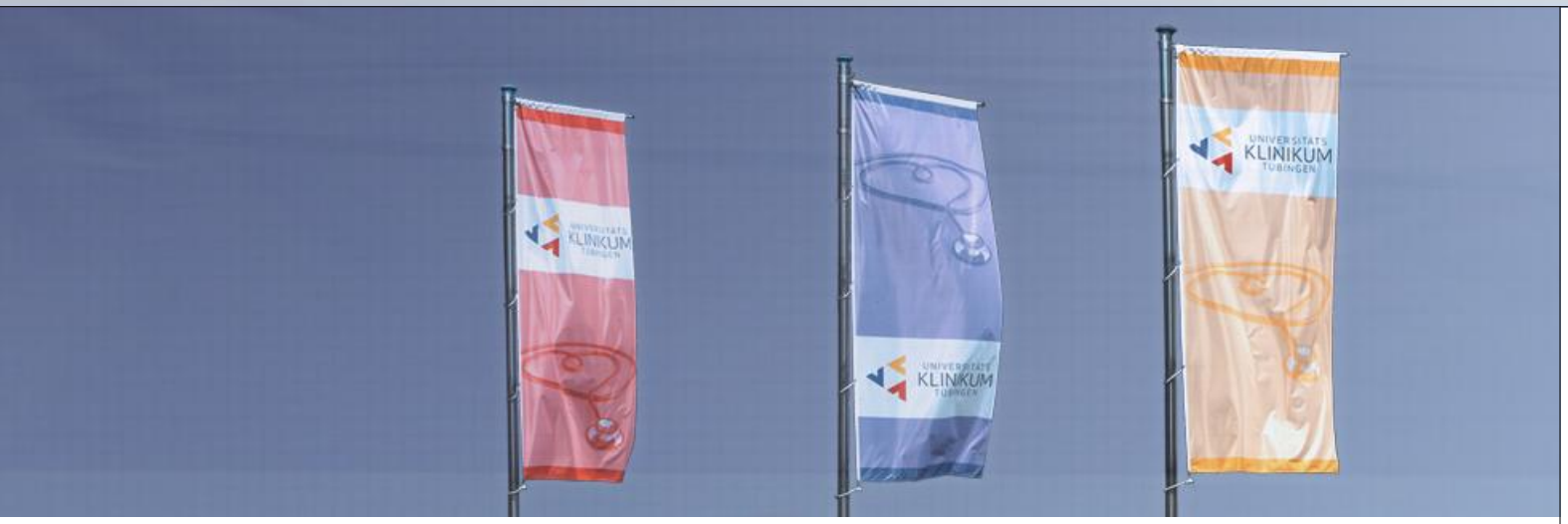

Chronisch entzündliche Darmerkrankungen

Dr. med. Thomas Klag

Arbeitsgruppe Univ. Prof. Dr. med. Jan Wehkamp

Universitätsklinikum Tübingen

Abteilung Innere Medizin I

Hepatologie, Gastroenterologie, Infektiologie

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Chronisch entzündliche Darmerkrankungen und Infektionsmedizin

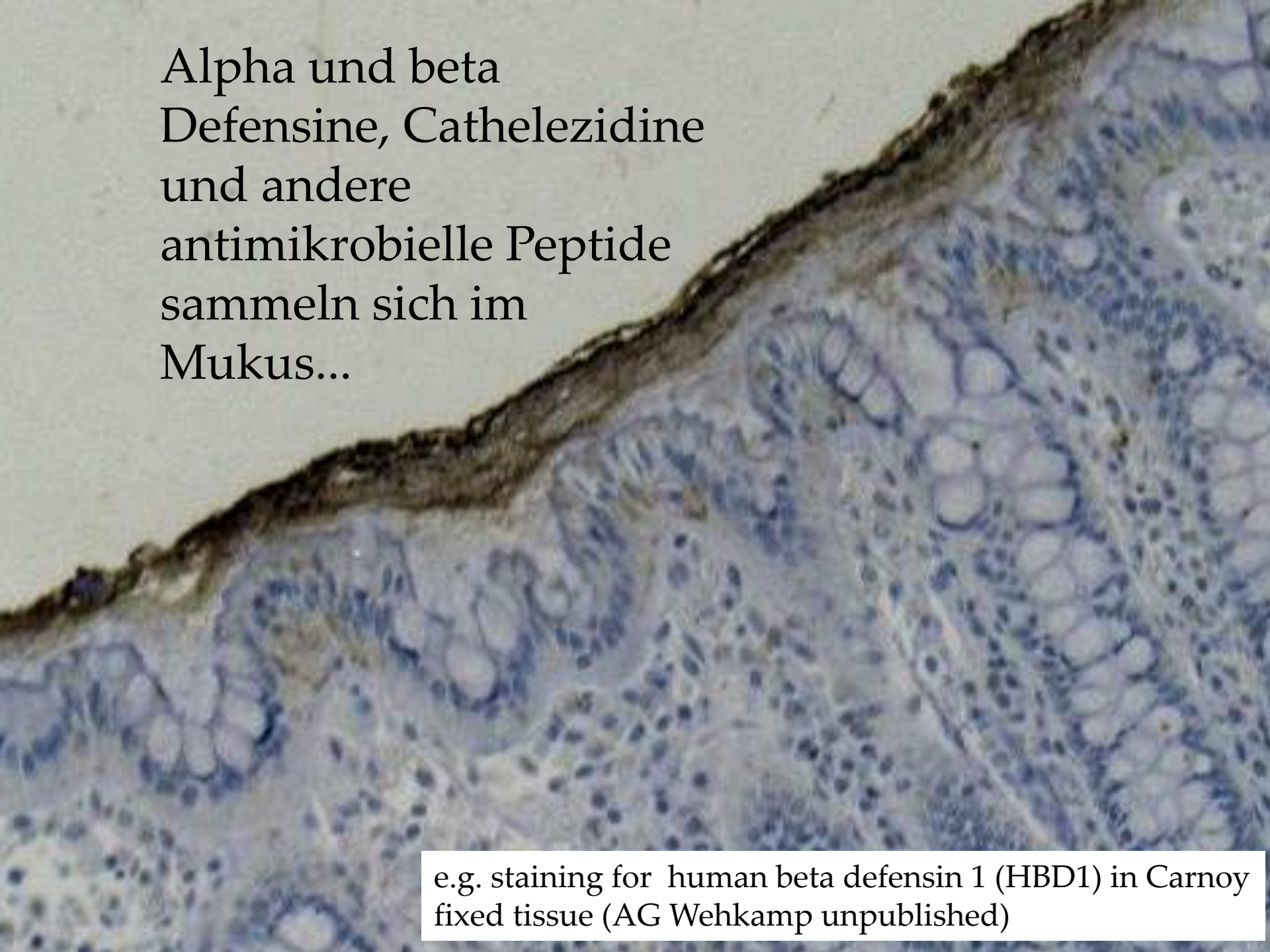
- Darmbarriere als *„first line of defense“* gegen Darmmikrobiom
- Komplikationen von CED: Abszesse, Fisteln, Peritonitis, toxisches Megakolon
- Therapie im Spannungsfeld zwischen Immunsuppression und Infektion
- Therapie assoziierte infektiologische Komplikationen:
  - opportunistische Infektionen unter Mehrfachimmunsuppression
  - Reaktivierung latenter Infektionen (TBC, Hepatitis B)
- Komplikativer Verlauf: CMV-Colitis, Clostridium difficile Infektionen
- Probleme bei der initialen differentialdiagnostischen Abgrenzung:
  - Yersiniose, atypische Mykobakteriose, TBC, infektiöse Colitis, post-infektiöses Reizdarmsyndrom

Chronisch entzündliche Darmerkrankungen und Infektionsmedizin

Darmbarriere als *„first line of defense“*

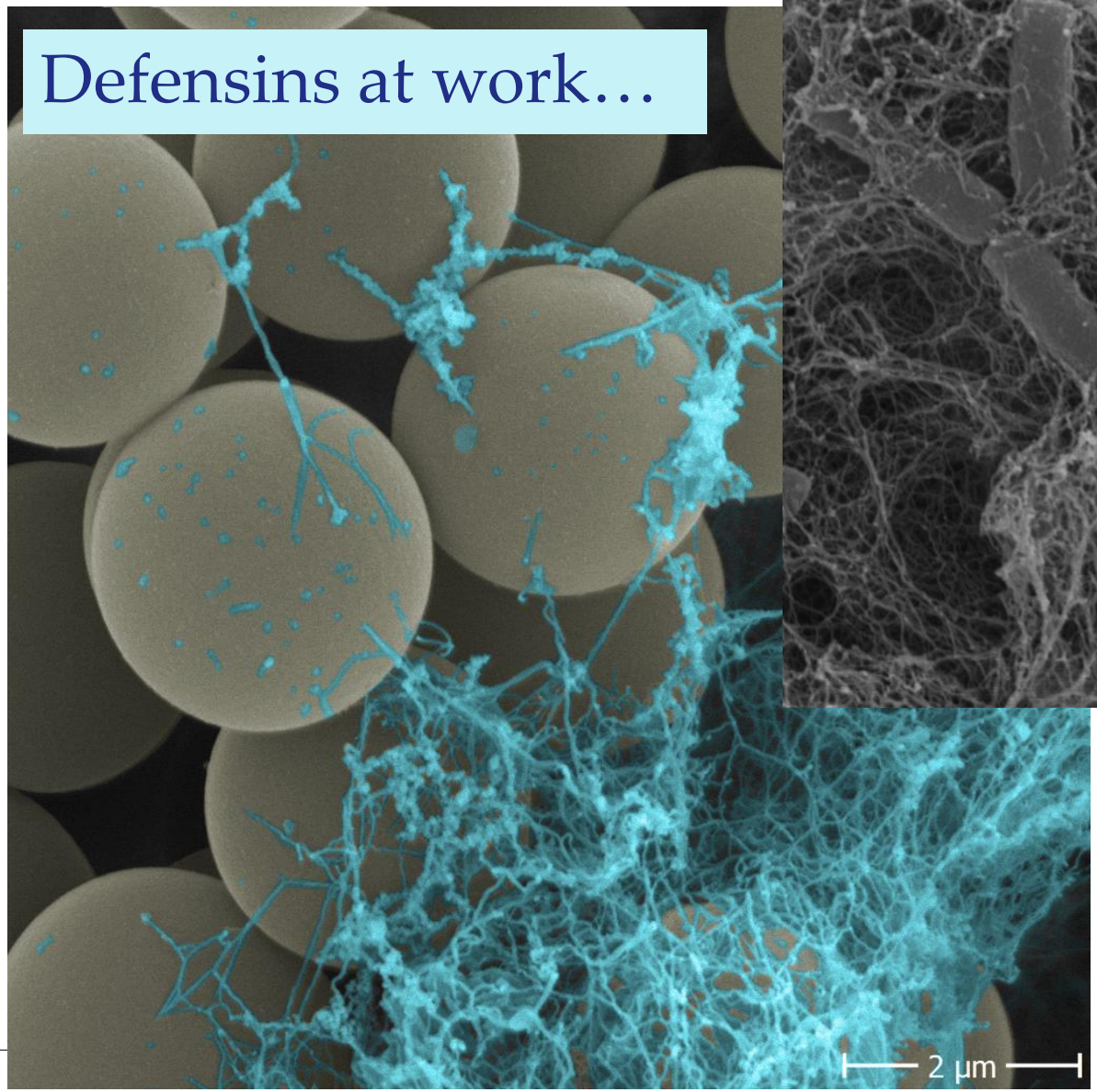
- **Pathophysiologische Bedeutung bei CED**
- **Therapeutische Implikationen bei CED**

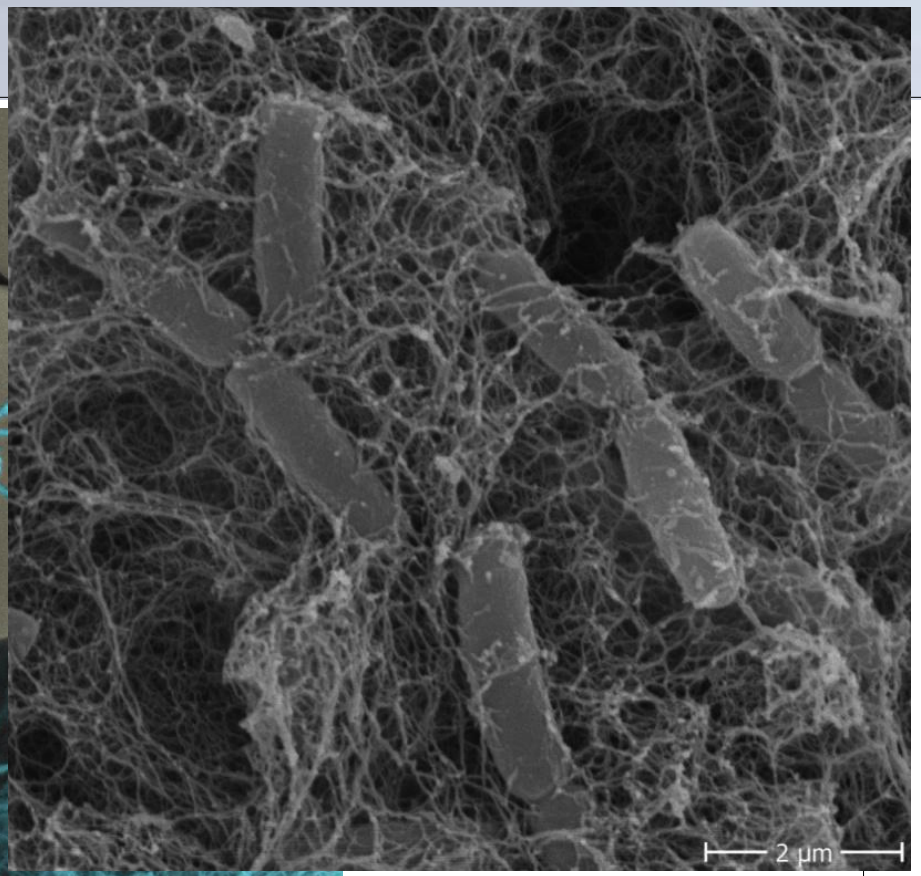
Alpha und beta Defensine, Cathelezidine und andere antimikrobielle Peptide sammeln sich im Mukus...



e.g. staining for human beta defensin 1 (HBD1) in Carnoy fixed tissue (AG Wehkamp unpublished)

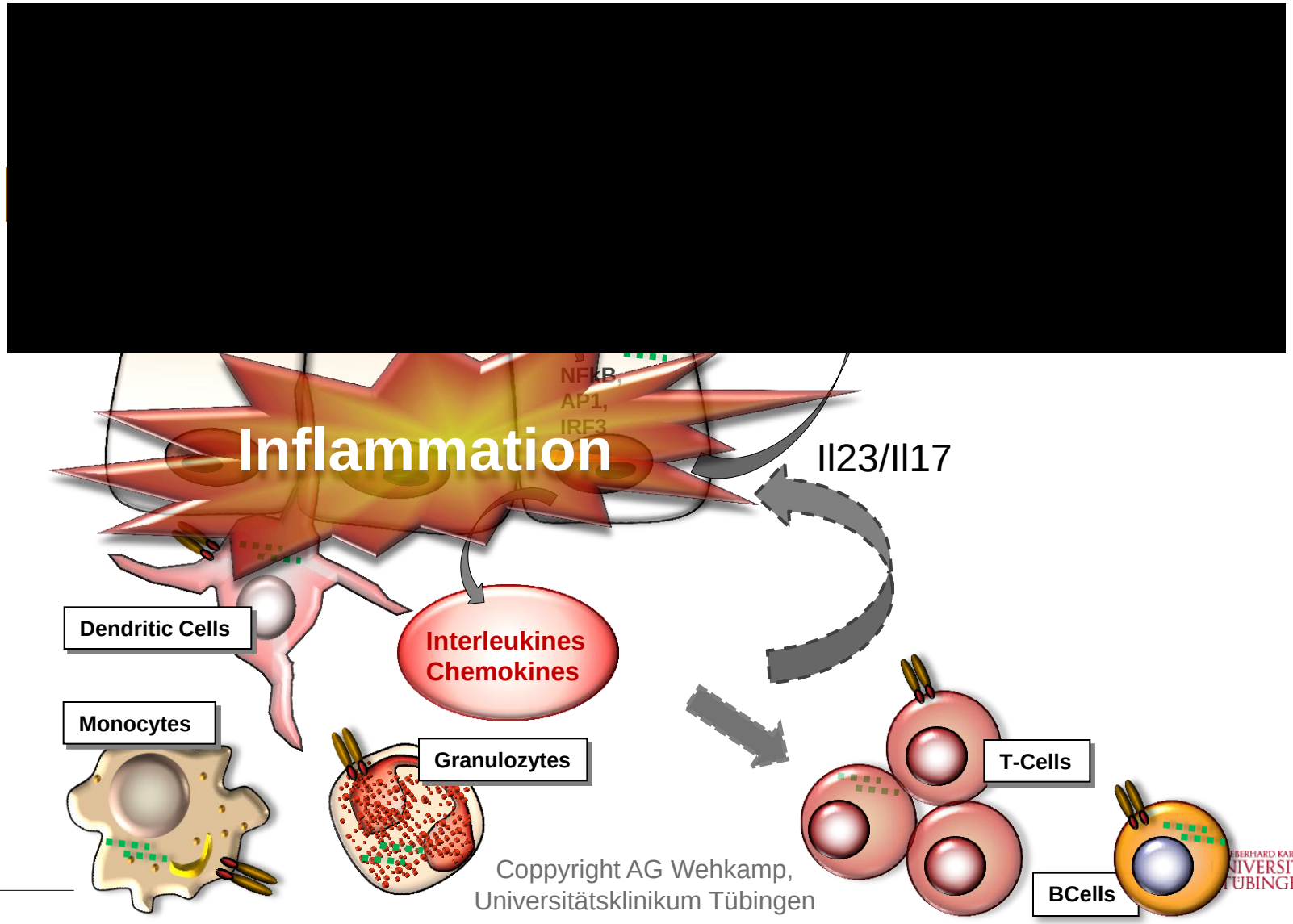
Understanding mechanism (s) of action of antimicrobial peptides: netting the enemy



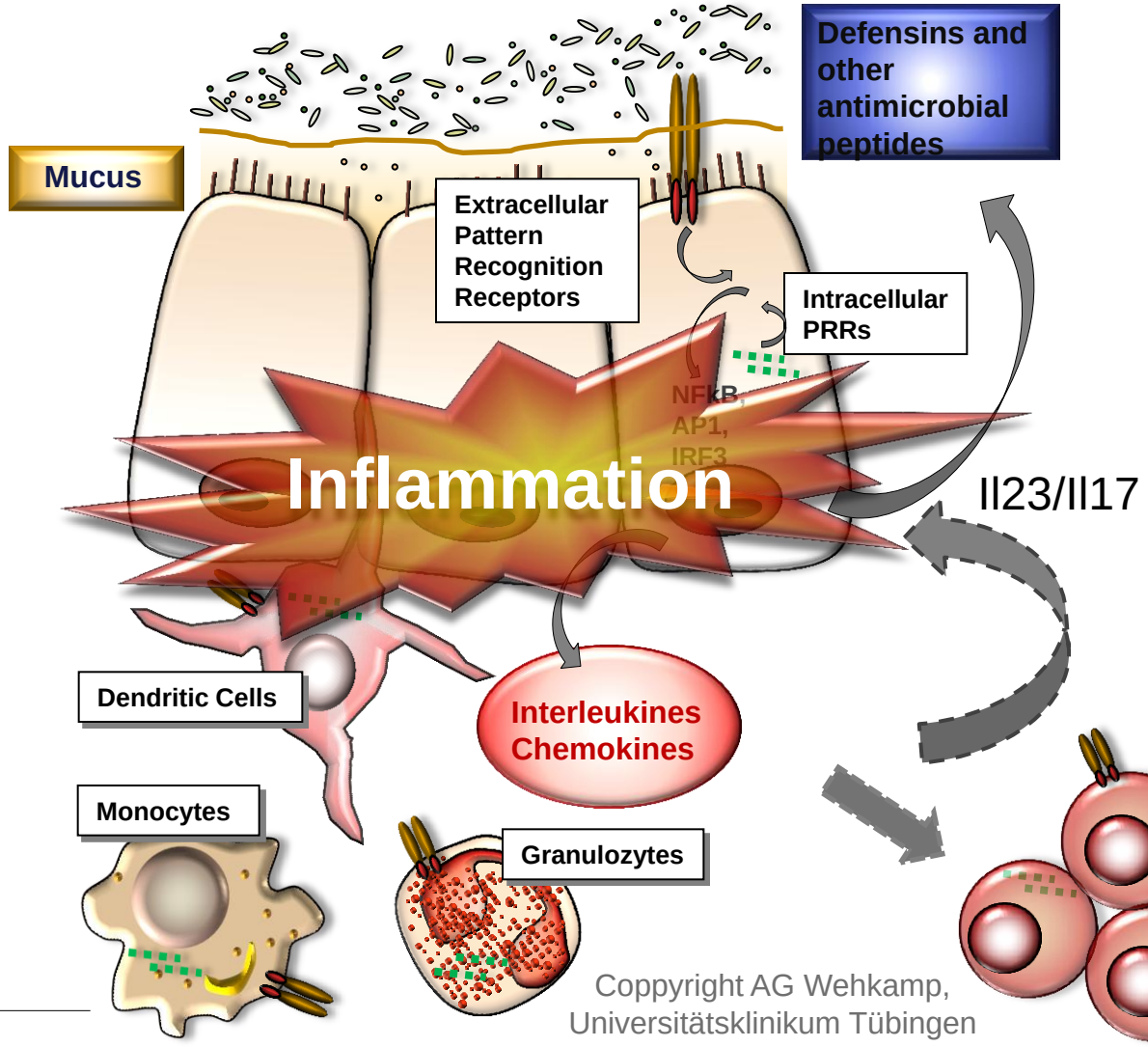


Raschig et al.
PloS Pathogens,
March 2017
modified Art version for
title illustration (left)

Paradigmenwechsel im Verständnis chronisch entzündlicher Darmerkrankungen



Paradigmenwechsel im Verständnis chronisch entzündlicher Darmerkrankungen

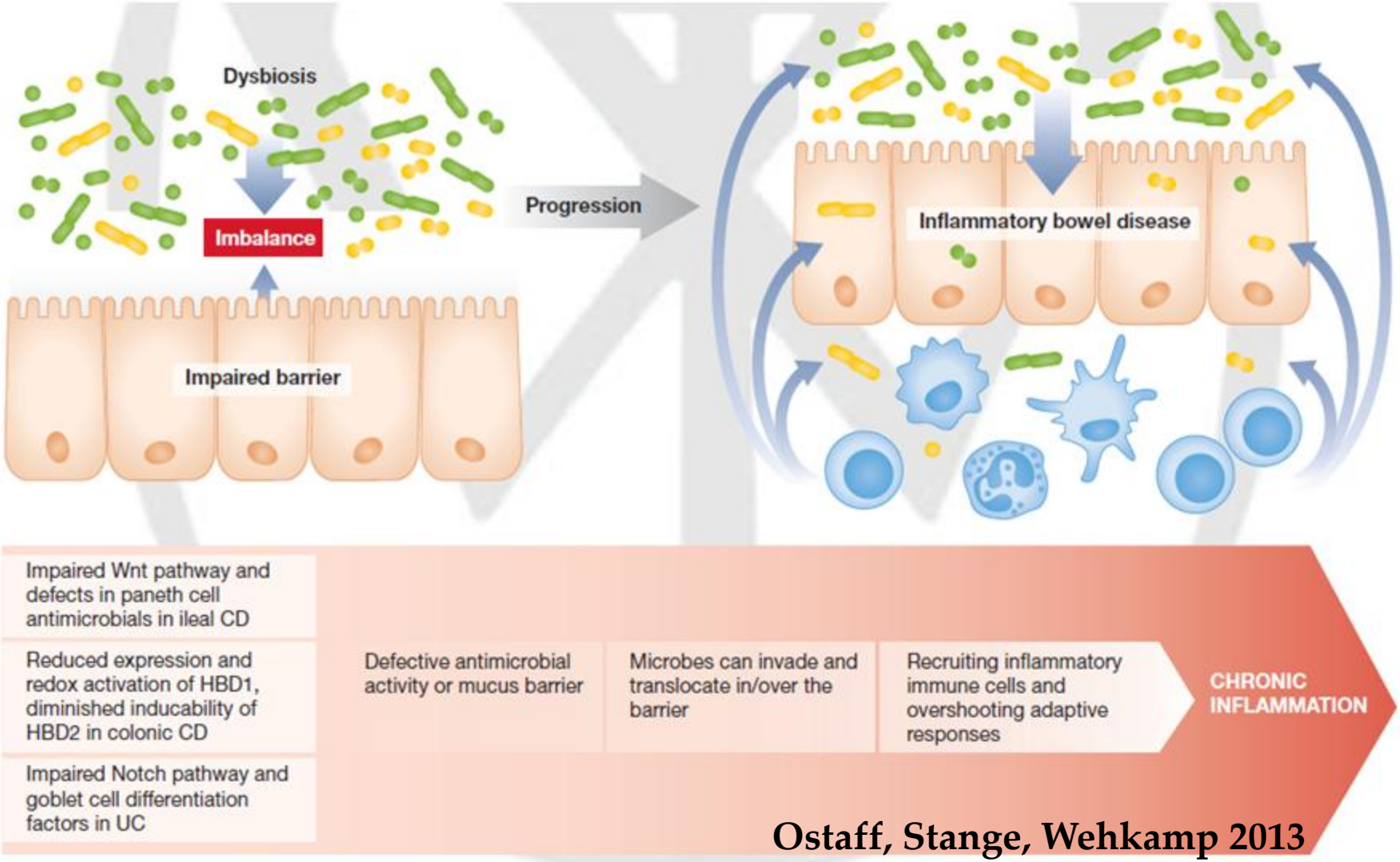


...from „*autoimmune*“ to defective barrier disease

EMBO Molecular Medicine
Review Series
Host–pathogen interactions

Intakte antimikrobielle Barriere schützt uns vor Entzündung und Tod

- Wandel der Krankheitskonzepte - Forschung am UKT



Ostaff, Stange, Wehkamp 2013

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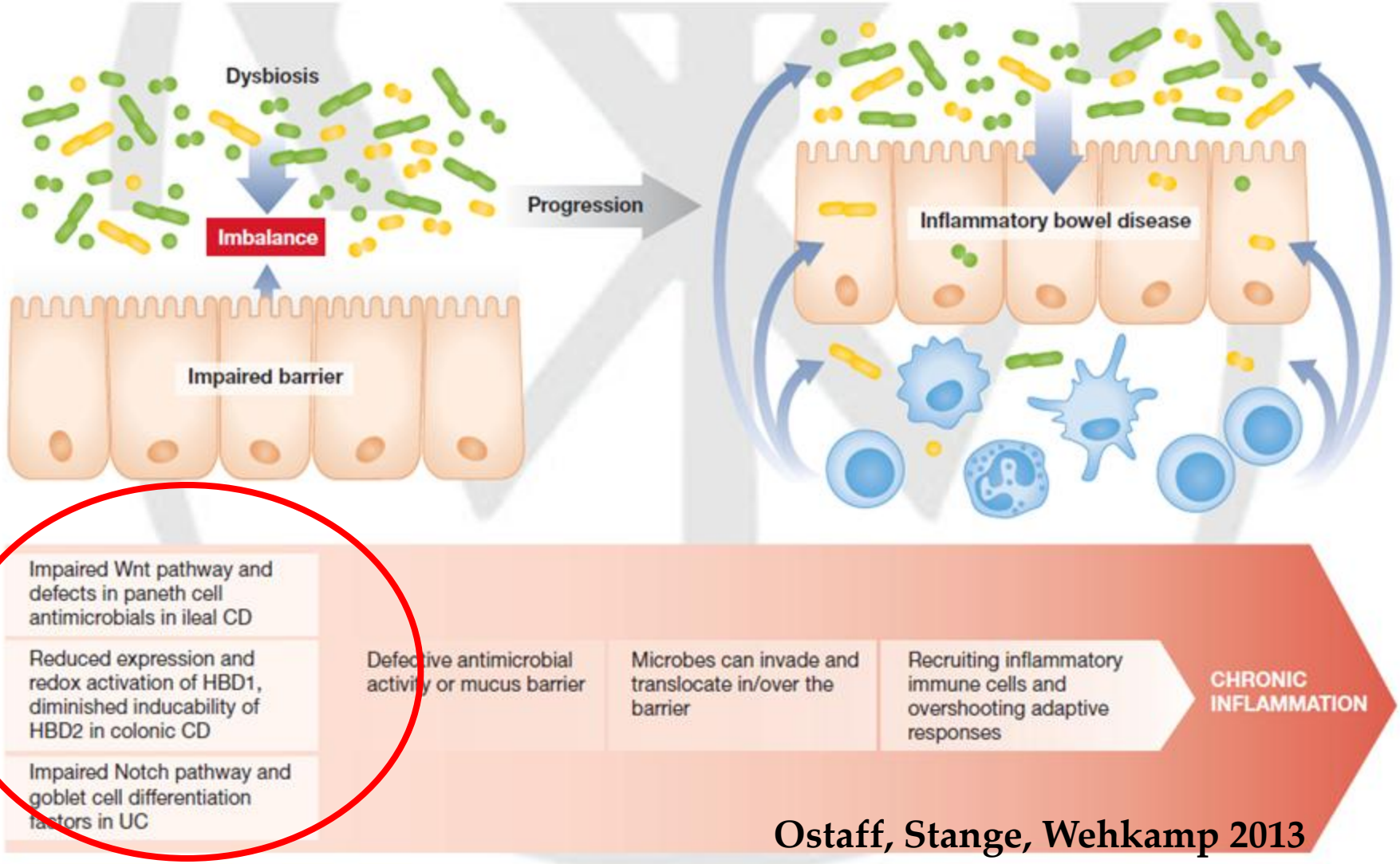
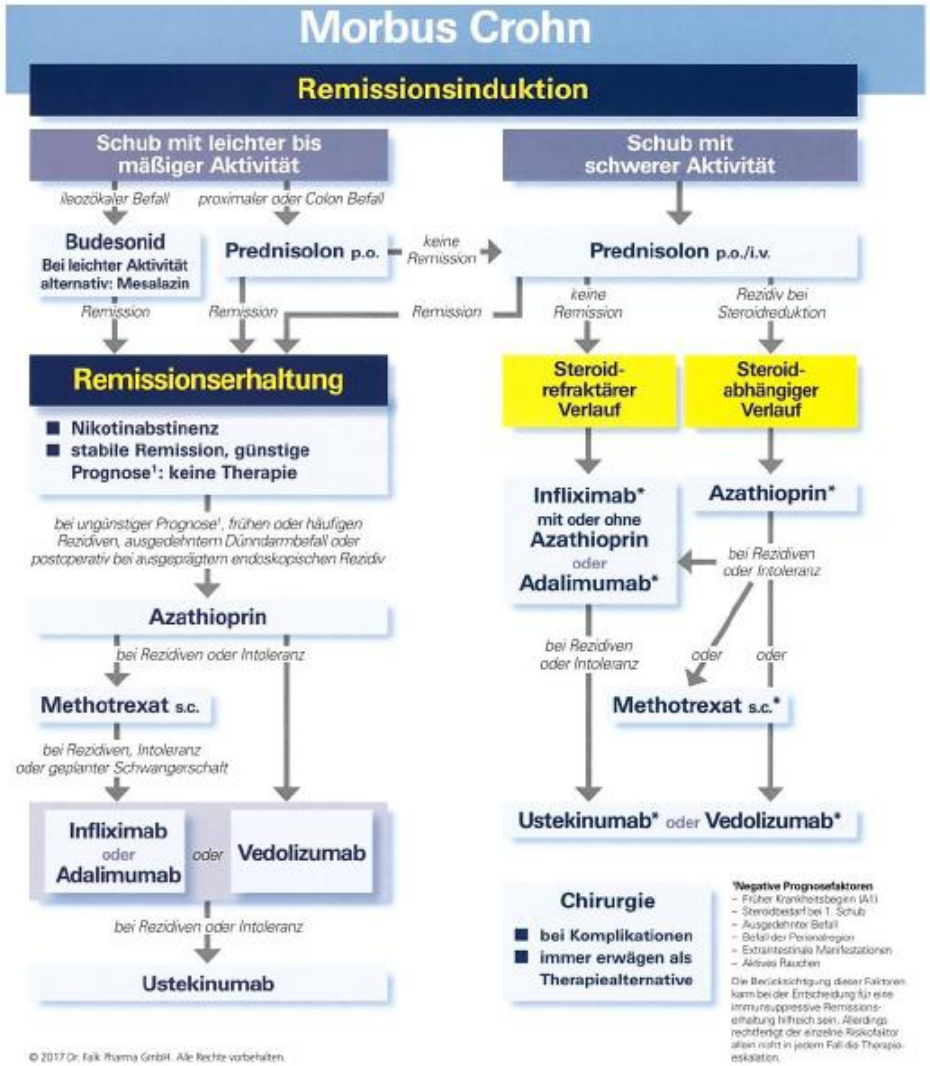
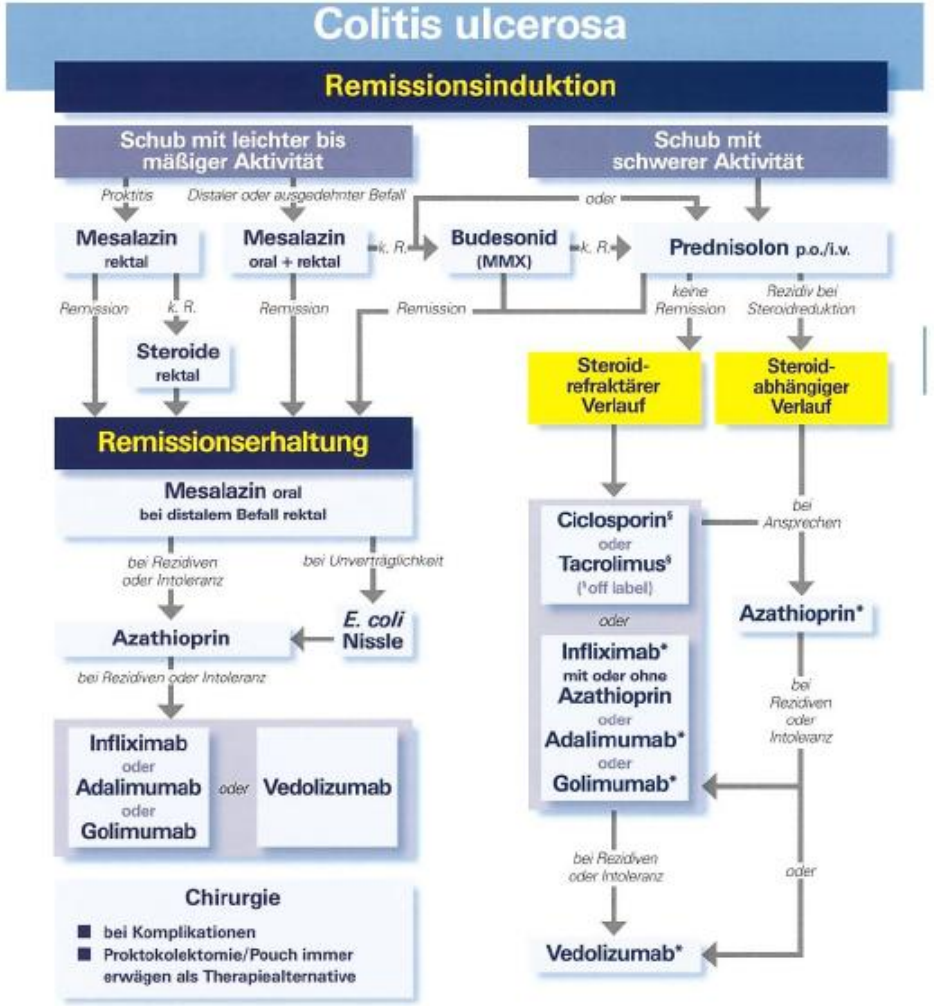


Ostaff, Stange, Wehkamp 2013

Paradigmenwechsel im Verständnis chronisch entzündlicher Darmerkrankungen - Therapie?





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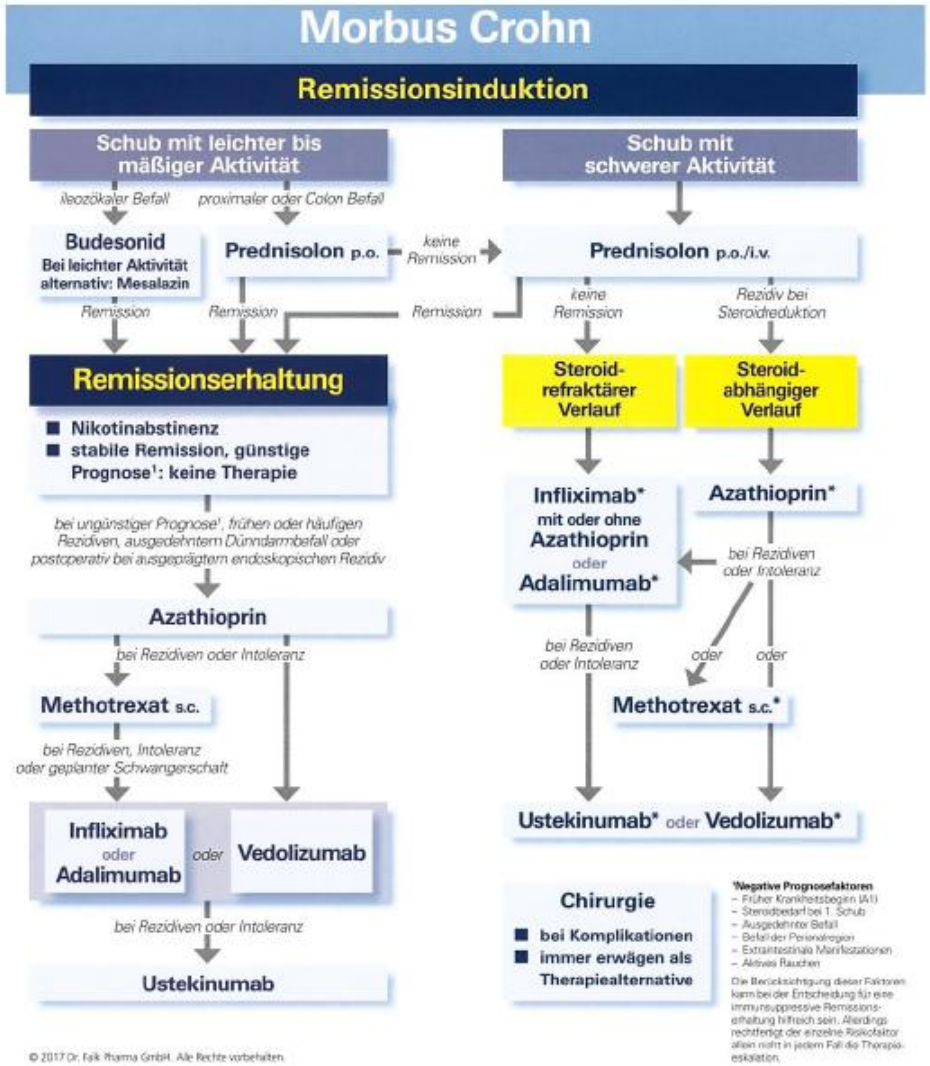

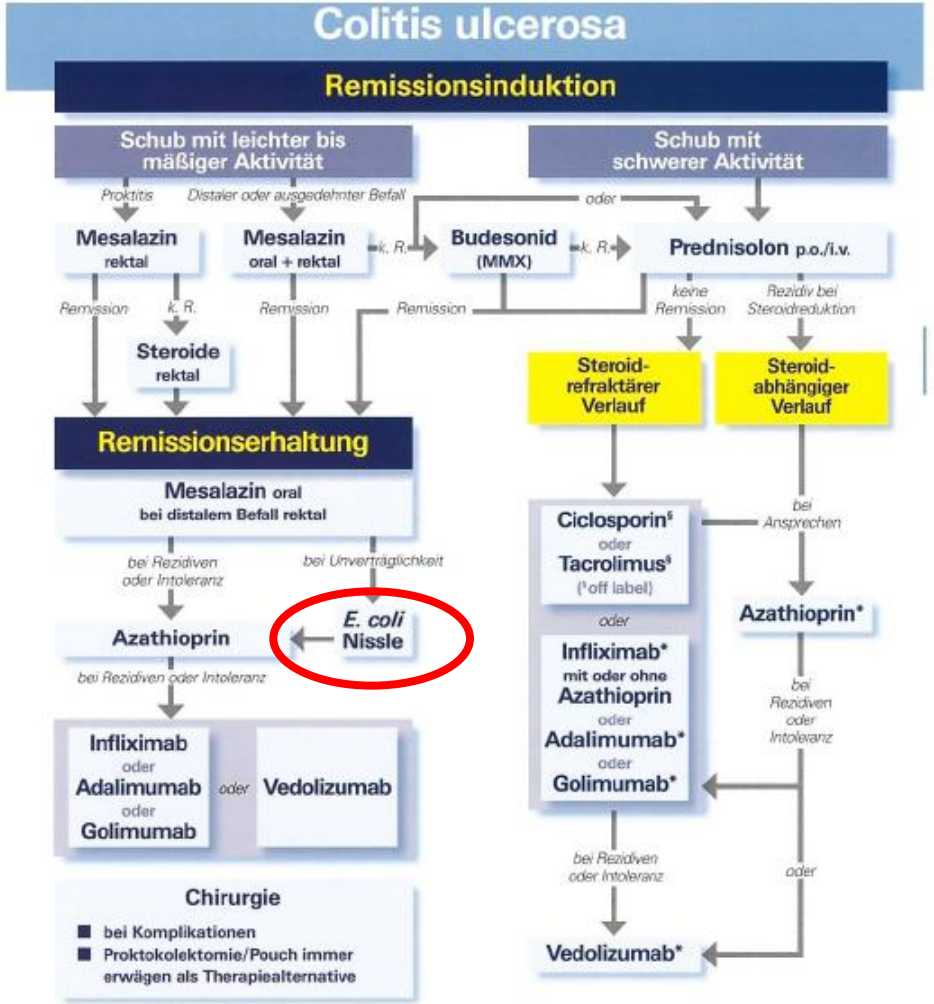

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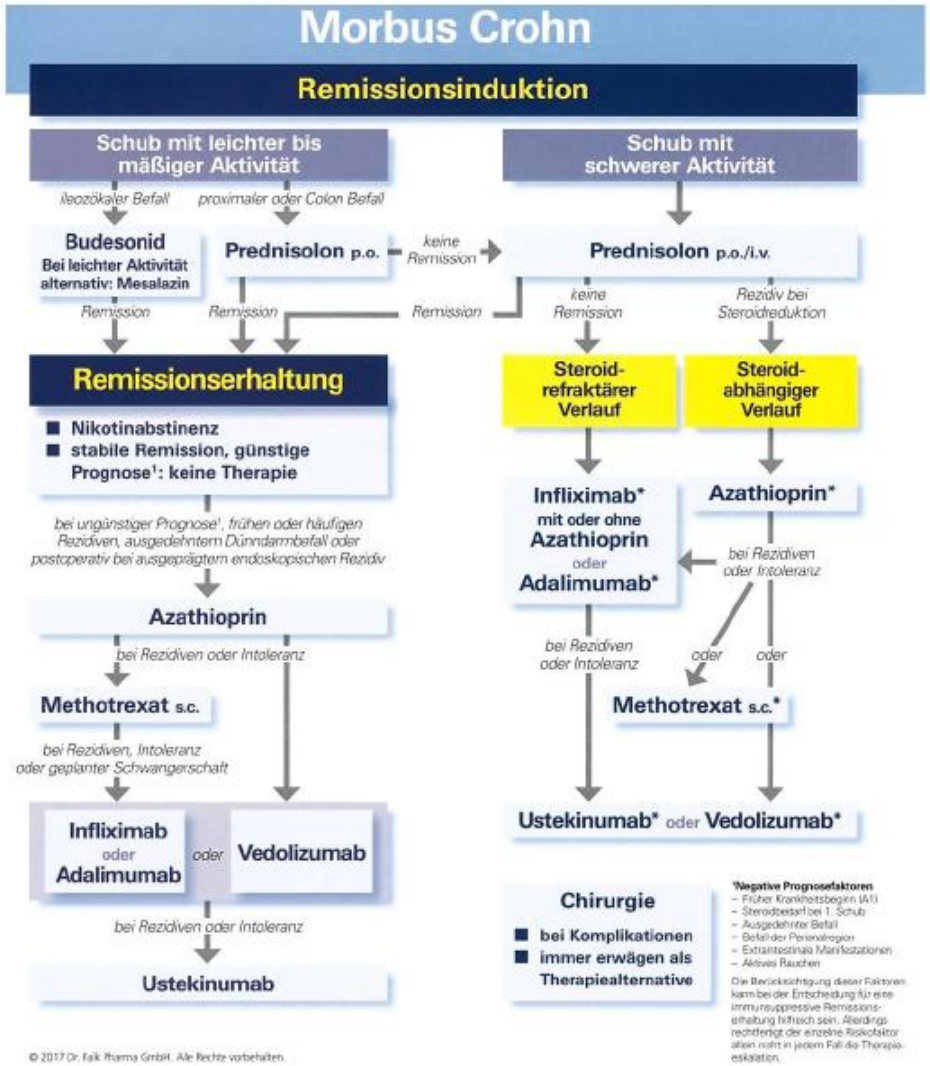

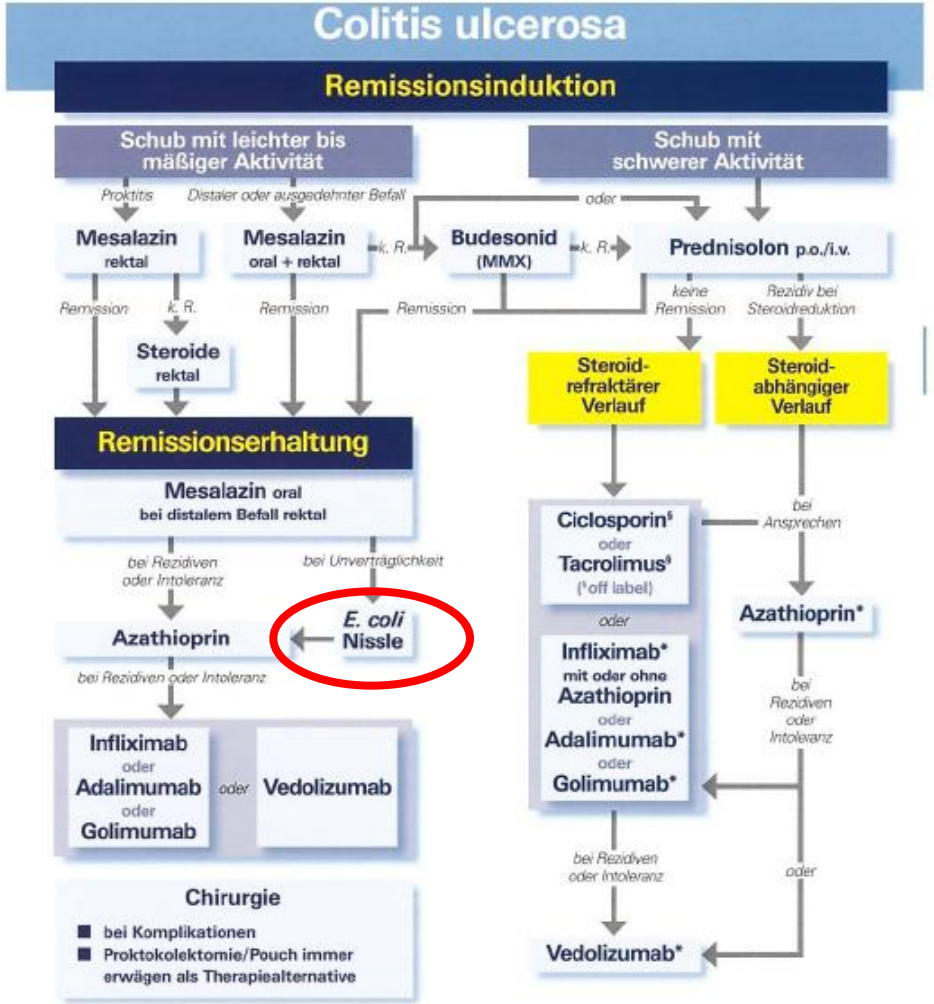

Bisher wenig Translation in die Therapie!

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Understanding disease pathogenesis-
Pioneering new treatment strategies

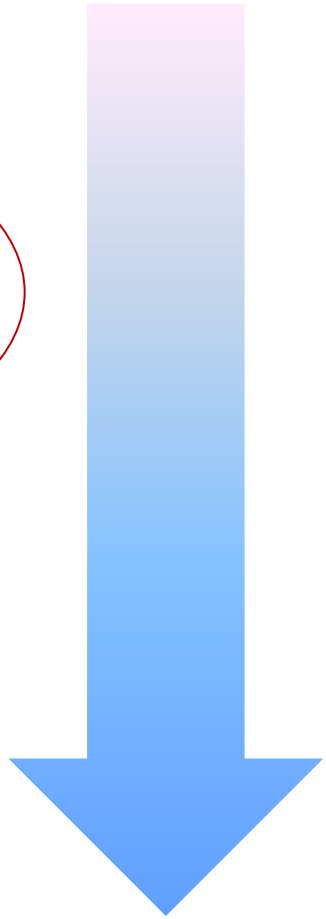
Anti- Infection

commensals/pathogens

microbiome

Anti-

Inflammation



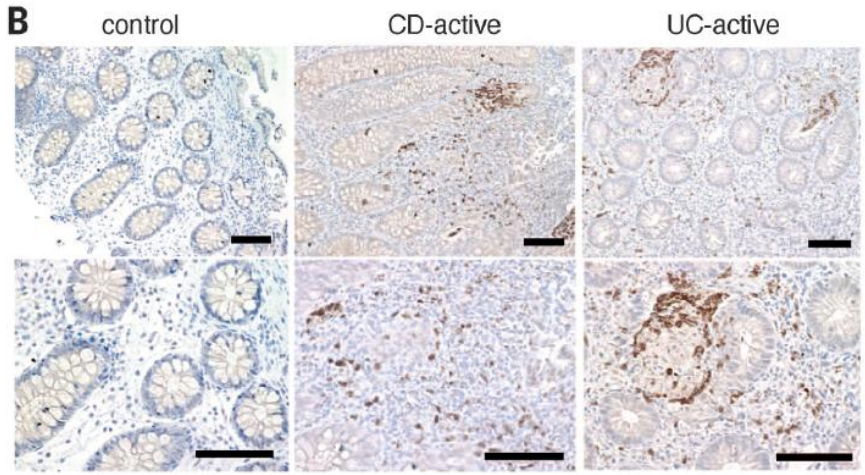
Sind anti-inflammatorische Biologika wirklich nur anti-inflammatorisch?

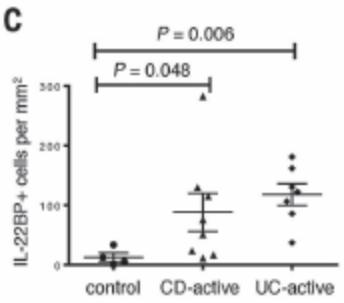
Verbindung zu Barriereprotektion vorhanden?

MUCOSAL IMMUNITY

A pathogenic role for T cell–derived IL-22BP in inflammatory bowel disease

Penelope Pelczar,[1*] Mario Witkowski,[1,2*] Laura Garcia Perez,[1*] Jan Kempski,[1] Anna G. Hammel,[1†] Leonie Brockmann,[1] Dörte Kleinschmidt,[1] Sandra Wende,[1] Cathleen Haueis,[1] Tanja Bedke,[1] Marco Witkowski,[3] Susanne Krasemann,[4] Stefan Steurer,[5] Carmen J. Booth,[6] Philipp Busch,[7] Alexandra König,[7‡] Ursula Rauch,[3] Daniel Benten,[1] Jakob R. Izbicki,[7] Thomas Rösch,[8] Ansgar W. Lohse,[1] Till Strowig,[9] Nicola Gagliani,[1,7§] Richard A. Flavell,[10§||] Samuel Huber[1§||]





MUCOSAL IMMUNITY

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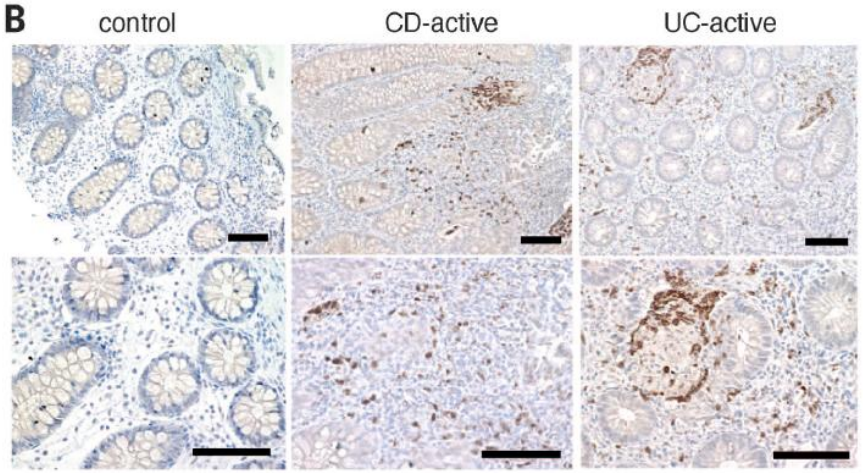

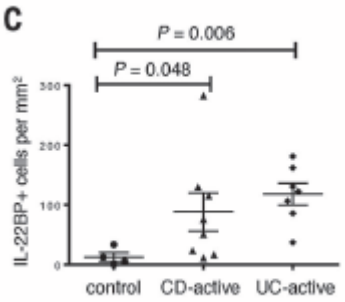

Protektives IL-22 wird bei CED durch hochreguliertes IL-22BP (binding protein) reduziert!

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Fig. 4. Anti–TNF-α therapy correlates with reduced IL-22BP expression by CD4$^+$ T cells in IBD (UC and CD) patients. (**A**) Correlation between *TNFα* and *IL22BP* mRNA expression, as measured by RT-PCR ($P = 0.004$; $r = 0.36$) of specimens from the intestines of patients with active IBD. In (B) to

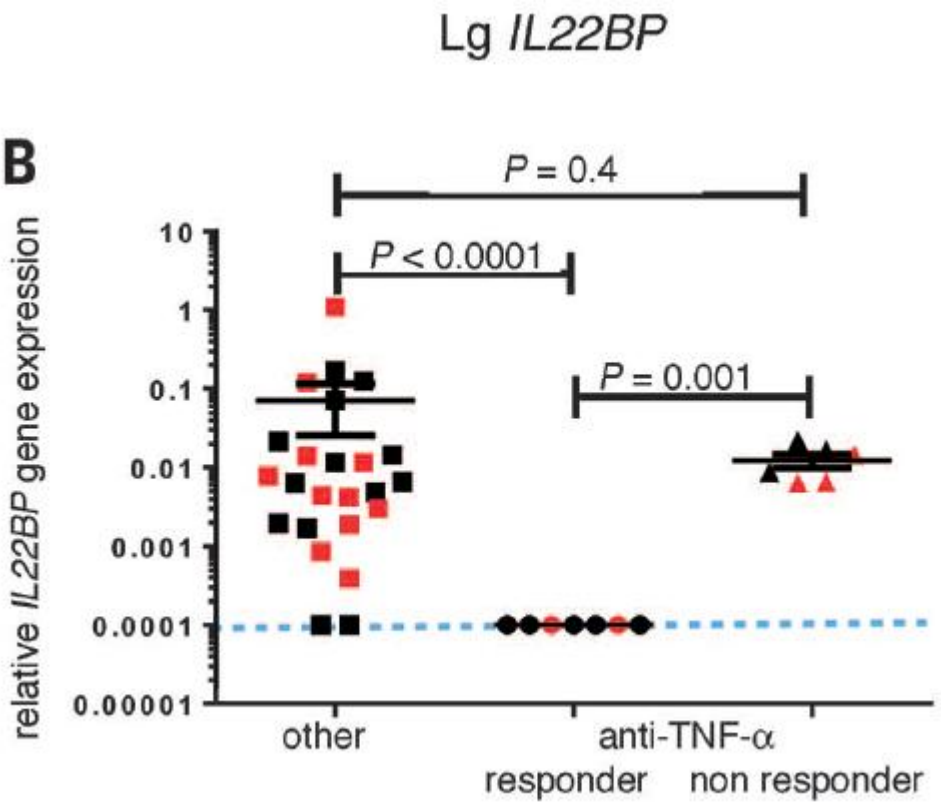
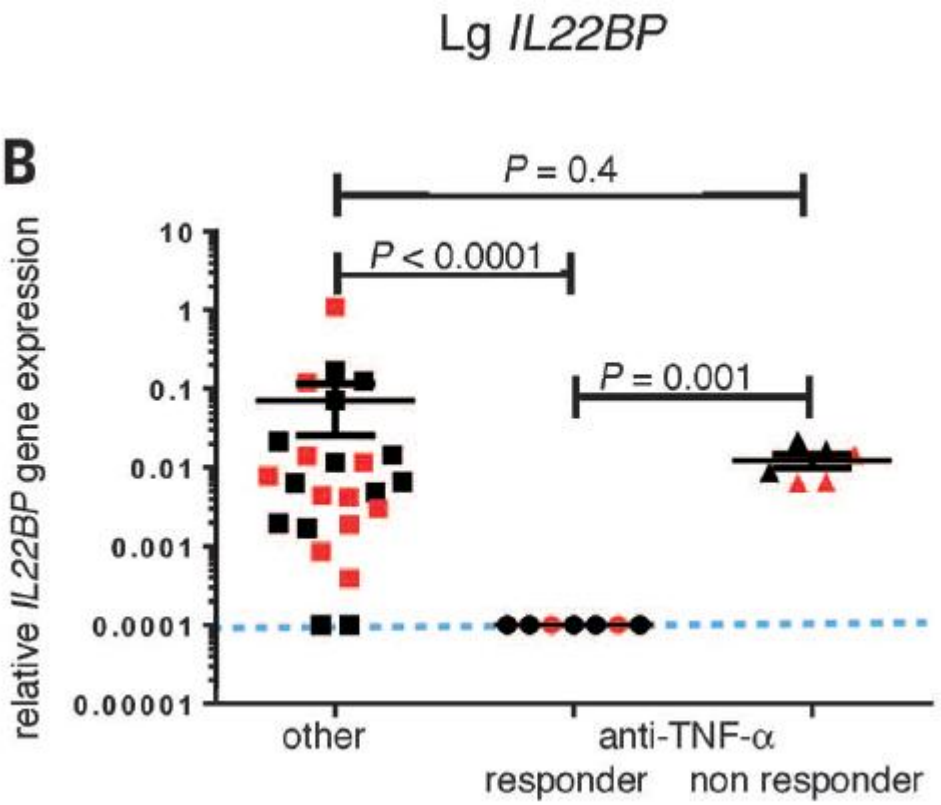


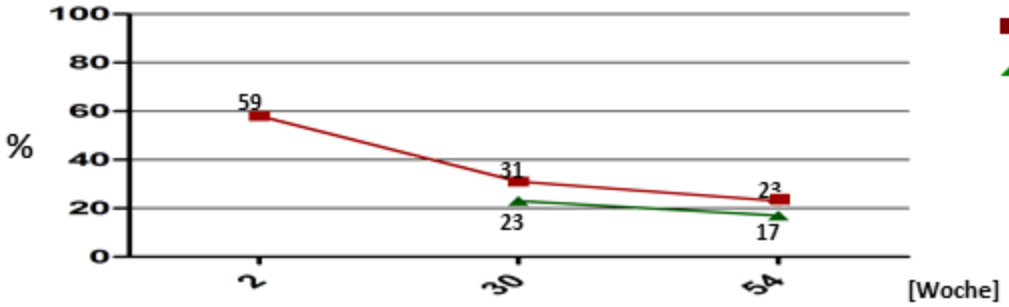
Fig. 4. Anti–TNF-α therapy correlates with reduced IL-22BP expression by CD4$^+$ T cells in IBD (UC and CD) patients. (**A**) Correlation between *TNFα* and *IL22BP* mRNA expression, as measured by RT-PCR ($P = 0.004$; $r = 0.36$) of specimens from the intestines of patients with active IBD. In (B) to



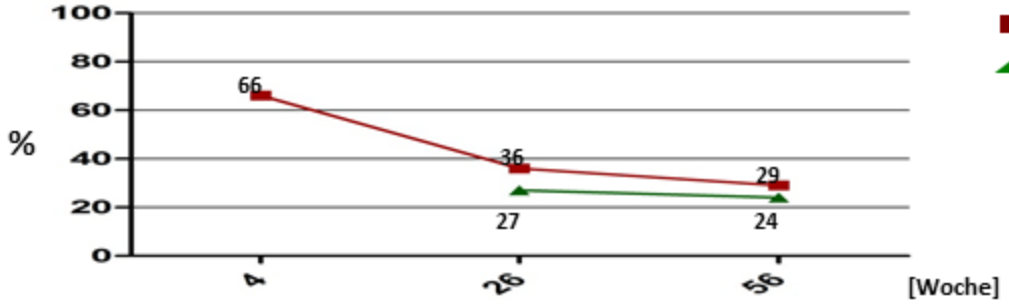
Ansprechen auf eine anti-TNF Therapie ist mit der verminderten Expression von IL-22BP assoziiert!

Sind die anti-inflammatorischen Medikamente, die verfügbar sind, ausreichend?

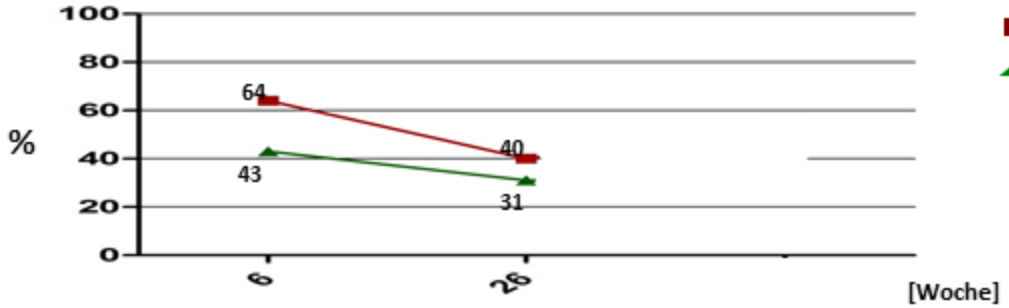
Morbus Crohn



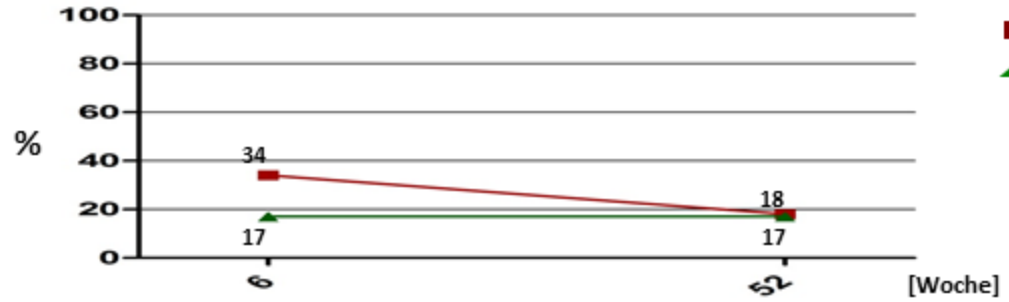
Infliximab
ACCENT 1
(5 mg/kg/8Wo)



Adalimumab
CHARM
(40 mg/2Wo)



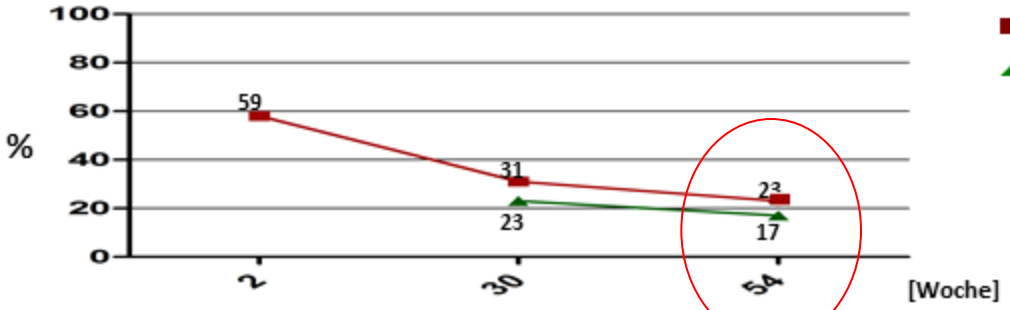
Certolizumab
PRECISE 2
(400 mg/4Wo)



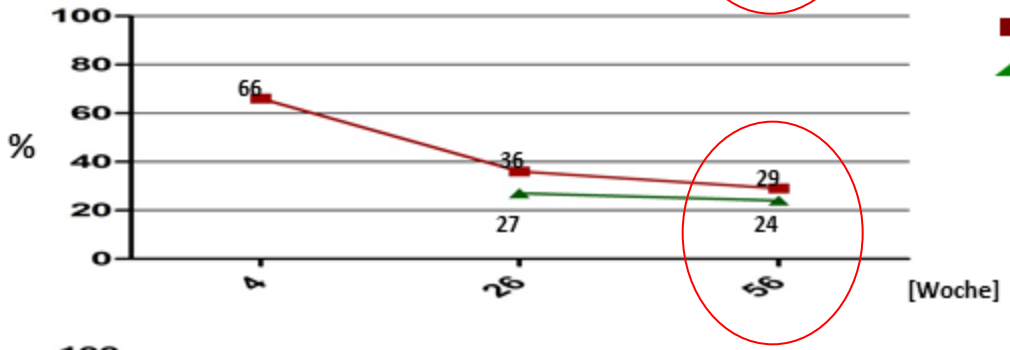
Vedolizumab
GEMINI 2
(300 mg/4Wo)

Zusammenstellung Stange, Klag, Wehkamp 2013

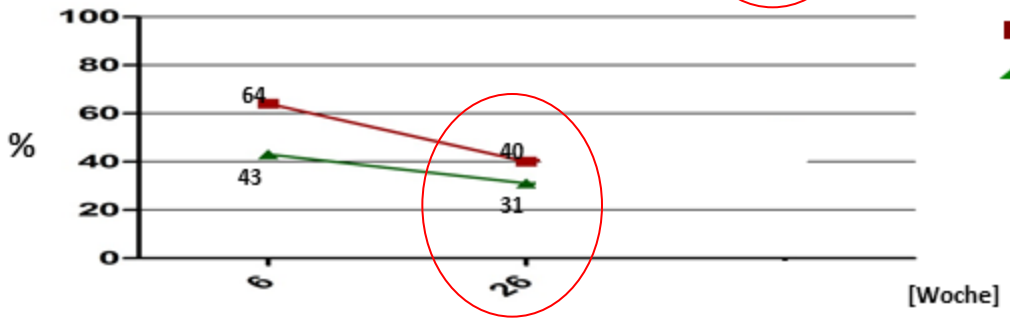
Morbus Crohn



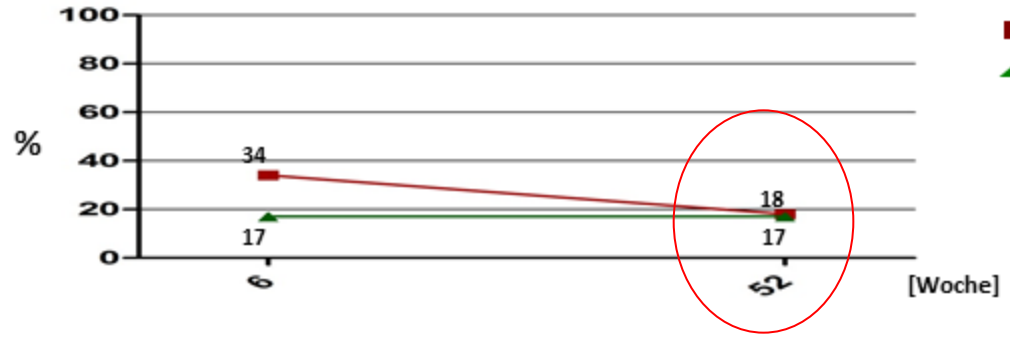
Infliximab
ACCENT 1
(5 mg/kg/8Wo)



Adalimumab
CHARM
(40 mg/2Wo)



Certolizumab
PRECISE 2
(400 mg/4Wo)



Vedolizumab
GEMINI 2
(300 mg/4Wo)

Zusammenstellung Stange, Klag, Wehkamp 2013

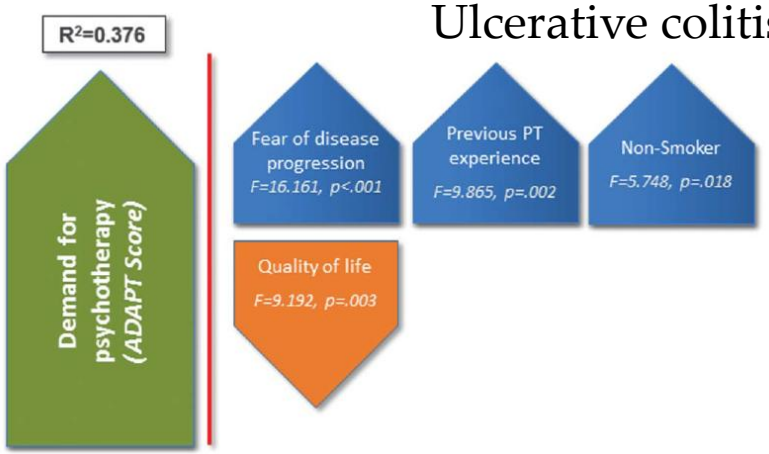
High Demand for Psychotherapy in Patients with Inflammatory Bowel Disease

Thomas Klag, MD, Nazar Mazurak, MD,† Laura Fantasia,* Juliane Schwille-Kiuntke, MD,† Andreas Kirschniak, MD,‡ Claudius Falch, MD,‡ Martin Goetz, MD,* Nisar P. Malek, MD,* Paul Enck, Dip Psych,† and Jan Wehkamp, MD**

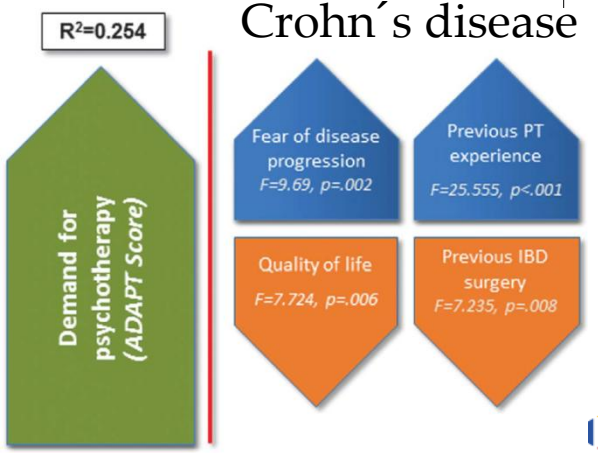
Results: n = 631 patients responded, and complete data from n = 578 (356 Crohn's disease, 219 ulcerative colitis, 3 unclear) were available for analysis. n = 296 had previous experiences with psychotherapy, whereas n = 282 had not. This distribution clearly determined the factor "demand for psychotherapy" (chi-square = 23.7, $P < 0.001$). When all available data were entered into a (stepwise-forward) regression model, psychotherapy demand was dependent on previous experience ($P < 0.001$), fear of progression ($P < 0.001$), quality of life ($P = 0.001$), smoking ($P = 0.003$), and previous surgery ($P = 0.005$) with the total model explaining 29.7% of the variance. The total explained variance of this model was higher in ulcerative colitis (37.6%) than in Crohn's disease alone (25.4%).

Conclusions: The demand for psychotherapy as additional therapy in IBD depends on previous experience with psychotherapy, fear for disease progression but also other disease or social characteristics and quality of life.

Ulcerative colitis



Crohn´s disease



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Was ist mit Mikrobiom modulierenden Therapieansätzen?

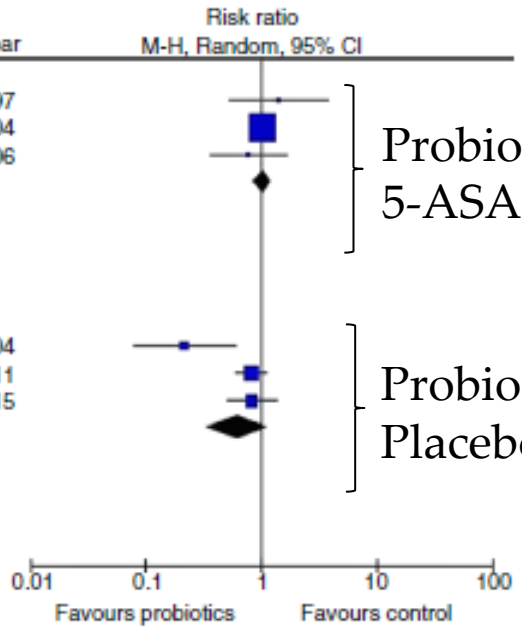
Probiotika zur Behandlung von chronisch entzündlichen Darmerkrankungen?

2017 WILEY APT Alimentary Pharmacology & Therapeutics

Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease

Y. Derwa[1,2,*] | D. J. Gracie[1,2,*] | P. J. Hamlin[1] | A. C. Ford[1,2]

Study or subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
4.2.1 Probiotics vs. 5-ASA							
Kruis (1997)	8	50	6	53	3.5%	1.41 [0.53, 3.79]	1997
Kruis (2004)	92	162	91	165	90.8%	1.03 [0.85, 1.25]	2004
Zocco (2006)	10	65	12	60	5.8%	0.77 [0.36, 1.65]	2006
Subtotal (95% CI)		277		278	100.0%	1.02 [0.85, 1.23]	
Test events	110		109				
Heterogeneity: τ^2=.00, χ^2=.96, df=2 (*P*=.62), I^2=0%							
Test for overall effect: *Z*=.25 (*P*=.80)							
4.2.2 Probiotics vs. control							
Cui (2004)	3	15	14	15	21.0%	0.21 [0.08, 0.59]	2004
Wildt (2011)	15	20	11	12	42.4%	0.82 [0.60, 1.11]	2011
Yoshimatsu (2015)	14	30	17	30	36.5%	0.82 [0.50, 1.35]	2015
Subtotal (95% CI)		65		57	100.0%	0.62 [0.33, 1.16]	
Test events	32		42				
Heterogeneity: τ^2=.22, χ^2=8.19, df=2 (*P*=.02), I^2=76%							
Test for overall effect: *Z*=1.50 (*P*=.13)							
Test for subgroup differences: χ^2=2.27, df=1 (*P*=.13), I^2=55.9%							



- **Wirksam bei der Remissionserhaltung bei Colitis ulcerosa, (nicht wirksam zur Remissionsinduktion).**
- **Keine Wirksamkeit bei Morbus Crohn.**

The Current Landscape and Lessons from Fecal Microbiota Transplantation for Inflammatory Bowel Disease: Past, Present, and Future

Jessica Allegretti, MD, MPH,[*,†] Lindsay M. Eysenbach, BA,[‡,§] Najwa El-Nachef, MD,[‖] Monika Fischer, MD, MSc,[¶] Colleen Kelly, MD,[**] and Zain Kassam, MD, MPH[†]*

TABLE 1. Summary of Randomized Controlled Trials for UC

Study	n	Disease Activity for Inclusion	Concurrent Medications Allowed	FMT Delivery	Dosing	Donor Stool	Control	Outcome Assessed	*P*
Moayyedi et al 2015[2]	65	Mayo clinical score ≥4	Oral mesalamine, glucocorticoids, Azathioprine Anti-tnfs	Enema (50 mL)	1/week	Unrelated volunteers	Water enema	Complete Mayo score <3 and a endoscopic subscore = 0 At week 6	FMT group: 9/38, control group: 2/37, $P = 0.03$
Rossen et al 2015[3]	48	SCCAI ≥4 and ≤11	Thiopurines, mesalamine, corticosteroids	Nasoduodenal (500 mL)	Week 0 and week 3	Patient directed donors	Autologous stool	SCCAI ≤2, and ≥1-point improvement in Mayo endoscopic subscore at week 12	FMT group: 7/23, control group: 5/25, $P = 0.29$
Paramsothy et al 2017[4]	81	Mayo Clinical score 4–10 and endoscopic subscore ≥1	Oral mesalamine thiopurines methotrexate prednisone (fixed taper during study)	Initial colonoscopy (150 mL), maintenance enemas	5/week	Mixed unrelated donors (3–7 donors per patient)	Saline enema	Total Mayo Score ≤2 with all 4 subscores ≤1 and ≥1 point reduction in endoscopic subscore	FMT group: 11/41, control group: 3/40, $P = 0.02$
Costello et al 2017[26]	73	Mayo score 3–10 and endoscopic subscore ≥2	Oral and rectal mesalamine, thiopurines, methotrexate, infliximab, or vedolizumab.	Initial colonoscopy, 2 enemas at week 1	Baseline, week 1	Anaerobically prepared pooled (3–4) unrelated donors	Autologous stool	Mayo score <2 and a Mayo endoscopic subscore of <1 at week 8	FMT group: 12/38, control group: 3/35, $P = 0.02$

Colitis ulcerosa→
(25-30%) Ansprechen

Morbus Crohn → unklar

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Study	n	Disease Activity for Inclusion	Concurrent Medications Allowed	FMT Delivery	Dosing	Donor Stool	Control	Outcome Assessed	*P*
Moayyedi et al 2015[2]	65	Mayo clinical score ≥4	Oral mesalamine, glucocorticoids, Azathioprine Anti-tnfs	Enema (50 mL)	1/week	Unrelated volunteers	Water enema	Complete Mayo score <3 and a endoscopic subscore = 0 At week 6	FMT group: 9/38, control group: 2/37, $P = 0.03$
Rossen et al 2015[3]	48	SCCAI ≥4 and ≤11	Thiopurines, mesalamine, corticosteroids	Nasoduodenal (500 mL)	Week 0 and week 3	Patient directed donors	Autologous stool	SCCAI ≤2, and ≥1-point improvement in Mayo endoscopic subscore at week 12	FMT group: 7/23, control group: 5/25, $P = 0.29$
Paramsothy et al 2017[4]	81	Mayo Clinical score 4–10 and endoscopic subscore ≥1	Oral mesalamine thiopurines methotrexate prednisone (fixed taper during study)	Initial colonoscopy (150 mL), maintenance enemas	5/week	Mixed unrelated donors (3–7 donors per patient)	Saline enema	Total Mayo Score ≤2 with all 4 subscores ≤1 and ≥1 point reduction in endoscopic subscore	FMT group: 11/41, control group: 3/40, $P = 0.02$
Costello et al 2017[26]	73	Mayo score 3–10 and endoscopic subscore ≥2	Oral and rectal mesalamine, thiopurines, methotrexate, infliximab, or vedolizumab.	Initial colonoscopy, 2 enemas at week 1	Baseline, week 1	Anaerobically prepared pooled (3–4) unrelated donors	Autologous stool	Mayo score <2 and a Mayo endoscopic subscore of <1 at week 8	FMT group: 12/38, control group: 3/35, $P = 0.02$

Wie? Was? Von wem? Wie oft?

Colitis ulcerosa→ (25-30%) Ansprechen

Morbus Crohn → unklar

Open
see related editorial on page 1052

First Multicenter Study of Modified Release Phosphatidylcholine "LT-02" in Ulcerative Colitis: A Randomized, Placebo-Controlled Trial in Mesalazine-Refractory Courses

Max Karner, MD[1,2], Andreas Kocjan, MD[3], Juergen Stein, MD, PhD[4], Stefan Schreiber, MD, PhD[5], Georg von Boyen, MD, PhD[6,7], Peter Uebel, MD[8], Carsten Schmidt, MD, PhD, MA[9,10], Limas Kupcinskas, MD, PhD[11], Ion Dina, MD, PhD[12,13], Frank Zuelch, PhD[14], Gerhard Keilhauer, PhD[14] and Wolfgang Stremmel, MD, PhD[1]

OBJECTIVES: **Phosphatidylcholine is a key component of the mucosal barrier. Treatment with modified release phosphatidylcholine aims to improve the impaired barrier function. The primary objective is to evaluate the efficacy of LT-02, a newly designed modified release phosphatidylcholine formula, in a multicenter setting.**

METHODS: **This is a double-blinded, randomized, placebo-controlled, superiority study conducted in 24 ambulatory referral centers in Germany, Lithuania, and Romania. A total of 156 patients with an inadequate response to mesalazine, a disease activity score (Simple Clinical Colitis Activity Index (SCCAI)) of ≥5, and bloody diarrhea underwent treatment with 0, 0.8, 1.6, or 3.2 g LT-02. The primary end point was defined *a priori* as changes in SCCAI from baseline to the end of treatment. The primary statistical model was a general linear least-squares model. The study was funded by the sponsor Lipid Therapeutics, Heidelberg, Germany, and registered at http://clinicaltrials.gov/show/NCT01011322.**

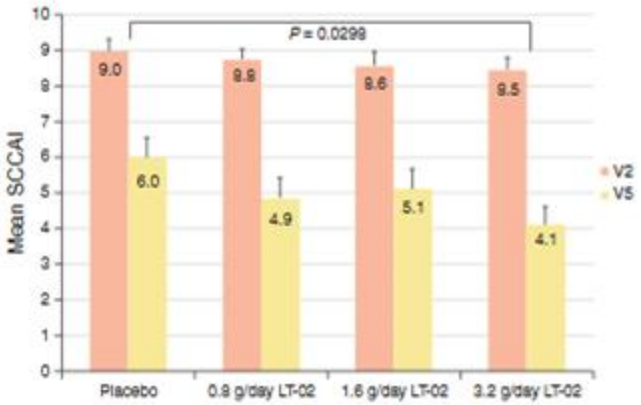


Table 5. Phosphatidylcholine (PC) for active ulcerative colitis [21]

	Placebo (n = 40)	PC 0.8 g (n = 40)	PC 1.6 g (n = 40)	PC 3.2 g (n = 35)
Δ SCCAI	−3.0	−3.9	−3.4	−4.3[1]
Remission, %	15.0	27.5	22.0	31.4

SCCAI = Simple clinical colitis activity index. [1] Dose response more impressive in patients without 5-ASA!

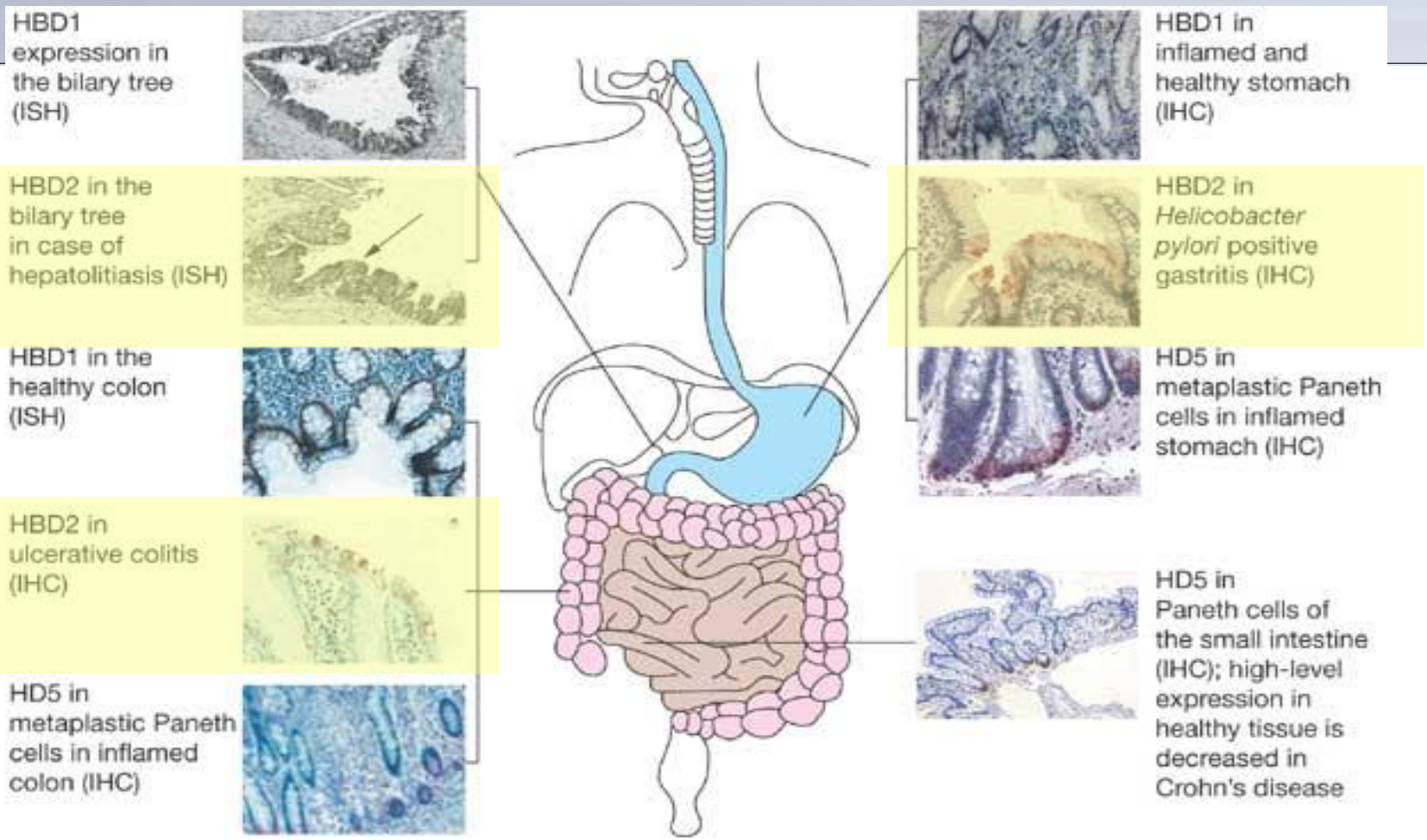
Am J Gastroenterol. 2014

Verminderte Induzierbarkeit von beta-Defensinen bei Morbus Crohn

–

Substitution?

The impact of human beta defensine 2 (hBD2)

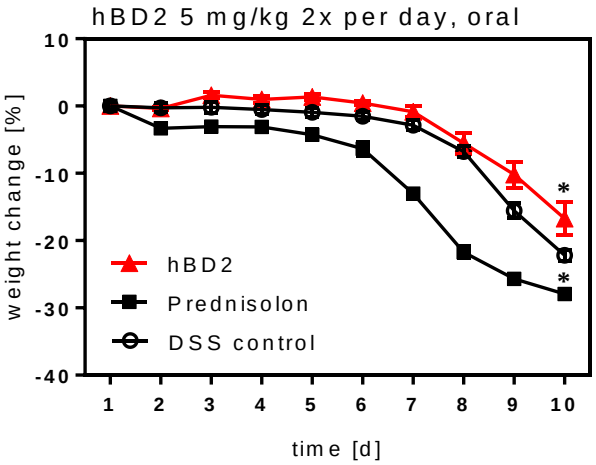


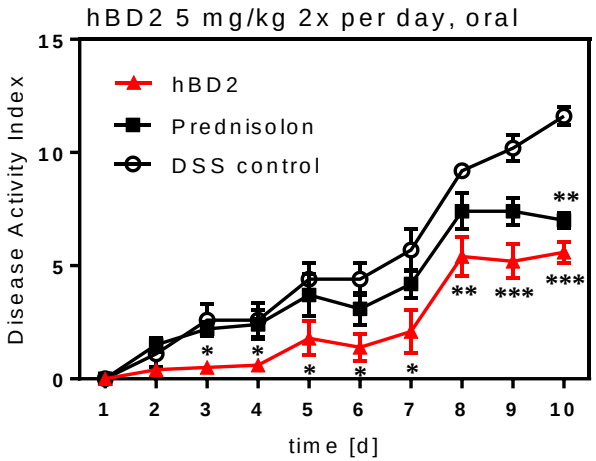
- hBD2 ubiquitously expressed by human epithelia (not only intestine!)
- *inducible on demand , Broad antimicrobial activity!*

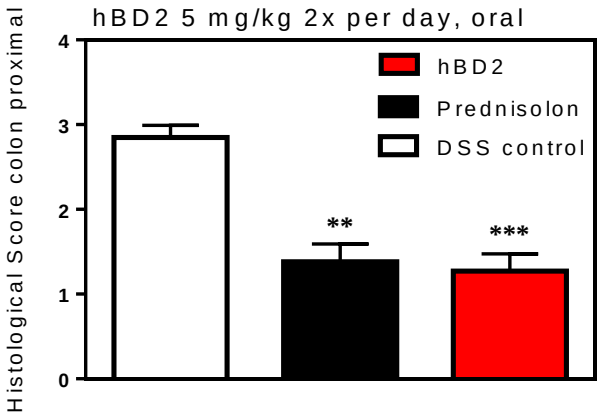
Wehkamp et al. Nature clin. Practice 2005

Oral appliziertes hBD2 ist effektiv im Mausmodell der Colitis

DSS colitis

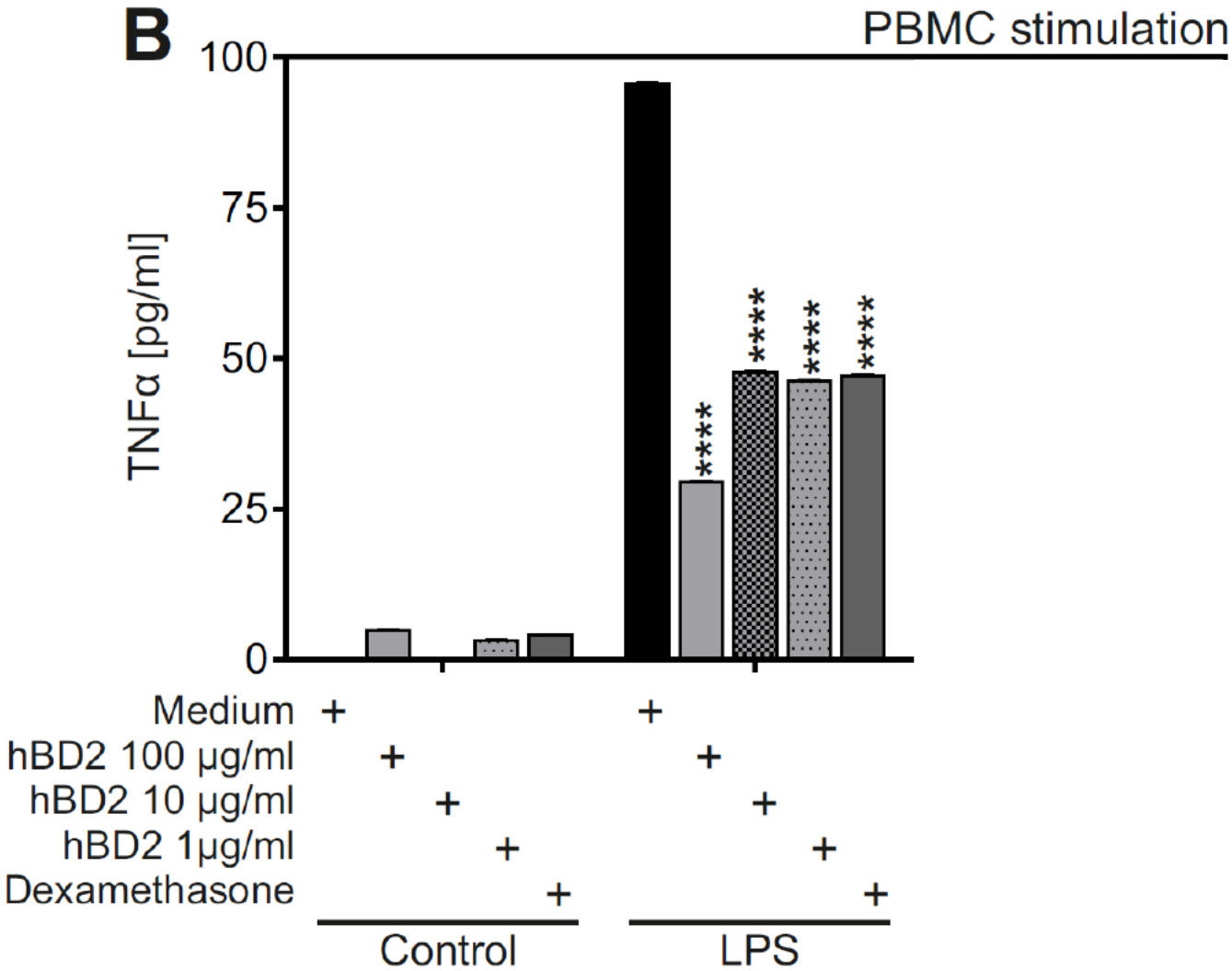






Armbruster et al. AG Wehkamp, unpublished

Weitere Mechanismen von hBD2?
- anti-inflammatorisch -

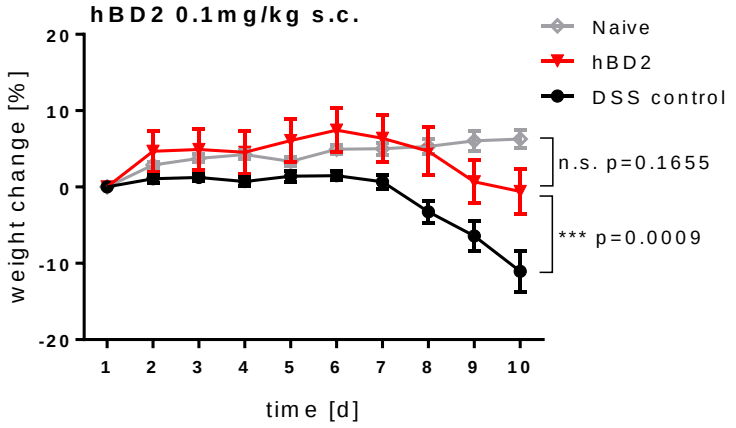


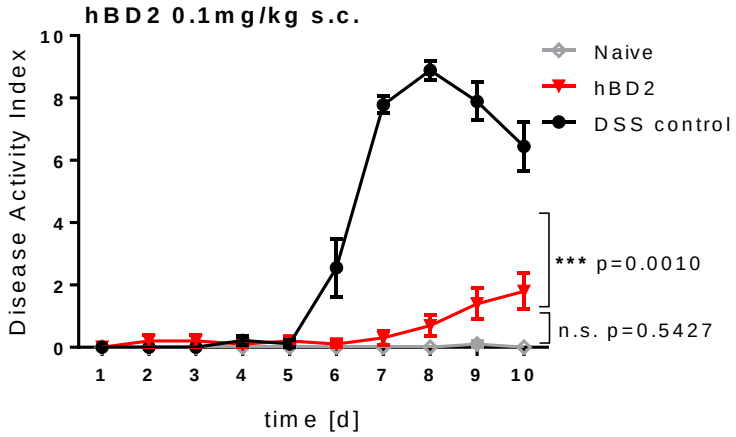
Armbruster et al. , manuscript in preparation

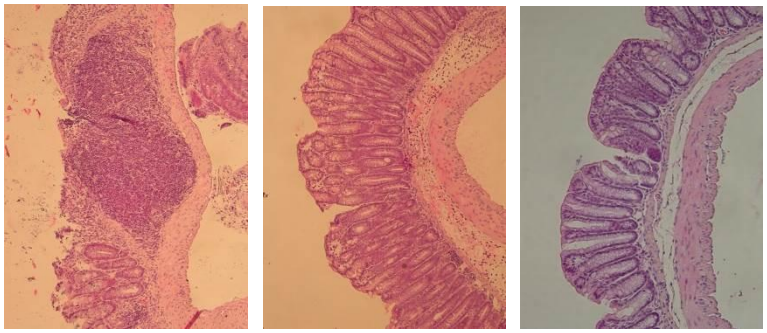
Wenn hBD2 die Bildung von TNFa vermindert – besteht dann auch eine systemische Wirkung s.c.?

S.c. hBD2 Behandlung ist effektiv in der experimentellen Colitis

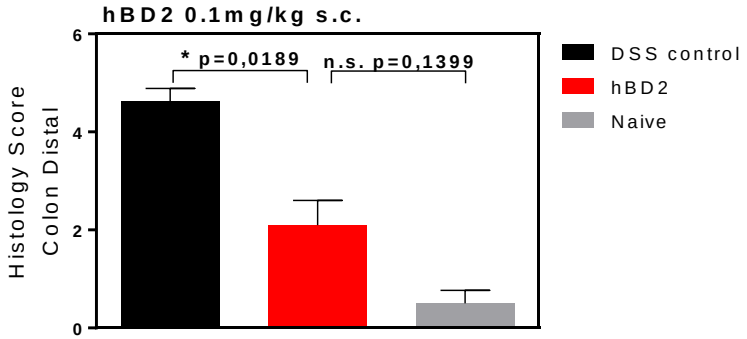
DSS colitis







DSS control | s.c. hBD2 | Naive

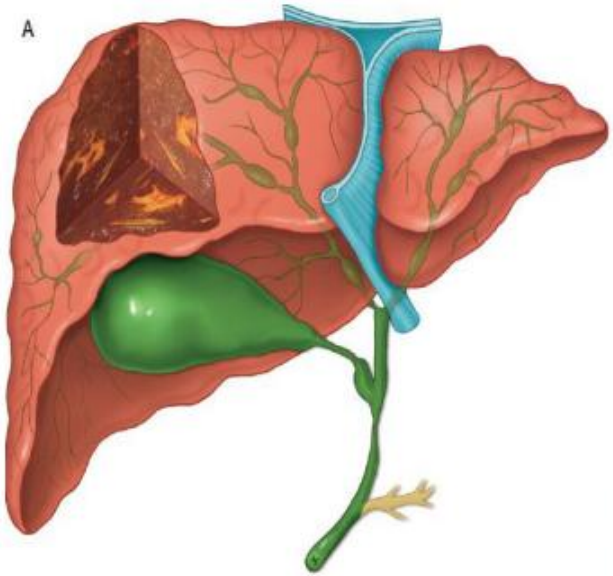


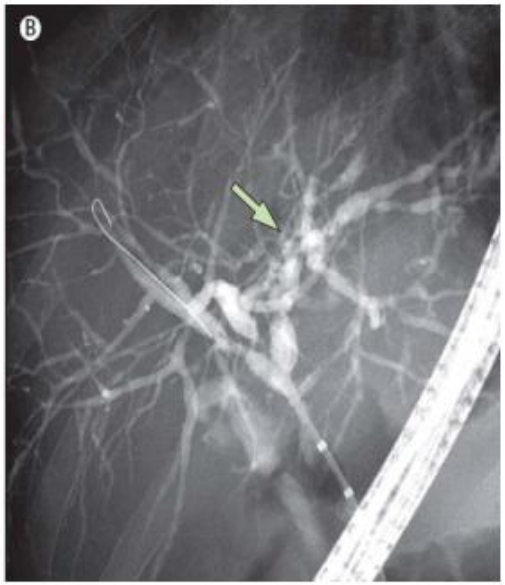
Armbruster et al. AG Wehkamp, manuscript in preparation

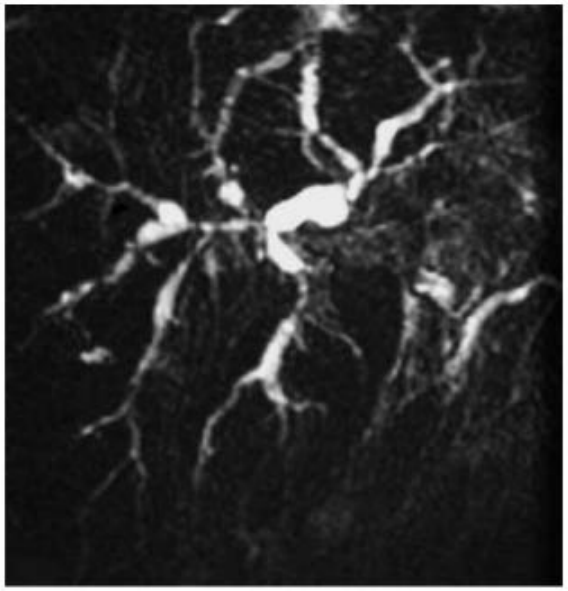
Exkurs – extraintestinale CED Manifestationen

Können antimikrobielle Peptide auch bei anderen Manifestationen chronisch entzündlicher Darmerkrankungen eine Rolle spielen?

Extraintestinale Manifestationen - spielen Defensine auch hier eine potentielle Rolle?







ERCP MRCP

Assoziation mit chronisch entzündlichen Darmerkrankungen

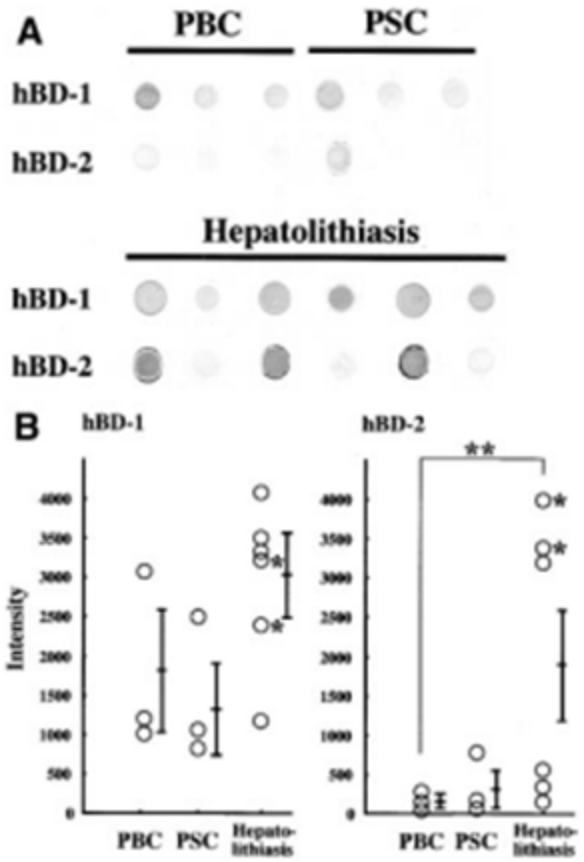
- 60-80% der Fälle in Nordeuropa mit CED assoziiert
- davon 75% mit Colitis ulcerosa (häufig Pancolitis ulcerosa), 25% mit M. Crohn

Rothfuss K.; in Stange EF. Chronisch entzündliche Darmerkrankungen; Schattauer 2015

Peptide Antibiotic Human Beta-Defensin-1 and -2 Contribute to Antimicrobial Defense of the Intrahepatic Biliary Tree

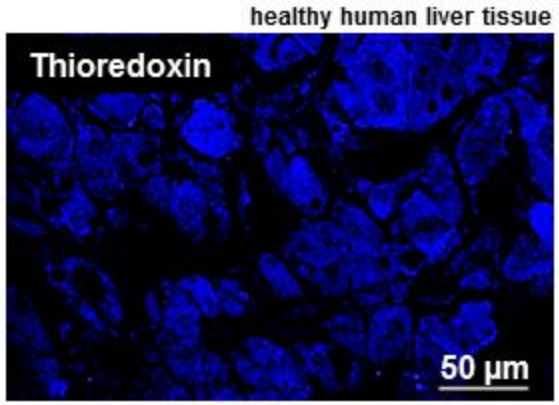
Kenichi Harada,[1] Kazuo Ohba,[1] Satoru Ozaki,[1] Kumiko Isse,[1] Toshiya Hirayama,[2] Akihiro Wada,[2] and Yasuni Nakanuma[1]

hBD1 und hBD2 sind in der Gallenflüssigkeit vermindert bei Cholestase im Rahmen von PSC und PBC!

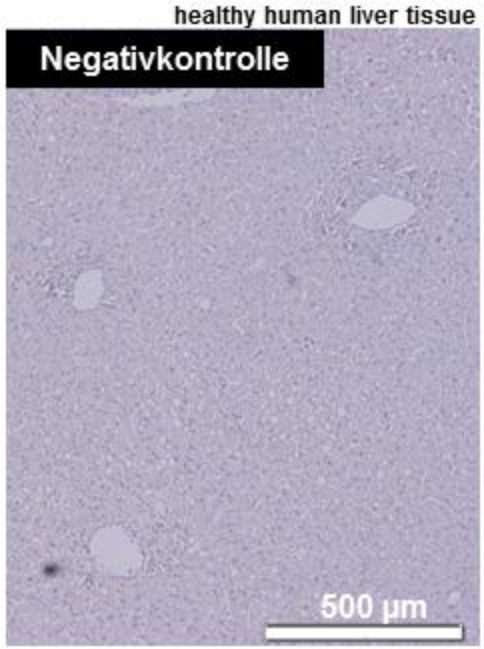


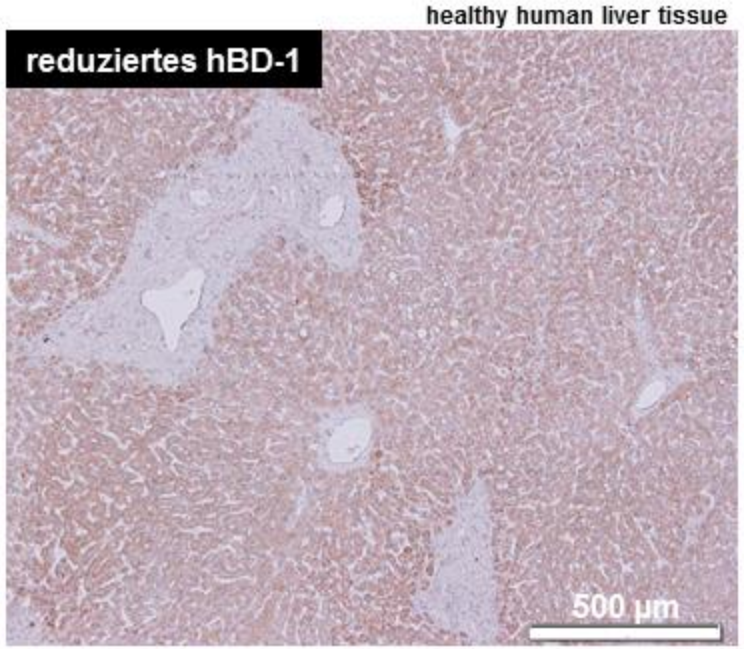
Hepatology 2004

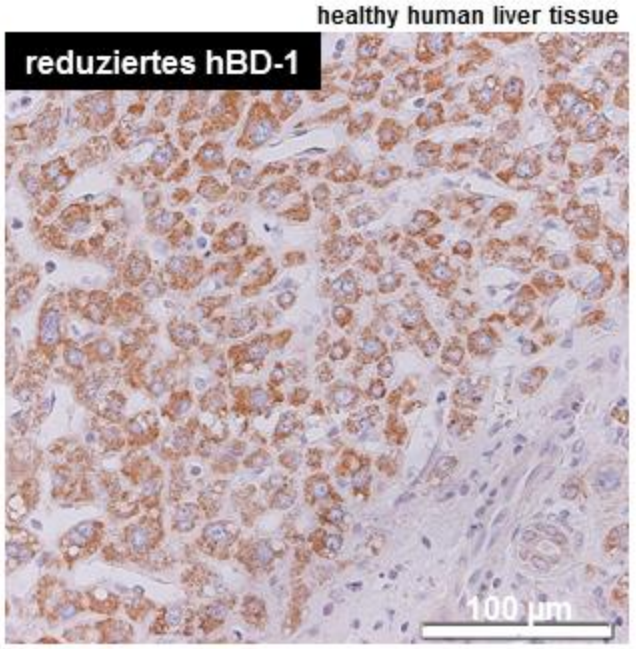
Antimikrobiell aktives hBD-1 und Thioredoxin (TXN) werden in Hepatozyten exprimiert



Thioredoxin und chemisch reduziertes, antimikrobiell aktives hBD-1 werden in der Leber ubiquitär exprimiert!







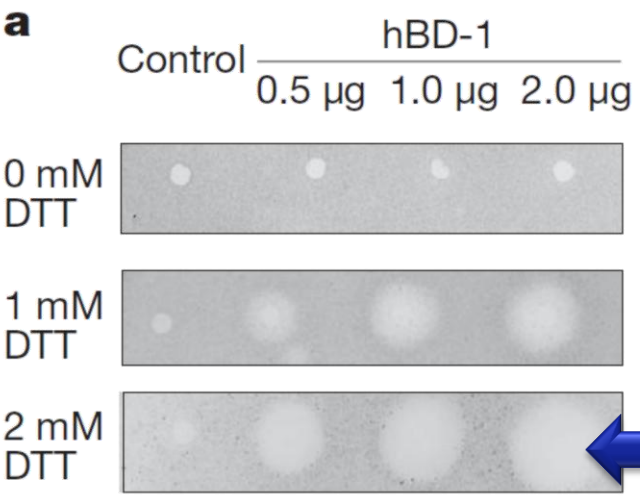
Klag et al; unpublished data

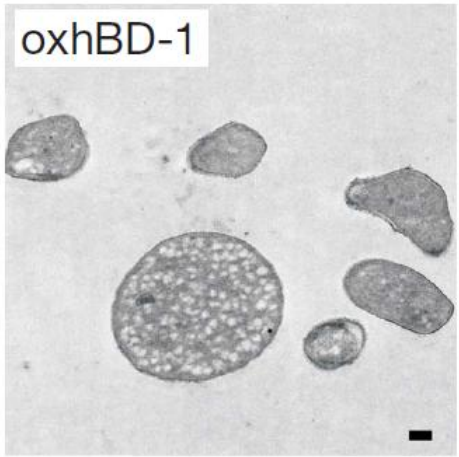
Umgebungsmilieu kontrolliert Wirts-Abwehr - Aktivierung durch chemische Reduktion: ubiquitäres Prinzip

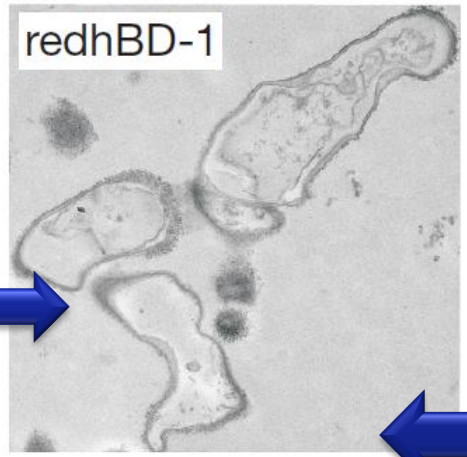
Reduction of disulphide bonds unmasks potent antimicrobial activity of human β-defensin 1

Bjoern O. Schroeder[1,2], Zhihong Wu[3], Sabine Nuding[1,2], Sandra Groscurth[4]†, Moritz Marcinowski[5], Julia Beisner[1,2], Johannes Buchner[5], Martin Schaller[6], Eduard F. Stange[7] & Jan Wehkamp[1,2,7]

Chemische Reduktion aktiviert hBD-1







Schroeder *et al.*, Nature 2011

IMMUNOLOGY

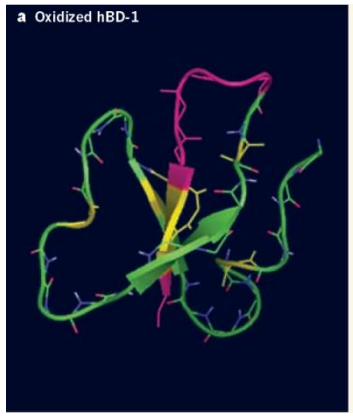
Peptide gets in shape for self-defence

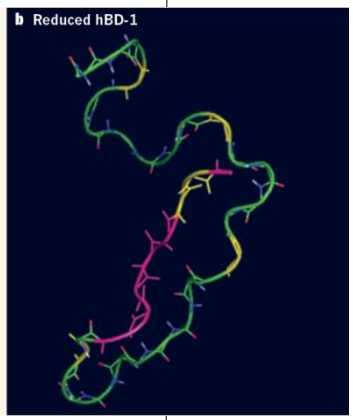
The transformation of tadpole to frog and of caterpillar to butterfly are two of the more obvious examples of metamorphosis. But molecular shape-shifting may occur in each of us as part of our innate antibacterial defence system. SEE LETTER P.419

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-

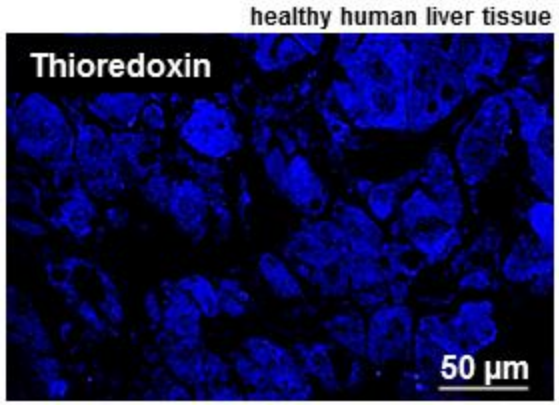




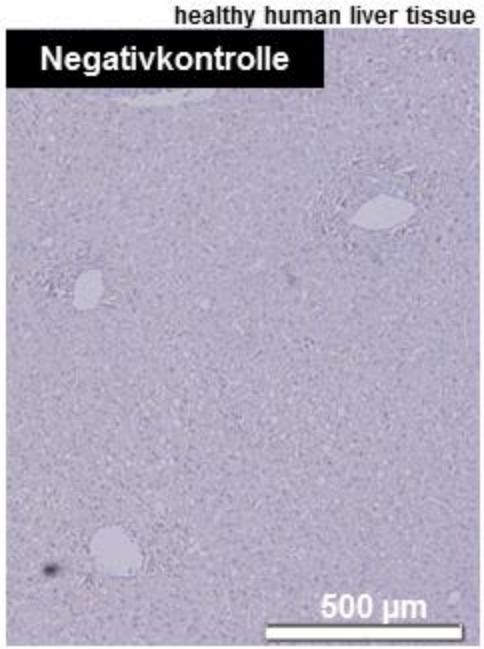
Lehrer, Nature N&V 2011

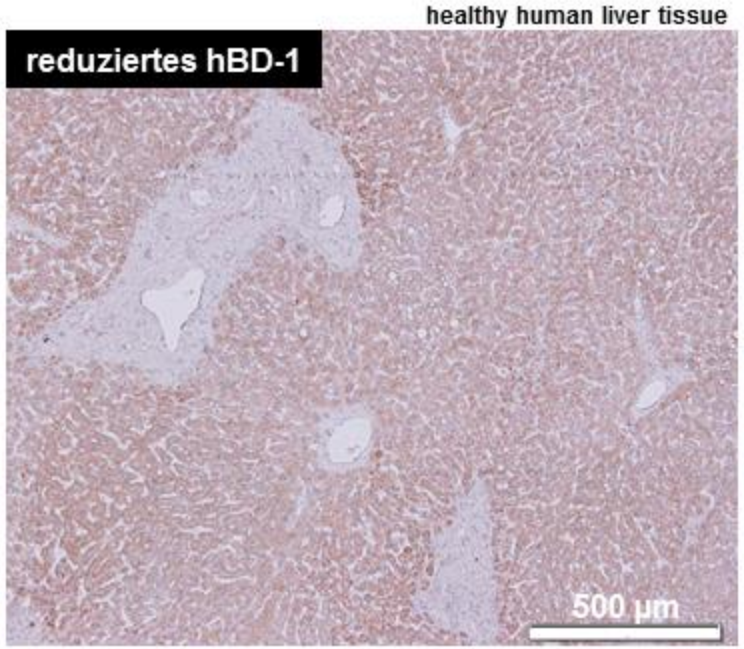
UNIVERSITÄTS KLINIKUM TÜBINGEN

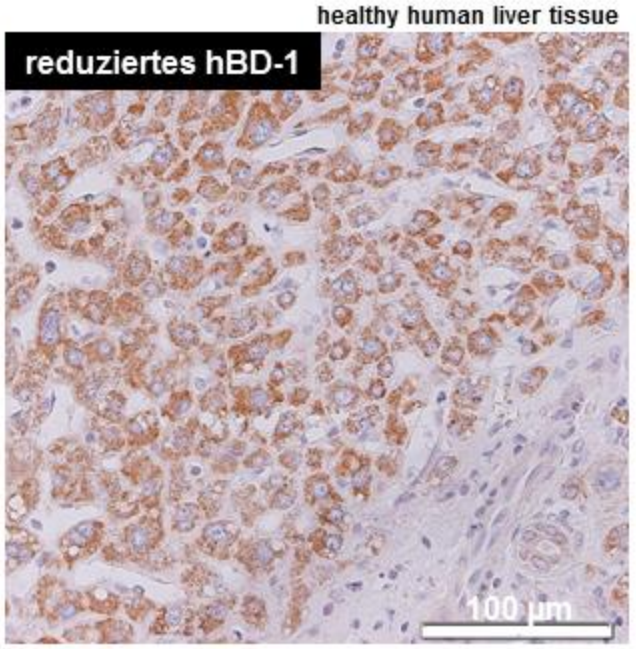
Antimikrobiell aktives hBD-1 und Thioredoxin (TXN) werden in Hepatozyten exprimiert



Thioredoxin und chemisch reduziertes, antimikrobiell aktives hBD-1 werden in der Leber ubiquitär exprimiert!

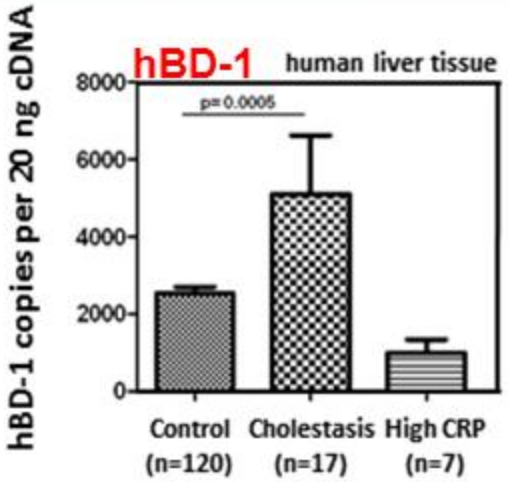


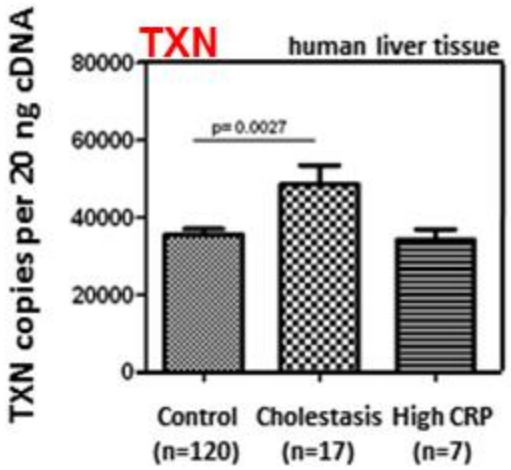


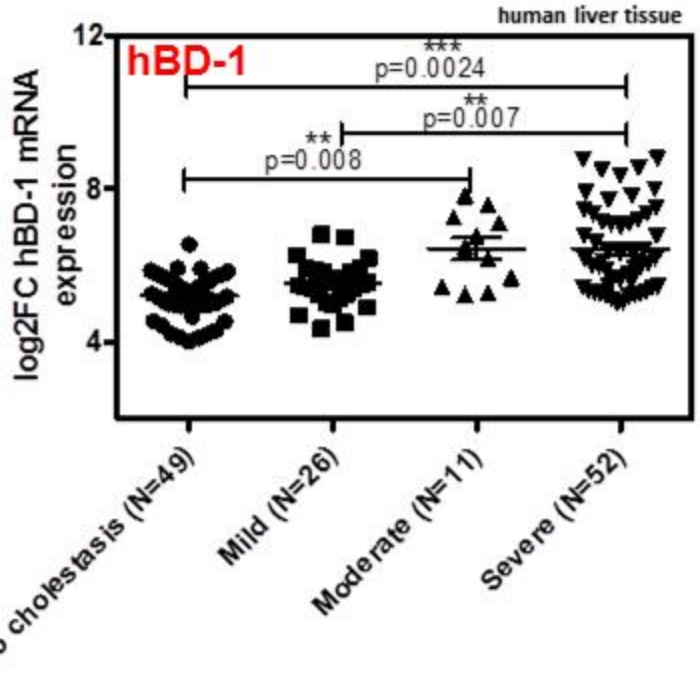


Klag et al; unpublished data

Cholestase ist assoziiert mit einer Induktion der Expression von hBD-1 und Thioredoxin



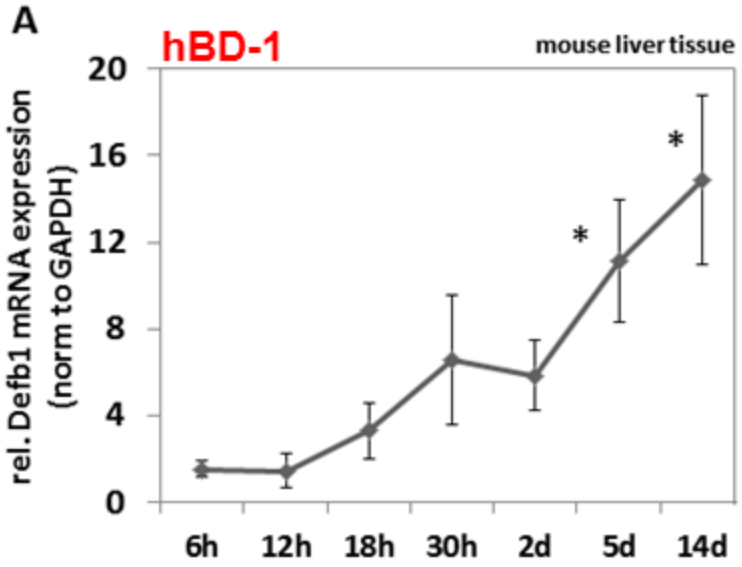


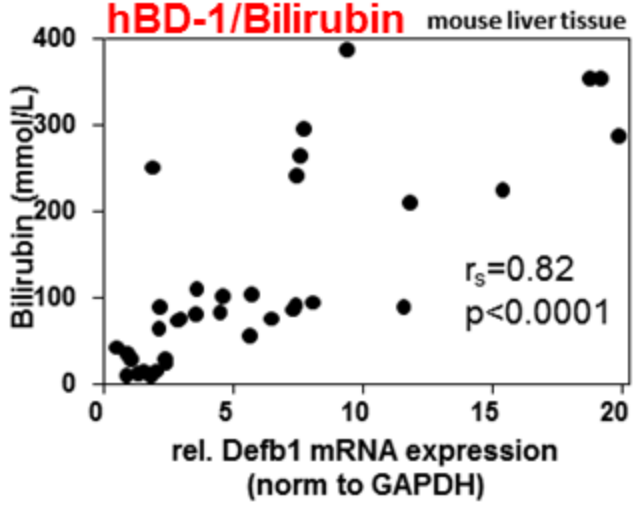


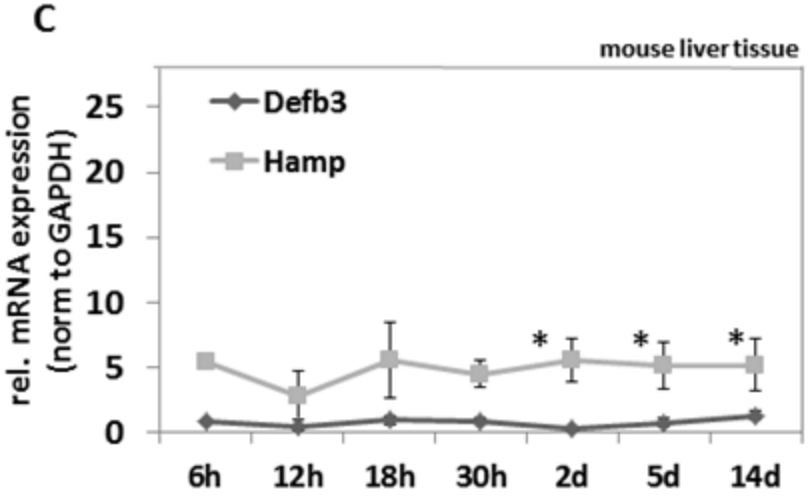
Die Expression von hBD-1 korreliert signifikant mit dem Grad der Cholestase und dem Serumbilirubin (p<0,001).

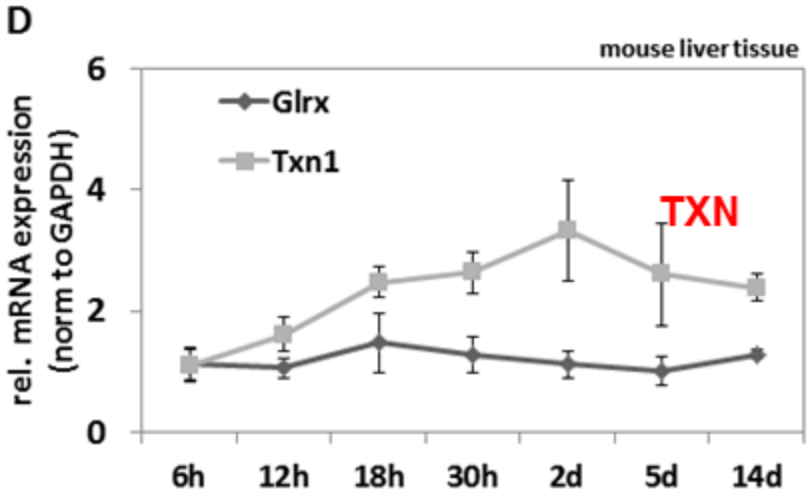
Klag et al; unpublished data

Cholestase in *bile duct ligated mice* führt zur Induktion des murinen antimikrobiellen Peptids Defb1 (hBD-1)



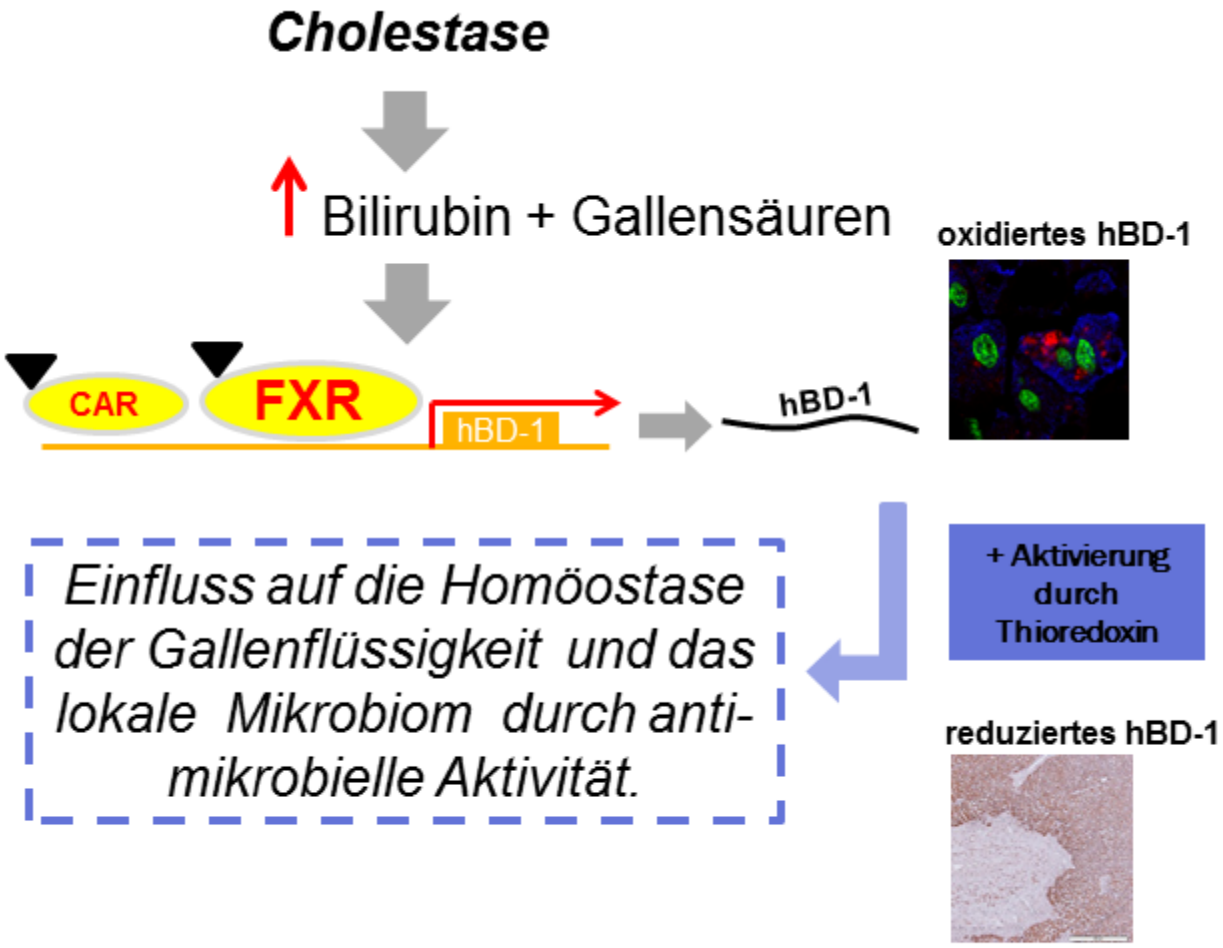




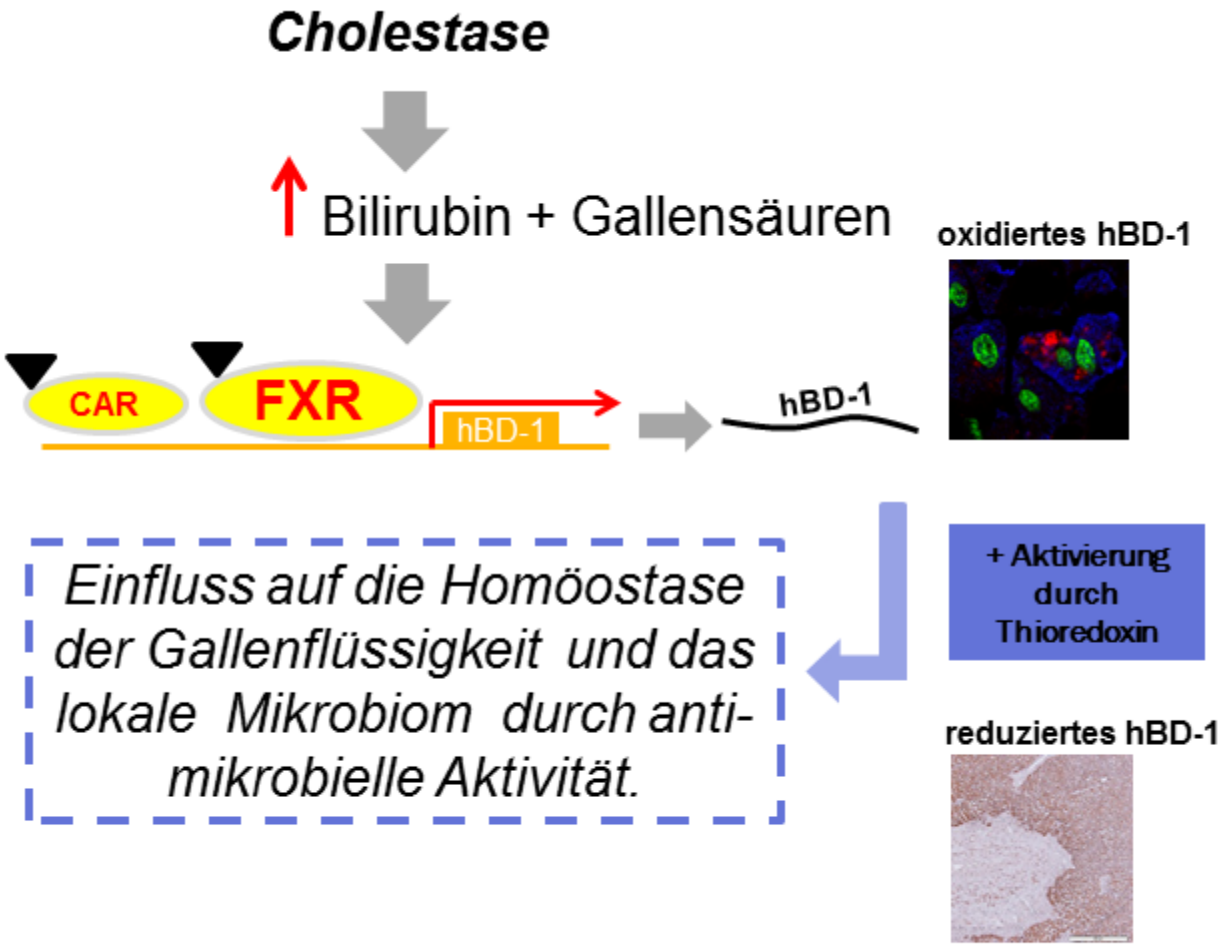


Klag et al; unpublished data

Regulation von hBD1 in der Cholestase

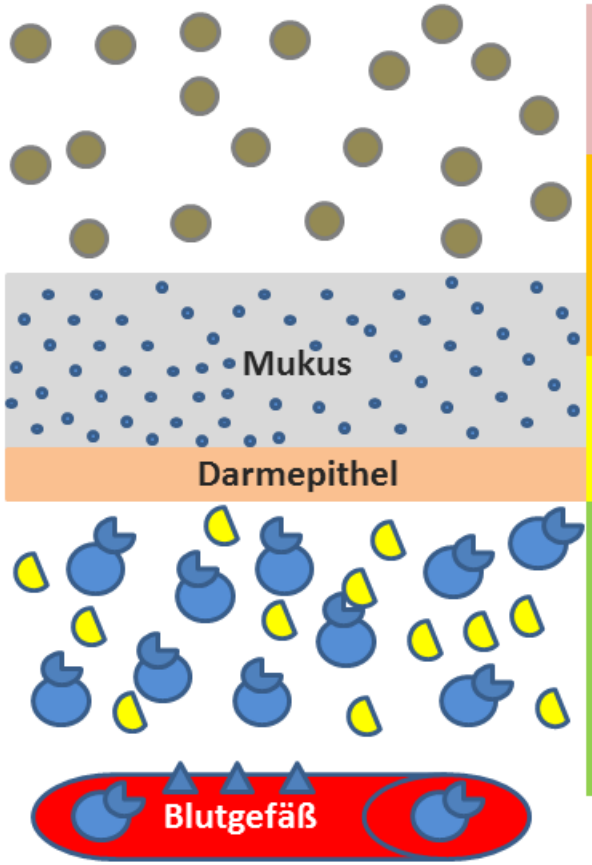


Regulation von hBD1 in der Cholestase



Defekte bei PSC/PBC in diesem System?

Zusammenfassung – chronisch entzündliche Darmerkrankungen



Modulation des Mikrobioms
- Fremdstuhltransfer, Antibiotika (z.B. Rifaximin)
- Probiotika (z.B. E. coli Nissle; VSL3#3)

Substitution der Barriere
- Defensine?
- Lecithin
- Interleukin-22?

Stimulation der unspezifischen Immunantwort
- E. coli Nissle
- VSL3#3

Anti-Inflammatorische Therapie
- Steroide, Azathioprin, Methotrexat
- Anti-TNF-Antikörper
- Anti-Integrin-Antikörper
- Anti-IL12/IL23-Antikörper
- Neuere Substanzen, siehe Tabelle 1.

Bakterium
Antimikrobielles Peptid
Rezeptor zur Lymphozytenmigration
Zelle der adaptiven Immunantwort
Zytokin

Klag, Wehkamp; DMW, under review 2018

Vielen Dank

für Ihre Aufmerksamkeit!

Universitätsklinikum Tübingen

Kompetenz mit Herz

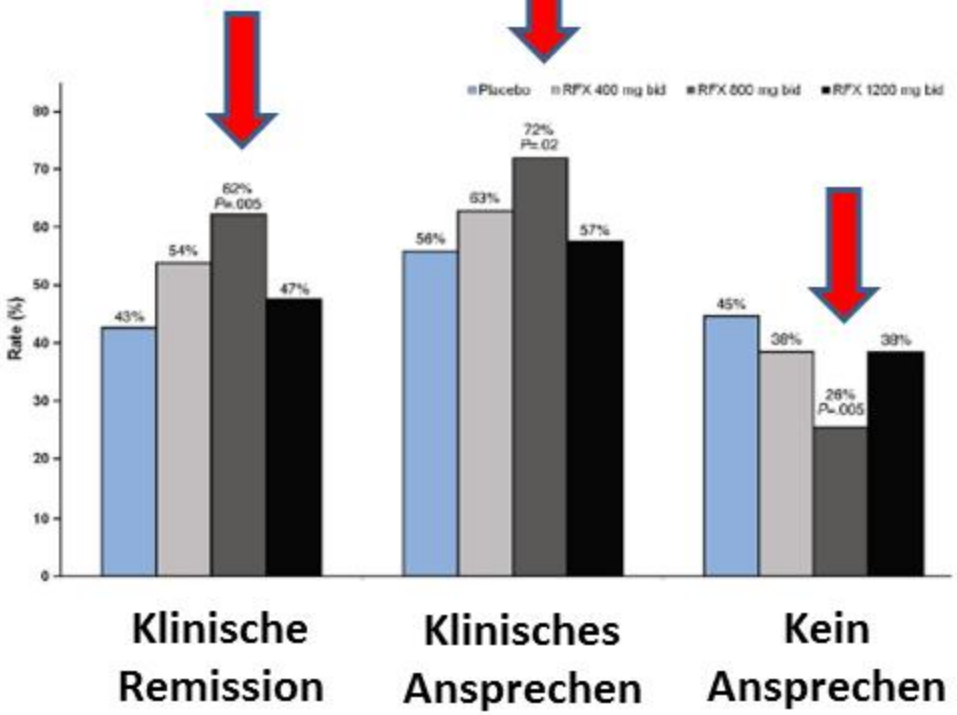
www.uniklinikum-tuebingen.de

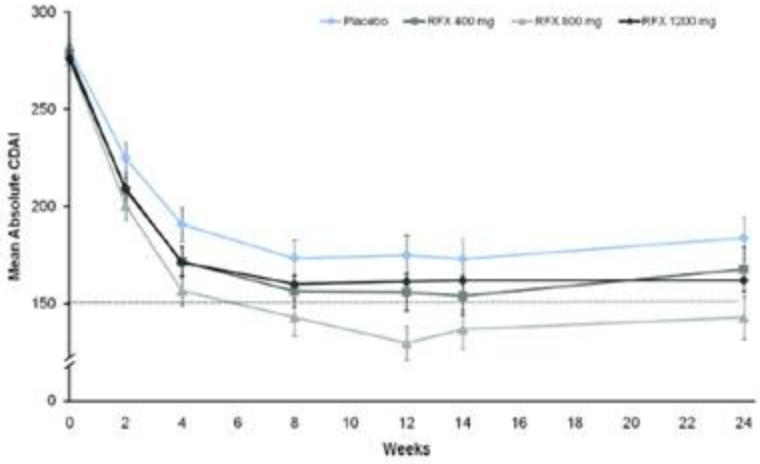
Rifaximin-Extended Intestinal Release Induces Remission in Patients With Moderately Active Crohn's Disease

COSIMO PRANTERA,* HERBERT LOCHS,‡ MARIA GRIMALDI,§ SILVIO DANESE,# MARIA LIA SCRIBANO,* and PAOLO GIONCHETTI,¶ on Behalf of the Retic Study Group (Rifaximin-Eir Treatment in Crohn's Disease)

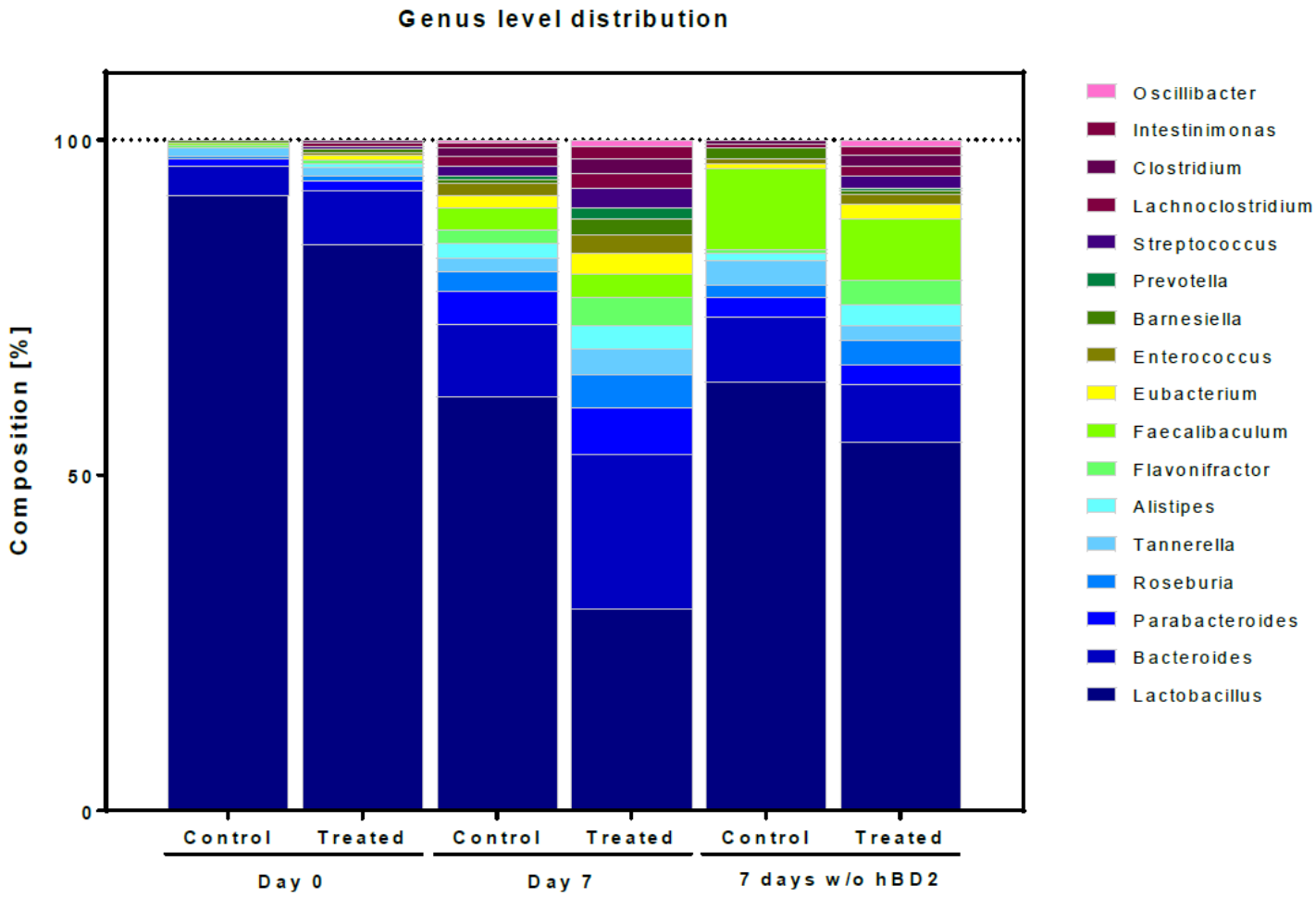
*Gastroenterology Unit, San Camillo Forlanini Hospital, Rome, Italy; ‡Rektorat Medizinische Universität Innsbruck, Innsbruck, Austria; §Department of Clinical Research, Alfa Wassermann SpA, Bologna, Italy; #IBD Center, Department of Gastroenterology, Istituto Clinico Humanitas, Rozzano, Milan, Italy; ¶IBD Unit, Department of Clinical Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

Rifaximin 800 mg 1-0-1





hBD2 verändert das Mikrobiom



Potent –short term-modification

Köninger et al AG Wehkamp
unpublished

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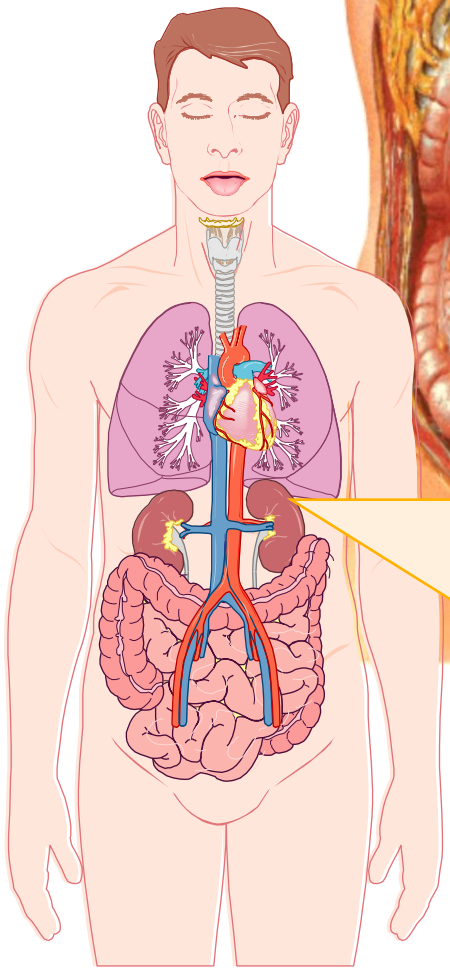
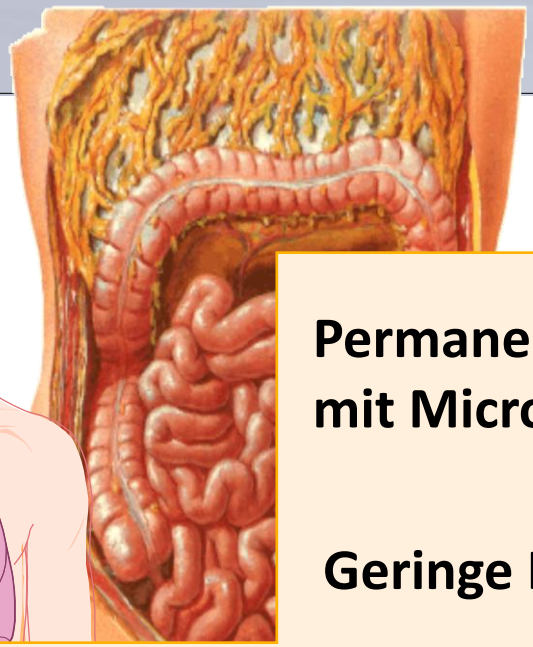
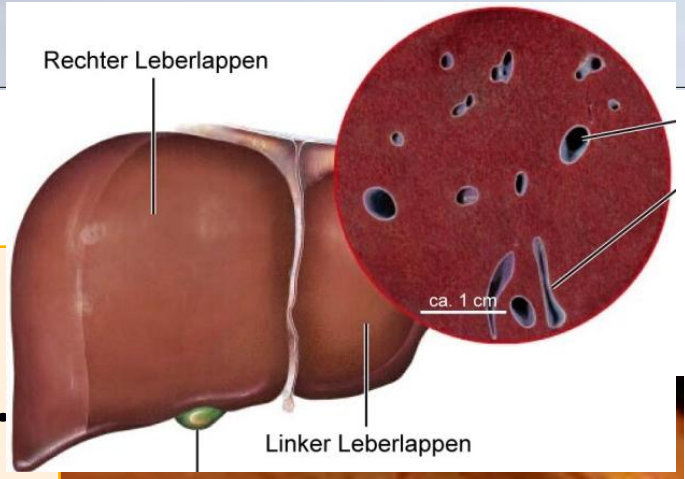
Von der Natur lernen- Schleimhäute des Menschen:



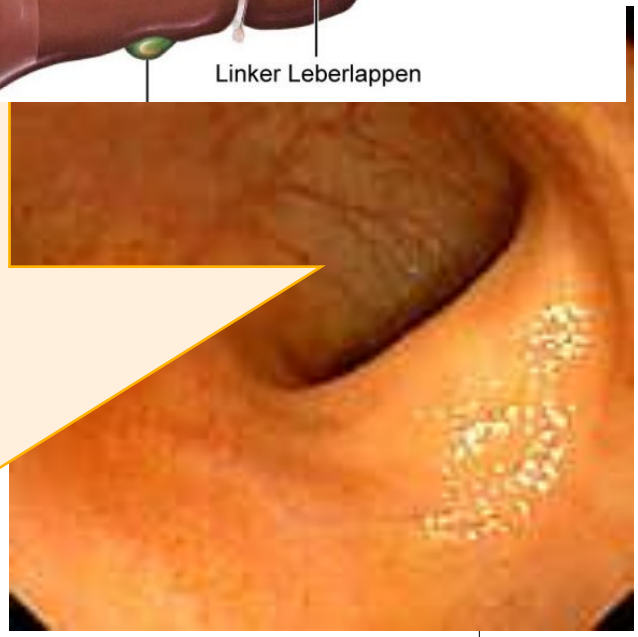




Permanenter Kontakt mit Microorganismen.

Geringe Infektionsrate.

Inflammation ist die Ausnahme, nicht die Regel!



Effective mucosal defense strategies!