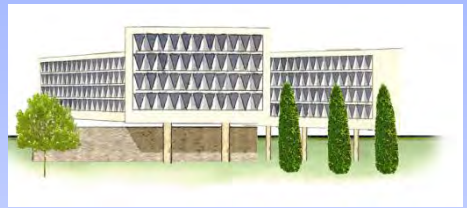
Telle flore, tel foie



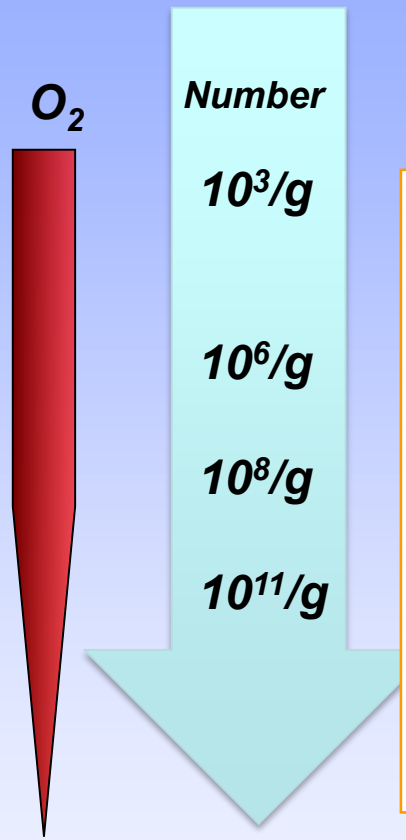
Hepato-gastroenterology
Antoine-Béclère
Clamart

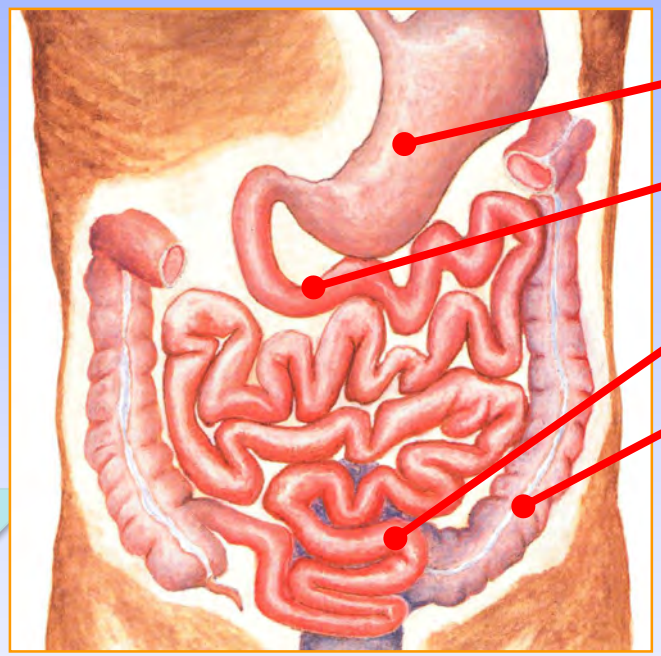
INSERM U996
Clamart

Gabriel Perlemuter

Gut microbiota

➡ **The gut contains around 10^{14} bacteria**





Stomach : 10^2 à 10^3 bacteria/g

Duodenum : 10^4 à 10^5 bacteria/g

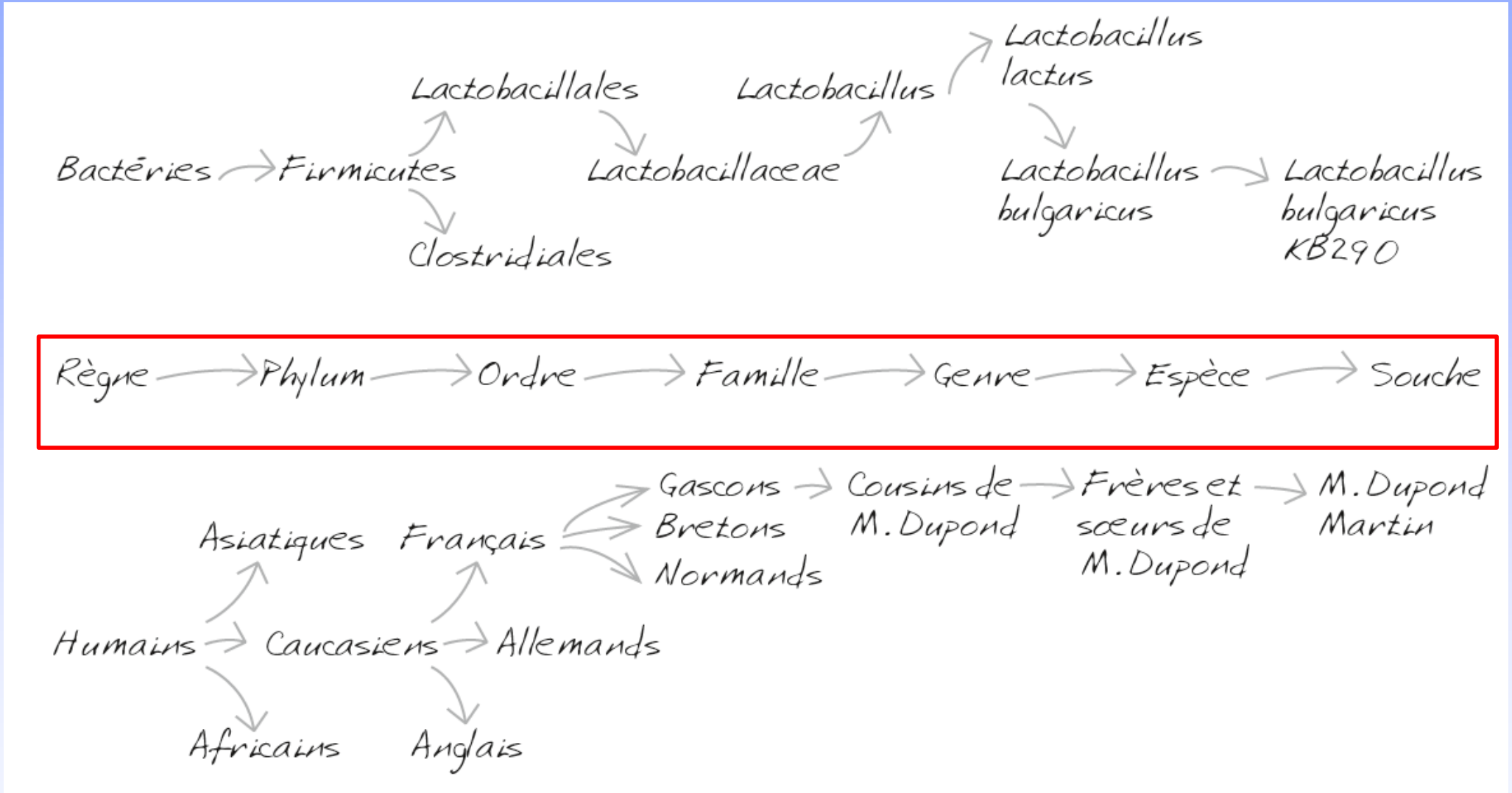
Ileum : 10^5 à 10^8 bacteria/g

Colon : 10^{10} à 10^{11} bacteria/g

➡ **10 times more bacteria than human cells**

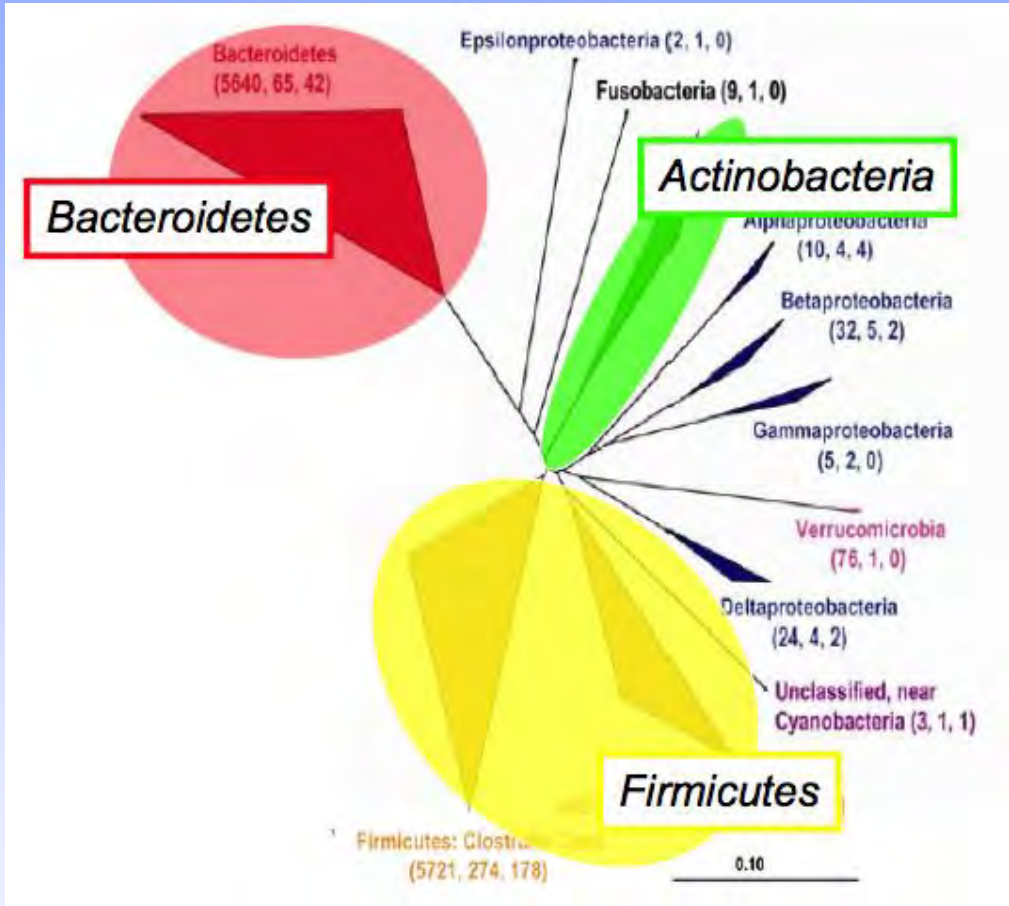
➡ **Gut microbiota: an organ with a high genetic content**

Classement des bactéries



Perlemuter, Cassard. Les bactéries, des amies qui vous veulent du bien. Solar 2016

Human gut microbiota contains few known bacterial phyla

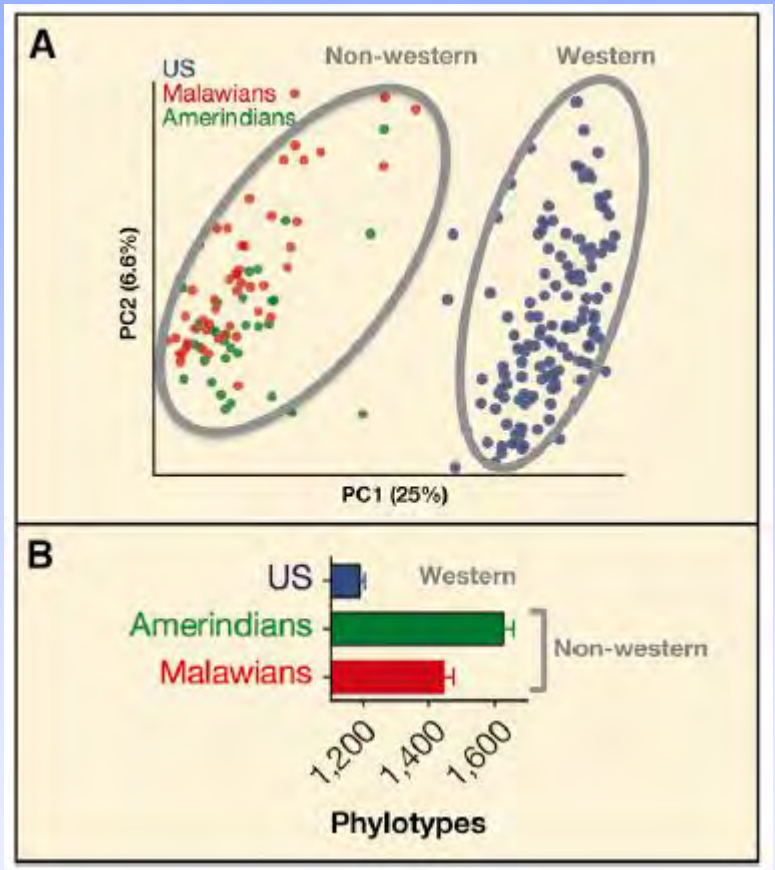


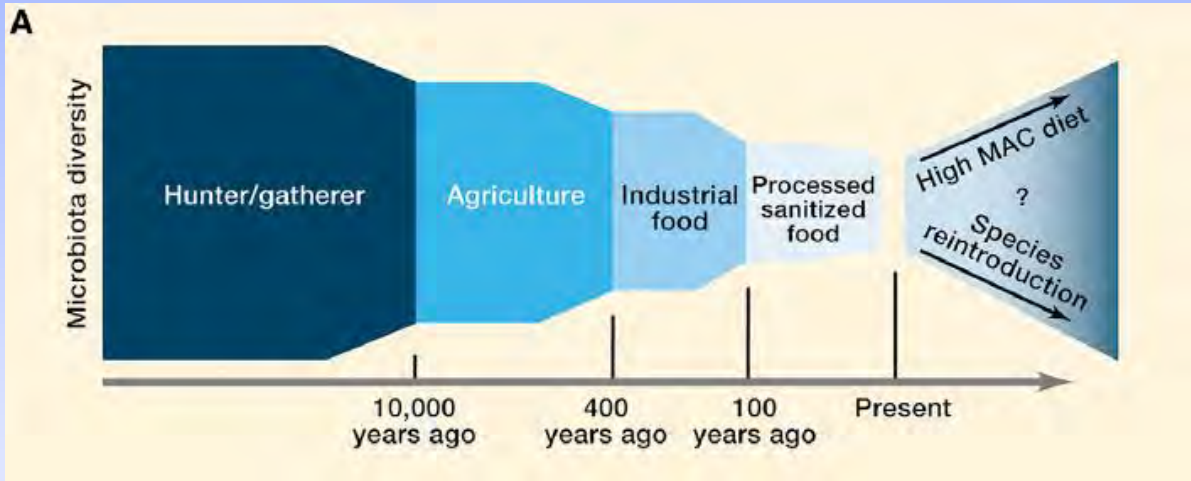
Wilson *et al* 1996
Suau *et al* 1999
Bonnet *et al* 2002
Hold *et al* 2002
Hayashi *et al* 2002
Hayashi *et al* 2003
Wang *et al* 2003
Mangin *et al* 2004
Manichanh *et al* 2006

≈ 1250 species
> 50 bacteria phyla
3 major phyla

Eckburg *et al*. 2005 (11831 sequences ; 391 species)

Western microbiota

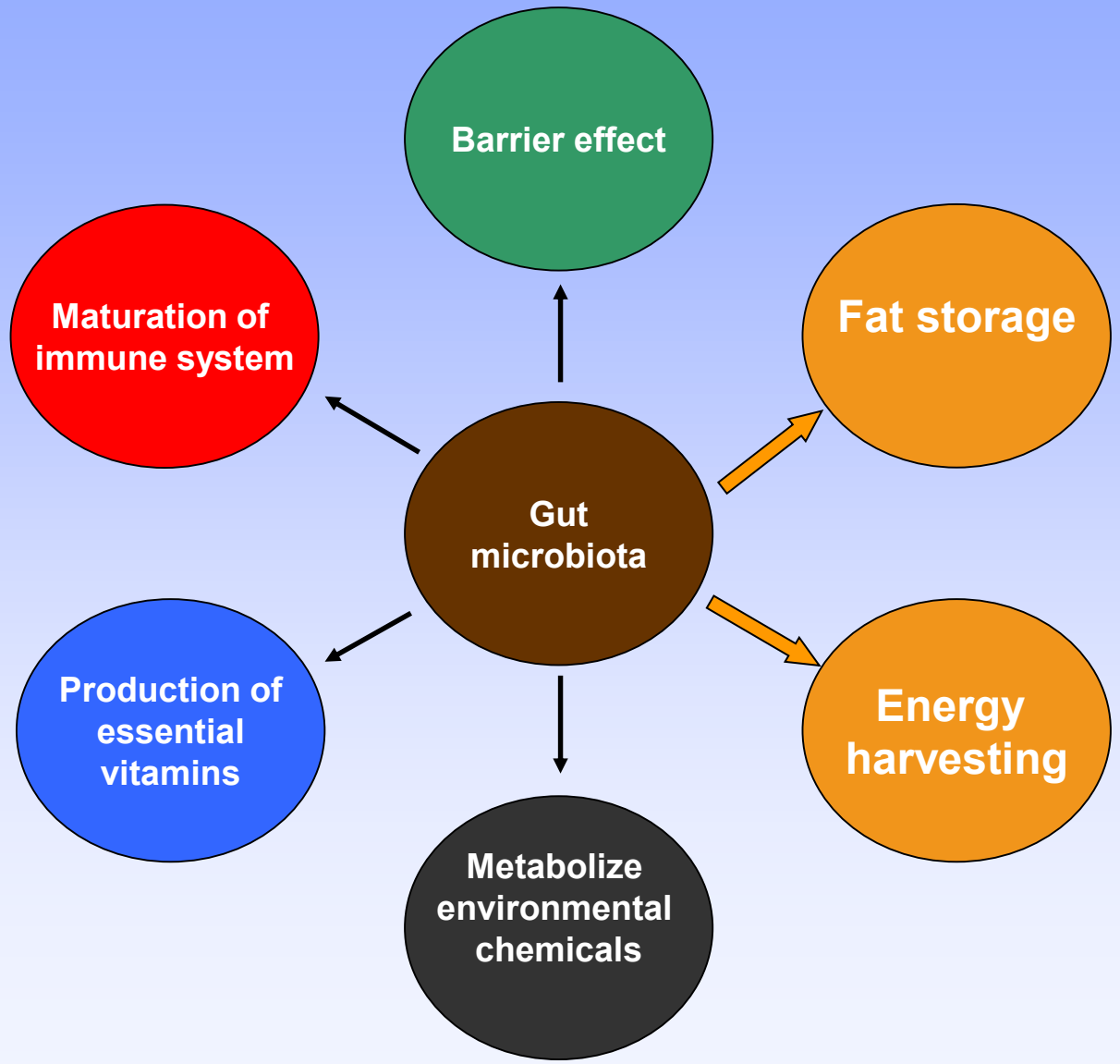




Western microbiota:
- is different
- has a low diversity

Yatsunenko Nature 2012

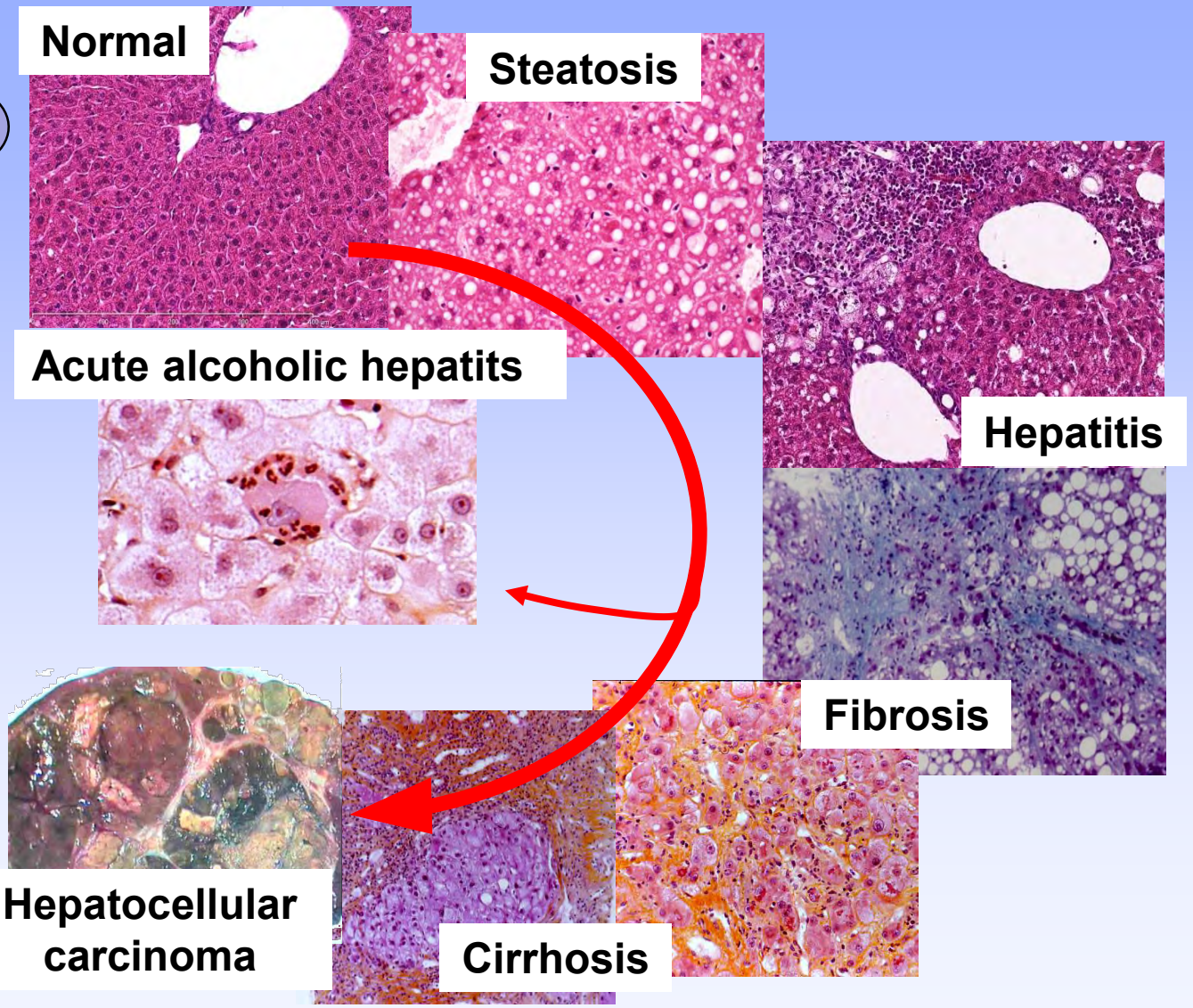
Gut microbiota functions



Three key years or 1000 key days

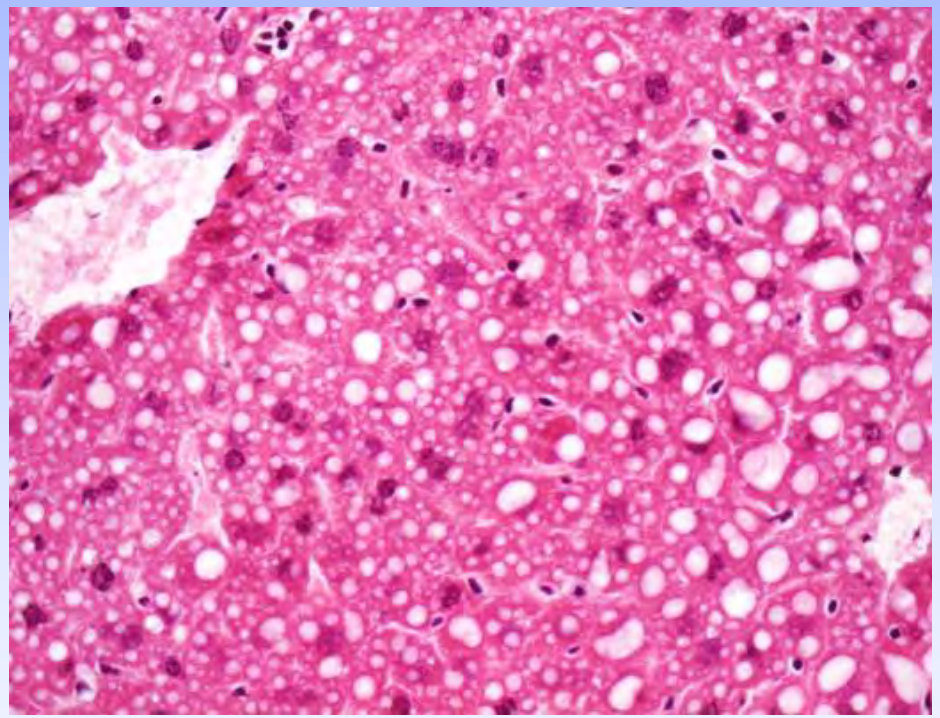
Liver lesions in nutritional liver diseases

What about our liver ?



ALD
NAFLD

Microbiota and steatosis



Does intestinal microbiota predispose to type 2 diabetes and steatosis ?

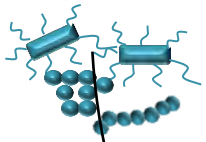
Individual data of conventional mice after 4 months of high-fat diet

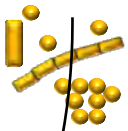
Experimental design (IM transplantation)

Non-Responser mice

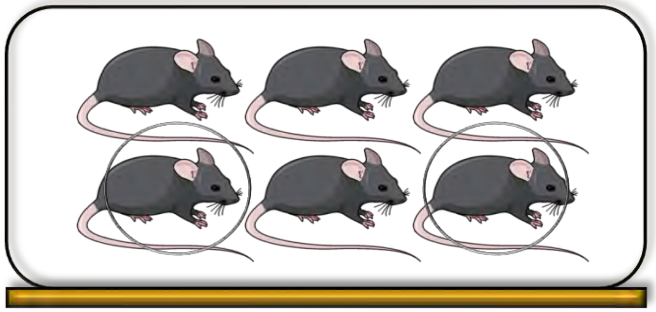
1 : Selection of 2 conventional mice after 16 weeks of high fat diet, based on the response to the diet

Responder mice

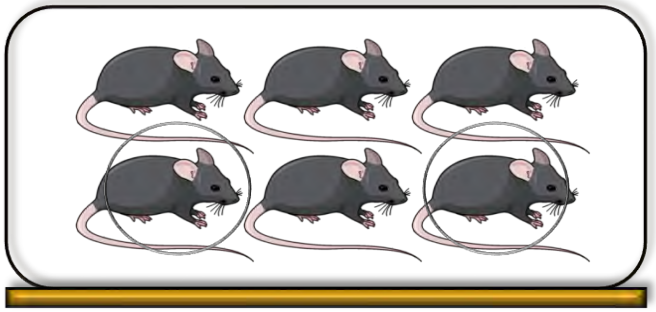




2 : Transfer of gut microbiota to germ-free mice by oral gavage with the cecal content

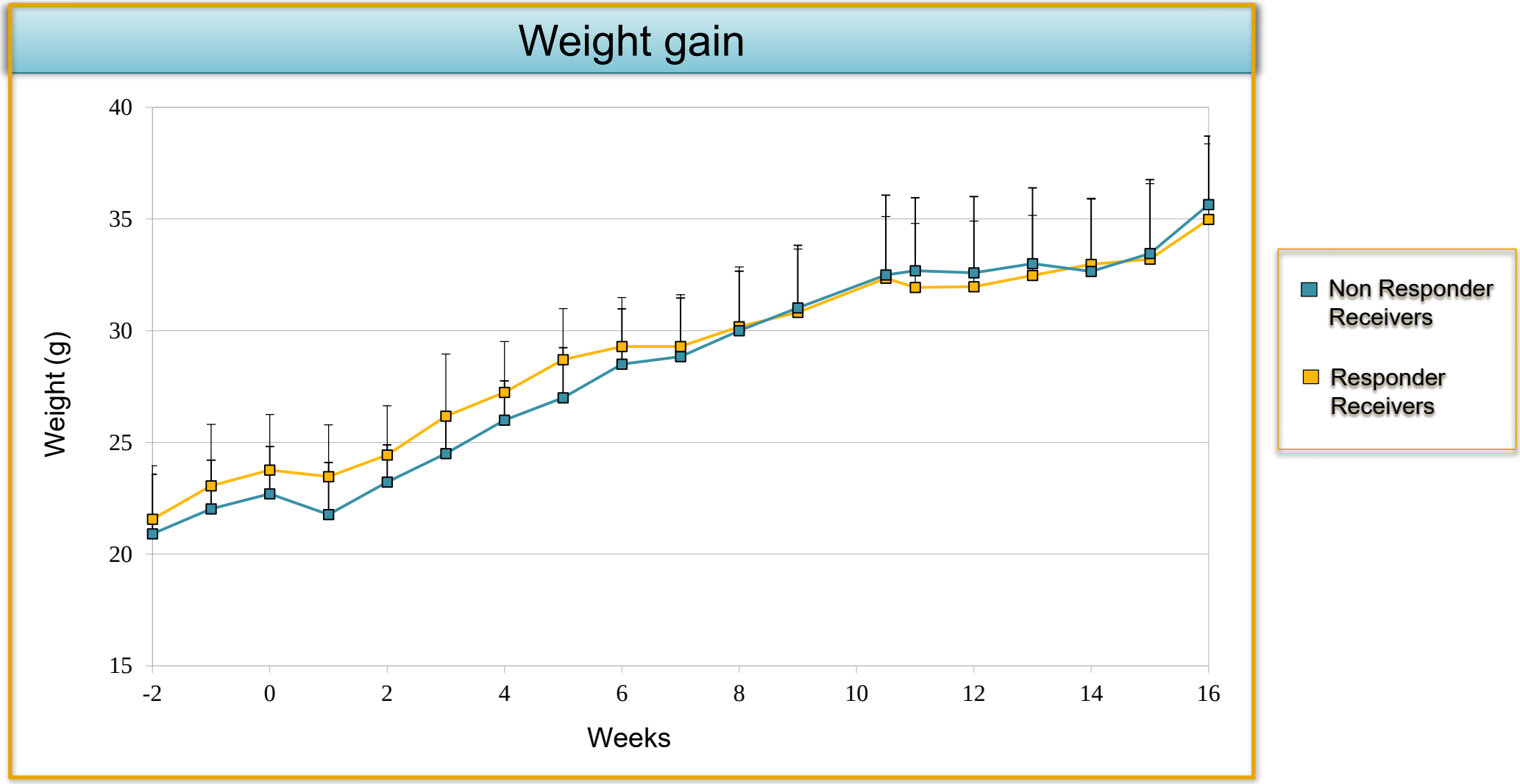


Non-Responder mice Axenic Mice

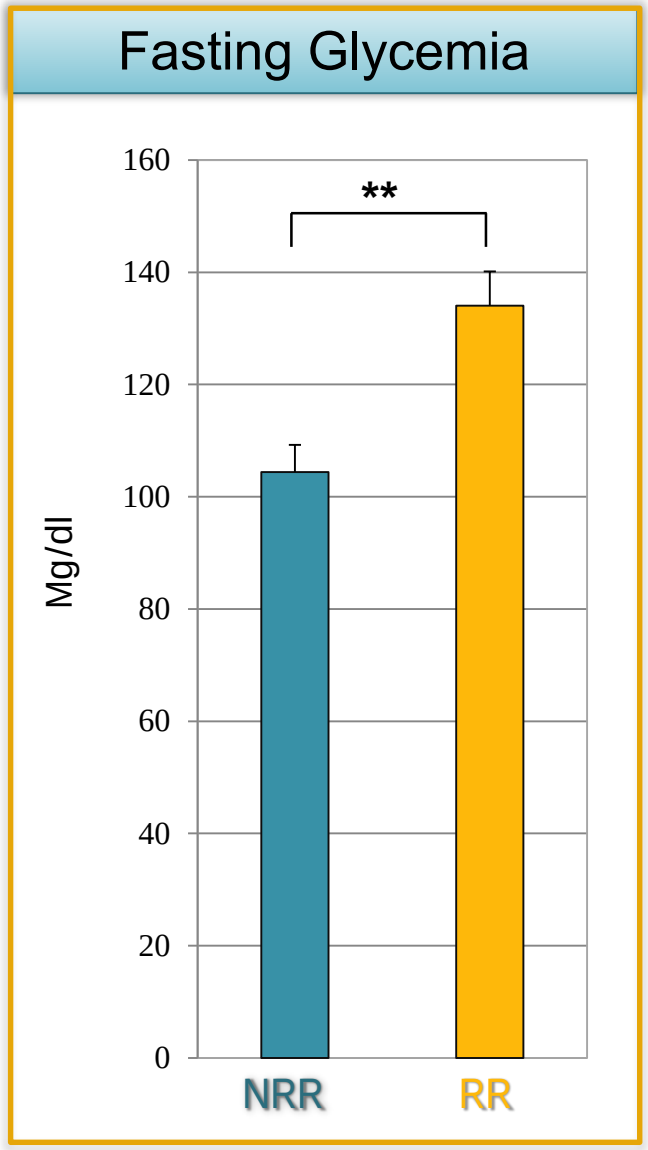


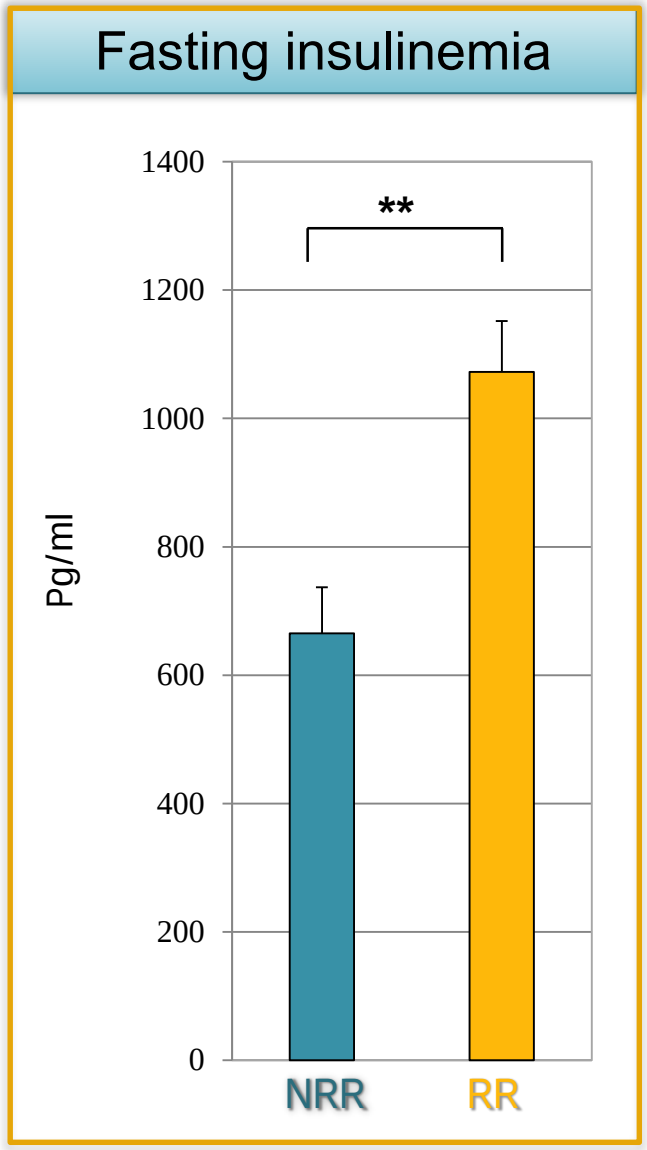
Responder mice Axenic Mice

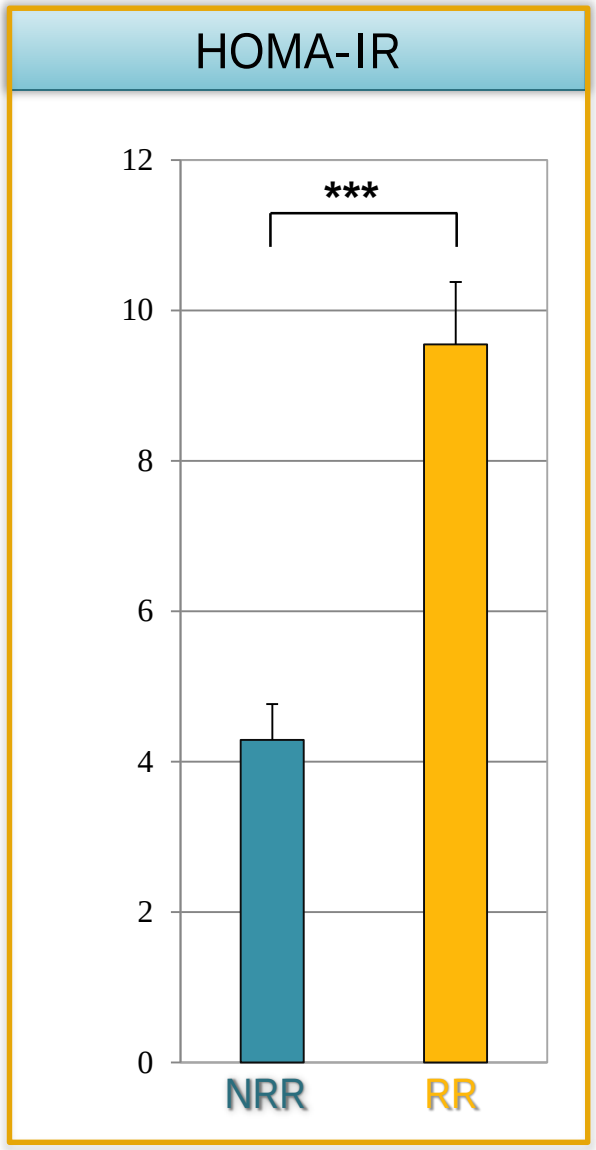
Response of receiver mice to high-fat diet



Response of receiver mice to high-fat diet







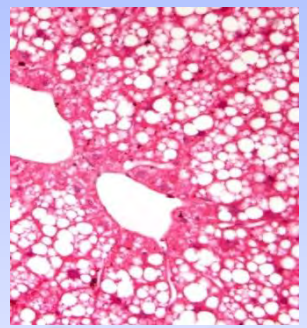
Le Roy et al, *Gut 2013*

** $p \leq 0{,}01$

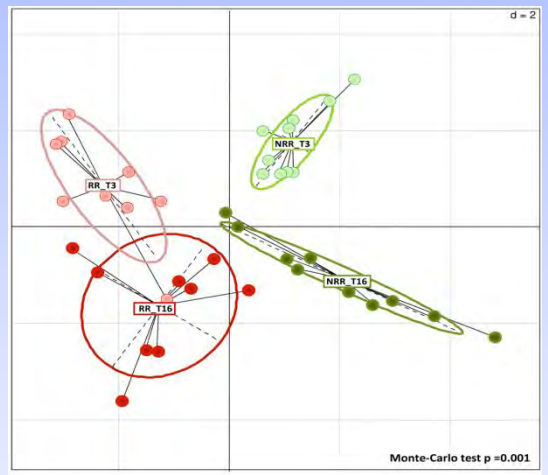
*** $p \leq 0{,}001$

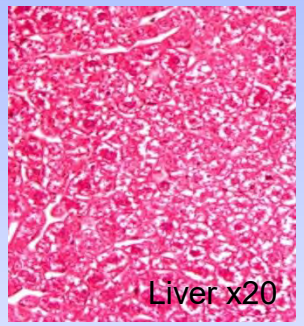
Microbiota of responder mice induces steatosis in receiver mice

➡ Dysregulation of liver genes involved in lipid metabolism



Responder Receivers





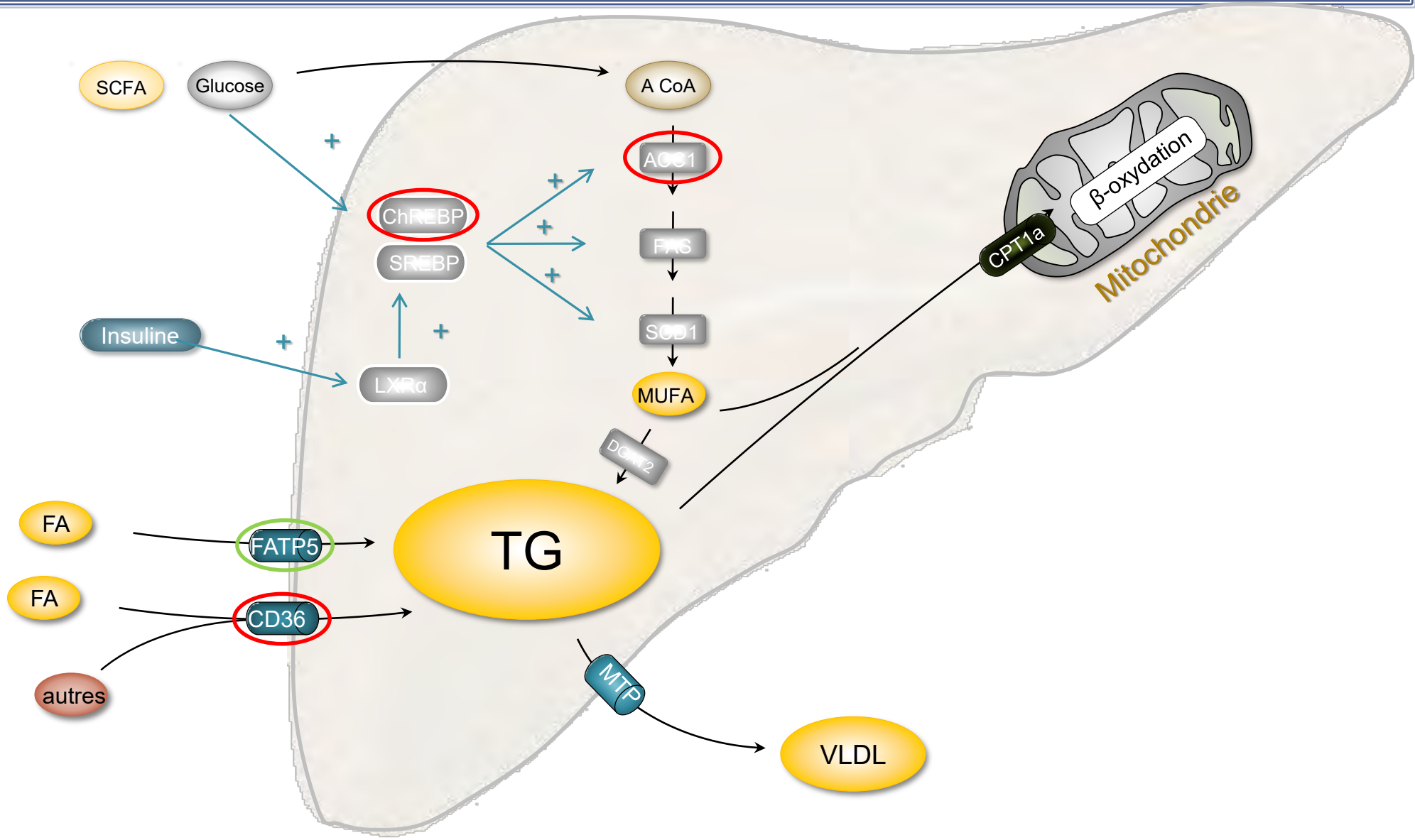
Non Responder Receivers

➡ Unclassified *Lachnospiraceae bacterium 609 (Clostridium)*

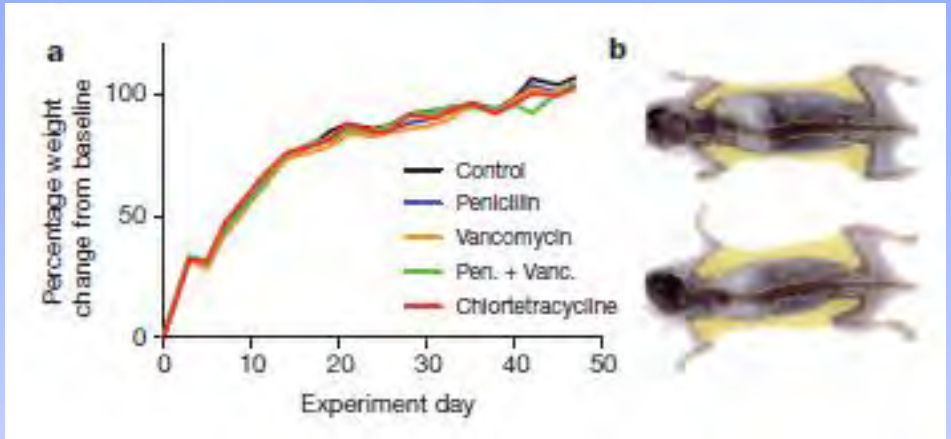
➡ Increase of sequences related to *Bacteroides vulgatus*

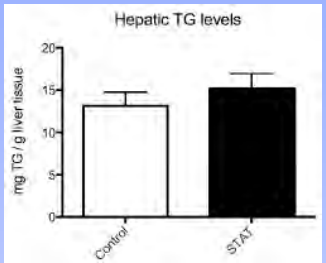
Le Roy et al, *Gut 2013*

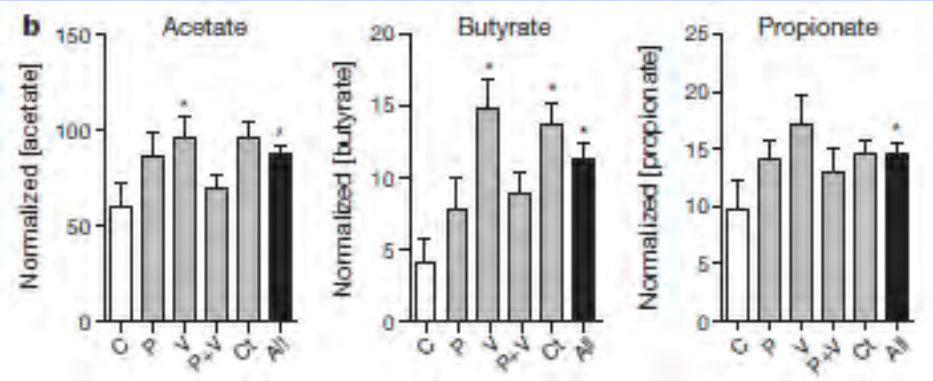
Modulation of genes involved in lipogenesis and lipid transport

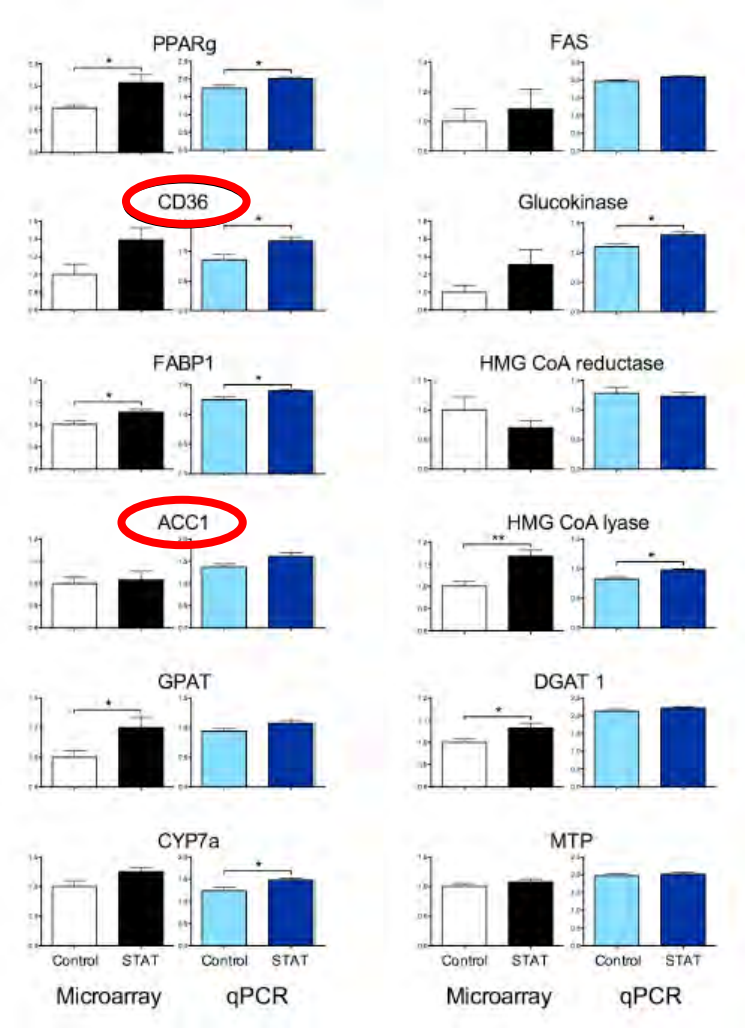


Subtherapeutic antibiotic treatment





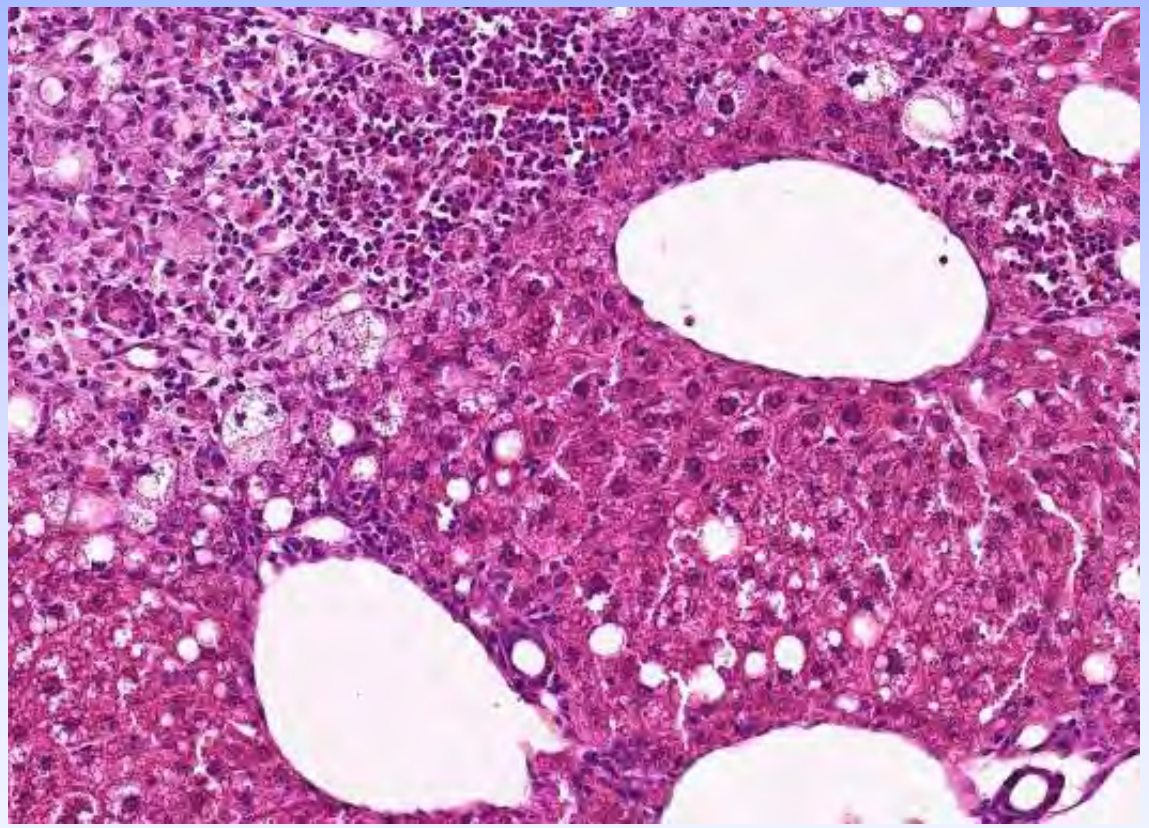




Increase *Lachnospiraceae*

Cho *Nature* 2012

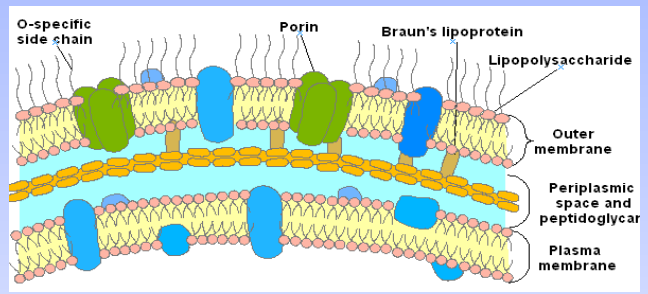
Microbiota and Inflammation/NASH



Innate immunity

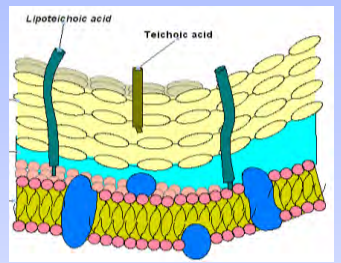
Recognitions of bacterial patterns by immune system

PAMP: Microbial/Pathogen Associated Molecular Pattern



LPS (TLR4)

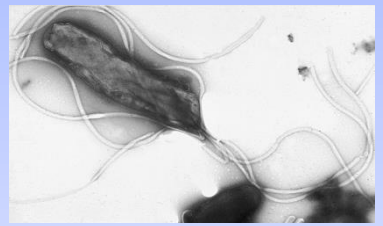
Lipopolysaccharide



PG

Peptidoglycan

ADN CpG
ARNdb



Flagelline
(TLR5)

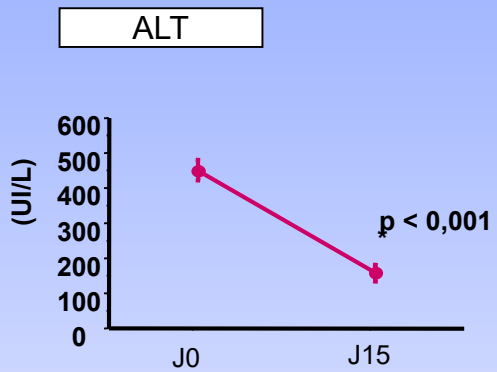
PRR: Pattern Recognition Receptors

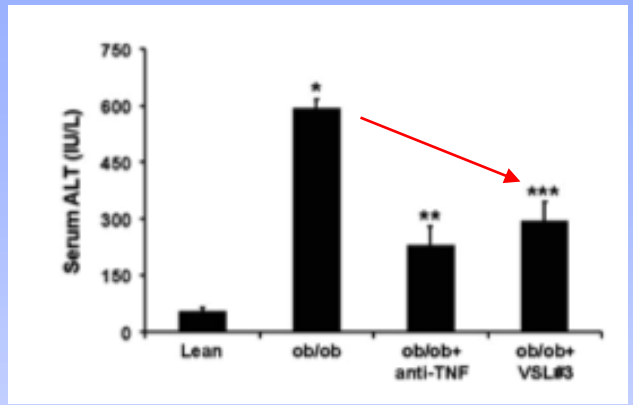
Transmembrane: TLR *(Toll-like Receptors)*;

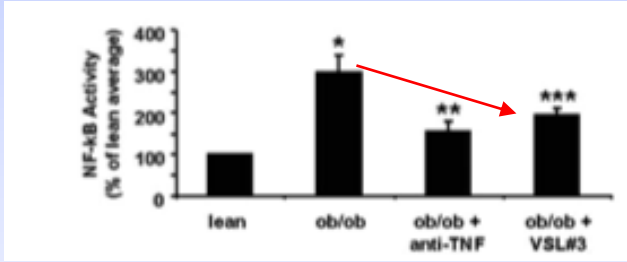
Intra-cellular: NLR/NOD *(Nucleotide oligodimerization domain)* → **Inflammasome**

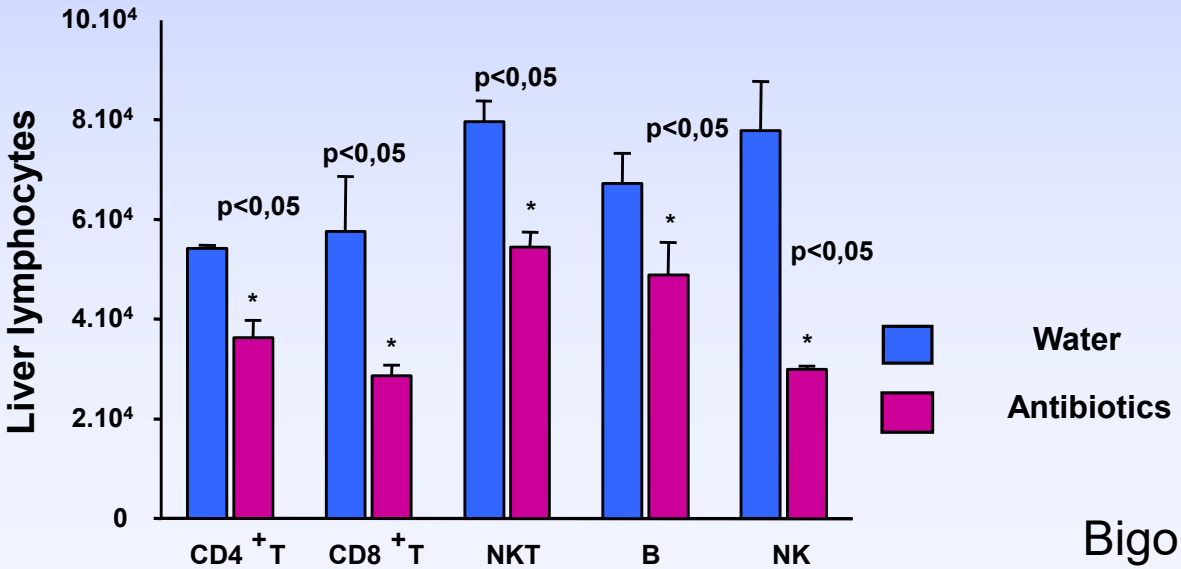
Neish *Gastroenterology* 2009

Oral antibiotic/probiotic treatment decreases obesity-related liver inflammation





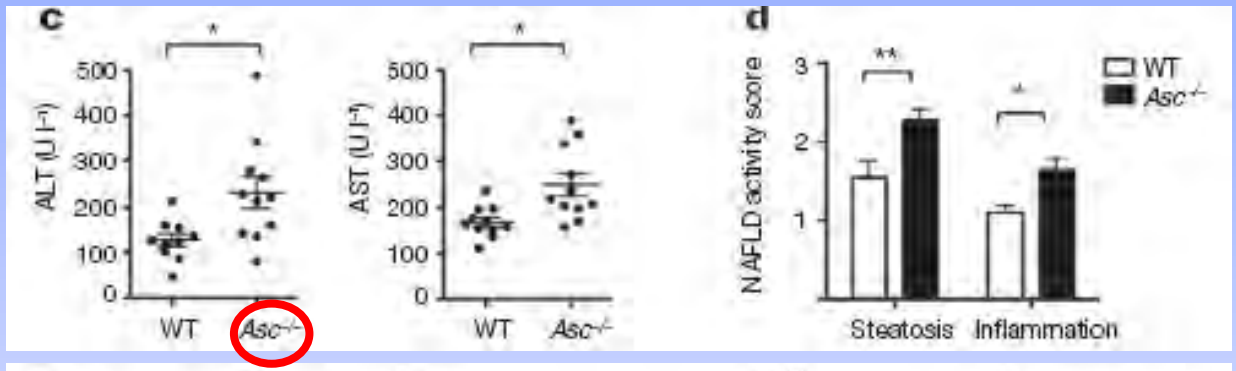




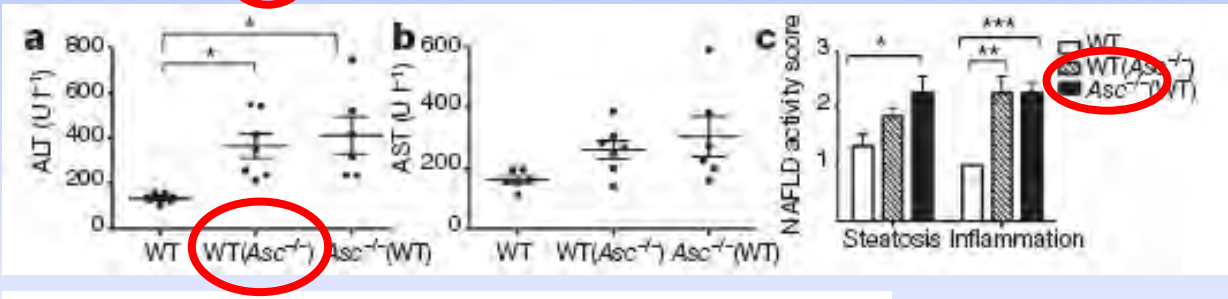
Li *Hepatology 2003*

Bigorgne, Perlemuter *Gastroenterology* 2007

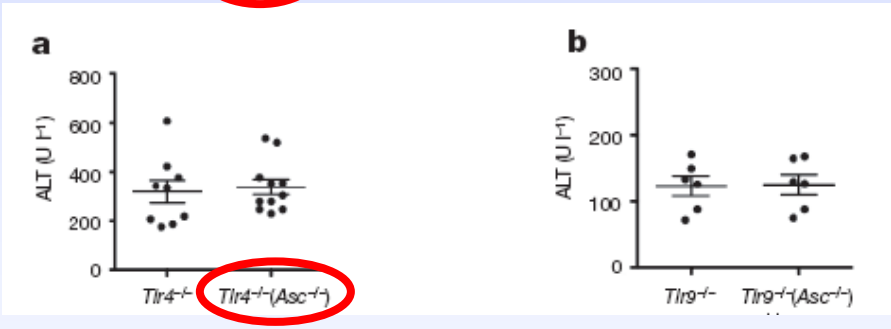
Inflammasome deficiency and intestinal microbiota



Increased liver steatosis and inflammation in inflammasome-deficient mice



Transmission of the disease in co-housed animals

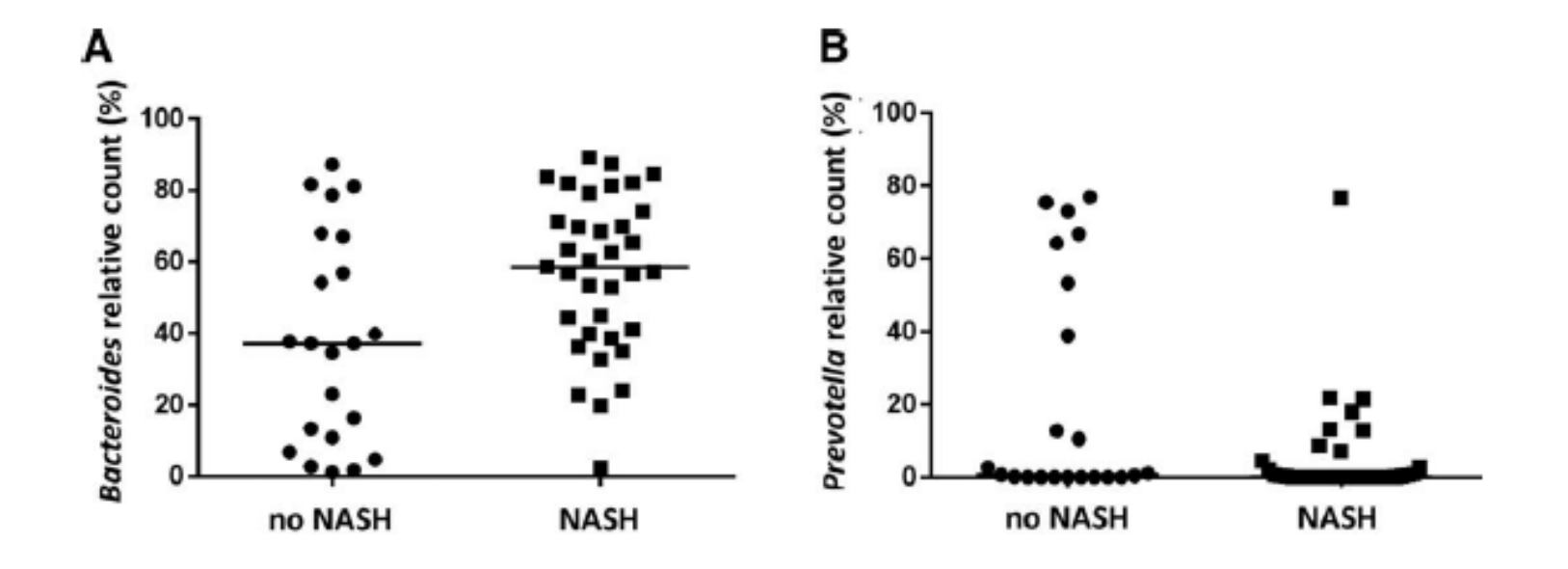


Involvement of TLR4 and TLR9 in disease transfer

Henao-Mejia *Nature* 2012

Interrelationship between liver inflammation and intestinal microbiota

A specific dysbiosis is associated with NASH



***Bacteroides* (*family*) and *Prevotella* have an inverse relationship**

Boursier *Hepatology* 2016

Dysbiosis is associated with a shift in the metabolic functions

TABLE 4. Functional Profile of the Gut Microbiota From NASH or F≥2 Patients

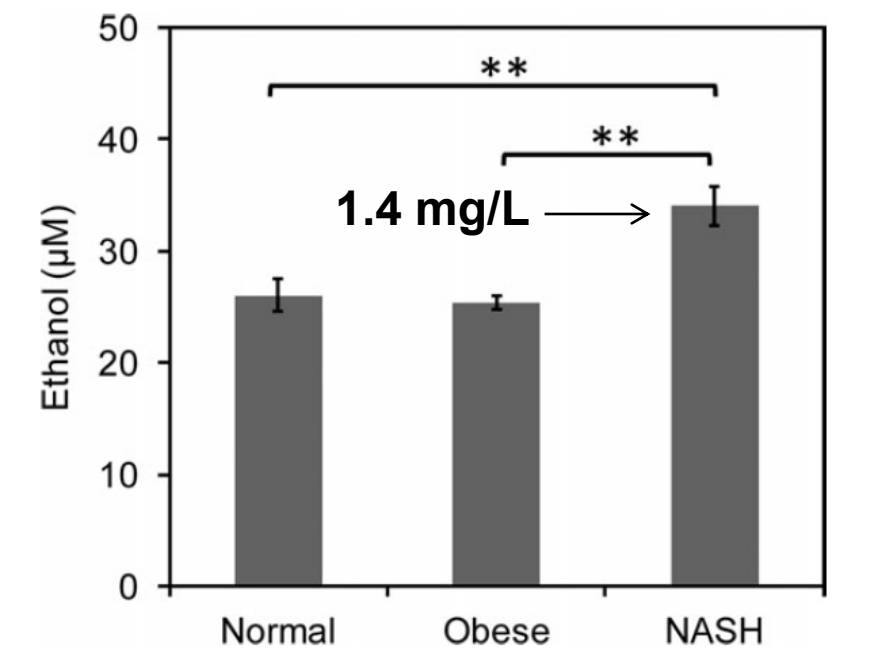
KO Functional Categories Level 2	Level 3	NASH vs. No NASH		F≥2 vs. F0/F1	
		LDA	*P* Value	LDA	*P* Value
Biosynthesis of other secondary metabolites	Phenylpropanoid biosynthesis	2.34	0.03	—	—
Carbohydrate metabolism	Glyoxylate and dicarboxylate metabolism	2.28	0.03	2.28	0.02
Carbohydrate metabolism	Pentose and glucuronate interconversions	—	—	2.74	0.02
Carbohydrate metabolism	Pentose phosphate pathway	—	—	2.44	0.01
Carbohydrate metabolism	Starch and sucrose metabolism	2.68	0.01	—	—
Carbohydrate metabolism	Unclassified	2.22	0.02	2.27	0.01
Lipid metabolism	Fatty acid biosynthesis	—	—	2.10	0.03
Lipid metabolism	Lipid biosynthesis proteins	—	—	2.07	0.03
Lipid metabolism	Sphingolipid metabolism	2.45	0.04	—	—
Metabolism of other amino acids	Cyanoamino acid metabolism	2.27	0.03	—	—
Translation	Translation factors	—	—	-2.25	0.05
Replication and repair	DNA replication proteins	—	—	-2.55	0.04

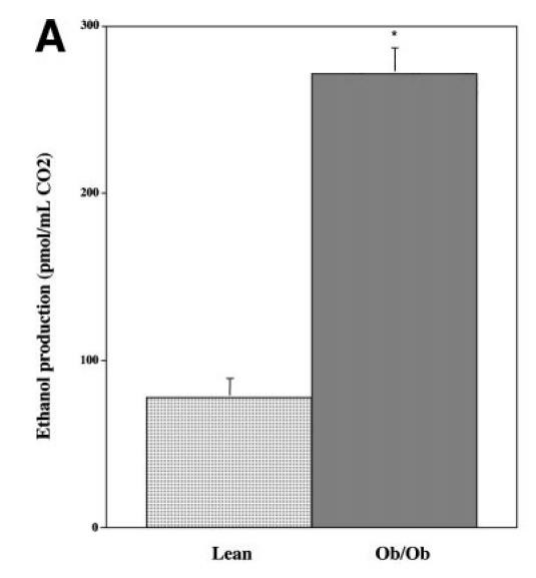
KEGG pathways were inferred from 16s rRNA gene sequences using PICRUSt. Functional categories significantly enriched or depleted in NASH patients or patients with F≥2 fibrosis were assessed with LEfSE ($P \leq 0.05$; LDA, >2). NASH and F≥2 fibrosis were associated with microbiota enrichment in KEGG categories related to metabolic functions.
Abbreviation: KO, KEGG orthology.

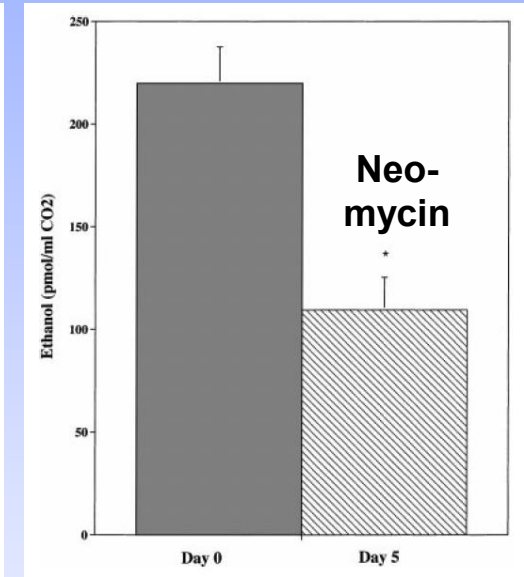
Modifications of carbohydrate, lipid and amino acid metabolism

Boursier *Hepatology* 2016

Ethanol production by microbiota







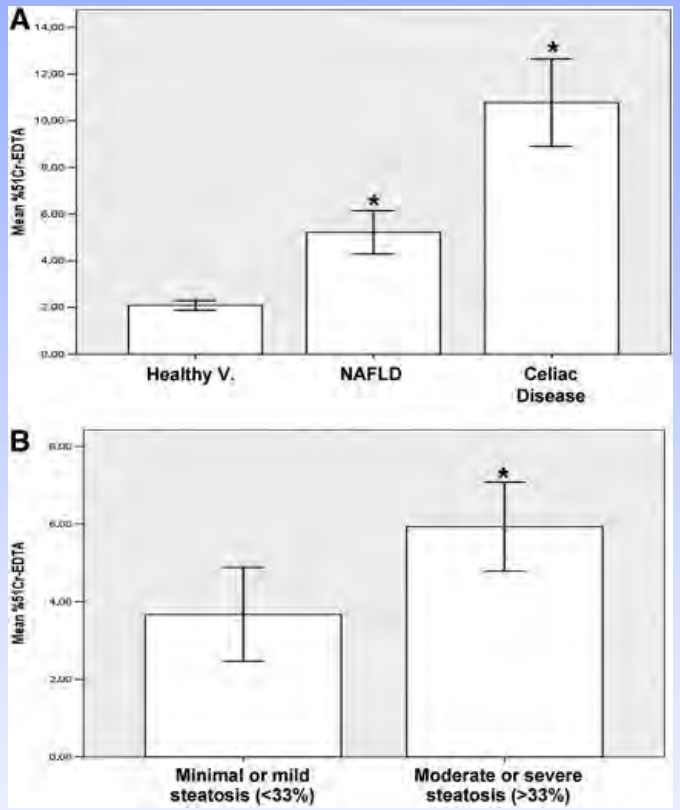
Production of ethanol by the microbiota

Cope *Gastroenterology* 2000

Zhu *Hepatology* 2013

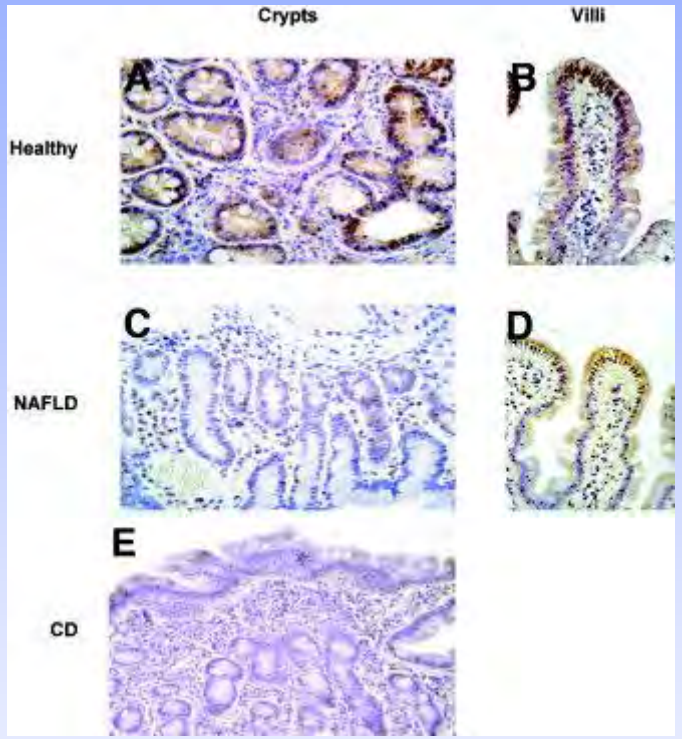
NASH and intestinal permeability

Intestinal permeability



Wigg *Gut* 2001

Zonula occludens 1



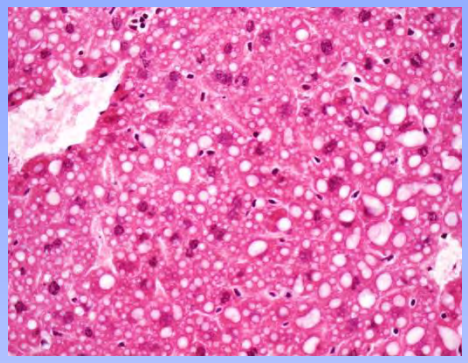
Miele *Hepatology* 2009

Bacterial overgrowth associated with NASH

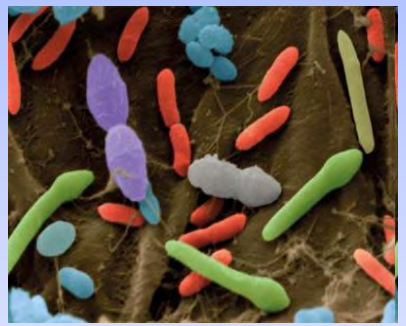
Et mon foie ?

L'absinthe - **Degas**

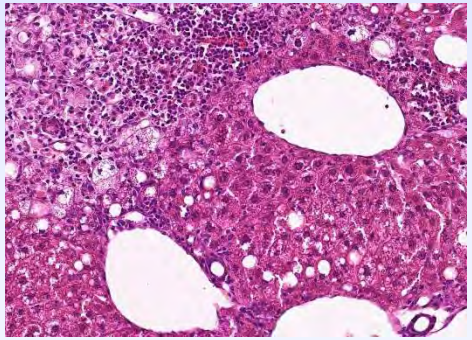
80 %

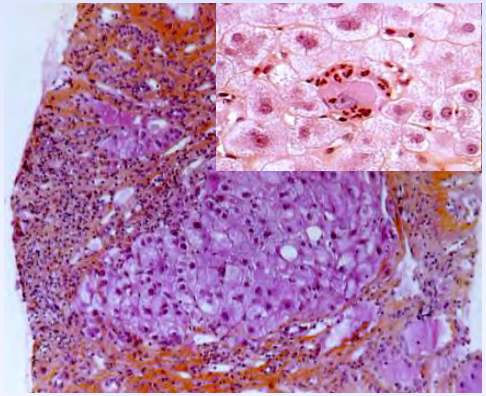


?



20 %





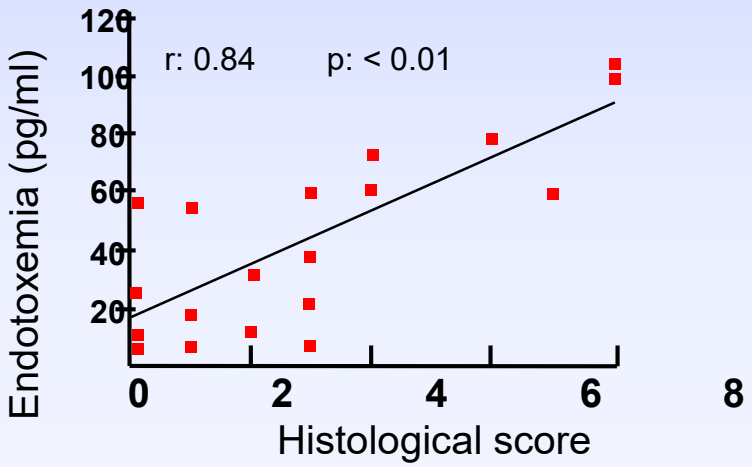
Evidences for a role of gut microbiota in ALD

➠ **The liver could be directly impacted by bacteria coming from the intestin via the portal vein**

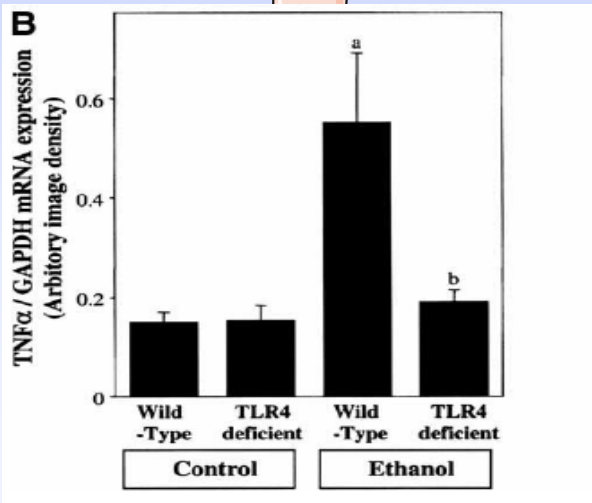
➠ **First evidences**

➠ **Increase of the intestinal permeabilty**

➠ **Correlation between endotoxemia and liver injury**



Nanji AA et al. Am J Pathol.1993



Uesugi *Hepatology* 2001

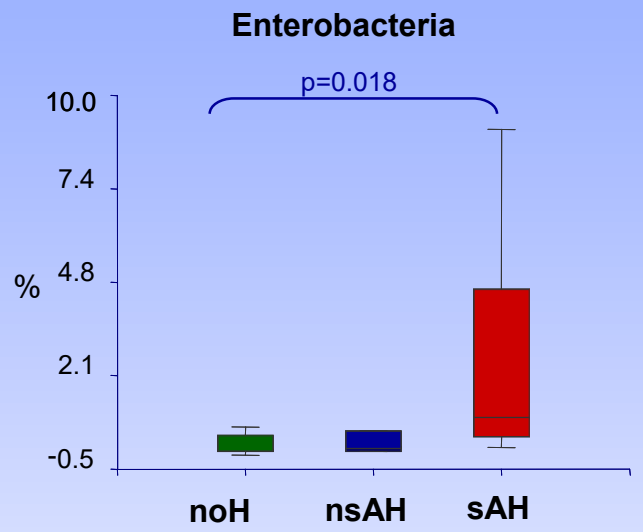
Mathurin et al. Hepatology, 2000

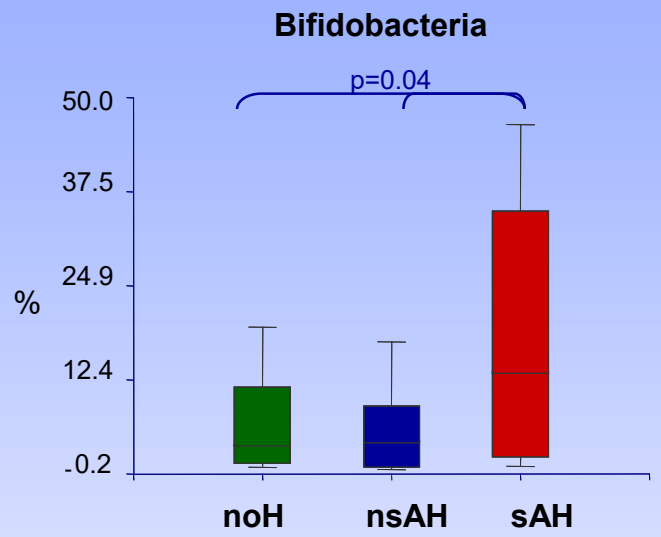
Characteristics of alcoholic patients

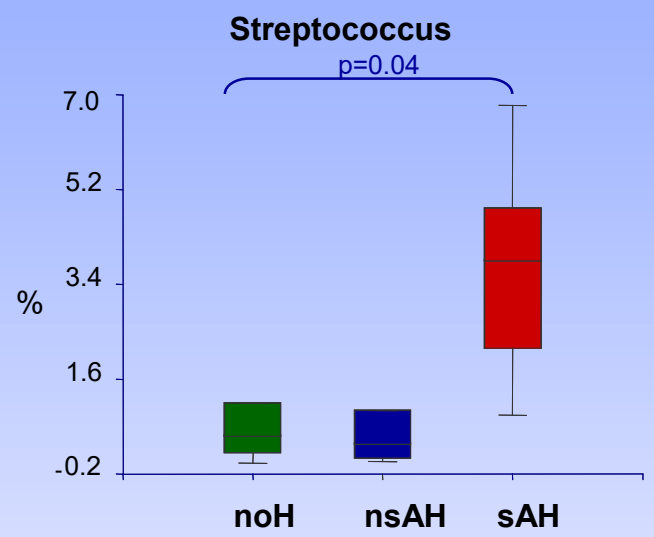
	noAH n=16	nsAH n=12	sAH n=10
Age (yr)	55 ± 3	50 ± 3	59 ± 8.8
Alcohol consumption (g/dy)	155 ± 37.9	185 ± 20.8	101 ± 16.2
Alcoholisation duration (yr)	16 ± 4	28 ± 5	23 ± 5
BMI (kg/m^2)	23.5 ± 4.5	24 ± 3.2	26.5 ±7.8
ALT (IU/L)	57 ± 18	93 ± 20	44 ± 8.8
AST (IU/L)	68 ± 27	163 ± 39.9	99 ± 36
Albumin (g/L)	38.3 ± 1.7	36.7 ± 2	28.7 ± 2.9
Blood glucose (mmol/L)	5.15 ± 0.34	5.27 ± 0.28	5.1 ± 0.5
Triglycerides (g/L)	1.38 ± 0.16	1.41 ± 0.4	0.46 ± 0.01
Prothrombin Time (%)	87 ± 13	79 ±7	35 ± 14
Bilirubin (µmol/L)	21 ± 10	30 ± 10	105 ± 16
Maddrey discriminant function	11.0 ± 7.5	16.4 ± 13.2	40 ± 11

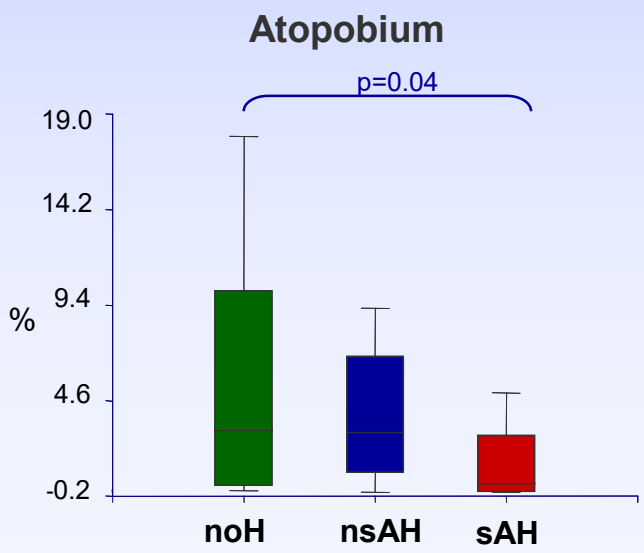
RESULTS

Differences in fecal microbiota of alcoholic patients according to the severity of alcoholic hepatitis





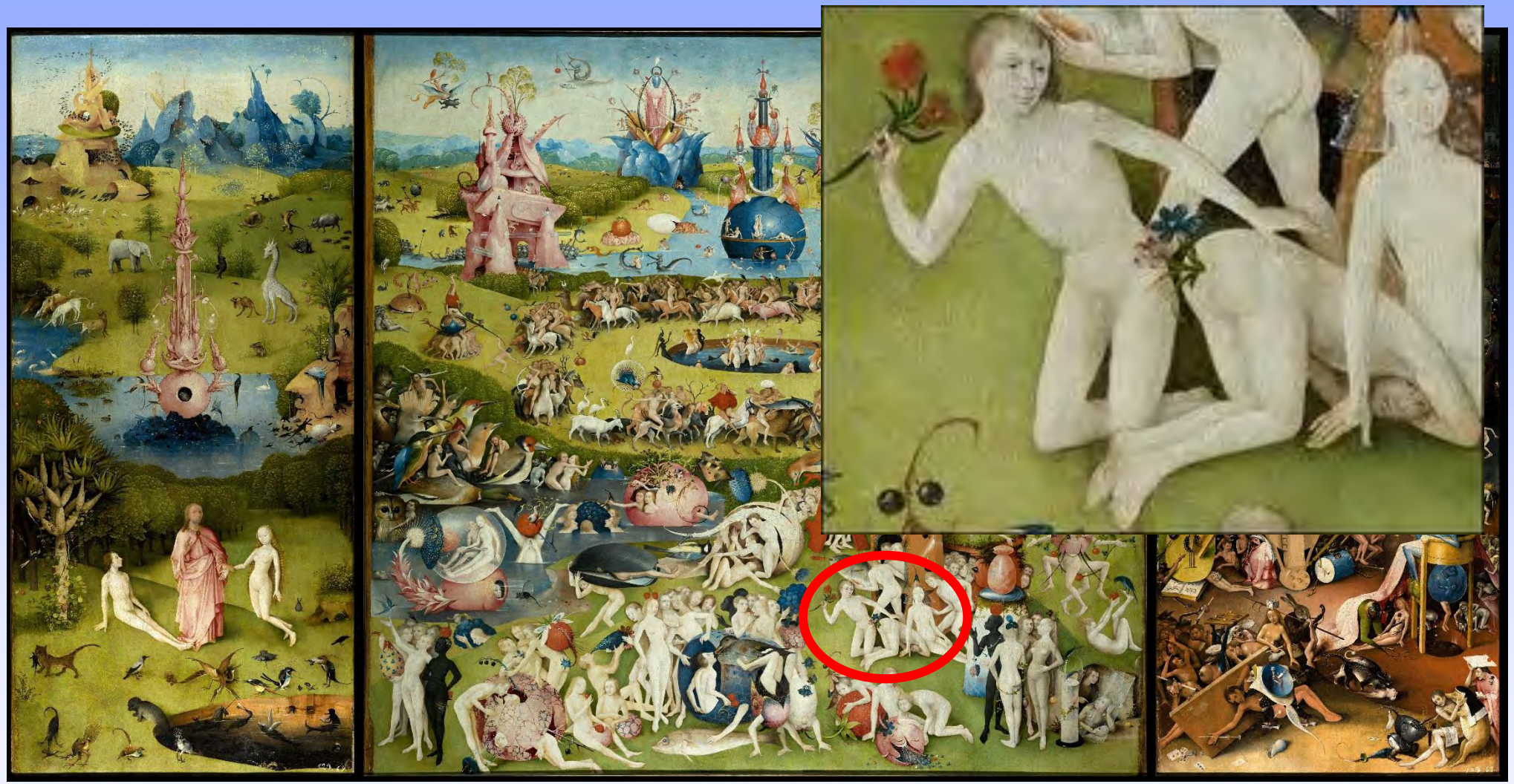




Alcoholic patients with severe acute alcoholic hepatitis have a profile of gut microbiota statistically different from alcoholic patients with less severe forms of liver lesion.

Data are expressed as median and 25th, 75th percentiles.

Experimental design (GM transplantation)

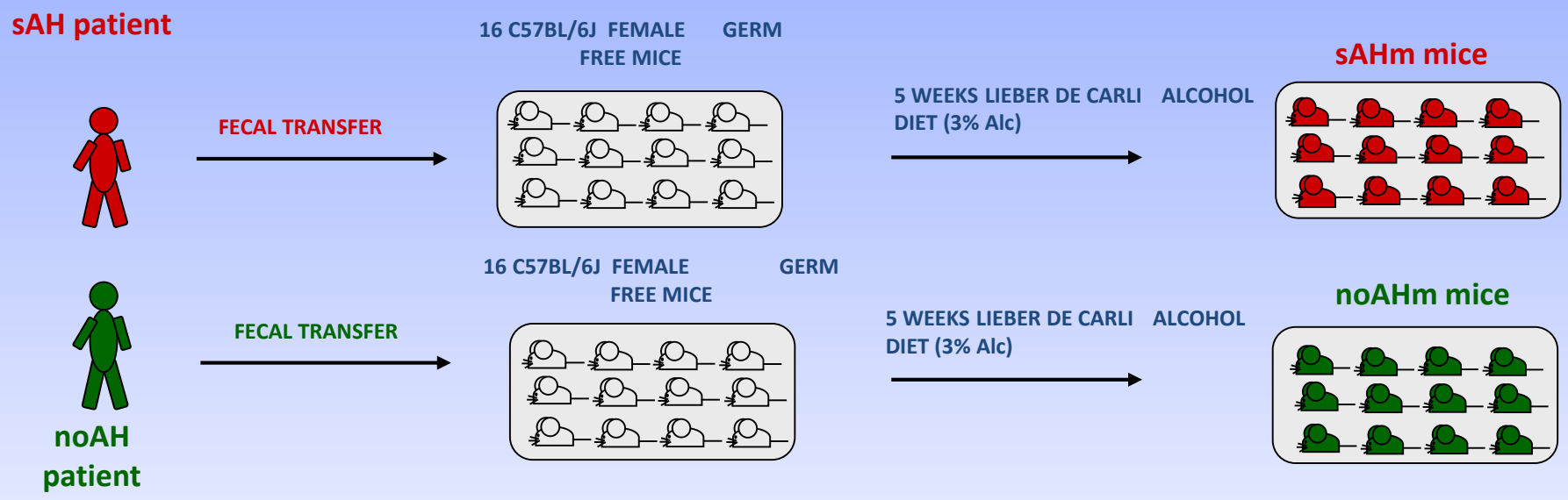


Garden of Eden – Jerome Bosch 1503-1504 – Prado - Madrid

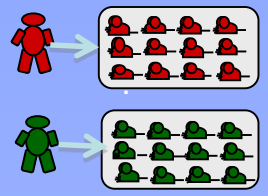
Gut microbiota transfer to germfree mice

Inoculation of cecal suspensions to germ-free mice

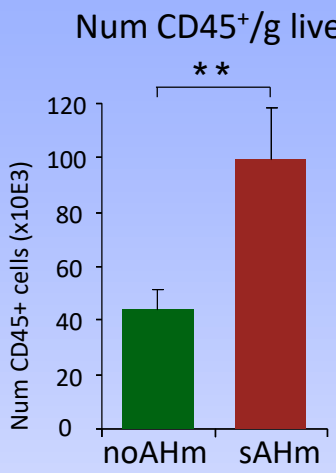
Transplantation of fecal microbiota human-mice

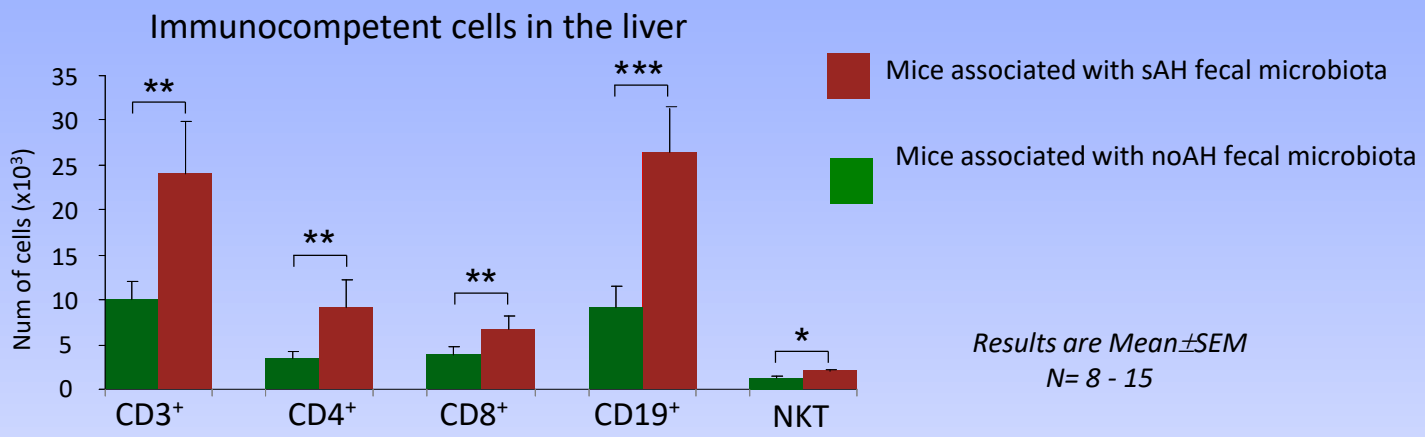


Liver inflammation in humanized mice

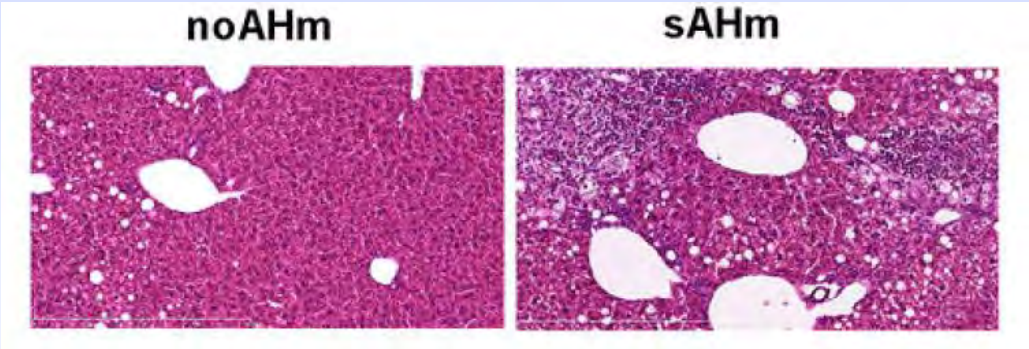


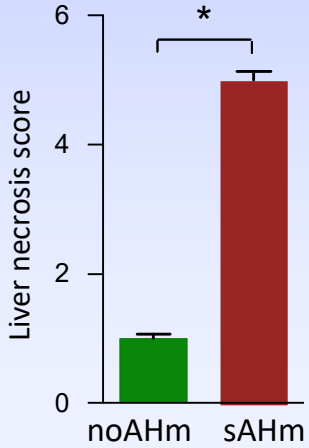
Quantification of liver inflammatory cells by flow cytometry





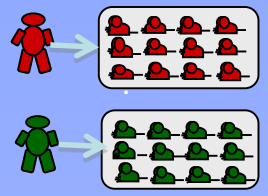
Results are Mean±SEM
N= 8 - 15

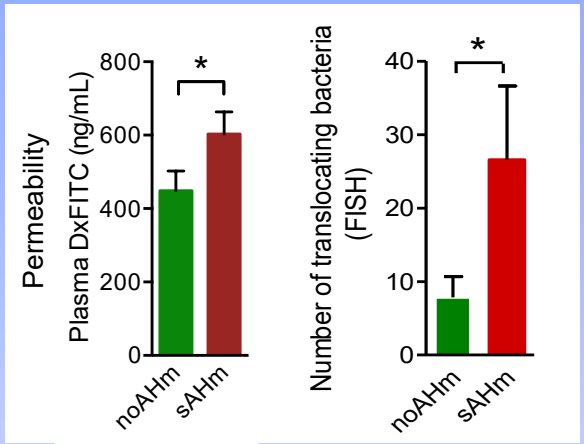


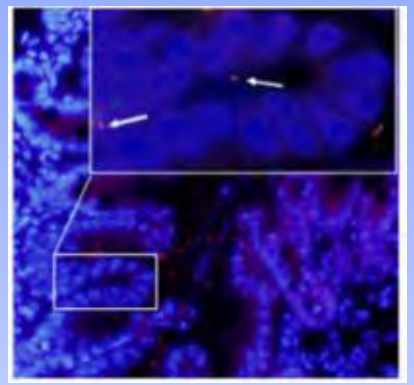


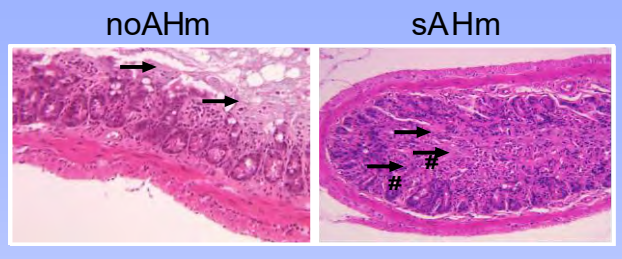
Livers of mice associated with the microbiota of the sAH patient have more recruitment of inflammatory cells than livers of mice from the no AH group.

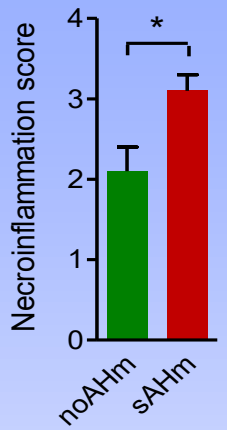
Intestinal and extra-intestinal affection in humanized mice



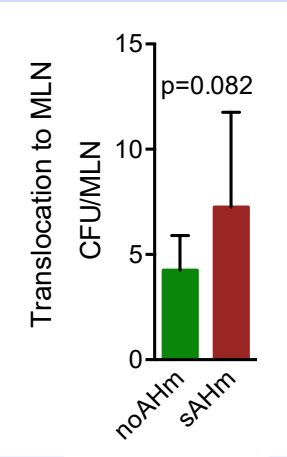


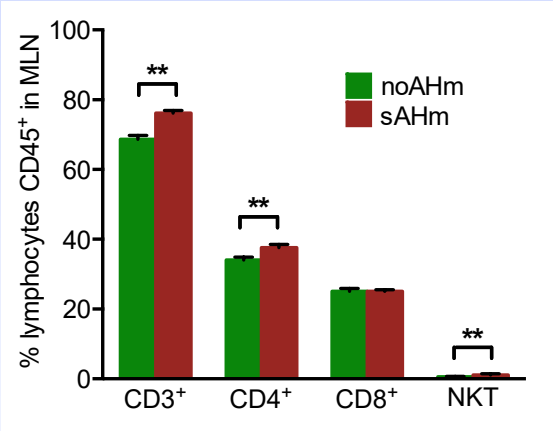


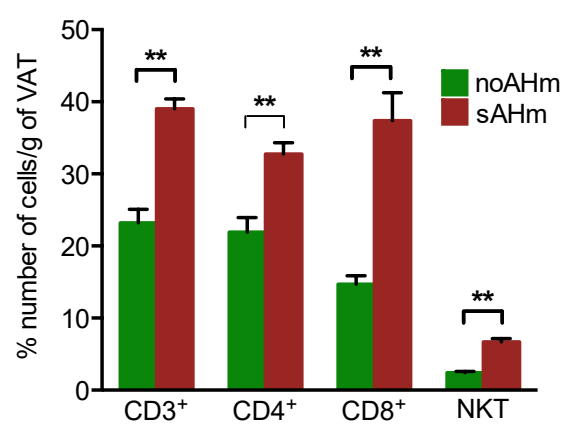




As in patients, alcohol-induced liver lesion is related to the impairment of the intestinal mucosa integrity.

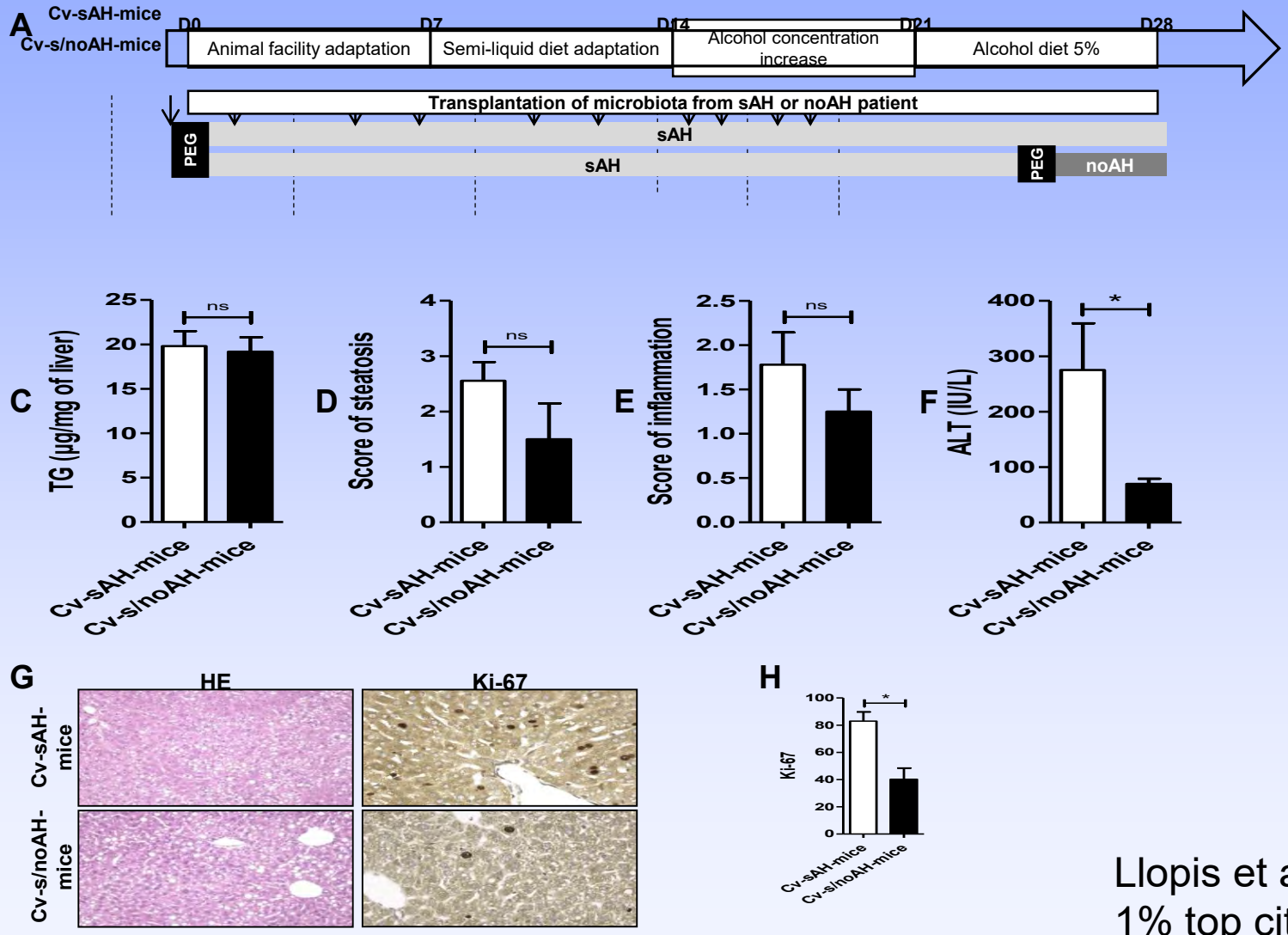






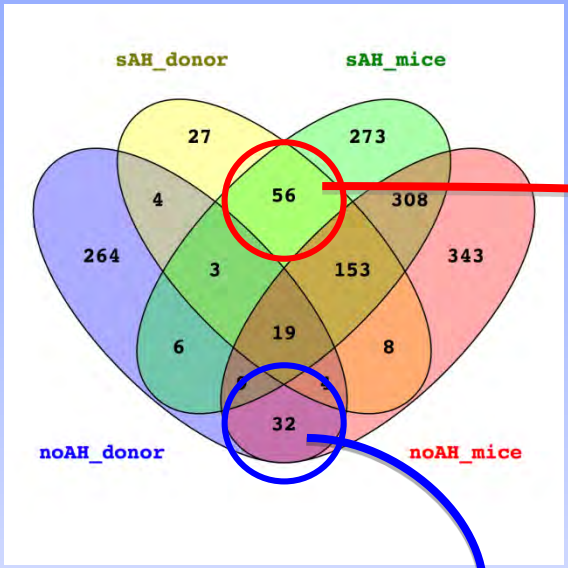
Inflammation extends to sites distal from the initial site of colonization.

Intestinal microbiota may improve alcohol-induced liver lesions



Llopis et al. *Gut* 2016
1% top cited papers

Protective bacteria and deleterious bacteria



- **Firmicutes**
  - *Clostridium nexile*
  - *Clostridium boltae*
  - *Clostridium symbiosae*
- **Bacteroidetes**
  - *Parabacteroides distasonis*
  - *Bacteroides fragilis*
- **Proteobacteries**
  - *E. coli*

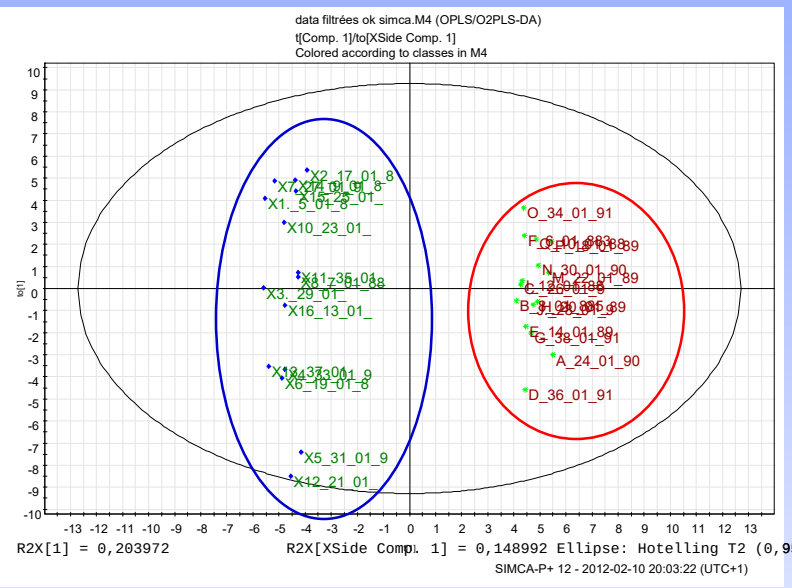
- **Firmicutes**
  - *Parabacteroides johnsonii*
  - *Bacteroides massiliensis*
- **Bacteroidetes**
  - *Faecalibacterium prausnitzii*
  - *Gemmiger formicilis*
- **Proteobacteries**
  - *Desulfovibrio sp*

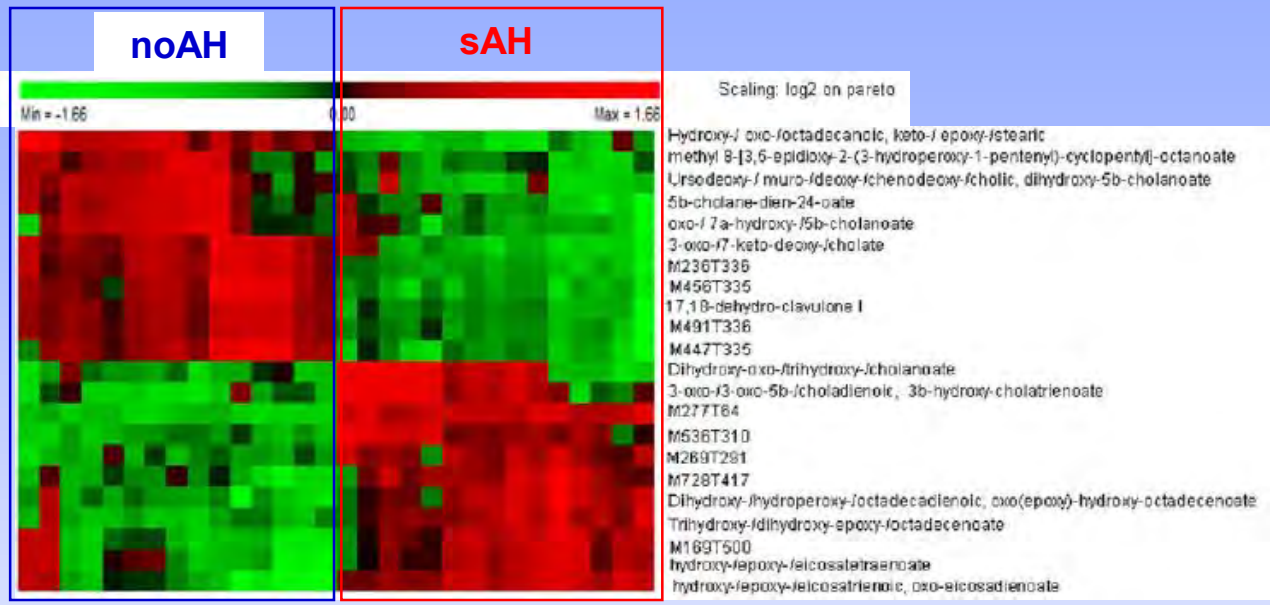
➡ **Identify a bacterial cocktail which could be protective**

Llopis et al. *Gut* 2016 1% top cited papers

Metabolomic analyses

noAH sAH





UDCA: increased in noAH

Bile acids are discriminant fecal metabolites

Llopis et al. *Gut* 2016
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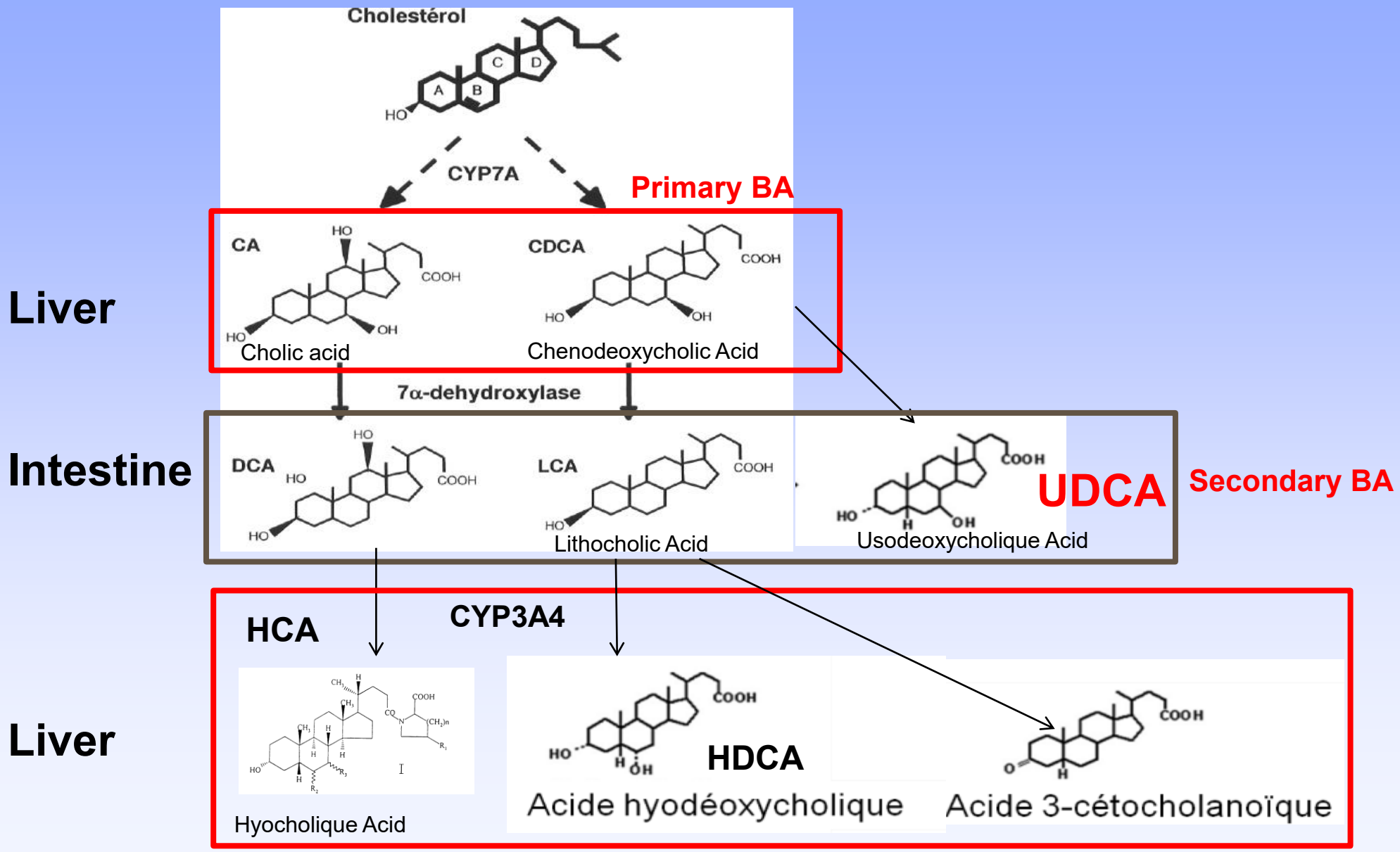
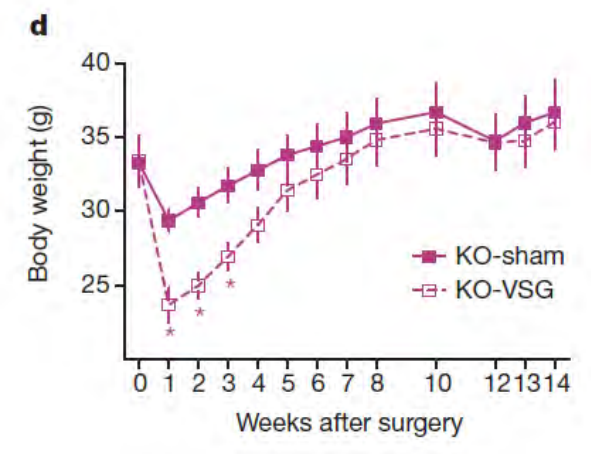
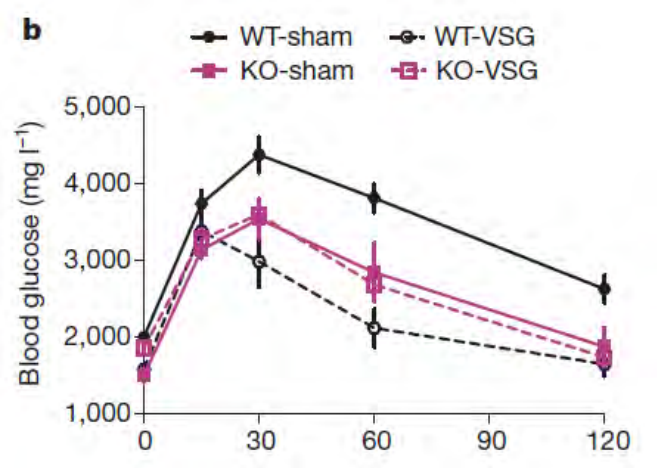
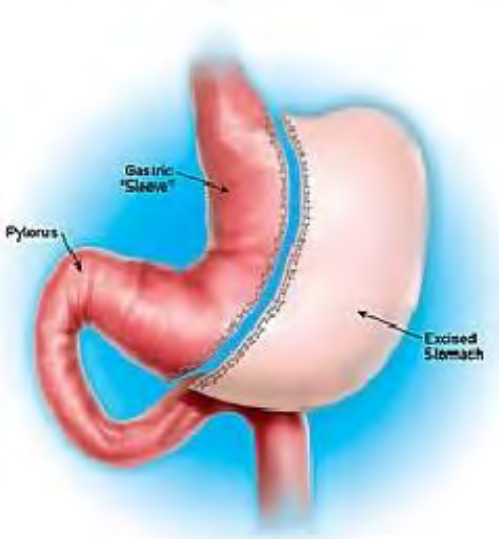
Entero-hepatic cycle of bile acids



FXR – microbiota interactions







Sleeve gastrectomy efficacy involves FXR signaling

Ryan *Nature* 2014

Bile acids, microbiota and cirrhosis

Median values in µg/100 mg dry stool	Controls (n = 14)	Early cirrhosis (n = 23)	Advanced cirrhosis (n = 24)
Total bile acids	206.5	156.1	39.0*
Primary			
CA (% in whom detected)	36.0 (14)	64.6 (22)	16.0 (71)*†
CDCA (% in whom detected)	3.1 (51)	10.1 (57)	12.4 (83)*†
Secondary			
LCA (% in whom detected)	83.2 (100)	63.8 (87)	12.7 (46)*†
DCA (% in whom detected)	110.7 (100)	35.8 (83)	8.3 (50)*†
Secondary/primary ratios			
LCA/CDCA	39.7	7.6	2.2*
DCA/CA	6.3	3.2	0.9*
LCA + DCA/CDCA + CA	79.8	9.6	0.004*

*p <0.05 between groups on Kruskall–Wallis tests on median concentrations.
†p <0.05 between groups on percent in whom the respective bile acids were detected.
CA, cholic acid; CDCA, chenodeoxycholic acid; LCA, lithocholic acid; DCA, deoxycholic acid.

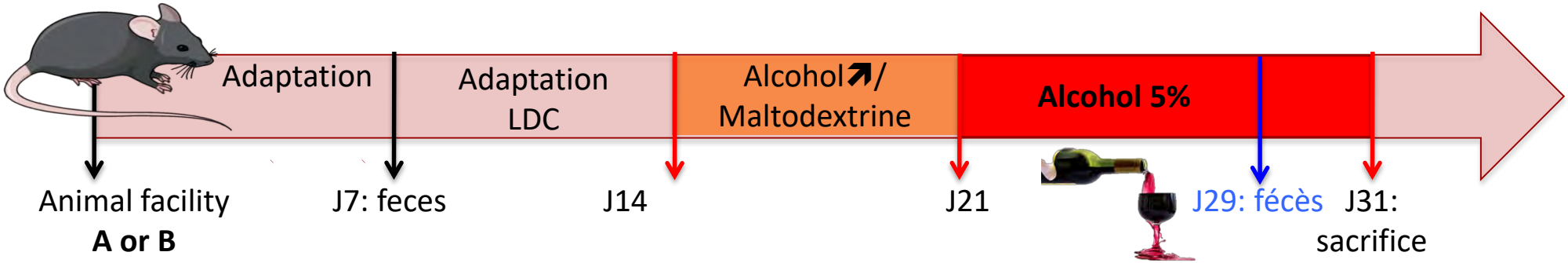
Cirrhose is associated with a decreased conversion of primary to secondary fecal bile acids

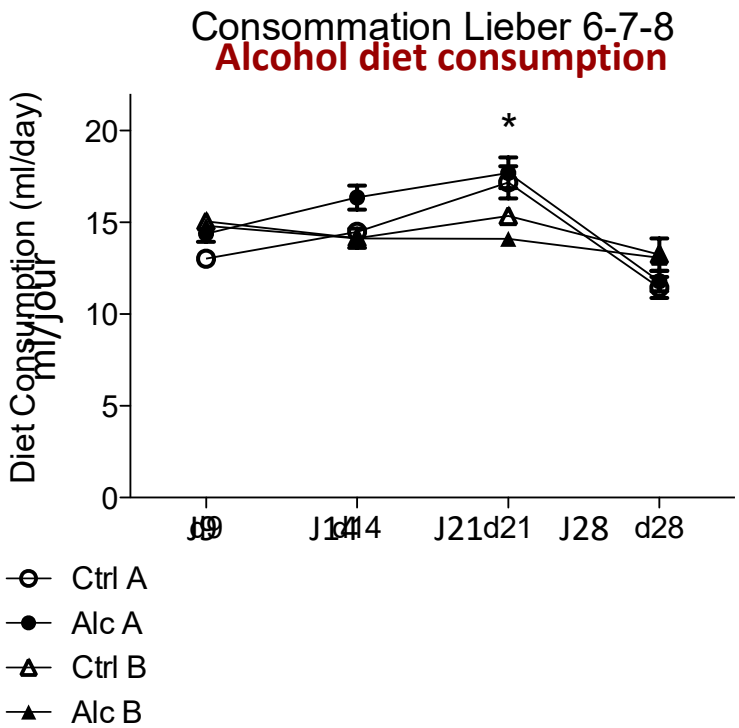
- acide deoxycholique
- acide lithocholique

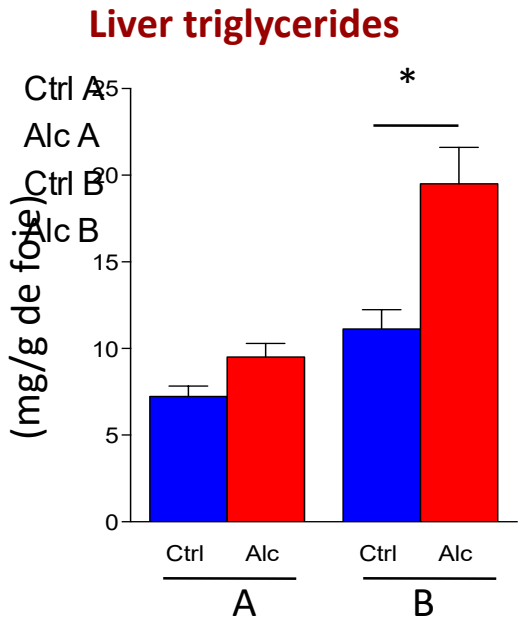
More cirrhosis is severe, more abnormalities are observed

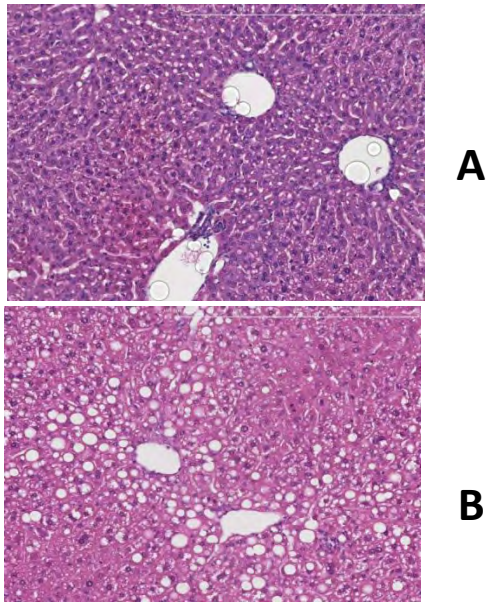
Kakiyama *J Hepatol* 2013

Mice behave like humans

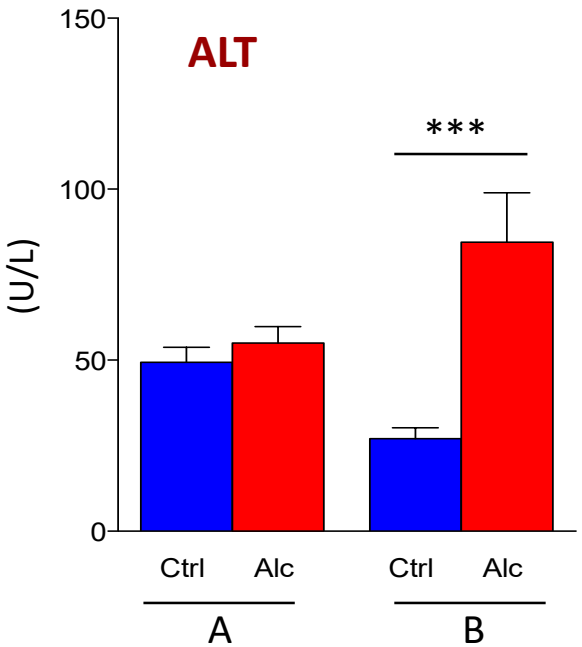


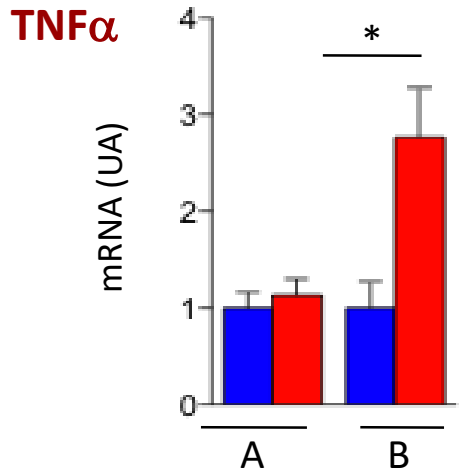


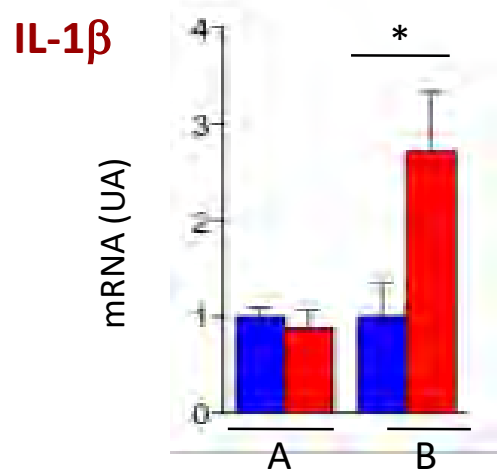


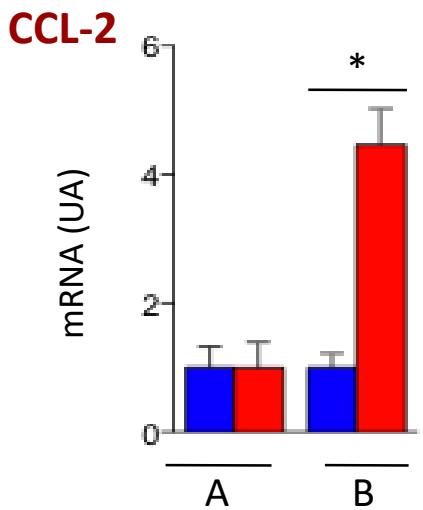


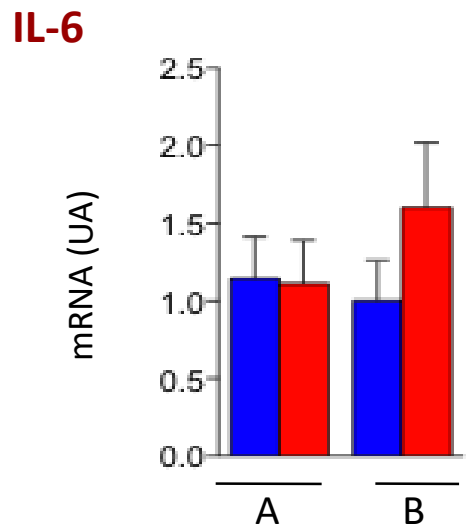
Mice behave like humans





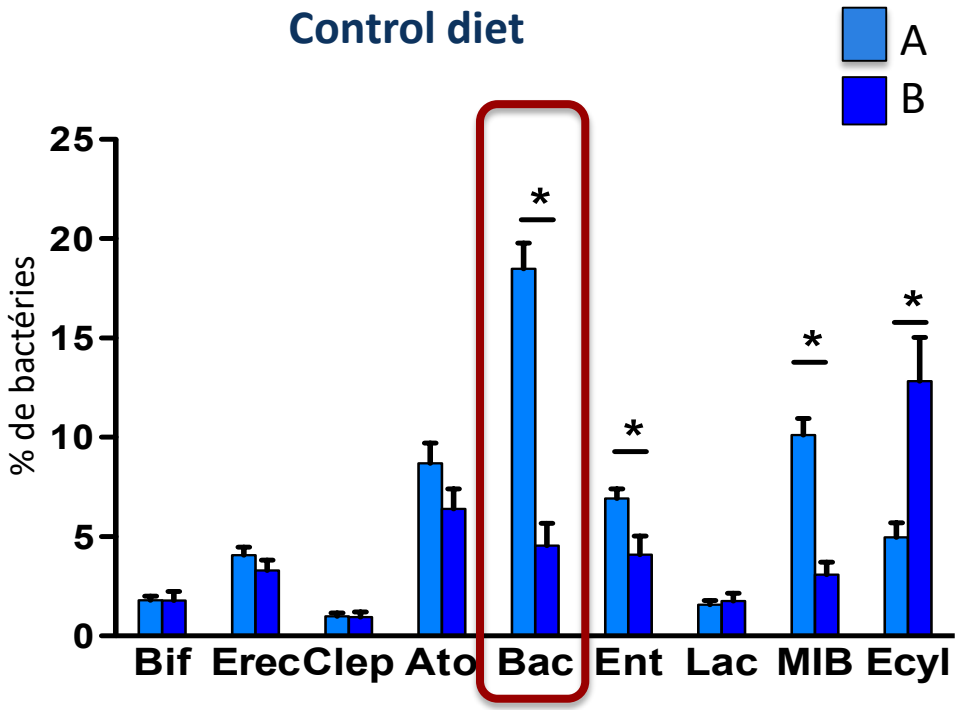


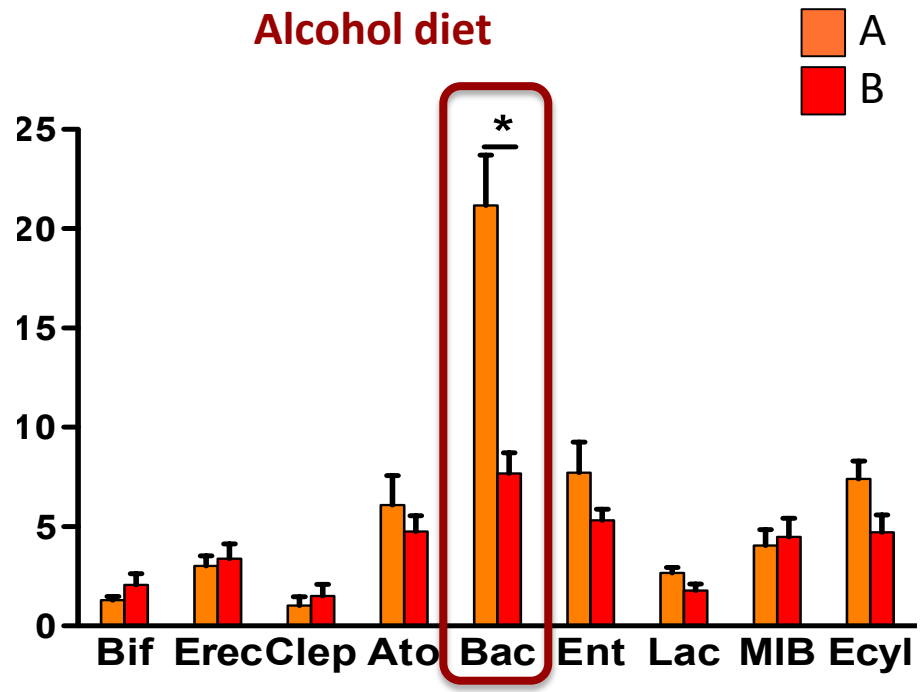




Individual susceptibility to alcohol-induced liver injury according to the animal facilities

Different intestinal microbiota in the 2 animal facilities

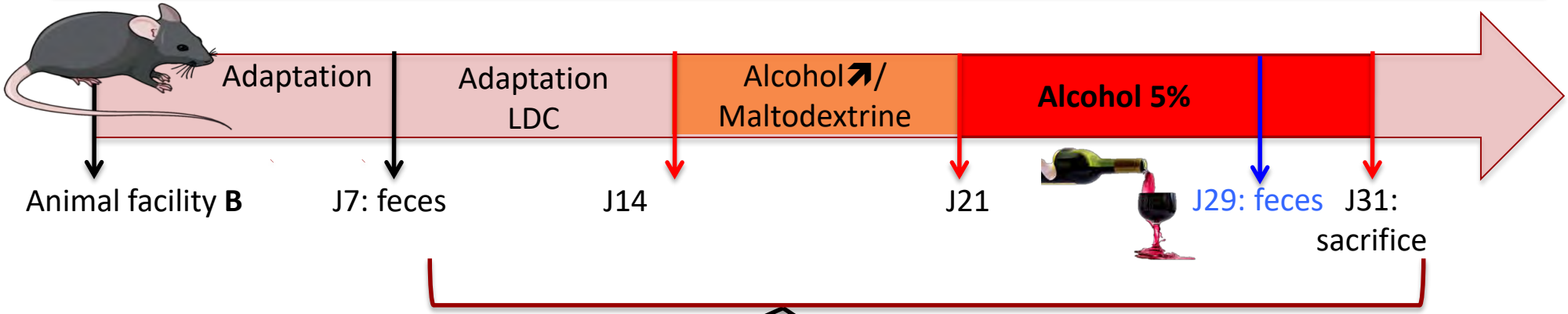


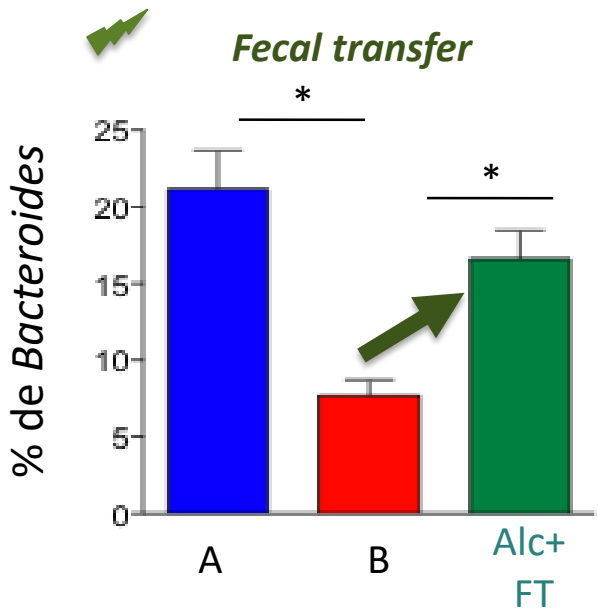


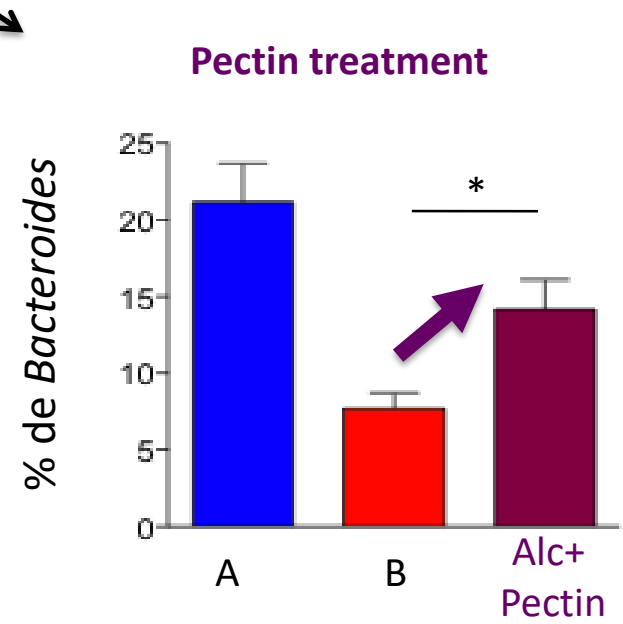
Decrease bacteroidetes is correlated with animal facilities

Decrease bacteroidetes is correlated with liver lesions

Fecal transfer (FT) / Pectin treatment



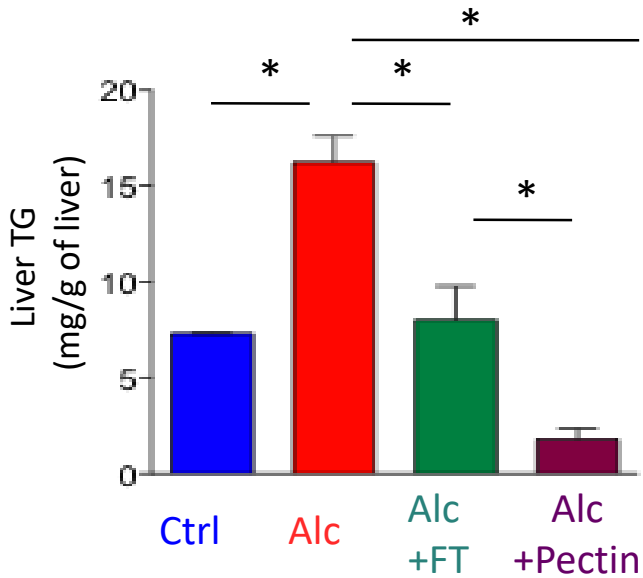


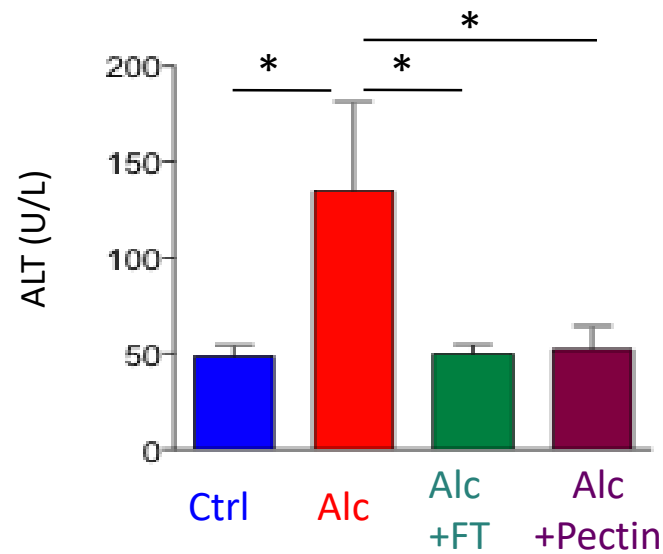


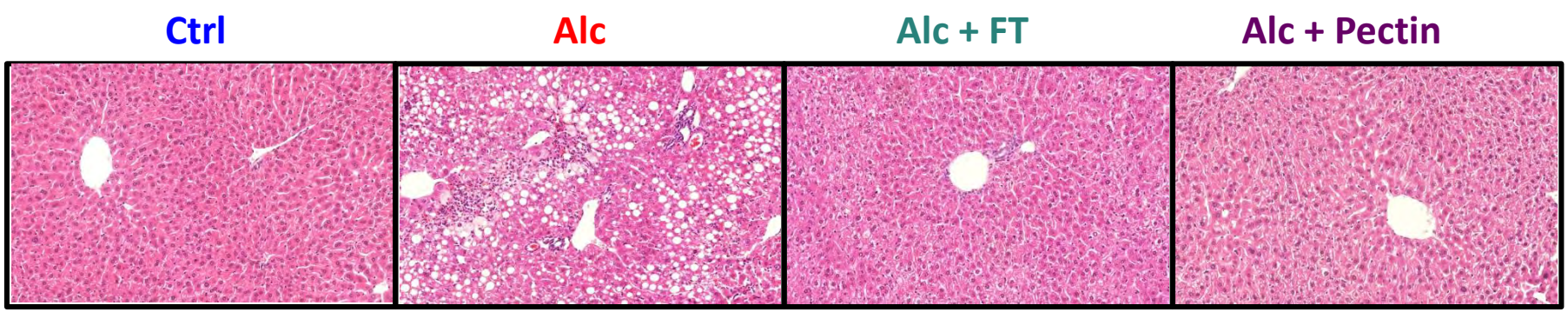
***Bacteroides* level is maintained with FT and pectin treatment**

Ferrere et al *J Hepatol* 2017
1 % top cited papers

Targeting microbiome improves alcohol-induced liver lesions



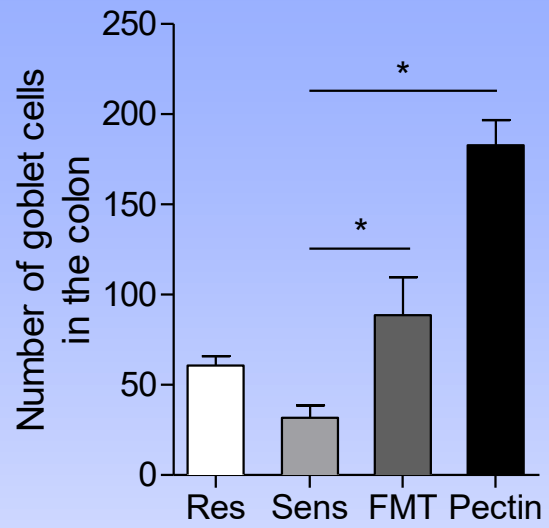


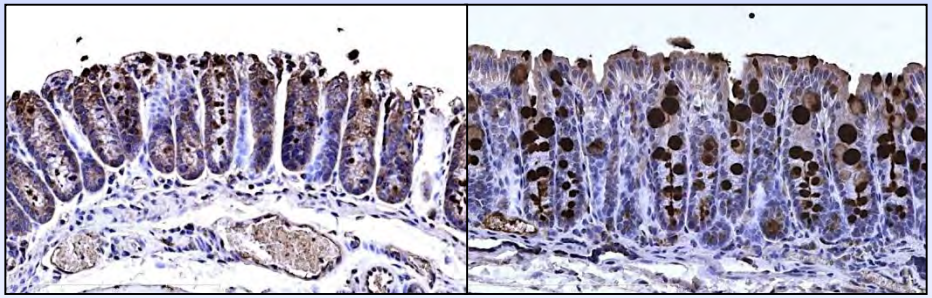


A high level of *Bacteroides* prevents steatosis

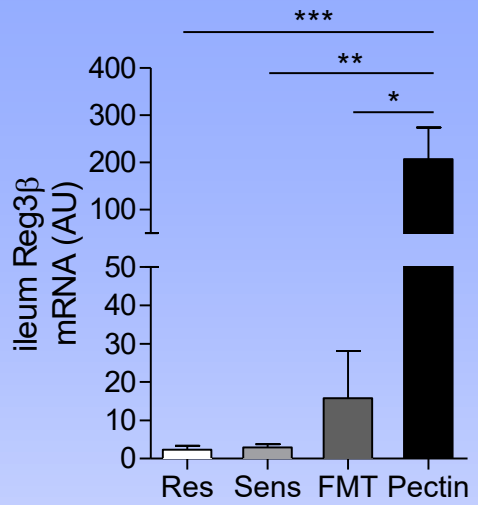
Ferrere et al *J Hepatol* 2017 1% top cited papers

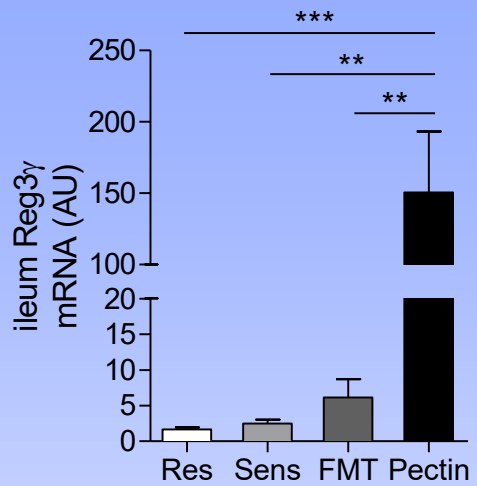
Impact of treatments in ALD on the gut epithelium

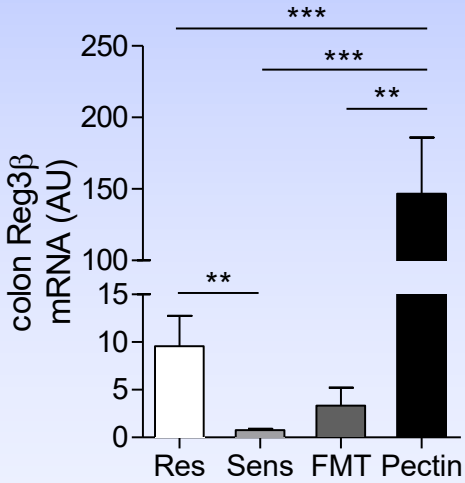


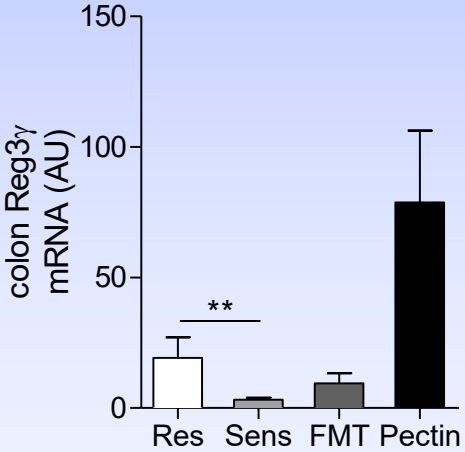


Muc 2 labeling in goblet cells





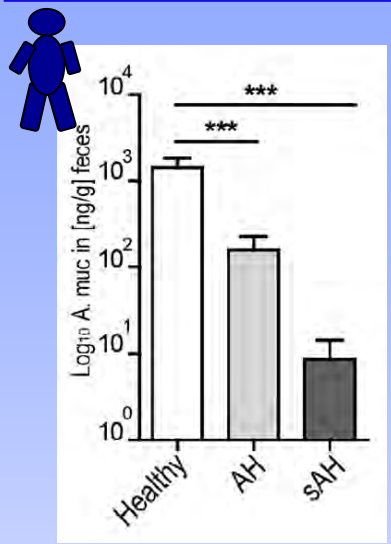


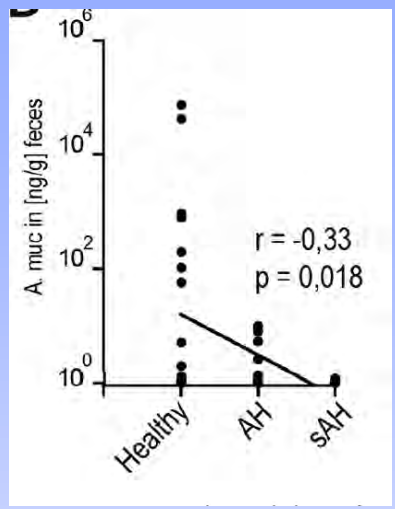


➡ **Improvement of the mucus layer and high level of anti-bacterial peptides**

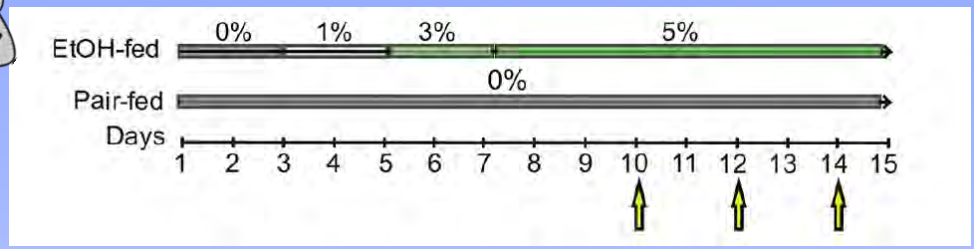
Ferrere et al. J. Hepatol 2017

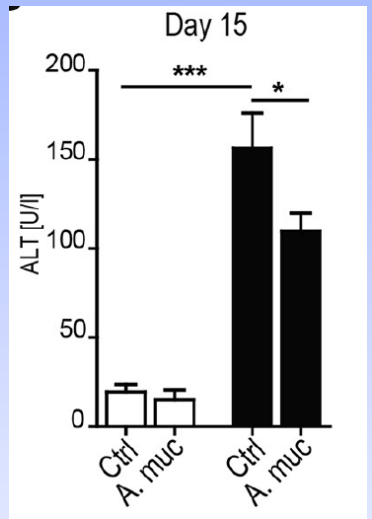
Impact of Akkermansia on the mucus layer

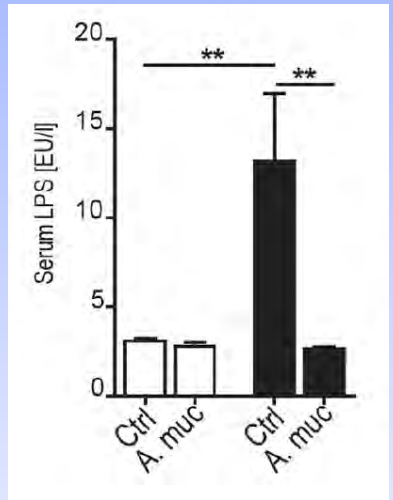


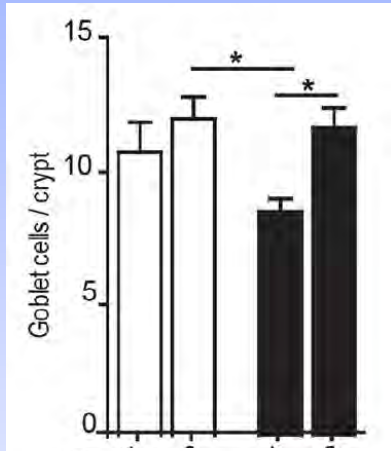


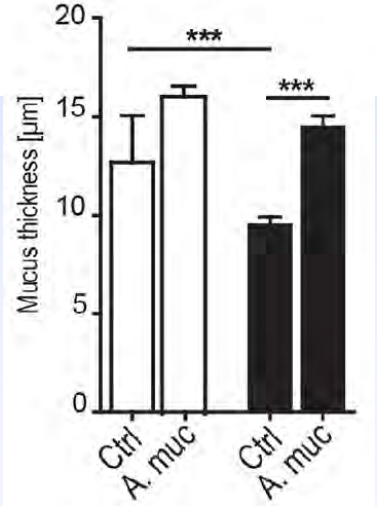
➡ **decrease of Akkermansia correlated to the severity of AH**









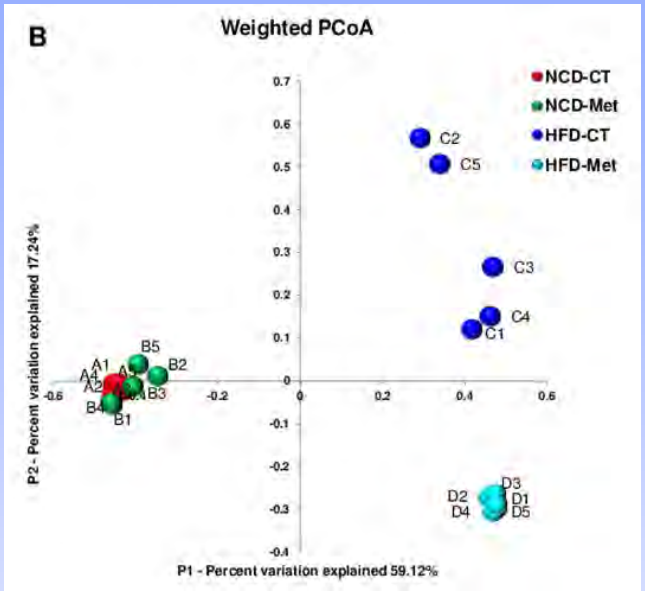


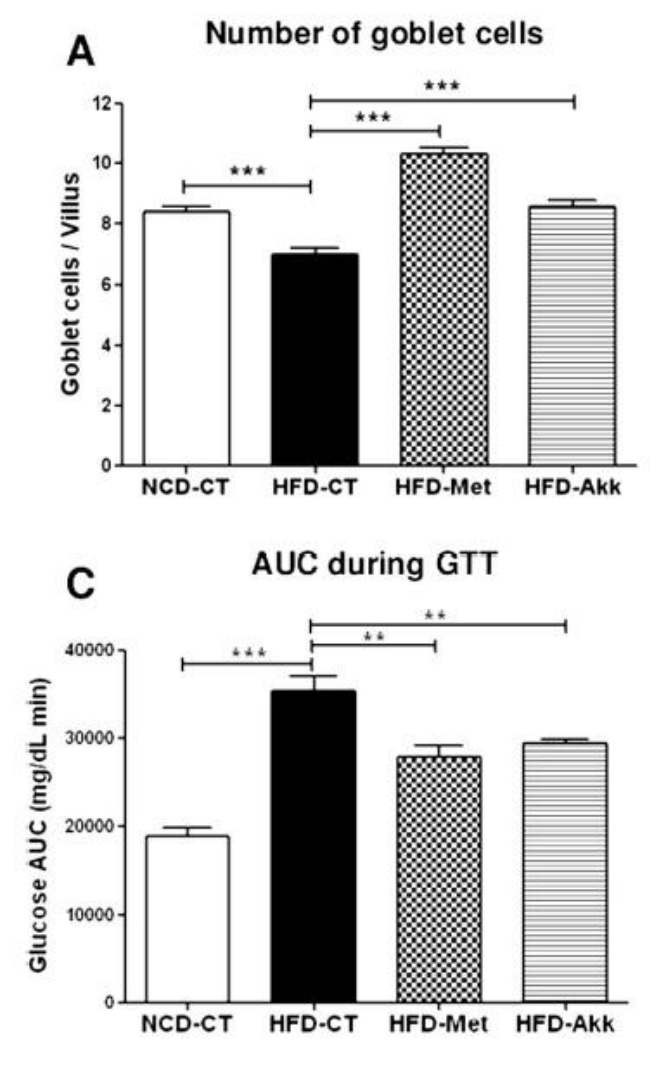
➡ **Akkermansia treatment improves liver injury**

➡ **Associated with an increase of the mucus layer protective**

Grander et al. Gut. 2017

Metformin Microbiome





- Increase of *Akkermansia* abundance and globlet cells in Metformin-treated mice
- *Akkermansia* improves glucose tolerance

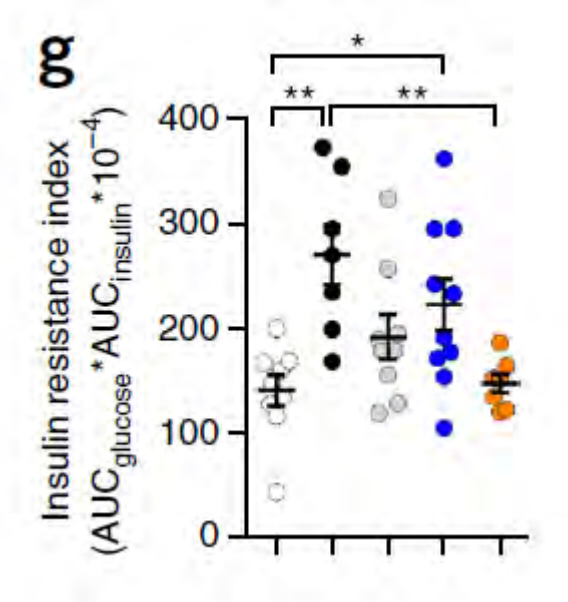
Microbiota changes:

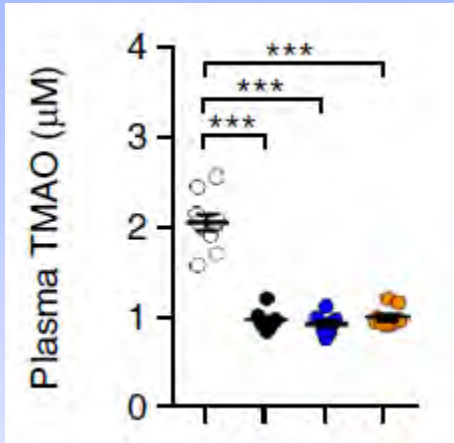
- Improve glucose tolerance
- Are responsible of side effects

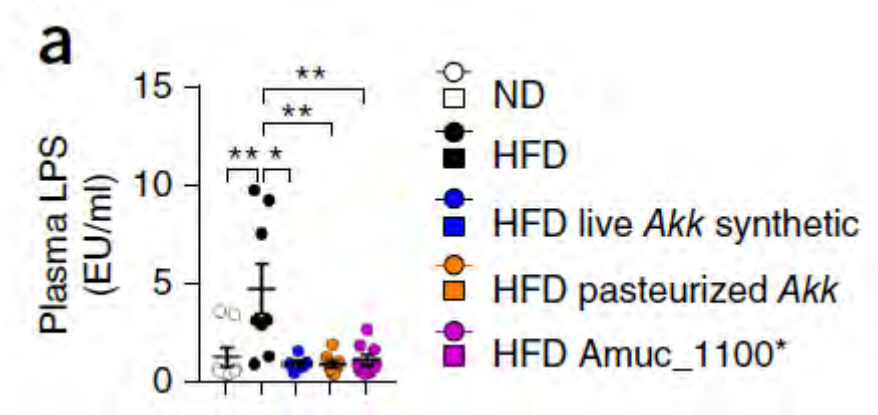
Forslund *Nature* 2015
Cabreiro *Cell Host Microb* 2016

Shin N-R *Gut* 2014

Akkermansia muciniphila improves metabolism



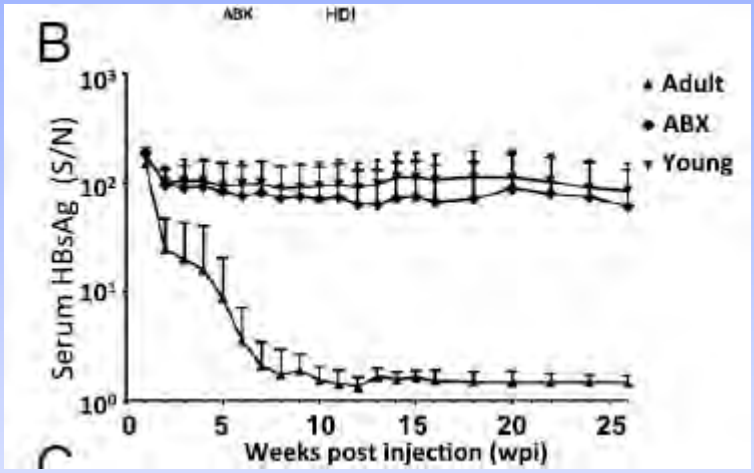


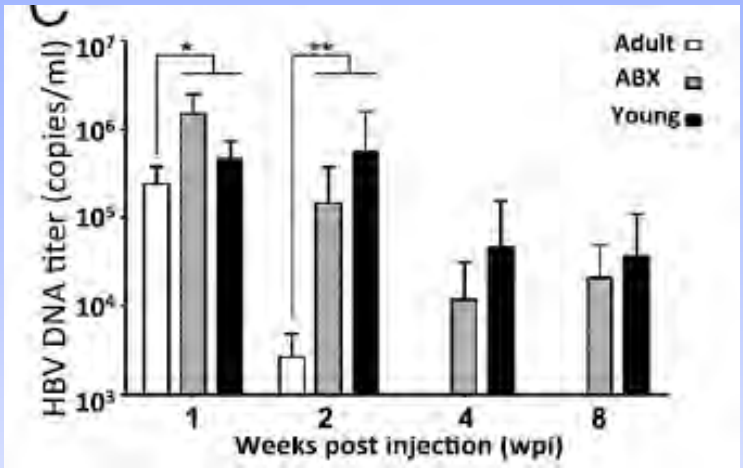


Akkermansia muciniphila **: a therapeutic option for diabetes and NAFLD ?**

Plovier *Nat Med* 2017

Clearance HBV and microbiota

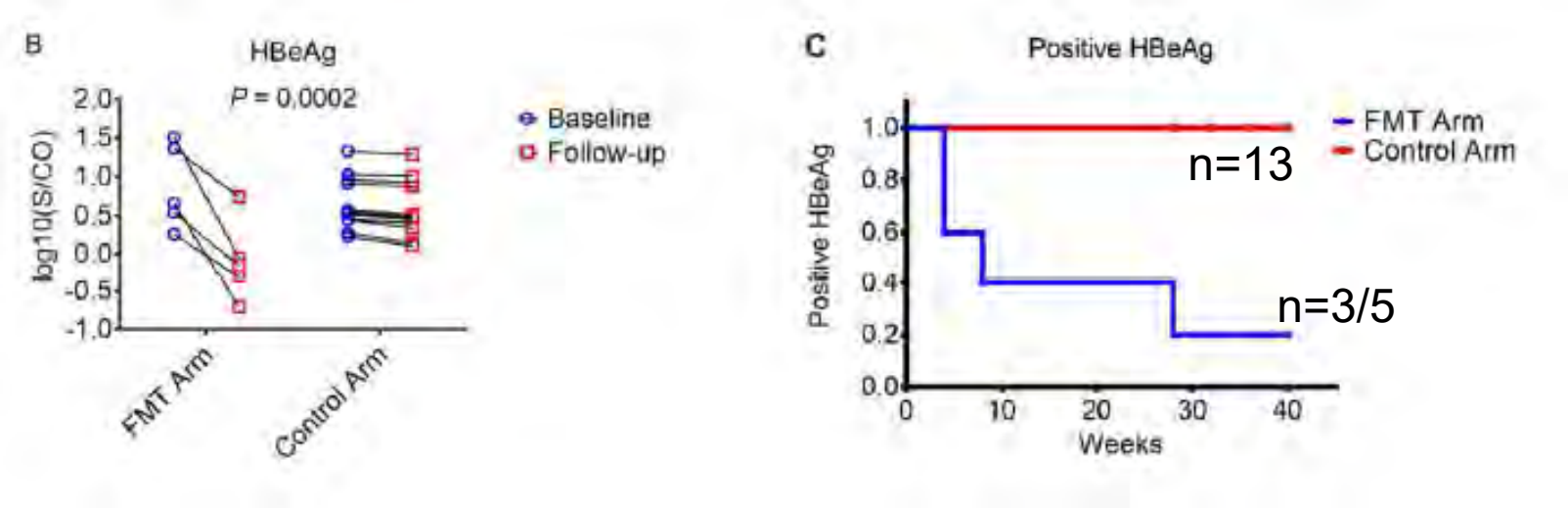




- Intestinal microbiota influences immune response
- In adults, depletion of IM restores liver tolerance

Chou HH *PNAS* 2015

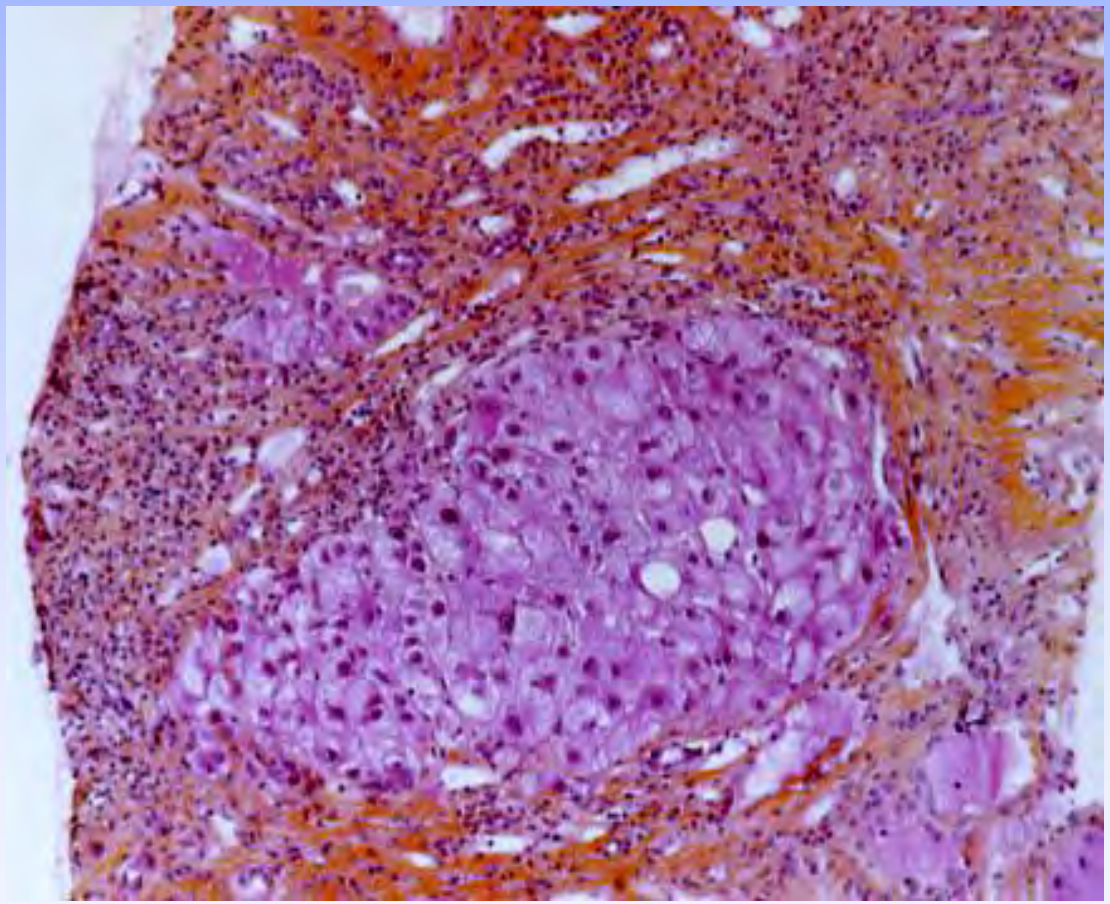
Fecal transfer and hepatitis B



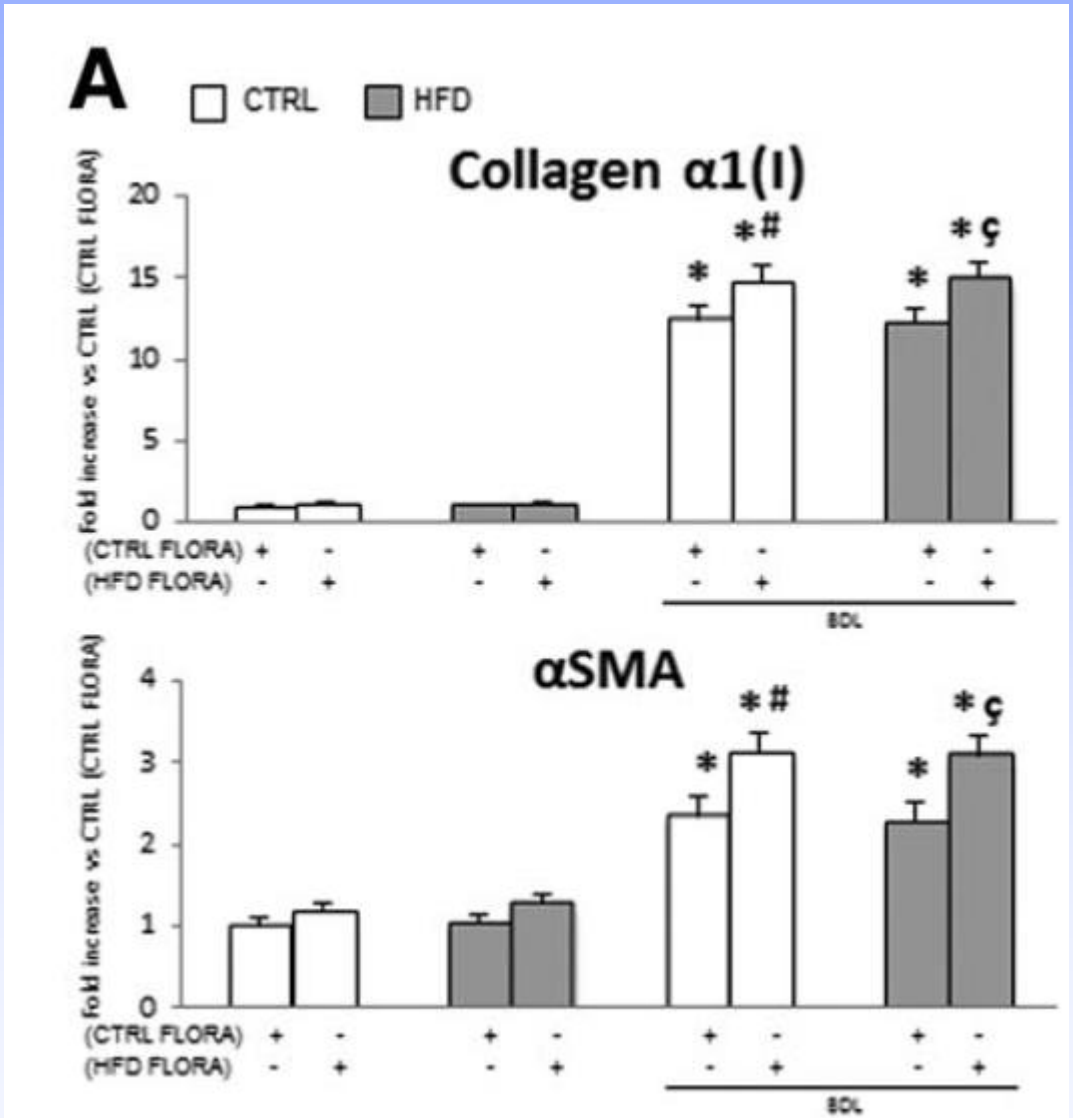
- AgHBe + despite ETV or TDF > 3 yrs
- Fecal transfer every 4 weeks by gastroscopy until AgHBe -
- HBV DNA < 500 IU/mL

Ren YD *Hepatology* 2017

Microbiota and Fibrosis



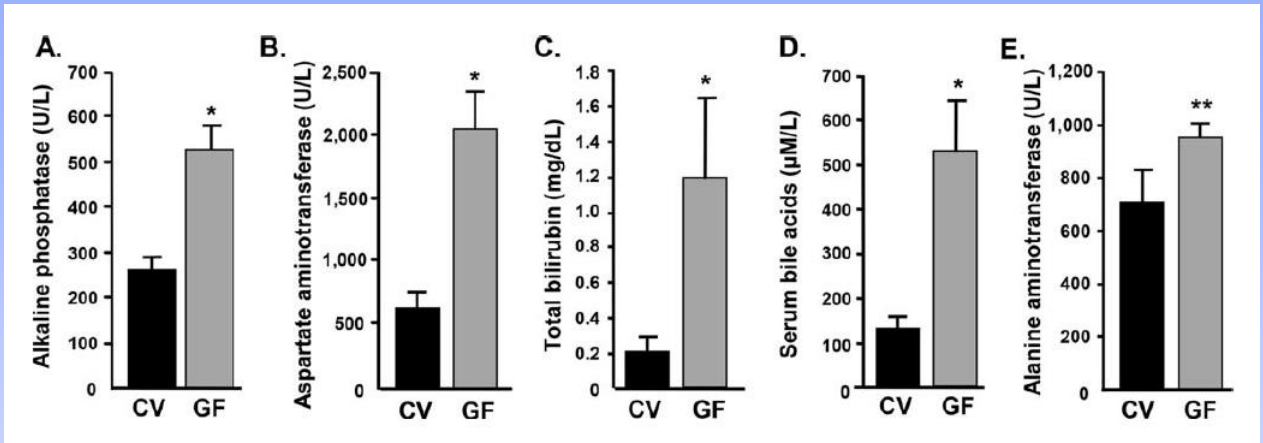
NASH, microbiota and fibrosis



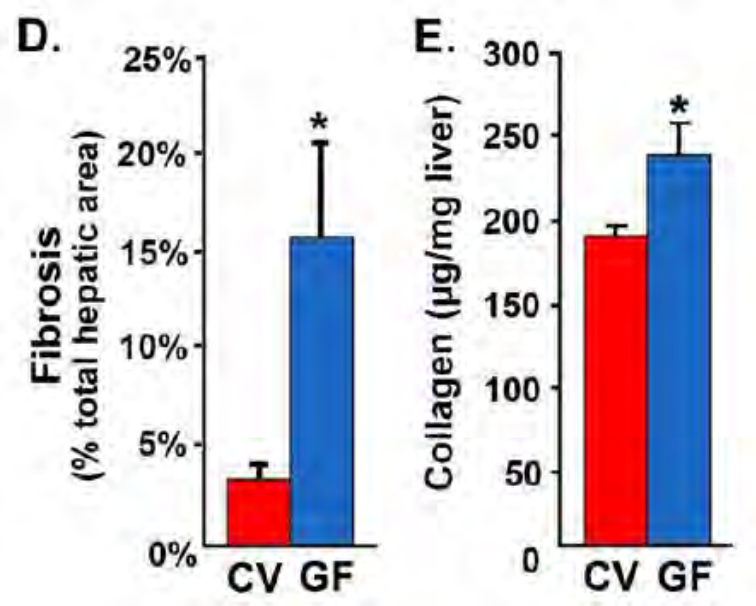
Direct involvement of the microbiota in liver fibrosis
Role of HFD-induced dysbiosis

Minicis *Hepatology* 2014

Primary biliary cirrhosis

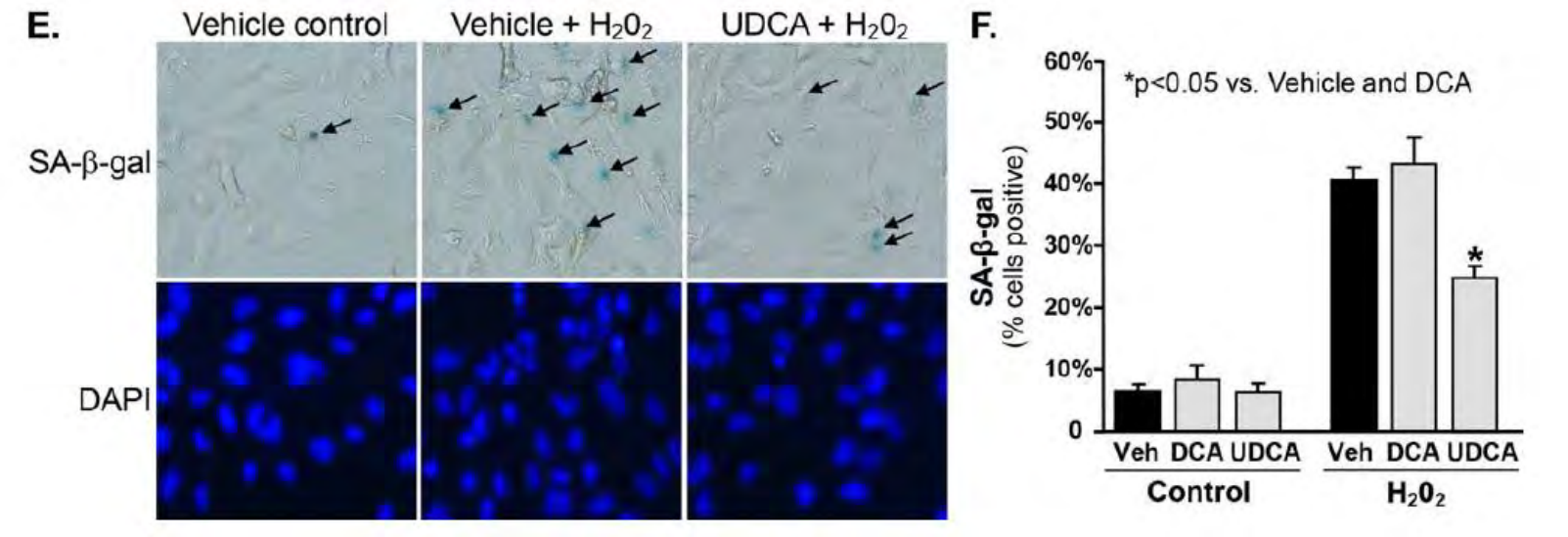


Mdr2$^{-/-}$ conv vs GF



Tabiban *Hepatology 2016*

Primary biliary cirrhosis

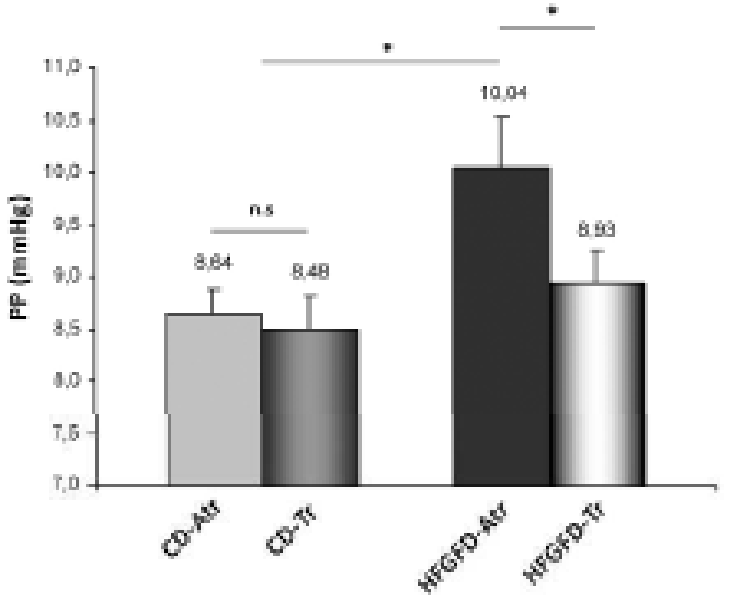


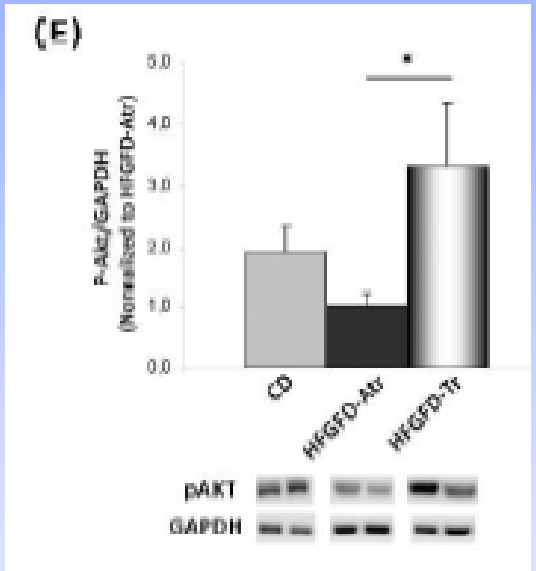
Mdr2$^{-/-}$ conv vs GF

- Absence of commensal bacteria:
  - > more severe biliary injury
  - > cholangiocyte senescence
- **UDCA, absent in GF mice**, improves cholangiocyte senesence

Tabiban *Hepatology 2016*

Microbiota and portal hypertension in a rat model of NAFLD

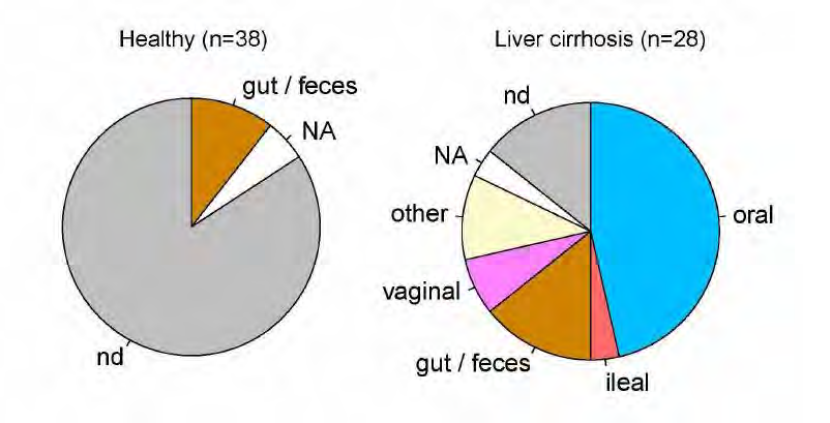


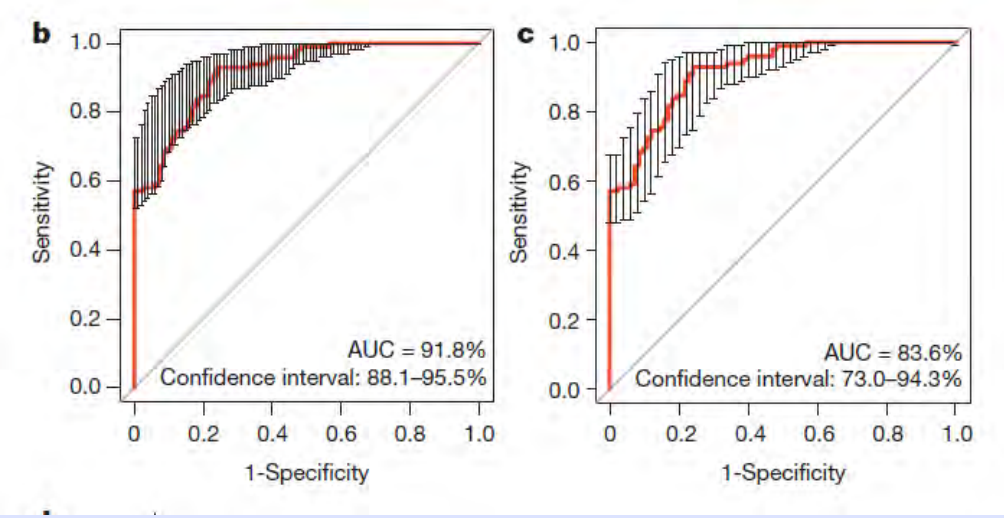


Intestinal microbiota influences portal hypertension:
- independently of liver fibrosis
- via the hepatic Akt signaling pathway

Garcia-Lezana
Hepatology 2017

Clinical perspectives: diagnosis





- Major changes in the gut microbiota in patients with cirrhosis
- Translocation of oral microbiota inside the gut
- 15 biomarkers may diagnose cirrhosis
- Clinical utility ?
- Predictive factor ?

Qin *Nature* 2014

Stool microbiota: a signature of fibrosis in NAFLD?

Table 1. Baseline Characteristics of Patients with Biopsy-Proven NAFLD

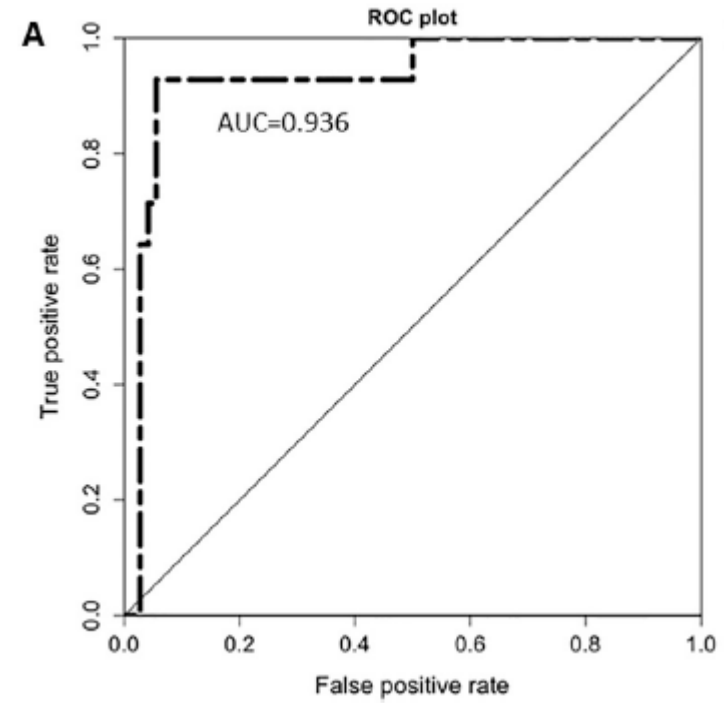
Characteristics	All Patients; N = 86	Stage 0–2, NAFLD; N = 72	Stage 3–4, Advanced Fibrosis; N = 14	p Value, Student's t Test
Demographics				
Age (mean ± SD)	48 ± 1.4	49.3 ± 12.6	63.4 ± 3	1.5e−12
Male n (%)	38 (44.2%)	36 (50%)	2 (14.3%)	0.030
White n (%)	40 (46.5%)	33 (40.2%)	7 (50%)	1.000
Hispanic n (%)	29 (33.7%)	23 (31.9%)	6 (42.9%)	0.630
Clinical				
Type 2 diabetes n (%)	20 (23.3%)	14 (19.4%)	6 (42.9%)	0.126
Anthropometric, Mean ± SD				
Body mass index (kg/m2)	31.2 ± 5.5	31.0 ± 5.4	32.2 ±± 6.0	0.503
Waist circumference (cm)	102.4 ± 16.3	101.5 ± 19.2	107.1 ± 17.3	0.823
Hepatology Panel, Mean ± SD				
AST (U/L)	41.0 ± 30.0	35 ± 24.5	72 ± 36.8	0.002
ALT (U/L)	57.0 ± 55.2	53.8 ± 54.3	73.8 ± 55.2	0.253
AST/ALT	0.72	0.65	0.98	–
Bilirubin, direct (mg/dL)	0.16 ± 0.12	0.13 ± 0.06	0.29 ± 0.23	0.033

Loomba *Cell Metab* 2017

Stool microbiota: a signature of fibrosis in NAFLD?

Table 3. Taxonomic Composition

Phylum	G1 Median, SD	G2 Median, SD	p Value
Firmicutes	58.81% (20.8)	42.61% (23.9)	0.01520
Proteobacteria	1.85% (15.3)	4.54% (22.9)	0.04004
Bacteroidetes	23.62% (18.1)	28.46% (27.4)	0.57840
Actinobacteria	2.67% (4.1)	2.02% (7.4)	0.78340
Species			
Ruminococcus obeum CAG:39	0.06% (0.54)	0.01% (0.02)	0.00005*
Ruminococcus obeum	0.29% (0.90)	0.11% (0.15)	0.00009*
Eubacterium rectale	2.56% (5.66)	0.12% (1.35)	0.00009*
Faecalibacterium prausnitzii	1.63% (4.07)	0.34% (3.07)	0.01961
Escherichia coli	0.29% (15.8)	0.99% (25.3)	0.44330
Bacteroides vulgatus	1.76% (4.56)	2.19% (7.04)	0.85610



Fecal-microbiome-derived metagenomic signature for advanced fibrosis in NAFLD

Age, BMI
Shannon diversity
37 species

Loomba *Cell Metab* 2017

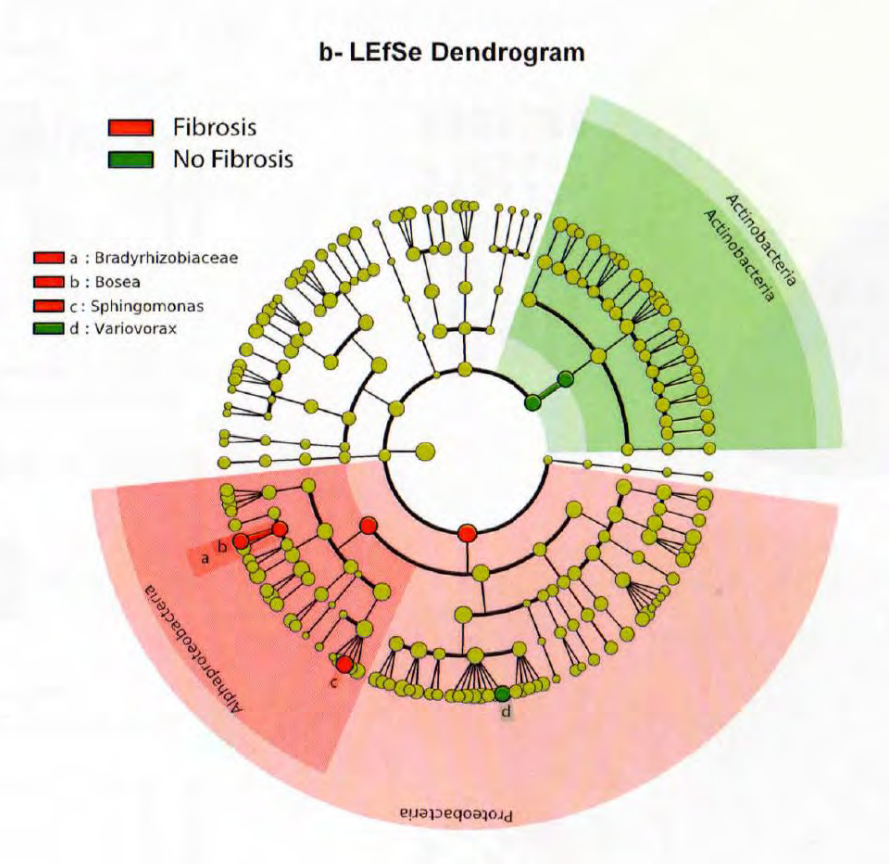
Blood microbiota: a signature of fibrosis in NAFLD?

Table 2: Characteristics of the Italian study population

	Controls (No fibrosis)		*Cases (Fibrosis)*		Cases vs controls
Total (n)	**60**		**11**		
Categorical variables	**n**	**%**	**n**	**%**	***p* (Fisher)**
Men	18	30.0	3	27.3	1.00
Women	42	70.0	8	72.7	1.00
Smoking status					
Never smoked	20	33.3	3	27.3	1.00
Former smoker	18	30.0	3	27.3	
Current smoker	22	36.7	5	45.4	
Treated hypertension	9	15.0	4	36.4	0.11
Treated diabetes	0	0	0	0	1.00
Treated dyslipidemia	0	0	1	9.1	0.02
Quantitative variables	**Mean**	**SD**	**Mean**	**SD**	***p* (Mann-Whitney, t)**
Age (years)	39.8	9.5	41.0	11.5	0.85
Body mass index (kg/m^2)	48.2	7,0	48.8	6.3	0.52
Total cholesterol (mg/dl)*	200.3	39.6	186.1	23.7	0.26
HDL cholesterol (mg/dl)*	45.7	12.84	43.2	10.1	0.68
GPT (U/l)	42.2	23.4	48.7	33.2	0.54
GGT (U/l)*	39.8	22.8	49.6	31.5	0.33
Glucose (mg/dl)	98.27	18.1	102.1	17,0	0.47
C reactive protein (mg/dl)*	2.4	4.2	2.7	4.3	0.95
Hematocrit (%)	40.9	3.1	42.5	2.4	0.07
Leukocyte (10^3/µl)	8.1	2.1	10,0	4.4	0.3
Neutrophil (10^3/µl)	5.2	1.9	5.5	2.8	0.48
Blood 16S DNA (copies/µl)	**2.4**	**0.7**	**3.1**	**1.4**	**0.0057**

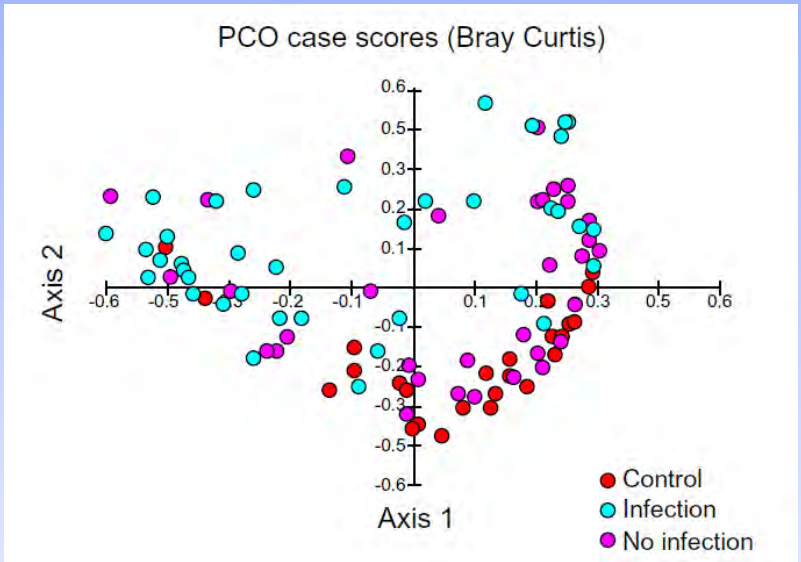
GPT: Glutamic-Pyruvic Transaminase, GGT: Gamma-glutamyl transpeptidase, HDL: High-density lipoprotein.

*Data is missing for one or two patients.



Lelouvier *Hepatology* 2016

Clinical perspectives: cirrhosis dybiosis ratio



	Cirrhosis with infection (n = 38)	Cirrhosis without infection (n = 38)
Age (yr)	56.0 ± 6.9	58.4 ± 6.8
Sex (Male/female)	21/17	25/13
Race (Caucasian/African-American/Hispanic/other)	21/9/5/3	20/13/8/0
BMI	29.2 ± 6.7	30.1 ± 6.5
Cirrhosis etiology (HCV, alcohol, HCV + alcohol, NASH, others)	11/12/6/6/1	16/9/6/5/2
MELD score	18.2 ± 6.2	18.4 ± 6.8
History of		
Variceal bleeding	5 (13%)	4 (11%)
Hepatic encephalopathy	28 (73%)	23 (61%)
Medications		
Proton pump inhibitors	25 (66%)	24 (63%)
Non-selective beta-blockers	16 (42%)	14 (36%)
Lactulose	15 (40%)	18 (47%)
Rifaximin	17 (45%)	14 (37%)
On SBP prophylaxis	3 (8%)	6 (15%)
Endotoxin (EU/ml)	1.60 ± 1.2	0.65 ± 0.45***
Microbiota (median % abundance Phylum_Taxon)		
Phylum Actinobacteria		
Actinobacteria_Coriobacteriaceae	0.2	0.5*
Phylum Bacteroidetes		
Bacteroidetes_Bacteroidaceae	4.3	21.1
Phylum Firmicutes		
Firmicutes_Streptococcaceae	0.0	1.0
Firmicutes_Clostridiales_XIV	0.0	2.4***
Firmicutes_Lachnospiraceae	3.1	14.4***
Firmicutes_Ruminococcaceae	0.7	5.0***
Firmicutes_Veillonellaceae	0.0	1.6***
Phylum Proteobacteria		
Protoebacteria_Enterobacteriaceae	1.4	0.0*
Cirrhosis Dysbiosis Ratio	0.34	0.78***

There are no significant differences in the demographics, cirrhosis severity and medication use between the groups.
Only microbiota with an abundance ≥ 1% in any group are shown.
*p <0.05-0.01.
***p <0.0001.

- Progressive changes in the gut microbiome in cirrhosis and in cirrhosis wth decompensation.
- Proposal of a score: cirrhosis dysbiosis ratio (CDR)

Bajaj *J Hepatol* 2014

Fungal dysbiosis in cirrhosis

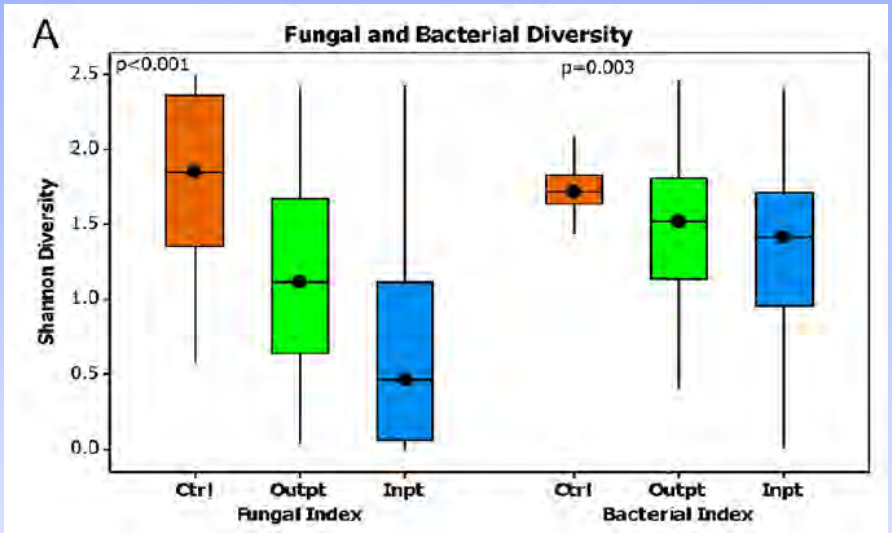


Table 2 Characteristics of patients who were admitted within 90 days

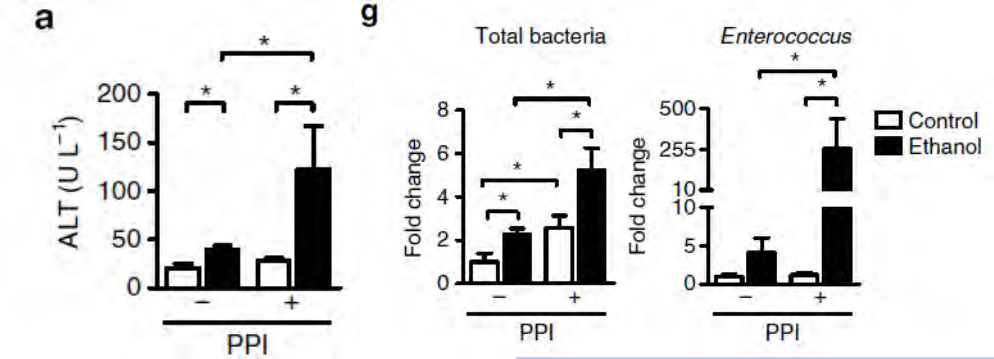
	Not readmitted (n=96)	Readmitted (n=27)
Clinical parameters		
Age (years)	57.9±7.4	55.2±7.5
Gender (men/women)	81/15	14/13*
Aetiology (HCV, alcohol, HCV+alcohol, NAFLD, others)	38/10/15/21/12	7/7/4/4/3
MELD score	15.3±6.9	17.5±8.1
Prior hepatic encephalopathy	35	14*
Lactulose alone/any rifaximin	15/20	11/3*
SBP prophylaxis	10	3
Proton pump inhibitors	46	14
Non-selective beta-blockers	39	10
Diabetes	26	8
Infection	23	15*
Inpatient group	34	17*
Microbiota parameters		
Fungal Shannon index	1.0±0.7	0.71±0.4*
All Ascomycota (median relative abundance)	76%	98%*
All Basidiomycota (median relative abundance)	0%	0.1%
Basidiomycota/Ascomycota ratio	0.3±0.8	0.06±0.10*
All Proteobacteria (median relative abundance)	2%	7%*
All Bacteroidetes (median relative abundance)	40%	8%*
All Firmicutes (median relative abundance)	39%	45%

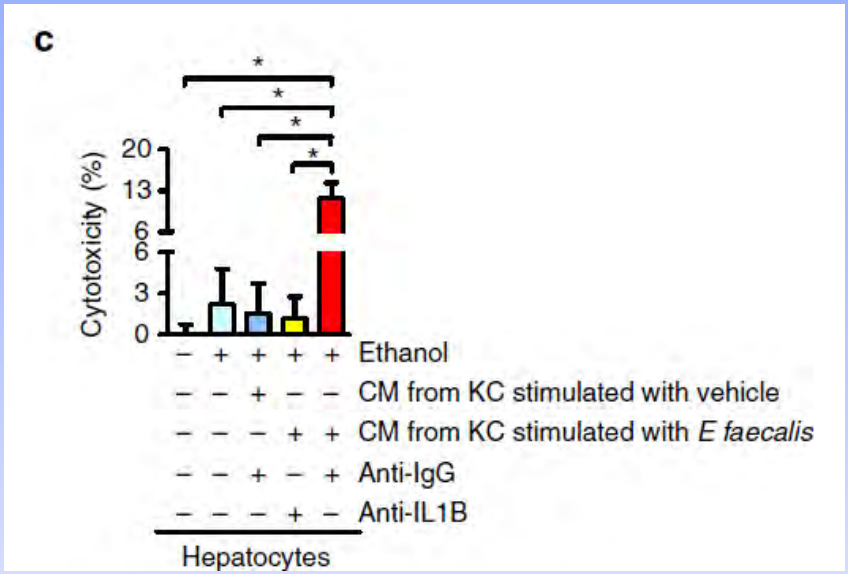
MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; SBP, spontaneous bacterial peritonitis.

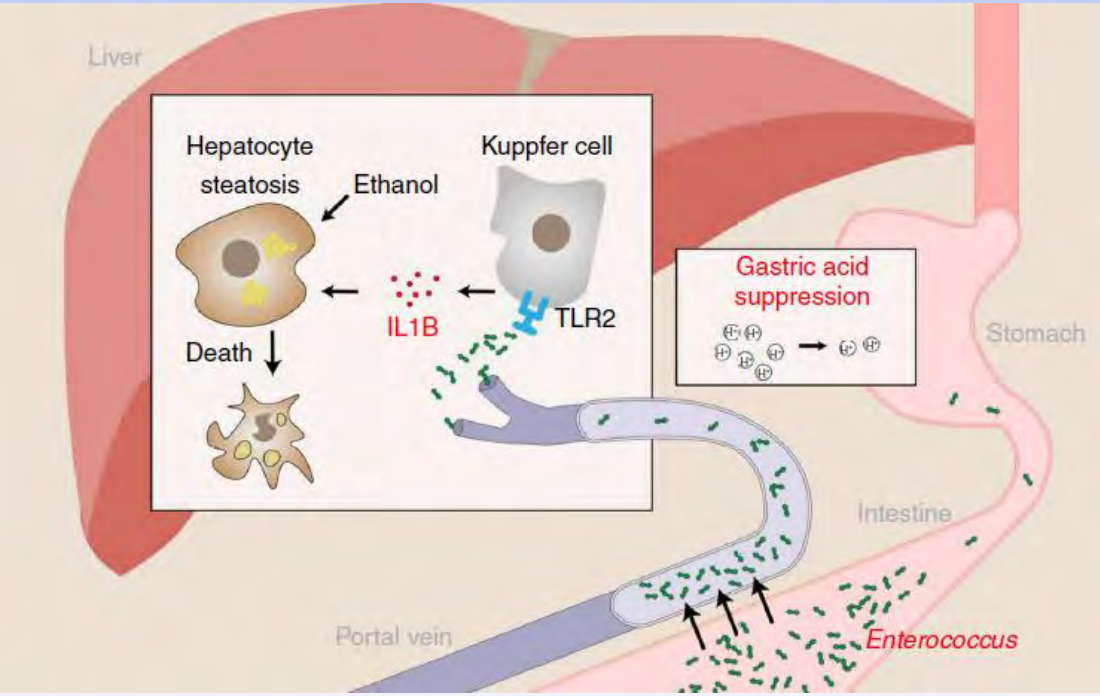
- Bacteroidetes/Ascomycota, can predict 90-day hospitalisations
- Outpatient antibiotic use in patients with cirrhosis leads to fungal diversity reduction

Bajaj *Gut* 2017

Inhibition of gastric acid secretion and liver disease



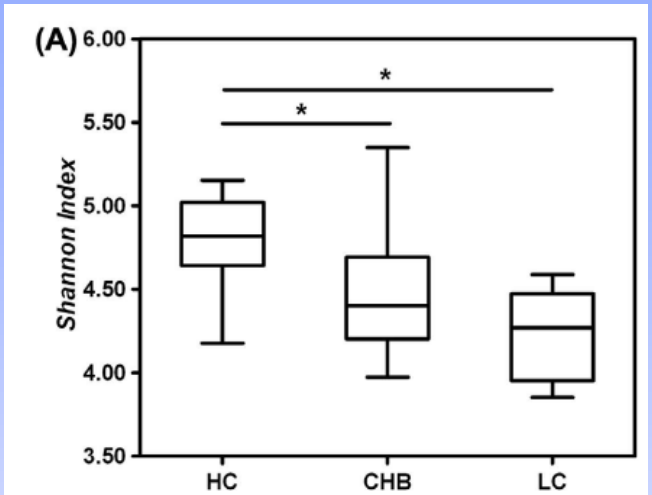




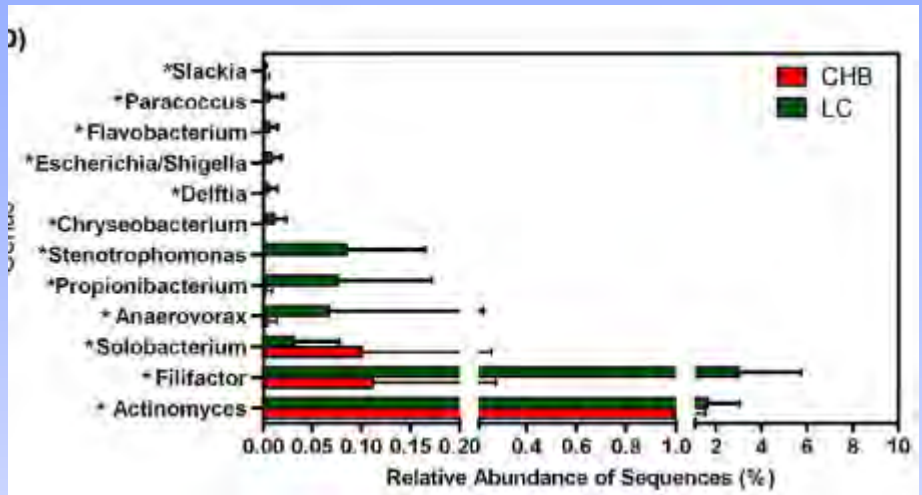
- PPI increases Enterococcus spp. growth
- Enterococcus spp. exacerbates ALD in mice

Llorente *Nat Commun* 2017

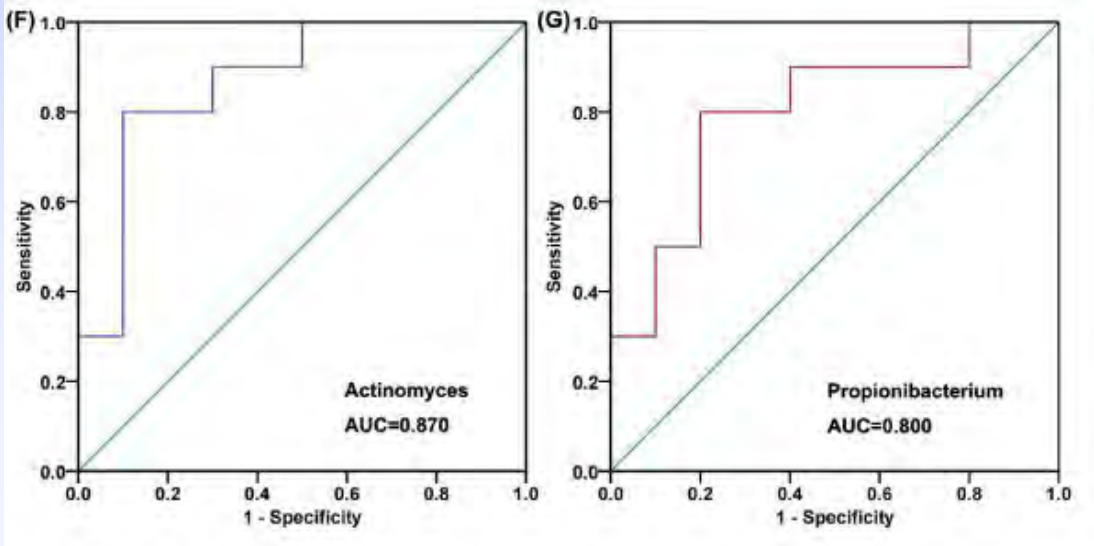
Oral microbiota and HBV-induced cirrhosis



Decreased diversity



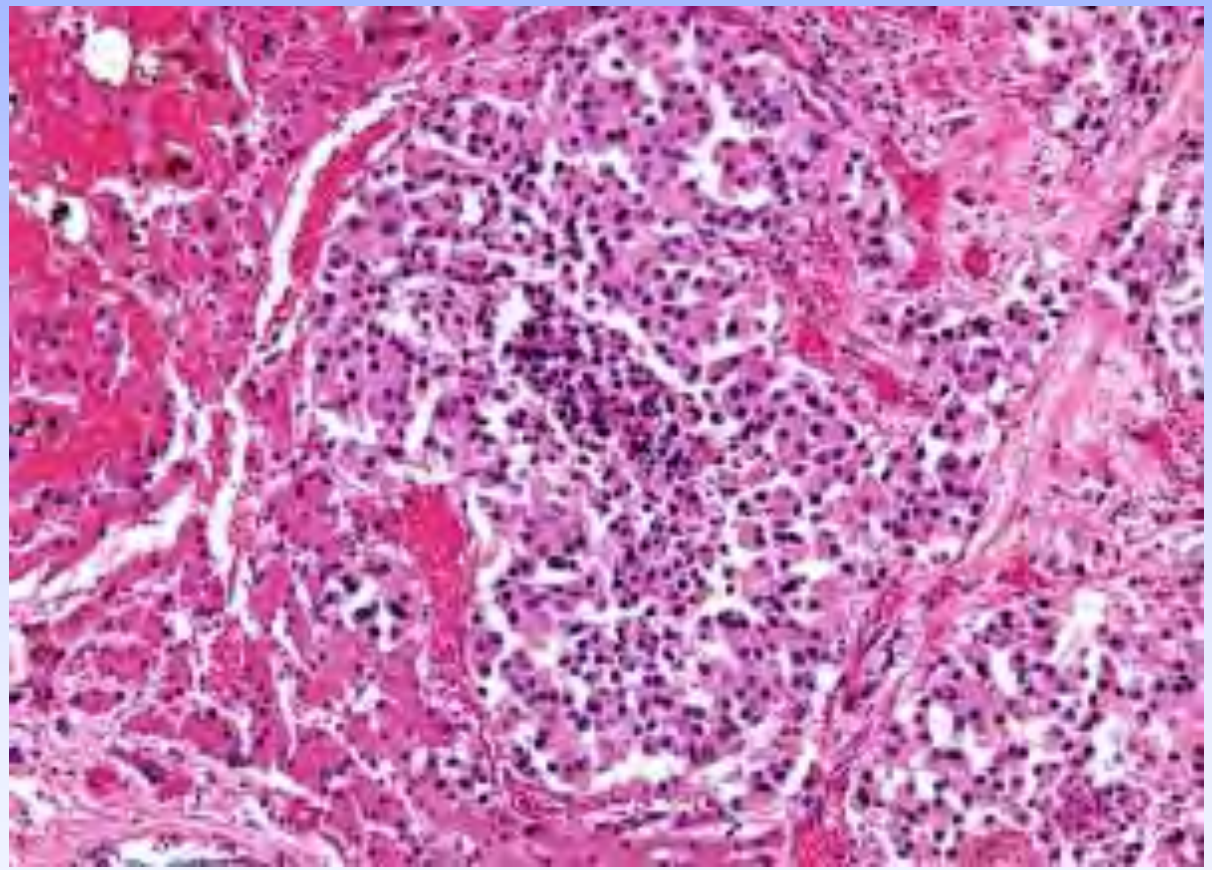
Genus level



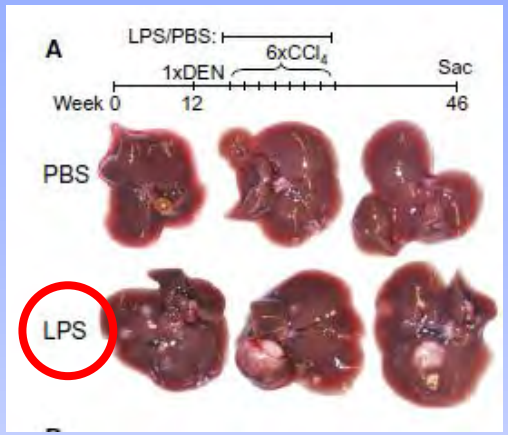
Actinomyces, *Propionylbacterium*, *Stenotrophomonas* and *Chryseobacteria*
Good cutoff to distinguish liver cirrhosis from chronic hepatitis B

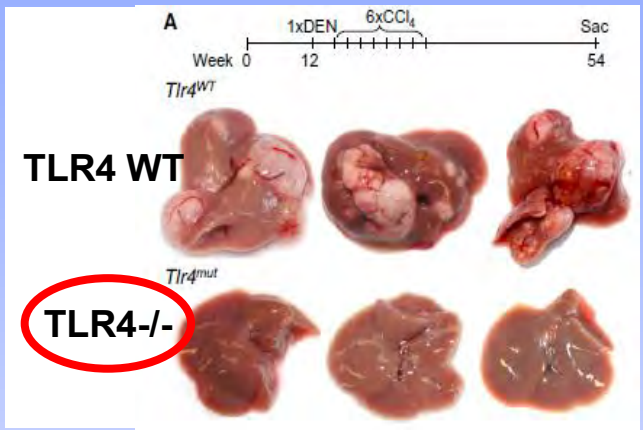
Ling *Scientific reports 2015*

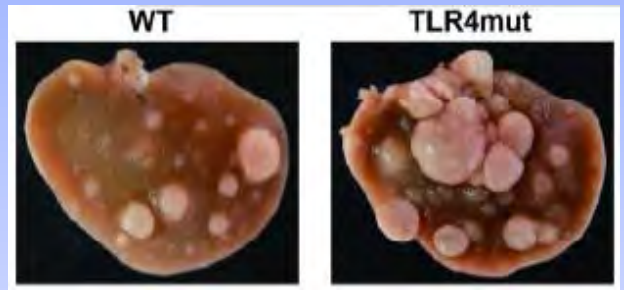
Microbiota and HCC



Intestinal microbiota and HCC : indirect evidences







➠ **LPS promote HCC**

➠ **TLR4 deficiency protects from HCC**

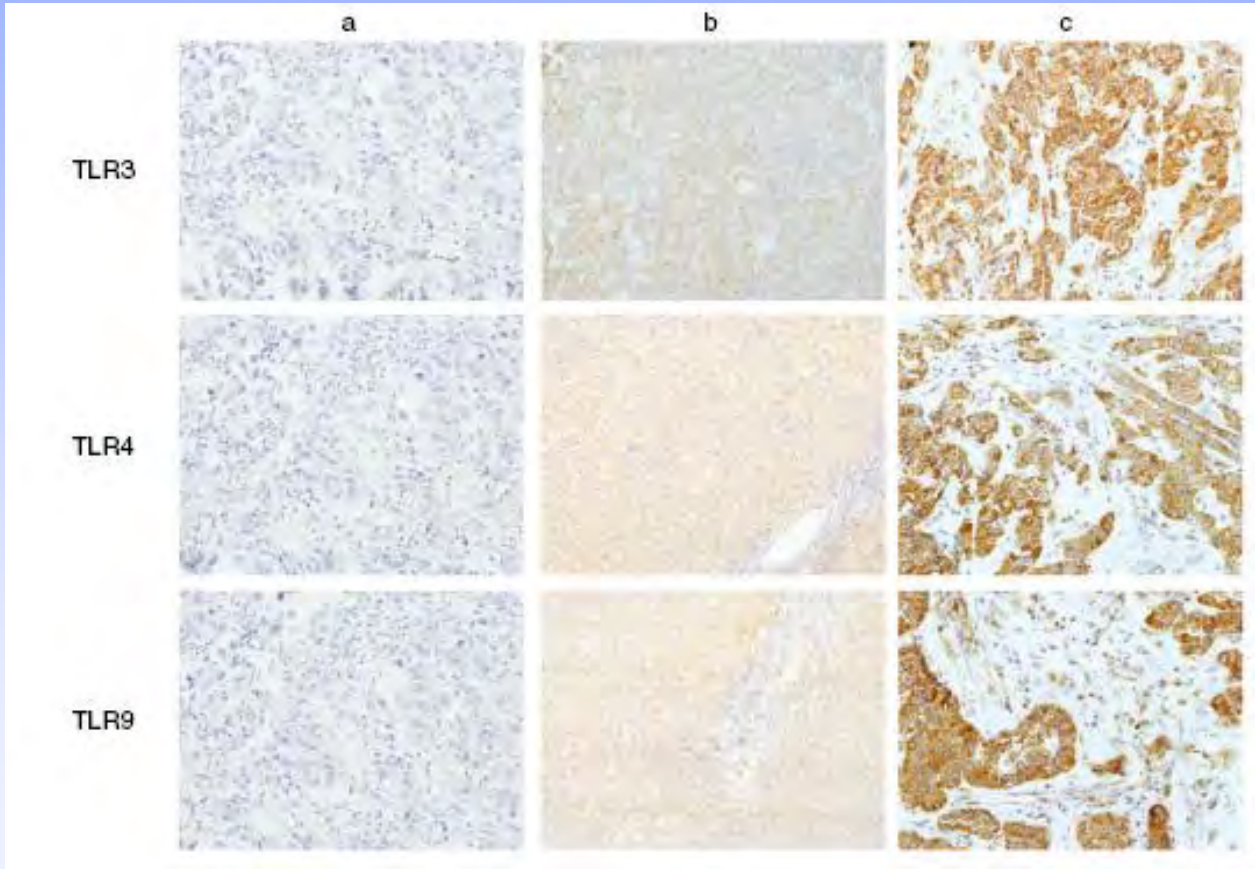
➠ **Antibiotics protect from HCC in late stages of carcinogenesis**

Dapito Cancer Cell 2012

➠ **TLR4 deficiency enhances development of HCC**

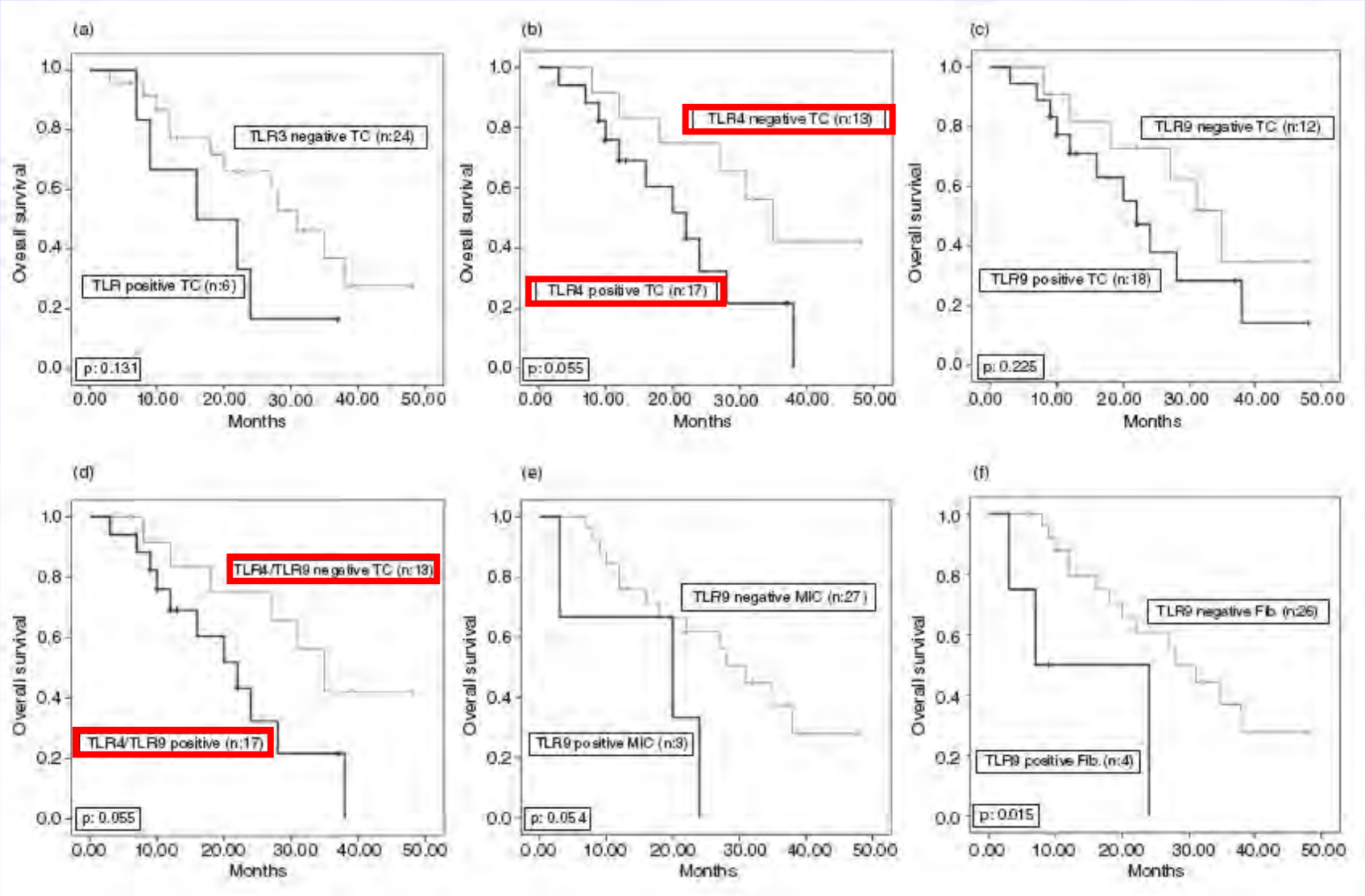
Wang *Hepatology* 2013

TLR 3, 4 and 9 are expressed in human liver hepatocellular carcinoma



Eiro *Hepatology Research* 2013

TLR 3, 4 and 9 expression and patient survival in hepatocellular carcinoma



Eiro *Hepatology Research* 2013

LPS, flagellin and HCC

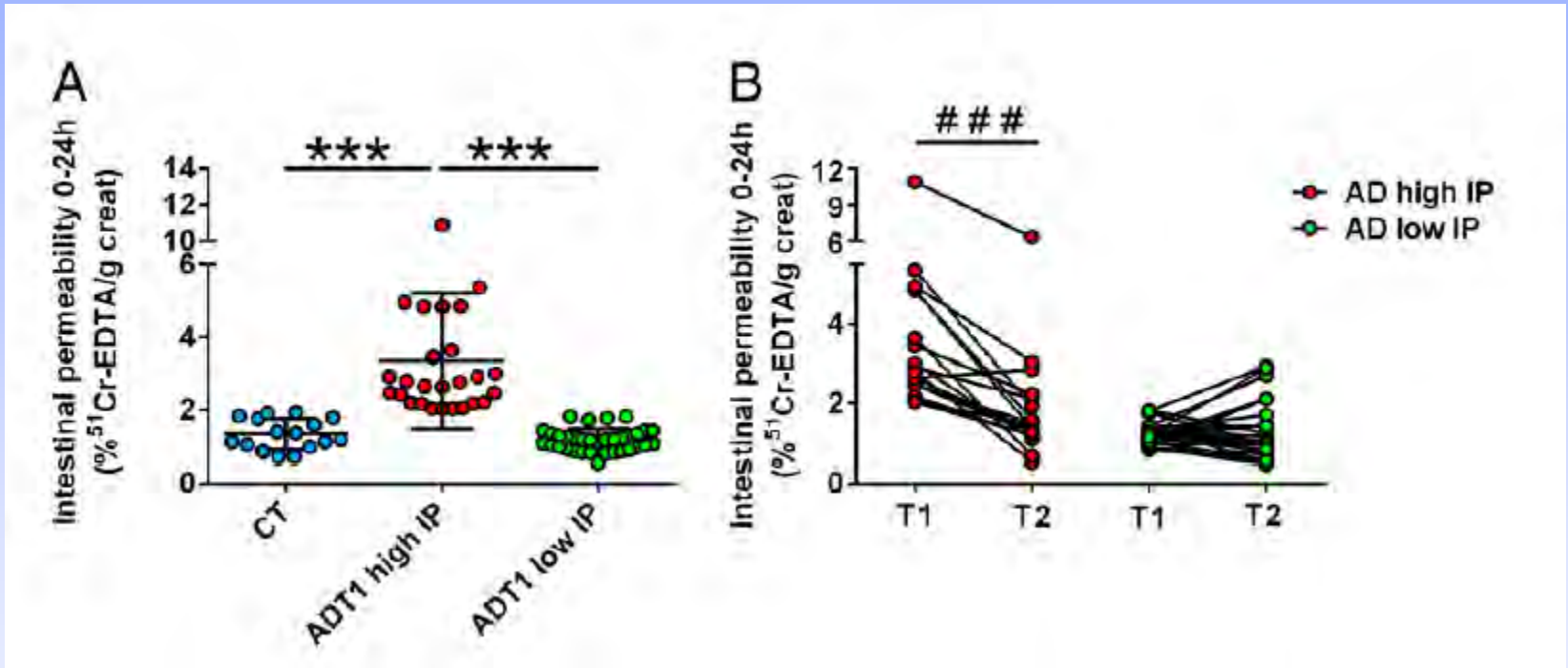
Table 3 Incidence rate ratios (IRR) and 95% confidence intervals of hepatocellular carcinoma according to categories of and per 1 unit increase in serum anti-LPS and anti-flagellin immunoglobulin levels, EPIC study, 1992–2010

Biomarker	IRR (95% CI)					OR per ↑1 unit
	Q1	Q2	Q3	Q4	P_{trend}	
Anti-LPS IgG + IgA, *n* case/control	20/35	25/34	35/35	59/35		
Matching factors[a]	Ref.	1.34 (0.61–2.98)	2.74 (1.13–6.65)	11.17 (3.46–36.00)	<0.0001	2.19 (1.59–3.03)
Multivariable[b]	Ref.	1.64 (0.56–4.83)	2.52 (0.76–8.39)	17.16 (3.52–83.50)	0.001	2.58 (1.65–4.03)
+ dietary factors[c]	Ref.	1.65 (0.54–5.04)	2.67 (0.77–9.31)	20.06 (3.88–103.0)	0.001	2.68 (1.69–4.23)
+ Fischer's ratio[d]	Ref.	2.52 (0.70–9.08)	2.17 (0.55–8.63)	13.65 (1.91–97.80)	0.017	2.05 (1.25–3.36)
Anti-Flagellin IgG + IgA, *n* case/control	22/34	25/36	37/35	55/34		
Matching factors[a]	Ref.	1.09 (0.5–2.38)	2.35 (1.03–5.37)	7.11 (2.46–20.55)	<0.0001	2.18 (1.56–3.06)
Multivariable[b]	Ref.	1.05 (0.37–2.93)	2.87 (1.00–8.20)	7.78 (2.19–27.57)	0.001	2.31 (1.51–3.54)
+ dietary factors[c]	Ref.	1.21 (0.40–3.59)	3.07 (1.05–9.01)	6.72 (1.88–24.02)	0.003	2.25 (1.47–3.47)
+ Fischer's ratio[d]	Ref.	1.52 (0.43–5.37)	4.37 (1.21–15.84)	3.59 (0.79–16.35)	0.025	1.80 (1.12–2.90)
Anti-LPS IgG + Anti-Flagellin IgG, *n* case/control	24/34	29/36	40/34	46/35		
Matching factors[a]	Ref.	1.23 (0.58–2.63)	2.11 (0.99–4.52)	4.08 (1.43–11.64)	0.006	2.02 (1.43–2.85)
Multivariable[b]	Ref.	1.40 (0.53–3.68)	2.92 (1.06–8.06)	5.80 (1.46–23.02)	0.007	2.47 (1.56–3.91)
+ dietary factors[c]	Ref.	1.43 (0.52–3.92)	3.45 (1.18–10.07)	5.37 (1.31–22.10)	0.007	2.57 (1.60–4.12)
+ Fischer's ratio[d]	Ref.	1.18 (0.39–3.60)	3.89 (1.12–13.58)	2.71 (0.42–17.29)	0.056	1.97 (1.15–3.36)
Anti-LPS IgA + Anti-Flagellin IgA, *n* case/control	18/35	27/34	27/35	67/35		
Matching factors[a]	Ref.	2.16 (0.82–5.72)	2.23 (0.85–5.87)	8.47 (3.01–23.86)	<0.0001	1.83 (1.43–2.36)
Multivariable[b]	Ref.	4.00 (0.96–16.63)	4.91 (1.15–20.9)	14.22 (3.02–66.90)	0.001	1.99 (1.39–2.86)
+ dietary factors[c]	Ref.	5.34 (1.21–23.68)	4.73 (1.06–21.16)	14.97 (3.04–73.50)	0.001	1.98 (1.37–2.86)
+ Fischer's ratio[d]	Ref.	2.65 (0.55–12.84)	4.49 (0.94–21.6)	8.40 (1.64–43.12)	0.009	1.65 (1.11–2.45)
Anti-LPS IgG + IgA + Anti-Flagellin IgG + IgA, *n* case/control	23/34	22/35	37/35	57/35		
Matching factors[a]	Ref.	0.97 (0.46–2.08)	2.25 (1.03–4.91)	8.72 (2.78–27.29)	<.00001	1.57 (1.31–1.88)
Multivariable[b]	Ref.	1.54 (0.59–4.02)	2.78 (0.94–8.21)	14.01 (2.99–65.60)	0.001	1.72 (1.34–2.21)
+ dietary factors[c]	Ref.	1.71 (0.63–4.68)	2.78 (0.92–8.35)	13.31 (2.78–63.70)	0.002	1.71 (1.33–2.21)
+ Fischer's ratio[d]	Ref.	1.75 (0.58–5.27)	2.19 (0.63–7.66)	11.76 (1.70–81.40)	0.021	1.48 (1.13–1.94)

Association of gut-derived products and HCC

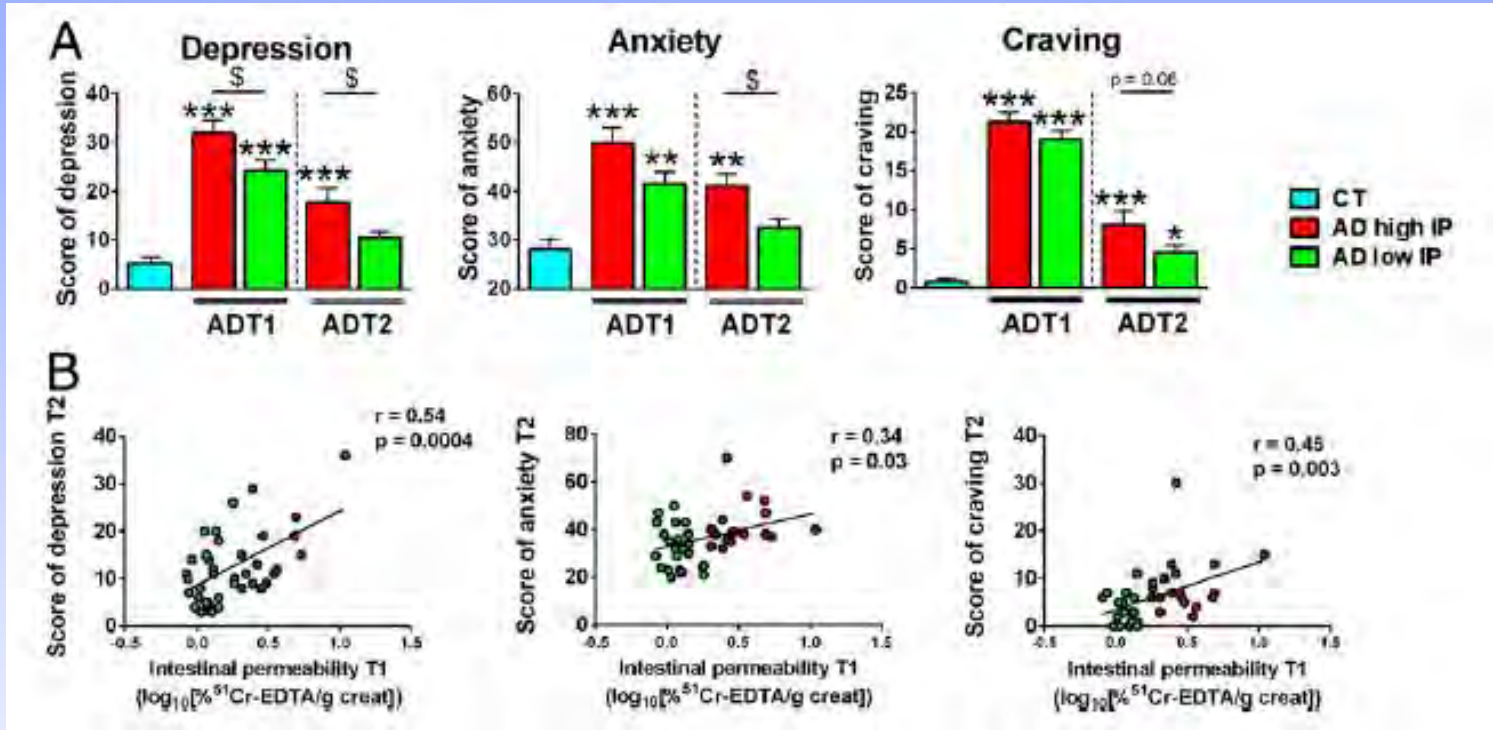
Fedirko *BMC Medicine* 2017

Dépendance à l'alcool et perméabilité intestinale



Leclerq *Proc Natl Acad Sci USA* 2014

Dépendance à l'alcool et perméabilité intestinale

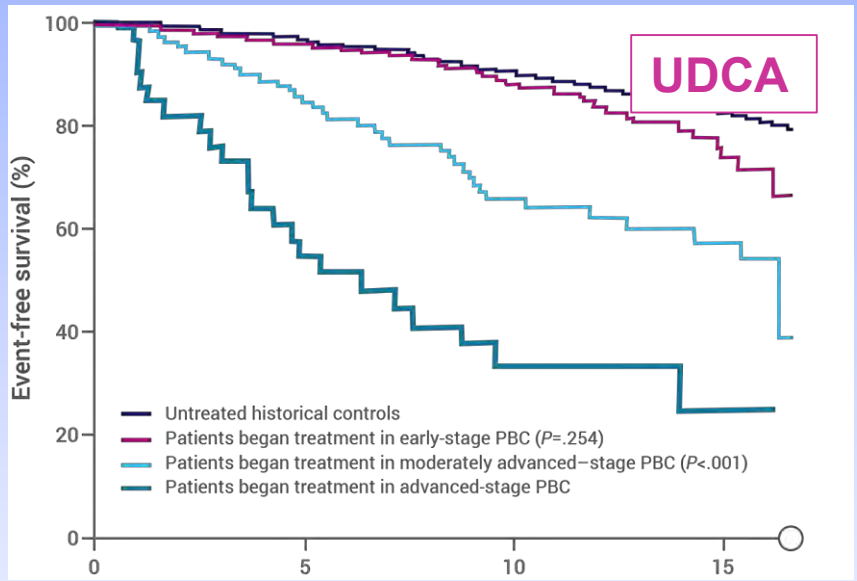


→ **Effet du microbiote et de la perméabilité sur la dépendance ?**

Leclerq *Proc Natl Acad Sci USA* 2014

Postbiotiques - UDCA

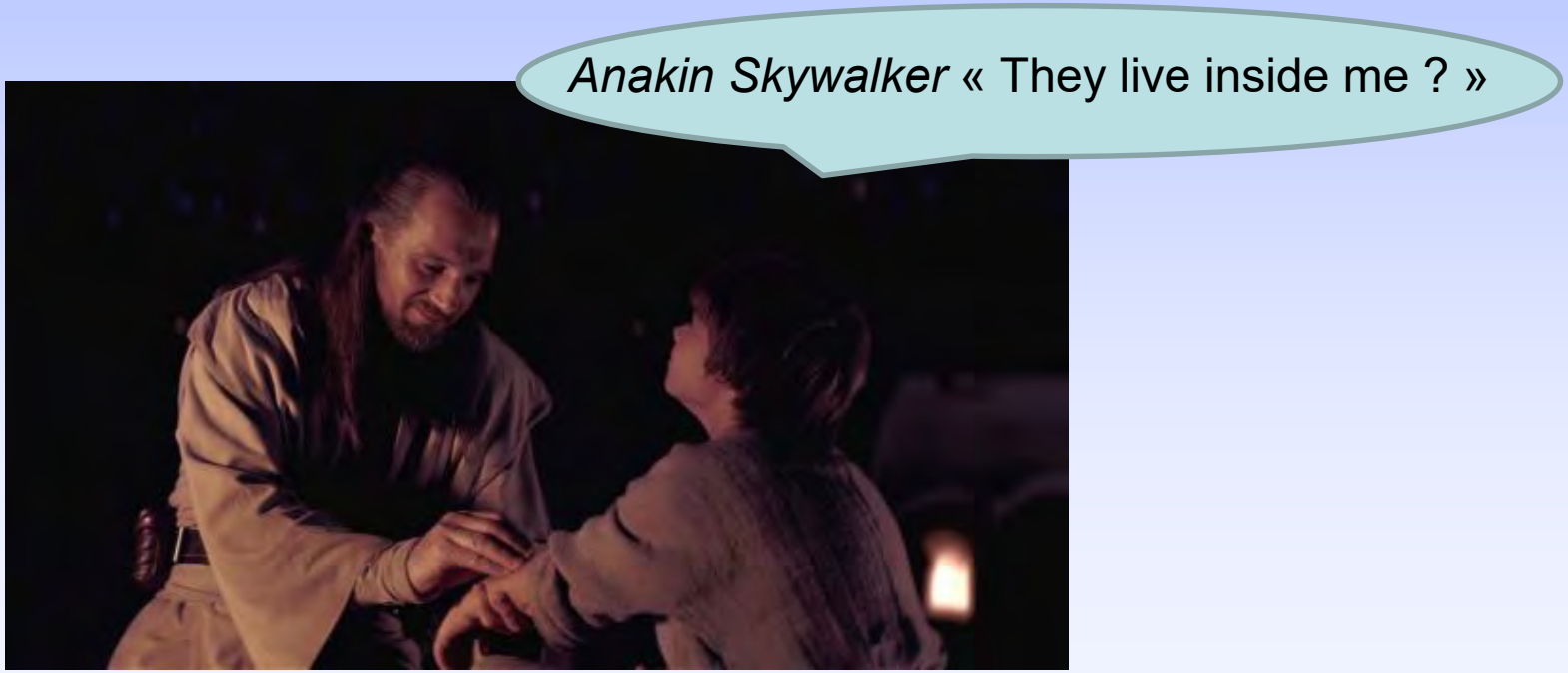
Empereur Tai Zong
Dynastie Tang – 627-649



Can you become Jedi ?

From Louis Pasteur to Georges Lucas

- **Midi-chlorians**
  - Intelligent microscopic life forms
  - Are living symbiotically inside our cells

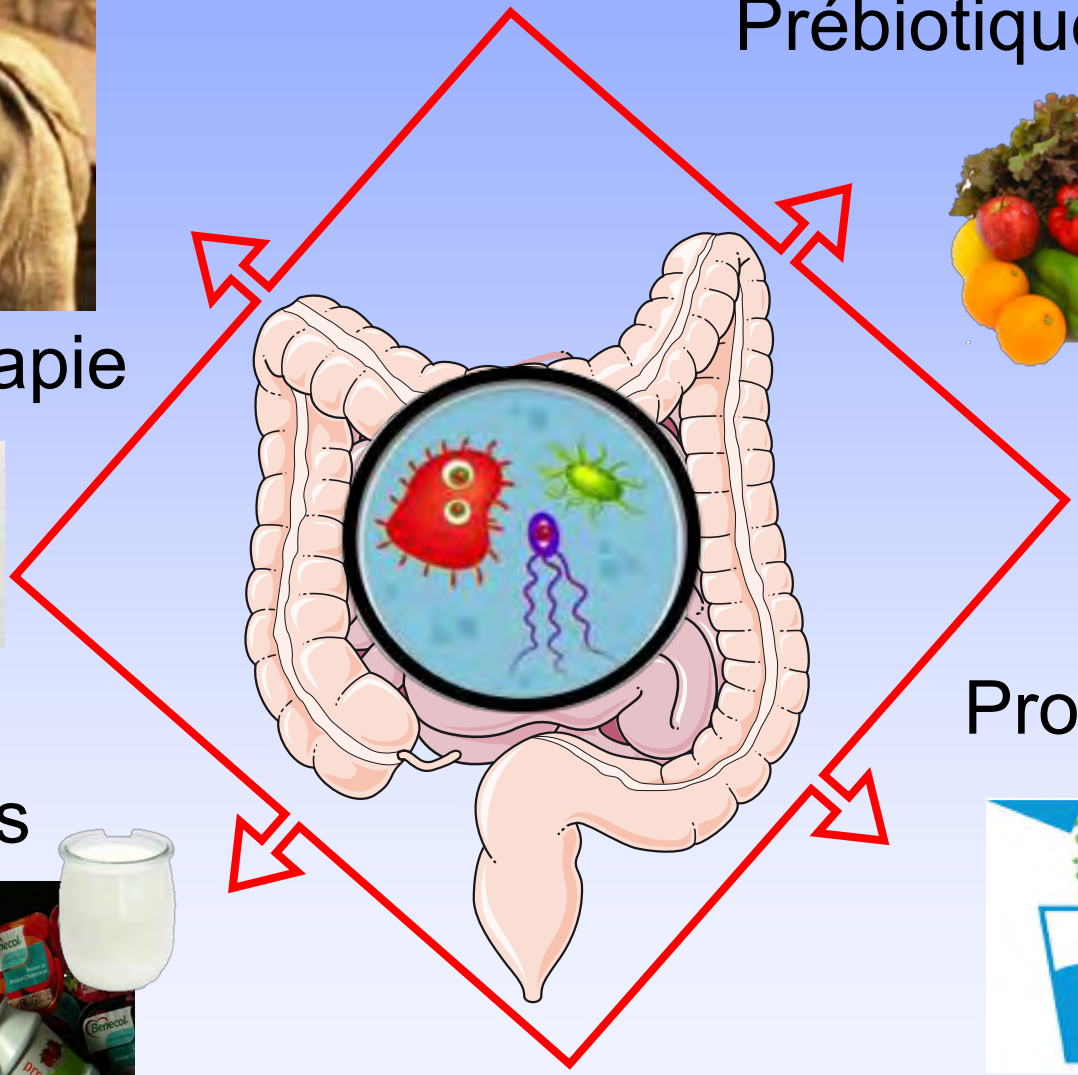


Georges Lucas. *Star Wars Episode I: The Phantom Menace*

Que la force soit avec vous

Prébiotiques

Fécalothérapie



Probiotiques

Symbiotiques

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Antoine-Béclère Bicêtre Paul-Brousse

INSERM UMR-S 996

Inserm

LabEx LERMIT

Intestinal microbiota, macrophages and liver inflammation

Hospital Antoine-Béclère
Hepato-Gastroenterology and Nutrition

Gabriel Perlemuter
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Amandine Lebrun
Axel Balian
Sylvie Naveau

Anne-Marie Cassard
Gabriel Perlemuter
Laura Wrzosek
Dragos Ciocan
Vanessa LeMoal
Gladys Ferrere
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Virginie Puchois
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