Basis of Immunology and Immunophysiopathology of Infectious Diseases

Jointly organized by
Institut Pasteur in Ho Chi Minh City and Institut Pasteur
with kind support from ANRS & Université Pierre et Marie Curie

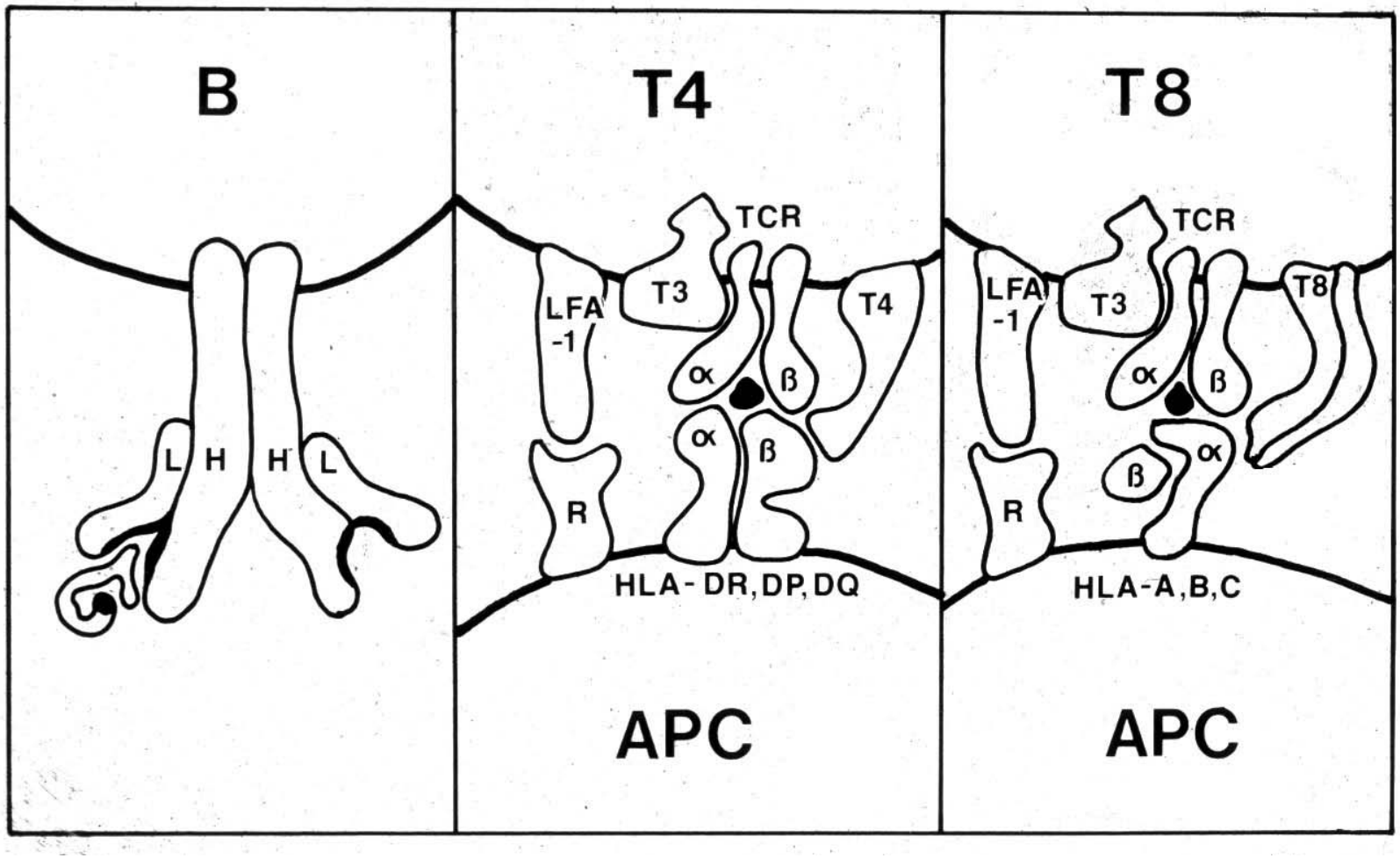
January 24 – February 5, 2005
at the Institut Pasteur in Ho Chi Minh City, Vietnam

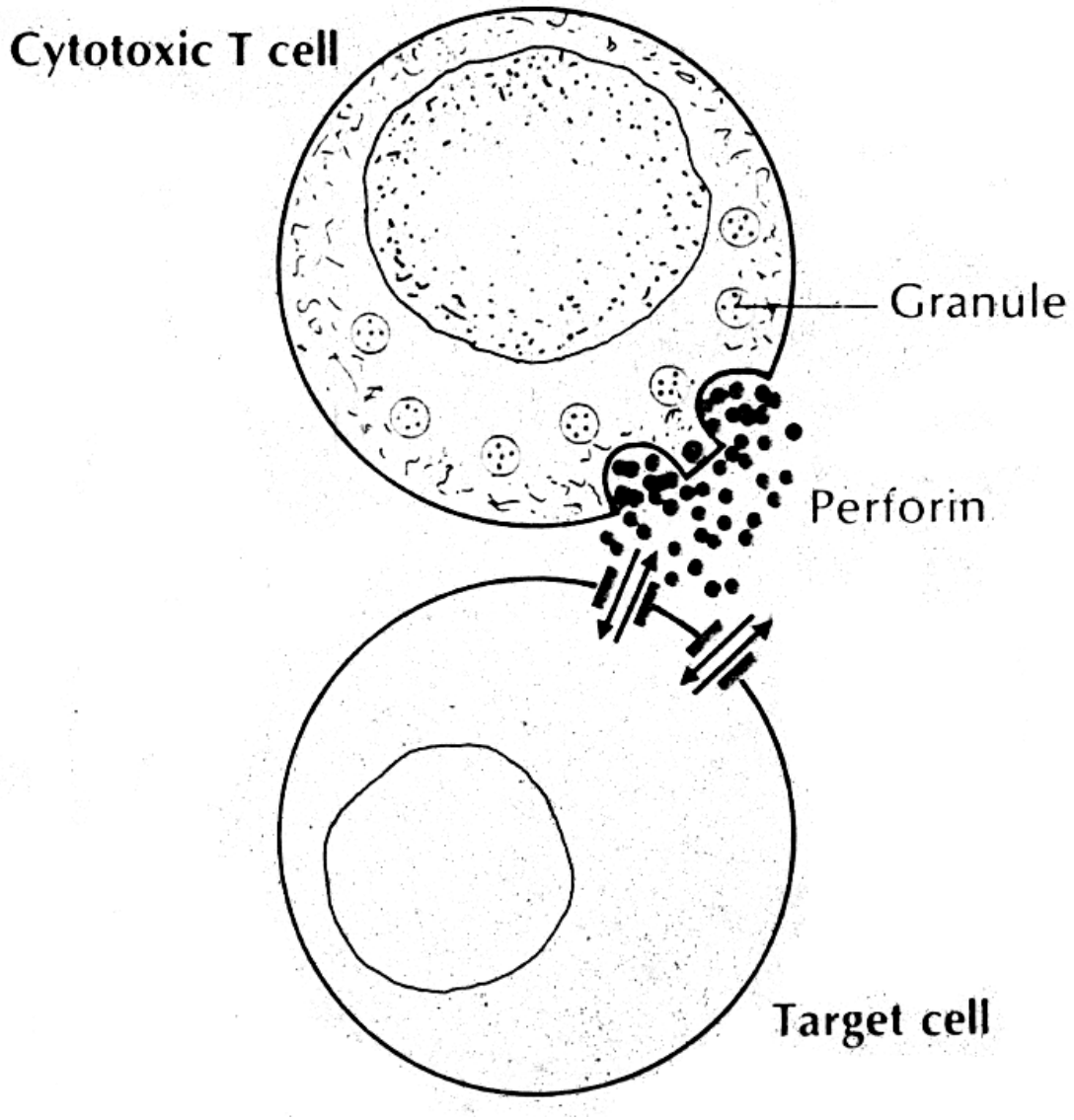
Lecture :

Activation of peripheral T lymphocytes

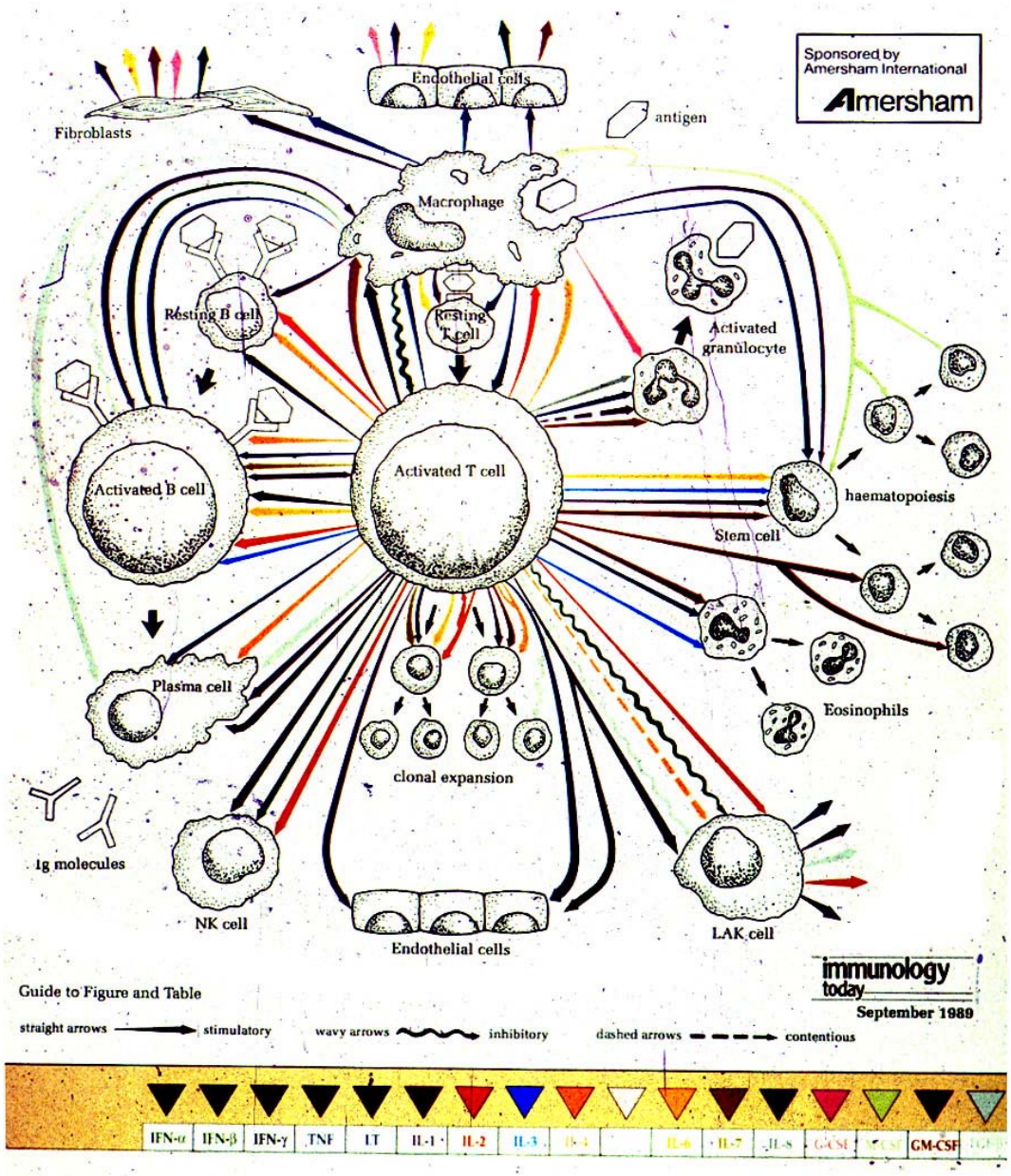
Prof. Jacques Louis

January 28, 2005

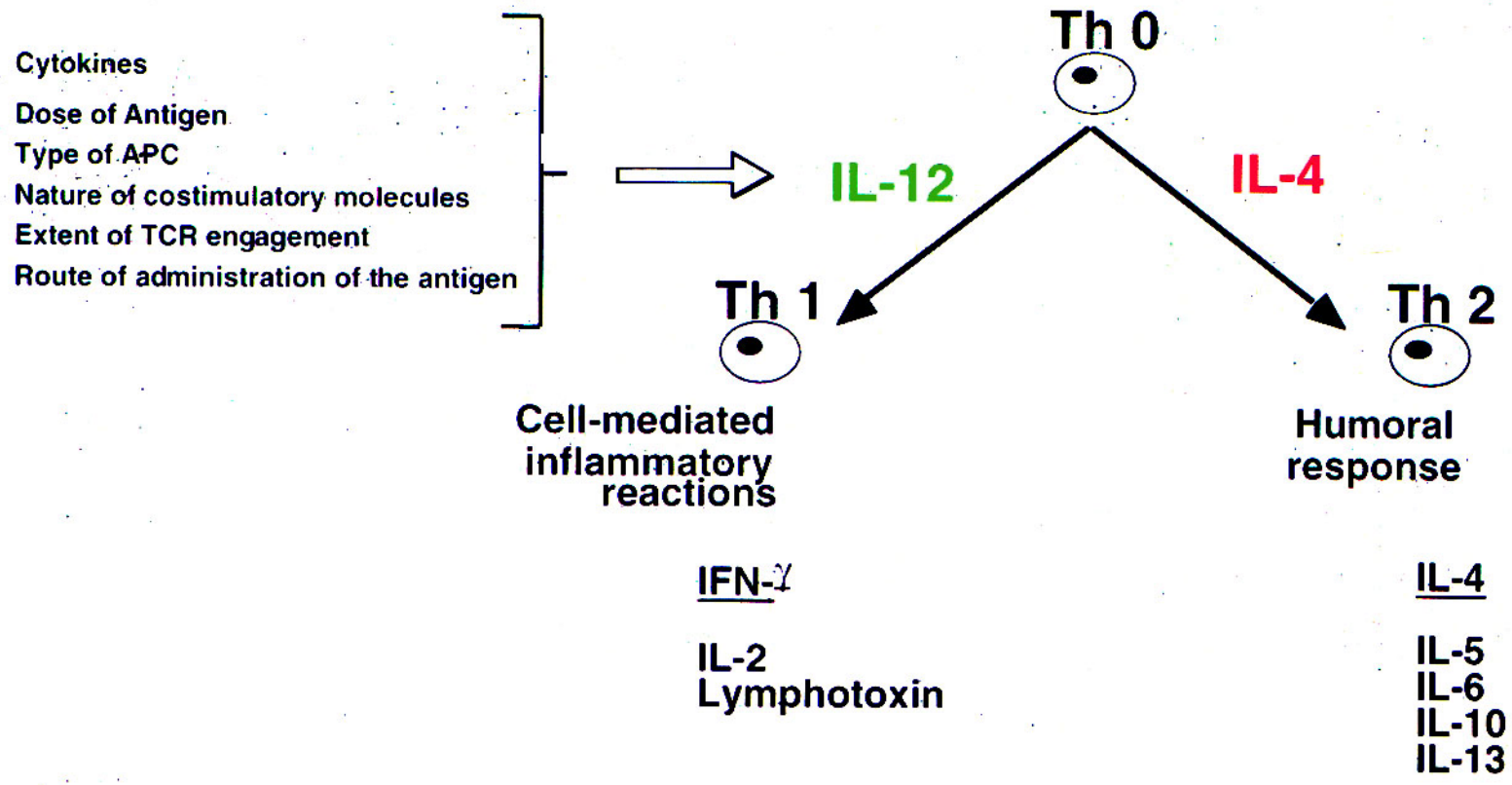

B
L
H
H
L
T4
TCR
LFA
-1
T3
T4
α
β
α
β
R
HLA - DR, DP, DQ
APC
T8
TCR
LFA
-1
T3
T8
α
β
β
α
R
HLA-A, B, C
APC

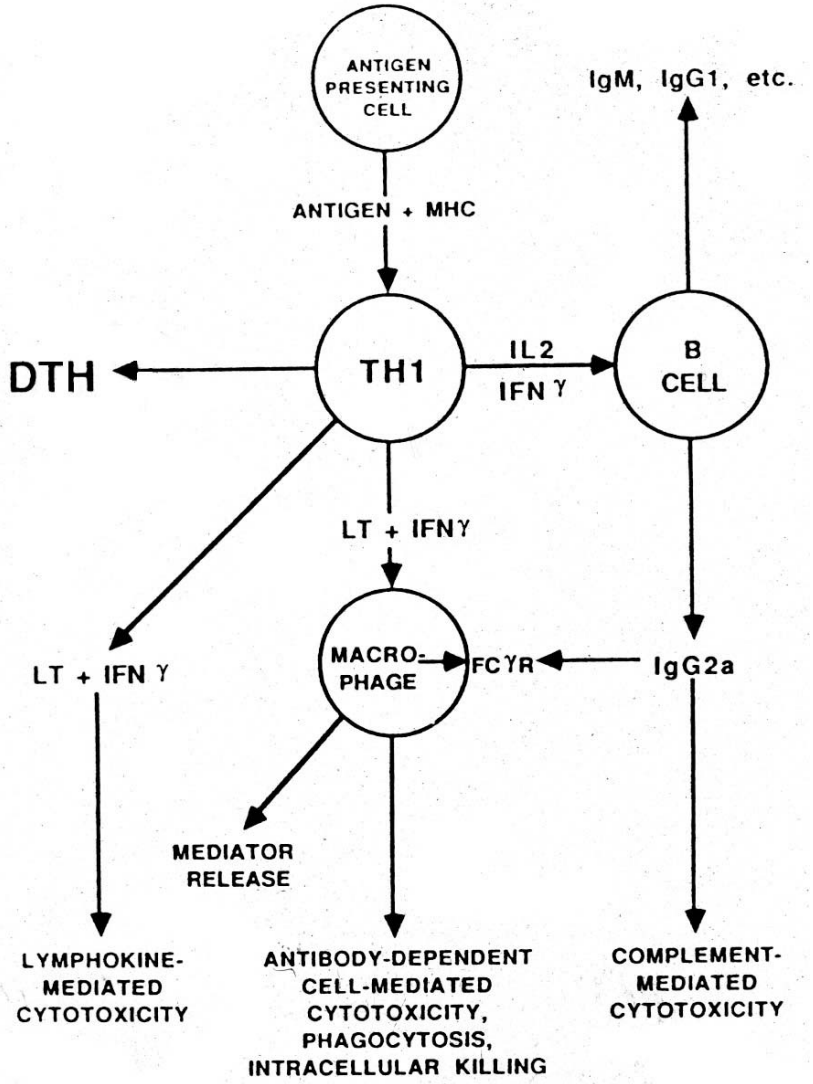

Cytotoxic T cell
Granule
Perforin
Target cell

The Cytokine Network

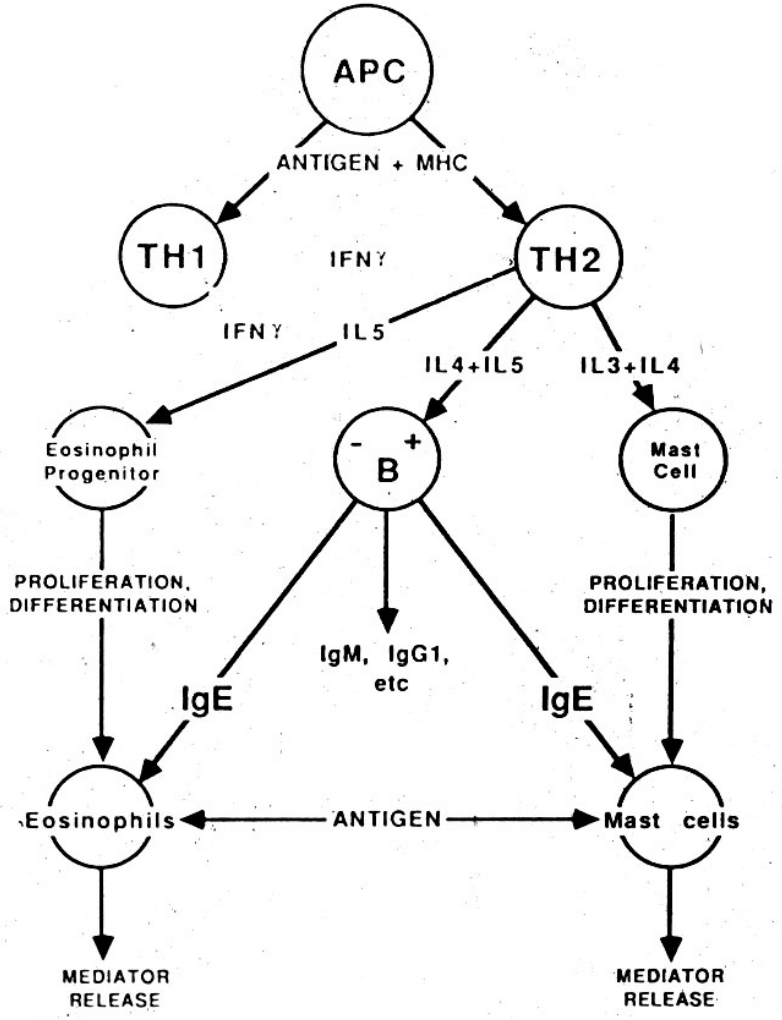


Th cells can develop into two different subsets of effector cells





TH1-mediated effector functions.

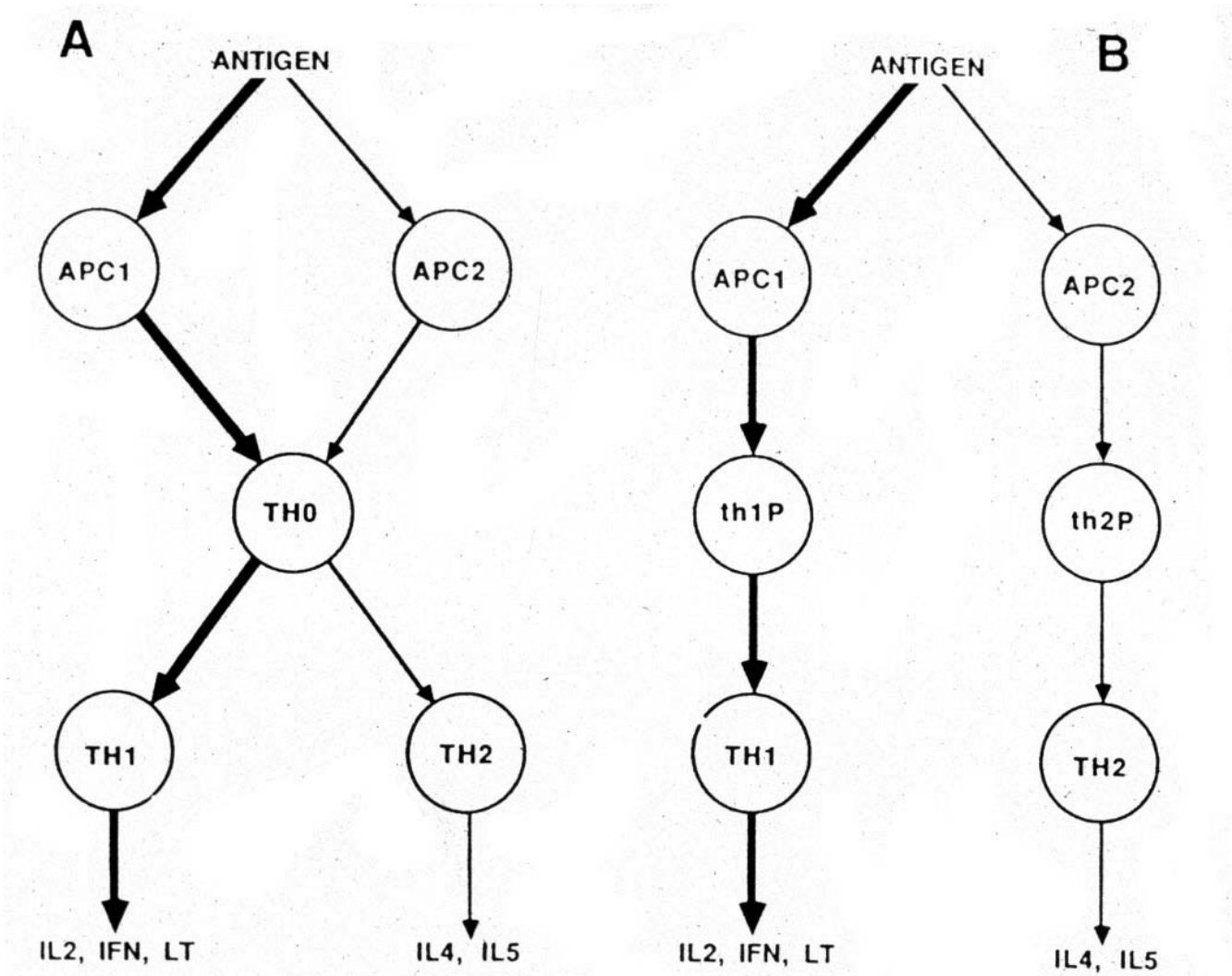


TH1 and TH2 regulation of IgE. Stippled arrows indicate inhibitory effects, and solid arrows show stimulatory effects.

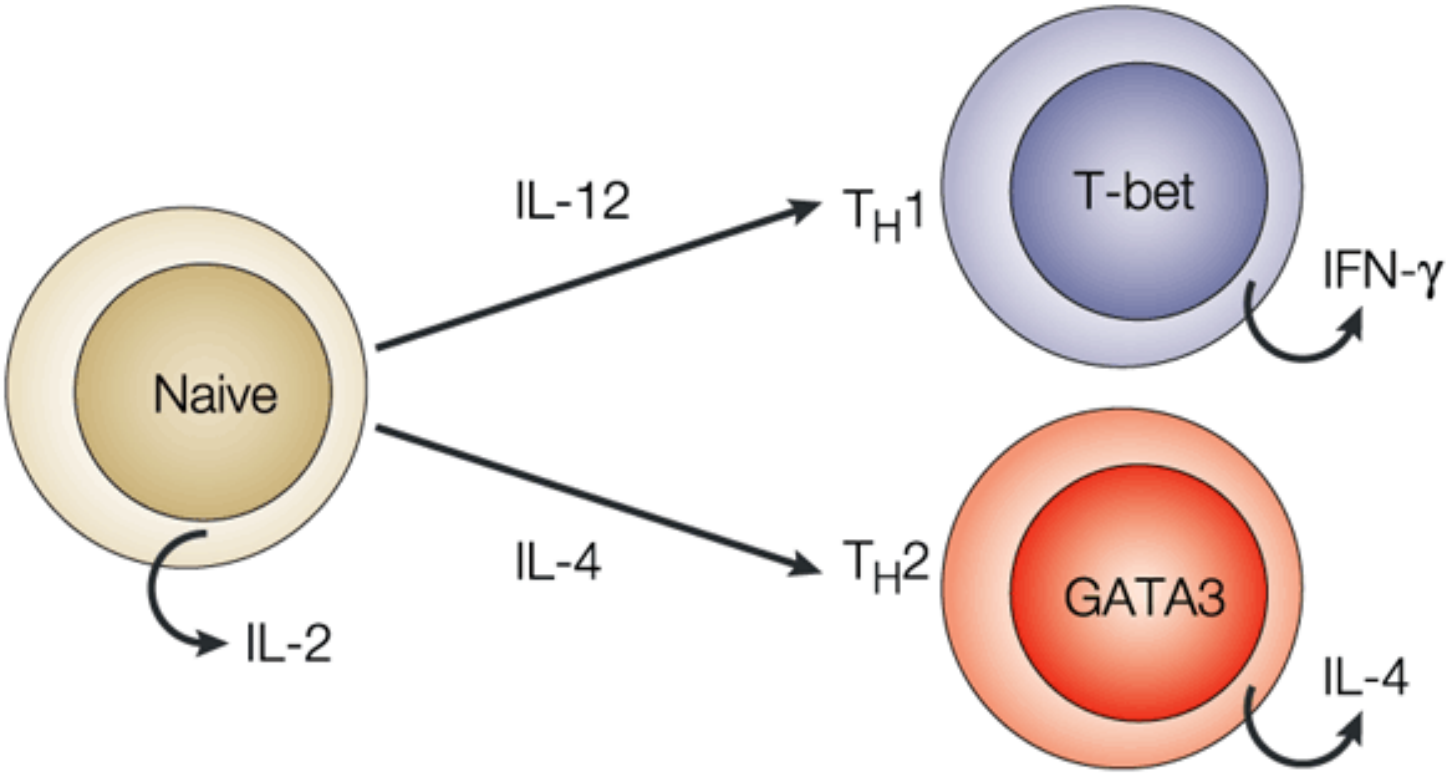
HEAVY CHAIN ISOTYPE SWITCHING INDUCED BY CYTOKINES

B cells cultured with:		Ig isotype secreted (% of total Ig)				
Polyclonal activator	*Cytokine*	*IgM*	*IgG1*	*IgG2a*	*IgGE*	*IgA*
LPS	None	85	2	<1	<1	<1
LPS	IL-4	70	20	<1	5	<1
LPS	IFN-γ	80	2	10	<1	<1
LPS	TGF-β + IL-2	75	2	<1	<1	15

Adapted from Abbas, Lichtman, & Pober, Cellular and Molecular Immunology



Possible TH1 and TH2 differentiation pathways.


IL-12
T_H1
T-bet
IFN-γ
Naive
IL-2
IL-4
T_H2
GATA3
IL-4
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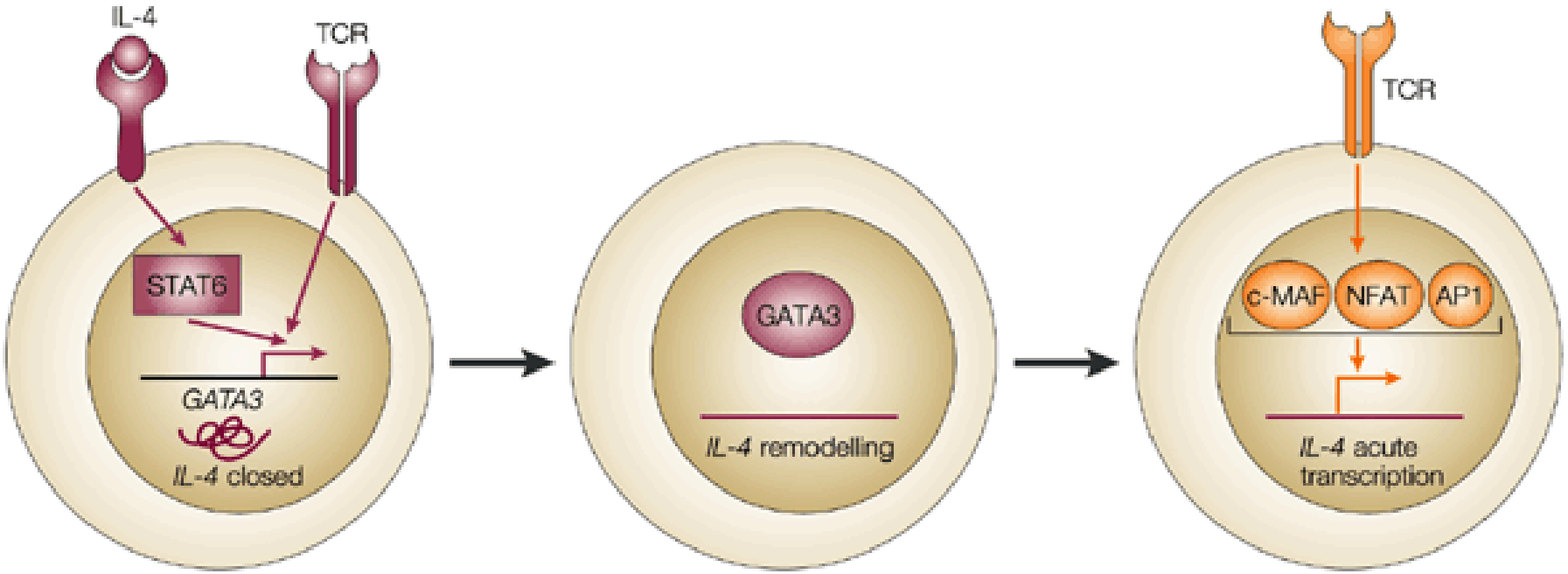

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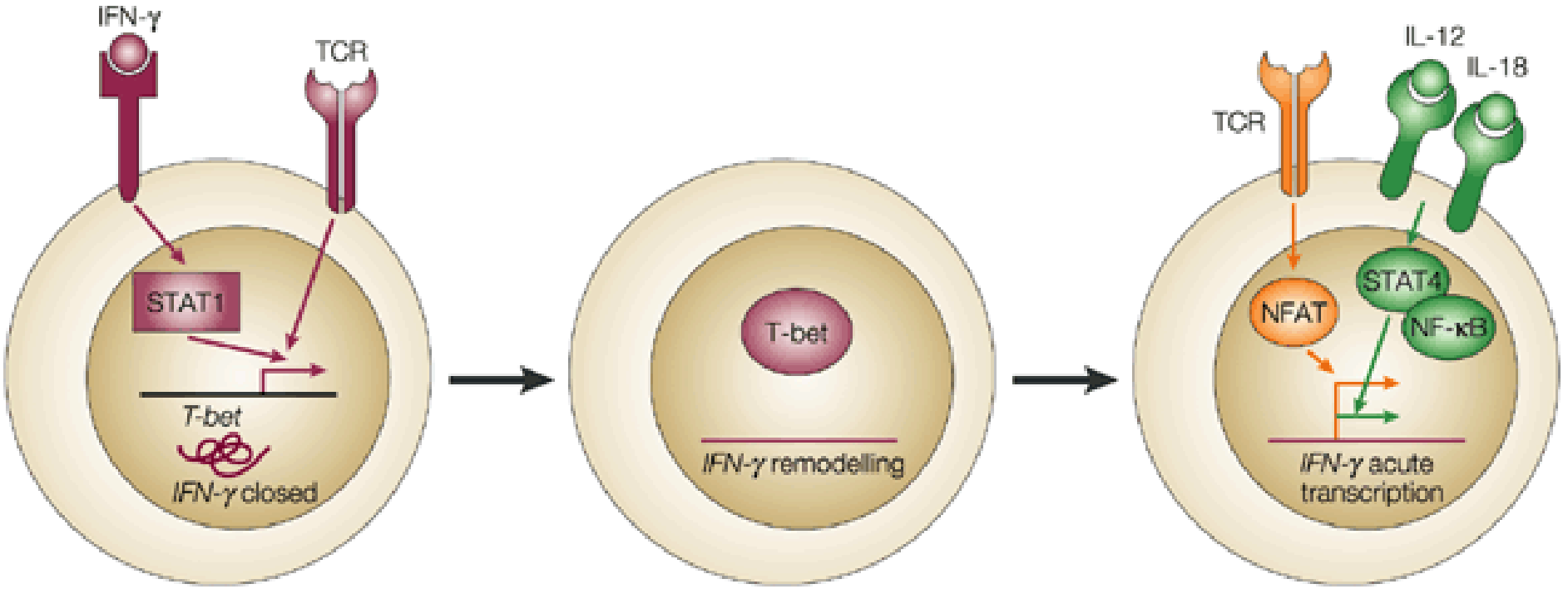

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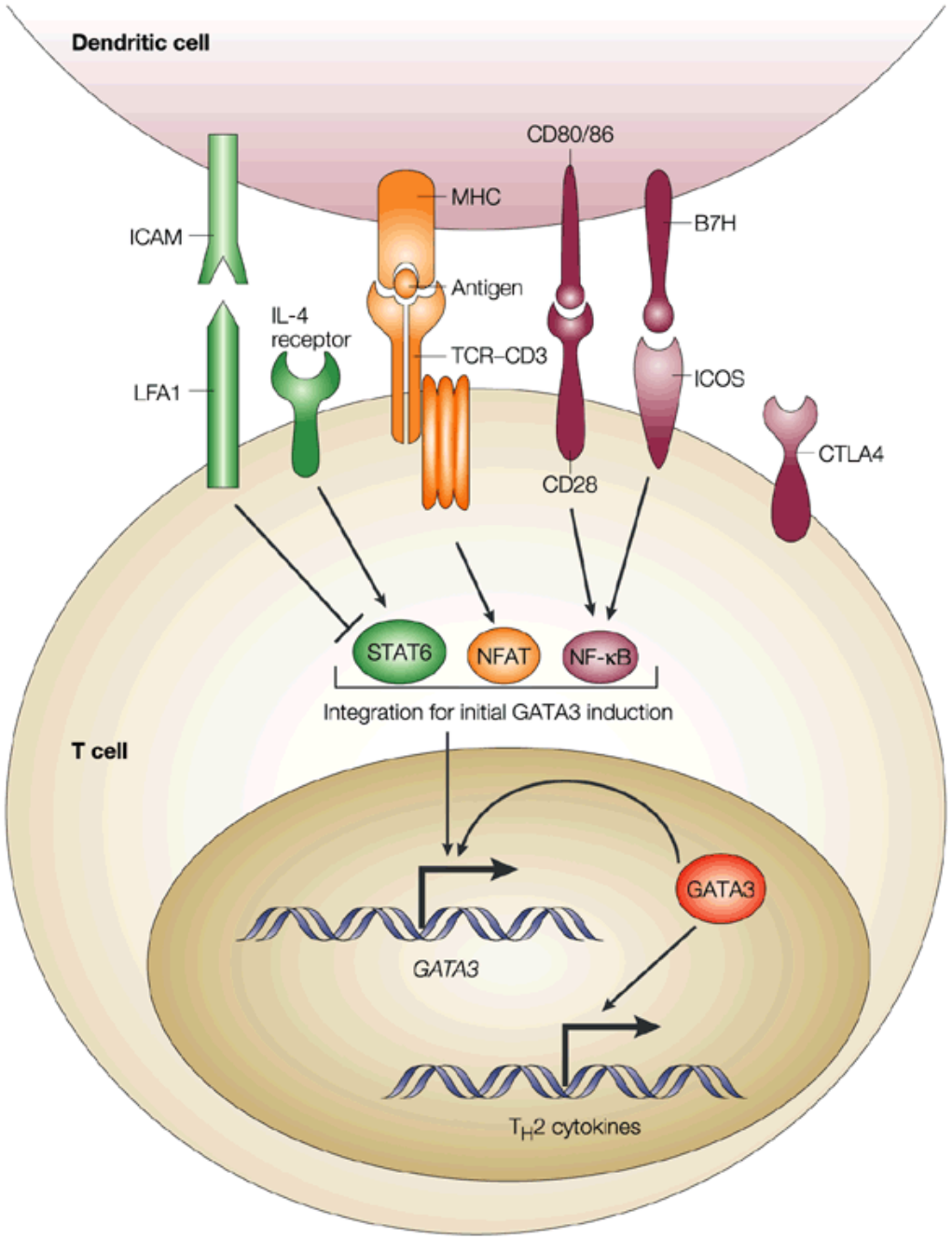
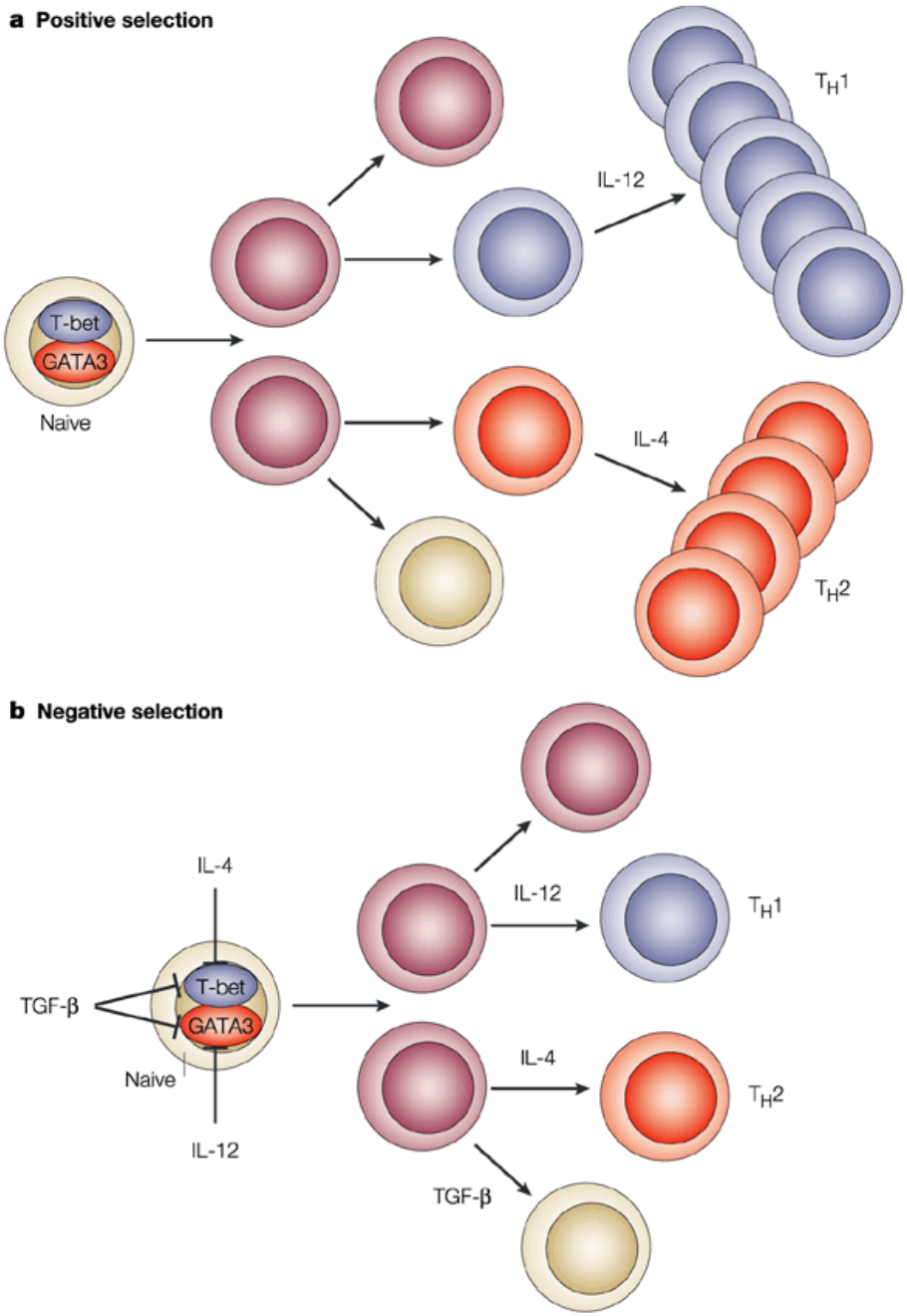
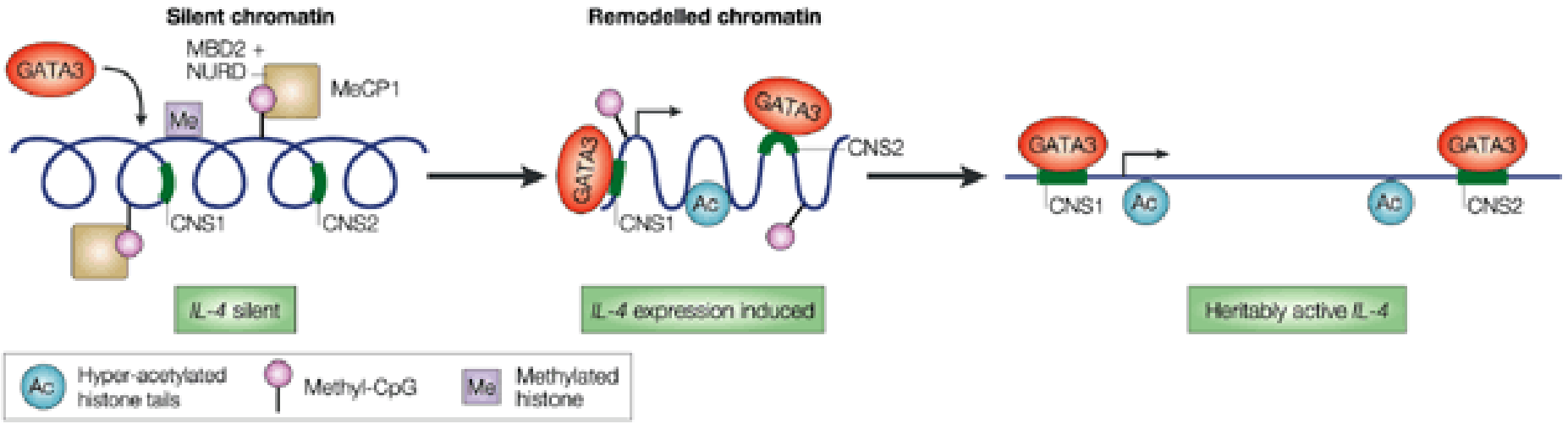

Dendritic cell
CD80/86
MHC
B7H
ICAM
Antigen
IL-4
receptor
TCR–CD3
LFA1
ICOS
CTLA4
CD28
STAT6
NFAT
NF-κB
Integration for initial GATA3 induction
T cell
GATA3
GATA3
TH2 cytokines


a Positive selection
T-bet
GATA3
Naive
IL-12
T_H1
IL-4
T_H2
b Negative selection
IL-4
TGF-β
T-bet
GATA3
Naive
IL-12
IL-12
T_H1
IL-4
T_H2
TGF-β



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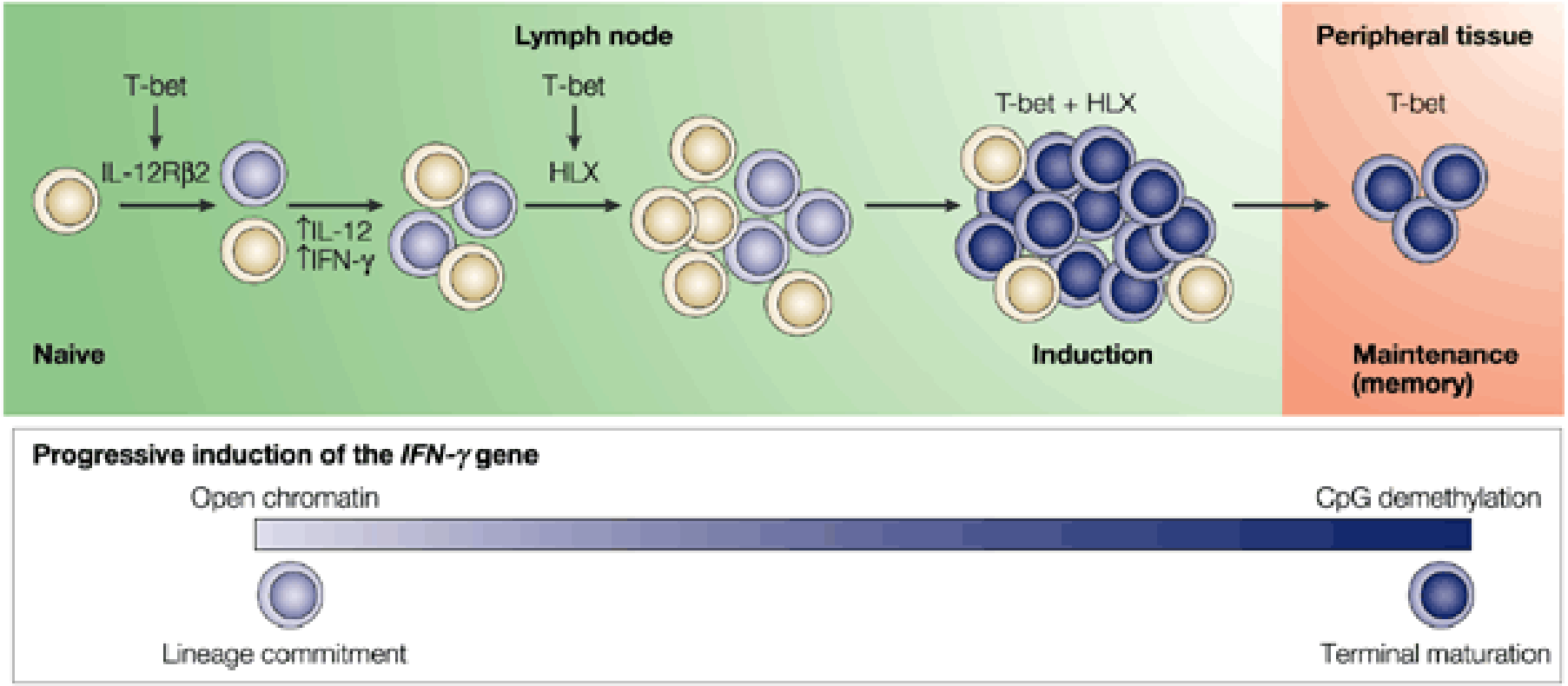

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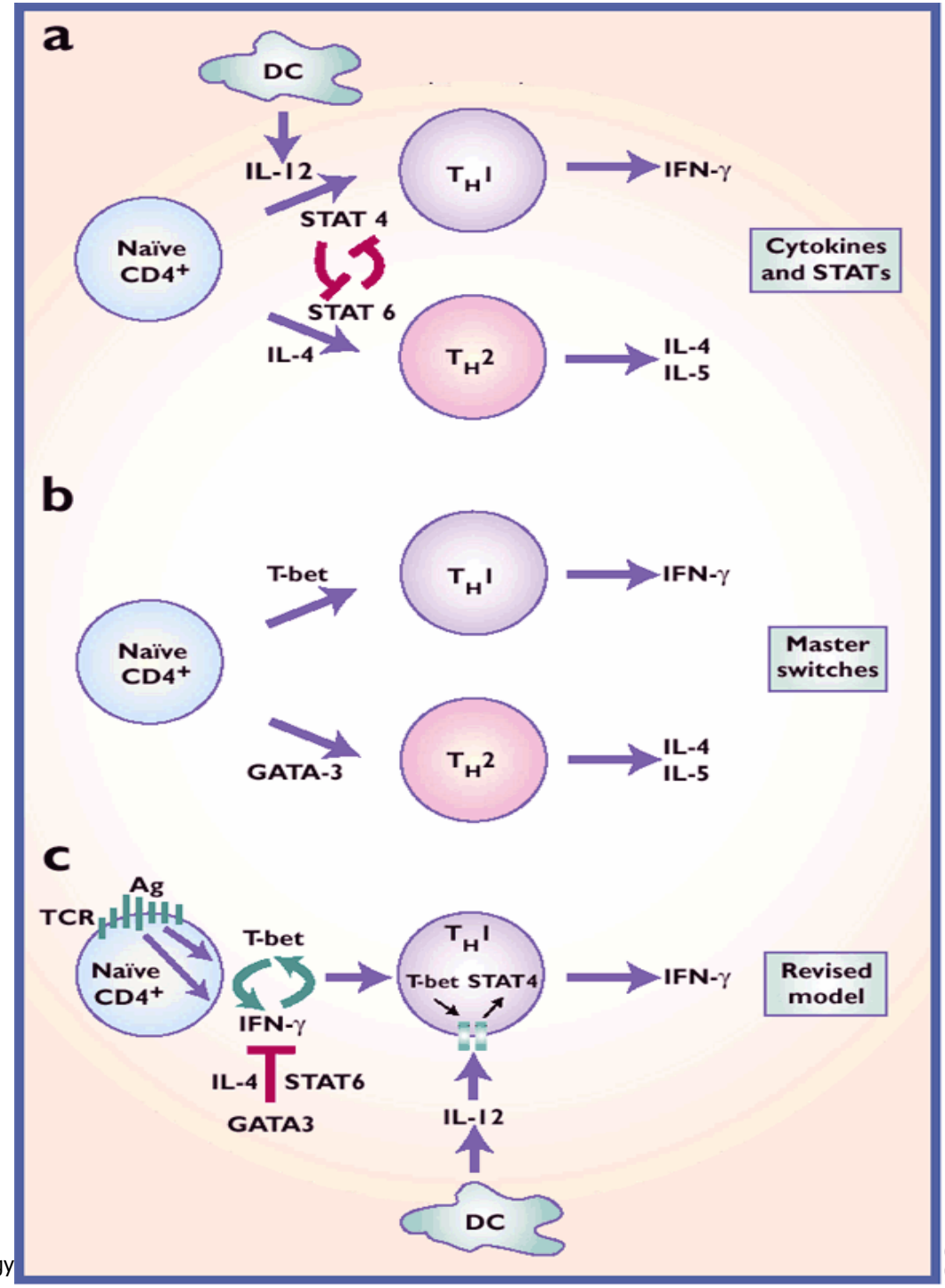
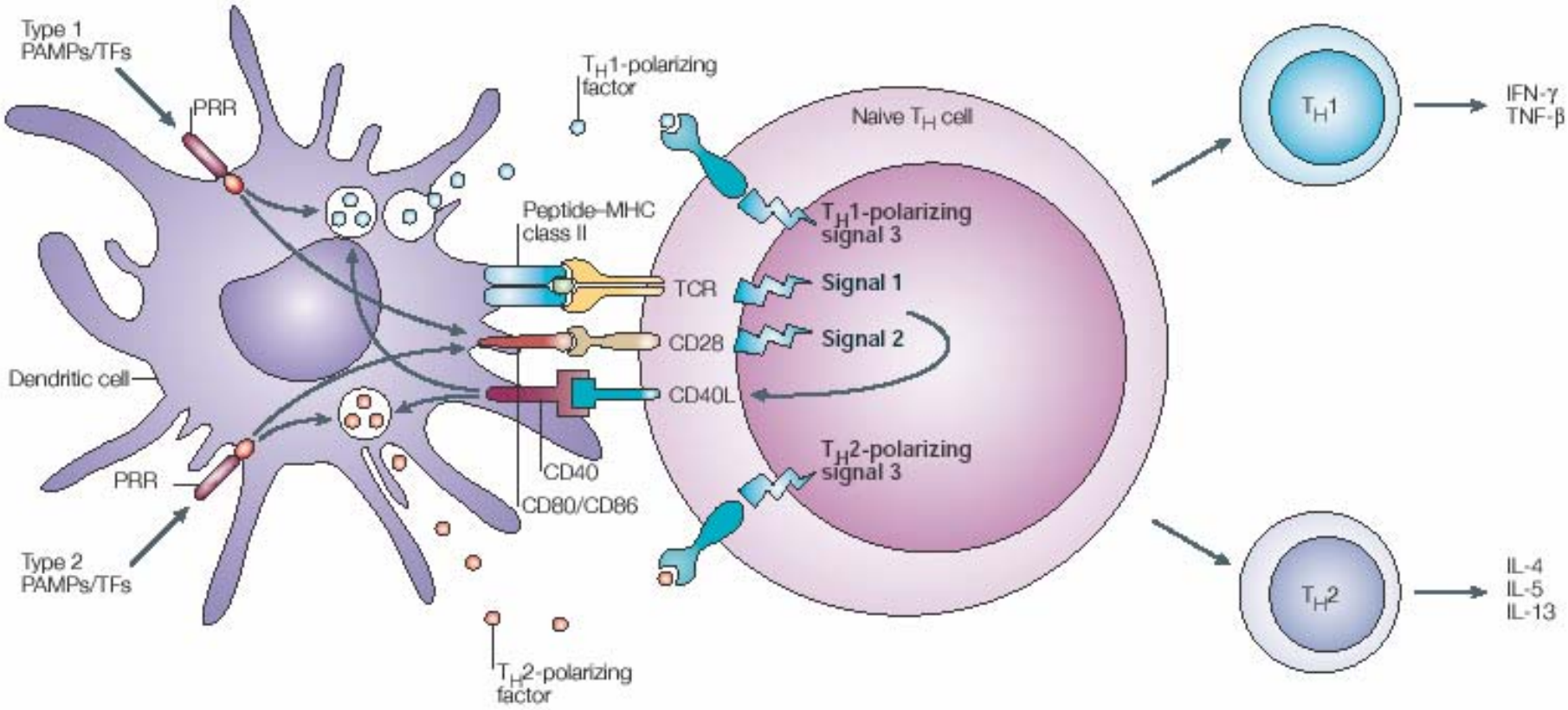

a
DC
IL-12
STAT 4
Naïve CD4+
STAT 6
IL-4
TH1
TH2
IFN-γ
IL-4
IL-5
Cytokines and STATs
b
T-bet
Naïve CD4+
GATA-3
TH1
TH2
IFN-γ
IL-4
IL-5
Master switches
c
Ag
TCR
Naïve CD4+
T-bet
IFN-γ
IL-4
STAT6
GATA3
TH1
T-bet STAT4
IFN-γ
IL-12
DC
Revised model


Type 1
PAMPs/TFs
PRR
T_H1-polarizing
factor
Naive T_H cell
Peptide–MHC
class II
T_H1-polarizing
signal 3
TCR
Signal 1
CD28
Signal 2
CD40L
Dendritic cell
T_H2-polarizing
signal 3
PRR
CD40
CD80/CD86
Type 2
PAMPs/TFs
T_H2-polarizing
factor
T_H1
IFN-γ
TNF-β
T_H2
IL-4
IL-5
IL-13

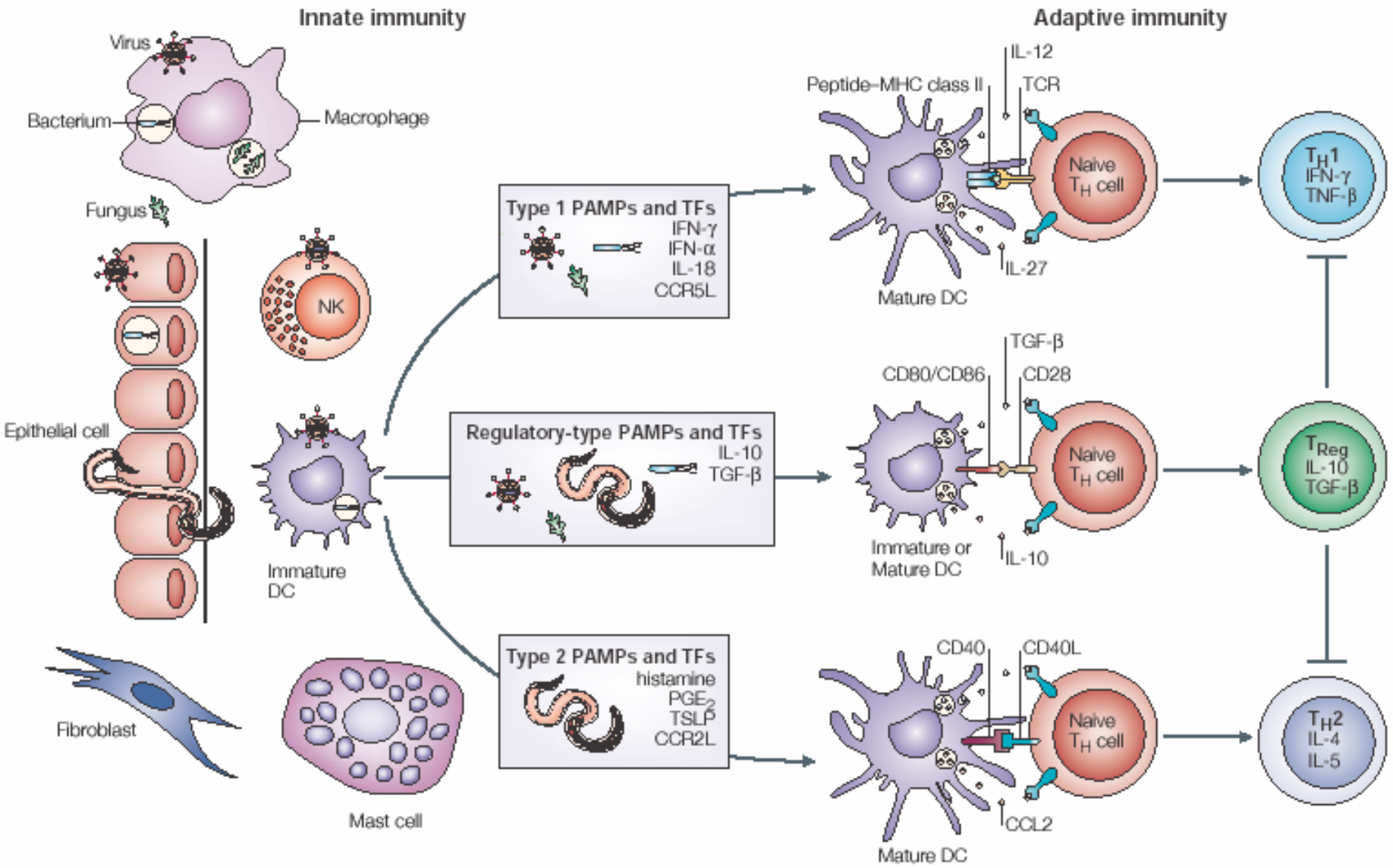
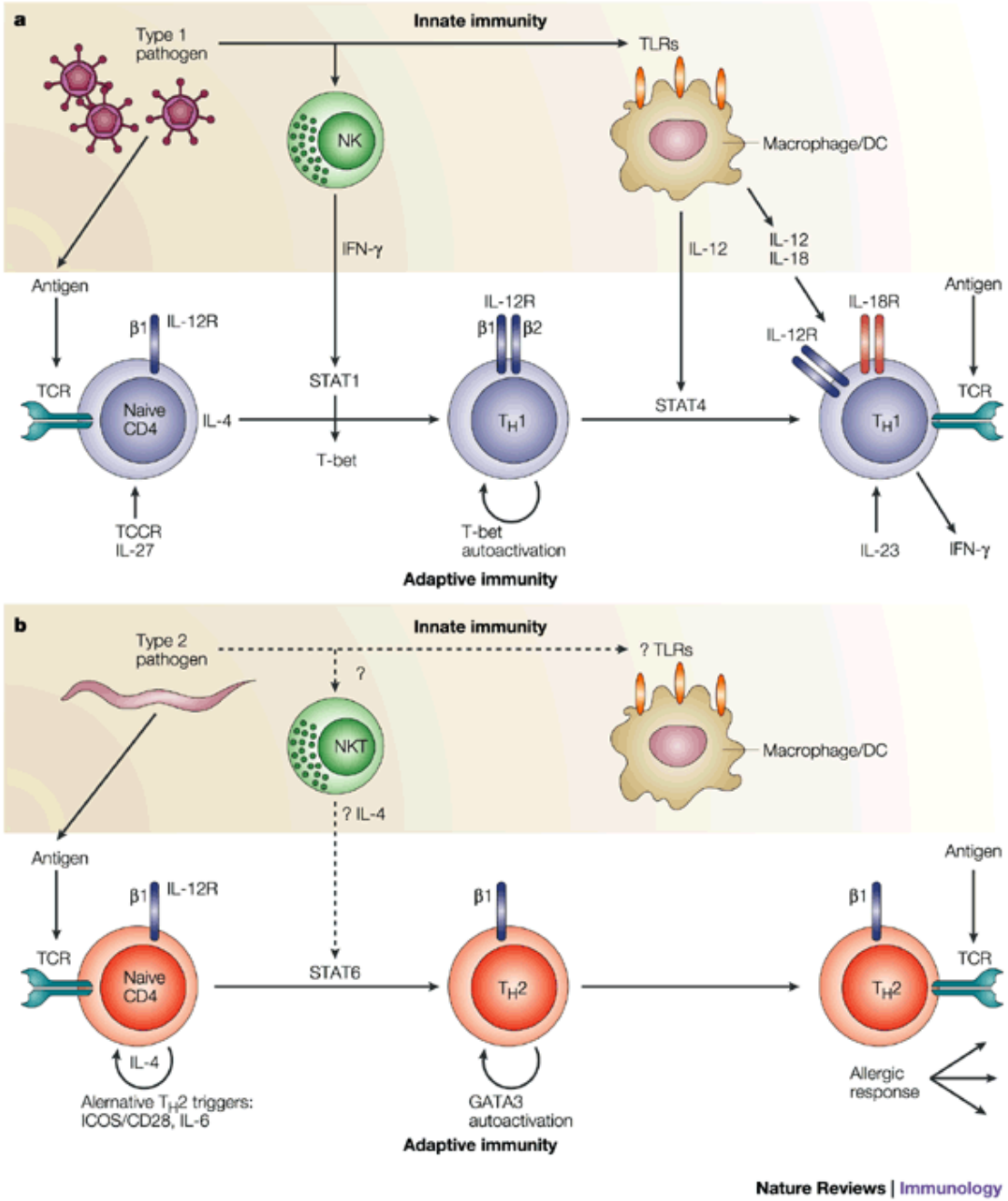

Innate immunity
Adaptive immunity
Virus
Bacterium
Macrophage
Fungus
NK
Epithelial cell
Immature DC
Fibroblast
Mast cell
Type 1 PAMPs and TFs
IFN-γ
IFN-α
IL-18
CCR5L
Regulatory-type PAMPs and TFs
IL-10
TGF-β
Type 2 PAMPs and TFs
histamine
PGE2
TSLP
CCR2L
Peptide–MHC class II
IL-12
TCR
Naive TH cell
IL-27
Mature DC
TH1
IFN-γ
TNF-β
TGF-β
CD80/CD86
CD28
Immature or Mature DC
IL-10
TReg
IL-10
TGF-β
CD40
CD40L
CCL2
TH2
IL-4
IL-5

Table 1 | **Type 1, type 2 and regulatory-type tissue factors**

Tissue factors	Type 1	Type 2	Regulatory
Cytokines	*IFN-γ[88], *IFN-α/β[120], IL-12p70, TNF-β, IL-18 (REF. 89), *IL-27	IL-4, IL-5, IL-9, IL-13, IL-25, *TSLP[92]	*IL-10 (REF. 94), *TGF-β[95], TSP1
Chemokines	CXCL9, CXCL10, CCL21	*CCL2, *CCL7, *CCL8, *CCL13 (REF. 93), CCL17	
Co-stimulatory factors	ICAM1	OX40L	PD1/PD2L, CTLA4, GITRL, CD47, SIRP-α
Eicosanoids		*PGE_2 (REF. 91)	
Others		*Histamine[90]	


a
Innate immunity
Type 1 pathogen
TLRs
NK
Macrophage/DC
IFN-γ
IL-12
IL-12
IL-18
Antigen
β1
IL-12R
IL-12R
β1
β2
IL-18R
IL-12R
Antigen
TCR
Naive CD4
IL-4
STAT1
STAT4
TCR
T-bet
TCCR
IL-27
T-bet autoactivation
IL-23
IFN-γ
Adaptive immunity
b
Innate immunity
Type 2 pathogen
?
? TLRs
NKT
Macrophage/DC
? IL-4
Antigen
β1
IL-12R
β1
β1
Antigen
TCR
Naive CD4
STAT6
TCR
IL-4
Alernative TH2 triggers: ICOS/CD28, IL-6
GATA3 autoactivation
Allergic response
Adaptive immunity
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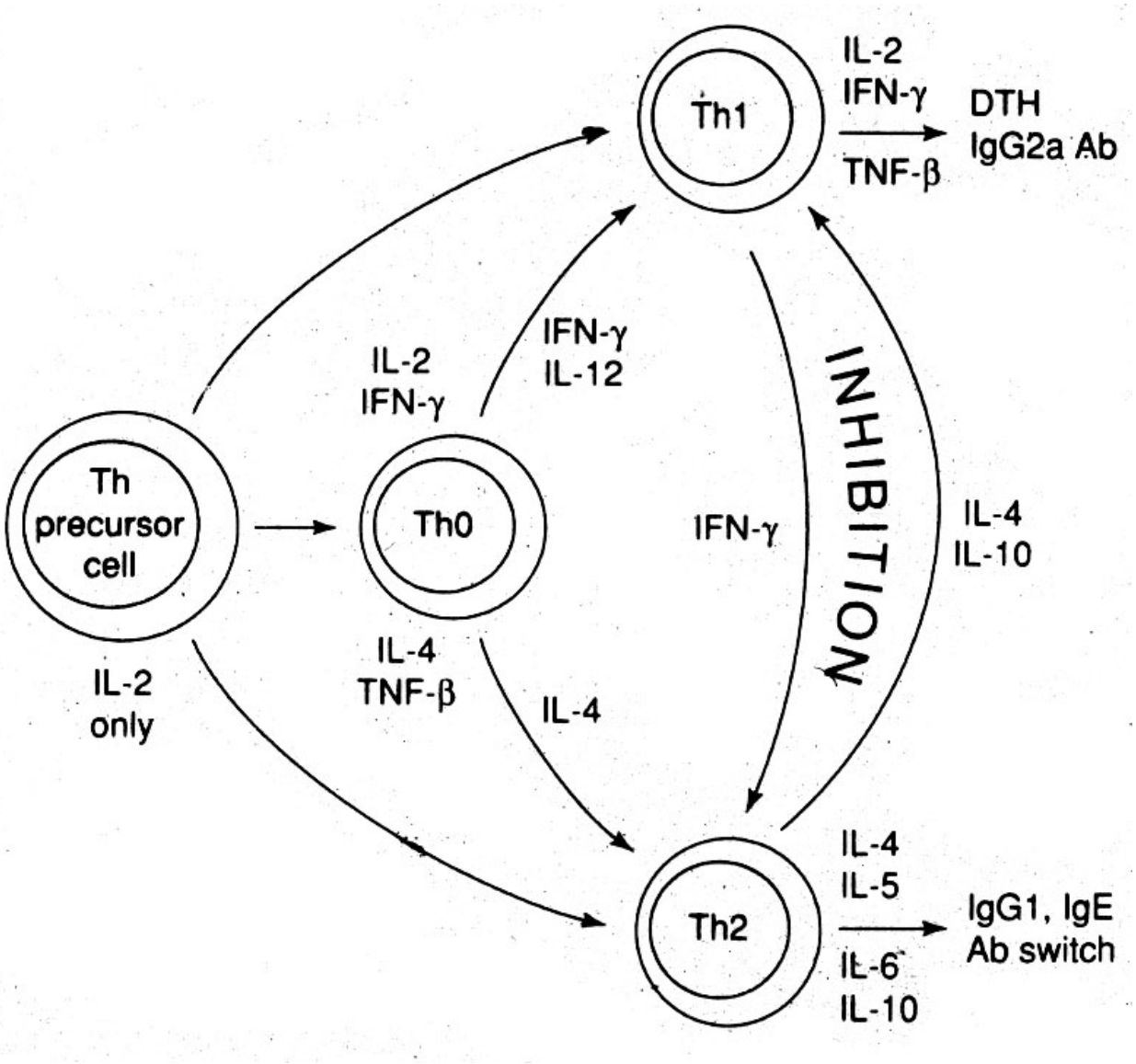
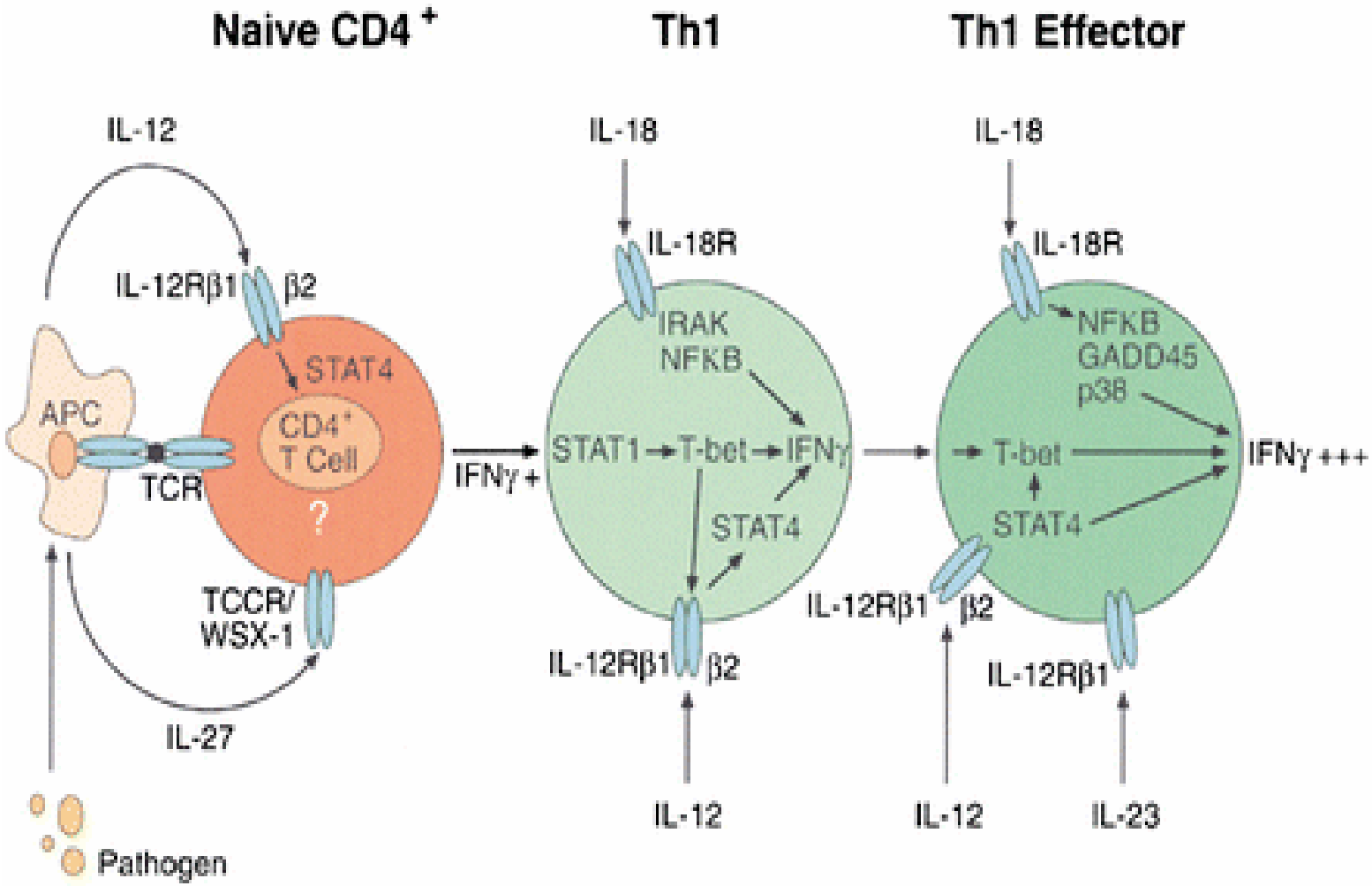
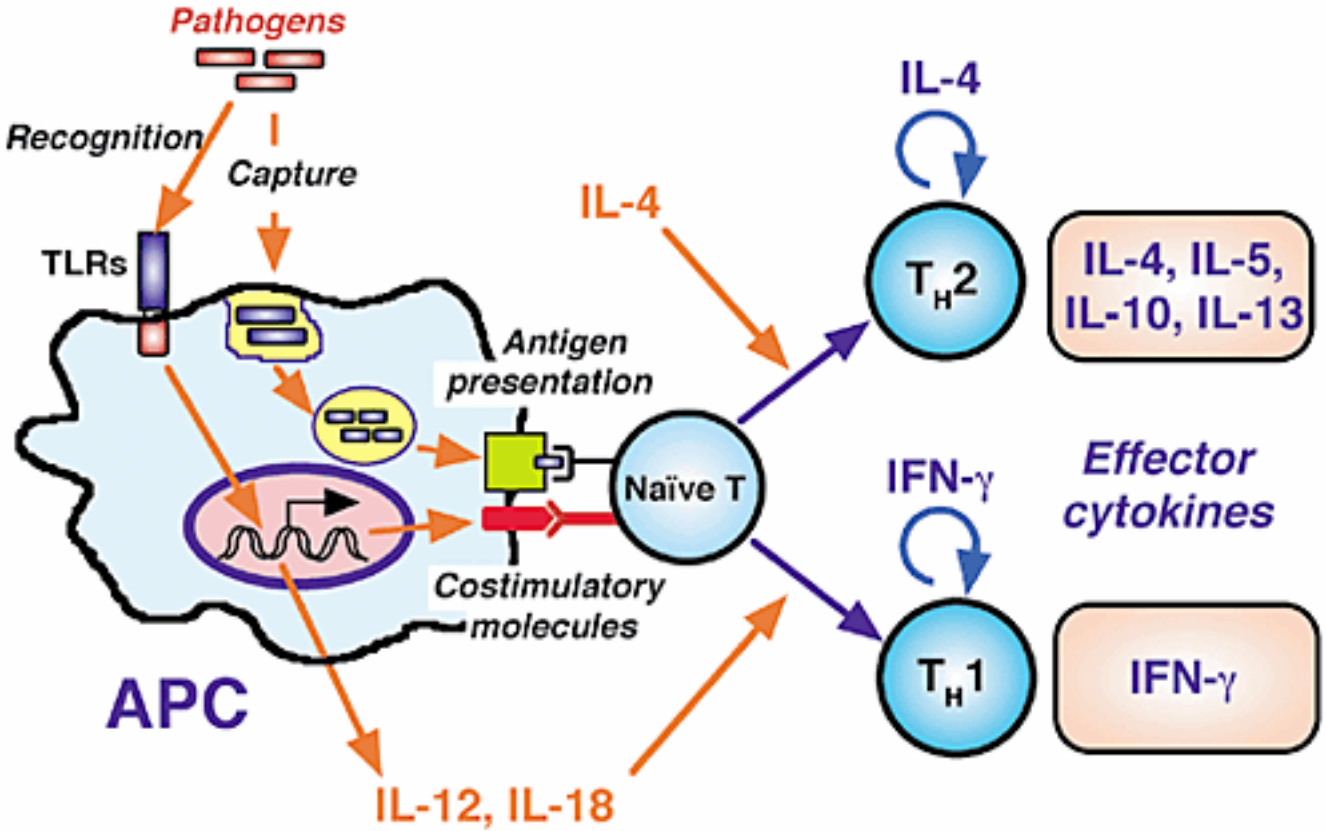

Th1
IL-2
IFN-γ
TNF-β
DTH
IgG2a Ab
IL-2
IFN-γ
IFN-γ
IL-12
INHIBITION
Th
precursor
cell
Th0
IFN-γ
IL-4
IL-10
IL-2
only
IL-4
TNF-β
IL-4
Th2
IL-4
IL-5
IL-6
IL-10
IgG1, IgE
Ab switch

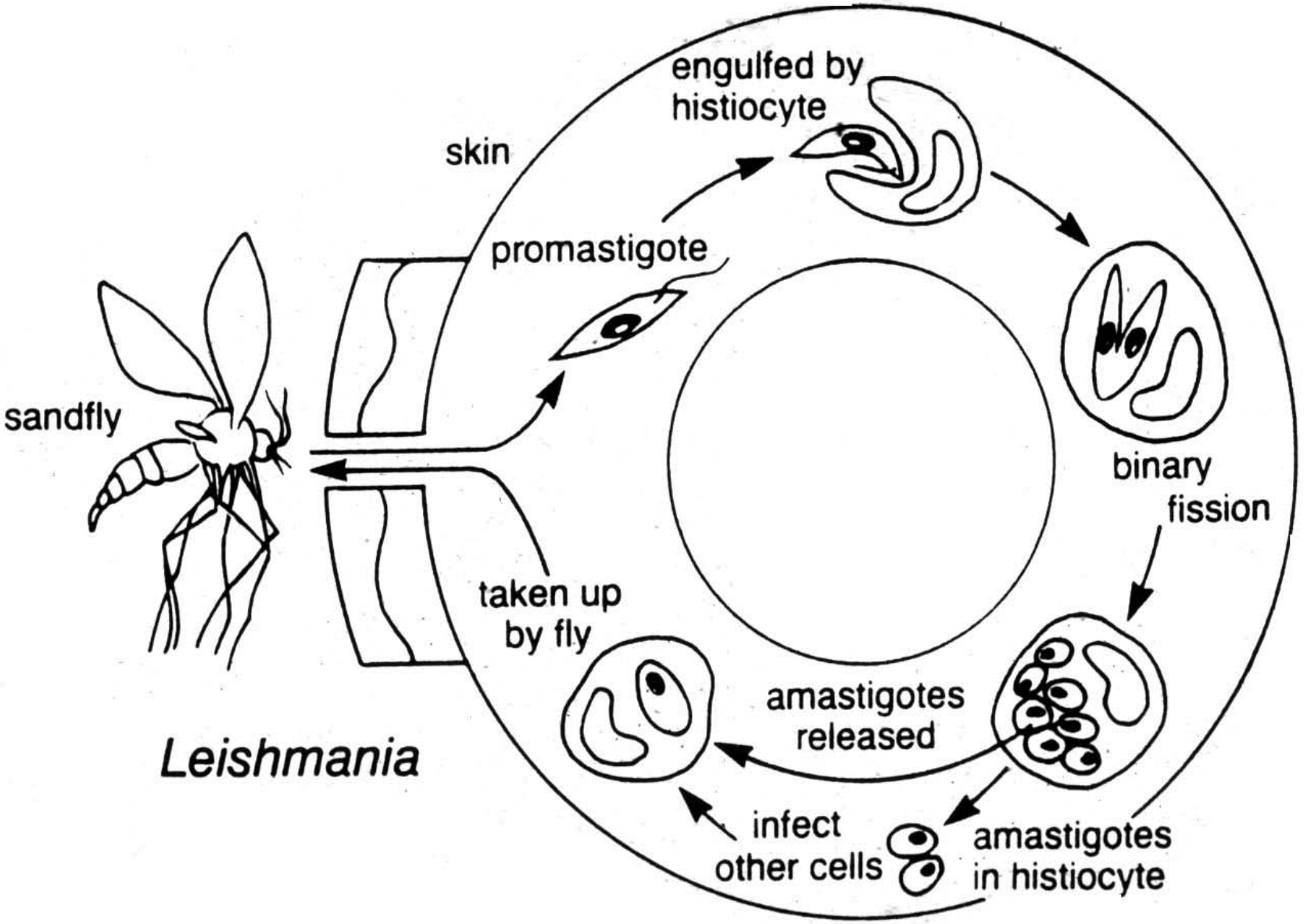

Naive CD4 +
Th1
Th1 Effector
IL-12
IL-12Rβ1
β2
STAT4
APC
CD4+
T Cell
TCR
?
TCCR/
WSX-1
IL-27
Pathogen
IFNγ +
IL-18
IL-18R
IRAK
NFKB
STAT1
T-bet
IFNγ
STAT4
IL-12Rβ1
β2
IL-12
IL-18
IL-18R
NFKB
GADD45
p38
T-bet
IFNγ +++
STAT4
IL-12Rβ1
β2
IL-12Rβ1
IL-12
IL-23

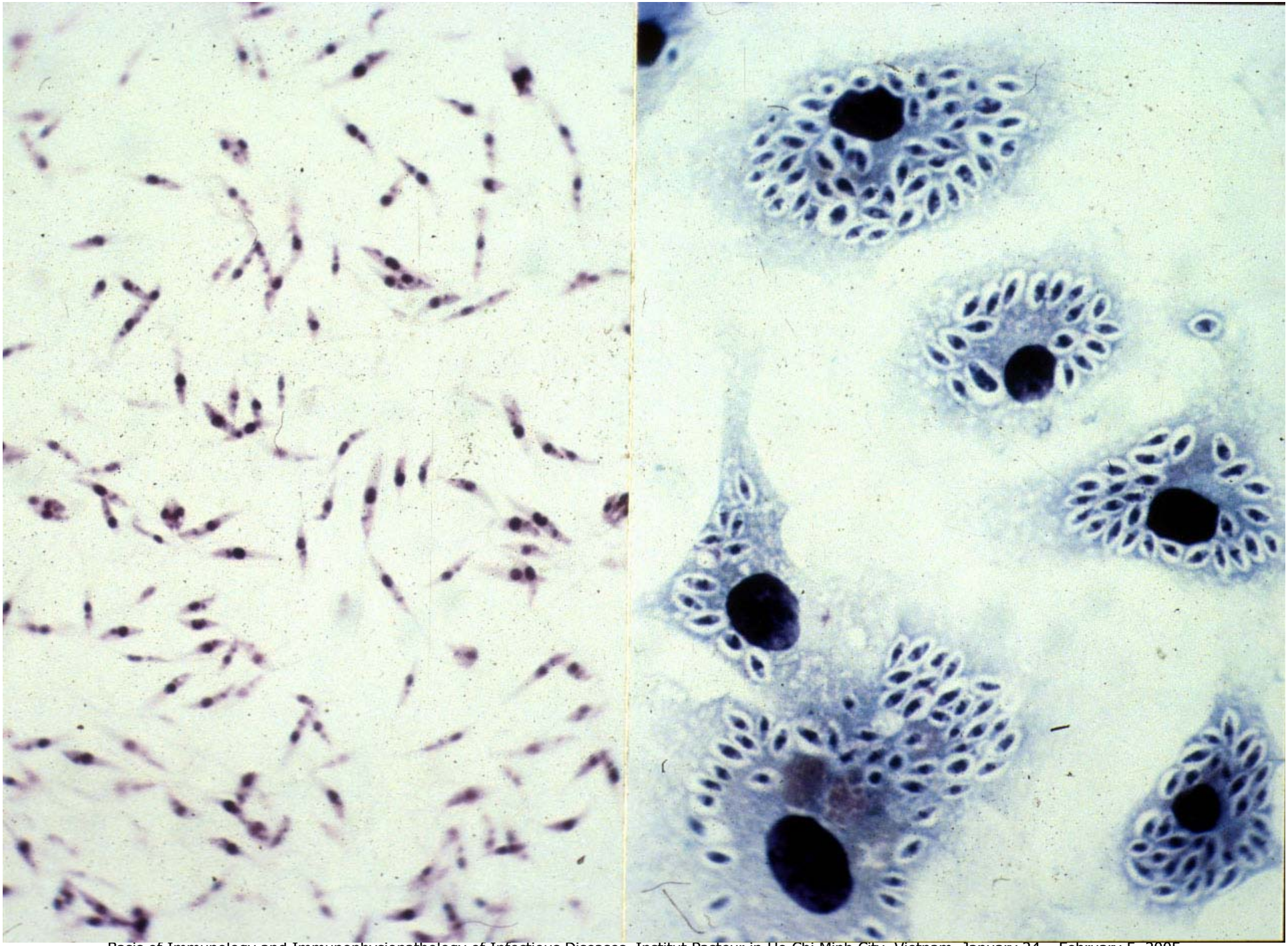

Pathogens
Recognition
Capture
TLRs
Antigen presentation
Naïve T
Costimulatory molecules
APC
IL-12, IL-18
IL-4
IL-4
T_H2
IL-4, IL-5, IL-10, IL-13
IFN-γ
Effector cytokines
T_H1
IFN-γ

Toll and control of adaptive $CD4^+$ T cell responses

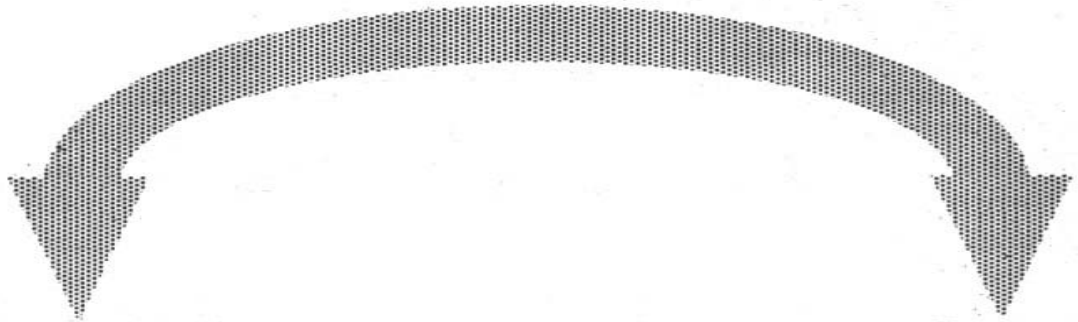
*** Th1 responses are Toll-dependent responses**

*** Th2 responses are Toll-independent responses**


engulfed by
histiocyte
skin
promastigote
sandfly
binary
fission
taken up
by fly
amastigotes
released
Leishmania
infect
other cells
amastigotes
in histiocyte

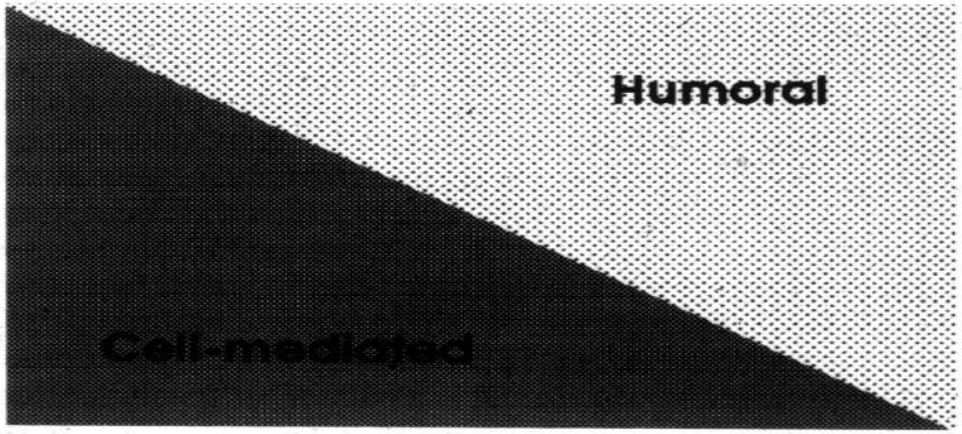


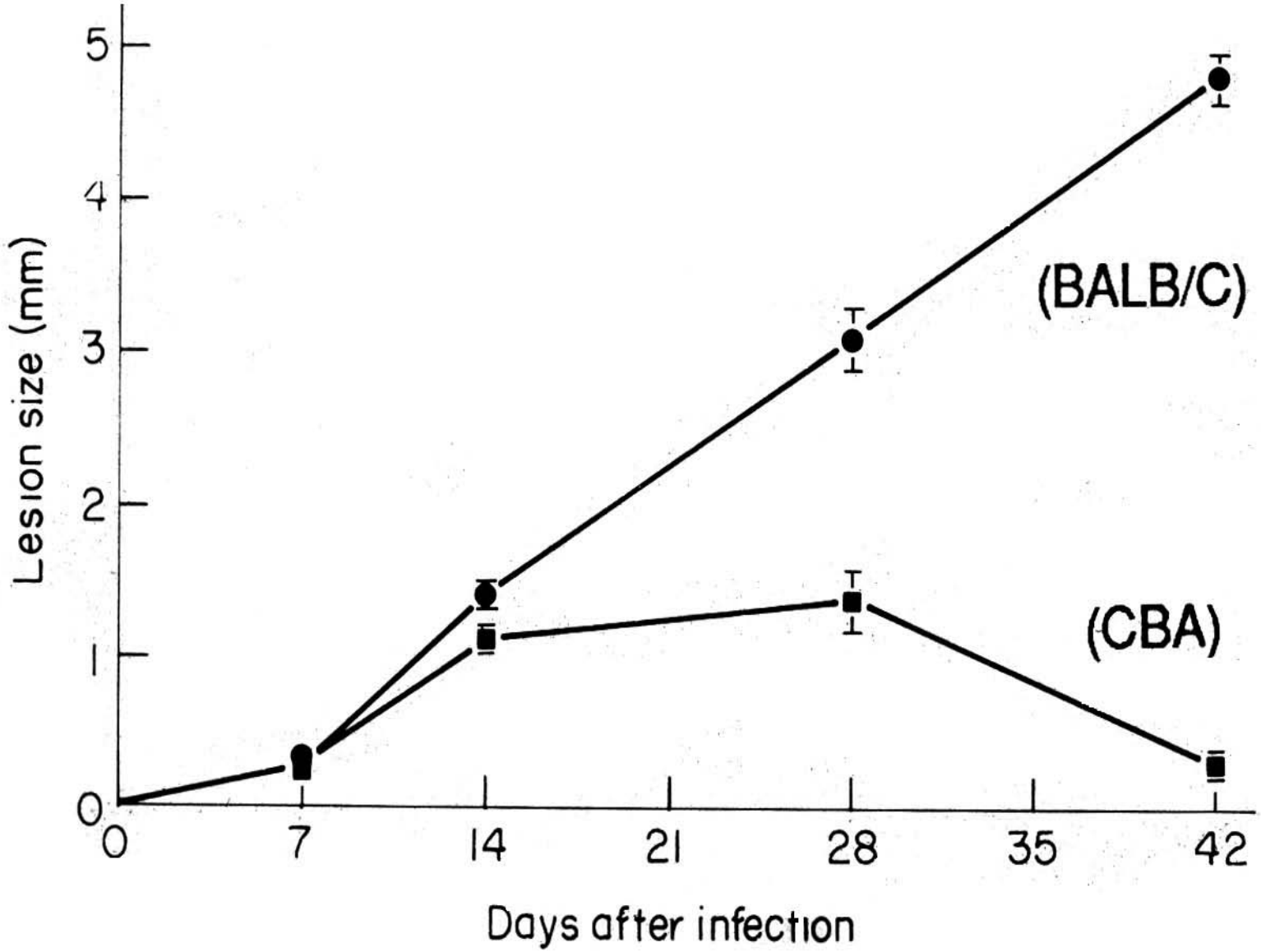
Spectrum of clinical manifestations of infection with *Leishmania*



- ✔ Localized cutaneous lesion
- ✔ Generalized systemic disease

Type of immune response which predominates



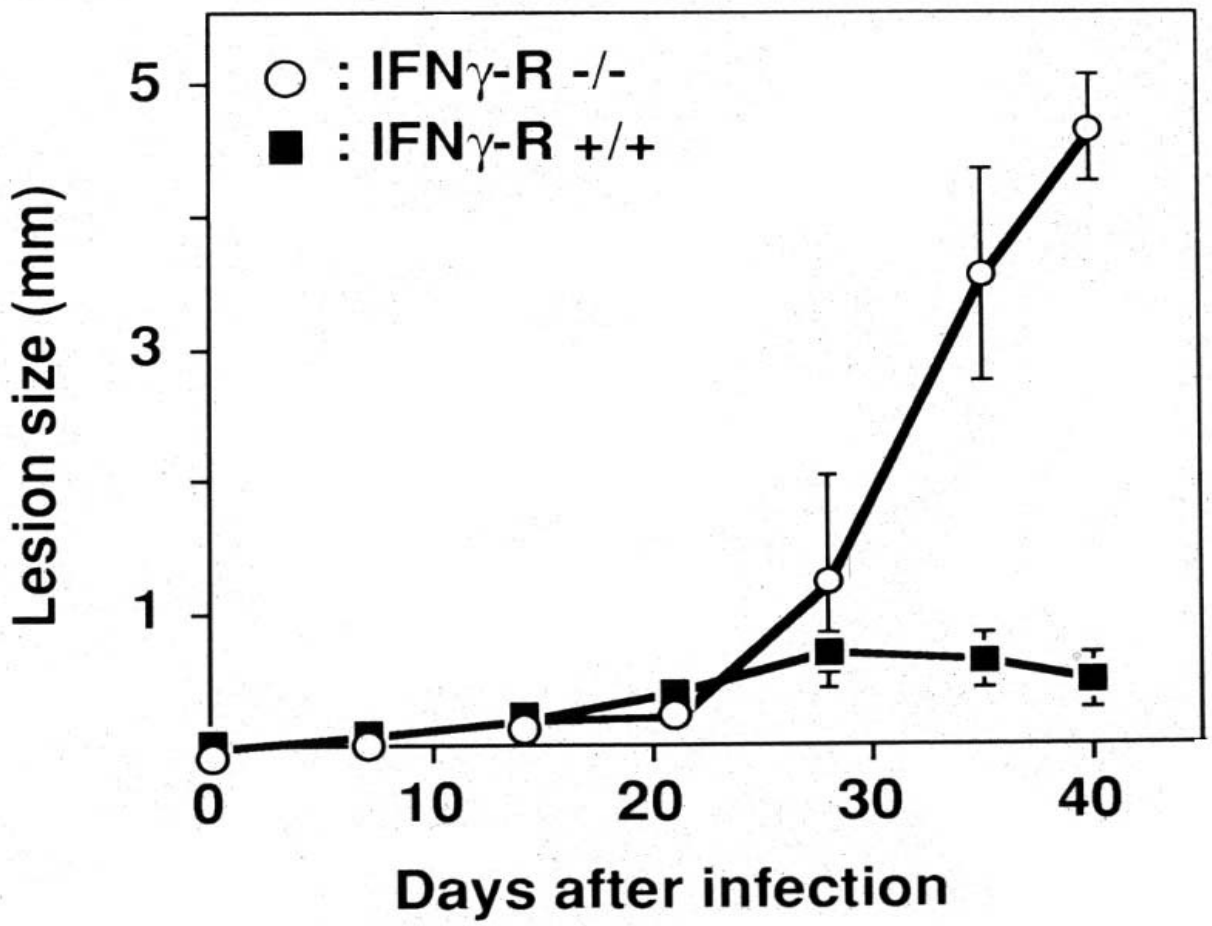

Lesion size (mm)
0
1
2
3
4
5
0
7
14
21
28
35
42
Days after infection
(BALB/C)
(CBA)

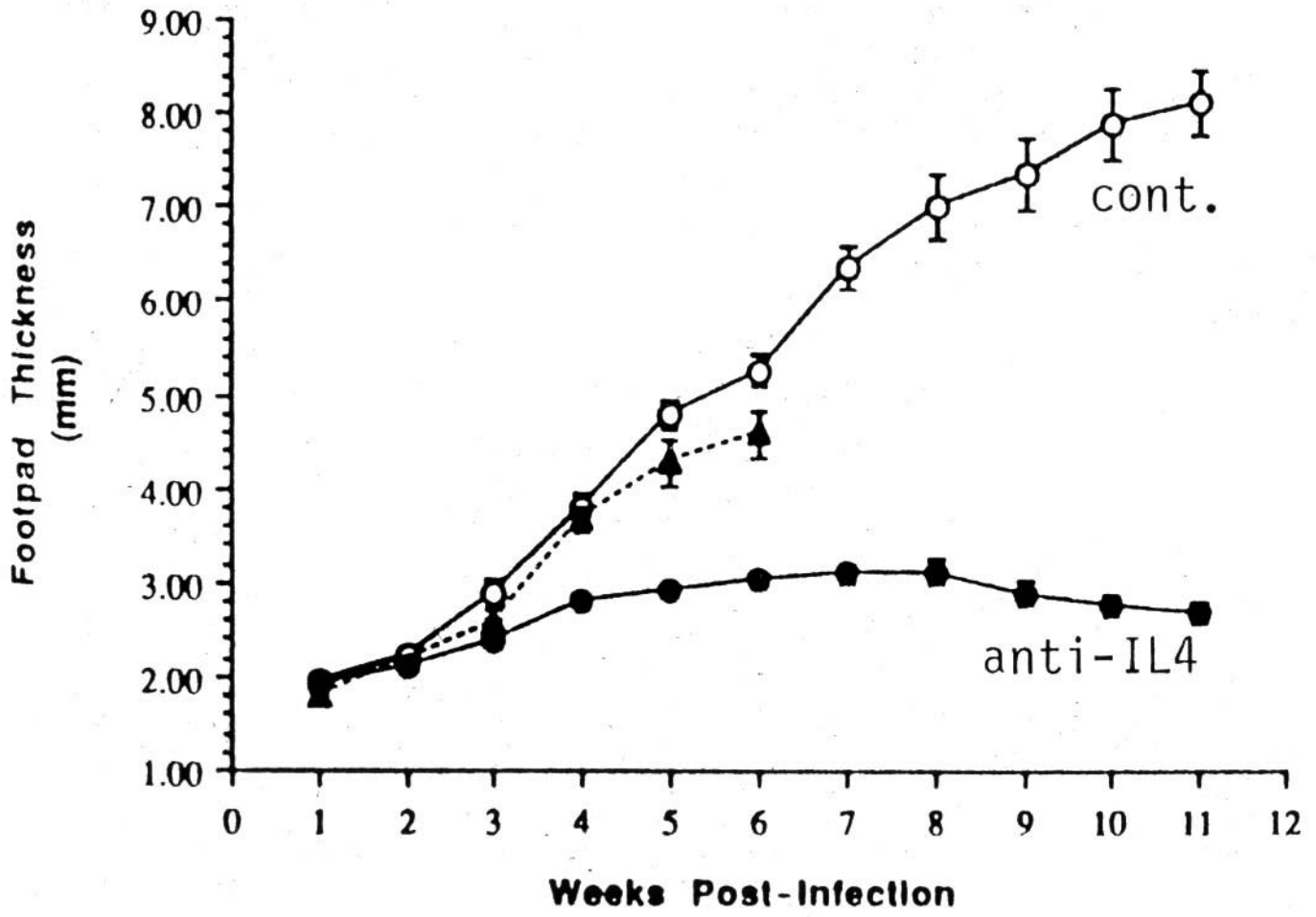
Characteristics of the T Cell Response in Mice Infected with *Leishmania major*.

Resistant Phenotype: Preferential expansion of **TH1** cells.

Susceptible Phenotype: Preferential expansion of **TH2** cells.

Development of Lesion induced by *L.major* in Mice From a Genetically Resistant Strain Lacking IFNγreceptor





From Sadick et al.: J.Ex.Med,I990,I7I,II5

Factors Influencing the Functional Differentiation of CD4 T Cells

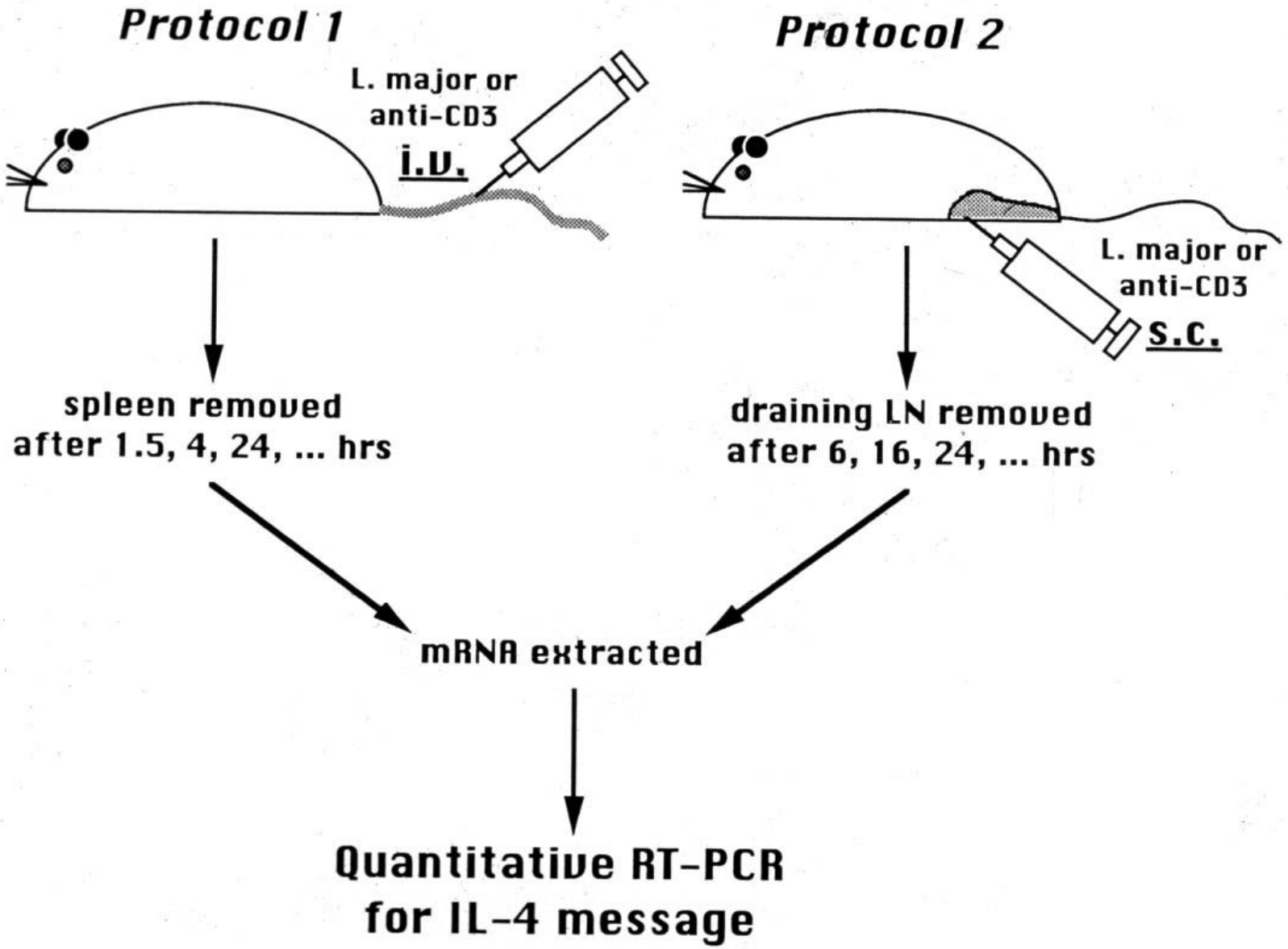
- ✔ Antigen structure
- ✔ Route of administration of antigen
- ✔ Genetic background
- ✔ Type of antigen presenting cells
- ✔ Costimulatory signals
- ✔ **Cytokines environment**

Importance of cytokines in the differentiation of CD4$^+$ T cell precursors towards the Th1 or Th2 functional phenotype

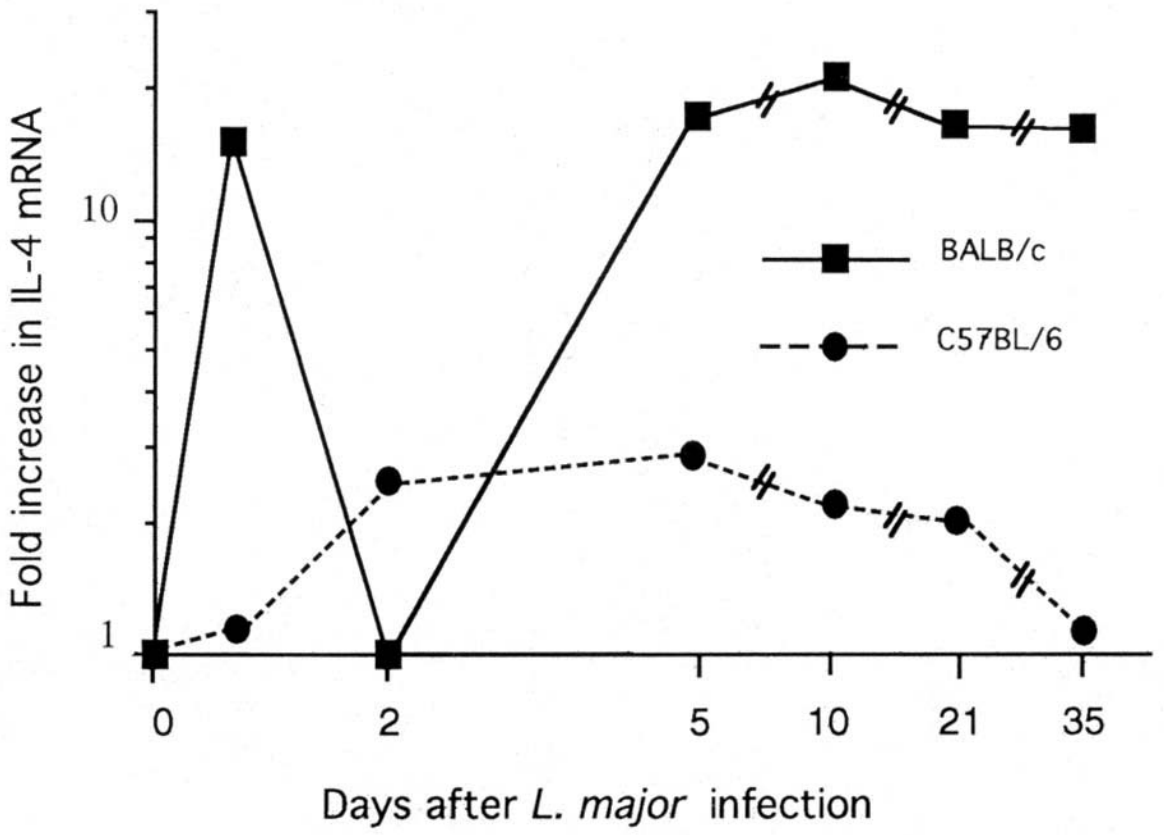
IL-4: Critical for priming CD4$^+$ T cells to become IL-4 producers (Th2)

IL-12: Enhances priming for IFNγ-producing CD4$^+$ T cells (Th1)

IFNγ: Plays a role in Th1 cell development, but is not sufficient. Differences between strains of mice in the IFNγ requirement for the development of Th1 responses ?


Protocol 1
L. major or
anti-CD3
i.v.
spleen removed
after 1.5, 4, 24, ... hrs
Protocol 2
L. major or
anti-CD3
S.C.
draining LN removed
after 6, 16, 24, ... hrs
mRNA extracted
Quantitative RT-PCR
for IL-4 message

Kinetics of IL-4 mRNA expression in lymph nodes of susceptible and resistant mice following infection with *L. major*



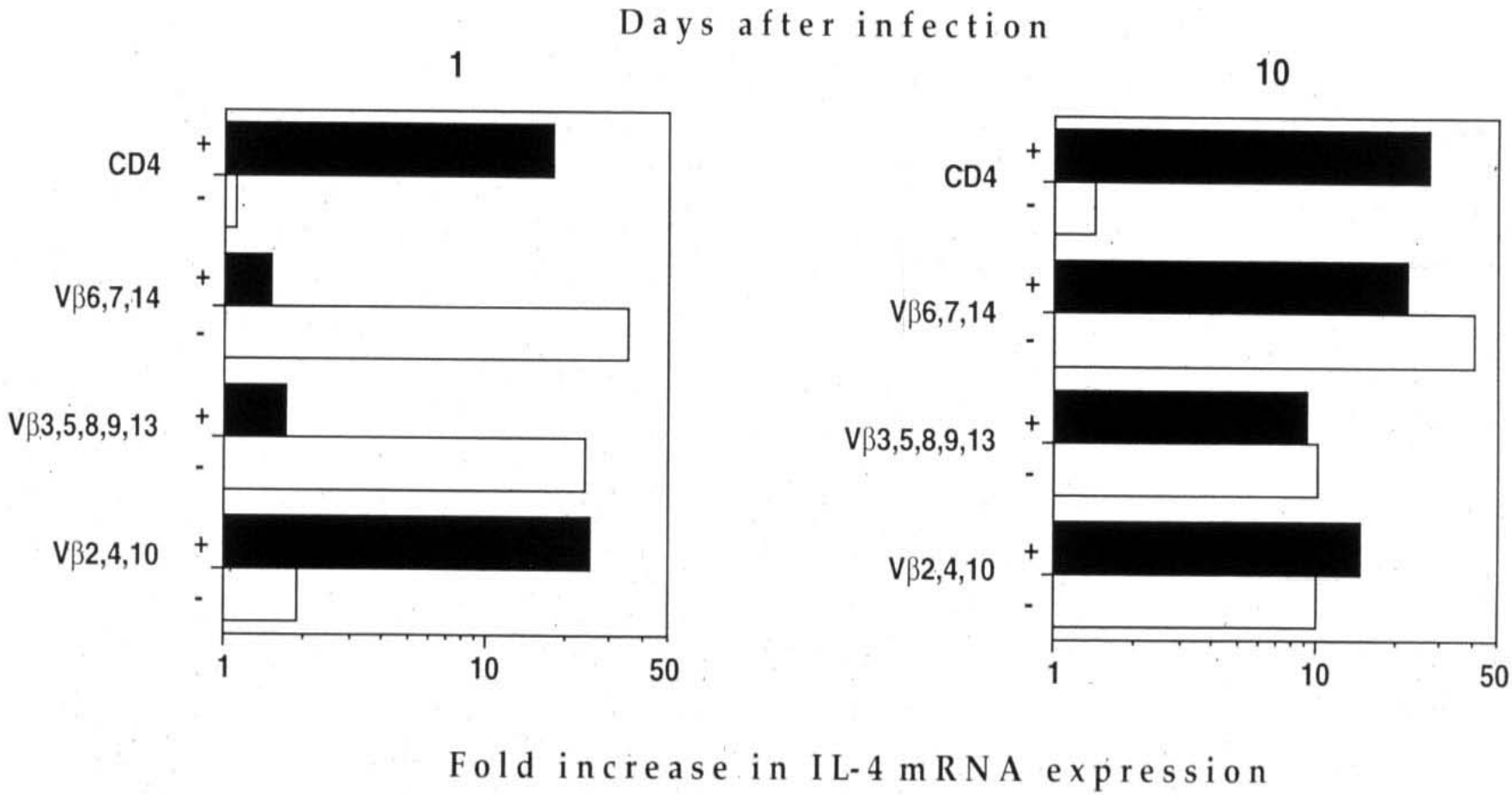
Possible cellular origin of cytokines involved in the differentiation of CD4+ T cell precursors

IL-12: Macrophages

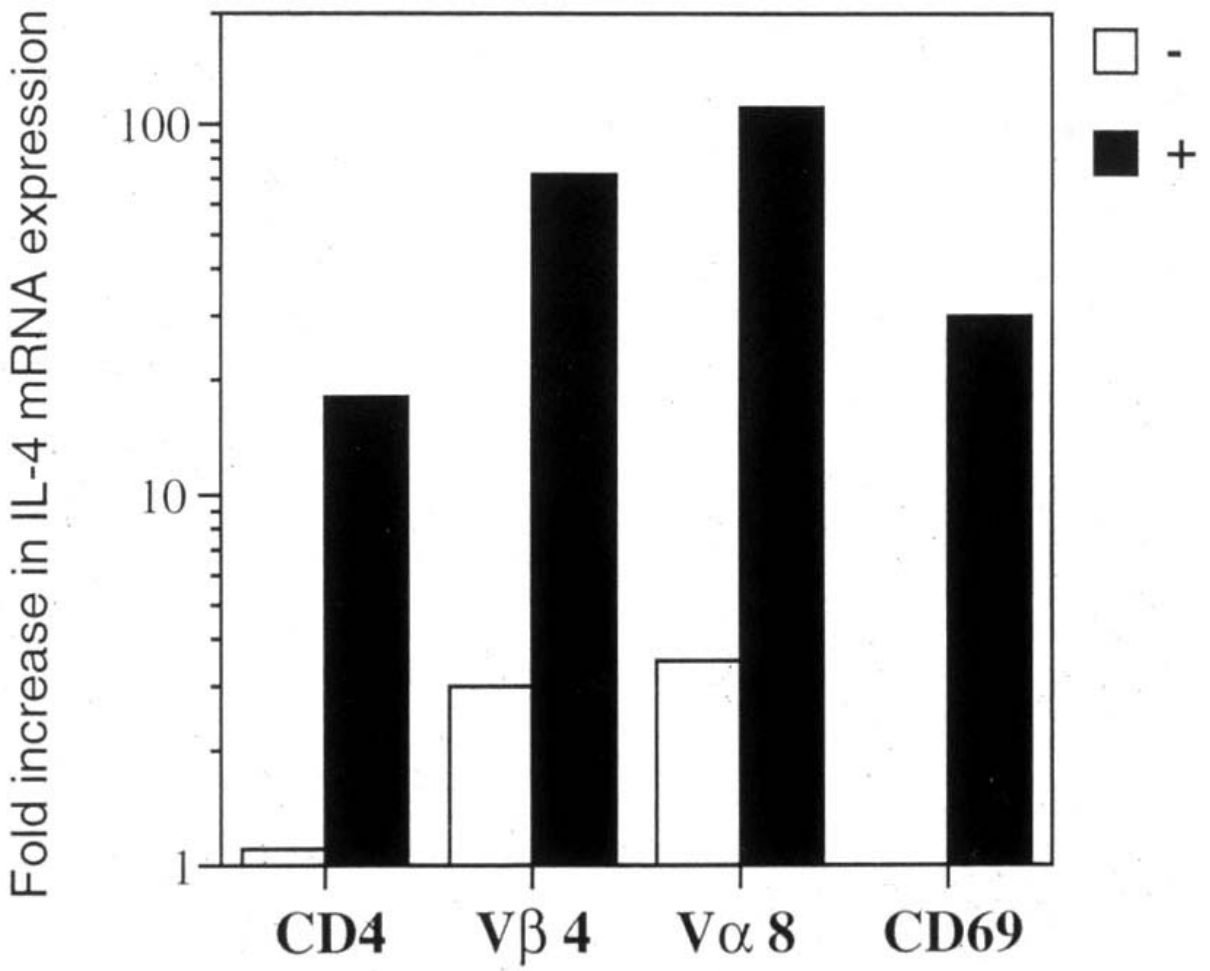
IFNγ: NK cells
CD4+ T cells

IL-4:
- Mast cells, basophils (stimulated to produce IL-4 by cross-linkage of FcεRI or FcγRII/III)
- Activated (memory) CD4+ T cells
- NK1.1pos CD4+ cells

Characteristics of the T cells producing IL-4 in BALB/c mice infected with *L. major*



Phenotype of CD4+ cells producing IL-4 in lymph nodes 16 hrs after infection with *L. major*

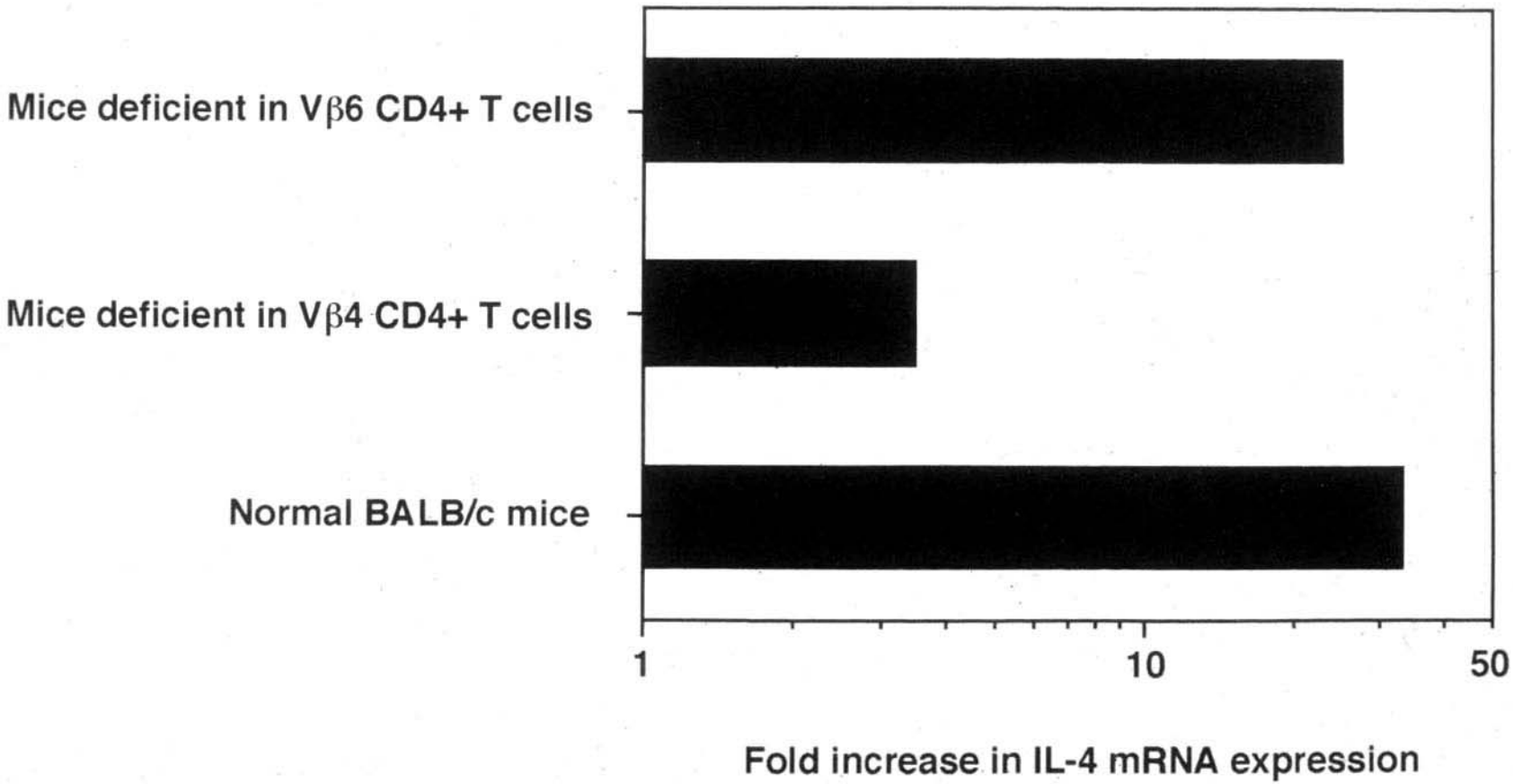


BALB/c mice deficient in T cells expressing the Vβ4 TCR chain

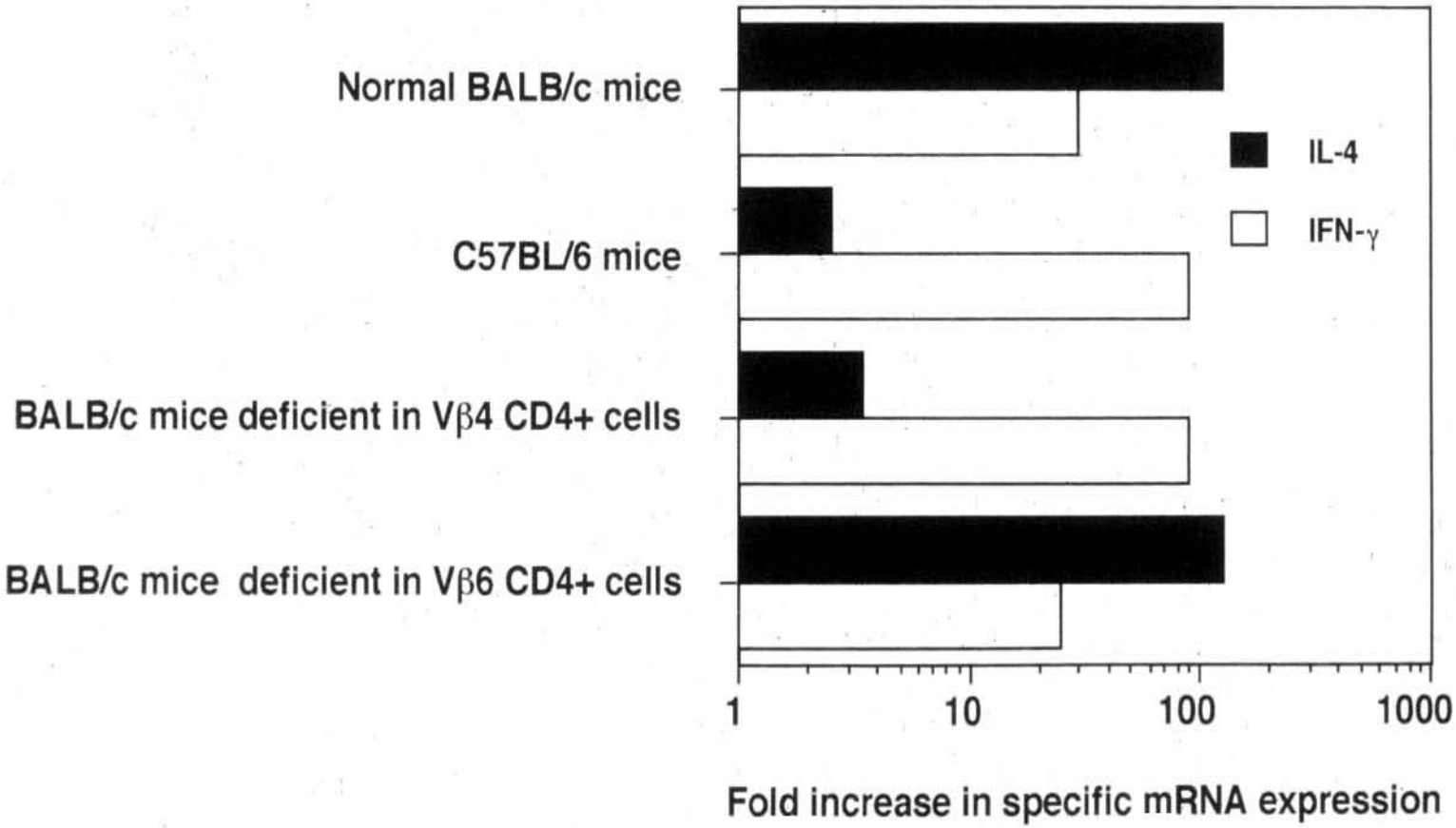
Mouse mammary tumor viruses (MMTV) encode a superantigen that ultimately leads to systemic deletion of CD4+ T cells expressing the Vβ TCR chain reacting with this superantigen

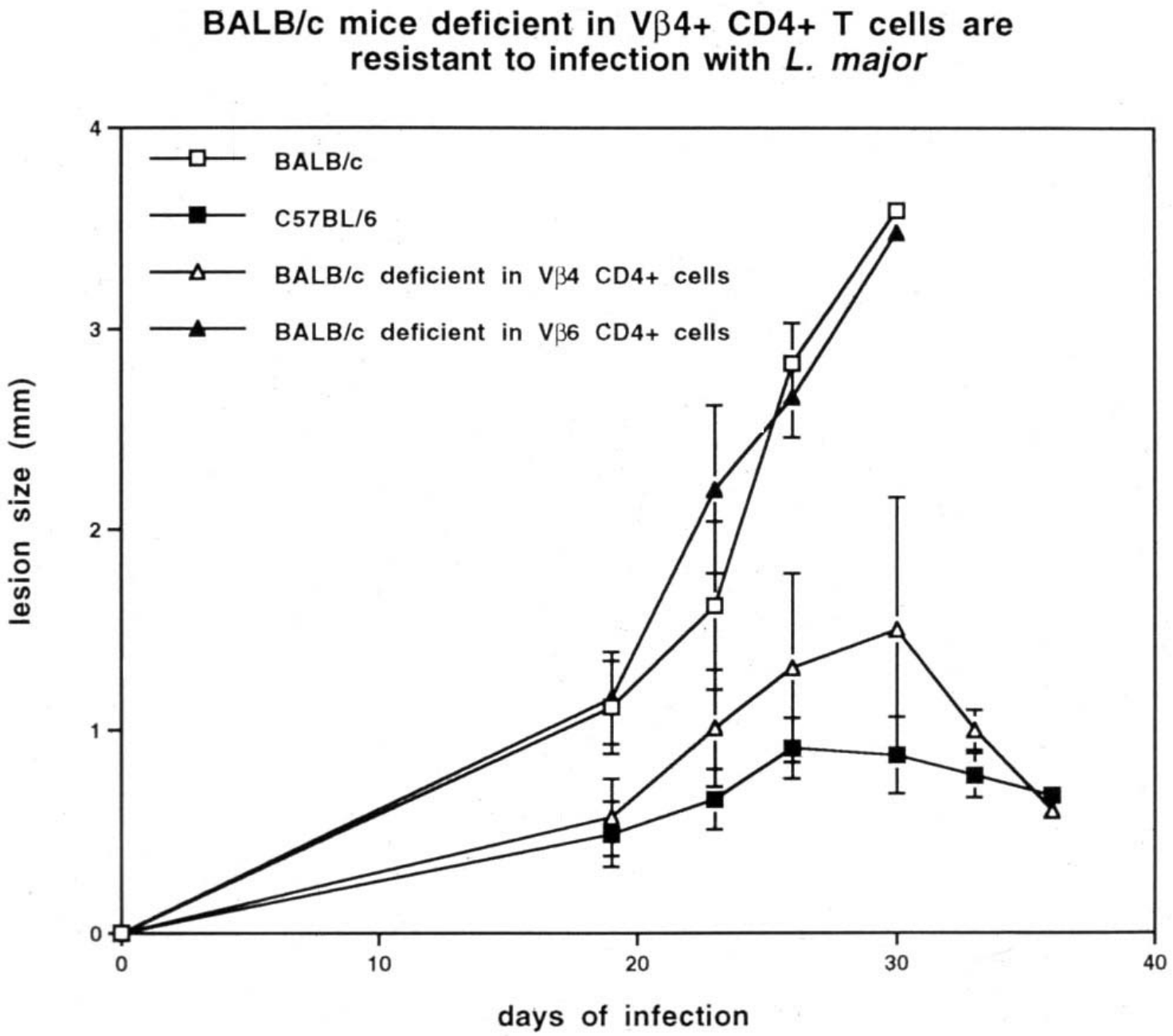
- **MMTV-SIM** encodes a superantigen leading to systemic deletion of **Vβ4+** CD4+ T cells *(Maillard, I. et al., Eur. J. Immunol. 1996, 26, 1000).*
- **MMTV-SW** encodes a superantigen leading to systemic deletion of **Vβ6+** CD4+ T cells *(Held, W. et al., J. Exp. Med. 1992, 175, 1623).*

BALB/c mice deficient in Vβ4+ CD4+ T cells do not exhibit early (16hrs) IL-4 mRNA expression following infection with *L. major*

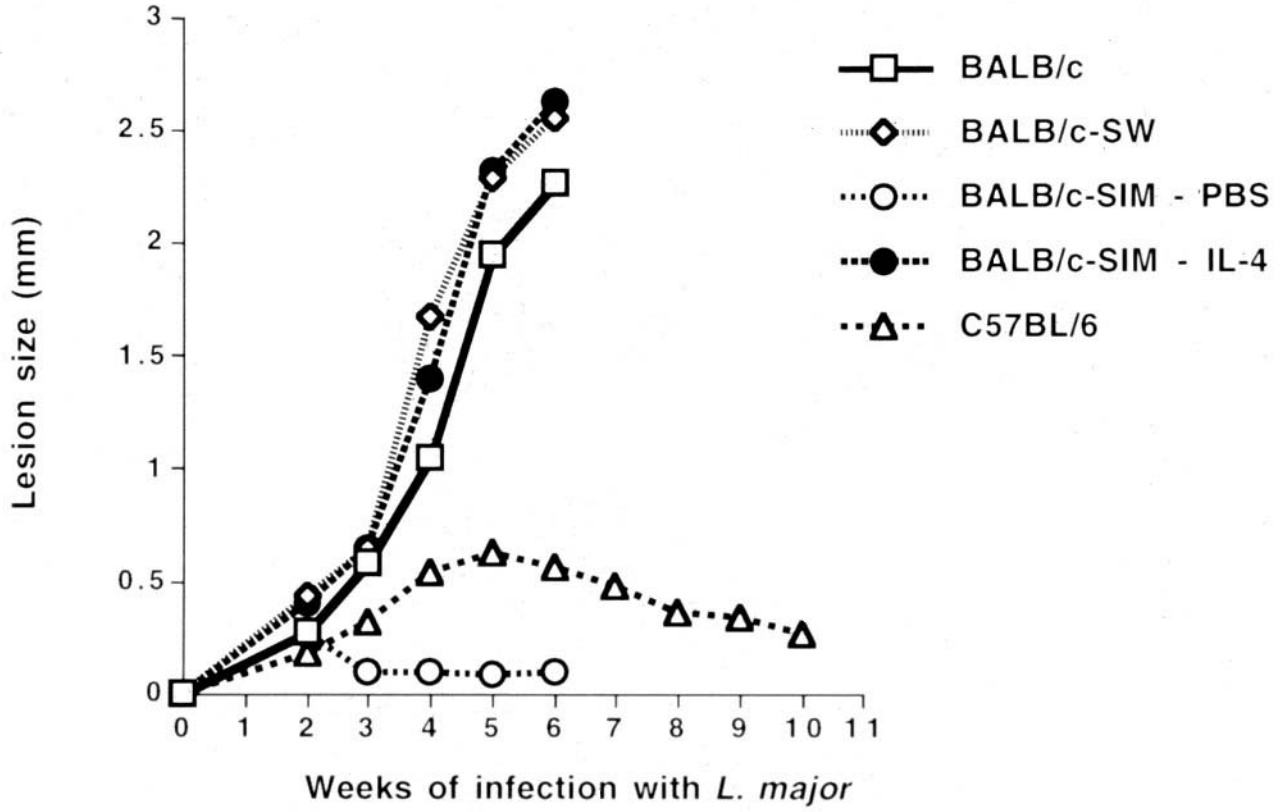


Th2 cell development does not occur in BALB/c mice deficient in Vβ4+ CD4+ T cells following infection with *L. major*

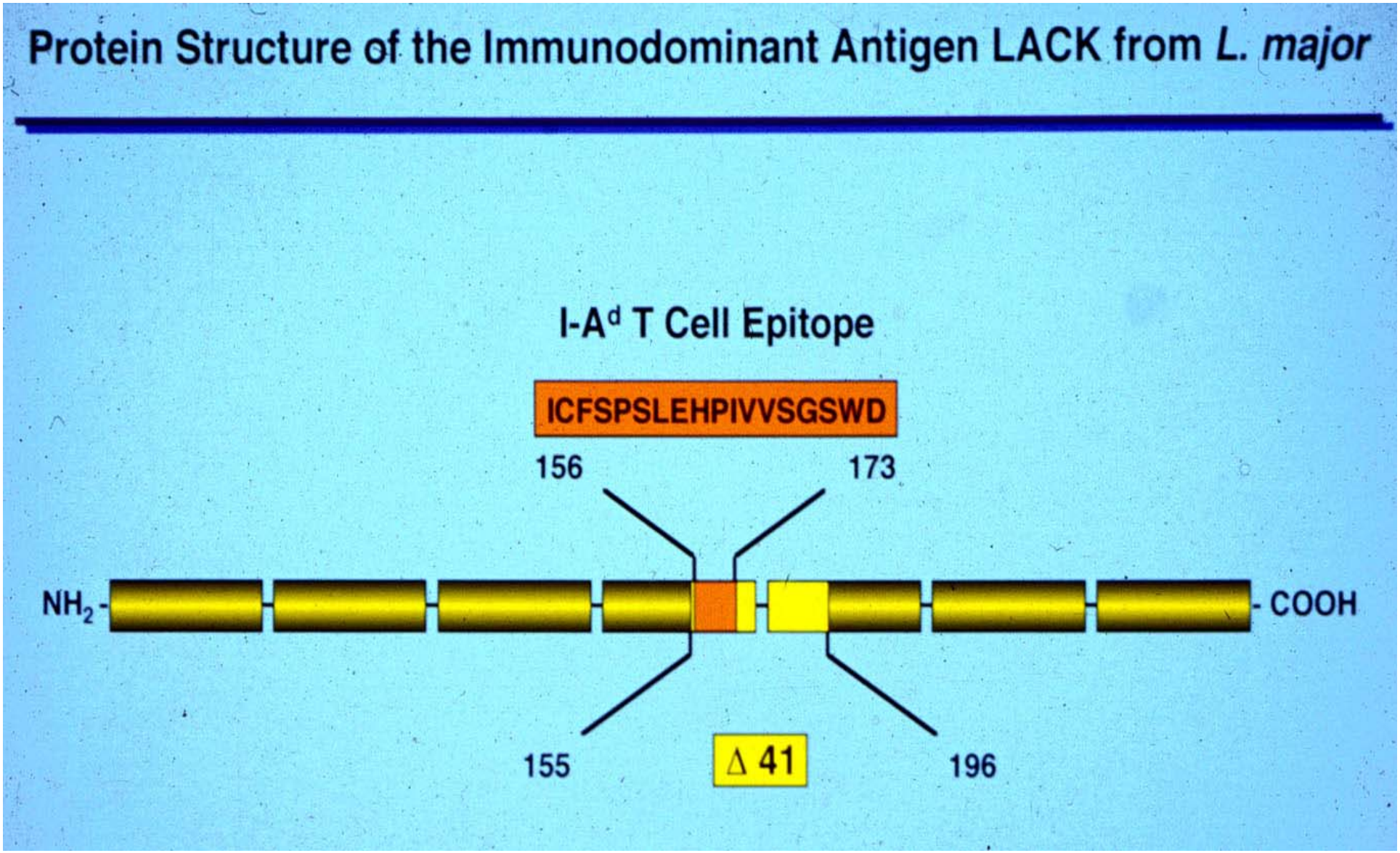



BALB/c mice deficient in Vβ4+ CD4+ T cells are resistant to infection with L. major
BALB/c
C57BL/6
BALB/c deficient in Vβ4 CD4+ cells
BALB/c deficient in Vβ6 CD4+ cells
lesion size (mm)
0
1
2
3
4
0
10
20
30
40
days of infection

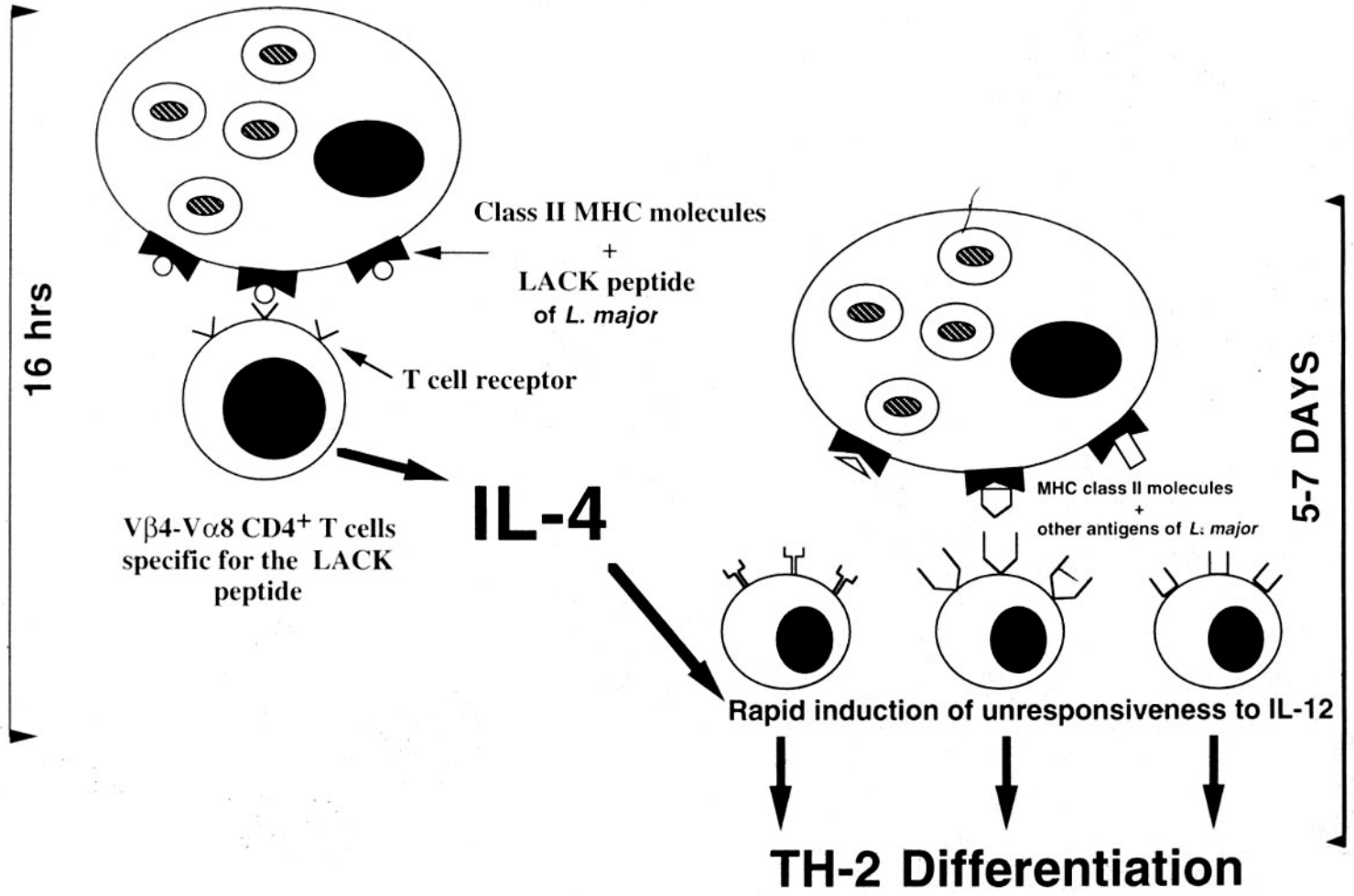
IL-4 during the early stage of infection is necessary and sufficient to instruct Th2 development and susceptibility to *Leishmania major* in BALB/c mice



Protein Structure of the Immunodominant Antigen LACK from *L. major*



IL-4 rapidly produced by Vβ4Vα8 CD4+ T cells intructs Th2 cell development and the susceptibility to L. major in BALB/c mice

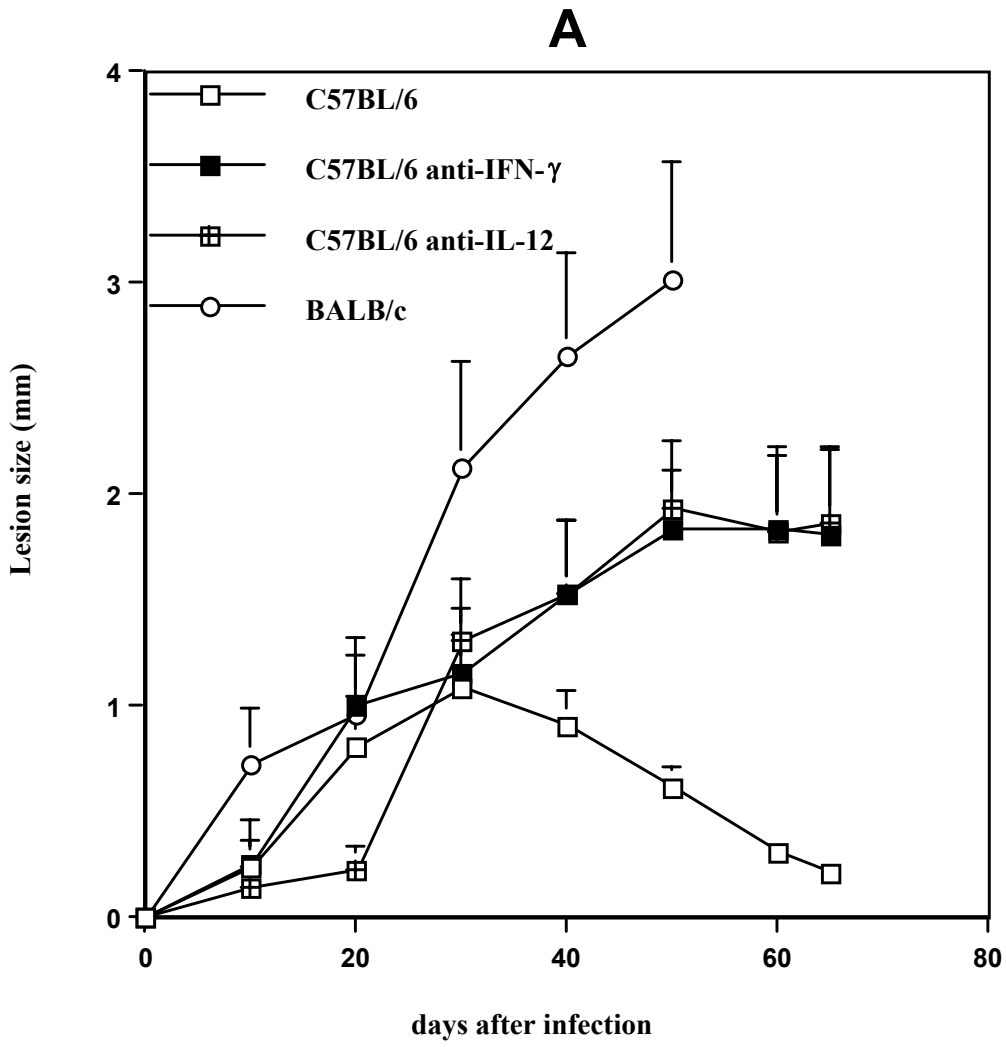


What might underlie susceptibility to infection with L. major in BALB strain mice ?

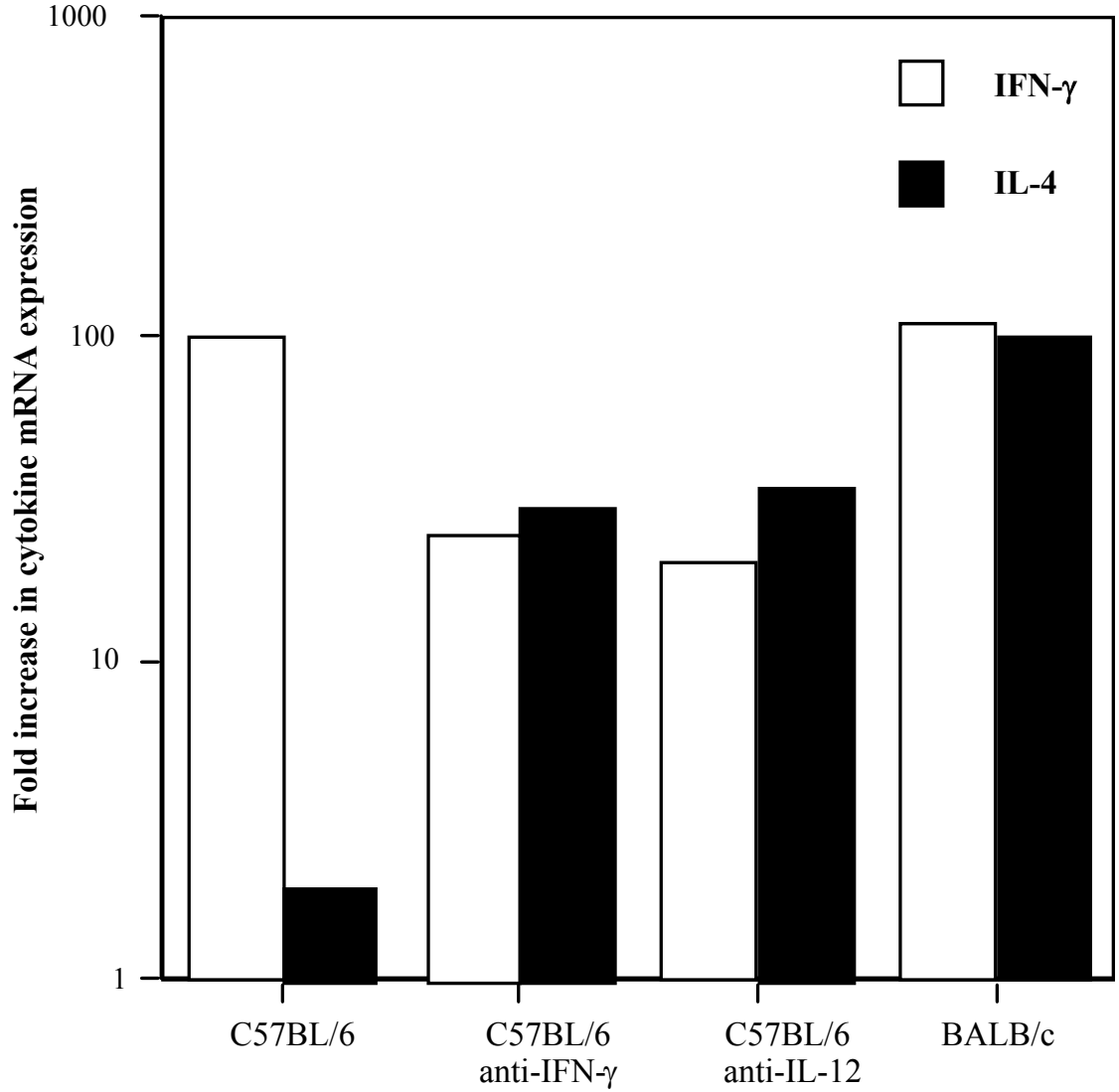
- A greater LACK-specific T cell precursor frequency could account for the capacity of the initial IL-4 production in response to LACK to exceed the threshold required for Th2 lineage commitment.

- Susceptibility of BALB mice might be linked to an inability to down-regulate early IL-4 production by LACK-reactive cells.

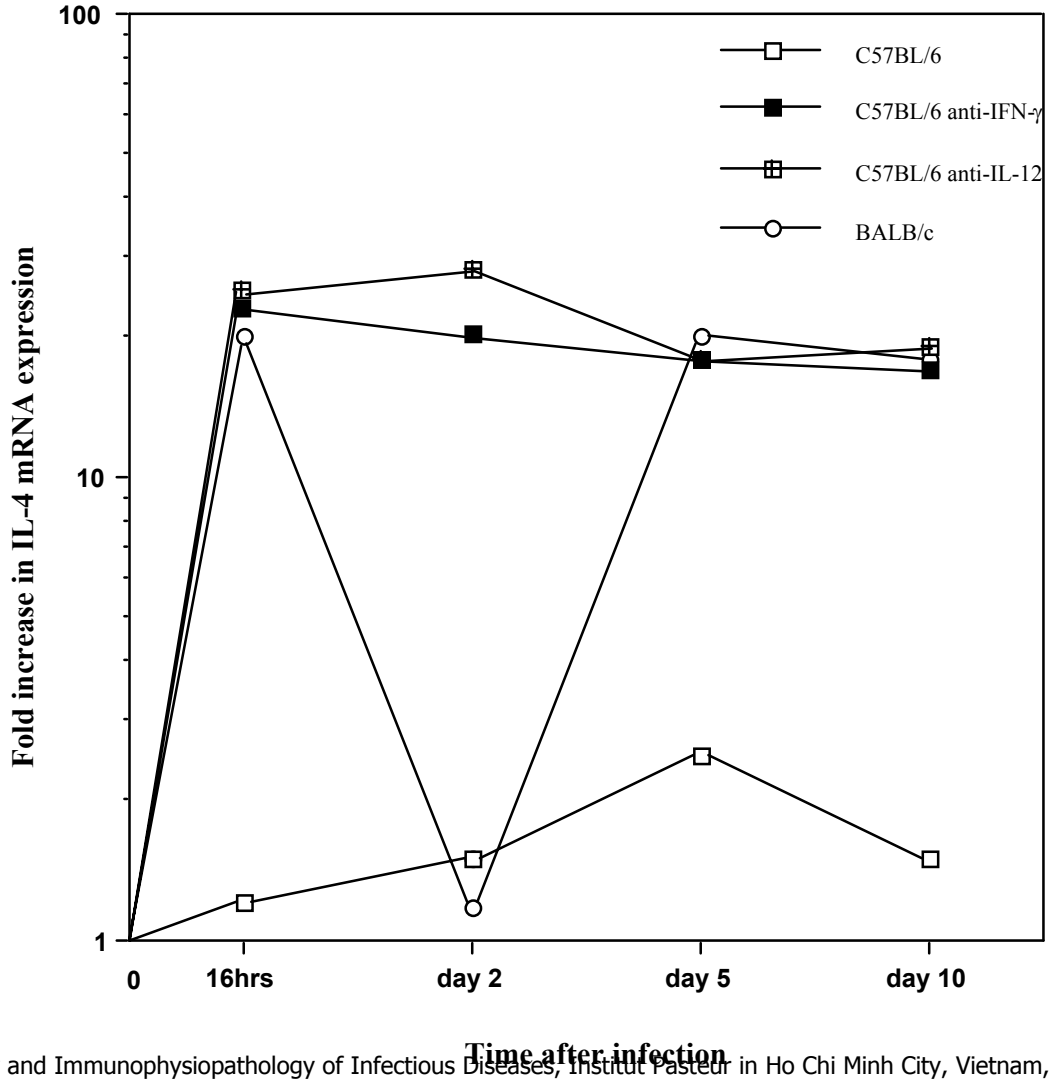
Lesions'development in C57BL/6 mice treated with anti-IL-12 or -IFN-γ at the onset of infection with L. major



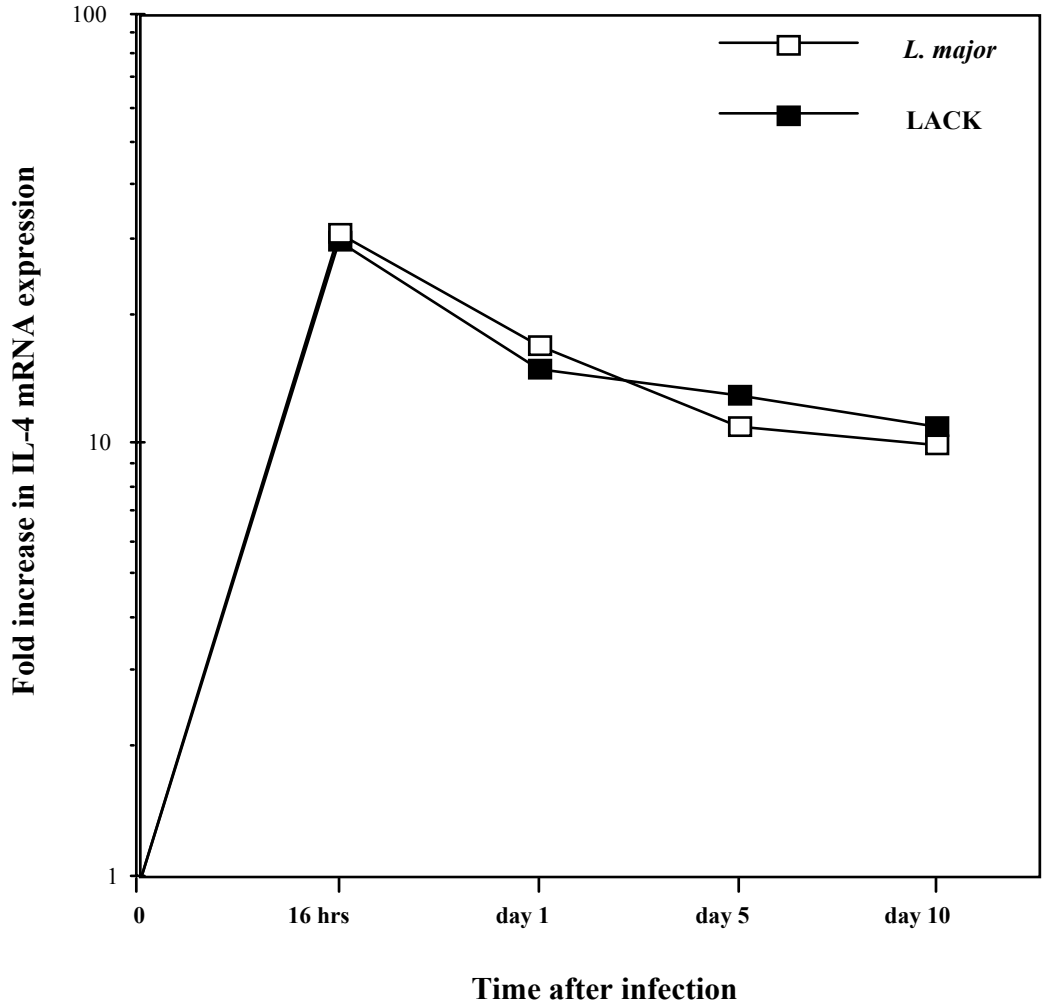
Cytokines transcripts in draining lymph nodes 45 days after infection with L. major in C57BL/6 mice treated with anti-IL-12 or IFN-γ



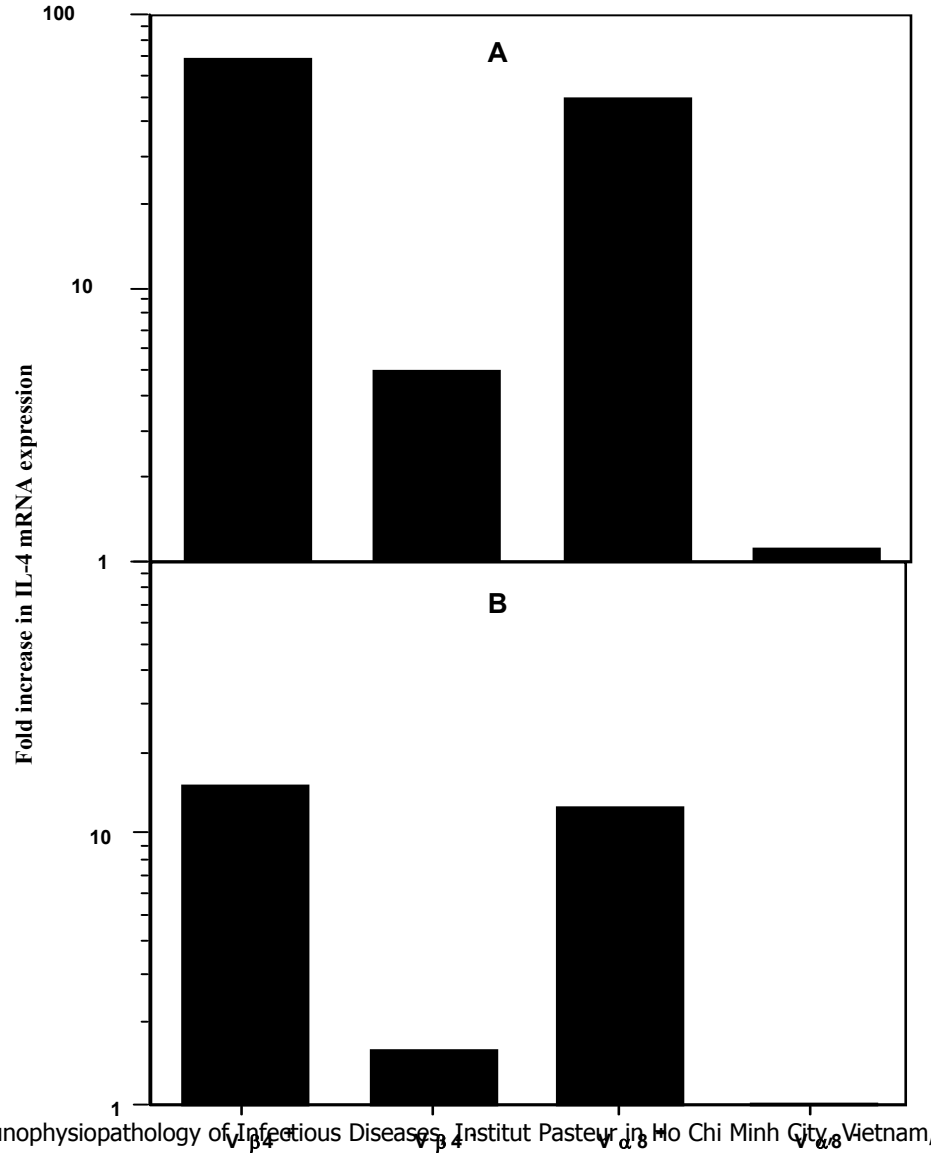
Kinetics of IL-4 mRNA expression in lymph nodes of C57BL/6 mice treated with anti-IFN-γ or-IL-12 at the onset of infection with Leishmania major



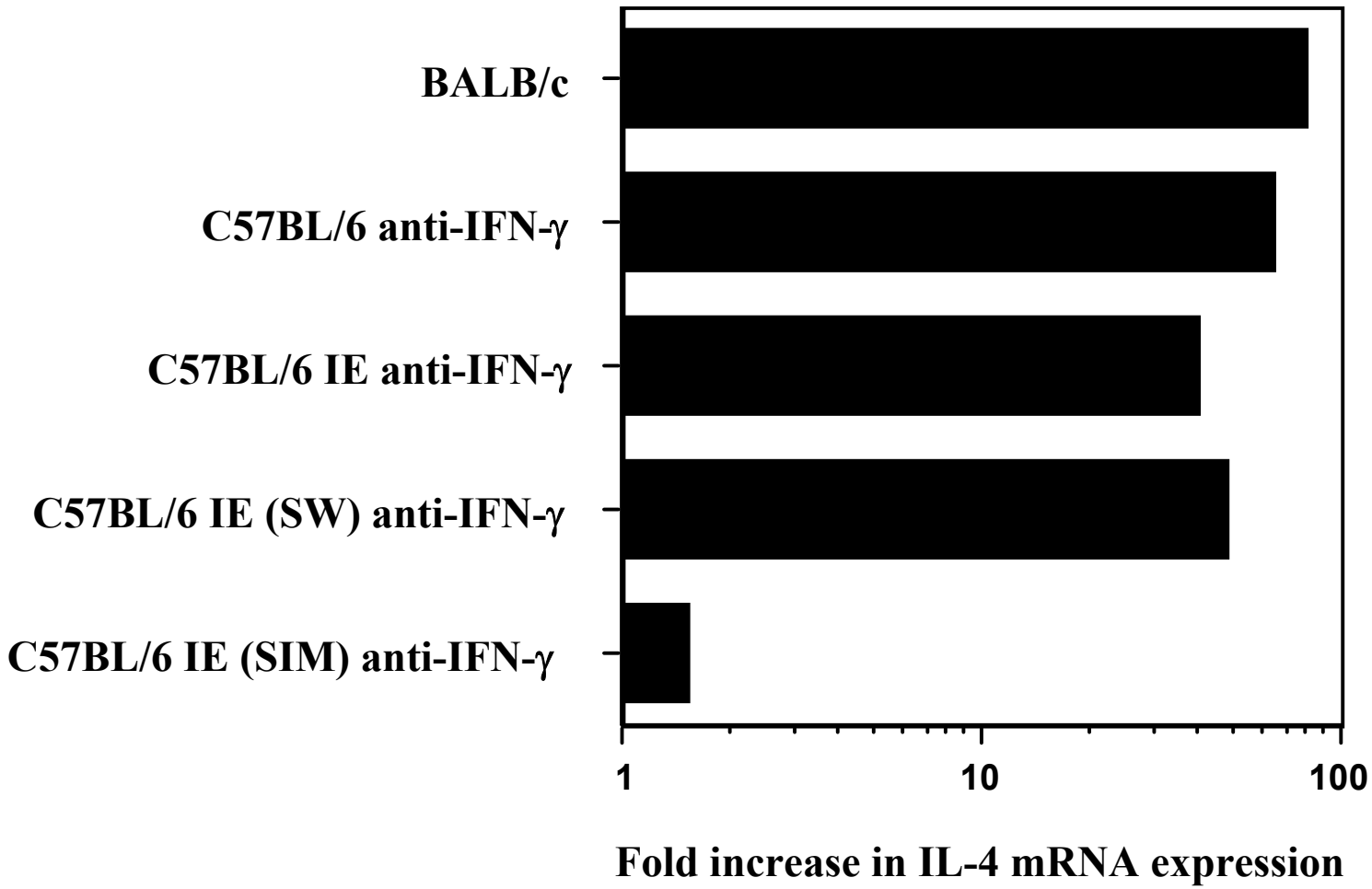
LACK induces a rapid IL-4 response in draining lymph node cells from C57BL/6 mice treated with anti-IL-12 or -IFN-γ



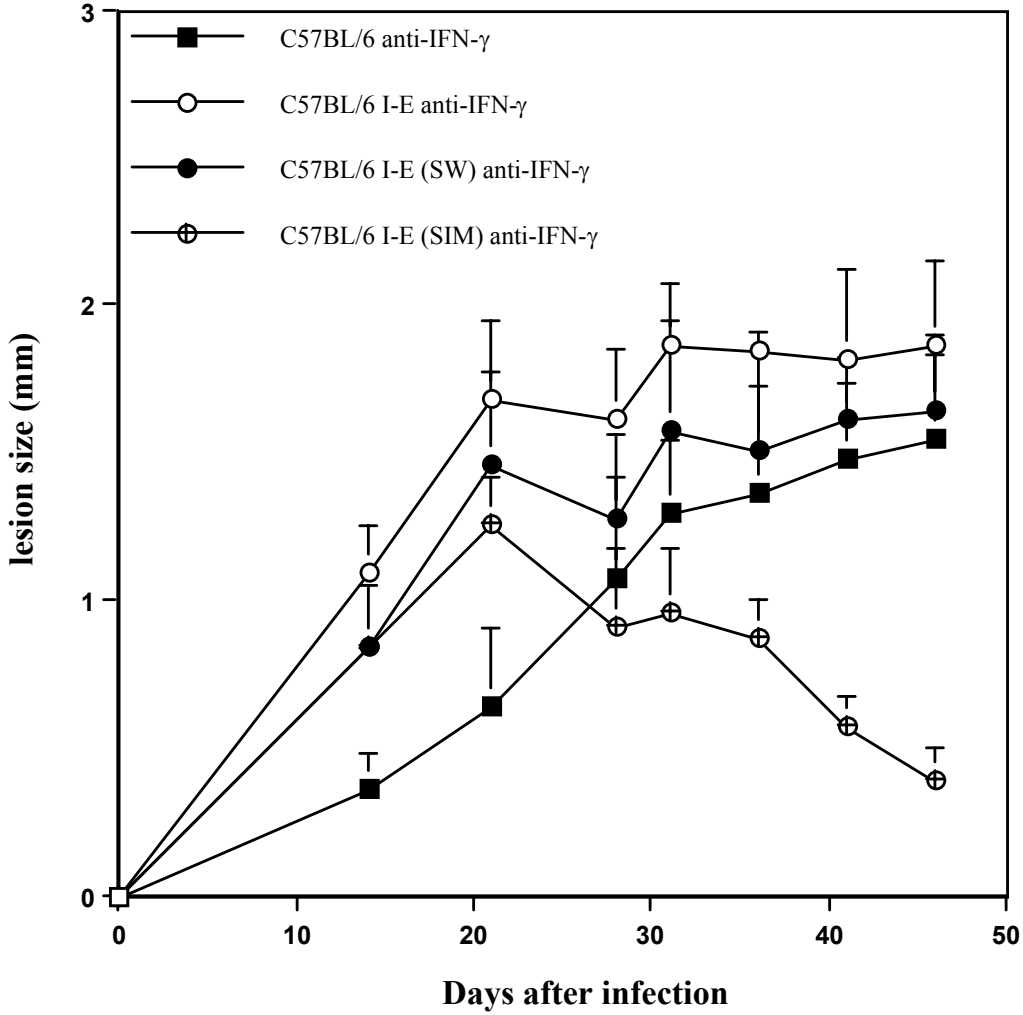
The CD4 cells producing IL-4 in response to L. major in C57BL/6 mice treated with anti-IL-12 at the onset of infection express the Vβ4-Vα8 TCR chains



Early IL-4 mRNA expression in response to L. major does not occur in Vβ4-deficient C57BL/6 mice treated with anti-IFN-γ at the initiation of infection



Lesions'development in anti-IFN-γ treated I-E transgenic C57BL/6 mice deficient in Vβ4 CD4 T cells



Treatment of Vβ4-deficient I-E transgenic C57BL/6 mice with anti-IFN-γ before infection with L. major does not interfere with Th1 cell development