The approval of vascular endothelial growth factor (VEGF) inhibitors Macugen® (2004) and Lucentis® (2006) by the United States Food and Drug Administration to treat age related macular degeneration paved the way for the development of numerous other therapeutic agents including VEGF Trap, VEGF siRNA, and receptor tyrosine kinase inhibitors to inhibit VEGF and a variety of other growth factors implicated in retinal neovascular disorders. Recently, sphingosine 1 phosphate receptor 2 (S1P2R) has been implicated in the retinal pathological angiogenesis (1), indicating the potential usefulness of S1P2R inhibitors in treating retinal neovascular disorders. In addition, amyloid-beta peptides have been shown to be associated with optic nerve damage, suggesting the potential usefulness of anti-Alzheimer drugs in treating glaucoma associated optic nerve damage (2). Eye is the first organ for the introduction of novel nucleic acid based drugs such as antisense oligonucleotides (Vitravene®, 1998) and aptamers (Macugen). Potentially, it will also be the first organ for the application of siRNA therapeutics. While the new targets provide great opportunities in developing new drug candidates for treating disorders of the back of the eye, safe, efficient, and patient friendly drug delivery over prolonged periods is rate-limiting for the development of any new drug candidate.

Interestingly, a variety of innovative drug delivery systems were first introduced for ophthalmic applications. The examples include Ocusert® (1974) placed in the conjunctival cul-de-sac for constant release of pilocarpine for 1 week; Vitrasert® (1996) placed surgically in the pars plana area of vitreous for constant release of ganciclovir for about 6 months; and Retisert® (2005), smaller but similar to Vitrasert for constant release of fluocinolone acetonide for about 2.5 years, to name a few. An intravitreally injectable, biodegradable implant is currently undergoing Phase III Clinical trials in the USA for treating persistent macular edema. This implant sustains dexamethasone delivery for about 5 weeks and the effects for 6 months (Posurdex®). Injectable non-degradable implants (Medidur®) are also under development for sustaining drug release for a few years. Despite the advances, all the above approaches intended for the treatment of the back of the eye require intravitreal administration. Some of the above systems require surgical administration and removal (Vitrasert® and Retisert®). Others employ non-degradable, injectable systems that might remain in the eye for years (Medidur®). All delivery systems require repeated administrations at some frequency. With such repeated administrations, the complications associated with the procedures including cataracts, endophthalmitis, and retinal detachment escalate. Indeed, several of the above systems, while efficacious, suffer from safety concerns due to administration procedure, drug, or device.

Transscleral drug delivery to the back of the eye is considered a safer alternative to repeated intravitreal injections (3). This route, although more efficient in drug delivery compared to systemic or topical routes in general, is much less efficient than intravitreal route for retinal drug delivery. Modifications of the above non-degradable systems, tailored for unidirectional drug release towards the sclera are useful in enhancing and sustaining transscleral drug delivery. An alternative to non-degradable delivery systems is the use of biodegradable nanoparticles and microparticles encapsulating the drug of interest in the periocular region for transscleral delivery (3). Such systems do not require surgical placement. Due to their degradable nature, they do not require removal after the drug release is com-

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These particulate systems are particularly useful for drugs that are rapidly cleared from the site of administration. While small 20 nm particles are removed rapidly from the periocular site of administration, particles of size 200 nm and above are retained for prolonged periods and allow sustained transscleral drug delivery to the retina for a few months (4,5). Drug containing nanoparticles and microparticles can be prepared using biodegradable carriers including synthetic polymers, albumin, and lipids (6). However, a precise control of drug release from these systems over prolonged periods is more difficult.

In general, for sustaining drug release over prolonged periods, larger delivery systems are better than smaller systems (i.e., non-degradable implants are better than microparticles, which are better than nanoparticles). If the goal of the therapy is to increase cellular uptake, and if the drug by itself does not have adequate cell penetration, nanoparticle approaches would be particularly useful (7). Nanoparticle systems, while capable of enhancing the delivery of poorly permeable molecules, may not enhance the uptake of well permeable drugs. However, they can reduce the clearance of macromolecules as well as small molecules from within the cells or tissues. When topically administered as an eye drop, the corneal uptake of even very small nanoparticles is only 2% due to rapid precorneal clearance (8). Interestingly, upon surface functionalization of nanoparticles with ligands for cell surface receptors, their uptake by cornea can be increased up to 16% within 5 min. The functionalized nanoparticles enter and cross the conjunctiva even better. It remains to be seen if such functionalized nanoparticles allow non-invasive drug delivery via the conjunctiva and sclera to the back of the eye from an eye drop. In the long run, patients are likely to accept non-invasive approaches the best. However, unless the systemic entry of the drugs is minimized from eye drops, non-invasive approaches might result in systemic toxicity, especially upon chronic administration.

To match the exciting scientific advances in the identification of new, druggable targets for disorders of the back of the eye, there is a great need for improving drug delivery to the back of the eye. Nanoparticle technologies offer one such avenue for improving non-invasive drug delivery to the back of the eye.

**REFERENCES**


