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| **Institution: Queen Mary University of London** | | |
| **Unit of Assessment: UoA 12** | | |
| **Title of case study: Inductigraft™/AltaPore™ and Actifuse™: Synthetic bone graft substitutes with enhanced bioactivity for improved bone regeneration** | | |
| **Period when the underpinning research was undertaken: 2000-31 Dec 2020** | | |
| **Details of staff conducting the underpinning research from the submitting unit:** | | |
| **Name(s):** | **Role(s) (e.g. job title):** | **Period(s) employed by submitting HEI:** |
| Dr Karin Hing | Reader in Biomedical Materials | Oct 1995-present |
| **Period when the claimed impact occurred: August 2013-31 Jul 2020** | | |
| **Is this case study continued from a case study submitted in 2014? Y** | | |

**1. Summary of the impact** (indicative maximum 100 words)

Collaborative research led by Queen Mary and Baxter, which, in 2010, acquired the Queen Mary spin-out ApaTech™, which was set up in 2001 to commercialise Queen Mary research, resulted in the UK launch of the synthetic bone graft substitute Inductigraft™ in 2013. Inductigraft has enhanced bioactivity comprising equivalent performance to the gold standard, autograft, and superior performance to other commercial synthetic bone graft (SBG) materials and allografts (treated donor bone). It was launched in the US under the trade name AltaPore™, with FDA approval granted for use in orthopaedic procedures in extremities and the pelvis in 2017, and posterolateral spine fusion in September 2018. In 2018, a 'flow' version of Actifuse™ (initially launched in 2005 by ApaTech, also based on Queen Mary research) was launched, which provides a finer fraction of granules for narrow bore application. Approximately 24,000 procedures take place every year using Baxter products with 98.9% fusion rates. The move from autograft to Baxter synthetic bone grafts has led to reduced complication rates and enhanced patient outcomes. In 2019, a Royal Mail stamp, dedicated to the innovation of Actifuse™/Inductigraft™/AltaPore™ SBGs, was issued as part of the British Engineering Stamp collection.

**2. Underpinning research** (indicative maximum 500 words)

Synthetic bone grafts (SBGs) are highly porous materials (>60% porous) often consisting of a ceramic with a calcium-phosphate-based chemistry and an open foam-like porous structure, which mimics cancellous bone (the internal tissue of skeletal bone). The purpose of a SBG is to stimulate bone healing or regeneration where the skeleton's natural regenerative abilities are impaired or insufficient. Early SBGs were variable in both effectiveness and reliability due to a lack of understanding of the body's biological response to these materials and their characteristics.

The QMUL spin-out ApaTech™ was established in 2001, built on the research undertaken under the directorship of Prof William Bonfield and Prof Serena Best, both at Queen Mary until 1999, working in collaboration with Prof Iain Gibson and Dr Hing. The team optimised graft chemistry and structure, and developed novel processing technology to deliver superior synthetic bone graft substitutes, ApaPore™ (2001) and Actifuse™ (2005), to the clinical market. The company was acquired by Baxter inc. in 2010. Since 2000, Dr Karin Hing at Queen Mary has built on the teams pioneering research, in response to earlier observations of the sensitivity of bone regeneration to graft chemistry, macro-pore structure and strut permeability. Dr Hing has investigated the mechanisms through which minor fluctuations in SBG chemistry and strut porosity can either enhance or impair bone healing. This has led to work that demonstrates that bone regeneration can be further enhanced by manipulating the exact structural characteristics of the porous ceramic foam. This has led to further refinement of graft structure, resulting in SBGs with enhanced bioactivity, and the clinical launch of Inductigraft™/AltaPore™.

Dr. Hing's work led to the understanding that the sensitivity of bioactivity to chemistry is dependent on both the pattern of inorganic ion exchange and surface selectivity of key proteins, which synergistically direct bone cell recruitment, metabolism and function [3.1]. Further research demonstrated that increasing strut porosity in SBGs enables a synthetic graft to stimulate osteoinductive-like behaviour when implanted ectopically in a recognised model of osteoinductivity, and facilitates faster and more reliable bone regeneration [3.2]. This is particularly

important in the treatment of patients with impaired bone biology, multi-level spinal fusions or complicated trauma injuries. This work led to the successful filing of a patent by ApaTech/Baxter [5.1]. The launch of Inductigraft/AltaPore was underpinned by studies that (1) show efficacy of SBGs with increased strut-porosity in a critical defect orthotopic model, as both an autograft extender (using 'patient's' own bone), as a standalone SBG [3.3] and in a challenging spine fusion model [3.4] and (2) further probe the relative roles of graft chemistry [3.5] and structure in enhancing bone growth [3.6].

**3. References to the research** (indicative maximum of six references)

[3.1] Guth K, Campion C, Buckland T, Hing KA. (2010). Effect of Silicate-Substitution on Attachment and Early Development of Human Osteoblast-Like Cells Seeded on Microporous Hydroxyapatite Discs. *Adv Eng Mater, 12,* B26–B36. https://doi.org/10.1002/adem.200980003

[3.2] Coathup, M.J., S. Samizadeh, Y.S. Fang, T. Buckland, K.A. Hing, G.W. Blunn, (2011). The Osteoinductivity of Silicate-Substituted Calcium Phosphate. *J Bone Joint Surg, A93 A(23),* 2219-26. https://doi.org/10.2106/jbjs.i.01623

[3.3] Hutchens, S. A., Campion, C., Assad, M., Chagnon, M., & Hing, K. A. (2016). Efficacy of silicate-substituted calcium phosphate with enhanced strut porosity as a standalone bone graft substitute and autograft extender in an ovine distal femoral critical defect model. *J Maters Sci: Maters Med, 27(1)*, 1-12. https://doi.org/10.1007/s10856-015-5559-3

[3.4] Coathup, M. J., Blunn, G. W., Campion, C., Ho, C. Y., & Hing, K. A. (2017). The effect of increased microporosity on bone formation within silicate-substituted scaffolds in an ovine posterolateral spinal fusion model. *Journal of Biomedical Materials Research - Part B Applied Biomaterials, 105(4),* 805-814. https://doi.org/10.1002/jbm.b.33614

[3.5] Mafina MK.; Sulivan AC.; Hing KA. (2017). Use of a fluorescent probe to monitor the enhanced affinity of rh-BMP-2 to silicated-calcium phosphate synthetic bone graft substitutes under competitive conditions. *Materials Science and Engineering: C, 80*, 207-212. https://doi.org/10.1016/j.msec.2017.05.142

[3.6] F. Yang, S.C.F. Rawlinson, K.A. Hing (2018). The synergistic effect of combined bone graft scaffold (BGS) architecture and mechanical environment on hMSCs differentiation in vitro. *8th World Congress of Biomechanics, Dublin, Ireland*. http://wcb2018.com/wp-content/uploads/2018/07/13028-WCB2018-Programme_Web.pdf

**Evidence of quality of the research:**

[EQR. 1] G Blunn. K Hing (December 2008-September 2009). Ectopic and Orthotopic Bone Formation with Actifuse Bone Graft Substitute Materials. *ApaTech Ltd*. Industrial Research Contract. GBP162,516.

[EQR. 2] KA Hing. G Davis. (September 2009-September 2013). Development of AnalyticalTechniques to Monitor Bone Penetration in 3D via Computer Tomography Analysis. *ApaTech Ltd*. PhD studentship. GBP100,000.

[EQR. 3] KA Hing. A Sullivan. (September 2009-September 2013). The Role of Chemistry and Strut Porosity and the Influence of Serum Proteins in Modulating Cellular Response to Bone Graft Substitutes. *ApaTech Ltd*. PhD studentship. GBP90,000.

[EQR. 4] KA Hing. L Jenis. (March 2010-December 2010). SpineJenes. *ApaTech Ltd*. Industrial Research Contract. GBP94,385.

[EQR. 5] KA Hing. SCF Rawlinson. (October 2015-September 2019). D Ikramova. *EPSRC/Baxter*. DTP CASE Studentship. GBP154,222.

**4. Details of the impact** (indicative maximum 750 words)

Inductigraft (AltaPore in the US) is a bone void filler intended for gaps that are not intrinsic to the stability of the bony structure. These defects may be surgically created or from traumatic injury. The product is reabsorbed and replaced by bone during the healing process.

Inductigraft and AltaPore are delivered through Baxter, and are based on the 2003 and 2009 ApaTech/Baxter patents [5.1]. AltaPore received FDA approval for use in orthopaedic procedures in extremities and the pelvis in 2013 and posterolateral spine fusions in September 2018 [5.2]. The Shape version (malleable putty instead of granules delivered dry or in a sculptable carrier, ABX) was launched in 2019.

**Enhanced patient health and well-being**

*Clinical superiority of Inductigraft/Altapore*

Inductigraft/AltaPore has been clinically reported to have "excellent fusion rates" [5.3] according to Michael Mokawem, Consultant Orthopaedic and Spinal Surgeon, Royal National Orthopaedic Hospital NHS Trust, with 98.9% fusion rates in transforaminal lumbar interbody fusion and lateral lumbar interbody fusion surgery.

Mr. Mokawem further reported "12 months CT scans showing close to 100% fusion (1 out of 150 failed), whereas for other SBGs it would be 80-92%." Mr. Mokawem added that the Baxter products' optimised levels of silicate and pore structures (to facilitate development of interpenetrating vascular networks) to "provide a microenvironment that facilitates osteoblasts to start bone formation" and have, thus, more reliable outcomes in surgery. The chemistry (apatite based rather than tricalcium phosphate/calcium sulphate/calcium carbonate based) means that these materials do not degrade chemically in the physiological environment. Any remodelling that happens is entirely cell mediated (use of chemically biodegradable materials can result in complications). Additionally, unlike traditional growth factor based treatments, Inductigraft/AltaPore is not contraindicated in skeletally immature individuals, which has enabled successful treatment of children and adolescents [5.4].

*Improved patient outcomes*

First, with use of Inductigraft/AltaPore, the surgeon is "able to reliably use Inductigraft without the need to harvest iliac crest bone to achieve excellent fusion rates, so eliminating the need for a second donor site with associated risks of infection, pain and complications associated with donor site morbidity," according to Robert Lee, Consultant spinal surgeon at the Royal National Orthopaedic Hospital Stanmore [5.5]. Additionally, the use of SBGs means there is a reduced need for anaesthesia and, thus, reduced surgical risks to patients. This is because without the need to obtain autograft bone (from the iliac crest), the operative procedure is shorter so patients are anaesthetised for a reduced length of time.

Second, a patient treated with Inductigraft/AltaPore has a greater chance of avoiding reoperation or revision surgery because "the excellent fusion rates significantly contribute to the improvement in patient reported outcomes," according to Mr. Lee [5.5]. Further, patients are typically released from hospital two to three days earlier, which has a positive effect on both the patient's quality of life and that of their family, friends and work colleagues.

Finally, in clinical trials at month 12 post fusion, clinically significant decreases in disability were observed. Patients also reported reductions in pain and an improved quality of life post-surgery. Motor, sensory functions, reflexes, straight leg raise and femoral stretches were either maintained, or improved in over half of patients [5.6].

**Improved health economics [5.4]**

Use of autograft involves two surgeries (harvesting of the bone followed by implantation), meaning

- The operation itself is prolonged
- Autograft harvesting procedures routinely have complications

For allograft and autograft, the risk of infection or immune rejection is significant vs SBGs where it is virtually zero. The percentage of patients returning with complications and requiring further surgery is therefore higher for allo/autograft, as, in the case of allografts, the bone has to be treated and sterilised before it is used. The faster bone growth associated with Baxter products also means that there is a reduced need for hardware, for example the insertion of metal supports.

The associated cost implications of the above are detailed in the table below:

| Item | Baxter | Autograft | Growth factor therapy |
|---|---|---|---|
| **Material cost /procedure** | USD600-800 | N/A | USD4,000-8,000 |
| **Operation time** | 20% less than autograft, an average of 3 hours | +USD1,000/operation | |
| **Recovery time** | 2-3 days less than autograft, saving USD280/day | +USD840/operation | |
| **Complications** | 21% less than autograft | +USD6,000/operation | Potential for complications in 50% of cases |

Based on approximately 24,000 procedures per year, Baxter products are estimated to save

- USD31,000,000 per year when compared to autograft-based procedures
- USD74,000,000 per year when compared to growth factor-based procedures

**Continued use of Actifuse™ (launched in 2005) in the current REF time period**

Actifuse, launched in 2005 and the subject of a Queen Mary REF 2014 impact case study, is continuing to have a health impact. This is now expanding to areas outside of spinal injuries to knee injuries. A clinical study conducted between 2012 and 2015 found that clinical function outcomes after knee surgery using Actifuse vs autograft were comparable 3 years after surgery. The average operative time in the autograft group was 114 minutes, nearly double that in the Actifuse group (64 minutes), as using the SBG is a technically less demanding procedure than using harvested cancellous bone from the iliac crest. No complications occurred in the Actifuse group. In contrast, 1/20 patients in the autograft group required revision surgery at the donor site [5.8].

In 2018, a 'flow' version of Actifuse was launched, which provides a finer fraction of granules for narrow bore application. It is unique in that it is non-setting when injected [5.4]. Actifuse Flow comes ready to use with no mixing or preparation involved and maintains its consistency throughout surgery. The SBG is delivered directly from a pre-loaded syringe with the ability to start and stop delivery, making use of Actifuse compatible with minimally invasive surgical techniques in addition to more traditional open surgery, increasing potential market size.

**Stimulated academic and public interest and attracted national/international recognition**

In 2014, the Academia/Industry partnership, TERMIS-EU (Europe) and TERMIS-AM (Americas) Industry Committees used Baxter (and ApaTech) as a case study to demonstrate that there are a number of mechanisms by which industry can interact effectively with academia to transfer technologies to commercial partners [5.9].

Outside of Queen Mary, Baxter products have been used as a biomedical technology 'Laboratory Bench to Clinic' case study in the syllabus of various undergraduate biomaterials/bioengineering degree programmes across the country. This includes Kings College London (delivered to approx. 20 students, in 2017, 2019) and the University of Manchester (delivered to approx. 30 students from 2014 to 2019) [5.10] [5.11].


The development of Actifuse and Inductigraft/AltaPore bone graft substitutes has achieved national/international recognition though the issue of a Royal Mail stamp (priced at £1.60) dedicated to the innovation of SBG materials able to enhance bone growth. The stamp was released in the British Engineering Stamp Issue (May 2019) celebrating seven key British engineering achievements of the last 50 years [5.12] and was described by Mr Philip Parker (Stamp Strategy Manager, Royal Mail) as a "very well received and successful" [5.12] stamp issue.

**5. Sources to corroborate the impact** (indicative maximum of 10 references)

[5.1] Patents: Hing, K. A., & Buckland, T. (2003). Ceramic biomaterial (GB0325833D0) [withdrawn by ApaTech] & Buckland, T., & Campion, C. (2009). Porous biomaterial (US20110054615A1).

[5.2] US Food and Drug Administration (23 January 2013), *Traditional 510(k) Premarket Notification* (K1 30531 – ALTAPORE) and US Food and Drug Administration (31 August 2018), *Traditional 510(k) Premarket Notification* (K1 81225 – ALTAPORE)

[5.3] M. Mokawem, G. Katzouraki, C. L. Harman, R. Lee (2019). Lumbar interbody fusion rates with 3D-printed lamellar titanium cages using a silicate-substituted calcium phosphate bone graft, *Journal of Clinical Neuroscience, 68*, 134-139.https://doi.org/10.1016/j.jocn.2019.07.011

[5.4] Fresh Perspectiv (2020). *Impact Case Study: Synthetic Bone Grafts - ApaTech™.*

[5.5] R Lee. Consultant spinal surgeon. *Royal National Orthopaedic Hospital Stanmore* (testimonial letter, 16 July 2019). [Corroborator 1]

[5.6] Bolger C, Jones D, Czop S. (2019). Evaluation of an increased strut porosity silicate-substituted calcium phosphate, SiCaP EP, as a synthetic bone graft substitute in spinal fusion surgery: a prospective, open-label study. *European Spine Journal, volume 28,*1733–1742. https://doi.org/10.1007/s00586-019-05926-1

[5.7] D Johnson. Technology Development Manager. *Baxter Healthcare* (testimonial letter, 15 November 2019).

[5.8] von Recum J, Schwaab J, Guehring T, Grützner P A, Schnetzke M (2017). Bone Incorporation of Silicate-Substituted Calcium Phosphate in 2-Stage Revision Anterior Cruciate Ligament Reconstruction: A Histologic and Radiographic Study. Arthroscopy: *J Arthroscopic Rel Surgery, volume 33(4),* 819-827. https://doi.org/10.1016/j.arthro.2016.10.007

[5.9] Y Bayon, S Ellison, A Verte, A Ahmed, A J Coury, C Campion, T A. Bertram, K B. Hellman, (2014). Commercialization of Regenerative Products: The Academic/Industry Partnership. Tissue Engineering: Part B, volume 20(4), 243-245. https://doi.org/10.1089/ten.teb.2012.0683

[5.10] L Di Silvio. Professor of Tissue Engineering. *Kings College London* (testimonial letter, 29 August 2019). [Corroborator 2]

[5.11] J Gouch. Professor of Biomaterials and Tissue Engineering, Director of Undergraduate Studies. *University of Manchester* (testimonial letter, 29 July 2019). [Corroborator 3]

[5.12] Royal Academy of Engineering. (02 May 2019). *Royal Mail celebrates British engineering with set of special stamps*. https://www.raeng.org.uk/news/news-releases/2019/may/royal-mail-celebrates-british-engineering-with-set