BREAKTHROUGH NANOTECHNOLOGY ENHANCES DELIVERY TO THE FRONT AND BACK OF THE EYE

In this article, Hongming Chen, ScD, Executive Vice-President of Research at Kala Pharmaceuticals, and Robert Langer, ScD, Company Co-Founder and Board Member, discuss applications of the company's Mucus Penetrating Particle nanotechnology in ophthalmic drug delivery. Dr Langer believes the delivery technology has the potential to allow effective treatment of diseases of the back of the eye using topically administered formulations.

By Malaika I Hill, Medical Writer

Drug delivery in the eye has been a frustrating undertaking for eye-care professionals as current drug delivery methods are limited when considering convenience and bioavailability. The burgeoning field of nanotechnology could lead to better treatment for patients suffering from myriad ocular diseases.

NANOTECHNOLOGY

Nanotechnology, the science of engineering materials at the molecular and supramolecular scale, is on the cusp of forever changing the approach to current therapeutic challenges in eye care.[1] Nanotechnology is a major focus of one of history's most prolific inventors in medicine, Massachusetts Institute of Technology (MIT) Professor Robert Langer, ScD.

Dr Langer's research is focused on developing new nanoparticle delivery approaches to treat disease, including diseases of the eye, more effectively. One element of Dr Langer's research involves the design of polymer, lipid, and polymer-lipid hybrid nanocarriers for improved drug delivery, as well as controlled delivery systems for genetically engineered therapeutic proteins, DNA, and RNA. His work also involves the creation of novel approaches for engineering of new tissues and organs.

NANOTECHNOLOGY IN OPHTHALMOLOGY

Innovative treatments for ocular diseases are needed to address the significant unmet needs in both the front and the back of the eye. Kala Pharmaceuticals is rising to meet this challenge by developing a mucus penetrating particle (MPP) platform nanotechnology. MPPs are based on decade-long work at Johns Hopkins University (Baltimore, MD, US) by one of Dr Langer's former students, Dr Justin Hanes, which focused on developing systems to improve the delivery of drugs to mucus-protected tissues. With its proprietary MPP platform technology, Kala is building a diversified pipeline of ophthalmic products to include topical therapies for post-surgical inflammation, ocular surface diseases, and wet age-related macular degeneration (AMD).

By penetrating mucus layers in the eye, MPPs can dramatically transform treatments

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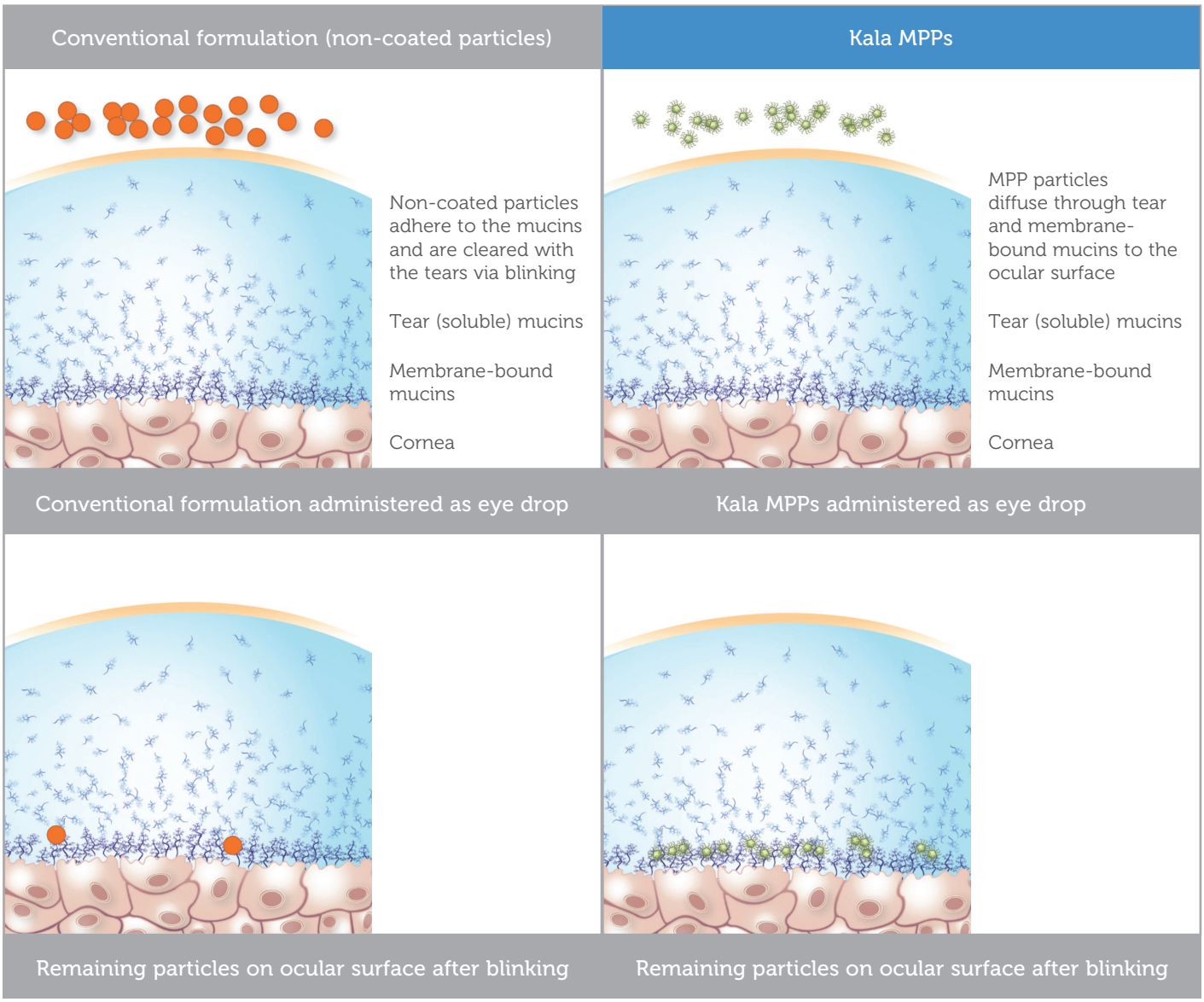

Figure 1: Mechanism of action of the mucus penetrating particle (MPP) platform nanotechnology (right), compared with conventional, non-coated particles (left).

for conditions affecting both the anterior and posterior segments of the eye. Mucus layers have been largely viewed as a limitation for drug efficacy for a variety of mucus protected tissues, including the lung, gastrointestinal tract, vaginal tract and the eye.

Mucus is a heterogeneous mesh of mucin fibers that defends against pathogens and other particles by sterically excluding particles larger than the pore size of the mucins and binding particles via the glycosylated macromolecules that are part of the meshwork. It serves as a primary defense mechanism in the body, protecting against pathogens and other foreign material and facilitating their clearance.

Particles trapped in the surface mucus layer of the tear film are cleared with blinking, which limits the delivery and efficacy of drug delivery with eye drops. The MPP platform technology enhances the penetration of drugs through the mucus layer by engineering the size and surface characteristics of the particles. For delivery to the eye, MPPs prevent therapeutic agents from being caught by the tear film and then cleared via blinking. This enhances the penetration and

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prolongs the drug's retention at the disease site.

"Nanotechnology will revolutionise ophthalmology because it offers a much more effective delivery to the front of the eye with longer action, and we can now apply the drug precisely where we want it to be," commented Langer. "I envision a new kind of eye drop that will tremendously enhance duration of action and localisation of action for delivery to the front or the back of the eye."

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MPPs were engineered combining nanometric particle size and proprietary surface engineering to achieve particles that can freely diffuse through the mucus layer. The process features the creation of a nanoparticle crystalline core consisting of the therapeutic agent, surrounded by surface-engineered polymers that allow the drug to be inert to the mucin fibers. MPP platform technology can deliver a wide variety of molecules and could also be amenable to the delivery of biologic agents and controlled delivery (see Figure 1).

"I believe we are about to see nanotechnology making a grand entry in ophthalmology and addressing the drug delivery challenge in the eye, one of the organs of the human body that is best protected," said Dr Hongming Chen, Kala's Executive Vice-President of Research, a 20-year industry veteran in drug delivery, and also one of Langer's former students.

PRODUCTS IN THE PIPELINE

Loteprednol etabonate ophthalmic suspension (marketed as Lotemax® by Bausch + Lomb) is a popular medication for reducing post-ocular inflammation. Kala is applying the MPP platform to enhance the delivery of loteprednol for a number of ocular diseases. Preclinical data has demonstrated pharmacokinetic and efficacy results for Kala's 1% formulation of loteprednol etabonate (1% LE-MPP) that are superior to that of current loteprednol products.

"In head-to-head preclinical studies, LE-MPP delivered significantly greater levels of drug to the aqueous humour, as well as the cornea, conjunctiva, and retina than either Lotemax® Suspension or Lotemax® Gel with similar dosing regimens. The objective of the upcoming clinical trial will be to demonstrate if twice-daily administration of 1% LE-MPP is effective in the treatment of inflammation and pain following cataract surgery. If successful, this would represent a significant dosing advantage compared to other topical steroids, which are currently indicated for four times a day dosing," said Kala's Chief Medical Officer, Dr Kim Brazzell.

It is set to enter a pivotal Phase II/III clinical study this year for post-operative pain and inflammation following cataract surgery, followed by a second Phase III trial to be completed in 2015. A 0.25% loteprednol etabonate-MPP formulation designed for treatment of dry eye and blepharitis is set to enter clinical trials this year as well.

Kala also plans to test MPPs ability to deliver drugs topically to the back of the eye, based on data demonstrating substantial levels of loteprednol and other drugs in the retina following topical administration. The trial could expand the possibilities for LE-MPP use for treating retinal diseases such diabetic macular edema (DME) and cystoid macular edema (CME).

Kala is also currently advancing toward selecting clinical candidates for a research phase programme featuring a topical receptor tyrosine kinase 1 (RTK1-MPP) for the treatment of wet AMD and other retinal diseases.

Although Kala's MPP technology platform internally focuses on ocular diseases, the company is also pursuing collaborations with partners to transform the therapeutic properties of both marketed drugs and compounds in development for a broad range of disease indications, including the gastrointestinal tract, airway, and cervicovaginal tract. An even mucosal coating is achieved in various tissues using MPP. For these indications, Kala will partner its technology with other companies rather than develop the applications internally.

Leading investors, including Lux Capital, Polaris Venture partners, Third Rock Ventures, and Crown Venture Fund.

REFERENCE:

1. *Zarbin MA, Montemagno C, Leary JF, Ritch R, "Nanotechnology in ophthalmology". Can J Ophthalmol, 2010, Vol 45(5), pp457-76.*