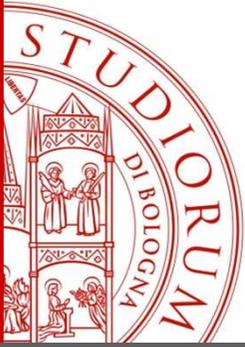
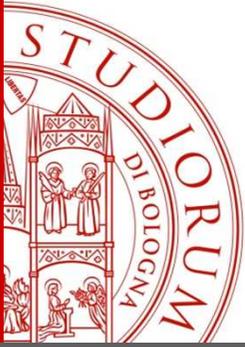


Therapeutic targeting of eosinophil adhesion and accumulation in allergic conjunctivitis

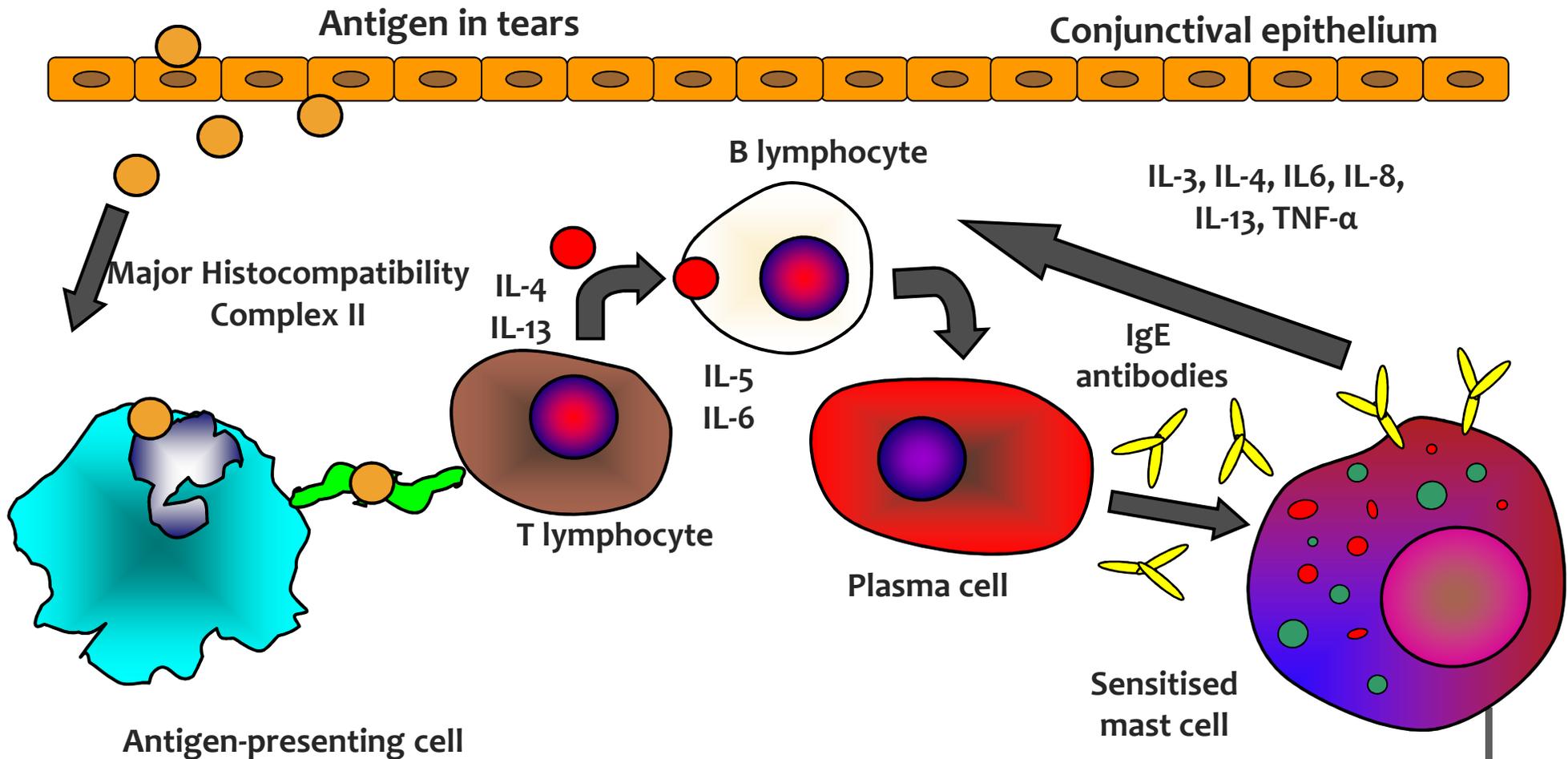


Allergy Inflammation - Medications

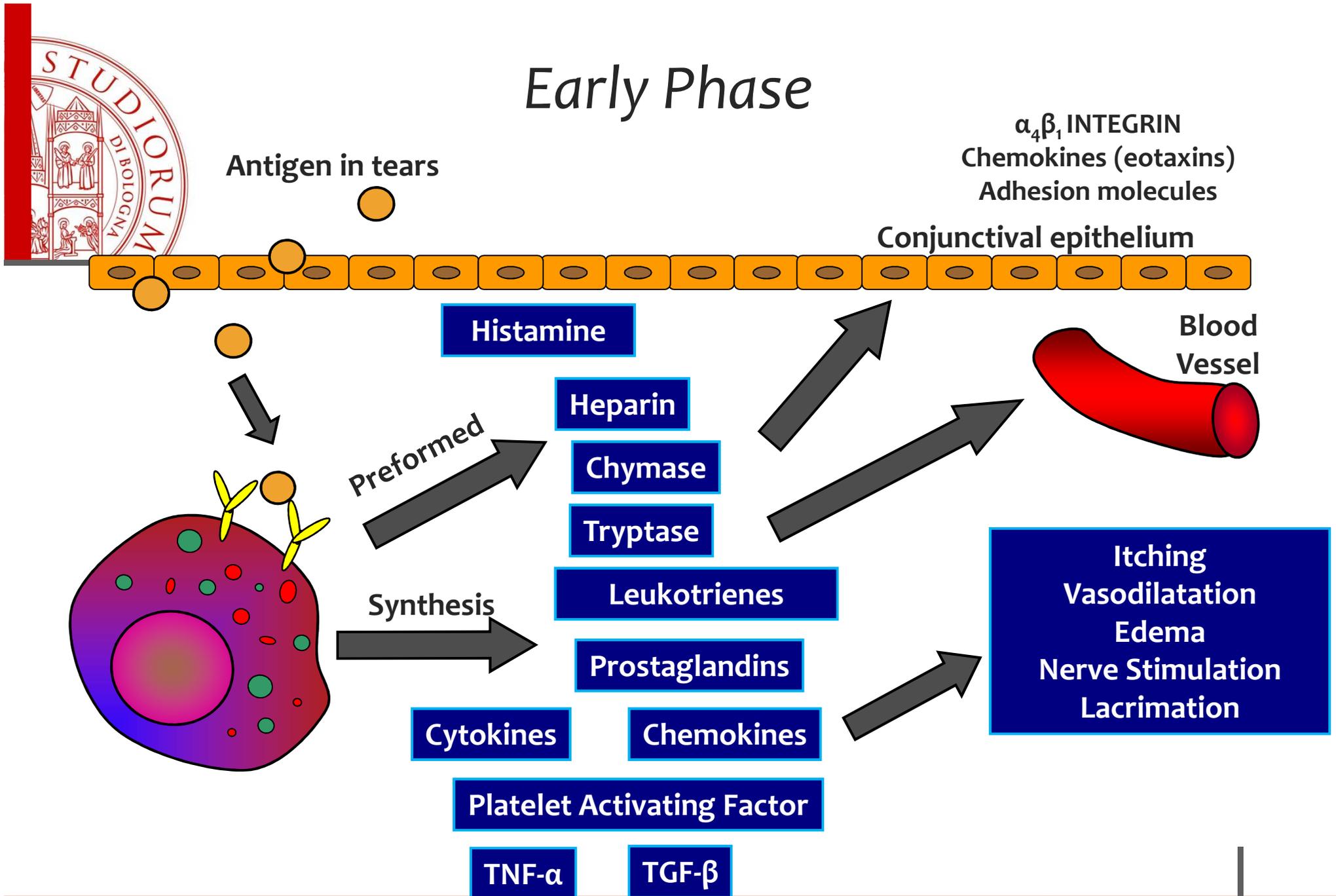
- ✘ Steroids
 - + Topical
 - + Systemic
- ✘ NSAIDs
 - + Topical
 - + systemic
- ✘ Antihistamines
 - + Topical
 - + Systemic
- ✘ Mast-Cell stabilizers
- ✘ Decongestants
- ✘ Cyclosporine



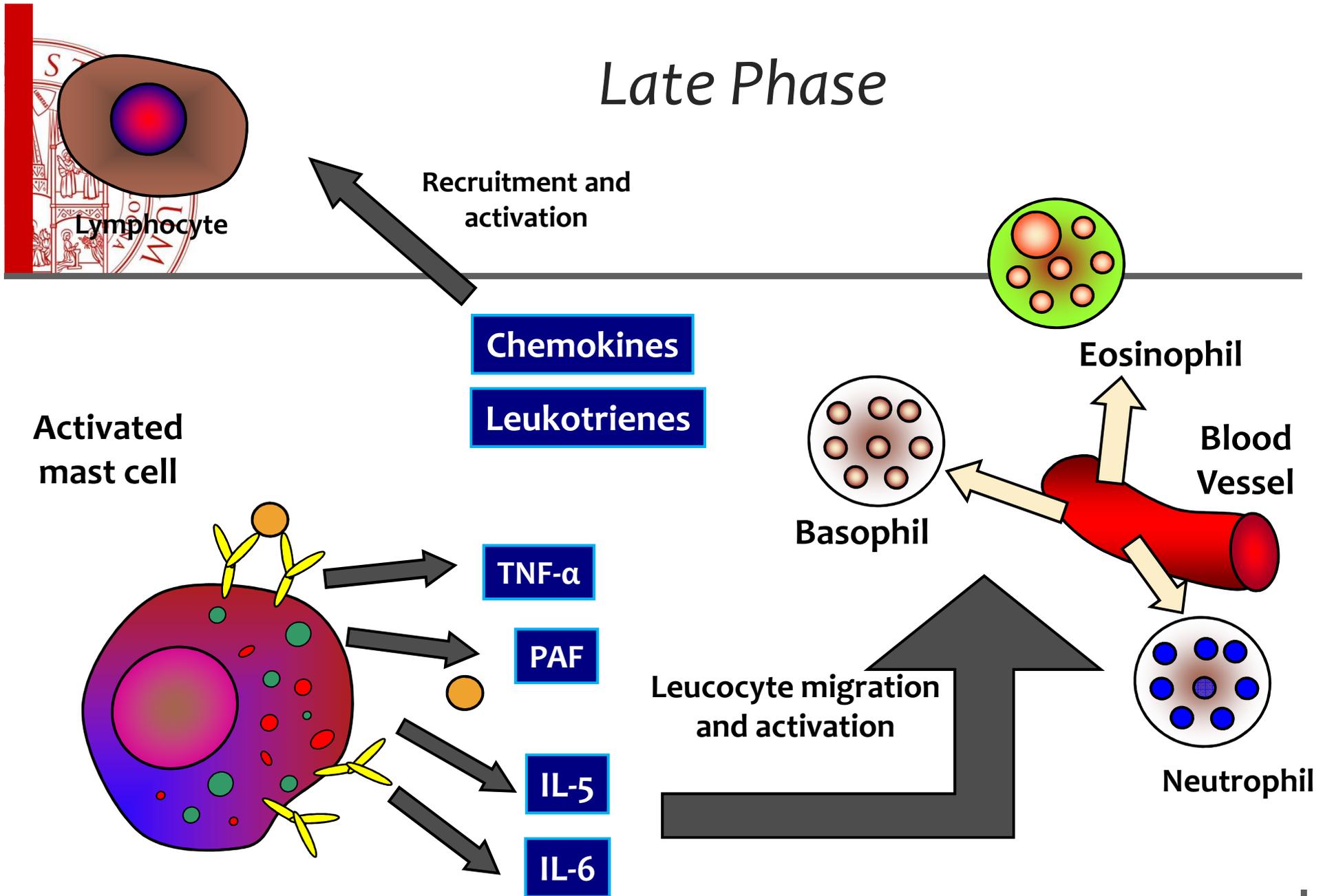
Allergic Conjunctivitis

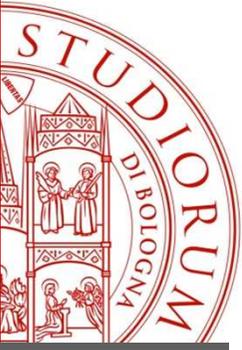


Early Phase

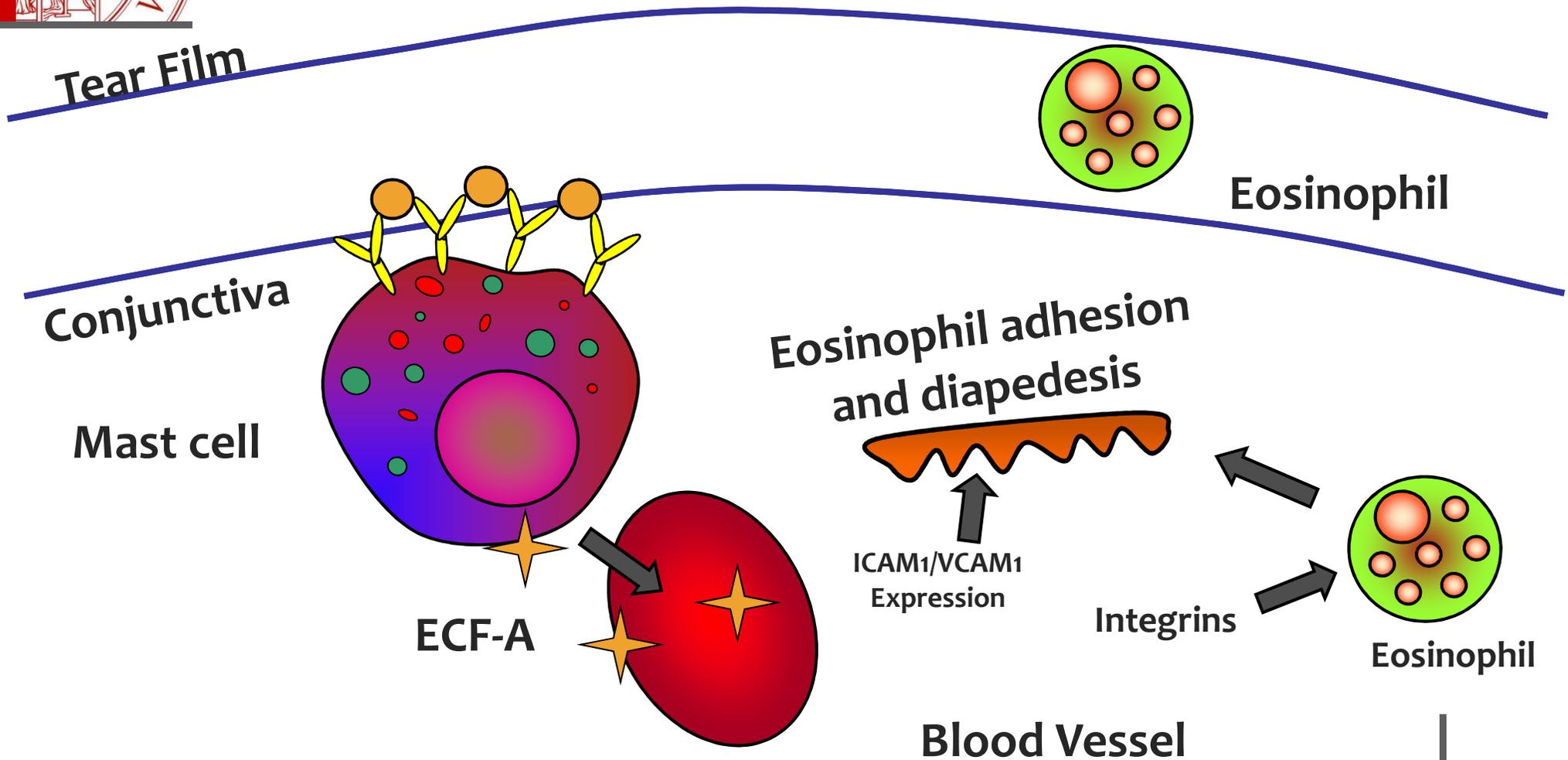


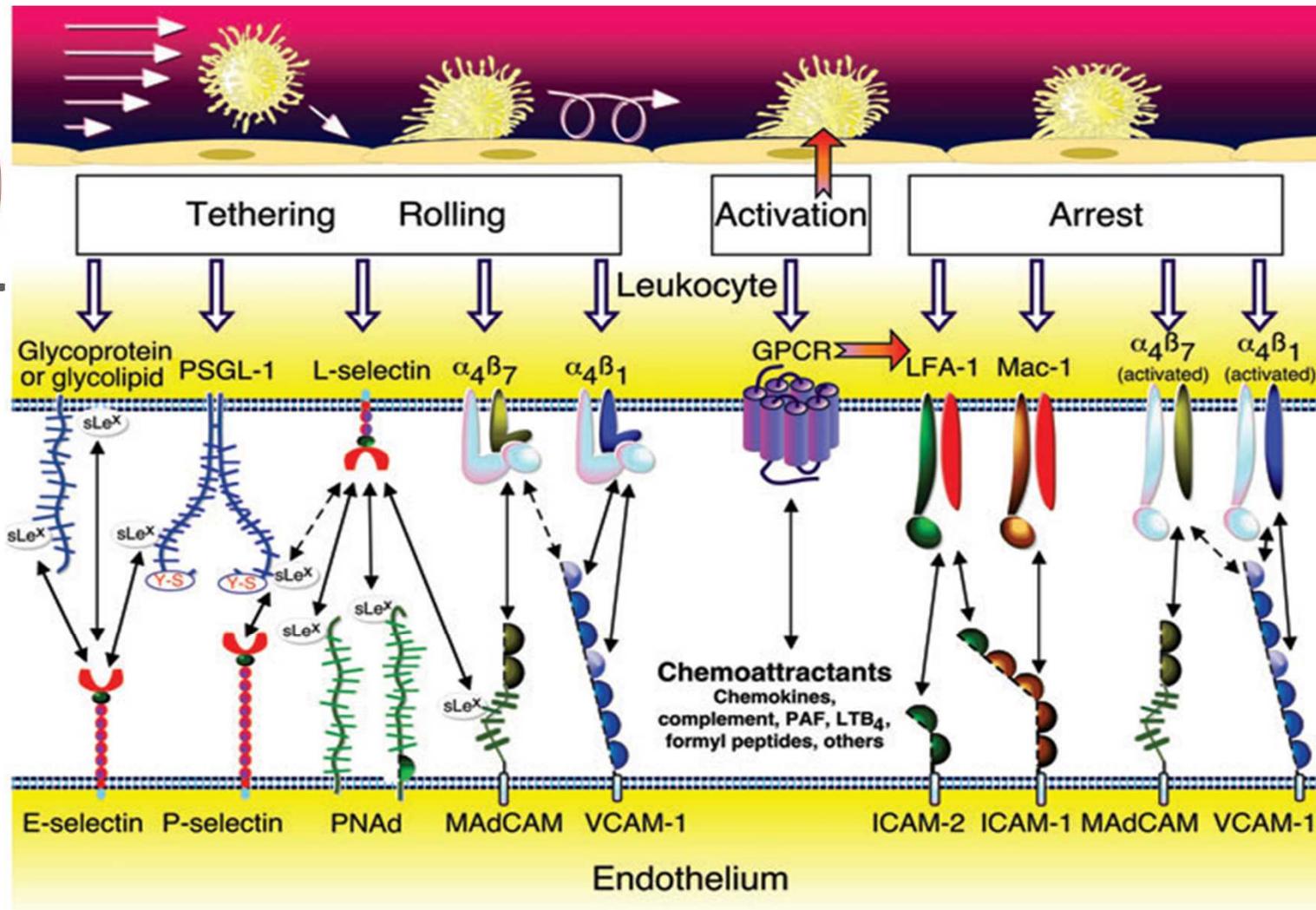
Late Phase



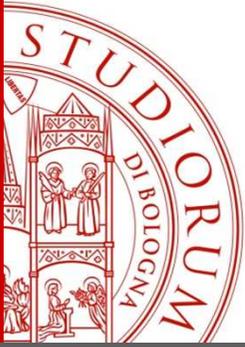


Eosinophil Recruitment





In figura sono schematizzati i 4 step a cui i leucociti vanno incontro durante il processo di accumulo nel vaso sanguigno; in basso, le molecole espresse dai leucociti con i rispettivi contro-recettori endoteliali.



Adhesion Molecules with a Critical Role in Inflammation

Selectins

E-selectin (on endothelium)

P-selectin (on endothelium & platelets; is preformed and stored in Weible Palade bodies)

L-selectin (leukocytes)

Ligands for E-and P-Selectins are sialylated glycoproteins (e.g **Sialylated Lewis X**)

Ligands for L-Selectin are Glycan-bearing molecules such as GlyCam-1, CD34, MadCam-1

Mucin-like glycoproteins

Heparan sulfate (endothelium)

Ligands for CD44 on leukocytes

Bind chemokines

Integrins ($\alpha + \beta$ chain)

Heterodimeric molecules

VLA-4 ($\beta 1$ integrin) binds to VCAM-1

LFA1 and MAC1 (CD11/CD18) = $\beta 2$ integrin bind to ICAM

Expressed on leukocytes

Immunoglobulin family

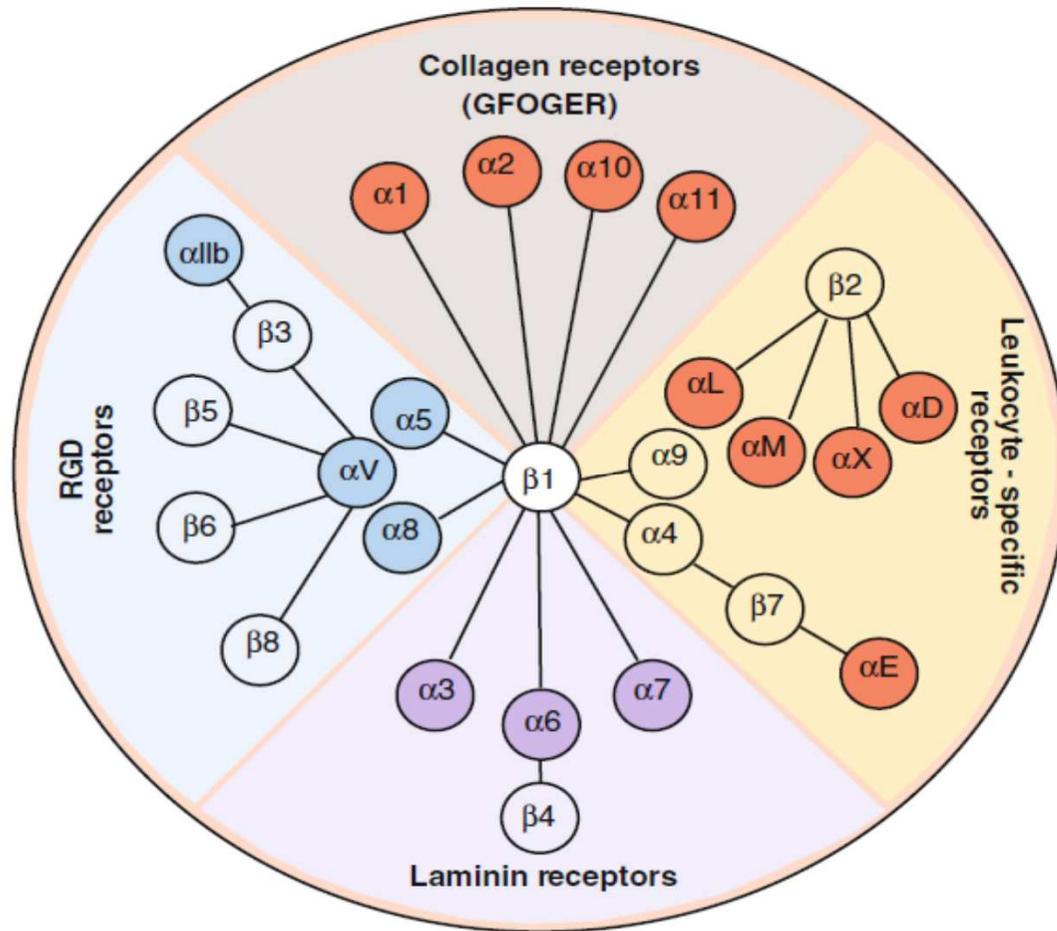
ICAM-1 (intercellular adhesion molecule 1)

VCAM-1 (vascular adhesion molecule 1)

Are expressed on activated endothelium

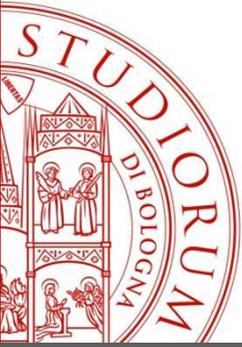
Ligands are integrins on leukocytes

LE INTEGRINE

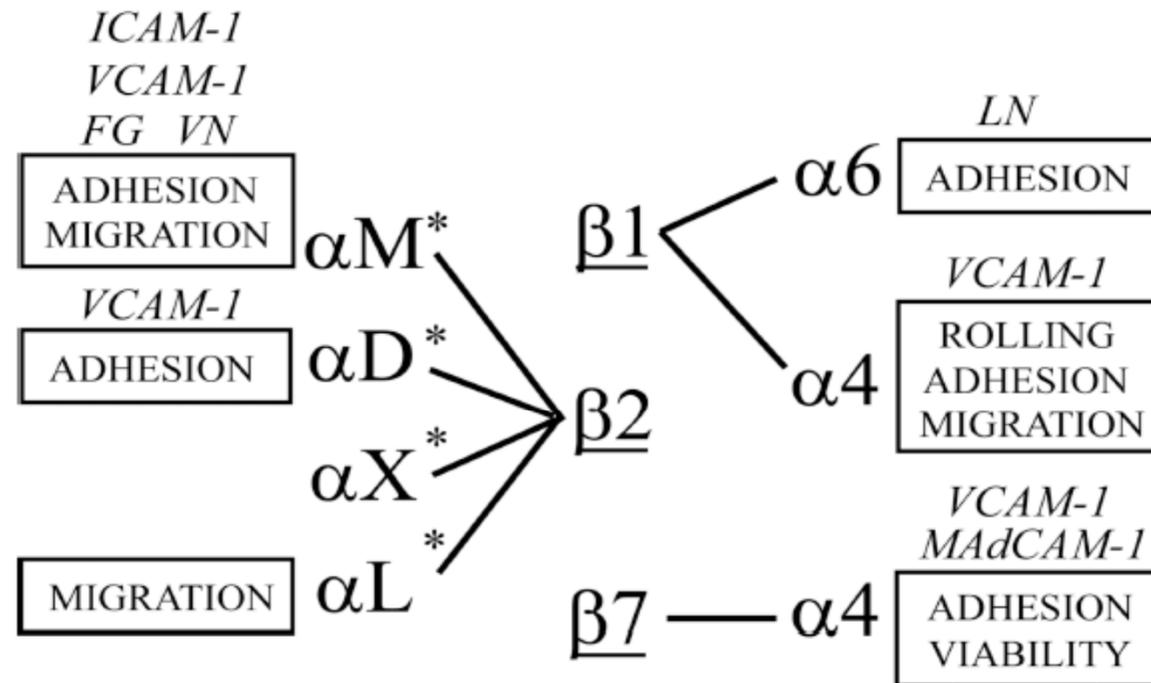


Recettori coinvolti nei processi di:

- ✓ Embriogenesi
- ✓ Morfogenesi tissutale
- ✓ Differenziamento cellulare
- ✓ Crescita cellulare
- ✓ Proliferazione cellulare
- ✓ Coagulazione

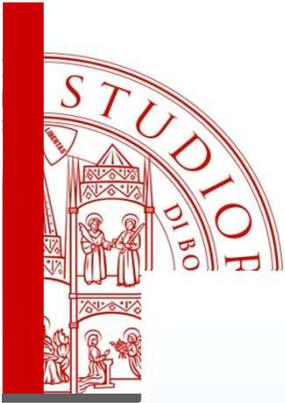


Integrins expressed in eosinophils

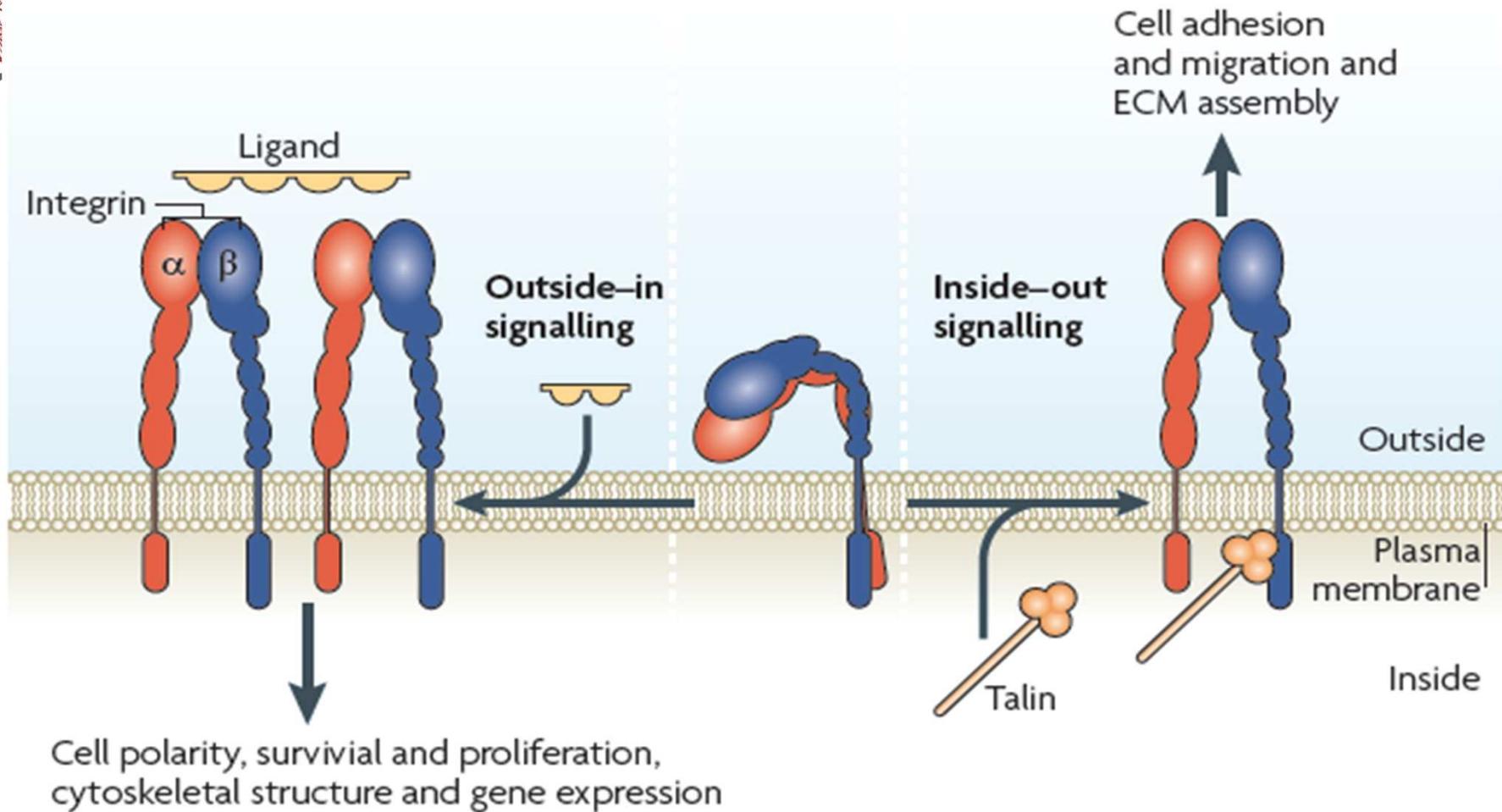


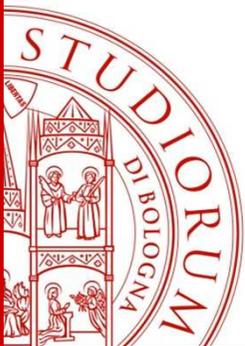
* subunits containing an I-domain

_ subunits containing an I-like domain

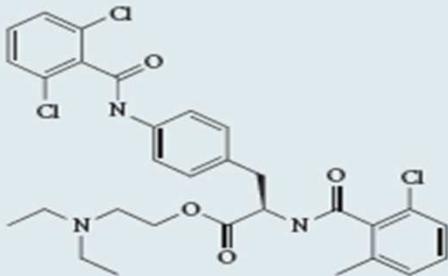
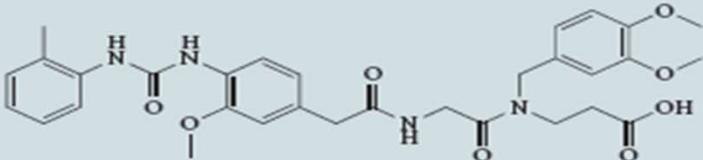
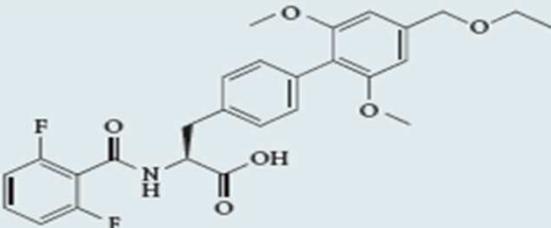


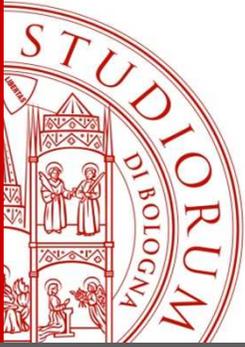
Integrin bidirectional signalling





L'integrina VLA-4 ($\alpha_4\beta_1$): target terapeutico

Name	Structure	Developer	Stage	Indication	Target
Valategrast (R411)		Roche	Terminated at Phase II	Asthma	$\alpha_4\beta_1$
IVL745		Sanofi-Aventis	Terminated at Phase II	Asthma	$\alpha_4\beta_1$
Firategrast (SB-683699)		GlaxoSmithKline	Phase II	Multiple sclerosis	$\alpha_4\beta_1$

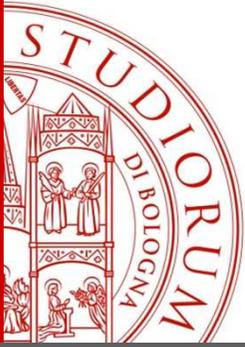


L'integrina VLA-4 ($\alpha_4\beta_1$): target terapeutico

Table 1
Stage of development of different alpha4 integrin antagonists for the treatment of Multiple Sclerosis (MS)

Company	Drug	Action	Clinical trial status
Biogen/Elan	Natalizumab(Tysabri [®])	α_4 antibody	Marketed
GSK	SB-683699 (Finategrast [®])	$\alpha_4\beta_1/\alpha_4\beta_7$ antagonist	Phase II
UCB/Biogen	CDP323	$\alpha_4\beta_1/\alpha_4\beta_7$ antagonist	Phase II
Encysive/ Schering Plough	TBC-4746	$\alpha_4\beta_1/\alpha_4\beta_7$ antagonist	Phase I

AJM300 [†]		Ajinomoto	Phase II	Ulcerative colitis	$\alpha_4\beta_1$
6-B345TTQ		University of California at San Diego, USA	Preclinical	Unknown	α_4 -paxillin interaction

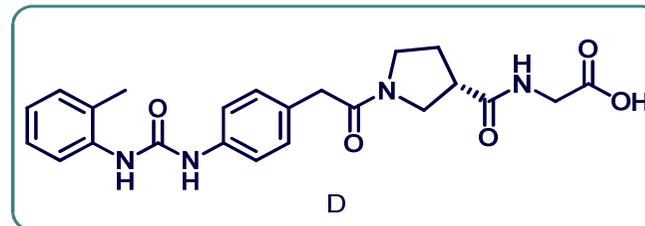


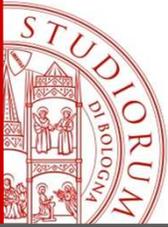
DS-70

DS 70 - UN NUOVO ANTAGONISTA DUALE DELLE INTEGRINE

$\alpha 4\beta 1$ e $\alpha 4\beta 7$

Inibisce *in vitro* l'adesione dei mastociti e degli eosinofili a VCAM-1





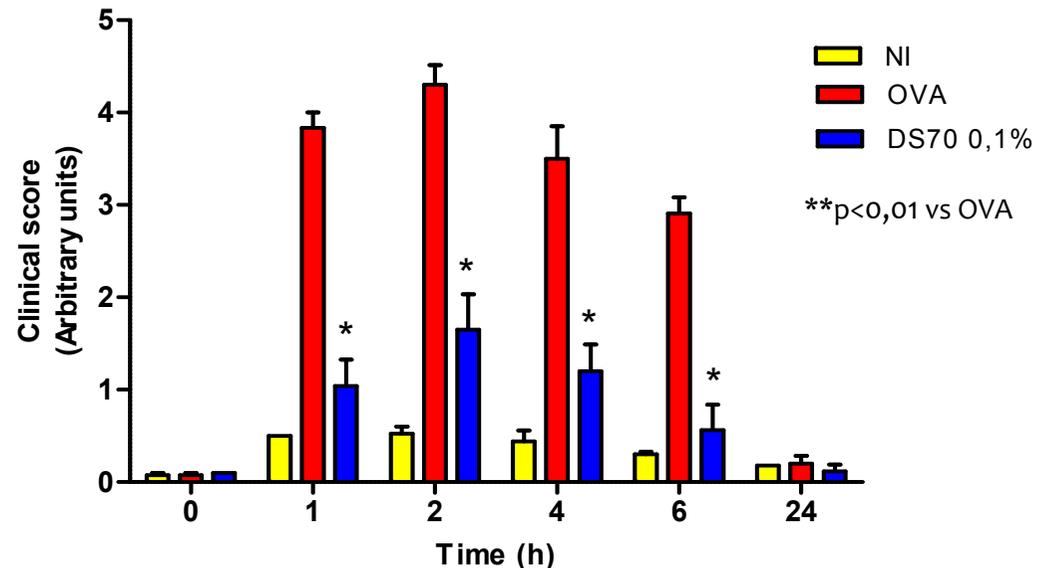
MODELLO DI CONGIUNTIVITE ALLERGICA INDOTTO IN CAVIE

Clinical score

Effetto del composto DS70 sui sintomi congiuntivali indotti dall'ovalbumina (OVA) nelle cavie. Ogni gruppo sperimentale comprendeva cinque animali. I dati presentati sono la media \pm SEM (sono stati valutati entrambi gli occhi).

- 0, assenza di sintomi;
- 1, lieve arrossamento congiuntivale con o senza lacrimazione;
- 2, moderato arrossamento congiuntivale con lacrimazione e lieve chemosi;
- 3, moderato arrossamento congiuntivale con lacrimazione e chemosi moderata;
- 4, severo arrossamento congiuntivale con lacrimazione e parziale eversione della palpebra;
- 5, severo arrossamento congiuntivale con lacrimazione e palpebre chiuse più della metà.

OVA: ovalbumina
NI: non immunizzato



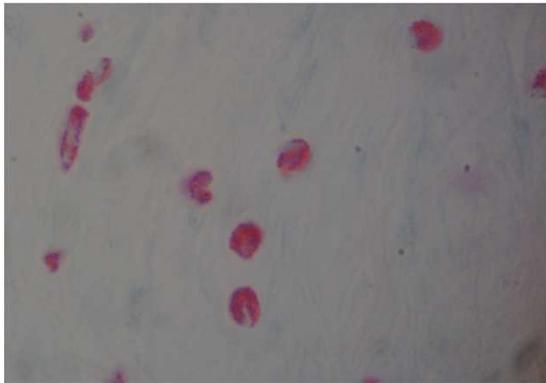
MODELLO DI CONGIUNTIVITE ALLERGICA INDOTTO IN CAVIE

Degranulazione dei mastociti a livello della congiuntiva

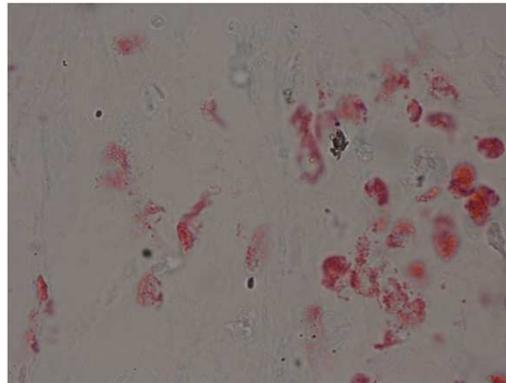
2 h post OVA

Giemsa staining

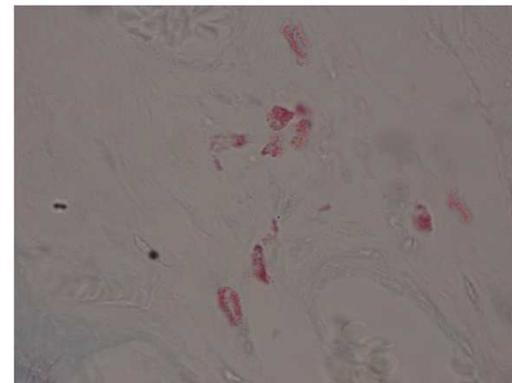
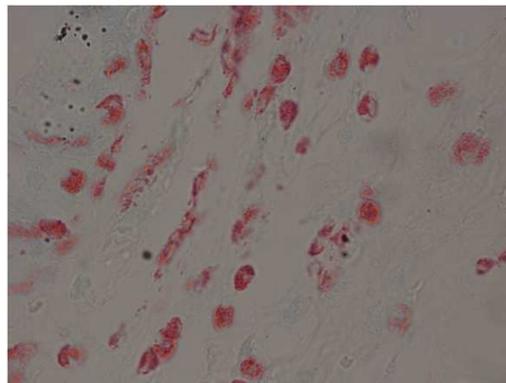
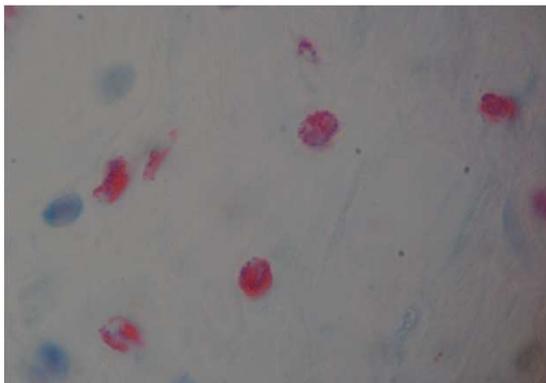
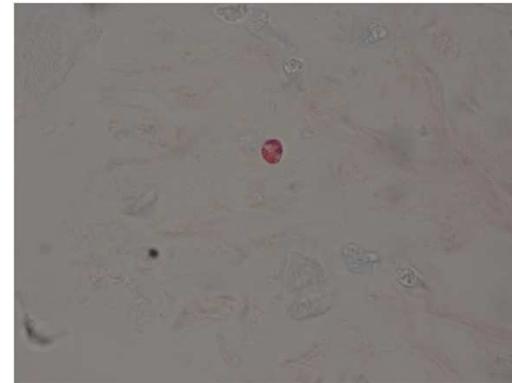
Non immunizzato

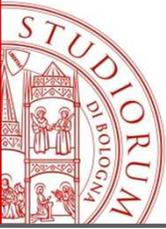


Ovalbumina



DS70 + ovalbumina



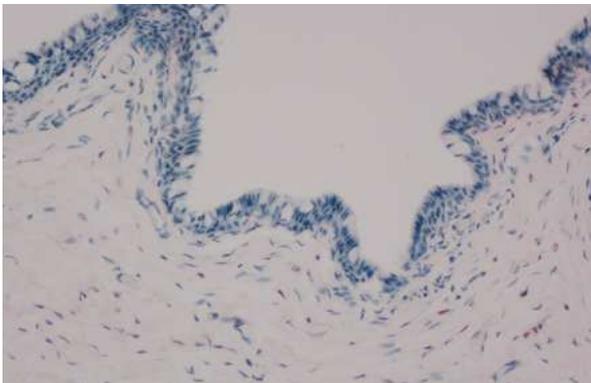


MODELLO DI CONGIUNTIVITE ALLERGICA INDOTTO IN CAVIE

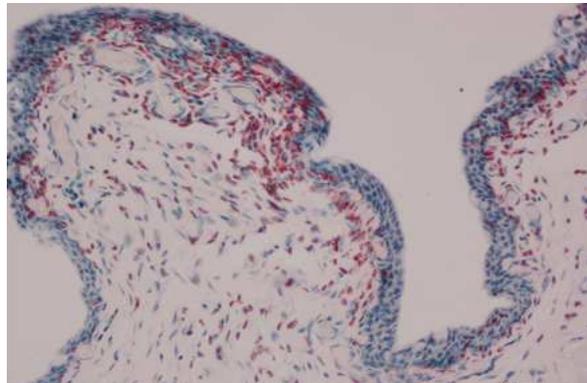
Infiltrazione degli eosinofili a livello della congiuntiva

Colorazione di Luna

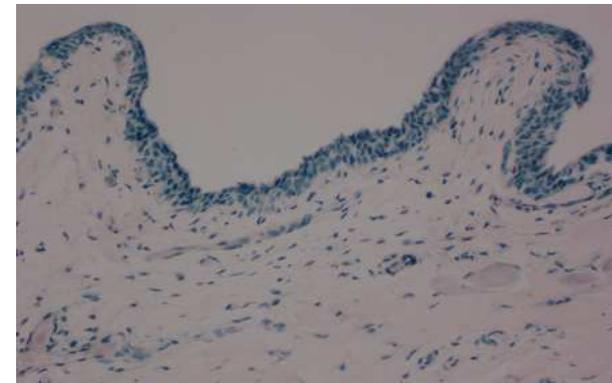
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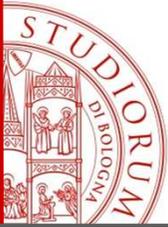


Ovalbumina



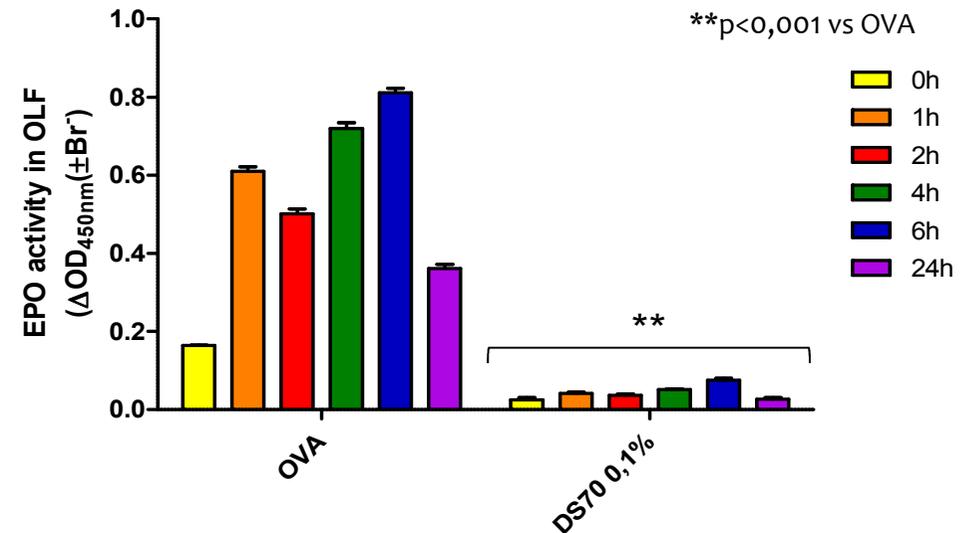
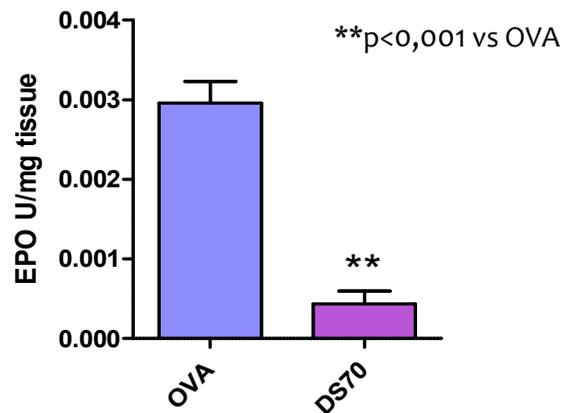
DS70 + ovalbumina





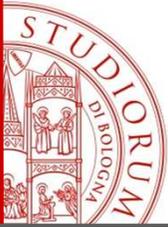
MODELLO DI CONGIUNTIVITE ALLERGICA INDOTTO IN CAVIE

Analisi della perossidasi nel tessuto congiuntivale e nelle lacrime



Effetto del composto DS70, entrambi alla concentrazione di 0,1%, sui livelli di perossidasi degli eosinofili (EPO), valutati **nelle congiuntive** di animali in cui, precedentemente, era stata indotta congiuntivite allergica mediante immunizzazione con ovalbumina (OVA).

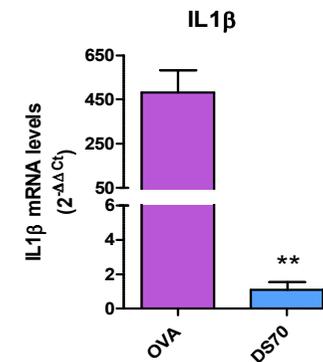
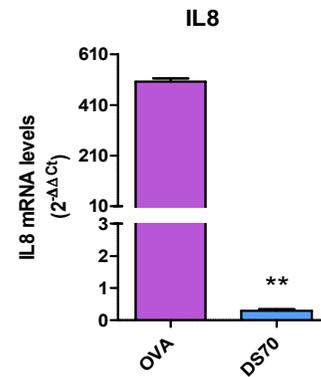
Attività della perossidasi degli eosinofili (EPO) valutata **nelle lacrime** prelevate da animali con congiuntivite allergica indotta da ovalbumina (OVA), **p < 0,001 vs OVA.



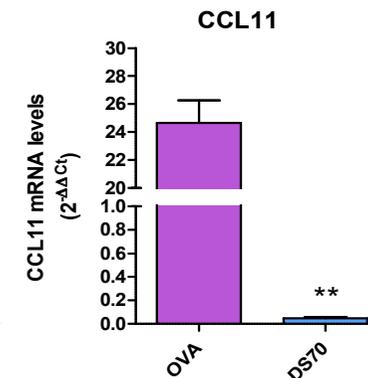
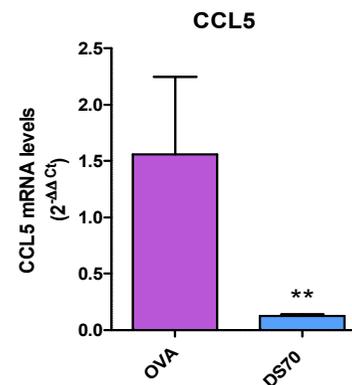
MODELLO DI CONGIUNTIVITE ALLERGICA INDOTTO IN CAVIE

Analisi chemochine e citochine pro-infiammatorie

Valutazione dell'espressione di chemochine e citochine pro-infiammatorie in campioni di **congiuntiva** provenienti da animali trattati e DS70, alla concentrazione 0,1%



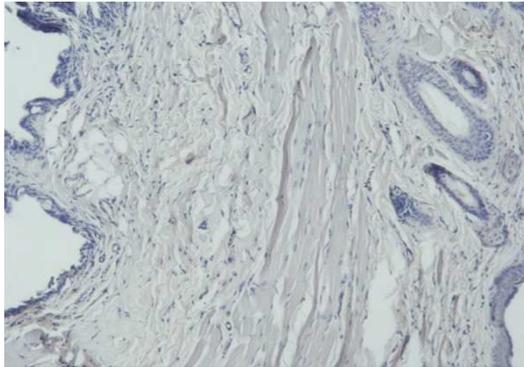
**p<0,001 vs OVA



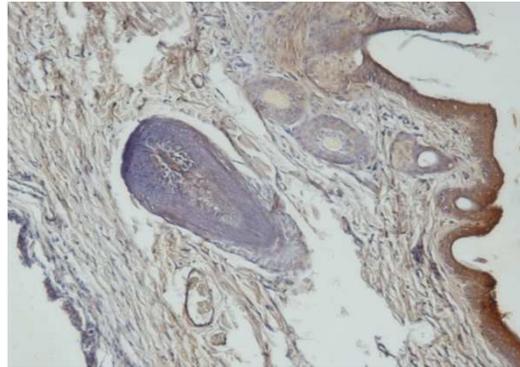
MODELLO DI CONGIUNTIVITE ALLERGICA INDOTTO IN CAVIE

Immunoistochimica – Integrina $\alpha_4\beta_1$

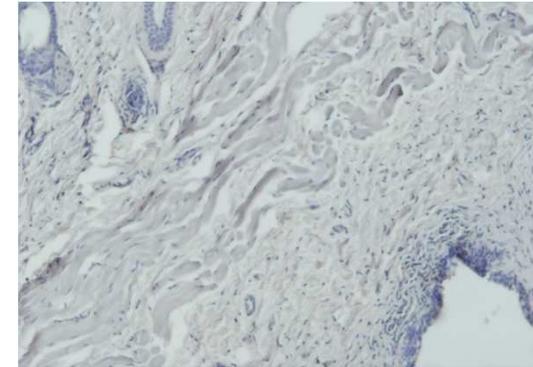
Non immunizzato

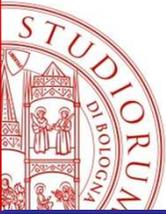


Ovalbumina

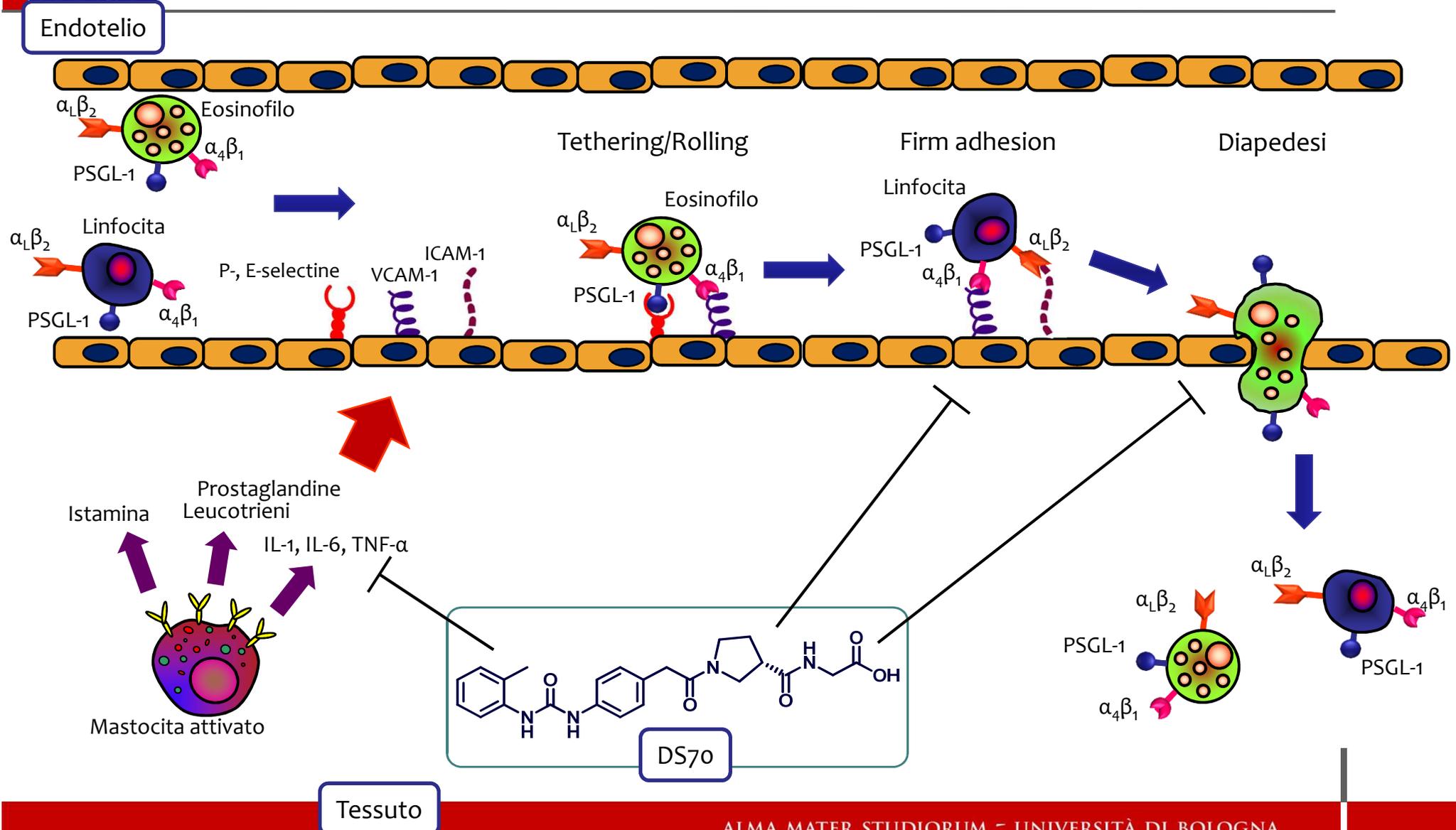


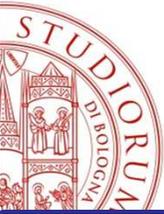
DS70 + ovalbumina





LA REAZIONE INFIAMMATORIA





LA REAZIONE INFIAMMATORIA

