

Pattern Recognition Receptors : From Discovery To Therapeutic Applications

Bruno Lemaitre

**Global Health Institute
*Ecole Polytechnique Fédérale de Lausanne***

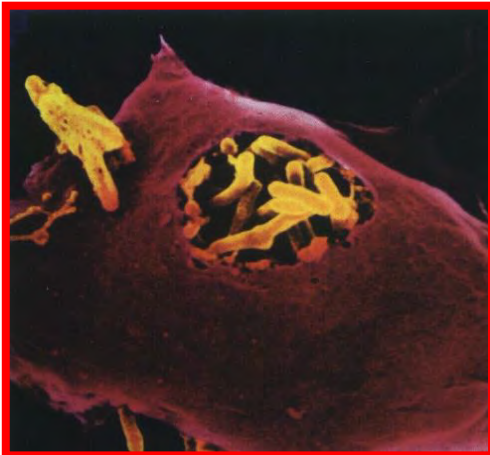
Outlines

- From *Drosophila* to vertebrate: the story of TLR discovery
- Mammalian PRRs
- How discoveries in innate immunity have reshaped our understanding of immune systems

Innate vs Adaptive Immunity

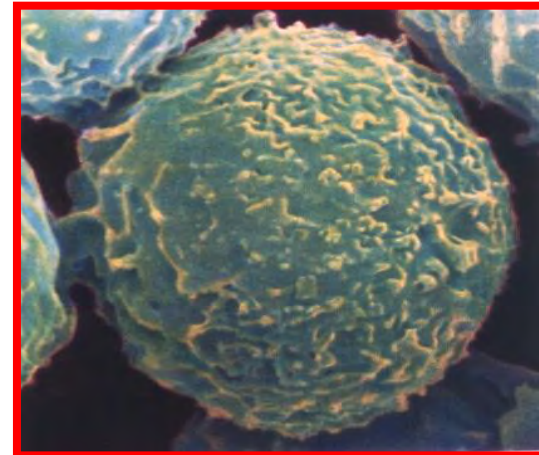
Innate Immunity

- Conserved throughout evolution
- Immediately active
- **No memory, no specificity**
- Phagocytosis, Natural Killer cells, antimicrobial peptides, Complement system ...

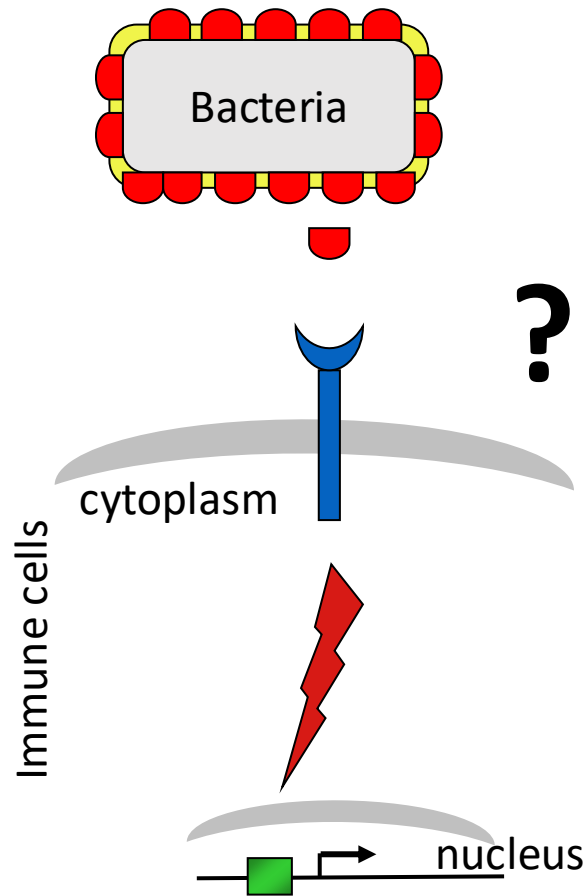


Adaptive Immunity

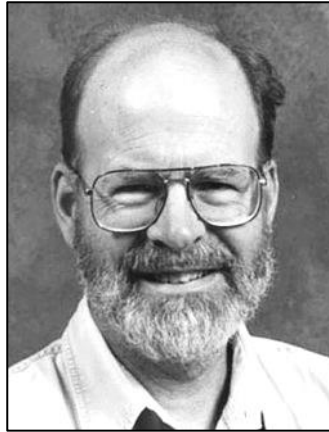
- Unique to vertebrates
- Antigen receptors by rearrangements of somatic genes
- Memory and specificity



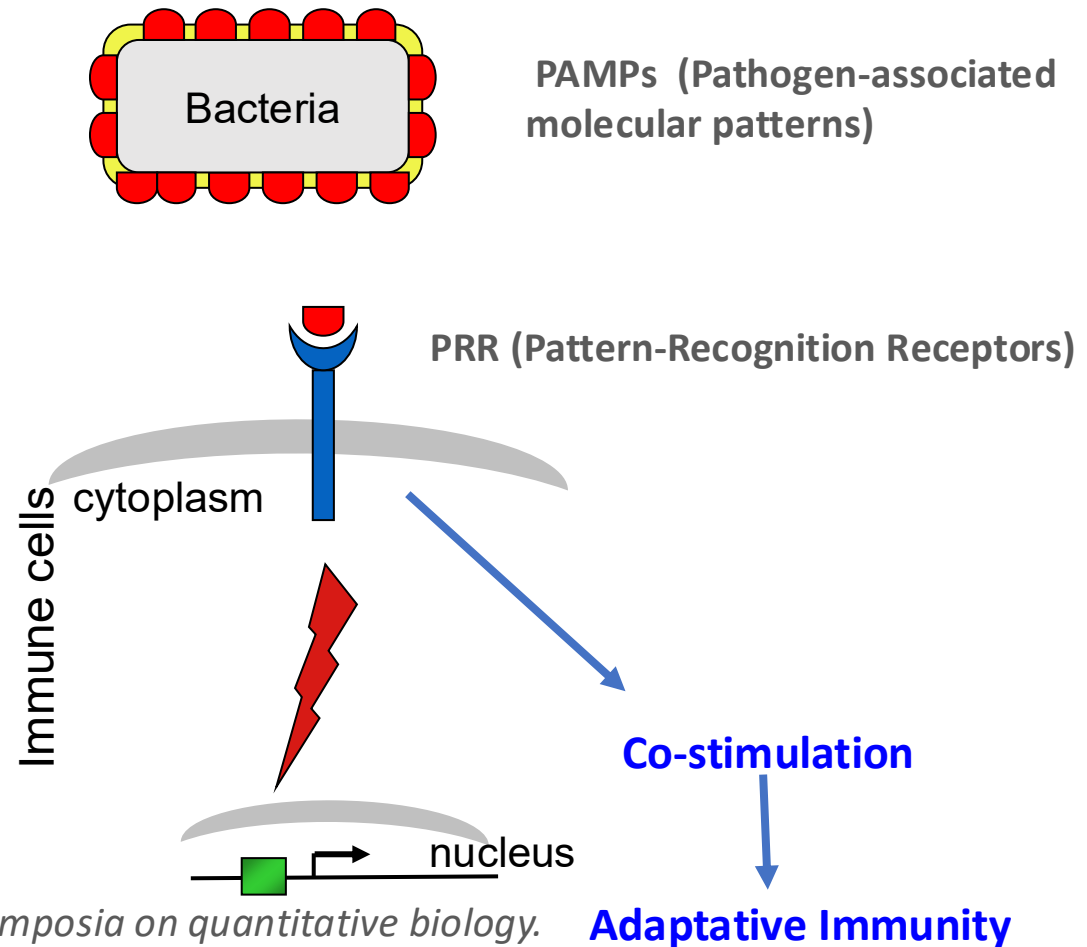
How do animals and plants recognize infectious agents?



The concept of Pattern-recognition receptor (Janeway 1989)



Charles Janeway
(1943-2003)



Janeway. (1989). In *Cold Spring Harbor symposia on quantitative biology*.
Medzhitov & Janeway. (1997). *Cell*.

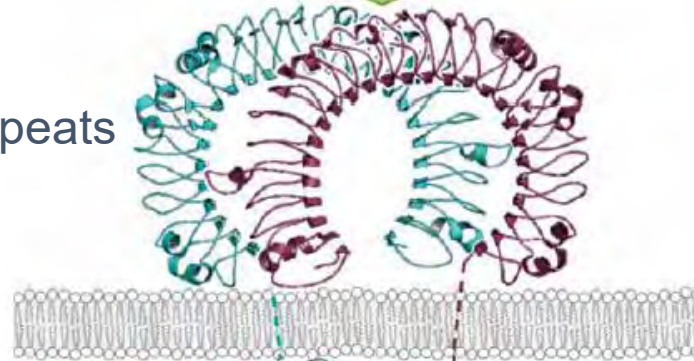
The road to Toll: 1995-2002

Microbial elicitors (LPS, dsRNA, lipoproteins...)



Extracellular

LRR: Leucin-Rich-Repeats



TIR : Toll/IL1R domain

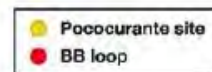
Receptor TIR



Intracellular



Adapter TIR

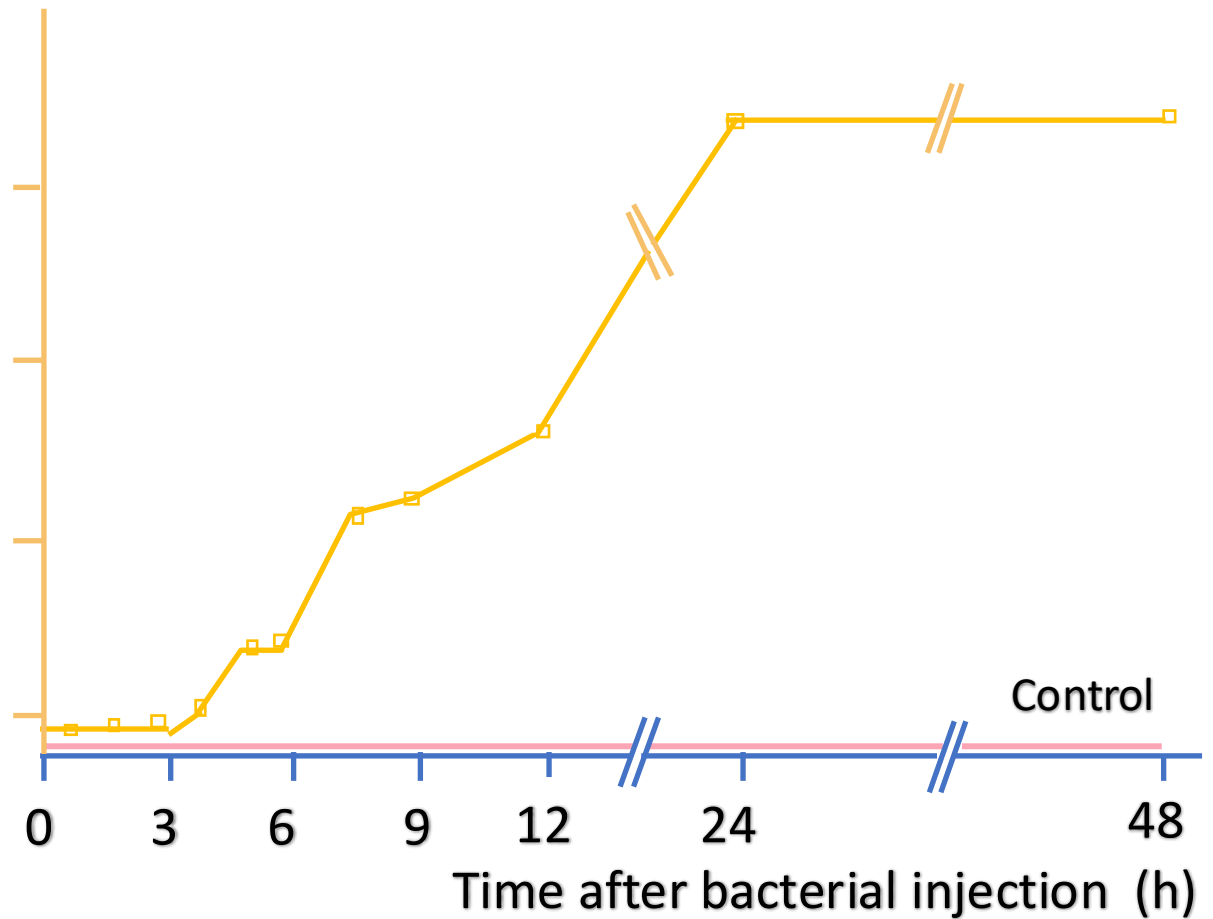


Activation of immune genes

1980-81: the discovery of antimicrobial peptides



Antimicrobial activity

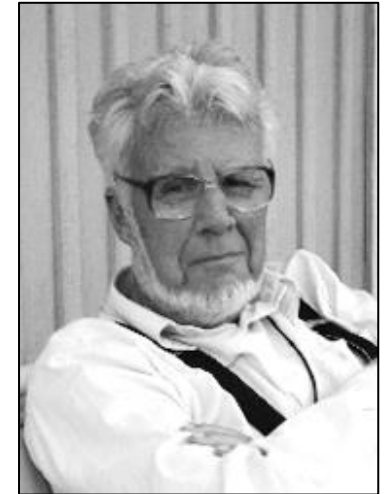


Coomassie

Bacterial overlay



Antimicrobial peptides



Hans G. Boman

(1924-2008)

with

Dan Hulmark

Ingrid Faye

Hakan Steiner

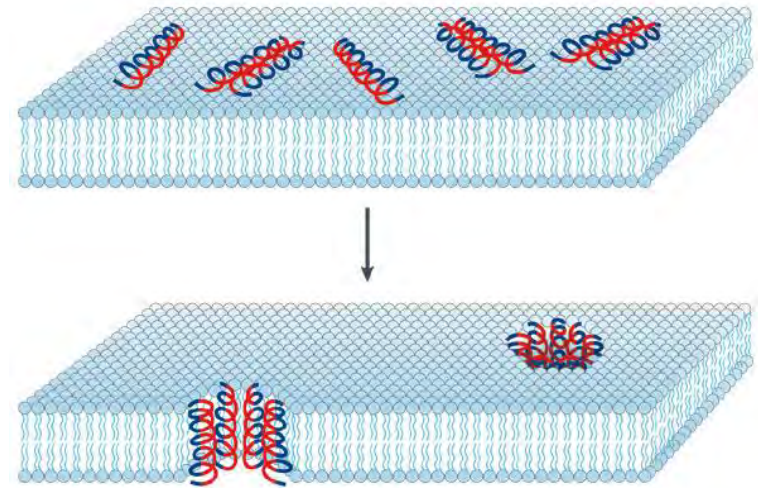
1981: insect cecropins from insect hemolymph [Steiner et al. (1981). *Nature*.]

1980-1984: vertebrate defensins from phagocytic cells [Lehrer et al. (1993). *Annual review of immunology*.]

Common structural features of antimicrobial peptides

AMPs are

- Short (12-50 amino acid)
- Positively charged (+2 - +9)
- Amphipathic structure



Nature Reviews | Microbiology

Mode(s) of action

- Disruption of membrane integrity
- *But some have specific targets*



Detergents are amphipathic

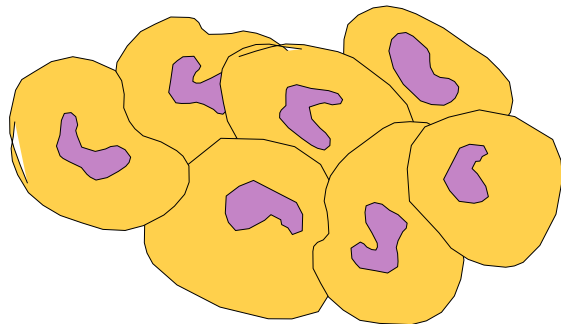
The systemic antimicrobial response of *Drosophila*



septic injury



Massive production of antimicrobial peptides by the fat body



Drosomycin

1994



Fungi

Metchnikowin

1995



Gram-positive bacteria

Defensin

1994



Cecropins

1990



Drosocin

1993



Gram-negative bacteria

Attacins

1995



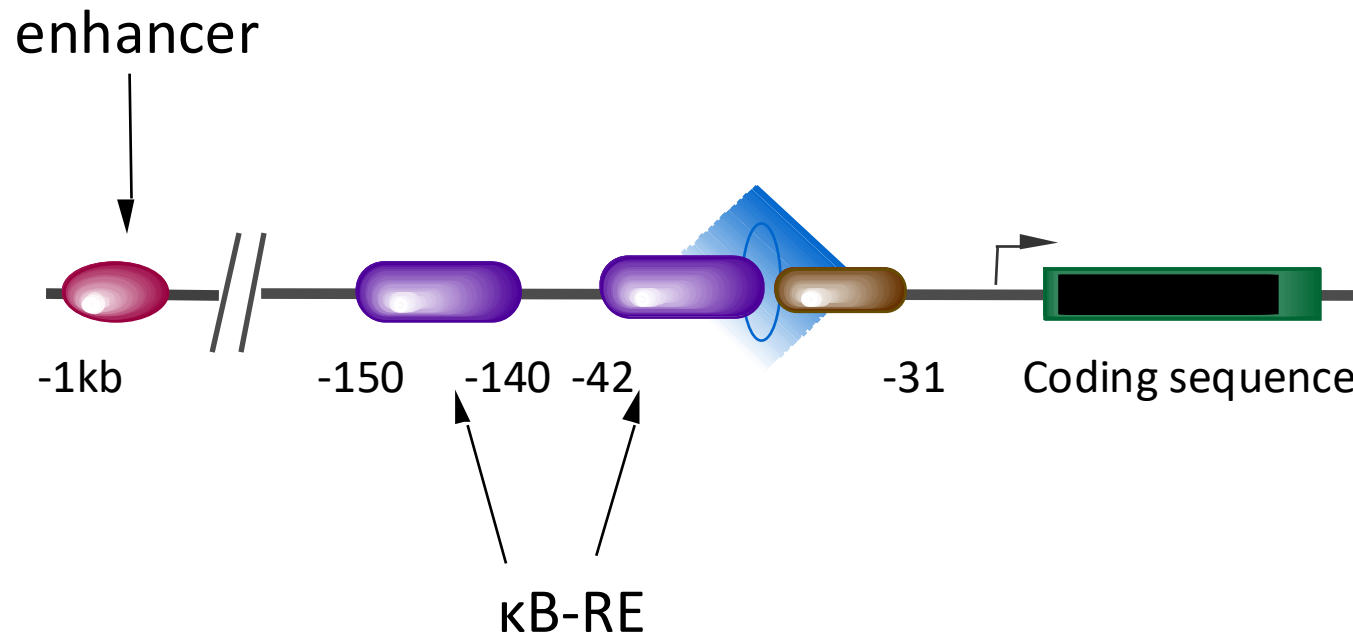
Diptericins

1990



What regulates the expression of antimicrobial peptides upon infection ?

Organization of the AMP gene promoter (*e.g. Diptericin*)



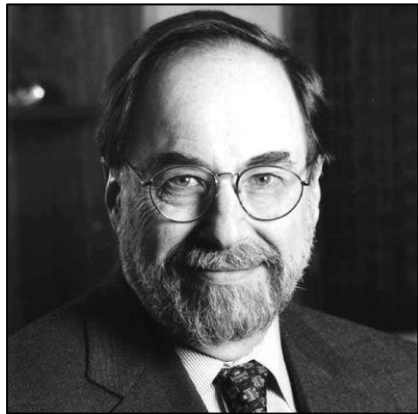
Sun, Asling, & Faye. (1991). *Journal of Biological Chemistry*.

Kappler et al. (1993). *The EMBO journal*.

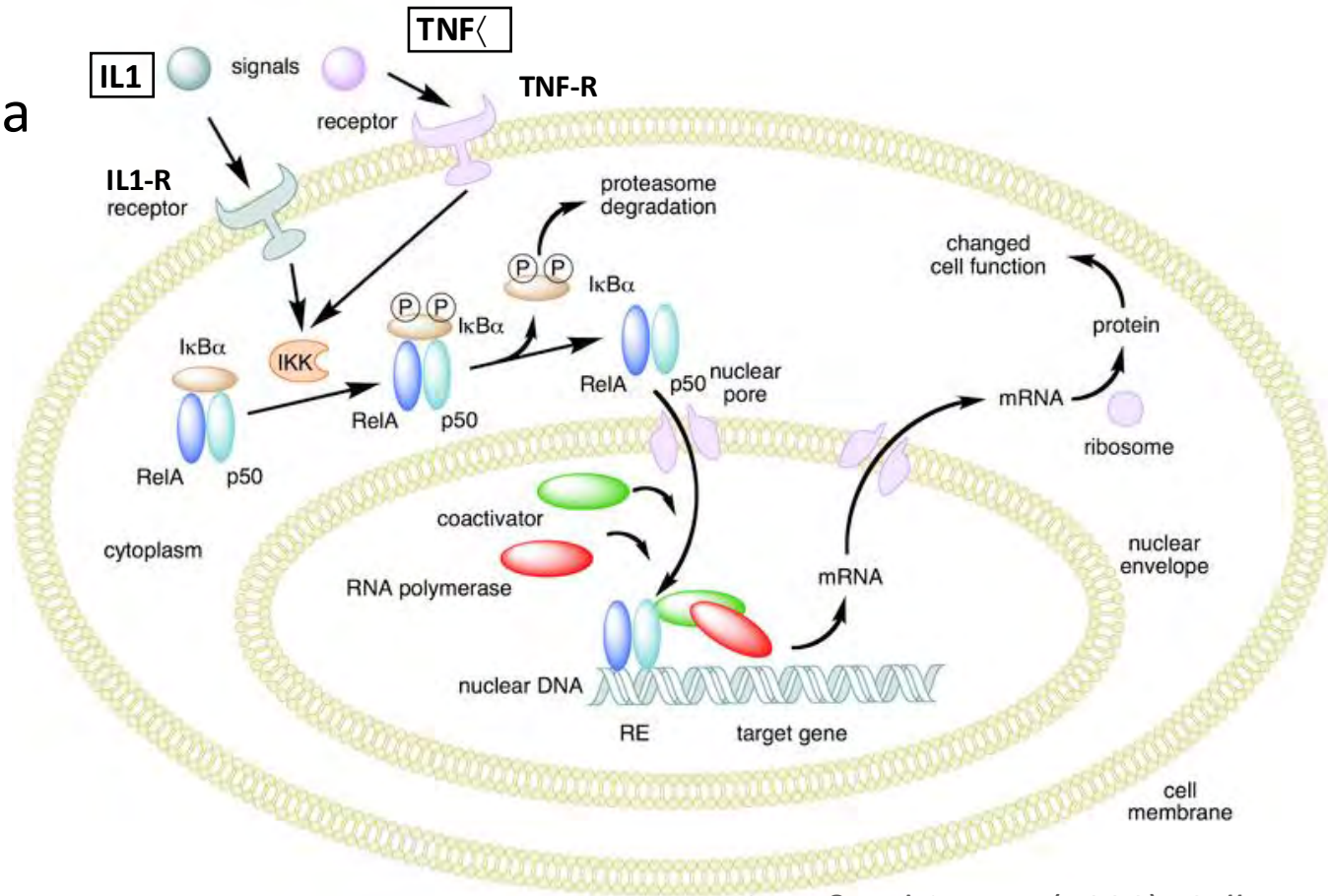
Engström et al. (1993). *Journal of Biological Chemistry*.

The transcription factors NF- κ B

- Discovered in 1986
- Cloned in 1990
- Activated by IL1 and TNF- α
- Regulate many inflammatory genes

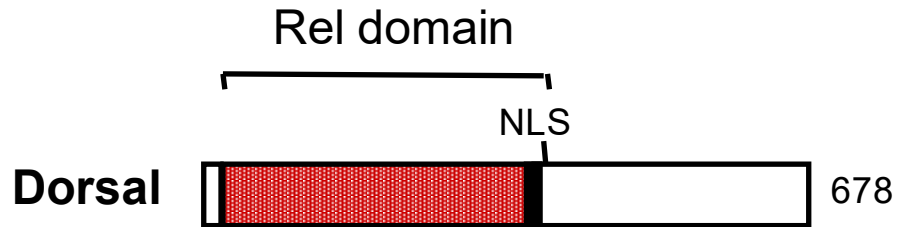


David Baltimore
(1938-2025)



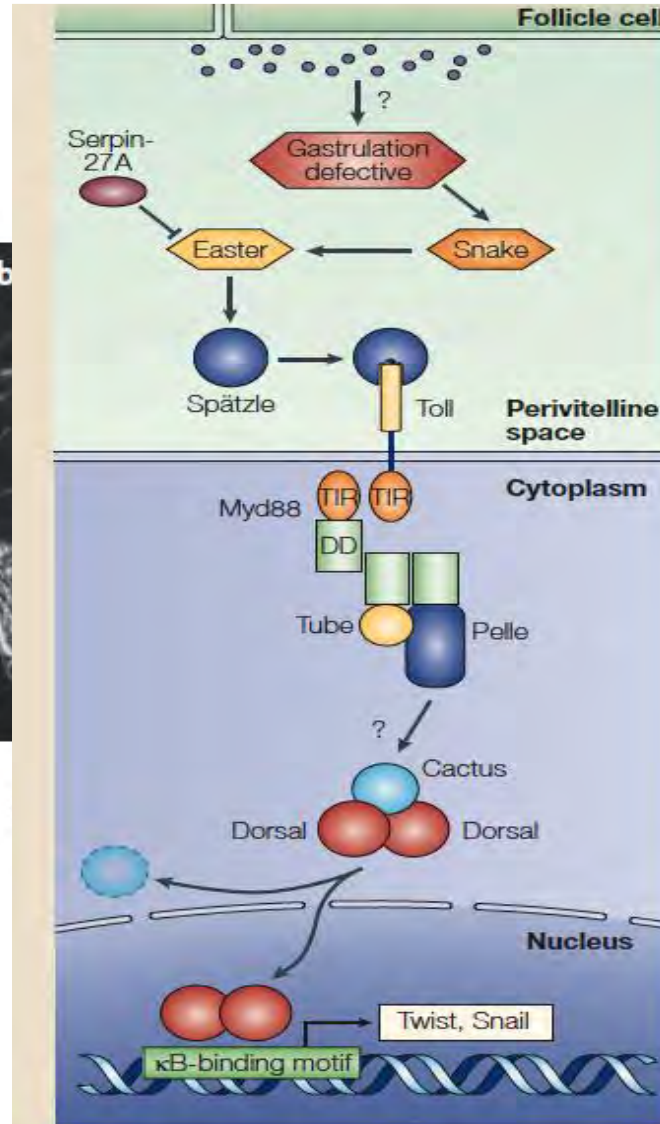
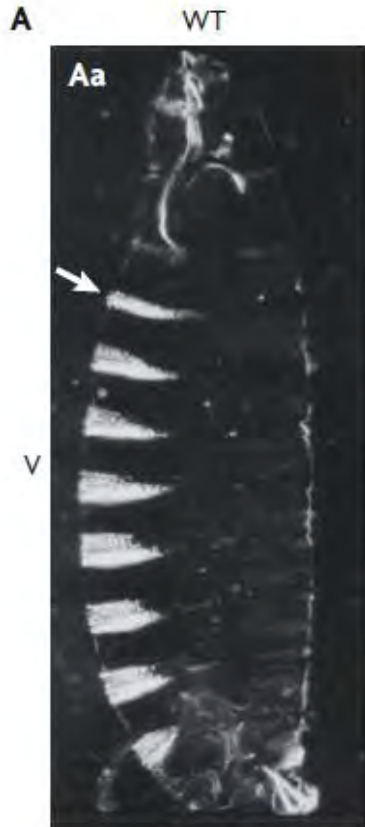
Sen, & Baltimore. (1986). *Cell*.
Ghosh et al. (1990). *Cell*.
Kieran et al. (1990). *Cell*.

Drosophila Rel/NF- κ B and I κ B proteins

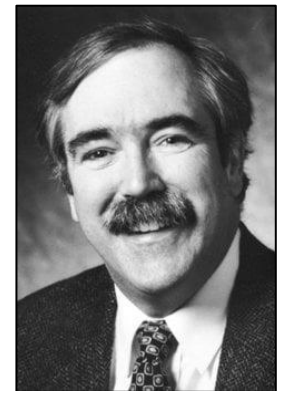


Nüsslein-Volhard. (1979). In *Determinants of Spatial Organisation*. Steward. (1987). *Science*.

The Toll pathway in *Drosophila* development



Christiane
Nüsslein-
Volhard



Eric F.
Wieschaus



Kathryn V.
Anderson
(1952-2020)

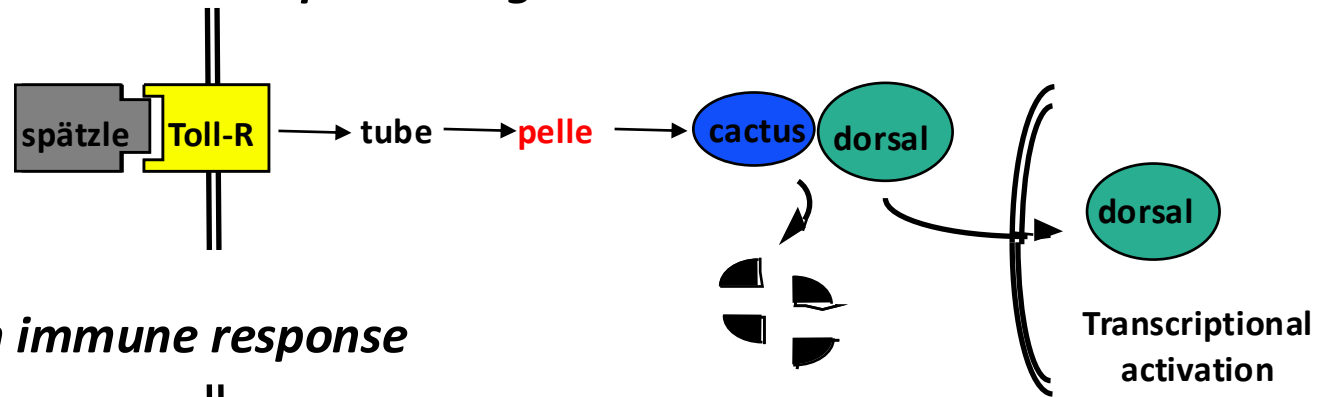
Anderson, K. V. & Nusslein-Volhard, 1984

Anderson, K. V., et al., *Cell* **1985**

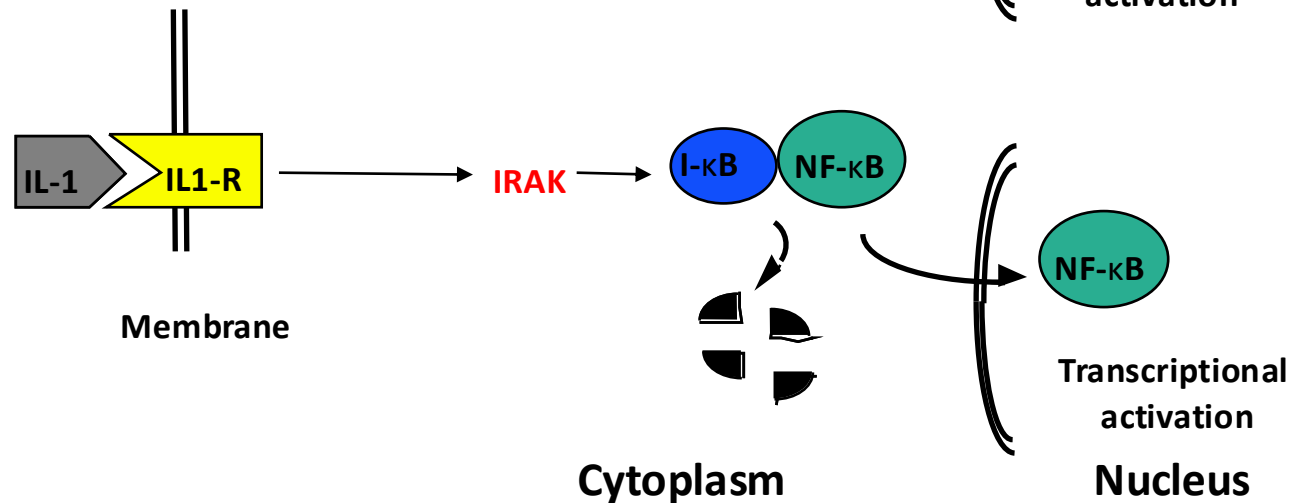
Hashimoto, et al., *Cell* **1988**

Conserved signaling pathways control Dorsal and NF-κB nuclear translocation

Drosophila dorso-ventral patterning



Mammalian immune response



Gay, & Keith. (1991). *Nature*.

Schneider et al. (1991). *Genes & development*.

**Searching for an immune function of the
Drosophila Toll:
from premise to demonstration**

Tübingen, 15.1.93

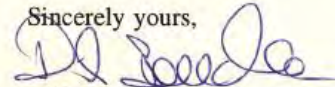
Dear Dr. Bruno Lemaitre

We are sending the stocks you requested:

our internal number	mutant allele	markers	balancer	remarks
M351	rch st e	TL ^{1-2x4}	ITM3.Sor	
M371	b st e	TL ⁷⁴⁴⁴	ITM3	
M701	b dl ⁰¹¹	pr	1Cy0	
M707	f b cact ⁰²⁶	an	1Cy0	
M713	f b cact ⁰¹³	pr	1Cy0	
M714	f b cact ⁰¹¹	pr	1Cy0	
M717	f b cact ⁴²	an	1Cy0	
M720	f b cact ⁴⁸	an bw	1Cy0	
M320	st ea ² e		ITM8	(still balanced?)
M369	f sp2 ⁶⁷	ca	ITM1	
M384	b st tu ²³⁸ e	TL ^{302E1}	ca ITM3,SS	(still balanced?)
M801	b st ea ⁸⁴ e		ITM3,SS	
M330	f e TL ^{40RE}	ca	ITM3	

In case they do not arrive in good shape, please let us know and we will send them again.

Sincerely yours,



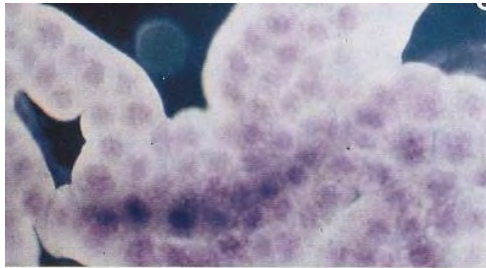
Dirk Beuchle
Stock keeper

P.S. I am sorry but we lost K305; M268 and M271

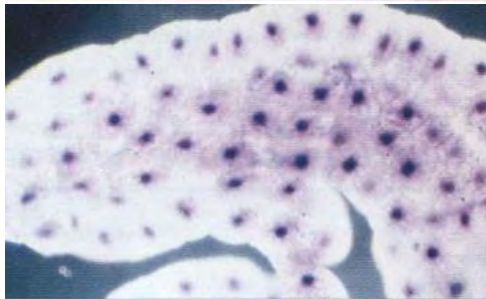
Fostering discovery: the
Drosophila community's
ethos of sharing

1993-1995: No overt role of Toll pathway in *Drosophila* immunity

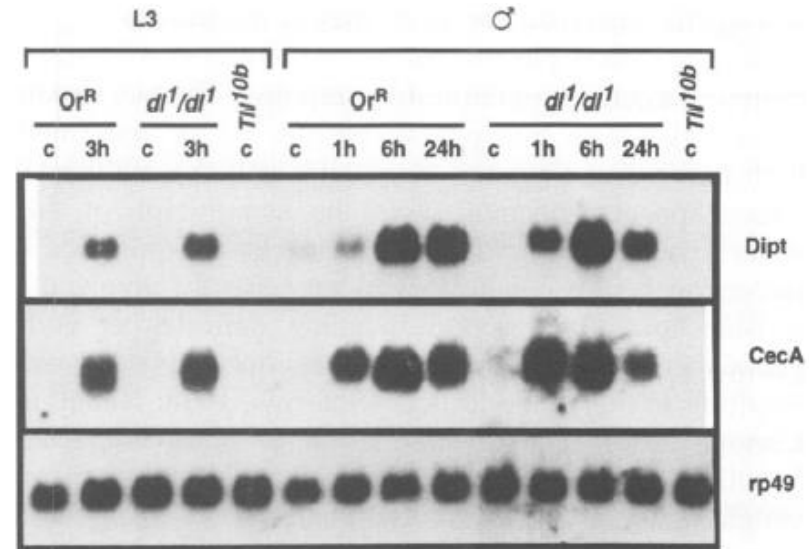
Control



Infected



But wild-type levels of induction of *Diptericin* in *dl1* mutant



272 P.S.

THE GENOME OF
Drosophila melanogaster

Bc: Black cells

location: 2-80.6.
origin: Induced by ethyl methanesulfonate.
references: Grell, 1969, DIS 44: 46.
Rizki, Rizki, and Grell, 1980, Wilhelm Roux's Arch.
Dev. Biol. 188: 91-99 (fig.).
phenotype: Quadrate crystalline bodies in crystal cells of
hemolymph replaced by amorphous melanotic mass.
Black cells appear in 11-hour embryos in Bc/B₁ and in

laced by
us black
pae, and
le larvae
nolymph
mediate
le adults
ly linked
: RK2 in



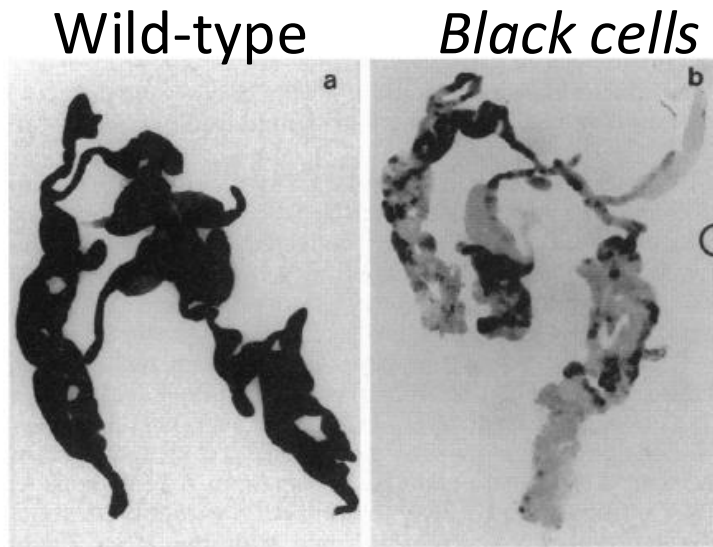
Black cells

(313)764-1492

maintaining
hemocyte
differences.
the photographs
are a manuscript
on observations

J. M. T. Lili

1994: serendipitous discovery of the first immune deficiency mutation (*Black cells*)



Diptericin-LacZ expression
6h post infection

17/1/94 10730 → 14420 Lab book: 17/1/1994

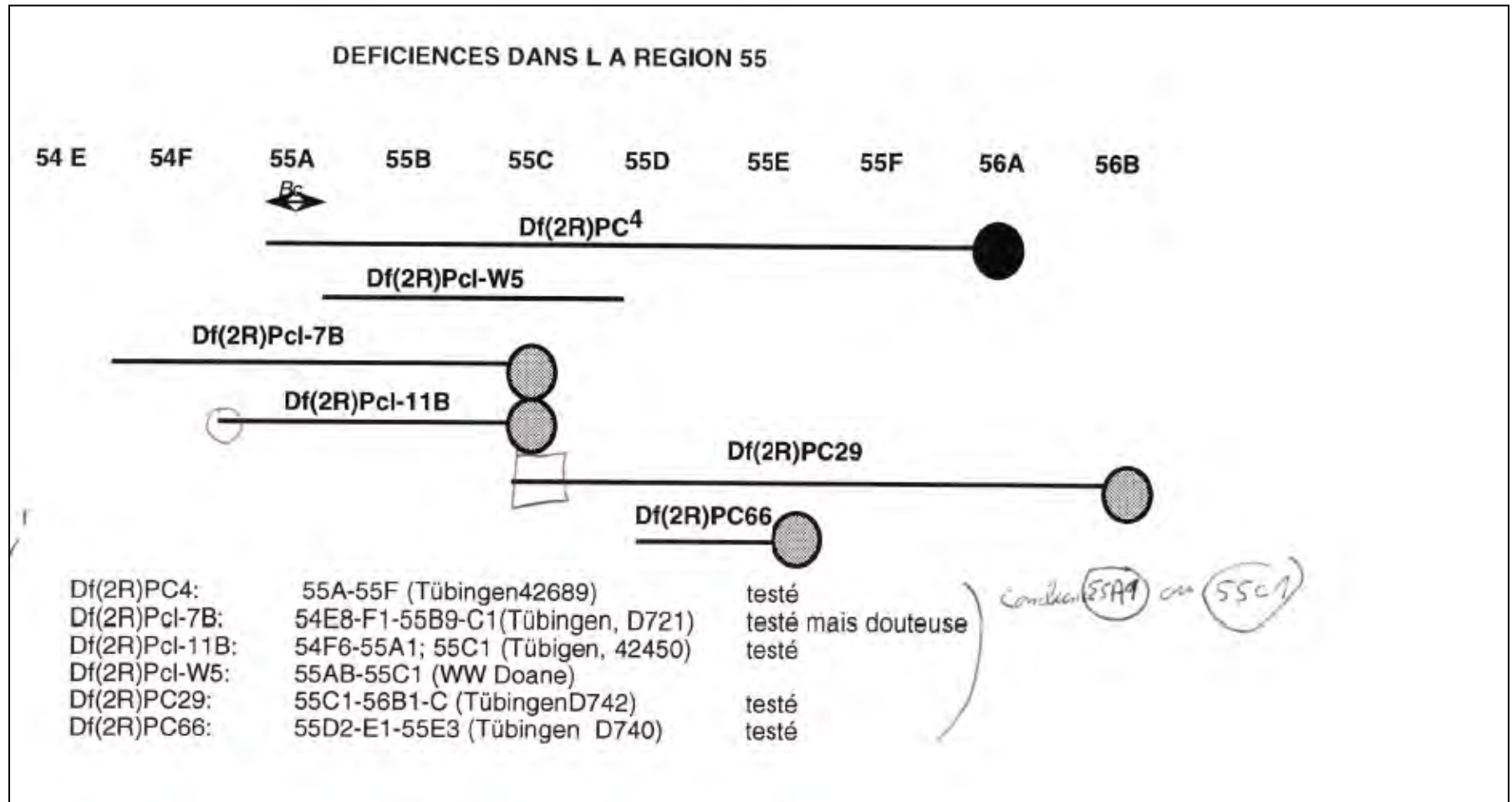
L3 piqne' 45 BT
 1 dpt¹ Bcl/Bc
 4 dpt¹ out
 5 dpt¹

W = 37°C at 7/4. OK

cdall piqne' 75
 dpt¹/Bc
 6pi¹/Bc
 dpt

Blae ←
 Bla
 Bla.

1994: “*imd*” is not “Black cells”



1994: “Two” pathways regulates antimicrobial peptides



Lydia Michaut

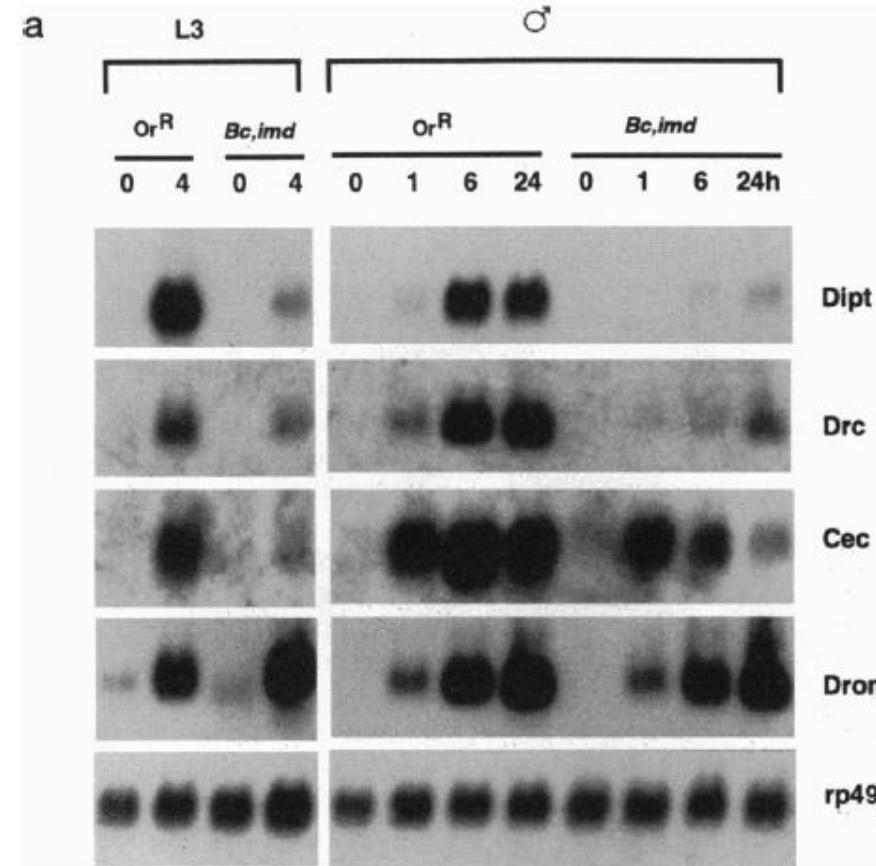
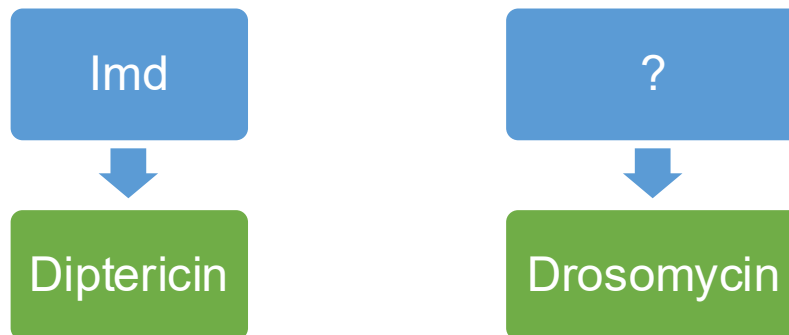
Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 9465–9469, October 1995
Genetics

A recessive mutation, immune deficiency (*imd*), defines two distinct control pathways in the *Drosophila* host defense

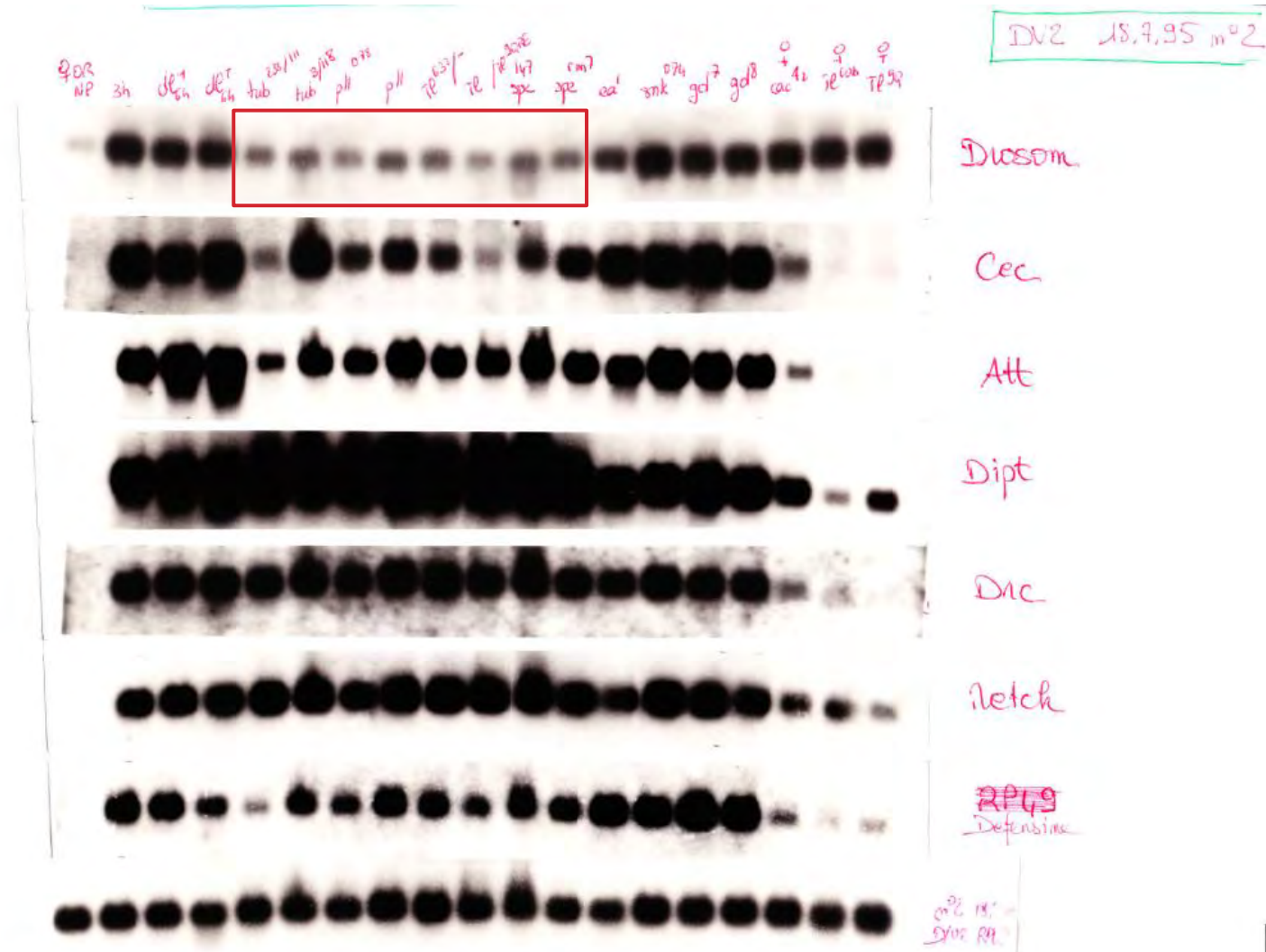
(antibacterial peptides/antifungal peptides/insect immunity)

BRUNO LEMAITRE*, ELISABETH KROMER-METZGER, LYDIA MICHAUT, EMMANUELLE NICOLAS, MARIE MEISTER, PHILIPPE GEORGEL, JEAN-MARC REICHHART, AND JULES A. HOFFMANN

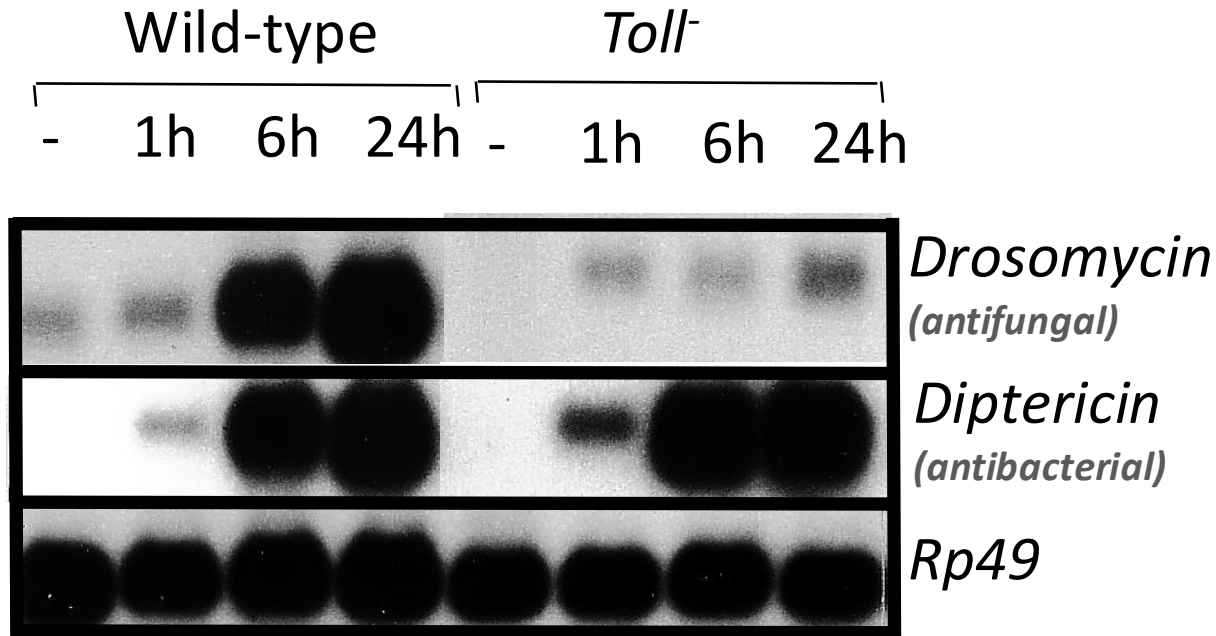
Institut de Biologie Moléculaire et Cellulaire, Unité Propre de Recherche 9022 du Centre National de la Recherche Scientifique, 15 rue René Descartes–67084, Strasbourg Cedex, France



July 1995: checking induction of AMP genes in *Toll* deficient mutants

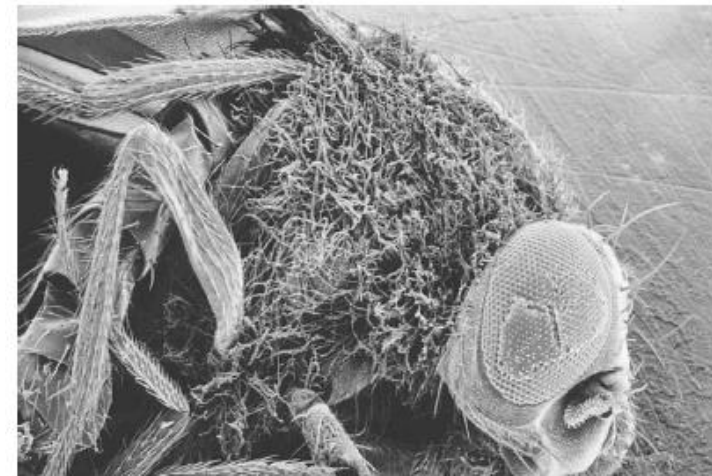


Toll regulates the *Drosophila* antifungal response



- : control

h : hours after infection



Susceptibility of *Toll* deficient mutants

The Dorsoventral Regulatory Gene Cassette *spätzle/Toll/cactus* Controls the Potent Antifungal Response in *Drosophila* Adults

Bruno Lemaitre, Emmanuelle Nicolas, Lydia Michaut,
Jean-Marc Reichhart, and Jules A. Hoffmann
Institut de Biologie Moléculaire et Cellulaire
UPR 9022 du Centre National de la Recherche
Scientifique
15 rue René Descartes
67084 Strasbourg Cedex
France



Lydia Michaut



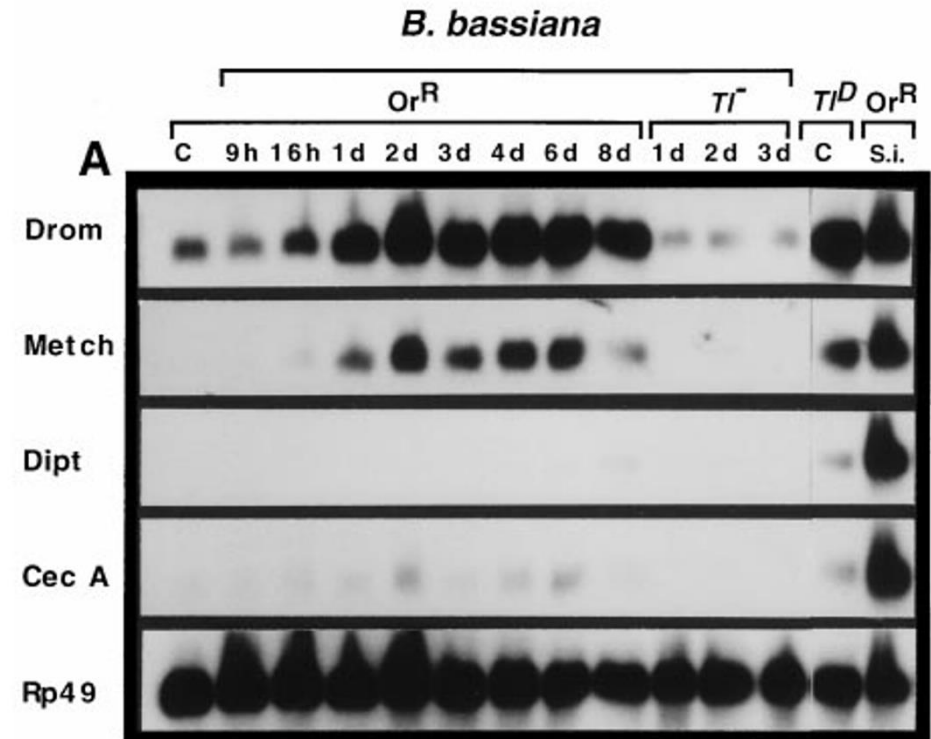
Why two pathways? Specificity of innate immune responses

Mixture of Gram-negative bacteria (*E. coli*) and Gram-positive bacteria (*M. luteus*)



Drosophila immune responses are adapted to the pathogen:

Natural infection by *B. bassiana*



Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 14614–14619, December 1997
Immunology

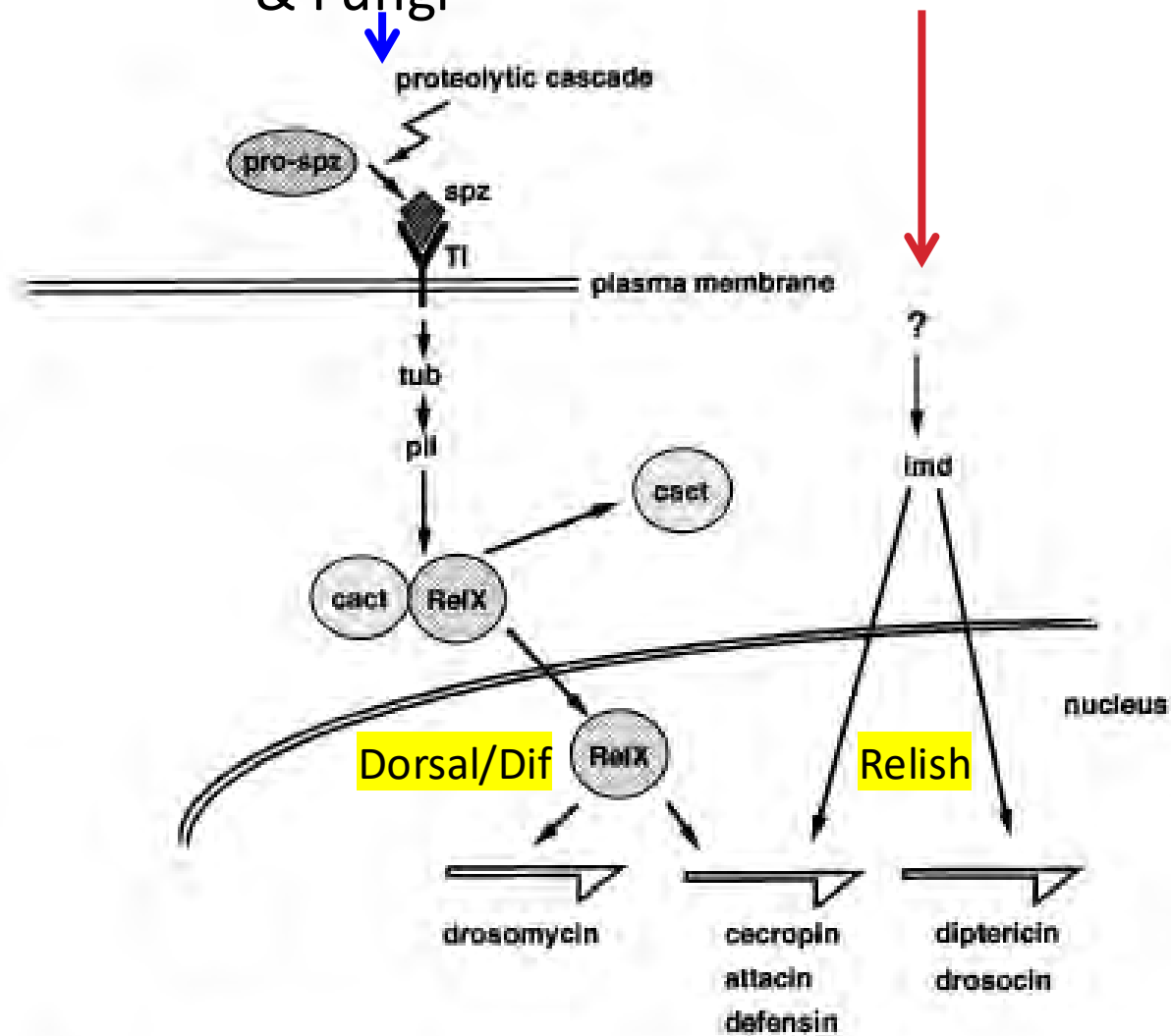
Drosophila host defense: Differential induction of antimicrobial peptide genes after infection by various classes of microorganisms

BRUNO LEMAITRE, JEAN-MARC REICHHART, AND JULES A. HOFFMANN*

Institut de Biologie Moléculaire et Cellulaire, Unité Propre de Recherche 9022 du Centre National de la Recherche Scientifique, 15 rue René Descartes, 67084 Strasbourg Cedex, France

Gram-positive bacteria & Fungi

Gram-negative bacteria



Lemaitre et al. (1995). *Proceedings of the national academy of sciences*.

Lemaitre et al. (1996). *Cell*.

Lemaitre et al. (1995). *Proceedings of the national academy of sciences*.

Hendegren et al. (1999). *Molecular cell*.

Manfruelli et al. (1999). *The EMBO journal*.

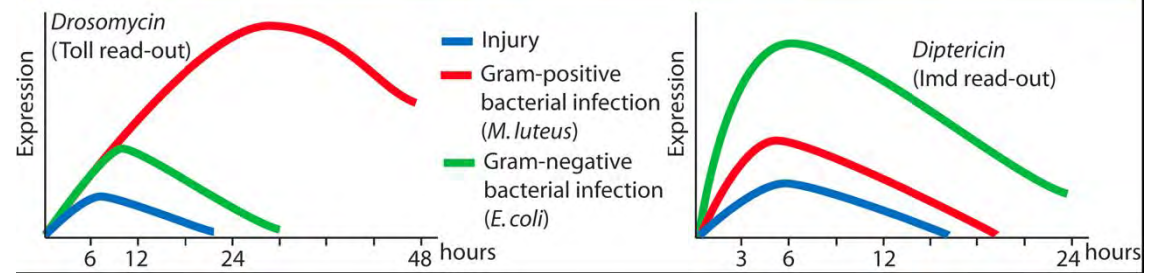
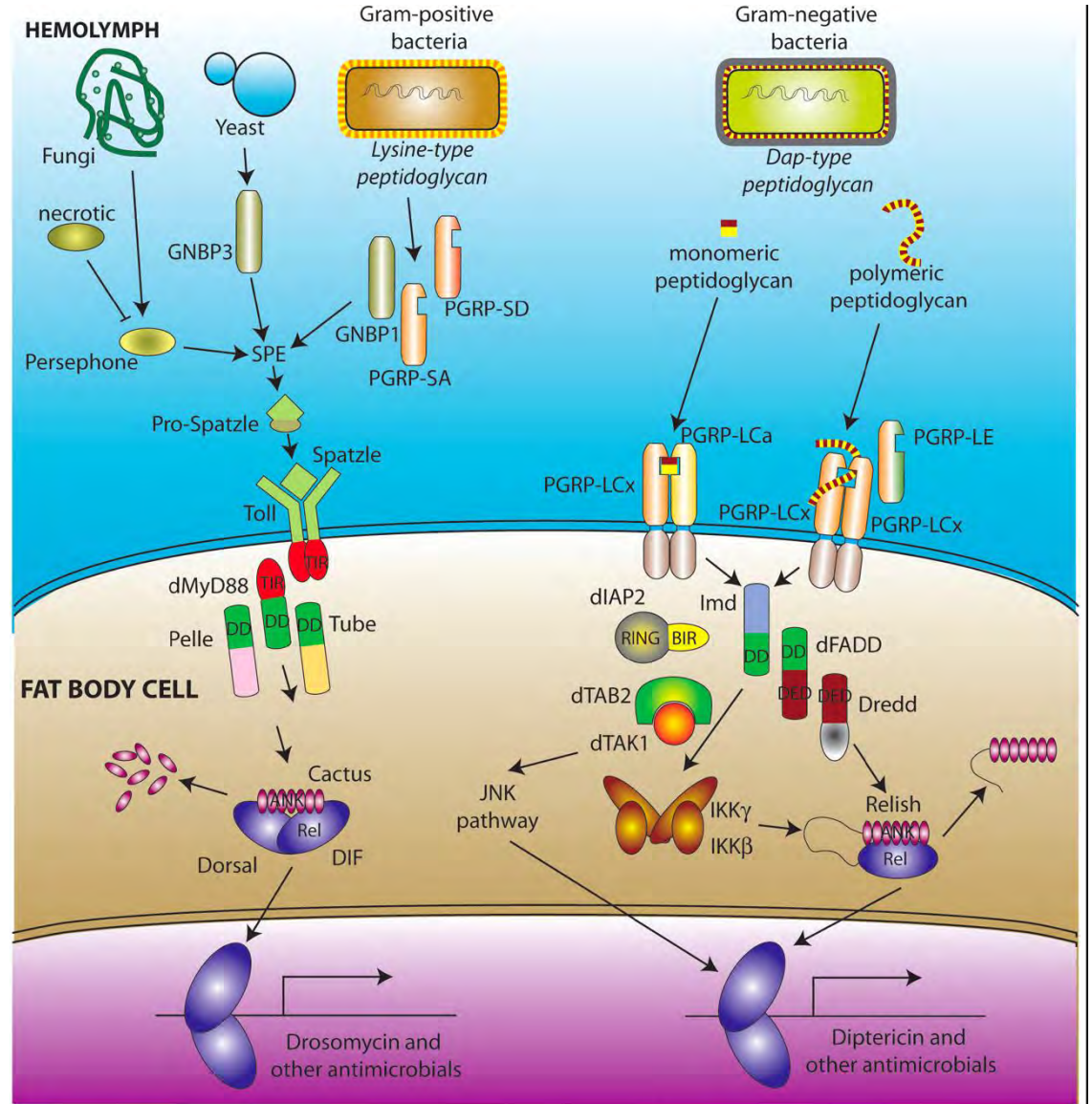
Meng et al. (1999). *Genes & development*.

Rutschmann et al. (2000). *Immunity*.

Leulier et al. (2000). *EMBO reports*.

The Toll and Imd pathways:

a paradigm of innate immunity

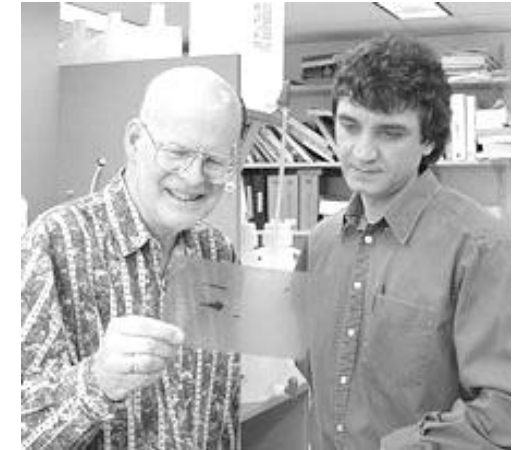
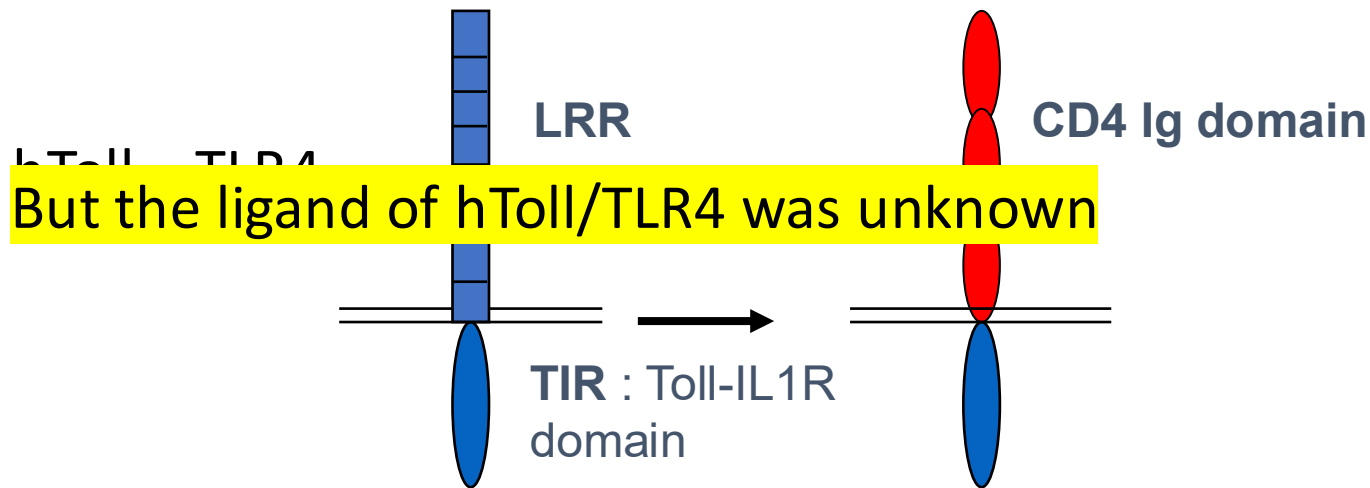


**1997-1999: the mammalian chapter of the
TLR story**

July 1997

A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity

Ruslan Medzhitov*, Paula Preston-Hurlburt & Charles A. Janeway Jr*

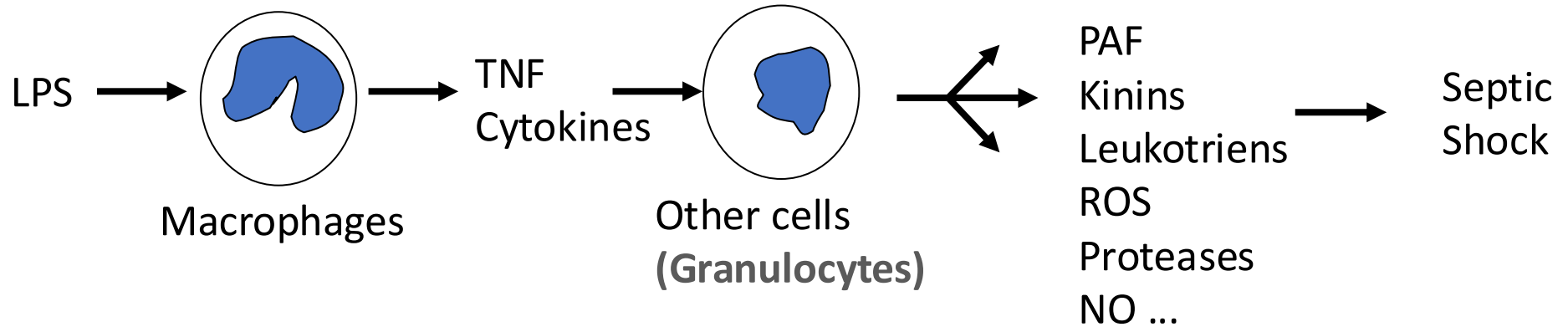


Charles Janeway
Ruslan Medzhitov

Cells expressing a chimeric construct CD4-hTOLL induce the expression of genes encoding IL-1, IL-8, B7.1 via NF-kB

- Conservation of Toll/NF-kB pathway in immunity
- Role of Toll in the activation of adaptative immune response

Mapping of the mouse LPS locus by reverse genetics



- Mouse *lps* locus (1977-79)
- Higher susceptibility to Gram-negative bacterial infection
 - Higher resistance to endotoxin (LPS)

Several groups were involved in the mapping of the *Lps* gene



**Bruce
Beutler**



**Stephanie
Vogel**



**Danielle
Malo**

Defective LPS Signaling in C3H/HeJ and C57BL/10ScCr Mice: Mutations in *Tlr4* Gene

Alexander Poltorak, Xiaolong He,* Irina Smirnova, Mu-Ya Liu,†
Christophe Van Huffel,‡ Xin Du, Dale Birdwell, Erica Alejos,
Maria Silva, Chris Galanos, Marina Freudenberg,
Paola Ricciardi-Castagnoli, Betsy Layton, Bruce Beutler§

Submitted 3 September 1998;
Accepted 3 November 1998;
Published 11 December 1998



Bruce Beutler

Endotoxin-tolerant Mice Have Mutations in Toll-like Receptor 4 (*Tlr4*)

By Salman T. Qureshi,*|| Line Larivière,|| Gary Leveque,||
Sophie Clermont,|| Karen J. Moore,¶ Philippe Gros,‡||
and Danielle Malo*§||

Submitted 25 November 1998;
Accepted 7 December 1998;
Published 15 February 1999



Danielle Malo

April 1999: Knock-out of *TLR4* block the host response to LPS

*The Journal of
Immunology*

BRIEF REPORT | APRIL 01 1999

Cutting Edge: Toll-Like Receptor 4 (TLR4)-Deficient Mice Are Hyporesponsive to Lipopolysaccharide: Evidence for TLR4 as the *Lps* Gene Product¹

Katsuaki Hoshino,^{*†§} Osamu Takeuchi,^{*§}
Taro Kawai,^{*§} Hideki Sanjo,^{*§} Tomohiko Ogawa,[‡]
Yoshifumi Takeda,[†] Kiyoshi Takeda,^{*§} and
Shizuo Akira^{2*§}

Submitted 15 December 1998;

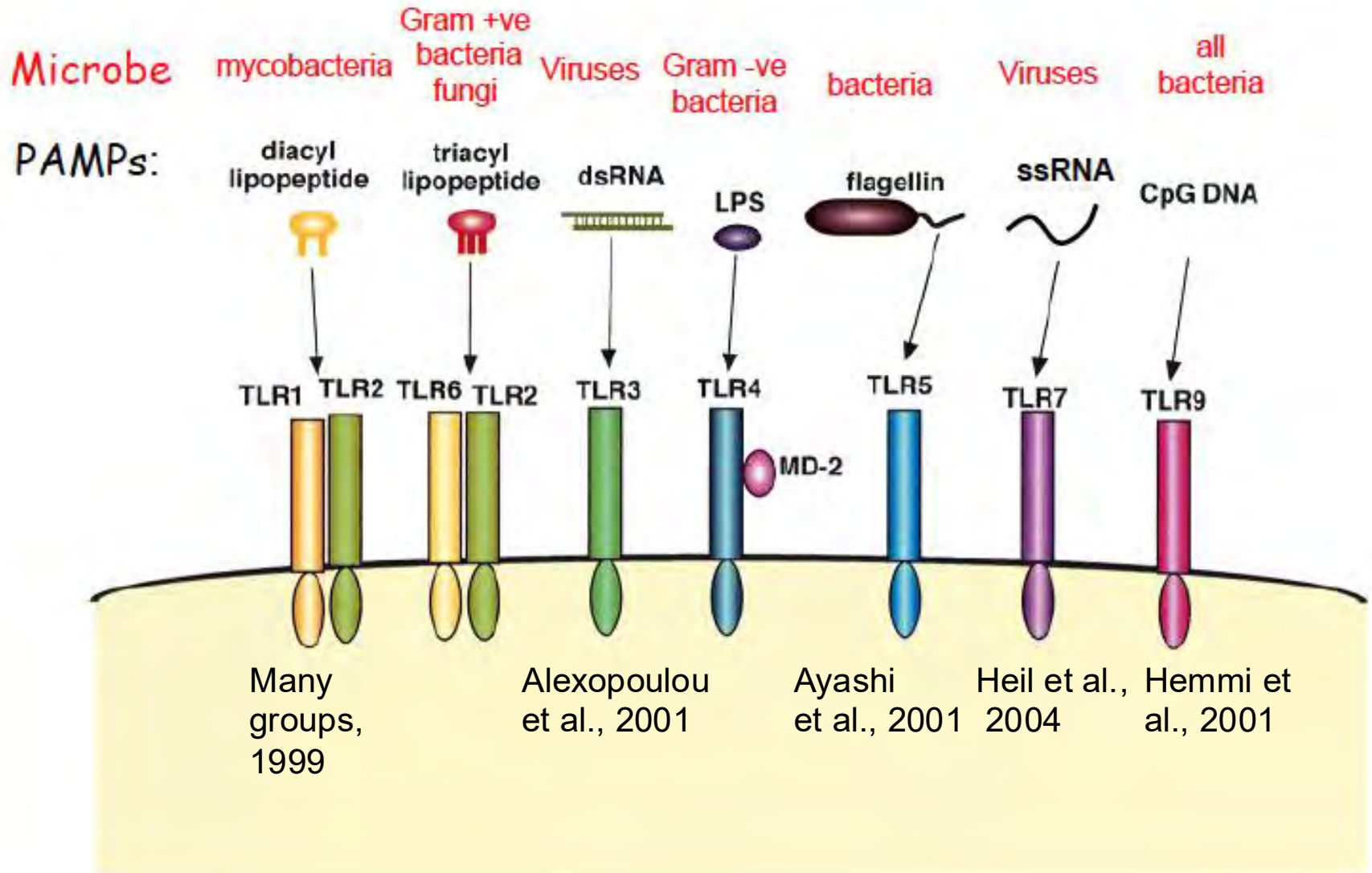
Accepted 19 January 1999;

Published 1 April 1999

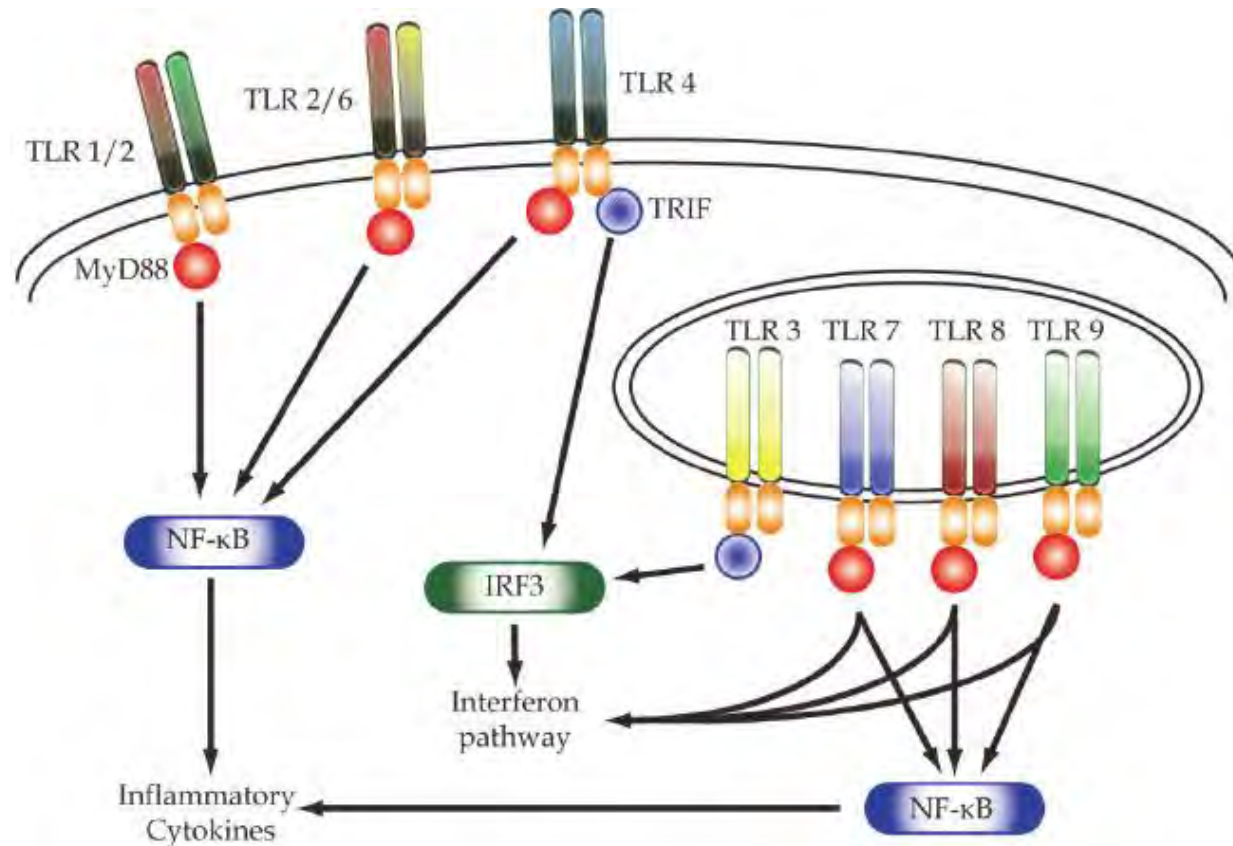


Shizuo Akira

1998-2004: Toll-like receptors (TLRs) and their respective ligands

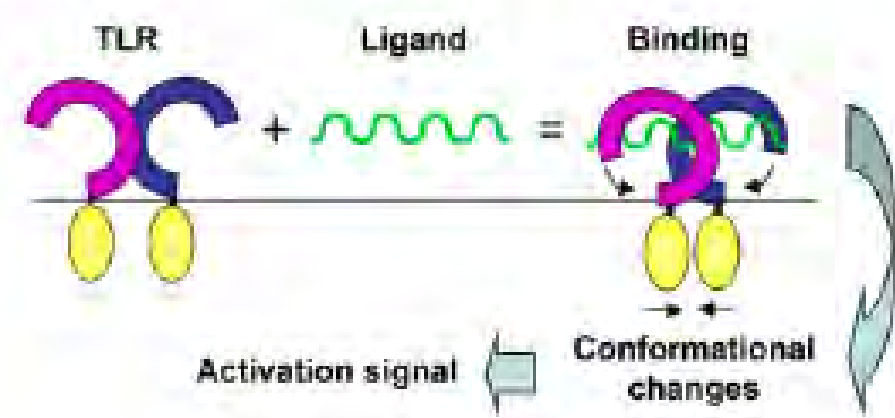
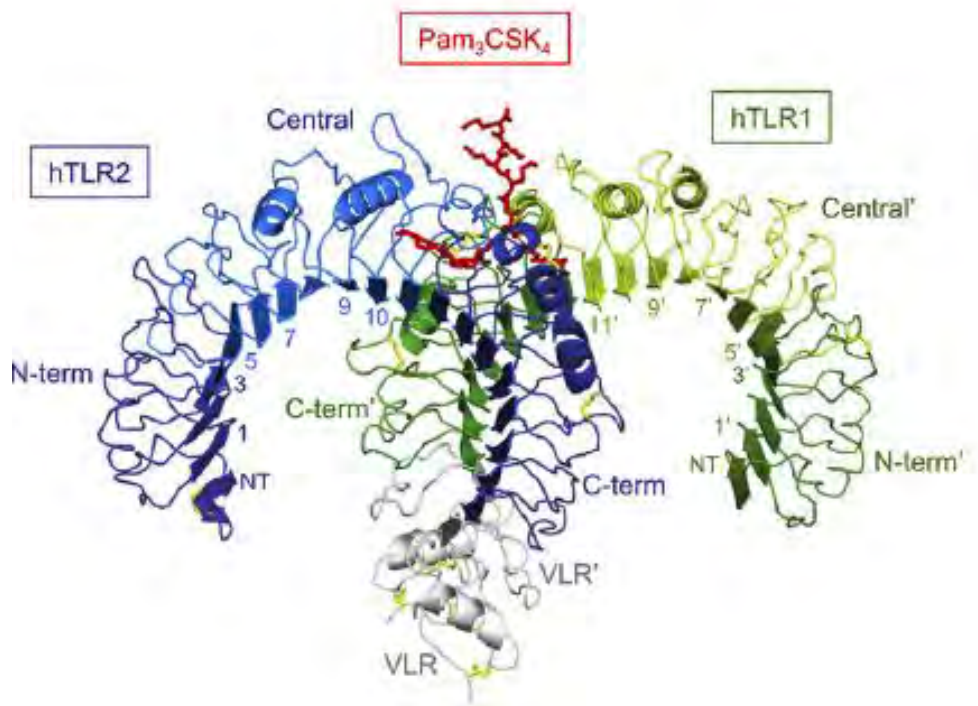


Different localizations of TLRs and distinct signaling cascades via the recruitment of distinct TIR domain adaptors



Boehme & Compton, 2004

Molecular Basis of TLR-Ligand Interaction (2007)

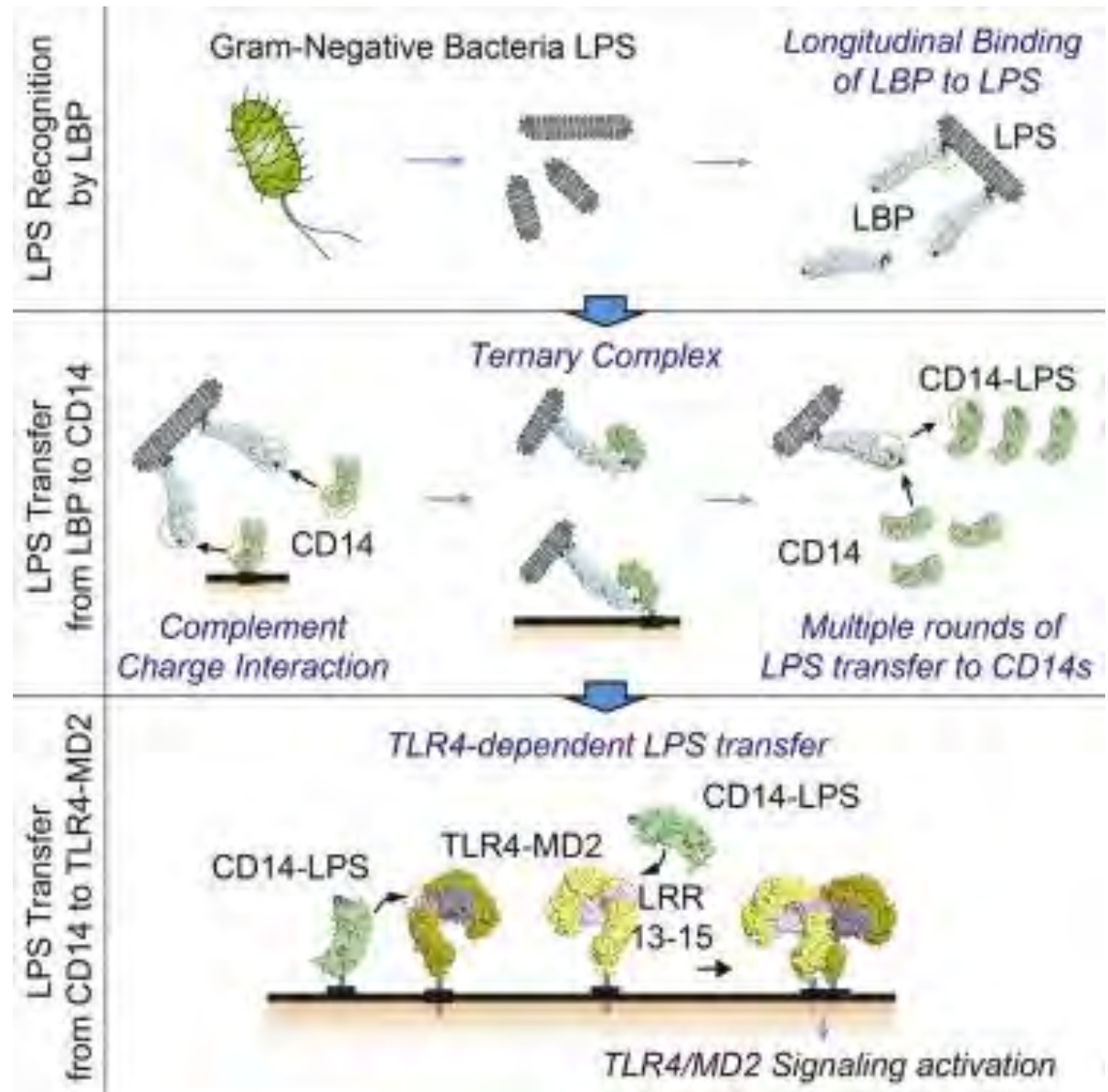


Crystal Structure of the TLR1-TLR2 Heterodimer Induced by Binding of a Tri-Acylated Lipopeptide

Derived from Ishii and Akira, Cell host and Microbes 2008

PRR Sensing is a multistep mechanism

LPS sensing by TLR4/MD2, with the help LBP and CD14



Relevance of TLRs in Human host defense

TLR3 Deficiency in Patients with Herpes Simplex Encephalitis

Shen-Ying Zhang,^{1,2,3} Emmanuelle Jouanguy,^{1,2,3} Sophie Ugolini,⁴ Asma Smahi,⁵ Gaëlle Elain,⁶ Pedro Romero,⁷ David Segal,⁸ Vanessa Sancho-Shimizu,^{1,2} Lazaro Lorenzo,^{1,2} Anne Puel,^{1,2} Capucine Picard,^{1,2,9} Ariane Chaggier,^{1,2} Sabine Plancoulaine,^{1,2} Matthias Titeux,¹⁰ Céline Cognet,⁴ Horst von Bernuth,^{1,2} Cheng-Lung Ku,^{1,2} Armanda Casrouge,^{1,2} Xin-Xin Zhang,³ Luis Barreiro,¹¹ Joshua Leonard,⁸ Claire Hamilton,^{1,2} Pierre Lebon,¹² Bénédicte Héron,¹³ Louis Vallée,¹⁴ Lluís Quintana-Murci,¹¹ Alain Hovnanian,¹⁰ Flore Rozenberg,¹² Eric Vivier,⁴ Frédéric Geissmann,⁶ Marc Tardieu,¹⁵ Laurent Abel,^{1,2} Jean-Laurent Casanova^{1,2,3,16*}

Science 2007

Detection of Toll-like receptor 2 (TLR2) mutation in thelepromatous leprosy patients

Tae-Jin Kang, Gue-Tae Chae *

Institute of Hansen's Disease, Department of Pathology, College of Medicine, The Catholic University of Korea, 505 Banpo-Dong, South Korea

First published online 29 May 2001

TLR4 mutations are associated with endotoxin hyporesponsiveness in humans

Nancy C. Arbour^{1*}, Eva Lorenz^{1*}, Brian C. Schutte^{2*}, Joseph Zabner¹, Joel N. Kline¹, Michael Jones³, Kathy Frees¹, Janet L. Watt¹ & David A. Schwartz¹

**These authors contributed equally to this manuscript.*

Implication of TLRs in auto-immune diseases (2021)

Article

***TLR7* gain-of-function genetic variation causes human lupus**


<https://doi.org/10.1038/s41586-022-04642-z>

Received: 20 January 2021

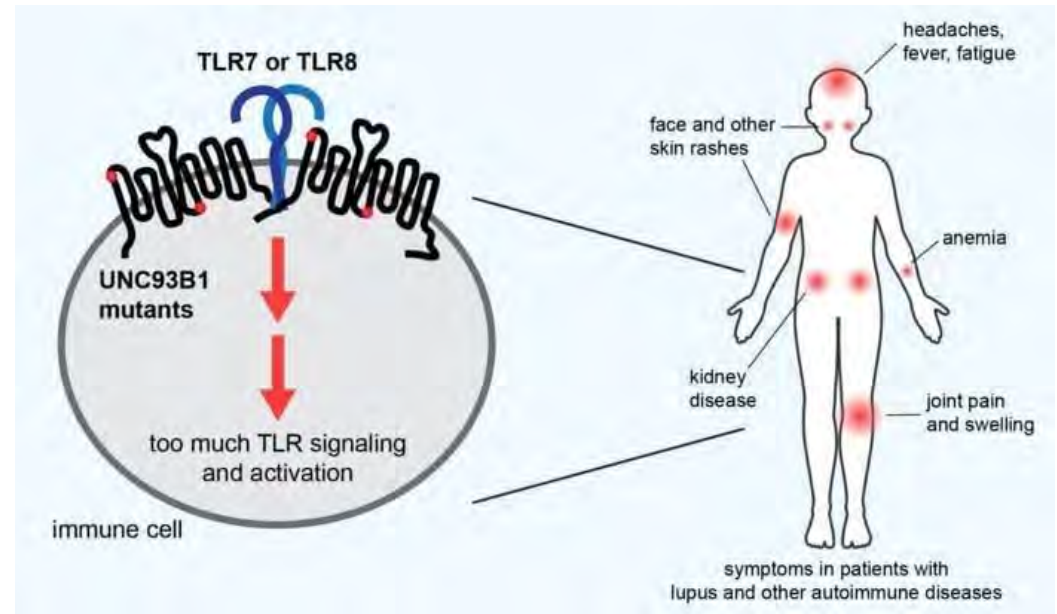
Accepted: 10 March 2022

Published online: 27 April 2022

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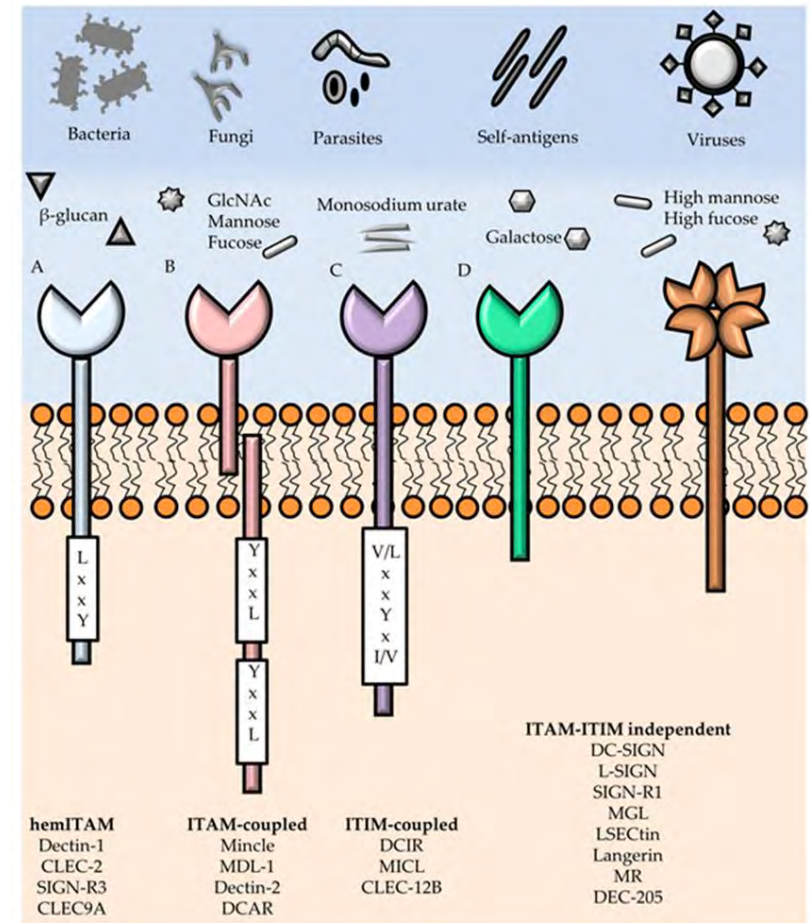


- Identification of a missense TLR7^{Y264H} variant in patients with lupus.
- The TLR7^{Y264H} variant selectively increased sensing of TLR7 ligand
- LR7^{Y264H} is sufficient to cause lupus when introduced into mice.
- TLR7 localization on the X would explain the predominance of Lupus in women

Other membrane bound PRRs: C-type lectin Receptors (CLRs)

2007

- Dectin 1 bind to β -glucan of fungi
- Dectin-2 recognizes α -mannan structures
- Mannose Receptor
- Involved in phagocytosis
- High number of membrane-bound and secreted lectins
- Contribute to host defense, and have implicated in psoriasis, atopic dermatitis, and tumors



The Nod Like Receptor family

- **Nod1 and Nod2**
- **NLR and Inflammasome**

The NLR protein family

Effector binding domain

Oligo-merization domain

Ligand recognition domain

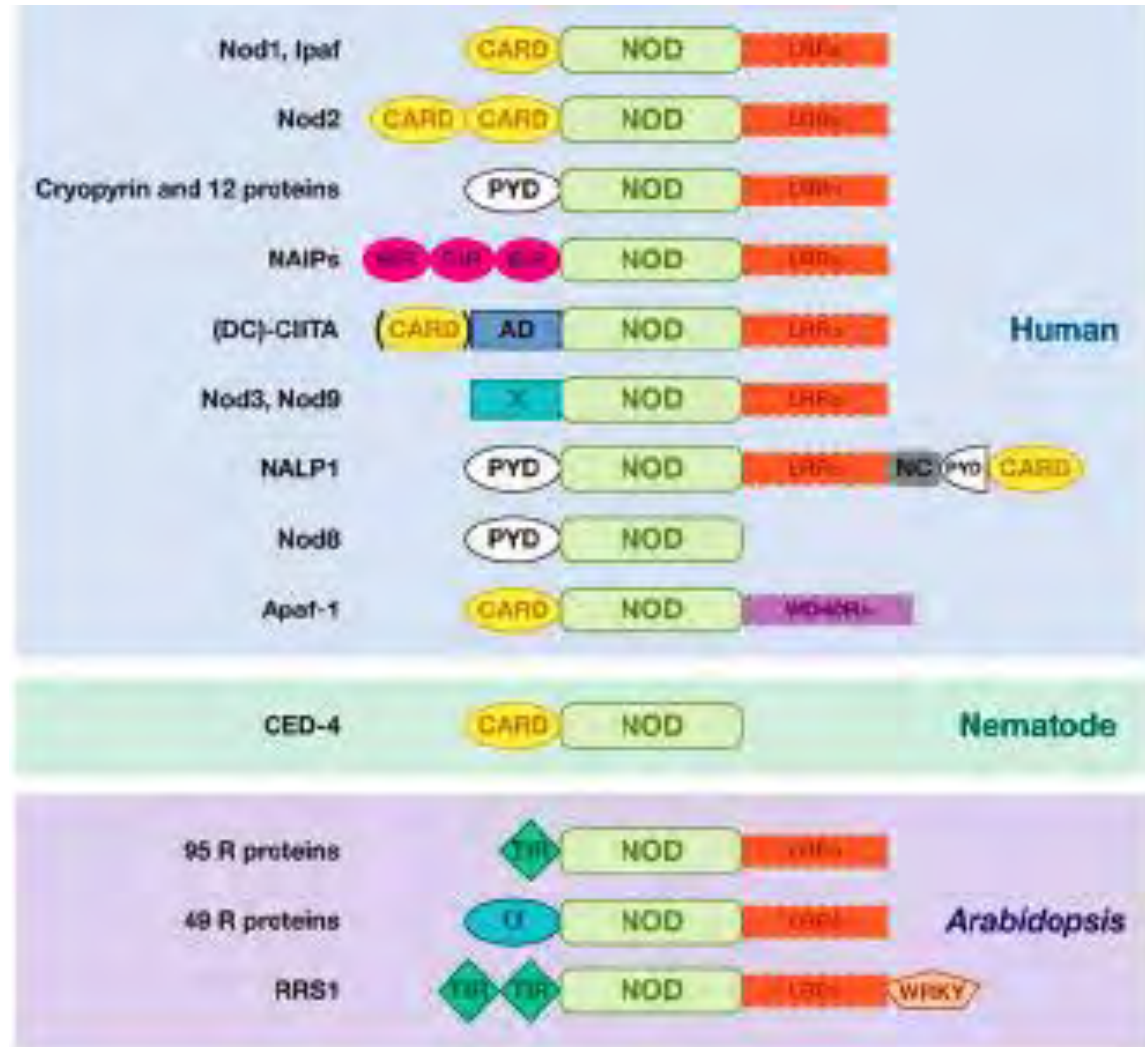
Cytosolic proteins

Contains

- a LRR recognition domain
- a nucleotide-binding Oligomerization Domain (=NACHT/NOD)
- an effector binding domain (signaling)

-shares similarity with R proteins of plants

-Involved in PAMPs sensing, activation of inflammatory and apoptotic caspases



NALP = NLRP (Pyrin)

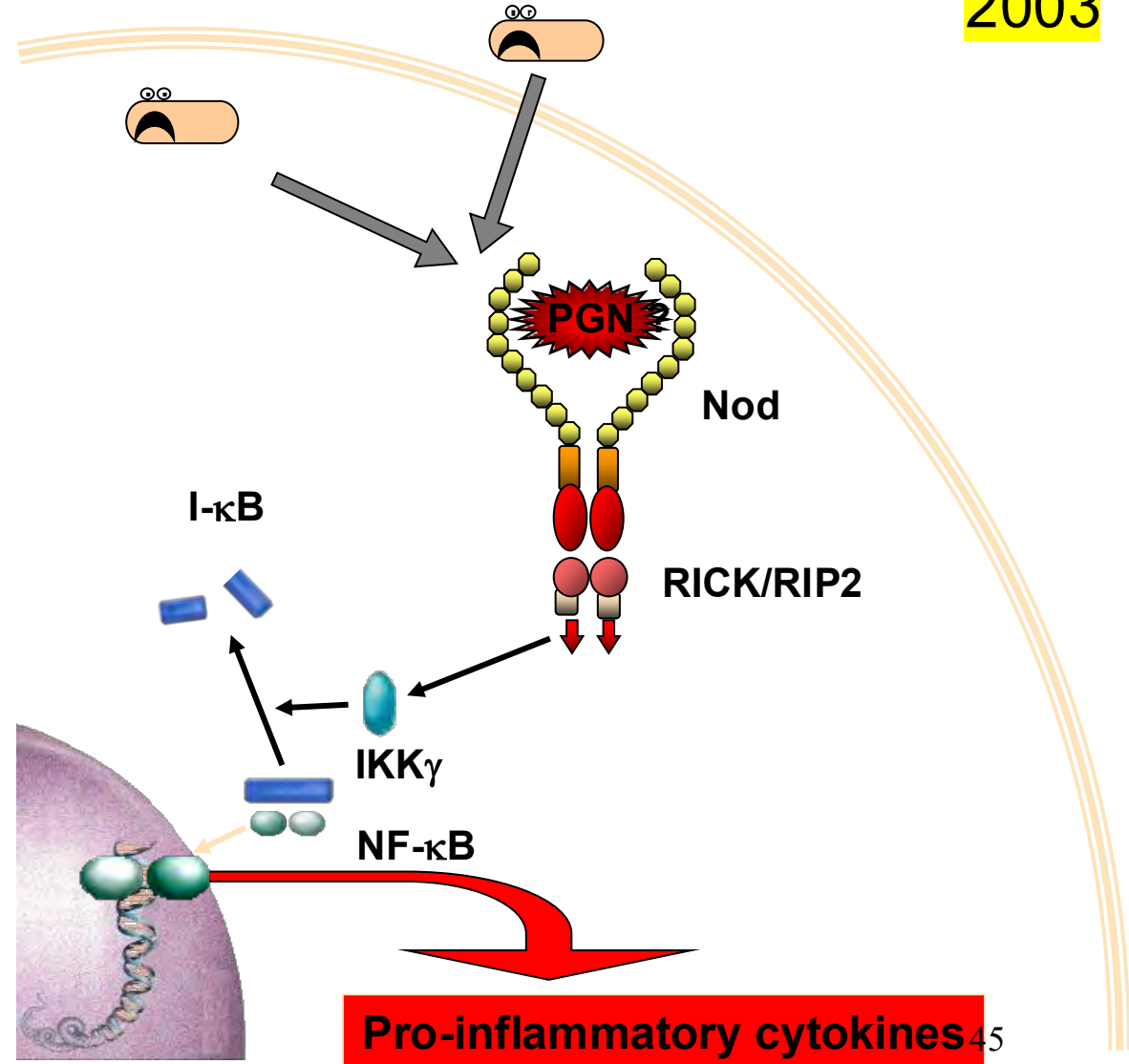
NOD = NLRC (Card)

Nod1 and Nod2 are intracellular PRRs for peptidoglycan

2003

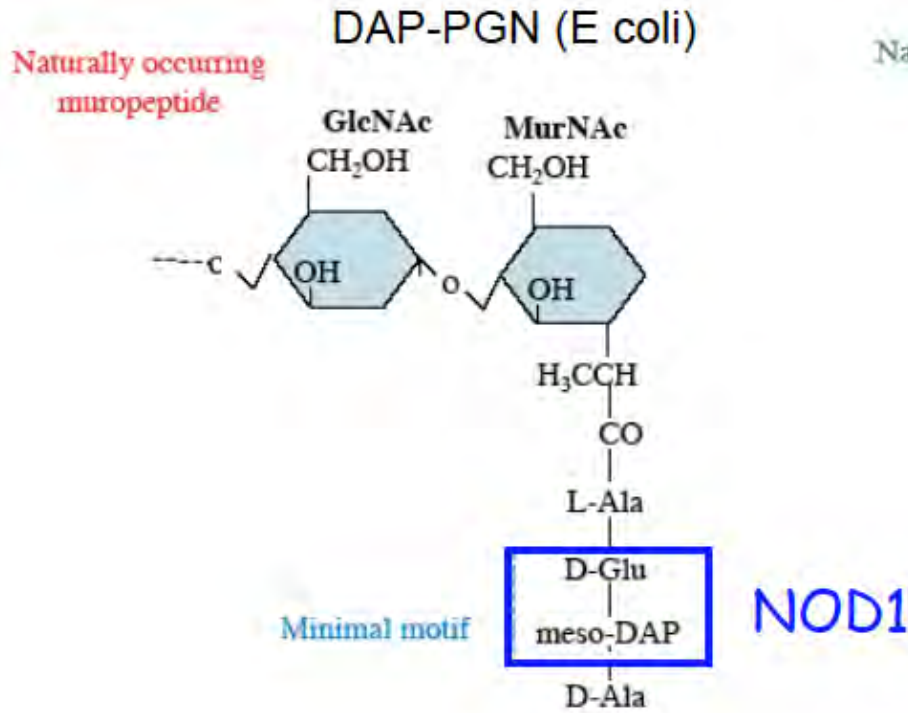


Dana Philppot
Stephan Girardin
(& Gabriel Munez)

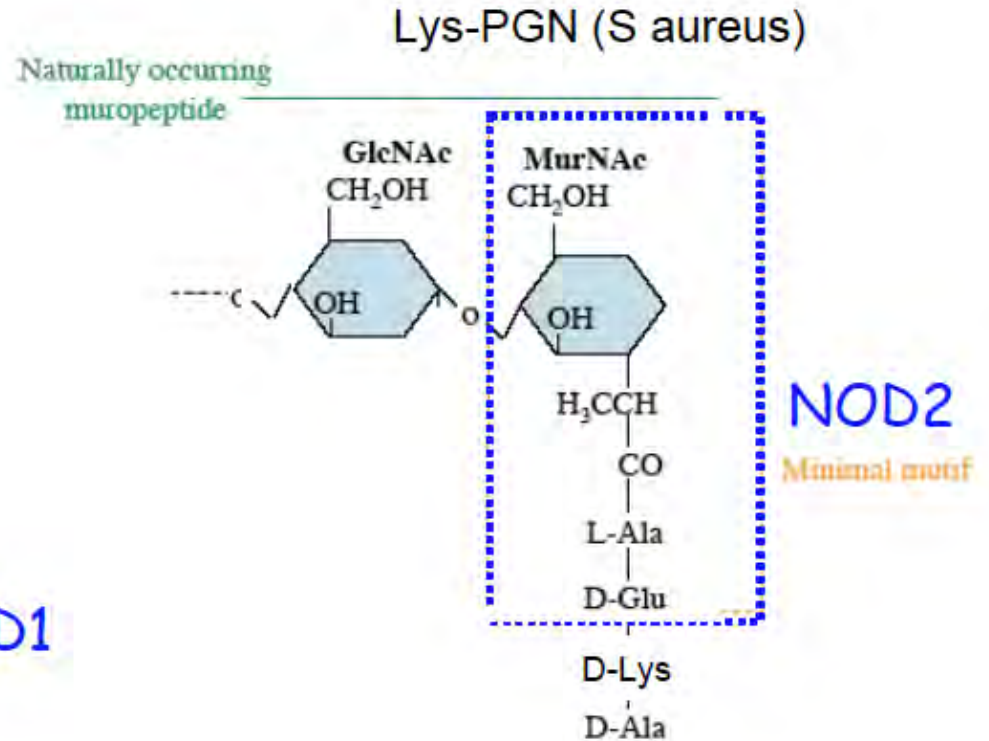


Pro-inflammatory cytokines⁴⁵

NOD1 and NOD2 recognize bacterial peptidoglycans

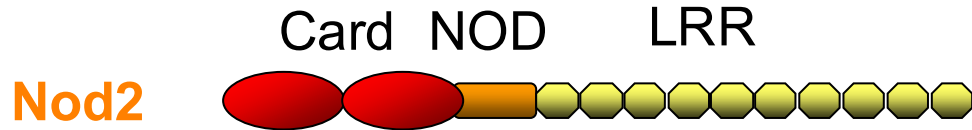


NOD1 binds meso-diaminopimelic acid (DAP, Gram negative bacteria and bacillus)



NOD2 binds muramyl dipeptide (MDP, all bacteria)

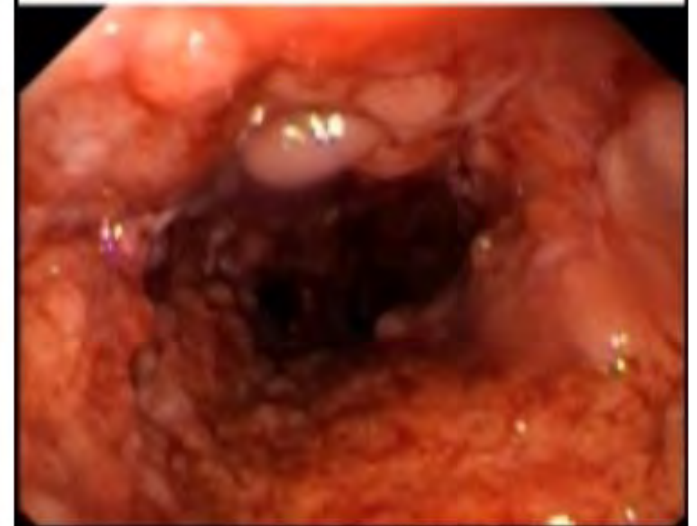
Nod2: Major susceptibility gene in Crohn's disease (and Blau syndrome)



-NOD2 mutations are found in 20% of Caucasian population

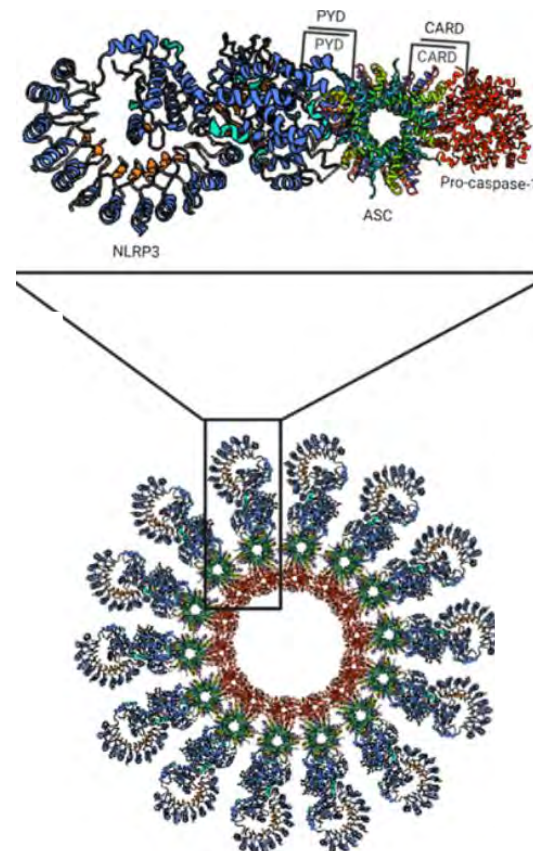
-Loss-of-function mutations in NOD2 are implicated in 10% of case. Hypothesis: an initial failure in bacterial clearance resulting in a more severe inflammation...

-Gain of function allele of Nod2 are linked to Blau Syndrom (inflammation of joints, eye)

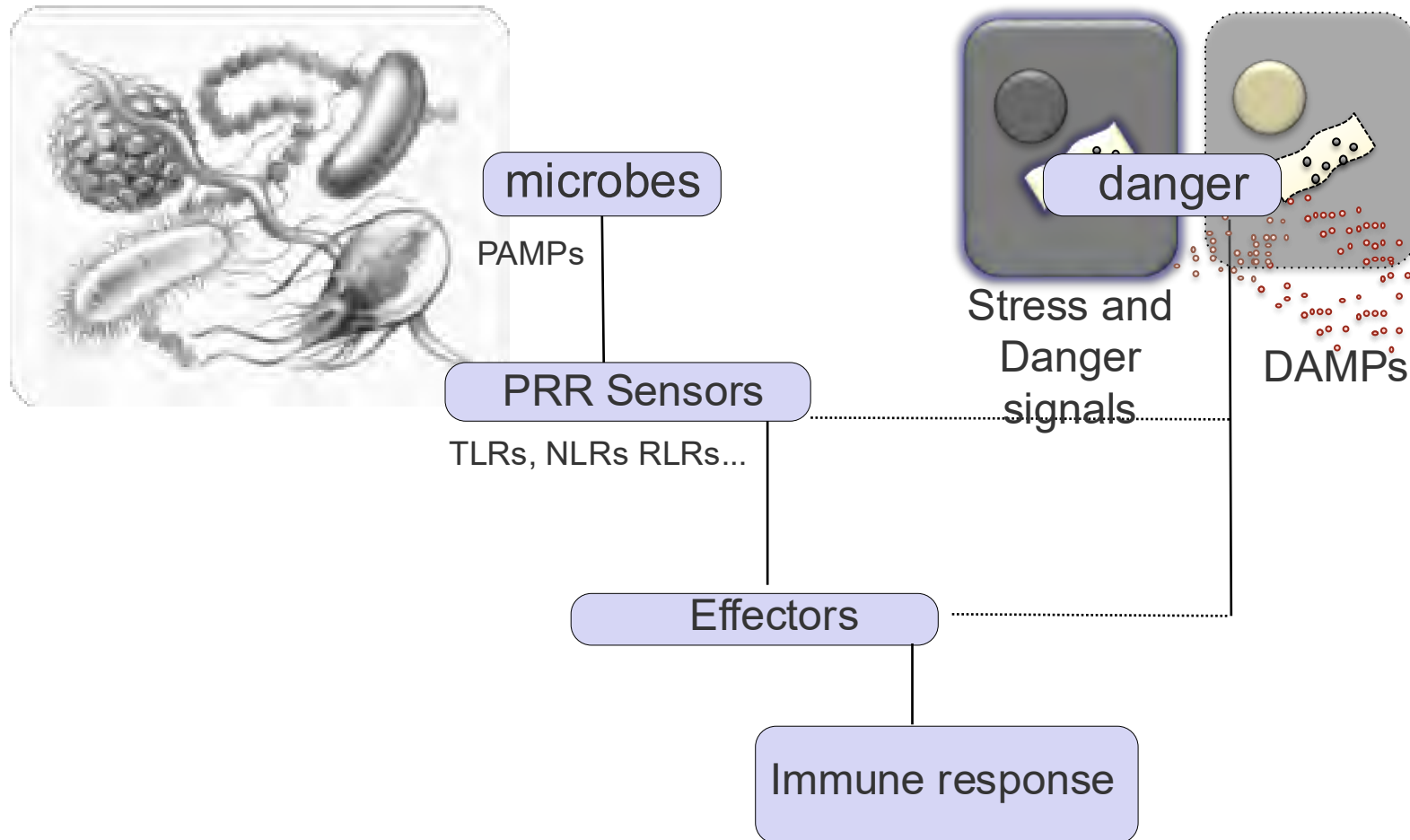


The Nod Like Receptor family

- Nod1 and Nod2
- **NLR and Inflammasome**

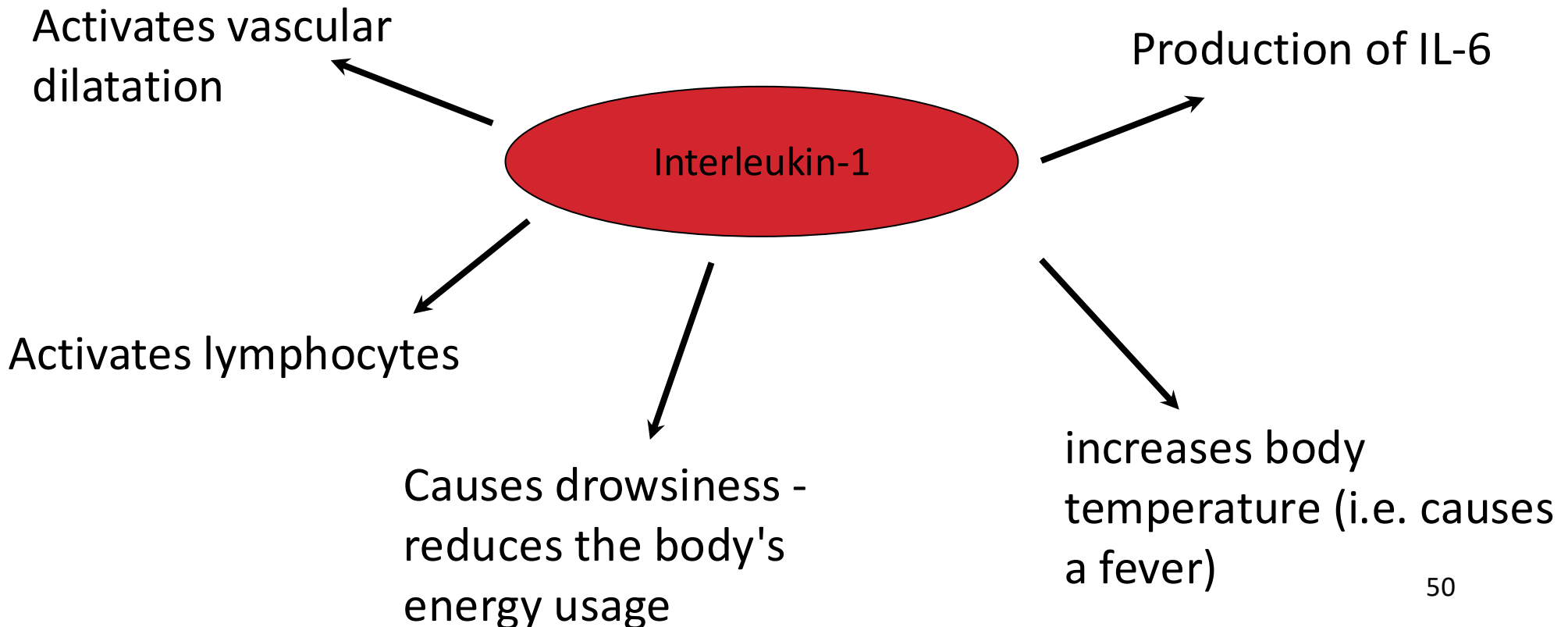


Basics of innate immunity: Capturing danger, identifying microbes

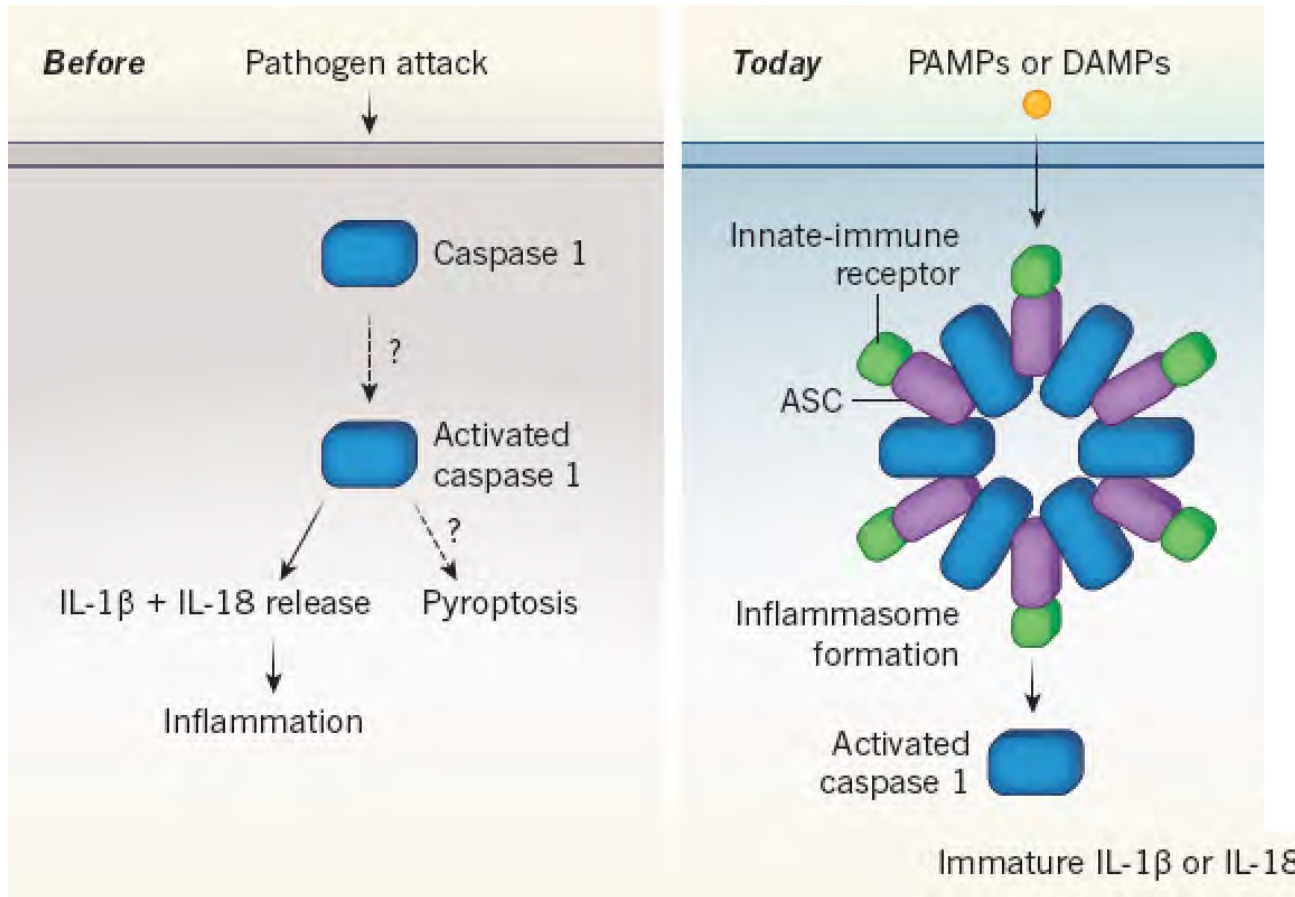


Multiple Function of Interleukin-1 (1984)

- IL-1 is a generic name for IL-1a and IL-1b
- Engages the IL1-Receptor that activate NF- κ B
- Activate local and systemic response
- Produced by macrophages and dendritic cell upon microbial recognition
- Maturation of proIL-1 β (31kDa) to its 17kDA active form by Caspase 1



2002: the discovery of inflammasome

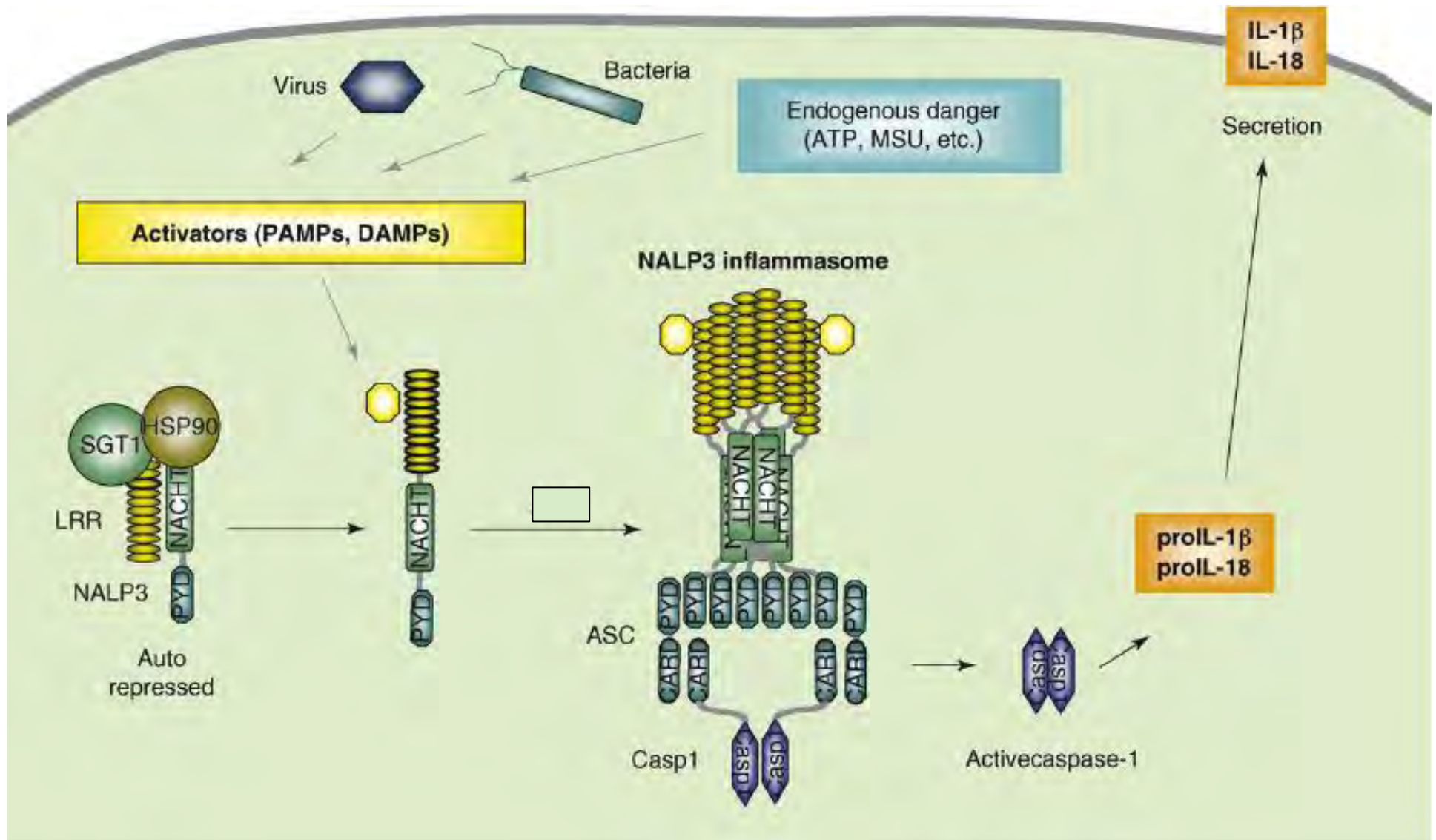


Jürg Tschopp
(1951-2011)



Fabio Martinon

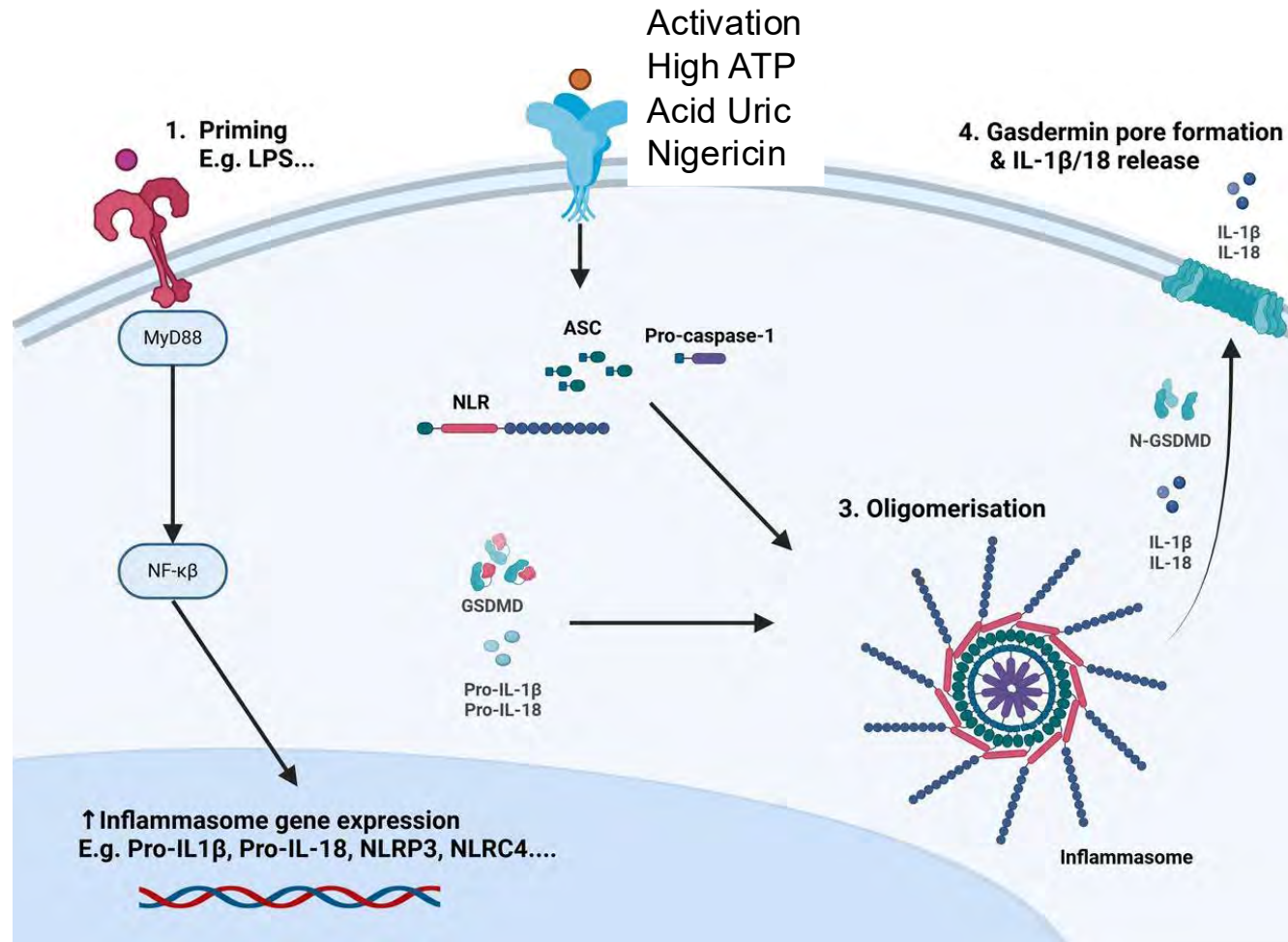
Activation of NLRs



Expression and Maturation of IL-1 β

Three levels:

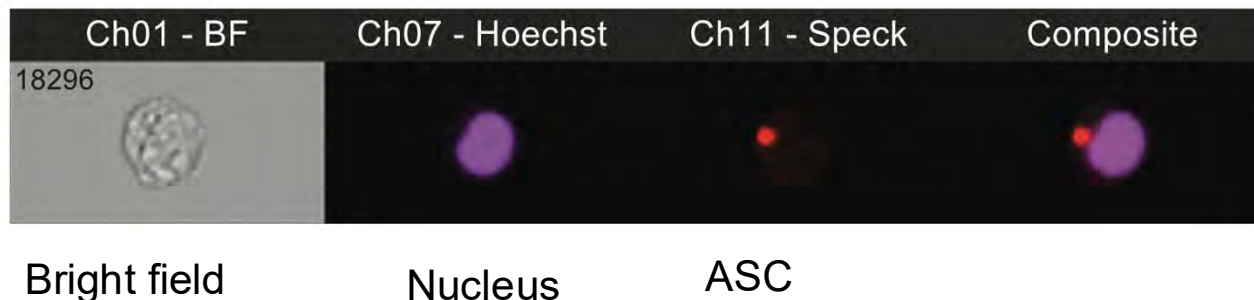
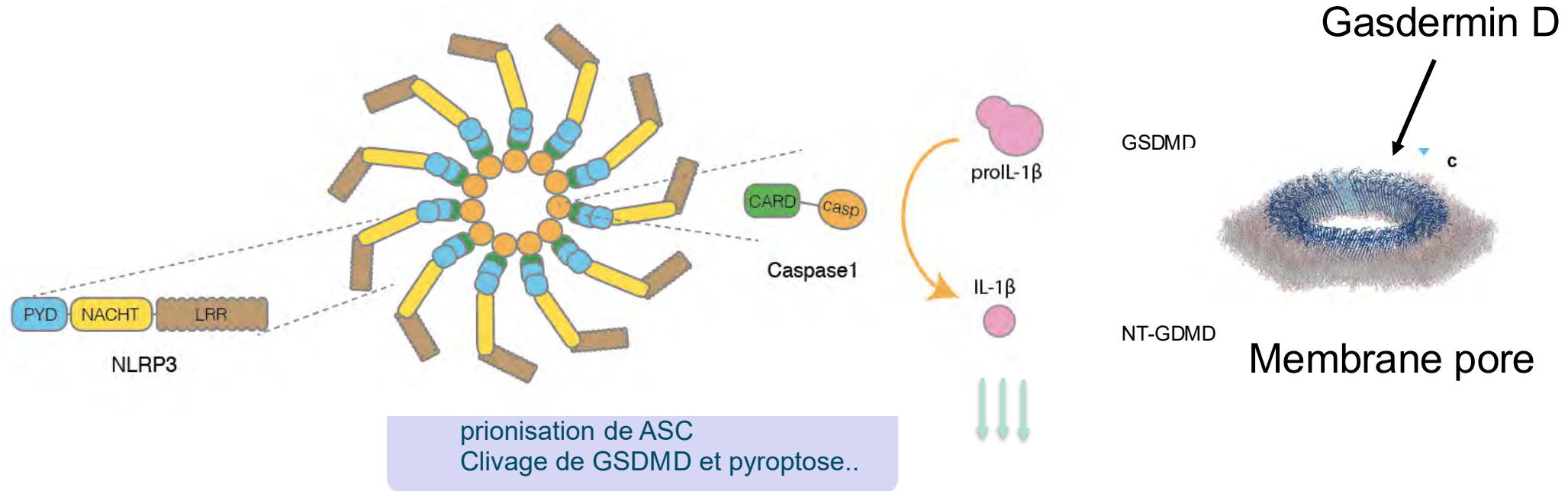
- 1. Priming: IL1 gene expression (by TLRs)
- 2. IL1-Maturation by caspase 1 (by inflammasome)
- 3. IL-1 Secretion through Gasdermin D pore (by inflammasome)



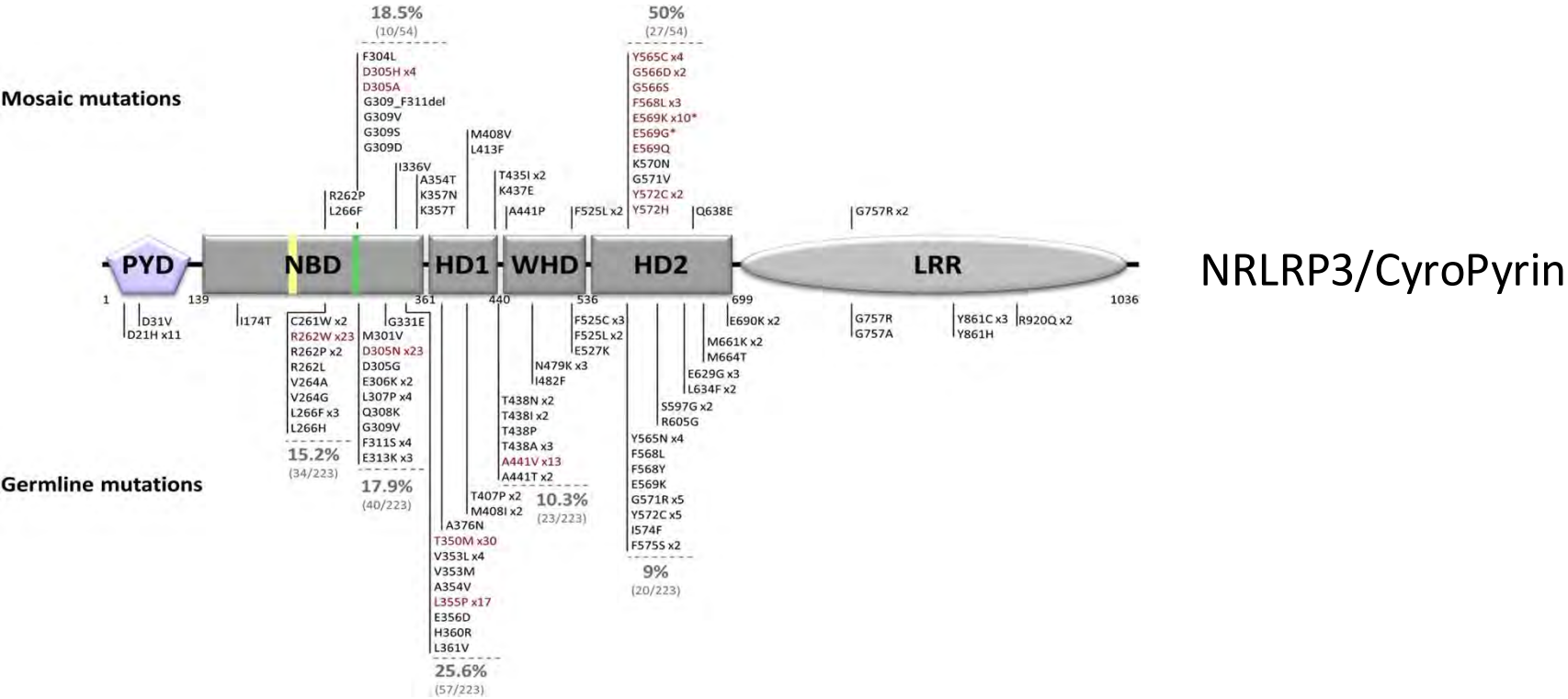
Macrophages
Cellules
dendritiques

↑ Inflammasome gene expression
E.g. Pro-IL1 β , Pro-IL-18, NLRP3, NLRC4....

The Inflammasome NLRP3 matures both IL1 and Gasdermin D



Mutations in the NLRP3/cryopyrin gene are associated with auto-inflammatory diseases



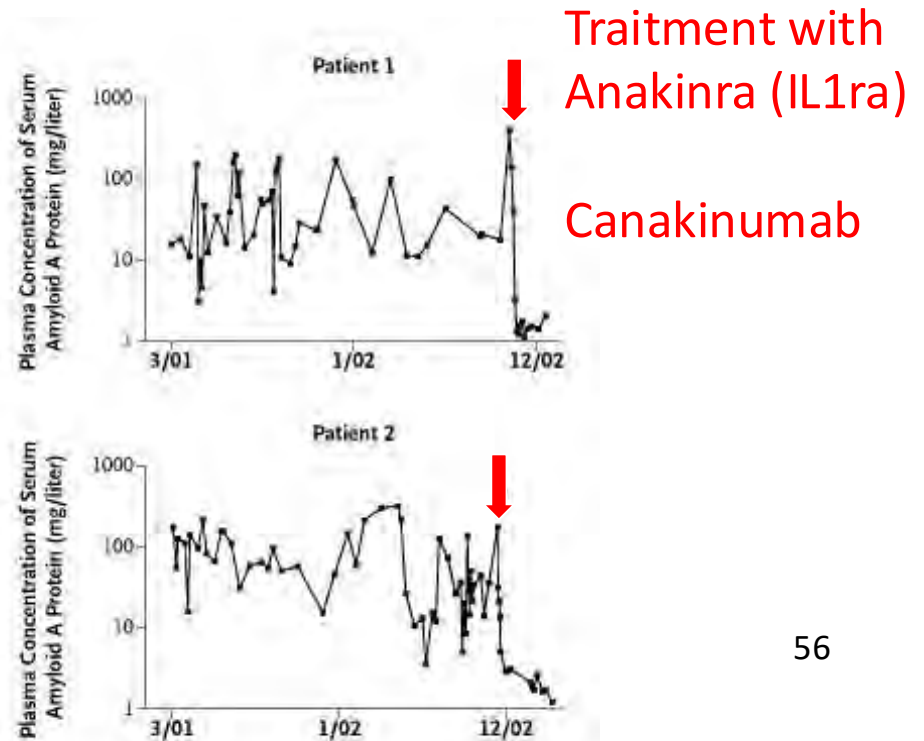
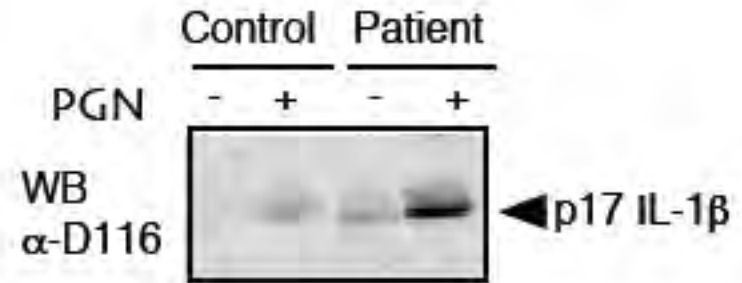
NLRP3/CryoPyrin

CAPS (CryoPyrin-associated Periodic Syndrome)

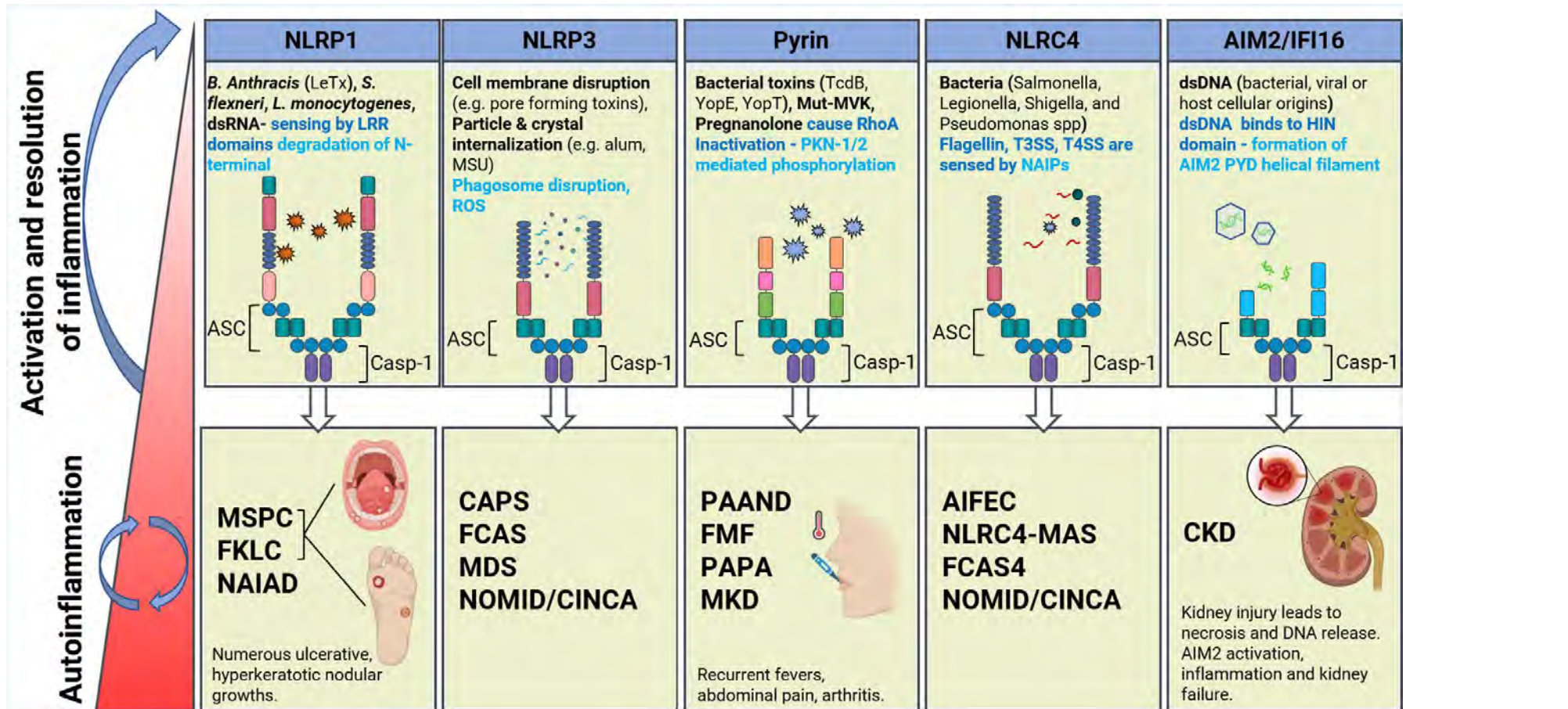
- Familial cold autoinflammatory syndrome (FCAS, FCU)
- Muckle-wells syndrome (MWS)
- Chronic infantile neurological cutaneous and articular syndrome (CINCA, NOMID)

NALP3 and Muckle-wells syndrome (MWS)

- Autosomal dominant mutation in NALP3
- Periodic fever, rash, arthritis, conjunctivitis...
- Spontaneous production of IL1 β



Several inflammasomes with various triggers



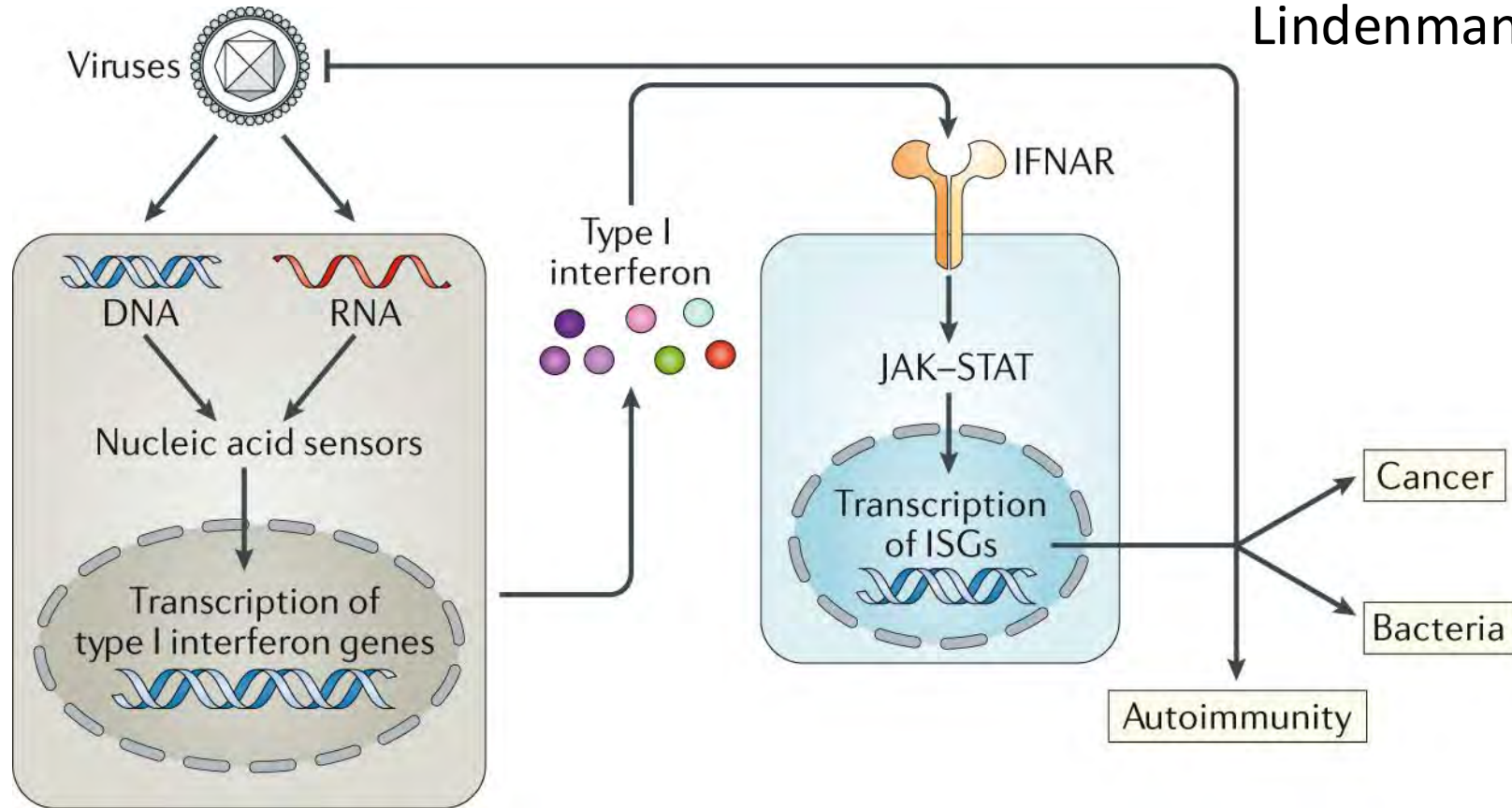
MSPC: Multiple palmoplantar carcinoma;
 FKLC: Familial keratosis lichenoides chronica;
 NAIAD: NLRP1-associated autoinflammation with arthritis and dyskeratosis;
 MWS: Muckle–Wells syndrome;
 FCAS: familial cold autoinflammatory syndrome; MDS: myelodysplastic syndromes
 CINCA/ NOMID: chronic infantile neurological cutaneous and articular
 PAAND, pyrin associated autoinflammation with neutrophilic dermatosis

FMF: familial mediterranean fever;
 PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne;
 MKD: mevalonate kinase deficiency;
 AIFEC: autoinflammation and infantile enterocolitis; NLRC4-
 syndrome; CKD, chronic kidney disease

Cytoplasmic Nucleic Acid Sensors

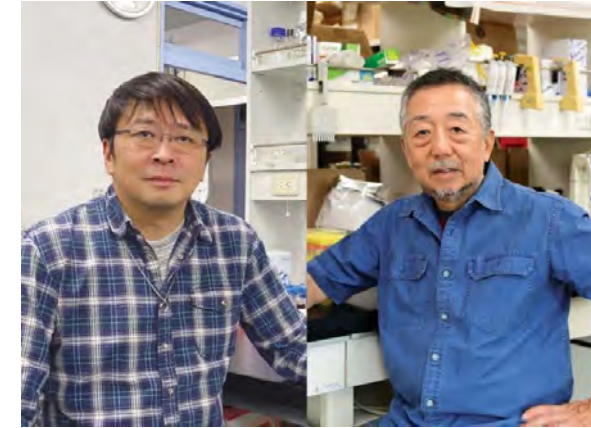
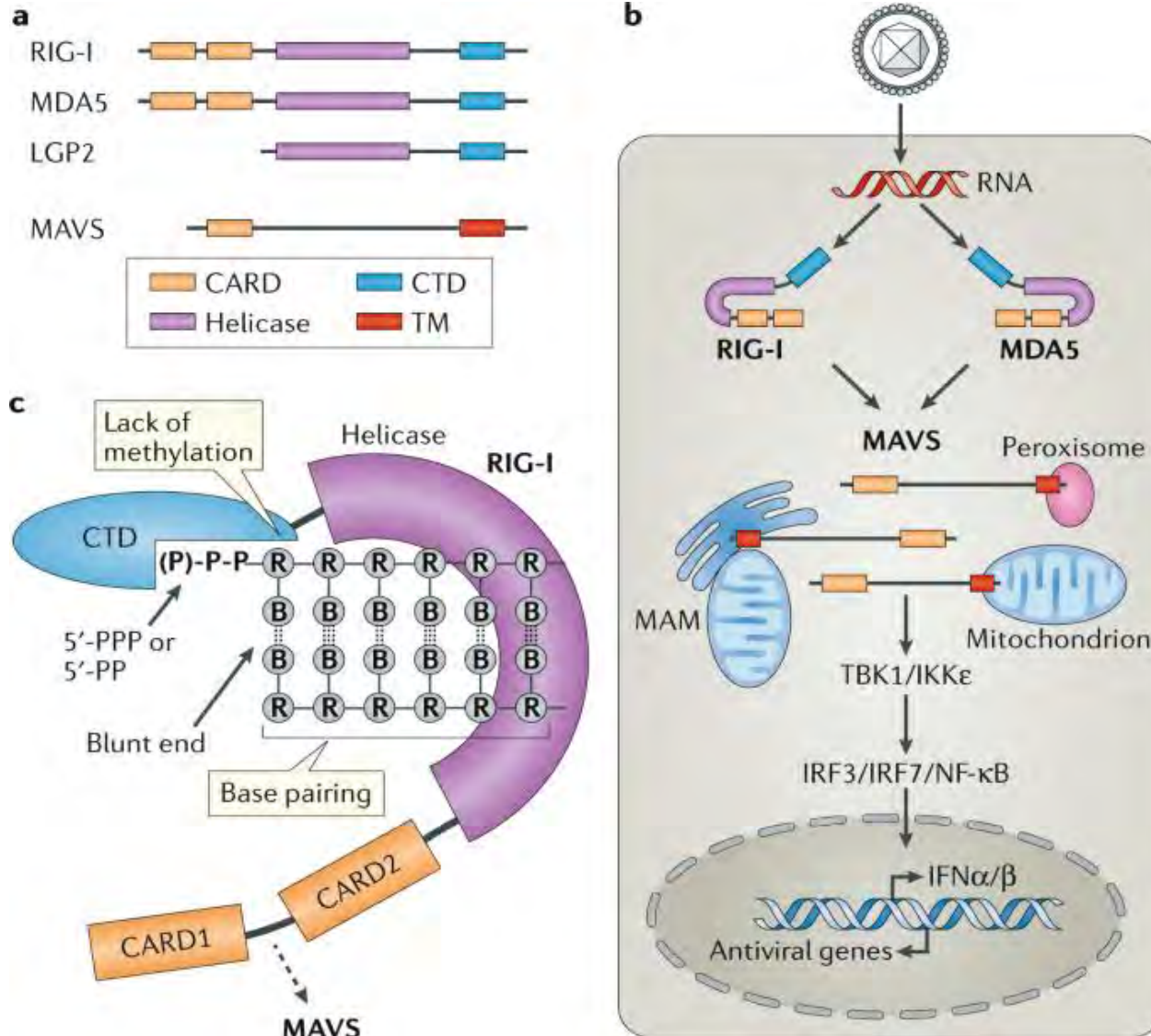
The type I interferon response to viruses

1957: interferon by
Isaacs and
Lindenmann



The helicase proteins RIG-I and MDA5 senses cytoplasmic viral RNA

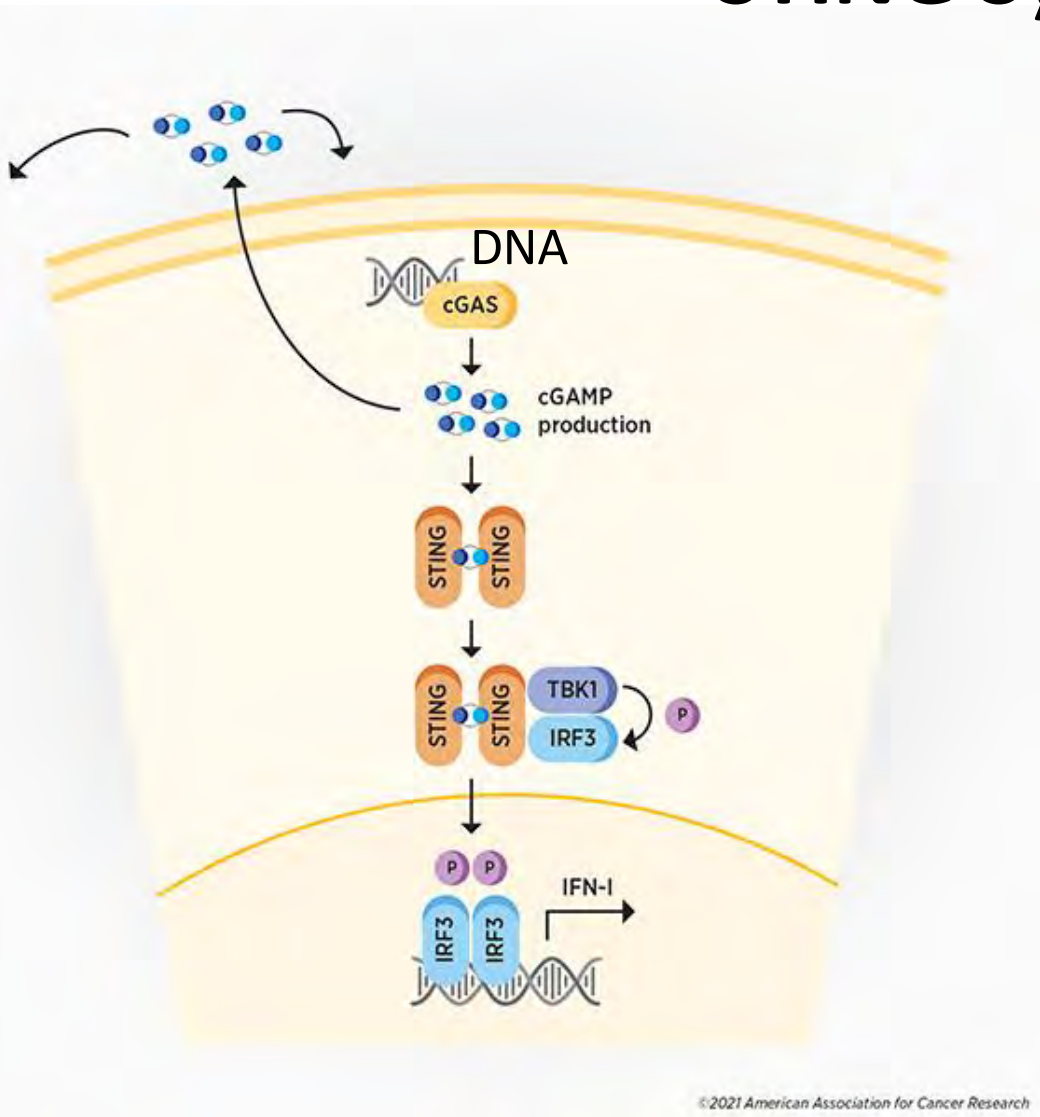
2004-2006



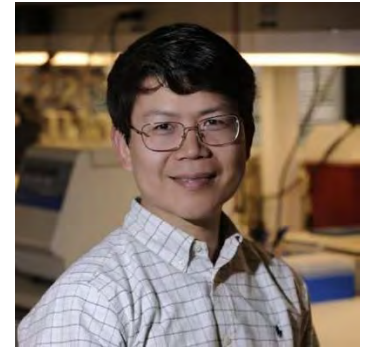
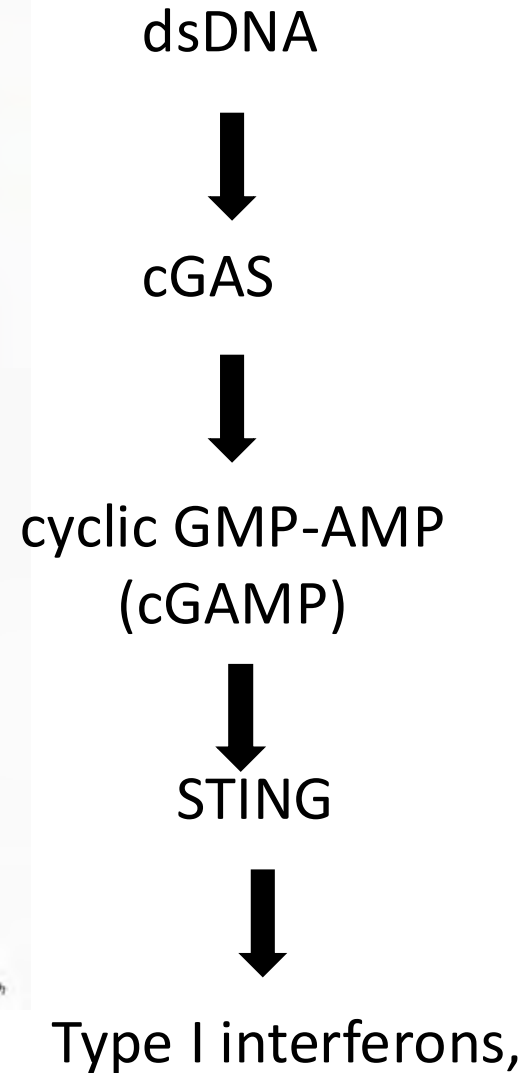
Mitsutoshi Yoneyama
and Takashi Fujita (RIG-I)

Sensing of cytoplasmic DNA by the cGAS-STING System

2013

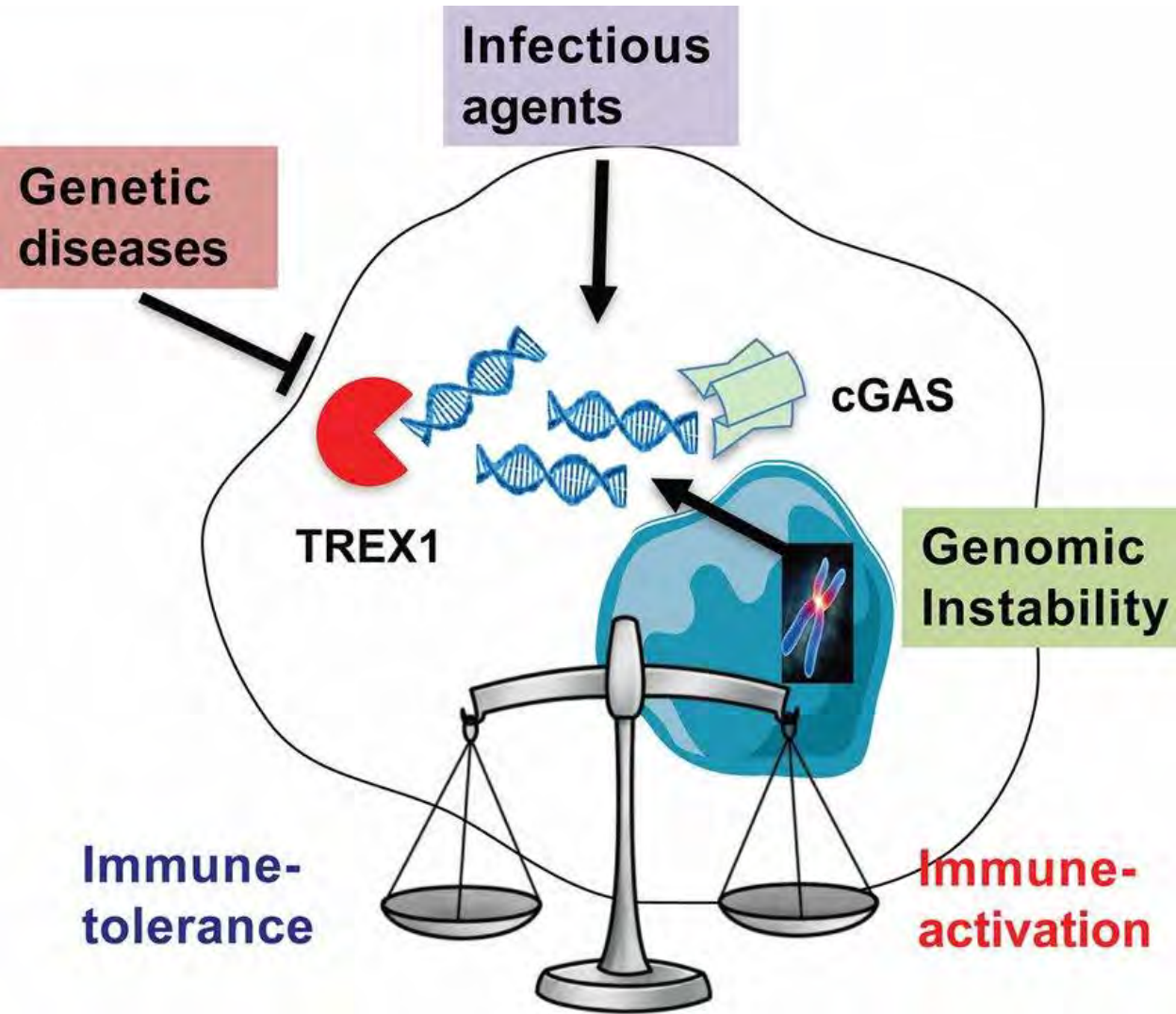


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Zhijian "James" Chen

Loss-of-function TREG1 mutations cause interferon-driven diseases (Aicardi-Goutières syndrome, lupus...)



Pattern recognition receptor-targeting therapeutic strategies

- PRRs stimulate both innate and adaptive immune responses to combat pathogens, but also induce the production of inflammatory cytokines, that can lead to tissue damage.
- PRR agonists to boost immune responses: vaccin, immunotherapy
- PRR antagonists to inhibit inflammatory and auto-immune diseases

Many molecules in clinical trials

3

Table 3. Treatment with PRRs' agonists and antagonists in clinical trials

Disease type	Category of PRRs	Agonists	Study type/phase	ClinicalTrials.gov Identifier			
Cancers							
Acute myelogenous leukemia	TLRs	GNKG168	Interventional/phase 1	NCT01743807			
Acute lymphoblastic leukemia	TLR7/8	Imiquimod	Interventional/phase 2	NCT03559413			
Breast cancer	TLR7	Imiquimod	Interventional/phase 2	NCT01421017			
				NCT00899574			
				NCT03982004			
				NCT00821964			
Colorectal cancer	TLR7	852 A	Interventional/phase 2	NCT00319748			
				NCT05954143			
	TLR7	Imiquimod	Interventional/phase 3	NCT00785122			
				NCT02135419			
Cutaneous T-cell lymphoma	TLR9	IMO 2055	Interventional/phase 2	NCT00719199			
				TLR3	Poly ICLC	Interventional/phase 1	NCT02061449
	TLR4	G100 agent	Interventional/phase 2				NCT03742804
				TLR7	Imiquimod	Interventional/early phase 1	NCT03116659
Mantle cell lymphoma	TLR7/8	Resiquimod	Interventional/phase 1				NCT01676831
				TLR9	PF-03512676	Interventional/phase 2	NCT00490529
							TLR9
				NCT02927964			
Chronic lymphocytic leukemia	TLR7	Imiquimod	Interventional/phase 2	NCT00596336			
				NCT00319748			
Endometrial cancer	TLR7	852 A	Interventional/phase 2	NCT00319748			
Head and neck cancer	TLR5	Entolimod	Interventional/phase 1	NCT01728480			
				NCT03906526			
Pancreatic cancer	TLR3	Rintatolimod	Interventional/phase 1	NCT05927142			
				TLR9	SD-101	Interventional/phase 1	NCT04050085
							NCT04364230
Melanoma	TLR3	Poly-ICLC	Interventional/phase 2	NCT04364230			
				TLR	MEL60	Interventional/phase 2	NCT02126579
	TLR4	GLA-SE	Interventional/early phase 1				NCT02320305
				TLR7/8	Resiquimod	Interventional/phase 2	NCT00960752
	TLR7/8	Imiquimod	Interventional/phase 1				NCT01748747
				Lentigo malignant	TLR7/8	Imiquimod	Interventional/phase 1
NCT03276832							
NCT04530500							
NCT00651703							
NCT00273910							
NCT00273910							
NCT01264731							
NCT01191034							
NCT00118313							
NCT00470379							
NCT00821652							
NCT05061017							
Oral cancer	TLR9	Icatimod	Interventional/phase 2	NCT05061017			
				TLR	MEL58	Interventional/phase 1	NCT01585350
							TLR7/8
				NCT01161888			
Ovarian cancer	TLR7/8	Imiquimod	Interventional/early Phase 1	NCT01161888			
				TLR3	Ampligen	Interventional/phase 2	NCT01720407
							TLR7
				NCT00707174			
Ovarian cancer	TLR7/8	Imiquimod	Interventional/early Phase 1	NCT04883645			
				TLR3	Ampligen	Interventional/phase 2	NCT01312389
							TLR7
				TLR7	852 A	Interventional/phase 2	
TLR8	VTX-2337	Interventional/phase 1	NCT01294293				
			NCT01666444				
NCT02431559							

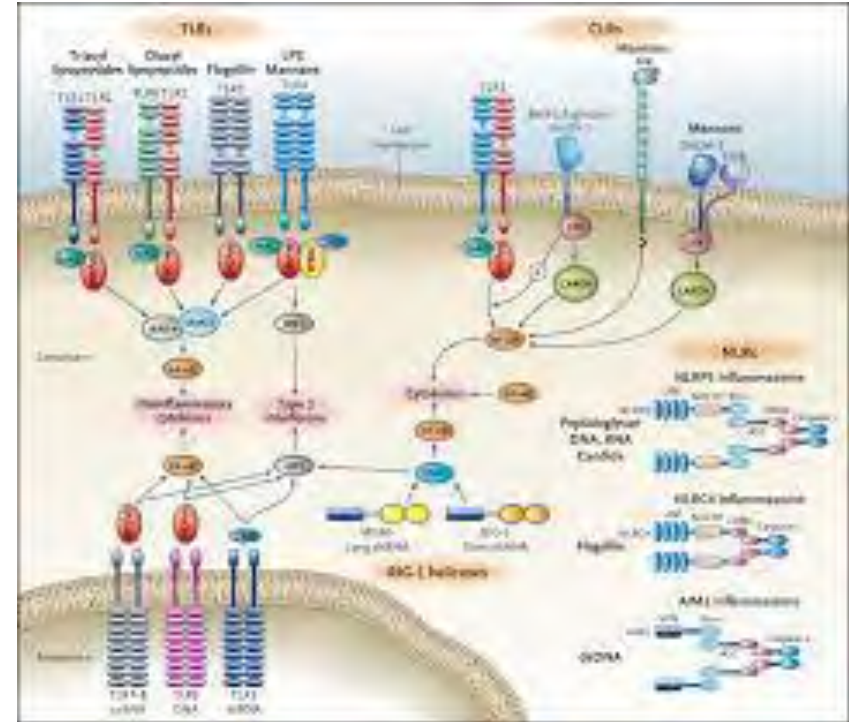
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Table 3. continued

Disease type	Category of PRRs	Agonists	Study type/phase	ClinicalTrials.gov Identifier			
Vulvar intraepithelial neoplasia	TLR7/8	Imiquimod	Interventional/phase 3	NCT01861535			
				NCT00941811			
Cervical intraepithelial neoplasia	TLR7/8	Imiquimod	Interventional/NA	NCT03206138			
				NCT02864147			
				NCT02329171			
				NCT02917746			
				NCT02669459			
				NCT02130323			
				NCT01283763			
				NCT00988559			
				NCT00941252			
				NCT00788164			
				NCT00031759			
				NCT06356012			
NCT03196180							
NCT05405270							
NCT03233412							
NCT04859361							
Cervical cancer	TLR7	852 A	Interventional/phase 2	NCT00319748			
				VTX-2337			
Peritoneal carcinomatosis	TLR5	VTX-2337	Interventional/phase 1	NCT01294293			
				TLR3	Ampligen	Interventional/phase 2	NCT01312389
Fallopian tube cancer	TLR8	VTX-2337	Interventional/phase 1	NCT01294293			
				NCT01666444			
Lung cancer	TLR3	Ampligen	Interventional/phase 2	NCT01312389			
				TLR8	VTX-2337	Interventional/phase 2	NCT01666444
Bladder cancer	TLR7	BNT411	Interventional/phase 2	NCT01013537			
				TLR7/8	EIK1001	Interventional/phase 2	NCT06246110
							TLR7/8
				TLR9	DV281	Interventional/phase 1	
Glioblastoma	TLR7/8	Imiquimod	Interventional/phase 1	NCT05375803			
				NCT01731652			
Cutaneous neurofibromas	TLR3	Poly-ICLC	Interventional/phase 2	NCT02754362			
				TLR7	Imiquimod	Interventional/phase 1	NCT01403285
Recurrent gliomas	TLR7	Imiquimod	Interventional/phase 1	NCT02078648			
				NCT01808820			
Prostate cancer	TLR7	Imiquimod	Interventional/phase 1	NCT00865644			
				TLR7/8	Imiquimod	Interventional/early Phase 1	NCT01678352
Soft tissue sarcomas	TLR7	Imiquimod	Interventional/phase 2	NCT04808245			
				TLR7	STM-416p	Interventional/phase 2	NCT02452307
							TLR9
				Vidutolimod	Interventional/phase 2	NCT06450106	
Basal cell carcinoma	TLR4	GLA-SE	Interventional/phase 1	NCT03007732			
				TLR7	Imiquimod	Interventional/phase 1	NCT05445609
Basal cell carcinoma	TLR7/8	Resiquimod	Interventional/phase 2	NCT02180698			
				NCT01803152			
Basal cell carcinoma	TLR7/8	Imiquimod	Interventional/phase 3	NCT01808950			
				NCT00079300			
				NCT00668872			
				NCT05212246			
				NCT06252857			
				NCT00803907			
				NCT03534947			
				NCT02242929			
				NCT00463359			
				NCT00314756			
				NCT00204555			
				NCT00189306			
NCT00189280							
NCT00189241							
NCT00129519							
NCT00581425							

1989-2024: a revolution in immunology

- Identification of the PRR receptors that sense microbial infection
- Immunity is an universal phenomenon in all living things. Adaptive immunity (B and T cells) is a fascinating but tiny part of immunity.
- Innate immunity is diverse and complex, local and systemic



Netea et al., N Engl J Med 2011;364:60-70

1989-2024: a revolution in immunology

- The concepts of "memory" and "specificity" have been found to be generally applicable to innate immunity.
- Immunity goes far beyond simply defending against pathogens: role in tissue homeostasis, symbiosis, and implication in many non-immune diseases
- Many other processes cooperate with the immune system in host defense: tolerance mechanism, symbiont-mediated immunity, and behavioral immunity

Immunology & psychology of science

Acknowledgments

Marie Meister

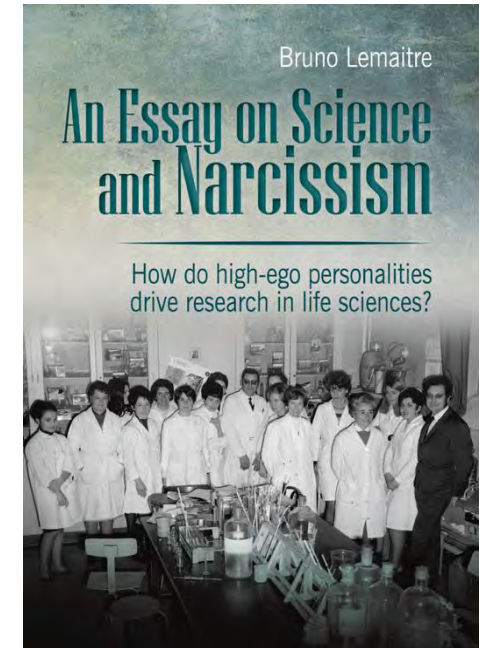
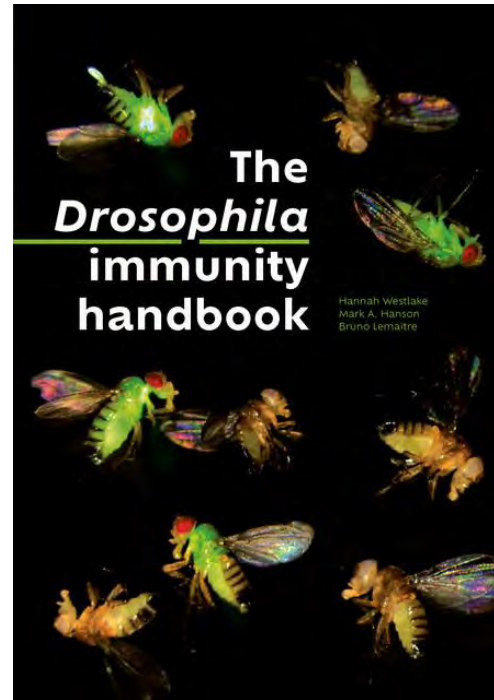
Lydia Michaut

Raymonde Syllas

Reine Clock

Emmanuelle Nicolas

Jules Hoffmann lab



Pdf freely available

The road to Toll (2004) Nature Reviews Immunology 4 (7), 521-527

BBC: Interview on the Toll story
<https://www.bbc.co.uk/programmes/w3ct4r4r>

The conceptual foundations of innate immunity.

Pradeu , Thomma, Girardin, Lemaître (2024) Immunity. 57(4):613

Science, narcissism and the quest for visibility (2017) FEBS journal. 284:875-882

Innate versus adaptative

« Perhaps the most radical conceptual transformation in the field has been the questioning of the definition of innate immunity as such. Innate immunity was originally defined by what it was seen to lack: memory and specificity. This vision has perished as these concepts have been found to be generally applicable to innate immunity. Thus, reconceptualizing innate immunity is a necessity. In our view, the two terms “specific” and “adaptive” are not adequate to distinguish the innate immune system from the adaptative immune system, except when taken in the implicit sense of the clonal selection of a repertoire of immune genes.