



# 21° Congresso Nazionale

Società Italiana di Tossicologia

**Pericolo, rischio  
e rapporto  
rischio-beneficio**

**BOLOGNA**

20-22 Febbraio 2023

[www.sitox.org](http://www.sitox.org)

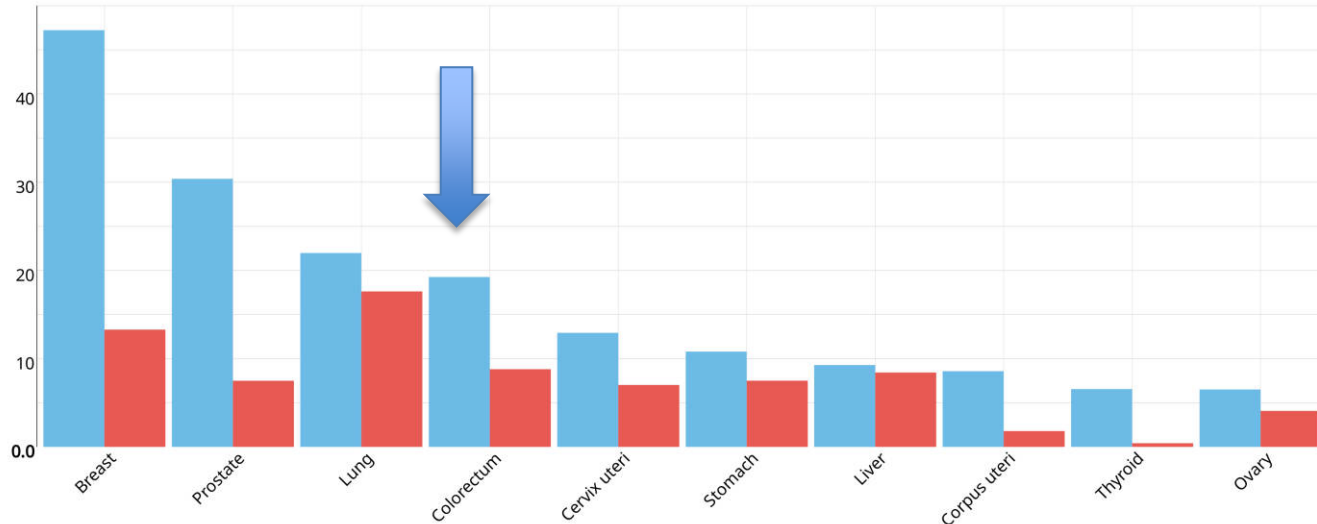
# **Il microbioma intestinale media l'effetto della dieta sul rischio di sviluppare cancro del colon: confronto tra diete a base di carne e dieta pesco-vegetariana in un modello di cancerogenesi sperimentale**

Sofia Chioccioli

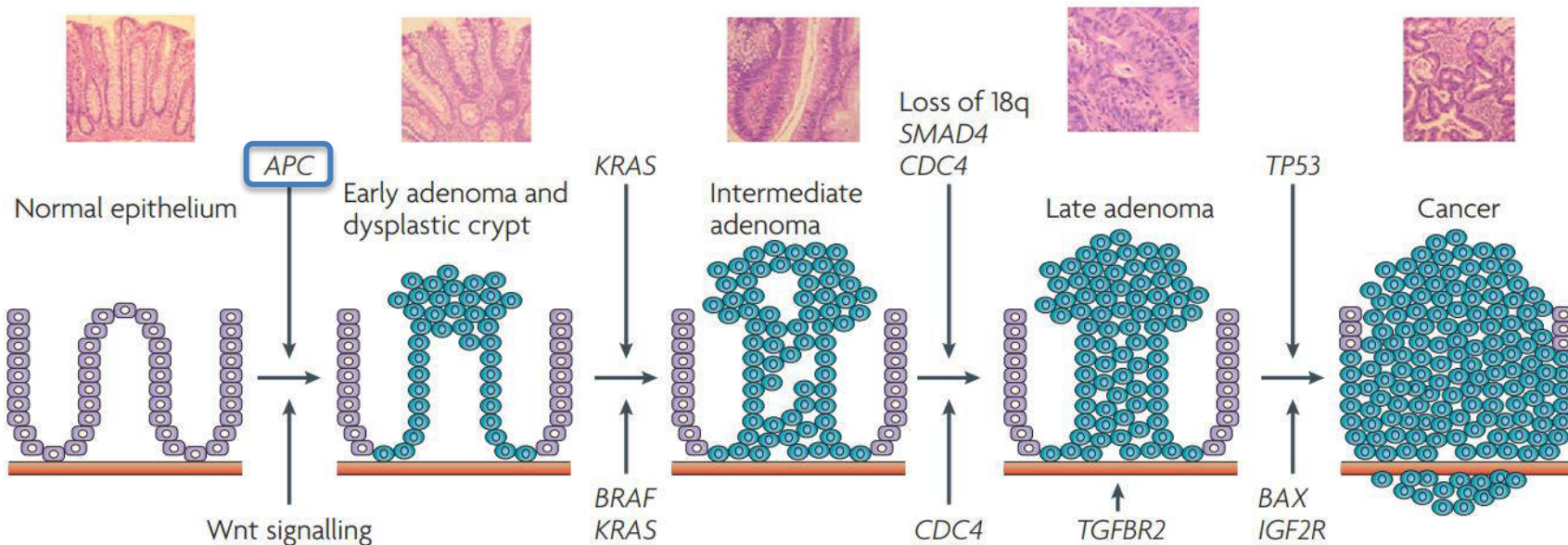
Bologna, 22 Febbraio 2023

# Il Cancro del Colon (CRC)

Estimated age-standardized incidence and mortality rates (World) in 2020, World, Italy, both sexes, all ages



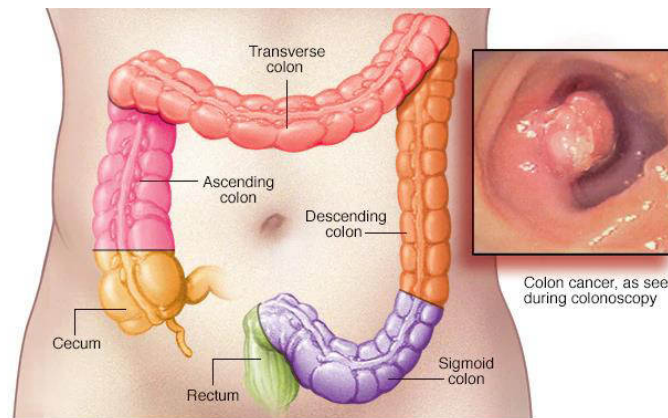
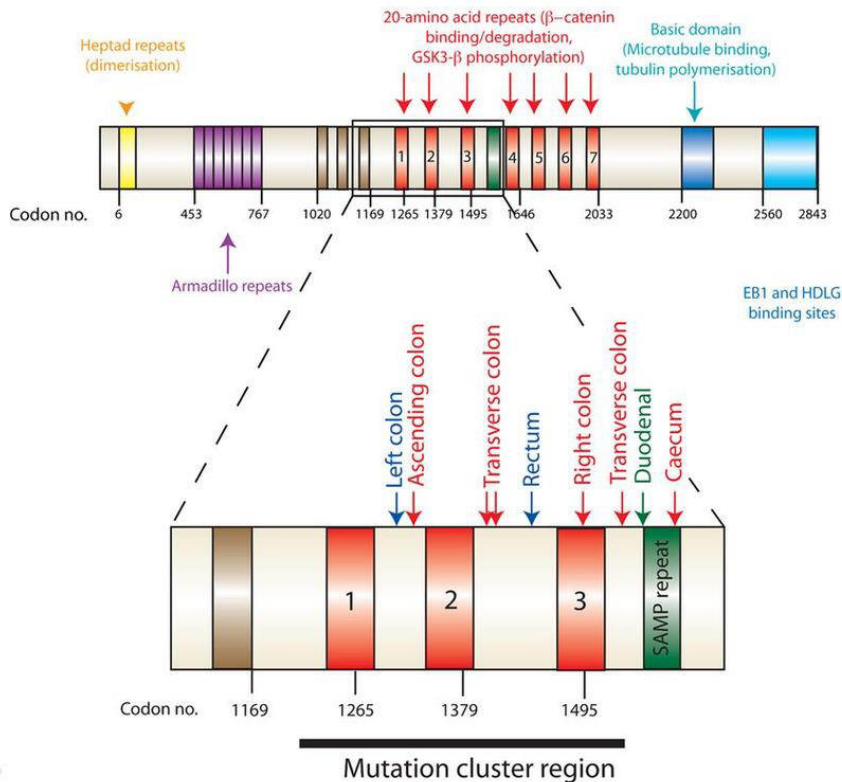
## Sequenza adenoma-carcinoma



Walther et al., 2009

### Fattori genetici

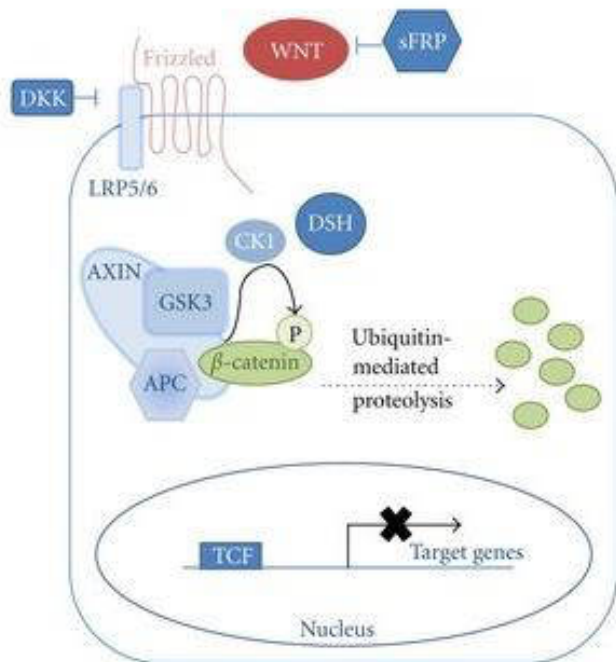
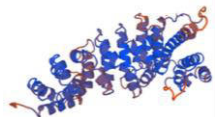
## Il gene *Apc*



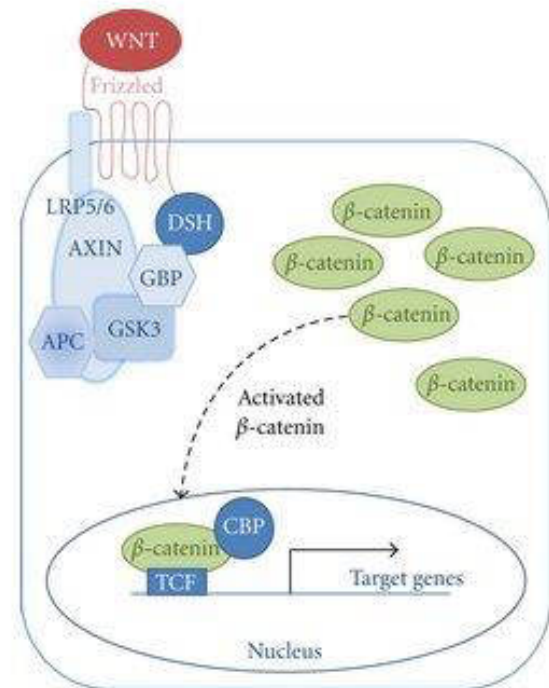
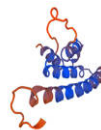
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# Pathway WNT/ $\beta$ -catenina

APC WT



APC troncata



Fattori ambientali

2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing	Physical activity	Processed meat Alcoholic drinks Body fatness Adult attained height
	Probable	Wholegrains Foods containing dietary fibre Dairy products Calcium supplements	Red meat
LIMITED EVIDENCE	Limited – suggestive	Foods containing vitamin C Fish Vitamin D Multivitamin supplements	Low intakes of non-starchy vegetables Low intakes of fruits Foods containing haem iron
	Limited – no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopen; retinol; energy intake; meal frequency; dietary pattern	
STRONG EVIDENCE	Substantial effect on risk unlikely		

2017

# DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER

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World Cancer Research Fund (WCRF, 2020).



2017

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2017

DIET, NUTRITION, PHYSICAL ACTIVITY  
AND COLORECTAL CANCER

DECREASES RISK

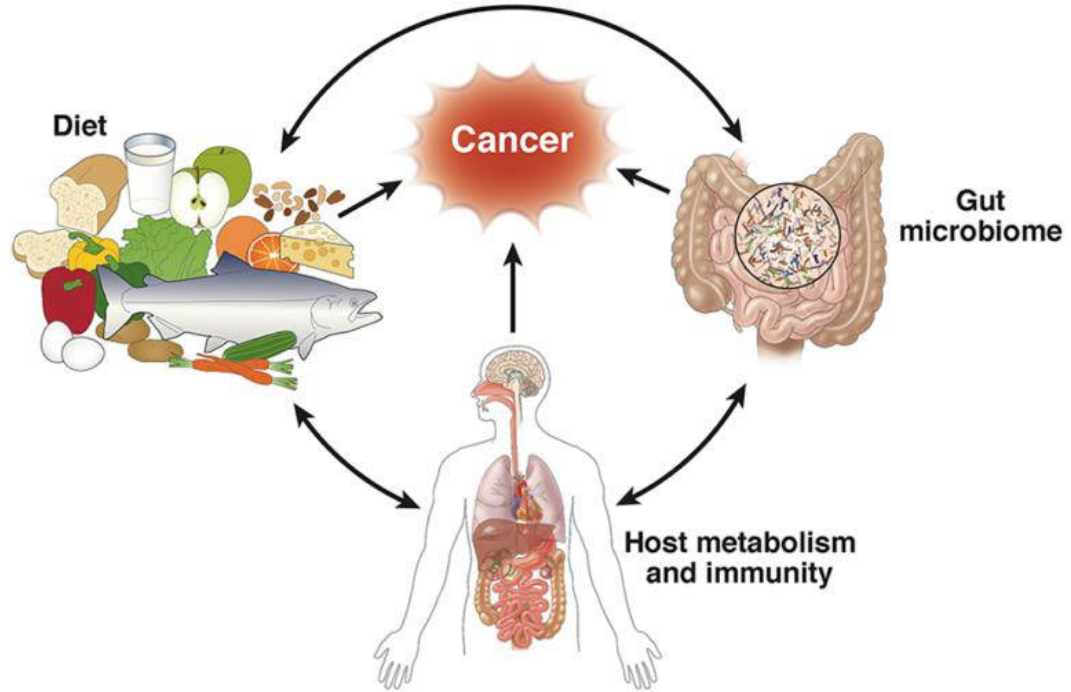
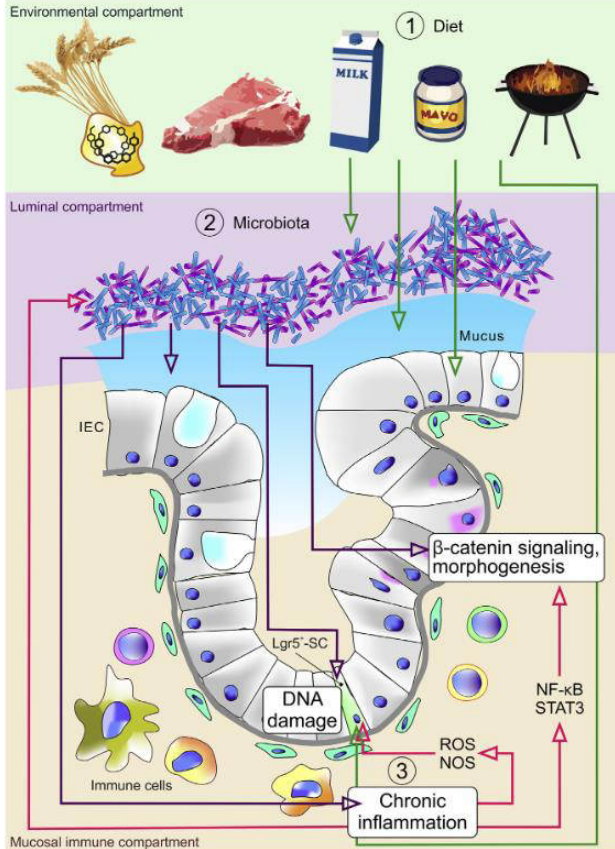
INCREASES RISK

<b>LIMITED EVIDENCE</b>	<b>Limited – suggestive</b>	<p>Foods containing vitamin C</p> <p>Fish</p> <p>Vitamin D</p> <p>Multivitamin supplements</p>	<p>Low intakes of non-starchy vegetables</p> <p>Low intakes of fruits</p> <p>Foods containing haem iron</p>
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<b>STRONG EVIDENCE</b>	<b>Substantial effect on risk unlikely</b>		

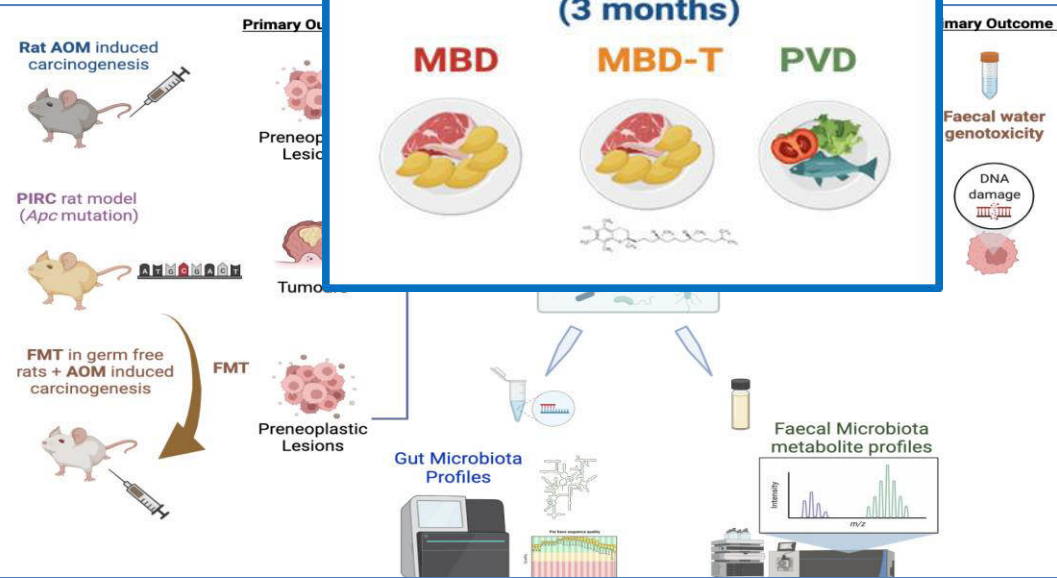
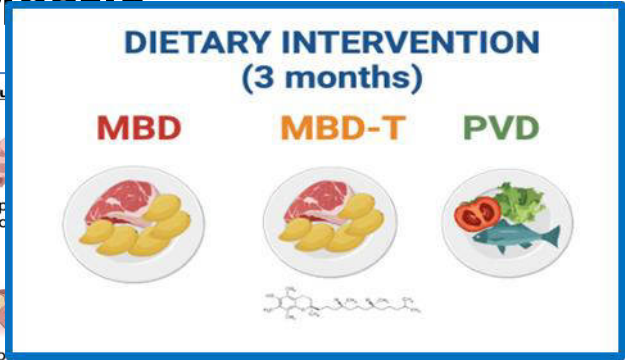
STRONG EVIDENCE

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World Cancer Research Fund (WCRF, 2020).



# Progetto Meistic

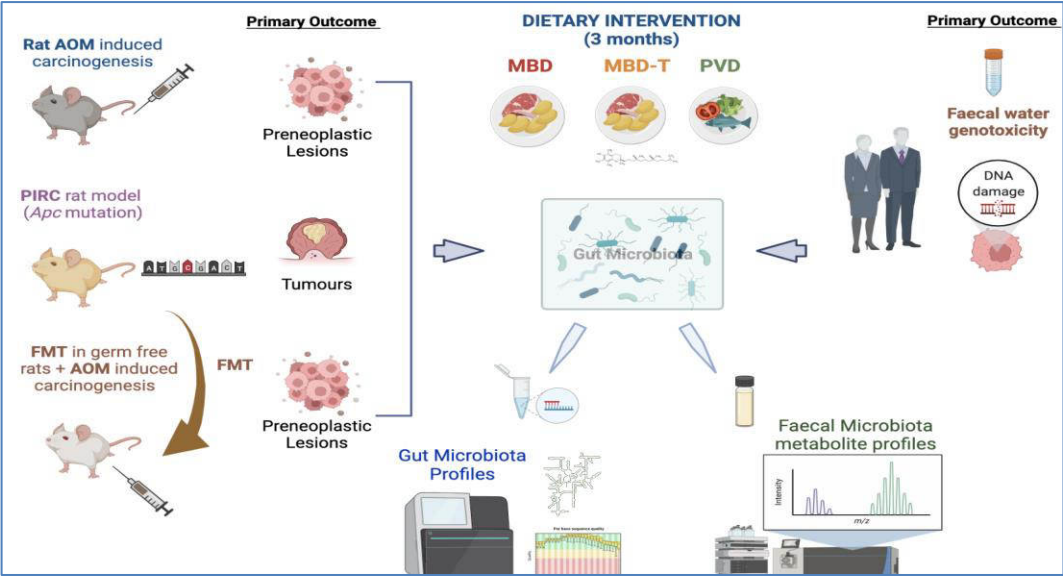


Valutazione dell'impatto del microbioma sul rischio di CRC associato alla **DIETA**



# Progetto Meatic

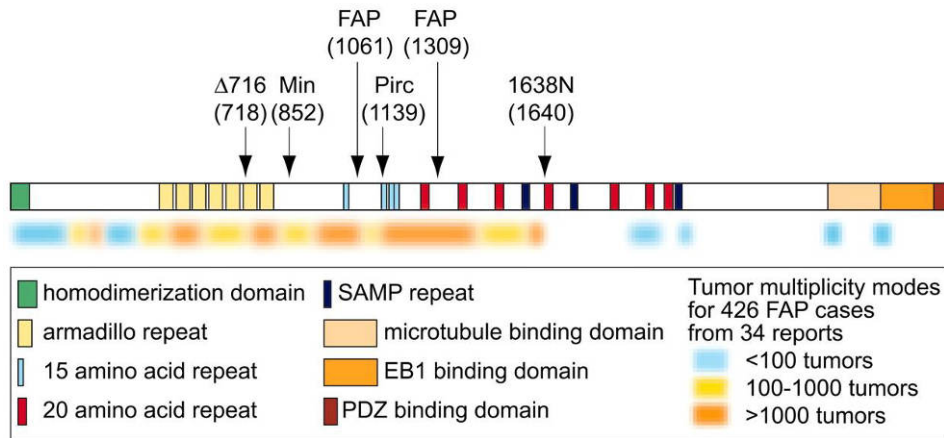
Valutazione dell'impatto del microbioma sul rischio di CRC associato alla **DIETA**



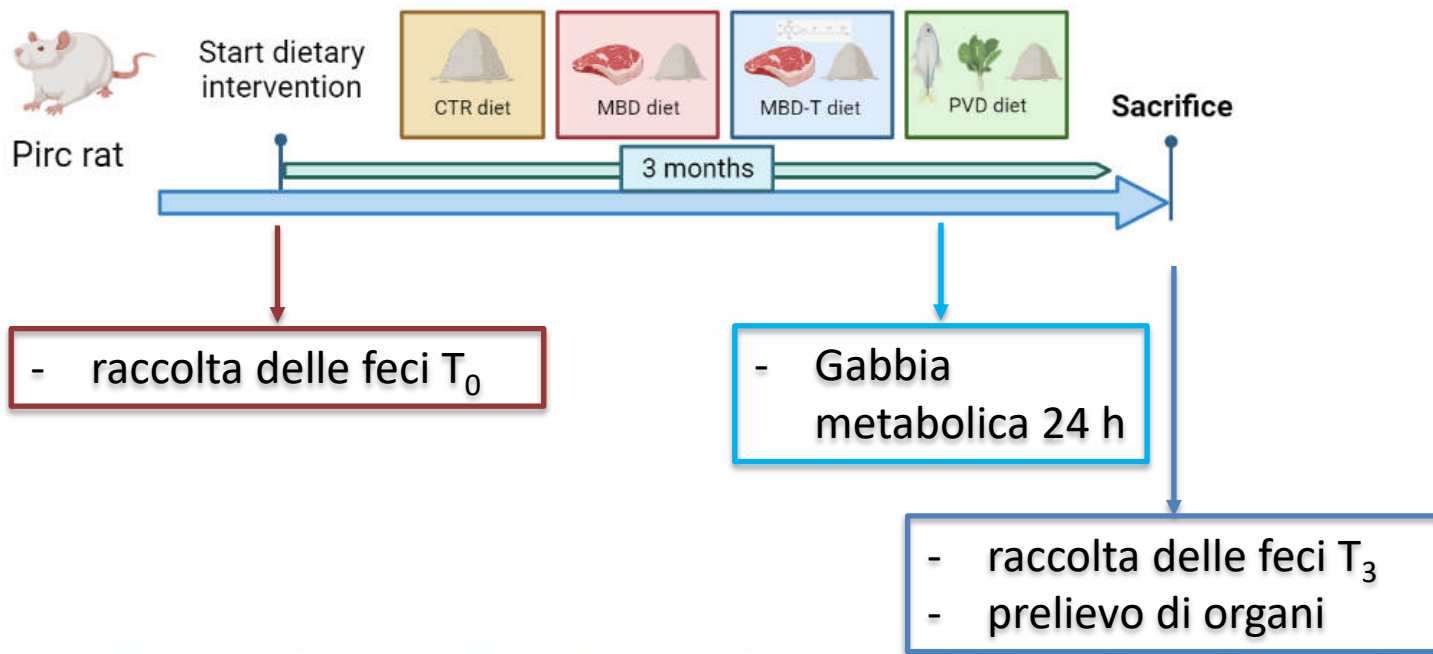
# Il ratto Pirc



F344-*Apc*<sup>am1137/+</sup>



## Disegno sperimentale

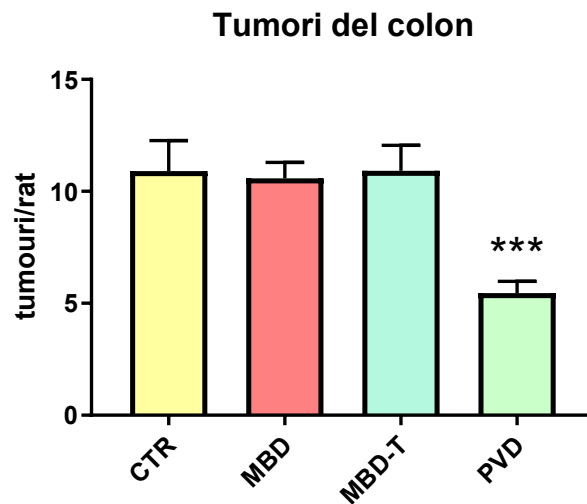




Colon



## Colon tumorigenesi



\*\*\*  $p < 0.011$  vs CTR; MBD, MBD-T

by one-way ANOVA and  
Tukey's multiple comparisons test

# Perossidazione lipidica

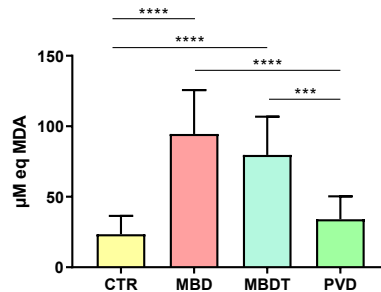


Fecal water  
urine  
faecal pellets

## Raccolta feci e urine delle 24h

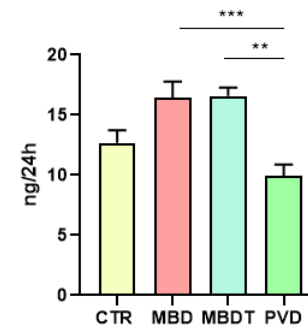
**TBARS**= Thiobarbituric acid reactive substances  
**HNE**= 4-Hydroxynonenal  
**DHN-MA**= 1,4-Dihydroxynonane mercapturic acid  
**8-isoPGF<sub>2</sub>α**= 8-isoprostane

### Fecal TBARS



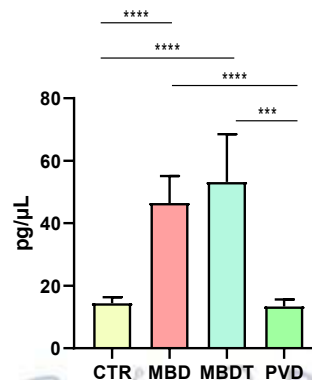
\*\*\*\* p<0.0001 CTR vs MBD-MBDT, MBD vs PVD  
\*\*\* p<0.0005 MBDT vs PVD

### urinary 8-isoPGF<sub>2</sub>α



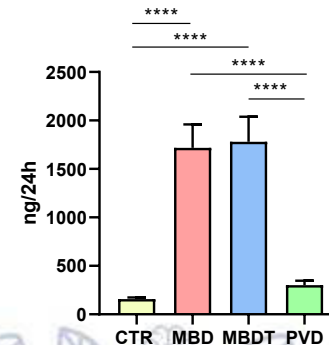
\*\*\* p=0.006 MBD vs PVD  
\*\* p=0.003 MBDT vs PVD

### HNE in FW



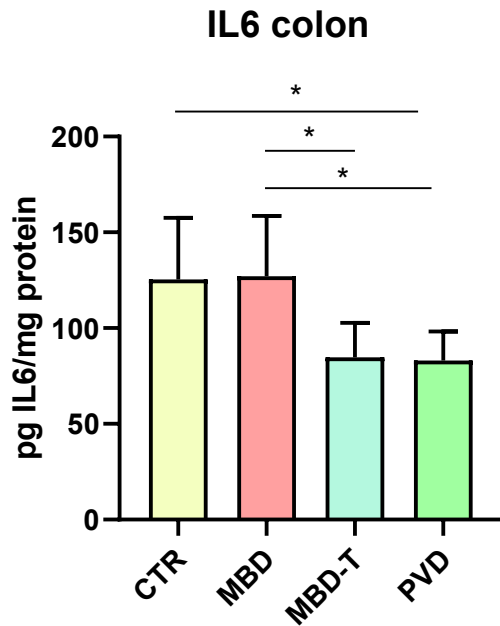
\*p<0.05 CTR vs MBD-MBDT, MBD-MBDT vs PVD

### Urinary DHN-MA

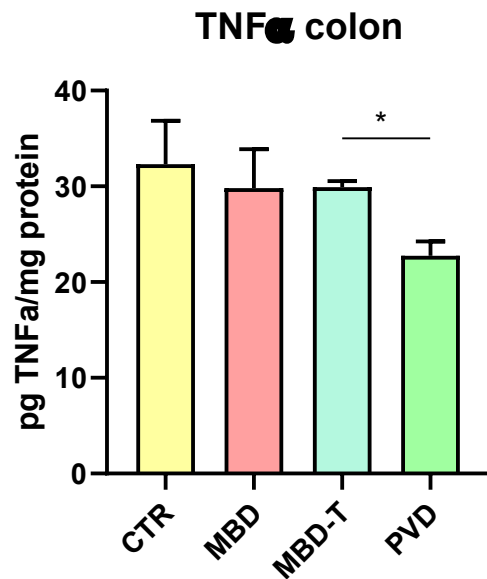


\*\*\*\* p<0.0001 CTR vs MBD-MBDT, MBD-MBDT vs VD

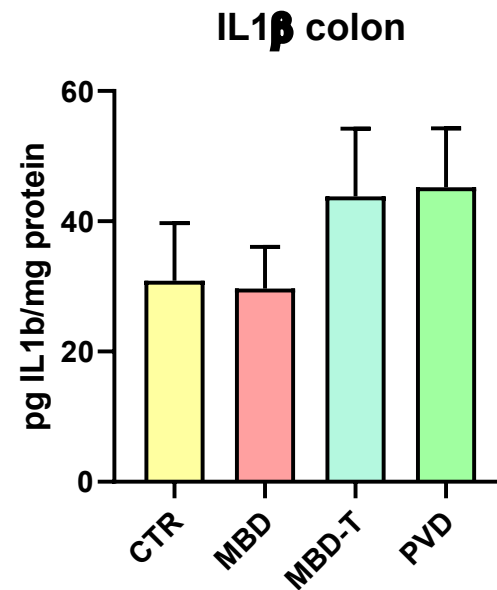
# Citochine del colon (mucosa normale)



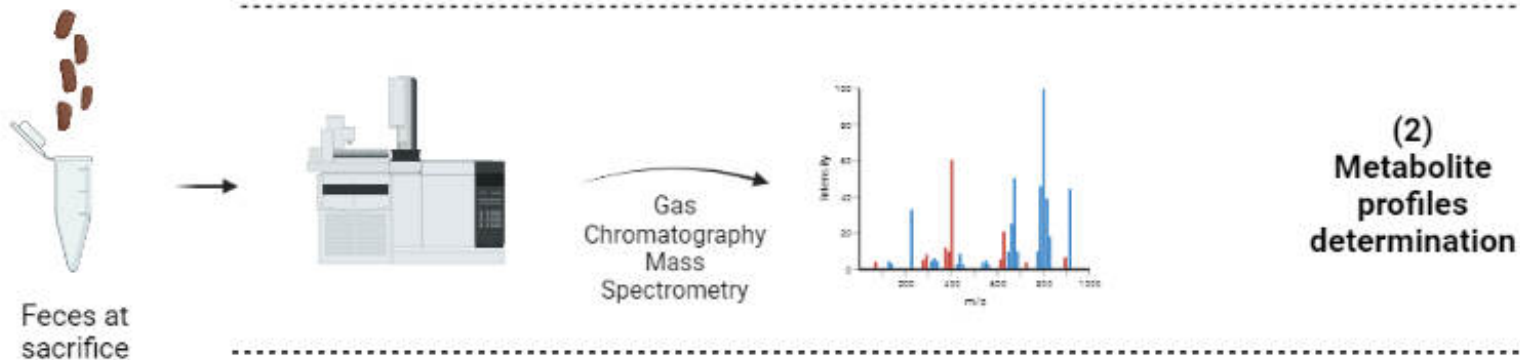
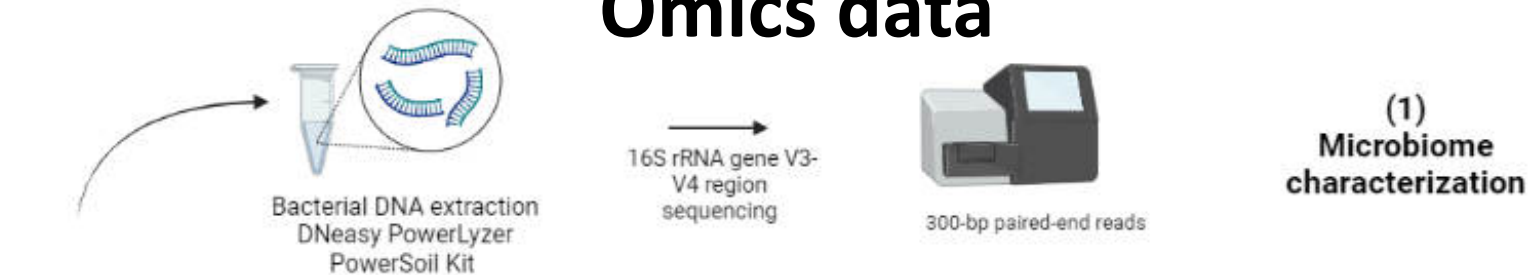
ANOVA P=0.008



ANOVA P = 0.02

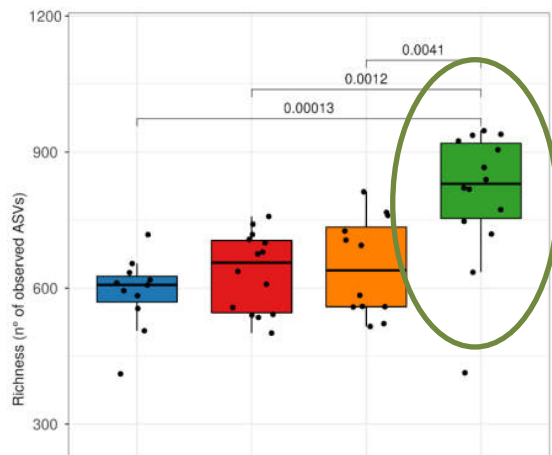


# Omics data

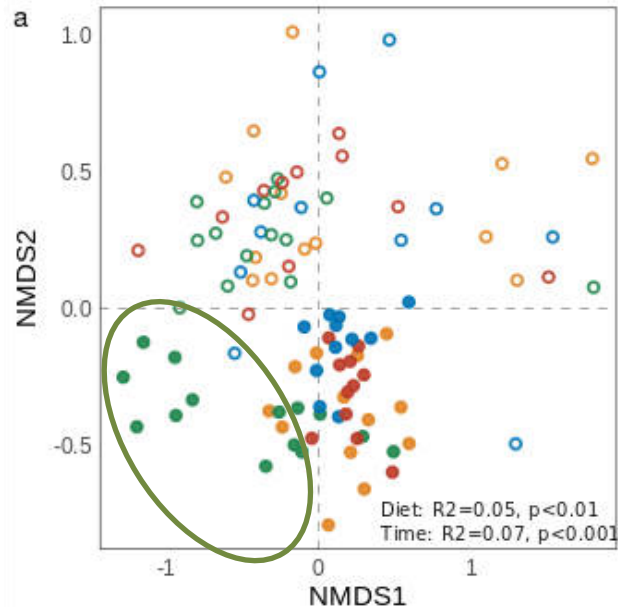


# (1) Caratterizzazione del microbioma

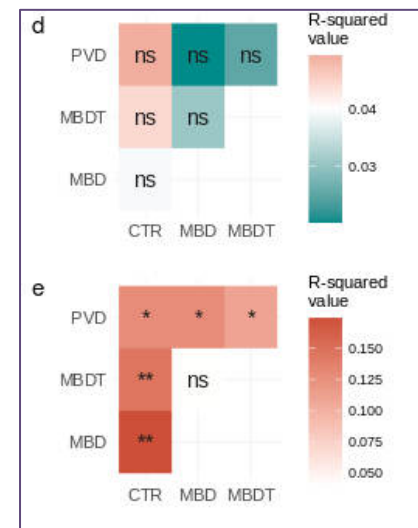
## Alpha-Diversity



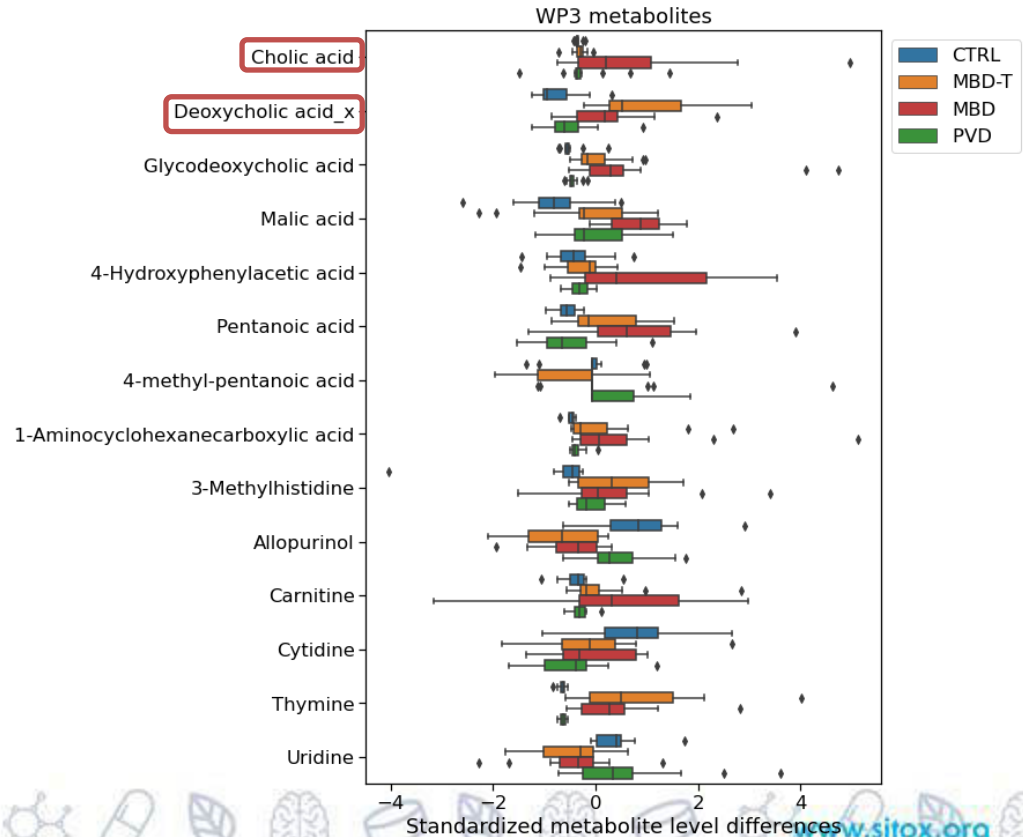
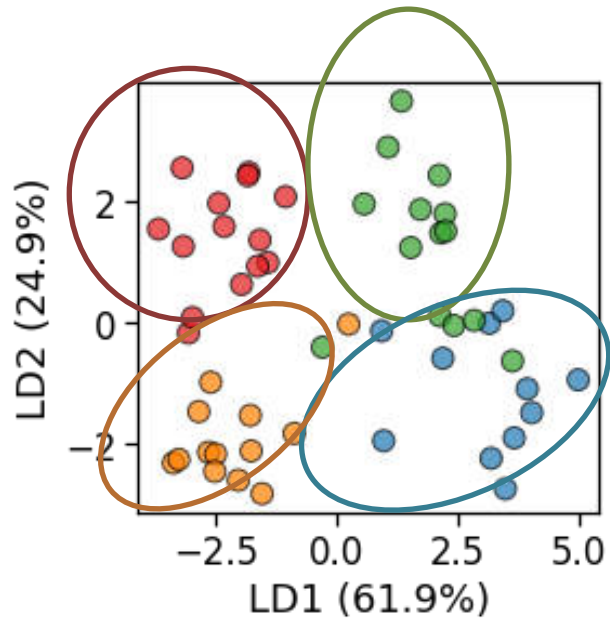
## Beta-Diversity



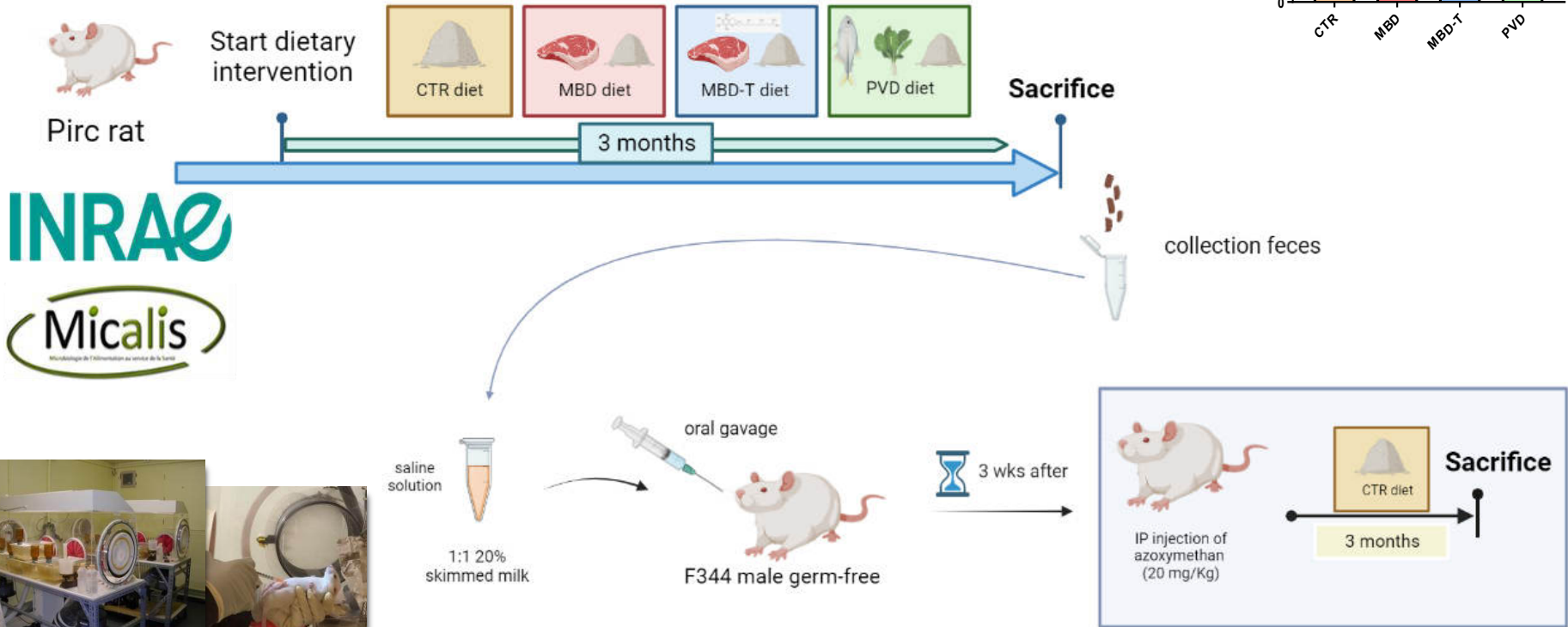
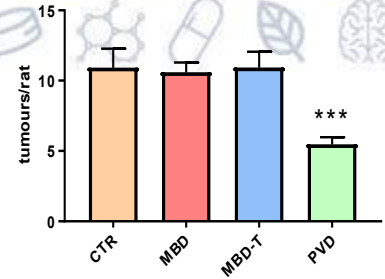
## PERMANOVA



## (2) Caratterizzazione dei metaboliti



### (3) Faecal Microbiota Transplantation (FMT)



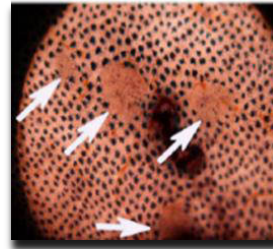
INRAE

Micalis

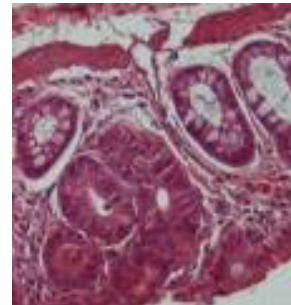


## MDF= Mucin Depleted Foci

- Lesioni preneoplastiche presenti sia negli uomini sia negli animali.
- Ridotta produzione di mucina.
- Formati da cripte che appaiono distorte quando comparate con le cripte vicine.



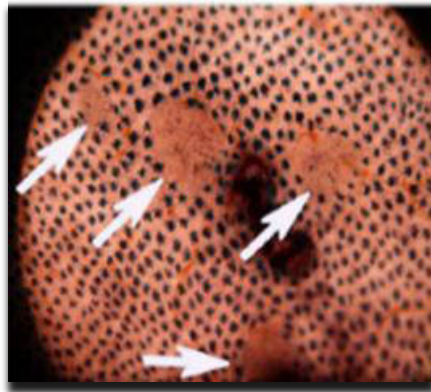
high-iron diamine Alcian blue staining (HID-AB)



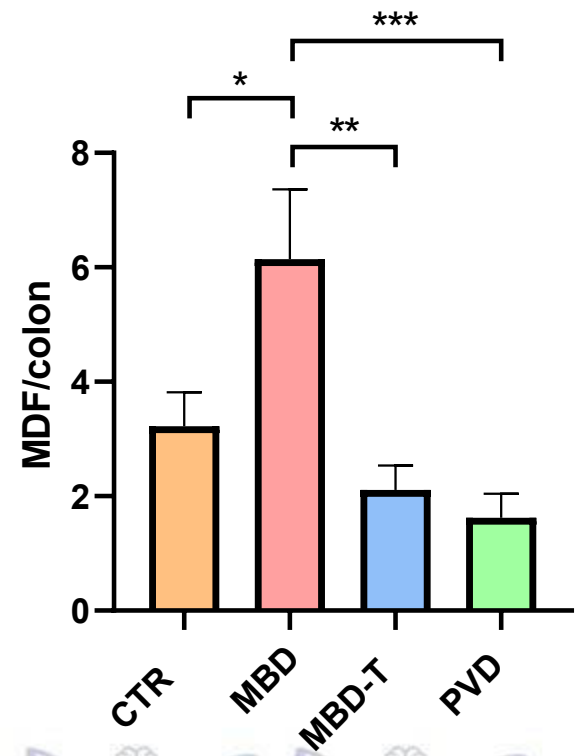
H&E staining



### (3) Faecal Microbiota Transplantation (FMT)



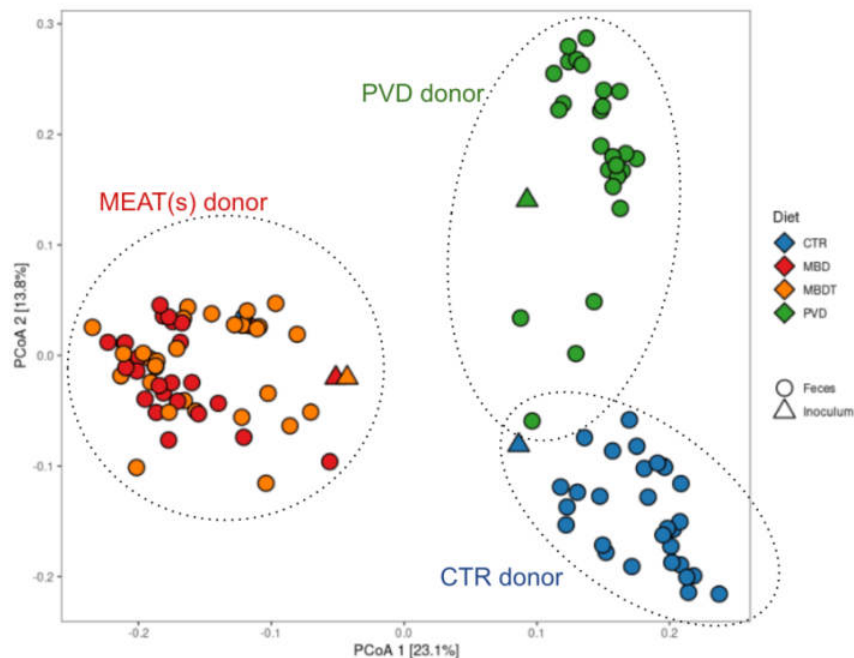
MDF/colon



\* p=0.03  
 \*\* p= 0.002  
 \*\*\* p= 0.001

### (3) Faecal Microbiota Transplantation (FMT)

#### Beta-Diversity



# Conclusioni

- La dieta PVD mostra un forte effetto protettivo sulla cancerogenesi intestinale.
- La dieta è in grado di modulare la composizione del microbioma intestinale.
- Il contenuto intestinale (microbioma e metaboloma) è capace di trasmettere i fattori di rischio di CRC associati alla dieta.

# Grazie per l'attenzione



UNIVERSITÀ  
DEGLI STUDI  
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DIPARTIMENTO DI NEUROSCIENZE,  
PSICOLOGIA, AREA DEL FARMACO  
E SALUTE DEL BAMBINO

**INRAE**

**Toxalim**  
RESEARCH CENTRE IN FOOD TOXICOLOGY

**Fabrice Pierre**  
Francoise Gueraud  
Nathalie Naud

**INRAE**

**Micalis**  
Microbiologie de l'Alimentation au service de la Santé

**Philippe Gerard**  
Camille Etienne

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Laura Pucci  
Francesco Vitali

**Giovanna Caderni**  
Francesco Sofi  
Monica Dinu  
Lisa Giovannelli  
Sofia Chioccioli

# **Il microbioma intestinale media l'effetto della dieta sul rischio di sviluppare cancro del colon: confronto tra diete a base di carne e dieta pesco-vegetariana in un modello di cancerogenesi sperimentale**

Sofia Chioccioli

Bologna, 22 Febbraio 2023



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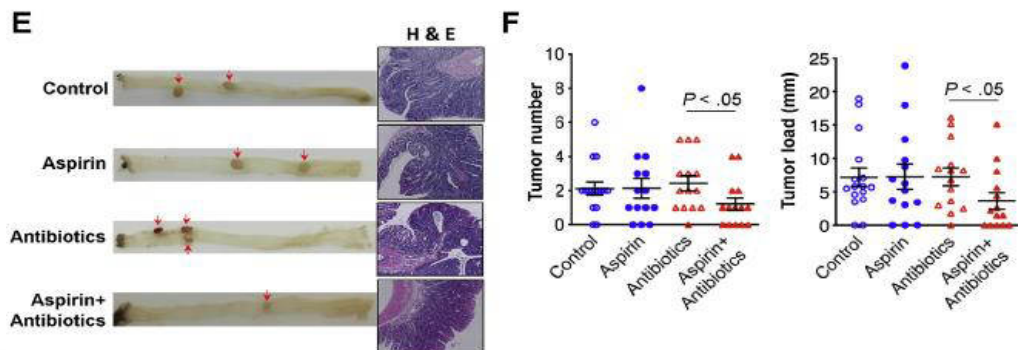
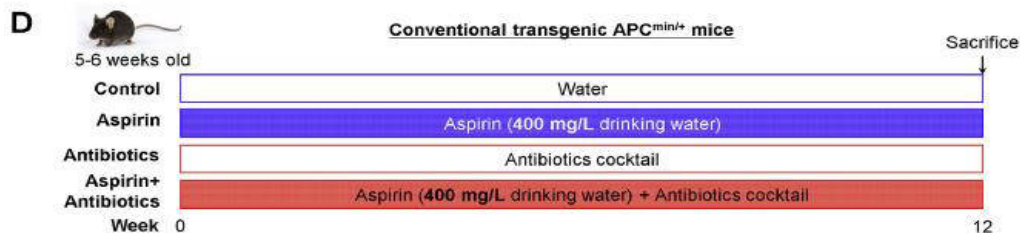
**BOLOGNA**

20-22 Febbraio 2023

[www.sitox.org](http://www.sitox.org)

## Aspirin Reduces Colorectal Tumor Development in Mice and Gut Microbes Reduce its Bioavailability and Chemopreventive Effects

Risheng Zhao<sup>1</sup>, Olabisi Oluwabukola Coker<sup>1</sup>, Jianlin Wu<sup>2</sup>, Yunfei Zhou<sup>1</sup>, Liuyang Zhao<sup>1</sup>, Geicho Nakatsu<sup>1</sup>, Xiqing Bian<sup>2</sup>, Hong Wei<sup>3</sup>, Anthony W H Chan<sup>4</sup>, Joseph J Y Sung<sup>1</sup>, Francis K L Chan<sup>1</sup>, Emad El-Omar<sup>5</sup>, Jun Yu<sup>6</sup>



Administration of ASA reduced the colorectal tumours number and load in APC<sup>min/+</sup> and mice given AOM and DSS that had been given antibiotics but not in mice with intact microbiota.





# NSDAIDs in combination with chemopreventive diet

DOLOGNA 20-22 Febbraio 2023

Pericolo, rischio e rapporto rischio-beneficio

## Aspirin (ASA)



Male Piric rats

Start dietary intervention  
1 month old

CTR diet

CTR diet + ASA 800 ppm

CTR diet + ASA 1600 ppm

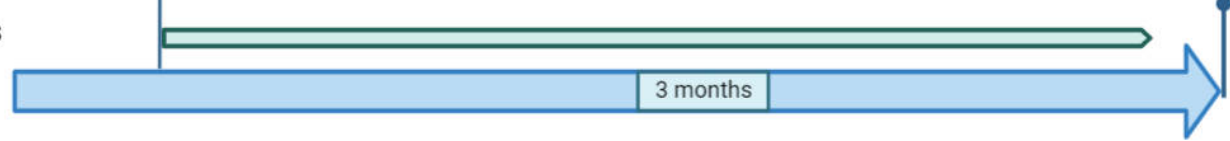
PVD diet

PVD diet + ASA 800 ppm

PVD diet + ASA 1600 ppm



Sacrifice



## Sulindac (SU)



Male Piric rats

Start dietary intervention  
1 month old

CTR diet

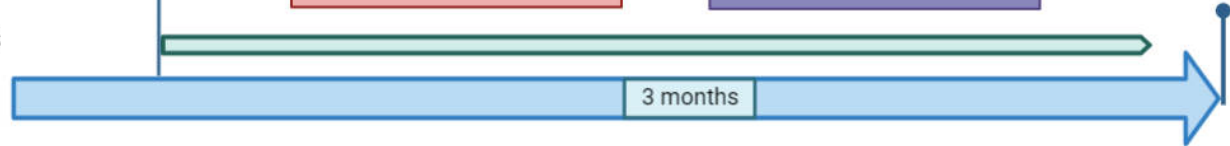
CTR diet + SU 80 ppm

PVD diet

PVD diet + SU 80 ppm



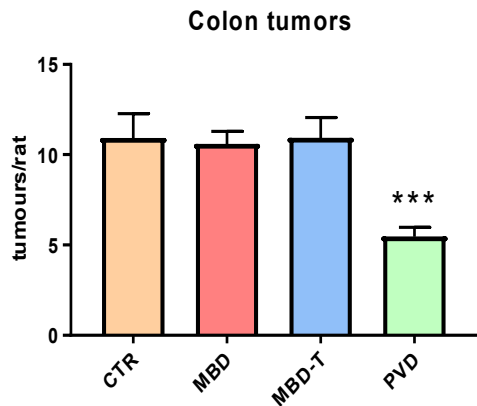
Sacrifice





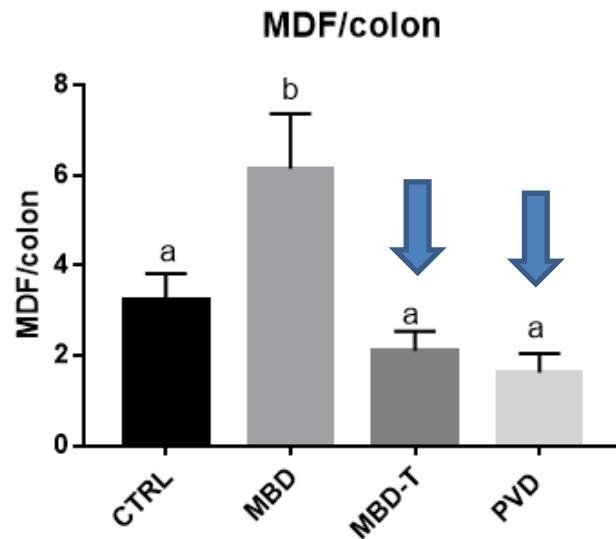
# Calcium and $\alpha$ -tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers

Fabrice H F Pierre<sup>1</sup>, Océane C B Martin, Raphaëlle L Santarelli, Sylviane Taché, Nathalie Naud, Françoise Guéraud, Marc Audebert, Jacques Dupuy, Nathalie Meunier, Didier Attaix, Jean-Luc Vendeuvre, Sidney S Mirvish, Gunter C G Kuhnle, Noel Cano, Denis E Corpet



\*\*\*  $p < 0.011$  vs CTR; MBD, MBD-T

No differences  
in MBD-T  
group.



ANOVA:  $P = 0.0017$

by one-way ANOVA and  
Tukey's multiple comparisons test



Pirc rat

Start dietary intervention



CTR diet



MBD diet



MBD-T diet



PVD diet

Sacrifice

3 months

**From 0,1%  
tocopherol**

**To 0,4%  
tocopherol**



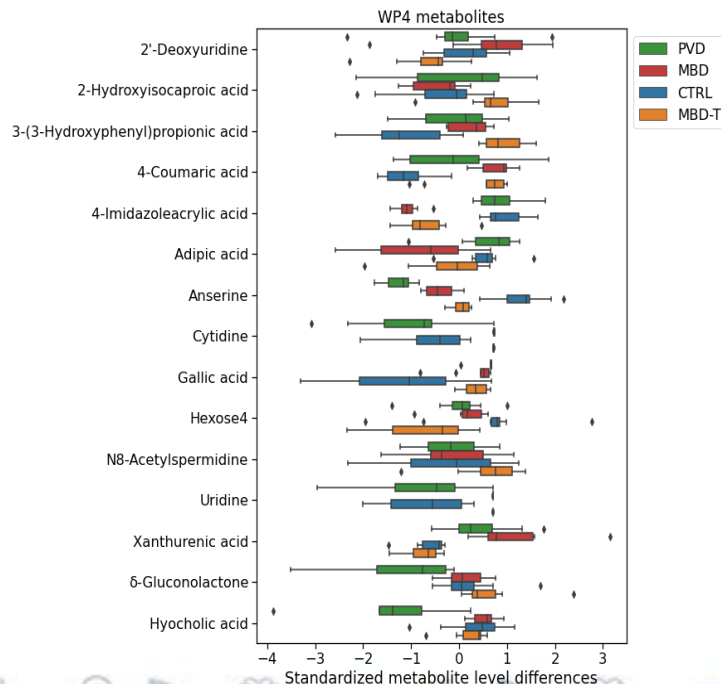
MBD-T diet

Additional group

(g)

# Composizione delle diete

	Diets		
	CON	MBD (T)	PVD
Casein	31,66	0,00	0,00
Corn starch	15,00	15,00	15,00
Sucrose	27,90	24,72	24,72
Cellulose	5,00	5,00	5,00
Methionine	0,30	0,30	0,30
AIN76 Mineral mix without Ca	3,50	3,50	3,50
AIN76 vitamin mix	1,00	1,00	1,00
Choline bitartrate	0,20	0,20	0,20
Ca phosphate	0,28	0,28	0,28
<b>Tot powder</b>	<b>84,84</b>	<b>50,00</b>	<b>50,00</b>
Safflower oil	5,00	5,00	5,00
Lard	10,16		0,00
Beef/ ham (dry matter)	0,00	45,00	
Fish (dry matter)			36,80
Spinach (dry matter)			8,20
<b>Tot additions</b>	<b>15,16</b>	<b>50,00</b>	<b>50,00</b>
<b>Total diet</b>	<b>100,00</b>	<b>100,00</b>	<b>100,00</b>



Dietary uridine, which is teratogenic in mice, decreases intestinal tumor formation in the ApcMin/+ mouse model.

Dietary uridine mimics the effect of the common methylene tetrahydrofolate reductase (MTHFR) C677T variant in protecting against colorectal cancer

Field, Martha S et al. Current developments in nutrition vol. 2,5 nzy013. 13 Mar. 2018