Institution: University of Sheffield

Unit of Assessment: 3A - Allied Health Professions, Dentistry, Nursing and Pharmacy: Dentistry

Title of case study: Clinical & Commercial Impact of a new Regenerative Bone Cement for Middle Ear Surgery

1. Summary of the impact

Research into the biocompatibility of glass-ionomer bone cements conducted at the School of Clinical Dentistry led directly to the start-up of a UK company to manufacture a new medical device, creating jobs in the supply chain and wealth creation via international sales. The new bone cement is safe and clinically effective, and has maintained or restored hearing to improve the quality of life of over 10,000 patients worldwide since 1st January 2008. In the course of supporting this commercial partner, Sheffield's staff also contributed to other non-academic tasks.

2. Underpinning research

Glass-ionomer cement technology has been used to repair tooth tissue in dentistry for over 40 years, but attempts to utilise these biomaterials in bone repair were not successful for much of this period. This failure was due to a lack of understanding of the interaction of the cement with living tissues, and a lack of data on biocompatibility prevented the optimisation of a formulation for use in bone tissue repair and regeneration. Academic staff (Paul Hatton and Ian Brook) based in Sheffield's School of Clinical Dentistry have been working on these challenges since the late 1980's. Since then, research undertaken by them and sometimes with collaborators underpinned the development of an optimised ionomeric bone cement composition by establishing that:

- The biocompatibility of ionomeric bone cements is related to glass composition, with mechanisms based on both ion release and selective protein adsorption [R1,R2]. Furthermore, biocompatibility may be optimised and/or modified by different strategies including compositional changes and controlled glass crystallisation [R1-R3].
- Aluminium ions are generally considered essential for cement setting, but also cause mineral defects in new bone [R1,R2] while their release is associated with neurotoxicity [R6]. Aluminium is very difficult to remove from the formulation, but our research identified an optimised composition with good biocompatibility and reduced aluminium ion release [R2,R4, R5].
- Some cement compositions may be neurotoxic if used incorrectly [R6]: An important finding, as a number of patients died following complications related to the use of a similar material developed in Germany (see Section 4). This material, that was named Ionocem®, was understandably withdrawn from the market. Our research was an important contributor to explaining the scientific basis for this medical device disaster and subsequently identifying a safer, optimised composition.

Key papers (including R4 and R5) relating to the discovery of the optimised composition were written as a result of a multi-partner investigation supported by European funding (EC Brite EuRam grant no. 6062-92, contract BRE2.CT92.0349). The discovery of the optimised composition arose specifically as a result of collaboration between the University of Sheffield, Limerick University in Ireland, and the Royal Free Hospital in London, who were academic partners on this EC-sponsored project. Sheffield led on the determination of the biocompatibility of cements, and as a result we identified the most promising glass composition and contributed significantly to the ionomer glass design work that was based in Limerick with Robert Hill.

3. References to the research

R1. CARTER, D. H., SLOAN, P., BROOK, I. M. & HATTON, P. V. 1997. Role of aluminium in the integration of ionomeric (glass polyalkenoate) bone substitutes. *Biomaterials* 18 459-466. doi: 10.1016/S0142-9612(96)00150-0

R2. BROOK, I. M. & HATTON, P. V. 1998. Glass ionomers - bioactive implant materials. *Biomaterials* 19, 565-571. doi: 10.1016/S0142-9612(98)00138-0

R3. K. HURRELL-GILLINGHAM, I. M. REANEY, C.A.MILLER, A. CRAWFORD & P.V.HATTON. 2003. Devitrification of ionomer glass and its effect on the *in vitro* biocompatibility of glass-ionomer cements. *Biomaterials* 24, 3153-3160. doi: 10.1016/S0142-9612(03)00124-8

R4. JOHAL, K.K, CRAIG, G.T., DEVLIN, A.J., BROOK, I.M., & HILL, R. 1995. *In vivo* response to ionomeric cements: Effect of glass-composition, increasing soda or calcium fluoride content. *Journal of Materials Science: Materials in Medicine* 6 690-694. doi: 10.1007/BF00134302

R5. DEVLIN, A. J., HATTON, P. V. & BROOK, I. M. 1998. Dependence of *in vitro* biocompatibility of ionomeric cements on ion release. *Journal of Materials Science: Materials in Medicine* 9, 737-741.

R6. LOESCHER, AR, ROBINSON, PP & BROOK, IM. 1994. The effects of implanted ionomeric and acrylic bone cements on peripheral nerve function. *Journal of Materials Science: Materials in Medicine*, 5 108-112. (DOI: 10.1007/BF00121699)

4. Details of the impact

Pathway to impact: After undertaking early work with funding from Pfizer Howmedica Ltd and the Medical Research Council, in 1992 staff at Sheffield (Hatton & Brook) were successful in securing funding as part of a European consortium to work on the optimisation of glass-ionomer cements for new clinical applications including bone repair (EC Brite EuRam grant no. 6062-92). One important output from this project was the identification of an optimised composition for bone cementation in middle ear surgery, and Hatton and Brook initially considered forming their own company to commercialise this under the trade name “Biocem”. However, following discussions with a commercial contact, the decision was taken instead to licence the optimised composition to a new start-up company, Corinthian Medical, which was formed specifically to take this new cement to the market. The new company was started in 1997, with an agreement to pay royalties from sales to Sheffield University who would distribute this fund to the other institutions (University of Limerick and Royal Free Hospital) in accordance with the original European project consortium agreement. The cement was originally placed on the market in 1997 with the name Biocem, but this was later changed to SerenoCem® because another company had already registered the former name for the Swiss market.

Healthcare impact: The cement is used in bone repair or device fixation in middle ear surgery, and Corinthian estimate that it has been used in at least 10,000 clinical procedures worldwide since 1st January 2008 [S1]. The cement is now used in a large number of clinical procedures in otorhinolaryngology including repair of the ossicular chain, occlusion of bony defects, and fixation of other medical devices such as the Cochlear implant [S2-S7]. Clinical research papers from centres throughout Europe and the USA are included in the supporting evidence (see Section 5). There are many independent clinical evaluations of performance in a large number of otological surgical procedures published in the leading ENT journals, and together they demonstrate the versatility and excellent performance of the new bone cement [S2-S8]. With respect to versatility, it is also possible to use the cement as a pre-set granular bone graft substitute [S3,S4]. Several of these clinical reports and studies were published in this REF period, with four examples provided

here [S5-S8]. These more recent papers also report the use of ionomeric bone cement in successful reconstruction of the incus [S5], and revision stapes surgery where significant hearing improvement was identified along with a reduction in morbidity [S6]. In comparative studies for incudostapedial joint reconstruction, cement was used in 31 out of 66 patients, and improvements in hearing were greater in the cement group [S7]. In addition, the product based on Sheffield's glass-ionomer technology consistently provided the best clinical results in type 2 ossiculoplasty [S8]. No fatalities or serious adverse incidents have been reported to date (unlike the previous commercial cement formulation, Ionocem®)*.

*Sheffield research (identified in Section 3 above as R6) identified the neurotoxic potential in a previous otological cement, albeit too late to save the lives of a number of patients in France and Belgium who the same year underwent surgery where the cement was placed in contact with brain tissue (Renard *et al*. Post-otoneurosurgery aluminium encephalopathy. *Lancet* 344:63-64.)

Commercial impact: The decision by Sheffield University to licence this new, optimised composition was in part driven by the need to replace Ionocem® with a demonstrably safer formulation. The licensing of the new cement formulation led directly to the start-up of a new UK company (Corinthian Medical Ltd., later called Corinthian Surgical), created solely for the purpose of placing our cement on the market [S1]. The founder and Managing Director of Corinthian Surgical Ltd. has testified:

> *"The optimised composition for an ionomeric bone cement licensed to Corinthian by the University of Sheffield remains a unique and significant innovation in the field of otology that has transformed the lives of thousands of patients worldwide. Corinthian Surgical Ltd. is indebted to Paul Hatton and Ian Brook for identifying the formulation for our bone cement, SerenoCem®, as I would not have been able to start up my company without their insight and support. While we are an SME, employing 5 persons including myself as Managing Director, I should point out that we inevitably contribute to many more jobs in a complex supply chain that includes glass-making, polymer synthesis, capsule manufacture, distribution, regulatory compliance, and financial services."* [S1]

With our further assistance, Corinthian Surgical obtained approval to place our optimised composition on the market in Europe and the USA. Hatton and Brook contributed significantly to the company gaining a CE mark and FDA approval via a 510(k) submission (for example, Hatton presented to the US FDA in Washington as an expert witness), we advised on packaging and sterilisation, and we advised on the wording for clinical contra-indications that are identified on the packaging of the device at sale (important given the previous deaths following use of a competitor product) [S1]. Sales of the cement have generated £65,000 royalties to date [S1]. In addition to job creation noted above, wealth has been generated via sales including exports. In addition to Europe and the USA, the medical device is exported to several other countries including Australia, Turkey, New Zealand, and Saudi Arabia [S1]. The culmination of Sheffield's more recent work resulted in research leading to 2 new patent applications [S9, S10] for novel formulations based on aluminium-free bioactive glass compositions, and we are currently working with Corinthian to develop new medical device products based on this intellectual property.

5. Sources to corroborate the impact

S1. Letter from the Founder and Managing Director of Corinthian Surgical Ltd. corroborates the claims of commercial and healthcare impact as detailed above.

S2. Ossicular Reconstruction Using Bone Cement. Babu, S. & Seidman, M.D. 2004. *Otology and Neurotology* 25(2) 98-101. This clinical paper corroborates the claim that the cement may be used in ossicular reconstruction with good clinical results, and with the other clinical papers here corroborates the broad claim that this is safe and versatile cement technology.

S3. SerenoCem™-glass ionomeric granules: a 3-year follow-up assessment of their effectiveness in mastoid obliteration. M.P.A. Clark and I. Bottrill. 2007. *Clinical Otolaryngology* 32(4) 287-290. This clinical paper corroborates the claim that the cement may be used as a pre-set bone graft substitute.

S4. SerenoCem glass ionomeric granules: a 3-year follow-up assessment of their effectiveness in mastoid obliteration. 2007. *Clinical Otolaryngology* 32(4):287-90. This clinical paper corroborates the claim that the cement is sufficiently versatile to be used as a pre-set bone graft substitute.

S5. Technical Refinements and Precautions During Ionomeric Cement Reconstruction of Incus Erosion During Revision Stapedectomy. Douglas A. Chen & Moisés A. Arriaga. 2009. *The Laryngoscope* 113(5) 848-852. This clinical paper corroborates the claim that the cement may be used successfully in incus repair, and with the other clinical papers here corroborates the claim that this is safe and versatile cement technology.

S6. Utilisation d'un ciment ionomère: résultats préliminaires: dans la chirurgie de révision d'otospongiose (= Use of inomeric cement: Preliminary results in revision stapes surgery). AUBIN A., BAKHOS D., KIM S., LESCANNE E., & ROBIER A. 2012. *Revue de laryngologie, d'otologie et de rhinologie* 133(2), 71-75. This clinical paper corroborates the claim that the cement may be used in this otology procedure to substantially improve hearing and reduce post-operative morbidity. With the other clinical papers listed here, it also corroborates the broad claim that this is safe and versatile cement technology.

S7. The impact of fixated glass ionomer cement and springy cortical bone incudostapedial joint reconstruction on hearing results. H. Celik, S. Sevim, A. Felek, A. Islam, M. Demirci, E. Samim. 2009. *Acta Oto-laryngologica* 129(12) 1368-1373. This clinical paper corroborates the claim that the cement may be used in this surgical procedure with evidence for improvements in hearing.

S8. Type 2 ossiculoplasty: prognostic determination of hearing results by middle ear risk index. Sevim Aslan Felek, Hatice Celik, Ahmet Islam, Atilla H. Elhan, Munir Demirci, Erdal Samim. 2010. *American Journal of Otolaryngology*, 31(5) 325-331. This clinical paper corroborates the claim that the cement may be used in this procedure where it provided the best clinical results, and with the other clinical papers here corroborates the broad claim that this is safe and versatile cement technology.

S9. UK Patent application 1223509.9 filed on 31st December 2012. This patent application corroborates the claim that we have identified new, innovative cement designs for further commercialisation.

S10. UK Patent Application No. 1311648.8 filed on 28th June 2012. This patent application corroborates the claim that we have identified new, innovative cement designs for further commercialisation.