Institution: Aston University

Unit of Assessment: 15: General Engineering

Title of case study: More comfortable contact lenses modelled on Nature's principles

1. Summary of the impact

The impact we describe arose from research led by Professor Brian Tighe between 1998 and 2013 involving research students and fellows of Aston Biomaterials Research Unit (BRU). We proposed [3.1] that responsive polymers modelled on nature's macromolecules would be required for successful synthesis of biomaterials analogues of natural systems. This led to health and economic impacts in the area of vision care, specifically: *a commercially successful family of daily disposable contact lenses (current annual sales > 2 billion lenses), which use blink-activated release of hydrophilic macromolecules from contact lenses to mimic aspects of the corneal surface thereby enhancing ocular comfort.*

2. Underpinning research

In the last decade (2000-2013) B. Tighe (Professor, 1990-present) initially working with S. Tonge (Research Student 1995 –1998, PDRA 1999 – 2002), and subsequently C. Maissa (Research Student 1997-2000) and V. Rebeix (Research Visitor 1998) developed and elaborated a concept first described in 2001 (invited contribution - impact factor 14 journal): "If we are to advance in the design of polymers to interface with, and mimic biological systems, we need to develop responsive polymers" [3.1]. This proposition emerged from our longstanding work and resultant understanding of the principles and biomimetic applications of hydrated polymers in biomaterials science, ranging from synthetic work [3.2] to modelling of corneal transport processes [3.3]. Similar molecular and biochemical principles are involved in the design of materials for contact lenses, wound dressings and dermal delivery systems. BRU has exploited responsive biomaterials in two broad areas.

(A) RESPONSIVE CONTACT LENSES THAT MIMIC THE CORNEA.

BRU identified, explained and extended an in-eye release mechanism activated by the eyelid in a polyvinyl alcohol-based contact lens that was first marketed by CIBA VISION (CIBA DAILIES^{TM}) in 1996. The manufacturer initially claimed that the material was fully cross-linked [5.10b]. BRU, however, identified the fact that linear soluble PVA was released from the lens matrix [5.10c] and proposed the extension of this into a blink-activated mechanism with analogies to the action of mucin at the corneal surface, thus maintaining an aqueous hydrodynamic boundary layer. The research involved development of an effective in vitro model and a demonstration of the in vivo role and persistence of adsorbed macromolecules at contact lens surfaces [3.4]. This underpinned the development of successive generations of CIBA single-use contact lenses (Section 4 A).

(B) RESPONSIVE GAG MIMICS FOR OCULAR, ORTHOPAEDIC AND DERMAL APPLICATIONS

Research building on our 2001 proposition relating to the need for responsive polymers was extended to the use of the C-linked sulphonate group as a biomimetic surrogate for the O-linked sulphate group found in glycosaminoglycans (GAGs). The GAG components of proteoglycans provide the osmotically responsive hydration engine in many body sites. We have applied this biomimetic principle to dermal sites (wound dressings), ocular sites (contact lenses and intraocular lenses) and to the spine (injectable intervertebral disc nucleus repair) [3.5, 3.6].

Underpinning research led by BRU on the application of GAG analogues to the spine was funded by EPSRC (grant GR/S41173/01: 2004–2007, £247k to Aston) "New Clinical Materials for Biomimetic Repair of Intervertebral Disc" involving Dr Jill Urban (Oxford) and Professor Sally Roberts (Robert Jones and Agnes Hunt Hospital, Oswestry) and two clinical centres. The GR/S41173/01 final report was judged "outstanding".

In summary, our initial proposition was that if we are to advance in the design of polymers to

interface with and mimic biological systems, we need to develop responsive polymers [3.1]. This underpinning concept has already been successfully applied to soft contact lens surfaces that mimic aspects of the corneal behaviour (Section 4A) where the claimed impact is well-established. The significance of BRU research in the biomimetic design of soft tissue analogues was recognised by: the inaugural award of Inaugural UK Society for Biomaterials Presidents Prize (2002), the BCLA Gold Medal (2003), and the IOM^3 Chapman Medal for innovation in biomaterials (2006).

3. References to the research (the 3 marked * are best indicators of research quality)

3.1 Tonge SR, Tighe BJ. Responsive hydrophobically associating polymers: a review of structure and properties, Advanced Drug Delivery Reviews 2001; 53:109-122. doi.org/10.1016/S0169-409X(01)00223-X

*3.2 *Oxley HR, Corkhill PH, Fitton JH and Tighe BJ.: Macroporous hydrogels for biomedical applications: Methods and morphology, Biomaterials 1993, 14:1064-1072. doi.org/10.1016/0142-9612(93)90207-I*

*3.3 *Li LY and Tighe BJ Numerical simulation of corneal transport processes, J. Royal. Soc. Interface 2006, 3(7), 303-310. doi:10.1098/rsif.2005.0085*

*3.4 *Tonge SR, Jones L, Goodall S and Tighe BJ et al. The ex vivo wettability of soft contact lenses, Curr Eye Res 2001, 23 (1): 51-59, doi/abs/10.1076/ceyr.23.1.51.5418*

3.5 Tighe BJ, Bramhill J and Campbell D, Proteoglycan analogues for ophthalmic and orthopaedic applications. Advanced materials research 2012, 506,3-6. doi.org/506: 3-6. 10.4028/www.scientific.net/AMR.506.3

3.6 Tighe BJ and Mann A, Sulphonated biomaterials as glycosaminoglycan mimics in wound healing, Chapter 13 in Advanced wound repair therapies, D Farrar (Ed), Woodhead Publishing Limited, Cambridge (2011). (PDF available on file).

This underpinning research has been supported by both BBSRC (e.g. “An integrative approach to the development of a novel biomimetic keratoprosthesis”, £188,675, 01/02/1999) and EPSRC (e.g. “New Clinical Materials for Biomimetic Repair of Intervertebral Disc”, £247,411.00, 24/07/2003) through peer-reviewed research grants. Results were published (e.g. 3.2) in the leading (web of science) biomedical materials journal with an invited overview (3.1) in a 14 impact factor journal.

4. Details of the impact

The business and health benefits

(A) RESPONSIVE MACROMOLECULAR RELEASE: A PLATFORM FOR MORE COMFORTABLE CONTACT LENSES

BRU research is regularly presented to the mixed commercial, clinical and academic audience at the annual Clinical Conference of the British Contact Lens Association (BCLA) by Tighe and co-workers. The relevance of BRU work to both UK and US ophthalmic industry and clinical community is reflected in the reporting of such presentations on websites sponsored by major companies. [e.g. 5.1] Through this mechanism the commercial and clinical relevance of BRU work is recognised. The development of a series of daily disposable contact lenses [5.2] (e.g. CIBA DAILIES™ All Day Comfort™ and CIBA DAILIES™ Aqua Comfort Plus™), which incorporate the concept of blink-activated release of linear polyvinyl alcohol by a reptation mechanism, arose from this process. The consequent corneal mimicry dramatically reduces the end of day discomfort that limits the wear duration of the unmodified lens.

CIBA personnel [5.10] first became aware of, and identified the importance of BRU research,

through reference [5.10c] presented at the 1998 BCLA conference. Following a visit to BRU where the blink activation process and its potential enhancement in PVA-containing lenses was explained, CIBA began to embody the principles in their products. In consequence CIBA made unrestricted research donations to BRU which for a ten year period supported a PDRA working on ocular biomaterials research at Aston.

The more recent CIBA product variant (CIBA DAILIES™ Aqua Comfort Plus™) uses two polymers (polyvinyl alcohol and polyethylene glycol) within the lens matrix and a third surface-active polymer added to the lens packing solution. BRU has developed unique methodology demonstrating the in-eye duration and effectiveness of such surface-active polymers adsorbed onto the lens surface [3.4]. The CIBA DAILIES™ products couple this mechanism with blink-activated release of polymers from the lens matrix. The release mechanism that we proposed is incorporated in a marketing claim that the lens "moisturises at every blink" [5.2].

The latest DAILIES product (launched 2012) is a silicone hydrogel lens known as DAILIES Total 1™. This product contains phosphatidylcholine; intended to be ocularly released; so as to stabilise the aqueous tear film. This contribution, too, can be directly attributed to BRU influence and supporting research. In fact, CIBA VISION has sought out BRU assistance in pre- and post-market support in this arena [5.10].

BRU's research in identifying and quantifying the blink-activated release of polyvinyl alcohol, and the mechanism of macromolecular modification of the lens surface has had significant health and commercial impacts. It underpinned the blink activation principle, which now characterises all CIBA DAILIES™ lenses, sold in more than 70 countries with an annual 'DAILIES' PVA-only production (2011) of over **2 billion lenses** [5.4]. CIBA has a market share of **ca 25% of the worldwide contact lens market, now estimated at $6.8 billion**. Daily disposable lenses account for 15% of lenses fitted, but almost 35% of soft lens revenue [5.3, 5.4]. CIBA Vision has recognised BRU's contribution in presentations and publications and key CIBA personnel involved will provide verification "to any review panel" [5.10].

(B) RESPONSIVE GAG MIMICS IN OCULAR, ORTHOPAEDIC AND DERMAL APPLICATIONS

Ongoing biomimetic design of other soft tissue GAG analogues has included a long-term relationship with SME, First Water Ltd, a specialist UK manufacturer of wound dressings, skin adhesives and conductive hydrogels. Commercial outcomes were recognised by EPSRC via their national Knowledge Transfer Challenge competition and this impact that has continued throughout the impact period, was described (archived EPSRC website) as first-class interaction between researchers and industry [5.5].

A novel intervertebral disc application involves an injectable pre-gel avoiding the need for major surgical intervention and, by mimicking the natural GAGs, restores osmotic responsiveness and disc height. The exploitation potential of the fundamental work (Section 3) was recognised by an EPSRC "follow-on" award, given to develop IP and subsequent commercialisation [5.6]. The novelty of the resultant patent [5.7] was recognised in the US "Best Spine Technologies of 2009" awards by the US orthopaedics industry journal, Orthopaedics This Week, where it was highlighted as one of the top three regenerative spinal technologies of the year [5.8]. Long-term studies of biomechanical stability are in progress.

BRU studies of the application of responsive GAG analogues to therapeutic and cosmetic contact lenses for dry eye symptomatology, including a process development programme, supported by J&J Vision Care has led to joint intellectual property [5.9].

During the impact period there have been further awards to Prof Tighe, recognising the significance and commercial importance of BRU achievements, including the European Contact Lens Industry (EFCLIN) Technology Award (2008) and the ISCLR (predominantly funded by the international contact lens industry) Research Medal (2009).

5. Sources to corroborate the impact

5.1 http://www.thevisioncareinstitute.co.uk/sites/default/files/content/uk/doc/111215%20TVCI%20Assottica.pdf.

5.2. *Advance to DAILIES® brand contact lenses*
The only contact lenses with blink-activated moisture (accessed 14th May 2012): http://www.dailies.com/for-ecp/for-ecp-technology.shtml

DAILIES® AquaComfort Plus® Contact Lenses
Brand new lens every day, refreshing all day (accessed 14th May 2012): http://www.dailies.com/products/dailies-aquacomfort-plus.shtml

5.3 *Contact Lenses 2011: Market and survey data*
Nichols, JJ Contact Lens Spectrum, Volume: 27 , Issue: January 2012, page(s): 20-25.

5.4. *CIBA Vision Overview (accessed 14th May 2012): http://www.cibavision.com/about-us/worldwide-locations.shtml*

5.5 *Faster and more effective treatment for wounds - an example of first-class interaction between researchers and industry. EPSRC March 2007 (accessed 14th May 2012):* http://www.epsrc.ac.uk/newsevents/casestudies/2007/Pages/wounds.aspx

5.6 *12 month EPSRC Follow-on grant: Clinical Materials for Biomimetic Repair of Intervertebral Disc, Value £259K*
Awarded to Prof B. J. Tighe (EP/G006202/1) Start date October 2009

5.7. *PATENT: Tighe, B J, Franklin V J, Lydon F J, Roberts S, Urban J P G and Sarit S (2009), 'Intervertebral Disc and Intraocular Lens', WO/2009/127844. (US 2011/0118379 published 05/19/2011)*

5.8 *Orthopaedics this week*
Award-Winning Biomaterial Heals Discs (accessed 14th May 2012): http://ryortho.com/spine.php?news=300_AwardWinning-Biomaterial-Heals-Discs

5.9. *PATENT: Tighe B J, Nasso M Benning B and Molock F J, 'Polymeric compositions comprising at least one volume excluding polymer,' US 20080114123 (2008)* ***Granted May 2011*** *AND DIVISIONAL US20130289135 A1, Publication Date Oct 31 2013.*

5.10 *The former Global Head R&D Strategy and Business Alliances (LCW), and Global Head of Research (JML), CIBA VISION (now Alcon CIBA) principal authors of the CIBA publication (a) below "will be happy to validate all of this information to any group or review board". [email addresses placed on file].*

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CIBA publication (b) explicitly presents the original CIBA assertion that was challenged by the BRU research, first reported in publication (c) that led to the claimed impact. Reference (c) is a pdf provided by the former CIBA Global Head of Research showing the poster annotated with JML's first circulation of the information with CIBA Vision. References (a-c) were suggested by CIBA personnel LCW and JML as corroborations of the route to impact.

(a) Winterton, LC, Lally, JM, Sentell, KB, Chapoy LL, The elution of poly (vinyl alcohol) from a contact lens: The realisation of a time release moisturising agent/artificial tear, Journal of Biomedical Materials Research Part B: Applied Biomaterials (2007) Volume 80B, Issue 2, pages 424–432. DOI: 10.1002/jbm.b.30613

(b) Nelfilcon A, A New Material for Contact Lenses. Chimia 53: (1999) 269 -274 (pdf saved).

(c) Maissa C, Tonge S, Guillon M, Tighe B. Surface properties of daily disposable contact lenses. Contact lens & Ant. Eye (1998) 21: 138. (pdf - annotated by JML)