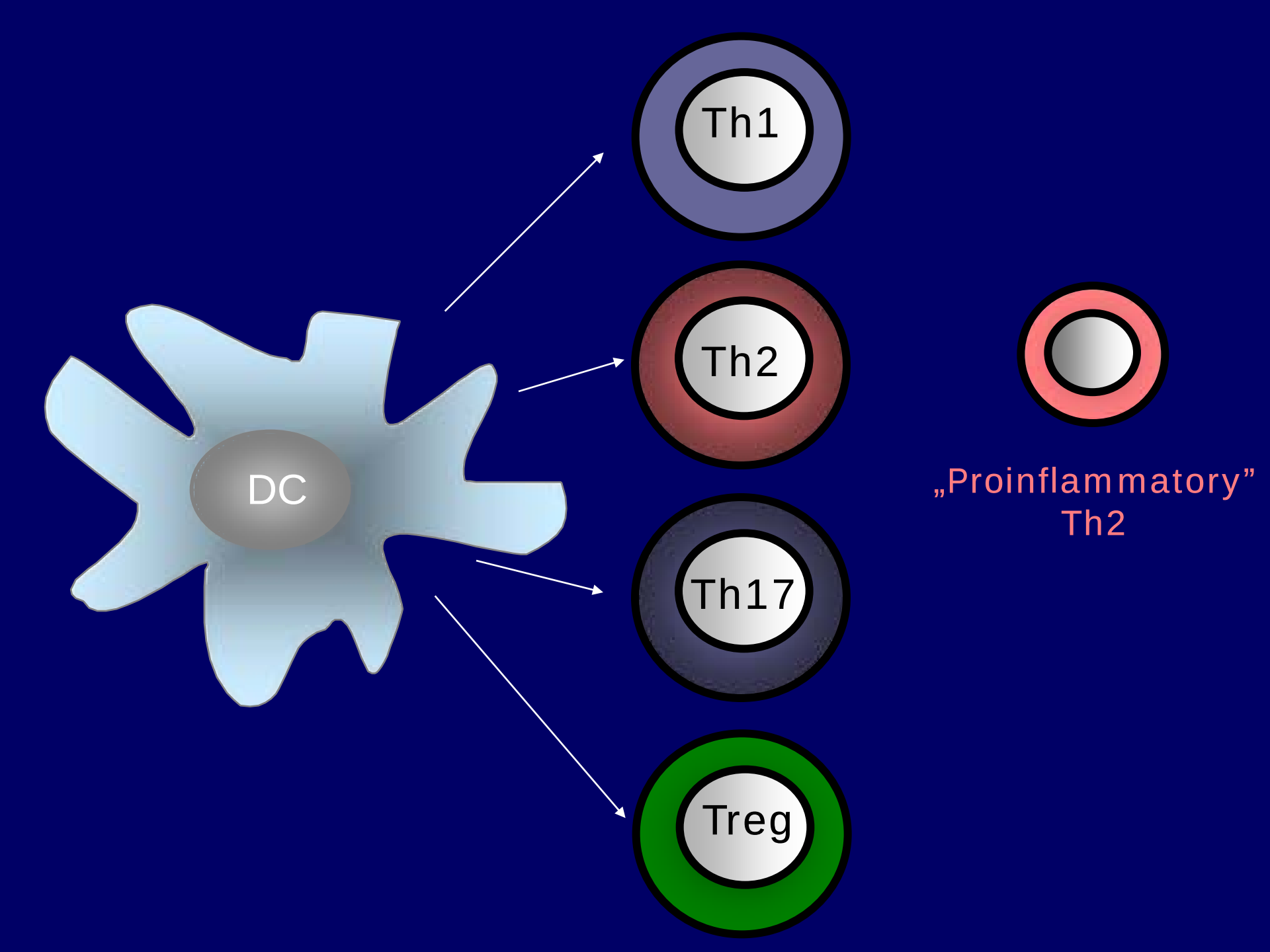
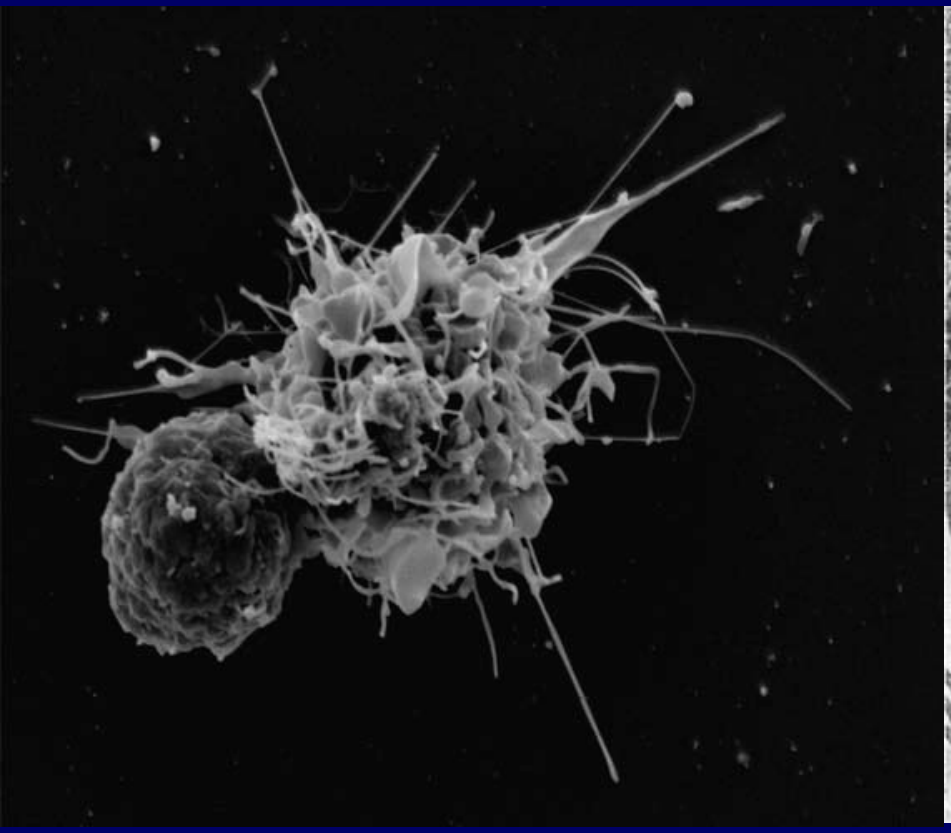
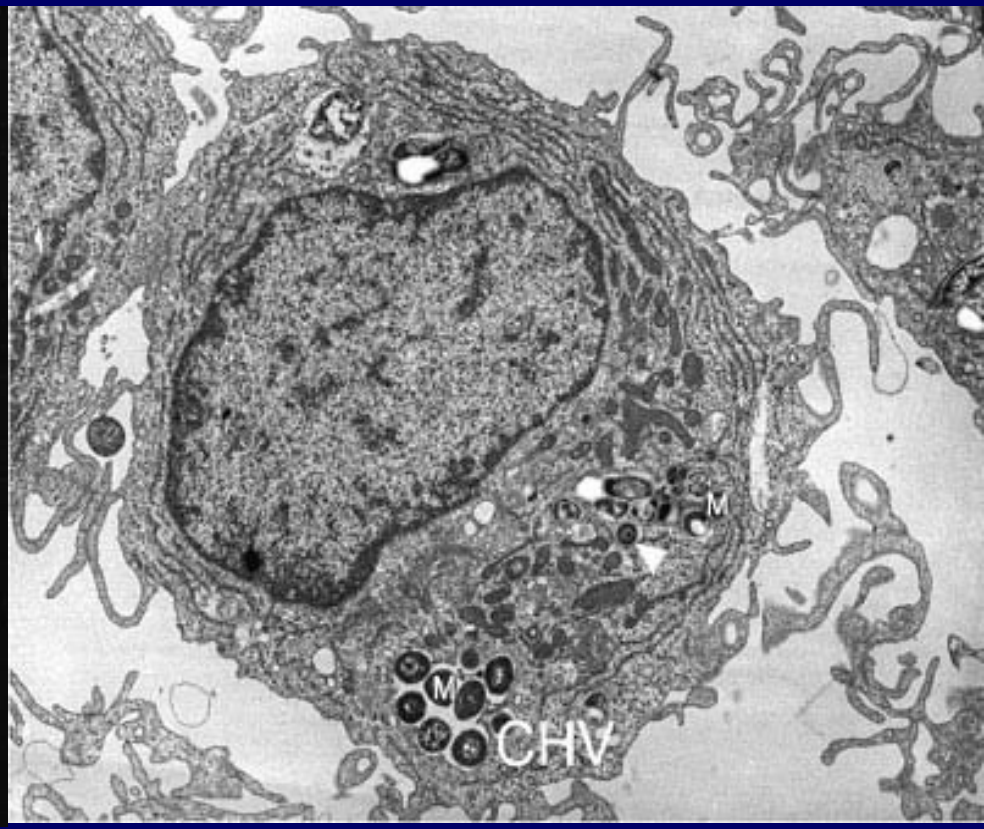
Regulatory T cells
Tregs
in antitumor response

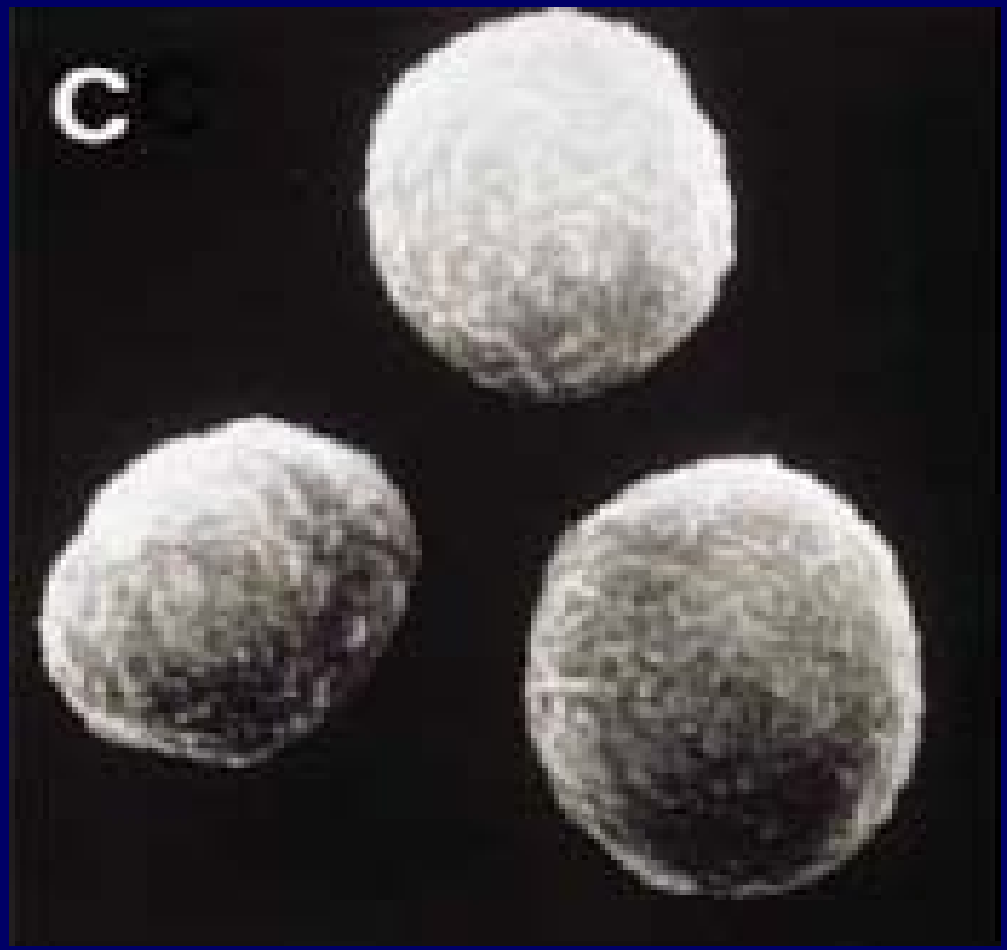

Th1
Th2
DC
Th17
Treg
„Proinflammatory”
Th2

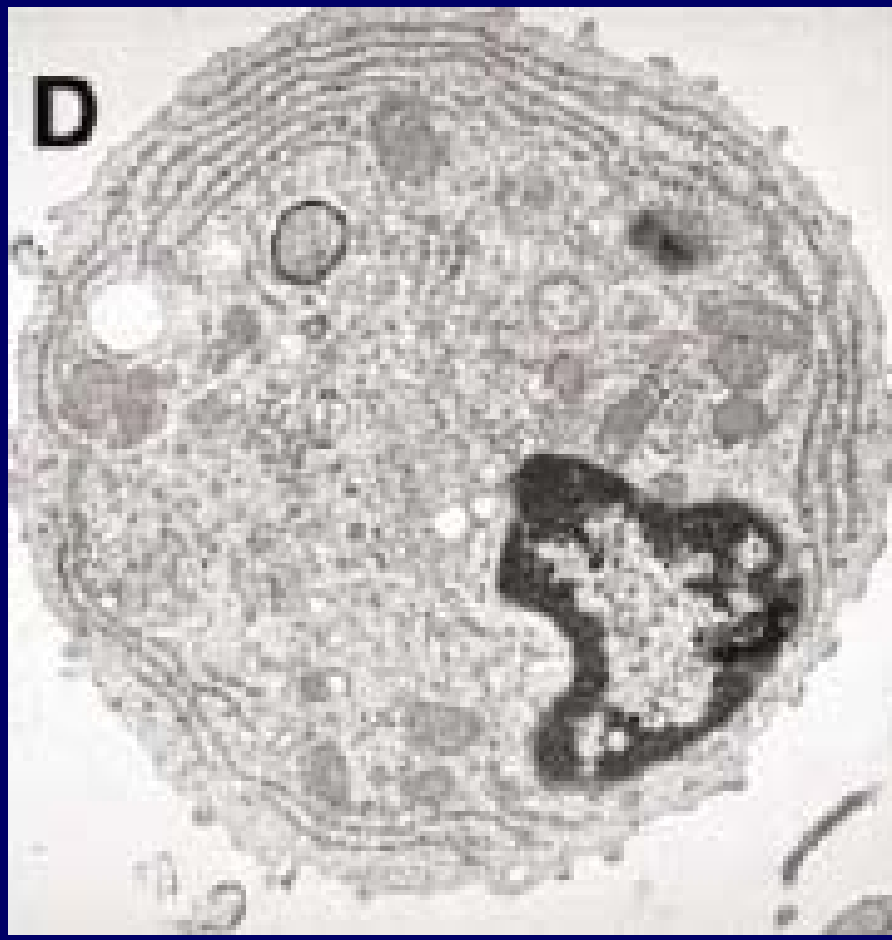
Mieloid DC





Plasmocytoid DC

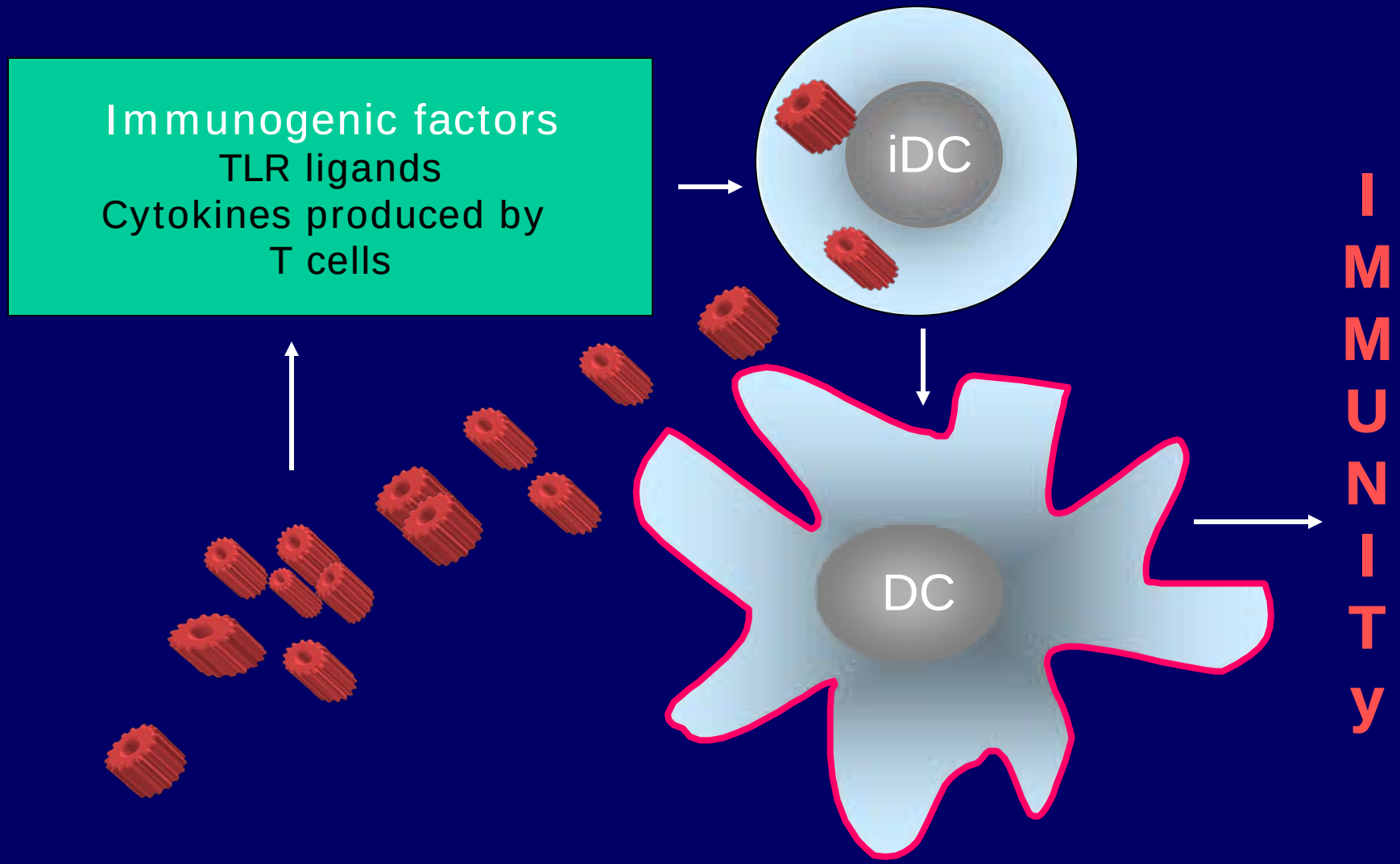


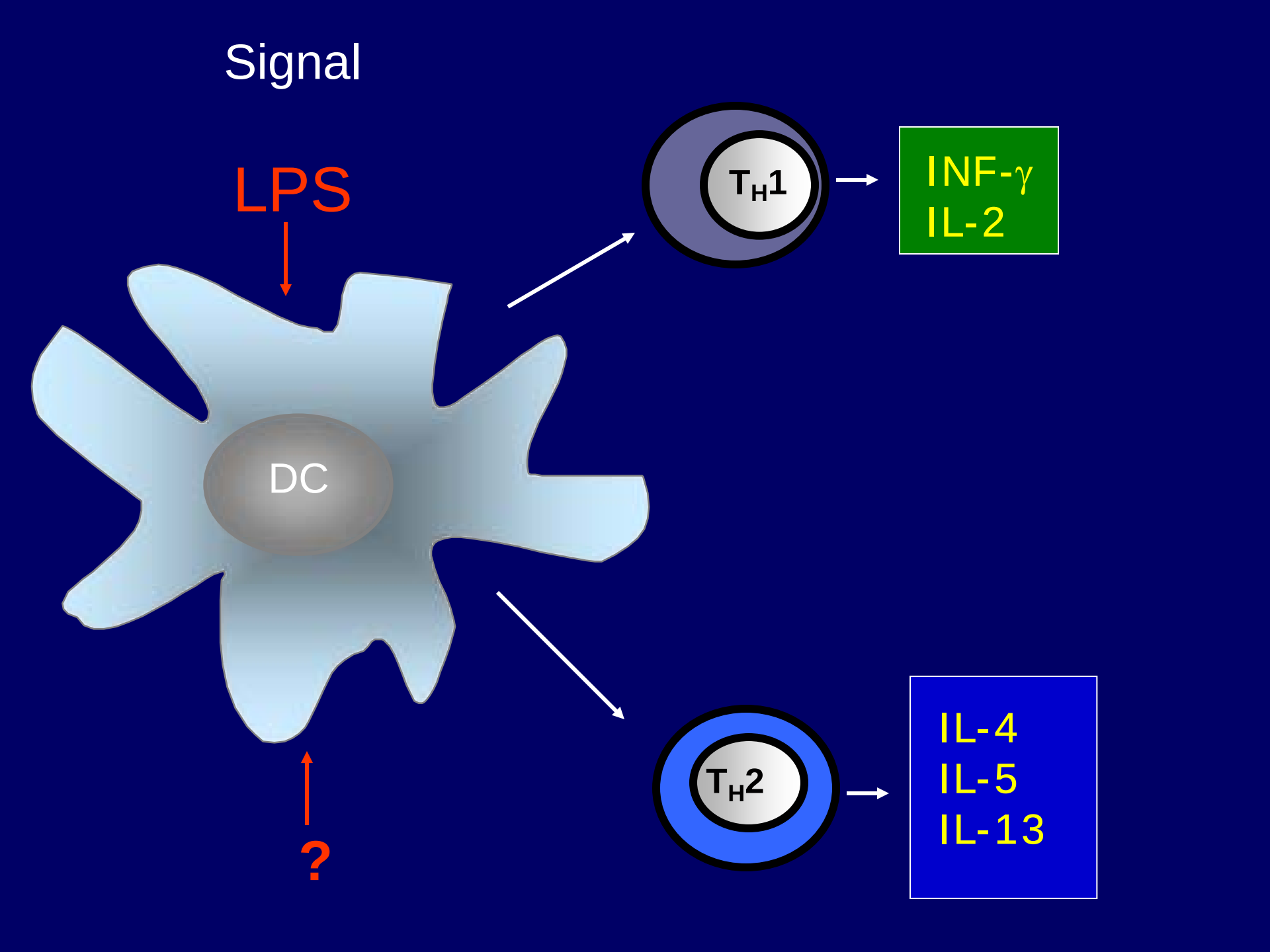


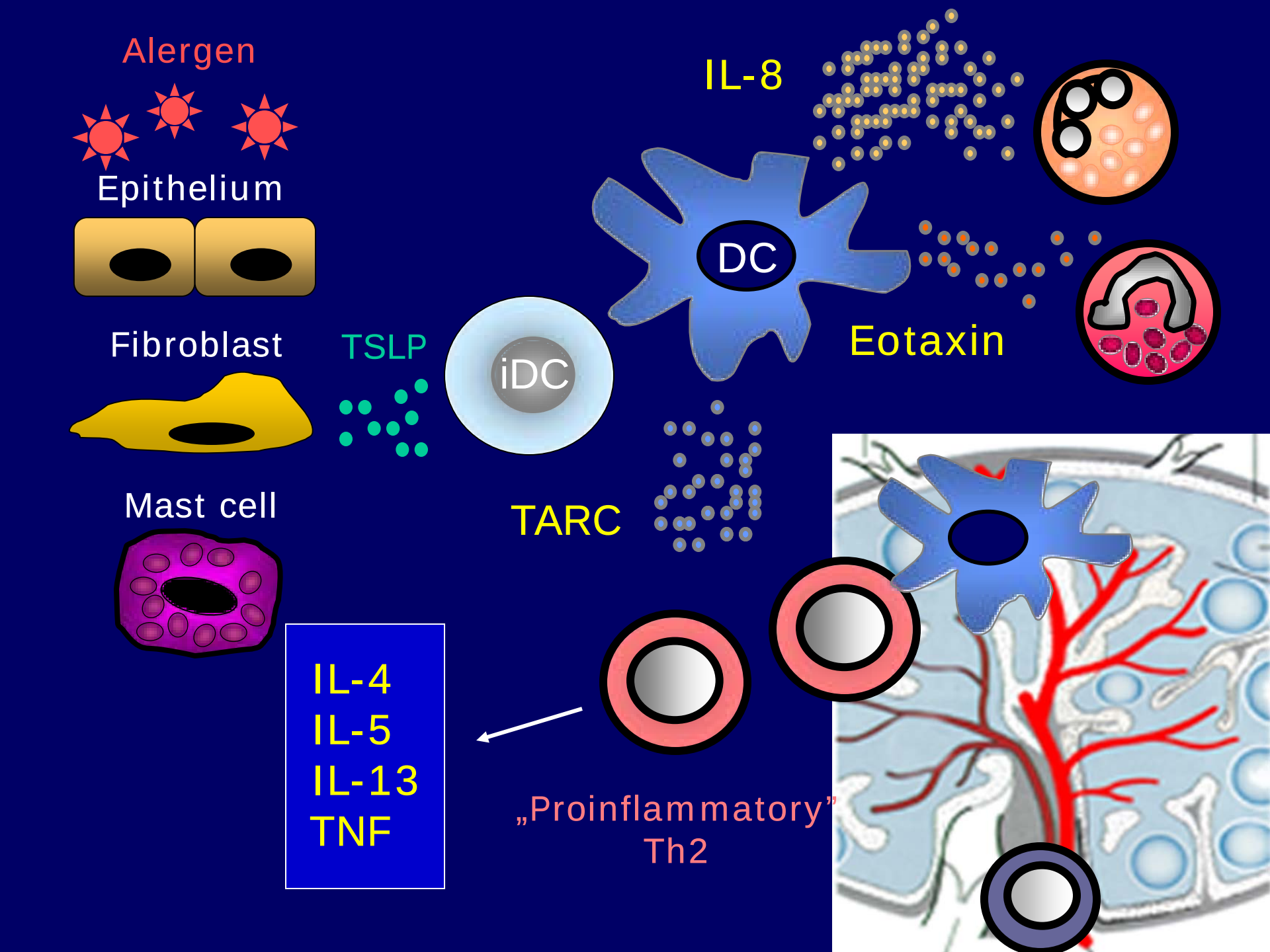
Human DC

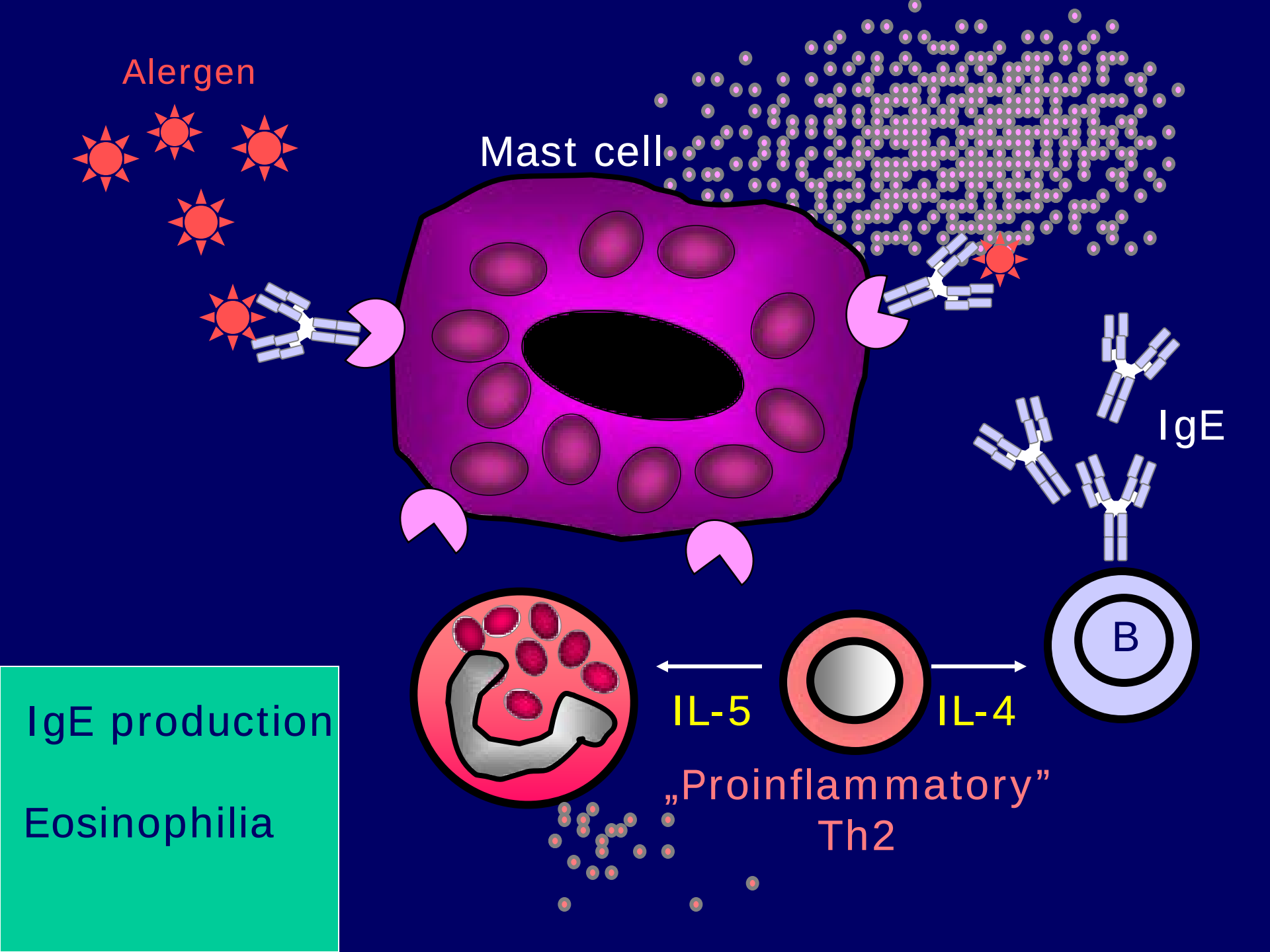
Phenotype	pDC/IPC	Monocytes	CD11c$^+$ immature DC
Myeloid marker			
CD11b	−	+	+
CD11c	−	+	+
CD13	−	+	+
CD14	−	+	−
CD33	−	+	+
Lymphoid marker			
Pre-Ta	+	−	−
Ig1-like 14.1	+	−	−
Spi-B	+	−	−
Pattern recognition receptors			
TLR1	+	++	+
TLR2	−	++	+
TLR3	−	−	++
TLR4	−	++	+
TLR5	−	+	+
TLR6	+	+	+
TLR7	++	−	−
TLR8	−	++	++
TLR9	++	−	−
TLR10	+	−	+
Mannose R	−	+/−	+/−
BDCA2	+	−	−
CD1a, b, c, d	−	+/−	+/−
Other differentially expressed antigens			
CD4	++	+	+
CD45RA	+	−	−
CD45RO	−	+	+
IL-3R	+++	+	+
GM-CSFR	+	++	++
Function			
IFN-α/β production	++++	+	+
IL-12 production	−	++	++
phagocytosis	−	++	++

DC in immunity




Signal
LPS
DC
?
T_H1
INF-γ
IL-2
T_H2
IL-4
IL-5
IL-13

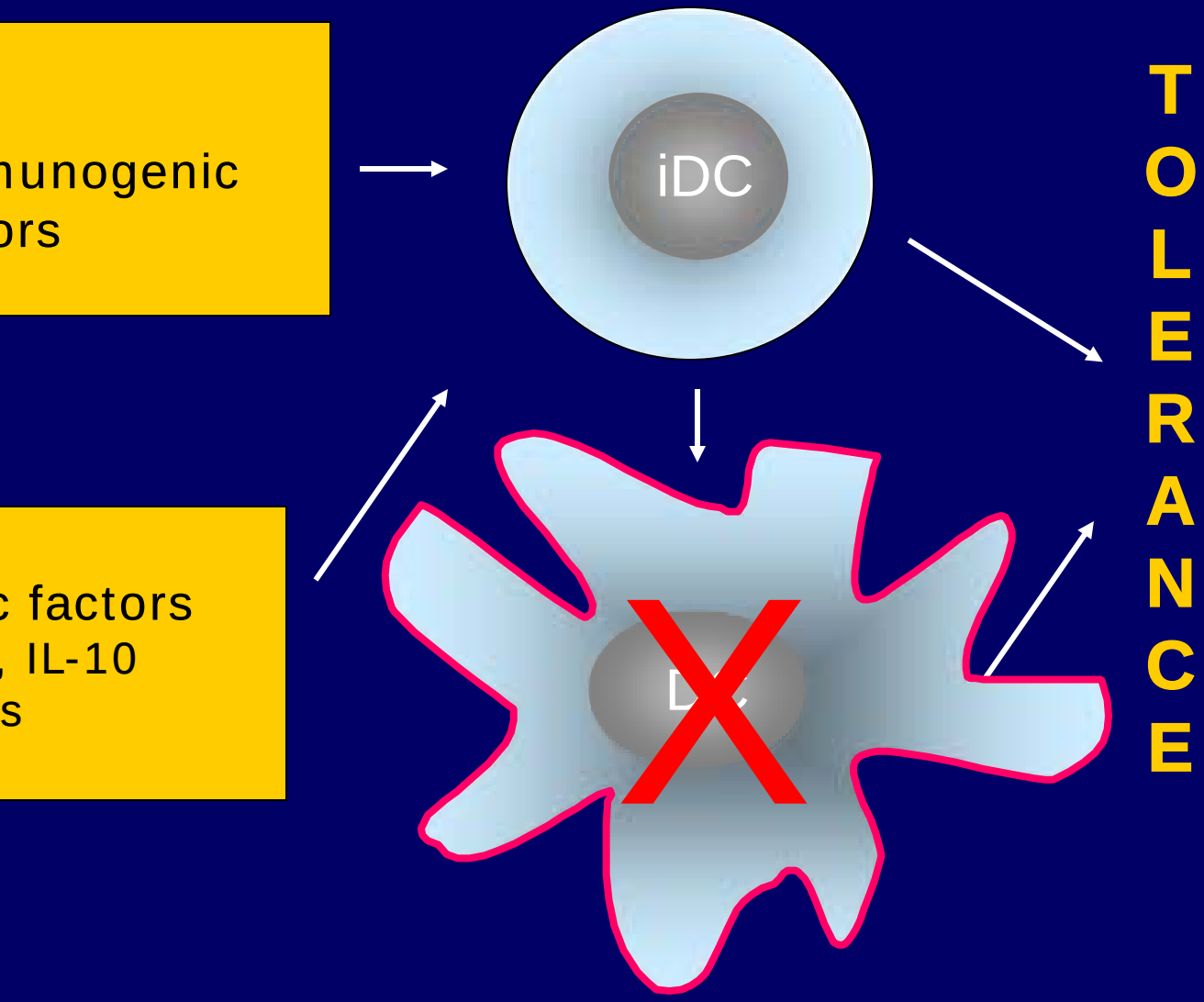

Alergen
Epithelium
Fibroblast
Mast cell
TSLP
iDC
DC
IL-8
Eotaxin
TARC
IL-4
IL-5
IL-13
TNF
„Proinflammatory"
Th2


Alergen
Mast cell
IgE
B
IL-5
IL-4
„Proinflammatory”
Th2
IgE production
Eosinophilia

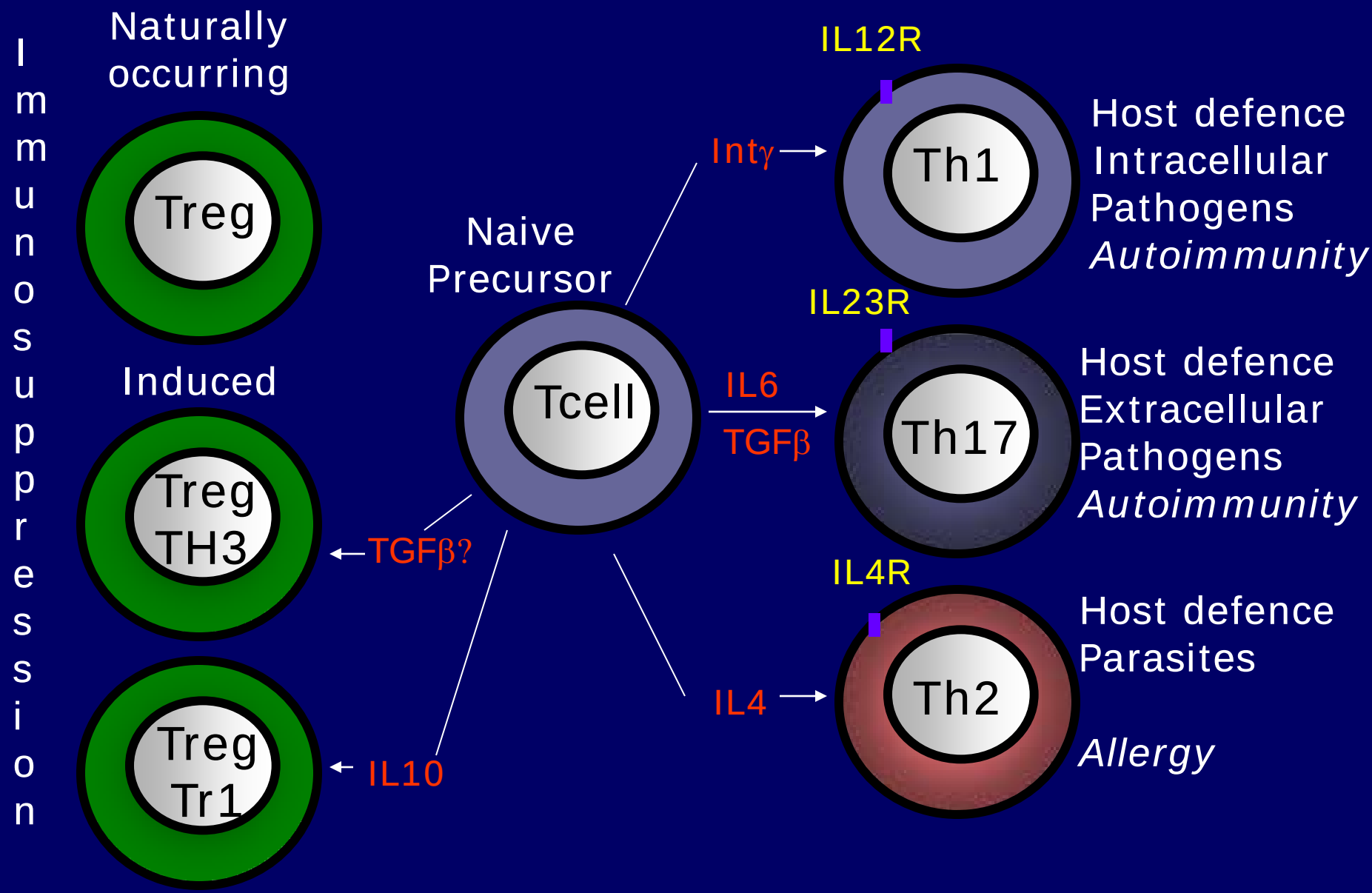
DC in tolerance

Lack of immunogenic factors

Tolerogenic factors
TGF-beta, IL-10
Tregs



Generation of CD4 T cell lineages



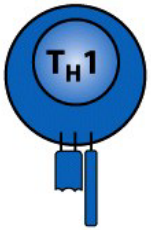
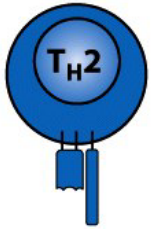
	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	CD4 regulatory T cells (various types)
Types of effector T cell					
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	Extracellular bacteria (e.g. *Salmonella enterica*)	

Figure 8-1 Immunobiology, 7ed. (© Garland Science 2008)

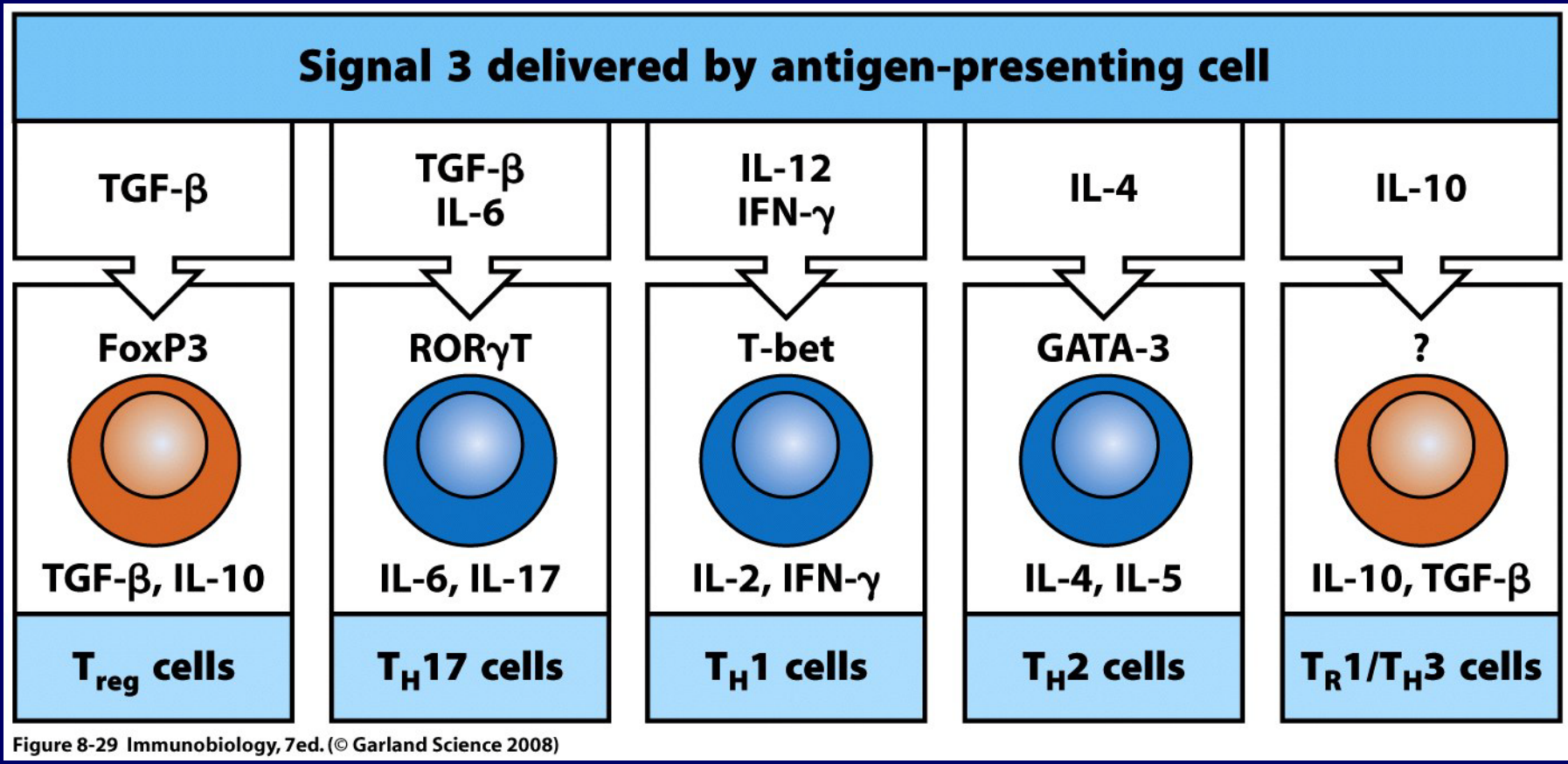
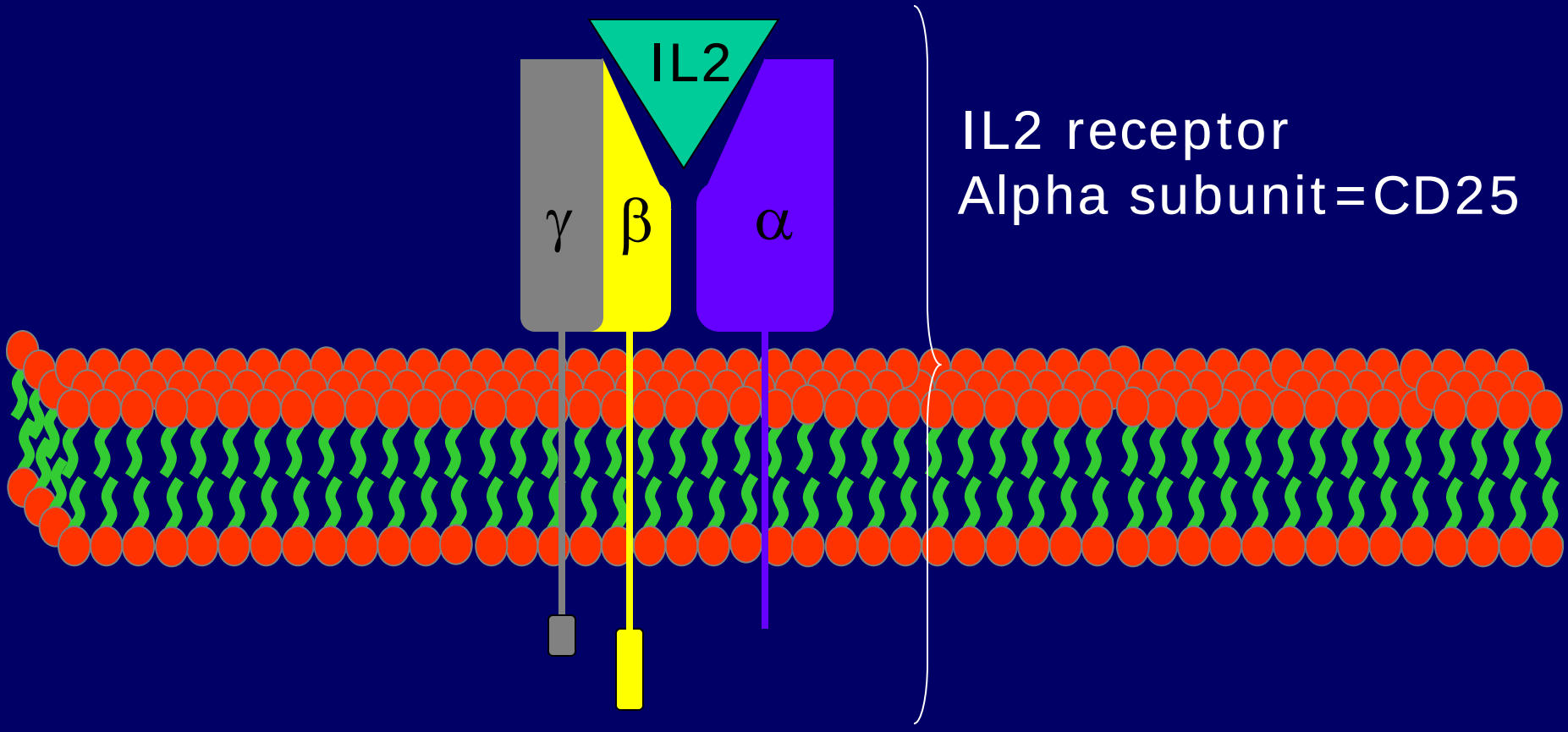


Figure 8-29 Immunobiology, 7ed. (© Garland Science 2008)

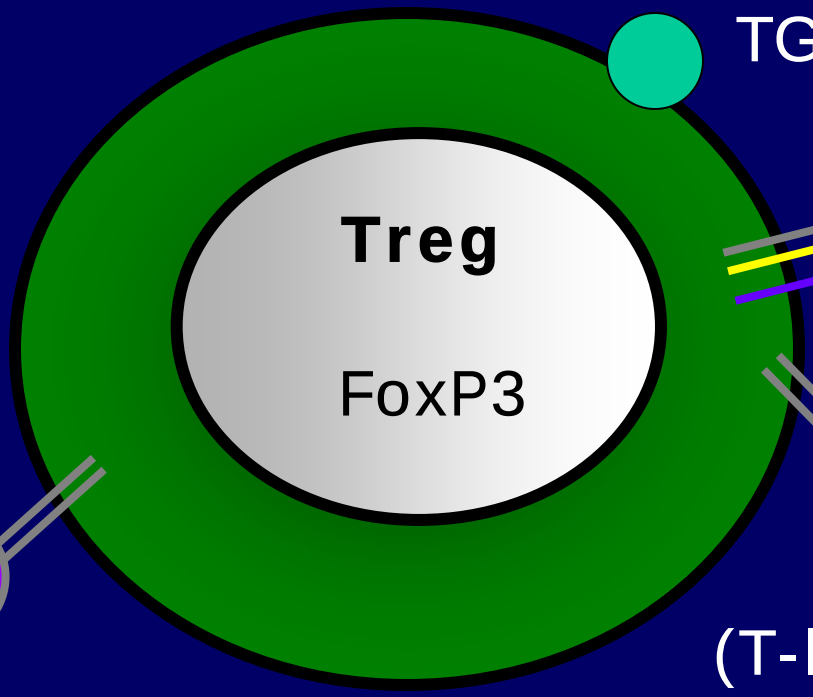
High-affinity IL-2 receptors are 3-chain structures



Tregs-few facts

- Tregs are a distinct lymphocyte lineage endowed with regulatory properties
- IL2 is crucial for Tregs homeostasis and co-stimulatory molecules CD80 and CD40 are required for peripheral Tregs maintenance
- Naturally occurring Tregs are generated in thymus
- Induced Tregs probably can be generated in the periphery from naïve T cells
- Tregs account for 5-10% of the circulating CD4 T cell population

Phenotype of Tregs



TGFβ

(80% of Tregs)

IL2 receptor
CD25

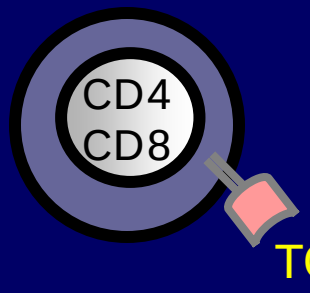
CTLA-4 (CD152)
(T-lymphocyte-associated
protein 4)

GITR
Glucocorticoid-induced
TNF receptor

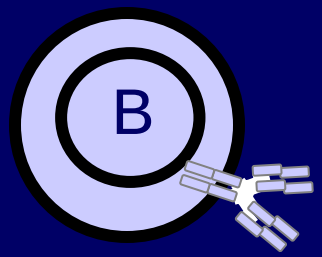
Transcription factor forkhead box P3 (Foxp3)

- A disease-causative gene in Scurfy mice, which spontaneously develop severe autoimmunity/inflammation
- The key controlling factor in a development and function of natural Tregs
- Foxp3 up-regulates Tregs-associated molecules (CD25, CTLA-4, GITR) and down-regulates IL2, IL4 and Intγ
- Expression of Foxp3 in naïve T cells is sufficient to convert them into phenotypically and functionally Treg-like cells

Tregs inhibit:

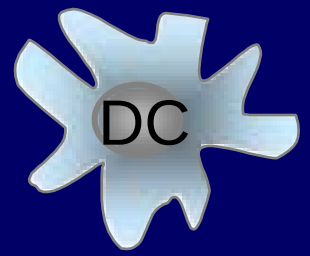


Activation, proliferation, cytokine formation



Proliferation, Ig production, class switching

Cytotoxic function

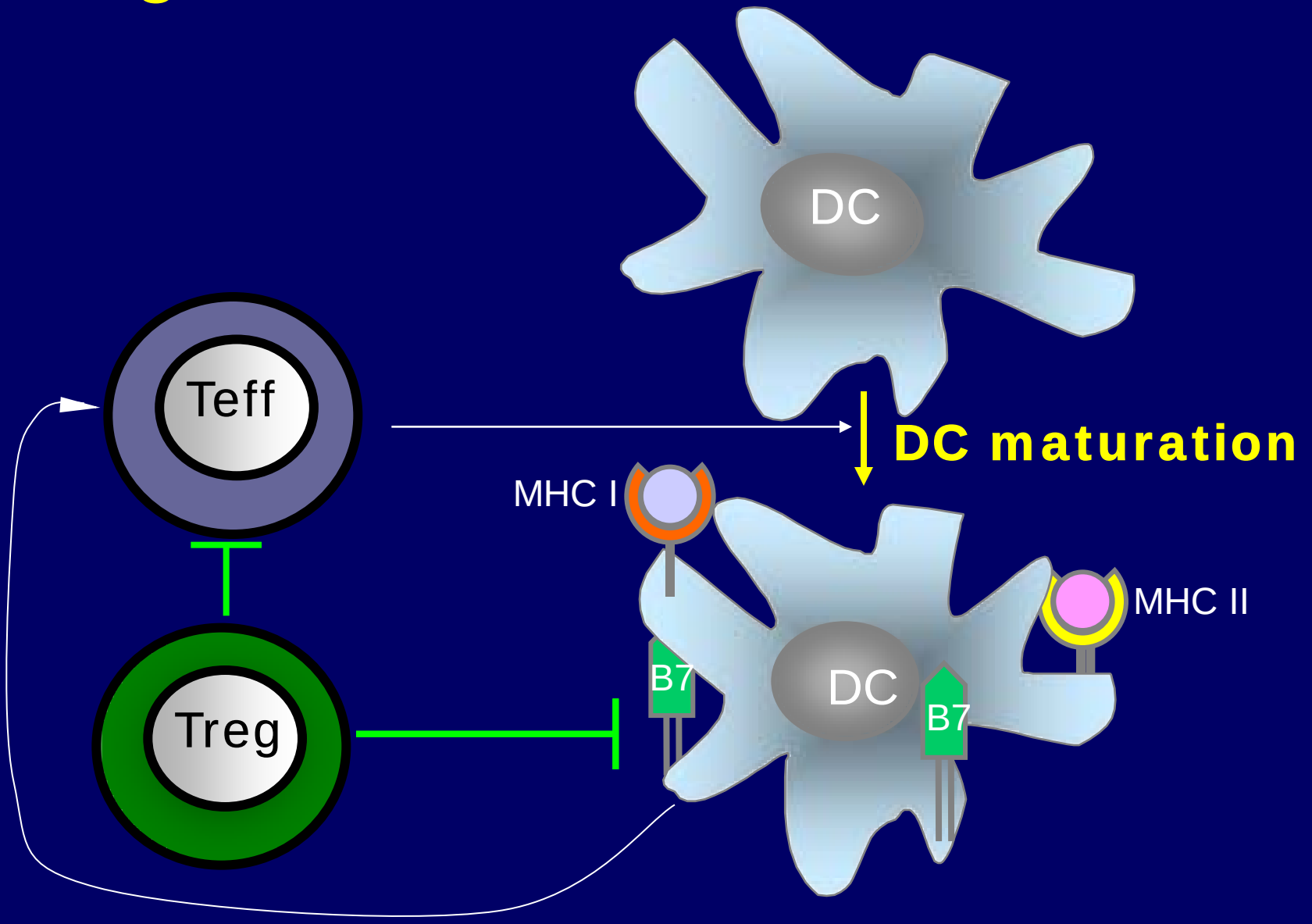


Function and maturation

Treg cell depletion induces:

- Polyclonal T cell activation
- Systemic DC expansion and maturation

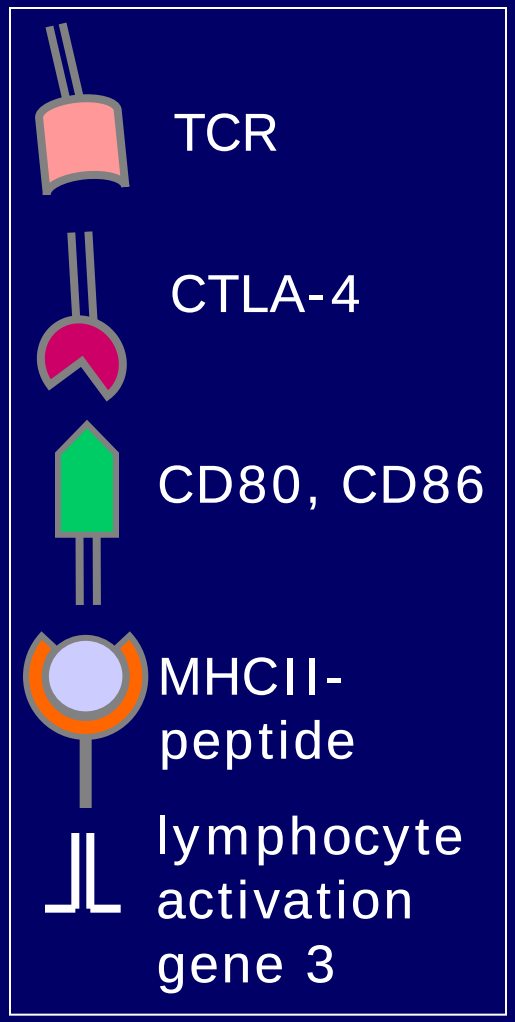
Treg-mediated control of DC

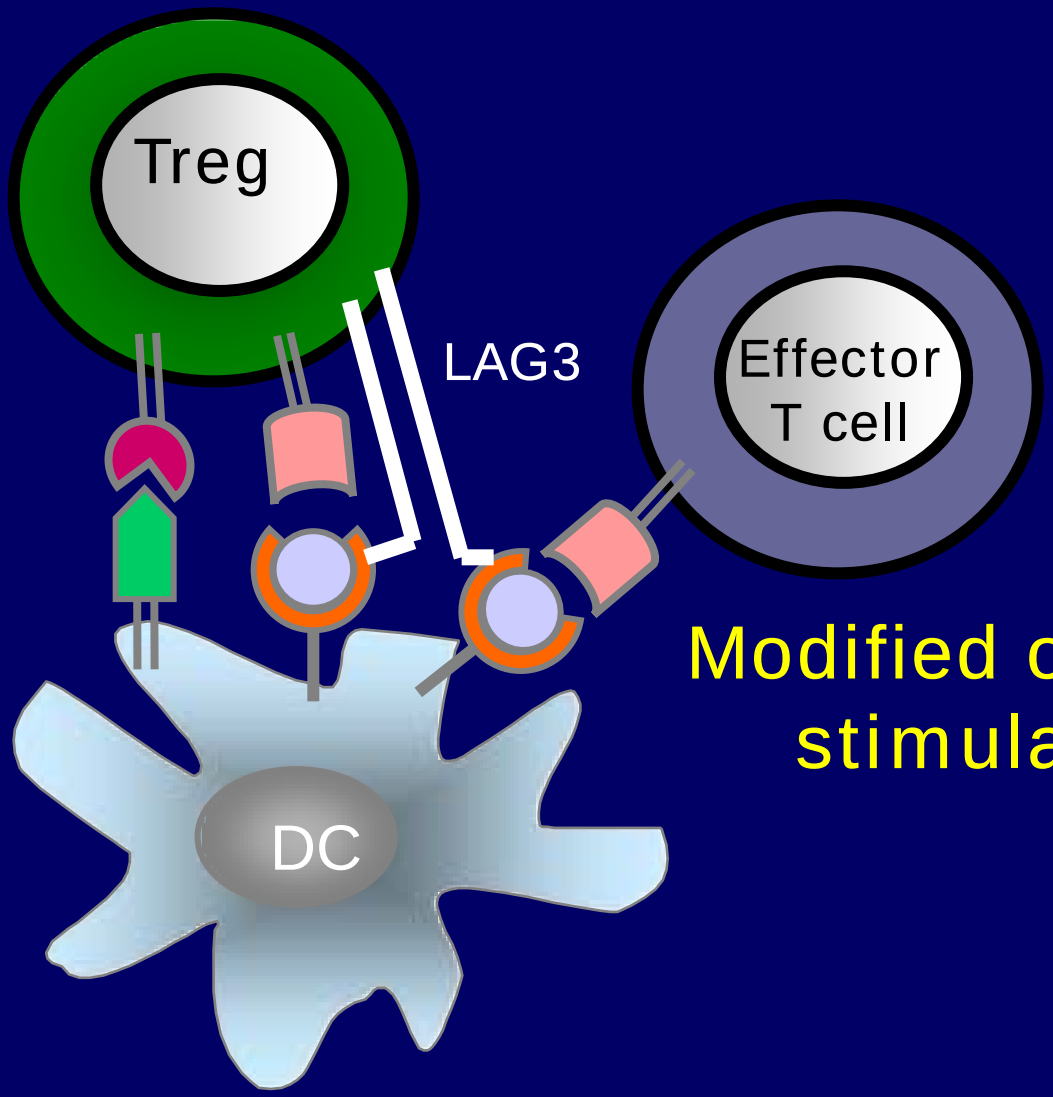


Critical role of CTLA-4 in Treg-mediated supression

- Tregs (Foxp3+CD25+CD4+) constitutively express high levels of CTLA-4, Foxp3 upregulates CTLA-4 expression
- Blockade of CTLA-4 produces organ-specific autoimmunity (IBD, diabetes)
- Mice lacking CTLA-4 in Treg cells, similarily to Foxp3-deficient mice develop lymphoproliferation, autoimmune diseases and IgE hyperproduction

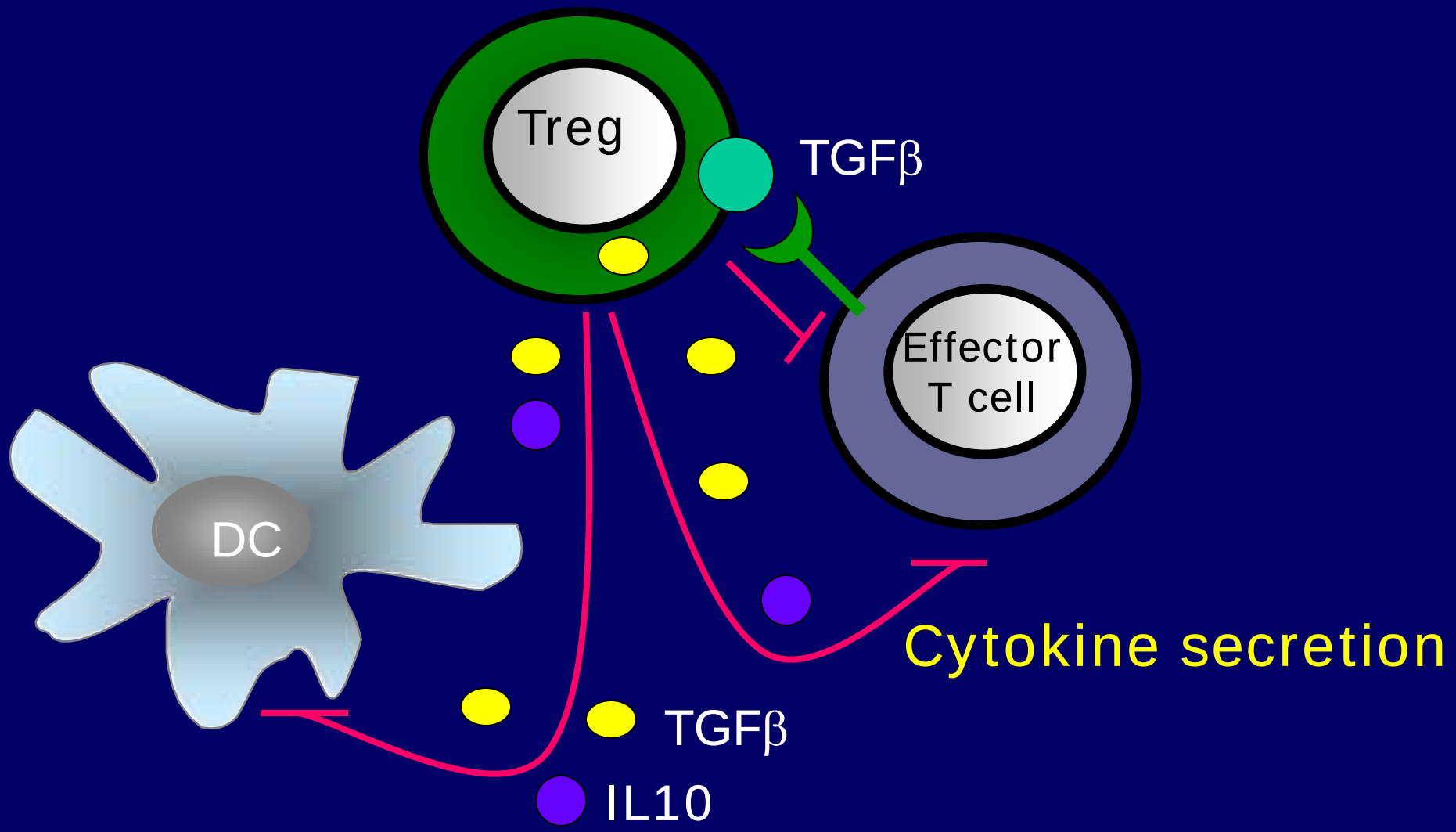
Potential mechanisms of Tregs-mediated suppression



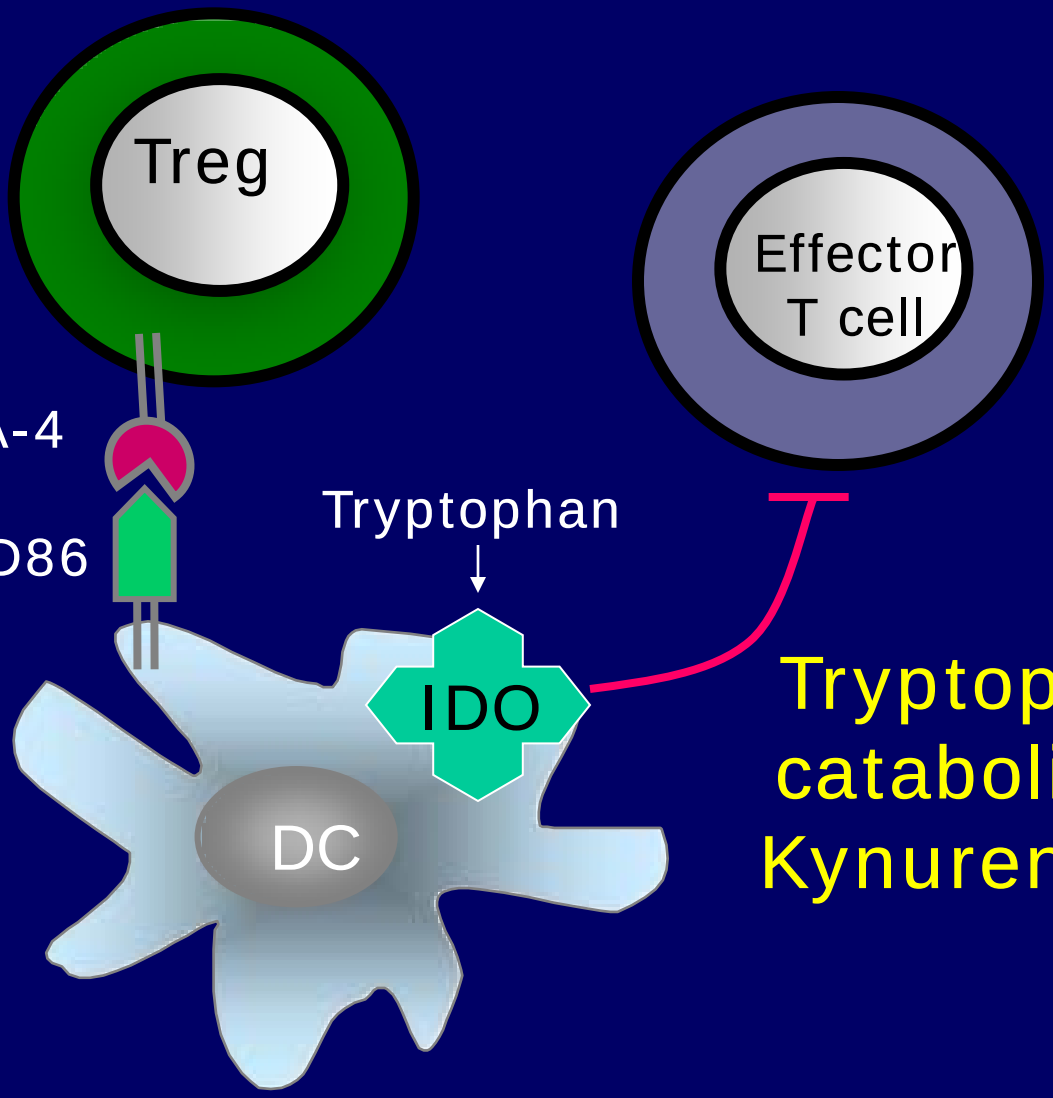


Modified or week stimulation

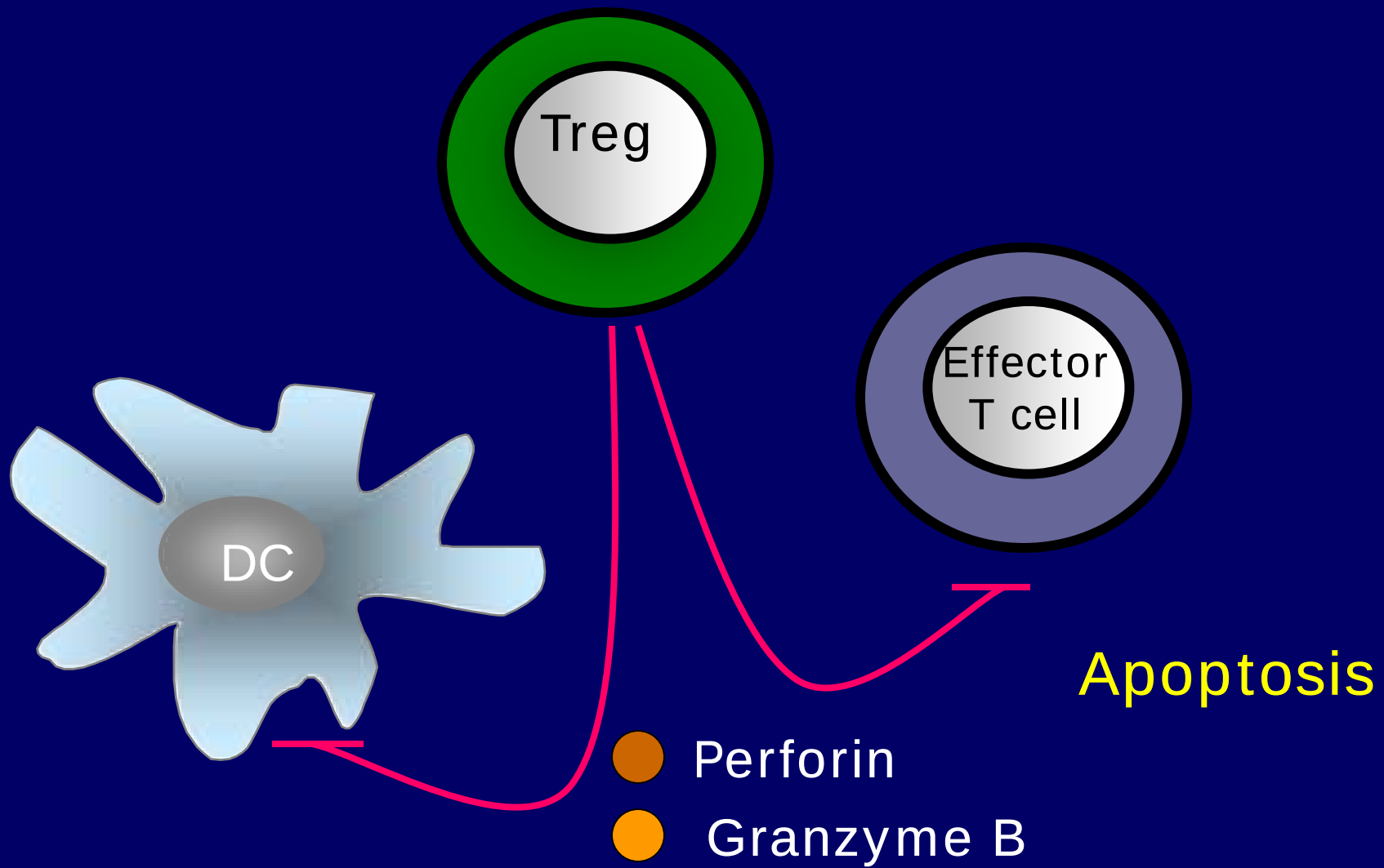
Potential mechanisms of Tregs-mediated suppression



Potential mechanisms of Tregs-mediated suppression



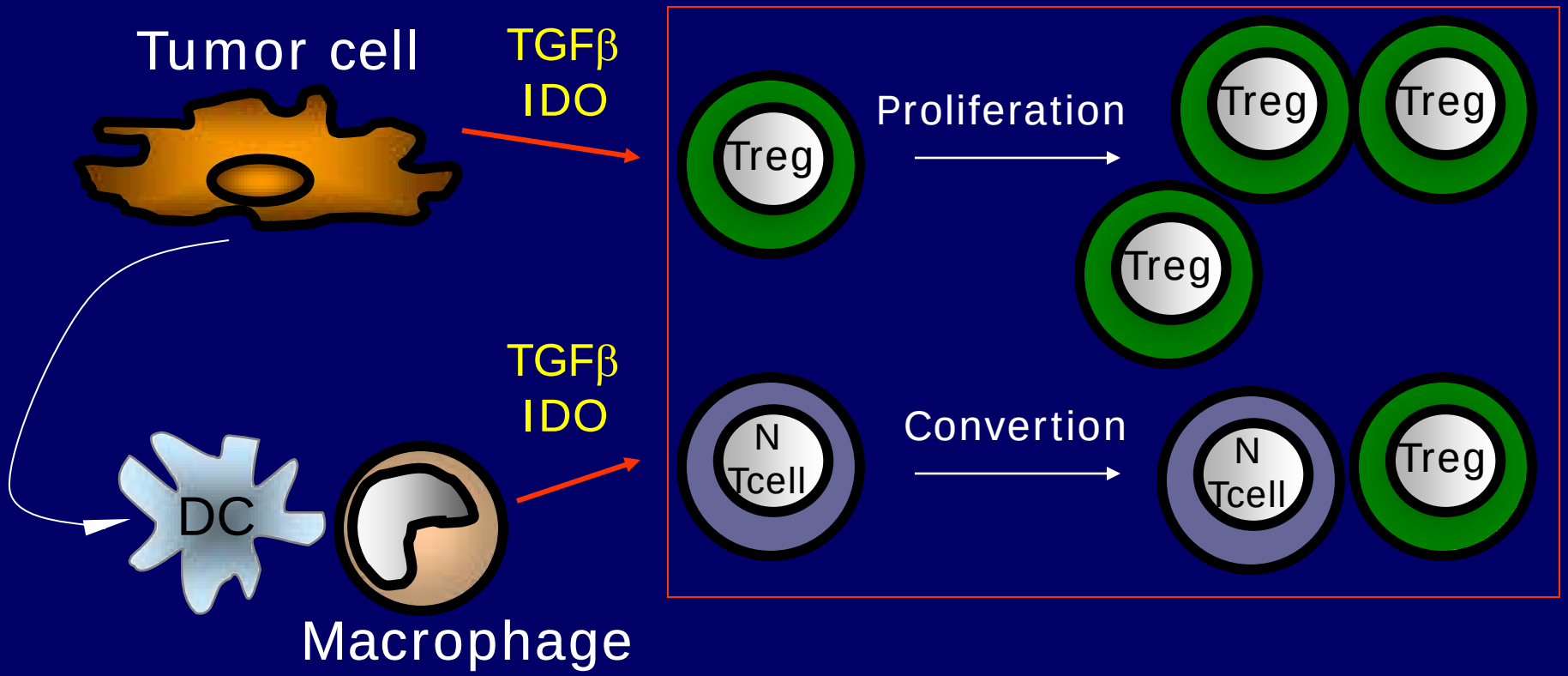
Potential mechanisms of Tregs-mediated suppression



Tumors perturb Tregs homeostasis

- During tumor progression, the initial immunity is finally subverted by CD4 T cell-mediated immune suppression, suggesting that effector and suppressor subpopulations might be functionally predominant at different stages of tumor progression
- Suppression of immunity occurs when Tregs outnumber effector T cells
- The increase in Tregs is not unlimited and does not exceed 50% of the CD4 population
- Tregs accumulation and compartmentalization can vary among different cancers

Tregs in tumor immunity



Tregs functional inactivation