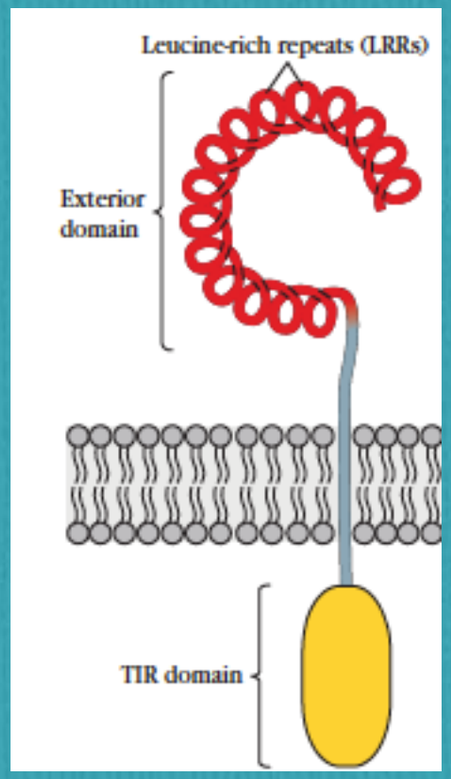
Programa de Pôs-graduação em Imunologia ICB/USP
Disciplina BMI 5904 – Reconhecimento no Sistema Imune

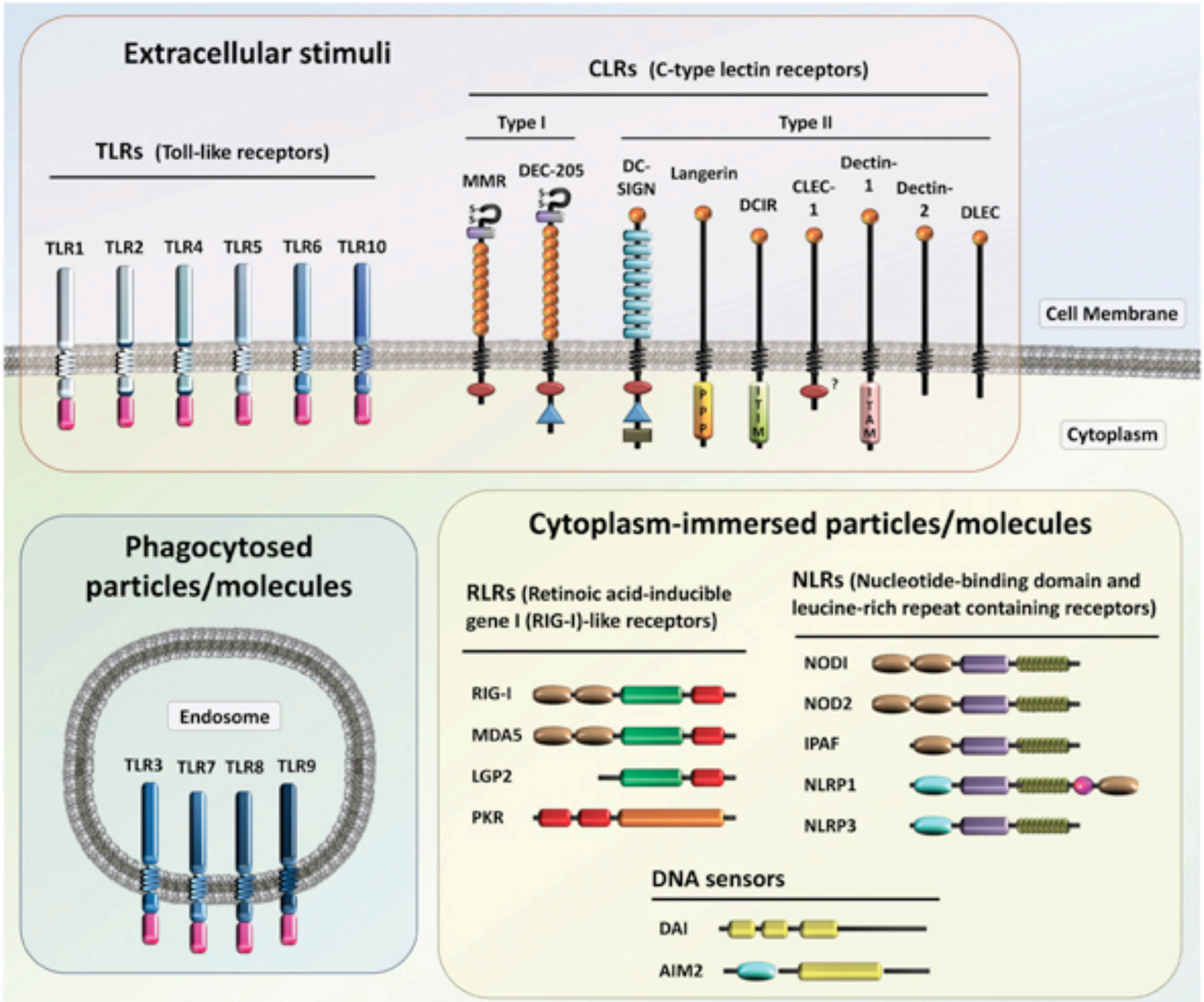


Aula 4

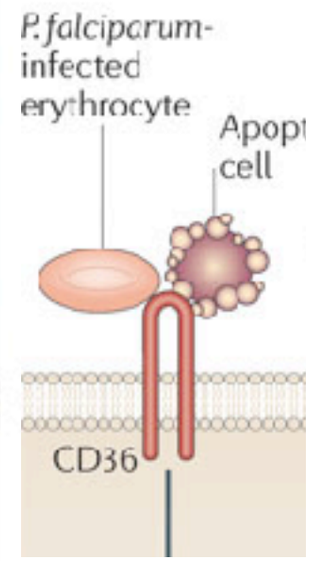
Alessandra Pontillo

Lab. Imunogenetica/Dep.Imunologia/ICB/USP

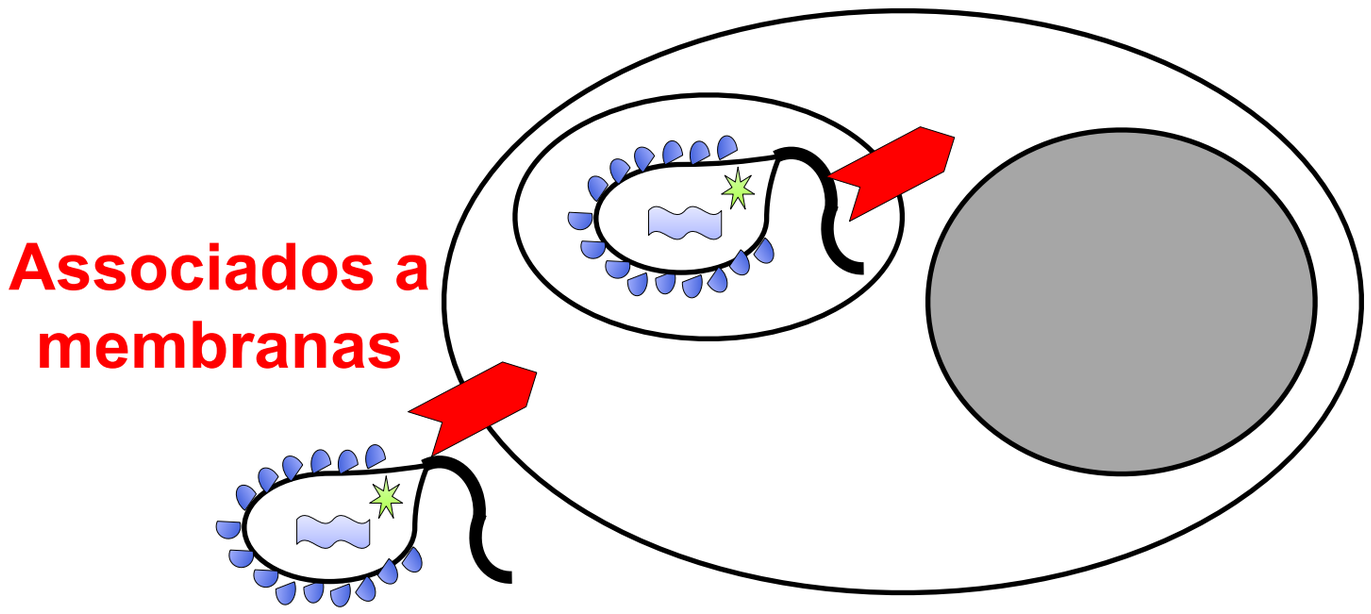
PRRs



Scavanger



PRRs



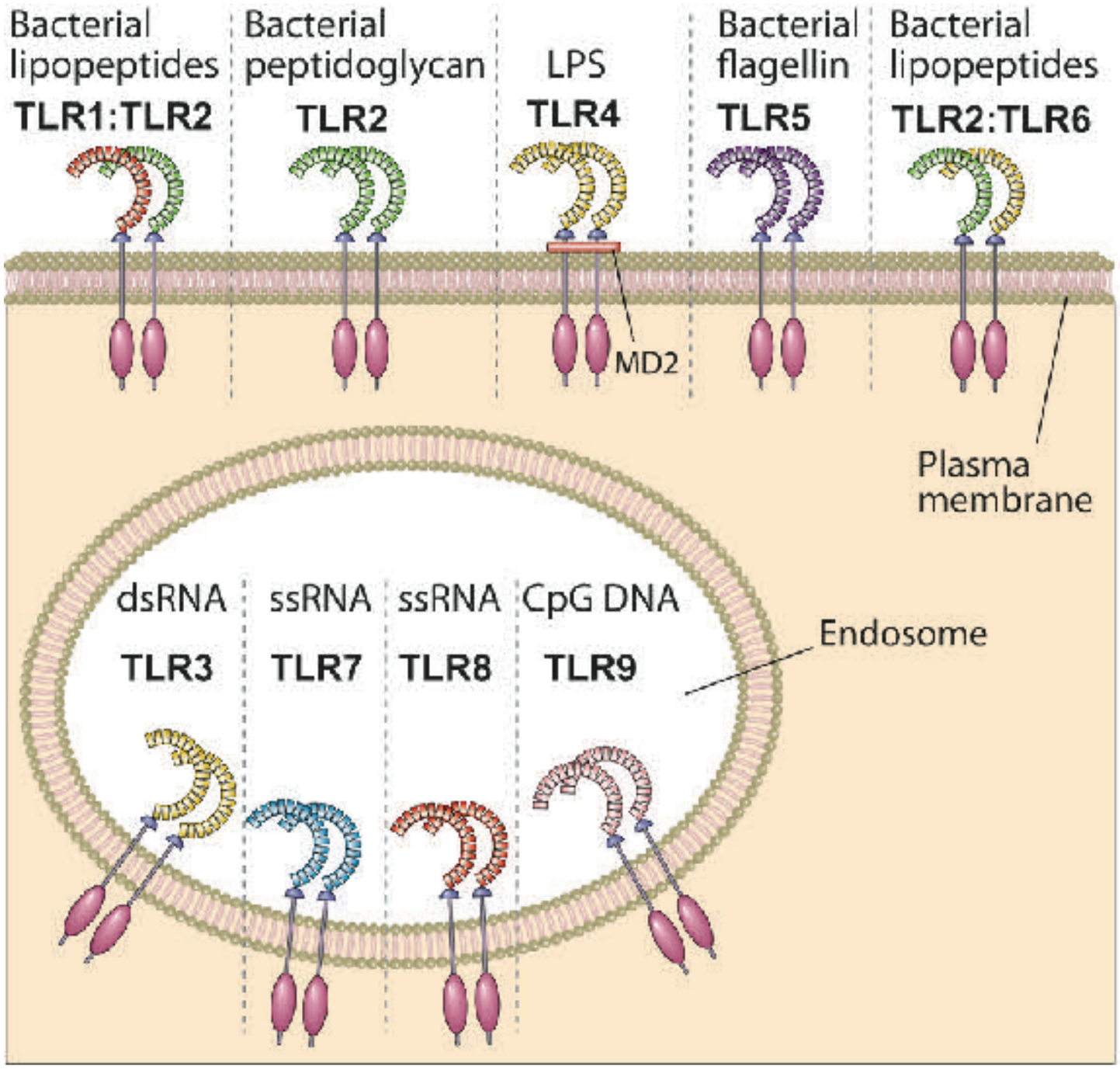
RECEPTORES DE FAGOCITOSE

Receptores de carboidratos (CLRs)
Receptores Scavenger

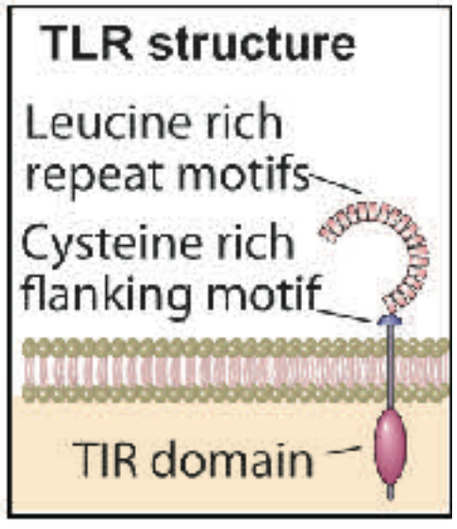
RECEPTORES DE SINALIZACAO

TLRs

Receptores semelhantes a Toll (TLRs)



- Dimeros (homo ou hetero)
- Membrana celular (bacteria PAMPs)
- Endosomes (viral PAMPs)

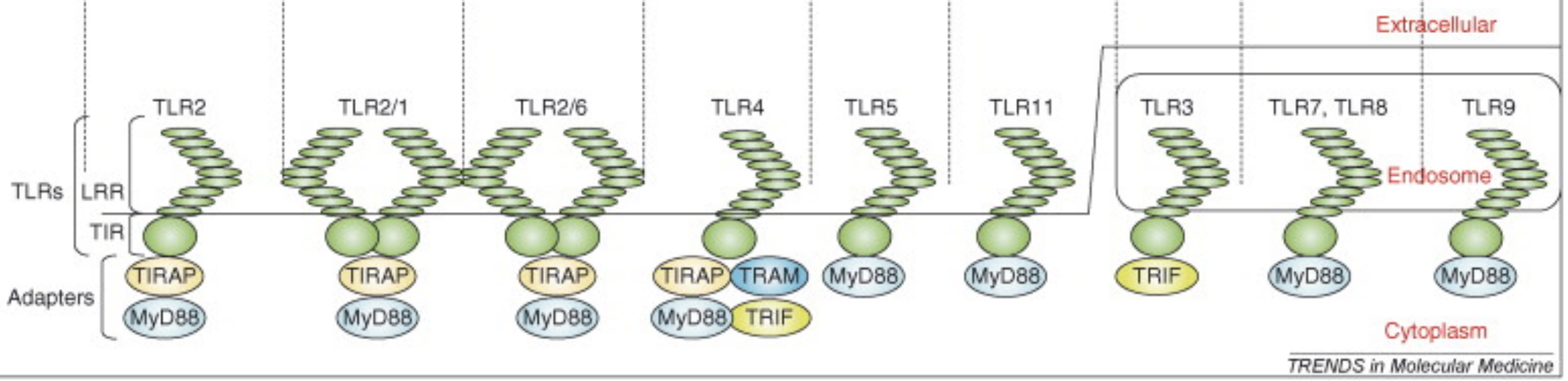


TLRs

TLRs	PAMPs	Synthetic ligands	DAMPs
TLR1/2	Triacyl lipopeptides	Pam_3CSK_4, BLP	β-defensin-3
TLR2/2	Peptidoglycan (PGN), glycolipids	Zymosan	Monosodium urate, Pancreatic adeno-carcinoma upregulated factor (PAUF), Serum amyloid A, neutrophil elastase, HSP60, HSP70, gp96, surfactants A/D, eosinophil-derived neurotoxin, biglycan, hyaluronic acid, HMBG1, MMP-2
TLR2/6	Diacyl lipopeptides, lipteichoic acid	Pam_2CSK_4, FSL1, BPP	Versican
TLR3	Double stranded RNA	Poly-(I:C)/-(A:U)	Tumor derived dsRNA and siRNAs
TLR4	LPS from Gram-negative bacteria	MPLA, Lipid A	HMGB1, gp96, HSP22, HSP60, HSP70, HSP72, HSP90, hyaluronan, heparan sulfate, fibrinogen, monosodium urate, peroxiredoxin, biglycan, neutrophil elastase, serum amyloid A, oxidized LDL, fibronectin EDA, fibrinogen, tenascin-C, lactoferrin, β-defensin-2, saturated fatty acids, surfactant protein-A, HMGN1
TLR5	Flagellin	–	–
TLR7	Single stranded RNA	Imiquimod (R-837), Resquimod (R-848), Gardiquimod, Loxoribine, Bropirimine	Tumor derived ssRNA and siRNAs, anti-phospholipid antibodies, miRNAs
TLR8	Single stranded RNA	Gardiquimod, Resquimod (R-848), Poly (dT)-ODN, Bropirimine	Tumor derived ssRNA and siRNAs, anti-phospholipid antibodies, Human cardiac myosin, miRNAs
TLR9	ss/ds DNA, hemozoin	ODN: CpG-, AT-	Tumor mtDNA, HMGB1, IgG-chromatin
TLR10	Unknown	–	–
TLR11	Profilin	–	–
TLR12	Profilin	–	–
TLR13	23S rRNA	–	–

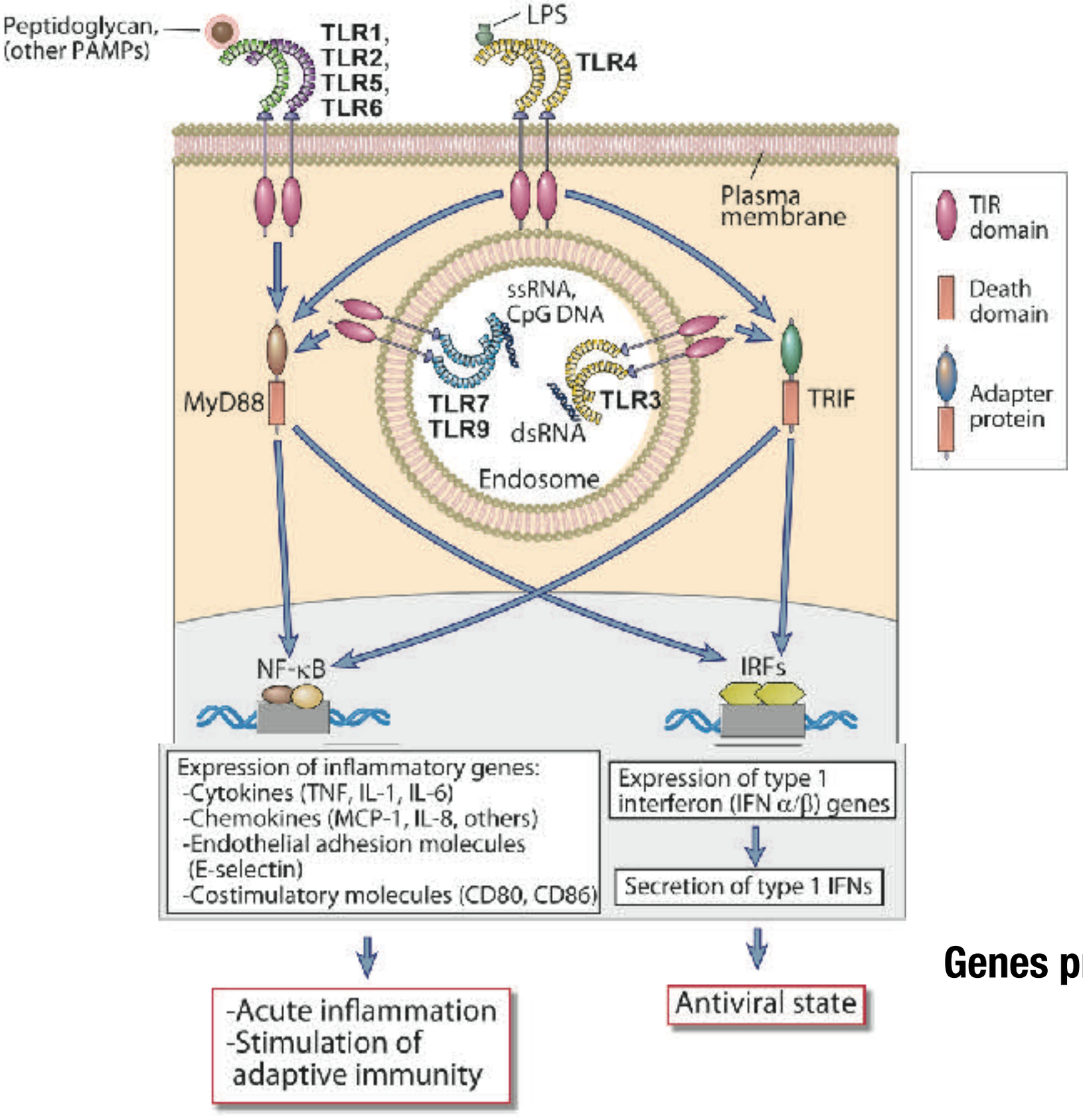
TLRs

Bacteria	Peptidoglycan (gram-positive bacteria) Lipoarabinomannan (mycobacteria)	Triacyl lipopeptide (bacteria, *mycoplasma*)	Diacyl lipopeptide (*mycoplasma*)	LPS (gram-negative bacteria)	Flagellin	Uropathogenic bacteria components			CpG DNA
Viruses	Hemagglutinin protein (measles virus)			Envelope proteins (RSV, MMTV)			dsRNA	ssRNA	DNA
Parasites	tGPI-mutin (*trypanosoma*)					Profilin-like molecules (*toxoplasma gongii*)			Hemozoin (*plasmodium*)
Fungus			Zymozan (*s. cerevisiae*)						
Synthetic compounds				MPLA			Poly IC	Imidazoquinolines	



TRENDS in Molecular Medicine

TLRs



Dimerização

Sinalização Myd88,TRIF

NF-kB **IRFs**

Expressão genica

Genes pro-inflamatorios **Interferon de tipo I**

Receptores & Sinalização

Respostas rápidas

NF-kB

IRF3

Proinflammatory cytokines Type 1 interferons

IFN-I

IFNRs

Fatores de restrição viral

Resposta antiviral

Resposta inflamatoria

IL-6R **TNFR** **IL1R**

AP-1

NF-kB

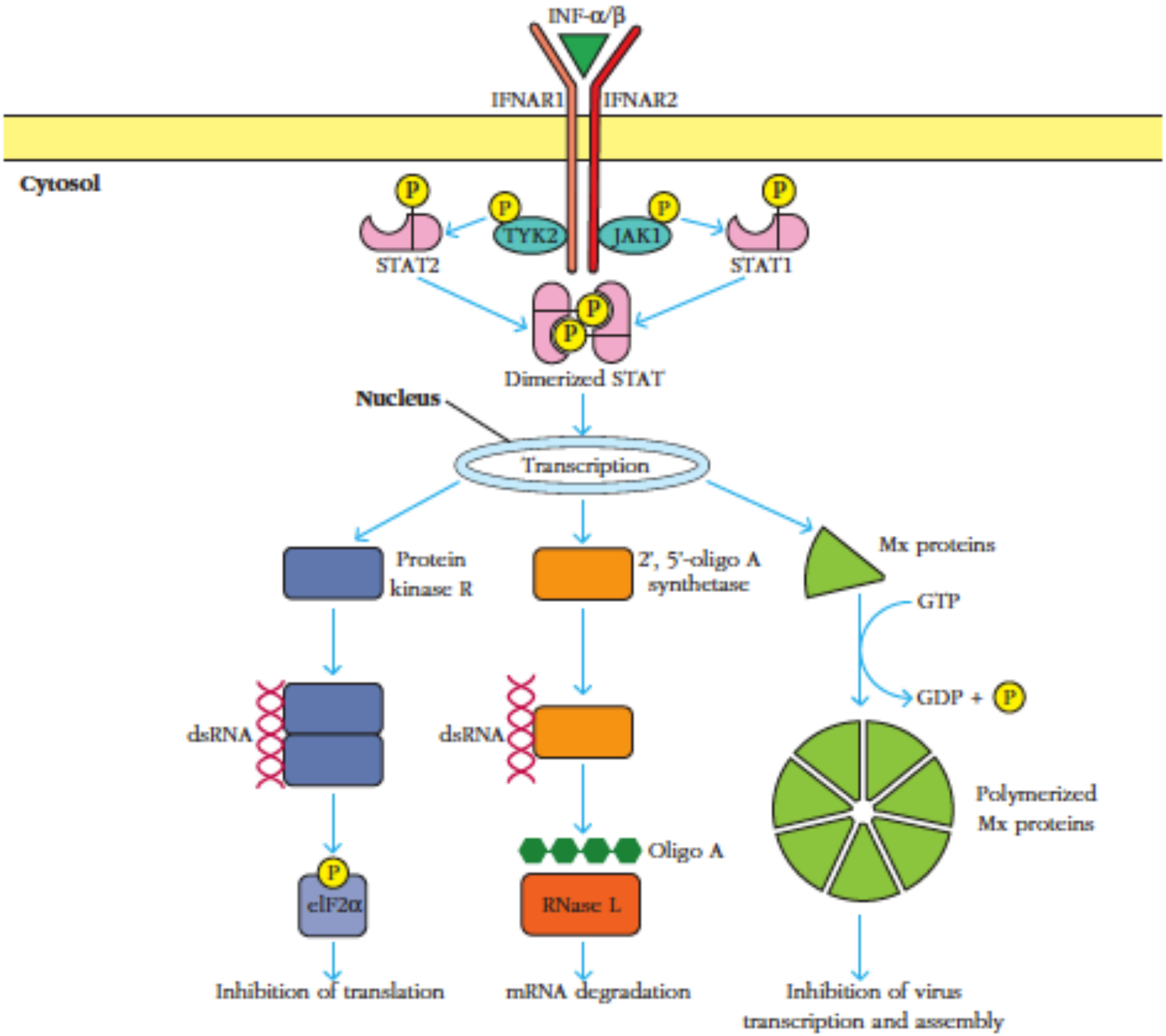
SOCS

Inflamassoma

Moleculas antimicrobianas
Enzimas
Citocinas, Quimiocinas
Sist.Complem., APPs

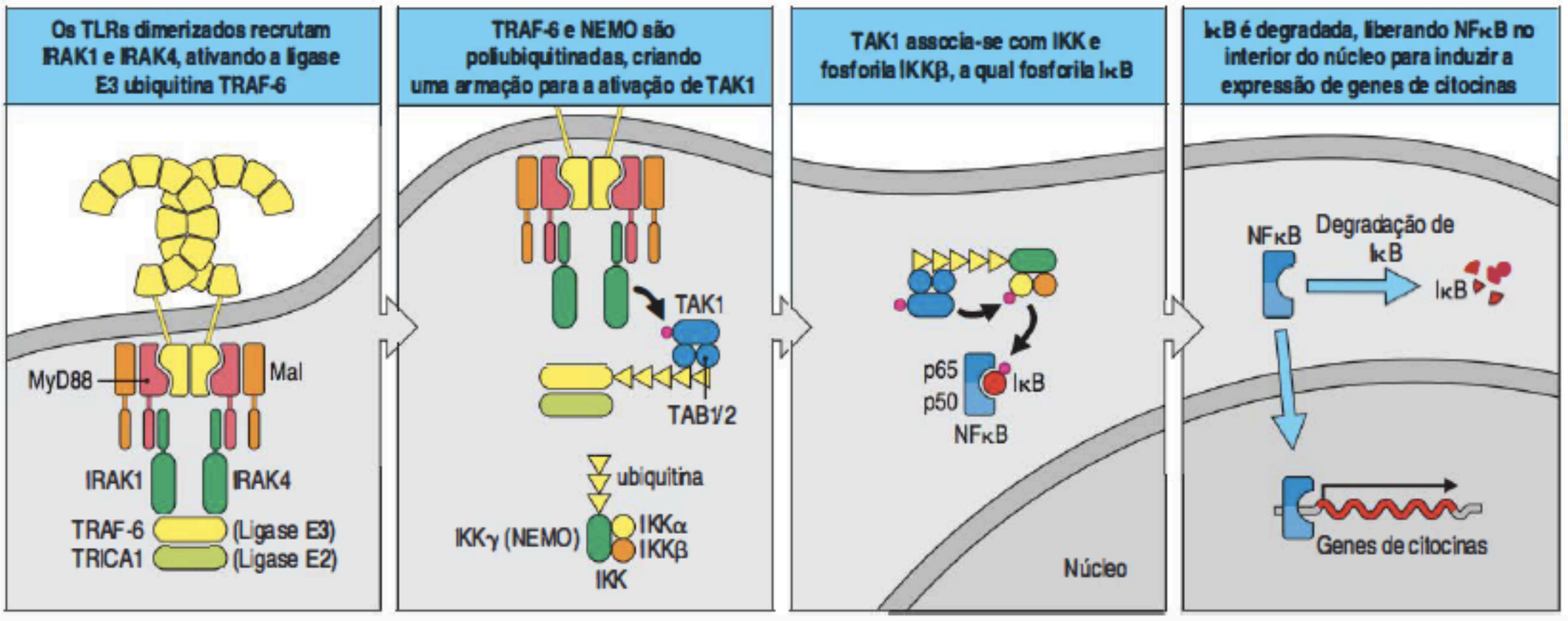
IL-1ß
IL-18
TNF
IL-6

Ação anti-viral dos IFN tipo I

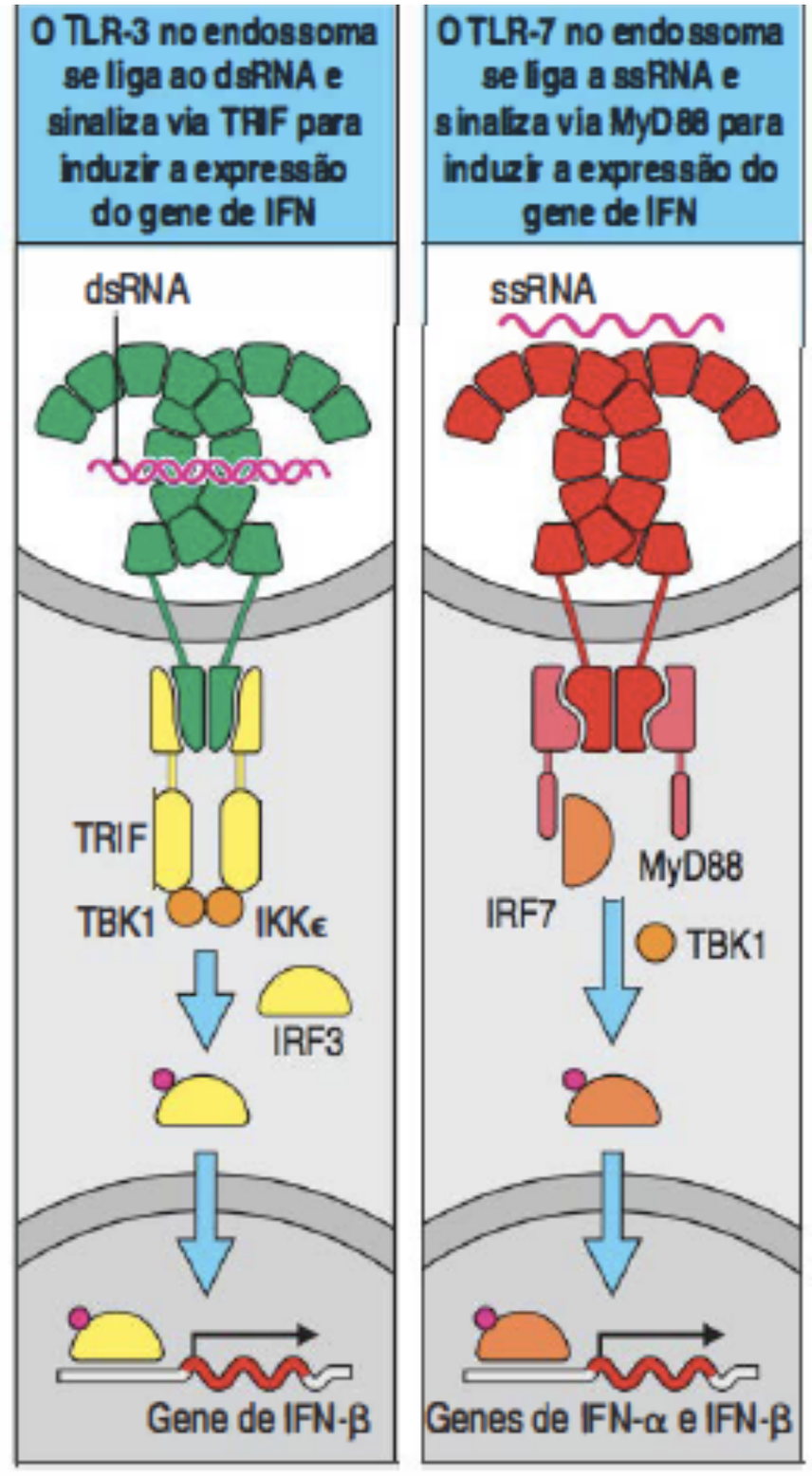


TLRs

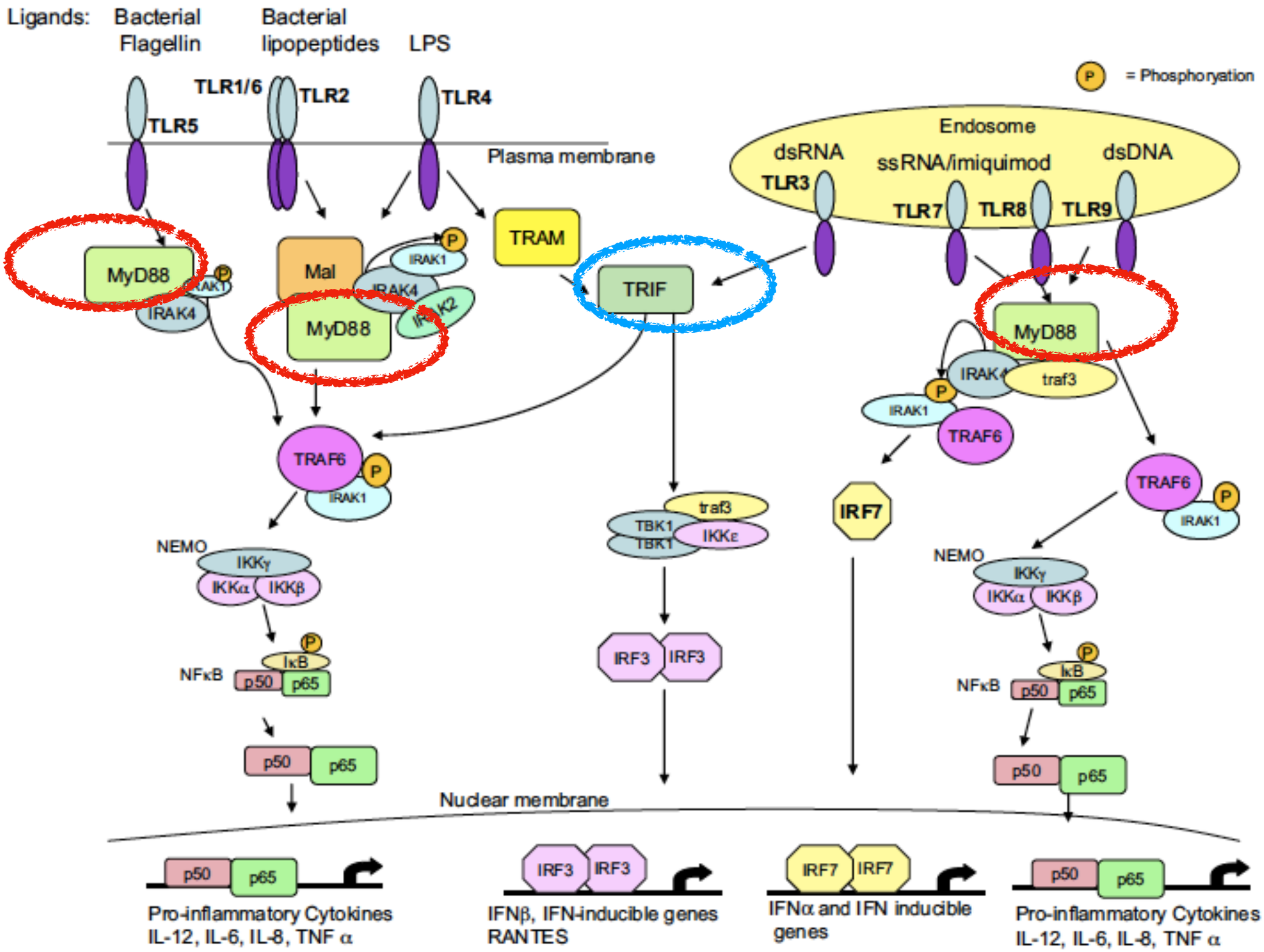
TLR-5, -7 e -9: Myd88
TLR-3: TRIF
TLR-2/-1, TLR-2/-6: Myd88/Mal
TLR-4: Myd88/TRIF



TLRs

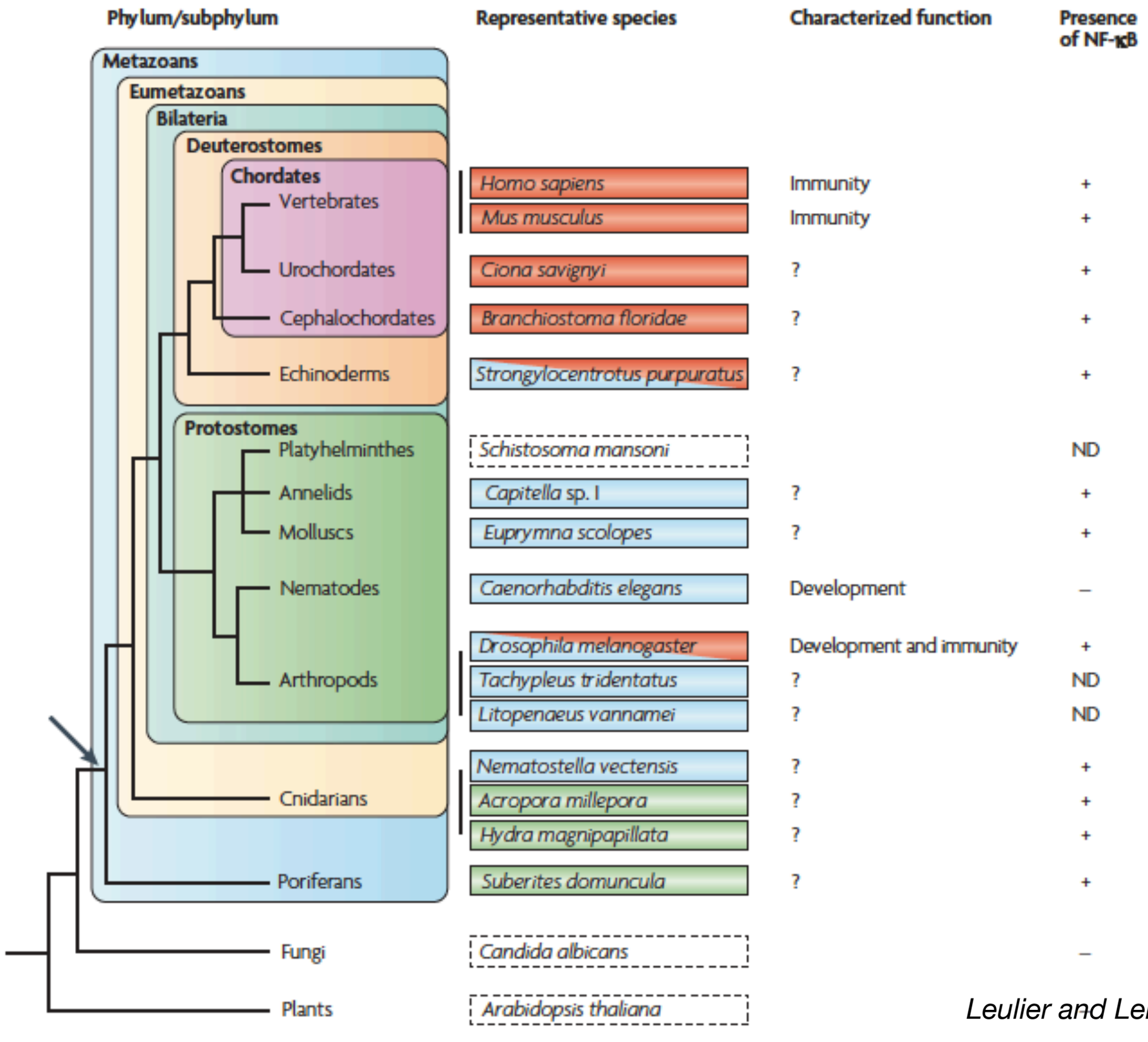

O TLR-3 no endossoma se liga ao dsRNA e sinaliza via TRIF para induzir a expressão do gene de IFN
dsRNA
TRIF
TBK1
IKKε
IRF3
Gene de IFN-β
O TLR-7 no endossoma se liga a ssRNA e sinaliza via MyD88 para induzir a expressão do gene de IFN
ssRNA
MyD88
IRF7
TBK1
Genes de IFN-α e IFN-β

TLRs



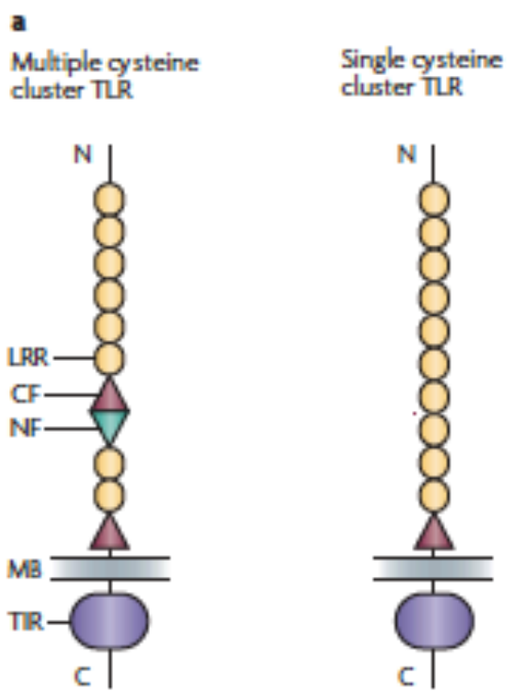
O'Neill et al 2009

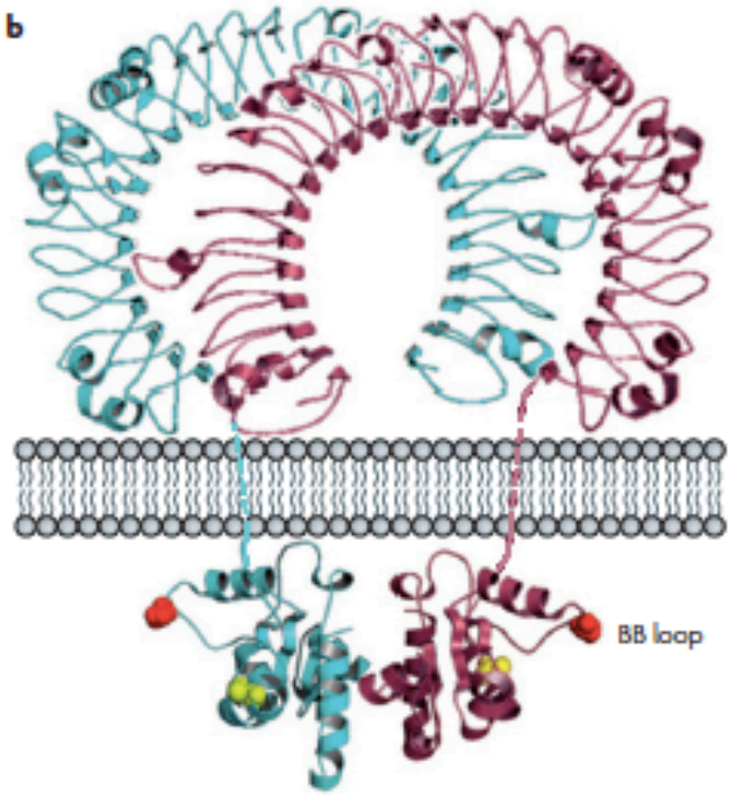
TLRs



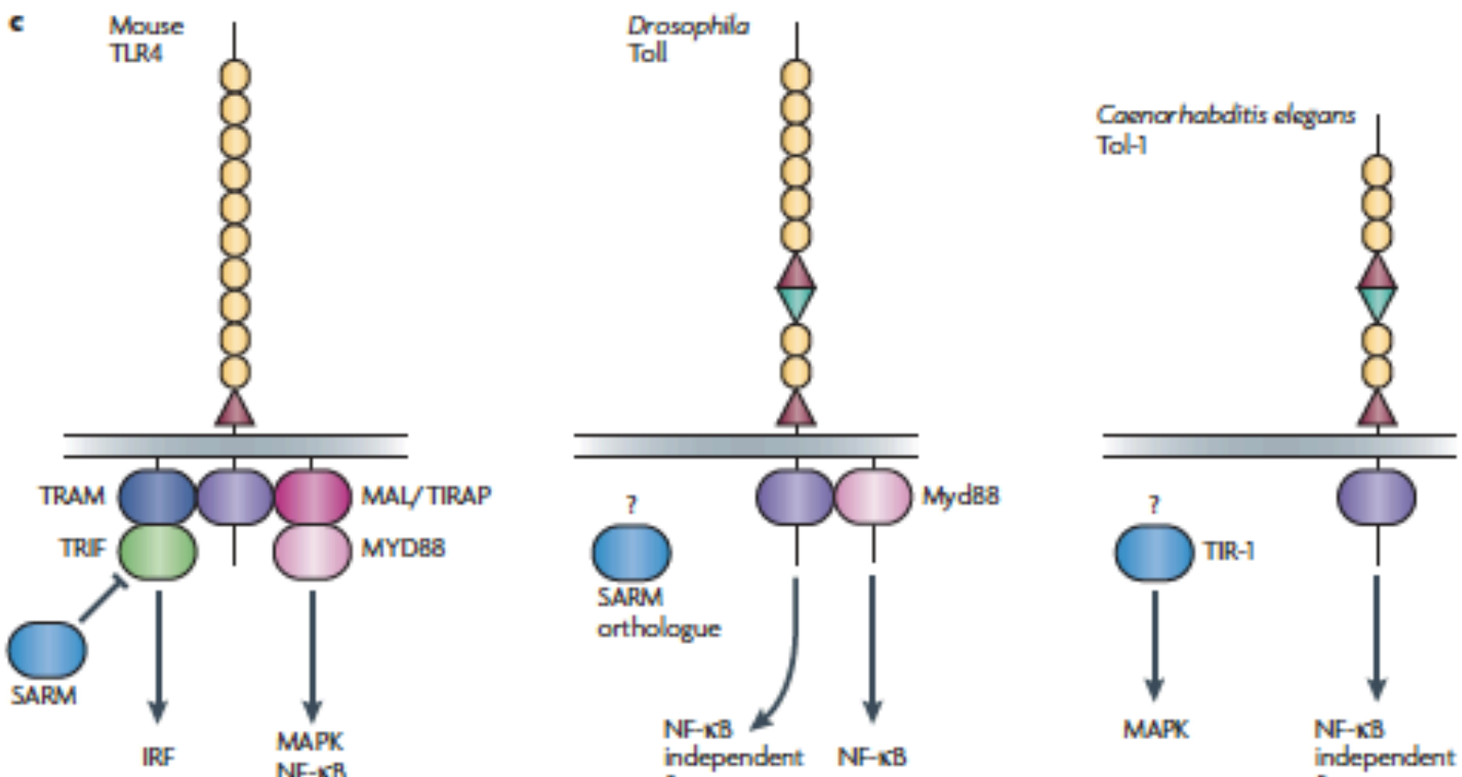
Leulier and Lemaitre, Nature 2008

TLRs





Reconhecimento



Leulier and Lemaitre, Nature 2008

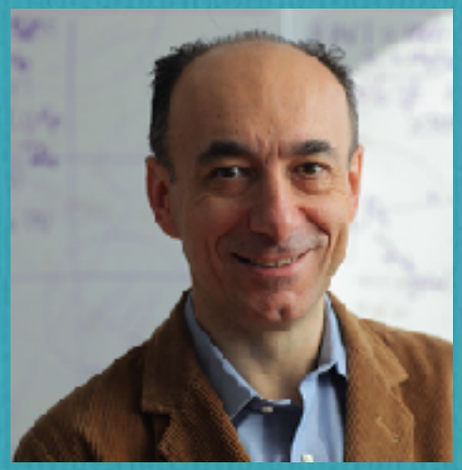
TLRs

Table 2 | **Loss-of-function analysis of Toll-like receptor genes**

Gene	Species	Major loss-of-function phenotypes	Ref.
Toll	*Drosophila melanogaster*	Dorsalization of the embryo	1
		Defects in motor-neuron number	44
		Improper muscle patterning	44
		Improper motor-neuron synaptogenesis	46
		Incomplete dorsal-vessel formation (embryonic)	47
		Reduced number of circulating cells	54
		Defective antimicrobial-gene regulation (adult)	6
		Defective larval development	2
		Defective pupal development	43
Toll2 (*18 wheeler*)	*Drosophila melanogaster*	Defective morphogenesis	3
		Defective epithelial morphogenesis	57
Toll8 (Tollo)	*Drosophila melanogaster*	Loss of neural-specific glycosylation	59
Toll5A	*Aedes aegypti*	Susceptibility to fungal infection (adult)	72
Tol-1	*Caenorhabditis elegans*	Embryonic lethality	73
		Pathogen-avoidance defects (adult)	73
Tlr1	*Mus musculus*	Defective triacyl lipopeptide response	112
Tlr2	*Mus musculus*	Defective lipopeptide response	110
Tlr3	*Mus musculus*	Defective dsRNA response	116
Tlr4	*Mus musculus*	Defective lipopolysaccharide response	107
Tlr5	*Mus musculus*	Defective bacterial flagellin response	113
Tlr6	*Mus musculus*	Defective diacyl lipopeptide response	111
Tlr7	*Mus musculus*	Defective ssRNA response	121
Tlr9	*Mus musculus*	Defective bacterial-DNA response	122
		Defective viral-DNA response	123
Tlr11	*Mus musculus*	Susceptibility to uropathogenic bacteria	114
		Defective response to a profilin-like protein from *Toxoplasma gondii*	115
TLR3	*Homo sapiens*	Herpes simplex encephalitis	92

Leulier and Lemaitre, Nature 2008

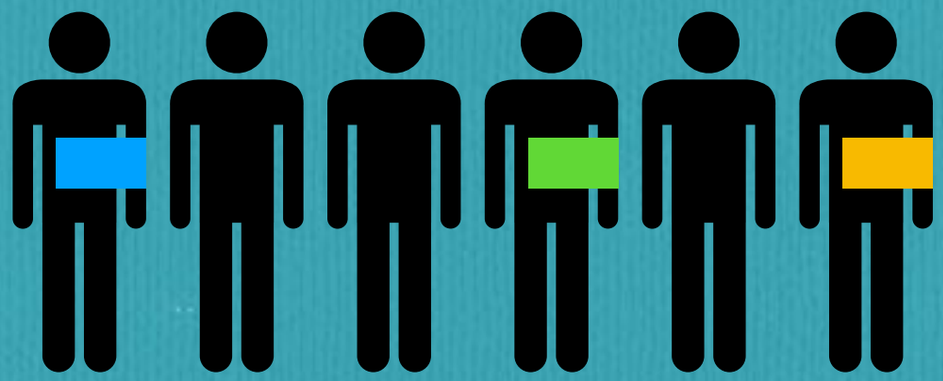
TLRs: protegem mesmo?



JL Casanova

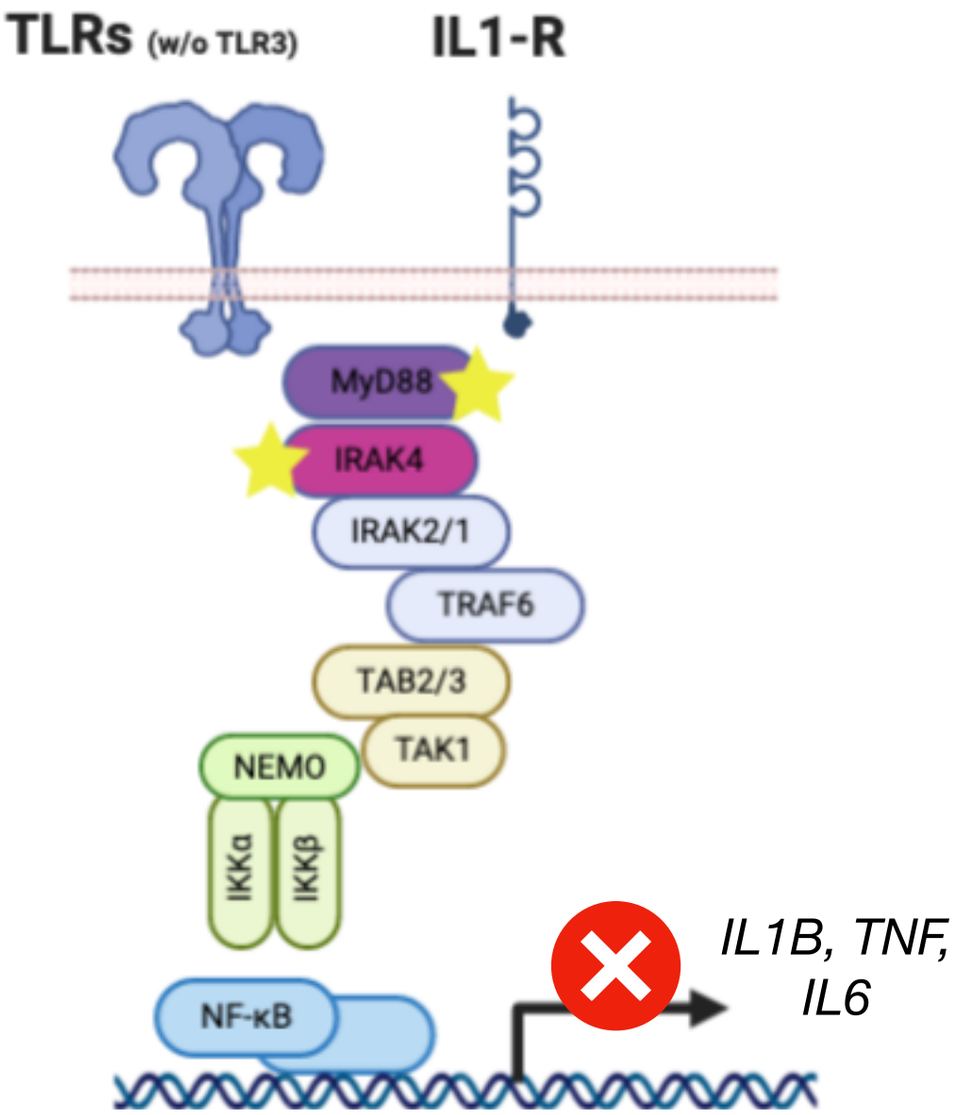
L Abel

Individues aparentemente saudáveis apresentam doenças graves frente a infeções por um tipo ou um numero limitado de patogenos

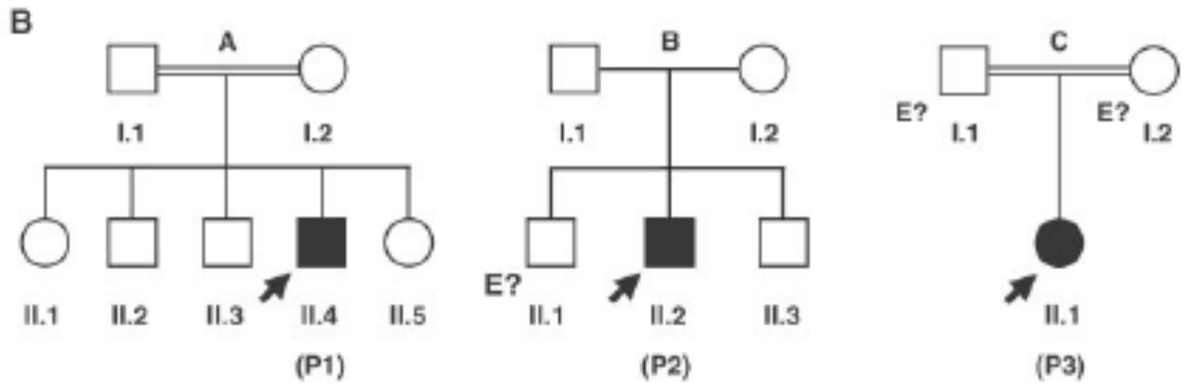


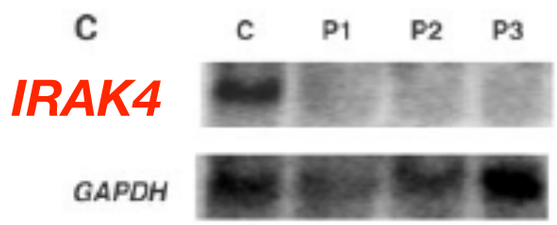
Doença pneumocócica invasiva

Autosomica dominante por mutações na sinalização Myd88

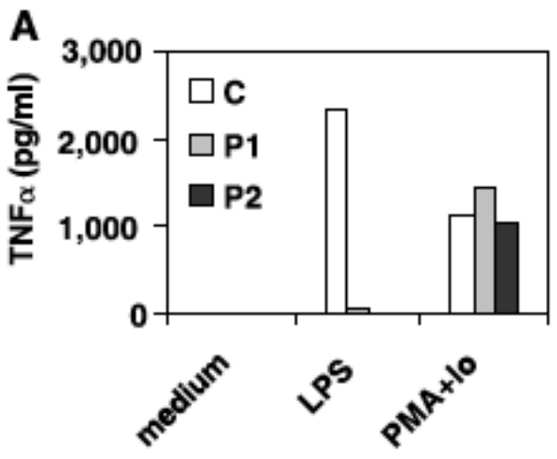


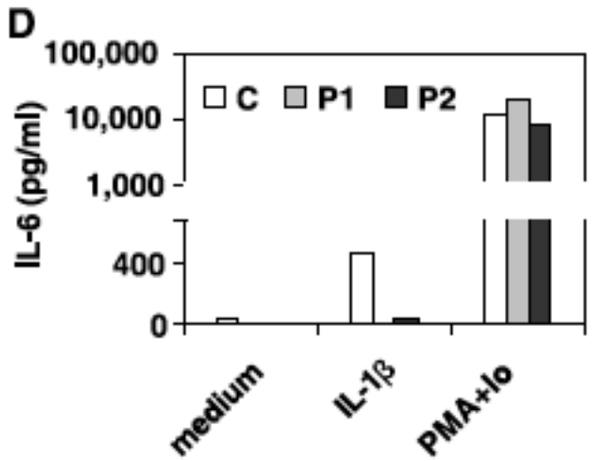
Suscetibilidade a bacteria piogenica
(Gram+ S pneumoniae and S aureus)





AR
P1 - 821delT (exon 7)
P2/3 - Q293X (exon 8)

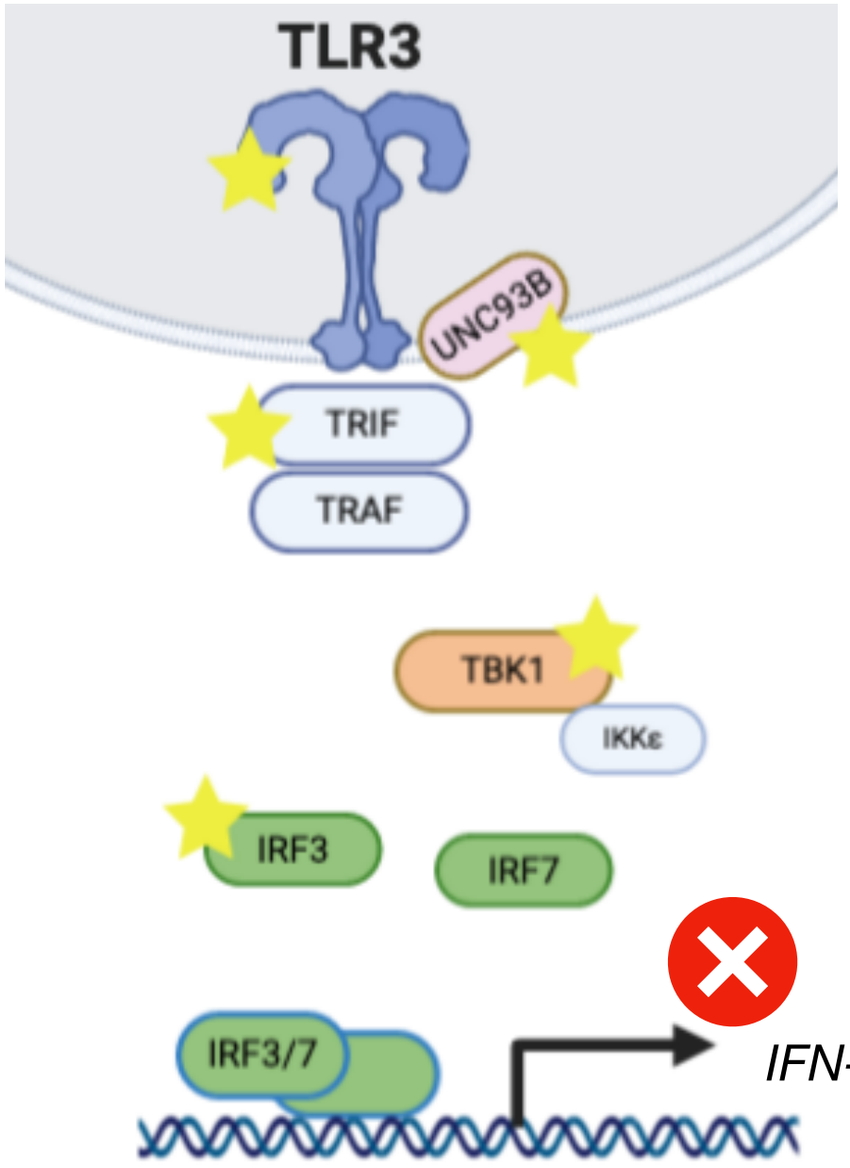


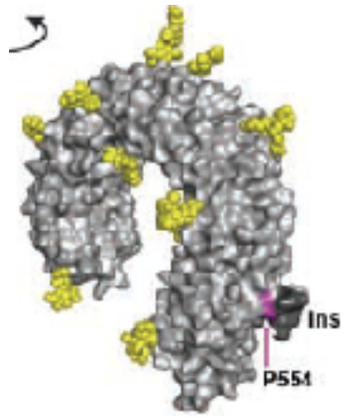


Picard, [], Casanova. Science (299) 2003

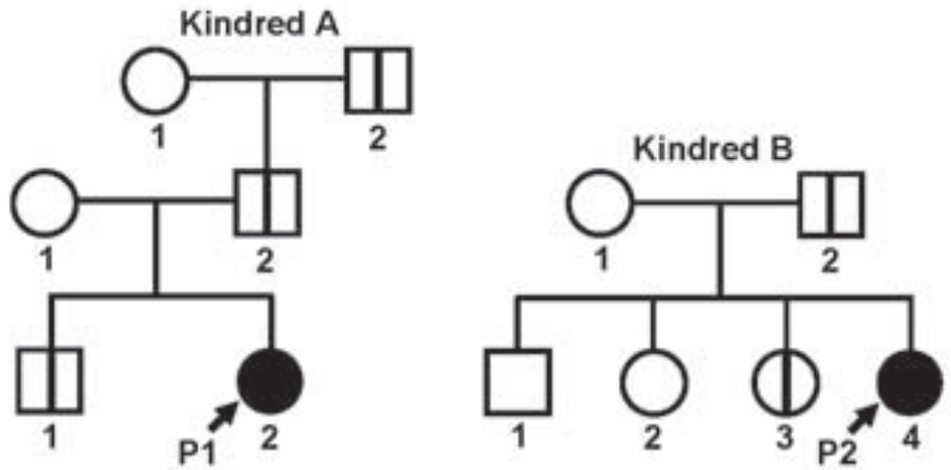
Encefalite associada a HSV-1

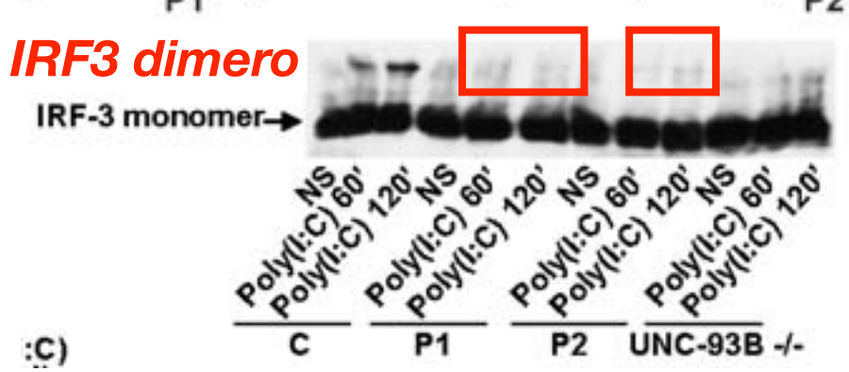
Autosomica dominante por mutações na via do TLR3

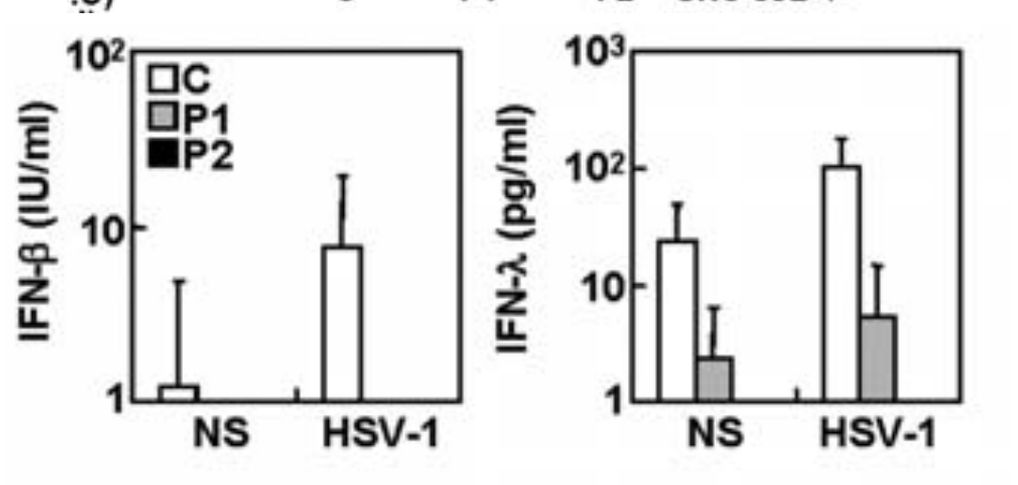




***TLR3 HZ* P554S**





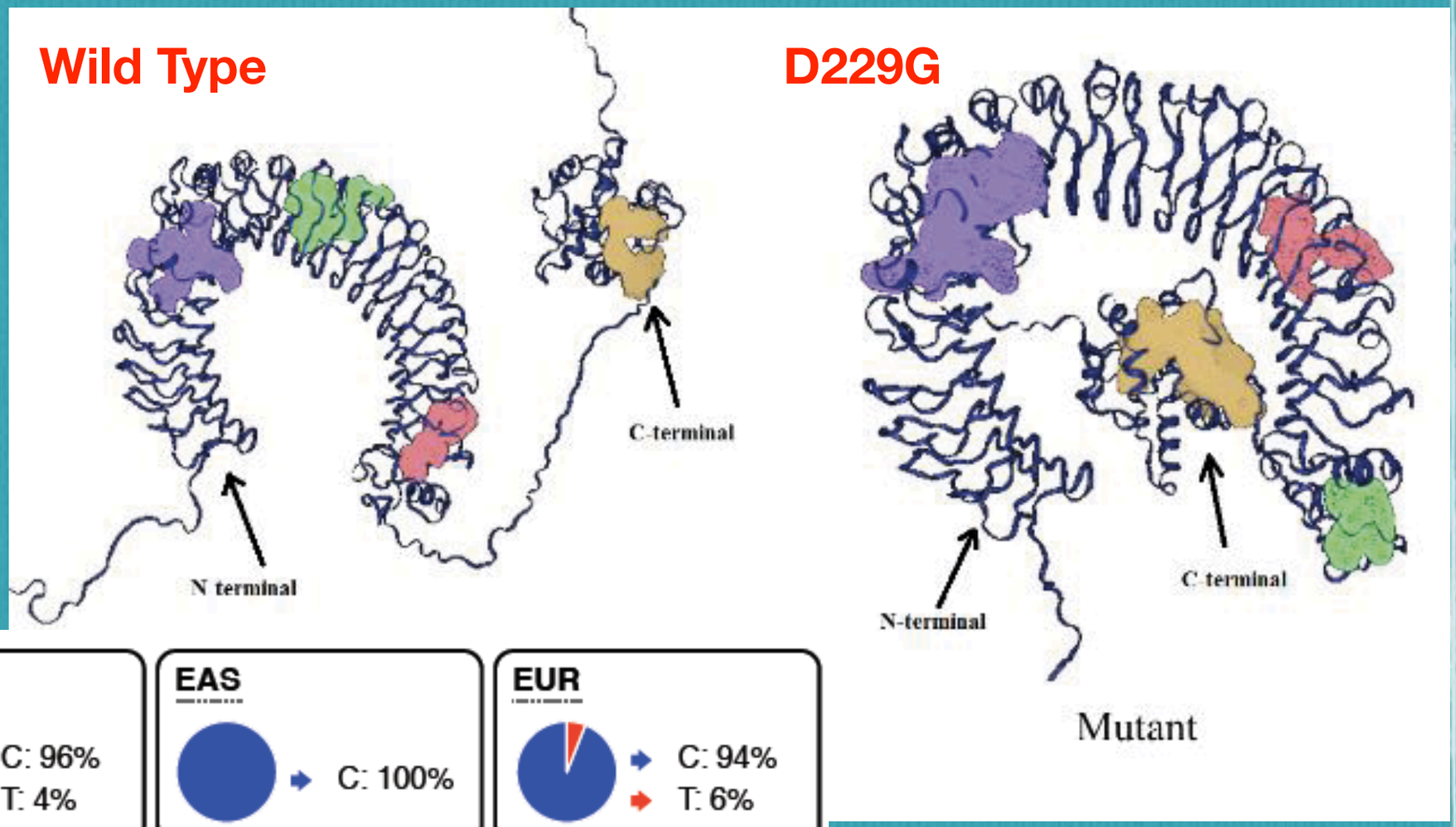


Zhang, [], Casanova. Science (317) 2007

TLRs: protegem mesmo?

Variantes perda-de-função no gene TLR4

Asp299Gly (D229G)
Thr399Ile (T399I)



TLRs: protegem mesmo?

Variantes perda-de-função no gene TLR4

↑ infecçoes (LPS)
↓ Legionella

↓ atherosclerosis, RA

TLR4	D299G rs4986790	Decreases the risk of atherosclerosis Improves resistance to rheumatoid arthritis Reduces inflammatory responses to *Plasmodium falciparum* Results in linkage disequilibrium and reduced response to LPS in human Children inherited with this polymorphism are prone to invasive meningococcal disease Provide resistance to infection by *Legionella pneumophila* Results in susceptibility to inflammatory bowel disease. Increasing the level of Chronic periodontitis
	T399I rs4986791	Results in reduced response to LPS in human Reduced inflammatory responses to *P falciparum* Amplify susceptibility to respiratory syncytial virus infection Increases susceptibility to atherosclerosis

Mukherjee, Scand J Immunol. 2019