New Strategies to Prevent Posterior Capsule Opacification

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Cataracts

- any opacity of the crystalline lens
  - caused by ageing, ultraviolet irradiation, oxidative stress, metabolic disorders, genetics...
- most common cause of blindness in humans and dogs
Cataracts

- surgical removal of cataracts is the only way to effectively restore vision
- removal of lens fibres and lens epithelial cells (LEC)
- implantation of intraocular lens
Posterior Capsule Opacification (PCO)

- remaining LEC undergo proliferation and migration
- results in a progressive decrease in visual acuity
  - in dogs: 80 – 100% incidence
  - in adults: 30 – 50% incidence
  - in pediatrics: 80 – 100% incidence
Current PCO Treatment

- Nd:YAG laser posterior capsulotomy
- Surgery is not without complications
- Cost!!
- Unsuccessful in dogs
Surgical PCO Prevention Strategies

“power wash” the capsule

Unpublished data. Work performed by Dr. E. Curto, et al. 2013
Surgical PCO Prevention Strategies

- capsular tension rings
- intraocular lens design
Surgical PCO Prevention Strategies

Unpublished data. Work performed by Dr. S Hoy, et al. 2009
Pharmacologic PCO Prevention

• key elements:
  • targeted death of LEC (via programmed cell death)
  • not harmful to the corneal endothelial cells
  • long term efficacy

• ideally, will help to reduce post-operative inflammation
Cyclosporine A

- cyclosporine A (CsA) has varied effects
  - induces programmed cell death in multiple epithelial cell types
  - potent immunomodulator frequently used to control uveitis
  - previously reported to reduce PCO formation in a rabbit model

- serendipity
can intracapsular release of high dose CsA delay or prevent PCO formation ex vivo?
Pharmacologic PCO Prevention

• **Goal:**
  • can intracapsular CsA treatment reduce LEC viability or prevent LEC migration and proliferation?

• **Expected Outcome:**
  • increased rates of cytotoxicity in a dose dependent fashion with daily CsA treatment *ex vivo*
Effects of CsA on LEC

Effects of CsA on LEC

- performed histology on all samples
- count LEC present within four different regions of the capsule
Effects of CsA on LEC

Effects of CsA on Long-term PCO Formation

• unrealistic to imaging lifetime of sustained drug release
• what happens after the drug is no longer present?

Effects of CsA on Long-term PCO Formation

Length of CsA Exposure on PCO Formation

Pharmacologic PCO Prevention

Goal:
- does exposure to high doses of CsA decrease viability in the corneal endothelium

Rationale:
- corneal endothelial cells are the most susceptible to toxicity
- loss of endothelial cells results in corneal edema and impaired corneal function
Effects of CsA on the Corneal Endothelium

viability staining (via trypan blue and alizarin red) is performed on the corneal endothelial cells and percent toxicity is calculated.

- negative control (stain only)
- negative control (vehicle only)
- positive control (toxic MMC)
- 20 µg/mL CsA
- 40 µg/mL CsA
- 100 µg/mL CsA
Effects of CsA on the Corneal Endothelium

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Effects of CsA on the Corneal Endothelium

Unpublished data. Work performed by Dr. E Curto, et al. 2013
Cyclosporine Conclusions & Future Directions

- CsA is capable of pharmacologically preventing PCO formation *ex vivo*
  - dose dependent response
  - acute drug release can prevent cellular repopulation of the capsule
  - negligible toxicity to the corneal endothelium
- does "chronic" exposure to CsA cause harm to the endothelium
- how do we deliver CsA to the lens epithelium *in vivo*?
Intraocular Drug Delivery

• possibilities:
  • topical application
  • scleral implants
  • circulating fluid within the capsule following cataract surgery
Cataract Surgery

- during cataract surgery, viscoelastic material is used
- viscoelastic is commonly left behind in the lens capsule following cataract surgery
Cataract Surgery

- hyaluronic acid (HA) is a main component in viscoelastics
- HA is a large protein that can induce migration and proliferation
if hyaluronic acid induces migration & proliferation...

does exogenous hyaluronic acid induce posterior capsule opacification in vitro?
Hyaluronic Acid & PCO

• **Goal:**
  - to determine if different HA concentrations can alter the rate of proliferation and migration in LEC

• **Rationale:**
  - if migration and proliferation of LEC can be induced by HA, it is possible that introduction of exogenous HA, in surgical viscoelastics, may increase the rate of PCO formation
Hyaluronic Acid Treatment

1.0 mg/mL HA – 16 h
0.5 mg/mL HA – 16 h
control – 16 h

initial appearance

control – 16 h
0.5 mg/mL HA – 16 h
1.0 mg/mL HA – 16 h
Hyaluronic Acid Treatment

LEC Treatment with Viscoelastic
LEC Treatment with Viscoelastic

<table>
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<th>Condition</th>
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LEC Treatment with Surgical Viscoelastic

Hyaluronic Acid Conclusions

• treatment with HA significantly increased LEC migration and proliferation
• surgical viscoelastics containing higher concentrations of HA significantly increased PCO formation *in vitro*
• it is possible that use of viscoelastics intraoperatively could promote PCO formation *in vivo*
Overall Conclusions

- CsA is capable of pharmacologically preventing PCO \textit{ex vivo}.
- Intraocular drug release is not likely to be achieved via release from surgical viscoelastic.
What Does the Future Bring?

• development of alternative intraocular delivery methods via the IOL
What Does the Future Bring?

What Does the Future Bring?

- use of a thermal biodegradable gel to be used for intracapsular drug release
- influence of aqueous humor dynamics
- taking *in vitro* data and translating it to *in vivo*
- further understanding of the mechanism of PCO (and cataract) formation
Acknowledgments

- Elizabeth Curto, DVM
- Rachel Matusow, DVM
- Elizabeth Lutz, DVM
- DJ Haeussler, DVM, MS
- Celeste Quinones, DVM
- David Wilkie, DVM, MS, DACVO
- Brian Gilger, DVM, MS, DACVO
- Anne Gemensky-Metzler, DVM, MS, DACVO
- Miru Thangavelu, MS
- Christie Grieshop, BS
- Tim Vojt, MS

Funding provided by:
- American Kennel Club, Canine Health Foundation
- Acrivet, S &V Technologies AG Hennigsdorf, Germany
- American College of Veterinary Ophthalmologists Vision for Animals Foundation
- Scynexis, Inc.
- Inson Medical Systems
Questions?