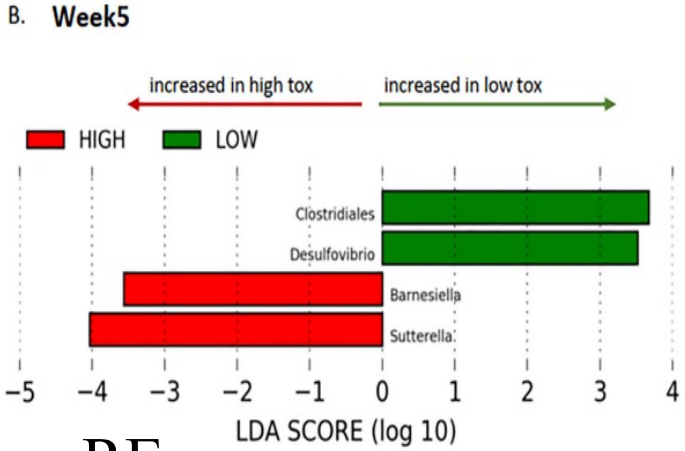




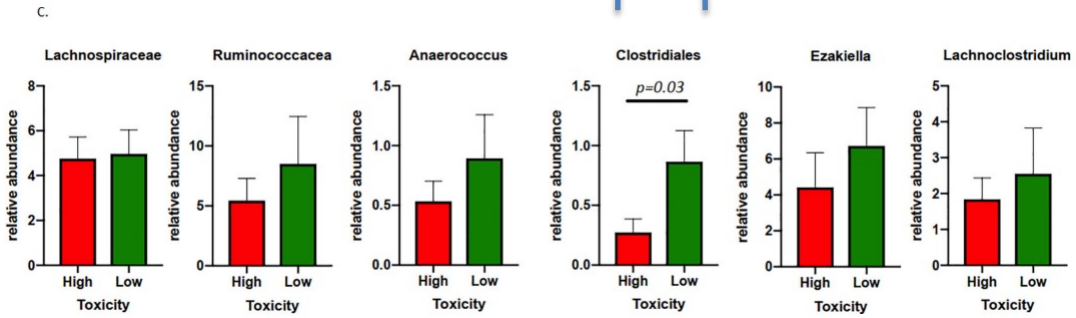
Mitra A, IJROBP 2020

Microbioma and toxicity





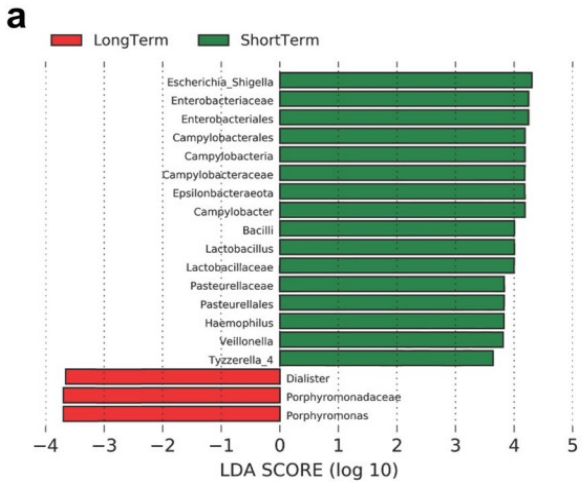
Less at risk of developing RE

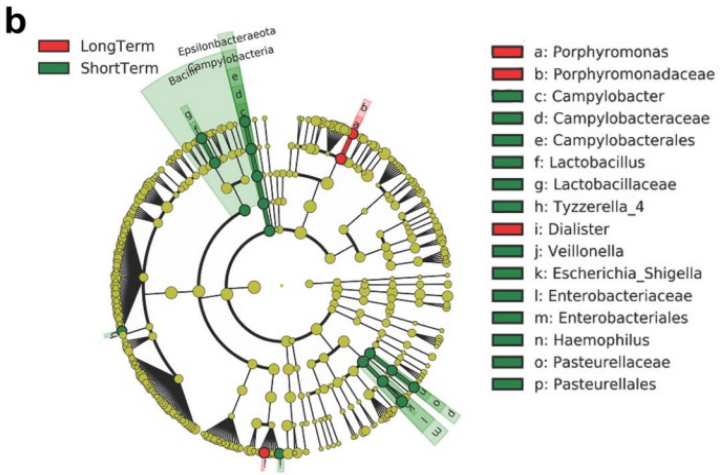


Mitra A, IJROBP 2020

Gut microbiome diversity is an independent predictor of survival in cervical cancer patients receiving chemoradiation

communications biology





Sims TT, 2021

Gut microbiome diversity is an independent predictor of survival in cervical cancer patients receiving chemoradiation

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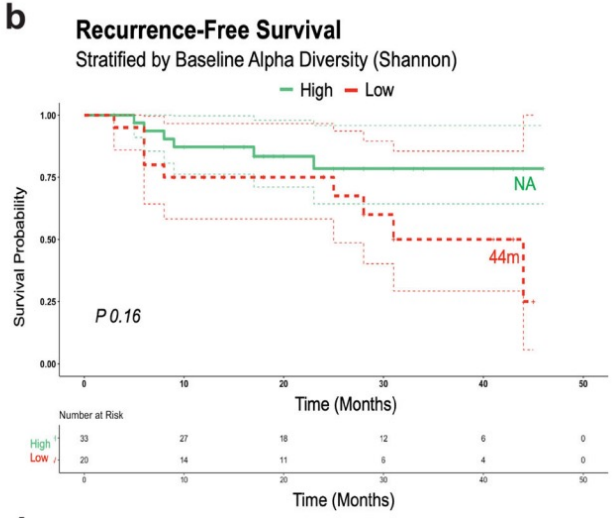
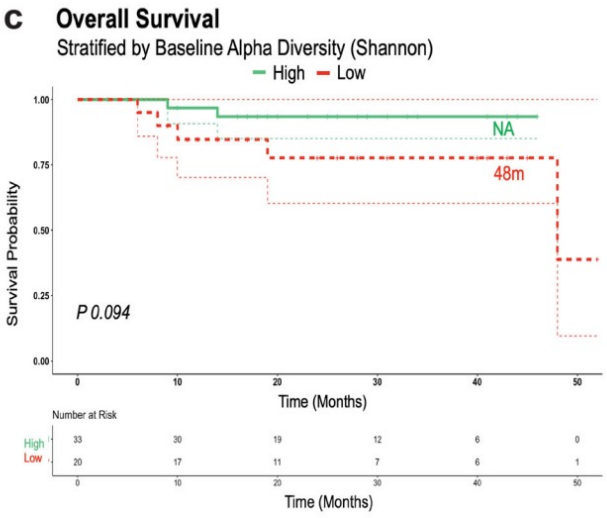
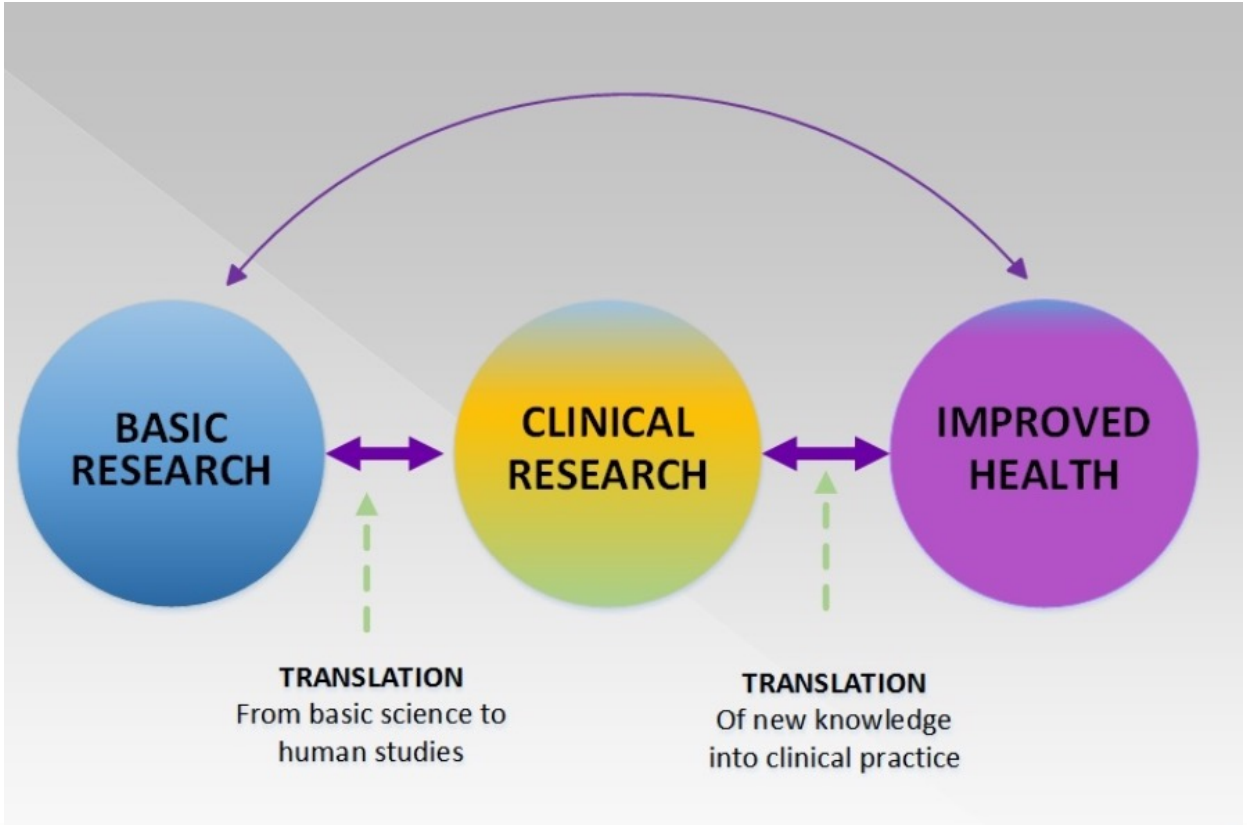
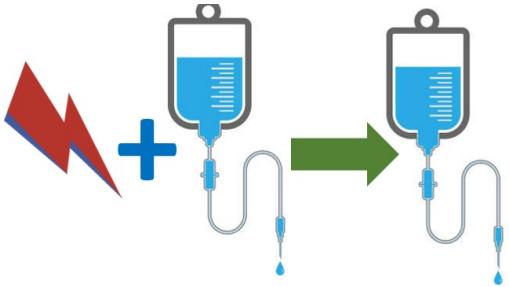
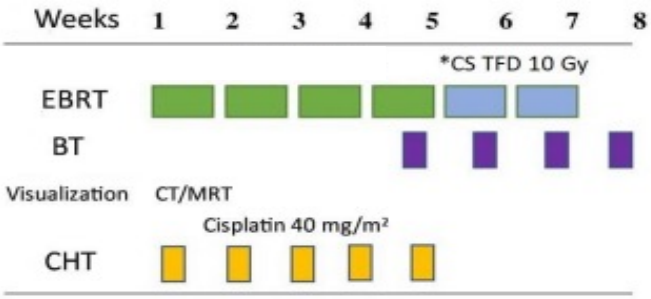


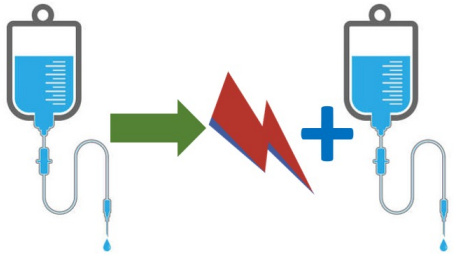


Sims TT, 2021


BASIC RESEARCH
CLINICAL RESEARCH
IMPROVED HEALTH
TRANSLATION
From basic science to human studies
TRANSLATION
Of new knowledge into clinical practice



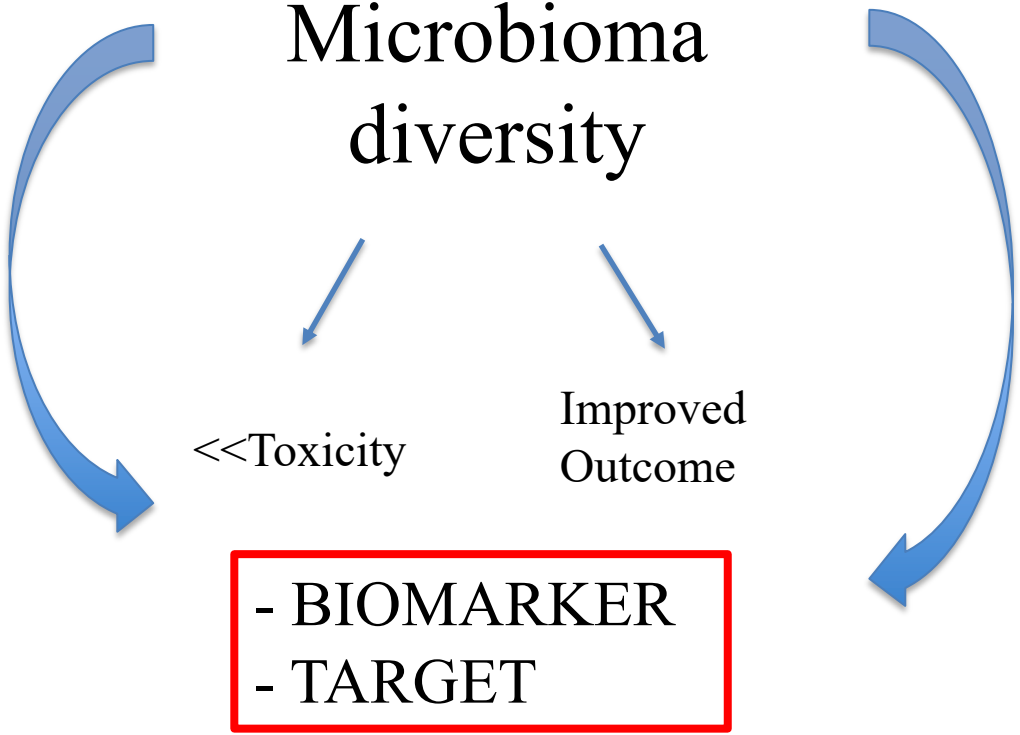




Adding NAD:
- phase II trials negative
- INTERLACE ongoing

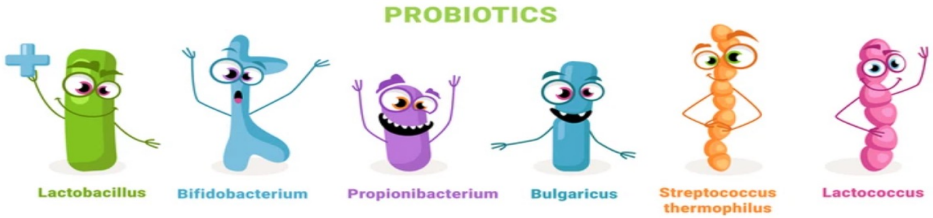
Reducing toxicities through new technologies

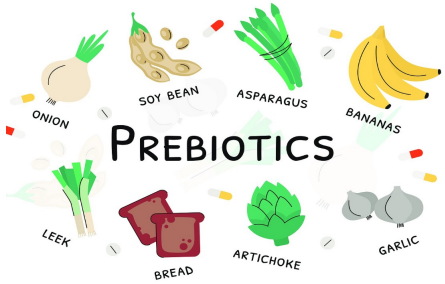
Adding AT (chemo or immunotp):
- OUTBACK trial negative
- CALLA trial negative
- Keynote A18 trial positive (PFS experimental arm: 67.8 vs57.3, HR0.7, p=0.002)


Microbioma
diversity
<<Toxicity
Improved
Outcome
- BIOMARKER
- TARGET

Modulating microbioma

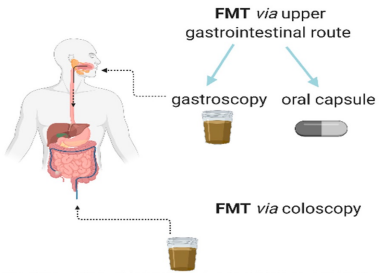
«live microorganisms that, when administered in adequate amounts confer a health benefit on the host»



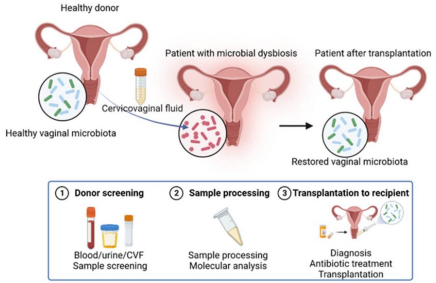


«indigestible carbohydrates which promote the growth of healthy bacteria already present in the body»

Fecal microbioma trasplant

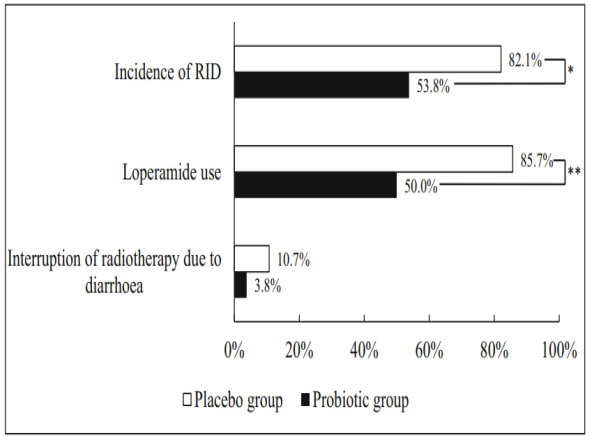


Vaginal microbioma trasplant



To reduce toxicity

PROBIOTICS



* = $p < 0.05$, ** = $p < 0.01$

Linn YH, Probiotics Antimicro 2019
Delia P, World J Gastroenterol 2007

PREBIOTICS

- ✓High fibre diet may decrease toxicity and associated symptoms
- ✓Fibre intake reduced the frequency of diarrhoea
- ✓Inuline improved stool consistency

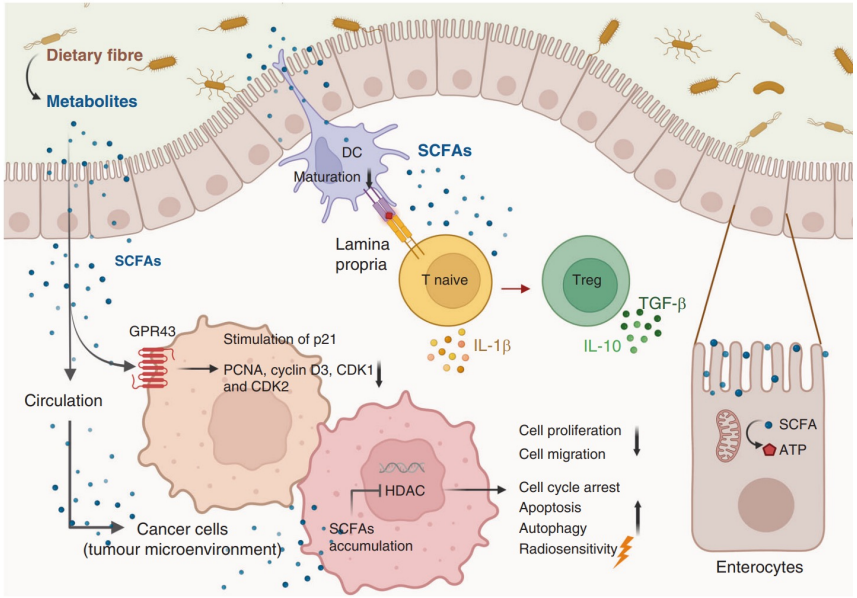
Wedlake L, Am J Clin Nutr 2017
Deleemans JM, Integr Cancer Ther 2021
Garcia Peris P, Eur J Clin Nutr 2016

FMT

In a 5 patients pilot study 3 patients responded to FMT (reduction of endoscopic mucosal damage); the benefit was temporary

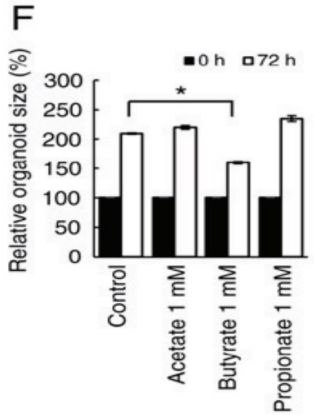
Ding X, Radioth Oncol 2020

...to enhance tumor response



Eaton SE, British J of Cancer 2022

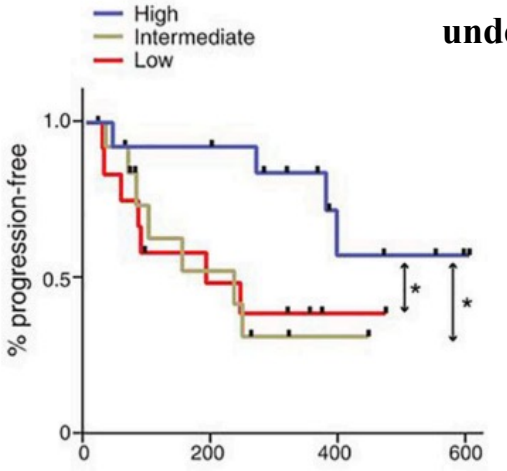
Butyrate showed anticancer effects

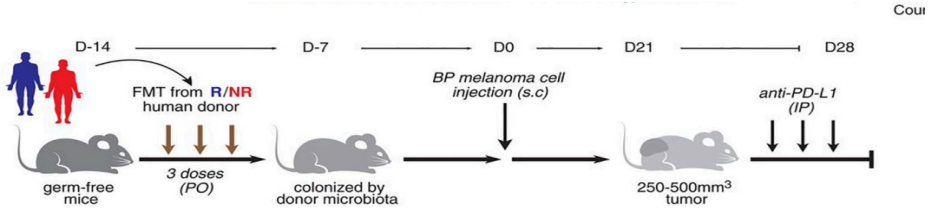


Park M Int J Oncol 2020

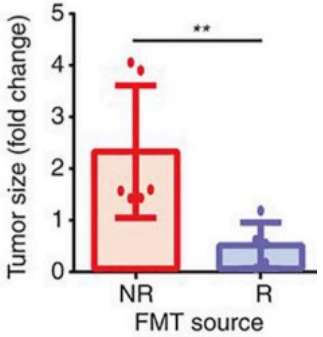
...to enhance immune-response

Gut diversity improves PFS in advanced melanoma patients undergoing ICIs





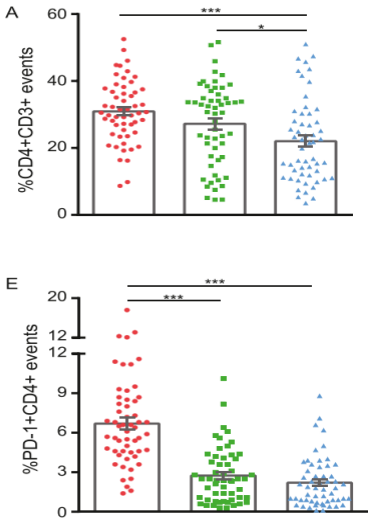
FMT from Responders donor in mice obtained regression of tumor

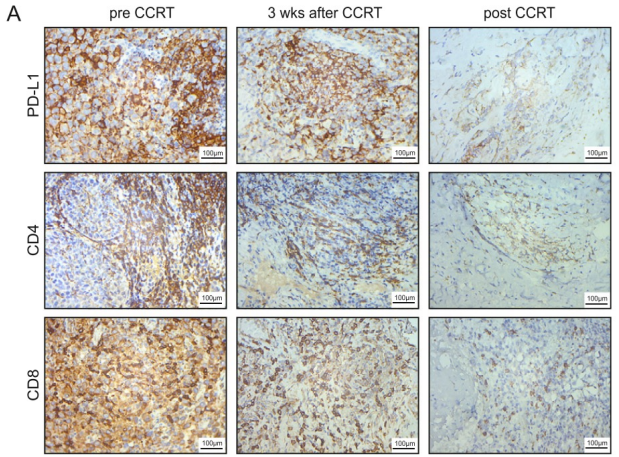


Gopalakrishnan V 2018

...to improve microenvironment

During CCRT a suppression of T-cell immunity has been documented





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AIRO2023

Radioterapia Oncologica:
l'evoluzione al servizio dei pazienti

...to improve microenvironment

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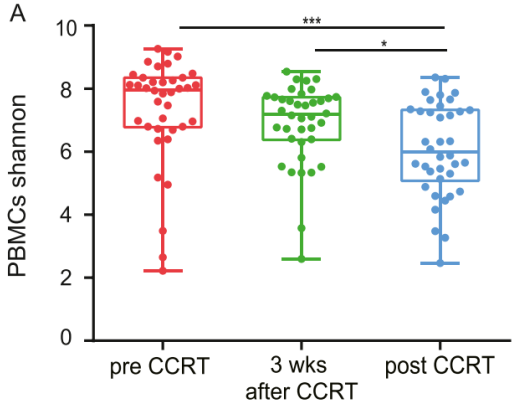

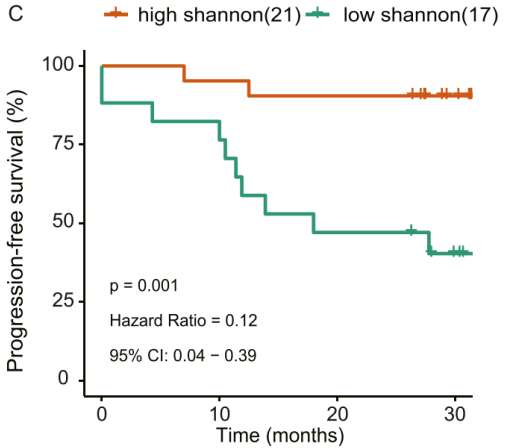

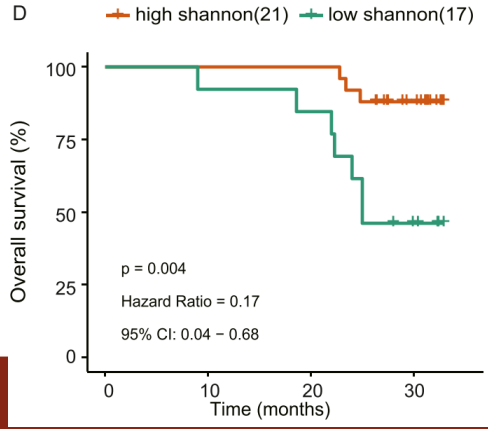

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Gut diversity and increased tumor infiltration of lymphocytes in cervical cancer patients

	P value*
CD4+ Ki.67+ at T4	0.004‡
CD4+ CD69+ at T3	0.004‡
CD4+ PD1+ at T3	0.0367‡
CD4+ CTLA4+ at T3	0.057
CD4+	—

Sims TT, 2021

Conclusions

Microbioma plays a major role in treatment of gynecological cancer
Alpha diversity showed to be related to toxicity and to response to treatment

Microbioma focused research should be increased but:
- longitudinal data
- explore mechanism
- metagenomics and metabolomics to better define microbioma