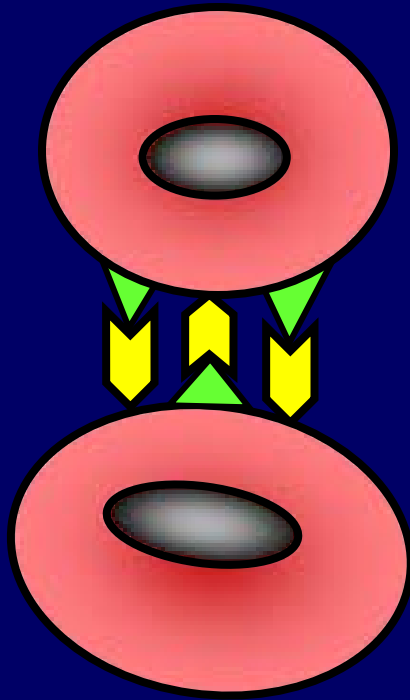
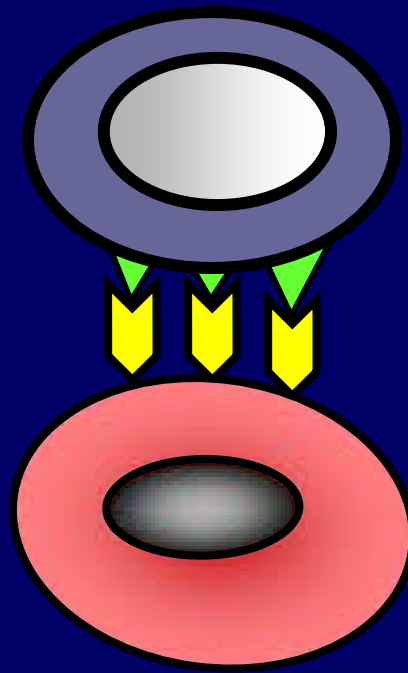


# Cellular Interactions

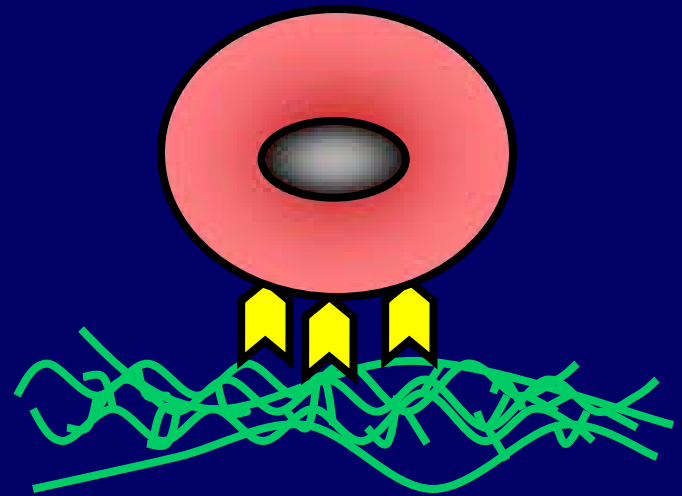
Homotypic



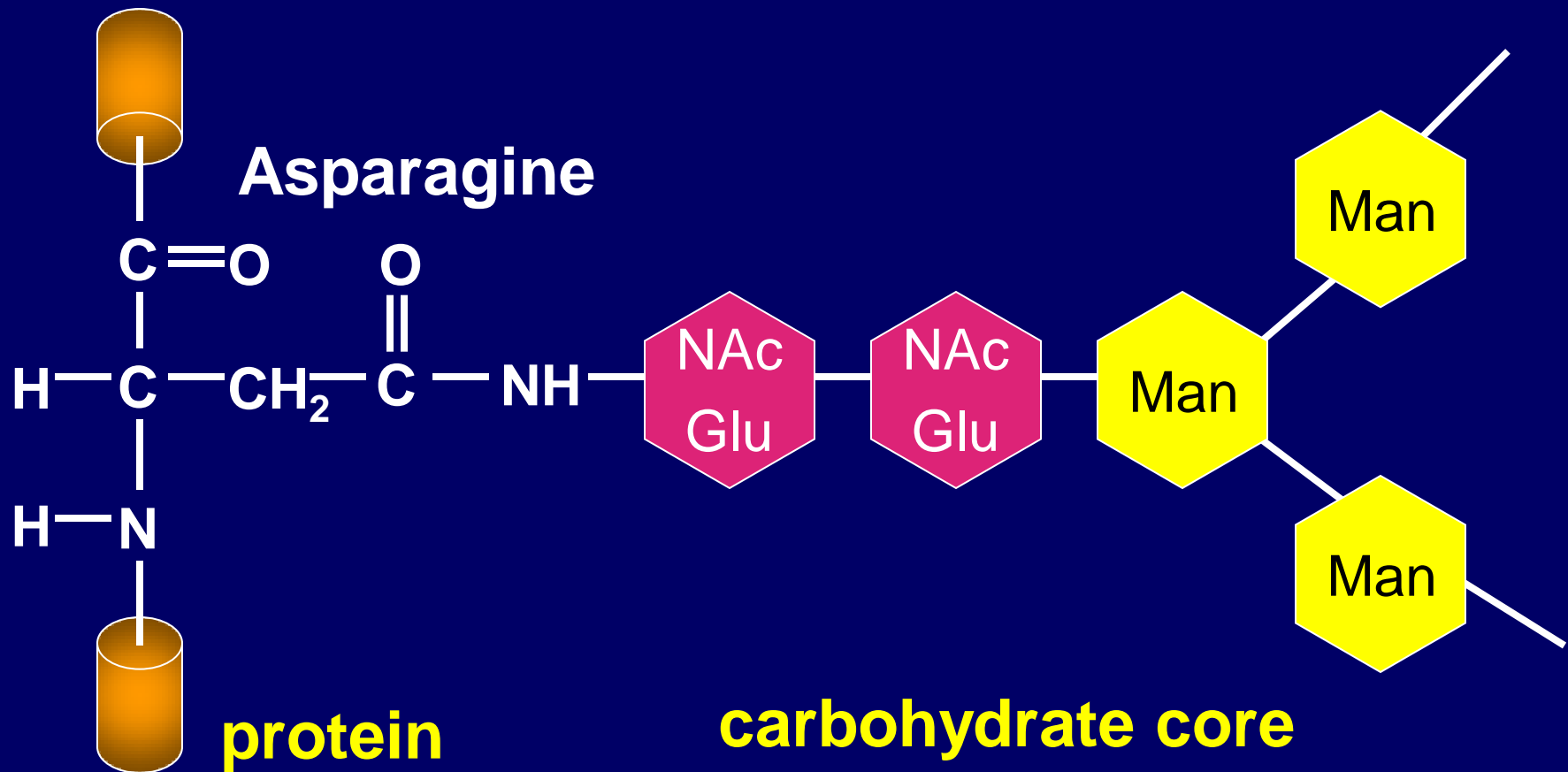
Heterotypic



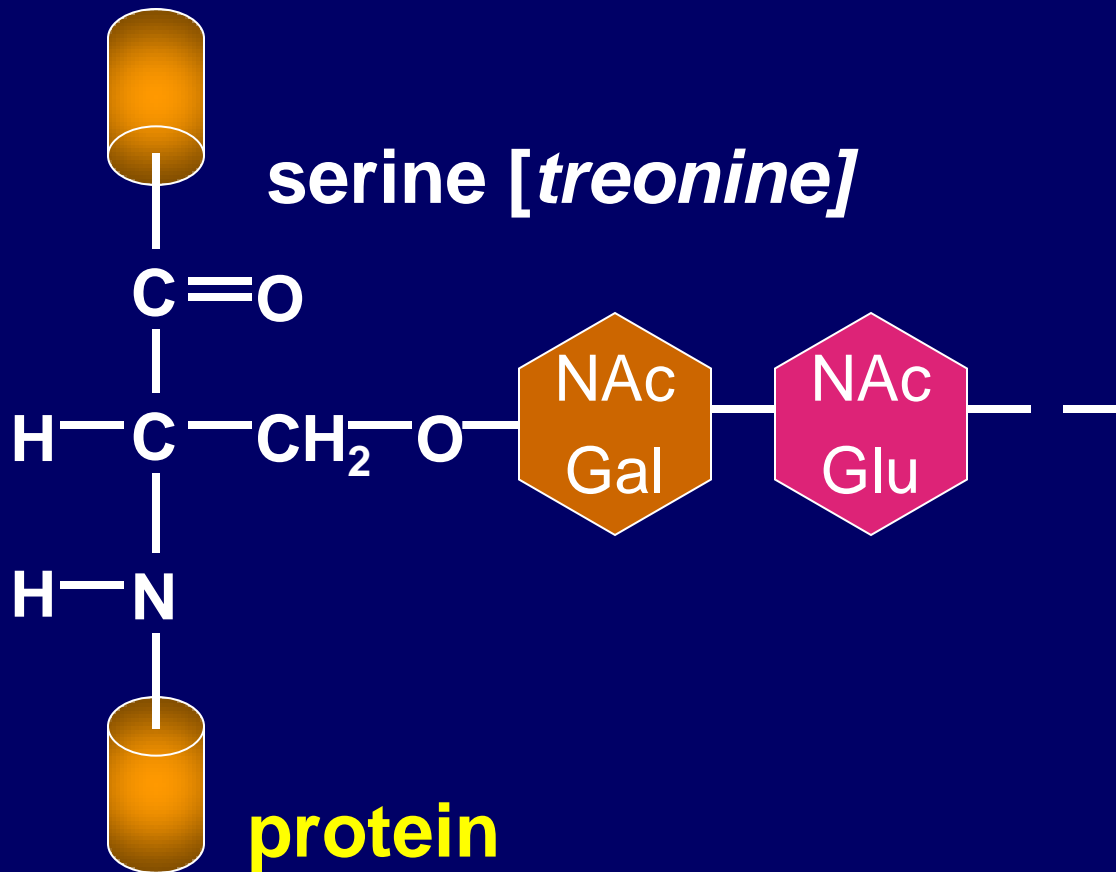
Cell-ECM



# N-glycosylation



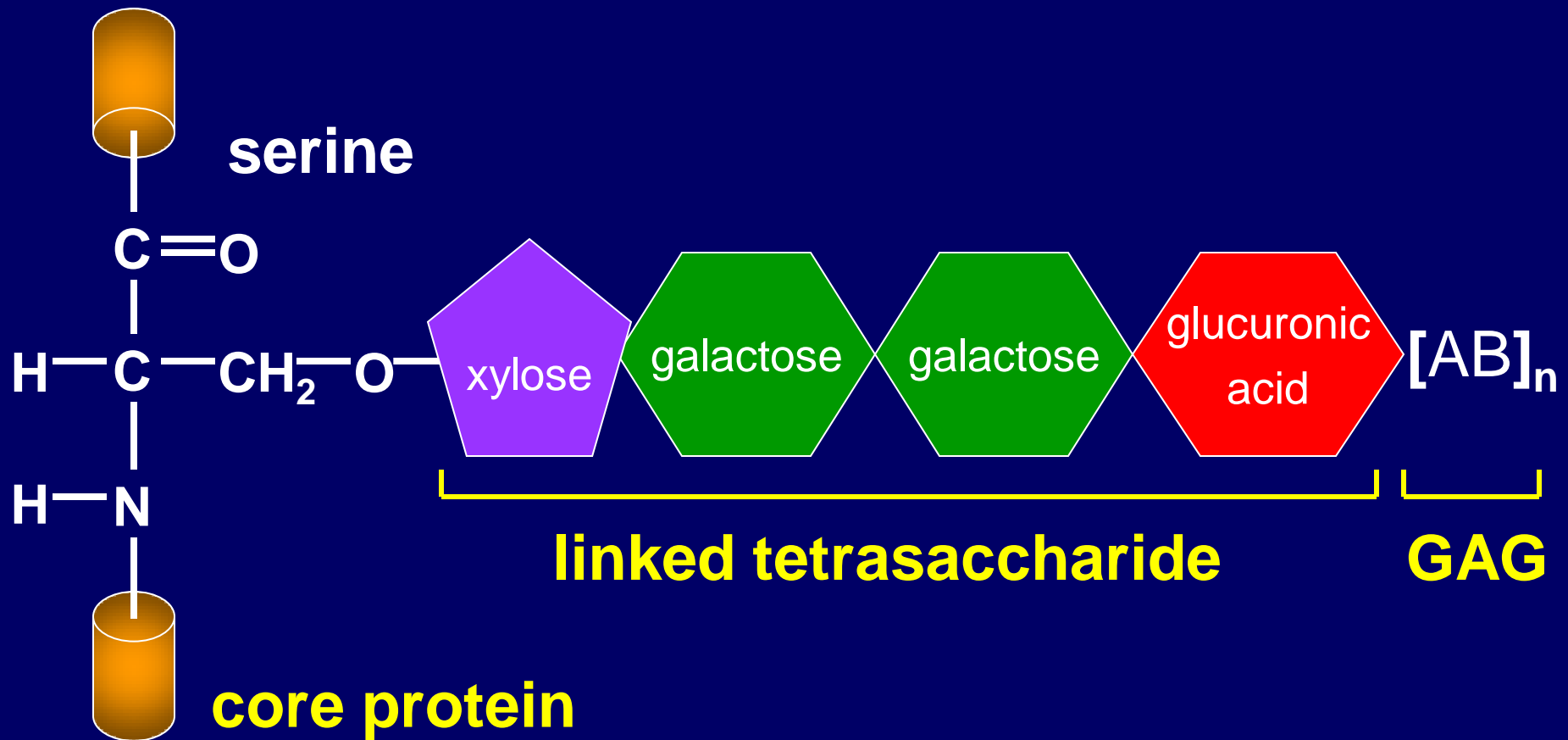
# O-glycosylation



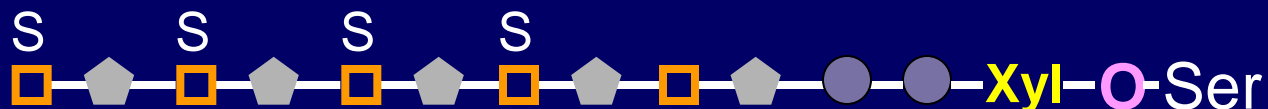
# The Glycosaminoglycans

Glycosamino- glycan	MW [kDa]	Repeating Disaccharide(A-B) <sub>n</sub>		Sulfates per (A-B) unit	Linked to protein
		Monosaccharide A	Monosaccharide B		
Hyaluronic acid	4-8000	D-glucuronic acid	N-acetyl- D-glucosamine	0	-
Chondroitin sulfate	5-50	D-glucuronic acid	N-acetyl- D-galactosamine	0.2-2.3	+
Dermatan sulfate	15-40	D-glucuronic acid or L-iduronic acid	N-acetyl- D-galactosamine	1.0-2.0	+
Heparan sulfate	5-12	D-glucuronic acid or L-iduronic acid	N-acetyl- D-glucosamine	0.2-2.0	+
Heparin	6-25	D-glucuronic acid or L-iduronic acid	N-acetyl- D-glucosamine	2.0-3.0	+
Keratan sulfate	4-19	D-galactose	N-acetyl- D-glucosamine	0.9-1.8	+

# The linkage between a GAG chain and its core protein

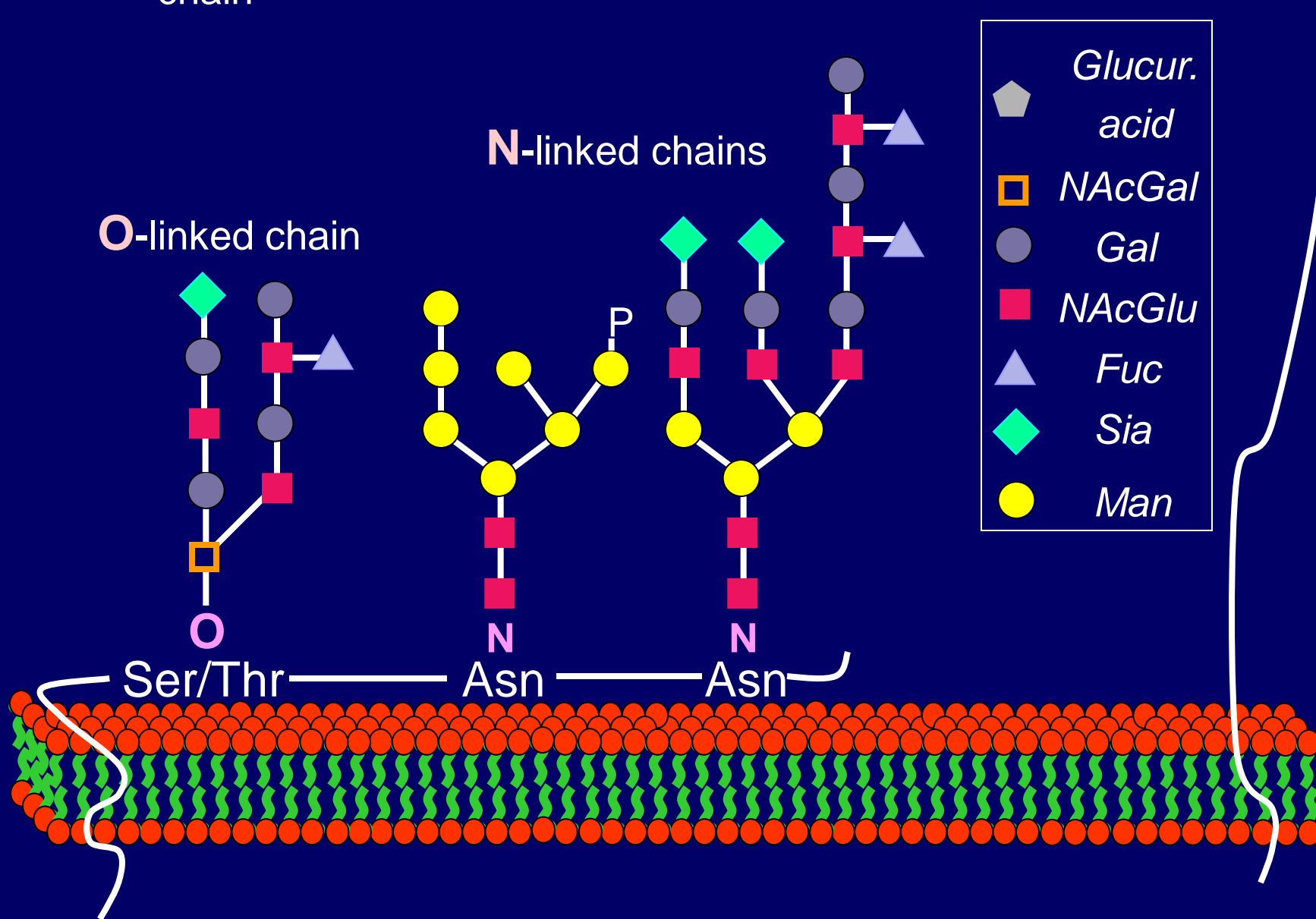
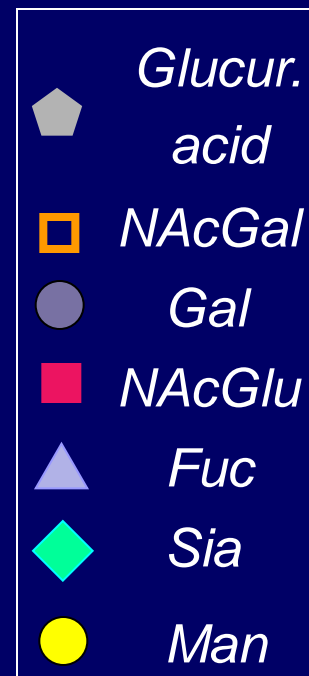


Glycosaminoglycan  
chain



N-linked chains

O-linked chain



# Adhesion molecules

- Integrins
- Immunoglobulin Superfamily
- Selectins
- Mucin-like molecules
- Cadherins
- Cartilage link proteins

# The Integrin Family

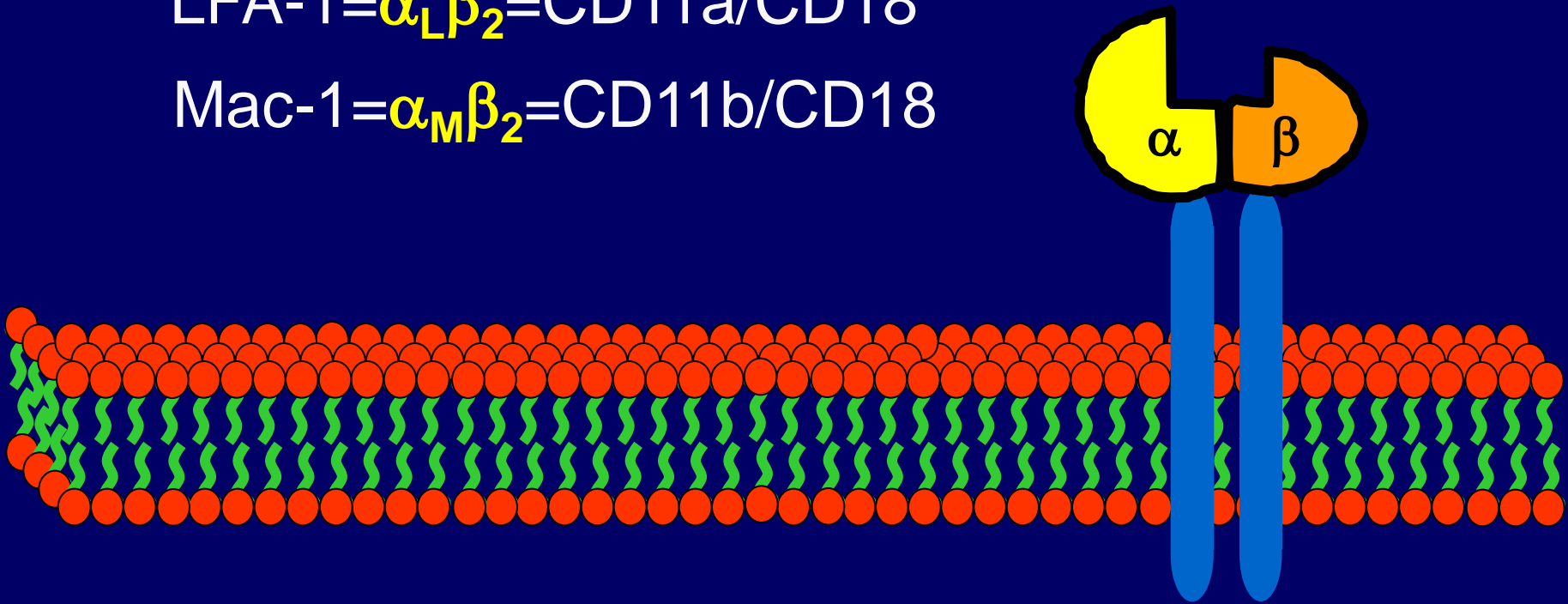
- Are composed of two subunits,  $\alpha$  and  $\beta$ , that traverse the cell membrane and are characterized by noncovalent interactions
- Can be subdivided into groups based on  $\beta$  subunits
- Are dependent on divalent cations
- Play a critical role in cell-cell and cell-ECM interactions



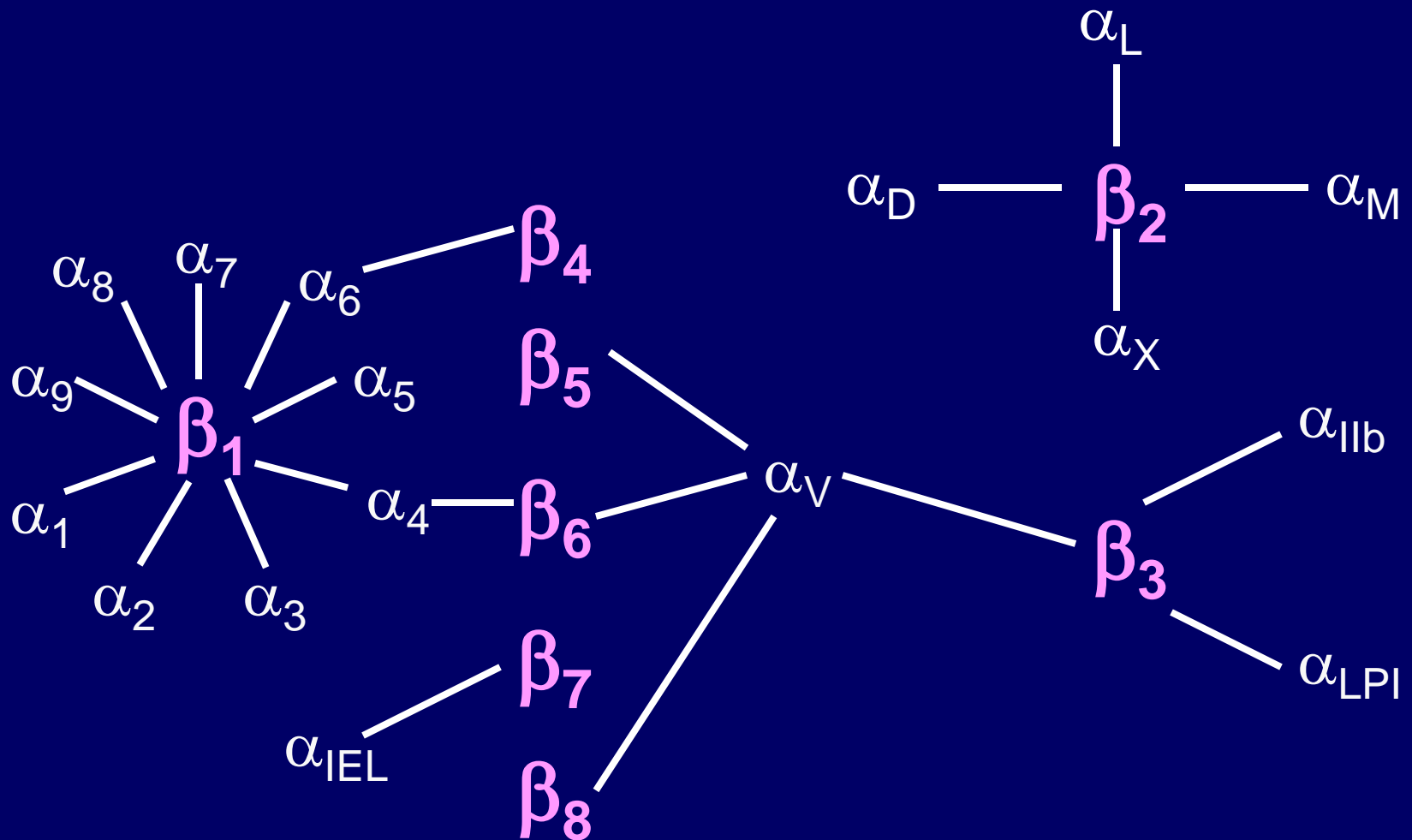
# The Integrins

LFA-1 =  $\alpha_L\beta_2$  = CD11a/CD18

Mac-1 =  $\alpha_M\beta_2$  = CD11b/CD18



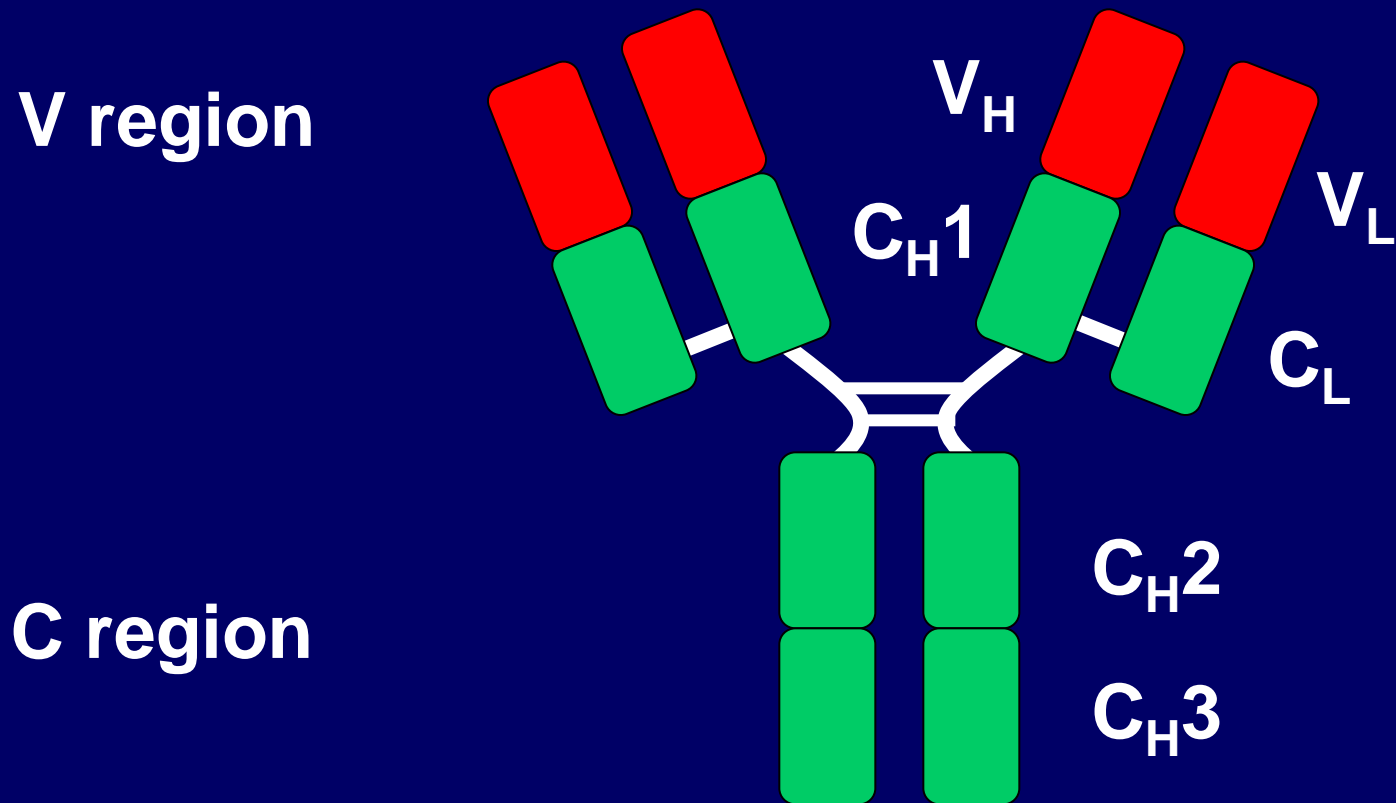
# Organization of the integrin family



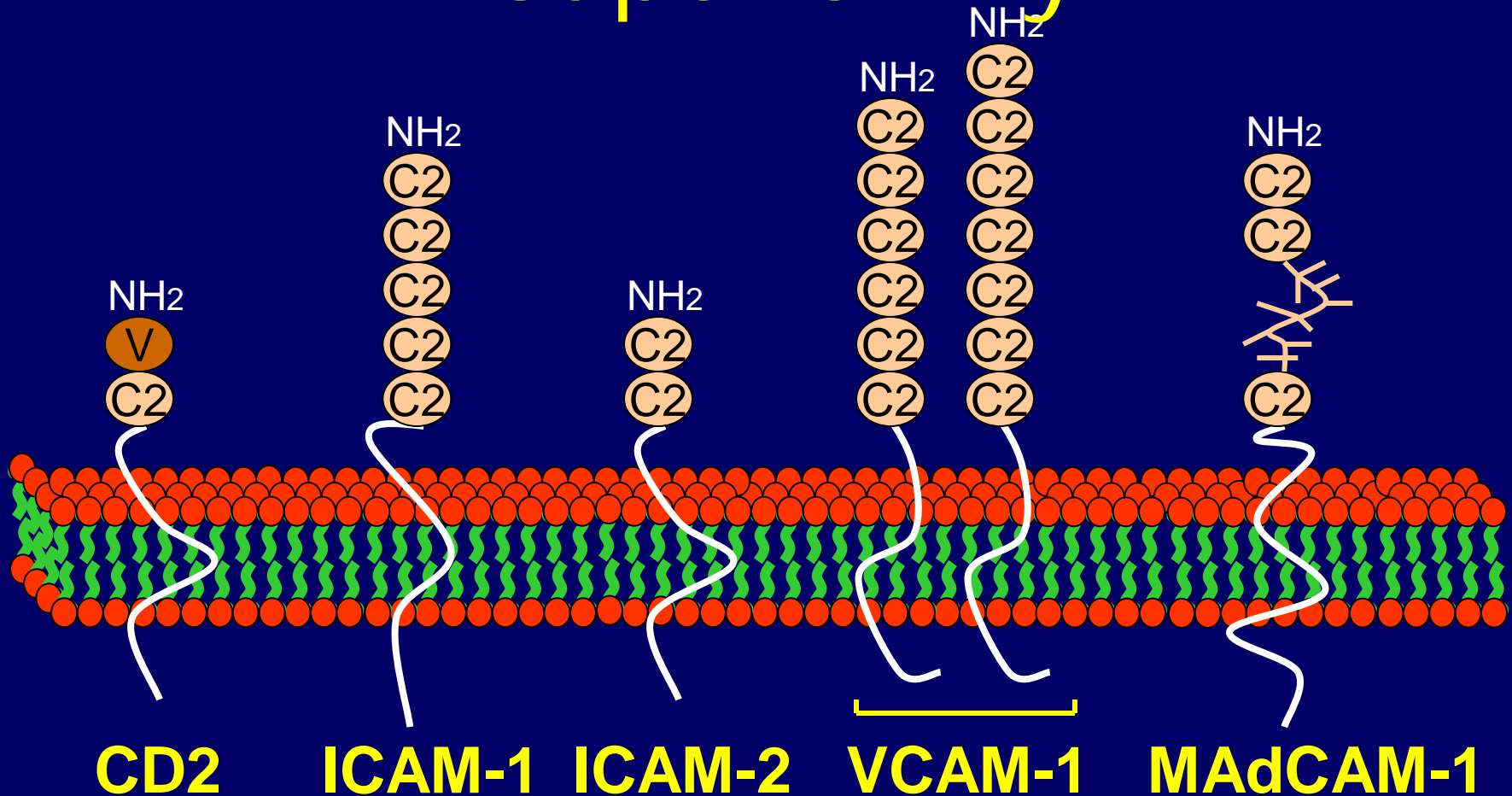
# The Immunoglobulin Superfamily

- Contain one or more of a common Ig-like repeat that is characterized by two cysteines separated by 55 to 75 aa
- Generally they span the cell membrane and contain only a short cytoplasmic tail
- Some are directly involved in Ag recognition [MHC, CD4, CD8]
- Play a key role in immune responses

# Structure of Ig



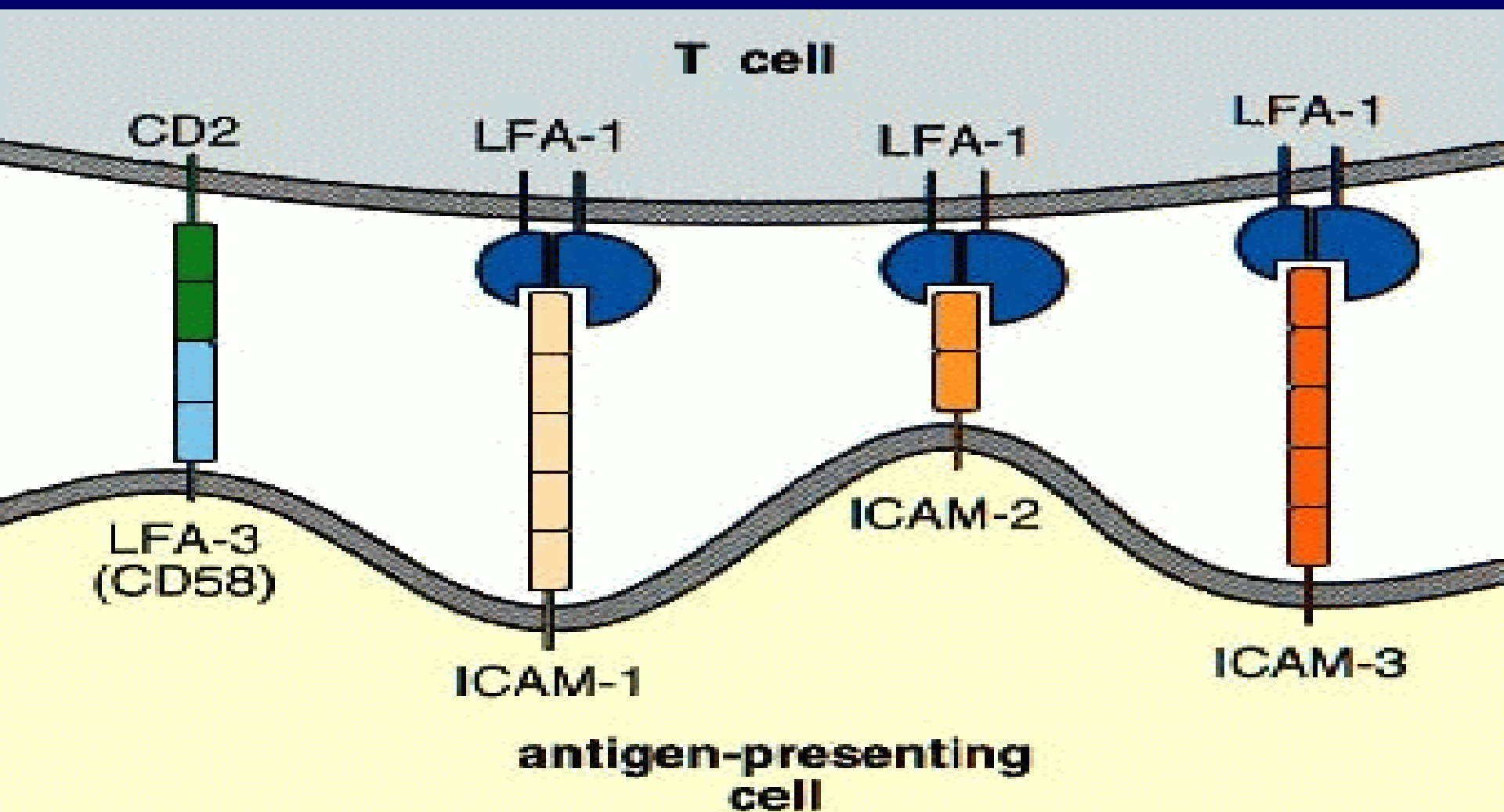
# Members of the Ig superfamily



# Cellular integrin ligands

Ligand	Expression levels	Function
ICAM-1	Broad tissue expression	Leukocyte recruitment to inflammatory sites
ICAM-2	Endothelium, Leukocytes	Leukocyte trafficking, Lymphocyte activation
ICAM-3	Leukocytes	Lymphocyte activation
VCAM-1	Inflammed endothelium, DC	Leukocyte recruitment to inflammatory sites, Leukocyte trafficking
MAdCAM-1	HEV of PP and MLN	Leukocyte recruitment to intestinal tissues
E-Cadherin	Epithelial cells	Adhesion

**Cell-surface molecules of the immunoglobulin superfamily are important in the interactions of lymphocytes with antigen-presenting cells.**



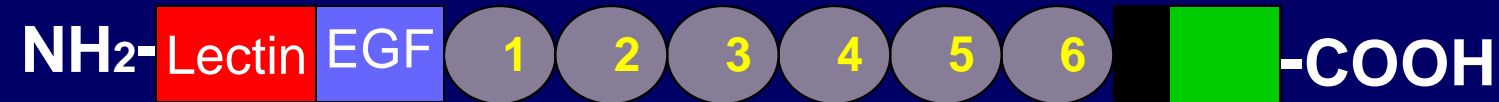
# Selectin Family

- Are  $\text{Ca}^{2+}$  dependent
- Bind carbohydrate ligands [sLe<sup>x</sup>]
- Low ligand affinity, rapid interactions with ligand

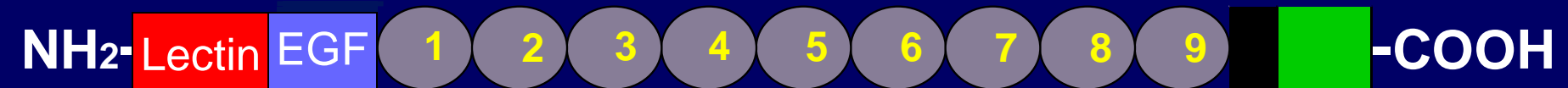


# The selectin family

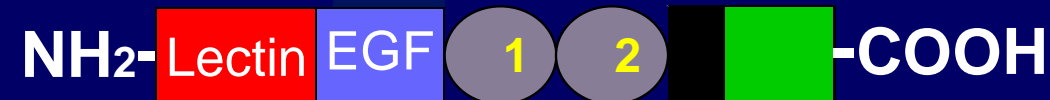
## E-selectin



## P-selectin



## L-selectin

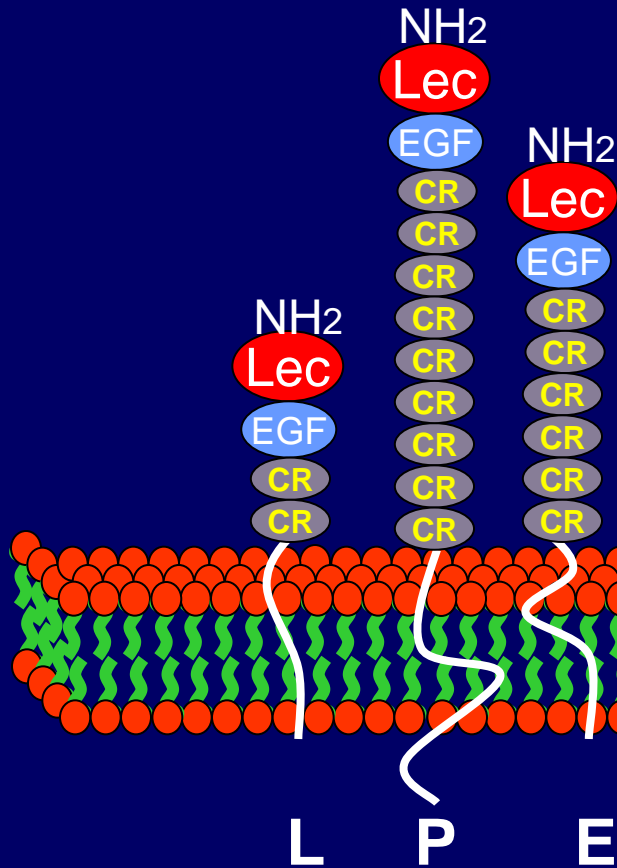


 = Complement Regulatory-Like Modules

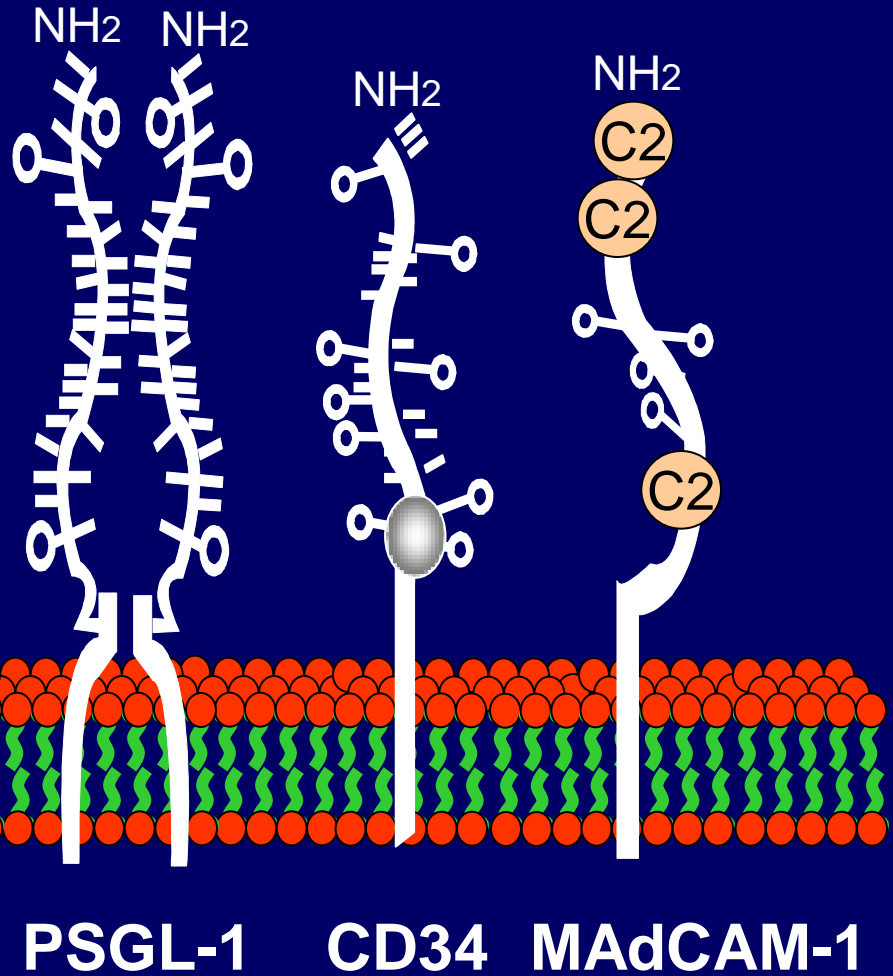
# Mucin-like molecules

- Are rich in serine and treonine
- Are heavily glycosylated (O-linked carbohydrates)

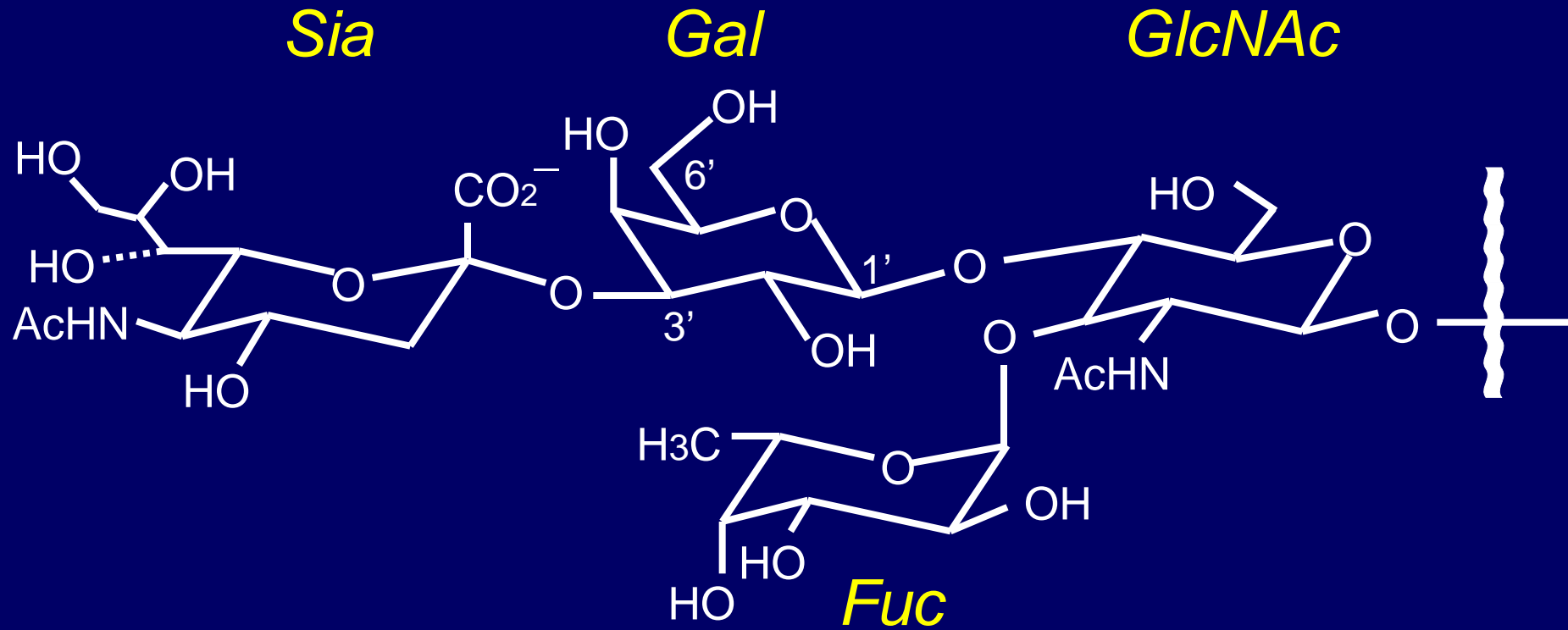
## Selectins



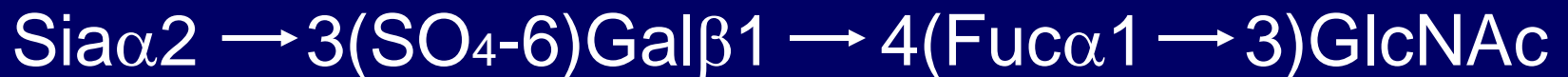
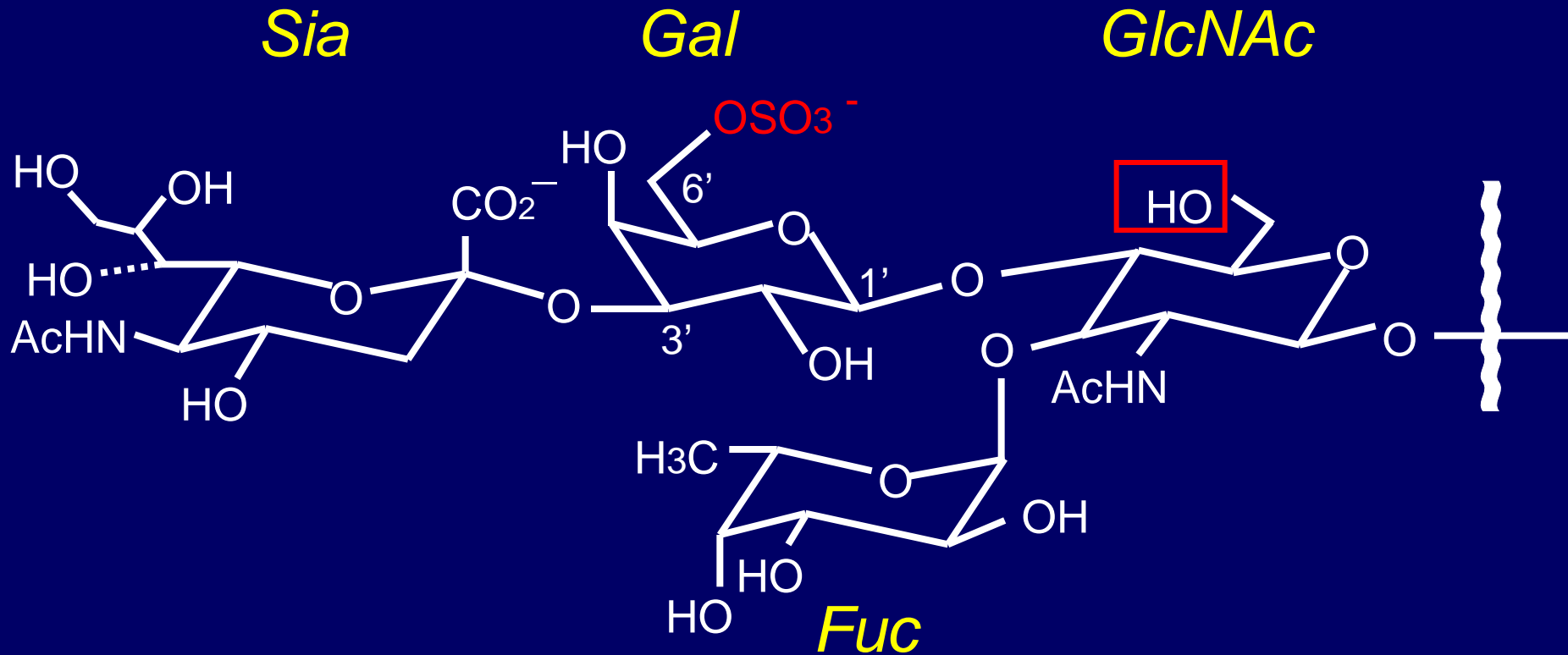
## Mucin-like molecules



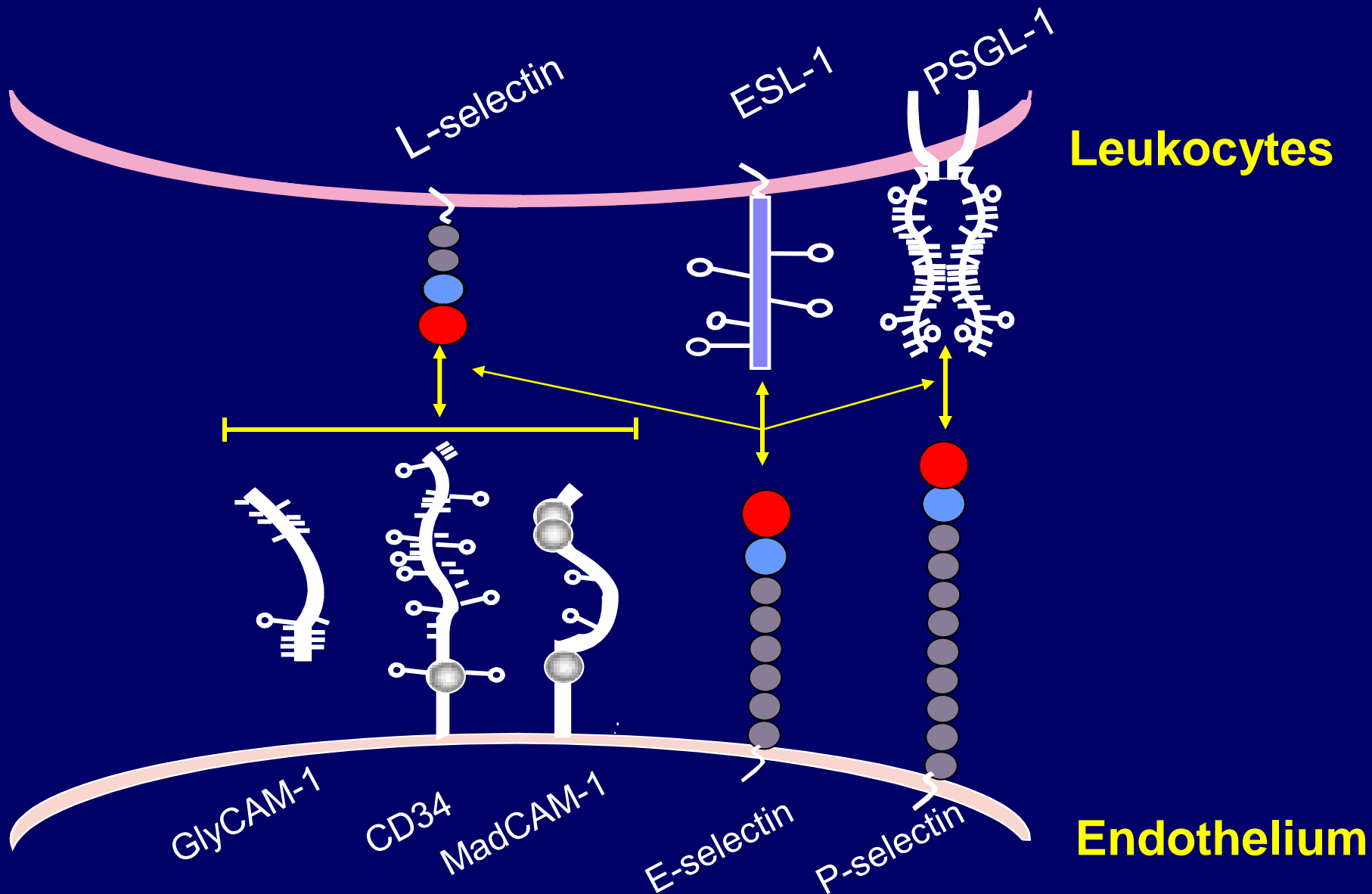
# Sialyl Lewis x



# 6'-Sulfated sLe<sup>x</sup>



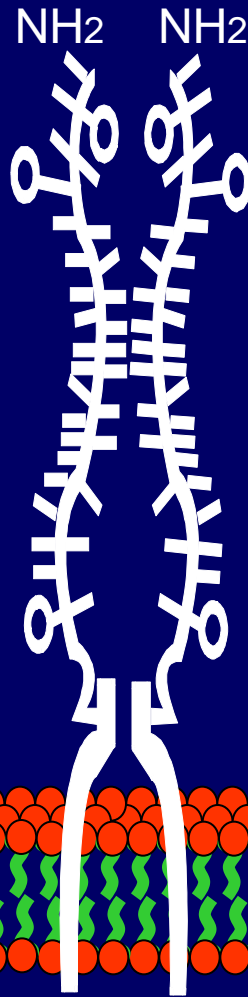
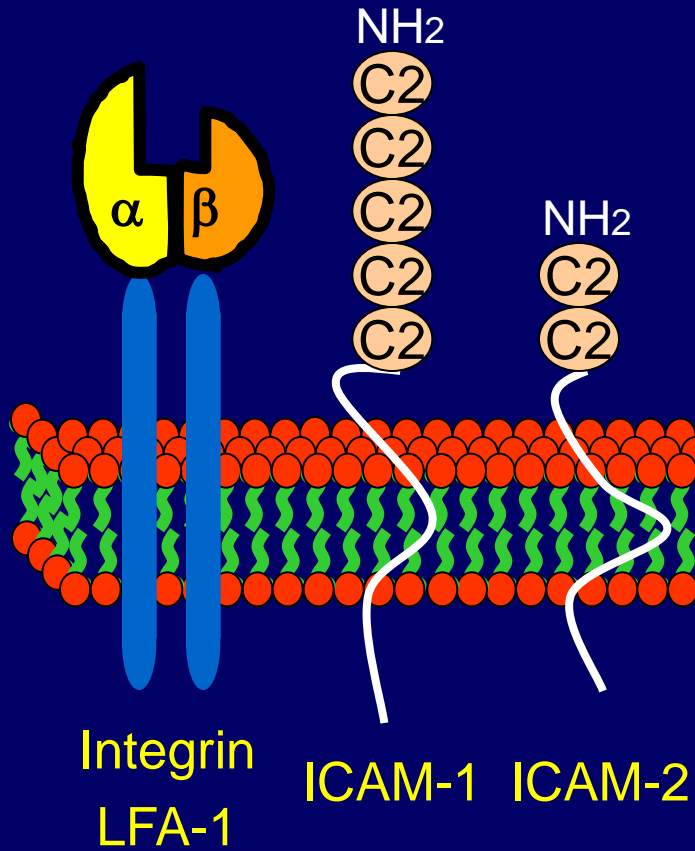
# Selectin ligands



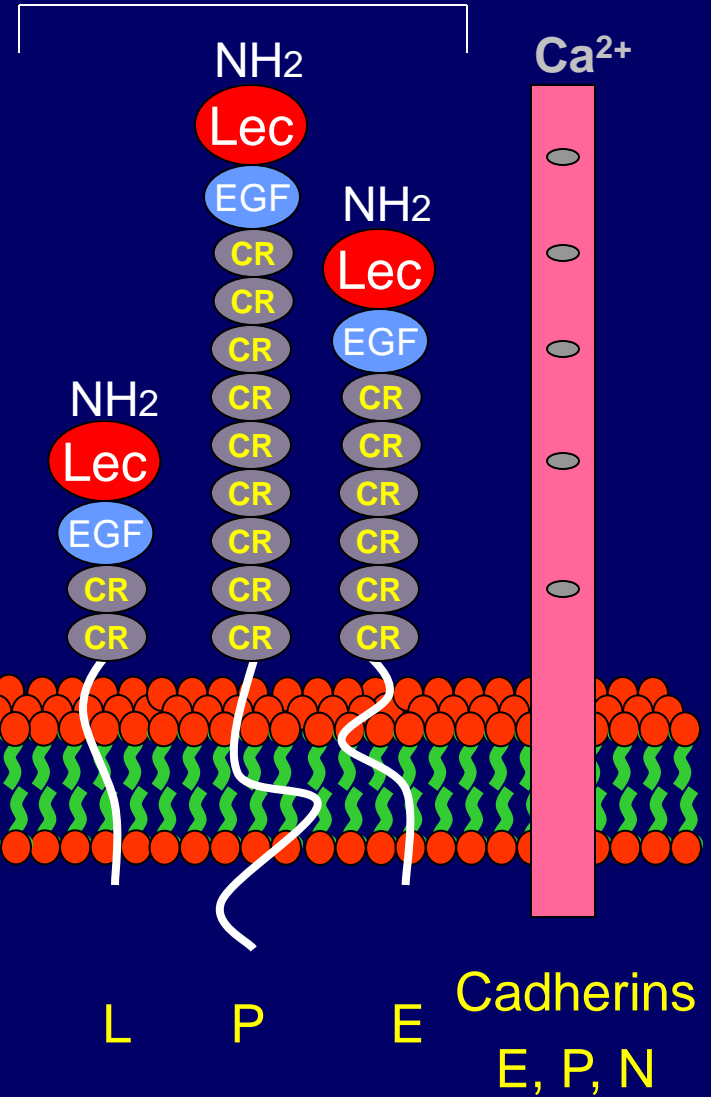
# Cadherin Family

- Mediate homotypic cellular interactions by binding to their homologues on an adjacent cell
- $\text{Ca}^{2+}$  is critical to their function and serves to maintain the structural integrity of the protein
- Are comprised of E-(epithelial), P-(placental), N-(neural) cadherins

## Ig Family



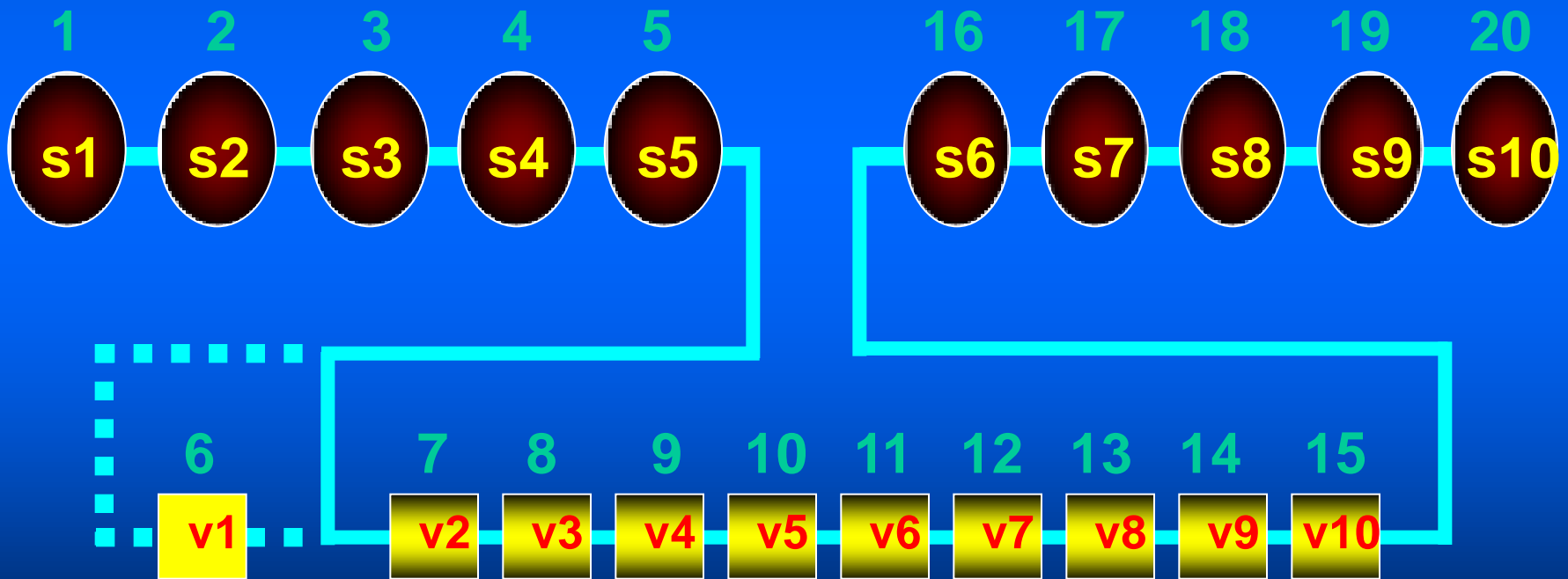
## Selectins





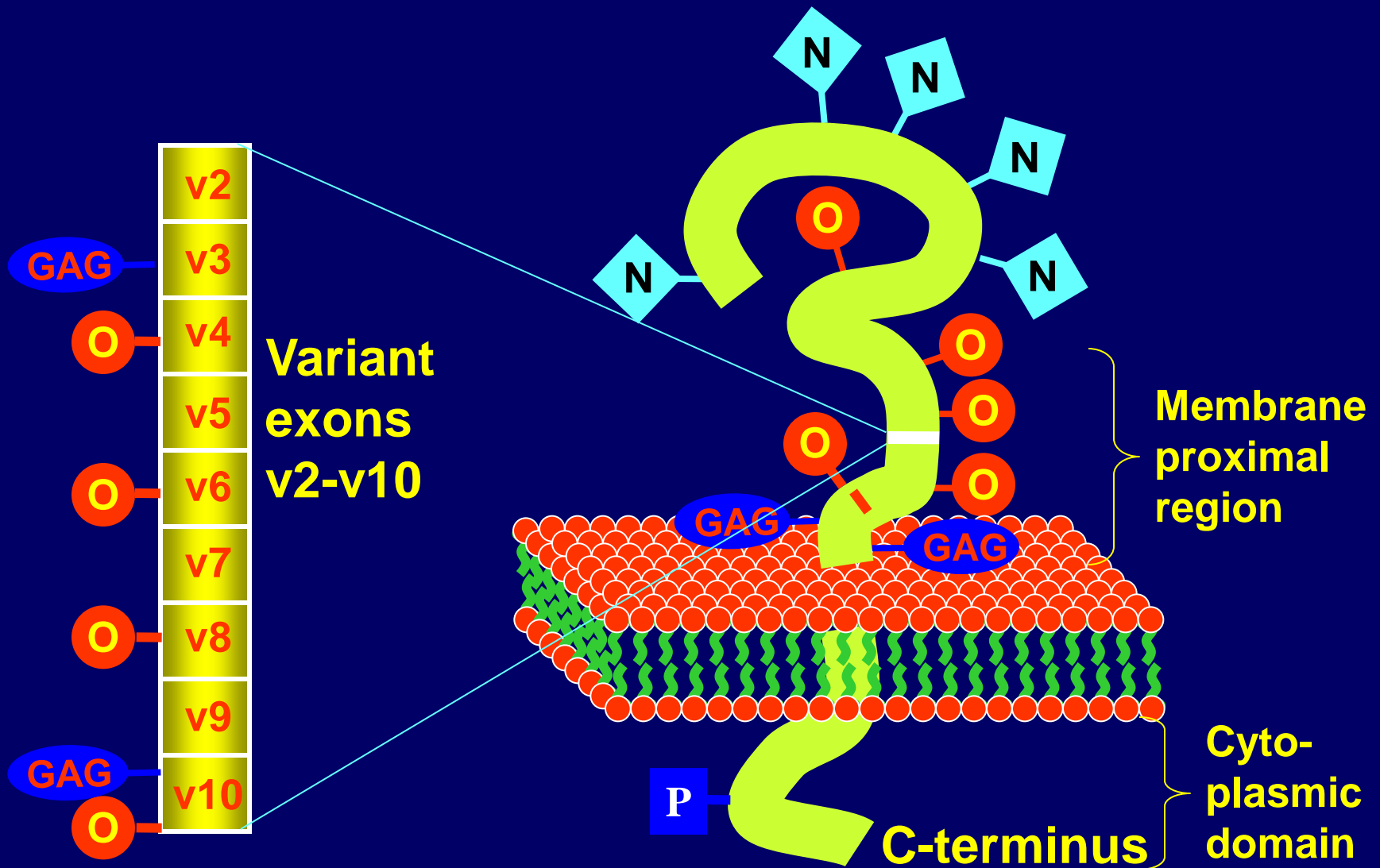
# CD44 gene

Standard exons (CD44s = 363 amino acids = 37 kDa)

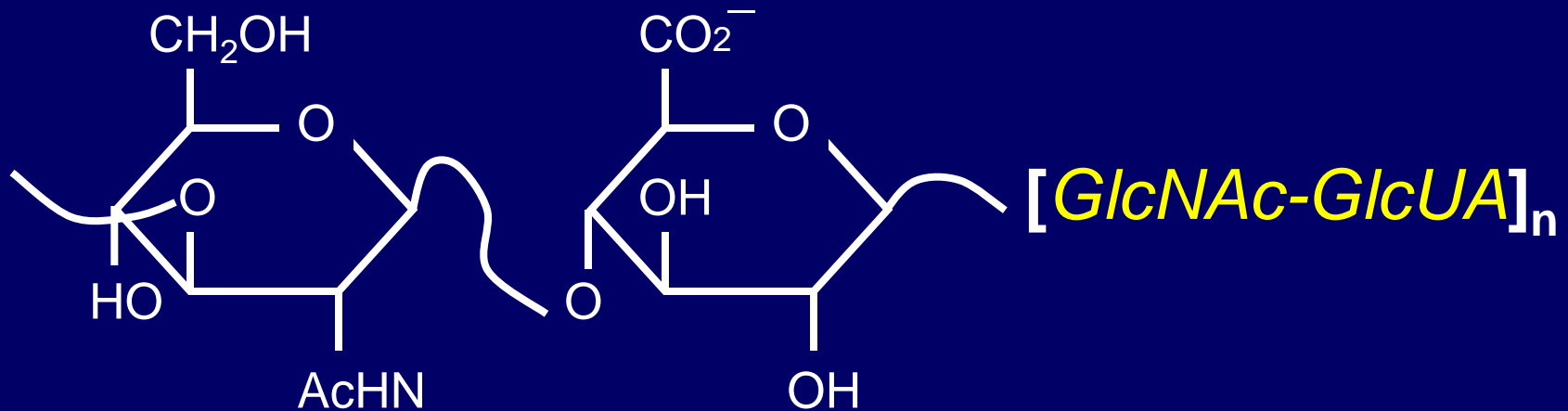


Variant exons (381 amino acids = 39 kDa)

# CD44 protein



# Hyaluronan



N-acetylglucosamine    Glucuronic acid

*GlcNAc*

*GlcUA*

# Chemokines

- A group of small (~8-14 kDa), structurally related molecules that regulate directional migration-chemotaxis
- Are divided into subfamilies based on the arrangement of the two N-terminal cysteine residues [CCL, CXCL, CX<sub>3</sub>CL, CL]

# The chemokines

CC	MCP-1, 2, 3, 4	Monocyte chemotactic peptide 1, 2, 3, 4
	RANTES	Regulated on activation, normal T cell expressed and secreted
	MIP-1 $\alpha$ , -1 $\beta$	Macrophage inflammatory protein 1 $\alpha$ , 1 $\beta$
	Eotaxin	Eosinophil chemoattractant protein
	I309	Intercrine- $\beta$ glycoprotein 309
	TARC (CCL17)	Thymus and activation-regulated chemokine
	MDC	Macrophage-derived chemokine
	LARC	Liver and activation-regulated chemokine
	ELC	EBL1-ligand chemokine
	SLC (CCL21)	Secondary lymphoid tissue chemokine

# The chemokines

CXC	IL-8	Interleukin-8
	GRO $\alpha, \beta, \gamma$	Growth related protein $\alpha, \beta, \gamma$
	NAP-2	Neutrophil-activating peptide 2
	ENA-78	Epithelial cell-derived neutrophil-activating peptide 78
	GCP-1	Granulocyte chemotactic protein 2
	IP-10	IFN $\gamma$ -inducible 10 kDa protein
	MIG	Monocyte/Mac activating IFN $\gamma$ -inducible protein
	I-TAC	IFN $\gamma$ -inducible, T cell activating $\alpha$ chemokine
	SDF-1 (CXCL12)	Stromal cell-derived factor 1
	BCA-1 (CXCL13)	B cell-attracting chemokine 1

# The chemokines

<b>CX<sub>3</sub> C</b>	Fractalkine/Neurotactin
<b>C</b>	Ltn Lymphotactin

# Chemokines and their receptors involved in leukocyte trafficking

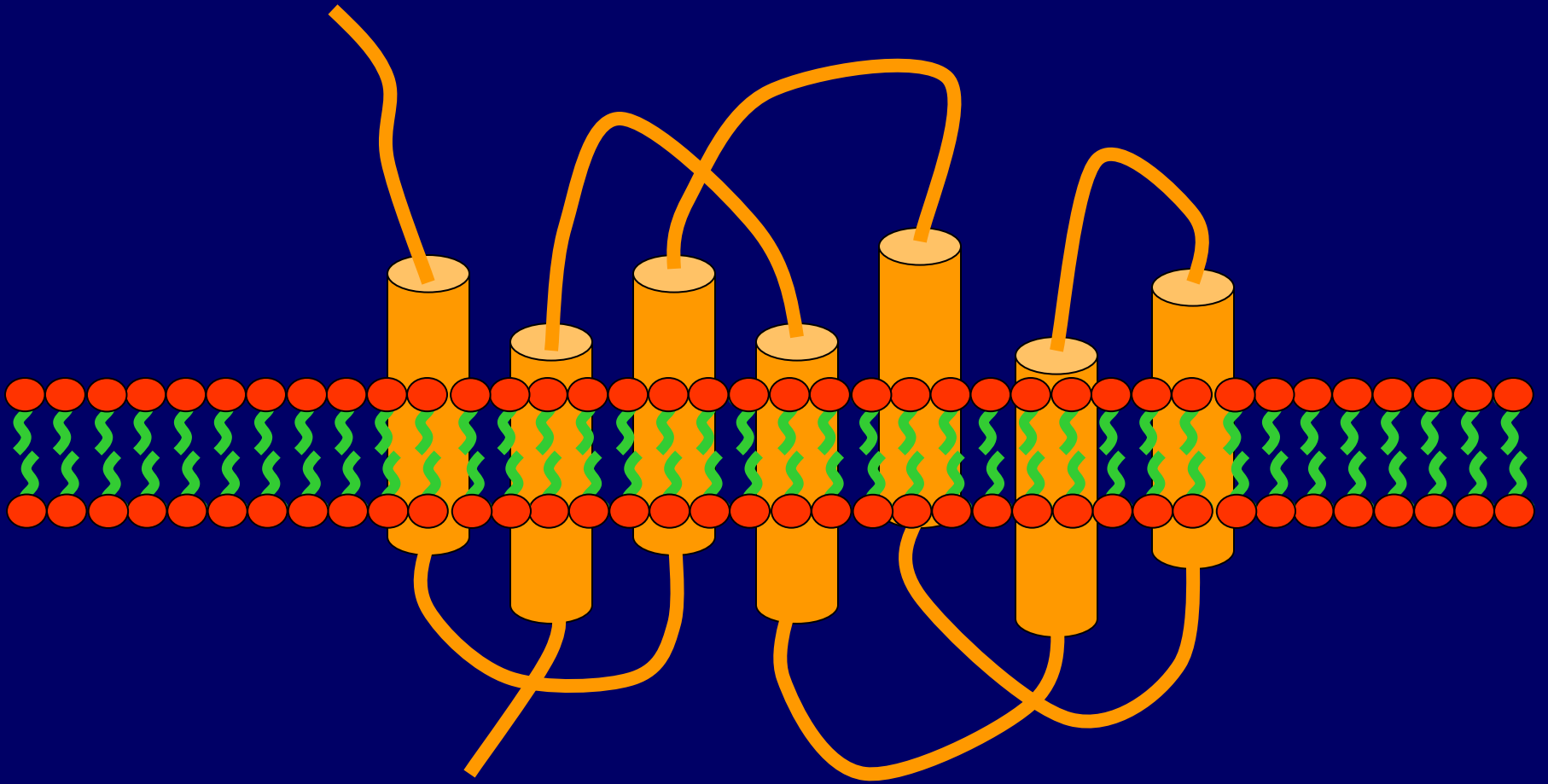
Inflammatory	Chemokines	Receptors	Functions
	I-TAC, MIG, IP10	CXCR <sub>3</sub>	Effector T cells
	CXCL <sub>16</sub>	CXCR <sub>16</sub>	Effector T cells
	RANTES, MIP-1 $\alpha$ , MCP-2, MCP-3	CCR <sub>1</sub>	Effector T cells
	MCP-1, MCP-2, MCP-3, MCP-4	CCR <sub>2</sub>	Effector T cells
	Eotaxin-1, -2, -3, RANTES, MCP-2	CCR <sub>3</sub>	Effector T cells (T <sub>H</sub> 2)
	MCP-3, MCP-4, MEC, RANTES, MIP-1 $\alpha$ , MIP-1 $\beta$ , MCP-2	CCR <sub>5</sub>	Effector T cells (T <sub>H</sub> 1)
	I309	CCR <sub>8</sub>	Effector T cells (T <sub>H</sub> 2)
	Fractalkine	CX <sub>3</sub> CR1	Effector T cells



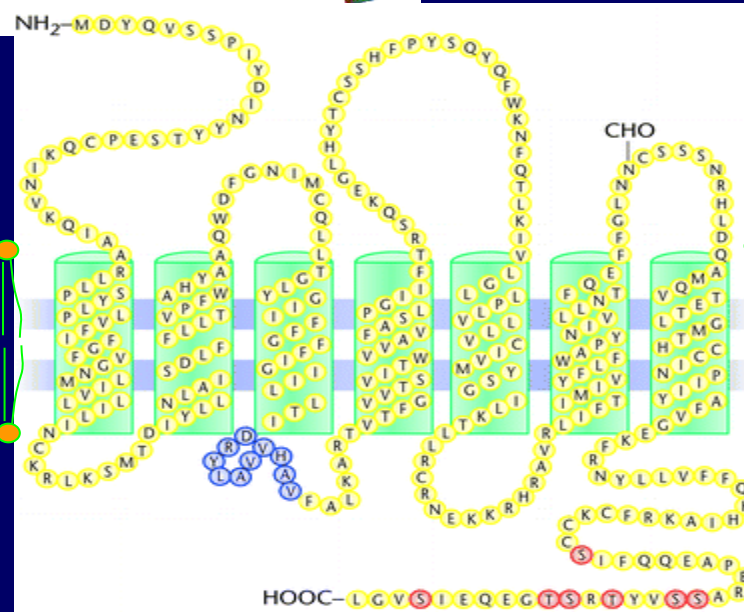
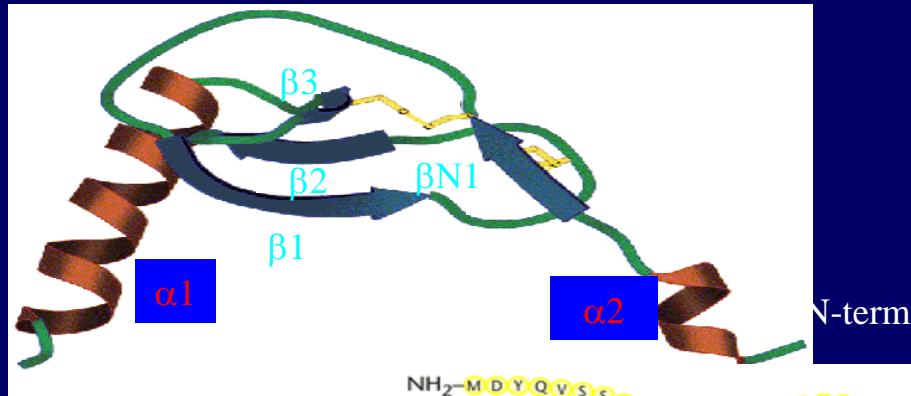
# Chemokines and their receptors involved in leukocyte trafficking

	Chemokines	Receptors	Functions
Homeostatic	CTACK, MEC	CCR <sub>10</sub>	Memory T cells (CLA)
	SDF-1	CXCR <sub>4</sub>	Naive, memory T cells, B cells, thymocytes
	BCA-1	CXCR <sub>5</sub>	Follicular B helper T cells, B cells
	SLC, ELC	CCR <sub>7</sub>	Naive, central memory T cells, B cells, thymocytes
	TECK	CCR <sub>9</sub>	Memory T cells ( $\alpha_4\beta_7$ ), B cells, immature thymocytes
	DC-CK1	CCR <sub>5</sub>	Naive T cells
	MDC, TARC	CCR <sub>8</sub>	Effector T cells (T <sub>H</sub> 1, T <sub>H</sub> 2), Memory T cells (CLA), thymocytes
H and I	LARC	CX <sub>3</sub> CR1	Effector T cells, B cells, memory T cells (CLA, $\alpha_4\beta_7$ )

# Chemokine receptors



# Chemokines and Chemokine Receptors



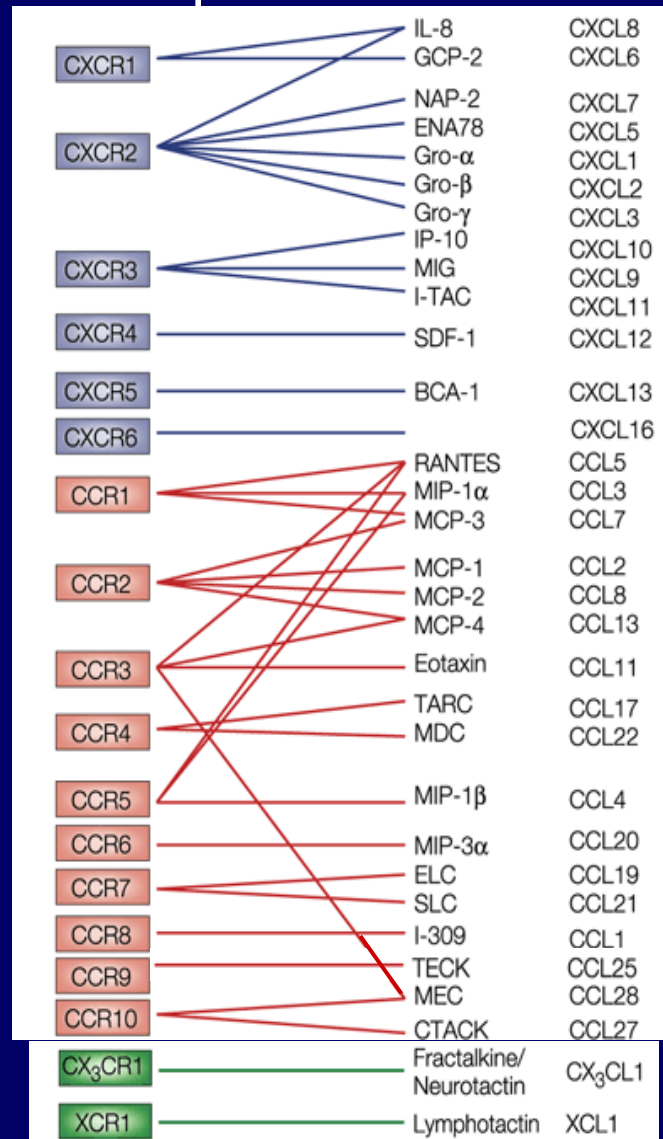
Adhesion  
Migration

Signaling



# Chemokines and Chemokine Receptors

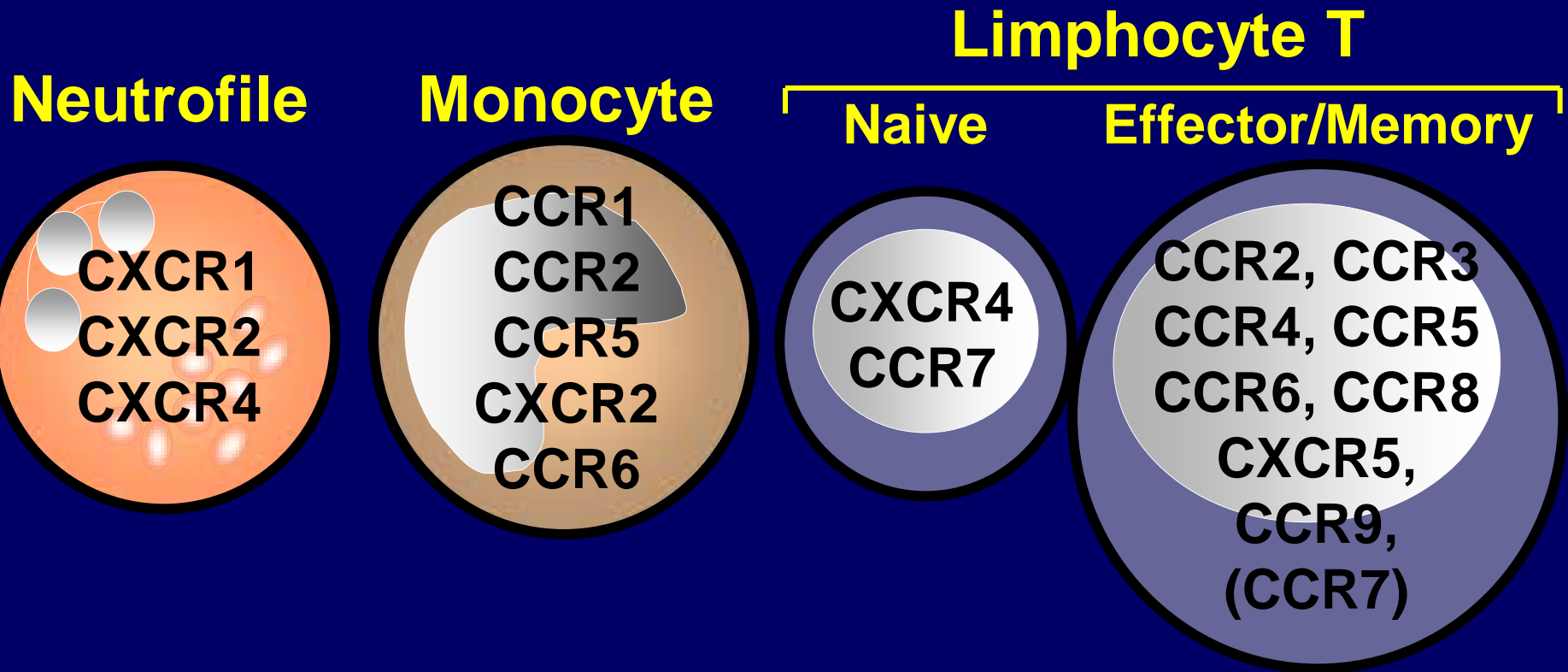
## Receptor Chemokine



Many chemokine receptors are selectively expressed by different leukocyte subsets

Chemokines are expressed differentially in tissues

# Chemokine Receptors in leukocytes



# Biological functions of chemokines

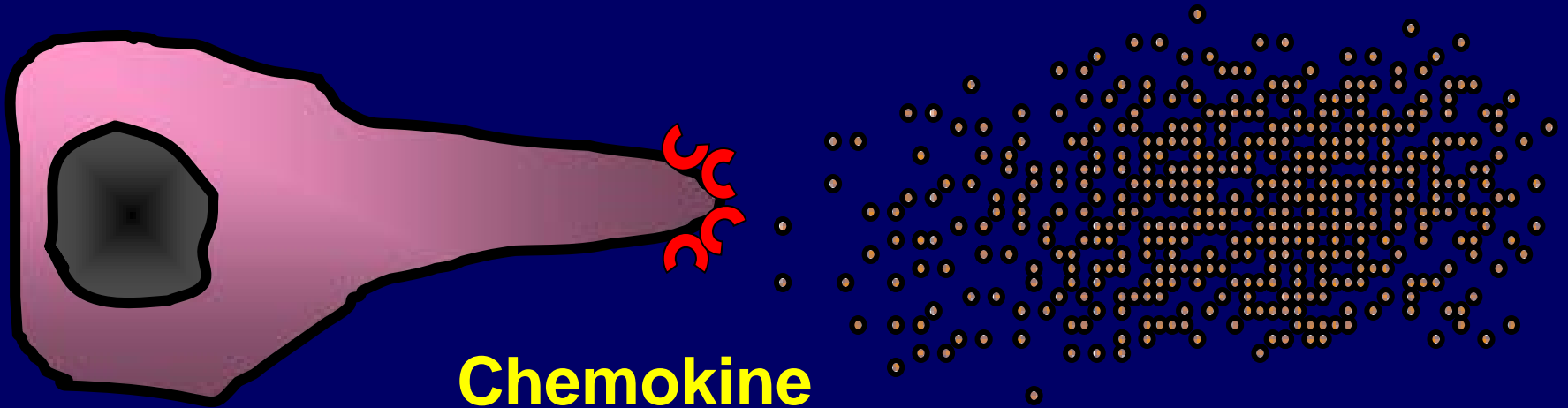
## Leukocyte chemotaxis

**Trailing  
edge**

**Leading  
edge**

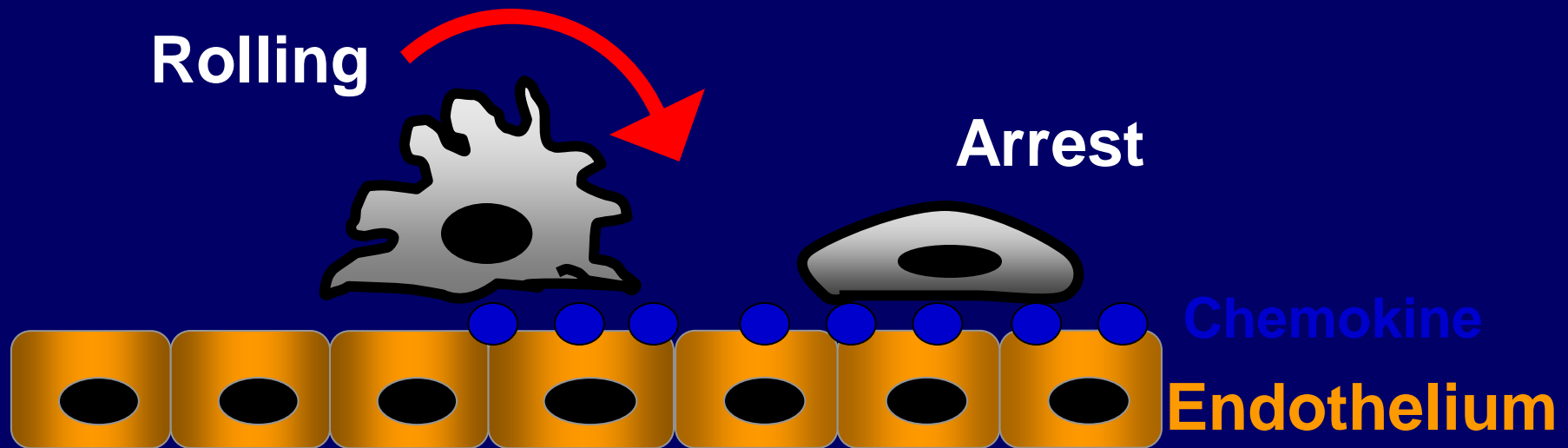
**Chemokine  
receptors**

**Chemokine gradient**



# Biological functions of chemokines

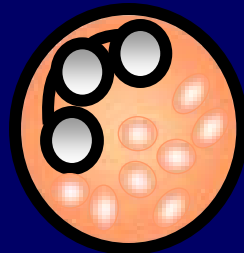
Integrin activation during leukocyte-endothelial interactions



# Biological functions of chemokines

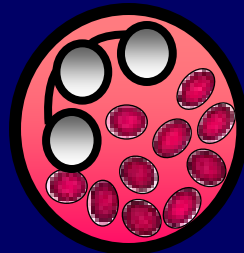
## Leukocyte degranulation and mediator release

**PMN**



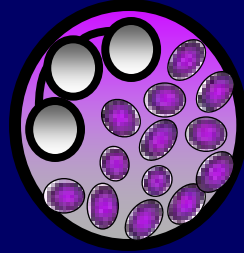
**Myeloperoxidase,  
elastase**

**Eosinophil**



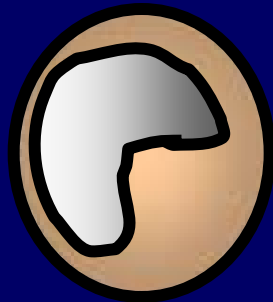
**Cationic proteins,  
peroxidases**

**Mast cell  
basophil**



**Histamine**

**Macrophage**

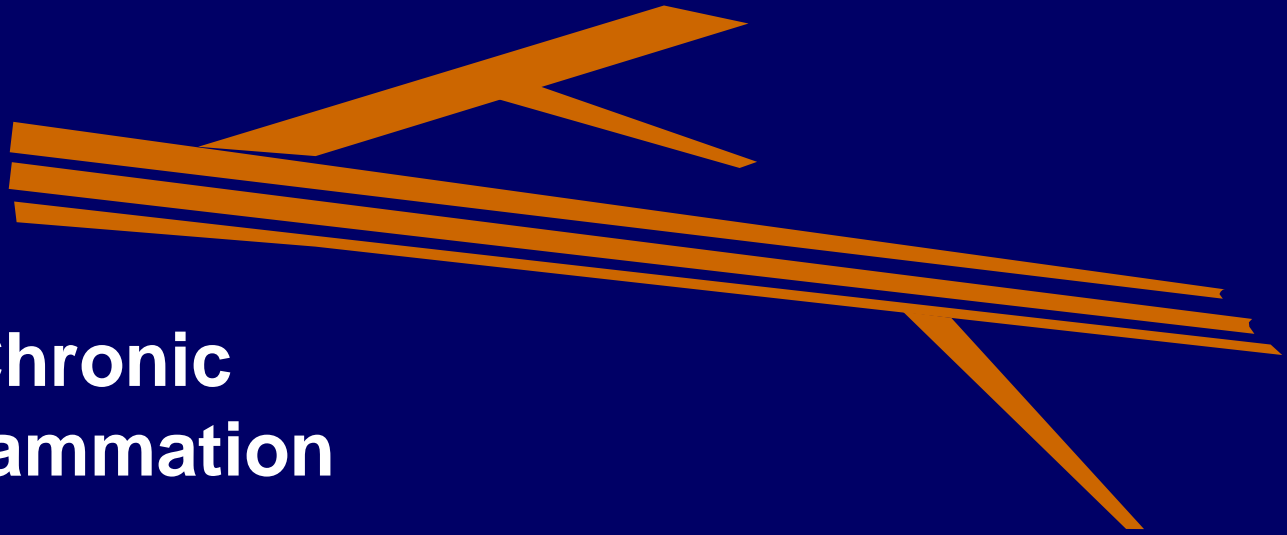


**Respiratory burst**



# Biological functions of chemokines

Angiogenesis or angiostasis



**Chronic  
inflammation**

**Suppression  
of tumor growth**

# Proposed scheme for interaction of HIV with CD4 and CXCR4

