Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Development of Novel Tamponade Agents has Improved the Treatment of Retinal Detachment

1. Summary of the impact

The University of Liverpool (UoL) has developed novel tamponade agents used to treat retinal detachments. They are modified silicone oils that have an increased extensional viscosity. This makes it easier to inject into the eye by the vitreoretinal surgeons and, experimentally, they have an increased emulsification resistance. This technology has been licenced to Fluoron GmbH who manufacture these products under the name Siluron® 2000 and Siluron® Xtra. Siluron® 2000 has been on the market worldwide since 2008 and used to treat patients providing an impact to health by enhancing the clinical outcome for retinal detachment patients. Siluron® Xtra was launched in July 2013.

2. Underpinning research

Retinal detachment is an important cause of blindness in the western world. It is the final common pathway for many disease processes including diabetic retinopathy and age-related macular degeneration. Treatment involves the removal of the vitreous from the eye and its replacement with silicone oil to cause closure of the retinal tear. The emulsification of silicone oil-based tamponade agents, which are used in the treatment of complex retinal detachments, is a significant clinical problem. This causes problems of clouding of vision and adverse biological responses including inflammatory reactions and blocking of the fluid outflow from the eye potentially leading to glaucoma. Currently, high shear viscosity oils are used to counter emulsification but the higher the shear viscosity the more difficult the oils are to inject and remove from the eye.

This project took a multidisciplinary approach involving Prof Rachel Williams (then a senior lecturer in Department of Clinical Engineering, UoL) and Dr Michael Garvey (then a Senior Research Fellow in the Department of Physics, UoL) in collaboration with Prof David Wong, Consultant Vitreoretinal surgeon, University of Hong Kong and Honorary Professor (UoL), and Mr Theodor Stappler, Honorary Lecturer (Clinical, Royal Liverpool University Hospital) who provided strong clinical input. A highly qualified surfactant chemist (Dr Michael Day: Postdoctoral research associate, UoL) studied the mechanisms involved in the formation of the emulsions in the eye. The research showed that the process of emulsification in the eye results from the oscillation of the silicone/water interface under a shear force which leads to the pulling out of filaments of the oil into the aqueous phase which snap resulting in the formation of satellite silicone droplets which will persist in the aqueous phase. The addition of very high molecular weight polymers to the oil increases the extensional viscosity and prevents filament snapping and satellite droplet formation. The increase in extensional viscosity was achieved by adding a range of high molecular weight additives of varying molecular weight at different concentrations to clinical grade silicone oil. The underpinning research was funded by EPSRC (EP/C546679-1) in 2005-2006 under the post-doctoral mobility scheme to allow Dr Day to use his expertise to address a cross-disciplinary problem.

The project demonstrated that modification of standard clinical grade silicone oil tamponade agent (Siluron® 1000, Fluoron GmbH) with a low percentage of a very high molecular weight (423k) polymer of the same chemistry increased the extensional viscosity of the oil and reduced its emulsification [1,4]. Furthermore these silicone oil blend have a lower shear viscosity than Siluron® 5000 (Fluoron GmbH), the current high viscosity clinical grade silicone oil, and thus are advantageous in terms of ease of injection into and removal from the eye [2]. A patent [3] has been filed to protect these findings (WO 06/413269) in the EU, US and Canada and has been granted in Australia, China, Hong Kong and Japan (15/02/2013). Further funding was received from Fluoron GmbH (£58,629, 2007) to develop a product.

3. References to the research

Key Outputs

1. **Williams RL**, **Day M**, **Garvey MJ**, English R, **Wong D**. Increasing the extensional viscosity of silicone oil reduces the tendency for emulsification. Retina 30(2):300-304, 2010 DOI: 10.1097/IAE.0b013e3181babe0c. Citations: 9 Impact Factor: 2.825
2. **Williams RL**, **Day M**, **Garvey MJ**, Morphis G, Irigoyen C, **Wong D** and **Stappler T**. Injectability of silicone oil-based tamponade agents. B. J. Ophthalmol. 95: 273-276, 2011 DOI: 10.1136/bjo.2010.192344 Citations: 3 Impact Factor: 2.725
3. **Garvey MJ**, **Williams RL** and Day M. Composition for treatment of a detached retina and method of production thereof WO 06/413269 May 2006
4. **Day M**, Blanchard RL, English R, Dobbie T, Williams R, **Garvey M** and Wong D, Shear and Extensional Rheometry of PDMS Tamponade Agents Used in Vitroretinal Surgery, AIP Conference Proceedings 1027, 1411 (2008); doi: 10.1063/1.2964592

Original grants

2005-2006. **EPSRC**. Identification of colloid science routes to improve the clinical performance of tamponade agents, £65,717, PI **RL Williams**, CoIs **MJ Garvey**, **M Day**

2007-2008. **Fluoron GmbH.** Producing novel tamponade agents**,** £58,629 PI **RL Williams**

4. Details of the impact

This project developed a new tamponade agent to enhance the clinical outcome after treatment of retinal detachments. Standard tamponade agents are based on silicone oils which can emulsify in the eye and cause adverse side effects. The underpinning research provided proof of principle that a silicone oil with an increased extensional viscosity had an increased resistance to emulsification. This was achieved by the addition of a low percentage of a very high molecular weight polymer of the same chemistry to the silicone oil. Following on from this the UoL established that the extensional viscosity property of the blend also made the material easier to inject in comparison with an equivalent silicone oil with the same shear viscosity but without the high molecular weight additive.

An additional benefit of this approach is that since there has been no chemically different material added to the clinical grade silicone oil the regulatory requirements were easier. In 2007 a collaboration was established with Fluoron GmbH, a silicone oil tamponade manufacturer, to develop the proof of principle prototype into a clinical grade product. Fluoron GmbH licensed the technology from the University and have since contributed a minimum payment of £10k pa and paid all patent costs.

Fluoron GmbH launched the product named Siluron® 2000 in 2008 (EC certification: CE 575554) [4,6]. It accounted for 32% of its sales by units in the period 2008-13 with 34,208 sales by 30th September 2013 [11]. A second product named Siluron® Xtra based on this technology was launched for sale in July 2013 (EC certification: CE 575554). This product has 10% of the high molecular weight additive further increasing the resistance to emulsification while maintaining the ease of injection within the range of current clinical products. Fluoron GmbH have brought this second product to market in response to requests from vitreoretinal surgeons [5] and it has sold 1,145 units part way through its first year of introduction [11]. These products have enabled Fluoron to gain new customers and reduce complaint rates by 40% [11].

The ultimate beneficiaries will be patients. Current tamponade agents are either made from 1000mPas silicone oil that is known to emulsify in the eye and cause adverse effects for the patient or 5000mPas silicone oil that is very viscous and difficult to inject. All silicone oils are currently removed after 3-6 months because of the risk of emulsification leading to complications. The new Siluron® 2000 has a shear viscosity of 2000mPas making it easier to inject than 5000mPas oil but

because of the increased emulsification resistance will be less likely to cause adverse effects to the patient [9,10]. Another major advantage of Siluron® 2000 is that its extensional viscosity makes it easier to inject than an equivalent oil meaning that smaller gauge instruments can be used to inject and remove it from the eye causing a significant reduction in trauma to the patient's eye due to the surgery. This also fits very well with the general move, within vitreoretinal surgery, to the use of smaller gauge instruments. Siluron® Xtra has a shear viscosity of 5000mPas and can therefore be injected and removed using existing surgical equipment but has been requested by clinicians owing to its enhanced resistance to emulsification and thus improved clinical outcome for patients.

The market for silicone oil tamponades is not large but is valuable because the patients requiring this treatment would go blind if not treated. The incidence of retinal detachment is reported as 1 per 10,000 of population pa and of these 15-20% are treated with silicone oil tamponades. Some vitreoretinal surgeons will not use oils because of the oil related complications and therefore the availability of an oil with increased emulsification resistance is expected to increase this treatment option. This is the first product specifically designed to address this problem. Fluoron GmbH has sold over 25,000 units of Siluron® 2000. In 2012 the units were sold across 37 different countries with the largest numbers going to Germany and Egypt and substantial numbers going to Singapore, Italy, Belgium and Switzerland. They have recently (August 2013) received a licence to sell Siluron® 2000 and Xtra in China and believe this to be a substantial market, expecting to sell over 1000 units in the first year. An audit of its use in St Paul's Eye Unit at Royal Liverpool University Hospital on 20 patients reported "Clinically it proved easy to inject and remove in a small-gauge setup. Anatomical success rates were comparable to our experience with standard 5000cst silicone oil, so was its safety profile." [7].

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

4. Fluoron GmbH website description of Siluron® 2000 and Siluron® Xtra http://www.geuder.de/media/raw/RZ_Brochure_Siluron_GB_25072013.pdf demonstrating commercial promotion of the products

5. Fluoron GmbH website user report on Siluron family of products http://www.geuder.de/media/raw/User_Report_Siluron_Xtra_by_Stappler_2013_E.pdf providing a clinical testimonial of the product

6. EC-Certificate for Siluron® 2000 and Siluron® Xtra http://www.fluoron.de/index.php?myID=56&sprache=en demonstrating compliance with EU regulations

7. **Theodor Stappler**, Lazaros Konstantinidis and **David Wong** Siluron 2000 Novel-Generation Silicone Oil: Proof of Concept and One Year Clinical Results *Invest Ophthalmol Vis Sci* 2012;53: E-Abstract 5792 providing evidence of clinical acceptability. This is an audited clinical study that used the new oil and evaluated clinical outcomes.

8. Caramoy A. Schröder S. Fauser S. and Kirchhof B. (2010) In vitro emulsification assessment of new silicone oils. Br. J. Ophthalmol. 94(4):509-512 **DOI:** 10.1136/bjo.2009.170852 demonstrating emulsification resistance in comparison with other tamponade agents evaluated by a different research group

9. Caramoy A. Hagedorn N. Fauser S. Kugler W. Groβ T and Kirchhof B. (2011) Development of emulsification-resistant silicone oils: Can we go beyond 200mPas silicone oil. Invest. Ophthalmol. Vis. Sci. 52(8):5432-5436 **DOI:** 10.1167/iovs.11-7250 Further demonstration of emulsification resistance by a different group

10. Yau Kei Chan, Chiu-On Ng, Paul Knox, **Michael Garvey**, **Rachel Williams**, and **David Wong** (2011) Emulsification of silicone oil and eye movements Invest. Ophthalmol. Vis. Sci. 52:9721-9727 **DOI:** 10.1167/iovs.11-8586 demonstrating emulsification resistance using a different model designed by scientists at the University of Hong Kong to mimic clinical eye movement and its influence on oil emulsification.

11. Letter: Geuder (Fluoron) dated 30th October 2013 and accompanying sales data.