INSTITUT PASTEUR

Quand les microbes dialoguent avec le système immunitaire

Gérard EBERL

Unité du Développement des Tissus Lymphoïdes
Departement d'Immunologie

1. **Où sont les microbes?**

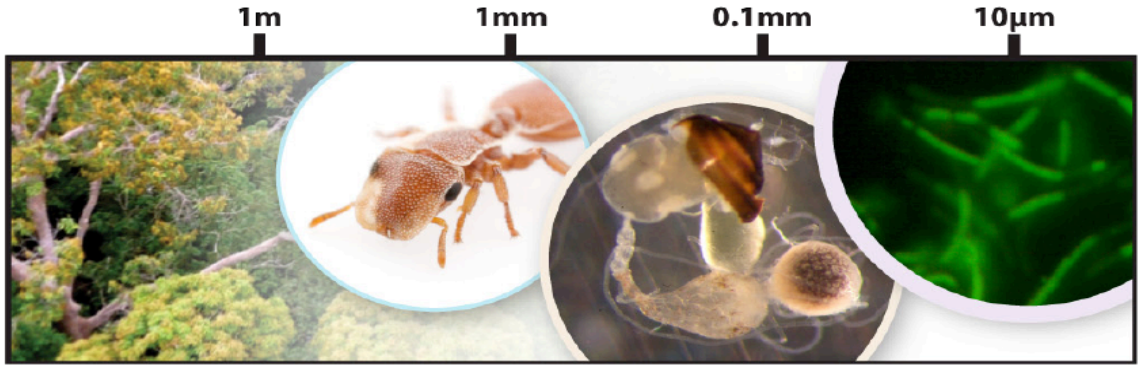
2. **Que fait le système immunitaire?**

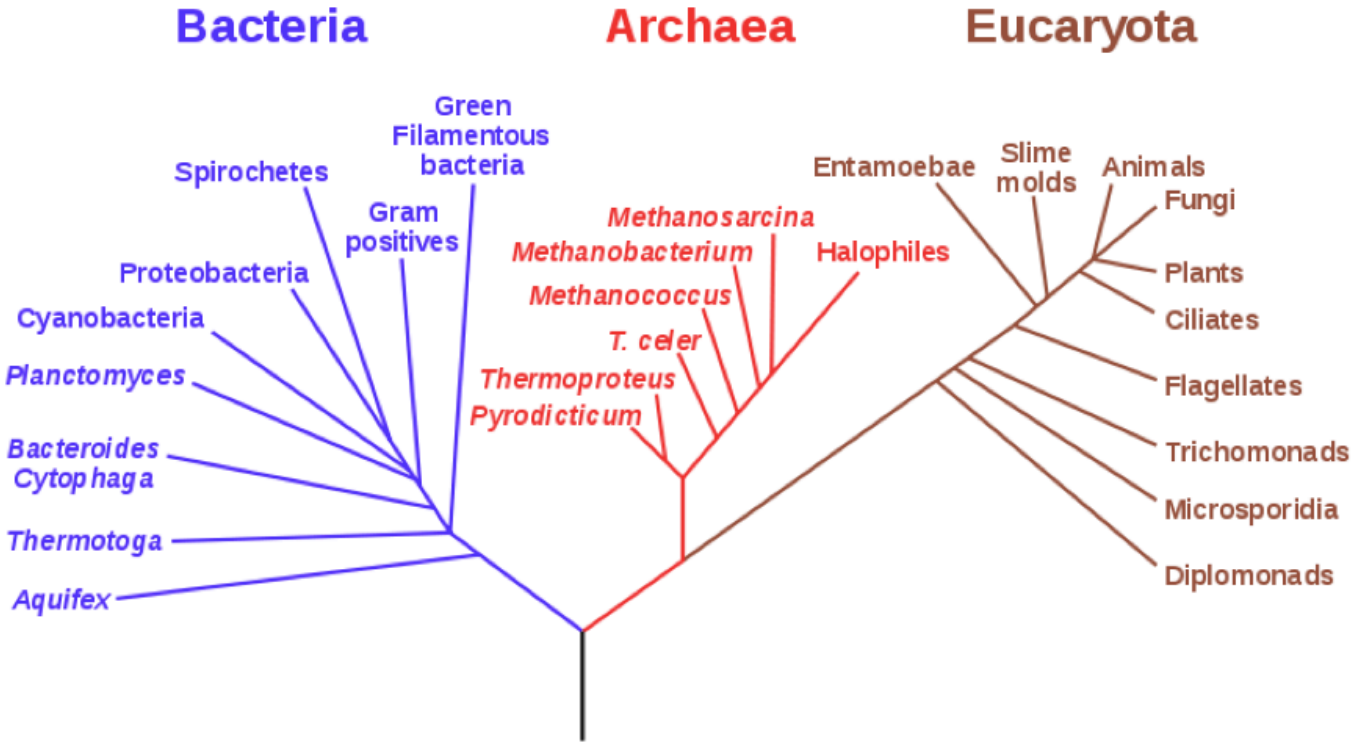
3. **Les microbes et le développement du système immunitaire**

– 1 –

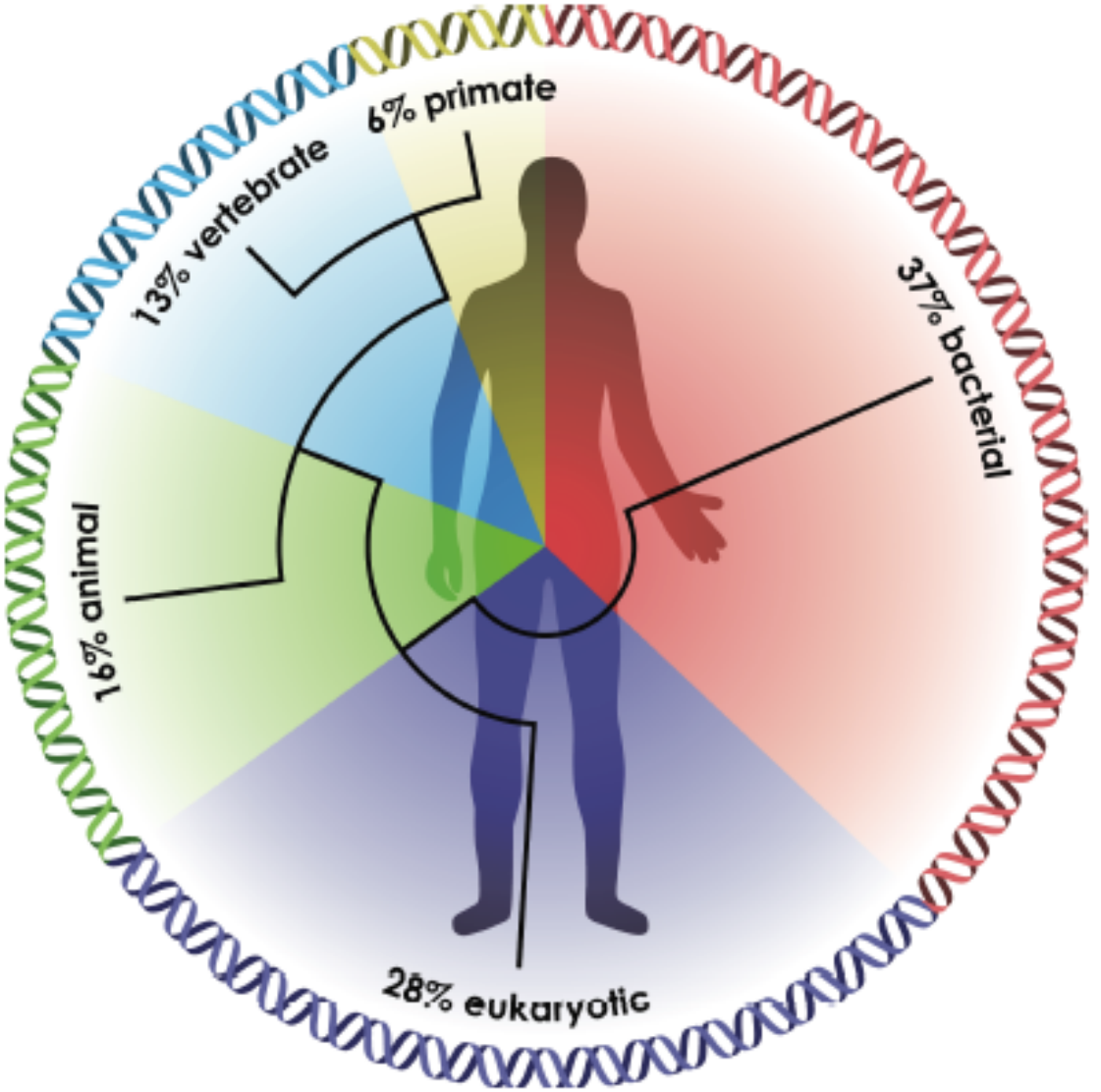
Où sont les microbes?

Notre environnement est essentiellement microbien

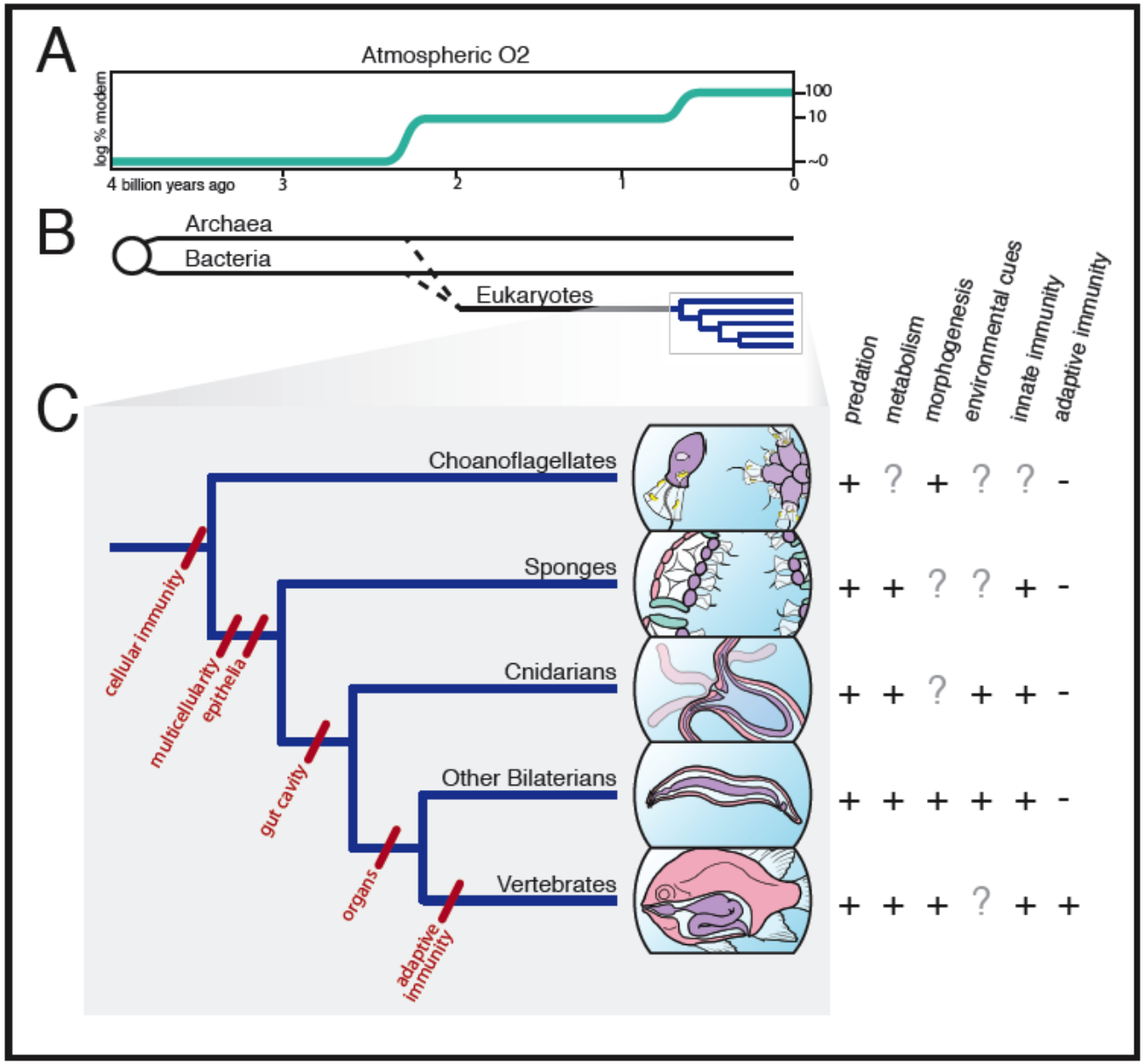




Nous sommes génétiquement très microbes



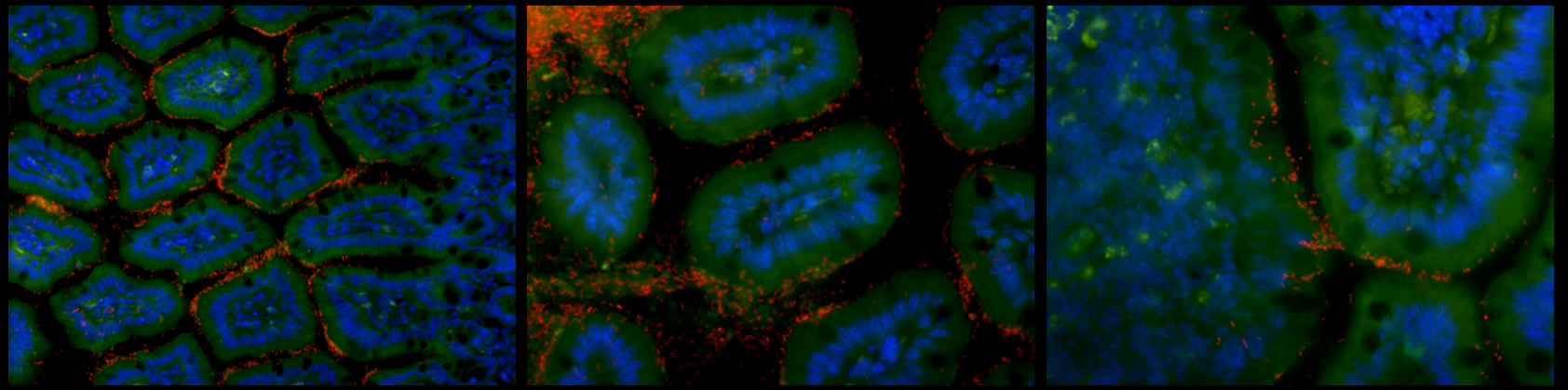
Les microbes dans l'évolution des animaux



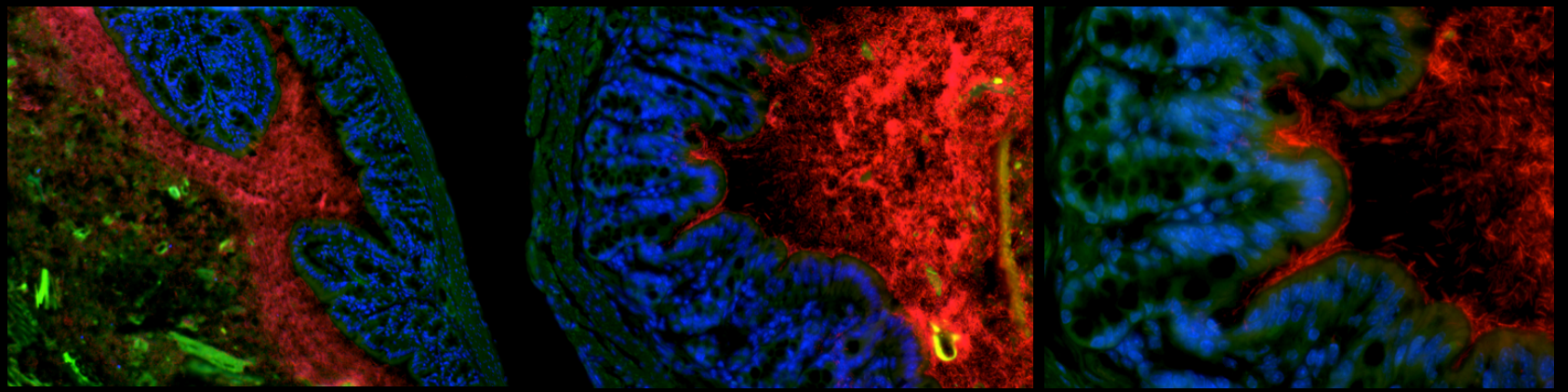
Les bactéries dans l'intestin

AutoF Bact 16S DAPI

Ileum

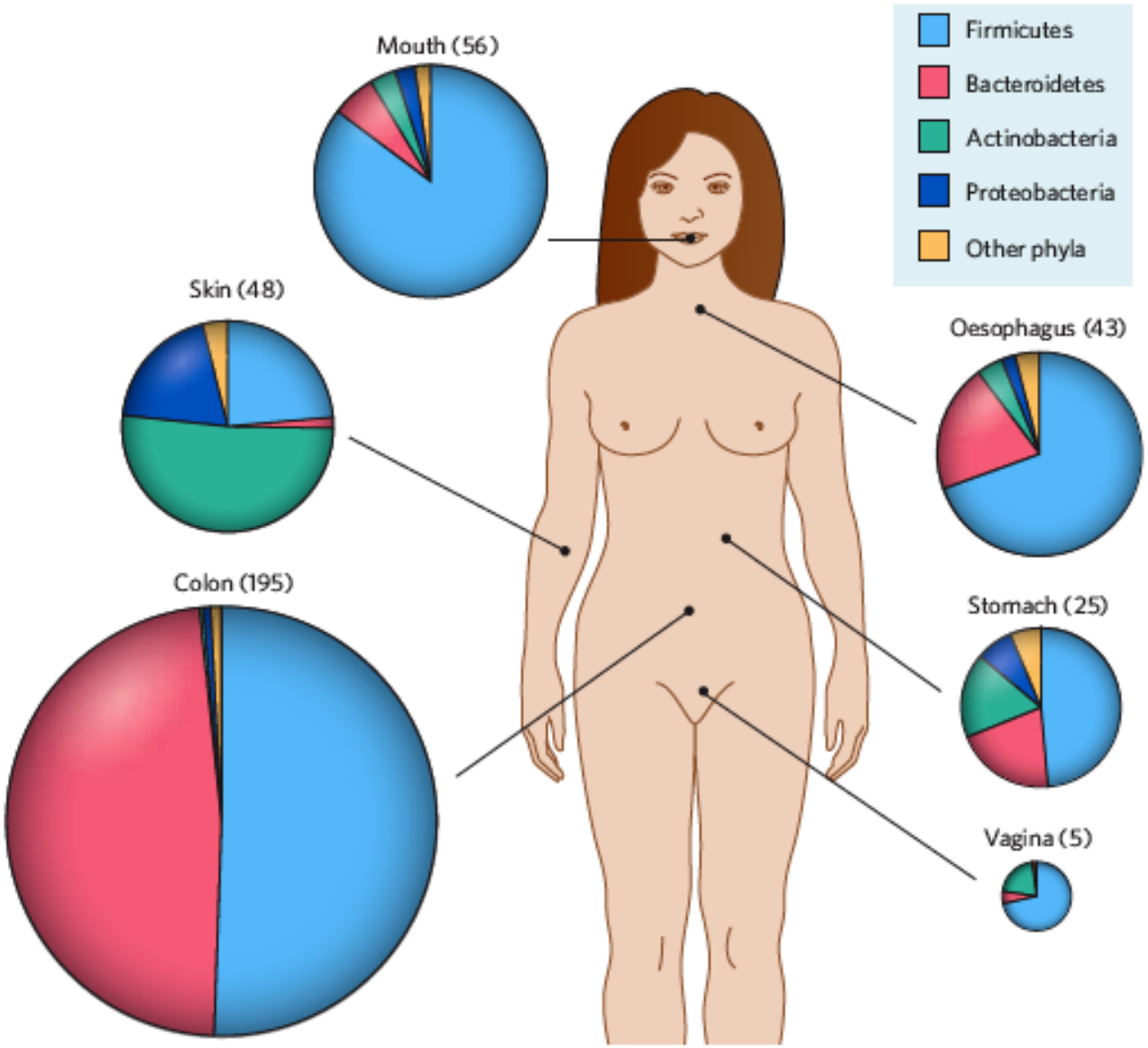


Colon



~10^{14} bactéries and ~10^{12} cellules eucaryotes

Symbiontes bactériens du corps humain



Clostridium
Bacillus
- **Lactobacillus**
- **Enterococcus**
- **(Listeria)**
- **(Staphylococcus)**

Bacteroides

Mycobacterium
Streptomyces
Bifidobacteriales

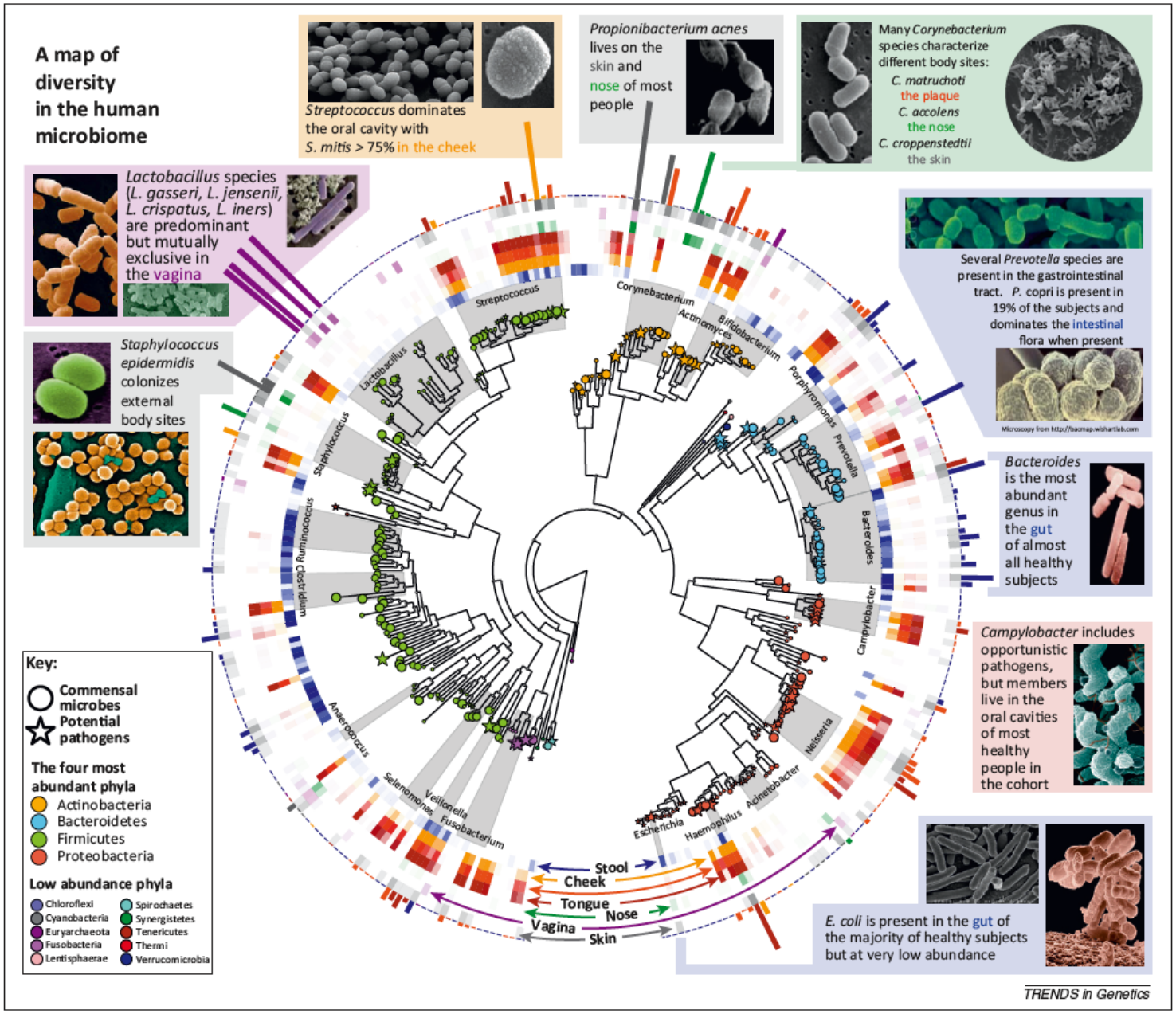
Escherichia
(Salmonella)
(Vibrio)
(Helicobacter)
(Bordetella)
(Neisseria)

Symbiontes bactériens du corps humain

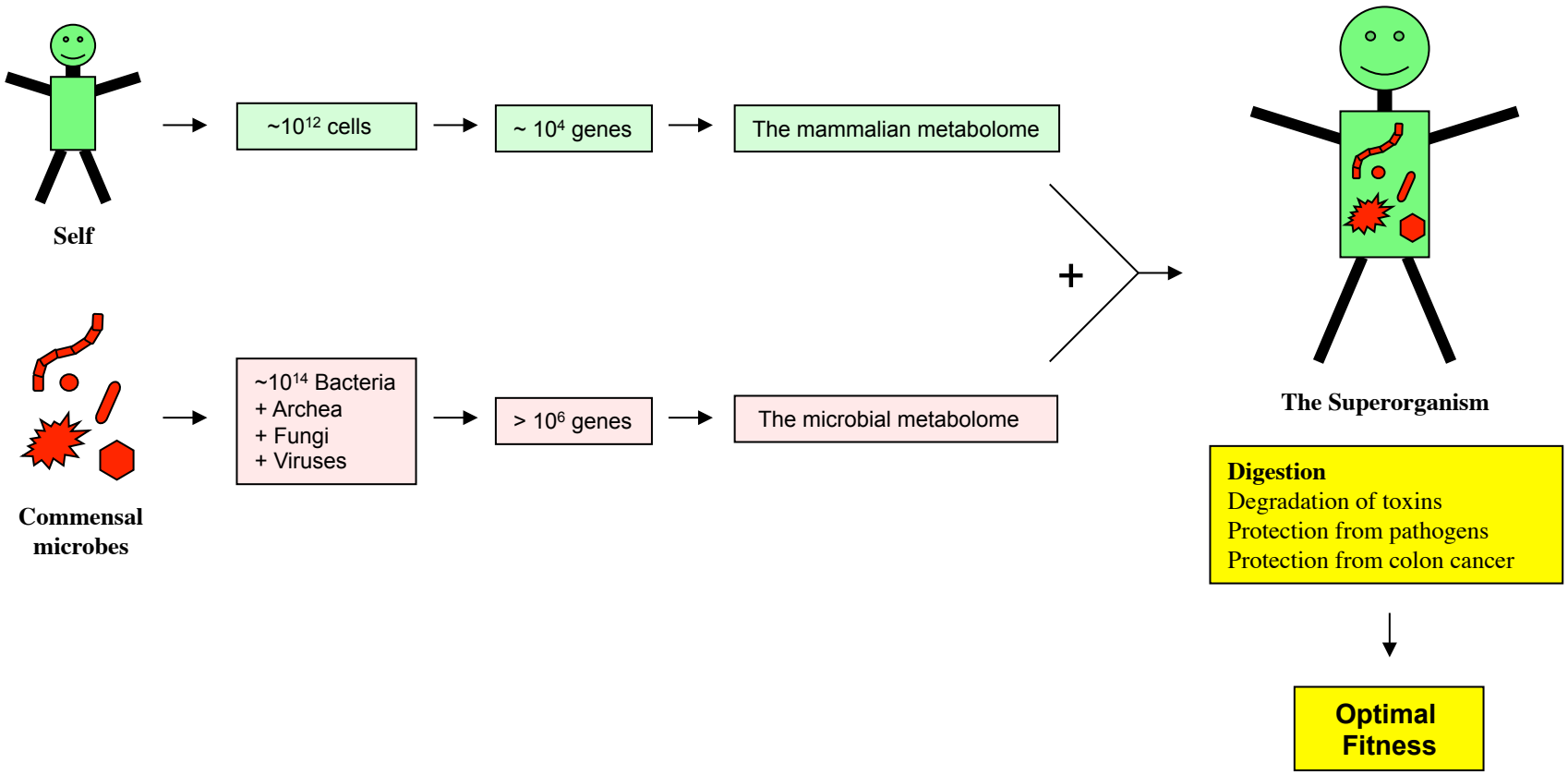
Biodiversity and functional genomics in the human microbiome

Xochitl C. Morgan[1], Nicola Segata[1], and Curtis Huttenhower[1,2]

[1] Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115, USA
[2] Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA 02142, USA



Le superorganisme hôte-microbe



Eberl, Mucosal Immunology 2010

Symbiosis

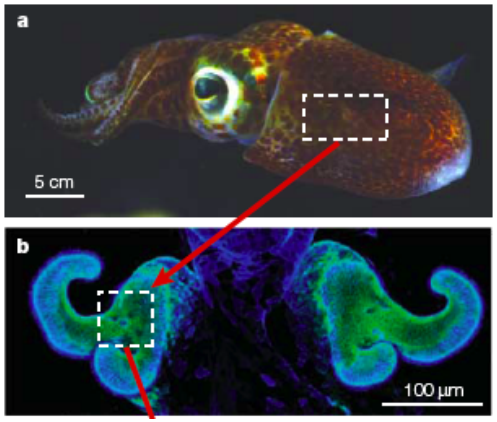
from the Greek:
σύν syn "with"*; and βίωσις biosis* "living"

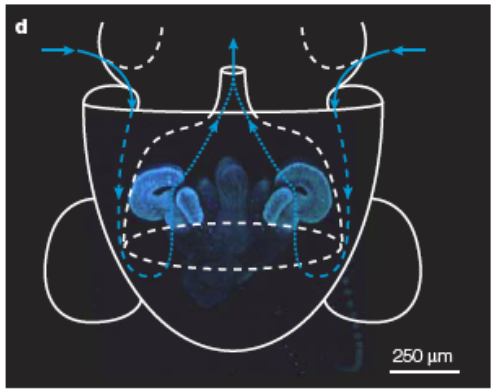
1. Mutualism
2. Commensalism
3. Parasitism

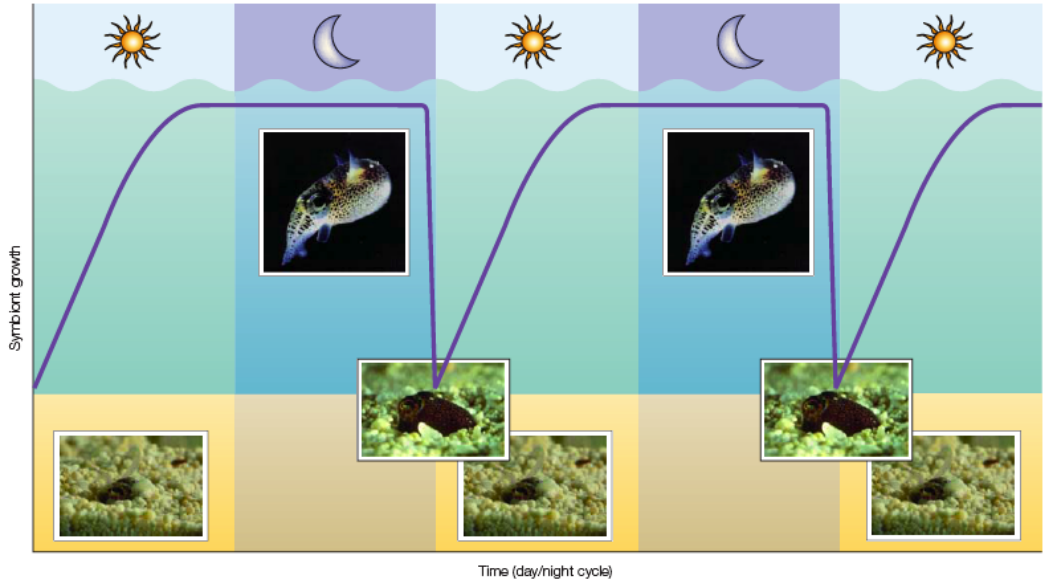
Microbial Factor-Mediated Development in a Host-Bacterial Mutualism

Tanya A. Koropatnick,[1] Jacquelyn T. Engle,[2] Michael A. Apicella,[3]
Eric V. Stabb,[4] William E. Goldman,[2] Margaret J. McFall-Ngai[1,5*]

Science 2004



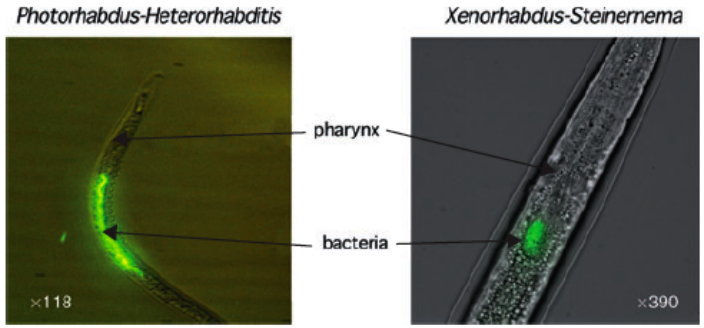


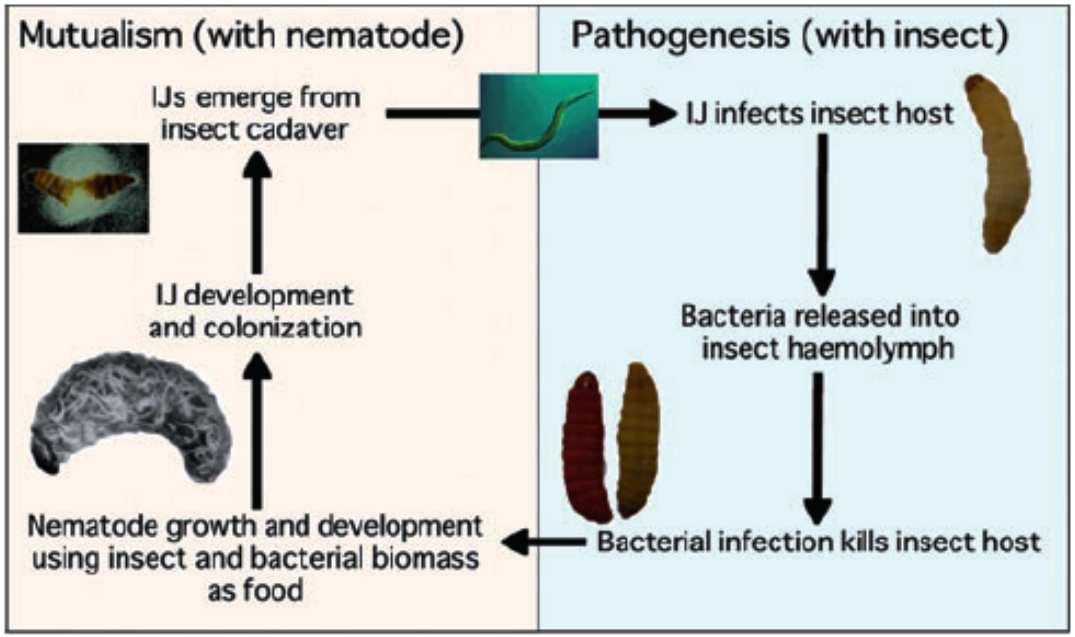


Mutualism and pathogenesis in *Xenorhabdus* and *Photorhabdus*: two roads to the same destination

Heidi Goodrich-Blair[1] and David J. Clarke[2]*
[1]*Department of Bacteriology, University of Wisconsin, Madison, WI, USA.*
[2]*Department of Microbiology, University College Cork, Ireland.*

Mol Micr 2007

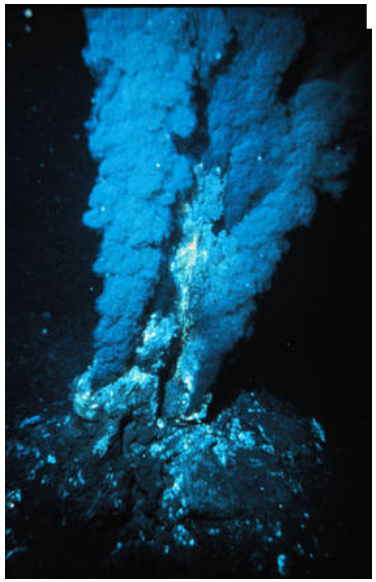


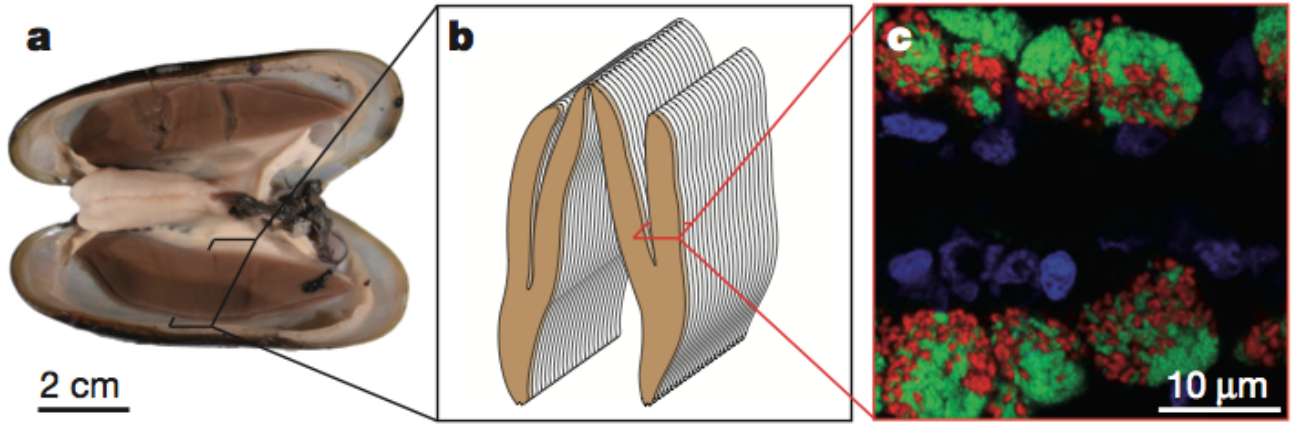


Hydrogen is an energy source for hydrothermal vent symbioses

Nature 2011

Jillian M. Petersen[1]*, Frank U. Zielinski[1,2]*, Thomas Pape[3], Richard Seifert[4], Cristina Moraru[1], Rudolf Amann[1], Stephane Hourdez[5], Peter R. Girguis[6], Scott D. Wankel[6], Valerie Barbe[7], Eric Pelletier[7], Dennis Fink[1], Christian Borowski[1], Wolfgang Bach[8] & Nicole Dubilier[1]

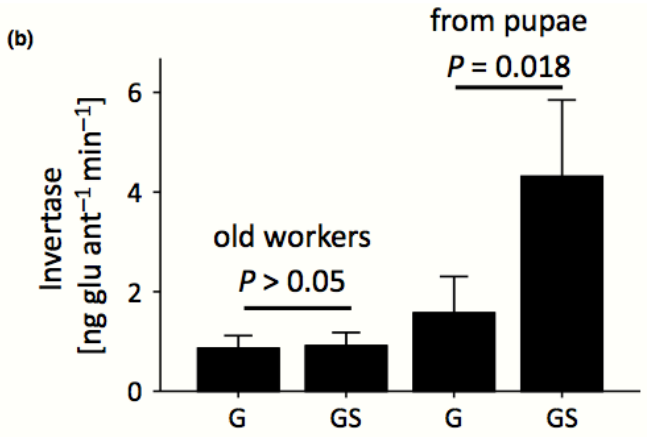


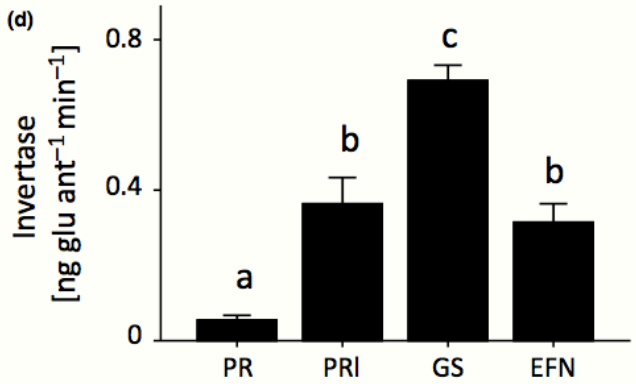


ECOLOGY LETTERS

Ecology Letters, (2013) doi: 10.1111/

Partner manipulation stabilises a horizontally transmitted mutualism

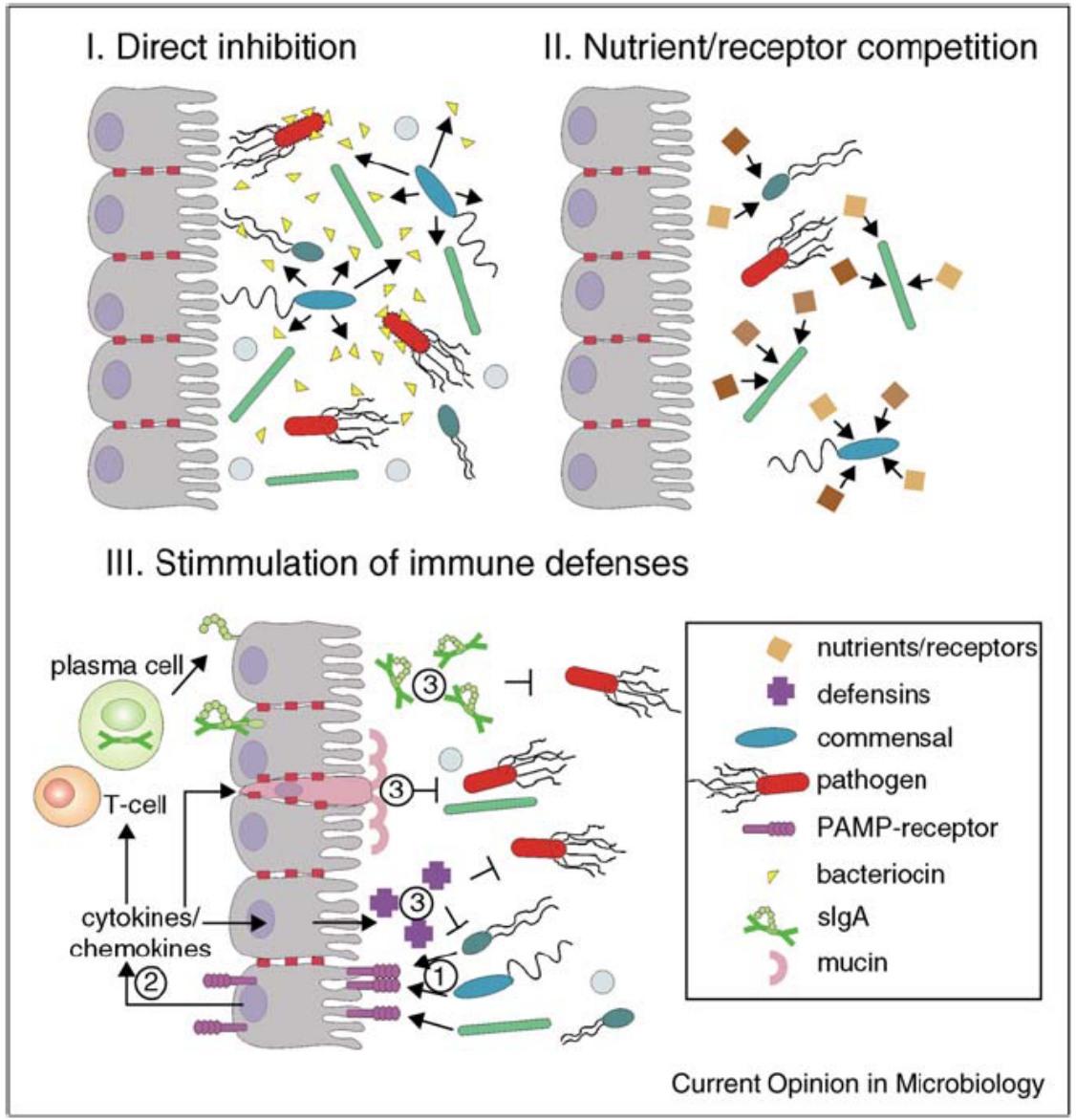




Le rôle des symbiontes bactériens

1. Digestion (extraction d'énergie)
2. Synthèse de métabolites
3. Degradation de toxines
4. Régulation de l'épithélium
5. Protection contre les pathogènes

5. Symbiontes intestinaux et défense



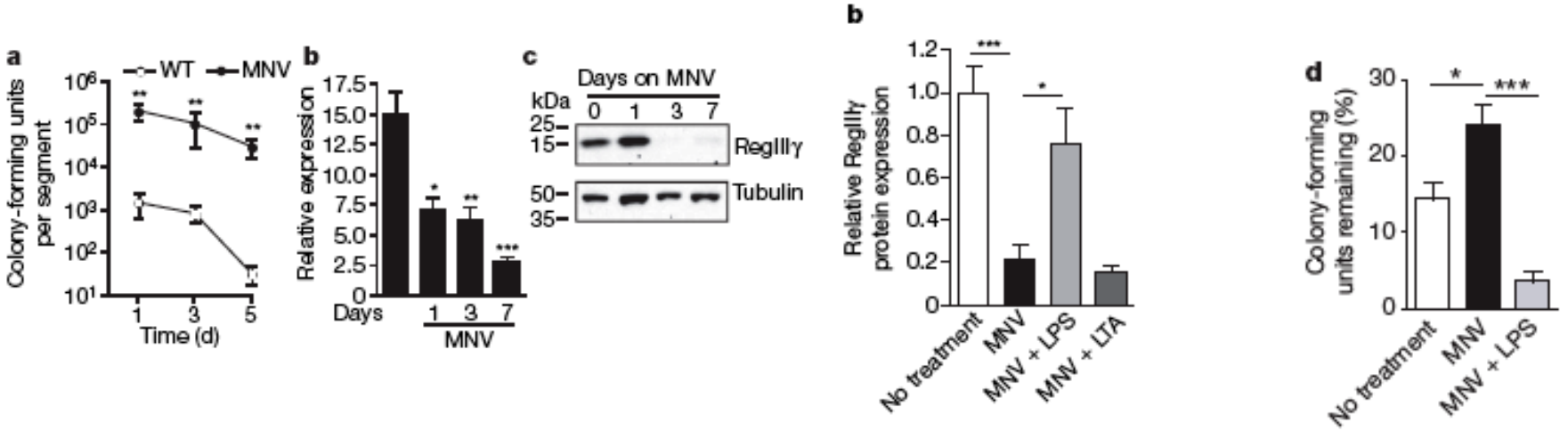
Mechanisms controlling pathogen colonization of the gut
Bärbel Stecher[1] and Wolf-Dietrich Hardt[2]

5. Symbiontes intestinaux et défense induite

Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits

Katharina Brandl[1]†, George Plitas[2], Coralia N. Mihu[1]†, Carles Ubeda[1], Ting Jia[1], Martin Fleisher[3], Bernd Schnabl[4]†, Ronald P. DeMatteo[2] & Eric G. Pamer[1,3]

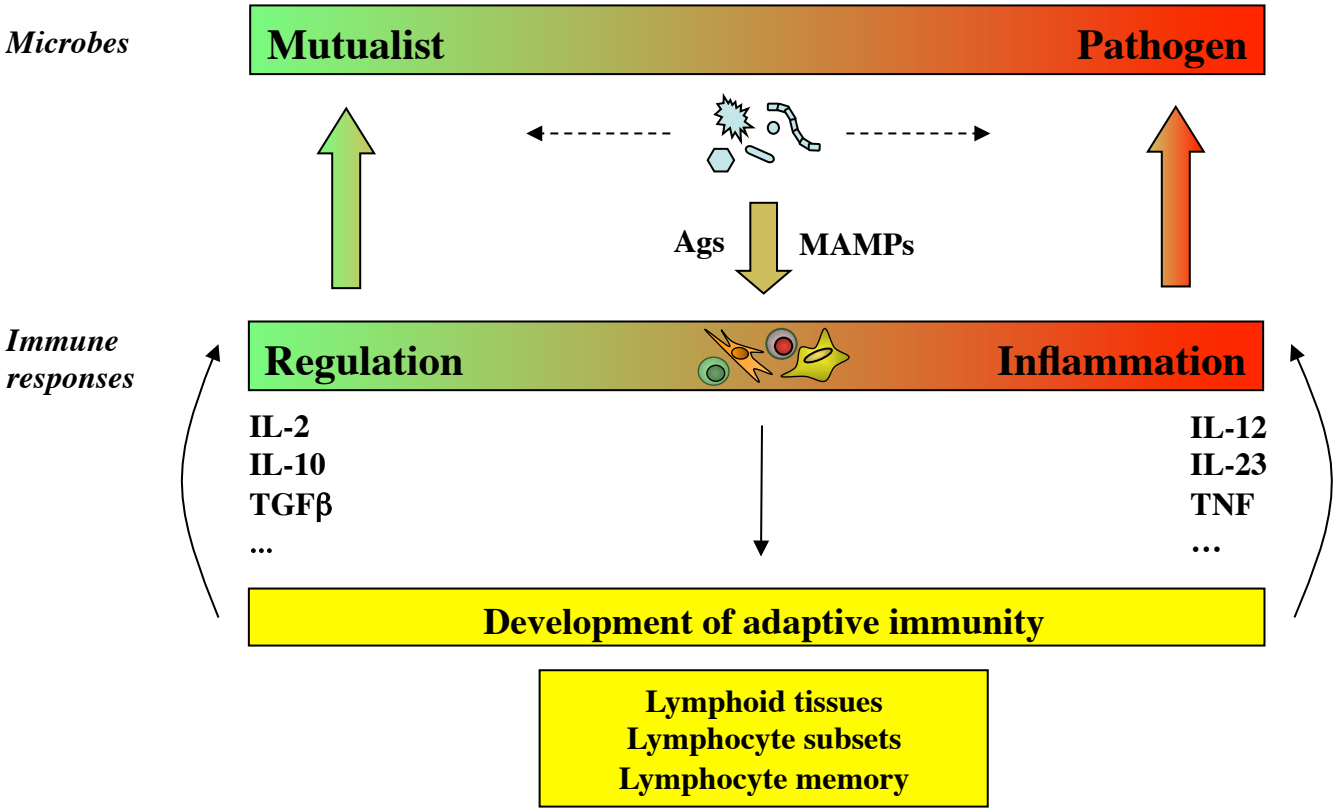
Nature 2008



– 2 –

Que fait le système immunitaire?

Le système immunitaire maintient l'équilibre

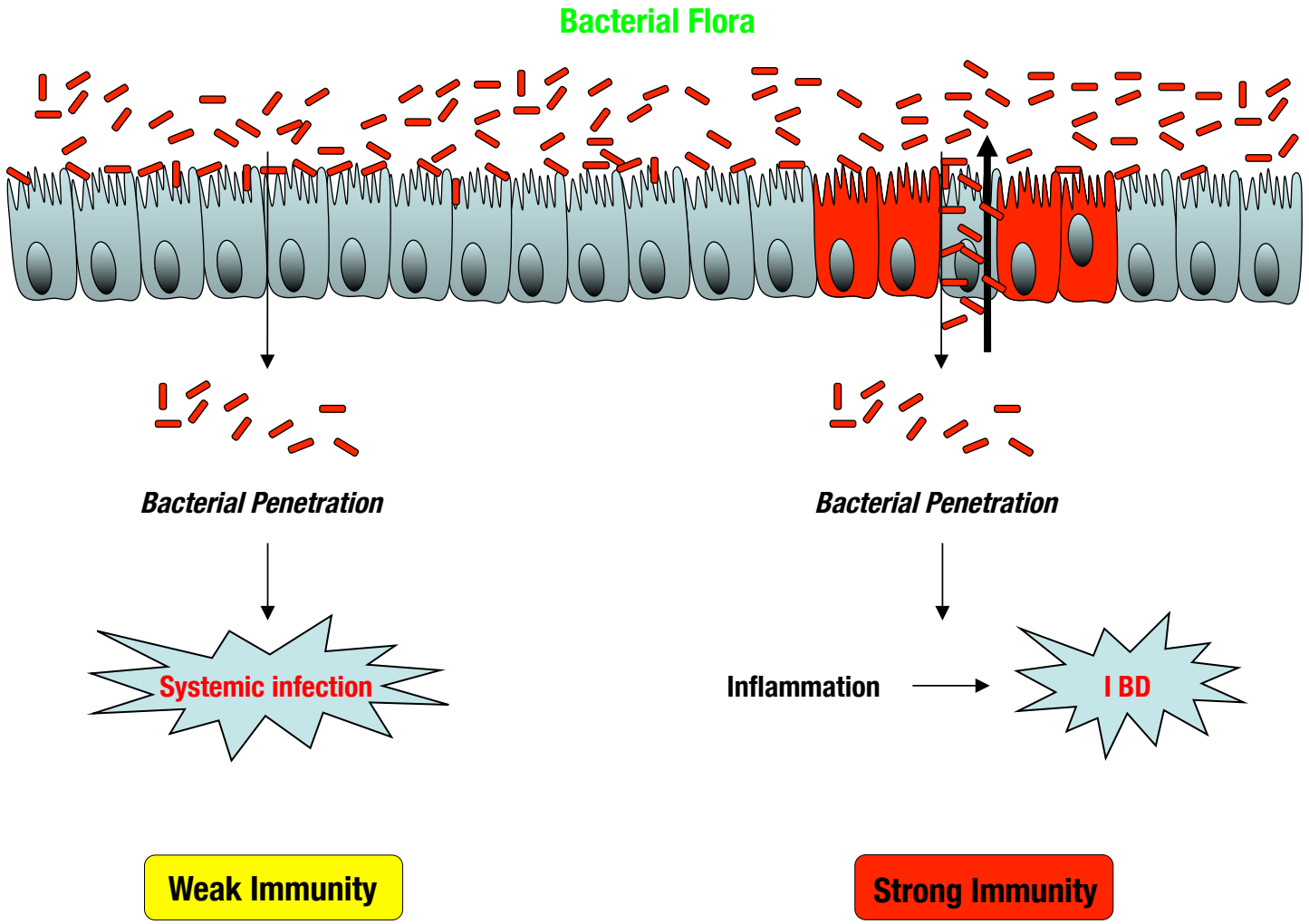


G. Eberl, Mucosal Immunol 2010

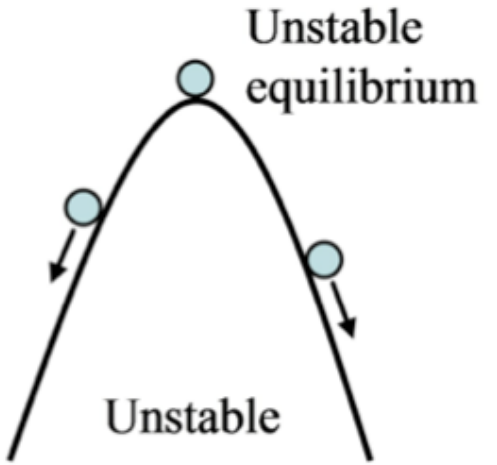
L’équilibre hôte-symbionte: la clé de la santé

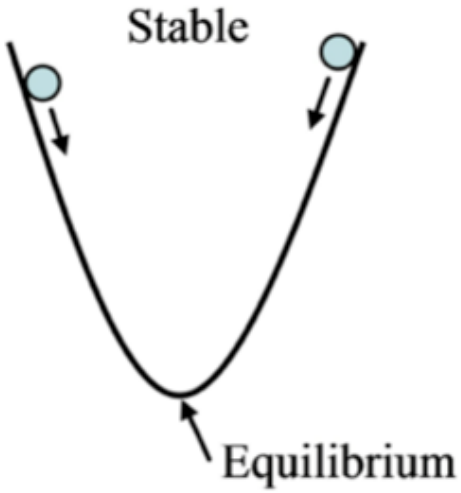
L’outil de l’hôte: le système immunitaire

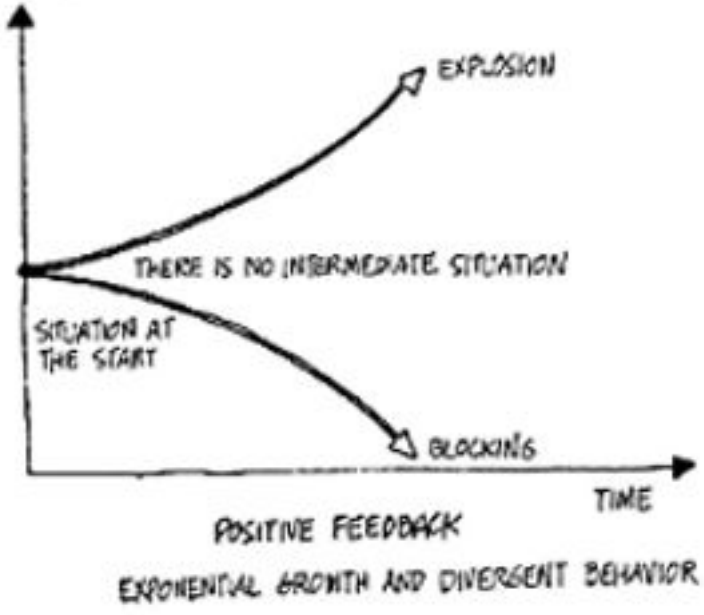
L’équilibre entre le microbiote intestinal et le système immunitaire

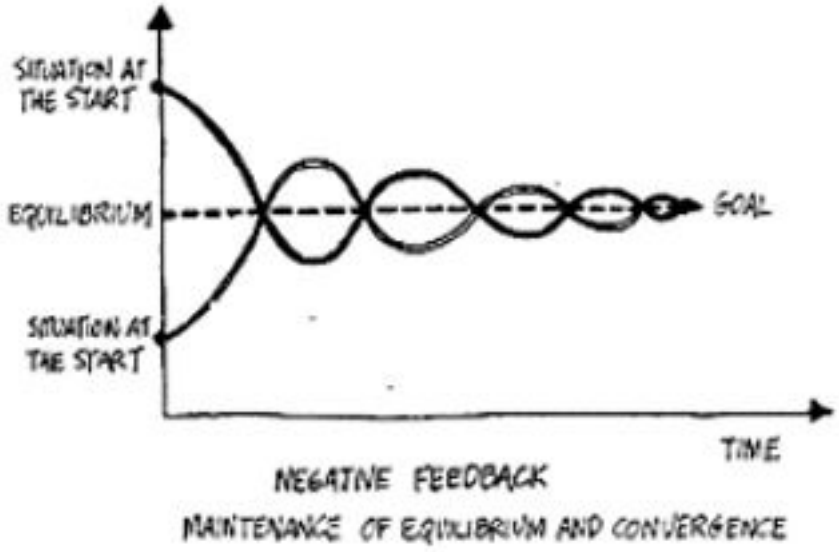


L’équilibre hôte-microbe est en général robuste





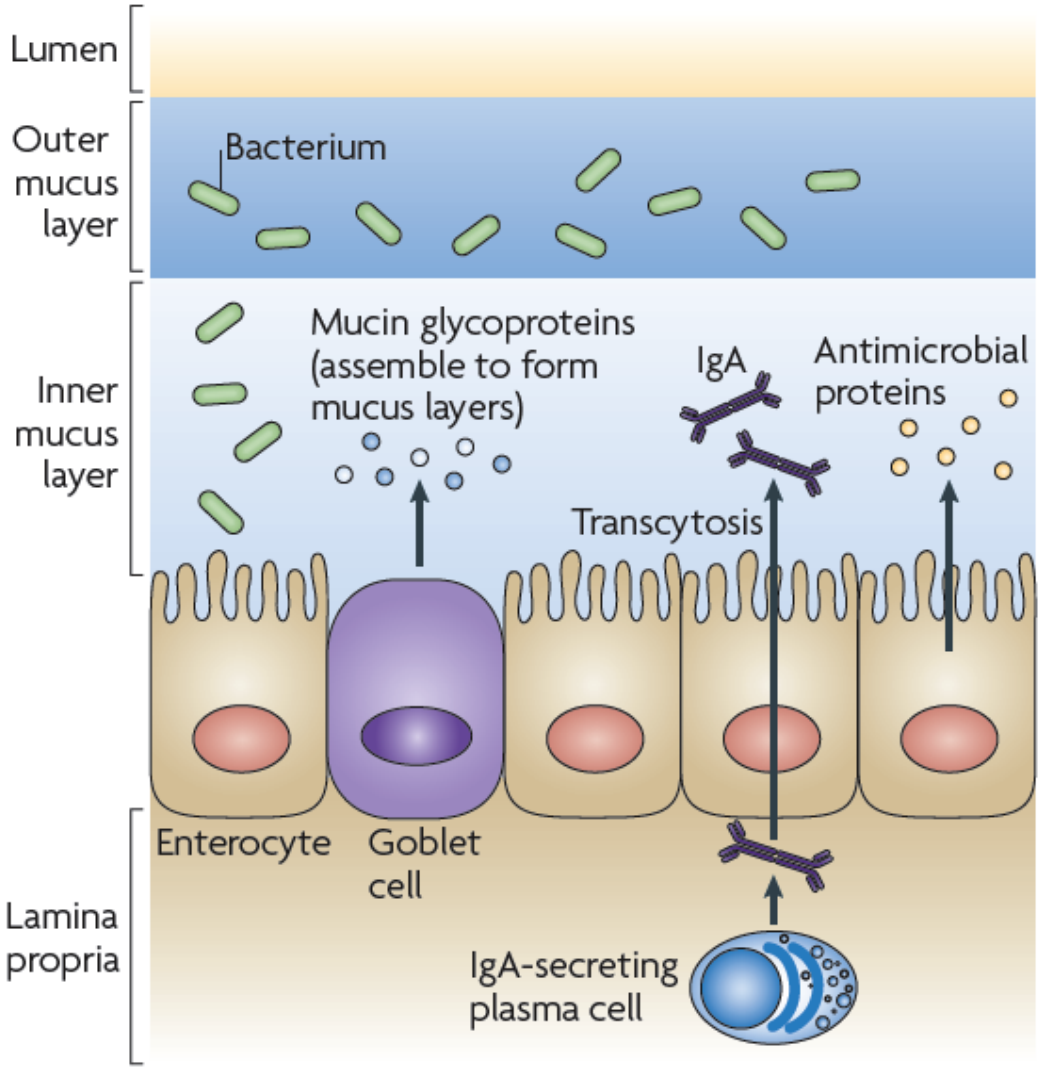


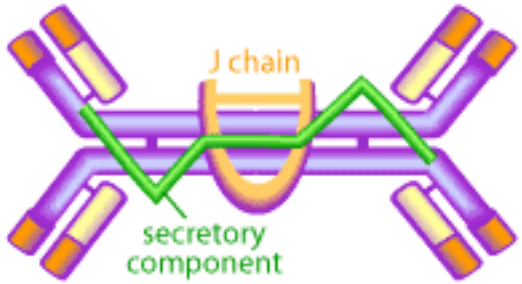


Le système immunitaire intestinal

1. Immunité innée
2. Immunité adaptative

La barrière intestinale établie par le système immunitaire





Immune adaptations that maintain homeostasis with the intestinal microbiota

Lora V. Hooper and Andrew J. Macpherson‡*

PRIMATE DEFENSINS

FOCUS ON ANTIMICROBIAL STRATEGIES

Nat Rev Med 2004

Robert I. Lehrer

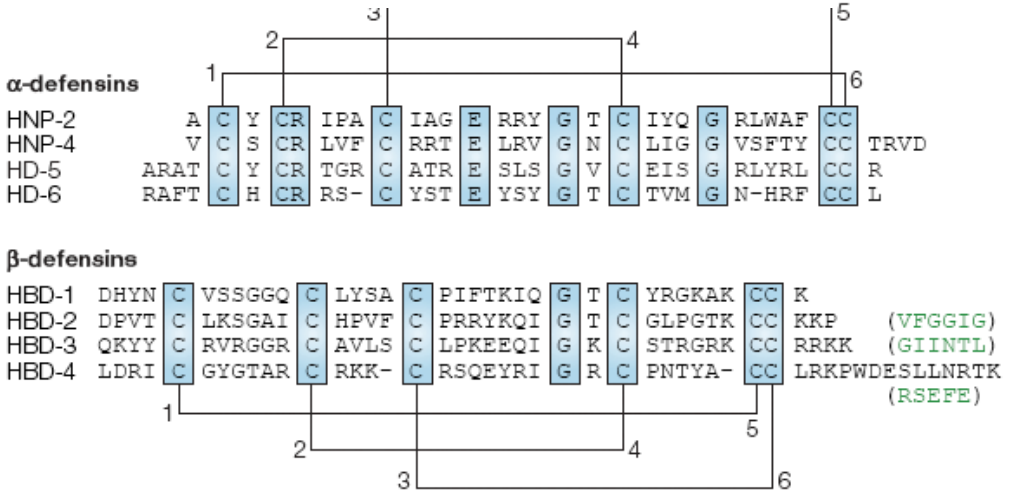
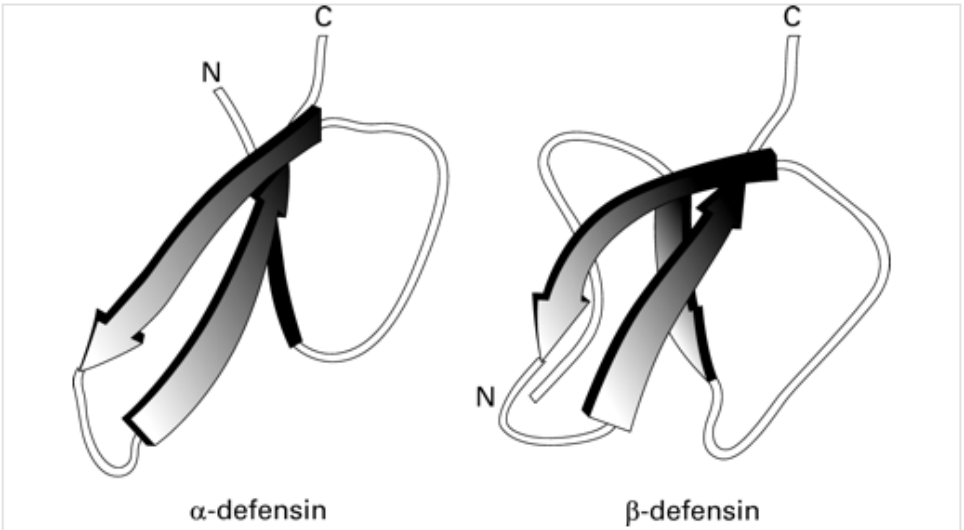
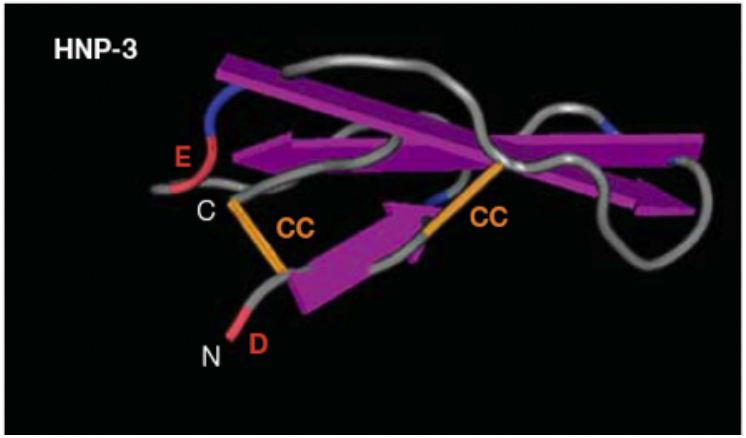
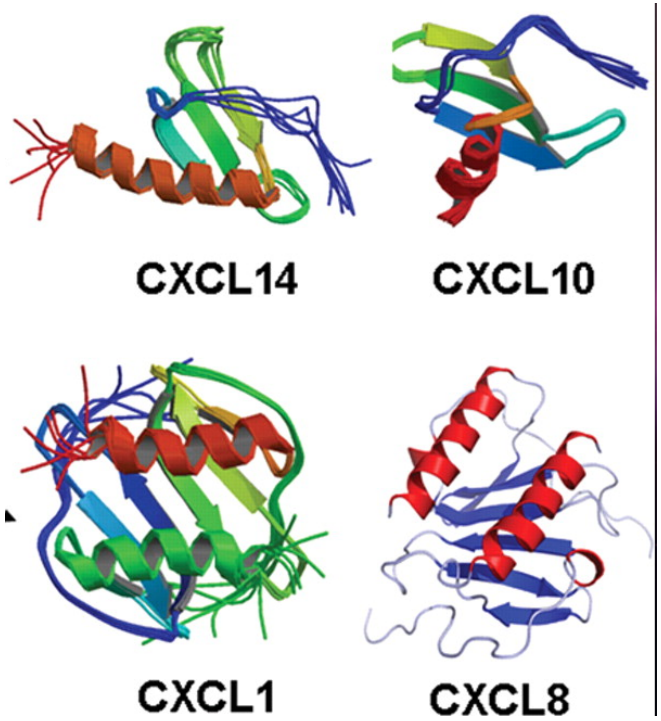


Figure 2 | **The sequence and cysteine bonding of four human α-defensins (HNP-2, HNP-4, HD-5 and HD-6) and four human β-defensins (HBD-1–4).** HNP-2 and -4 are expressed in

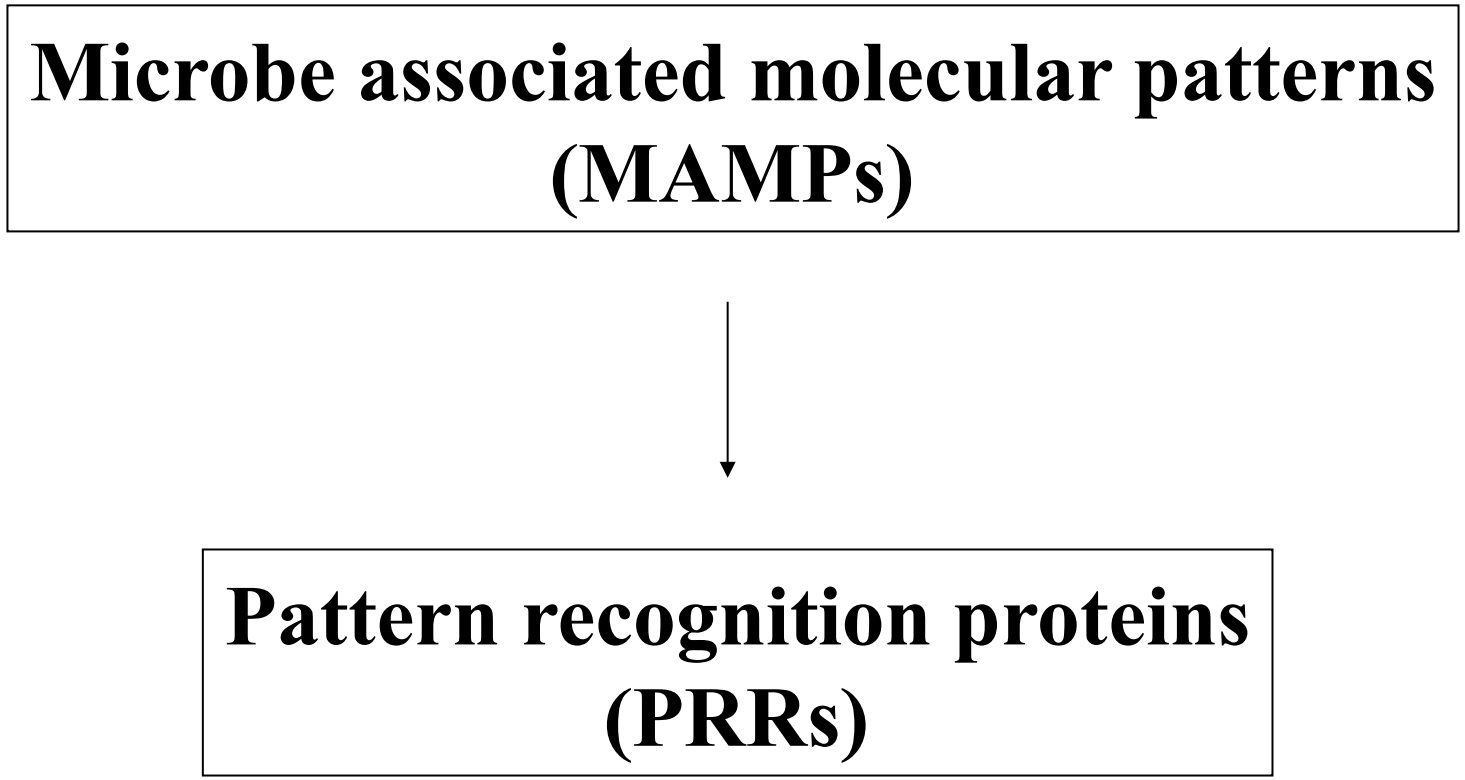






La majorité des chimiokines sont des défensines

Chemokine		Calculated	Antimicrobial activity (% Killed, mean±SD)*	
Family	Member	pI	*E. coli*	*S. aureus*
CXC	CXCL1/Groα	9.80	++++ (87±13)	+ (22±11)
	CXCL2/Groβ	10.27	+++ (78±9)	+ (26±9)
	CXCL3/Groγ	9.85	+++ (64±11)	+ (39±10)
	CXCL6/GCP-2	9.06	– (0)	– (0)
	CXCL8/IL-8	8.97	– (0)	– (0)
	CXCL9/MIG	10.83	++++ (100)	++++ (81±11)
	CXCL10/IP-10	10.52	++++ (100)	+++ (77±12)
	CXCL11/I-TAC	10.48	+++ (72±10)	+++ (69±9)
	CXCL12/SDF-1†	10.51	++++ (86±12)	++ (59±7)
	CXCL13/BCA-1	10.91	++++ (83±9)	++ (50±10)
	CXCL14/BRAK	10.28	++ (50±10)	+ (35±8)
CX3C	CX3CL1/fractalkine‡	9.78	– (0)	– (0)
C	XCL1/lymphotactin	11.35	++++ (100)	++ (47±9)
CC	CCL1/I-309	10.10	++++ (88±12)	+ (37±5)
	CCL2/MCP-1	9.58	– (0)	– (0)
	CCL3/MIP-1α	4.60	– (0)	– (0)
	CCL5/RANTES	9.25	– (0)	– (0)
	CCL7/MCP-3	10.10	– (0)	– (0)
	CCL8/MCP-2	10.38	+ (26±12)	– (0)
	CCL11/eotaxin	10.35	+++ (66±7)	++ (49±10)
	CCL13/MCP-4	10.40	+++ (76±9)	– (0)
	CCL16/LEC	8.71	– (0)	– (0)
	CCL17/TARC	9.29	+++ (59±10)	++ (46±8)
	CCL18/PARC	9.39	++++ (100)	+++ (69±9)
	CCL19/MIP-3β	10.16	++++ (82±10)	– (0)
	CCL20/MIP-3α	10.08	++++ (100)	++ (51±7)
	CCL21/SLC	10.46	++ (45±9)	+++ (75±8)
	CCL22/MDC	9.04	++++ (100)	+++ (74±11)
	CCL25/TECK	10.69	+++ (68±13)	++ (48±12)
	CCL27/CTAK	9.11	– (0)	– (0)


Microbe associated molecular patterns (MAMPs)
Pattern recognition proteins (PRRs)

Détecteurs innés (Prix Nobel de Médecine 2011)

Jules Hofmann, ***Bruno Lemaître*** *(Strasbourg)*

Bruce Beutler (Scripps, CA)

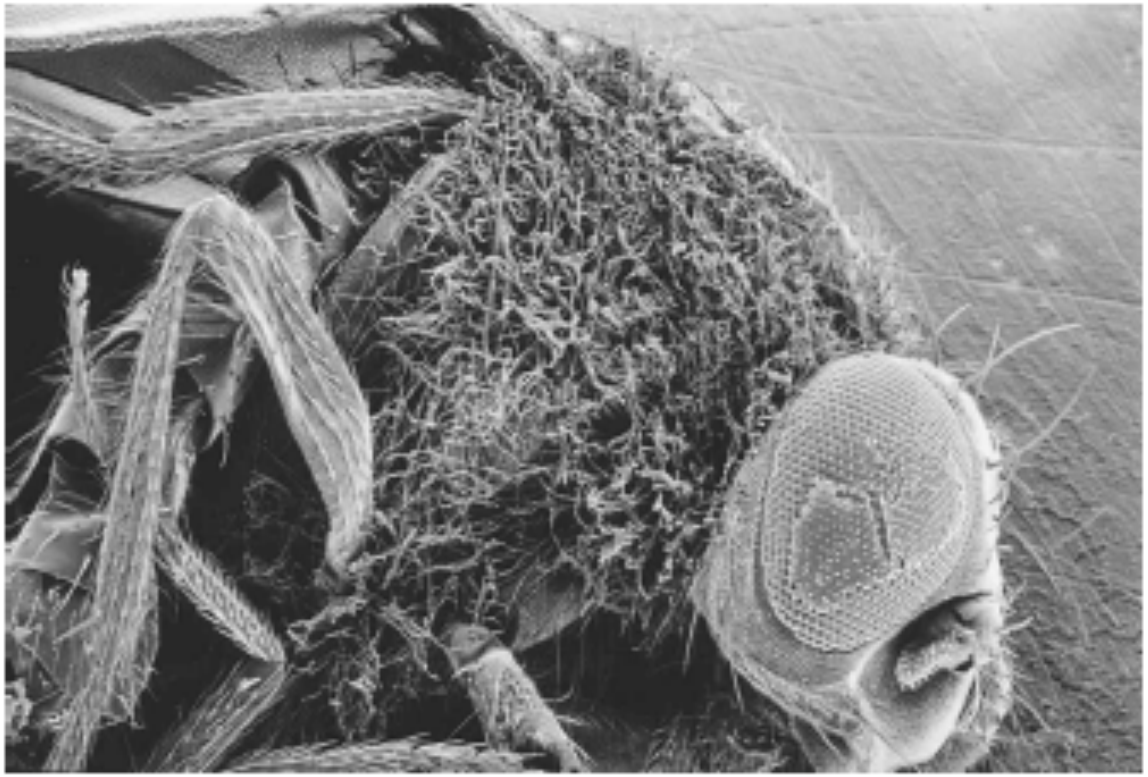


Figure 5. Germinating Hyphes of A. fumigatus on a Dead Drosophila
Scanning electron micrograph of a Drosophila adult that succumbed to infection by A. fumigatus and is covered with germinating hyphae (200× magnification).

A quoi sert l'immunité adaptative?

NATURE|Vol 445|11 January 2007

ESSAY

ADAPTIVE IMMUNITY

Care for the community

A memory-based immune system may have evolved in vertebrates because of the need to recognize and manage complex communities of beneficial microbes.

Margaret McFall-Ngai

– 3 –

Les microbes et le développement du système immunitaire

Microbial Factor-Mediated Development in a Host-Bacterial Mutualism

Tanya A. Koropatnick,[1] Jacquelyn T. Engle,[2] Michael A. Apicella,[3] Eric V. Stabb,[4] William E. Goldman,[2] Margaret J. McFall-Ngai[1,5]*

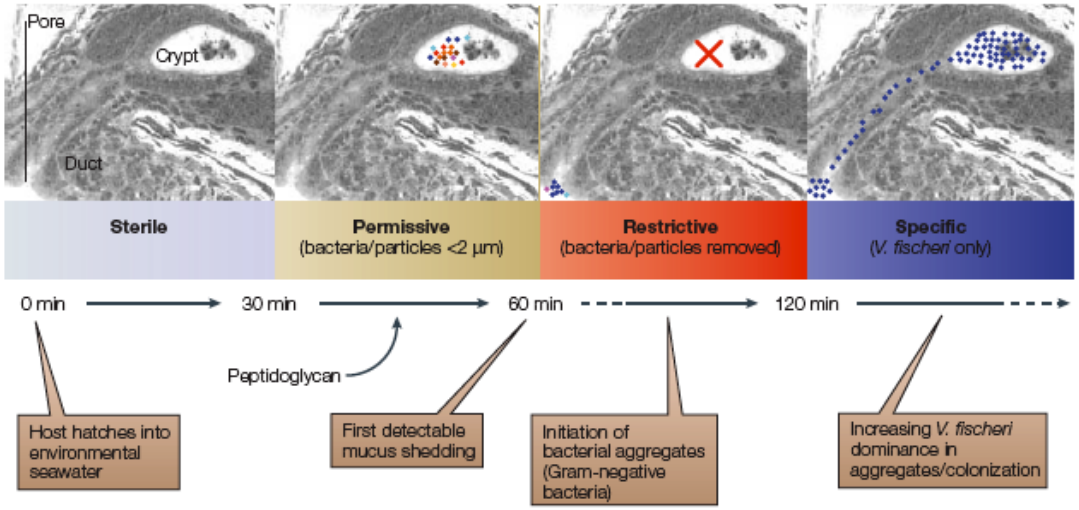
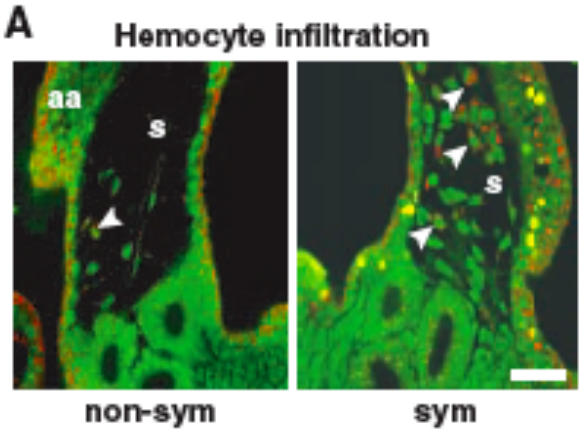
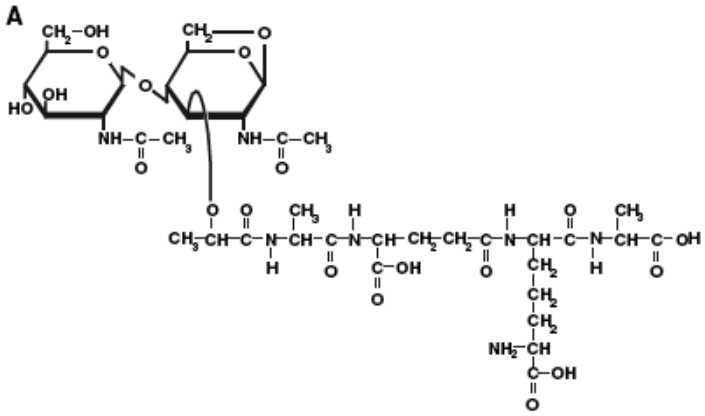


Figure 3 | **The initial interactions of the juvenile host with the environment.** Between 30 and 60 minutes after hatching, the light-organ crypts are open to small numbers (1–3) of bacterial cells or particles less than 2 µm in diameter. These initial entrants are later removed by an as-yet-unknown mechanism. After 1 hour, the host sheds mucus in response to bacterial peptidoglycan and by 2 hours, *V. fischeri* (~1 µm in diameter) begin to aggregate above the pore and then migrate through the duct before colonizing the crypt epithelium. At this point, the light organ transforms from a 'permissive' environment to an environment that is exclusive to the symbiont.

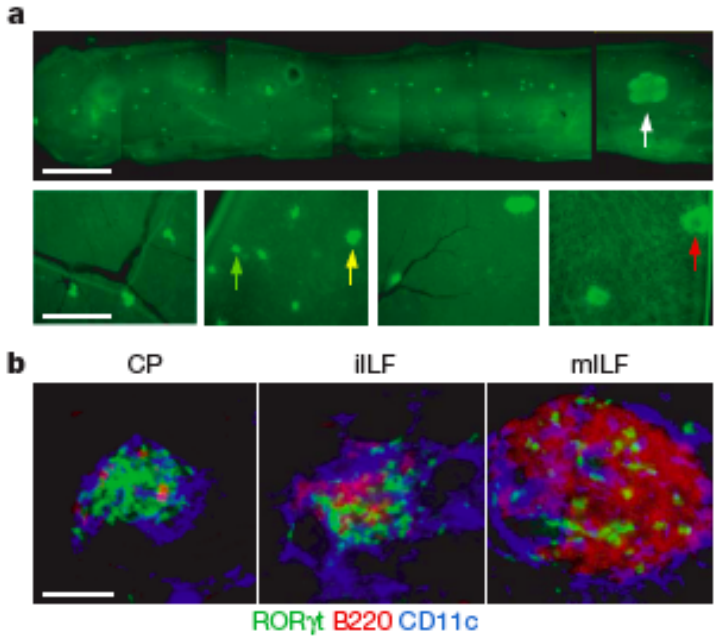


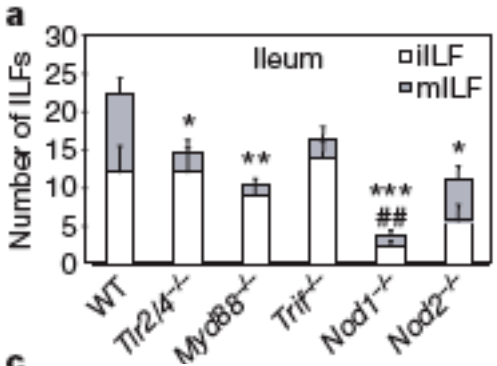


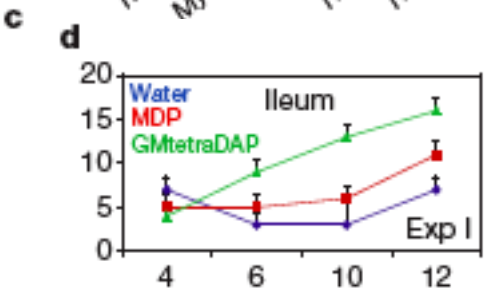
Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis

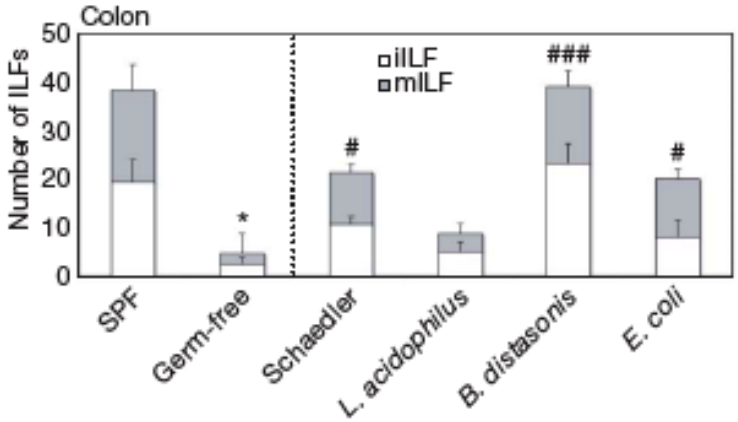
Nature 2008

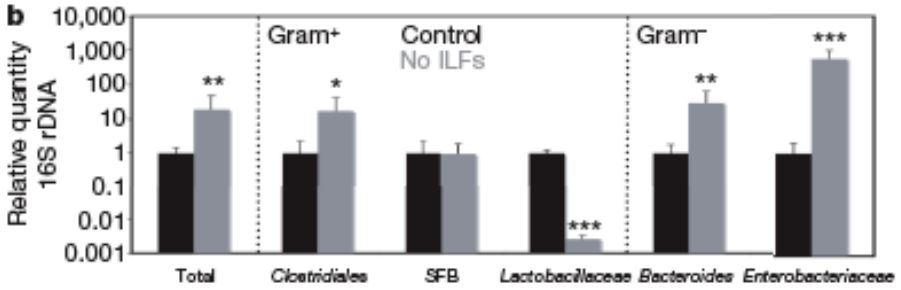
Djahida Bouskra[1], Christophe Brézillon[2], Marion Bérard[3], Catherine Werts[4,6], Rosa Varona[5], Ivo Gomperts Boneca[4,6] & Gérard Eberl[1]



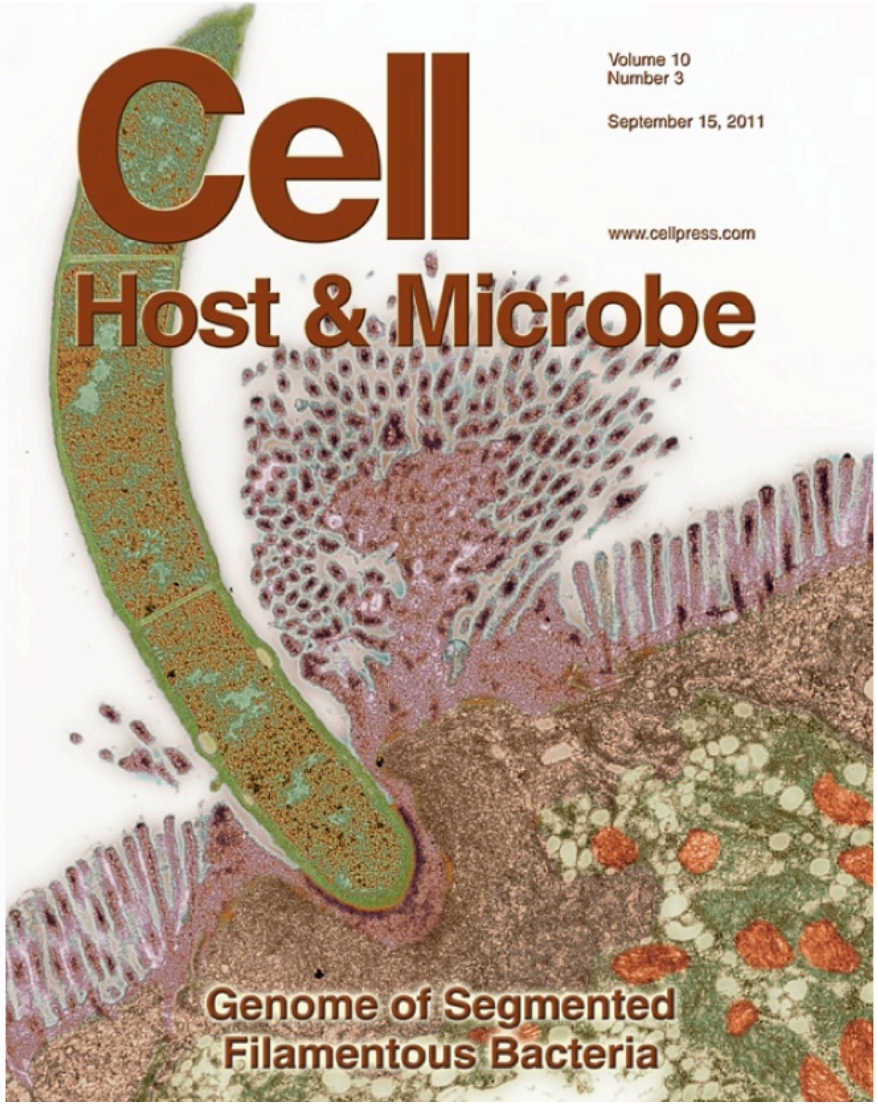


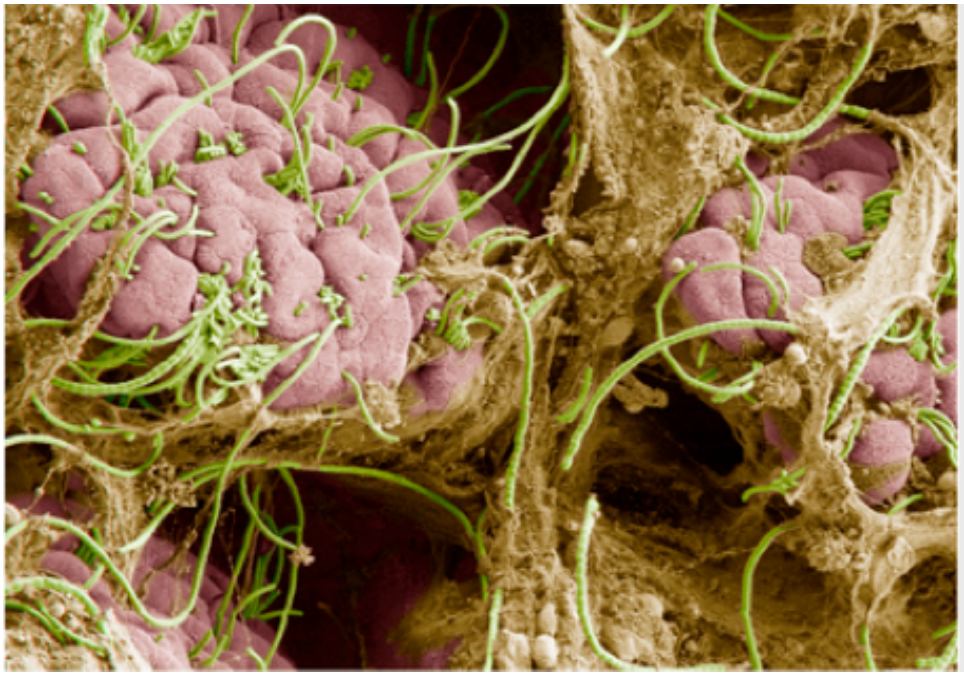


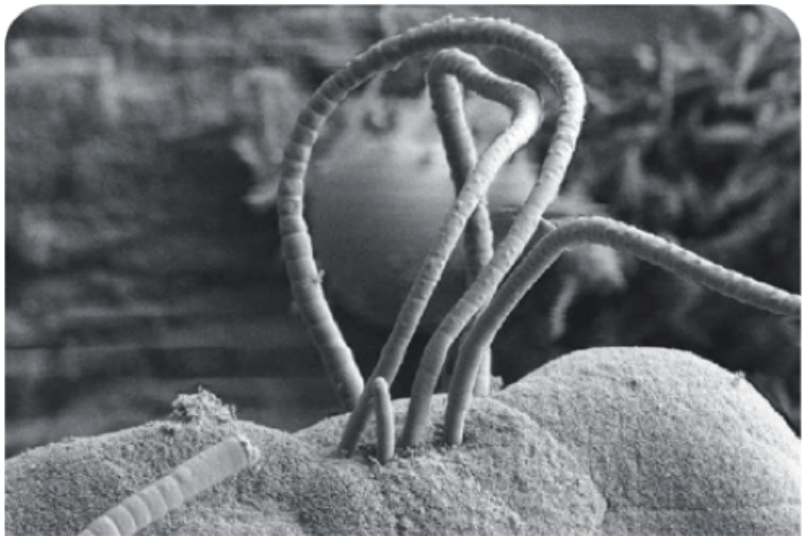




Bactéries Segmentées Filamenteuses (SFB)







INFECTION AND IMMUNITY, Apr. 1999, p. 1992–2000
0019-9567/99/$04.00+0

Segmented Filamentous Bacteria Are Potent Stimuli of a Physiologically Normal State of the Murine Gut Mucosal Immune System

GWEN L. TALHAM,[1]† HAN-QING JIANG,[1] NICOLAAS A. BOS,[2] AND JOHN J. CEBRA[1]*

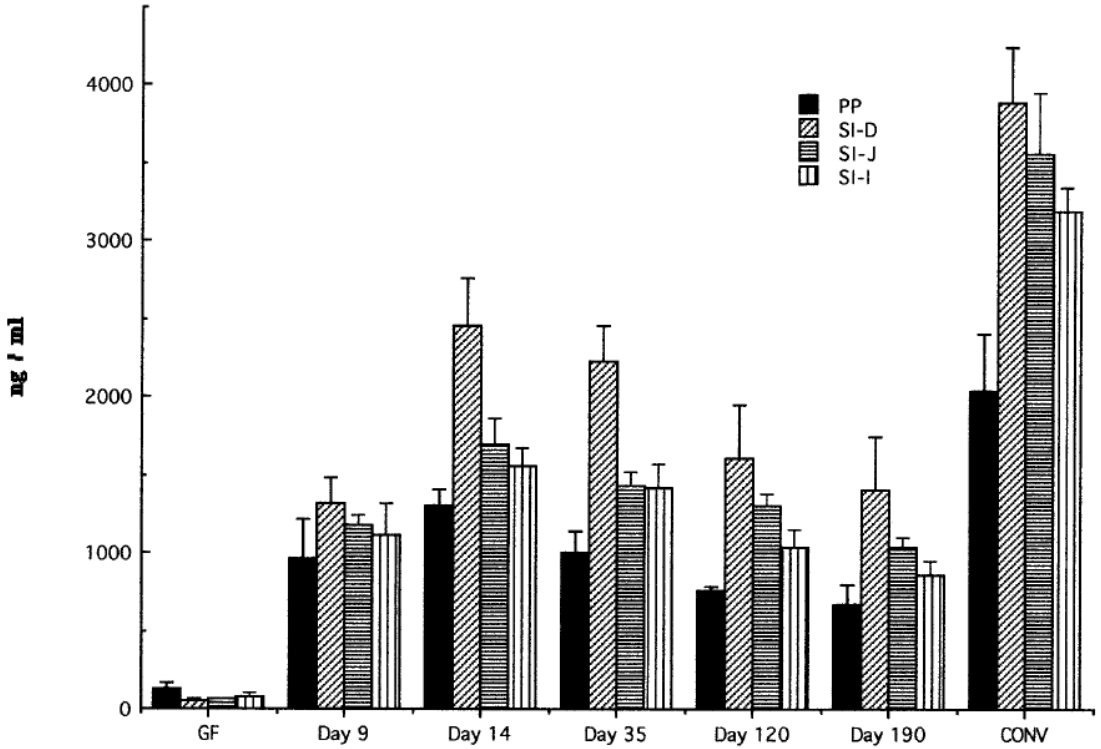
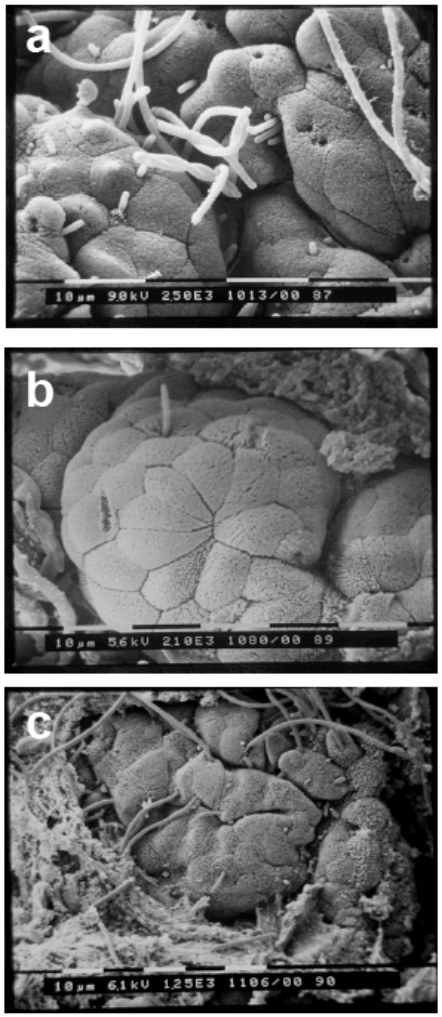
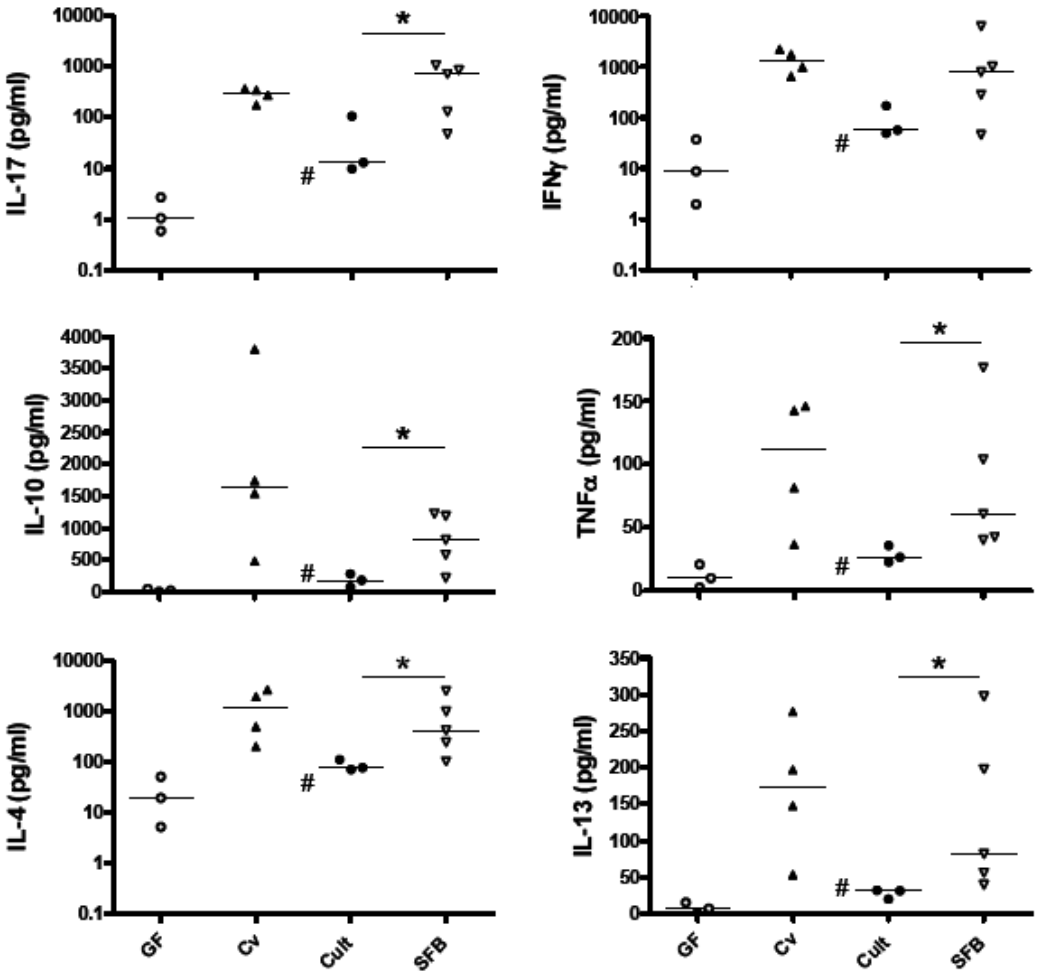


FIG. 2. Production of total IgA in supernatant of organ fragment cultures of PP and small intestine of GF, conventionally reared (CONV), and SFB-monoassociated C3H/HeN mice at various time points. RIA was used to detect IgA. Data are means ± standard errors of the mean. SI, small intestine; D, duodenum; J, jejunum; I, ileum. The number of fragment cultures per tissue per time point ranged from 4 to 14.

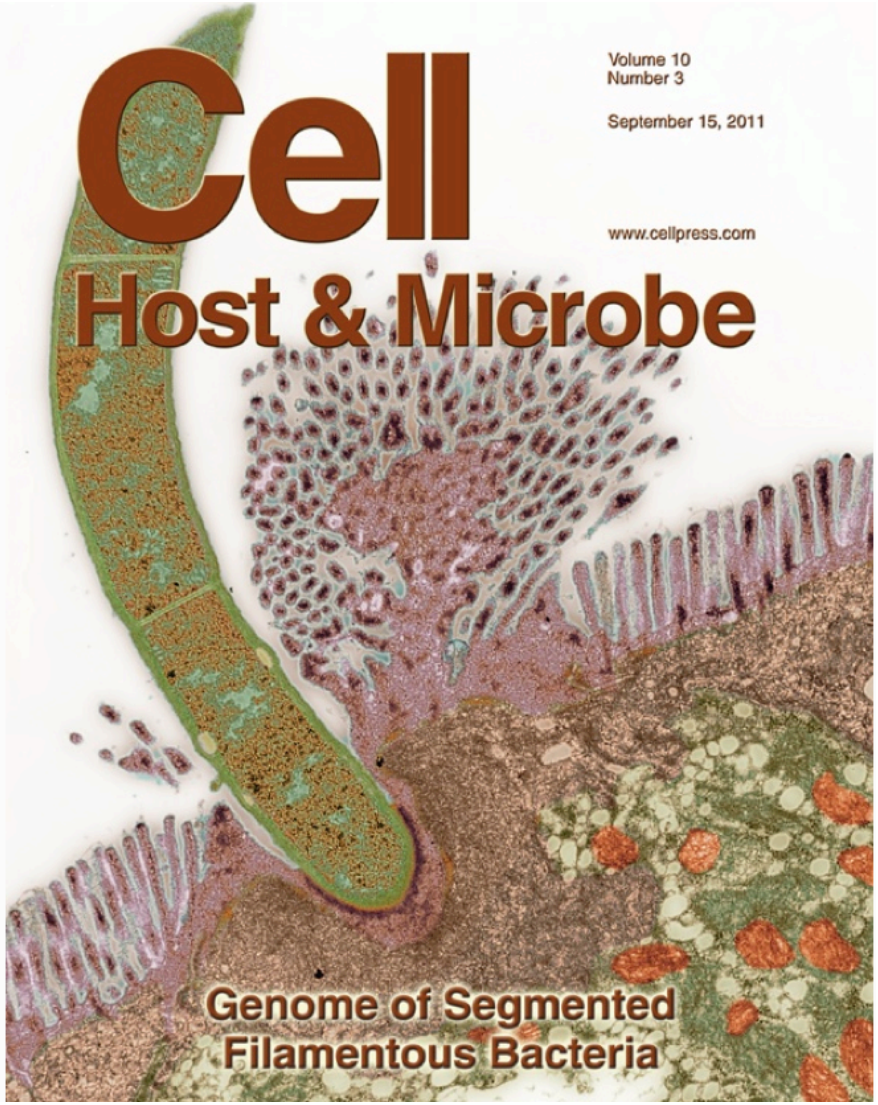
Les SFB induisent fortement les réponses adaptatives

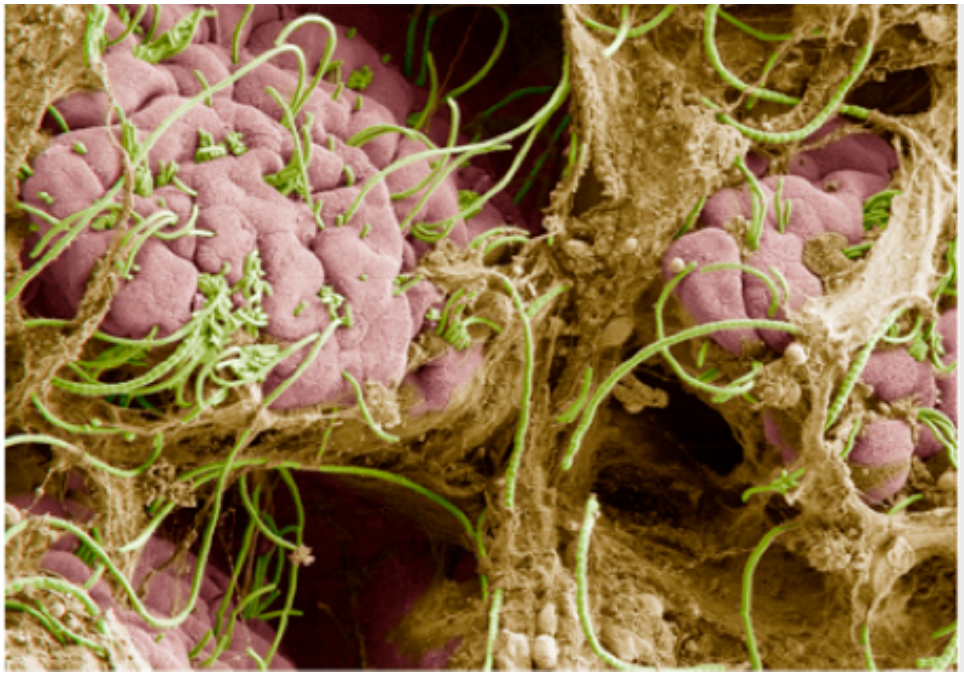


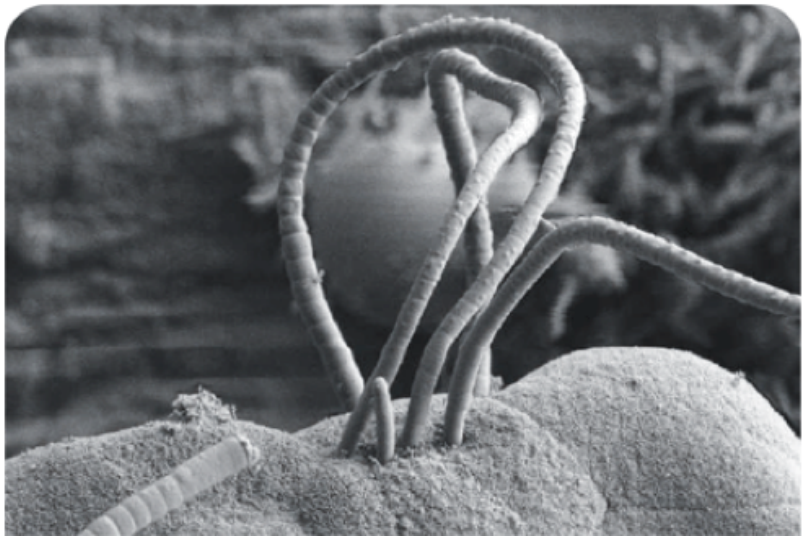


Valérie Gaboriau-Routhiau, Nadine Cerf-Bensussan, Immunity 2009

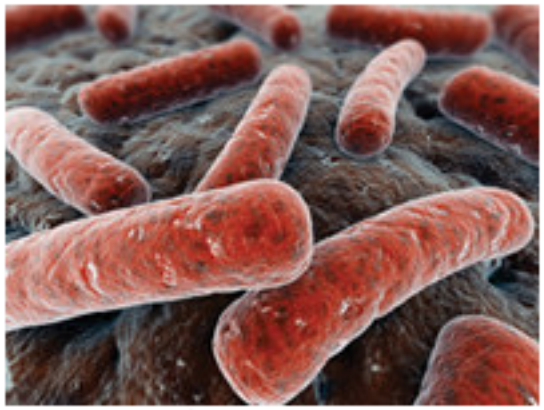
Les SFB élèvent le niveau d'alerte du système immunitaire

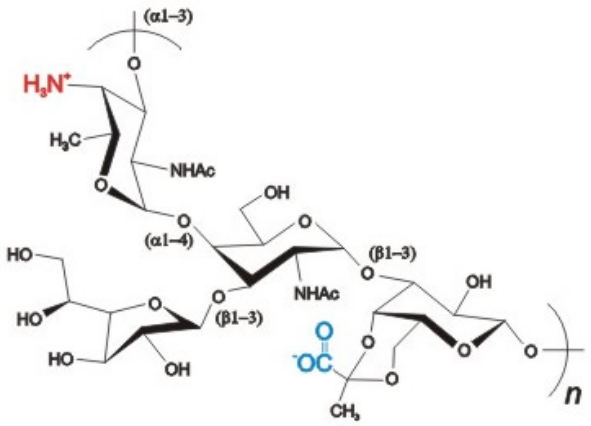


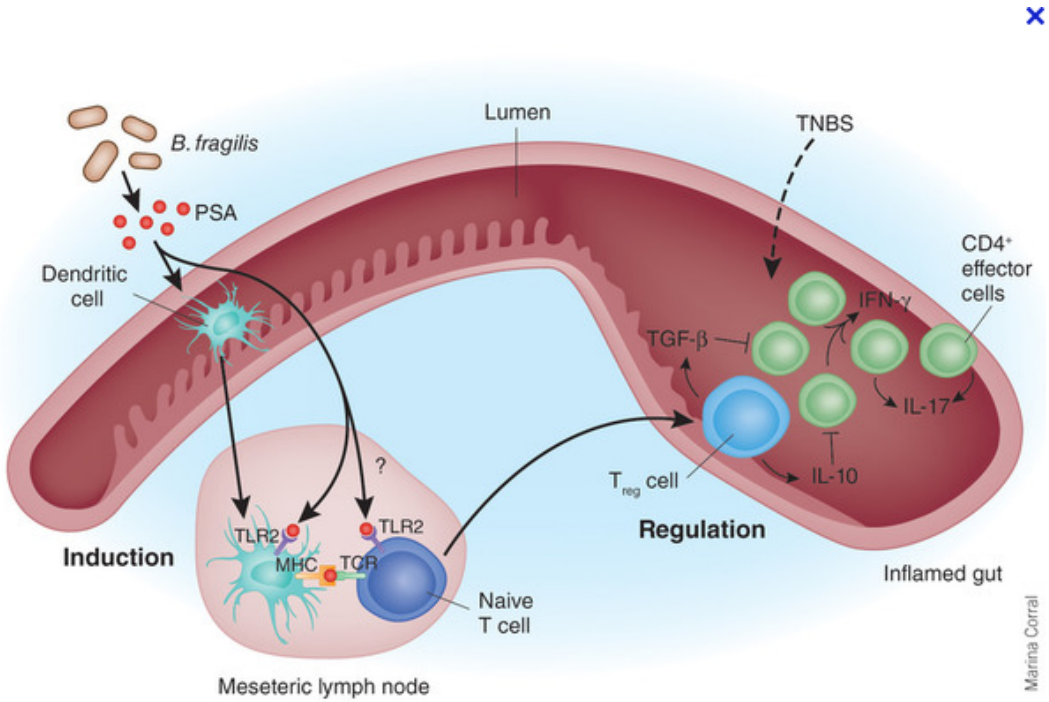




Bacteroides fragilis et le PSA



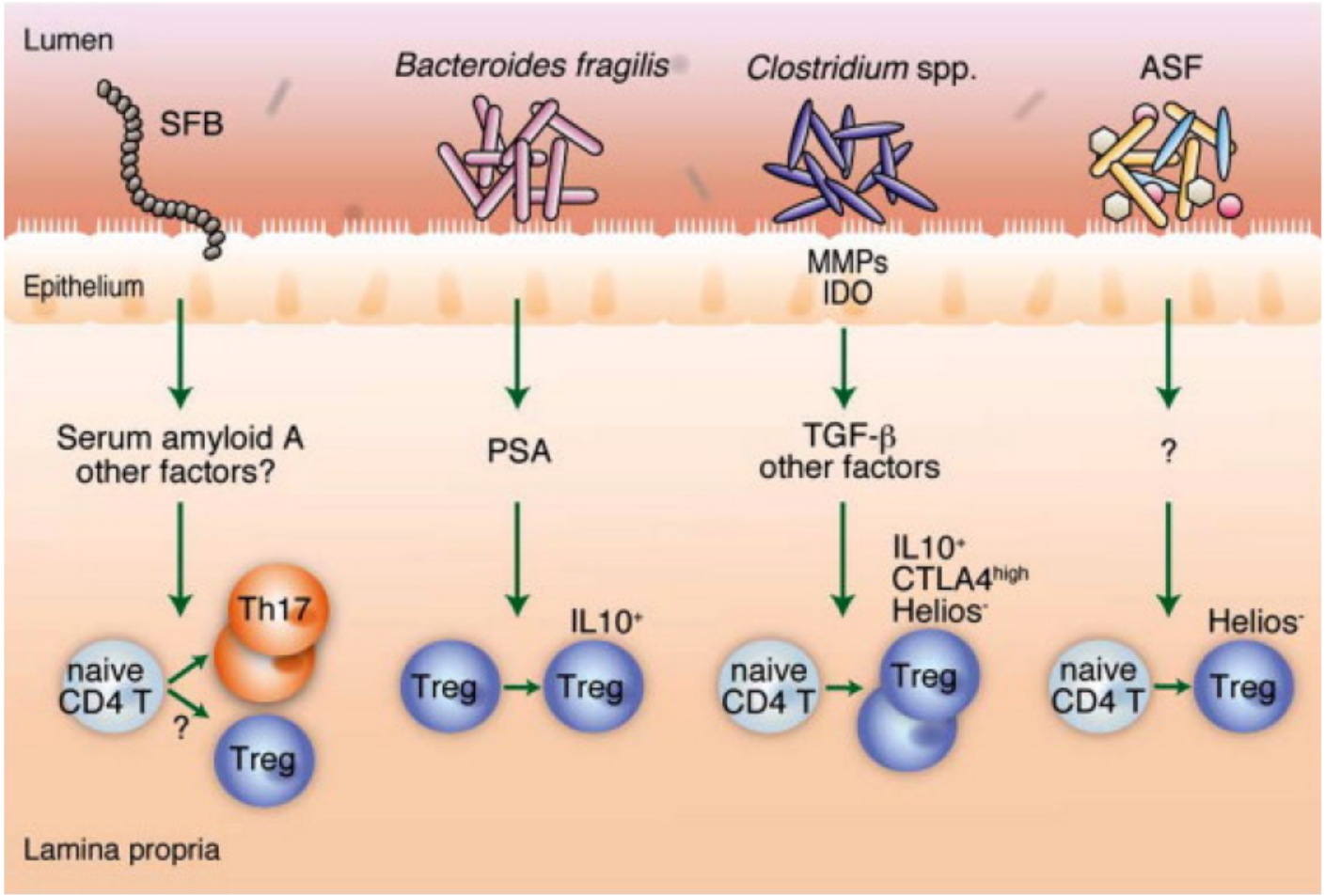




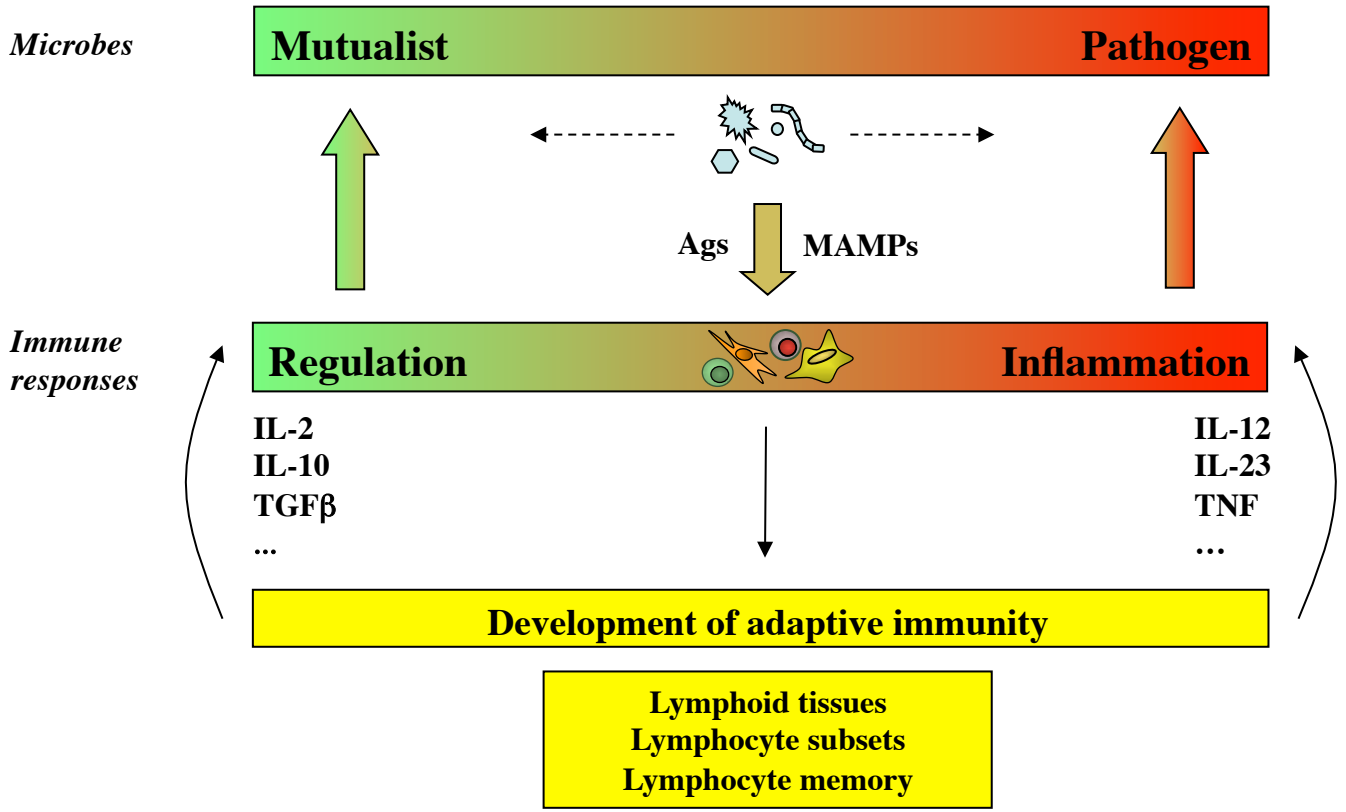
Sarkis Mazmanian (CalTech)

Induction of Treg cells in the mouse colonic mucosa: A central mechanism to maintain host–microbiota homeostasis

Takeshi Tanoue, Kenya Honda



La construction du système immunitaire



G. Eberl, Mucosal Immunol 2010

Redefining Chronic Viral Infection

Herbert W. Virgin,[1,*] E. John Wherry,[2,*] and Rafi Ahmed[3,*]
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[2]Immunology Program, The Wistar Institute, Philadelphia, PA 19104, USA
[3]Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA

Cell 2009

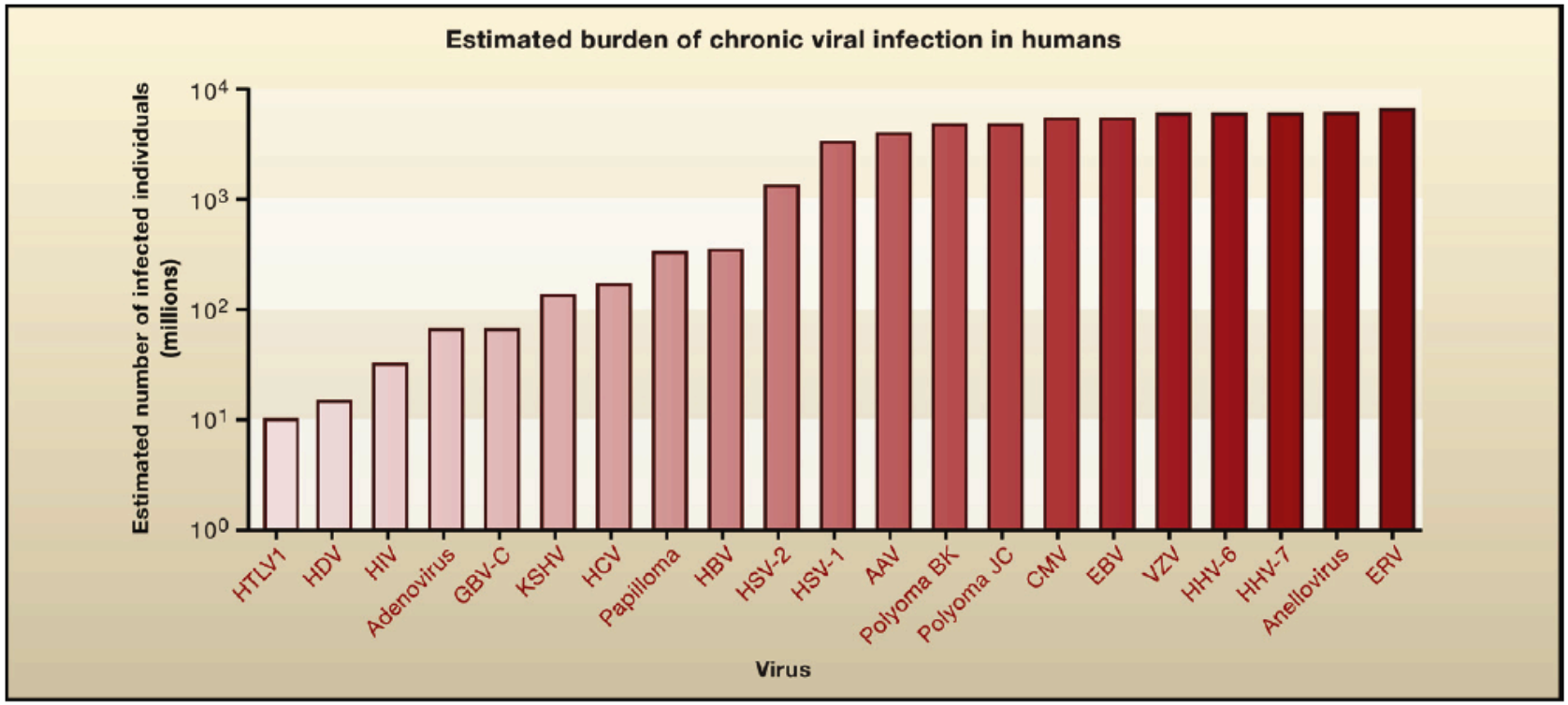
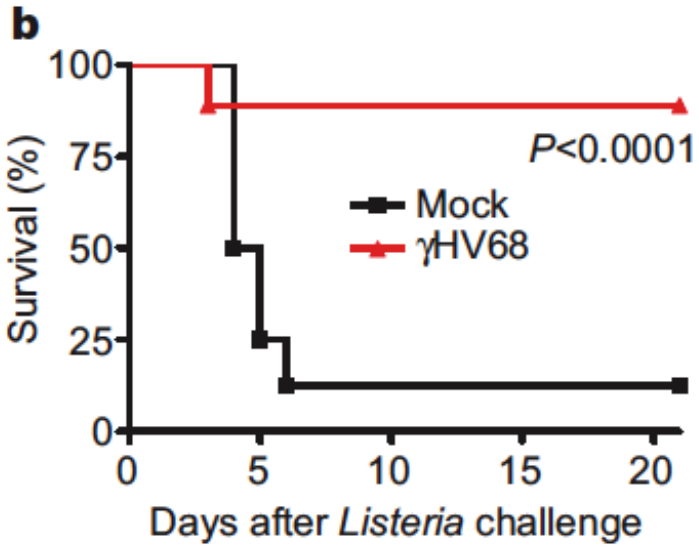


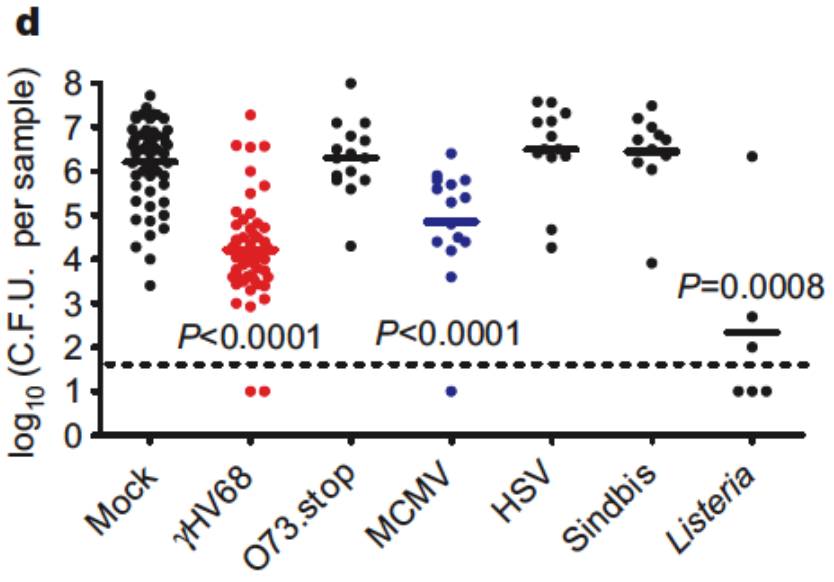
Figure 2. Chronic Viral Infections in Humans

Herpesvirus latency confers symbiotic protection from bacterial infection

Erik S. Barton[1]†, Douglas W. White[1,5], Jason S. Cathelyn[2], Kelly A. Brett-McClellan[1], Michael Engle[3], Michael S. Diamond[1,2,3], Virginia L. Miller[2,4] & Herbert W. Virgin IV[1,2]

Nature 2007





Ilya Illitch Metchnikof (1845-1916) et les probiotics