# Gene Vector Delivery Platform Targets Retinal Diseases

The LentiVector technology delivers genes into retinal cells efficiently and stably.

**BY JENNIFER KREATSOULAS, PHD, NEWS & CONTRIBUTING EDITOR**

The LentiVector (Oxford BioMedica plc, Oxford, England) is being evaluated in preclinical trials as a mechanism to deliver genetic material to the specialized, nondividing cells of the retina for the treatment of chronic, degenerative diseases such as wet age-related macular degeneration (AMD). For other indications, the LentiVector has been shown to efficiently and effectively deliver genes to a target site. For example, results from a phase 1/2 clinical trial using the LentiVector to deliver ProSavin (Oxford BioMedica) to patients with Parkinson's disease showed that patients achieved and maintained a 30% improvement in motor function from month 6 through month 12.

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*Retina Today* recently spoke with Stuart Naylor, PhD, Chief Scientific Officer and Executive Director of Oxford BioMedica, and his colleague Nick Woolf, Chief Business

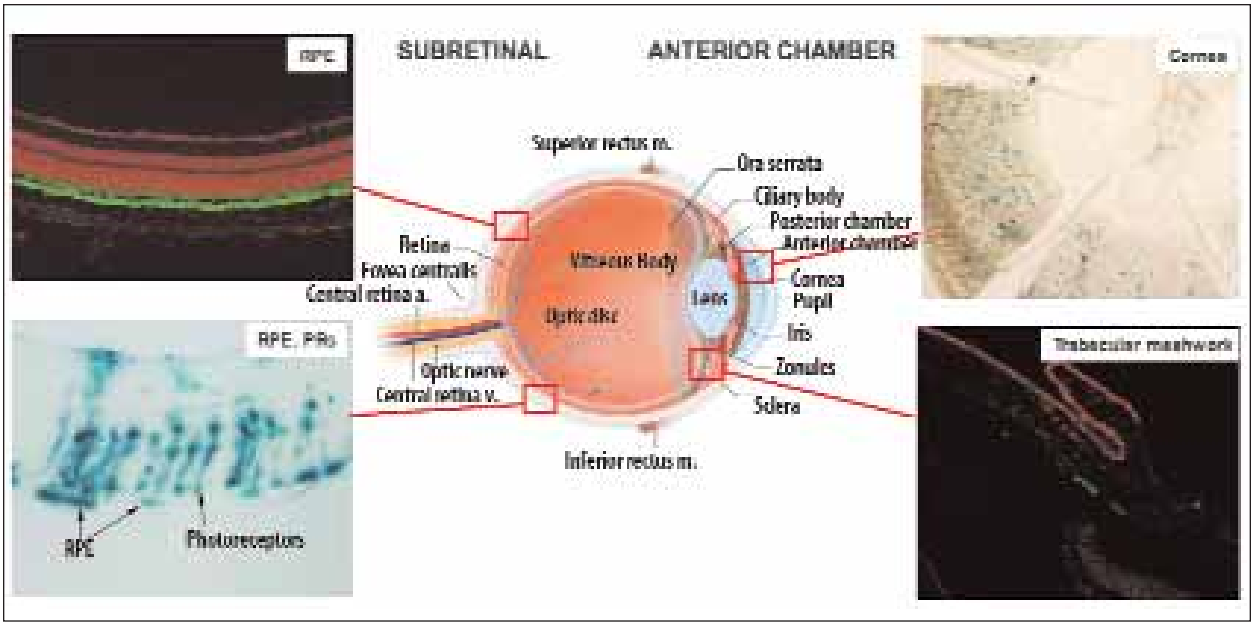


**Figure 1. Sites of LentiVector delivery and expression.**

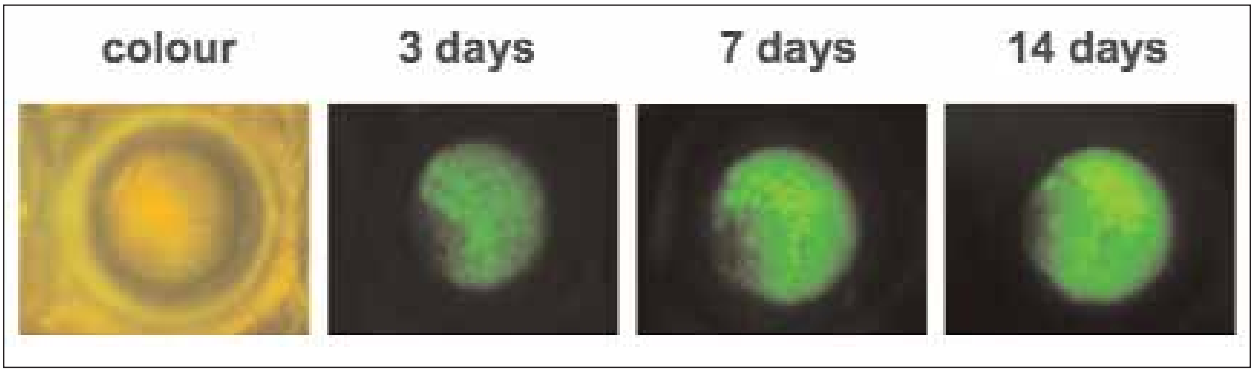


**Figure 2. Fundus images of gene expression over a 14-day period in a mouse retina.**

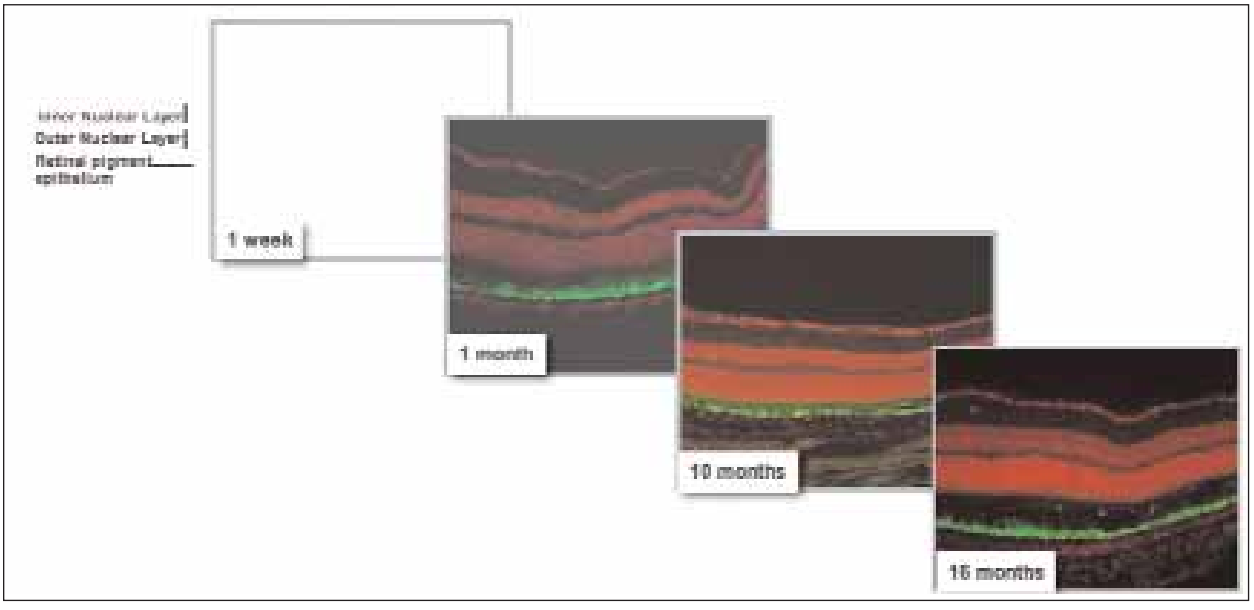


**Figure 3. Gene expression from 1 week through 16 months in a mouse retina.**

Officer, about how the LentiVector works in ocular indications and the advantages that it may have over other therapies for targeting diseases of the eye.

## THE SCIENCE

The LentiVector technology is a proprietary gene transfer system based on the lentivirus equine infectious anemia virus (EIAV). Applications for the gene vector system include gene therapy, transgenesis, stem cell manipulation, somatic disease models, target validation, and gene discovery. In ocular indications, however, the primary application of the LentiVector system is to either establish a "local factory" to produce therapeutic molecules (such as antiangiogenic factors) or to reprogram pathology-causing parent retinal cells by neutralizing the effect of mutant genes with corrected versions of the appropriate gene.

The therapeutic genes are engineered into a viral vector genome that has been stripped of all of its native genetic information, and it is then packaged using the normal structural proteins of the lentivirus. These therapeutic vectors are administered into the subretinal space between the photoreceptors and the retinal pigment epithelium (RPE) cells (Figure 1). The laminated structure of the retina squeezes tiny amounts of viral vector across the globe. Efficient gene transfer and expression takes place primarily in the RPE and photoreceptor cells as the vector envelope fuses with the target cells. The therapeutic genetic contents of the viral vector then go into the target cell, are transported to the nucleus, and become permanently integrated into the genome of the cell, resulting in efficient, effective, sustained gene expression (Figure 2).

## THE LONGEVITY FACTOR

The treatment regimen for Lucentis (ranibizumab; Genentech Inc.)—the current gold-standard in wet AMD treatment—requires patients to receive intravitreal injections every 4 weeks. Preclinical mouse models using the LentiVector system demonstrated long-term expression and therapeutic efficacy for nearly 3.5 years in the brain and for 16 months in the retina (Figure 3). With further study, Dr. Naylor said he is confident that gene expression and efficacy will be sustainable for at least 2 years in the retina, if not for life.

"In the case of treating wet AMD, this strategy aims to deliver the genes for two antiangiogenic proteins—angiostatin and endostatin—to the retina by essentially setting up a genetic implant in the back of the eye that constantly produces even levels of the angiostatic products, which combat proangiogenic signals in a broad way," Dr. Naylor stated. "As a result, a permanent guardian of the retina is created, eliminating the need for frequent readministration. Our LentiVector system offers patients and ophthalmologists a long-term fix for this chronic disease."

## PRECLINICAL PRODUCT CANDIDATES FOR RETINAL DISEASES

Currently, Oxford BioMedica has four gene-based ocular product candidates in preclinical testing: RetinoStat for the treatment of wet AMD; StarGen for Stargardt disease; UshStat for Usher syndrome 1B; and EncorStat for corneal graft rejection. RetinoStat aims to preserve and improve the vision of patients with wet AMD through antiangiogenesis by delivering endostatin and angiostatin genes directly to the retina. The Stargardt disease therapy, StarGen, uses the LentiVector system to deliver a corrected version of the ABCR gene to the retina. UshStat uses the gene delivery system to transport a corrected version of the MYO7A gene to the retina. EncorStat is a modified version of RetinoStat that aims to inhibit neovascularization in the cornea after corneal transplant surgery.

## COLLABORATORS

Oxford BioMedica recently entered into a collaboration agreement with sanofi-aventis SA (Paris, France) to develop these ocular therapies with an option for further development, manufacture, and commercialization on a worldwide basis pending results of phase 1/2 human clinical trials. The companies plan to begin phase 1/2 trials of RetinoStat and StarGen by the end of 2010.

"We are delighted to be working with sanofi-aventis on the advancement of our LentiVector system in the field of ophthalmology," Mr. Woolf said. "This collaboration enables us to accelerate the development of four novel gene therapies that have the potential to benefit patients with debilitating ocular diseases."

> "Our LentiVector system offers patients and ophthalmologists a long-term fix for this chronic disease."
> –Stuart Naylor, PhD

In addition to the support of sanofi-aventis, Oxford BioMedica is collaborating with Robin Ali, PhD (Institute of Ophthalmology, London), Jose Sahel, MD (Quinze Vingts, Paris), Rando Allikmets, PhD (Columbia University, New York, NY), David Williams, PhD (University of California, Los Angeles), Tim Stout, MD, PhD, MBA (Oregon Health and Science University, Portland), and Peter Campochiaro, MD (Wilmer Eye Institute at Johns Hopkins University, Baltimore, MD). The Foundation Fighting Blindness, a philanthropic organization in the United States, is also collaborating with Oxford BioMedica.

"The investment from sanofi-aventis is a wonderful boost for the development of Oxford BioMedica's gene therapy products and will greatly enhance our ability to move these emerging treatments into and through the clinical trial process," said Stephen Rose, PhD, Chief Research Officer of the Foundation Fighting Blindness. "This collaboration affirms the great potential for gene therapy to treat and cure a number of retinal degenerative diseases, including Stargardt disease and Usher syndrome that, as rare diseases, often do not receive the attention or investment necessary to bring about promising treatments." ■

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