Aus dem Institut für Klinische Physiologie
Medizinische Fakultät der Charité – Universitätsmedizin Berlin
Campus Benjamin Franklin
Direktor: Prof. Dr. Michael Fromm

Charakterisierung bakterieller Translokation am Kolonepithelmodell – Induktion von *focal leaks* durch *E. coli*-α-Hämolysin

Inaugural-Dissertation
zur Erlangung des Grades
Doctor rerum medicarum
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vorgelegt von Jan Frank Richter
aus Jena

Referent: Prof. Dr. Michael Fromm

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Meinen Eltern und Großeltern

INHALTSVERZEICHNIS

6 Anhang

6.1 Publikationsliste

Publikationen von Jan F. Richter mit methodischem und/oder inhaltlichem Bezug zur vorliegenden Dissertation

Originalarbeiten:

1. Heller F, Florian P, Bojarski C, Richter JF, Christ M, Hillenbrand B, Mankertz J, Gitter AH, Bürgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD (2005) Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis and cell restitution. *Gastroenterology* **129**(2): 550-564

2. Günzel D* / Florian P* (*equally contrib.), Richter JF, Troeger H, Schulzke JD, Fromm M, Gitter AH (2006) Restitution of single-cell defects in the mouse colon epithelium differs from that of cultured cells. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **290**: 1496-1507

3. Zeissig S, Bürgel N, Günzel D, Richter JF, Mankertz J, Wahnschaffe U, Kroesen AJ, Zeitz M, Fromm M, Schulzke JD (2006) Changes in expression and distribution of claudin-2, -5 and -8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut* (in press, online publiziert 05.07.06)

4. Troeger H* / Richter JF* (*equally contrib.), Beutin L, Günzel D, Florian P, Epple HJ, Gitter AH, Zeitz M, Fromm M, Schulzke JD (2006) E. coli α-hemolysin induces focal leaks in colonic epithelium – a novel mechanism of cytokine-facilitated bacterial translocation. (Eingereicht *Cellular Microbiology*)

Abstracts:

1. Richter JF, Troeger H, Beutin H, Epple HJ, Florian P, Schulzke JD, Fromm M (2004) Bacterial translocation across colonic epithelial cells. *Pflügers Arch.* **447**: 41 (Dt. Physiol. Ges., Vortrag)

2. Günzel D, Melovski M, Richter JF, Amasheh S, Schulzke JD, Fromm M (2004) The tight junction protein claudin-16, stably expressed in MDCK cells, causes a paracellular Mg^{2+} conductance. *Pflügers Arch.* **447**: 41 (Dt. Physiol. Ges., Vortrag)

3. Florian P, Richter JF, Schulzke JD, Fromm M, Gitter AH (2004) Apoptosis and single-cell repair in colon epithelium. *Pflügers Arch.* **447**: 79 (Dt. Physiol. Ges., Poster)

4. Richter JF, Troeger H, Beutin H, Epple HJ, Florian P, Schulzke JD, Fromm M (2004) Bacterial translocation in a colonic epithelial cell model. *J. Physiol. Biochem.* **60**(2): 136 (Eur. Intest. Transport Group, Vortrag)

5. Günzel D, Melovski M, Richter JF, Amasheh S, Schulzke JD, Fromm M (2004) Functional properties of claudin-16 in a tight epithelial cell model. *J. Physiol. Biochem.* **60**(2): 183 (Eur. Intest. Transport Group, Poster)

6. Günzel D, Richter JF, Amasheh S, Hunziker W, Pfaffenbach W, Wurps H, Schulzke JD, Fromm M (2005) Stable expression of claudin-16 in MDCK cells: effects on paracellular Mg^{2+} transport and a transcellular Mg^{2+}-induced current. *Pflügers Arch.* **449**: 99 (Dt. Physiol. Ges., Poster)

7. Troeger H, Richter JF, Schulzke JD, Fromm M (2005) Diarrhea mechanism caused by Giardia lamblia. *Pflügers Arch.* **449**: 93 (Dt. Physiol. Ges., Poster)

6.2 Abkürzungsverzeichnis

* in Biowissenschaften feststehende Begriffe / Abkürzungen wurden in englischer Sprache aufgeführt

AK	Antikörper
afa	afimbrial adhesine
ANOVA	analysis of variance
BCA	Bicinchoninsäure
Bp	Basenpaare
BSA	bovine serum albumin
cAMP	cyclic adenosine monophosphate
CD	cluster of differentiation
CED	chronisch entzündliche Darmerkrankung
CFU	colony forming units
CSF	colony stimulating factor
CU	Colitis ulcerosa
DAEC	diffusely adhering E.coli
DAPI	4´,6-Diamin-2´-Phenylindol-Dihydrochlorid
ddH_2O	bidestiliertes Wasser
DMEM	Dulbecco's modified Eagle's medium
DMSO	Dimethylsulfoxid
DNA	desoxyribonucleic acid
DNP	Dinitrophenol
E.coli	Escherichia coli
EHly	Enterohämolysin
ETEC	enterotoxigenic *E. coli*
ExPEC	extraintestinal pathogenic *E. coli*
Fab	Antigen-bindendes Fragment
Fas / Apo	fibroblast associated apoptosis receptor (CD95)
FKS	fötales Kälberserum
FMLP	N-Formyl-Methionyl-Leucyl-Phenylalanin
g	Leitwert (mS)
G_A	apparente Leitfähigkeit (mS cm^{-2})
GALT	gut associated lymphoid tissue
GPI	Glykosyl-Phosphatidyl-Inositol
GTP	Guanintriphosphat
GvHD	graft-versus-host disease
HIV	human immunodeficiency virus
HlyA	α-Hämolysin
hlya	Hämolysinoperon
I	elektrischer Strom (A)
IFN	interferon
IgG	Immunglobulin G
IL	interleukin
IpaH	invasion plasmid antigen H
I_{SC}	Kurzschlussstrom, bezogen auf 1 cm^2 Fläche ($\mu A \cdot h^{-1} \cdot cm^{-2}$)
JAM	junctional adhesion molecule
k	spezifische Leitfähigkeit
KBE	Kolonie-bildende Einheiten

LB	Luria-Bertani-Medium
LPS	Lipopolysaccharid
mAk	monoklonaler Antikörper
MC	Morbus Crohn
MEM	minimum essential Eagle's medium
MLN	mesenteric lymph node
MOI	multiplicity of infection
mbCD	Methyl-β-Cyclodextrin
NA	numerische Apertur
NOD2	nucleotide oligodimerisation domain
OD	optische Dichte
PAF	platelet activating factor
PAI	pathogenicity island
pAk	polyklonales Antikörperserum
PBST	phosphate buffered saline with Tween
PCF	Polykarbonat
PCR	polymerase chain reaction
PFGE	pulsed field gel electrophoresis
POD	Peroxidase
r	Korrelationskoeffizient
RPM	rounds per minute
RPMI	Roswell Memorial Park Institute (-medium)
R^t	transepithelialer Widerstand, bezogen auf 1 cm^2 Fläche ($\Omega \cdot cm^2$)
RT	Raumtemperatur
RTX	repeats in toxin
SDS	Sodiumdodecylsulfat
SEM	standard error of the mean
SIRS	systemic inflammatory response syndrome
SOLAS	Society of Laboratory Animal Science
stx	shiga-Toxin
Tbl	Tablette
TEMED	N,N,N,N-Tetramethylendiamin
TNFR1	p55 TNF-Rezeptor-Typ-1 (CD120a)
TNFα	tumor necrosis factor alpha
tRNA	transfer- ribonucleic acid
U	elektrische Spannung (mV)
ÜN	Übernachtkultur
VF	Virulenzfaktor
VK	Vorkultur
vs	versus
WD	Arbeitsabstand (working distance)
YfgL	outer membrane protein gramnegativer Bakterien
ZO-1(-2,-3)	Zonula occludens-Protein 1 (-2,-3)
λ_{EM}	Emissionswellenlänge
λ_{EX}	Anregungswellenlänge

6.3 Danksagung

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6.4 Curriculum vitae

Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht.

6.5 Eidesstattliche Erklärung:

Ich, Jan Frank Richter, erkläre an Eides statt, dass ich die vorgelegte Dissertationsschrift mit dem Thema: "*Charakterisierung bakterieller Translokation am Kolonepithelmodell – Induktion von focal leaks durch E. coli α-Hämolysin"* selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Datum: 05.06.07 **Unterschrift:**

6.6 Literaturverzeichnis

1. Cortajarena AL, Goñi FM, Ostolaza H (2001) Glycophorin as a receptor for E. coli α-haemolysin in erythrocytes. *J. Biol. Chem.* **276:** 12513-12519
2. Ahdieh M, Vandenbos T, Youakim A (2001) Lung epithelial barrier function and wound healing are decreased by IL-4 and IL-13 and enhanced by IFN-gamma. *Am. J. Physiol. Cell. Physiol.* **281**(6): 2029-2038.
3. Alexander JW, Boyce ST, Babcock GF (1990) The process of microbial translocation. *Ann. Surg.* **212**: 496–510.
4. Amasheh S, Meiri N, Gitter AH, Schöneberg T, Mankertz J, Schulzke JD, Fromm M (2002) Claudin-2 expression induces cation-selective channels in tight junctions of epithelial cells. *J. Cell Sci.* **115**(24): 4969-4976
5. Amy M, Velge P, Senocq D, Bottreau E, Mompart F, Virlogeux-Payant I (2004) Identification of a new *Salmonella enterica* serovar Enteritidis locus involved in cell invasion and in the colonisation of chicks. *Res. Microbiol*. **155:** 543-552
6. Anderson JM, van Itallie CM (1995) Tight junctions and the molecular basis for regulation of paracellular permeability. *Am. J. Physiol.* **269**(4 Pt 1): 467-475.
7. Anderson RG (1998) The caveolae membrane system. *Annu. Rev. Biochem*. **67**: 199-225.
8. Barmeyer C (2002) Diarrhoe und Malabsorption bei Colitis ulcerosa und zugrunde liegende Mechanismen in den Modellen der Interleukin-2-defizienten Maus und der Zytokin-exponierten Kolonmucosa der Ratte. Dissertation, Freie Universität Berlin
9. Bendfeldt K (2000) Tumornekrosefaktor- (TNFα-) induzierte Barrierestörung an menschlichen Kolonzellen HT-29/B6: Lokalisierung mittels Conductance scanning. Dissertation, Freie Universität Berlin
10. Bendfeldt K, Gitter AH, Fromm M (1998) Trans- and paracellular conductivity of HT-29/B6 cells measured by high-resolution Conductance scanning. *Ann. N. Y. Acad. Sci.* **17:** 295-299
11. Berg RD, Garlington AW (1979) Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect. Immun*. **23**(2): 403-411

12. Bettelheim KA, Beutin L, Gleier K, Pearce JL, Luke RK, Zimmermann S (2003) Serotypes of *Escherichia coli* isolated from healthy infants in Berlin, Germany and Melbourne, Australia. *Comp. Immunol. Microbiol. Infect. Dis.* **26**(1): 55-63.

13. Bhakdi S, Muhly M, Korom S, Schmidt G (1990) Effects of Escherichia coli hemolysin on human monocytes. Cytocidal action and stimulation of interleukin 1 release. *J. Clin. Invest*. **85**(6): 1746-1753

14. Blum G, Marre R, Hacker J (1995) Properties of Escherichia coli strains of serotype O6. *Infection* **23**(4): 234-236.

15. Blum G, Ott M, Lischewski A, Ritter A, Imrich H, Tschape H, Hacker J (1994) Excision of large DNA regions termed pathogenicity islands from tRNA-specific loci in the chromosome of an Escherichia coli wild-type pathogen. *Infect. Immun.* **62**(2): 606-614.

16. Bode H. Der Effekt von Interleukin-1 auf den epithelialen Ionentransport im menschlichen Colon. (1997) Dissertation, Freie Universität Berlin

17. Bojarski C, Gitter AH, Bendfeldt K, Mankertz J, Schmitz H, Wagner S, Fromm M, Schulzke JD (2001) Permeability of human HT-29/B6 colonic epithelium as a function of apoptosis. *J. Physiol*. **535**(Pt 2): 541-552

18. Boudeau J, Glasser AL, Julien S, Colombel JF, Darfeuille-Michaud A (2003) Inhibitory effect of probiotic Escherichia coli strain Nissle 1917 on adhesion to and invasion of intestinal epithelial cells by adherent-invasive E. coli strains isolated from patients with Crohn's disease. *Aliment. Pharmacol. Ther*. **18**(1): 45-56.

19. Boudeau J, Glasser AL, Masseret E, Joly B, Darfeuille-Michaud A (1999) Invasive ability of an Escherichia coli strain isolated from the ileal mucosa of a patient with Crohn's disease. *Infect. Immun*. **67**(9): 4499-4509.

20. Braegger CP, MacDonald TT (1994) Immune mechanisms in chronic inflammatory bowel disease. *Ann. Allergy*. **72**(2): 135-141.

21. Brathwaite CE, Ross SE, Nagele R, Mure AJ, O´Malley KF, Garcia-Perez FA (1993) Bacterial translocation occurs in humans after traumatic injury: evidence using immunofluorescence. *J. Trauma.* **34**(4): 586-589

22. Brook I, MacVittie TJ, Walker RI (1984) Recovery of aerobic and anaerobic bacteria from irradiated mice. *Infect. Immun*. **46**: 270–271.

23. Bruewer M, Luegering A, Kucharzik T, Parkos CA, Madara JL, Hopkins AM, Nusrat A (2001) Proinflammatory cytokines disrupt epithelial barrier function by apoptosis-independent mechanisms. *J. Immunol*. **171**(11): 6164-6172

24. Bürgel N, Bojarski C, Mankertz J, Zeitz M, Fromm M, Schulzke JD (2002) Mechanisms of diarrhea in collagenous colitis. *Gastroent*. **123**(2): 433-443

25. Burns JL, Griffith A, Barry JJ, Jonas M, Chi EY, Transcytosis of gastrointestinal epithelial cells by Escherichia coli K1. (2001) *Pediatr. Res.* **49**(1): 30-37

26. Buyse M, Tsocas A, Walker F, Merlin D, Bado A (2002) PepT1-mediated fMLP transport induces intestinal inflammation in vivo. *Am. J. Physiol. Cell. Physiol.* **283**(6): 1795-1800

27. Ceponis PJ, Botelho F, Richards CD, McKay DM (2000) Interleukins 4 and 13 increase intestinal epithelial permeability by a phosphatidylinositol 3-kinase pathway. Lack of evidence for STAT 6 involvement. *J. Biol. Chem.* **275**: 29132–29137

28. Cereijido M, Valdes J, Shoshani L, Conteras RG (1998) Role of tight junctions in establishing and maintaining cell polarity. *Annu. Rev. Physiol.* **60**: 161-177

29. Christian AE, Haynes MP, Phillips MC, Rothblat GH (1997) Use of cyclodextrins for manipulating cellular cholesterol content. *J. Lipid Res.* **38**: 2264-2272

30. Clark E,Hoare C, Tanianis-Hughes J, Carlson GL, Warhurst G (2005) Interferon gamma induces translocation of commensal Escherichia coli across gut epithelial cells via a lipid raft-mediated process. *Gastroent*. **128**(5): 1258-1267

31. Clark EC, Patel SD, Chadwick PR, Warhurst G, Curry A, Carlson GL (2003) Glutamine deprivation facilitates tumour necrosis factor induced bacterial translocation in Caco-2 cells by depletion of enterocyte fuel substrate. *Gut* **52**(2): 224-230.

32. Colonna B, Ranucci L, Fradiani PA, Casalino M, Calconi A, Nicoletti M (1992) Organization of aerobactin, hemolysin, and antibacterial resistance genes in lactose-negative Escherichia coli strains of serotype O4 isolated from children with diarrhea. *Infect. Immun.* **60**: 5224-5231.

33. Cruz N, Qi L, Alvarez X, Berg RD, Deitch EA (1994) The Caco-2 cell monolayer system as an in vitro model for studying bacterial-enterocyte interactions and bacterial translocation. *J. Burn. Care. Rehabil*. **15**(3): 207-212

34. Deitch EA (2002) Bacterial translocation or lymphatic drainage of toxic products from the gut: what is important in human beings? *Surgery* **131**(3): 241-244.

35. Diamond JM (1977) The epithelial junction: bridge, gate and fence. *Physiologist* **20**: 10-18

36. Eckmann L, Kagnoff MF, Fierer J (1995) Intestinal epithelial cells as watchdogs for the natural immune system. *Trends Microbiol*. **3**(3): 118-120

37. Emody L, Kerenyi M, Nagy G (2003) Virulence factors of uropathogenic Escherichia coli. *Int. J. Antimicrob. Agents* **22**(2): 29-33

38. Emori TG, Gaynes RP (1993) An overview of nosocomial infections, including the role of the microbiology laboratory. *Clin. Microbiol. Rev*. **6**(4): 428-442

39. Epple HJ (1993) Experimentelle Untersuchungen zum Mechanismus der mineralocorticoiden Wirkung von Carbenoxolon am menschlichen Dickdarm *in vitro*. Dissertation, Freie Universität Berlin

40. Falbo V, Famiglietti M, Caprioli A (1992) Gene block encoding production of cytotoxic necrotizing factor 1 and hemolysin in *Escherichia coli* isolates from extraintestinal infections. *Infect. Immun.* **60**: 2182-2187.

41. Fasano A, Nataro JP (2004) Intestinal epithelial tight junctions as targets for enteric bacteria-derived toxins. *Adv. Drug Deliv. Rev*. **56**(6): 795-807.

42. Felmlee T, Pellett S, Lee EY, Welch RA (1985) Escherichia coli hemolysin is released extracellularly without cleavage of a signal peptide. *J. Bacteriol.* **163**(1): 88-93

43. Felmlee T, Pellett S, Welch RA (1985) Nucleotide sequence of an *Escherichia coli* chromosomal hemolysin. *J. Bacteriol*. **163**(1): 94-105

44. Feltis BA, Wiesner SM, Kim AS (2000) Clostridium difficile toxins A and B can alter epithelial permeability and promote bacterial paracellular migration through HT-29 enterocytes. *Shock* **14**: 629-634

45. Flexner S (1895) Peritonitis caused by the invasion of the micrococcus Lanceolatus from the intestine. *John Hopkins Hosp. Bull.* **6:** 64-67

46. Florian P, Schoneberg T, Schulzke JD, Fromm M, Gitter AH (2002) Single-cell epithelial defects close rapidly by an actinomyosin purse string mechanism with functional tight junctions. *J. Physiol.* **545**(2): 485-499

47. Florian P (2002) Restitution von Einzelzell-Läsionen im Kolonepithel. Dissertation, Freie Universität Berlin

48. Foxman B, Zhang L, Palin K, Tallman P, Marrs CF (1995) Bacterial virulence characteristics of Escherichia coli isolates from first-time urinary tract infection. *J. Infect. Dis*. **171**(6): 1514-1521.

49. Frainkel A (1891) Über peritoneale Infektion, *Wien. Klin. Wochenschr.* **4**: 241, 265, 285

50. Frizzell RA, Koch MJ, Schultz SG (1976) Ion transport by rabbit colon. I. Active and passive components. *J. Membr. Biol*. **27**(3): 297-316

51. Frömter E, Diamond J (1972) Route of passive ion permeation in epithelia. *Nat. New. Biol.* **235**(53): 9-13

52. Furuse M , Fujita K , Hiiragi T , Fujimoto K , Tsukita S (1998) Claudin-1 and -2: Novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin. *J. Cell. Biol.* **141**: 1539–1550

53. Furuse M, Hirase T, Itoh M, Nagafuchi A, Yonemura S, Tsukita S, Tsukita S (1993) Occludin: a novel integral membrane protein localizing at tight junctions. *J. Cell. Biol.* **123**(6): 1777-1788.

54. Gekle M, Wünsch S, Oberleithner H, Silbernagl S (1994) Characterization of two MDCK-cell subtypes as a model system to study principal cell and intercalated cell properties. *Pflügers Arch.* **428**: 157 -162

55. Girardin SE, Boneca IG, Viala J, Chamaillard M, Labigne A, Thomas G, Philpott DJ, Sansonetti PJ (2003) Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. *J. Biol. Chem.* **278**: 8869–8872

56. Gitter AH, Bendfeldt K, Schulzke JD, Fromm M (2000) Leaks in the epithelial barrier caused by spontaneous and TNF-alpha-induced single-cell apoptosis. *FASEB J*. **14**(12): 1749-1753.

57. Gitter AH, Bendfeldt K, Schulzke JD, Fromm M (2000) Trans/paracellular, surface/crypt, and epithelial/subepithelial resistances of mammalian colonic epithelia. *Pflügers Arch.* **439**: 477-482

58. Gitter AH, Bertog M, Schulzke J, Fromm M (1997) Measurement of paracellular epithelial conductivity by Conductance scanning. *Pflügers Arch.* **434**: 830-840

59. Gitter AH, Wullstein F, Fromm M, Schulzke JD (2001) Epithelial barrier defects in ulcerative colitis: characterization and quantification by electrophysiological imaging. *Gastroent.* **121**(6): 1320-1328.

60. Gleason TG, Houlgrave CW, May AK, Crabtree TD, Sawyer RG, Denham W, Norman JG, Pruett TL (1998) Hemolytically active (acylated) alpha-hemolysin elicits interleukin-1beta (IL-1beta) but augments the lethality of Escherichia coli by an IL-1- and tumor necrosis factor-independent mechanism. *Infect. Immun.* **66**(9): 4215-4221

61. Grassl GA, Bohn E, Müller Y, Bühler OT, Autenrieth IB (2003) Interaction of Yersinia enterocolitica with epithelial cells: invasin beyond invasion. *Int. J. Med. Microbiol*. **293**(1): 41-54

62. Grimminger F, Rose F, Sibelius U, Meinhardt M, Potzsch B, Spriestersbach R, Bhakdi S, Suttorp N, Seeger W (1997) Human endothelial cell activation and mediator release in response to the bacterial exotoxins Escherichia coli hemolysin and staphylococcal alpha-toxin. *J. Immunol*. **159**(4): 1909-1916

63. Groisman EA, Ochman H (1996) Pathogenicity islands: bacterial evolution in quantum leaps. *Cell* **87**(5): 791-794

64. Gross RJ, Cheasty T, Rowe B (1977) Isolation of Bacteriophages Specific for the K1 Polysaccharide Antigen of *Escherichia coli*. *J. Clin. Microbiol.* **6**(6): 548-550

65. Grotjohann I, Gitter AH, Hoppe B, Schulzke JD, Fromm M (1998) Ion transport in rat colon measured by medium-resolution Conductance scanning. *Ann. N. Y. Acad. Sci*. **859**: 300-303

66. Grotjohann I, Gitter AH, Köckerling A, Bertog M, Schulzke JD, Fromm M (1998) Localization of cAMP- and aldosterone-induced K+ secretion in rat distal colon by Conductance scanning. *J. Physiol.* **507**(2): 561-570

67. Grunig GG, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, Sheppard D, Mohrs M, Donaldson D, Locksley RM, Corry DB (1998) Requirements for IL-13 independently of IL-4 in experimental asthma. *Science* **282**: 2160–2163

68. Guignot J, Bernet-Camard MF, Pous C, Plancon L, Le Bougenec C, Servin AL (2001) Polarized entry of uropathogenic Afa/Dr diffusely adhering Escherichia coli strain IH11128 into human epithelial cells: evidence for alpha5beta1 integrin recognition and subsequent internalization through a pathway involving caveolae and dynamic unstable microtubules. *Infect. Immun.* **69**(3): 1856-1868

69. Guignot J, Breard J, Bernet-Camard MF, Peiffer I, Nowicki BJ, Servin AL, Blanc-Potard AB (2000) Pyelonephritogenic diffusely adhering Escherichia coli EC7372 harboring Dr-II adhesin carries classical uropathogenic virulence genes and promotes cell lysis and apoptosis in polarized epithelial caco-2/TC7 cells. *Infect. Immun.* **68**(12): 7018-7027

70. Günzel D* / Florian P* (*equally contrib.), Richter JF, Troeger H, Schulzke JD, Fromm M, Gitter AH (2006) Restitution of single-cell defects in the mouse colon epithelium differs from that of cultured cells. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **290**: 1496-1507

71. Hacker J, Knapp S, Goebel W (1983) Spontaneous deletions and flanking regions of the chromosomally inherited hemolysin determinant of an Escherichia coli O6 strain. *Bacteriol.* **154**(3): 1145-1152

72. Hacker J, Schroter G, Schrettenbrunner A, Hughes C, Goebel W (1983) Hemolytic Escherichia coli strains in the human fecal flora as potential urinary pathogens. *Zentralbl. Bakteriol. Mikrobiol. Hyg.* **254** (3): 370-378

73. Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ (1981) Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflugers Arch*. **391**(2): 85-100

74. Hecht G (2001) Microbes and microbial toxins: paradigms for microbial-mucosal toxins. VII: Enteropathogenic Escherichia coli: physiological alterations from an extracellular position. *Am. J. Physiol. Gastrointest. Liver Physiol.* **281**: 1-7

75. Hegel U, Fromm M. Electrical measurements in large intestine. *Methods Enzymol.* **192**: 459-484

76. Heiskala M, Peterson PA, Yang Y (2001) The roles of claudin superfamily proteins in paracellular transport. *Traffic* **2**(2): 93-98

77. Heller F, Florian P, Bojarski C, Richter JF, Christ M, Hillenbrand B, Mankertz J, Gitter A, Burgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD (2005) Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroent.* **129**(2): 550-64

78. Hermiston ML, Gordon JL (1995) Inflammatory bowel disease and adenomas in mice expressing a dominant negative N-cadherin. *Science* **270**(5239): 1203-1207

79. Hoffmann JC, Pawlowski NN, Kuhl AA, Hohne W, Zeitz M (2002) Animal models of inflammatory bowel disease: an overview. *Pathobiology* **70**(3):121-130

80. Hollander D (1999) Intestinal permeability, leaky gut, and intestinal disorders. *Curr. Gastroenterol. Rep.* **1**(5): 410-416

81. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O´Morain CA, Gassul M, Binder V, Finkel Y, Cortot A, Modigliane R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* **411**(6837): 599-603

82. Ikenouchi J, Furuse M, Furuse K, Sasaki H, Tsukita S (2005) Tricellulin constitutes a novel barrier at tricellular contacts of epithelial cells. *J. Cell. Biol*. ***171***(6): 939-945

83. Island MD, Cui X, Foxman B, Marrs CF, Stamm WE, Stapleton AE, Warren JW (1998) Cytotoxicity of hemolytic, cytotoxic necrotizing factor 1-positive and-negative Escherichia coli to human T24 bladder cells. *Infect. Immun.* **66**: 3384-3389

84. Johnson JR (1991) Virulence factors in Escherichia coli urinary tract infection. *Clin. Microbiol. Rev*. **4**(1): 80-128

85. Johnson JR, Delavari P, Kuskowski M, Stell AL (2001) Phylogenetic distribution of extraintestinal virulence-associated traits in Escherichia coli. *J. Infect. Dis*. **183**(1): 78-88

86. Kilsdonk EP, Yancey PG, Stoudt GW, Bangerter FW, Johnson WJ, Phillips MC, Rothblat GH (1995) Cellular cholesterol efflux mediated by cyclodextrins. *J. Biol. Chem*. **270:** 17250-17256

87. Kim KS (2002) Strategy of *Escherichia coli* for crossing the blood-brain barrier. *J. Infect. Dis.* **186**(2): 220-224

88. Köckerling A, Fromm M (1993) Origin of cAMP-dependent Cl- secretion from both crypts and surface epithelia of rat intestine. *Am. J. Physiol*. **264**(5): 1294-1301

89. Köckerling A, Sorgenfrei D, Fromm M (1993) Electrogenic Na+ absorption of rat distal colon is confined to surface epithelium: a voltage-scanning study. *Am. J. Physiol*. **264**(5): 1285-1293

90. Konig B, Konig W, Scheffer J, Hacker J, Goebel W (1986) Role of Escherichia coli alpha-hemolysin and bacterial adherence in infection: requirement for release of inflammatory mediators from granulocytes and mast cells. *Infect. Immun*. **54**(3): 886-892

91. Konig B, Konig W (1991) Roles of human peripheral blood leukocyte protein kinase C and G proteins in inflammatory mediator release by isogenic Escherichia coli strains. *Infect. Immun*. **59**(10): 3801-3810

92. Kopecko DJ, Hu L, Zaal KJ (2001) Campylobacter jejuni-microtubule-dependent invasion.*Trends Microbiol*. **9**(8): 389-396

93. Korczak B, Frey J, Schrenzel J, Pluschke G, Pfister R, Ehricht R, Kuhnert P (2005) Use of diagnostic microarrays for determination of virulence gene patterns of Escherichia coli K1, a major cause of neonatal meningitis. *J. Clin. Microbiol*. **43**(3): 1024-1031

94. Kraehenbuhl JP, Neutra MR (2000) Epithelial M cells: differentiation and function. *Annu. Rev. Cell. Dev. Biol.* **16**: 301-32

95. Kreusel KM, Fromm M, Schulzke JD, Hegel U (1991) Cl- secretion in epithelial monolayers of mucus-forming human colon cell (HT-29/B6). *Am. J. Physiol.* **261**: 574-582

96. Kruis W, Fric P, Pokrotnieks J, Lukas M, Fixa B, Kascak M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J (2004) Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* **53**(11): 1617-1623

97. Kucharzik T, Lugering N, Rautenberg K, Lugering A, Schmidt MA, Stoll R, Domschke W (2000) Role of M cells in intestinal barrier function. *Ann. N. Y. Acad. Sci.* **915**: 171-183

98. Laemmli UK (1970) Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* **227**(5259): 680-685

99. Le TL, Yap AS, Stow JL (1999) Recycling of E-cadherin: a potential mechanism for regulating cadherin dynamics. *J. Cell. Biol*. **146**(1): 219-232

100. Lecuit M, Vandormael-Pournin S, Lefort J, Huerre M, Gounon P, Dupuy C, Babinet C, Cossart P (2001) A transgenic model for listeriosis: role of internalin in crossing the intestinal barrier. *Science* **292**(5522): 1722-1725

101. Leeds JA, Welch RA (1996) RfaH enhances elongation of Escherichia coli hlyCABD mRNA. *J. Bacteriol.* **178**(7): 1850-1857 Erratum in: *J. Bacteriol.* (1996) 178(13): 3989

102. Lemaire LC, van Lanschot JJ, Stoutenbeek CP, van Deventer SJ, Wells CL, Gouma DJ (1997) Bacterial translocation in multiple organ failure: cause or epiphenomenon still unproven. *Br. J. Surg*. **84**(10): 1340-1350

103. Lencer WI (2001) Microbes and microbial toxins: paradigms for microbial-mucosal toxins. V. Cholera: invasion of the intestinal epithelial barrier by a stably folded protein toxin. *Am. J. Physiol. Gastrointest. Liver. Physiol.* **280**: 781-786

104. Louvois J (1994) Acute bacterial meningitis in the newborn. *J. Antimicrob. Chemother.* **34**: 61-73

105. Ludwig A, Garcia F, Bauer S, Jarchau T, Benz R, Hoppe J, Goebel W (1996) Analysis of the in vivo activation of hemolysin (HlyA) from Escherichia coli. *J. Bacteriol.* **178**(18): 5422-5430

106. Ludwig A, Goebel W (1999) The family of the multigenic encoded RTX toxins. *The comprehensive sourcebook of bacterial protein toxins, 2 nd edition (Alouf, J.E., Freer, J.H. Eds.) Academic Press London*: 330-348

107. Ludwig A, Goebel W (2000) Dangerous signals from E. coli toxin. *Nat. Med.* **6**(7): 741-742

108. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P (1999) Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut* **45**(2): 223-228

109. Mack DR, Michail S, Wei S, McDougall L, Hollingsworth MA (1999) Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression. *Am. J. Physiol*. **276**(4): 941-950

110. Macpherson AJ, Uhr T (2004) Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science* **303**(5664): 1662-1665

111. Madsen KL, Malfair D, Gray D, Doyle JS, Jewell LD, Fedorak RN (1999) Interleukin-10 gene-deficient mice develop a primary intestinal permeability defect in response to enteric microflora. *Inflamm. Bowel Dis*. **5**(4): 262-270

112. Marshall JC, Christou NV, Meakins JL (1993) The gastrointestinal tract. The "undrained abscess" of multiple organ failure. *Ann. Surg.* **218**(2): 111-119

113. Martin HM, Campbell BJ, Hart CA, Mpofu C, Nayar M, Singh R, Englyst H, Williams HF, Rhodes JM (2004) Enhanced Escherichia coli adherence and invasion in Crohn's disease and colon cancer. *Gastroent*. **127**(1): 80-93

114. Martin-Padura I, Lostaglio S, Schneemann M, Williams L, Romano M, Fruscella P, Panzeri C, Stoppacciaro A, Ruco L, Villa A, Simmons D, Dejana E (1998) Junctional adhesion molecule, a novel member of the immunoglobulin superfamily that distributes at intercellular junctions and modulates monocyte transmigration. *J. Cell. Biol*. **142**(1): 117-127

115. Mavris M, Sansonetti P (2004) Microbial-gut interactions in health and disease. Epithelial cell responses. *Best. Pract. Res. Clin. Gastroenterol.* **18**(2): 373-386

116. May AK, Gleason TG, Sawyer RG, Pruett TL (2000) Contribution of Escherichia coli alpha-hemolysin to bacterial virulence and to intraperitoneal alterations in peritonitis. *Infect. Immun*. **68**(1): 176-183

117. Mayer K, Temmesfeld-Wollbruck B, Friedland A, Olschewski H, Reich M, Seeger W, Grimminger AF (1999) Severe microcirculatory abnormalities elicited by E. coli hemolysin in the rabbit ileum mucosa. *Am. J. Respir. Crit. Care Med*. **160**(4): 1171-1178

118. McKay DM (1999) intestinal inflammation and the gut microflora. *Can. J. Gastroenterol.* **13**(6): 509-516

119. Mitic LL, Anderson JM (1998) Molecular architecture of tight junctions. *Annu. Rev. Physiol*. **60**: 121-142

120. Moayyedi P, Axon A (1995) Helicobacter pylori: the research explosion. *Curr. Opin. Infect. Dis.* **8**: 374-379

121. Morales J, Kibsey P, Thomas PD, Poznansky MJ, Hamilton SM (1992) The effects of ischemia and ischemia- reperfusion on bacterial translocation, lipid peroxidation, and gut histology: Studies on hemorrhagic shock in pigs. *J. Trauma* **33**: 221-226

122. Nazli A, Yang PC, Jury J, Howe K, Watson JL, Soderholm JD, Sherman PM, Perdue MH (2004) Epithelia under metabolic stress perceive commensal bacteria as a threat. *Am. J. Pathol.* **164**(3): 947-957

123. Neutra MR, Frey A, Kraehenbuhl JP (1996) Epithelial M cells: gateways for mucosal infection and immunization. *Cell* **86**(3): 345-348

124. O'Boyle CJ, MacFie J, Mitchell CJ, Johnstone D, Sagar PM, Sedman PC (1998) Microbiology of bacterial translocation in humans. *Gut* **42**(1): 29-35

125. Ogata Y, Nishi M, Nakayama H, Kuwahara T, Ohnishi Y, Tashiro S (2003) Role of bile in intestinal barrier function and its inhibitory effect on bacterial translocation in obstructive jaundice in rats. *J. Surg. Res.* **115**(1): 18-23

126. Ørskov I, Ørskov F, Jann B, Jann K (1977) Serology, chemistry and genetics of O and K antigens of Escherichia coli. *Bact. Rev.* **41**: 667-710

127. Owens WE and Berg RD (1980) Bacterial translocation from the gastrointestinal tract of athymic (nu/nu) mice. *Infect. Immun.* **27:** 461–467

128. Panwala CM, Jones JC, Viney JL (1998) A novel model of inflammatory bowel disease: mice deficient for the multiple drug resistance gene, mdr1a, spontaneously develop colitis. *J. Immunol.* **161**(10): 5733-5744

129. Pentecost M, Otto G, Theriot JA, Amieva MR (2006) Listeria monocytogenes invades the epithelial junctions at sites of cell extrusion. *PLoS. Pathog*. **2**(1): e3

130. Powell DW, Barrier function of epithelia (1981) *Am. J. Physiol.* **241**(4): 275-288

131. Prasad S, Mingrino R, Kaukinen K, Hayes KL, Powel RM, Macdonald TT, Collins JE (2005) Inflammatory processes have differential effects on claudins 2, 3 and 4 in colonic epithelial cells. *Lab. Invest*. **85**(9): 1139-1162

132. Rembacken BJ, Snelling AM, Hawkey PM, Chalmers DM, Axon AT (1999) Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* **354**(9179): 635-639

133. Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R, Granucci F, Kraehenbuhl JP, Ricciardi-Castagnoli P (2001) Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. *Nat. Immunol*. **2**(4): 361-367

134. Riecken EO, Zeitz M, Ullrich R (1990) Opportunistic causes of diarrhoea in HIV infection. *Baillieres Clin. Gastroenterol.* **4**(2): 385-403

135. Rizzo G, Di Biase C (1976) Haemolysin production in Escherichia coli strains isolated from urinary tract infection, infantile enteritis and commensal flora *Ann. Sclavo*. **18**(6): 841-848

136. Rodal SK, Skretting G, Garred O, Vilhardt F, van Deurs B, Sandvig K (1999) Extraction of cholesterol with methyl-beta-cyclodextrin perturbs formation of clathrin-coated endocytic vesicles. *Mol. Biol. Cell*. **10**(4): 961-974

137. Rolhion N, Barnich N, Claret L, Darfeuille-Michaud A (2005) Strong decrease in invasive ability and outer membrane vesicle release in Crohn's disease-associated adherent-invasive Escherichia coli strain LF82 with the yfgL gene deleted. *J. Bacteriol.* **187**(7): 2286-2296

138. Russo TA, Johnson JR (2000) A Proposal for a new inclusive designation for extraintestinal pathogenic isolates of Escherichia coli: ExPEC. *J. Infect. Dis*. **181**(5): 1753-1754

139. Sadlak B, Merz H, Schorle H, Schimpl A, Feller AC, Horak I (1993) Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* **75**(2): 253-261

140. Sandle GI, Higgs N, Crowe P, Marsh MN, Venkatesan S, Peters TJ (1990) Cellular basis for defective electrolyte transport in inflamed human colon. *Gastroent.* **99**(1): 97-105

141. Sansonetti PJ (2001) Microbes and microbial toxins: paradigms for microbial-mucosal interactions III. Shigellosis: from symptoms to molecular pathogenesis. *Am. J. Physiol. Gastrointest. Liver Physiol*. **280**(3): 319-323

142. Sartor RB (2003) Targeting enteric bacteria in treatment of inflammatory bowel diseases: why, how, and when. *Curr. Opin. Gastroenterol.* **19**(4): 358-365

143. Schatten WE, Desprez JD, Holden WD (1955) A bacteriologic study of portal-vein blood in man. *AMA Arch. Surg*. **71**(3): 404-409

144. Schmitz H, Fromm M, Bentzel CJ, Scholz P, Detjen K, Mankertz J, Bode H, Epple HJ, Riecken EO, Schulzke JD (1999) Tumor necrosis factor-alpha (TNFα) regulates the epithelial barrier in the human intestinal cell line HT-29/B6. *J. Cell Sci.* **112**(1): 137-146

145. Schmitz H, Fromm M, Bode H, Scholz P, Riecken EO, Schulzke JD (1996) Tumor necrosis factor-alpha induces Cl^- and K^+ secretion in human distal colon driven by prostaglandin E2. *Am. J. Physiol.* **271**(4): 669-674

146. Schmitz H, Rokos K, Florian P, Gitter AH, Fromm M, Scholz P, Ullrich R, Zeitz M, Pauli G, Schulzke JD (2002) Supernatants of HIV-infected immune cells affect the barrier function of human HT-29/B6 intestinal epithelial cells. *AIDS* **16**(7): 983-991

147. Schulzke JD, Fromm M, Hegel U (1986) Epithelial and subepithelial resistance of rat large intestine: segmental differences, effect of stripping, time course, and action of aldosterone. *Pflugers Arch*. **407**(6): 632-637

148. Schwab M, Schaeffeler E, Marx C, Fromm MF, Kaskas B, Metzler J, Stange E, Herfarth H, Schoelmerich J, Gregor M, Walker S, Cascorbi I, Roots I, Brinkmann U, Zanger UM, Eichelbaum M (2003) Association between the C3435T MDR1 gene polymorphism and susceptibility for ulcerative colitis. *Gastroent*. **124**(1): 26-33

149. Schweinburg FB, Frank HA, Frank ED, Heimberg F, Fine J (1949) Transmural migration of intestinal bacteria during peritoneal irrigation in uremic dogs. *Proc. Soc. Exp. Biol. Med.* **71**: 150-153

150. Sears CL (2000) Molecular physiology and pathophysiology of tight junctions. V: Assault of the tight junction by enteric pathogens. *Am. J. Physiol. Gastrointest. Liver Physiol.* **279**: 1129-1134

151. Sedman PC, Macfie J, Sagar P, Mitchell CJ, May J, Mancey-Jones B, Johnstone D (1994) The prevalence of gut translocation in humans. *Gastroent*. **107**(3): 643-649

152. Shin JS, Abraham SN (2001) Caveolae as portals of entry for microbes. *Microbes. Infect.* **3**(9): 755-761

153. Siitonen A (1992) Escherichia coli in fecal flora of healthy adults: serotypes, P and type 1C fimbriae, non-P mannose-resistant adhesins, and hemolytic activity.*J. Infect. Dis*. **166**(5):1058-1065

154. Simon GL, Gorbach SL (1986) The human intestinal microflora. *Dig. Dis. Sci*. **31**(9): 147-162

155. Smale S, Bjarnason I (2003) Determining small bowel integrity following drug treatment. *Br. J. Clin. Pharmacol.* **56**(3): 284-291

156. Smith PK, Krohn RI, Hermanson GT, Mallia AK, Gartner FH, Provenzano MD, Fujimoto EK, Goeke NM, Olson BJ, Klenk DC (1987) Measurement of protein using bicinchoninic acid. *Anal. Biochem*. **150**(1):76-85. Erratum in*: Anal. Biochem.* (1987) 163(1): 279

157. Soderblom T, Laestadius A, Oxhamre C, Aperia A, Richter-Dahlfors A (2002) Toxin-induced calcium oscillations: a novel strategy to affect gene regulation in target cells. *Int. J. Med. Microbiol.* **291**(6): 511-515

158. Soderholm JD, Olaison G, Lindberg E, Hannestad U, Vindels A, Tysk C, Jarnerod G, Sjodahl R (1999) Different intestinal permeability patterns in relatives and spouses of patients with Crohn's disease: an inherited defect in mucosal defence? *Gut* **44**(1): 96-100

159. Souba WW (1997) Nutritional support. *N. Engl. J. Med.* **336**(1): 41-48

160. Spahn TW, Kucharzik T (2004) Modulating the intestinal immune system: the role of lymphotoxin and GALT organs. *Gut* **53**(3): 456-465

161. Staehelin LA (1974) Structure and function of intercellular junctions. *Int. Rev. Cytol.* **39**: 191-283

162. Stein J, Bolder U (2000) Intestinale Funktionen beim kritisch kranken Patienten, *Chir. Gastroenterol.* **16**(1): 13-22

163. Stephen J (2001) Pathogenesis of infectious diarrhea. *Can. J. Gastroenterol*. **15**(10): 669-683

164. Sun R, Anderson TJ, Erickson AK, Nelson EA, Francis DH (2000) Inhibition of adhesion of Escherichia coli k88ac fimbria to its receptor, intestinal mucin-type glycoproteins, by a monoclonal antibody directed against a variable domain of the fimbria. *Infect. Immun*. **68**(6): 3509-3515

165. Suttorp N, Floer B, Schnittler H, Seeger W, Bhakdi S (1990) Effects of Escherichia coli hemolysin on endothelial cell function. *Infect. Immun.* **58**(11): 3796-3801

166. Swidsinski A, Khilkin M, Kerjaschki D, Schreiber S, Ortner M, Weber J, Lochs H (1998) Association between intraepithelial Escherichia coli and colorectal cancer. *Gastroent.* **115**(2): 281-286

167. Swidsinski A, Weber J, loening-Baucke V, Hale LP, Lochs H (2005) Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. *J. Clin. Microbiol*. **43**(7): 3380-3389

168. Thjodleifsson B, Sigthorsson G, Cariglia N, Reynissdottir I, Gudbjartsson DF, Kristjansson K, Meddings JB, Gudnason V, Wandall JH, Andersen LP, Sherwood R, Kjeld M, Oddson E, Gudjonsson H, Bjarnason I (2003) Subclinical intestinal inflammation: an inherited abnormality in Crohn's disease relatives? *Gastroent.* **124**(7): 1728-1737

169. Tsukita S, Furuse M (2000) The structure and function of claudins, cell adhesion molecules at tight junctions. *Ann. N. Y. Acad. Sci.* **915**: 129-35

170. Tsukita S, Furuse M, Itoh M *(2001),* Multifunctional strands in tight junctions. *Nature Rev. Molec. Cell Biol.* **2***: 285-293*

171. Tullus K, Jacobson SH, Katouli M, Brauner A (1995) Relative importance of eight virulence characteristics of pyelonephritogenic Escherichia coli strains assessed by multivariate statistical analysis. *J. Infect. Dis*. **171**(6): 1514-1521

172. Uhlen P, Laestadius A, Jahnukainen T, Soderblom T, Backhed F, Celsi G, Brismar H, Normark S, Aperia A, Richter-Dahlfors A (2000) Alpha-haemolysin of uropathogenic E. coli induces Ca2+ oscillations in renal epithelial cells. *Nature* **405**(6787): 694-697

173. Ussing HH, Zerahn K (1951) Active transport of sodium as the source of electric current in the short-circuited isolated frog skin. *Acta Physiol. Scand.* **23**: 110-127

174. Van Itallie CM, Anderson JM (2006) Claudins and epithelial paracellular transport. *Annu. Rev. Physiol.* **68**: 403-429

175. Vaughan WG, Horton JW, Walker PB (1992) Allopurinol prevents intestinal permeability changes after ischemia-reperfusion injury. *J. Pediatr. Surg.* **27**(8): 968-972

176. Walev I, Vollmer P, Palmer M, Bhakdi S, Rose-John S (1996) Pore-forming toxins trigger shedding of receptors for interleukin 6 and lipopolysaccharide. *Proc. Natl. Acad. Sci. U S A* **93**(15): 7882-7887

177. Welch RA, Dellinger EP, Minshew B, Falkow S (1981) Haemolysin contributes to virulence of extra-intestinal E. coli infections. *Nature* **294**(5842): 665-667

178. Welch RA (1991) Pore-forming cytolysins of gram-negative bacteria. *Mol. Microbiol*. **5**(3): 521-528

179. Wells CL, Hess DJ, Erlandsen SL (2004) Impact of the indigenous flora in animal models of shock and sepsis. *Shock* **22**(6): 562-568

180. Wells CL, Maddaus MA, Reynolds CM (1987) Role of anaerobic flora in the translocation of aerobic and facultatively anaerobic intestinal bacteria. *Infect. Immun.* **55**: 2689–2694

181. Wells CL (1990) Relationship between intestinal microecology and the translocation of intestinal bacteria. *Antonie van Leeuwenhoek* **58**: 87–93

182. Wiest R, Rath HC (2003) Gastrointestinal disorders of the critically ill. Bacterial translocation in the gut. *Best. Pract. Res. Clin. Gastroenterol*. **17**(3): 397-425

183. Wittig BM, Zeitz M (2002) The gut as an organ of immunology. *Int. J. Colorectal. Dis.* **18**(3): 181-187

184. Wold AE, Caugant DA, Lidin-Janson G, de Man P, Svanborg C (1992) Resident colonic Escherichia coli strains frequently display uropathogenic characteristics. *J. Infect. Dis*. **165**(1): 46-52

185. Zeissig S, Bojarski C, Buergel N, Mankertz J, Zeitz M, Fromm M, Schulzke JD (2004) Downregulation of epithelial apoptosis and barrier repair in active Crohn's disease by tumour necrosis factor alpha antibody treatment. *Gut* **53**(9): 1295-1302

186. Zeng J, Teng F, Weinstock GM, Murray BE (2004) Translocation of Enterococcus faecalis strains across a monolayer of polarized human enterocyte-like T84 cells. *J. Clin. Microbiol.* **42**(3): 1149-1154

187. Bennet JD, Brinkmann M. Treatment of ulcerative colitis by implantation of normal colonic flora. (1989) *Lancet* **1**(8630): 164

188. Borody TJ, George L, Andrews P, Brandl S, Noonan S, Cole P, Hyland L; Morgan A, Maysey J, Moore-Jones D (1989) Bowel-flora alteration: a potential cure for inflammatory bowel disease and irritable bowel syndrome? *Med. J. Aust.* **150**(10): 604