

REVERSING RETINAL ISCHEMIA

Using encapsulated cell technology, a novel device may some day be used to treat inadequate oxygenation associated with common diseases.

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Decreased blood flow to the retina is the underlying pathophysiology in a number of major retinal diseases, including diabetic retinopathy, retinal vascular occlusive disease, and retinopathy of prematurity. This tissue ischemia

causes a cascade of cellular events, most notable among these the overproduction of VEGF, which causes neovascularization and increased vessel permeability. Current treatments for these diseases include laser, vitrectomy, and intravitreal anti-VEGF injections. Although these are all effective, they do not address the underlying pathophysiology: decreased tissue oxygen.

TARGETING RETINAL ISCHEMIA

Encapsulated cell technology (ECT) was first reported by Vincenzo Bisceglie in 1934 as a solution to overcoming immunologic rejection to nonself cells, tissues, or organisms.¹ This treatment mechanism holds promise for a variety of human diseases including diabetes, hemophilia, and Parkinson disease.²⁻⁴

Clinical studies involving the implantation of a ciliary neurotrophic factor ECT (NT-501, Neurotech) for the treatment of retinal degenerative conditions are ongoing. This ECT implant contains genetically modified human cells within a semipermeable membrane, and these cells produce a factor to prevent retinal cell death.^{5,6} In general, ECT allows bidirectional mass transport, which permits passage of nutrients and oxygen to the cells but prevents immune cells and antibodies from destroying the cells inside the membrane.⁷

OXYCELL DEVICE

OxyCell is a novel implant that was designed and tested at the University of Colorado Eye Center. It uses ECT to deliver oxygen intraocularly. OxyCell is an encapsulated intraocular bioimplant that contains oxygen-producing cyanobacteria inside a semipermeable dialysis membrane. These nonpathogenic, single-celled organisms originate from the *Synechococcus* strain, which is ubiquitous in oceans and freshwater environments all over the world. For more than

4 billion years, cyanobacteria have been performing a single metabolic feat: using sunlight to convert carbon dioxide and water into oxygen and simple sugars. The intraocular environment provides a similarly hospitable milieu. Encased in a microdialysis membrane, the organisms can produce oxygen when stimulated by ambient light.

DEVELOPMENT

In designing the OxyCell device, it was advantageous to have a large surface-to-volume ratio and a sustained, continuous release. An initial prototype was constructed out of polyvinyl chloride tubing with a nanofiltration membrane (NF90) secured with cyanoacrylate adhesive. After several iterations, it is now a compact bundle of microdialysis fibers (Figure).

In vitro testing showed a pure *Synechococcus* cell culture to have an elevated partial pressure oxygen reading. When a vial containing *Synechococcus* sp. cells was exposed to light and temperature, there was a statistically significant increase in the oxygen content compared with baseline. There was no statistically significant change from baseline in a sterile saline control group. Testing with the *Synechococcus* sp. in the implant demonstrated an increase in oxygen concentration in a 4-mL saline bath.

Ex vivo testing in freshly enucleated porcine eyes showed



AT A GLANCE

- Retinal ischemia is the underlying pathophysiology in diabetic retinopathy, retinal vascular occlusive disease, and retinopathy of prematurity.
- The OxyCell implant contains oxygen-producing cyanobacteria and uses encapsulated cell technology to deliver oxygen intraocularly.
- If it is shown to be safe and effective, the OxyCell implant may have applications in retinal ischemic conditions.

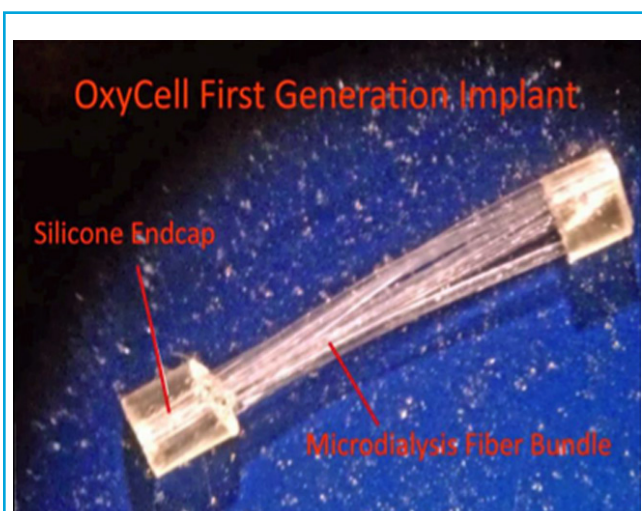


Figure. First-generation OxyCell implant.

an increase in vitreous oxygen concentration for the first 4 days after implantation. The oxygen concentration increase was sustained for the entire 15-day study period. This finding indicated that the cyanobacteria continued to produce oxygen inside the implanted eye over a period of time and that oxygen levels in the eye were significantly higher than in eyes that did not contain a bioimplant.

IN VIVO STUDIES

Initial in vivo studies have provided a proof of concept to demonstrate the feasibility of oxygen delivery with the intra-vitreous implant device. In a rabbit model, a central retinal artery occlusion (CRAO) was induced by raising intraocular pressure to 90 mm Hg. Animals were randomly assigned to receive no implant, an empty implant, or an implant with *Synechococcus* sp. cells. Intraocular oxygen measurements were taken before and after the procedure at various time points for 15 days. Sham implant animals had a hollow polysulfone fiber membrane tube implanted for a total of 30 minutes. After the animals were euthanized, microscopic analysis of retinal thickness was performed.

The oxygen concentration 30 minutes after reperfusion showed a significant increase in vitreous oxygenation in the active implant group, almost three times the oxygen content of the sham group and 14 times the oxygen content in the control group. There were no differences in concentration at days 3, 7, 10, and 15 of follow-up.

These initial studies indicate that the prototype is successful at producing oxygen in the vitreous cavity and suggest that it may prove useful for diseases such as diabetic retinopathy in which the retina receives inadequate oxygenation.

CONCLUSION

The retina has the highest rate of oxygen consumption in the body at 13 mL/100 g/min, making it sensitive to any variation in the oxygen supply.⁸ Current treatment options for

CRAO vary widely, with no standard of care and generally poor outcomes. In CRAO, the inner retinal layers normally served by the inner circulation lose viability, and loss of vision results.⁸

The use of an external source of oxygen to improve retinal oxygenation during and after exposure to an ischemic injury has been the aim of studies for many decades, with hyperbaric oxygen being the mechanism most extensively studied.⁹ Nevertheless, the systemic complications associated with sustained delivery of hyperbaric oxygen and its technical difficulties have limited its widespread use in clinical practice and prevented randomized controlled trials.¹⁰

The cyanobacteria-containing bioimplant is a novel approach to oxygen delivery directly to the vitreous cavity. We successfully demonstrated that oxygen can be produced in vitro and expressed in high quantities by a bioimplant made of a semipermeable membrane and *Synechococcus* sp. cells activated by light exposure. In addition, we demonstrated the technique for placing the bioimplant in an ex vivo setting with a resulting increase in vitreous cavity oxygen concentration. While the true biocompatibility of the membrane material has yet to be established, if it is shown to be safe and effective, the bioimplant has several promising investigational and clinical applications for retinal ischemic conditions. ■

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