

# Investigational platforms deliver site-specific treatment

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THE ideal pharmacological treatment for chronic retinal diseases would provide site-specific, controlled, sustained delivery of the intended drug to minimise systemic exposure using technology that could be introduced in a minimally invasive procedure.

Research presented at the annual meeting of the Association for Research in Vision and Ophthalmology indicates various groups of investigators are making significant progress toward reaching that goal with their development of innovative delivery platforms.

Investigators at the Doheny Retina Institute, Keck School of Medicine, University of Southern California, Los Angeles, have been working in collaboration with researchers from SurModics, Eden Prairie MN, to optimise a subretinal drug delivery system that can provide sustained, targeted exposure of ocular tissues to therapeutic drug concentrations.

They have been evaluating several prototypes constructed from various materials and of different designs, and they have also been experimenting with different surgical techniques to identify the most successful approach for implantation.

"Based on the studies completed to date, we have demonstrated it is feasible to surgically implant one of these devices using a fairly straightforward procedure. Moreover, both the biodegradable and non-biodegradable materials we are investigating appear very well tolerated in the subretinal space and are performing as predicted to deliver a drug over a sustained period of time," said Signe E Varner PhD, Director of Research and Development, Ophthalmology, SurModics.

The materials used for the prototype systems include both flexible biodegradable materials (polycaprolactone) embedded with a drug and a rigid backbone (Nitinol) covered with a non-biodegradable polymer-based drug coating. They have been fabricated into rod-shaped

devices that have been implanted through a sclerotomy accessed via a superior conjunctival peritomy.

The implantation has been performed both with and without vitrectomy and by preparing the implantation site either by creating a local retinal fluid detachment, a retinotomy, or using the implant tip itself first to puncture the retina and then act as a tunnelling device.

Stability of the implanted devices and damage to adjacent tissue were studied over four weeks using fundus photography, fluorescein angiography, and optical coherence tomography in the live animals and then after the eyes were collected for histological evaluation.

"Our studies indicate each of the approaches we evaluated has its own advantages and disadvantages. However, all have been generally safe as we have noted only some limited photoreceptor damage in the area directly overlying the implant, but no problems with subretinal fluid accumulation, exudate formation, haemorrhage, local fibrosis, inflammation, or migration," Dr Varner reported.

## Vitrectomy improves outcome

She noted that implantation was easiest and associated with the most reproducible results when the surgery included vitrectomy and creation of a subretinal fluid detachment. Retinotomy didn't improve surgical outcome.

"We found vitrectomy useful because the vitreous in the rabbit eye was an unforgiving mucous-adhesive barrier that complicated precise positioning of the subretinal implant," Dr Varner said.

With respect to materials and design, the flexible implants had the benefit of allowing conformal positioning in the subretinal space and allowed use of implant lengths between 2.0 and 2.5 mm without risk of epiretinal protrusion. Incorporation of a tapered tip was found essential for facilitating implantation when the device was used for self-starting a retinotomy. The more rigid Nitinol devices were easier to implant

relative to the more flexible devices, but were associated with a risk of penetration into deeper tissue layers.

"We are still becoming familiar with the different techniques and each will be evaluated further, but it appears we can improve the accuracy of placement with the rigid implants by creating a subretinal bleb," Dr Varner said.

The group also presented drug elution data which demonstrated the ability to achieve sustained release of both triamcinolone and sirolimus with this technology. Drug loading of the implants was performed using different polymer formulations that offer either fast or slow release profiles.

The amount of drug released over time was determined by using reverse phase HPLC to analyse the remaining content in devices explanted after 30 days. The results showed the devices performed as predicted in delivering their drug contents, and that with the use of the slow release polymer, implants could be constructed that would deliver approximately half of their medication load over 30 days, Dr Varner reported.

"Those data suggest this initial prototype could be used to provide sustained drug delivery for a period of several months," she said.

Currently, the researchers are moving forward to optimise the specifications for a commercially viable device. They are defining appropriate release characteristics and toxicity profiles as well as deciding what drugs to incorporate in the system.

## Refillable episcleral drug delivery device

Researchers from Johns Hopkins University, Baltimore MD, and their corporate partners at Targeted Therapy Technologies LLC, Irvine, CA, reported on their project to create a refillable episcleral drug delivery device intended to provide unidirectional and controlled transscleral drug administration. The implantable system encapsulates the drug in a reservoir that is sealed to the scleral surface so that only the target tissue (the sclera) is exposed to its contents.

Studies performed so far demonstrate that prototype

devices constructed of polyethylene or silicone elastomer can be fit onto the eye securely enough to avoid drug leakage into the periorbital space and without development of encapsulation of the drug diffusion window that would alter the kinetics of drug delivery.

"The results from these early experiments are promising in suggesting that this technology might be used to provide safe and effective control of intraocular pharmacokinetics after periorbital delivery" said Ricardo A P de Carvalho MD PhD Wilmer Eye Institute, Johns Hopkins University, Baltimore.

The devices were designed to fit onto the scleral surface of infant and adult eyes. Dimensions of the system were based on measurements in eyes enucleated for treatment of retinoblastoma and simulation of fit in its positive moulds.

## Laboratory studies

The researchers conducted studies investigating the adequacy of the seal and episcleral drug delivery in rabbit eyes using devices loaded with agents that could be detected by CT imaging (iohexol or carboplatin) or by fluorescence microscopy (sodium fluorescein or FITC-dextran 10 KDa). Control eyes received periorbital injections with the same compounds. After those studies were completed, the eyes were enucleated for histological evaluation to characterise biocompatibility.

Imaging studies performed up to three weeks after placement of the episcleral drug delivery device revealed that the signal contrast from the reservoir decreased over time but could be detected during the entire follow-up. Those findings were in contrast to the outcomes in the control eyes in which the injected material was only diffusely detectable after three hours and had disappeared by 24 hours.

The fluorescence microscopy studies demonstrated target specific delivery was achieved with higher concentration of the fluorescent material observed within the sclera, choroid, and retina overlying the implant whereas there was much greater loss of the injected

material through the periorbital space in the control eyes, Dr de Carvalho reported.

Histology evaluation of enucleated eyes up to three months after implantation demonstrated the biocompatibility of the system and absence of encapsulation of the drug diffusion window by inflammatory membranes or fibrotic tissue.

"The materials that we are using to construct the episcleral delivery devices have a long history of use in retinal detachment surgery and we know they are well-tolerated. However, our concerns with biocompatibility relate to the potential for encapsulation of the drug diffusion window as that could alter drug delivery over time. So far, it appears that problem can be prevented if the device is sealed to the eye so that only the reservoir is exposed to the sclera," Dr de Carvalho said.

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