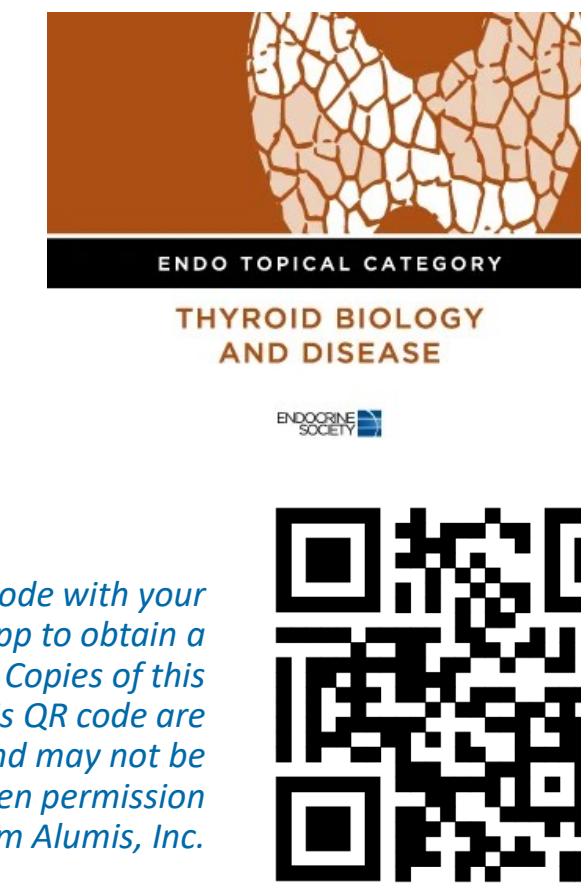


# Lonigutamab (Anti-IGF-1R Monoclonal Antibody) Reduces IGF-1–Mediated Hyaluronan Production in Thyroid Eye Disease Orbital Fibroblasts



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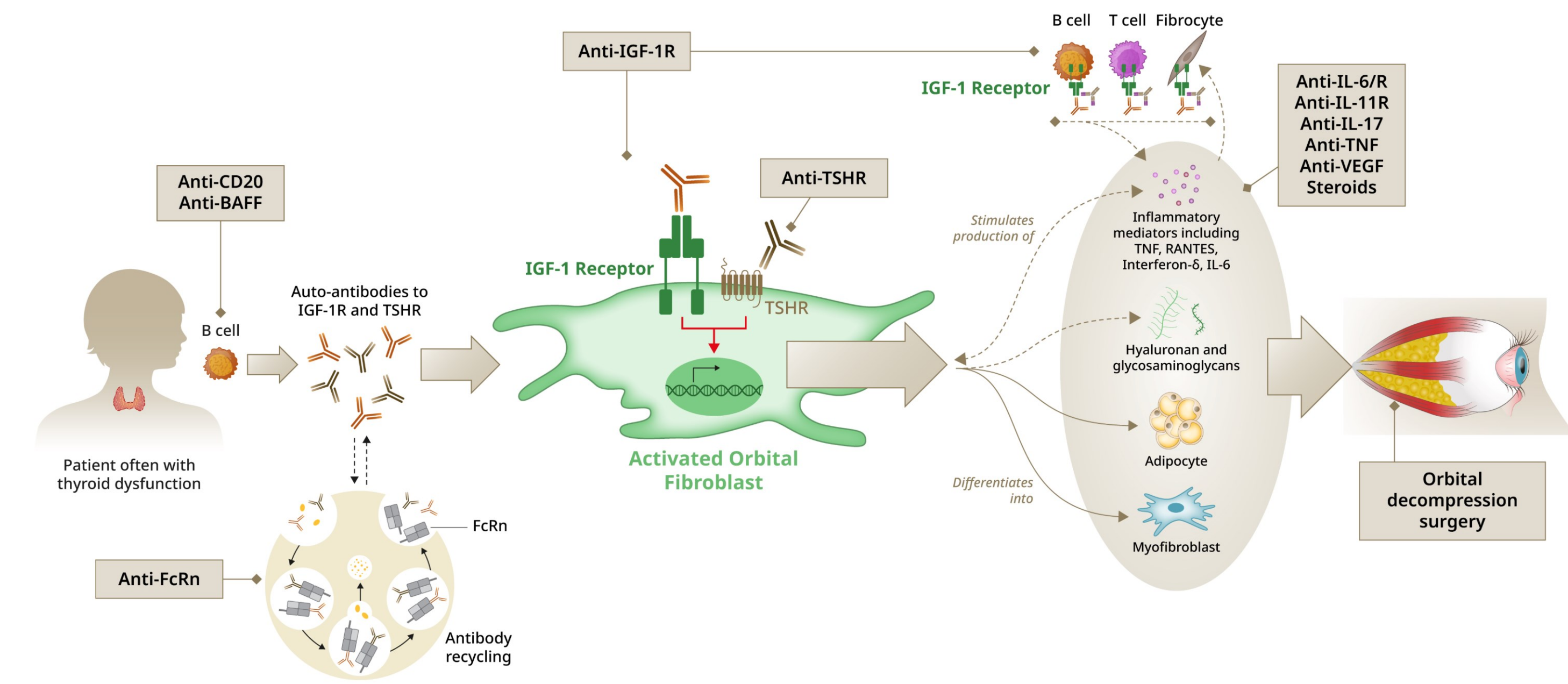
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Please refer to the Meeting App for conflict of interest disclosures.

ENDO 2025 Annual Meeting  
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## Background

- Thyroid eye disease (TED) is a chronic, debilitating, and vision-threatening condition characterized by aberrant stimulation of the insulin-like growth factor 1 receptor (IGF-1R) pathway<sup>1,2</sup>
- IGF-1R signaling promotes TED pathogenesis in part through activating orbital fibroblasts to produce excessive hyaluronan and other glycosaminoglycans, leading to interstitial edema and extraocular muscle expansion<sup>3-5</sup>
- IGF-1R is a clinically validated therapeutic target in TED<sup>1,6</sup>

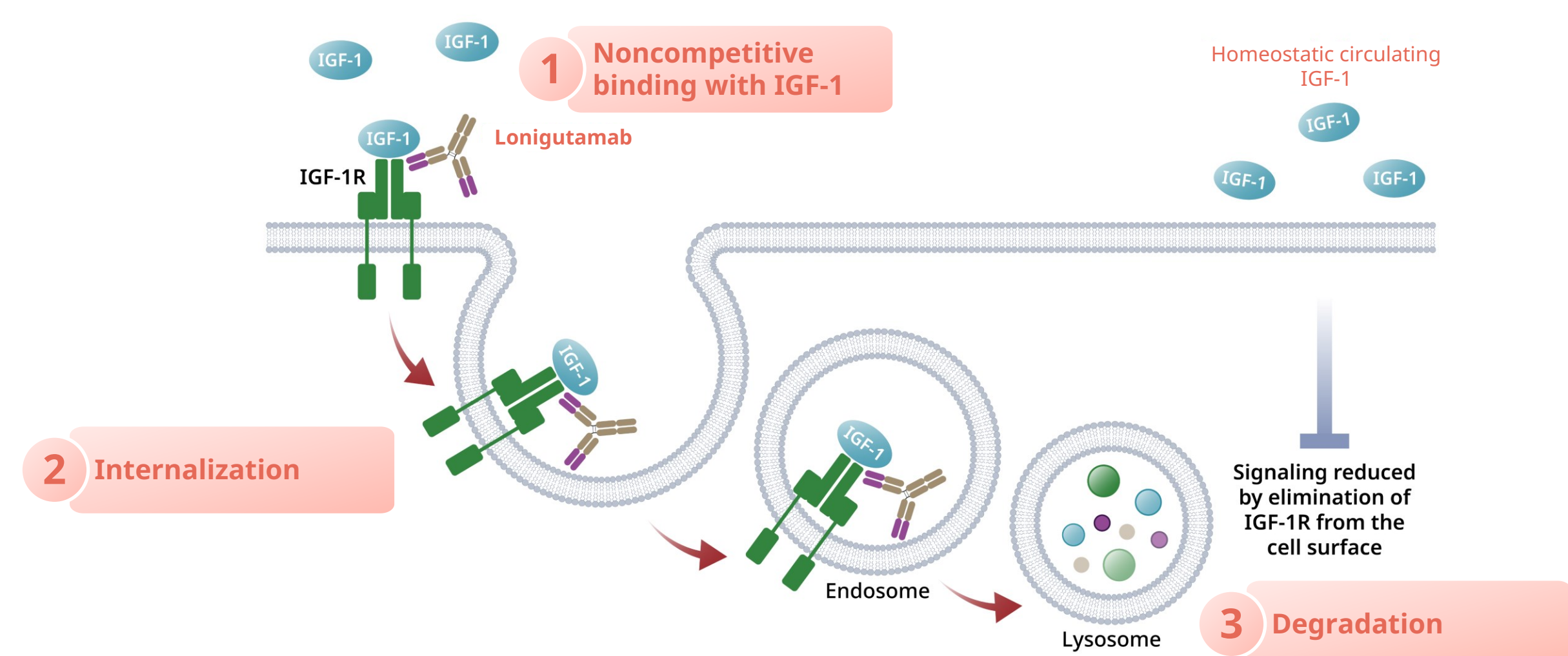
Figure 1. IGF-1R Is Central to TED Pathogenesis



ACELYRIN-commissioned figure. BAFF, B-cell activating factor; CD, cluster of differentiation; FcRn, neonatal fragment crystallizable receptor; IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; IL, interleukin; IL-6R, IL-6 receptor; IL-11R, IL-11 receptor; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; TED, thyroid eye disease; TNF, tumor necrosis factor; TSHR, thyroid-stimulating hormone receptor; VEGF, vascular endothelial growth factor.

- Lonigutamab is a novel, high-affinity, subcutaneously administered, anti-IGF-1R monoclonal antibody with a unique noncompetitive mechanism of action<sup>7,8</sup>
  - Lonigutamab has shown preliminary efficacy in a phase 1/2 study of patients with TED<sup>9</sup> and is continuing to be explored as a potential therapeutic for TED

Figure 2. Lonigutamab Mechanism of Action



**Lonigutamab Potential Therapeutic Benefits**

Convenient Subcutaneous Administration	Unique MoA	Potentially Improved Benefit/Risk Profile
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IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; MoA, mechanism of action.

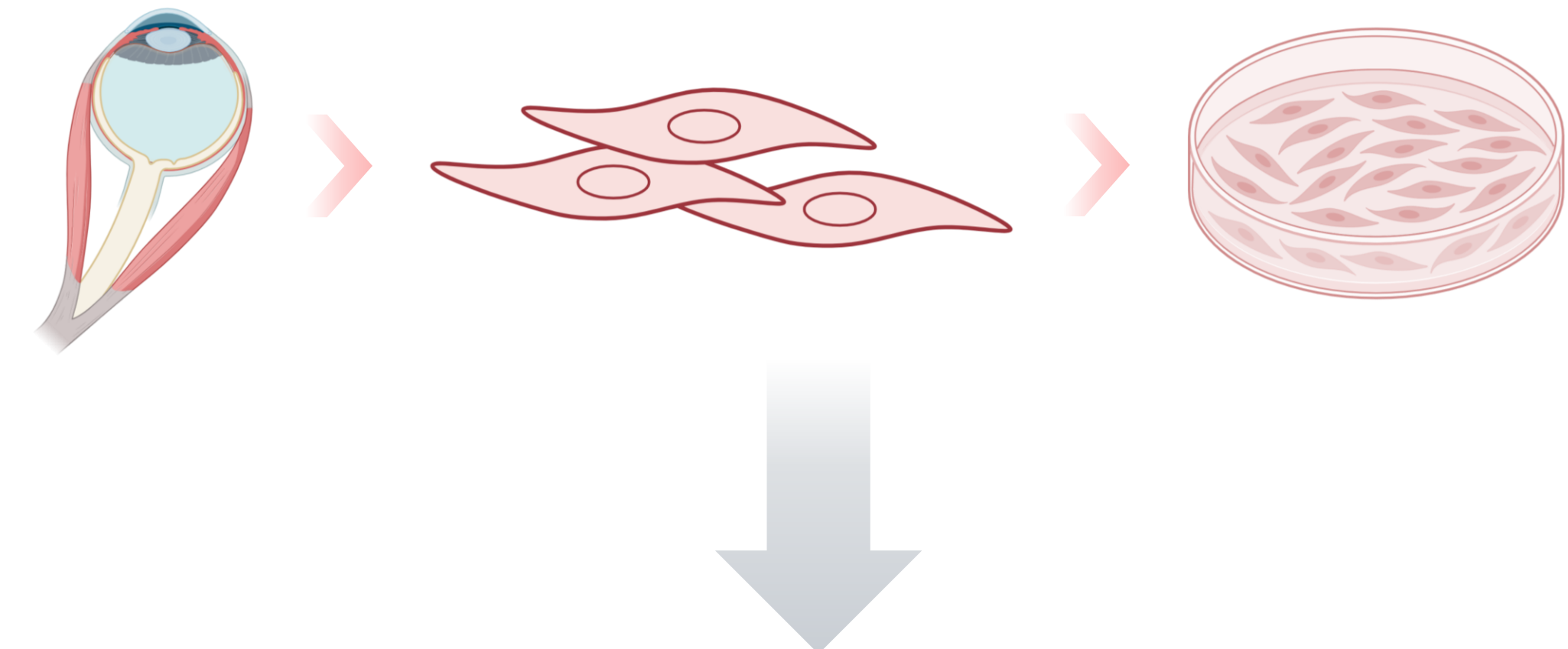
## Objective

This study characterizes the effect of lonigutamab-mediated inhibition of IGF-1R on hyaluronan production in TED orbital fibroblasts.

## Methods

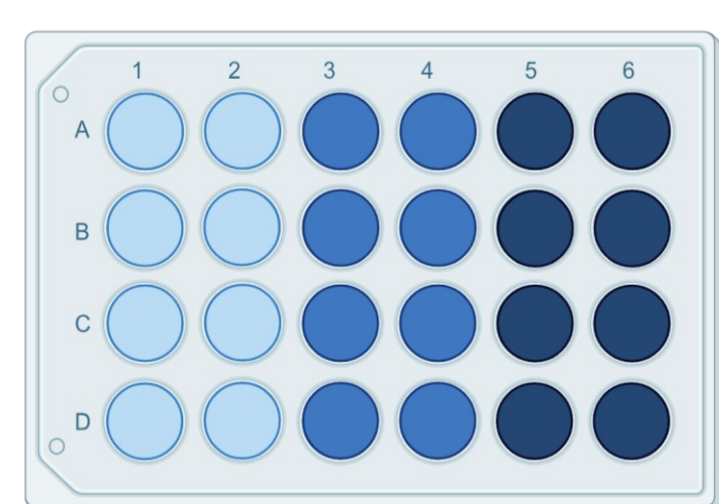
### Cell Culture

- Primary human orbital fibroblasts from patients with TED were harvested and cultured in Dulbecco's Modified Eagle's Medium supplemented with 10% fetal bovine serum and antibiotics



### Treatment

- Orbital fibroblasts (passages 4–10 post explant) were pretreated with vehicle (0.1% bovine serum albumin-phosphate-buffered saline) or lonigutamab for 1 hour
- Orbital fibroblasts were then incubated with vehicle or IGF-1 (10 or 25 ng/mL) for 48 to 72 hours



### Hyaluronan Assessments

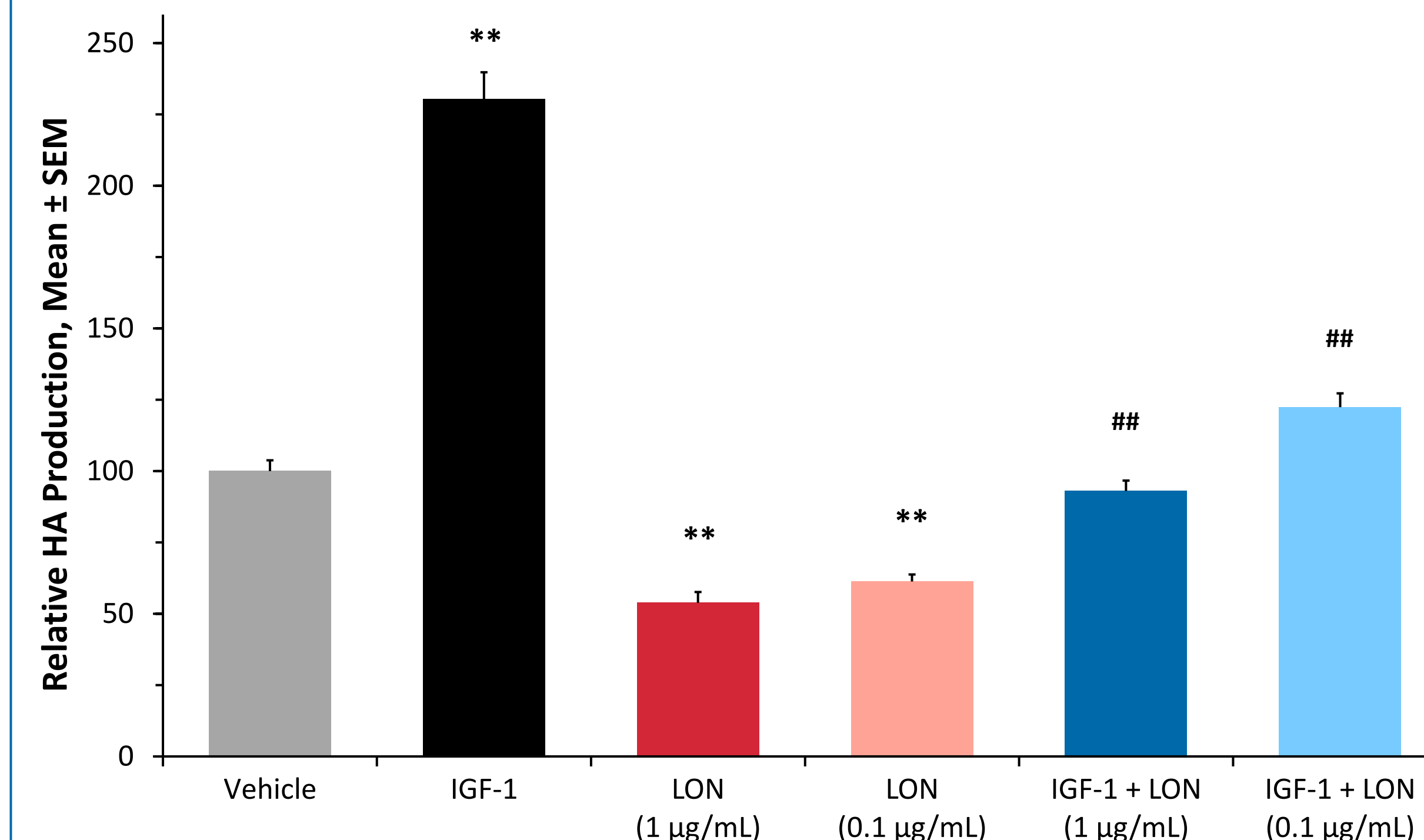
- Hyaluronan was quantified from cell supernatants by enzyme-linked immunosorbent assay (Echelon Biosciences, Inc. [Salt Lake City, UT])
- Hyaluronan molecular weight was examined by agarose gel electrophoresis following digestion with proteinase K



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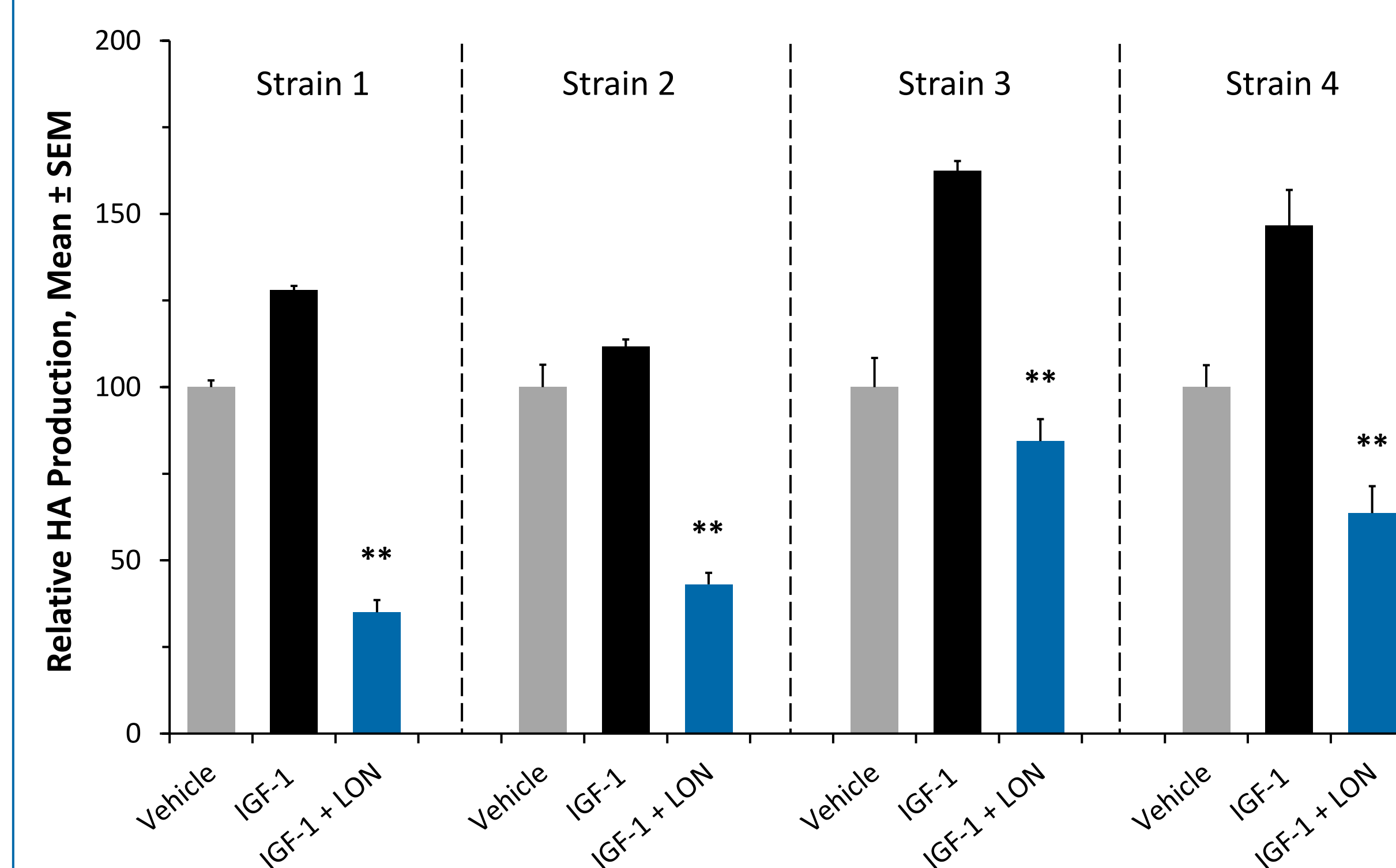
## Results

Figure 3. Lonigutamab Significantly Reduced Basal and IGF-1–Induced Hyaluronan Production in TED Orbital Fibroblasts



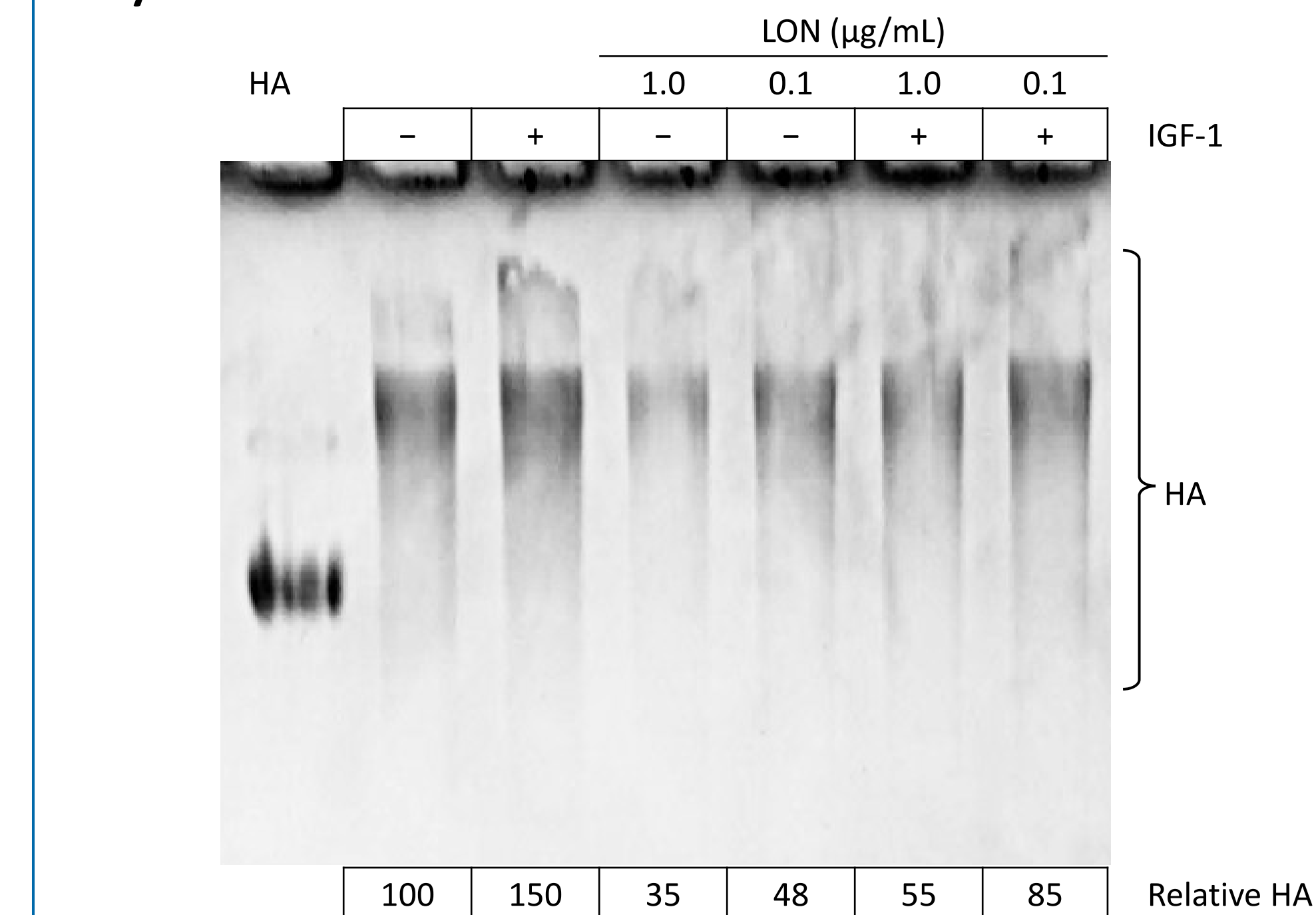
TED orbital fibroblasts were treated with either vehicle (0.1% BSA-PBS) or IGF-1 (25 ng/mL) for 72 hours. Some cells were pretreated with LON (0.1 or 1.0 µg/mL) for 1 hour before the addition of IGF-1. Cell culture supernatant was collected, and HA production was analyzed by ELISA. N = 3 samples per group. \*\*P<0.01 vs vehicle. ##P<0.01 vs IGF-1 alone, one-way ANOVA, Tukey post hoc test. ANOVA, analysis of variance; BSA, bovine serum albumin; ELISA, enzyme-linked immunosorbent assay; HA, hyaluronan; IGF-1, insulin-like growth factor 1; LON, lonigutamab; PBS, phosphate-buffered saline; SEM, standard error of the mean; TED, thyroid eye disease.

Figure 4. Lonigutamab Significantly Reduced IGF-1–Induced Hyaluronan Production in Multiple Strains of TED Orbital Fibroblasts



Four different strains of TED orbital fibroblasts were treated with either vehicle or IGF-1 (10 ng/mL) for 72 hours. Some cells were pretreated with 2 µg/mL LON for 1 hour before the addition of IGF-1. Afterwards, cell culture supernatant was collected, and HA production was analyzed by ELISA. N = 3 samples per group. \*\*P<0.01 vs IGF-1 alone, one-way ANOVA, Tukey post hoc test. ANOVA, analysis of variance; ELISA, enzyme-linked immunosorbent assay; HA, hyaluronan; IGF-1, insulin-like growth factor 1; LON, lonigutamab; SEM, standard error of the mean; TED, thyroid eye disease.

Figure 5. Lonigutamab Treatment Did Not Alter Hyaluronan Polymer Size



TED orbital fibroblasts were plated and grown to confluence. Fresh media containing vehicle or LON (1.0 or 0.1 µg/mL) was added. After 1 hour, vehicle or IGF-1 (25 ng/mL) was added for an additional 48 hours. Afterwards, cell lysate and cell culture supernatants were collected and analyzed for HA levels by agarose gel electrophoresis. High molecular weight HA standard is 1000 kDa. HA, hyaluronan; IGF-1, insulin-like growth factor 1; LON, lonigutamab; TED, thyroid eye disease.

## Conclusions

- Lonigutamab, a high-affinity, subcutaneous, noncompetitive, next-generation, anti-IGF-1R monoclonal antibody, decreased basal and IGF-1–mediated hyaluronan production without altering hyaluronan polymer size in orbital fibroblasts from patients with TED
- The lonigutamab-mediated reduction in hyaluronan in IGF-1–stimulated orbital fibroblasts was replicated in orbital fibroblasts from multiple patients with TED
- These results highlight lonigutamab's potential to modulate a crucial pathogenic disease process and provide mechanistic insights that support the observed preliminary clinical activity of lonigutamab in TED
- To learn more about lonigutamab's mechanism of action, see our oral presentation on lonigutamab-mediated IGF-1R degradation
  - Thyroid Biology and Disease: New Therapies in Graves' Orbitopathy; July 14, 2025, 1:45–3:15 PM, room 208, #OR31-06

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