Targeted optic nerve head delivery in pig

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INTRODUCTION

- Diseases of the optic nerve head (ONH, such as glaucoma, ischemic optic neuropathy, and metabolic optic neuropathy) are leading causes of vision loss and blindness.
- There are few treatments for optic neuropathies and none directly treat the diseased ONH tissue
- Targeted ONH delivery of therapeutics may enable disease-modifying neuroprotective and/or neuroregenerative strategies in the management of optic neuropathy
- We have developed a drug delivery system that enables targeted ONH delivery in rabbits. Rabbits eye size is on the same order of magnitude as human eye size, but rabbits lack a collagenous lamina cribrosa
- In this study, we further develop a targeted ONH delivery system in pig.

DESIGN & METHODS

- Targeted ONH delivery achieved with Suprachoroidal-to-Optic-NervE (SCONE) delivery in rabbit:

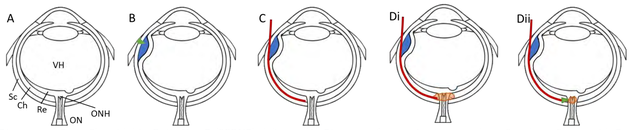
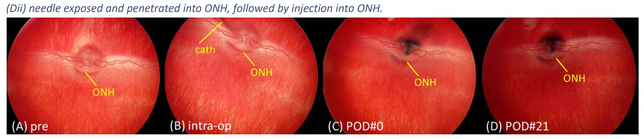


Diagram of SupraChoroidal-to-Optic-NervE (SCONE) delivery. (A) Diagram of eye prior to procedure. Sc-sclera, Ch-choroid, Re-retina, VH-vitreous humor, ON-optic nerve, ONH-optic nerve head. (B) Microneedle used to inject viscoelastic into suprachoroidal space (SCS). (C) Catheter introduced into SCS directed toward ONH. Can either proceed with (Di) injection into peripapillary SCS, or (Dii) needle exposed and penetrated into ONH, followed by injection into ONH.

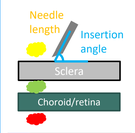


Fundus photo in same albino rabbit (A) before, (B) during, (C) immediately after, and (D) 21 days after SCONE delivery of India ink. ONH = optic nerve head; cath = catheter

- We optimized SCONE delivery in pig by breaking the procedure down into three steps:
  - **Step 1: Entering the suprachoroidal space**
    - Vary microneedle length and insertion angle to determine success in entering the suprachoroidal space
    - Location of microneedle tip (outside eye, within suprachoroidal space, or intravitreal) determined for each condition (N=6 per condition)
  - **Step 2: Passing through the suprachoroidal space**
    - Cut segment of sclera/choroid/retina and introduce catheter tip into suprachoroidal space at one edge and measure distance traveled before penetrating through choroid/retina or up to 20mm
    - Vary catheter bevel angle, presence/absence of sheath around catheter, and catheter gauge (N=6 per condition)
  - **Step 3: Delivery into or around the optic nerve head.**
    - 8-mm trephine to isolate optic nerve head and introduce catheter tip into suprachoroidal space.
    - Vary catheter bevel angle and presence/absence of sheath and inject fluorescent particles (N=6 per condition)
    - Snap freeze eye and use cryostat to section through eye every 200um

RESULTS

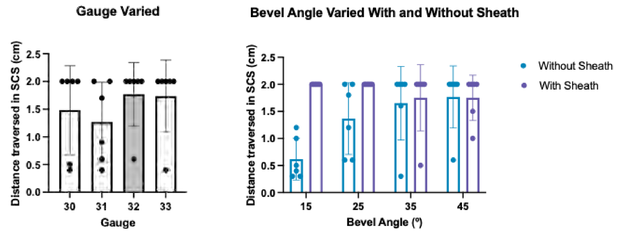
Step 1: Parameters affecting microneedle injection into suprachoroidal space



Needle length (µm)	90°	71.5°	60.9°	52.1°	45°
0	V	V	V	V	V
400	V	V	V	V	V
800	V	V	V	V	V
1200	V	V	V	V	V
1600	V	V	V	V	V
2000	X	V	X	O	O
2400	X	X	X	X	X

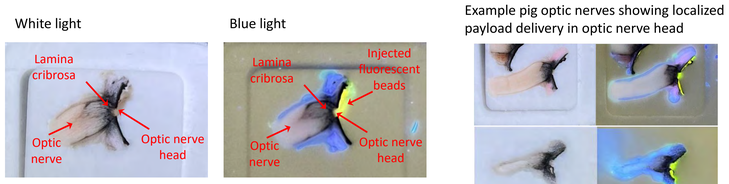
By varying microneedle length and insertion angle, we found that needle length of 2000um and insertion angle of 45° was successful in accessing the suprachoroidal space of pig.

Step 2: Parameters affecting traveling through suprachoroidal space



By varying catheter gauge, catheter bevel angle, and presence/absence of sheath, we were able to maximize passage through the suprachoroidal space with a catheter gauge of 32G and catheter bevel angle of 45°.

Step 3: Parameters affecting delivery to optic nerve head



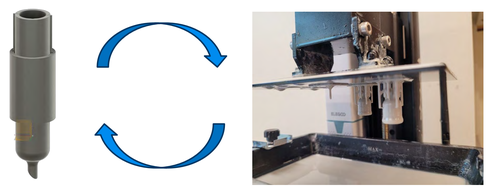
Example pig optic nerves showing localized payload delivery in optic nerve head

Catheter angle (°)	Sheath? yes	Sheath? no
15°	83%	50%
35°	83%	100%
45°	100%	100%

By varying catheter bevel angle, and presence/absence of sheath, we were able to maximize delivery to optic nerve head tissue while minimizing delivery to retrolaminar optic nerve and intravitreally with a catheter bevel angle of 45°.

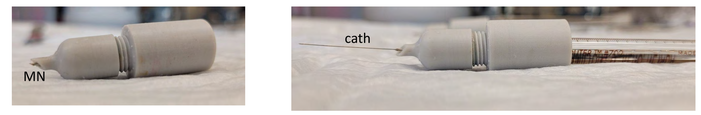
Step 4: Putting it all together

(LEFT) Computer-Aided-Design (CAD) design of SCONE injector combined the parameters identified in Steps 1-3, and (RIGHT) a SCONE injector was 3D printed with an SLA 3D printer. The design was iteratively improved.

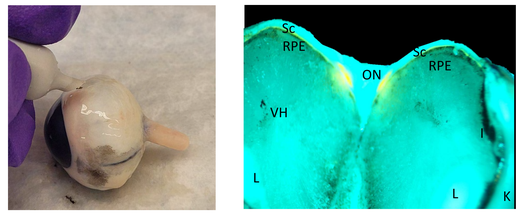


RESULTS

Ex vivo pig eye after SCONE delivery of fluorescent particles



(LEFT) Custom SCONE injector with microneedle of length and insertion angle determined in Step i. (RIGHT) Catheter inserting through lumen of microneedle with catheter gauge, catheter bevel angle, and catheter length determined in Step ii and iii. MN=microneedle; cath=catheter



(LEFT) Ex vivo pig eye of SCONE delivery being performed with injector. (RIGHT) After SCONE delivery performed with custom injector. Note that fluorescence is targeted to optic nerve head and trace fluorescence is between sclera and pigmented RPE in suprachoroidal space. Eye was frozen after injection and cut in half longitudinally and both sides are shown. Sc=sclera; RPE=retinal pigment epithelium; VH=vitreous humor; ON=optic nerve; L=lens; I=Iris; K=cornea

CONCLUSIONS

- Targeted optic nerve head delivery in rabbits and pig has been successfully achieved with SCONE delivery.
- Further validation *in vivo* and determination of VEP changes with SCONE delivery are needed.
- Targeted ONH delivery of therapeutics may enable disease-modifying neuroprotective and/or neuroregenerative strategies in the management of optic neuropathy.

NEXT STEPS

- Further develop and validate targeted ONH delivery strategies, including SCONE and others.
- Identify therapeutic compounds that may require targeted delivery to treat animal models of optic neuropathies.
- Apply for R01 funding to investigate targeted delivery of therapeutic compounds in animal models of optic neuropathy.

ACKNOWLEDGEMENTS

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OO, KH, RD, YL, DM, JLG have no disclosures to report.