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Dysmetabolism of Bile Acids in feces: implications in human colon pathologies

SCD, Friday 30 January 2015, Girona

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CRI
CENTRE de RECHERCHE
sur l'INFLAMMATION

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Dysmetabolism of Bile Acids in feces : implications in human colon pathologies

1) Bile acids: metabolism, original functions

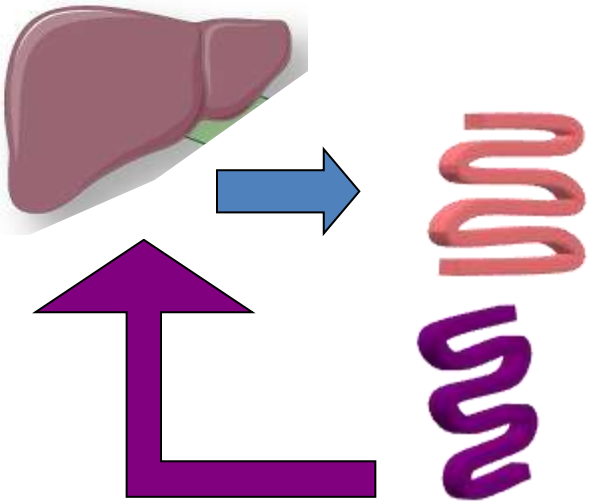
2) Bile acids and the gut : « The News »

3) Bile acids «Dysmetabolism»

- *Irritable Bowel Syndrome*
- *Inflammatory Bowel Diseases*

1) Bile acids : metabolism, original functions

BILE ACIDS METABOLISM IN HUMAN



- Synthesized by liver from cholesterol

- Secreted in gut lumen during digestion

- Allow lipid absorption by fat micellization

-95 % reabsorption by terminal ileum and return to the liver

Permanent recirculation : effective pool >>> quantitative pool

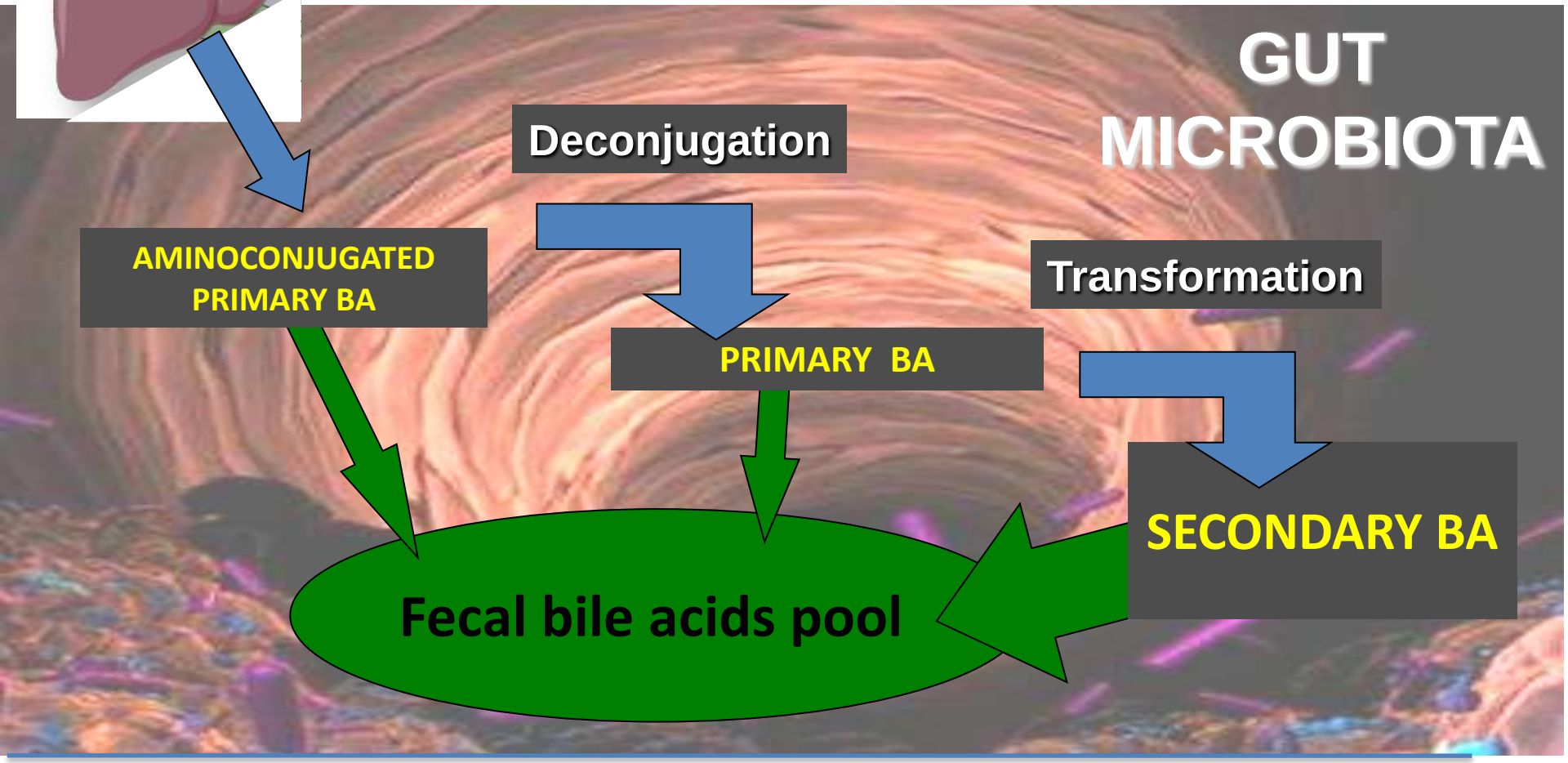
5 % faecal excretion

- **Bile Acids are endogenous laxatives**

- **Expansion of Bile Acids pool size causes diarrhoea (Bile Acids Malabsorption)**

Laxative effect varies with the species of bile acids

BILE ACIDS METABOLISM



4 main bile acids subtypes in human

Cholic acid	→	Deoxycholic acid
Chenodeoxycholic acid	→	Lithocholic acid

2) Bile acids and the gut : « The News »

FGF 19 and Bile Acids Malabsorption : the GHOST Slide

2) Bile acids and the gut : « The News »

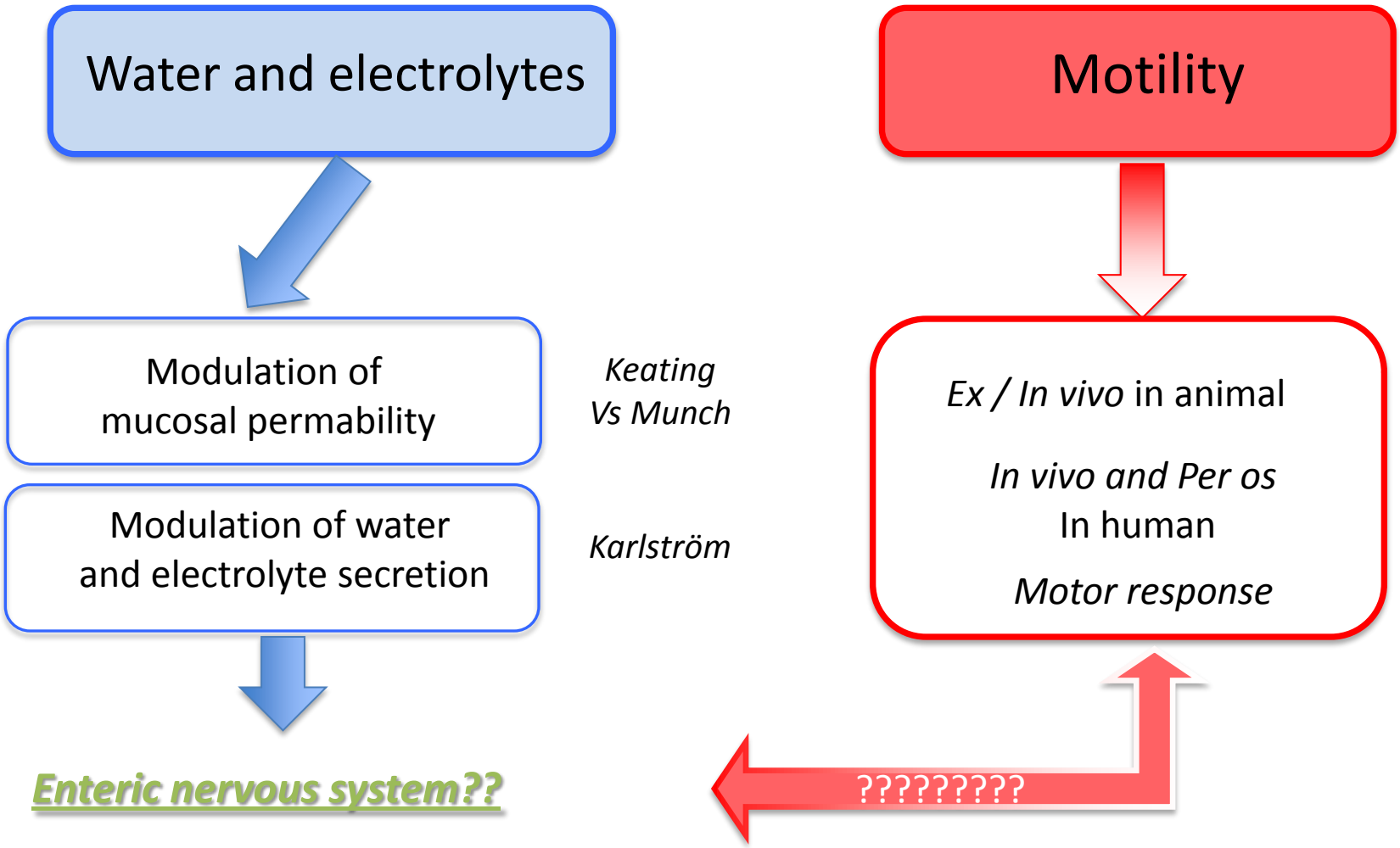
With the discovery of bile acids receptors FXR and TGR5,
Bile Acids became *HORMONES*

2 receptors - NUCLEAR: FXR
- MEMBRANAR : TGR5

Linked to -basal metabolism regulation
- Fats storage (liver and peripheral fat
- Inflammation

Bile Acids in the Colon

Bile acids are endogenous laxatives ?

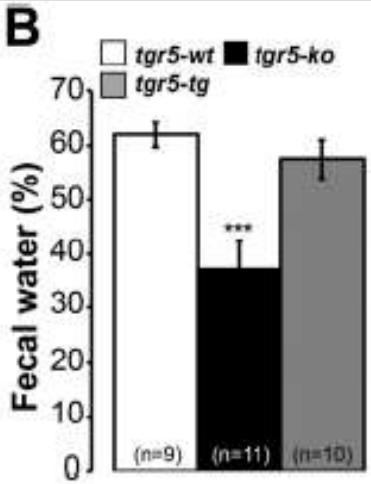


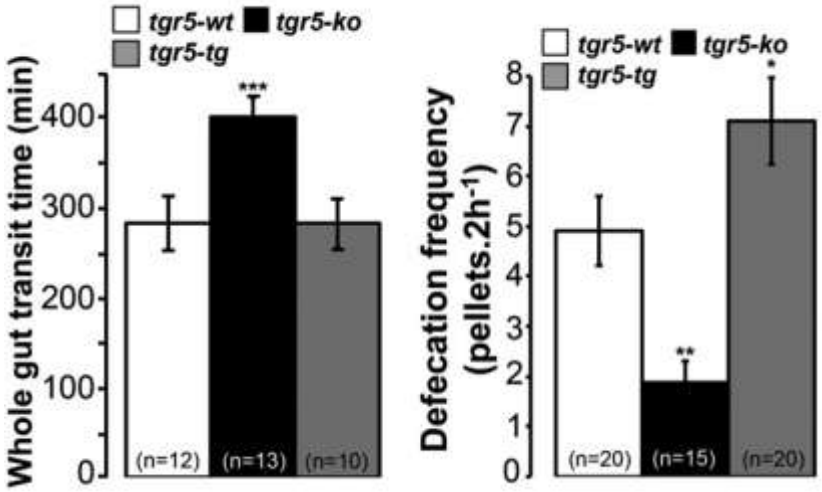
Bile Acids in the colon

Endogenous laxatives: a role for the TGR5 receptor

Water and electrolytes

Motility



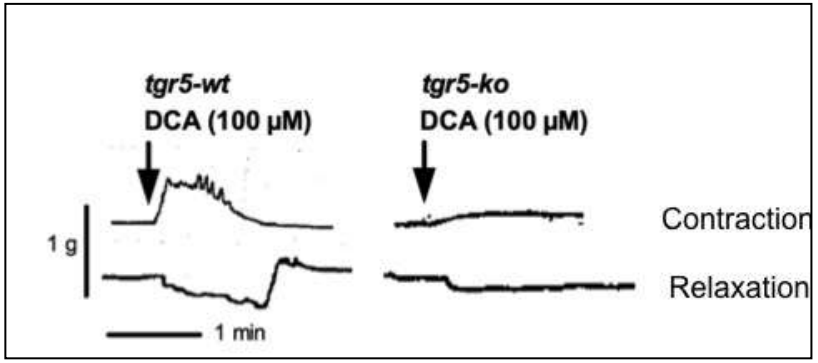


The Receptor TGR5 Mediates the Prokinetic Actions of Intestinal Bile Acids and Is Required for Normal Defecation in Mice

FARZAD ALEMI,[1] DANIEL P. POOLE,[2] JONATHAN CHIU,[1] KRISTINA SCHOONJANS,[3] FIORE CATTARUZZA,[1] JOHN R. GRIDER,[4] NIGEL W. BUNNETT,[5] and CARLOS U. CORVERA[1,6]

Gastroenterology

2013;144:145–154



Firt Study in IBS : AIMS

- To compare the composition of faecal bile acid pool between IBS-D patients and healthy subjects.
- Microbiota analysis in the same stool samples
- Look for correlation between fecal bile acids species and symptoms

Neurogastroenterology & Motility

Increase in fecal primary bile acids and dysbiosis in patients with diarrhea-predominant irritable bowel syndrome

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PATIENTS AND METHODS

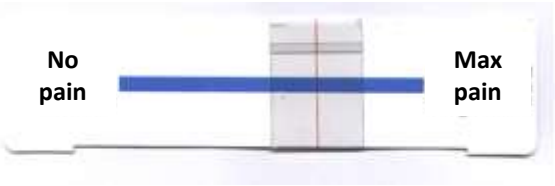
PATIENTS

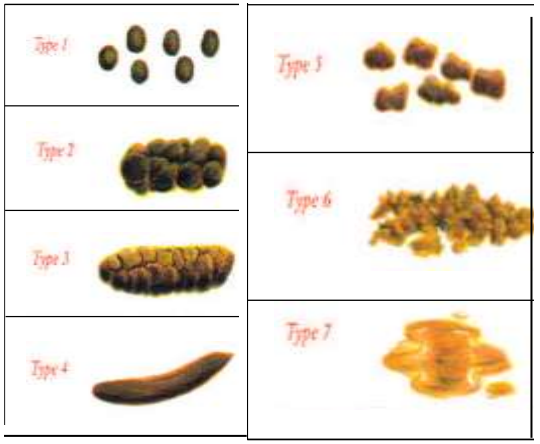
- 14 Diarrhoea predominant IBS vs 18 HS
- 18 - 75 years old, no previous treatment 3 monthes before

(Antibiotics, transit modulator, corticotherapy, probiotics)

CLINICAL DATAS the week before sampling

- Bristol stool scale
- Stool frequency / day
- Abdominal pain score / day
- Bloating score / day

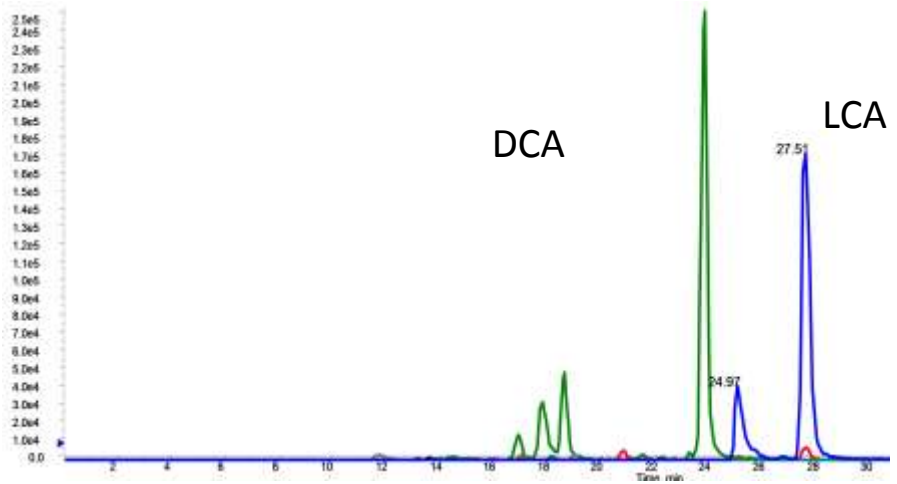




Bile acids and microbiota analysis

- **Measure of faecal Bile Acids** (HPLC MS / MS)

Normal fecal BA profil
by HPLC MS/MS



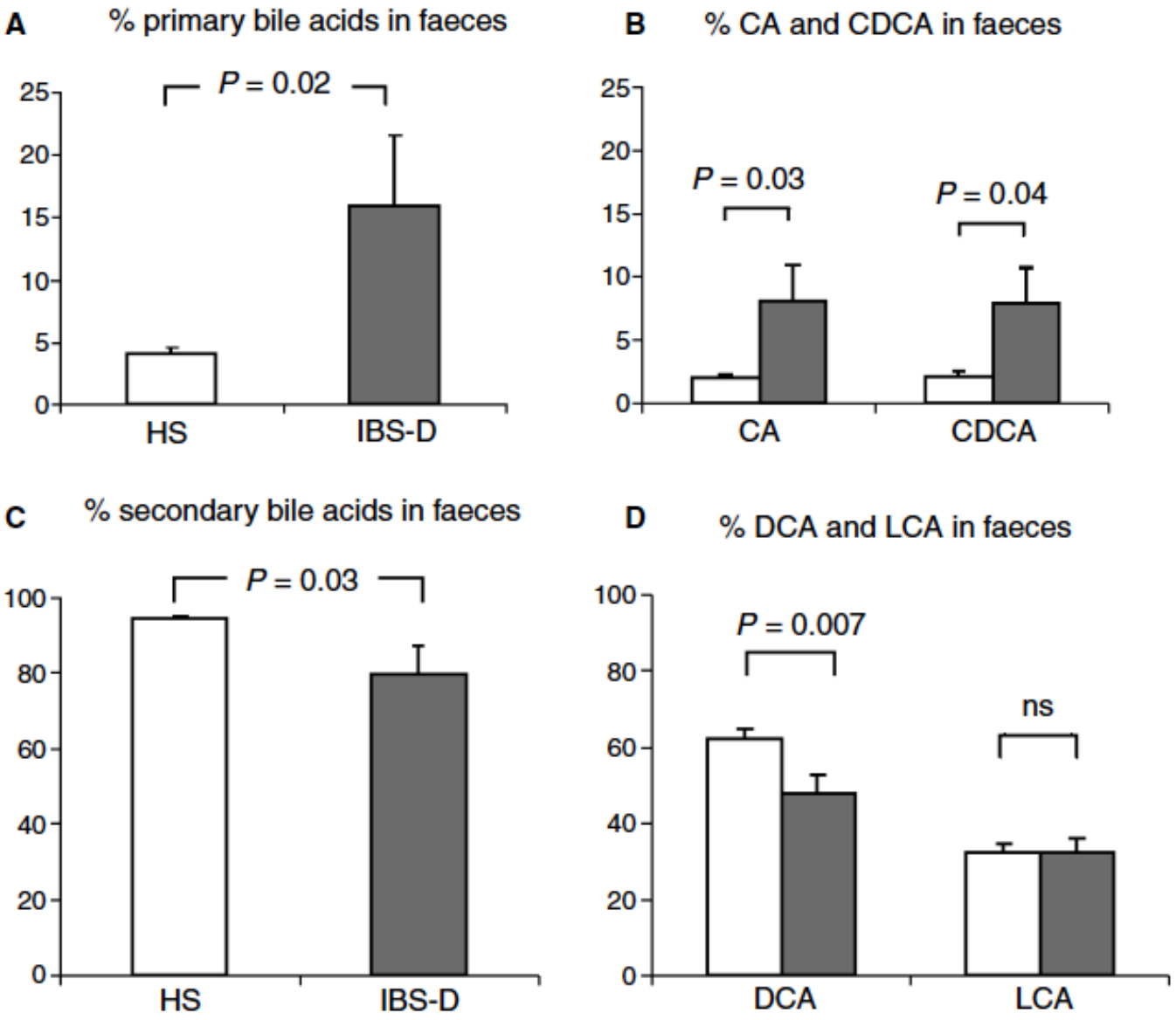
- **Microbiota by qPCR**

- *Bacteria*
- Bifidobacterium
- Lactobacillus
- *F.prausnitzii*

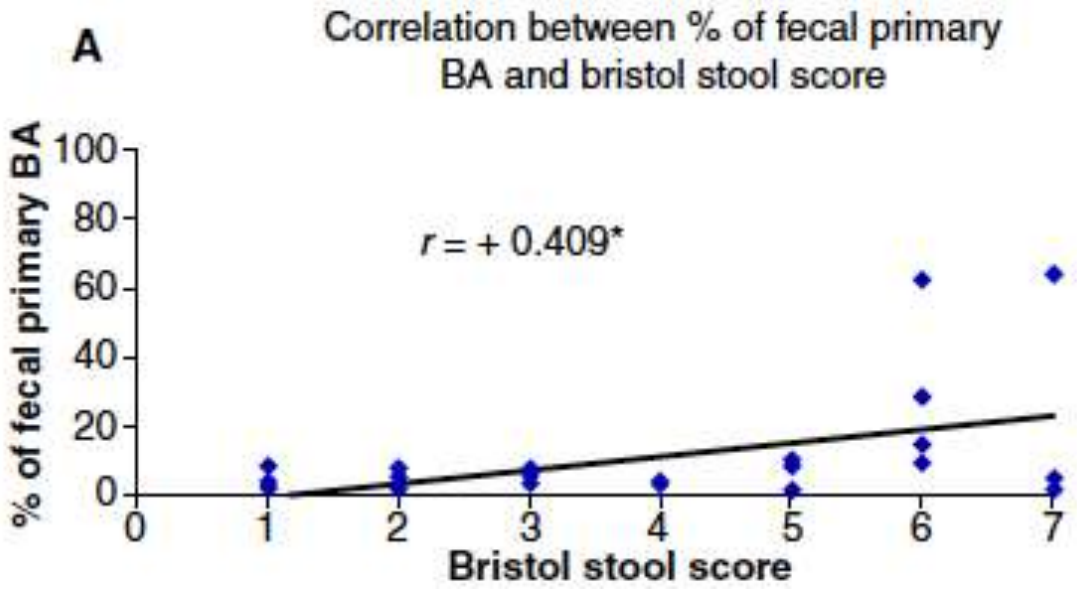
- Leptum
- Bacteroides
- *E.coli*
- Coccoides

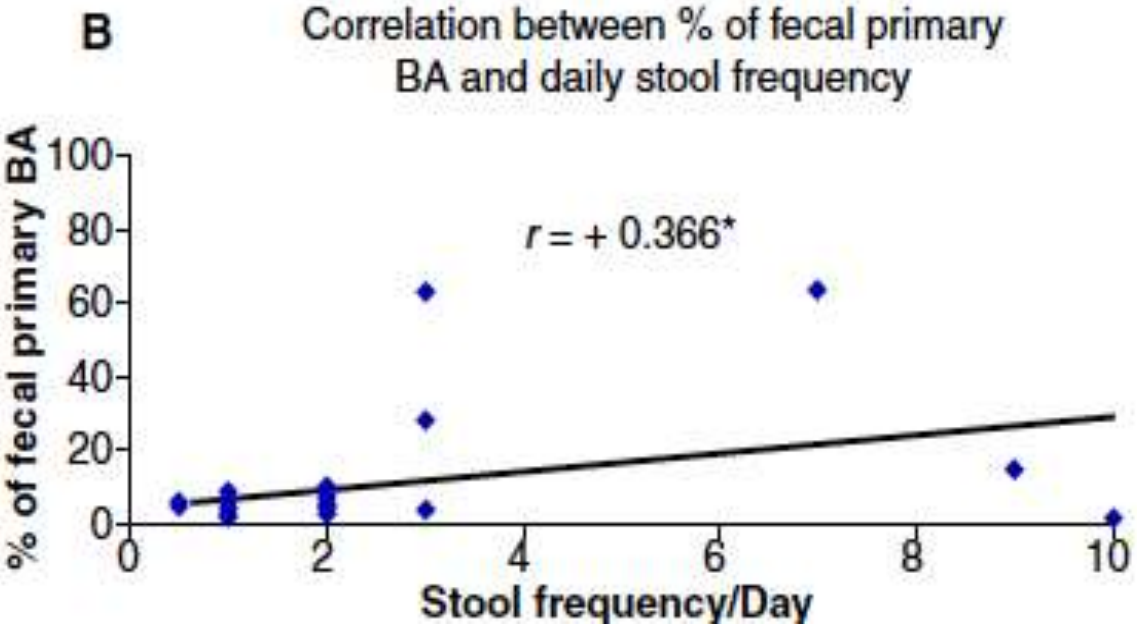
Bacterial species implicated in Bile acid Transformation

Bile acids in feces :

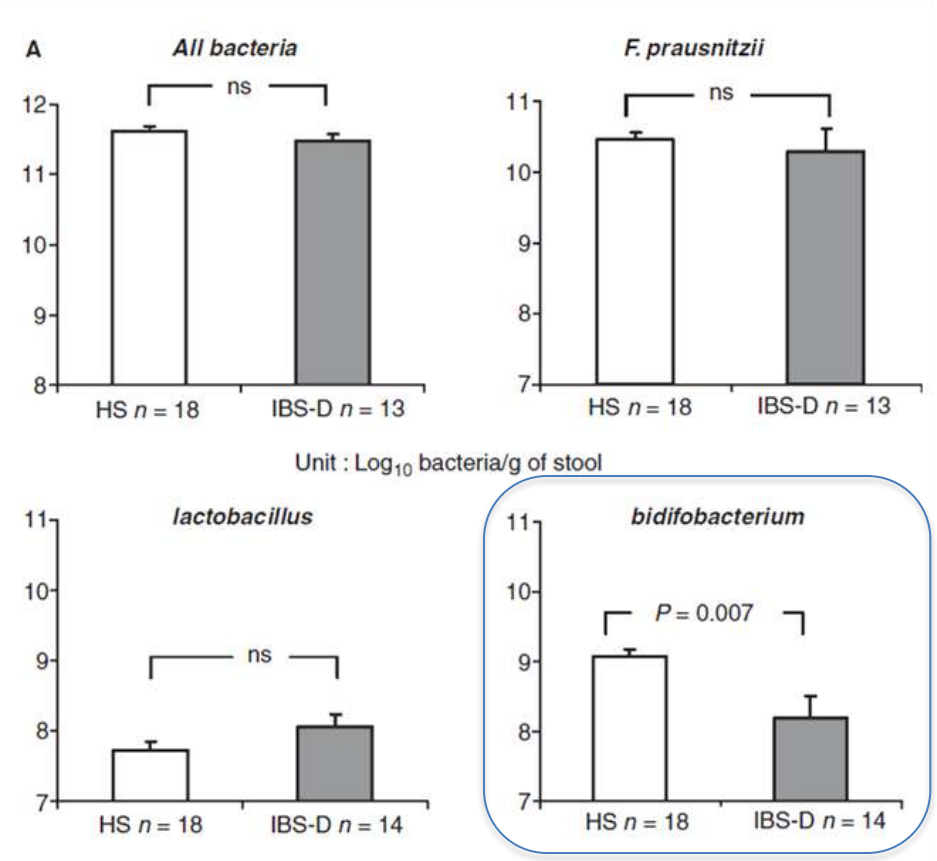


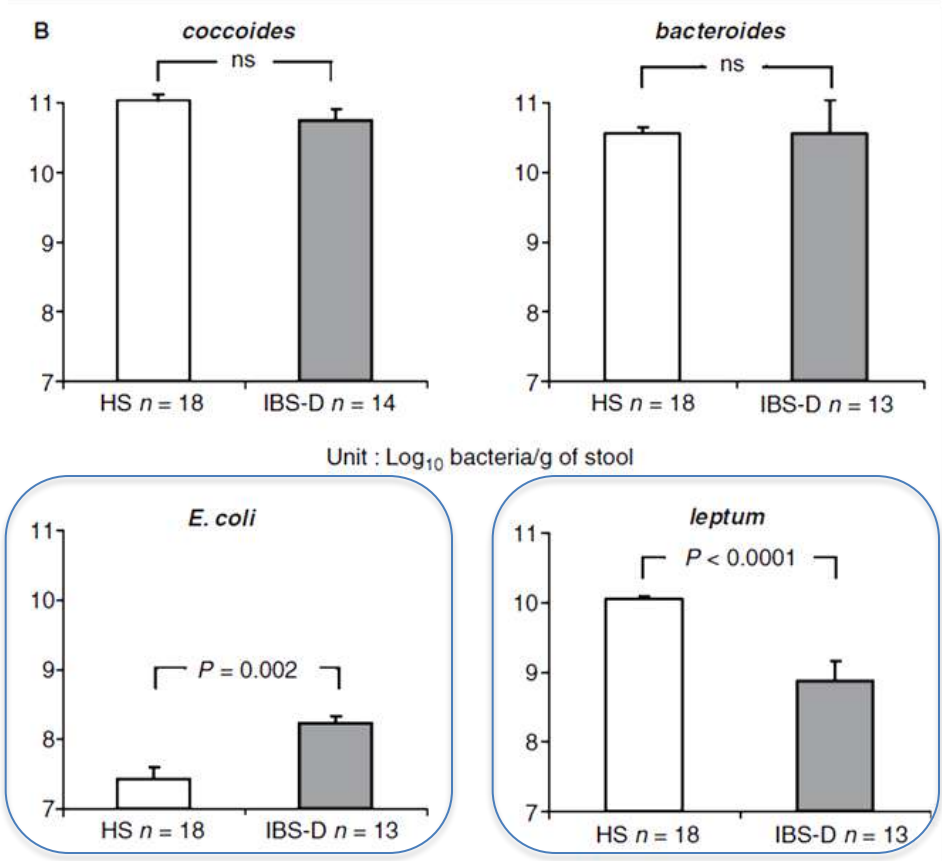
Correlation between % of primary BA and symptoms





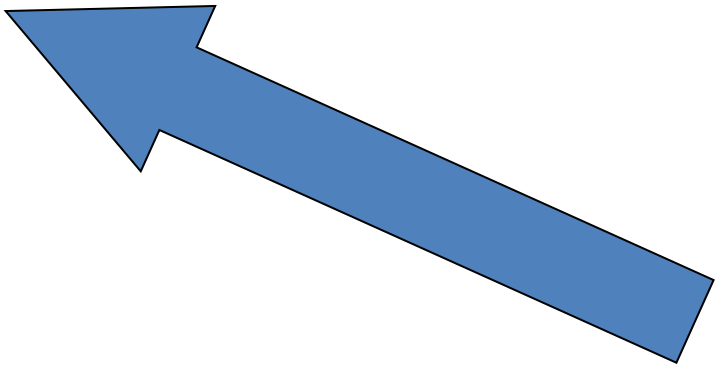
Dysbiosis in IBS-D patients





Perspectives : Mechanism ?

SHORTER
TRANSIT TIME



Less secondary BA
More primary BA
(CDCA)

Lower bacterial Bile Acids transformation

(due to decrease in Leptum group ?)

Primitive gut microbiota dysbiosis in IBS -D

- Incoming publication in IBS-C patients
- Role of TGR5?

Second Study in IBD

Colonic IBD: **23 flares, 19 remission, 29 HS** / **12 CD , 32 UC**

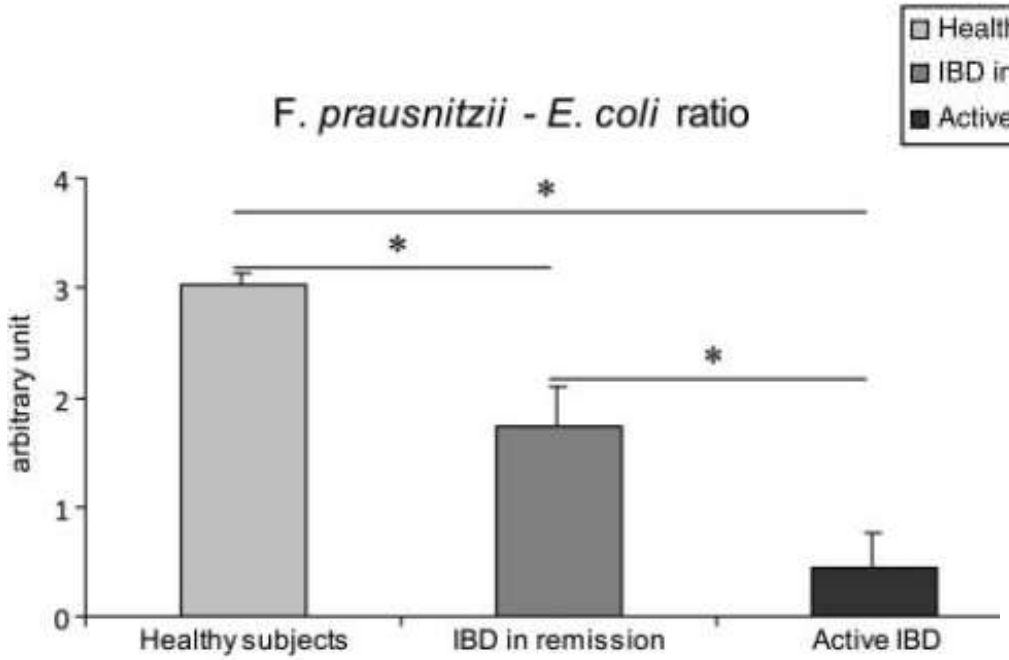
	Active CD	Active UC	Total	Remission CD	Remission UC	Total	Healthy subjects
IBD							
n (%)	7 (17)	16 (38)	23 (55)	5 (12)	14 (33)	19 (45)	29
Mean age (±SEM)	37.6±19	36.0±14	37.0±15	42.1±19	37.5±12	38.7±14	34.6±14
Male %	43	44	43	40	64	58	38
Montreal classification							
L1	0	–	0	0	–	0	–
L2 (%)	7 (17)	–	7 (17)	5(12)	–	5(12)	–
L3	0	–	0	0	–	0	–
E1 (%)	–	2 (5)	2 (5)	–	0	0	–
E2 (%)	–	6 (14)	6 (14)	–	4 (10)	4 (10)	–
E3 (%)	–	7 (17)	7 (17)	–	8 (17)	8 (17)	–
Treatment							
Corticosteroids (%)	3 (7)	8 (19)	11(26)	0	1 (2)	1 (2)	–
Mesalazine (%)	1 (2)	5 (12)	6 (14)	1 (2)	6 (14)	7 (17)	–
Methotrexate (%)	1 (2)	3 (7)	4 (10)	0	0	0	–
Purine analogues (%)	1 (2)	1 (2)	2 (5)	2 (5)	5 (12)	7 (17)	–
Infliximab (%)	3 (7)	7 (17)	10 (24)	2 (5)	5 (12)	7 (17)	–
Adalimumab (%)	0	0	0	0	2 (5)	2 (5)	–
Certolizumab (%)	0	0	0	1 (2)	0	1 (2)	
Ciclosporin (%)	0	1 (2)	1 (2)	0	1 (2)	1 (2)	–
Antibiotics	0	0	0	0	0	0	0

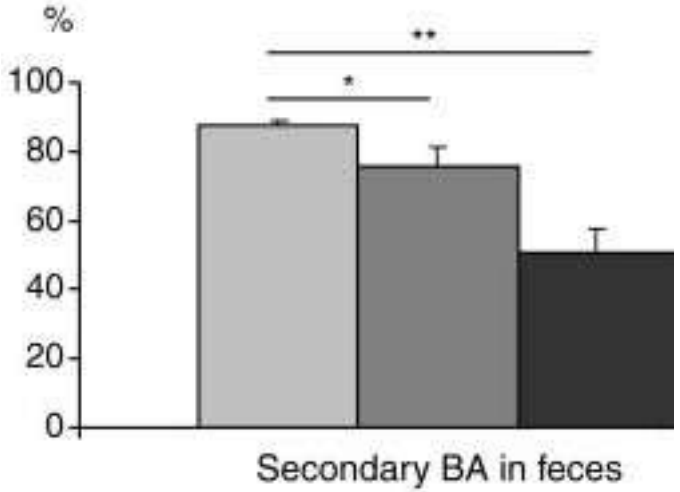
Gut

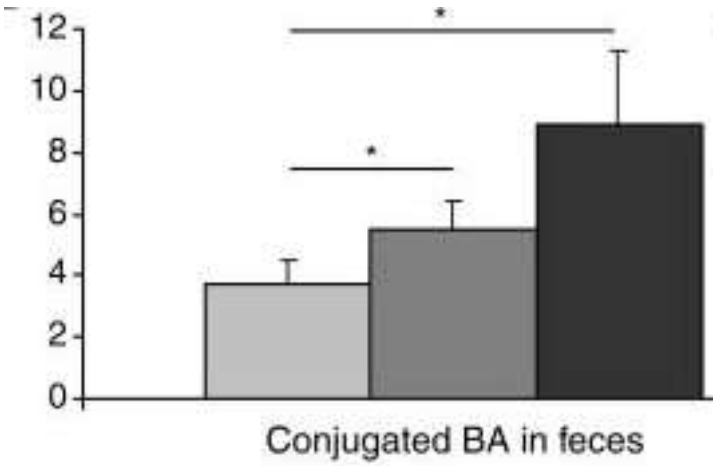
Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases

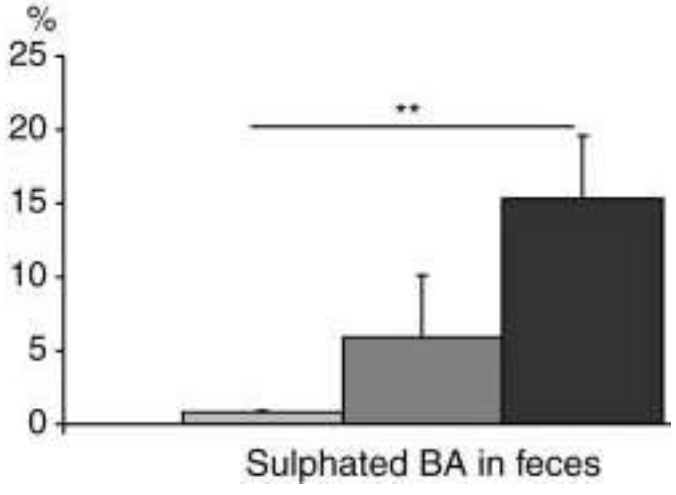
Henri Duboc,[1,2,3] Sylvie Rajca,[1,2,3] Dominique Rainteau,[1,2,4] David Benarous,[5] Marie-Anne Maubert,[1,2,4] Elodie Quervain,[1,2] Ginette Thomas,[1,2,4] Véronique Barbu,[4] Lydie Humbert,[1,2,4] Guillaume Despras,[2] Chantal Bridonneau,[6] Fabien Dumetz,[6] Jean-Pierre Grill,[1,2] Joëlle Masliah,[1,2,4] Laurent Beaugerie,[1,2,3] Jacques Cosnes,[1,2,3] Olivier Chazouillères,[7] Raoul Poupon,[7] Claude Wolf,[1] Jean-Maurice Mallet,[2] Philippe Langella,[6] Germain Trugnan,[1,2,4] Harry Sokol,[1,2,3] Philippe Seksik[1,2,3]

Dysbiosis and dysmetabolism in IBD :

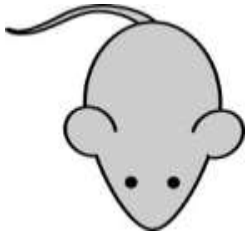


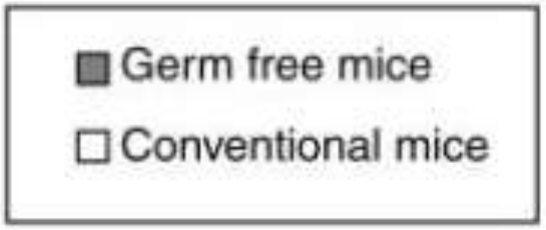


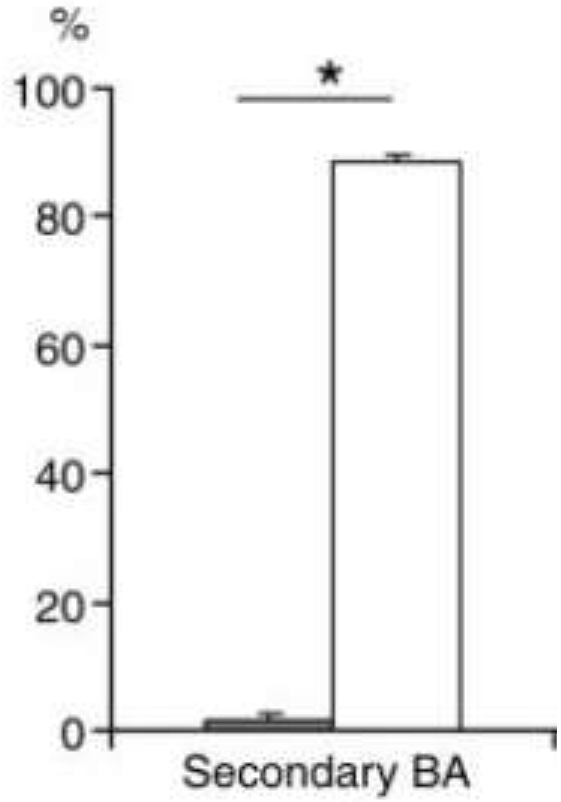




Does the dysbiosis lead to dysmetabolism ?

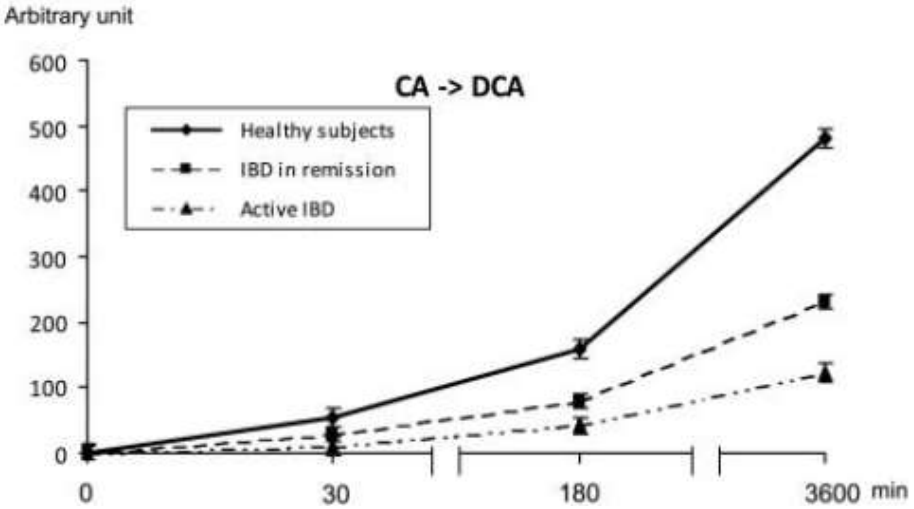






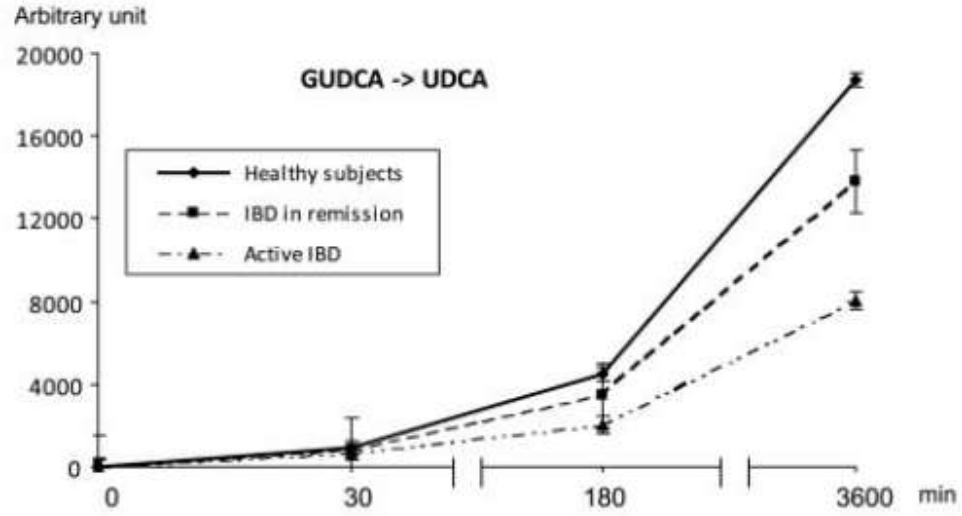
Does the dysbiosis lead to dysmetabolism ?

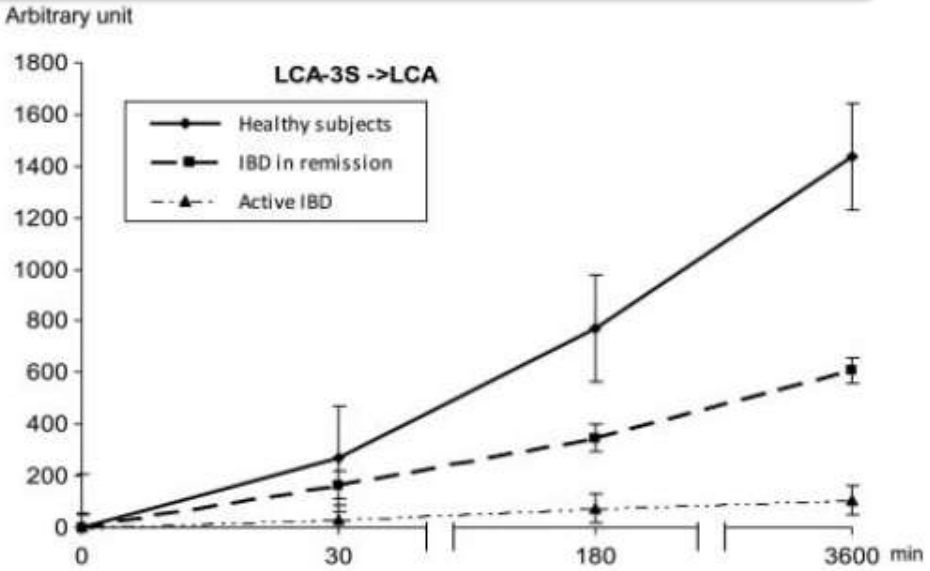
Experiments with dried feces of HS, IBD in remission and Active IBD



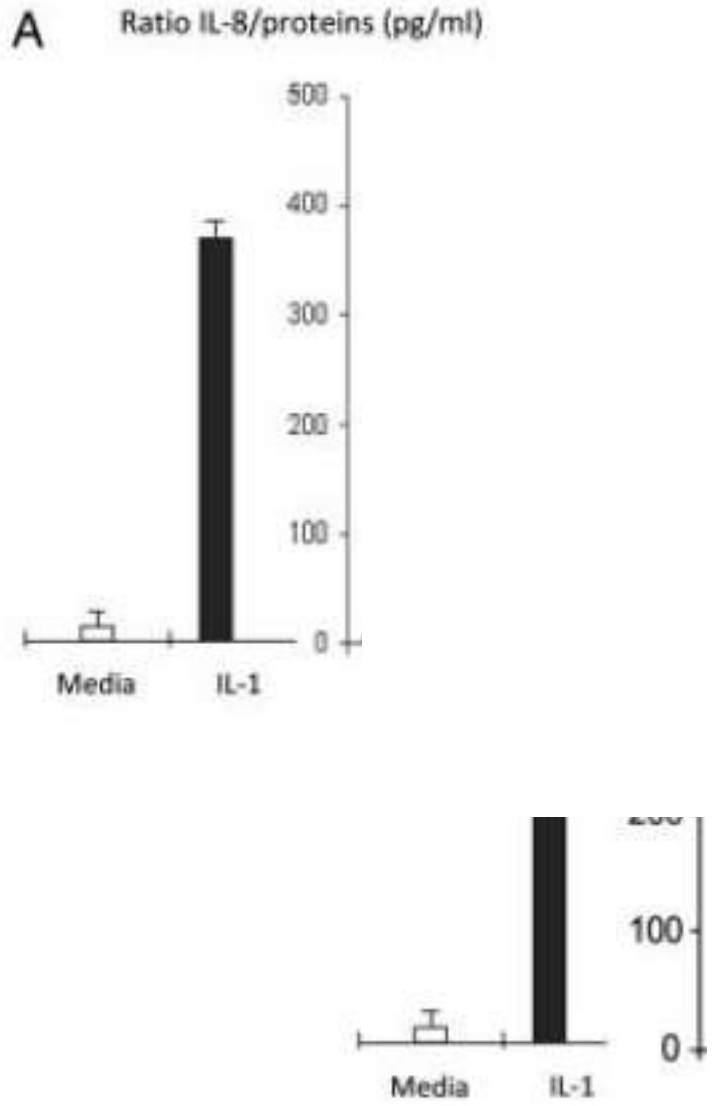
- **Transformation deficiency**
- **Deconjugation deficiency**
- **Desulfation deficiency**

The dysmetabolism depends of the disease activity





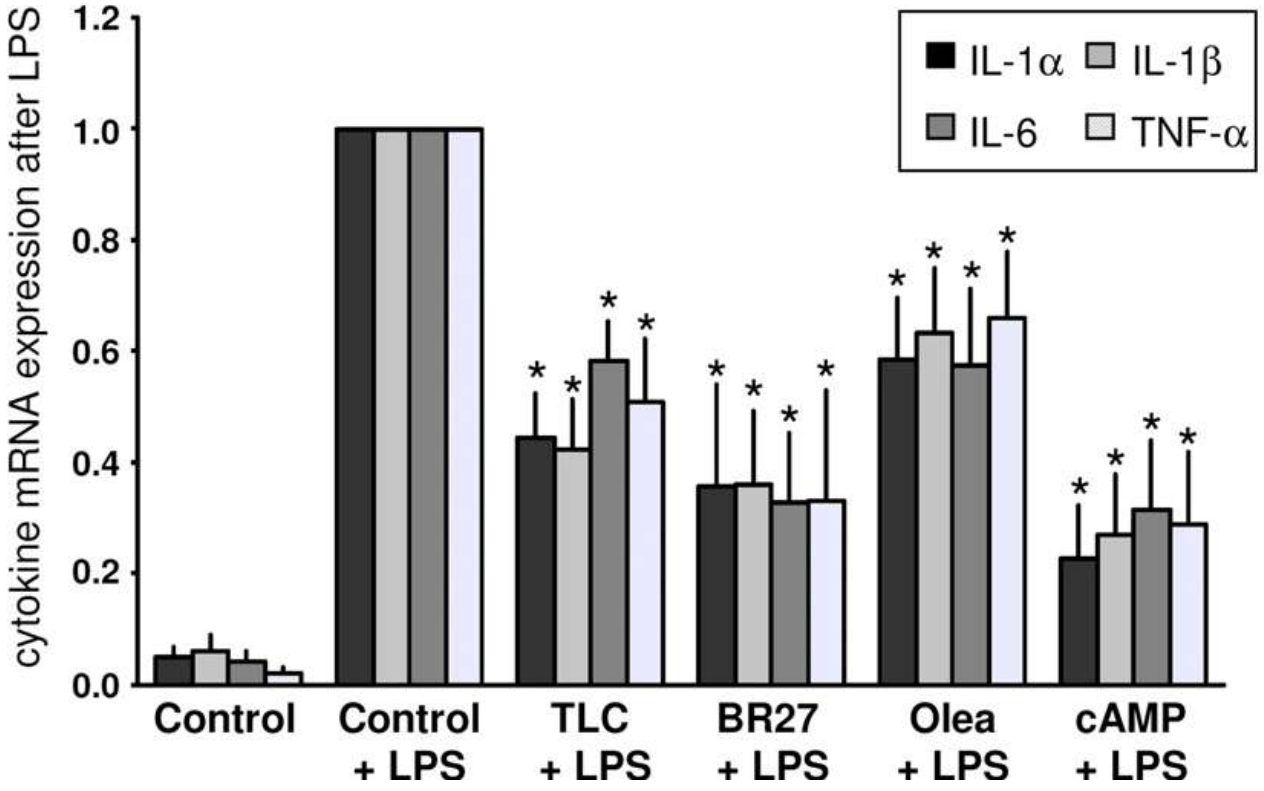
Does the changes in BA can be involved in the inflammatory loop ?



A TGR5 pathway ?

→ The anti-inflammatory effect of BAs, (decreased secretion of TNFα, Interleukin-1β, interleukin-6) in macrophages and monocytes have been described 20 years ago

TGR5 decrease the release of proinflammatory cytokines by Kupffer cells (liver macrophages)



Keitel V et Al . Expression and function of the bile acid receptor TGR5 in Kupffer cells. Biochem Biophys Res Commun. 2008 Jul 18;372(1):78-84.

The chicken and the egg?

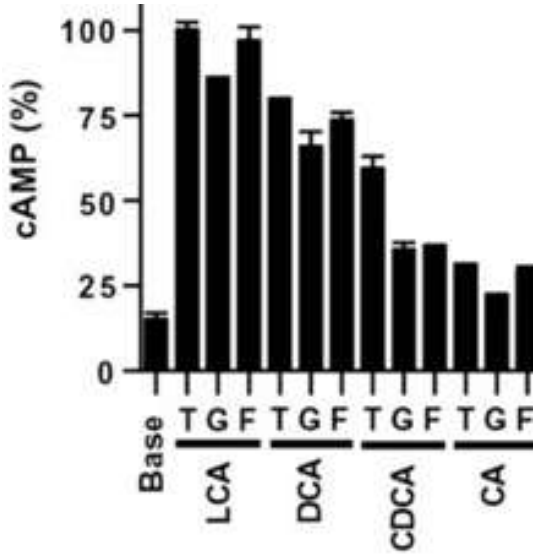
→ Parallèle entre profondeur de la dysbiose, du dysmétabolisme des acides biliaires, et de l'activité de la maladie

→Mesure d'activité enzymatiques fécales = permet de s'affranchir du temps de transit.

→ Dépistage de BAM: moins d'intêret dans cette population

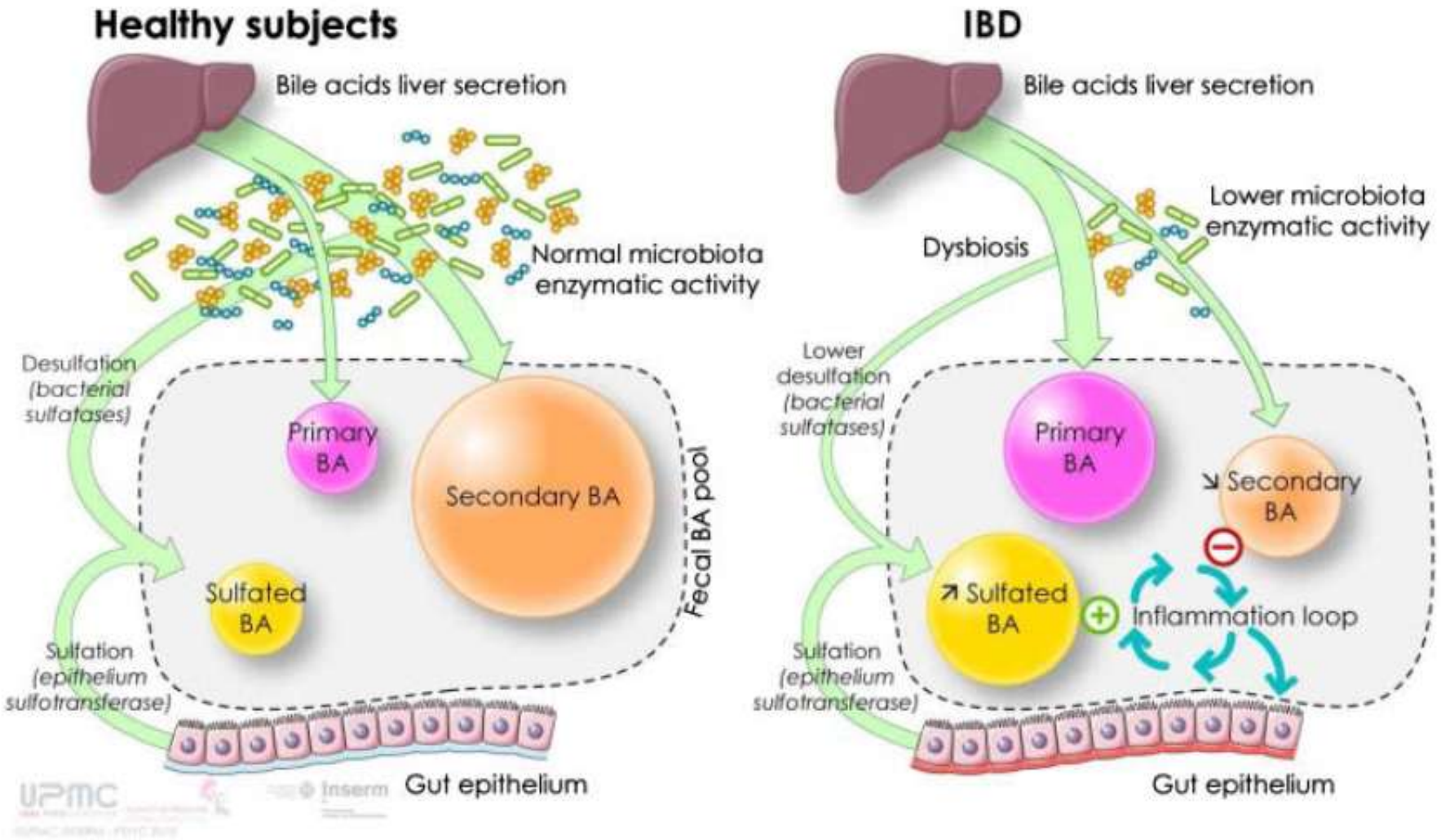
Effet anti inflammatoire: Perspective TGR5 ?

LCA et DCA sont les plus puissants ligands de TGR5



Kawamata et Al, 2003

A Model ?

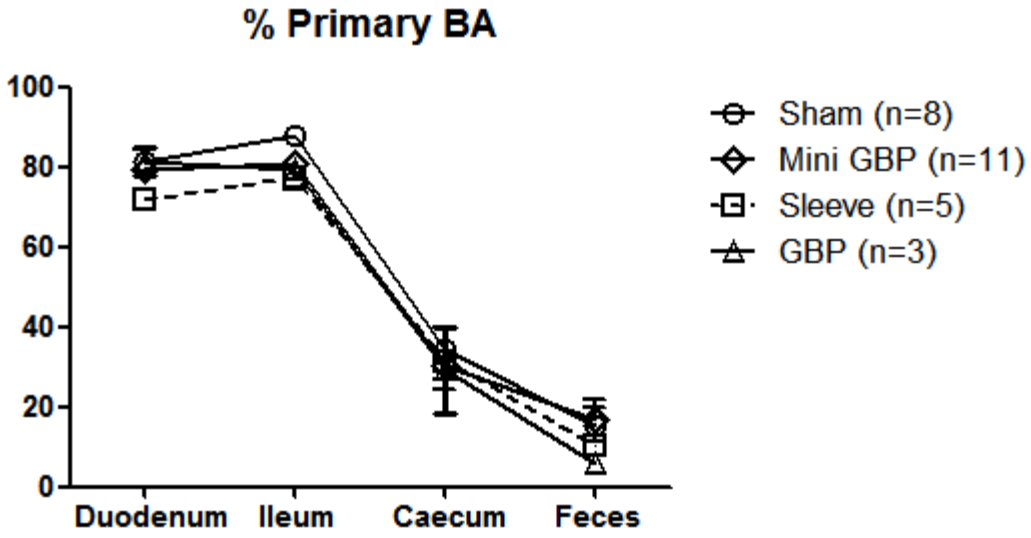

Healthy subjects
Bile acids liver secretion
Normal microbiota enzymatic activity
Desulfation (bacterial sulfatases)
Primary BA
Secondary BA
Sulfated BA
Fecal BA pool
Sulfation (epithelium sulfotransferase)
Gut epithelium
IBD
Bile acids liver secretion
Dysbiosis
Lower microbiota enzymatic activity
Lower desulfation (bacterial sulfatases)
Primary BA
↘ Secondary BA
↗ Sulfated BA
Inflammation loop
Sulfation (epithelium sulfotransferase)
Gut epithelium

Conclusion

Dysbiosis and Dysmetabolims of bile acids:

Strong arguments, > IBD than IBS, and maybe and a possible role in inflammation

But… a story to be continued



Thank you very much for your attention