Inhibition of corneal fibrosis with a miR-29 mimic

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Oligonucleotide Therapeutics Society 14th Annual Meeting
October 1, 2018
microRNA Therapeutics Regulate Systems Biology to Modify Disease

- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes
- microRNAs regulate complex biological systems
- microRNA-targeted therapies are intrinsically focused on disease-relevant pathways
- microRNA therapeutics particularly suited for complex, multigenic disorders
miR-29 Pathways and Systems Control

![Diagram](image)

**miR-29**
- **TGF-β + Diseased ECM**
- **Inflammation**

**Growth factors**
in vivo Validated Targets
- TGF-β2, TGF-β3, EGF, IGF2, IGFBP5, PDGFA, PDGFC

**Collagen transcription/translation**
- COL1A1, 1A2, 3A1, 5A1, 5A2, 5A3, 6A4, 6A5, 6A6, 8A1, 8A2, 9A1, 11A1, 12A1, 14A1, 22A1, 28A1

**Post-translational modification & triple helix formation**
- HSP47, P4HA2, P4HA3, PLOD2

**N- and C-terminal cleavage & secretion**
- PCOLCE2

**Fibril cross-linking**
- LOXL2

**Mature collagen fibrils**
miR-29 Pathways and Systems Control

Remlarsen (MRG-201) (promiR-29)

- Growth factors
  - in vivo Validated Targets
    - TGF-β2, TGF-β3, EGF, IGF2, IGFBP5, PDGFA, PDGFC
  - COL1A1, 1A2, 3A1, 5A1, 5A2, 5A3, 6A4, 6A5, 6A6, 8A1, 8A2, 9A1, 11A1, 12A1, 14A1, 22A1, 28A1

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Fibrotic Diseases in Which Reduced miR-29 Has Been Implicated

- Keloid scar. → Phase 2 clinical trial ongoing: NCT03601052
- Hypertrophic scar. → Phase 1 clinical trial complete: NCT02603224
- Scleroderma.
- Cardiac fibrosis.
- Pulmonary fibrosis – IPF, CTD-associated.
- Liver fibrosis – cirrhosis, NASH, viral.
- Kidney fibrosis – diabetic nephropathy, IgA.
- Retinal fibrosis.
- Glaucoma. Trabeculectomy bleb failure. → Multiple opportunities in ophthalmology
- Fuch’s Endothelial Corneal Dystrophy.
The Eye is a Preferred Target Organ for microRNA Therapeutics

- **Delivery** to multiple compartments of the eye, and via multiple routes of administration including injection and topical drops

- **Stability** due to reduced nuclease concentration enables long duration of action and infrequent dosing

- **Reduced liability** for toxicities due to local administration with limited systemic exposure
Remlarsen Uptake in Alkali Burned Cornea

- Animal model: Rat alkali burn
- Distribution of Remlarsen (MRG-201) to all layers of the cornea, including corneal endothelium after drop administration
Uptake of remlarsen in alkali burned cornea is high, but diminishes after re-establishment of the corneal epithelium and/or tear film post-burn.

**miR-29b levels in rat cornea**

- **Saline:** + + + +
- **Remlarsen:** + + + +

<table>
<thead>
<tr>
<th>Time</th>
<th>Saline</th>
<th>Remlarsen</th>
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<tbody>
<tr>
<td>24h</td>
<td>+</td>
<td>+</td>
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<tr>
<td>48h</td>
<td>+</td>
<td>+</td>
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<tr>
<td>4D</td>
<td>+</td>
<td>+</td>
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<tr>
<td>7D</td>
<td>+</td>
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**miR-29 Levels**

- **Control:**
- **Saline:**
- **Day 10:**
- **Day 14:**
- **Day 21:**
- **Day 28:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Saline</th>
<th>Day 10</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>$11x$</td>
<td>$14x$</td>
<td>$2.4x$</td>
<td>$5.7x$</td>
<td>$7.3x$</td>
<td>$2.1x$</td>
<td>$1.7x$</td>
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</table>
Remlarsen as an Anti-Fibrotic in the Cornea

- Damage is reduced in remlarsen treated alkali burned eyes
  - Epithelium re-established more quickly
  - Less damage to the stroma, decreased cellularity
  - Reduced inflammation
Remlarsen as an Anti-Fibrotic in the Cornea

- Wound healing is accelerated in remlarsen treated alkali burned eyes
  - Epithelium re-established more quickly
  - Reduced stromal thickness results
Remlarsen as an Anti-Fibrotic in the Cornea

- Scarring is reduced in remlarsen treated alkali burned eyes

![Graph showing hazing/scarring proportion of samples over time with remlarsen treatments](image-url)

Day 14

- Unburned cornea, No treatment
- Saline treated burned cornea
- Remlarsen treated burned cornea
Remlarsen as an Anti-Fibrotic in the Cornea

- $\alpha$-SMA staining is reduced by remlarsen treatment

$\alpha$-smooth muscle actin

Least staining in cohort

Most staining in cohort

Day 14

Day 28
mRNA Expression (Fold Change)

**Day 7**

- Saline
- Remlarsen  

**Day 10**

- Saline
- Remlarsen

**Day 14**

- Saline
- Remlarsen

**Study 1**

- p = 0.0350
- p = 0.0003

**Study 2**

- p < 0.0001

- COL1A1
- COL1A2
- COL5A2
- FN1
- TGFB2
- MMP2

miR-29b PD biomarkers are repressed following twice daily remlarsen drop treatments

- Consistent in multiple studies
- Multiple collagens and pro-fibrotic factors are affected
Conclusions

- miR-29b mimics are well taken up by a damaged/ulcerated cornea following drop administration
- Remlarsen uptake is sustained in the alkali burn model until the corneal epithelium and tear film are fully established post-burn
- Remlarsen treatment reduces the severity of alkali burn, accelerates repair vs. vehicle
- Remlarsen treatment reduces corneal hazing/scarring, decreases the corneal stromal thickness, and reduces $\alpha$-SMA staining post-burn
- Remlarsen engages its pharmacodynamic targets and reduces collagen/ECM expression in vivo
- Remlarsen represents a potential therapeutic for corneal scarring regardless of the etiology:
  - Infectious keratitis, surgery, trauma, genetic disease
  - Translatable to other compartments of the eye – trabecular meshwork, conjunctiva, retina, choroid