Importance of bowel barrier function in IBD

Jean-Frederic Colombel, MD
Director of The Susan and Leonard Feinstein IBD Clinical Center
and The Leona M & Harry B Helmsley Charitable Trust IBD Center

Icahn School of Medicine, Mount Sinai Hospital
New York

Mount
Sinai

Conflicts of interest

Jean-Frederic Colombel has served as consultant, advisory board member or speaker for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Immunic, Janssen and Janssen, Lilly, Medimmune, Merck & Co., Pfizer, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag, Theravance Biopharma.

Speaker for

AbbVie, Ferring, Pfizer, Takeda, Shire

Speaker's bureau for

Amgen

Stock options:

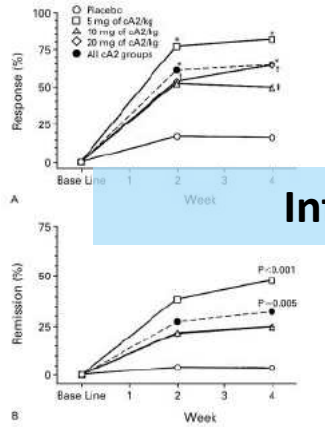
Intestinal Biotech Development, Genfit

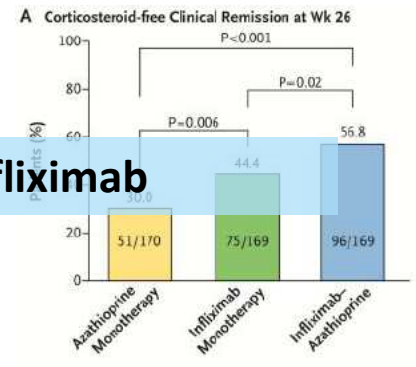
Research Grants:

AbbVie, Takeda, Janssen and Janssen

The care of IBD: what did we achieve?

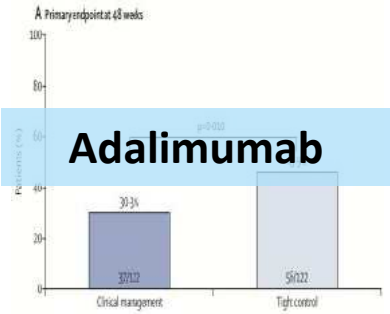
Progress over last two decades





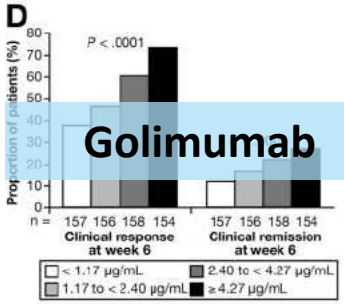
Infliximab

SONIC
Colombel et al, NEJM 2010



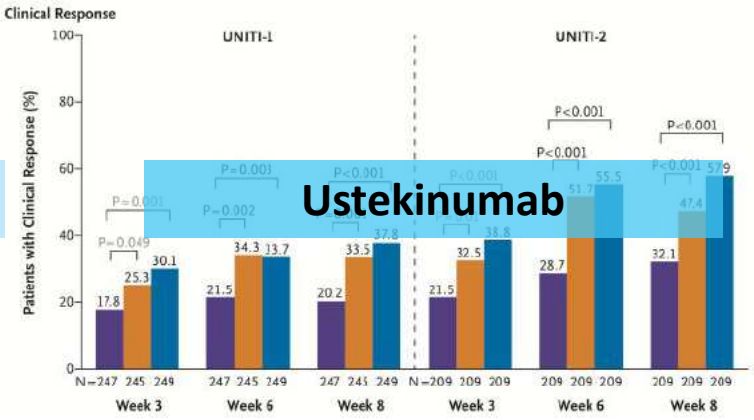
Adalimumab

CALM
Colombel et al, Lancet 2018



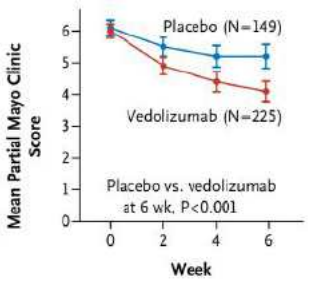
Golimumab

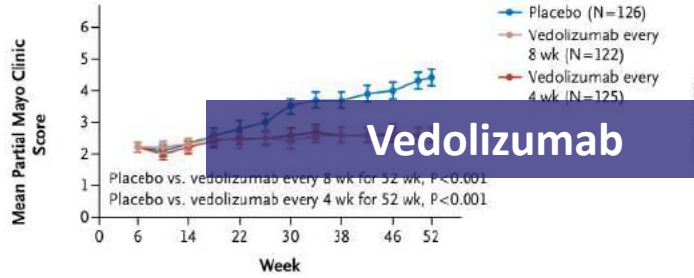
PURSUIT
Sandborn et al, Gastro 2014



Ustekinumab

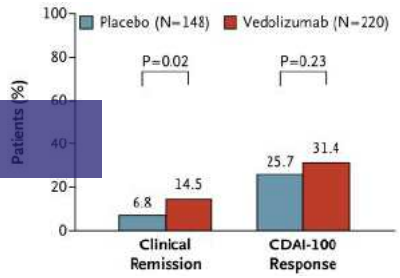
UNITI
Feagan et al, NEJM 2016



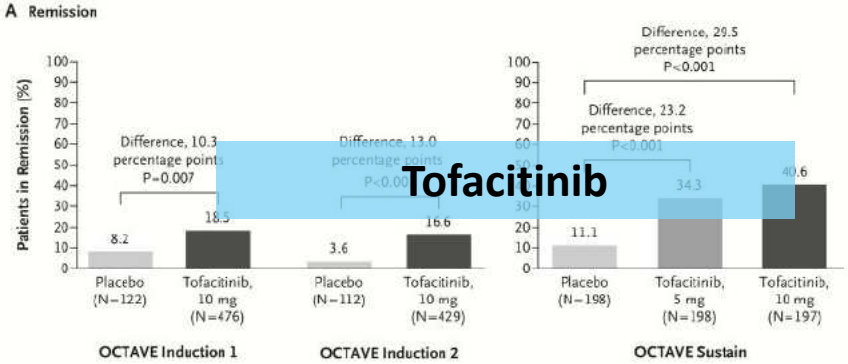


Vedolizumab

GEMINI
Feagan et al, NEJM 2013



GEMINI
Sandborn et al, NEJM 2013



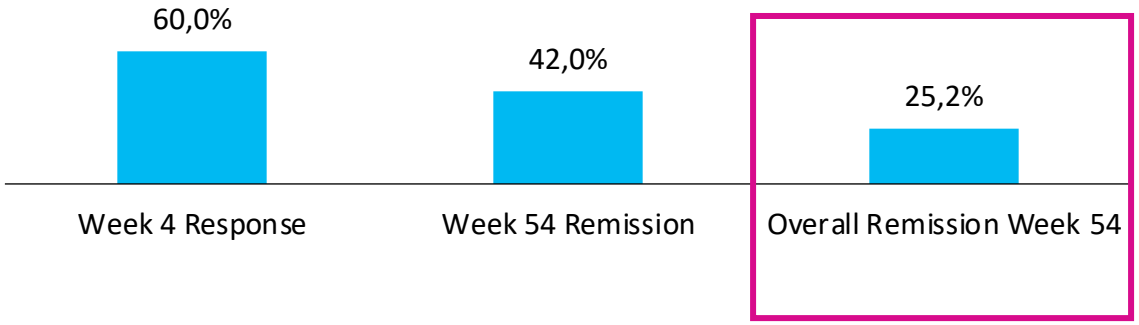
Tofacitinib

OCTAVE
Sandborn et al, NEJM 2017

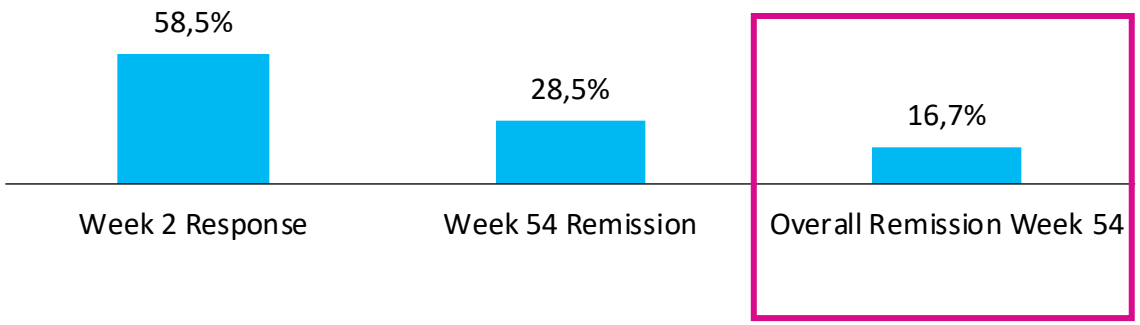
We are plateauing

Pivotal Crohn's Disease Trials: Anti-TNF Naïve Population with anchoring

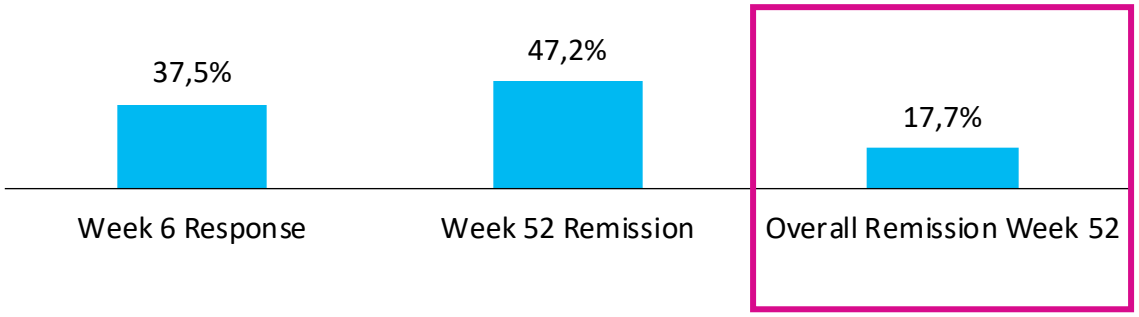
CHARM – Adalimumab



ACCENT I – Infliximab

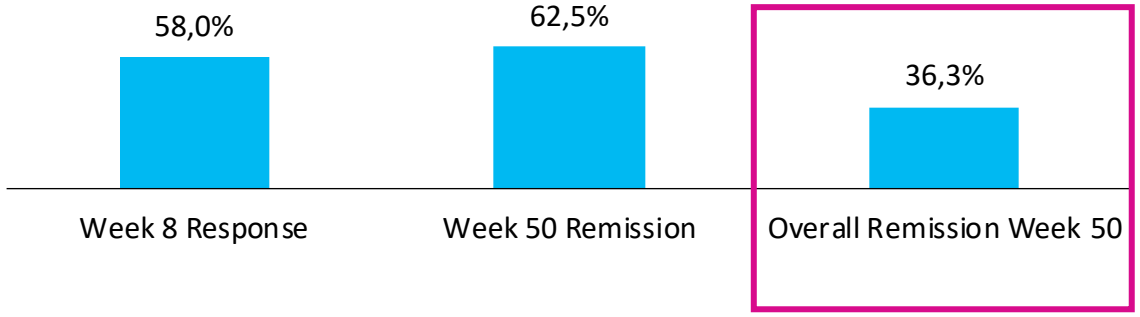


GEMINI II – Vedolizumab



- VDZ Q4W or Q8W for maint.

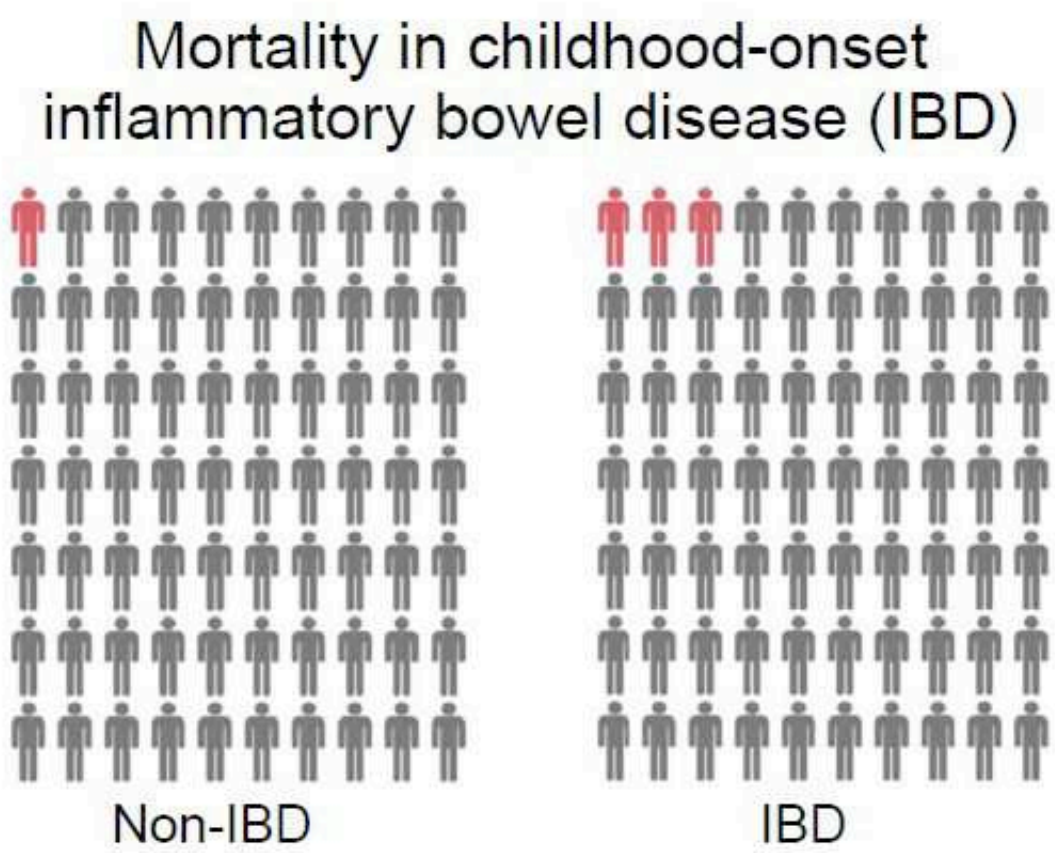
UNITI-2 – Ustekinumab*

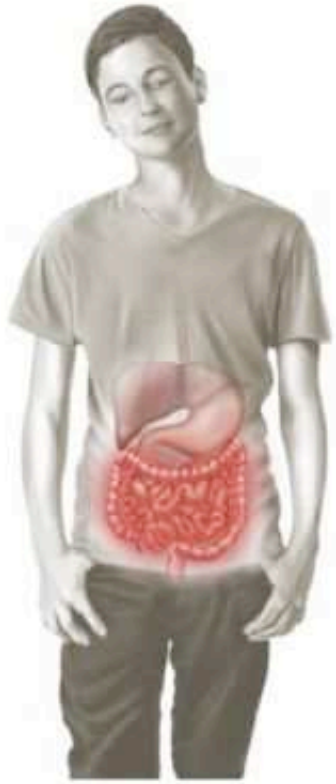


- 130 mg with 47% and 6 mg/kg with 58% response rate
- 50 weeks 90 mg/Q12 at 56.9% and Q8 at 62.5%

Ungaro R et al. DDW 2019

IBD childhood mortality: 2019





Deaths in childhood-onset IBD and matched general population reference individuals during 20 years of follow-up

Gastroenterology

Olen O et al. Gastroenterology 2019

Risk of lymphoma in IBD

Nation wide French cohort of 189289 patients

Table 3. HRs Comparing the Risk of Lymphoma in Patients Exposed to Thiopurine Monotherapy, Anti-TNF Monotherapy, and Combination Therapy vs Unexposed Patients

Lymphoma Type	Exposed to Thiopurine Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Anti-TNF Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Combination Therapy vs Unexposed to Thiopurines or Anti-TNF Agents	
	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
All Patients						
All lymphoma	2.06 (1.58-2.70)	2.60 (1.96-3.44)	1.57 (1.08-2.28)	2.41 (1.60-3.64)	3.60 (2.10-6.19)	6.11 (3.46-10.8)
Hodgkin lymphoma	2.78 (1.45-5.33)	2.83 (1.37-5.84)	2.21 (0.92-5.35)	2.23 (0.81-6.13)	11.4 (4.76-27.2)	12.1 (4.46-33.1)
Non-Hodgkin lymphoma	1.95 (1.45-2.62)	2.57 (1.90-3.49)	1.47 (0.97-2.22)	2.48 (1.58-3.89)	2.38 (1.17-4.84)	4.48 (2.15-9.34)
Patients With Incident IBD						
All lymphoma	1.58 (0.84-3.00)	2.35 (1.16-4.75)	0.98 (0.39-2.48)	1.49 (0.54-4.12)	3.14 (1.13-8.71)	5.90 (1.79-19.4)

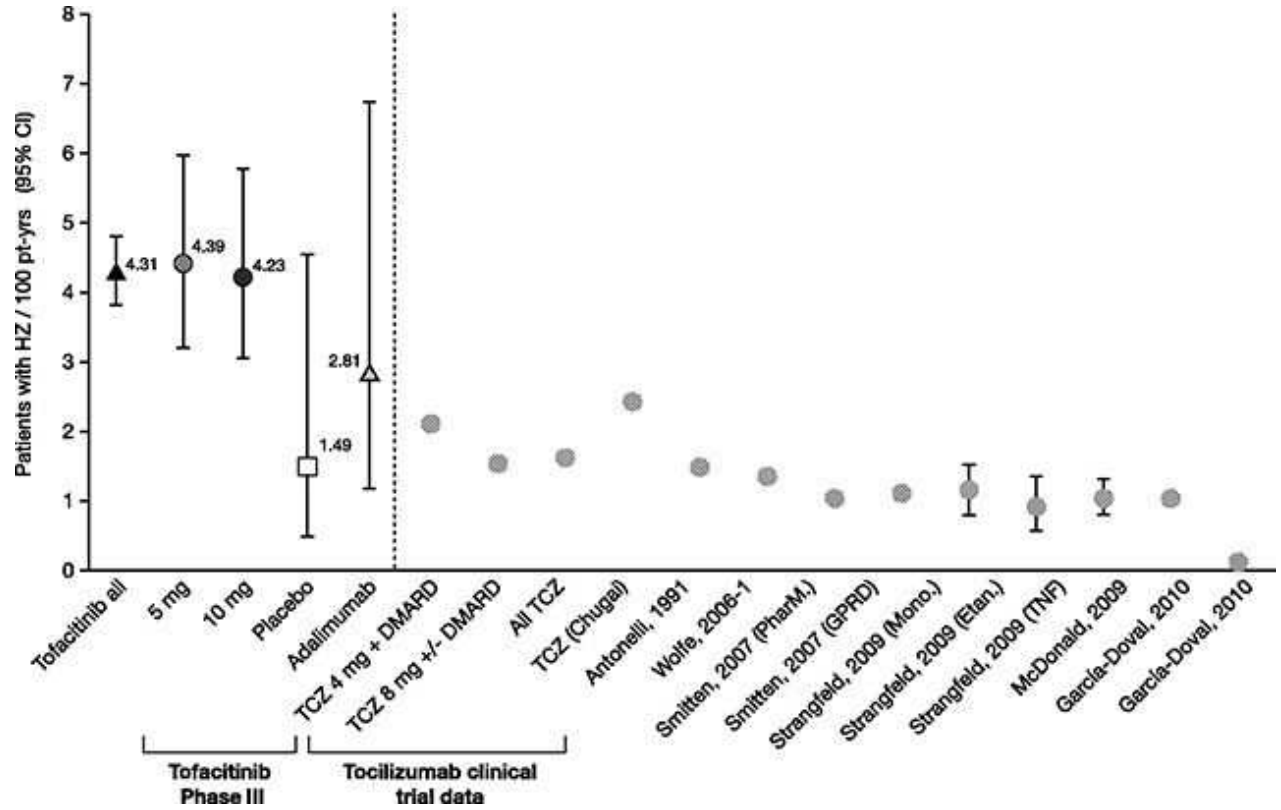
Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

[a] Multivariable Cox model adjusted for baseline characteristics including sex, age, affiliation to Complementary Universal Health Insurance, IBD diagnosis and duration, exposure to methotrexate and aminosalicylates, comorbidities and time-dependent covariates including exposure to corticosteroids, and IBD-related hospitalizations and surgical procedures.

Lemaitre M et al. JAMA 2017

Main Risk of Novel JAK-Inhibitors

4-in-100 Treatment Years Zoster Reactivation



Reference: Winthrop et al. Herpes Zoster and Tofacitinib: Clinical Outcomes and the Risk of Concomitant Therapy. *Arthritis Rheumatol*. 2017;69(10):1960-1968.

Crude incidence rates of herpes zoster (HZ) in the Tofacitinib Rheumatoid Arthritis (RA) Development Program (left of broken line) and in published studies of patients with RA treated with nonbiologic and biologic disease-modifying agents (right of broken line)

Impaired Response to Vaccines During IBD Therapy with Immunosuppressants

Table 3. Pneumococcal Vaccine (PPSV23) in IBD

	Controls[a]	Azathioprine	Infliximab	Combined[b]
Total population (N)	35	19	26	16
Dose/duration before baseline	N/A	2-2.5 mg/kg for at least 24 wk	5 mg/kg for at least 16 wk	Same
Response rate (*P*-value)	88.6% (N/A)	78.9% (*P* = .43)	57.7% (*P* = .008)	62.5% (*P* = .02)
Average antibody titer vs. baseline	5.71-fold increase	3.25-fold increase	2.69-fold increase	2.84-fold increase

[a] Control: anti-inflammatory, but not immunosuppressant therapy (e.g., mesalamine).
[b] Combined: azathioprine plus infliximab, same doses.
N/A: not applicable; IBD: inflammatory bowel disease (Crohn's disease and ulcerative colitis).
Source: Reference 7.

Reference: Gupta et al. Incidence and Risk Factors for Herpes Zoster Among Patients With Inflammatory Bowel Disease. Clinical Gastroenterology and Hepatology, Volume 4, Issue 12, 1483 - 1490

Update on Impact of COVID-19 in Inflammatory Bowel Disease Patients

Erica Brenner, MD (University of North Carolina at Chapel Hill)
Ryan Ungaro, MD MS (Icahn School of Medicine at Mount Sinai, New York)
Jean-Frederic Colombel, MD (Icahn School of Medicine at Mount Sinai, New York)
Michael Kappelman MD, MPH (University of North Carolina at Chapel Hill)

Brenner E et al. Gastroenterology in press.

Multivariable Analysis

Variable (Referent group)[a]	ICU/Vent/Death Odds Ratio (95% CI) (n = 517)	p	Hospitalization or Death Odds Ratio (95% CI) (n =517)	p	Death Odds Ratio (95% CI) (n = 513)	p
Age	1.04 (1.01-1.06)	0.002	1.03 (1.01-1.04)	<0.001	1.07 (1.03-1.11)	<0.001
Male (Female[b])	1.20 (0.55-2.60)	0.65	1.38 (0.89-2.15)	0.15	2.78 (0.76-10.14)	0.12
Diagnosis						
Crohn's disease (ulcerative colitis/IBD unspecified)	0.76 (0.31-1.85)	0.54	0.84 (0.51-1.38)	0.49	1.64 (0.42-6.43)	0.48
Disease severity[c] (remission)						
Active disease	1.14 (0.49-2.66)	0.76	1.96 (1.23-3.11)	0.005	0.97 (0.26-3.62)	0.96
Systemic corticosteroid (none)	6.87 (2.30-20.51)	<0.001	6.46 (2.74-15.23)	<0.001	11.62 (2.09-64.74)	0.005
TNF antagonist (none)	0.90 (0.37-2.17)	0.81	0.60 (0.38-0.96)	0.03	0.99 (0.23-4.23)	0.99
Current smoker	0.55 (0.06-4.94)	0.59	2.38 (0.92-6.16)	0.07	1.47 (0.12-17.53)	0.76
BMI ≥ 30	2.00 (0.72-5.51)	0.18	1.18 (0.61-2.31)	0.63	1.58 (0.28-8.80)	0.60
Comorbidities (none)						
1	1.22 (0.45-3.26)	0.70	1.29 (0.76-2.20)	0.34	1.64 (0.35-7.67)	0.53
≥2	2.87 (1.05-7.85)	0.04	4.42 (2.16-9.06)	<0.001	2.51 (0.56-11.24)	0.23
5-ASA/sulfasalazine (none)	3.14 (1.28-7.71)	0.01	1.77 (1.00-3.12)	0.05	1.71 (0.46-6.38)	0.43

What gastroenterologists want!

Crohn's disease

- 10-40% of moderate-severe patients do not respond to any remission induction therapy
- 24–46% develop secondary loss of response within the first year after drug-induced remission or surgery
- ~10% stop maintenance treatment due to adverse drug reactions or tolerability issues

Physician ranked unmet needs in CD:

1. **Agents to maintain remission without immunosuppression**
2. An effective treatment for fistulizing disease
3. Predicting response to biologic therapy
4. An effective cost-saving nonbiologic
5. Better activity measures in clinical trials
6. Drugs targeted for the mild patient population

Ulcerative colitis

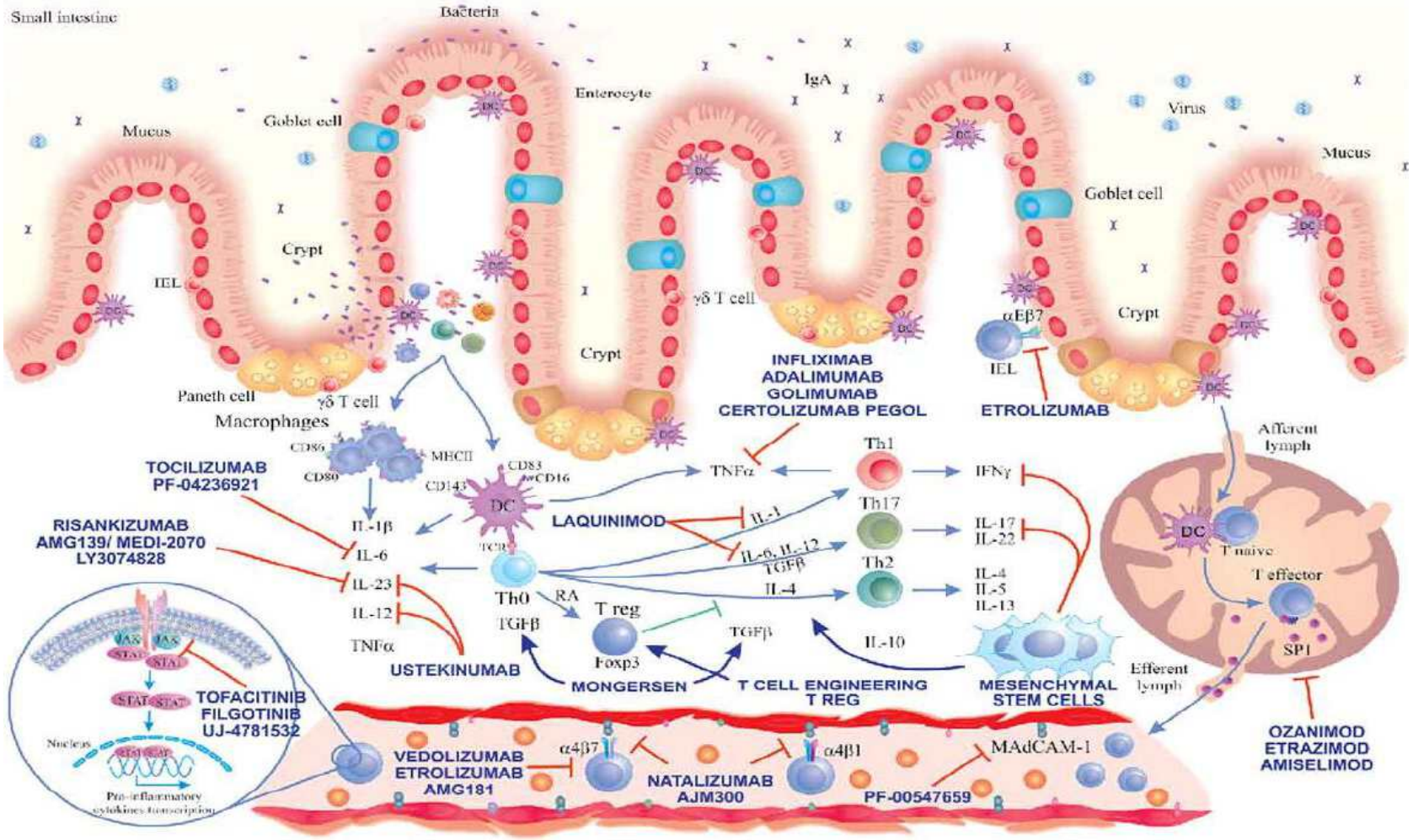
- ~30% patients are primary non-responders (PNR) to anti-TNF biologics
- ~15-30% lose response (LOR) over time or become intolerant to anti-TNFs
- PNR patients are less likely to respond to 2nd-line therapy as compared to patients with prior loss of response or intolerance

Physician ranked unmet needs in UC:

1. A well-tolerated treatment for inducing remission quickly
2. Effective treatments for refractory patients
3. **A non-steroid oral maintenance drug**
4. Disease-modifying drugs
5. An effective cost-saving nonbiologic
6. Simple blood tests that indicate disease activity

Reference: Datamonitor, Gastroenterologist survey 2016

The expanding IBD pipeline: most targeting immune system!



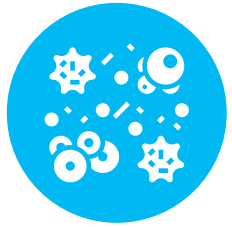
Need for new therapeutic options in IBD

That allow the long-term treatment of gastrointestinal diseases without impairing the immune system

---

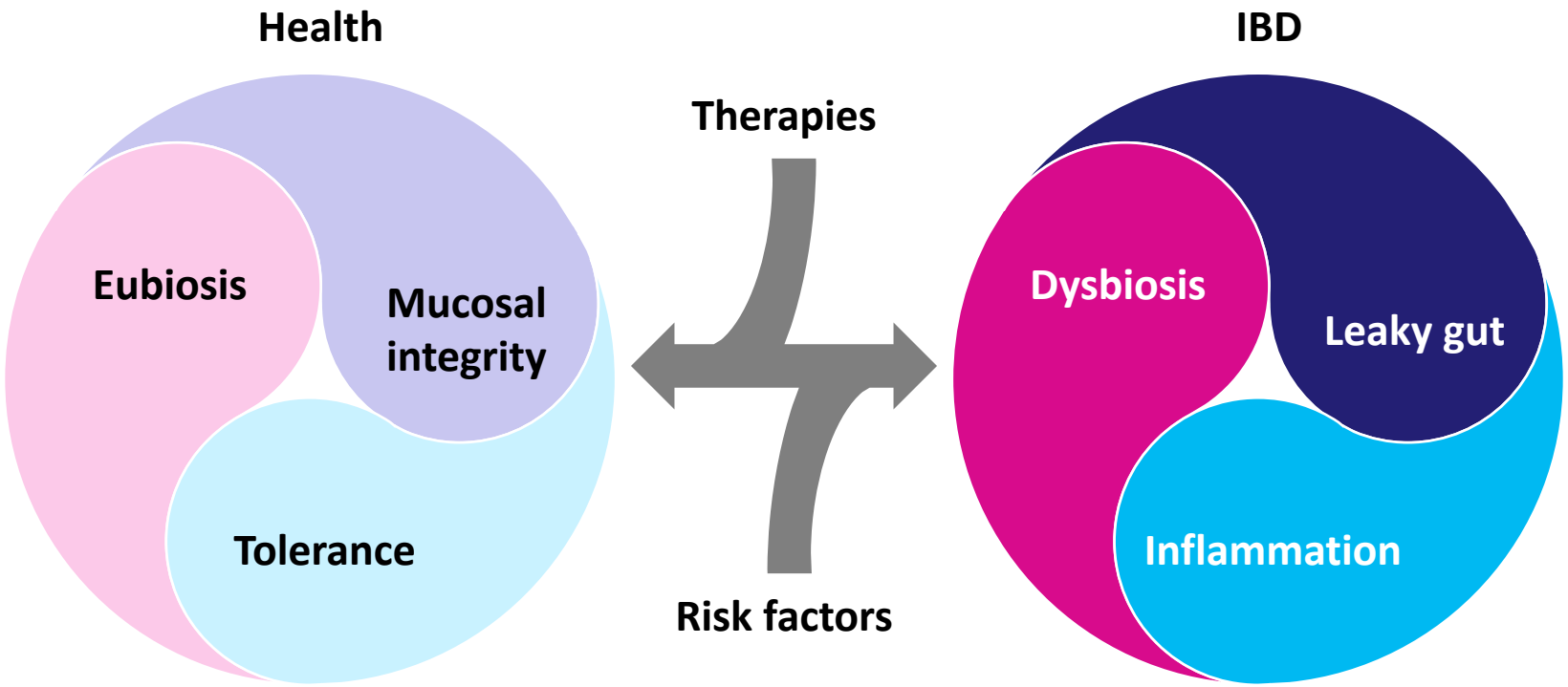
Concept of bowel permeability is central to many gastrointestinal diseases

---



Impaired bowel barrier function allows the microbiome to interact with the immune system

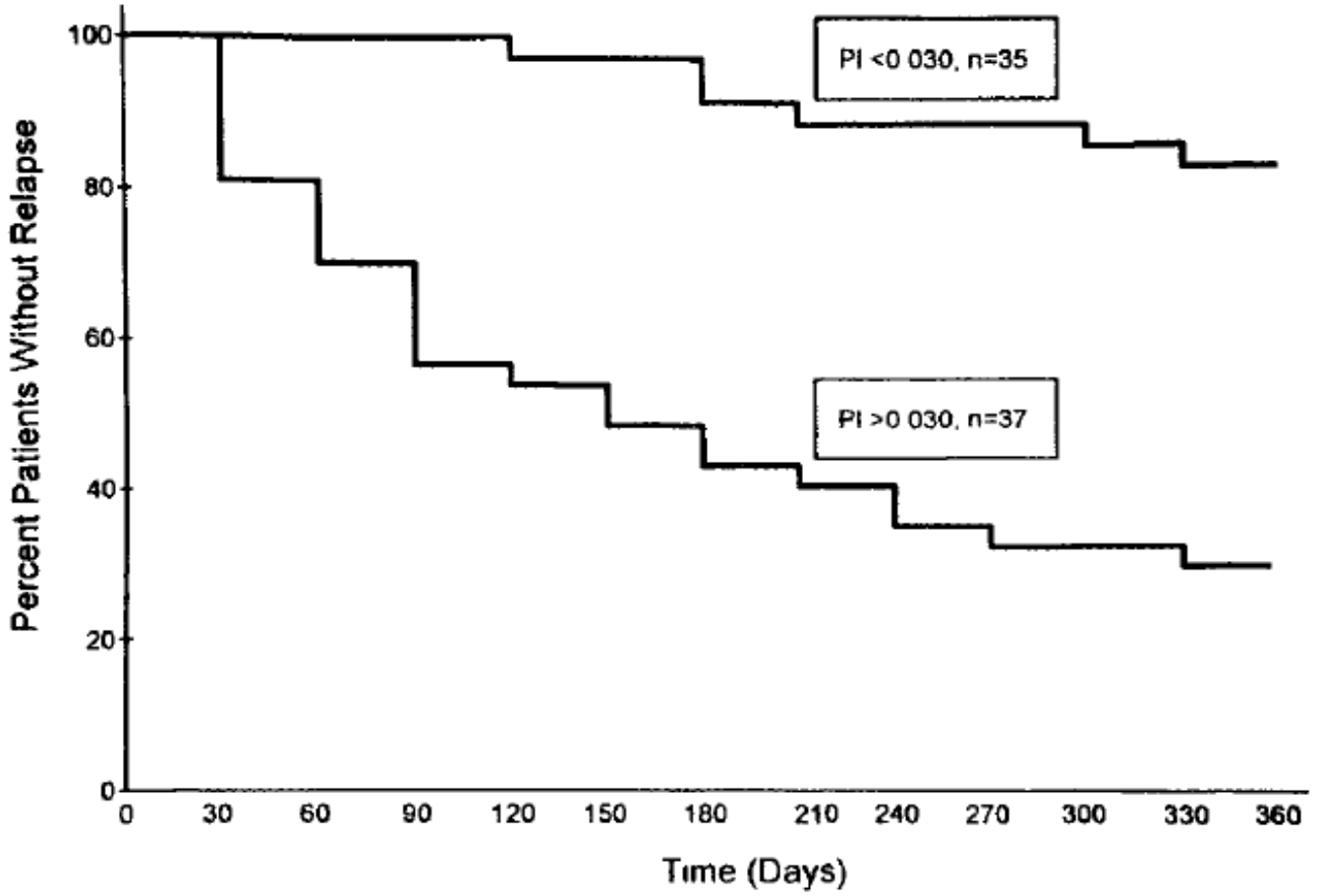
The tripartite pathophysiological circuit of IBD



The tripartite pathophysiological circuit of inflammatory bowel disease (IBD)

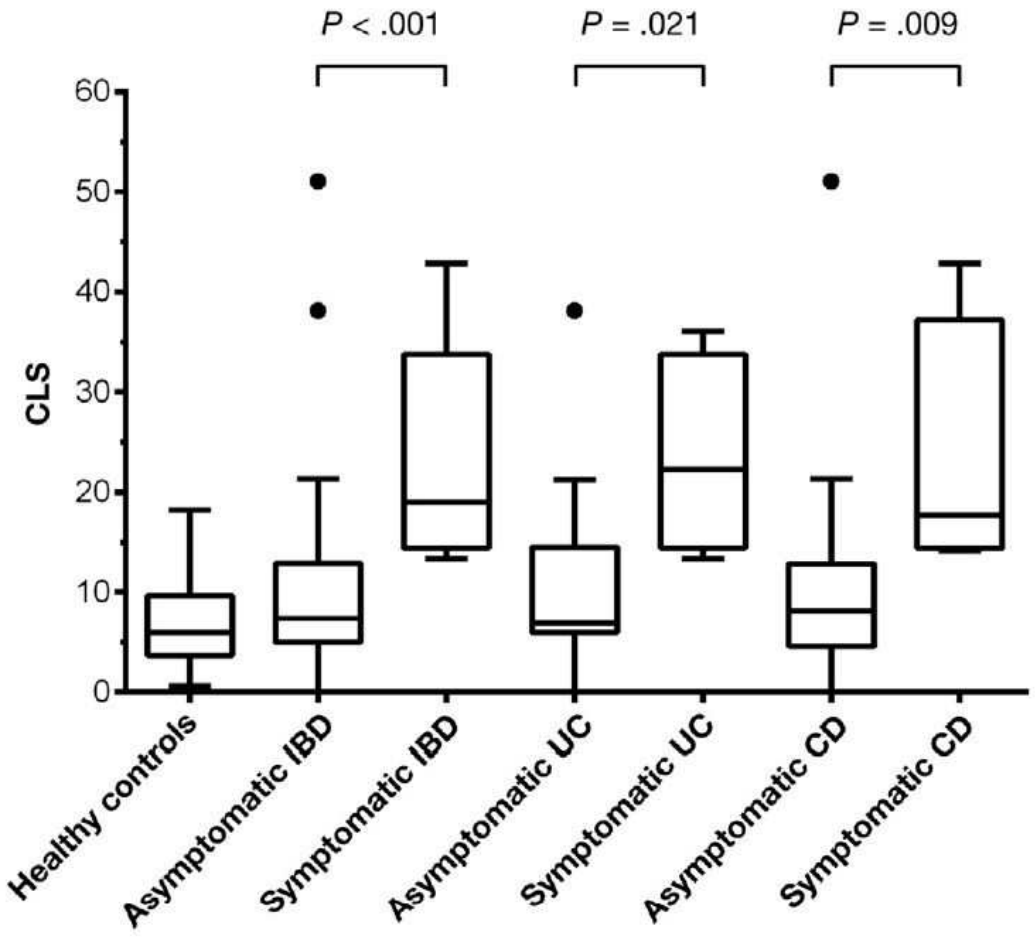
Dysfunction in each of these physiological components (dysbiosis, leaky gut, and inflammation) contributes in a mutually interdependent manner to IBD onset and exacerbation. (Vindigni et al. 2016)

Crohn's disease – patient with increased bowel permeability have higher probability for relapse



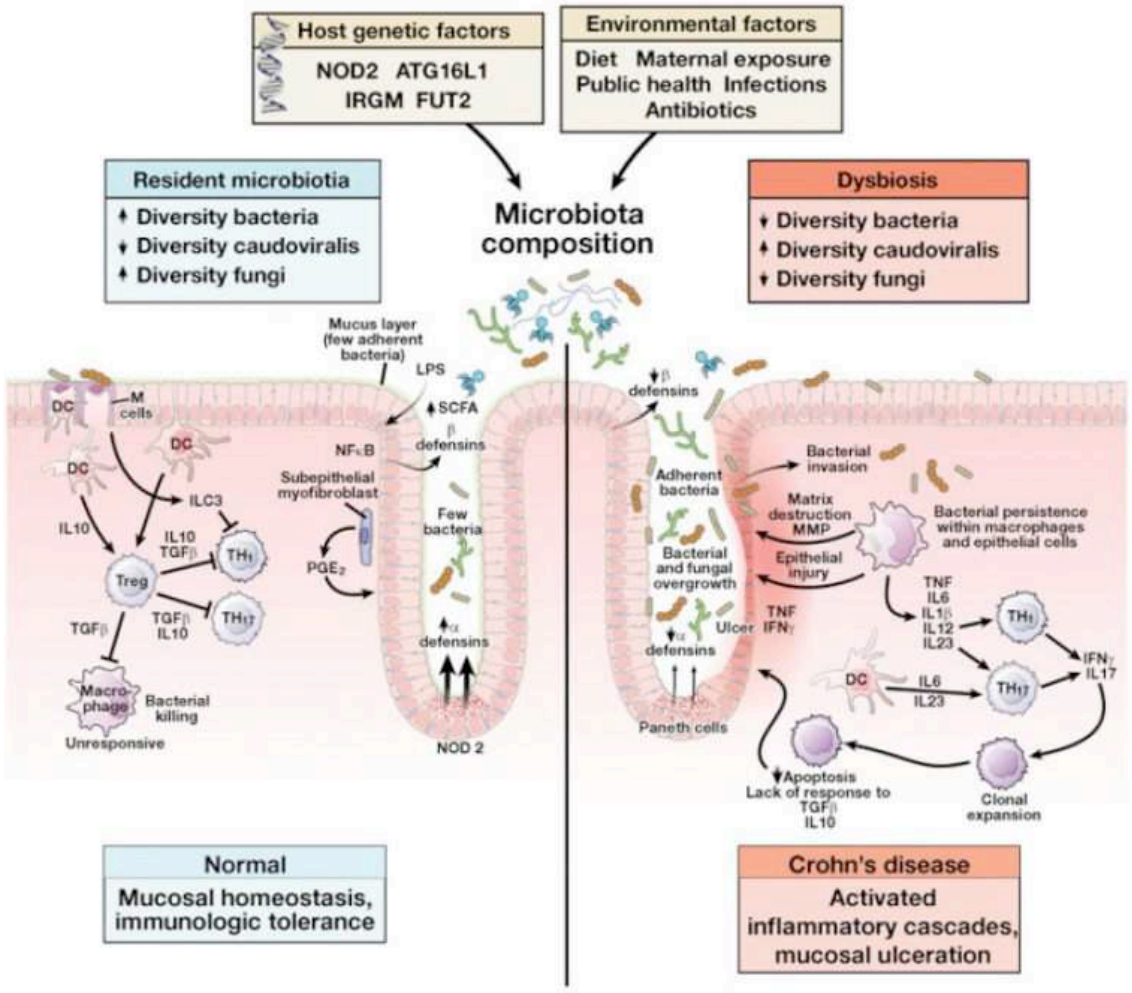
Wyatt et al. Lancet 1993

CD/UC– high bowel permeability correlates with symptoms



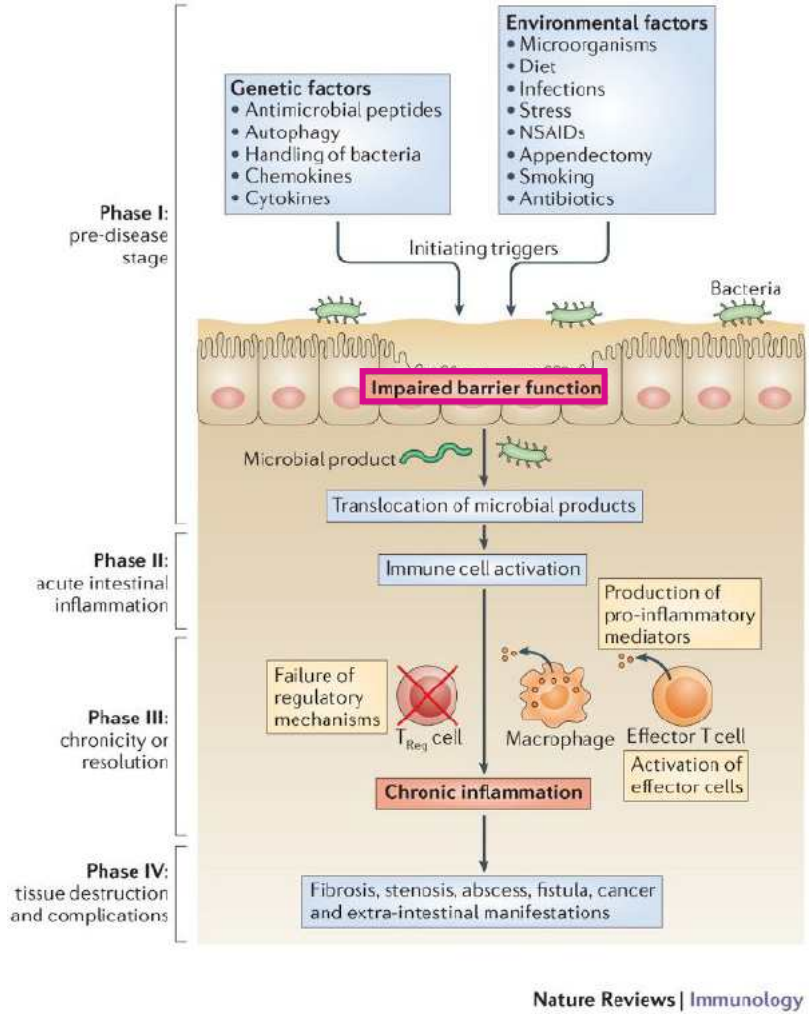
Chang et al. Gastroenterology 2017

Early events in IBD: dysbiosis, altered IP?



Sartor B et al. Gastroenterology 2017

Presumed Trigger for IBD: Bacterial penetration through weakened tight junctions causes immune overstimulation

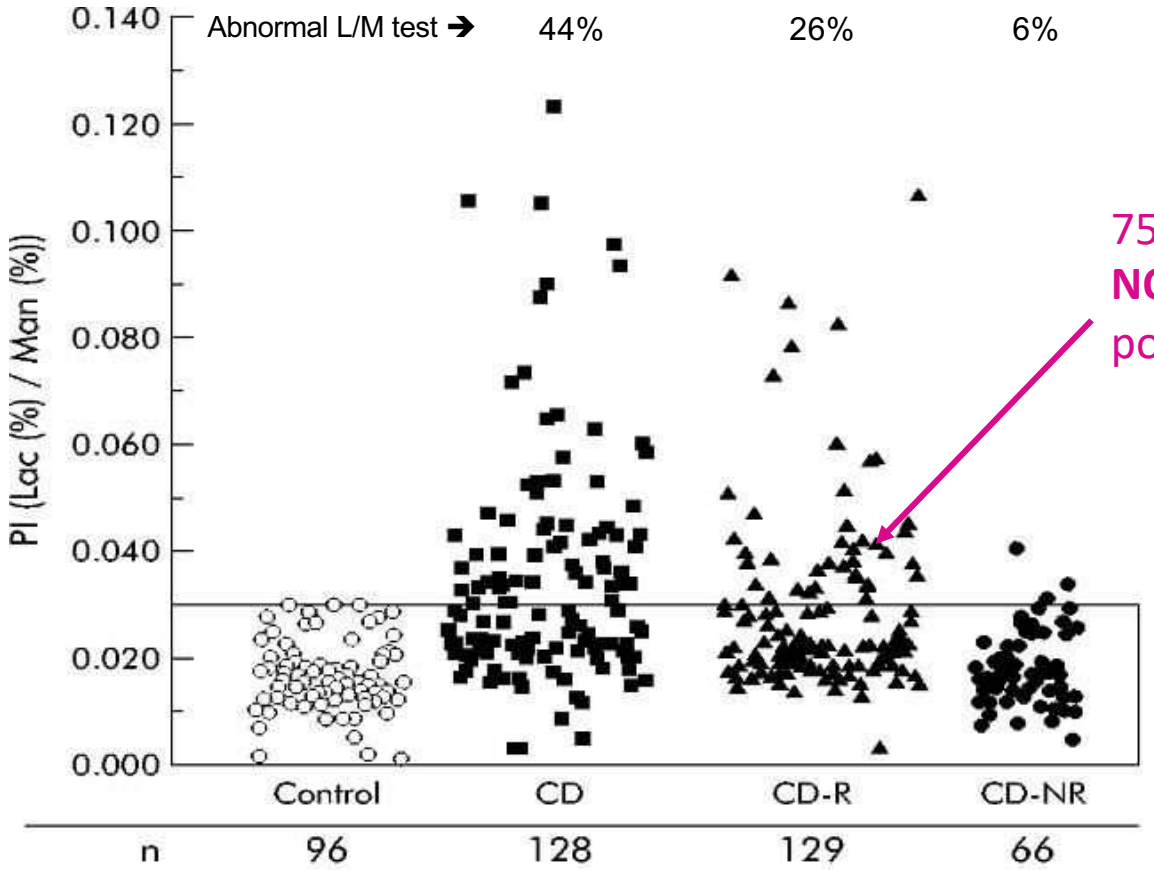


Reference: Neurath MF. Cytokines in inflammatory bowel disease. Nat Rev Immunol. 2014 May;14(5):329-42.

Enhanced *E. coli* LF82 Translocation through the Follicle-associated Epithelium in Crohn's Disease is Dependent on Long Polar Fimbriae and CEACAM6 expression, and Increases Paracellular Permeability

Åsa V. Keita,[a] Lina Yakymenko Alkaissi,[a] Elin B. Holm,[a] Stéphanie D. S. Heil,[a] Benoit Chassaing,[b] Arlette Darfeuille-Michaud,[c,†] Derek M. McKay,[d] Johan D. Söderholm[a,e]

First degree relatives IBD patients have increased intestinal permeability

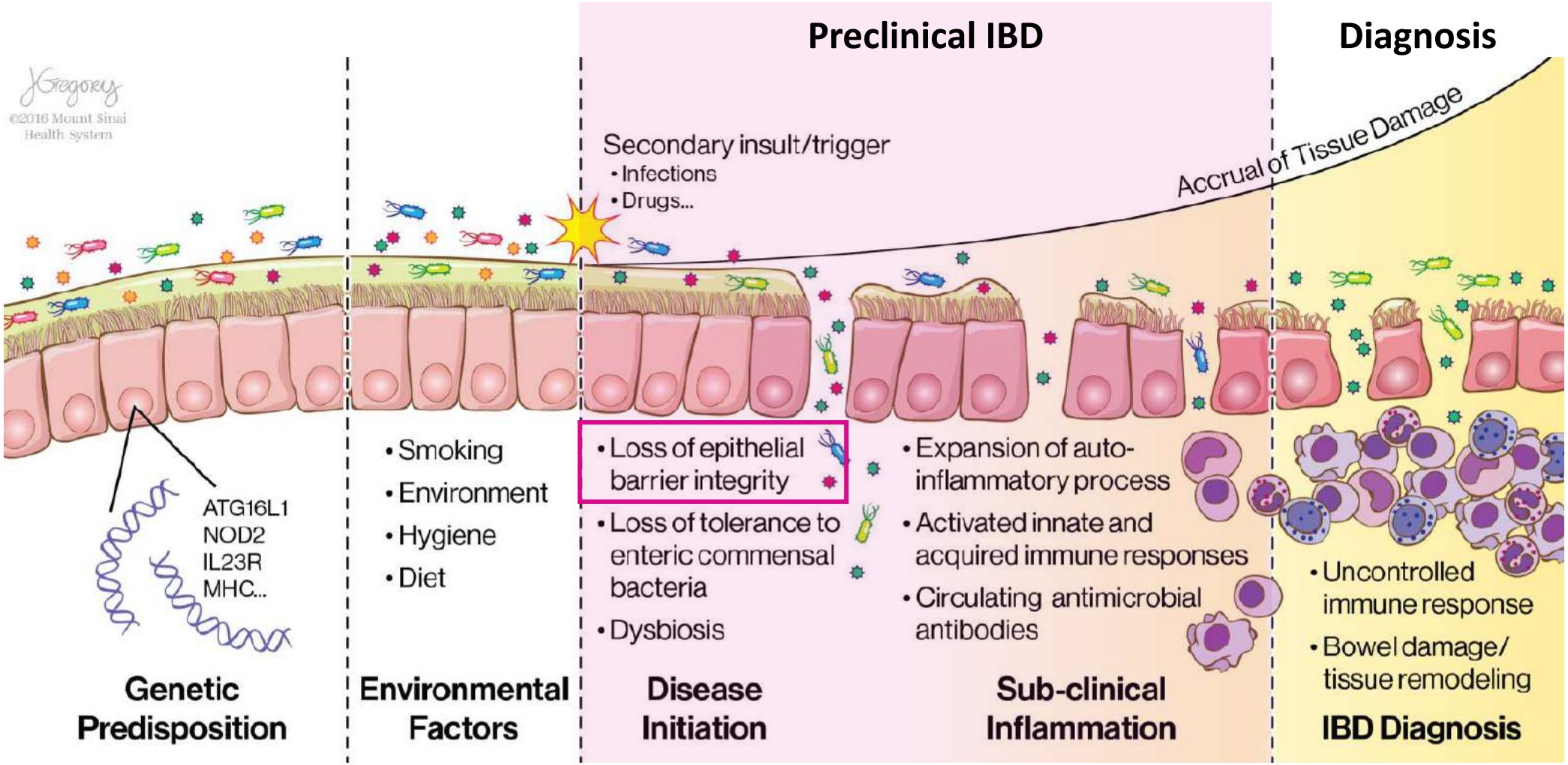


75% with **NOD-2** polymorfisms

CD - Crohn's disease (CD)
CDR - first degree relatives
CD-NR - non-blood relatives

Buhner S et al. Gut 2006;55:342-347

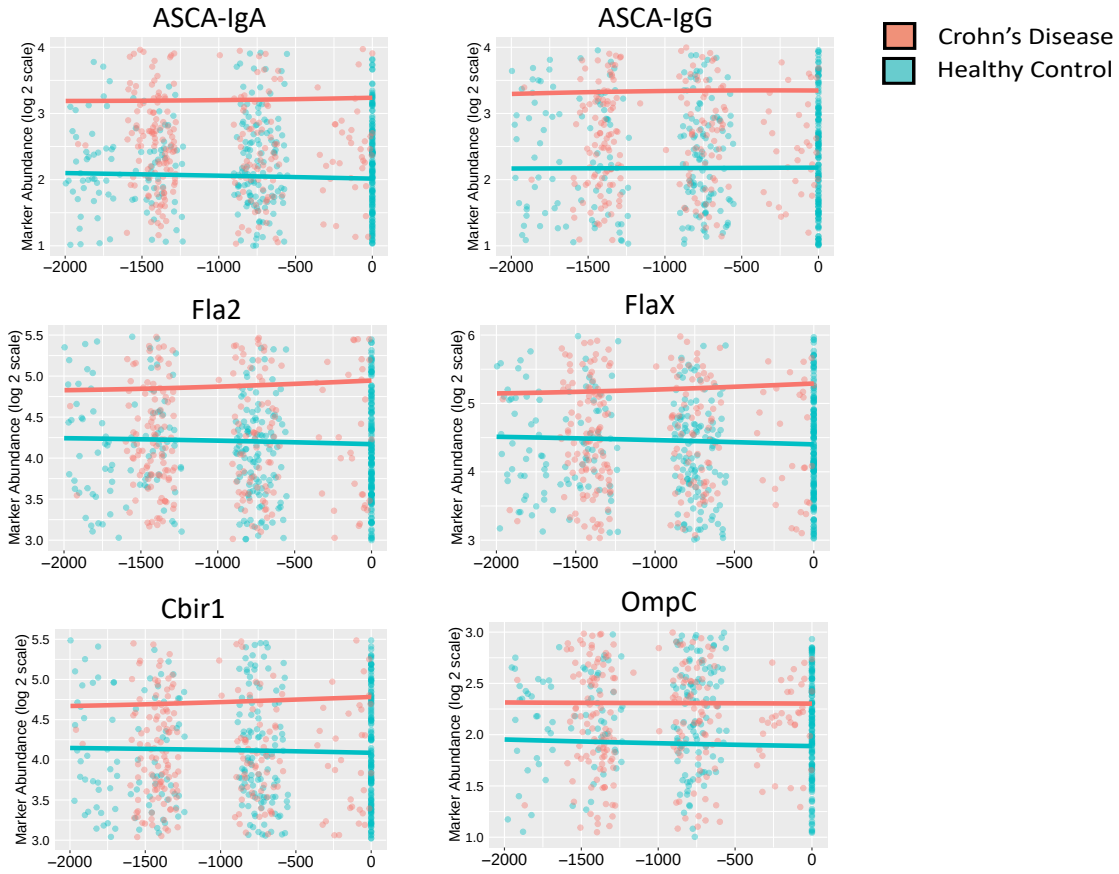
The rationale: IBD as other immune-mediated diseases have a preclinical period that can be targeted



Torres J. et al Gut 2016

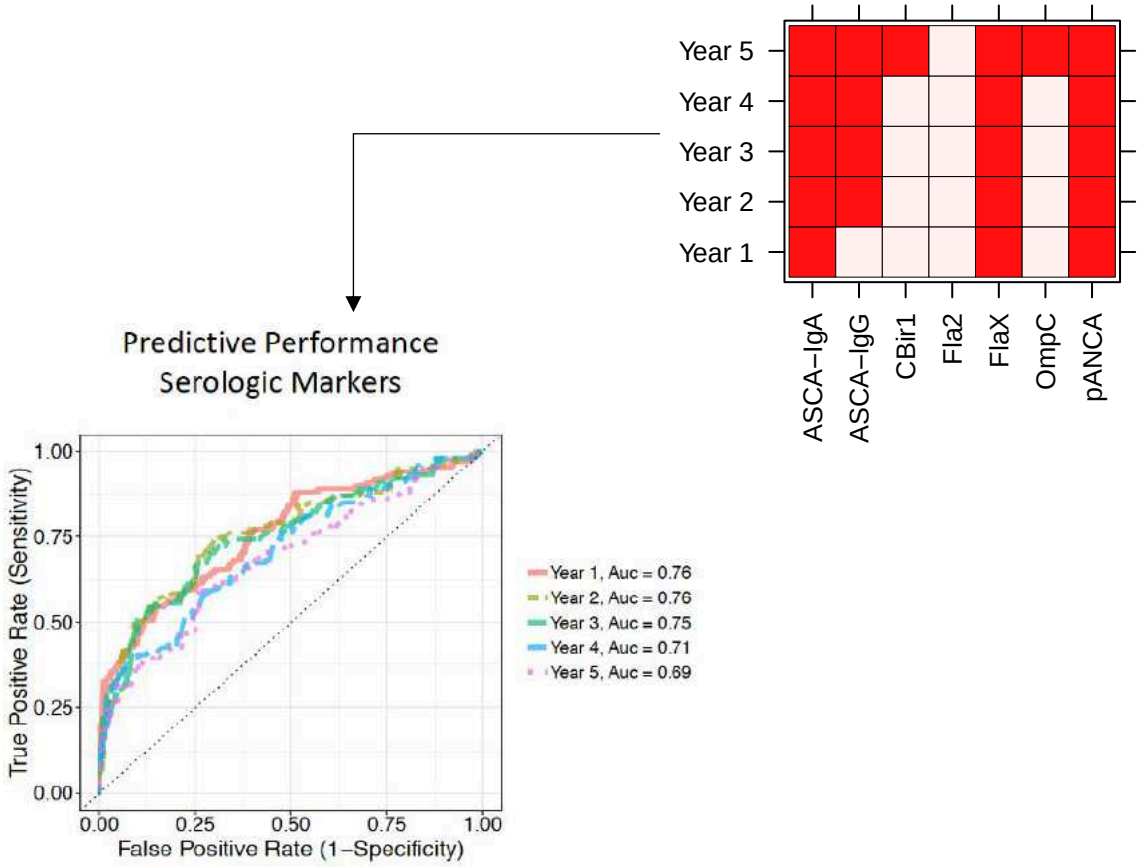
Crohn´s disease: Anti-microbial markers are elevated many years before diagnosis

Time-varying trajectory of antimicrobial antibodies*



Univariate analysis

Selected markers (multivariate analysis)



Multivariate analysis

* Derived using functional PCA in training data and evaluated in the testing data

Torres J et al. Gastroenterology 2020

The GEM project

Find 75 healthy subjects who go on to develop disease and compare with healthy subjects

75 new cases and 300 controls

Risk of Crohn's in FDR = 0.3% per year

5000 healthy Sibs

and Offspring

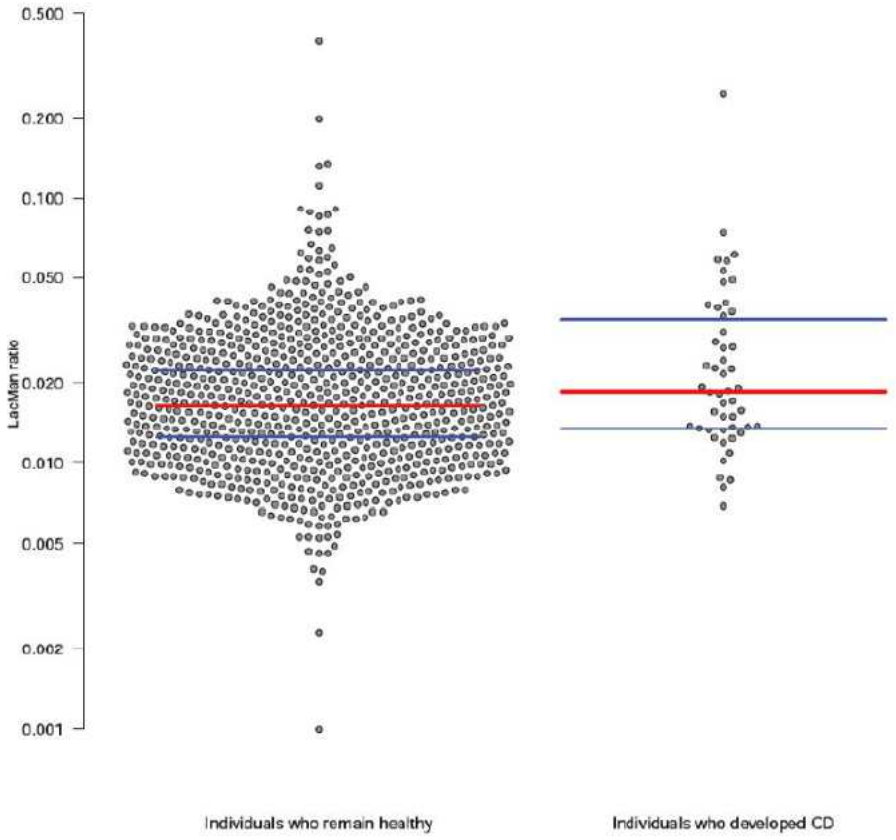
Completed

Being from multiplex family, intestinal permeability and microbiome diversity may be risk factors for development of CD

Courtesy K Croitoru

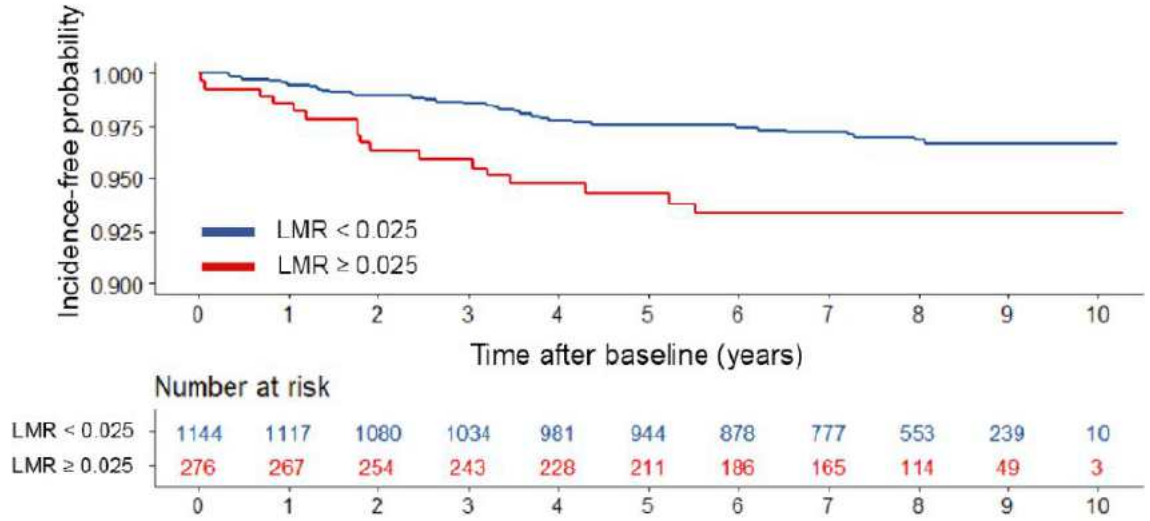
Increased IP precedes development of Crohn's disease

Follow up of 1420 FDRs – 50 developed IBD



LMR test

Risk of developing CD



HR : 3.03 CI (1.94-5.63)

Courtesy K Croitoru

Discussion: Potential use in Crohn's Disease

01

Mild CD disease

- The "mesalazine" of CD?

02

Post-operative setting

- Endpoint: avoid recurrence of local disease

03

Maintenance of remission in CD

- Monotherapy in remission
- Combination therapy in active disease

04

Prevention?