Basic Immunology

Lecture 7th

Communication between cellular components of the immune system.

Co-receptors and adhesion molecules.

Mediators of cell-cell interactions: „cross-talk”

- **Direct interaction:** adhesion molecules
- **Soluble mediators:** cytokines, chemokines, interleukins, interferons, growth factors

Where?

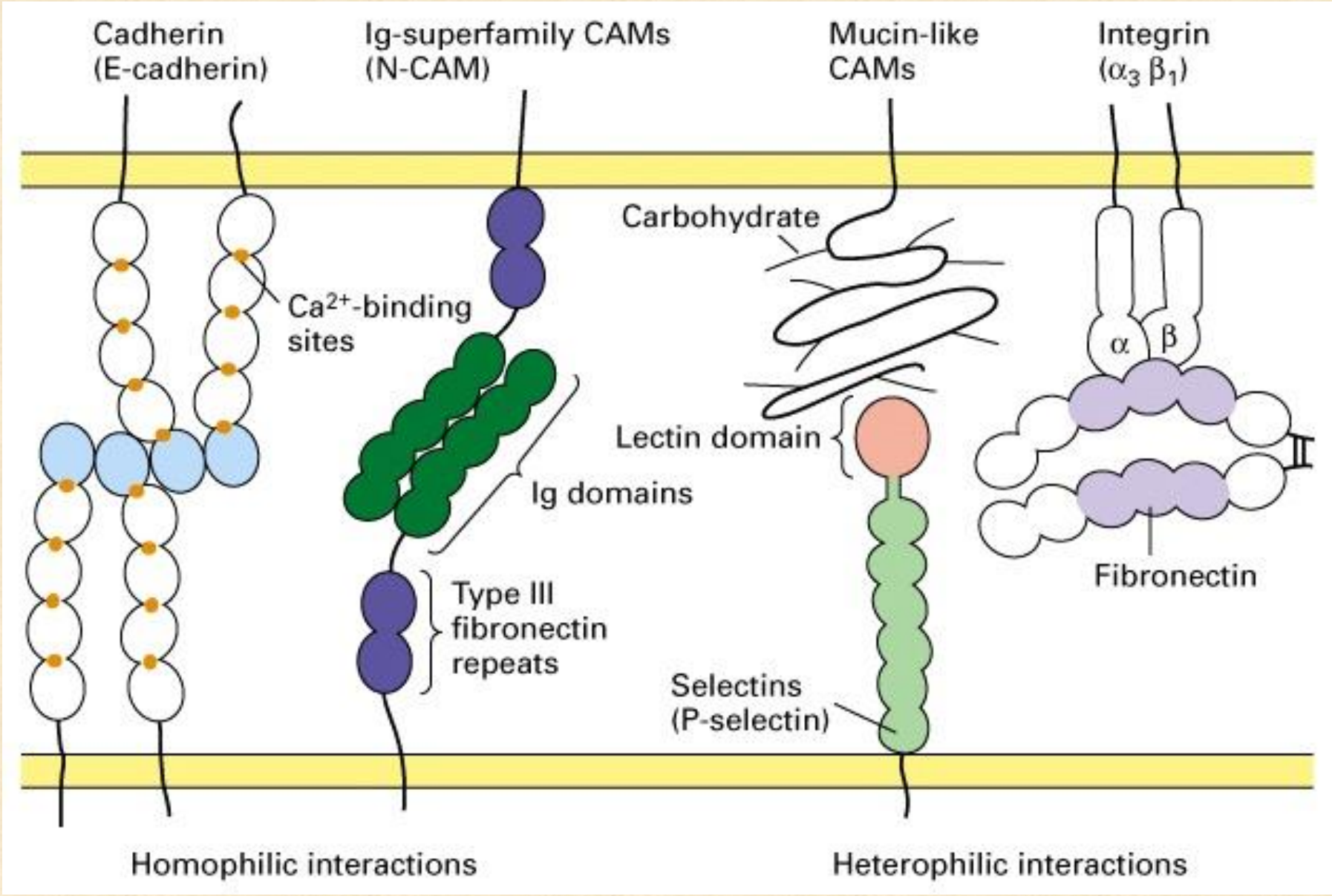
- **Haematopoiesis: adhesion between stroma cell – differentiating leukocytes**
- **Lymphocyte recirculation: adhesion between endothel – circulating leukocytes**
- **Immune response: T cell - APC/B cell interactions, cytotoxic reactions**

Adhesion molecules

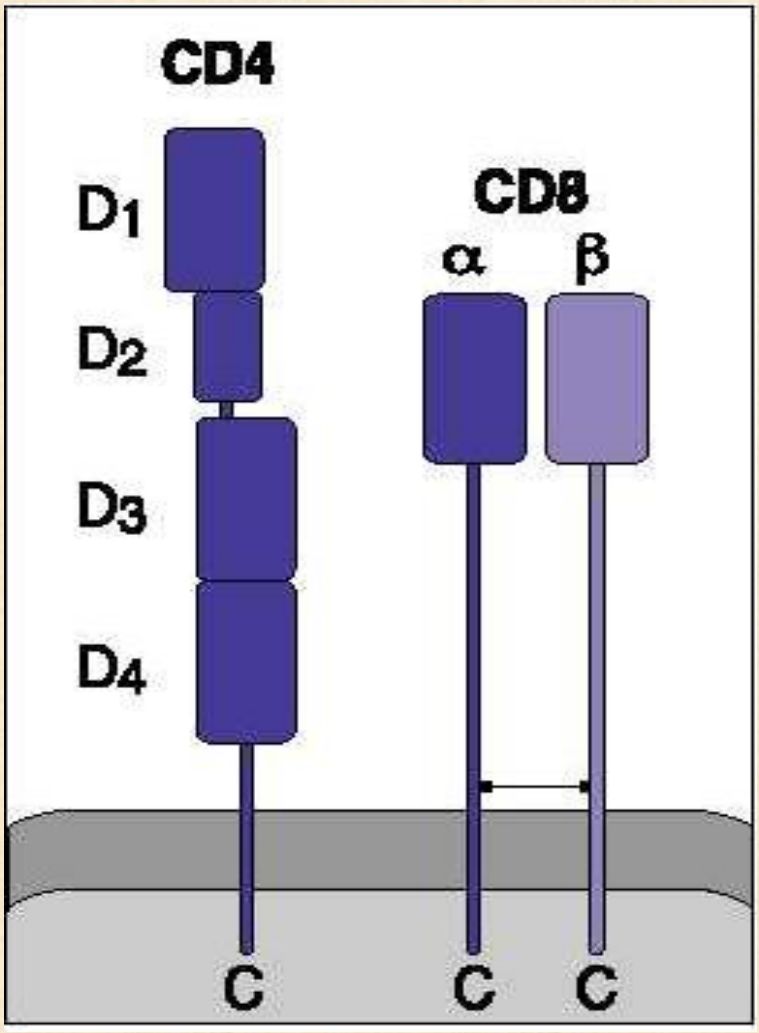
Cell surface molecules whose function is to promote adhesive interactions with other cells or the extracellular matrix and initiate signal transduction.

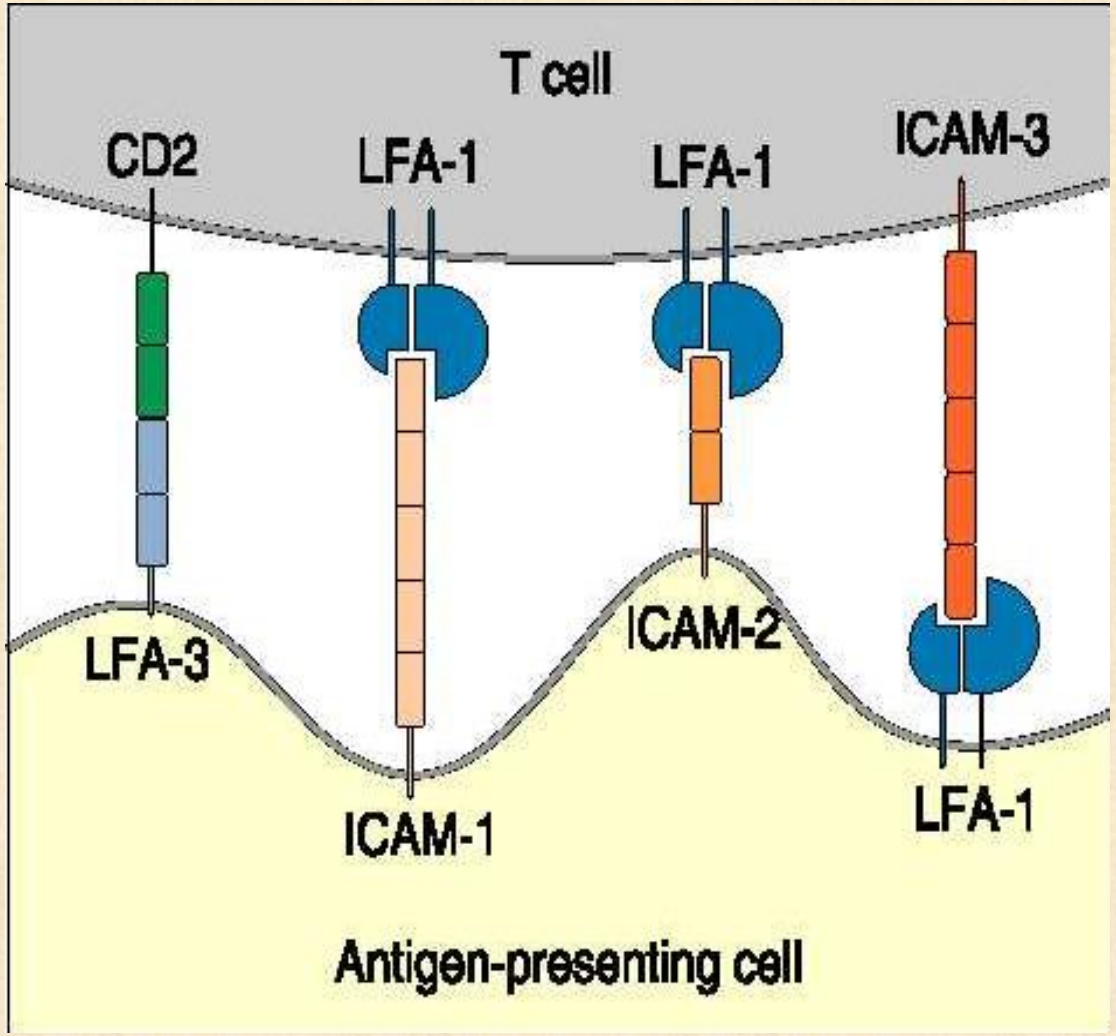
Leukocytes express various types of adhesion molecules, such as *selectins*, *integrins*, and members of the *Ig superfamily*, and these molecules play crucial role in cell migration and cellular activation both in innate and adaptive immune response.

Cell adhesion molecules



Accessory molecules on T cells

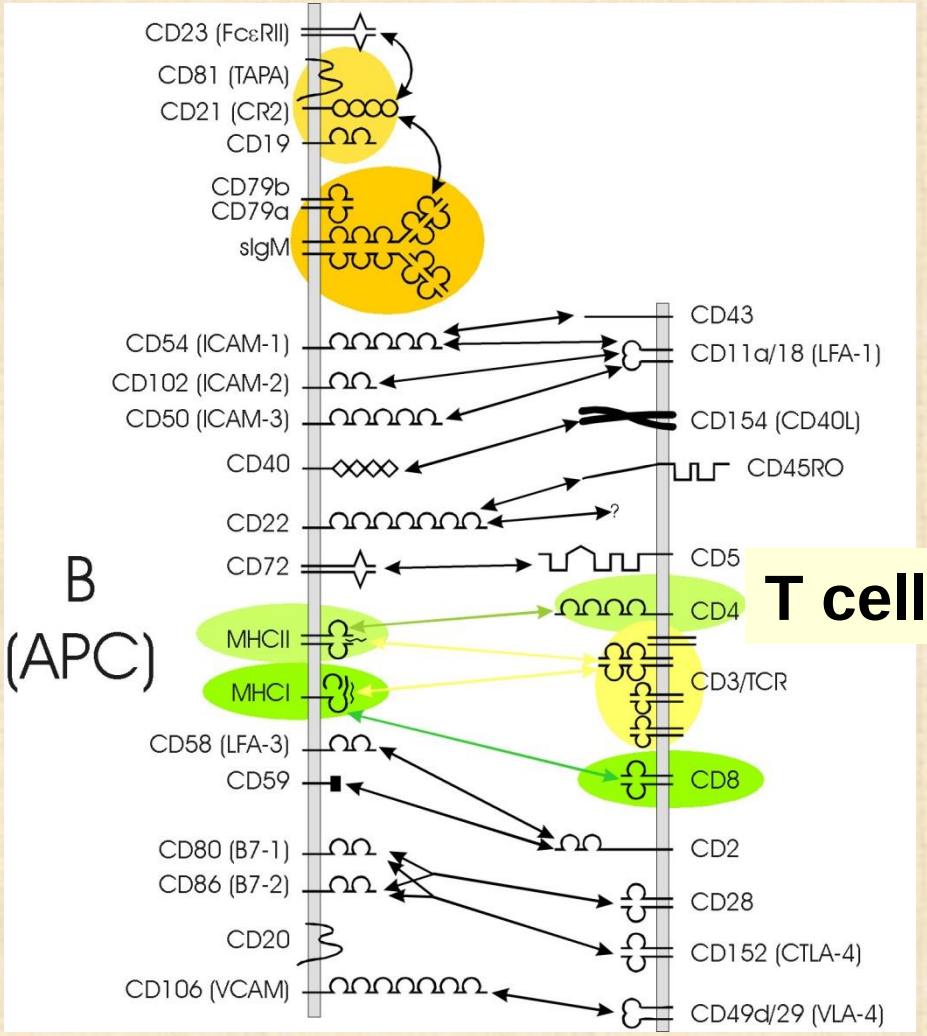




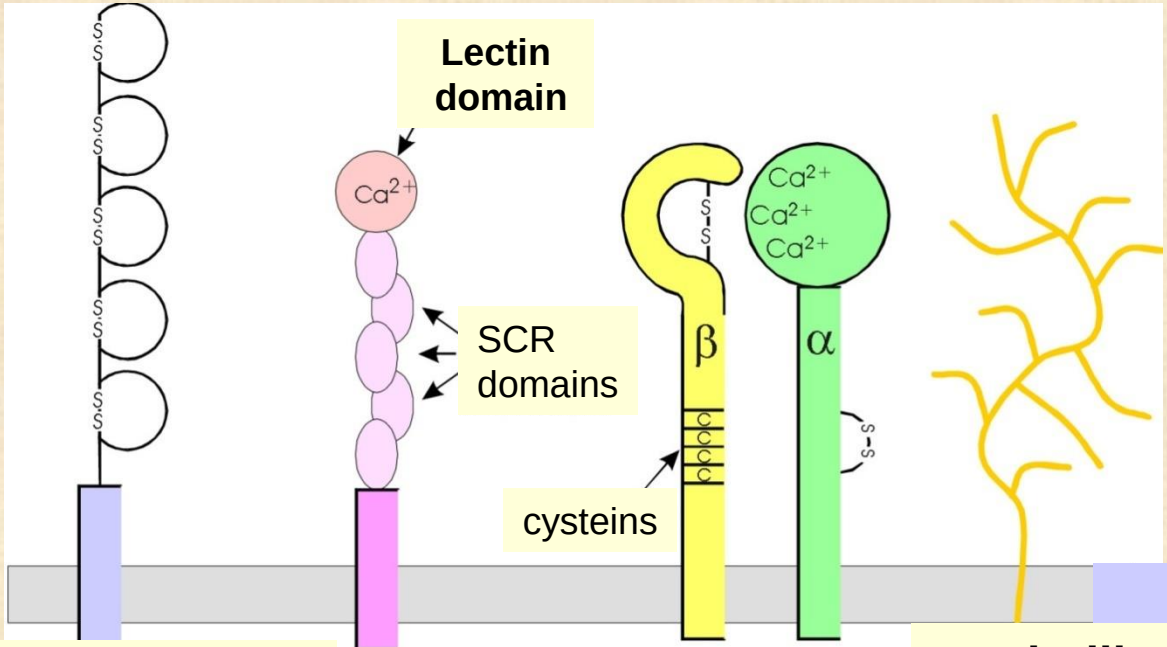
Family of accessory molecules, adhesion molecules, co-receptors

Common characteristics:

1. Molecules, responsible for the <u>direct interaction</u> of the immune cells
2. Their interaction is not antigen-specific
2. Low-affinity, reversible association
4. Increase the antigen-specific interaction
5. *Co-receptors:* - signaling function
6. *Co-stimulatory* molecules: help cell activation
7. Non-polymorphic



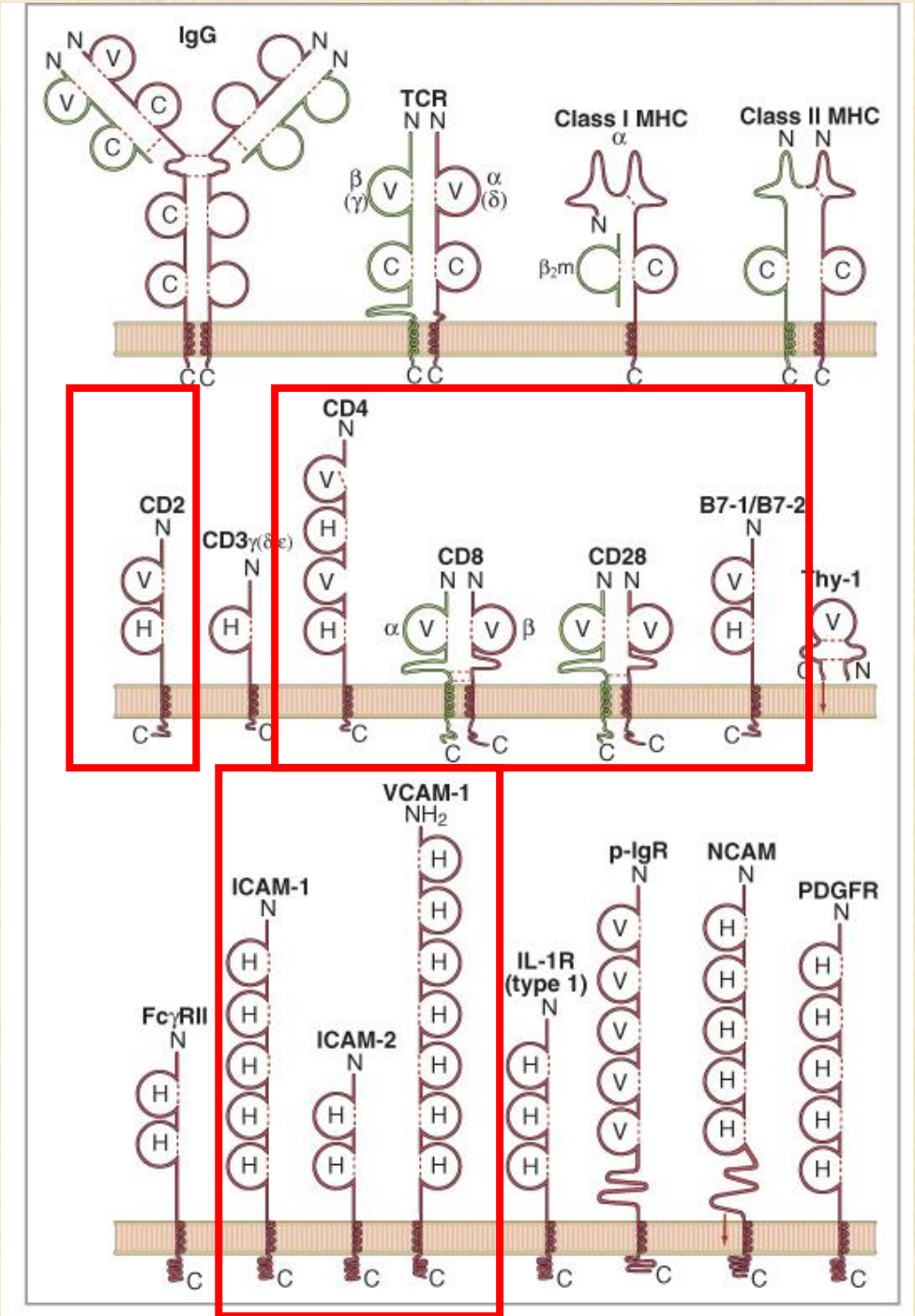
Families of adhesion molecules



„other" accessory molecules

Ig-superfamily members	Selectins	Integrins	Mucin-like molecules
CD2	L selectin	VLA	„vascular addressins"
CD4	E selectin	LFA	
CD8	P selectin	Mac1	
B7			
CD28			
CTLA 4			
ICAM			

CD45
CD44
CD40, CD40L
CD19/CD21/CD81
CD22



Immunglobulin-superfamily members

Ig-superfamily members

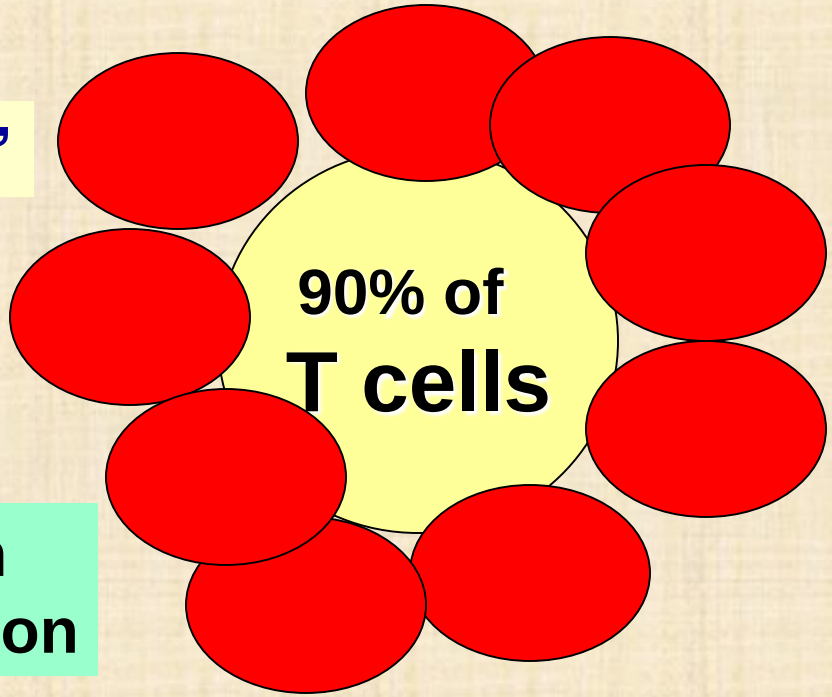
CD2

„sheep red-blood cell receptor”

Binds CD58

(LFA3)

„T cell rosette”



Adhesion
Cell activation

T cell activation, CTL- and NK-mediated lysis

CD4 and CD8:

extracellular domain: binding to MHC constant domain
intracellular domain: signal transduction, binding kinases

Differentiation markers

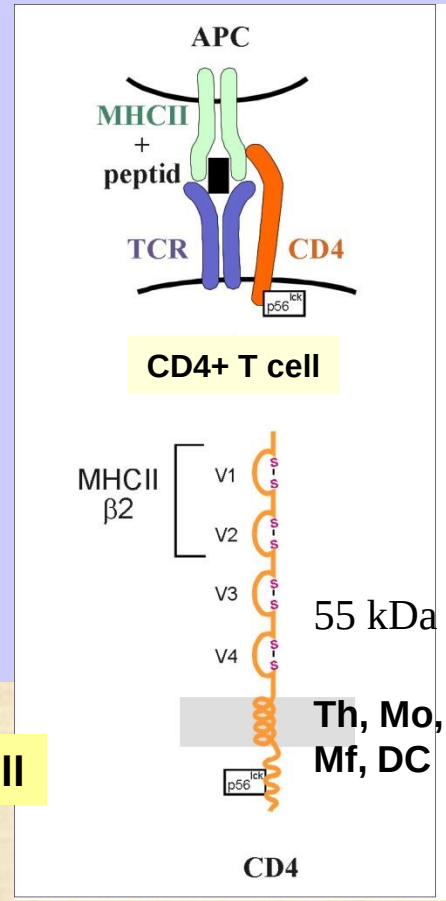
At different stages of T cell maturation

CD4 and **CD8 together**
„double positive”
in thymus

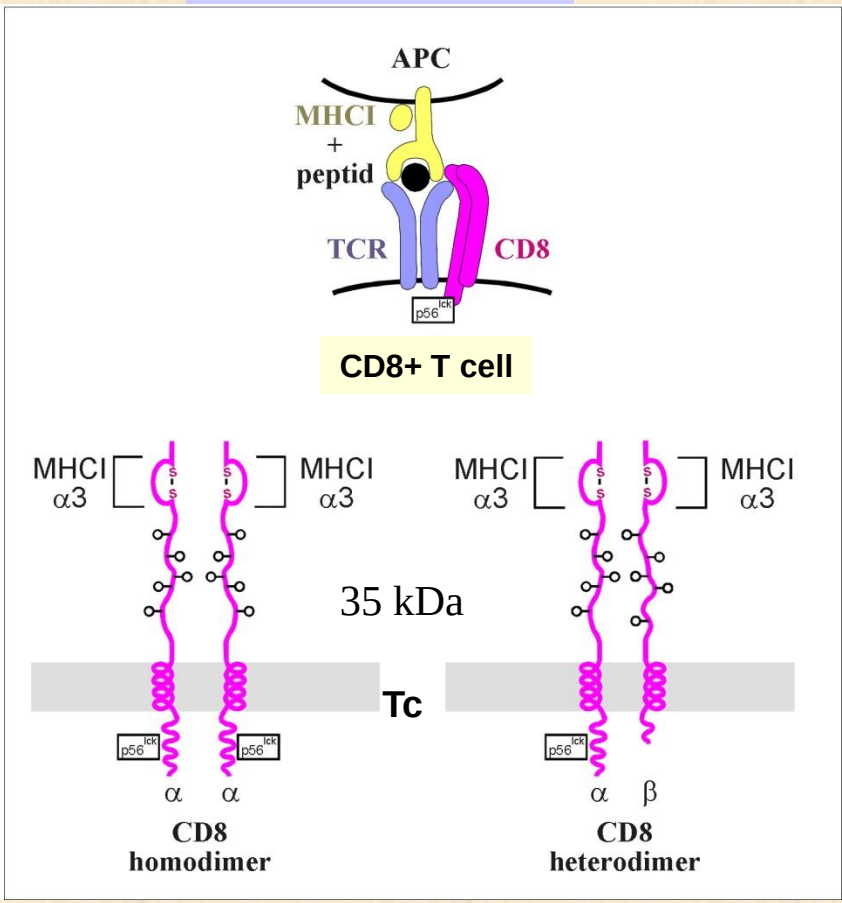
At the periphery*:*
„single positive”
T helper: CD4
T cytotoxic: CD8

CD4 - HIV-receptor as well

CD4 - MHCII

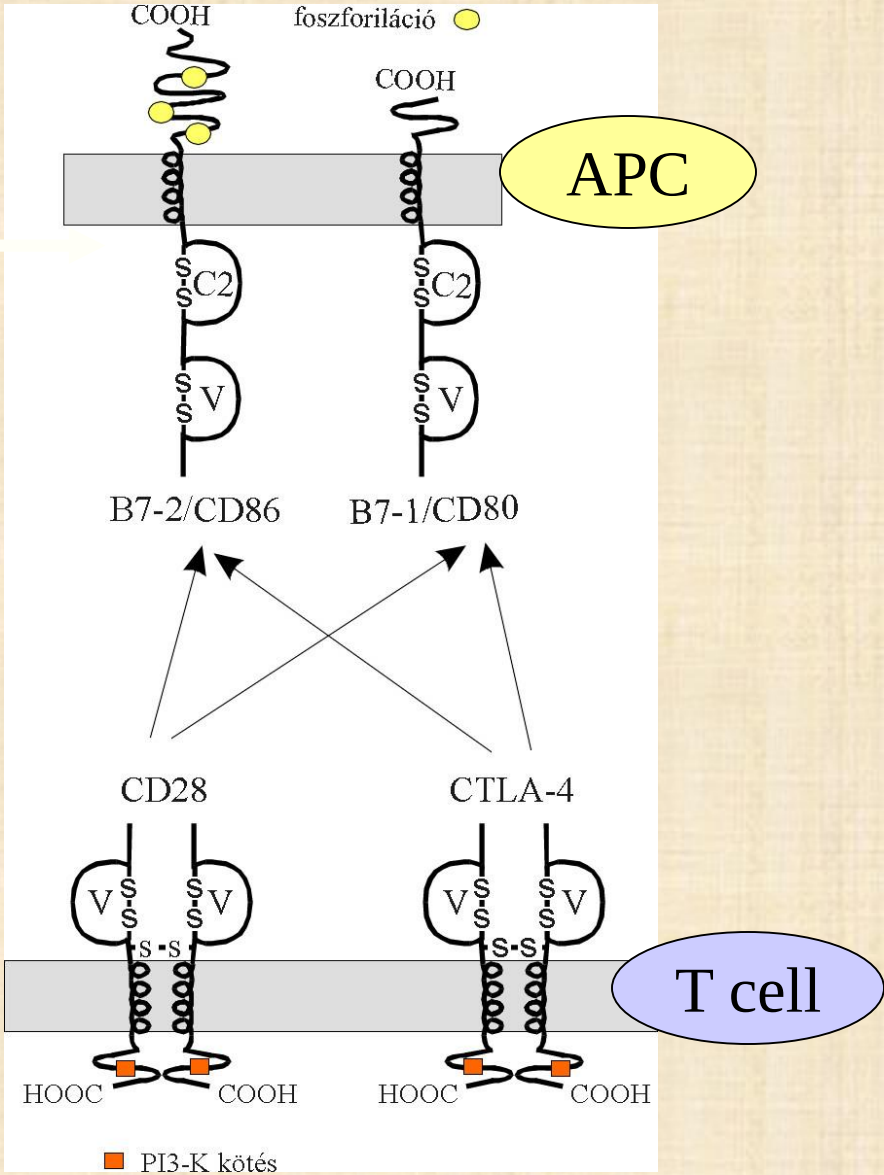


CD8 - MHCI



B7 (CD80, CD86), CD28 and CTLA-4 molecules

CD28 and CTLA-4 of T cells bind to the **B7-1** (CD80), **B7-2** (CD86) molecules of the APC

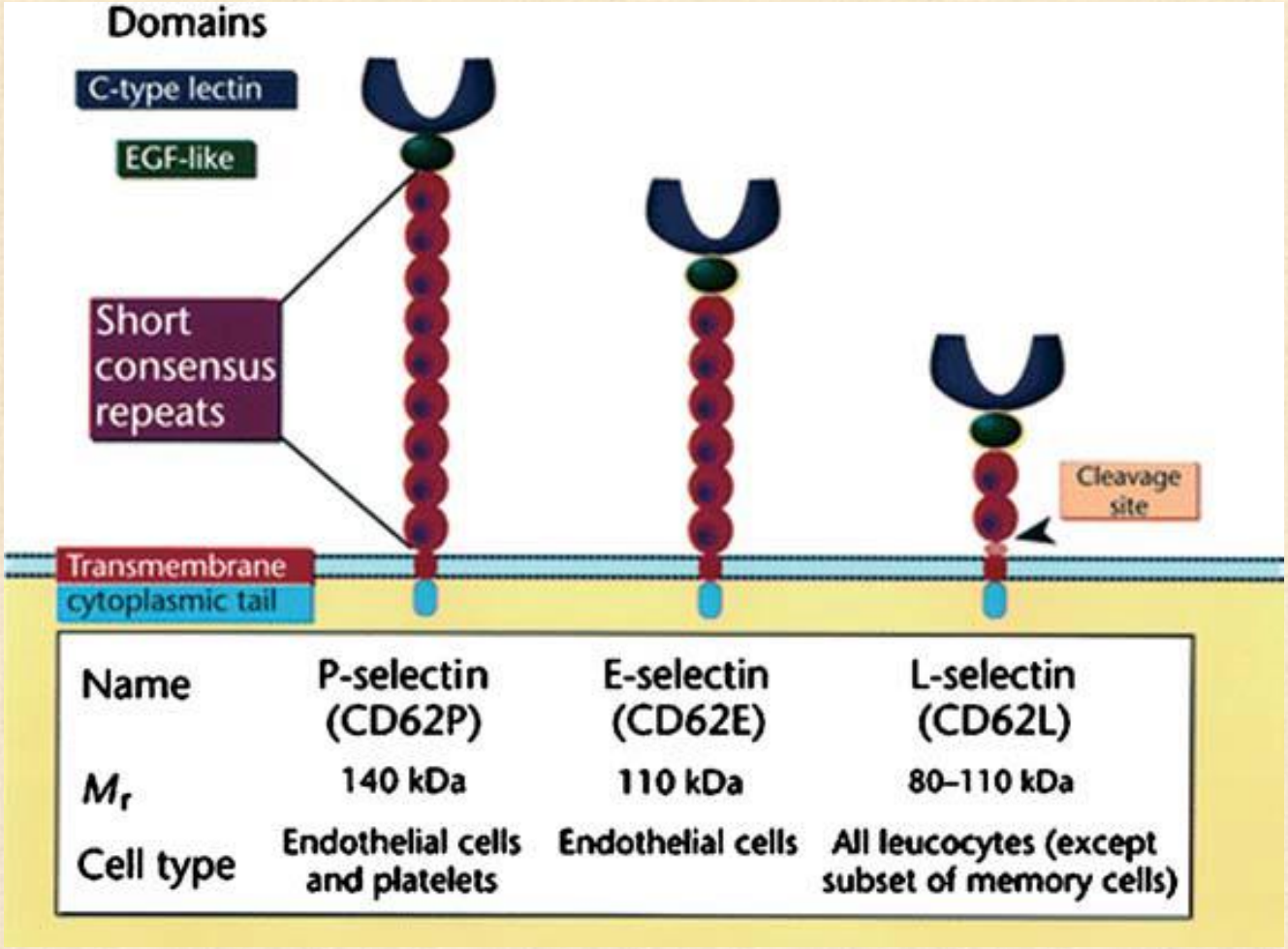


CD28: - co-stimulatory molecule in T cell activation
- Increases IL-2 and IL-2R expression,
- Induces T cell proliferation

CTLA-4 (CD152): - expressed in a later phase of the T cell activation
- inhibitory function

CTLA: **Cytolytic T lymphocyte associated Antigen**

Selectins



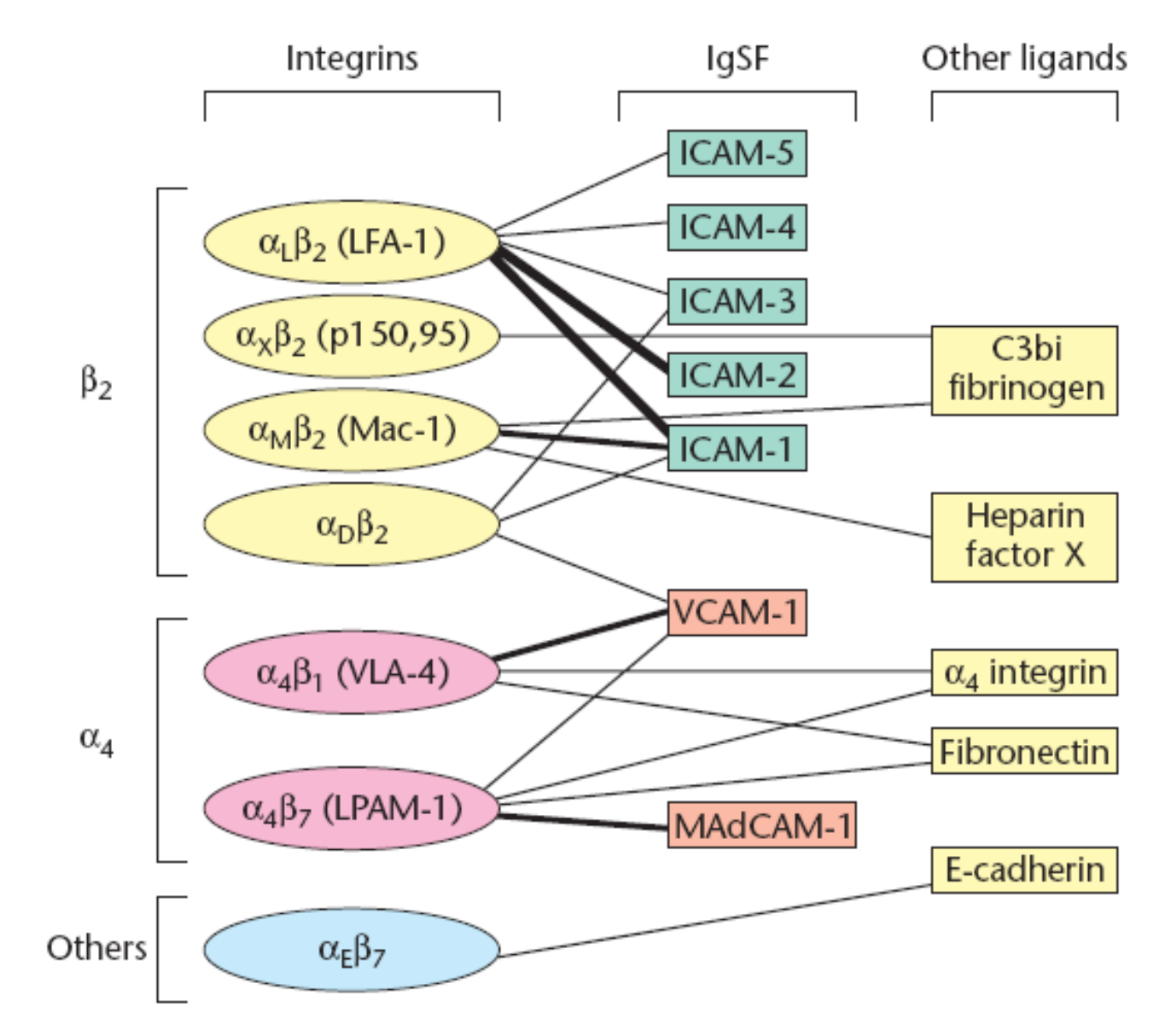
Name	P-selectin (CD62P)	E-selectin (CD62E)	L-selectin (CD62L)
M_r	140 kDa	110 kDa	80–110 kDa
Cell type	Endothelial cells and platelets	Endothelial cells	All leucocytes (except subset of memory cells)

L-Selektin: Myeloid Zellen, naive und Gedächtnis T- Lymphozyten

E-Selektin: Hautgefäße, entzündete Gefäße

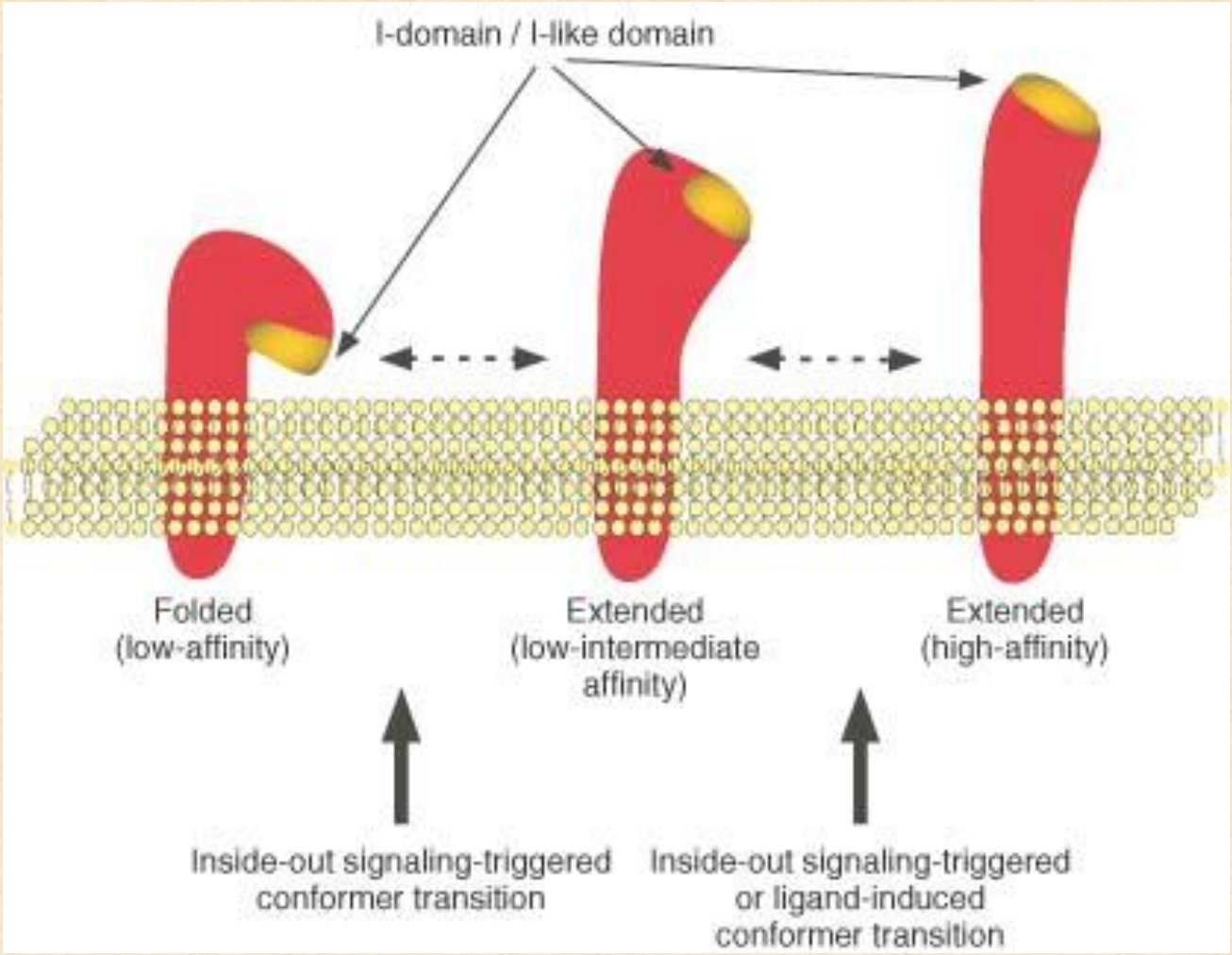
P-Selektin: Endothelien, Thrombozyten

Integrins


Integrins
IgSF
Other ligands
β2
α4
Others
αLβ2 (LFA-1)
αXβ2 (p150,95)
αMβ2 (Mac-1)
αDβ2
α4β1 (VLA-4)
α4β7 (LPAM-1)
αEβ7
ICAM-5
ICAM-4
ICAM-3
ICAM-2
ICAM-1
VCAM-1
MAdCAM-1
C3bi
fibrinogen
Heparin
factor X
α4 integrin
Fibronectin
E-cadherin

Activation of integrins

- **L**ymphocyte **F**unction-associated **A**ntigen
- **I**nter **C**ellular **A**dhesion **M**loecule

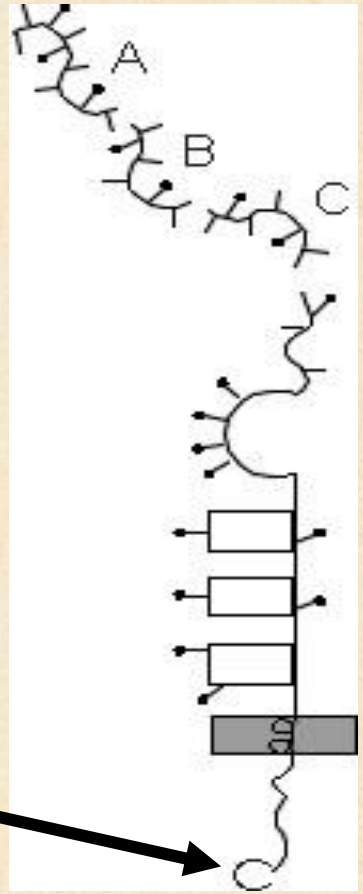


„OTHER” accessory molecules

CD45

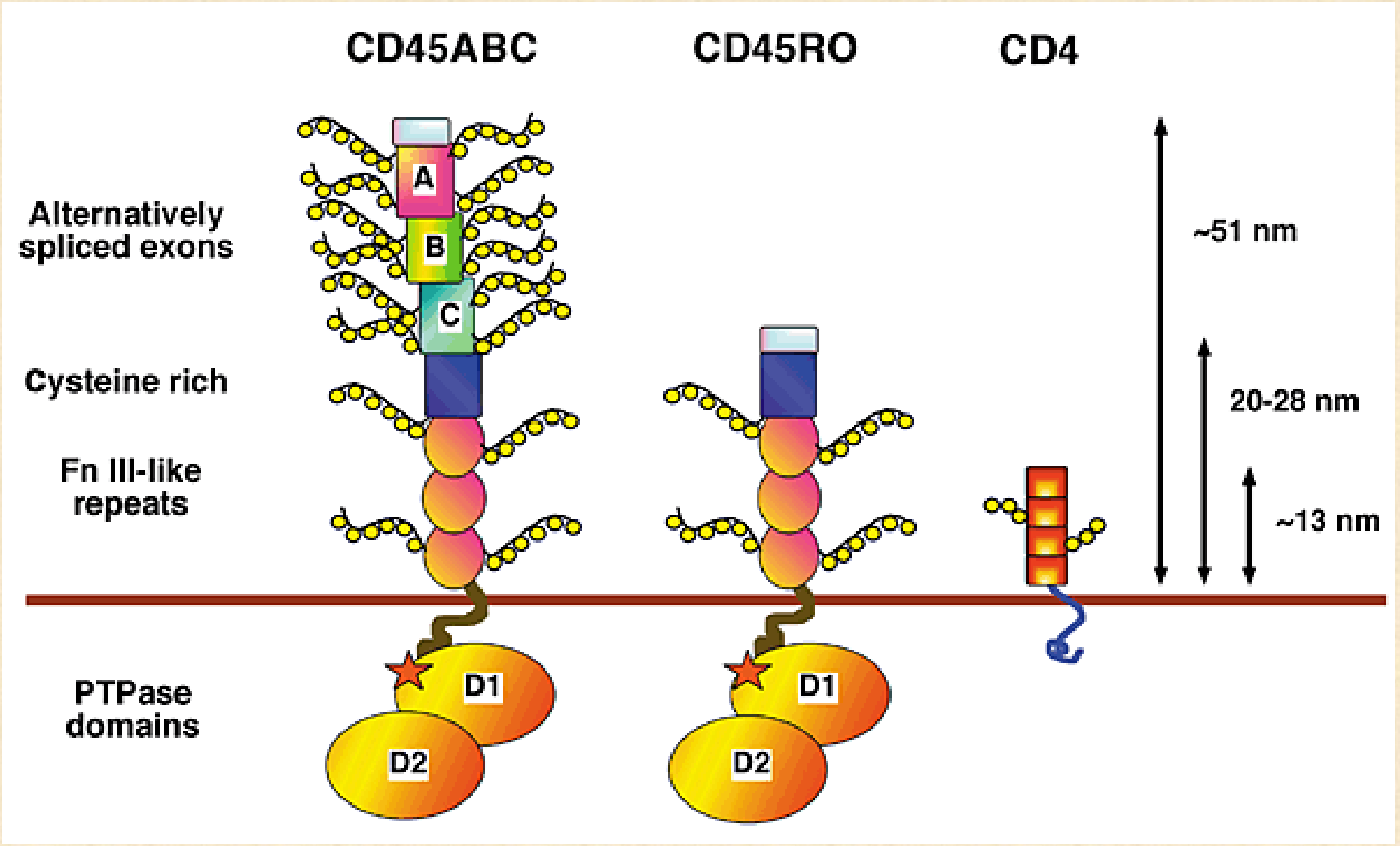
Expressed on every leukocyte
“pan-leukocyte marker”
- Highly glycosylated,
- More isoforms (180, 190, 200, 205, 220 kDa)
- alternative splicing

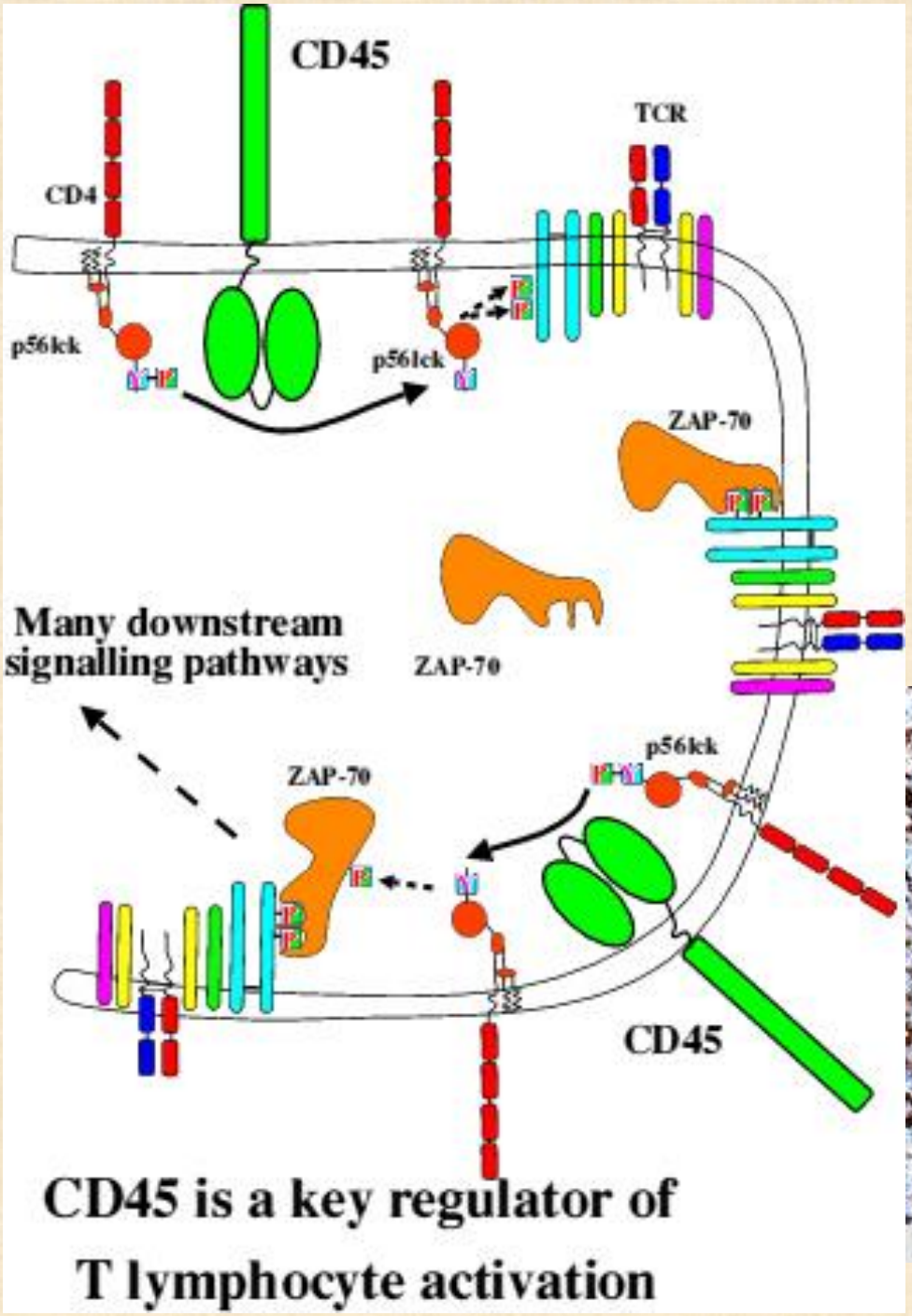
Plays important role in cell activation and in regulation of signal transduction
- ***tyrosine–phosphatase domain:***
dephosphorylation



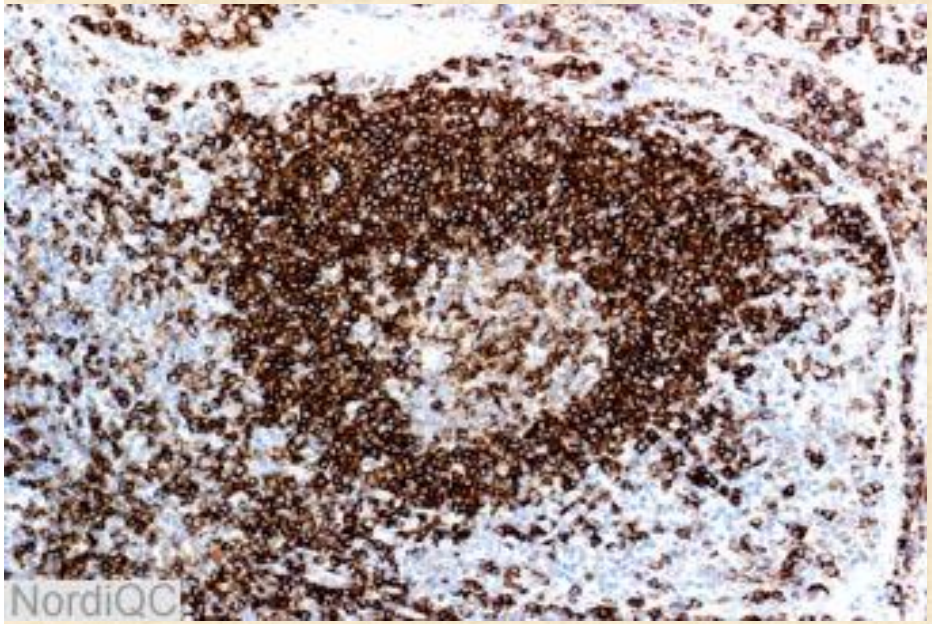
CD45

CD45 isoforms




CD45
TCR
CD4
p56lck
p561ck
ZAP-70
Many downstream
signalling pathways
ZAP-70
p56kk
ZAP-70
CD45
CD45 is a key regulator of
T lymphocyte activation

CD45


NordiQC

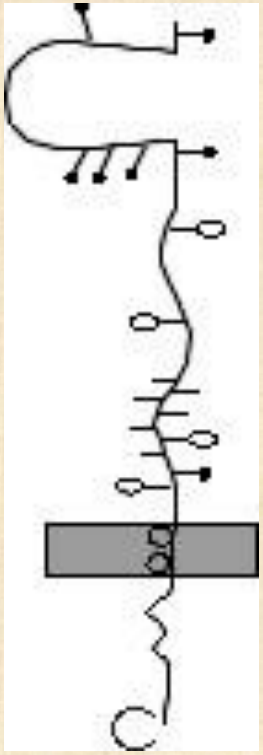
„OTHER” accessory molecules

CD44

Expressed on activated and memory T- and B-cells, phagocytes, fibroblasts, neuronal cells

More isoforms - *alternative splicing*

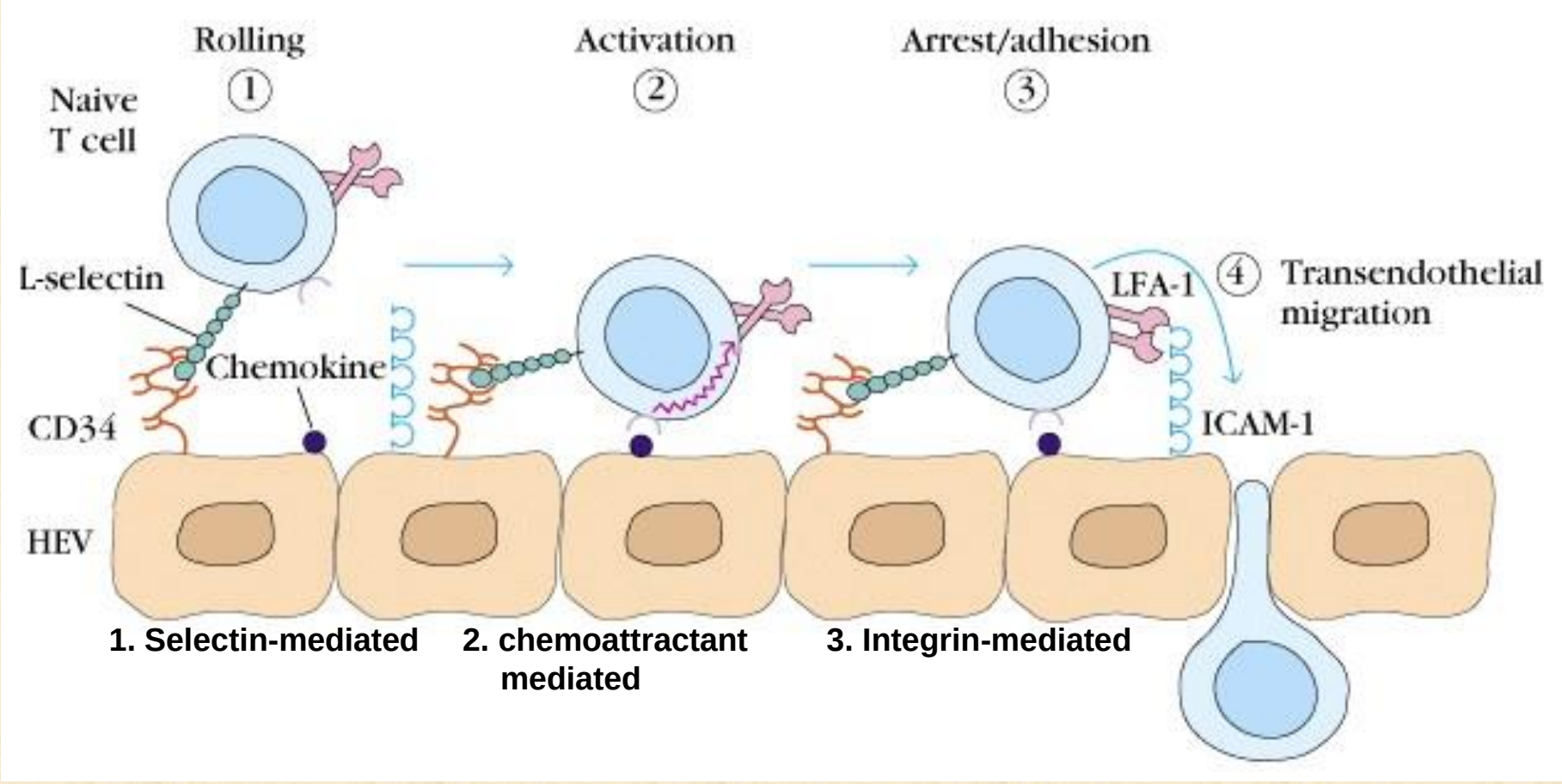
Important in „homing” of leukocytes



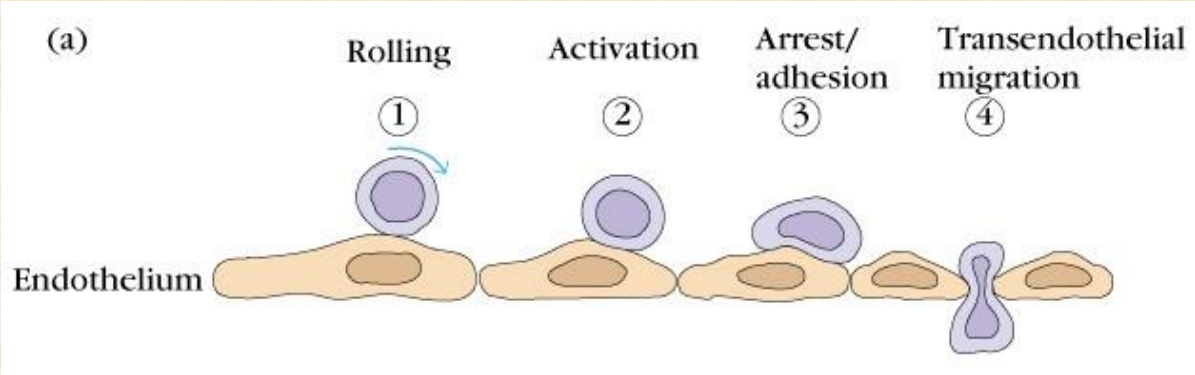
CD44

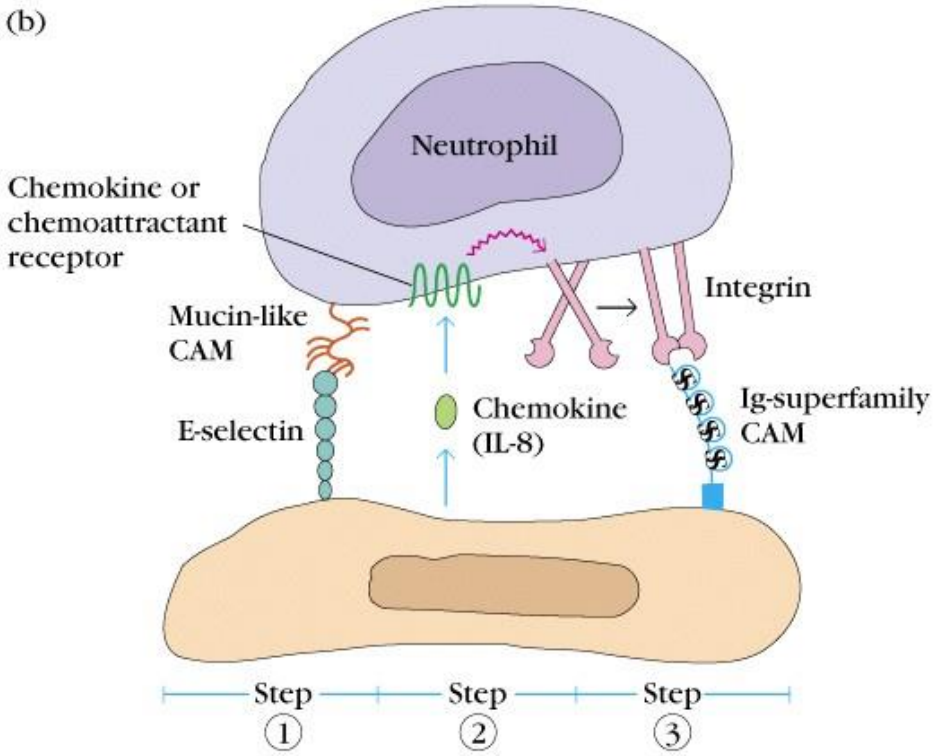
Naive lymphocytes migrating to the peripheral lymphatis tissues:

The role of the hugh endothelial venules (HEV), and the adhesion molecules:

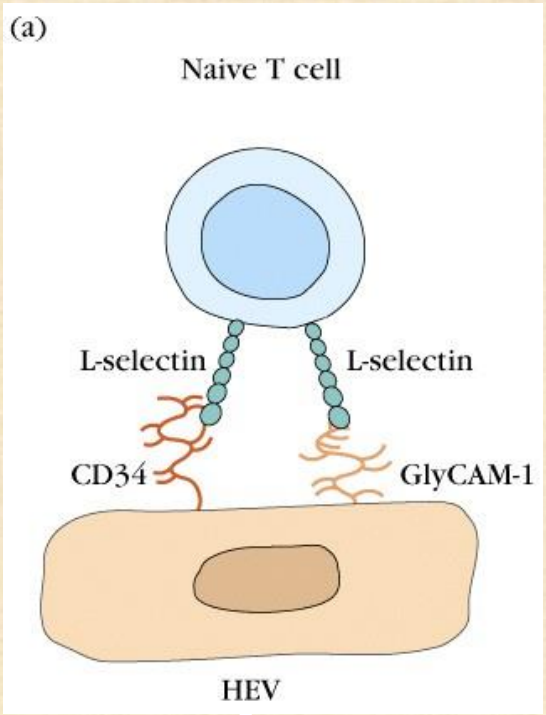


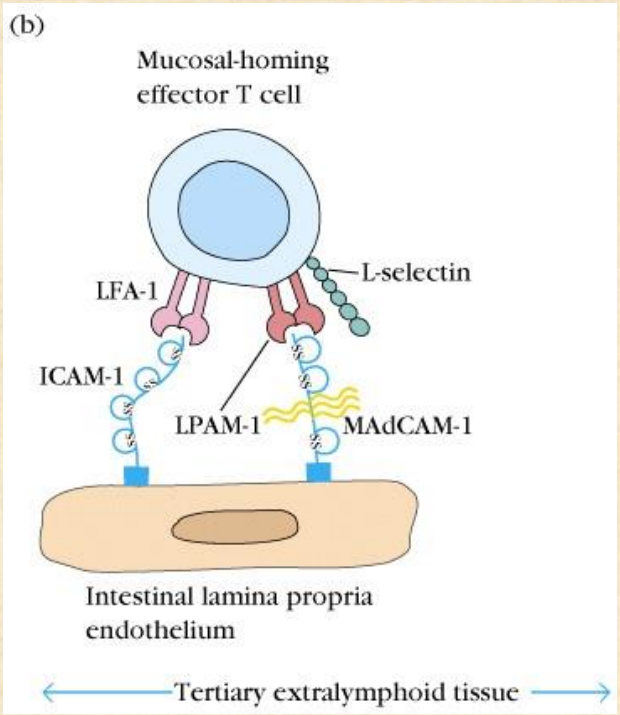
Migration of neutrophil granulocytes to the inflammed tissues throgh the endothel

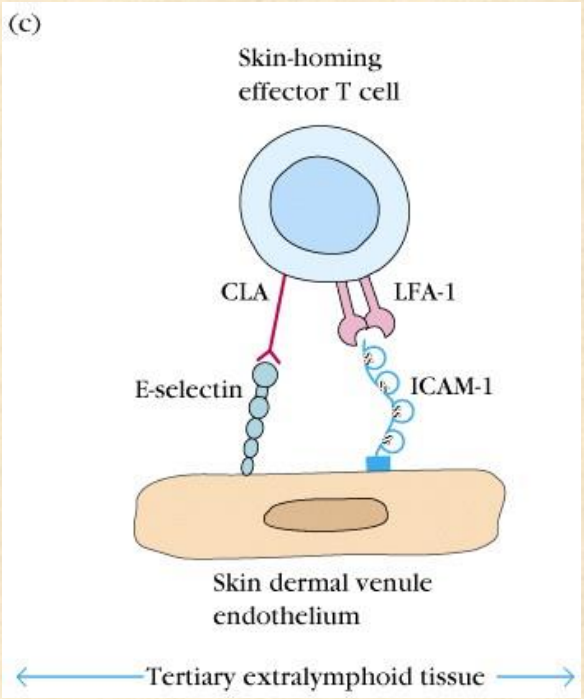




Different adhesion molecules determine the migration of naive and memory (effector) cells







Peripheral lymphatic tissue

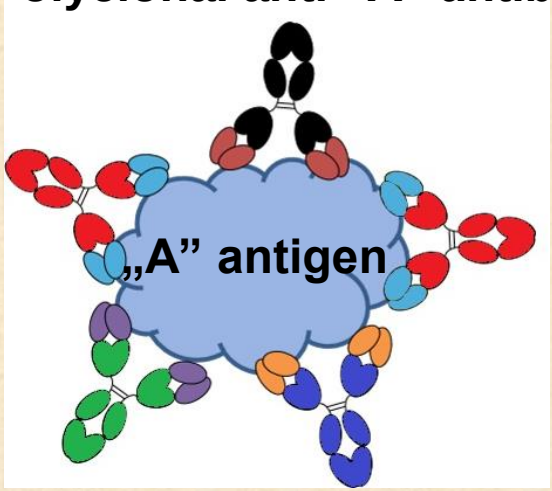
Inflammatory tissue

Some important accessory molecules

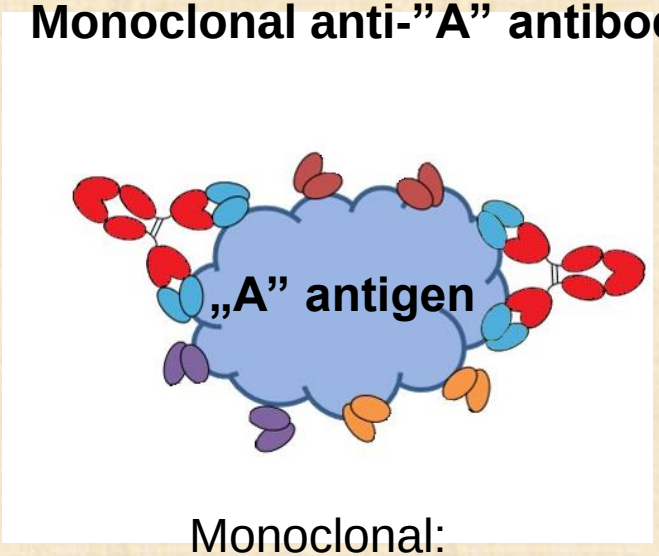
- CD4 and CD8
- CD28
- CD80/86 (B7.1 and B7.2)
- CD152 (CTLA4)
- CD45RA/RO
- CD40/CD154 (CD40 Ligand)

Comparison of monoclonal and polyclonal antibodies

Polyclonal anti-”A” antibody



Monoclonal anti-”A” antibody



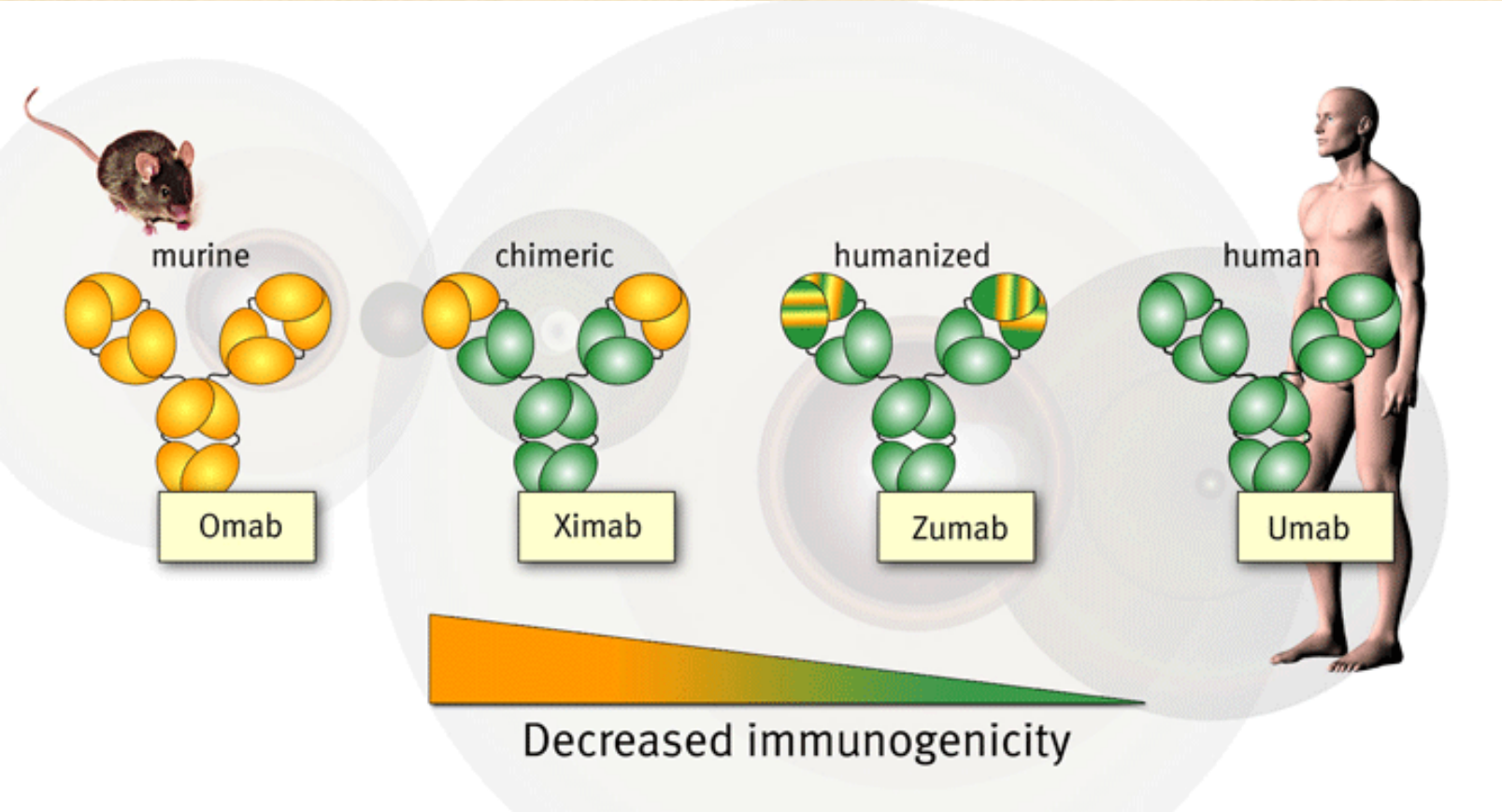
Polyclonal:

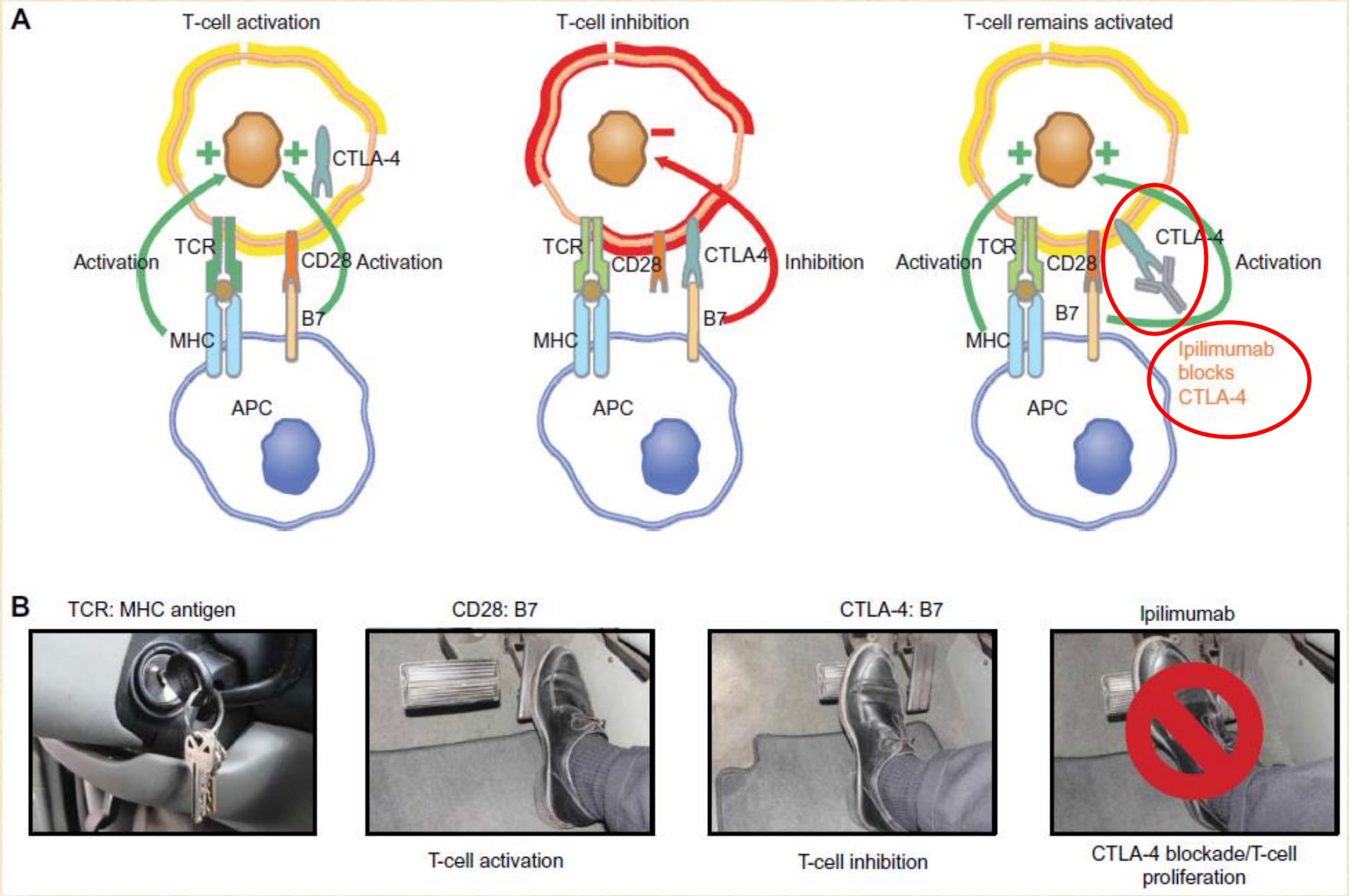
- Product of **several B cell clones**
- Recognize **different epitopes** of the target antigen
- Varying specificity and affinity
- (Consider them a mixture of different monoclonal antibodies)

Monoclonal:

- Product of **a single B cell clone**
- Recognize a **single specific epitope** of the antigen
- Antibodies have the **same specificity** and **affinity**

Therápiás célokra használt monoklonális ellenanyagok II: nomenklatúra



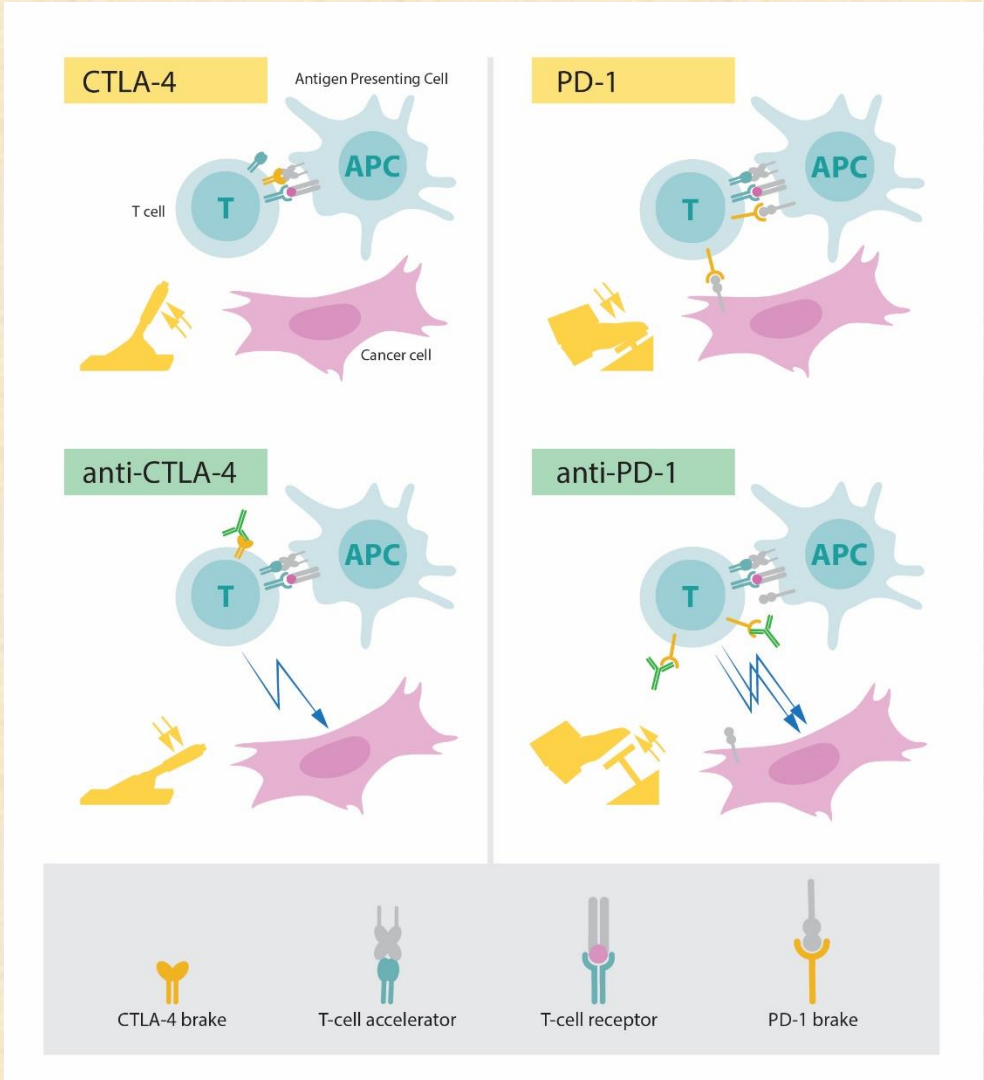

A
T-cell activation
CTLA-4
Activation
TCR
CD28
Activation
B7
MHC
APC
T-cell inhibition
TCR
CD28
CTLA4
Inhibition
B7
MHC
APC
T-cell remains activated
Activation
TCR
CTLA-4
CD28
Activation
B7
MHC
APC
Ipilimumab
blocks
CTLA-4
B
TCR: MHC antigen
CD28: B7
T-cell activation
CTLA-4: B7
T-cell inhibition
Ipilimumab
CTLA-4 blockade/T-cell
proliferation

Adhesion/co-stimulation, as therapeutic target

Name	Target	Effect	Application
Anti-α4 integrin (natalizumab)	α4 integrin	Inhibition of adhesion	Autoimmunity (SM, Morbus Crohn)
CTLA4-Ig (Abatacept)	B7	T-cell inhibition	Autoimmunity (RA)
Anti-CTLA4 (Ipilimumab)	CTLA4	T-cell activation	Tumor (melanom, NSCLC, SCLC)
Anti-PD-1 (Nivolumab)	PD-1	T-cell activation	Tumor (melanom, NSCLC, RCC)

Nobel Laureates in 2018 for medicine and physiology

James P. Allison



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