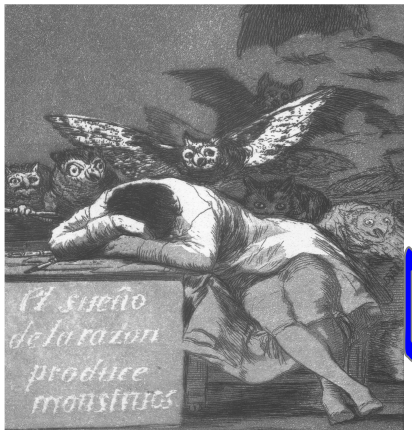


University of Florence
Dept. of Experimental and Clinical Medicine
Centre of Excellence DENOthe

Gli Interferoni
come meccanismo di difesa dai patogeni

Paola Parronchi

' IGRAs nella diagnosi e monitoraggio delle malattie infettive ' , Trento, 19 Aprile 2013

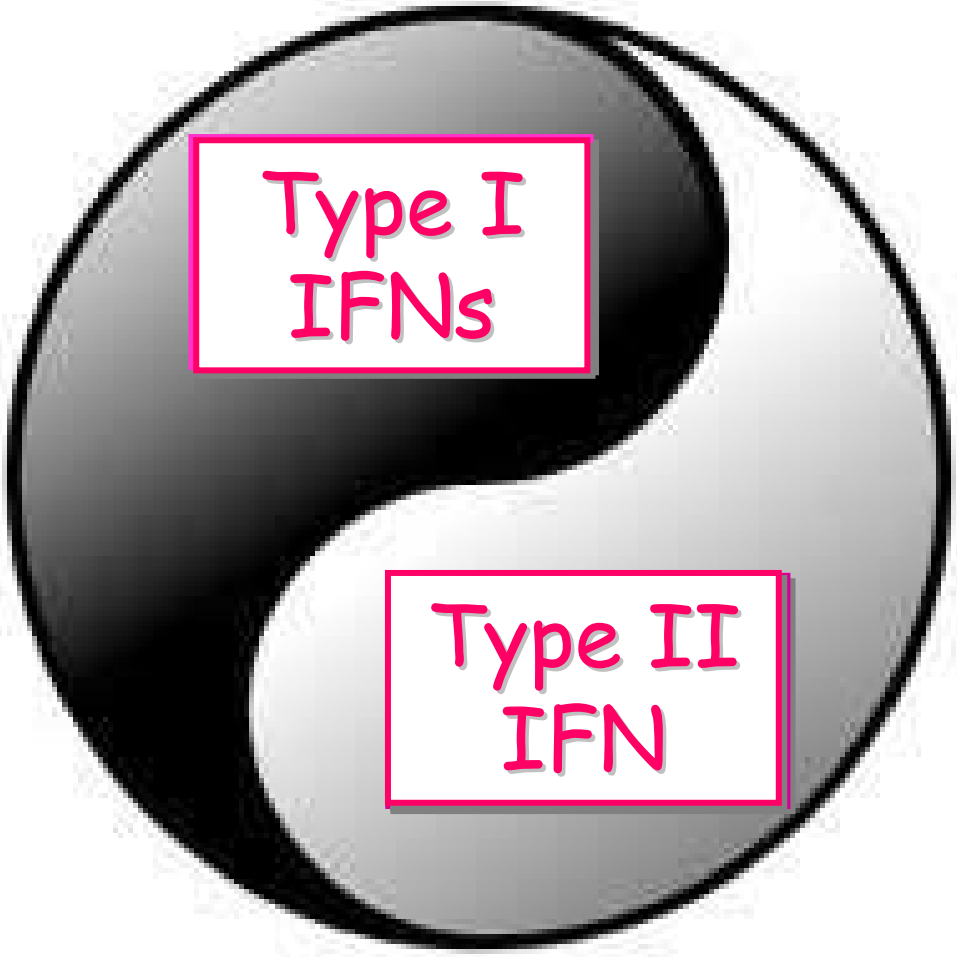
The mission of immune system

Druides militiae vacationem omniumque rerum habent immunitatem.
Caes

The mission of immune system

→ *Garanzia protettiva*

The two levels for immune defense

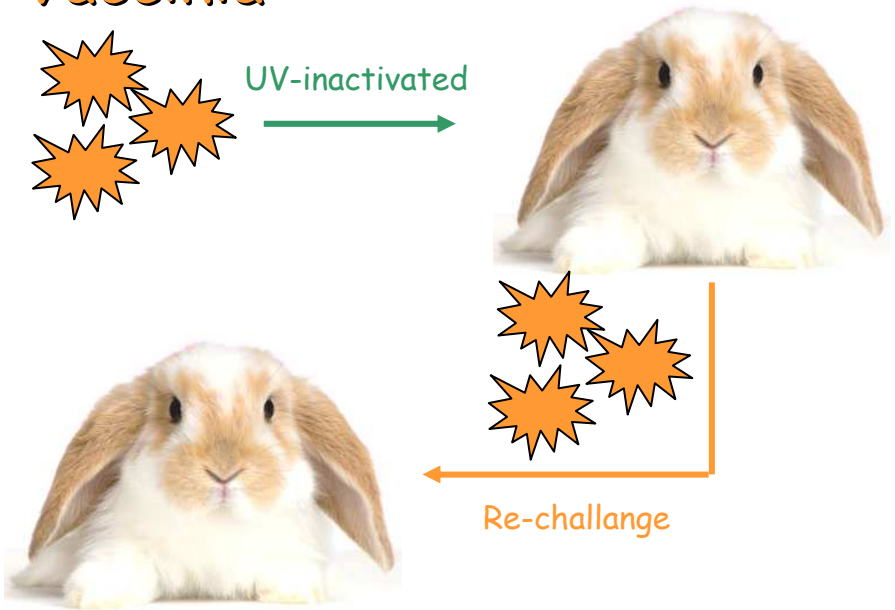


Crucial involvement of the interferon family in host defense

1954

"*facteur inhibiteur*"

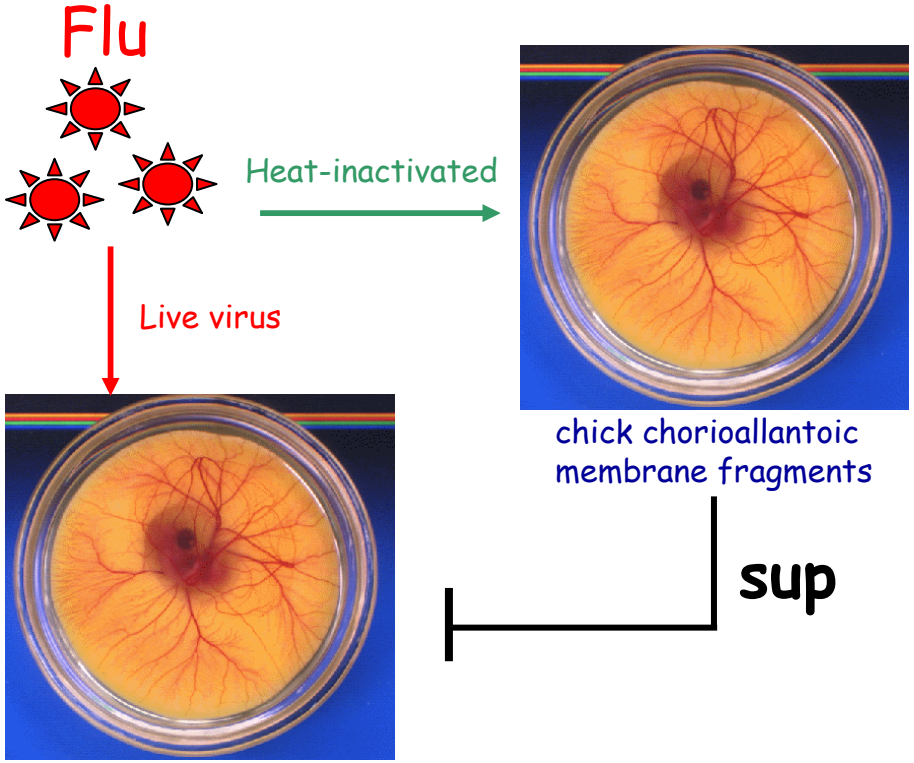
Vaccinia



Yasu-ichi Nagano and Yasuhiko Kojima
University of Tokyo

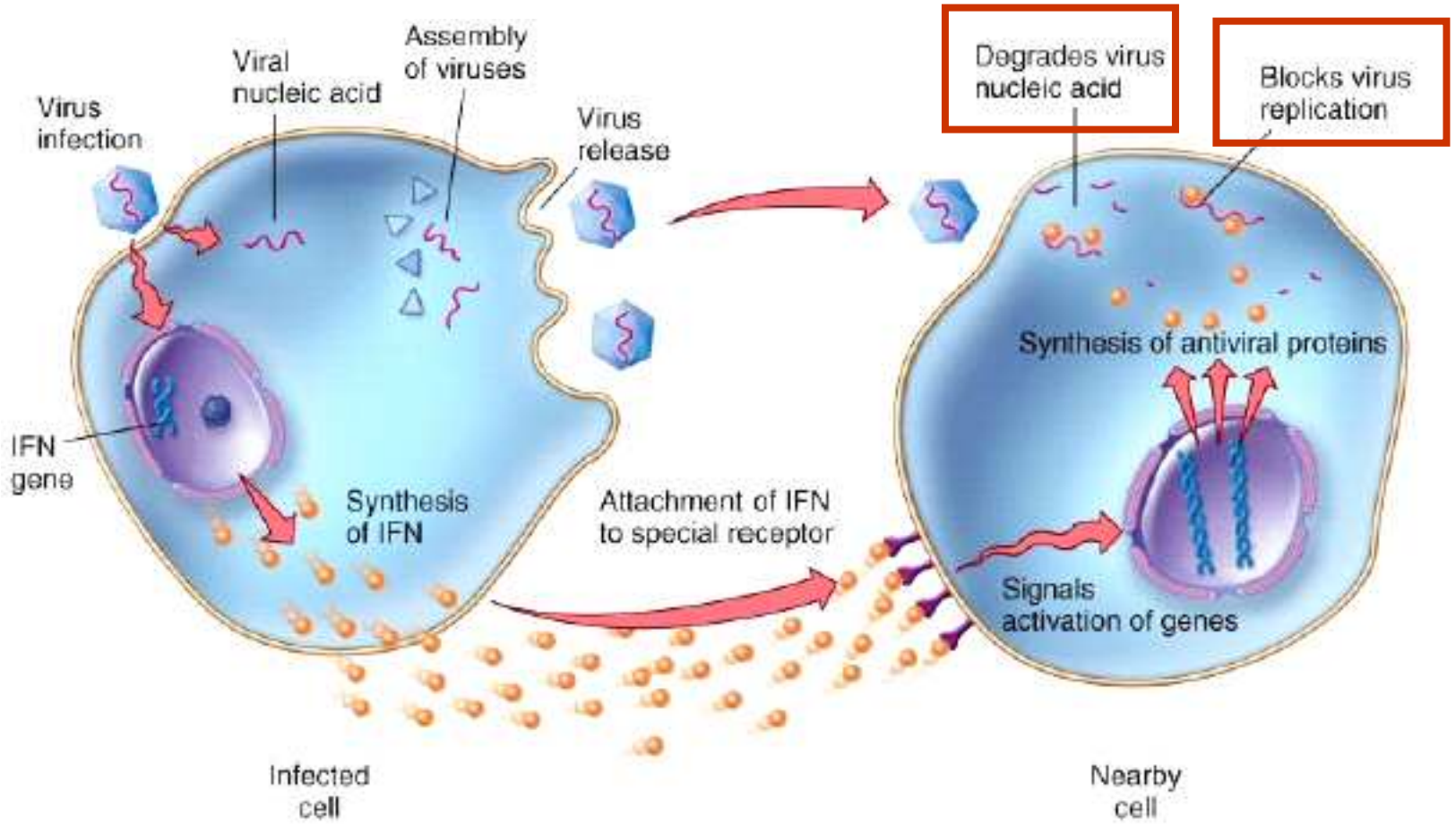
1957

viral interference



Alick Isaacs and Jean Lindenmann

Interferons in the mechanisms of innate immunity



The Interferon story is characterized by

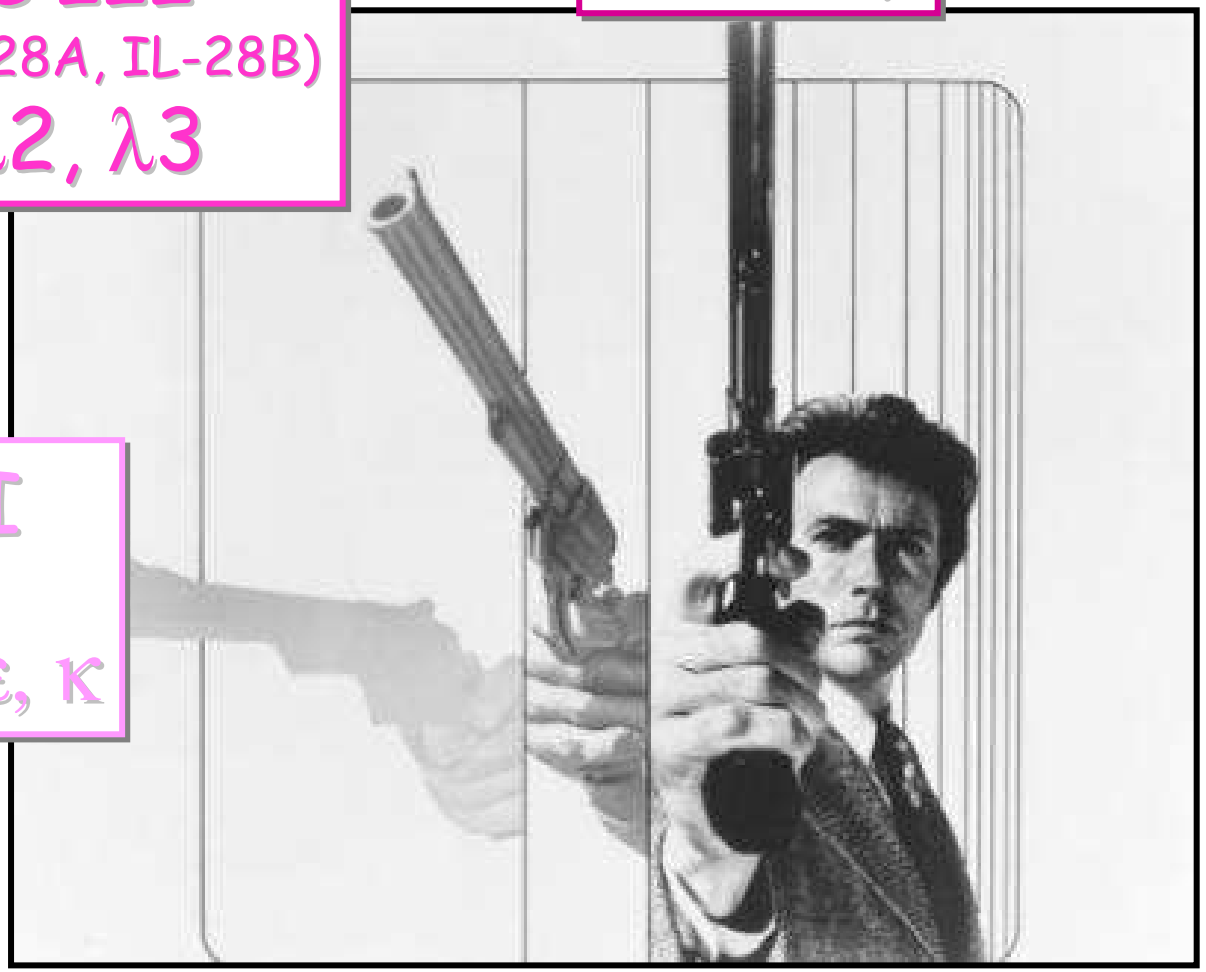
MULTIPLICITY

of molecules

The three types of Interferons for the immune defense

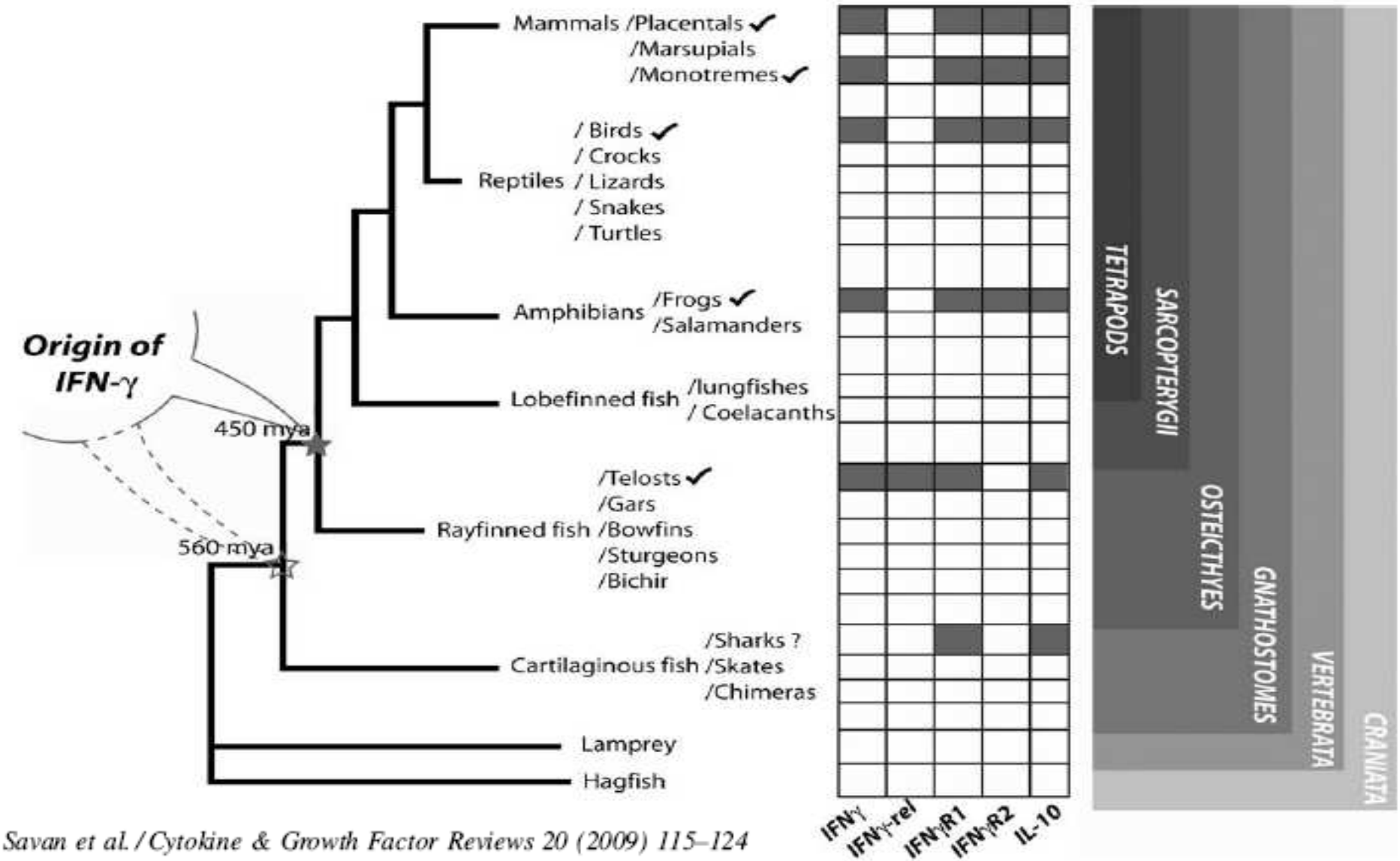
Type II
(immune) γ

Type III
(IL-29, IL-28A, IL-28B)
λ1, λ2, λ3



Type I
(innate)
α, β, ϖ, ε, κ

The phylogenetic tree of class II cytokine family genes



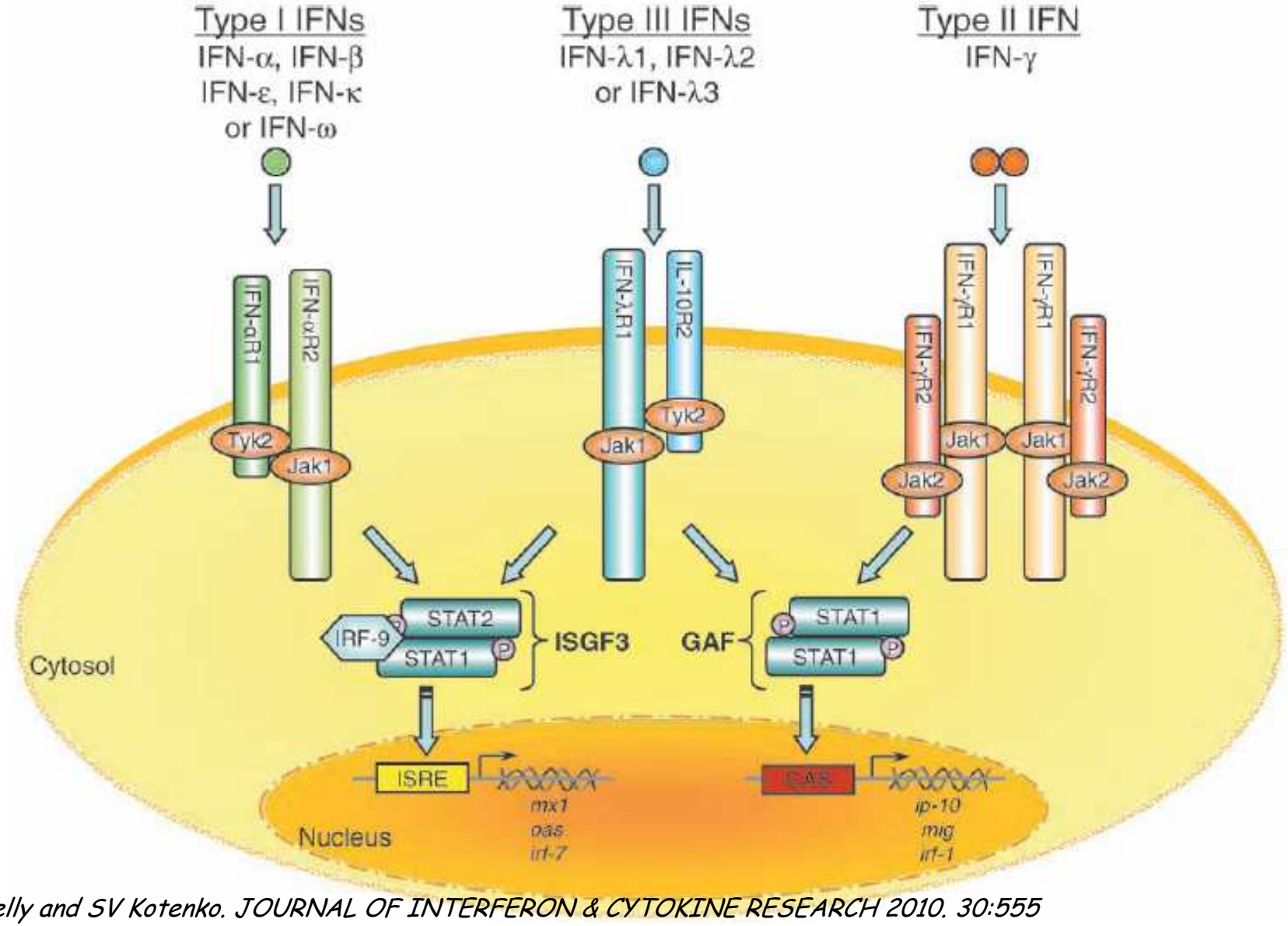
R. Savan et al. / Cytokine & Growth Factor Reviews 20 (2009) 115–124

The Interferon story is characterized by

MULTIPLICITY

of receptors

Receptors of type I, II and III Interferons



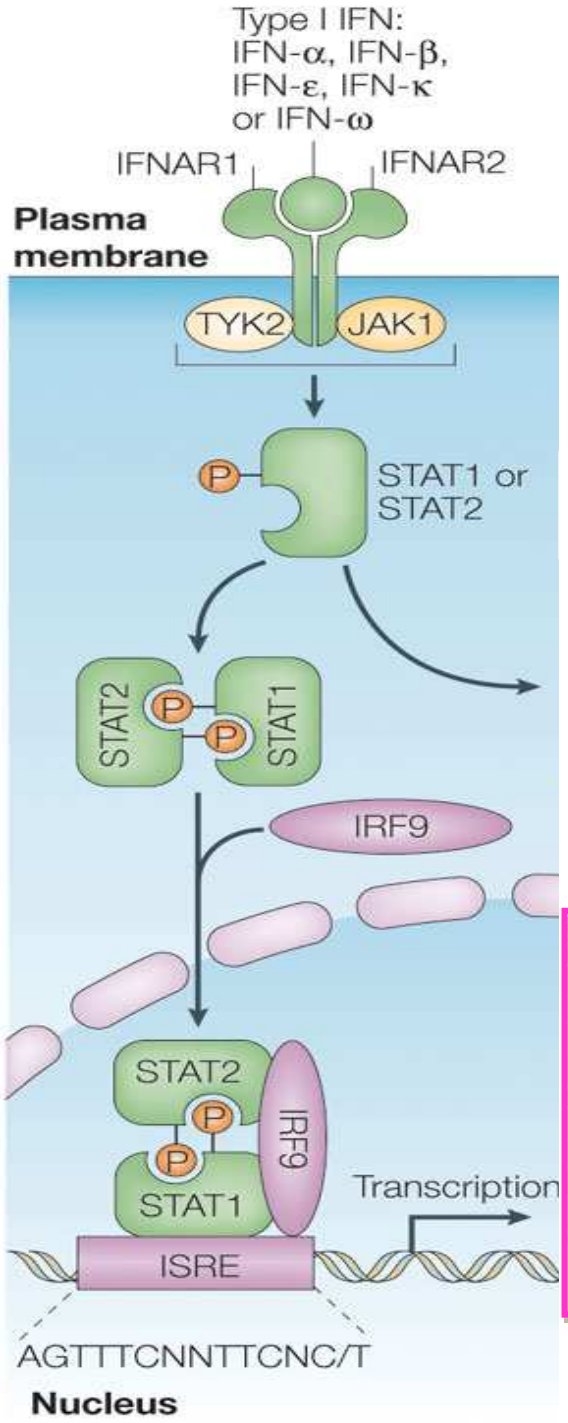
RP Donnelly and SV Kotenko. JOURNAL OF INTERFERON & CYTOKINE RESEARCH 2010. 30:555

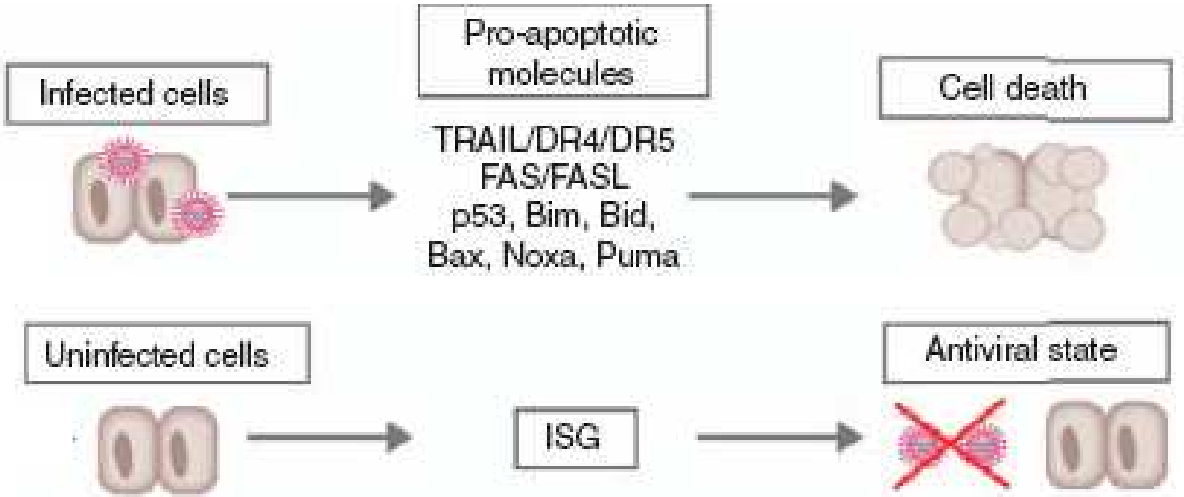
The Interferon story is characterized by

MULTIPLICITY

of effects

Effects of IFNs

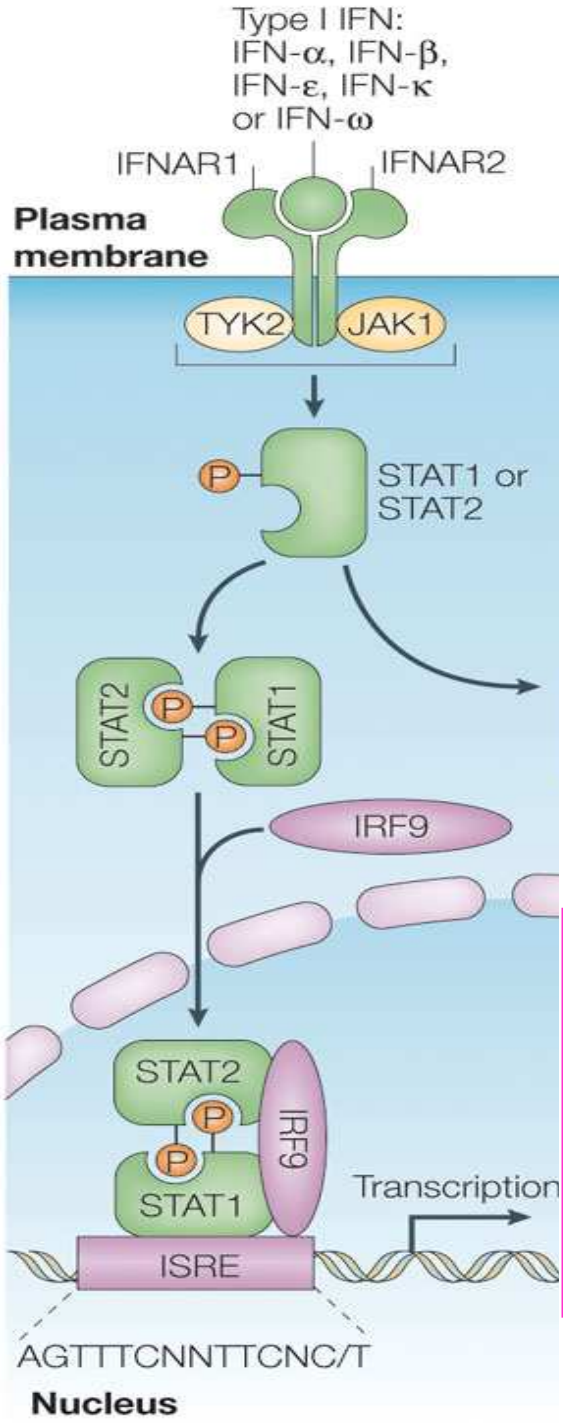


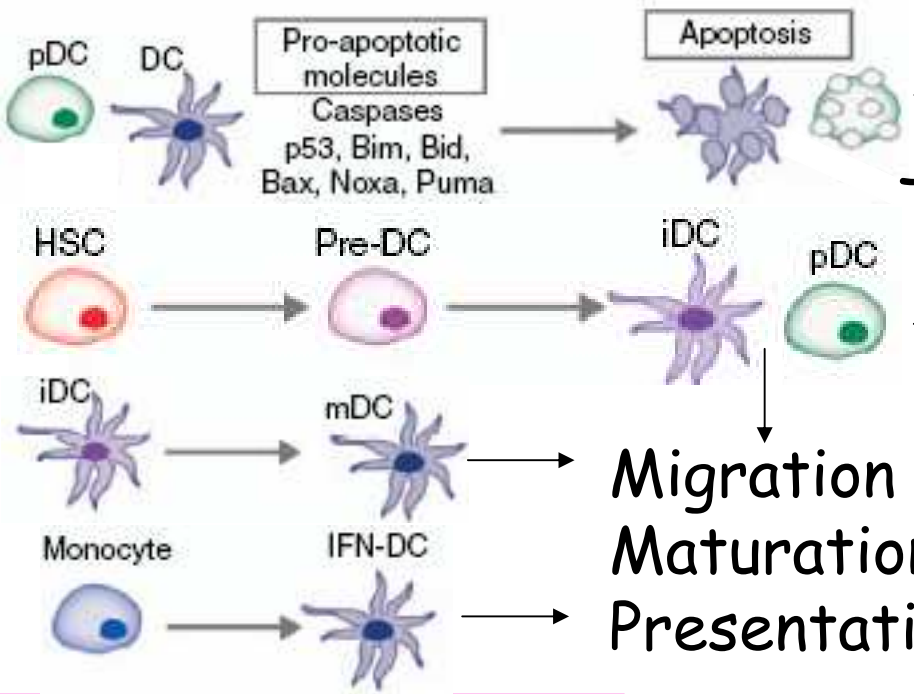


- IRF3 and IRF7 expression
- DC activation
- T-cell survival
- NK-cell activation
- Chemokine expression
- Lymph-node retention
- Antiproliferative and antiviral effects

Adapted from **Nature Reviews | Immunology**
Current Opinion in Virology 2011, 1:463–475

Effects of IFNs





- IRF3 and IRF7 expression
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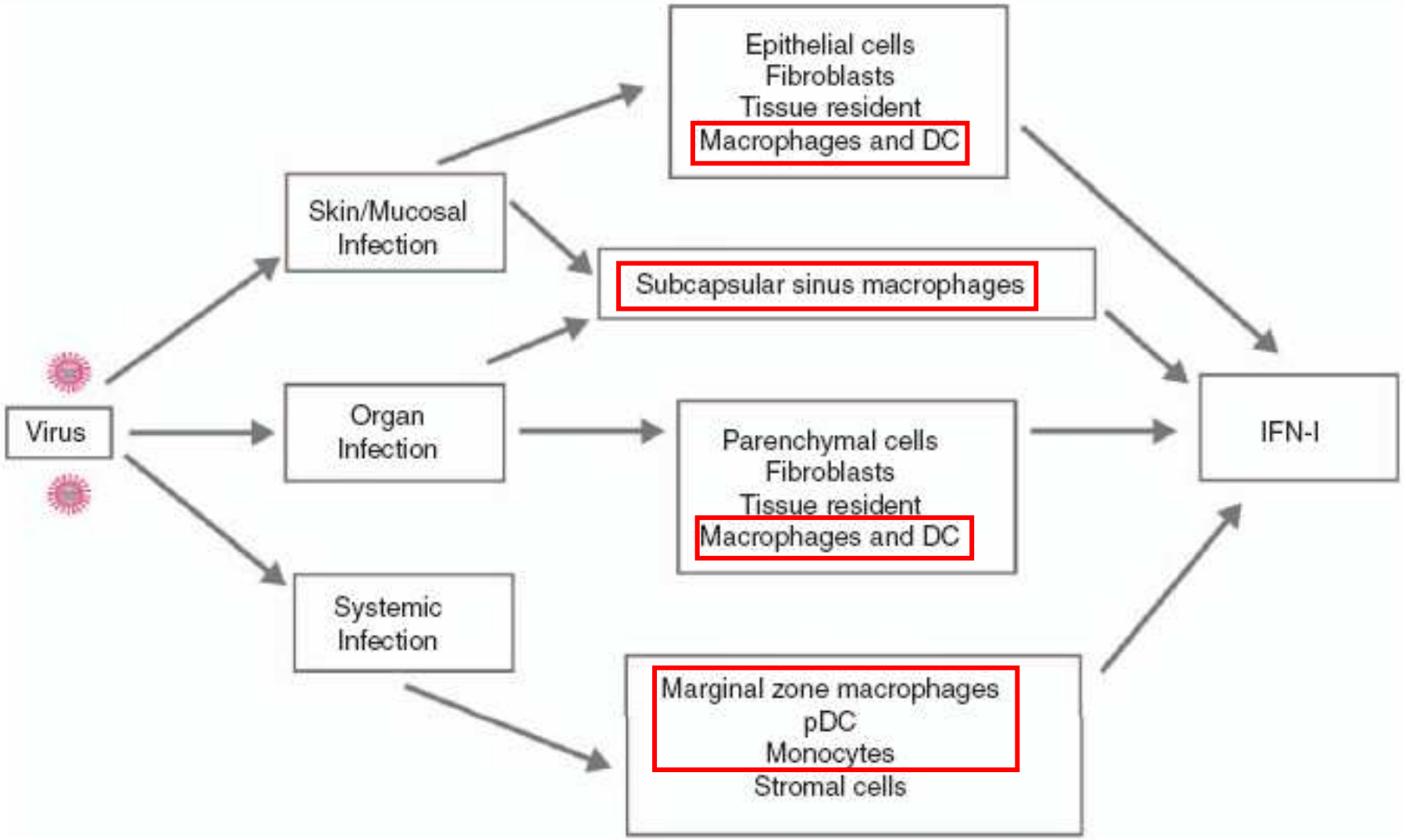
Adapted from Nature Reviews | Immunology
Current Opinion in Virology 2011, 1:463–475

The Interferon story is characterized by

MULTIPLICITY

of sources

Cellular sources of Type I Interferons



Melissa Swiecki and Marco Colonna Current Opinion in Virology 2011, 1:463–475

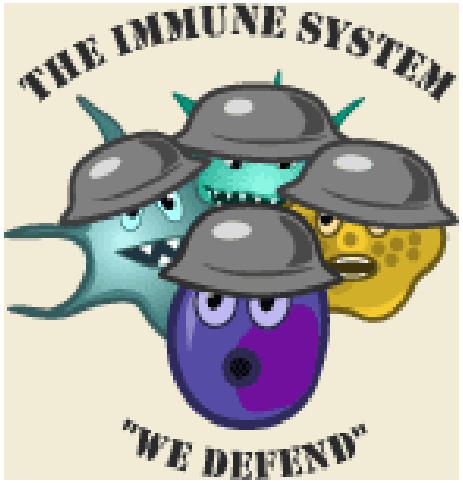
The Interferon story is characterized by

MULTIPLICITY

of sensors

The 'ordinary' view of innate immunity

- Invariant (aspecific)
- Rapid (minutes to hours)
- Generalized



The 'ordinary' view of innate immunity

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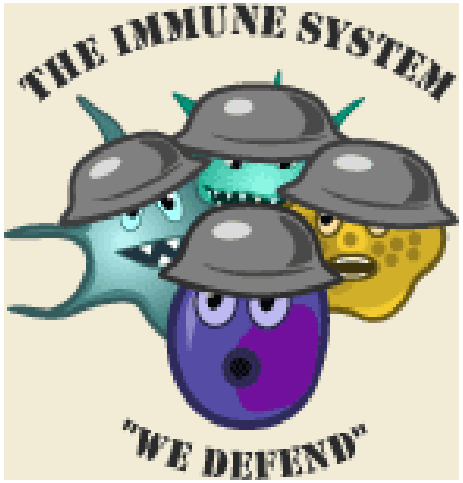
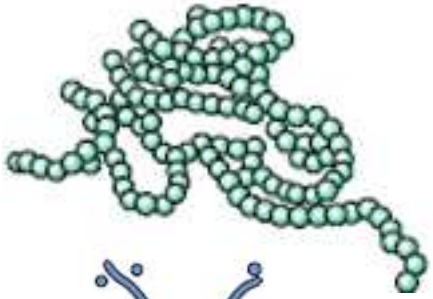
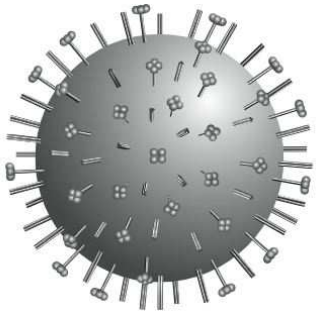


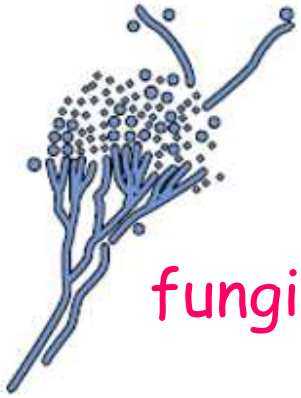

worms

bacteria



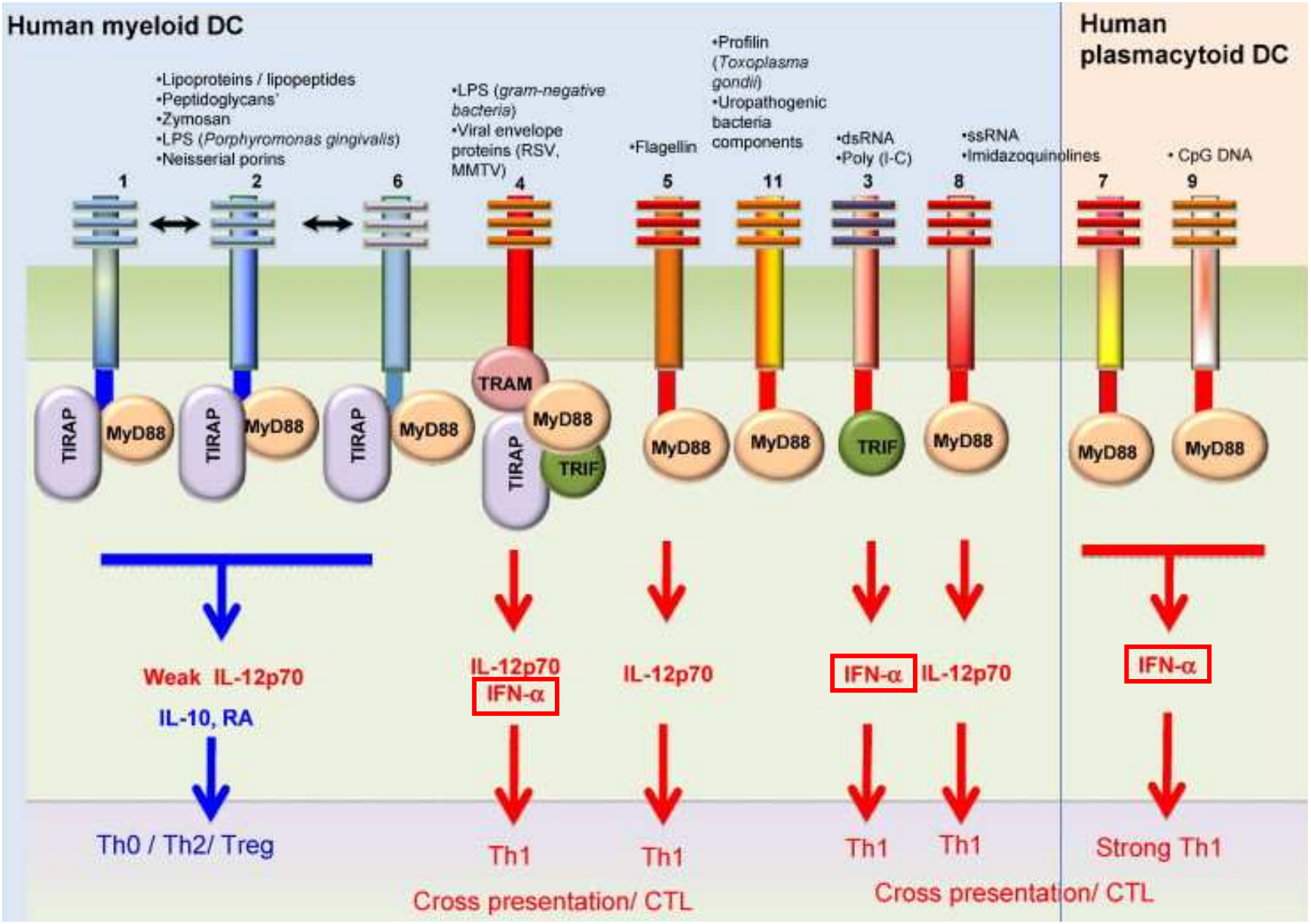
viruses




fungi

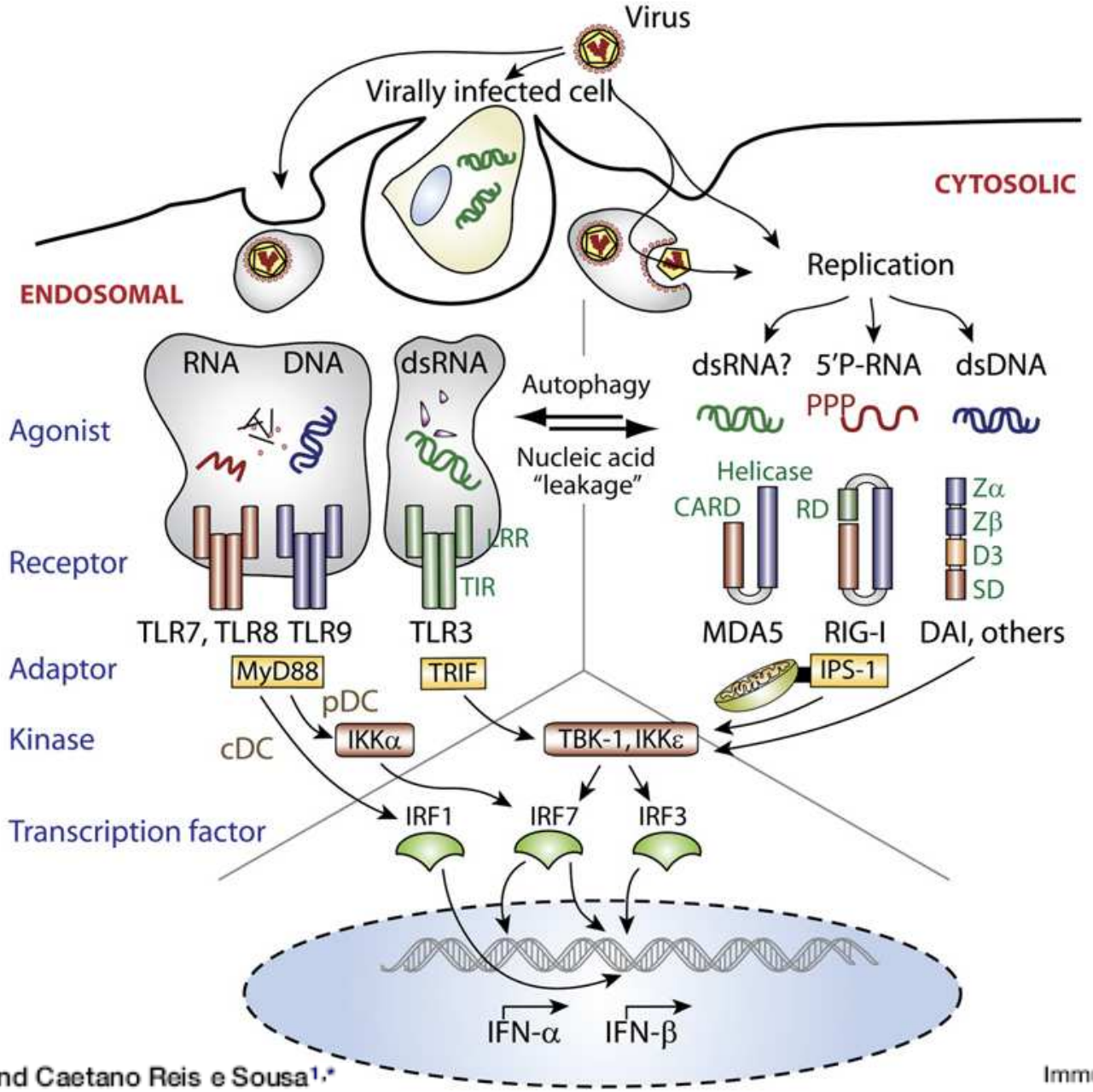
They share common recognition patterns
(Pathogen-Associated Molecular Patterns-**PAMPs**)
recognized by
specific Pattern Recognition Receptors-**PRRs**

TLR signalling in conventional APCs



Seminars in Immunology 2009. 21:185-193

Cytosolic sensors of nucleic acids



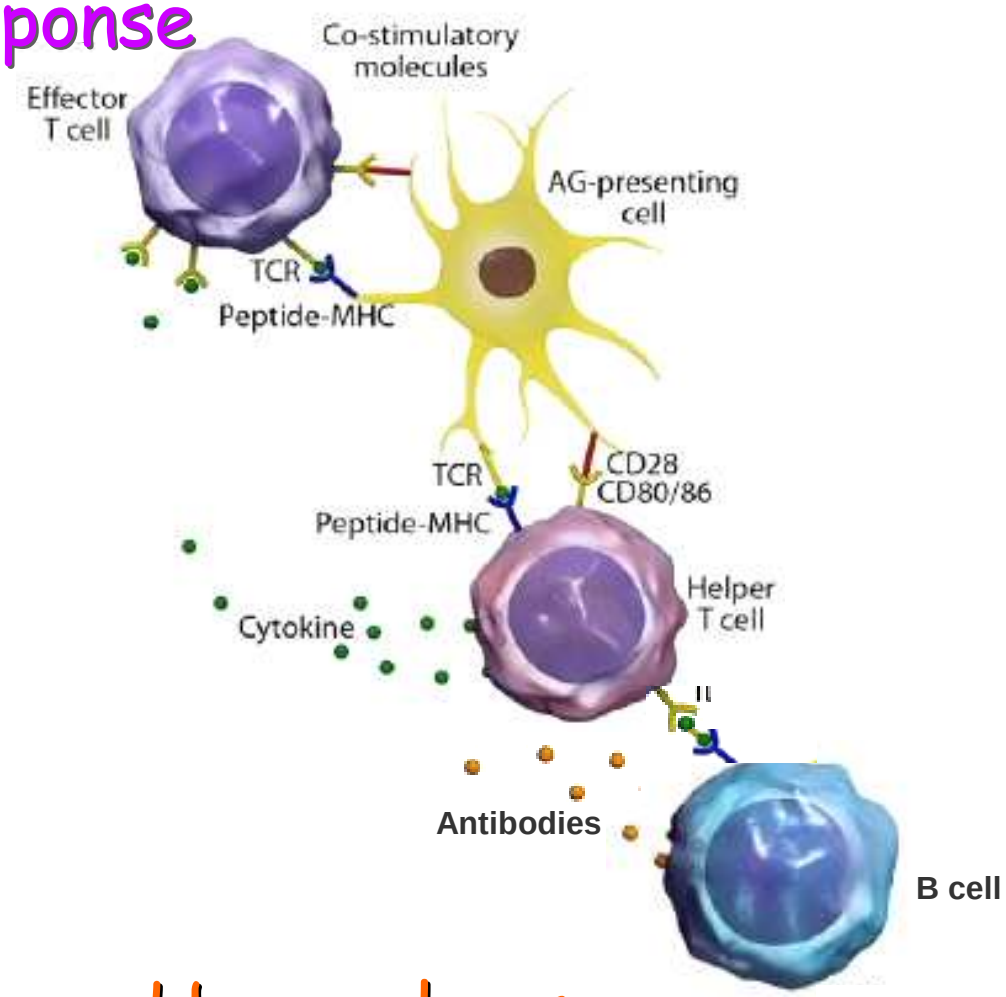
Inducers of type I IFN and producing cells

Inducer	Source	Receptor	Localization	Responding cell
ssRNA, dsRNA	Viruses	RIG-I and MDA5	Cytoplasm	Multiple cell types
Cytosolic DNA	Viruses or bacteria	STING, DAI and RNA polymerase III	Cytoplasm	Multiple cell types
dsRNA	Viruses	TLR3–TRIF	Endosomes	Macrophages, cDCs and epithelial cells
LPS	Gram-negative bacteria	TLR4–TRIF	Plasma membrane	Macrophages and cDCs
Viral glycolipids	Viruses	TLR4–TRIF	Plasma membrane	Macrophages and cDCs
ssRNA	Viruses or damaged host cells	TLR7–MYD88	Endosomes	pDCs, cDCs and macrophages
Imiquimod	Synthetic	TLR7–MYD88	Endosomes	pDCs, cDCs and macrophages
ssRNA	Viruses	TLR8–MYD88	Endosomes	cDCs
CpG DNA	Bacteria or viruses	TLR9–MYD88	Endosomes	pDCs, cDCs and macrophages

The two levels for immune defense

Mechanisms of immunity

Cellular response



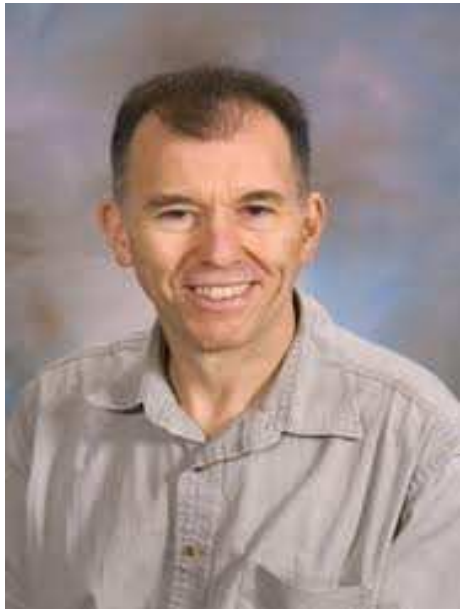
Humoral response

Mod from Burks AW et al, JACI 2008

The T_H1/T_H2 story

W.E. Paul

R.L. Coffman



T.R. Mosmann

0022-1767/86/1367-2348$02.00/0
THE JOURNAL OF IMMUNOLOGY

Vol. 136, No. 7, April 1, 1986
Printed in U.S.A.

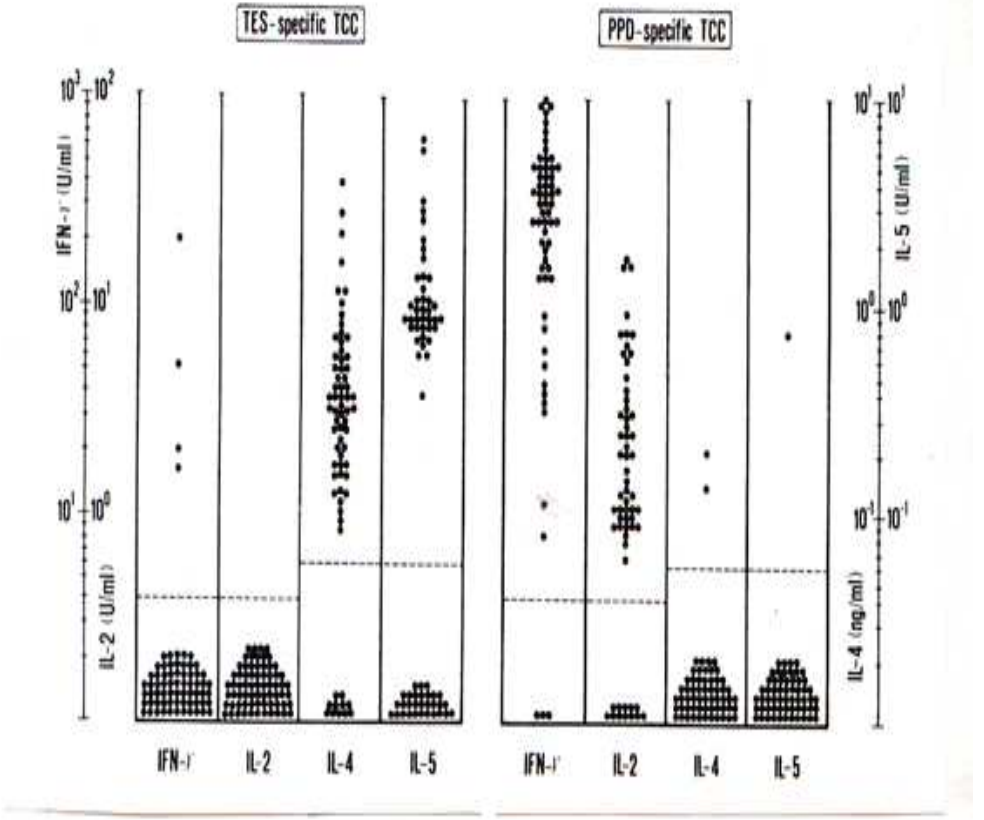
TWO TYPES OF MURINE HELPER T CELL CLONE

I. Definition According to Profiles of Lymphokine Activities and Secreted Proteins

TIMOTHY R. MOSMANN,[1] HOLLY CHERWINSKI, MARTHA W. BOND, MARTIN A. GIEDLIN,[2] AND ROBERT L. COFFMAN

From the DNAX Research Institute of Molecular and Cellular Biology, Inc., 901 California Ave, Palo Alto, CA 94304

Different antigens expand human T-cell clones with opposite (Th1 *vs* Th2) profile of cytokine production

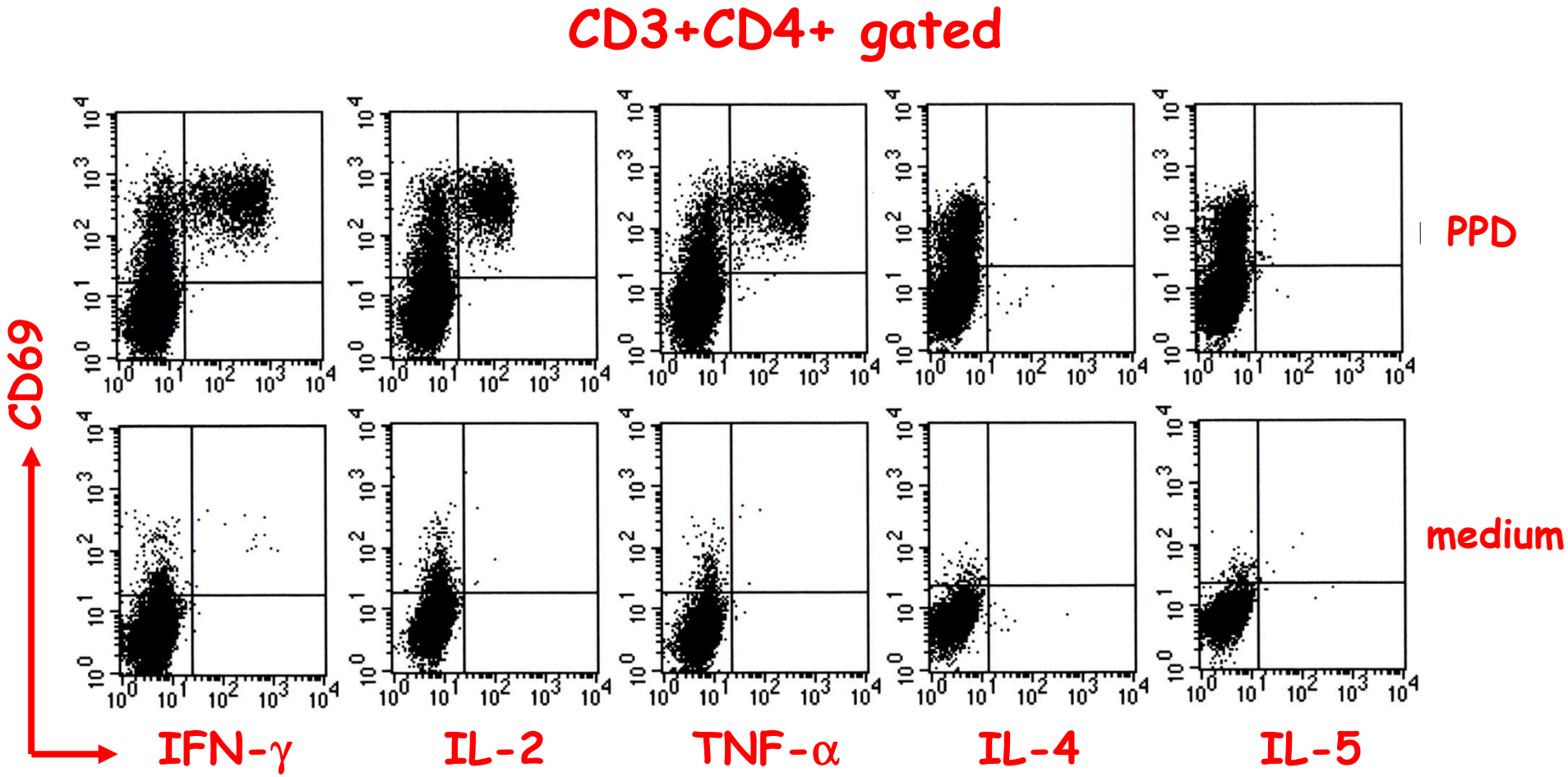


Del Prete et al., J.Clin.Invest. 88: 346-350, 1991

TCC	Antigen specificity	Cytokine production* IL-4, pg/ml	Cytokine production* IFN-γ, unit(s)/ml	IgE synthesis by autologous B cells,† ng/ml
None	—	—	—	0.2
FS 47	*D. pteronyssinus*	793	2	2.3
FS 35	*D. pteronyssinus*	325	1	4.1
FS 18	*D. pteronyssinus*	436	1	3.3
FS 14	*D. pteronyssinus*	3223	2	15.1
FS 21	*D. pteronyssinus*	4125	3	9.8
FS 4	Tetanus toxoid	10	85	0.2
FS 3	Tetanus toxoid	1186	12	14.9
FS 8	Tetanus toxoid	460	10	9.4
FS 10	Tetanus toxoid	10	137	0.2
FS 17	Tetanus toxoid	1298	46	0.6
None	—	—	—	0.3
AM 41	*L. perenne* group I	2052	2	6.2
AM 15	*L. perenne* group I	6272	9	7.4
AM 65	*L. perenne* group I	4320	4	2.7
AM 57	*L. perenne* group I	5440	5	4.1
AM 29	PPD	1000	28	2.9
AM 16	PPD	19	236	0.9
AM 17	PPD	112	225	0.3
AM 50	PPD	415	240	0.3

Parronchi et al., PNAS 88: 4538-4542, 1991

Flow cytometric evaluation of cytokines producing cells upon 8h PPD stimulation of PB from an active TB patient



The Th1/Th2 paradigm has become an established fact

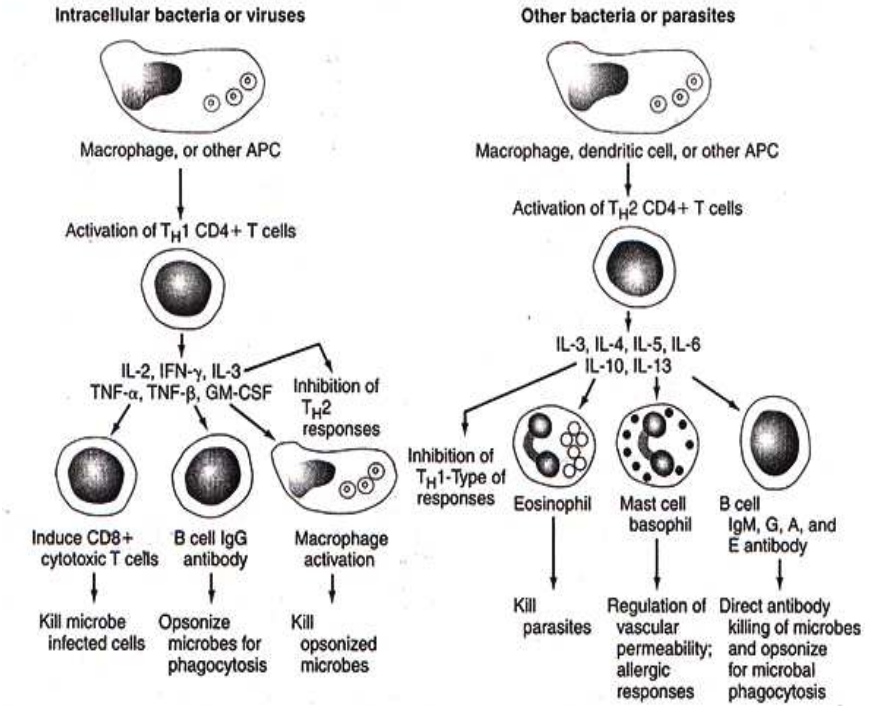


FIGURE 305-13 CD4+ helper T 1 (T_H1) cells and T_H2 T cells secrete distinct but overlapping sets of cytokines. T_H1 CD4+ cells are frequently activated in immune and inflammatory reactions against intracellular bacteria or viruses, while T_H2 CD4+ cells are frequently activated for certain types of antibody production against parasites and extracellular encapsulated bacteria; they are also activated in allergic diseases. APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

15th edition, 2001, p.1826

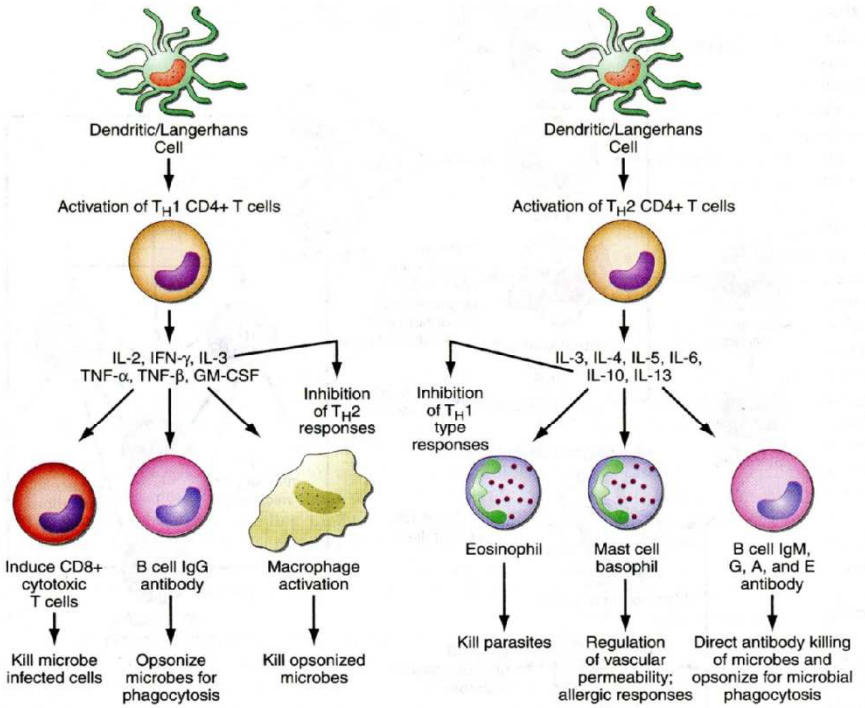
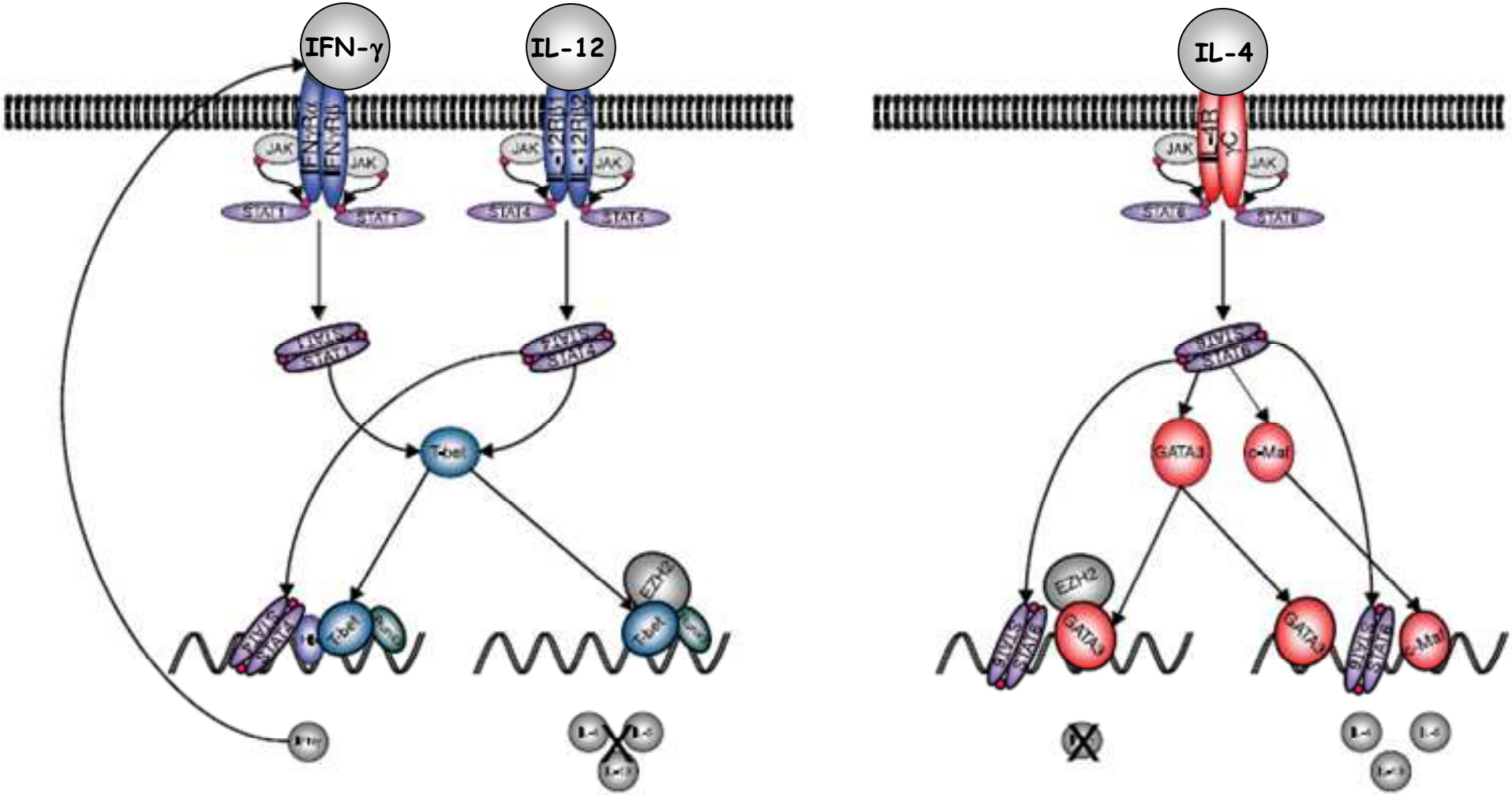


FIGURE 295-11 CD4+ helper T 1 (T_H1) cells and T_H2 T cells secrete distinct but overlapping sets of cytokines. T_H1 CD4+ cells are frequently activated in immune and inflammatory reactions against intracellular bacteria or viruses, while T_H2 CD4+ cells are frequently activated for certain types of antibody production against parasites and extracellular encapsulated bacteria; they are also activated in allergic diseases. GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor. *[Adapted from S Romagnani: CD4 effector cells, in J Gallin, R Snyderman (eds): Inflammation: Basic Principles and Clinical Correlates, 3d ed. Philadelphia, Lippincott Williams & Wilkins, 1999; with permission.]*

16th edition, 2004, p.1924

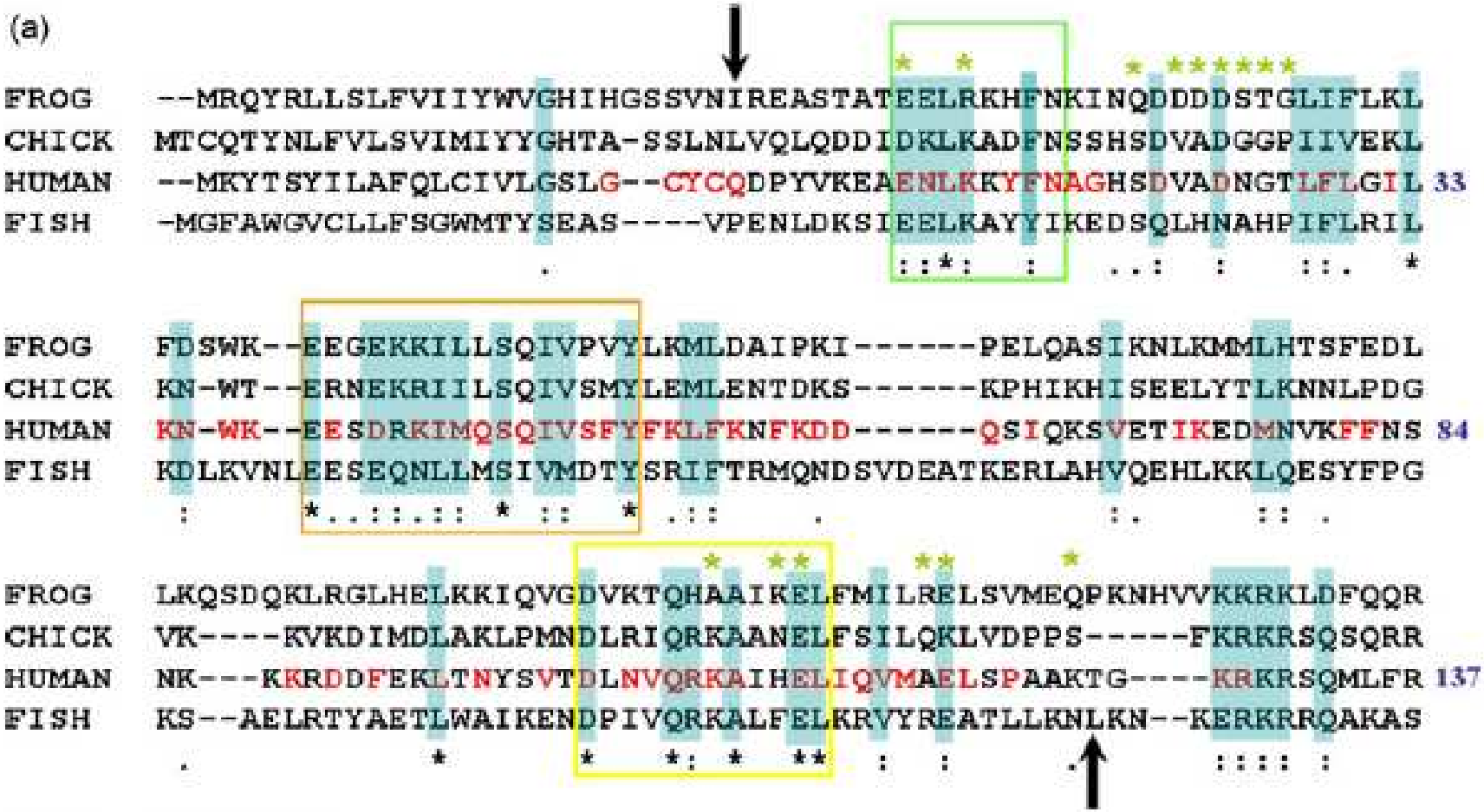
Harrison's. Principles of Internal Medicine (adapted from Romagnani, 1999)

Mutually exclusive expression of transcription factors in T_H1 and T_H2 cells



H. Bowen, A. Kelly, T. Lee and P. Lavender 2008. Clinical and Experimental Allergy, 38, 1422–1431

IFN-γ is highly conserved among species

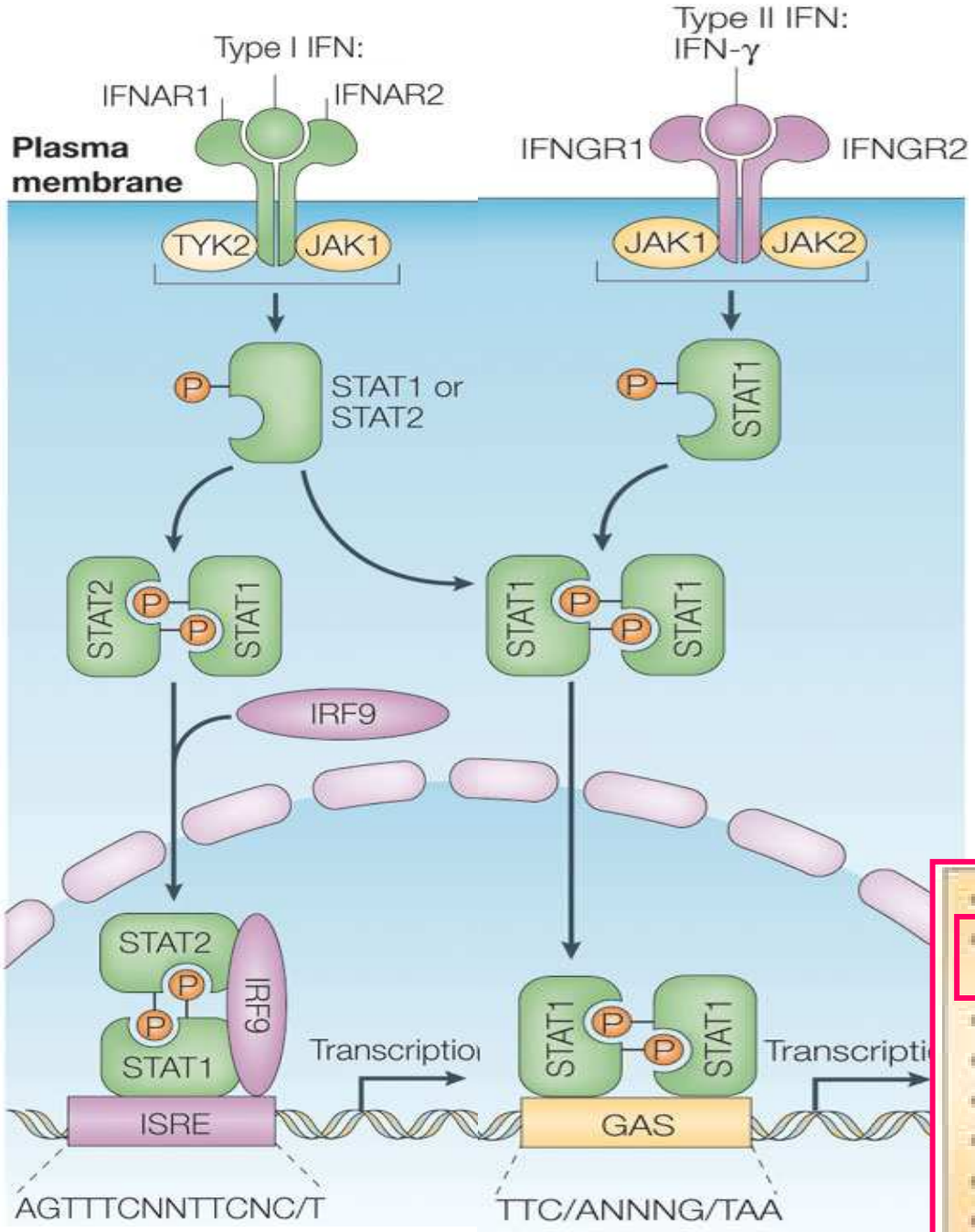


R. Savan et al. / Cytokine & Growth Factor Reviews 20 (2009) 115–124

Interferon-γ

- is the sole Type II IFN
- is structurally unrelated to Type I IFN
- is encoded by a separate chromosomal locus
- binds to different receptor

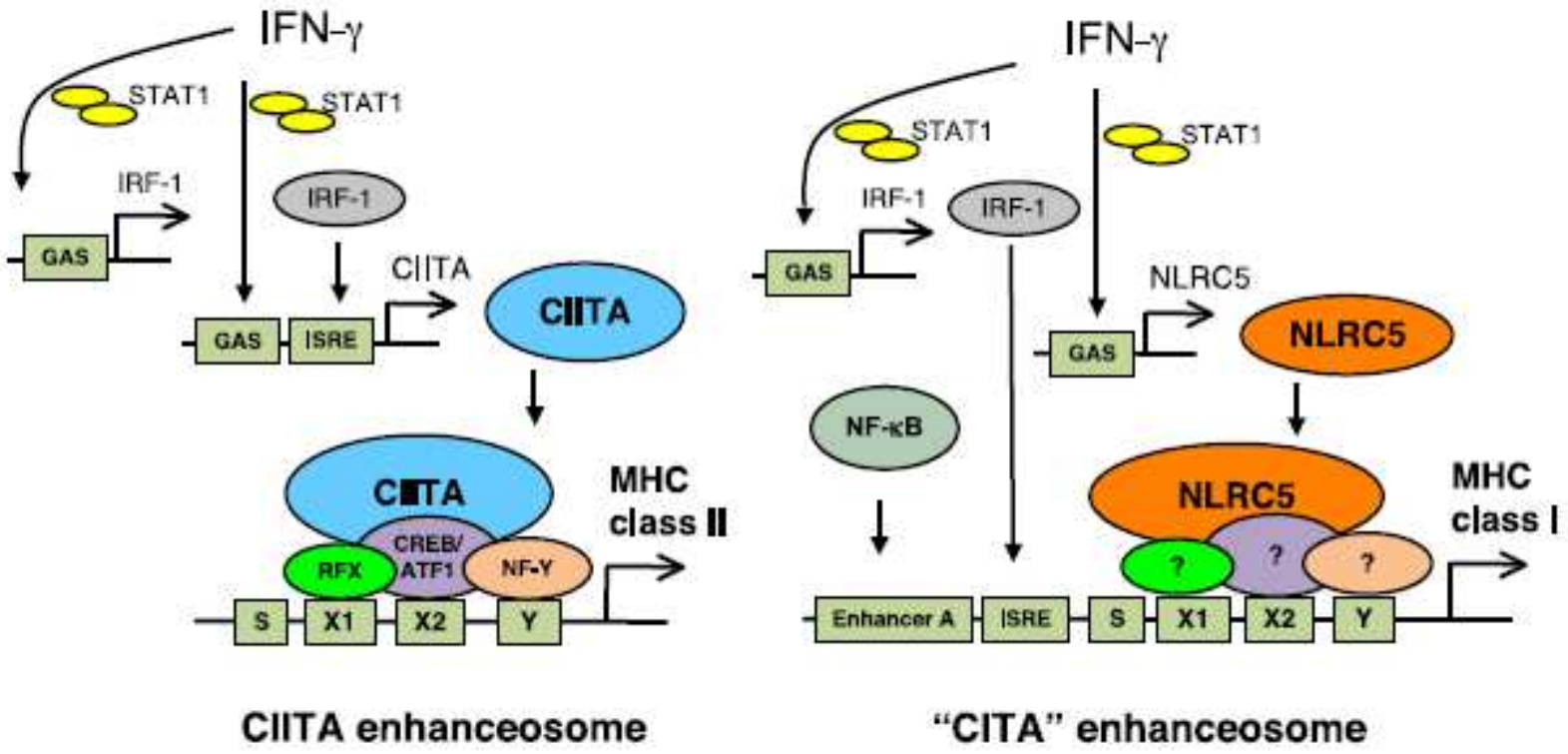
The cross-talk between IFN-α/β and IFN-γ pathways



- IRF1 expression
- MHC class I and class II pathway upregulation
- Chemokine expression
- Co-stimulation
- T_{Reg}-cell inhibition
- T_H1-cell differentiation
- CTL activation and differentiation
- Antiproliferative effects

Nature Reviews | Immunology

Class I and II presentation pathways are influenced by type II IFN

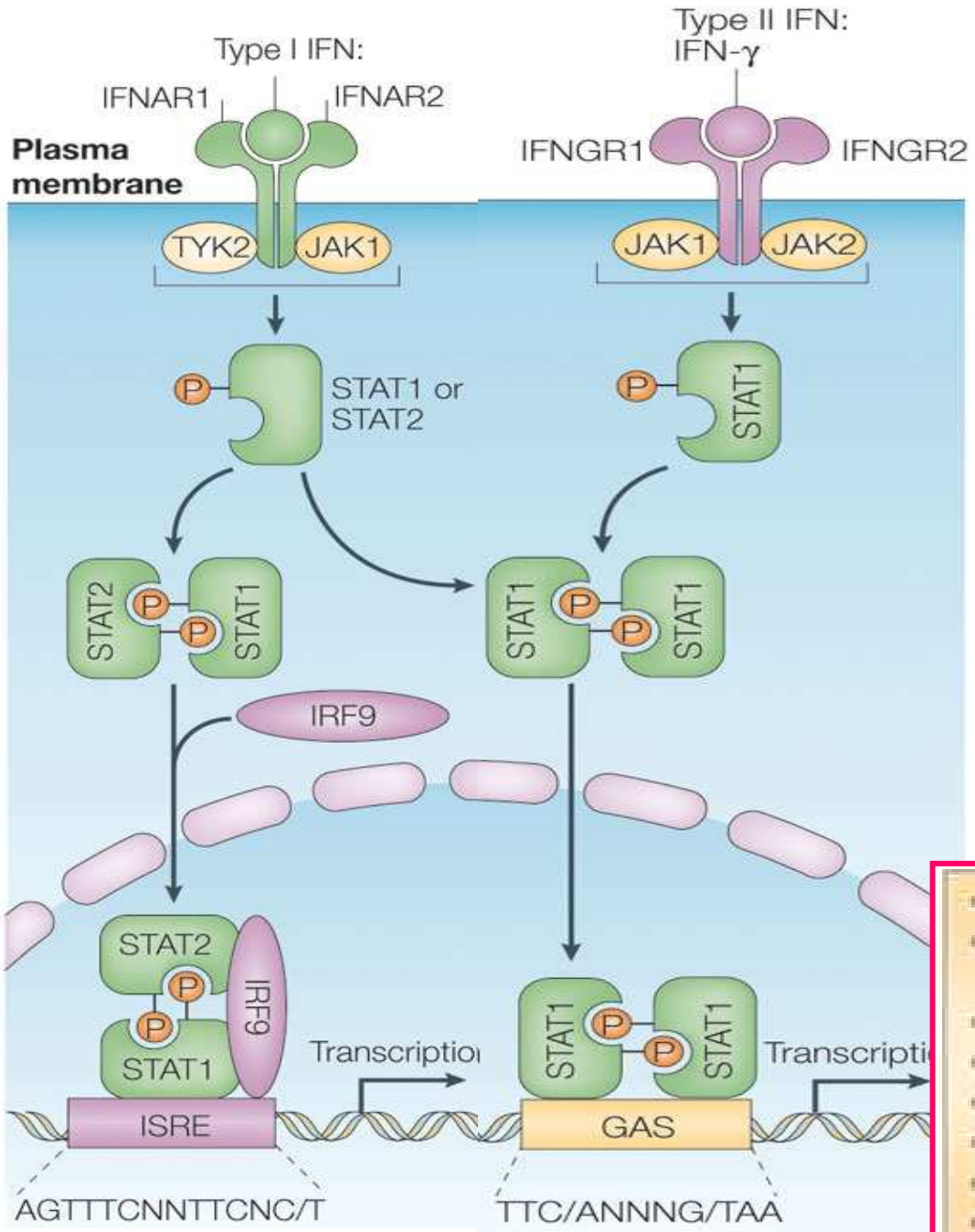


T.B. Meissner et al. / Microbes and Infection 14 (2012) 477–484

Class I and II presentation pathways are influenced by type II IFN

MHC class I		MHC class II	
LMP-2, LMP-7, MECL-1	Enzymatic proteasome subunits	α and β chains	Constituents of MHC
PA28a, PA28b	Proteasome activators	Ii chain, DM	
TAP-1, TAP-2	Transporter proteins	Cathepsins B, H, L	Involved in peptide production
Class I MHC heavy chain		CIITA	Master of regulator
Tapasin	Chaperone in ER		

The cross-talk between IFN-α/β and IFN-γ pathways



- IRF1 expression
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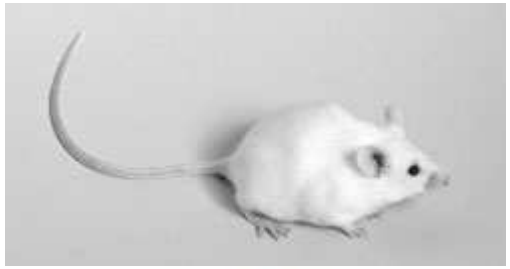
Nature Reviews | Immunology

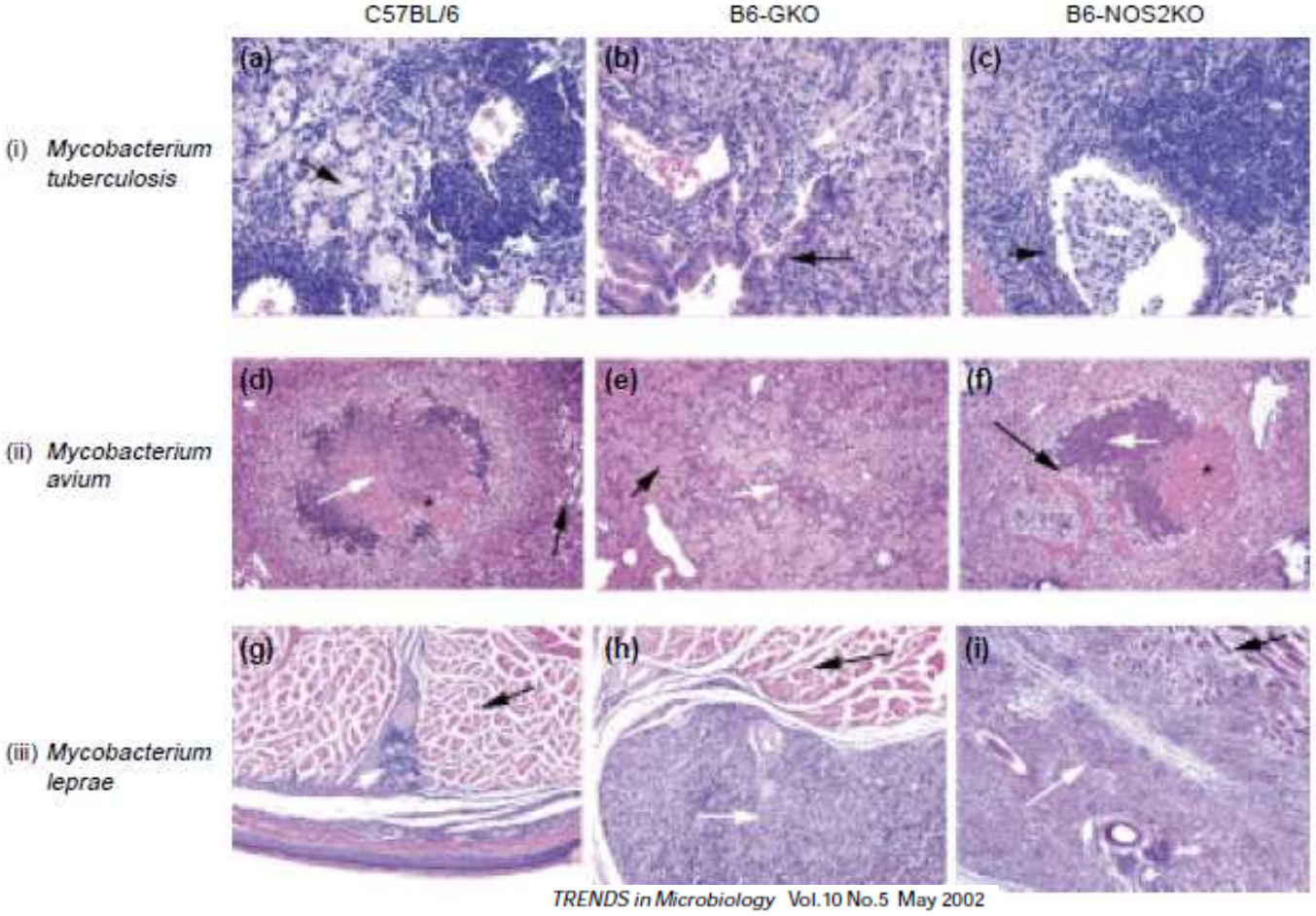
Effects of IFN-γ on antibacterial and antiviral response

Other antimicrobial mechanisms

Gene/protein up-regulated by IFN-γ	Function
NRAMP1	The natural resistance-associated macrophage protein (NRAMP1) confers resistance to macrophage intracellular pathogens by largely unknown mechanisms.
FcRγI	Expression of the high-affinity Fc receptor (FcγRI) is increased in myeloid cells by IFN-γ stimulation. FcRγI binds extracellular pathogens via IgG in the adaptive phase of the immune response.
C2, C4, Factor B	Complement proteins are secreted by macrophages and fibroblasts in response to IFN-γ. Complement functions to opsonize extracellular pathogen for receptor-mediated phagocytosis by mononuclear phagocytes.
Complement receptor CR3 (Mac-1)	Complement receptors of mononuclear phagocytes are up-regulated by IFN-γ to promote receptor-mediated phagocytosis of opsonized extracellular pathogens.

The examples of IFN-γ k.o. mice





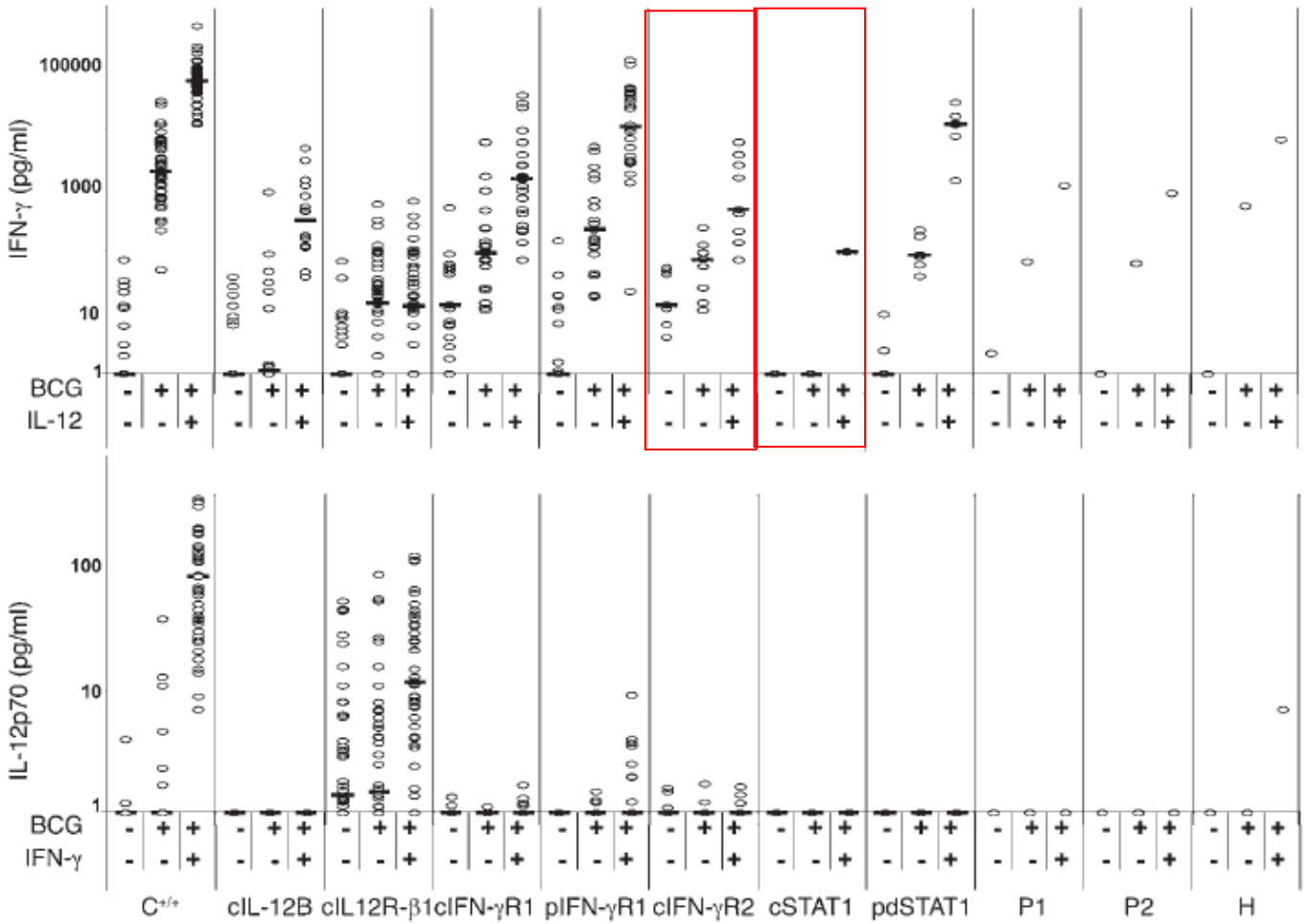
TRENDS in Microbiology Vol.10 No.5 May 2002

Effects of Interferon deficiencies

IL-12 and IL-23 receptor deficiency	L + NK	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	Elastase *IL-12Rβ1*:IL12 and IL23 receptor β1 chain
IL-12p40 deficiency	M	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*	AR	*IL-12p40* subunit of IL12/IL23: IL12/IL23 production
IFN-γ receptor deficiencies	M + L	IFN-γ binding or signaling	Susceptibility to *Mycobacteria* and *Salmonella*	AR, AD*	*IFN-γR1*: IFN-γR binding chain
				AR	*IFN-γR2*: IFN-γR *signaling chain*
STAT1 deficiency(2 forms)	M + L	-IFN α/β/γ signaling IFN-γ signaling	Susceptibility to *Mycobacteria*, *Salmonella*, and viruses Susceptibility to *Mycobacteria* and *Salmonella*	AR AD*	STAT1: STAT1

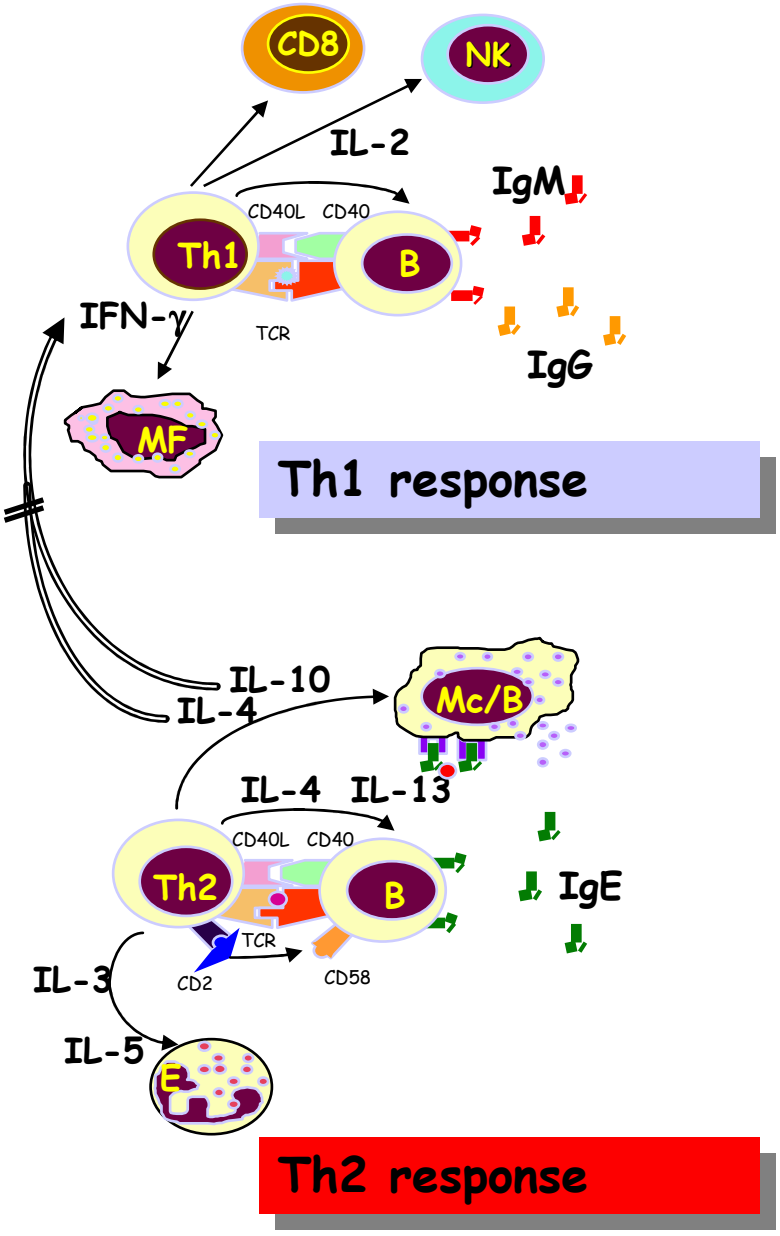
STAT1 deficiency is associated with susceptibility to mycobacterial and viral diseases

The Journal of Clinical Investigation http://www.jci.org Volume 119 Number 6 June 2009



The Th1/Th2 paradigm

(Romagnani S. Immunol. Today 18, 263, 1997)



Th1 response

Th2 response

Th1-associated conditions

Organ-specific autoimmune diseases	Some unexplained recurrent abortion
Rheumatoid arthritis	Proliferative glomerulonephritis
Sarcoidosis	Crohn's disease
Atherosclerosis	Helicobacter pylori-induced peptic ulcer
Acute allograft rejection	

Th2-associated conditions

Omenn's syndrome	Atopic disorders
Some idiopathic hyper-eosinophilic syndromes	Chronic GVHD
Vernal conjunctivitis	Progressive systemic sclerosis
Progression to AIDS of HIV infection	Idiopathic fibrosizing alveolitis

The Interferon story is characterized by

PLASTICITY

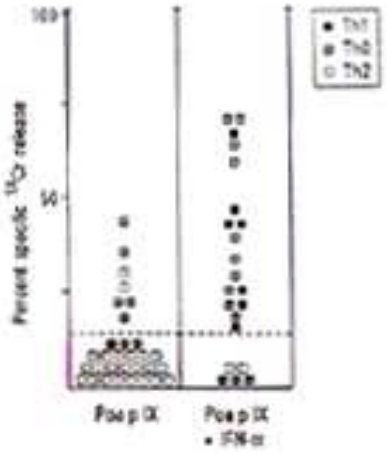
Eur Cytokine Net 1994 Jan-Feb;5(1):7-12.

Human T_H1 and T_H2 subsets: "eppur si muove"!

Romagnani S.
Division of Clinical Immunology and Allergy, University of Florence, Italy.

Innate cytokines promote the T_H1/T_H2 shift

IFN-α



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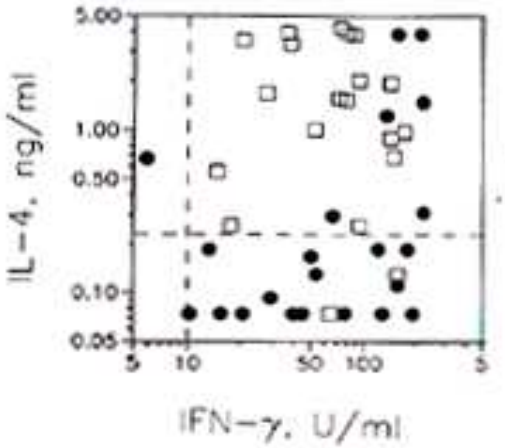
J. Immunol. 149:2977,1992

IL-12



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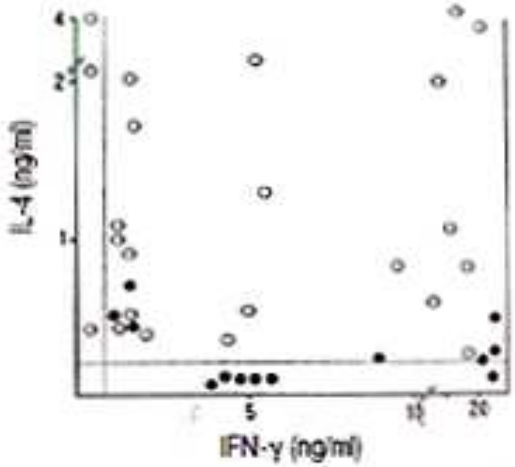
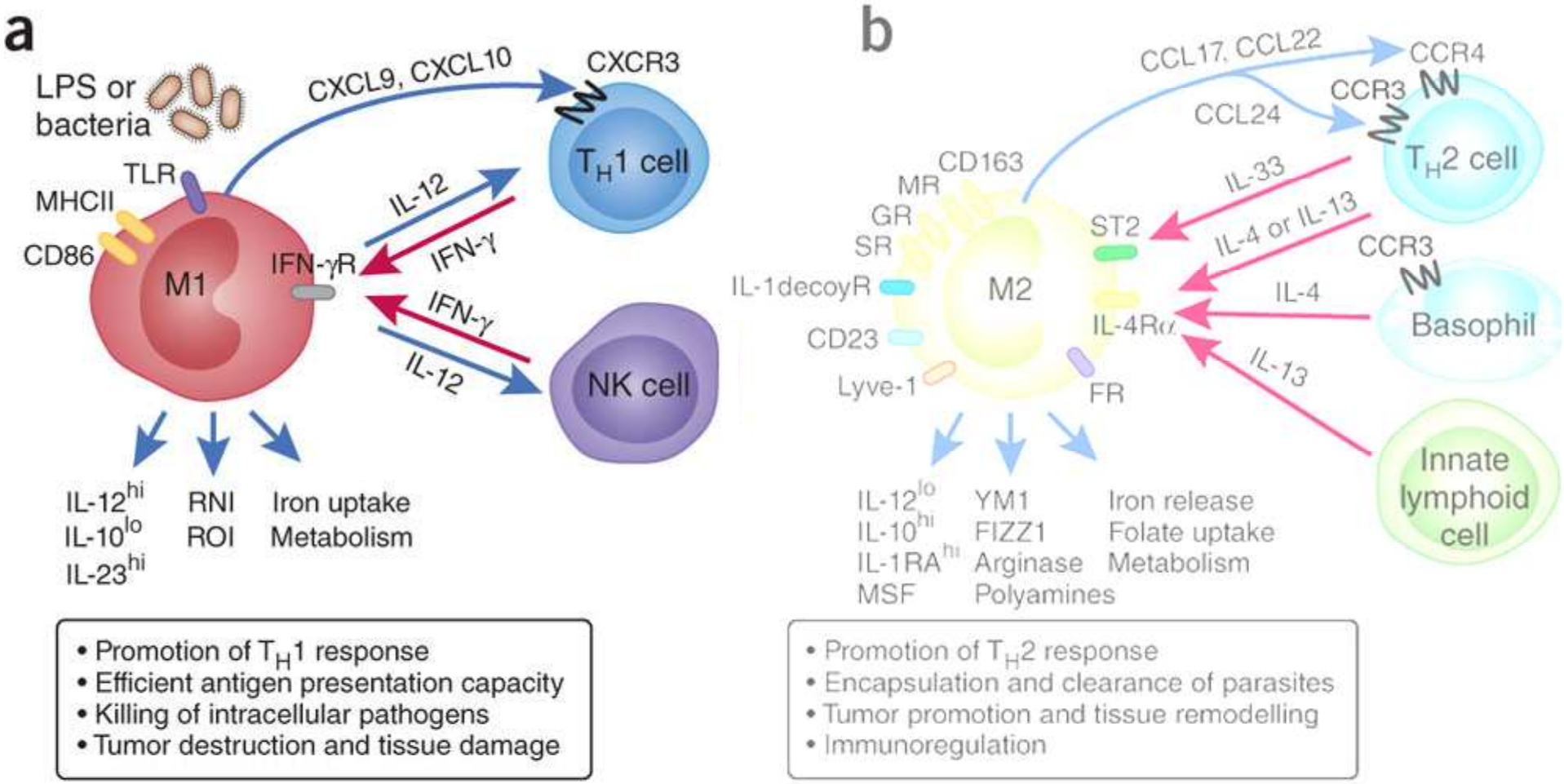
J. Exp. Med. 177:1199,1993

Poly I:C



Manetti et al.,
Eur. J. Immunol. 25:2656,1995

The orchestration of macrophage activation and polarization by lymphoid cells



Mod from Nature Immunology 11: 889-896 (2010)

Concluding remarks

Class I antigen presentation pathway

Class II antigen presentation pathway

The IFN-induced antiviral state

Cell cycle, growth, and apoptosis

Activation of microbicidal effector functions

Immunomodulation and leukocyte trafficking

IFN-γ priming of the macrophage LPS response

IFN-γ and development of Th1 response

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