

LABORATÓRIO DE BIOLOGIA CELULAR E MOLECULAR
Instituto de Ciências Biomédicas
Universidade de São Paulo



Mecanismos de tolerância periférica

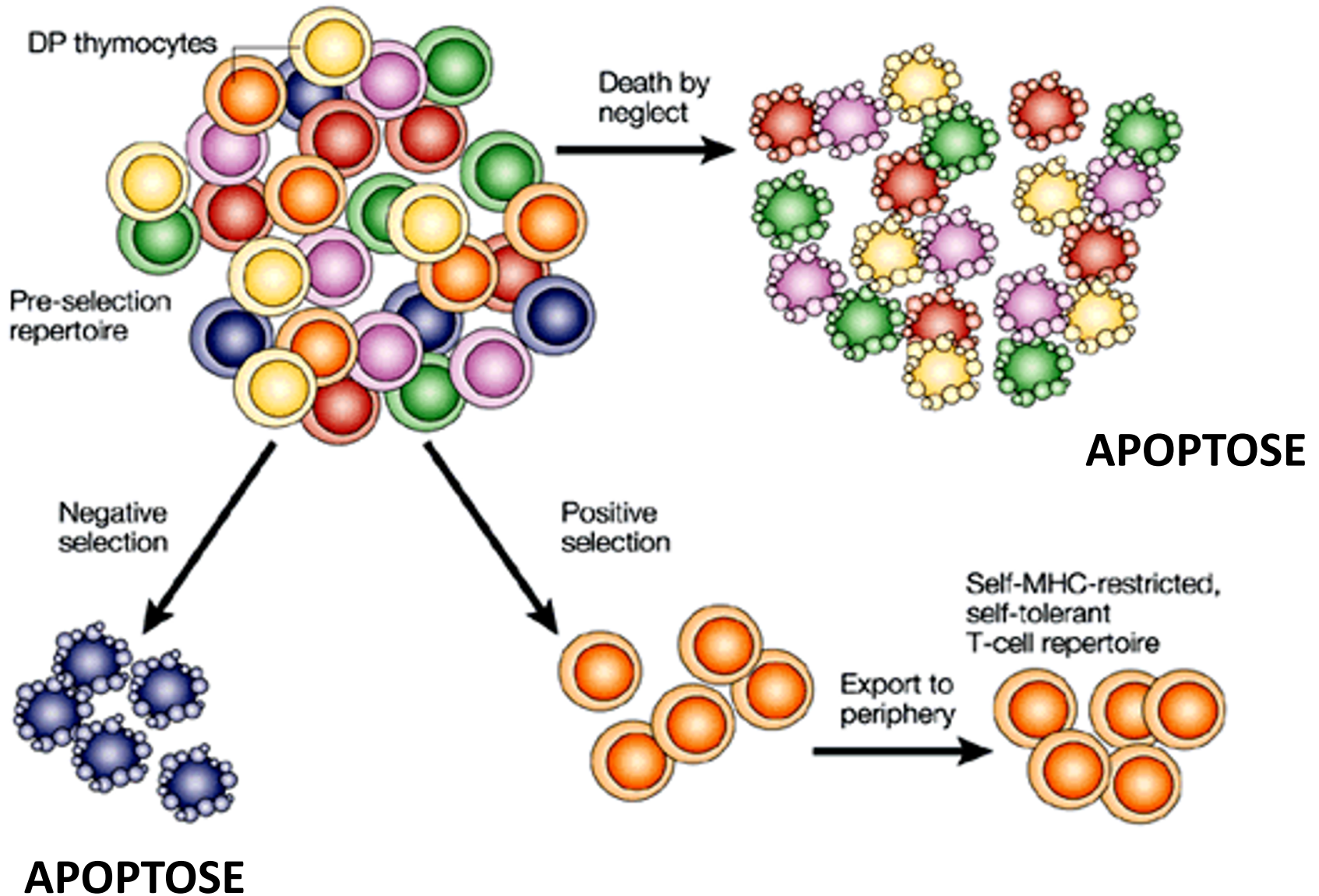
Prof. Dr. Gustavo P. Amarante-Mendes
Disciplina BMI-0256 – Imunologia
Nutrição Noturno - 2021



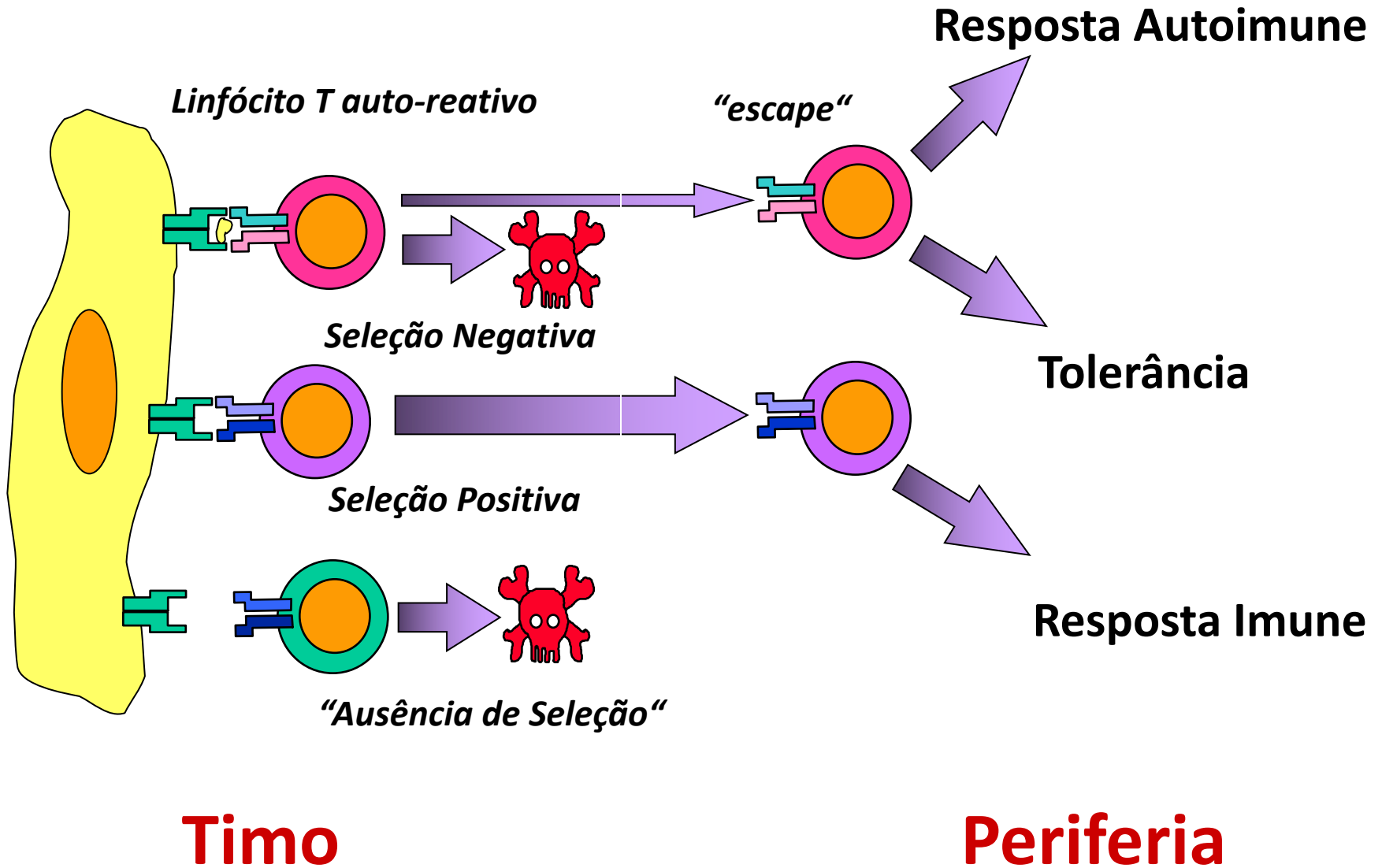
O Problema: Discriminação “self-non-self”

- O Sistema Imune responde a antígenos estranhos (patógenos) mas não a antígenos próprios
- Os linfócitos em desenvolvimento expressam uma ampla diversidade de receptores de maneira aleatória
- Portanto, todos os indivíduos produzem linfócitos com capacidade de reconhecer antígenos próprios
- Salvo exceções, antígenos próprios tem acesso ao Sistema Imune
- Consequentemente, linfócitos auto-reativos precisam ser eliminados ou inativados para prevenir reações autoimunes

Educação Tímica



Tolerância Central não é completa



Tolerância Periférica

Anergia

Ignorância/Imunoprivilégio

Desvio Imunológico

Deleção Clonal

Supressão/Regulação

Sinais para ativação de LTs

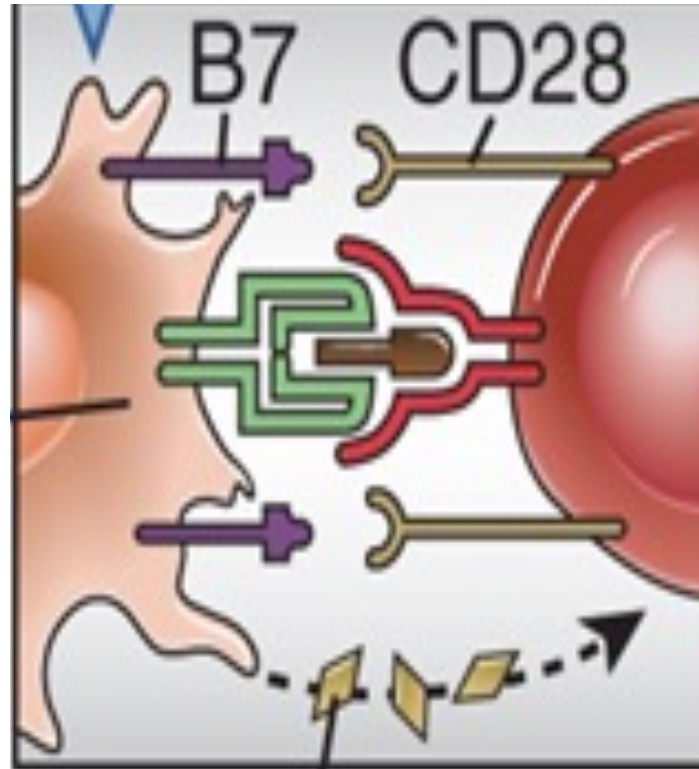
Célula dendríticas

Linfócito T *naive*

(2) Moléculas co-estimuladoras (B7-1/B7-2);

(1) Antígeno ligado ao MHC

3) Citocinas (DC e outras células) - p.ex. IL-12, IFN- γ , IL-4, IL-1/IL-6, etc



(2) CD28 (+) / CTLA-4 (-)

**IMUNIDADE ou
TOLERÂNCIA**

(1) Receptor de células T

ESPECIFICIDADE

(3) Receptores de citocinas

DIFERENCIAÇÃO

CITOCINAS

Anergia

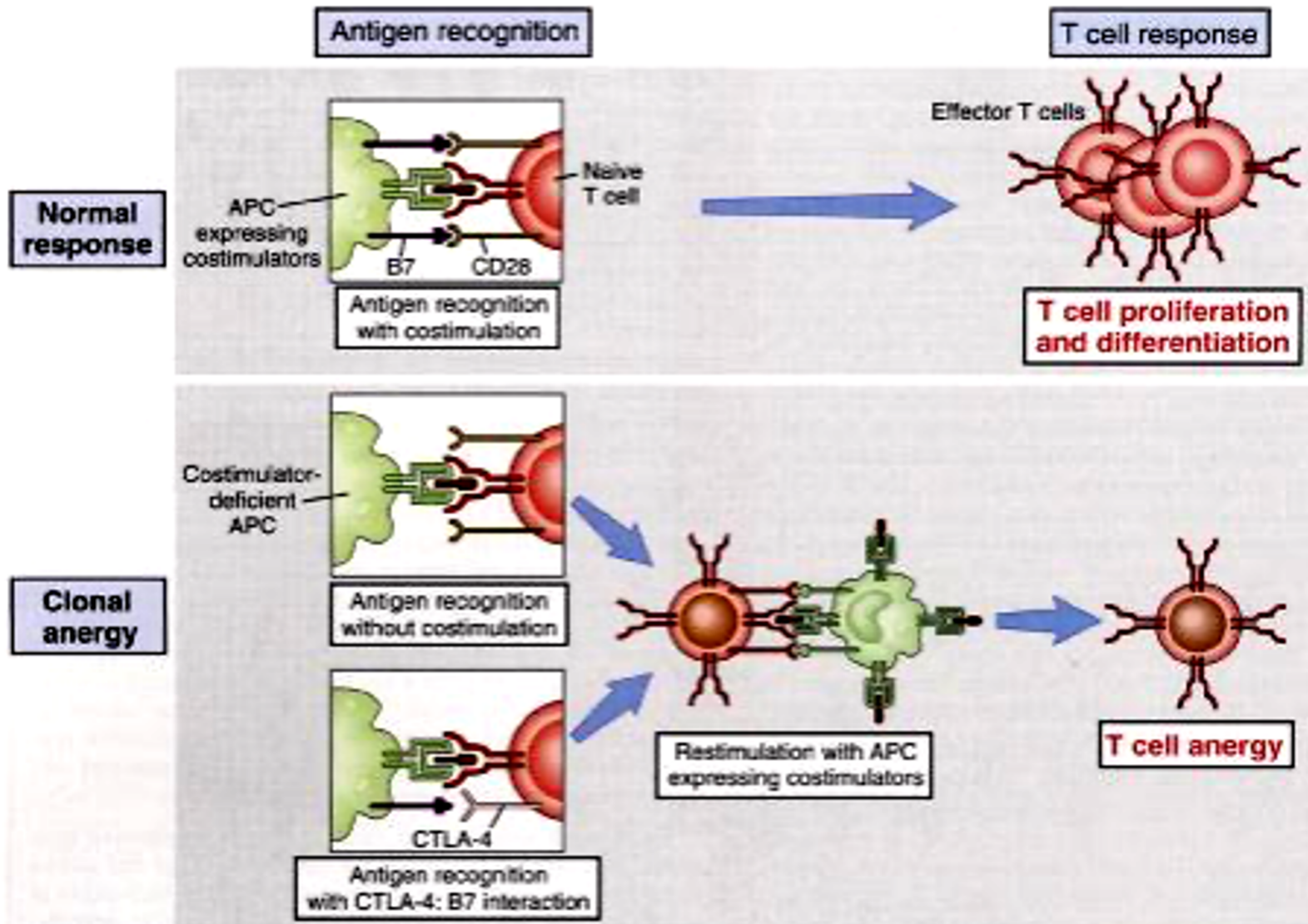
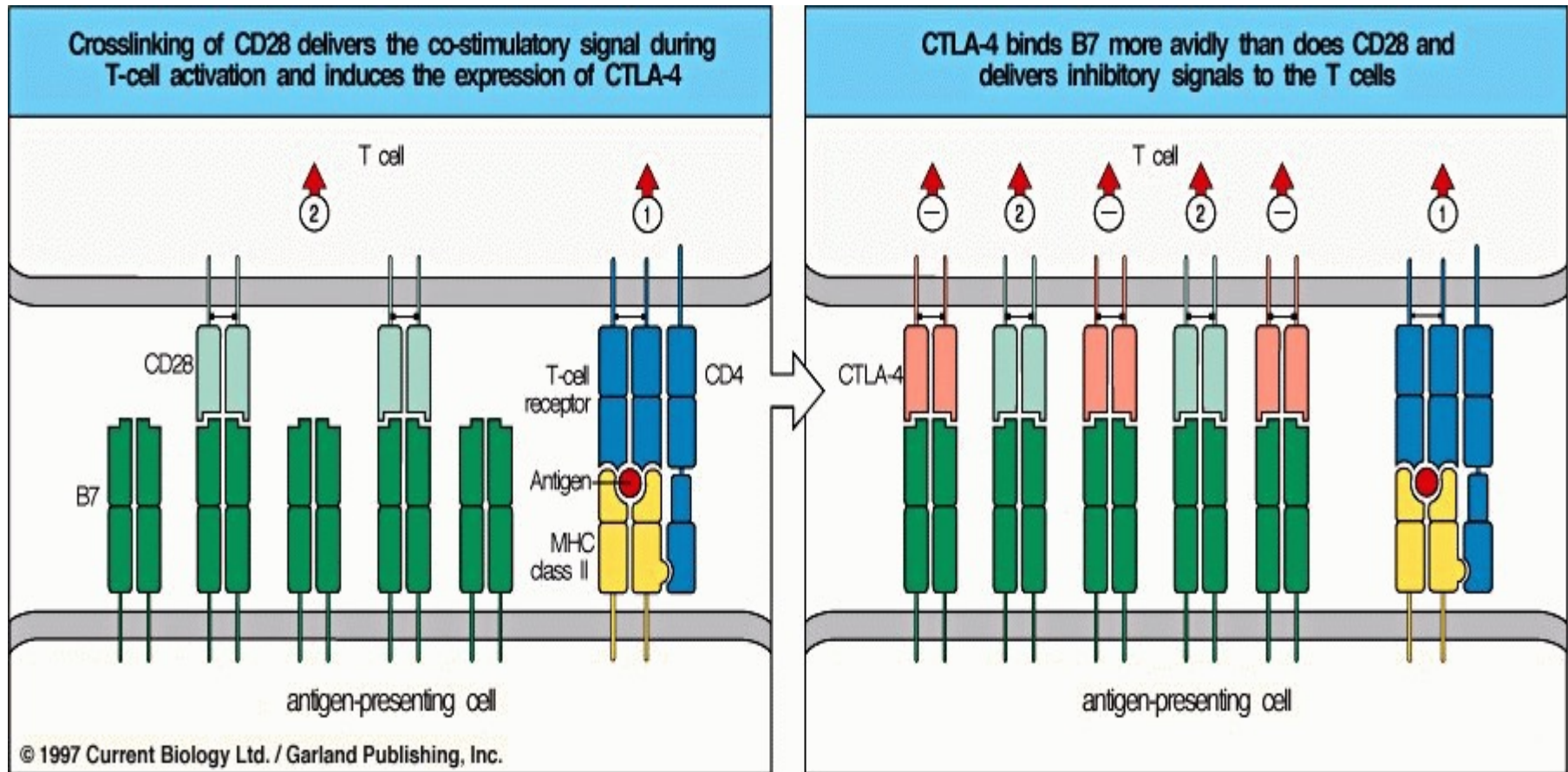


Figure 10-4 T cell anergy.

Sinais inibitórios

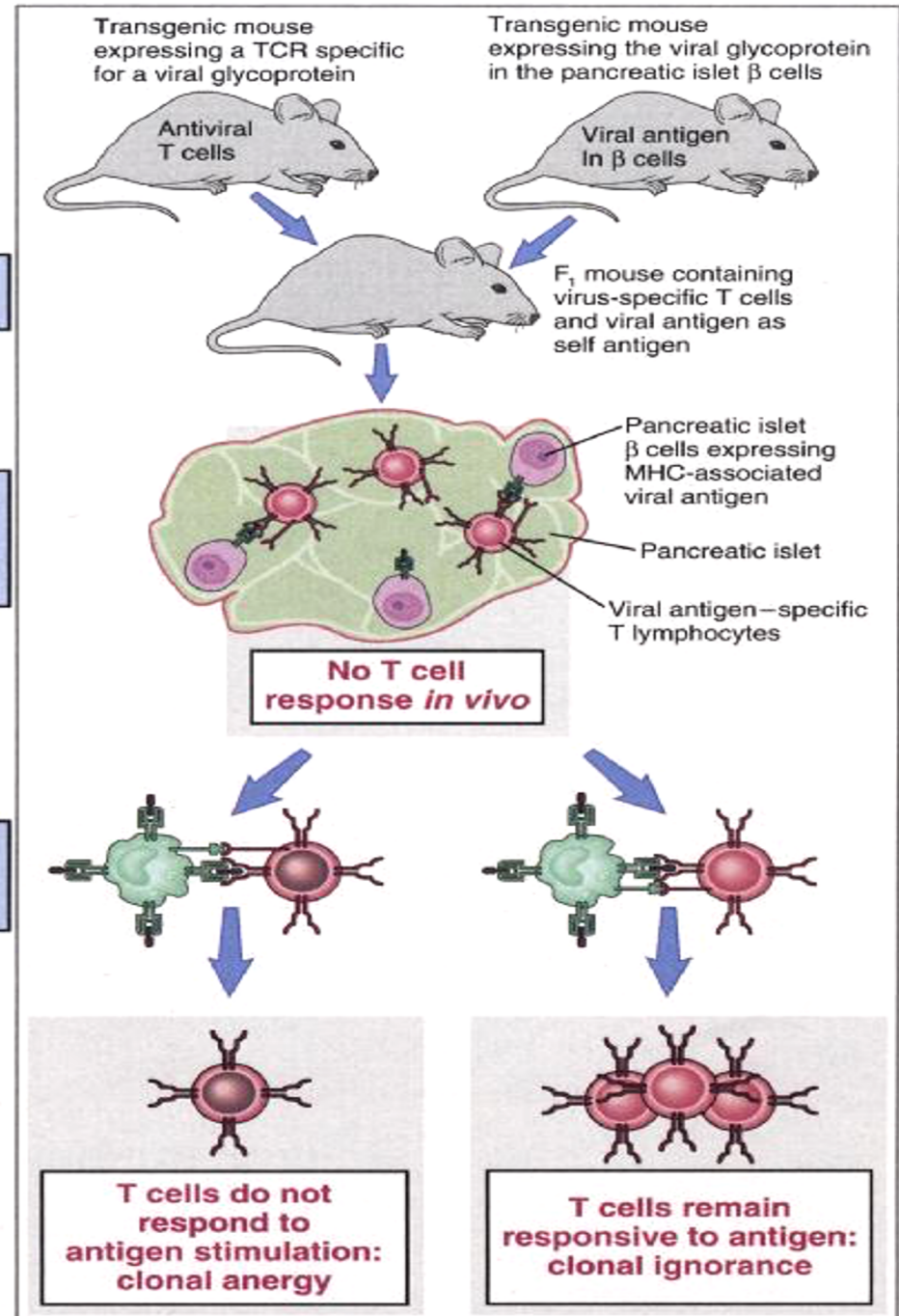


Anergia x Ignorância

Interbreeding of transgenic mice

Virus-specific T cells encounter viral antigen on islet β cells or in draining lymph nodes

Stimulation of recovered virus-specific T cells with viral antigen *ex vivo*



Sítios Imunoprivilegiados

Locais de difícil acesso para o sistema imune. Possuem antígenos “sequestrados”: Cérebro, Olhos, Testículos, Útero/feto

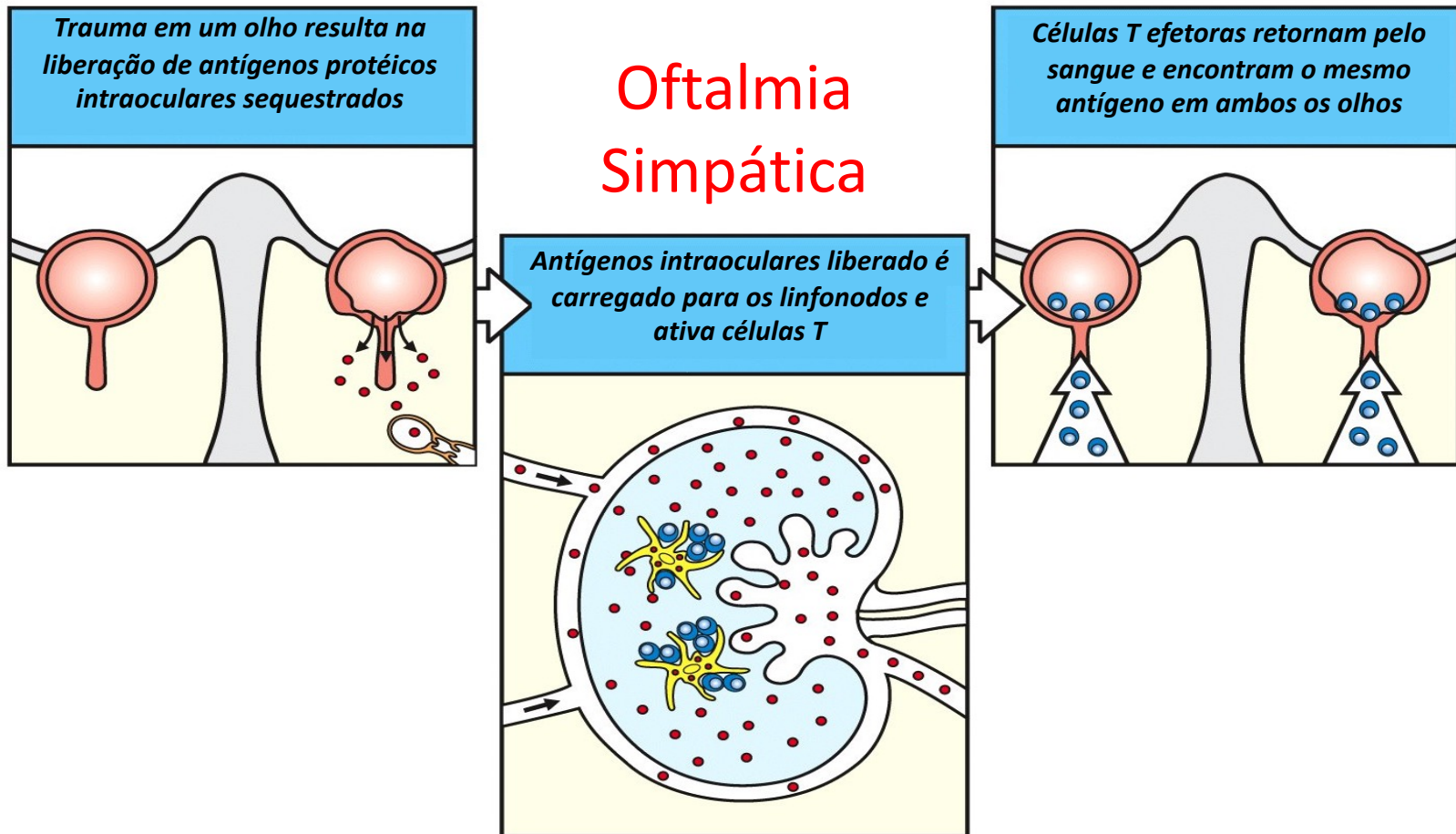
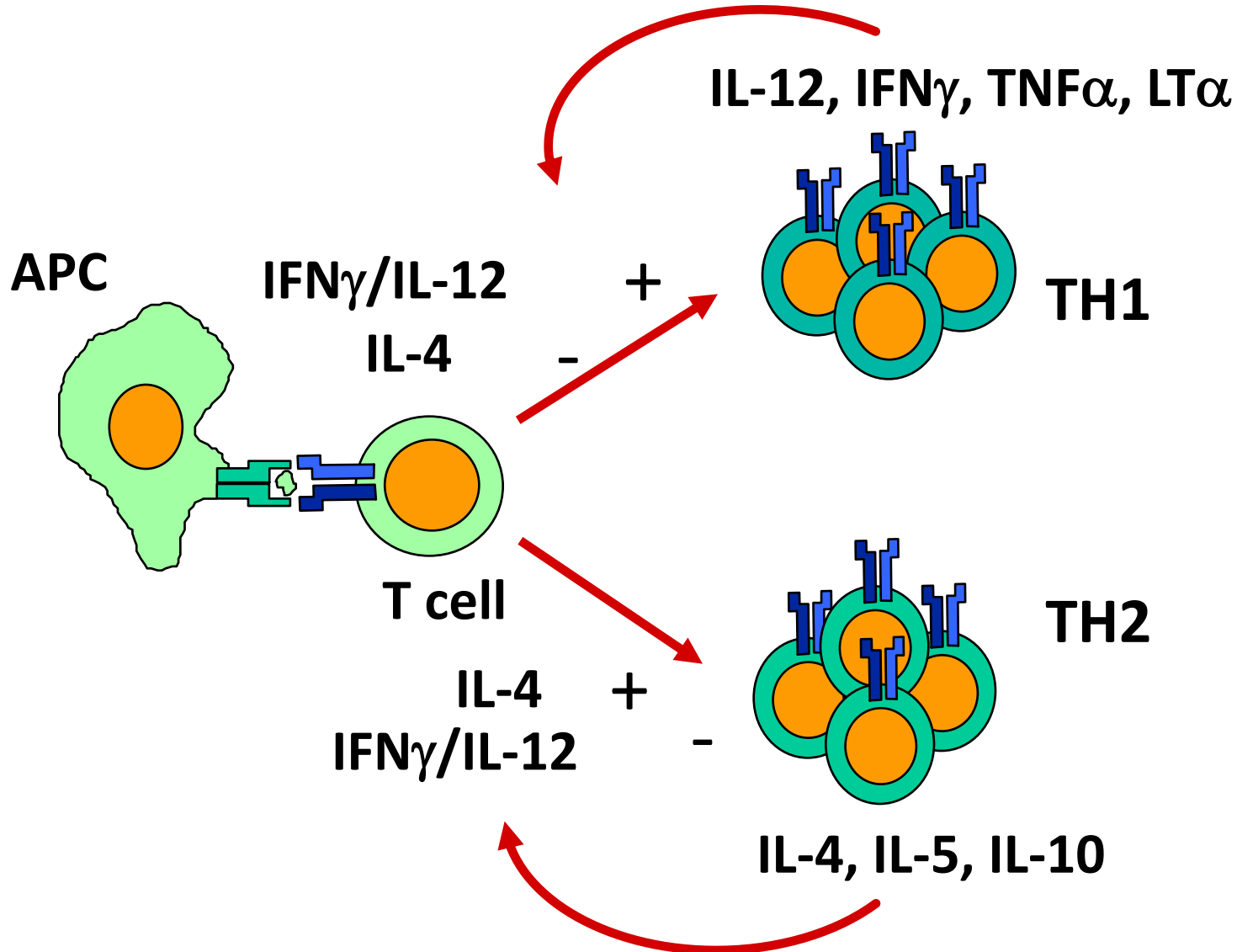
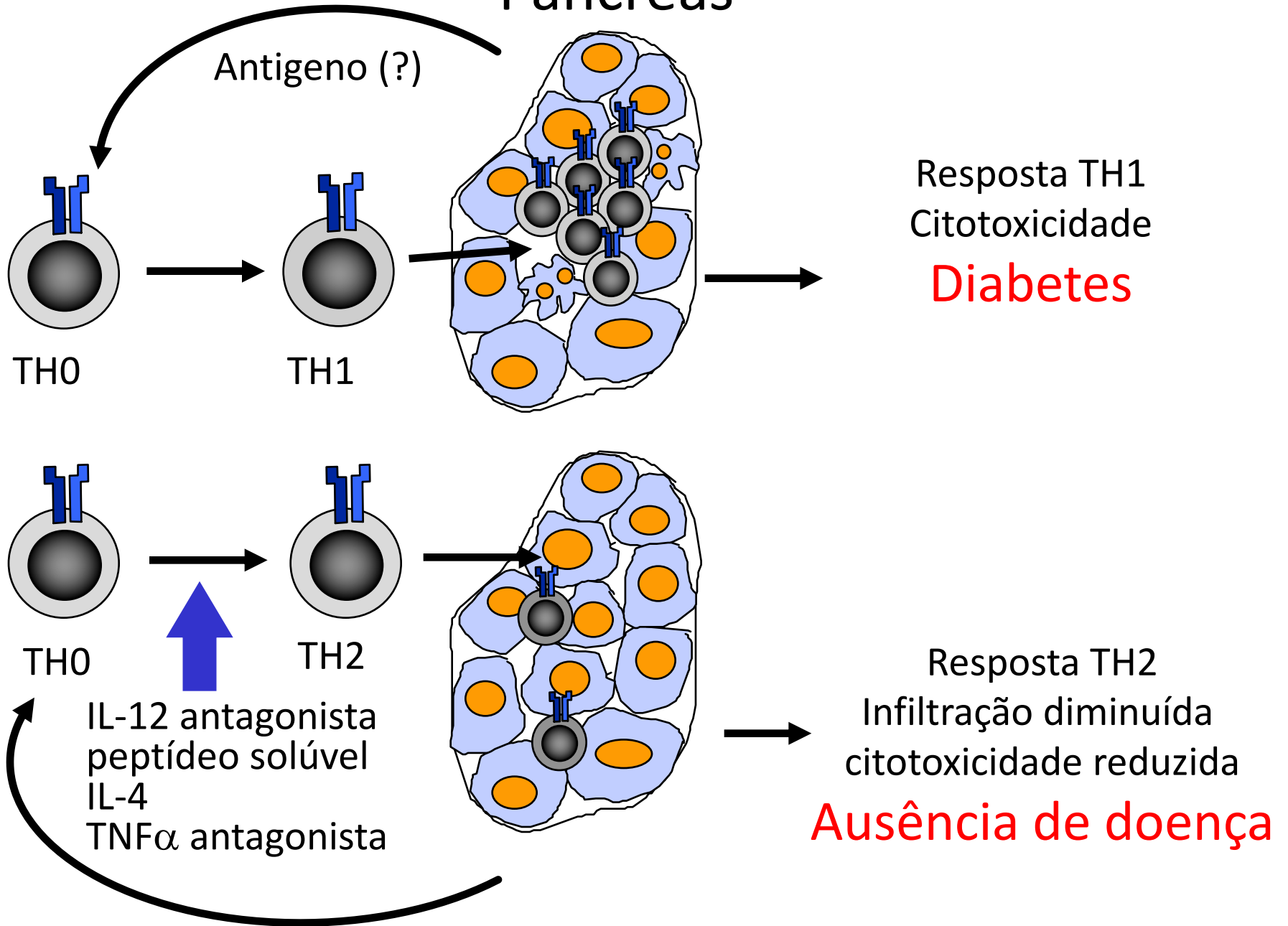


Figure 13-13 Immunobiology, 6/e. (© Garland Science 2005)

Desvio Imunológico

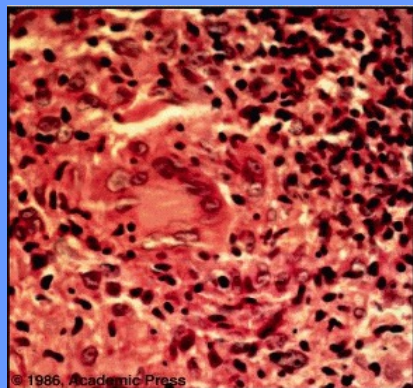


Pâncreas

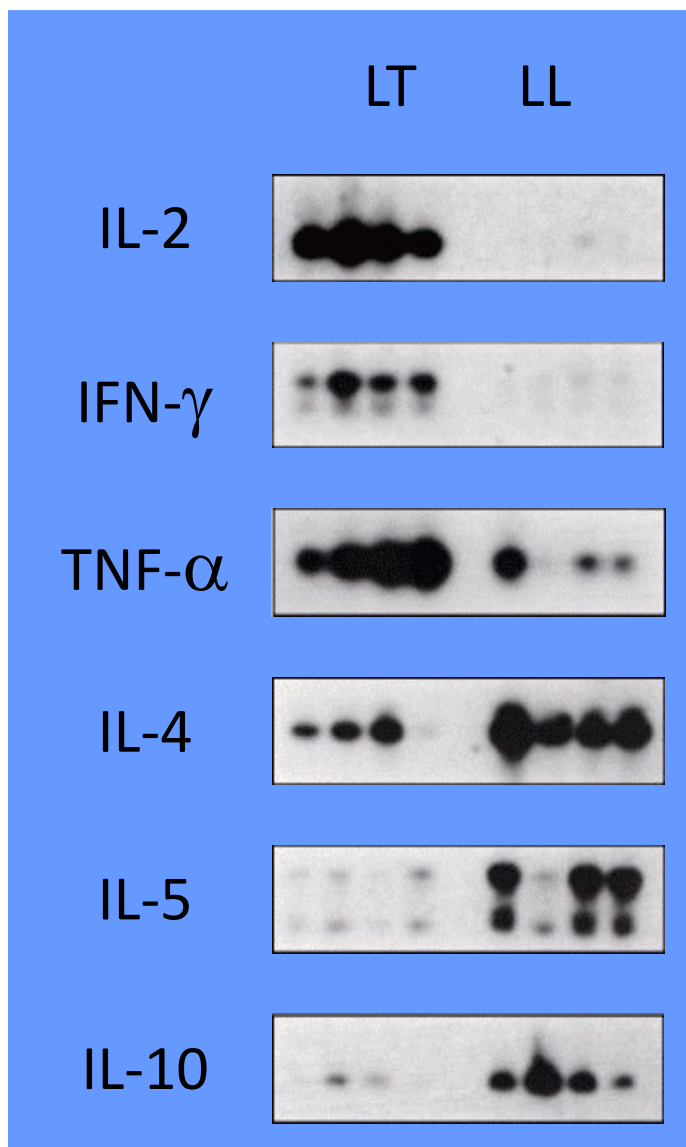
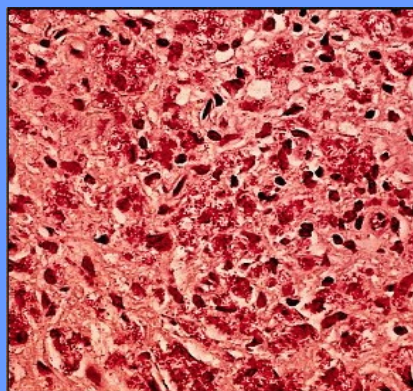


Desvio imunológico e o desenvolvimento de doenças infecciosas.

**Lepra tuberculóide
(restrita)**

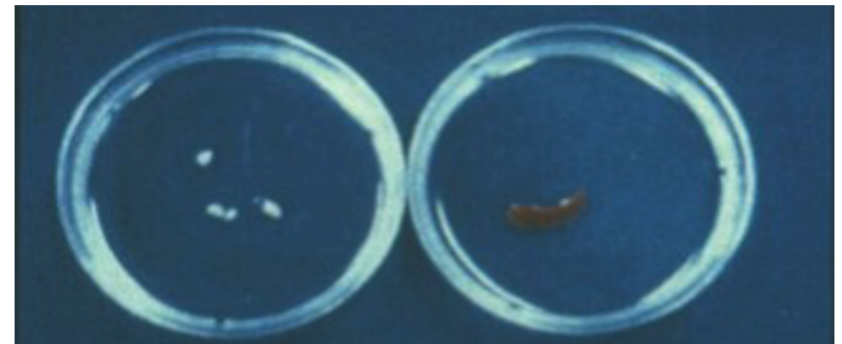


**Lepra lepromatosa
(disseminada)**

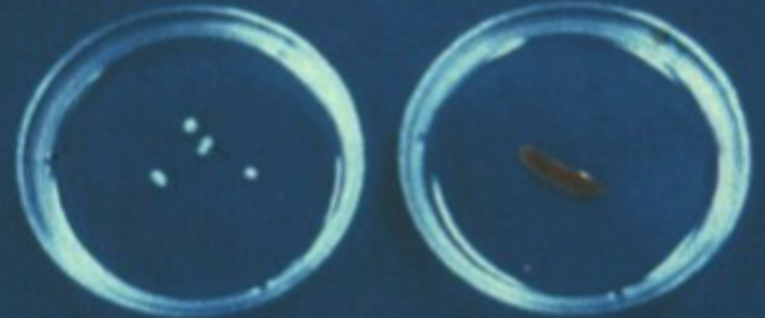


Regulação da
sobrevivência
celular por
Fas (CD95)
ou
FasL (CD95L)

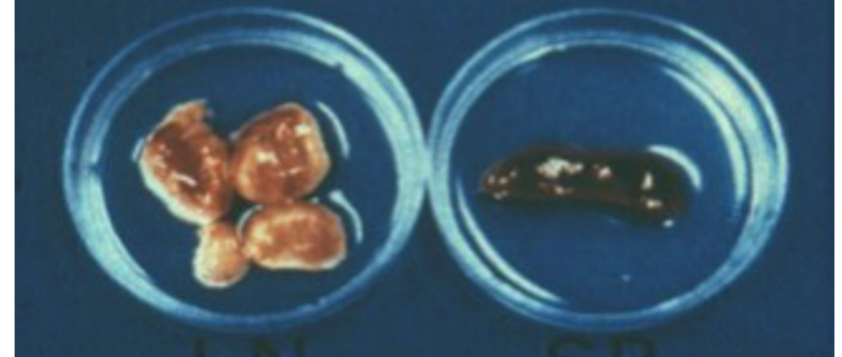
+/+



+/-



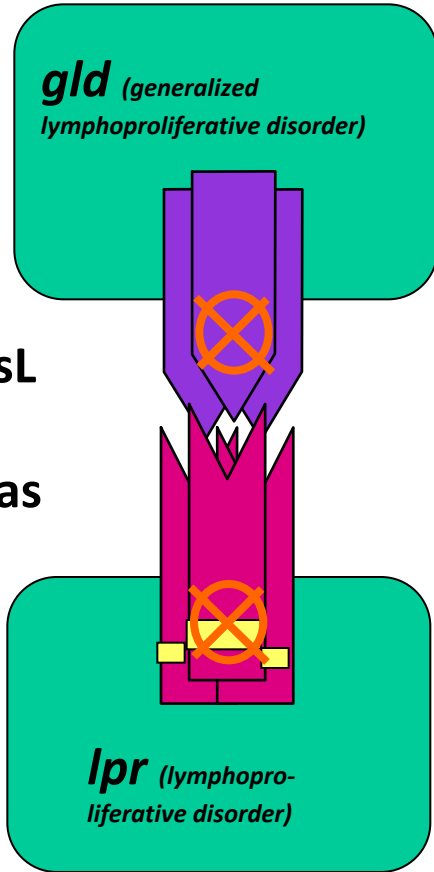
-/-



LN

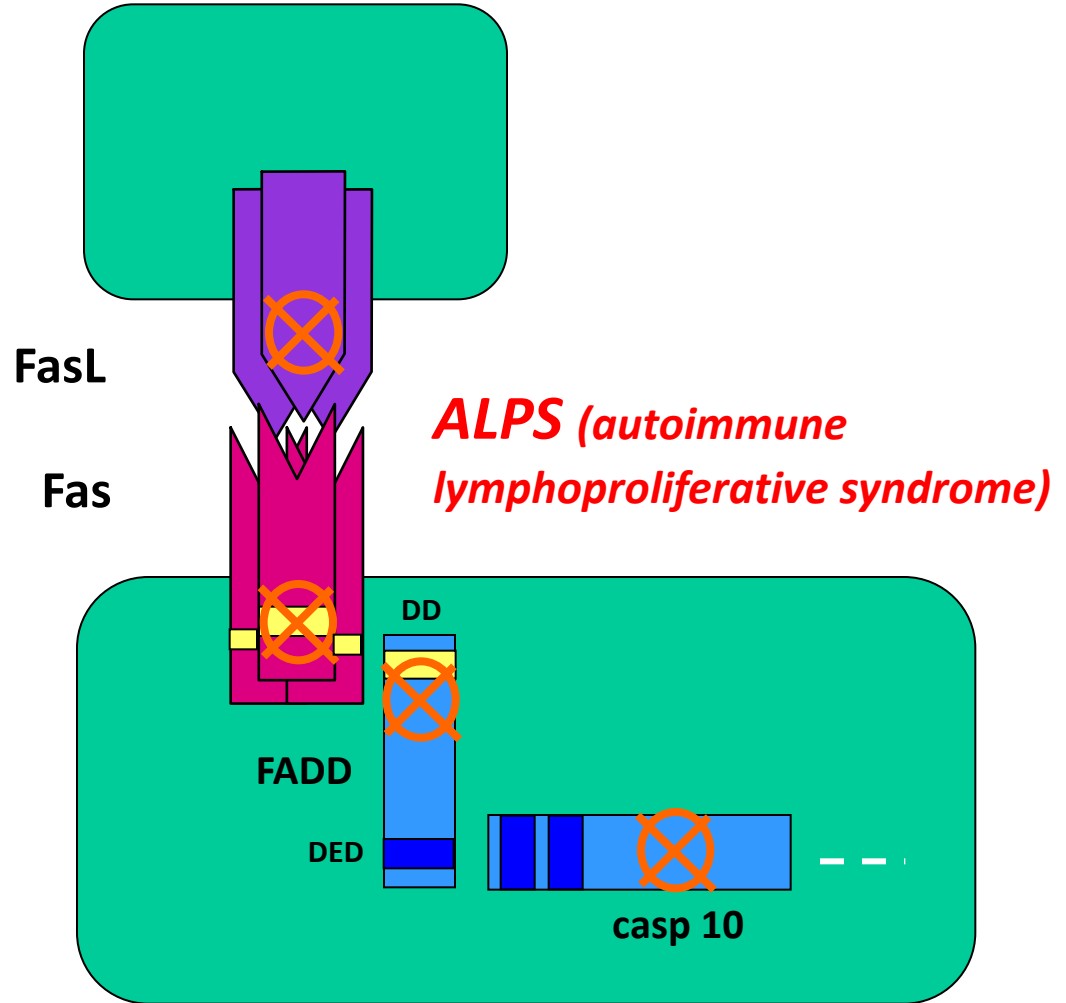
SP

Doenças Autoimunes associadas à mutações em proteínas relacionadas à apoptose



 Mutação/deleção

camundongo

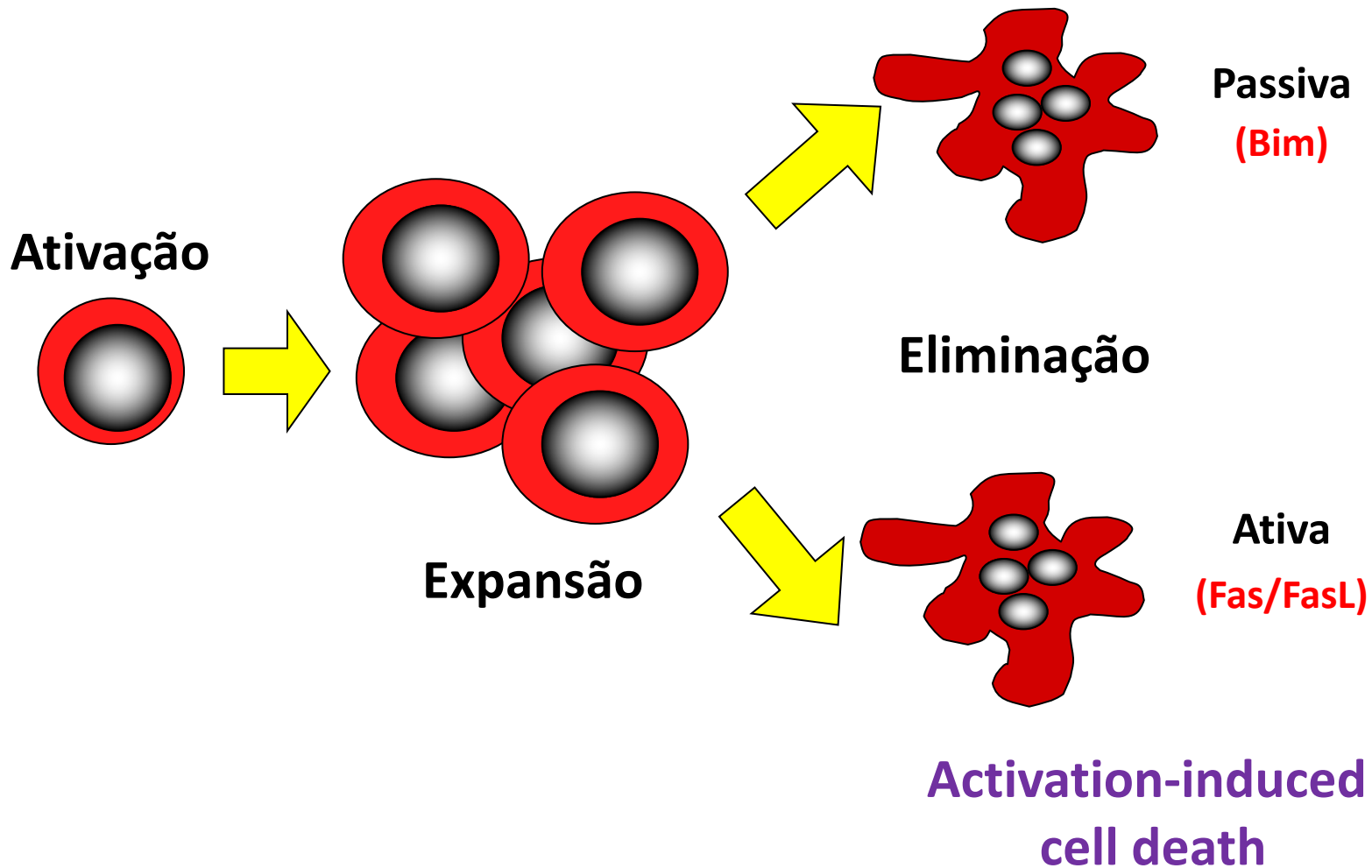


ser humano

Apoptose homeostática de linfócitos T

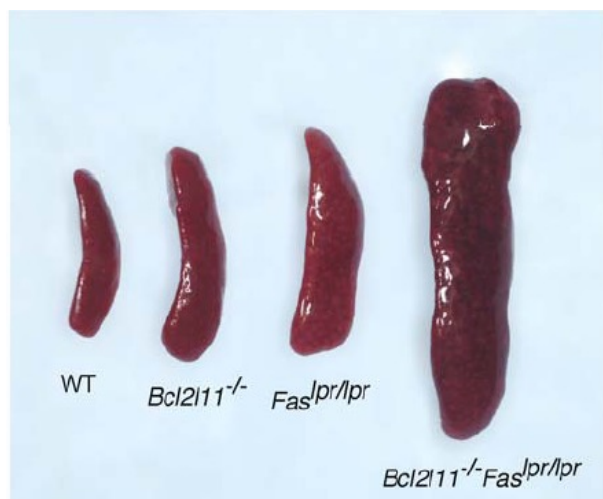
Activated T cell autonomous death

(retirada de fator de crescimento,
desaparecimento do Ag)





Bcl2l11^{-/-} *Bcl2l11*^{+/-}*Fas*^{lpr/lpr} *Fas*^{lpr/lpr}

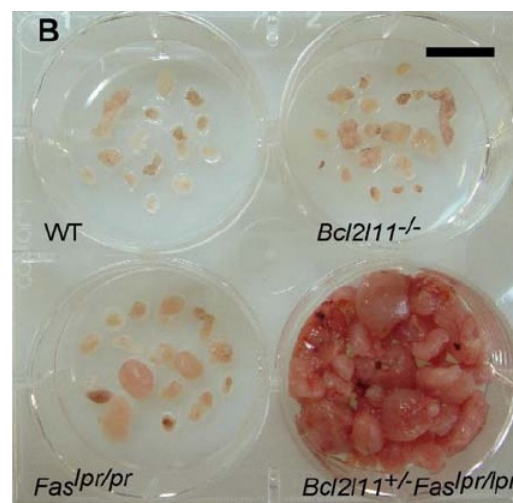


WT

Bcl2l11^{-/-}

Fas^{lpr/lpr}

Bcl2l11^{-/-}*Fas*^{lpr/lpr}



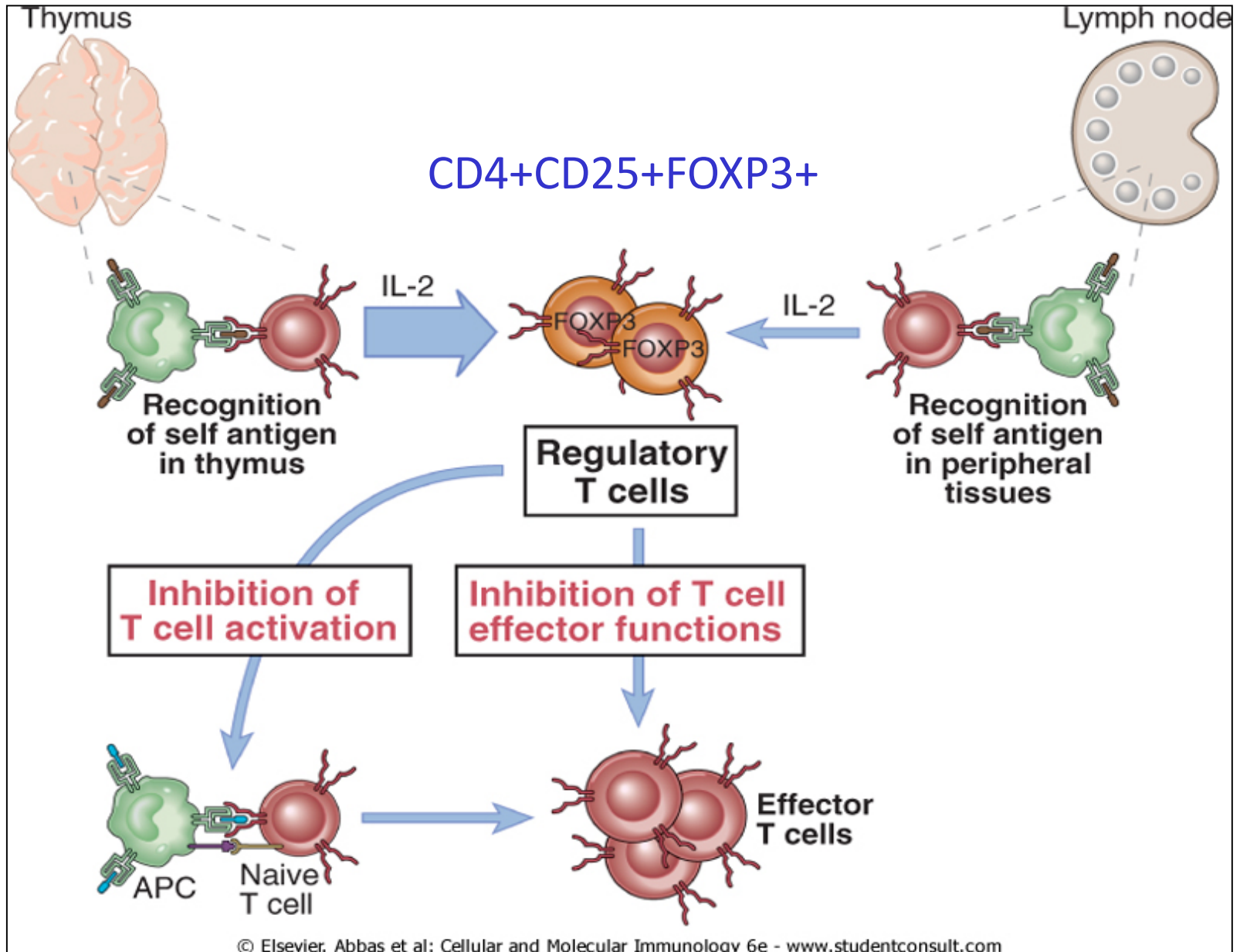
WT

Bcl2l11^{-/-}

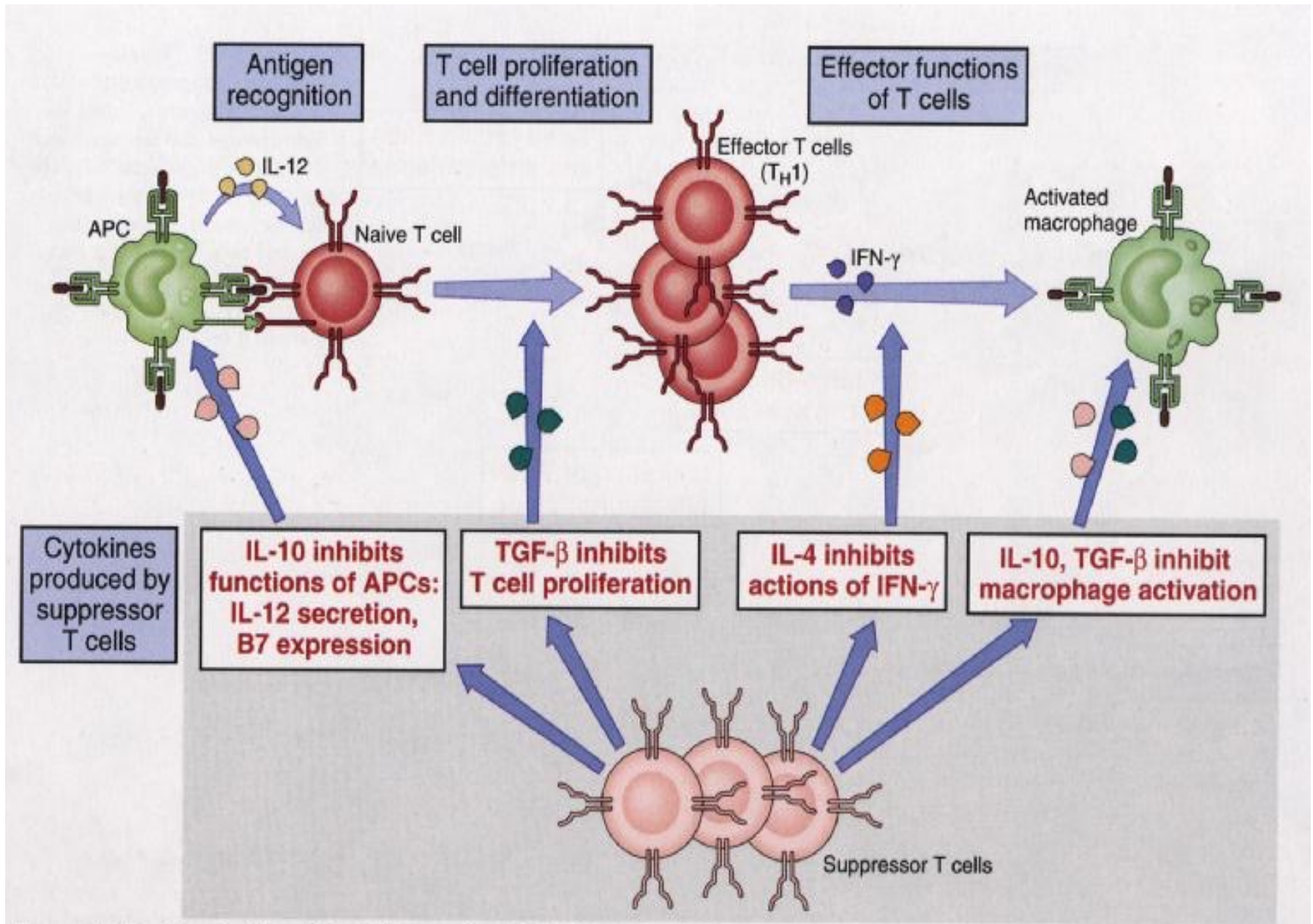
Fas^{lpr/lpr}

Bcl2l11^{+/-}*Fas*^{lpr/lpr}

Supressão/Regulação



Supressão/Regulação

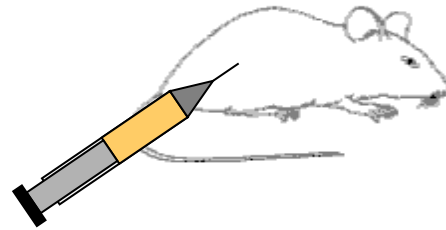
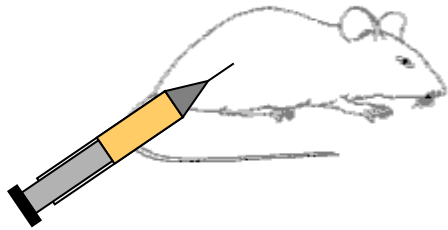


Tolerância Oral/Mucosa

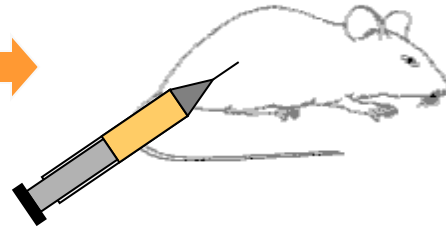
Primeiro contato

Segundo contato

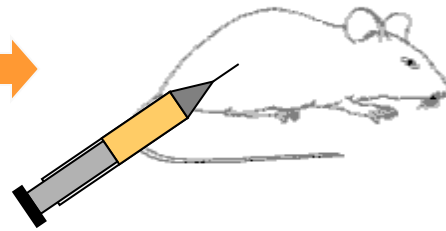
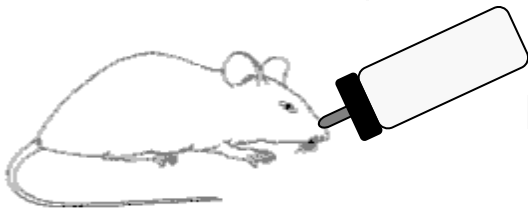
Resposta imune



+ + +

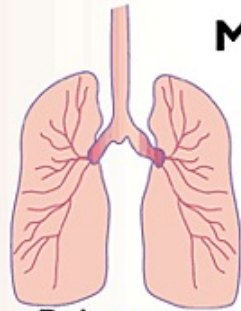


-/+

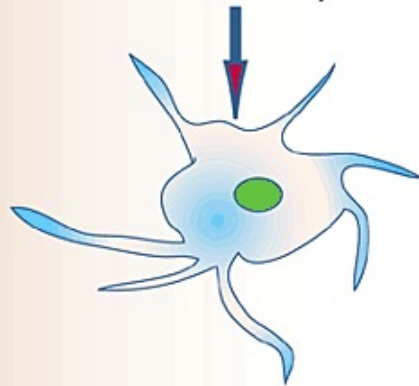


-/+

Mucosal tolerance



Pulmonary



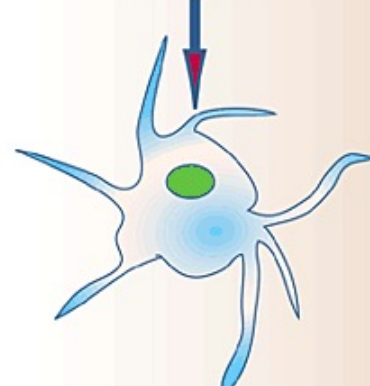
Dendritic cell

IL-10

T_R1 regulatory cell



Small intestine



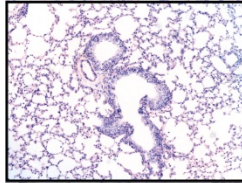
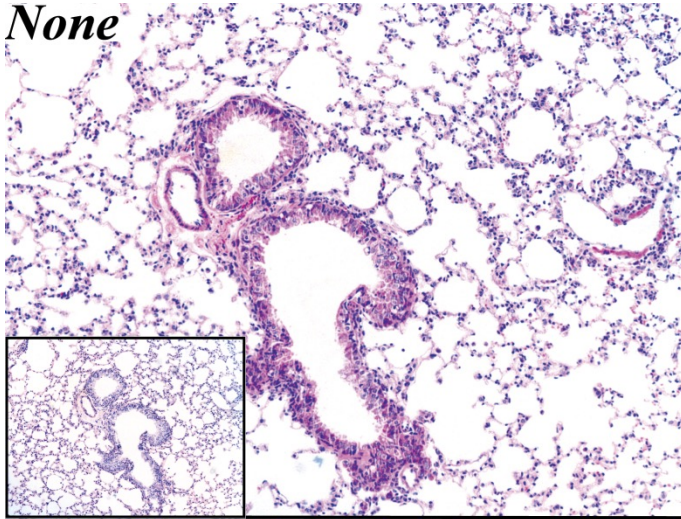
Dendritic cell

TGF- β

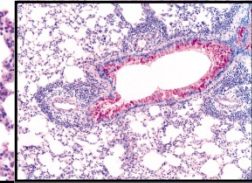
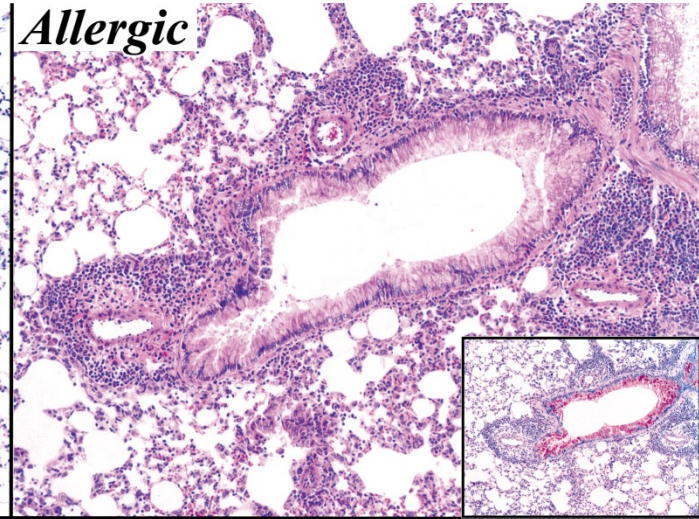
T_H3 regulatory cell

Tolerância Oral/Mucosa

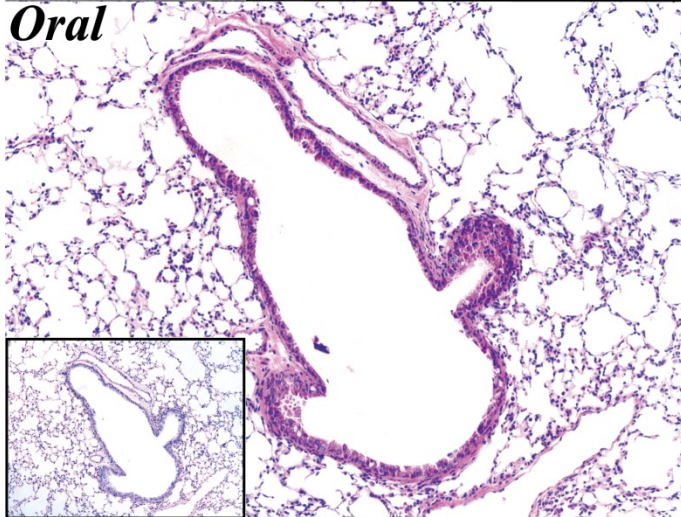
None



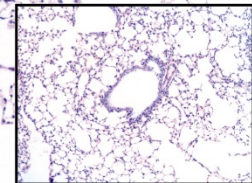
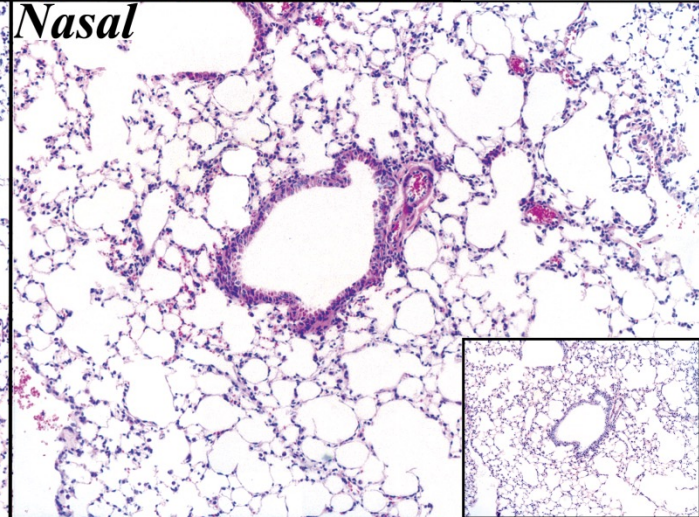
Allergic



Oral



Nasal



Qual é o mecanismo????

“Quebra” da auto-tolerância

Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Release of sequestered self antigen; activation of non-tolerized cells	Induction of co-stimulator activity	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	Sympathetic ophthalmia	Effect of adjuvants: induction of EAE	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis
	