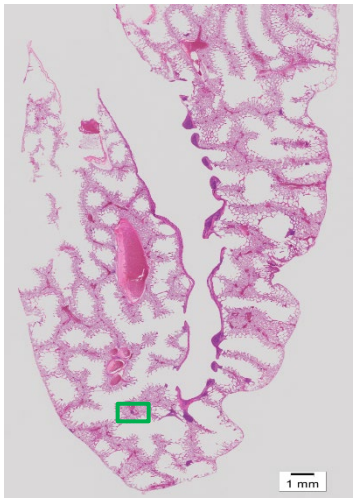
LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Das Mikrobiom: Wirt - Mikrobiom Interaktionen

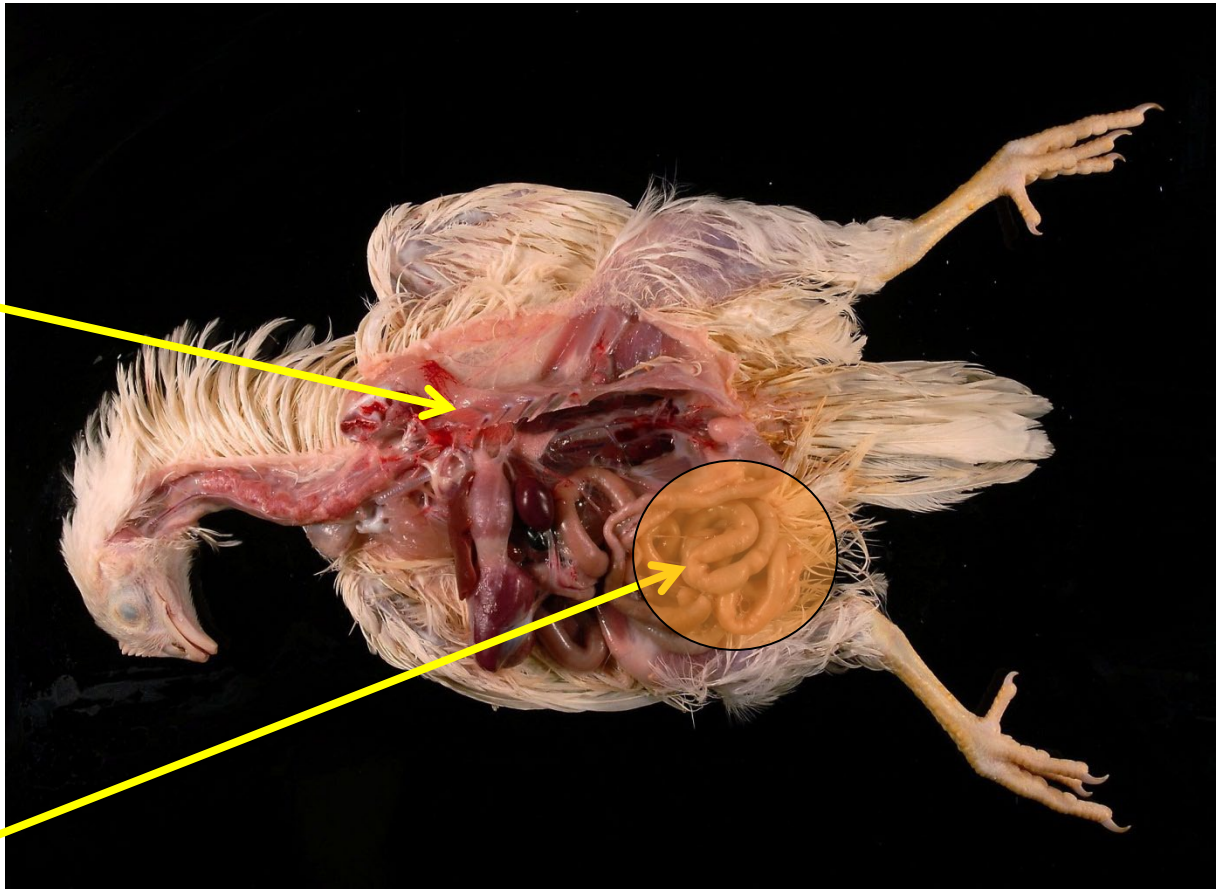
Bernd Kaspers, Department for Veterinary Sciences

University of Munich

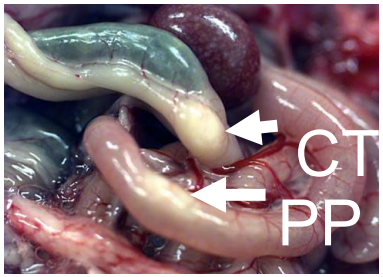
Bakterielle Besiedelung



Lunge

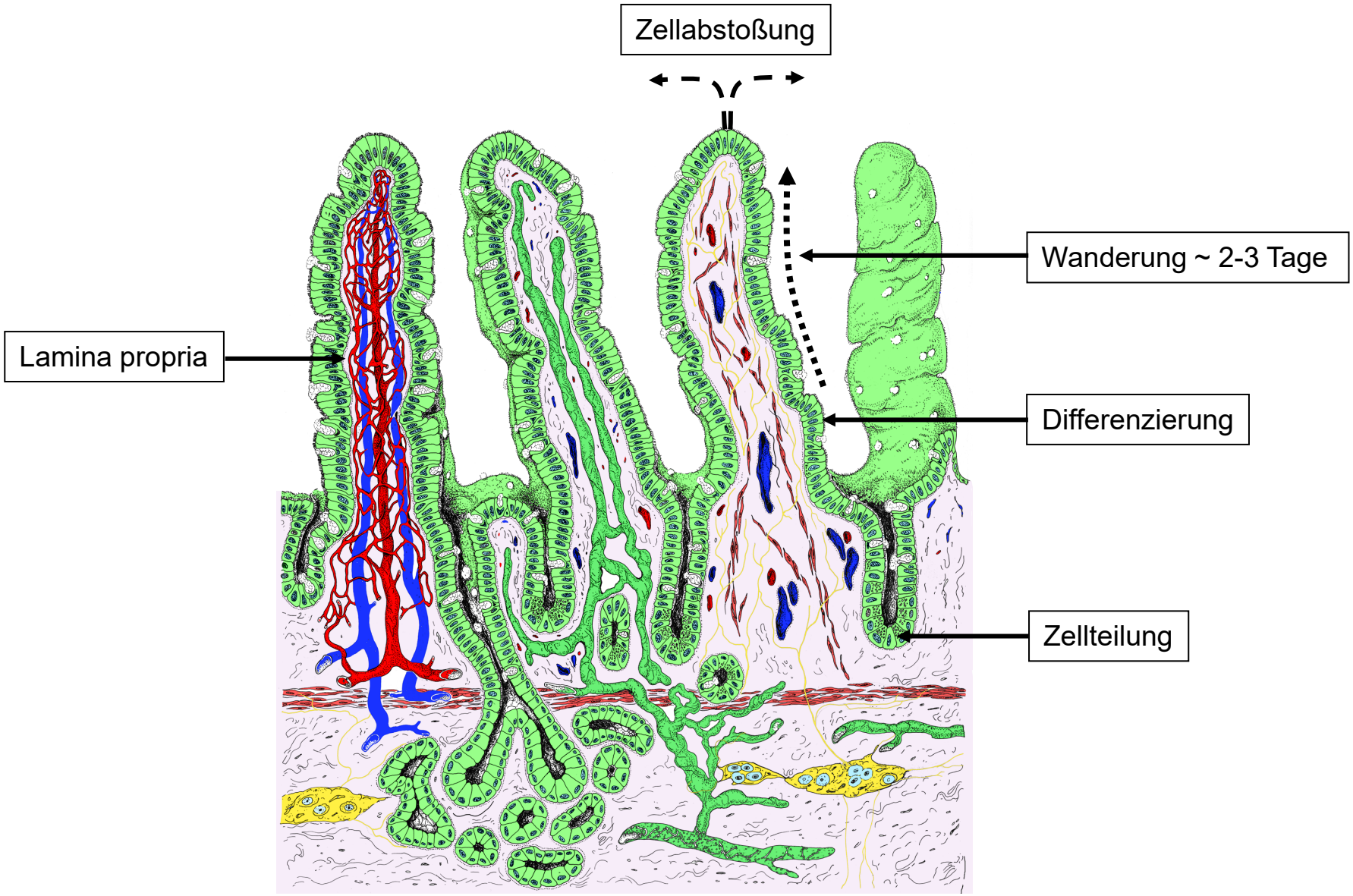


Darm

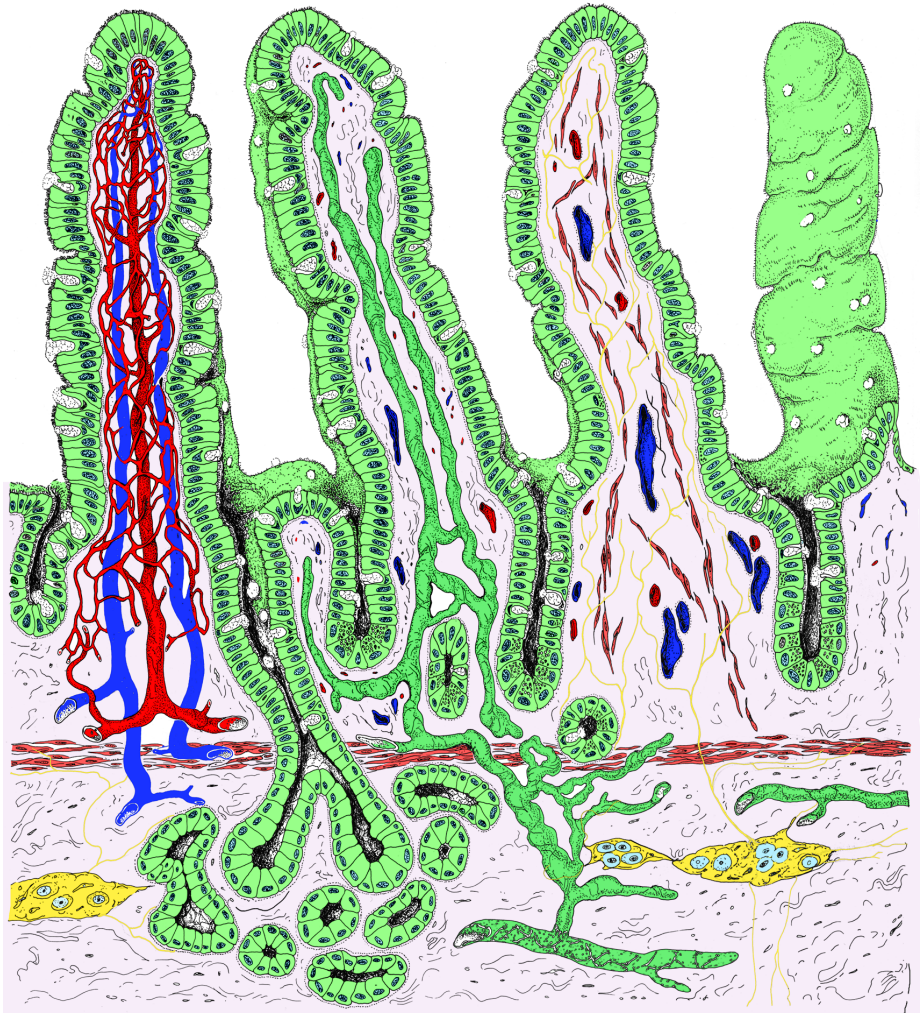


Reproduktions-trakt

Morphologie



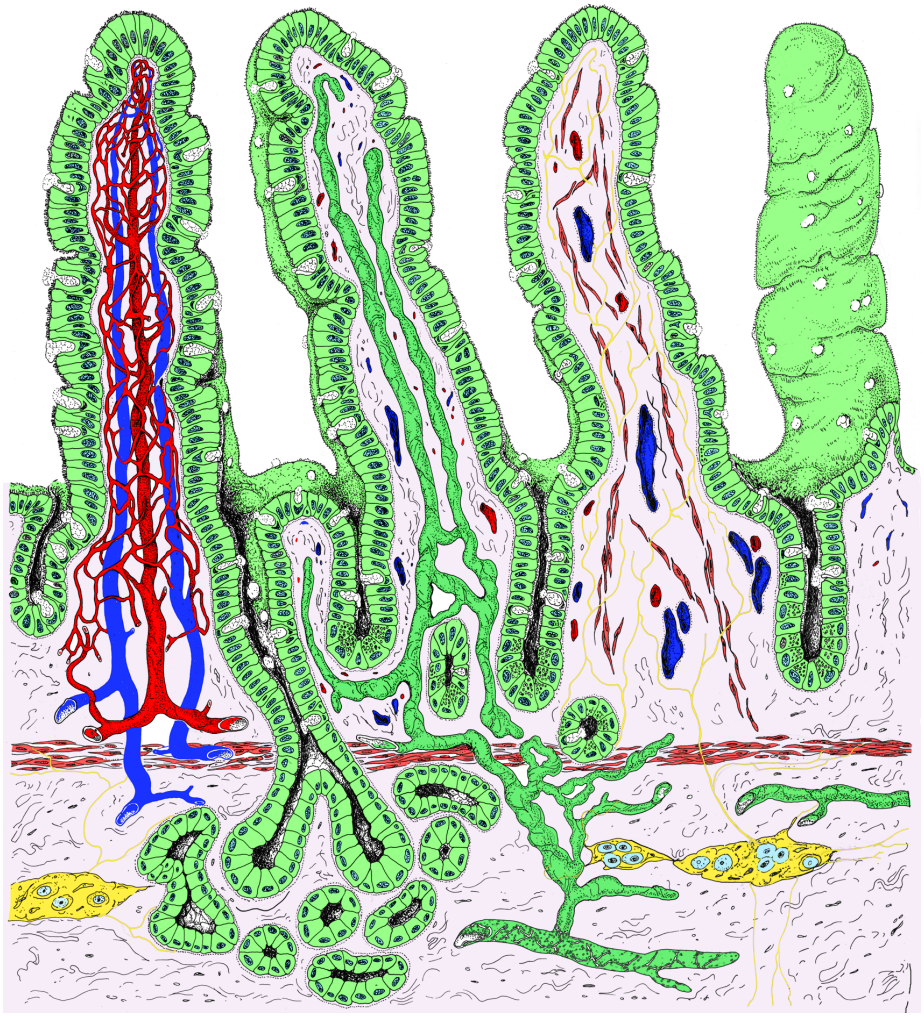
Aufgaben des Darmepithels



- Mechanischer Schutz
- Schutz vor Toxinen
- Schutz vor Pathogenen
- Kontrolle der Darmflora

- Sekretion
- Absorption
- Regulation der Verdauung

Mikrobiota



10 – 100 x 10^12 Mikroorganismen

Bakterien, Viren, Eukaryota, Archaea

500 – 1000 bacterial species

↓

Aufschluss von Nährstoffen

Competitive exclusion

Reifung und Funktion der Darmbarriere

Zellen des Darmepithels

Enterozyten

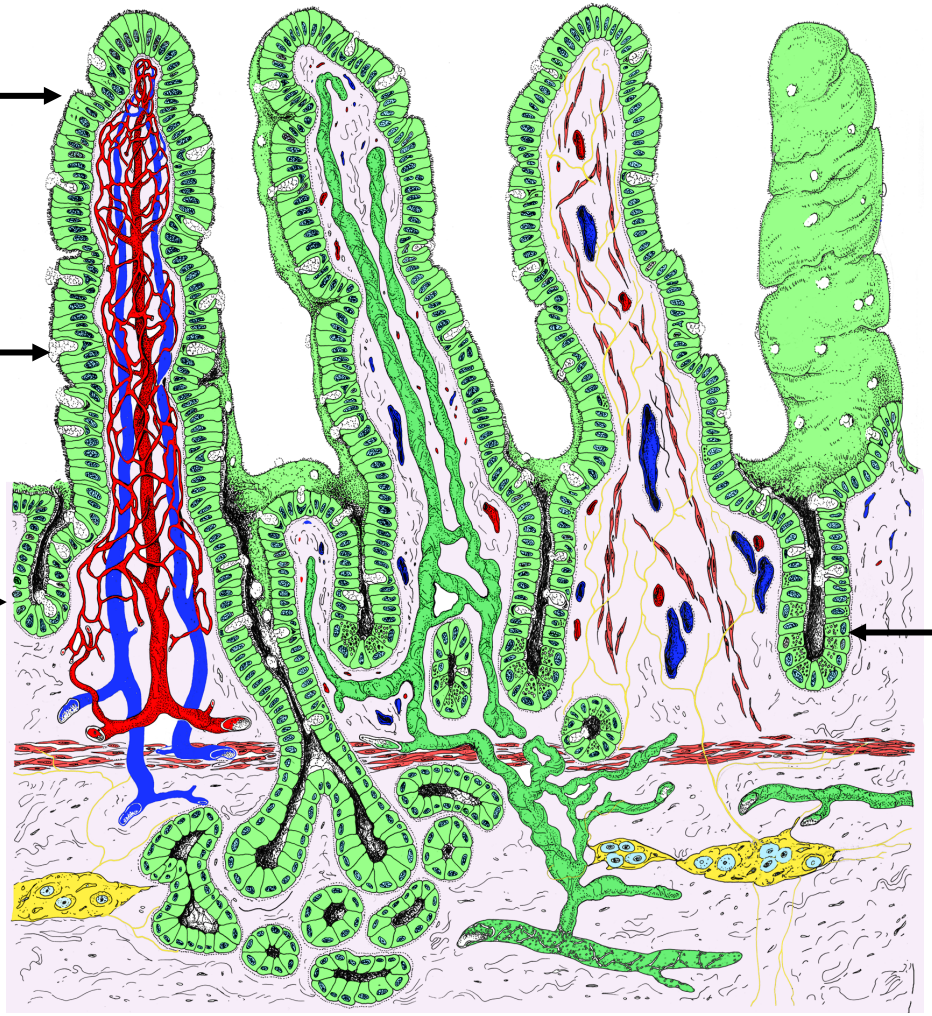
Absorption von Nährstoffen

Becherzellen

Schleimbildung

endokrine Zellen

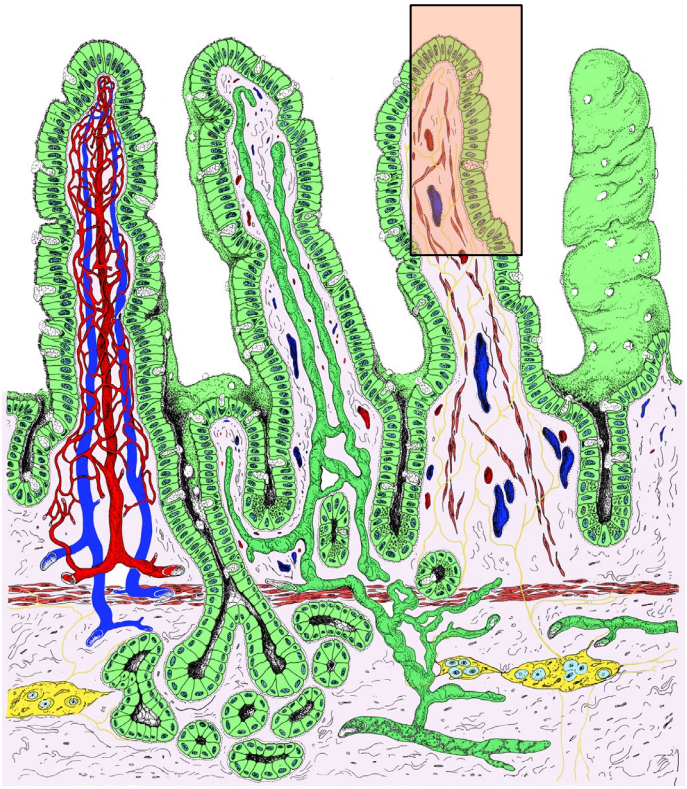
gastro-intestinale Hormone

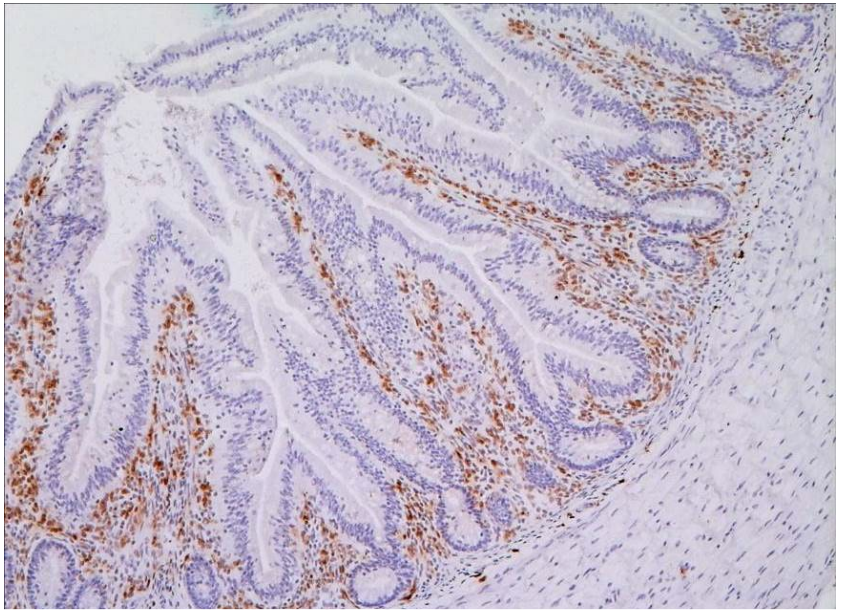


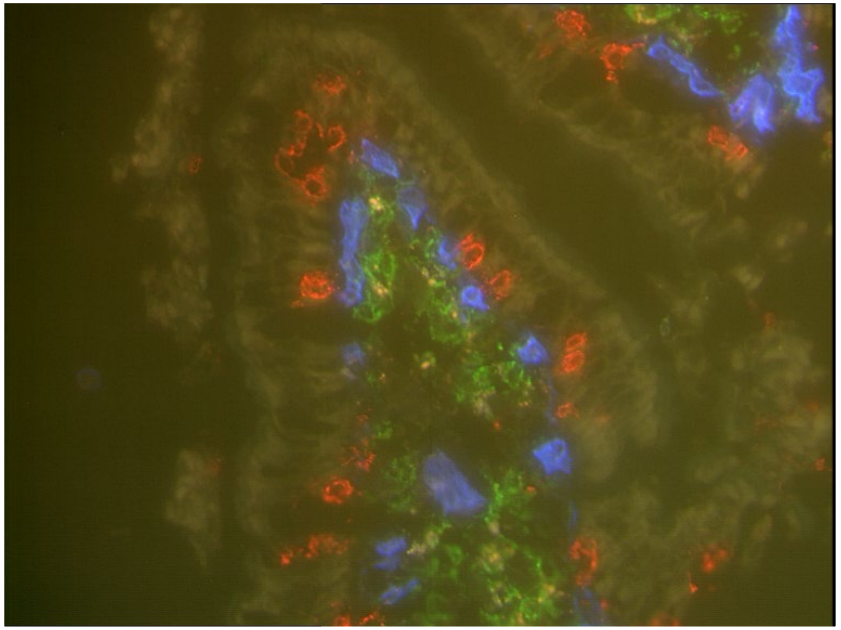
Kryptenepithel

Salz- und Wasser-Sekretion

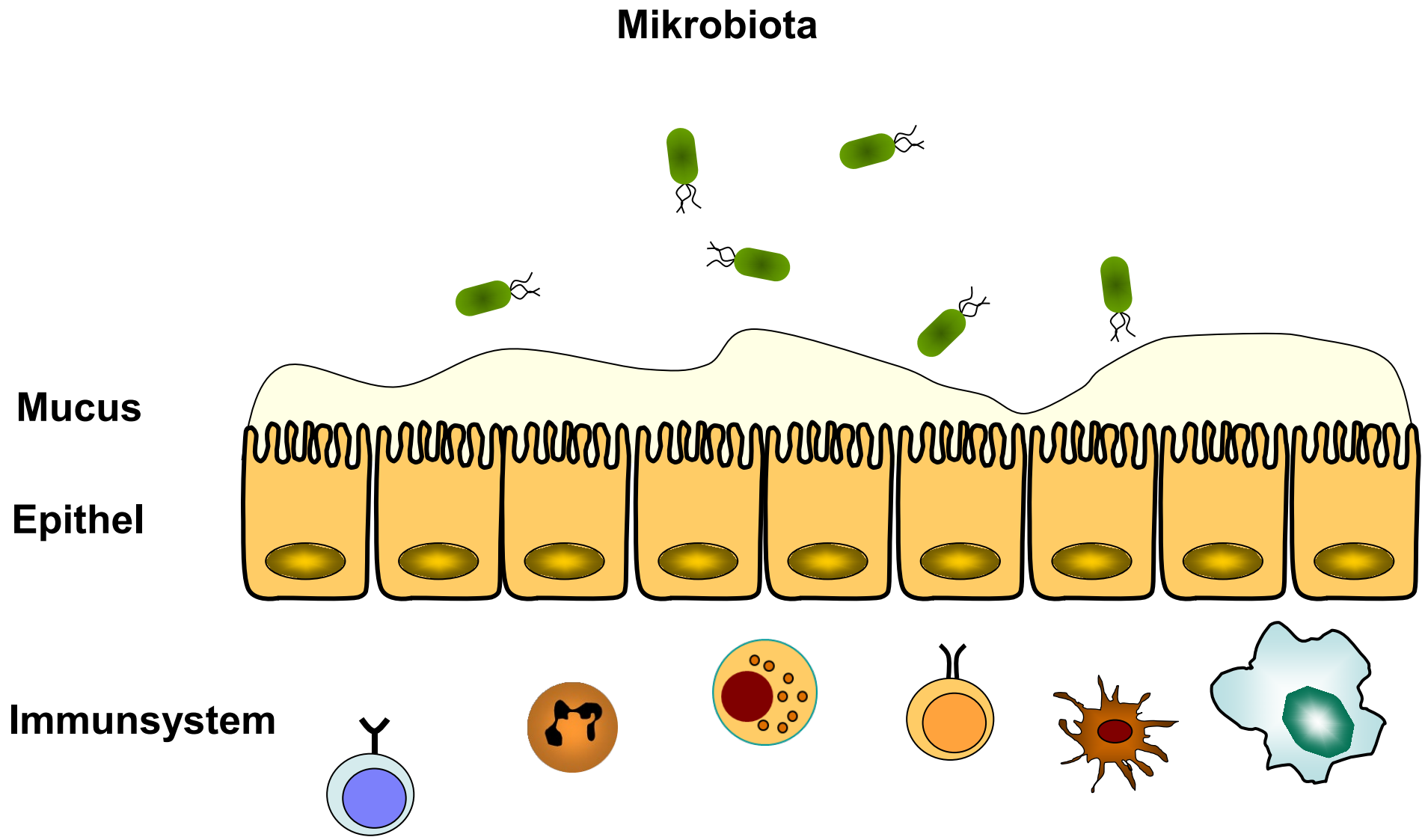
Zellen des Immunsystems



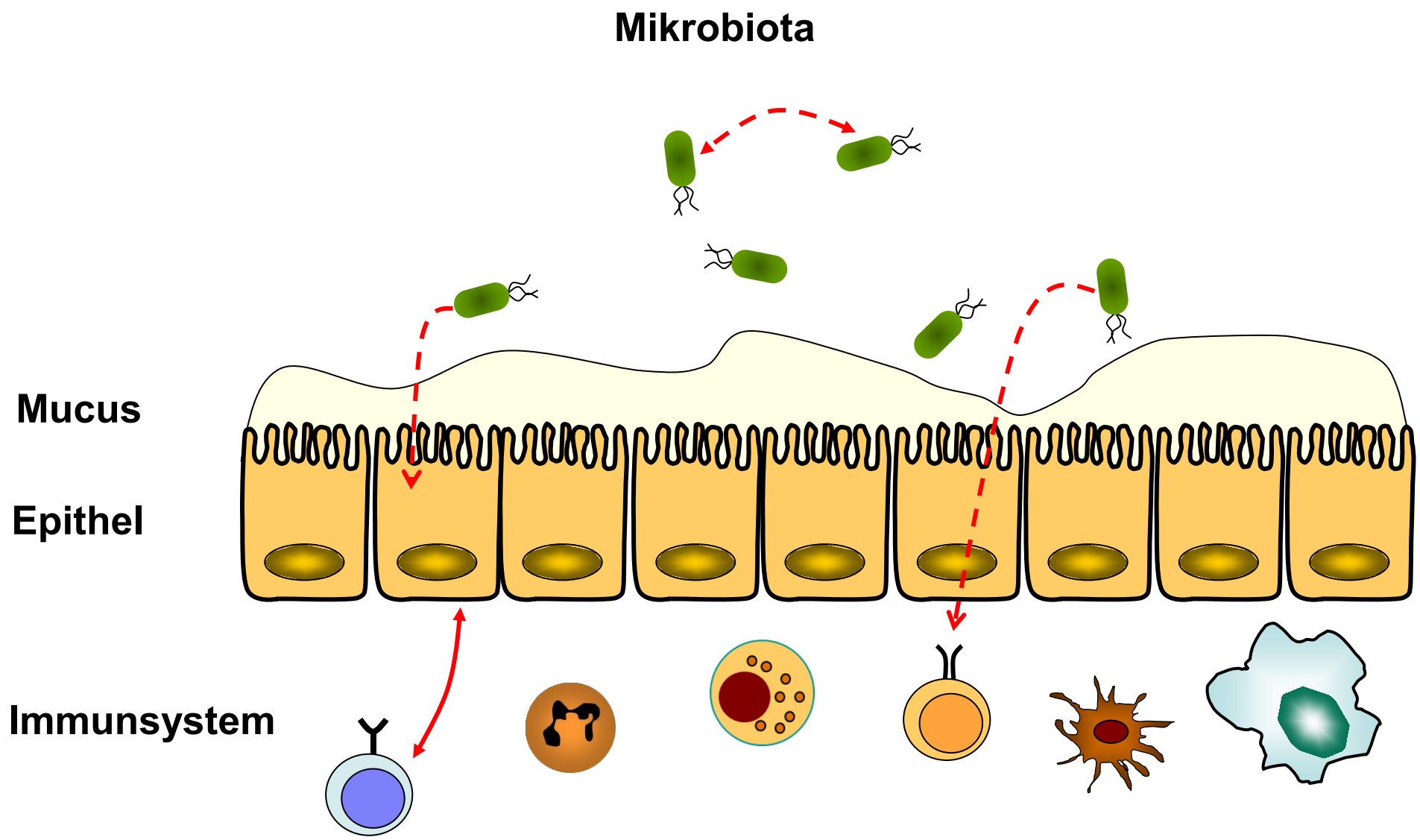




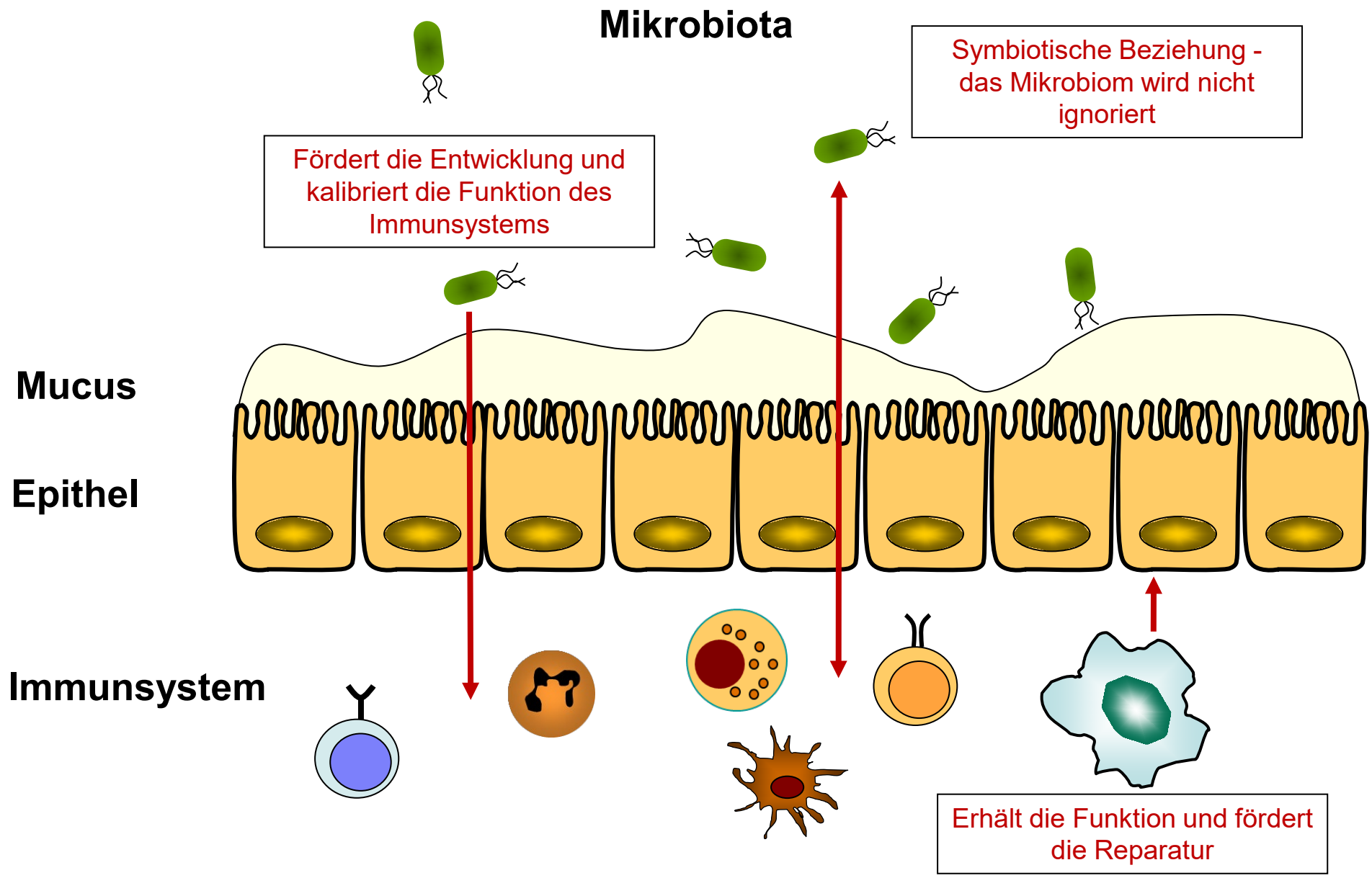
Die mukosale Barriere



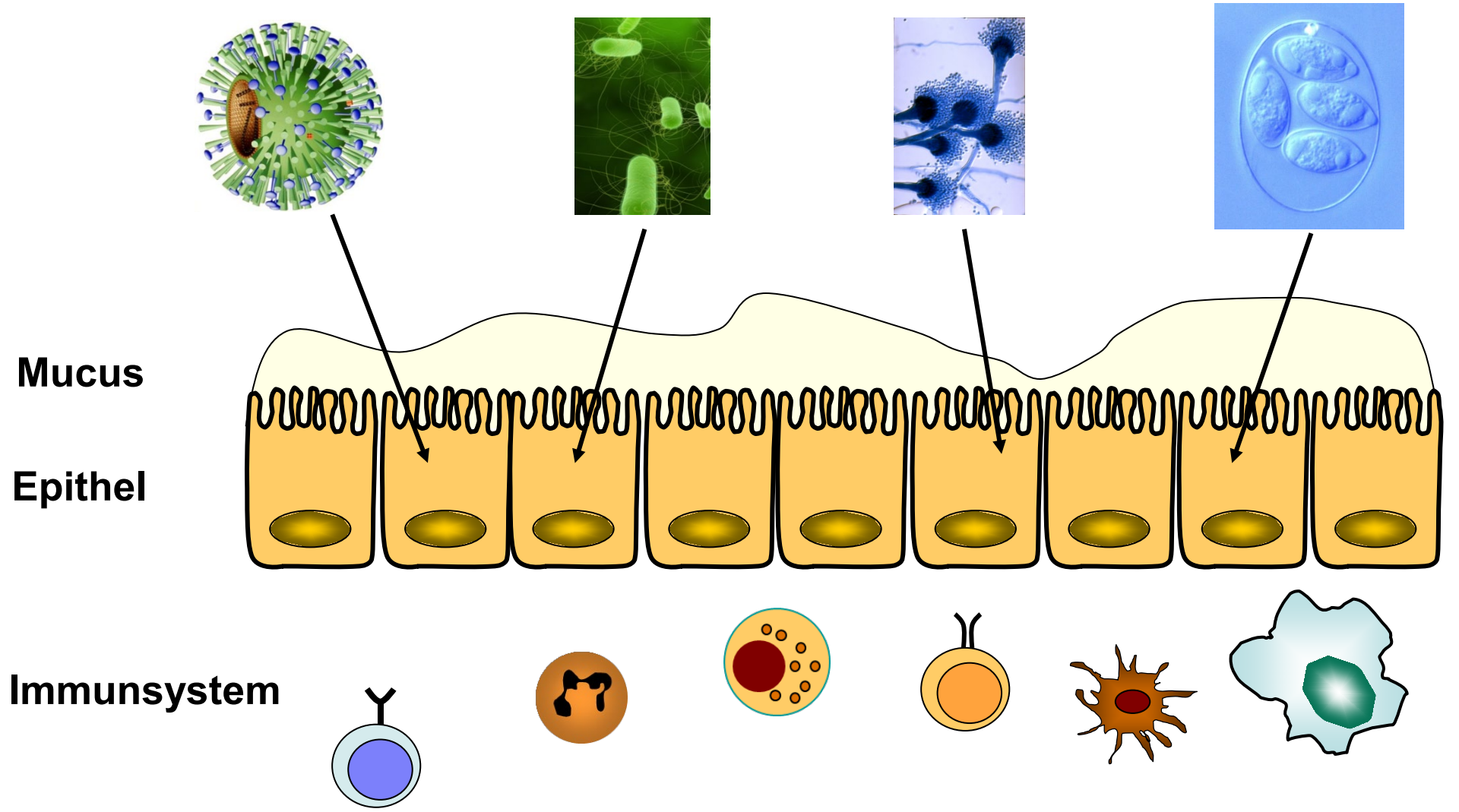
Mikrobiota-Wirt Interaktion



Mikrobiota-Wirt Interaktion

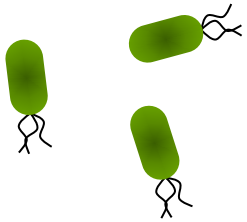


Die mukosale Barriere

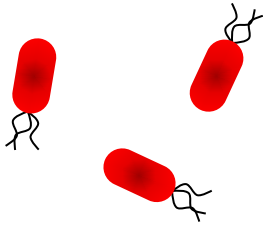


Die Reaktion auf:

Kommensale Mikrobiota



Pathogene



Keine Entzündungsreaktion

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Homeostatic immunity

Entzündung

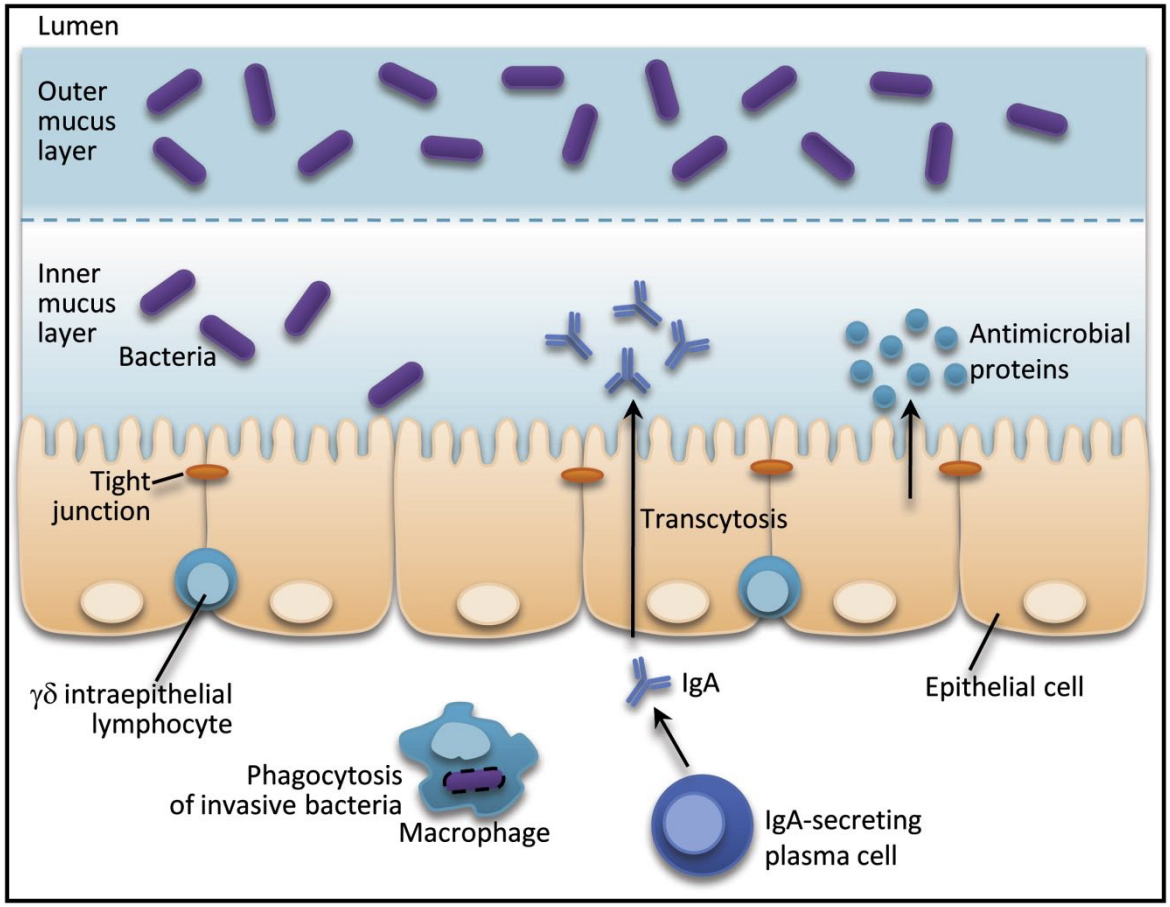
↓

Verlust der Gewebehomöostase

↓

Kontrolle der Entzündung

Schleimschicht

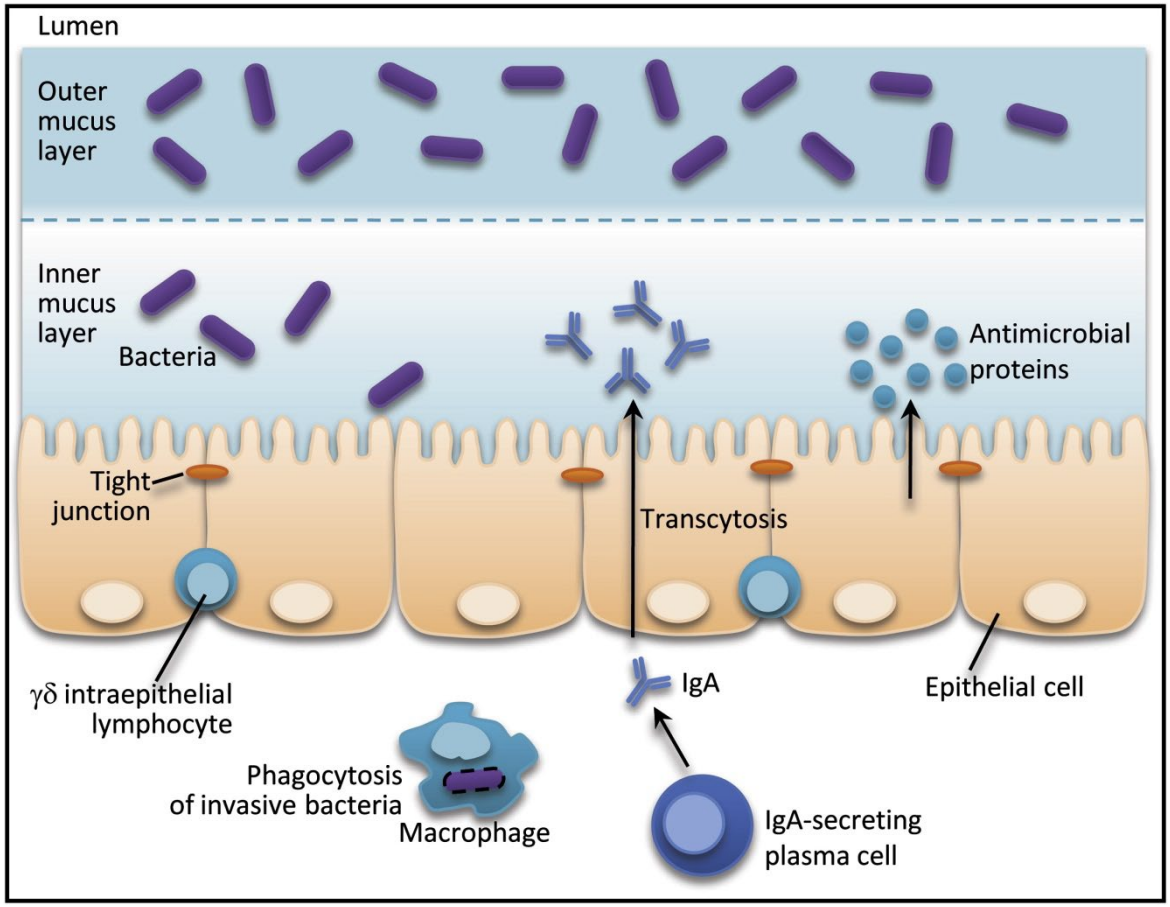


flüssig, viele Bakterien

nur sehr wenige Bakterien

MUC2 $^{-/-}$ Mäuse entwickeln schwere Darmentzündungen

Antimikrobielle Peptide



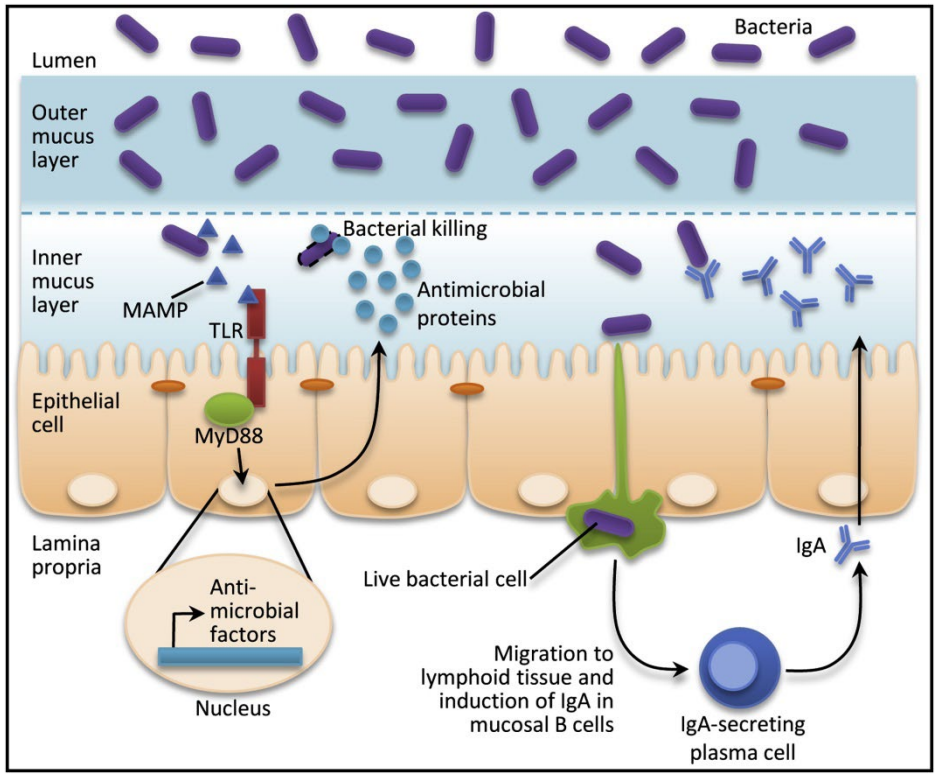
Antimikrobielle Peptide werden von speziellen Epithelzellen gebildet

Sie reduzieren die Bakterienzahl praktisch auf Null

Mäuse ohne Panethzellen zeigen einen erhöhten Übertritt von Bakterien in den Körper

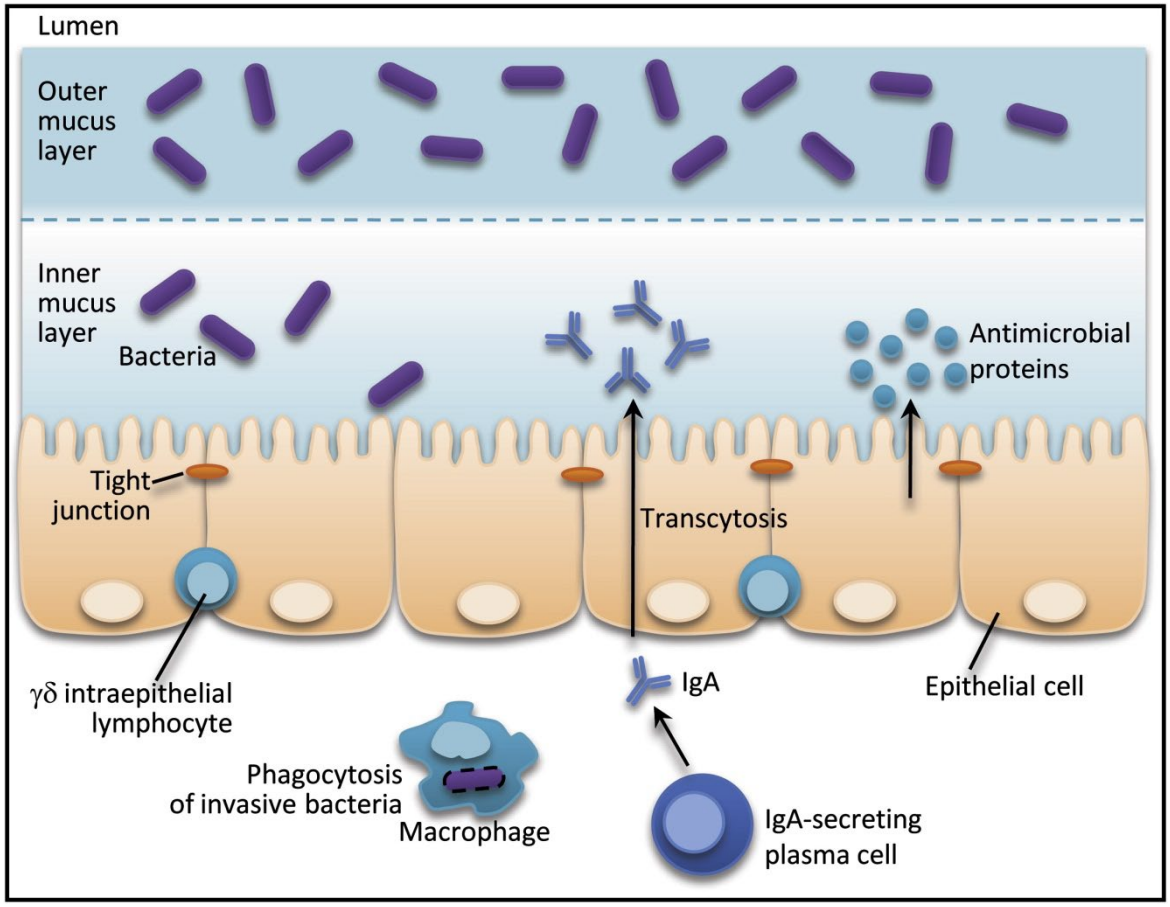
- Defensine
- Lysozym
- Lektine (RegIIIγ)

Antimikrobielle Peptide



- Epithelzellen erkennen Bakterien, die das Epithel erreichen
- Sie sezernieren daraufhin antimikrobielle Peptide. RegIIIγ wird beim Absetzen von Mäusen ~ 3000x hochreguliert
- Antimikrobielle Peptide sind mit der inneren Mucusschicht assoziiert
- Sie kontrollieren so die Zahl der Bakterien auf der Epitheloberfläche und verhindern deren Invasion

IgA



B-Zellen in der Lamina propria bilden bakterien-spezifisches IgA

IgA-Defizienz führt zu einem erhöhten Übertritt von Bakterien in den Körper

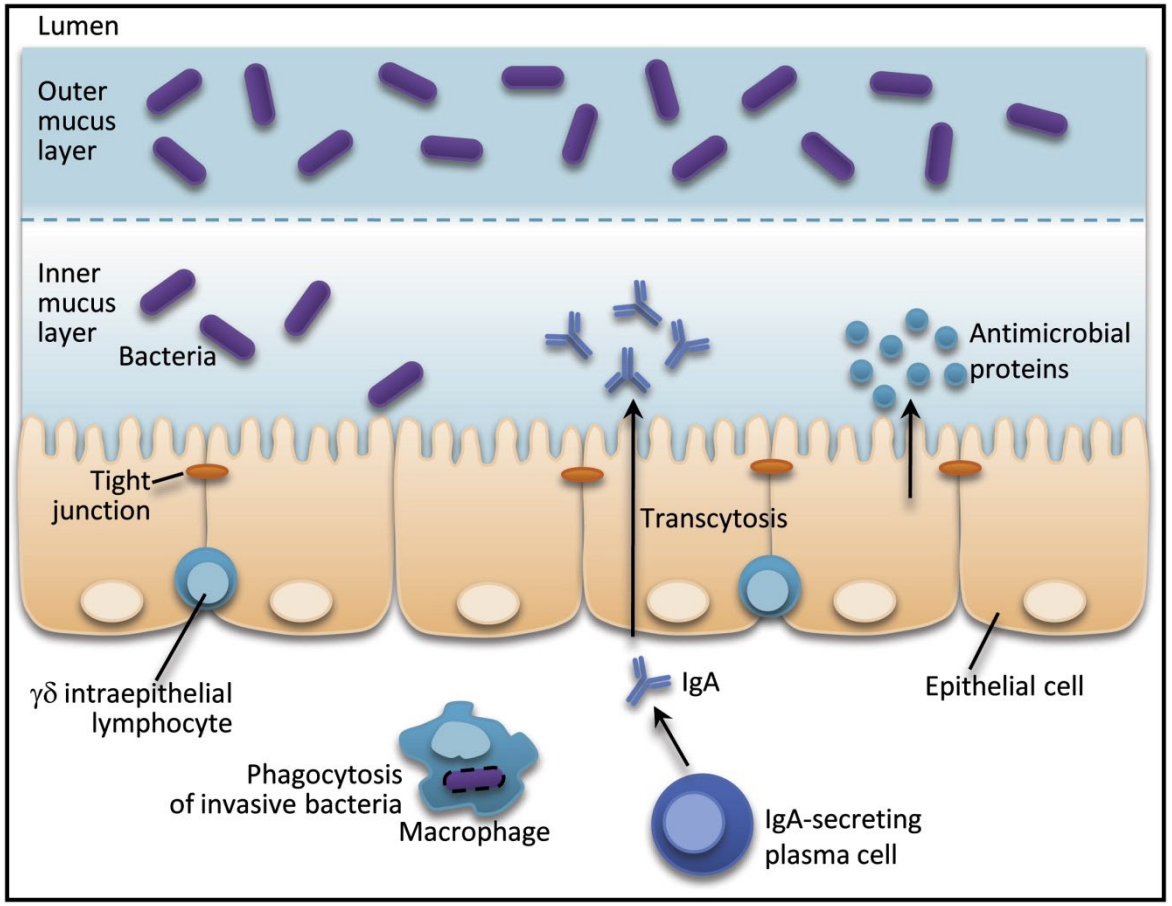
IgA wirkt möglicherweise über

- das Fangen von Bakterien im Mucus
- Complementaktivierung
- Opsonisierung für Makrophagen

IgA reguliert auch die Zusammensetzung der Darmflora

Der Mechanismus ist noch unverstanden.

γ/δ-Zellen und Makrophagen



γ/δ-Zellen sind wesentlich an der Reparatur von Epithelschäden beteiligt

Sie bilden epitheliale Wachstumsfaktoren

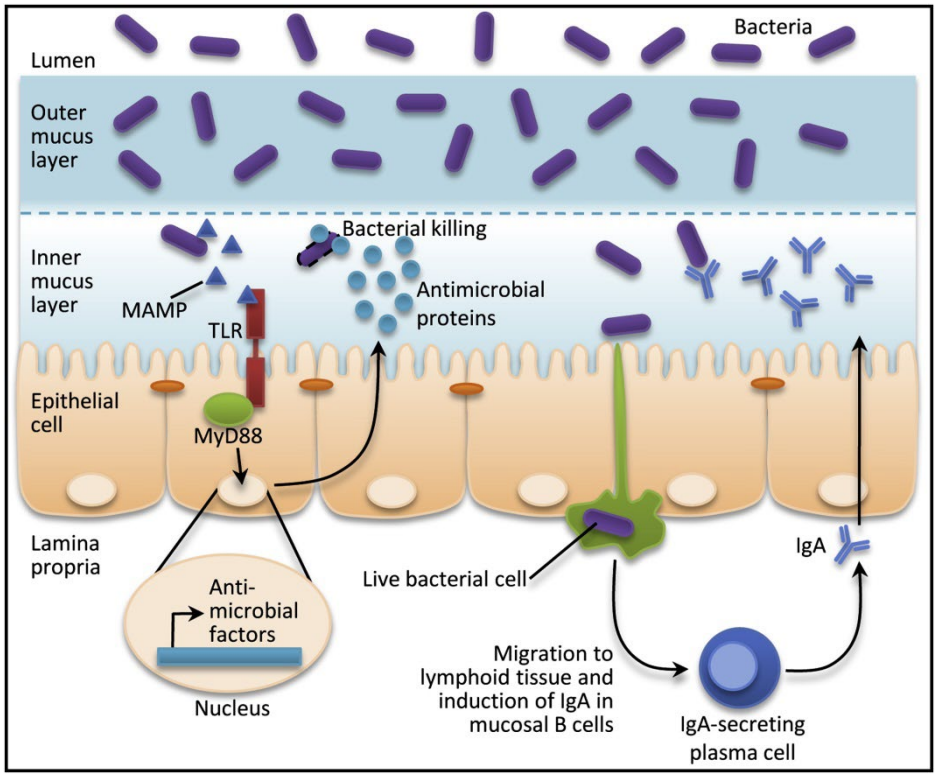
Sie exprimieren zahlreiche inflammatorische und antimikrobielle Faktoren

Makrophagen eliminieren eingedrungene Symbionten

Diese weisen eine hohe Empfindlichkeit auf

Koevolution?

Feedbackregulation

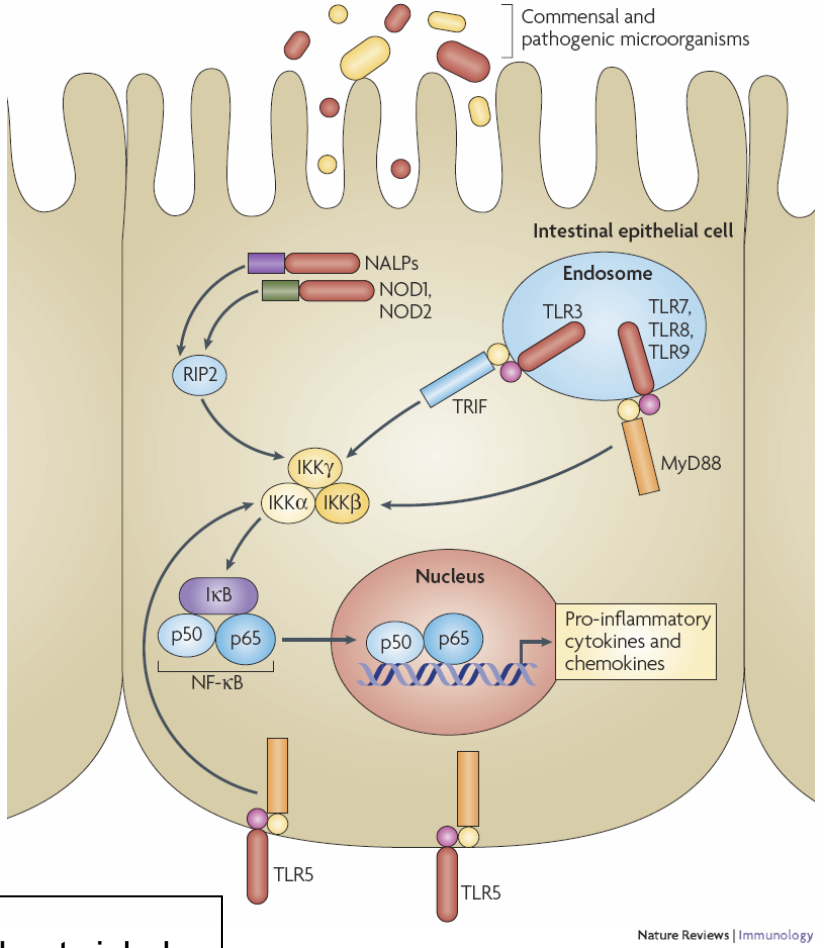


- DCs sammeln Bakterien
- Sie induzieren eine bakterienspezifische IgA-Bildung
- IgA reguliert die Dichte der Bakterien
- IgA reguliert die Zusammensetzung der Flora

- Expression eines spezies-spezifischen monoklonalen IgA führt zur Selektion gegen das Bakterium

Warum haben wir nicht permanent Darmentzündungen?

- PPRs sind nicht auf Epithelzellen exprimiert (TLR4)
- PPRs sind nur zytoplasmatisch oder auf der basolateralen Seite exprimiert (TLR5)
- Epithelzellen reagieren daher nicht auf die symbiontischen Bakterien
- Sie reagieren nur auf Bakterien, die auf die basolaterale Seite gelangt sind

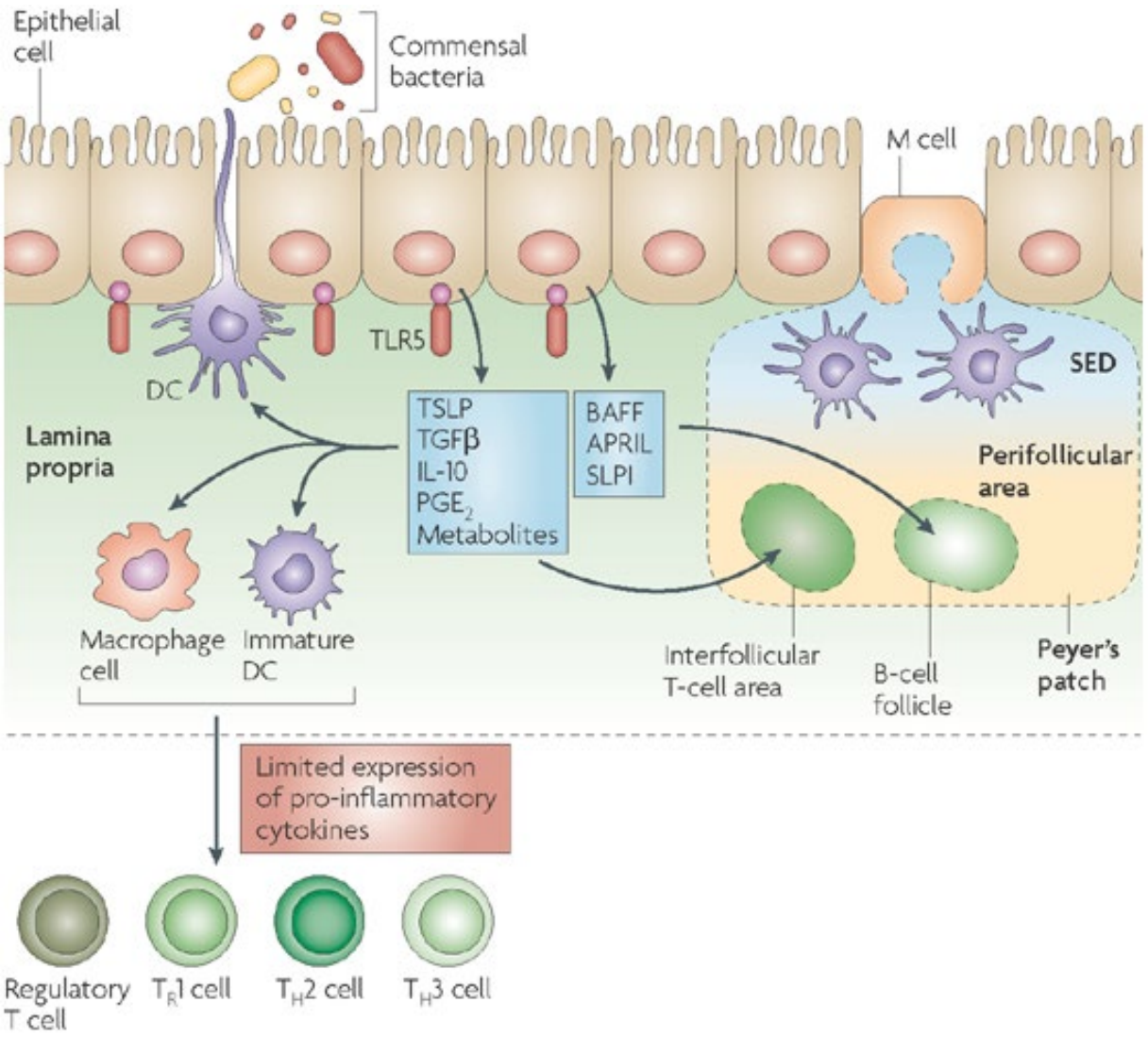


TLR5 $^{-/-}$ Mäuse haben eine veränderte Darmflora und entwickeln:

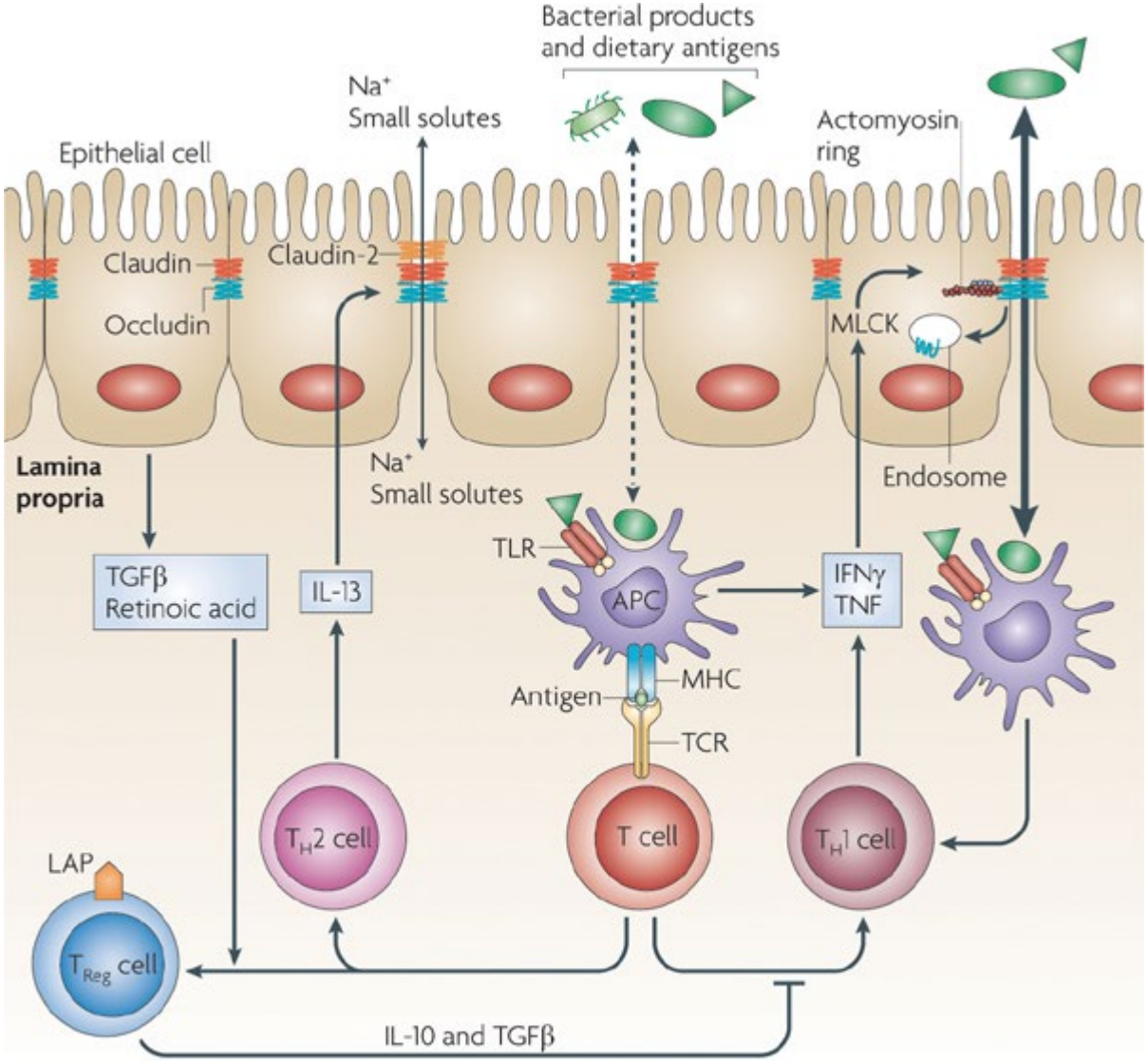
- Hyperphagie und Fettleibigkeit
- Metabolisches Syndrom und Insulinresistenz

→ dieses Krankheitsbild kann mit der Darmflora übertragen werden

Homöostatische Regulation des Darmimmunsystems



Homöostatische Regulation des Darmimmunsystems



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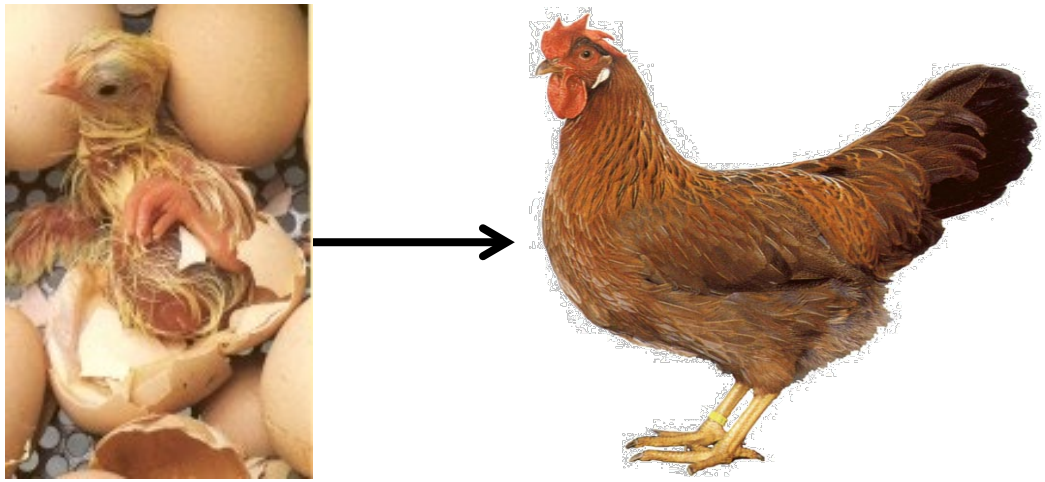
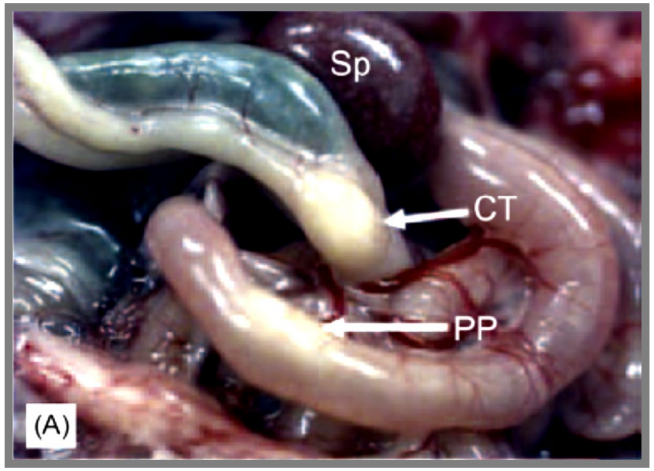
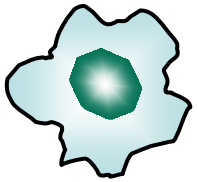
Wie entwickelt sich das Darmimmunsystem?



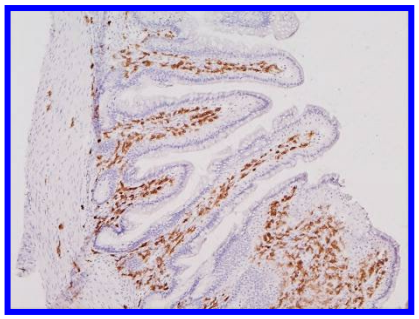


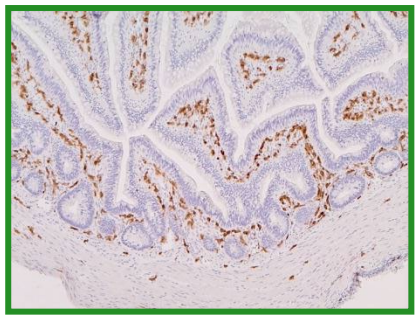
Entwicklung nach dem Schlupf

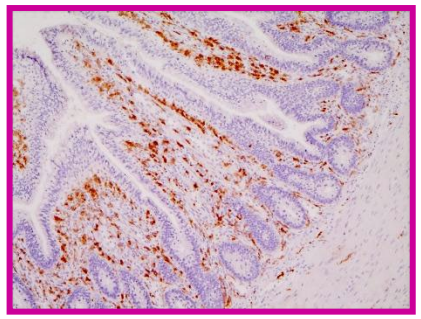
3d 7d 14d 21d

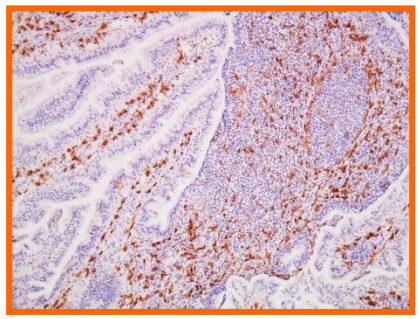


Makro-
phagen

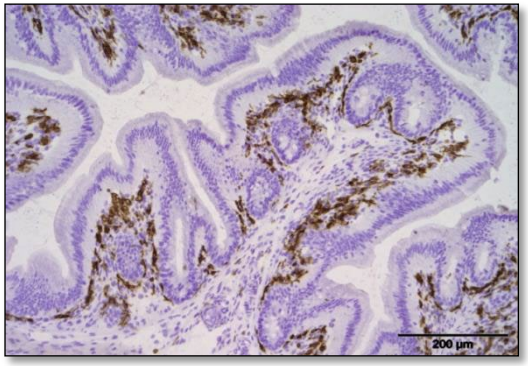




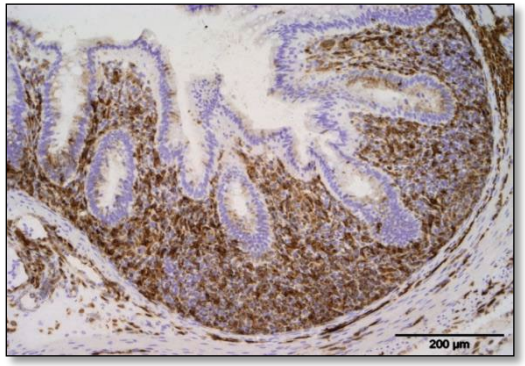


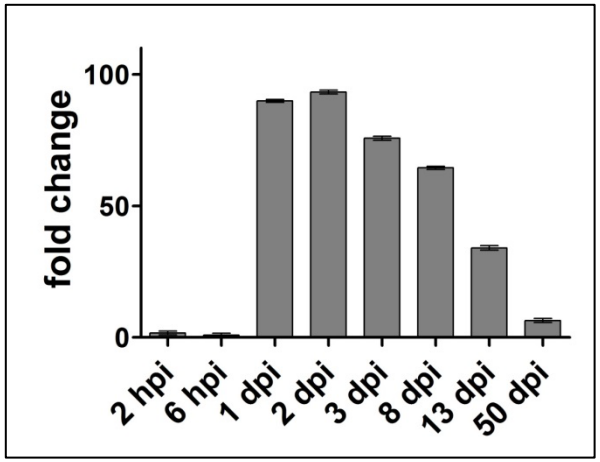


Kontrolle

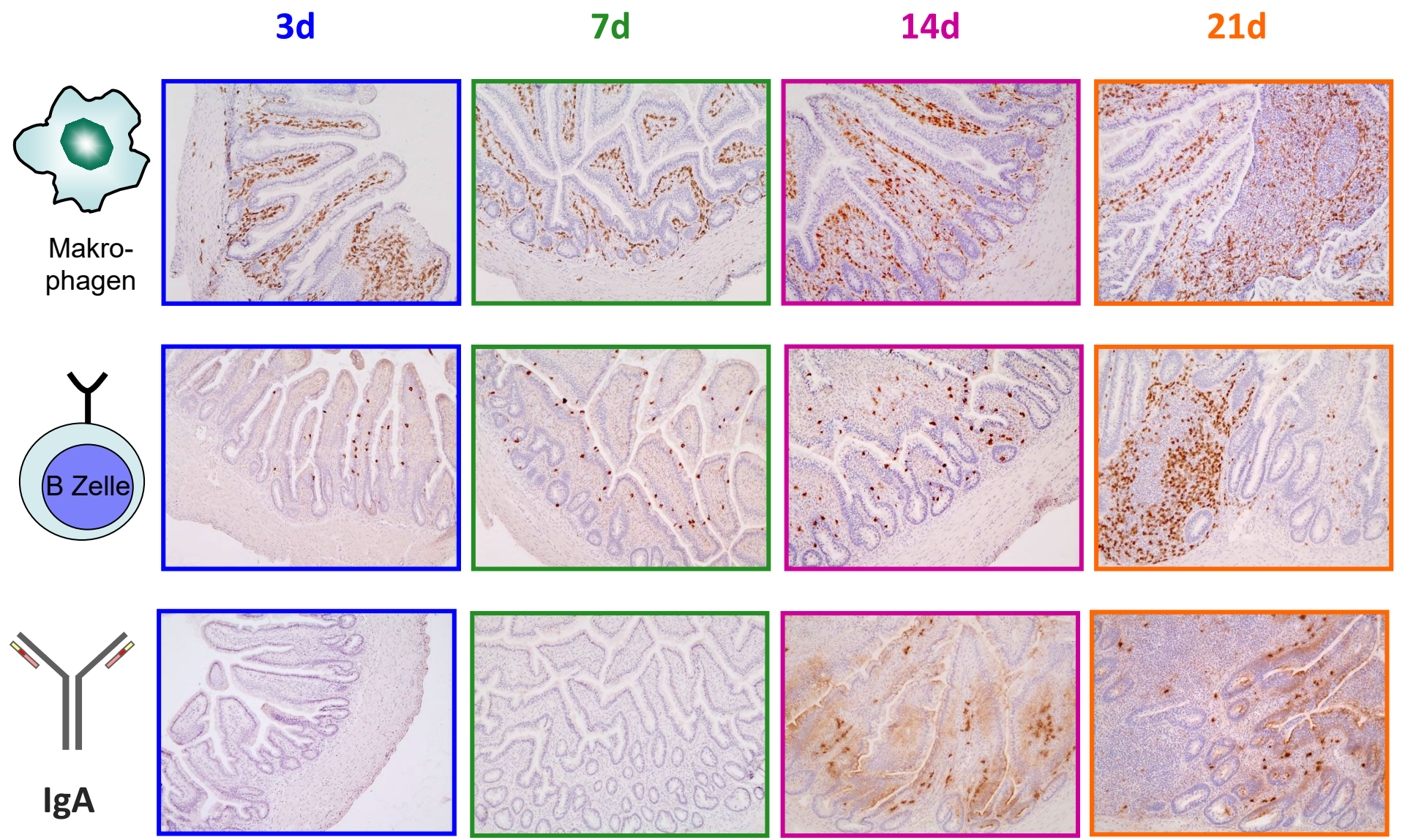


S. enteritidis

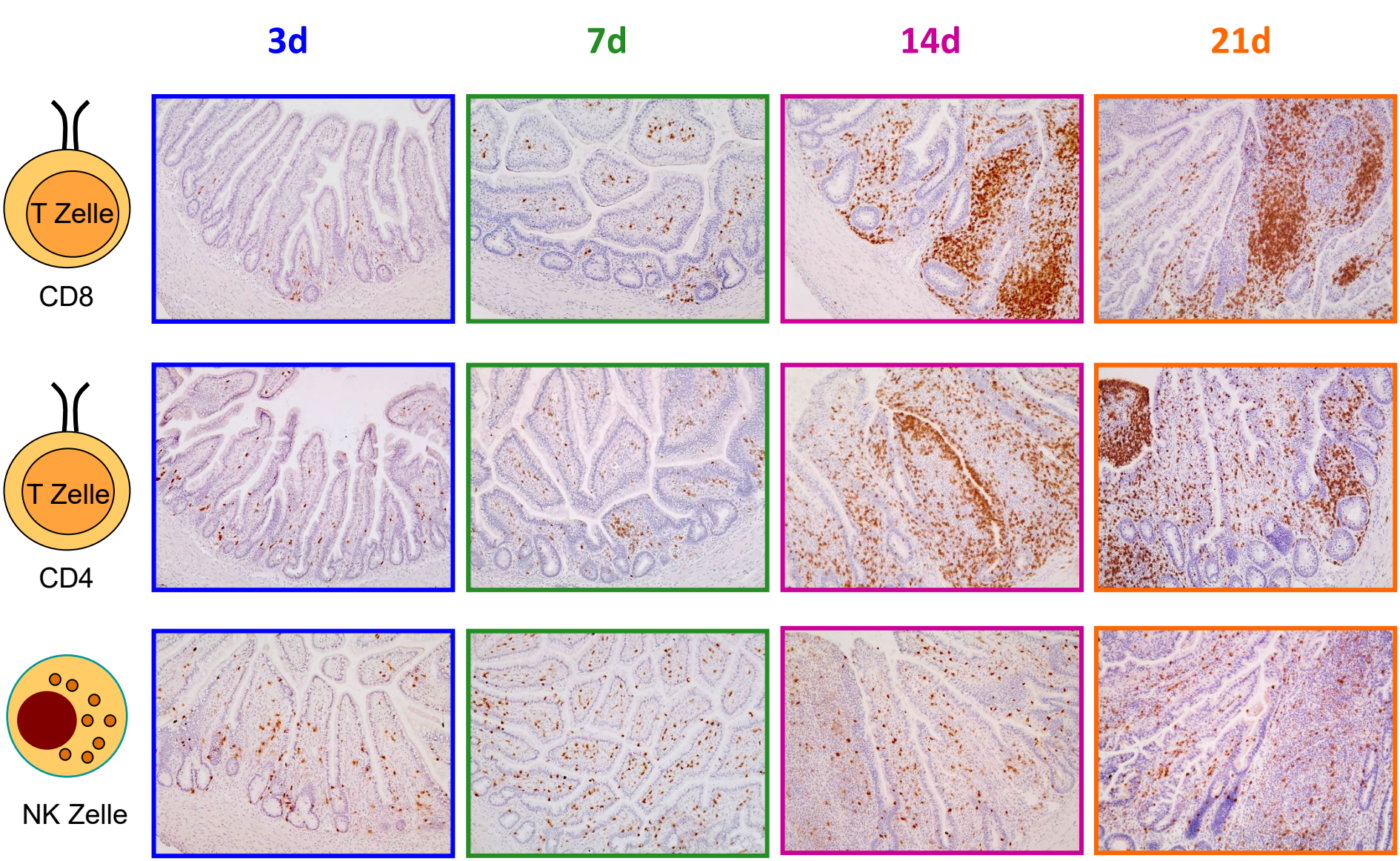




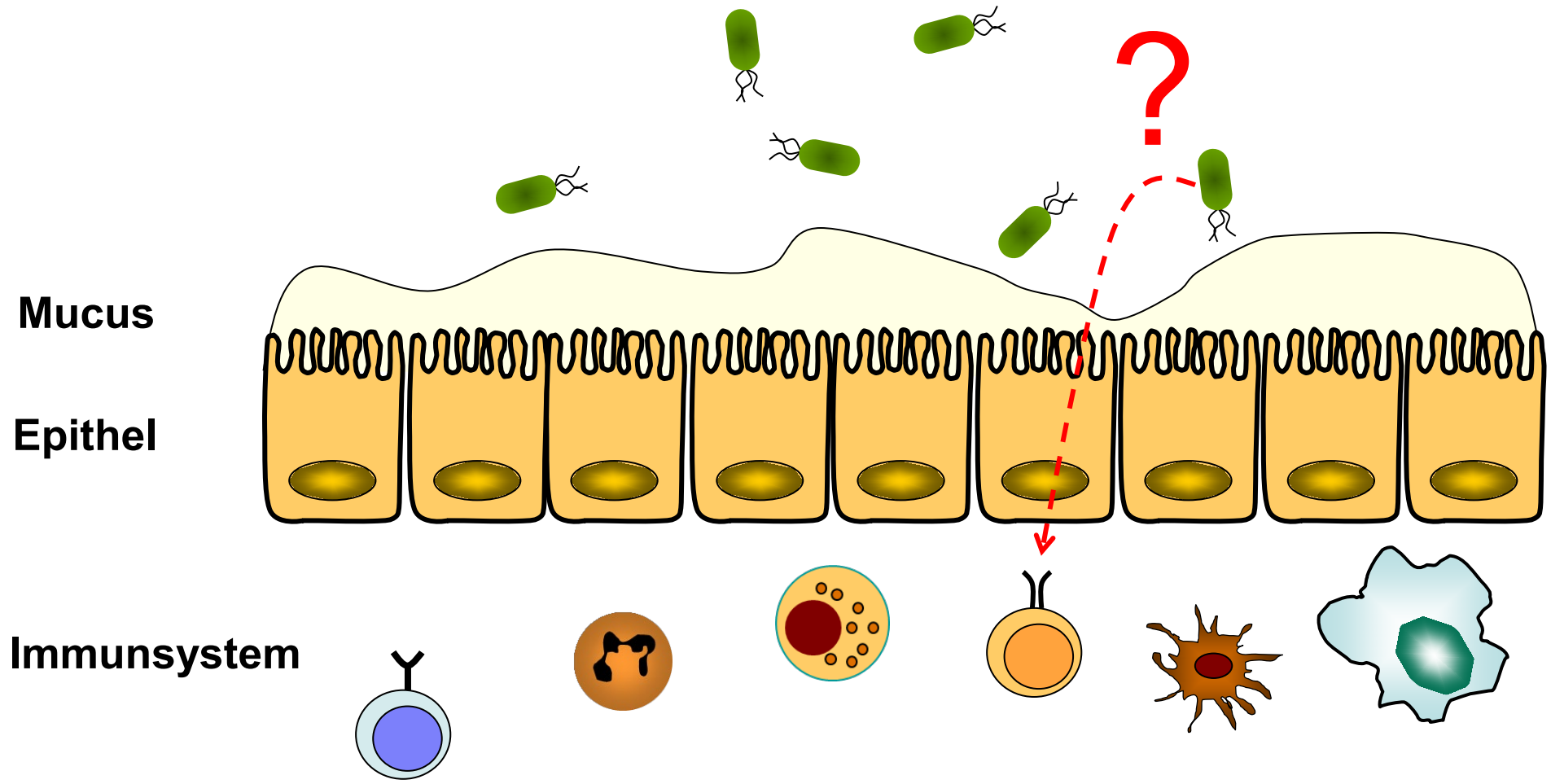
Entwicklung nach dem Schlupf



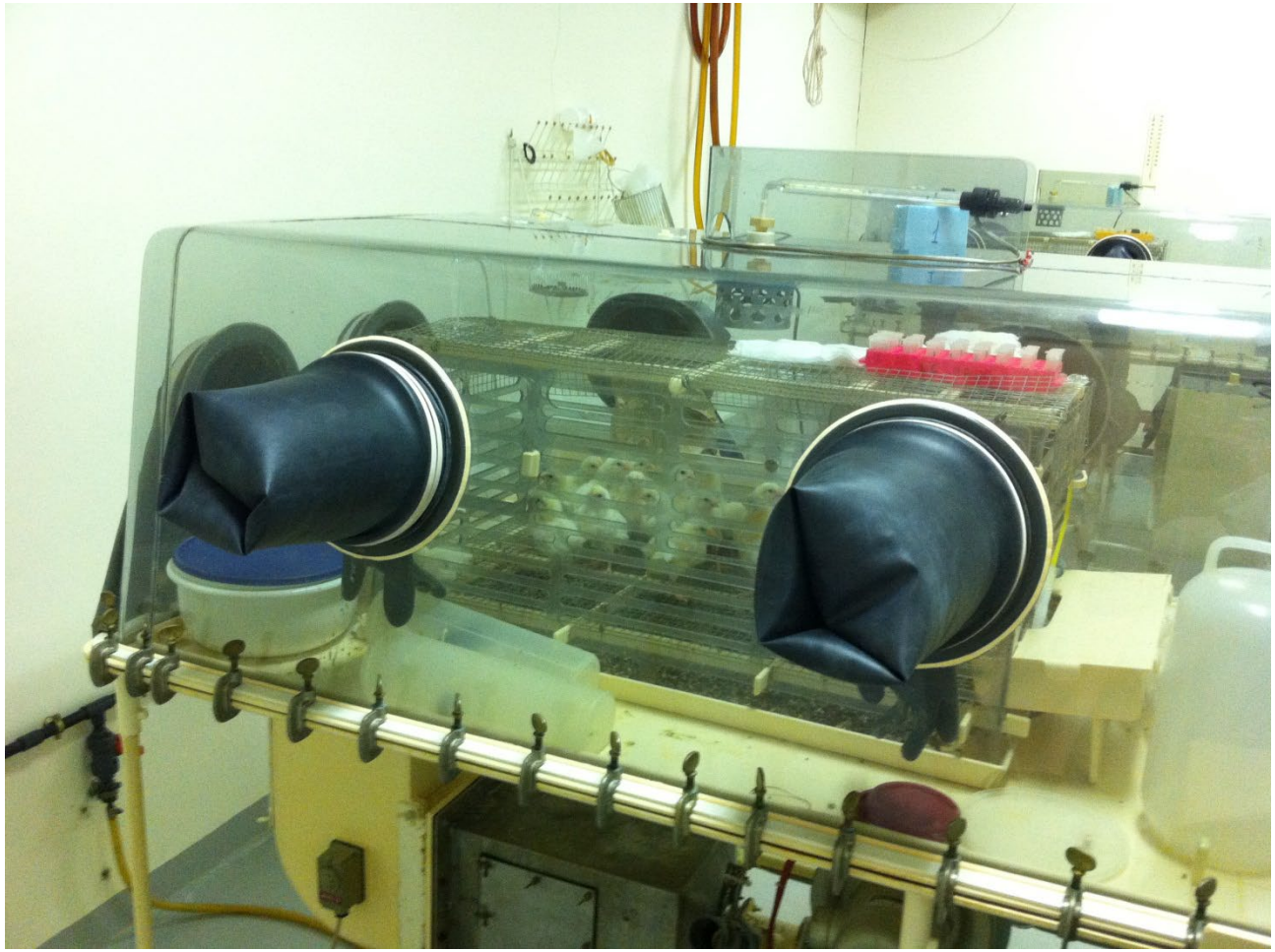
Entwicklung nach dem Schlupf



Beeinflusst die Mikrobiota die Entwicklung?



Keimfrei-Studien



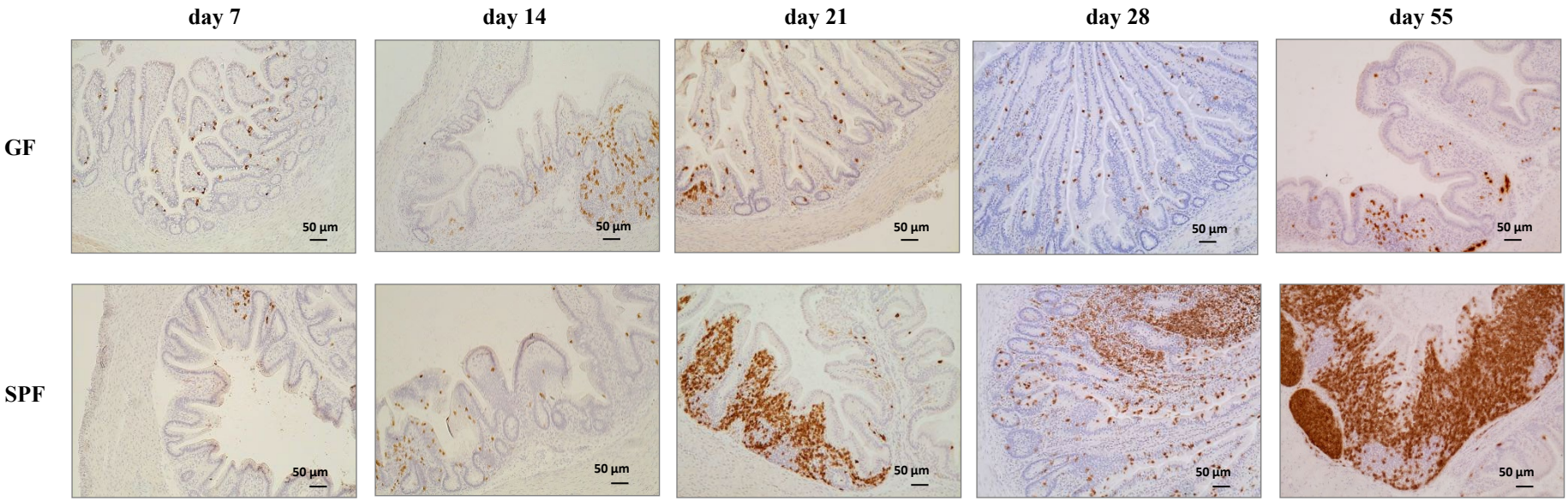
Versuchsaufbau - 1

SPF eggs

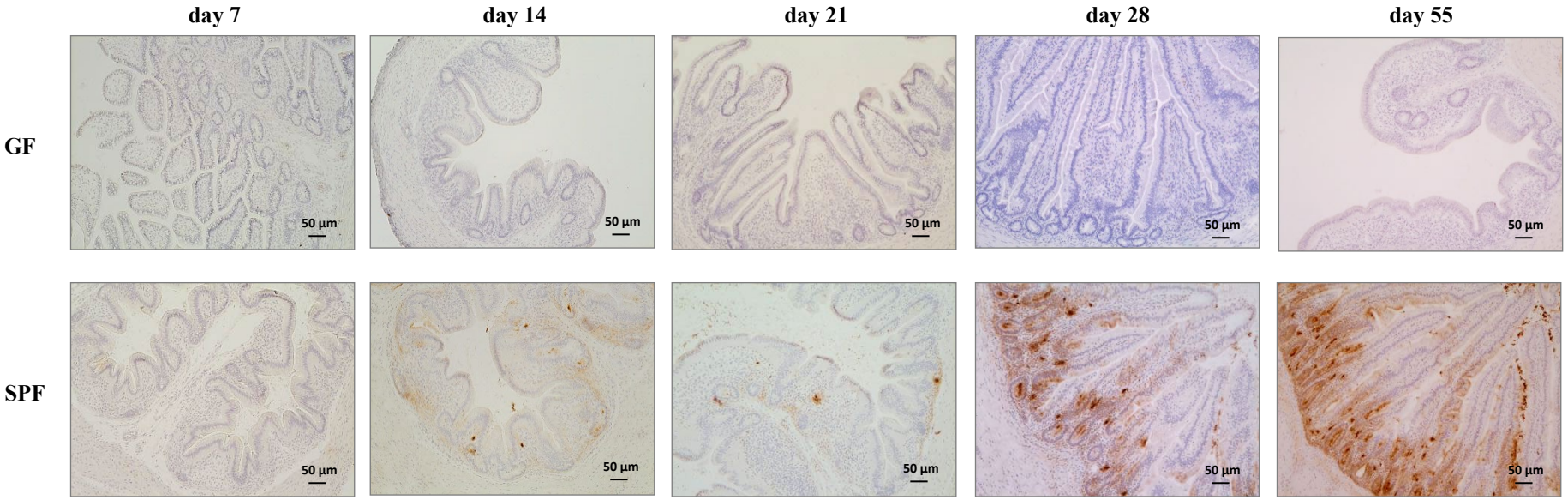
hatched under germ free conditions

sampling at day 14, 28 and 55 post hatch

Entwicklung des B-Zell Systems



Entwicklung des IgA Systems



Versuchsaufbau -2

SPF eggs

hatched under germ free conditions

SPF HOUSING

+ E.coli Nissle, *Enterococcus faecium, Clostridium butyricum, Lactobacillus rhamnosus*

RECONSTITUTED WITH 4 BACTERIA

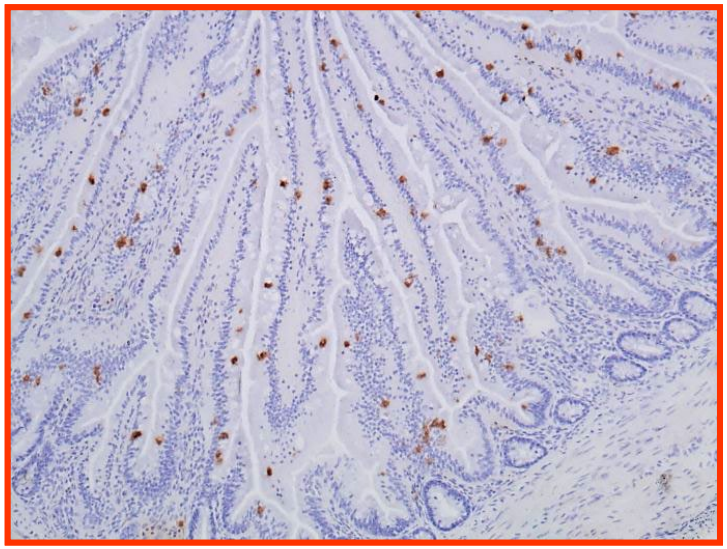
MONO-RECONSTITUTED WITH *E. COLI* NISSLE

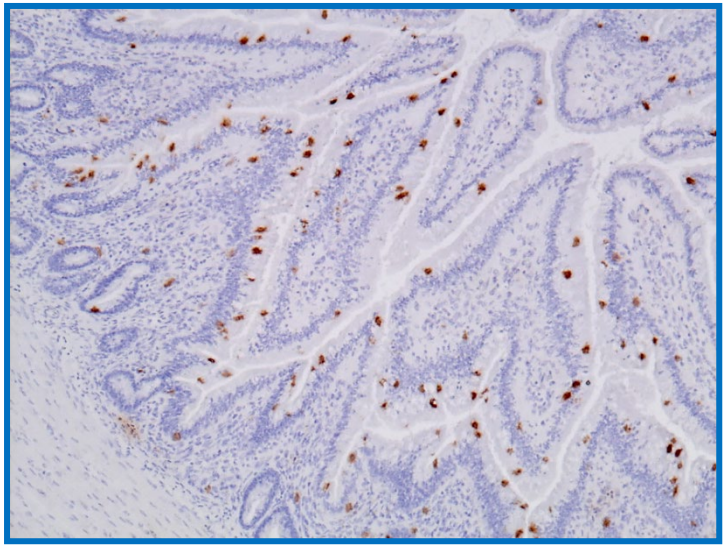
GERM FREE HOUSING

sampling at day 14, 28 and 55 post hatch

B-Zellen an Tag 28

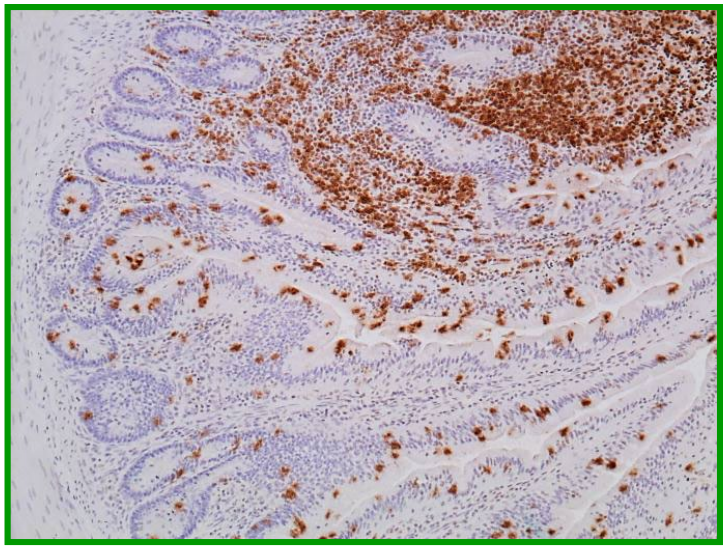
Germ free

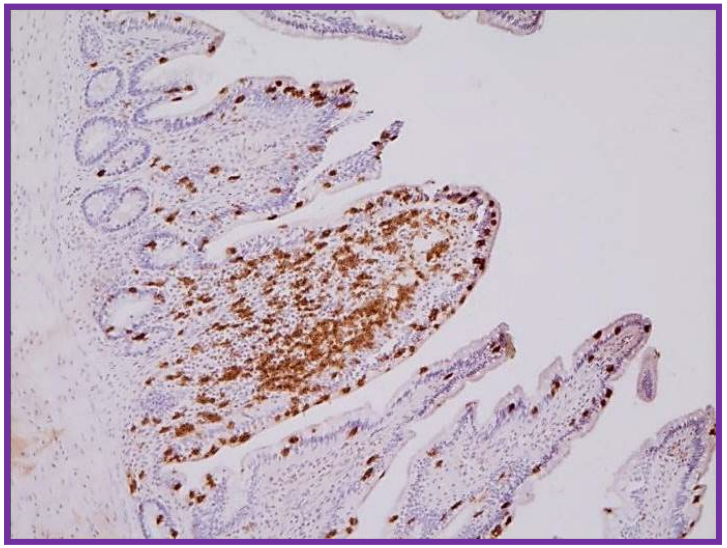




+ E.coli
Nissle

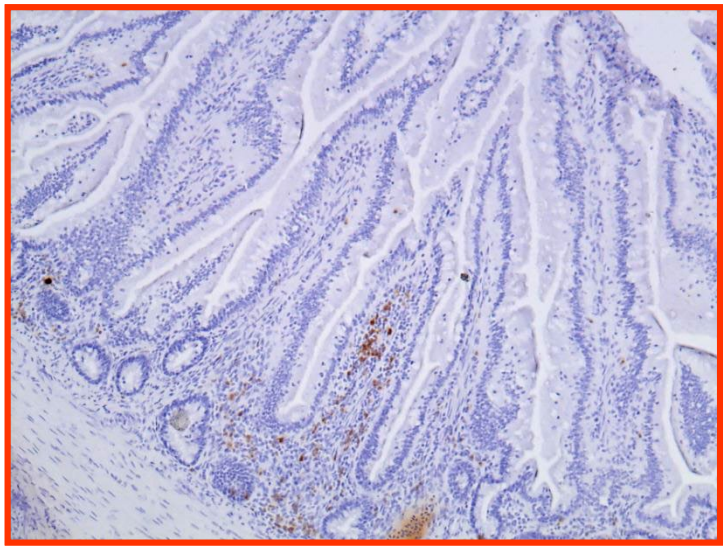
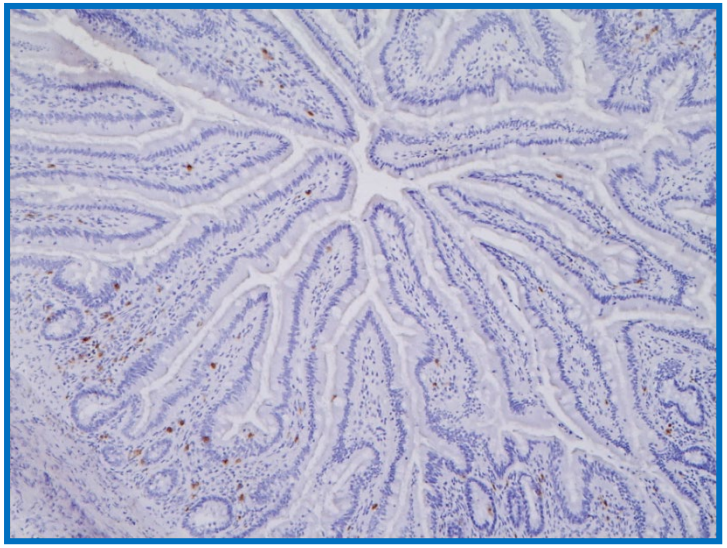
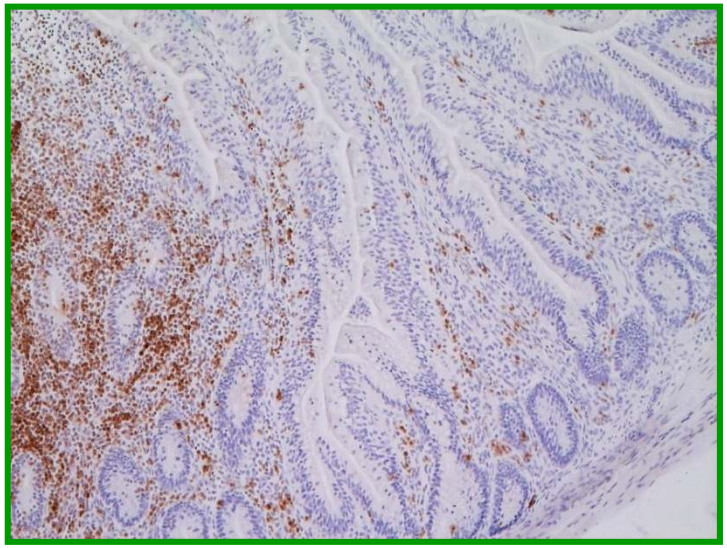
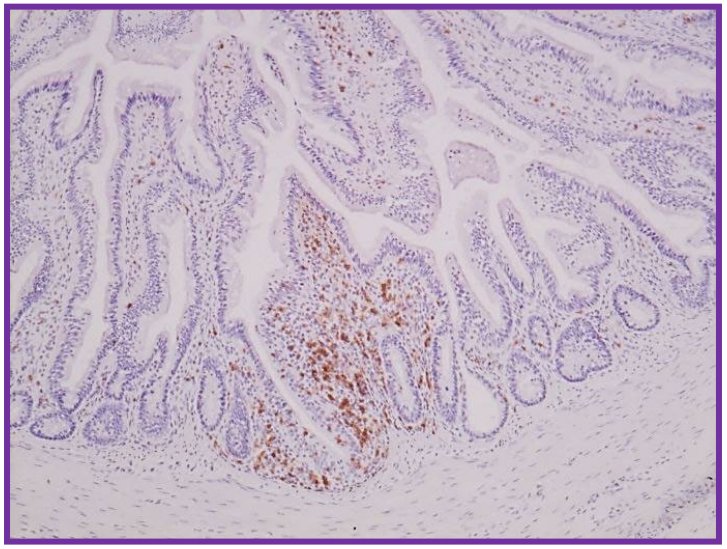
SPF





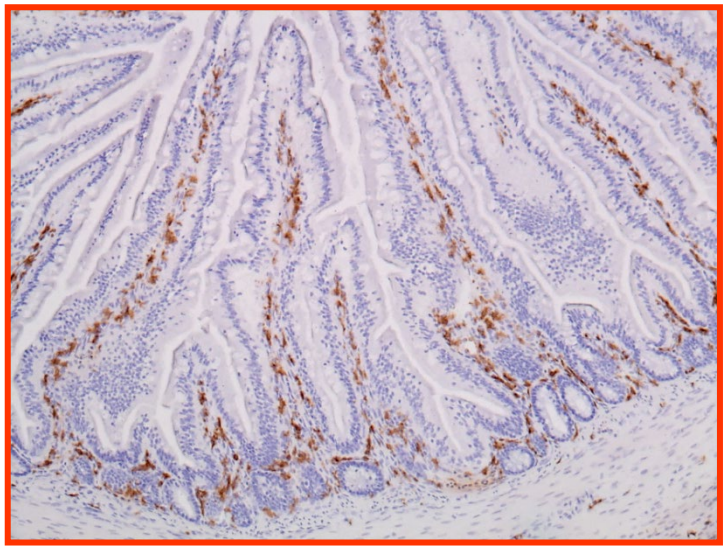
+ E.coli
Nissle,
Enterococcus faecium, Clostridium butyricum, Lactobacillus rhamnosus

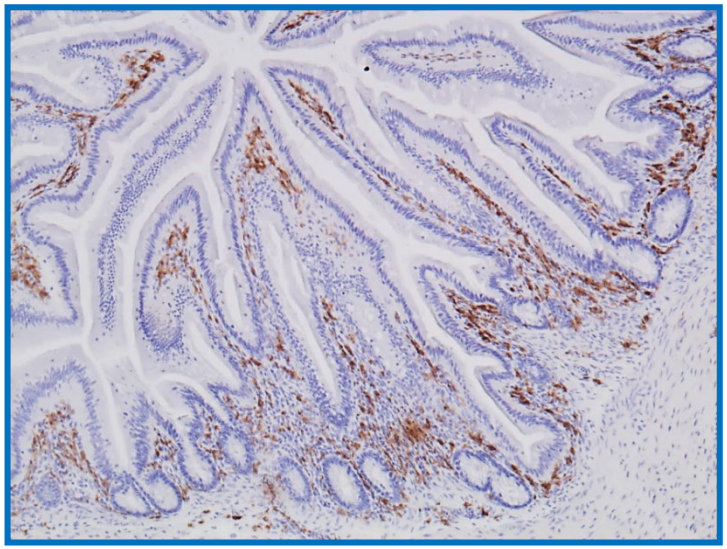
α/β T Zellen an Tag 28

Germ free			*+ E.coli* Nissle
SPF			*+ E.coli* Nissle, *Enterococcus faecium, Clostridium butyricum, Lactobacillus rhamnosus*

Makrophagen an Tag 28

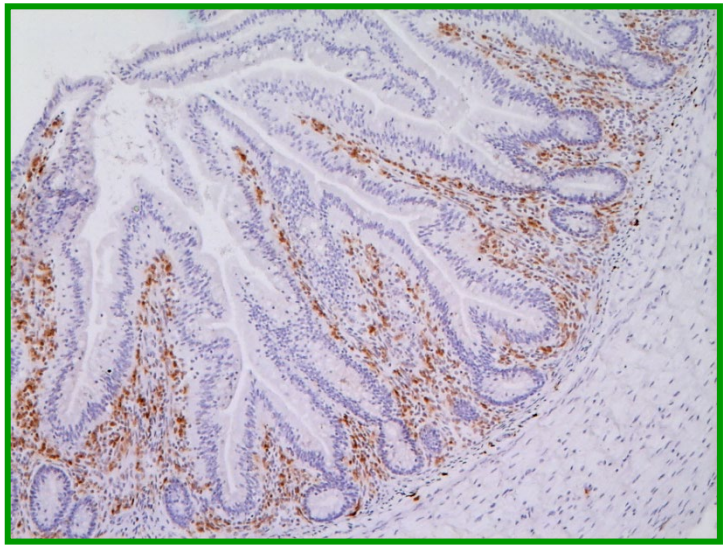
Germ free

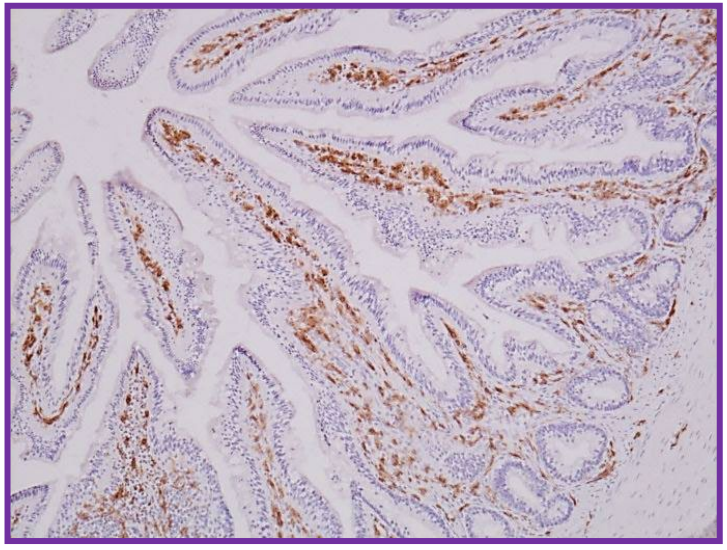




+ E.coli
Nissle

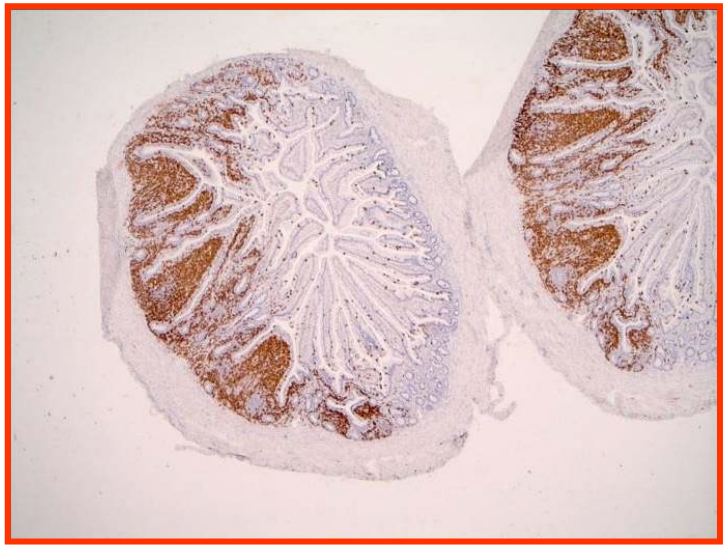
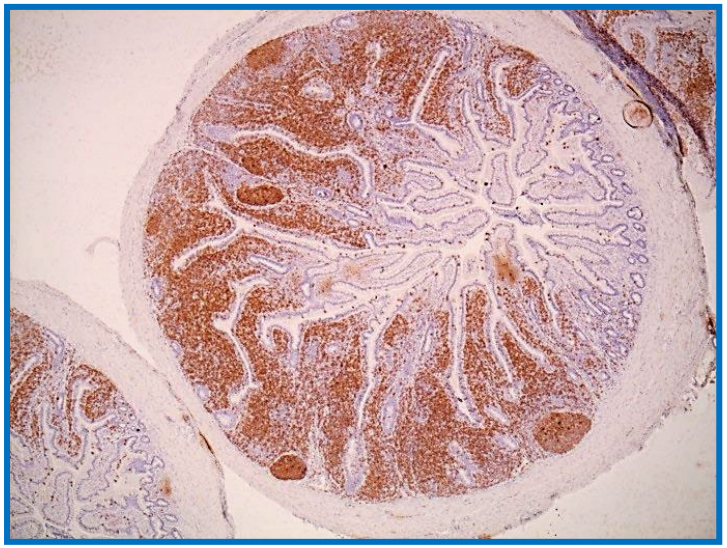
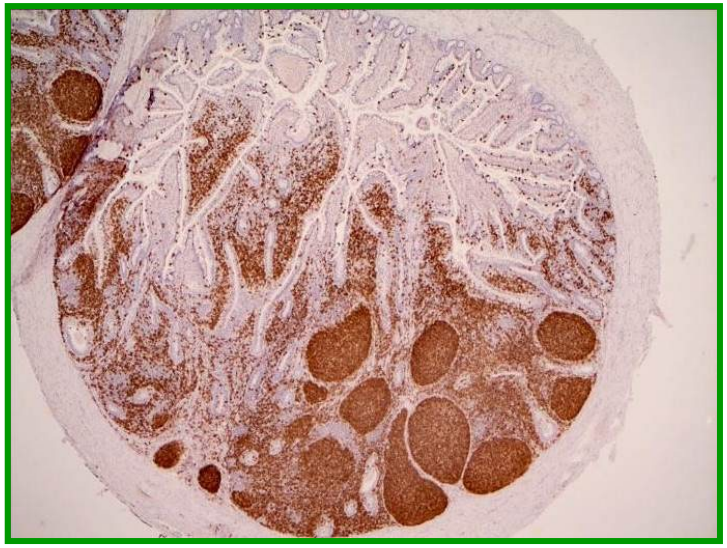
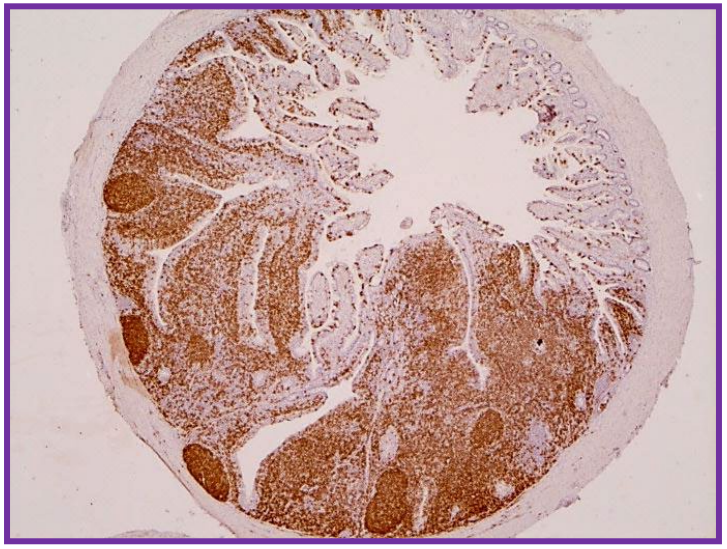
SPF





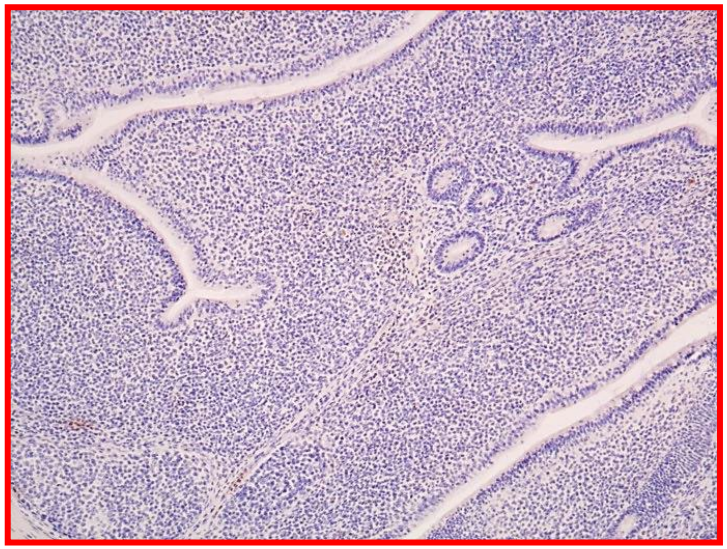
+ E.coli
Nissle,
Enterococcus faecium, Clostridium butyricum, Lactobacillus rhamnosus

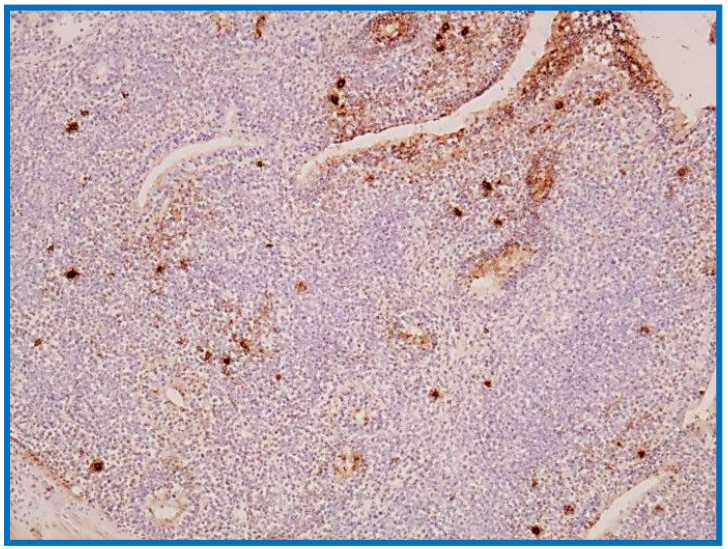
B Zellen in der Zäkaltonsille an Tag 28

Germ free			*+ E.coli* Nissle
SPF			*+ E.coli* Nissle, *Enterococcus faecium, Clostridium butyricum, Lactobacillus rhamnosus*

IgA in der Zäkaltonsille an Tag 28

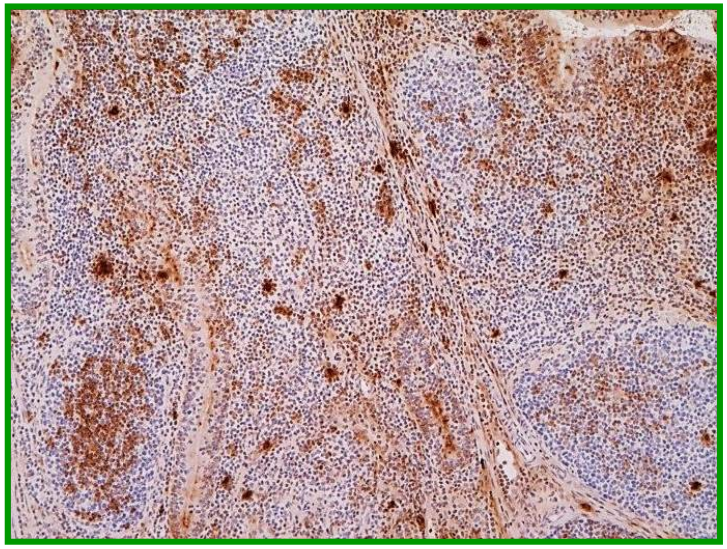
Germ free

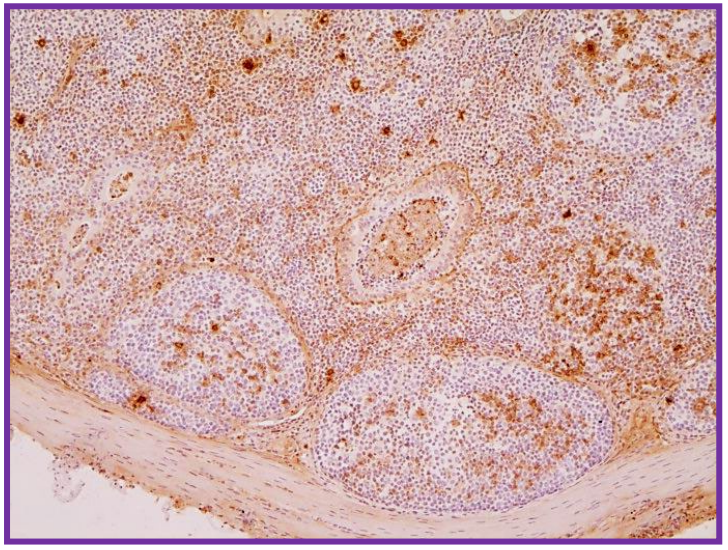




+ E.coli
Nissle

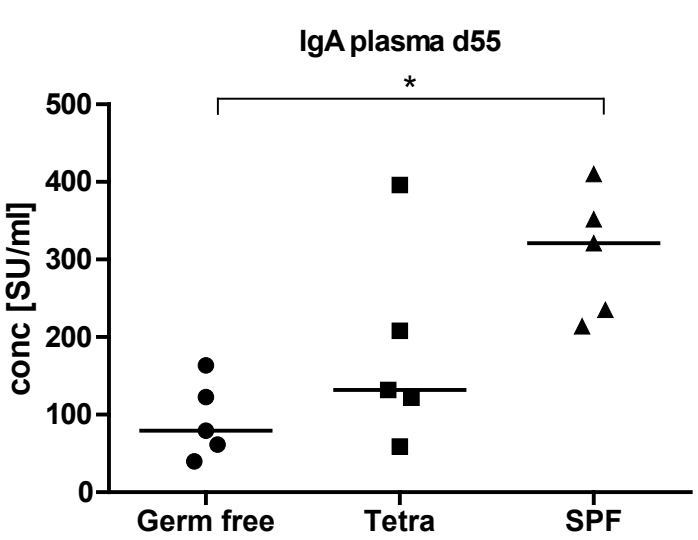
SPF

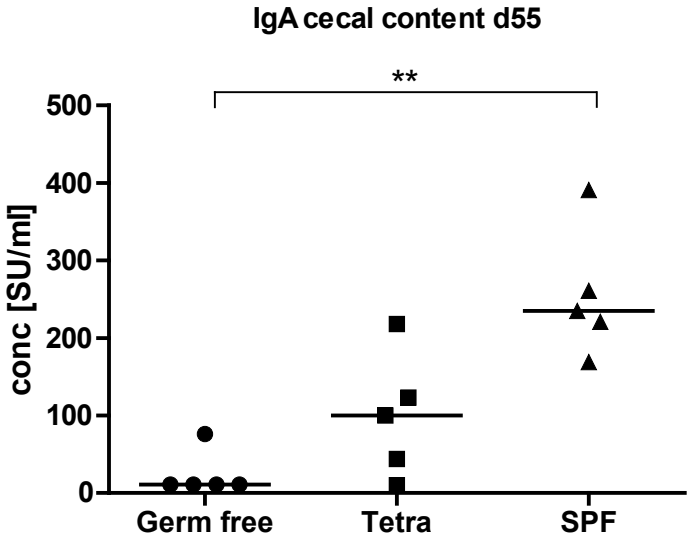




+ E.coli
Nissle,
Enterococcus faecium, Clostridium butyricum, Lactobacillus rhamnosus

IgA Konzentration





Übertragung einer maternalen Mikrobiota

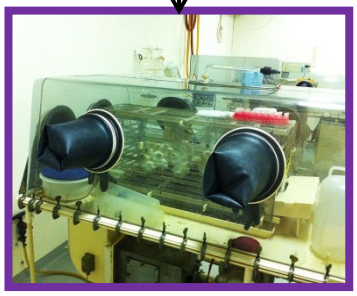
Versuchsaufbau - 3

Line PA-12 eggs

↓

Hatched under germ free conditions

GERM FREE

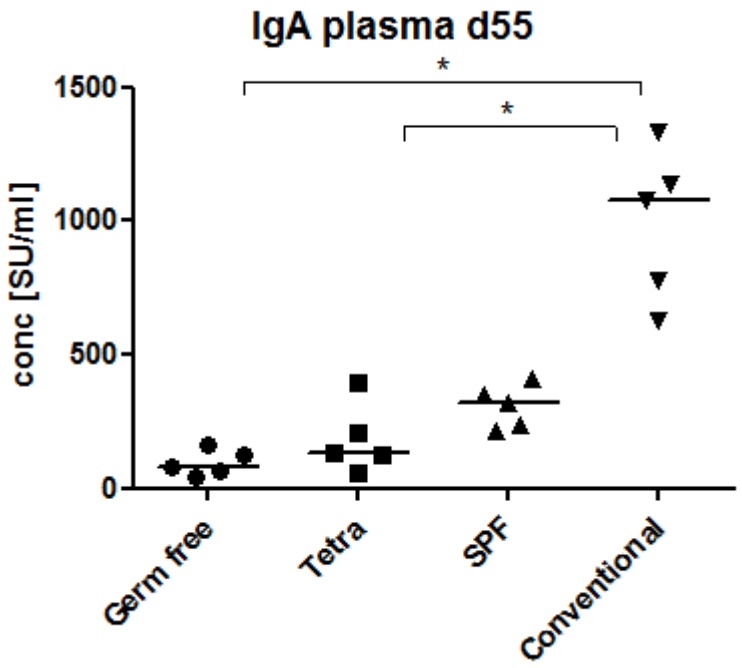


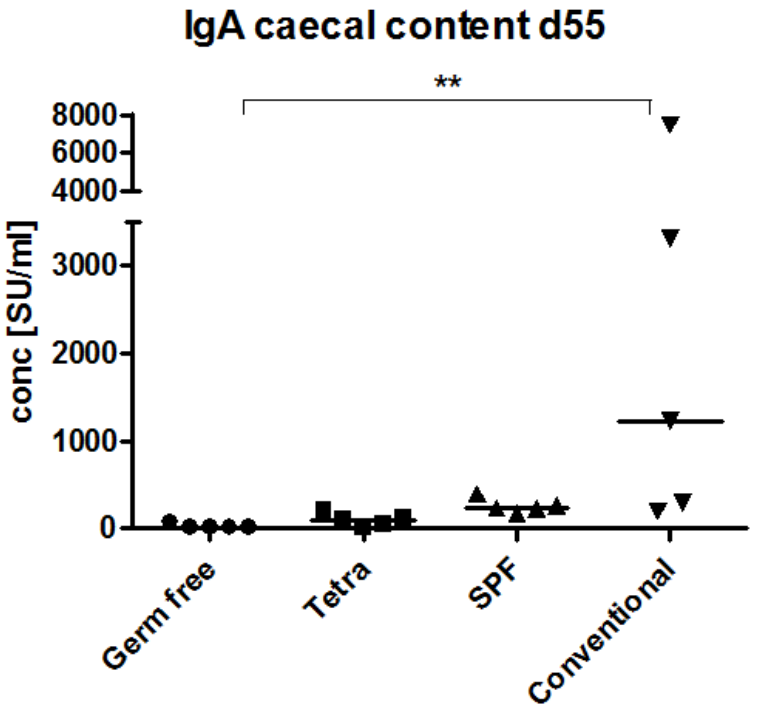
RECONSTITUTED WITH 4 BACTERIA

SPF CONDITIONS

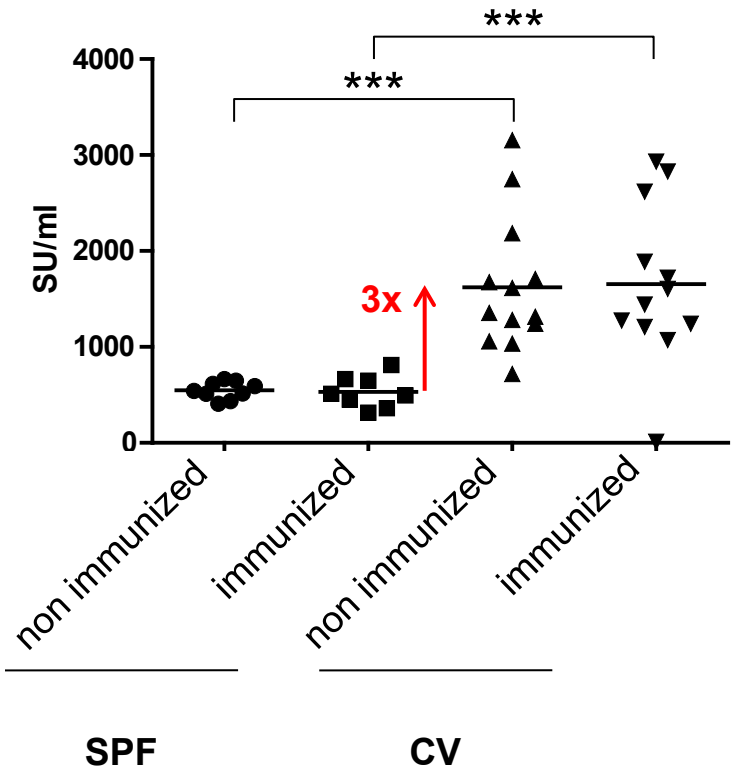
CONVENTIONAL

IgA Konzentration im Plasma

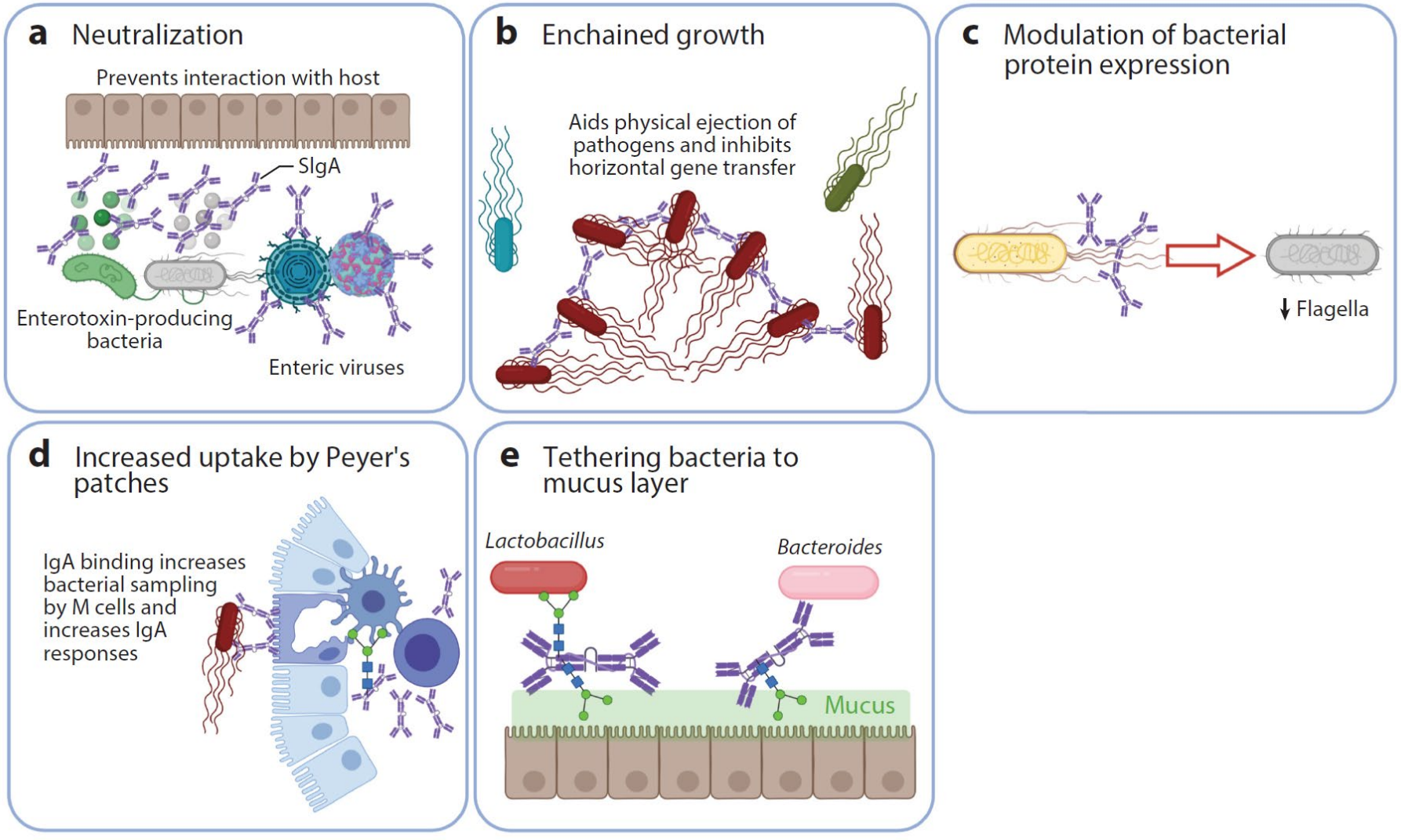




IgA Konzentration im Plasma

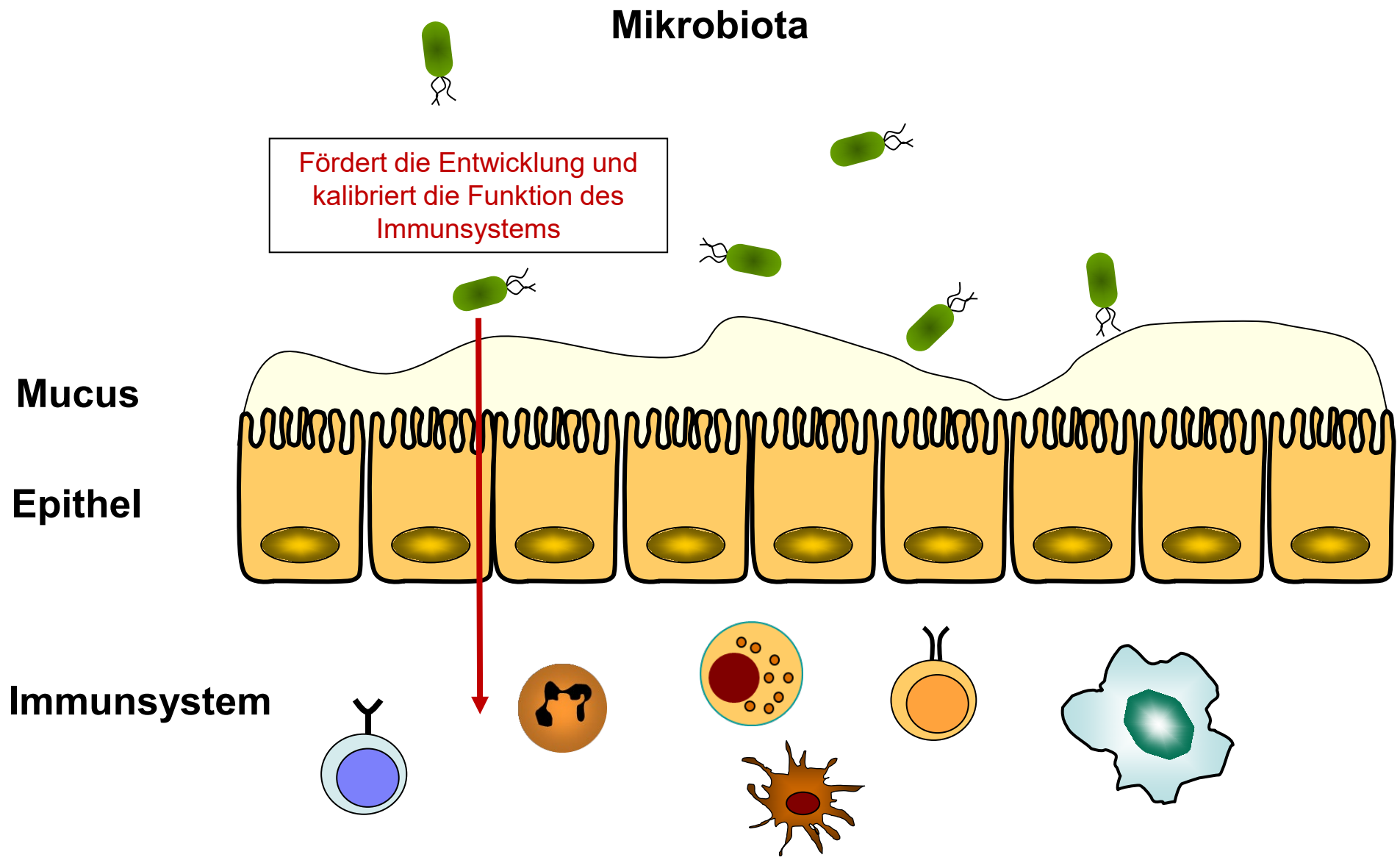


Die Funktion von IgA im Darm

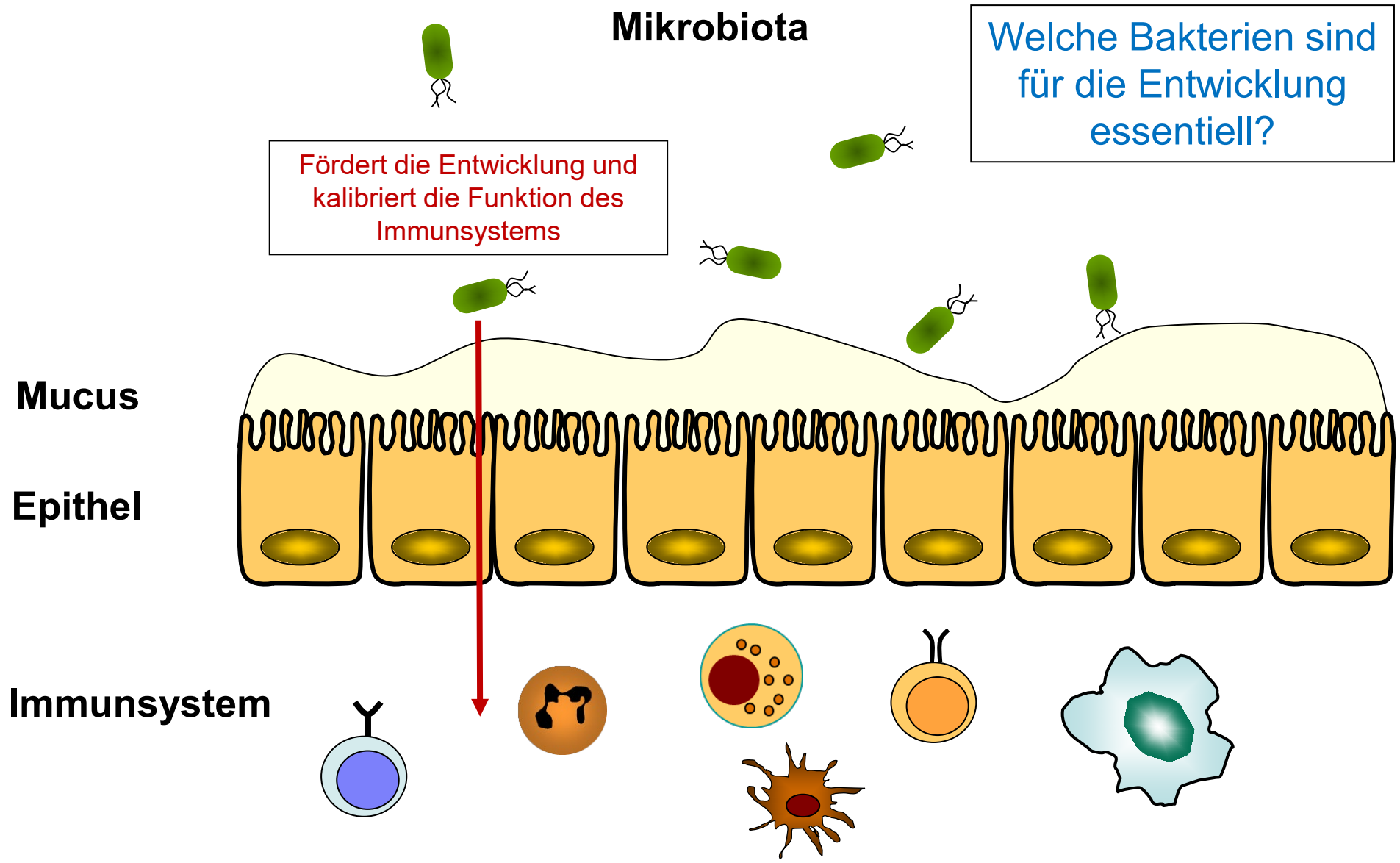


Annu. Rev. Immunol. 2021. 39:695–718

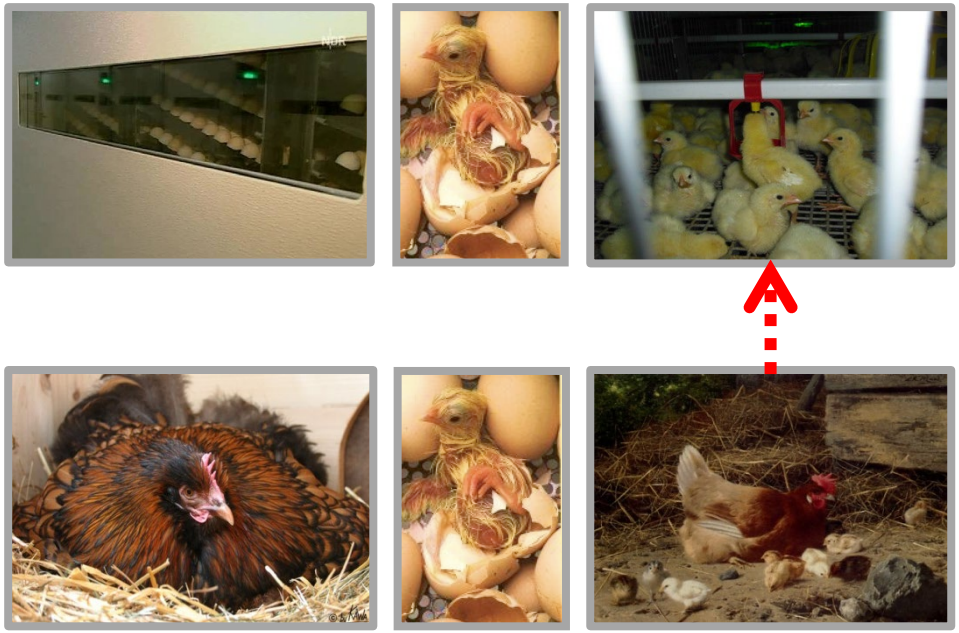
Mikrobiota-Wirt Interaktion



Mikrobiota-Wirt Interaktion



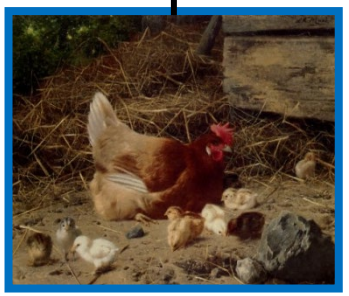
Übertragung einer maternalen Flora



GERM FREE

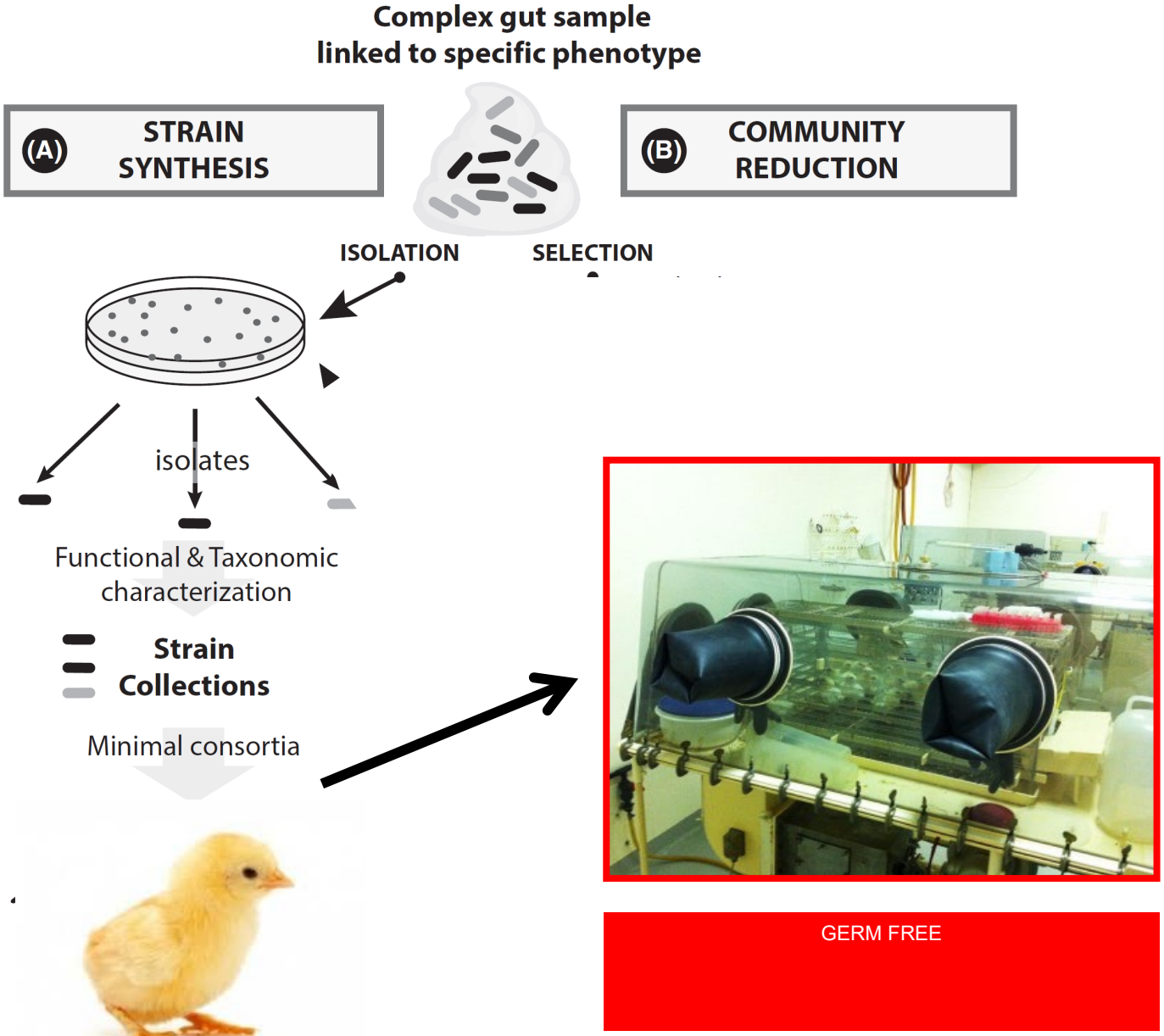
RECONSTITUTED WITH 4 BACTERIA

IDENTIFY THE OPTIMAL FLORA



CONVENTIONAL

Wie können wir das machen?



Clavel et al, Immunological Reviews 2017, 279: 8-22

Minimales Konsortium

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RESEARCH ARTICLE

Early-Life Immune System Maturation in Chickens Using a Synthetic Community of Cultured Gut Bacteria

Christian Zenner,[a,b] Thomas C. A. Hitch,[b] Thomas Riedel,[c,d] Esther Wortmann,[b] Stefan Tiede,[c,d] Eva M. Buhl,[e] Birte Abt,[c,d] Klaus Neuhaus,[f] Philippe Velge,[g] Jörg Overmann,[c,d,h] Bernd Kaspers,[a] Thomas Clavel[b]

[a]Department for Veterinary Sciences, Veterinary Immunology Study Group, Ludwig-Maximilians-University Munich, Munich, Germany
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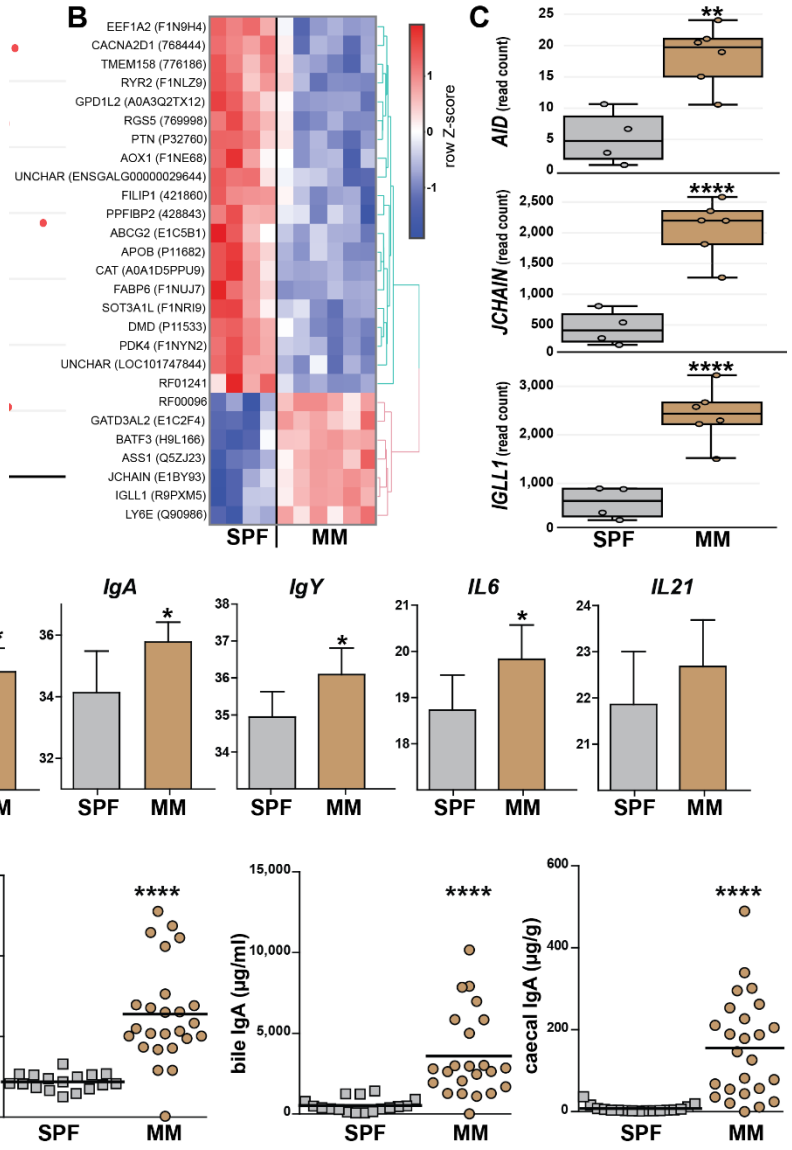
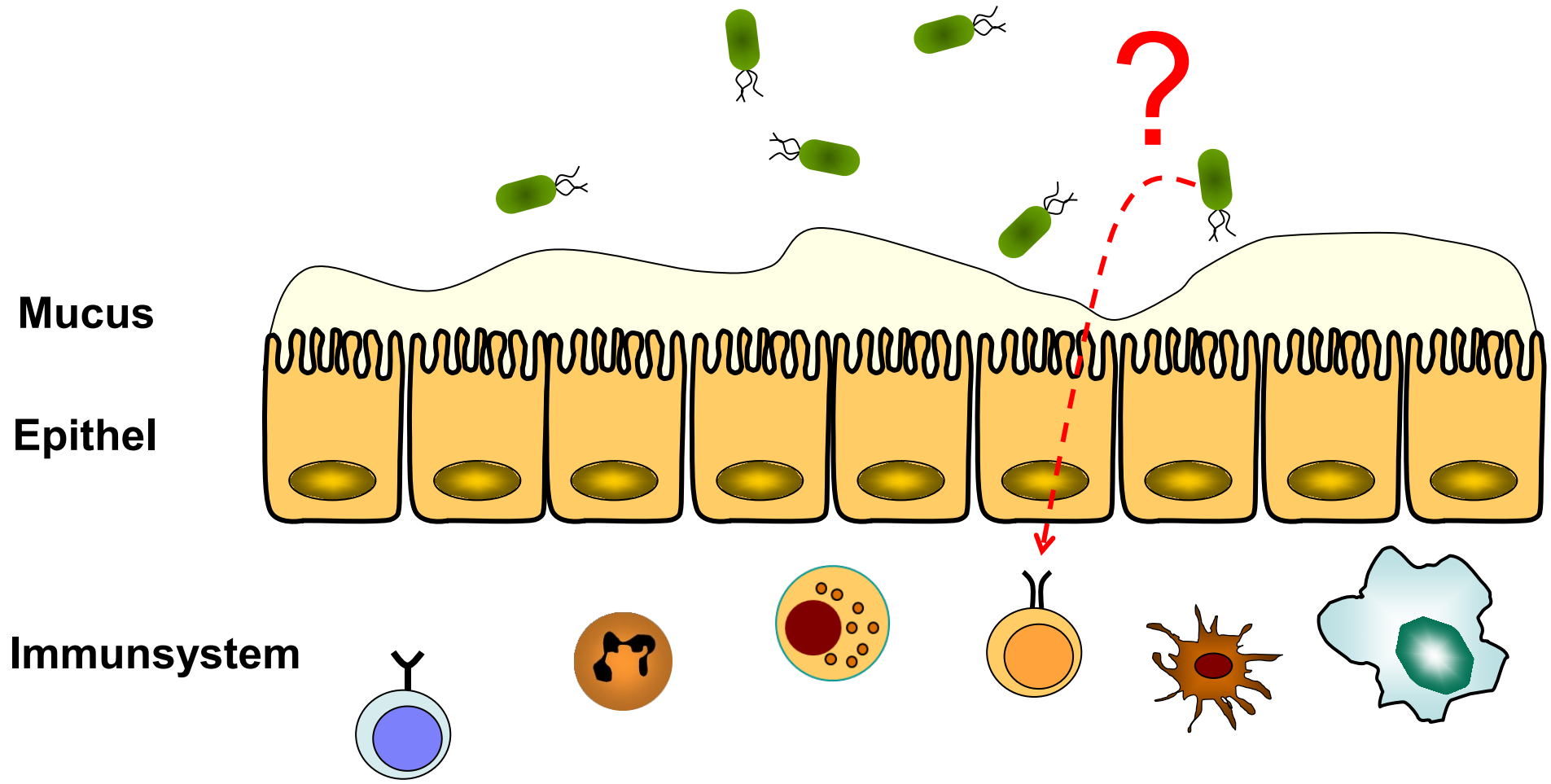
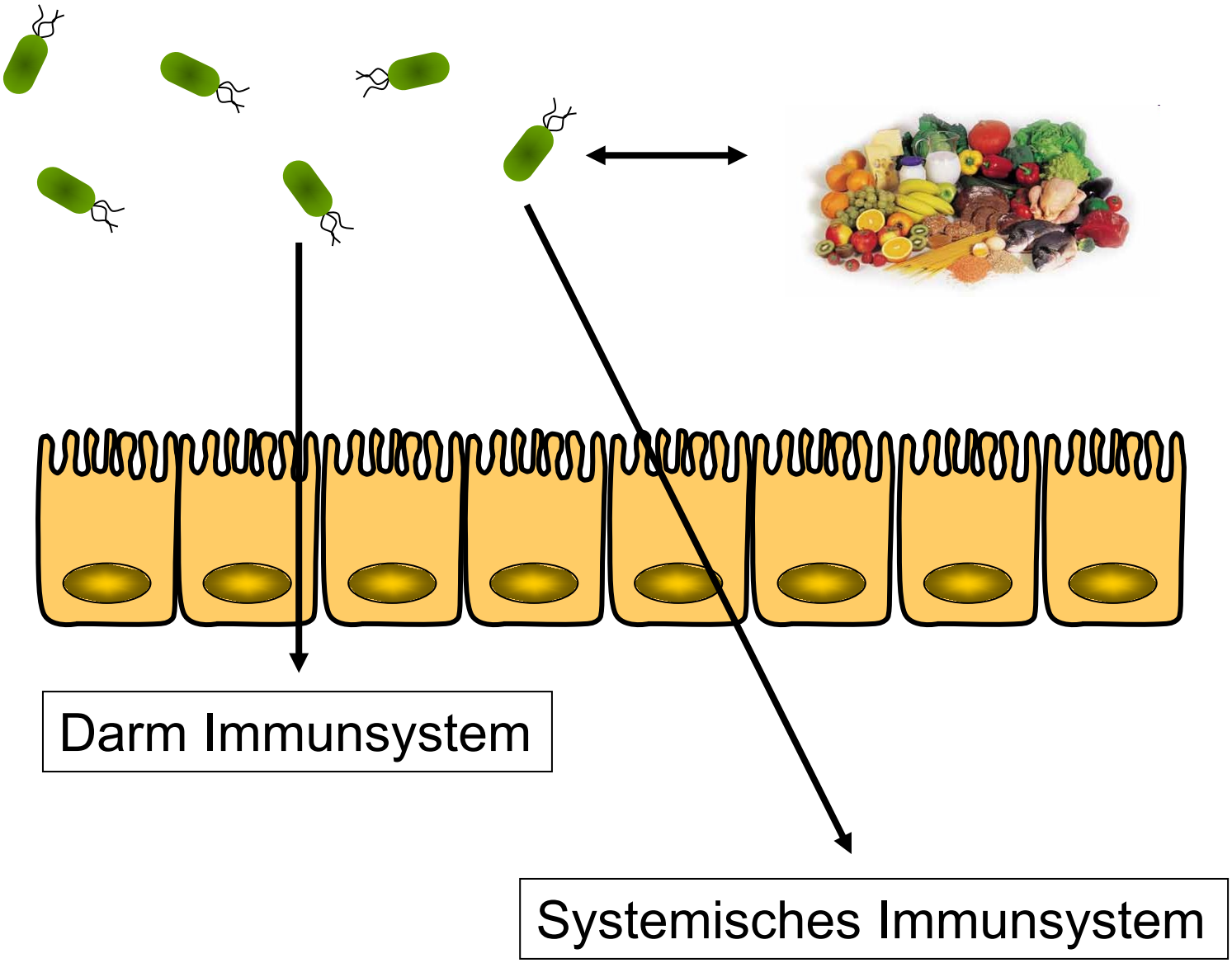
[c]Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany
[d]German Center for Infection Research (DZIF), Partner site Hannover-Braunschweig, Braunschweig, Germany
[e]Electron Microscopy Facility, Institute of Pathology, RWTH University Hospital Aachen, Aachen, Germany
[f]Core Facility Microbiome, ZIEL Institute for Food & Health, Technical University of Munich, Freising, Germany
[g]ISP, INRAE, Université François Rabelais de Tours, UMR 1282, Nouzilly, France
[h]Faculty of Life Sciences, Braunschweig University of Technology, Braunschweig, Germany



Wie beeinflusst die Mikrobiota die Entwicklung

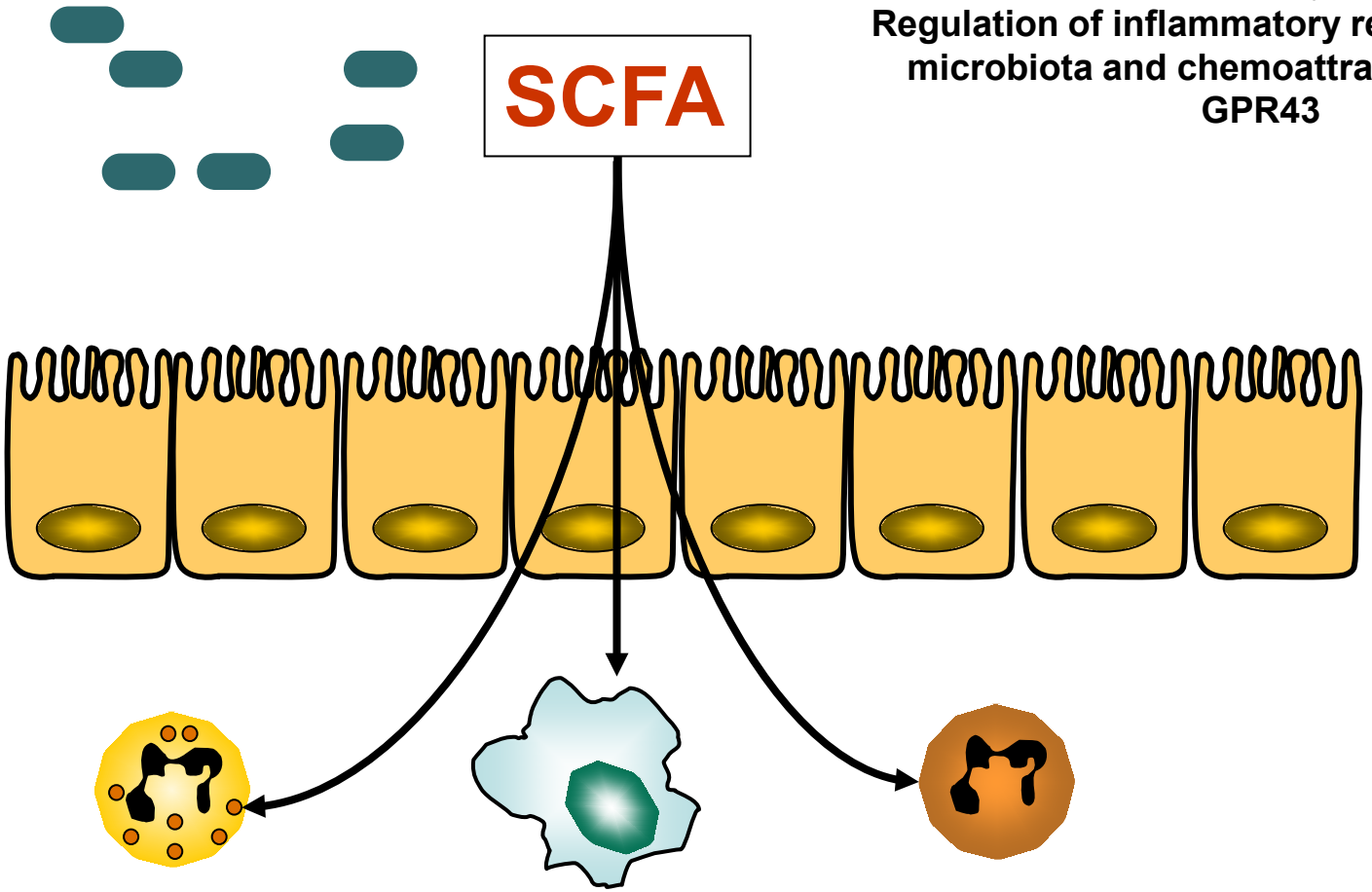


Mikrobielle Metaboliten



SCFA

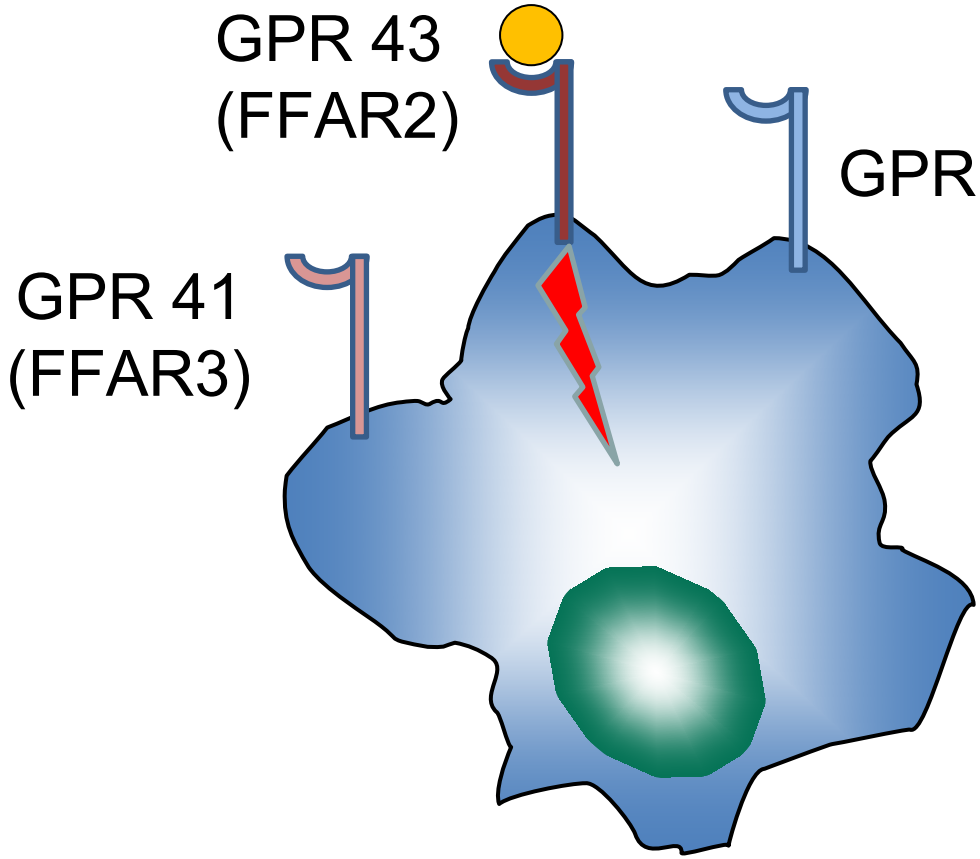
Nature **461**, 1282-1286 (29 October 2009)
Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43



SCFA bind to GPR43 → anti-inflammatory response

GPR $^{-/-}$ mice show increased inflammation
They are unabale to control induced athritis and lung inflammation

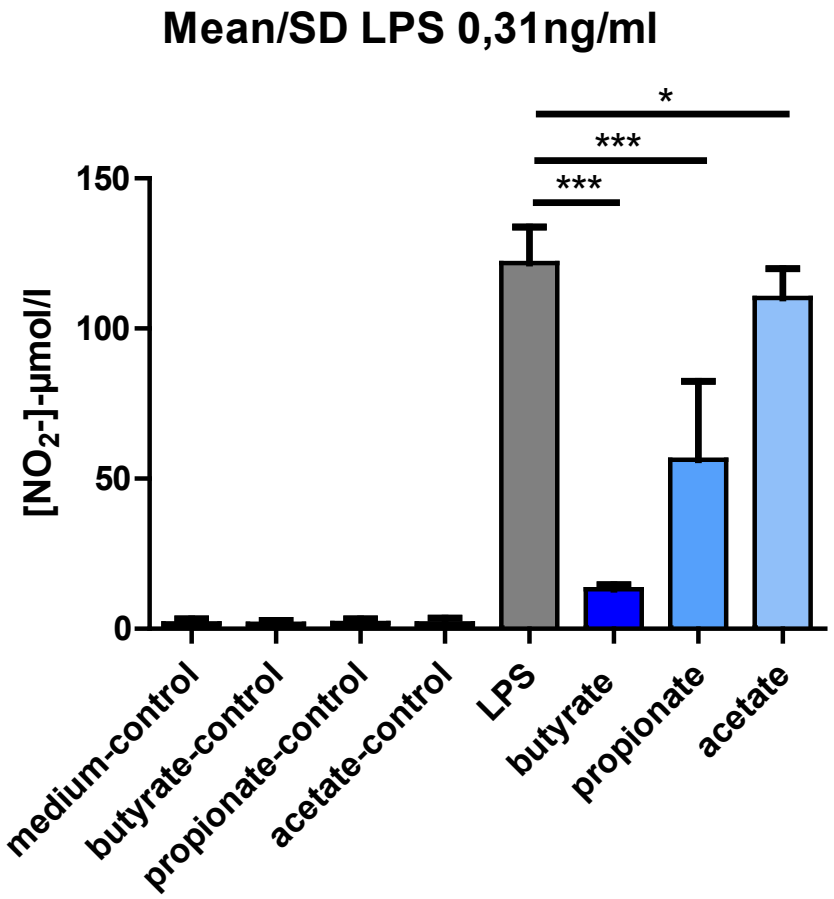
SCFA

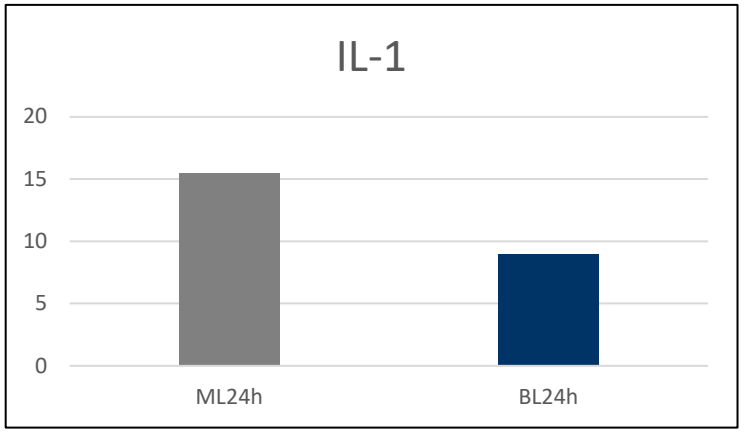


Anti-Entzündlich

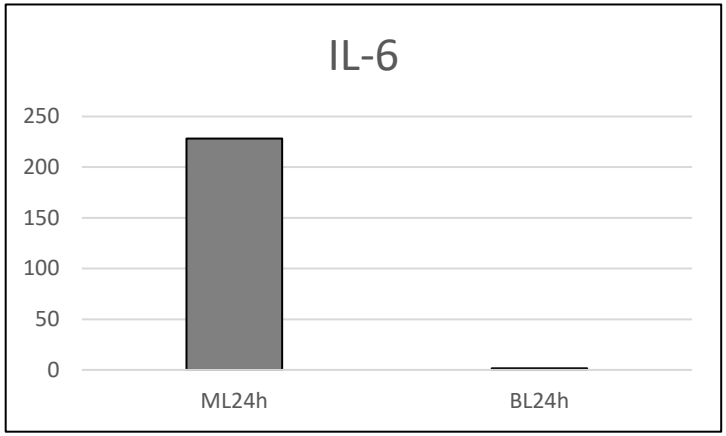
Anti-mikrobiell
(anti-microbial peptides)

SCFA – anti-entzündliche Wirkung

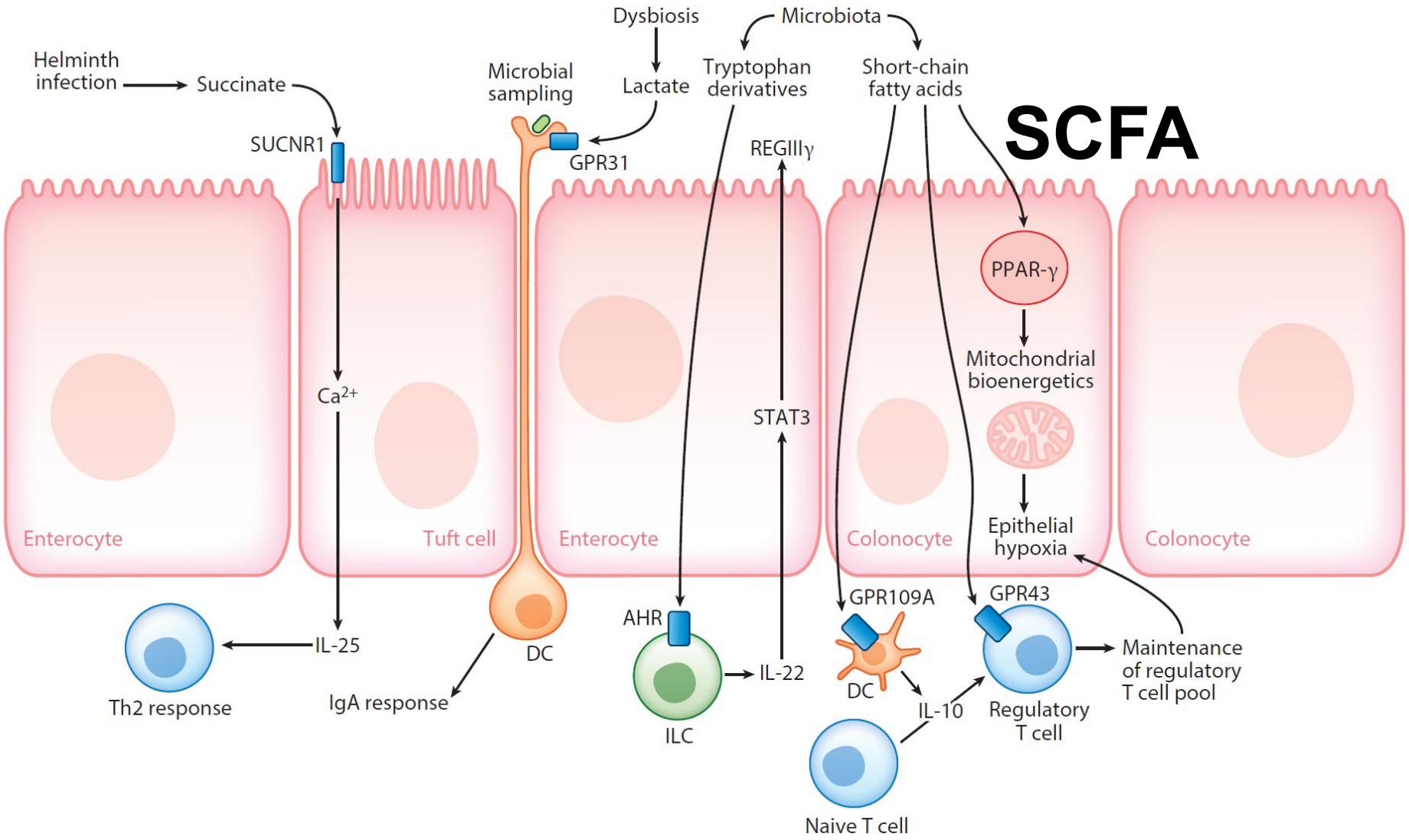




Fold changes



Mikrobielle Metaboliten



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Thanks to

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Sonja Härtle

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Philippe Velge

UNIKLINIK RWTH AACHEN

Thomas Clavel
Christian Zenner