

# Neuroinflammationens ABC

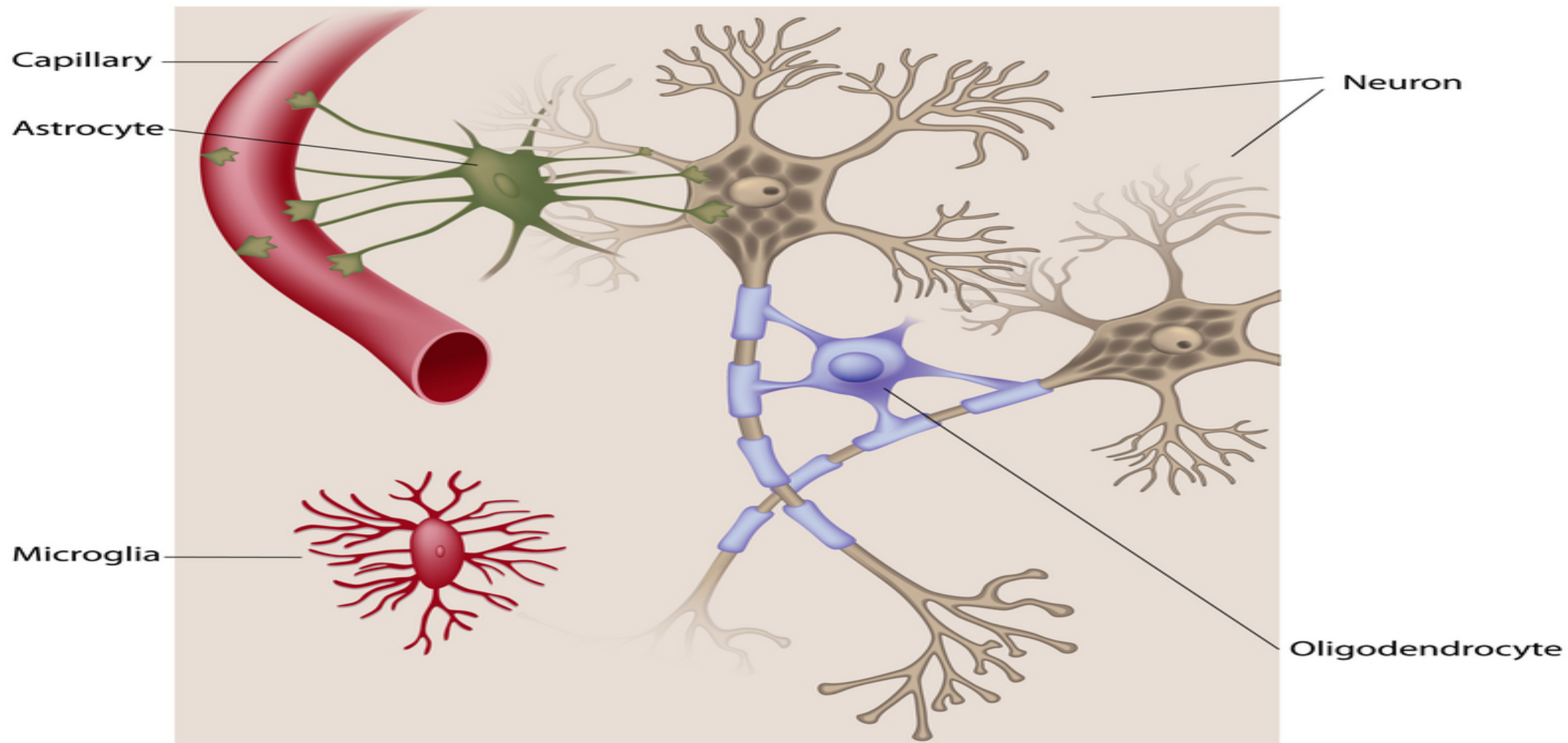
*Alex Karlsson-Parra, MD, PhD*

*Adjungerad Professor*

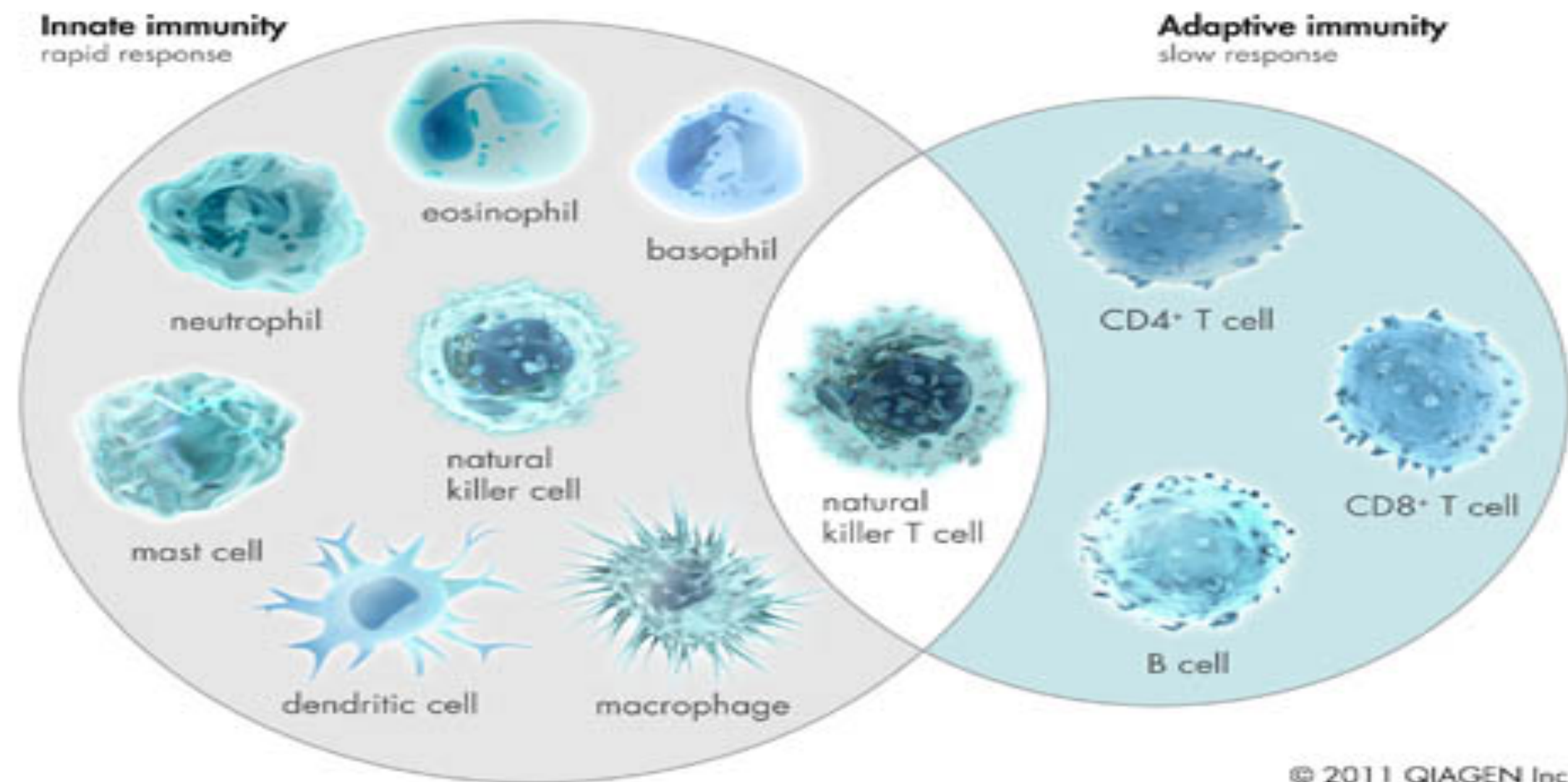
*Institutionen för Immunologi, Genetik och Patologi*

*Uppsala Universitet*

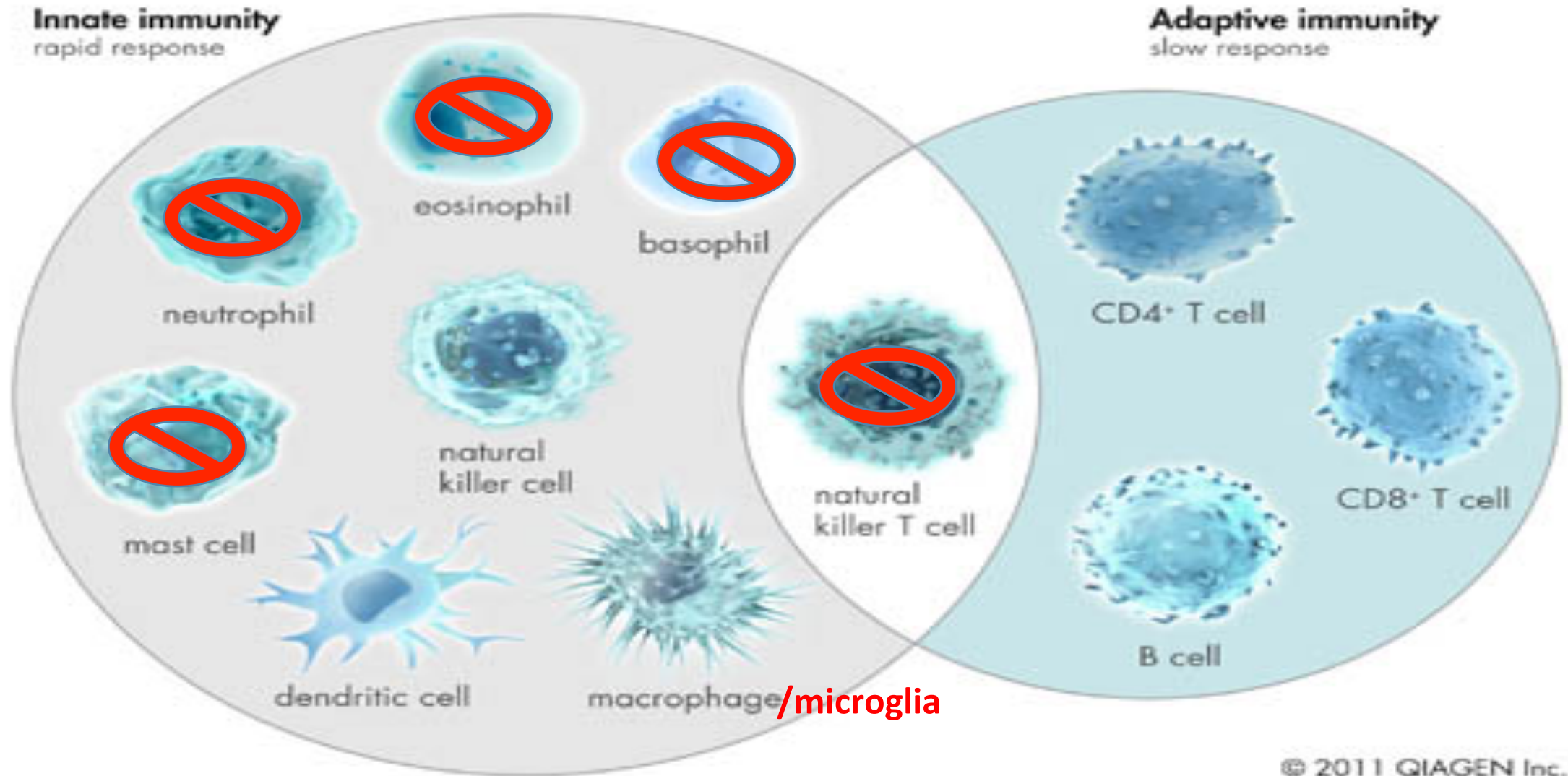
# Cells of the Central Nervous System



# Innate and adaptive immunity



# Innate and adaptive immunity in neuroinflammation





# Alzheimer vs Multiple Sclerosis

- Alzheimer: Dysregulated innate immune response
- Multiple Sclerosis: Dysregulated adaptive immune response

# Alzheimer

## Amyloid cascade hypothesis

Missense mutations in *APP*, *PS1*, or *PS2* genes



Increased Aβ<sub>42</sub> production and accumulation



Aβ<sub>42</sub> oligomerization and deposition  
as diffuse plaques



Subtle effects of Aβ oligomers on synapses



Microglial and astrocytic activation  
(complement factors, cytokines, etc.)



Progressive synaptic and neuritic injury



Altered neuronal ionic homeostasis;  
oxidative injury



Altered kinase/phosphatase activities ➤ tangles



Widespread neuronal/neuritic dysfunction  
and cell death with transmitter deficits



Dementia

Hardy and Selkoe, Science 2002

# Alzheimer – focus on microglia

The normal housekeeping role of microglia

- Assist synapse formation between neurons by secreting growth hormones and thrombospondins
- Constantly scan for dysfunctional synapses, which they are able to eliminate by phagocytosis
- Secretion of brain-derived neurotrophic factor (BDNF), a molecule that is crucial for learning-dependent synapse formation

# Alzheimer – focus on microglia

## Activation of microglia in Alzheimer disease

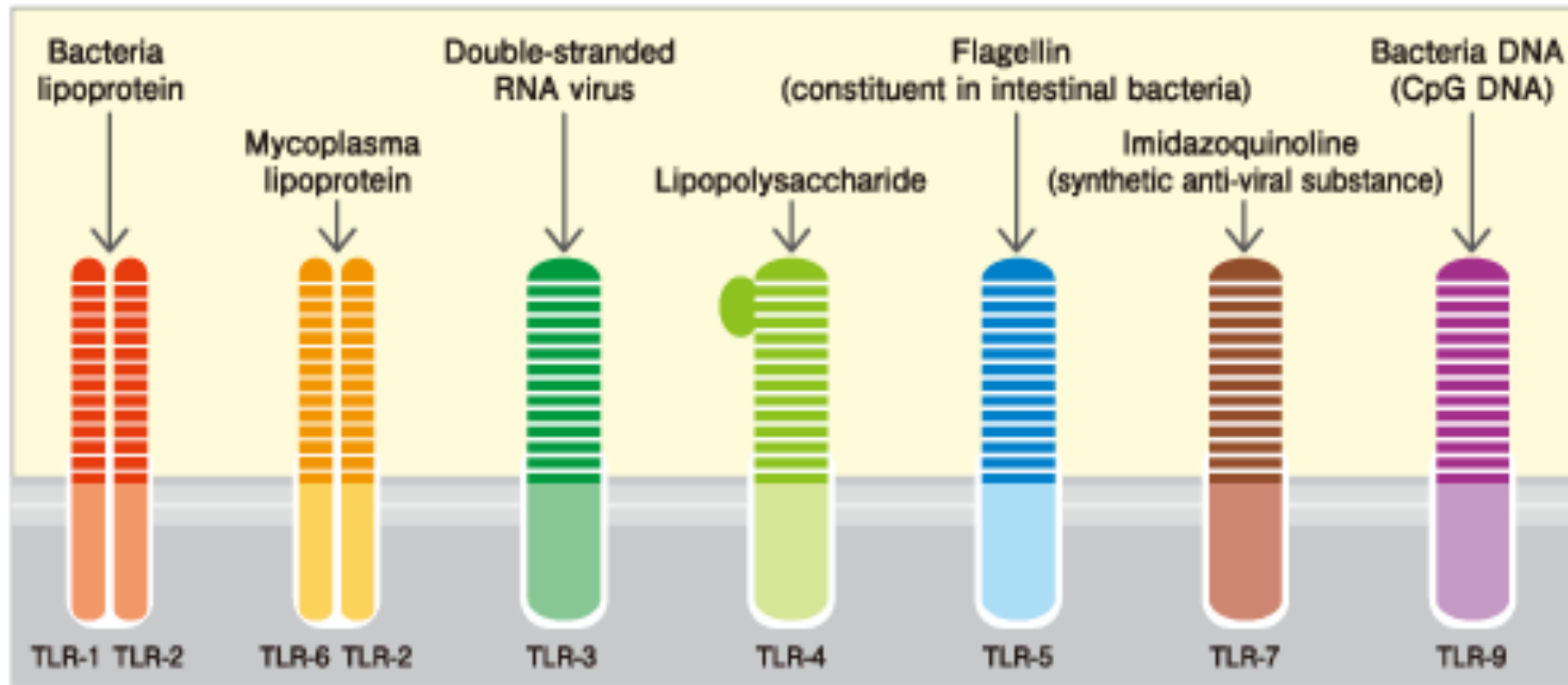
- Promotes excessive production and release of pro-inflammatory cytokines of the interleukin-1 $\beta$  (IL-1 $\beta$ ) family, including IL-1 $\beta$  and IL-18
- Promotes their release of reactive oxygen species (ROS) and nitric oxide (NO)
- Retraction of their processes, which is a phenotypic change that may correlate with an impaired ability to remodel synapses
- Neuroinflammation restricts the supply of neurotrophic factors to glial cells and probably affects physiological processes that are important for intraneuronal protein handling
- Increased cytokine concentrations are suggested to be responsible for insufficient microglial phagocytic capacity



# TOLL LIKE RECEPTORS

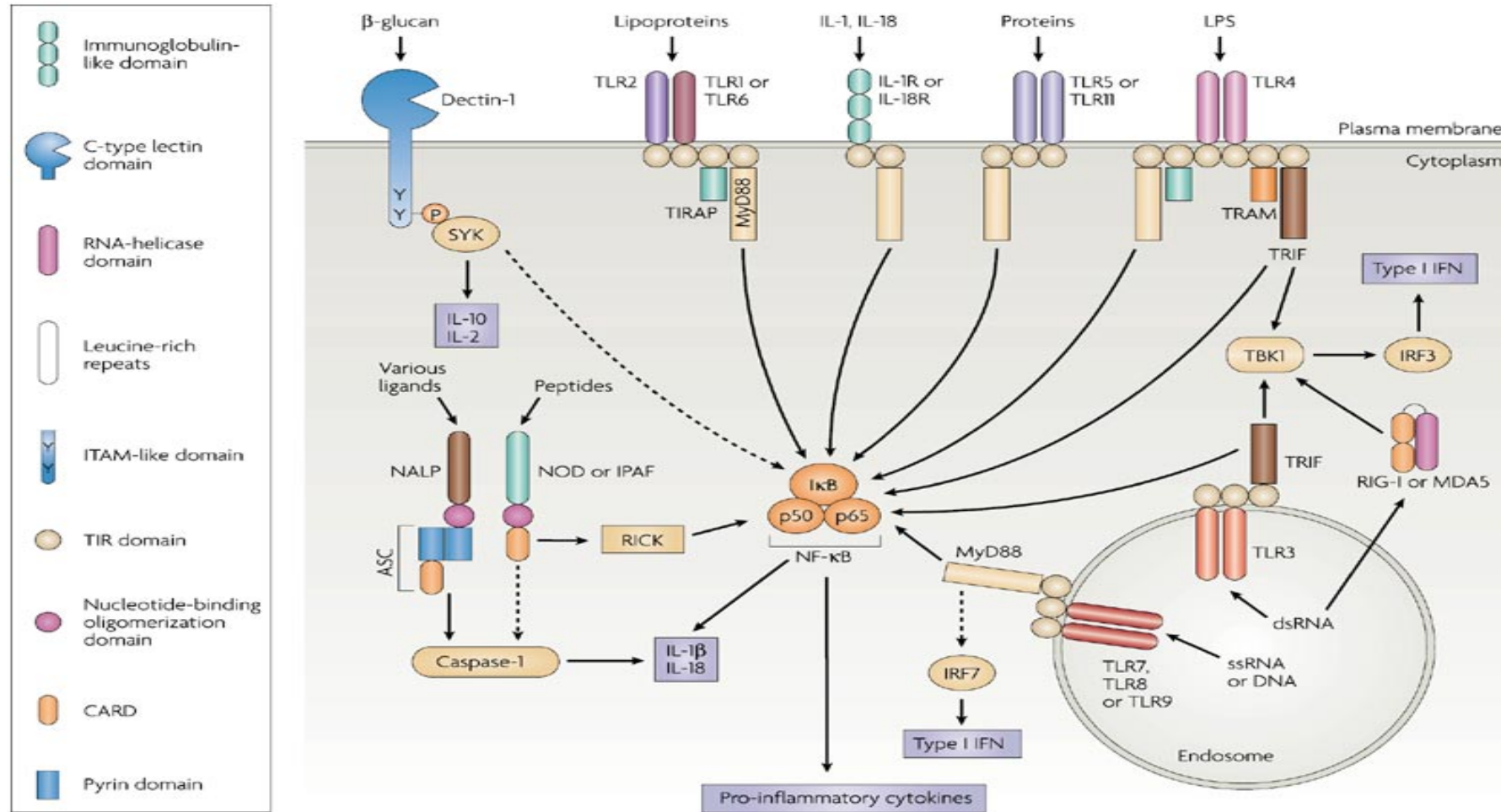


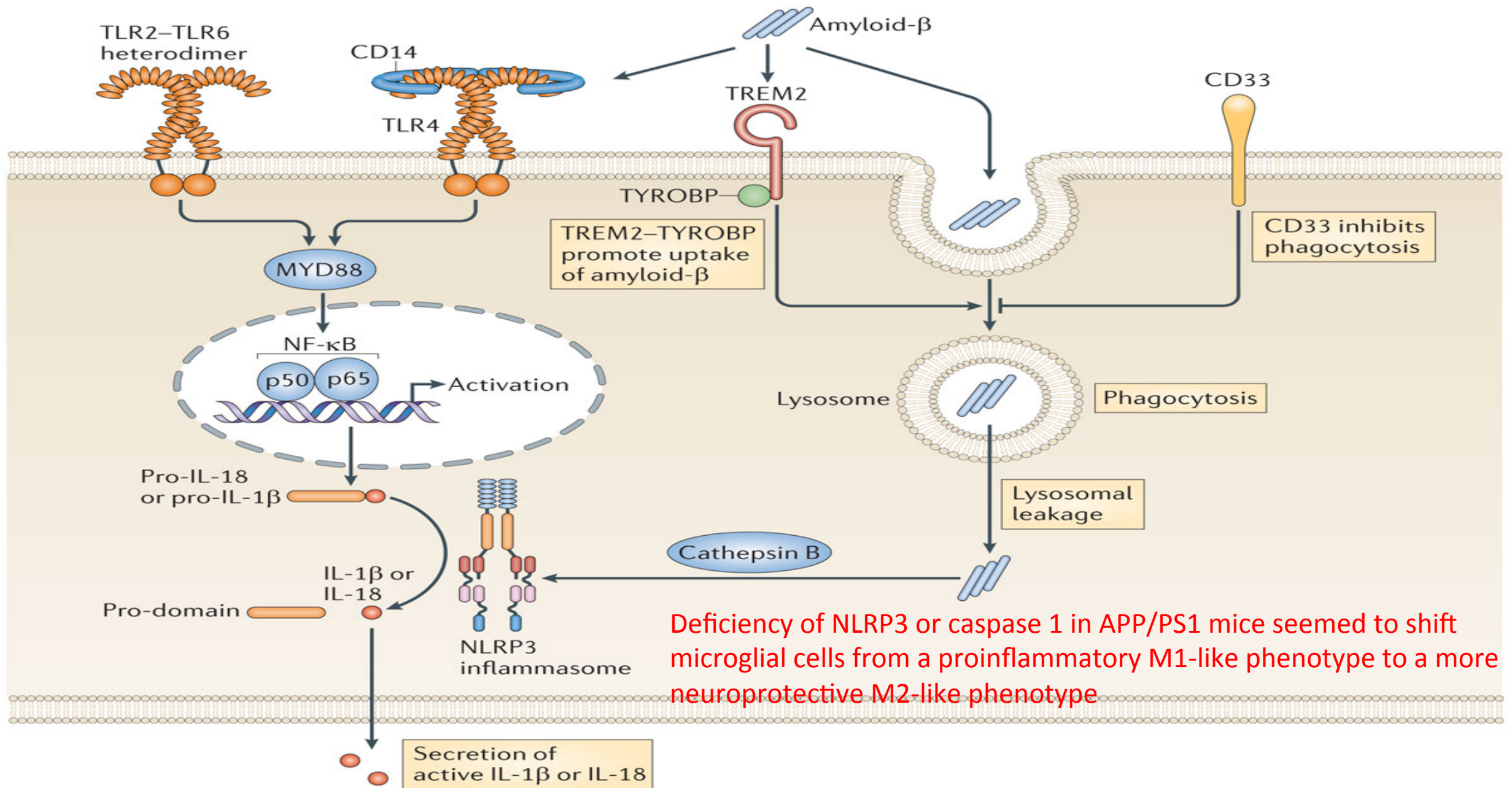
# Toll-like receptors (TLRs)



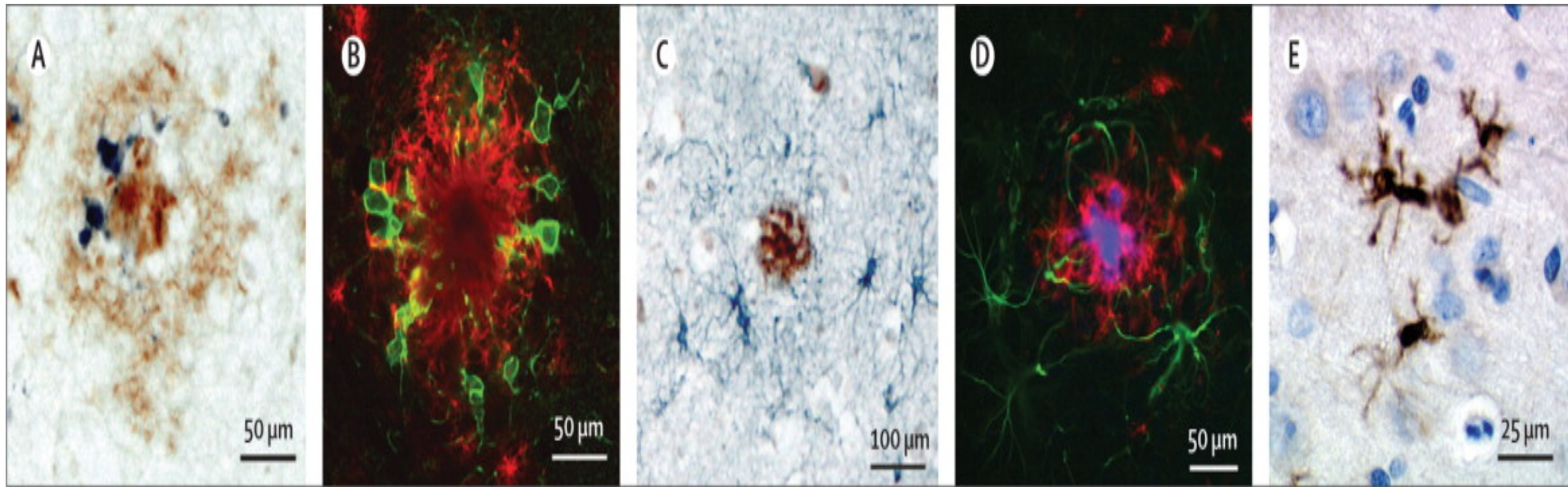
Toll-like receptor family and known active ingredients

# Pattern-recognition receptors (PRRs)

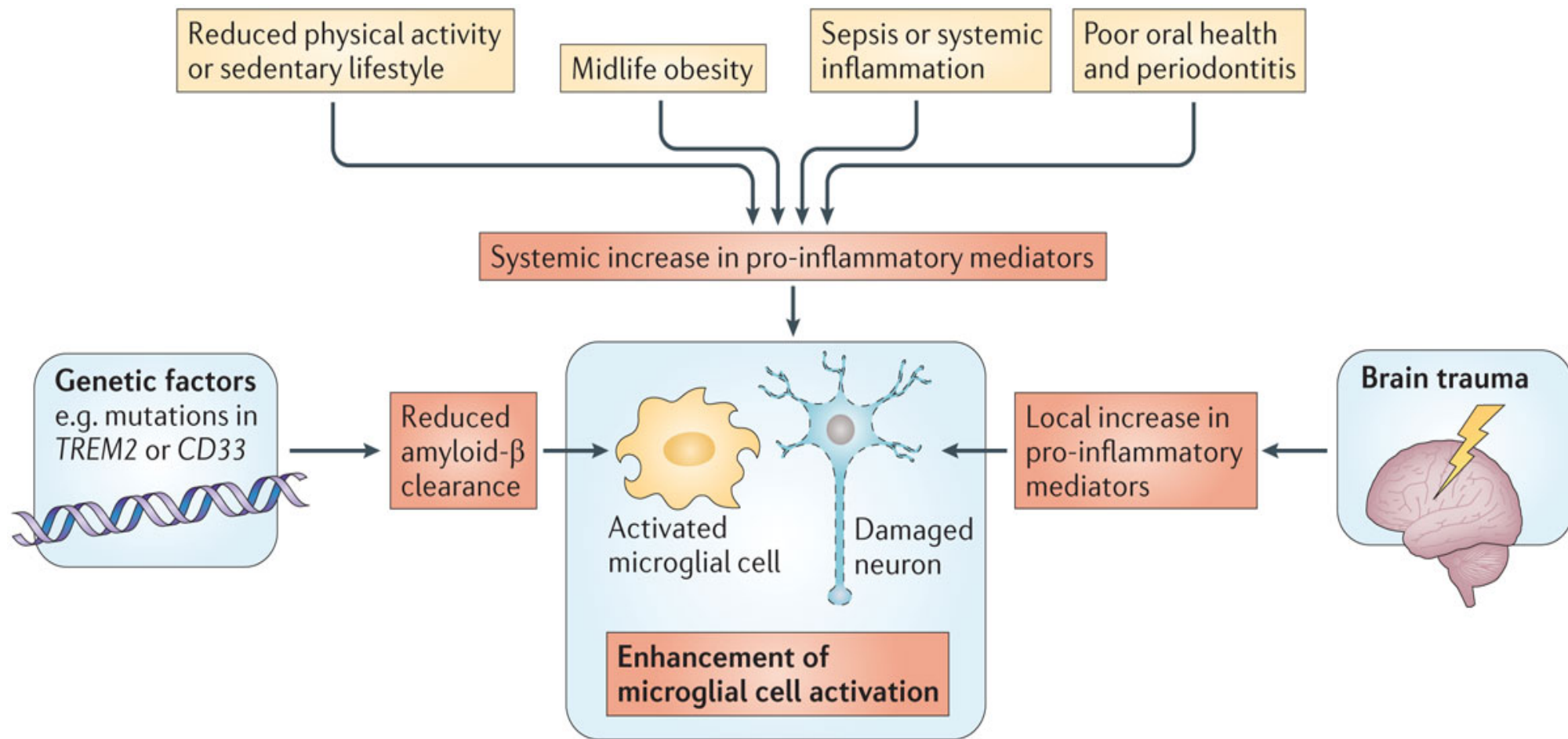




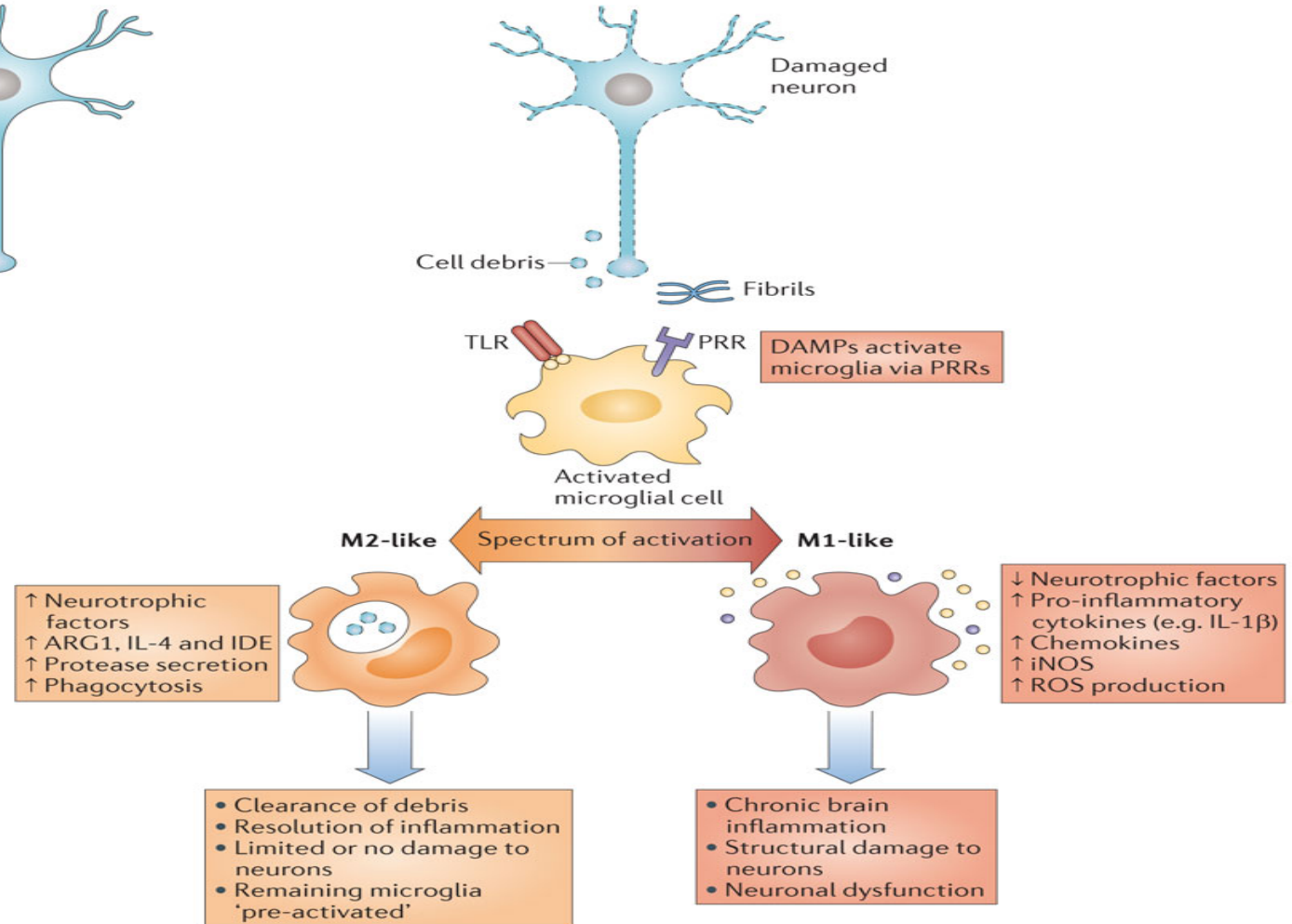
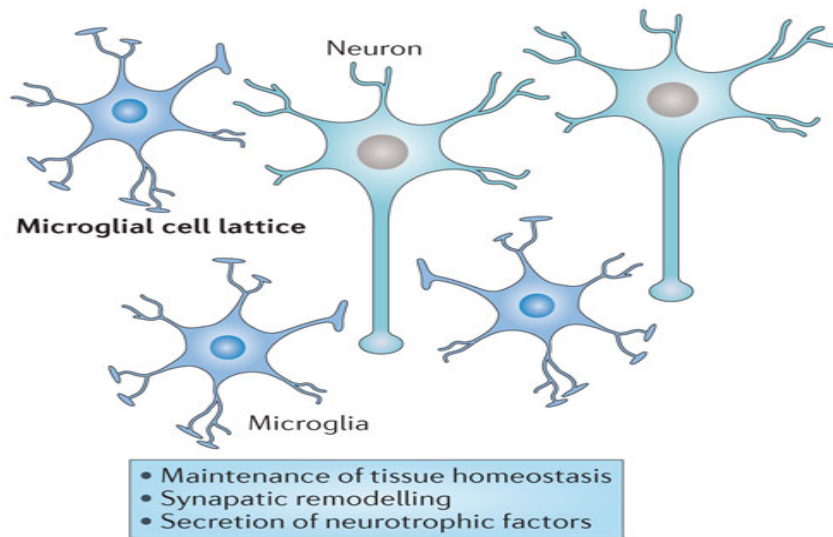




Heneka et al, Lancet Neurology, 2015

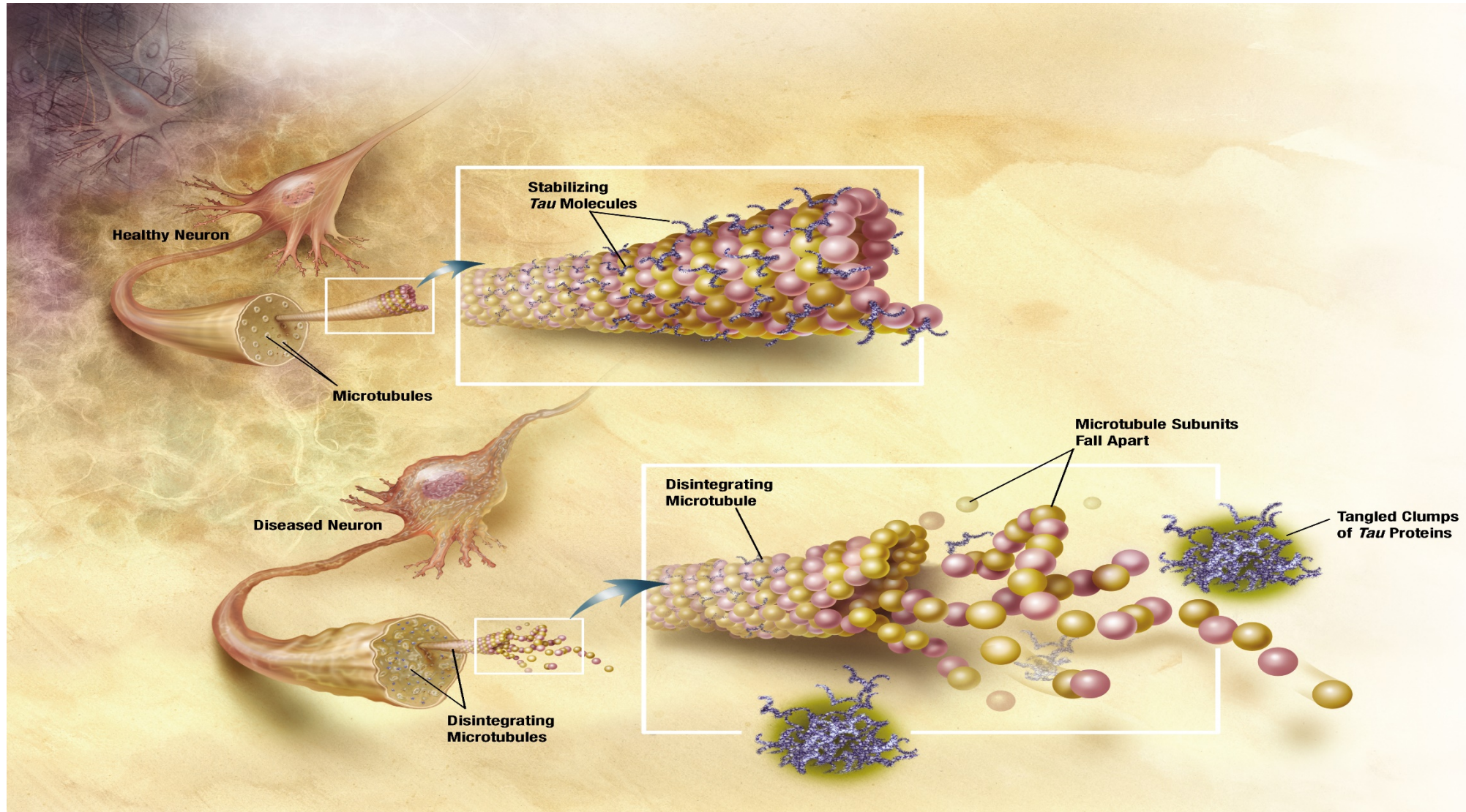


Heneka et al, 2014, *Nature Reviews* | Immunology





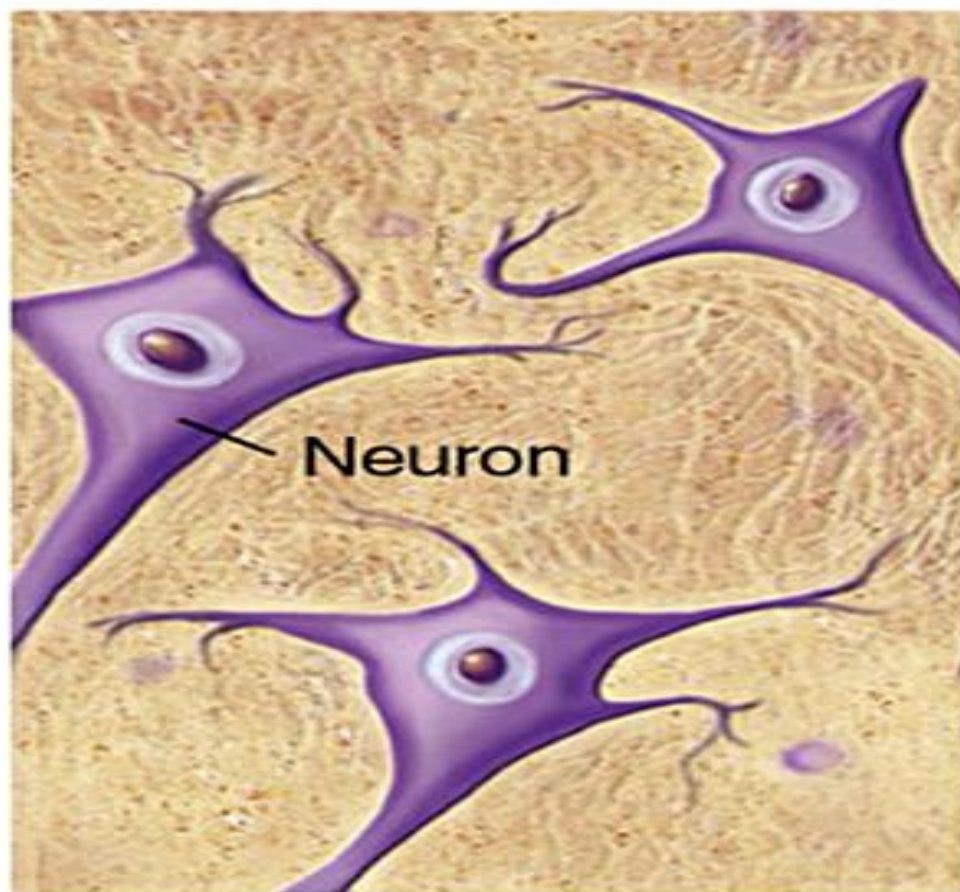
# Alzheimer- disintegrated neuron microtubuli



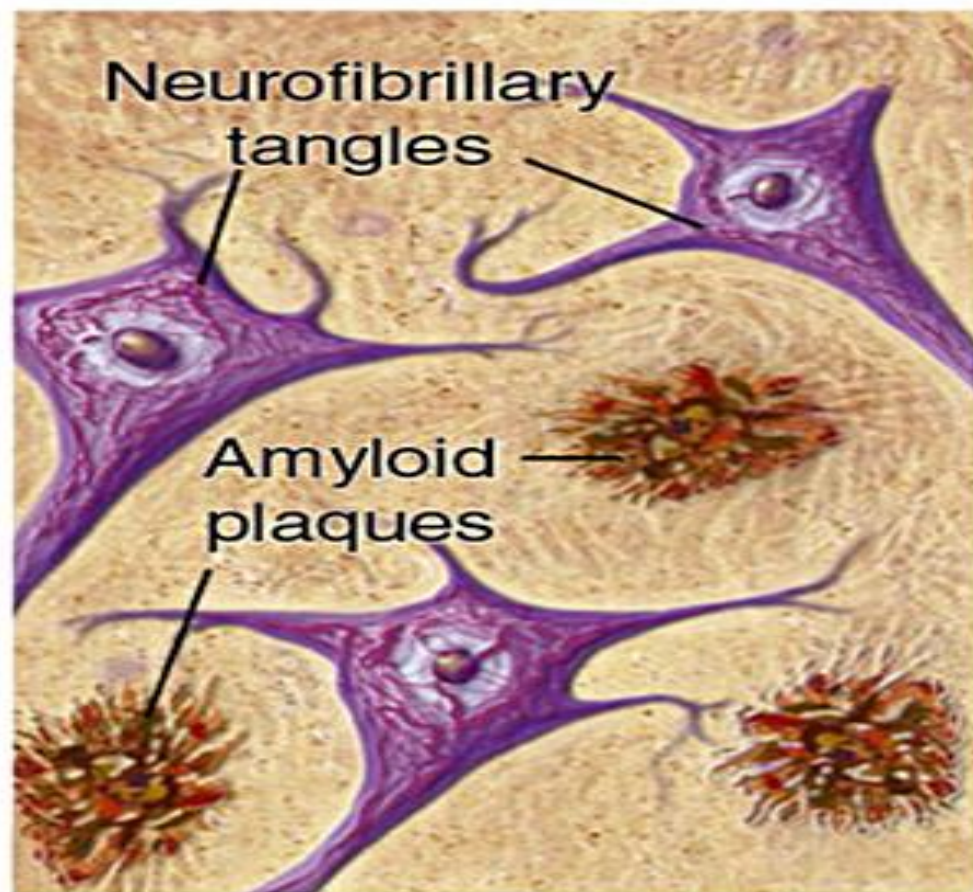


# Normal vs. Alzheimer's Diseased Brain

**Normal**

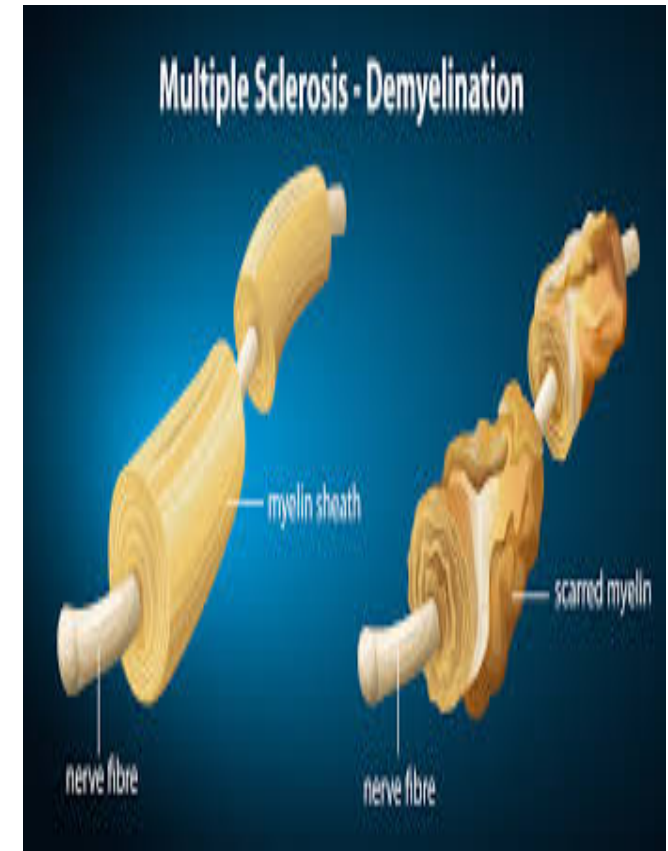
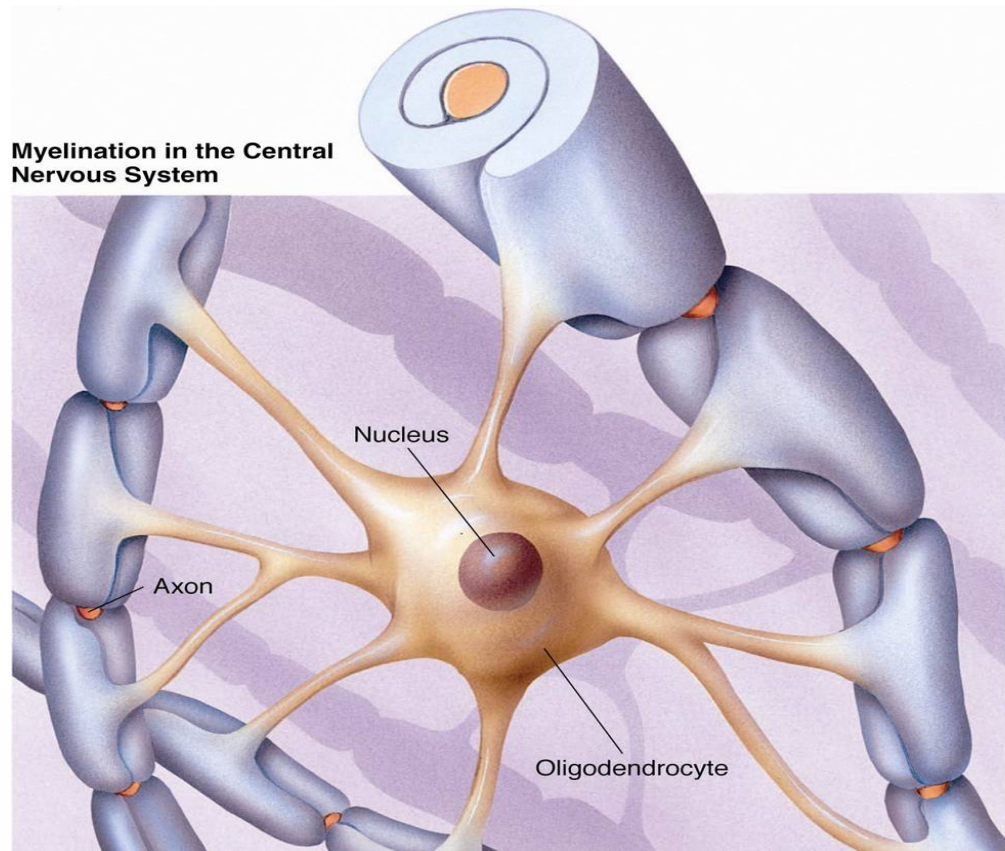


**Alzheimer's**



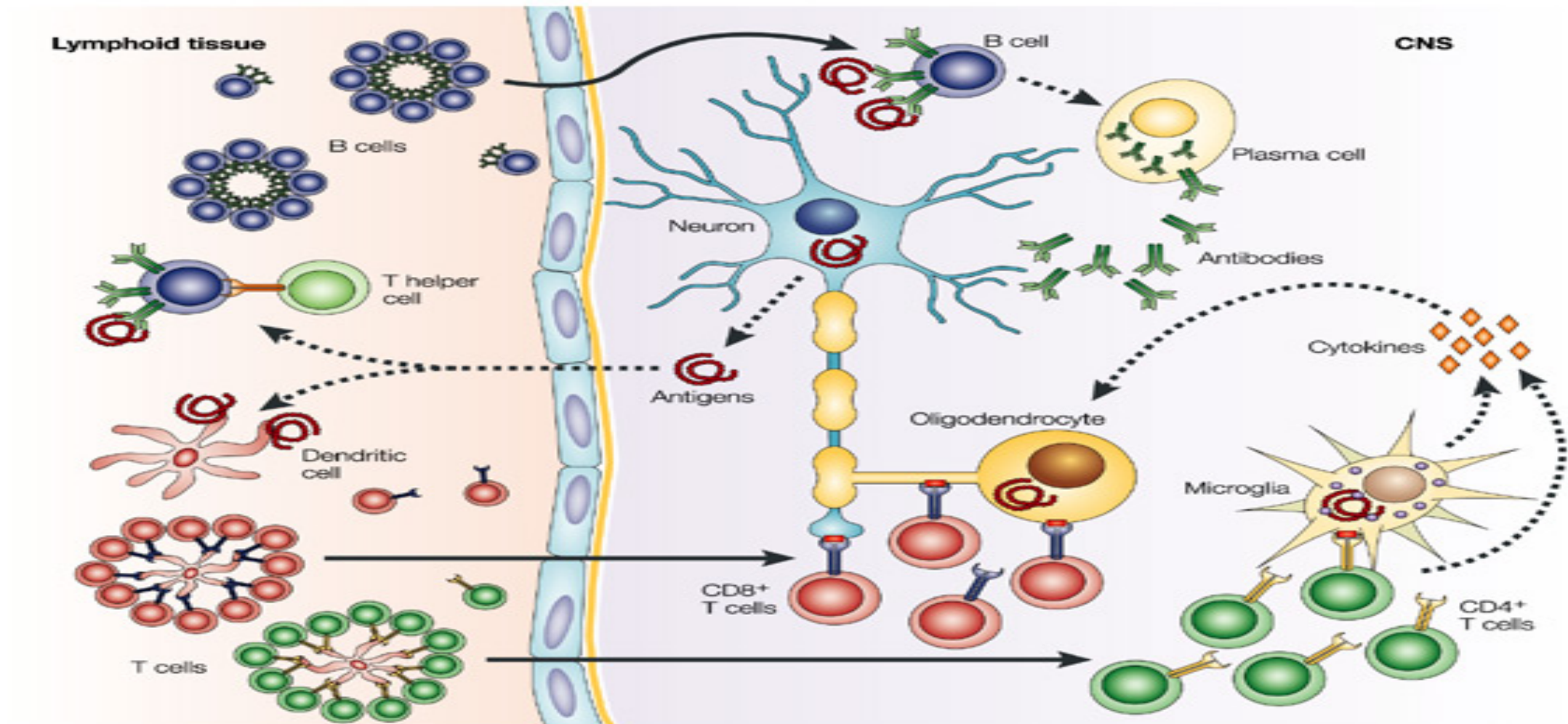
# Multiple sclerosis

Dysregulated adaptive immune responses (autoimmune) mainly attacking the oligodendrocyte leading to demyelination





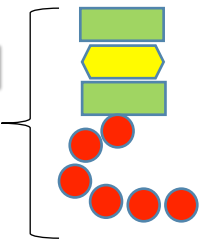
# Multiple sclerosis – a disease with a dysregulated adaptive immunity (autoimmunity)



Some basic immunology.. 😊



Microbial  
antigen



Carbohydrate

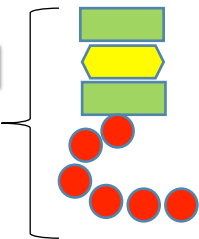
Lipid

Protein

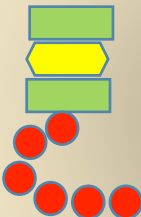
Dendritic cell (DC)

MHC II

Microbial  
antigen



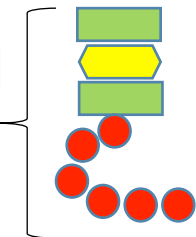
Dendritic cell (DC)



MHC II

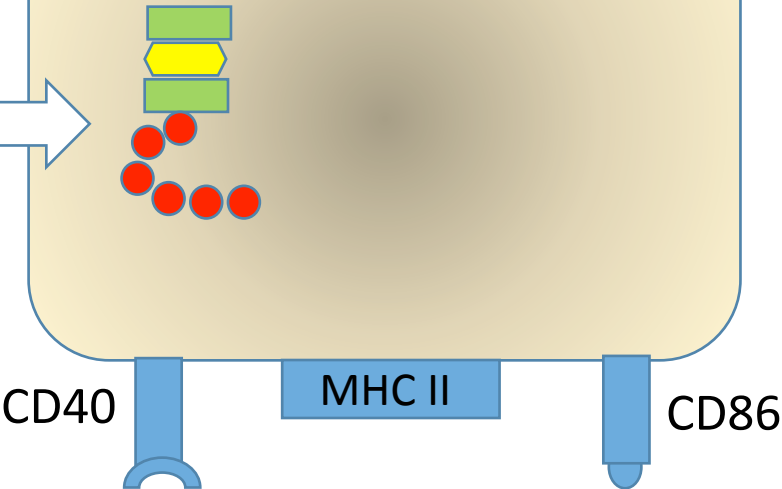
- Carbohydrate
- Lipid
- Protein

Microbial  
antigen

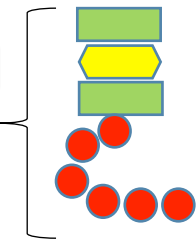


- Carbohydrate
- Lipid
- Protein

Dendritic cell (DC)



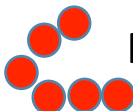
Microbial  
antigen



Carbohydrate

Lipid

Protein

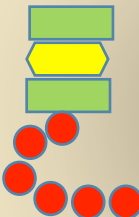


Dendritic cell (DC)

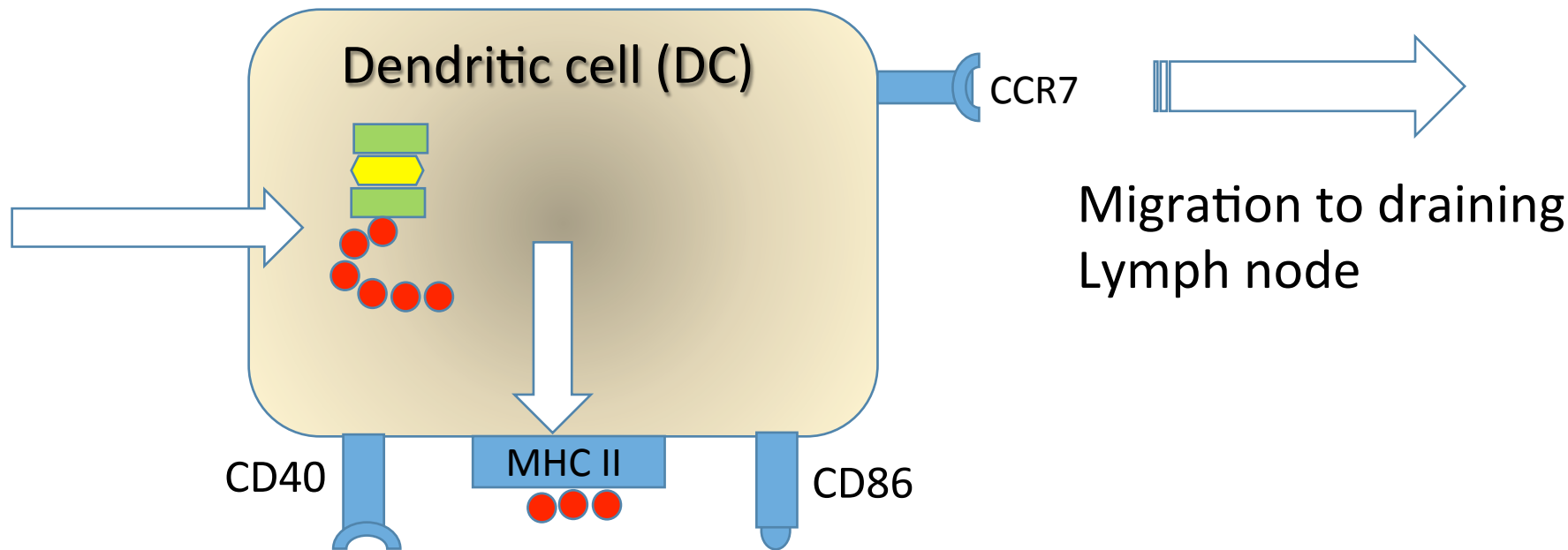
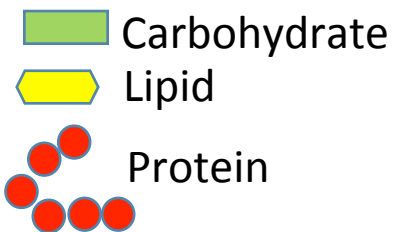
CD40

MHC II

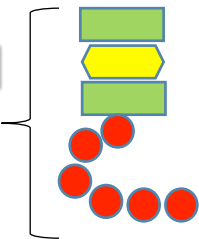
CD86



Microbial  
antigen



Microbial  
antigen



Carbohydrate

Lipid

Protein

Dendritic cell (DC)

CD40

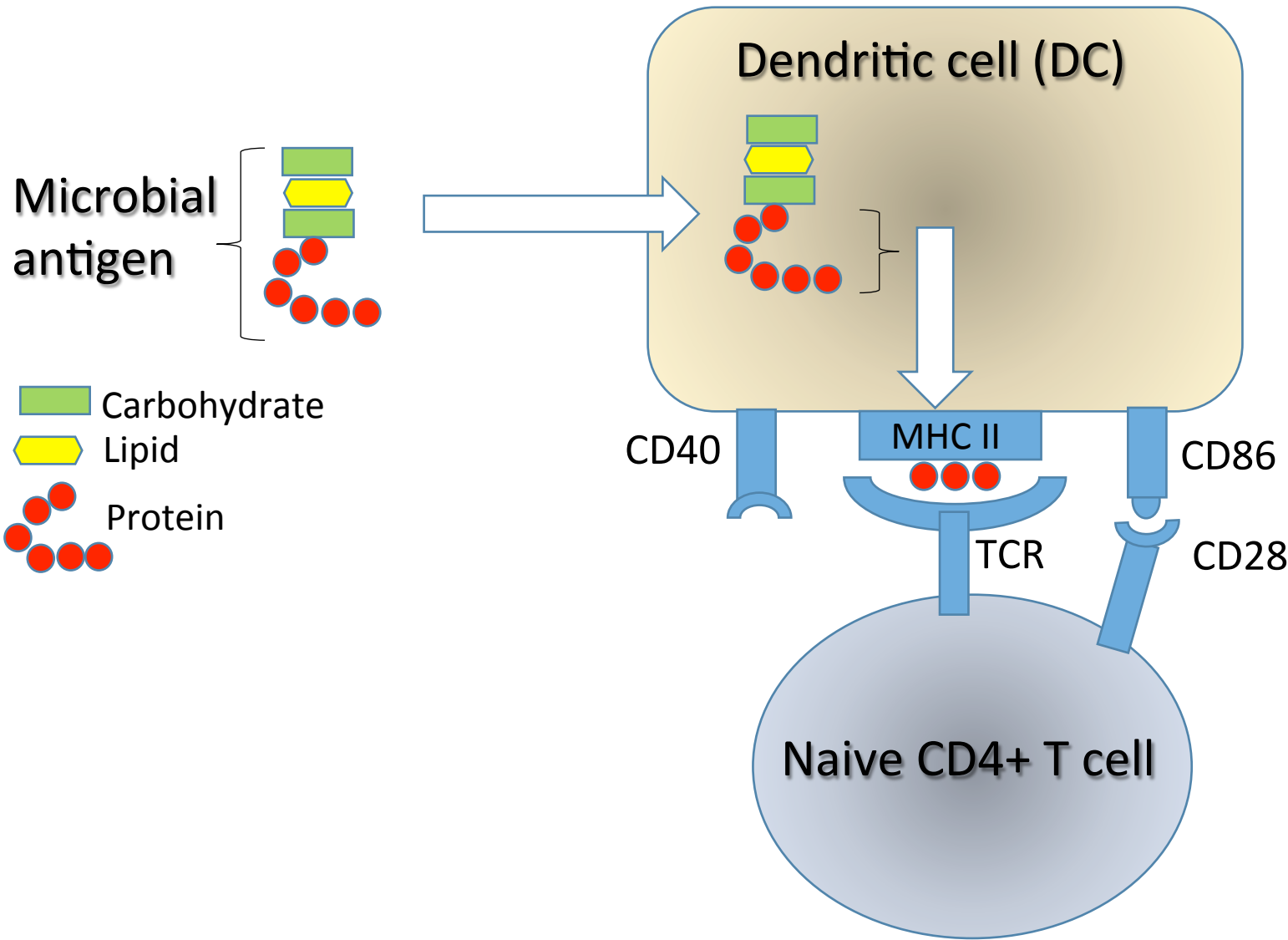
MHC II

TCR

CD86

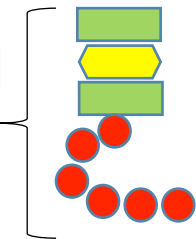
CD28

Naive CD4+ T cell





Microbial  
antigen



Carbohydrate

Lipid

Protein

Dendritic cell (DC)

CD40

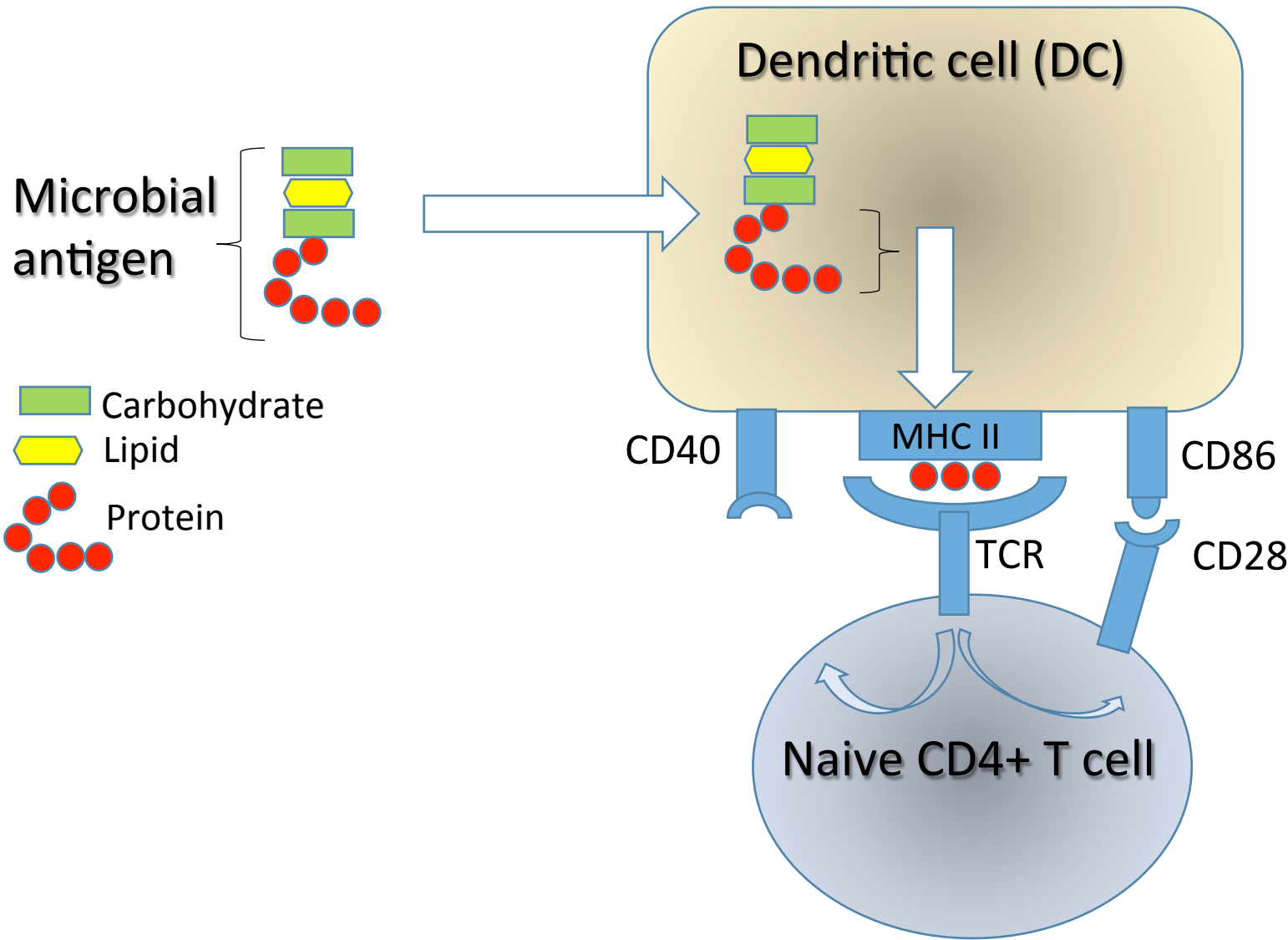
MHC II

CD86

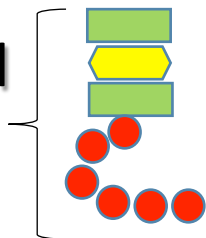
CD28

TCR

Naive CD4+ T cell



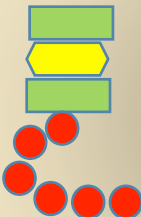
Microbial  
antigen



- Carbohydrate
- Lipid
- Protein



Dendritic cell (DC)



MHC II



CD40

CD40-L

TCR

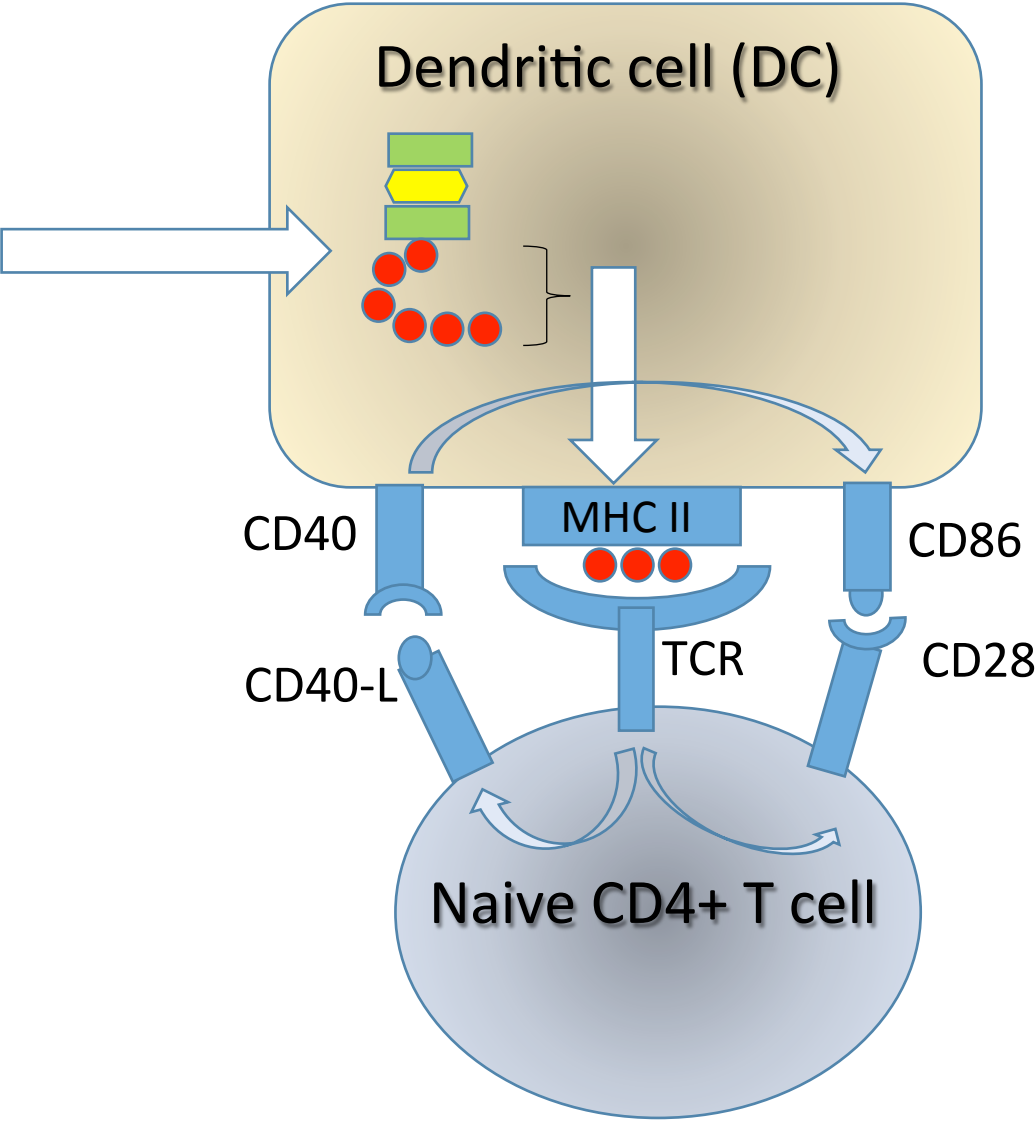
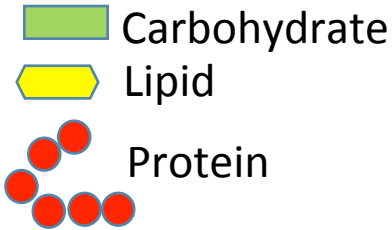
CD86

CD28

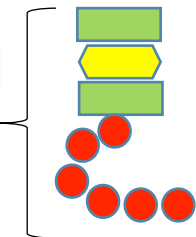
Naive CD4+ T cell



Microbial  
antigen



Microbial  
antigen

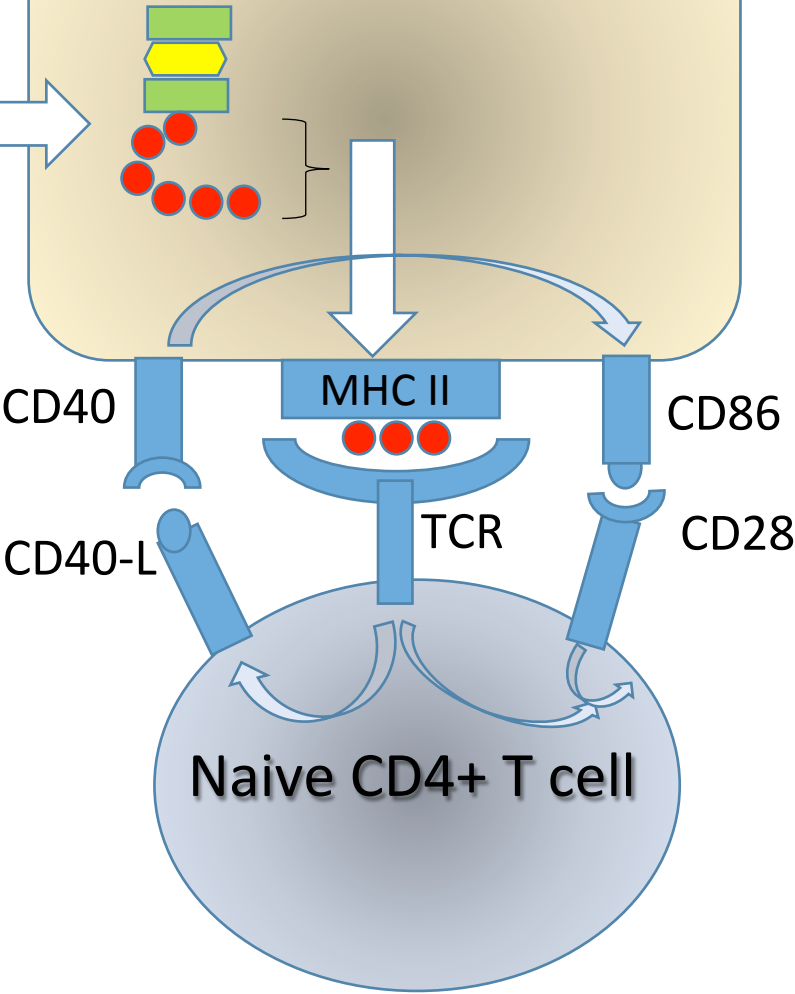


Carbohydrate

Lipid

Protein

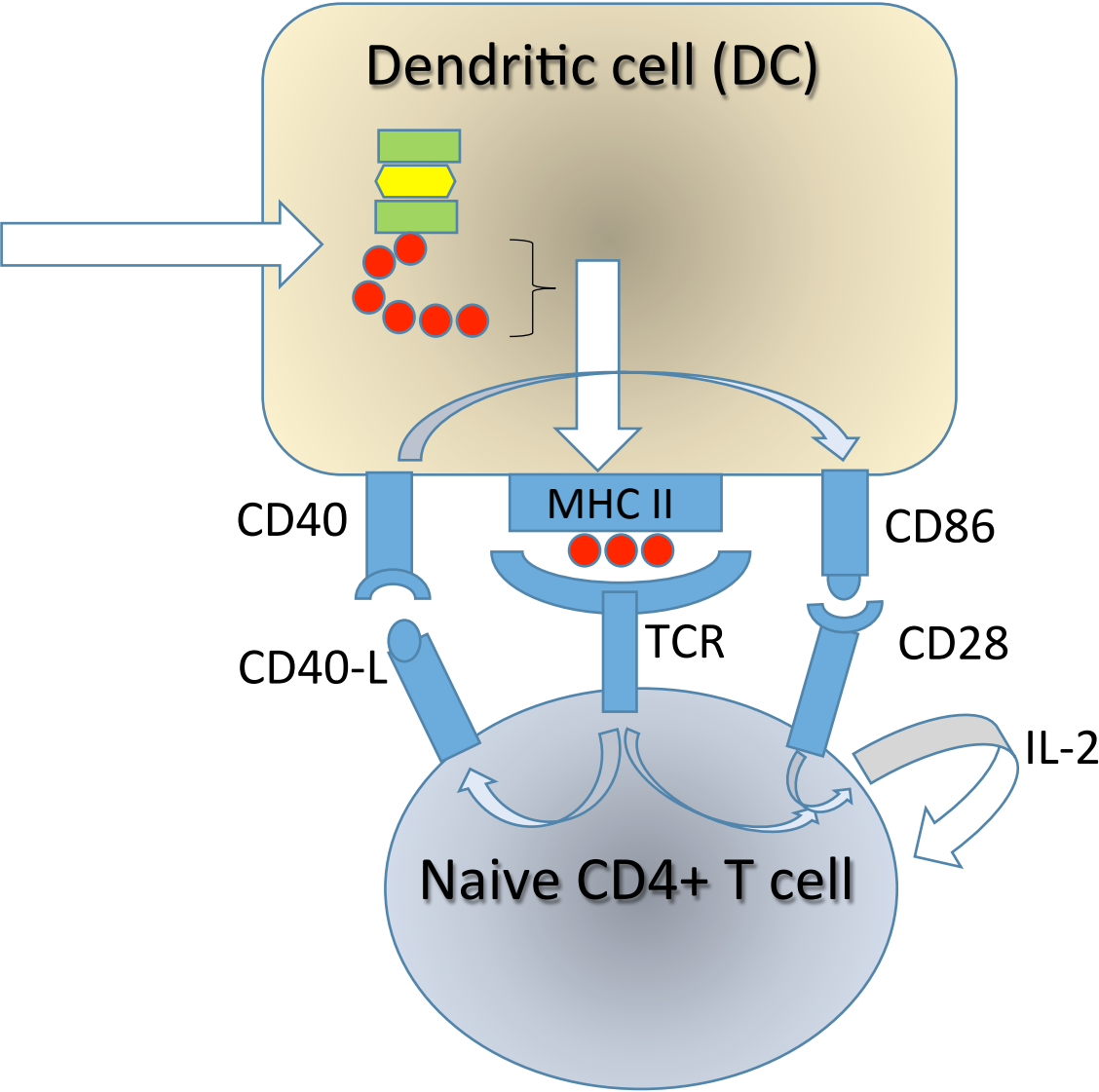
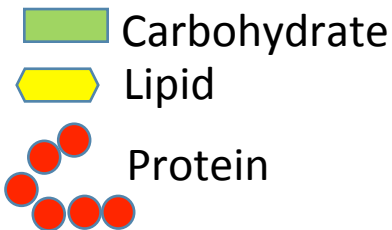
Dendritic cell (DC)



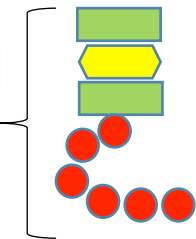
Naive CD4+ T cell



Microbial  
antigen



Microbial  
antigen



Carbohydrate

Lipid

Protein

Dendritic cell (DC)

CD40

MHC II

CD86

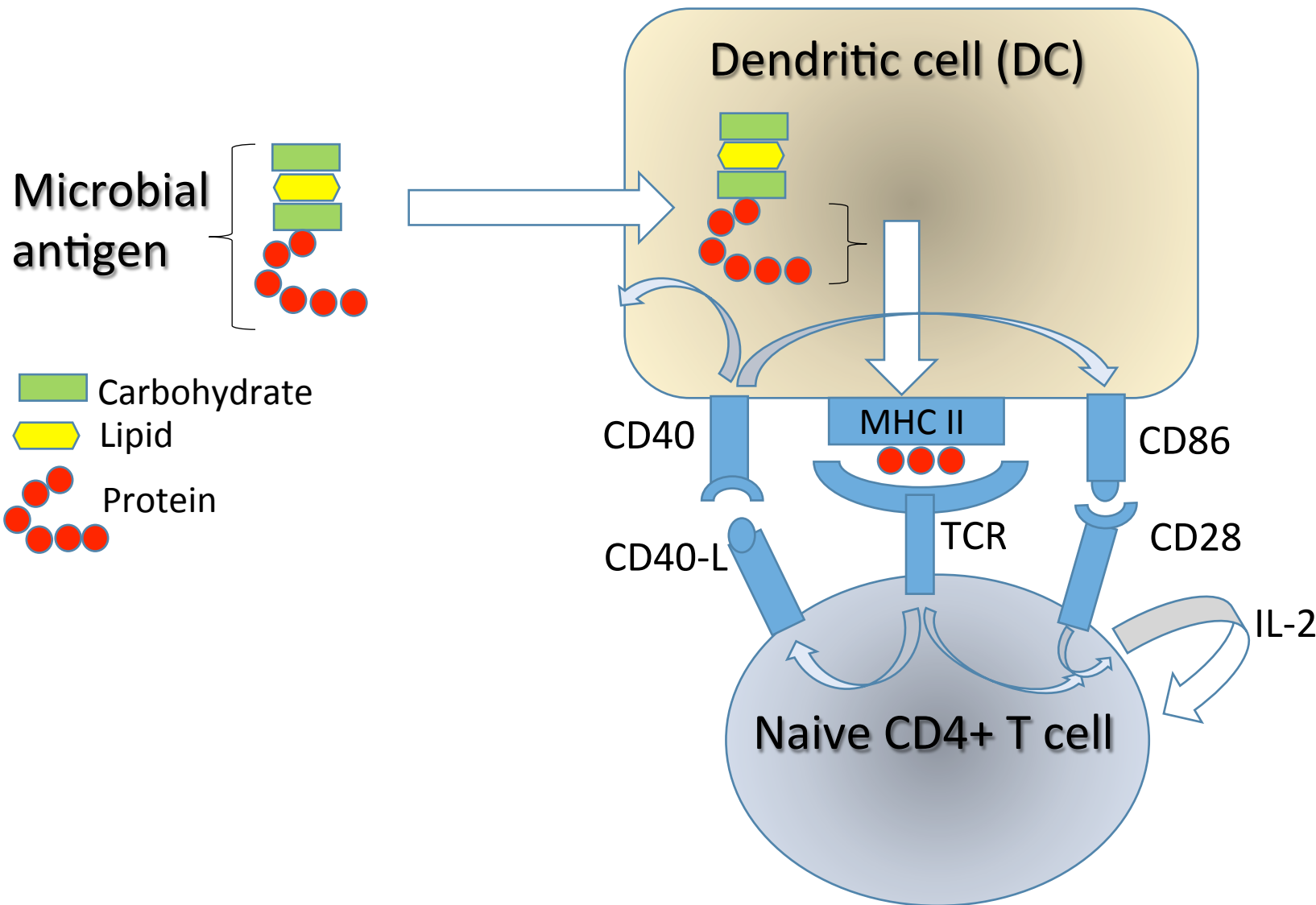
CD40-L

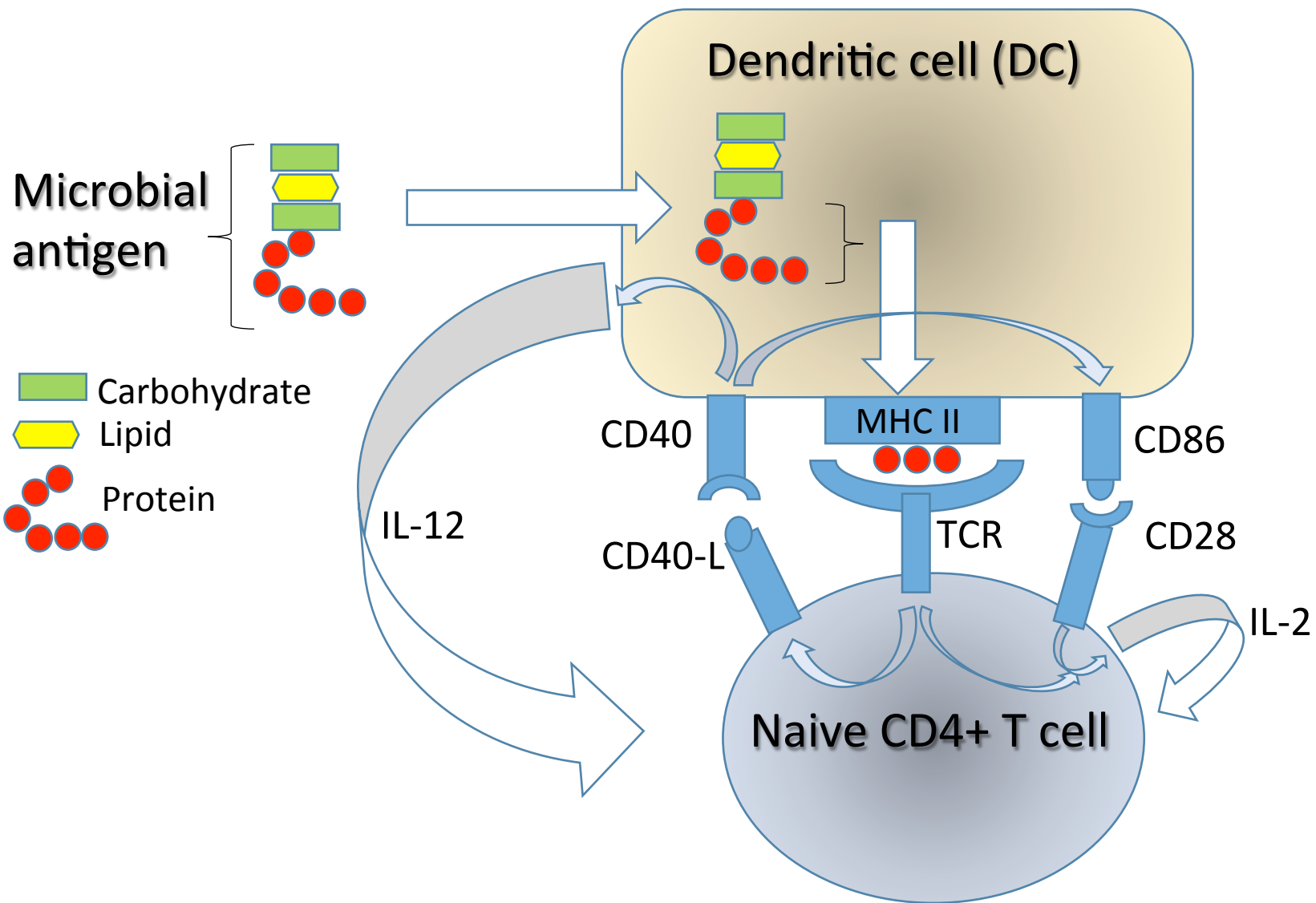
TCR

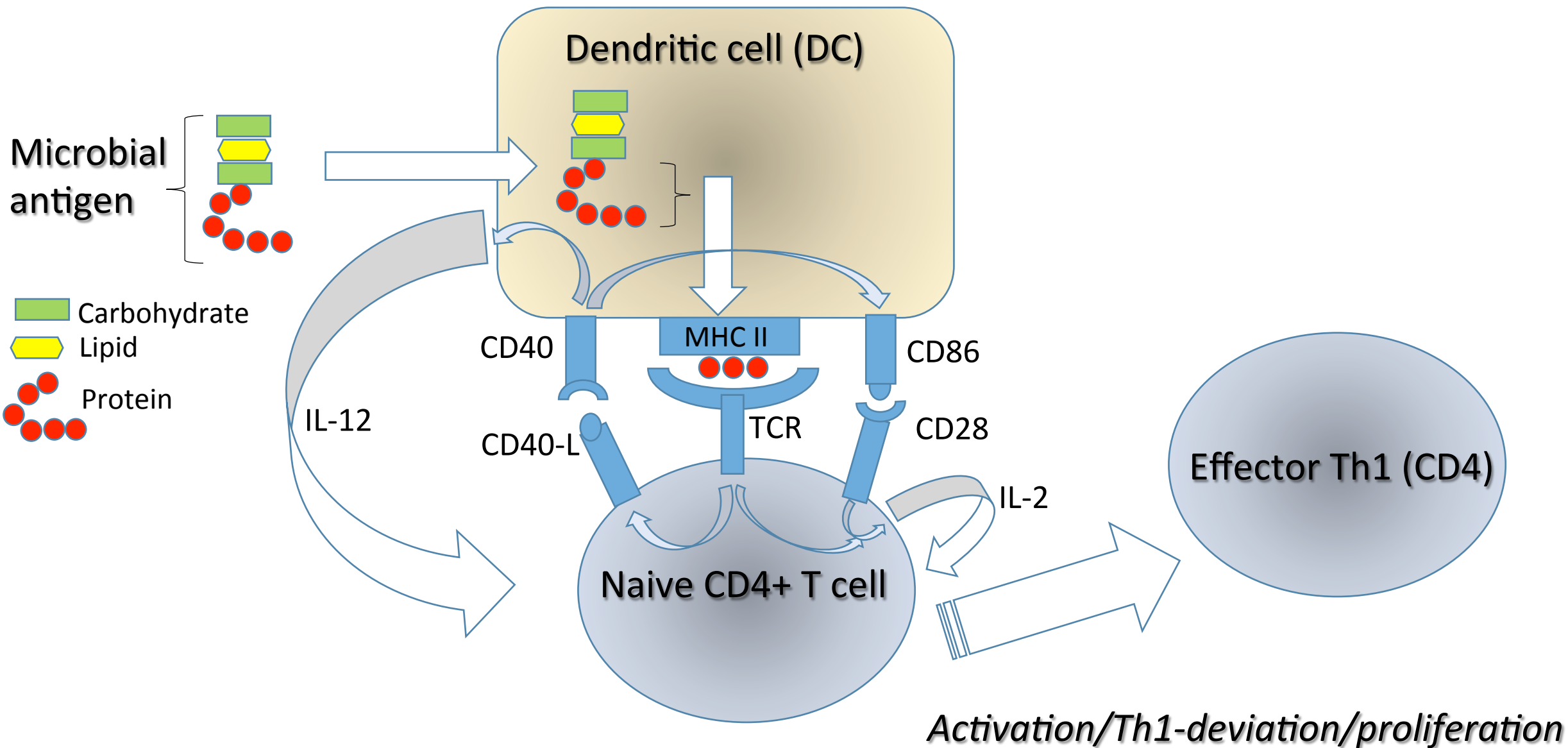
CD28

IL-2

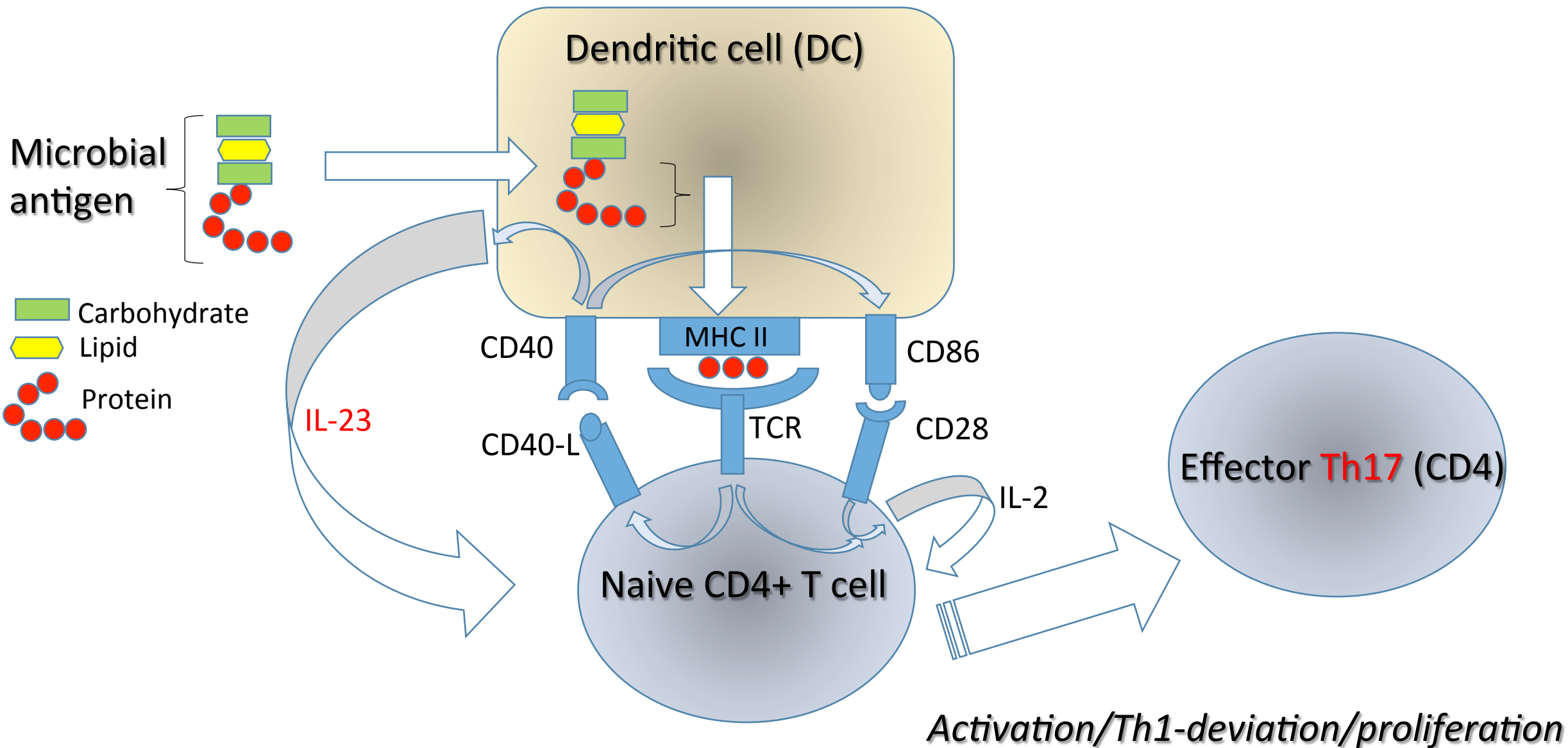
Naive CD4+ T cell



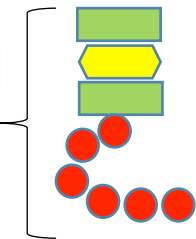








Microbial  
antigen

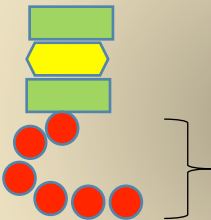


Carbohydrate

Lipid

Protein

Dendritic cell (DC)

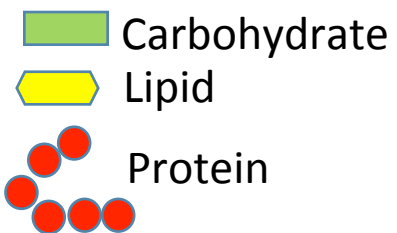


CD40

MHC I

CD86

Microbial  
antigen



Dendritic cell (DC)

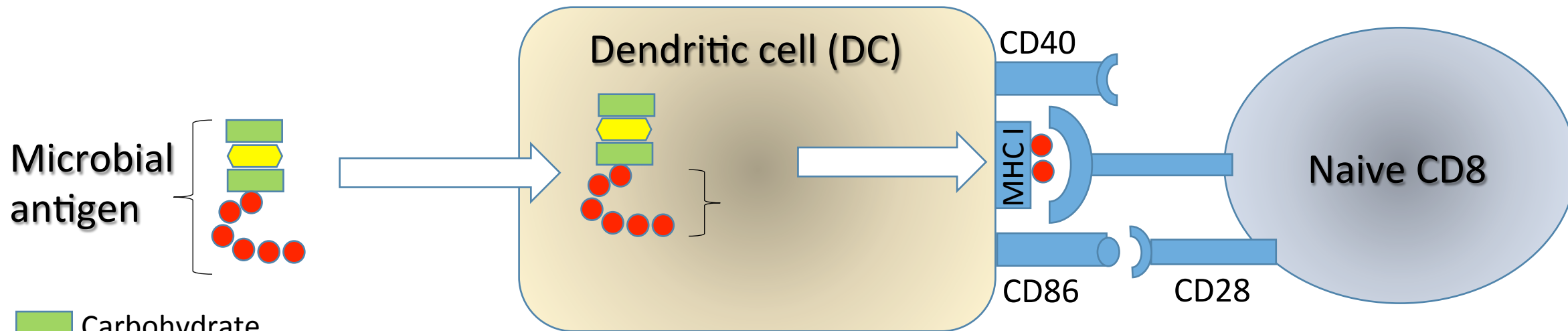
CD40

MHC I

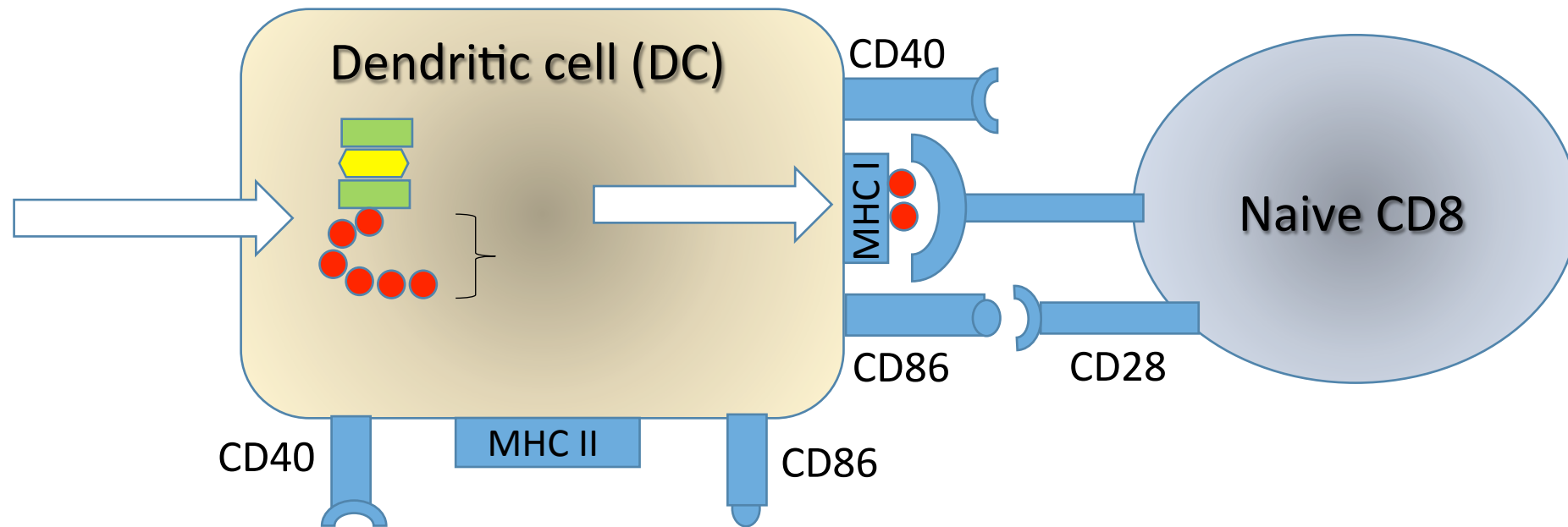
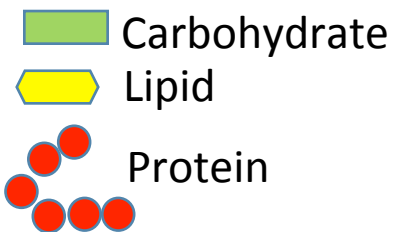
CD86

CD28

Naive CD8

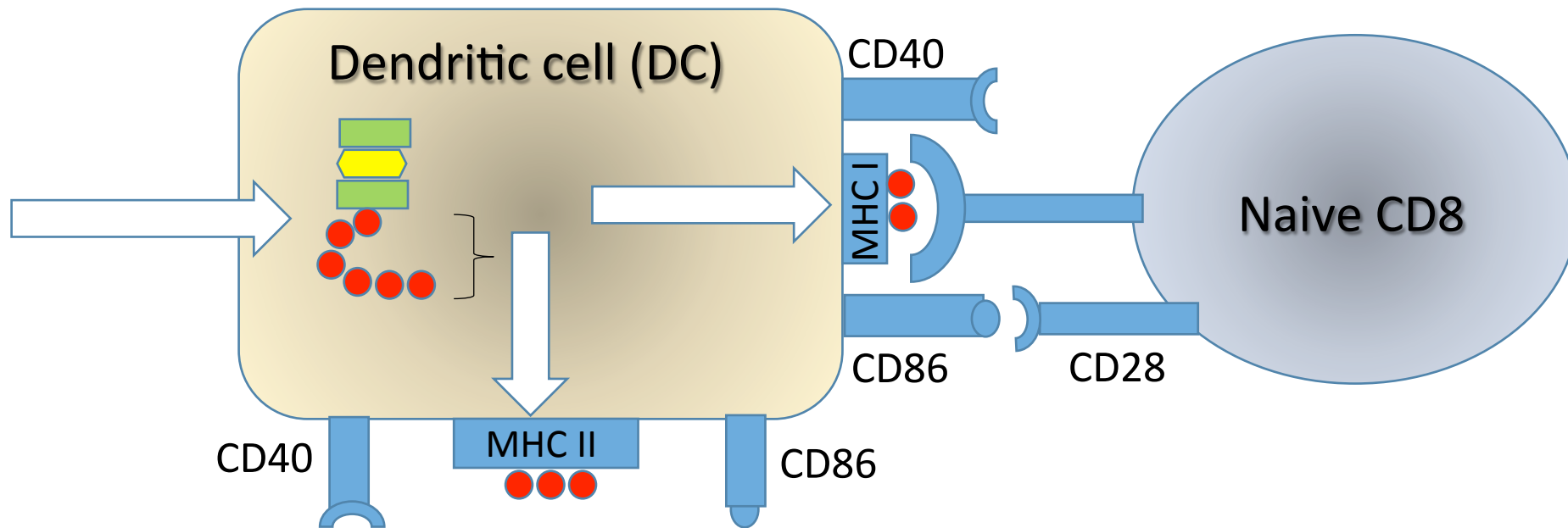
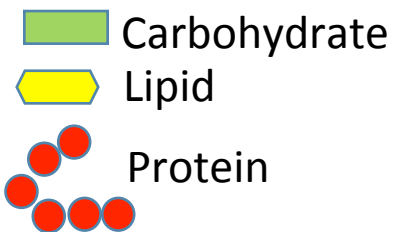


Microbial  
antigen

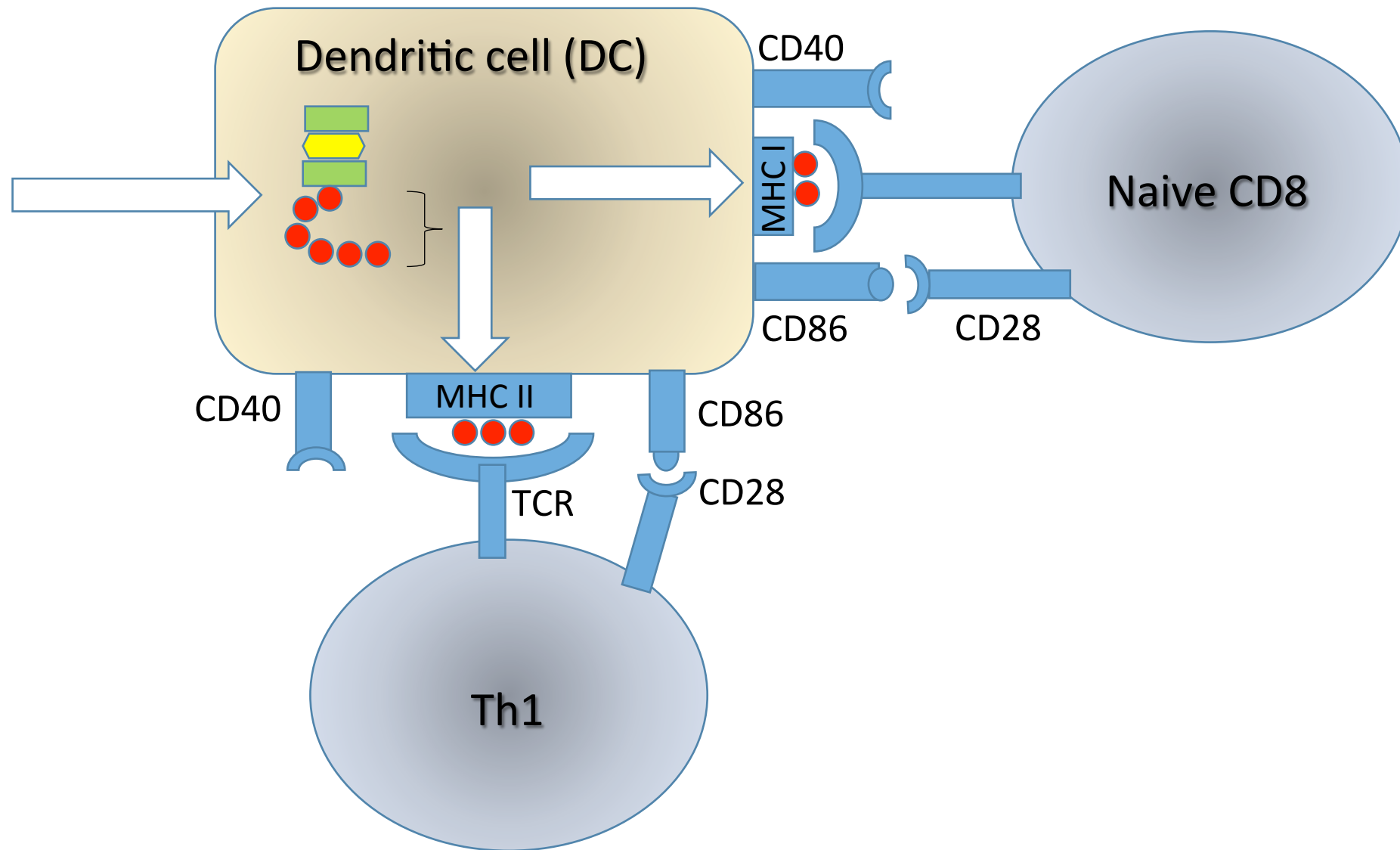
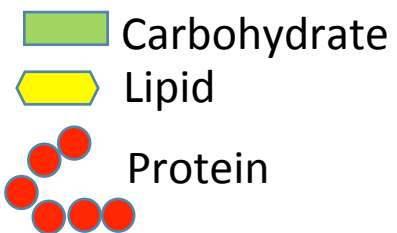




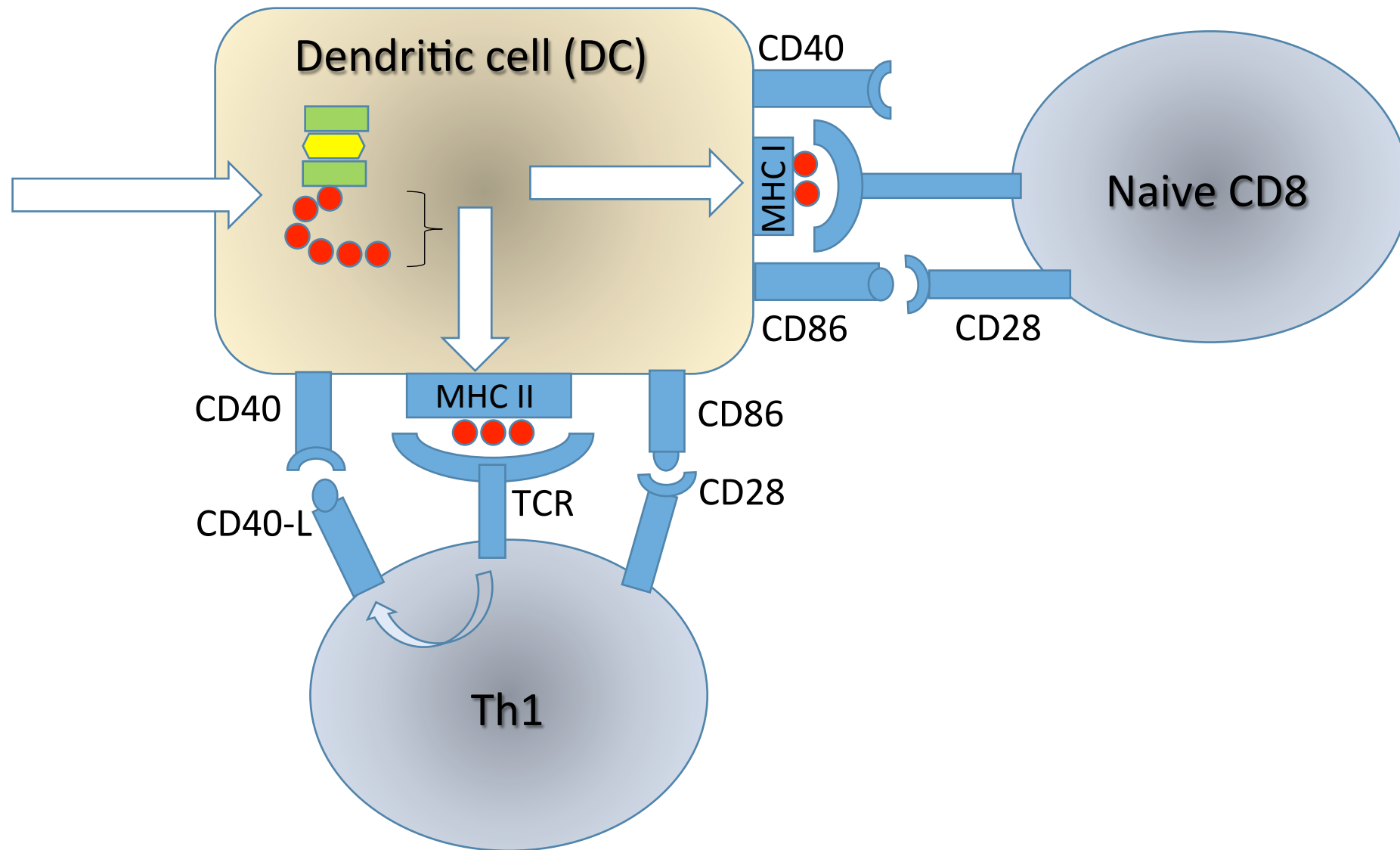
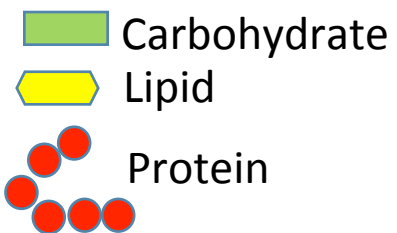
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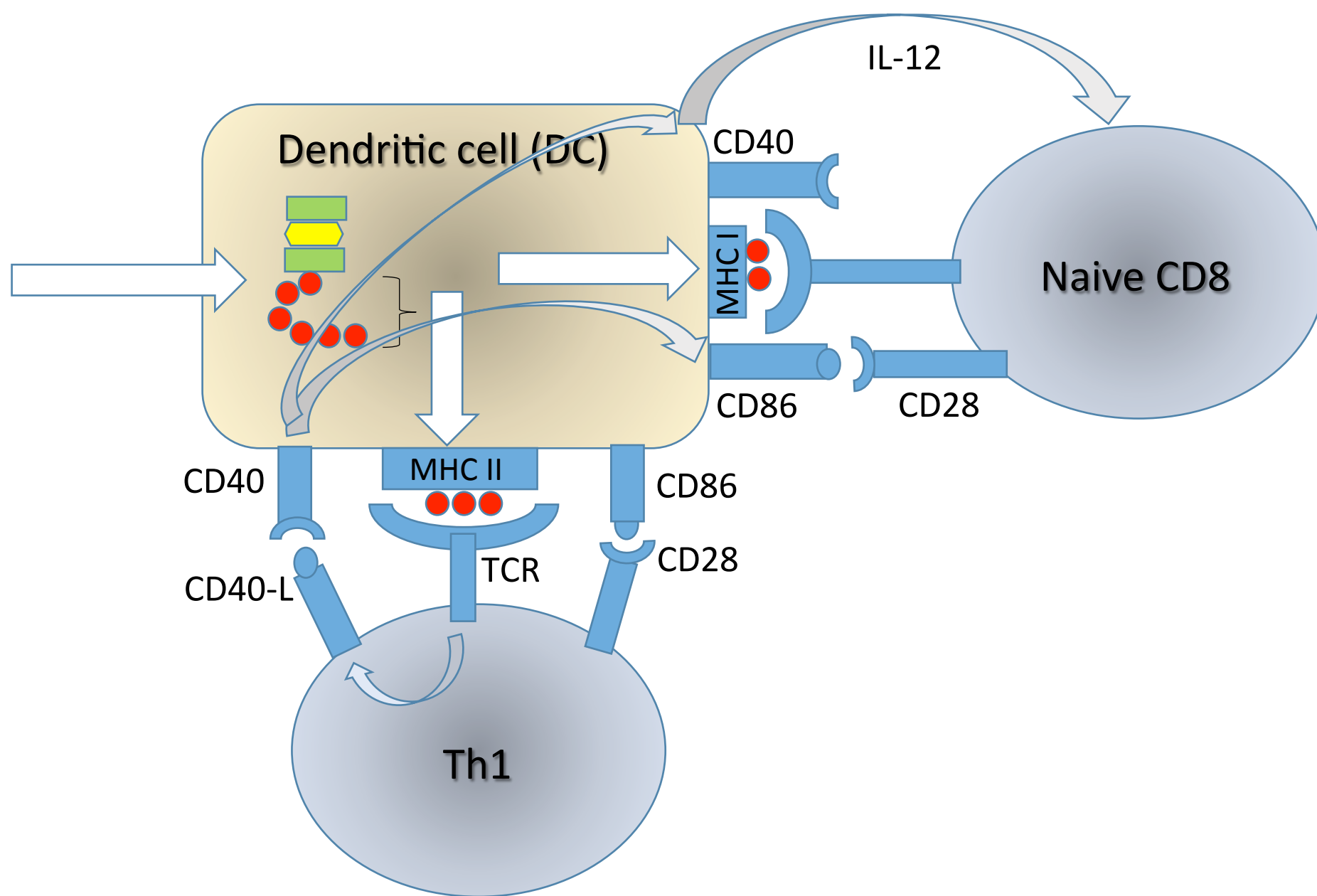
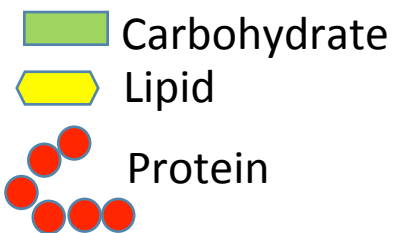
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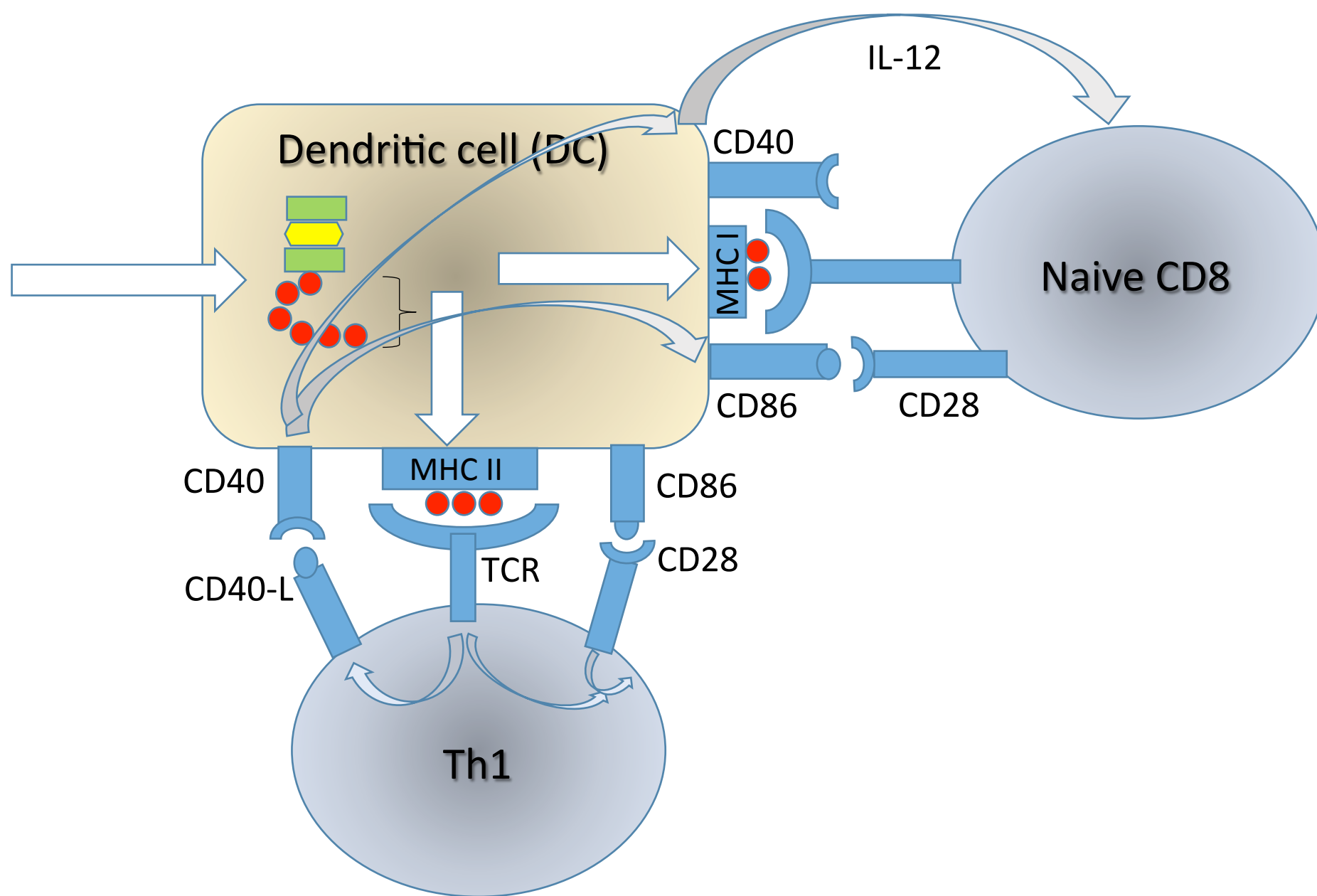
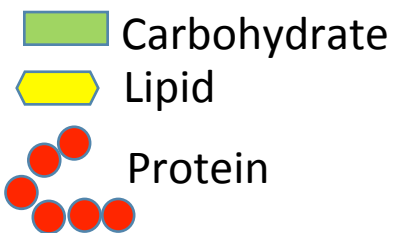
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Microbial  
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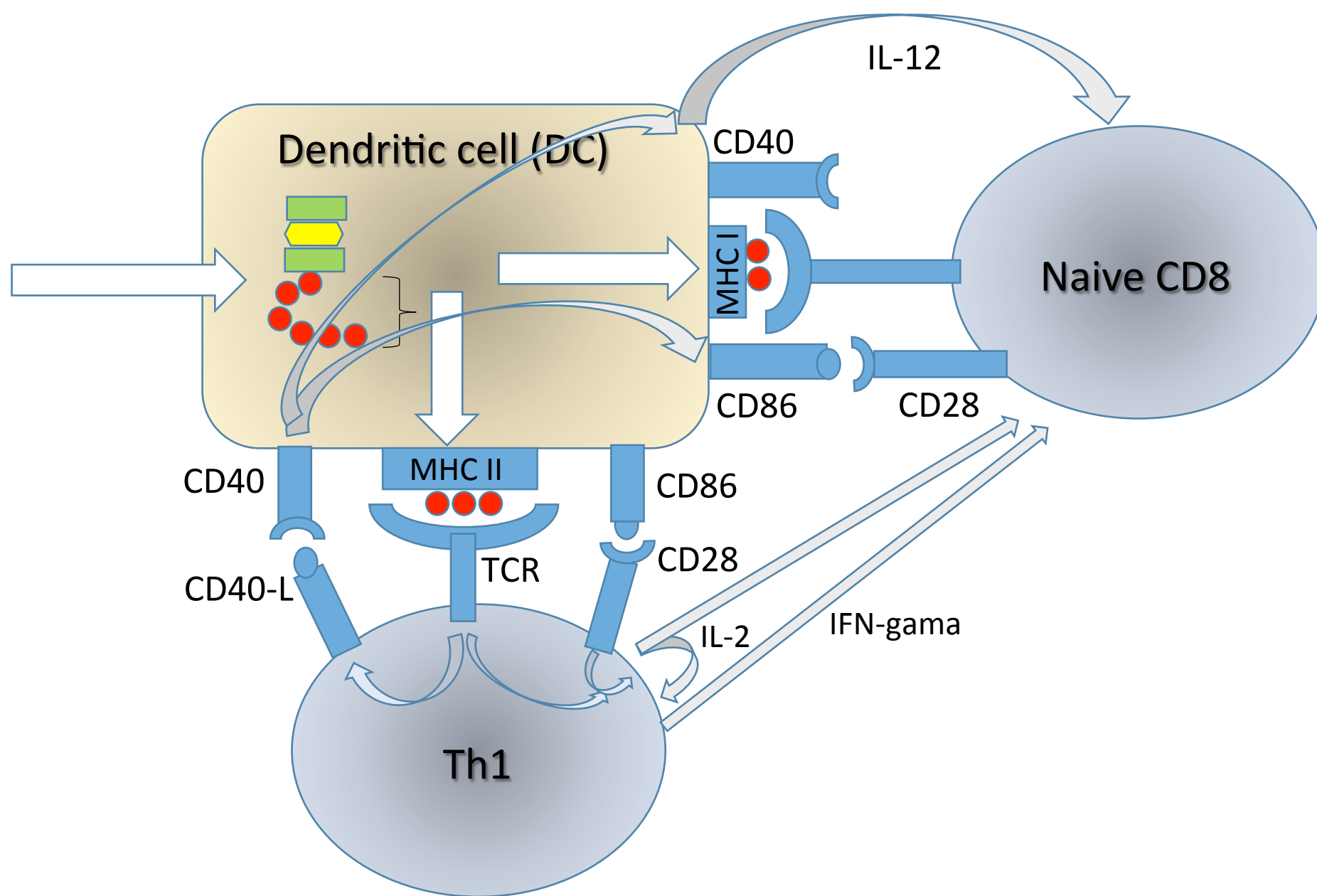
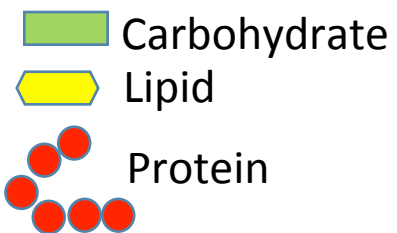


Microbial  
antigen

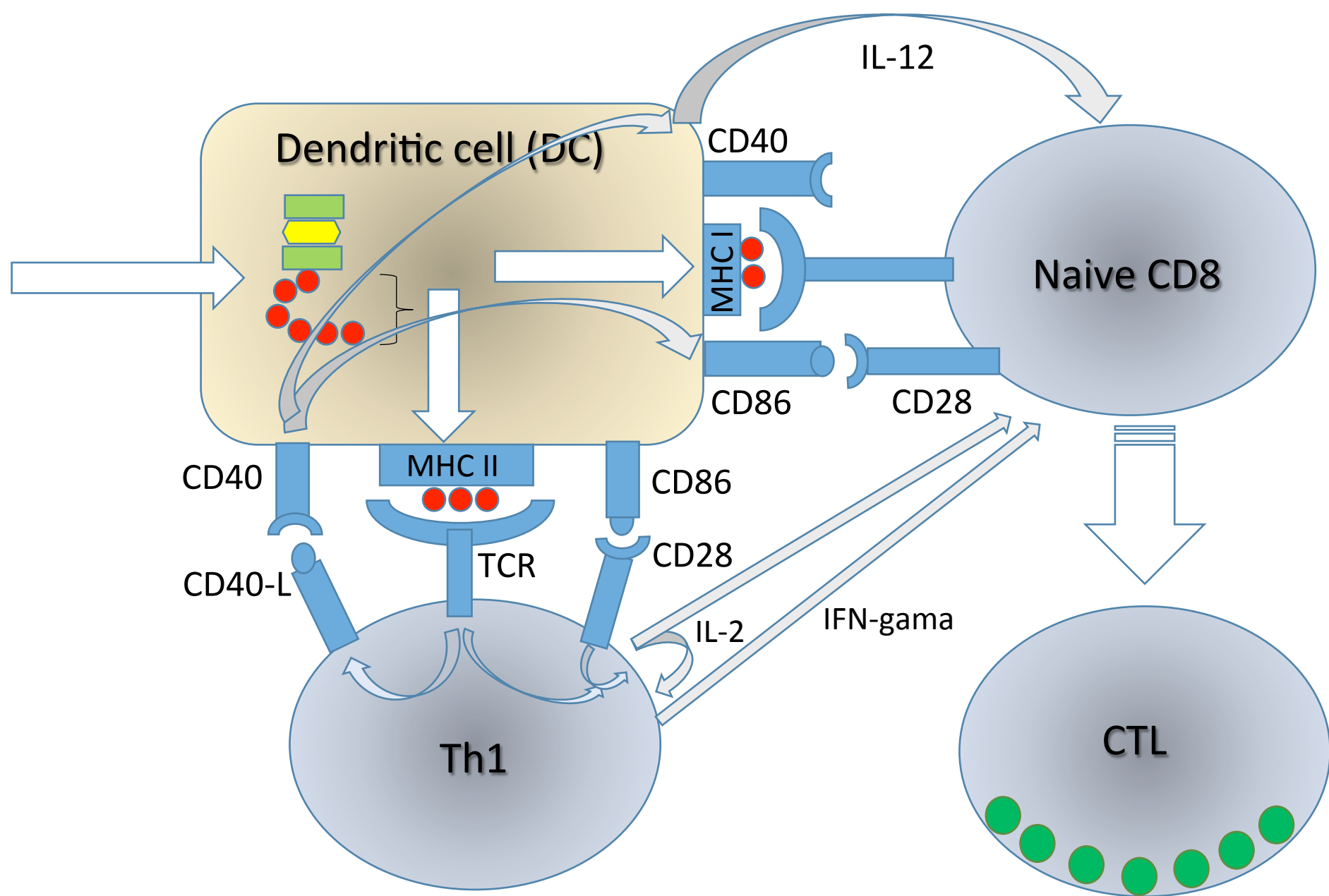
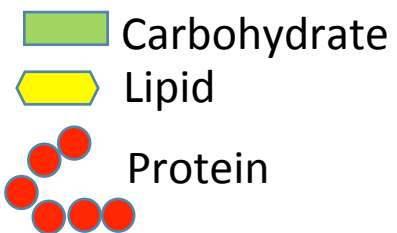


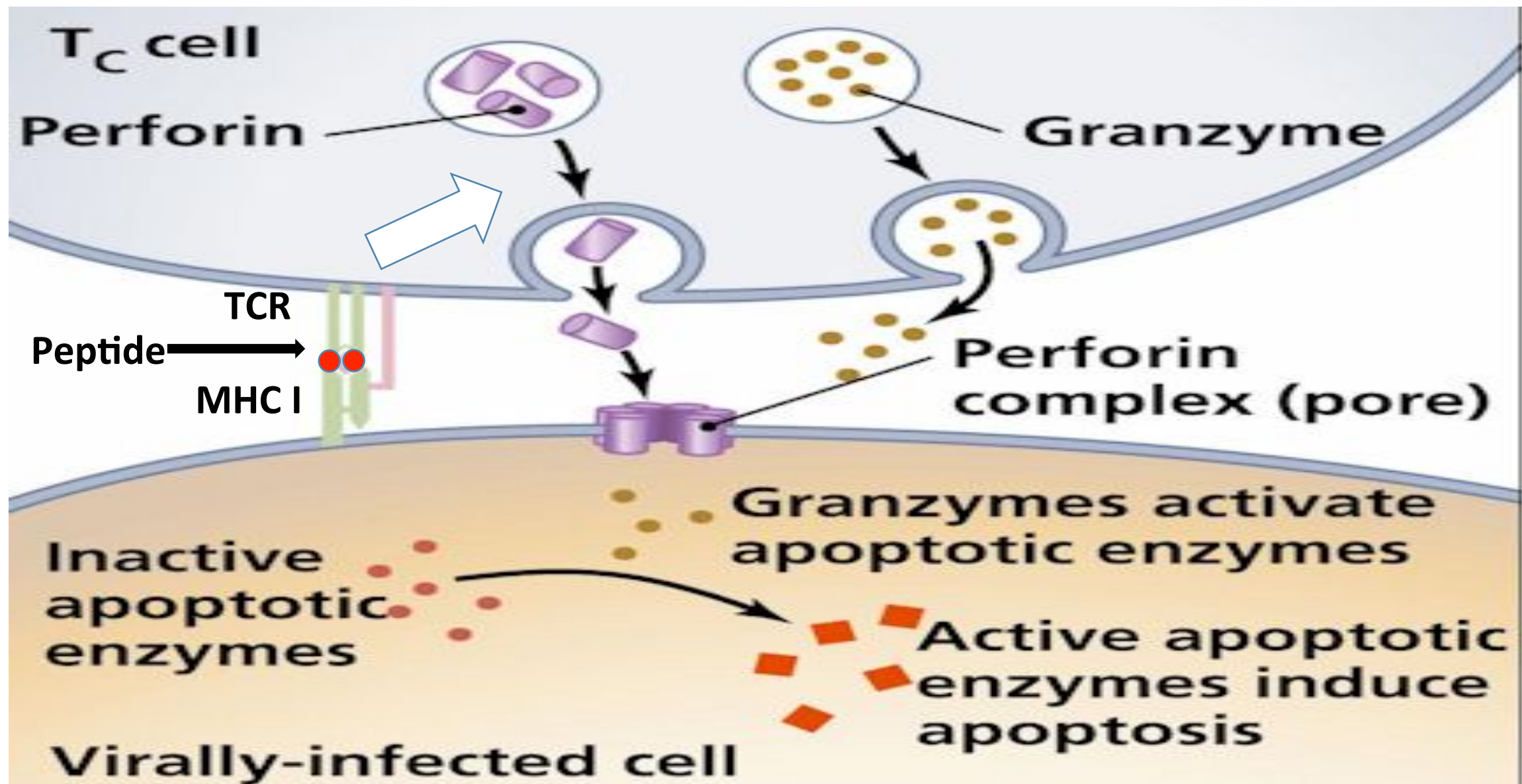


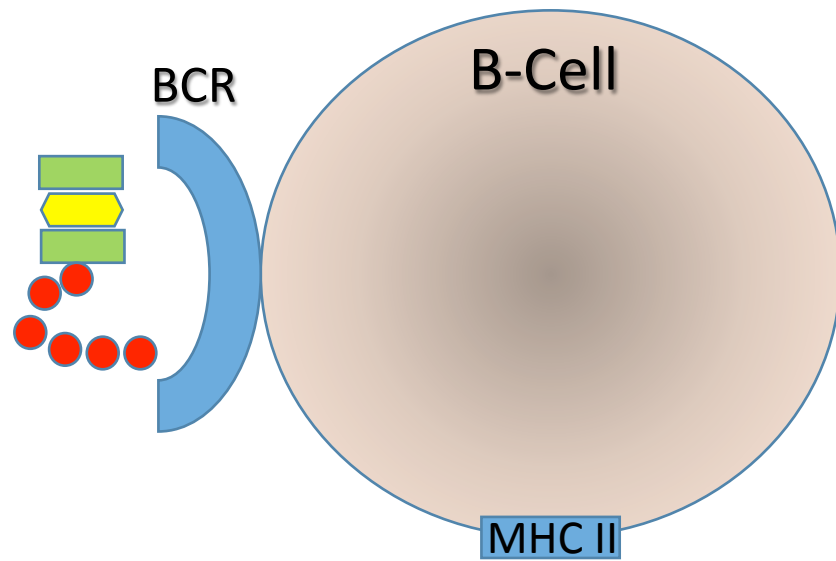
Microbial  
antigen

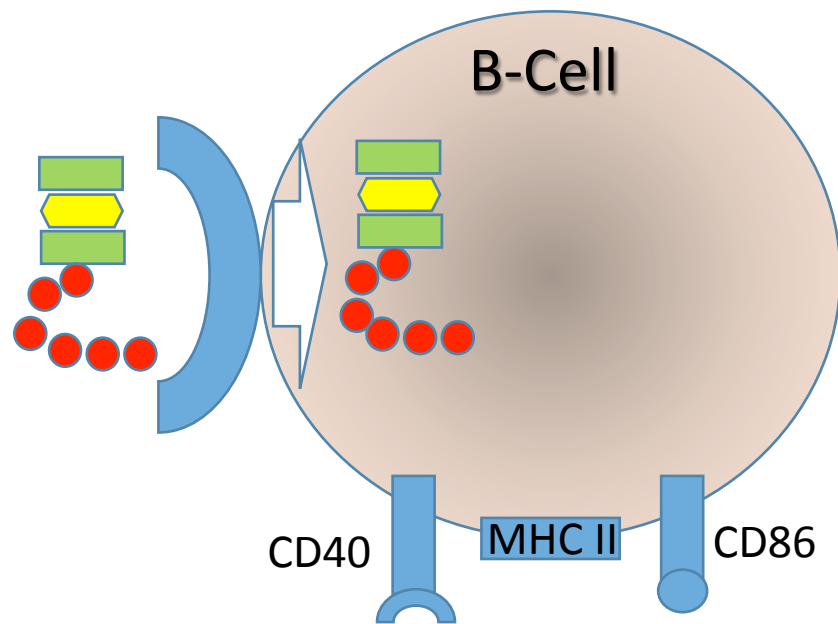


Microbial  
antigen

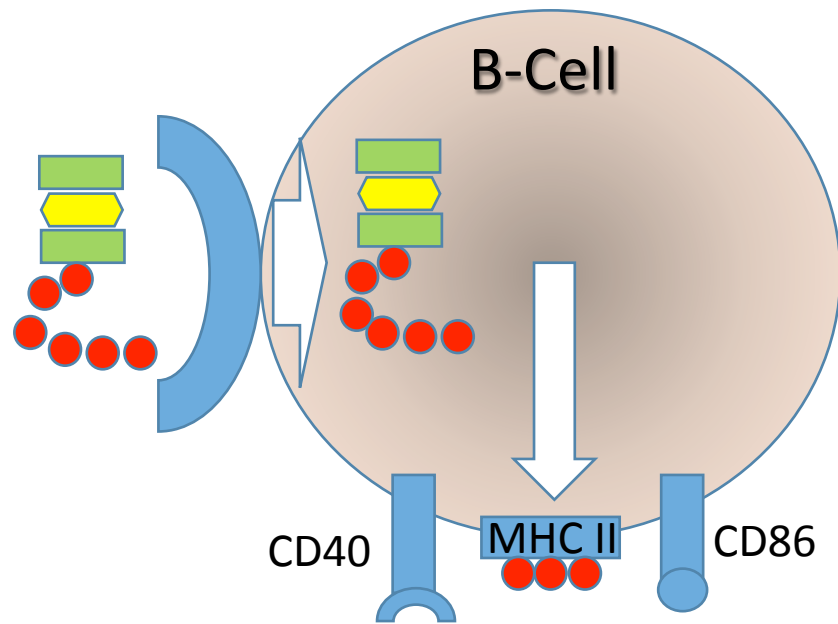


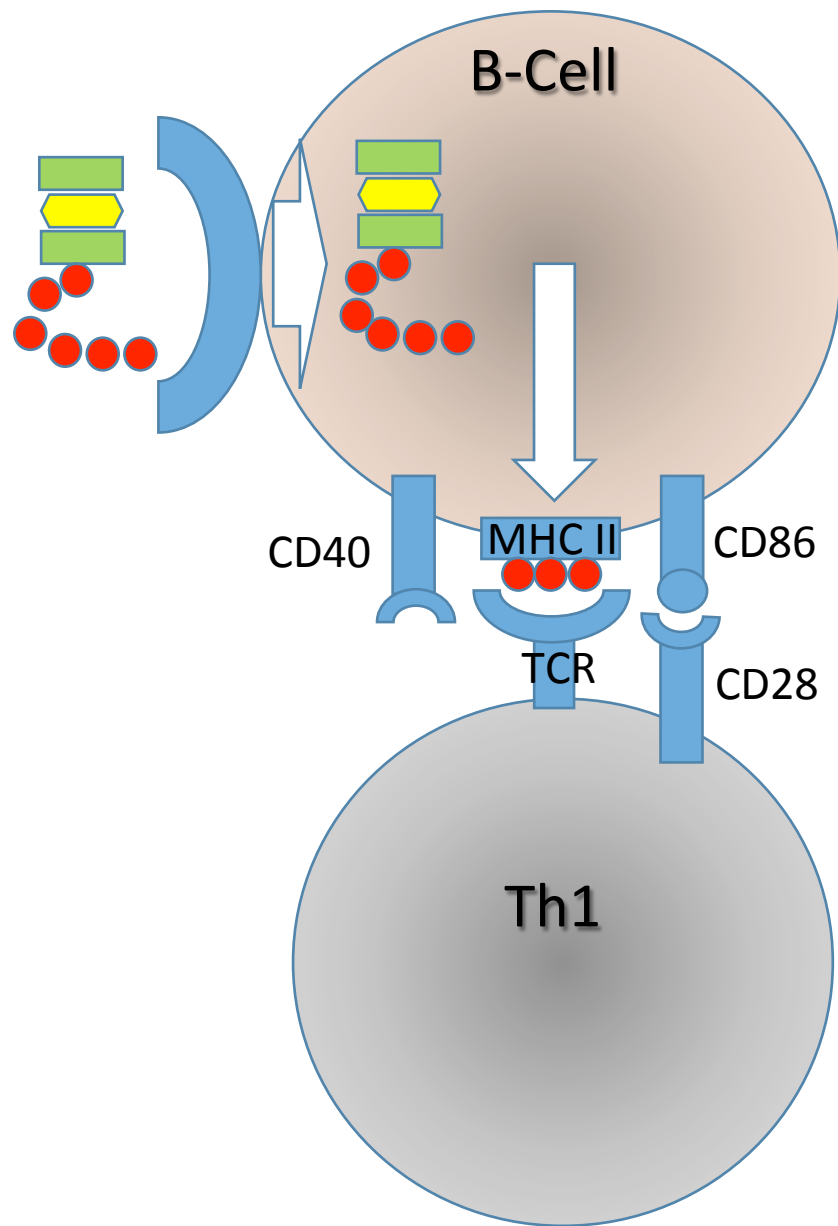


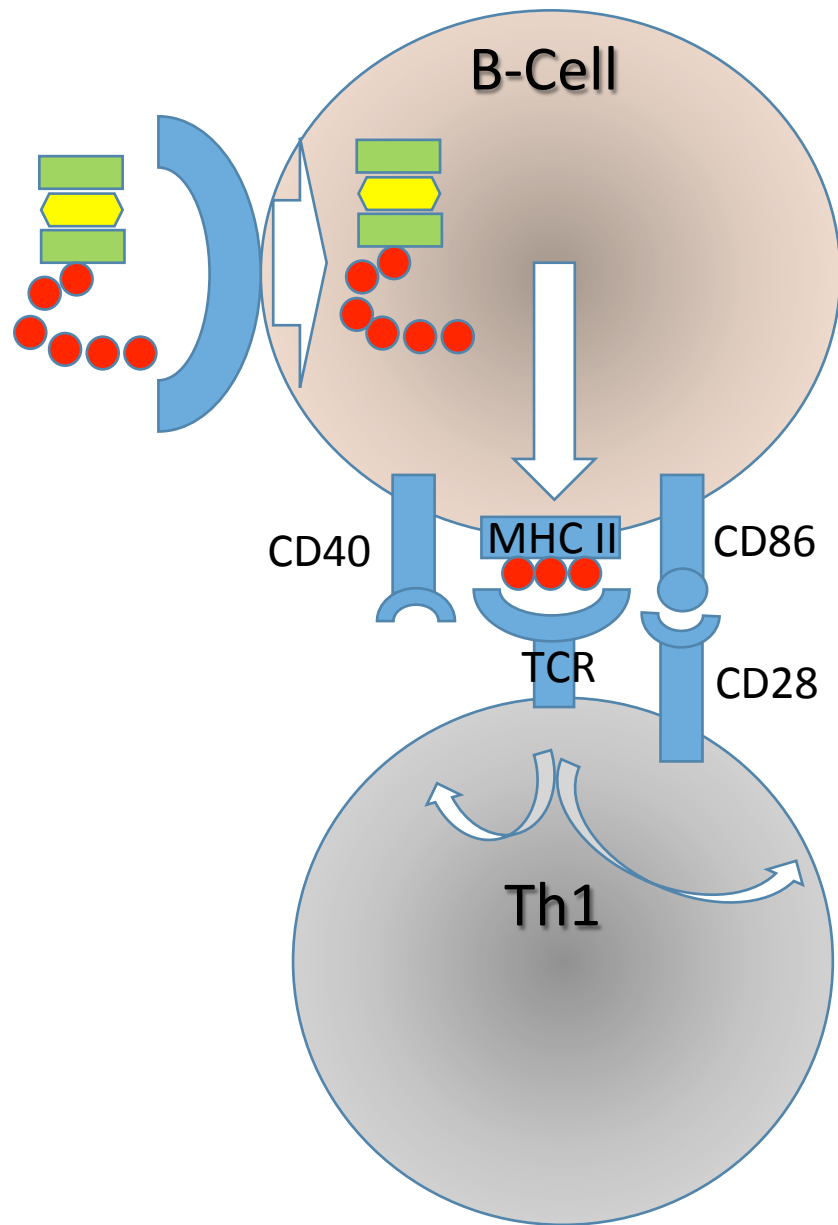


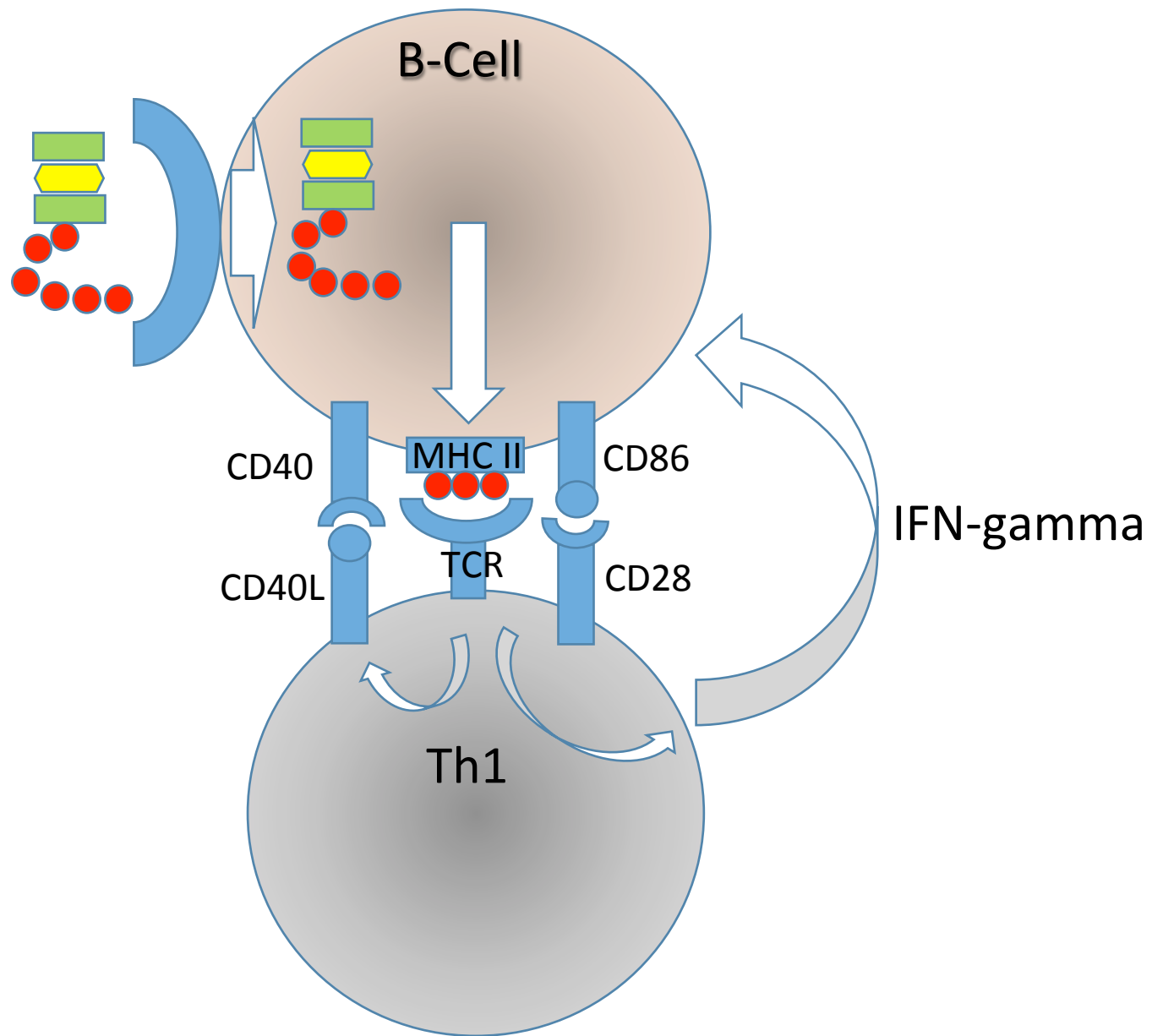


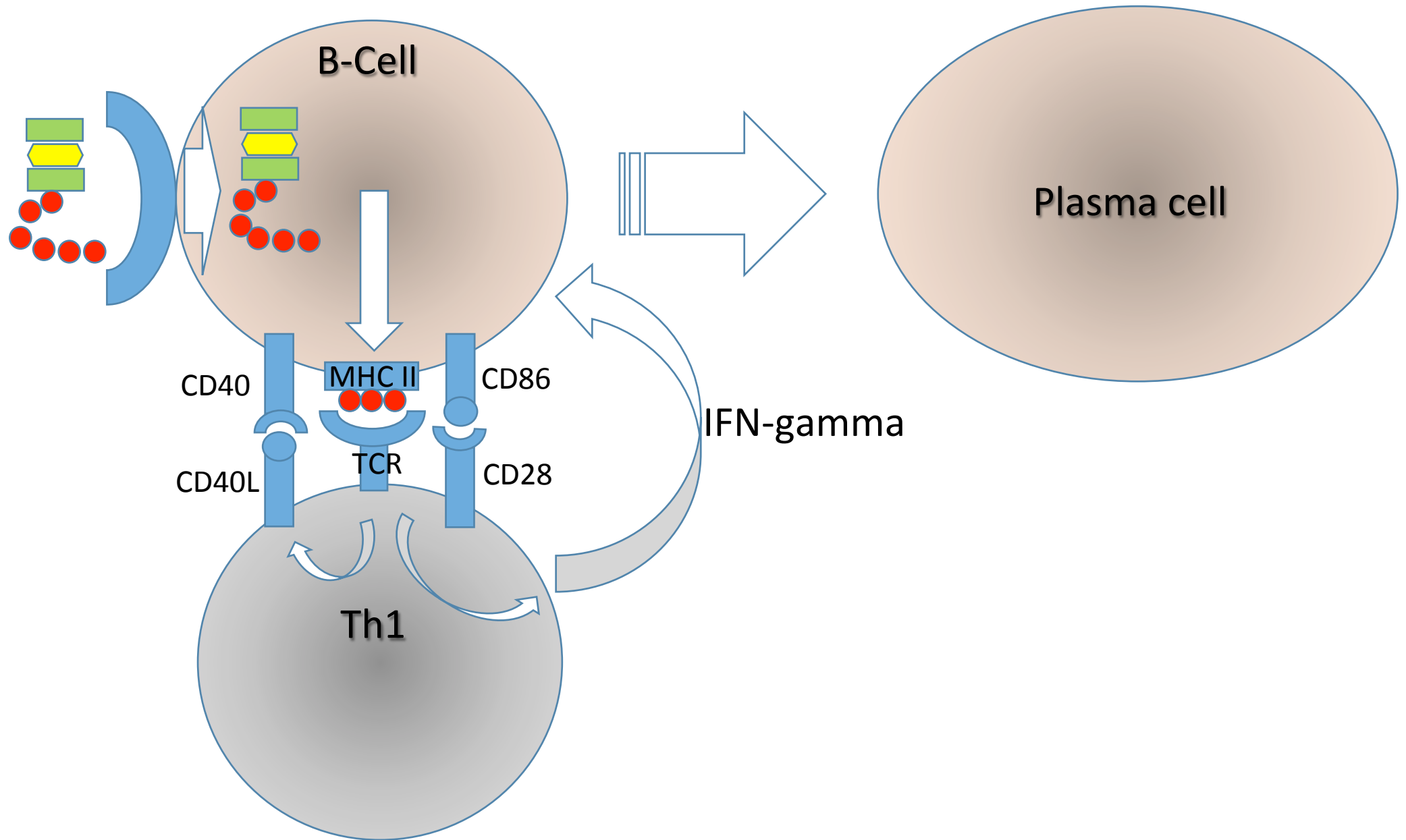




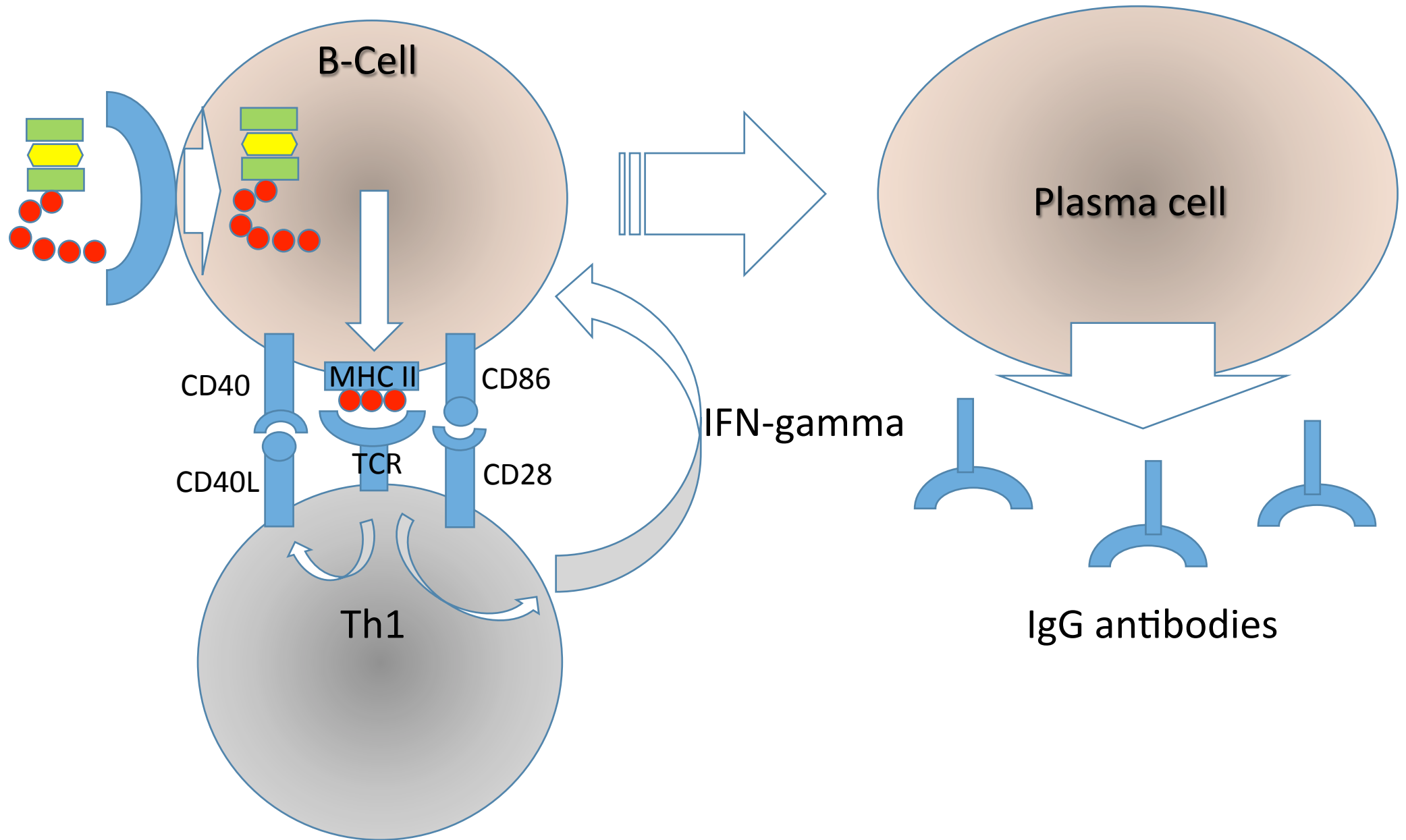


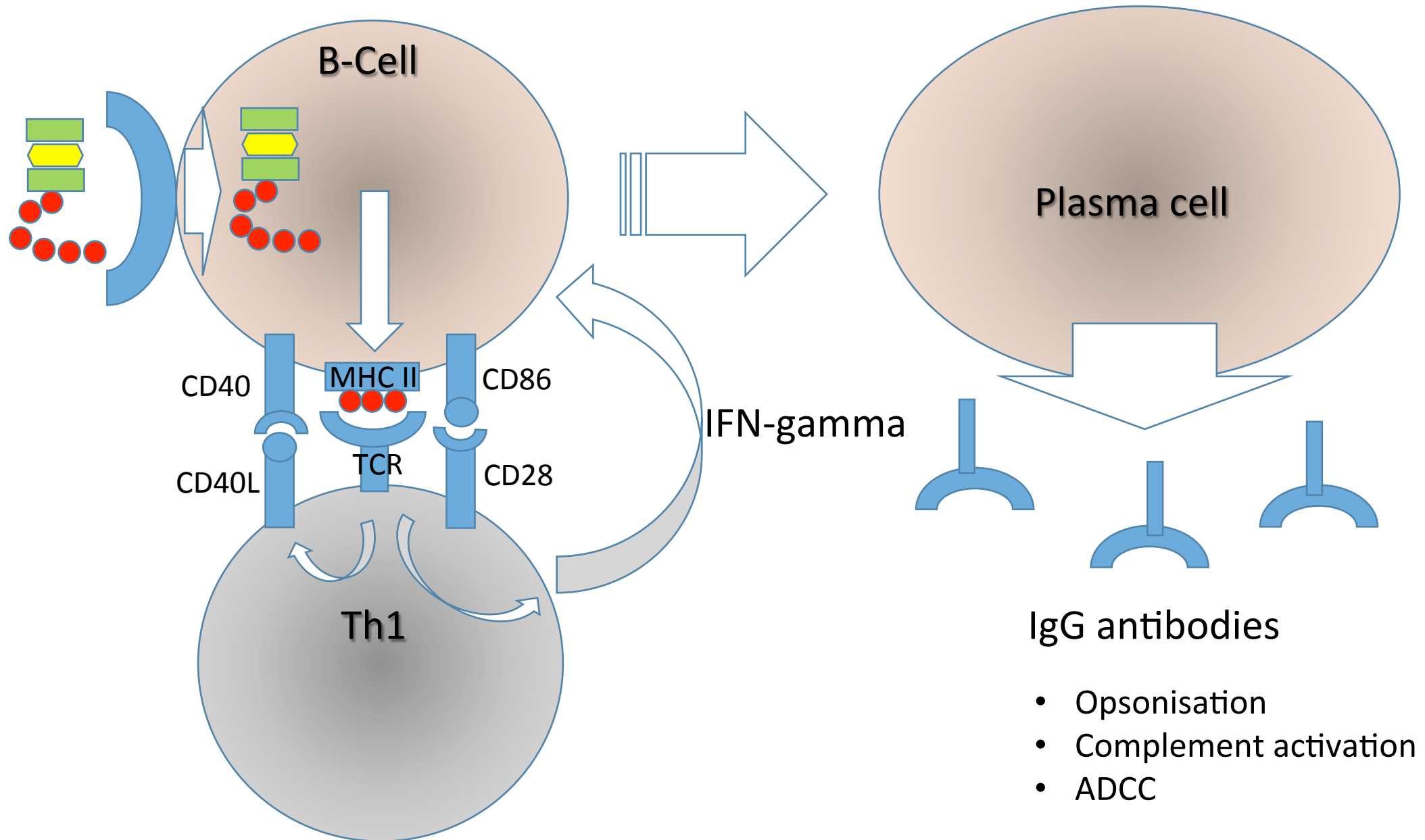




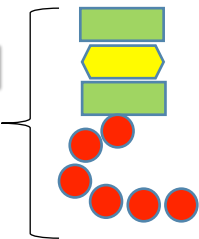








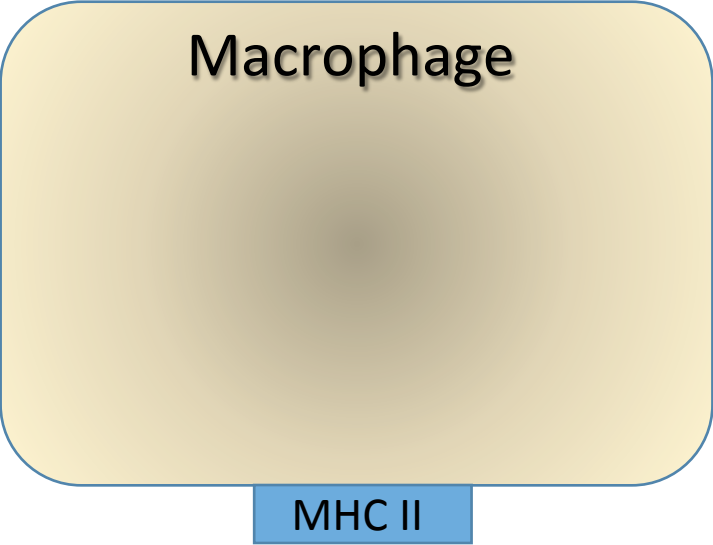
Microbial  
antigen



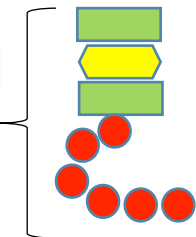
Carbohydrate




Lipid

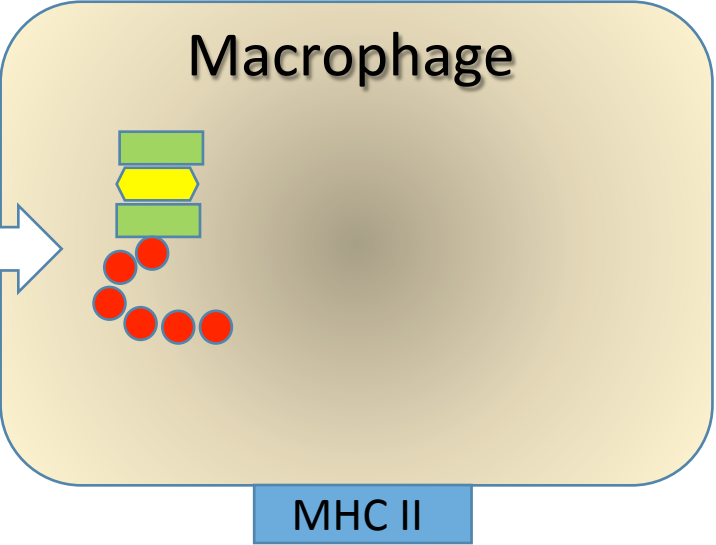
Protein



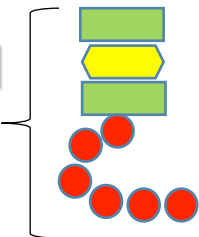
Microbial  
antigen



-  Carbohydrate
-  Lipid
-  Protein



Microbial  
antigen



Carbohydrate

Lipid

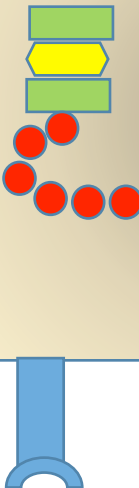
Protein

Macrophage

CD40

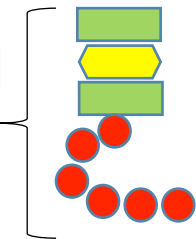
MHC II

CD86





Microbial  
antigen



Carbohydrate

Lipid

Protein

Macrophage

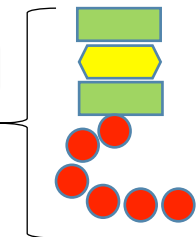
CD40

MHC II

CD86



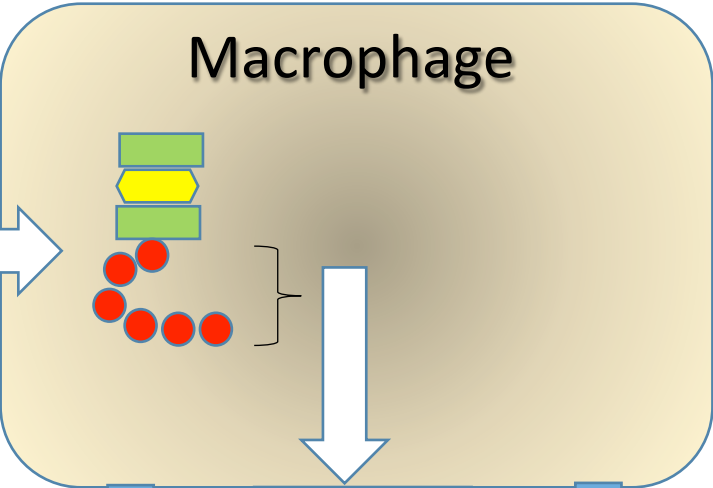
Microbial  
antigen



Carbohydrate

Lipid

Protein



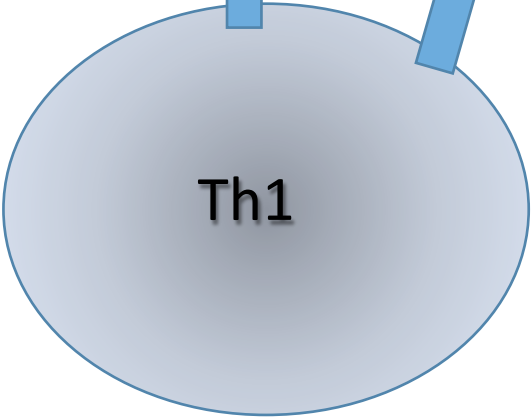
CD40

MHC II

CD86

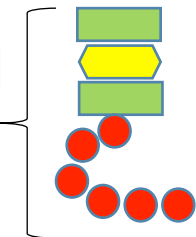
TCR

CD28



Th1

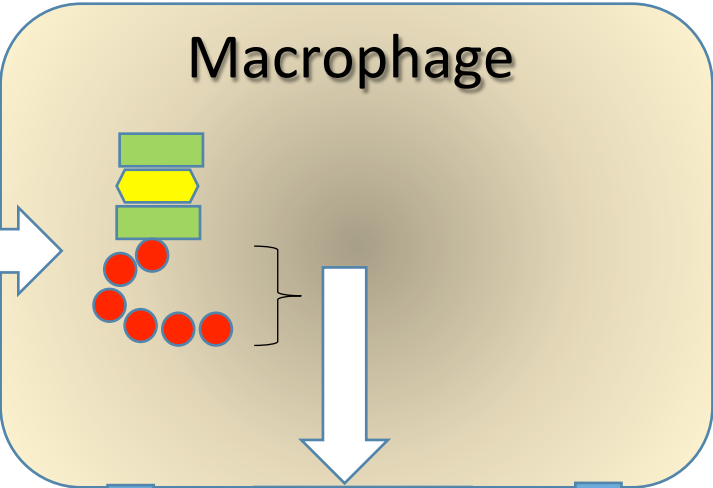
Microbial  
antigen



Carbohydrate

Lipid

Protein



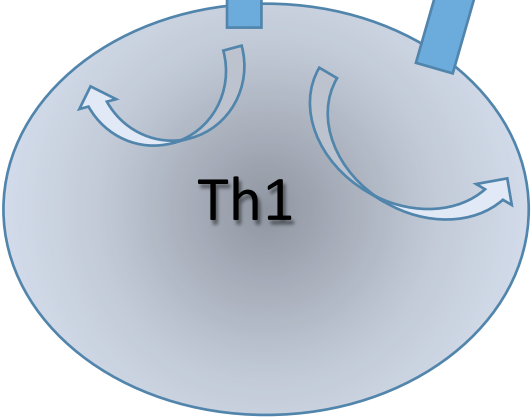
CD40

MHC II

CD86

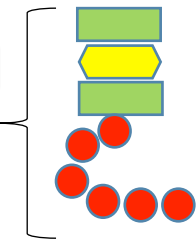
TCR

CD28



Th1

Microbial  
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Carbohydrate

Lipid

Protein

Macrophage

CD40

MHC II

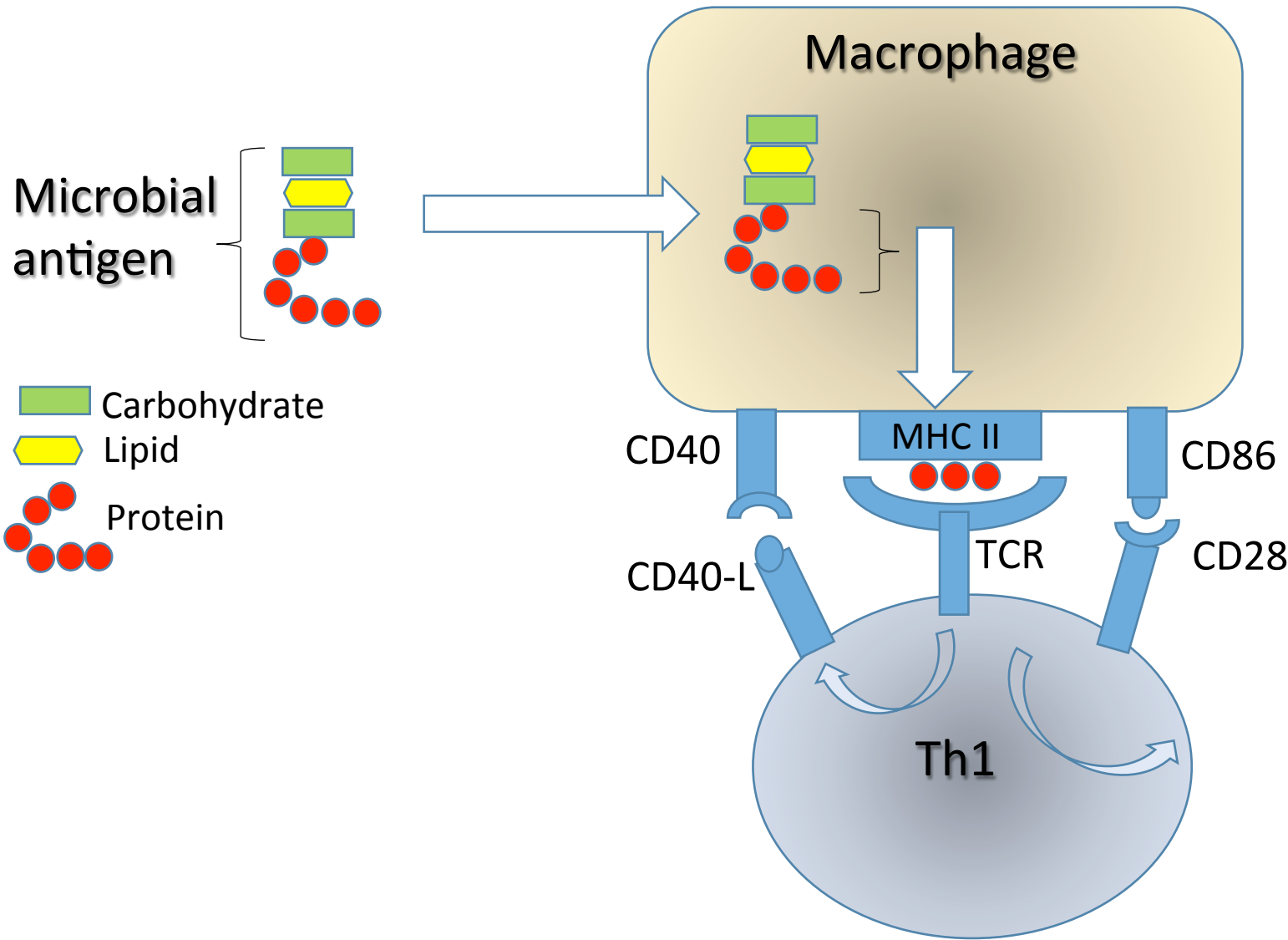
CD86

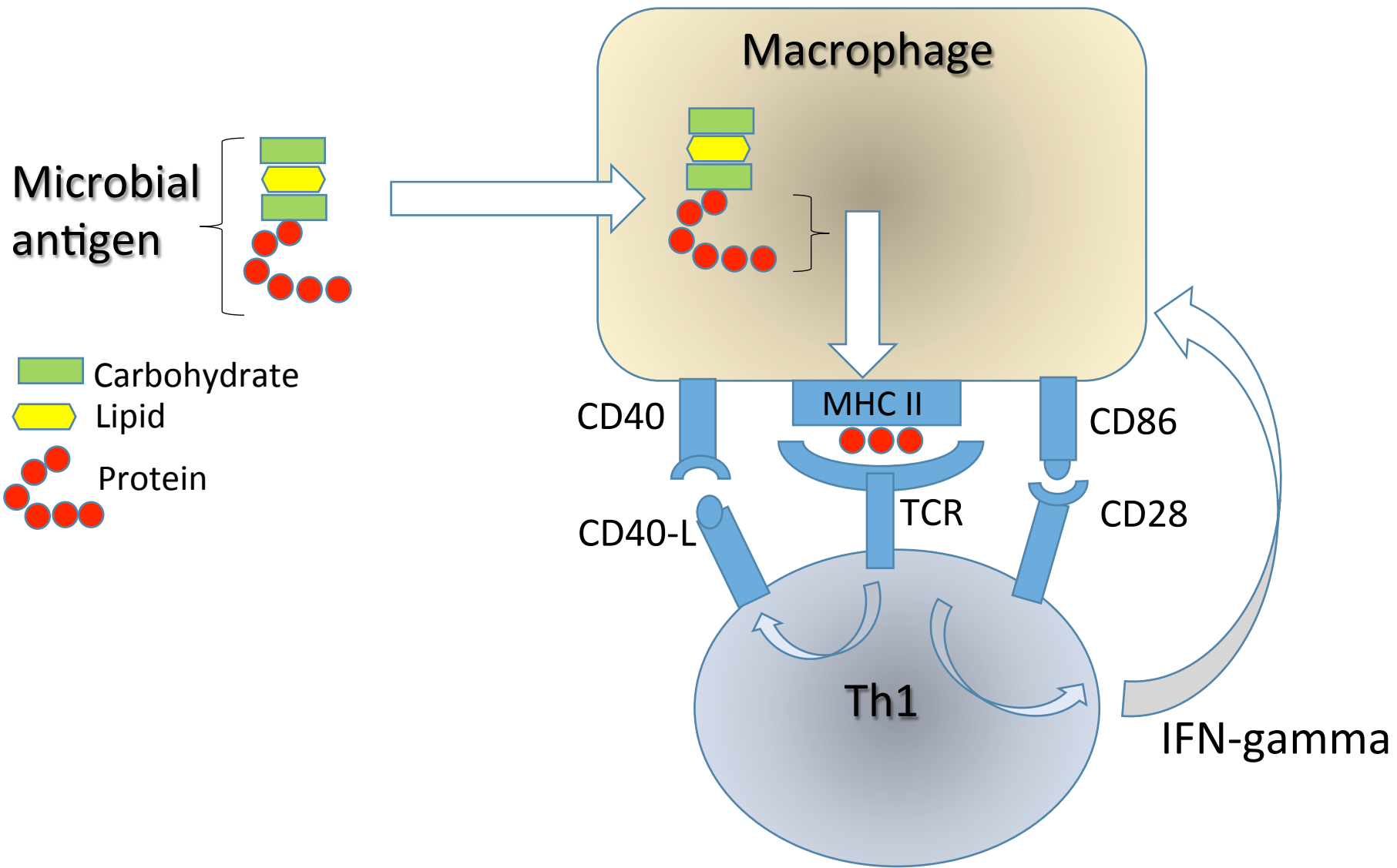
CD40-L

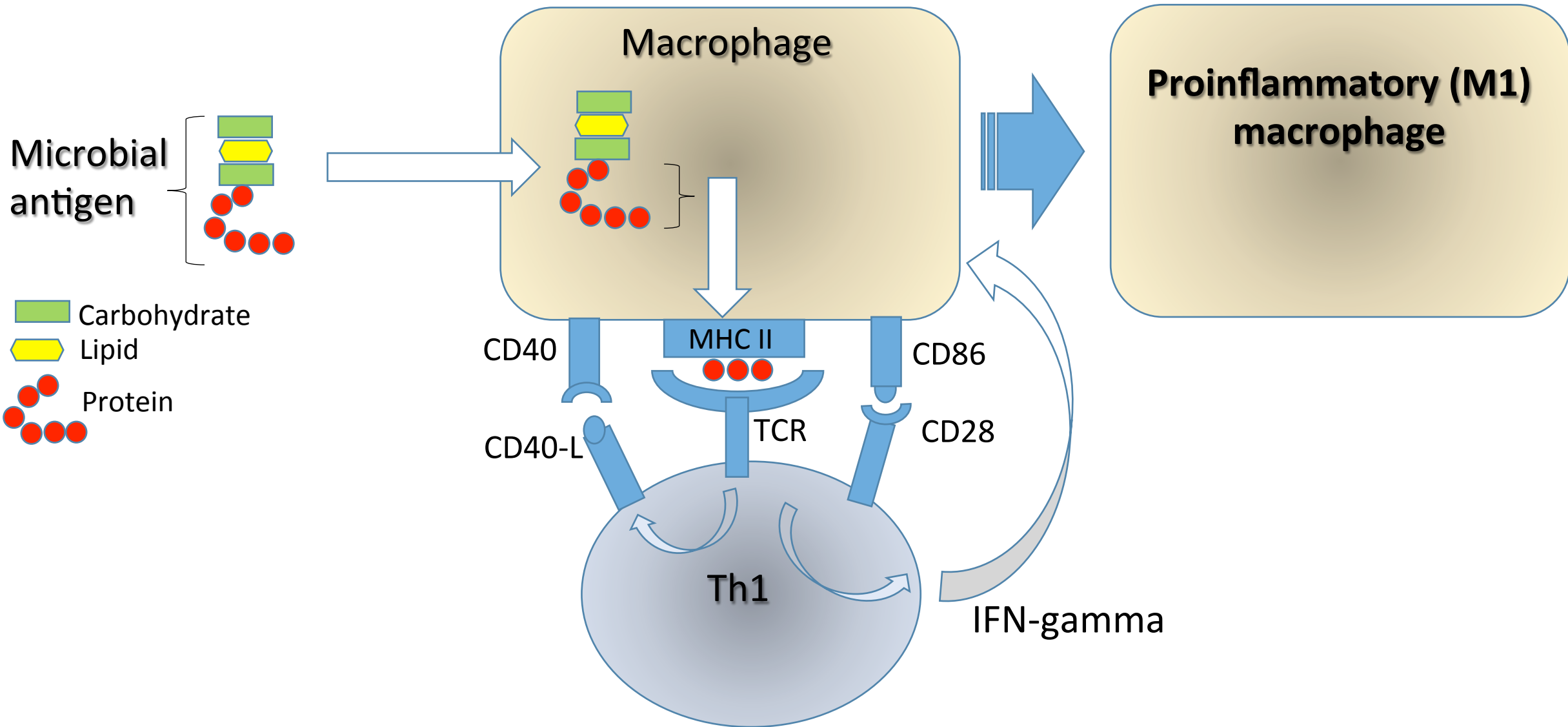
TCR

CD28

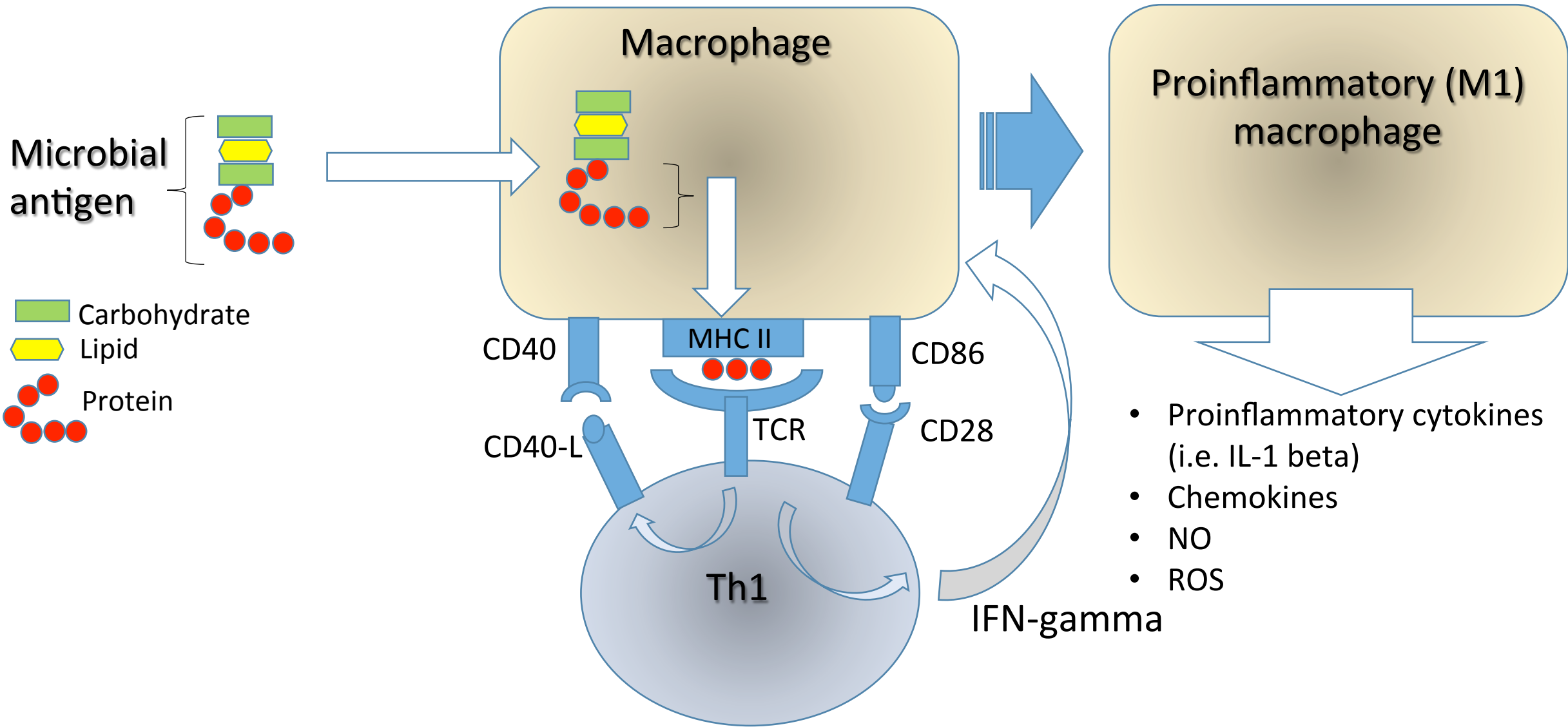
Th1











# The pathogenic mechanism underlying Multiple Sclerosis

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- The exact pathogenic mechanisms underlying MS remains unknown!
- MBP shares extensive homologies at the amino acid level with a number of common pathogens including measles, hepatitis B, influenza virus, and adenovirus
- CD4+ T cells activated in the periphery by a microbial mimic home to the CNS, become attached to receptors on endothelial cells, and then proceed to cross the blood-brain barrier (BBB) directly into the interstitial matrix
- CD4+ T cells become reactivated in-situ by fragments of myelin antigens exposed in the context of MHC class II molecules on the surface of microglia
- Reactivation induces the release of proinflammatory cytokines that open further the BBB and stimulate chemotaxis, resulting in a second, larger wave of inflammatory cell recruitment and leakage of pathogenic antibodies and other plasma proteins into the nervous system.

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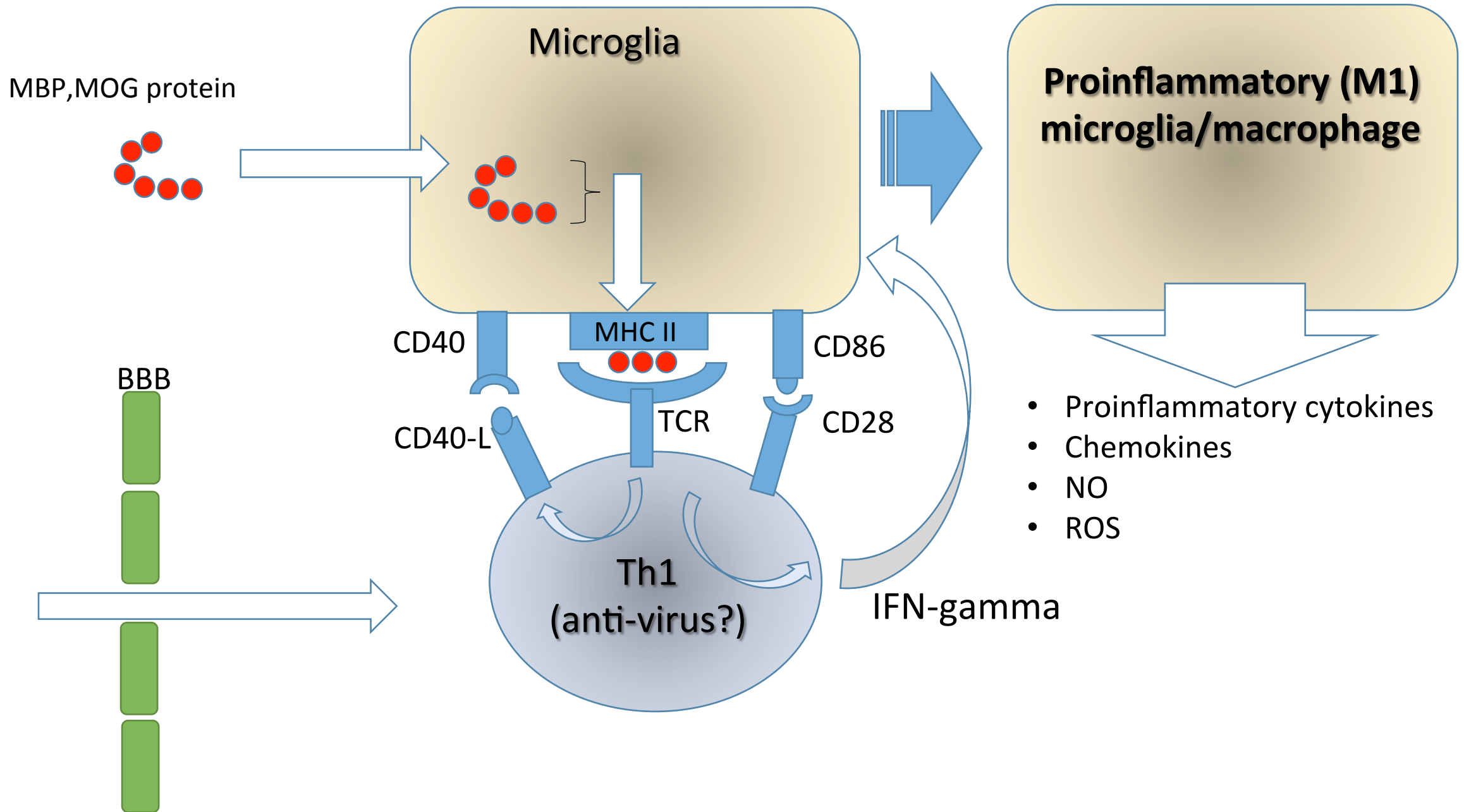
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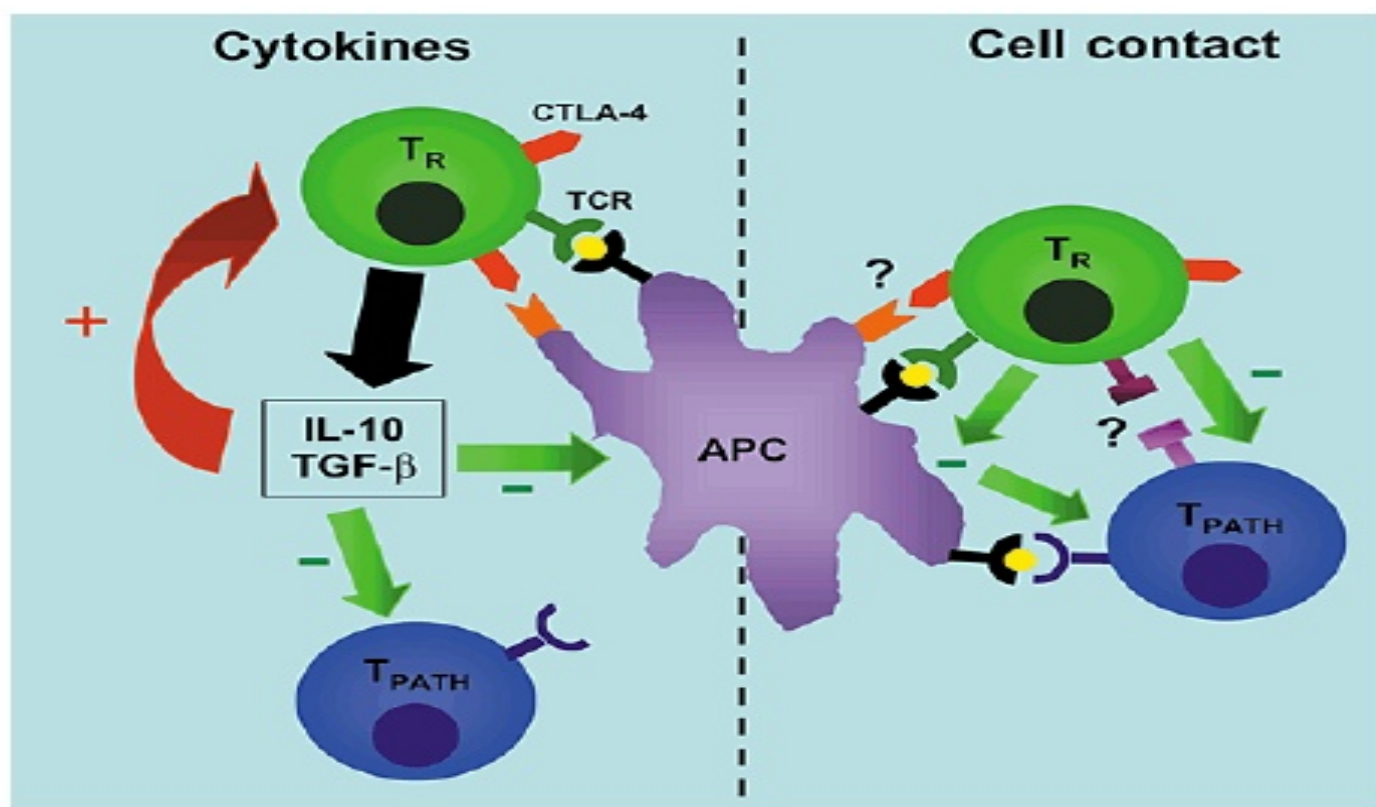
# The role of B-cells/antibodies

- Class-switched antibodies reactive with CNS components including MBP and MOG are detected as oligoclonal bands in the cerebrospinal fluid of MS patients
- IgG antibodies from MS patients caused demyelination in a complement-dependent manner when using both *in vivo* and *in vitro* models.
- Plasmapheresis and immunoadsorption in order to remove antibodies and complement factors have shown promising results as treatment for MS patients with steroid-resistant relapses
- Additional to antigen-presentation molecules, costimulatory molecules, such as CD80, CD86, and CD40, are expressed on B cells and contribute to optimal T cell activation
- B cells are essential for the generation of optimal pathogenic CD4<sup>+</sup> T cell responses and differentiation of myelin reactive Th1 and Th17 cells.

# The role of CD8<sup>+</sup> T cells

- On the genetic level, positivity for the HLA class I allele A3 increases one's risk of developing MS
- Myelin-specific CD8<sup>+</sup> T cells show oligoclonal expansion in plaques, cerebrospinal fluid (CSF), and blood of MS patients, and the frequency of CD8<sup>+</sup> T cells greatly exceeds that of CD4<sup>+</sup> T cells in acute MS lesions
- Granzyme B-positive CD8<sup>+</sup> T cells are found in close proximity to demyelinated axons in MS lesions and their cytolytic granules appear to be polarized toward the site of injury
- CSF levels of granzymes A and B are elevated during active MS
- Various cells of the CNS, including oligodendrocytes, can be induced to express MHC class I on their surface in the context of an inflammatory response.

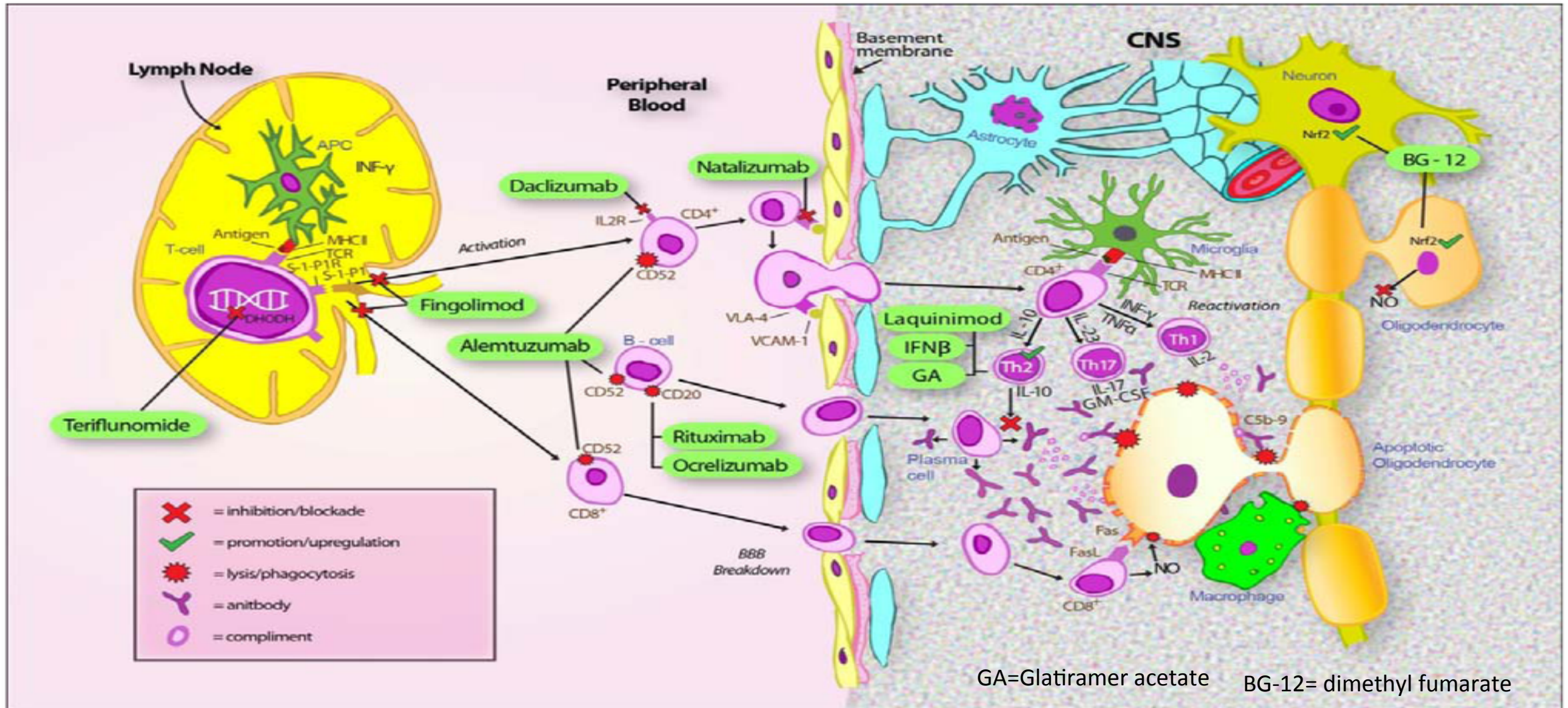
## T Regulatory Cells ( $T_R$ )



Maloy and Powrie, Nature Immunol. 2:816



# Mode of action of different MS-drugs





Tack för  
uppmärksamheten!