A New Paradigm for Treatment of Glaucoma

Robert L. Galloway IEEE Fellow, Michael Delisi, Eva M. Harth, and Louise A. Mawn

***Abstract*—Glaucoma is the leading irreversible cause of blindness in the world. We are developing a new image-guidance system to deliver a neuroprotective drug in a controlled release nanosponge. The system consists of a magnetically tracked image-guidance system, the nanosponge material and the drug. We have characterized the performance of each aspect in phantoms, animals and ex-vivo human tissue.**

I. Introduction

Optic neuropathies occur when the optic nerve is damaged causing a functional loss. The majority of optic neuropathies: glaucomatous, ischemic, traumatic, and Leber's hereditary optic neuropathy have, at present, no viable therapeutic options. Glaucoma, which for years has been treated as a disease of hypertension of the globe, was recently identified by the National Eye Institute (NEI) as a *neuropathy* with the following statement:

> **"On the basis of the recommendation from both this workshop and the NAEC (National Advisory Eye Council) that glaucoma be viewed as an optic neuropathy and be studied within that context, the Program will be expanded to include research on all optic neuropathies."**

This addresses the reality that with present treatments of glaucoma, visual field loss and retinal ganglion cell (RGC) death continue despite well-controlled intraocular pressure.[1,2] While the system under development could have application for all neuropathies and even for certain forms of macular degeneration, we focus on glaucoma.

It is estimated that more than 2.2 million Americans have glaucoma, approximately 70 million worldwide. While cataracts are the number one cause of blindness, that is reversible. Glaucoma is then the number one irreversible cause of blindness. Glaucoma has progressed to blindness in 120,000 living Americans and roughly 8 million living worldwide. Present therapeutic progresses can slow the progression of glaucoma but even with perfect therapeutic compliance 27% will progress to blindness. Most of the length of the optic nerve axons resides behind the eye presenting a significant challenge for drug delivery. Eye drops applied to the front surface of the eye are attenuated by tear turnover, corneal epithelium barriers and drainage. Geroski and Edelhauser [3] estimate that less than 5% of a topically applied drug reaches intraocular tissue. Intraocular, intravital or peribulbar injections can increase the availability of intraocular drugs but have both a significant complication rate and patient resistance [4,5]. And these studies do not address the issue of getting drugs into either the macula or the optic nerve.

Since the exact mechanism of the nerve damage is unknown, a new approach, neuroprotection, has been developed for treatment of optic neuropathies. The goals are to protect undamaged RGCs and their axons and to rescue their injured counterparts. Many candidate therapies have been successful in animal models of acute and chronic neurodegenerative processes of the optic nerve and tremendous effort continues in pursuit of translating this success to clinical trials [5,6].

While a number of drugs have shown optic neuroprotective properties [7,8] there have been challenges in their delivery to the eye. Local administration such as topical drops or injections such as sub-conjunctival, sub-Tenon's, and intravitreal injections either deliver low concentrations, have a significant complication rates [4] or poor patient compliance. Systemic administration of many potential neuroprotective therapeutics will frequently be prohibited by the side effect profile given the high, frequent dosing required to overcome barriers to CNS and ocular tissues [8].

Our work was to develop a minimally-invasive, safe, quick-to-learn method of delivering a drug aliquot to the retrobulbar space. By developing such a drug delivery we hypothesize that we can get higher concentration of the drug in the optic nerve without a significant circulating concentration. In addition we believe that the clinical impact will be magnified if we can develop a sustained release mechanism which would then minimize the need for frequent refreshment of the aliquot.

II. Methods

A. Approach

The system is composed of a magnetically tracked endoscope coupled with the delivery of nanoparticle encapsulated neuroprotective drug. We have several investigational steps which had to be performed prior to human application.

Research supported by in part by the Research to Prevent Blindness Physician Scientist Award, the Unrestricted Grant from Research to Prevent Blindness to the Vanderbilt Eye Institute, and the NIH under Grant R21 RR025806.

RL Galloway and Michael Delisi are with the Vanderbilt Dept. of BME, Nashville TN (615-343-8102; fax 615-343-7919; email bob.galloway@vanderbilt.edu) (email: michael.p.deLisi@vanderbilt.edu). Eva Harth is with the Vanderbilt Dept. of Chemistry (email: eva.m.harth@vanderbilt.edu).
Louise Mawn is with the Vanderbilt Dept. of Ophthalmology (email: louise.a.mawn@vanderbilt.edu)

B. Tracked Endoscope.

Working with collaborators from Northern Digital Inc (Waterloo, Ontario, CA) and Karl Storz (El Segundo, Ca.) we embedded an Aurora® 6 DOF PCB Sensor in the distal end of a 3.9mm x 24cm flexible hysteroscope. The computer system is a MainGear custom built computer with a Eusys Piccolo frame grabber card and NVIDIA GTX GPU. The video input is a Storz DXII telecam system connected to a single chip Telecam head. Please see Figure 1.

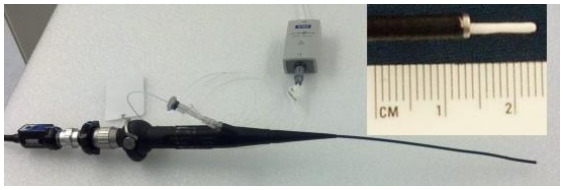

Figure 1. Flexible endoscope with magnetic sensor inserted down the working channel. The box in the upper right corner shows the sensor protruding slightly from the scope.

C. Nanosponge controlled release

The nanosponge (NP) delivery system is derived from a known FDA-approved polymer backbone. Such polyesters are based on the valerolactone family and are connected through a network architecture that advances controlled drug release, kinetics, adjustments of size and drug loading capacity. The optimized delivery system was developed to overcome the limitations of widely known drug delivery particles such polyglycolic lactic acid (PGLA). The novel cross-linked connectivity of the nanosponge gives less crystalline particles and therefore have a higher degree of solubilization *in vivo* and contributes to the lower toxicity level of already established systems. Standard MMT cell viability assay showed a lower toxicity of the novel nanosponges than the FDA-approved PGLA degradable nanoparticles systems and those applied in tissue engineering. Another significant advantage of the NP over current drug release systems is that linear release rate can be tailored. This was pioneered for the nanosponges. [9,10]. All other known sustained delivery systems release the drug in a non-linear kinetic, known as the "burst" effect and leads to a fast release of the drug in the first 48 hours. Here, a meaningful clinical protocol cannot be developed. The nanosponge delivery system shows release profiles that can be individually tailored with one particle type of a specific crosslinking density or mixing particles of the same size in different quantities and crosslinking densities to give fast, medium and slow release as seen in Figure 2. Moreover, they show a linear release profile in contrast to known established degradable release systems that cannot be tailored towards specific release kinetics and lack a zero-order drug release kinetic. The tailored linear release offers to "personalize" for the first time drug delivery systems together with the increased efficacy of the drug. Clinical protocols can be developed that are tailored towards the drug released at a given time. Single and combination therapies can gain a higher efficacy. In addition, drug resistance, created by over or underdosing, can be limited. In our previous application of NP to cancer treatments, successful *in vivo* studies have been undertaken to attack several tumor types with a five times higher efficacy in comparison to traditional chemotherapy. [11] These promising results have encouraged us to apply the nanosponge to other diseases that require a controlled release and high efficacy of a drug as in the treatment of glaucoma.

So far we have tested one distinct particle size of 50 nm with brimonidine as the drug incorporated. Brimonidine is our first choice because of its ability to function as a neuroprotective as well as reducing the intraocular pressure. Since the preliminary data suggested that the drug is released and then crosses the dura, we hypothesize that we can optimize the drug delivery system towards larger particles and prepare a panel of nanoparticle sizes of 50, 400 and 700 nm. The larger sizes afford a higher drug loading and the direct delivery with the endoscope to the retrobulbar region, targets the particles for drug release. In preliminary studies we have verified that the loading capacity is increased as the particles get larger and is also depended on the chosen crosslinking density and chemical nature of the incorporated drug. Please see Figure 2.

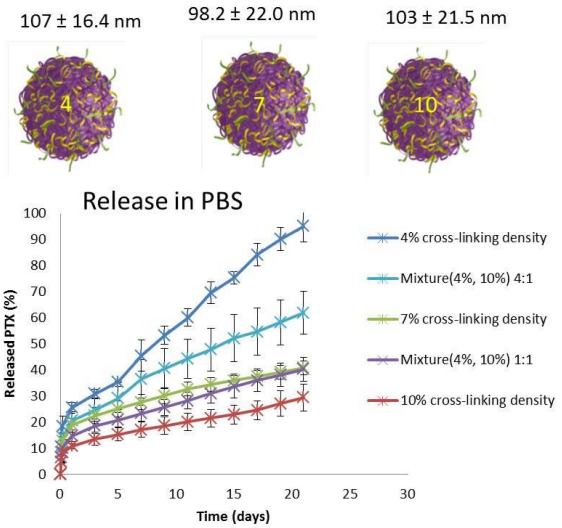

Figure 2 Cumulative release of individual and a mixture of particles loaded with paclitaxel with crosslinking densities of 4%, 7% and 10% measured in PBS. [10]

D. Experiments

We have guidance experiments on phantoms and in a living animal model. We have a drug transfer experiment in ex-vivo human tissue. The phantom experiments consist of a an anthropomorphic skull phantom with a silicon eye and a 3 mm diameter cord serving as an optic nerve surrogate. The retrobulbar area is filled with white stellate beads which both obscure the visualization of the target and yet can be parted by standard endoscopic insufflation gases. Also in the retrobulbar space there are four differently colored stellate beads one of which has been treated with barium (the target) to make it lucent on a CT scan. In a series of experiments we measured accuracy of finding the target, average time to target with image guidance and with a video augmentation.

In an additional experiment we measured the forces exerted by the endoscope on the optic nerve surrogate.

After the phantom experiments we tested the accuracy and time to target of a skilled user in a living animal model. Here two small vials were placed in the retrobulbar space of the animal model in an IACUC approved trial. One of the bulbs contained MR contrast agent, the other did not. The

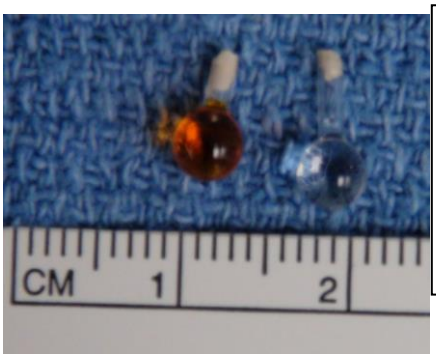

Figure 3. Microsphere bulbs filled with dyed and clear solutions.

relationship of visible color to contrast agent was blinded from the surgeon. See Figure 3.The challenge to the surgeon was to use the guidance system to reach the MR lucent target and report the color.

One question to be addressed was whether a drug delivered to the outside of the optic nerve dura could cross the dura and enter the optic nerve. We tested this with a two chamber system. The chambers were separated by a sample

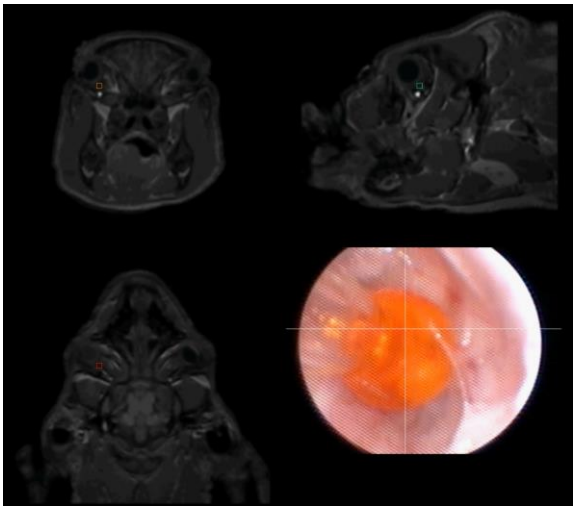

Figure 4: Screen capture of guidance system as target is found.

of human dura acquired during a therapeutic enucleation. Then our first trial drug, brimonidine, was placed in the donor chamber and its concentration was tracked via serial samples and a UV-vis spectrophotometer.

III. Results.

We have reported before on the value of image guidance in this application [12]. One of the strongest findings was the learning curve demonstrated by surgeons at every training level. So the for experiment where we have added video augmentation to the image guidance we reduced the number of surgeons to 16 but gave them 8 trials each.

As reported in [13] using video augmentation resulted significantly (p = 0.02) faster average times and less "searching" by the surgeons.

The next step was to take this to trial in a live animal. The biggest hurdle in validating such a process is establishing a target [14]. Because the fat and the optic nerve can move, a rigid object cannot be attached to them.

Placing a target anchored to the bone makes the task artificially easy. We elected to "float" one of the microspheres shown in Figure 3 and to task the surgeon with finding it and report its color. Our animal model was porcine.

Figure 4 shows a screen capture from the experiment. The upper and lower left quadrants are cardinal plane MRI images. Probe location is shown by the box and the endoscope image is live in the lower right quadrant. In it the microsphere can be seen.

Figure 5 shows a box plot of the results of time to target with a significantly ($p<0.02$) reduced result with the augmented guidance. This work is covered in greater detail in [15].

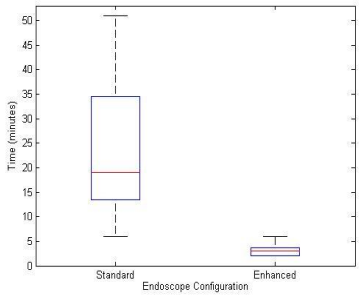

Figure 5. Transorbital procedure times in pigs, with and without enhanced endoscopy

We also examined the pressure effects of introducing an endoscope into the orbit. Although this has been done clinically in several cases [16-18] there has not been a rigorous testing. Since our intent is the preservation of sight we wanted to measure the pressures on a optic nerve phantom. Our phantom was designed in such a manner as to give us a worst-case measurement. Figure 6 shows our

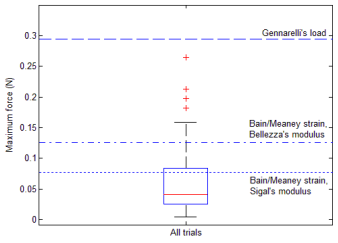

Figure 6: Boxplot of maximum force observed over all trials with reference to injury thresholds

results compared to other published measures values.

This work is explored in detail in [19].

So we can rapidly and safely guide our device to be adjacent to the optic nerve in order to deposit a time release drug. Our two chamber experiment allowed us to determine

if the drug would cross the human dura. These results are shown in Figure 7 and described more explicitly in [19].

A second time/concentration experiment was run with nanoparticle encased drug. Here we saw very similar results with 2.3 times increase in the time constant, entirely consistent with the controlled release properties of the nanosponge.

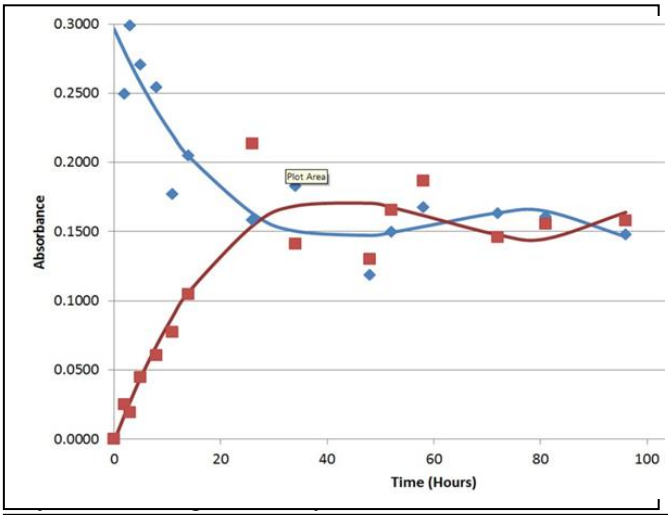

Figure 7 – Time /Concentration curves for human dural diffusion. The red line is the receiver concentration and the blue line is the donor chamber concentration.

measure uptake and distribution in the optic nerve of an animal. It is expected that by the August meeting we will be able to show these results.

If that trial proves successful, we will begin the process of getting clearance for human testing.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of Martha Ingram, Debbie Deskins, Dahl Irvine, Amy Nunnally, Jamie Yates, Dr. Seth Smith and Phil Williams.

REFERENCES

[1] Levin LA. "Axonal loss and neuroprotection in optic neuropathies." *Can J Ophthalmol*. 2007;42:403-408.

[2] Bessero AC, Clarke PG. "Neuroprotection for optic nerve disorders". *Curr Opin Neurol*. 2010;23:10-15.

[3] Geroski DH, Edelhauser HF. "Drug delivery for posterior segment eye disease". *Invest Ophthalmol Vis Sci. 2000;* 41:961–*964.*

[4] *Current Opinion in Ophthalmology*: May 2010 - Volume 21 - Issue 3 - p 178–183.

[5] Baltmr A, Duggan J, Nizari S, Salt TE, Cordeiro MF. "Neuroprotection in glaucoma - is there a future role?" *Experimental Eye Research*. 2010;91:554-566.

[6] Cheung W, Guo L, Cordeiro MF. "Neuroprotection in glaucoma: drug-based approaches". *Optom Vis Sci.* 2008 Jun;85(6):406-16.

[7] Saylor M, McLoon LK, Harrison AR, Lee MS. Experimental and clinical evidence for brimonidine as an optic nerve and retinal neuroprotective agent: An evidence-based review. *Arch Ophthalmol*. 2009; 127: 402-406.

[8] Diebold Y, Calonge M. Applications of nanoparticles in ophthalmology. *Prog Retin Eye Res*. 2010;29:596-609.

[9] Van der Ende A.E., Kravitz E. J., E. Harth, *J Am Chem Soc*, 2008, 130, 8706-8713.

[10] Stevens D.M., Gilmore K.A, Harth E. "An assessment of nanosponges for intravenous and oral drug delivery of BCS class IV drugs: Drug delivery kinetics and solubilisation, *Poly. Chem*, 2014 , Asap

[11] Passarella R. J., Spratt D. E., van der Ende A. E., Phillips J. G., Wu H. M., Sathiyakumar V., Zhou L., Hallahan D. E., Harth E., Diaz R. *Cancer Res* 2010, *70*, 4550.

[12] Ingram ME, Atuegwu NC, Mawn LA, Galloway RL, "Transorbital Therapy Delivery – Phantom Testing" *Proc SPIE 7964. Medical Imaging 2011*. KH Wong DR Holmes (eds)

[13] Delisi MP, Mawn LA, Galloway RL "Image-Guided Transorbital Procedures With Endoscopic Video Augmentation" International Journal of Medical Physics Research and Practice. In Review

[14] Robert L. Galloway, Michael P. DeLisi, Louise A. Mawn, Validation of targeting accuracy in a non-rigid milieu IJCARS June 2013, Volume 8, Issue 1 Supplement, pp 209-212

[15] DeLisi MP, Galloway RL, Mawn LA. Transorbital Targeted Navigation in the Porcine Model with Endoscopic Video Augmentation . IJCARS in review

[16] Mawn LA, Shen JH, Jordan DR, Joos KM. Development of an Orbital Endoscope for Use with the Free Electron Laser Ophthalmic Plastic & Reconstructive Surgery: (2004) Vol 20. No. 2. pp 150-157

[17] Rivkin MA, Turtz AR, Morgenstern KE. Transorbital endoscopic removal of posterior lateral orbital mass. *Laryngoscope*. 2013 123(12):3001-4.Luxenberger W, Stammberger H, Jebeles JA, Walch C.Endoscopic optic nerve decompression: the Graz experience. *Laryngoscope*. 1998 Jun;108(6):873-82.

[18] Delisi MP, Mawn LA, Galloway RL" Characterization Of Optic Nerve Impacts During Transorbital Endoscopic Interventions" Journal of Medical Devices. In review.

[19] Grove KS, Dobish J , Harth EM, Ingram MC, Galloway RL, Mawn LA. Trans-meningeal Drug Delivery to Optic Nerve Ganglion Cell Axons Using a Nanoparticle Drug Delivery System. *Experimental Eye Research* Vol. 118, January 2014, Pages 42–45.