Animal Disease Models in Ocular Drug Development

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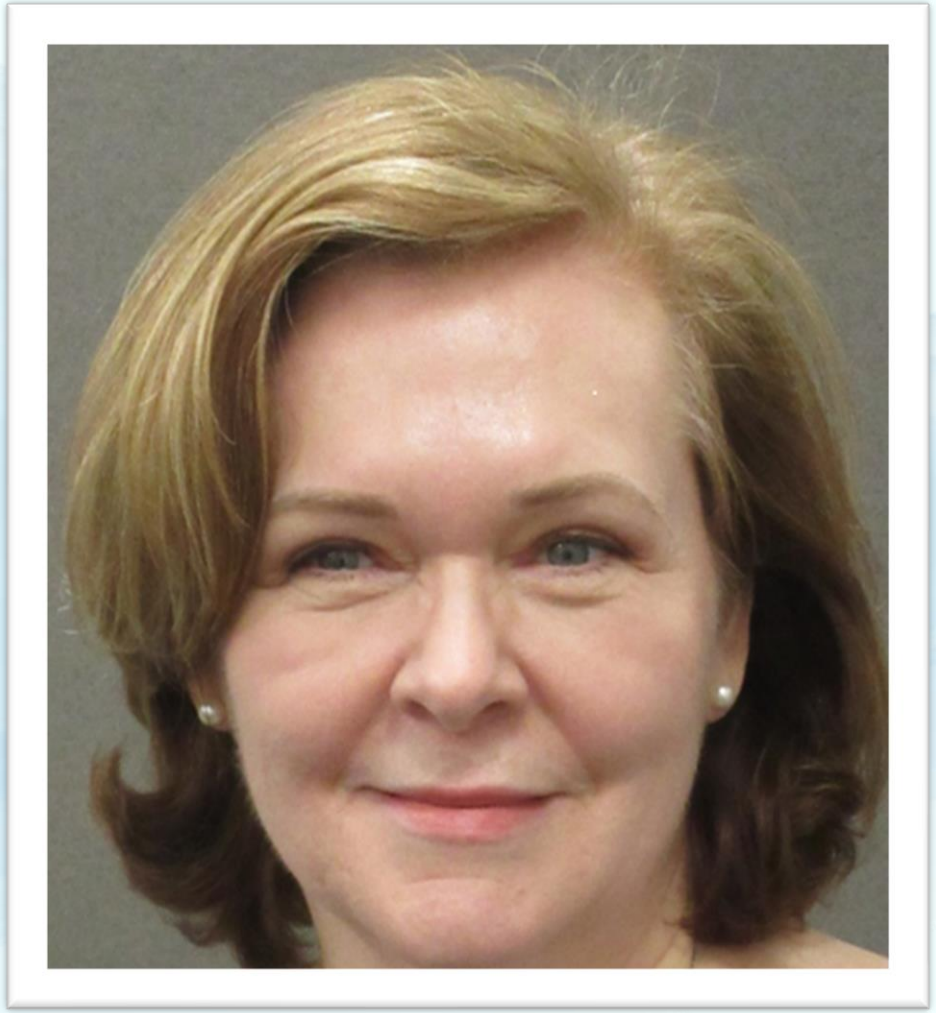

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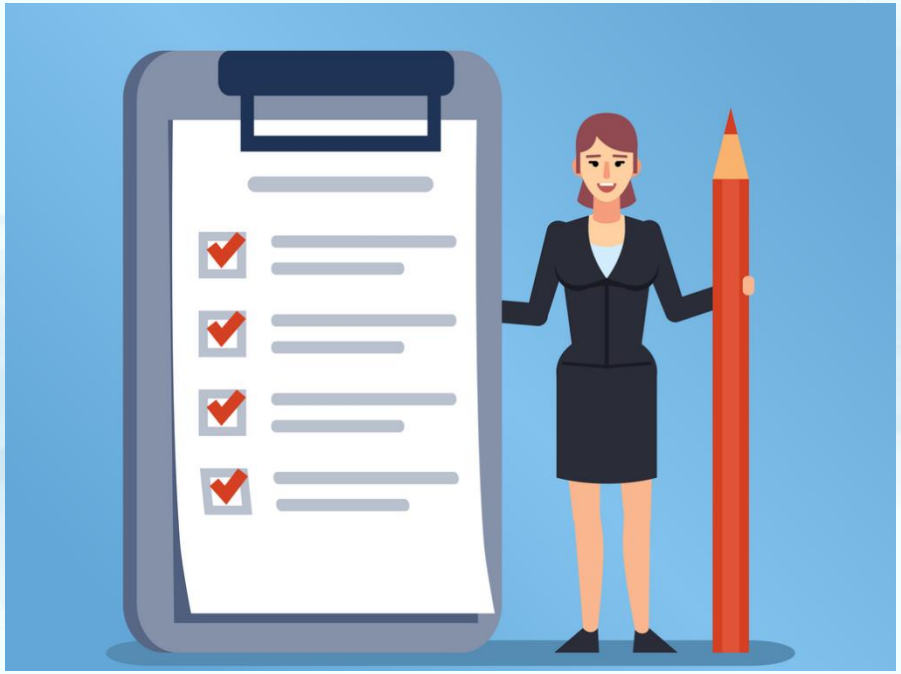
Objective

To demonstrate how early preclinical studies using disease models, surgically altered or transgenic animals can inform the design of pivotal toxicology studies and improve translation of ocular drugs to the clinic

Agenda

- Challenges Unique to Ocular Drug Development
- Ocular Anatomy and Routes of Administration
- Case Studies
- Summary



Challenges in Ocular Drug Development – Big Picture

- Anatomical and Physiological Barriers
- Drug Delivery Methods
- Patient Compliance
- Manufacturing and Regulatory Hurdles
- Understanding Disease Pathogenesis
- Animal Models

Overview of General Preclinical Development

Pharmacology

- Primary pharmacodynamics – efficacy studies on the intended indication
- Secondary pharmacodynamics – off-target effects
- Safety pharmacology – effects on critical systems (CV, respiratory, CNS)

Pharmacokinetics

- Repeat dose PK in toxicology species to characterize ADME/exposure
- Protein binding, metID, etc.

Toxicology

- Species based on metabolism (SM) or pharmacological relevance (LM)
- One rodent and one non-rodent species for SM, usually rat and dog
- One pharmacologically relevant species for LM, often NHP
- Route of administration, schedule and duration based on clinical plan
- Dose levels sufficient to achieve 10x safety margins

Additional Considerations for Ocular Drugs

Study Level Challenges

Pharmacology

- Early studies often in rodent disease or transgenic models
- Rabbits, dogs and NHP models also used

Pharmacokinetics

- Rabbits are commonly used for ADME in ocular compartments
- Protein binding, specifically for melanin is needed

Toxicology

- Rodents are not practical for ocular tox studies due to size of eye, limits dose volumes
- Rabbits can be used for SM studies; may not be useful for LM due to profound immune response
- If drug binds melanin, a pigmented (second) species is needed (Dutch-belted rabbit, dog, pig, NHP)
- Systemic route in one species to assess systemic toxicity (for novel drugs)

Additional Considerations for Ocular Drugs

Study level challenges

Dose Volume Limitation for Topical and Intraocular Routes

Topical:

- Average eye drop is 30-50 µL, the tear film capacity of the human eye is only 6-8 µL
- Only 1-5% of the administered drug in a standard eye drop is absorbed at the site of action

Intraocular:

- The maximum volume that can be injected without causing a spike in intraocular pressure (50 uL),
- The maximum concentration based on the limit of solubility of a SM or feasibility of manufacturing a LM at concentrations that are usually only slightly higher than the clinical concentration
- The tolerability of the intraocular drug product, which includes excipients or, in the case of biologics, host cell proteins, and endotoxin.

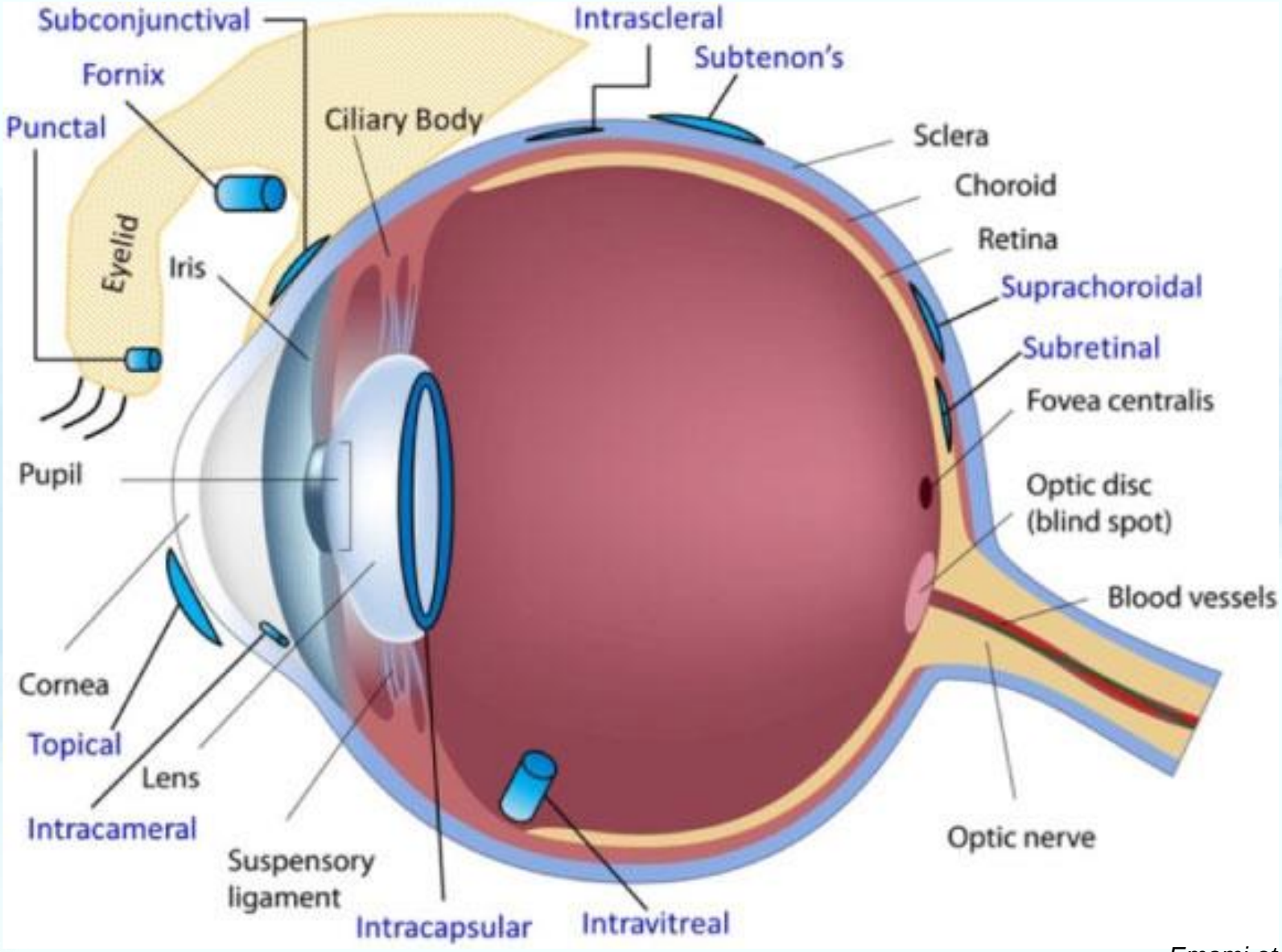
Often only a 2- or 3-fold multiple of the maximal anticipated human dose is achieved in intraocular toxicity studies.

Ocular Case Studies

Specific drug/indication level challenges

Disease Impacts the PK Profile of the Drug:	Topical Drug for Neurotrophic Keratitis (NK): A toxicity study need to consider PK profile change
Common Surgical Procedure in Glaucoma Patients Impacts PK/PD Profile of the Drug:	Subconjunctival Drug for Glaucoma: Introduction of a glaucoma filtration surgery (trabeculectomy) and its impact on the PK/PD profile
Gene Therapy Protein Product is an Antibody:	Subretinal Gene Therapy for Wet AMD: Protein product is anti-VEGF Ab. Humanized VEGF mice (efficacy model) provides a target for the Ab

Ocular Anatomy and Routes of Administration

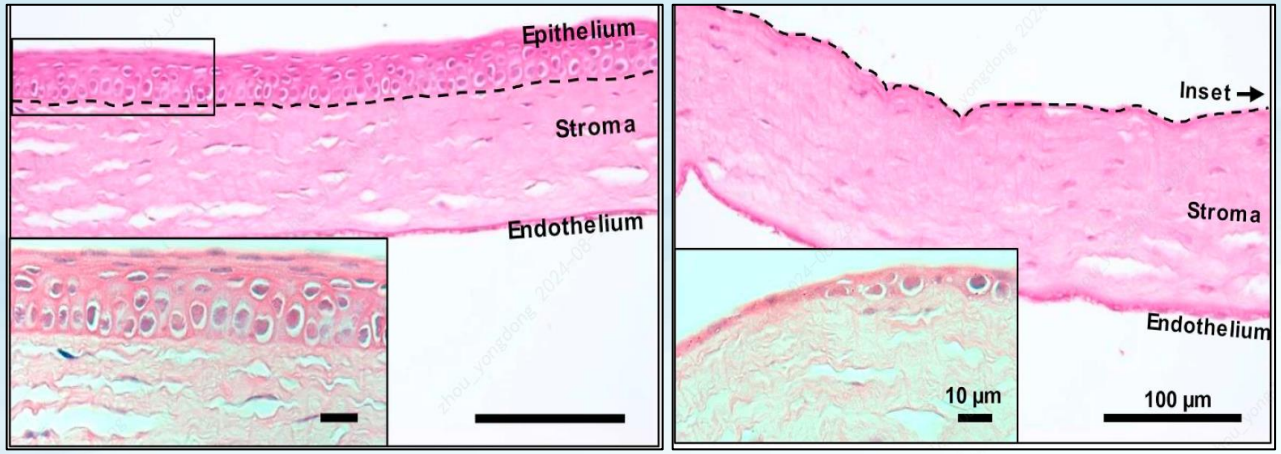


Emami et al, Int J Tox, 2018

Case 1　Eye Drops for Neurotrophic Keratitis (NK）

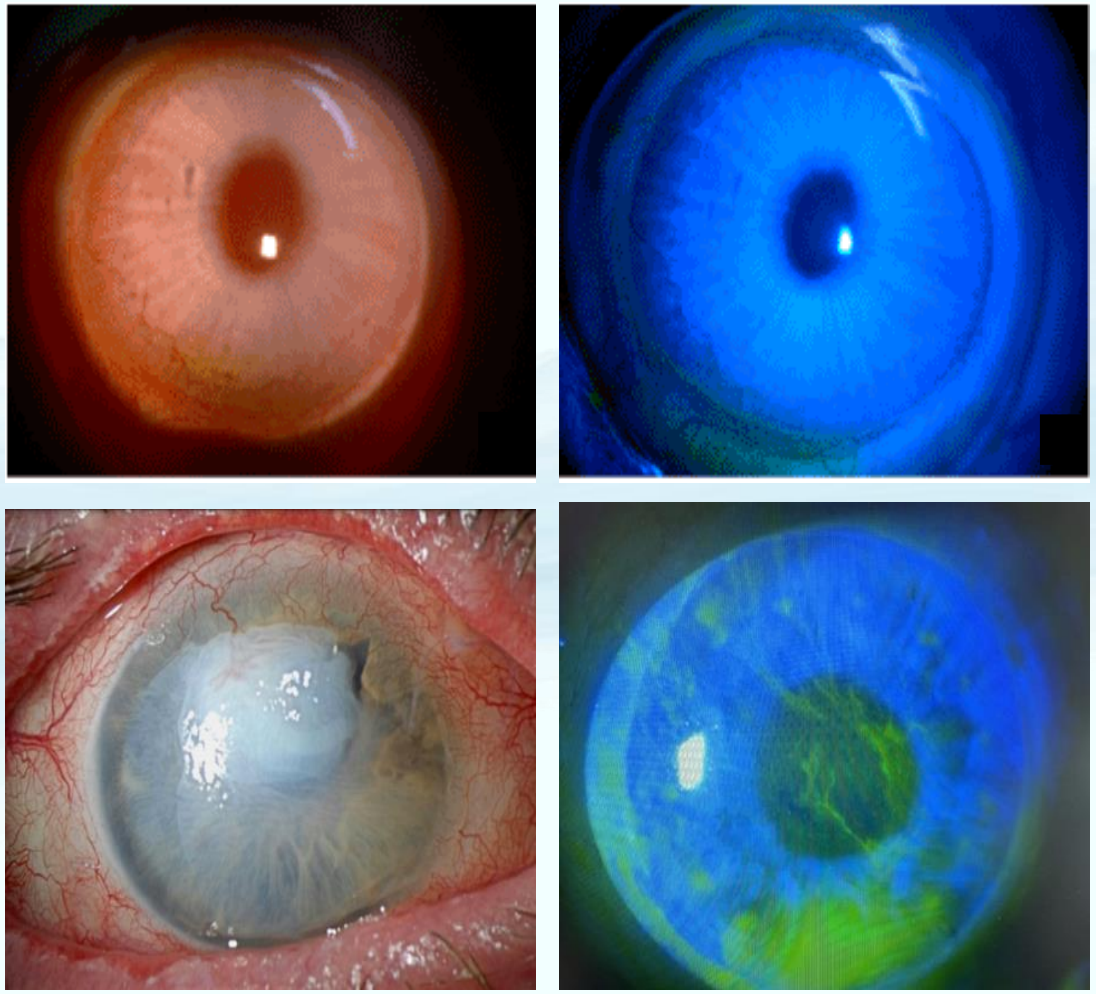
Background:

- NK is a degenerative disease of the cornea caused by damage of the trigeminal nerve, which results in impairment of corneal sensitivity, spontaneous corneal epithelium breakdown, poor corneal healing and development of corneal ulceration, melting and perforation.
- In the pharmacodynamic (PD) study, the concentrations of test article (TA) in the corneas of NK modeling animals were 10 folds higher than those in the corneas of healthy control animals due to loss of barrier.
- What should be considered in a pre-clinical safety evaluation?



Control　　Cornea epithelium defect

Richard Zhang *et al*. The ocular surface 2020, 18;158-169



Uma L Balakrishnan, *et al*. Neurotrophic Keratitis: Exploring the Therapeutic Landscape. touchREVIEWS in Ophthalmology. 2023;17(1):36–41

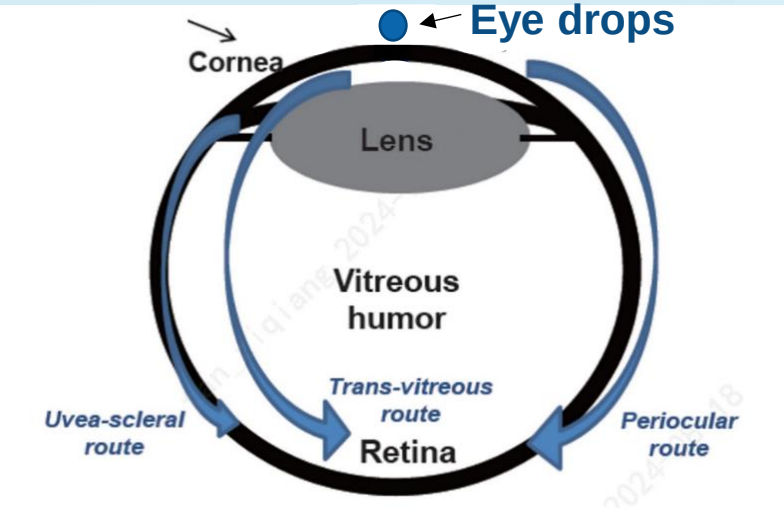
Consideration for Study Design: (PK/PD+Tox)

- Characteristics of pharmacokinetics (PK) and biodistribution of the TA. The maximum concentration limited by the feasibility of manufacturing.
- Higher TA concentration in the cornea may cause higher TA exposure in the eye (anterior chamber and posterior segment of the eye).
- Options:

1) PD+Tox, SD rats, NK modeling from Day -3, topical instillation, four groups

1. vehicle with modeling;
2. TA-low dose with modeling;
3. TA-mid dose with modeling;
4. TA-high dose with modeling.

IND TOX followed using normal dogs and rabbits for ocular route and rats for systemic (iv or oral) route.



2) Biodistribution of TA does not change significantly in the eye. Ocular toxicity study design is like common eye drops. Use normal dogs and rabbits for ocular route and rats for systemic (iv or oral) route.

Four groups

1. vehicle;
2. TA-low dose;
3. TA-mid dose;
4. TA-high dose.

3) Biodistribution of TA changes significantly in the eye. Use normal dogs and rabbits for ocular route and rats for systemic (iv or oral) route. An alternate ROA group to achieve higher exposure in the eye will be added.

Five groups

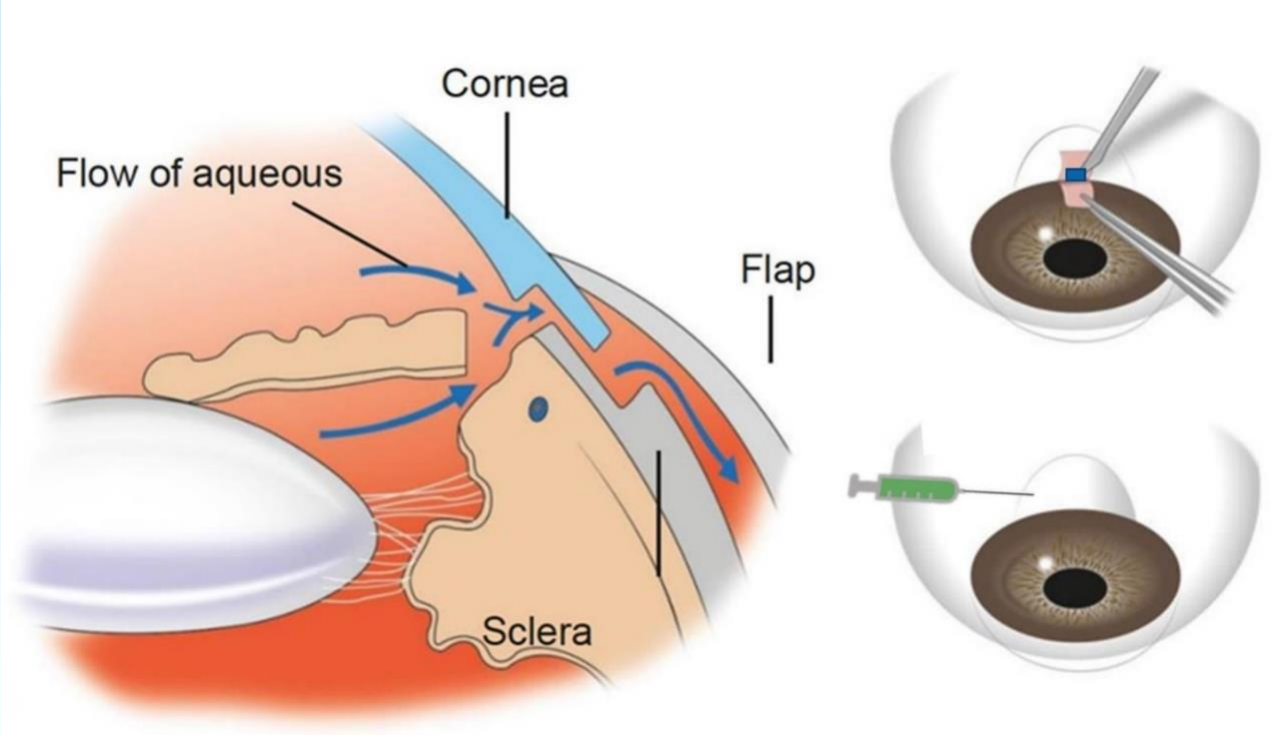
1. vehicle (topical);
2. TA-low dose (topical);
3. TA-mid dose (topical);
4. TA-high dose (topical).
5. TA-high dose (intracameral).

Endpoints: Ophthalmic examination; Draize; Corneal fluorescein staining; Intraocular pressure; OCT; Electroretinography; Histopathology; Toxicokinetics.

Case 2 Subconjunctival Injection for Glaucoma

Background:

- Glaucoma is a common eye condition where the optic nerve becomes damaged. It's usually caused by fluid building up in the front part of the eye, which increases pressure inside the eye. Glaucoma can lead to loss of vision if it's not diagnosed and treated early.
- Trabeculectomy is a type of glaucoma surgery performed on the eye that creates a new pathway for fluid inside the eye to be drained to reduce intraocular pressure (IOP).
- Episcleral and subconjunctival scarring post-trabeculectomy.
- TA will be delivered subconjunctivally after trabeculectomy to prevent fibrosis.
- What should be considered in a pre-clinical safety evaluation?



Consideration for Study Design: (PK/PD+Tox)

- Rabbits

  1) creating a fistula connecting the anterior chamber and the subconjunctival space;

  2) normal
- Subconjunctival injection (100 μL)
- Characteristics of pharmacokinetics (PK) and biodistribution of the TA.
- Modeling group had higher TA concentration in the eye (anterior chamber and posterior segment of the eye).

- Options:

  1) PD+Tox, rabbits, trabeculectomy, four groups

  1. vehicle;
  2. TA-low dose;
  3. TA-mid dose;
  4. TA-high dose.

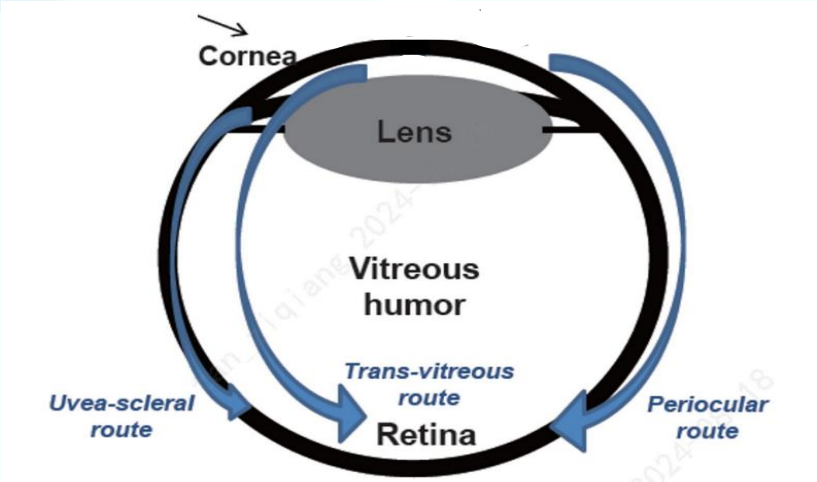
2) Biodistribution of TA does not change significantly in the eye. IND Tox is standard study design in normal animals.

3) Biodistribution of TA changes significantly in the eye. Use normal rabbits and add an alternate ROA group to achieve higher exposure in the eye for IND studies.

Five groups

1. vehicle (subconjunctival);
2. TA-low dose (subconjunctival);
3. TA-mid dose (subconjunctival);
4. TA-high dose (subconjunctival);
5. TA-high dose (intracameral).

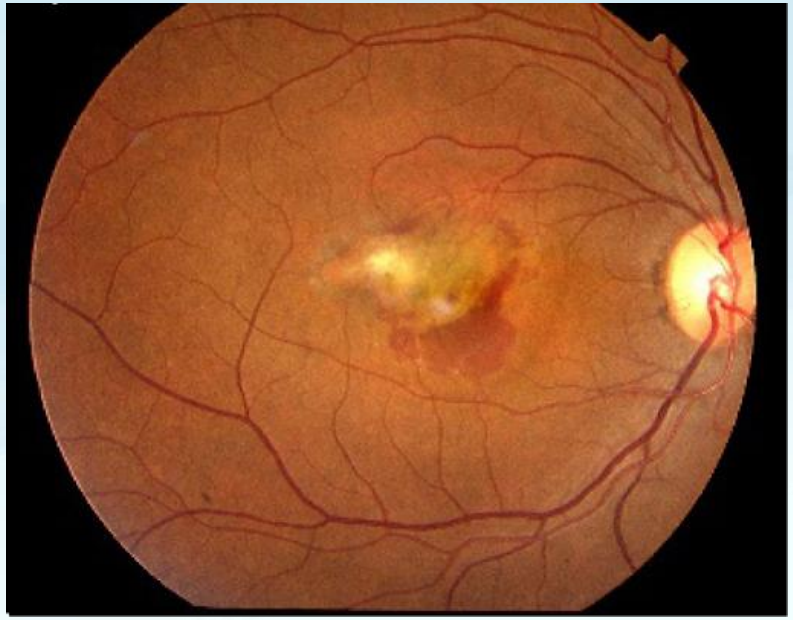
Endpoints: Ophthalmic examination; Draize; Corneal fluorescein staining; IOP; Electroretinography; OCT; Histopathology; Toxicokinetics.

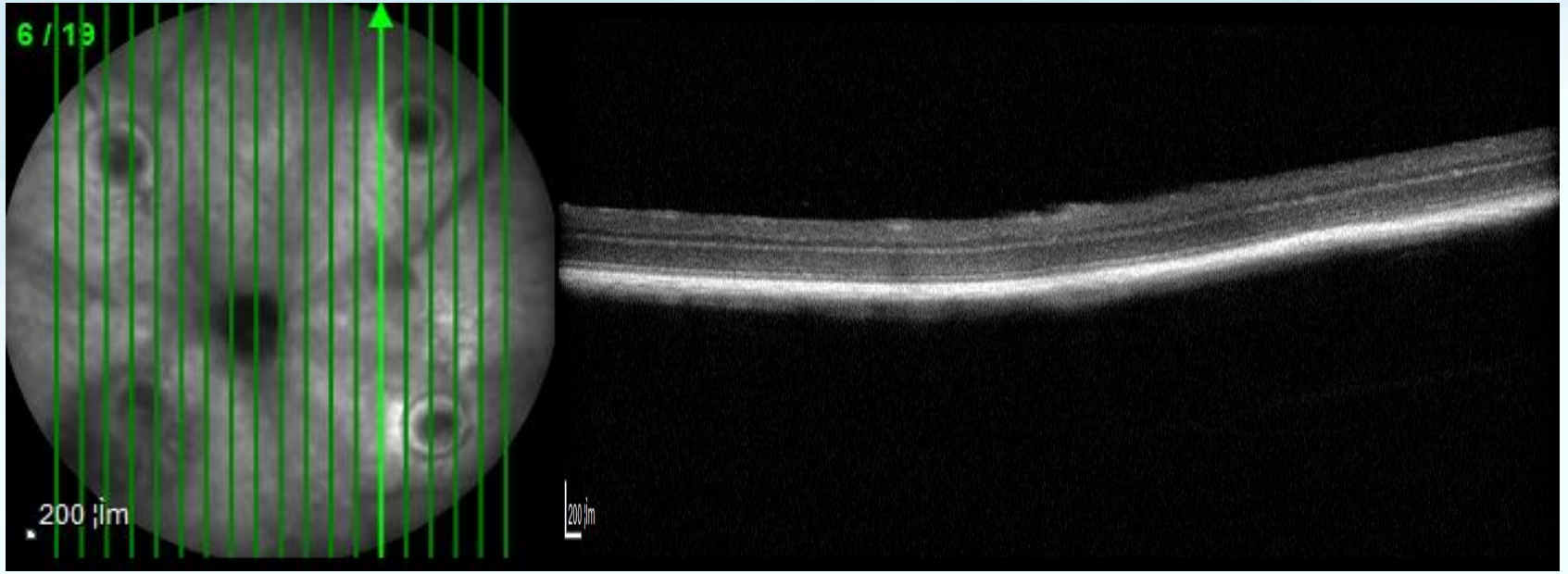


Case 3 Gene Therapy for Wet Age-Related Macular Degeneration (AMD)

Background:

- Wet AMD causes abnormal blood vessels to grow in the back of the eye. These blood vessels can leak fluid and blood, damaging the macula and leading to rapid vision loss
- Laser-induced choroidal vascularization (CNV) model in mice.
- Gene therapy (AAV) used to inhibit CNV development and avoid repeated injection in the eye.
- H-VEGF model mice used.
- What should be considered in a pre-clinical safety evaluation?



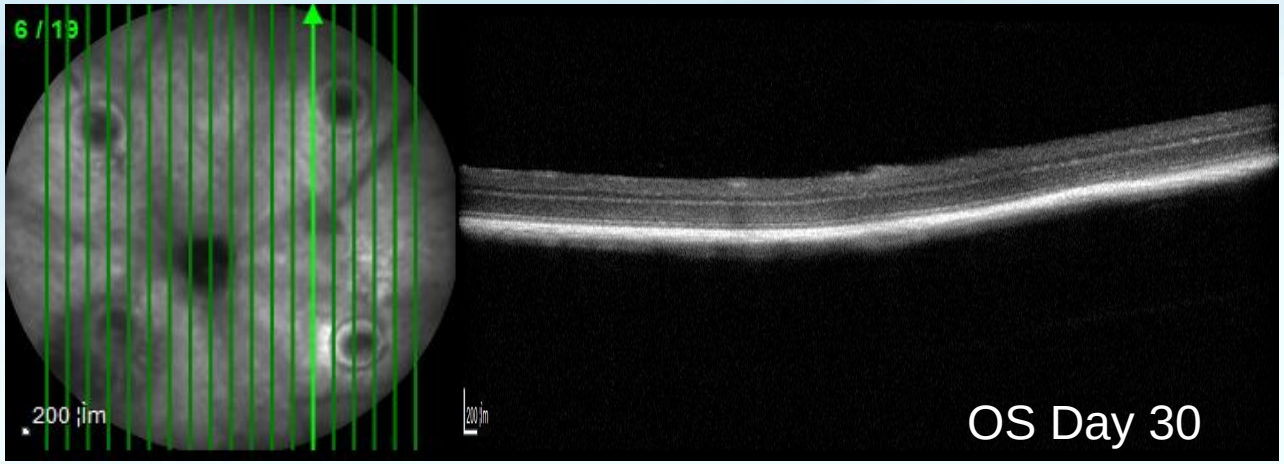


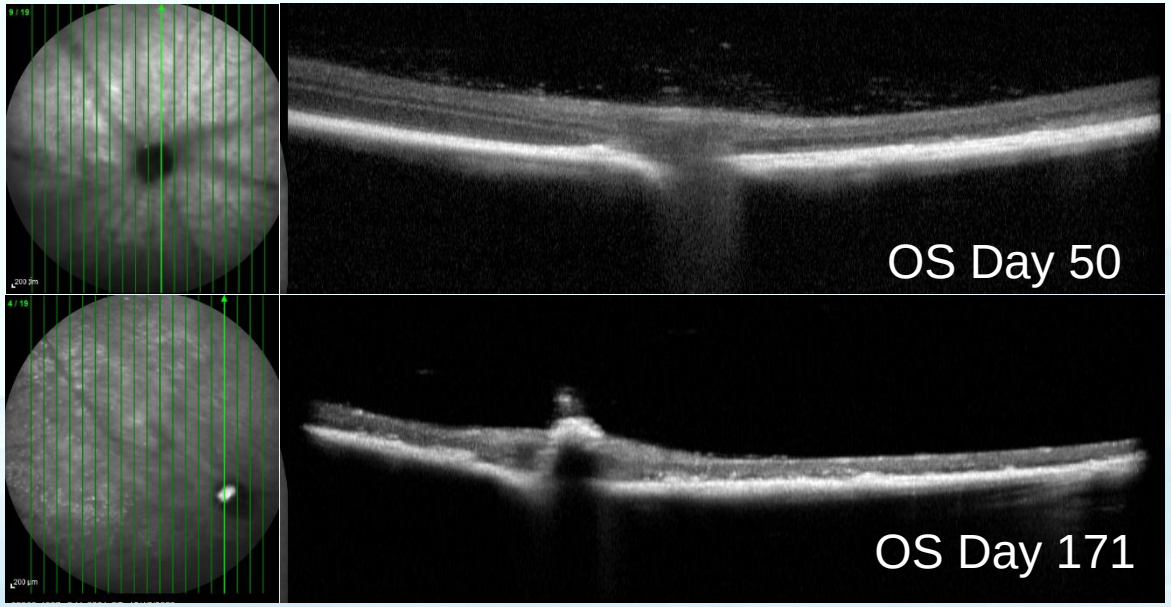
Consideration for Study Design: (BD/PD+Tox)

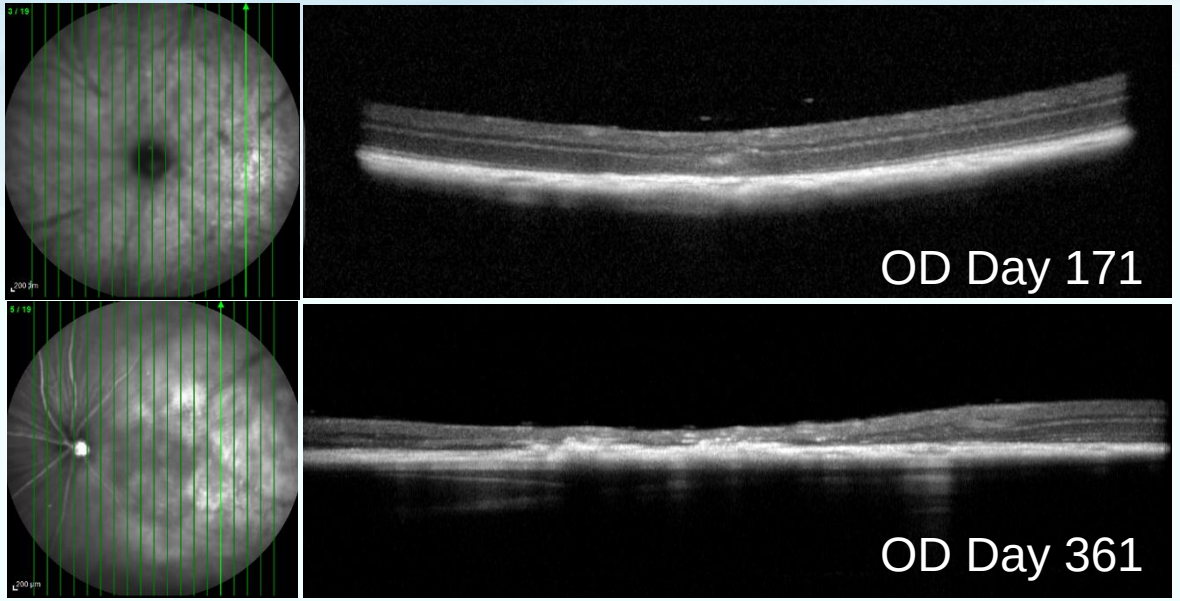
- Subretinal injection, test PD and BD in the retina
- Long-term observation (1 year)
- PD+Tox, h-VEGF model mice, laser-induced CNV in five groups (Day 30 and 340).
    1. vehicle with modeling;
    2. Positive control with modeling;
    3. TA-low dose with modeling;
    4. TA-mid dose with modeling;
    5. TA-high dose with modeling.

Endpoints: Ophthalmic examination; Fundus fluorescence angiography; Intraocular pressure; OCT; Electroretinography; Histopathology; Bioanalysis.

Results:







Case 3 – Options for IND program?

Gene therapy / large molecule combo?

Option 1. The sponsor selected NHPs and rabbits

1) If the sponsor selected normal mice, then rabbits would be better than mice due to more similarities to human eyes and suitable for ocular ROA.

2) In an IND species selection, NHPs meet the relevant species, rabbits are not relevant but can test the non-pharmacological aspects of the TA.

3) Usually sponsors choose option 1 since the genetic mice are expensive and may not meet the product number of the mice in a short period.

4) One relevant species especially NHPs, and one non-relevant species, combinate in an IND program also meet requirements in gene therapy or oligo/nucleotide programs.

Case 3 – Options for IND program?

Gene therapy / large molecule combo?

Option 2. Use h-VEGF A mice and normal monkey

- AAV-directed gene therapy that encodes anti-VEGF; the target of the gene therapy is VEGF.
- Pharmacology studies performed in humanized (h-VEGF) with laser-induced AMD; humanized mice needed to provide the target for the encoded antibody.
- Most AAV gene therapy toxicology studies are done in NHPs.
- IND studies for ocular ROA are not usually performed in rodents. However, gene therapy programs have more flexibility.
- Assuming the NHP VEGF protein is cross reactive/homologous to human VEGF, the NHP is a pharmacologically relevant species for the therapy.
- Do you need pharmacological relevance for this gene therapy? If this gene product is expressed and translated in the eye in order to bind VEGF, don't you need that interaction to occur to assess safety within the eye?
- Would you propose the h-VEGF mouse and the NHP for this program? Or rabbit?
- What do *you* think?

Summary

- Ocular drug development has challenges related to delivery to target cells, incomplete understanding of pathogenesis, and translatability of animal models.
- Early studies using animal models that mimic the patient situation can inform IND-enabling programs and improve translation to the clinic.
- Sufficient exposure can be difficult due to anatomical barriers and compartment sizes.
- Exposure issues can be improved by increasing TA concentration and alternate ROA.

Summary Continued

- IND-enabling study designs of new ocular drugs will depend on the TA type and the specific target cells in the eye.
- Ocular IND programs usually utilize rabbits, minipigs, dogs and NHPs; rodents can also be used and are more commonly used to assess systemic toxicity.
- Always review your IND design with the FDA at your Pre-IND meeting.

Q&A

QUESTIONS