Development and Characterization of Trabecular Meshwork Targeted RNAi Molecule Platform via Intracameral Administration for Glaucoma

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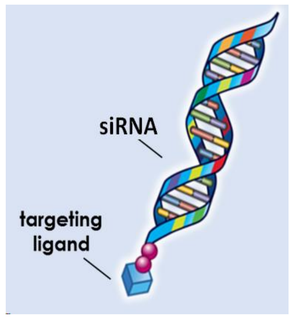
Overview

- The trabecular meshwork (TM) regulates the intraocular pressure (IOP) by draining aqueous humor. Dysfunction of the trabecular meshwork will cause high IOP, the major risk factor of glaucoma.
- Although many medical and surgical treatment options are available, glaucoma patients are still at high risk of progressive visual impairment.
- We developed a proprietary Trabecular Meshwork Targeted RNAi Molecule (**TRiM™**) Platform to silence a target gene in trabecular meshwork for potential treatment of glaucoma.

Trabecular Meshwork TRiM™

- Optimized and simplified trabecular meshwork-targeted conjugate
- Robust and durable target mRNA reduction
- Specific delivery to target tissue
- Favorable safety profile
- Potential infrequent dosing

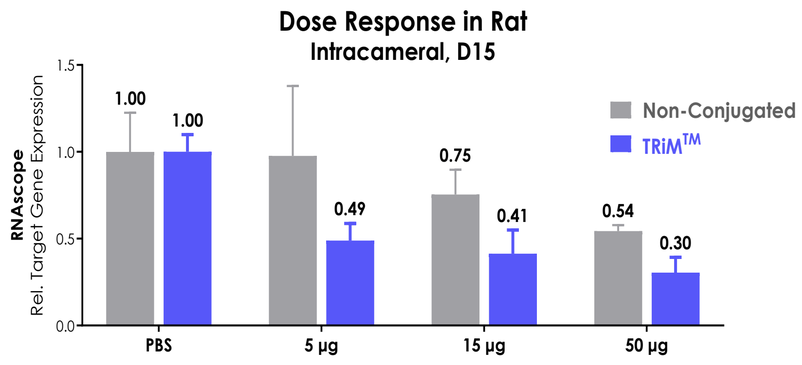


Methods

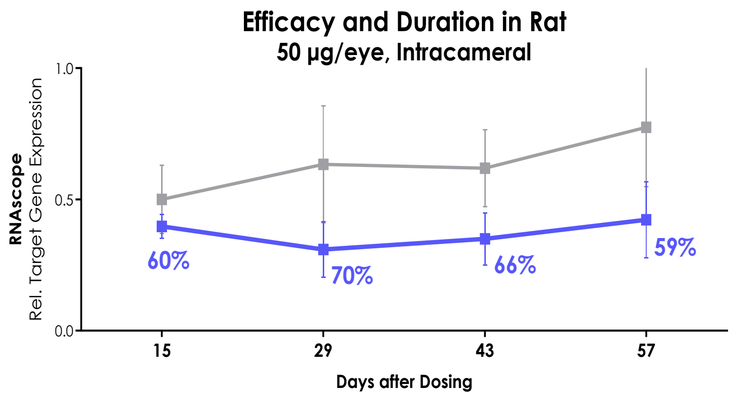
- **PD Study in Rat**
  - Sprague-Dawley rats received a single intracameral injection of 50 µg /eye trabecular meshwork TRiM™
  - The target gene knockdown is evaluated by RNAscope
- **Safety Study in Rabbit**
  - Rabbits received up to 7 mg/eye as a single intracameral injection of trabecular meshwork TRiM™
  - The ADME properties are characterized by HPLC/MS
  - The safety profile is determined by ocular exam, fundus/optical coherence tomography (OCT) imaging, and histopathology
- **PD Study in Non-Human Primates (NHP)**
  - Cynomolgus monkeys received up to 1.0 mg/eye as a single intracameral injection of trabecular meshwork TRiM™
  - The target gene knockdown is evaluated by quantitative polymerase chain reaction (qPCR) and RNAscope
  - Protein expression in TM is analyzed by western blot
  - The tolerability was determined by histopathology

Ligand-Mediated Delivery by TRiM™ Enables Durable Knockdown

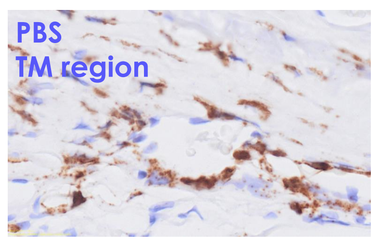
- TRiM™ increased silencing activity over non-conjugated siRNA at three dose levels, N=5
  - The dose response confirms targeted delivery is necessary for optimal efficacy

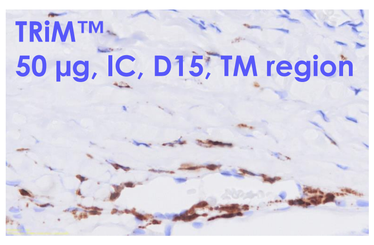


- After a single 50 µg intracameral dose, TRiM™:
  - Enabled 70% target gene reduction at nadir on D29, N=5
  - Maintained ~60% efficacy through D57



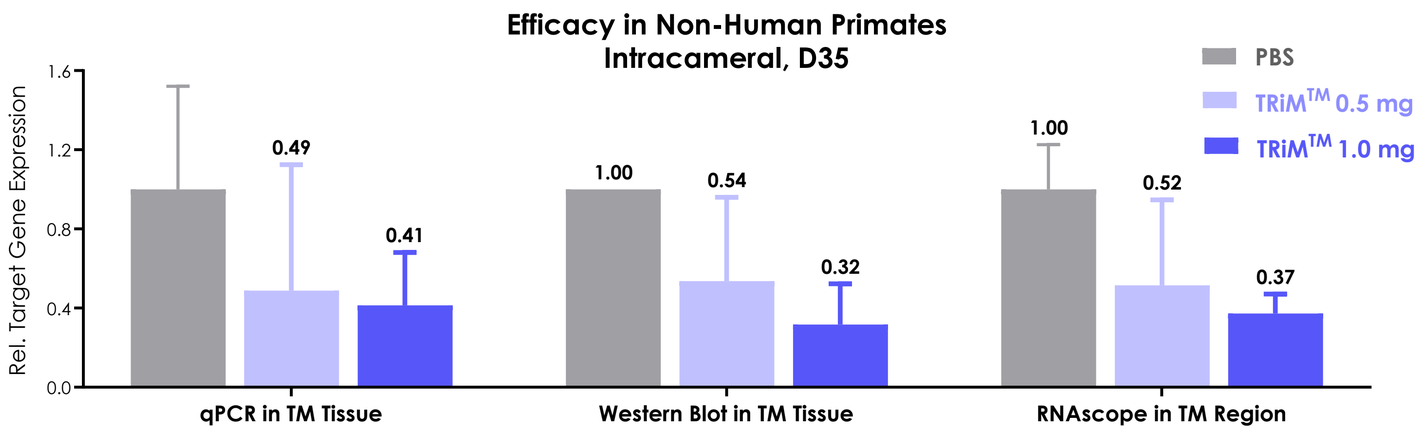
- RNAscope confirms notable TM region transcript reduction





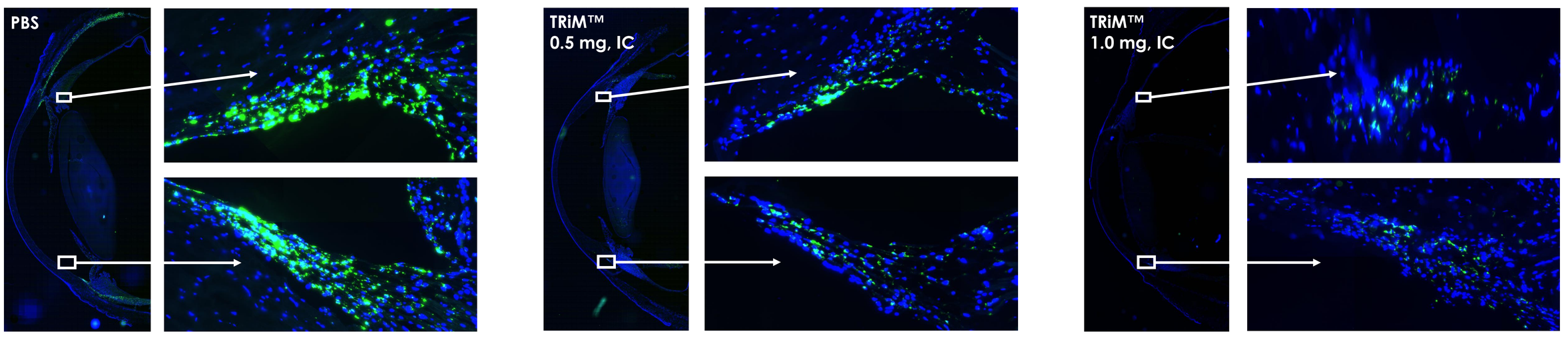
TRiM™ Demonstrated Deep Knockdown in Non-Human Primates

- Cynomolgus monkeys received a single intracameral injection of TRiM™, N=3
  - Target transcript expression: up to 59% mRNA knockdown in dissected TM tissue by qPCR
  - Target protein expression: up to 68% protein knockdown in dissected TM tissue by western blot
  - Efficacy confirmed with up to 63% knockdown in TM region by RNAscope



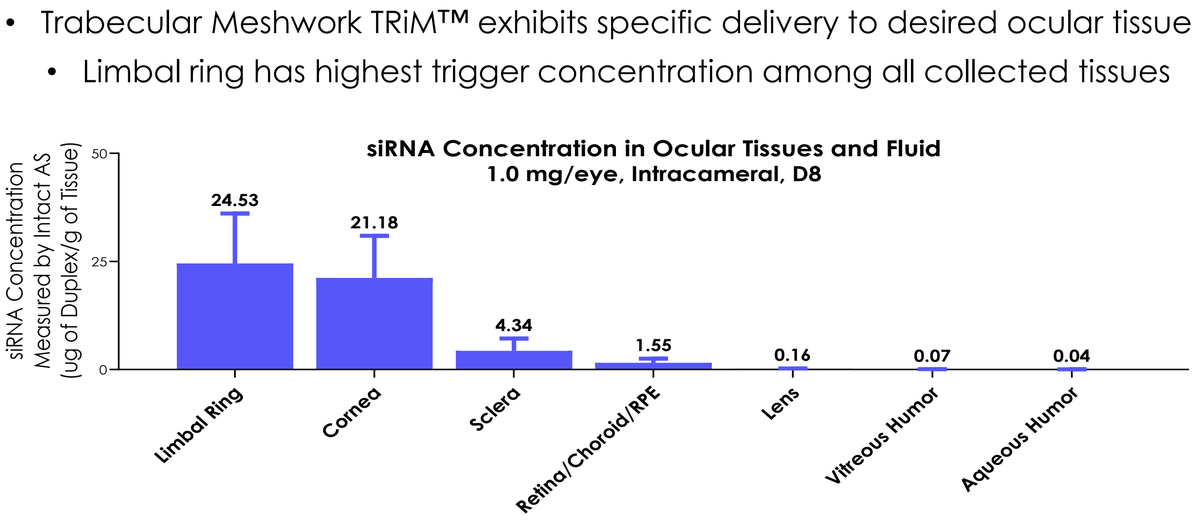
Conclusion

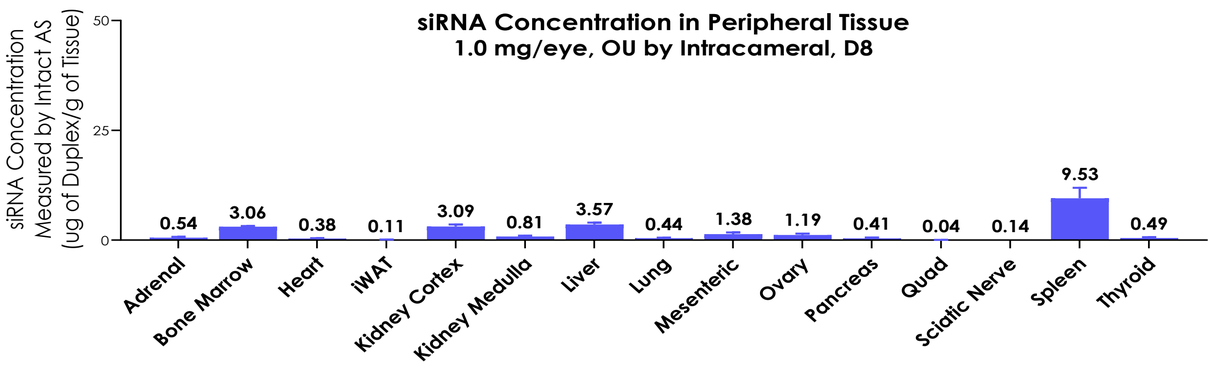
- We have demonstrated that targeted siRNA could be a new therapeutic approach for glaucoma
  - TRiM™ demonstrated deep and durable gene knockdown in trabecular meshwork
  - Successful translation from rodent to cyno
  - Favorable preliminary ADME and non-GLP toxicologic profile
  - Potential for less frequent dosing
- Arrowhead's Trabecular Meshwork TRiM™ platform represents a new opportunity for other ocular indications



TRiM™ Enabled Delivery to Ocular Tissues

- Rabbits received 1 mg/eye TRiM™ on Day 1 via intracameral injection, N=6
  - Trabecular Meshwork TRiM™ exhibits specific delivery to desired ocular tissue
    - Limbal ring has highest trigger concentration among all collected tissues





Favorable Non-GLP Toxicologic Profile

- Rabbits received 3, 5, and 7 mg/eye TRiM™ via intracameral injection

	PBS	Trabecular Meshwork TRiM™ (N=5)
Ophthalmic Exams (Pretest and D2, 9, 22, 29)	D9, 22, 29 Corneal Opacity 0 mg – 2/5 animals	D22, 29 Corneal Opacity 3 mg – 1/5 animals
OCT (Pretest and D15, 29)	Normal	No Testing Article-Related Effects
Histopathology (D30/31)	Normal	No Testing Article-Related Effects
Corneal opacity is noticed as punctate, faint, white. G2 opacities in one animal shifts from OD to OS over time		

- NHP received 0.5 and 1.0 mg/eye TRiM™ via intracameral injection

	PBS	Trabecular Meshwork TRiM™ (N=3)
Histopathology (D35)	Normal	No Testing Article-Related Effects