Dry Eye: A Heterogenous Multifactorial Disease

Multiple causes → surface damage → chronic inflammation

Chronic Dry Eye Disease

- Epithelial cell damage
- Tear film disruption (goblet cells, Meibomian glands)
- Inflammation
  - Cytokines
  - Cellular response

Targeting multiple aspects of dry eye → improved outcomes:

- Epithelial cell damage
- Tear film disruption (goblet cells, Meibomian glands)
- Inflammation
  - Cytokines
  - Cellular response
Multiple Benefits of Adiponectin in Dry Eye Model

Therapeutic Effect of Topical Adiponectin in a Mouse Model of Desiccating Stress–Induced Dry Eye (Yoon, IOVS. 2013)

Key findings:

- ↓ Corneal damage (staining)
- ↓ Inflammatory cytokine levels
- ↓ T cell infiltrate (CD4+T cells)
- ↑ Goblet cell density (mucin)
- ↑ Tear integrity (breakup time)
- ↑ Tear volume

<table>
<thead>
<tr>
<th>IL-1β, TNF-α, and INF-γ (Conjunctiva)</th>
<th>pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT (normal)</td>
<td>1.08</td>
</tr>
<tr>
<td>EDE (untreated dry eye)</td>
<td>6.82</td>
</tr>
<tr>
<td>0.0001% adiponectin</td>
<td>6.81</td>
</tr>
<tr>
<td>0.001% adiponectin</td>
<td>1.30</td>
</tr>
<tr>
<td>0.01% adiponectin</td>
<td>1.22</td>
</tr>
</tbody>
</table>

* P < 0.05 vs BSS
† P < 0.05 vs EDE.
Adiponectin: A Unique “Protective” Hormone

**ADIPONECTIN**

- Major hormone produced by adipose and muscle
- Counteracts adverse effects of obesity
- Beneficial actions on multiple organs:
  - Reverses insulin resistance (AMPK)
  - Inhibit inflammation (cellular, cytokine) (NF-κb, TNF-α)
  - Epithelial cell regeneration following injury (Akt)

Similar benefits in the eye

Scherer J Mol Cell Bio 2016
ALY688: An Optimized Adiponectin Analogue

Adiponectin protein is a poor drug candidate

1.) Identification of Binding Domain

Adiponectin sequence (266 aa)

2.) Optimization

ALY688: peptide agonist

- Binds receptors (AdipoR1/R2)
- Stable in biological fluids
- Topical eye drop formulation (BID)

Scherer, Diabetes (2006)

Otvos, BMC Bio (2011)
ALY688 (vs Adipo) in Dry Eye

**ALY688 as effective as adipo protein:**
- Decreased corneal damage
- Increased tear volume
- Increase break up time

**ALY688 more effective than cyclosporin**

- **Corneal Staining (grade)**
- **Corneal Defects**
- **Staining Score (fluorescein)**

* P < 0.05 vs Dry Eye and Veh
**Similar Efficacy in Rabbit Dry Eye Model (Atropine)**

**ALY688** significantly better than **vehicle** in improving corneal staining, tear integrity, and tear volume.

- **Corneal Staining**
  - ALY688: 7
  - Vehicle: 6
  - Atropine: 5
  - Treatment

- **Tear Break-up Time**
  - ALY688: 6
  - Vehicle: 5
  - Atropine: 4
  - Treatment

- **Tear Volume**
  - ALY688: 8
  - Vehicle: 7
  - Atropine: 6
  - Treatment

(Crawford, 2019, ARVO)
ALY688 (and Adipo) Accelerates Corneal Healing Following Injury

Decrease in Area of Corneal Epithelial Defect following Alkali Burn

Rapid improvement in corneal defect size one day following injury

(Yoon, et.al. ARVO, 2018)
ALY688 Improves Multiple Aspects of Dry Eye Disease

**Inciting Factors:**
- Decrease tear production
- Increased tear evaporation
- Loss of tear integrity

**Inflammatory Cascade:**
- Cytokines
- WBCs

**Corneal surface damage**
- Promotes corneal healing
- Reduces inflammation

**Loss of tear integrity**
- Improves tear integrity and tear volume
Allysta Management and Advisors

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Summary

**ALY688—first potent and specific analogue of adiponectin**

Unique mechanism of action targets multiple critical aspects of dry eye:
- Reduce ocular surface inflammation (cellular and cytokine)
- Enhance corneal epithelial regeneration
- Improve tear integrity (goblet cells)

- IND and clinical studies: 4th qtr. 2019
- Series A lead: Morningside Ventures