



# eyevensys

## CREATING SUSTAINABLE BIOTHERAPEUTICS FACTORIES IN THE EYE TO TREAT MAJOR OPHTHALMIC DISEASES

In this article, Patricia Zilliox, PhD, Chief Executive Officer, Eyevensys, discusses the inherent difficulties in drug delivery to the back of the eye and how this creates an unmet need in ophthalmology. Dr Zilliox goes on to describe Eyevensys' novel solution to this problem, and the company's first lead product, EYS606.

### CURRENT DRUG DELIVERY METHODS IN OPHTHALMOLOGY

Traditionally, the eye has been an extremely difficult target for drug delivery due to its unique anatomy and physiology (Figure 1). It has a range of protective barriers, both static and dynamic (different layers of cornea, sclera and the blood-retina barrier), that unfortunately limit the therapeutic effectiveness of systemic drug delivery and make local drug delivery challenging.

Disorders that manifest at the back of the eye are particularly difficult to treat, as it is still not possible to administer the drugs needed to manage these conditions using methods typical to the front of the eye, such as eye drops, ointments or gels.

Traditionally such indications have been addressed using high doses administered by repeated intravitreal injections or by surgical intervention. Neither of these are ideal options for patients; intravitreal injections can have serious adverse consequences, such as intraocular infection (endophthalmitis), increased intraocular pressure and cataract formation. Even then, it remains difficult to sustain the appropriate concentration of the drug in the eye using these suboptimal methods.

Despite the success of current blockbuster drugs, such as Lucentis (ranibizumab) or Eylea (aflibercept), the ophthalmology industry is still facing a need to overcome the barriers to ocular drug delivery and improve ocular bioavailability for the treatment of back of the eye diseases, a need

which remains unmet. A number of innovative alternative approaches have recently been developed, such as free-floating intravitreal implants, scleral implant devices and biodegradable formulations. These innovative solutions have come to market,

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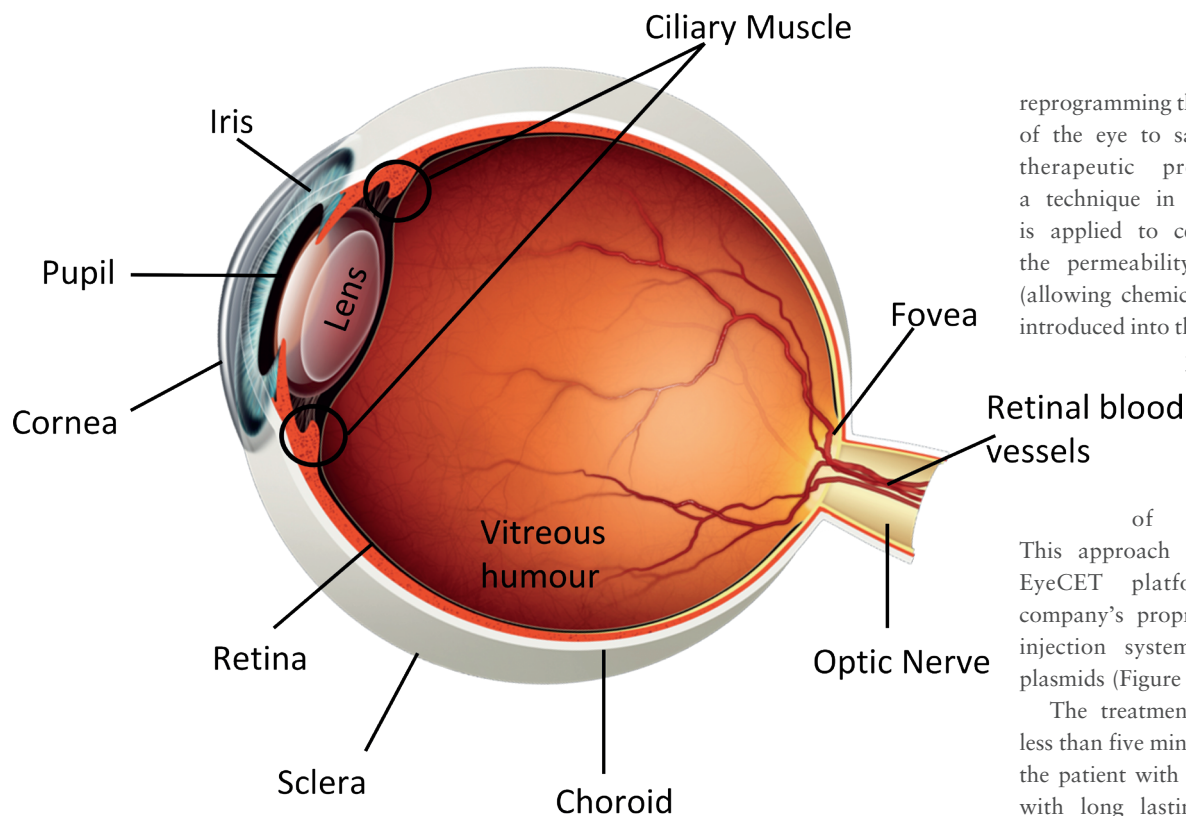


Figure 1: Simplified schematic of the human eye.

providing options for delivering precise microlitre volumes into the vitreous or choroidal chamber of the eye. However, all of these new treatments come with drawbacks, the primary culprit being that they require particularly invasive procedures. Additionally, predictable drug release from an implant is extremely difficult to achieve, given that it is a function of size and geometry and biological incompatibility can cause further inflammation for biodegradable formulations.

Despite various promising new options for back of the eye diseases, such as gene therapy, their clear limitations, especially in the drug delivery aspect, mean there is an urgency to improve the effectiveness of ocular therapies. To address this unmet medical need, Eyevensys has developed a truly innovative approach.

“A therapeutic “bio-factory” is created in the eye itself, a feat achieved by reprogramming the cells in the ciliary muscle of the eye to safely and locally produce therapeutic proteins.”

**EYEVENSYS’ NOVEL APPROACH**

Eyevensys has developed a method to treat back of the eye diseases whereby a therapeutic “bio-factory” is created in the eye itself, a feat achieved by

reprogramming the cells in the ciliary muscle of the eye to safely and locally produce therapeutic proteins. Electroporation, a technique in which an electrical field is applied to cells in order to increase the permeability of the cell membrane (allowing chemicals, drugs, or DNA to be introduced into the cell), is utilised to deliver protein coding plasmids into the ciliary muscle of the eye.

This enables local sustained production of therapeutic proteins. This approach is built upon Eyevensys’ EyeCET platform, which uses the company’s proprietary electro-transfection injection system (ETIS) to deliver the plasmids (Figure 2).

The treatment procedure, which takes less than five minutes, is designed to provide the patient with a safe and local treatment with long lasting effects between three to twelve months. The ETIS device is gently fixed to the eye and applies the electroporation technique to the ciliary muscle cells allowing the plasmids to penetrate the cells. The plasmids then encode the production of therapeutic proteins in the ciliary muscle. The ETIS device means that the process is easily controlled and reproduced.

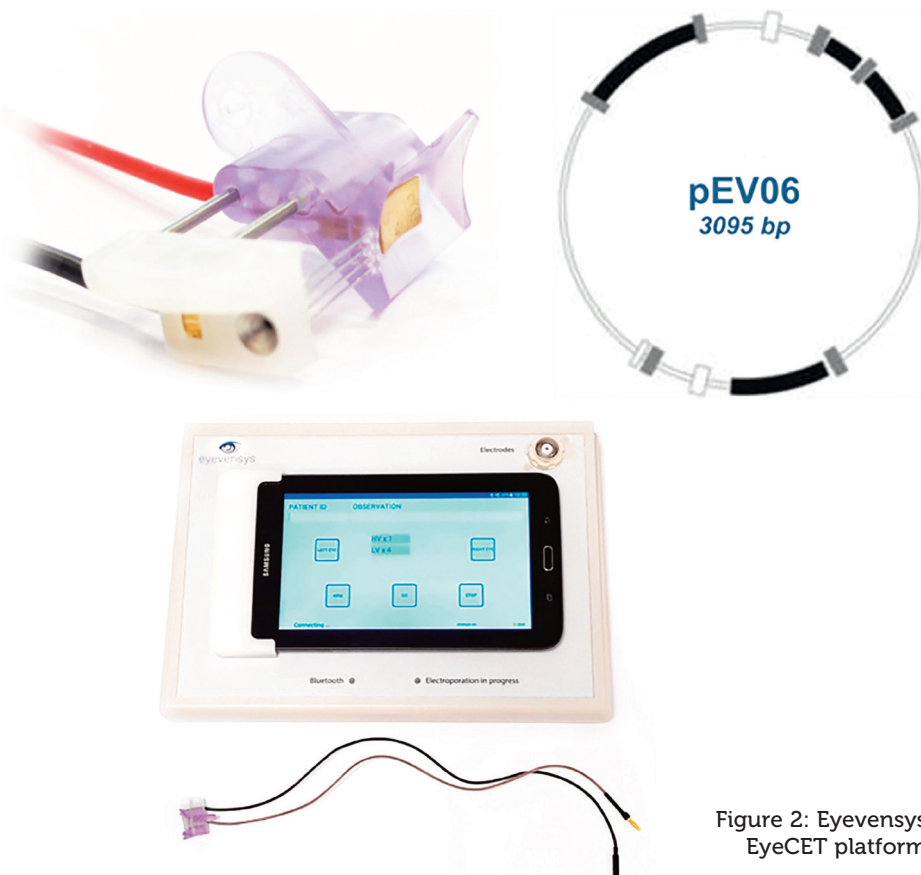


Figure 2: Eyevensys’ EyeCET platform.

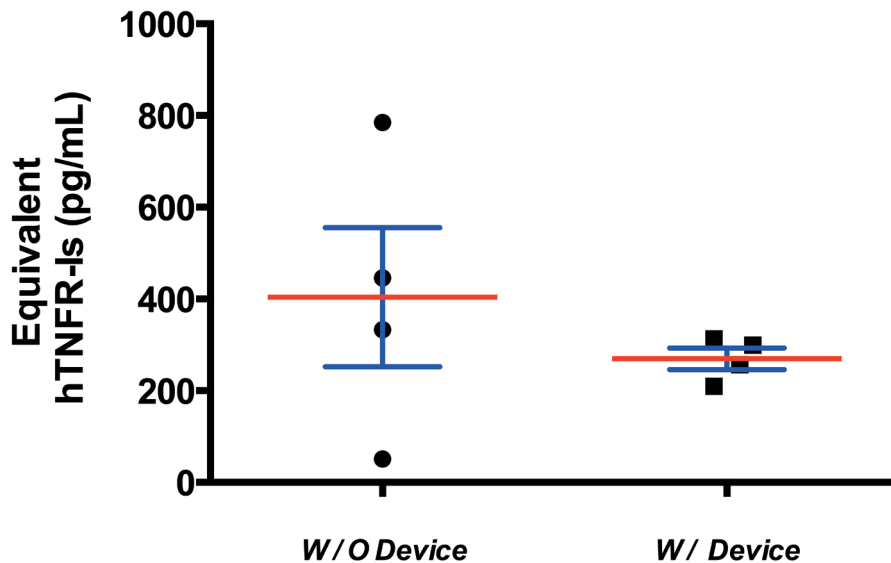


Figure 3: Comparison of the transfection reproducibility without and with an ocular device.

This translates into accurate and consistent expression of the therapeutic proteins (see Figure 3).

Eyevensys founder Dr Francine Behar-Cohen explained the thinking behind the technology thusly, “The idea was to use the only muscle inside the eye as a therapeutic producing cell, given that it was an ideal candidate for transduction, offered no visual risk and was easy to reach with minimally invasive procedure.” Dr Behar-Cohen also elaborated on the delivery method: “Electroporation is a well-known method that has been used in different parts of the human body, but which represents a revolution in the field of ophthalmology. Eyevensys’ technology is an innovation that applies electroporation in the ciliary muscle of the eye for the first time.”

#### A POTENTIAL NEW TREATMENT FOR NON-INFECTIOUS UVEITIS

Eyevensys’ first lead product, EYS606, is a potential new treatment for non-infectious uveitis (NIU). EYS606 has been granted an orphan designation by the EMA for the treatment of NIU and is currently being evaluated in a first-in-human Phase I/II clinical trial. EYS606 is the first non-viral product that has the potential to treat NIU patients for three to twelve months following an electro-transfection procedure.

EYS606 uses plasmid encoding for the production of inhibitors to suppress TNF- $\alpha$ , a pro-inflammatory cytokine that has been shown to play an important role enhancing intraocular cytotoxic events in immune diseases, including uveitis. Animal models of uveitis (EIU and EAU) have consistently

shown that the treatment efficiently reduces inflammation, significantly lowers inflammatory marker levels such as TNF- $\alpha$  and NOS2 (Nitrate Oxide Synthase 2), and protects the outer nuclear level (ONL) from degeneration.

#### EYEVENSYS’ AMBITIONS TO TREAT A RANGE OF MAJOR OPHTHALMIC DISEASES

Eyevensys aims to build a high value product pipeline by enabling sustained production of a number of therapeutic proteins in the eye, thus improving clinical outcomes and reducing the burden of frequent intravitreal or systemic injections in a range of important ophthalmic diseases.

Eyevensys is presently developing a preclinical pipeline where the expression of fully functional proteins has consistently been achieved in animal models.

This preclinical pipeline could lead to drug candidates to treat diseases including:

- Retinitis pigmentosa
- Dry age-related macular degeneration (AMD) & geographic atrophy
- Glaucoma
- Diabetic macular oedema
- Retinal vein occlusion (RVO/BRVO).

#### ABOUT THE COMPANY

Eyevensys is a private clinical-stage biotechnology company developing its EyeCET gene therapy electroporation technology to enable the sustained intraocular production of a range of therapeutic proteins. Eyevensys’ vision is

to use the EyeCET technology to develop a pipeline of products that address major unfulfilled needs in the treatment of sight threatening ophthalmic diseases. Eyevensys was founded in 2008 and is headquartered in Paris, France. It is funded by Boehringer Ingelheim Venture Fund, Bpifrance, CapDecisif, Inserm Transfert, and Pontifax.

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#### ABOUT THE AUTHOR

Patricia Zilliox, who joined the Eyevensys board in May 2016 and became CEO in December 2017, has over 25 years’ experience of global clinical development in ophthalmology. Prior to this position, Dr Zilliox served as Chief Drug Development Officer of the Clinical Research Institute, a division of the Foundation Fighting Blindness, Columbia, MD, US, where she led the financing of several start-ups in the field of gene therapy. She also spearheaded validation of a new clinical endpoint in the field of retinitis pigmentosa, opening the path for drug developers to focus on treatment of this rare condition of the retina. Previously, Dr Zilliox held several positions at Alcon/Novartis, including head of clinical development for ophthalmology.