

SEVENTH FRAMEWORK PROGRAMME
Marie Curie Actions: *People*
Marie Curie Intra European Fellowship (IEF)

ANNEX 4: FINAL REPORT



INDIVIDUAL FELLOWSHIP



1. Full Title: biomimetic therapeutic hydrogel layers for interaction with corneal tissues

a. Acronym: THERALENS

b. Scientific Panel: CHE

2. Proposal Number: 328708

3. Grant Agreement Number: PIEF-GA-2012-328708

4. Duration of the project: 24 months

5. Period covered: from May 1st 2013 to April 30st 2015

6. Beneficiary and Researcher:

a. Beneficiary: ASTON UNIVERSITY

b. Scientist in Charge: Prof. Brian Tighe

c. Name of Researcher: Dr. Virginia Saez

1. FINAL PUBLISHABLE SUMMARY REPORT

This section normally should not exceed 2 pages.

This is a comprehensive summary overview of results, conclusions and the socio-economic impacts of the project. The publishable report shall be formatted to be printed as a stand alone paper document. This report should address a wide audience, including the general public.

Please ensure that it:

- *Is of suitable quality to enable direct publication by the REA or the Commission.*
- *Is comprehensive, and describes the work carried out to achieve the project's objectives; the main results, conclusions and their potential impact and use and any socio-economic impact of the project. Please mention any target groups such as policy makers or civil society for whom the research could be relevant.*
- *Includes where appropriate, diagrams or photographs and the project logo, illustrating and promoting the work of the project.*
- *Provides the address of the project Website (if applicable) as well as relevant contact details.*

Delivering an effective dose to ocular tissues can be a challenge. The bioavailability of most topical ophthalmic medications is surprisingly limited. The major obstacle to targeting the eye with therapeutics is the presence of various barriers such as the epithelium tear film, which control the concentration and entry of solutes into the eye¹. These barriers impede the effective passage of many drugs leading to minimal dose absorption. Additionally solution drainage, lacrimation, tear dynamics, conjunctival absorption and the relative impermeability of the corneal epithelial membrane reduce the residence time, penetration and efficacy of topically applied molecules. Current pharmaceutical practise tries to resolve the problems of ineffective delivery by increasing the dose of the active with subsequent potential for toxic overdose.

Simpler, more effective methods of delivery of drugs, leading to better patient compliance would have both financial and quality of life benefits. Chronic ocular conditions require long-term pharmacologic treatment leading to compliance failures. This is an excellent potential application for the use of controlled-release, drug-eluting contact lenses. Contact lenses impregnated with drugs show efficacy equivalent to conventional therapy and no toxicity². Techniques to incorporate pharmaceutical agents into lenses include incorporation of drug microparticles and nanoparticles directly into the lens material; use of polymer and fibrin films; adding surfactants to control drug release; trapping the drug through polymerization, ion ligand-containing polymeric hydrogel; molecularly imprinting of drugs among others. All these approaches suffer from one major drawback. They either involve the fabrication of a new modified lens, or the use of toxic chemicals and sequential chemical reactions to bring about surface attachment. THERALENS suffers from neither of these drawbacks.

THERALENS has used novel biomimetic nanoparticles embedded within a lens coating. These amphiphilic structures have been made with the biocompatible hypercoiling polymer poly(styrene-co-maleic acid) or its ester derivative, and the phospholipid DMPC (1,2-dimyristoyl-sn-glycero-3-phosphocholine)³. The advantage of this nanostructured system is that it enables hydrophobic substances (e.g. drugs) to be dissolved into the central zone or bilayer and then be taken into solution in water, yielding vehicle for drug delivery. They can be freeze-dried and are smaller (size $\approx 50\text{nm}$) and more stable than liposomes⁴. Several active molecules with different hydrophilicities have been loaded and their controlled release from these nanoparticulate carriers has been studied.

A feature of commercial lens production that has been adopted by lens manufacturers is “*in package coating*”⁵. This is a means of applying a polymer coating to the lens during the final stages of lens production, the sterilisation step and the hydration / extraction stage. THERALENS project has exploited this generic “*in package*” coating technology to develop controlled release contact lenses, using existing prescription lenses as the substrate, which means that it does not involve the fabrication of a new lens. During this coating step, nanostructures loaded with hydrophobic or hydrophilic drugs have been incorporated into the coating as part of the coating process. Within these coating stages contact lenses have been treated with a range of polymer solutions of no more than 1 wt.% concentration, containing carboxyl, amide, and quaternium functional groups. Various conditions have been tested as part of each stage through process development. Treated lenses have been characterised by using dynamic and static contact angle and friction techniques, with additional dimensional and resistance to lipid analyses. A six-stage treatment process has been optimized and developed involving a first carboxylic acid pre-treatment in the hydration / extraction stage. The next step has been the entrapment of the drug-loaded nanocarriers within two oppositely charged coating layers of polyquaternium followed by a crosslinker layer of synthesized crosslinking macromers based on NMA (N-methylolacrylamide), the formulation being optimized within the project and the selected one being sodium acrylate-N-

¹ Urtti, A., Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv. Drug Deliv. Rev., 2006, 58: 1131-1135.

² Schultz et al. A medical device/drug delivery system for treatment of glaucoma. Clin Exp Optom. 2009; 92:343-8.

³ S.R. Tonge, B.J. Tighe, Responsive hydrophobically associating polymers: a review of structure and properties. Adv. Drug Deliv. Rev., 2001, 53: 109–122

⁴ S.R. Tonge, B.J. Tighe, lipid-containing compositions and use thereof. US6436905 B1, 2002.

⁵ Qiu Y et al., silicon hydrogel lens with crosslinked hydrophilic coating. US2012/0026457A1

methacrylamide-acrylamide copolymer p[NaA-b-(NMA-co-AM)] 80:10:10. This layer has helped to anchor and crosslink the final hydrophilic PVA layer added in the final sterilisation stage.

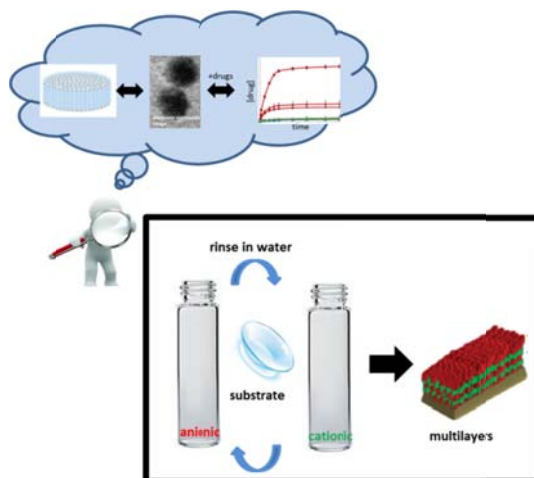


Figure 1: Scheme of coating technology extended to incorporation of drug-loaded nanostructures in contact lenses surface coating. (see attached document).

In addition to the controlled drug release properties observed in the new devices, the type of functional groups within the hydrophilic polymer has determined the quality of the surface improvements i.e. wettability, friction, and resistance to lipids. It must be taken into account that layer thickness and interaction with the preceding substrate / surface is influenced by the polymer concentration, solution pH, soak time in solution and temperature of the process. Properties of functional groups and charge density of polymers play a role in local mobility i.e. conformation of structure and access to attachment sites, and surface roughness. To sum up, the project has adapted the new coating system for contact lenses to enable hydrophilic and hydrophobic ophthalmic drugs and phospholipid supplements to the tear film.

The new procedure is currently under patenting process and several contact lenses companies have already shown their interest on it. The fluent relationship of the Fellow with these industrial partners and clinicians has helped to increase their interest in a deeper investigation of new types of contact lens coating materials for different purposes. With the contacts that the Fellow has made in the biomaterials community there will be other biomaterials that could need improved surface coatings. THERALENS scientific results are predicted to contribute to both European excellence and competitiveness by the development of more stable and therapeutically effective contact lenses, by keeping the costs effectiveness. The window of opportunity for this project is related to the expiry of the controlling Ciba patent that prevents competitors from using coatings on silicon-hydrogel contact lenses. The fact that the US has been in virtually sole control of this technology means that the expertise to take such developments forward did not exist in Europe until now. This project will make this a European focal point for advice in development of these complex materials. The results already obtained, and currently being generated, are expected to lead to a number of publications and one patent. THERALENS IP is expected to remain within the EU and thus any commercial products that arise from the results generated by the project will directly contribute to the competitiveness of the EU. The results of THERALENS have been disseminated to researchers at Sauflon Pharmaceuticals, and small in vitro test will be planned by them in the next few months. Different surrogate fluids will be used to establish differences in their interaction with inflammation-promoting and cell growth promoting proteins, and to study specific interfacial interactions and the effectiveness of the released drugs.

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