Institution: University of Reading

Unit of Assessment: 8 Chemistry

Title of case study: Biocompatible polymer coatings for the long-term implantation of biomedical devices in humans

1. Summary of the impact

Biomedical devices that need to be implanted into the body typically experience the so-called foreign-body reaction: proteins adhere to the surface of the devices, leading to rapid loss of function and, eventually, to a requirement for replacing the device. Between October 2006 and September 2011, The University of Reading, in collaboration with the UK SME *BioInteractions Ltd*., developed and evaluated a range of new polymers for coating implantable biomedical devices, especially coronary stents and catheters. The result was a coating system that can deliver a drug controllably over a pre-defined period, leading to the commercial biomaterials platforms Adapt^{TM} and Assist^{TM}. This work resulted in capital investment by Biointeractions Ltd and a substantial increase in their research staffing.

2. Underpinning research

Drug-eluting stents (DESs) – the use of which is regulated by the National Institute for Health and Care Excellence – represent a major treatment option for arterial coronary disease. DESs enable controlled drug-release from an implanted device (a stent) whose main function is to open up a partially-blocked artery. Substantial savings can be made if stent replacement is avoided within the first 3 years after initial implantation: up to £5000 per patient is saved if no re-stenting procedure is required in this period. However, most polymers used in coatings suffer from protein absorption and foreign-body rejection problems, and so need to be replaced earlier than this. Also, because most drugs are hydrophobic, and the polymer coatings generally used as *in situ* drug-delivery vehicles are not readily permeable to water, the majority of the drug remains encapsulated in the polymer and so is never delivered to the surrounding tissue. To address these issues, the research team set out to develop a more effective coating system for coronary stents that would allow efficient delivery of drugs into the bloodstream from the surface of the stent. Key targets were (a) to develop a material that allows complete release of the chosen therapeutic agent in a controlled manner, whilst (b) presenting a non-thrombogenic (i.e. non-protein-absorbing) surface to the blood vessel. Achieving these goals was seen as essential to the success of an advanced DES.

The research team [University of Reading and BioInteractions Ltd., funded by the Knowledge Transfer Partnership (KTP) programme], developed a series of polymer coatings containing hydrophilic subunits that were already approved for human use (so avoiding potential regulatory hurdles). The polymers were optimised to deliver over 80% of the encapsulated drug in a 30-day time window, and to ensure that no delamination of the polymer coating from the surface of the stent occurred. Thermomechanical analysis of the new polymers revealed that they are elastomeric and highly flexible (glass transition below room temperature). A low glass transition improves the rate of release of the drug: polymers with glass transition temperatures higher than ambient are rigid and so display a less satisfactory release profile. In fact, elution studies for the drugs paclitaxel and sirolimus demonstrated that 100% of the encapsulated drug was delivered from the new coating over a 30-day time period. The elution rate was further controlled by varying the ratio of hydrophilic to hydrophobic subunits in the polymer, allowing drug release for up to 10–15 days, and also by varying the structure of the drug via an enzyme-mediated modification, which allowed drug elution to be extended to around 30 days. The cytostatic drug sirolimus is also known as rapamycin, and the KTP programme led to the development of modified versions of rapamycin (carbonate esters) that are more suited to polymer-based release applications.[1] These technologies (trademarked as Adapt^{TM}) have now been commercialised by BioInteractions Ltd.

Further development was carried out by Dr Rasin-Dadre (KTP Associate and PhD student 2008–2011) as part of a follow-up collaboration between The University of Reading and BioInteractions Ltd. Development of one of the polymer technologies resulting from the first KTP led to the creation of a second-generation material with a substantially greater hydrophilic character.[2] The new polymer material contains a component that mimics the structure of the outer wall of cells and so is better tolerated by biological systems in terms of the foreign-body reaction. The surface of

this second-generation polymer is remarkably resistant to protein and cellular deposition because it promotes the formation of an extensive hydration layer that inhibits such deposition. Hence, the new material is highly biocompatible and its ability to retain a clean surface allows continuous elution of nonpolar drug substances. Apart from greater utility for the purposes of generating drug releasable stents, this new material has a potentially wide range of applications for any biomedical devices that need to be implanted in the body. A partnership between BioInteractions Ltd and a custom synthesis laboratory (IsleChem LLC; USA) will produce these materials at large scale for clinical evaluation. In particular, the main focus of product development from this technology is the manufacture of contact lenses for ocular drug delivery and of coatings for long-term implantable catheters (Assist™).

The project was developed by Simon Onis (Biology specialist, BioInteractions, 2006 – present), Alan Rhodes (KTP Associate and PhD student, 2006-2008; BioInteractions Senior Scientist, 2008 – present), Fanny Raisin-Dadre (KTP Associate and PhD student, 2008 – 2011; BioInteractions Research Scientist, 2011 – present), John Mckendrick (Lecturer/Associate Professor in Chemistry 2000 – present; academic supervisor to AR and FRD), Shivpal Sandhu (Research Director, BioInteractions, 2006 – 2008) and Ajay Luthra (CEO, BioInteractions, 2006 – present).

3. References to the research

This research has been internally assessed as of at least 2* quality.

[1] Rhodes, A.; Onis, S. J.; Sandhu, S.; Mckendrick. J. E. U.S. Patent Application number

US20090253733. Preparation of Rapamycin Carbonate Esters via Lipase-catalysed Condensation Reaction as Anti-tumour and Anti-bacterial Agents (2009).

[2] Sandhu, S.; Raisin-Dadre, F.; Mckendrick, J. E.; Rhodes, A.; Onis, S. J., PCT Int. Appl. WO 2012175923 A1. Biomimetic Ampholyte Compounds Comprising Phosphate and Quaternary Ammonium groups and Polymers Made Therefrom (2012). Also published as U.S. Patent Application US 20130053470 A1 (2013).

Grants: (i) "Synthesis and characterisation of biocompatible bioabsorbable polypeptide analogues", KTP 796, £100K (2005-2008); (ii) "Next generation biomimetic non-biological based biomaterials", KTP 7076, £130K (2008-2011).

4. Details of the impact

Medical devices are a $434 billion market worldwide, and coating systems for use in medical devices reached a market value of ~$5.3 billion/year in 2012 (Medical Market Outlook Report, Espicom Business Intelligence, 2013).

Given the very recent date of the fundamental research that underpins the technology, it is remarkable that it has already led to new products which are now being marketed actively by Biointeractions Ltd. Economic impacts of this work include the generation of new capital investment by Biointeractions and 3 new staff positions within the company.

New capital investment by BioInteractions, resulting from this work, has included the purchase of a Sono-Tek, ultrasonic spray stent-coating platform and the renting of clean room facilities for the coating of stents for human implantation, with 1000 stents having being coated at a cost of £200 per stent. Moreover, the polymer technology developed for coating coronary stents, as described above (Adapt™)[a],[b] has very recently been adapted – with a partner company – for use in implantable glucose sensors and catheters.[c] The glucose sensors, using the Adapt™ polymer coating system under license from BioInteractions, will allow the partner company to market an improved device with extended implantation lifetime. The range of clinical applications for such implantable devices is very significant, providing a significantly larger potential market for the commercialisation of the technology. A partnership agreement is expected to be in place by the

end of 2013, but details are commercially sensitive and so are confidential at present. The licensing agreement is expected to generate income of ~£150K/year from 2016 onwards.[d] The projected incomes from the lubricating coating system for catheters (Assist™)[c] developed from the Adapt™ technology, are £176K in 2015 and £590K in 2017.[d]

The second-generation coating system developed through the follow-up KTP programme requires approval for medical use in humans. BioInteractions is currently involved in the initial stages of clinical evaluation, and a partnership has been agreed with IsleChem LLC that will allow production of the materials on the scale needed for full clinical evaluation. The further capital investment required to bring this novel material to a point where BioInteractions can realise their investment through a technology licensing agreement is around £100K.[d] The company has heavily promoted this system as a base material for the development of contact lenses with long residence times in the eye, and the technology is also being applied to implantable stents for long-term use: in this case, revenue is expected to be generated within 6 years. These developments have led BioInteractions to increase the size of their research team by 150%.[e]

Biointeractions Ltd have actively promoted the products and technologies that arose from the research described here. Since 2008, the company has presented these new polymer technologies at 18 major international biomedical-device trade shows (often represented by the former KTP Associates): UK Biomaterials, Liverpool, 2008; Medical Device & Manufacturing (MD&M), Minneapolis, 2008; MEDTEC Ireland, Galway, 2009; MD&M, Minneapolis, 2009; Polymeric Biomaterials, Reading, 2010; UK Biomaterials, Glasgow, 2010; MD&M West, Anaheim, 2010; MD&M East, New York, 2010; MD&M, Minneapolis, 2010; Compamed (Medica), Düsseldorf, 2010; MD&M West, Anaheim, 2011; MD&M East, New York, 2011; Compamed (Medica), Düsseldorf, 2011; US Biomaterials, Florida, 2011; MD&M West, Anaheim, 2012; MD&M East, Philadelphia, 2012; Biointerfaces, Dublin, 2012 and MD&M West, Anaheim, 2013.

5. Sources to corroborate the impact *Contact details provided

Evidence of the material being brought to market can be obtained from:

[a]. Biointeractions Ltd: http://www.biointeractions.com/adapt.htm (Adapt™ technology)

[b]. Biointeractions Ltd: http://www.biointeractions.com/drug_delivery.htm (Drug delivery)

[c]. Biointeractions Ltd: http://www.biointeractions.com/assist.htm (Assist™ technology)

[d]. The CEO of BioInteractions Ltd*.

[e]. The KTP Associate working on KTP grant No. 796 (now a staff member at Biointeractions)*. This scientist was one of the Biointeractions team who won Best Biotechnology Award 2008 in the area of cardiovascular research (Medical Futures Innovation Award): http://www.medicalfutures.co.uk/2008.php

[f]. The first KTP research collaboration was judged by the KTP sponsorship panel to be so successful that it warranted publication of a case study: See: http://www.reading.ac.uk/web/FILES/ktc/BioInteractions_Ltd.pdf