RE·VANA
VISION IN THE FUTURE

BIODEGRADABLE IMPLANTS FOR SUSTAINED INTRAOCULAR DELIVERY OF SMALL AND LARGE MOLECULES

Presently, there is an unmet need for more effective methods of treating diseases that manifest in both the front and back of the eye. In this article, Raj Thakur, PhD, Chief Scientific Officer, and Prof David Jones, PhD, Chief Scientific Adviser, both co-founders of Re-Vana Therapeutics, discuss this issue and introduce a possible solution: OcuLief™ and EyeLief™, Re-Vana's two proprietary sustained-release platforms.

BACKGROUND

Diseases that originate in the back of the eye can cause permanent loss of vision if left untreated. In practice, untreated conditions, such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and uveitis, are a major cause of blindness. Worldwide estimates indicate that approximately 30-50 million people are affected by AMD.[1] Current therapies for the wet form of this disease require frequent intravitreal injections, which have been shown to prevent further vision loss and increase visual acuity. However, adverse events of frequent intravitreal injections include increased risk of infection, retinal detachment, haemorrhage, pain, discomfort and rise in intraocular pressure.

Chronic diseases manifesting in the front of the eye can also result in significant loss of vision. For example, glaucoma is the considered to be the second leading cause of blindness, affecting more than 60 million worldwide.[2] The application of topical eye drops daily and sometimes multiple times a day, in order to control raised intra-ocular pressure, is the standard method of treatment for this disease. However, this form of treatment has significant drawbacks, such as the potential for long-term side effects, reduced efficacy over time and a negative impact on patient compliance, which may lead to disease progression.

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These issues further escalate healthcare costs and create a significant burden on patients, carers and physicians. Therefore, the largest problem plaguing the development of ocular therapeutics is maintaining an effective concentration of the drug at its target site of action, in order to achieve the expected pharmacological response.

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SUSTAINED DRUG DELIVERY SYSTEMS

Biological barriers and faster drug clearance rates, coupled with conventional formulation approaches, have led to poor ocular bioavailability of both small- and large-molecule therapeutics. Therefore, frequent intravitreal injections of large molecules (e.g. ranibizumab) in treating back of the eye diseases or frequent eye drops of small molecules (e.g. latanoprost) in treating front of the eye diseases is necessary for the management of ocular conditions.

This has led to increased research in the area of sustained release systems. Sustained release drug delivery systems can achieve prolonged therapeutic drug concentrations in target ocular tissues, whilst both improving patient adherence to therapy and limiting adverse events caused by systemic exposure.

Formulation strategies that have been investigated to address this issue so far include:

- Surgically sutured implants
- Inserts (e.g. punctal plugs)
- Injectable implants
- Hydrogels
- Nano-/micro-particles
- Liposomes
- Iontophoresis
- Microneedles
- Ultrasound.

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Although significant research is ongoing in the development of novel sustained release systems, since 1995, only four implant-based sustained release systems have achieved both global regulatory approval and commercial success. These include:

- Sustained release non-biodegradable implants:
  - Vitrasert® (ganciclovir 4.5 mg) – approved in 1995 for AIDS-related cytomegalovirus retinitis with a six to eight month drug release profile.
  - Retisert® (fluocinolone 0.59 mg) – approved in 2005 for chronic non-infectious posterior uveitis with an approximately two-and-a-half year drug release profile.
  - Iluvien® (fluocinolone acetonide 0.19 mg) – approved in 2011 for DME with an approximately three year drug release profile.
- Sustained release biodegradable implants:
  - Ozurdex® (dexamethasone 0.7 mg) – approved in 2009 for macular oedema with an up to six month drug release profile.

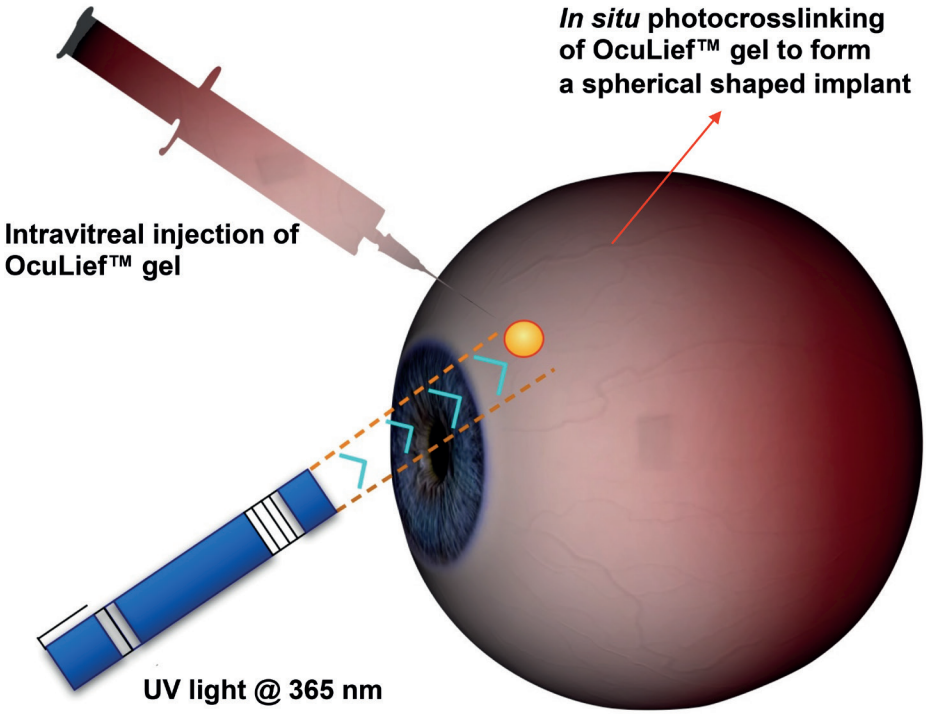

Figure 1: Schematic representation of *in situ* implant formation of OcuLief™.

Irrespective of ongoing developments, to date, there is no viable alternative to frequent intravitreal injection for the delivery of therapeutic proteins in treating back of the eye diseases or frequent eye drops in treating front of the eye diseases.

RE-VANA'S TECHNOLOGY

Re-Vana's proprietary sustained drug release technologies, OcuLief™ and EyeLief™, offer delivery of both small and large molecules with a wide range of physicochemical properties. The technologies are comprised of photosensitive polymeric materials that are selectively photocrosslinked to provide tailored release profiles for a wide range of therapeutics in the treatment of various ocular diseases. The platforms are both biodegradable and biocompatible in nature.

The first of the two technologies, OcuLief™, is a photosensitive, injectable gel-based platform. OcuLief™, is injected through the intravitreal route – using conventional hypodermic needles – followed by a short-term application of UV light to induce *in situ* photocrosslinking resulting in a photocrosslinked implant formation (Figure 1).

The second technology, EyeLief™, is a preformed photocrosslinked implant. EyeLief™ is engineered to allow intraocular administration to achieve sustained delivery of selected therapeutics.

Proof of Concept

Proof of concept data of Re-Vana's proprietary photocrosslinked sustained drug release systems have shown the ability to provide the release of small and large molecules for markedly extended periods. Using the OcuLief™ and EyeLief™ technologies, Re-Vana has demonstrated sustained release of candidate therapeutic molecules, including molecules that are employed in the treatment of both front and back of the eye diseases such as AMD, DR and glaucoma.

OcuLief™ is a polymeric gel-based formulation which, upon injection in the eye followed by UV light application,

forms a spherical photocrosslinked implant, *in situ*. Injections in the eye can be achieved using conventional narrow-bore hypodermic needles, such as those that are presently used in intraocular injections. Localised delivery of this platform technology achieves high drug levels at target tissues, prolonged delivery times, reduction in adverse events linked with systemic delivery and improved patient compliance.

EyeLief™ is a preformed implant (Figure 2) that can be administered intraocularly to achieve sustained delivery of a wide range of drug molecules. Being photosensitive, the implant can be selectively crosslinked so as to achieve the desired release rates over an extended period. EyeLief™ can be engineered into different shapes and sizes to accommodate desired routes of intraocular delivery.

Re-Vana does not employ extreme pH conditions or elevated temperatures in the engineering of its implants, which otherwise can cause issues when working with temperature or pH labile drugs, such as proteins. Furthermore, rapid crosslinking at physiological temperatures can swiftly entrap drug molecules, thereby reducing high burst release and thus sustaining drug delivery over a longer term. The degree of crosslinking of the implants influences their pore structure, which in turn controls the rate and extent of drug release. This technology has achieved sustained release, from two to twelve months, of therapeutic molecules such as triamcinolone acetonide (435 Da), dexamethasone (392 Da) and bevacizumab (Avastin®; 149 kDa). A sample *in vitro* release profile of bevacizumab is shown in Figure 3.

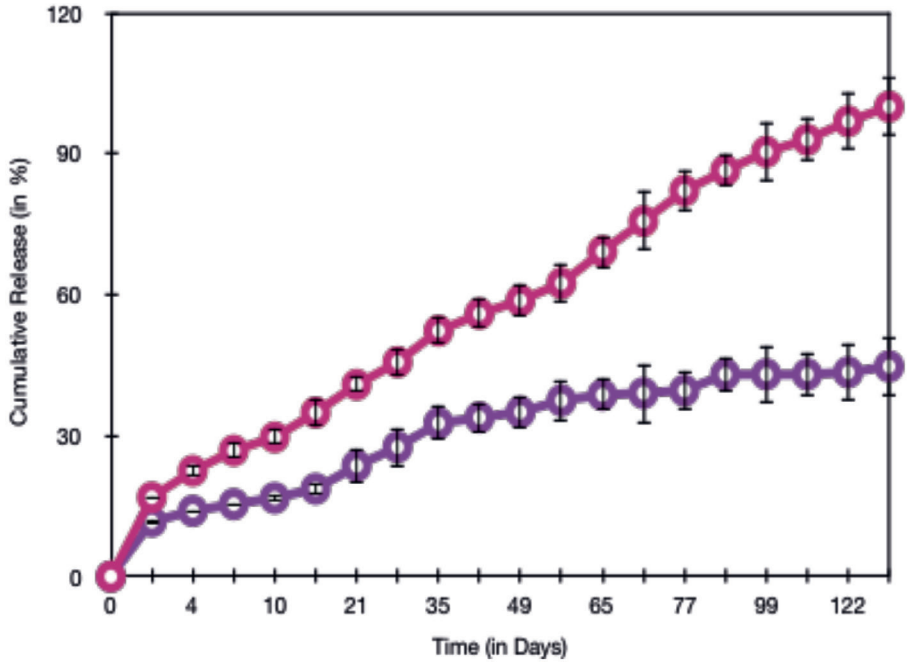

Figure 3: Tailored *in vitro* release profile of bevacizumab from OcuLief™ implants.

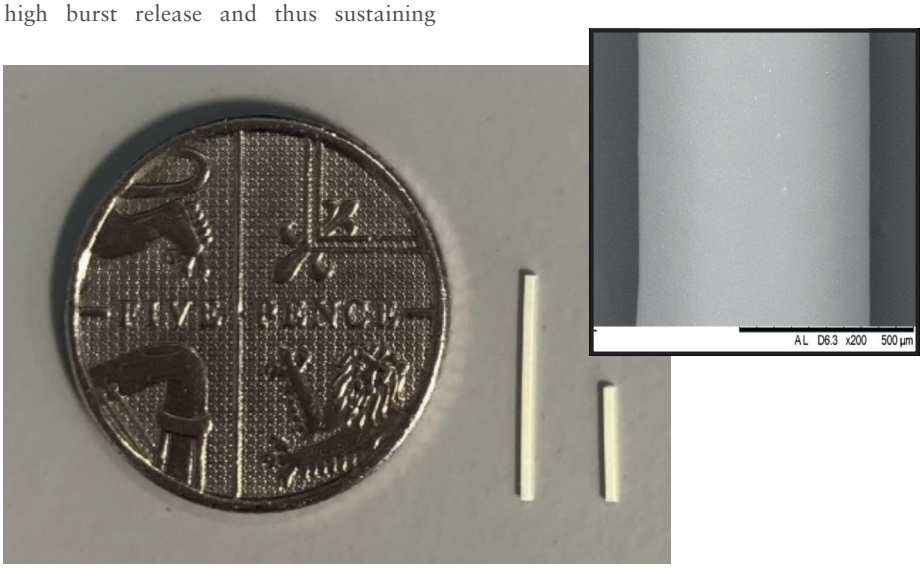

Figure 2: Preformed rod-shaped EyeLief™ implants adjacent to a UK five pence piece and imaged by an electron microscope.

VALUE PROPOSITION

- Proprietary photocrosslinked drug delivery platforms providing sustained, long-term drug delivery.
- Proven delivery of a range of small and large therapeutic molecules.
- Biocompatible and biodegradable drug delivery platforms.
- Ability to achieve tailored release profiles – with controlled burst release.
- Able to address both front and back of the eye diseases by delivery using different routes.

SUMMARY

Re-Vana Therapeutics has developed two proprietary photocrosslinked drug

delivery platforms that can sustain release of both small and large molecules.

The company has:

- Ongoing preclinical development programmes addressing both front and back of the eye diseases.
- Scientific and management team situated in both the UK and the US, experienced within the areas of ocular drug delivery systems, polymer science, regulation and commercialisation.
- Intellectual property rights protecting both platforms and routes for ocular applications.

ABOUT THE COMPANY

Re-Vana Therapeutics is an ocular pharmaceuticals and drug delivery company focused on the development and commercialisation of revolutionary long-acting biodegradable drug delivery platforms to treat chronic eye diseases such as AMD, DR, glaucoma and ocular infections. It is a spinout company from the School of Pharmacy, Queens University Belfast (UK).

REFERENCES

1. *Ozaki E et al, "Inflammation in age-related macular degeneration". Adv Exp Med Biol, 2014, Vol 801, pp 229-235.*
2. *Quigley HA, Broman AT, "The number of people with glaucoma worldwide in 2010 and 2020". Br J Ophthalmol, 2009, Vol 90(3), pp 262-267.*

ABOUT THE AUTHORS

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Professor David Jones is a Pro-Vice-Chancellor and holds the Chair in Biomaterial Science at Queen's University Belfast's School of Pharmacy (UK). He has a DSc in Biomaterial Science, PhD in Pharmaceutics, BSc in Pharmacy and a BA in Mathematics and Statistics. His research concerns the characterisation, formulation and engineering of pharmaceutical materials/dosage forms and biomedical devices. He is the author of three textbooks, 10 patents and over 400 research papers. He is a Chartered Engineer, a Chartered Statistician and a Chartered Chemist and is a former Royal Society Industry Fellow.