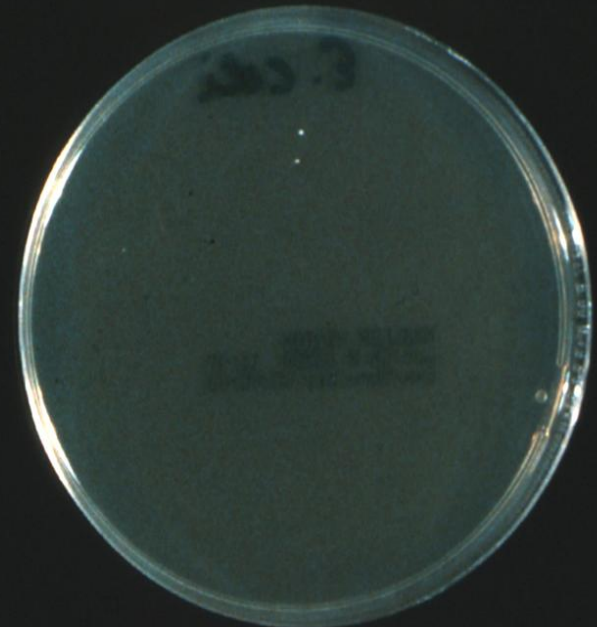


Menschliche Haut besitzt eine spezifische Resistenz gegenüber dem Darm-Keim *E. coli*

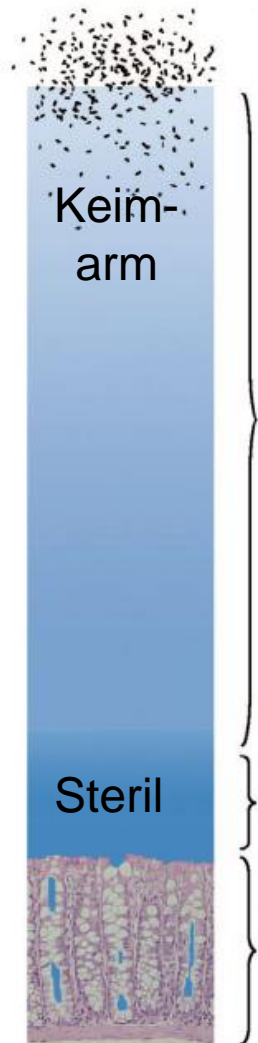
S. Aureus ATCC 6538



E. coli ATCC 11303

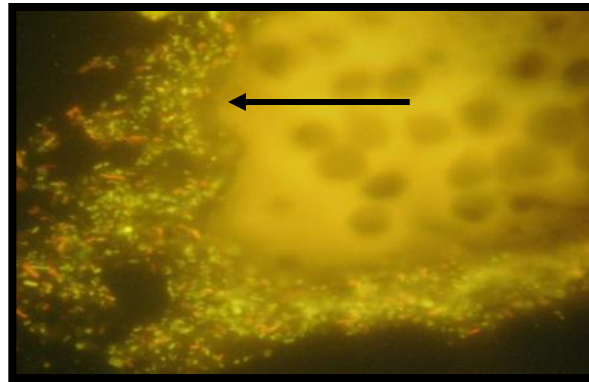


CED ist ein Barriereedefekt



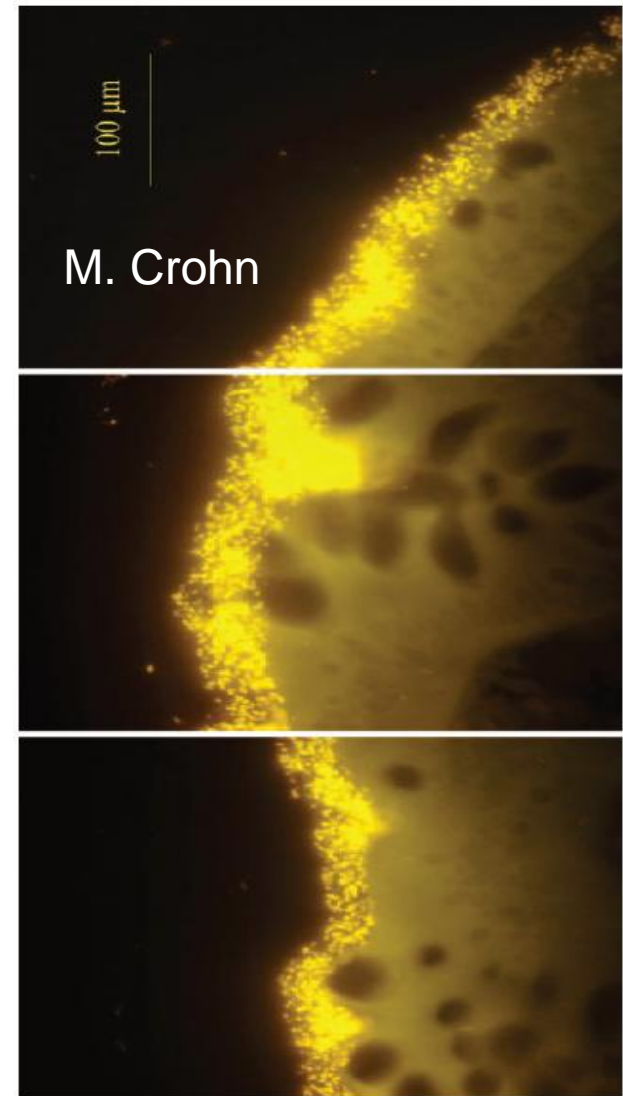
Intestinales Lumen
massenhaft aerobe Bakterien

Äussere Mucusschicht (700 μm)
antibakterielle Peptide
(Defensine, Cathelicidine)



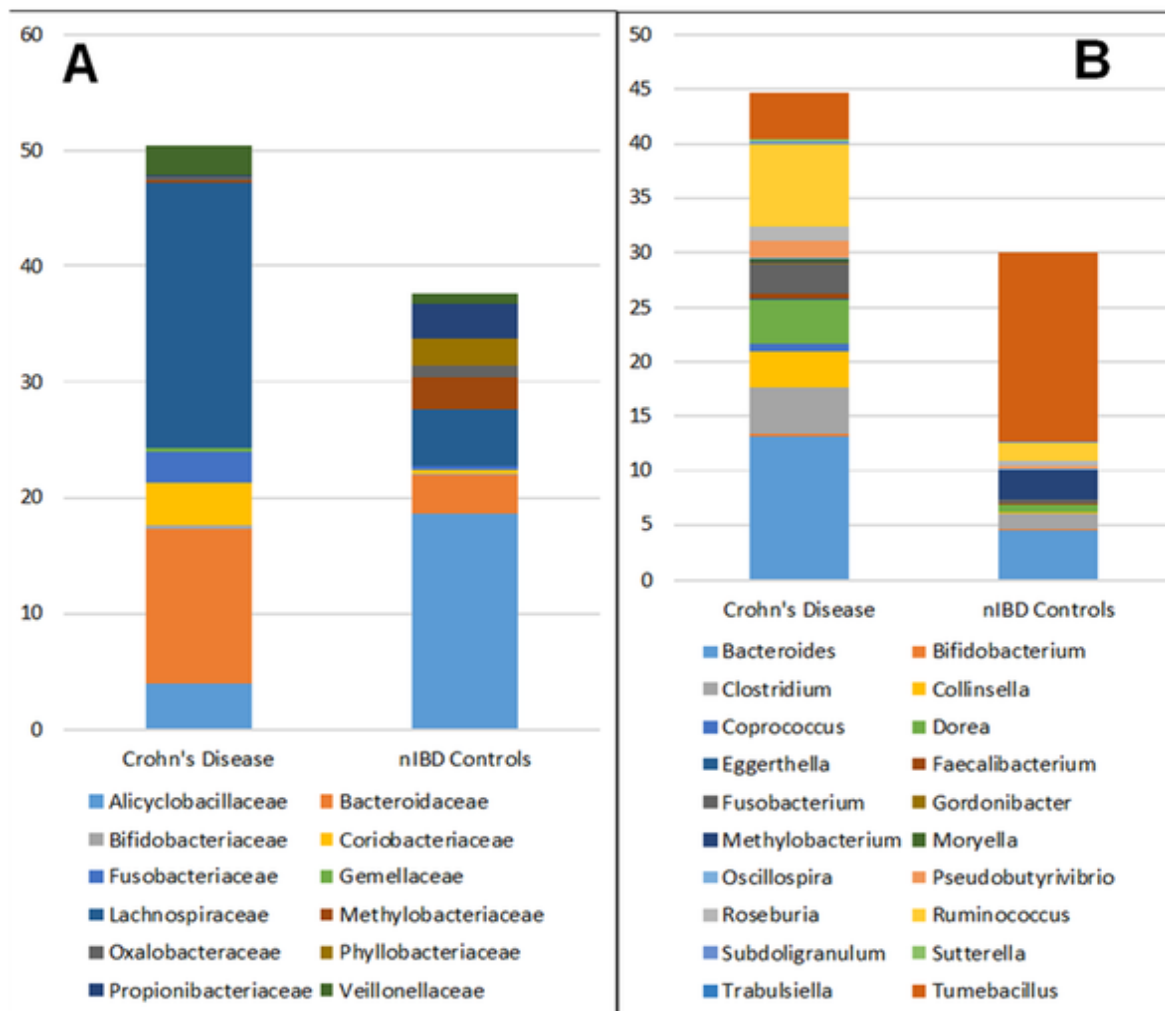
Innere Mucusschicht (100 μm)
Fest adhärent, reich in
antibakt. Peptiden

Colon-Crypten (200 μm)
Sekretion von Mucus
und antibakt. Peptide
Epithelzellbarriere



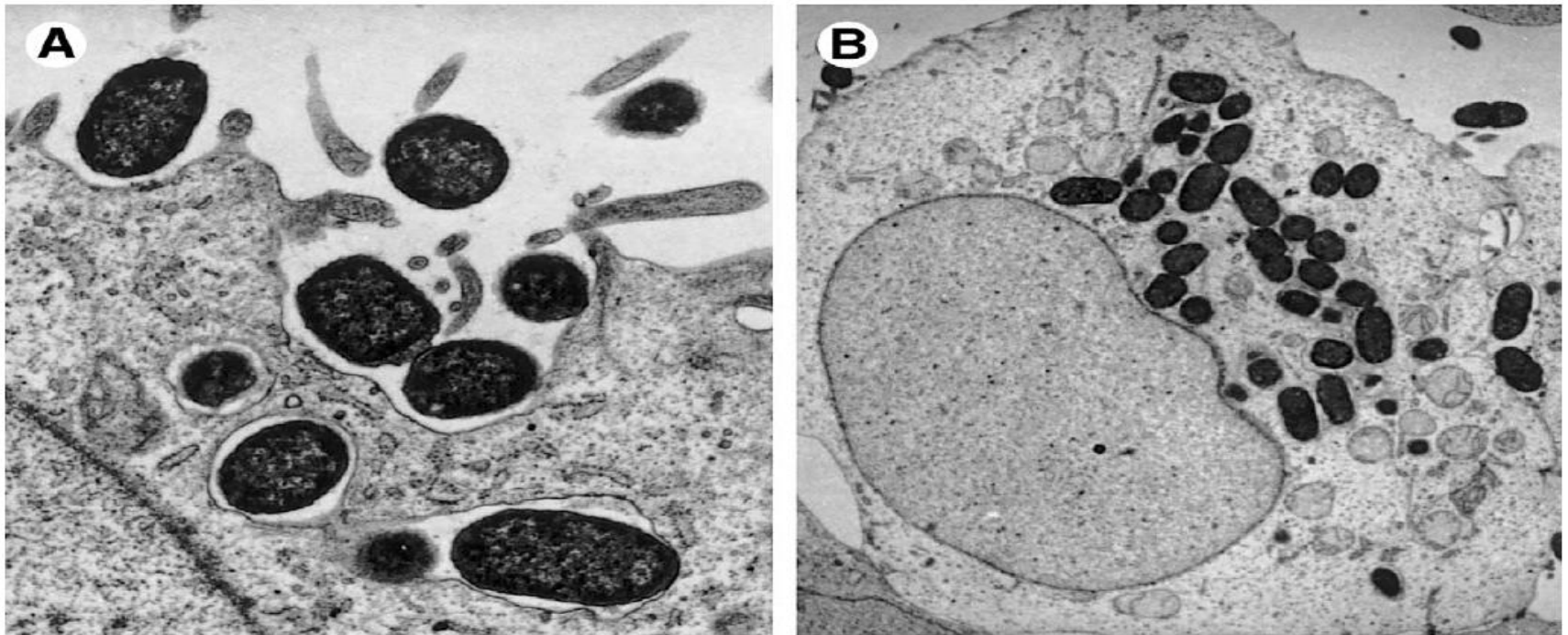
A. Swidsinski

Comparison of the relative abundance of bacterial Families (A) and Genera (B) within the submucosa of the diseased ileum in Crohn's disease as compared to the ileal submucosa in nIBD controls.



Chiodini RJ, Dowd SE, Chamberlin WM, Galandiuk S, Davis B, et al. (2015) Microbial Population Differentials between Mucosal and Submucosal Intestinal Tissues in Advanced Crohn's Disease of the Ileum. PLoS ONE 10(7): e0134382.

Adherent-invasive E. coli



AIEC in 21.7% of CD patients versus 6.2% of controls (ileal samples)
AIEC in 3.7% of CD patients versus 1.9% of controls (colonic samples)

Reversible following corticosteroid administration: secondary!

Darfeuille-Michaud et al., Gastro 2004
Swidsinski et al. IBD 2008

Microbiota sind das immunologische Target bei CED

- *Gnotobiotische Tiere refraktär gegenüber experimenteller Colitis*
- CED lokalisiert in Segmenten mit höchster Bakteriendichte
- Diversion (Stoma) führt meist zu distaler Abheilung, Rezidiv bei Aufhebung der Diversion
- Adhärente und abnorme Flora bei CED
- Serologische und T-Zell-Immunität gerichtet gegen bakterielle Antigene
- Risikogene der Bakterienerkennung (NOD2), intrazell. Degradation (ATG16L1) und extrazell. Abtötung (TCF4, LRP6 durch Panethzellen)
- Antibiotika wirksam bei Pouchitis und Prophylaxe postoperativ nach Ileumresektion

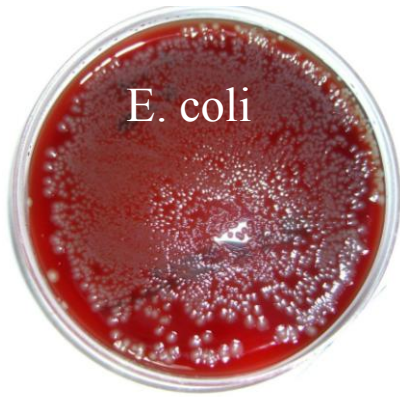
“Segmental vulnerability”



Same bacteria –
different mucosa
suggesting local
defect

Crohn's and Hirschsprung Disease
Dray IBD 2007

Verminderte antibakterielle Aktivität in Crohn-Mucosa



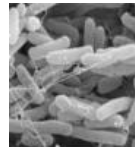
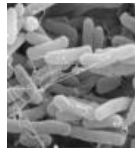
Added: **Buffer**

**Healthy mucosal
tissue extract**

**Ulcerative colitis mucosal
tissue extract**

**Crohn's disease mucosal
tissue extract**

Präinkubation von Bakterien
mit Biopsieextrakt

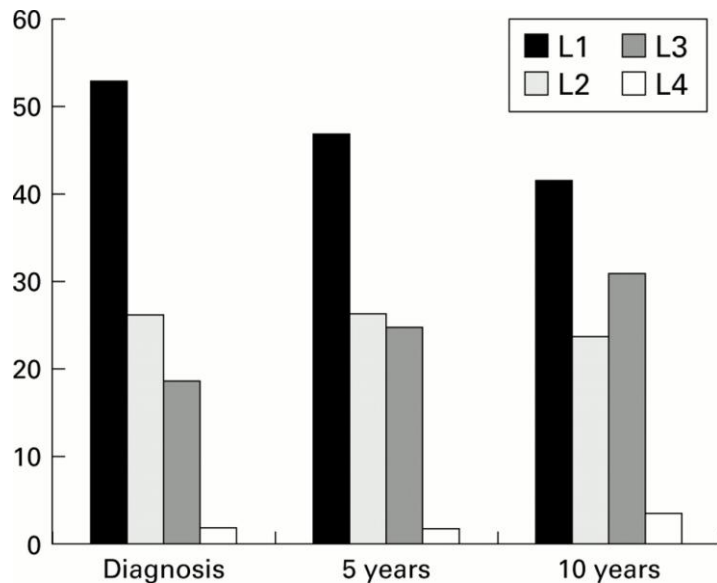
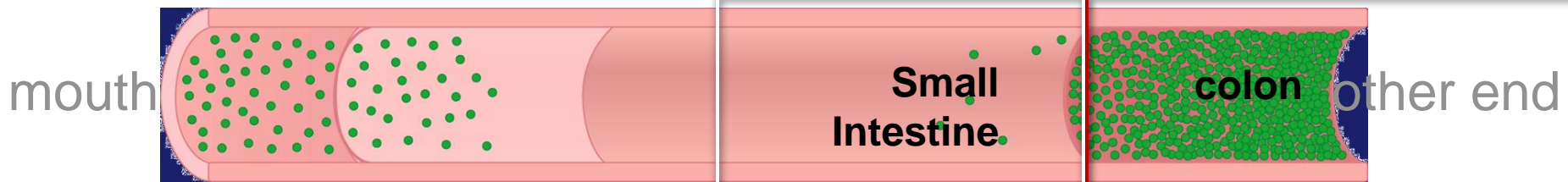


- Normale Mucosa tötet Bakterien ab
- verstärkt bei Colitis ulcerosa
- Defekt bei M. Crohn

Wehkamp et al. PNAS 2005

Nuding et al. Gut 2007

Crohn's diseases

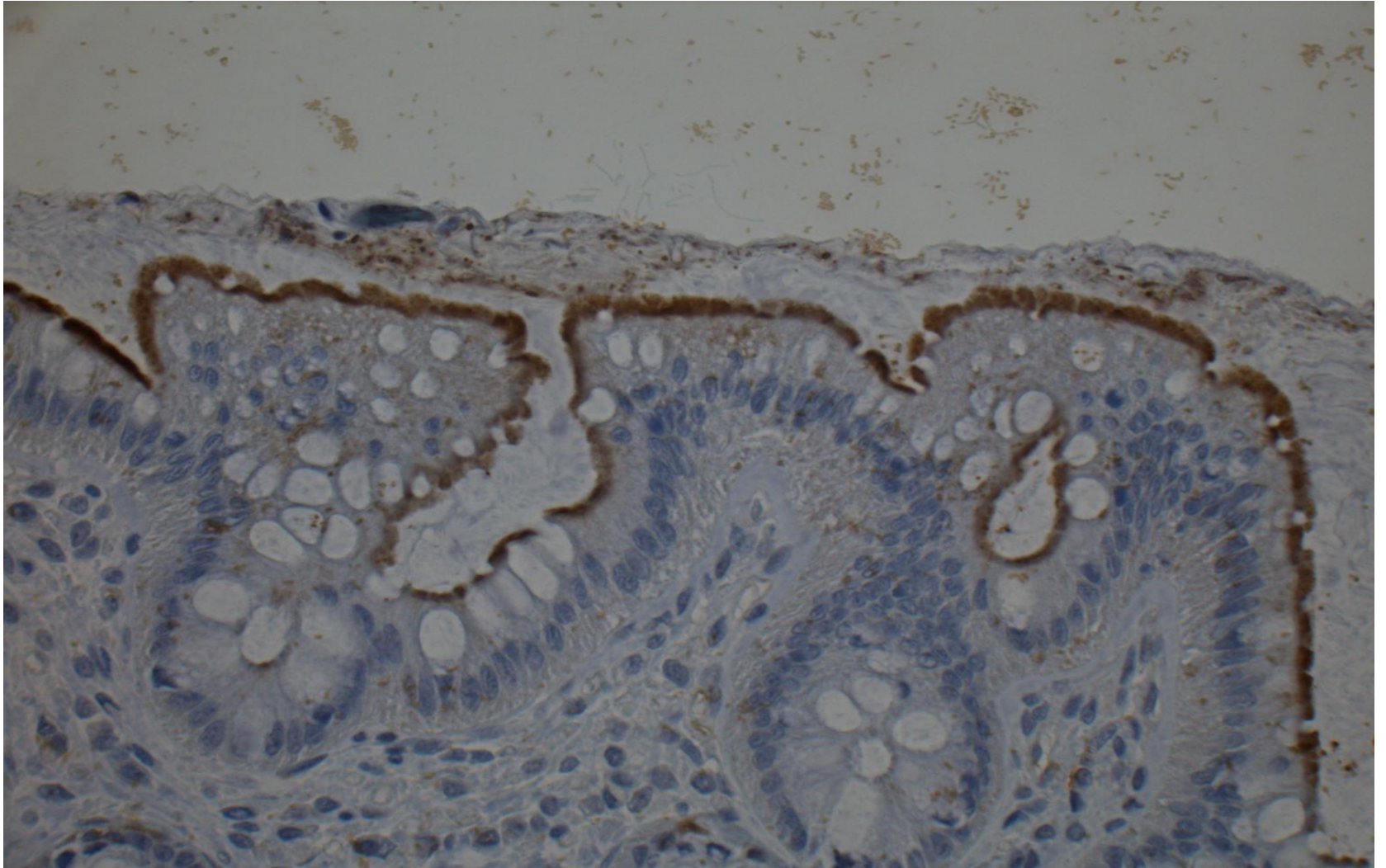


alpha-
-Defensins:
HD-5 and 6
(constitutive)

beta-Defensins:
HBD1
(constitutive)
HBD 2,3 and 4
(inducible)

Louis, E et al. Gut 2001; 49:777-782

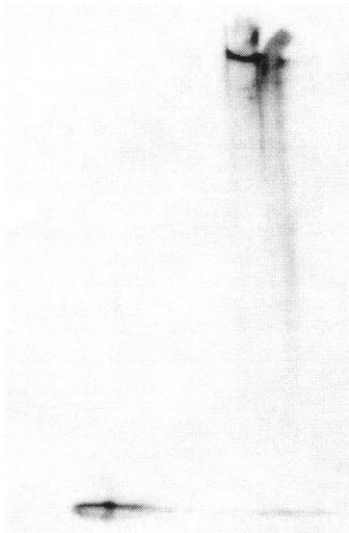
Humanes β -Defensin-1 im Colonepithel



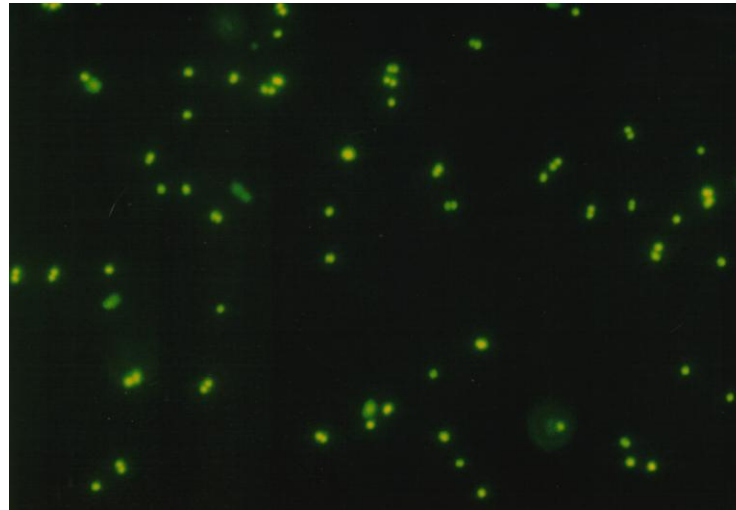
Binding of antimicrobial peptides to mucins in mucus while retaining functional activity

E. coli ATCC 29522

Mucins binding
HBD-2

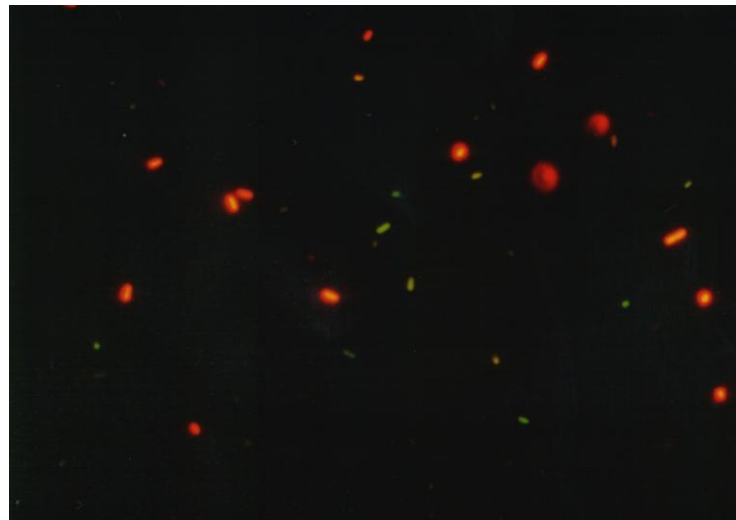


HBD-2



Staining with SYTO 9[®]
(living bacteria green) and
propidium iodide (dead
bacteria red)

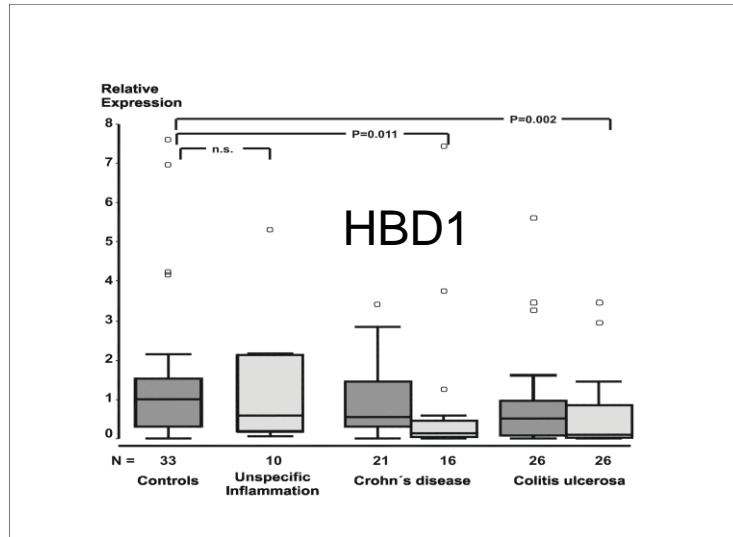
Untreated control



Incubated with colonic
mucus

Antoni et al.
J Crohn's Colitis 2013

Defensin expression in the colon

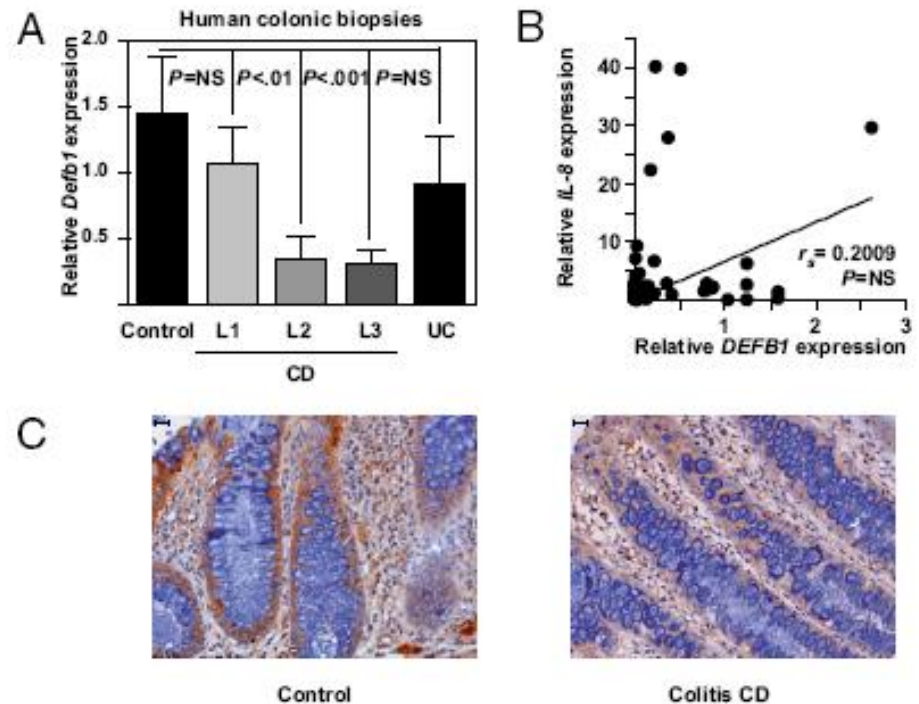


Wehkamp et al., IBD 2003

PNAS

Peroxisome proliferator-activated receptor gamma activation is required for maintenance of innate antimicrobial immunity in the colon

Laurent Peyrin-Biroulet^{a,b,c,1}, Julia Beisner^{d,e,1}, Guoxing Wang^{d,e,1}, Sabine Nuding^{d,e,f}, Sajit Thottathil Oommen^g, Denise Kelly^h, Erika Parmentier-Decrucq^{a,i}, Rodrigue Dessein^{i,j,k,l}, Emilie Merour^a, Philippe Chavatte^m, Teddy Grandjean^{i,j,k,l}, Aude Bressenotⁿ, Pierre Desreumaux^{a,i}, Jean-Frédéric Colombel^{a,i}, Béatrice Desvergne^g, Eduard F. Stange^f, Jan Wehkamp^{d,e,f,2,3}, and Mathias Chamailard^{i,j,k,l,2,3}



Scand J Gastroenterol. 2008;43(3):299-307.
Association of beta-defensin 1 single nucleotide polymorphisms with Crohn's disease.

[Kocsis AK](#), [Lakatos PL](#), et al.

Department of Medical Microbiology and Immunobiology,
University of Szeged, Szeged, Hungary.

Environment Controls Host Defence

nature

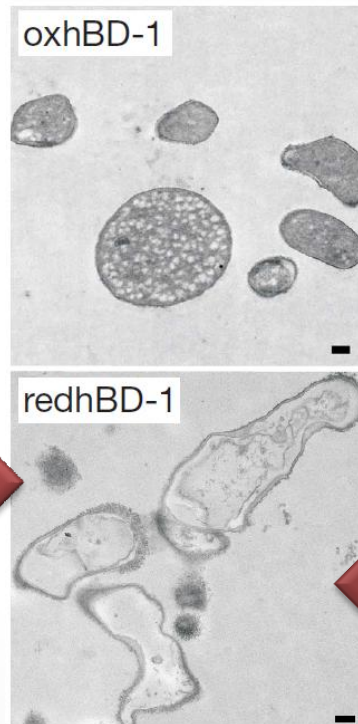
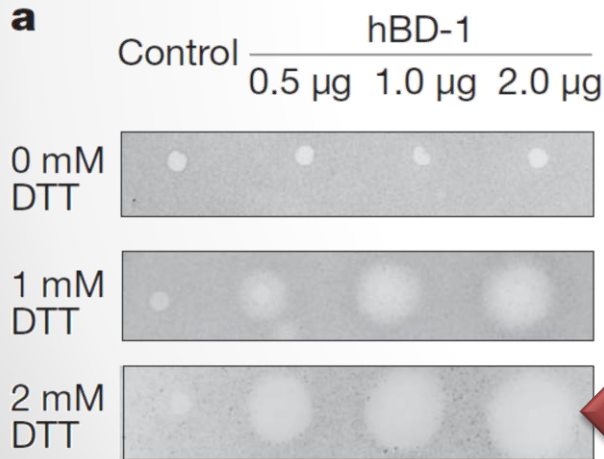
doi:10.1038/nature09674

Reduction of disulphide bonds unmask potent antimicrobial activity of human β -defensin 1

Bjoern O. Schroeder^{1,2}, Zhihong Wu³, Sabine Nuding^{1,2}, Sandra Grosecruth^{4,†}, Moritz Marcinowski⁵, Julia Beisner^{1,2}, Johannes Buchner⁵, Martin Schaller⁶, Eduard F. Stange⁷ & Jan Wehkamp^{1,2,7}

Human epithelia are permanently challenged by bacteria and fungi, including commensal and pathogenic microbiota^{1,2}. In the gut, the fraction of strict anaerobes increases from proximal to distal, reaching 99% of bacterial species in the colon³. At colonic

Because β -defensins contain three intramolecular disulphide-bridges¹³ we investigated the involvement of cystines for the observed antimicrobial effect. Therefore, we incubated hBD-1 with increasing concentrations of DTT and analysed samples using matrix-assisted laser



IMMUNOLOGY

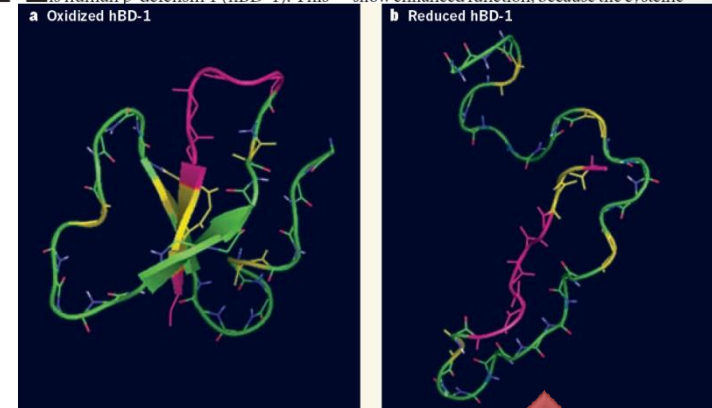
Peptide gets in shape for self-defence

The transformation of tadpole to frog and of caterpillar to butterfly are two of the more obvious examples of metamorphosis. But molecular shape-shifting may occur in each of us as part of our innate antibacterial defence system. [SEE LETTER P.419](#)

ROBERT I. LEHRER

Among the immune mediators that fight microorganisms within us, one is human β -defensin 1 (hBD-1). This

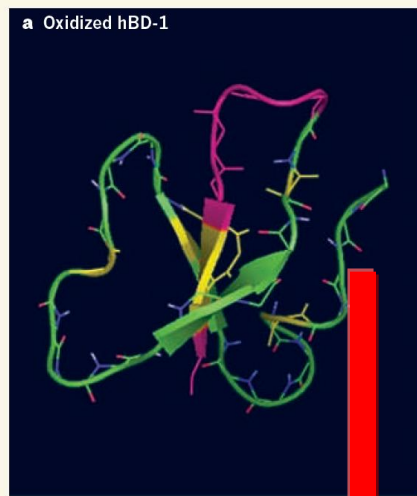
If shape change alone imparted the expanded antimicrobial range of hBD-1, then analogues of this peptide in which cysteine residues are replaced by other amino acids should also show enhanced function, because the cysteine-



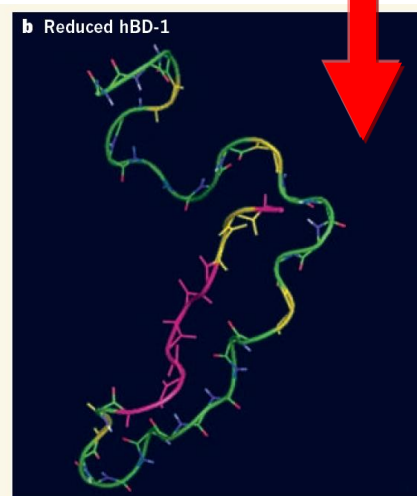
Peptide gets in shape for self-defence

The transformation of tadpole to frog and of caterpillar to butterfly are two of the more obvious examples of metamorphosis. But molecular shape-shifting may occur in each of us as part of our innate antibacterial defence system. [SEE LETTER P.419](#)

RESEARCH NEWS & VIEWS

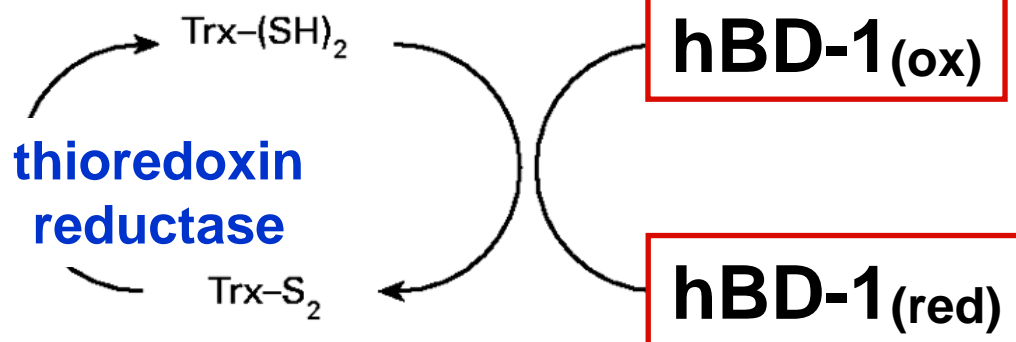


not
„active“



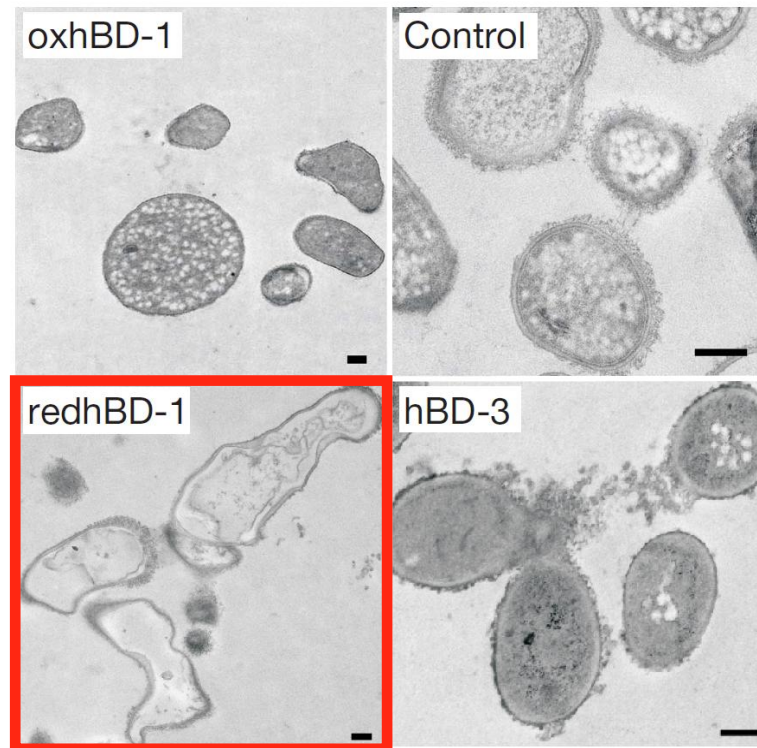
„active“

The thioredoxin (TRX) system



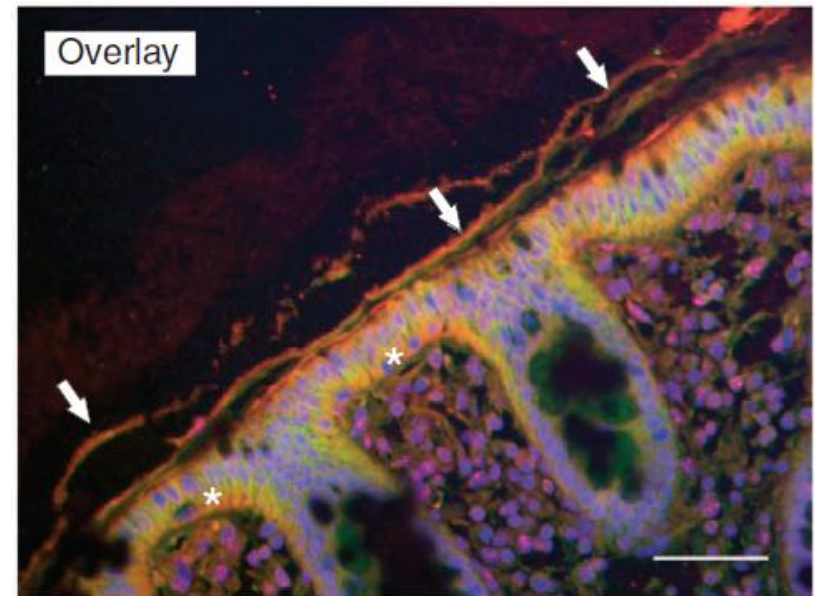
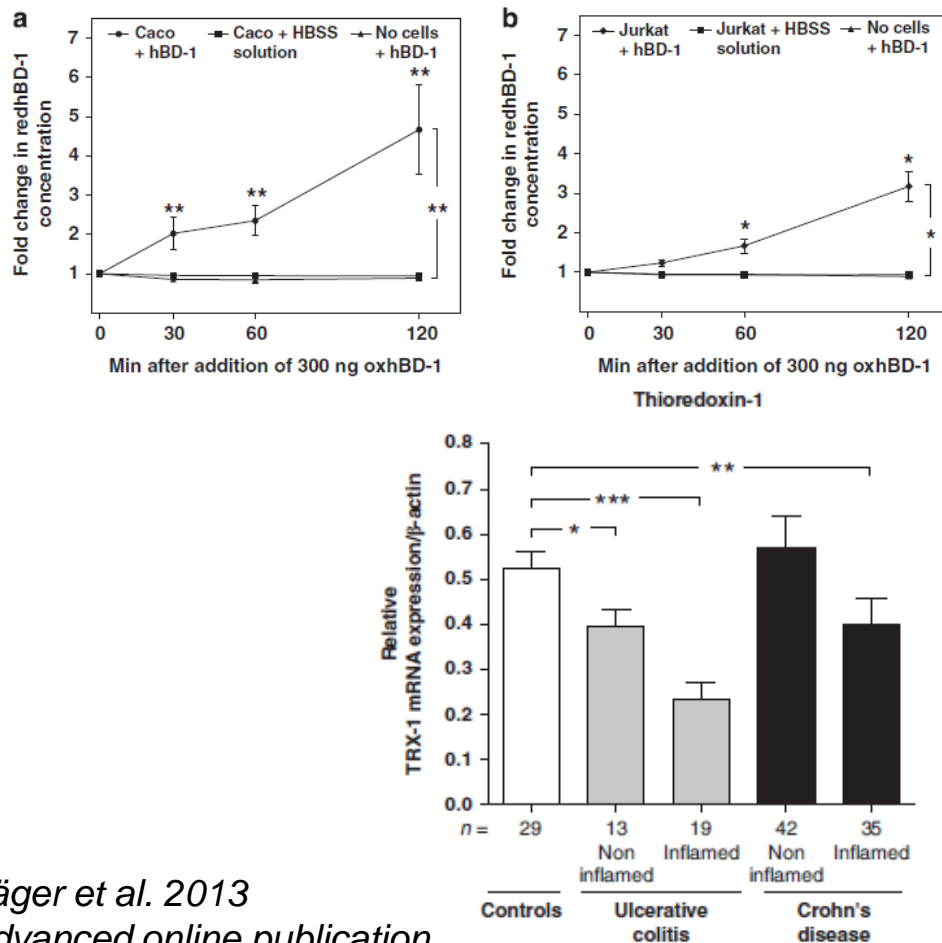
Schroeder et al., Nature 2011

electron microscopy



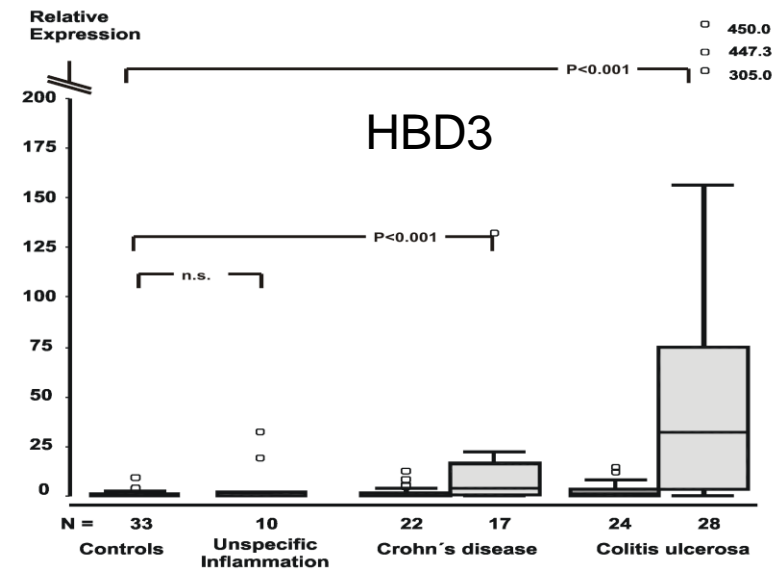
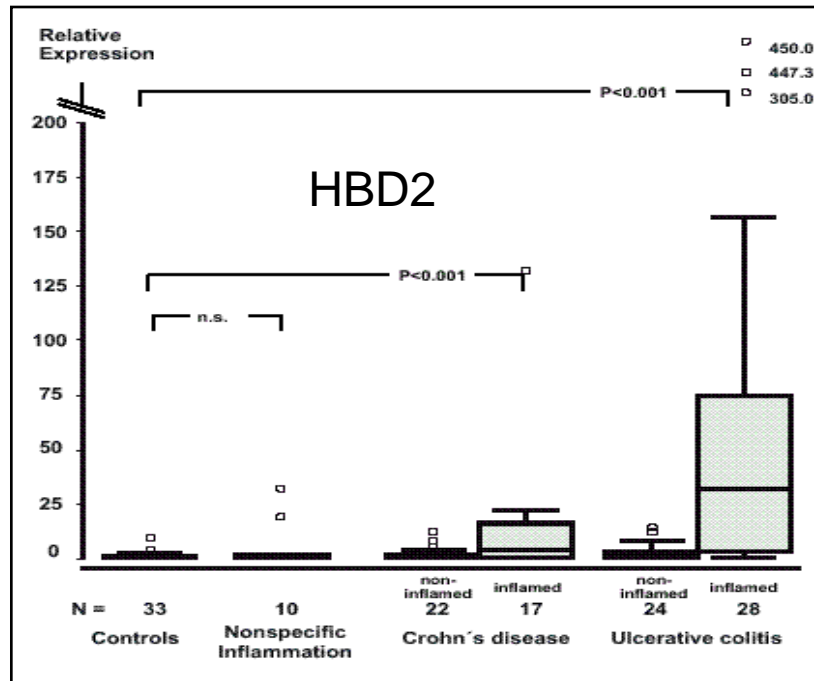
Cell-mediated reduction of human β -defensin 1: a major role for mucosal thioredoxin

SU Jaeger^{1,2}, BO Schroeder², U Meyer-Hoffert³, L Courth², SN Fehr², M Gerseemann¹, EF Stange¹ and J Wehkamp^{1,2}

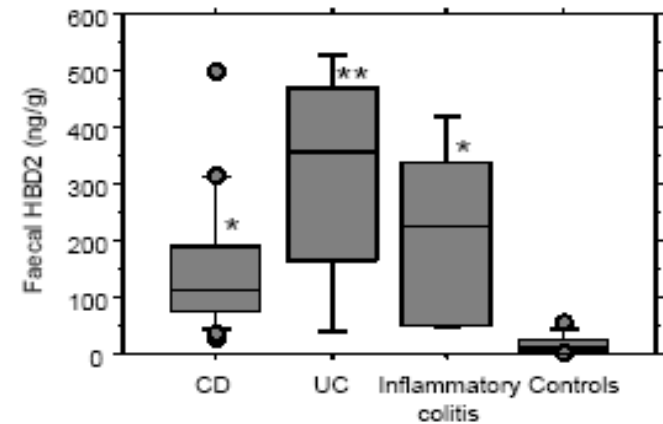
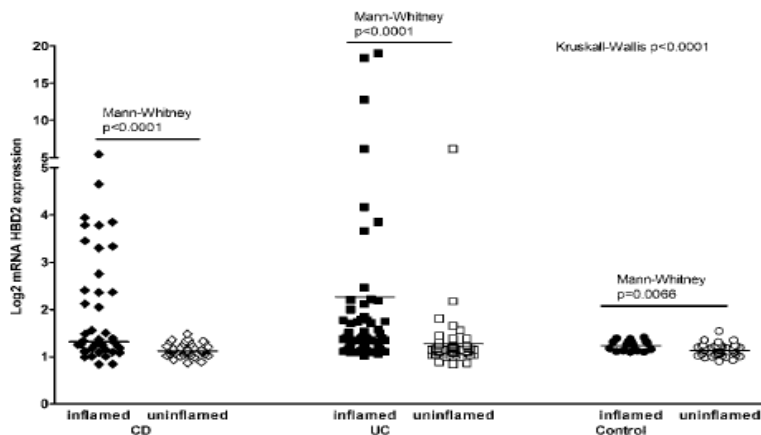


New mechanism:
Reduced luminal activation of antimicrobial activity due to lack of redox enzymatic activity

Defensinexpression im Colon bei M. Crohn und Colitis ulcerosa



Wehkamp et al., IBD 2003



OPEN ACCESS

PLOS one

Dysregulation of Human β -Defensin-2 Protein in Inflammatory Bowel Disease

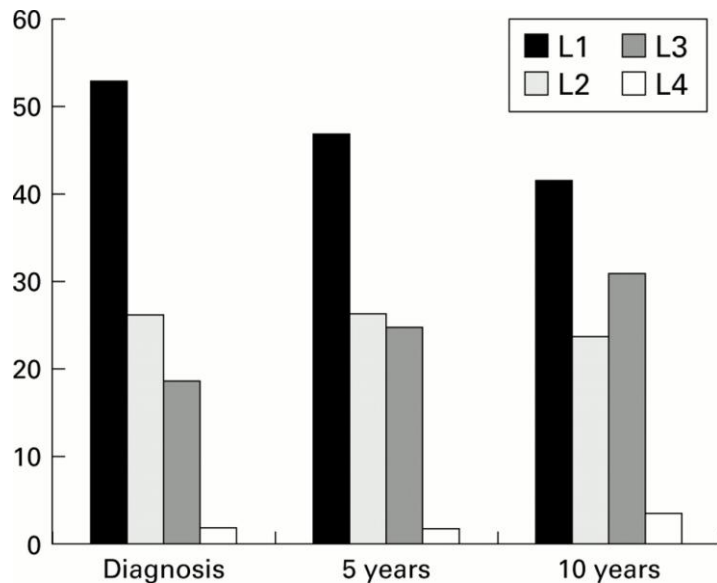
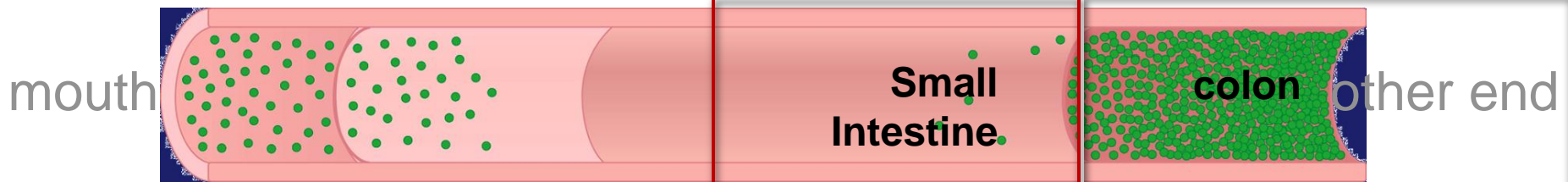
Marian C. Aldhous*, Colin L. Noble, Jack Satsangi

Gastrointestinal Unit, School of Clinical and Molecular Medicine, University of Edinburgh, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, Scotland, United Kingdom

Ruemmele et al.

J Pediatr Gastroenterol Nutr. 2009, 48(1):117-20

Crohn's diseases

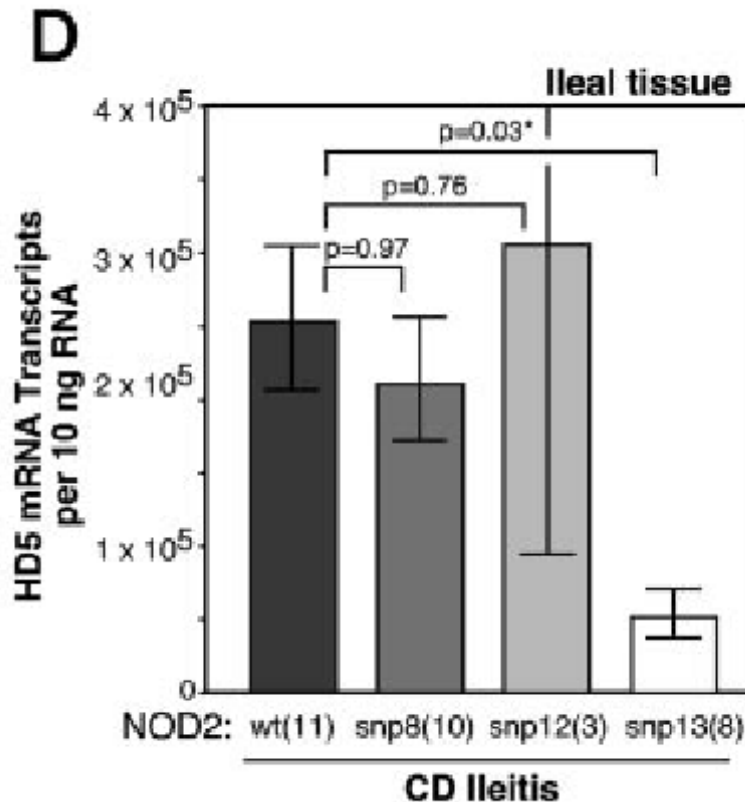
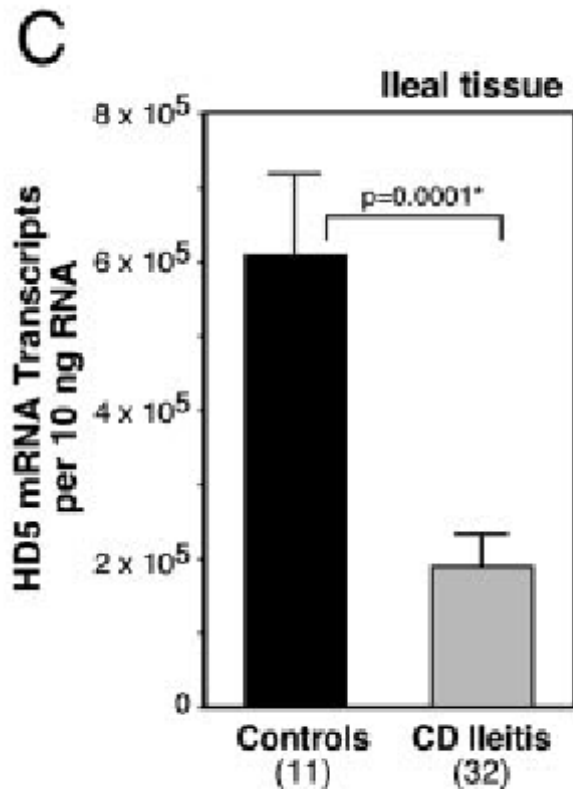


alpha-
-Defensins:
HD-5 and 6
(constitutive)

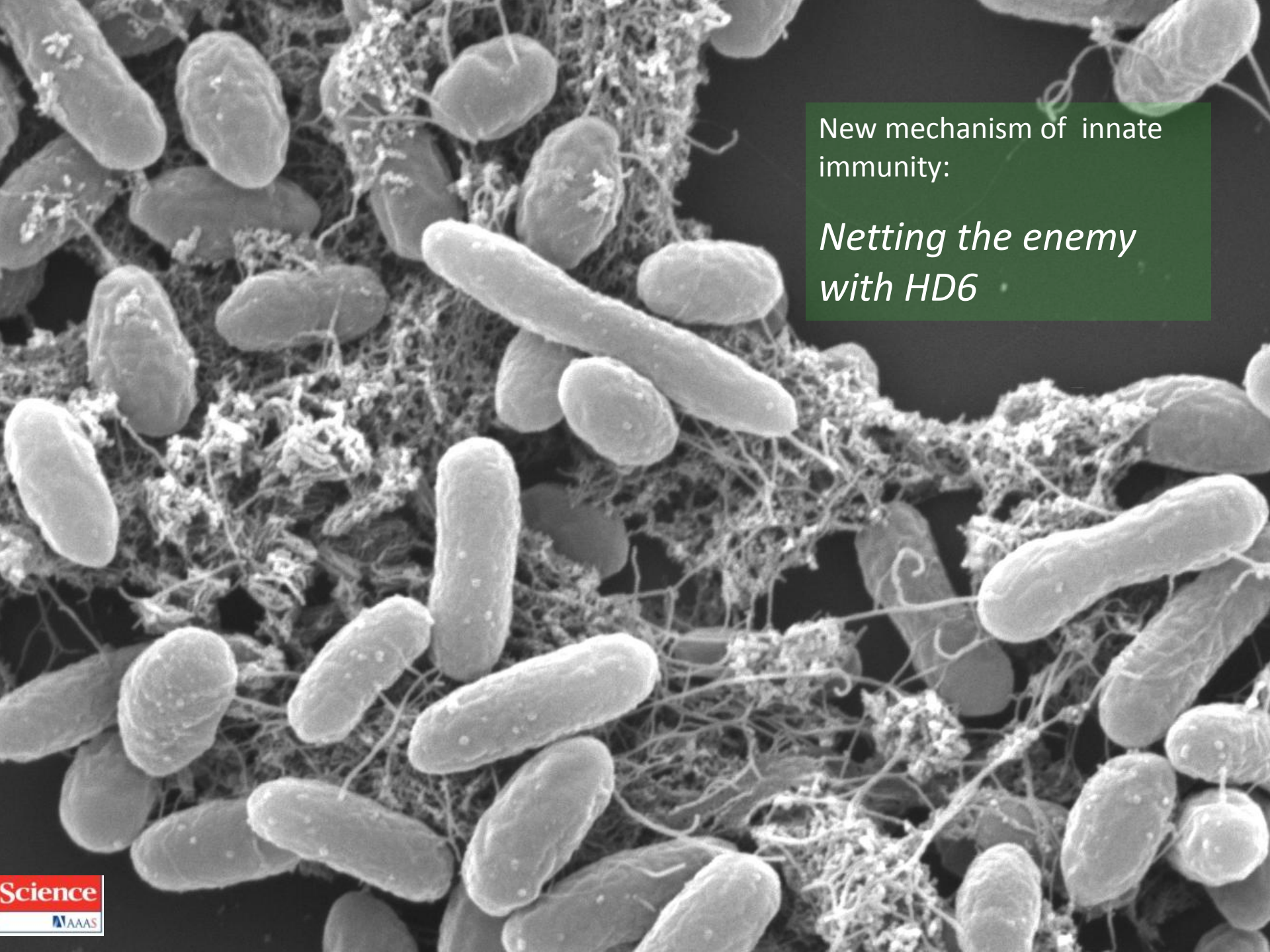
beta-Defensins:
HBD1
(constitutive)
HBD 2,3 and 4
(inducible)

Louis, E et al. Gut 2001; 49:777-782

Paneth cell defensins in Crohn's disease



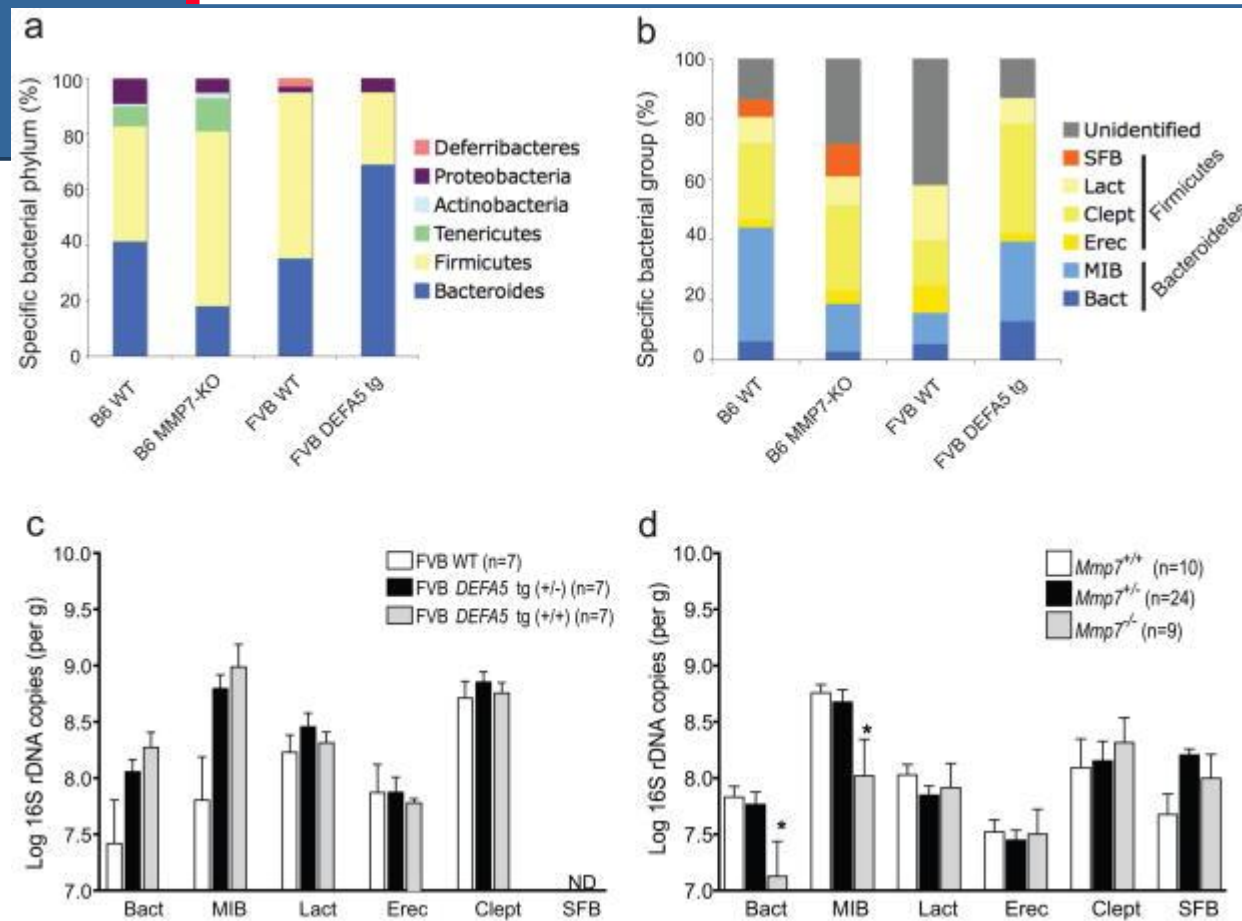
Wehkamp et al. *PNAS* 2005; 102:18129 -34.

A scanning electron micrograph showing numerous rod-shaped bacteria, likely E. coli, interacting with a complex, fibrous, net-like structure. The bacteria are of various sizes and orientations, some appearing to be caught or entangled in the fine threads of the net. The background is dark, highlighting the intricate details of the bacterial surfaces and the delicate structure of the net.

New mechanism of innate immunity:

*Netting the enemy
with HD6*

Enteric defensins are essential regulators of intestinal microbiology



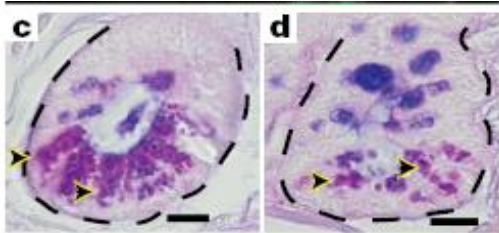
Paneth's disease

Jan Wehkamp ^{a,b,*}, Eduard F. Stange ^a

HD5-Mutation

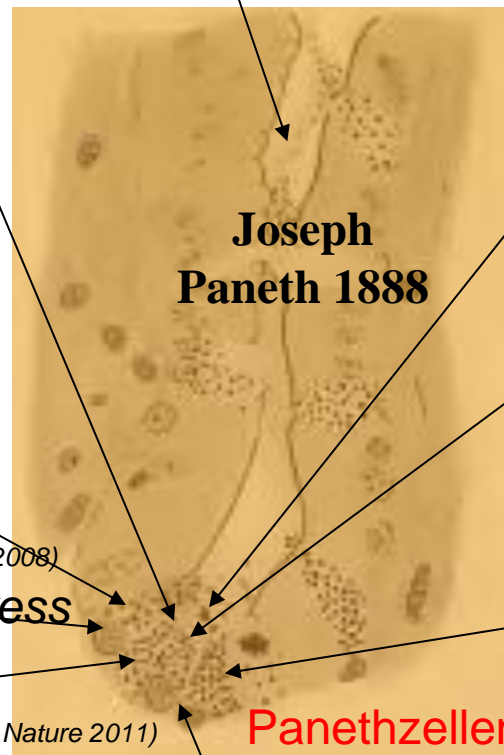
(Erik de Leeuw et al. FEBS letters 2009)

ATG16L1 (Cadwell et al. Nature 2008)
Granula-Exozytose



Tryptische Degradation und Proteasebindung von HD5

(Elphik et al. 2008 Am J Path)



KCNN4 (Simms et al. Am J Gas
Ca-aktivierter
Kaliumkanal

Crinophagie (Thachil et al. G
Granula-Autophag

XBP1 (Kaser et al. Cell 2008)
Endosomaler Stress

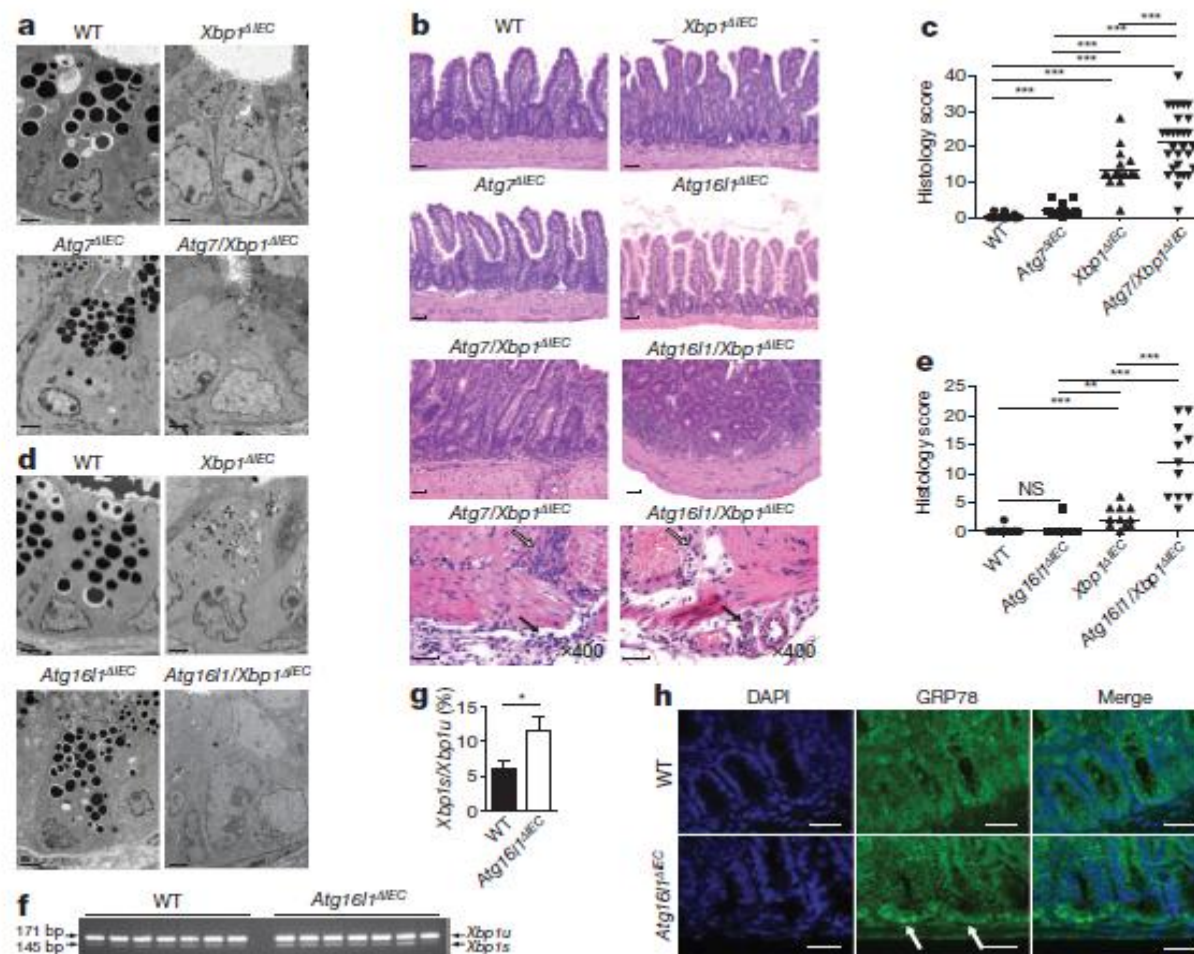
NOD2 (Wehkamp et al. Gut 2004)
Defensin-Synthese

Caspase 8 (Günther et al. Nature 2011)
TNF induzierte Nekroptose

TCF4 / LRP6 (Koslowski et al. 2010, Plos One, 2012 Plos Genetics)
Panethzell-Differenzierung aus Stammzellen

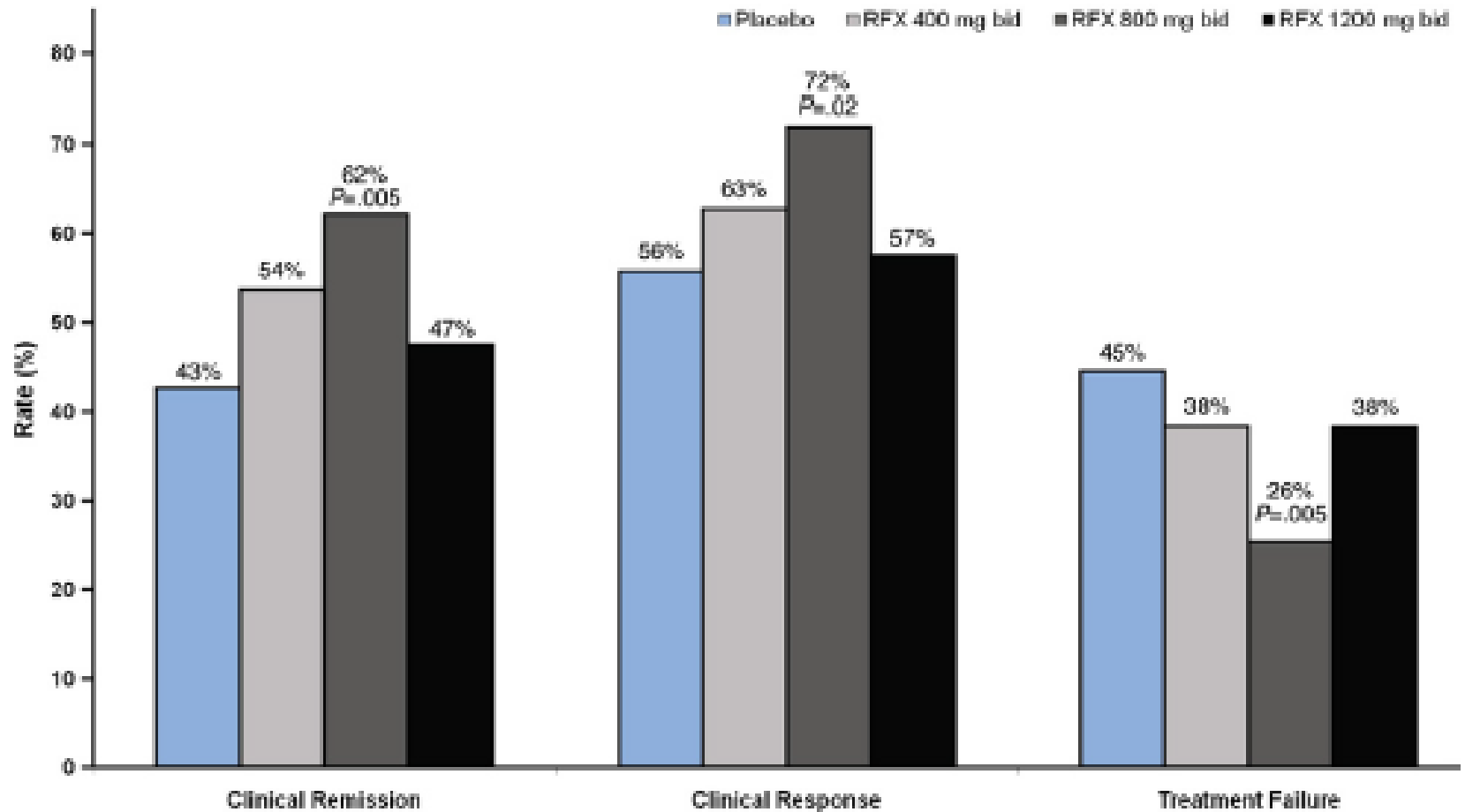
Paneth cells as a site of origin for intestinal inflammation

Timon E. Adolph^{1*}, Michal F. Tomczak^{2*}, Lukas Niederreiter^{1*}, Hyun-Jeong Ko^{2†*}, Janne Böck³, Eduardo Martinez-Naves⁴, Jonathan N. Glickman⁵, Markus Tschurtschenthaler^{1,6}, John Hartwig⁷, Shuhei Hosomi², Magdalena B. Flak², Jennifer L. Cusick², Kenji Kohno⁸, Takao Iwawaki^{9,10}, Susanne Billmann-Born³, Tim Raine¹, Richa Bharti³, Ralph Lucius¹¹, Mi-Na Kweon¹², Stefan J. Marciniak¹³, Augustine Choi¹⁴, Susan J. Hagen¹⁵, Stefan Schreiber³, Philip Rosenstiel³, Arthur Kaser^{1*} & Richard S. Blumberg^{2*}

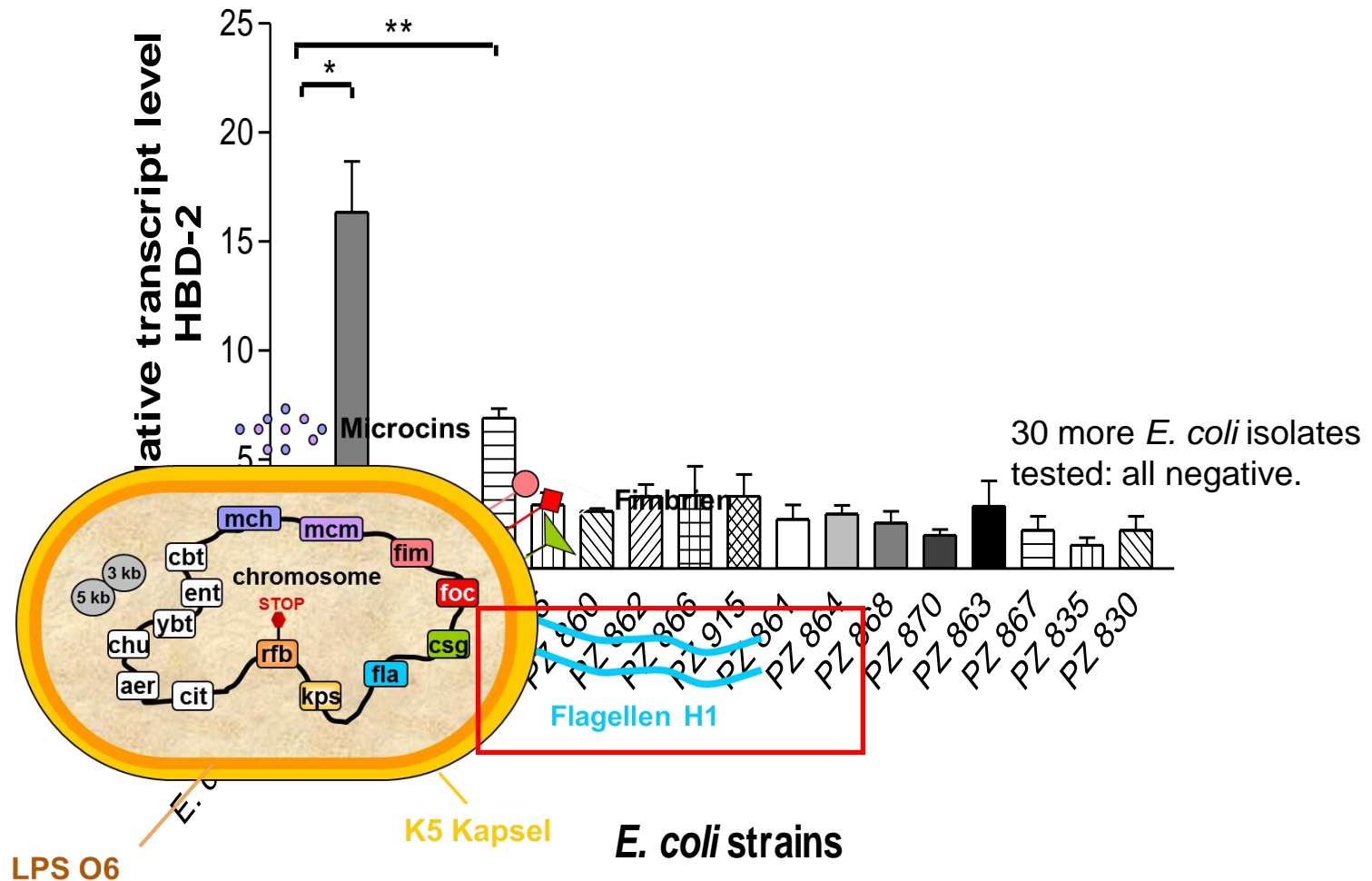


Nature
2013

Rifaximin in Crohn's disease



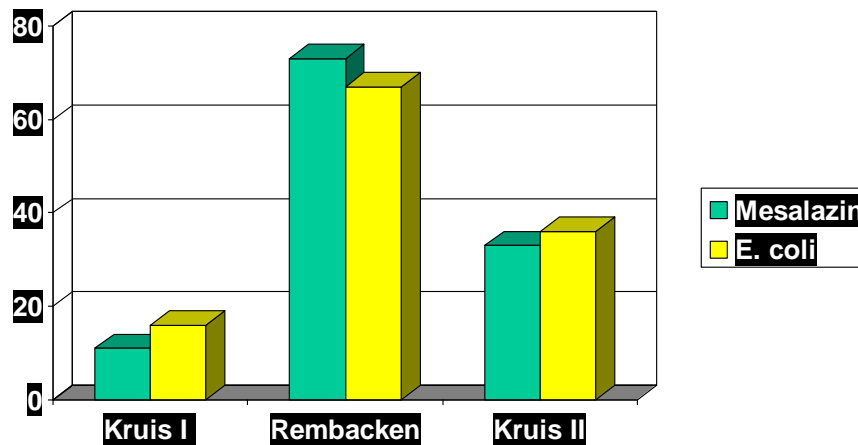
Induktion des humanen β -Defensin-2 durch *E. coli* Nissle



E. coli Nissle bei Colitis ulcerosa

Nissle 1917 (MUTAFLOR®)

A. Nissle (1918). Die antagonistische Behandlung chronischer Darmstörungen mit Colibakterien. Med. Klinik No 2:29-33.



Rembacken et al., Lancet 1999

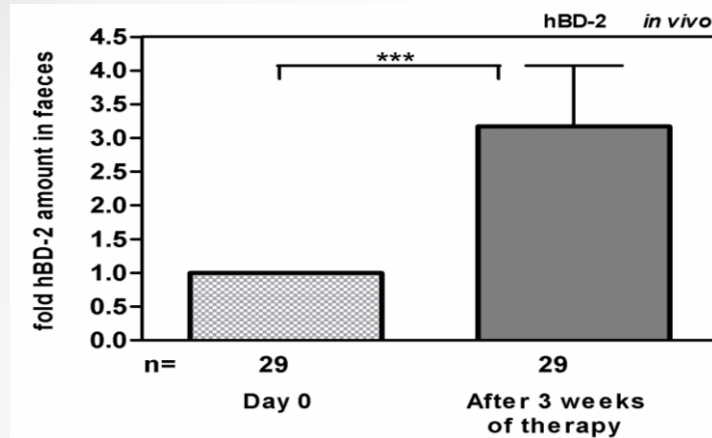
Kruis et al., Alimentary Pharmacol Ther 1997

Kruis et al., Gut 2005

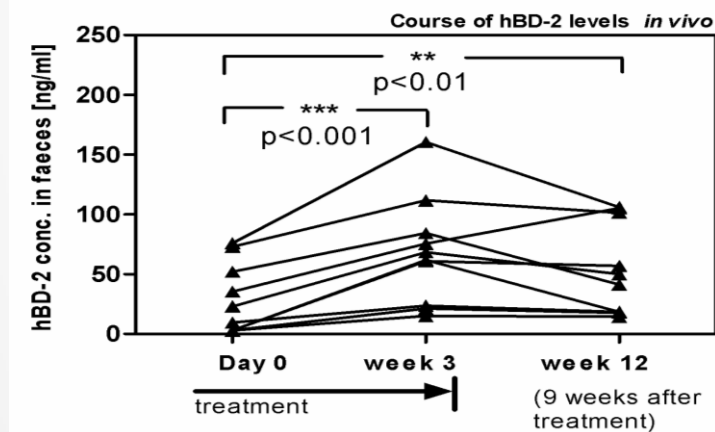
Nissle vergleichbar mit Mesalazin bzgl
Remissionserhaltung bei Colitis ulcerosa

Defensin-Induction- common mechanism of probiotic action

a

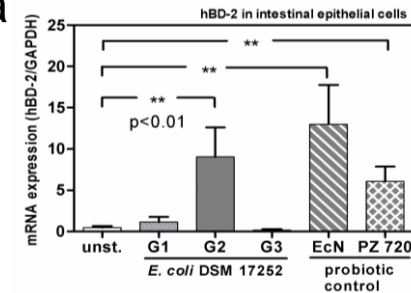


b

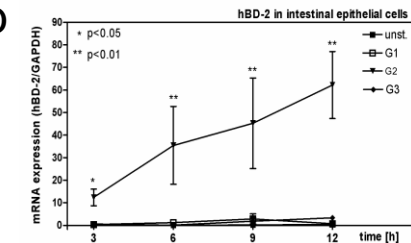


Symbioflor

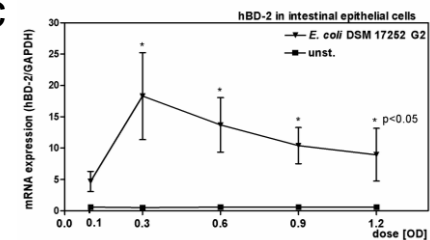
a



b



c



nature publishing group

ARTICLES

Probiotic *E. coli* treatment mediates antimicrobial human β -defensin synthesis and fecal excretion in humans

M Möndel¹, BO Schroeder¹, K Zimmermann², H Huber³, S Nuding¹, J Beisner¹, K Fellermann⁴, EF Stange⁴ and J Wehkamp^{1,4}

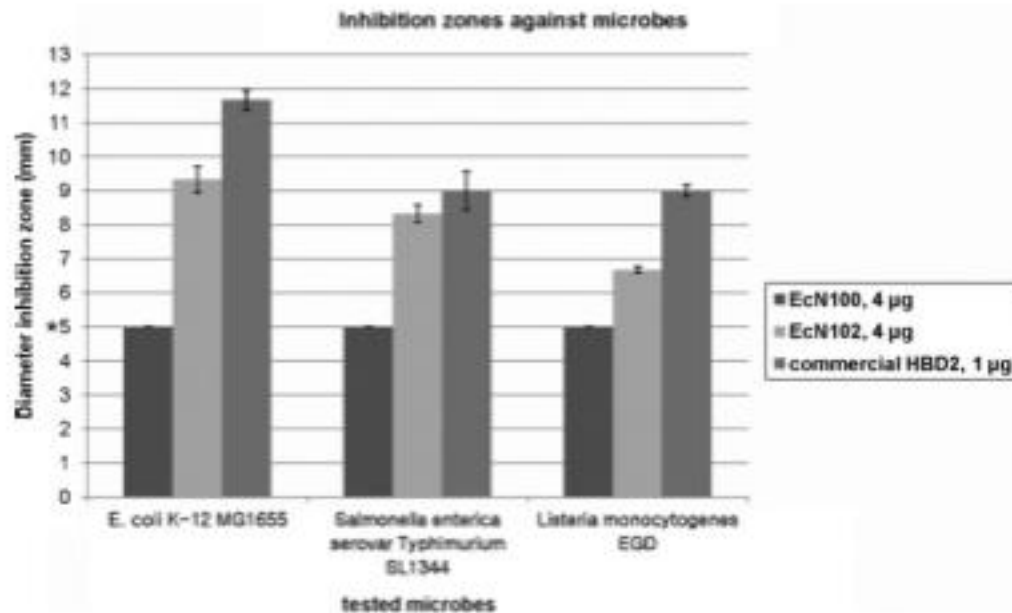
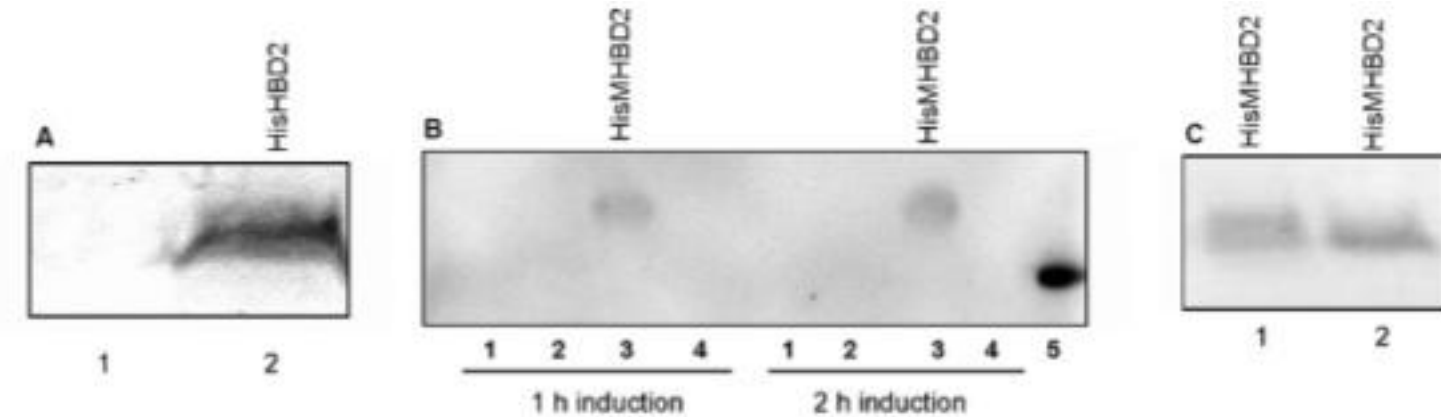
Wehkamp et al. *Infection and Immunity* 2004

Schlee et al. *Infection and Immunity* 2007

Möndel et al.; *Mucosal Immunology* 2009

Construction of recombinant *E. coli* Nissle 1917 (EcN) strains for the expression and secretion of defensins

Ean-jeong Seo^a, Stephanie Weibel^b, Jan Wehkamp^c, Tobias A. Oelschlaeger^{a,*}



HBD2 als YebF-Fusionsprotein sezerniert und antibakteriell aktiv

CED ein Defekt der antibakteriellen Barriere

Crohn: Defensine ↓

Colitis: Mucine ↓

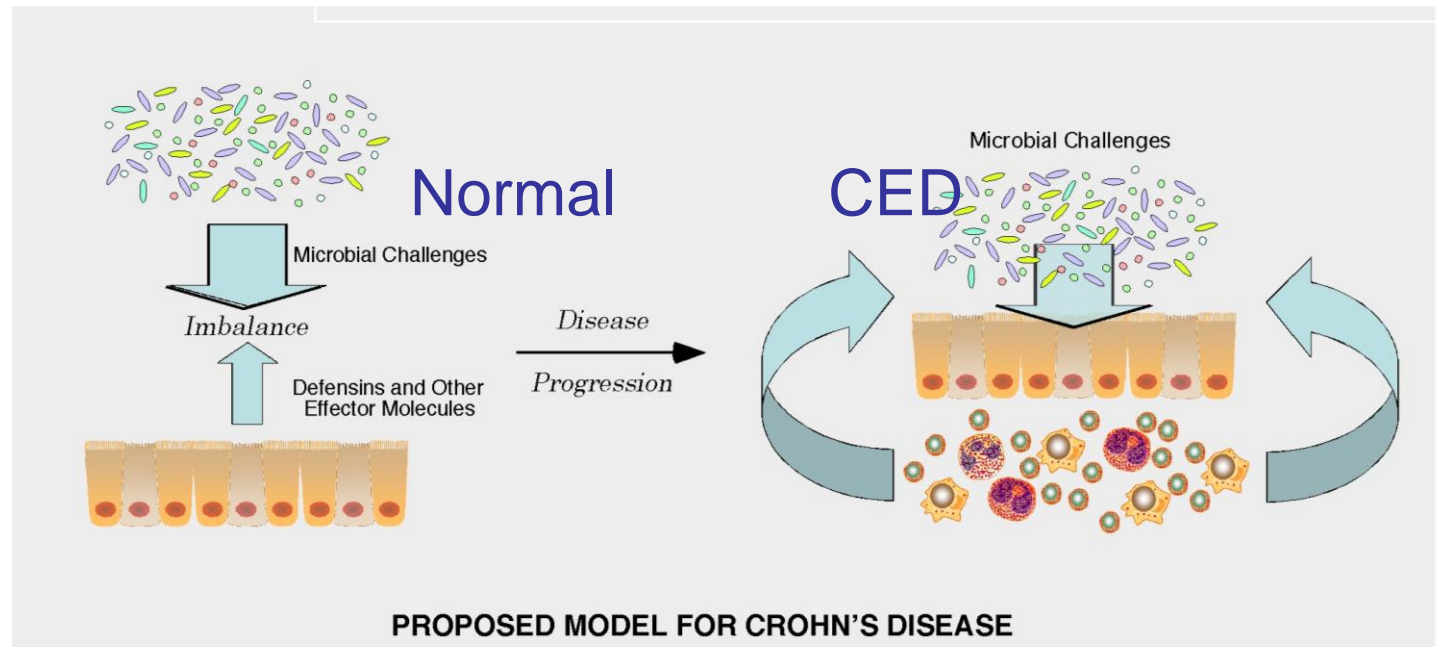
Gersemann et al. Differentiation 2009

Fellermann et al. 2003
Crohn's disease: a defensin deficiency syndrome?

Antibiotische Aktivität in Mucus/Mucosa ↓

Adherent-invasive Bakterien an der Mucosa

Immunreaktion gegen kommensale Flora



Wehkamp et al.
Nature Clin Pract
2006

