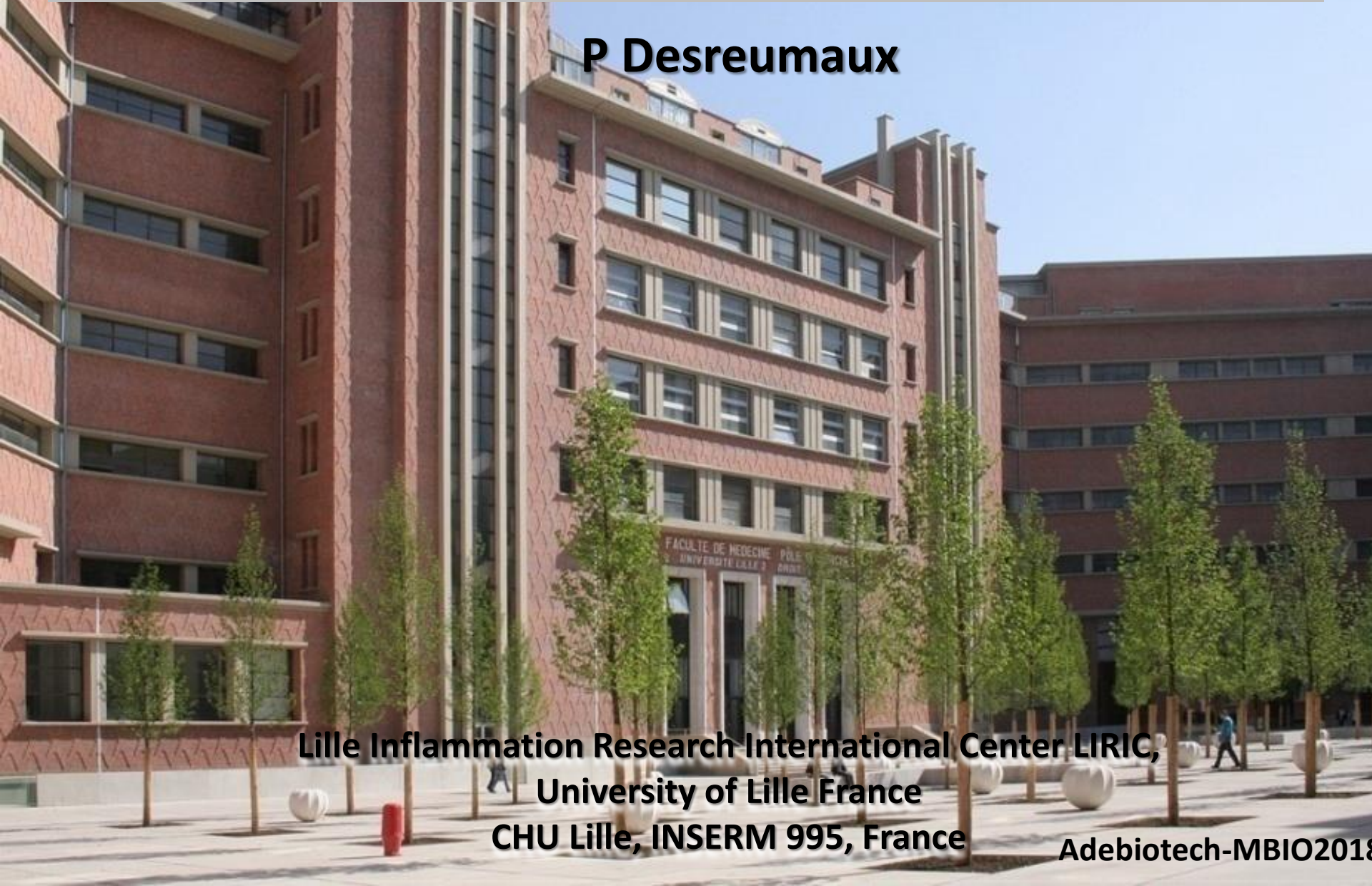


# Modulation des microbiotes en rapport avec les MICI

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**Adebiotech-MBIO2018**

## Liens d'intérêts

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P Desreumaux has served as consultant or advisory board member or speaker for Abbvie, Amgen, Biofortis, Boehringer Ingelheim, Danone, Ferring, Intralytix, Janssen, Kitozyme, Lesaffre, Neovacs, Nogra, Norgine, PPM, Roquette, Takeda, Tillotts, Trenker

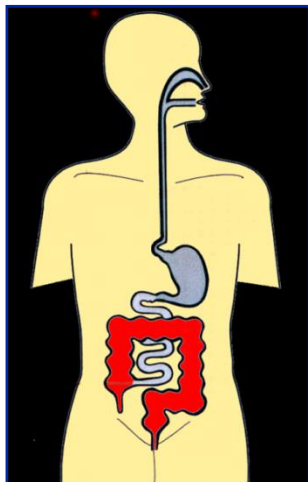
# Maladie de crohn et rectocolite hémorragique (RCH)

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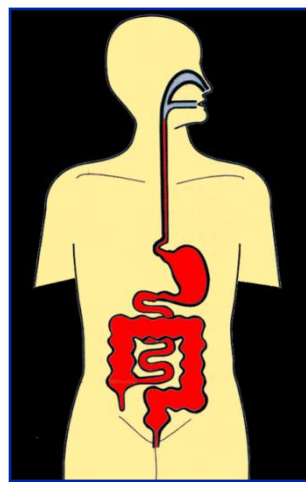
- Maladies chroniques, évoluant par poussées, entrecoupées de périodes de rémission
- Etiologie ? : environnement, génétique, immunologique

## Différences entre Crohn et rectocolite hémorragique

Localisation des lésions

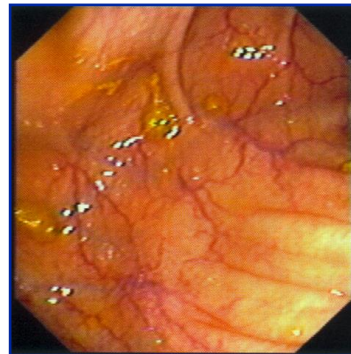


RCH



MC

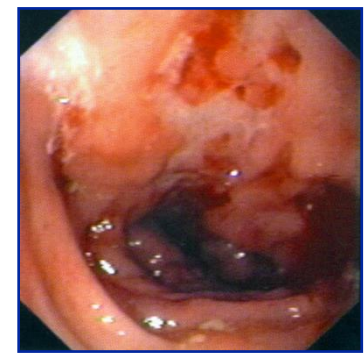
Profondeur des lésions



Témoins



RCH



MC

# Forte hétérogénéité des malades

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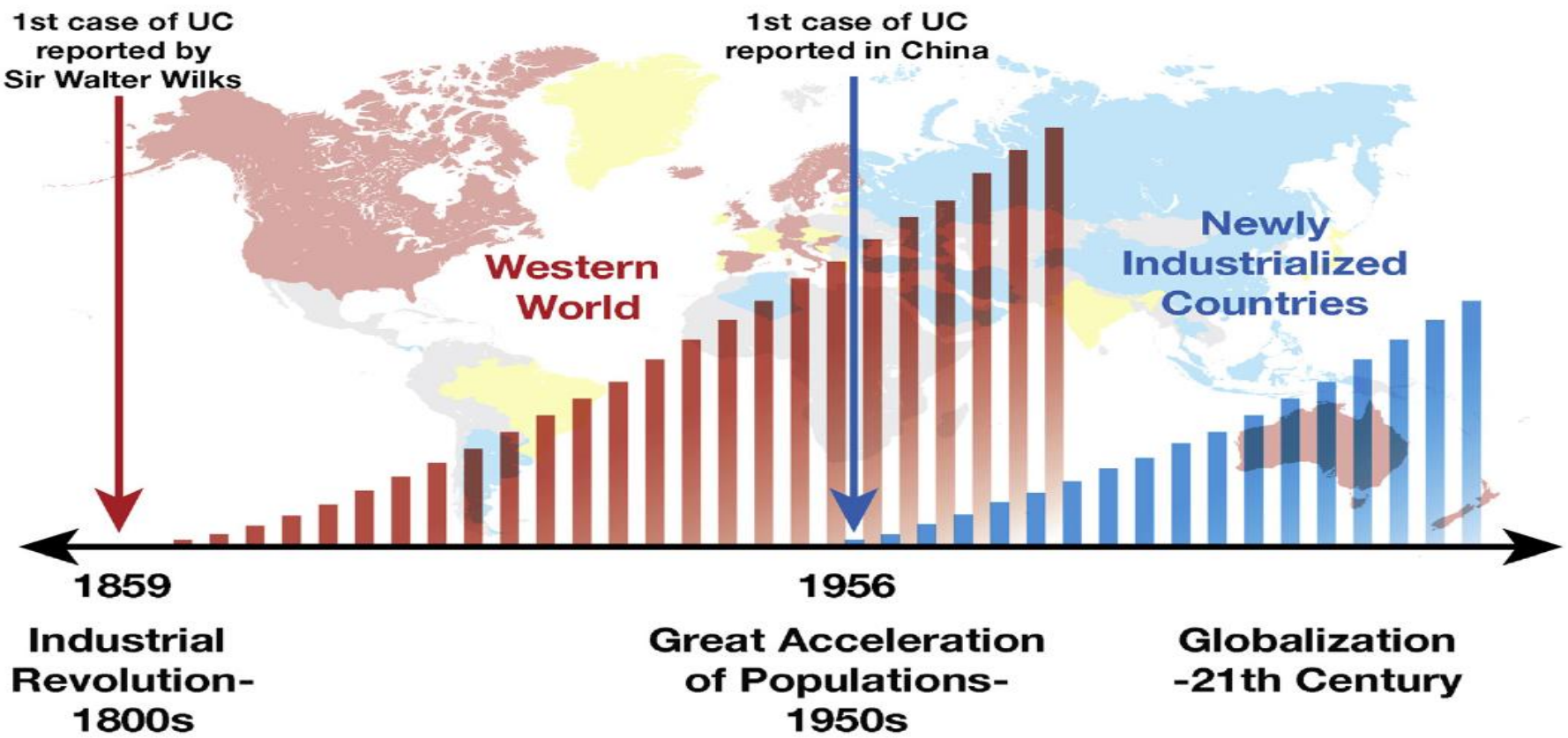
# Forte morbidité

## Federation of Crohn's and Ulcerative Colitis Association (EFCCA)

Effets de la poussée des symptômes de la maladie sur la qualité de vie des patients et sur leur activité professionnelle

Traitement actuel	Tous patient (n = 5576) n (%)	MC (n = 3025) n (%)	RCH (n = 2333) n (%)
Poussées tous les quelques mois	3870 (69,4)	2145 (71,0)	1580 (67,7)
Poussées tous les mois	611 (11,0)	383 (12,7)	201 (8,6)
Poussées toutes les semaines	534 (9,6)	348 (11,5)	162 (6,9)
Symptômes affectant la capacité à apprécier les loisirs	4213 (75,6)	2363 (78,1)	1693 (72,6)
Symptômes affectant la capacité à remplir ses fonctions professionnelles	3841 (68,9)	2168 (71,1)	1531 (65,6)
Symptômes ayant causé un changement dans le travail ou ayant altéré les responsabilités professionnelles	1872 (33,6)	1137 (37,6)	643 (27,6)

# Maladies de civilisation

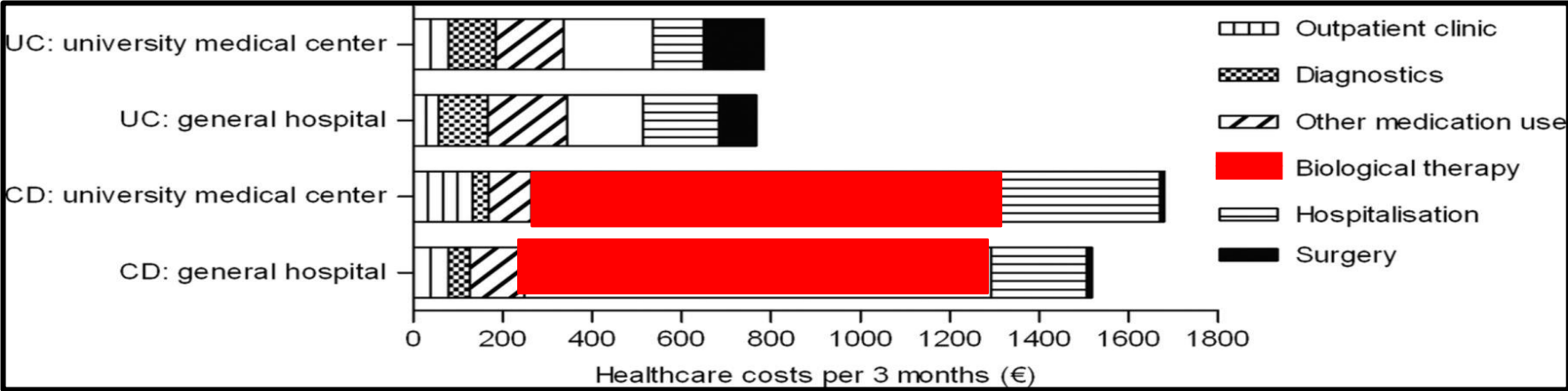


Kaplan G, Ng S. Gastroenterology 2017

# Cost societal important et croissant

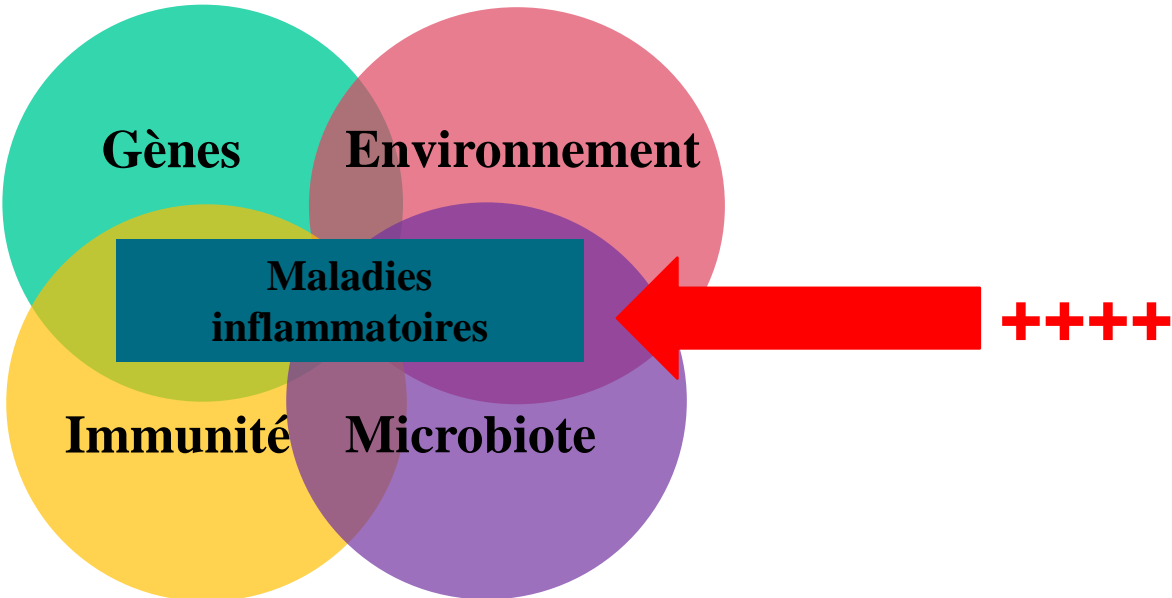
## An alarming growing cost *Real life data from The Netherlands*

1315 CD patients and 937 UC patients



# MICI: étiologie inconnue

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# MICI et microbiote en 2018: 3 hypothèses principales

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## 1. Existence d'un pathobionte (AIEC):

Nouveau pathovar *E. coli* ayant des propriétés adhésives et invasives (AIEC)

## 2. Diminution de *Faecalibacterium prausnitzii*:

Bactérie anaérobie « anti-inflammatoire régulatrice »

## 3. Dysbiosis (richesse en germes dominants, biodiversité, stabilité, résilience ...)

# Solutions thérapeutiques ciblées sur le microbiote ?

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## 1. AIEC:

**Antibiotiques, bloqueur de FimH, phages ...**

## 2. Diminution de *Faecalibacterium prausnitzii*:

**Probiotique ciblé (Harry Sokol, Philippe Langella ...)**

## 3. Dysbiosis (richesse en germes dominants, biodiversité, stabilité, résilience ...)

**Probiotiques ??**

**Transplantation fécale ?**

**Autres**

## (conventional) Probiotics at a glance in 2018 in IBD

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- Clinical trials in the last 20 years with probiotics in IBD are disappointing
- Absence of clear guidelines for the use of probiotics in Gastroenterology
- 70% of patients with IBD are spontaneously taken « probiotics » with personal satisfaction in more than 50%
- Main studies concerning probiotics are limited to *Lactobacillus*, *Bifidobacteria*, or cocktails containing at least one of these 2 bacteria (levels of  $10^{6-10}$  CFU / day)

# Human intestinal microbiota: basic data

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**Ingestion** (microbiota in transit)

$10^{10}$  bacteria / day



**Intestinal microbiota**

$10^{12-14}$  bacteria / g of stools

- 70% are unknown and non cultivable



Bacterial  
probiotic  $10^{10}$

Bacterial flora  $10^{15}$



# Transplantation fécale (1958 – 2017)

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# FMT in IBD in 2018: encouraging in UC

**CD:** only uncontrolled series, initial experience not encouraging

**UC:** uncontrolled series + 4 randomized controlled trials

	Moayyedi	Rossen	Paramsothy	Costello
FMT	Enema 1 weekly 6 weeks	Jejunal W0 and W3	Enema 5 weekly 8 weeks	Colonoscopy and 2 enema day7
Placebo	Water	autologous	Isotonic saline	autologous
Duration (W)	7	12	8	8
n	75	48	81	73
Remission	24% vs 5%	30% vs 20%	27% vs 8%	50% vs 17%
p	0,03	0,51	0,021	<0,01

Moayyedi et al. Gastroenterology 2015

Rossen et al. Gastroenterology 2015

Paramsothy et al. Lancet 2017

Costello et al. ECCO 2017

# FMT in IBD in 2018: many questions remain

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- Donor selection, process, pretreatment with gut lavage, concomitant therapy, long term efficacy ...?
- Concept of « super donor » and phage and yeast transmission
- Problems of safety: disease exacerbation leading to colectomy, abdominal pain, vomiting, novel occurrence of CD, CMV infection ...

# Traitement de la dysbiose dans les MICI ?

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- Probiotics are living **micro organisms (bacteria, virus, phages, parasites and/or yeasts)**, which, when ingested or locally applied in sufficient numbers confer one or more specified demonstrated functional or health benefits for the consumer
- Probiotics can match with a **multiple varieties of selected compounds** which are neglected but are becoming more and more important



# Connaissance composition du microbiote intestinal

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## Intestinal microbiota

**$10^{12-14}$  bacteria / g of stools**

- 70% are unknown and non cultivable

**$10^{13-15}$  virus / g of stools**

- 80% are phages (bacteriophages=bacteria-eater)

**$10^4$  yeast / g of stools**

- Mainly candida

# Microbiote fungal et ...

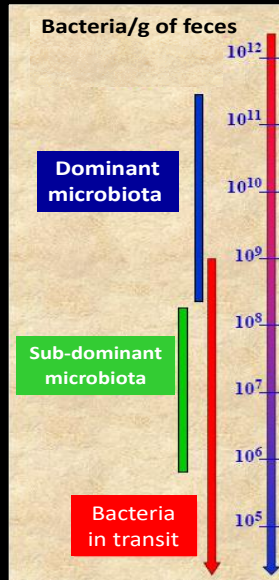
- $10^3$  levures / g selles, essentiellement **Candida**



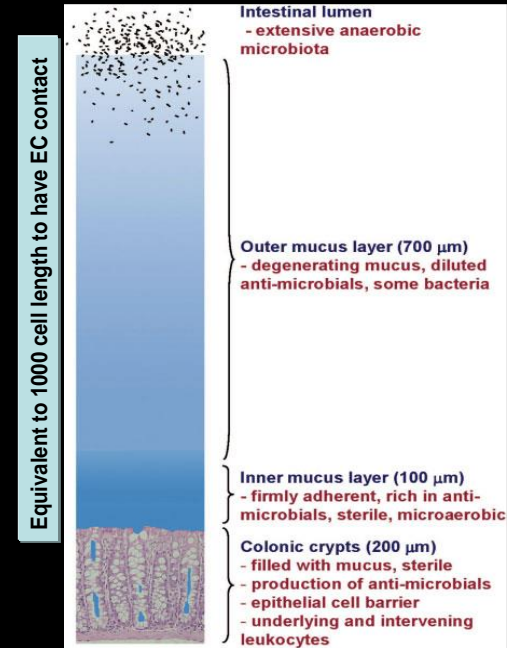
	Bacteria	Yeast	Advantage of yeast
Presence in intestinal flora	+++ $10^{14}$	+ (candida, no <i>Saccharomyces</i> ) $10^4$	Numerical predominance Less competition No colonisation
Cell size	$1\mu\text{m}$	$4\text{-}40\mu\text{m}$	> Surface area
Type	prokaryote	eukaryote	No genetic transfer No resistancy
Antibiotic resistancy	no	yes	Not weakend by ABT
Phage resistancy	no	yes	Robustness
Acid resistancy (gastric acid, bile acid ...)	no	yes	Higher natural resistancy Robustness
Immune stimulation	+	+++	Rumbo Martin et al, 2011

# Meilleure connaissance des microbiotes intestinaux

## LUMINAL



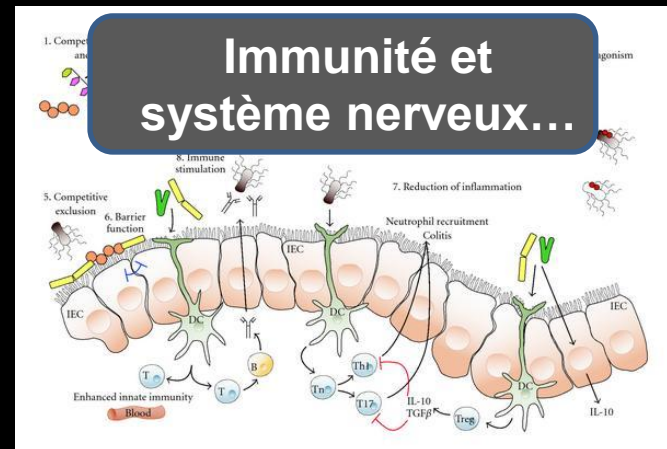
## ADHERENT ?



## Effet barrière



## Immunité et système nerveux...



# Conclusion (1)

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- High demand and high potential for probiotics in gastroenterology
- Main strength of probiotics: safety +++ (except fecal transplantation)
- Main weakness of classic probiotics in IBD: efficacy
- POC: fecal transplantation with > 90% efficacy in patients with *C. difficile* induced pseudomembranous colitis but
  - no insurance of (long term) safety
  - no efficacy marker (depends of the quality of donor stools)

## Conclusion (2)

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- Need to analyse the intestinal flora as a whole including in the microbiome the bacteriome, virome, phagome and fungome
- Need high quality studies, products and clinical trials
- Place for new forms of probiotics:
  - Isolated microorganisms: bacteria, phages and yeasts ...
  - Cocktails : oral capsules of known effective and safety micro-organisms containing bacteria, phages, yeasts and some of their metabolites according to appropriate conditions