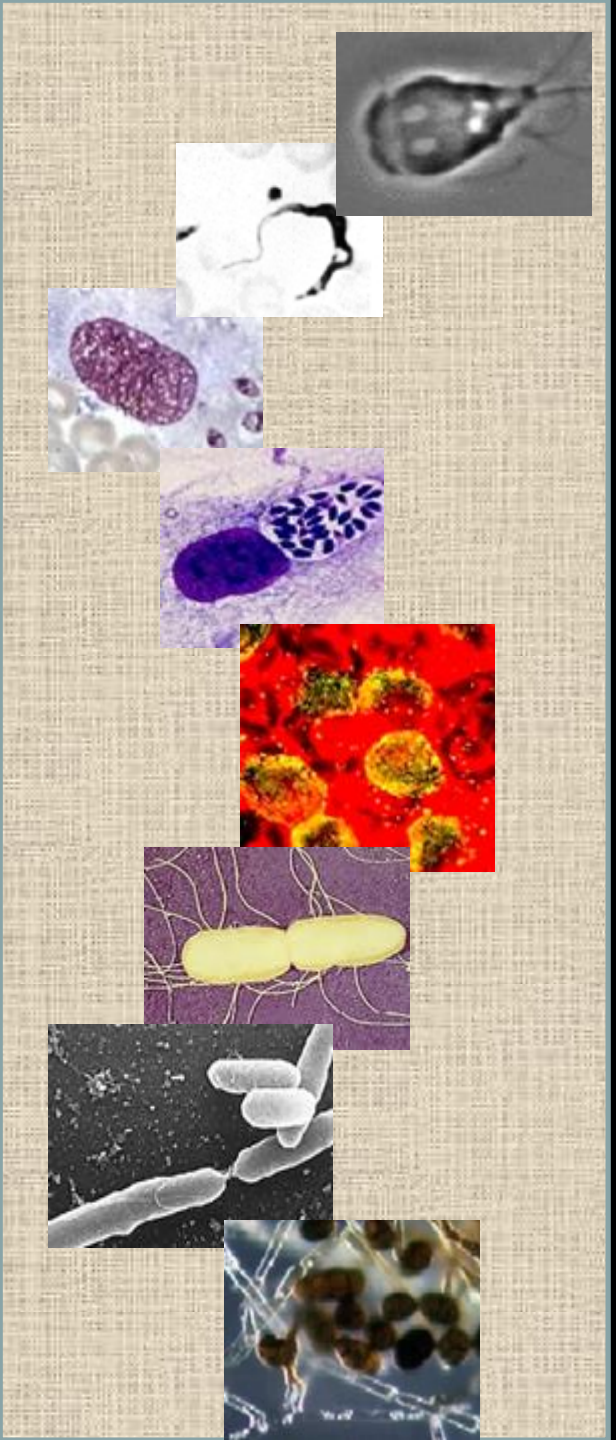


Imunidade Adaptativa

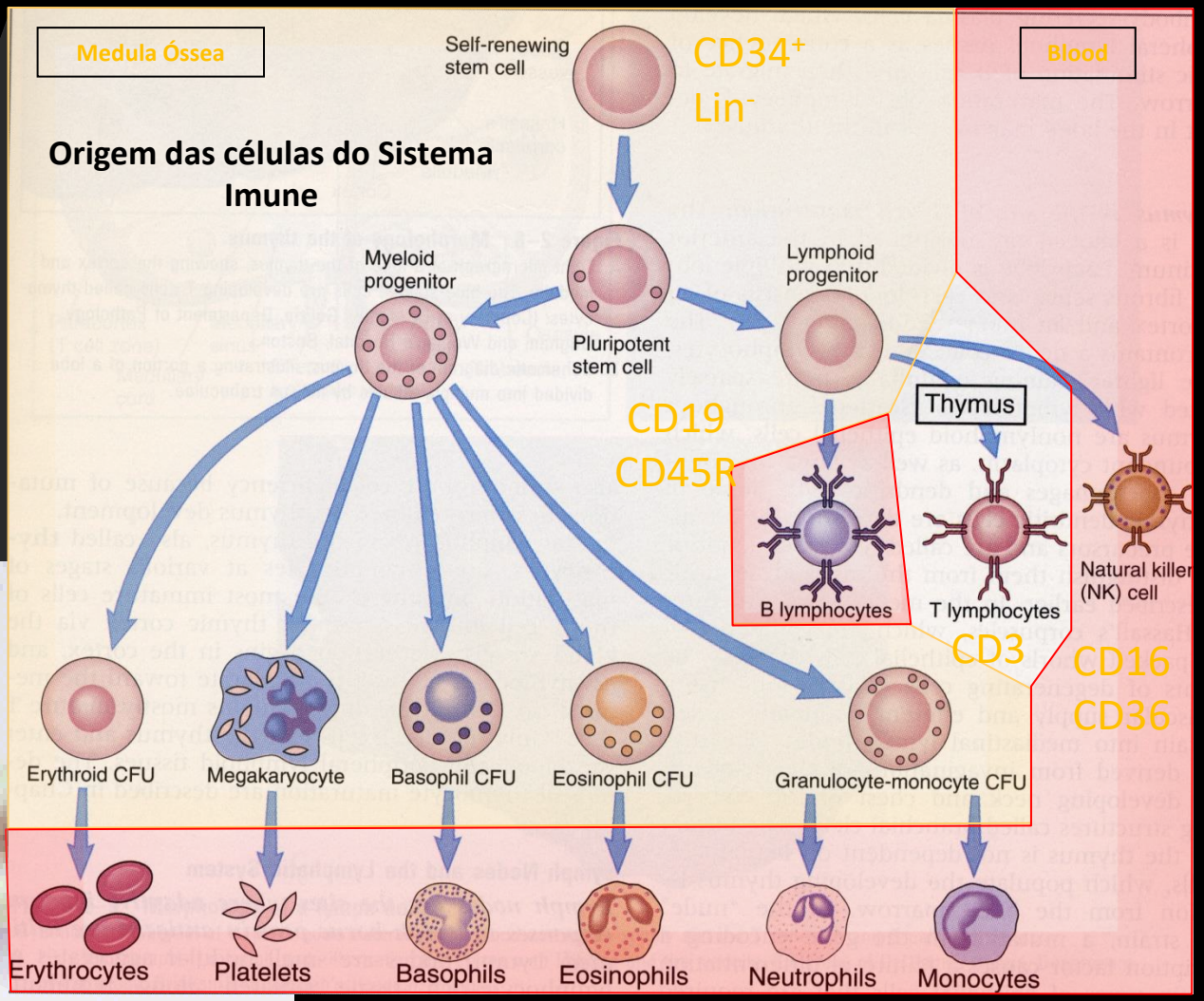
Dr. Jean Pierre Schatzmann Peron

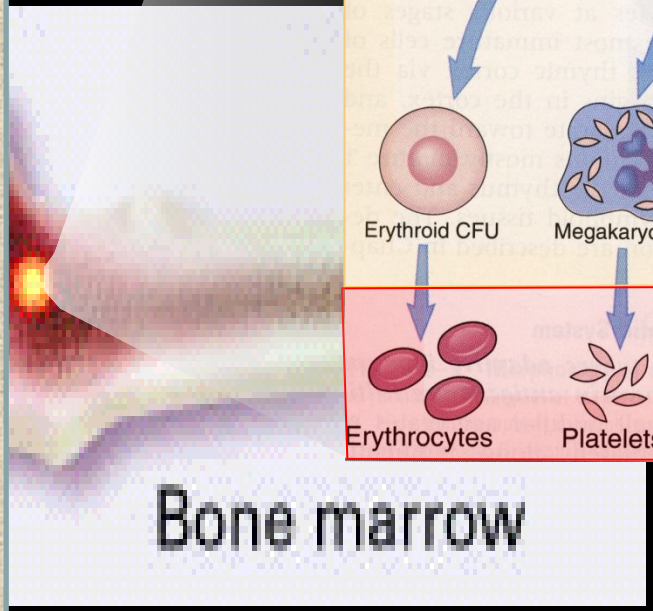
Laboratório de Interações Neuroimunes
Departamento de Imunologia
Universidade de São Paulo

Objetivos

- Células do Sistema Imune Adaptativo
- Geração e Localização
- Seus Receptores de Reconhecimento
- Apresentação de Antígenos
- Classificação Funcional dos Linfócitos T CD4 e Suas Funções

Medula Óssea – Orgão Linfóide Primário

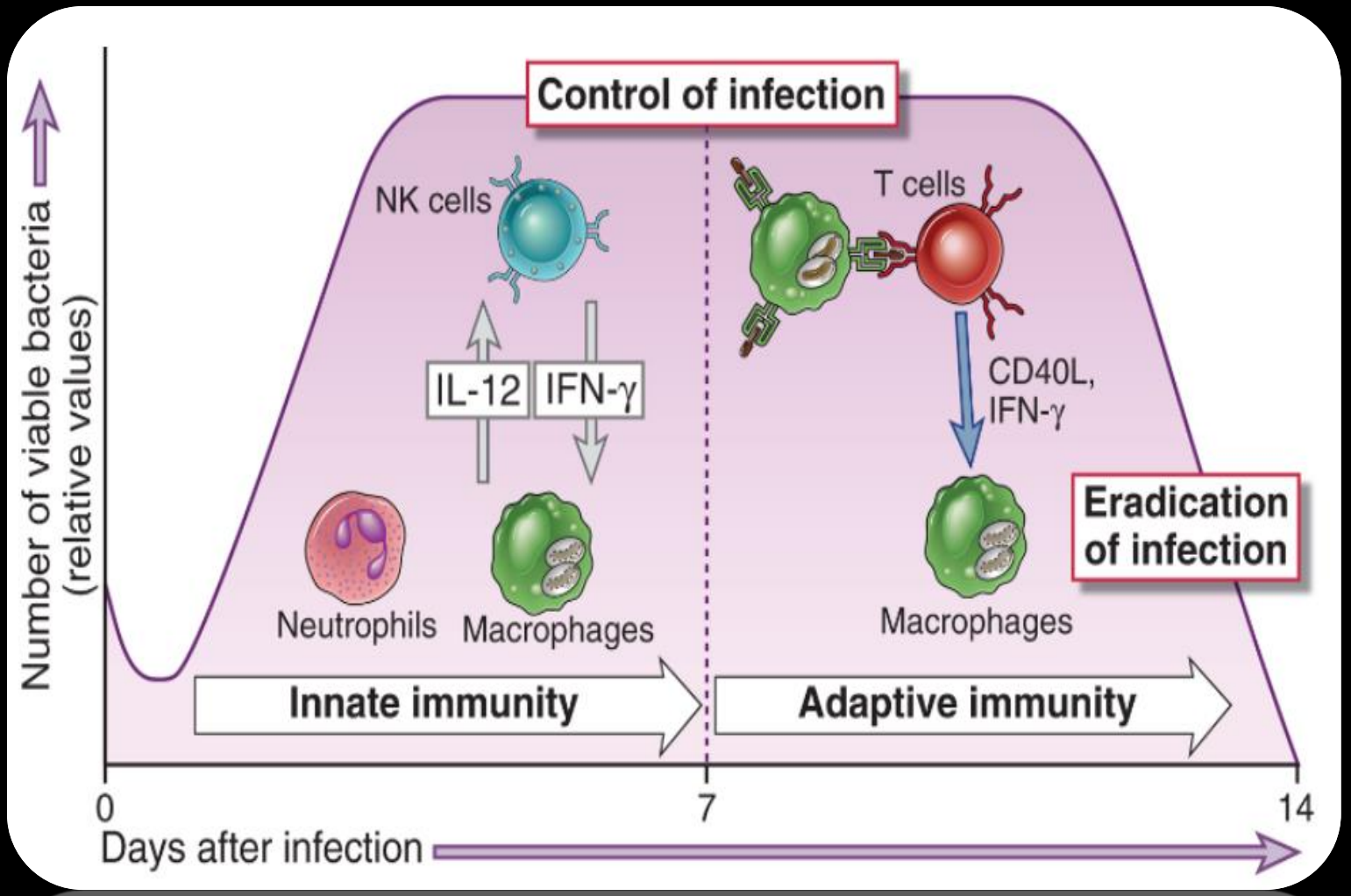




Abbas A. Cellular and Molecullar Immunology. 8th adition

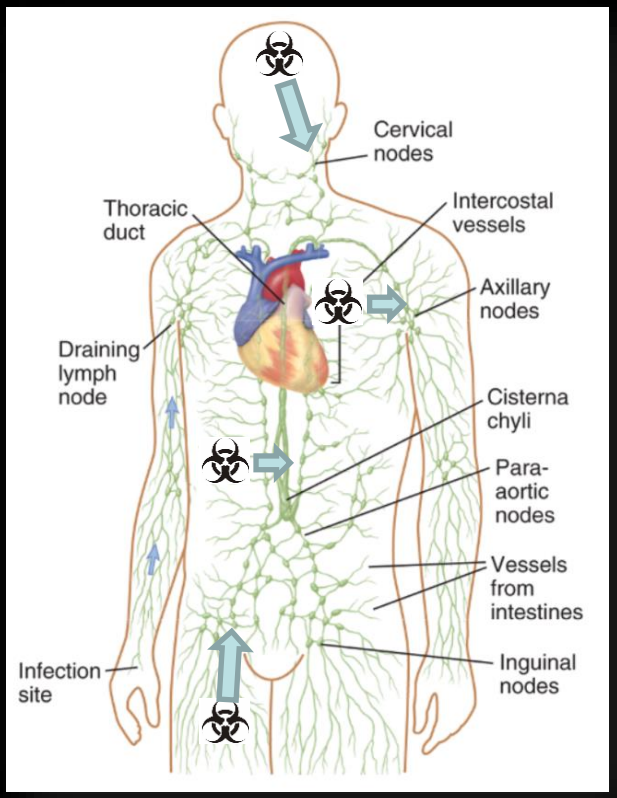
Resposta Imune

Inata X Adaptativa



Abbas A. Cellular and Molecullar Immunology. 8th adition

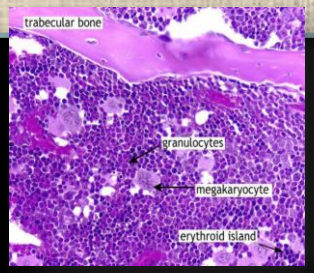
Sistema Linfático – Drena o Líquido Intersticial - LINFA



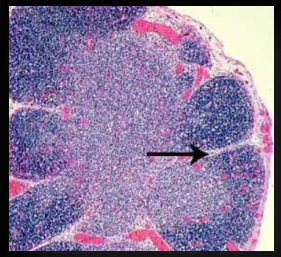
Abbas A. Cellular and Molecullar Immunology. 8th adition

Componentes do Sistema Imune

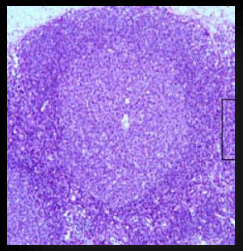
- Órgãos Linfóides
  - **Primários** – Timo e Medula Óssea
  - **Secundários** – Linfonodos, baço, Placas de Payer
  - **Terciários** – Tecidos ectópicos Ex: Esclerose múltipla, Tireoidite Hashimoto



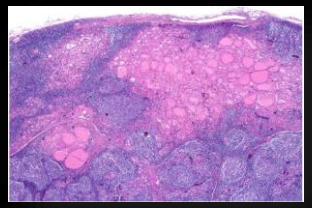
Medula Óssea


Timo

- **Células do Sistema Imune** – Evolutivamente Divididas em Imunidade Inata e Adaptativa
  - **Inata** – Macrófagos, Células Dendríticas, Neutrófilos, NKs, Basófilos, Eosinófinos, etc
  - **Adaptativa** – Linfócitos T e B


Linfonodos

- Células com FUNÇÃO IMUNE
  - Fibroblastos, hepatócitos, plaquetas, astrócitos, etc...


Folículos Linfóides

Estrutura das Moléculas de MHC I e II

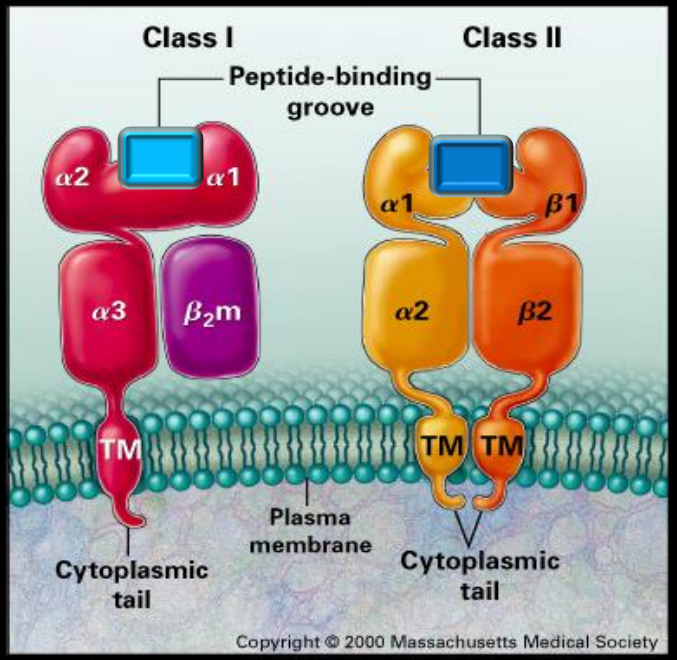
Apresentação de Antígenos

É Um Fenômeno Fisiológico

CONSTANTE

AUTO-ANTÍGENOS

Protéinas Endógenas Degradadas

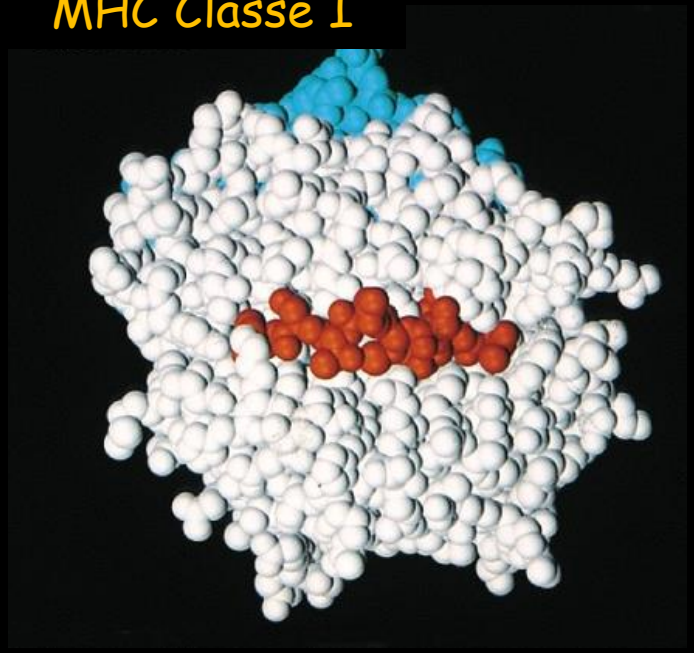


Klein J, Sato A. The HLA System. First of two parts. N Engl J Med 2000;343:702-9.

The New England Journal of Medicine

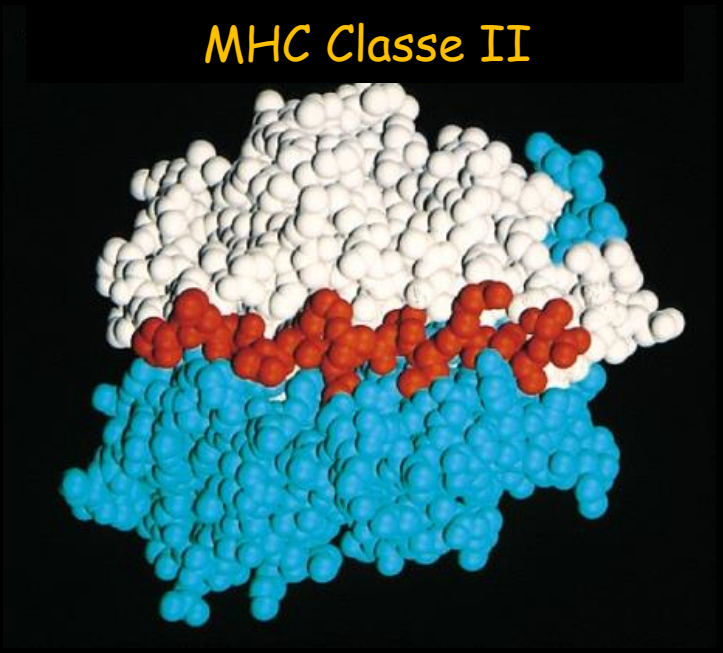
Estrutura das Moléculas de MHC I e II

MHC Classe I



Todas as células Nucleadas

MHC Classe II

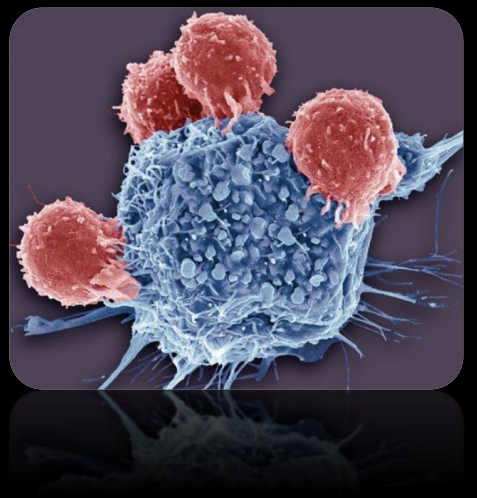


Apresentadoras de Antígeno Profissionais

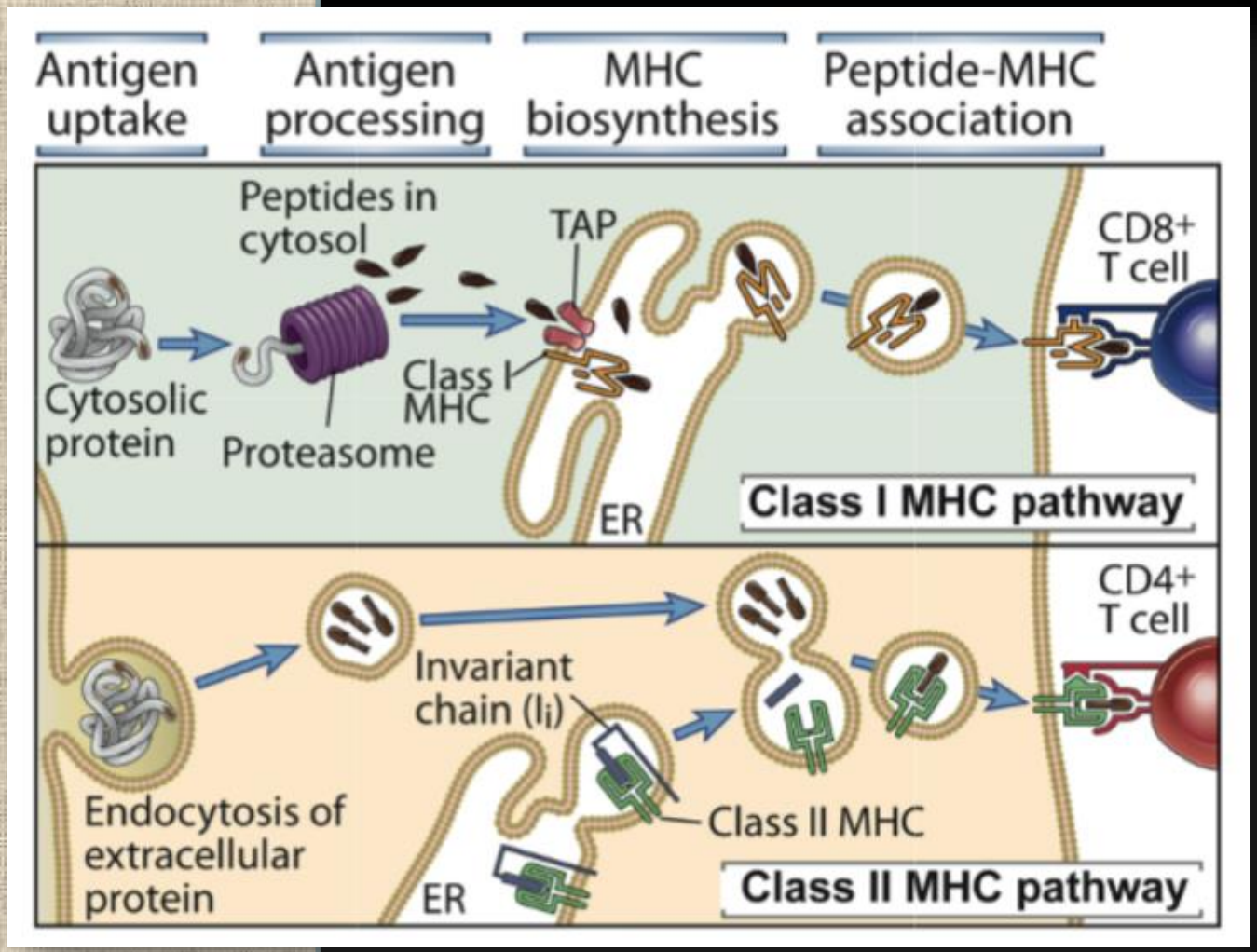
Abbas A. Cellular and Molecullar Immunology. 8th adition

As Moléculas do MHC

- são constantementMolécula de MHC I e II e sintetizadas;
- As mesmas não existem na AUSÊNCIA DE ANTÍGENO;
- 99,9% do tempo esses ANTÍGENOS SÃO PRÓPRIOS
- Moléculas MHC I apresentam Antígenos Citosólicos aos Linfócitos T CD8 (Citotóxicos);
- Moléculas MHC II apresentam Antígenos Internalizados aos Linfócitos T CD4 (FAGOCITOSE);



Apresentação de Antígenos



Antígenos Intracelulares

Actinas, miosinas, citocinas, fatores de transcrição, antígenos órgão específicos (Insulina, Mielina, Tropomiosina, IRBP...)

Antígenos Extracelulares

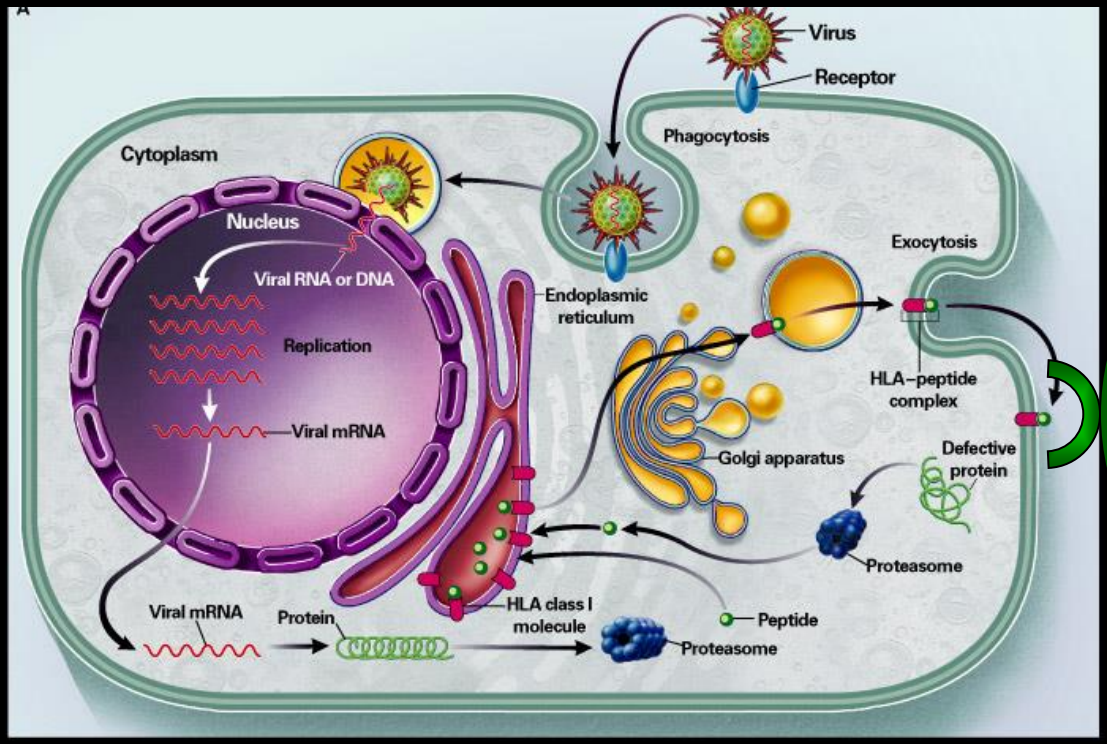
Internalizados

Debris celulares, células Em apoptose,

APRESENTAÇÃO CRUZADA

Abbas A. Cellular and Molecullar Immunology. 8th adition

Apresentação de Antígenos via MHC Classe I
HLA- A, B, C

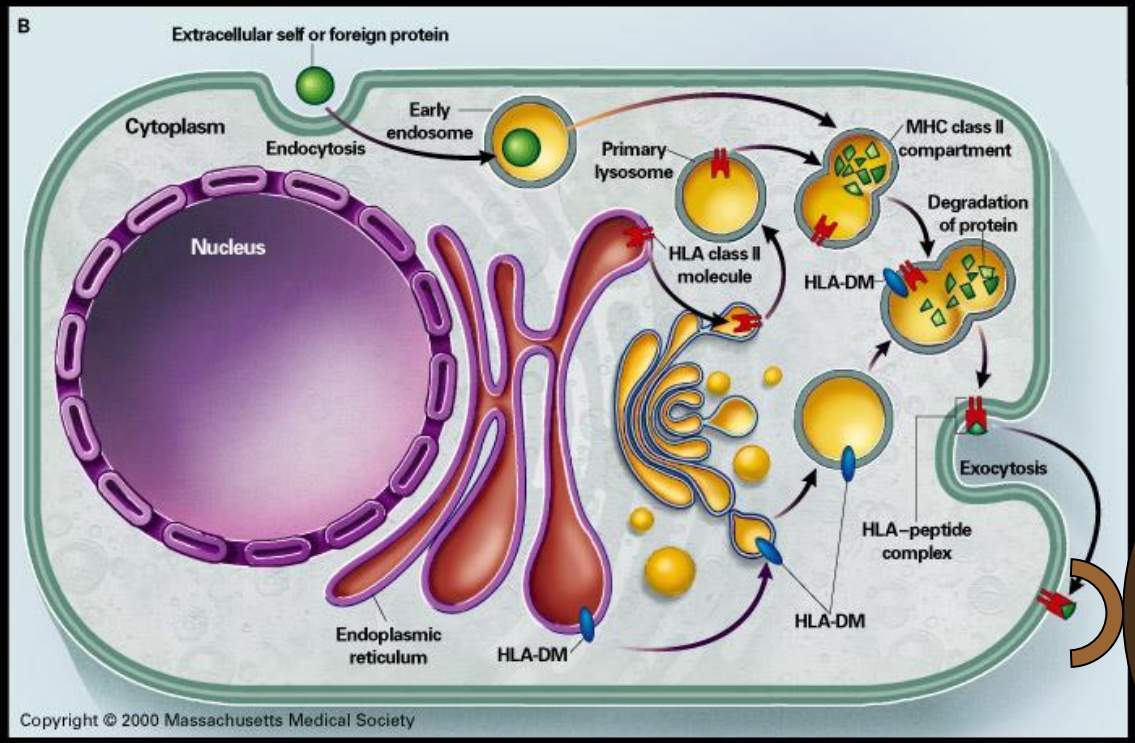


T CD8

Klein J, Sato A. The HLA System. First of two parts.
N Engl J Med 2000;343:702-9.

The New England Journal of Medicine

Apresentação via MHC Classe II
HLA-DP, DQ, DR

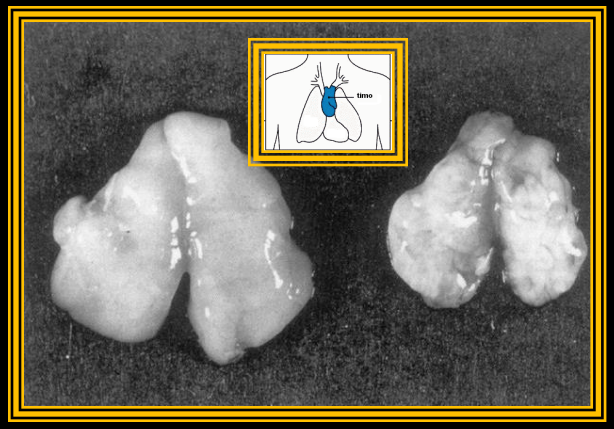


Klein J, Sato A. The HLA System. First of two parts.
N Engl J Med 2000;343:702-9.

The New England Journal of Medicine

T CD4

Estrutura Tímica

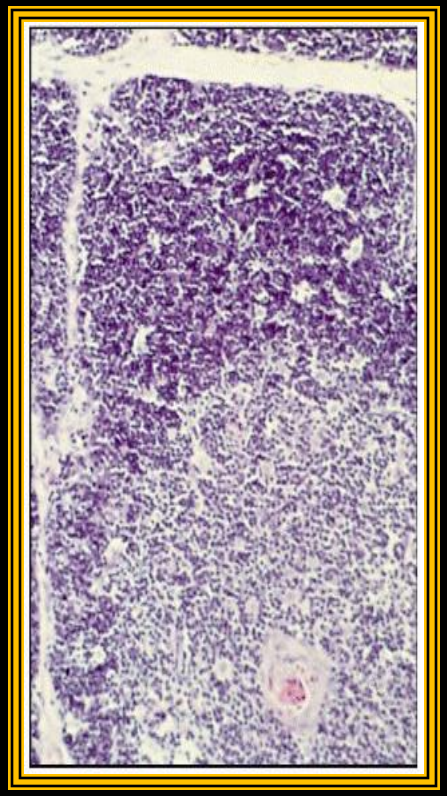


TECs –Células Epiteliais Timo

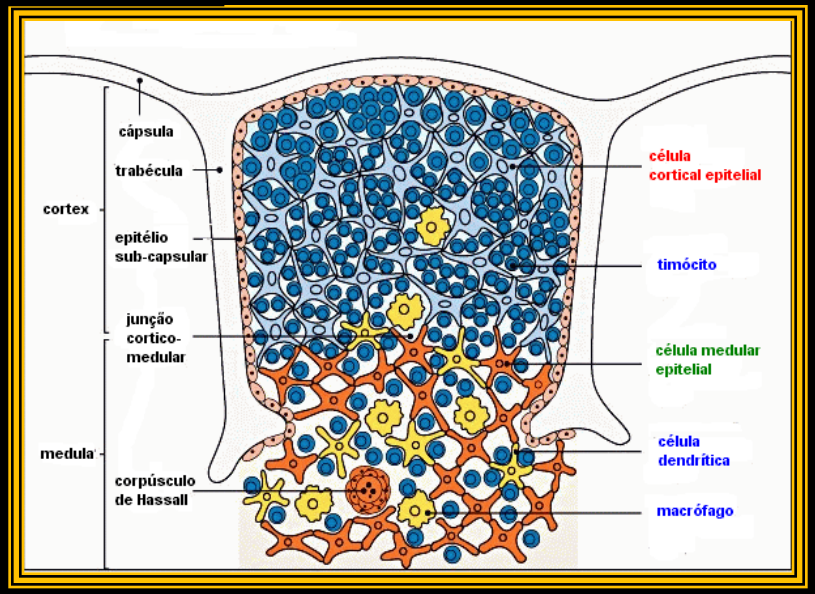
Expressão AIRE

Antígenos ÓRGÃO ESPECÍFICOS

SELEÇÃO NEGATIVA



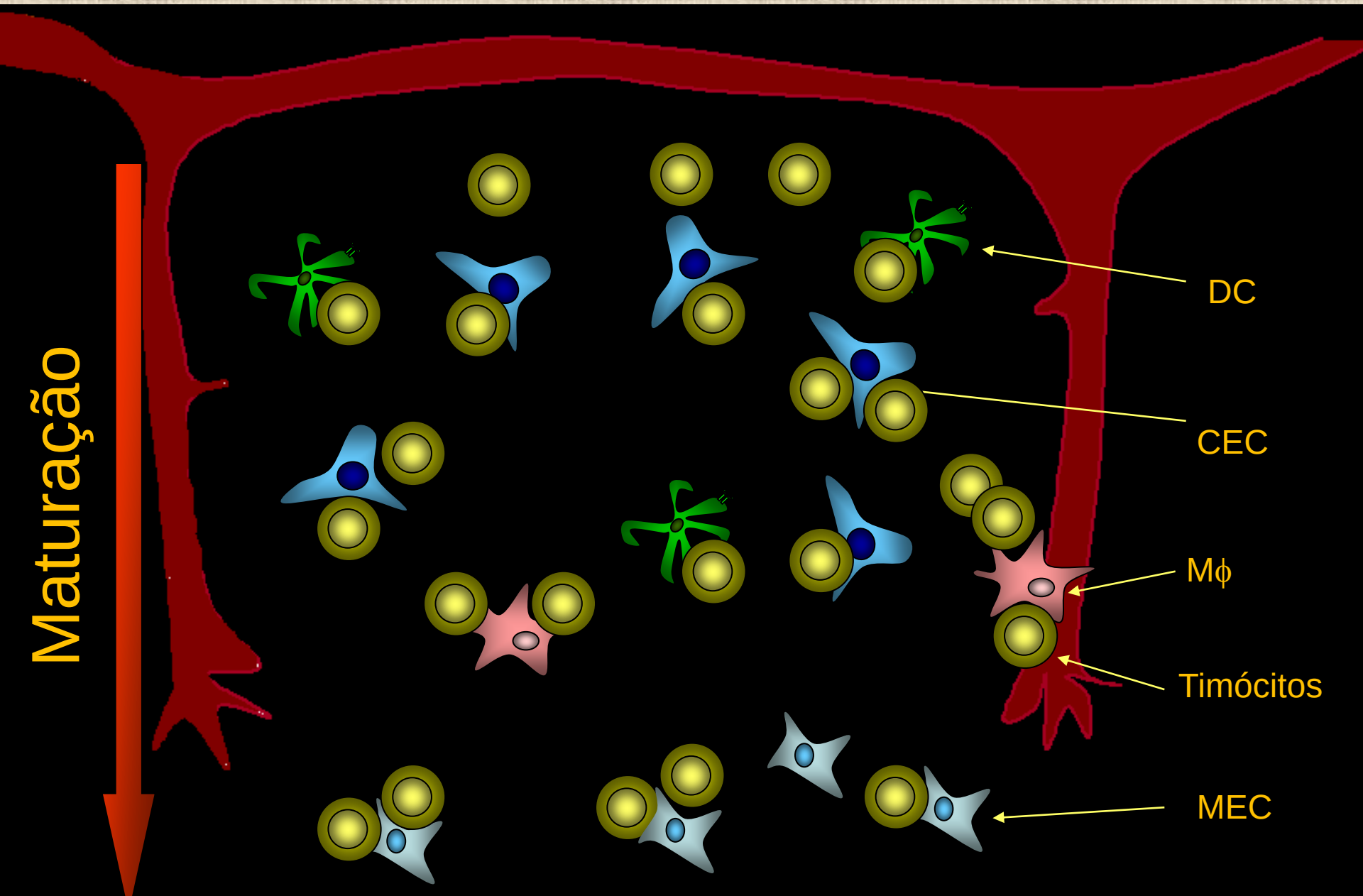
Idade em anos



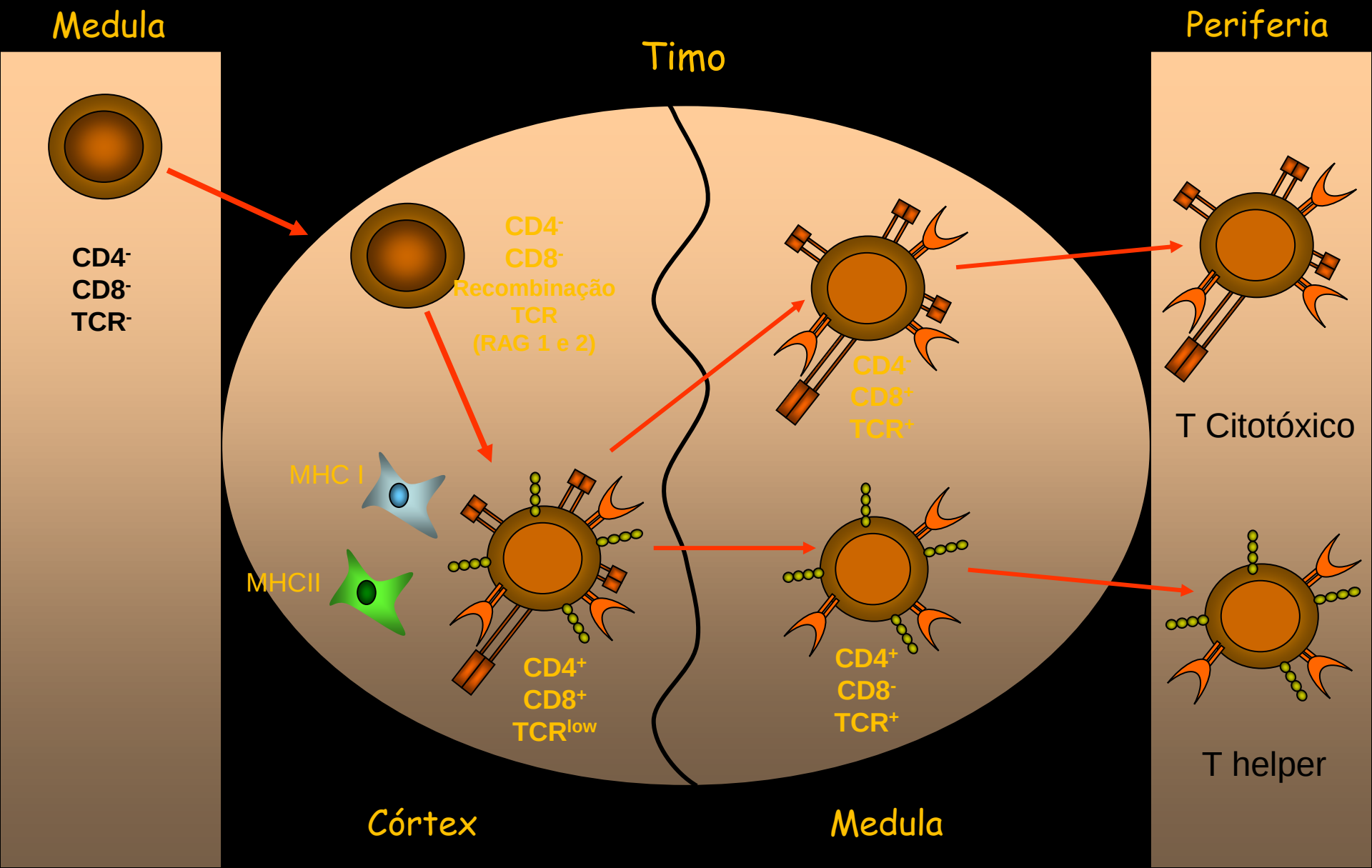
Imunobiologia de Janeway. – 8ª Ed. 2014

Precursores linfóides, agora chamados timócitos, migram da CÓRTEX PARA MEDULA e não expressam CD4 nem CD8

$CD4^{neg}$ $CD8^{pos}$



Ao adentrar o timo, timócitos passam a expressar $CD4^{pos}$ $CD8^{pos}$



Negligência

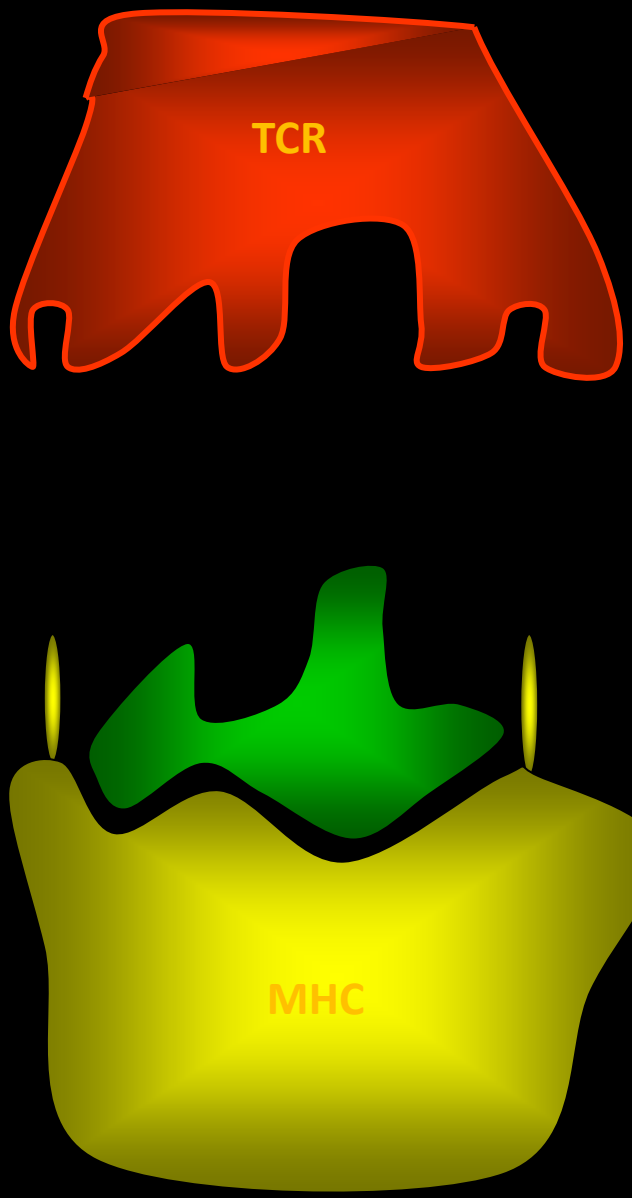
Nenhum Reconhecimento
Sinal de Morte
Morte por negligência

Seleção Negativa

Afinidade da interação
MCH-Peptídeo-TCR

Impede que clones auto-
reativos alcancem a periferia

Seleção Negativa

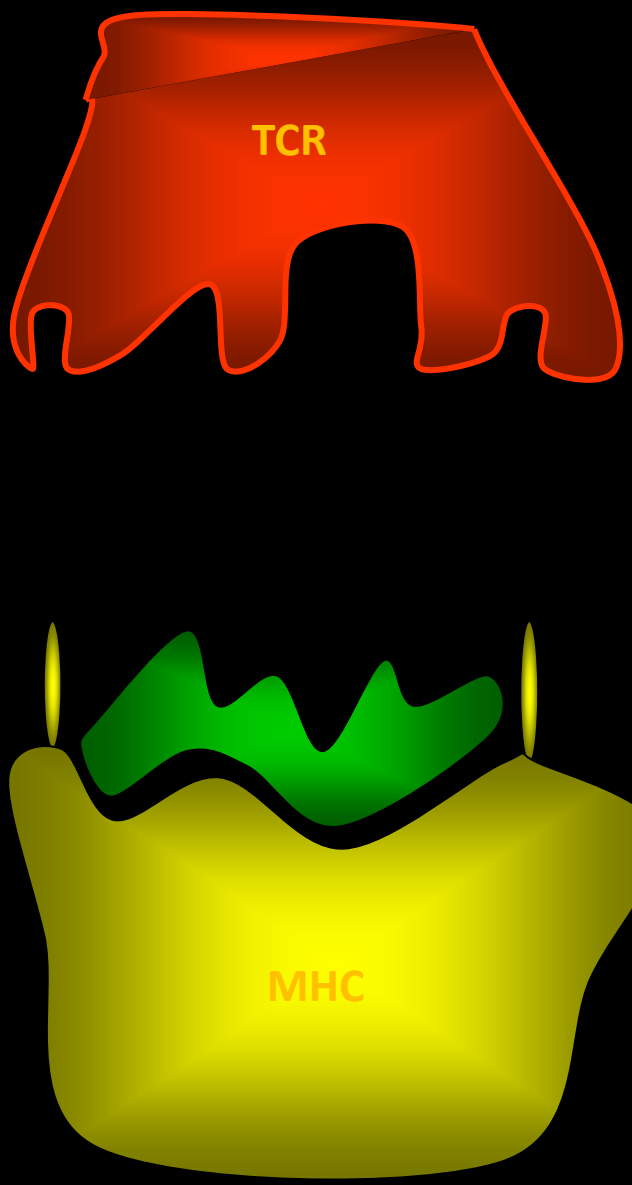


Sinal de Morte
Total
Complementaridade
Tregs

Seleção Positiva

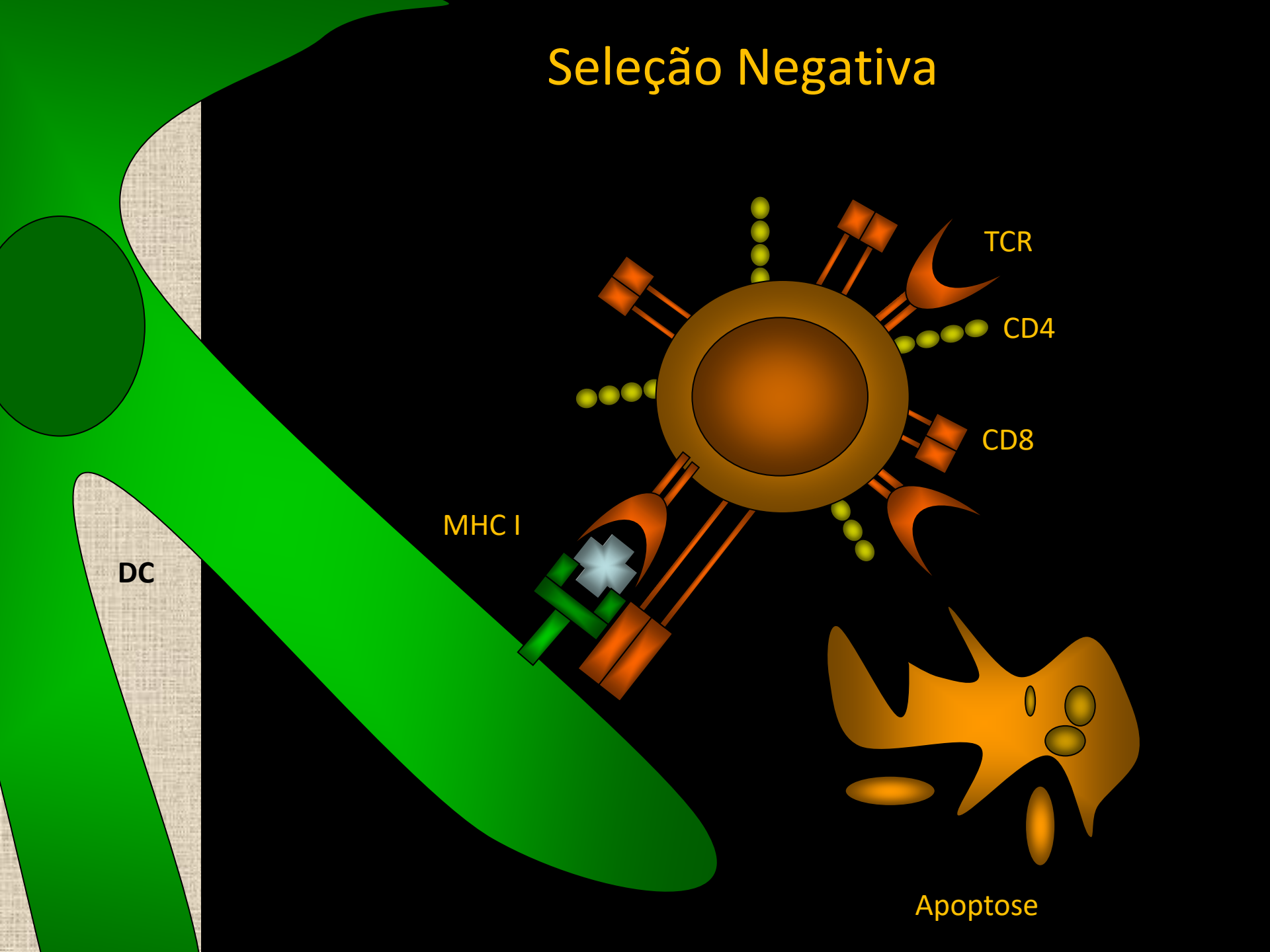
Sinal de Vida

Seleção Negativa

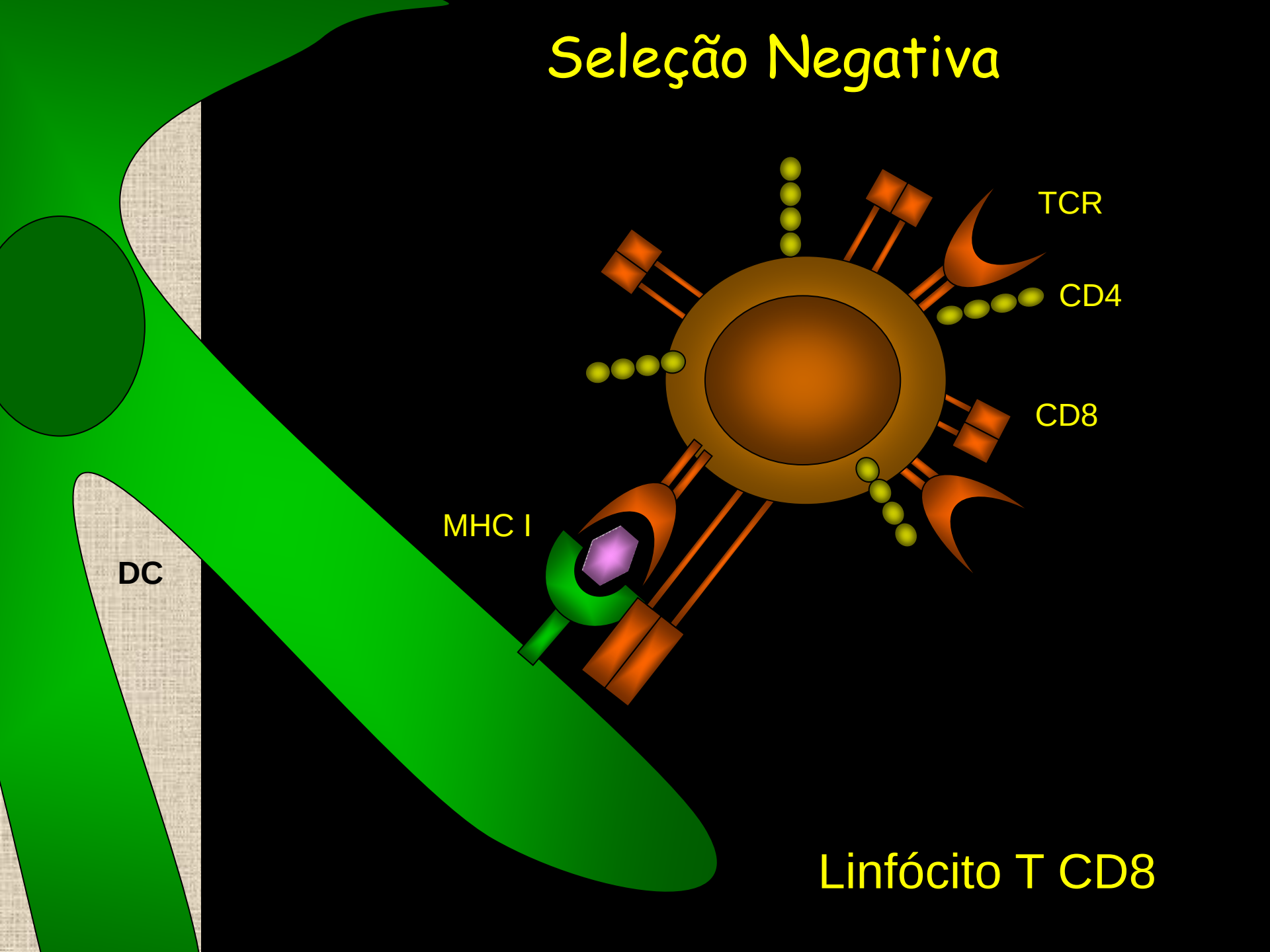


Sinal de vida

Seleção Negativa

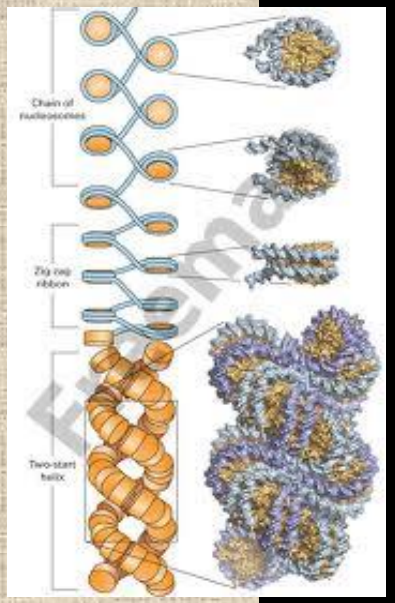


Seleção Negativa



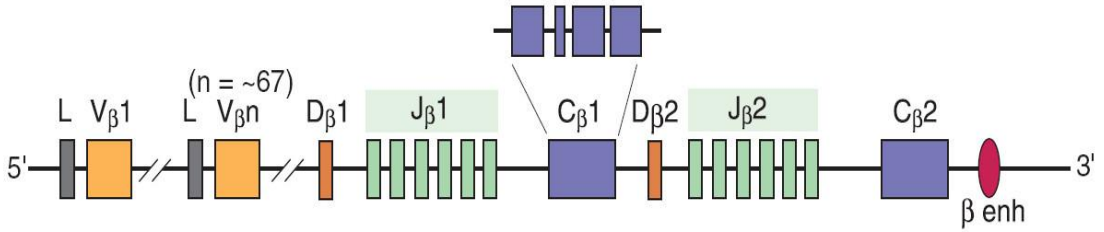
Limiar de Seleção Regido pela Força de Interação Entre os Linfócitos e Antígenos Próprios

Loci do TCR

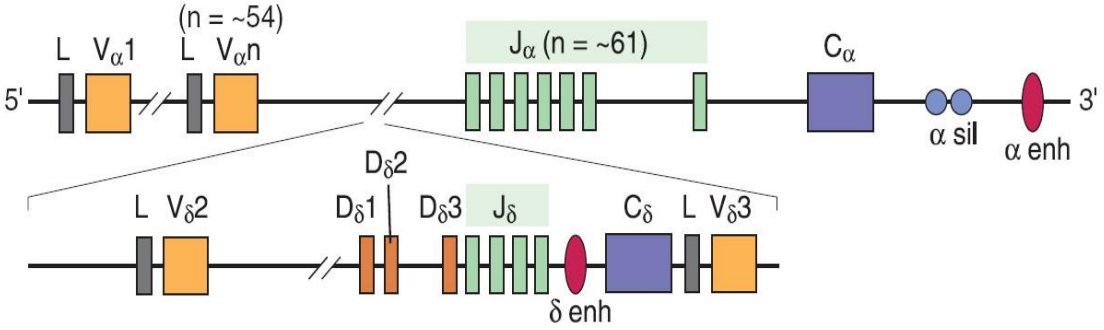


Imunologia Celular e Molecular
ISBN: 9788535222449
Elsevier Editora

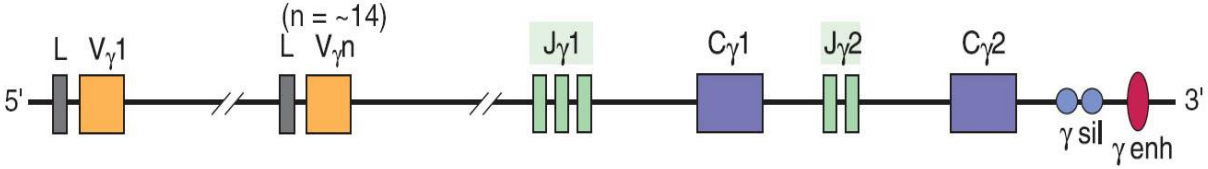
Locus da cadeia β do TCR humano (620 kb; cromossomo 7)



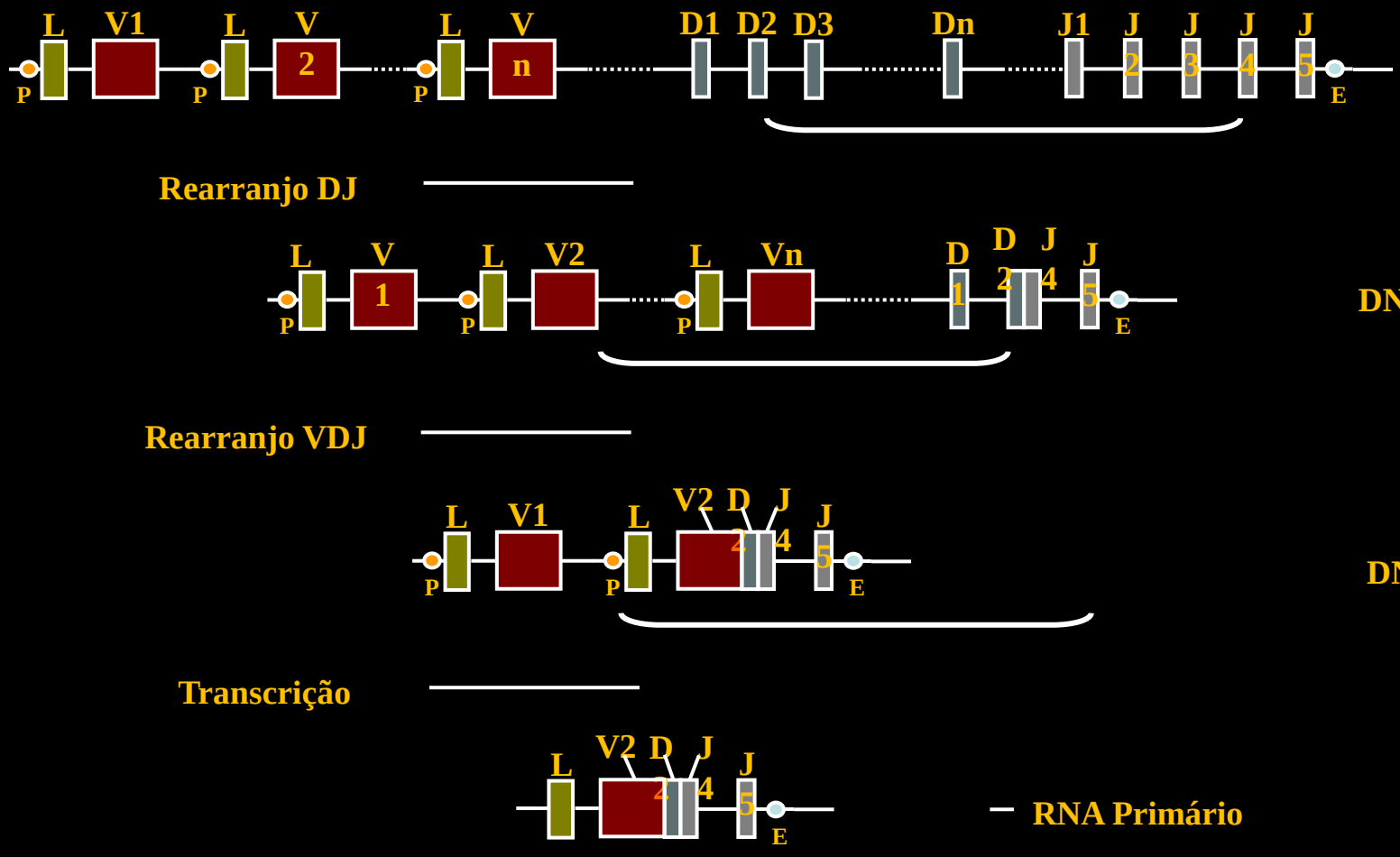
Locus das cadeias α e δ do TCR humano (1.000 kb; cromossomo 14)



Locus da cadeia γ do TCR humano (200 kb; cromossomo 7)



O TCR Sofre Rearranjo Gênico V(D)J



Isso Codificará as Proteínas do TCR

Estrutura dos Linfonodos

Zona Parafolicular – Linfócitos T

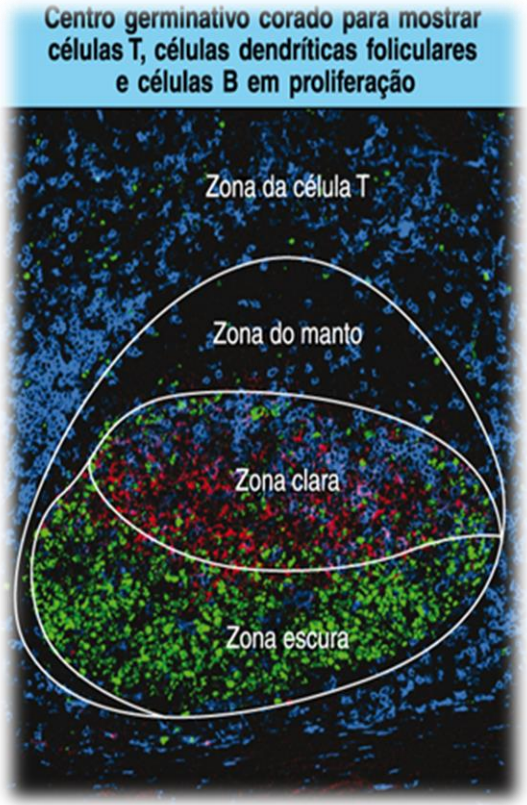
Circulação Linfática
Um Fenômeno Fisiológico

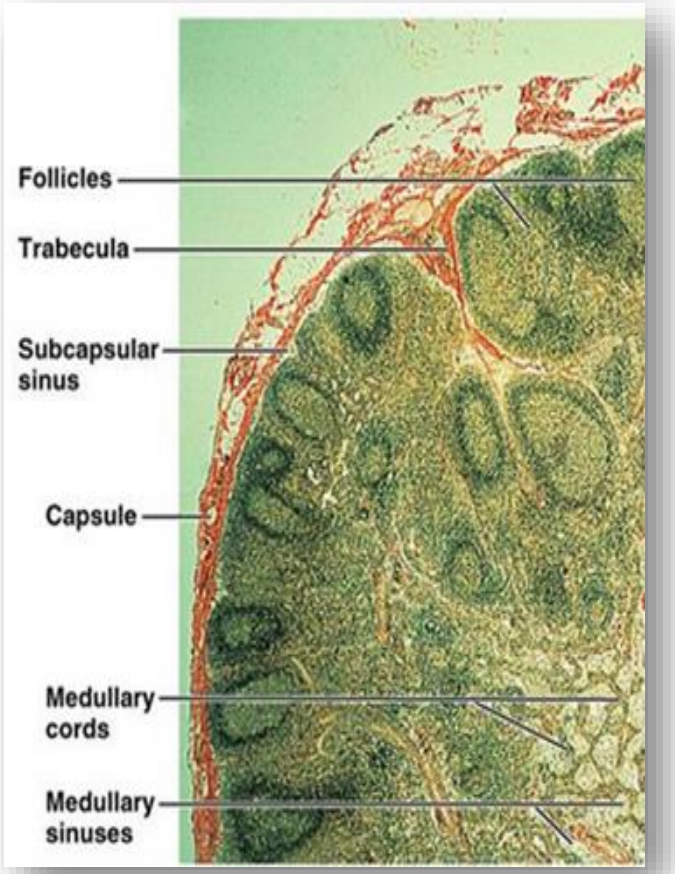
Constante Circulação de
Líquido Intersticial

Debris celulares, matriz
extracelular,
Produtos do metabolismo,
transporte de lipídeos, etc...

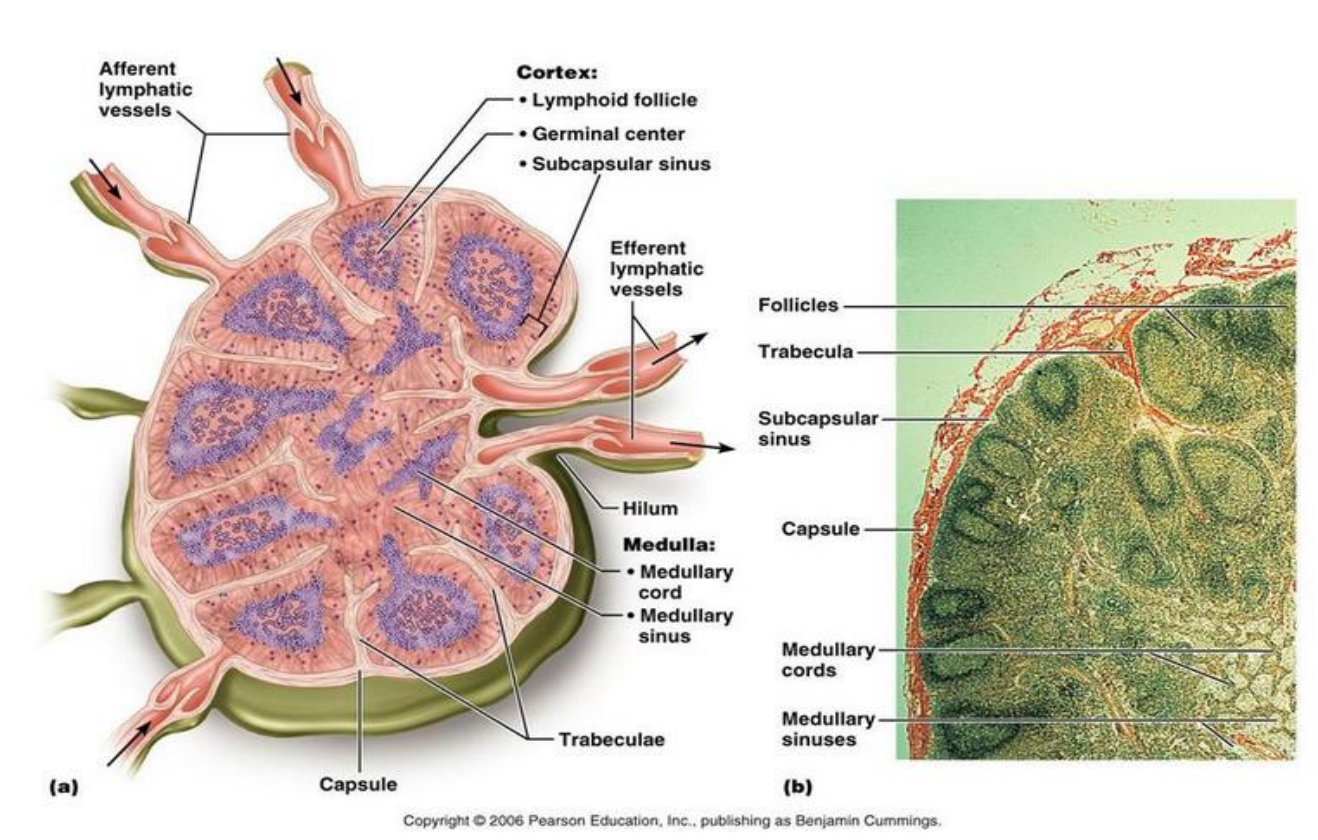
Logo...

Linfonodos Estão
Constantemente
Recebendo Essas
Moléculas e Células
Circulantes

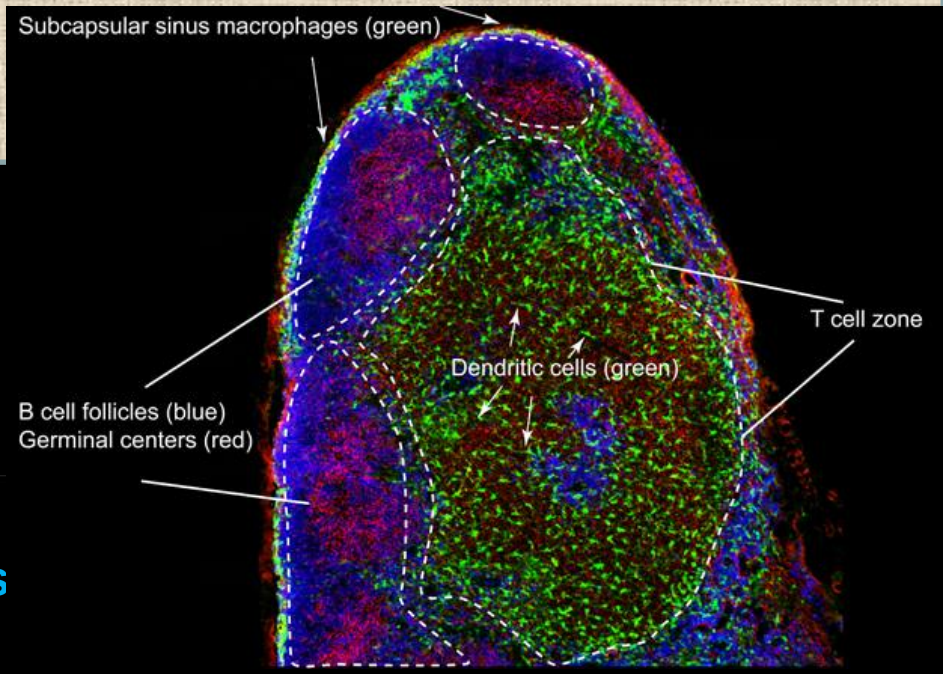


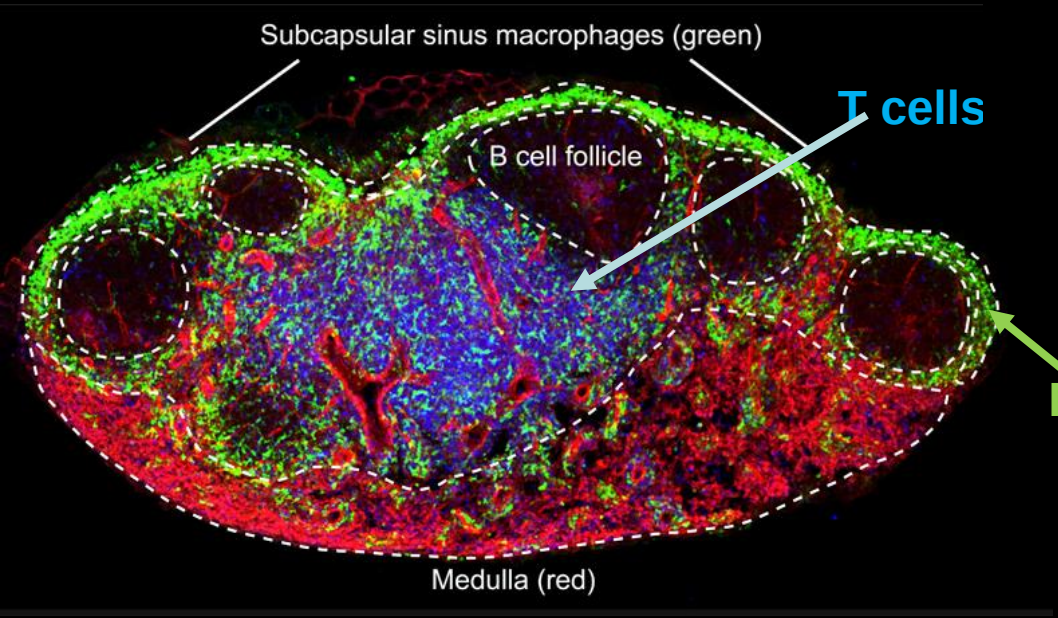


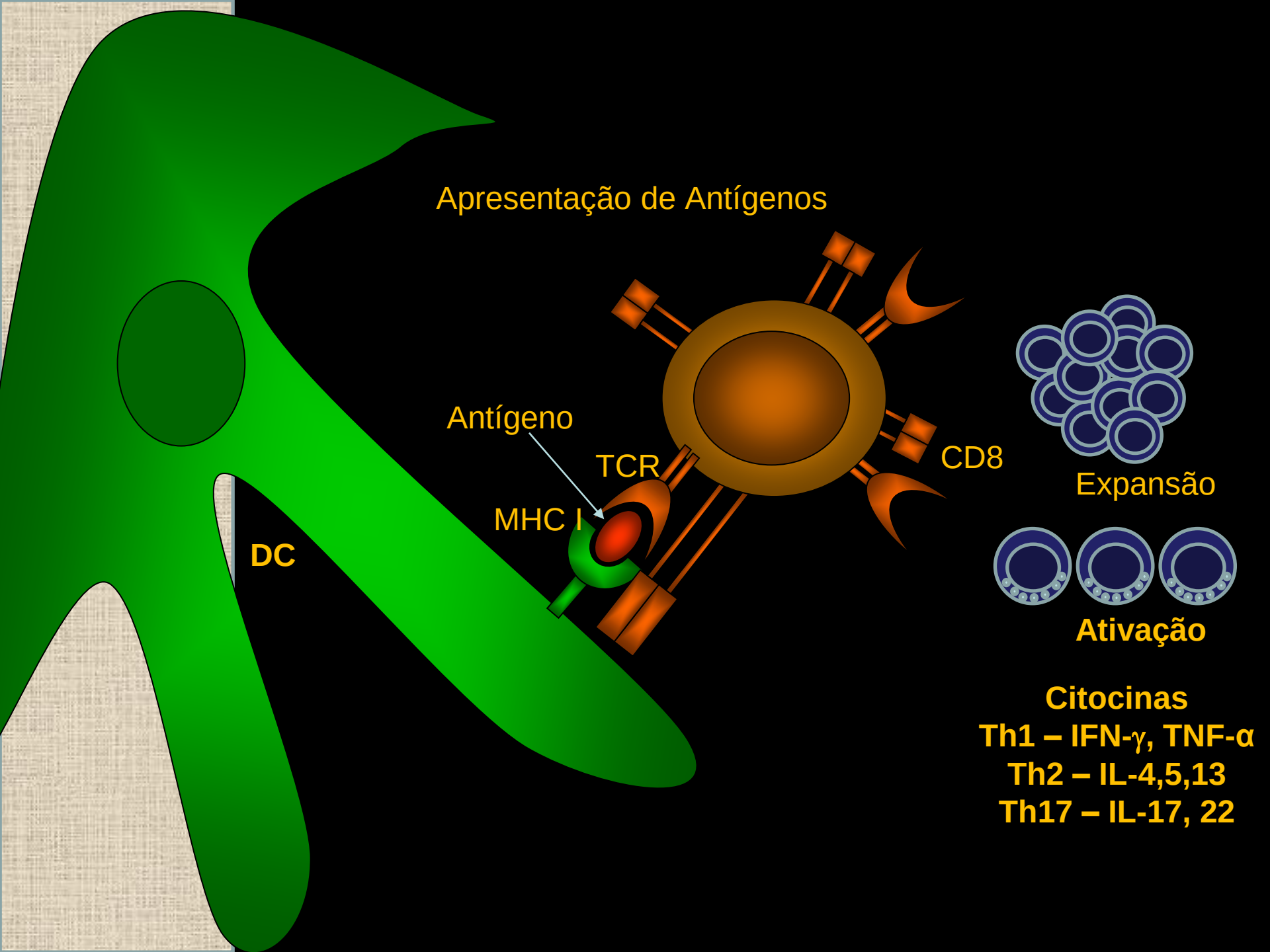
Drenagem de Antígenos – Solúveis ou Carreados por Células



Linfonodos e sua arquitetura






Apresentação de Antígenos
Antígeno
TCR
MHC I
CD8
DC
Expansão
Ativação
Citocinas
Th1 – IFN-γ, TNF-α
Th2 – IL-4,5,13
Th17 – IL-17, 22

Mas....

Qual é objetivo da
Apresentação de Antígenos ?

Quais seus resultados?

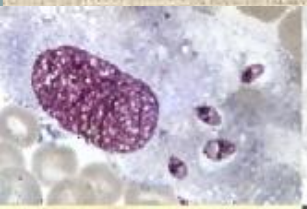
ATIVAÇÃO DA

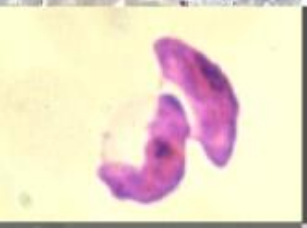
IMUNIDADE

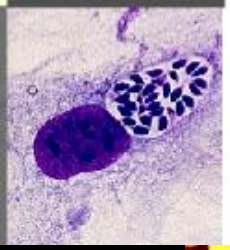
ADAPTATIVA

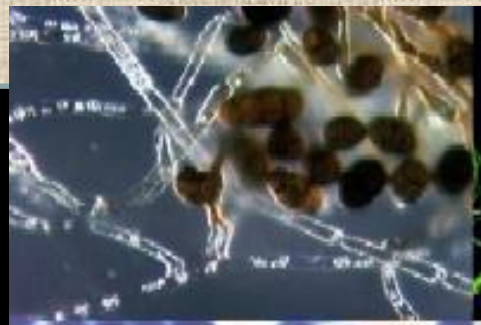
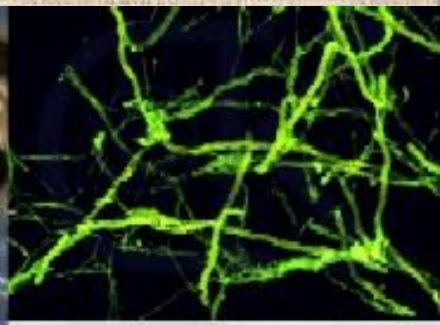
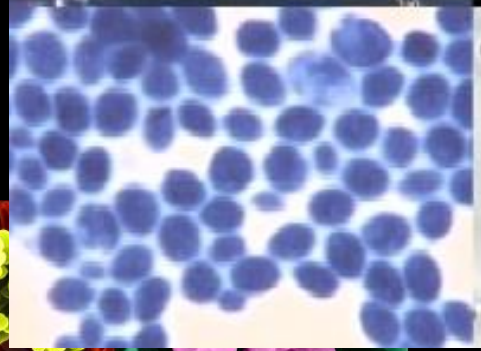
Foto: John Isaac

As Populações de Linfócitos T CD4 Existem para Adequar a Resposta Imune ao Patógeno Presente



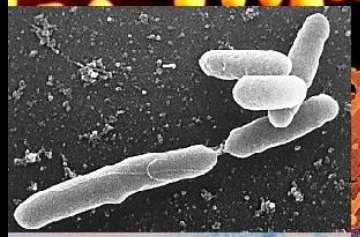
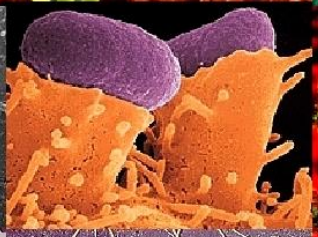
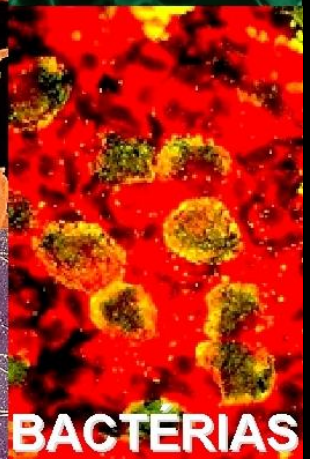
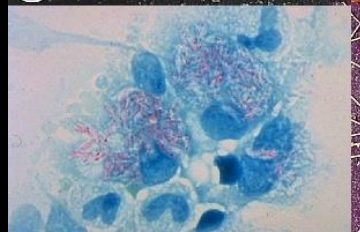
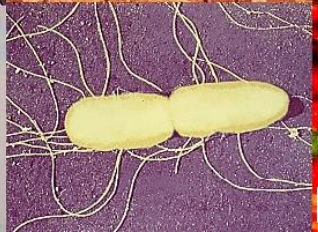


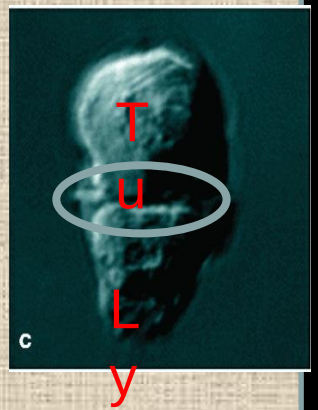


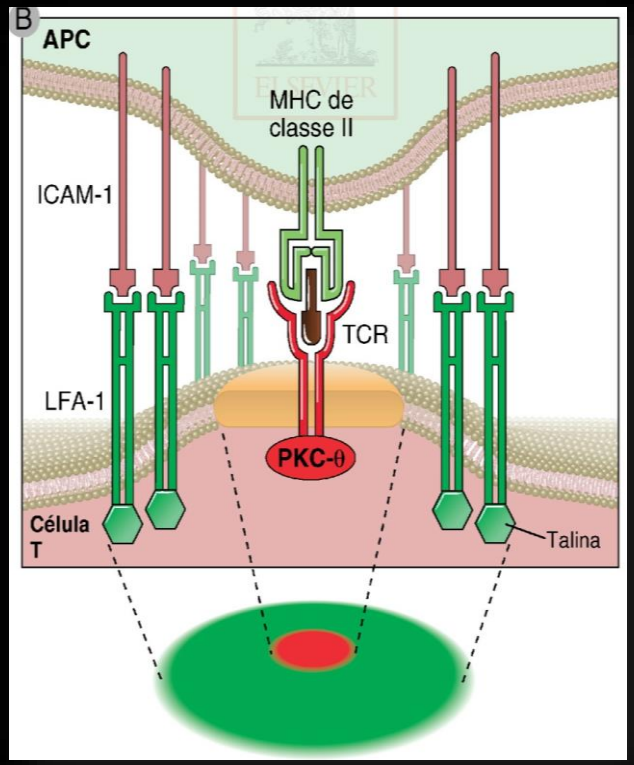


Sinapse Imunológica – Michael Dustin

Após a interação com MHC + Ag, há um rearranjo do CITOESQUELETO
Migração de MOLÉCULAS DE ATIVAÇÃO para o Local de Contato



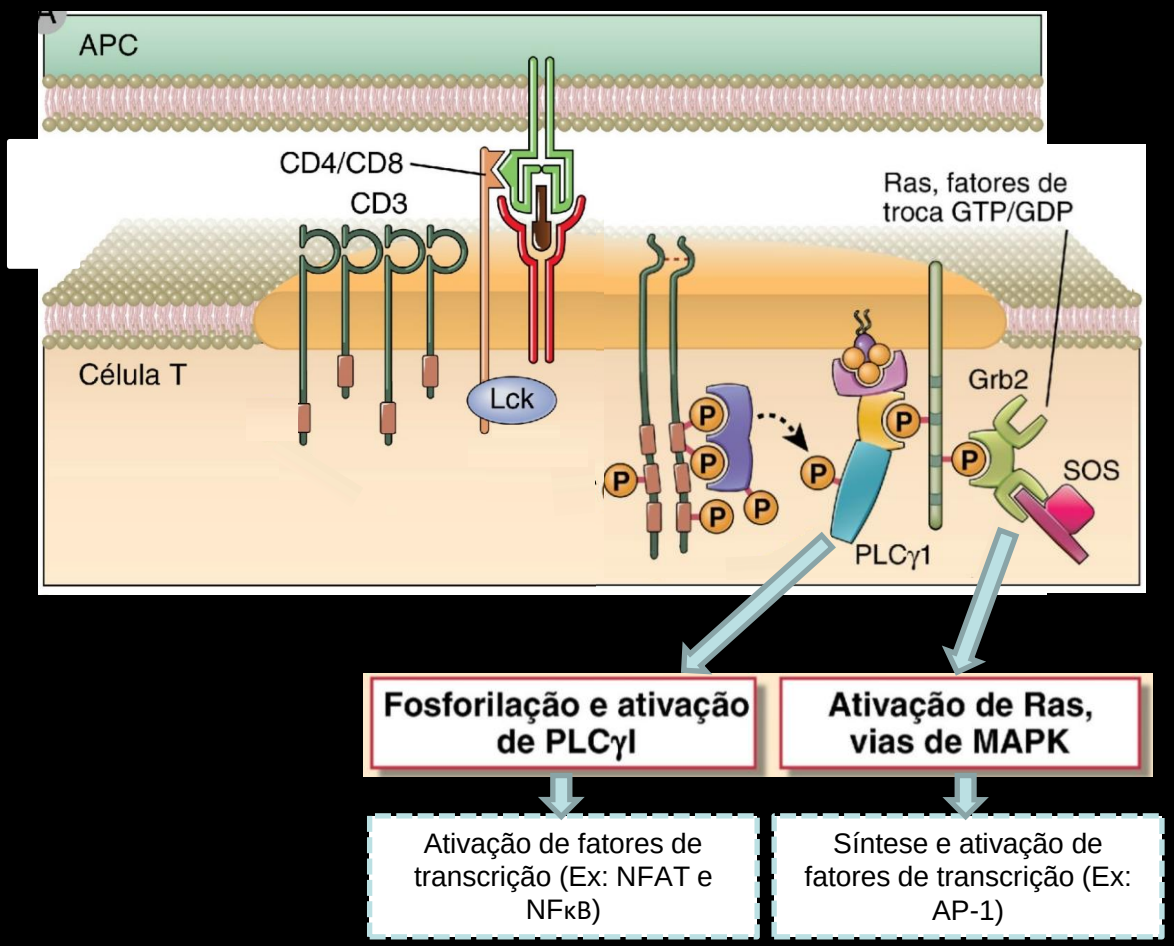


Aumenta/Reduz Interação Celular
Aumenta/Reduz Sinalização Intracelular

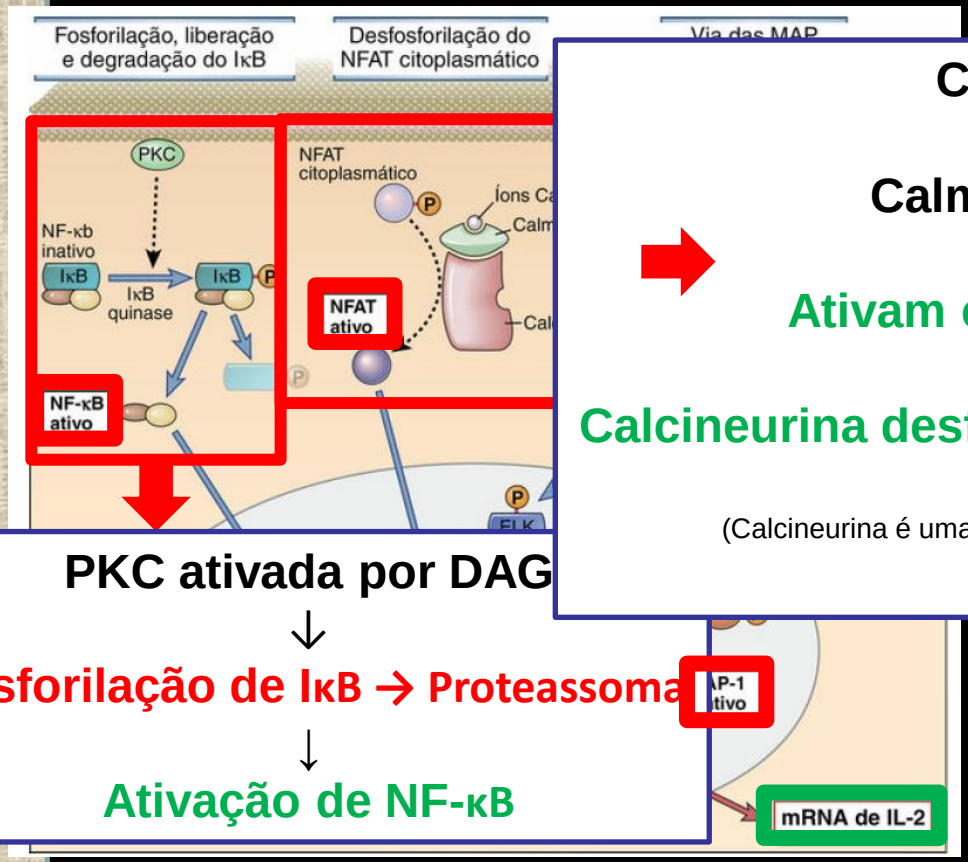
DEPENDENTE DAS MOLÉCULAS PRESENTES NAS SINAPSES

Dustin ML, Baldari CT. Methods Mol Biol. 2017;1584:1-5.

Sinalização Intracelular



Sinalização Intracelular



Cálcio

+

Calmodulina

↓

Ativam calcineurina

↓

Calcineurina desfosforila e ativa NFAT

(Calcineurina é uma fosfatase que ativa NFAT)

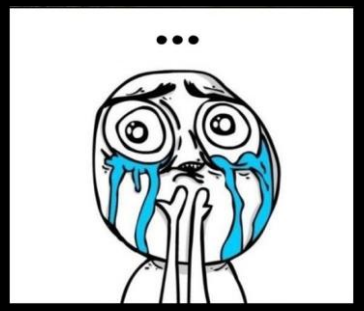
PKC ativada por DAG

↓

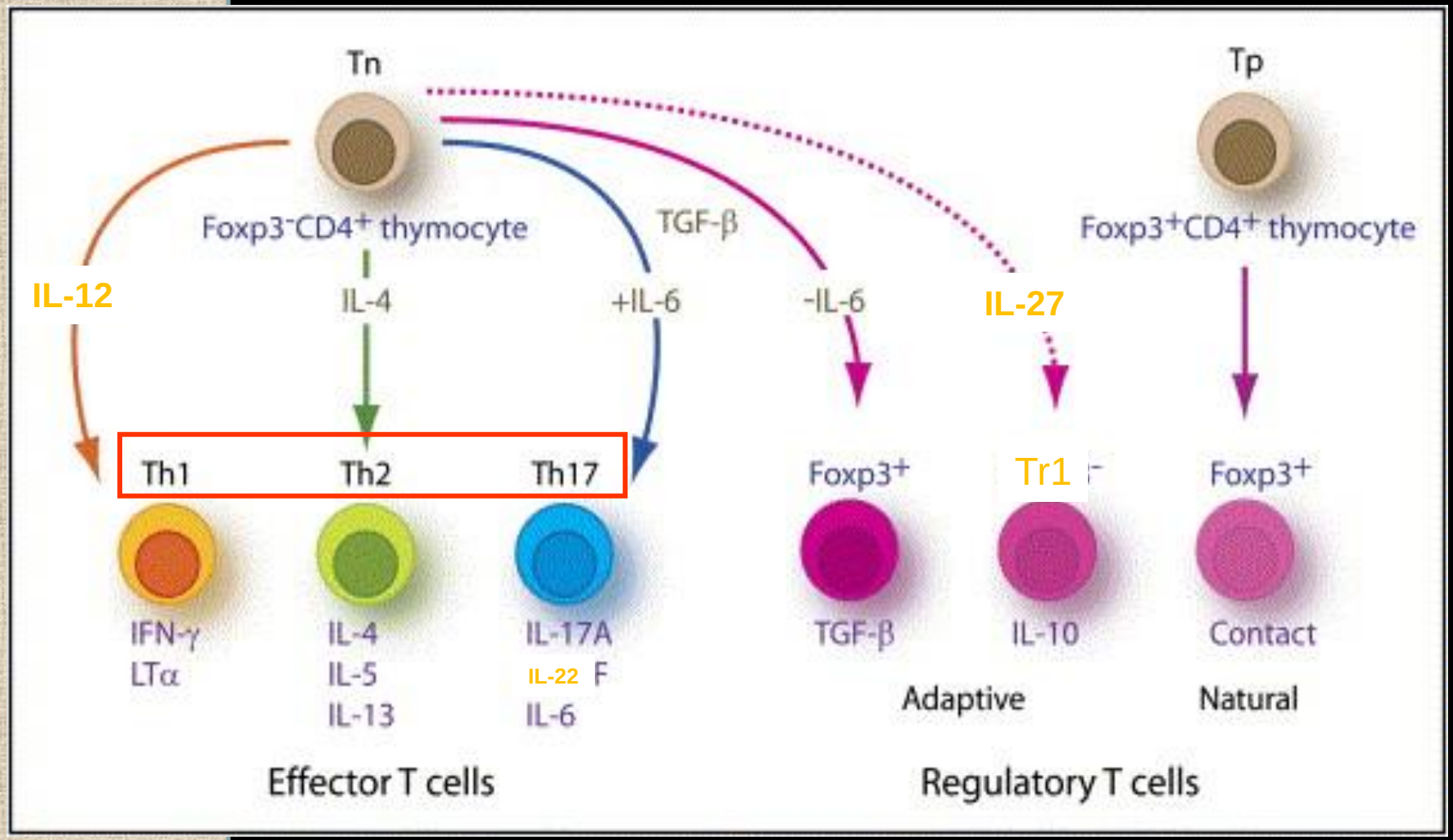
Fosforilação de IκB → Proteassoma

↓

Ativação de NF-κB



Populações de Células T



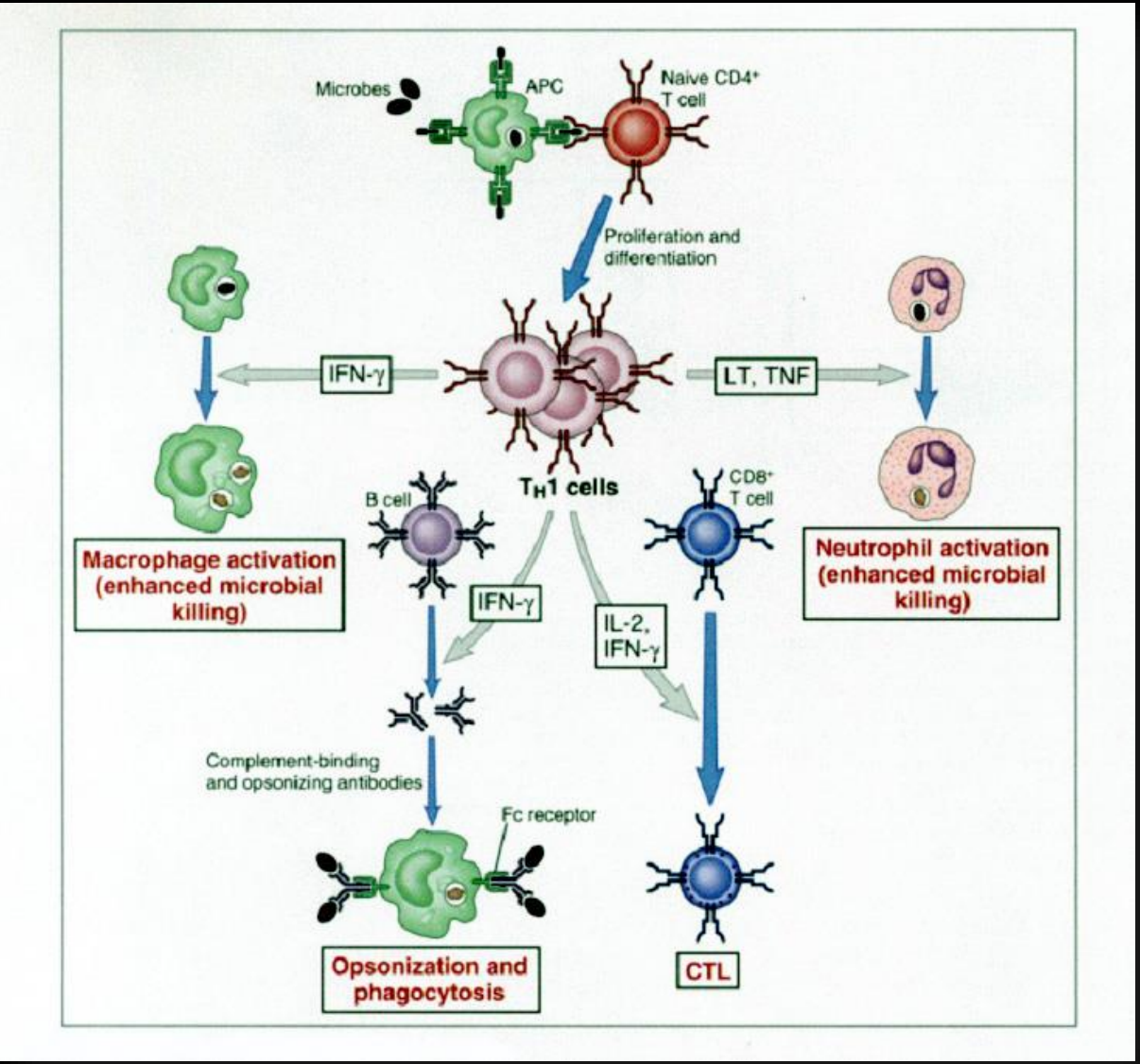
Weaber CT. Immunity. 2006 Jun;24(6):677-88

Tipos de Linfócitos T CD4 – Caracterização Funcional

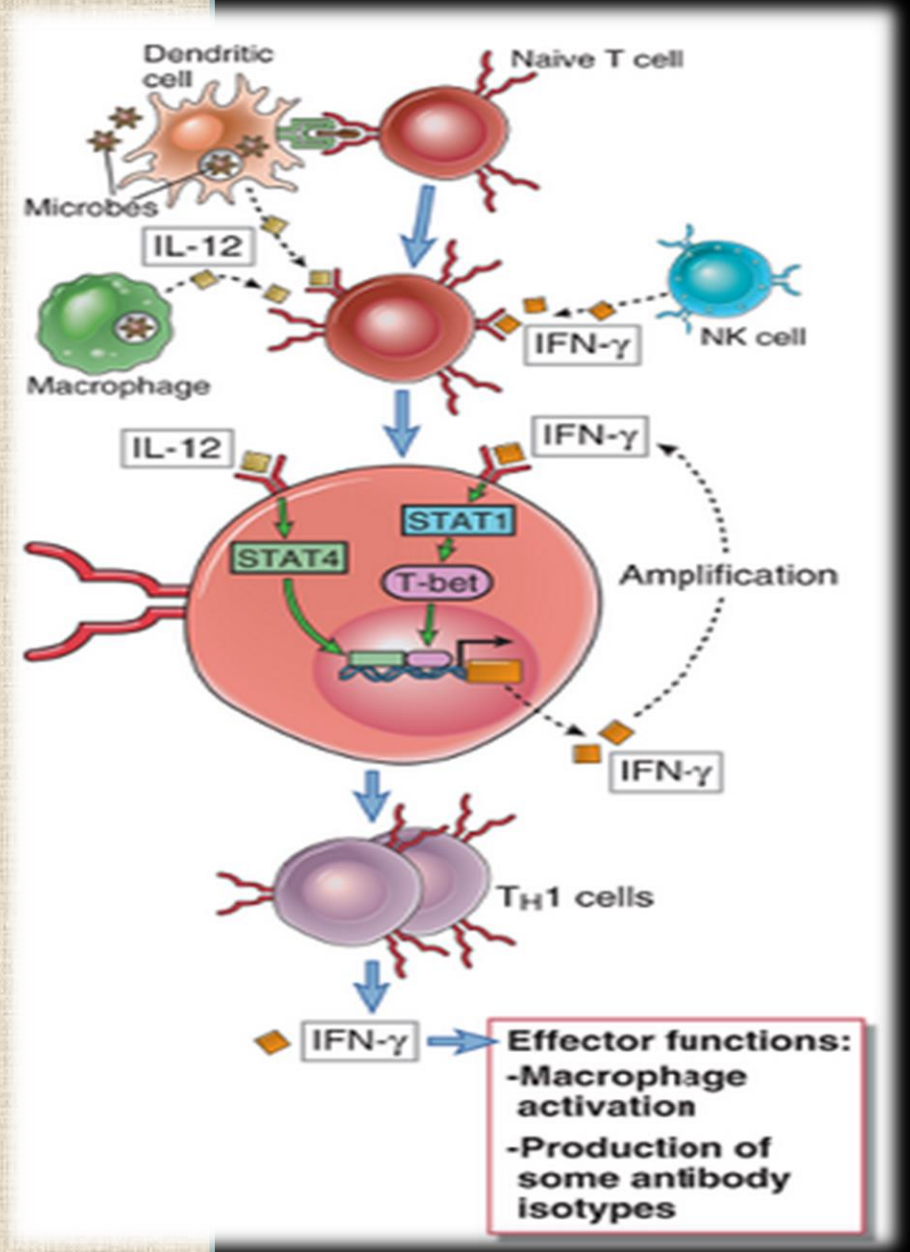
	Signature cytokines	Immune reactions	Host defense	Role in diseases
T_H1 cell	IFNγ	Macrophage activation; IgG production	Intracellular microbes	Autoimmune diseases; tissue damage associated with chronic infections
T_H2 cell	IL-4 IL-5 IL-13	Mast cell, eosinophil activation; IgE production; "alternative" macrophage activation	Helminthic parasites	Allergic diseases
T_H17 cell	IL-17A IL-17F IL-22	Neutrophilic, monocytic inflammation	Extracellular bacteria; fungi	Organ-specific autoimmunity

Cellular and molecular immunology. Abbas A. 8th Ed. 2016

Funções das Células Th1



Cellular and molecular immunology. Abbas A. 8th Ed. 2016



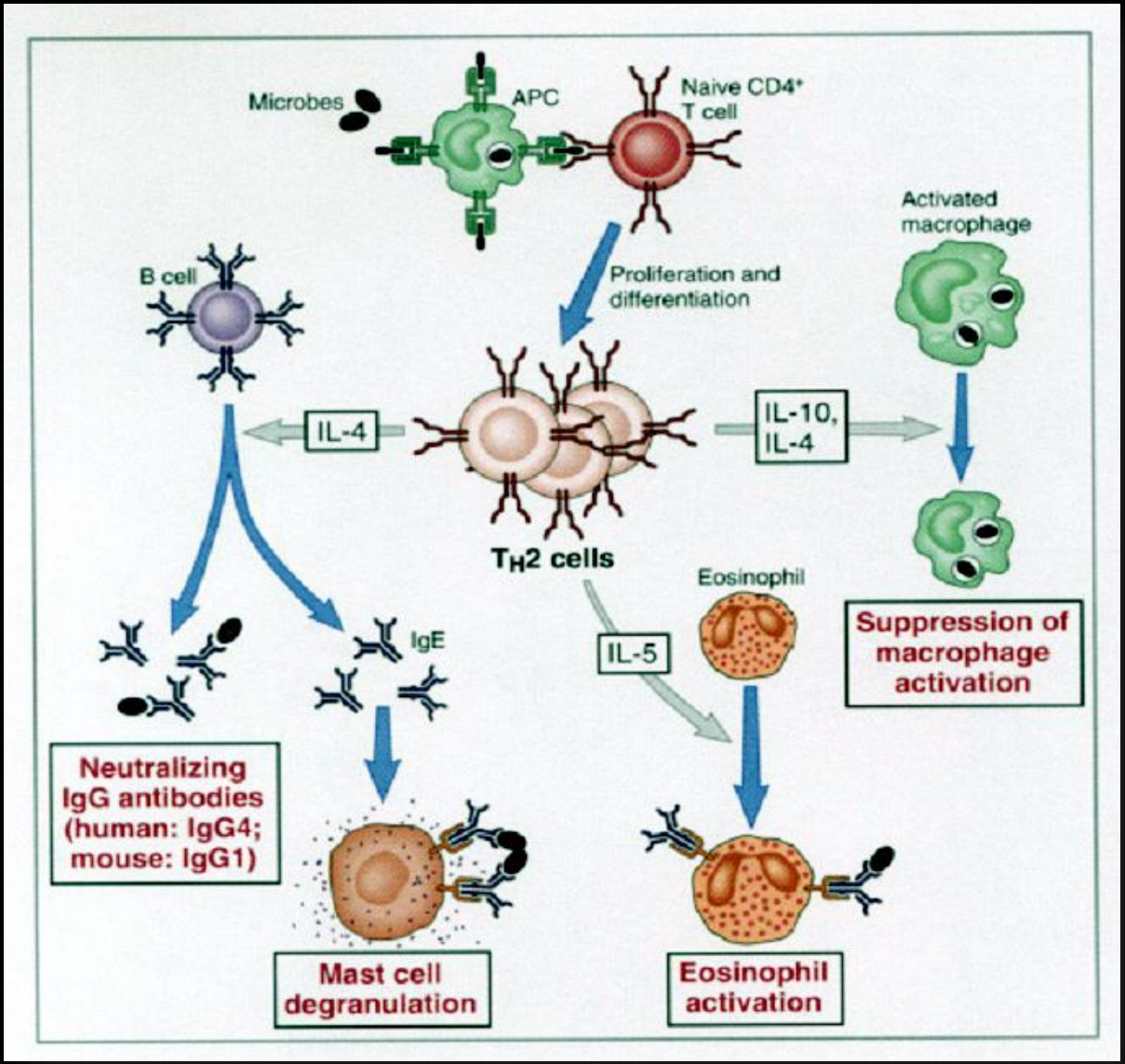
Resposta Th1

- Agentes Intra-celulares
- Ativação da Capacidade Fagocítica e de Degradação Intracelular
- Macrófagos Inflamatórios M1
- A tivação Células NK
- Citocinas principais
- IL-1, IL-12, IL-8, IL-18

IL-12, TNF-α, IFN-γ

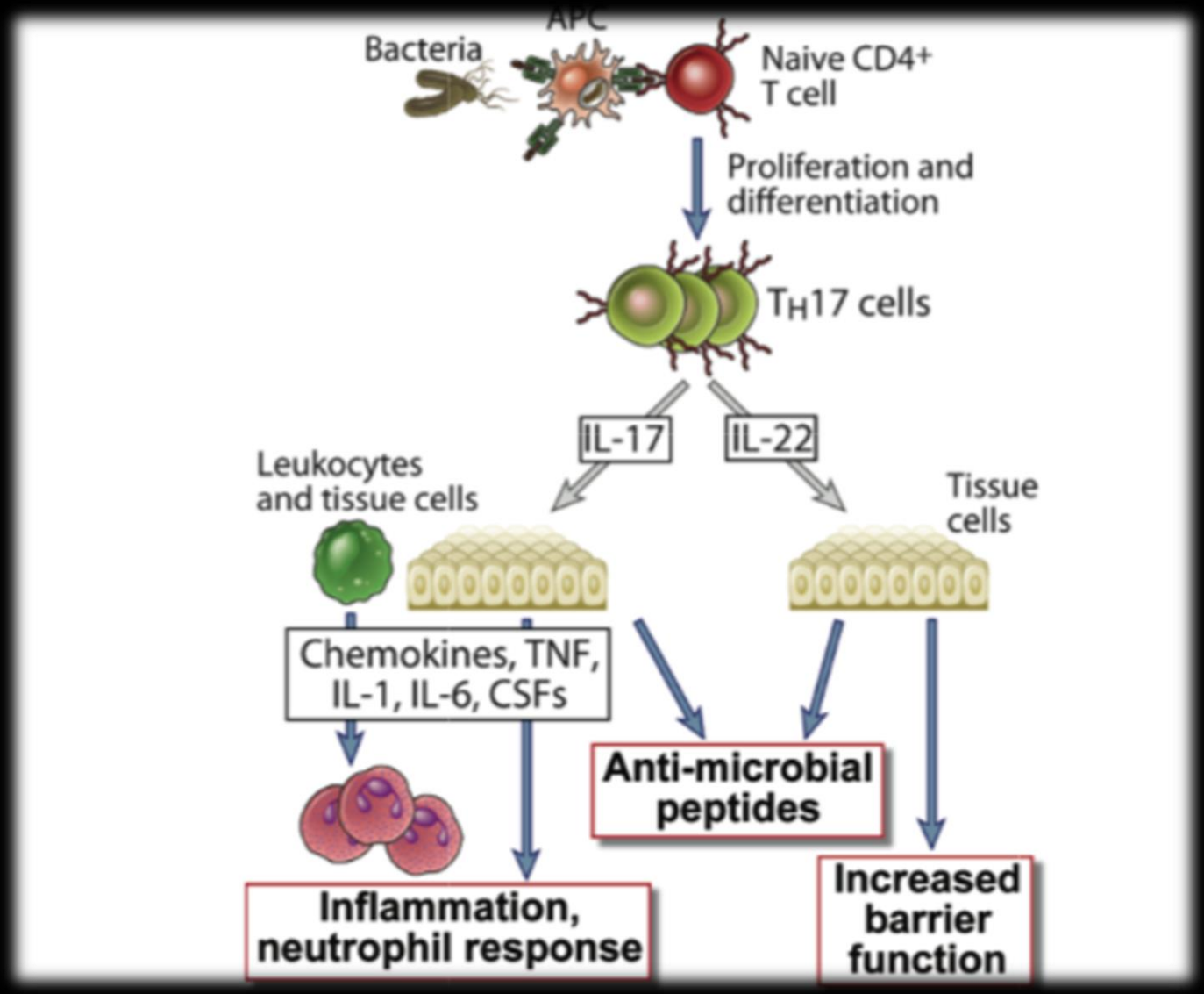
Cellular and molecular immunology. Abbas A. 8th Ed. 2016

Funções das Células Th2



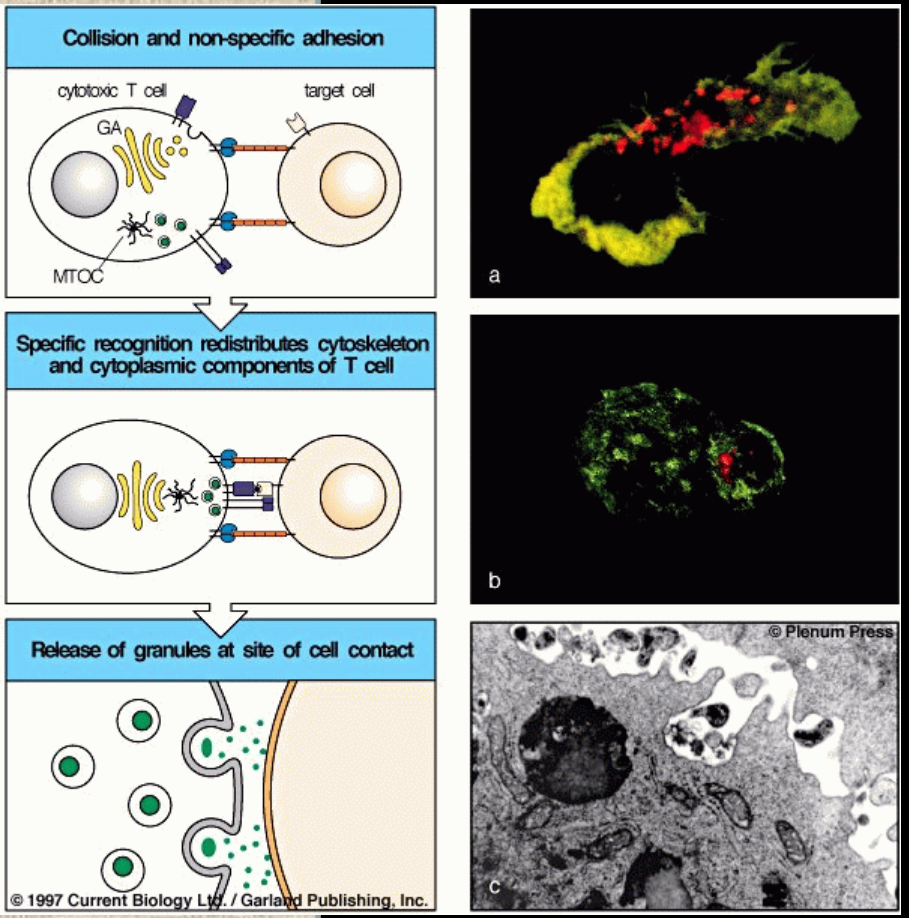
Cellular and molecular immunology. Abbas A. 8th Ed. 2016

Linfócitos Th17

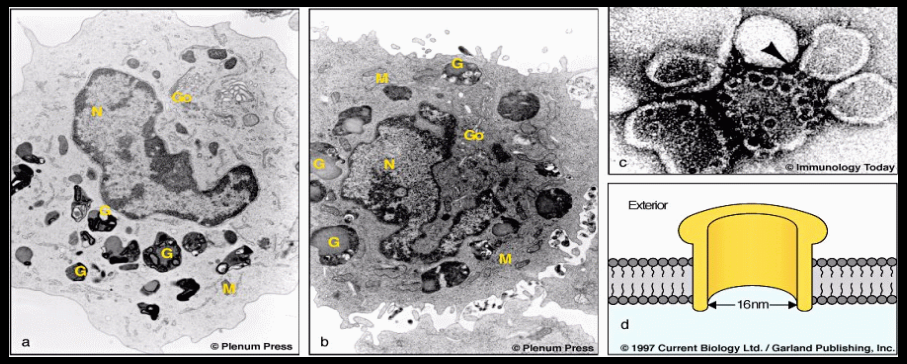


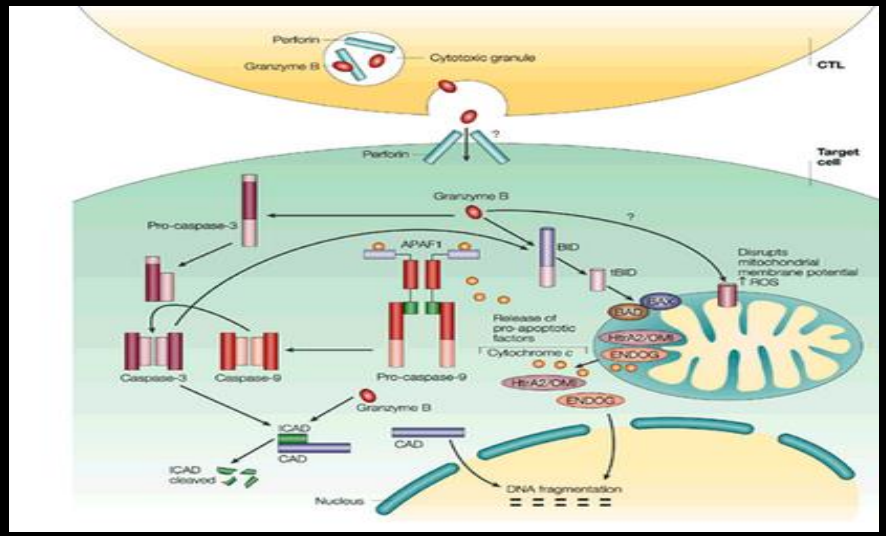
Cellular and molecular immunology. Abbas A. 8th Ed. 2016

Linfócitos T CD8

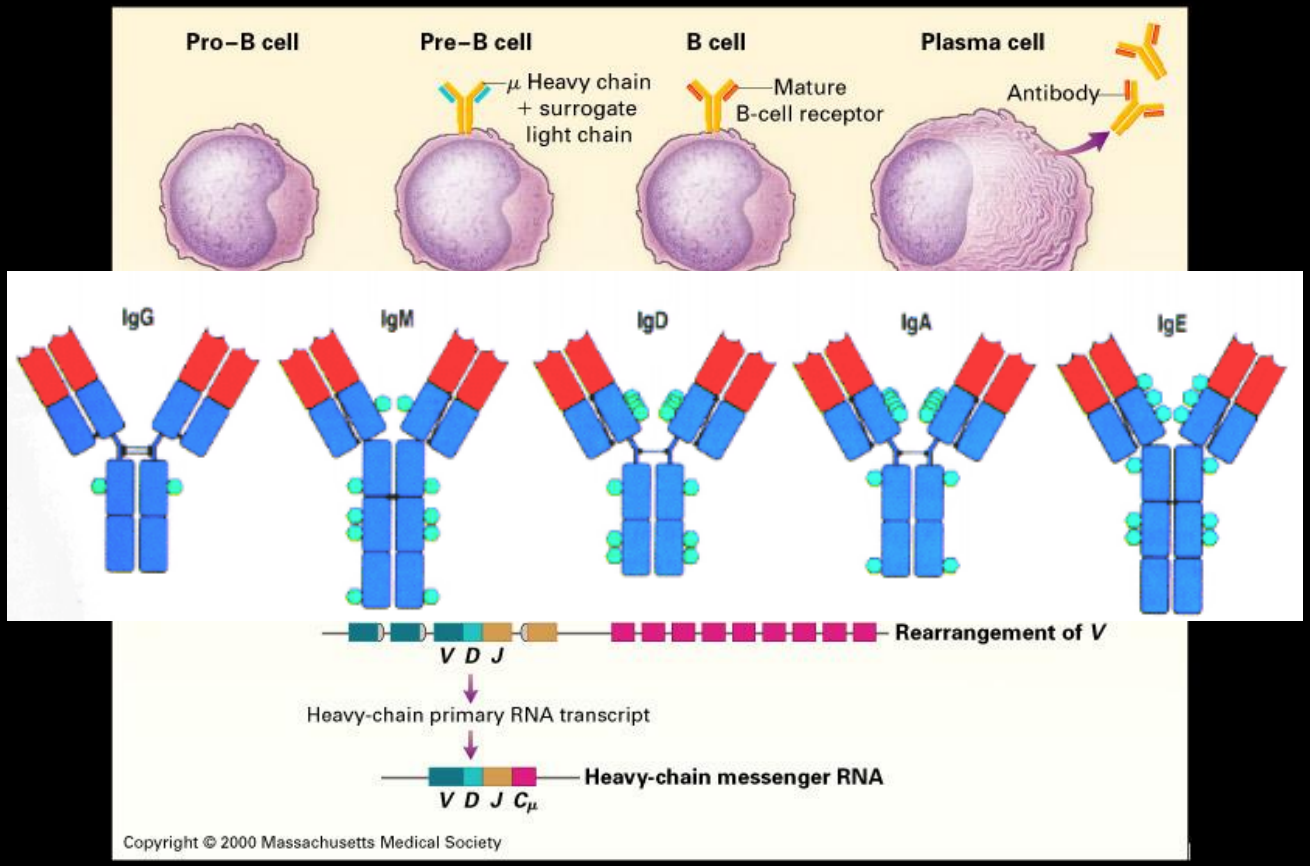


Granzimas e Perforinas





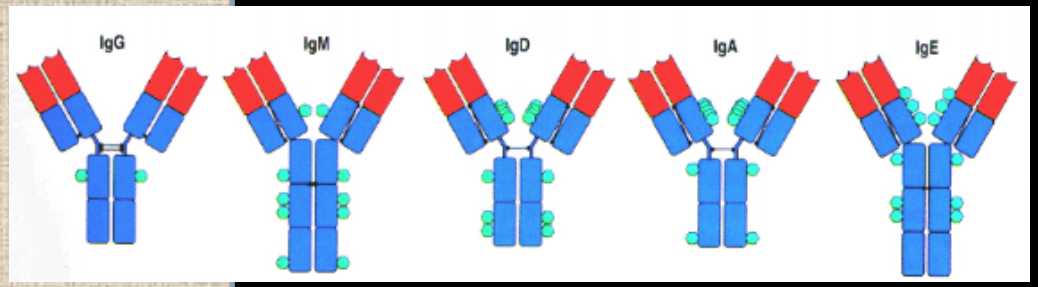
Linfócitos B

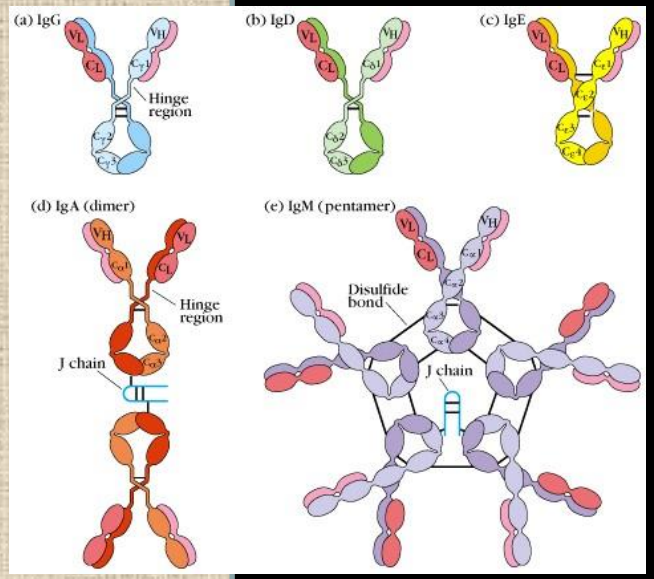


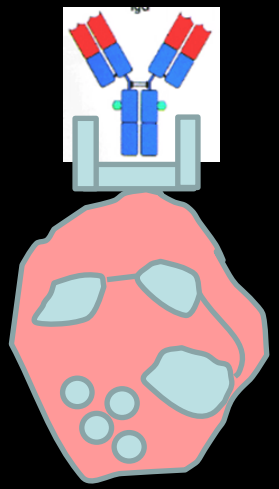
Delves PJ, Roitt IM. The Immune System (Part1).
N Engl J Med 2000;343:37-49.

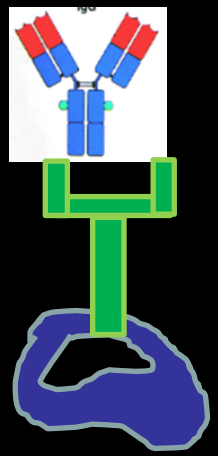
The New England Journal of Medicine

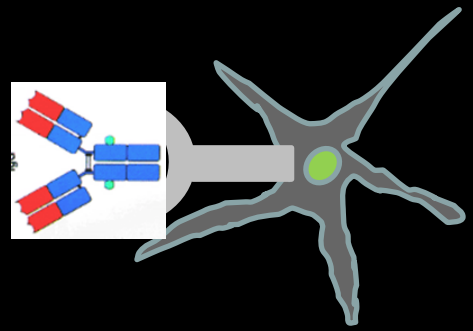
Anticorpos ou Imunoglobulinas e Seus Receptores Fc



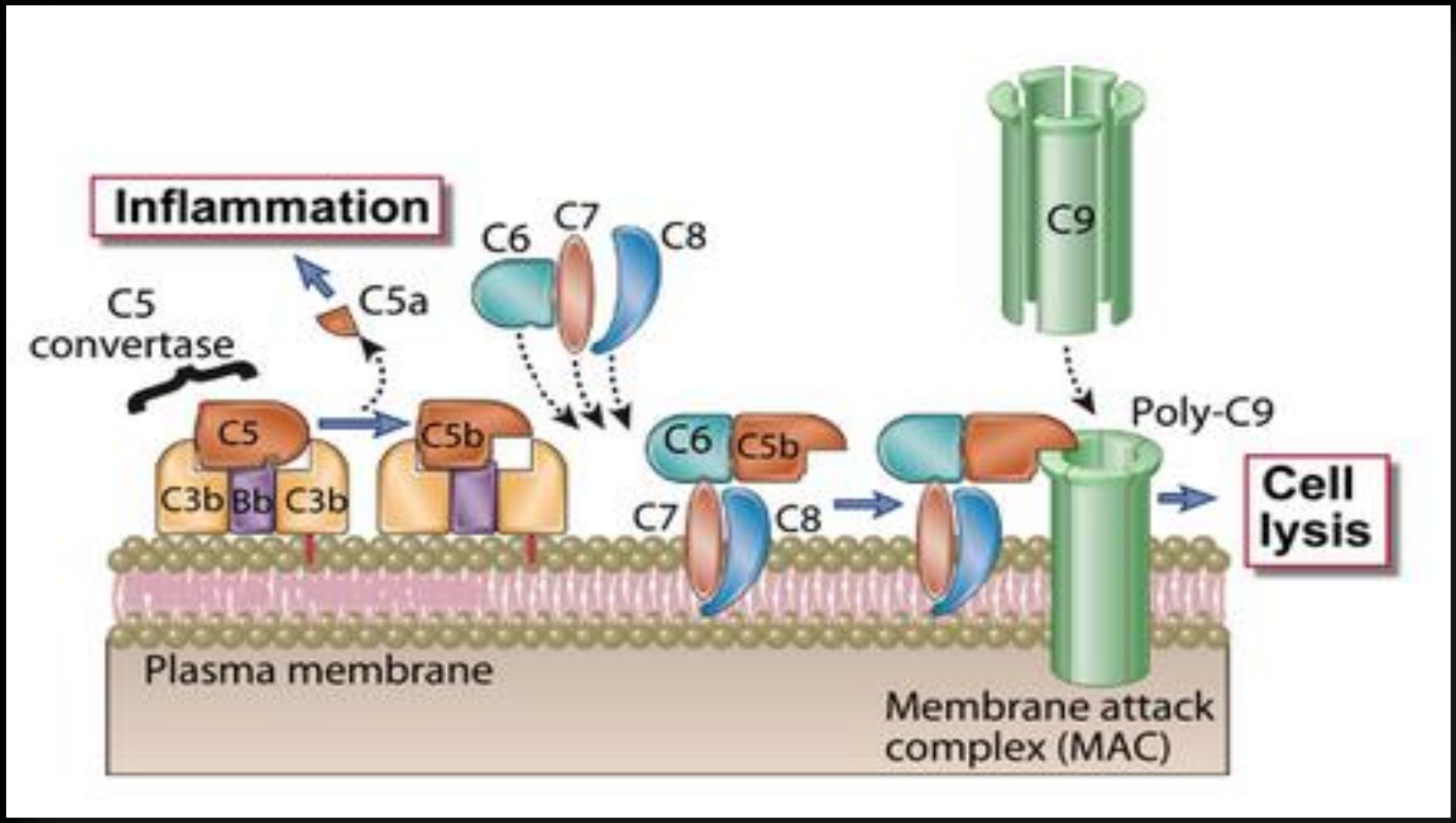






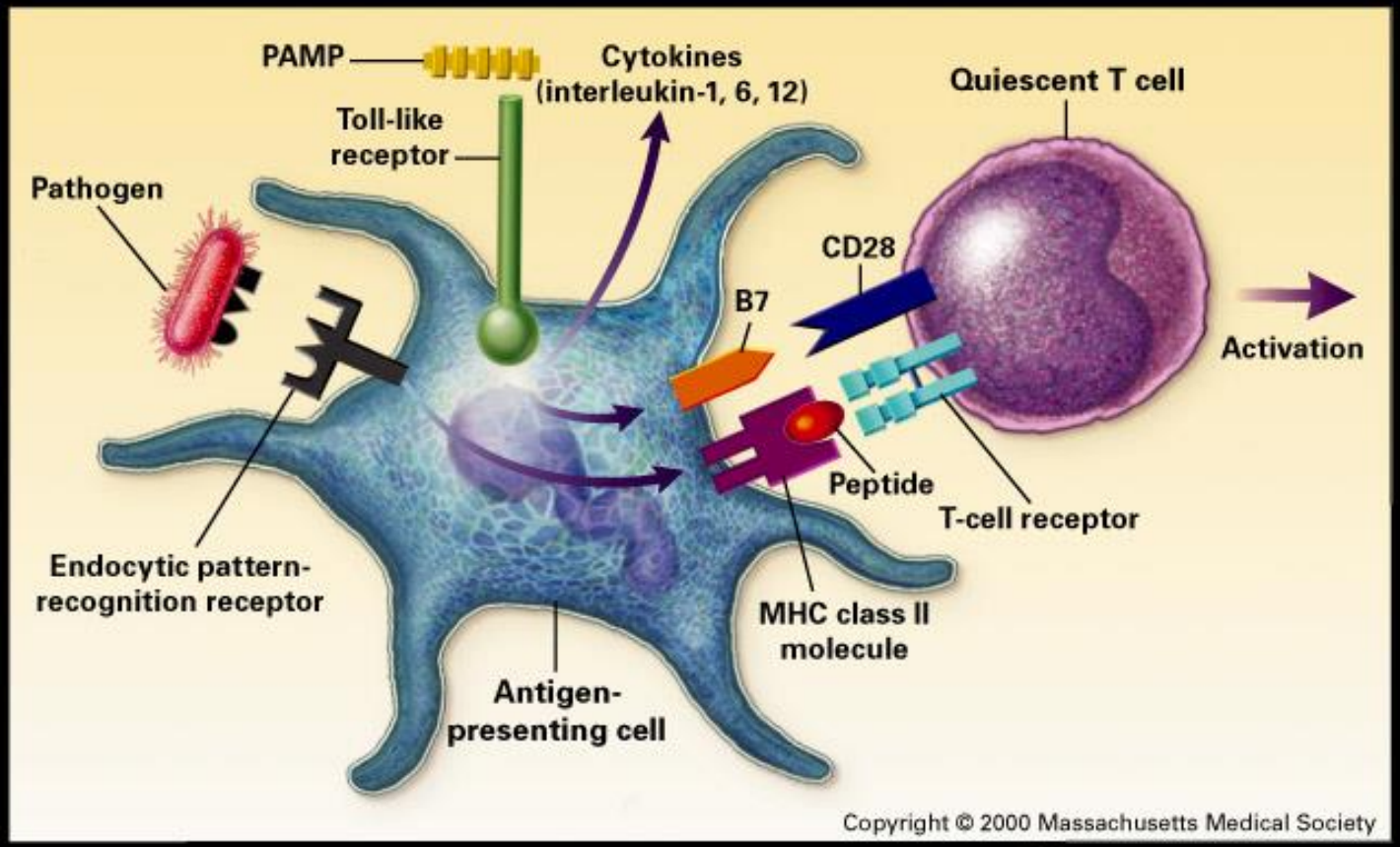


Anticorpos Ativam o Complemento – Via Clássica



Cellular and molecular immunology. Abbas A. 8th Ed. 2016

Link Entre a Imunidade Inata e a Adaptativa – ATIVAÇÂO DAS CÈLULAS DA IMUNIDADE INATA

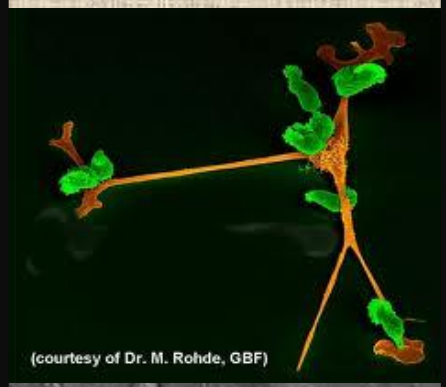


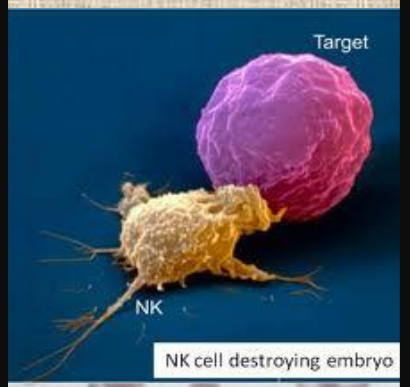
Medzhitov R, Janeway C Jr. Innate Immunity.
N Engl J Med 2000;343:338-44.

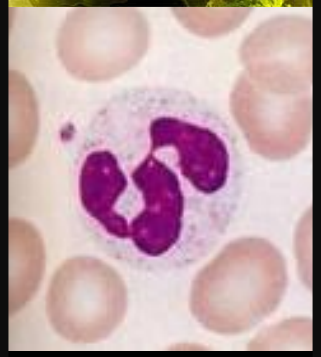
The New England Journal of Medicine

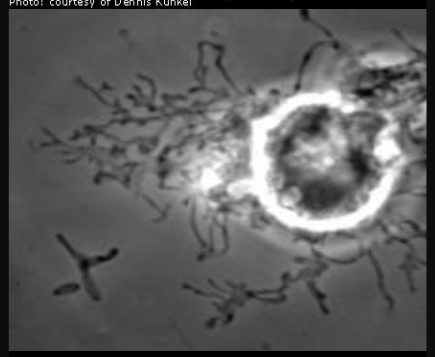
Tipo celular	Neutrófilo	Macrófago	Células dendríticas	Célula *natural killer*
Função	Fagocitose Espécies reativas de oxigênio e nitrogênio Peptídeos antimicrobianos	Fagocitose Mediadores inflamatórios Apresentação de antígenos Espécies reativas de oxigênio e nitrogênio Citocinas Proteínas do complemento	Apresentação de antígeno Sinais co-estimuladores Espécies reativas de oxigênio Interferon Citocinas	Lise da célula infectada por vírus Interferon Ativação de macrófagos

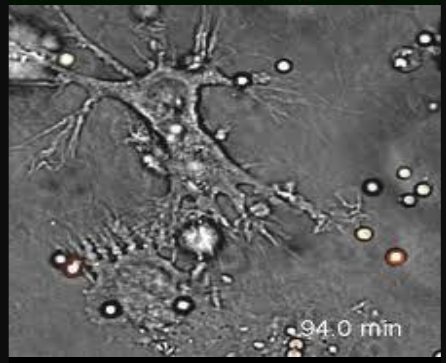
An activated macrophage phagocytosing bacteria upon contact
Photo: courtesy of Dennis Kunkel

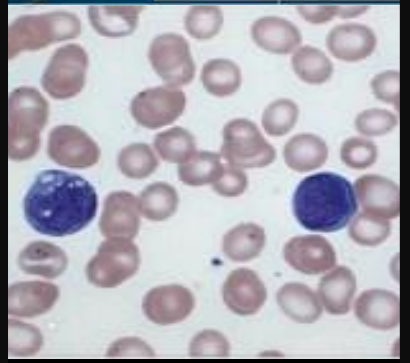




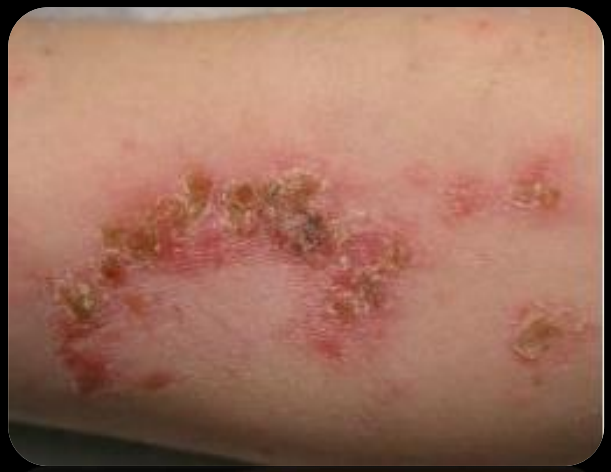




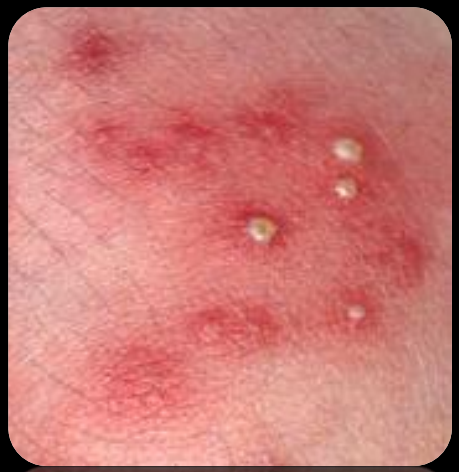




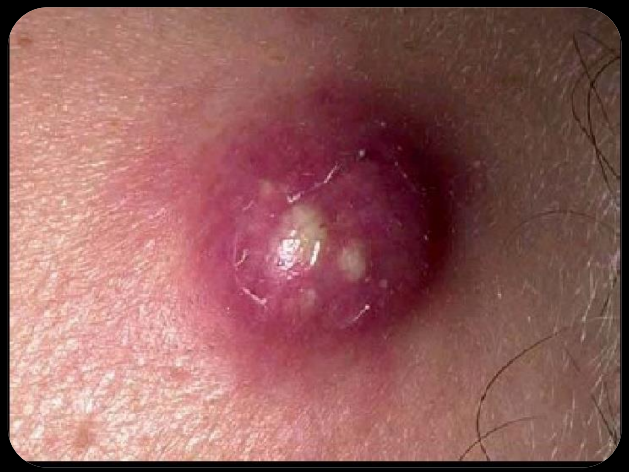
Imunopatologia



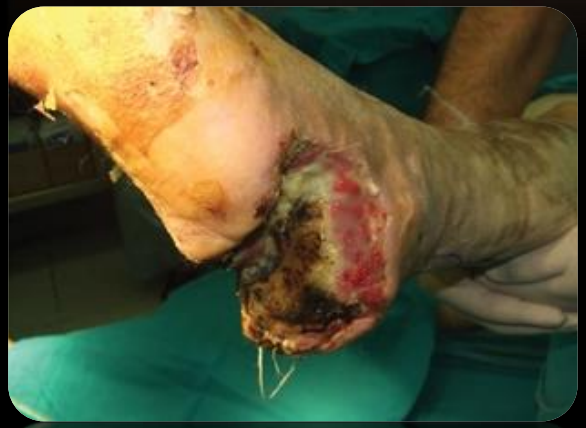
Impetigo



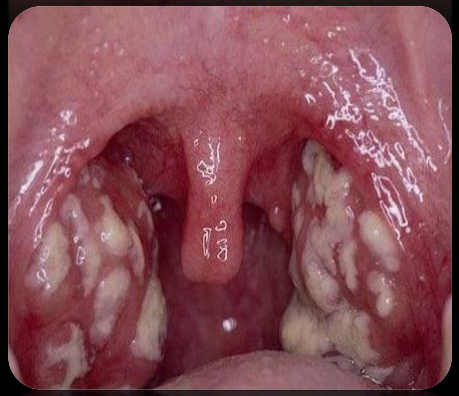
Foliculite



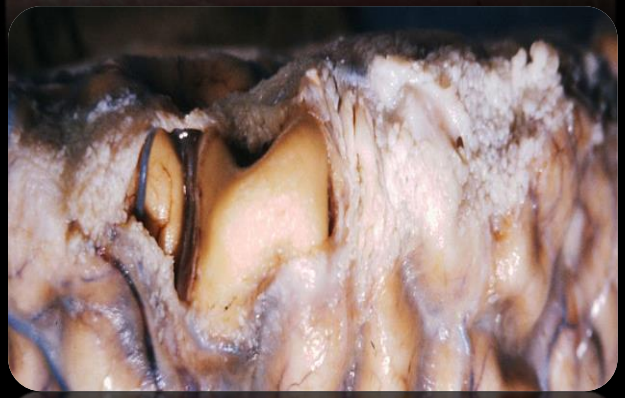
Furunculose



Osteomielite + pé-diabético



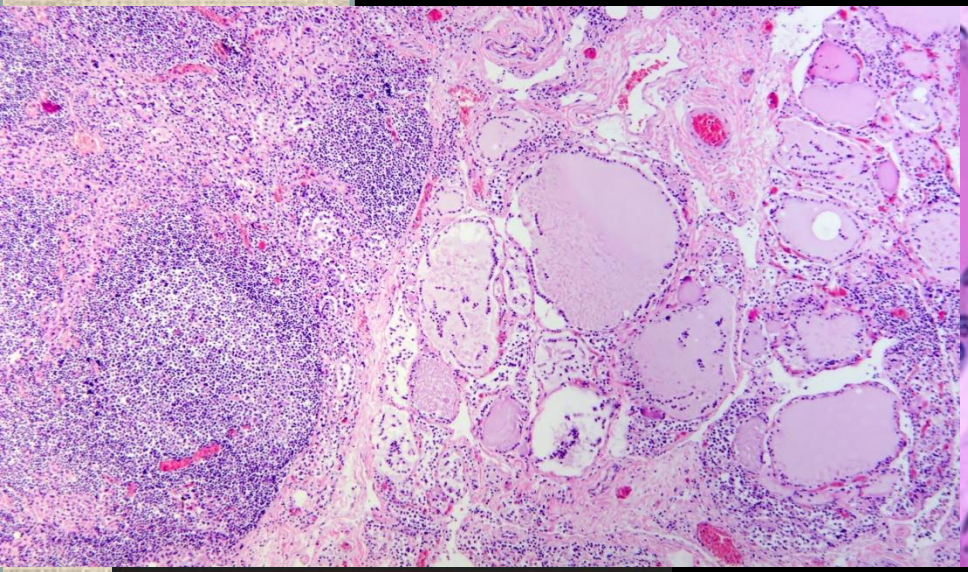
Amigdalite

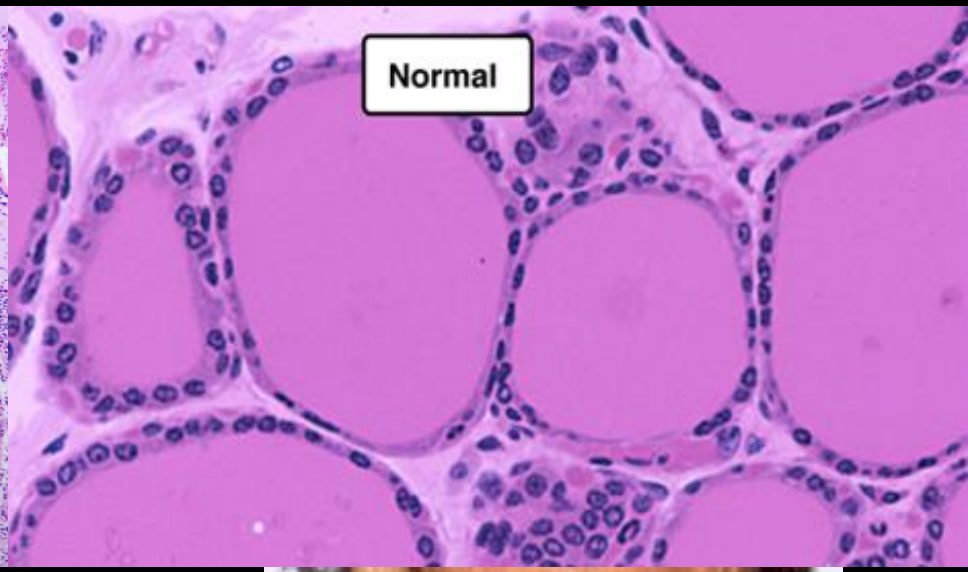


Meningite

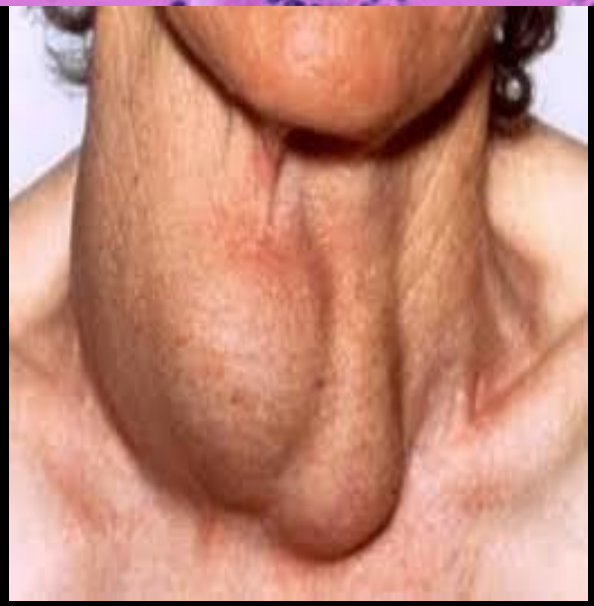
http://infectionnet.org/notes/staphylococci/

Autoimunidade – Tireoidite de Hashimoto



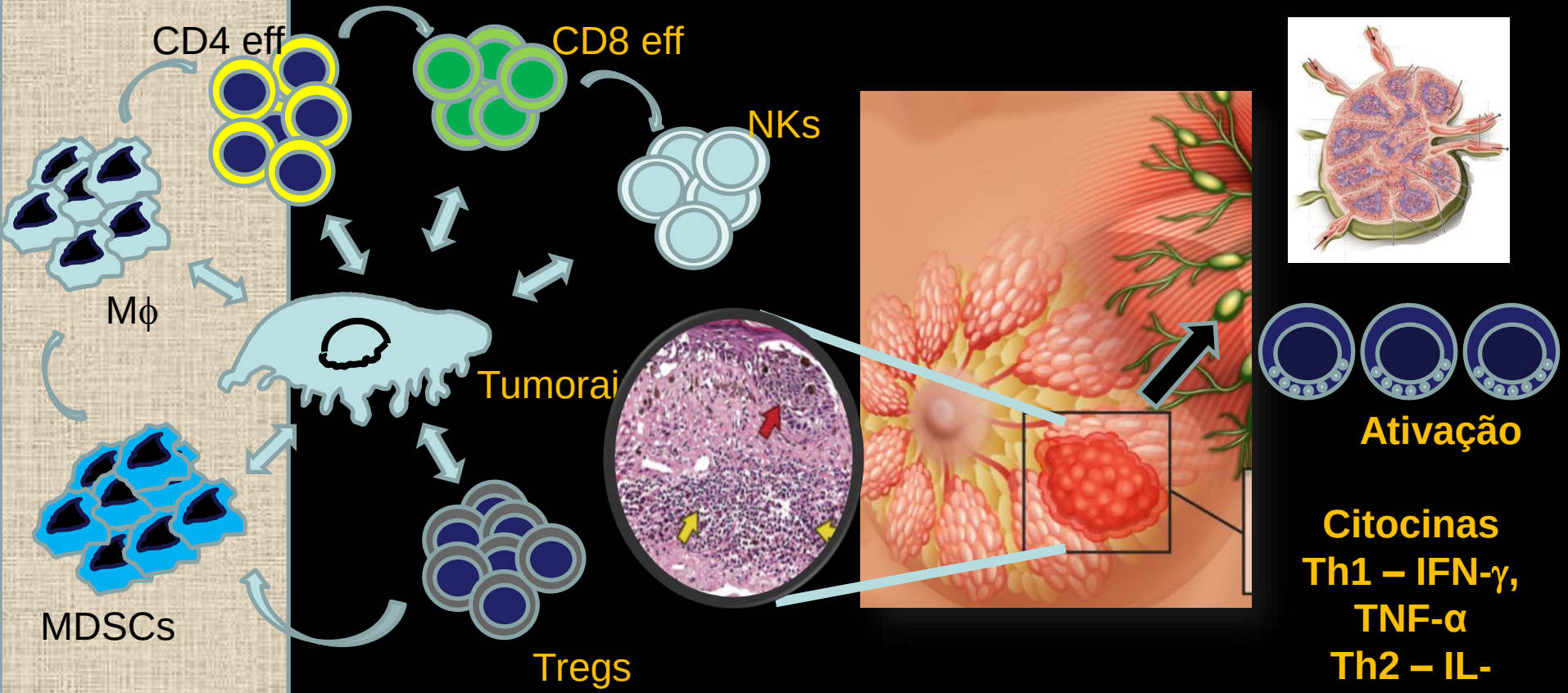


Hipotireoideo
Metabolismo Lento
Obeso



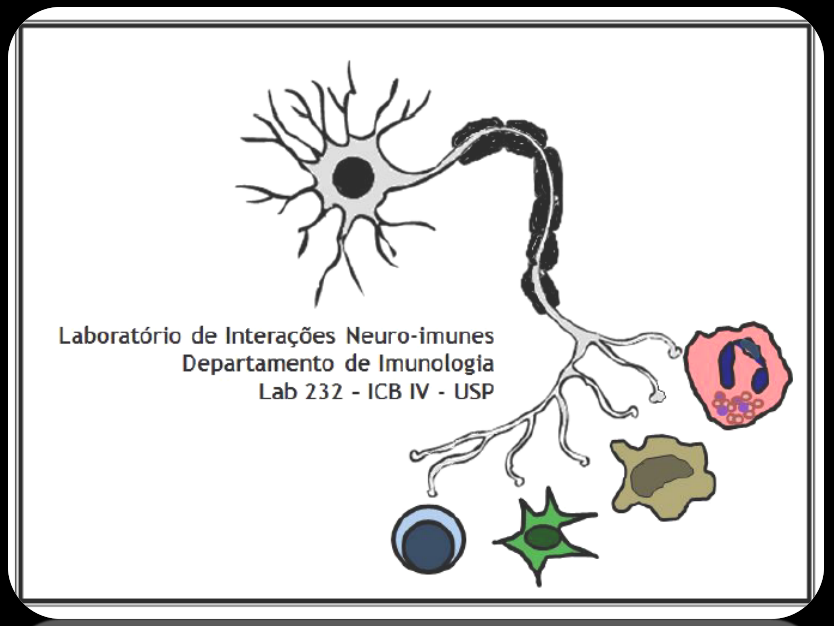
https://en.wikipedia.org/wiki/Hashimoto%27s_thyroiditis

Ambiente Tumoral – TILs (Tumor Infiltrating Lymphocytes)



Ativação

Citocinas
Th1 – IFN-γ, TNF-α
Th2 – IL-4,5,13
Th17 – IL-17, 22



DEPARTAMENTO DE Imunologia
INSTITUTO DE CIÊNCIAS BIOMÉDICAS | USP

Laboratório de Interações Neuroimunes

"...estudar as interações neuroimunes vigentes durante a resposta imune, assim como suas repercussões sobre a fisiologia do organismo".

jeanpierre@usp.br