

Biogel Release of Growth Factor to the Ocular Surface

Group Members:

John Byce (Co-Leader), Alex Johnson (BSAC) , Sarah Reichert (Co-Leader),
Jeff Hlinka (BWIG), Anthony Sprangers (Communicator)

Advisor:

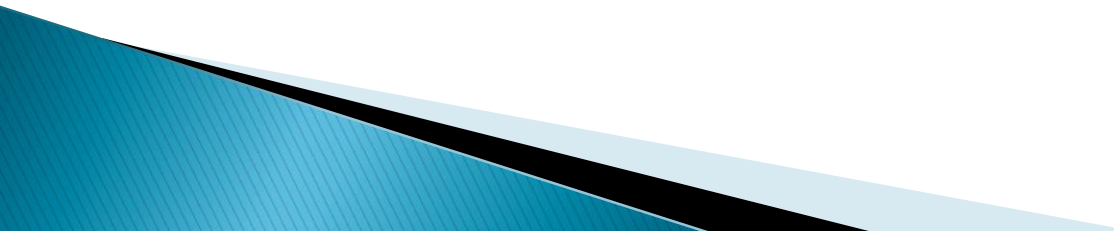
Professor Chris Brace

Client:

Dr. Neil Barney



Problem Motivation

- ▶ Dry Eye affects 10 million Americans
 - ▶ Chronic, incurable disease
 - ▶ Available treatments only for comfort
 - ▶ Growth factors for comfort and renewal
- 

What is a Biogel?

“A polymeric networks with 3D configuration capable of imbiding high amounts of water or biological fluids.”

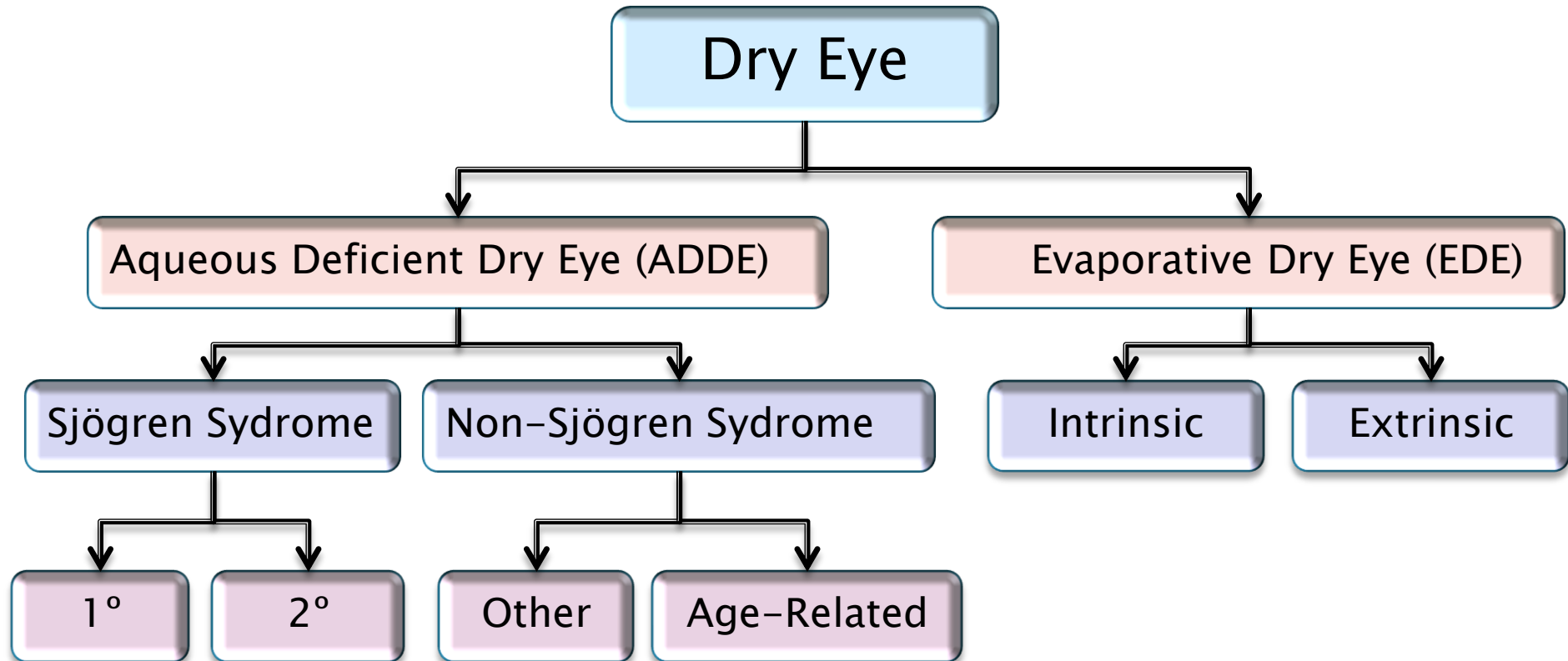
Hamidi, M., Azadi, A., & Rafiei, P. (2008). Hydrogel nanoparticles in drug delivery. *Advanced Drug Delivery Reviews*, 60(15), 1638-1649.

- ▶ Absorbs because of hydrophilic groups
- ▶ Structure resembles body tissue

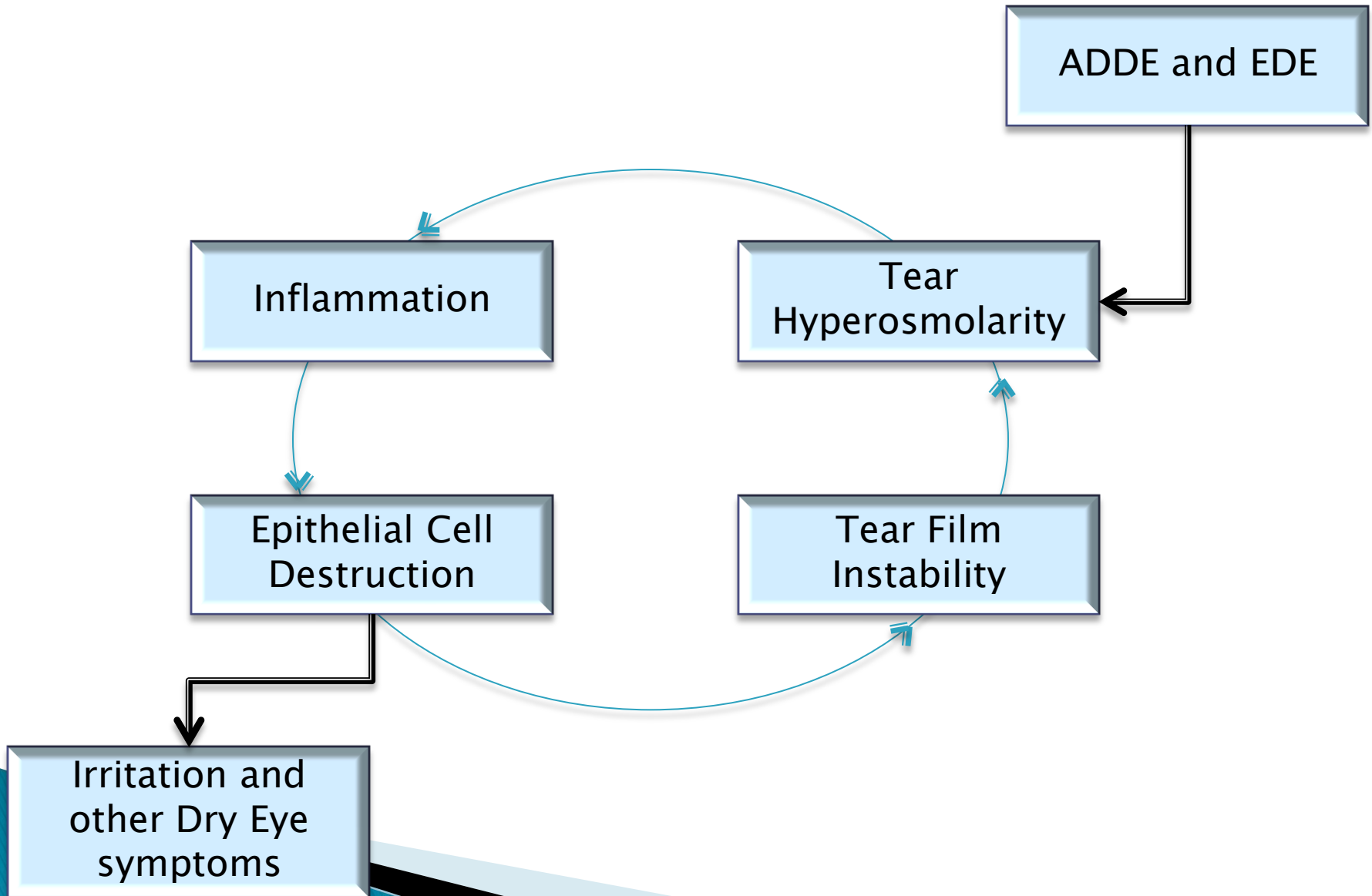


<http://www.pharmainfo.net/devisarvani/hydrogel-s-novel-drug-delivery-system>

Classification of Dry Eye

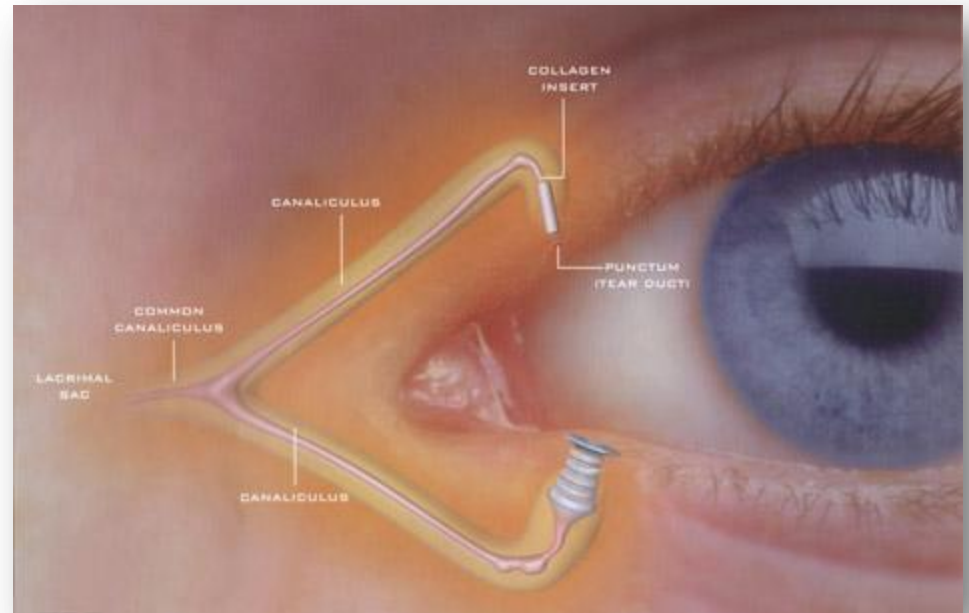


Causative Mechanism



Current Treatments

- ▶ Tear Supplementation
- ▶ Tear Secretagogues
- ▶ Tear Retention
 - Punctal Occlusion
 - Contact Lenses



Current Treatments

- ▶ Anti-inflammatory therapy
 - Cyclosporine
 - Corticosteroids
- ▶ Biological tear substitutes
 - Serum
 - Salivary Gland Autotransplantation



http://www.bausch.ca/en_CA/images/product_full_img/pharma/lotemax_lg_en.



<http://www.latisse.com/images/restasis.jpg>

Collagen Shield



www.oasismedical.com

▶ Pros

- Protein: Most abundant
- Natural: Non-antigenic
- Biodegradable, bioreabsorbable, biocompatible
- History

▶ Cons

- Variability of properties
- Hydrophilicity
- Ergonomics

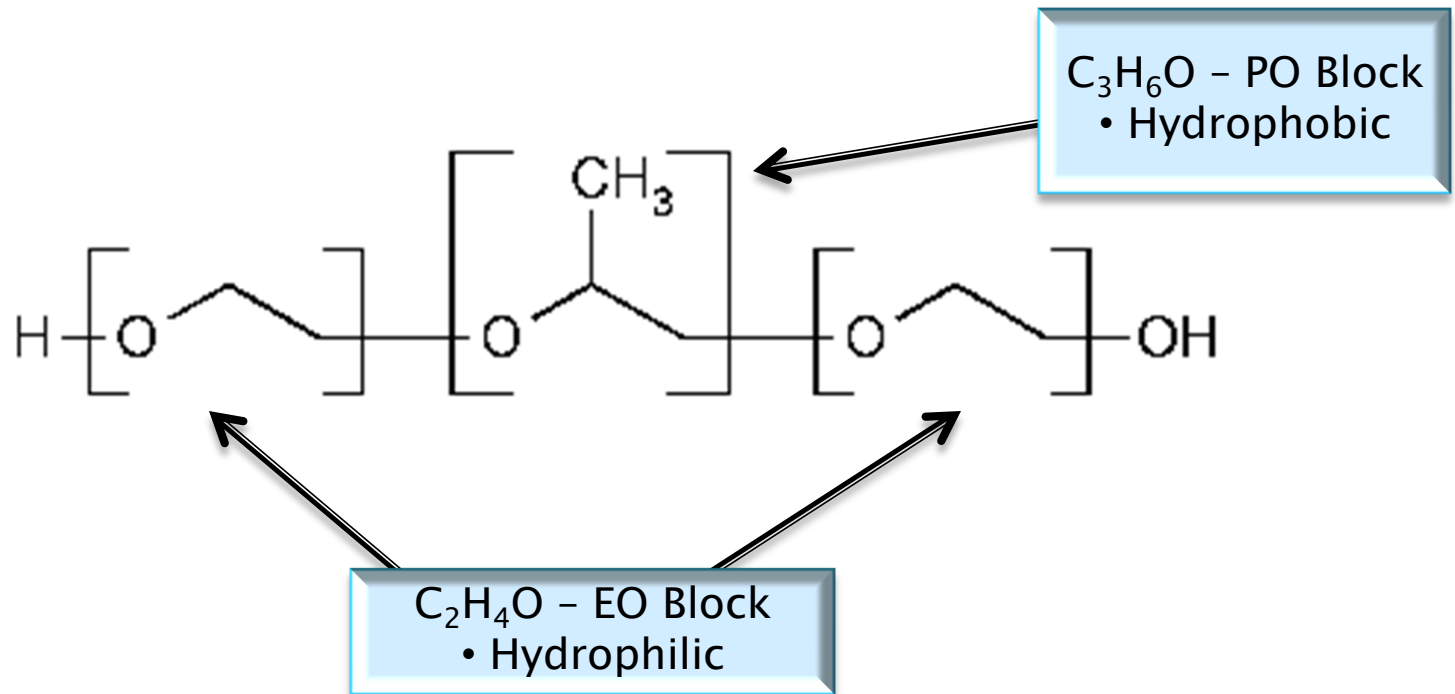
Collagen Shield

- ▶ Cross-Linking
 - Glutaraldehyde, chromium tanning
 - Entrapment
 - Increases durability, dissolving rate, drug release rate and drug contact time

- ▶ Degradation process
 - Breakdown cross-linked proteins
 - Surface layer replenished
 - Incorporation of EGF, possible other drugs

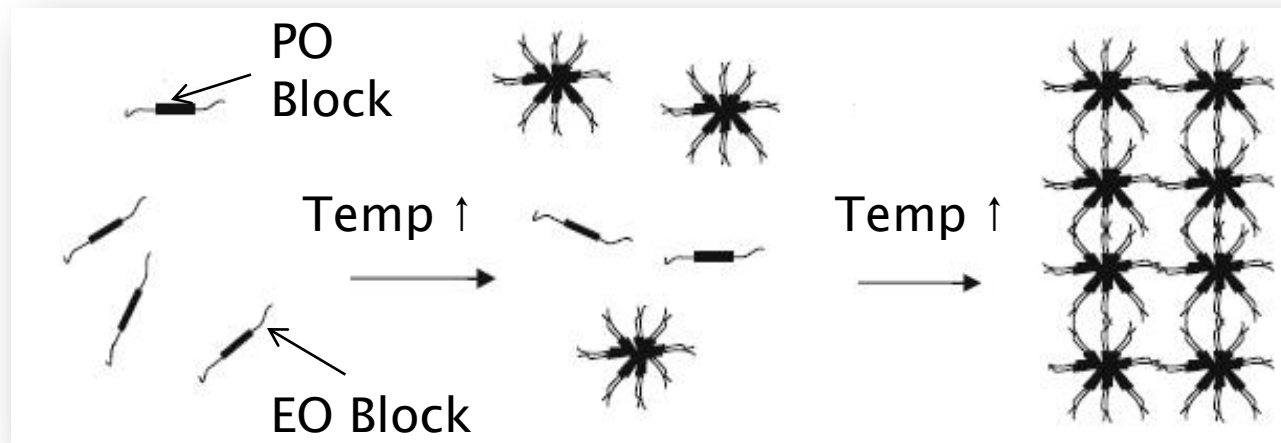
Ploxamer Hydrogel

Polyoxyethylene (EO) and Polyoxypropylene (PO) triblock copolymer.



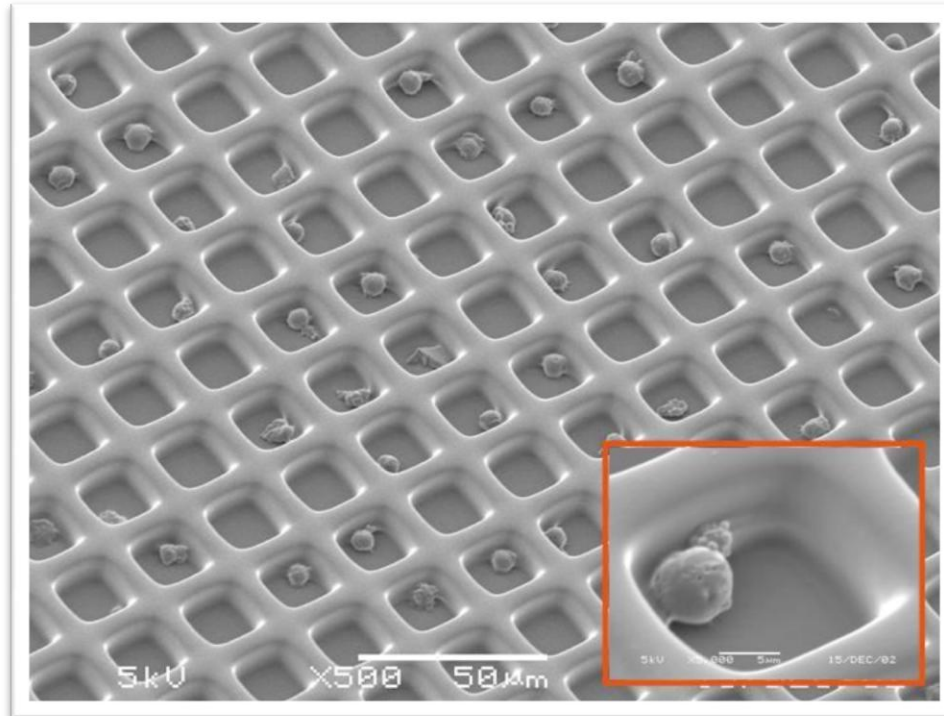
Plloxamer (407) Hydrogel

- ▶ Thermo-reversible property varies with concentration
- ▶ FDA considers inactive ingredient
- ▶ Gel dissolution \leq 12 hours



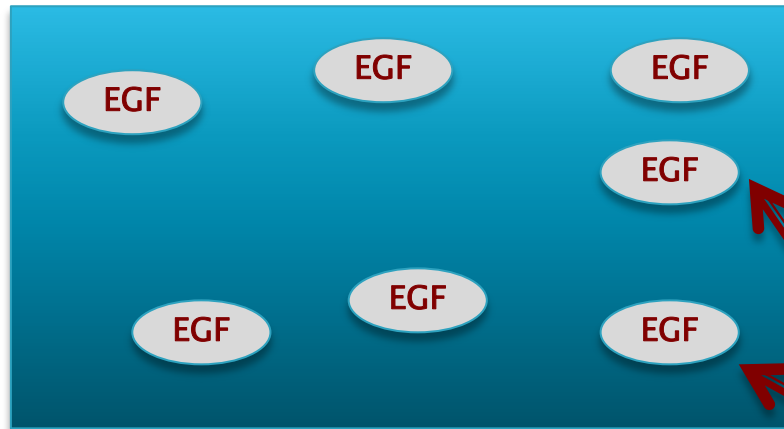
A review of Plloxamer 407 Pharmaceutical and Pharmacological Characteristics",
Pharmaceutical Research, Vol. 23, No. 12, December 2006.

Hydrogel Network



http://www.nibib.nih.gov/nibib/image/Research/P41Images/MToner_cellaray.jpg

POLY(ETHYLENE GLYCOL) GEL



**EPIDERMAL
GROWTH
FACTOR**



Design Matrix

	Poly(ethylene glycol) Gel	Poloxamer 407 Gel	Collagen Shield
Biocompatibility (25pts)	20	20	25
Degradation Control (25 pts)	25	15	20
Cost of Materials (5 pts)	5	5	2
Ergonomics (15 pts)	10	15	10
Drug Release Control (30 pts)	25	10	20
Total	85	70	77

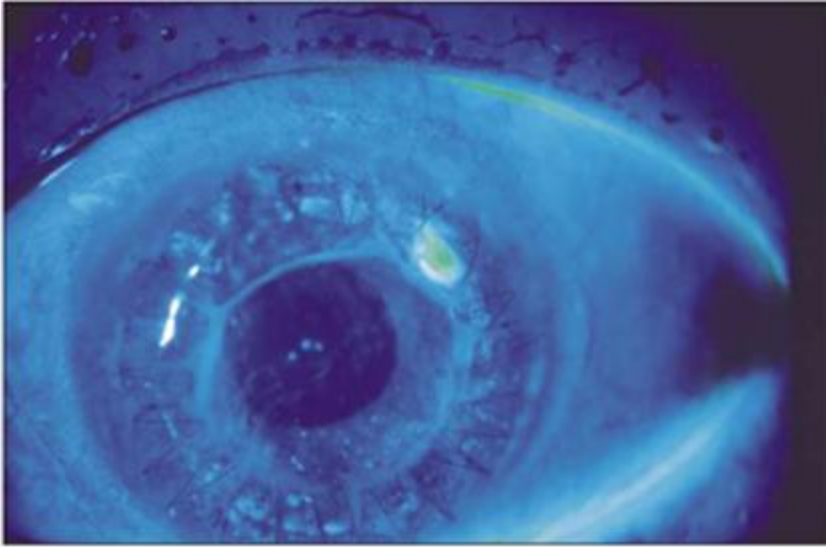
Growth Factors

Epidermal Growth Factor

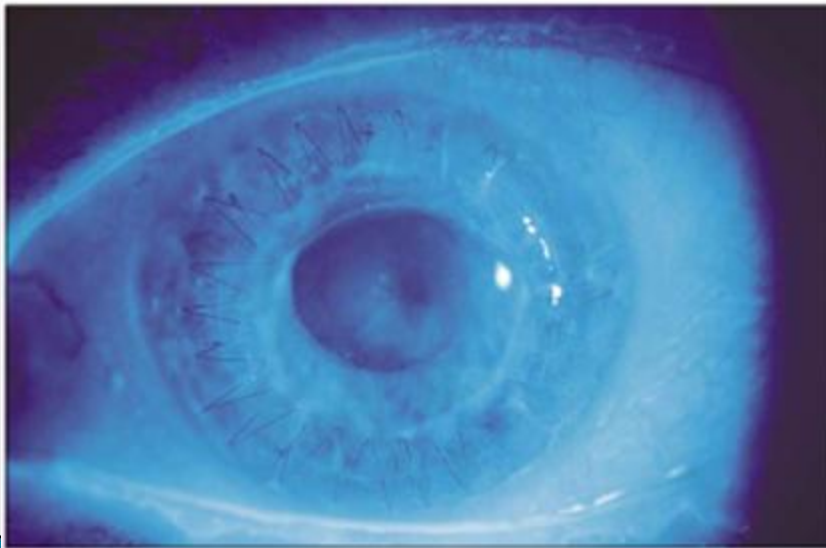
- Molecular weight of 6000 Da
- Differentiation and proliferation of epithelial cells
- Chain contains 53 amino acids

Additional Growth Factors

- Insulin-Like Growth Factor-1 (IGF-1)
 - Substance P
- 



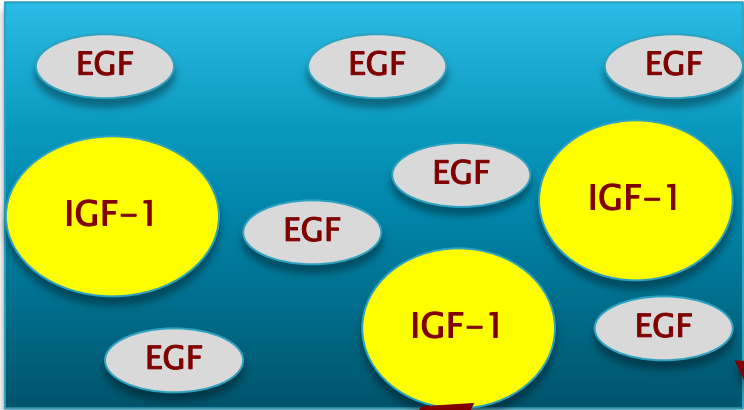
Corneal wound in
presenting patient



Healed corneal wound
after weeks treatment
of IGF-1 and Sub P

Barney, N. P., MD. (2002). Substance P, insulinlike growth factor 1, and surface healing. *Clinicopathologic Reports, Case Reports, and Small Case Series*, 120(FEB 2002), 215-216.

POLY(ETHYLENE GLYCOL) GEL



**INSULIN-LIKE
GROWTH
FACTOR-1**



**EPIDERMAL
GROWTH
FACTOR**



Projected Costs

Item	Cost
Epidermal Growth Factor	\$180 for 1 mg
Insulin-Like Growth Factor-1	\$150 for 1 mg
Substance P	\$75 for 1 mg
Total	\$180 (\$405)

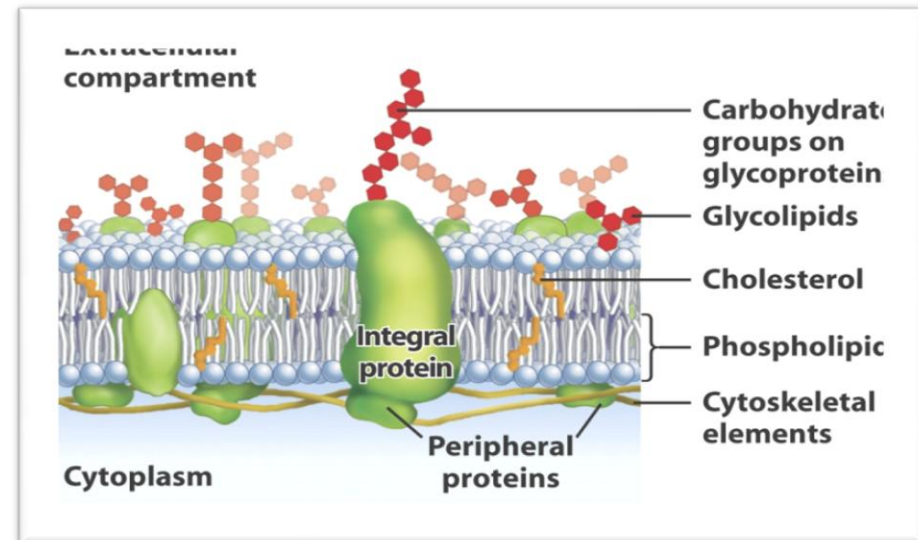
Future Work

▶ Testing

- Gel degradation
 - Wet mass (initial)
 - Dry mass – freeze drying
- Drug release
 - Release of Methyl Blue tested by spectrometer
 - Growth factor in human corneal epithelial cell cultures

▶ Gel additives

- Cell adhesion ligand
- Drug delivery vehicle
 - Alginate microspheres



References

- ▶ Pharmacopeia Online, "Poloxamer", [Online] available at http://www.uspbpep.com/usp28/v28230/usp28nf23s0_m66210.htm, [Accessed 25 Feb 2010]
- ▶ G. Dumortier, J. Grossiord, F. Agnely, and J. Chaumeil, "A review of Poloxamer 407 Pharmaceutical and Pharmacological Characteristics", *Pharmaceutical Research*, Vol. 23, No. 12, December 2006.
- ▶ E. Kim, Z. Gao, J. Park, H. Li, and K. Han, "rhEGF/HP- β -CD complex in poloxamer gel ophthalmic delivery", *International Journal of Pharmaceutics*, Vol. 233, Issues 1–2, 21 February 2002, pp 159–167.
- ▶ G. Niu et al., "Synthesis and characterization of reactive Poloxamer 407s for biomedical applications", *Journal of Controlled Release*, Vol. 138, 2009, pp 49–56.
- ▶ Cosmetic Ingredient Review Expert Panel, "Safety Assessment of Poloxamers 101, 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403, 407, Poloxamer 105 Benzoate, and Poloxamer 183 Dibenzoate as used in Cosmetics", *International Journal of Toxicology*, 2008, Vol. 27, pp 93–128.
- ▶ L. Stratton, A. Dong, M. Manning, and J. Carpenter, "Drug Delivery Matrix Containing Native Protein Precipitates Suspended in a Poloxamer Gel", *Journal of Pharmaceutical Sciences*, Vol. 86, No. 9 September 1997, pp 1006–1110.
- ▶ E. Fattal, G. De Rosa, and A. Bochot, "Gel and solid matrix systems for controlled delivery of drug carrier-associated nucleic acids", *international Journal of Pharmaceutics*, Vol. 277, 2004, pp 25–30.
- ▶ *Biotechnology*. (2009). Retrieved 03/01, 2010, from <http://www.nibib.nih.gov.ezproxy.library.wisc.edu/Research/ResourceCenters/ListState>
- ▶ Hudalla, G. A., Eng, T. S., & Murphy, W. L. (2008). An approach to modulate degradation and mesenchymal stem cell behavior in poly(ethylene glycol) networks. *Biomacromolecules*,9(3), 842–849.
- ▶ Hamidi, M., Azadi, A., & Rafiei, P. (2008). Hydrogel nanoparticles in drug delivery. *Advanced Drug Delivery Reviews*, 60(15), 1638–1649.
- ▶ Djalilian, A., Hamrah, P., & Pflugfelder, S. (2005). Disorders of tear production and the lacrimal unit. In J. Krachmer, M. Mannis & J. Hollan (Eds.), *Cornea: Fundamentals, diagnosis and management* (Second ed., pp. 521) Elsevier Mosby.
- ▶ Lemp, M. L., MD, & Foulks, G. N., MD. (2008). The definition & classification of dry eye disease. Guidelines from the 2007 International Dry Eye Workshop, (April 2008), 1–6.
- ▶ Sjögren's syndrome foundation. Retrieved 2/27, 2010, from <http://www.sjogrens.org/>
- ▶ Barney, N. P., MD. (2002). Substance P, insulin-like growth factor 1, and surface healing. *Clinicopathologic Reports, Case Reports, and Small Case Series*, 120(FEB 2002), 215–216.
- ▶ Epidermal growth factor (EGF). Retrieved 2/12, 2010, from <http://www.curehunter.com/public/keywordSummaryD004815.do>
- ▶ IGF-1 (mouse, rat) ELISA. Retrieved 2/15, 2010, from <http://www.alpco.com/single.asp?CatNumber=22-IG1MS-E01>