

Benoit Chassaing

*Mucosal microbiota in chronic inflammatory diseases*

INSERM U1016, Institut Cochin

# Host-Microbiota-Diet interaction

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*On our way to personalized care*



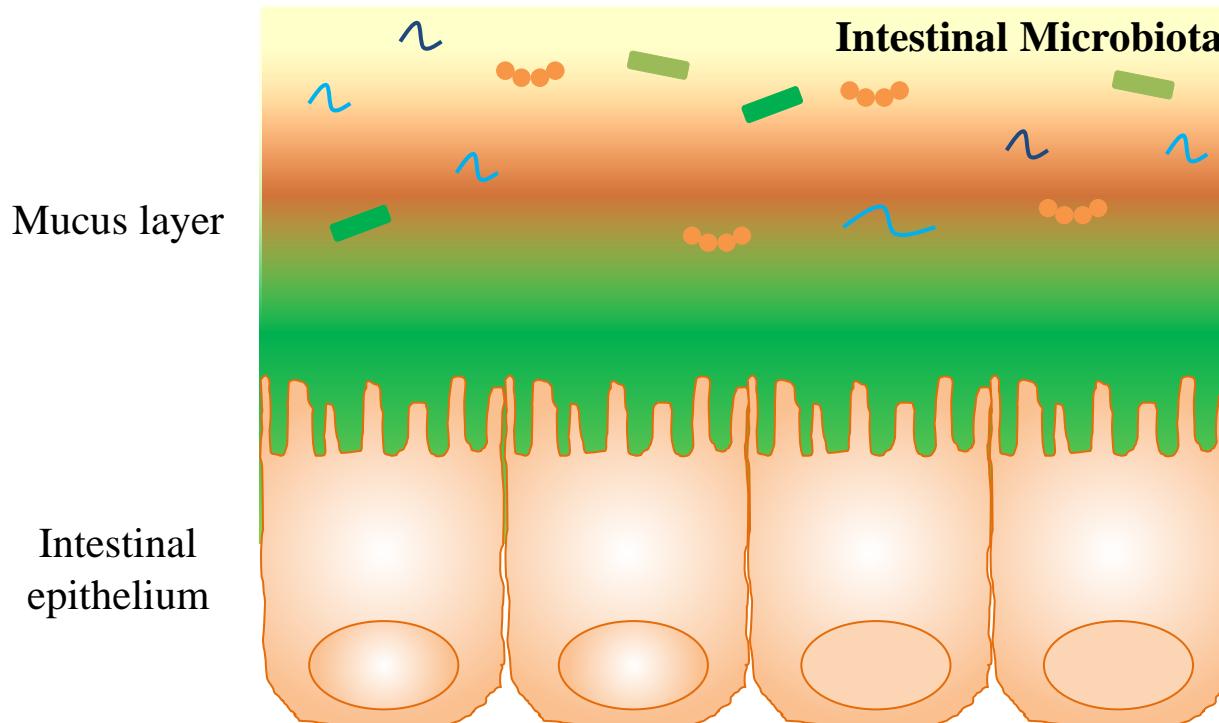
International Conference  
on Clinical Metagenomics

Banner-ICCMg



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# The intestinal microbiota in health and diseases



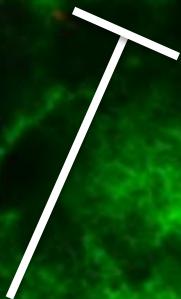
From Bretin, *Am J Physiol* 2018

## Beneficial roles

- Protection against pathogens
- Maturation of the immune system

## Detrimental roles

- Intestinal inflammation
- Metabolic deregulations



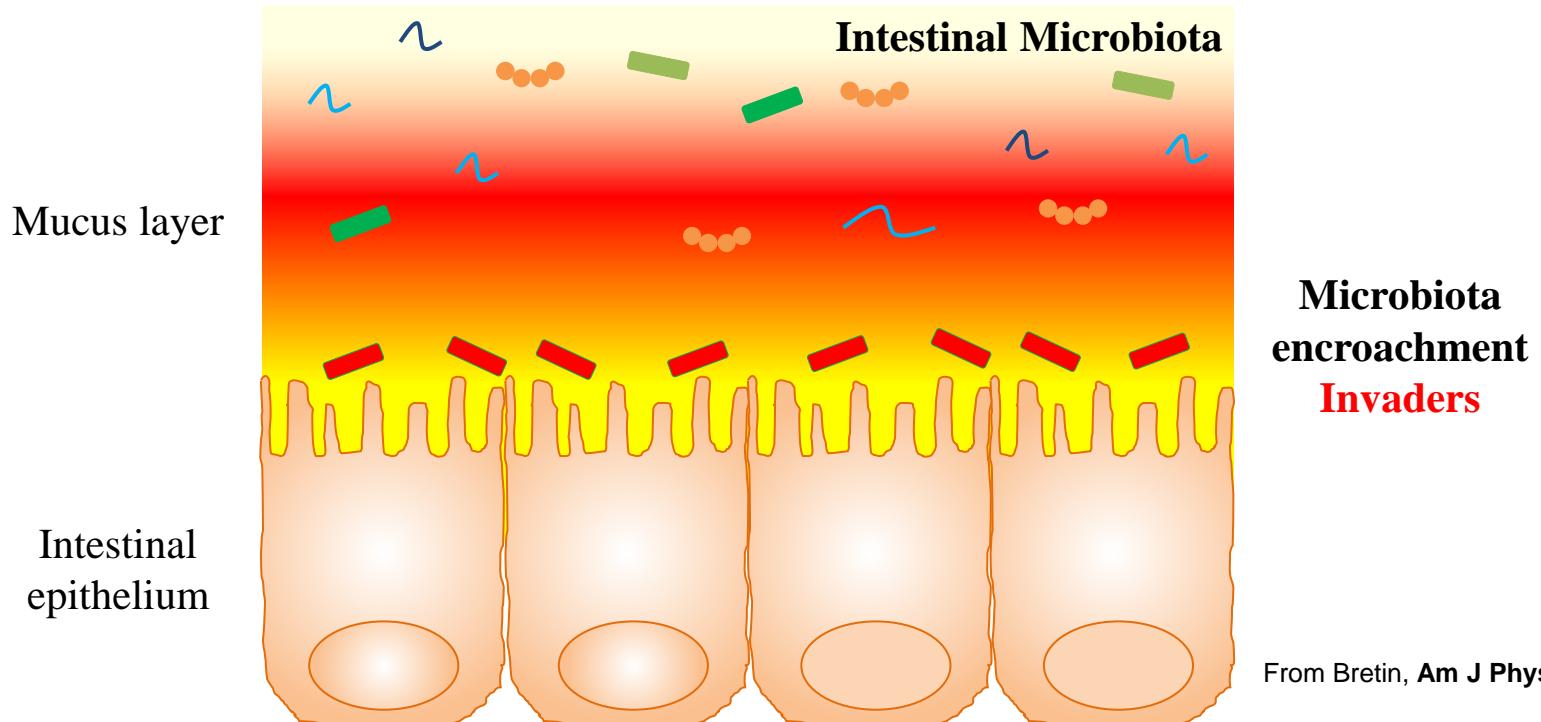
**Mucus layer**  
**Antimicrobial peptides**  
**IgA, IgG**

**TLRs / NLRs**



**Antimicrobial peptides**  
**Immune cell recruitment**

# The intestinal microbiota in health and diseases



## Beneficial roles

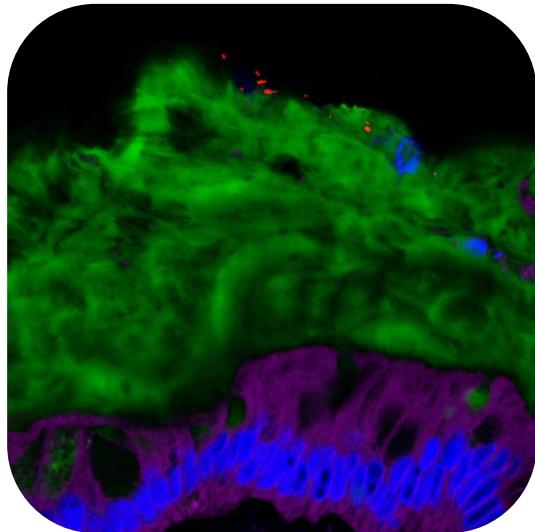
- Protection against pathogens
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## Detimental roles

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# The mucosal microbiota

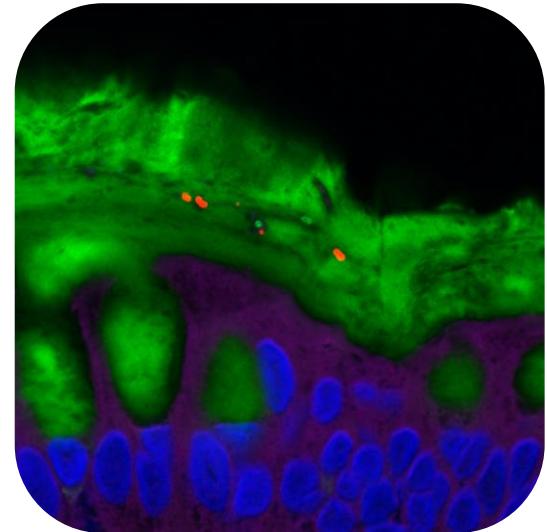
Inner mucus layer - Sterile



Mucus  
Actin

Bacteria  
DNA

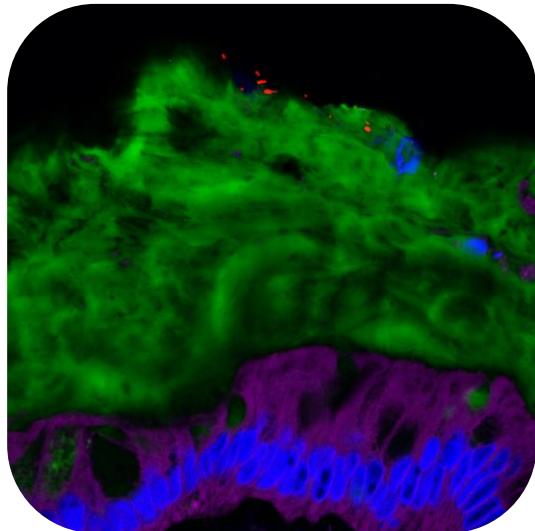
Microbiota encroachment  
**Invaders**



Intestinal inflammation

# The mucosal microbiota

Inner mucus layer - Sterile

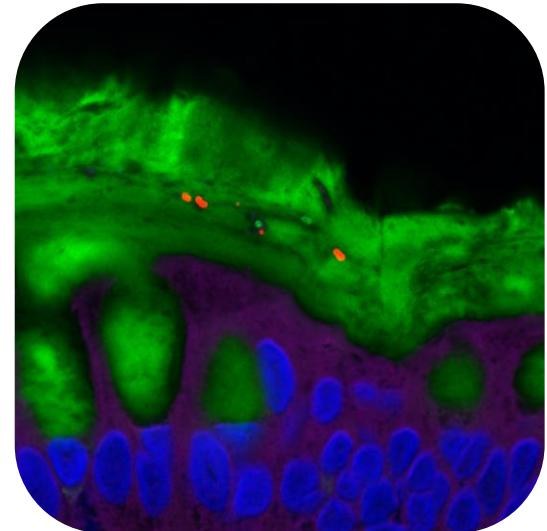


Mucus  
Actin

Bacteria  
DNA

Microbiota encroachment

Invaders



Dietary emulsifiers  
Genetical predisposition  
Lack of fiber  
Pathobiont infection



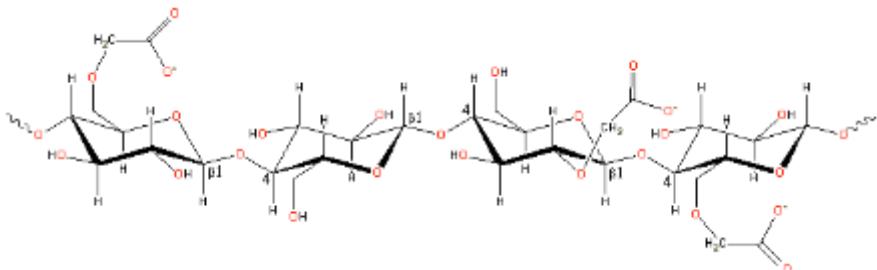
Intestinal inflammation

# Inflammatory Diseases – Impact of food additives

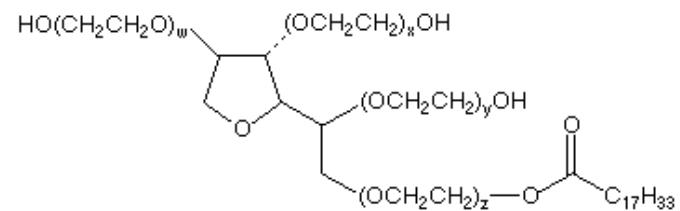
*Impact of emulsifiers on intestinal inflammation*



Dietary emulsifiers : food additives broadly used to improve texture and stabilize emulsion

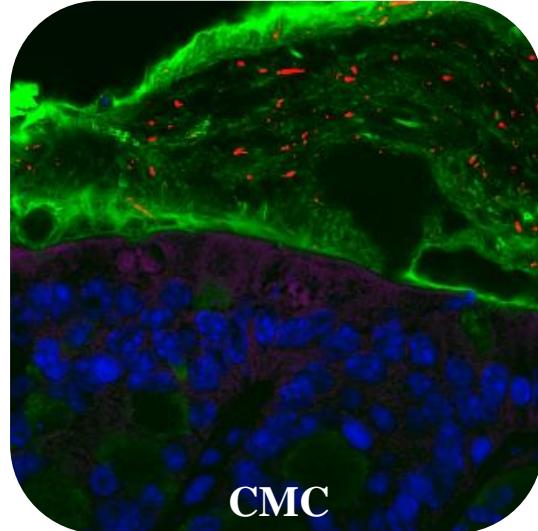
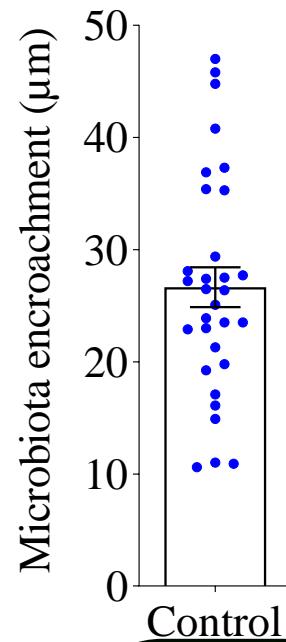


Carboxymethylcellulose (CMC)  
**E466**

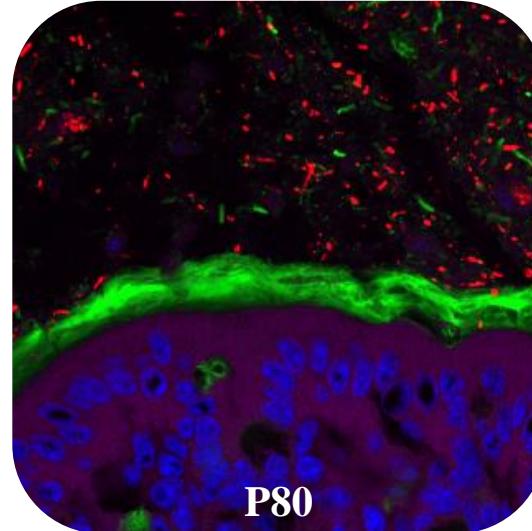
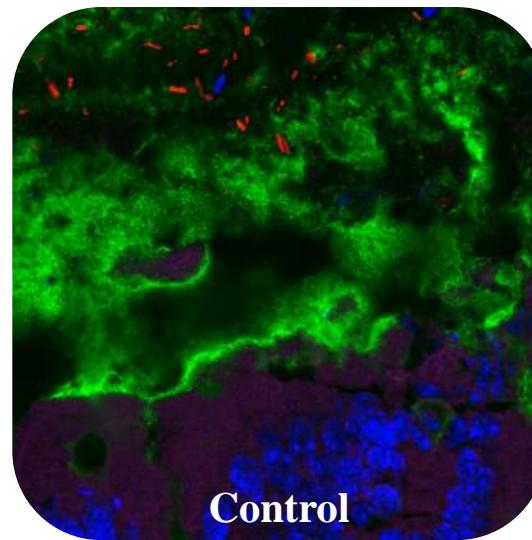


Polysorbate 80 (P80)  
**E433**

# Dietary emulsifying agents alter host / microbiota interaction

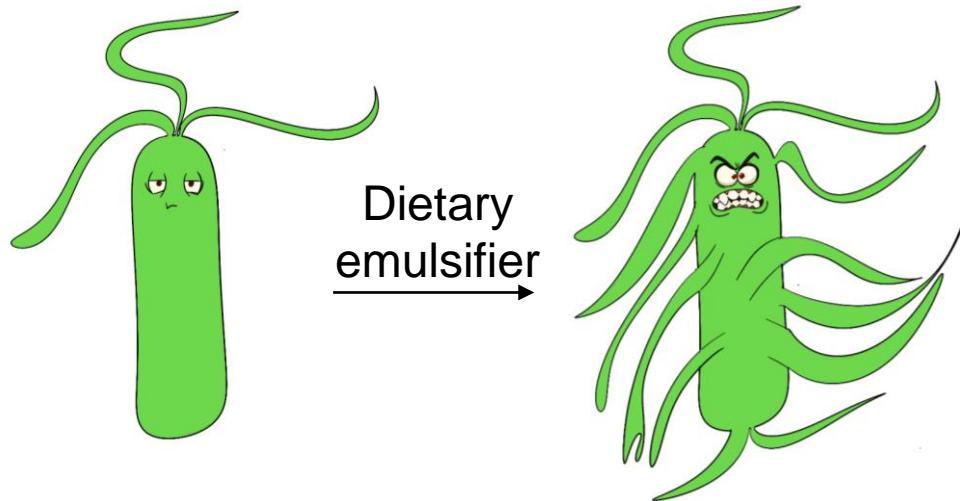
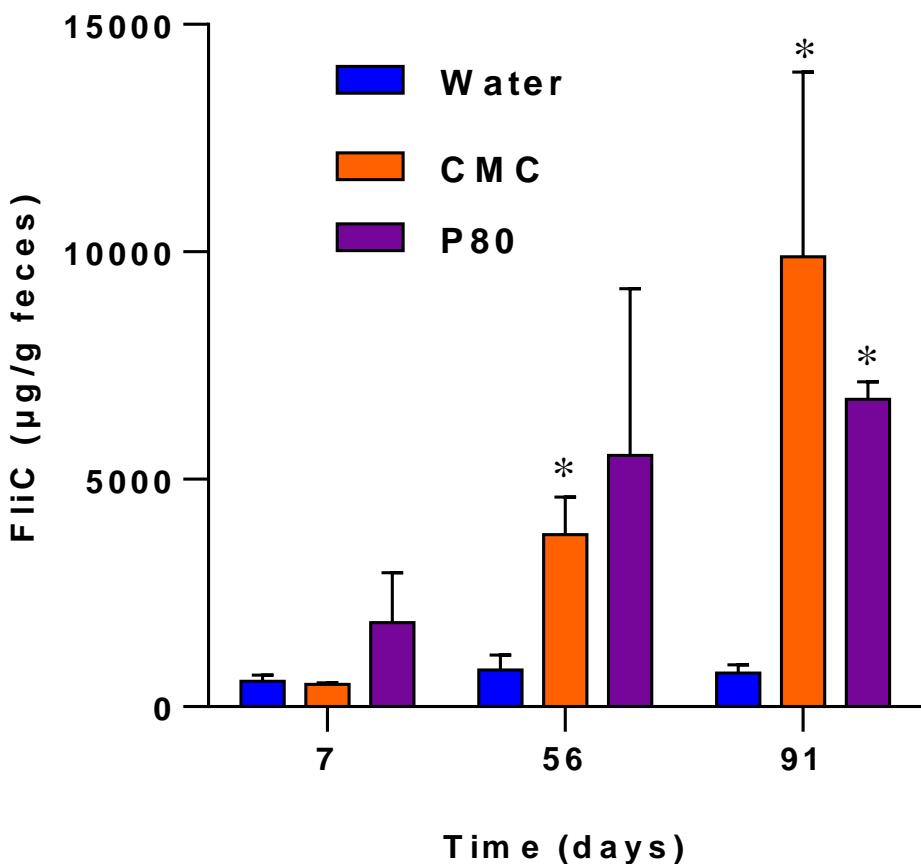


Microbiota  
encroachment  
**Invaders**



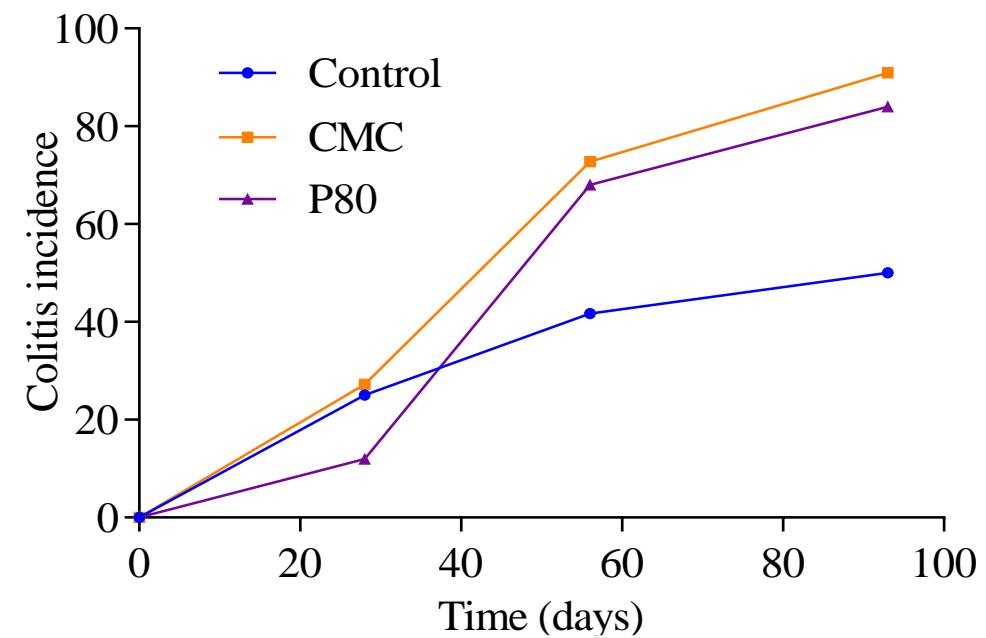
# Dietary emulsifying agents alter host / microbiota interaction

Microbiota pro-inflammatory potential



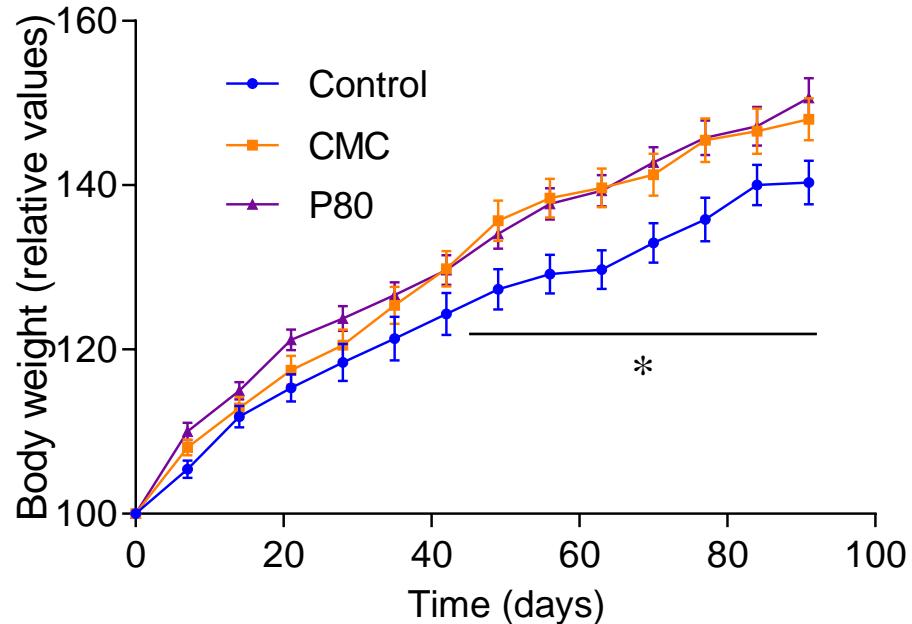
# Dietary emulsifiers promote inflammatory diseases

**IL10<sup>-/-</sup>**



**Colitis - IBD**

**WT**



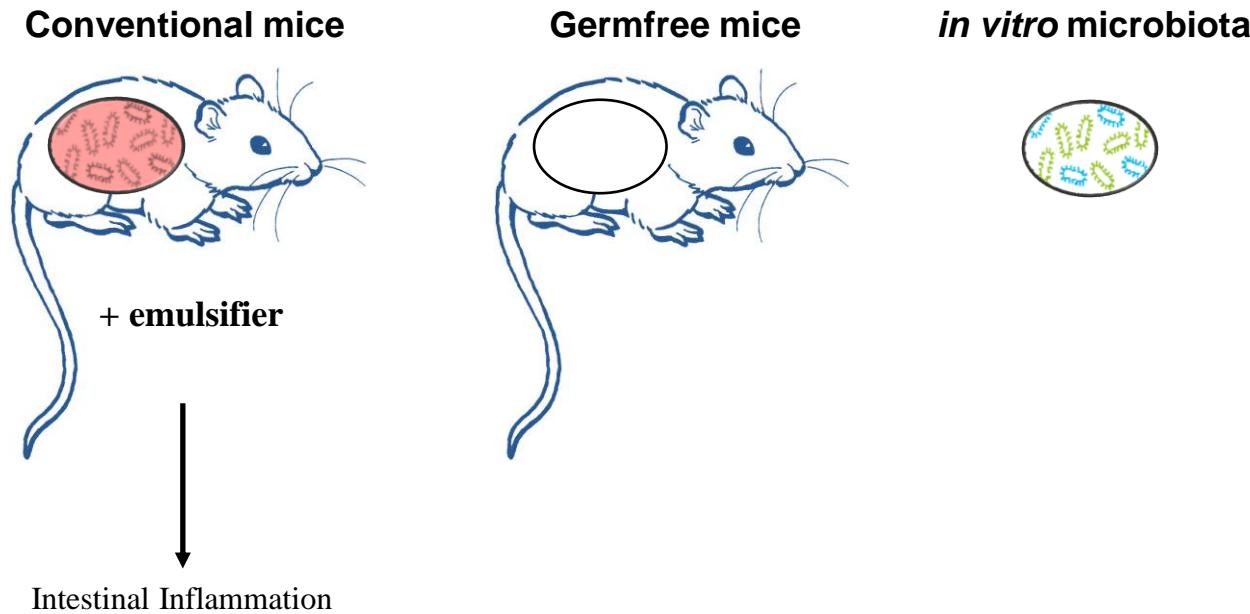
**Metabolic deregulation  
Obesity / Diabetes**

Chassaing et al, *Nature* 2015

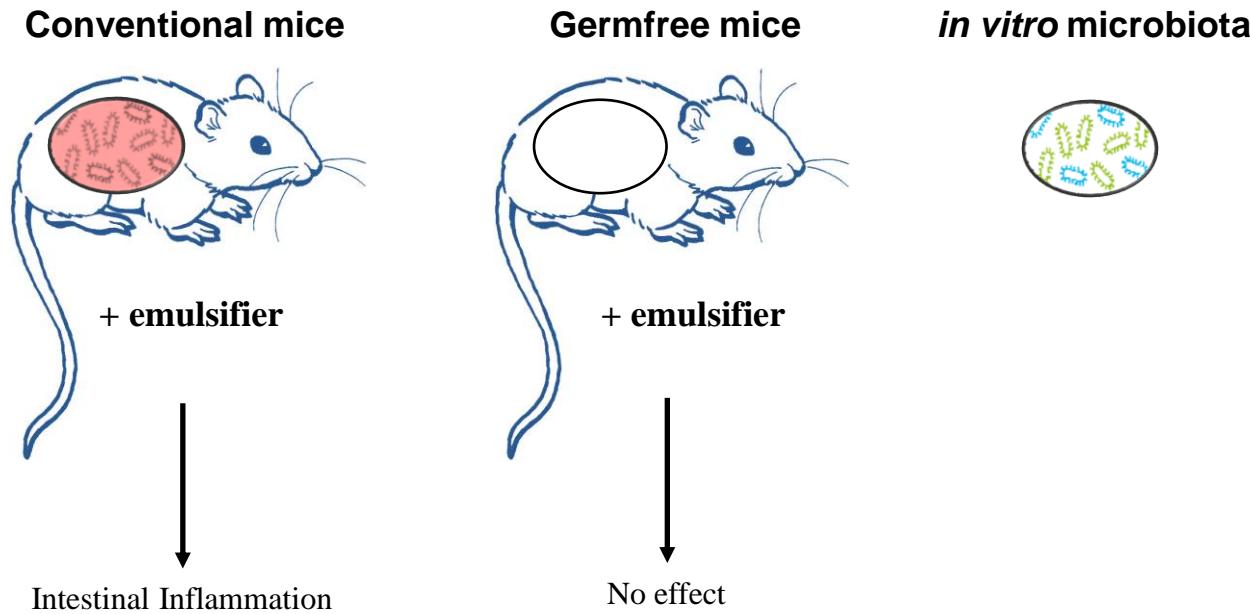
Chassaing et al, *Gut* 2017

Delaroque et al, *NPJ Biofilms and Microbiomes*, under revision

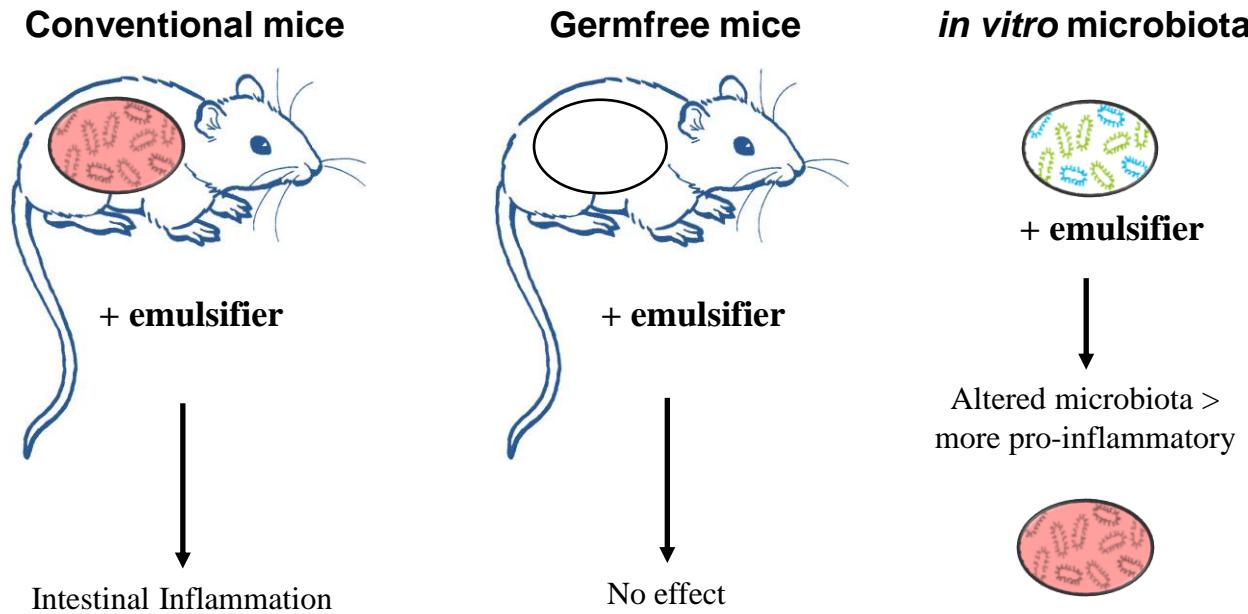
# Mechanism beyond dietary emulsifiers detrimental effects



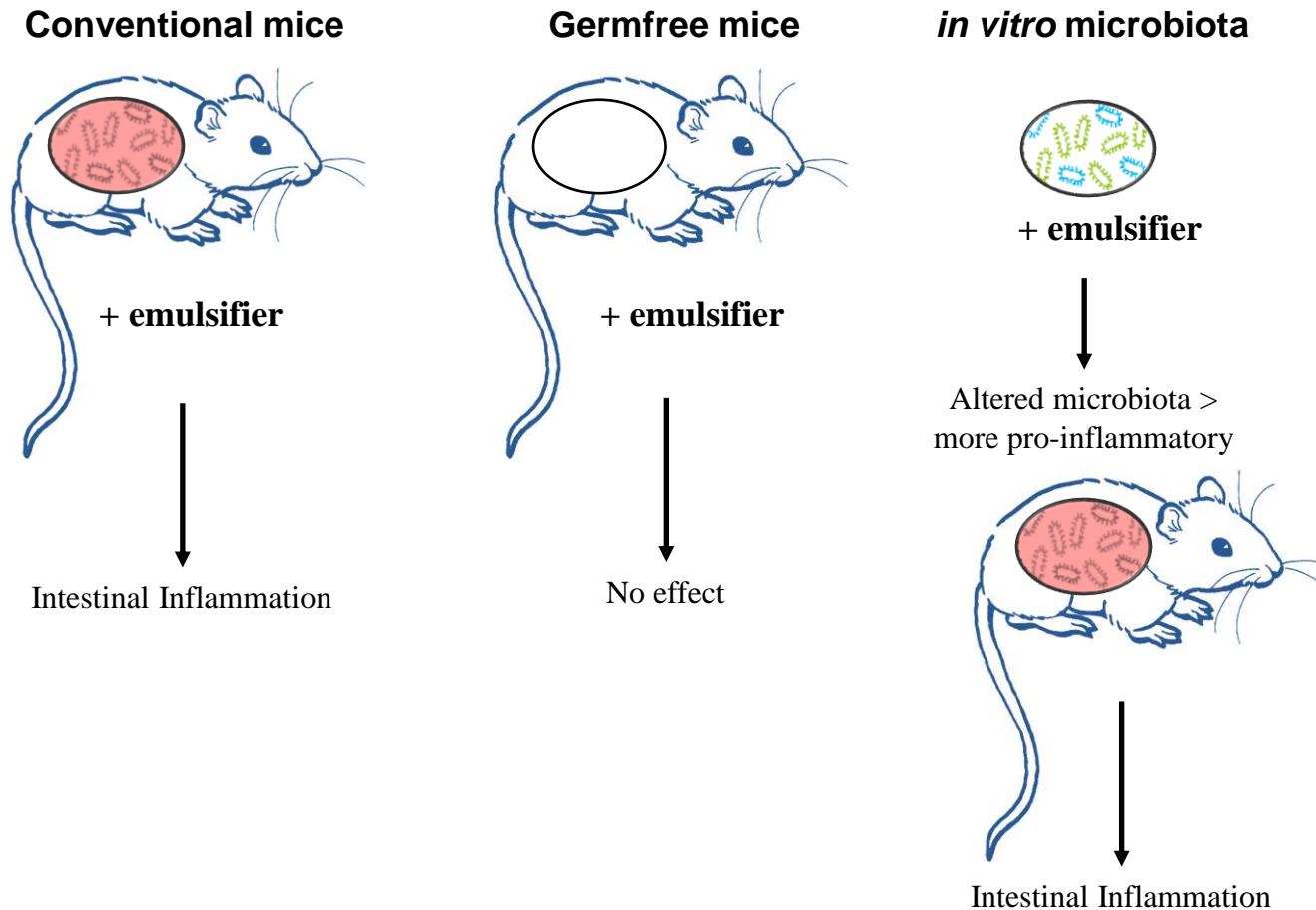
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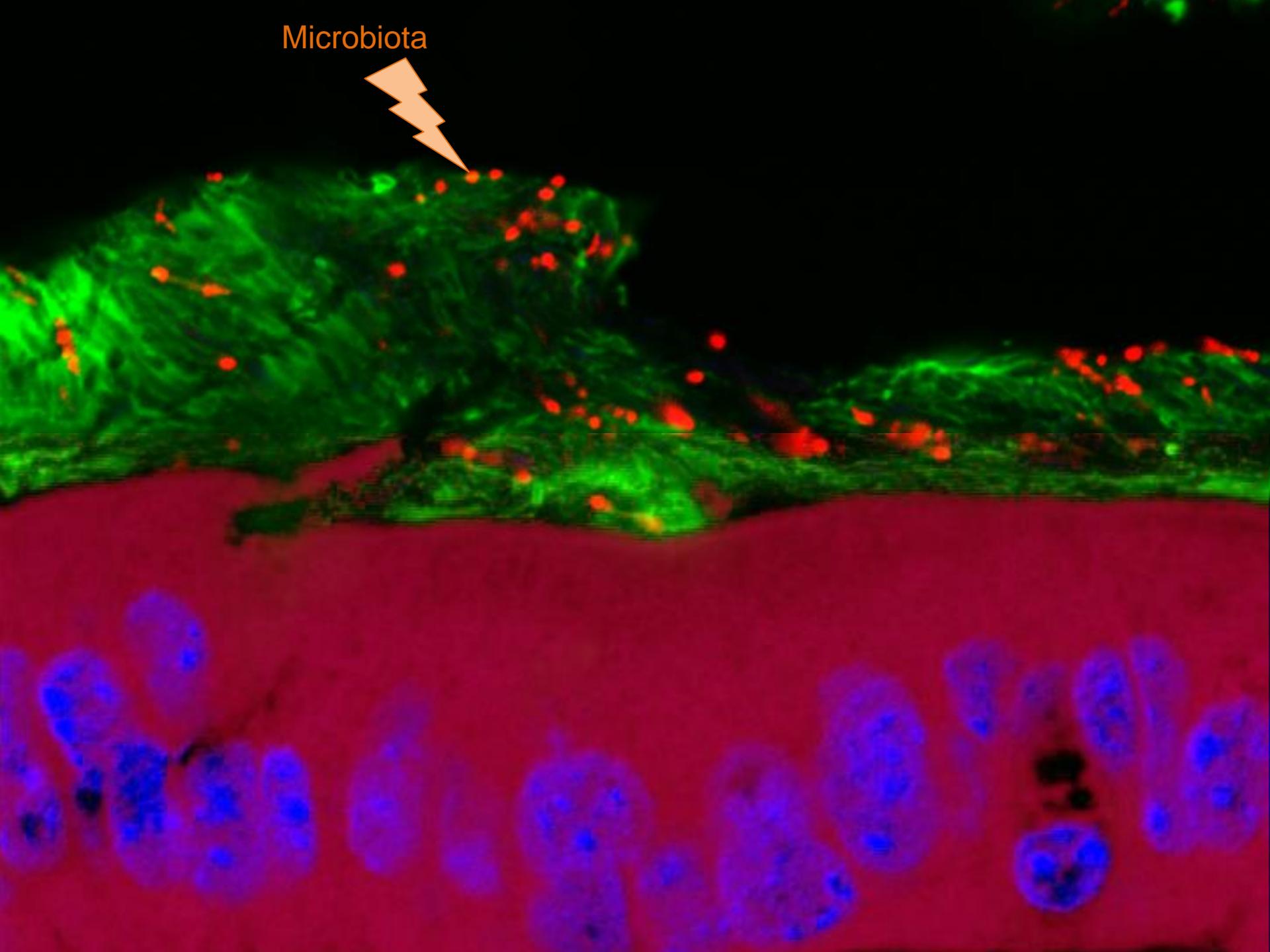
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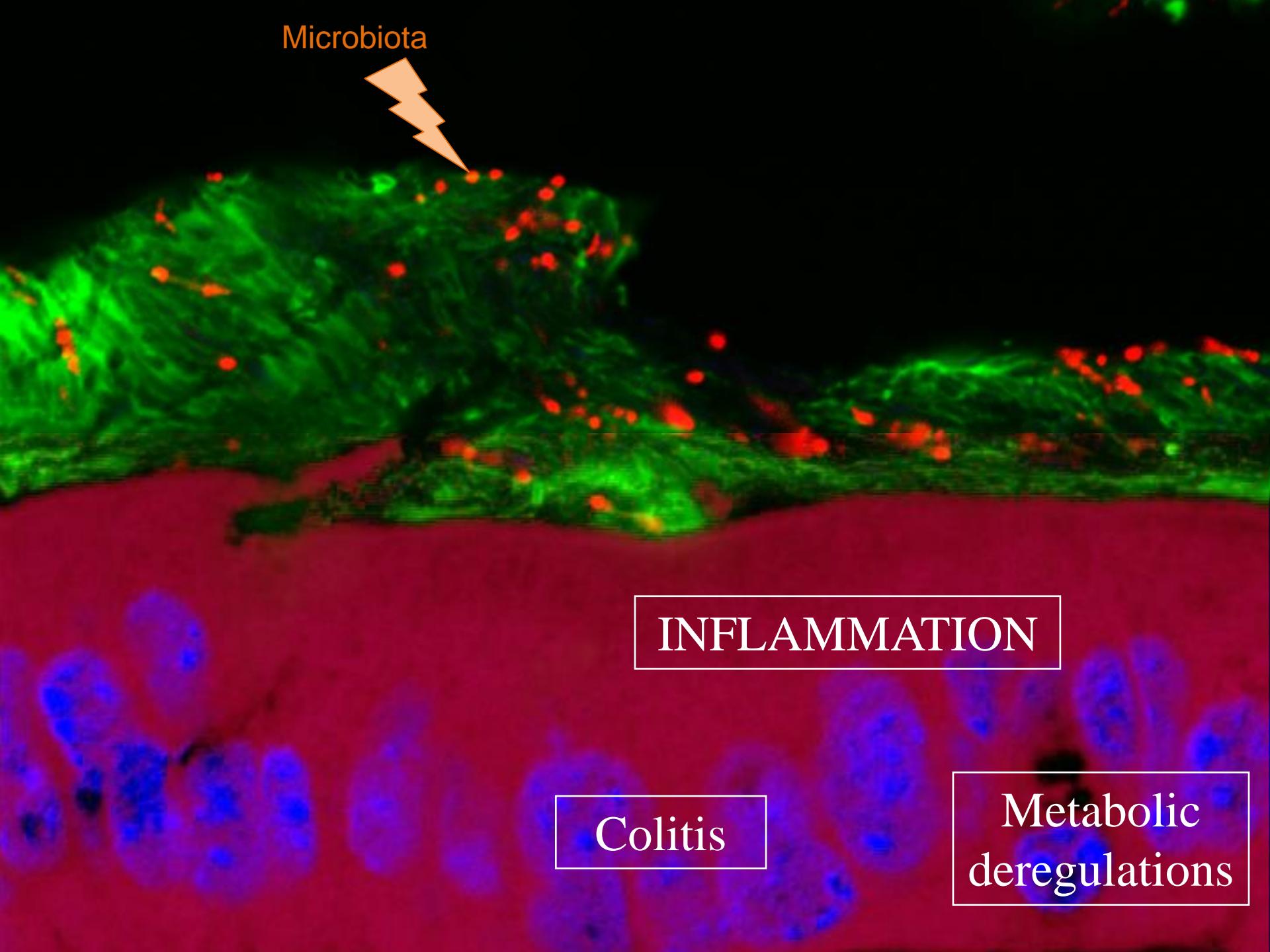


# Mechanism beyond dietary emulsifiers detrimental effects



Microbiota





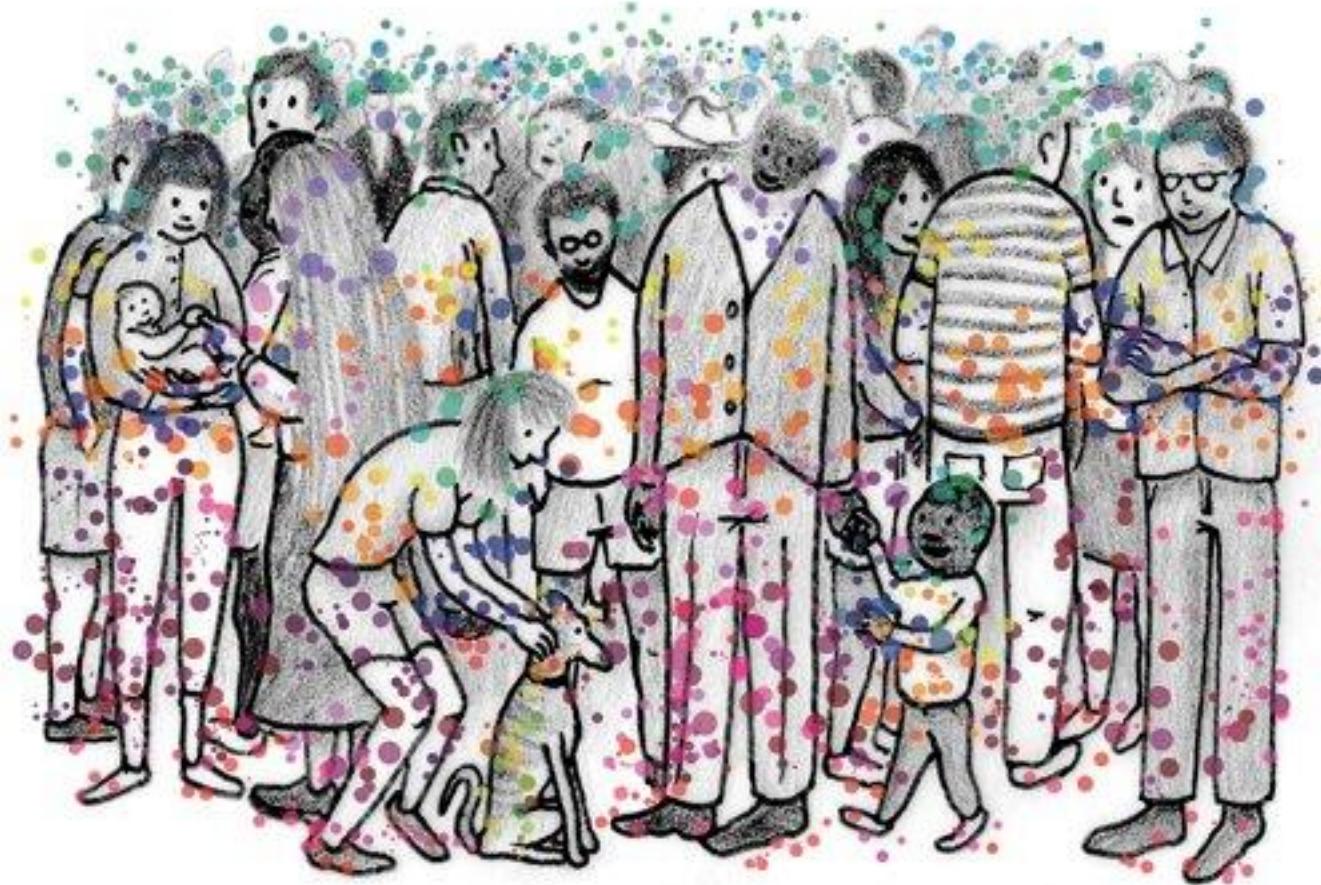
Microbiota



INFLAMMATION

Colitis

Metabolic  
deregulations



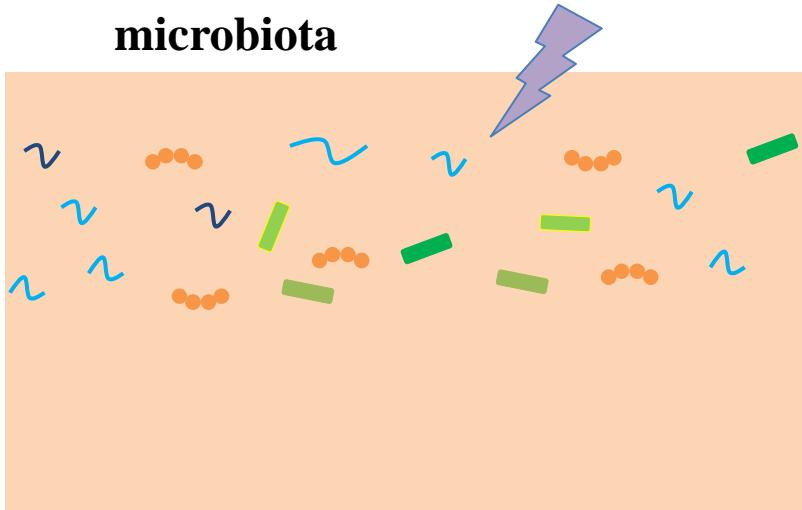
<https://learn.genetics.utah.edu/content/microbiome/changing>

# Emulsifiers directly impact the microbiota... but not all microbiota

ASF  
mice

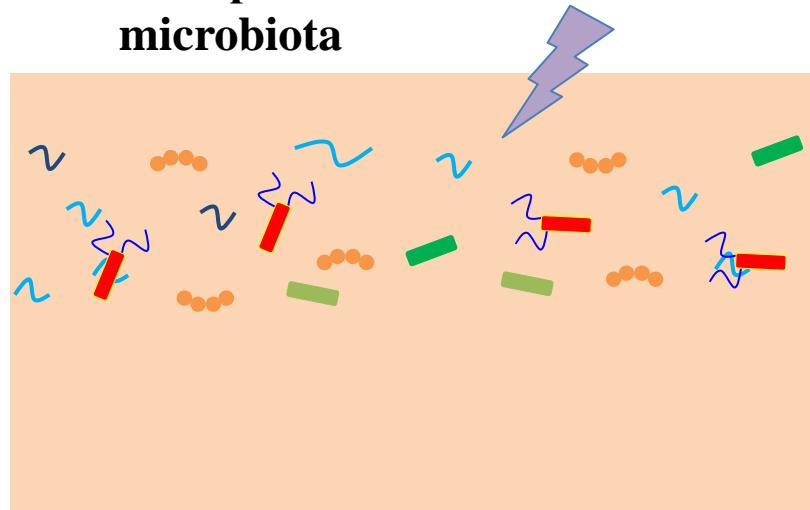
“Resistant”  
microbiota

Dietary  
emulsifier



“Susceptible”  
microbiota

Dietary  
emulsifier

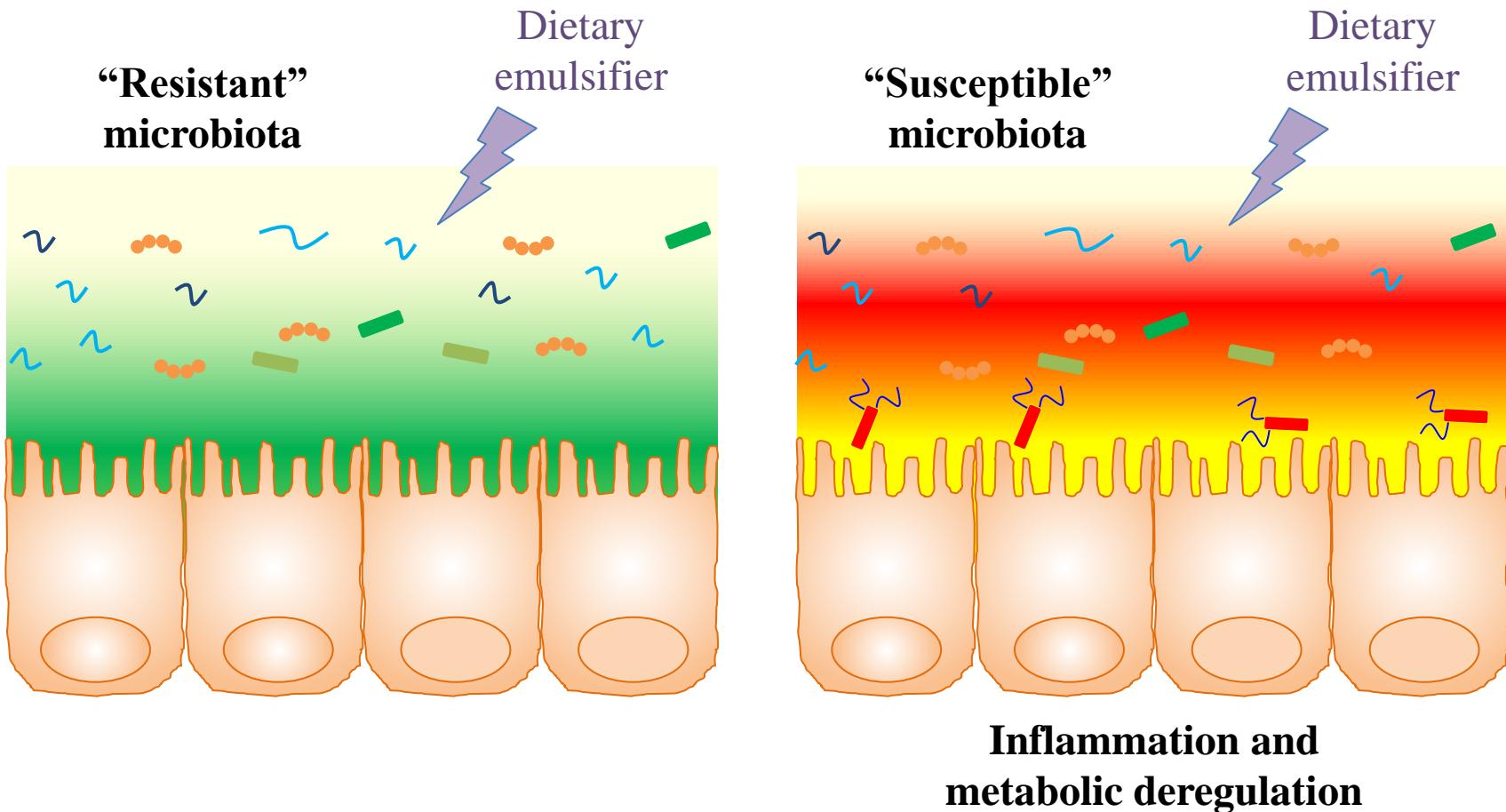


Chassaing *et al.* **Nature** 2015

Chassaing *et al.* **Gut** 2017

Chassaing *et al.* **Plos One** 2018

# Emulsifiers directly impact the microbiota... but not all microbiota

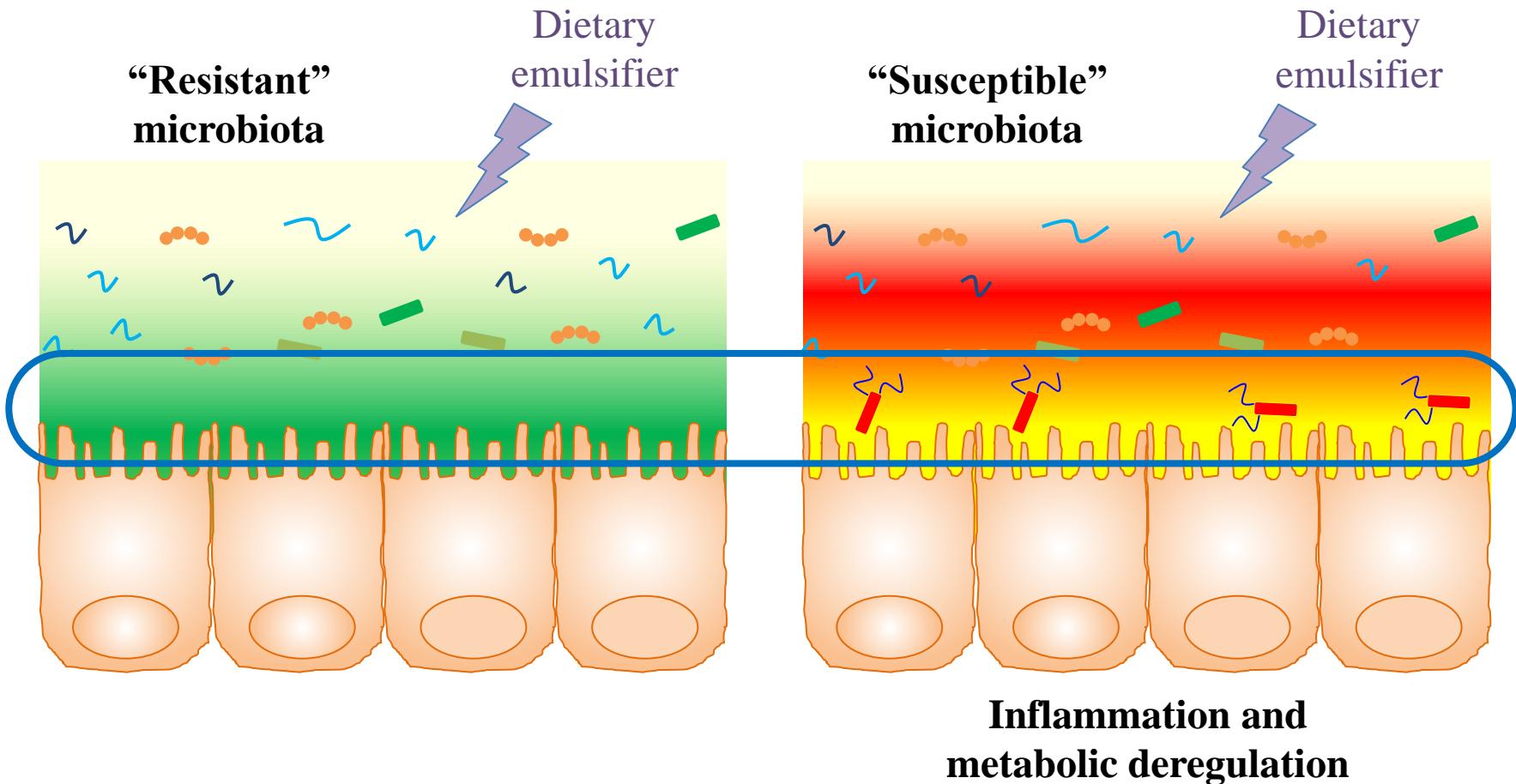


Chassaing *et al.* **Nature** 2015

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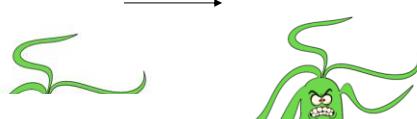
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# Emulsifiers directly impact the microbiota... but not all microbiota



Chassaing *et al.* **Nature** 2015  
Chassaing *et al.* **Gut** 2017  
Chassaing *et al.* **Plos One** 2018

Dietary  
emulsifier

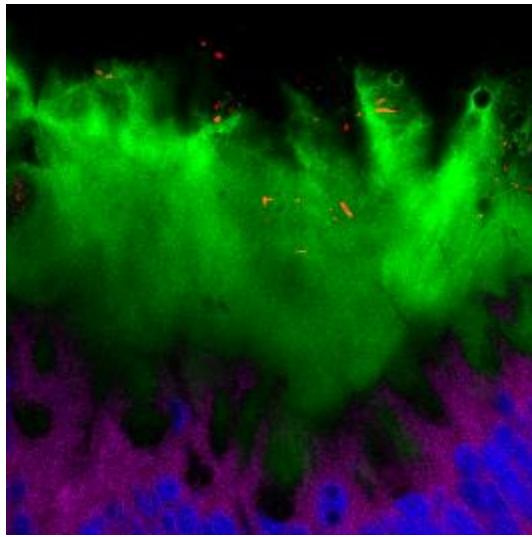


# Human relevance

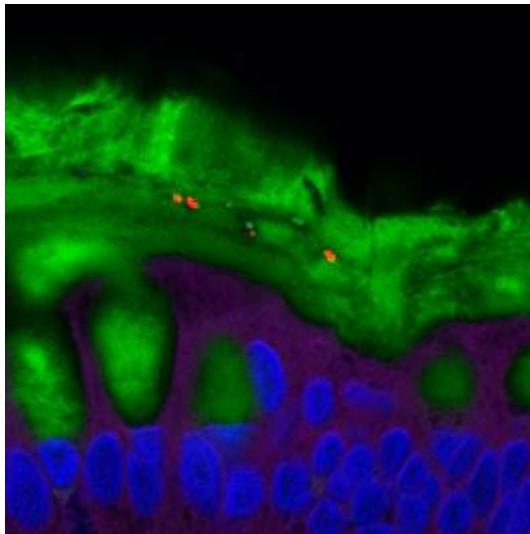
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# Human relevance

- Microbiota encroachment is a feature of metabolic syndrome **in humans**



Patient #13 BMI = 28.00, Glucose = 97  
HbA1C = 6.1, Diabetes mellitus = No

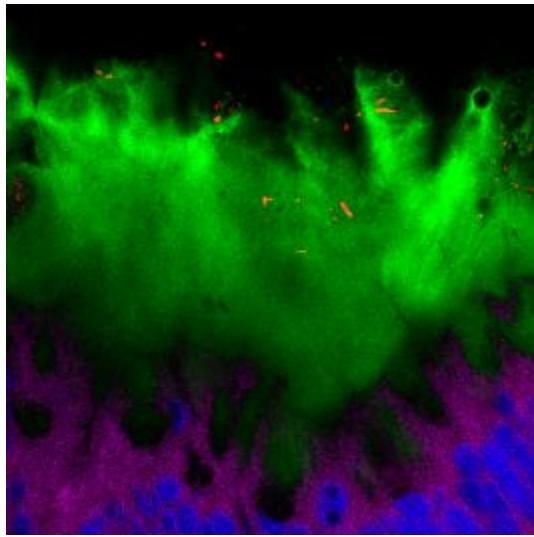


Patient #24 BMI = 38.20, Glucose = 70  
HbA1C = 8.2, Diabetes mellitus = Yes

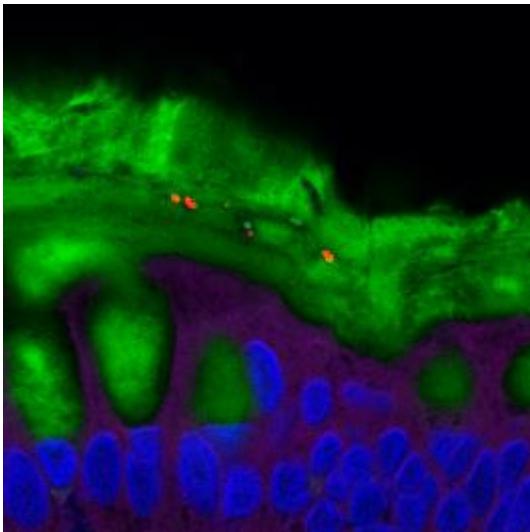
Chassaing, *et al*, **Cell Mol Gastro Hepatol** 2017

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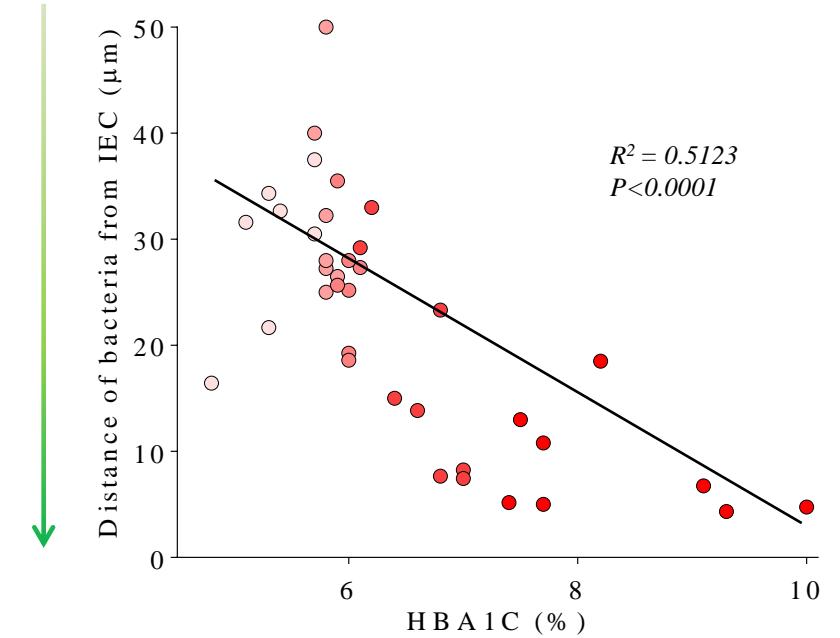


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Mucus layer penetration



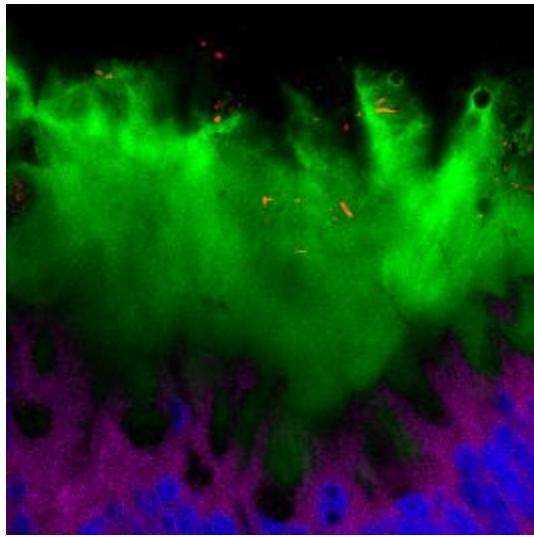
Metabolic dysfunction

Human

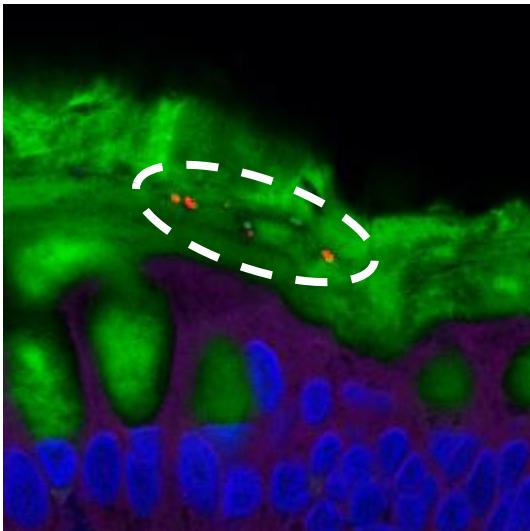
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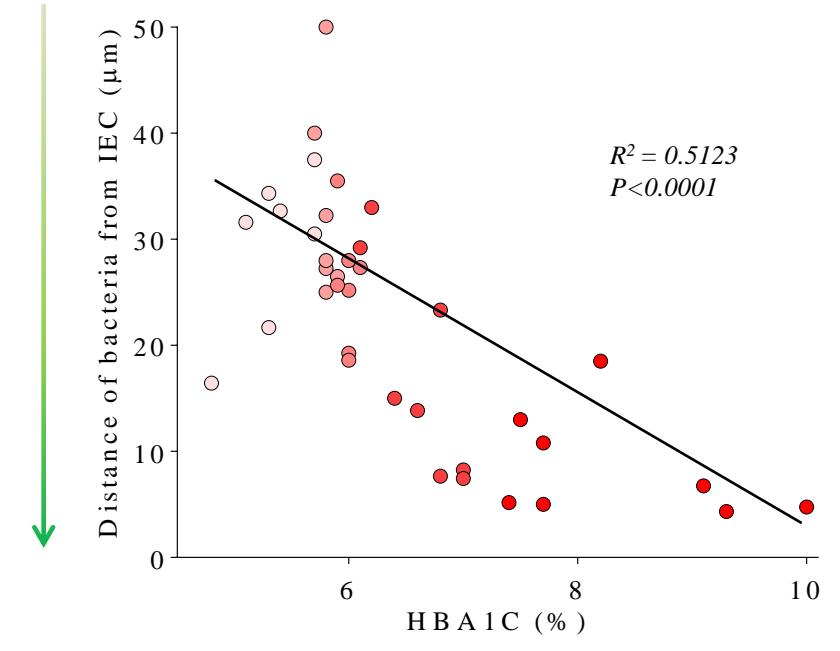


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Metabolic dysfunction

Human



OPEN ACCESS



Check for updates

## Food additive emulsifiers and risk of cardiovascular disease in the NutriNet-Santé cohort: prospective cohort study

Laury Sellem,<sup>1</sup> Bernard Srour,<sup>1</sup> Guillaume Javaux,<sup>1</sup> Eloi Chazelas,<sup>1</sup> Benoit Chassaing,<sup>2</sup> Emilie Viennois,<sup>3</sup> Charlotte Debras,<sup>1</sup> Clara Salamé,<sup>1</sup> Nathalie Druesne-Pecollo,<sup>1</sup> Younes Esseddik,<sup>1</sup> Fabien Szabo de Edelenyi,<sup>1</sup> Cédric Agaësse,<sup>1</sup> Alexandre De Sa,<sup>1</sup> Rebecca Lutchia,<sup>1</sup> Erwan Louveau,<sup>1</sup> Inge Huybrechts,<sup>4</sup> Fabrice Pierre,<sup>5</sup> Xavier Coumoul,<sup>6</sup> Léopold K Fezeu,<sup>1</sup> Chantal Julia,<sup>1,7</sup> Emmanuelle Kesse-Guyot,<sup>1</sup> Benjamin Allès,<sup>1</sup> Pilar Galan,<sup>1</sup> Serge Hercberg,<sup>1,7</sup> Mélanie Deschasaux-Tanguy,<sup>1</sup> Mathilde Touvier<sup>1</sup>

For numbered affiliations see  
end of the article

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[http://dx.doi.org/10.1136/  
bmj-2023-076058](http://dx.doi.org/10.1136/bmj-2023-076058)

Accepted: 16 August 2023

### ABSTRACT

### OBJECTIVE

To assess the associations between exposure to food additive emulsifiers and risk of cardiovascular disease (CVD).

### DESIGN

Prospective cohort study.

### SETTING

French NutriNet-Santé study, 2009-21.

### PARTICIPANTS

95 442 adults (>18 years) without prevalent CVD who completed at least three 24 hour dietary records during the first two years of follow-up.

### MAIN OUTCOME MEASURES

Associations between intake of food additive emulsifiers (continuous (mg/day)) and risk of CVD, coronary heart disease, and cerebrovascular disease characterised using multivariable proportional hazard Cox models to compute hazard ratios for each additional standard deviation (SD) of emulsifier intake, along with 95% confidence intervals.

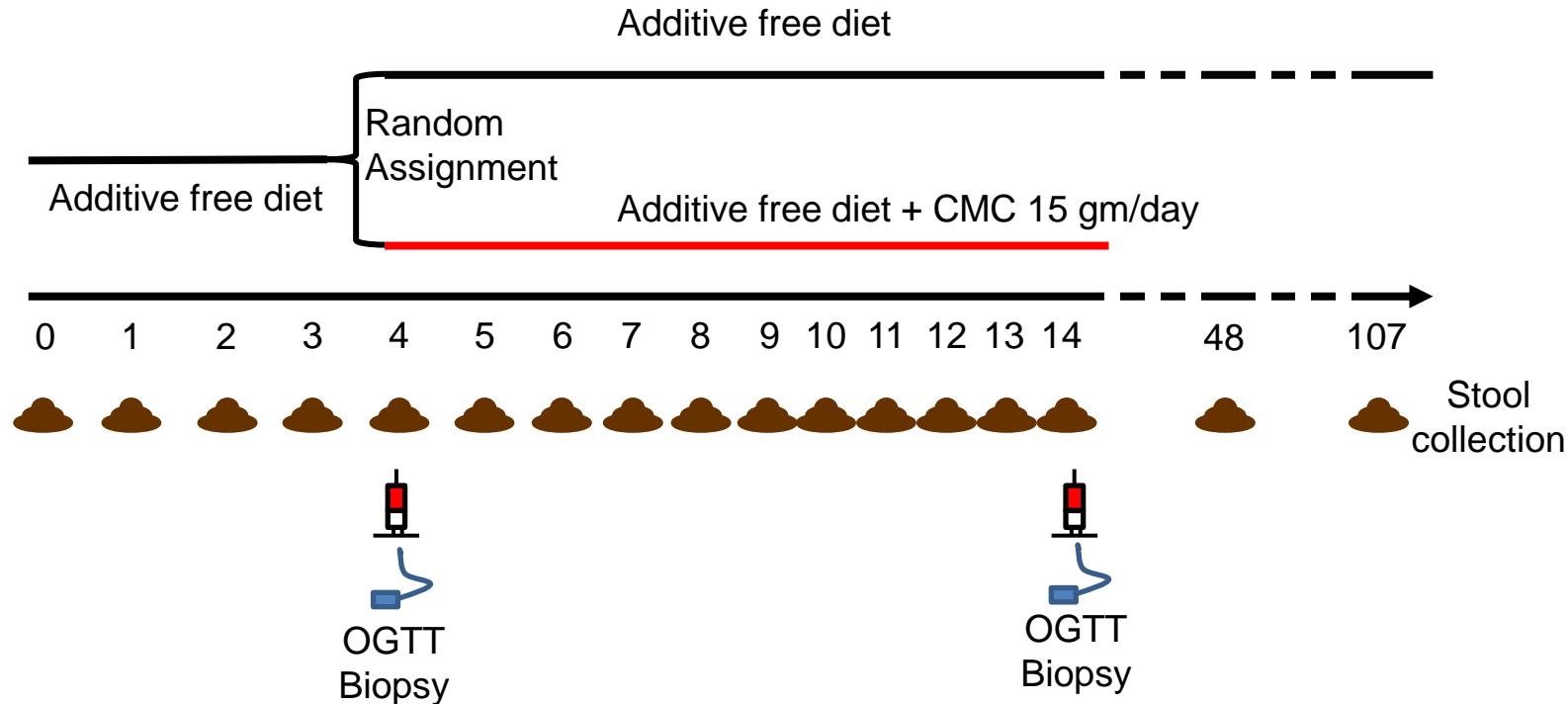
### RESULTS

disease events were diagnosed. Higher intake of celluloses (E460-E468) was found to be positively associated with higher risks of CVD (hazard ratio for an increase of 1 standard deviation 1.05, 95% confidence interval 1.02 to 1.09,  $P=0.003$ ) and coronary heart disease (1.07, 1.02 to 1.12,  $P=0.004$ ). Specifically, higher cellulose E460 intake was linked to higher risks of CVD (1.05, 1.01 to 1.09,  $P=0.007$ ) and coronary heart disease (1.07, 1.02 to 1.12,  $P=0.005$ ), and higher intake of carboxymethylcellulose (E466) was associated with higher risks of CVD (1.03, 1.01 to 1.05,  $P=0.004$ ) and coronary heart disease (1.04, 1.02 to 1.06,  $P=0.001$ ). Additionally, higher intakes of monoglycerides and diglycerides of fatty acids (E471 and E472) were associated with higher risks of all outcomes. Among these emulsifiers, lactic ester of monoglycerides and diglycerides of fatty acids (E472b) was associated with higher risks of CVD (1.06, 1.02 to 1.10,  $P=0.002$ ) and cerebrovascular disease (1.11, 1.06 to 1.16,  $P<0.001$ ), and citric acid ester of monoglycerides and diglycerides of fatty acids (E472c) was associated with higher risks of CVD (1.04, 1.02 to 1.07,  $P=0.004$ ) and coronary heart disease (1.06, 1.03 to 1.09,  $P<0.001$ ). High intake of

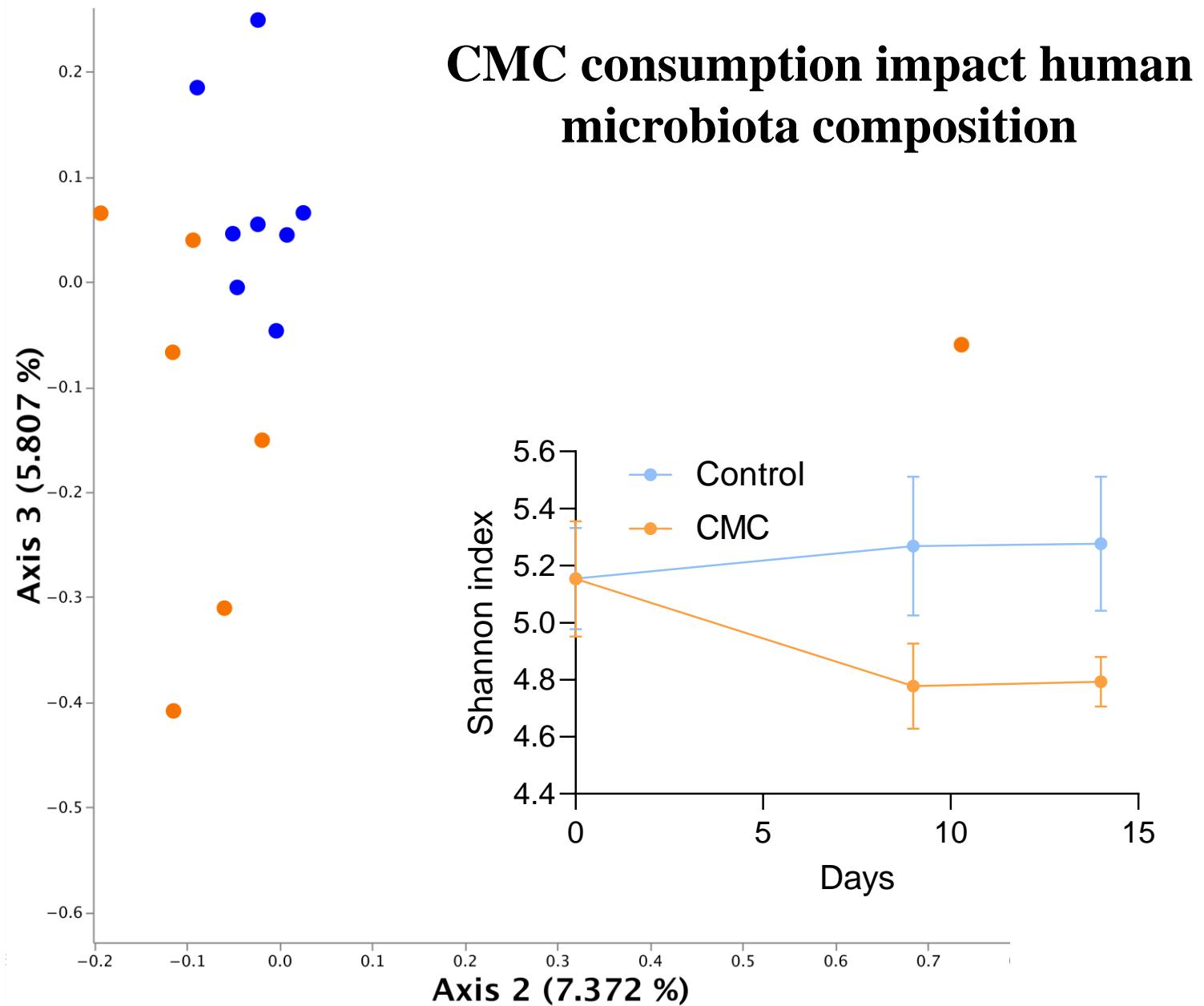
# Human relevance

## FRESH study = Functional Research on Emulsifiers in Humans

*In patient study*

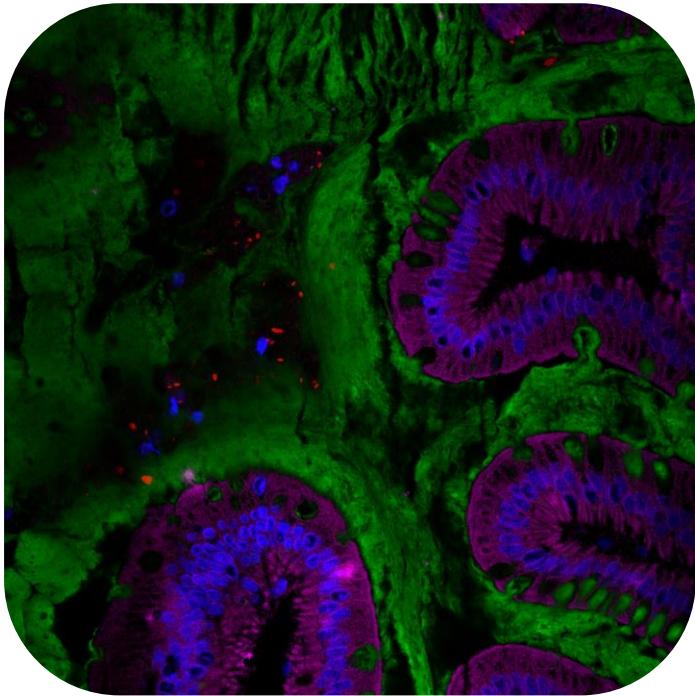


# Human relevance

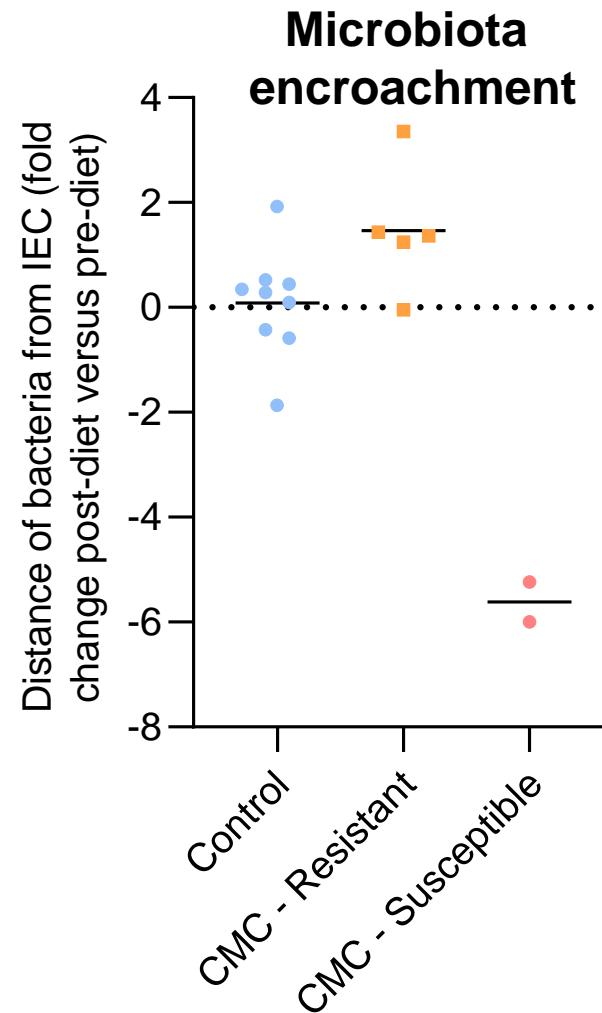
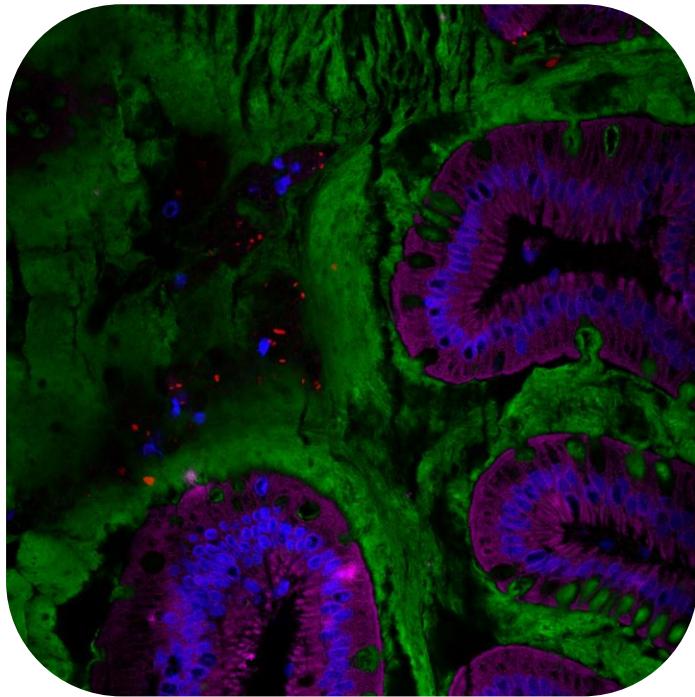


# Human relevance

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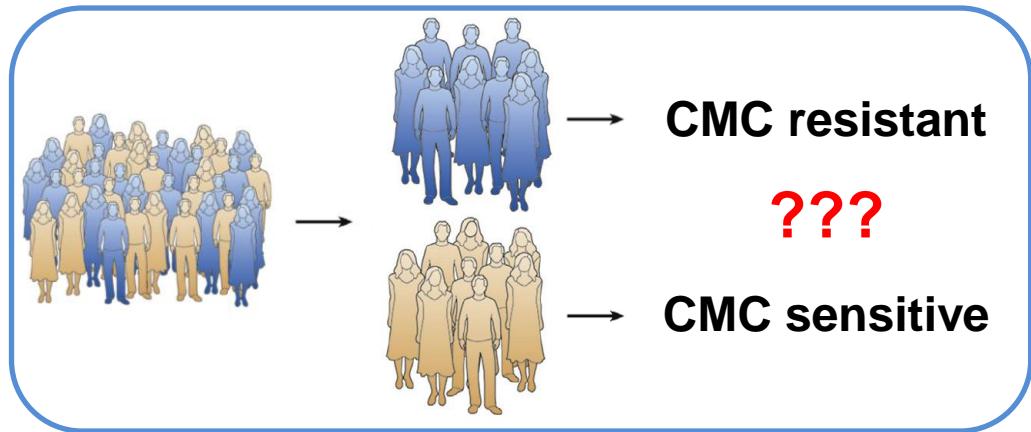
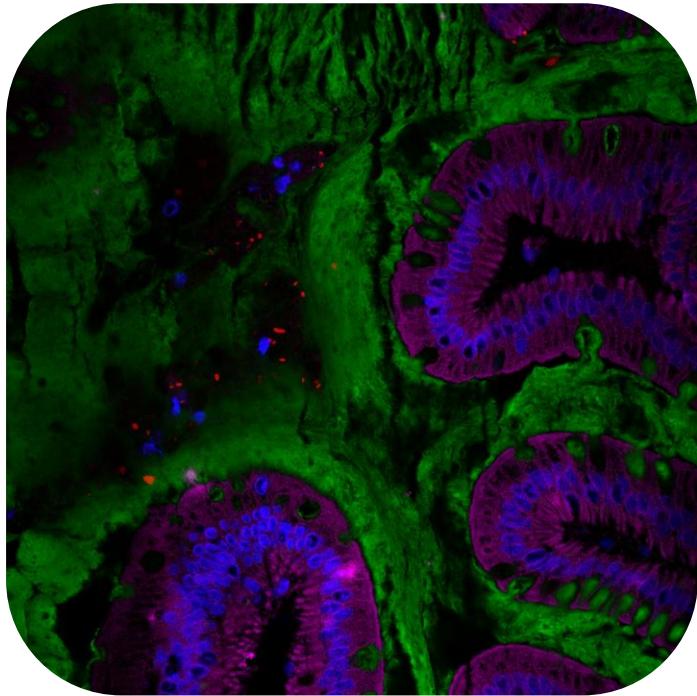


# Human relevance



In **select** individual, CMC consumption  
drive microbiota encroachment

# Human relevance



In **select** individual, CMC consumption  
drive microbiota encroachment

From human relevance > **BACK TO MICE !!**

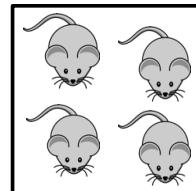
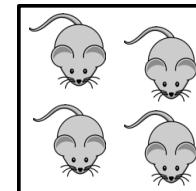
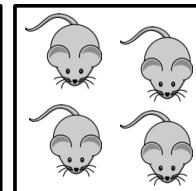
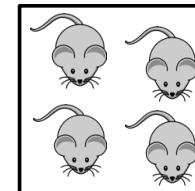
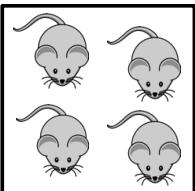
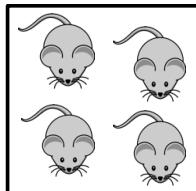
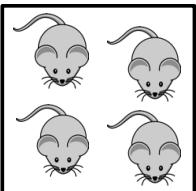
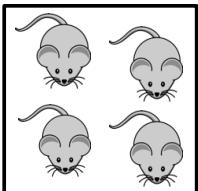
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@Noémie

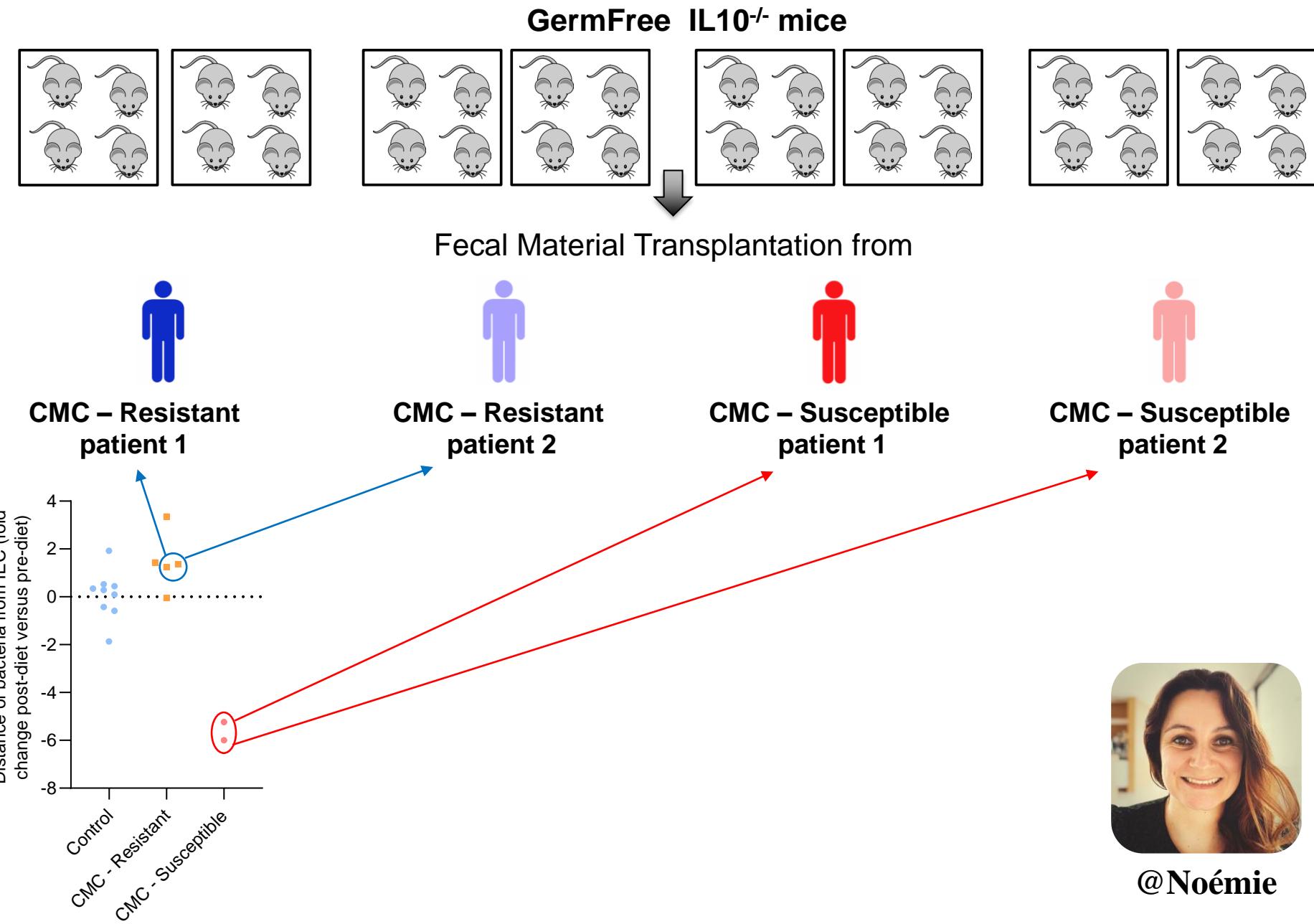
# From human relevance > BACK TO MICE !!

GermFree IL10<sup>-/-</sup> mice

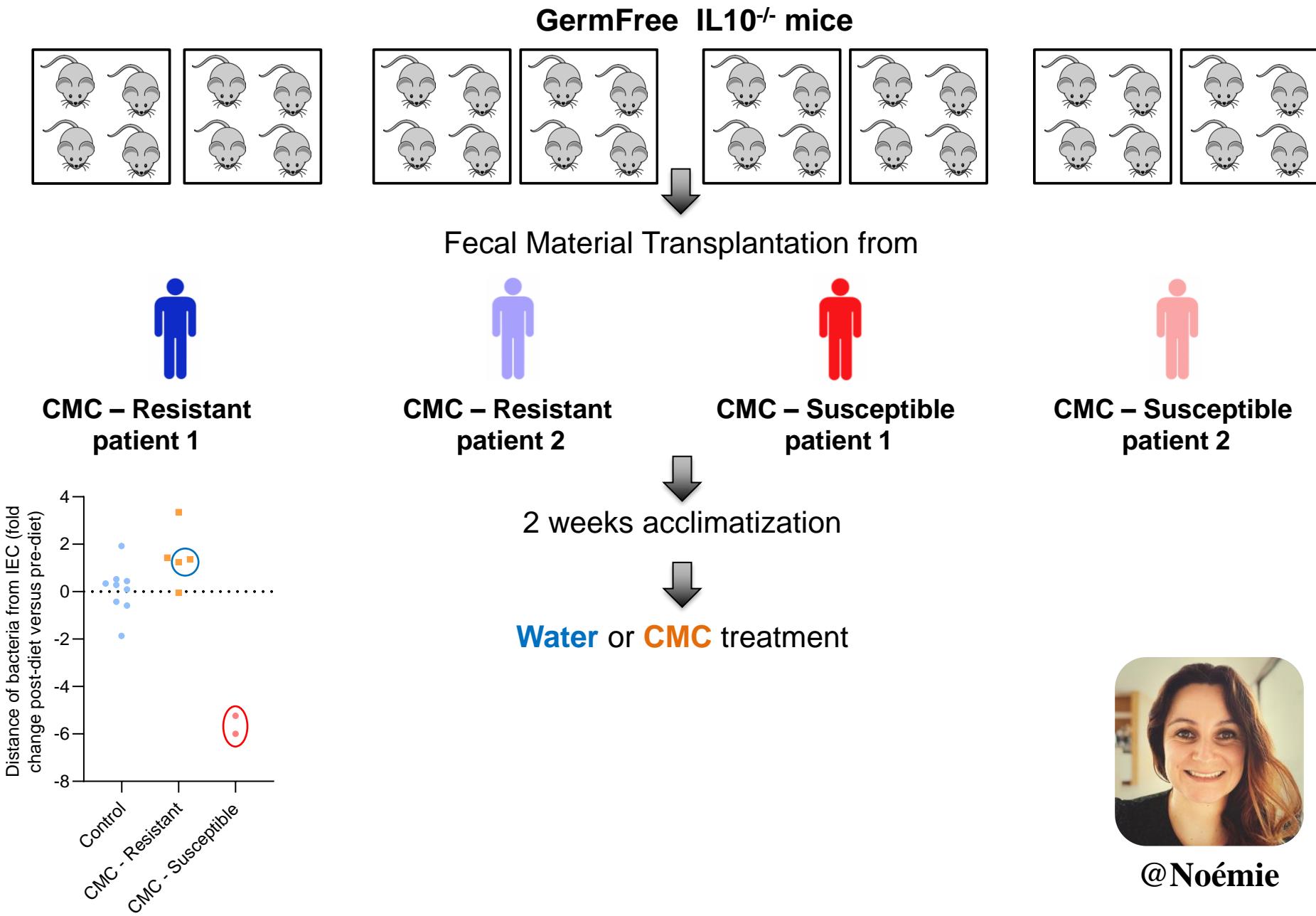


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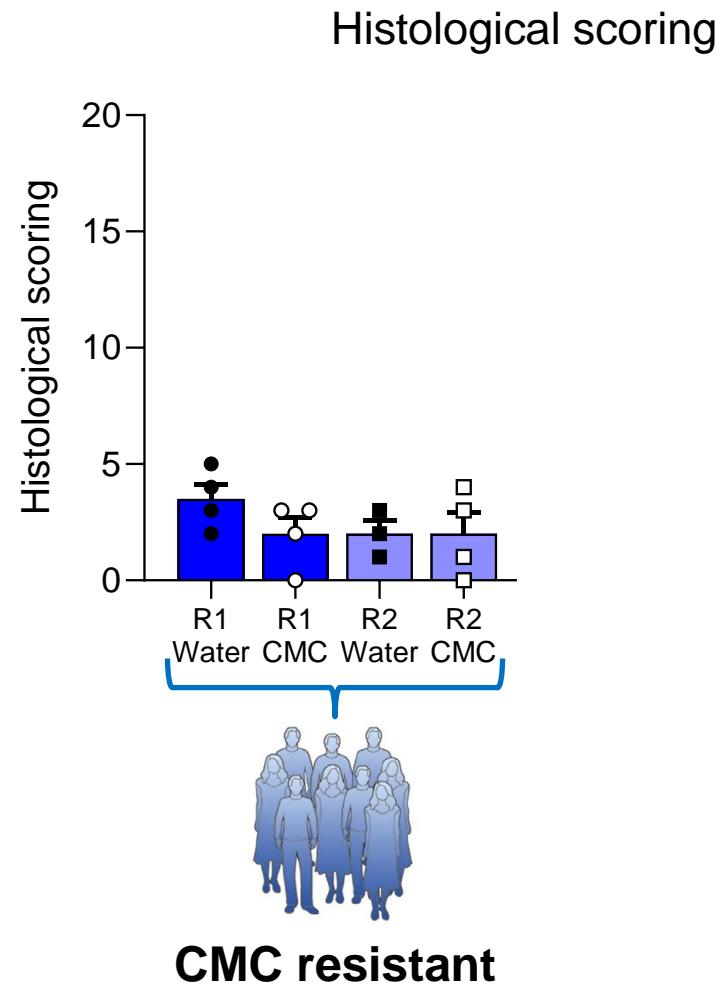
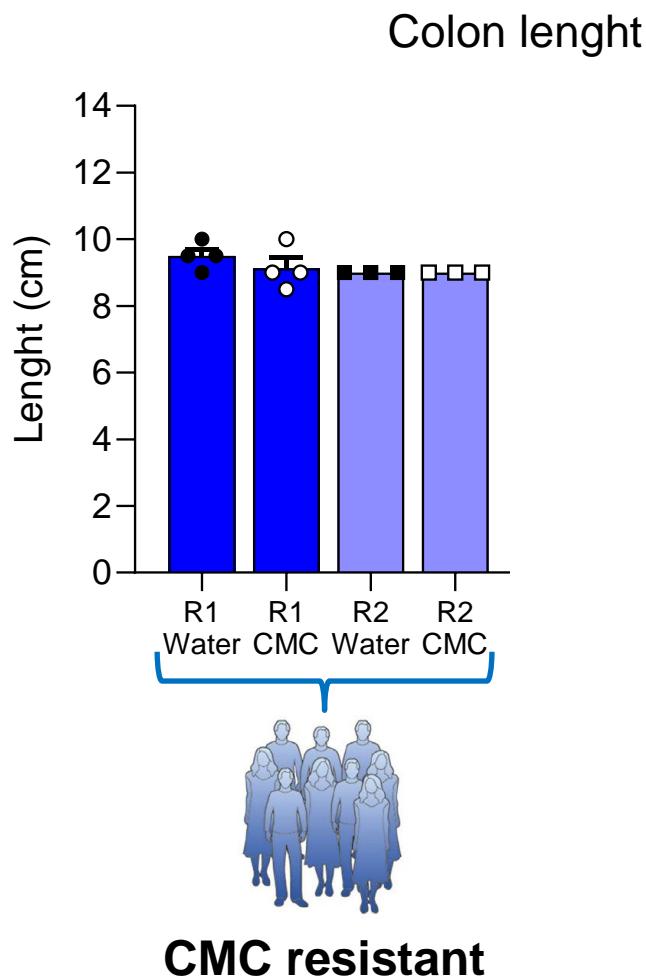
# From human relevance > BACK TO MICE !!



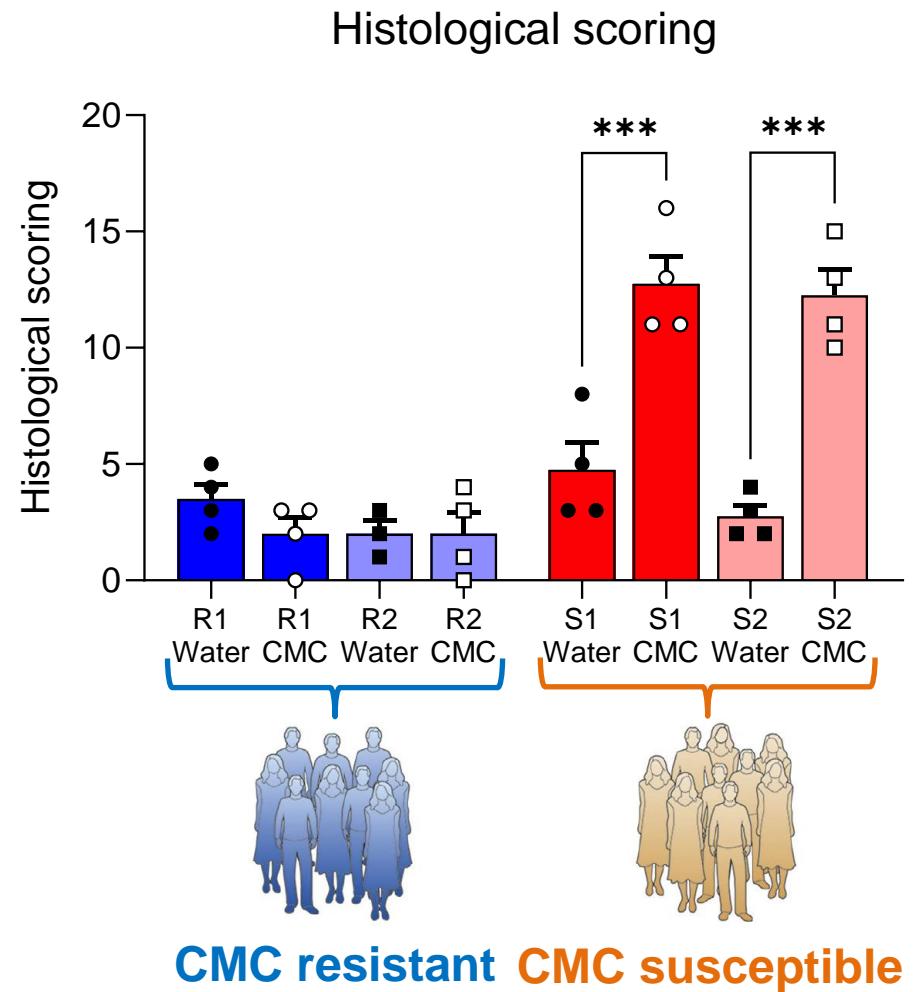
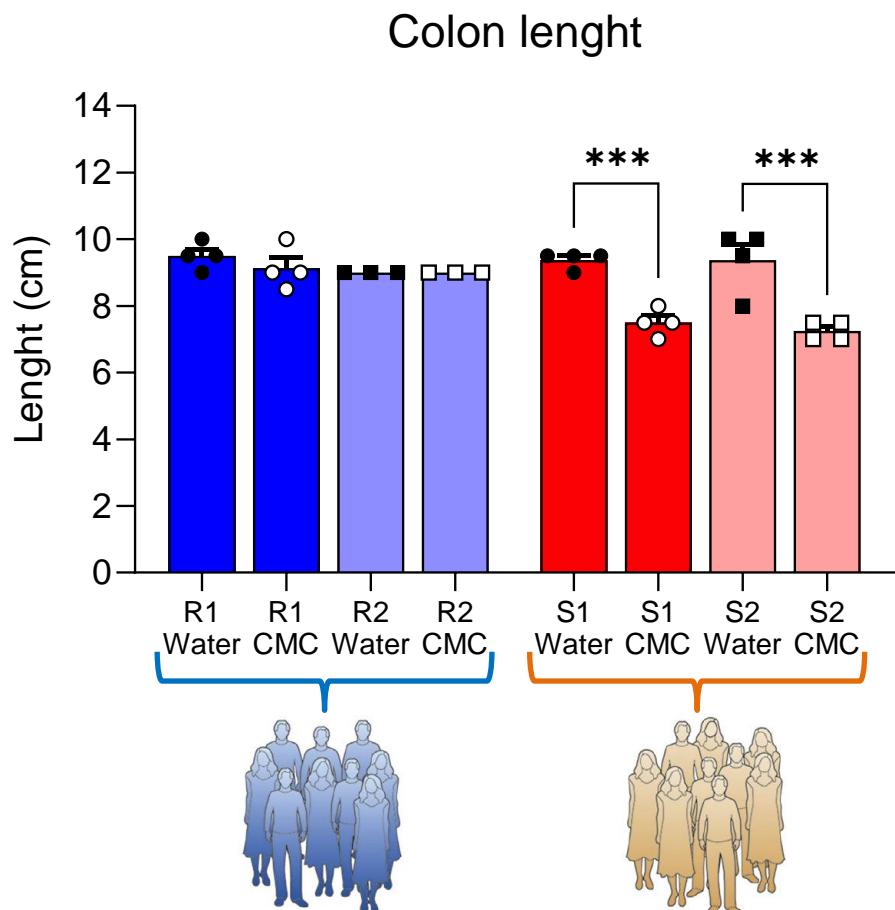
# From human relevance > BACK TO MICE !!



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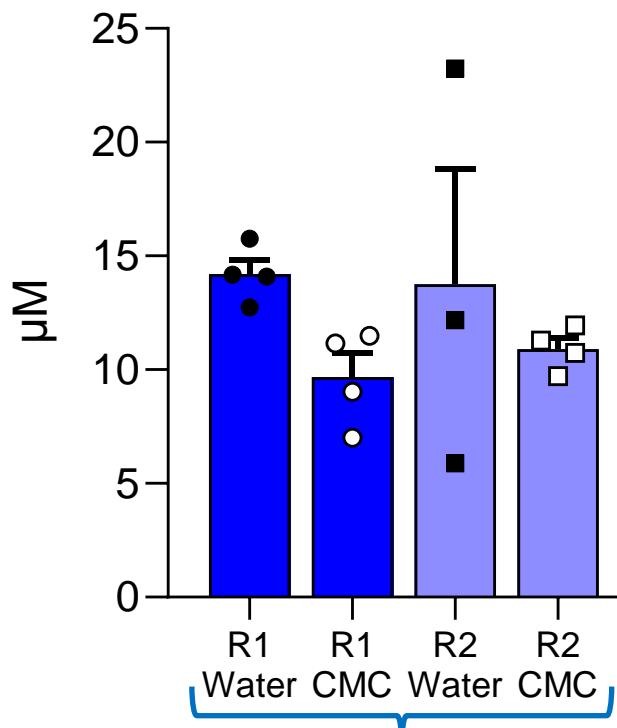
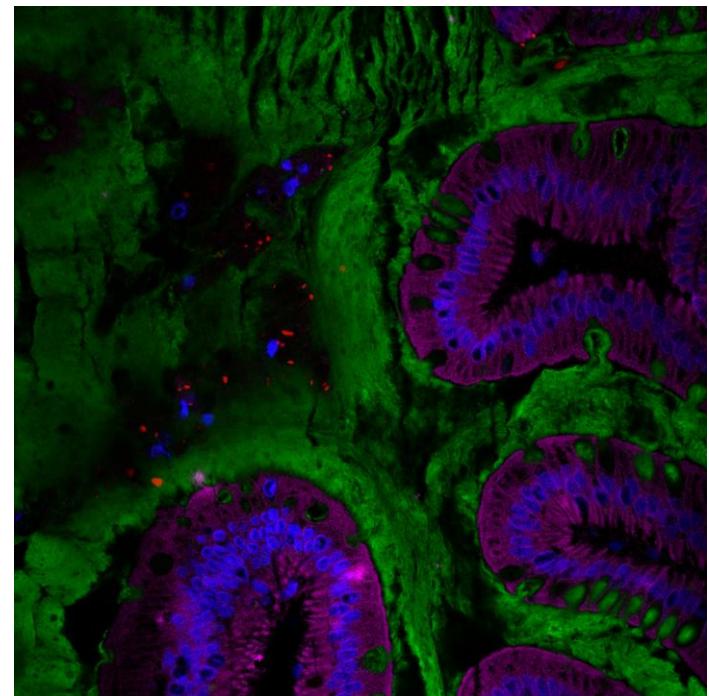


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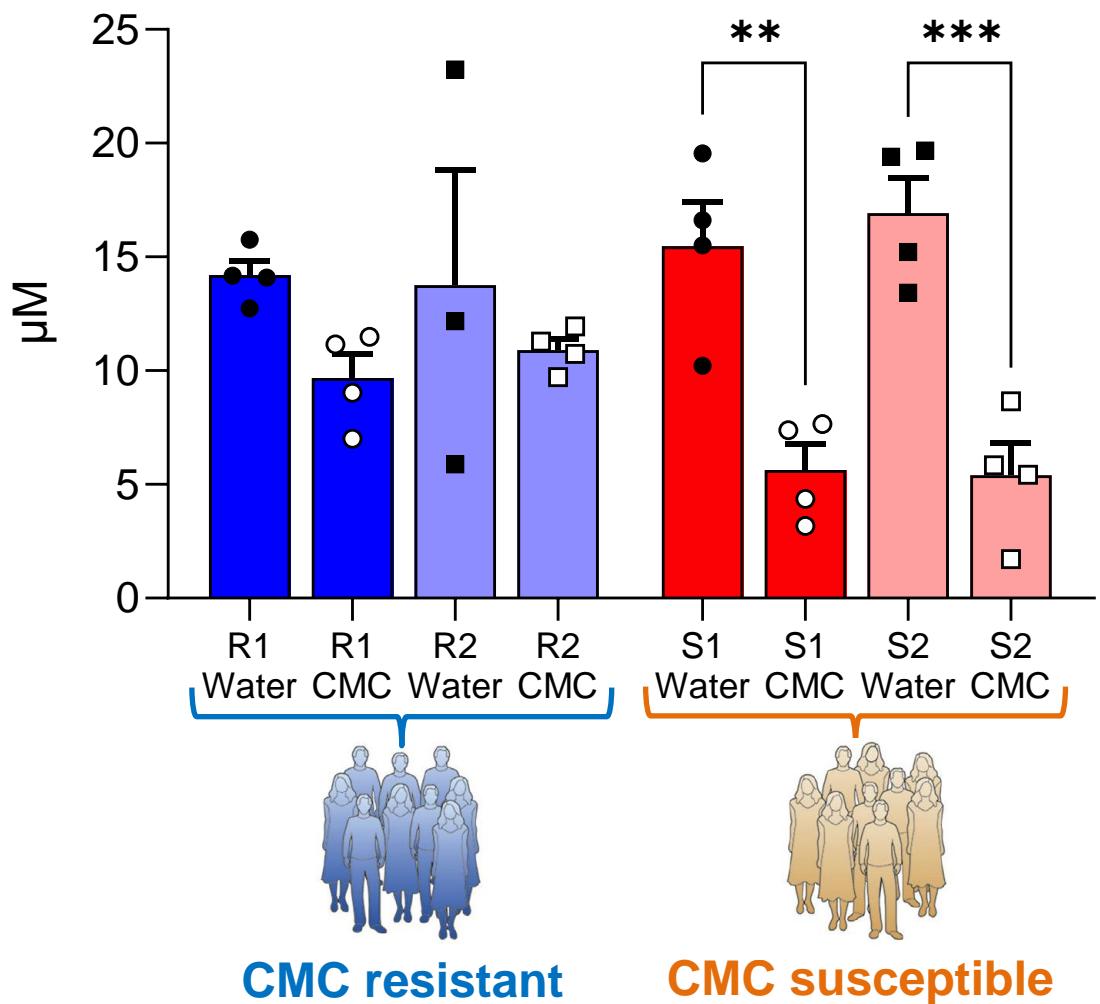
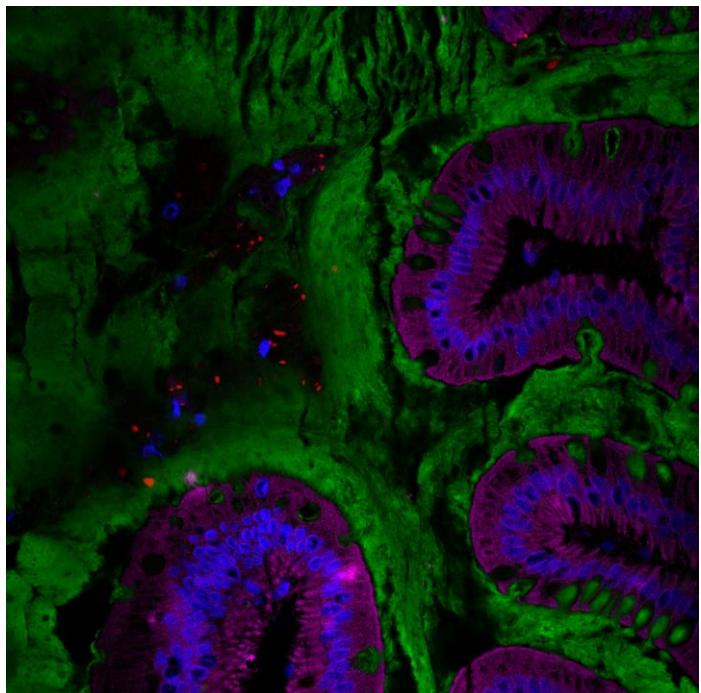
# From human relevance > BACK TO MICE !!

Distance of bacteria from IEC



# From human relevance > BACK TO MICE !!

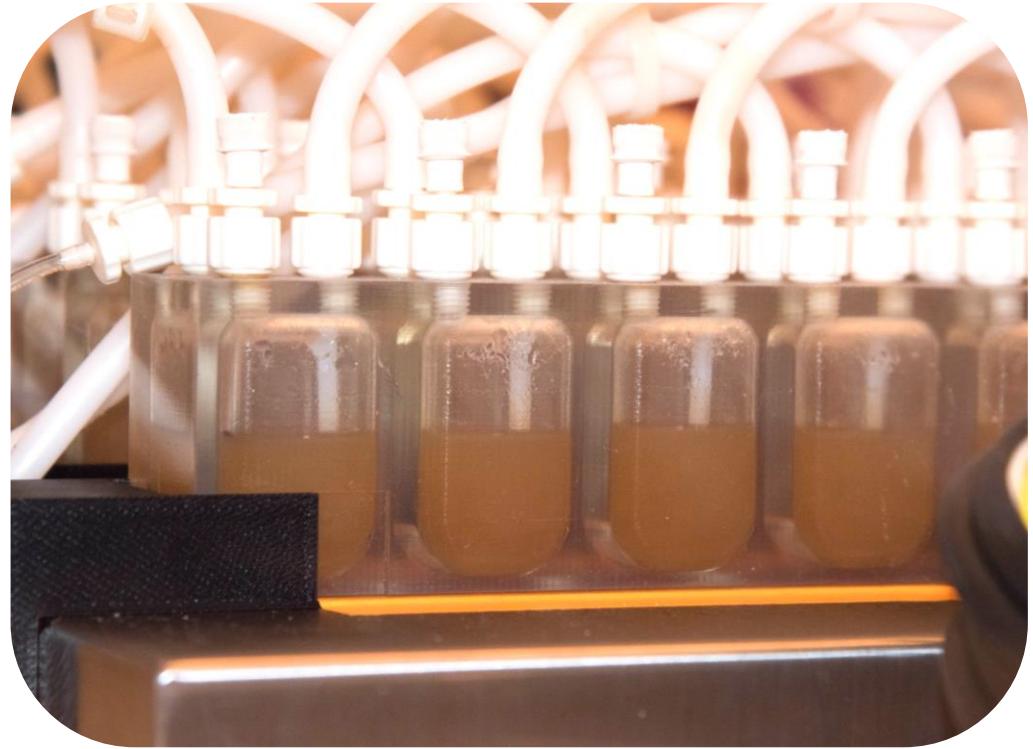
Distance of bacteria from IEC



From human relevance > BACK TO MICE >  
**BACK TO *IN VITRO* for mechanistic insights**

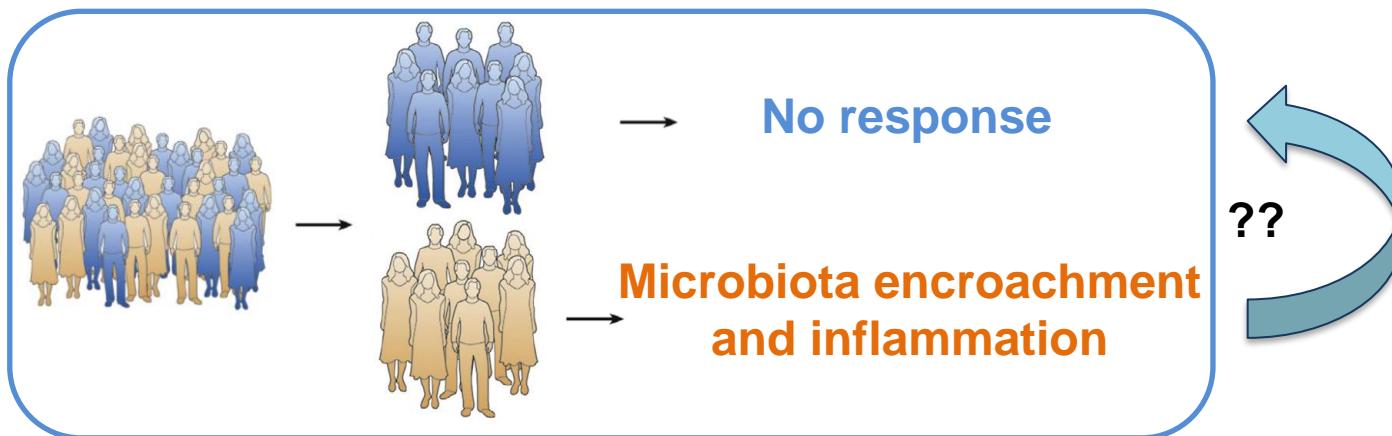


MiniBioReactor Arrays  
(MBRAs)



Auchtung *et al.* *Microbiome* 2015

# Therapeutic potential of mucus-associated microbial population

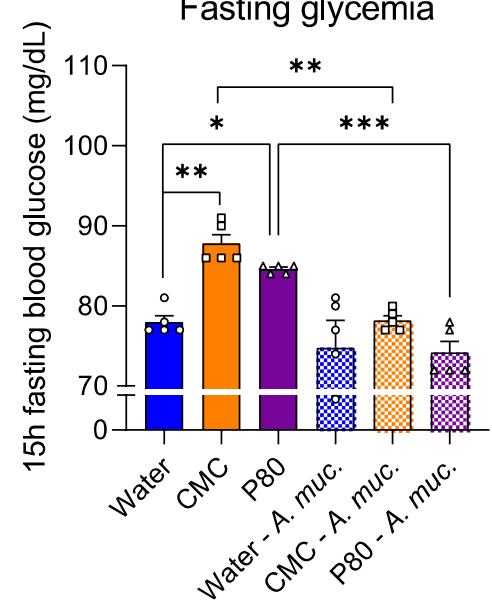
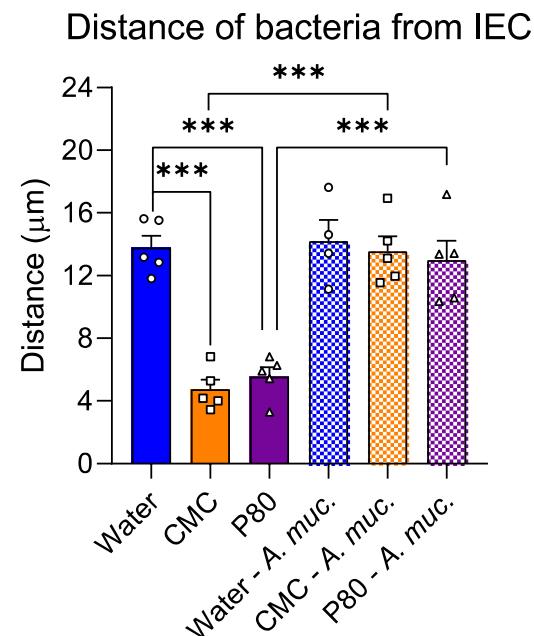
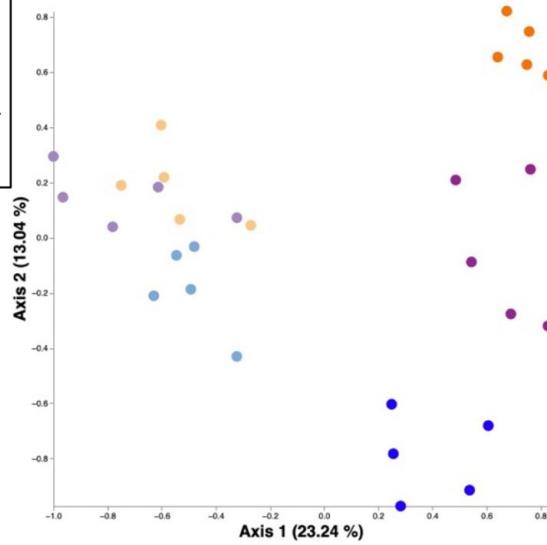


@Noémie

# Therapeutic potential of mucus-associated microbial population



- Water
- CMC
- P80
- Water - *A. muc.*
- CMC - *A. muc.*
- P80 - *A. muc.*



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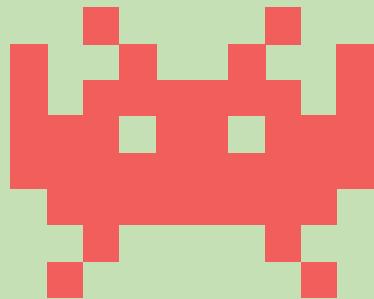
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