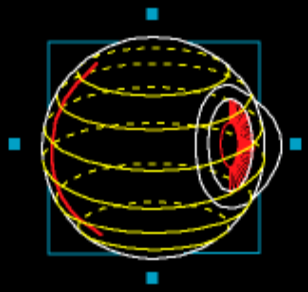
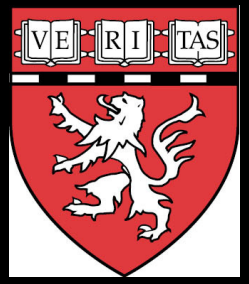
# Dry eye disease:
# A tear film and ocular surface challenge



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Disclosures: Singularis & TearLab

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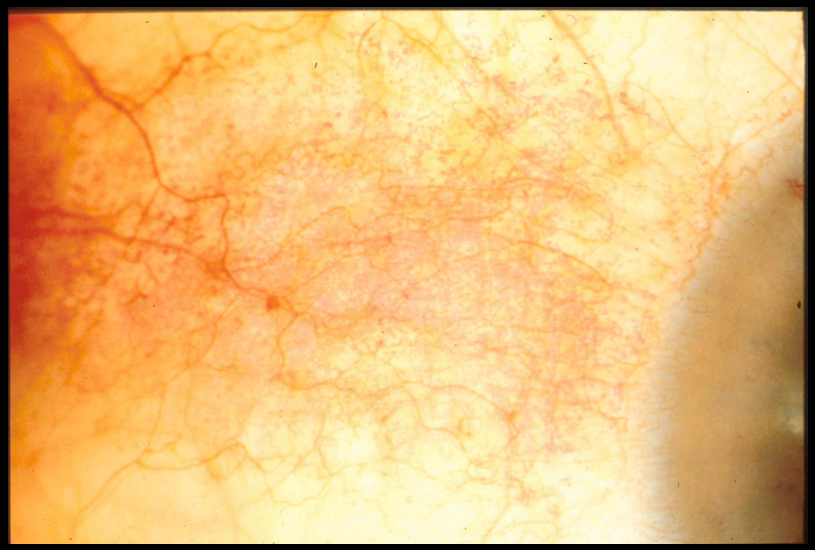
# Assignment

- Review the definition, impact, classification, mechanism & risk factors of dry eye disease
- Highlight the new therapeutic approaches and challenges for the treatment of dry eye disease

"Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is



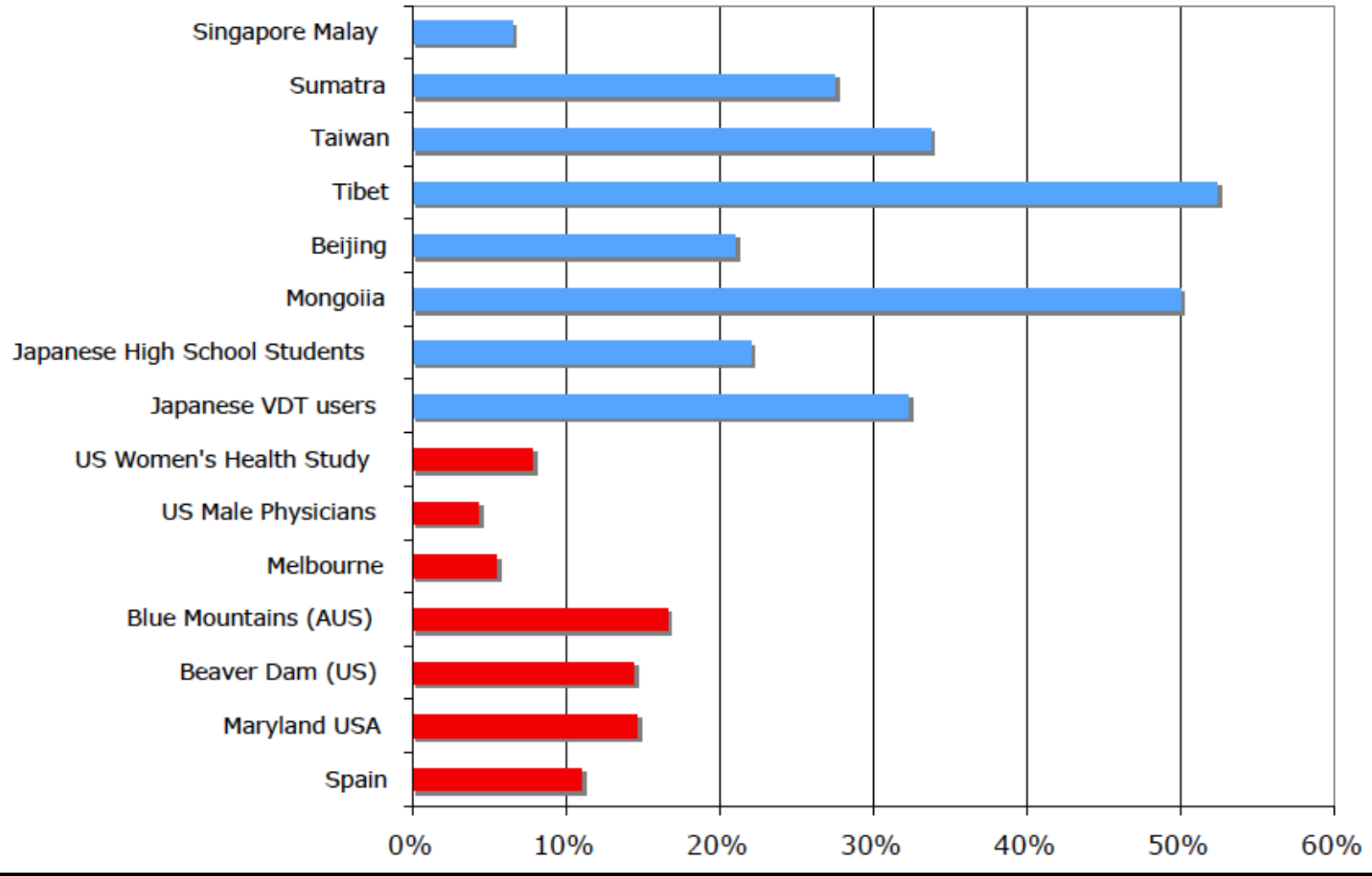
accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

TFOS DEWS, 2007

# Dry Eye Disease

- Afflicts > 40 million people in USA
- Leading cause of patient visits to eye care practitioners
- Has no cure

# Global Prevalence of Dry Eye in Adults

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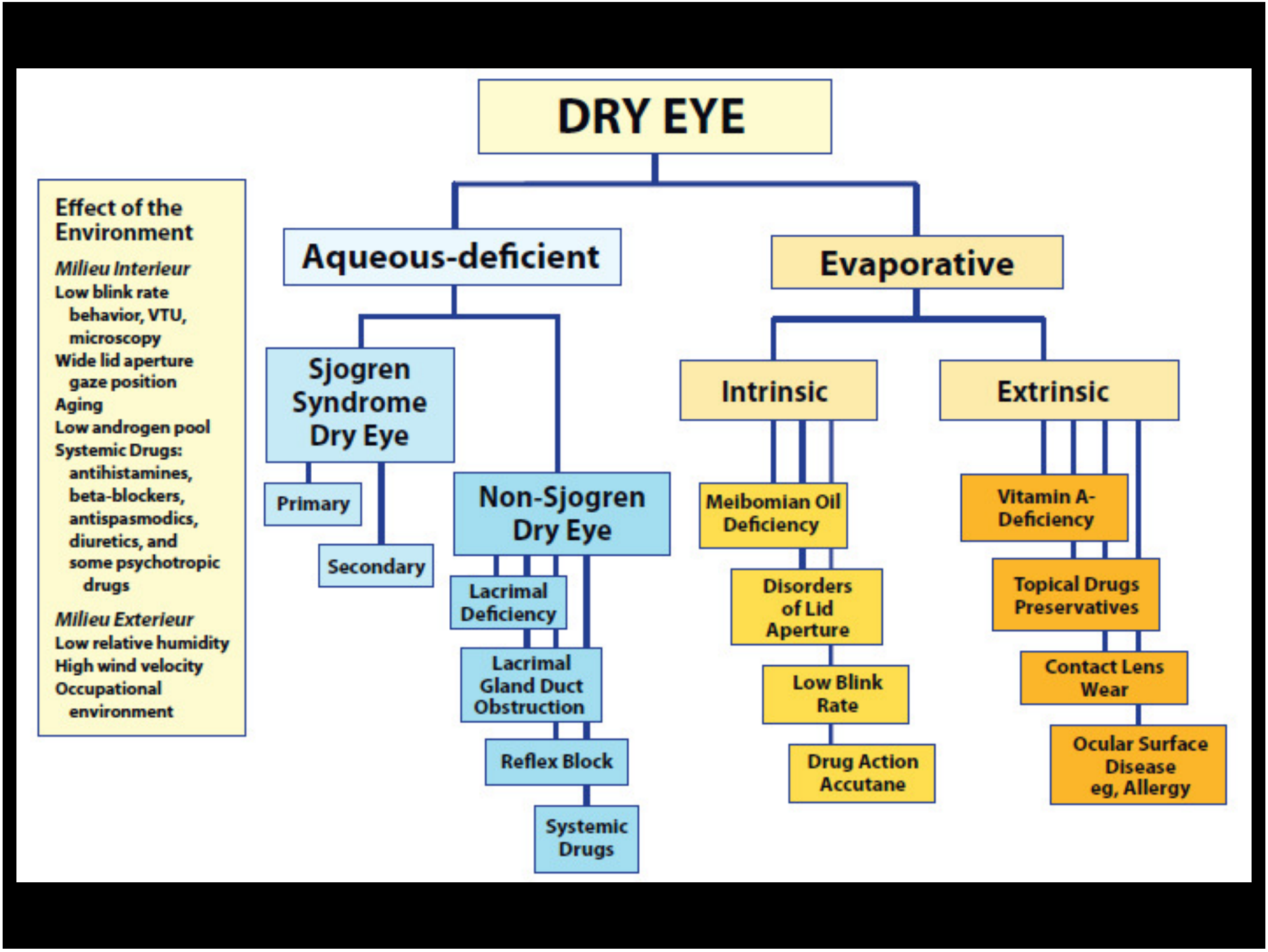
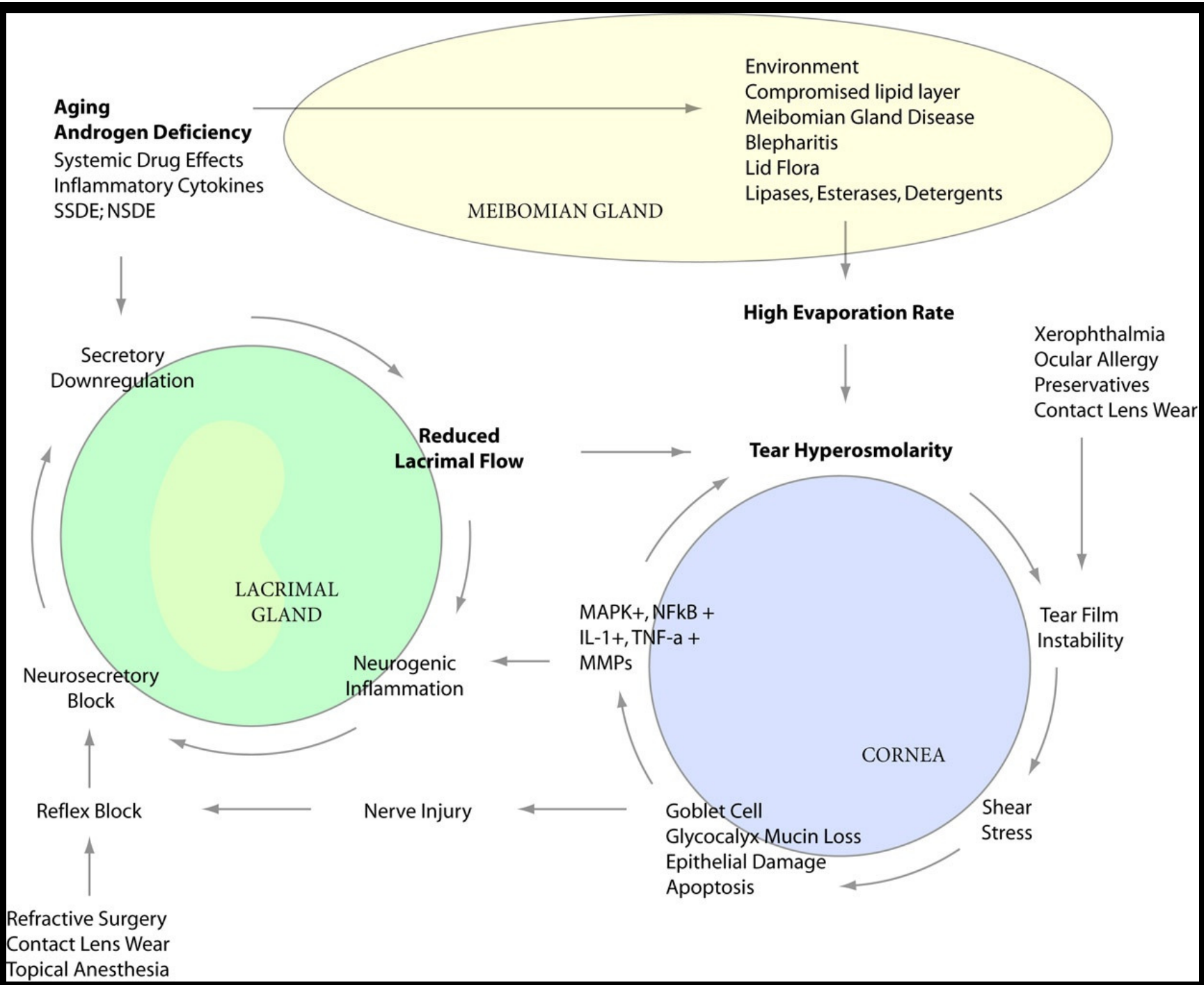
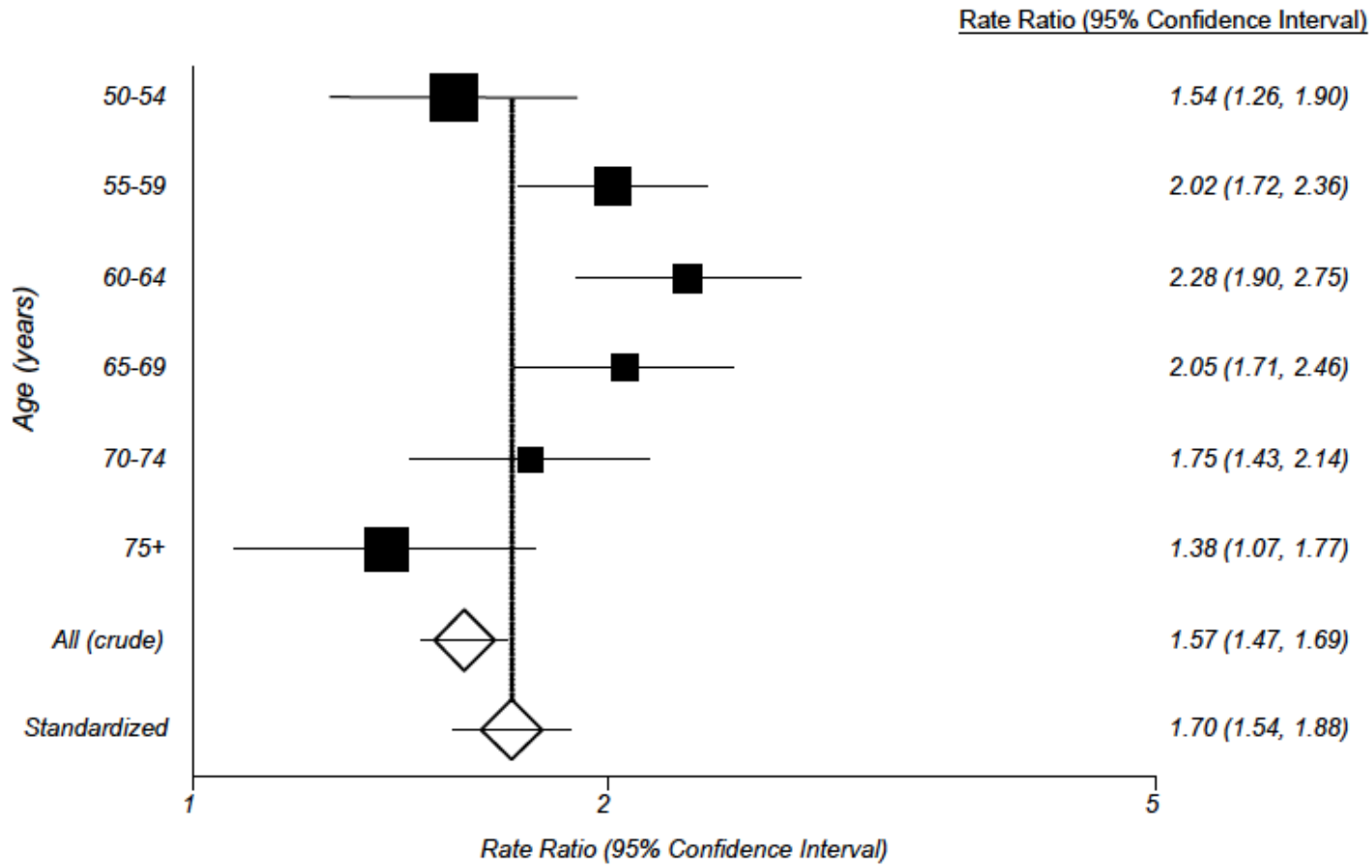

DRY EYE
Aqueous-deficient
Evaporative
Sjogren Syndrome Dry Eye
Primary
Secondary
Non-Sjogren Dry Eye
Lacrimal Deficiency
Lacrimal Gland Duct Obstruction
Reflex Block
Systemic Drugs
Intrinsic
Meibomian Oil Deficiency
Disorders of Lid Aperture
Low Blink Rate
Drug Action Accutane
Extrinsic
Vitamin A-Deficiency
Topical Drugs Preservatives
Contact Lens Wear
Ocular Surface Disease eg, Allergy
Effect of the Environment
Milieu Interieur
Low blink rate behavior, VTU, microscopy
Wide lid aperture gaze position
Aging
Low androgen pool
Systemic Drugs: antihistamines, beta-blockers, antispasmodics, diuretics, and some psychotropic drugs
Milieu Exterieur
Low relative humidity
High wind velocity
Occupational environment


Aging
Androgen Deficiency
Systemic Drug Effects
Inflammatory Cytokines
SSDE; NSDE
Environment
Compromised lipid layer
Meibomian Gland Disease
Blepharitis
Lid Flora
Lipases, Esterases, Detergents
MEIBOMIAN GLAND
High Evaporation Rate
Xerophthalmia
Ocular Allergy
Preservatives
Contact Lens Wear
Secretory
Downregulation
Reduced
Lacrimal Flow
Tear Hyperosmolarity
LACRIMAL
GLAND
MAPK+, NFkB +
IL-1+, TNF-a +
MMPs
Tear Film
Instability
Neurosecretory
Block
Neurogenic
Inflammation
CORNEA
Reflex Block
Nerve Injury
Goblet Cell
Glycocalyx Mucin Loss
Epithelial Damage
Apoptosis
Shear
Stress
Refractive Surgery
Contact Lens Wear
Topical Anesthesia

# Dry eye disease:
# Risk factors

# Sex Differences in DED Prevalence




Schaumberg DA, Dana R, Buring JE, Sullivan DA. Arch Ophthalmol. 2009 Jun;127(6):763-8.

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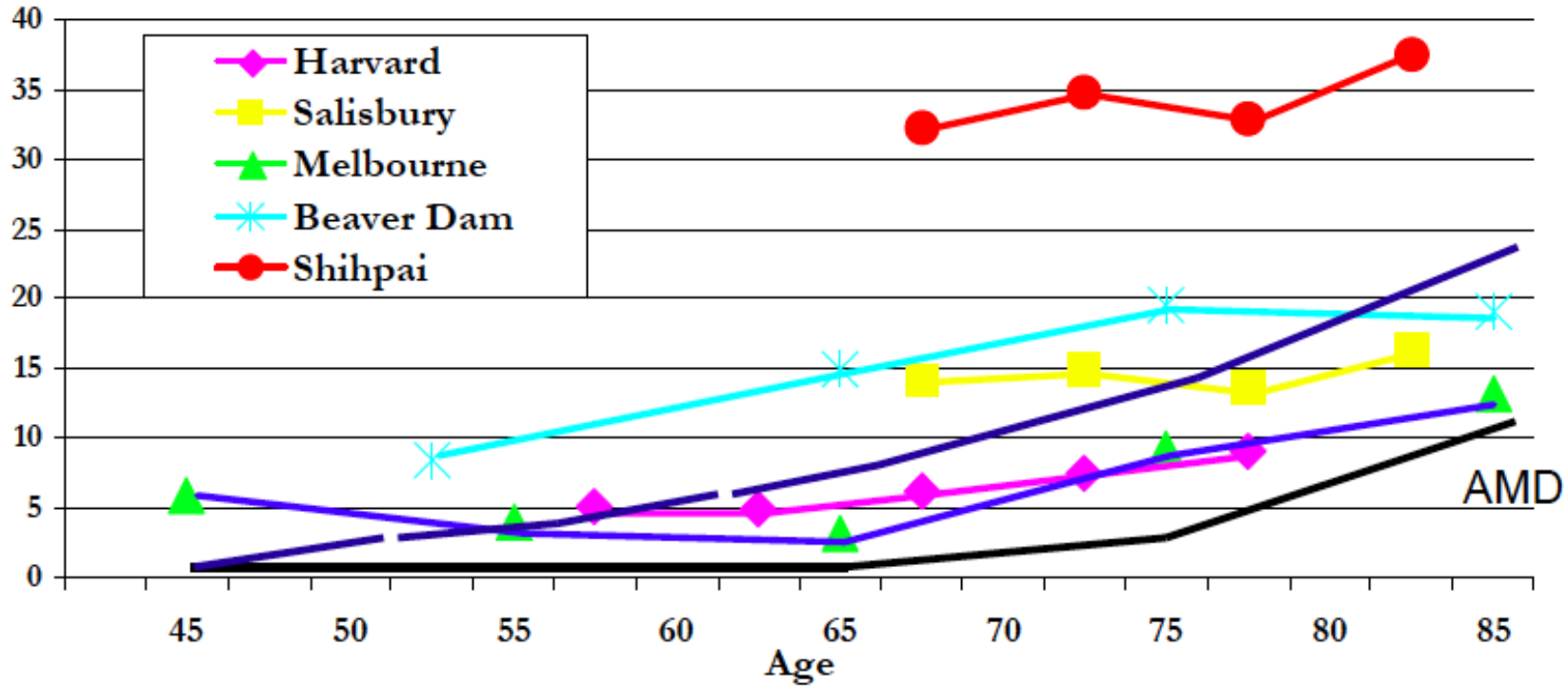
2010

# Prevalence of Dry Eye by Age

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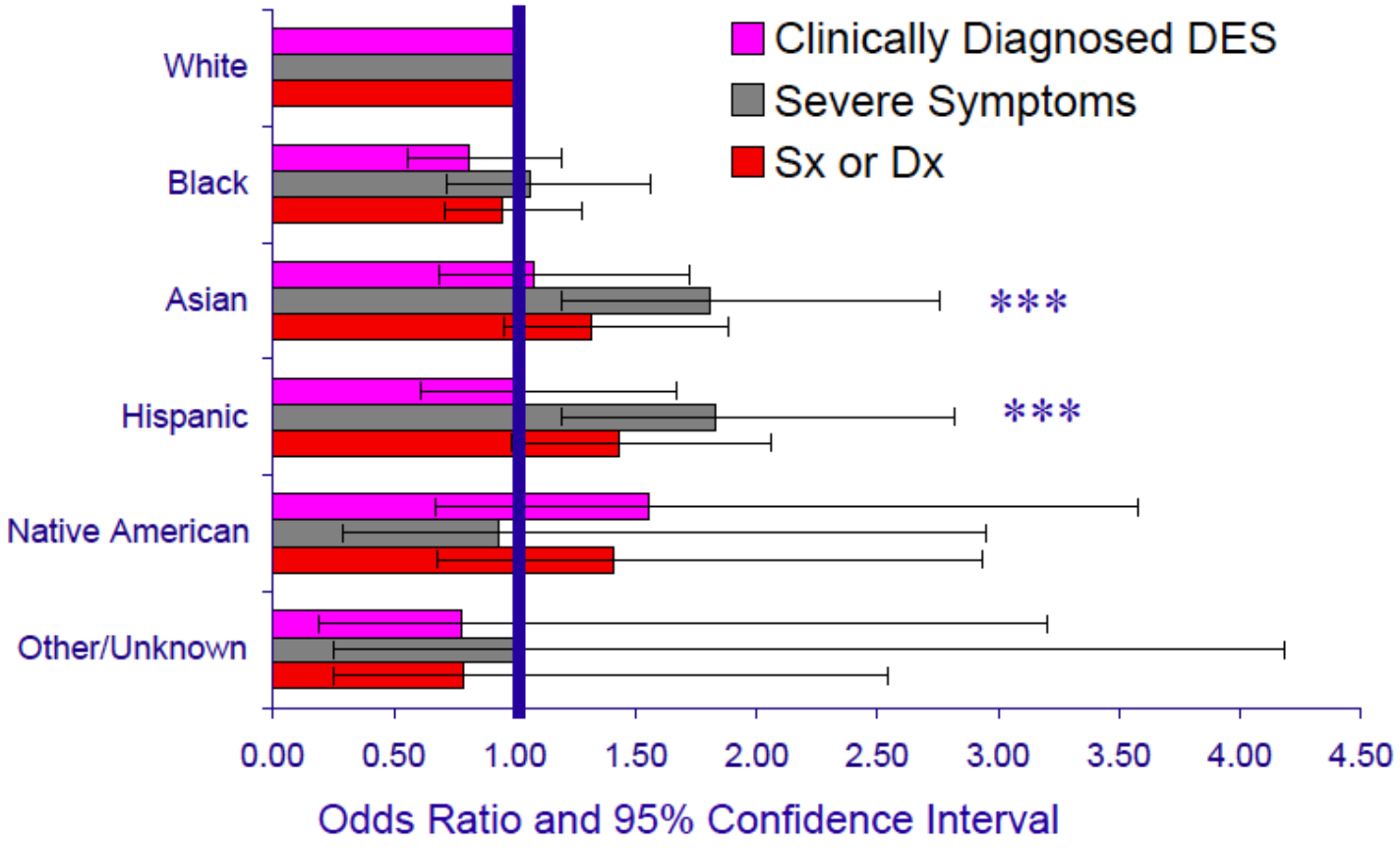
# Prevalence of Dry Eye in US, by Race




Schaumberg DA, Sullivan DA, Buring JE, Dana MR.Am J Ophthalmol. 2003 Aug;136(2):318-26.

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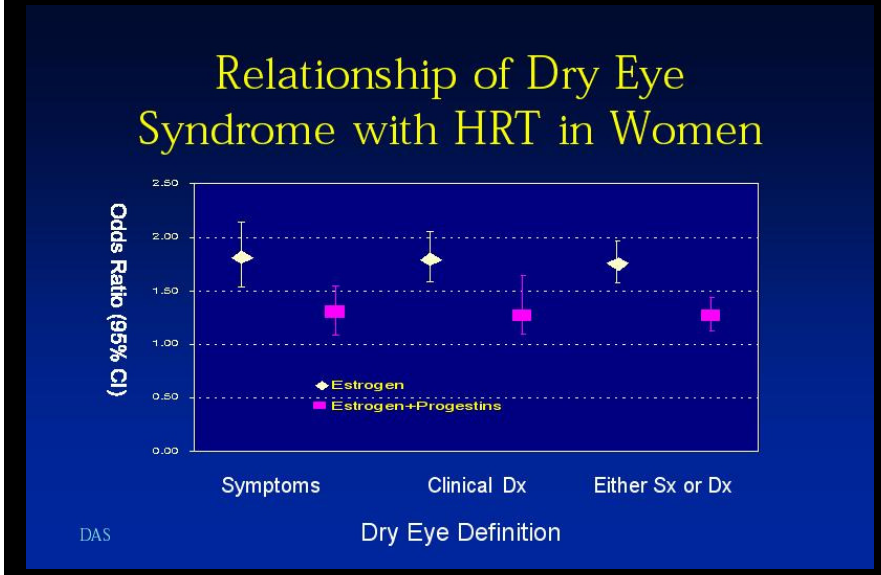
2010

# Additional risk factors for DED




- Androgen deficiency
- Estrogen replacement therapy
- Benign prostatic hyper-plasia & associated medications
- Hypertension
- Antidepressant medications

# Dry eye disease: Quality of life

# Dry eye & quality of life


- Impact of moderate to severe dry eye is comparable to dialysis and severe angina
- DED leads to problems with reading, computer use & work performance, and is associated with role limitations, lower vitality & poorer general health

# Dry eye disease: Approved treatments

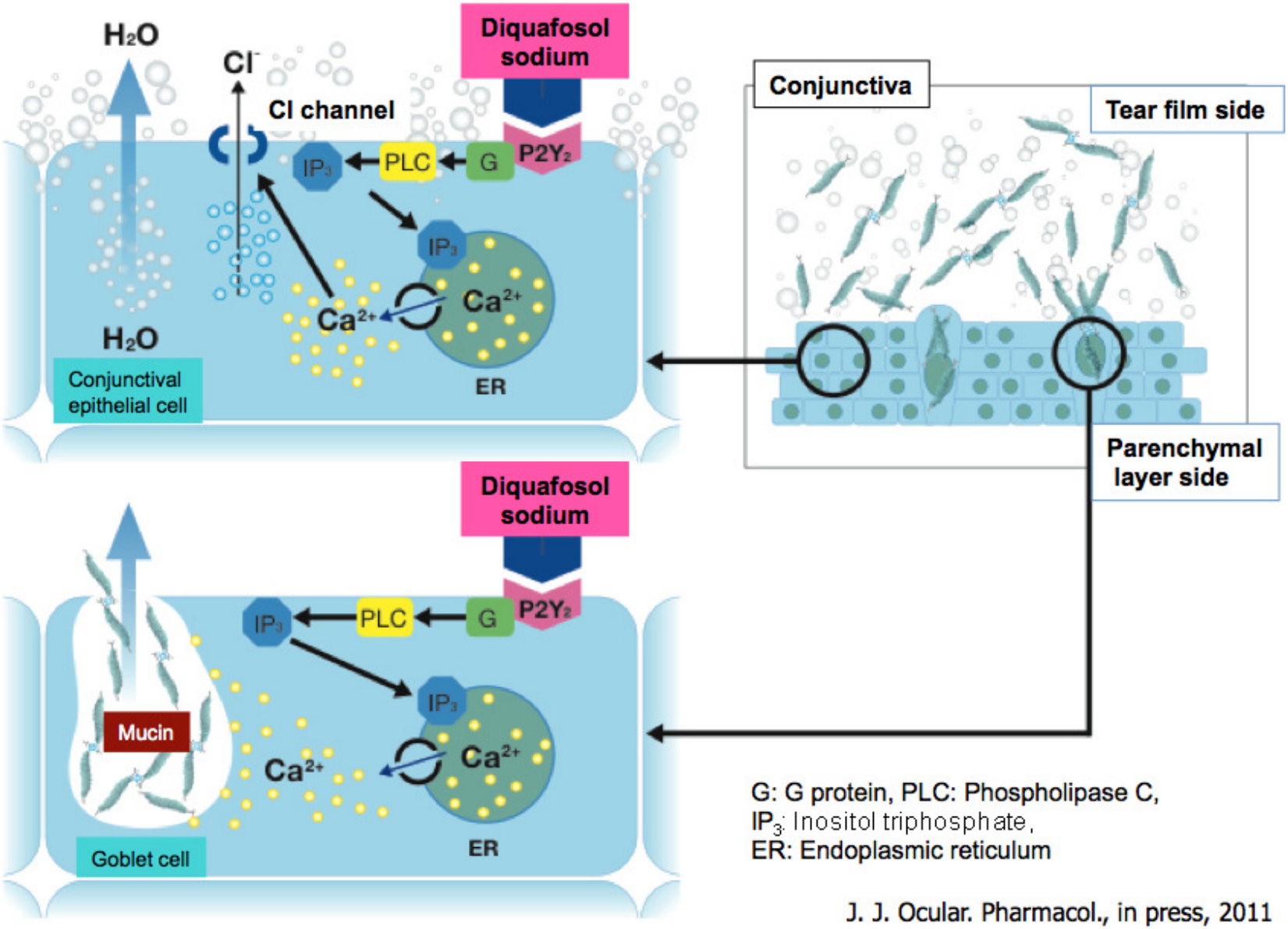
# Topical Restasis

"Restasis is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca."

# Restasis sales in 2010: > $700 million


"… statistically significant increases in Schirmer wetting of 10 mm versus vehicle…effect was seen in ~ 15% of RESTASIS® ophthalmic emulsion treated patients versus ~ 5% of vehicle treated patients."

# Mechanism of Action - Diquafosol tetrasodium -

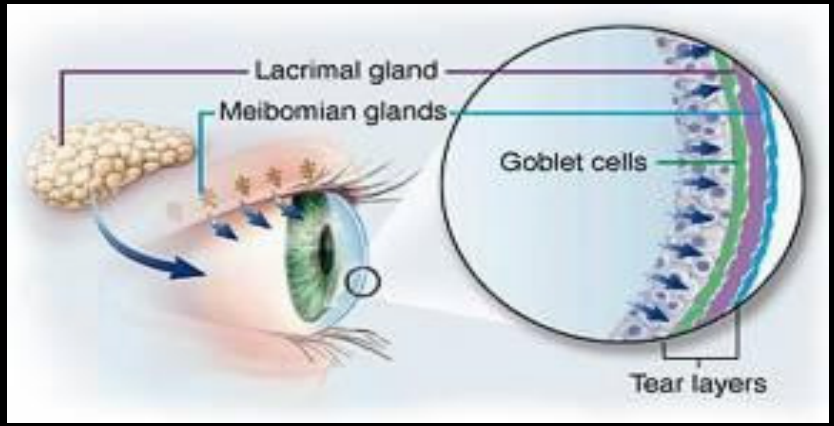



G: G protein, PLC: Phospholipase C,
$IP_3$: Inositol triphosphate,
ER: Endoplasmic reticulum

J. J. Ocular. Pharmacol., in press, 2011

# Dry eye disease: Potential treatments

# Treatment Targets




Mucin deficiency

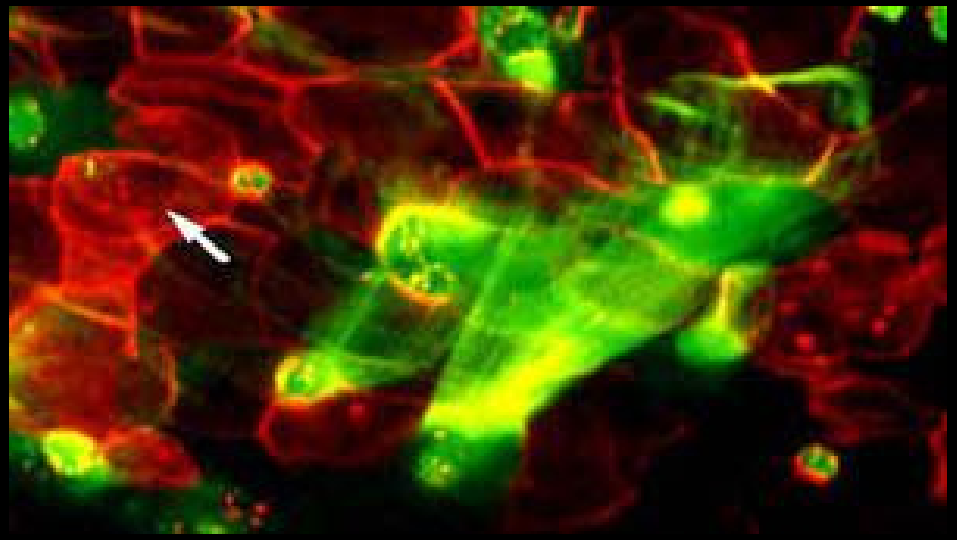
Aqueous tear deficiency

Lipid deficiency

Ocular surface damage

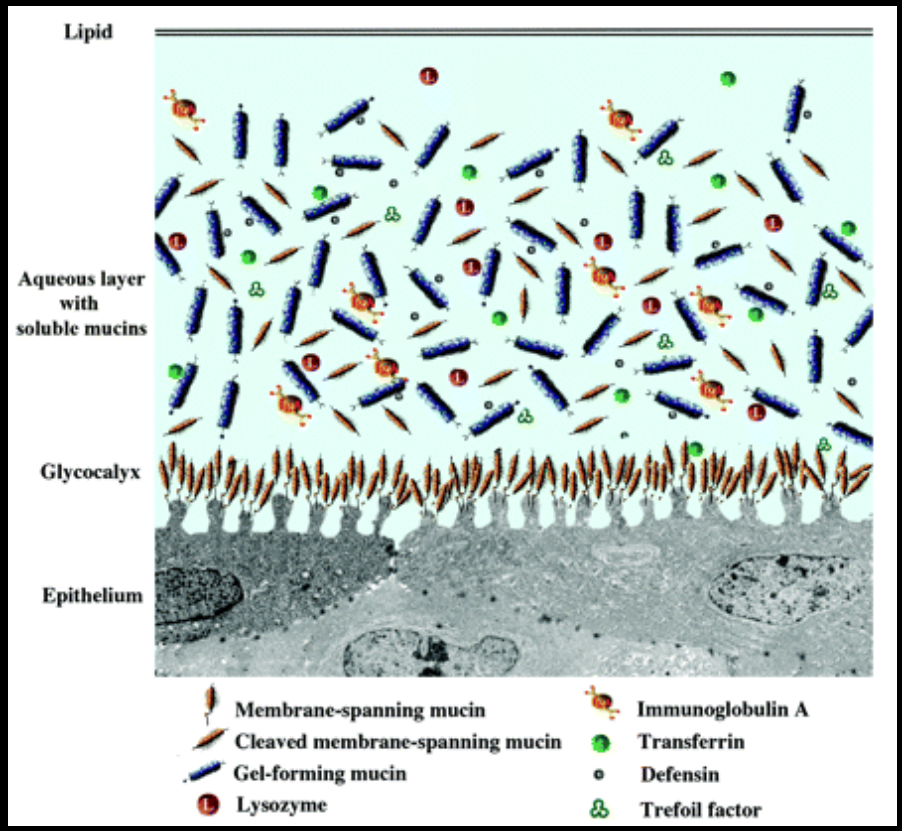
# New therapeutic approaches for the treatment of mucin deficiency

- Diquafasol
- Gefarnate
- Eupatilin
- Rebamipide
- Galectin 3
- Tamarind seed
- Trefoil factor family peptide 3 (TFMP3)
- Mycophenolate mofetil
- Nerve growth factor & mimetic



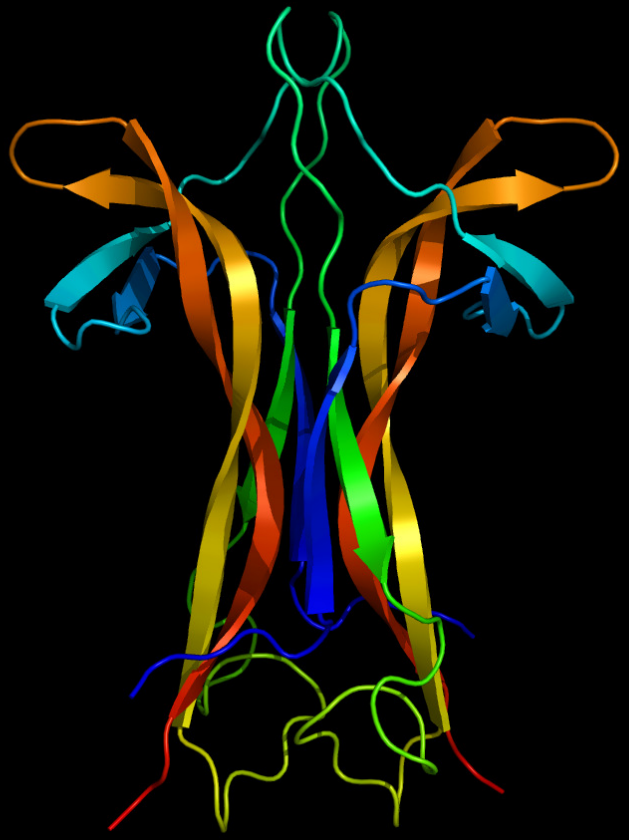
# Stimulation of ocular surface mucins

- Mycophenolate mofetil – ↑ MUC5AC in human conjunctiva
- DA-6034 (Eupatilin) – ↑ MUCs 1, 2, 4, 5AC, 5B & 16 in human conjunctiva
- Rebamipide – causes mucus secretion (activates cyclooxygenase 2)
- TFMP3 – stabilizes mucous layer




Gipson IK, IOVS 2007;48:4391-4398

# Nerve growth factor & mimetic



↑ Goblet cell number & MUC 5AC production

↑ Corneal sensitivity

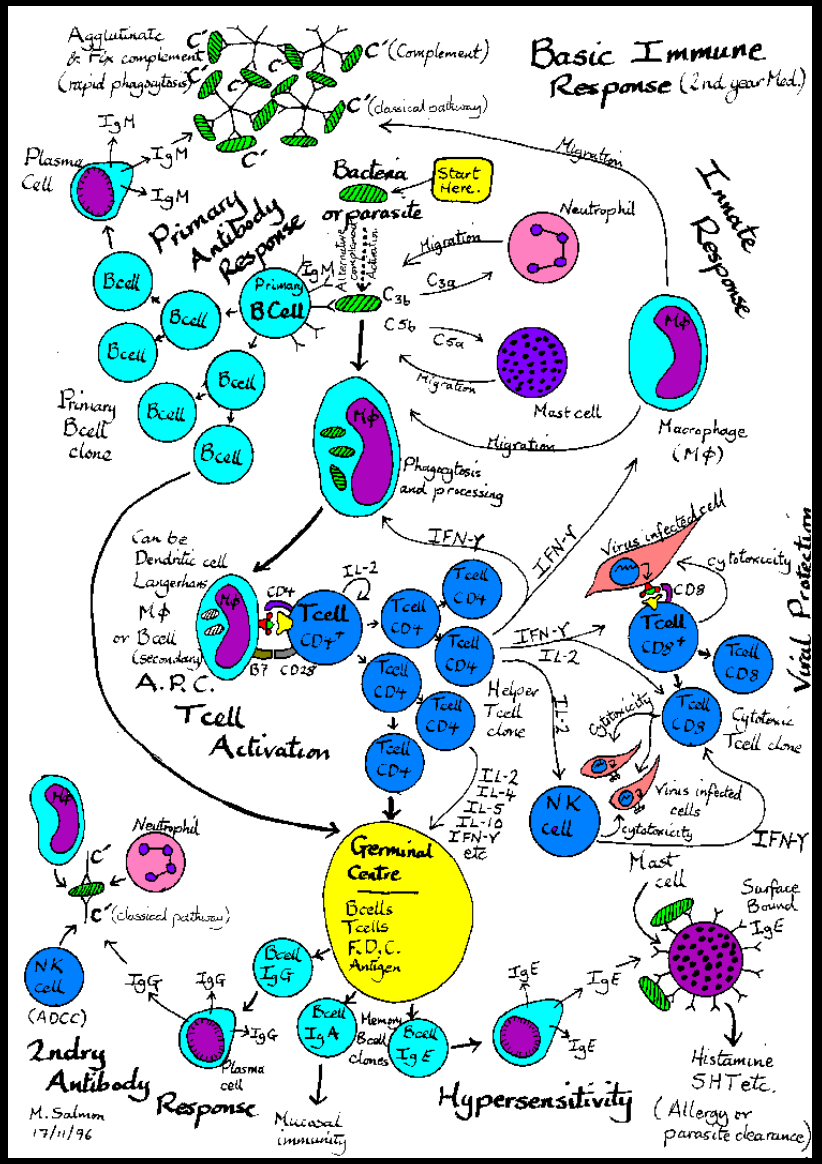
- Promotes corneal epithelial cell wound healing

# New approaches for the treatment of aqueous tear deficiency


Immunomodulation

Lacrimal gland stimulation

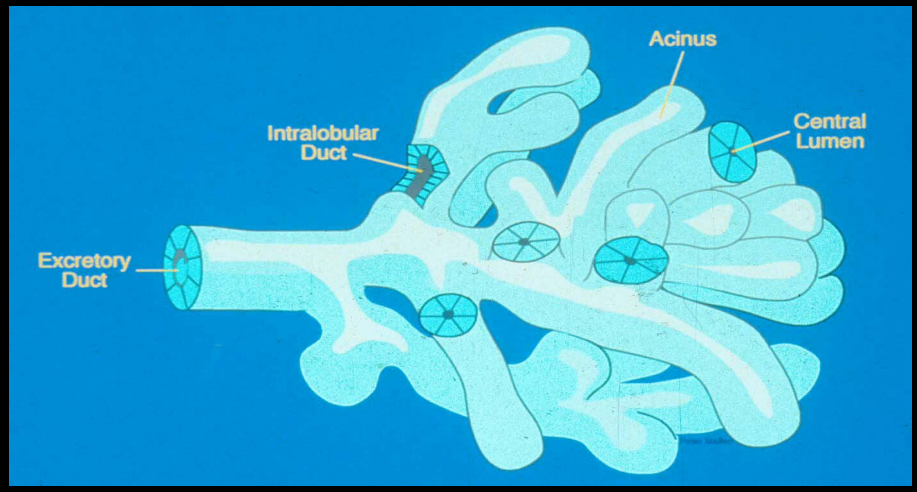
# Immunomodulation



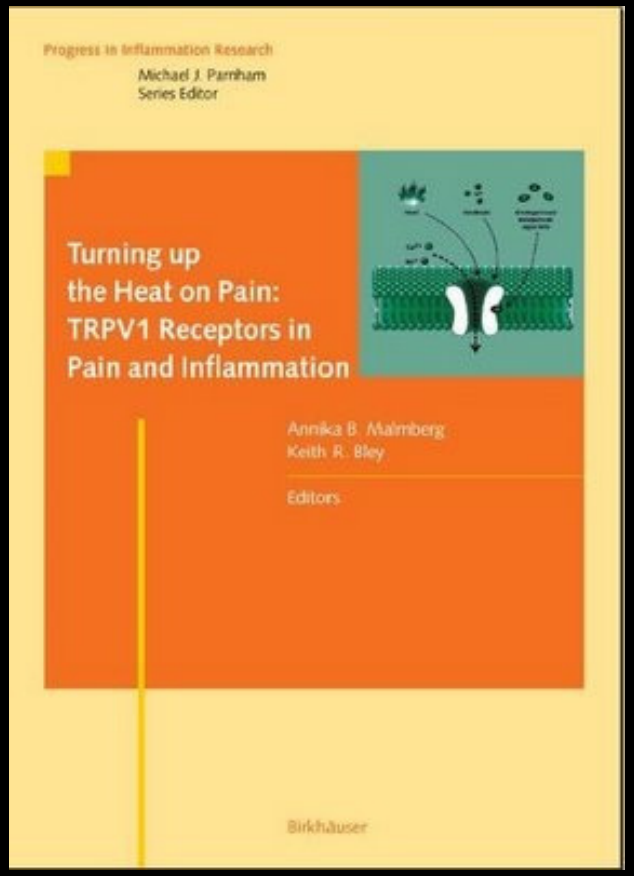

Webrheum.bham.uk/staff/mikessalmon/immune.htm

# Lacrimal Gland Stimulants

- TRPV1 receptor modulators
- Taste & salivation
- Anethol trithione
- Uridine
- Hydroxychloroquine
- Vitamin A
- Muscarinic receptor agonists
- Topical androgens



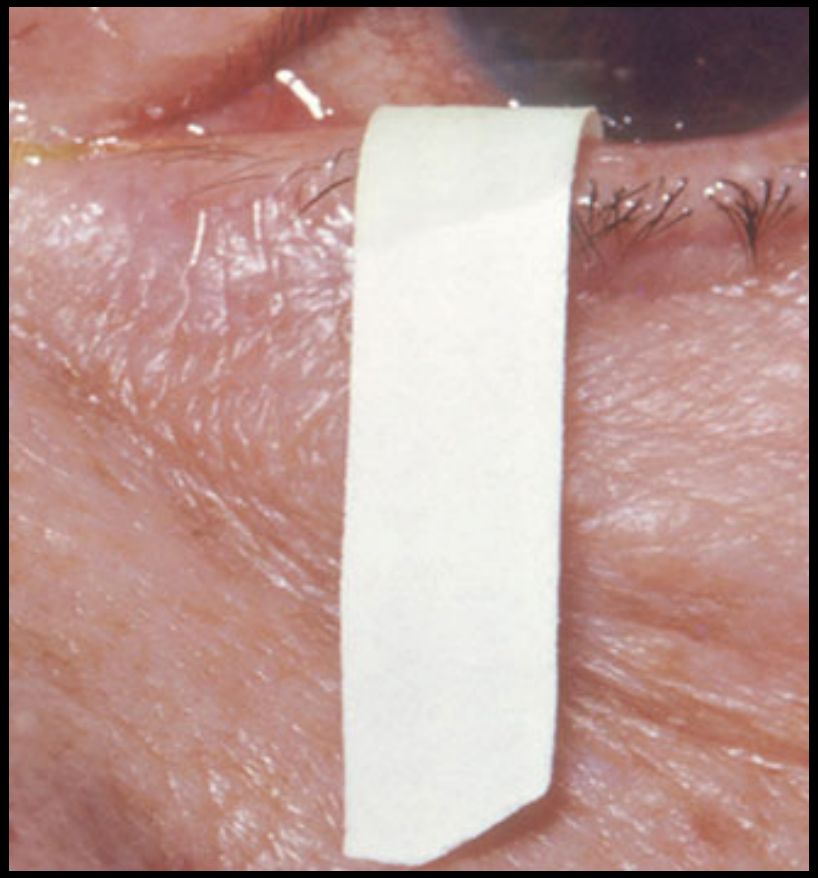
# Transient receptor potential vanilloid 1 (TRPV1) receptor modulator



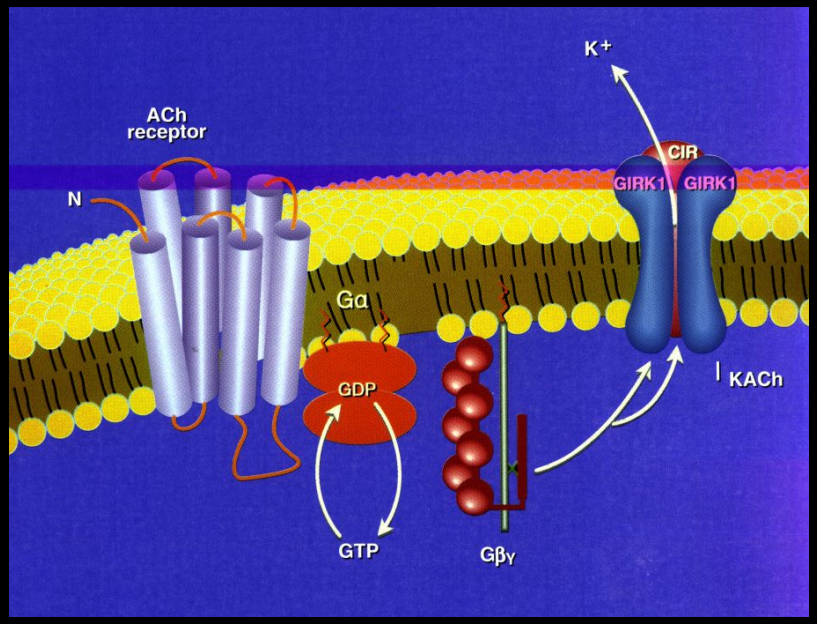

Intranasal application of Civamide, a TRPV1 receptor modulator, reportedly increases tear production. TRPV1 is a permeable, non-selective cation channel.

# Increased Schirmer Wetting Score

- Oral anethole triothine – a cholagogue
- Oral uridine – metabolized into P2Y2 agonist
- Oral hydroxychloroquine – in Sjögren's syndrome patients with α-fodrin antibodies
- Vitamin A – retinyl palmitate eye drops



# Muscarinic Receptor Agonists




Salagen (M3 agonist, oral pilocarpine)

Cevimeline (M1/M3 agonist)

# Oral Pilocarpine and Cevimeline

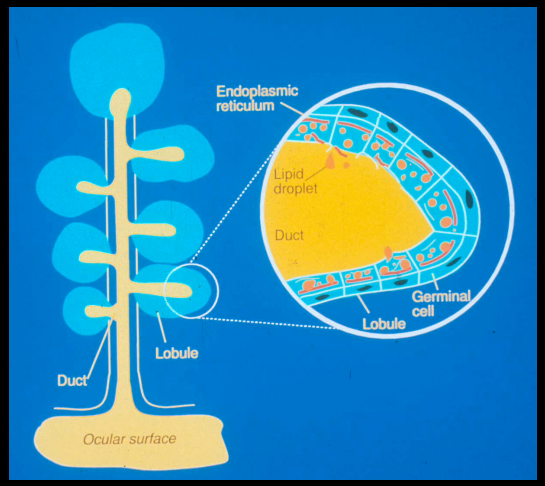
Sjögren's Syndrome:

Beneficial effect on subjective eye symptoms

No effect on tear volume

Pilocarpus pennatifolius

# New approaches for the treatment of lipid deficiency




LipiFlow & Maskin Intraductal Probe

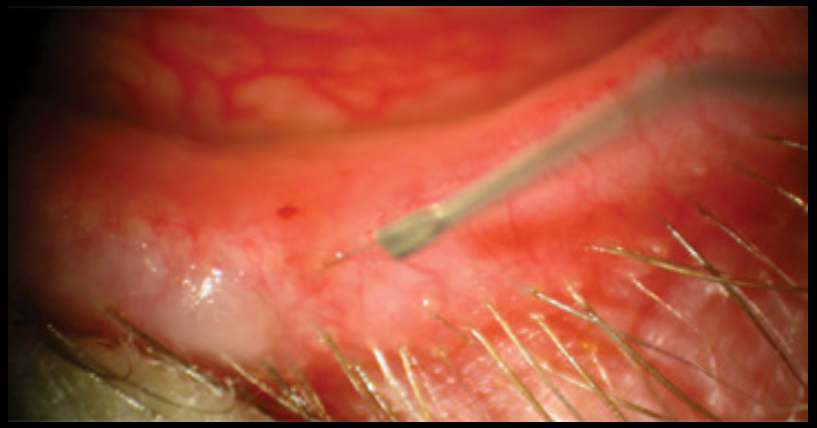
Azithromycin & IL-1Ra

Topical androgens

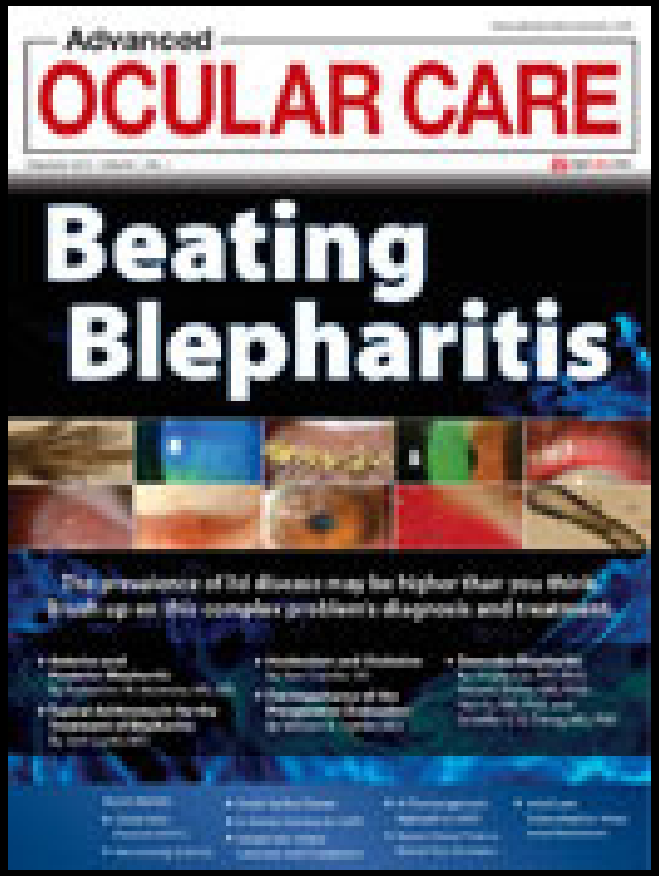
# Treatment of Meibomian Gland Duct Obstruction

TearScience LipiFlow

Maskin Intraductal Probe



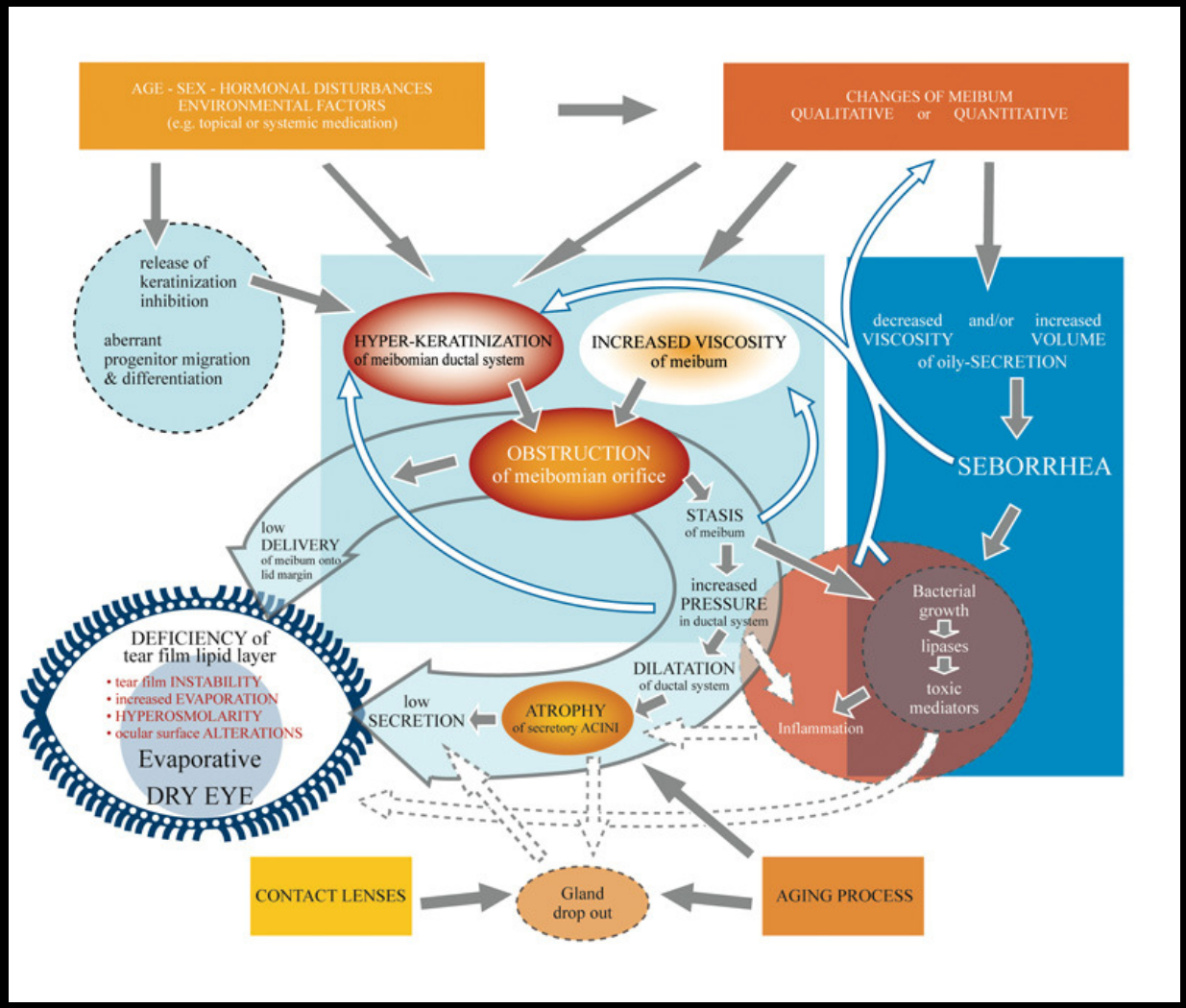
# Treatment of Posterior Blepharitis




Azithromycin (Azasite, Azyter)

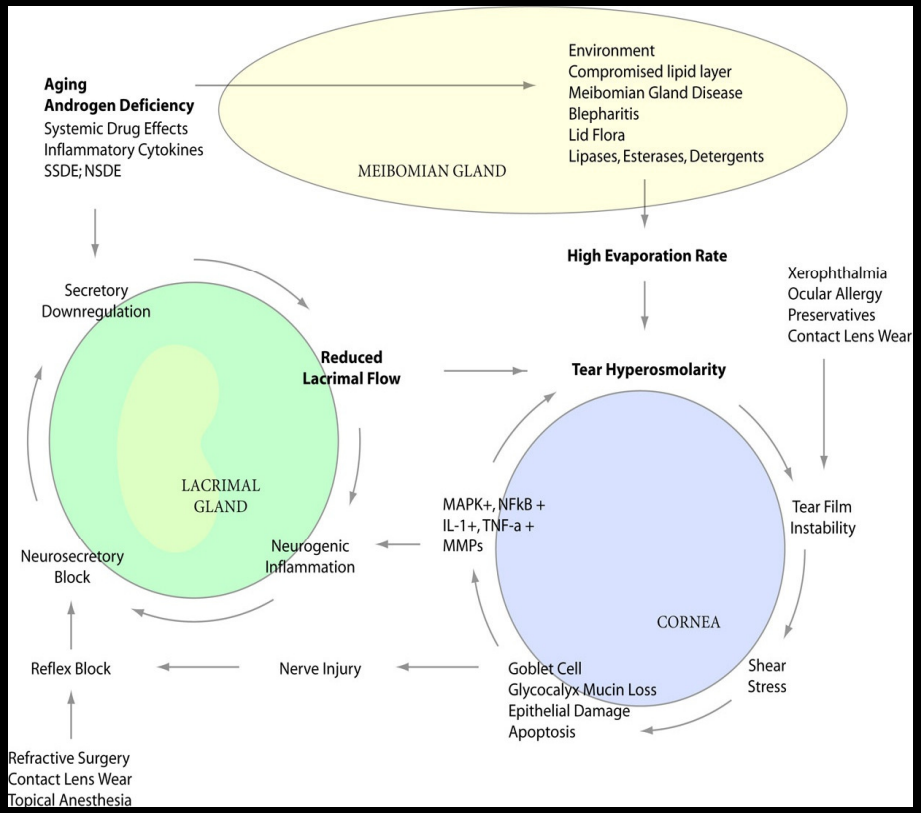
Interleukin-1 receptor antagonist

# Topical androgens: Treatment of meibomian gland dysfunction




TFOS MGD Report, 2010

# Treatment of Ocular Surface Damage

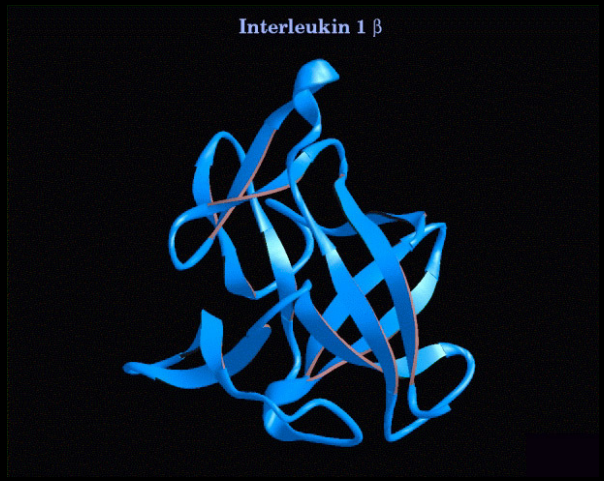



Immunomodulation

Hydration

Boundary Lubrication

# Immunomodulation




Omega 3 fatty acids & nutritional foods

Glucocorticoids

NSAIDs

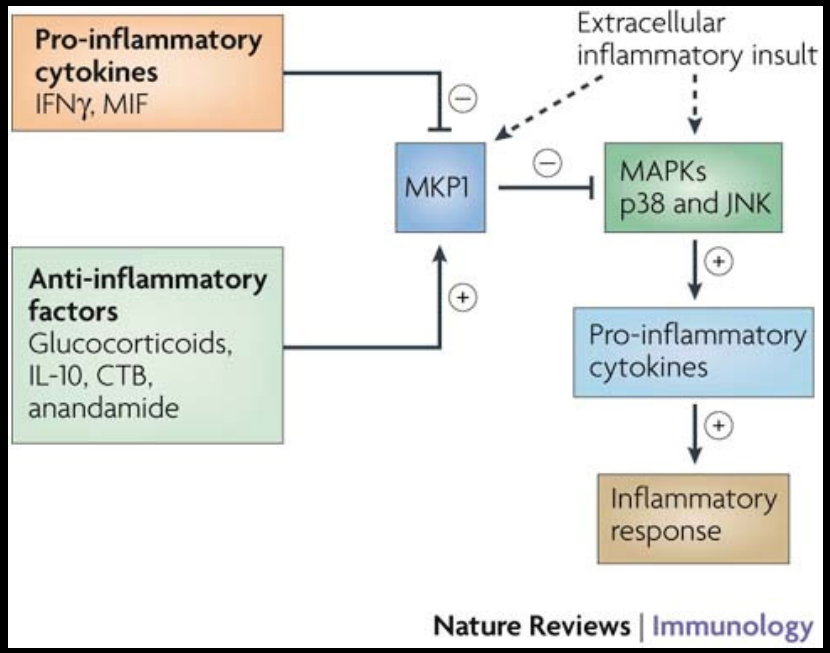
Calcineurin inhibitors

Antibodies & other drugs

# Omega 3 fatty acids & nutritional foods

# Glucocorticoids

- EGP-437 – EyeGate Pharma, dexamethasone & transscleral iontophoresis
- Mapracorat – B&L, selective glucocorticoid receptor agonist
- DE-110 – Santen, selective glucocorticoid receptor agonist
- Lotemax – B&L



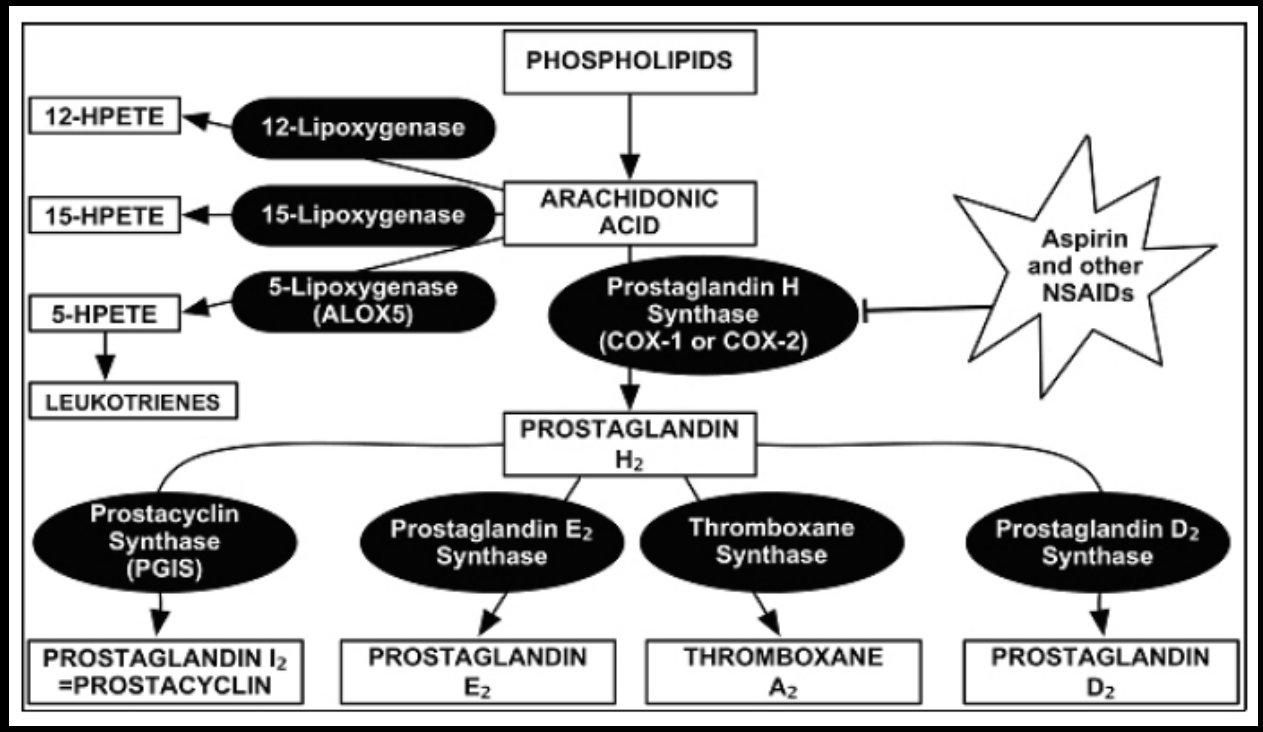

# Possible glucocorticoid side effects

Ocular side effects have included blurred vision, discharge, ocular pain and discomfort, increased intraocular pressure, foreign body sensation, pruritus, and hyperemia in 1% to 5% of patients.

Dry eye, tearing, conjunctival and corneal edema, keratitis, photophobia, corneal erosion, corneal ulcer, corneal staining, increased fibrin, tearing, photophobia, edema, irritation, browache, lid margin crusting, and infiltrate have been reported in less than 1% of patients.

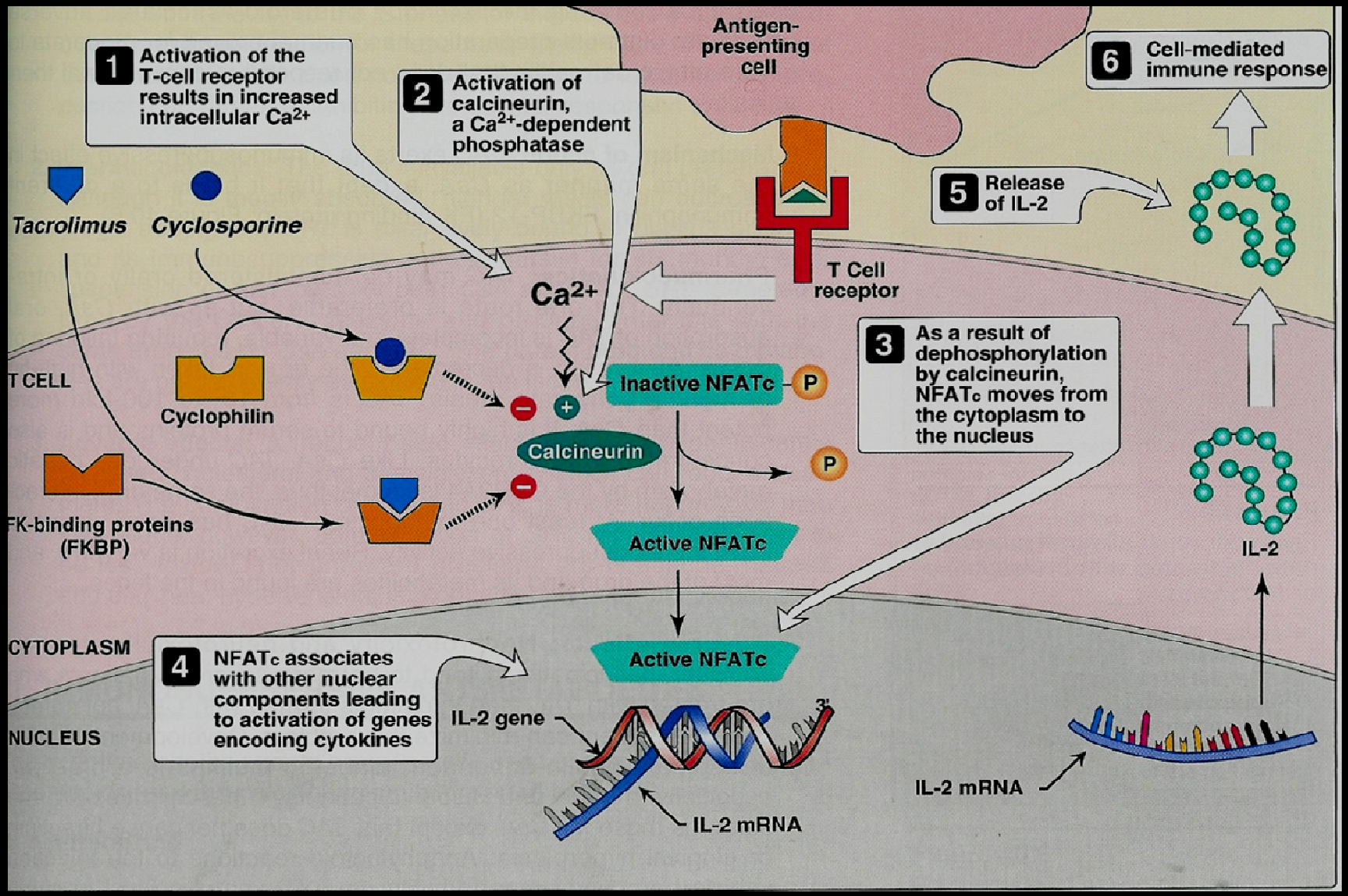
In addition, prolonged use of topical ophthalmic corticosteroids has caused ocular hypertension/glaucoma, optic nerve damage, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, and secondary infections of the eye. The use of topical corticosteroids has caused perforation of the globe where there is preexisting thinning of the cornea or sclera.

# Non-steroidal anti-inflammatory drugs



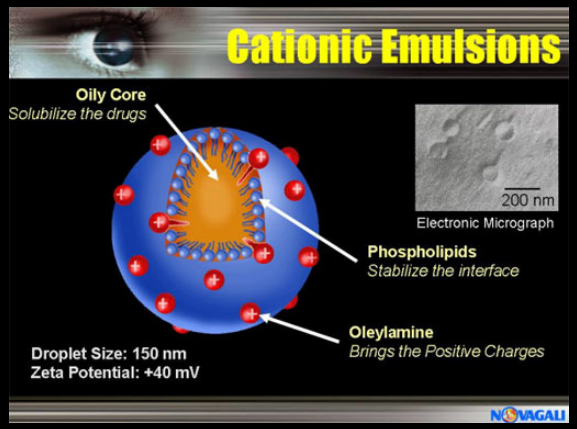

Remura (ISTA Pharmaceuticals) & ISV-101 (InSite Vision) – bromfenac, thought to inhibit cyclooxygenases 1 & 2

# Calcineurin inhibitors

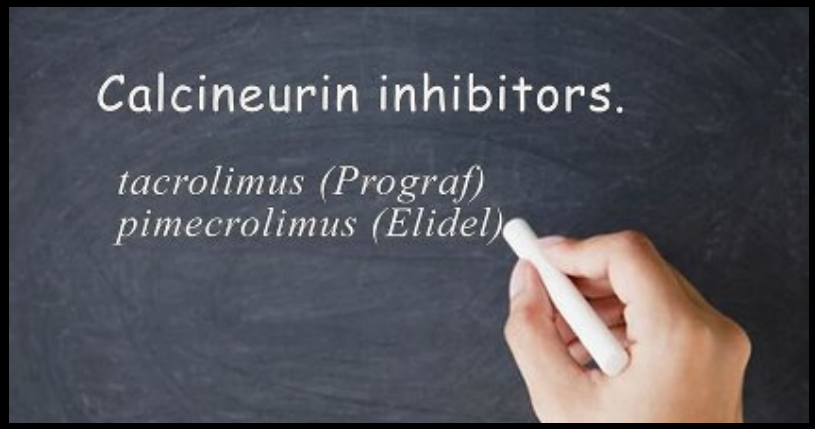


# Additional formulations

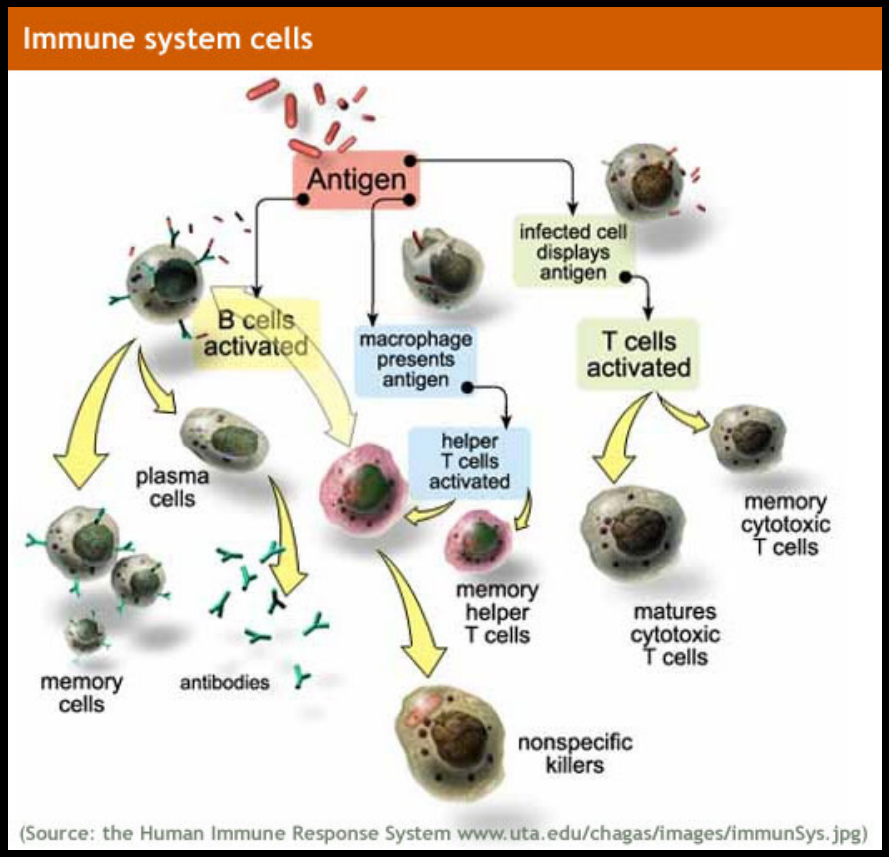
Novagali – Cyclokat, a cyclosporine




LuxBio – LX214, a voclosporine

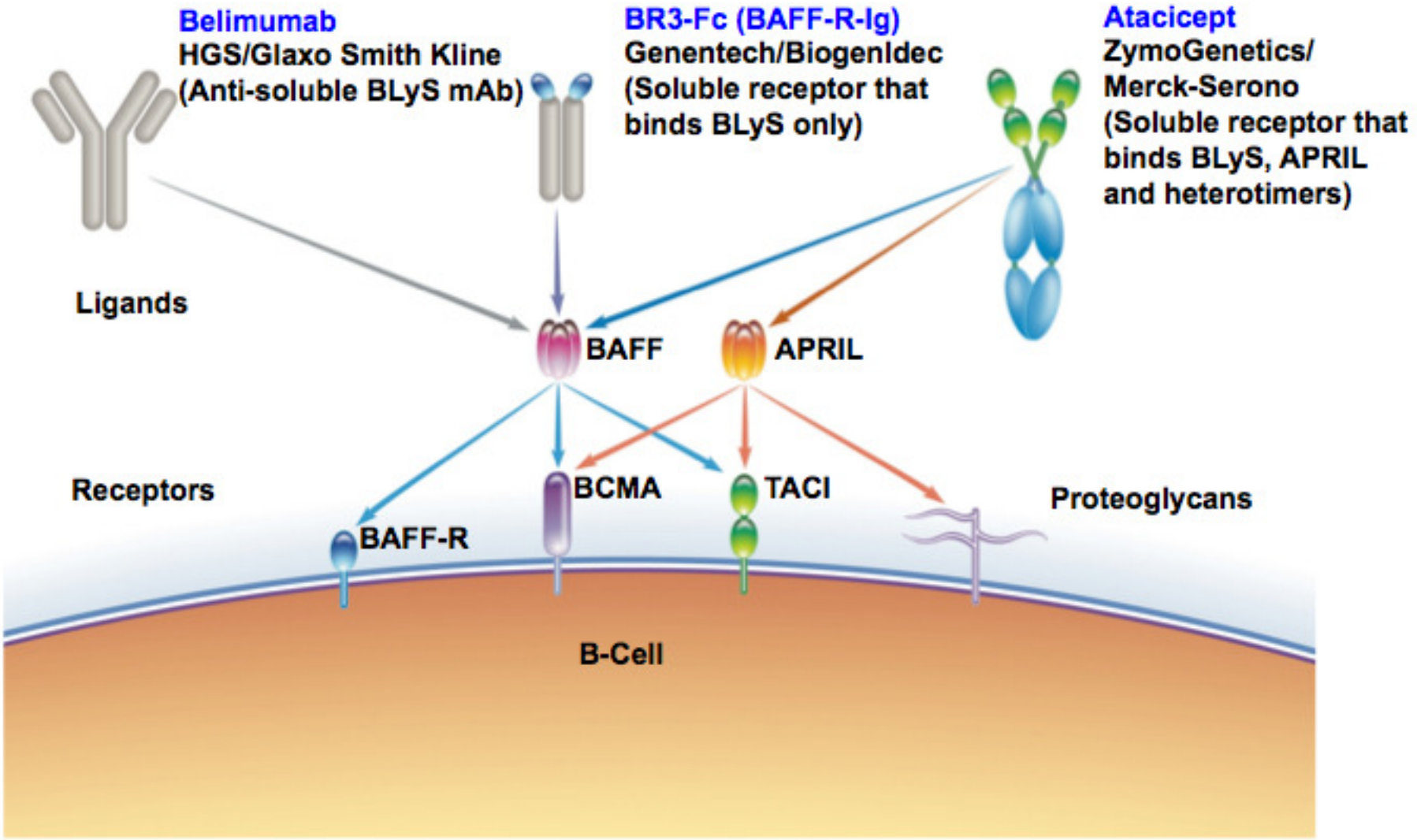


# Antibodies




- AIN457 (Novartis) – neutralizes IL-17A
- ESBA105 (Alcon) – fragment against TNF-α
- Belimumab (GSK) – human monoclonal inhibits B cell activation factor
- Rituximab (Biogen) – murine/human anti-CD20 monoclonal

# Inhibiting BAFF or BAFF + APRIL ?



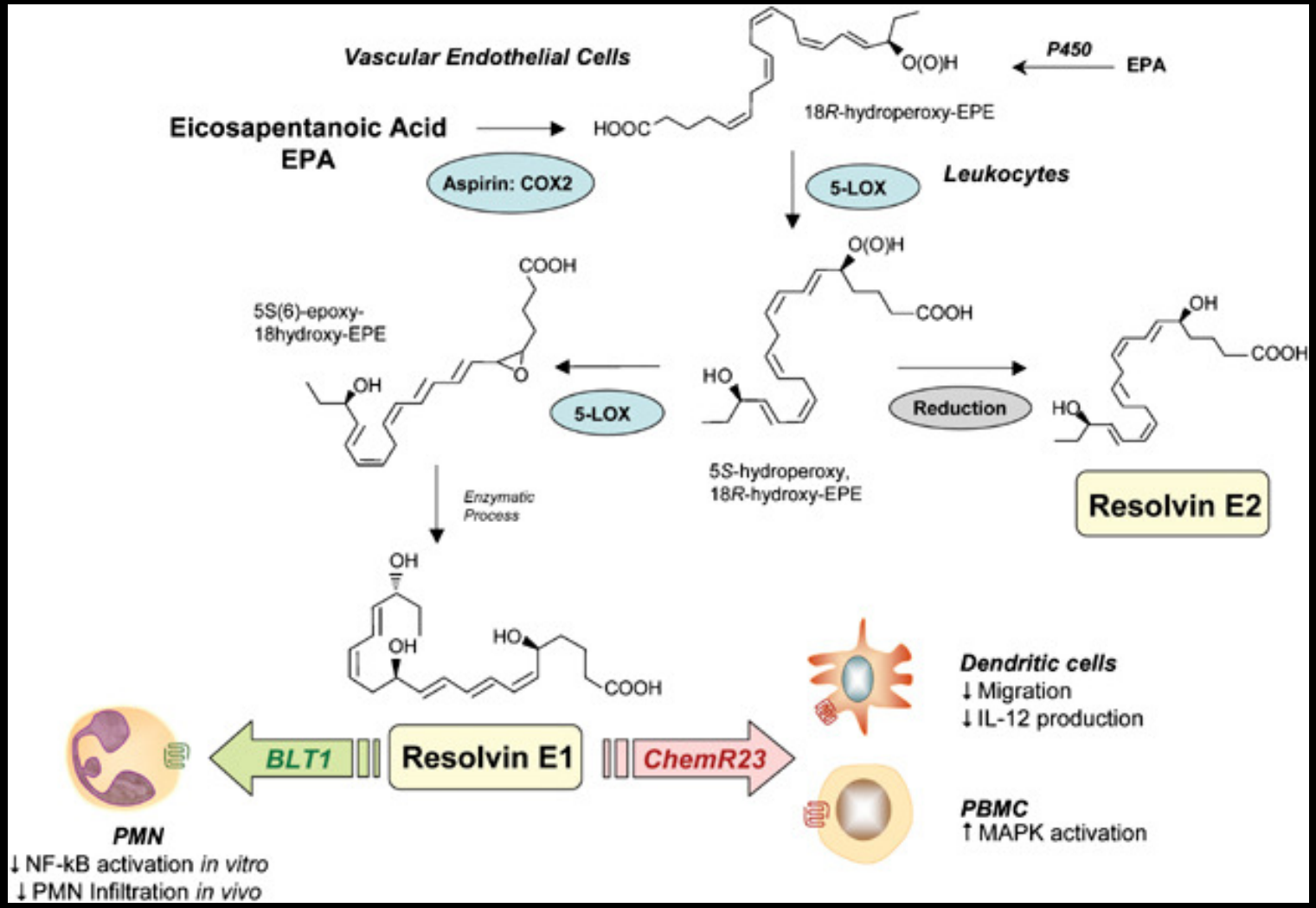
# Other anti-inflammatory drugs

CF-101 (CAN-FITE) – oral adenosine3 receptor agonist, induces inflammatory cell apoptosis

RGN259 (Regenerx) – topical thymosin β4

Perceiva (MacuSight) – sirolimus, subconjunctival injection, inhibits response to IL-2

# Resolvins

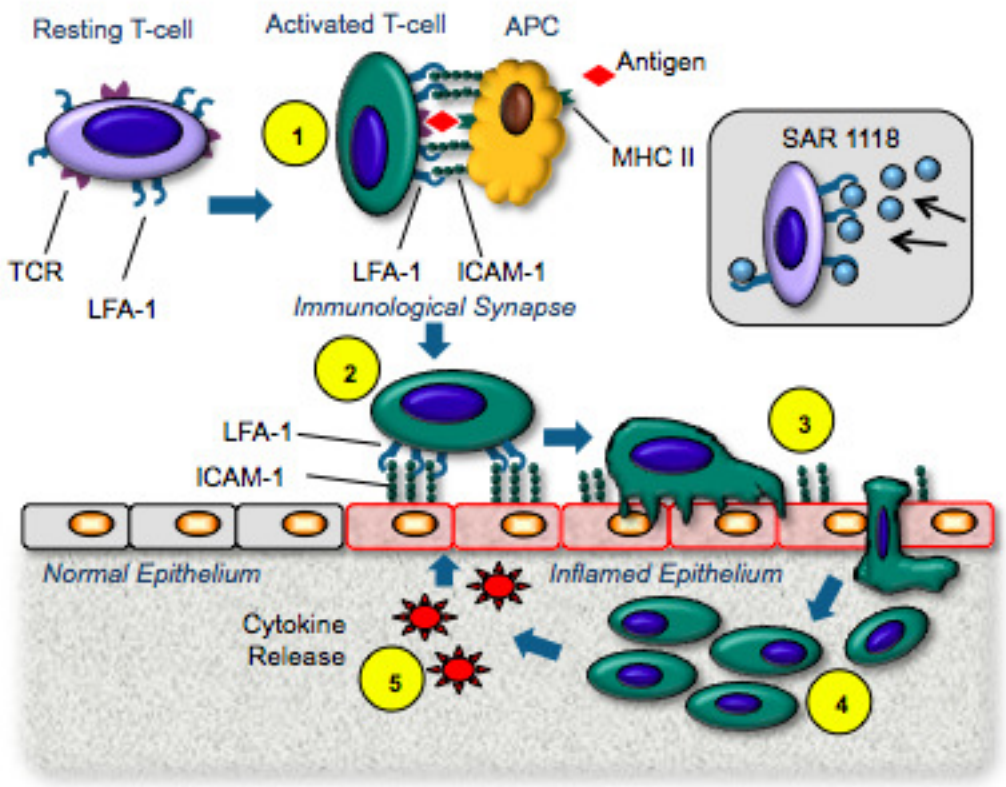

Vascular Endothelial Cells
P450
EPA
O(O)H
HOOC
18R-hydroperoxy-EPE
Eicosapentanoic Acid
EPA
Aspirin: COX2
5-LOX
Leukocytes
COOH
5S(6)-epoxy-
18hydroxy-EPE
OH
O
HO
5-LOX
Reduction
5S-hydroperoxy,
18R-hydroxy-EPE
Resolvin E2
Enzymatic
Process
OH
HO
COOH
BLT1
Resolvin E1
ChemR23
Dendritic cells
↓ Migration
↓ IL-12 production
PBMC
↑ MAPK activation
PMN
↓ NF-kB activation in vitro
↓ PMN Infiltration in vivo

# Goal – Break Cycle of Inflammation

*SAR 1118 Binds to LFA-1 on T-cells and Prevents Interaction with ICAM-1*

**SAR 1118 Inhibits T-cell**

1. LFA-1/ICAM-1
2. Adhesion
3. Migration
4. Proliferation
5. Cytokine Release




**LFA-1**: lymphocyte function-associated antigen-1 (CD11a/18; αLβ2)

**ICAM-1**: intercellular adhesion molecule-1 (CD54)

**TCR**: T cell receptor

**APC**: antigen presenting cell

**MHC II**: major histocompatibility complex class II

# Other anti-inflammatory compounds

- Rivoglitazone (Santen) – binds to PPARs
- Cilomilast (Alcon) – phosphodiesterase 4 inhibitor
- DA-6034 (Dong-A) – inhibits NF-κB activation
- Chitosan-N-acetylcysteine conjugate – thiolated polymer, suppresses inflammation, no effect on corneal staining
- Tranilast – inhibits lipid mediator and cytokine release
- N-acetyl aspartyl glutamic acid – neuropeptide
- Astaxanthin – oral carotenoid
- Curcumin - natural polyphenol extracted from turmeric
- Catechins – from green tea
- KLS-0611 & KCT-0809 (Kissei) - treat surface damage

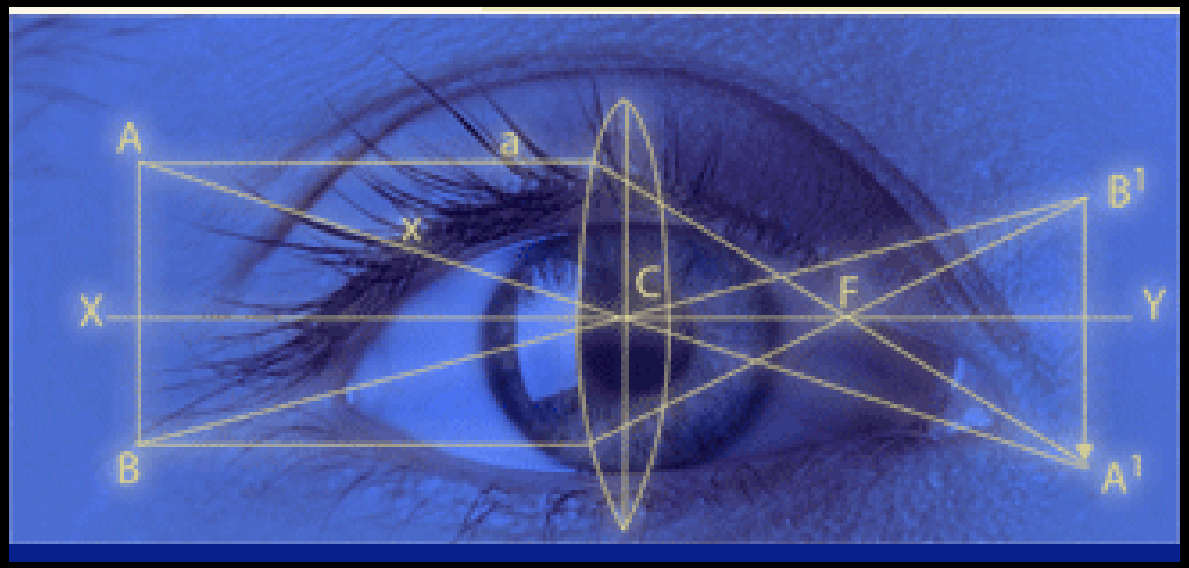
# Hydration

Oral sea buckthorn oil – reduces tear osmolarity

Lancutovide (Lantibio) – promotes hydration

Alpha eye dry eye relief mask – moisture barrier

# Boundary Lubrication



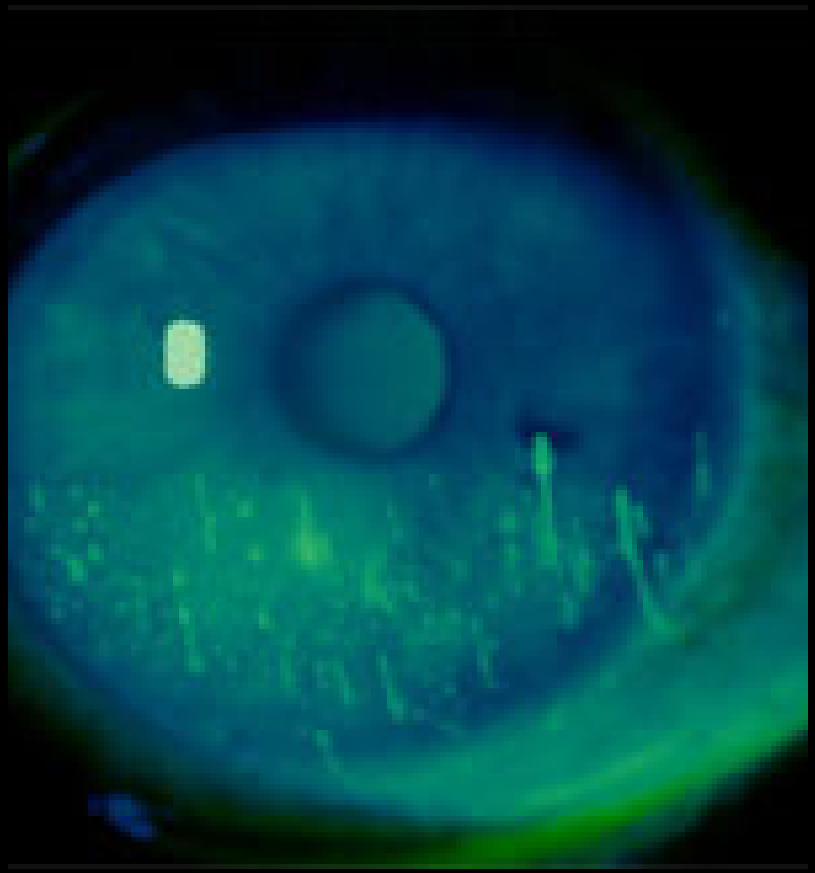

Lubricin -

- Protects against shear stress
- Addresses central causative mechanism (*i.e.* shear stress) of ocular surface damage in dry eye disease

# Virtual kaleidoscope of potential treatments for dry eye disease


CHALLENGE

# Common signs and symptoms of dry eye disease do not correlate



# Clinical Challenges in Dry Eye Therapeutics

- Existing treatments fail to address causative mechanisms
  - Inflammation is low gain, peripheral to central loop
- Difficult inclusion/exclusion criteria
  - Historically subjective signs
  - Symptoms & signs don't correlate
- Schirmer strips and corneal staining are primary endpoints in most clinical trials, but their diagnostic value is limited
- Symptoms alone are insufficient to track severity

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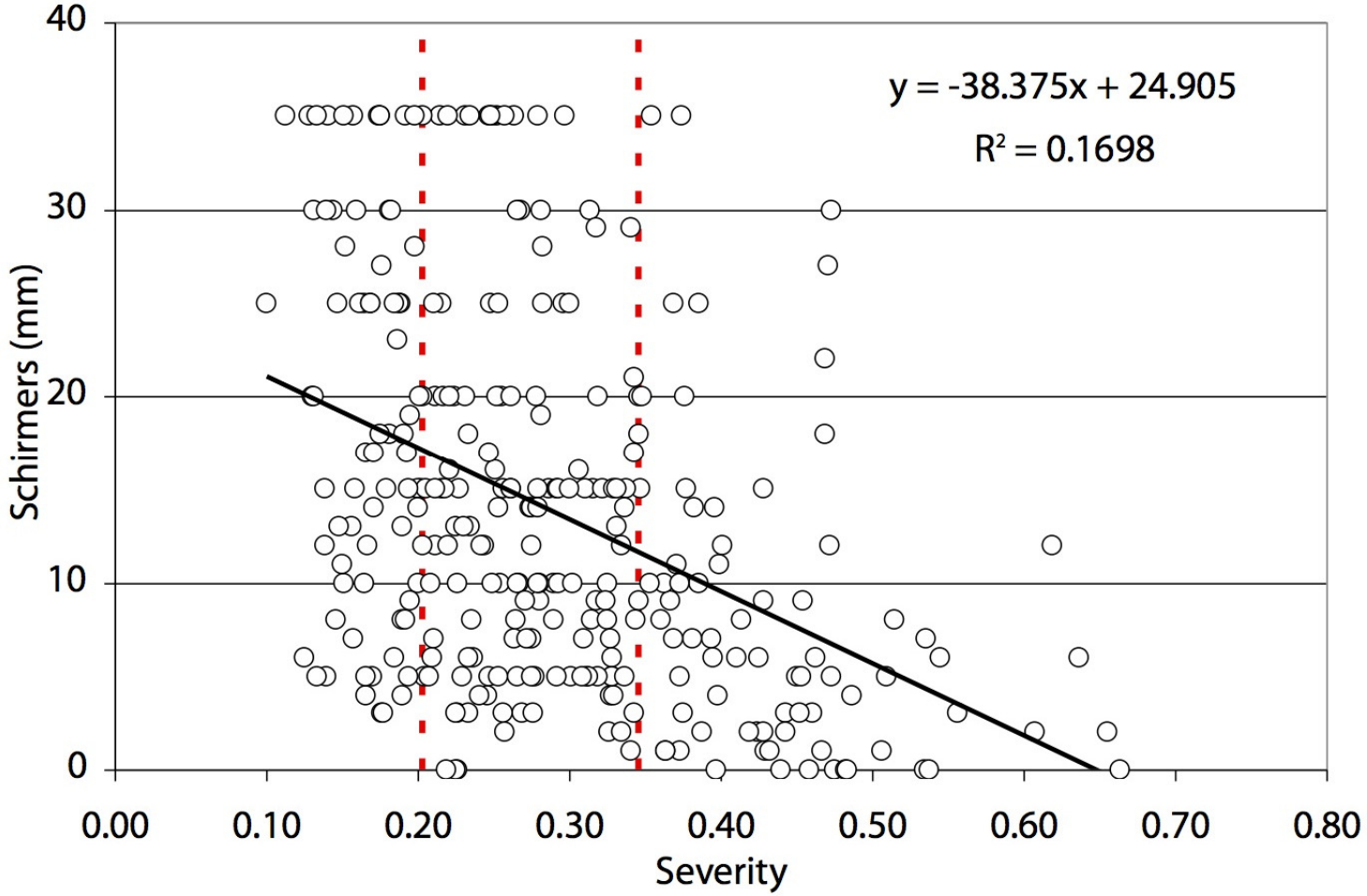
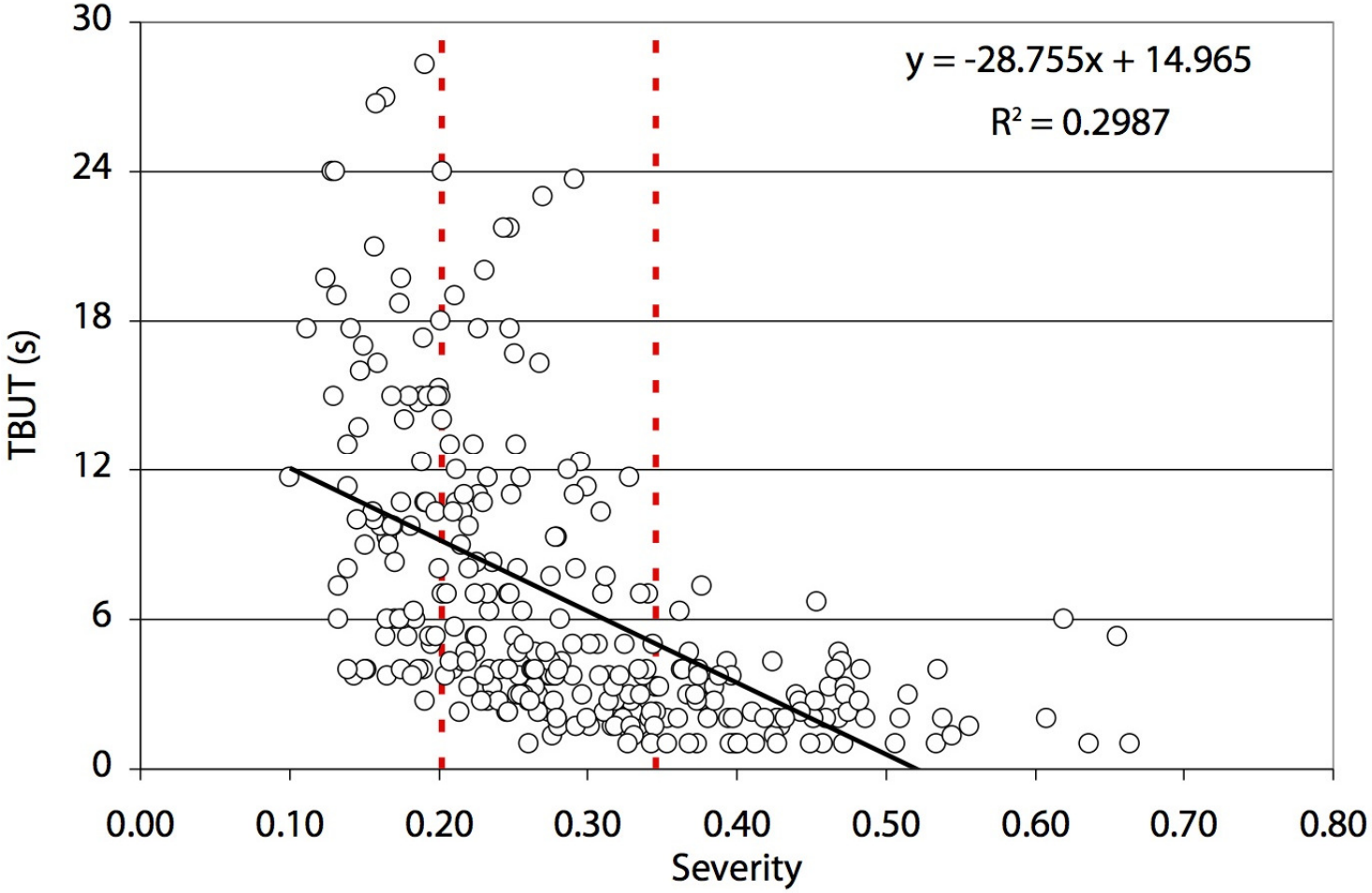
# Schirmer Strip Severity Analysis




*Disease severity is calculated as an unbiased, normalized composite of seven clinical signs & symptoms

Confidential

# Tear Film Breakup Time (TBUT) Severity Analysis

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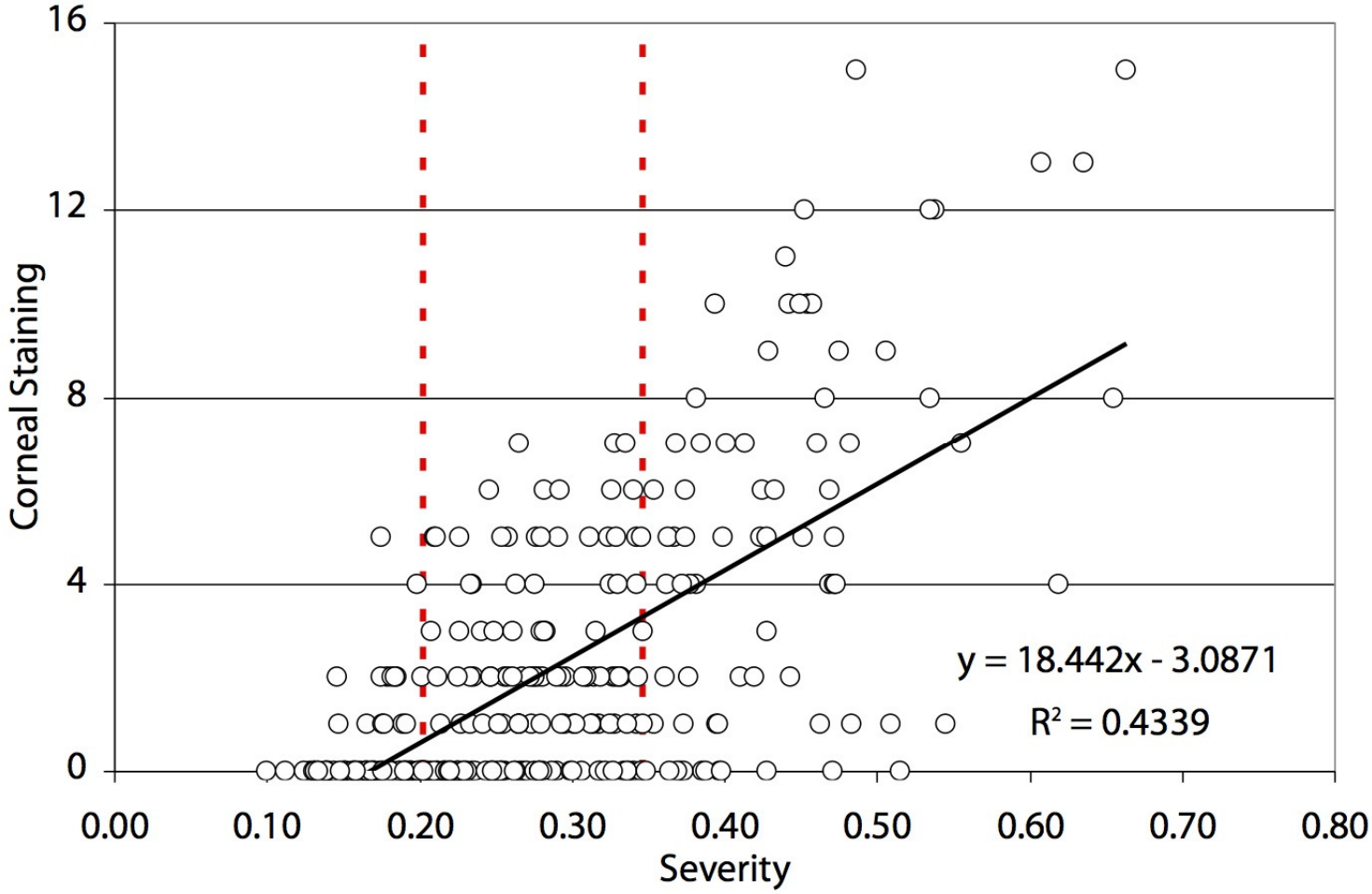
# Corneal Staining Severity Analysis

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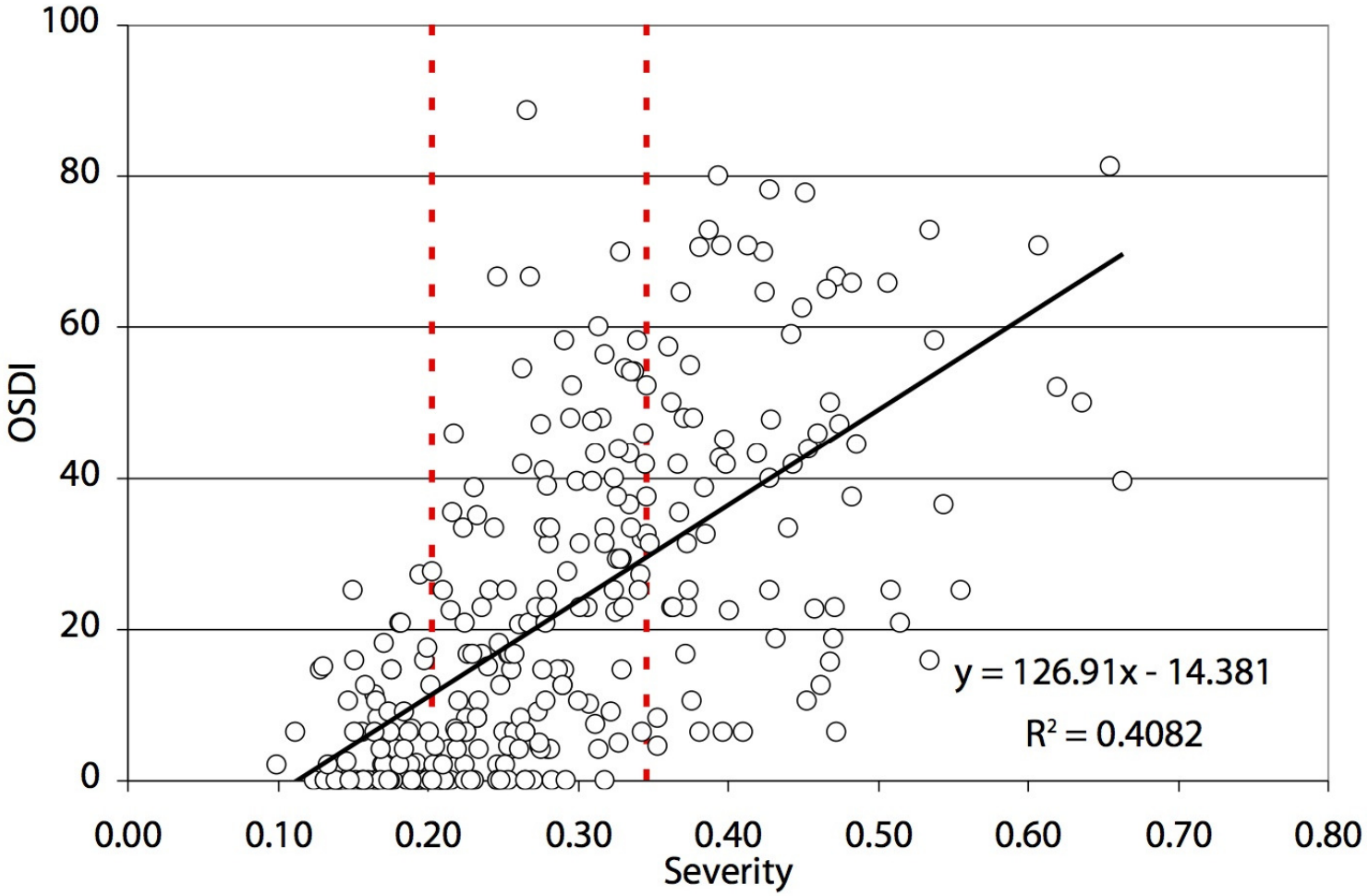
# Symptoms (OSDI) Severity Analysis

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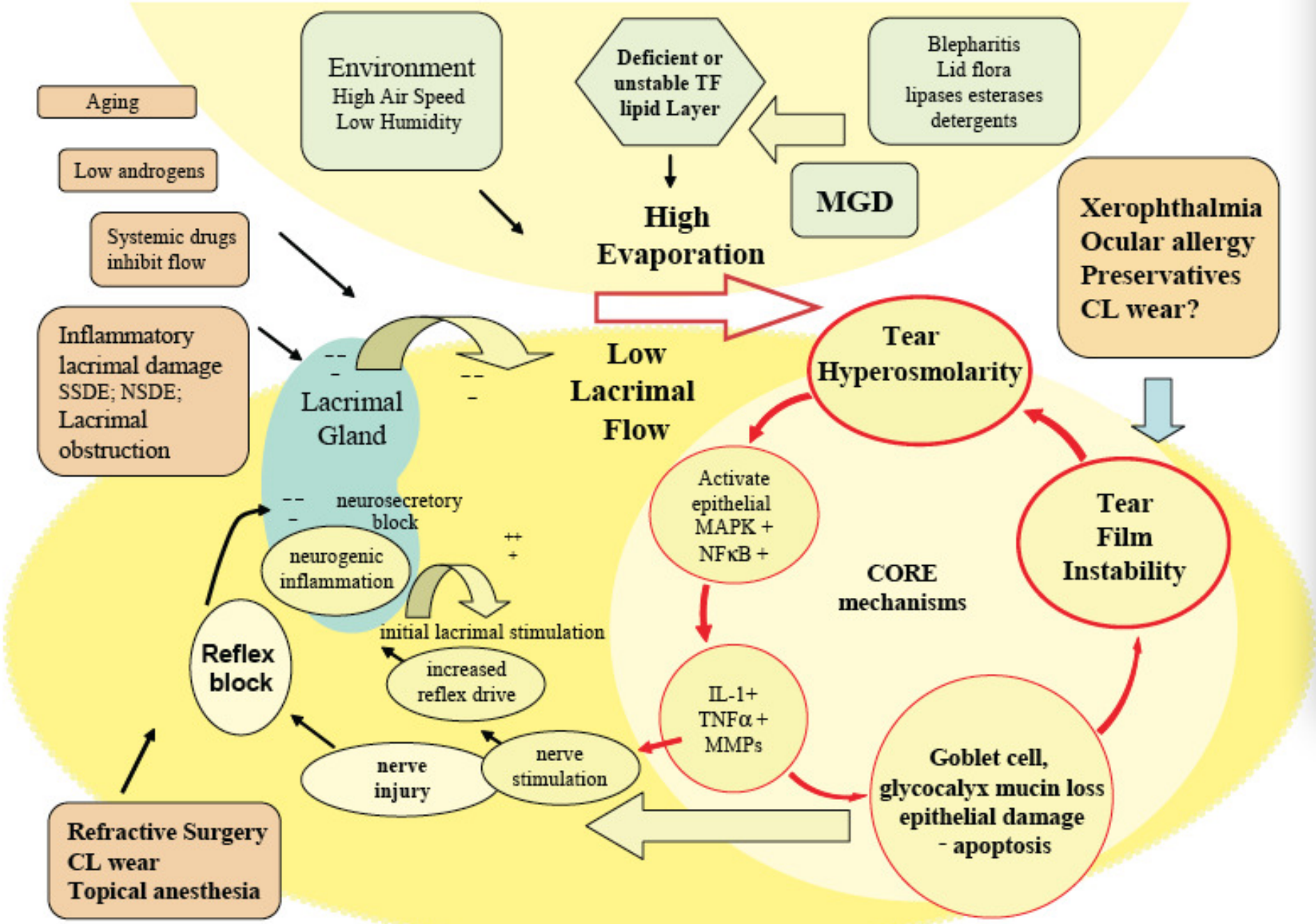


**Figure 2. Mechanisms of dry eye.**

# Hyperosmolarity is Bad

- Hyperosmolarity is recognized as the central pathogenetic mechanism of dry eye disease
- Hyperosmolarity is common across all forms of dry eye disease
- Hyperosmolarity causes epithelial cell death
- Hyperosmolarity causes inflammation
- Hyperosmolarity reduces the ability of mucins to lubricate
  - Loss of lubrication causes friction, which leads to wear
  - Wear roughens ocular surface
  - Rough ocular surface nucleates faster breakup times

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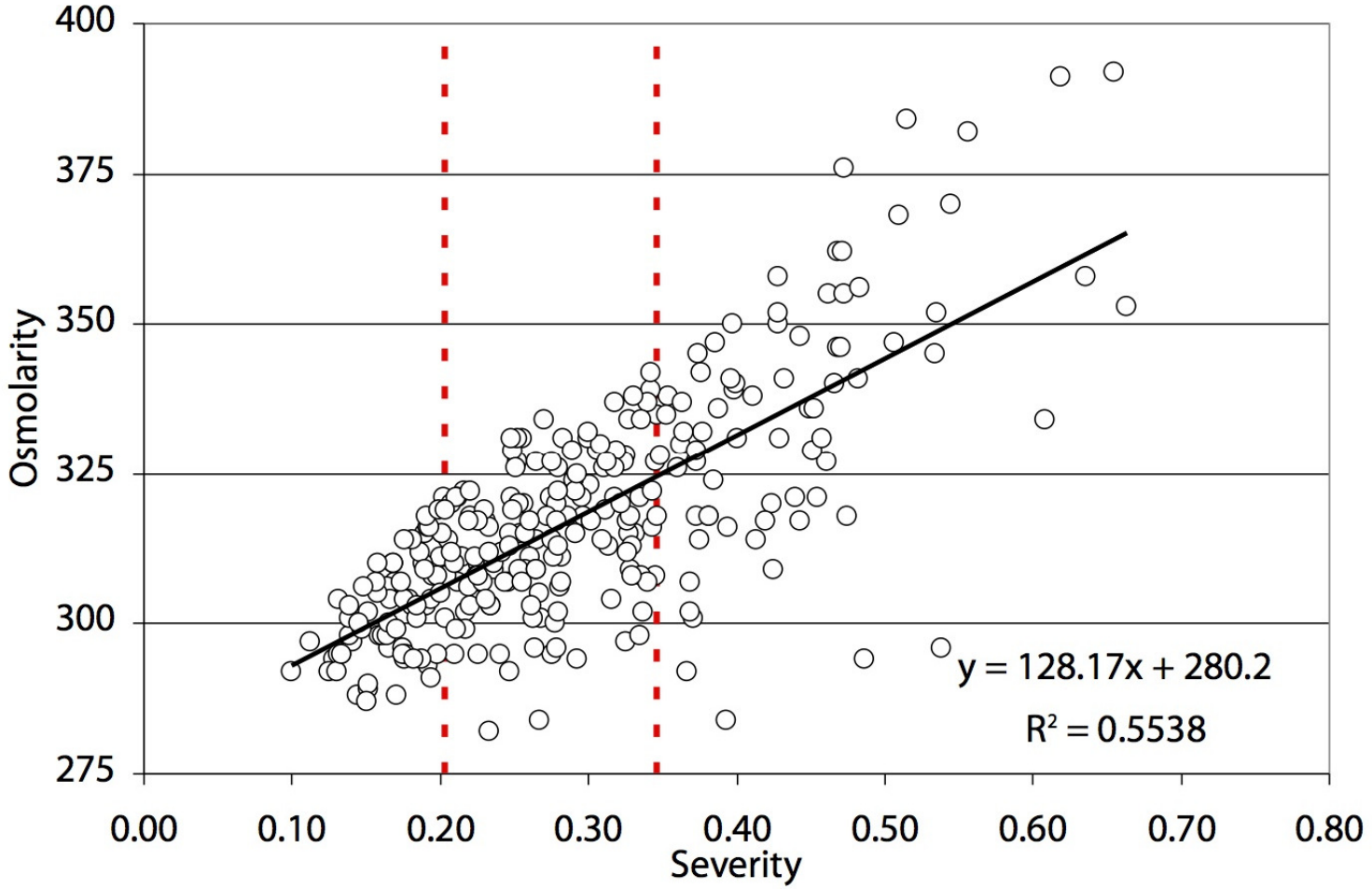
# Osmolarity Severity Analysis

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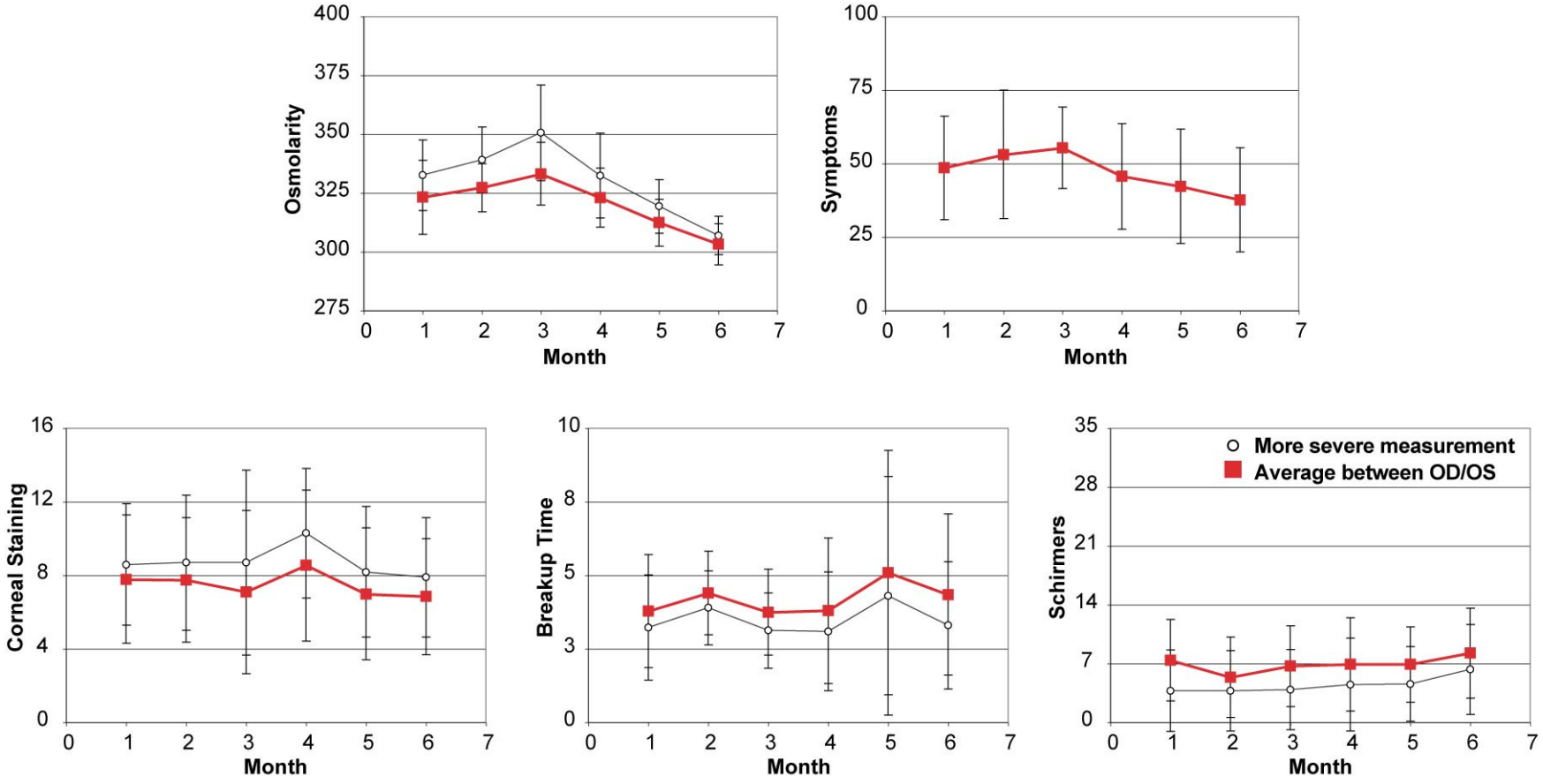
# Osmolarity is a Superior Marker of Therapeutic Efficacy

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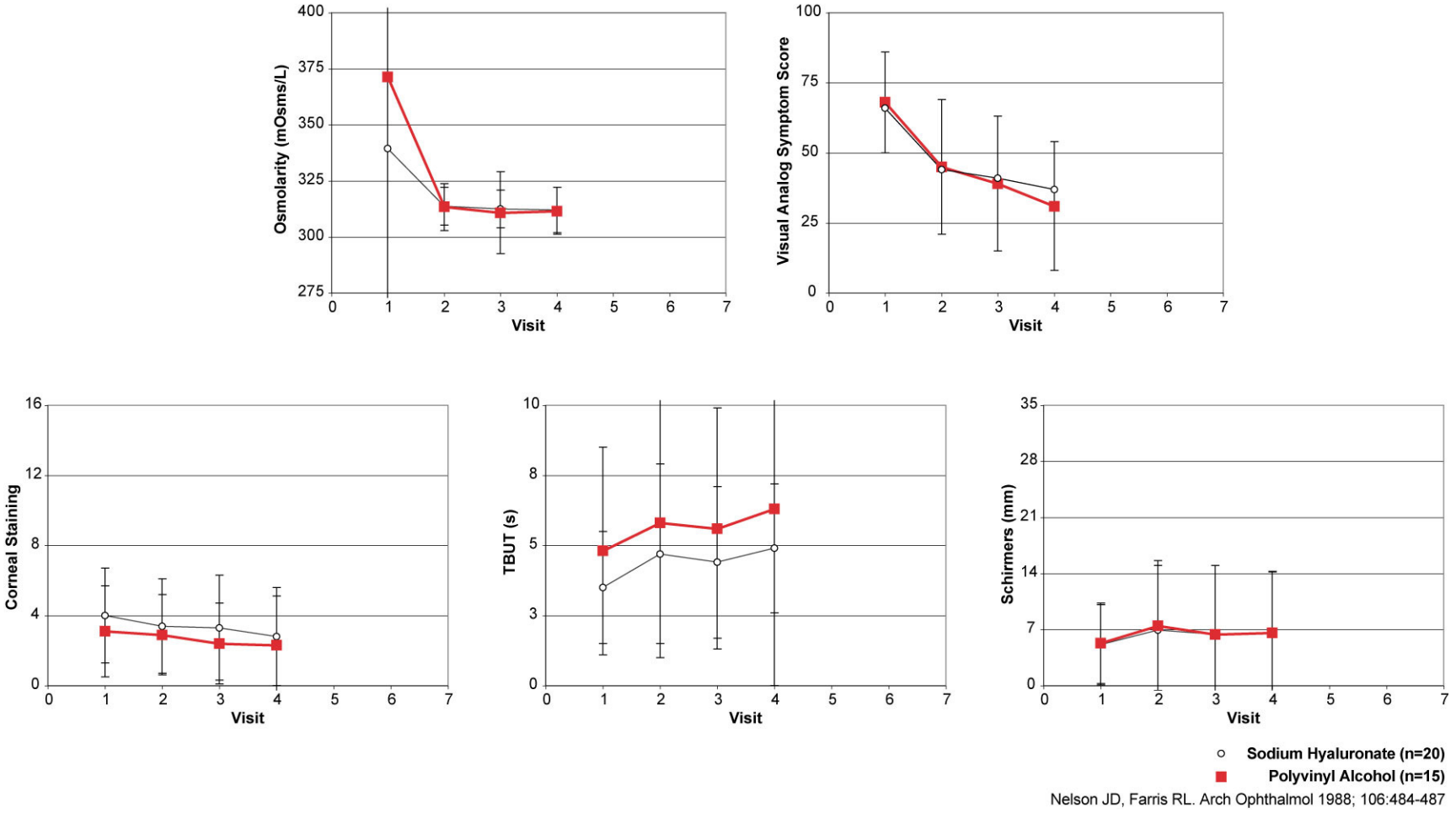
Data Courtesy Dr. Baris Sonmez, Ondokuz Mayis Universitesi

# Osmolarity is a Superior Marker of Therapeutic Efficacy




Nelson JD, Farris RL. Arch Ophthalmol 1988; 106:484-487

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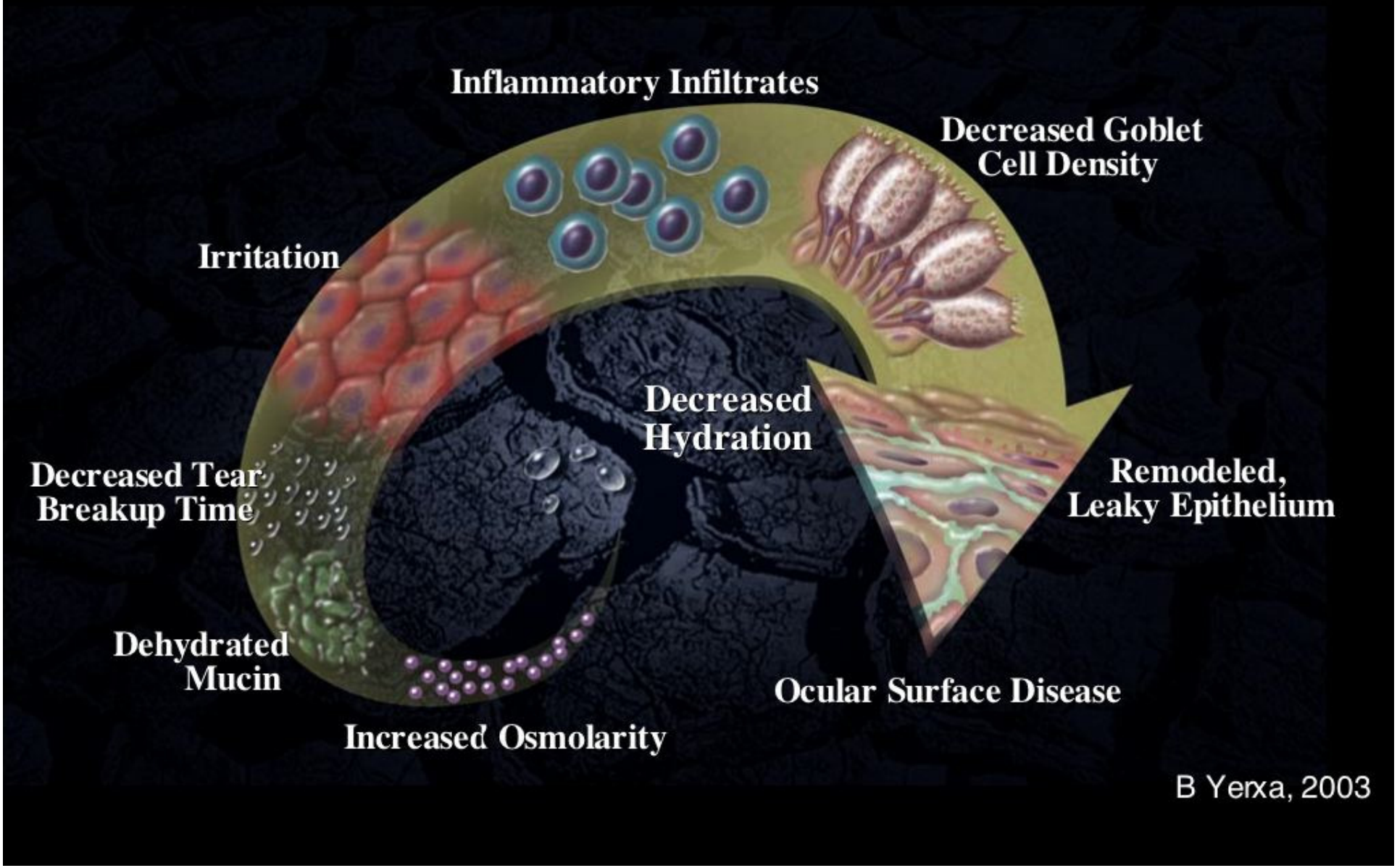
# We need new diagnostic approaches to help solve the puzzle of dry eye treatment

# *Ocular Surface Disease Spiral*



# Thank you for your attention