I. The Immune system

Innate Immunity ⟷ **Adaptive Immunity**

1) Cellular effectors:
- Phagocytes (Monocytes/Macrophages, Granulocytes);
- Killers (NK cells).

2) Soluble Effectors:
- Complement
- Defensins
- Interferons α, β
- Primary cytokines (IL-1, IL-6, TNF)
- Chemokines

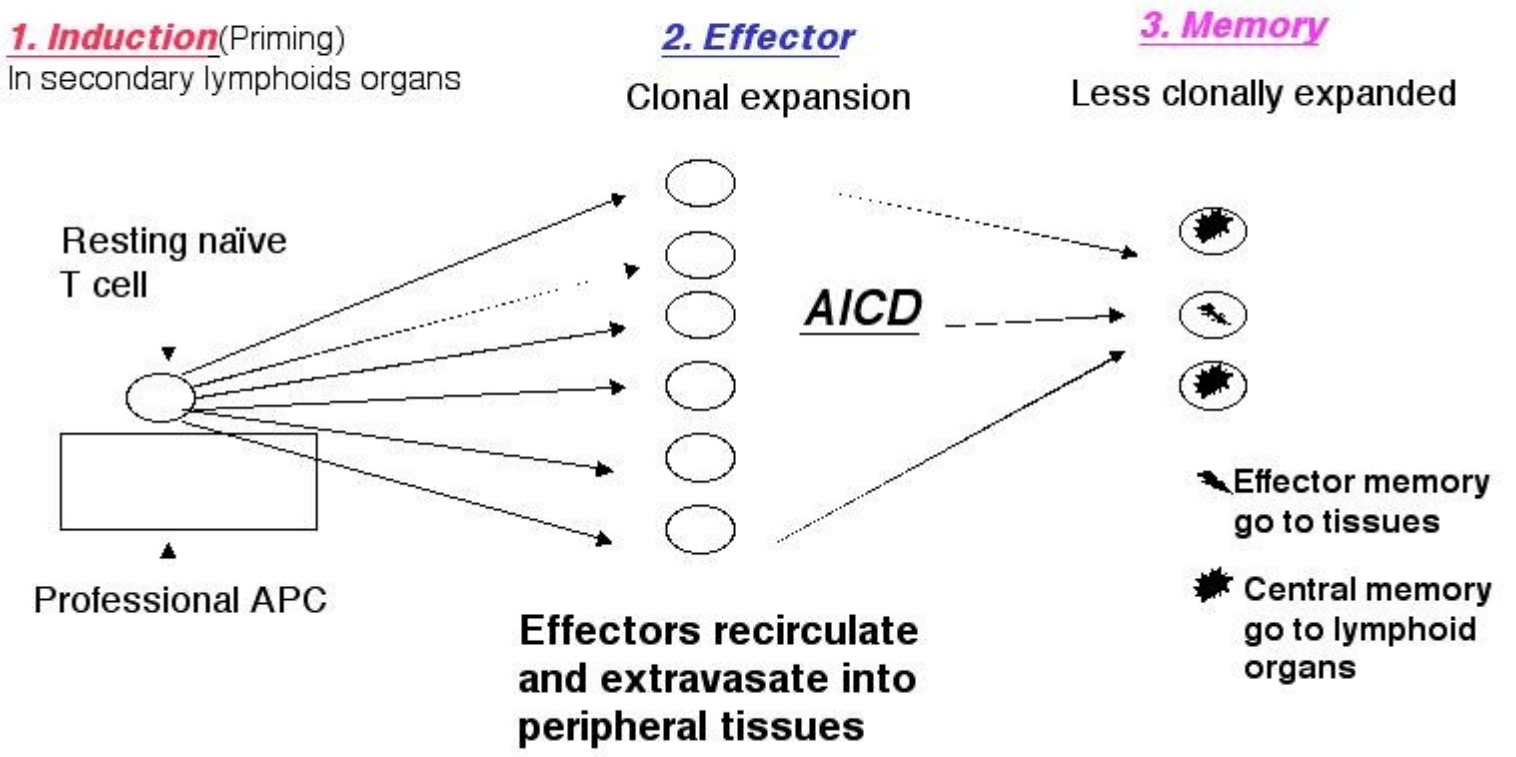
1) Cellular effectors:
- T lymphocytes
- B lymphocytes

2) Soluble Effectors:
- Immunoglobulins (B cells)
- Interferon-γ
- Secondary cytokines
- Chemokines

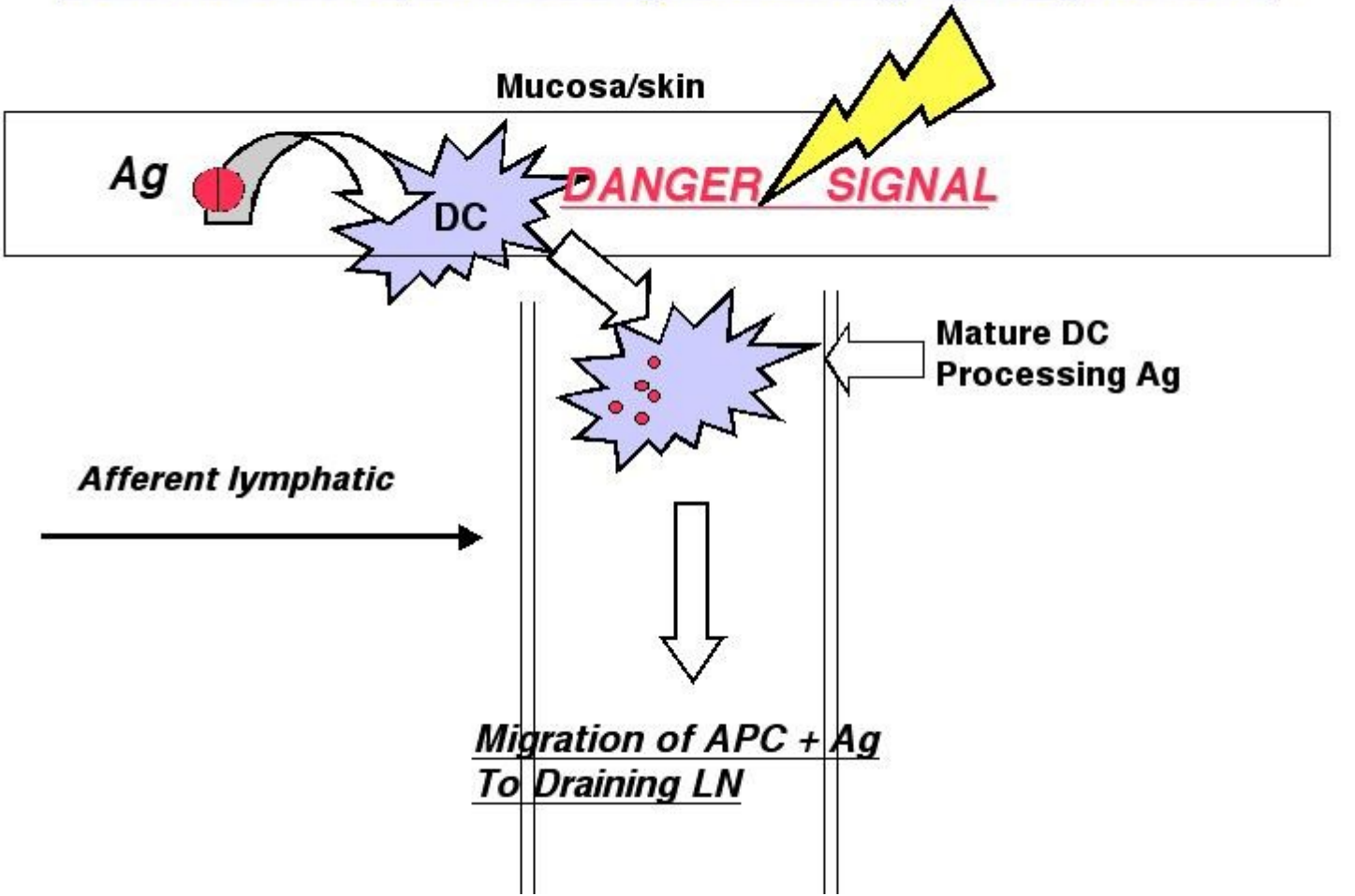
II. Phases of the Adaptive Response

1. Induction (Priming) →	***2. Effector*** →	***3. Memory***
Primary response		Secondary response
-Naïve cells	-Effector cells	-Activated cells
-Quiescent	-Hyper-Activated cells	- Quiescent,long lived
-Low precursor frequency ($10^{-5}/10^{-6}$ lymphocytes)	-Clonal expansion: cell cycle Highest precursor frequency (10^{-2} /10^{-4} lymphocytes)	-High precursor frequency (10^{-4} lymphocytes)
-Low avidity Ag Receptors	-Selecting high avidity Ag receptors	-High avidity Ag receptors
-No effector functions	-Effector functions (Cytokines, Help, Killing)	-Effector functions (Cytokines, Help, Killing)
-Stringent activation requirements	-Easy to trigger	
Where: Secondary lymphoid Organs	-Secondary lymphoid Organs (CD4 helper, B cells); -Tissues (CD4, CD8 T cells)	-Patrolling lymphoid organs and tissues (central memory or effector memory T cells) -Resident in Bone Marrow (B cells plasmacells)
How: Meeting with Ag+APC	-Meeting with target cells	-Re-induced by APC in secondary lymphoid organs

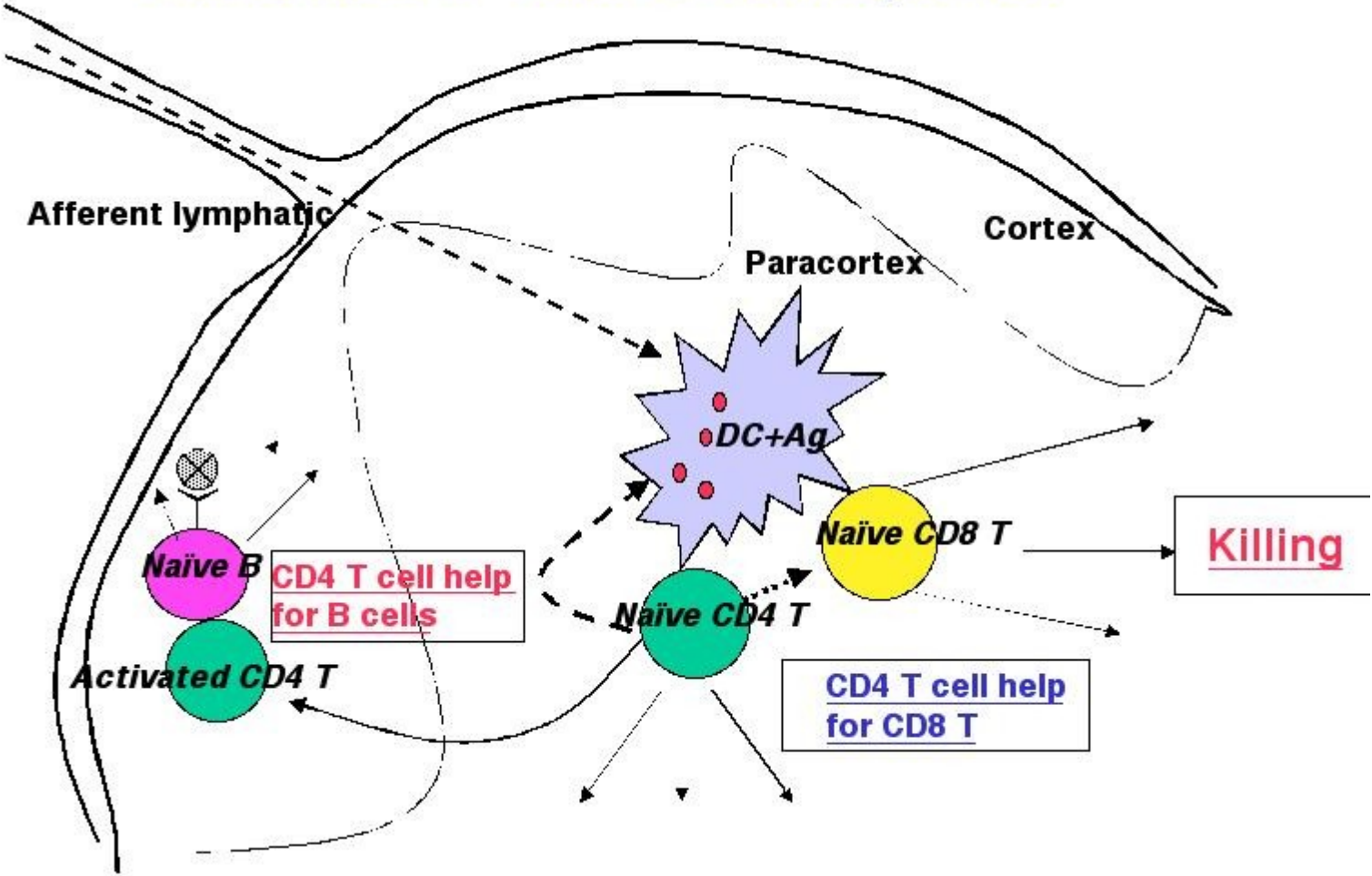
III. Phases of the Adaptive Response

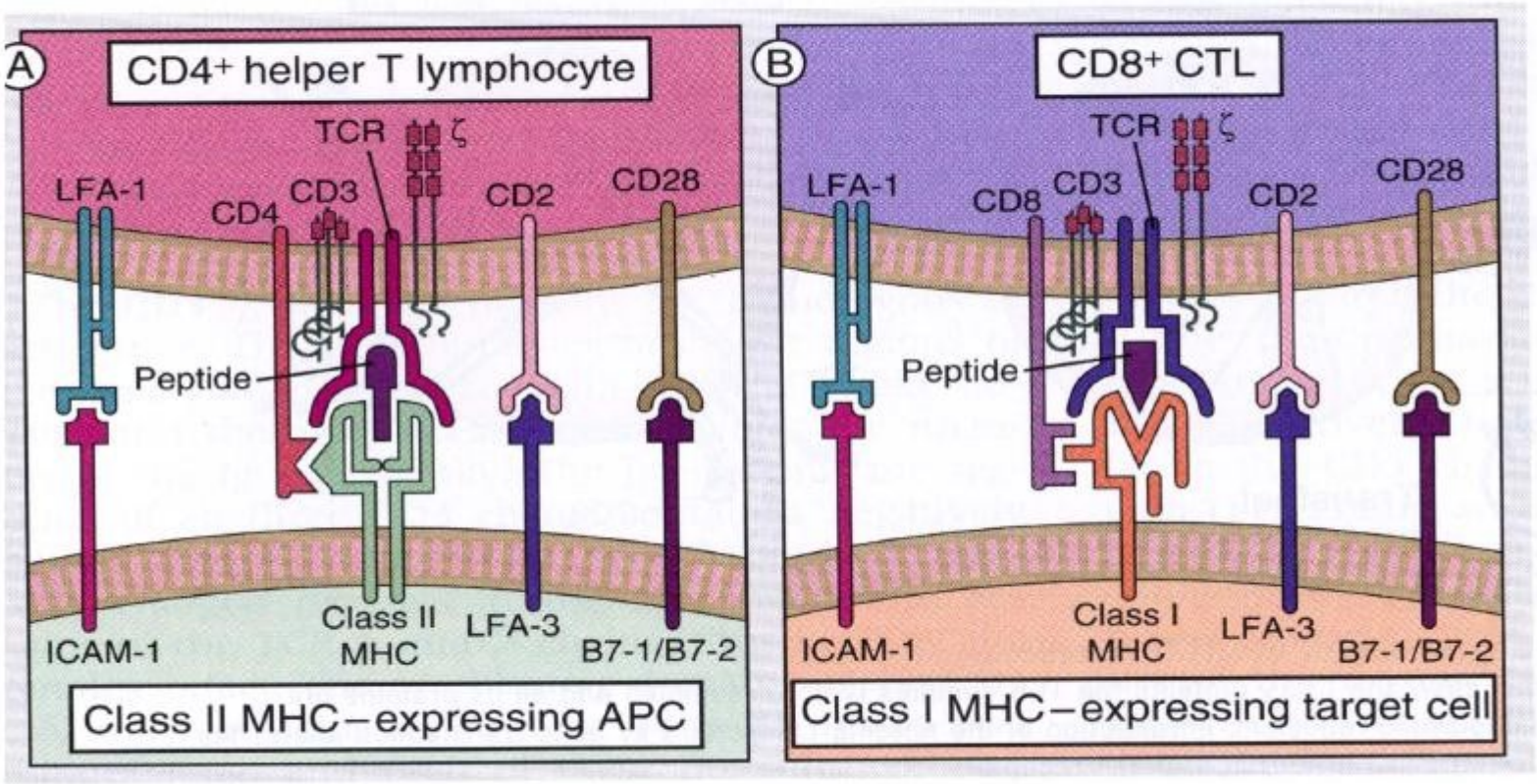


IV. How do Peripheral Antigens and Lymphocytes meet ?



V. Induction of T and B cell responses

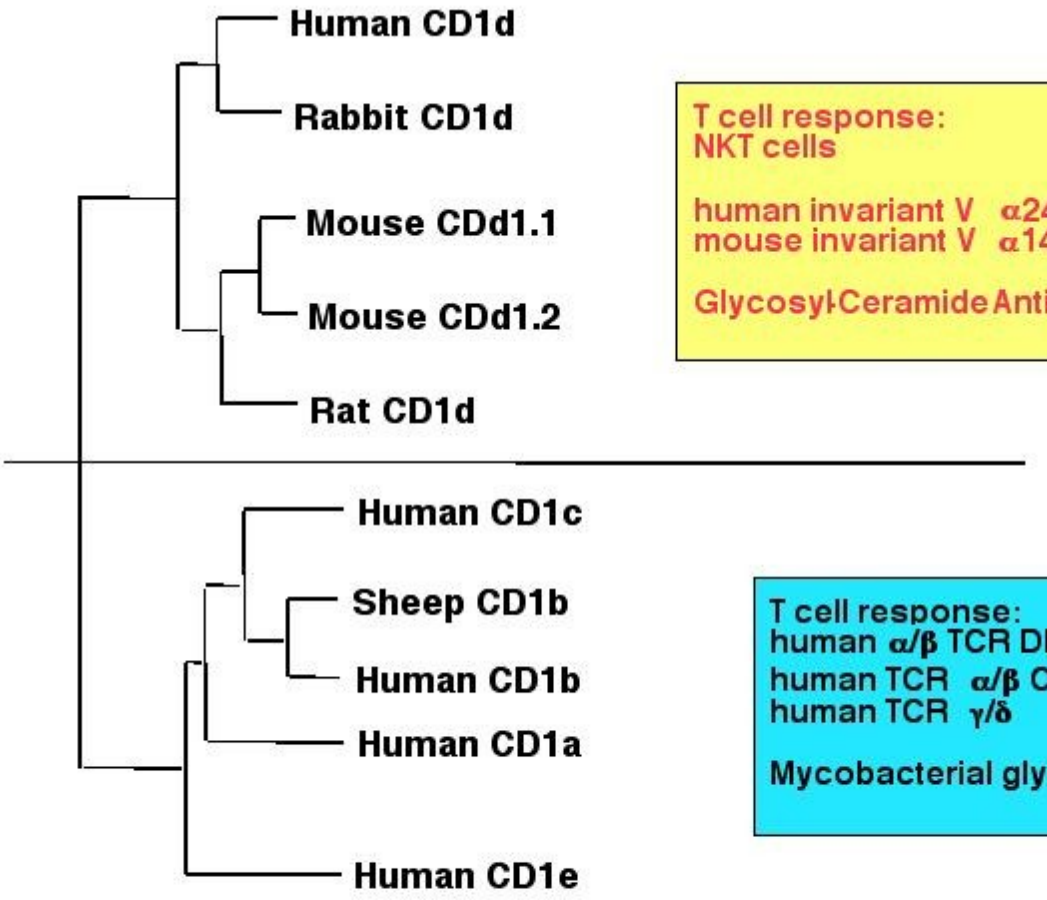



A
CD4+ helper T lymphocyte
TCR
ζ
LFA-1
CD4
CD3
CD2
CD28
Peptide
ICAM-1
Class II MHC
LFA-3
B7-1/B7-2
Class II MHC–expressing APC
B
CD8+ CTL
TCR
ζ
LFA-1
CD8
CD3
CD2
CD28
Peptide
ICAM-1
Class I MHC
LFA-3
B7-1/B7-2
Class I MHC–expressing target cell

NKT cells

T cells= α/β (γ/δ) TCR

NK cells= CD161 (NKPR1)



T cell response:
NKT cells 8

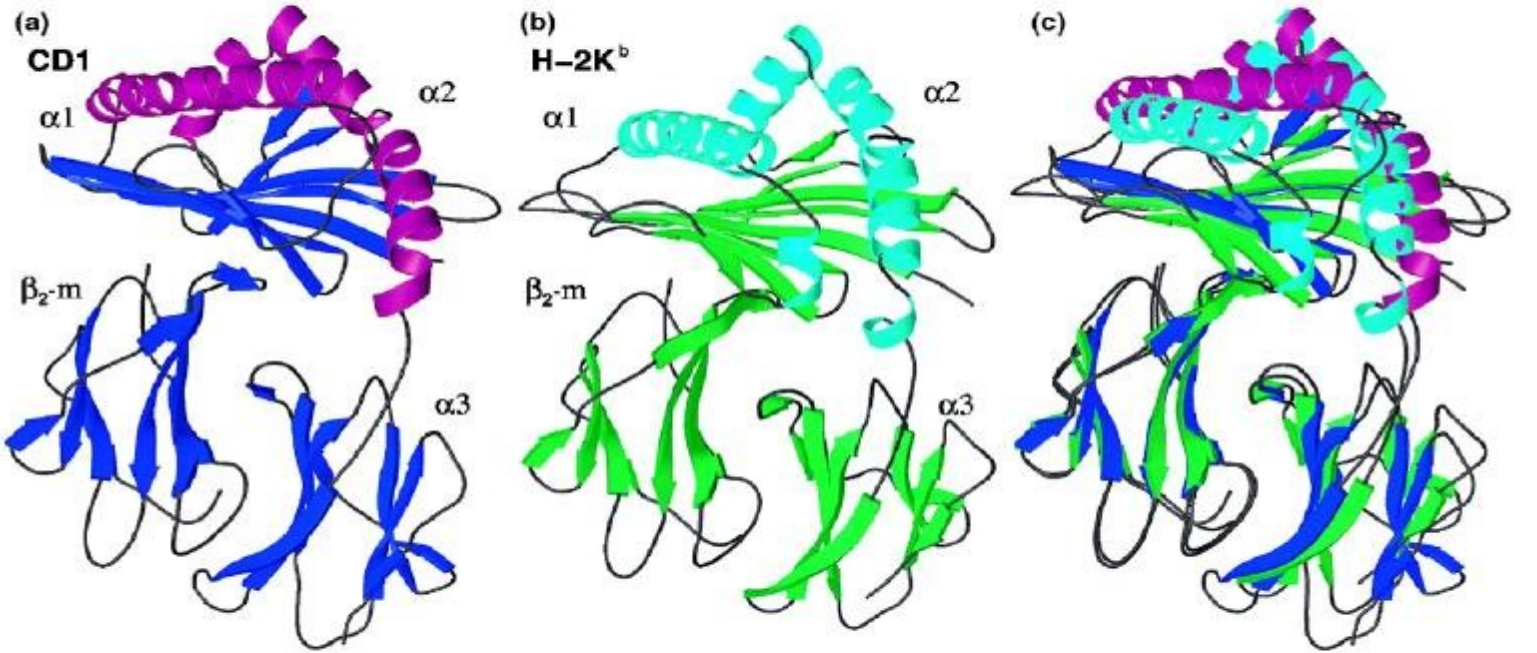
human invariant V α24-J αQ/V β11
mouse invariant V α14-J α281/V β

Glycosyl-Ceramide Antigens

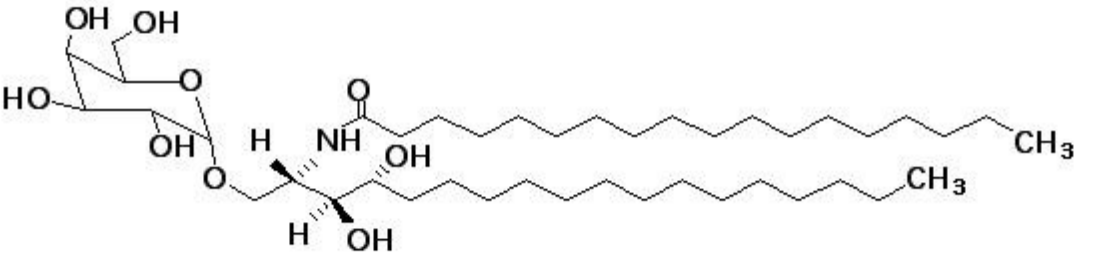
T cell response:
human α/β TCR DN
human TCR α/β CD8 +
human TCR γ/δ

Mycobacterial glycolipid Antigens

Human CD1 genes: chromosome 1
Mouse CD1 genes: chromosome 3


(a)
CD1
α1
α2
β2-m
α3
(b)
H–2K^b
α1
α2
β2-m
α3
(c)

α-GalCer KIRIN7000



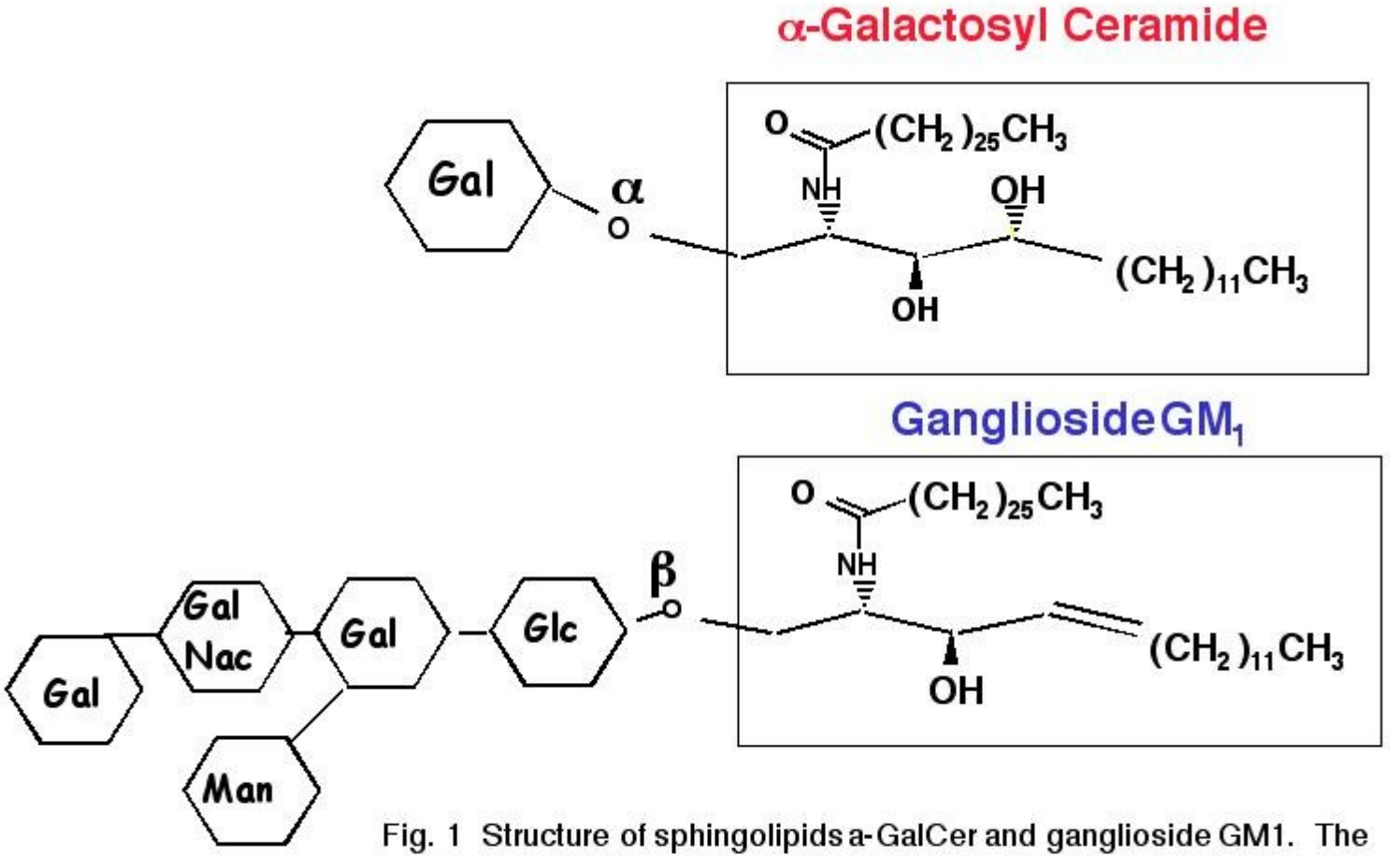
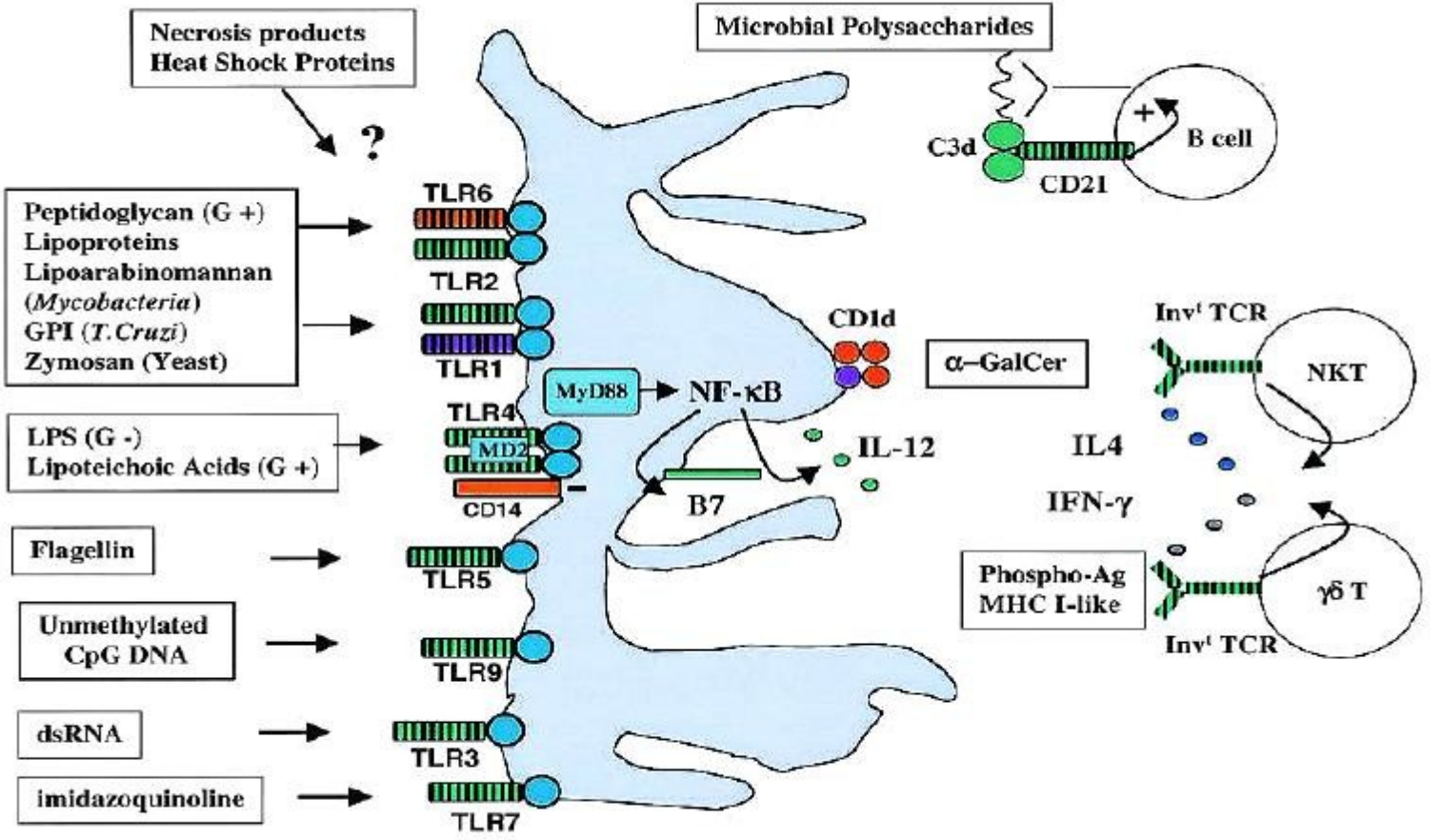


Fig. 1 Structure of sphingolipids a-GalCer and ganglioside GM1. The ceramide moiety is enclosed in the gray box and the a or banomeric linkage of the sugar is indicated.


Necrosis products
Heat Shock Proteins
?
Microbial Polysaccharides
C3d
CD21
B cell
+
Peptidoglycan (G +)
Lipoproteins
Lipoarabinomannan
(Mycobacteria)
GPI (T.Cruzi)
Zymosan (Yeast)
TLR6
TLR2
TLR1
CD1d
α–GalCer
Inv' TCR
NKT
MyD88
NF-κB
TLR4
MD2
CD14
LPS (G -)
Lipoteichoic Acids (G +)
IL-12
IL4
B7
IFN-γ
Flagellin
TLR5
Phospho-Ag
MHC I-like
γδ T
Inv' TCR
Unmethylated
CpG DNA
TLR9
dsRNA
TLR3
imidazoquinoline
TLR7

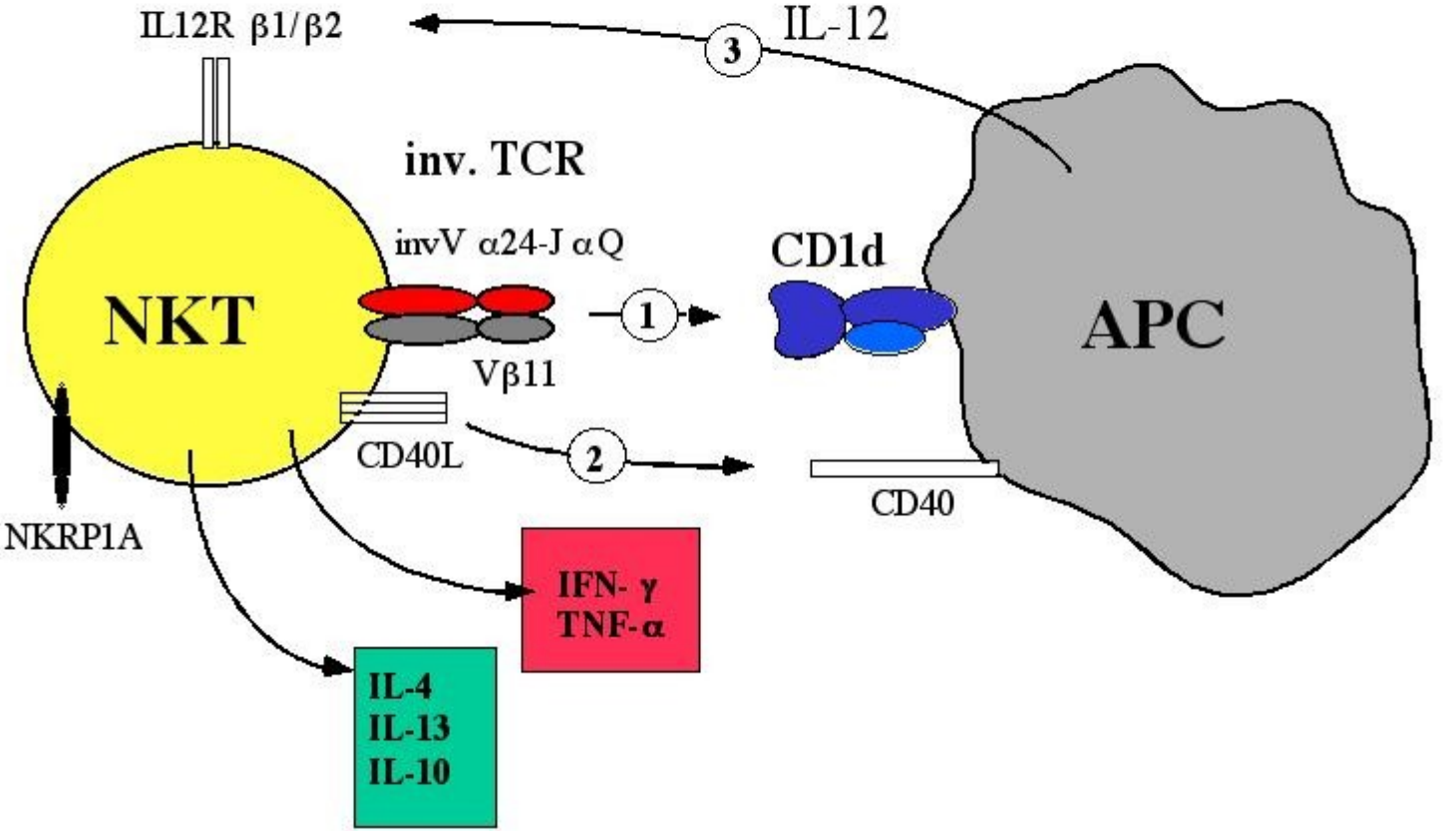
Le cellule NKT differiscono dalle T convenzionali, poiché

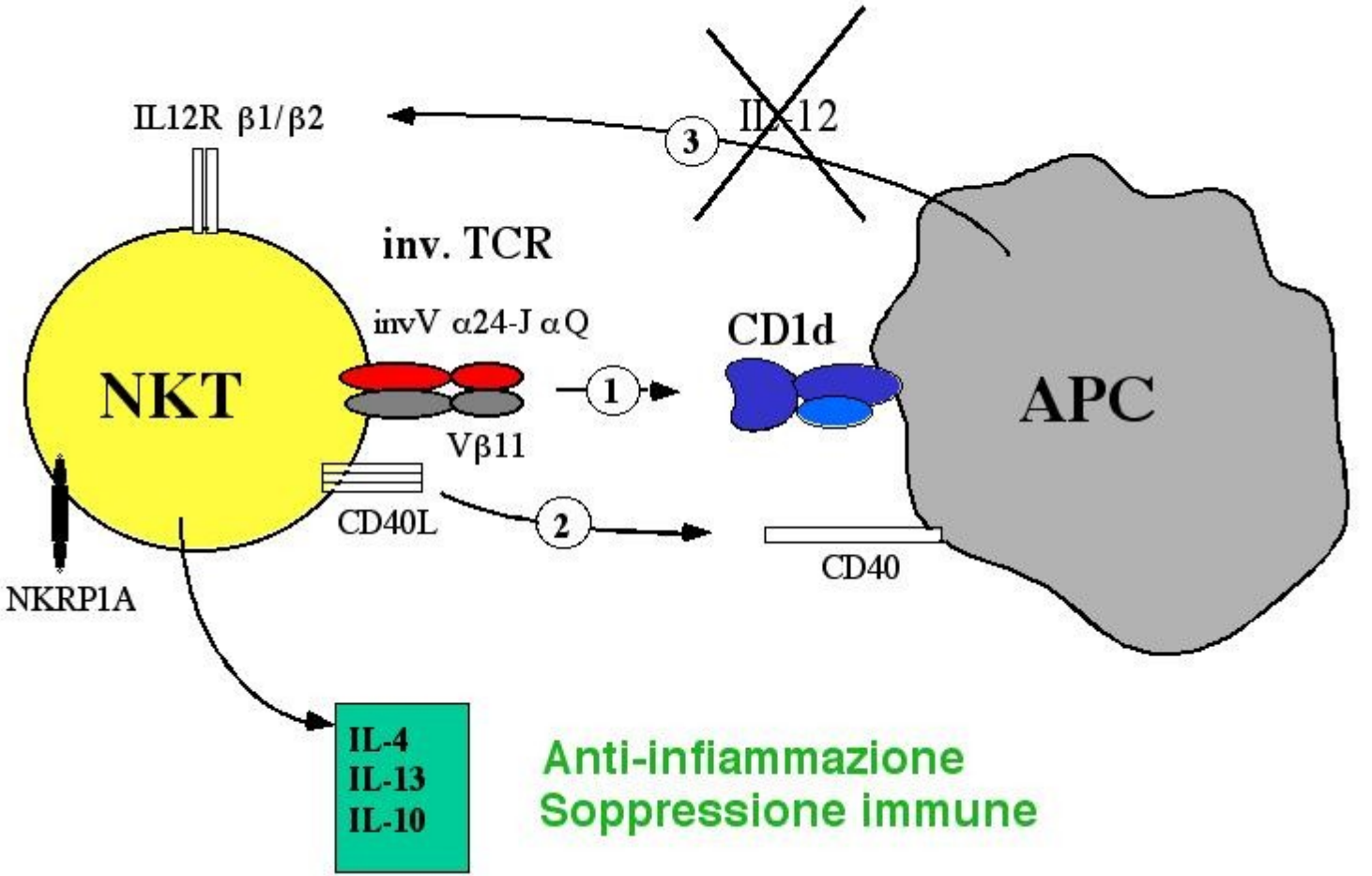
Sono sempre attivate

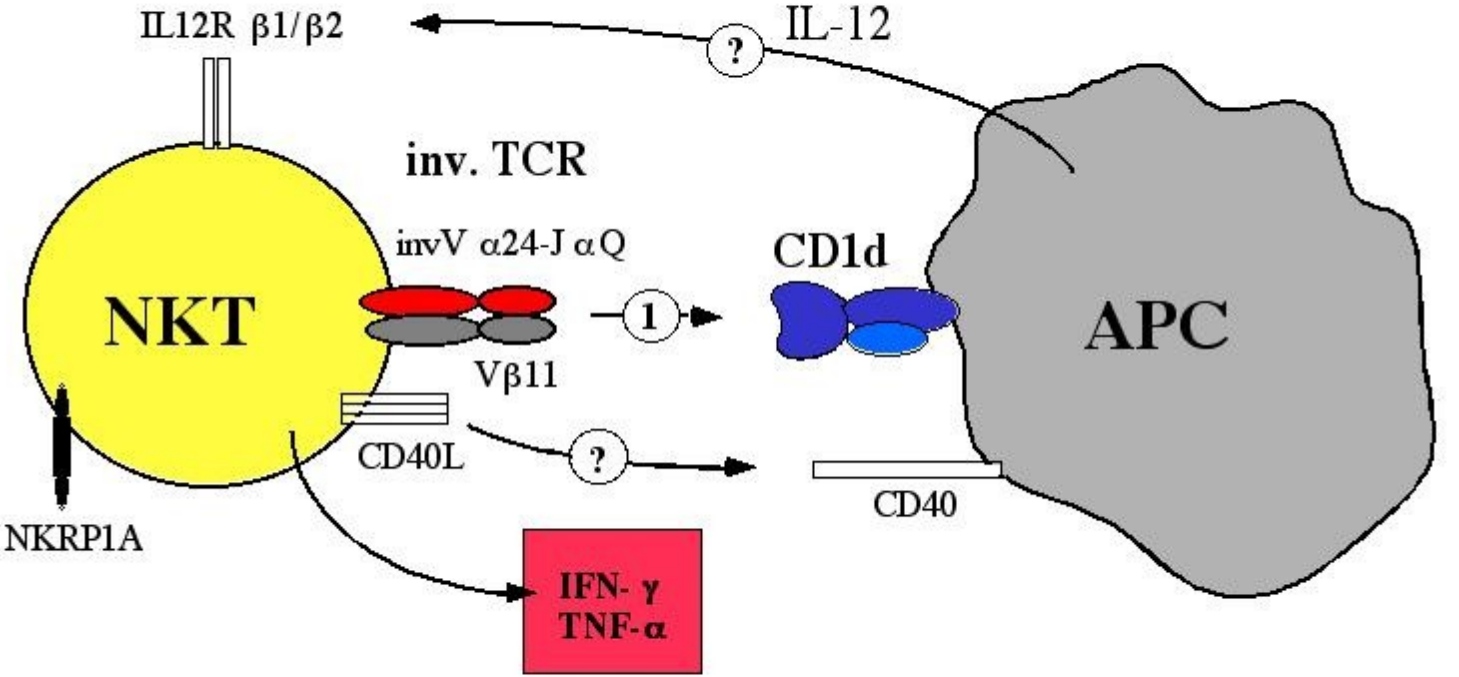
Sono già clonalmente espanse

Hanno sempre funzini effettrici immediate

In questo, sono simili alle cellule dell'immunita innata

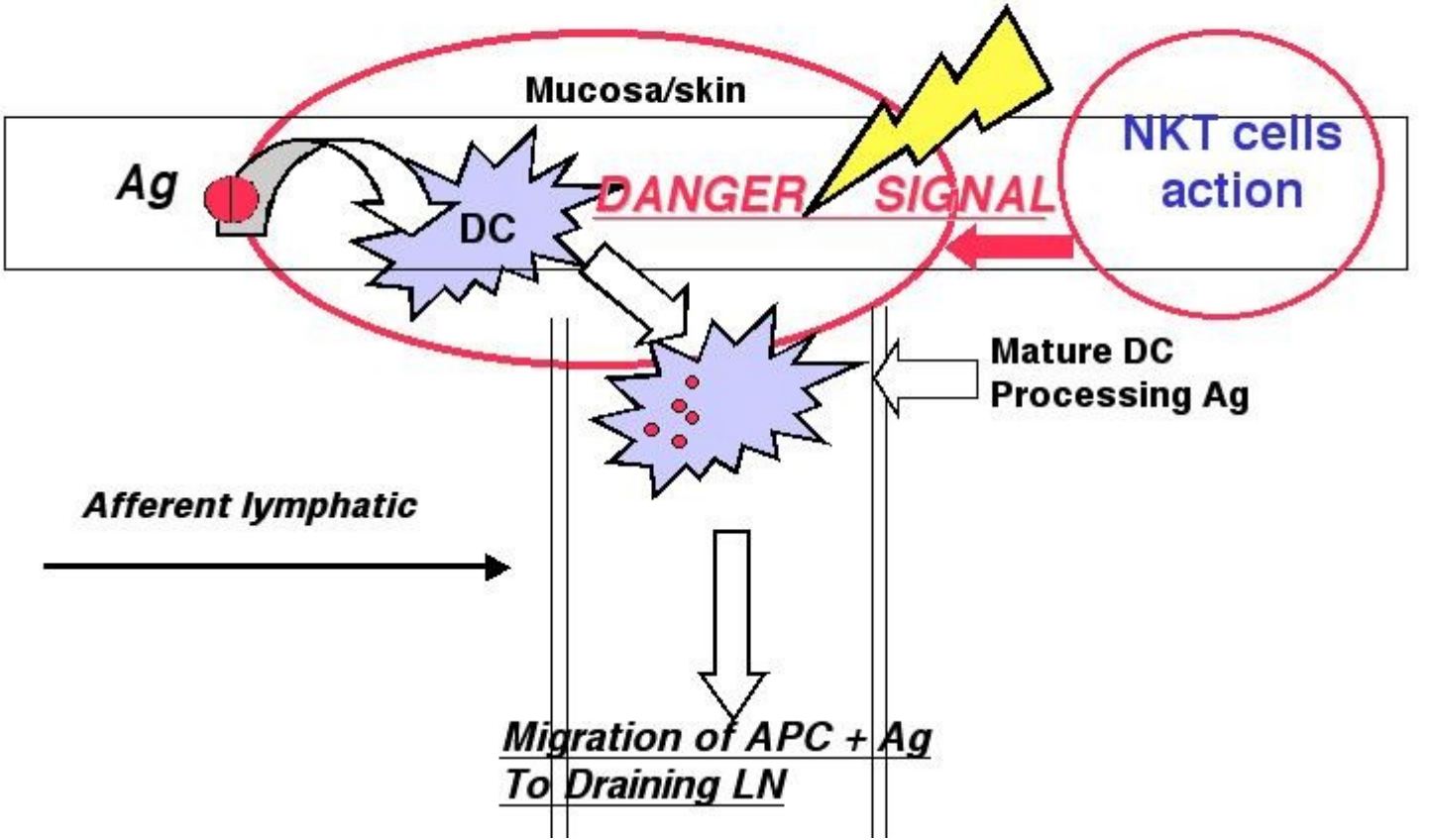

IL12R β1/β2
IL-12
3
inv. TCR
invV α24-J αQ
CD1d
NKT
APC
1
Vβ11
CD40L
2
CD40
NKRP1A
IFN- γ
TNF-α
IL-4
IL-13
IL-10


IL12R β1/β2
IL-12
3
inv. TCR
invV α24-J αQ
CD1d
NKT
APC
1
Vβ11
CD40L
2
CD40
NKRP1A
IL-4
IL-13
IL-10
Anti-infiammazione
Soppressione immune

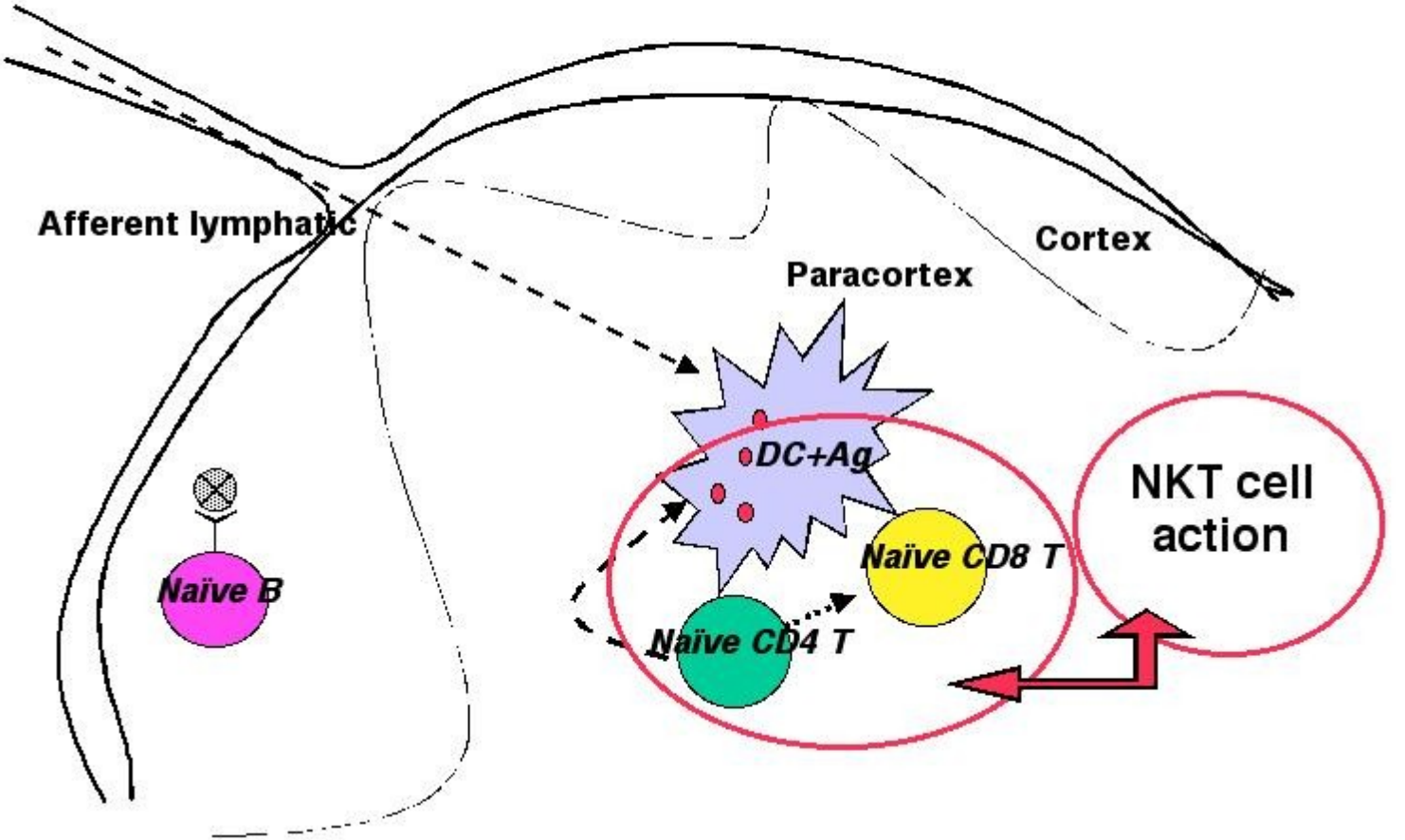


Infiammazione
Attivazione immune

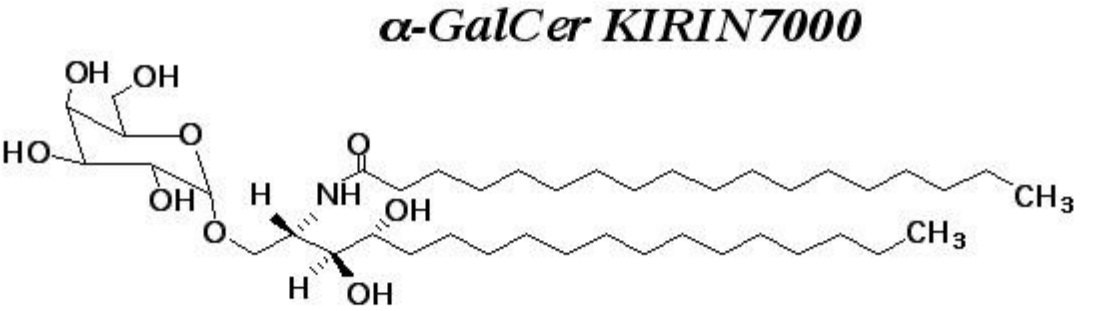
Cellule NKT possono ifluenzare la maturazione delle DC nelle mucose



Le cellule NKT possono influenzare l'induzione della risposta immune



α-Gal Cer come farmaco per attivare cellule NKT



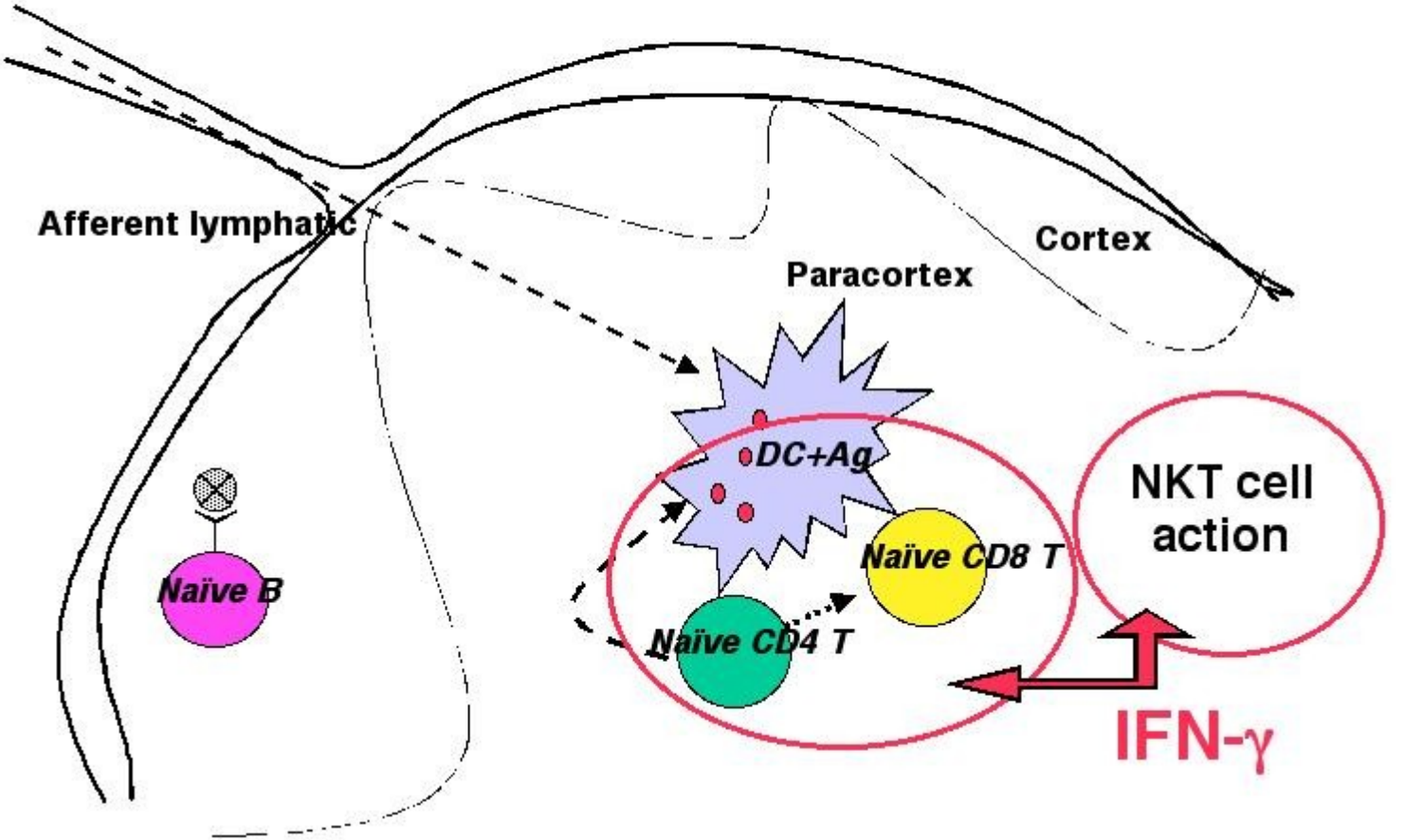
Regulatory activity by inv. NKT cells

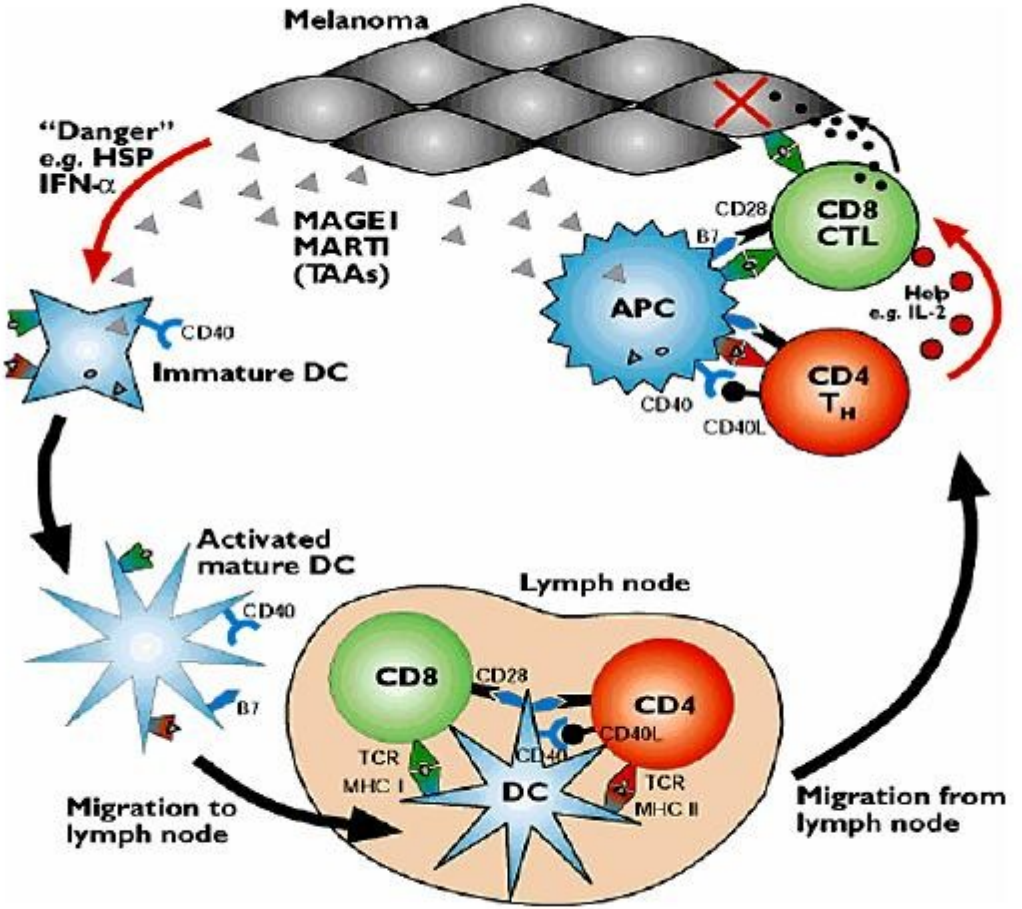
Activation of inv. NKT cells by α-Gal Cer:

Induces anti-tumor responses

Potentiate malaria vaccines

Le cellule NKT possono influenzare l'induzione della risposta immune




Melanoma
"Danger"
e.g. HSP
IFN-α
MAGE1
MARTI
(TAAs)
CD40
Immature DC
CD28
B7
CD8
CTL
APC
Help
e.g. IL-2
CD4
T_H
CD40
CD40L
Activated
mature DC
CD40
B7
Lymph node
CD8
CD28
CD4
CD40L
CD40
TCR
MHC I
DC
TCR
MHC II
Migration to
lymph node
Migration from
lymph node

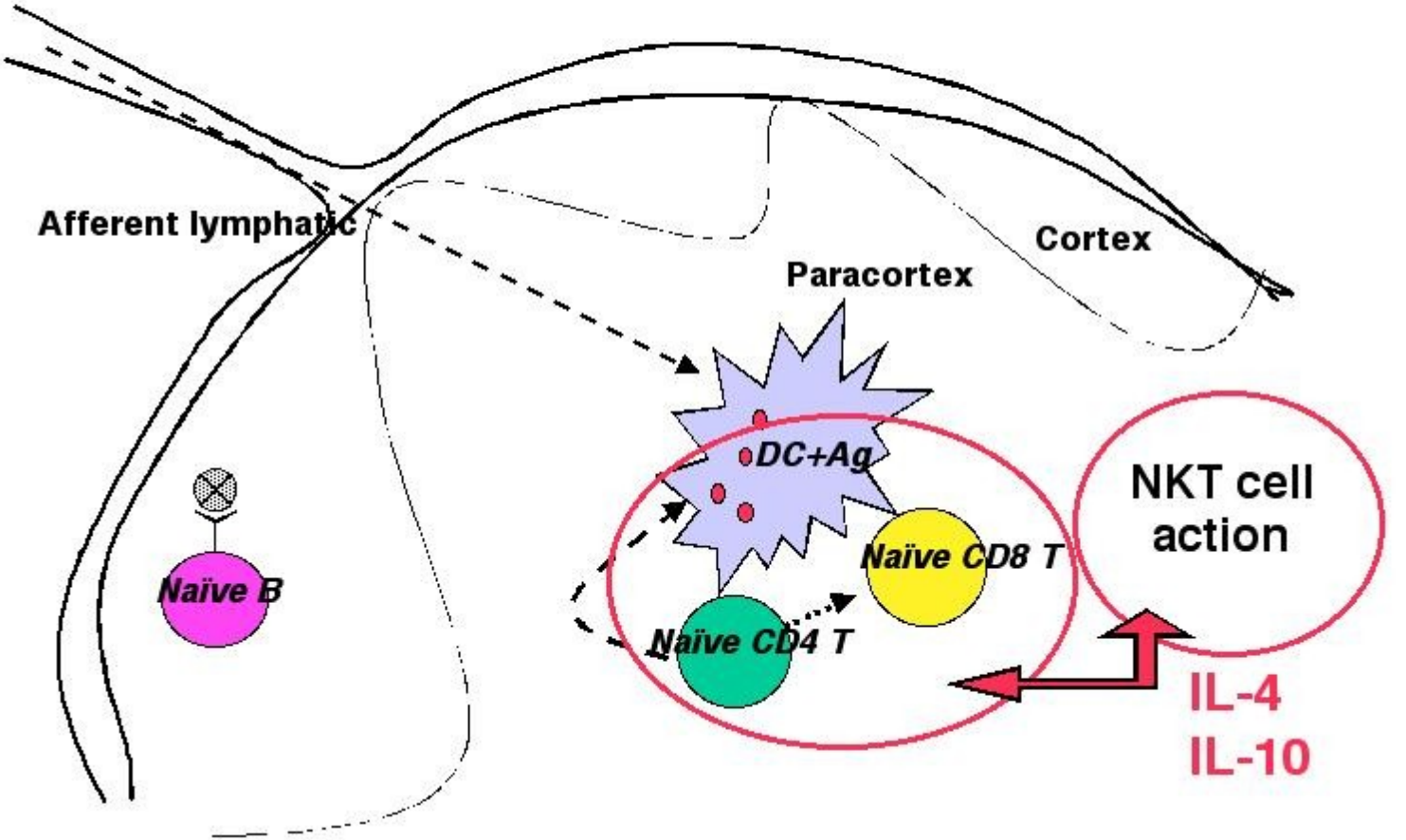
Regulatory activity by inv. NKT cells

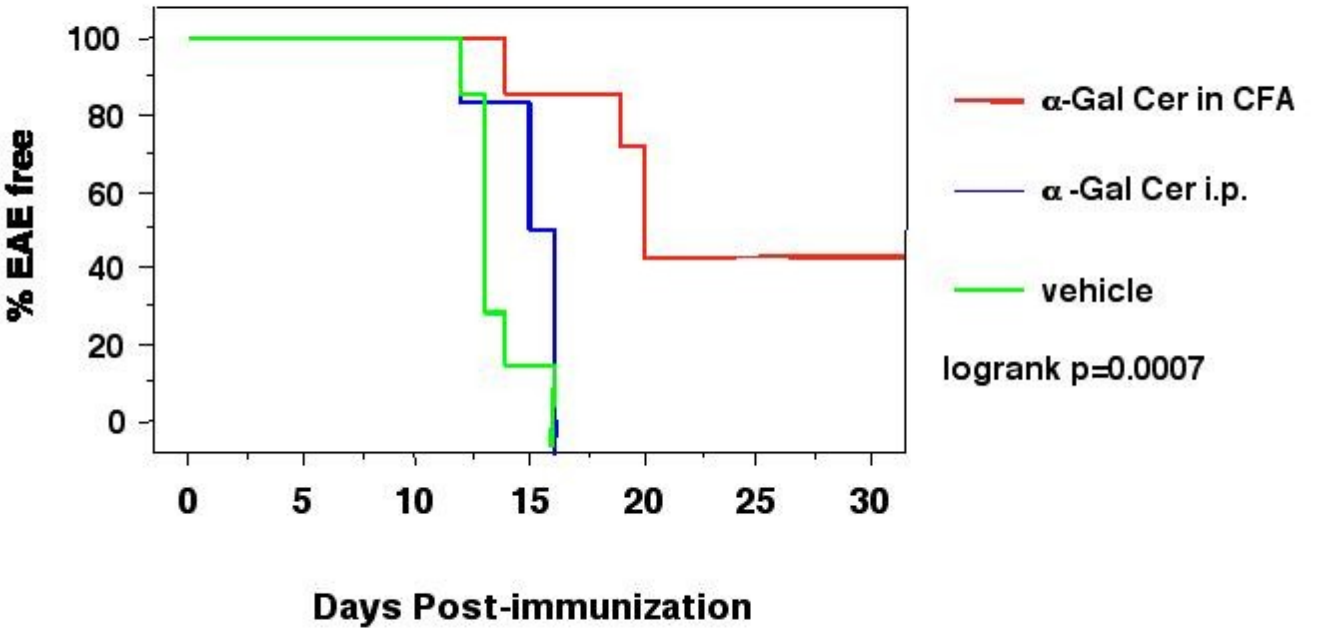
Activation of inv. NKT cells by α-Gal Cer:

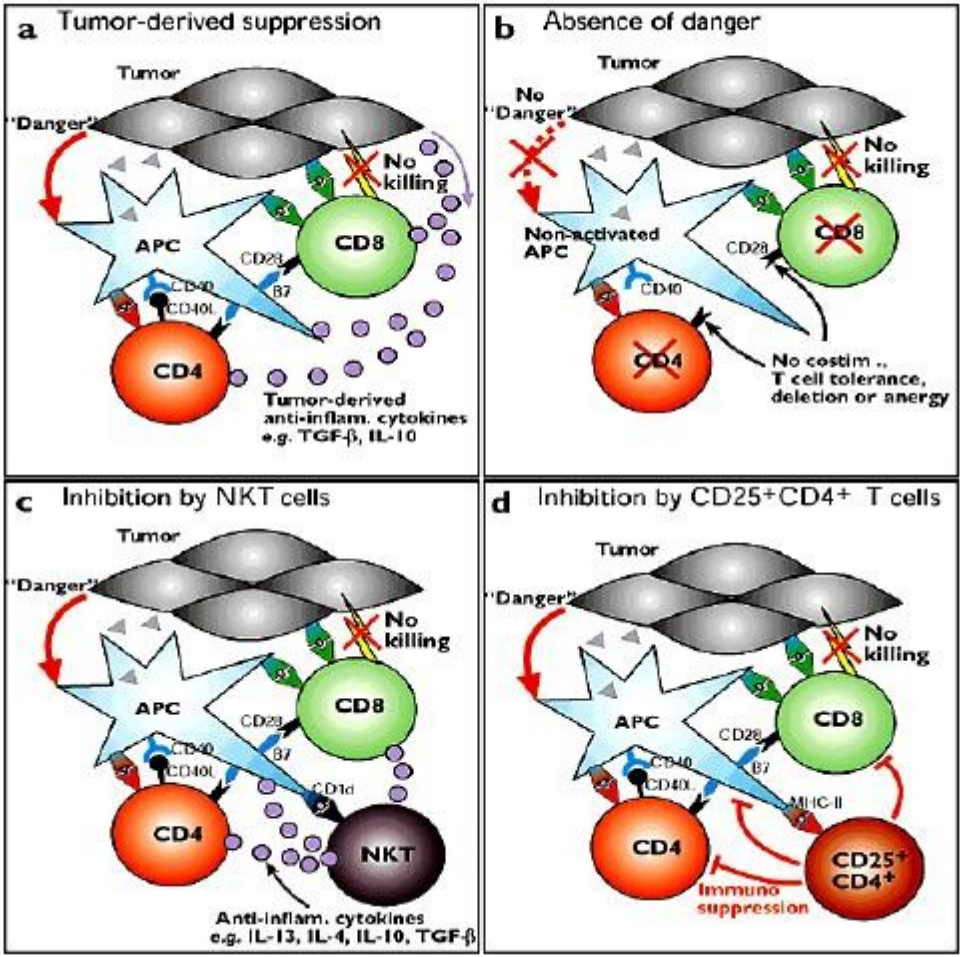
Suppresses/delays type I diabetes

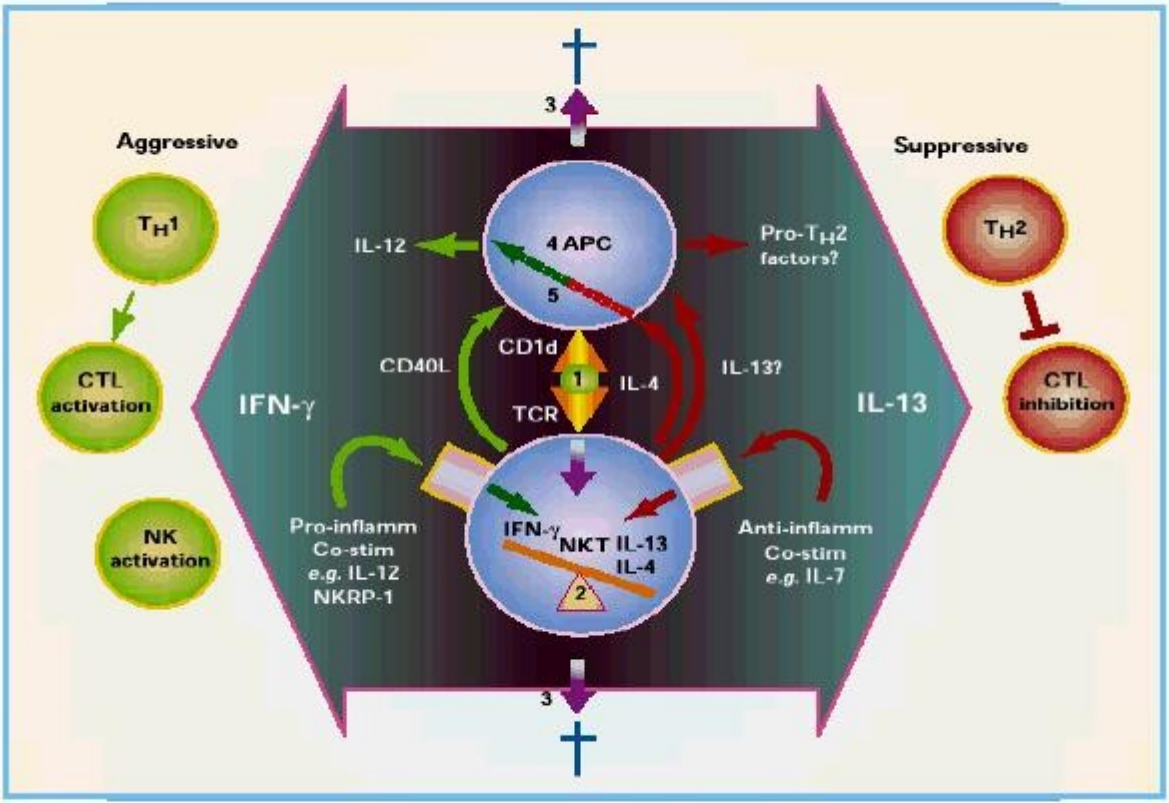
Suppresses/delays EAE

Le cellule NKT possono influenzare l'induzione della risposta immune




% EAE free
100
80
60
40
20
0
0
5
10
15
20
25
30
Days Post-immunization
α-Gal Cer in CFA
α -Gal Cer i.p.
vehicle
logrank p=0.0007

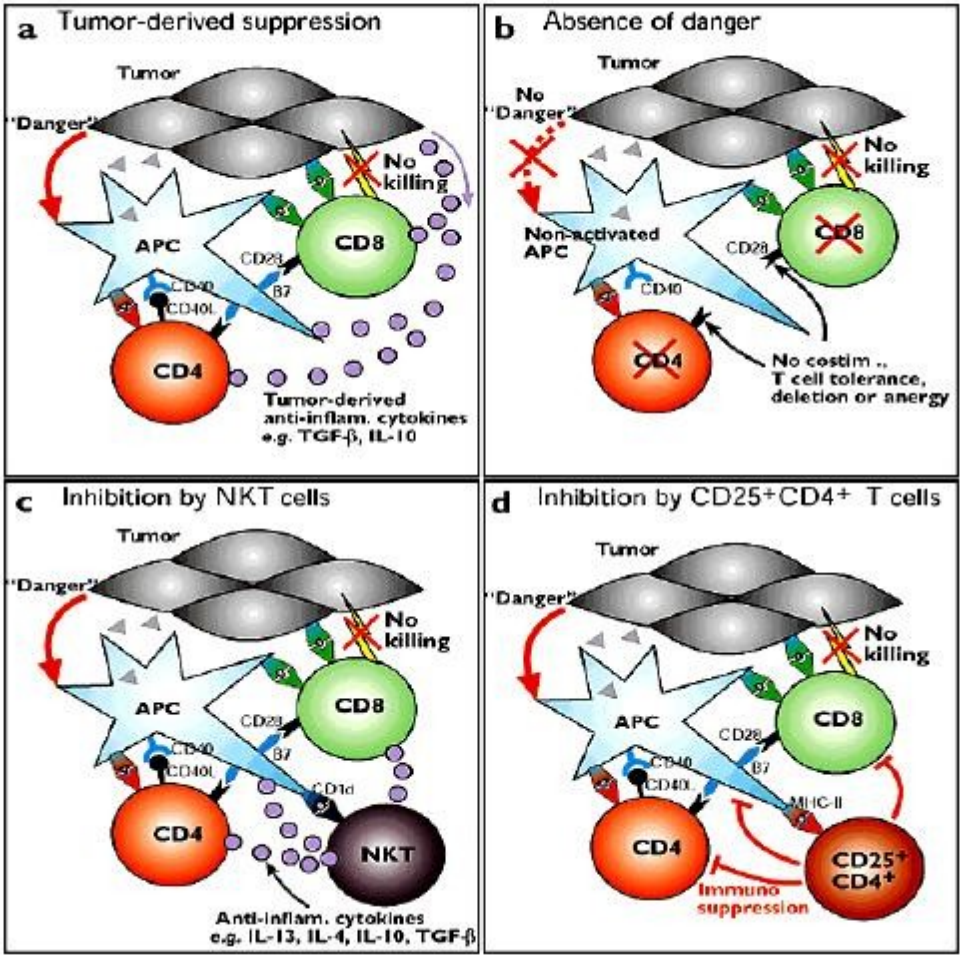

a Tumor-derived suppression
Tumor
"Danger"
No killing
APC
CD8
CD28
B7
CD40
CD40l
CD4
Tumor-derived anti-inflam. cytokines e.g. TGF-β, IL-10
b Absence of danger
Tumor
No "Danger"
No killing
Non-activated APC
CD8
CD28
CD40
CD4
No costim .. T cell tolerance, deletion or anergy
c Inhibition by NKT cells
Tumor
"Danger"
No killing
APC
CD8
CD28
B7
CD40
CD40l
CD1d
CD4
NKT
Anti-inflam. cytokines e.g. IL-13, IL-4, IL-10, TGF-β
d Inhibition by CD25+CD4+ T cells
Tumor
"Danger"
No killing
APC
CD8
CD28
B7
CD40
CD40l
MHC-II
CD4
CD25+ CD4+
Immuno suppression


Aggressive
Suppressive
T_H1
T_H2
CTL activation
CTL inhibition
NK activation
IL-12
4 APC
Pro-T_H2 factors?
5
CD40L
CD1d
1
IL-4
TCR
IL-13?
IFN-γ
IL-13
3
IFN-γ
NKT
IL-13
IL-4
2
Pro-inflamm Co-stim e.g. IL-12 NKRP-1
Anti-inflamm Co-stim e.g. IL-7
3

Le cellule NKT hanno caratteristiche tipiche sia dell'immunità innata che adattativa

Hanno funzione regolatoria, producendo citochine pro- ed anti- infiammatorie

La loro manipolazione è possibile, e potrebbe avere interessanti risvolti futuri in terapia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Tumor
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Tumor
No "Danger"
No killing
Non-activated APC
CD8
CD28
CD40
CD4
No costim .. T cell tolerance, deletion or anergy
c Inhibition by NKT cells
Tumor
"Danger"
No killing
APC
CD8
CD28
B7
CD40
CD40l
CD1d
CD4
NKT
Anti-inflam. cytokines e.g. IL-13, IL-4, IL-10, TGF-β
d Inhibition by CD25+CD4+ T cells
Tumor
"Danger"
No killing
APC
CD8
CD28
B7
CD40
CD40l
MHC-II
CD4
CD25+ CD4+
Immuno suppression