DDT Vol. 6, No. 1 January 2001

Encapsulated cell technology provides new treatment options

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Neurotech SA (Paris, France) and NSgene A/S (Copenhagen, Denmark) are developing an encapsulated cell technology (ECT) for the delivery of drugs to the eye and the brain. The two teams are currently working to develop long-lived cell lines that can be bound within a matrix-filled catheter device ready for implantation for the treatment of disorders such as age-related macular degeneration, retinitis pigmentosa, Parkinson's disease and epilepsy.

ECT is a potential solution to the problems of delivering drugs and molecules across both the blood–eye and the blood–brain barrier. By introducing a small, cell-containing semi-permeable capsule directly into these two body compartments, ECT delivers secreted factors to the required site. Furthermore, if problems arise during the treatment phase, the small capsule, complete with cells, can be removed quickly.

Lessons from an early Phase IIb trial

The ECT technology was acquired by Cytotherapeutics (Lincoln, RI, USA) in December 1999. Michael Lysaght (CEO at CytoTherapeutics and now Professor of Artificial Organs Research at Brown University, Providence, RI, USA), carried out the first transplantation of encapsulated cells in humans. 'Using ECT, graft rejection by the host is prevented by the semi-permeable barrier of the implant,' he explains. This work culminated in a Phase IIb trial for chronic pain in 1998. 'The intention was to block pain receptors and so reduce the chronic pain but the trial ran into several problems,' explains Tom Shepherd, CEO at Neurotech. The device used was small, was implanted

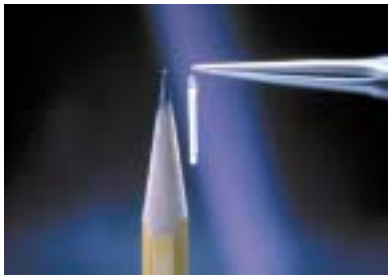

Figure 1. This shows the size of an encapsulated cell technology catheter for use in the human eye compared with an ordinary pencil point.

in the spine, and the factor secreted (noradrenaline) was low in potency. In the large volume of fluid within the CNS, the factor could not build up to high enough levels to have an effect. Although the trial was a failure in some respects, Shepherd stresses that the encapsulation device itself was validated in this trial, and that, with the right cells and a high potency factor in a smaller volume of fluid, the trial might have been more successful.

One of the problems with the trial was the choice of cells; bovine cells were seeded into the matrix of the implantable catheters. 'Using xenobiotic cells now poses ethical difficulties,' points out Shepherd and he confirms that current work to expand the applications of ECT is based on human cell lines that can live in an encapsulated matrix inside the body for at least 12 months. At the moment, neither company can discuss the details of the cells being used but Shepherd confirms that retinal cells are being used in the eye disorder studies. 'It seems to make sense to use cells that normally live in the environment that is under investigation,' he says.

ECT for eye disorders

Rebecca Li (Genetics Institute, MA, USA), who worked on ECT at Cytotherapeutics, developed several matrices specific for different cell types. 'The choice of encapsulation matrix has a profound effect on cell morphology, level of factor secreted and viability of encapsulated cells,' she explains. For example, when a collagen-coated polyethylene terephthalate (PET) yarn scaffold was compared with just collagen, the results showed that the PET scaffold enabled cells to release four times as much secreted ciliary-derived neurotrophic factor (CNTF) compared with the collagen matrix[1].

Shepherd and colleagues have now started preclinical work in a canine model of retinal degeneration. 'The dog model is providing information on how neuroprotective factors can protect against retinal damage,' he reports. Dogs of a few weeks old have received implants of encapsulated cells producing

Figure 2. This shows how the device is positioned in the eye.

1359-6446/01/$ – see front matter PII: S1359-6446(00)01621-4

CNTF. When injected into the eye, CTNF protects neurones and retinal cells but at the expense of serious side effects, says Shepherd. 'Using retinal cells within a device produces a very low level of side effects but enables high levels of CNTF to be delivered to the back of the eye,' says Shepherd. The 15-min procedure to implant the small catheter causes less pain than an injection and can be carried out under local anaesthetic. In humans, the implantable eye device is tiny and is inserted directly into the vitreous humour (Figs 1 and 2). The position of the device can be checked regularly using an ordinary opthalmoscope and it can be removed if there are problems. 'If preclinical work continues to go well, we could go into Phase I/II clinical trials within about 14–18 months,' says Shepherd.

ECT and Parkinson's

NSgene A/S are using ECT as a delivery system for factors to treat Parkinson's disease. Neublastin has already been shown to protect dopinergic neurones (see Box 1). 'ECT seems an ideal way of delivering neublastin across the blood–brain barrier; animal data and the Phase IIb trial carried out by CytoTherapeutics showed good efficacy and low toxicity,' says Lars Wahlberg, COO at NSgene.

Box 1. Neublastin: a potent neuroprotective factor

Neublastin is a glial cell line-derived neurotrophic factor (GDNF). *In vitro* results have shown that neublastin can increase the number of surviving tyrosine hydroxylase-immunoreactive neurones by ≈70% when added to cultures of fetal mesencephalic dopamine neurones[2]. *In vivo* studies using lentiviral vectors carrying cDNA for neublastin were injected into the striatum and ventral midbrain of rats and this was followed a week later by a selective lesion of the nigral dopamine neurones by an intrastriatal injection of 6-hydroxydopamine. Three weeks later, only about 20% of the nigral dopamine neurones were left in the control group, compared with 80–90% of dopamine neurones in the neublastin-treated group[2].

Insertion of the ECT device into the brain is more invasive than in the eye but uses standard stereotactic techniques. A frame is placed on the skull for reference points and then an MRI scan is used to create a system of coordinates to pinpoint specific areas in the brain. Under only a local anaesthetic, a small hole in the skull is made through which a catheter is inserted. 'Positioning the device is crucial to the success of the therapy; we aim to place the tip of the catheter within the striatum, the area rich in dopinergic neurones,' says Wahlberg. The catheter is secured under the skin of the skull so that it is stable but can be removed. 'This is a significant advantage of a delivery system over alternatives such as gene therapy, which is usually impossible to reverse,' he points out.

The future

Lysaght is encouraged by the progress being made so far. 'The new collaborative studies avoid the pitfalls of earlier clinical trials with encapsulated cells,' he says. Both Shepherd and Wahlberg hope that ECT implants will be permanent, or at least long lasting. 'Even if the implant has to be replaced annually, or every 18 months, that would be acceptable to most patients,' predicts Wahlberg.

References

1 Li, R. *et al.* (2000) Encapsulation matrices for neurotrophic factor-secreting myoblast cells. *Tissue Engineering* 6, 151–163

2 Rosenblad, C. *et al.* (2000) *In vivo* protection of nigral dopamine neurons by lentiviral gene transfer of the novel GDNF family member neublastin/artemin. *Mol. Cell. Neurosci.* 15, 199–214

Drug delivery collaborations…

Syngenix Ltd (Cambridge, UK) has signed an agreement with **GlaxoWellcome** (Research Triangle Park, NC, USA) for the drug delivery of one of GlaxoWellcome's drug candidates. Glaxo R&D will use the neuronal drug delivery technology from SynGenix, ProVector, to target their drug for neuropathic pain directly to sites within the nerve. This system is hoped to enable much higher therapeutic doses to be achieved while minimizing the potential for adverse effects. The system is also said to enable the delivery of large molecules that would otherwise be broken down in the body. The financial details of the agreement were not disclosed.

Bradford Particle Design (BPD; Bradford, UK) has signed a licensing agreement with **Bristol-Myers Squibb** (BMS; Princeton, NJ, USA) to provide BMS access to their supercritical fluid technology for controlling the formation of dry powder particles. BMS paid BPD an undisclosed up-front licence fee for the knowledge and equipment, and for clinical trial materials for specific collaborative projects. 'Engineered pharmaceutical powders are playing an increasingly important role in enabling new drugs and adding value to currently marketed products,' said Ronald L. Smith, Director of Exploratory Biopharmaceutics and Drug Delivery, BMS Research Institute. 'This agreement strengthens our research and pharmaceutical development platform by allowing us to apply proprietary technologies to our innovative drug products.'