

● PERSPECTIVE

Delivery of therapeutics to posterior eye segment: cell-encapsulating systems

Drug delivery to the posterior segment of the eye, especially the retina, faces the unique challenges of various anatomical and physiological barriers. Invasive intravitreal injection is currently the mainstream clinical approach to posterior eye diseases such as age-related macular degeneration, diabetic retinopathy, uveitis, and cytomegalovirus retinitis. Repeated injections could be complicated by endophthalmitis, intraocular pressure elevation, retinal vascular occlusion, and retinal detachment, let alone the psychological and economical burdens suffered by patients (Schwartz et al., 2014). In view of this, several extended release drug delivery systems have been devised and the idea of encapsulated-cell technology (ECT) has gained popularity in recent decades since its first proposal in the 1960s.

The pinnacle goal of ECT is to provide sustained delivery of fresh therapeutics secreted by the encapsulated cells at the target sites without causing any immune reactions. ECT is comprised of two parts as its name suggested, cells and encapsulation. Different cell types, with or without further genetic modifications, offer endless possibilities in the production of desired therapeutics. The essence of encapsulation is to provide an “immunoprivileged environment” for encapsulated cells to carry out their function, and at the same time, to isolate them from host immune system. An ECT drug delivery platform should offer selective permeability where nutrients and oxygen could diffuse in for nourishing encapsulated cells, while desired therapeutics and waste produced by cells could efflux; adequate immunoisolation to avoid triggering any host response; sufficient mechanical strength to hold shape and long-term device integrity to prevent leakage of cells (Wong and Lo, 2016).

ECT is being put to the test in its feasibility and ability to treat various diseases including diabetes, central nervous system neurological diseases, bone and cartilage defects. The eye, an immunoprivileged and anatomically easily accessible organ, provides an attractive target for the application of ECT. Several preclinical and clinical reports demonstrated the translational potential of ECT technology in treating sight-threatening diseases (Wong and Lo, 2016).

ECT in clinical studies: Two of the ECT devices developed by Neurotech Pharmaceuticals (Lincoln, RI) underwent clinical trials. They were NT-501 (also known as Renexus[®]) and NT-503, which delivered ciliary neurotrophic factor (CNTF) and a soluble anti-vascular endothelial growth factor receptor (VEGF-R) protein, respectively. NT-501 is a cylindrical device with 1 mm in diameter and 6 mm in length. It is composed of a semi-permeable polyethersulfone external membrane, an internal yarn of polyethylene terephthalate, and around 2×10^5 CNTF-secreting human retinal pigment epithelium (ARPE-19) cells. CNTF is a neurotrophic factor

that showed promising results in attenuating the progression of degenerative retinal diseases in rodent and canine models of retina degeneration. For anchorage to the sclera and easy retrieval after implantation, a titanium anchor was placed at one end of the device (Kauper et al., 2012). It was inserted 3.75 mm posterior to the limbus in the inferotemporal region by a 2 mm sclerotomy. On the other hand, NT-503 took a multi-chamber approach to increase the total number of encapsulated cells and pave the way for potential combination therapy. VEGF-R expressing ARPE-19 cells were encapsulated in a 5-chamber cartridge format in NT-503.

NT-501 has been tested in four previous clinical trials, including a 6 month Phase 1 study for retinitis pigmentosa (RP), 12-month Phase 2 studies for geographic atrophy (GA) and late-stage RP, and a 24-month Phase 2 study for early-stage RP (Kauper et al., 2012). As for NT-503, a Phase 2 clinical trial was halted as its performance was disappointing with larger than expected patients requiring rescue anti-VEGF injection in the treatment arm (Neurotech, 2016). Currently, only NT-501 is still undergoing Phase 2 trials in patients with macular telangiectasia (MacTel) and glaucoma.

Through various clinical trials, these devices had consistently shown safety and achieved localized secretion in the eye without the need of immunosuppressants (Zhang et al., 2011; Birch et al., 2013; Chew et al., 2015). There were no serious adverse events associated with the NT-501 device or the implantation procedures. No treatment-related adverse effects such as endophthalmitis, retinal detachment, and choroidal neovascularization were detected up to 12 months post-implantation. Serum CNTF, antibodies against CNTF or encapsulated cells were also undetectable. These findings showed that the device was well-tolerated, and ECT is a feasible route for sustained drug administration. However, efficacies of NT-501 on GA, late and early RP were mediocre. In the GA study, despite the increase in retinal thickness documented by optical coherence tomography and the stabilization of best corrected visual acuity reported in the high dose group, no significant difference was noted in the lesion size, electroretinogram evaluations and visual field sensitivity between sham and treated groups (Zhang et al., 2011). Similarly, no significant change in visual acuity was detected between sham and treated groups in the late-stage RP study (Birch et al., 2013). The early-stage RP study showed further deterioration in visual field sensitivity in the high-dose treatment group as compared with non-treated patients at one year (Birch et al., 2016). Interestingly, such deterioration was found to be reversed at 6 months post-explantation. Prolonged implantation of up to 96 months did not show improvements in visual acuity, visual field sensitivity and macula structure in RP patients compared with the sham group.

Besides RP and GA, NT-501 has been applied in clinical studies for glaucoma and MacTel, a rare degenerative retinal disease that causes progressive bilateral vision loss. As in previous trials, Phase I trial for MacTel showed good tolerability and safety towards the device (Chew et al., 2015). A Phase 2 MacTel trial is currently underway and two-year data is expected in mid 2017. As for glaucoma, early data from Phase 1 trial suggested that CNTF may promote retinal ganglion cell survival (Neurotech, 2016). A Phase 2 study is currently underway, aiming to recruit 60 patients, and is expected to be completed in 2020.



Although primary safety outcome of these clinical trials was satisfactory, therapeutic efficacy of CNTF failed to translate in GA and RP patients. This may be attributed to a lack of understanding in disease causal mechanism and the choice of therapeutic. To allow successful translation of novel drugs like CNTF, it is crucial to understand the correlations between animal and human disease mechanisms, and ensure biotargets identified play a similar role in disease model as in clinical conditions (Denayer et al., 2014). Furthermore, a more stringent success criteria during the non-clinical stages of drug development may reduce translation failure. Besides conducting histological evaluations, as with NT-501, further functional evaluations such as electroretinogram and optokinetic tracking are important to improve the predictability of these studies.

ECT in preclinical studies: Various ECT designs have been proposed in preclinical studies in the recent decade. In particular, biocompatible alginate and collagen-based hydrogel systems have shown promising results *in vitro* and *in vivo*. For alginate systems, polylysine coated microspheres supported protein drug production from modified ARPE-19 cells for at least 110 days *in vitro* (Wikstrom et al., 2008). When implanted in healthy rat eyes, a similar system with VEGF receptor 2-expressing myoblast delivered drug sustainably over 3 weeks of implantation (Santos et al., 2012). As for collagen systems, enhanced protein secretion rate and sustained drug delivery *in vitro* for up to 30 days from modified HEK293 cells was reported (Lee et al., 2009). Further inclusion of alginate improved the cell immobilization power. The authors have further developed the collagen-alginate composite ECT system into an intravitreally injectable gel for treating posterior eye disorders (Wong et al., 2016). Continuous GDNF delivery was achievable in culture and healthy rat eyes for at least 14 days. The gels were well-tolerated with no host tissue attachment and contained living cell colonies. Most importantly, when implanted in dystrophic Royal College of Surgeons rat eyes for 28 days, gels with higher initial cell number yielded better photoreceptor retention.

Although clinical trials on ocular cell-encapsulation therapy showed mild efficacy, preclinical and clinical studies demonstrated the safety and feasibility of these platforms for sustained drug delivery, circumventing repeated intravitreal injections. Further knowledge in the casual and progression mechanisms of eye diseases, treatment targets and therapeutic agents is essential to ensure successful application of these platforms. Moreover, studies with longer implantation duration in dystrophic models are warranted. It is important to understand how these systems perform and interact with host tissue under pathological environments. Also, the incorporation of “smart” functions, such as on/off switch, real time monitoring or reporter system, and controllable, patient-specific drug delivery can greatly expand the robustness of this technology for translational applications.

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