

- **What comprises ocular surface?**

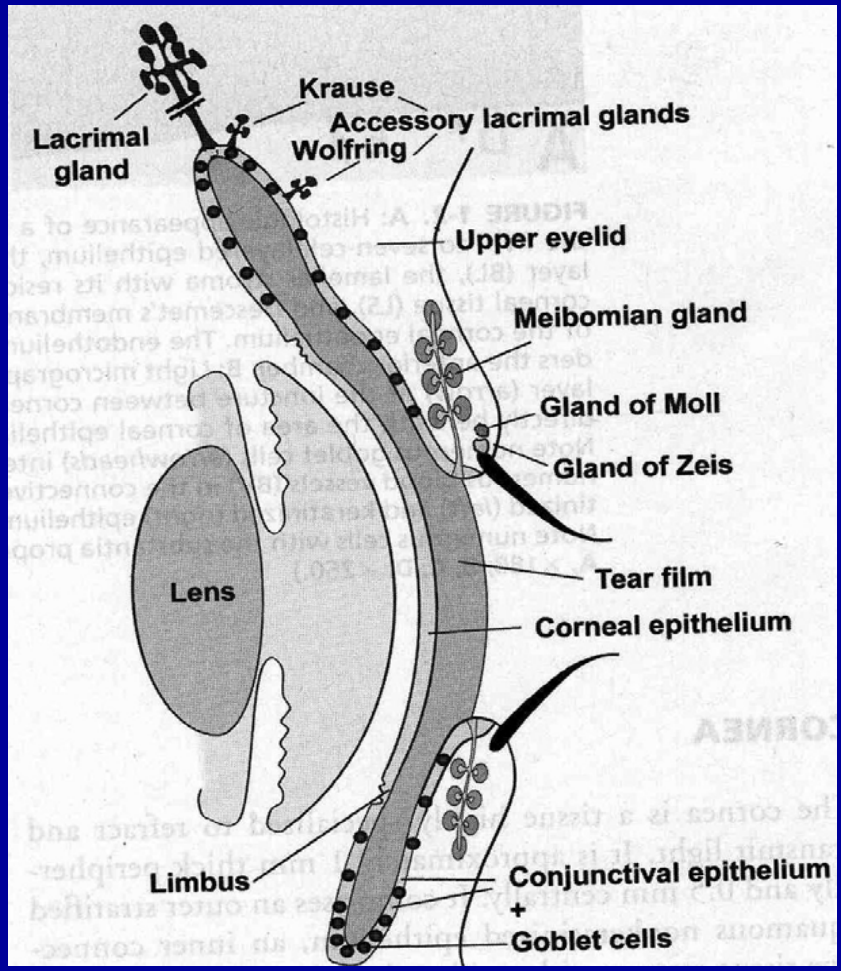
- Corneal and conjunctival epithelium and tear film

- **What are the functions of the tear film?**

- Smooth refractive surface for clear vision, Removal of debris, First line of defense and Supply of oxygen and growth factors.

- **Which glands contribute to the tear film ?**

- Goblet cells, Meibomian glands, Lacrimal glands, Accessory lacrimal glands (Krause and Wolfring), Sebaceous glands (Zeis and Moll)



**Describe the structure of the tear film and functions of each layer.**

**Mucin layer, aqueous layer and lipid layer.**

### **Functions**

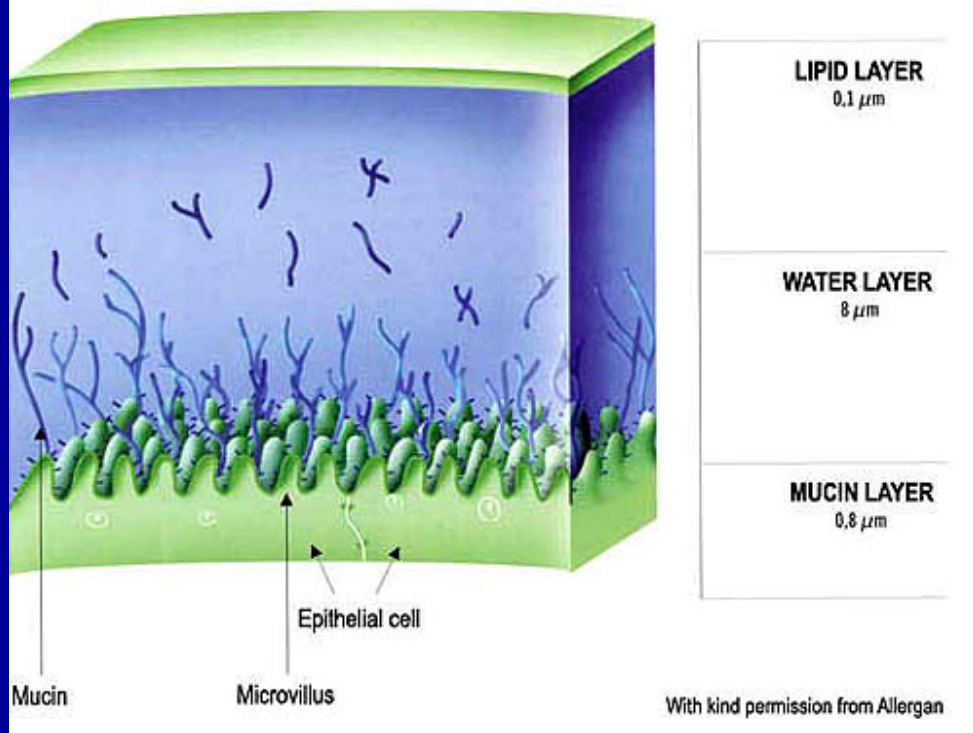
**Lipid layer: retards evaporation, optical properties, hydrophobic barrier to prevent tear overflow, prevent damage to lid margin skin**

**Aqueous layer: Oxygen supply, maintain electrolyte composition, antibactererila and antiviral, wash away debris**

**Mucin layer: trap cellular debris, foreign particles and bacteria, lubriacate the eyelids as they pass over the globe.**



## TEAR FILM



Meibomian Gland  
(lipid)

Lacrimal Gland  
(water)

Goblet Cell  
(mucin)

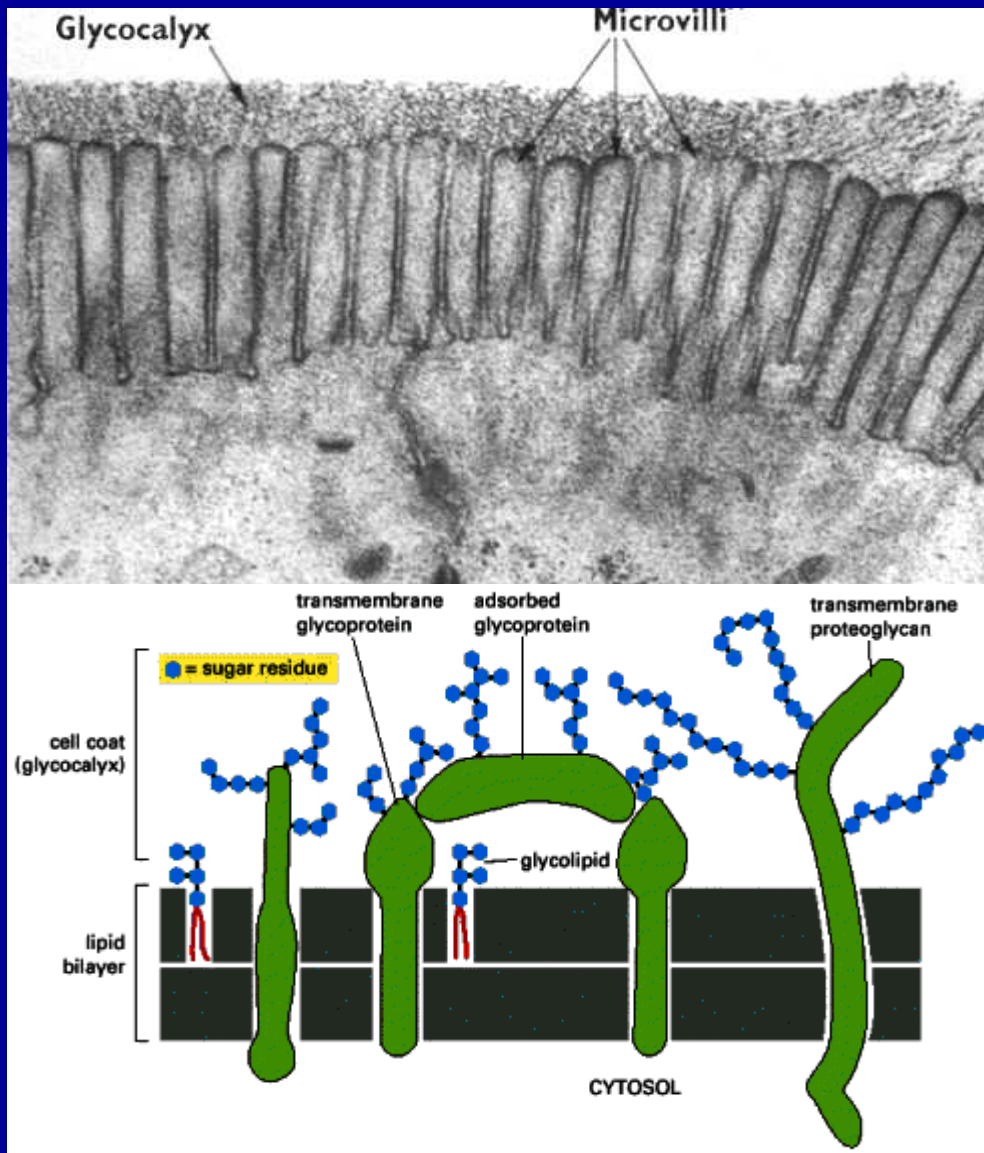
Failure to form adequate tear film results in dry eye (keratoconjunctivitis sicca).

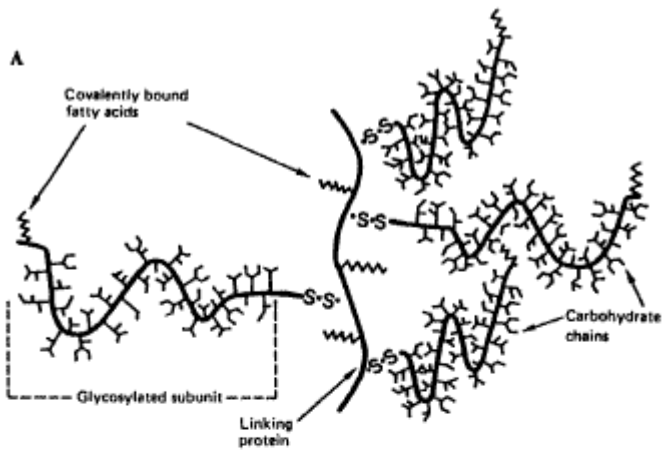
<b>Compostion</b>	<b>98.2 % water and 1.8 % solid</b>
<b>Volume</b>	<b>7.4 <math>\mu</math>l</b>
<b>Secretary rate</b>	<b>3.8 <math>\mu</math>l/ min</b>
<b>Turnover rate</b>	<b>12-16%/min</b>
<b>Evaporation rate</b>	<b>0.06 <math>\mu</math>l/cm<sup>2</sup>/min</b>
<b>Osmolarity</b>	<b>296-308 mOsm/L</b>
<b>pH</b>	<b>6.5-7.6</b>



<b>Tear layer</b>	<b>Origin</b>	<b>Components</b>	<b>Physiological functions</b>
Lipid layer	Meibomian gland Accessory lacrimal glands	Wax, cholesterol, fatty acid ester	Lubrication, prevention of evaporation, stabilization
Aqueous layer	Lacrimal gland Accessory lacrimal gland	Water Electrolyte: Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup> , Mg <sup>2+</sup> Proteins: albumin, lysozyme, lactoferrin, transferrin, ceruloplasmin, immunoglobulins (IgA, IgG, IgE, IgM) Cytokines, growth factors: EGF, TGF- $\alpha$ , TGF- $\beta$ 1, TGF- $\beta$ 2, bFGF, HGF, VEGF, substance P Other: glucose, vitamins	Lubrication, antimicrobial, bacteriostasis, oxygen supply, nutritional supply, mechanical clearance, regulation of cellular functions
Mucous layer	Conjunctival goblet cells, conjunctival epithelial cells, corneal epithelial cells	Sulfomucin, cyalomucin, MUC1, MUC4, MUC5AC	Lowered surface tension, stabilization of aqueous layer

# What provides stability to the tear film on the ocular surface





## MUC gene      Type

MUC1

Membrane bound

MUC2

Secretory,

MUC4

Membrane-bound, soluble form,

MUC5AC

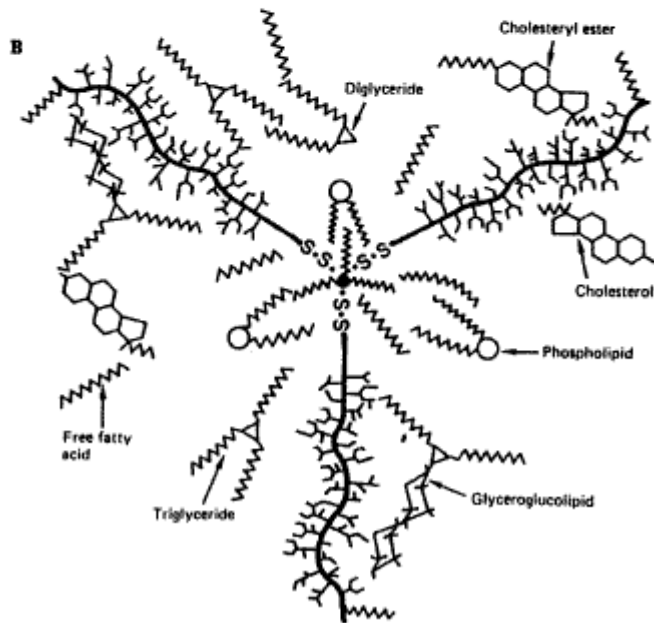
Secretory, gel forming

MUC5B

Secretory, gel forming

MUC7

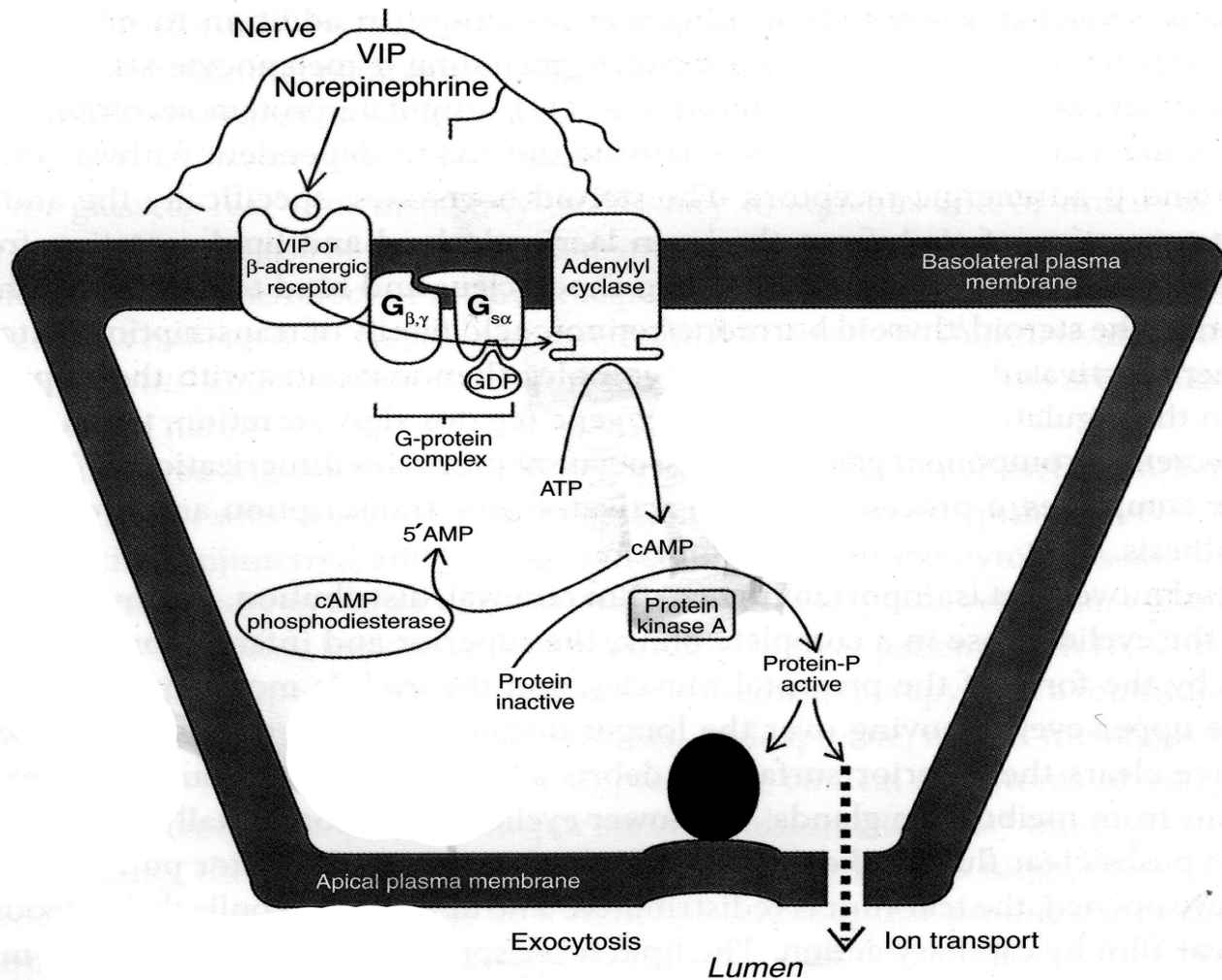
Secretory, soluble



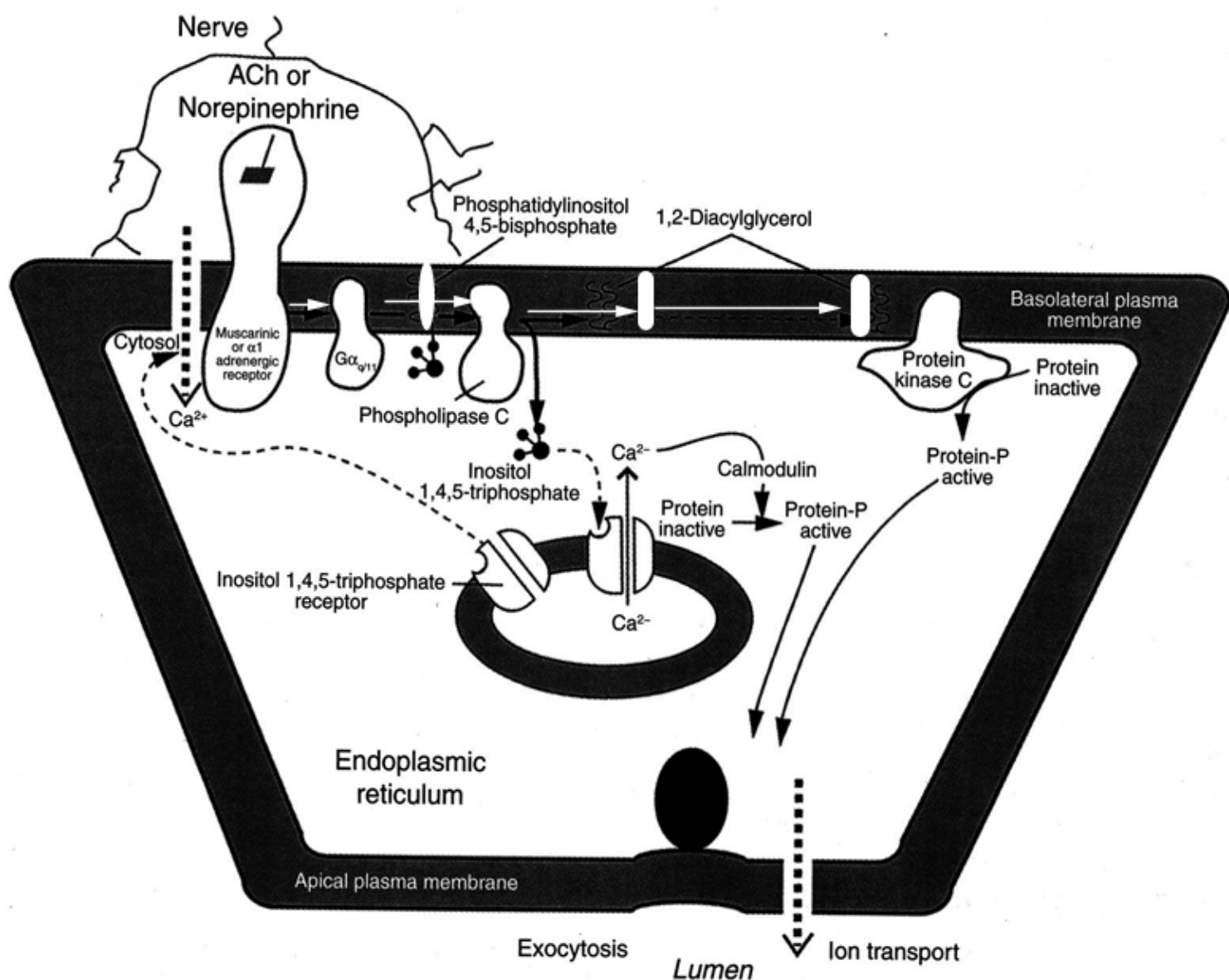




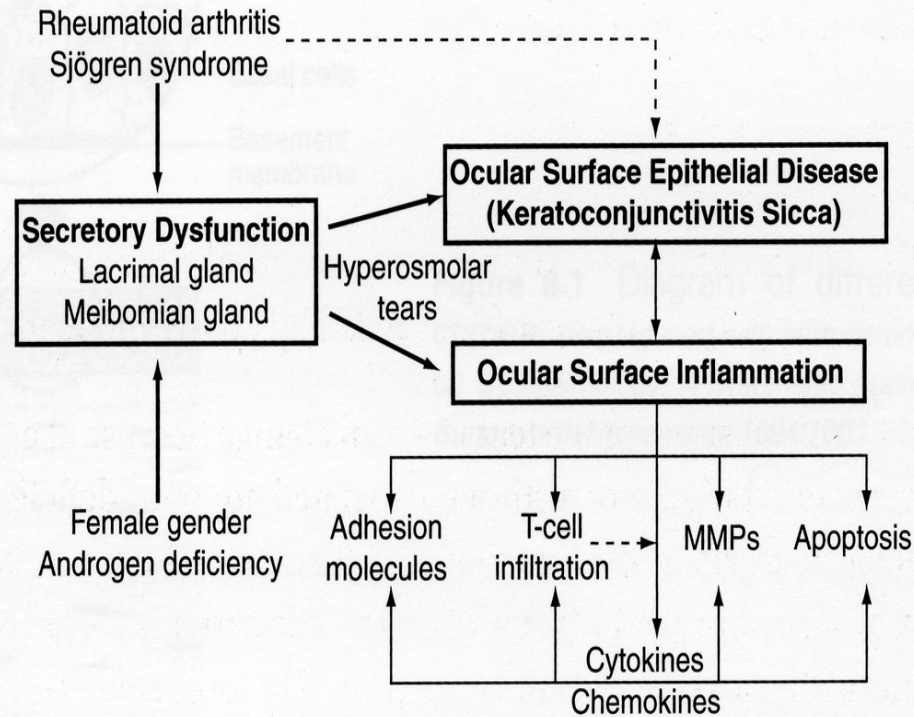
Functional peptides of tears	
Growth factors	Association
Epidermal growth factor (EGF) Transforming growth factor alpha (TGF- $\alpha$ ) Transforming growth factor beta-1 (TGF $\beta$ -1) Transforming growth factor beta-2 (TGF $\beta$ -2) Hepatocyte growth factor (HGF) Basic fibroblast growth factor (FGF-2) Vascular endothelial growth factor (VEGF) Platelet derived growth factor-BB	Epithelial wound healing. Tear concentration higher than saliva or serum Wound response Wound response Found in normal tears, increases after wounding Wound response Wound response Wound response, increases after wounding Did not change after PRK
<b>Neuropeptides</b> Substance P Calcitonin gene related peptide	Wound healing, neurogenic inflammation Wound healing, neurogenic inflammation
<b>Interleukins</b> IL-4 IL-1 $\alpha$ , IL-1 $\beta$ IL-2, IL-4, IL-6, IL-8, IL-10	Increases in vernal conjunctivitis Elevation of IL-1 in dry eye patients Increases with contact lens wear, ocular allergy
<b>Immunoglobulins</b> IgA, IgE, IgG(1-4) and complement	Ocular allergy
<b>Proteases</b> MMP-1, MMP-3, MMP-9, TIMP-1, capthepsin, alpha2-macroglobulin	Role in pterygium migration and vernal keratoconjunctivitis, protection of the ocular surface
<b>Antimicrobial Peptides</b> Lysozyme, lactoferrin, $\alpha$ and $\beta$ defensins, phospholipase A2	Increases in infections, wound healing, may decrease in dry eye



Epithelial cell. Schematic of 3',5'-cyclic adenosine monophosphate (*cAMP*)-dependent signaling pathway activated by vasoactive intestinal polypeptide (*VIP*) or norepinephrine to stimulate mucin, protein, or electrolyte and water secretion in epithelial cells. 5' AMP = adenosine 5'-monophosphate, ATP = adenosine 5'-triphosphate,  $G_{\beta,\gamma}$  =  $\beta$ - and  $\gamma$ -subunits of guanine nucleotide-binding protein,  $G_{s\alpha}$  = stimulatory  $\alpha$ -subunit of guanine nucleotide-binding protein, GDP = guanosine 5'-diphosphate, *Protein-P* = phosphorylated (activated) protein. (Modified from Dartt DA. Regulation of tear secretion. *Adv Exp Med Biol.* 1994;350:5.)



Epithelial cell. Schematic of  $\text{Ca}^{2+}$ /protein kinase C-dependent signal transduction pathway activated by cholinergic and  $\alpha_1$ -adrenergic agonists in epithelial cells to stimulate mucin, protein, or electrolyte and water secretion. *ACh* = acetylcholine,  $G_{\alpha_{q/11}}$  = q/11 subtype of guanine nucleotide-binding protein, *Protein-P* = phosphorylated (activated) protein. (From Dartt DA. Regulation of tear secretion. *Adv Exp Med Biol.* 1994;350:4.)



Inflammatory mediators in keratoconjunctivitis sicca. *MMPs* = matrix metalloproteinases. (Reproduced with permission from Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol. 2004;137(2):338.)

- **Tear Film Dysfunction will be discussed by:**
- Dr. Francis Mah
- Date: **08/26/2009 - 7:00am** Pharmacology/Dry Eye & Anti Inflammatory compounds

### ***TEAR SECRETION***

Schirmer I

Schirmer II (reflex tear secretion in response to nasal stimulation)

Phenol Red Thread Test

Meniscometry (tear meniscus radius)

### ***TEAR FILM STABILITY***

Tear Break-Up Time

Ocular Protection Index

Tear Film Stability Analysis System  
(videoscropy)

### ***TEAR TURNOVER***

### ***OCULAR SURFACE EVALUATION***

Fluorescein

Rose Bengal

Lissamine Green

### ***TEAR FILM OSMOLARITY***

Tear Film Osmolarity

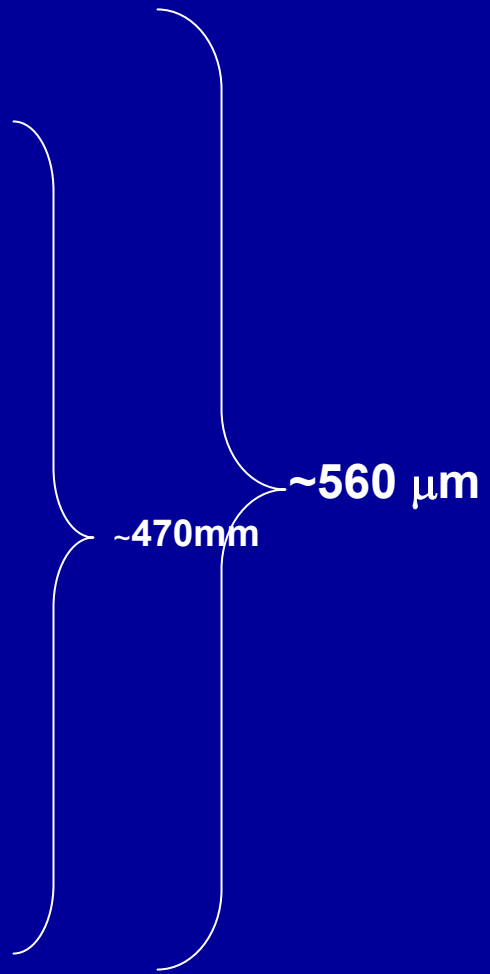
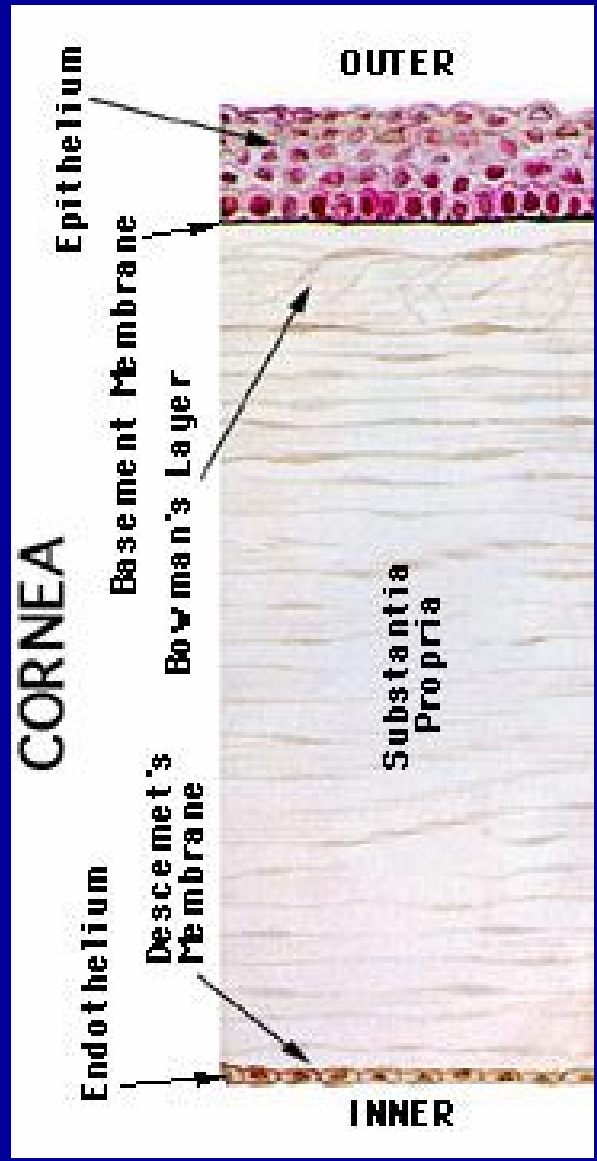
Tear Fering

Tear Evaporation

### ***LIPID LAYER EVALUATION***

Interferometry

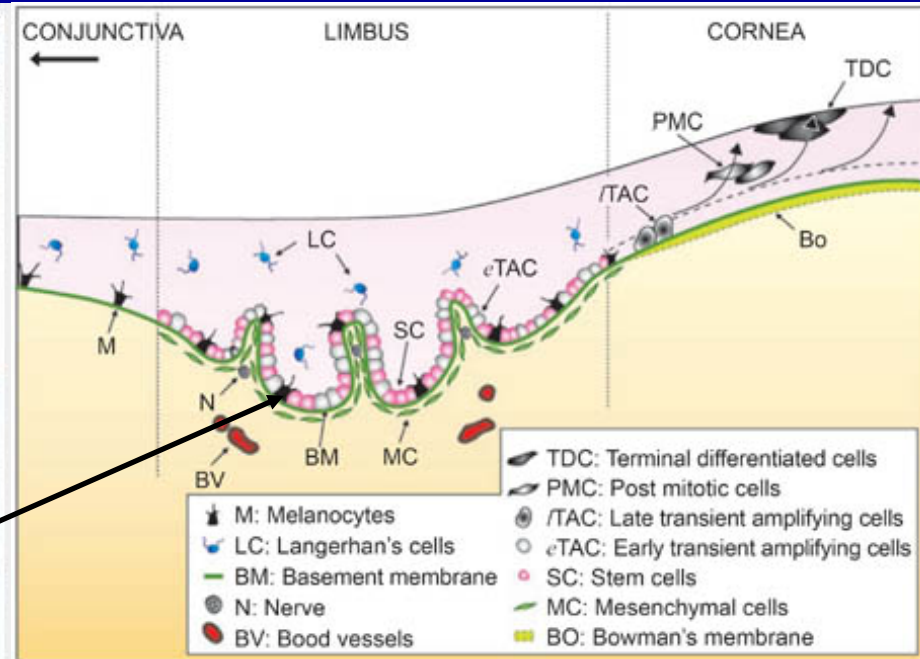
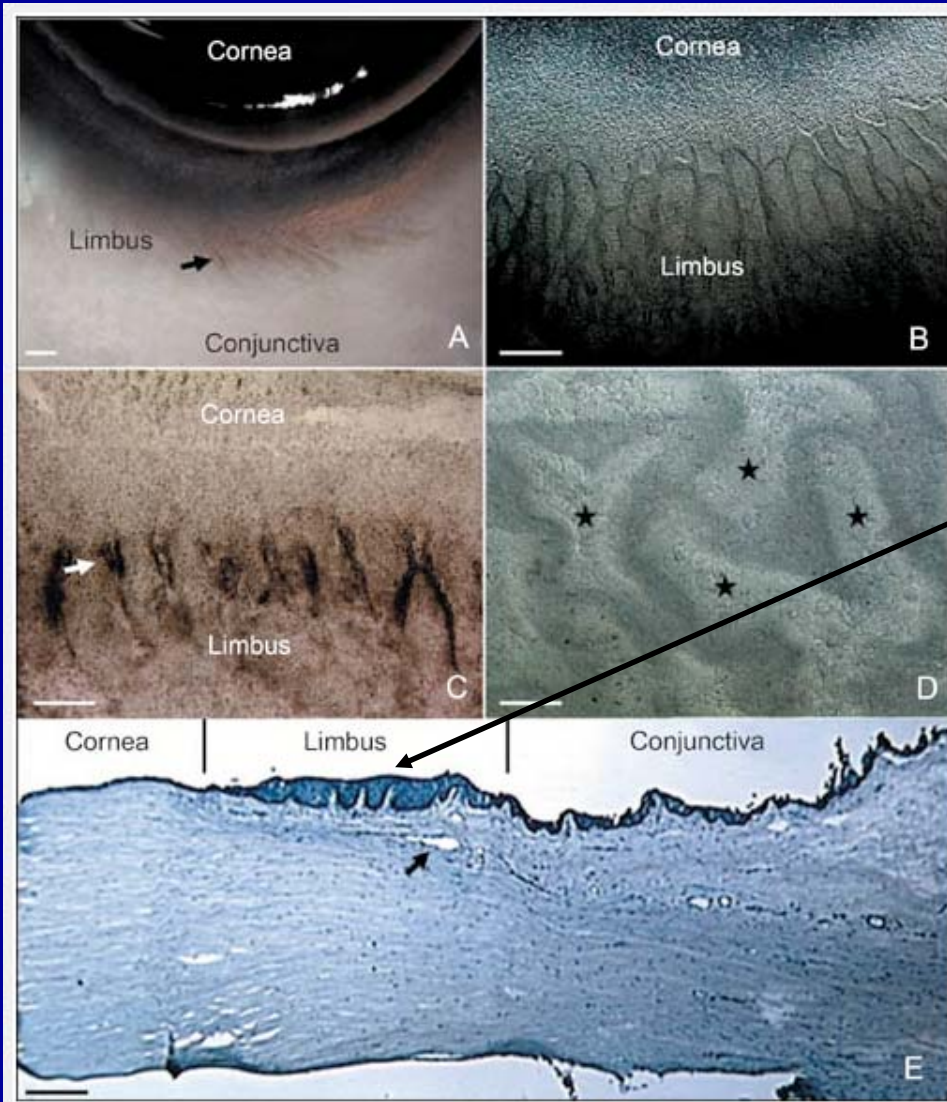
Meibometry



# Corneal epithelium is generated from Limbal Stem Cells

Views of the palisades of Vogt

Model of the limbal stem cell niche



Limbal Stem Cell Deficiency



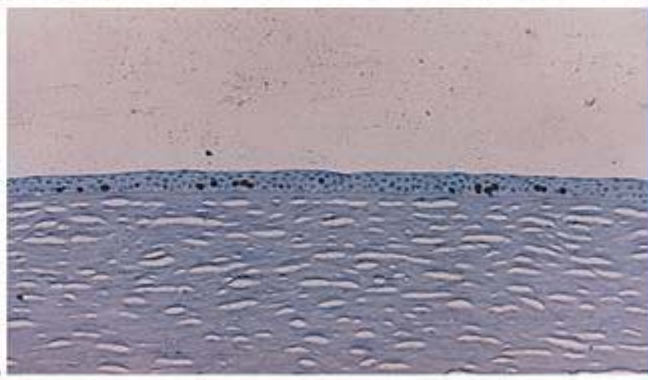
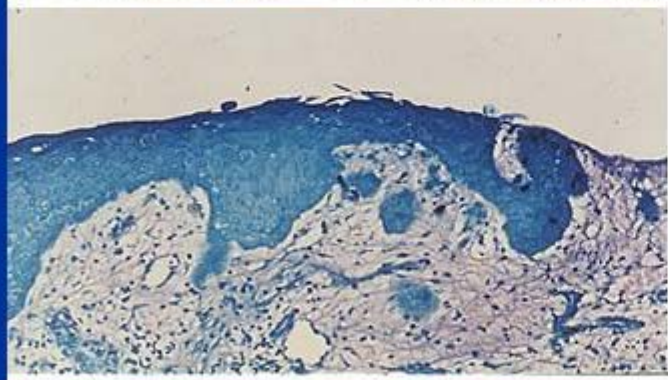
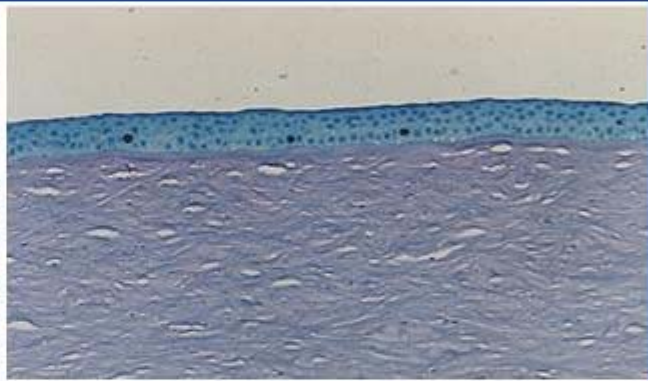
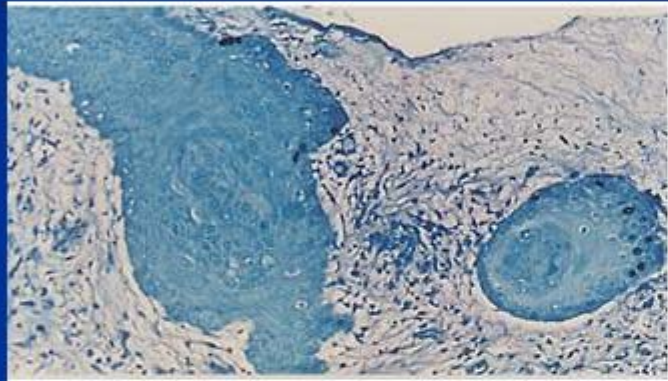
## Intrinsic differences between stem cells and transient amplifying cells

### Stem cells

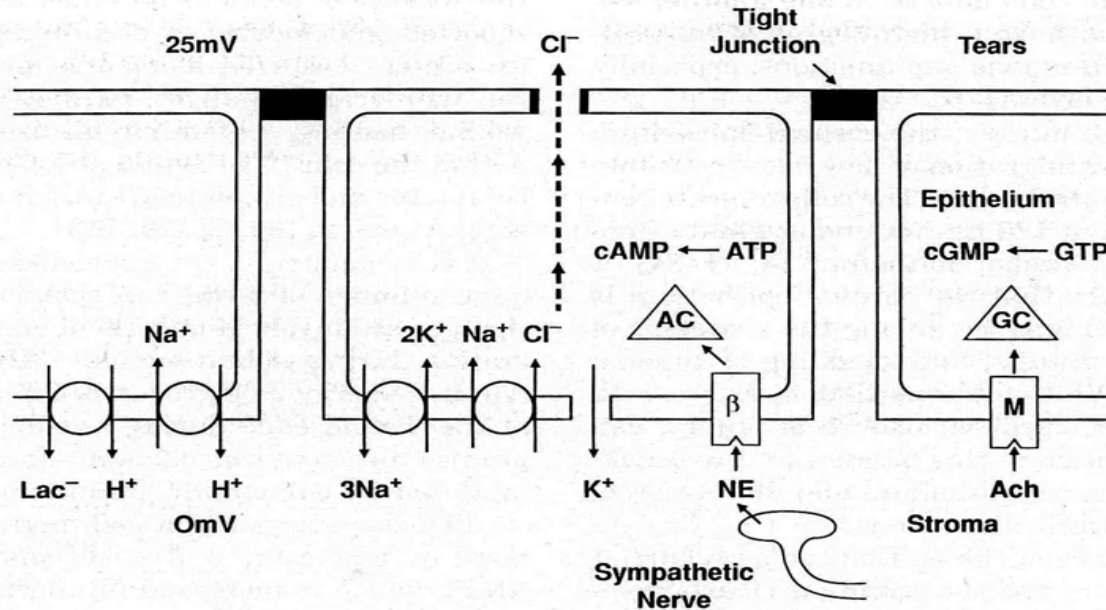
- Resistant to tumor promoters
- Poorly differentiated with primitive cytoplasm
- High capacity for error-free self renewal
- Slow cycling during homeostasis
- Long life span

### Transient amplifying cells

- Susceptible to tumor promoters
- Less primitive than differentiated cells
- Differentiate into post-mitotic and terminally differentiated cells
- Divide more frequently
- Limited proliferative potential



## Net negative 30 mV



Neurotransmitters and transport mechanisms in the corneal epithelium [5, 11, 17, 55, 57, 58, 104, 110]. *Ach* = acetylcholine; *AC* = adenylyate cyclase;  $\beta$  = beta receptor; *GC* = guanylate cyclase; *Lac* = lactate; *M* = muscarinic receptor; *NE* = norepinephrine; *cAMP* = adenosine 3':5'-cyclic phosphate; *ATP* = adenosine triphosphate; *cGMP* = guanosine 3':5' -cyclic phosphate; *GTP* = guanosine triphosphate.

Amphotericin B and  $\text{Ag}^+$  create cation channels

Ouabain inhibits  $\text{Na}^+$  transport inhibit

Catecholamines stimulate

Propranolol and timolol block

}  $\text{Cl}^-$  secretion

