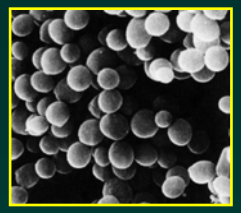
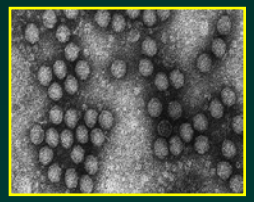
The Antimicrobial Defense of *Drosophila*, A Paradigm for Innate Immunity

Jules Hoffmann, Strasbourg, France

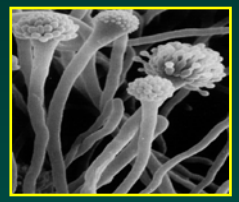


Bacteria



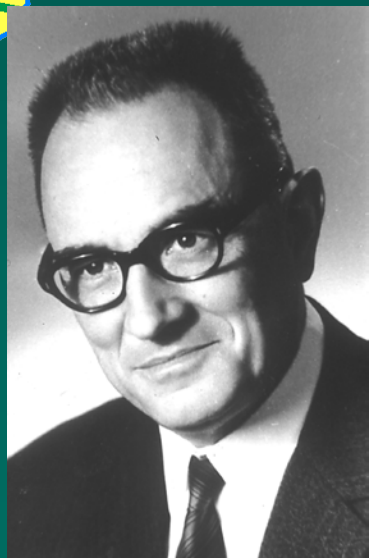
Viruses

Protozoa



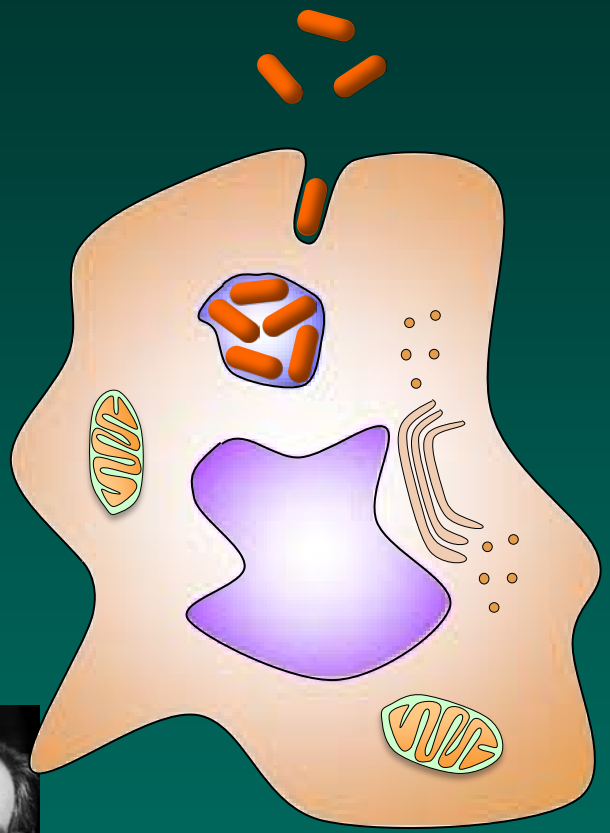
Fungi

Jos Hoffmann 1911-2000



Pierre Joly 1913-1996

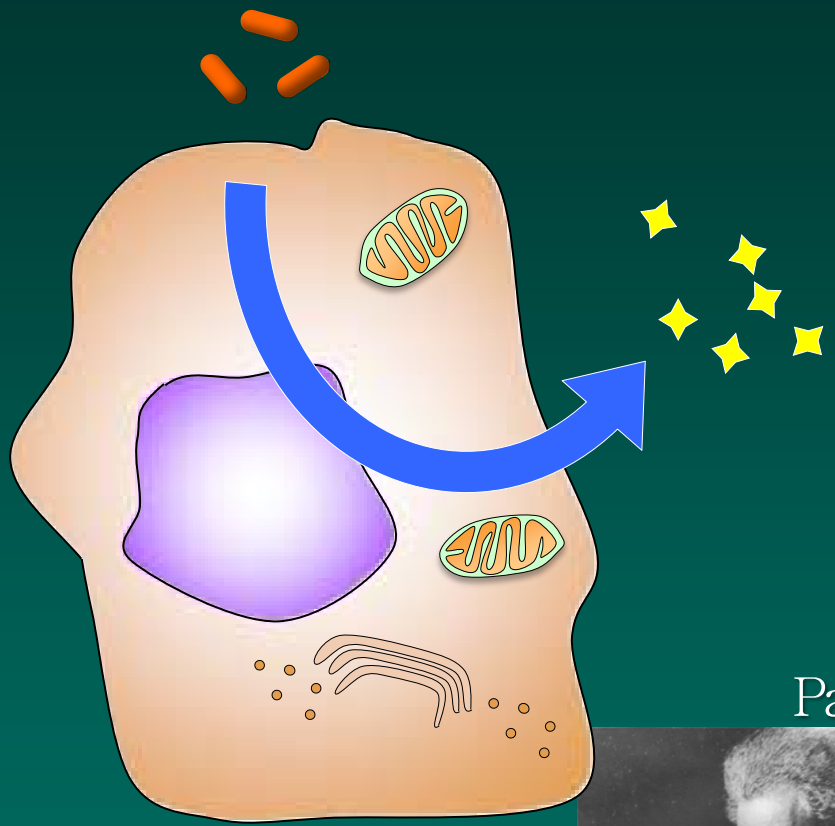
Antimicrobial Defenses in Insects : First Investigations



Phagocytosis

« Cellular Immunity »

Metchnikoff, 1880



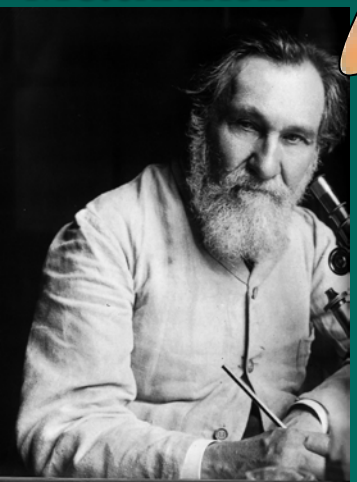
Antimicrobial substances in the blood

« Humoral Immunity»

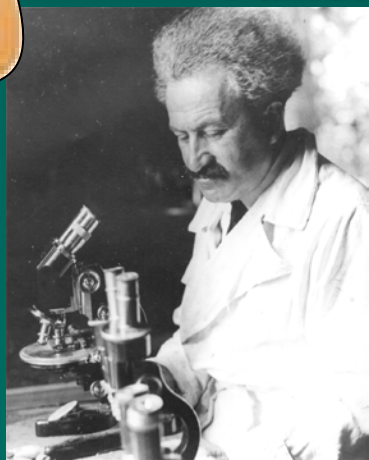
Paillot 1920-1935

Glaser

Metchnikoff



Paillot



Induction of an antimicrobial activity in Drosophila by an immune challenge

Hyalophora cecropia

Antimicrobial activity in the *cell-free hemolymph*

1

Injection of bacteria

2

3

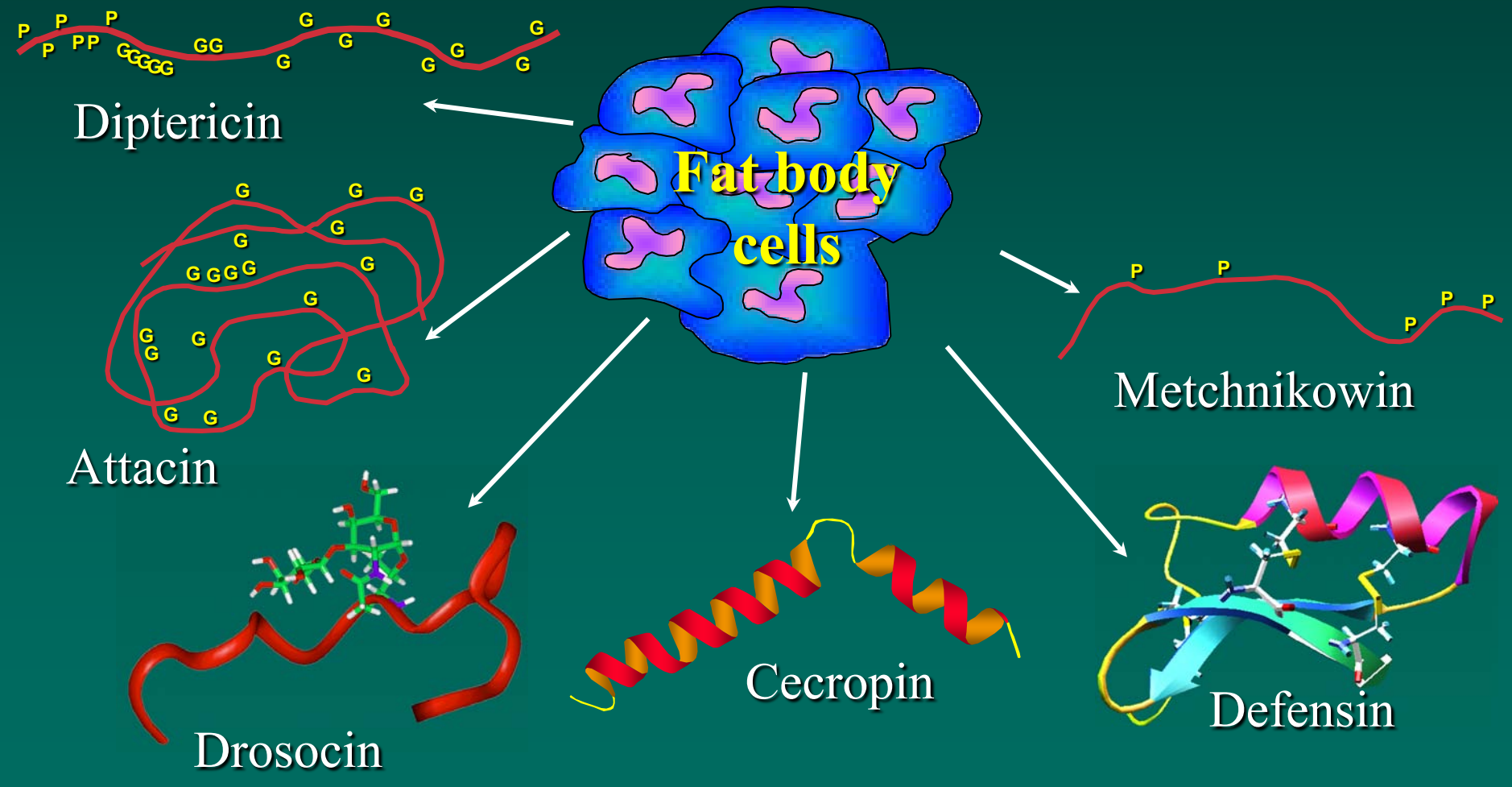
Control

0 3 6 9 12 24 48

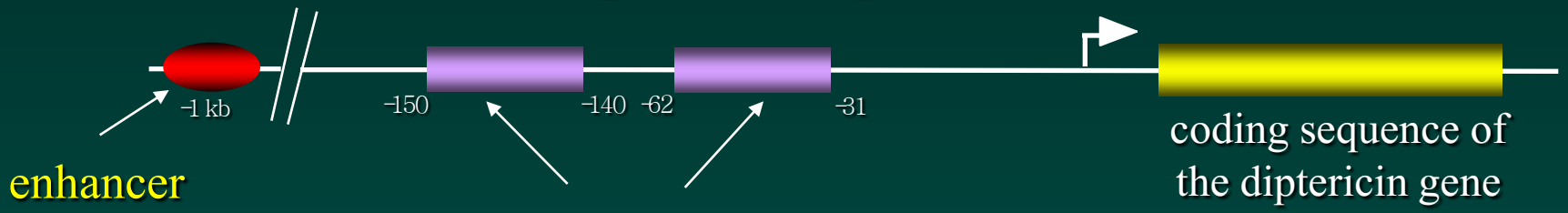
Time (h)

Hans Boman
1924–2008

Systemic ("humoral") antimicrobial response in Drosophila – *identification of antimicrobial peptides*

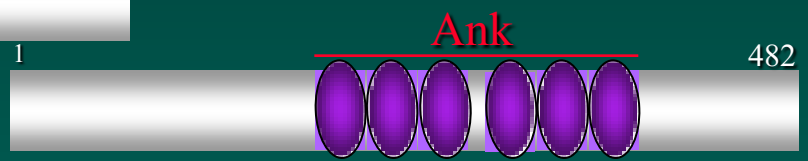


NF-κB response elements in the promoter of the diptericin gene



Stewart 1987

DORSAL



CACTUS

Unchallenged

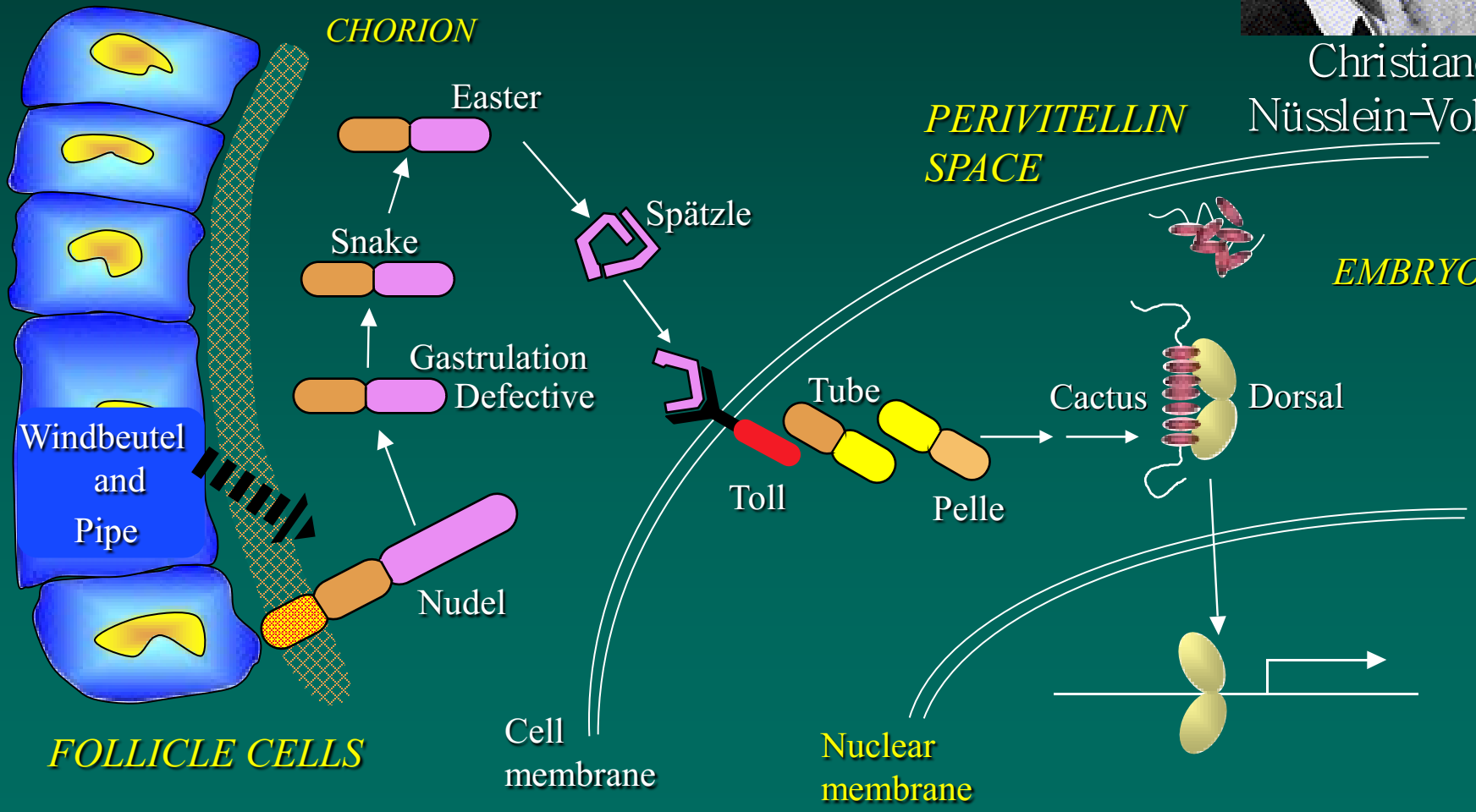
Diptericin-LacZ reporter gene

Challenged

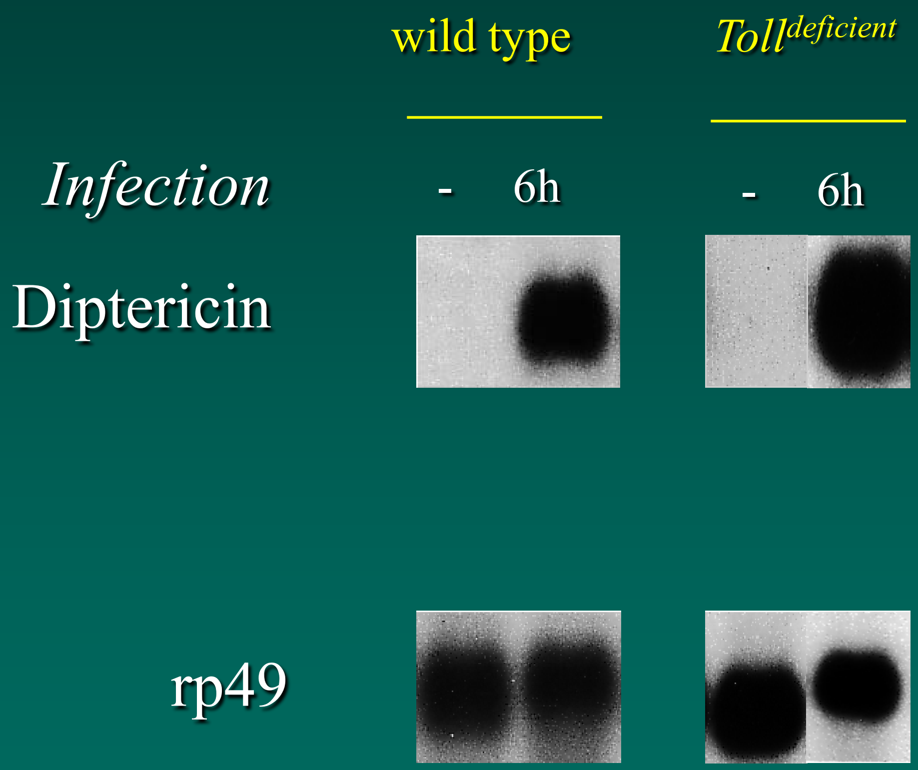
Versailles, 18 years ago, Innate Immunity Conference

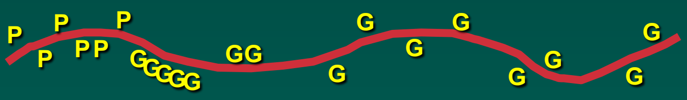
Gene cascade controlling the dorso-ventral axis in the Drosophila *embryo*

Christiane Nüsslein-Volhard

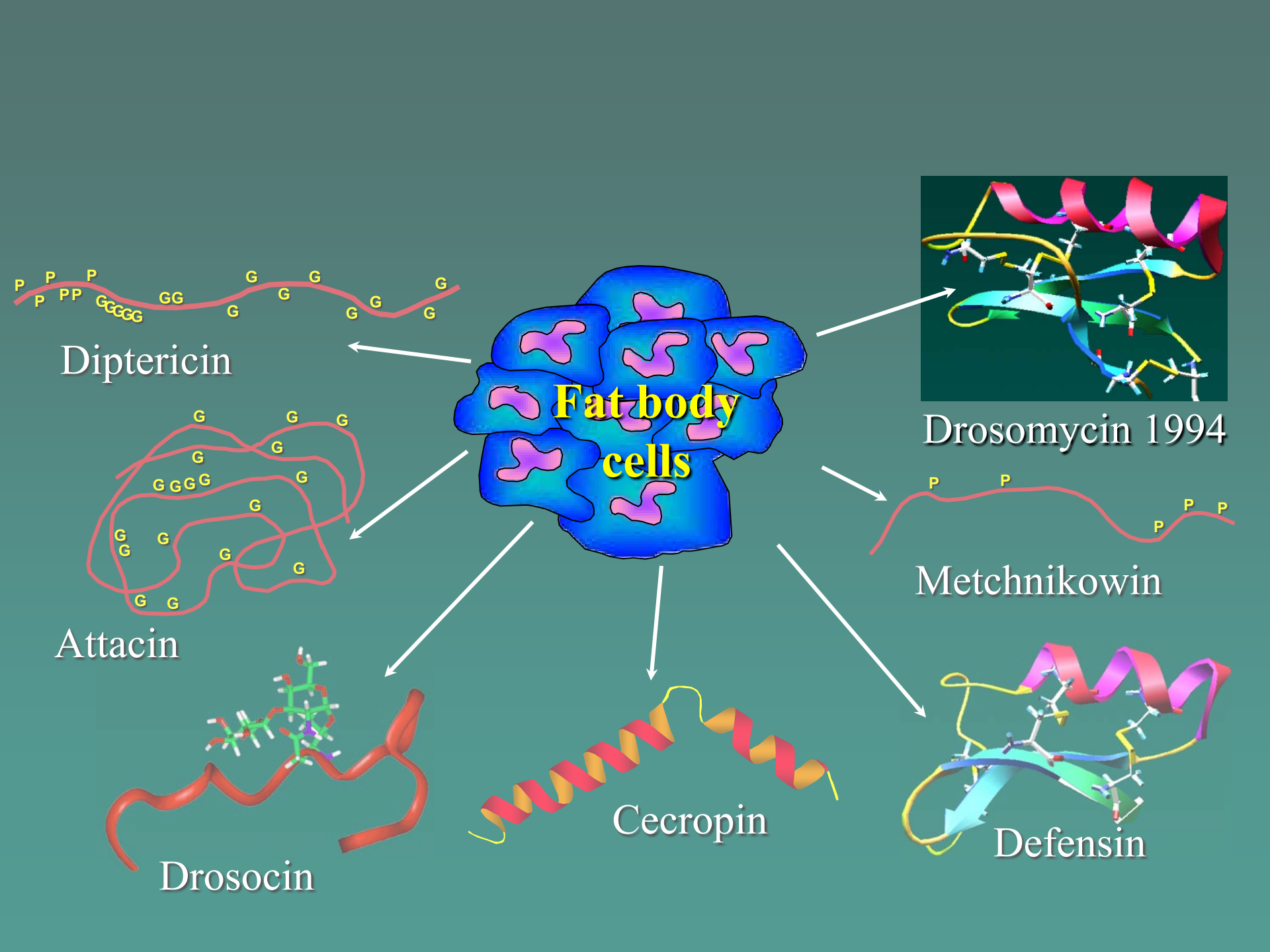


Do the genes of the Spätzle/Toll/Dorsal *cassette control the challenge-induced expression of diptericin ?*

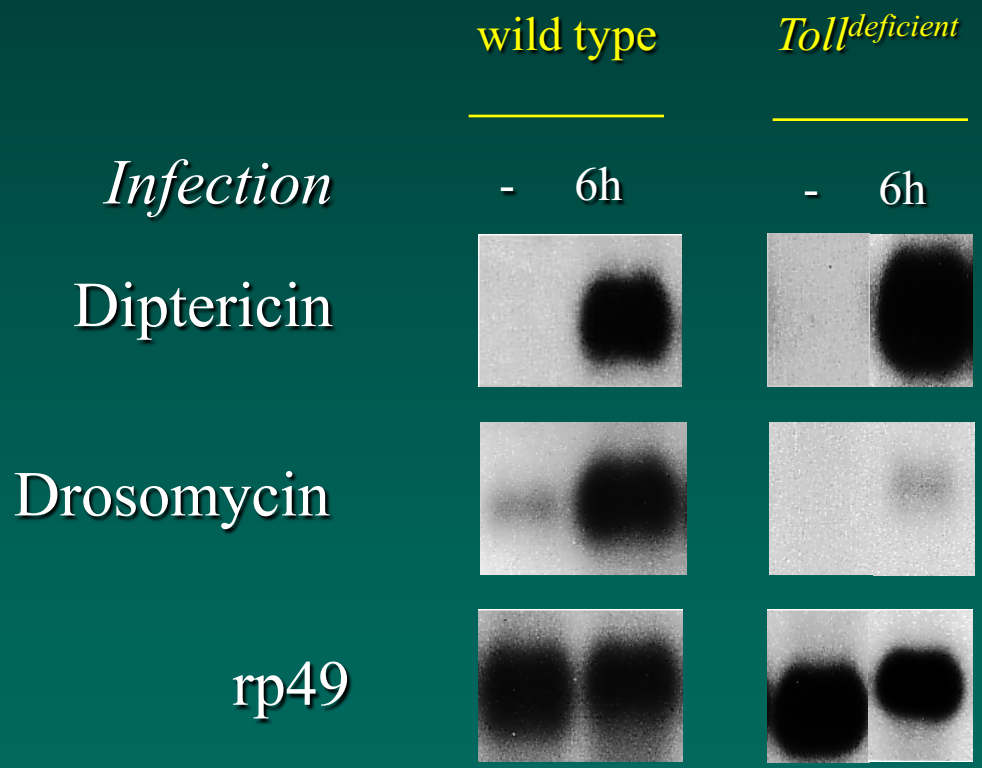


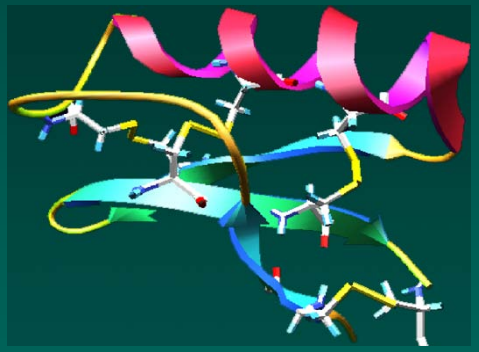


Diptericin 1990


Fat body cells
Diptericin
Drosomycin 1994
Attacin
Metchnikowin
Drosocin
Cecropin
Defensin

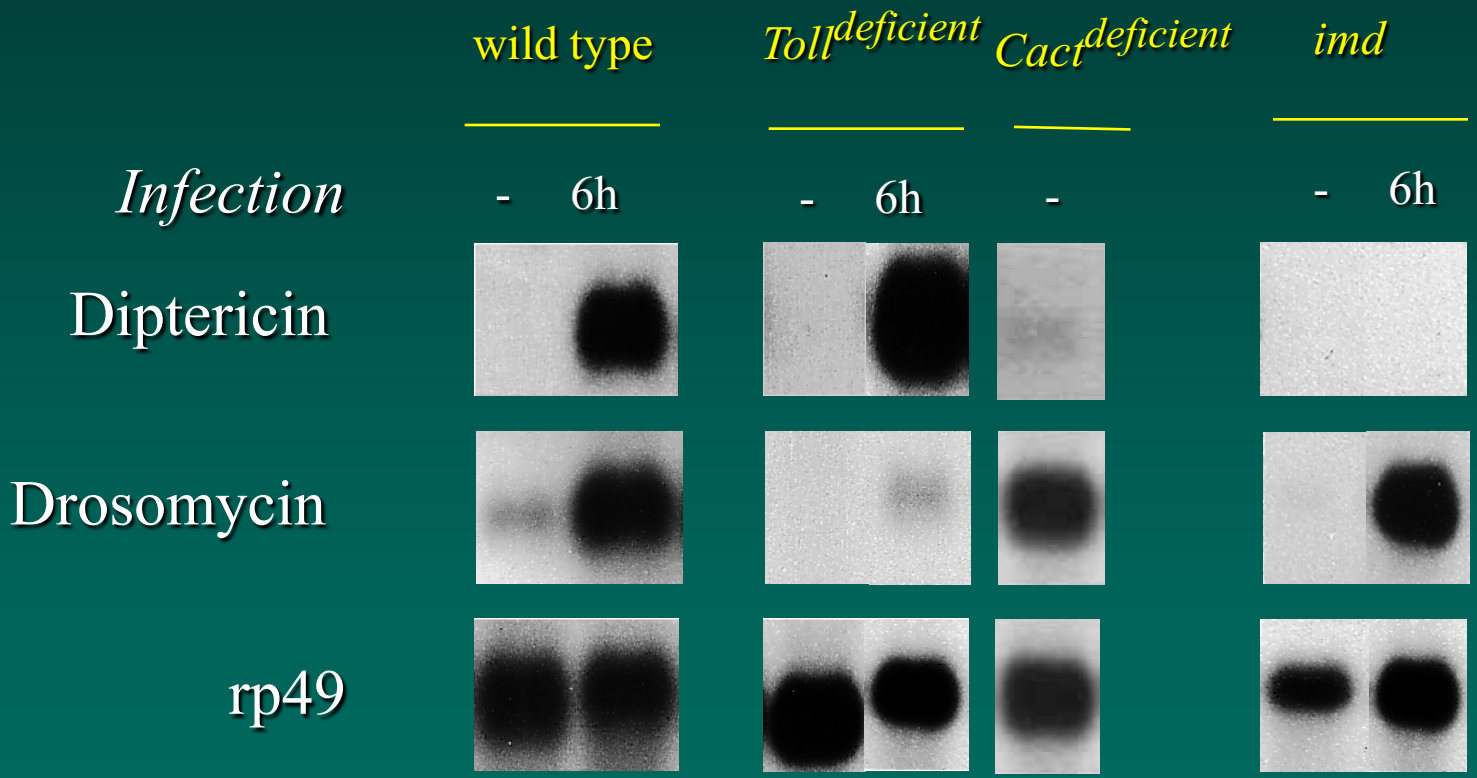
The challenge-induced expression of the Drosomycin *gene is dependent on the Toll pathway.*



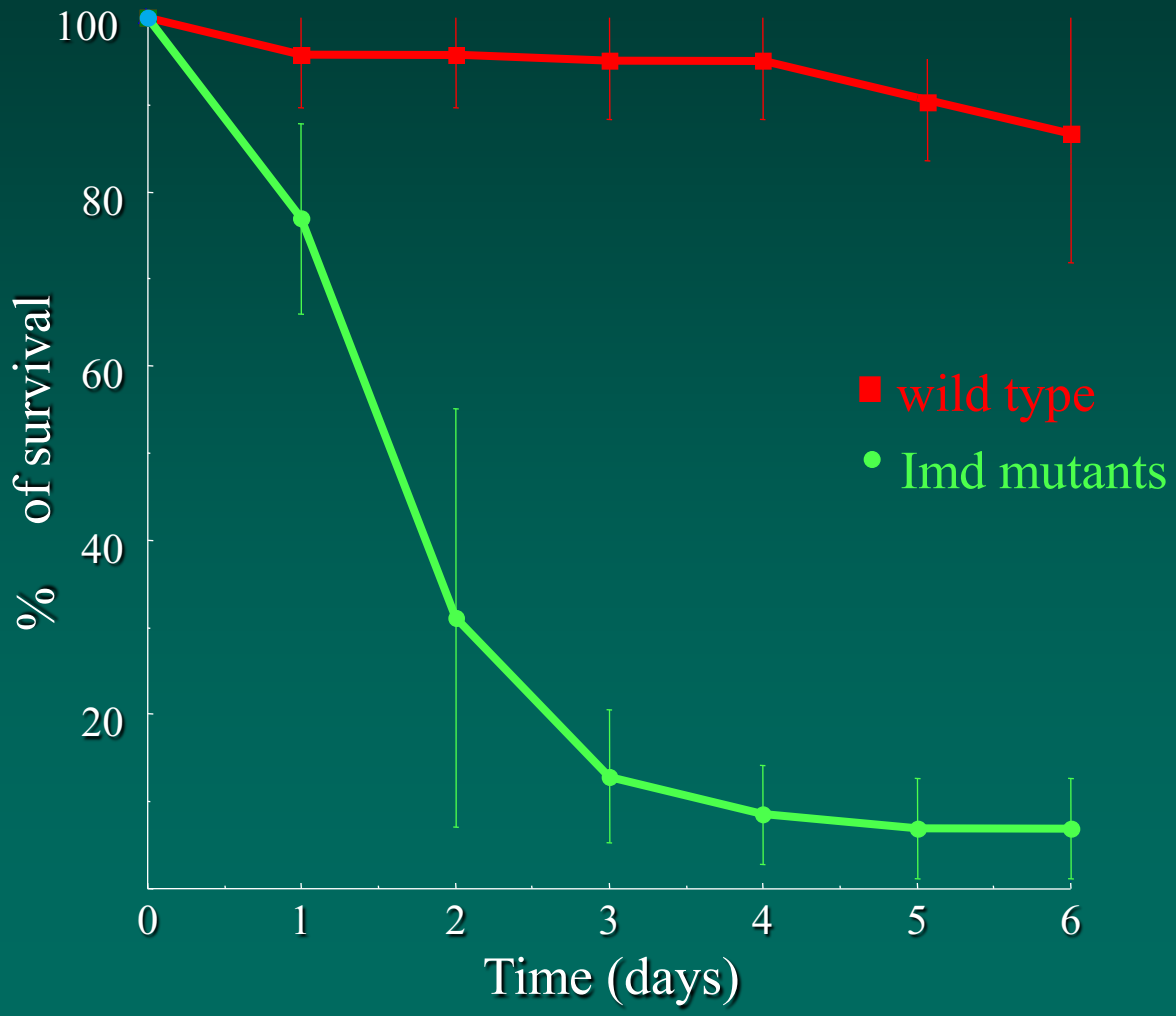


Drosomycin 1994

Two distinct pathways control the expression of antimicrobial peptides

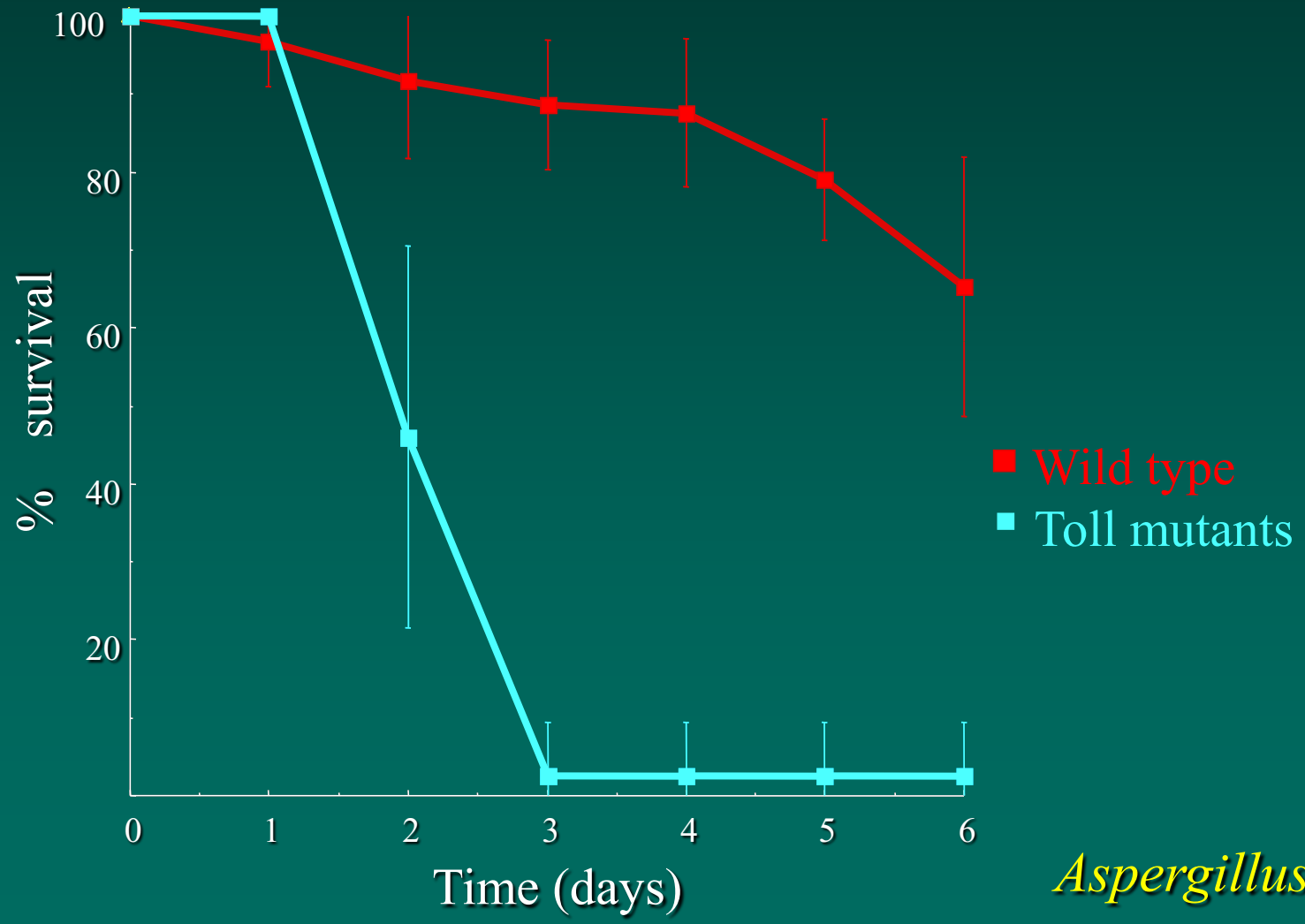


Imd pathway mutants are sensitive to bacterial infections



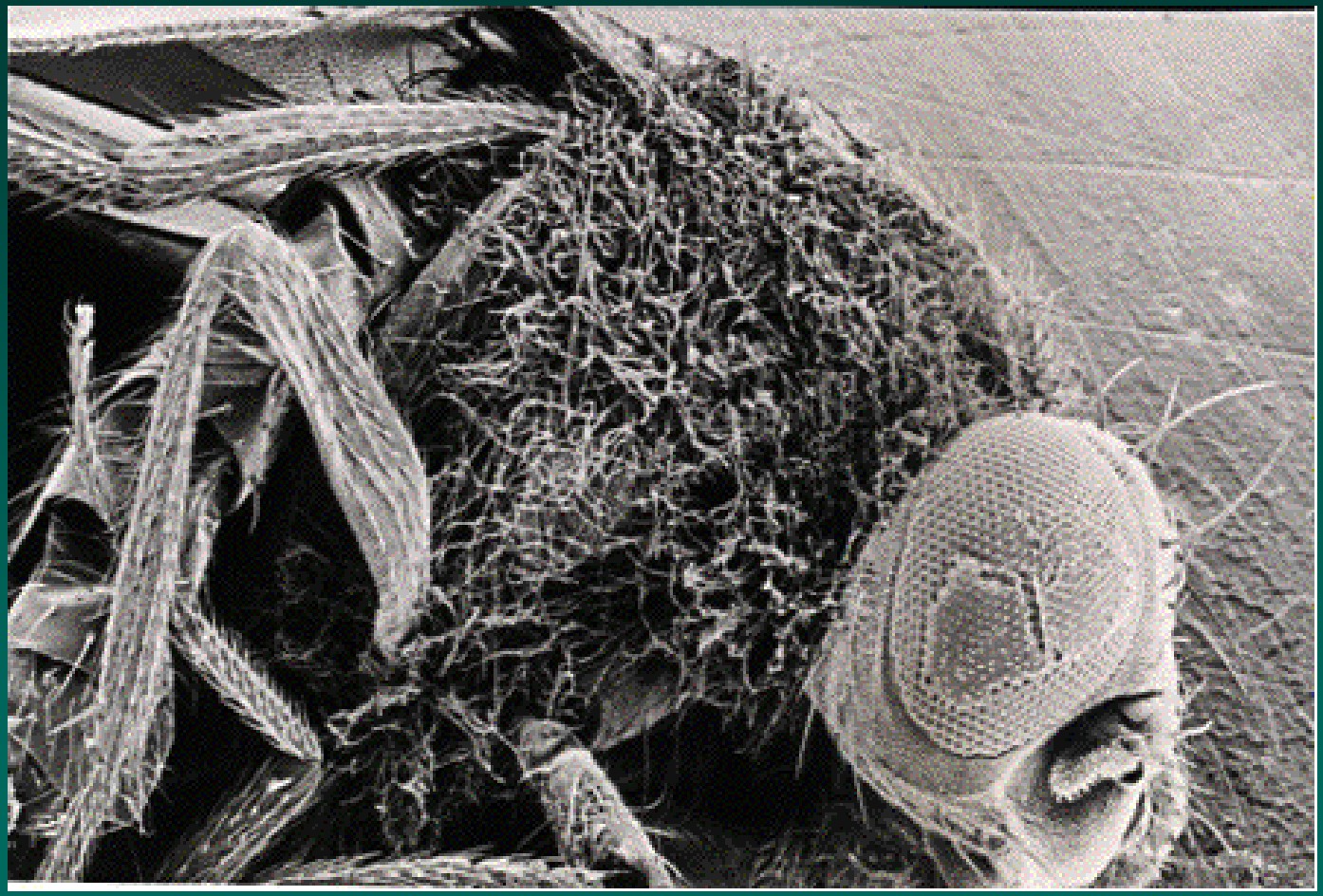
E. coli infection

Toll pathway mutants are sensitive to fungal infections



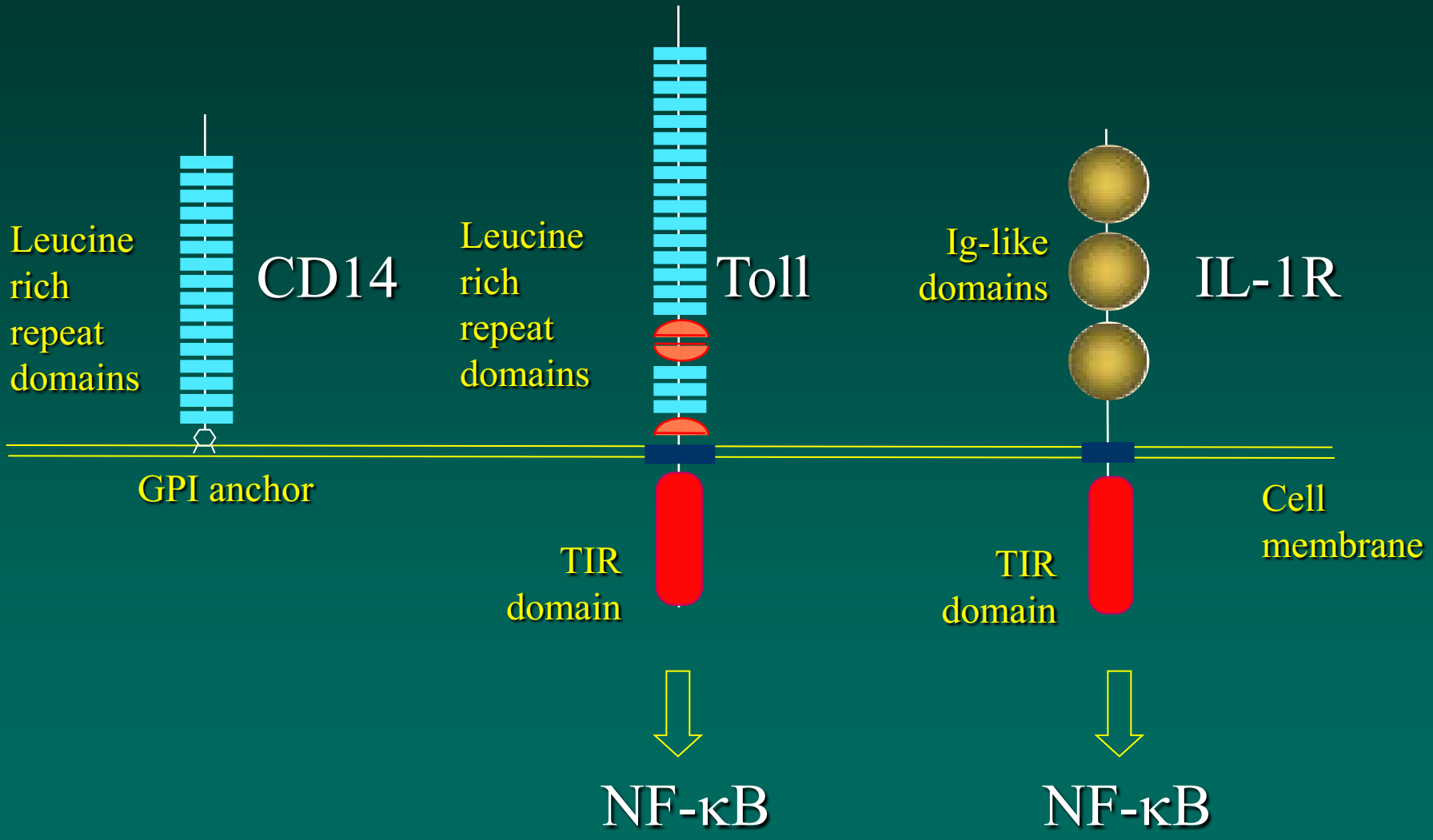
Aspergillus infection

Overwhelming fungal infection in a Toll deficient background

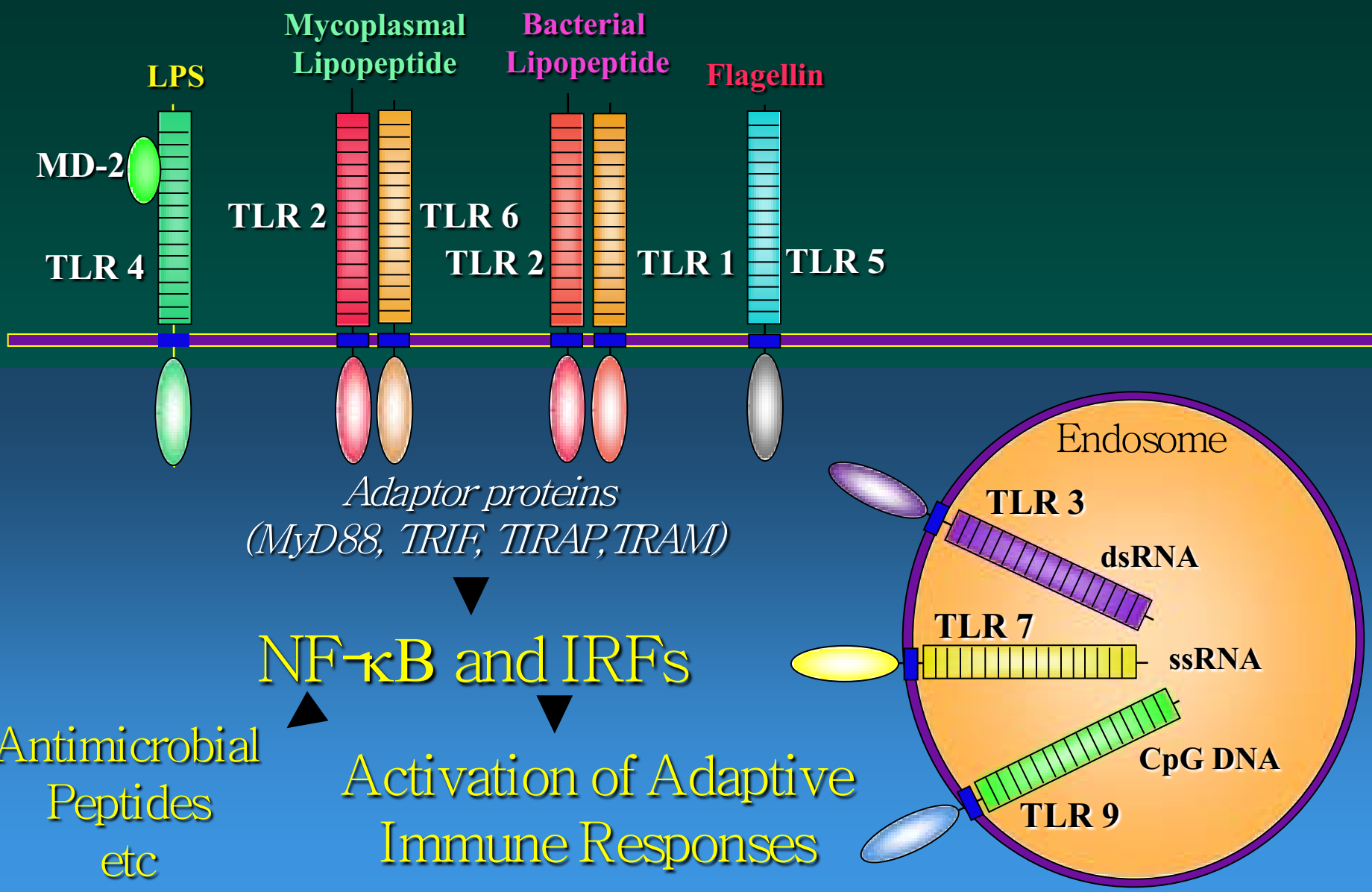


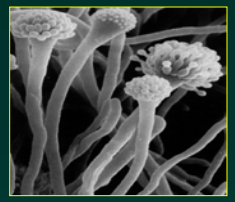
Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. *Cell, 1996, 20:973-83*

NF-κB activation by Toll and IL-1

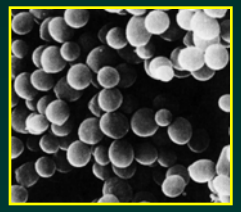


Activation of NF-κB by TLR family members





Fungi



Gram positive bacteria

Receptors

Proteolytic cascade

Spaetzle

Toll

Toll-2

Toll-3

Toll-4

Toll-5

Toll-6

Toll-7

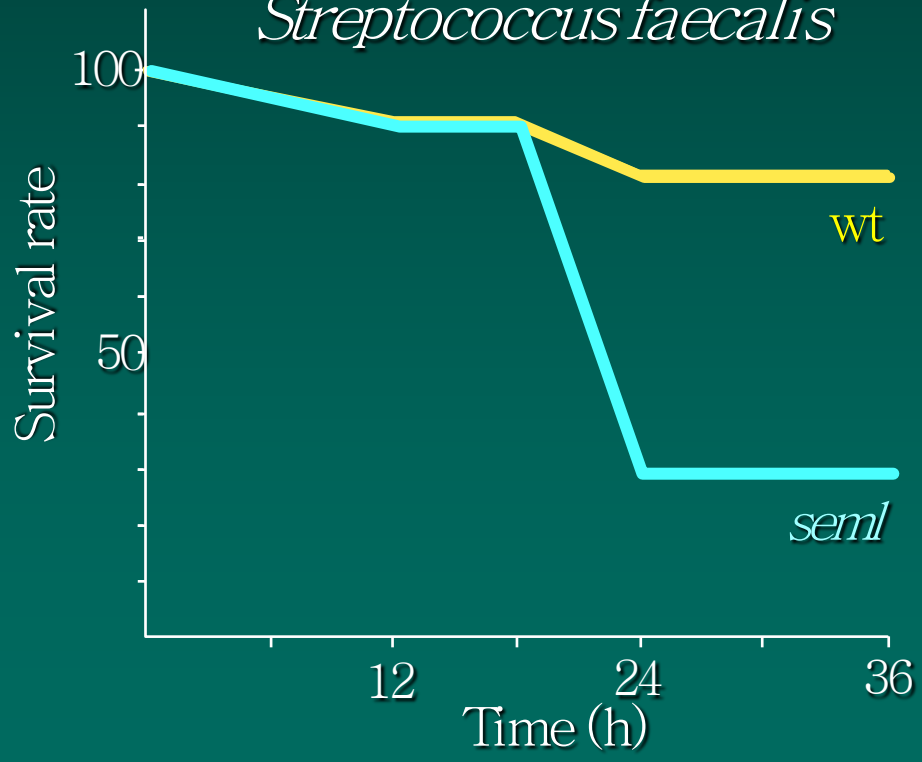
Toll-8

Toll-9

NF-κB

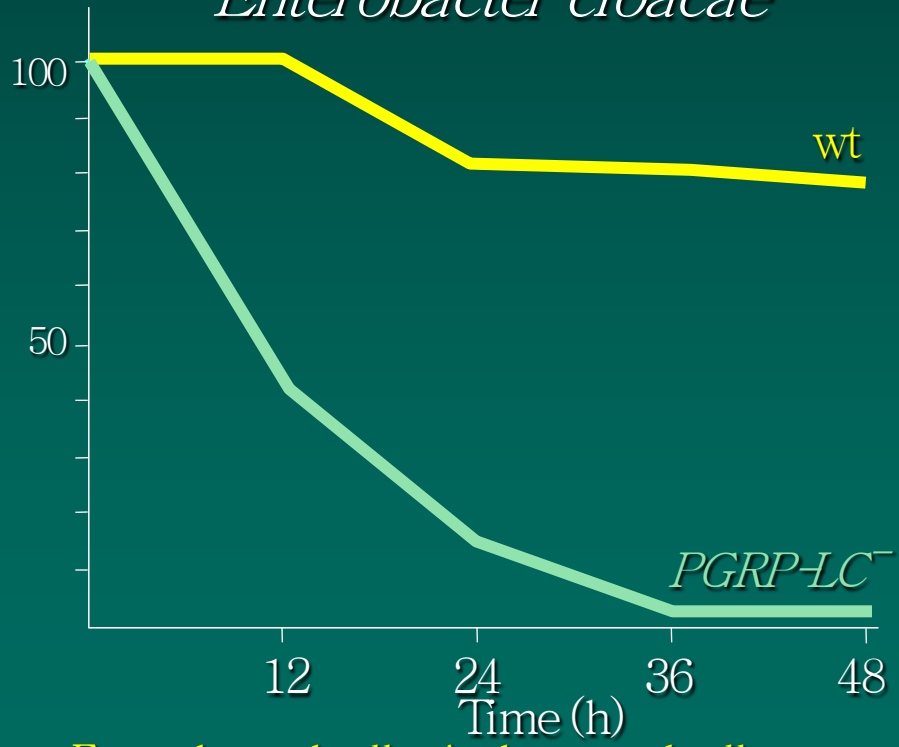
A mutation in the PGRP-SA gene (semmelweis) *compromises the anti-Gram-positive defense*

Infection by *Streptococcus faecalis*



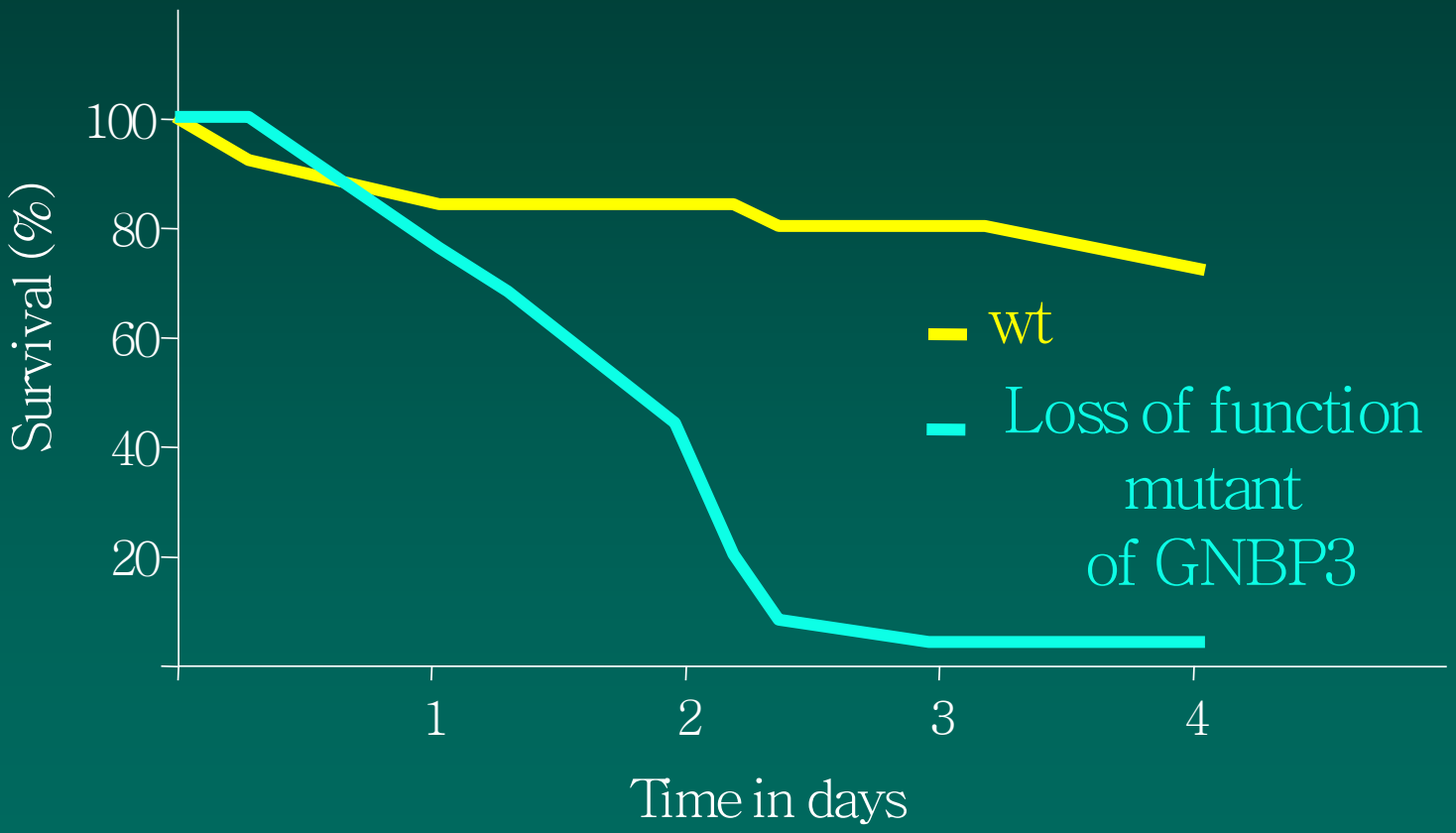
A mutation in the PGRP-LC gene compromises the defense against Gram-negative bacteria

Infection by *Enterobacter cloacae*



Royet and coll. 2001, Royet, Ferrandon and coll., Anderson and coll., Ezekowitz and coll. 2002

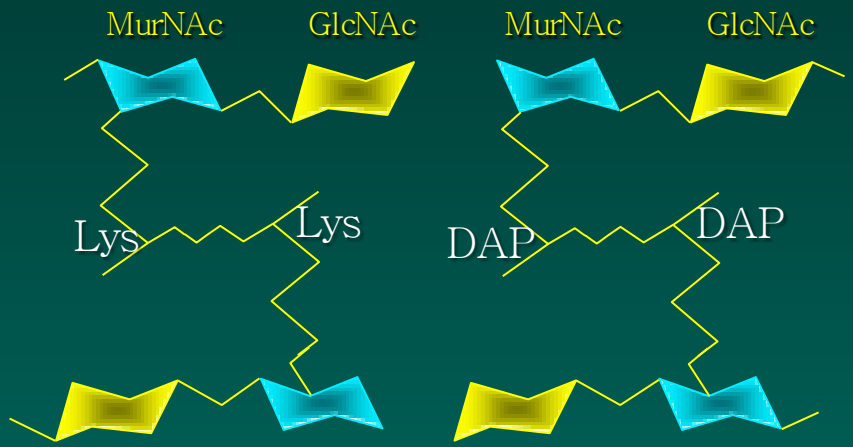
A mutation in the gene encoding GNBP3 *compromises resistance to* Candida *infections*



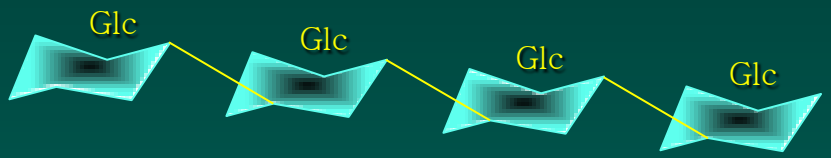
Microbial Inducers of Immune Responses and Cognate Receptors in Flies:

Peptidoglycan Recognition Proteins and Glucan Binding Proteins

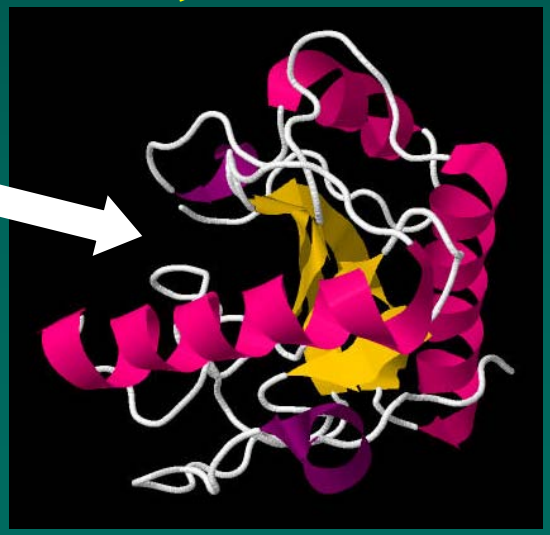
Peptidoglycan



β-(1,3) -Glucan



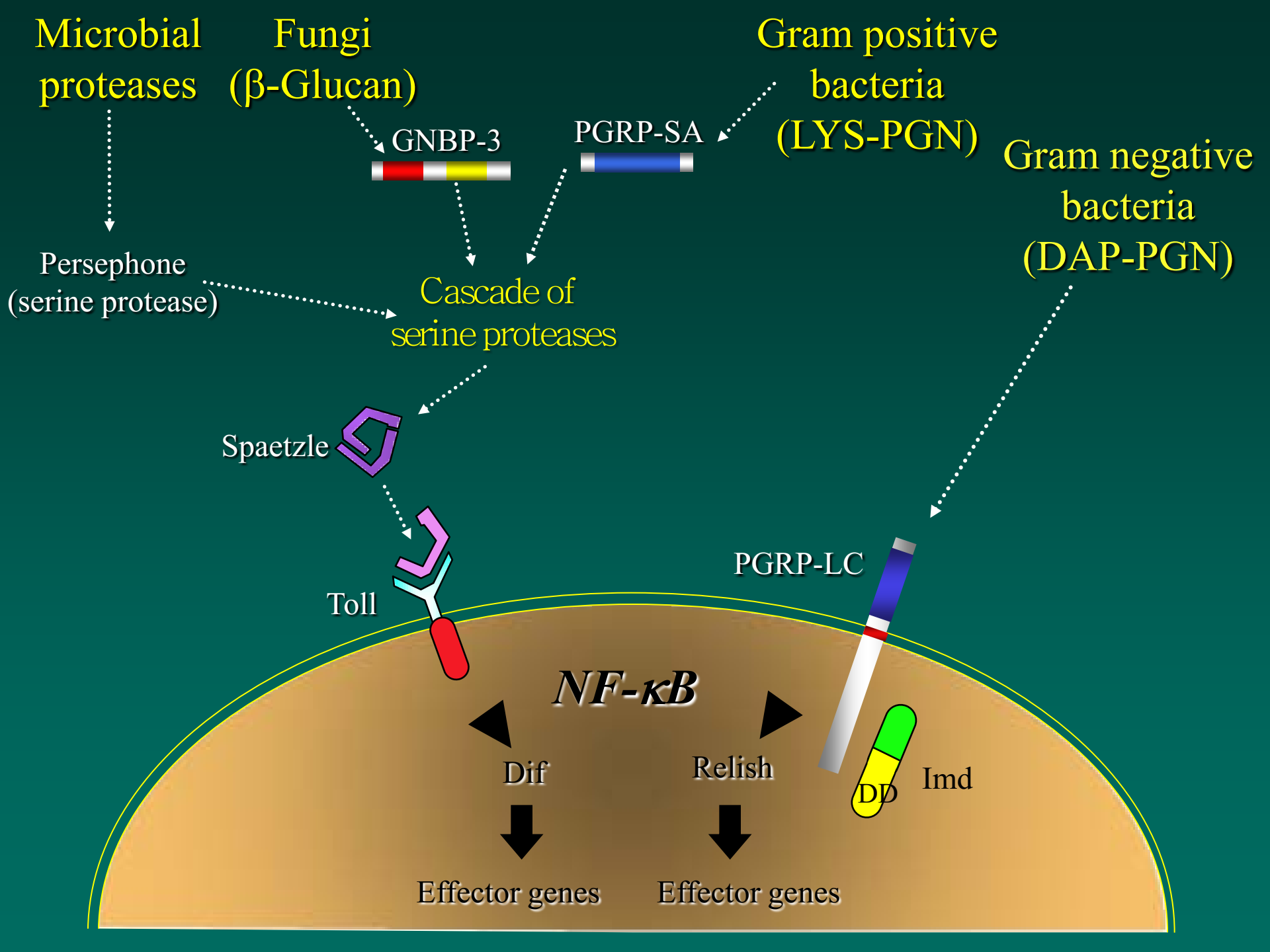
PGRP



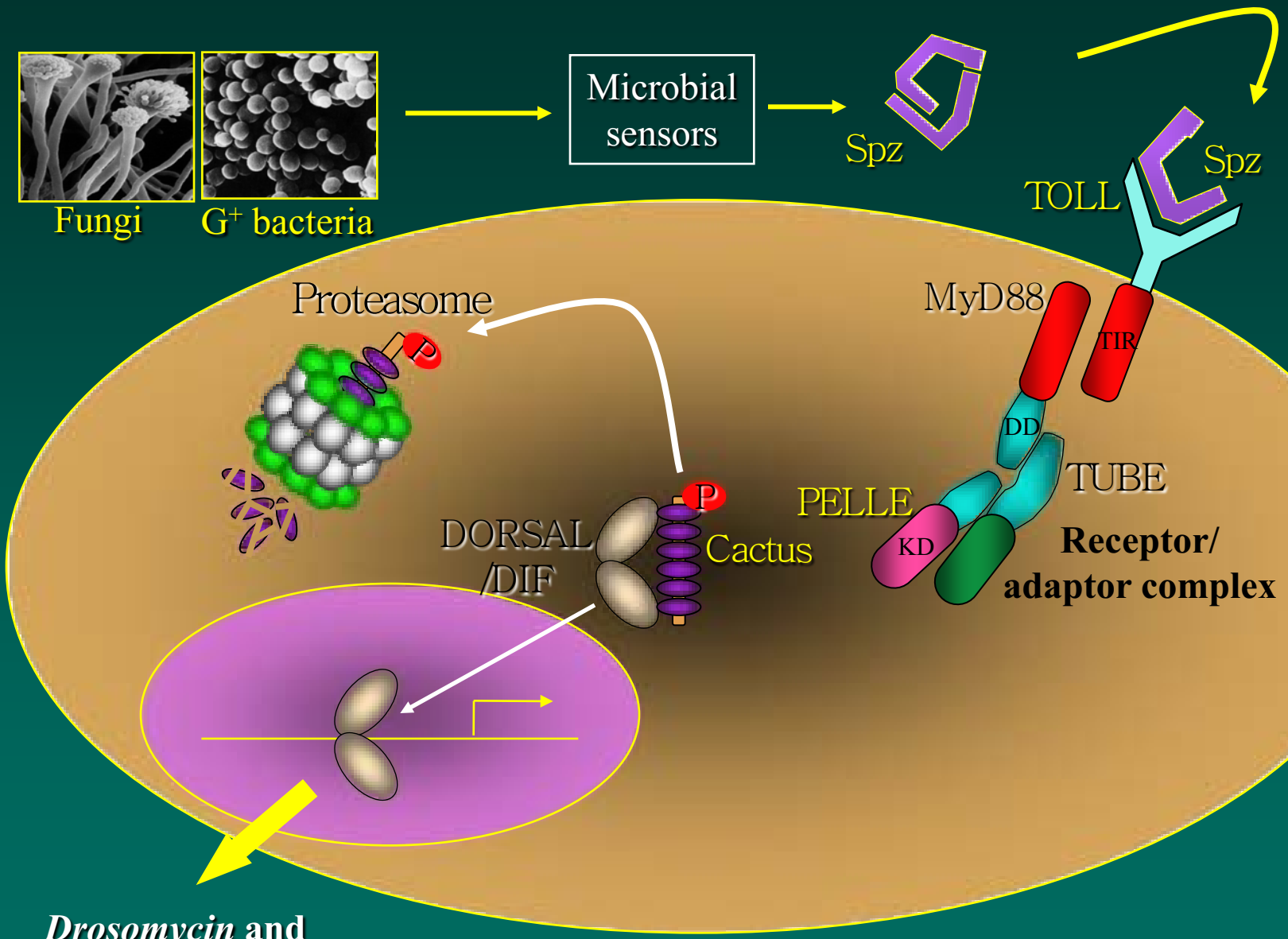
GNBP

Rousse/ and coll.

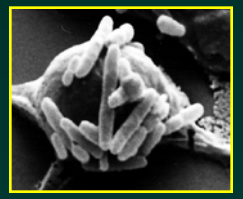
Werner and coll.; Kim and coll.; Reiser and coll.; Chang and coll.


Microbial proteases
Fungi (β-Glucan)
Gram positive bacteria (LYS-PGN)
GNBP-3
PGRP-SA
Gram negative bacteria (DAP-PGN)
Persephone (serine protease)
Cascade of serine proteases
Spaetzle
Toll
PGRP-LC
NF-κB
Dif
Relish
DD
Imd
Effector genes
Effector genes

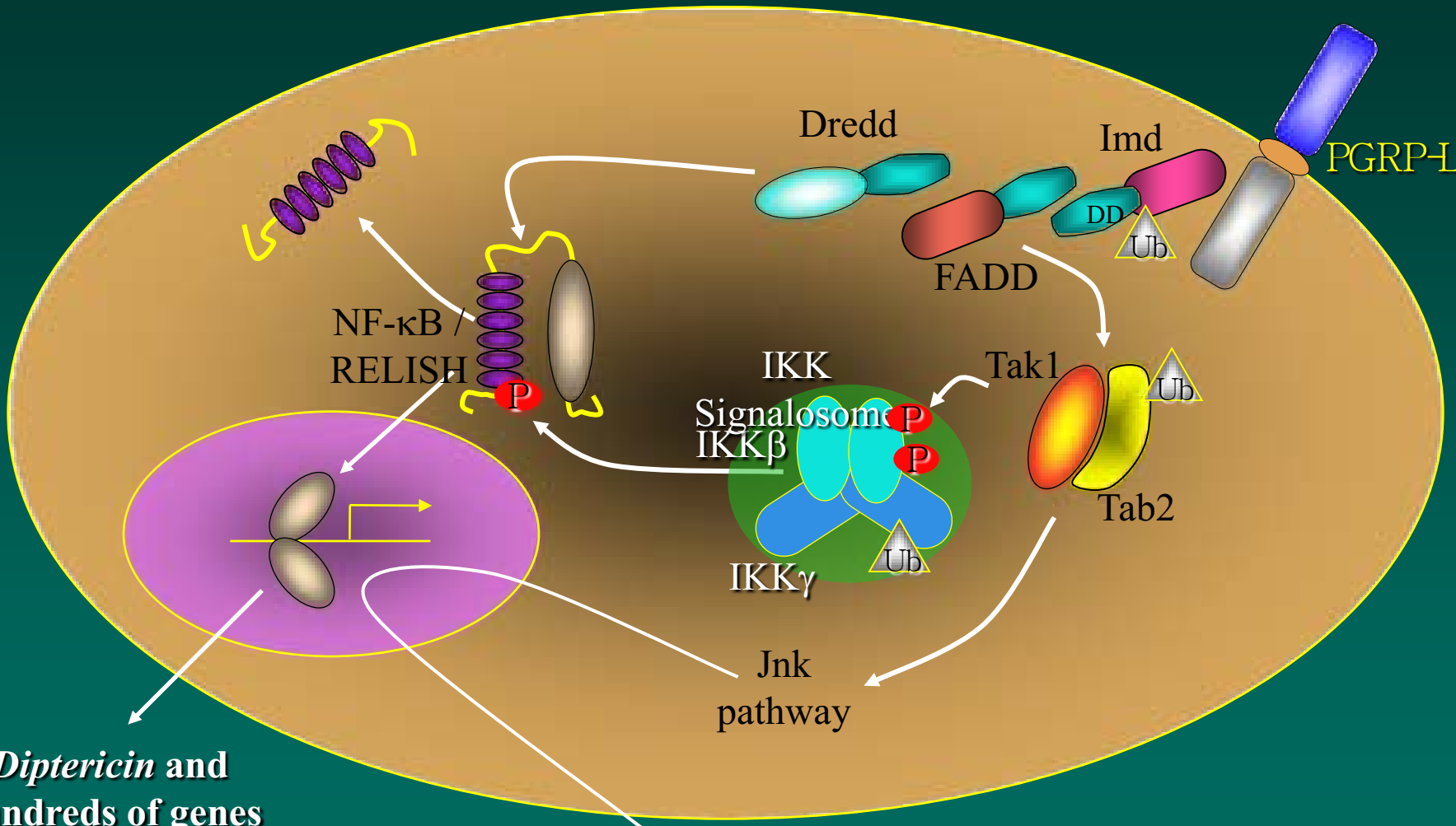
NF-κB activation by Toll in Drosophila

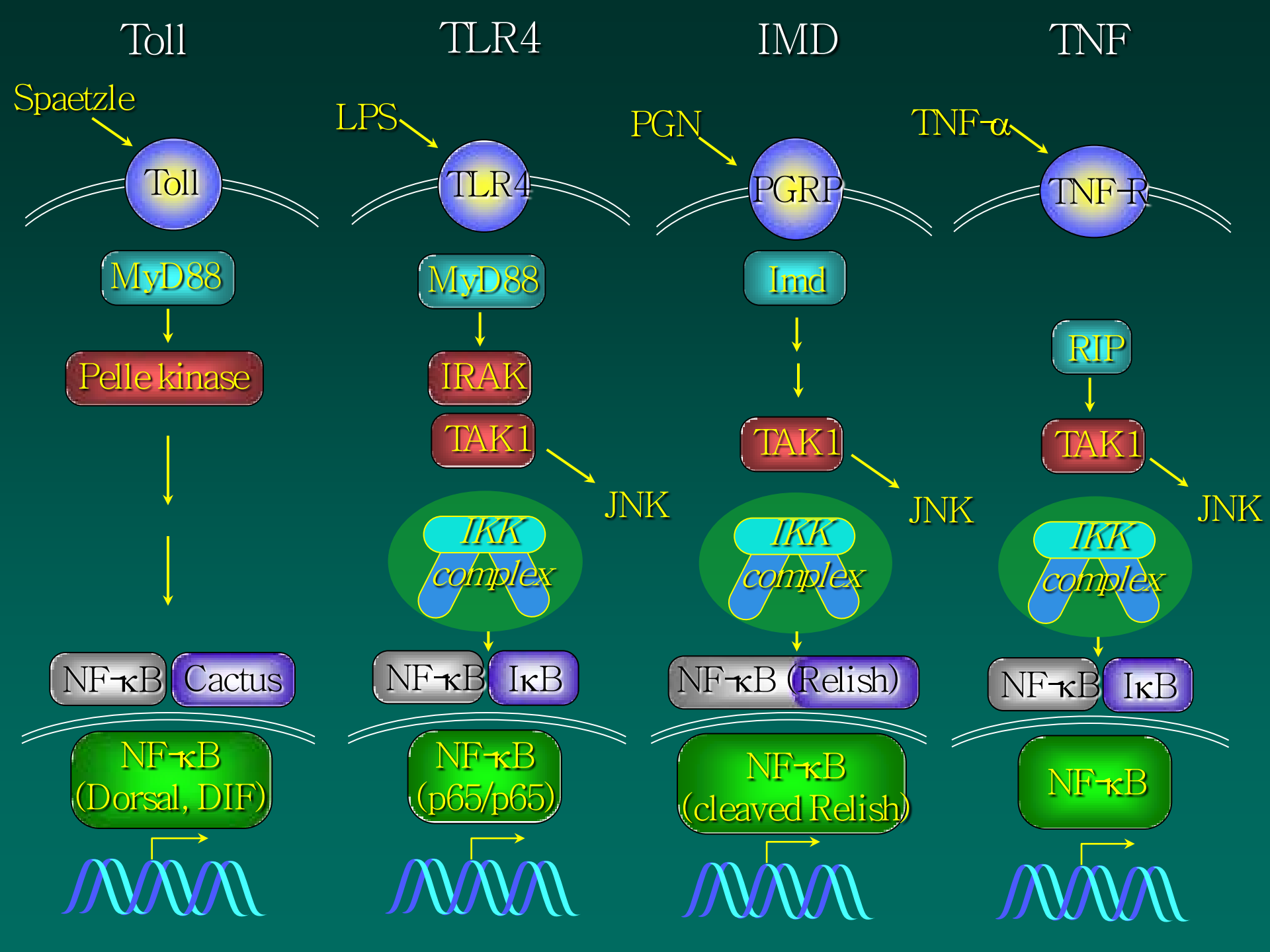


NF-κB activation by IMD in Drosophila

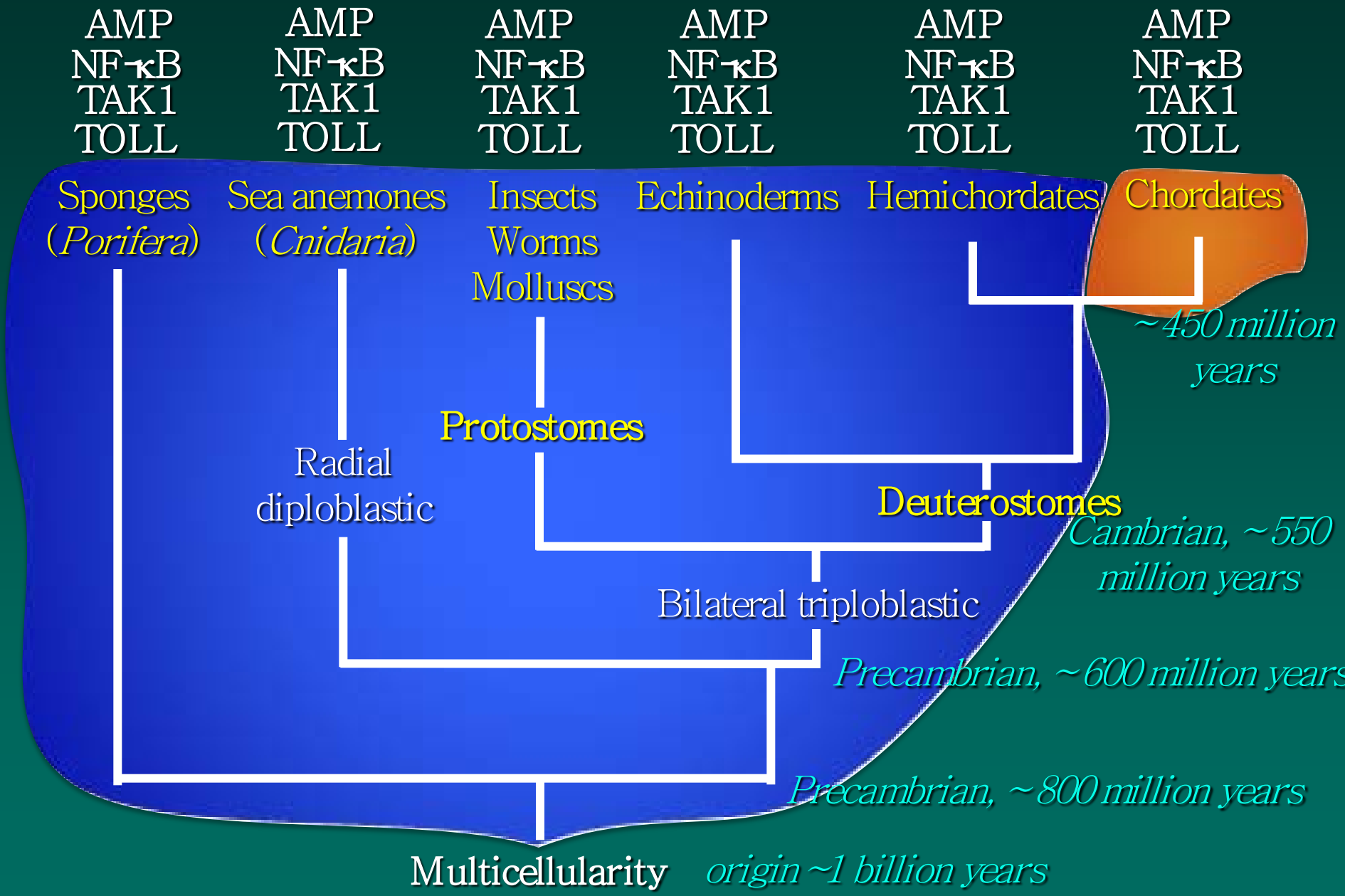


G- Bacteria



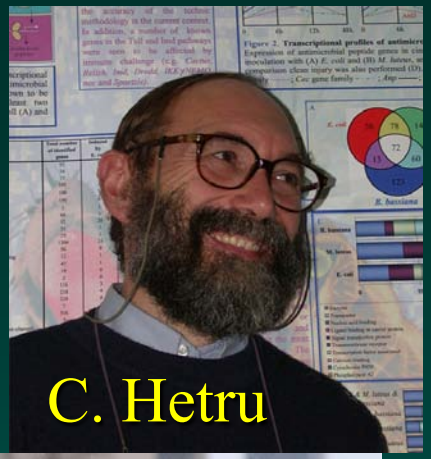

Toll
TLR4
IMD
TNF
Spaetzle
LPS
PGN
TNF-α
Toll
TLR4
PGRP
TNF-R
MyD88
MyD88
Imd
RIP
Pelle kinase
IRAK
TAK1
TAK1
TAK1
JNK
JNK
JNK
IKK complex
IKK complex
IKK complex
NF-κB
Cactus
NF-κB
IκB
NF-κB (Relish)
NF-κB
IκB
NF-κB (Dorsal, DIF)
NF-κB (p65/p65)
NF-κB (cleaved Relish)
NF-κB

Phylogeny of Innate Immune Defenses



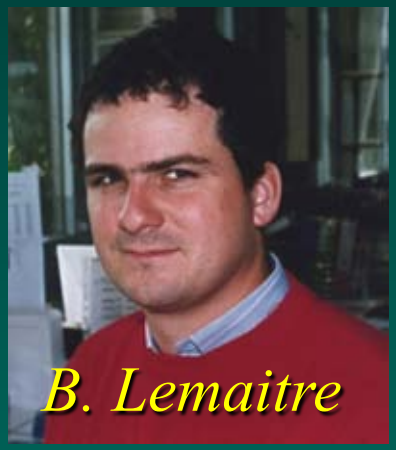
Acknowledgements


D. Hoffmann

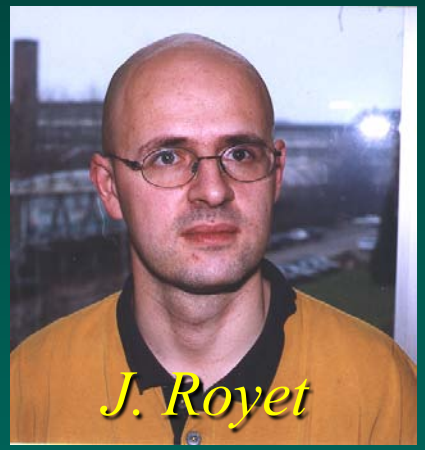

C. Hetru

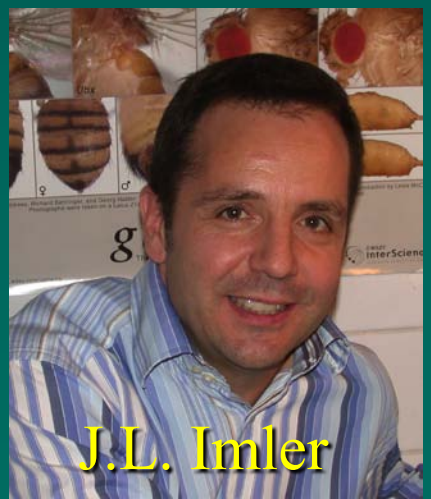

JL. Dimarcq


J.M. Reichhart


B. Lemaitre

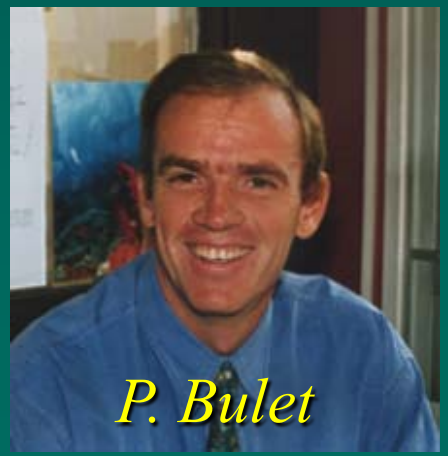

D. Ferrandon


J. Royet


J.L. Imler


E. Levashina


M. Lagueux


P. Bulet

Credits : Drosophila *immunity*

USA,

Kathryn Anderson
Carl Hashimoto
Steve Wasserman

Tony Ip

Ruth Stewart
Shuba Govind

Neal Silverman
Tom Maniatis

Alan Ezekowitz
Nathalie Franc
Linda Stuart
Christine Kocks

Norbert Perrimon
Herve Agaisse
Michael Boutros

David Schneider

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Hakan Steiner
Dan Hultmark
Ingrid Faye
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Ulli Theopold

Bruno Lemaitre
François Leulier
Julien Royet

Mika Ramet
Nick Gay

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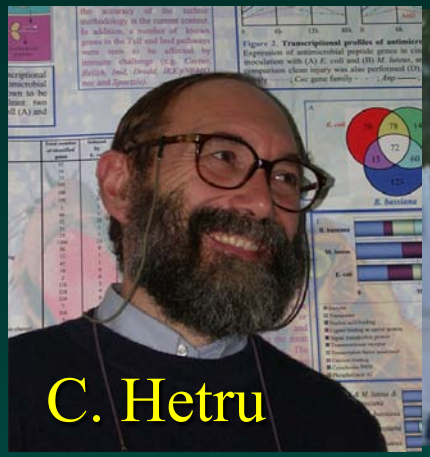
Shoichiro Kurata
Won-Jae Lee

Young-Joon Kim

Acknow-ledge-ments


D. Hoffmann


C. Hetru

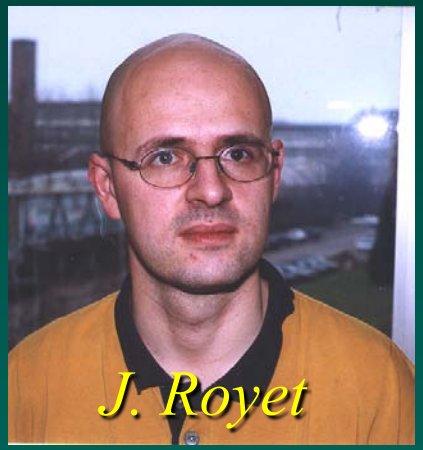

B. Lemaitre

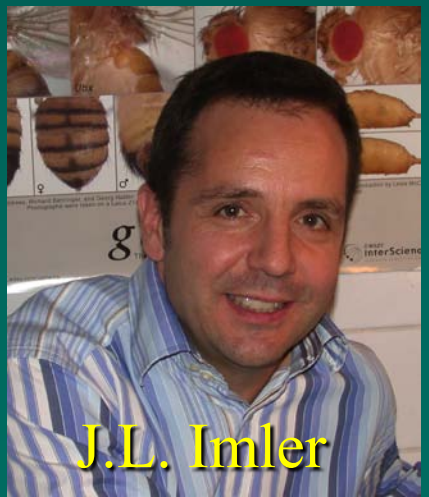

JL. Dimarcq


J.M. Reichhart


D. Ferrandon

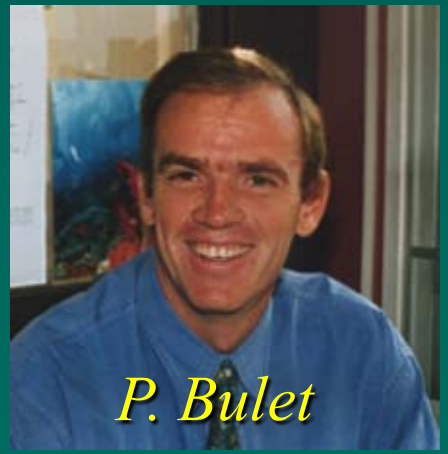

M. Meister


J. Royet

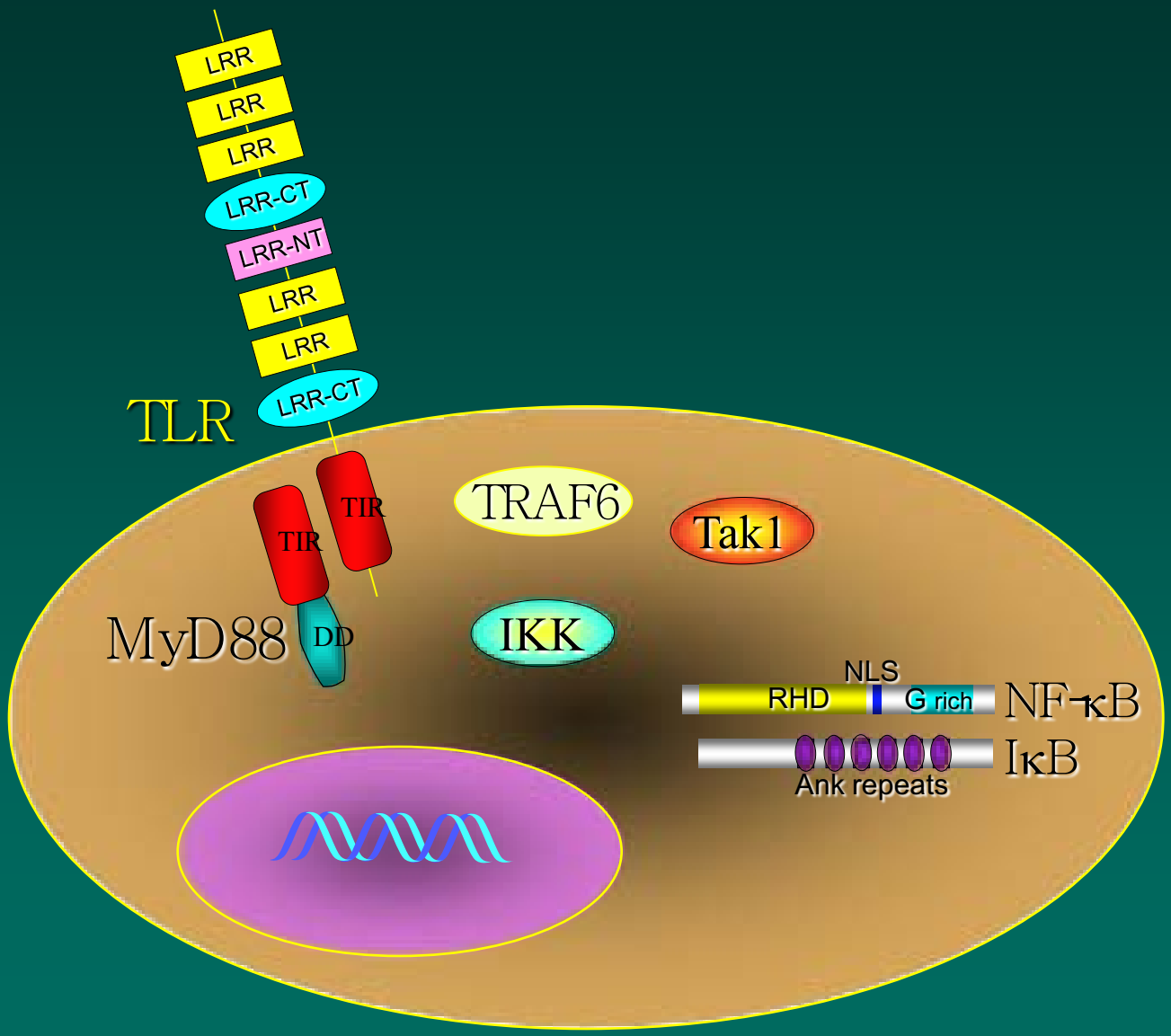

J.L. Imler


E. Levashina

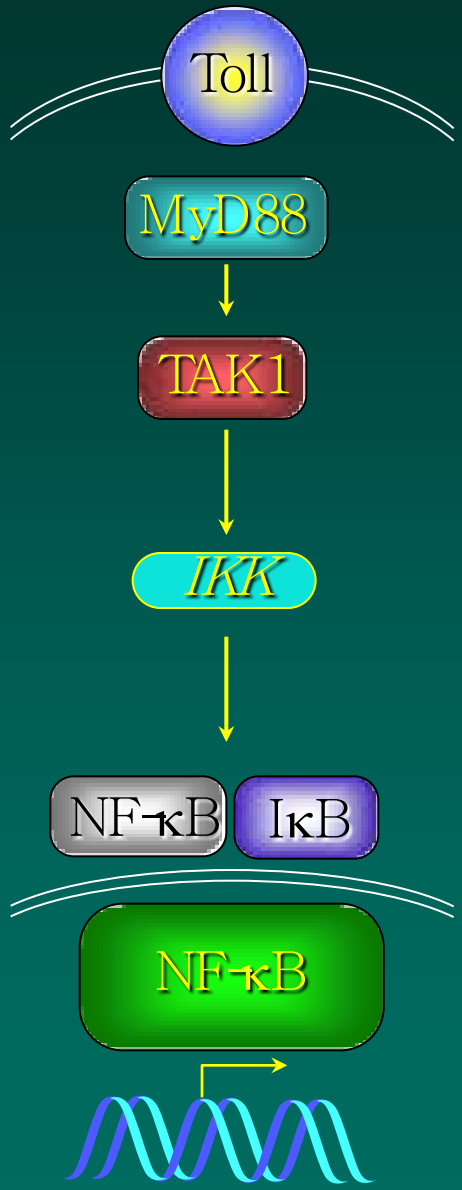

M. Lagueux

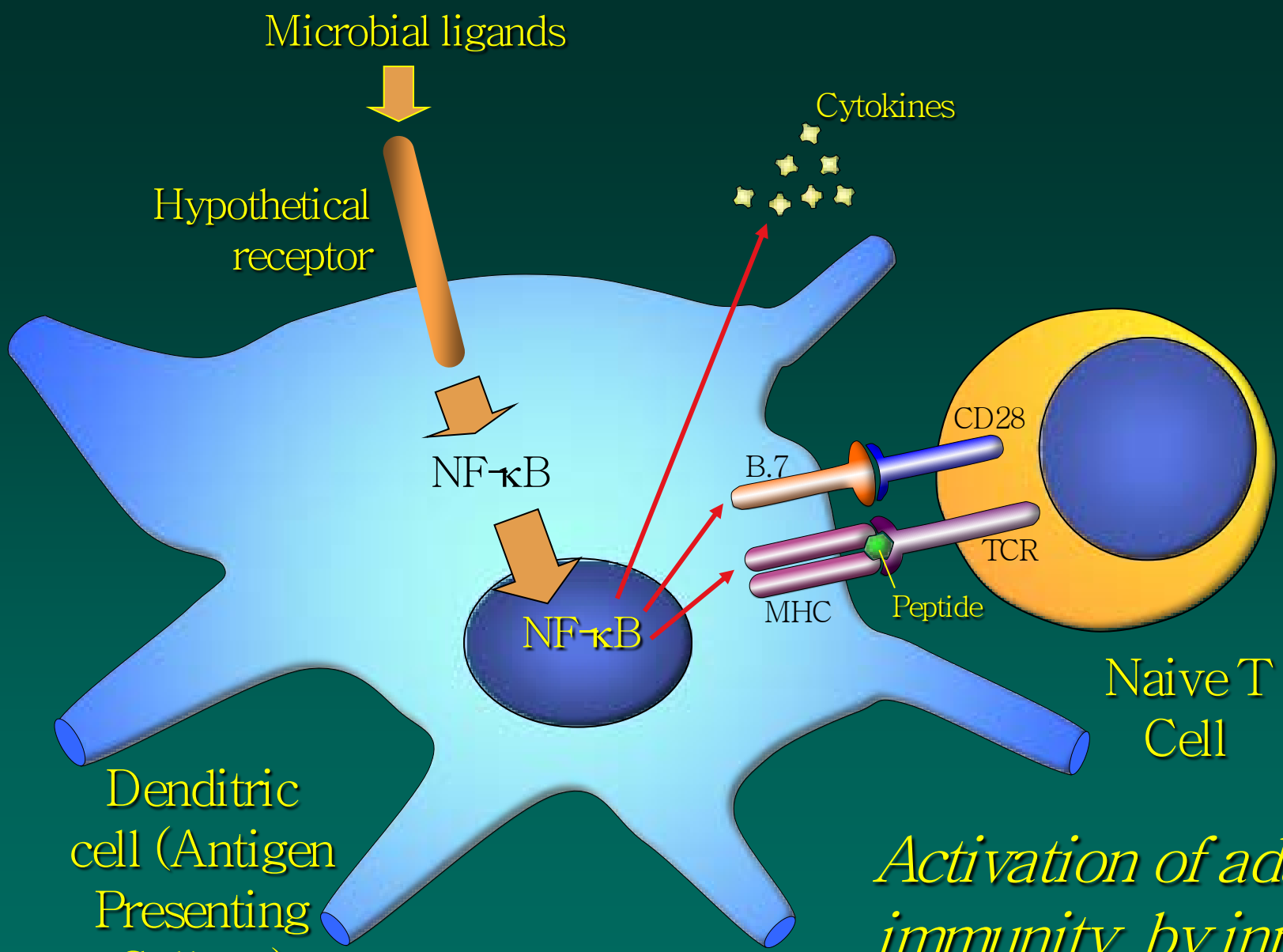

P. Bulet

The sea anemone Nematostella



Nematostella





Activation of adaptive immunity by innate immunity