RETINA

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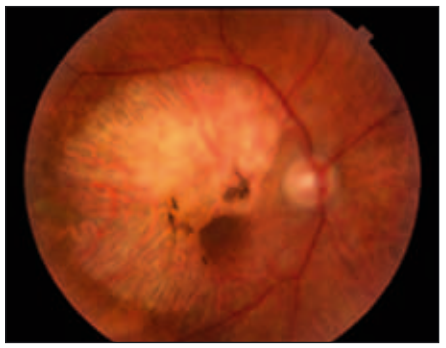
GEOGRAPHIC ATROPHY

Encapsulated cell therapy delivers nerve growth factors

by Sean Henahan in La Jolla



Credit: UCSD School of Medicine

Image showing geographic atrophy (GA)

Patients with advanced geographic atrophy associated with non-neovascular age-related macular degeneration (AMD) showed promising visual improvements when treated with an innovative approach known as encapsulated cell therapy that delivers neurotrophic factors to the back of the eye.

In a recent multicentre phase II clinical trial patients were implanted with a small capsule designed to release a steady stream of ciliary neurotrophic factor for at least one year. The design of the device, known as NT-501, is such that the implant can do its work without antibodies and immune cells attacking it, Kang Zhang MD, PhD, professor of ophthalmology and human genetics at the UCSD School of Medicine, and director of UCSD's Institute of Genomic Medicine, told *EuroTimes*.

"The study findings are very promising since both structural and functional improvements were demonstrated in a disease that is currently untreatable. These results support the initiation of larger confirmatory studies of NT-501 in patients with geographic atrophy," noted Dr Zhang, lead author of the study.

The intraocular implant device used in the study consists of human cells genetically modified to secrete ciliary neurotrophic factor (CNTF), a nerve growth factor capable of rescuing and protecting dying photoreceptors. It is a relatively simple surgical procedure, implanting the device via pars plana vitrectomy to position in the pars plana, and securing it with a single suture. It is placed outside of the main visual axis, he explained.

The 51 study participants were divided into three groups. One group received a high dose CNTF implant, another group received a low dose, and the third underwent sham surgery with no active drug.

The study results, reported recently in the Proceedings of the National Academy of Science (PNAS), showed a dose-dependent increase in retinal thickness suggesting increased photoreceptor metabolic activity. This increase was followed by visual acuity stabilisation (loss of fewer than three lines of vision, or 15 letters) of 96.3 per cent in the high-dose group compared to 83.3 per cent in the low-dose group and 75.0 per cent in the sham group.

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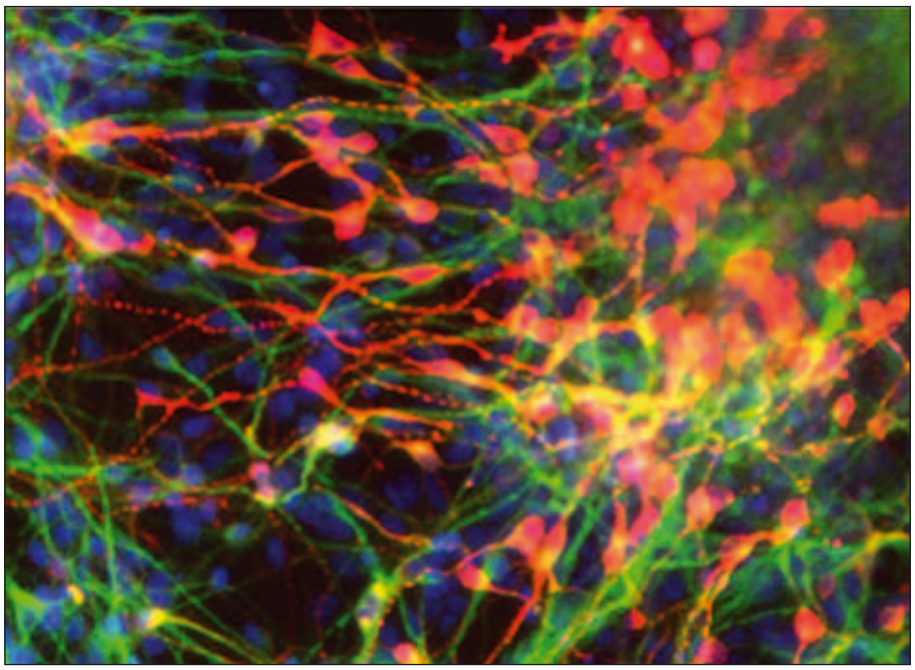

Stained mature neurons, derived from precursor cells, expressing the neurotransmitter dopamine
Credit: UCSD School of Medicine

Researchers measured retinal thickening using time domain optical coherence tomography. They measured lesion size using fundus photography. Patients in the high-dose group showed retinal thickening as early as four months after receiving the implant.

A sub-group analysis indicated that patients who began the trial with visual acuity of 20/63 or better tended to have better visual outcomes. All of the patients in the high-dose group maintained visual acuity stabilisation at one year, compared to 55.6 per cent of those in the combined low- and sham-treated groups. Patients receiving the high-dose had a 0.8 mean letter gain compared to a 9.7 mean letter loss in the combined low- and sham-treated groups.

"This makes sense, because if all the cells are gone there is no way for you to actually protect the cells. This approach will have more success with the cells that are near dying where you are able to keep them alive, and ultimately provide better vision," he told *EuroTimes*.

Additional data was presented at the recent ARVO meeting by Glenn Jaffe MD and colleagues, Duke University Eye Centre, Durham North Carolina, US. Eighteen-month data from the multicentre trial showed very similar results to those reported by Dr Zhang and colleagues, with lasting retinal thickening and stabilisation of vision in the high-dose patient group.

The device appeared to be safe and well tolerated with no reports of serious adverse events associated with the implant or implantation procedure. A few patients required explantation of the device. This gave the investigators a chance to check the patency of NT-501 device. These evaluations confirmed that the devices continued to show healthy cells and stable CNTF output for up to 12 months.

In another recent study *(Investigative Ophthalmology & Visual Science April, 2011, Vol. 52)*, researchers reported promising findings with NT-501 in patients with retinitis pigmentosa. The implant provided statistically significant cone photoreceptor preservation in two patients with retinitis pigmentosa and one patient with Usher syndrome. That study used adaptive optics scanning laser ophthalmoscopy to image and measure the rate of the progressive degeneration of cone photoreceptors.

Stem cell breakthrough Dr Zhang noted that he was also very excited about recent work in his lab on the creation of long-term, self-renewing, primitive neural precursor cells from human embryonic stem cells. In another study published recently in the *Proceedings of the National Academy of Sciences*, Dr Zhang and colleagues reported they had developed a relatively straightforward way to create these stem cells without any increased risk of tumour formation.

"It's a big step forward. It means we can generate stable, renewable neural stem cells or downstream products quickly, in great quantities and in a clinical grade – millions in less than a week – that can be used for clinical trials and, eventually, for clinical treatments. Until now, that has not been possible," Dr Zhang emphasised.

He told *EuroTimes* that research is already under way in his lab to develop an array of neural cells. On the ophthalmic front, this could lead to new approaches to the treatment of AMD, retinitis pigmentosa and glaucoma. Developing lines of motor neuron cells would open the way to new treatments for a host of neurological disease including Lou Gehrig's disease (ALS), and Parkinson's disease, he said.