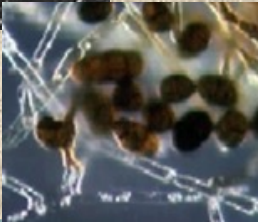
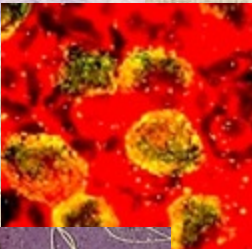
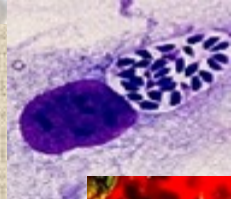
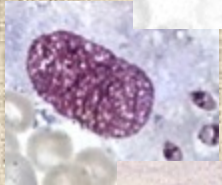
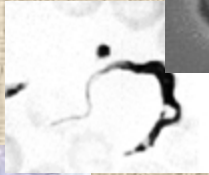
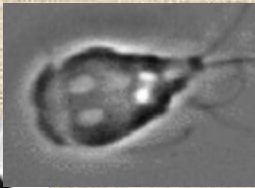


Imunidade Adaptativa

Dr. Jean Pierre Schatzmann Peron

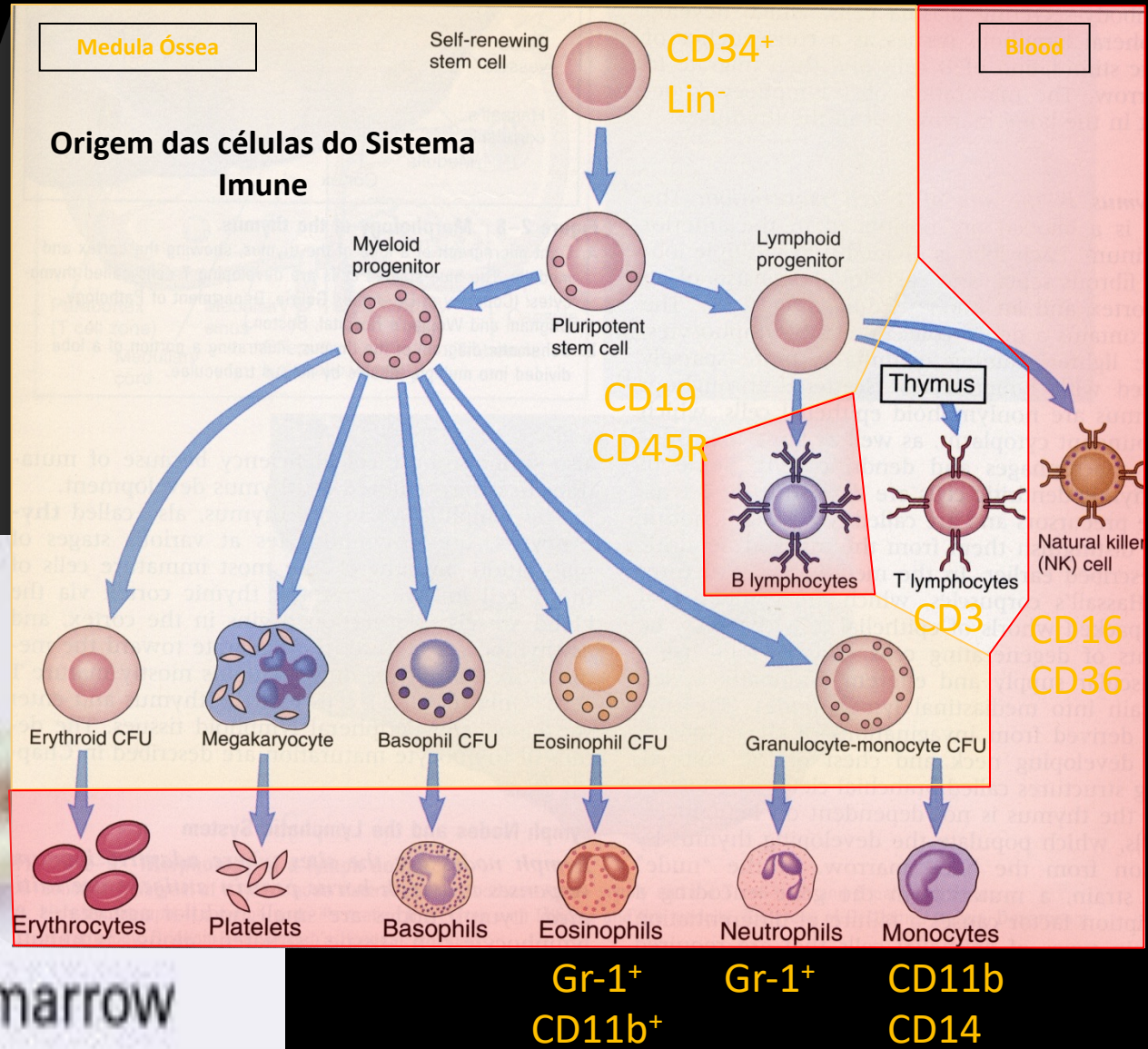
Laboratório de Interações Neuroimunes
Departamento de Imunologia
Universidade de São Paulo



Objetivos

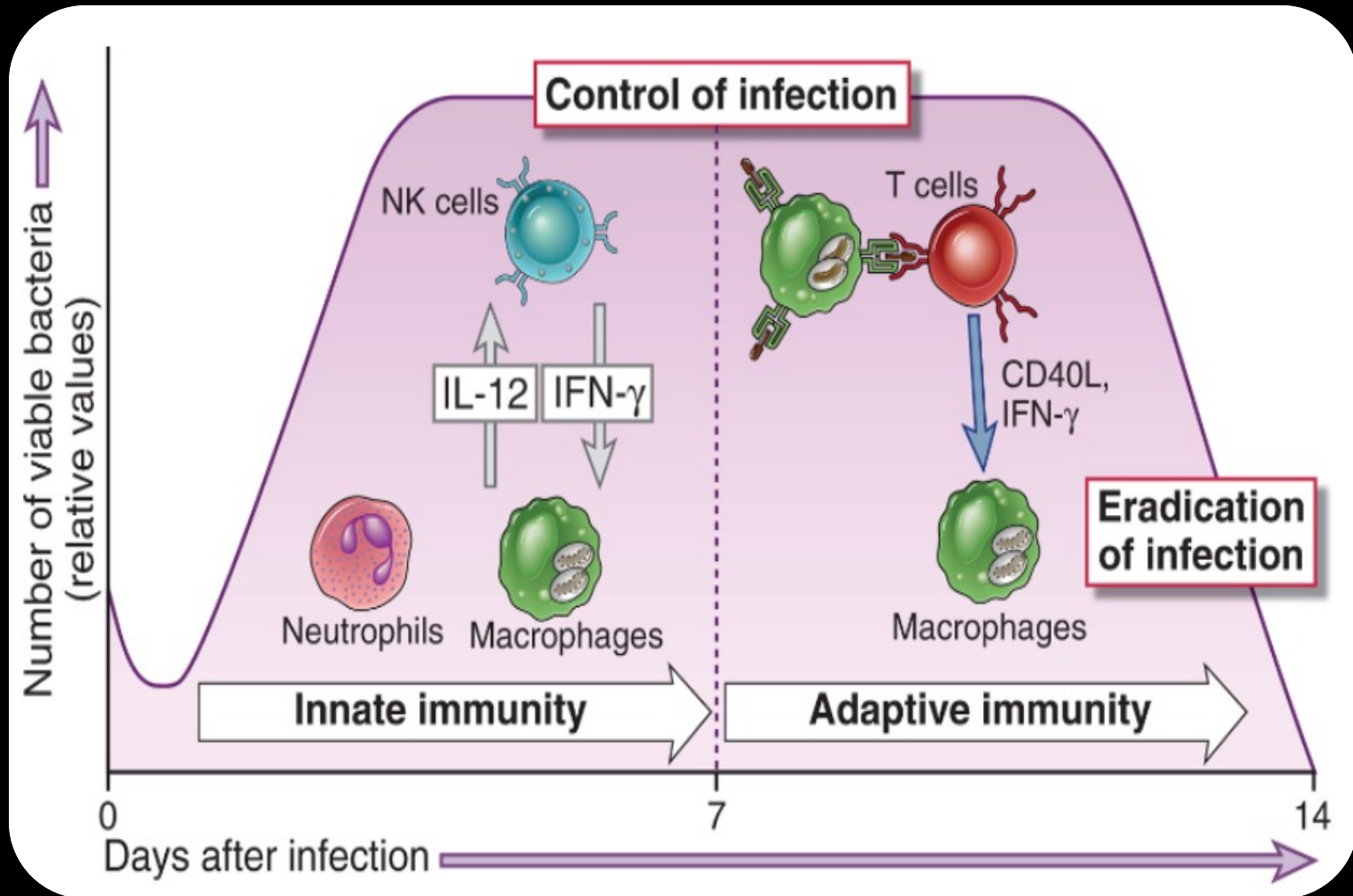
- Células do Sistema Imune Adaptativo
 - Geração e Localização
- Seus Receptores de Reconhecimento
 - Apresentação de Antígenos
- Classificação Funcional dos Linfócitos T CD4 e Suas Funções

Medula Óssea – Órgão Linfóide Primário



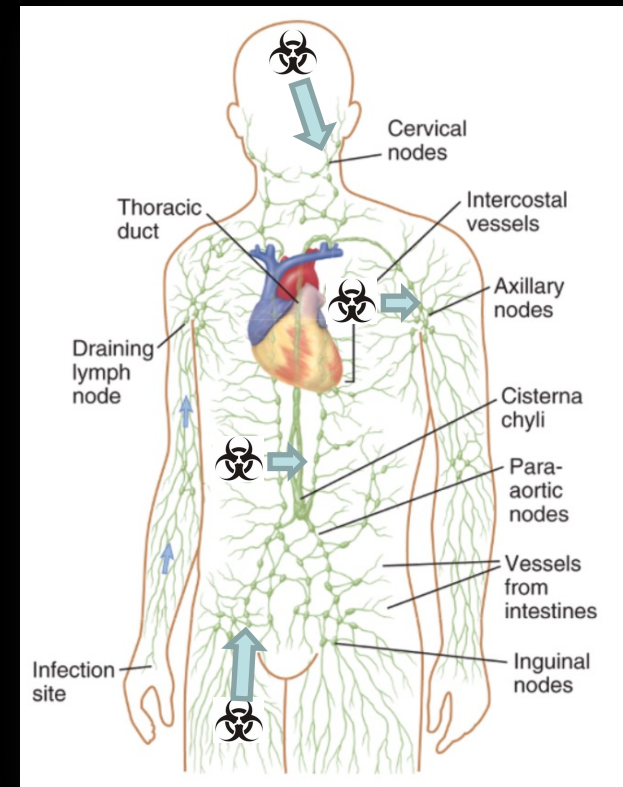
Resposta Imune

Inata X Adaptativa



Days after infection

Sistema Linfático – Drena o Líquido Intersticial - LINFA



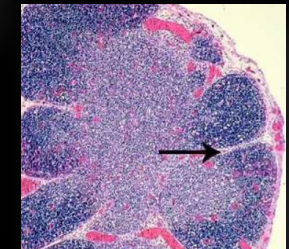
Componentes do Sistema Imune

- Órgãos Linfóides

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



Medula Óssea



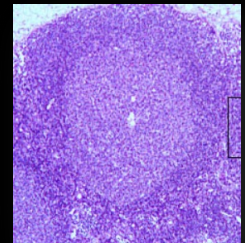
Timo

- **Células do Sistema Imune** – Evolutivamente Divididas em Imunidade Inata e Adaptativa

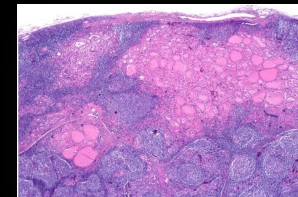
- **Inata** – Macrófagos, Células Dendríticas, Neutrófilos, NKs, Basófilos, Eosinófilos, etc
- **Adaptativa** – Linfócitos T e B

- **Células com FUNÇÃO IMUNE**

- Fibroblastos, hepatócitos, plaquetas, astrócitos, etc...



Linfonodos



Folículos Linfóides

Estrutura das Moléculas de MHC I e II

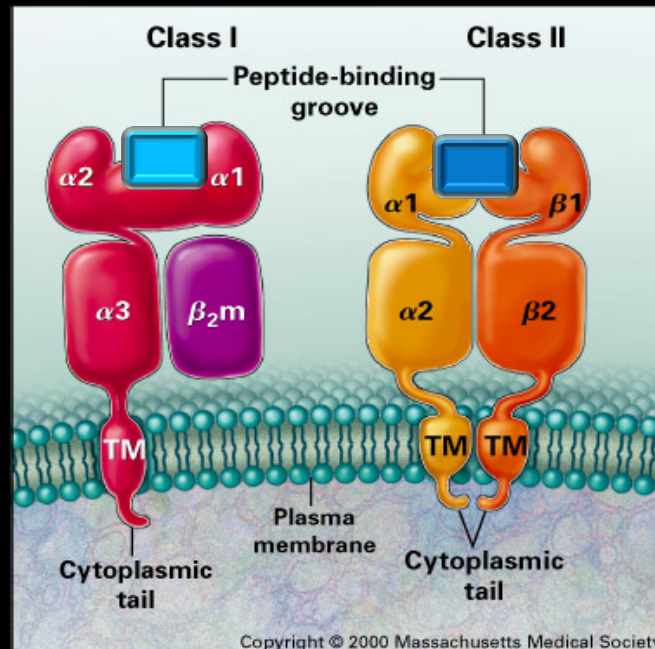
Apresentação de Antígenos

É Um Fenômeno Fisiológico

CONSTANTE

AUTO-ANTÍGENOS

Protéínas Endógenas
Degradadas



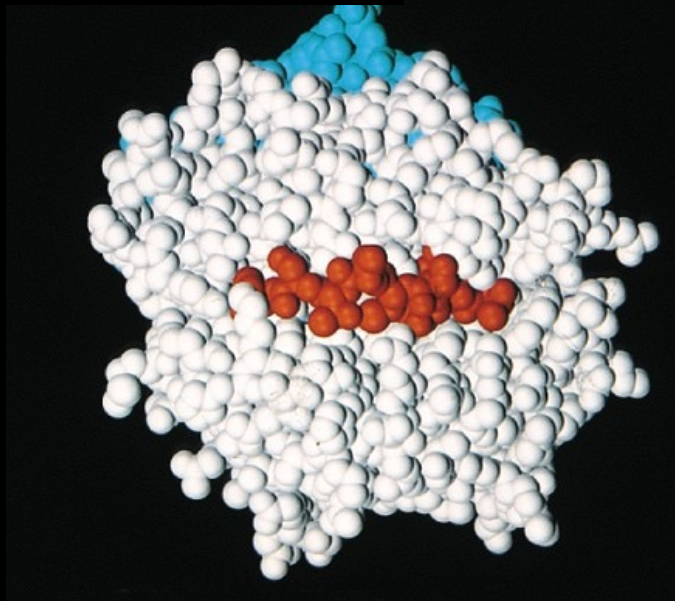
Klein J, Sato A. The HLA System. First of two parts. N Engl J Med 2000;343:702-9.



The New England
Journal of Medicine

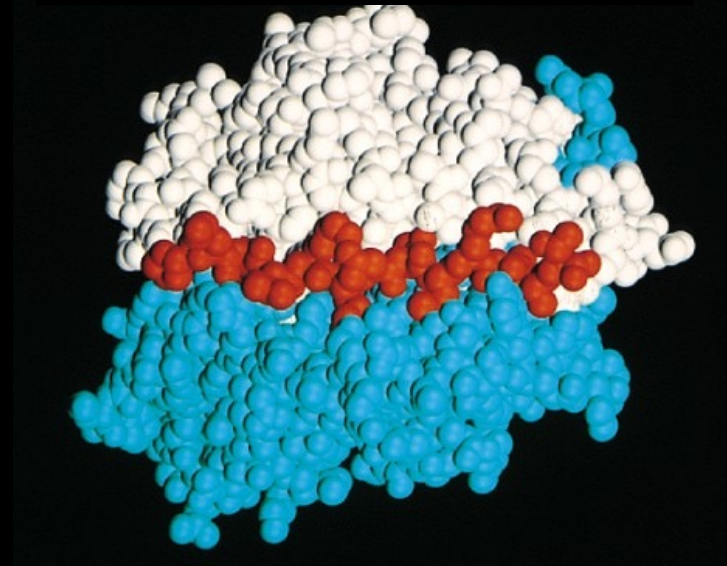
Estrutura das Moléculas de MHC I e II

MHC Classe I



Todas as células
Nucleadas

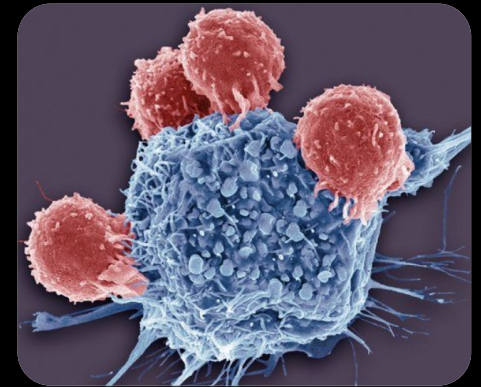
MHC Classe II



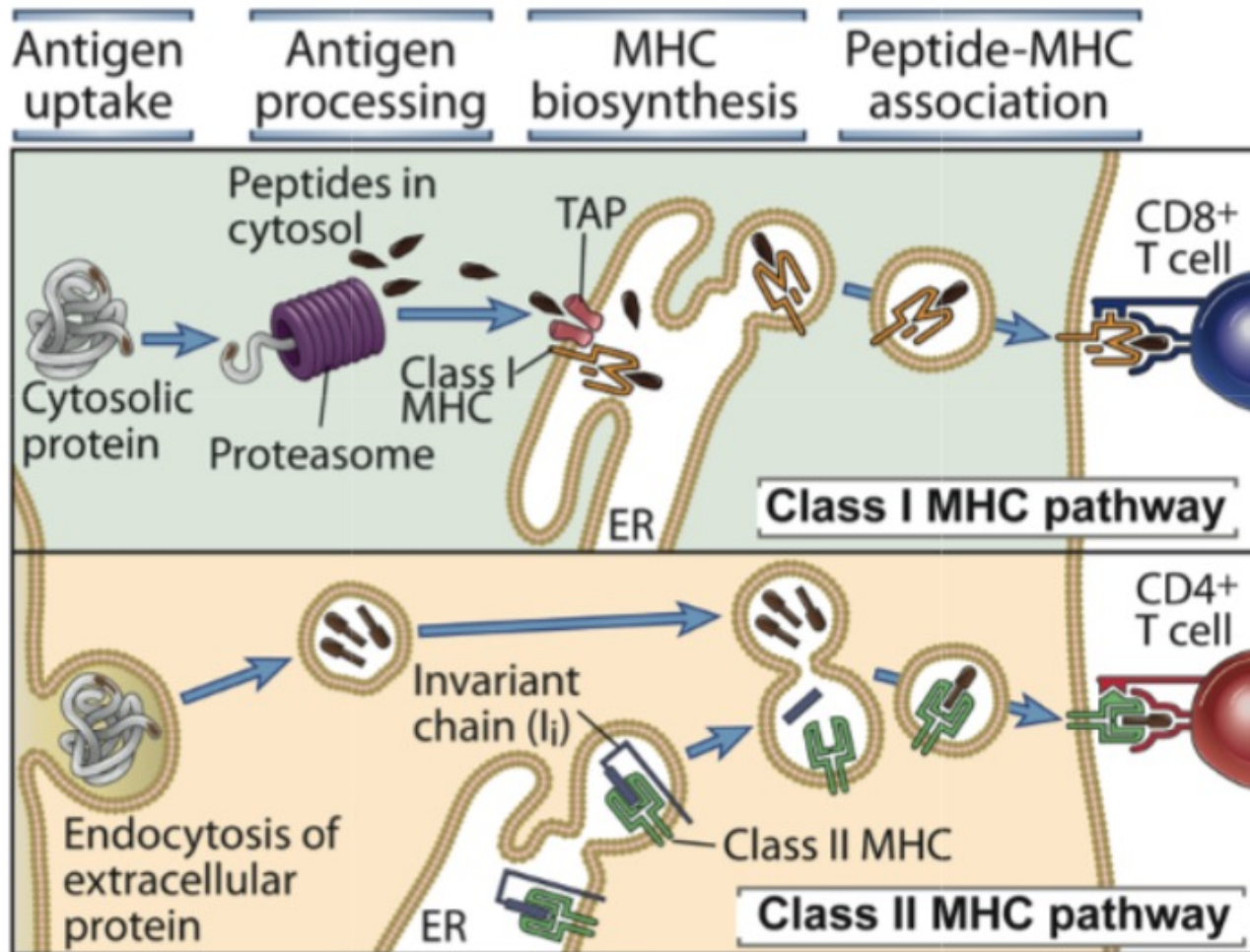
Apresentadoras de Antígeno
Profissionais

As Moléculas do MHC

- são constantemente 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...)

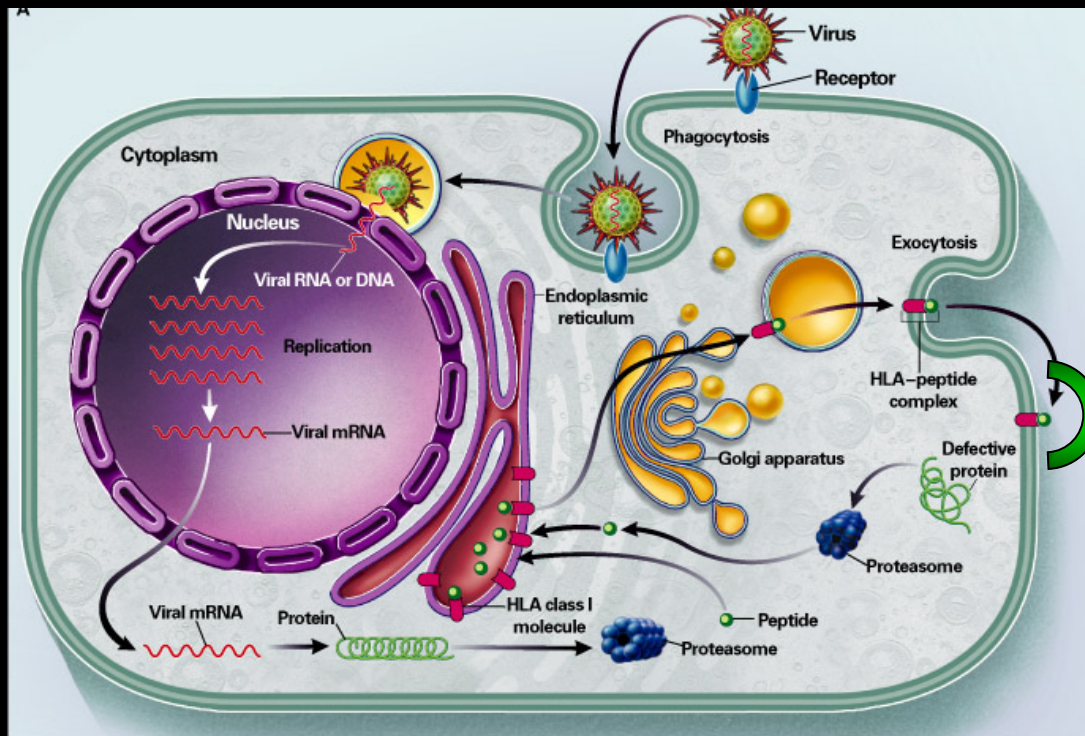
Antígenos Extracelulares

Internalizados

Debris celulares, células Em apoptose,

APRESENTAÇÃO CRUZADA

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

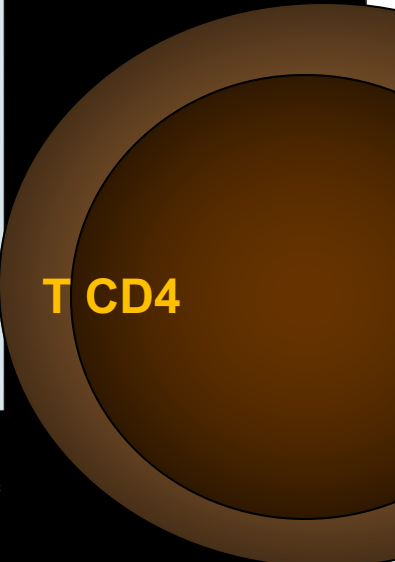
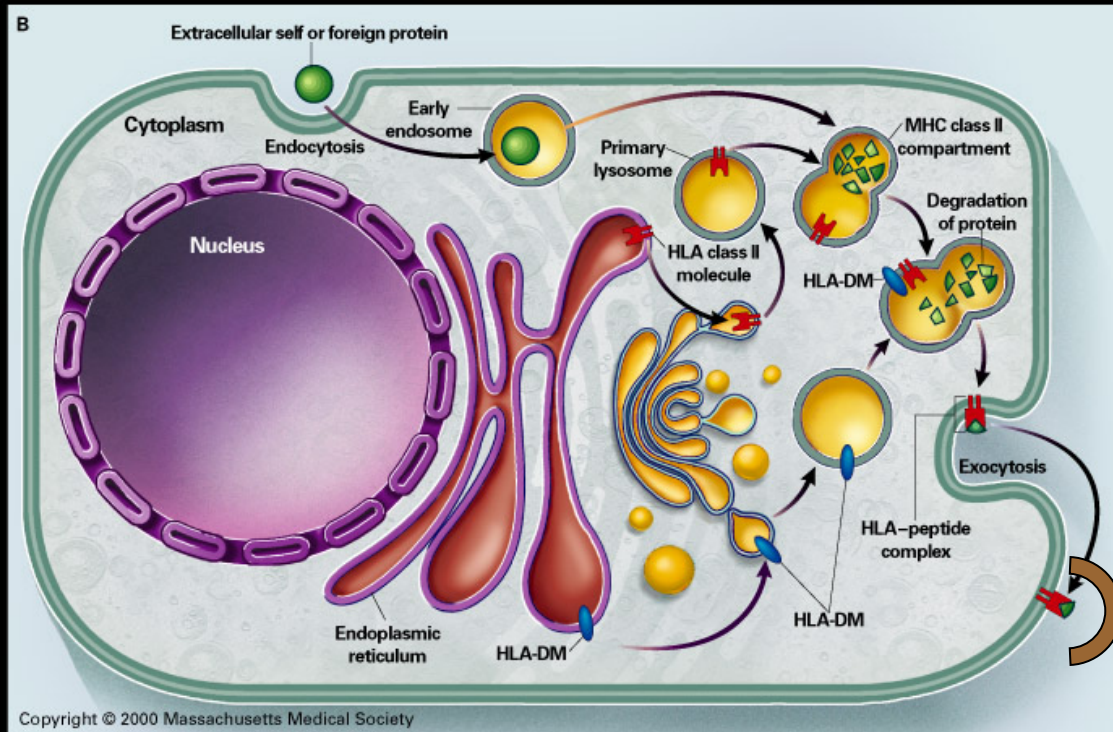


Klein J, Sato A. The HLA System. First of two parts.
N Engl J Med 2000;343:702-9.



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

Estrutura Tímica



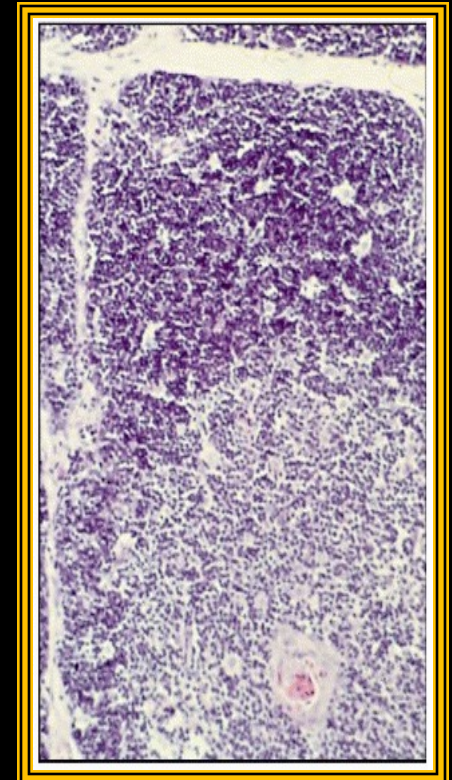
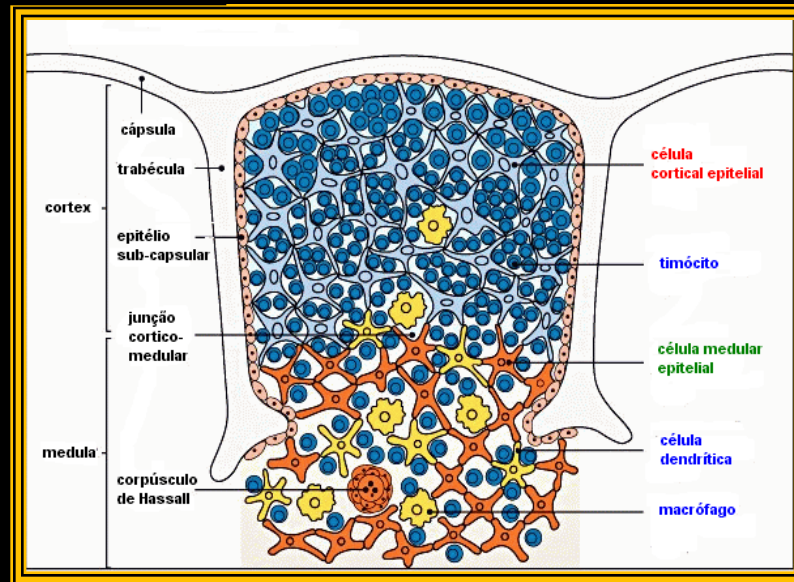
TECs –Células Epiteliais Timo

Expressão AIRE

Antígenos ÓRGÃO ESPECÍFICOS

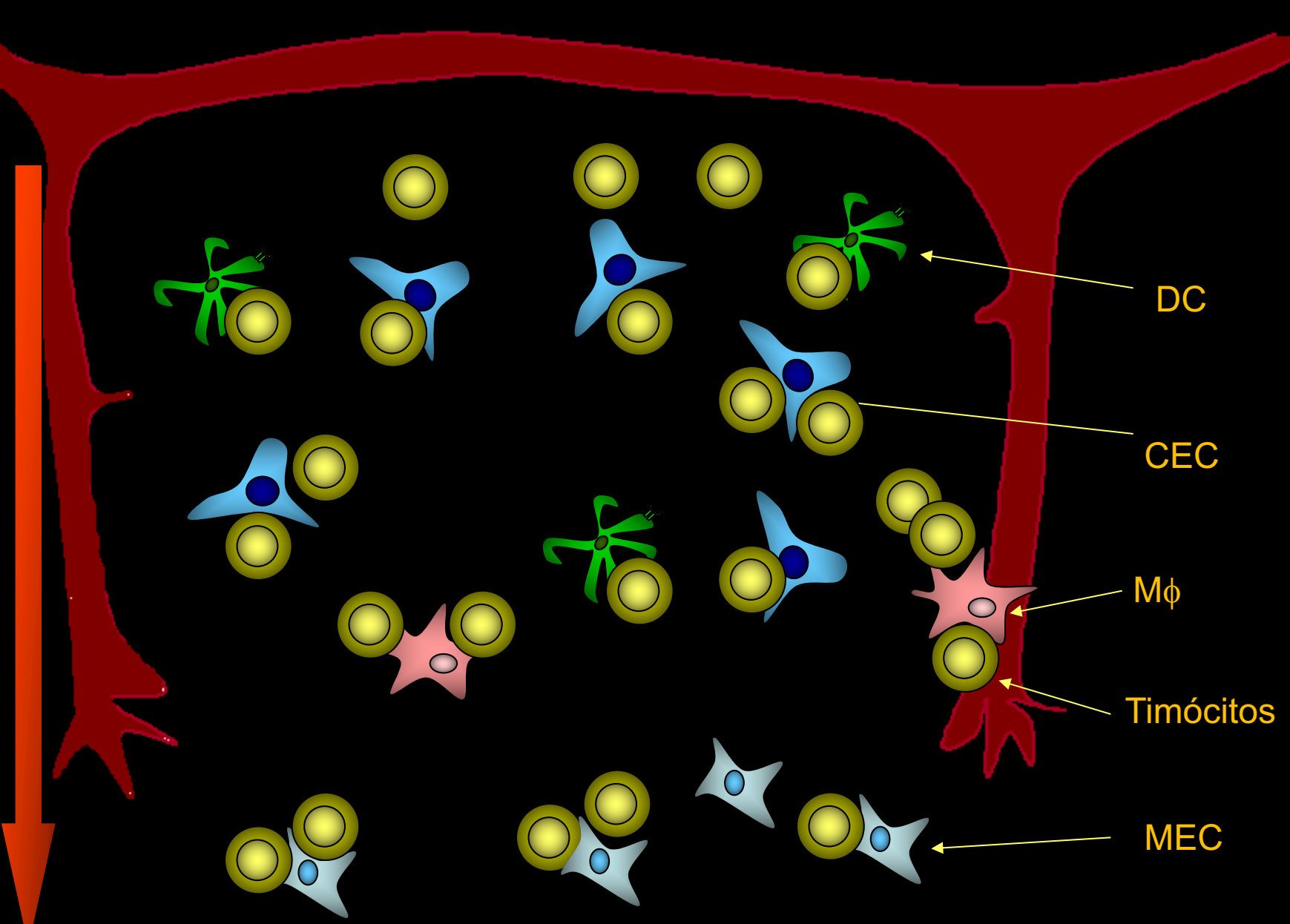
SELEÇÃO NEGATIVA

Idade em anos



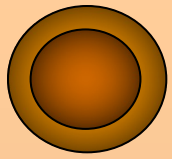
Precursores linfóides, agora chamados timócitos, migram da CÓRTEX
PARA MEDULA e não expressam CD4 nem CD8
CD4^{neg} CD8^{pos}

Maturação

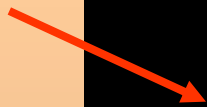


Ao adentrar o timo, timócitos passam a expressar $CD4^{pos} CD8^{pos}$

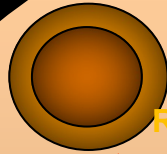
Medula



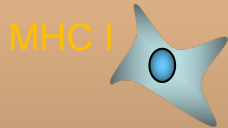
$CD4^{-}$
 $CD8^{-}$
 TCR^{-}



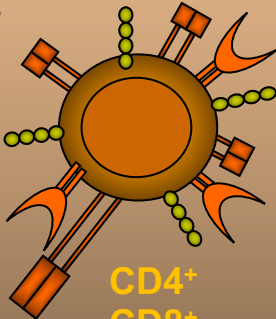
Timo



$CD4^{-}$
 $CD8^{-}$
Recombinação
TCR
(RAG 1 e 2)

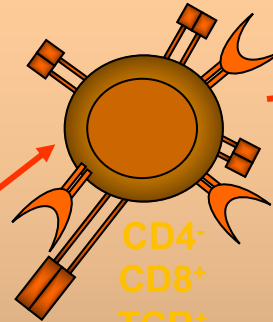


MHC I
MHC II

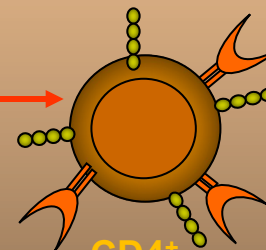


$CD4^{+}$
 $CD8^{+}$
 TCR^{low}

Córtex



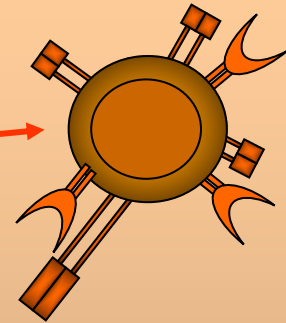
$CD4^{-}$
 $CD8^{+}$
 TCR^{+}



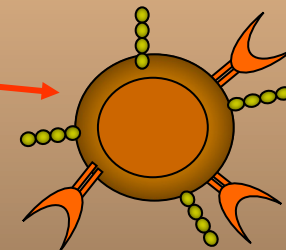
$CD4^{+}$
 $CD8^{-}$
 TCR^{+}

Medula

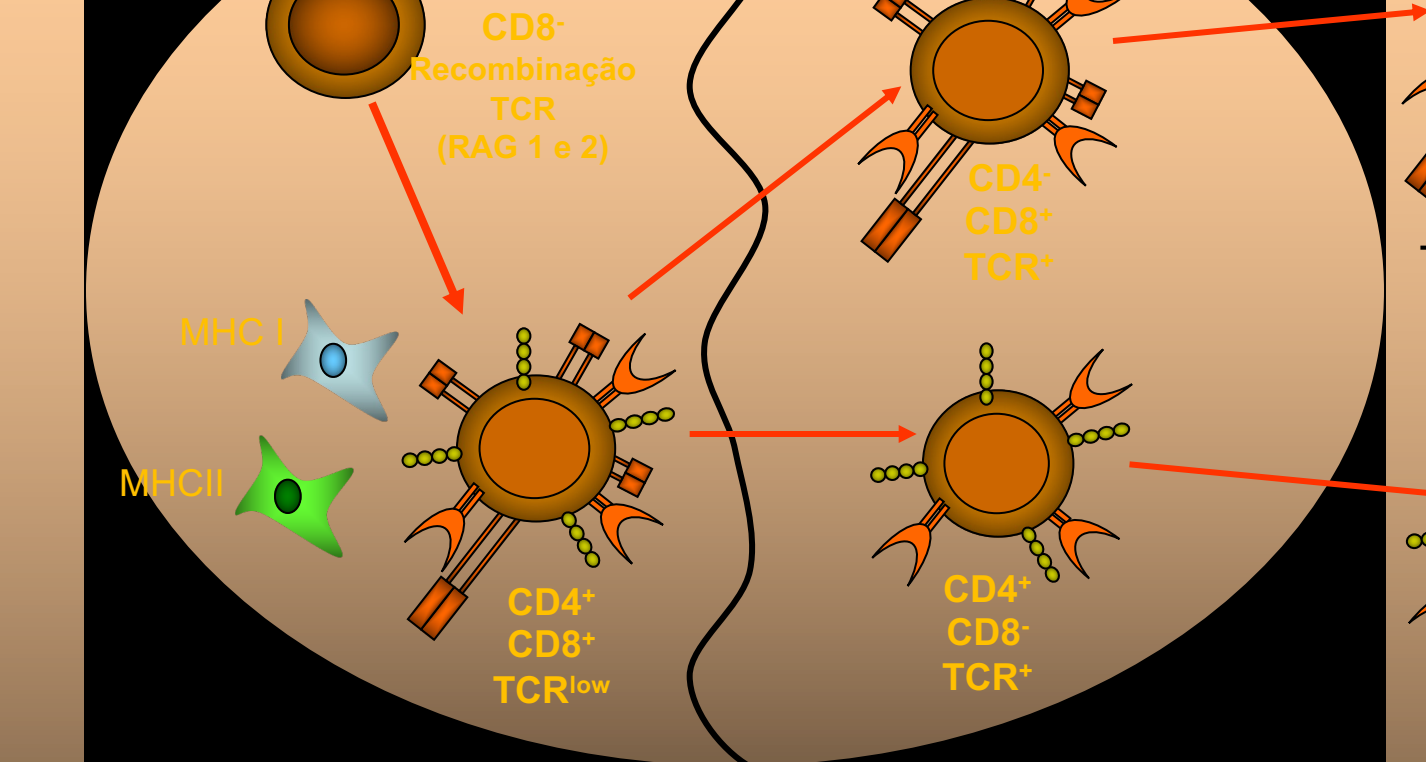
Periferia



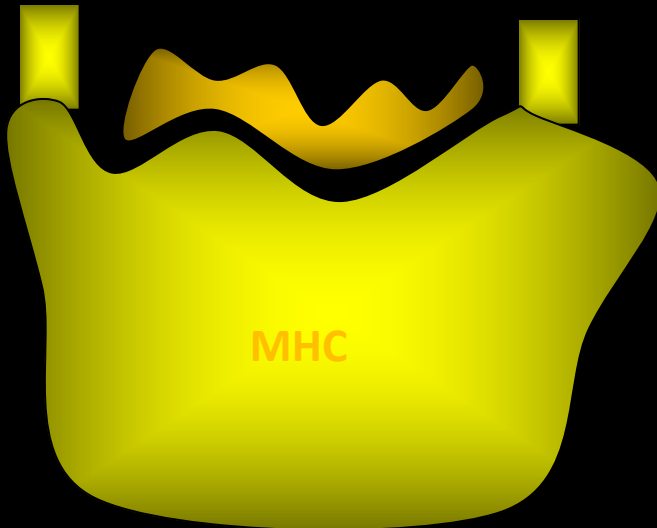
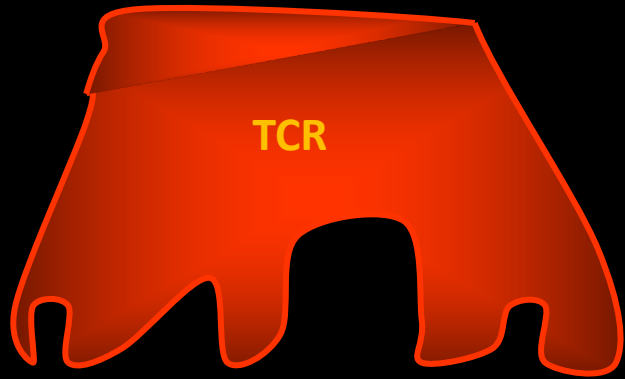
T Citotóxico



T helper



Negligência



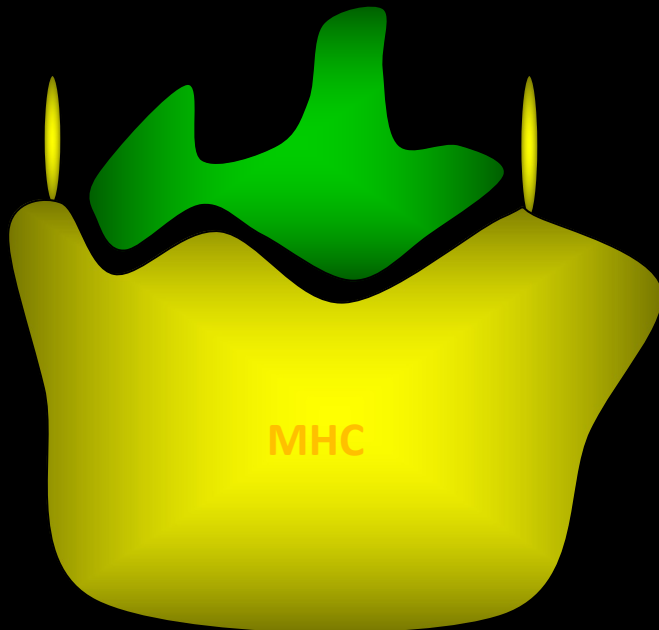
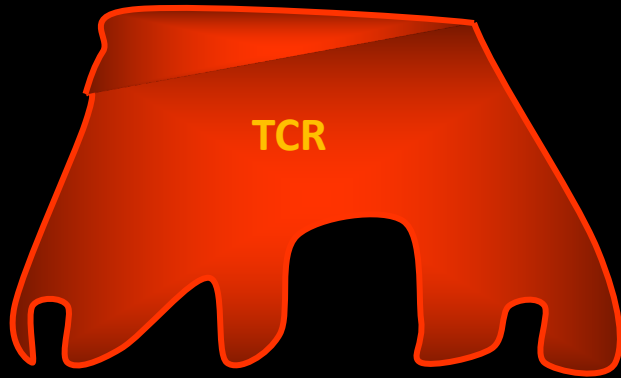
Nenhum Reconhecimento
Sinal de Morte
Morte por negligência

Seleção Negativa

Afinidade da interação
MCH-Peptídeo-TCR

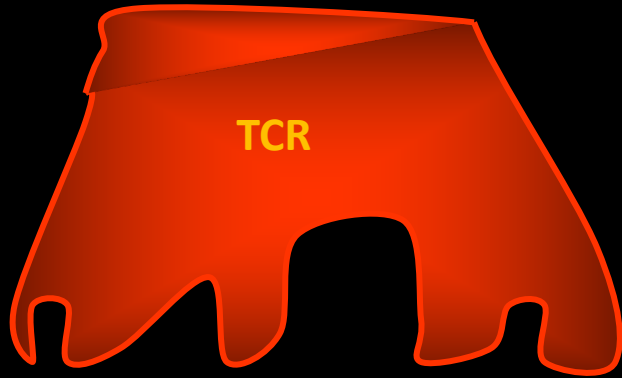
Impede que clones auto-
reativos alcancem a periferia

Seleção Negativa

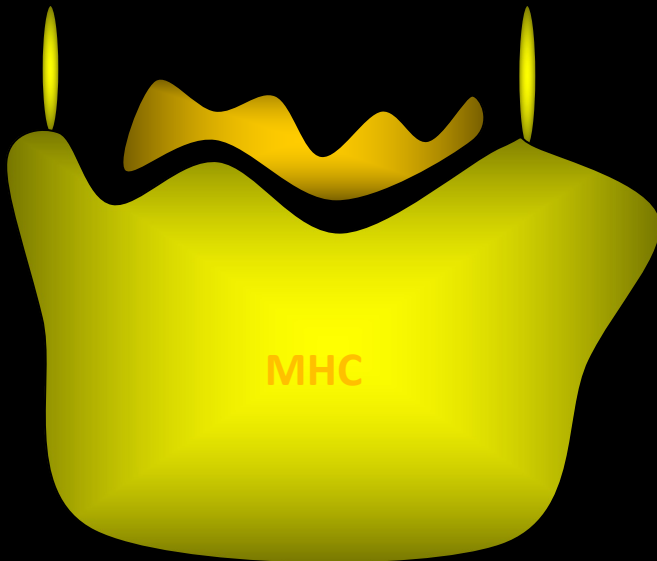


Sinal de Morte
Total
Complementaridade
Tregs

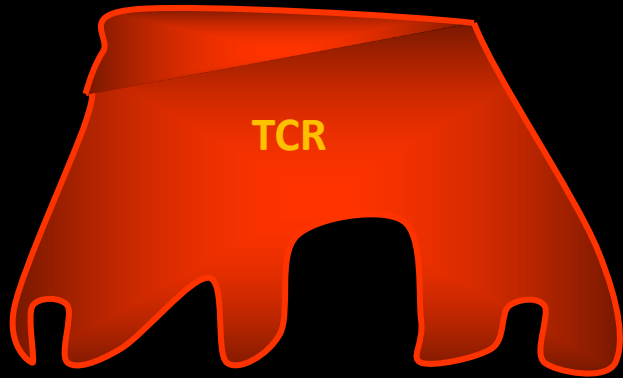
Seleção Positiva



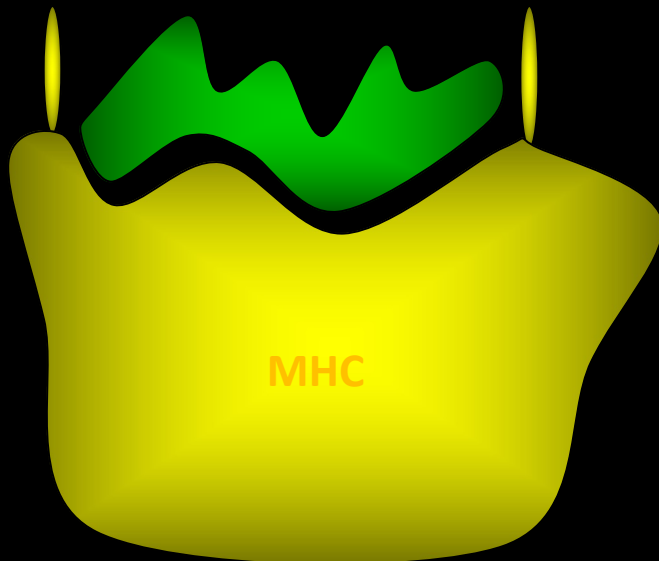
Sinal de Vida



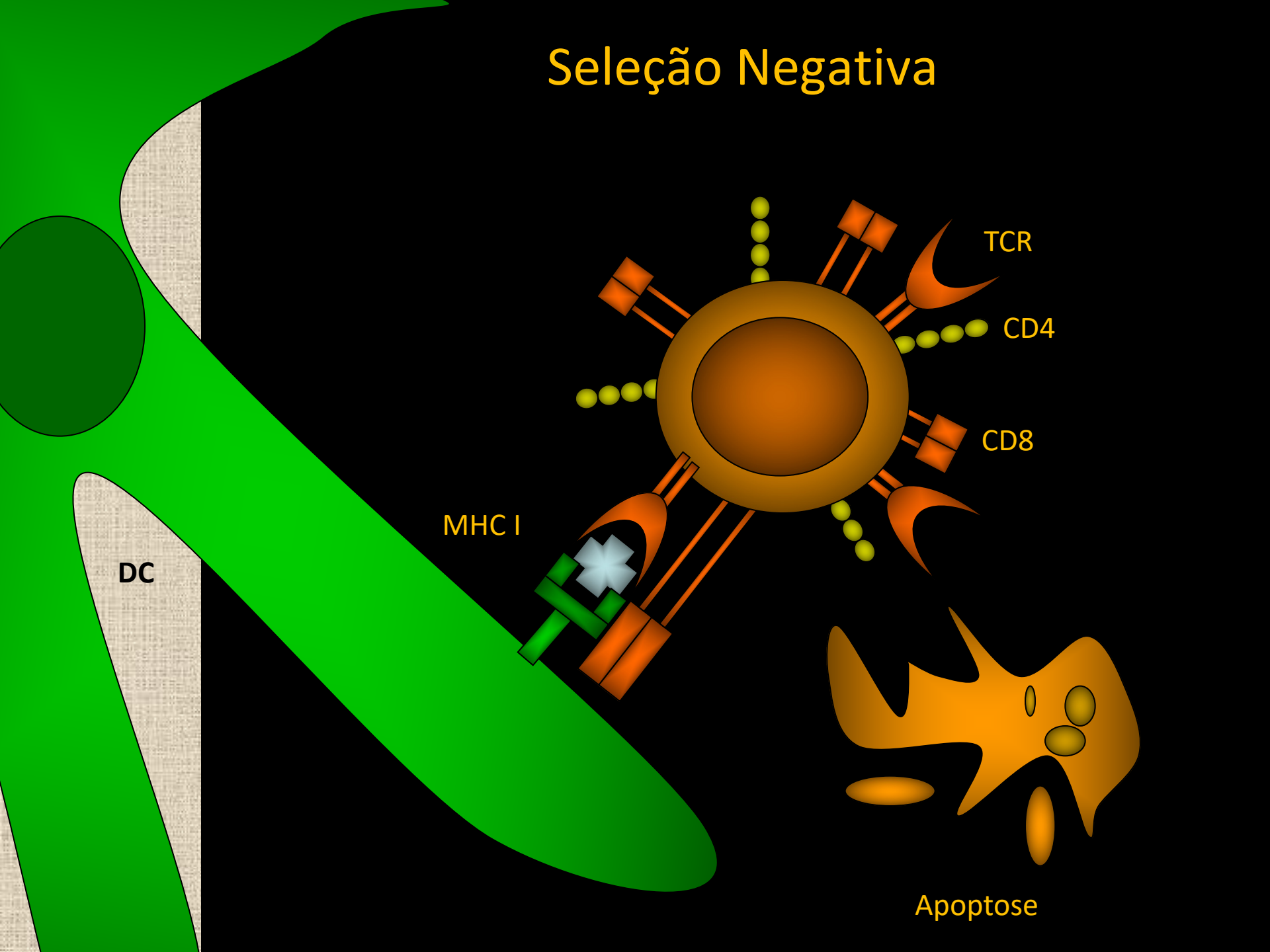
Seleção Negativa



Sinal de vida



Seleção Negativa



TCR

CD4

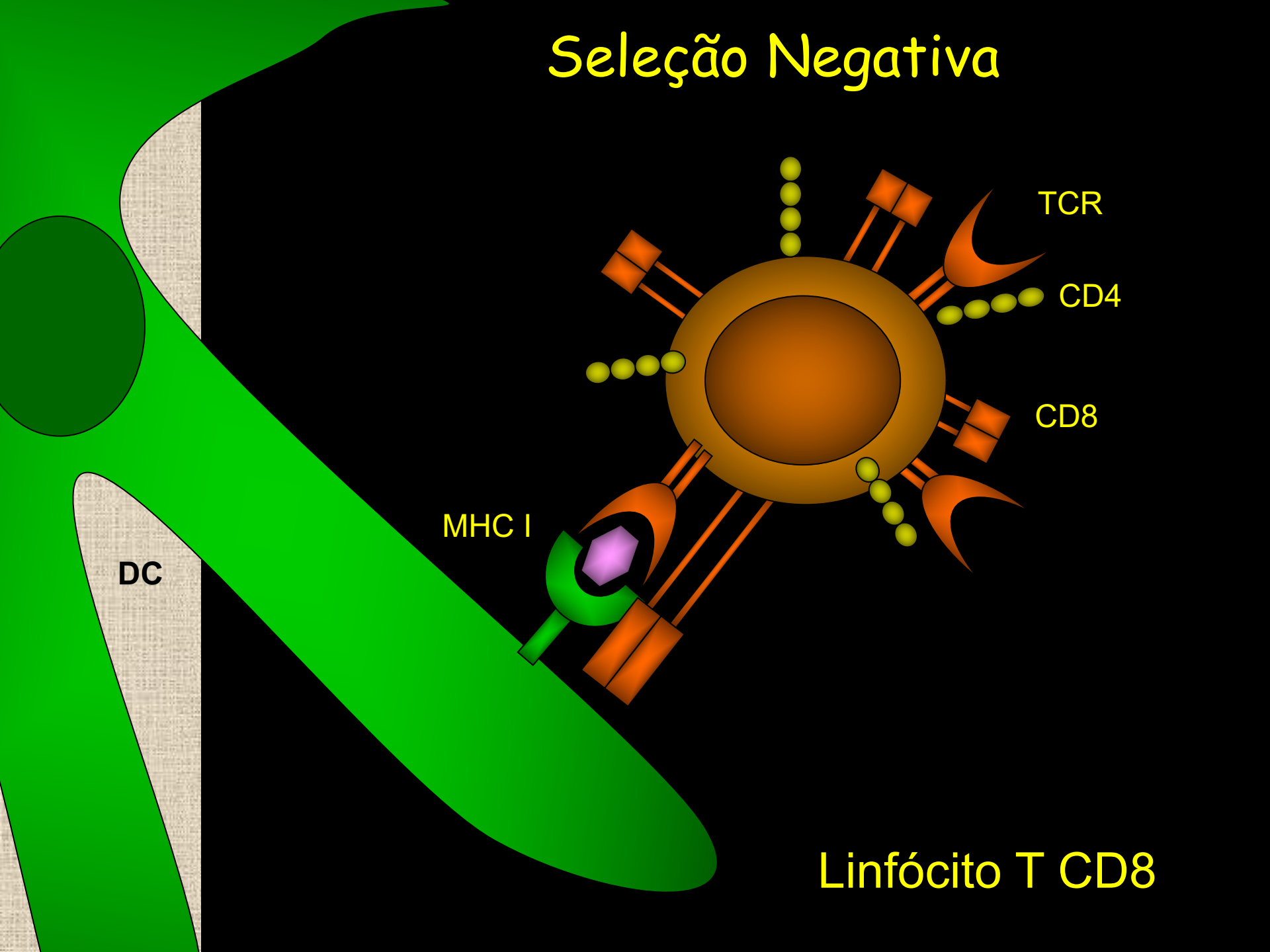
CD8

MHC I

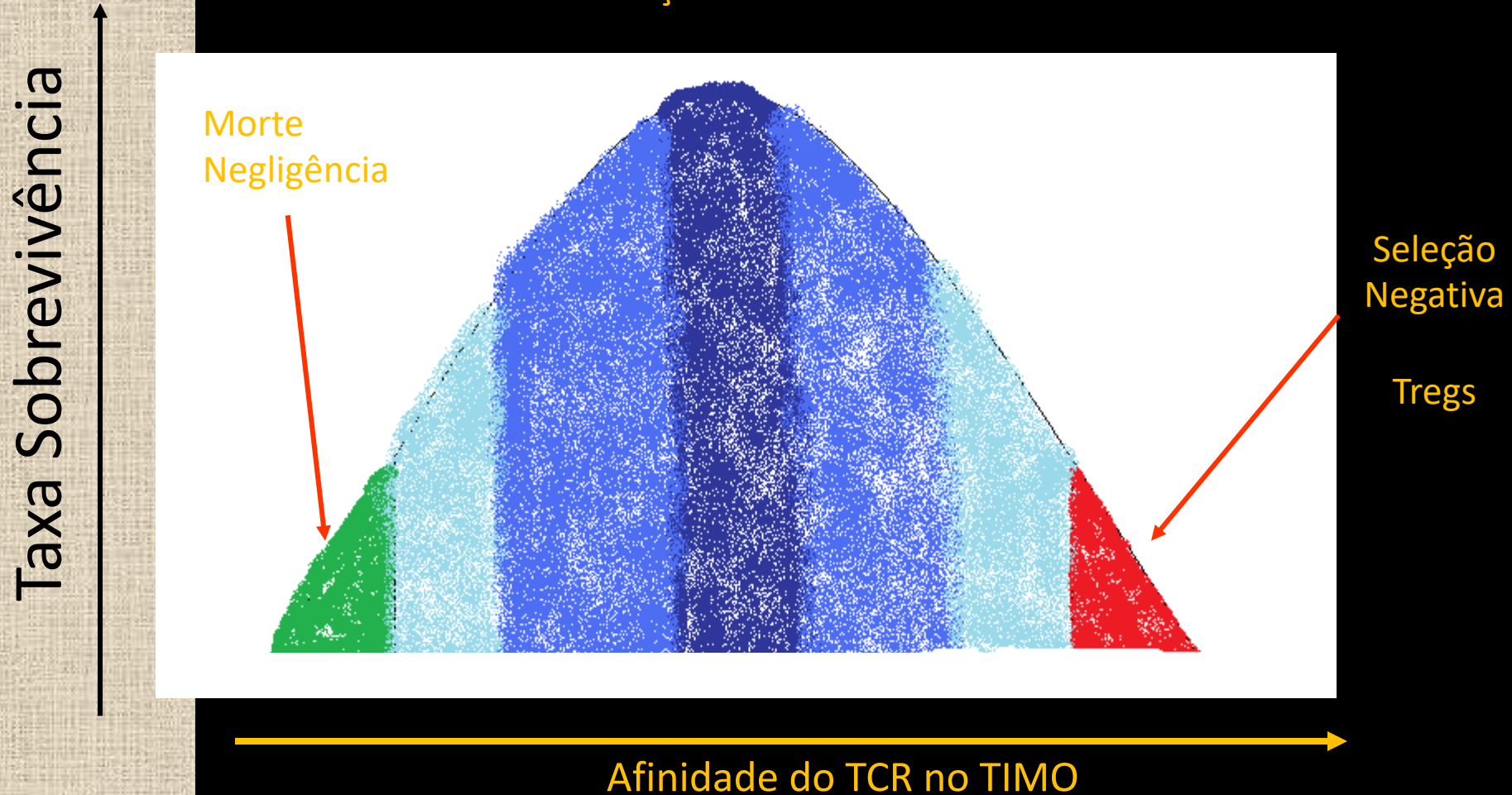
DC

Apoptose

Seleção Negativa



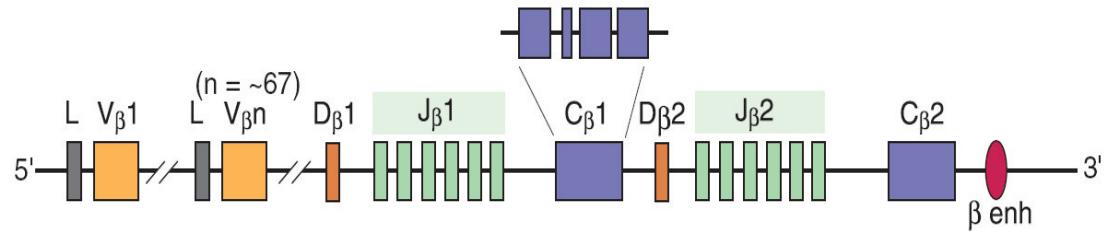
Limiar de Seleção Regido pela Força de Interação Entre os Linfócitos e Antígenos Próprios



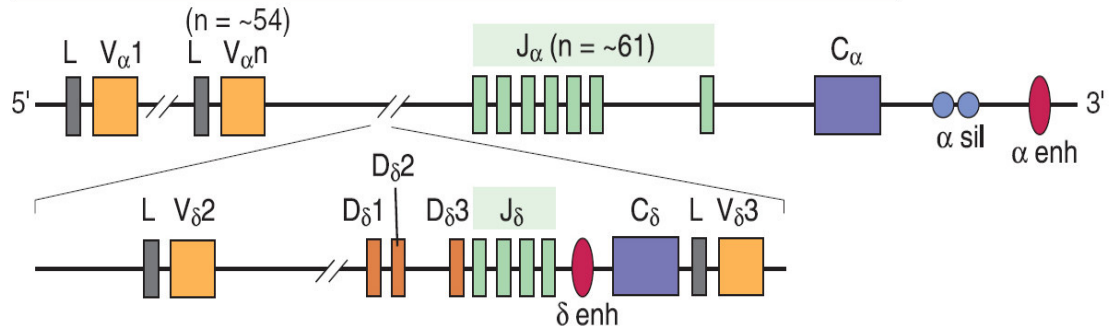
Loci do TCR

Imunologia Celular e Molecular
ISBN: 978853222449
Elsevier Editora

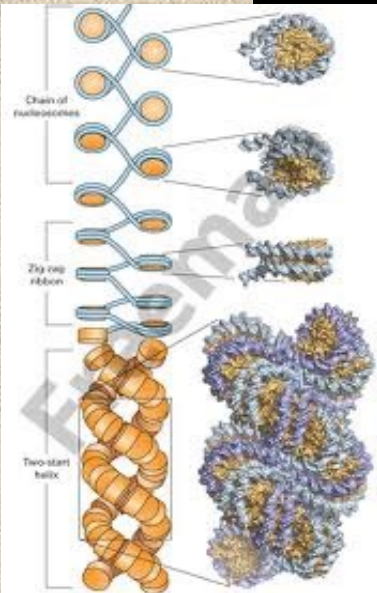
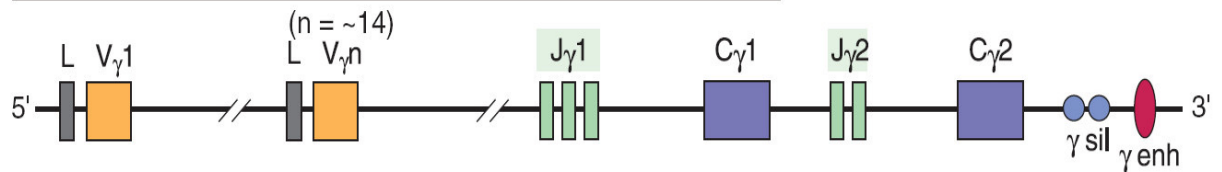
Locus da cadeia β do TCR humano (620 kb; cromossomo 7)



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



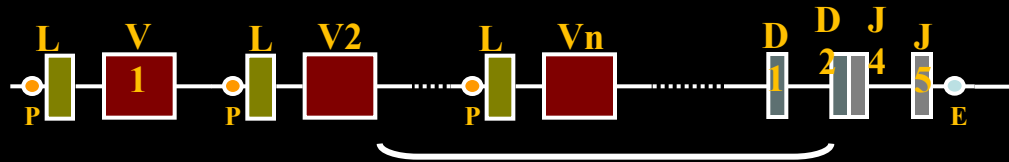
Locus da cadeia γ do TCR humano (200 kb; cromossomo 7)



O TCR Sofre Rearranjo Gênico V(D)J

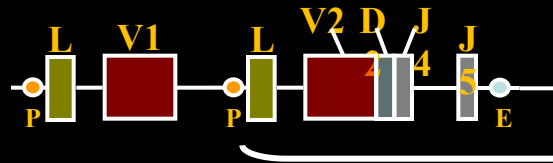


Rearranjo DJ



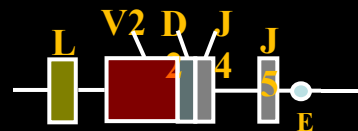
DNA

Rearranjo VDJ



DNA

Transcrição



— RNA Primário

Isso Codificará as Proteínas do TCR

Estrutura dos Linfonodos

Zona Parafolicular – Linfócitos T

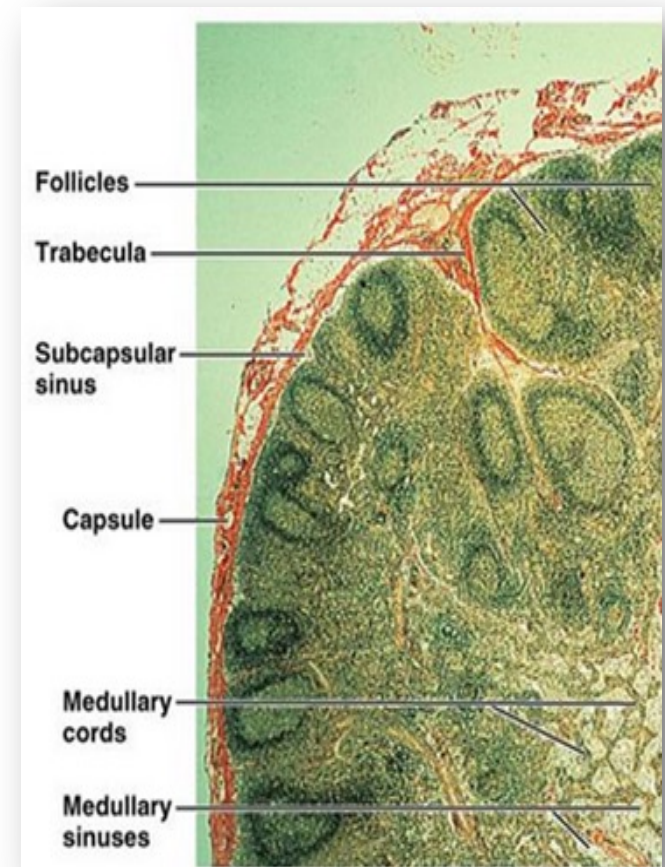
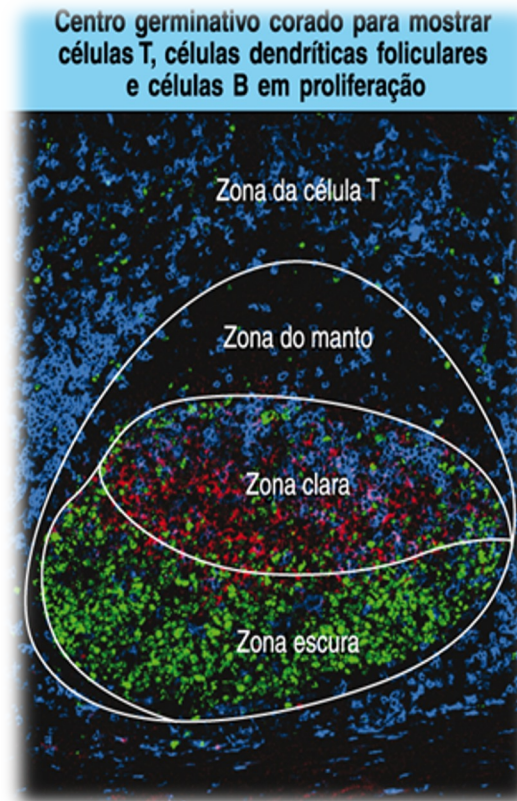
Circulação Linfática
Um Fenômeno Fisiológico

Constante Circulação de
Líquido Intersticial

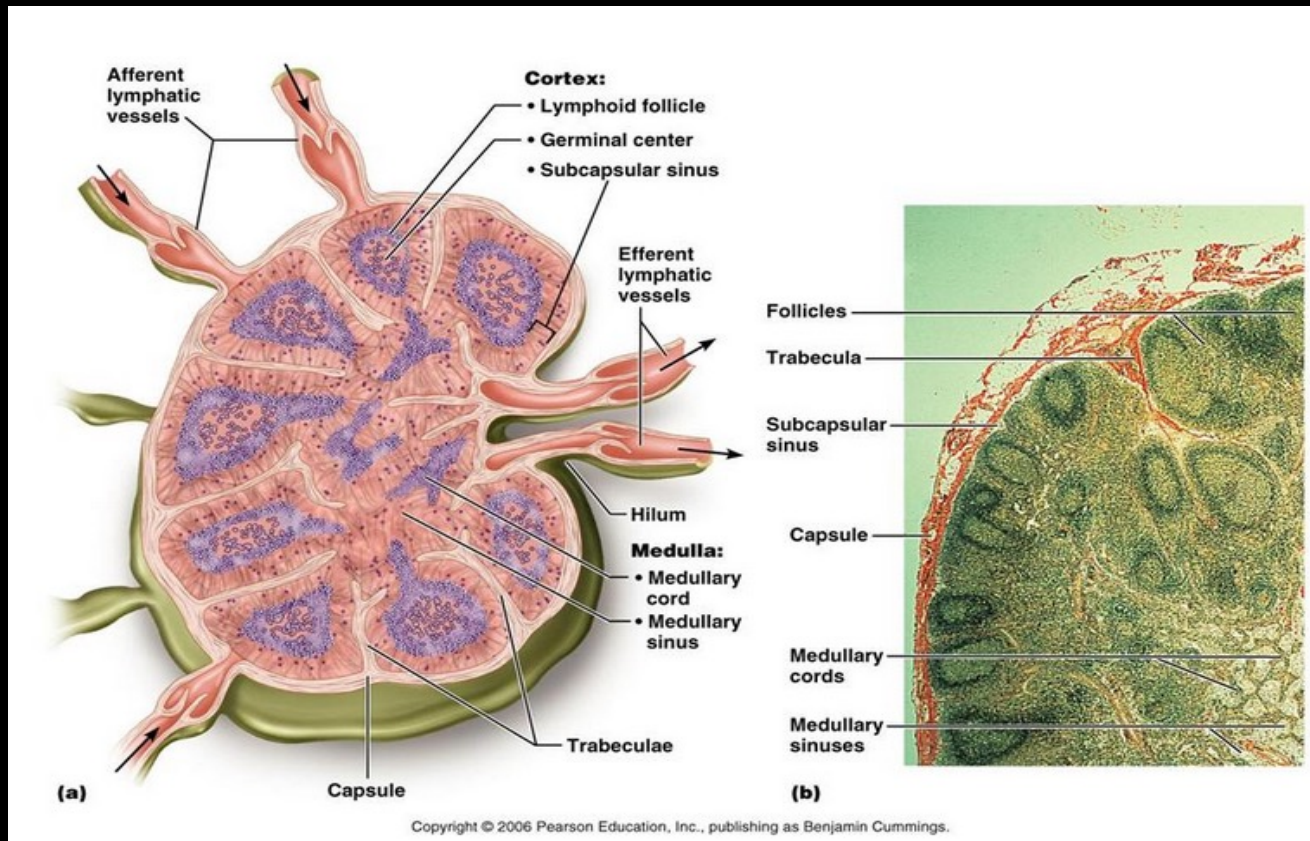
Debris celulares, matriz
extracelular,
Produtos do metabolismo,
transporte de lipídeos, etc...

Logo...

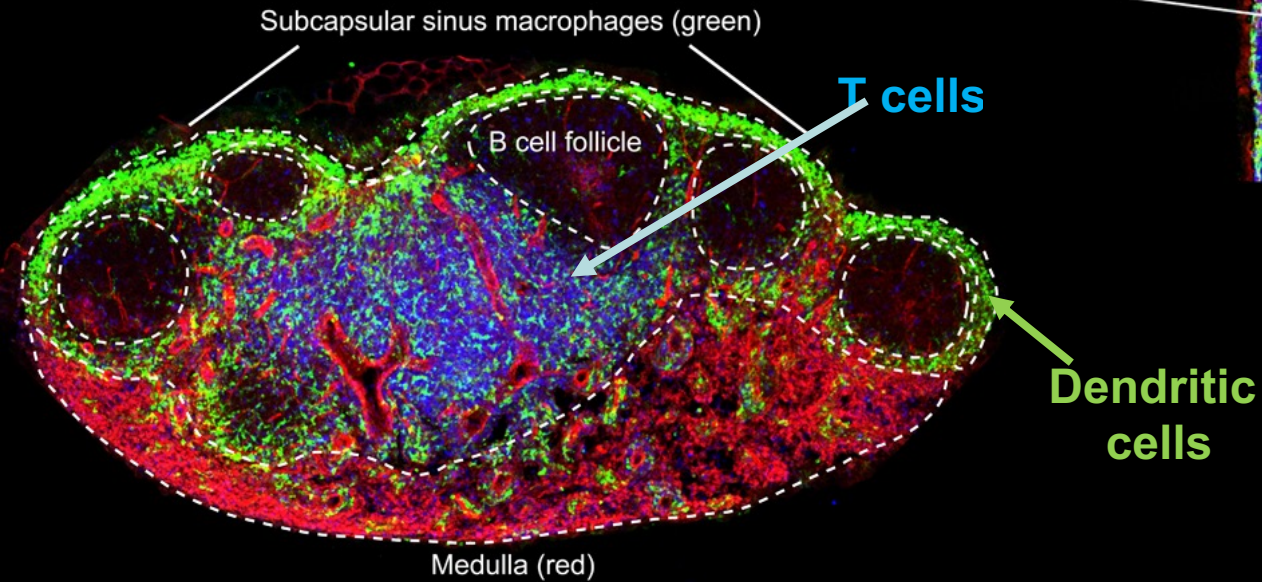
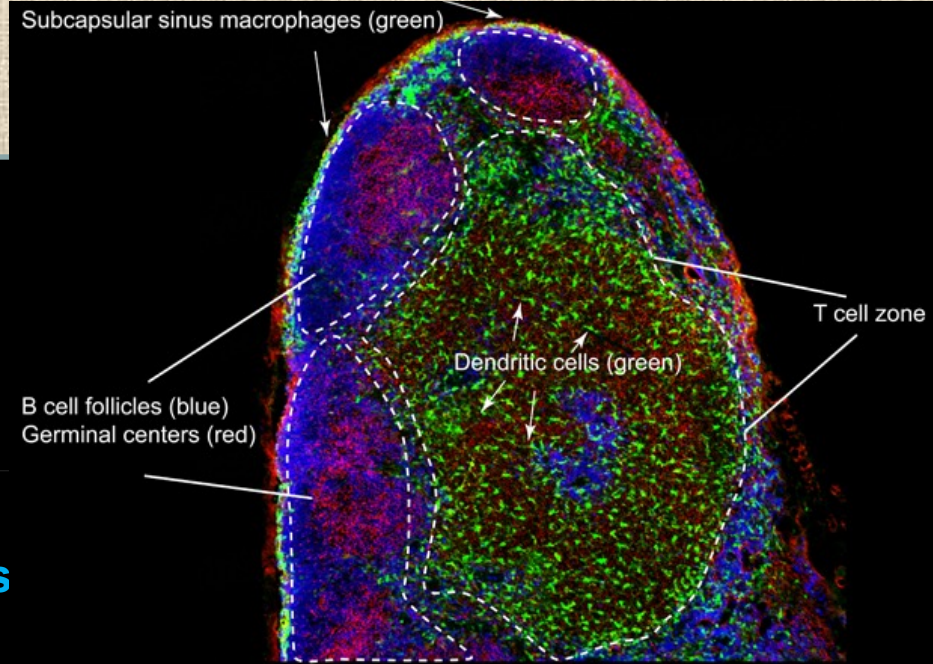
Linfonodos Estão
Constantemente
Recebendo Essas
Moléculas e Células
Circulantes



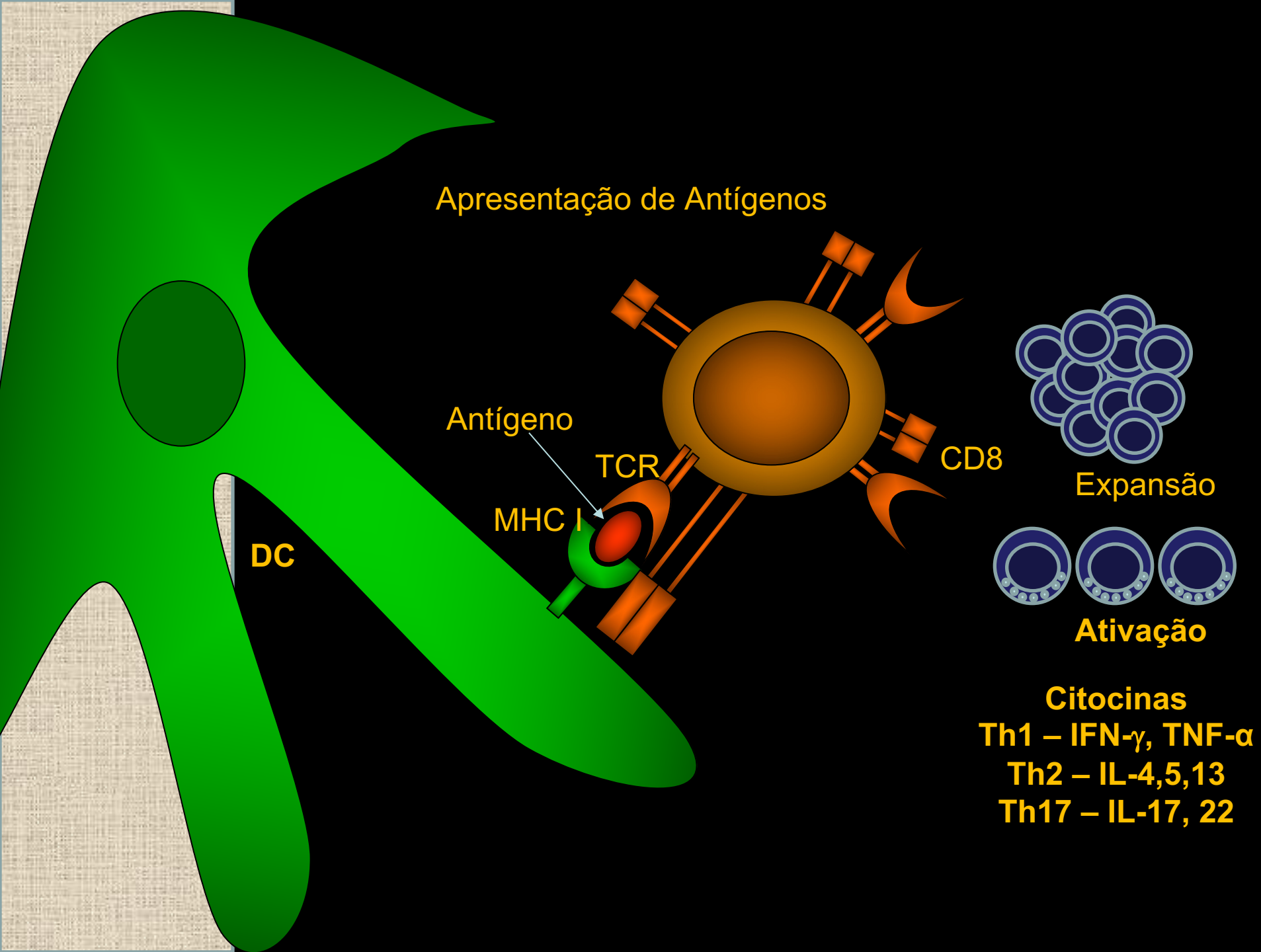
Drenagem de Antígenos – Solúveis ou Carreados por Células



Linfonodos e sua arquitetura



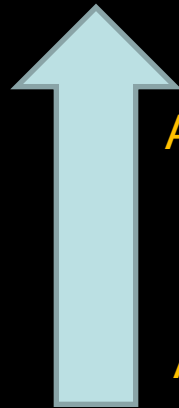
Apresentação de Antígenos



Mas....

Qual é objetivo da
Apresentação de Antígenos ?

Quais seus resultados?

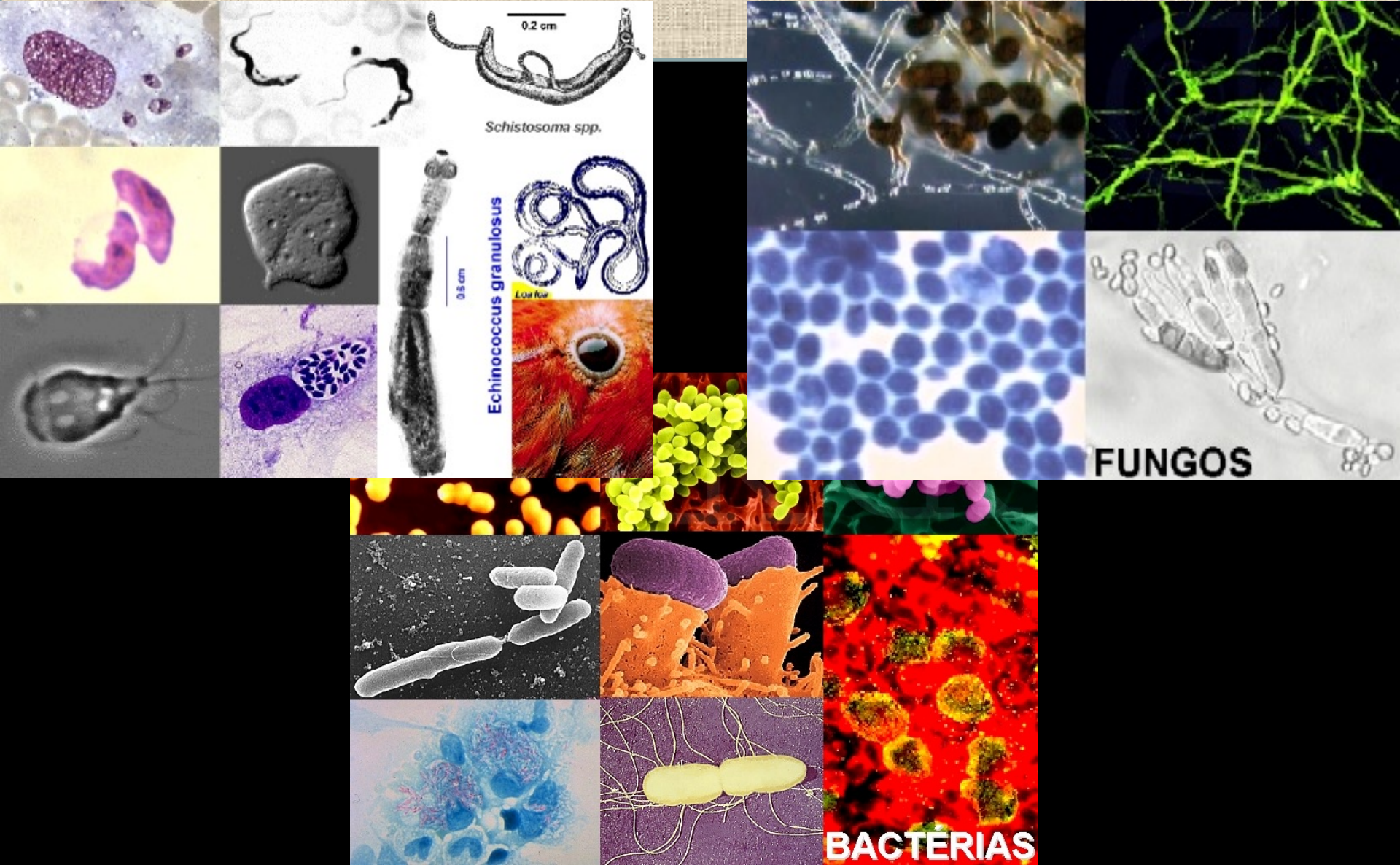


ATIVAÇÃO DA
IMUNIDADE
ADAPTATIVA



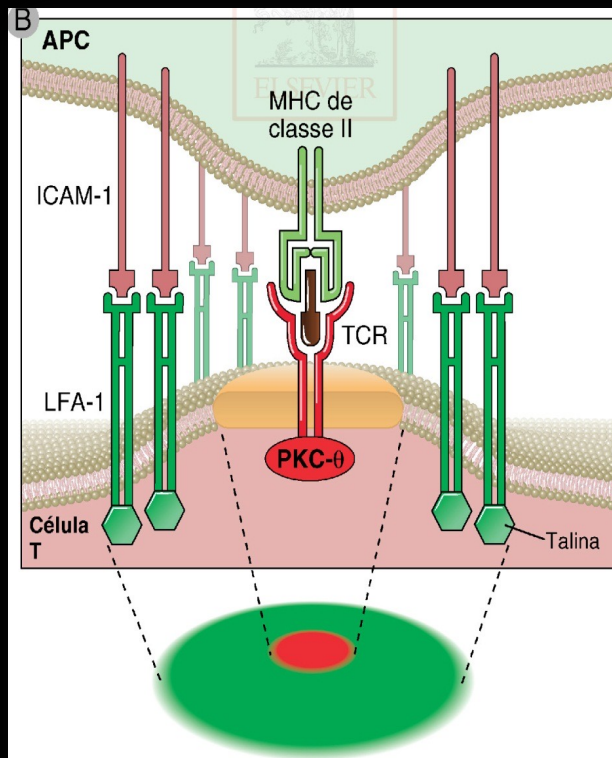
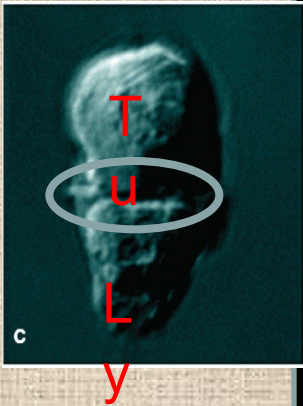
Foto: John Isaac

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

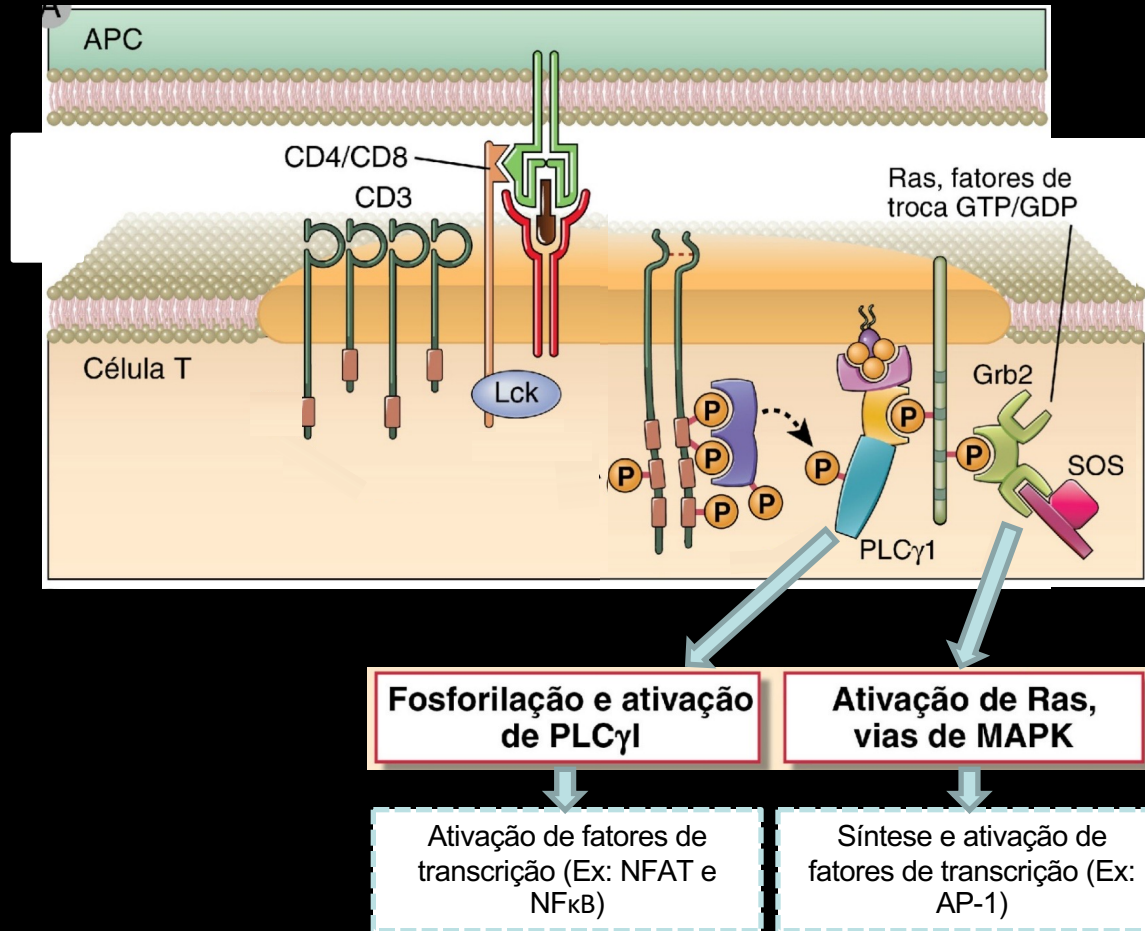


Aumenta/Reduz Interação Celular
Aumenta/Reduz Sinalização Intracelular

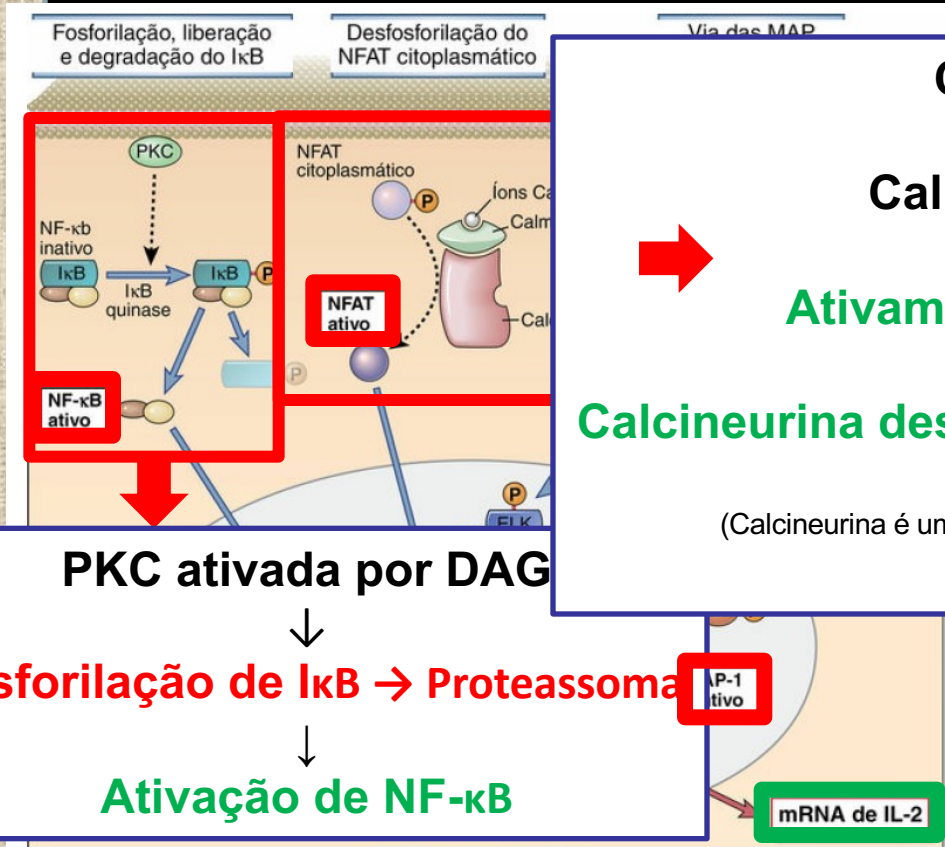


DEPENDENTE DAS MOLÉCULAS
PRESENTES NAS SINAPSES

Sinalização Intracelular



Sinalização Intracelular



Cálcio + Calmodulina

↓

Ativam calcineurina

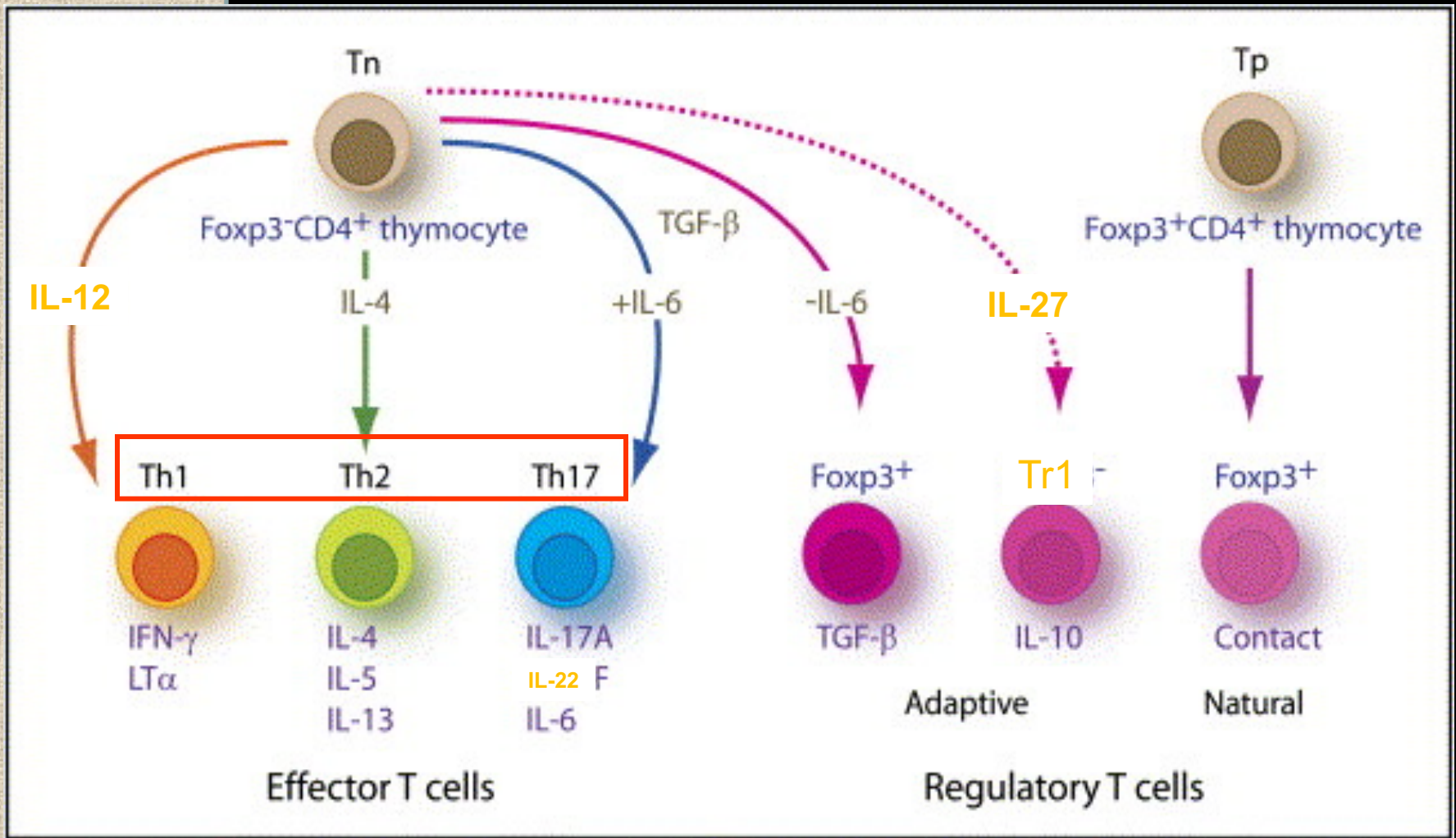
↓

Calcineurina desfosforila e ativa NFAT

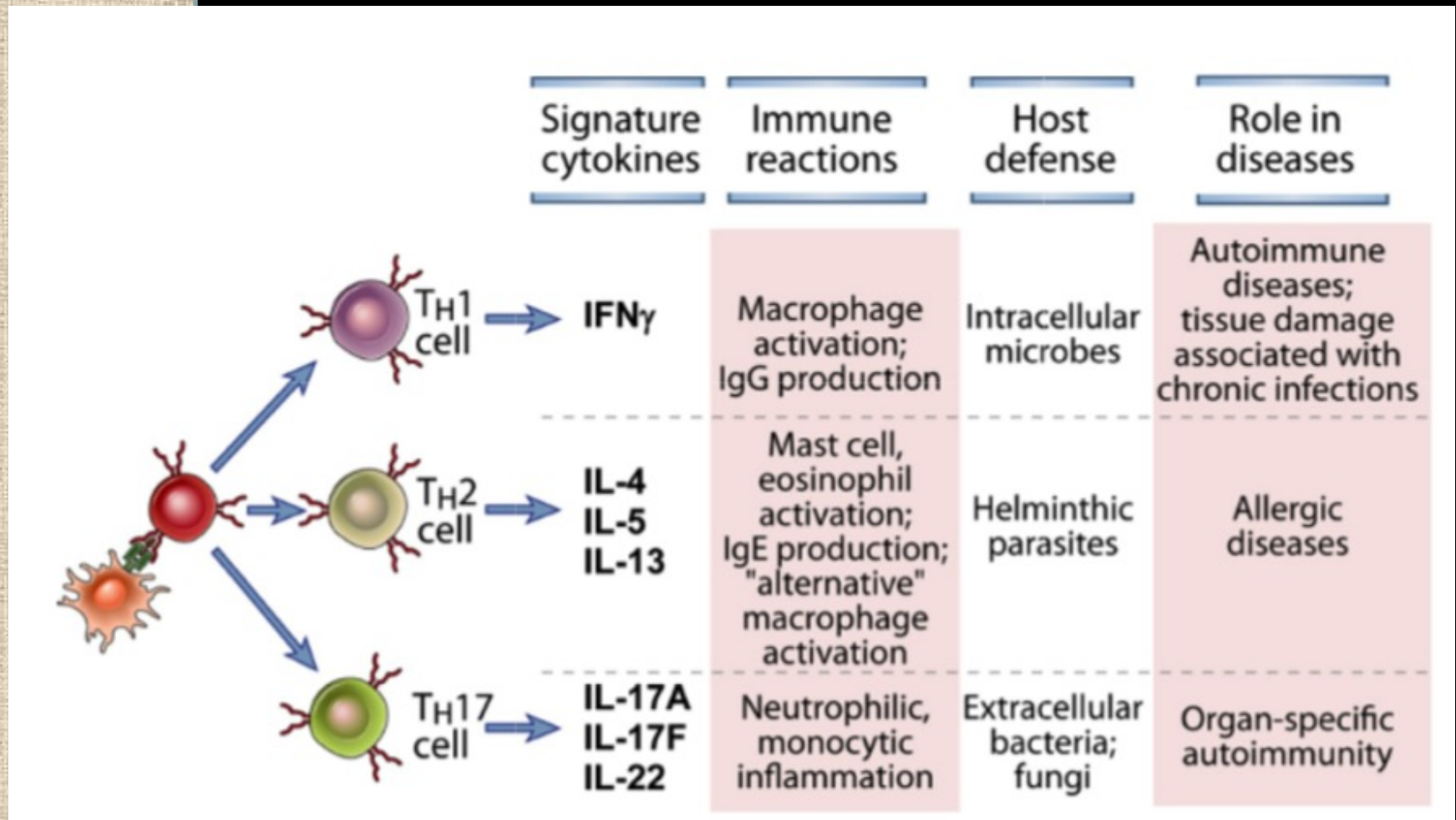
(Calcineurina é uma fosfatase que ativa NFAT)



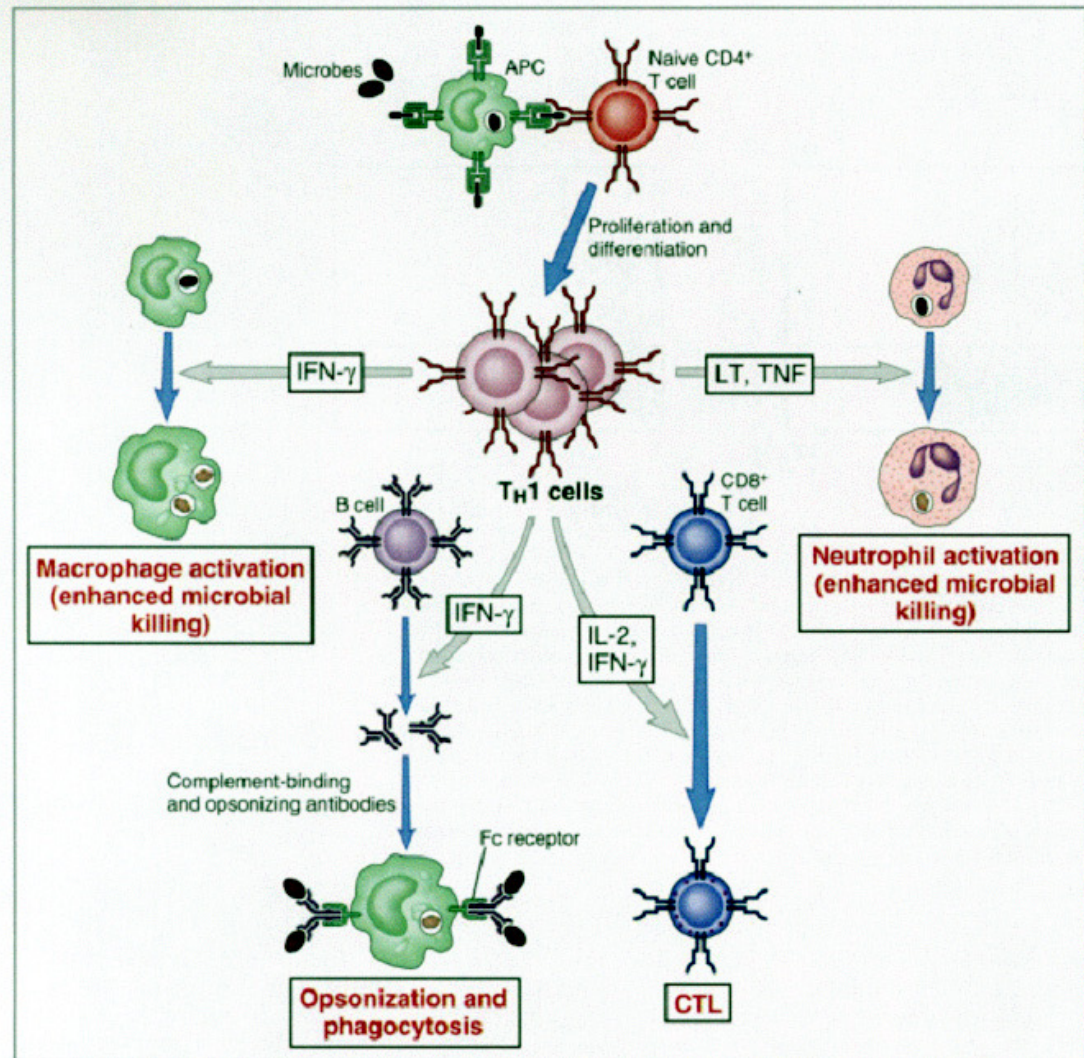
Populações de Células T

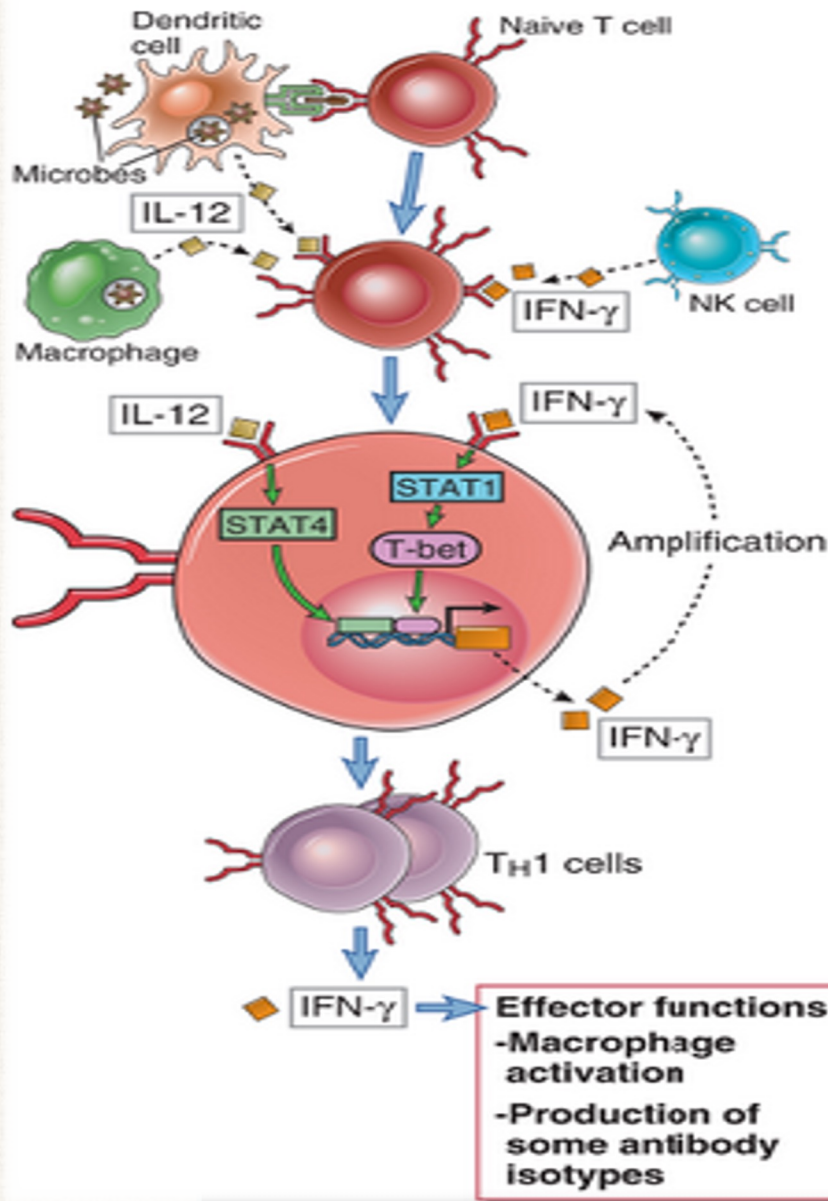


Tipos de Linfócitos T CD4 – Caracterização Funcional



Funções das Células Th1

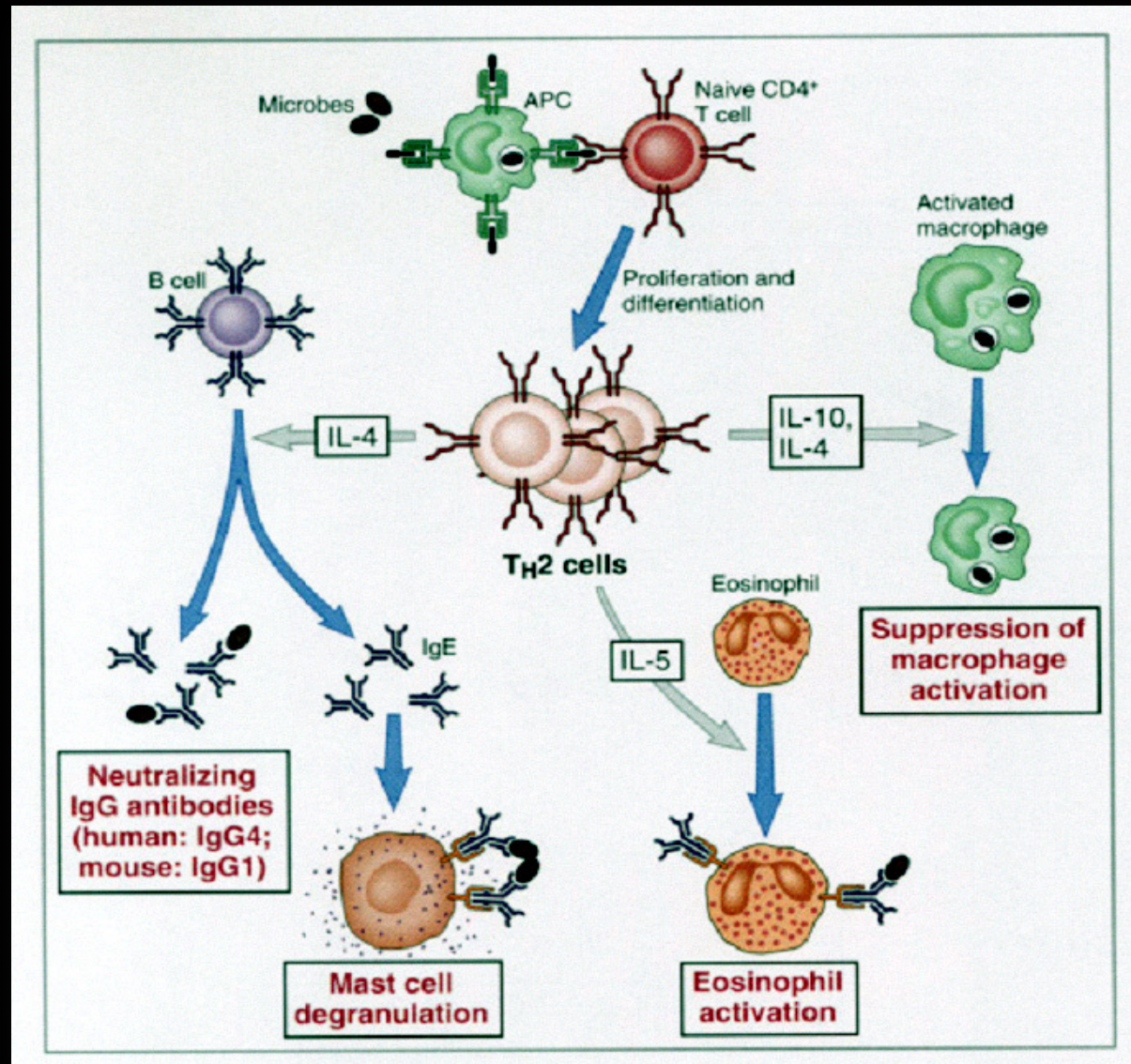




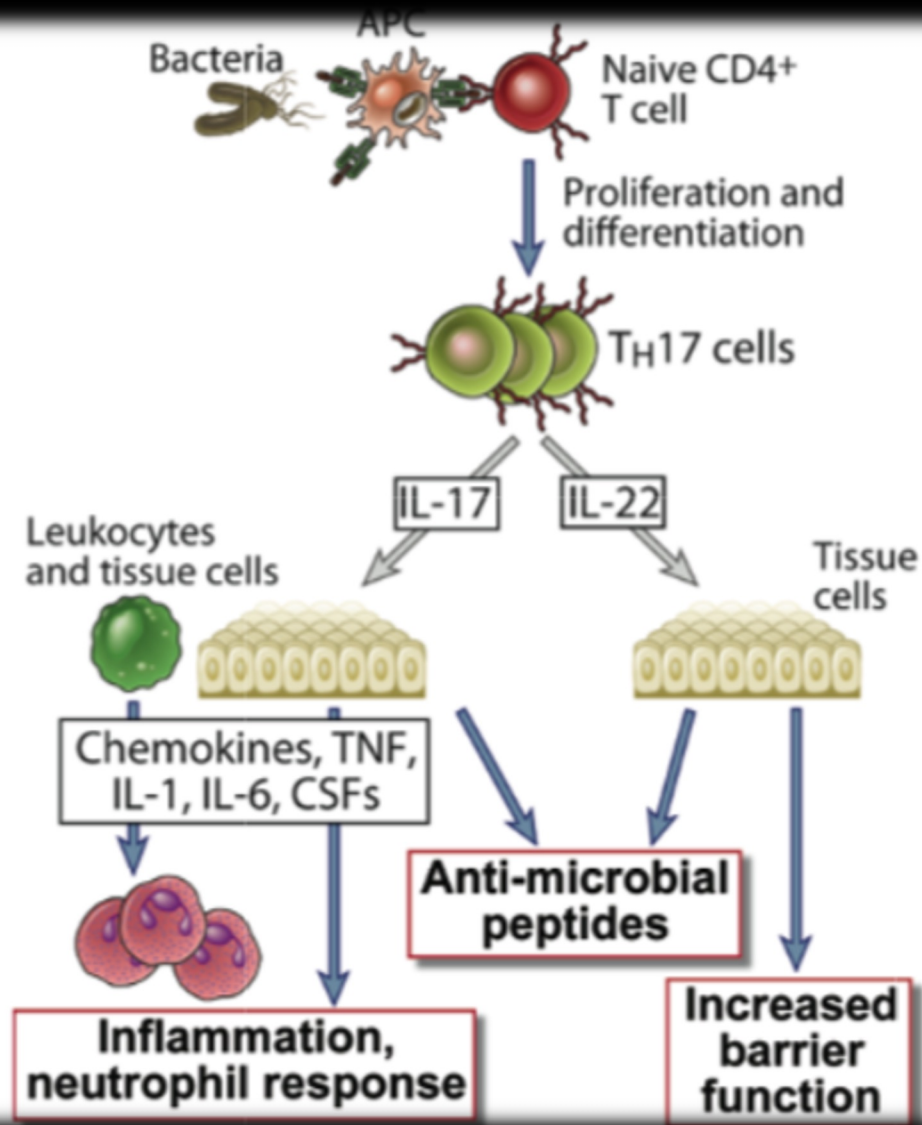
Resposta Th1

- 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

Funções das Células Th2

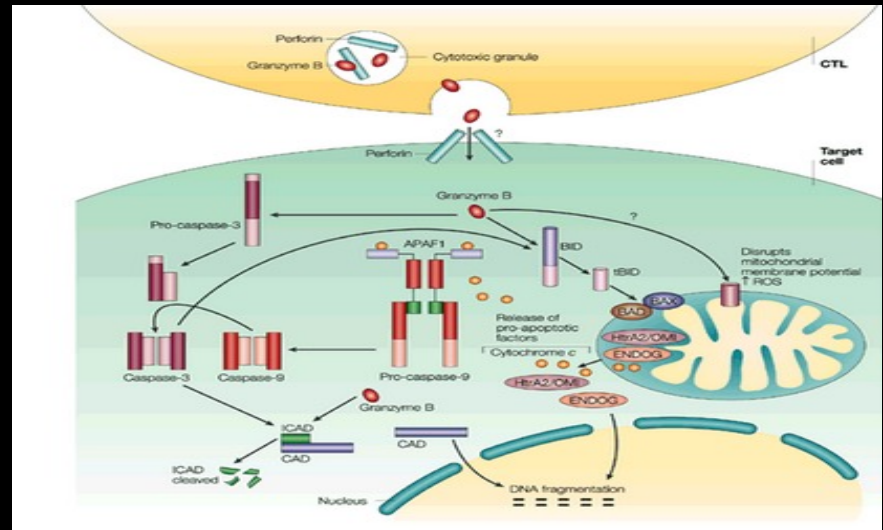
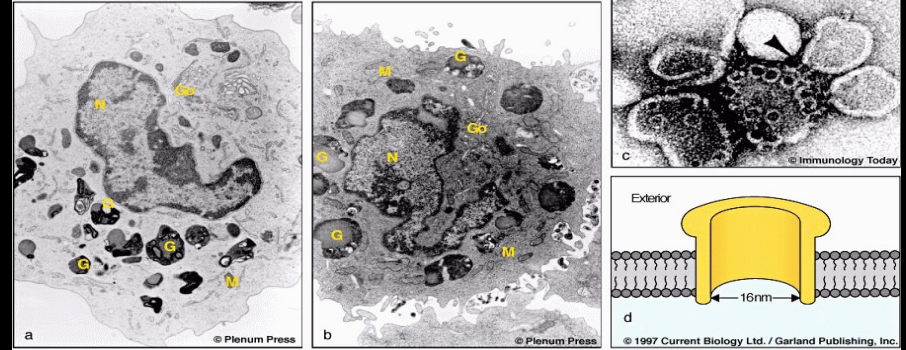
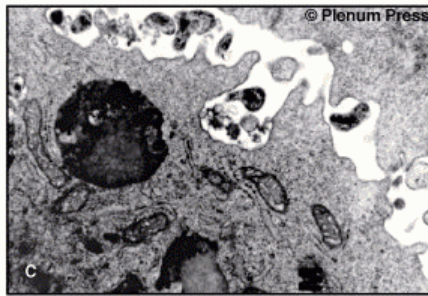
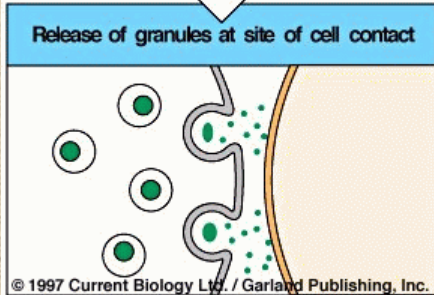
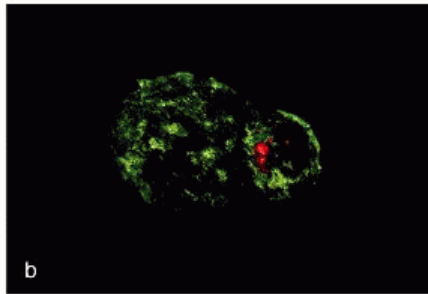
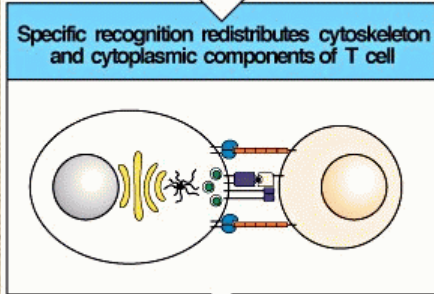
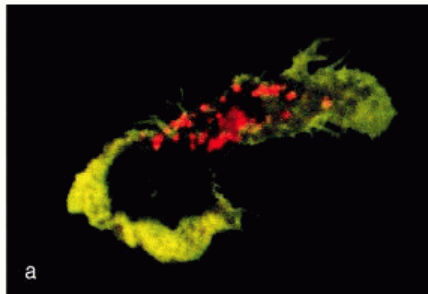
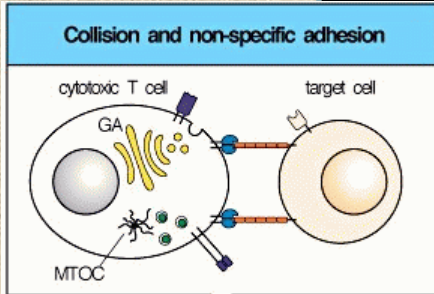


Linfócitos Th17

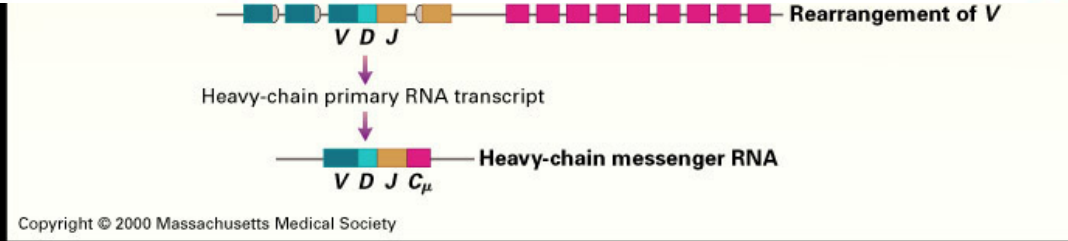
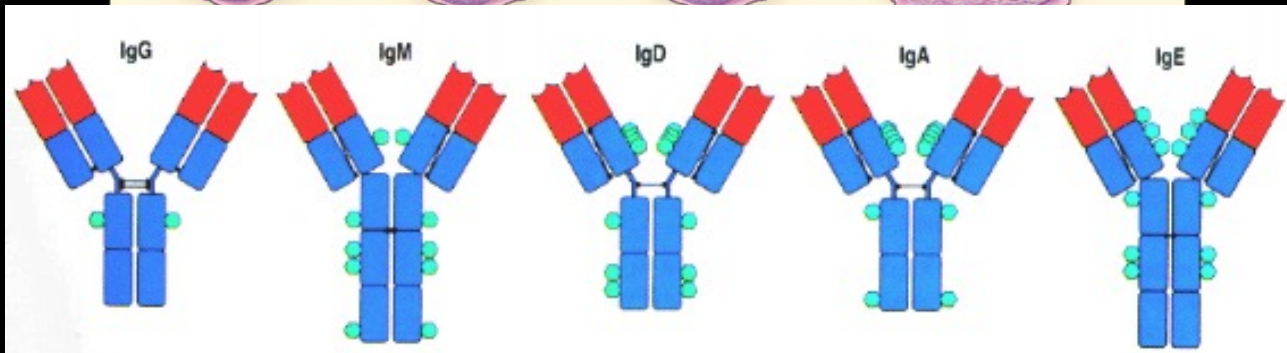
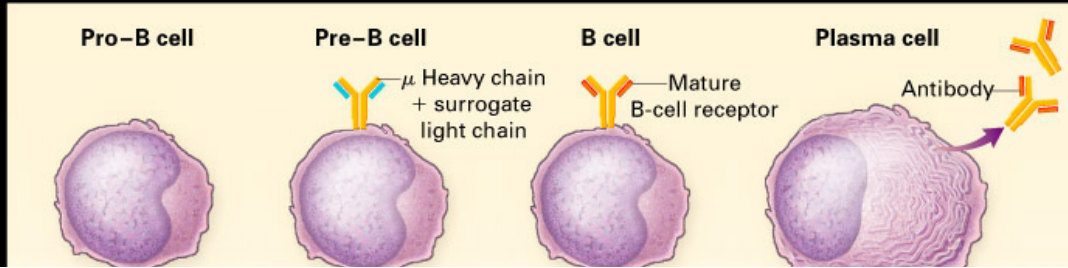


Linfócitos T CD8

Granzimas e Perforinas



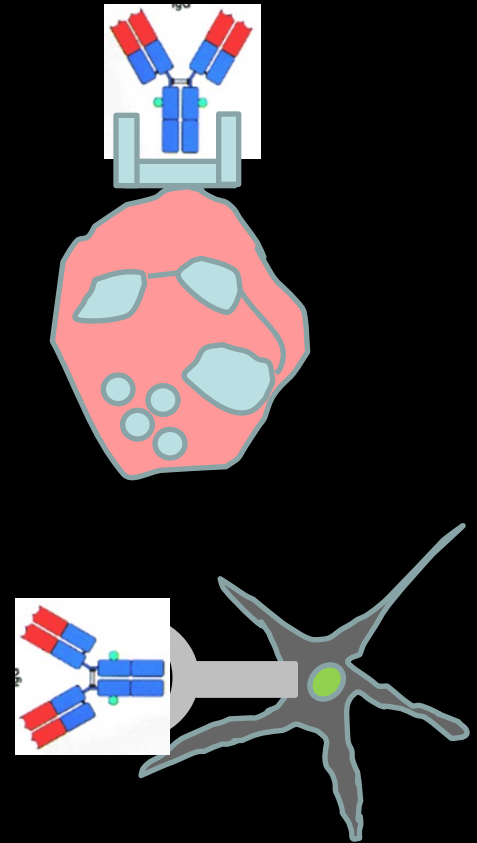
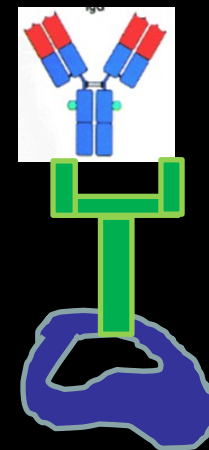
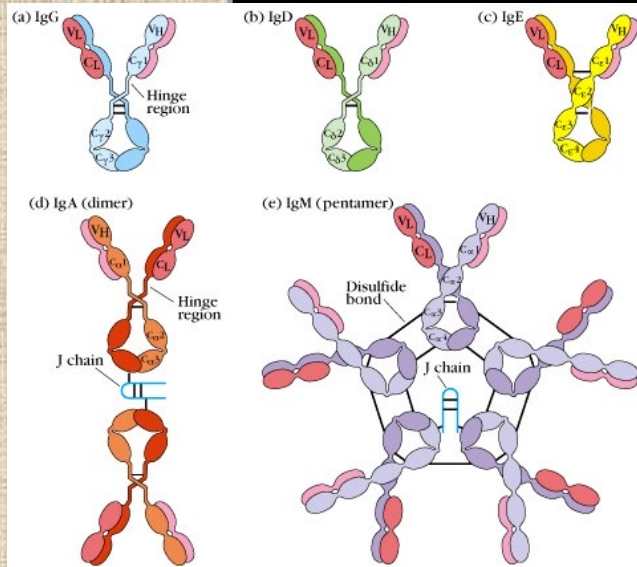
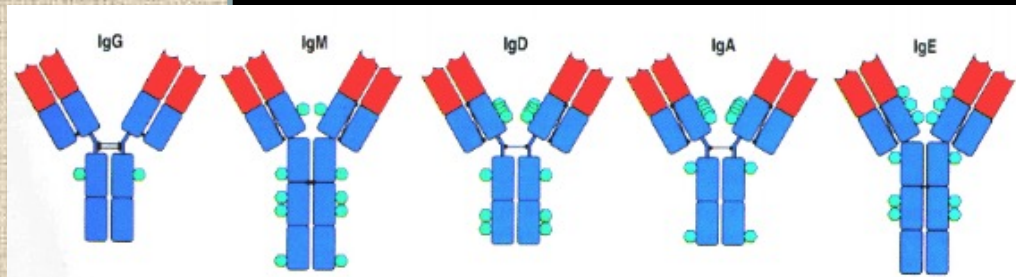
Linfócitos B



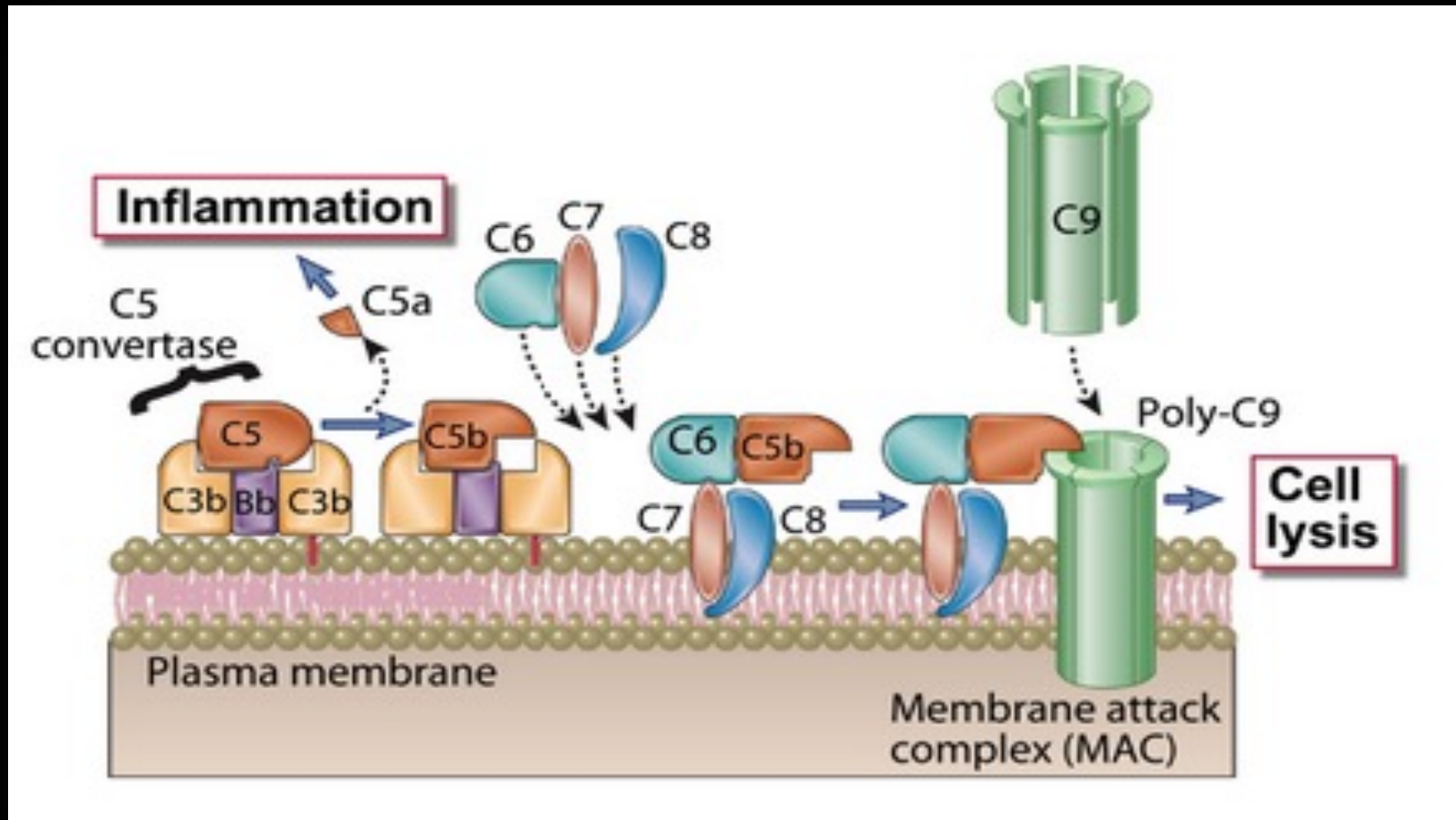
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Delves PJ, Roitt IM. The Immune System (Part1).
 N Engl J Med 2000;343:37-49.

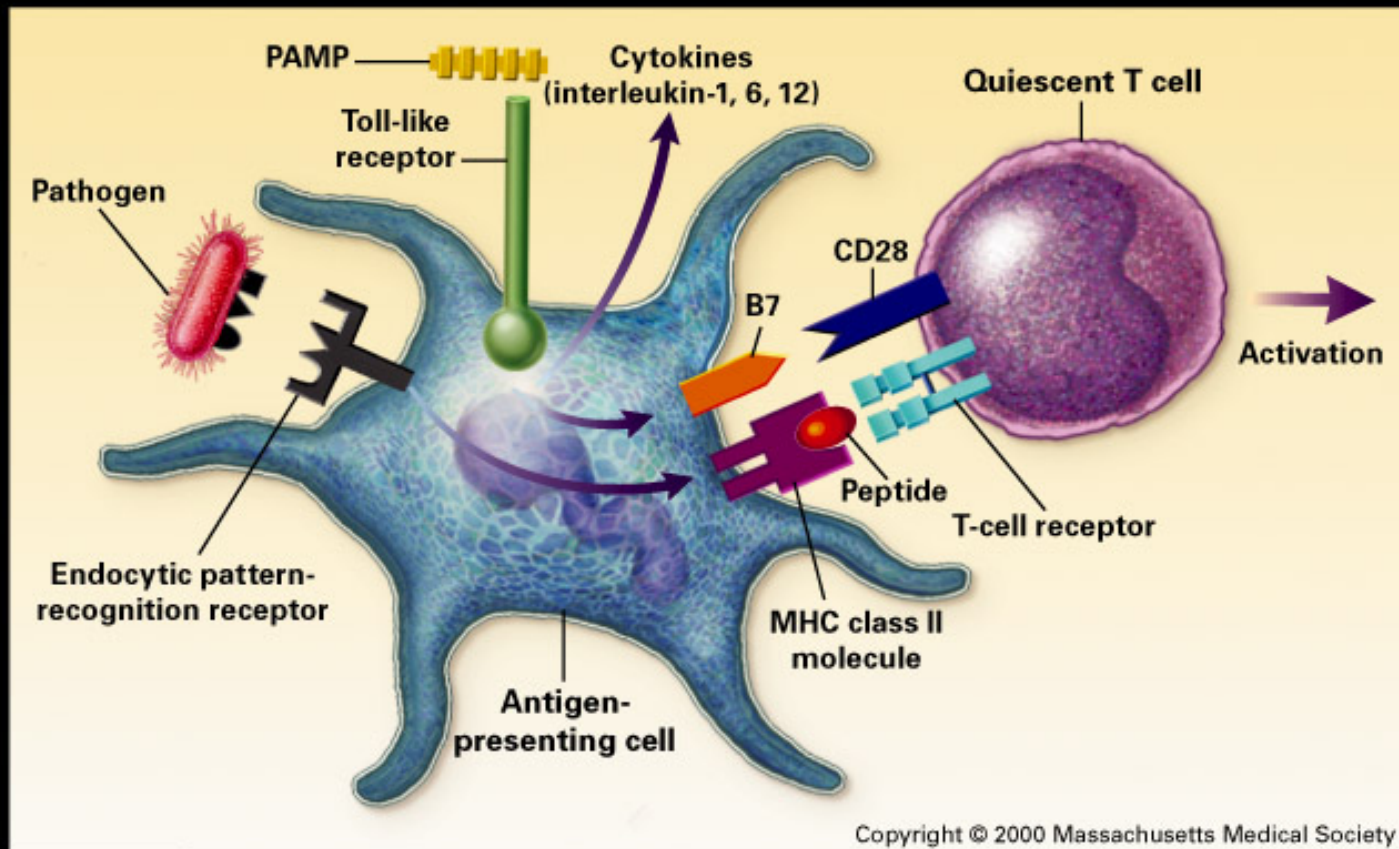
Anticorpos ou Imunoglobulinas e Seus Receptores Fc



Anticorpos Ativam o Complemento – Via Clássica



Link Entre a Imunidade Inata e a Adaptativa – ATIVACÃO DAS CÉLULAS DA IMUNIDADE INATA



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



The New England
Journal of Medicine

Tipo celular



Neutrófilo

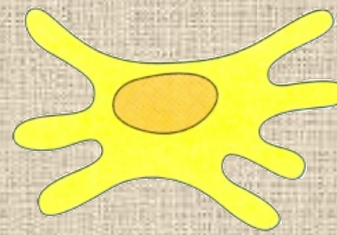
Função

Fagocitose
Espécies reativas de oxigênio e nitrogênio
Peptídeos antimicrobianos



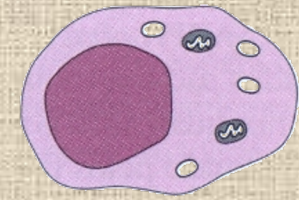
Macrófago

Fagocitose
Mediadores inflamatórios
Apresentação de antígenos
Espécies reativas de oxigênio e nitrogênio
Citocinas
Proteínas do complemento



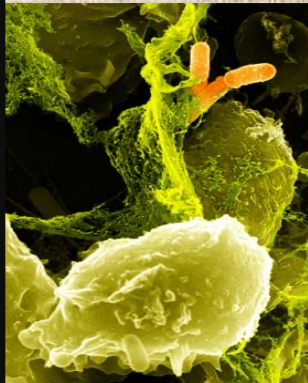
Células dendríticas

Apresentação de antígeno
Sinais co-estimuladores
Espécies reativas de oxigênio
Interferon
Citocinas



Célula natural killer

Lise da célula infectada por vírus
Interferon
Ativação de macrófagos



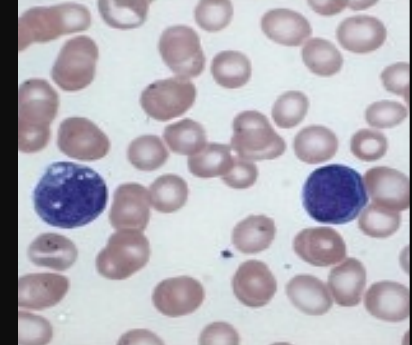
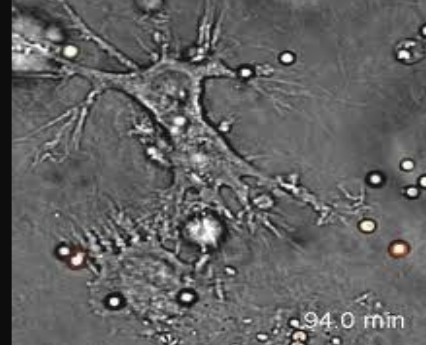
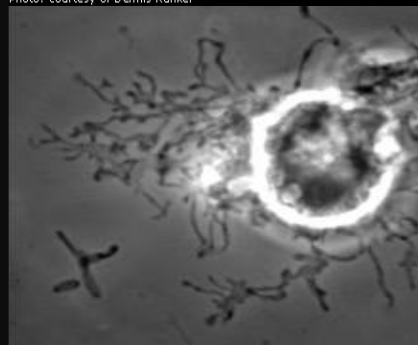
An activated macrophage phagocytosing bacteria upon contact
Photo: courtesy of Dennis Kunkel



(courtesy of Dr. M. Rohde, GBF)



NK cell destroying embryo



Imunopatologia



Impetigo



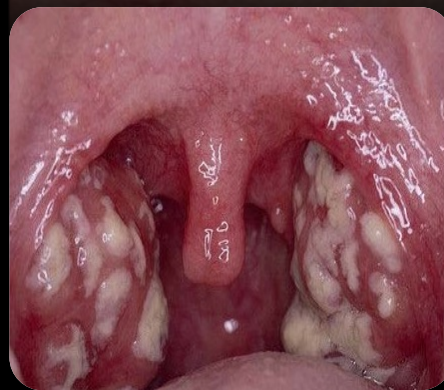
Foliculite



Furunculose



Osteomielite + pé-diabético

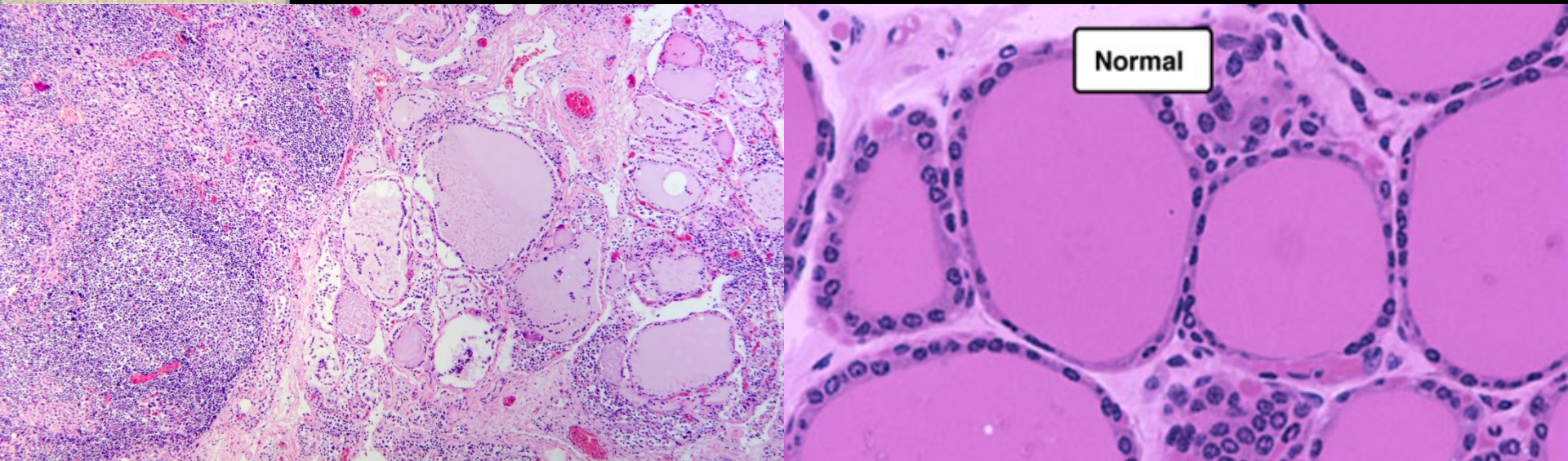


Amigdalite



Meningite

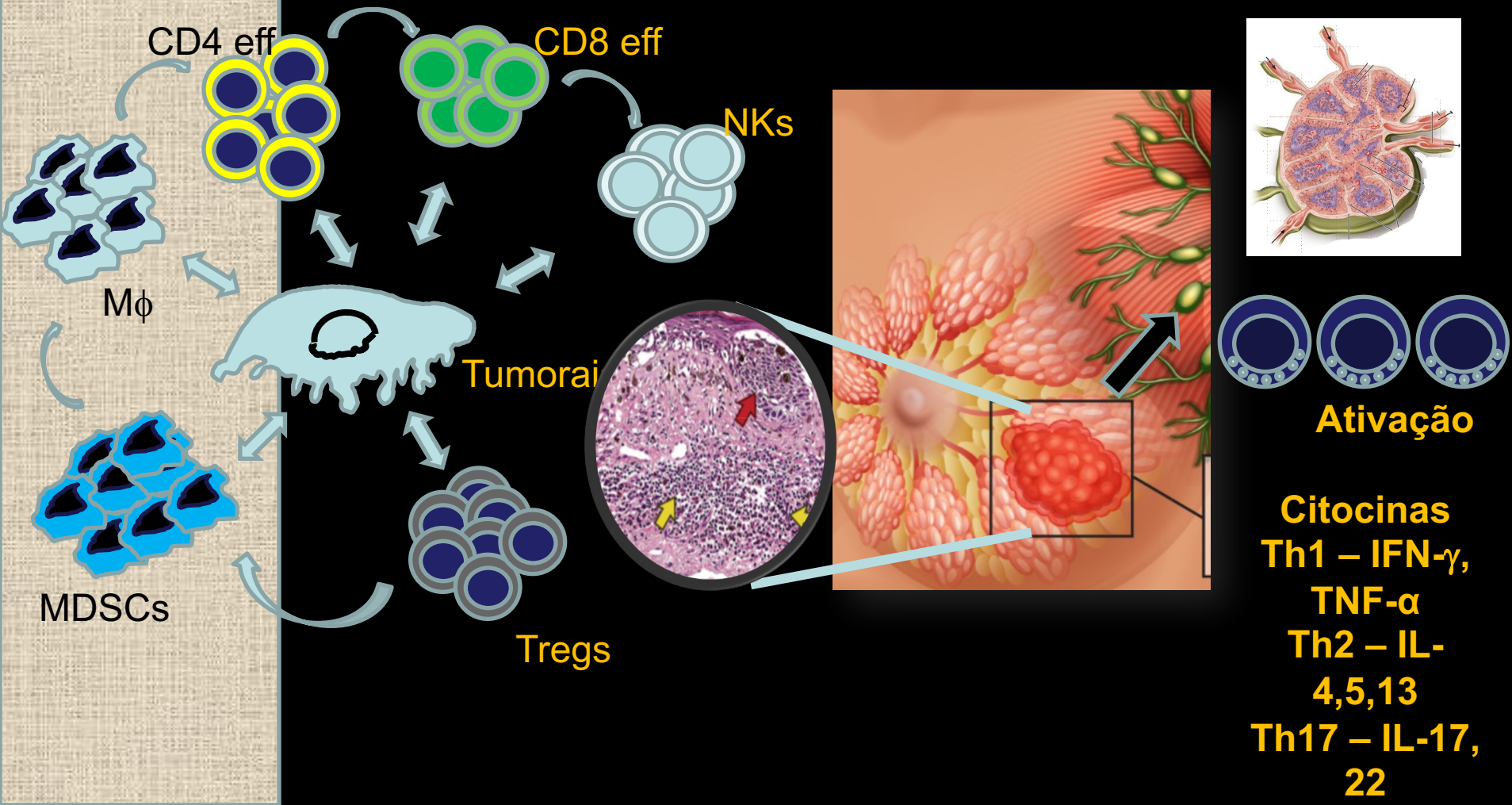
Autoimunidade – Tireoidite de Hashimoto

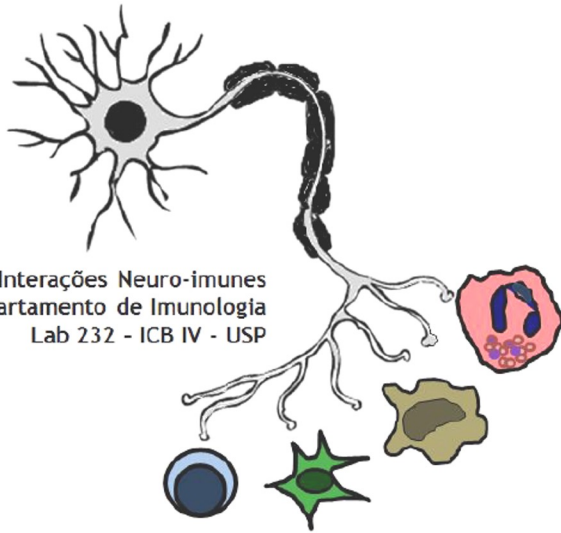


Hipotireoideo
Metabolismo Lento
Obeso



Ambiente Tumoral – TILs (Tumor Infiltrating Lymphocytes)





Laboratório de Interações Neuro-imunes
Departamento de Imunologia
Lab 232 - ICB IV - 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

