A T SEJTEK TÍPUSAI ÉS AKTIVÁCIÓJA

Buzás Edit

Genetikai, Sejt- és Immunbiológiai Intézet

A T limfociták

1. **A celluláris immunitás sejtjei**
2. **T sejt receptor van a felszínükön**
3. **A thymusban érnek**
4. **Típusaik:**

αβ T sejtek

T helper: segítség a B sejteknek vagy makrofágoknak/NK sejteknek

T citotoxikus: vírusfertőzött vagy tumoros sejtek elpusztítása

T reguláló: más T sejtek működésének gátlása

MHC molekulával bemutatott epitópot ismernek fel

γδ T sejtek

NKT sejtek

MAIT sejtek

T sejt receptor komplex

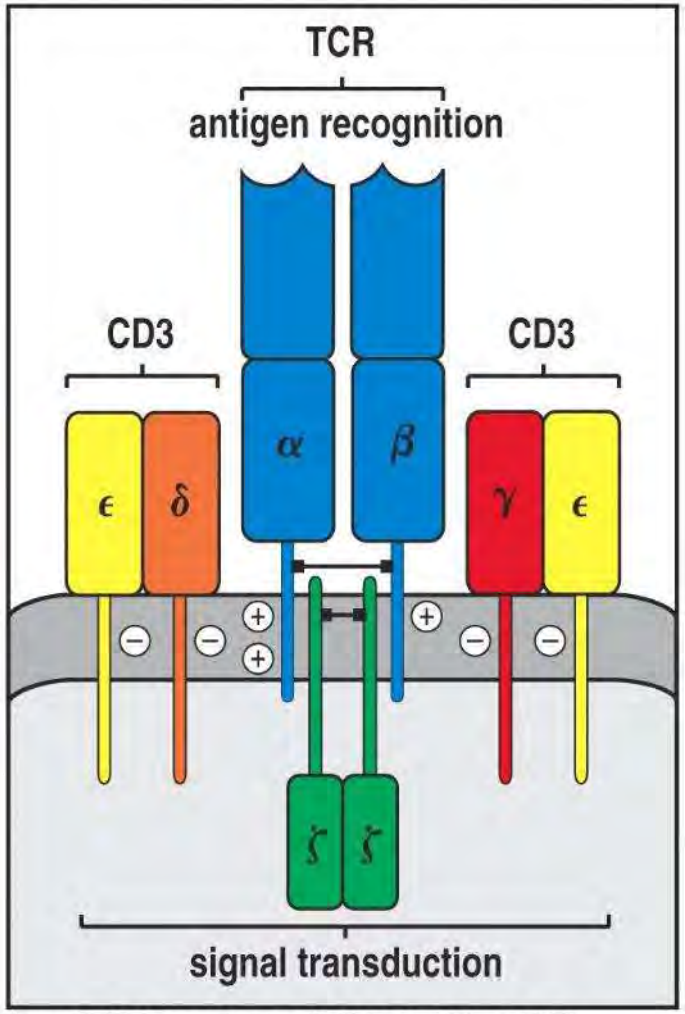


Figure 3-6 The Immune System, 2/e (© Garland Science 2005)

A T sejtek CD3+ sejtek

A T limfociták

1.T sejt ontogenezis (*thymus*)

2. T sejt aktiváció (*szekunder nyirokszervek*)

3. T sejttípusok és működésük (*szövetek*)

Thymus

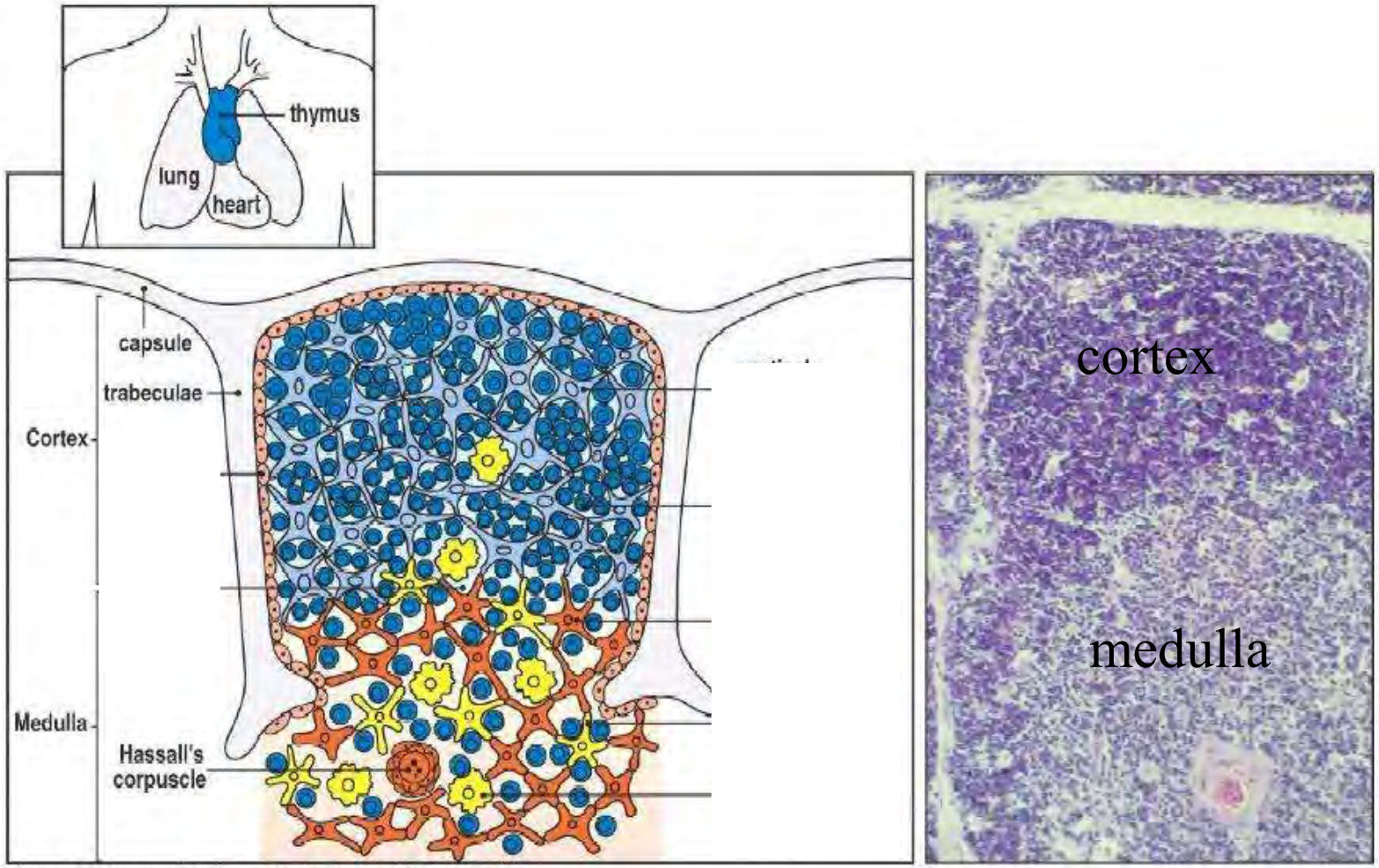
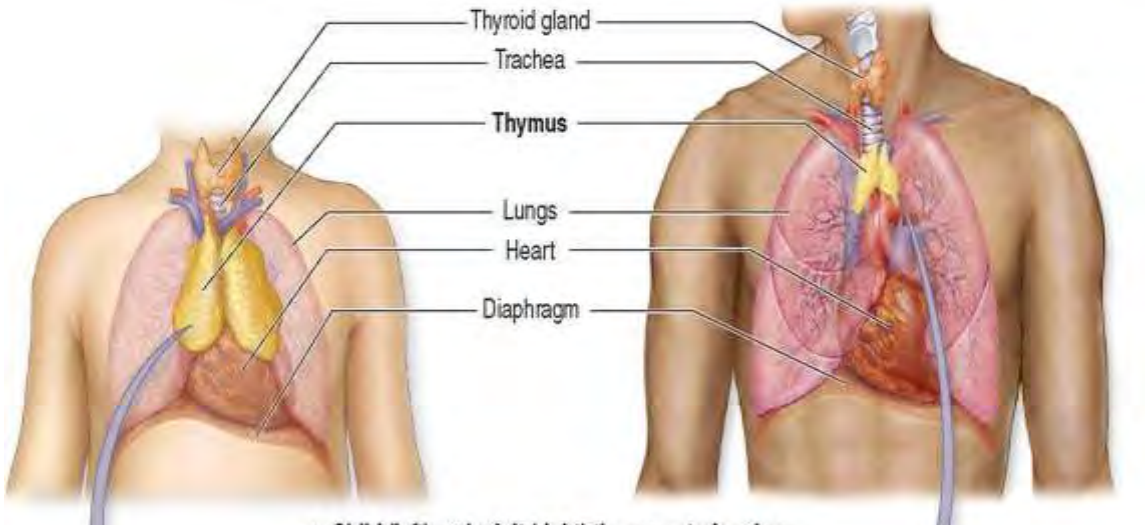
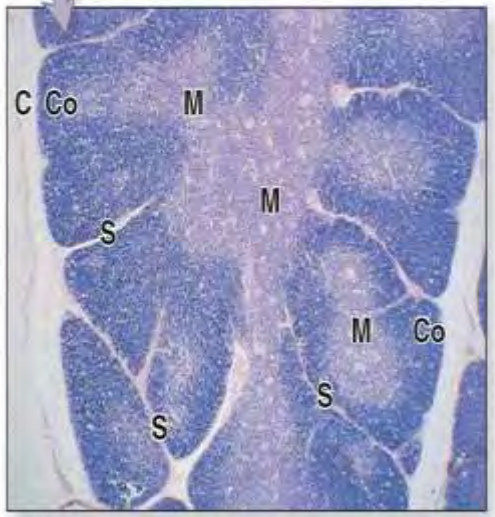


Figure 7-8 Immunobiology, 6/e. (© Garland Science 2005)

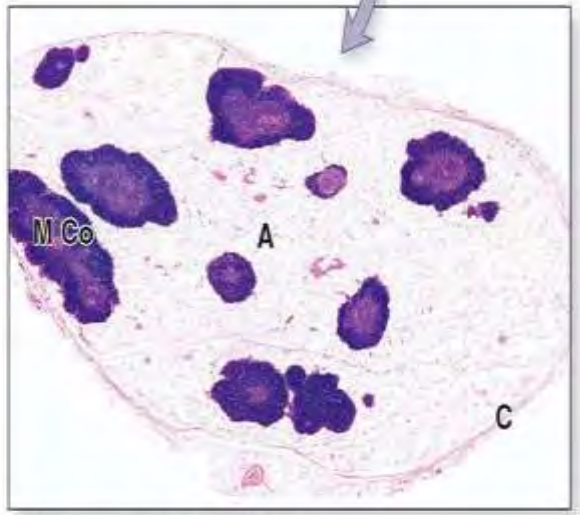
Thymus



a Child (left) and adult (right) thorax, anterior view

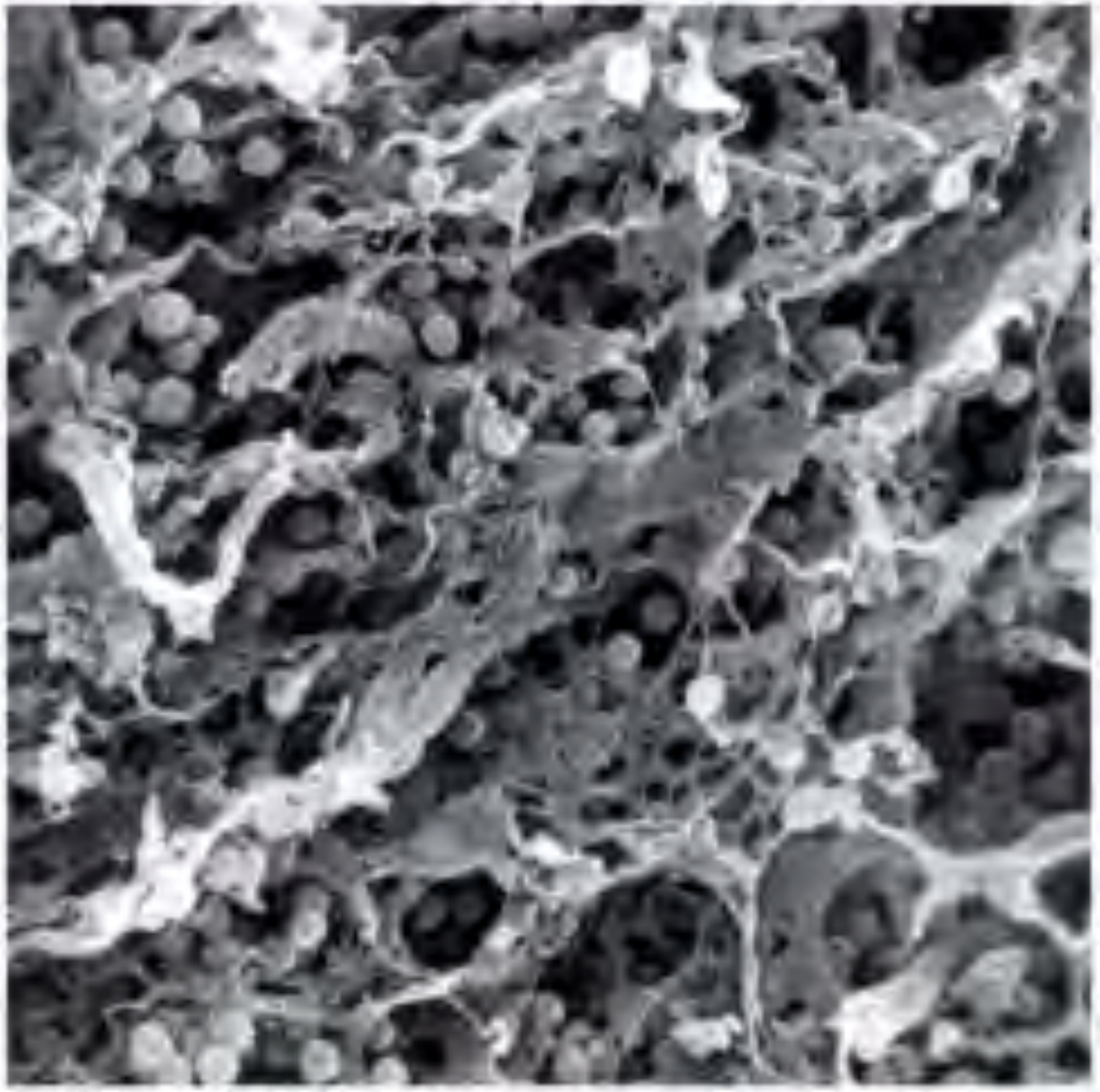


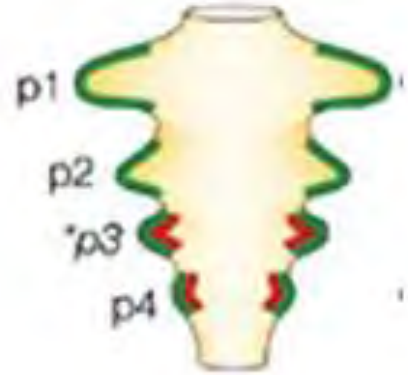
b Micrograph of child's thymus

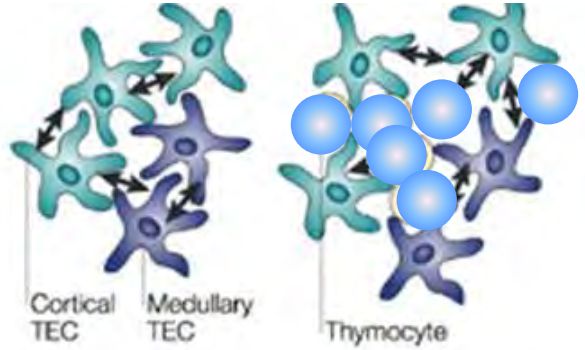


c Micrograph of adult's thymus

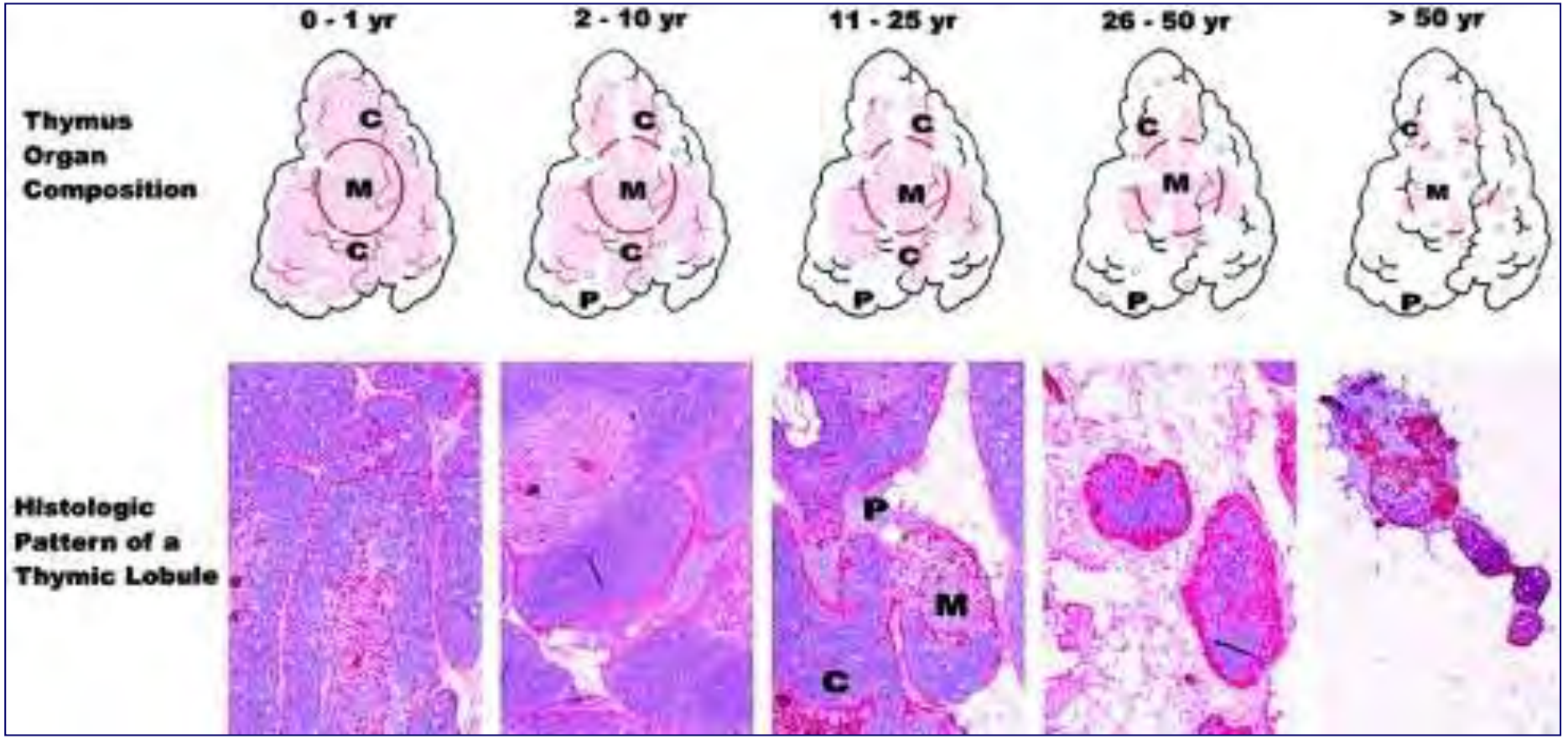
Thymus stroma: entodermális citoretikulum



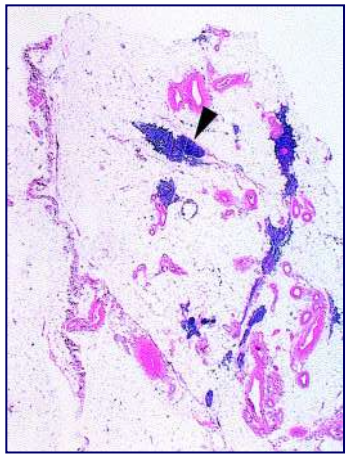




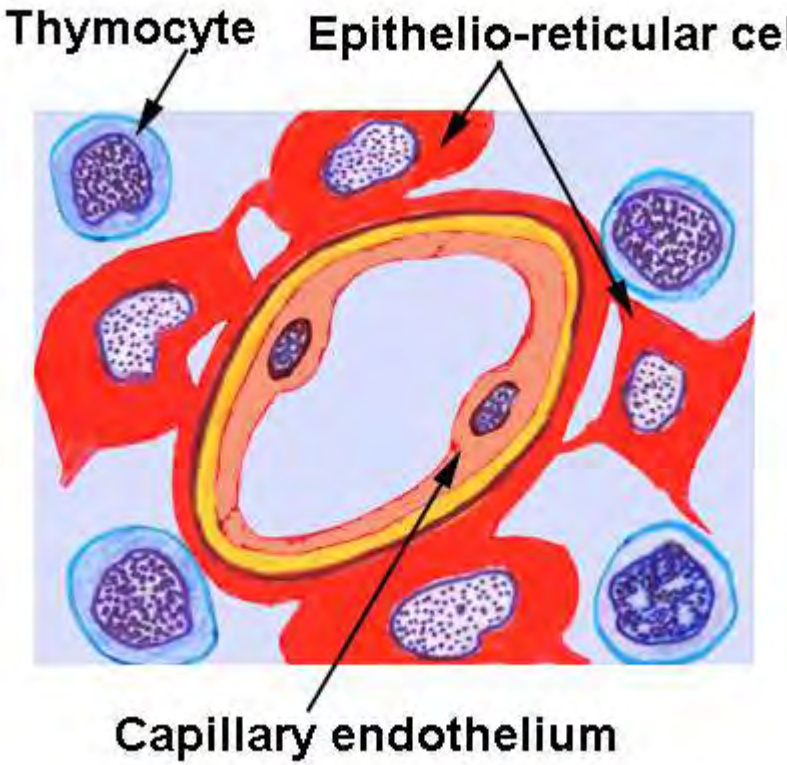
A thymus ontogenezise

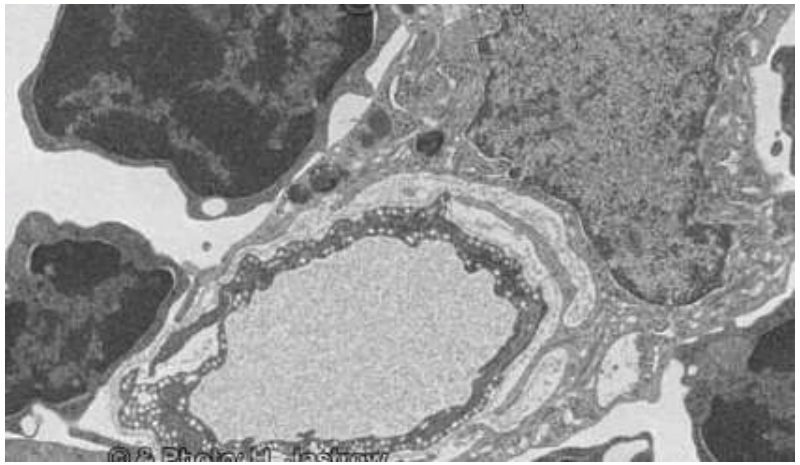


78 éves nő thymusa

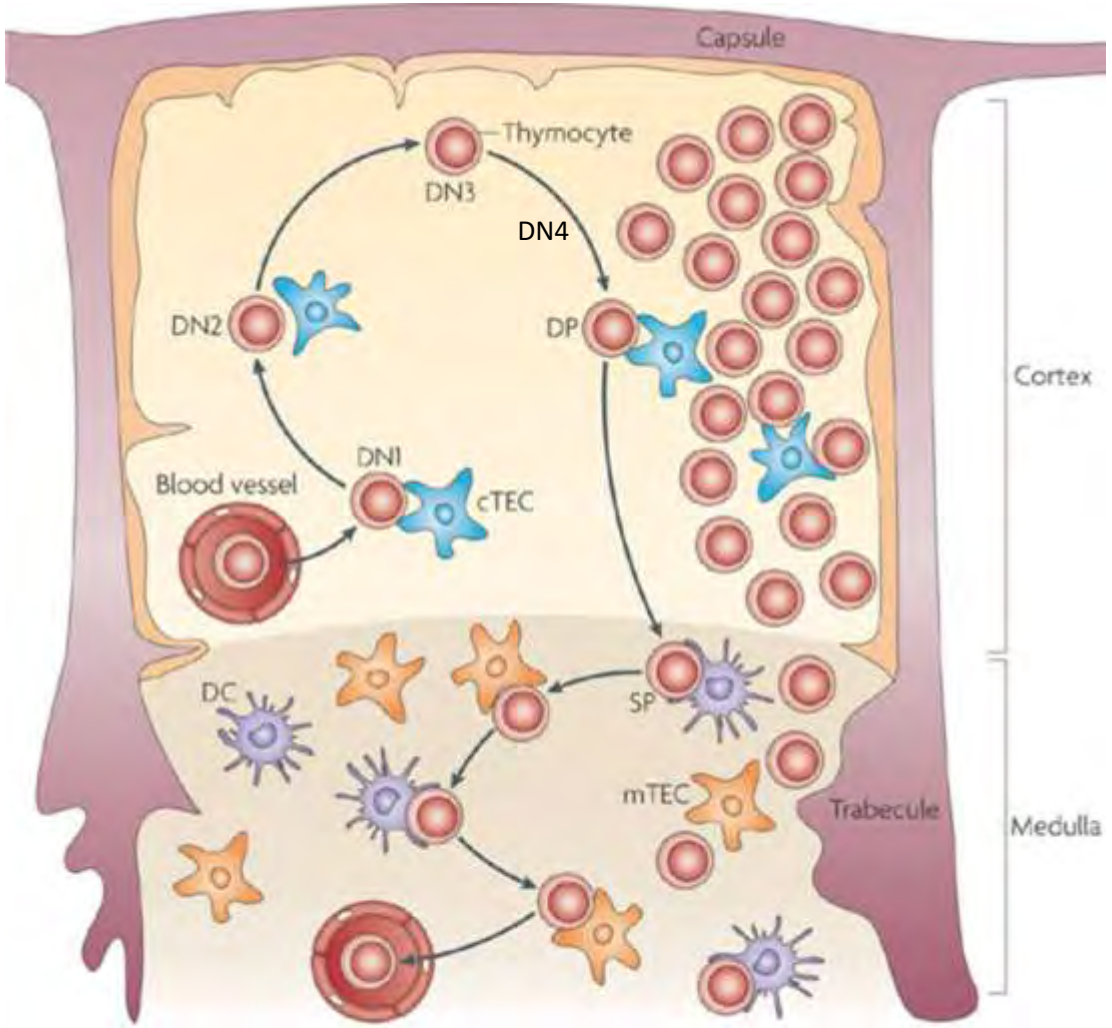


Vér-thymus gát





T sejt érés a thymusban

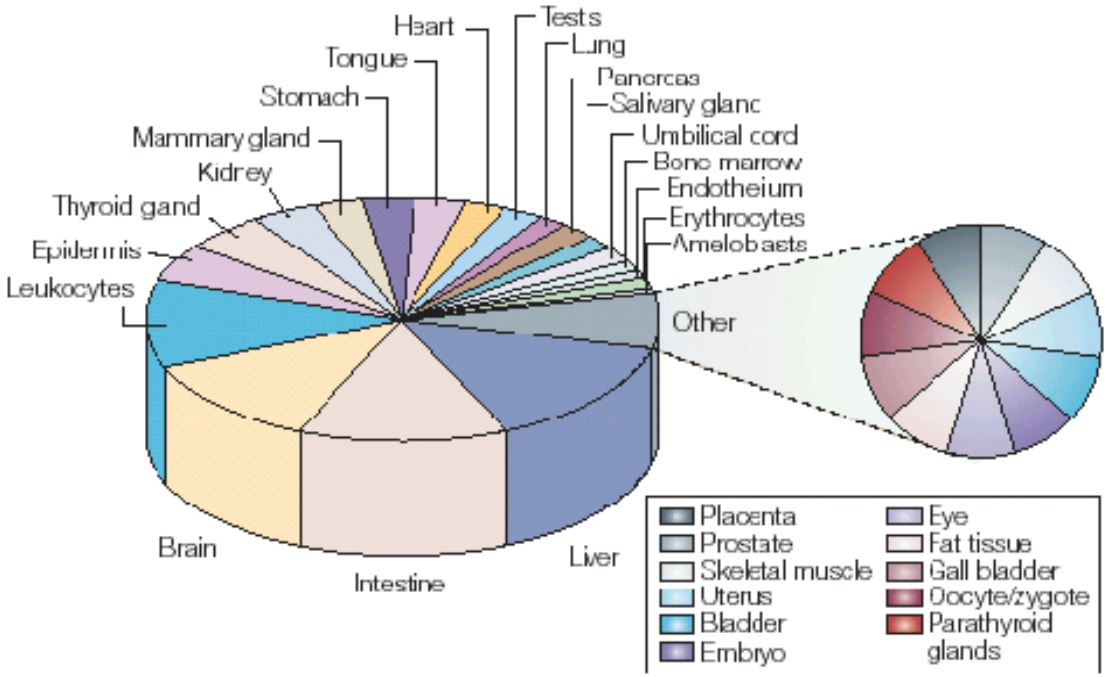


R.N. Germain, Nature Review 2002

mTEC: saját antigének kerülnek bemutatásra a thymusban: promiszkuus génexpresszió

5-10%-a (~3000 gén) expresszálódik:

Fő szabályozói az AIRE és a FEZF2 transzkripciós faktorok

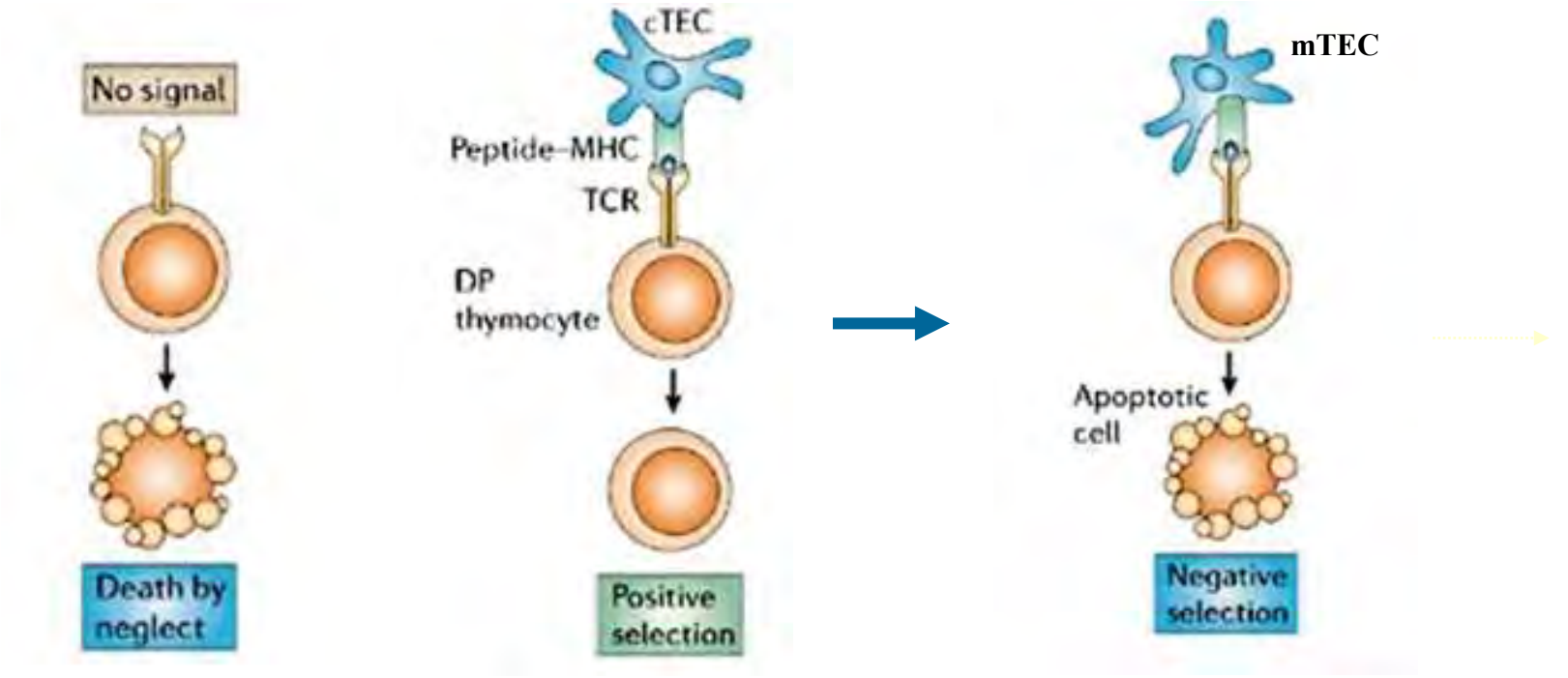


Nat Rev Immunol 2004. 4: 688-698.

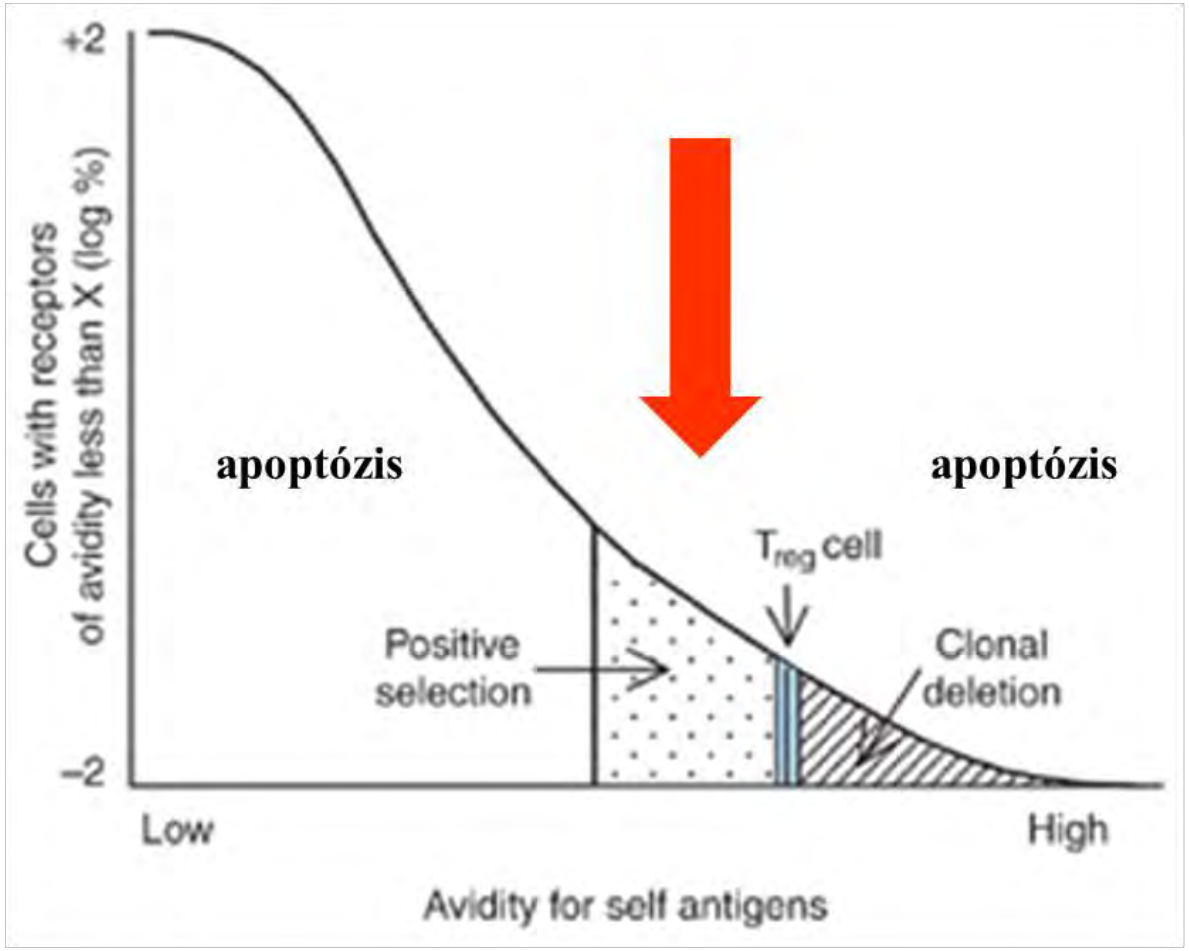
A saját peptid-saját MHC kötődés próbái

Pozitív szelekció

Negatív szelekció



Szelekció a TCR MHC_saját peptid komplex aviditása alapján a thymusban



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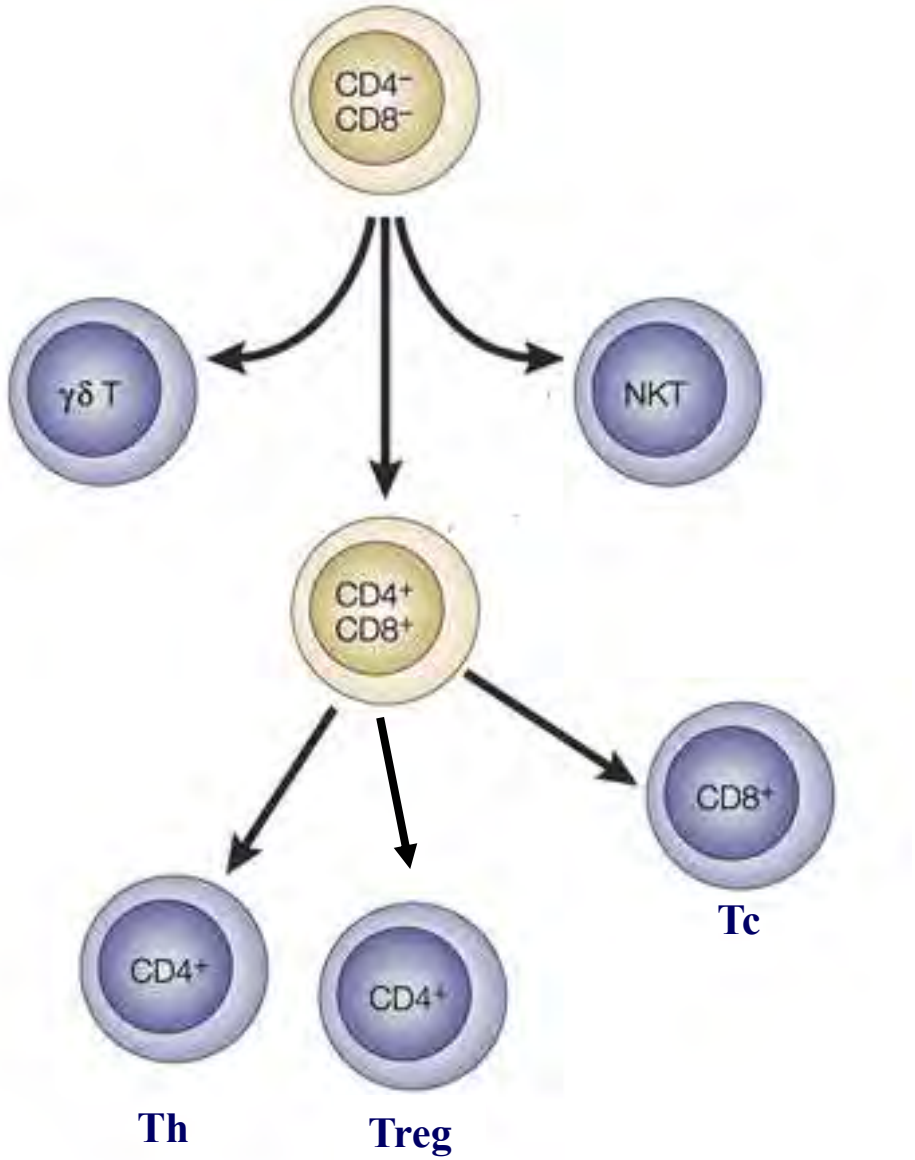
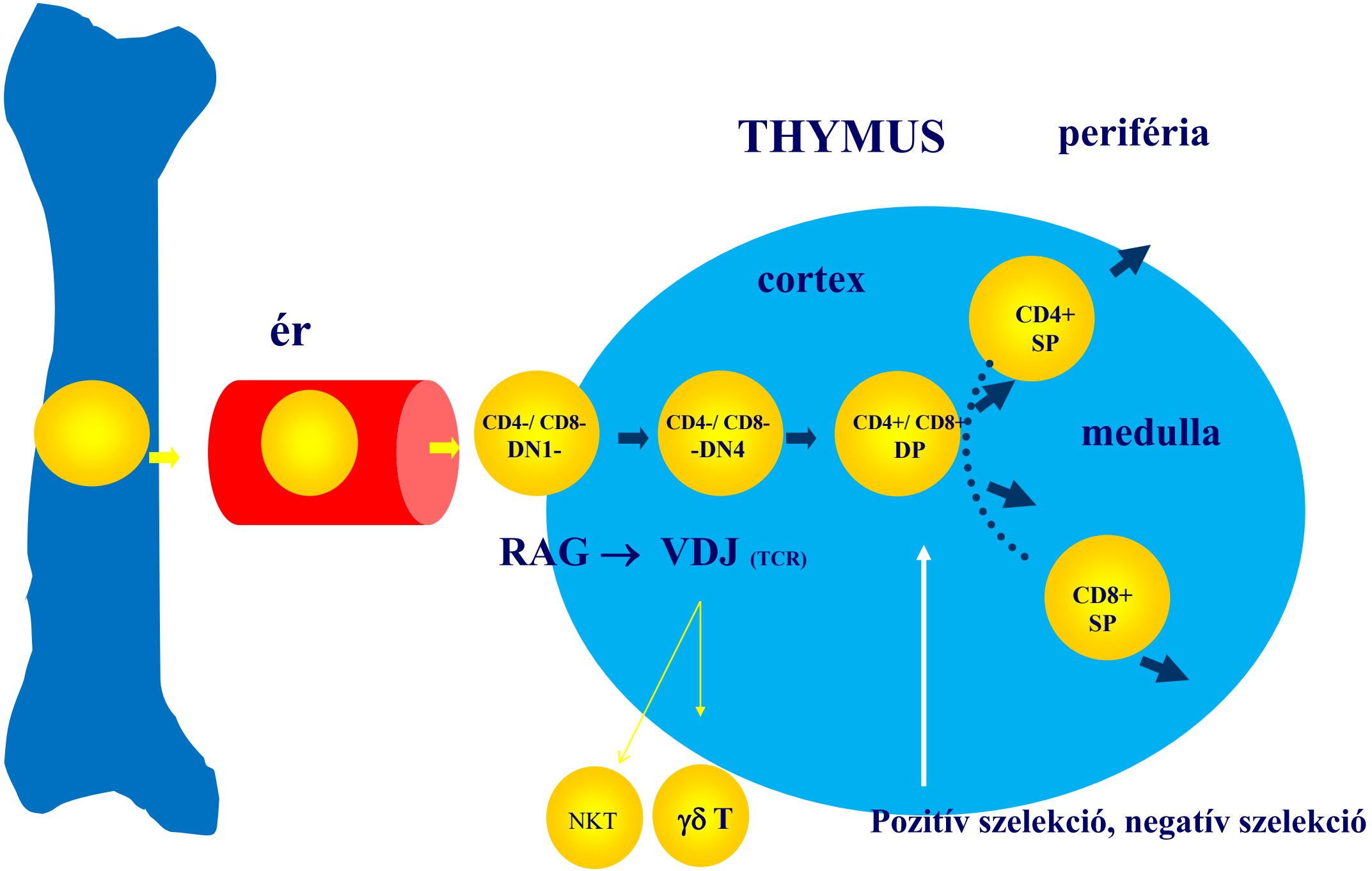
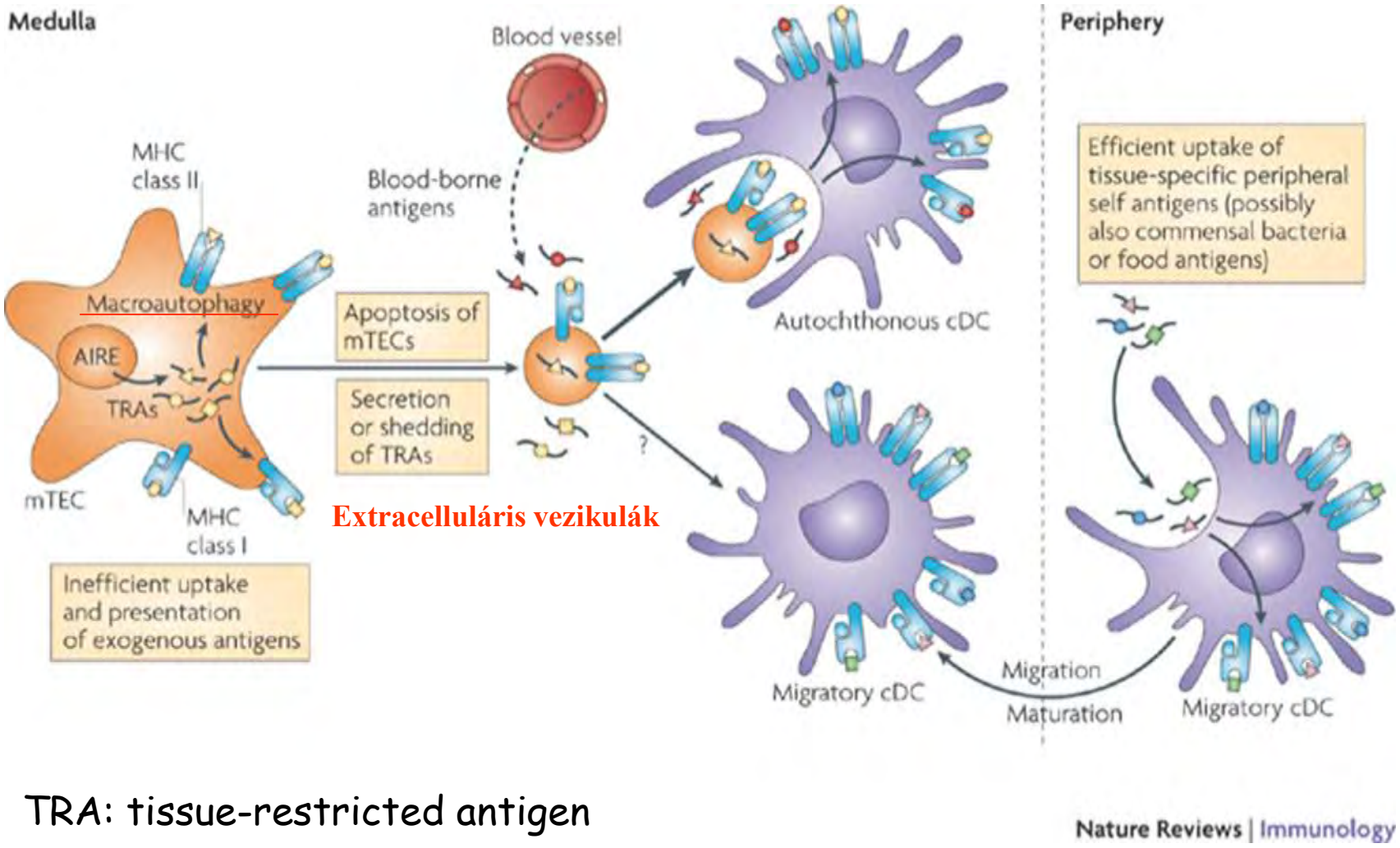

CD4⁻
CD8⁻
γδ T
NKT
CD4⁺
CD8⁺
CD8⁺
CD4⁺
CD4⁺
Th
Treg
Tc


THYMUS
periféria
cortex
ér
CD4+
SP
CD4-/ CD8-
DN1-
CD4-/ CD8-
-DN4
CD4+/ CD8+
DP
medulla
RAG → VDJ (TCR)
CD8+
SP
NKT
γδ T
Pozitív szelekció, negatív szelekció

A saját peptid-saját MHC kötődés próbái

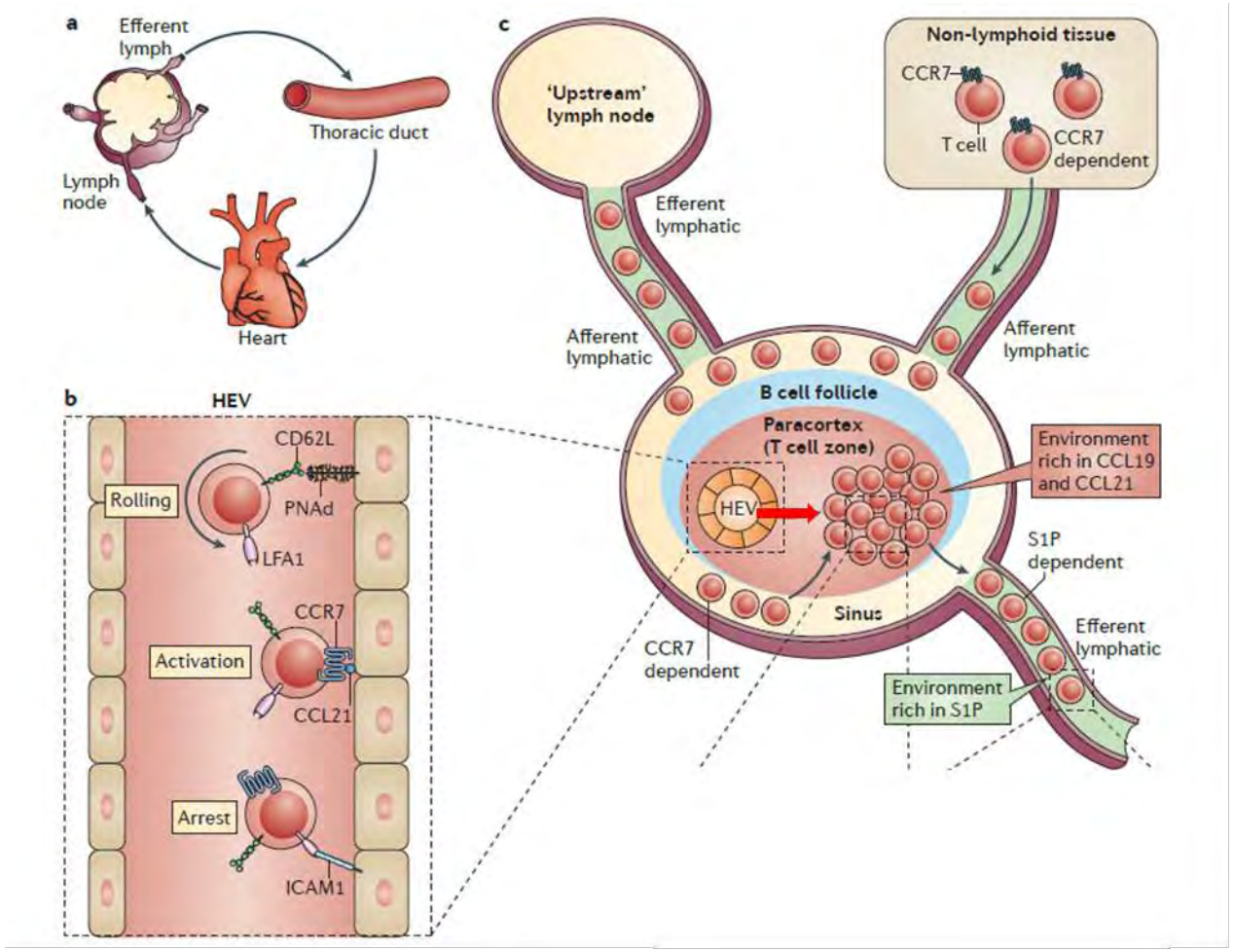


TRA: tissue-restricted antigen

A pozitív és negatív szelekciót a keletkezett T sejtek 5%-a éli túl

A pozitív és negatív szeklekciót túlélő T sejtek elhagyják a thymust és csatlakoznak a recirkuláló limfocita tömeghez

A naiv T sejtek migrációja a nyirokcsomókba



A naiv T sejteken L-szelektin (CD62L) és CCR7 homing receptorok vannak

A nyirokcsomókban addresszin molekulák expresszálódnak (CCL19 és CCL21)

Nature Reviews Immunology **13**, 309–320(2013)

Az éretlen dendritikus sejtek a perifériáról a nyirokcsomókba szállítják a felvett antigént

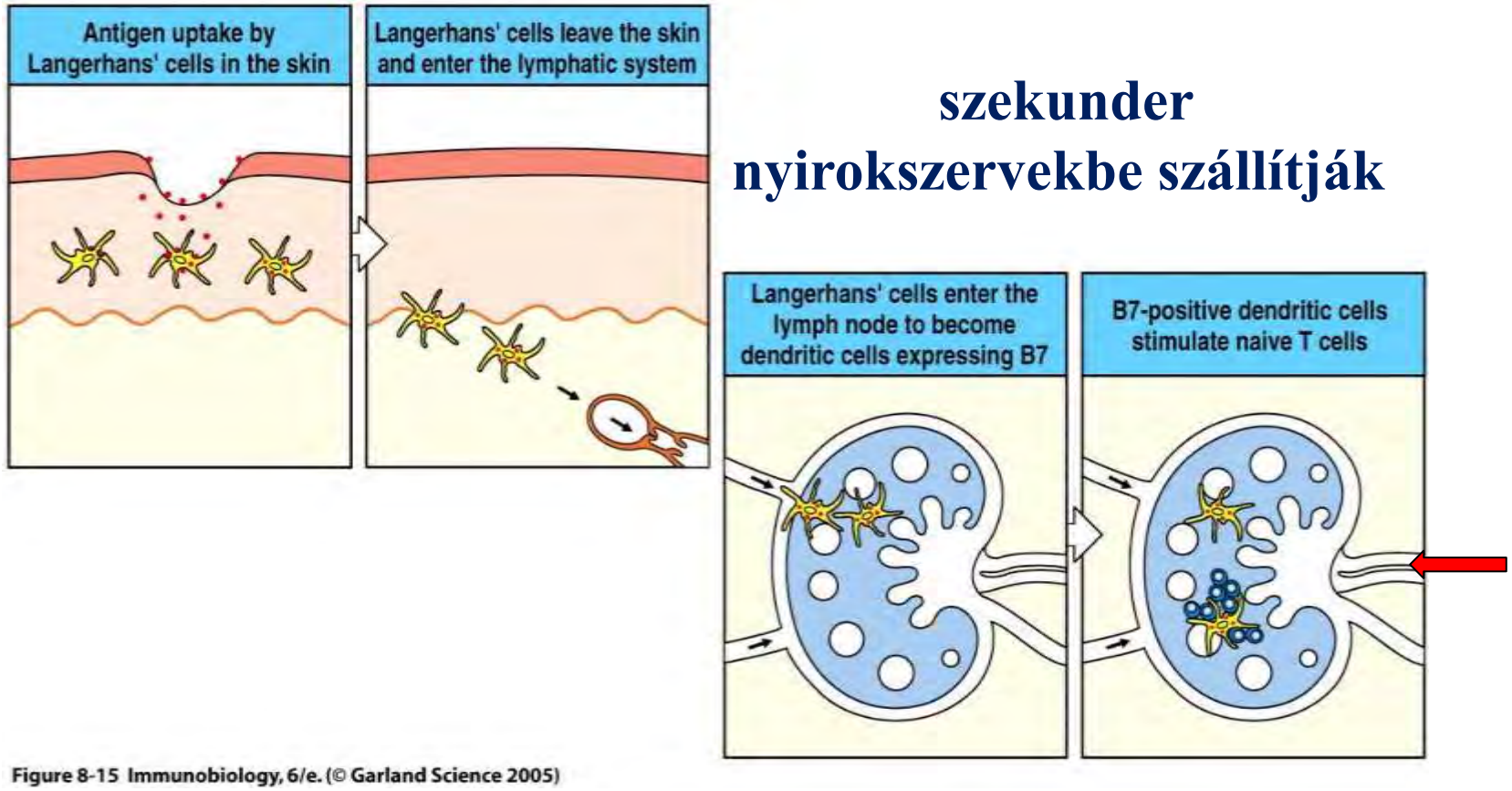
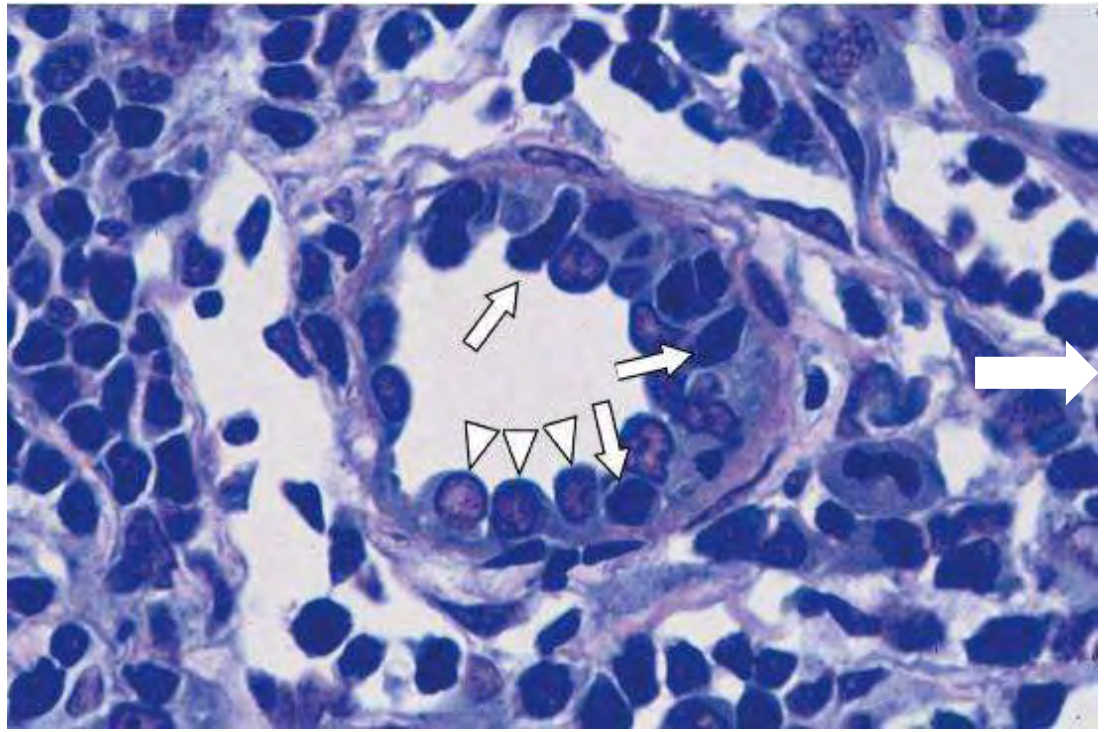


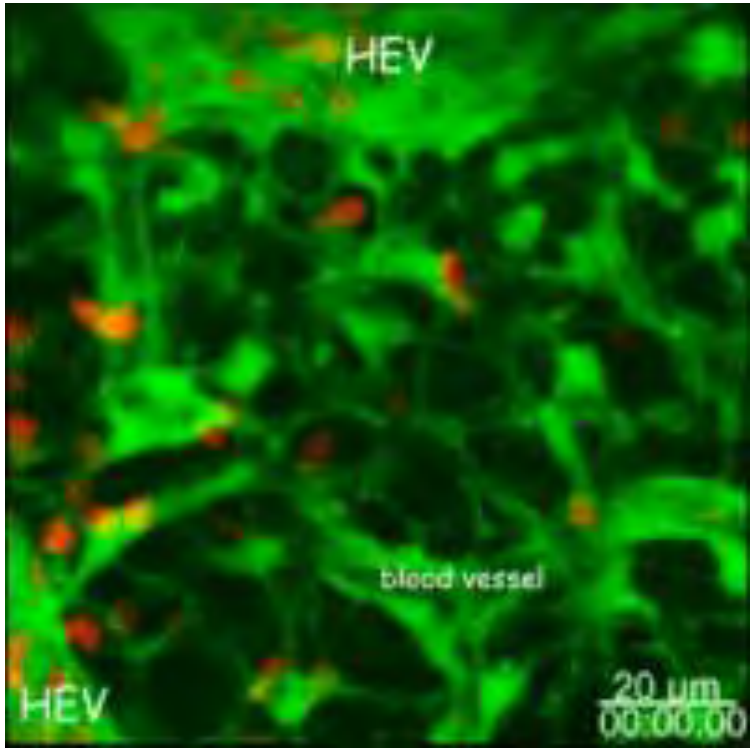
Figure 8-15 Immunobiology, 6/e. (© Garland Science 2005)

szekunder nyirokszervekbe szállítják

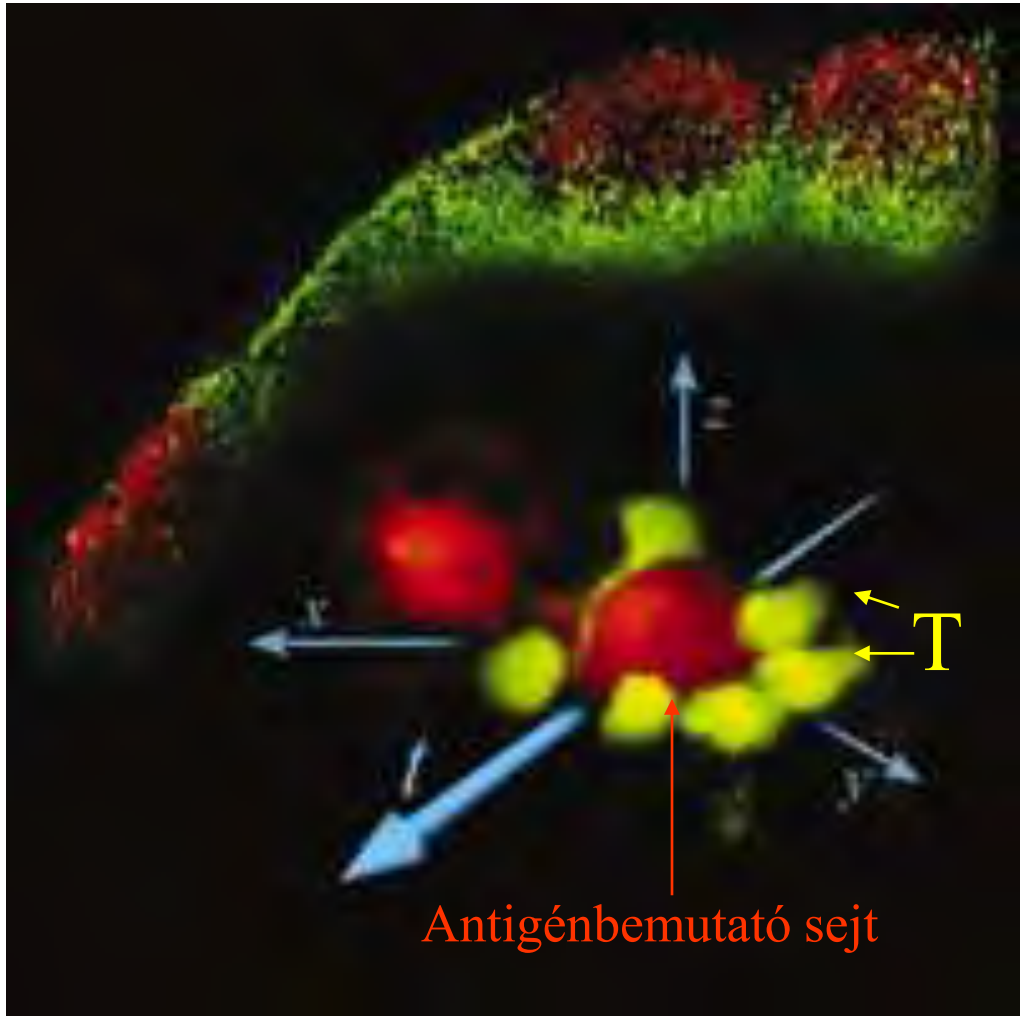
A megérett dendritikus sejtek bemutatják az antigént

A nyirokcsomó állományába a HEV-ek falán át lépnek be a T sejtek



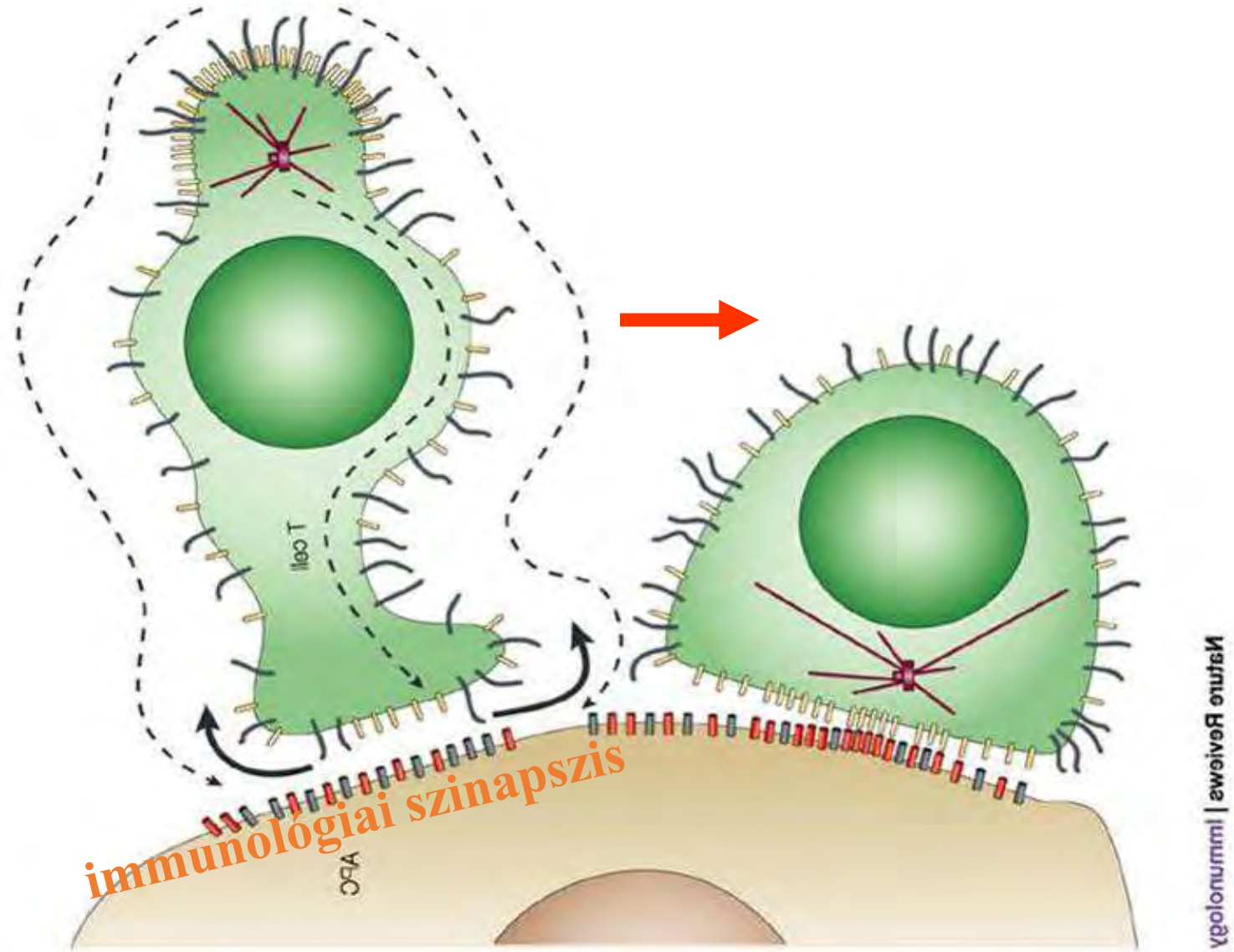


A nyirokcsomó paracortexébe a HEV-ek falán át lépnek a véráram útján érkezett T sejtek

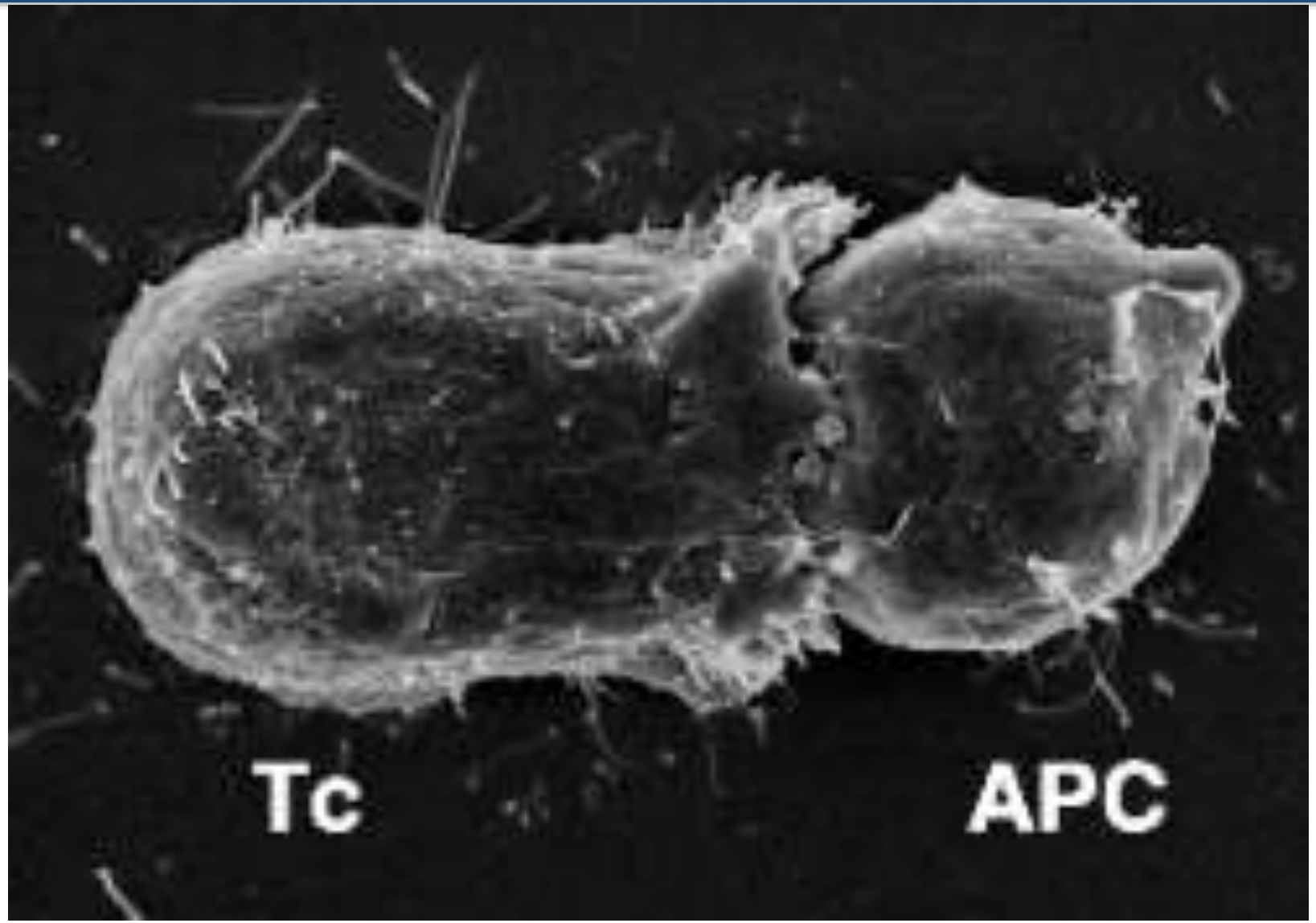


http://crt.biomol.uci.edu/images/intravital%20T%20HEV.jpg

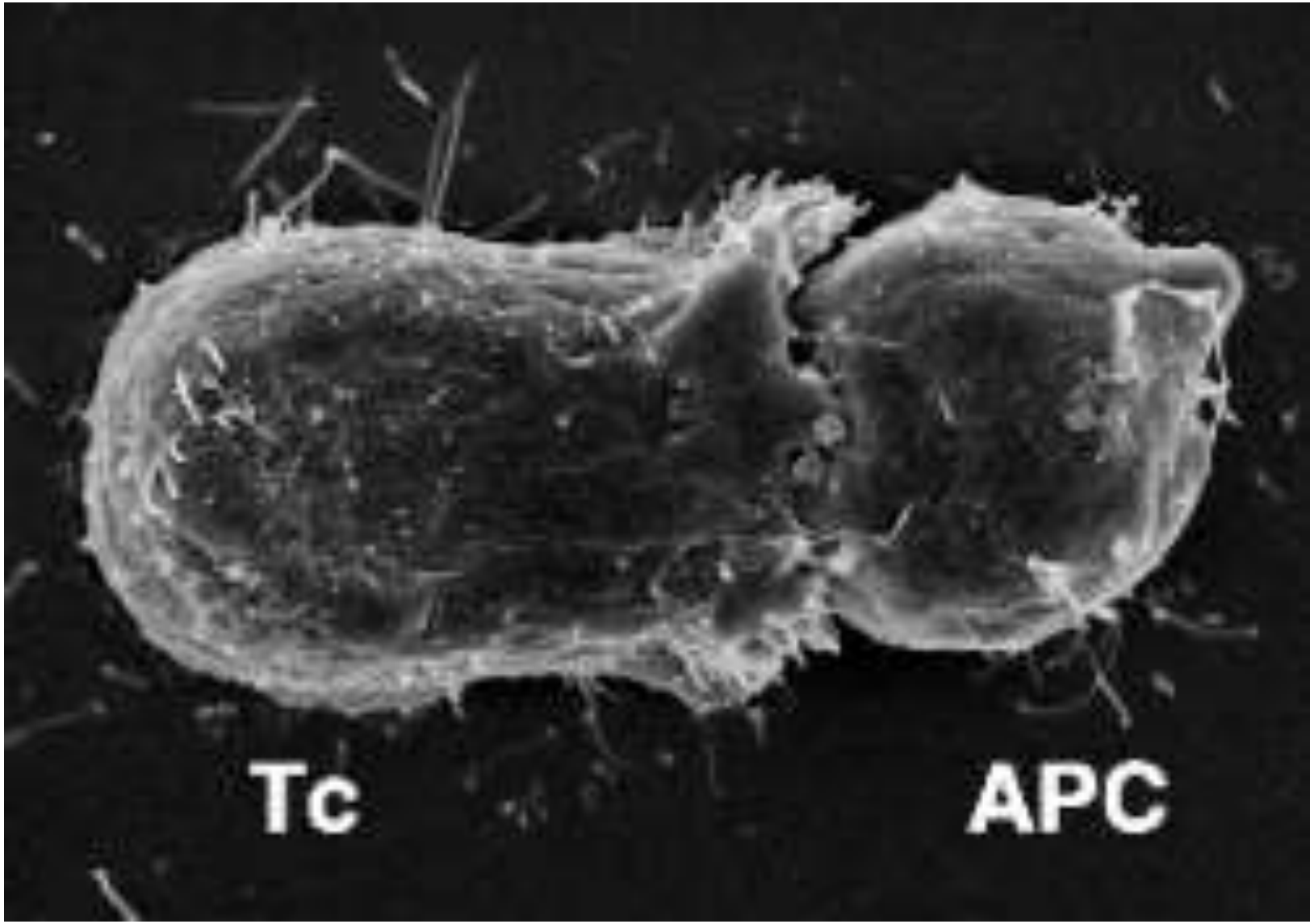
Az immunológiai szinapszis kialakulása



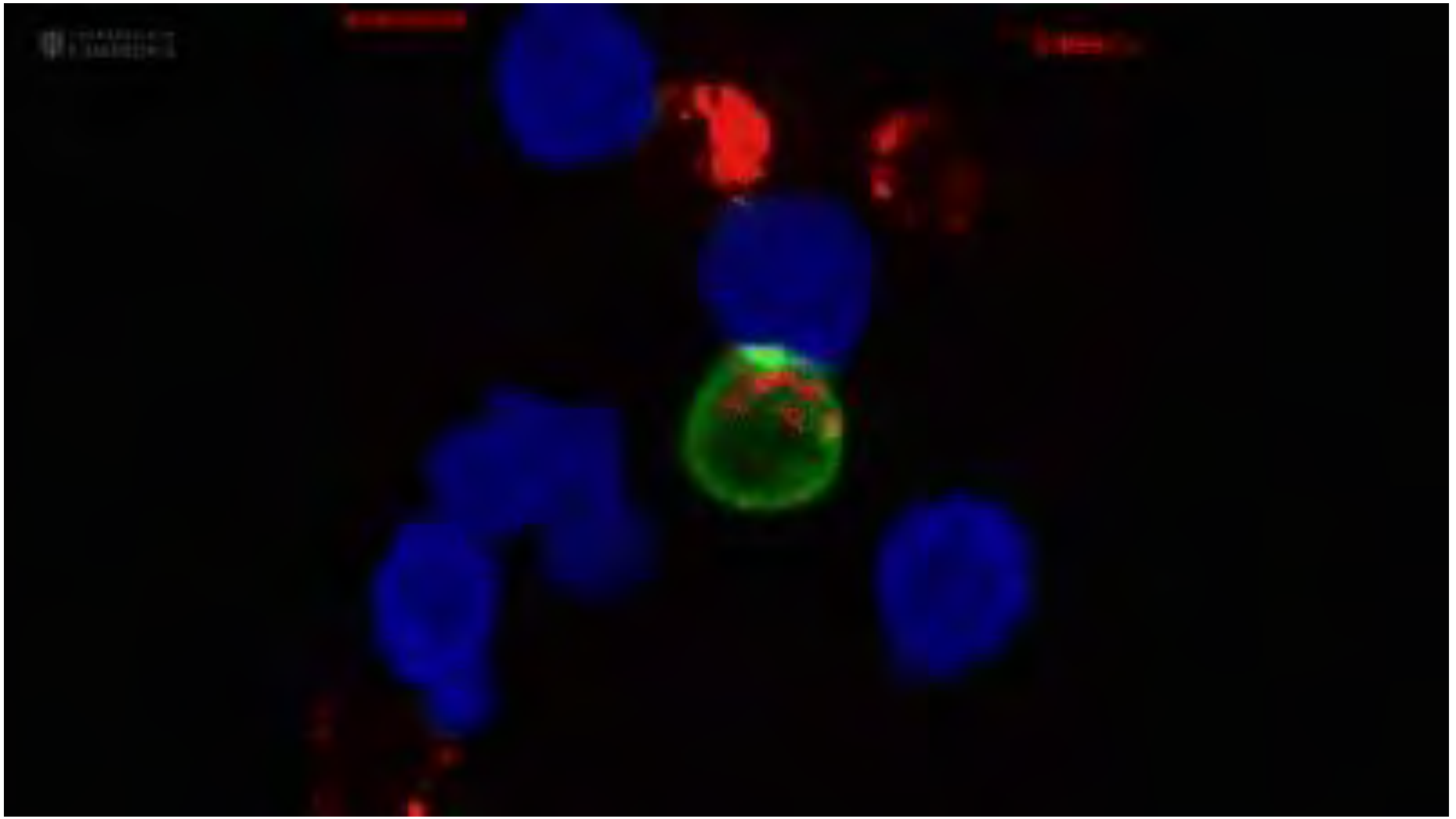
Az immunológiai szinapszis kialakulása



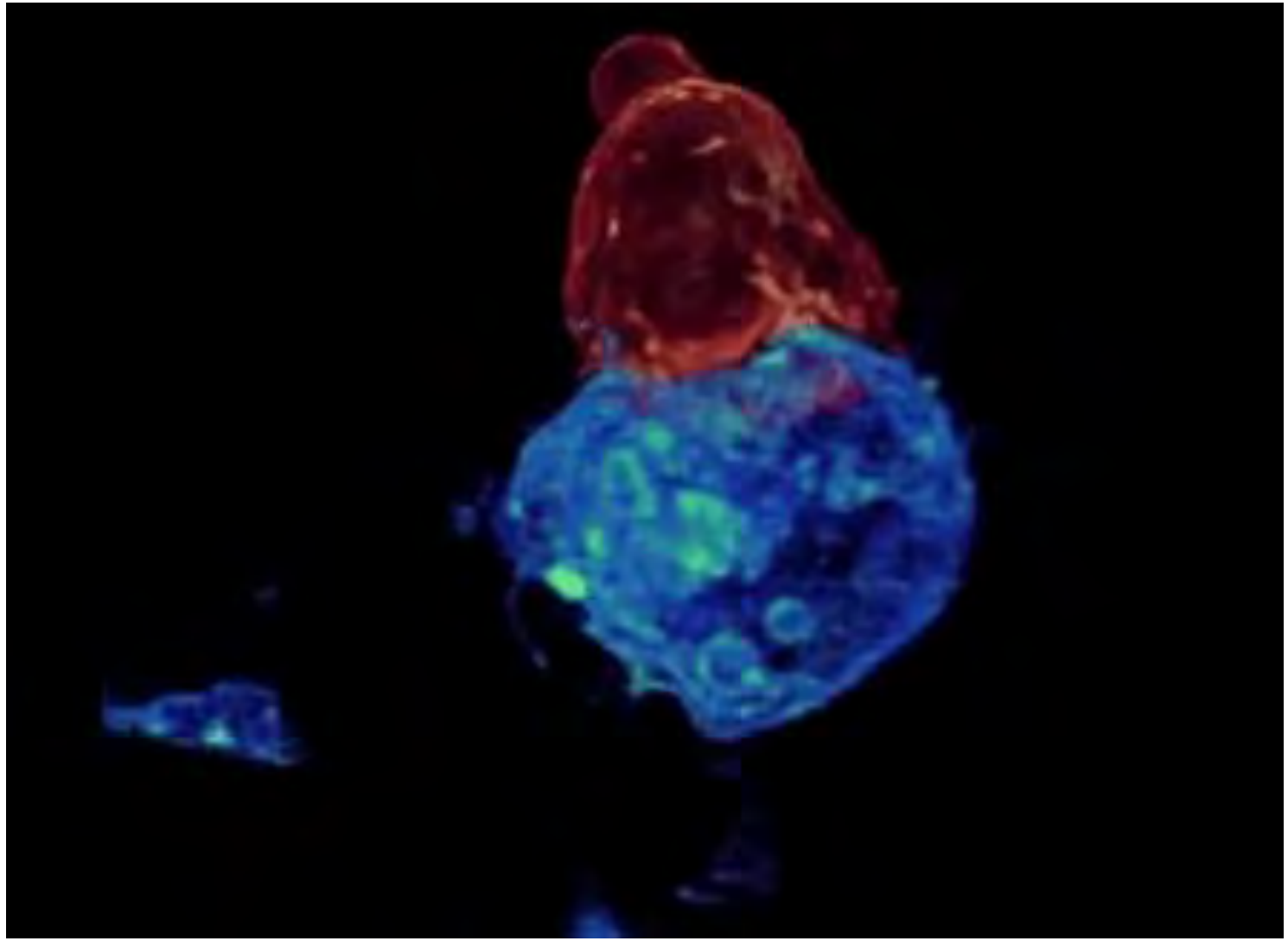
Az immunológiai szinapszis kialakulása

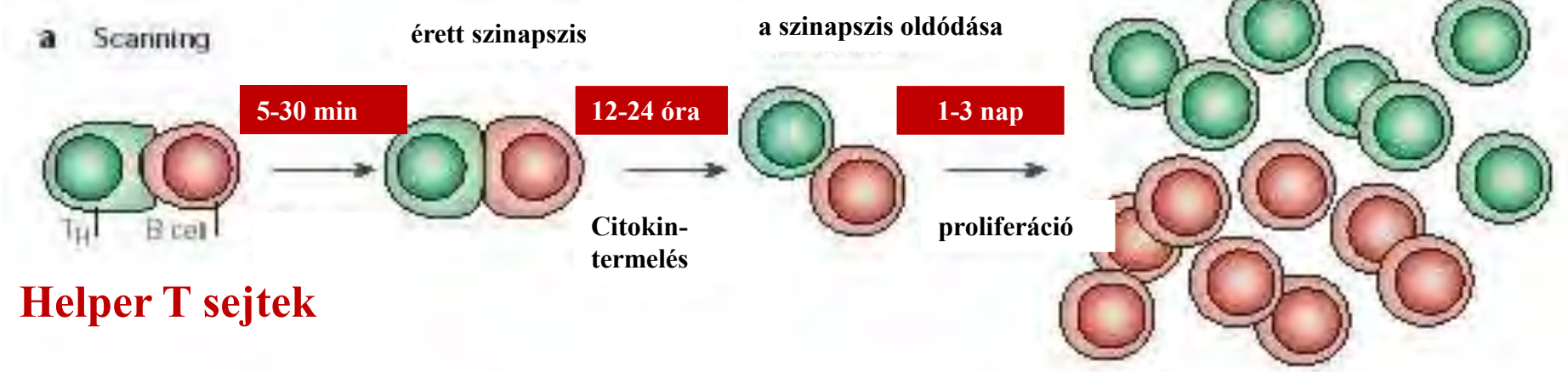


Az immunológiai szinapszis kialakulása

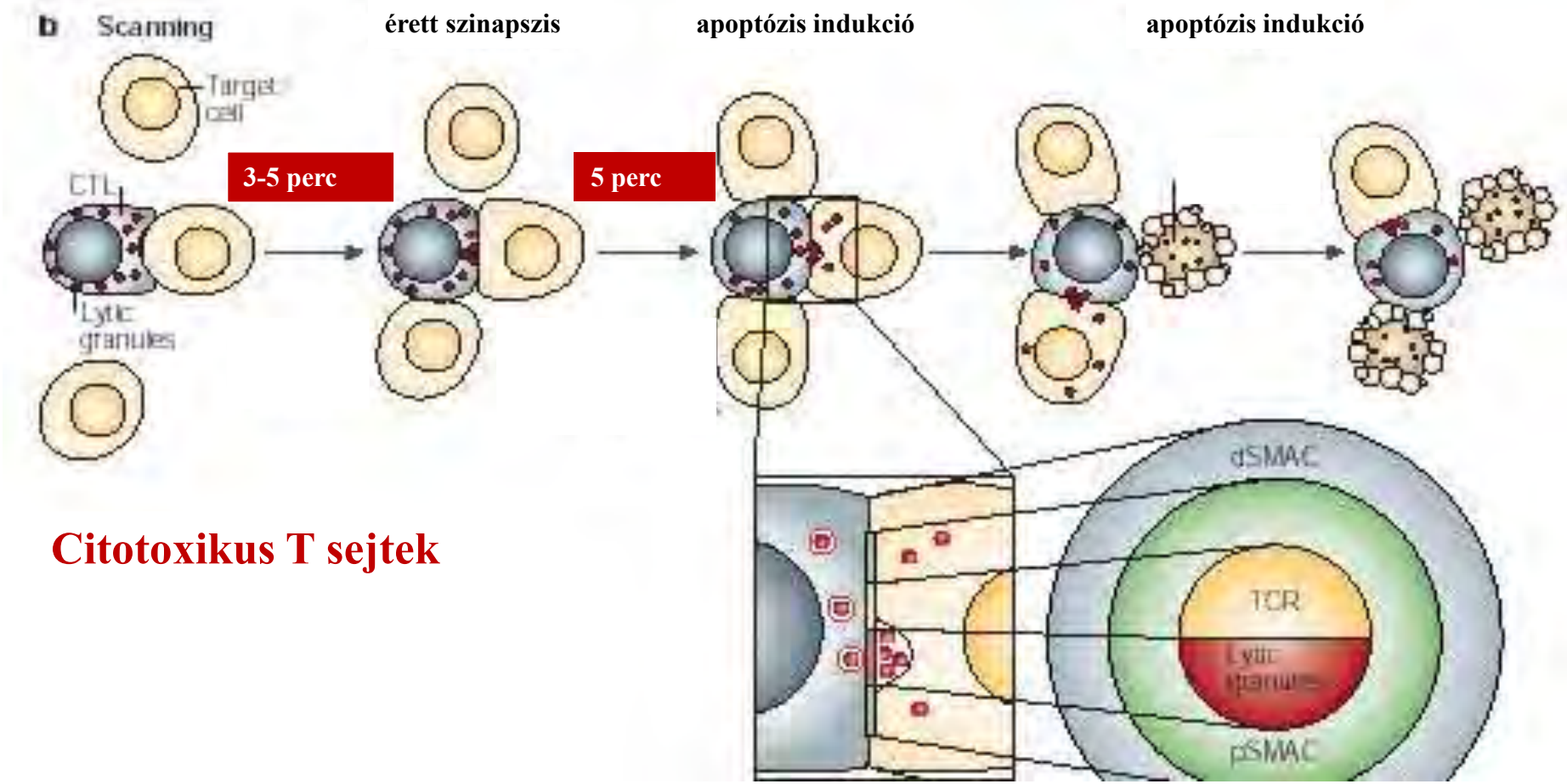


Az immunológiai szinapszis kialakulása



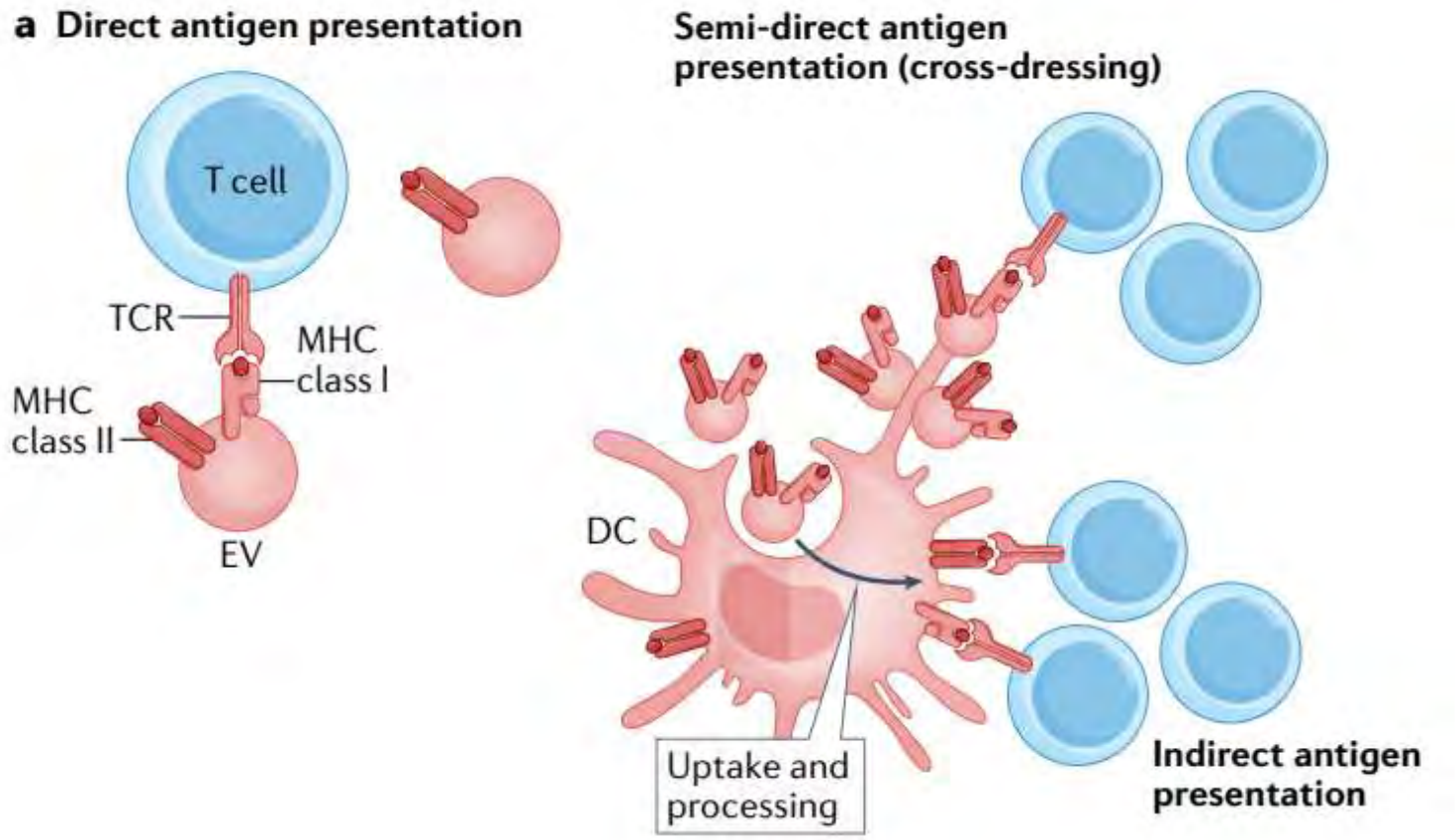


Helper T sejtek



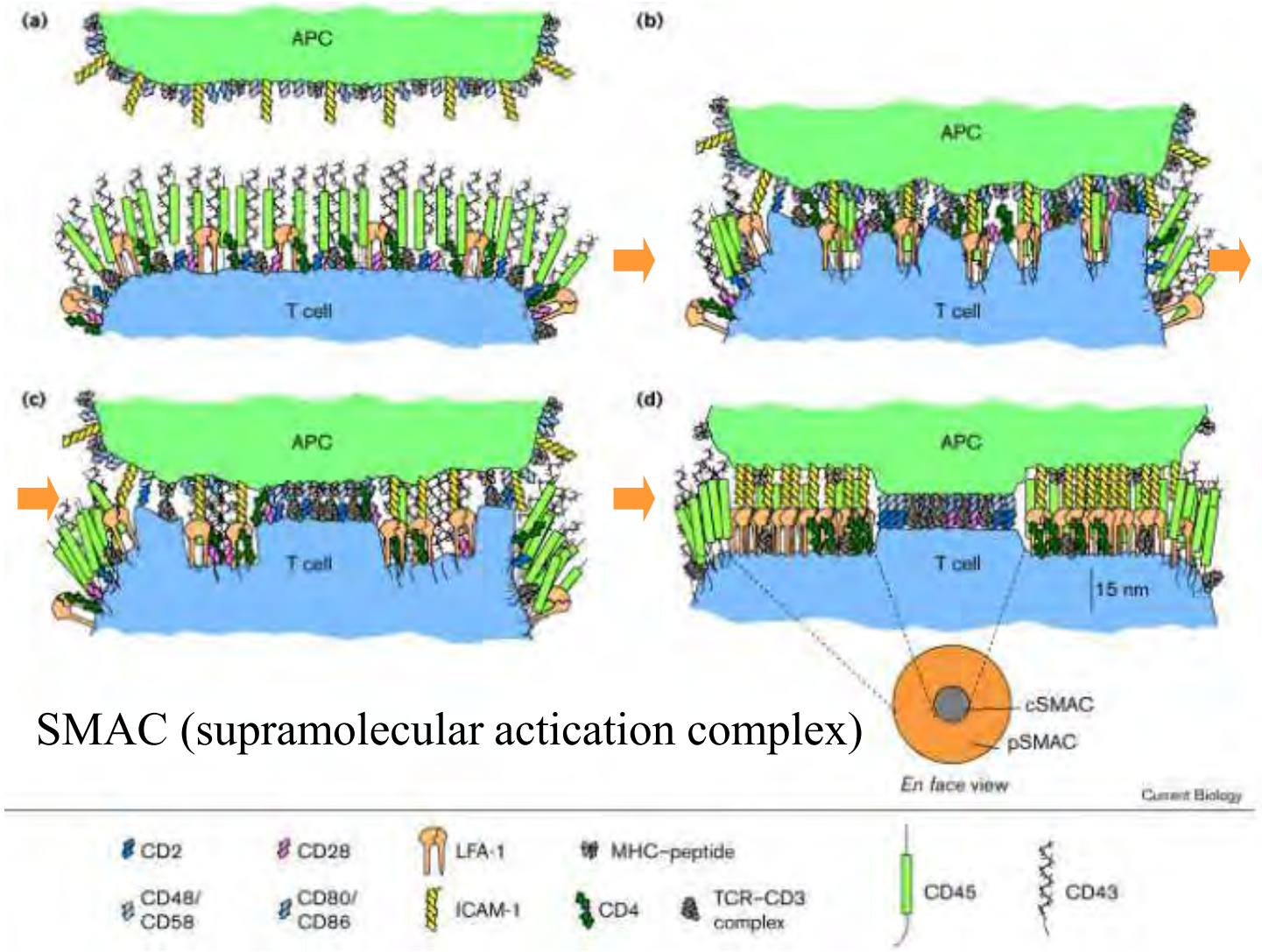
Citotoxikus T sejtek

The role of EVs in antigen presentation



Buzas E Nat Rev Immunol (2023)

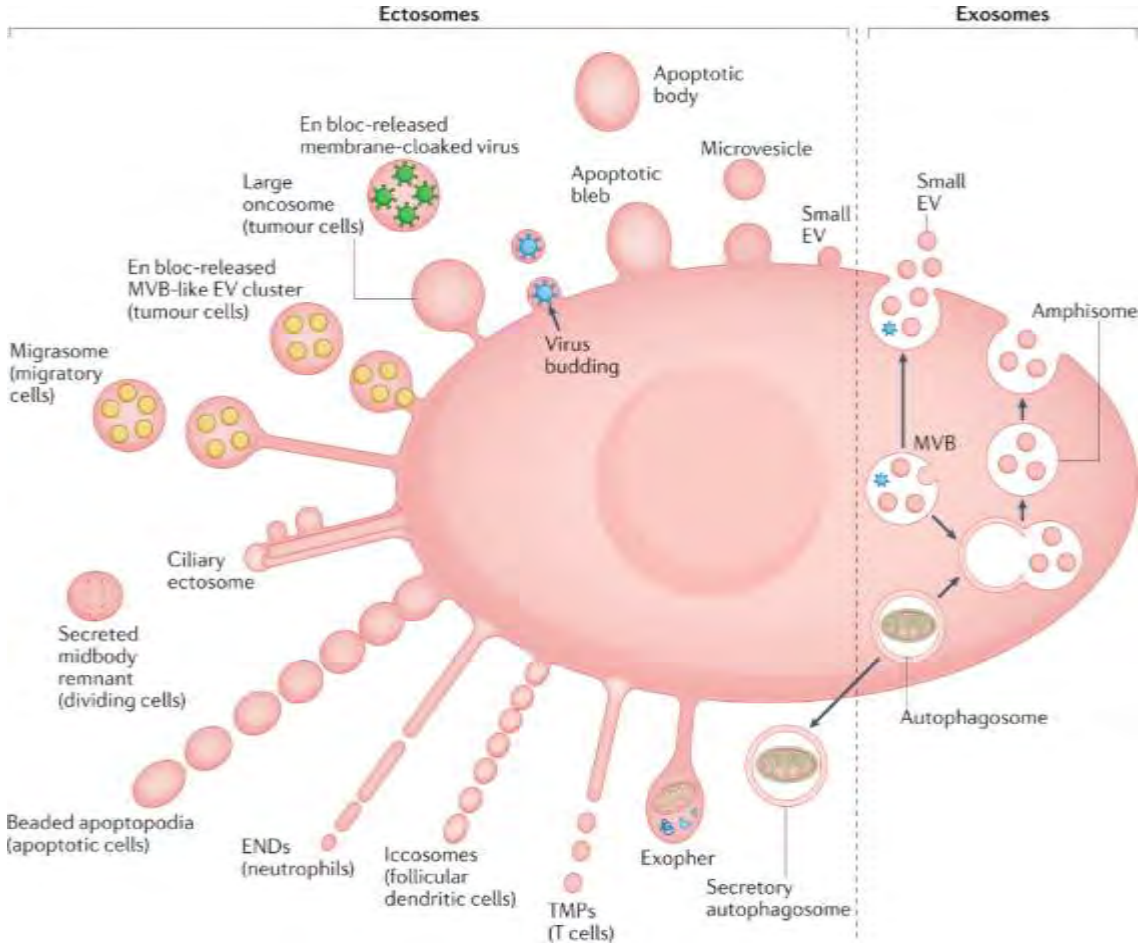
Az immunológiai szinapszis kialakulása



SMAC (supramolecular actication complex)

Delon and Germain, 2000

Extracelluláris vezikulák



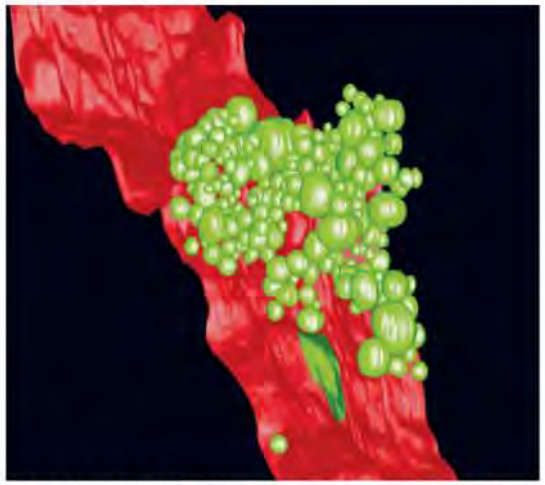
Buzas E Nat Rev Immunol (2023)

T sejt receptor ectocytosis az immunológiai szinapszisban

Immune synapse

https://doi.org/10.1038/s41577-023-00905-6

Serial killing enabled by T cell receptor ectocytosis



CD3ζ–APEX-labelled ectosomes (green) bud from the surface of a cytotoxic T lymphocyte (red) at the immune synapse with a target cell. Image courtesy of Gillian Griffiths.

The ability of a cytotoxic T lymphocyte (CTL) to kill multiple target cells requires a coordi-

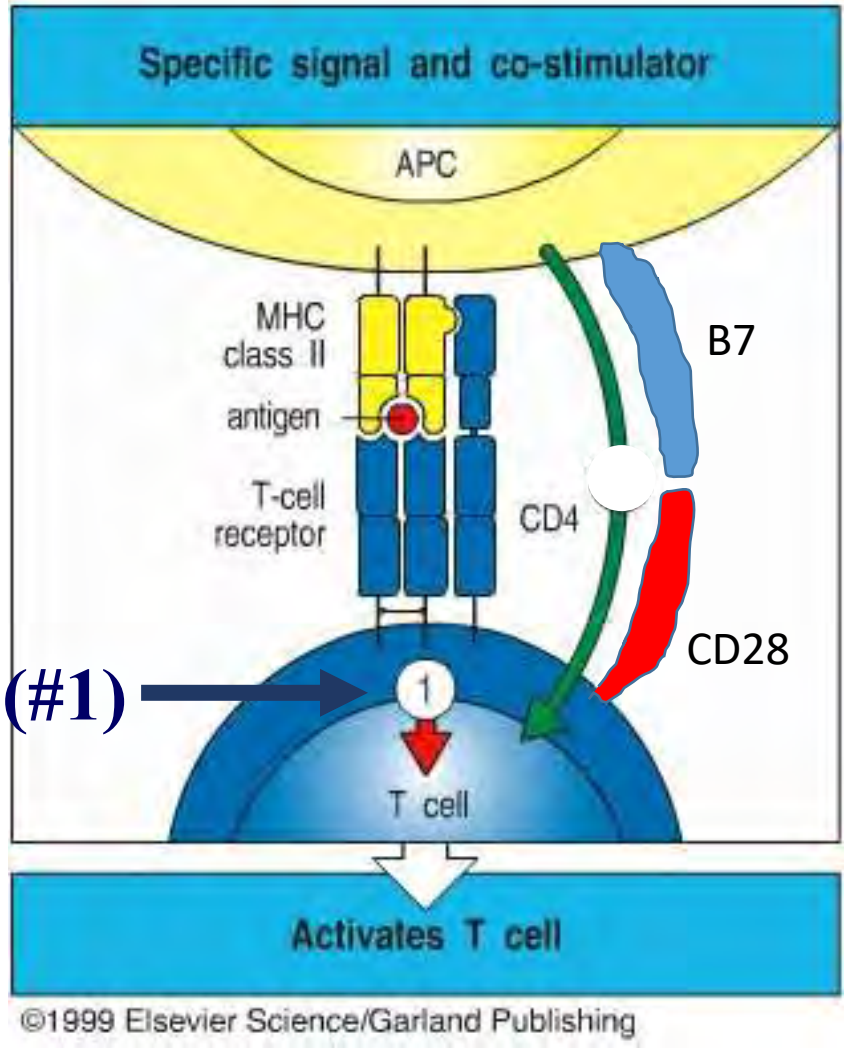
CD3ζ–APEX was found in ectosomes, suggesting that ectocytosis not endocytosis is the main mechanism of TCR down-regulation at the immune synapse.

The number of CD3ζ–APEX-labelled ectosomes increased with time and this correlated with decreased cell membrane-associated CD3ζ–APEX. As the ectosomes budded from the CTL surface, they created an area of localized cell separation that disrupted the close membrane contact with the target cell. Both ectocytosis and CTL detachment increased with TCR signal strength (as shown using peptides of different TCR affinity), which suggests that this mechanism of synapse disruption is activated by TCR signalling.

In keeping with this, the membrane lipid diacylglycerol (DAG), which accumulates at the immune synapse downstream of TCR signalling-induced phospholipase activa-

Nat Rev Immunol. 2023 Aug;23(8):475.

A T sejt aktivációhoz legalább két szignál kell (#1és #2)



szignál (#1)

Kostimulációs szignál (#2)

T sejt anergia

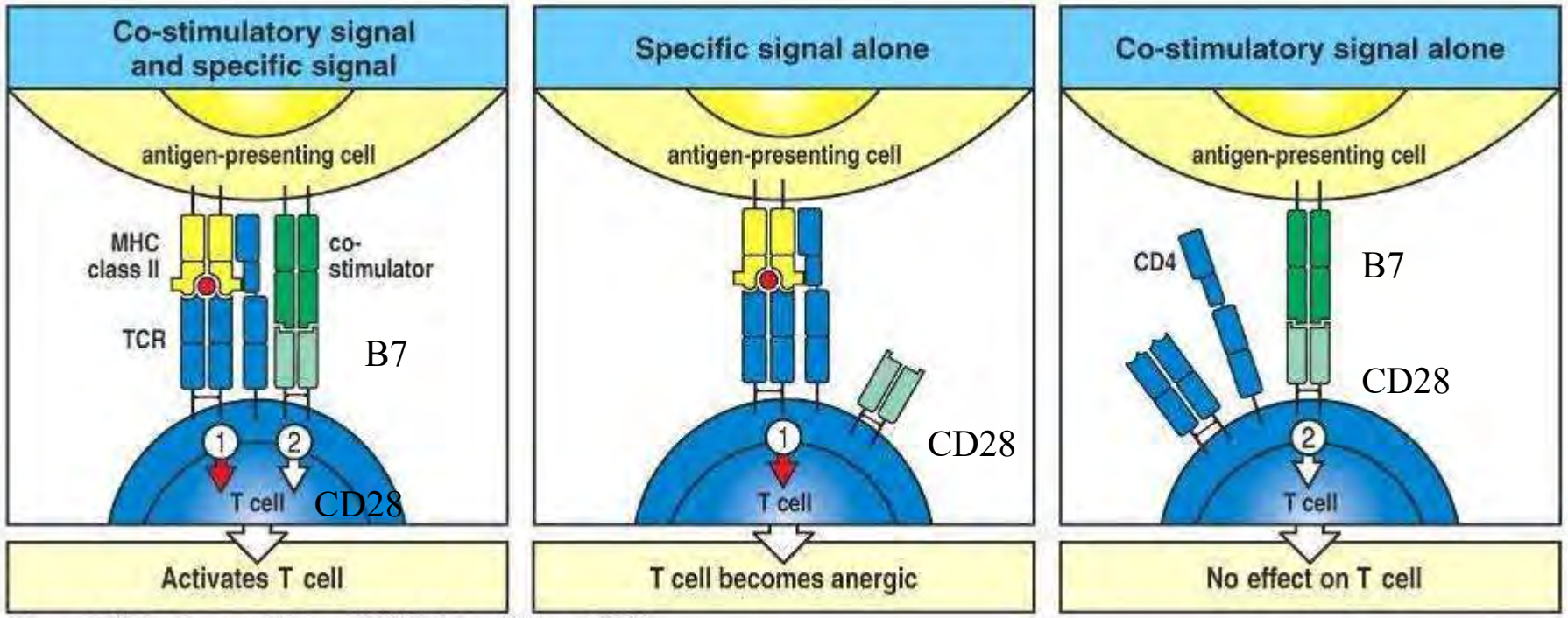
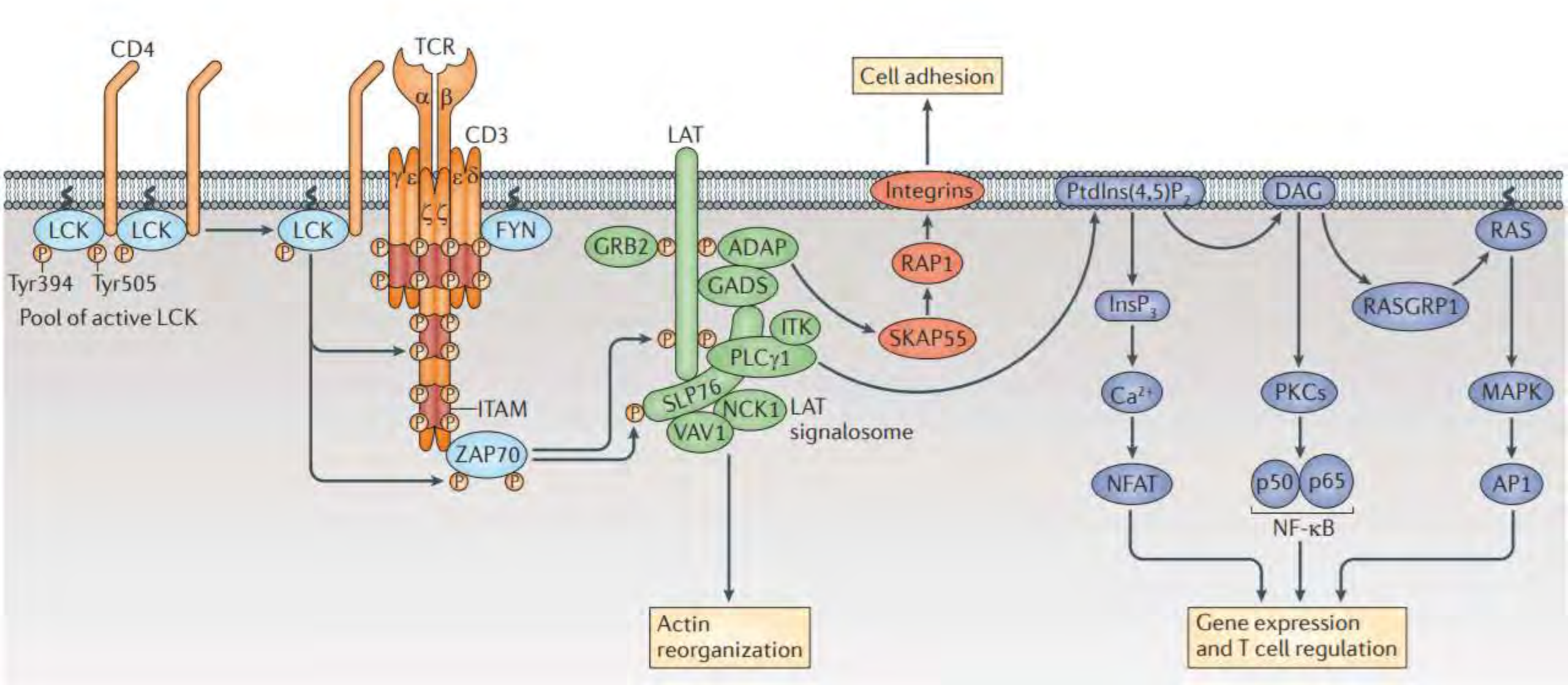
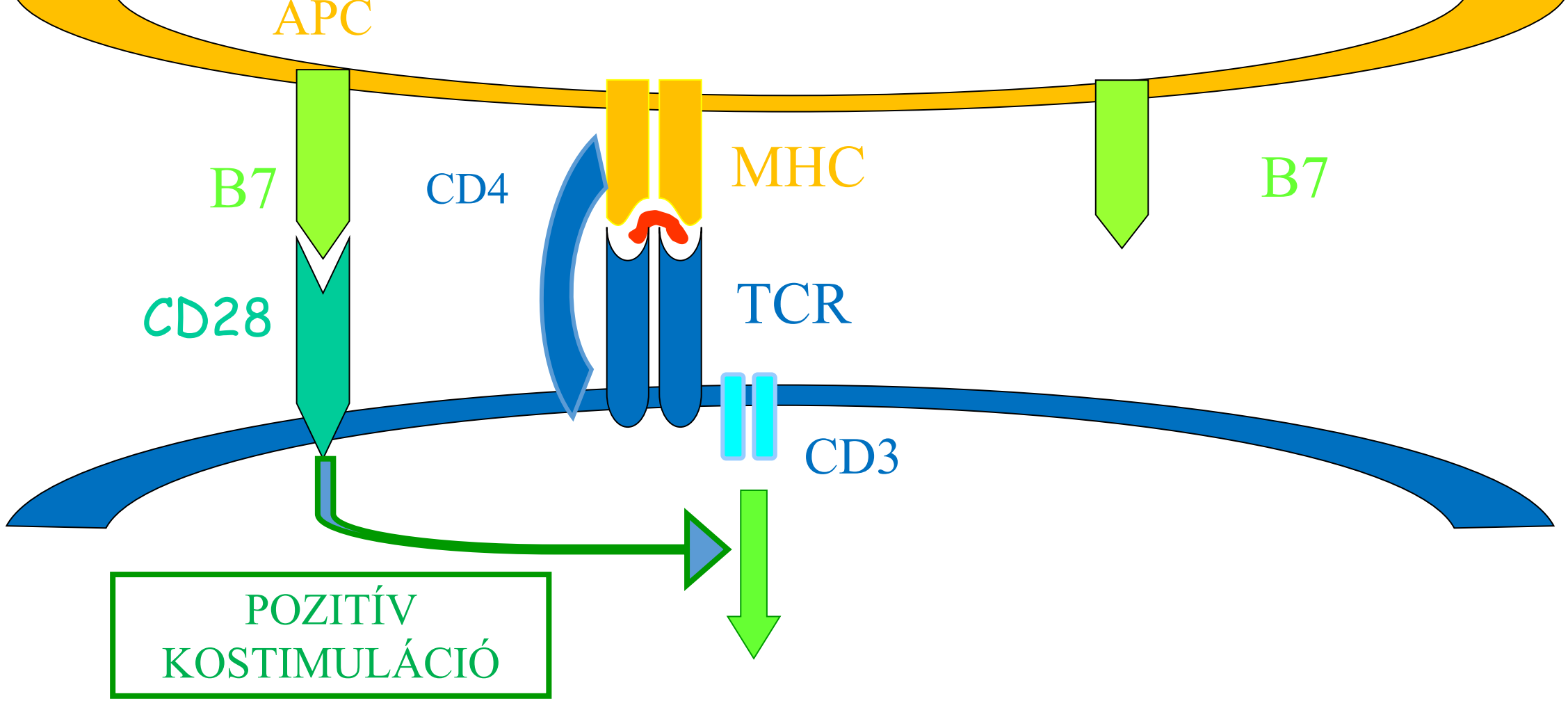


Figure 6-19 The Immune System, 2/e (© Garland Science 2005)

kostimulációs szignál hiányában

A TCR-en keresztüli jelátvitel

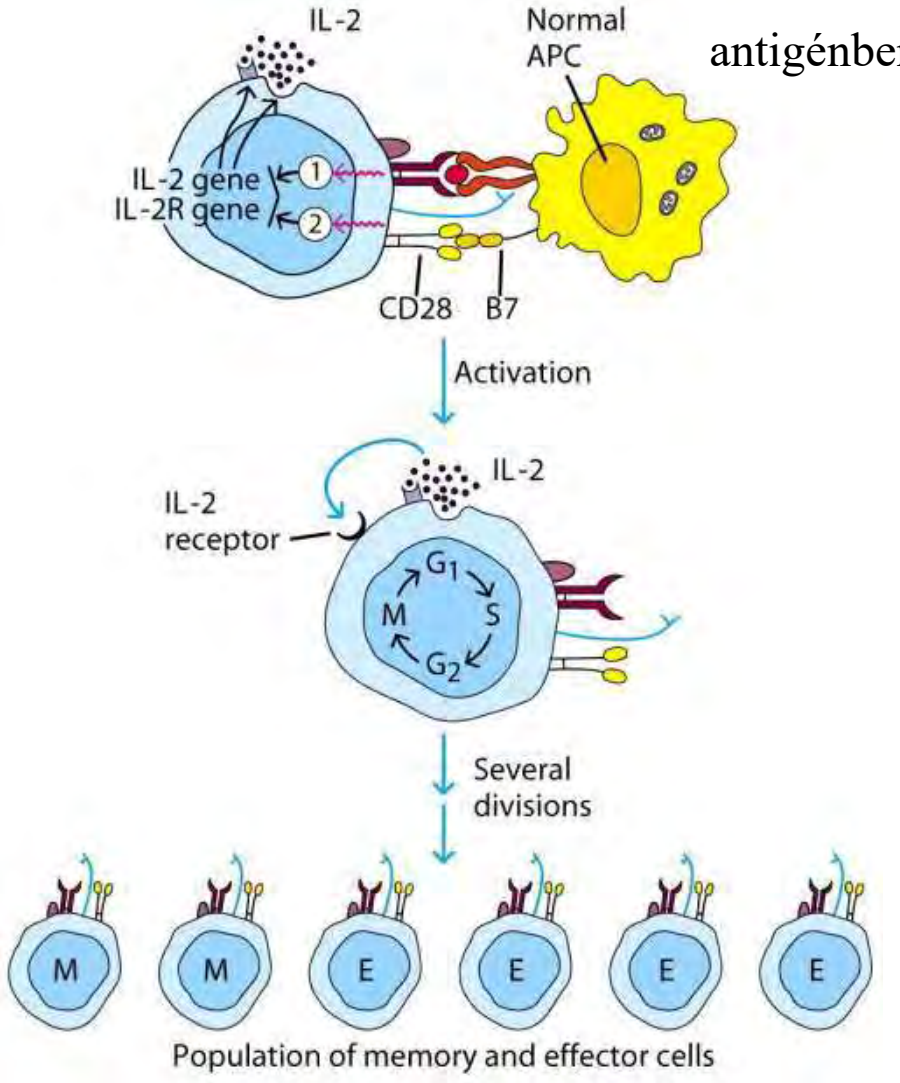



APC
B7
CD4
MHC
B7
CD28
TCR
CD3
POZITÍV
KOSTIMULÁCIÓ

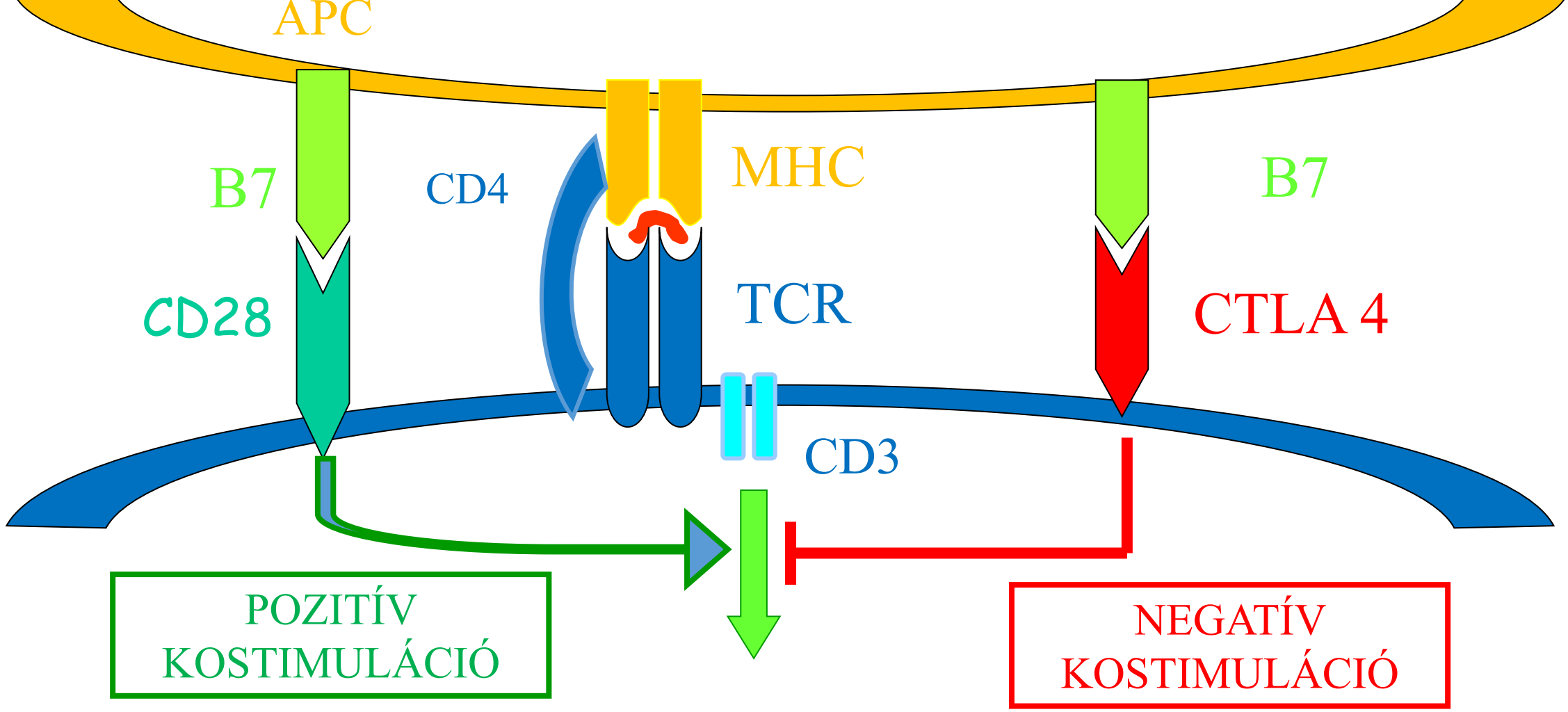

sejtmag
IL-2 mRNS

T sejt

Az IL-2 autokrin T sejt növekedési faktor

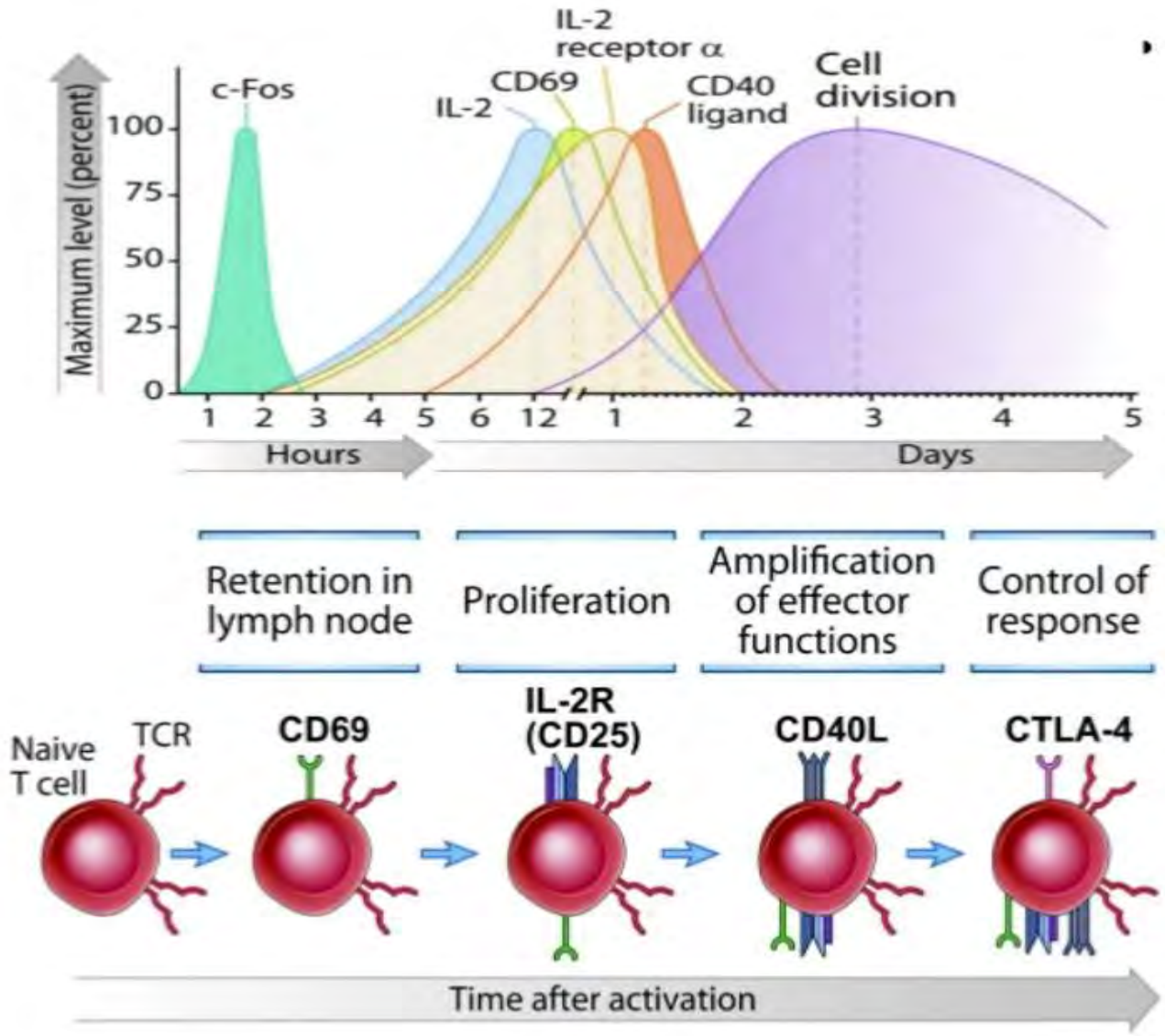


antigénbemutató sejt


APC
B7
CD4
MHC
B7
CD28
TCR
CTLA 4
CD3
POZITÍV
KOSTIMULÁCIÓ
NEGATÍV
KOSTIMULÁCIÓ


T sejt
sejtmag
IL-2 mRNS

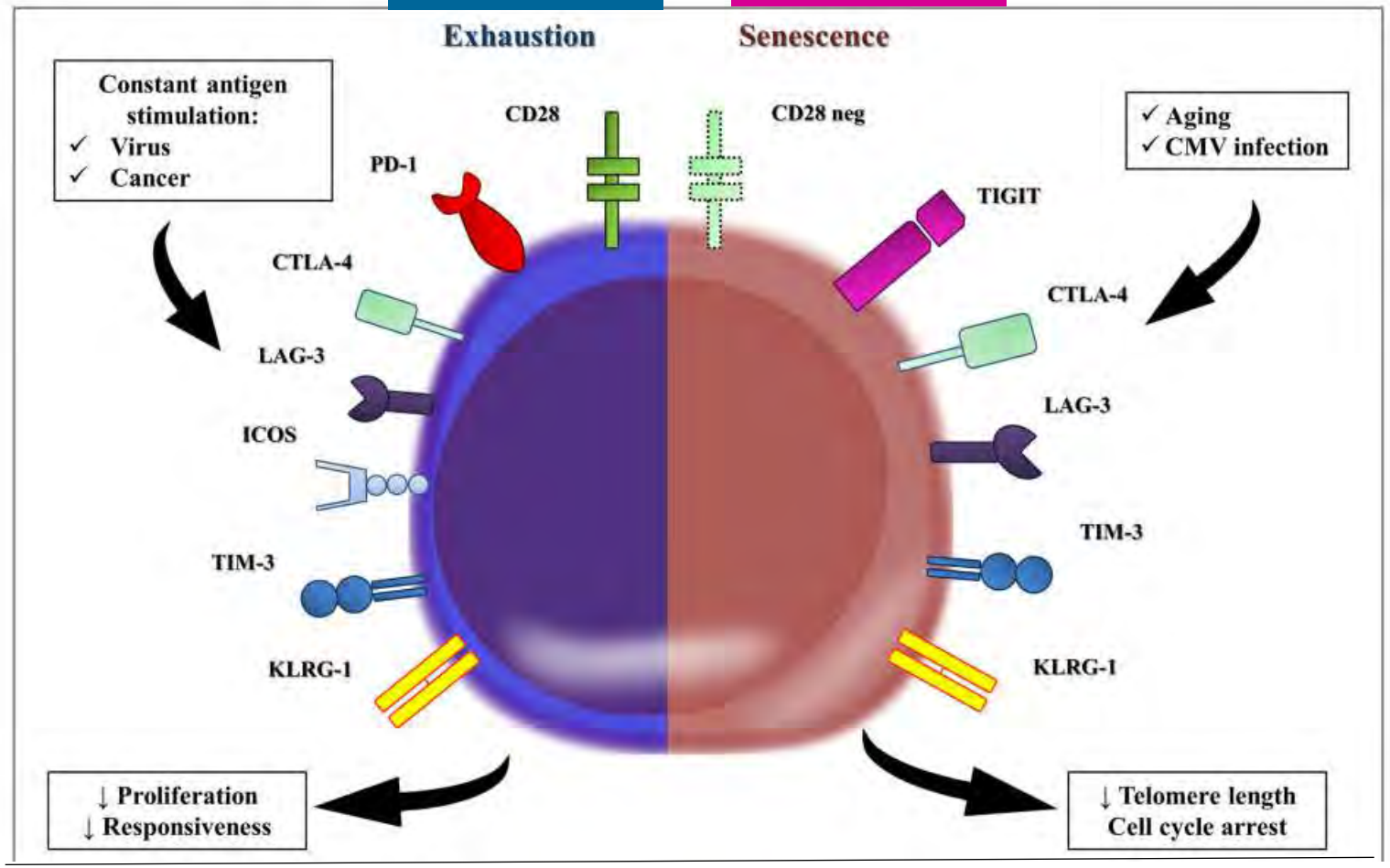
A T sejt aktiváció során bekövetkező génexpressziós változások



A T limfociták kimerülése és öregedése

Kimerült

Szeneszcens



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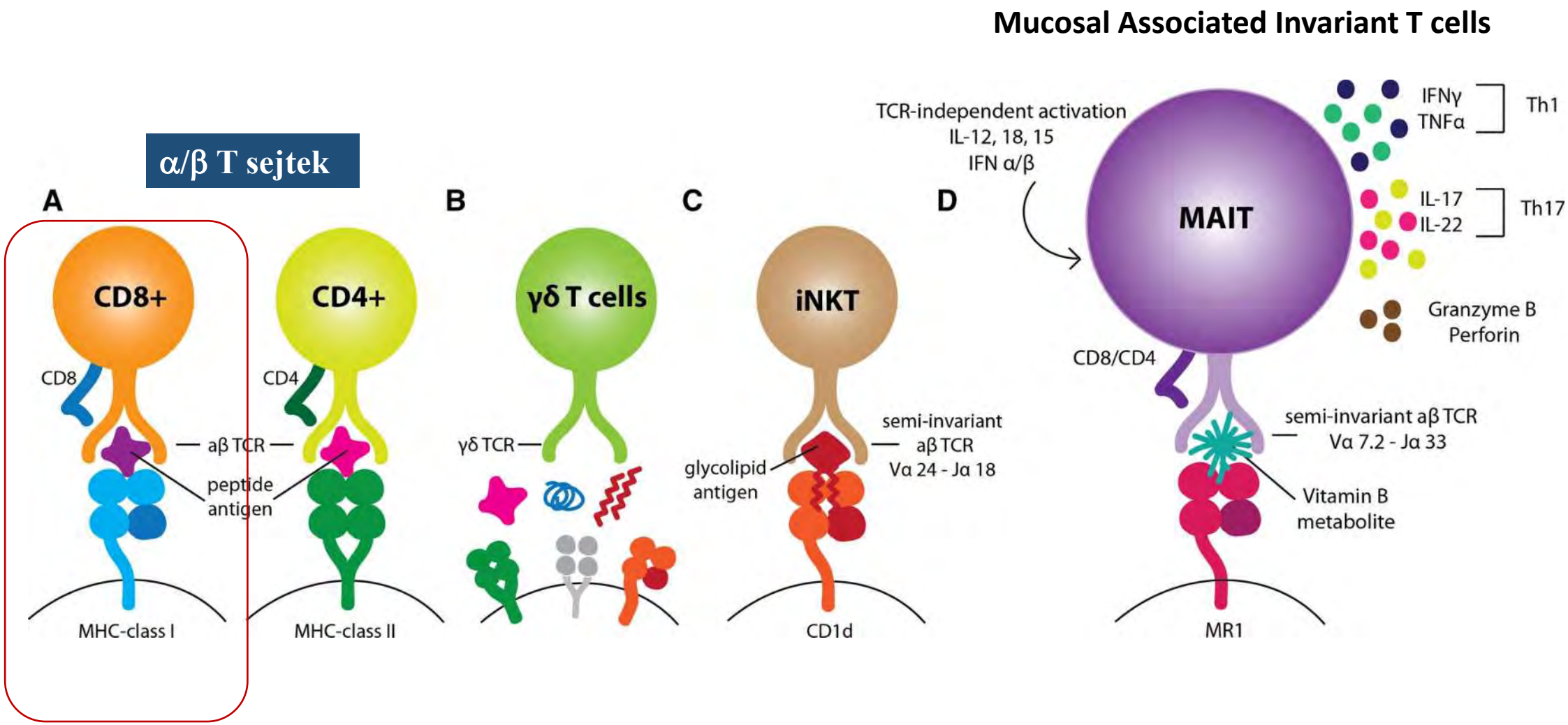
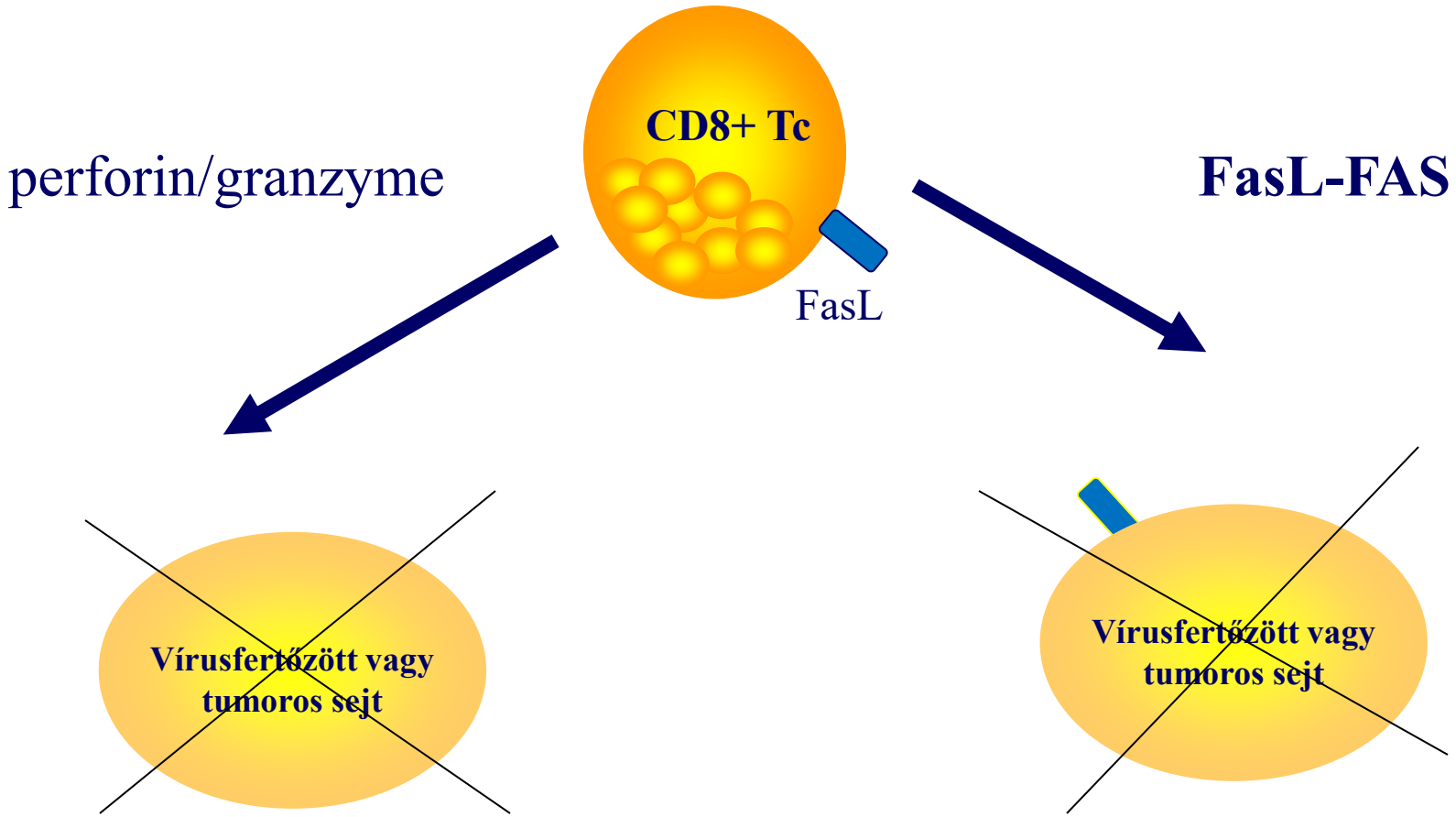
A T sejtek típusai

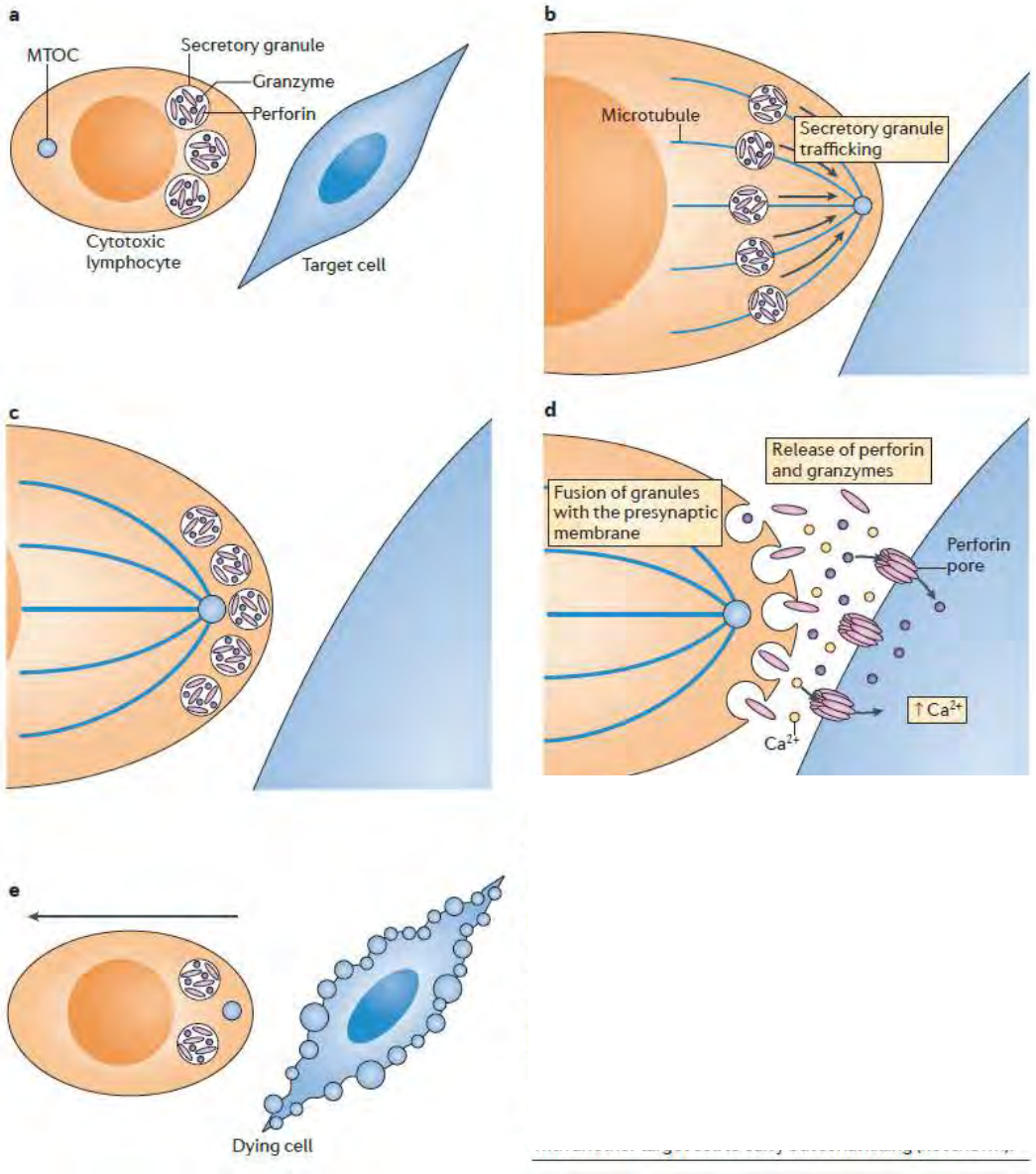


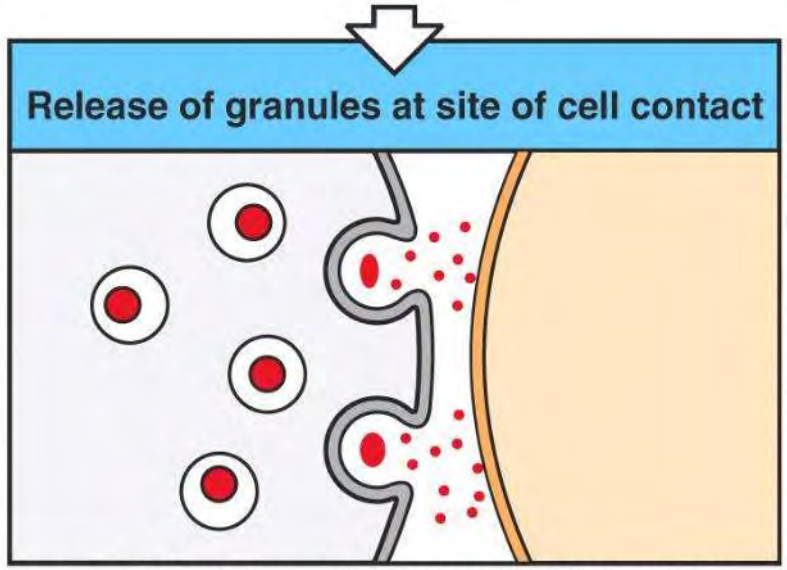
FEBS Letters 593 (2019) 1627–1640

CD8+ citotoxikus T sejt



Citotoxikus T sejtek





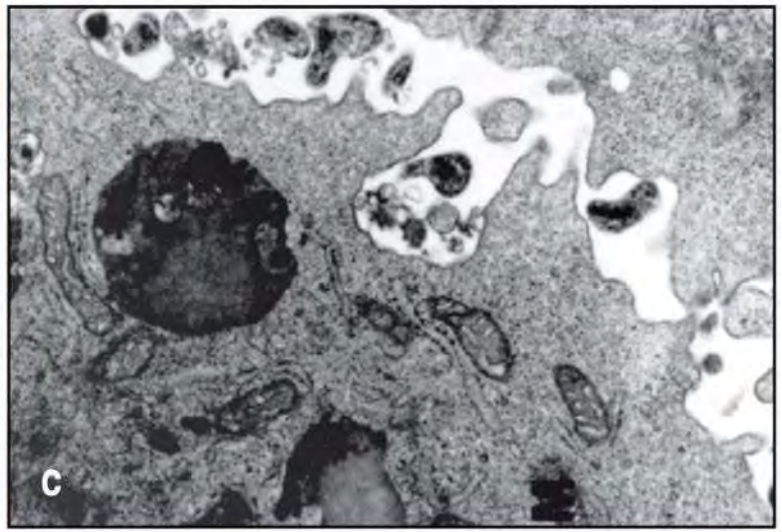
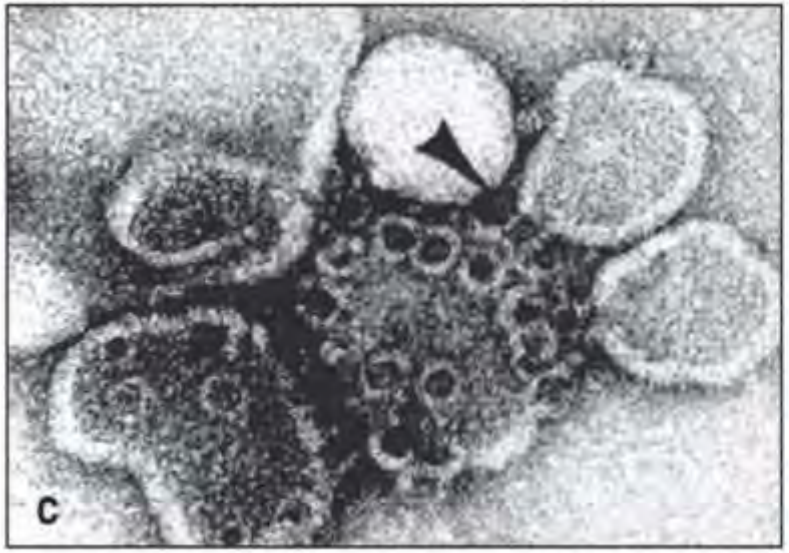


Figure 8-29 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)



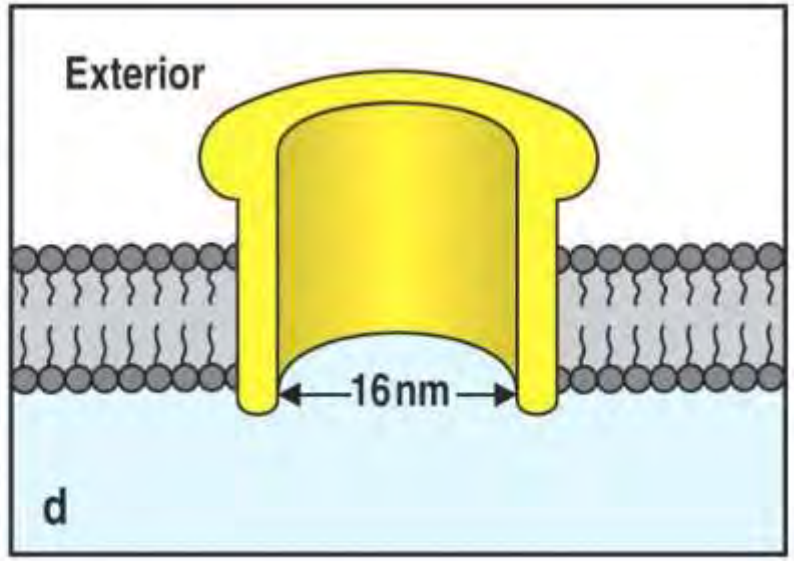
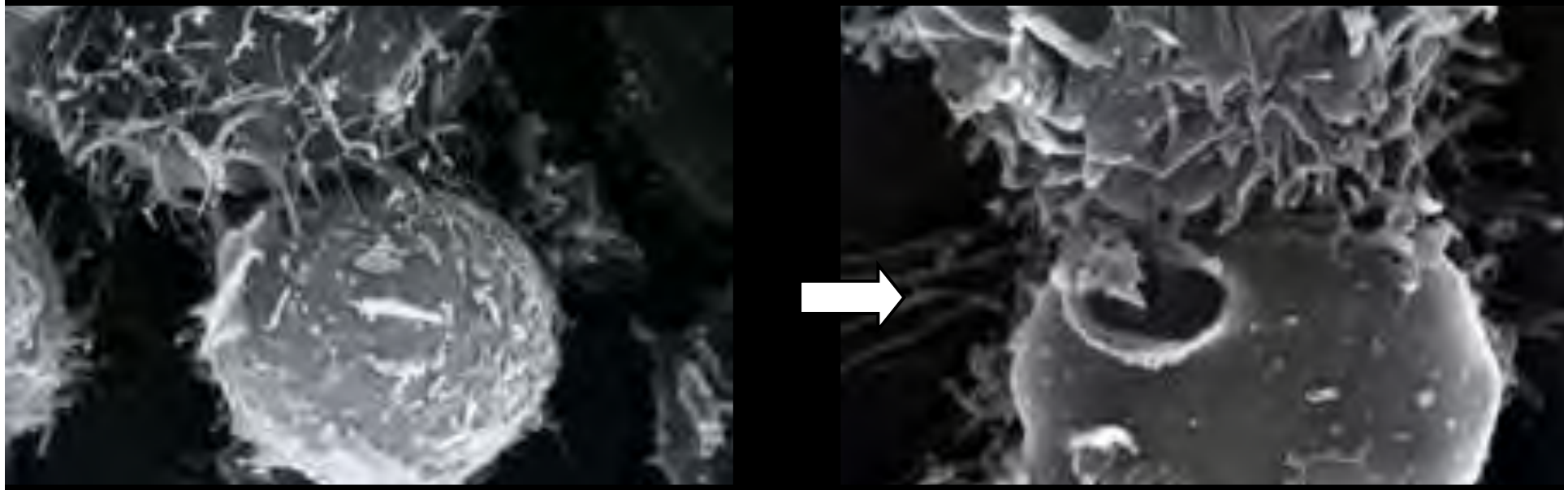
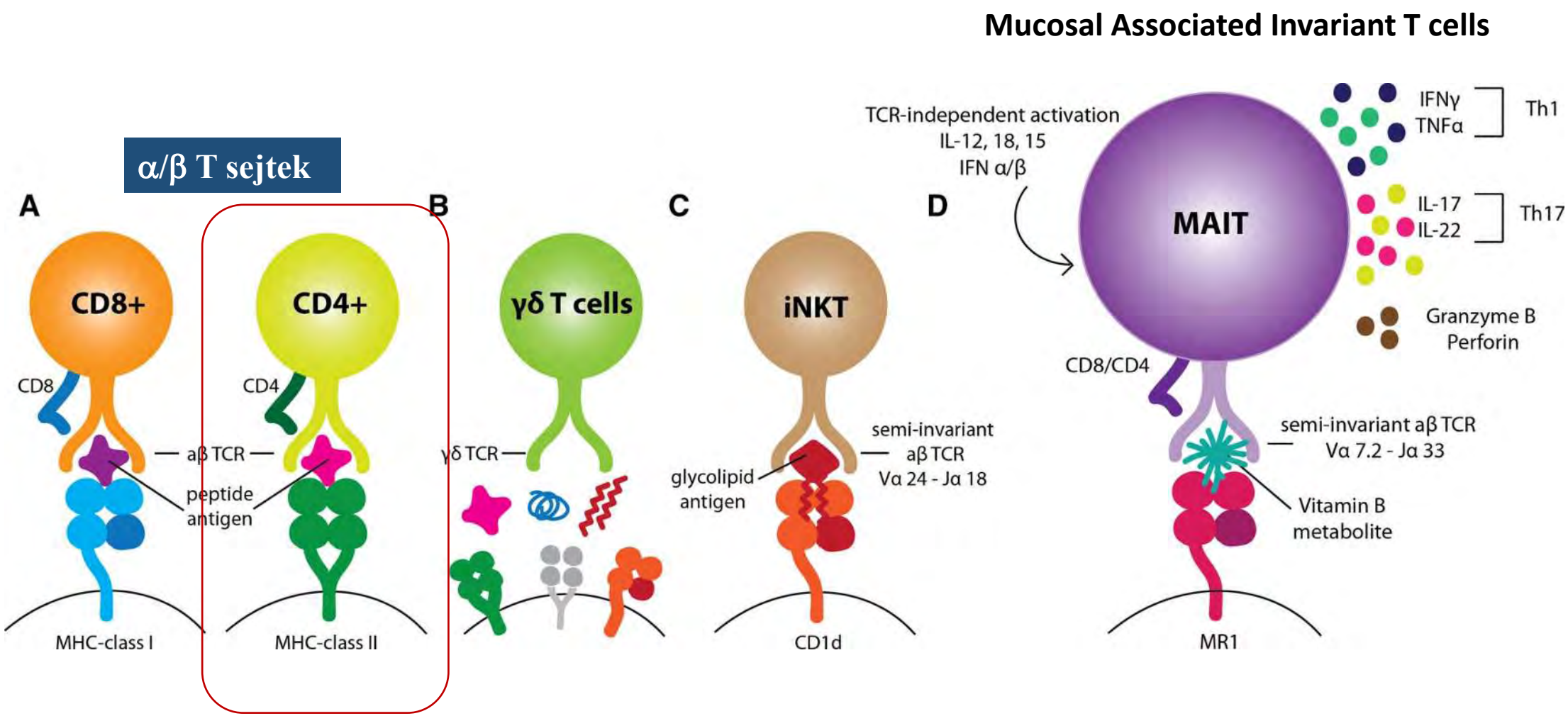


Figure 8-36 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)



A T sejtek típusai



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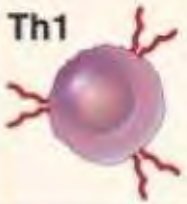
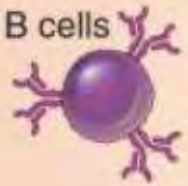
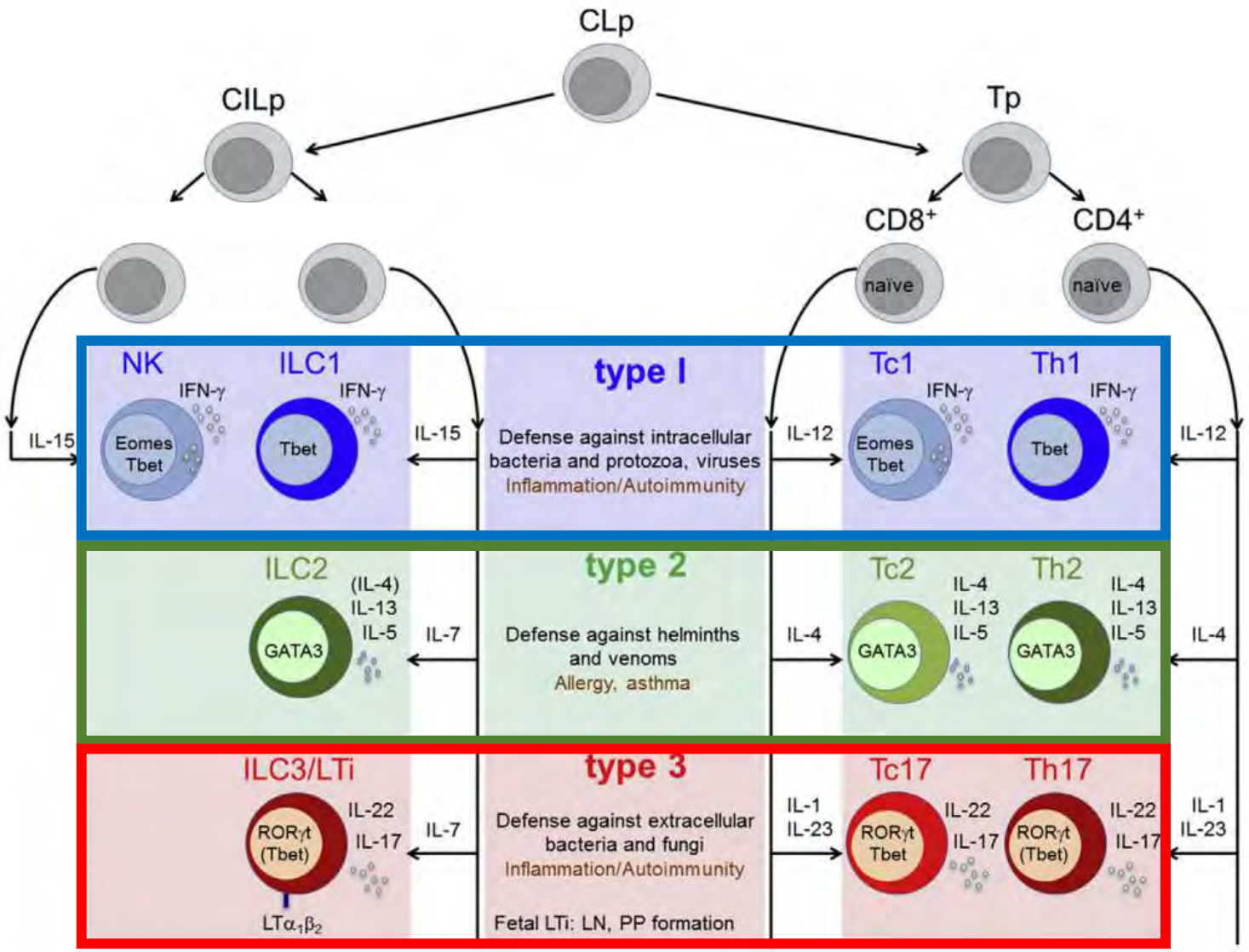
A CD4+ helper T sejtek fő típusai

Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1 	IFN-γ	Macrophages 	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2 	IL-4 IL-5 IL-13	Eosinophils 	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17 	IL-17 IL-22	Neutrophils 	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation
Tfh 	IL-21 (and IFN-γ or IL-4)	B cells 	Antibody production	Extracellular pathogens	Autoimmunity (autoantibodies)

Abbas AK, et al. Cellular and Molecular Immunology 9th edition

A háromféle immunitás



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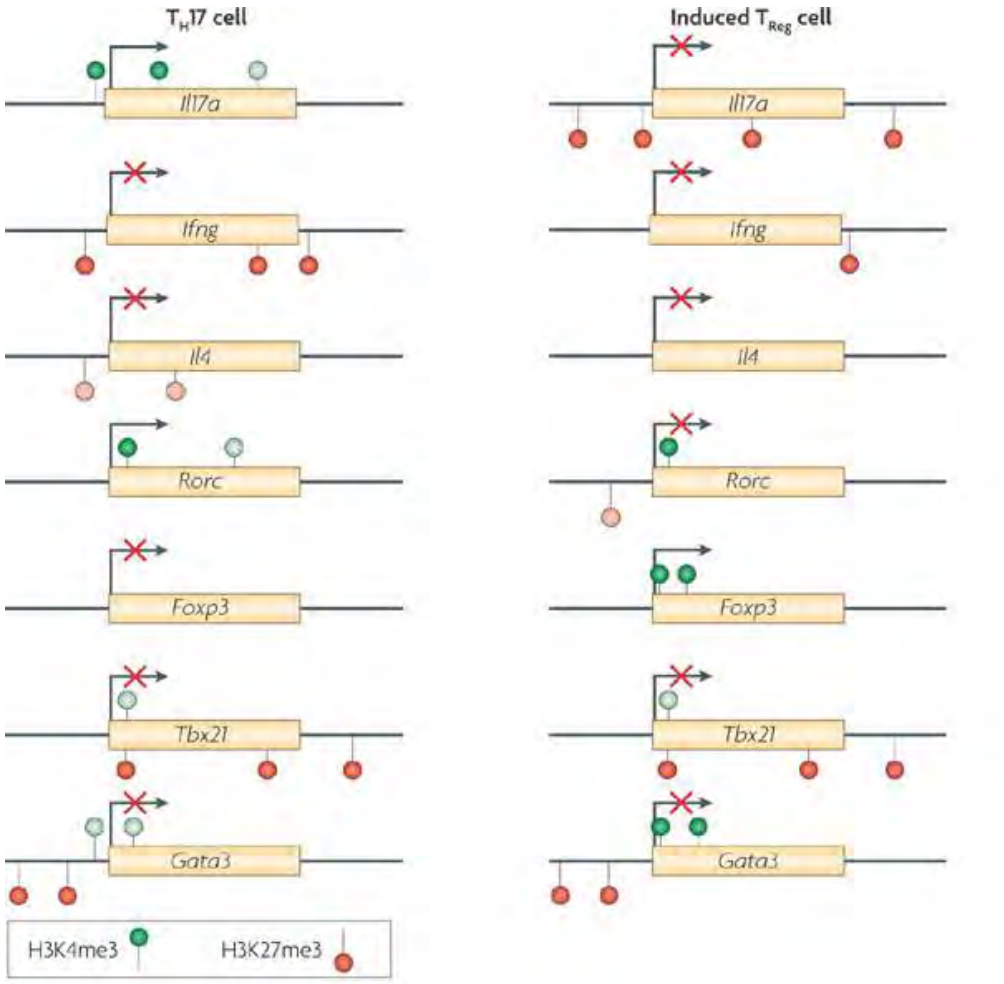
Epigenetikai változások felelősek a T sejt fenotípusok kialakításáért



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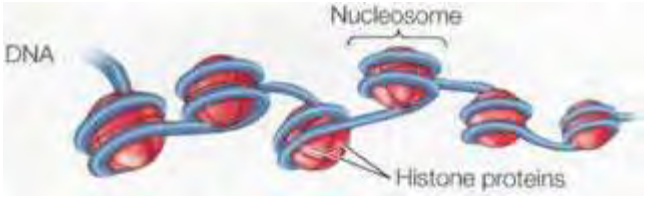
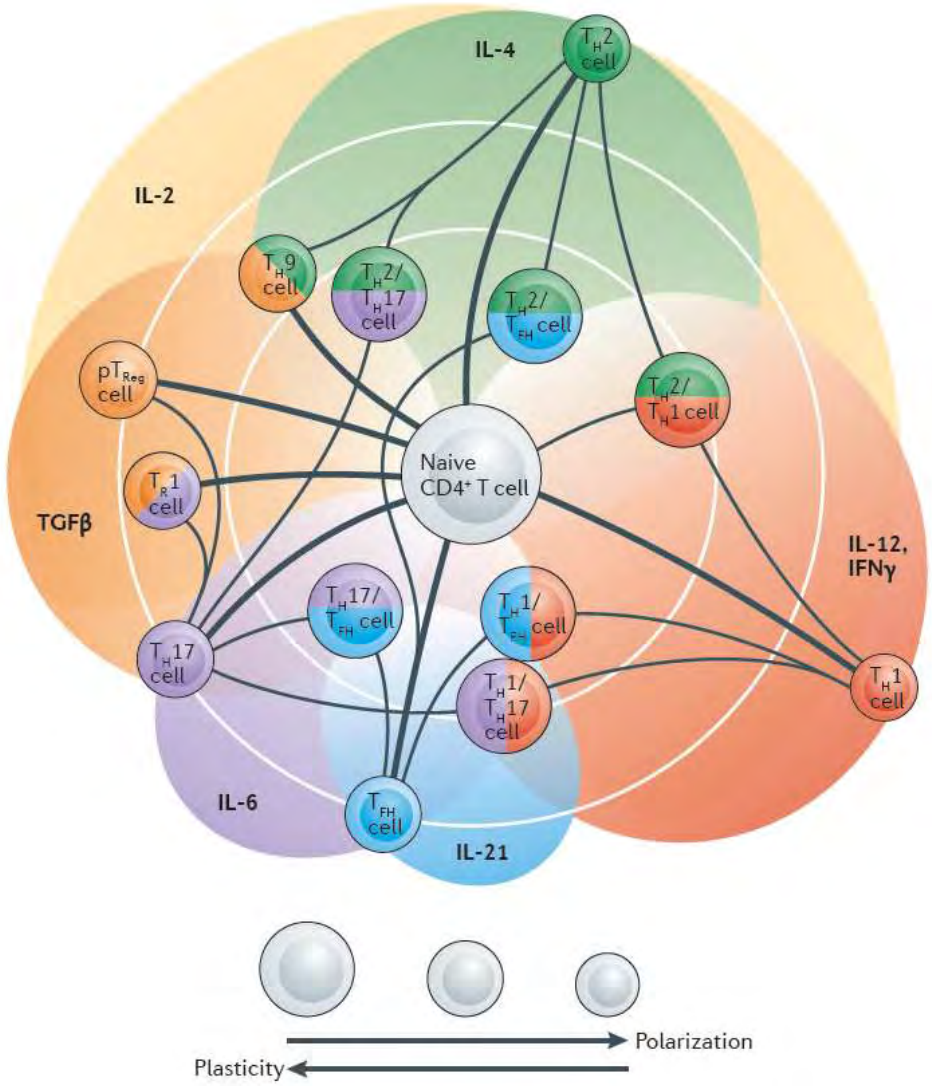
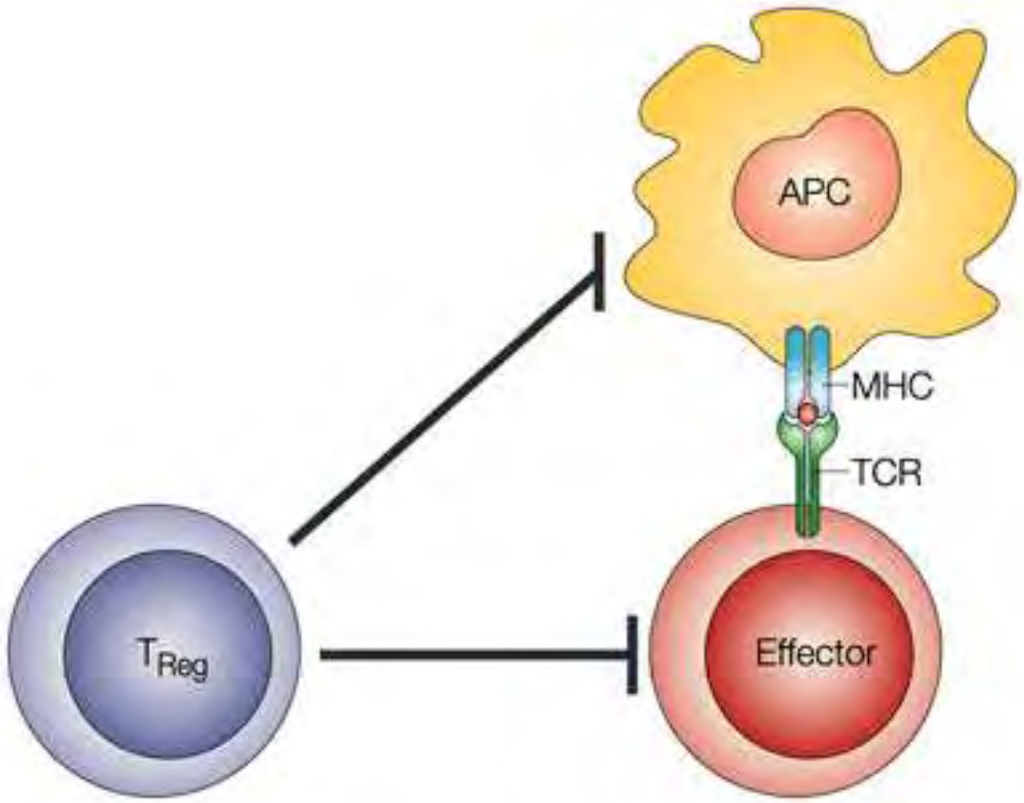


T sejt plaszticitás

Fenotípusos egymásba alakulás képessége



Reguláló T sejtek



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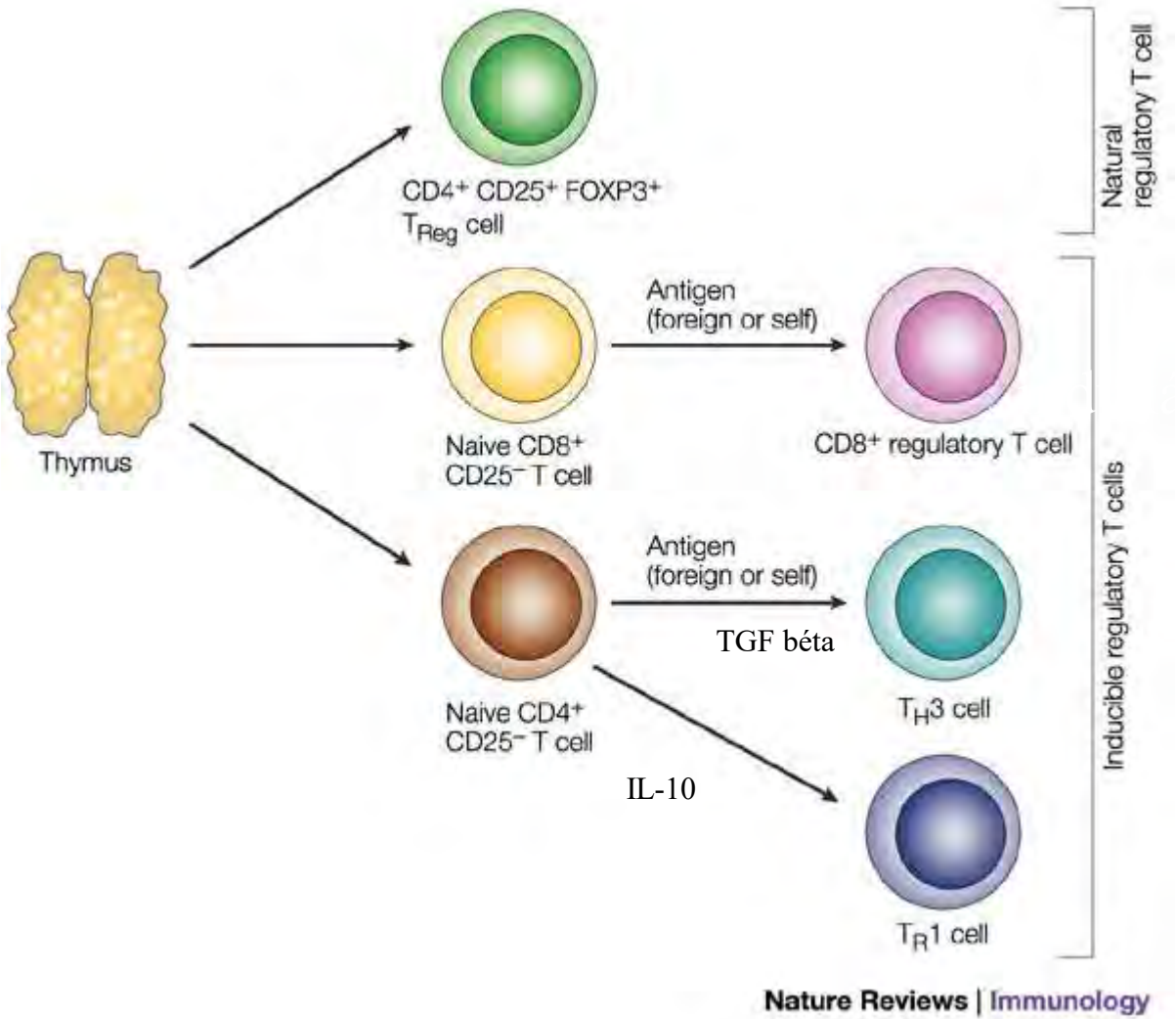

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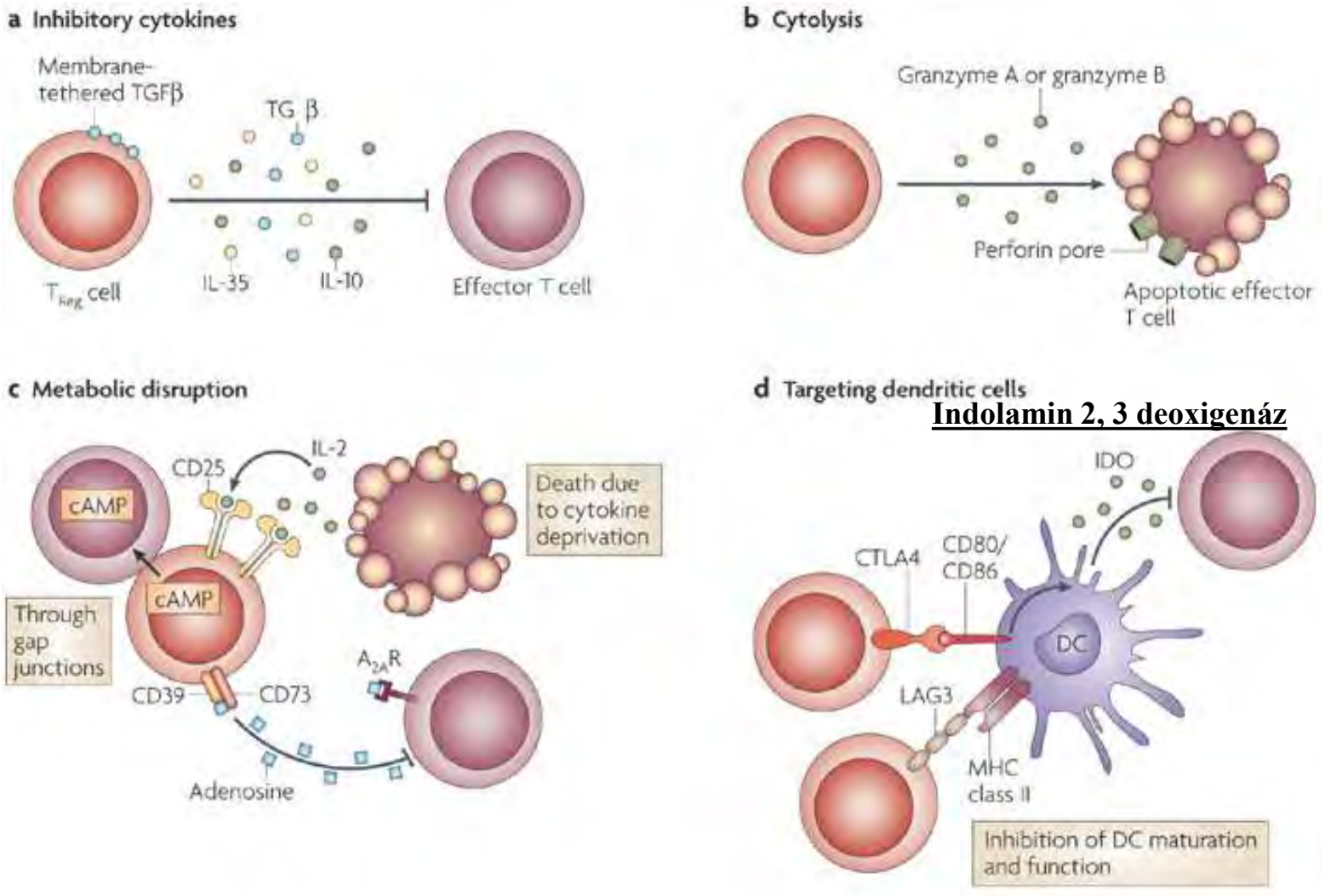

Nature Reviews Immunology 8, 523-532 (July 2008)

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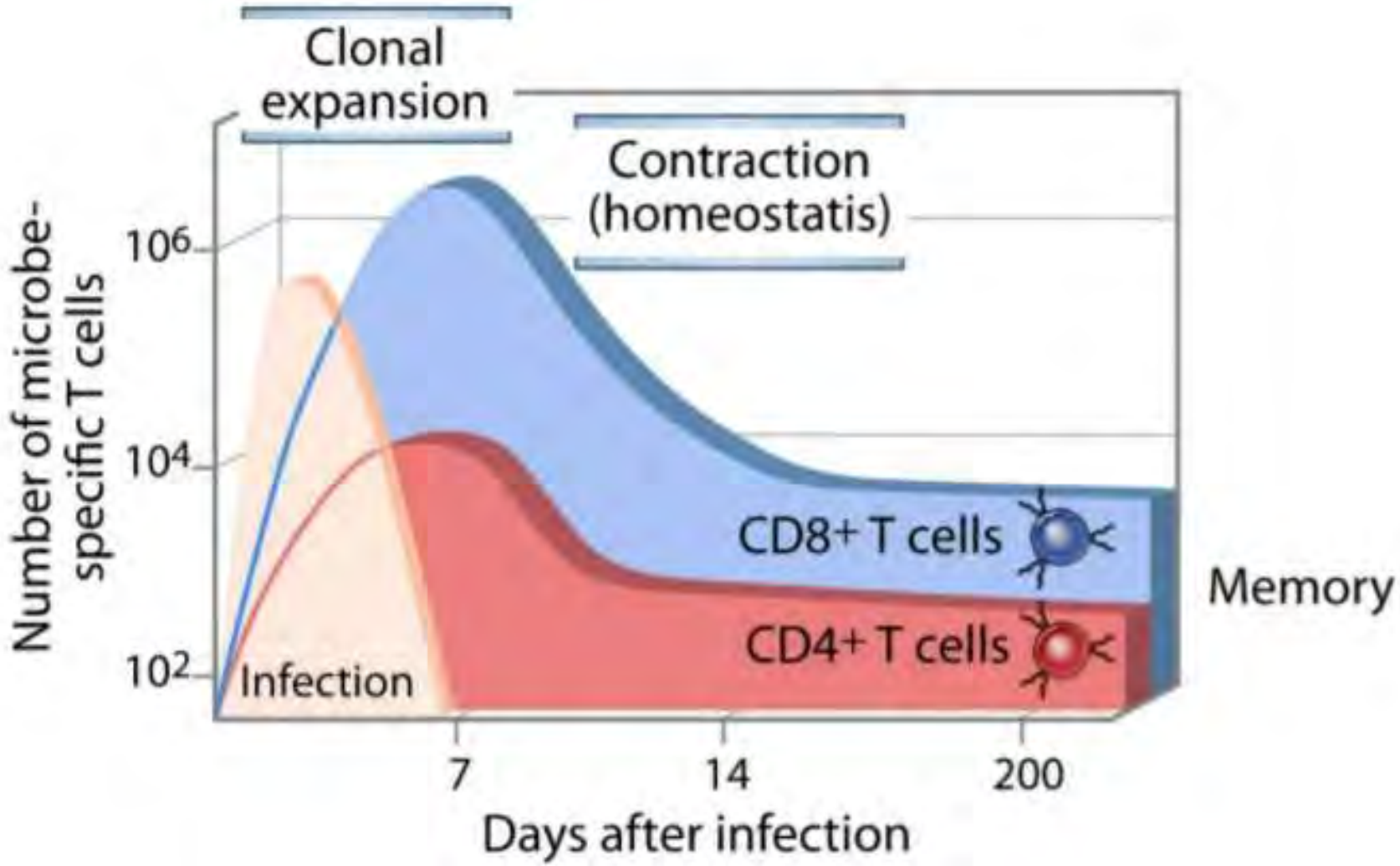
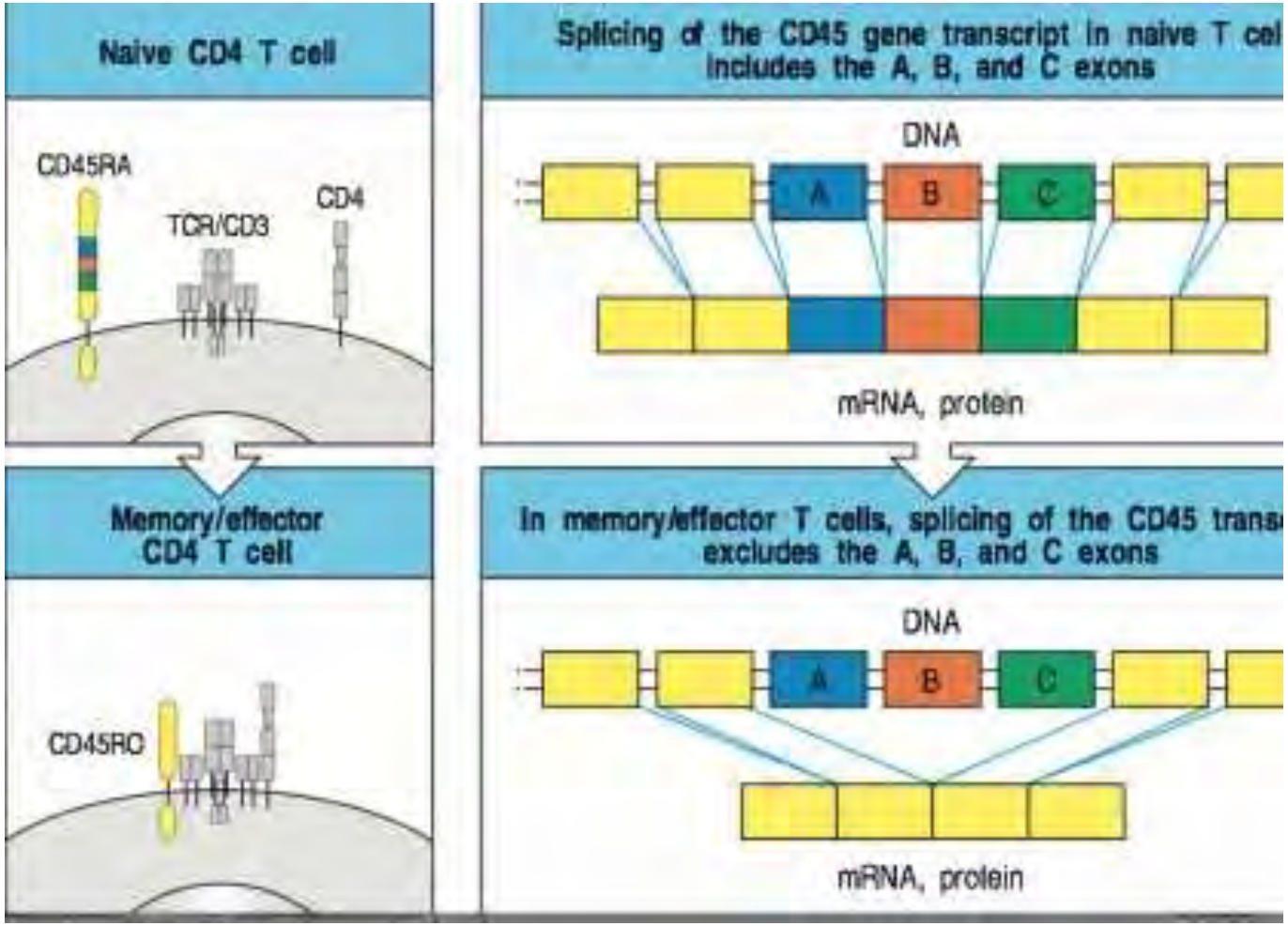
A T sejt válasz lefolyása



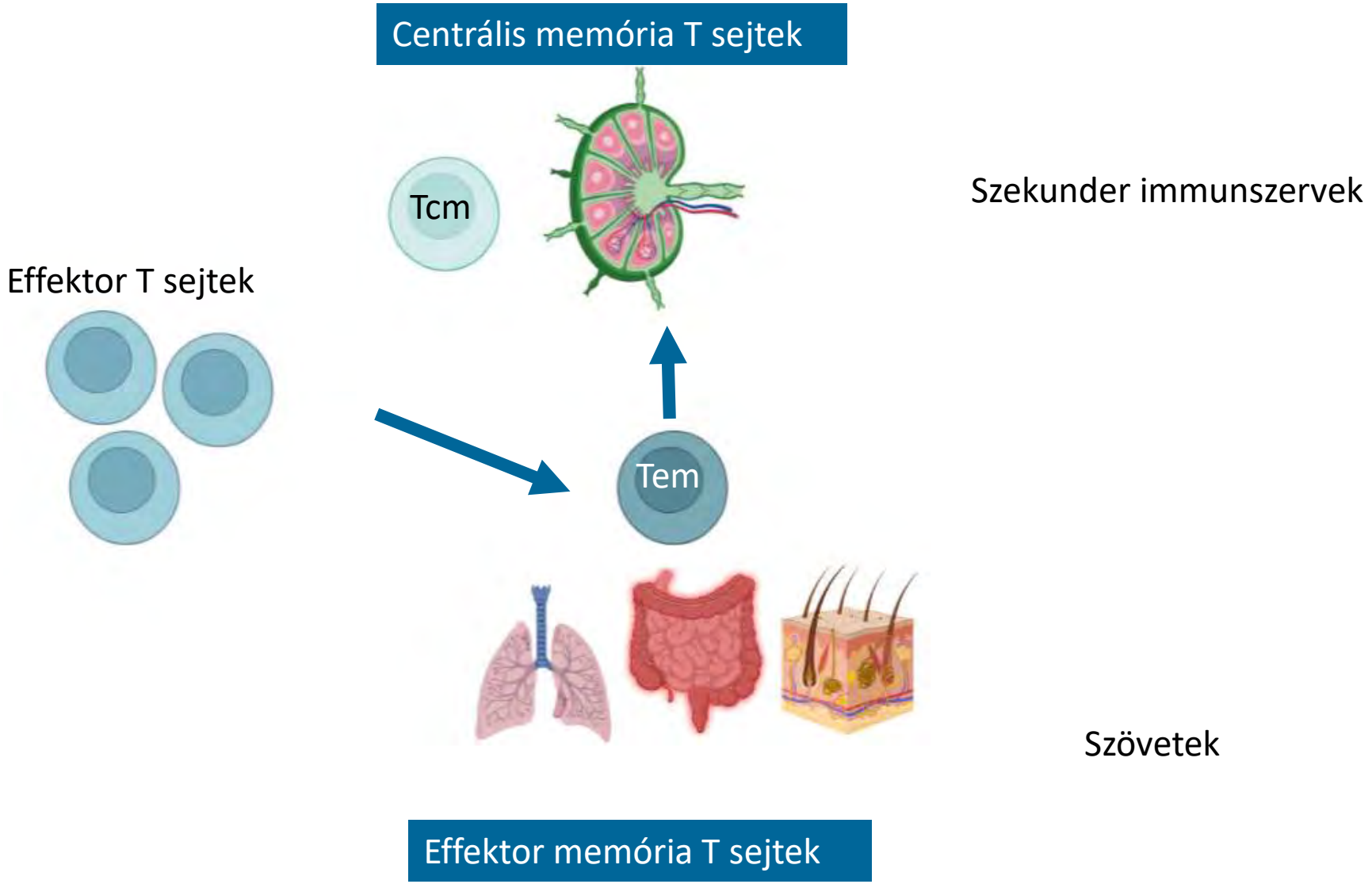
T sejt memória

naiv

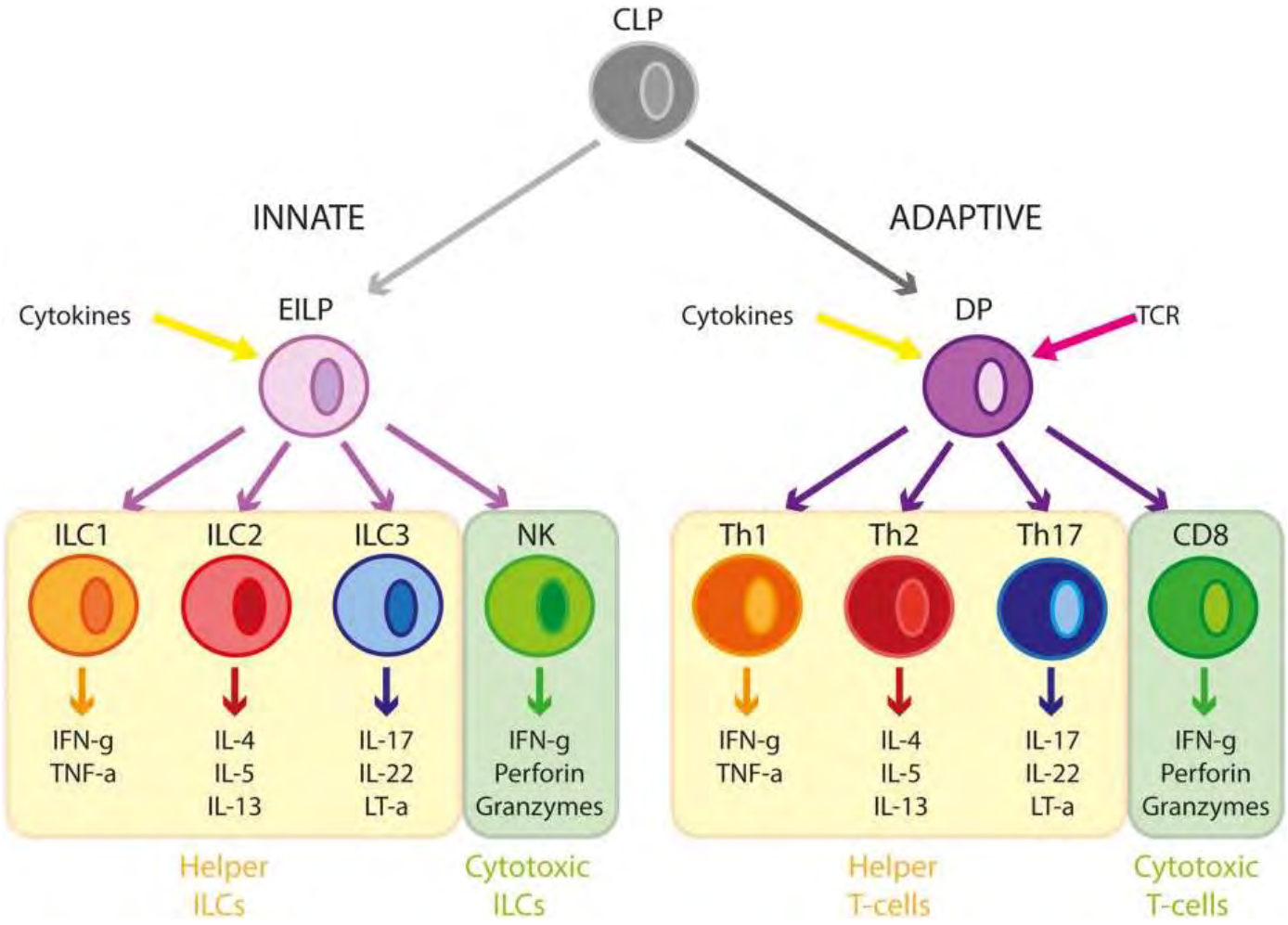
memória



Memória T sejtek



A T helper sejtek az Innate lymphoid sejtekkel együtt védik a szervezetet



https://doi.org/10.1002/cyto.b.2161

Nobel díj az immune checkpoint blokád felfedezéséért

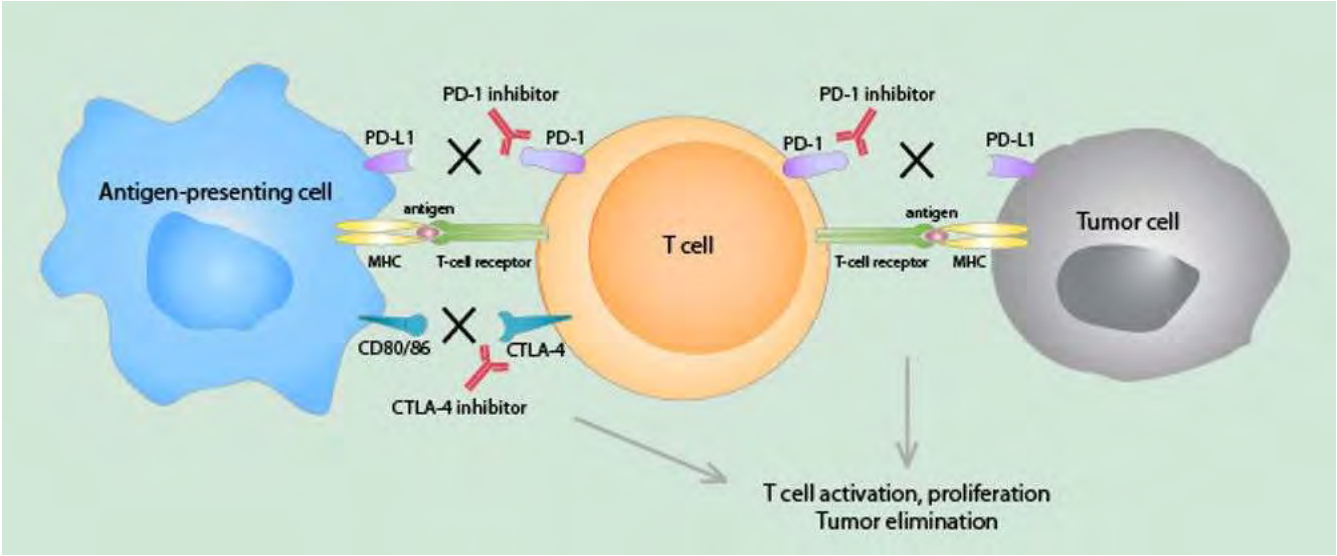
2018

Tasuku Honjo

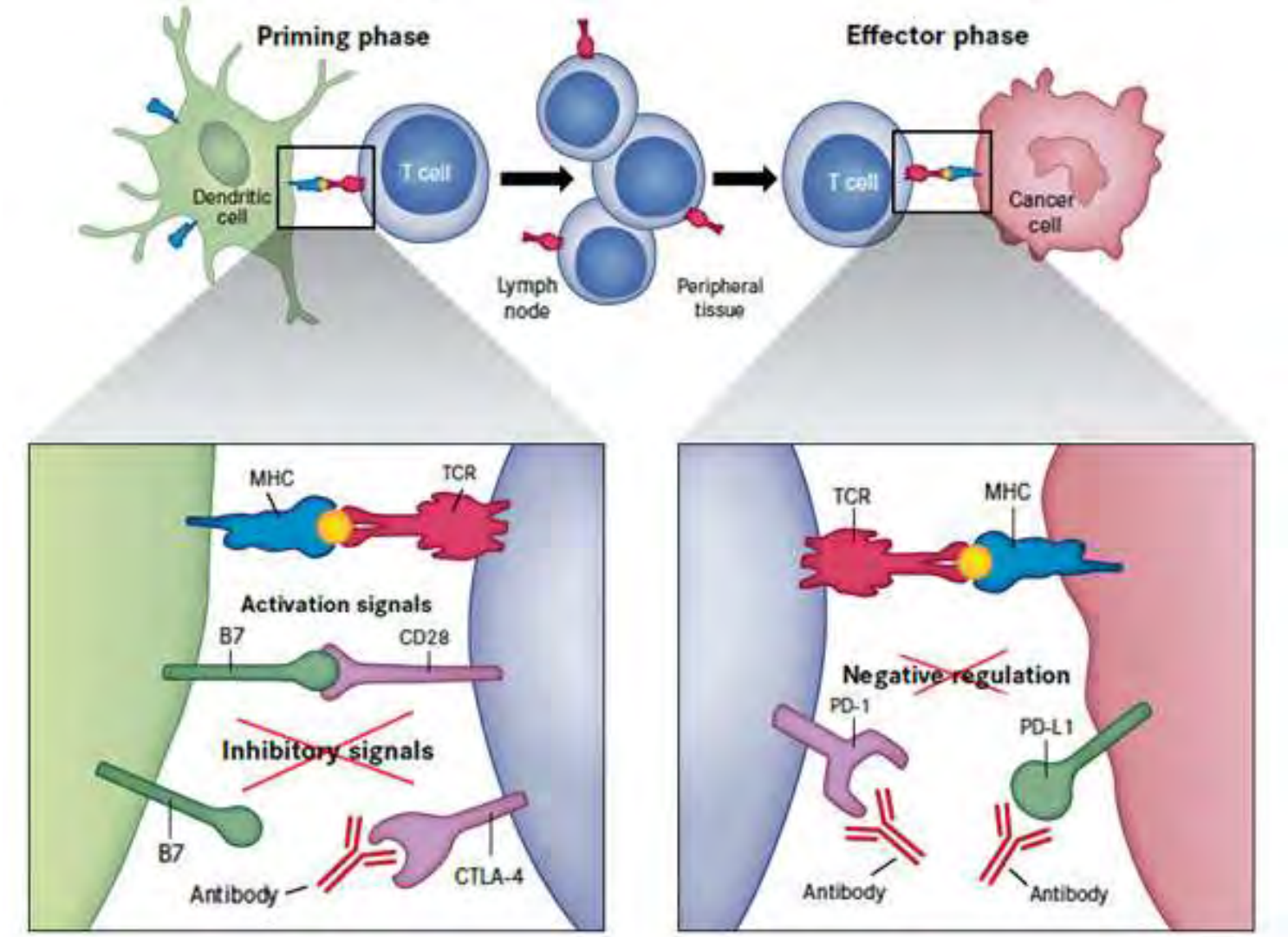
PD1

James Allison

CTLA-4



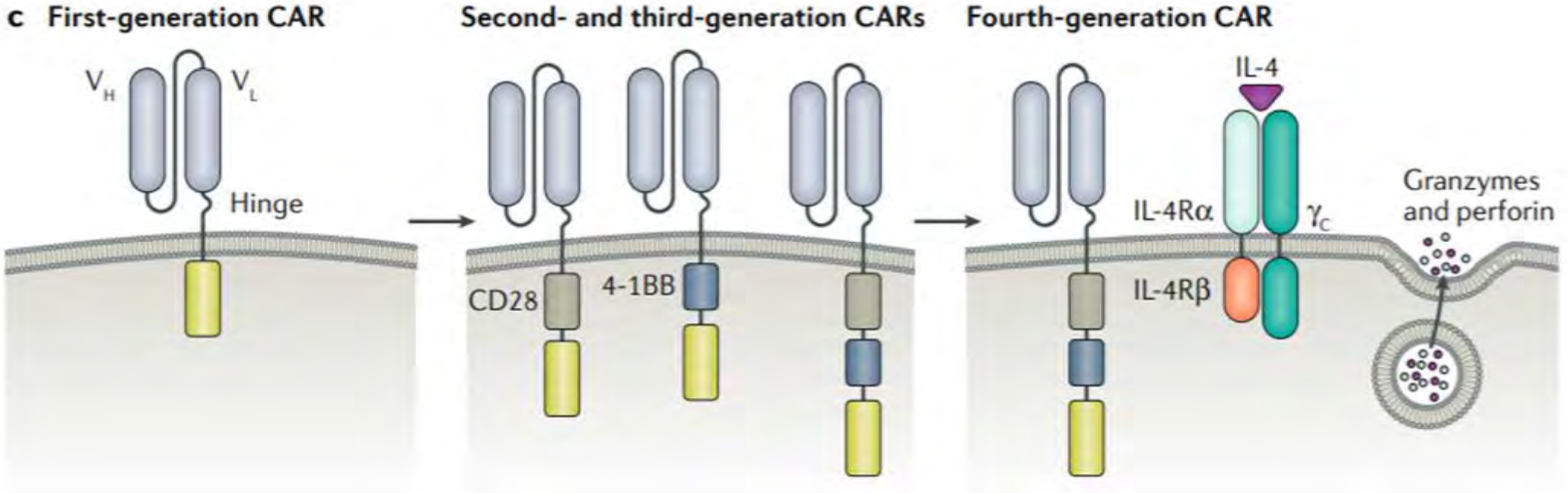
Checkpoint blokád



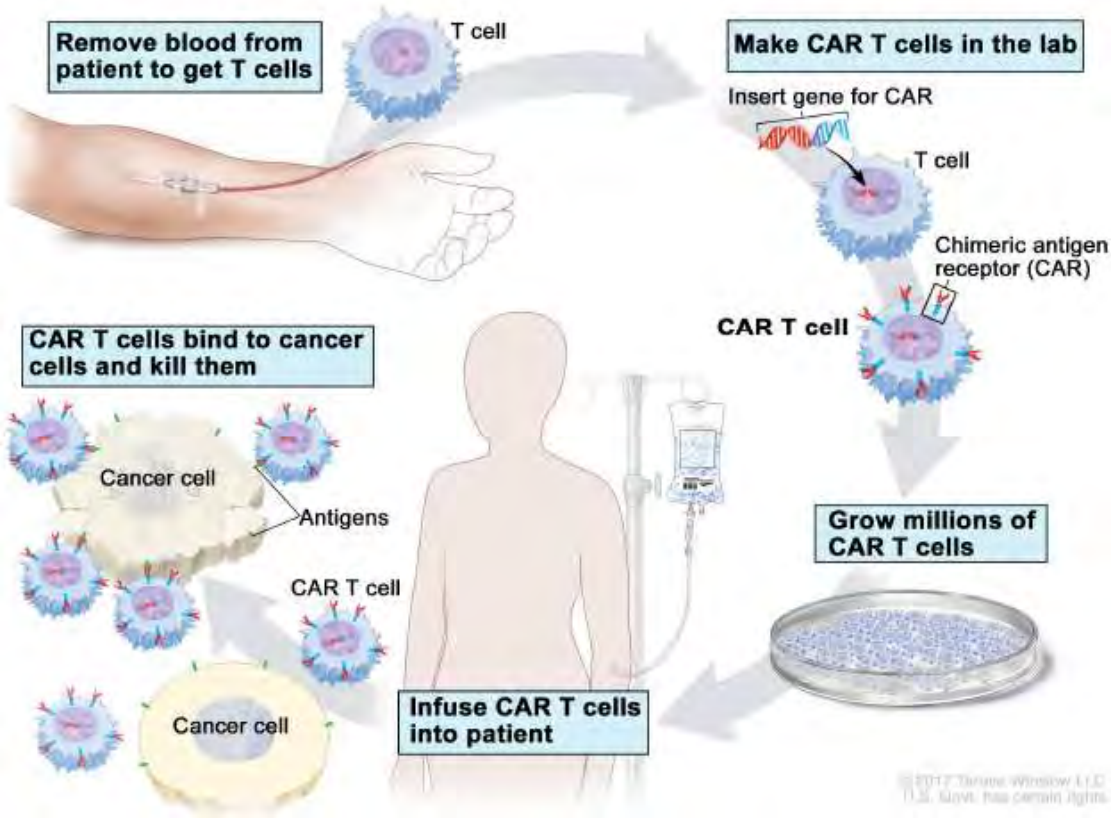
CAR T sejtek

“antitesttel-módosított” T sejtek

scFv: single chain variable fragment



CAR (chimeric antigen receptor) T sejtek)



2017-ben történt engedélyezése óta a CAR T-sejt terápiát > 30 000 hematológiai malignitásban szenvedő beteg esetében alkalmazták már az USA-ban

https://thermogenesis.com/the-successes-and-challenges-of-car-t-cell-therapy/

Köszönöm a figyelmüket!