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Novel TRiM™ Platform for Oligonucleotide Delivery to Trabecular Meshwork via Local Intracameral Administration

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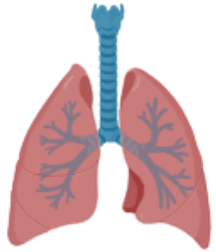
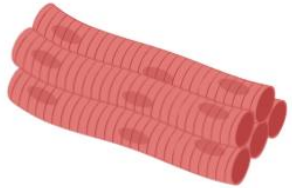
This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types

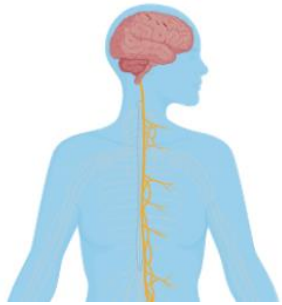
Clinical Stage



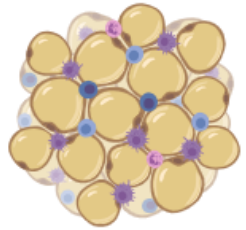
Clinical Stage



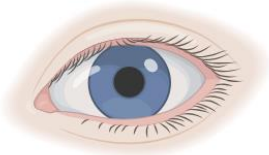
Clinical Stage



Preclinical Stage



Preclinical Stage



Preclinical Stage

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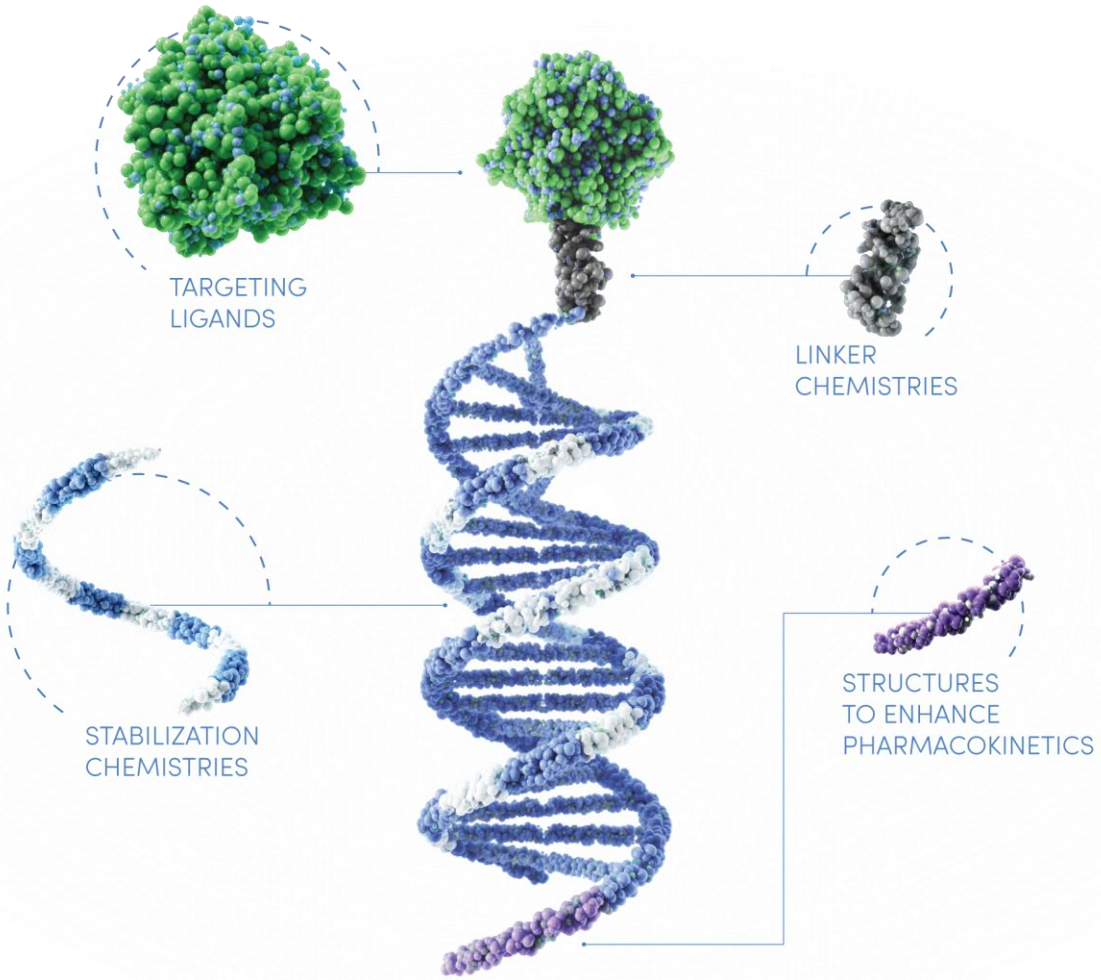
TRiM™ Platform: Targeted RNAi Molecule



A modular system with:

- Unique RNAi chemistry insights and expertise
- Powerful platform technology to maximize activity and stability employing:
  - Algorithmic approach to sequence selection and design
  - Stabilization chemistry
  - Targeting ligand
  - PK enhancers
  - Linker chemistry

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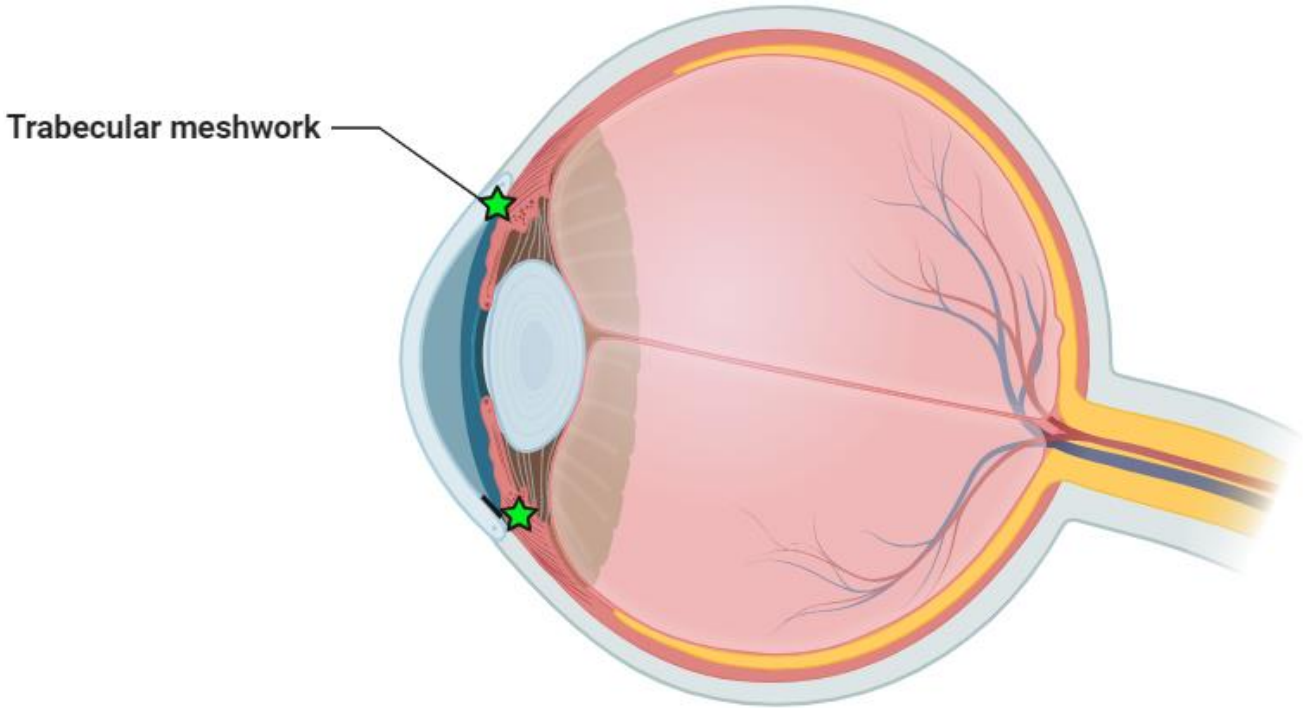
Agenda

TRiM™ Ocular Platform *to target trabecular meshwork (TM)*

- ✓ Demonstrated delivery
- ✓ Deep target gene knockdown
- ✓ Favorable ADME properties
- ✓ Good safety profile



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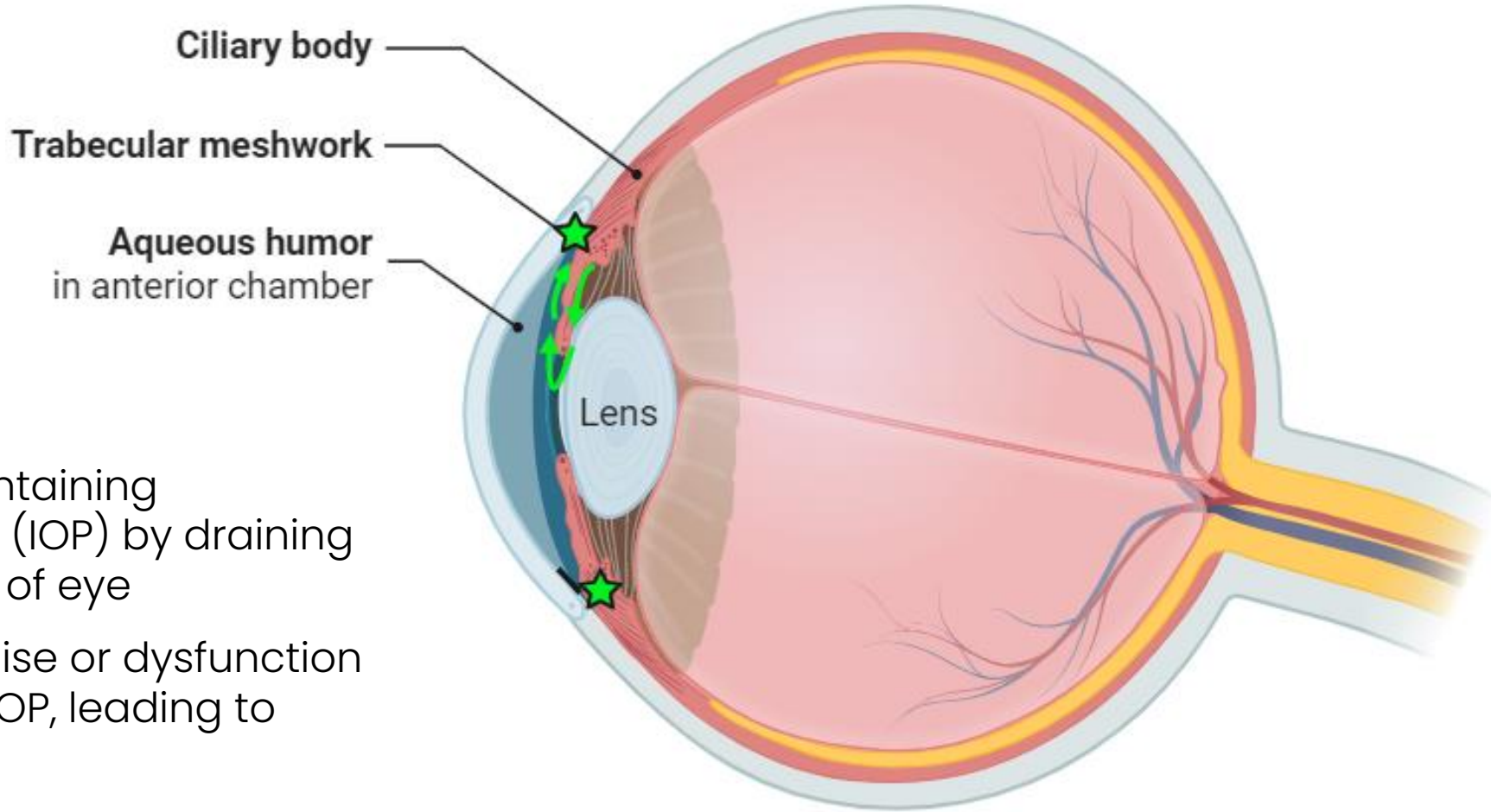
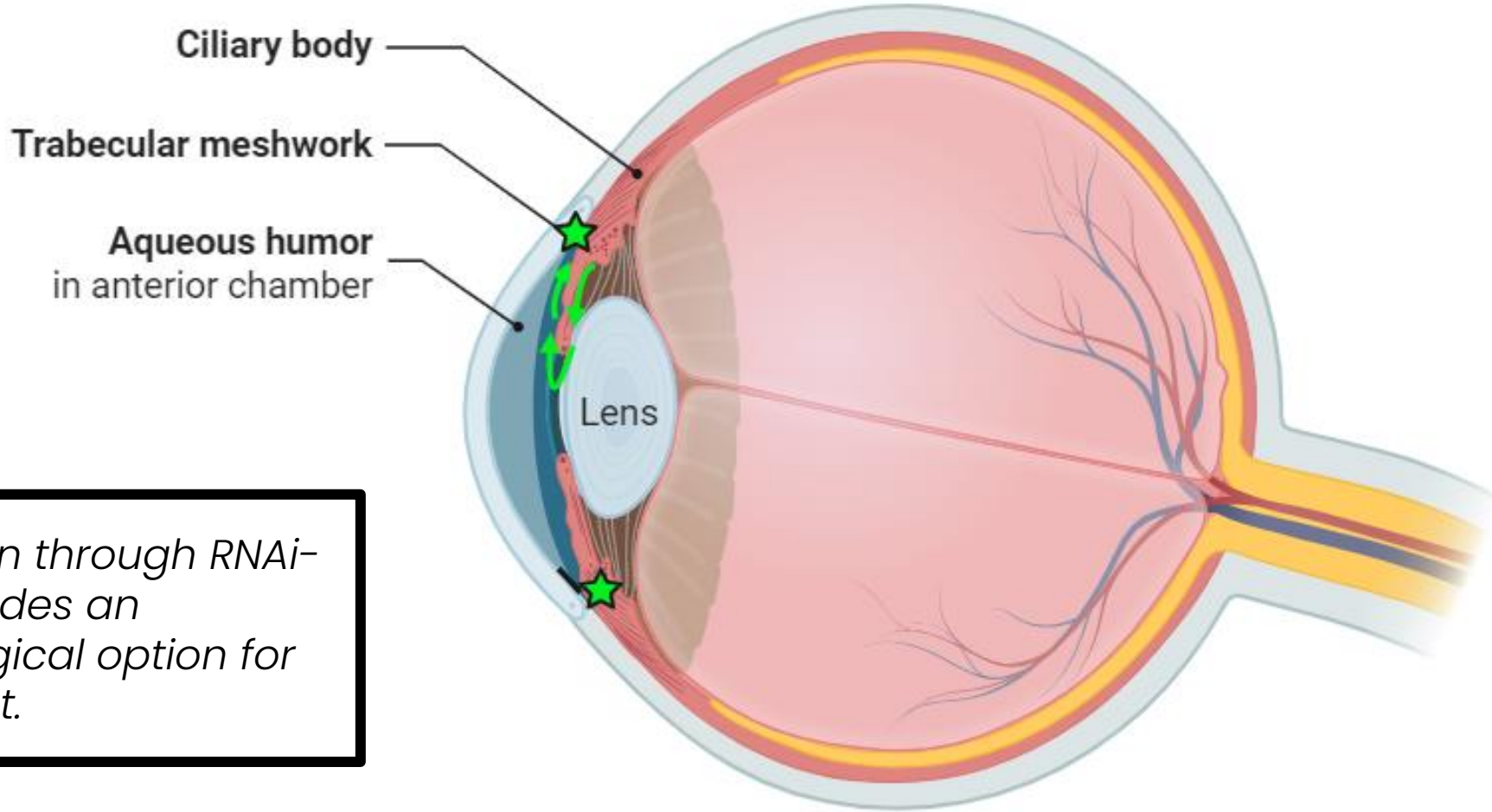
Endogenous Role of Trabecular Meshwork



- Responsible for maintaining intraocular pressure (IOP) by draining aqueous humor out of eye
- Structural compromise or dysfunction of TM can increase IOP, leading to glaucoma

Endogenous Role of Trabecular Meshwork



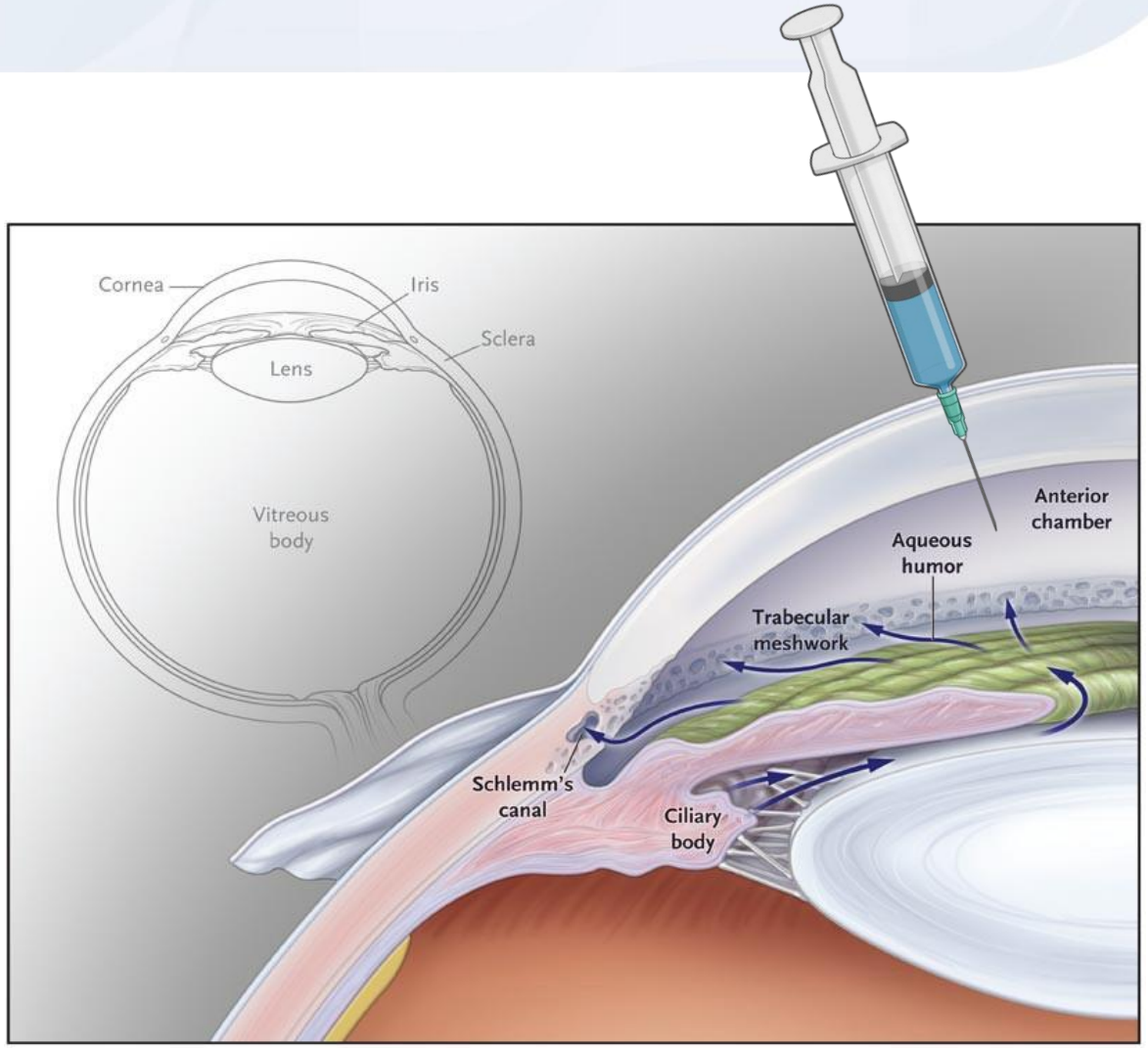
Restoring TM function through RNAi-based therapy provides an alternative, non-surgical option for glaucoma treatment.

Local Injection for Trabecular Meshwork-Targeting siRNA Therapeutic

Feasibility
Intracameral injection to aqueous humor is clinically feasible

Accessibility
Trabecular meshwork (TM) cells are directly accessible from aqueous humor (AH)

Targeted Delivery
Increase of delivery to TM cells through receptor-mediated uptake



N Engl J Med 2009; 360: 1113-1124.

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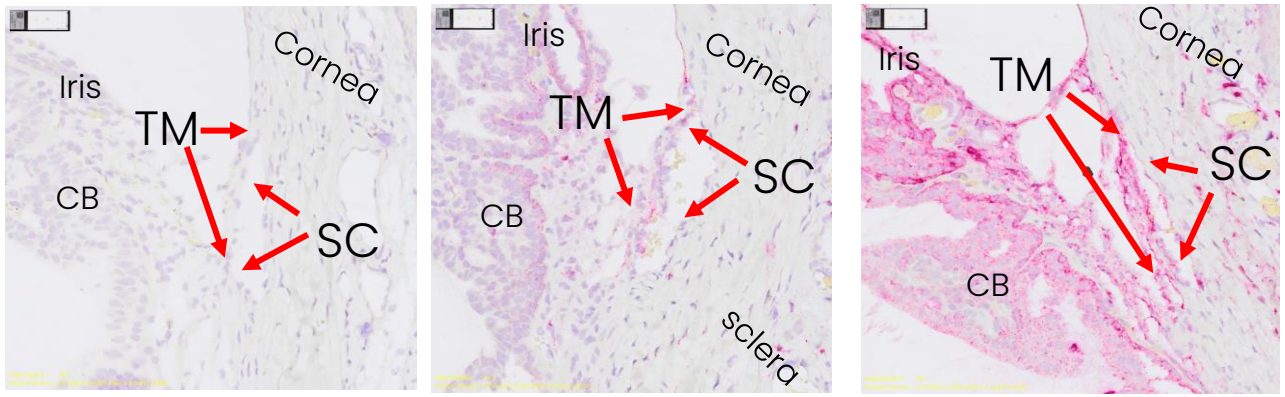
TRiM™ Ocular Platform Ligand Improves Oligonucleotide Delivery to Trabecular Meshwork in Rat

Groups treated with:

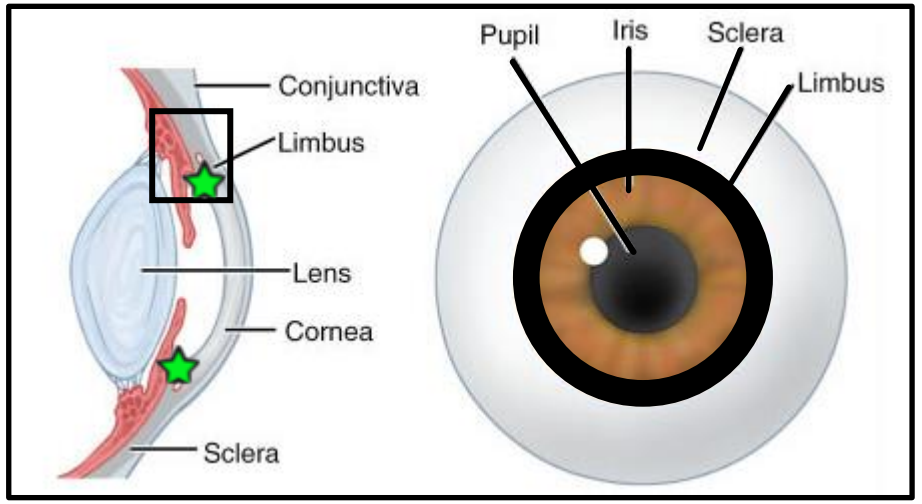
50 µg/eye OU, IC, D1
Sac D30

Rat miRNAscope™

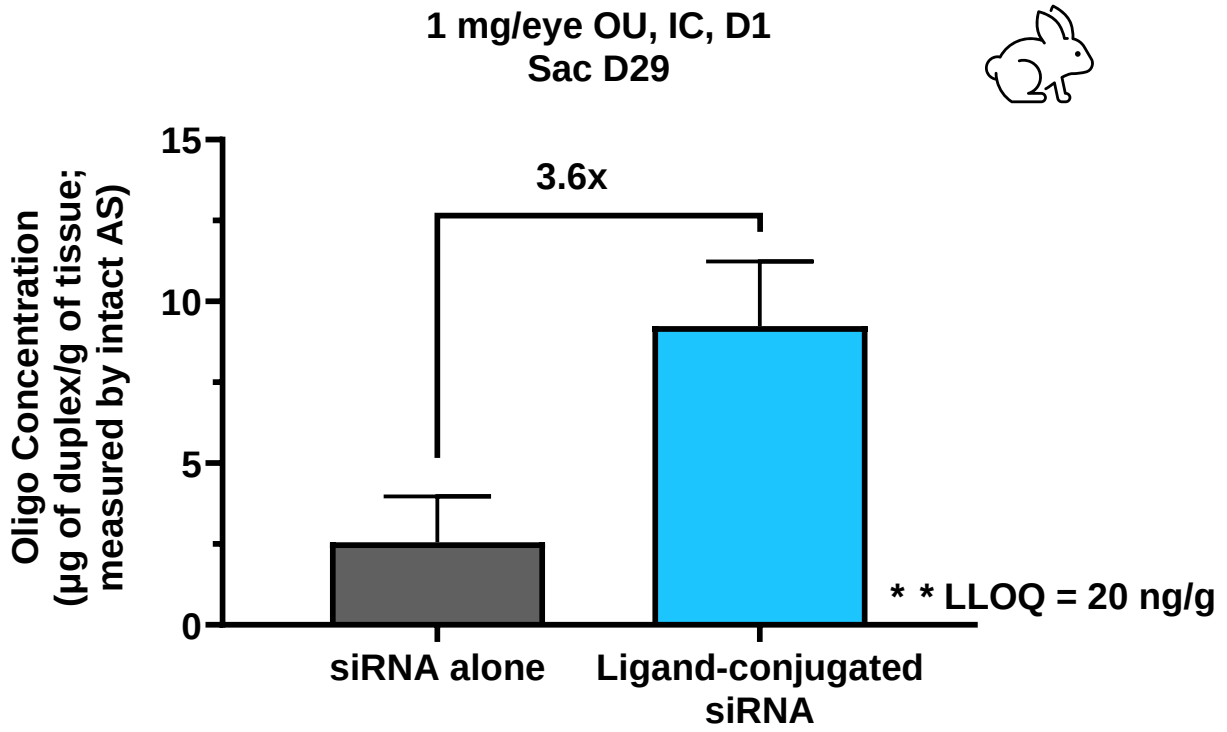


- No staining with PBS
- Slight staining in TM and iris/ciliary body with siRNA alone
- Strong staining in TM and iris/ciliary body with TRiM™ Ocular Platform ligand-conjugated siRNA

TRiM™ Ocular Platform Ligand Improves Oligonucleotide Delivery to Trabecular Meshwork in Rabbit



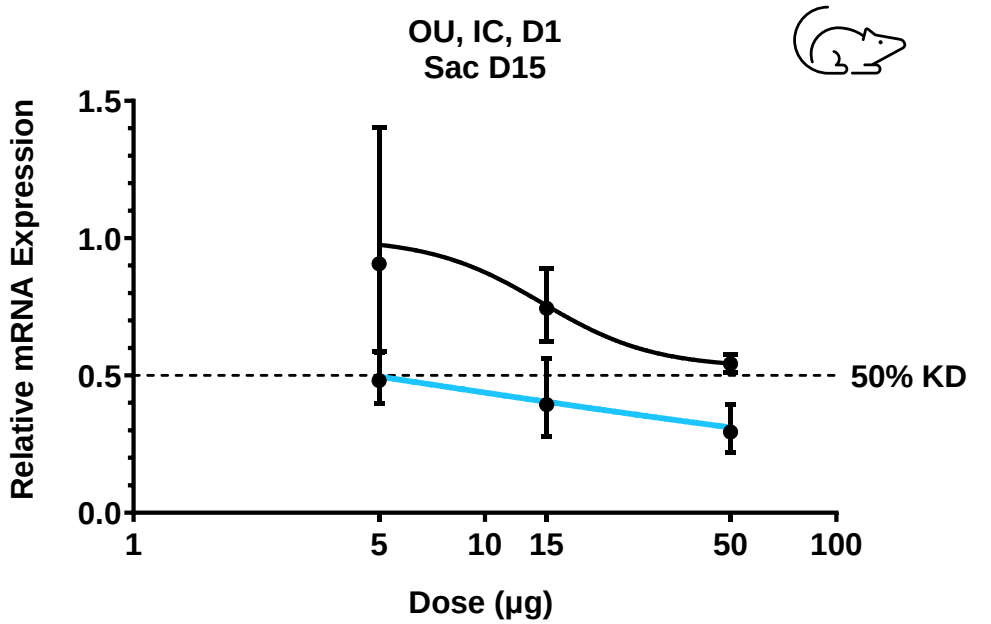
siRNA Concentration in Limbal Ring



- Improved oligo delivery in TM with TRiM™ Ocular Platform ligand-conjugated siRNA

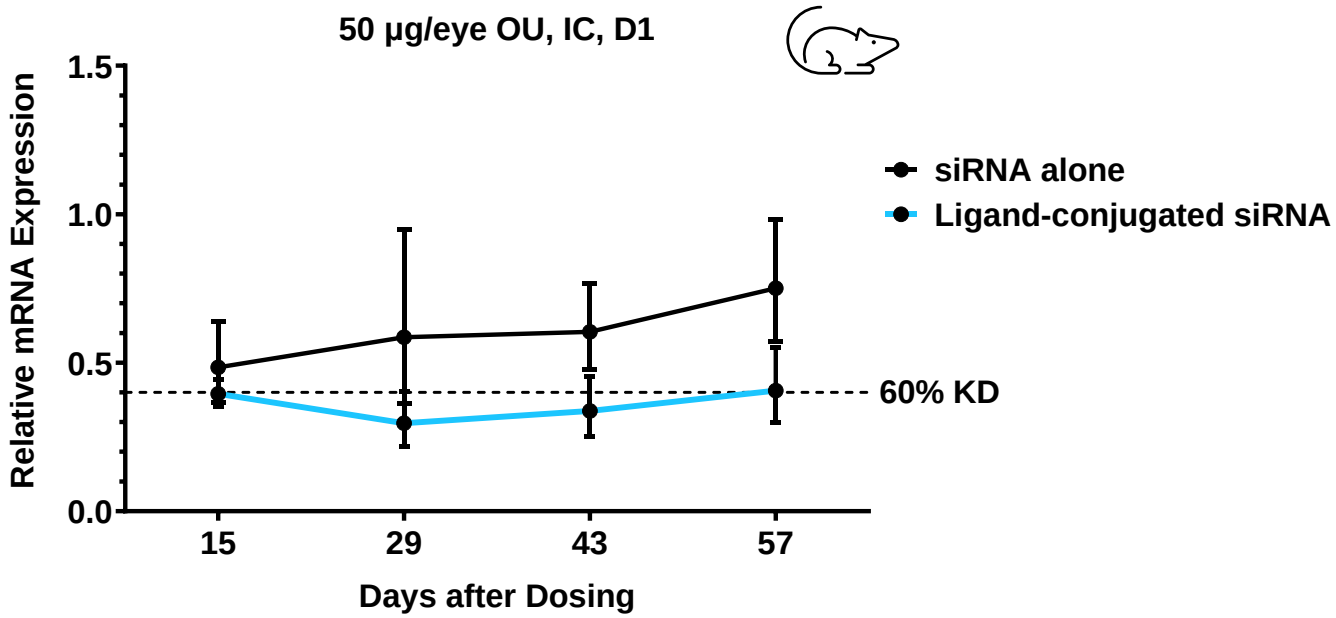
Improved Delivery to TM Translated to Improved Gene Silencing in Rat

Dose Response



- Enhanced knockdown (KD) of target gene with TRiM™ Ocular Platform ligand-conjugated siRNA across all 3 doses
- Up to 70% KD observed with TRiM™ Ocular Platform ligand-conjugated siRNA

Duration



- Up to 2-month duration observed with TRiM™ Ocular Platform ligand-conjugated siRNA
- Clear recovery observed with non-conjugated siRNA

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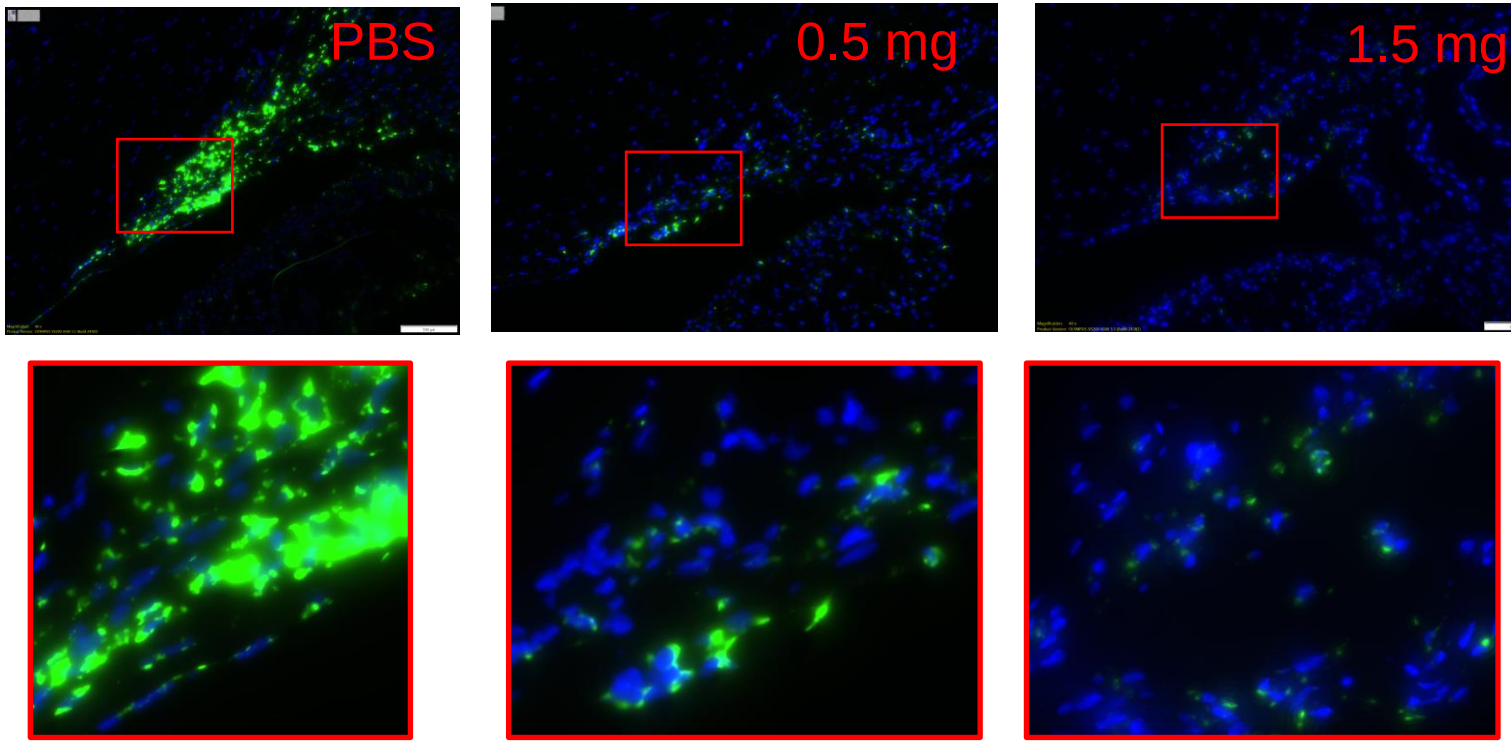
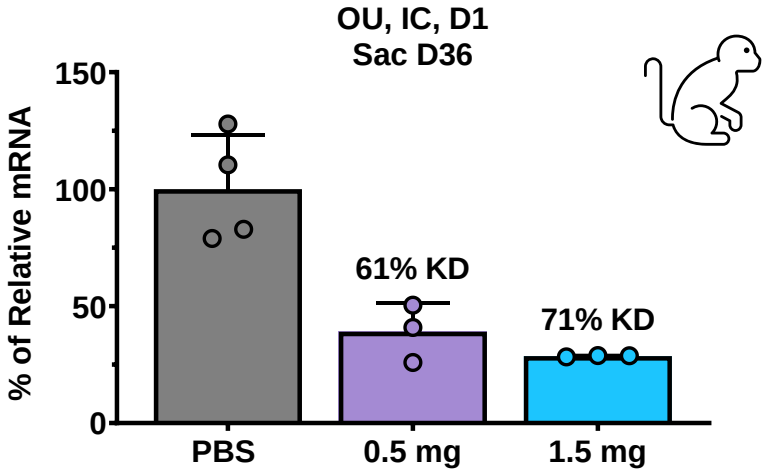
Deep Gene Silencing Achieved in Non-Human Primates

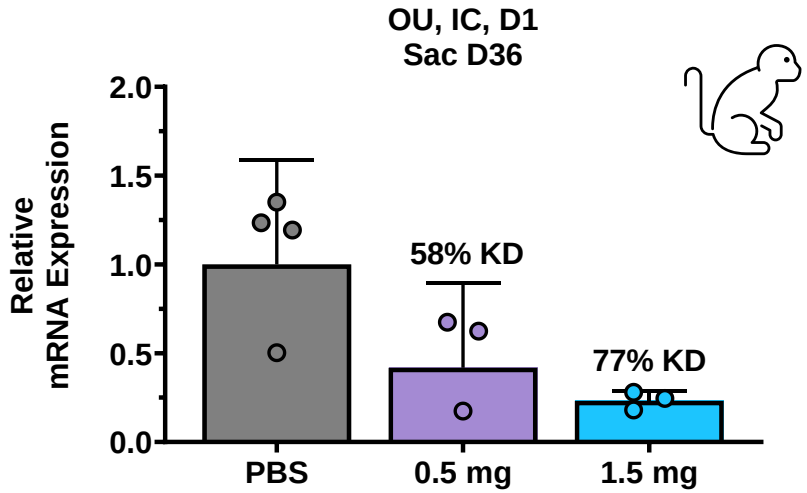


- mRNA gene KD demonstrated by RNAscope™ imaging of eye
- mRNA gene KD demonstrated by qPCR of TM tissue

mRNA Levels by Imaging



mRNA Levels by qPCR



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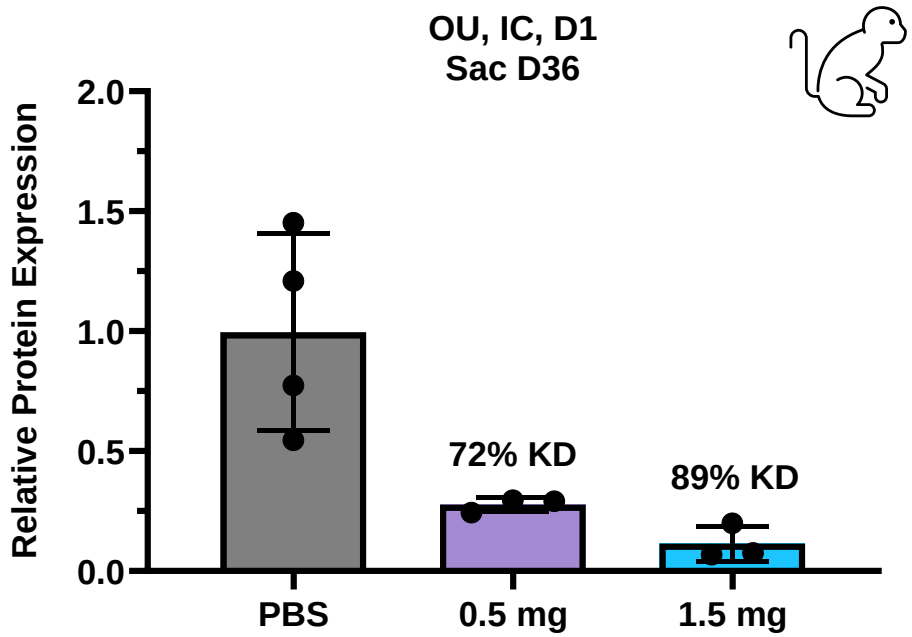
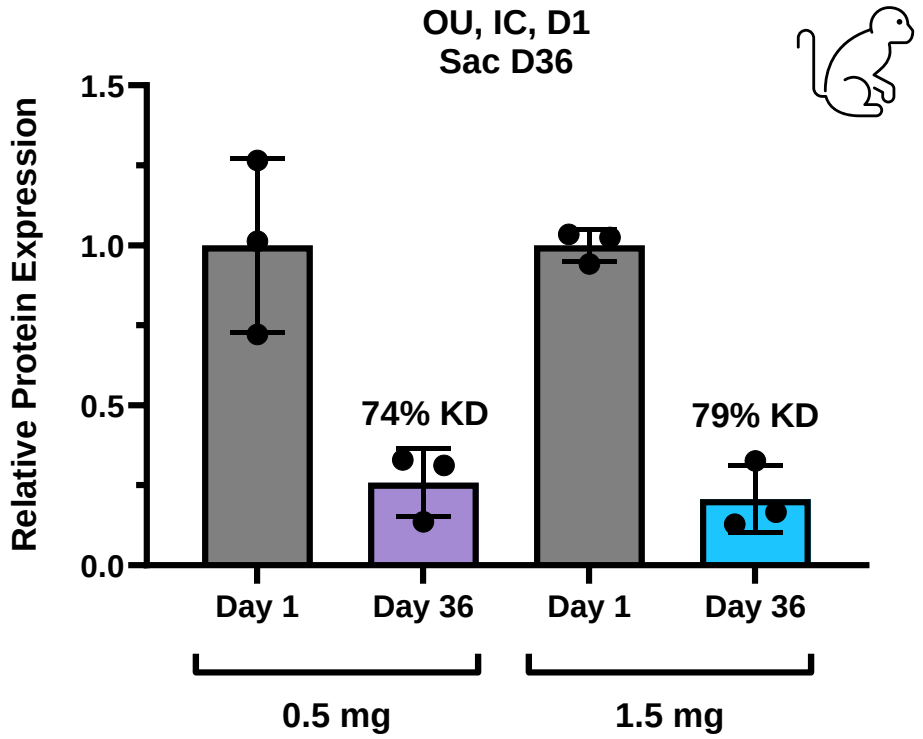
Deep Protein Knockdown Achieved in Non-Human Primates

Protein Levels in TM Tissue



- Deep protein knockdown achieved in trabecular meshwork
- Corroborates with mRNA gene KD

Protein Levels in Aqueous Humor



- Deep protein knockdown achieved in aqueous humor (biomarker readout)

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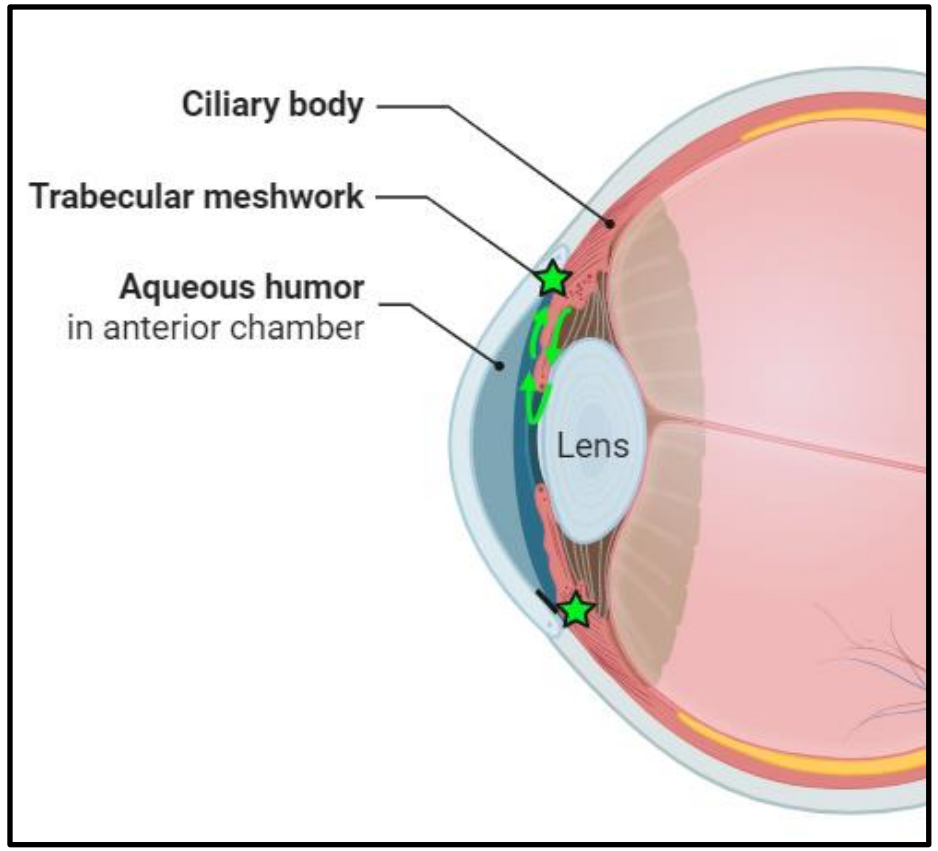
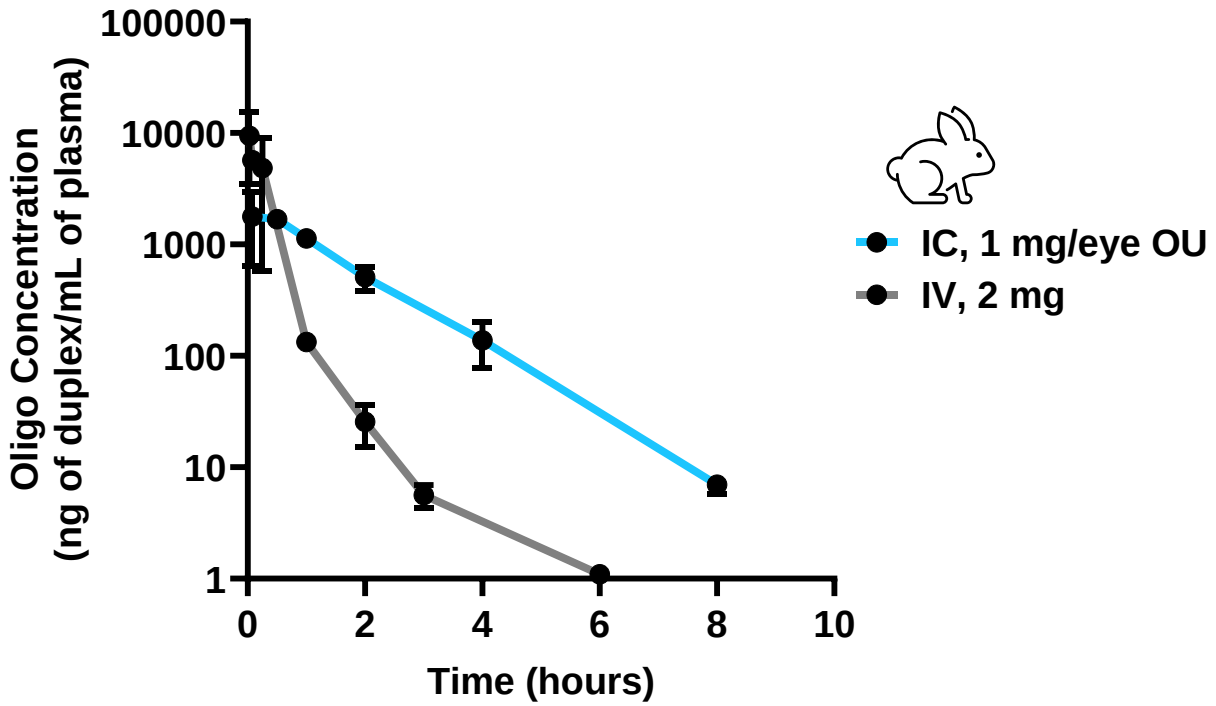
Clearance From Aqueous Humor and Plasma PK



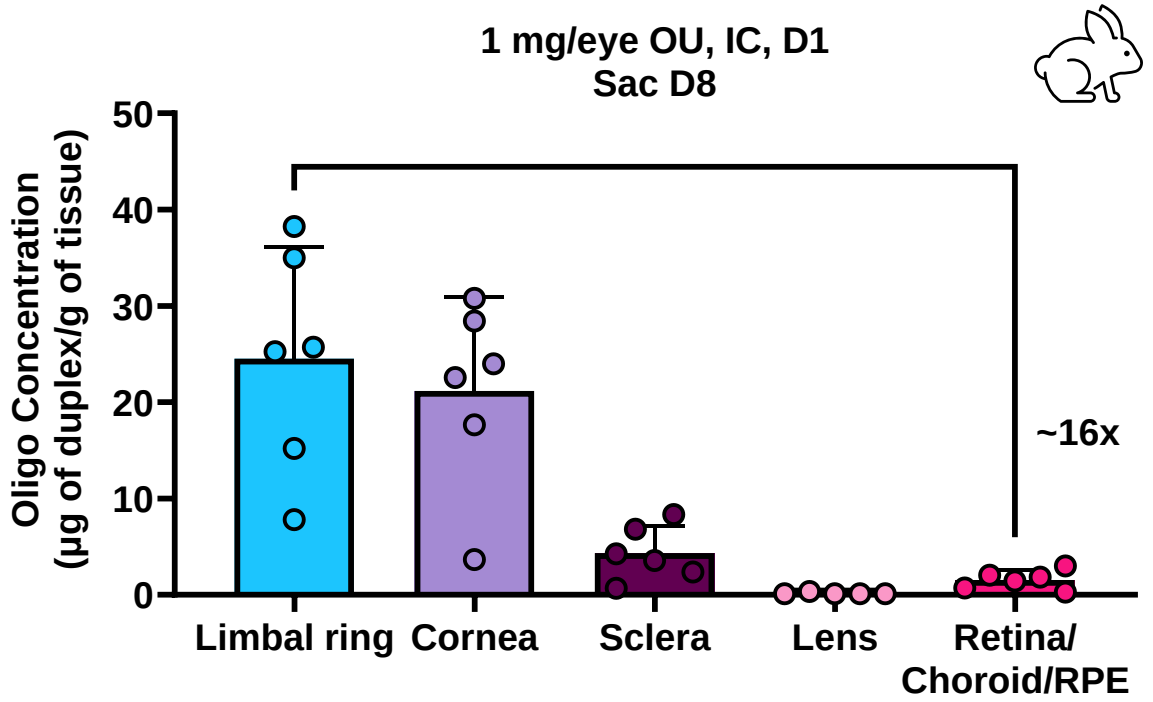
Plasma PK Profile



- 95% plasma bioavailability
- T_{max}: 5-30 min

Rabbit Ocular Distribution Profile

siRNA Concentrations in Ocular Tissues



- Highest concentration observed in limbal ring
- Minimal in lens and posterior section of the eye
- Similar results observed in cyno

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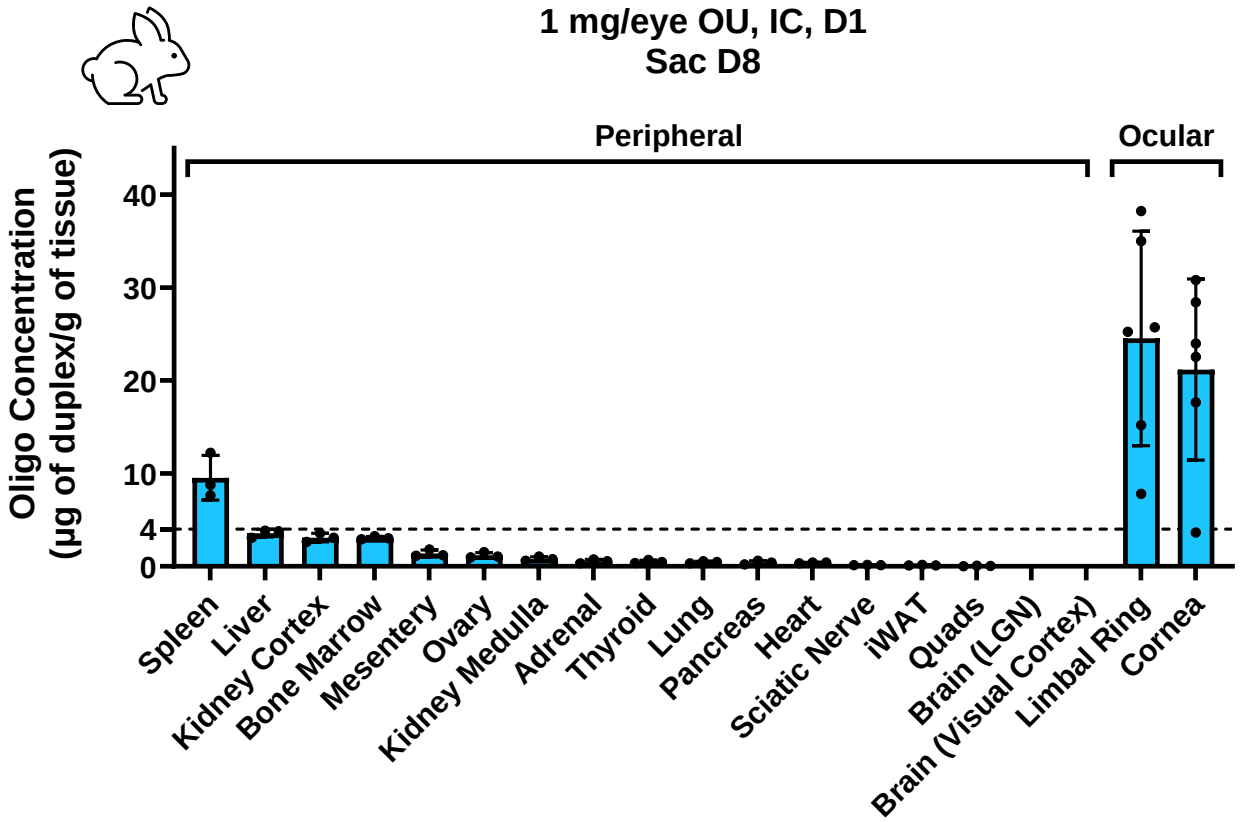
Rabbit Peripheral Biodistribution Profile

siRNA Concentrations in Rabbit Peripheral Tissues



- 13% of dose excreted in urine
- Broad distribution of oligo to peripheral organs
- Generally low concentrations in peripheral organs
  - Highest concentration observed in ocular tissue
  - >5x lower concentrations in peripheral organs except spleen
- Similar results in cyno
  - >10x lower concentrations in peripheral organs compared to ocular tissue
- Good tissue selectivity

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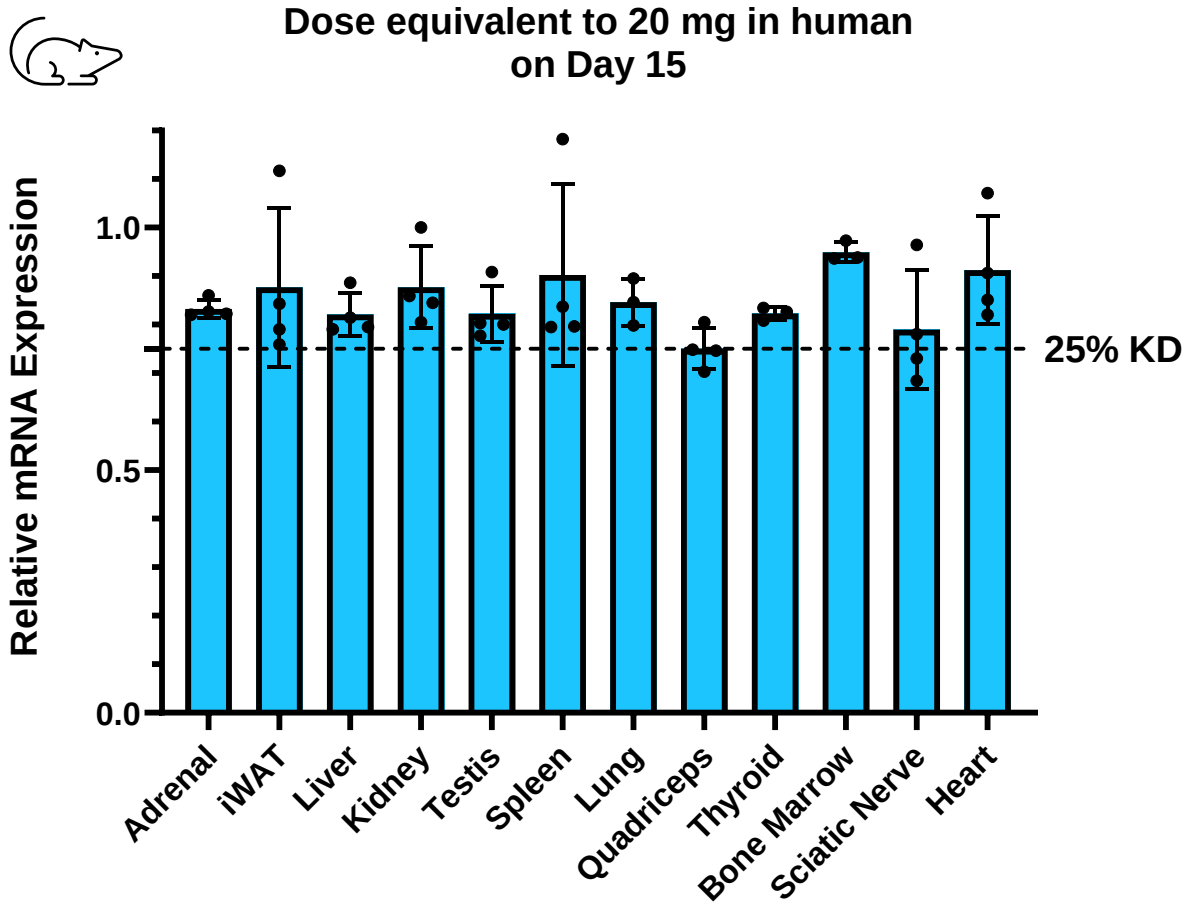
Functional Selectivity Demonstrated in Rat Peripheral Tissues

SOD1 mRNA Levels in Peripheral Tissues



- Gene silencing potential in peripheral organs evaluated in rats
  - SOD1-targeting trigger with TM platform ligand
- ≤25% KD in all tissues evaluated at highest dose
- Platform's limited peripheral tissue KD demonstrates good functional selectivity

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Tissue Clearance Profile

Tissue	Half-life (days)
Ocular limbal ring	20.86
Liver	6.34
Other peripheral organs	5 - 26

- Clearance evaluated in 20 organs/tissues in rabbit
- Tissue clearance half-lives range from 5-26 days
- Slow clearance of oligo in ocular limbal ring tissue
- High clearance of oligo in liver
- Relative clearance profile is attributed to higher accumulation of oligo in limbal ring relative to peripheral organs
- Minimal accumulation anticipated with a 2-month dosing regimen in rabbit

TRiM™ Ocular Platform Safety Profile in New Zealand White Rabbits

Test Article	Dose (mg/eye)	Number of Animals (Females)	Dose (40 µL)
Candidate	3.0, 5.0, 7.0	5/group	Single Intracameral Dose – Day 1

Findings:

The Arrowhead Trabecular Meshwork Platform candidate had no test article-related findings in ophthalmic examinations, intraocular pressure, optical coherence tomography, or ocular histopathology.

Summary

A new extrahepatic TRiM™ platform for siRNA delivery to ocular trabecular meshwork has been developed that achieves:

- ✓ Deep and durable target gene knockdown in rat
- ✓ Deep target gene knockdown in NHP
- ✓ Favorable biodistribution profile
- ✓ Minimal siRNA activity in peripheral organs
- ✓ Good safety profile in rabbit

Thank you! Questions?