Institution: Queen Mary University of London		
Unit of Assessment: 8		
Title of case study: A New Generation of Synthetic Bone Graft Material That More Reliably and Effectively Stimulates Natural Bone Healing (Inductigraft™/AltaPore™)		
Period when the underpinning research was undertaken: 01/01/2000 - 31/12/2013		
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:**
1) Alice Sullivan	1) Professor of Inorganic Chemistry	1) 1990 - 2013
Period when the claimed impact occurred: 01/08/2013 - 31/08/2020		
Is this case study continued from a case study submitted in 2014? Yes		

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

Synthetic bone graft materials stimulate natural bone healing and regeneration when the body's ability to heal itself is impaired due to disease or injury. Research by Prof. Sullivan and Dr. Hing at Queen Mary has led to the creation of a new-generation synthetic bone graft material that is more reliable and effective than previous generations. The new material, developed in collaboration with Baxter International, launched in the UK as Inductigraft™ in 2013 and in the US as AltaPore™ in 2017. The material was approved by the US Food and Drug Administration (FDA) for use in orthopaedic procedures in extremities and the pelvis in 2017 and posterolateral spine fusion in 2018. With an estimated 24,000 procedures taking place every year using Baxter products, Inductigraft™ and AltaPore™ have led to safer and more reliable surgery, improved outcomes and quality-of-life for patients after surgery, with 98.9% fusion rates. This has generated significant cost savings for healthcare providers. In 2019, Inductigraft™ was selected as one of seven innovations to be presented on Royal Mail Stamps celebrating 50 years of British engineering achievement.

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 an 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.

Research at Queen Mary led by Prof. Sullivan (Department of Chemistry) and Dr. Hing (School of Engineering and Materials Science) has led to the development of synthetic bone grafts that can stimulate natural bone healing and regeneration when the body's regenerative abilities are impaired or insufficient due to disease or injury.

Sullivan's research group described the first examples of silica and polysilsesquioxane materials having covalently attached phosphonate and phosphonic acid groups [3.1] and the synthesis of mesoporous phosphonic acid-modified silicas that show a clear relationship between loading and porosity [3.2]. This work underpinned a close collaboration with Hing, whose research group specialise in novel biomaterials. This resulted in the development of a highly porous phosphate-based ceramic foam for use in bone grafts [EQR.1]. This ceramic bone replacement material was launched in 2001 as ApaPore™, under the umbrella of ApaTech™, a Queen Mary spin-out company. In 2010, ApaTech™ was bought by the US medical products company Baxter International.

Building on this success, further research led by Sullivan and Hing in collaboration with Baxter International, demonstrated that silicate was essential for early bone development. As a result, silicate-substituted hydroxyapatite was employed in a new material. Hing's team established that an optimal level of silicate substitution was 0.8% silicon by weight [3.3]. This led to the initial launch of the synthetic bone graft product Actifuse™ in 2005. An optimally silicate-substituted

synthetic bone graft with 80% porosity was subsequently developed into the Actifuse-ABX™ and Actifuse-Shape™ formats, released to market in 2008 and 2009 [3.4].

In 2013, Sullivan and Hing published the results of their five-year study on the adsorption and de-adsorption of proteins to silicate-substituted ceramics, using benchmarked fluorescently-labelled proteins [3.5]. In 2017, they demonstrated that silicate substitution results in greater adsorption of bone morphogenic protein (rh-BMP-2) under physiologically relevant conditions [3.6]. This advance was important in providing a mode of action and optimising the silicate-substituted hydroxyapatite in promoting the induction of bone remodelling, showing efficacy of SBGs in a challenging spine fusion model [3.5, 3.6]. It is this new understanding of the chemistry of the inorganic substrate and its adsorption of bone morphogenic proteins and osteoblast cells that led to the development of a new improved bone graft ceramic material, with enhanced porosity and protein adsorption properties. This new product was launched in the UK as Inductigraft™ in 2013 and in the US as AltaPore™ in 2017.

These next generation synthetic bone graft materials have proven osteoinductivity, which arises from a combination of hierarchical porosity, silicon doping, protein adsorption, cell capturing and cell activating properties. It is these properties that have led to more reliable bone regeneration needed for treating patients with impaired bone biology, multi-level spinal fusions, or complicated trauma injuries.

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

[3.1] Aliev, A., Ou, D. L., Ormsby, B. & Sullivan, A. C. (2000). Porous silica and polysilsesquioxane with covalently linked phosphonates and phosphonic acids. *Journal of Materials Chemistry*, *10*, 2758-2764. https://doi.org/10.1039/B007452G
[3.2] Jurado-Gonzalez, M., Ou, D. L., Sullivan, A. C. & Wilson, J. R. H. (2002). Synthesis, characterisation and catalytic activity of porous vanadyl phosphonate-modified silicas. *Journal of Materials Chemistry*, *12*, 3605-3609. https://doi.org/10.1039/B207833C
[3.3] Hing, K. A., Revell, P. A., Smith, N. & Buckland, T. (2006). Effect of silicon level on rate, quality and progression of bone healing within silicate-substituted porous hydroxyapatite scaffolds. *Biomaterials*, *27*, 5014-5026. https://doi.org/10.1016/j.biomaterials.2006.05.039
[3.4] Hing, K. A., Annaz, B., Saeed, S., Revell, P. A. & Buckland, T. (2005). Microporosity enhances bioactivity of synthetic bone graft substitutes. *Journal of Materials Science: Materials Medicine, 16*, 467-475. https://doi.org/10.1007/s10856-005-6988-1
[3.5] Mafina, M.-K., Hing, K. A. & Sullivan, A. C. (2013). Development of novel fluorescent probes for the analysis of protein interactions under physiological conditions with medical devices. *Langmuir, 29* (5), 1420-1426. https://doi.org/10.1021/la304244s
[3.6] Mafina, M.-K., Sulivan, A. C. & Hing, K. A. (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 Engineering C*, *80*, 207-212. https://doi.org/10.1016/j.msec.2017.05.142

Evidence of quality of the research:

[EQR.1] Patent. Hing, K. A. & Buckland, T. (2003). *Ceramic biomaterial* (GB0325833D0).
[EQR.2] Hing, K. A. & Sullivan, A. (09/2009-09/2013). 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.

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

Research led by Queen Mary has resulted in the development of a synthetic bone graft (SBG) material with enhanced bone-forming capacity compared to previous-generation materials, being significantly greater at de-novo bone regeneration. The improved bone graft material is typically used in spinal surgery in the US and UK as a treatment for patients with debilitating degenerative diseases, traumatic injuries or scoliosis. This product more reliably and rapidly supports bone regeneration in these patients than previous generations of synthetic bone graft materials such as Actifuse™ (launched 2005). It is also safer and more cost-effective than autograft treatments, which use a patient's own bone, or growth factors. The new material was initially launched by ApaTech/Baxter in the UK in 2013 as Inductigraft™ [5.1]. After gaining FDA approval for use in

orthopaedic procedures in extremities and the pelvis in 2017, the material was launched in the US as AltaPore™. Its use in posterolateral spine fusion was approved by the FDA in 2018 [5.2]. Approximately 24,000 procedures per year are undertaken using Baxter bone graft products [5.3].

Enhancing patient wellbeing and improving clinical outcomes

Recent clinical publications demonstrate that Inductigraft™ is a more effective and reliable synthetic bone graft than other treatments, with:

- 86.3% fusion rates in posterolateral fusion surgery [5.4]
- 98.9% fusion rates in transforaminal lumbar interbody fusion and lateral lumbar interbody fusion surgery [5.5].

This leads to improved health outcomes and wellbeing for patients. Robert Lee, a consultant orthopaedic and spinal surgeon at the Royal National Orthopaedic Hospital (RNOH) NHS Trust, one of the leading hospitals for orthopaedic healthcare in the UK, says: "I am 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. Moreover, we believe that the excellent fusion rates significantly contribute to the improvement in patient-reported outcomes" [5.6].

In a clinical trial, the team at RNOH achieved a 99% successful fusion rate at 12 months post-surgery with Inductigraft™ [5.6]. Michael Mokawem, also a consultant orthopaedic and spinal surgeon at RNOH, explains how Inductigraft™ is superior to other SBGs [5.3]: "For Inductigraft, we have an excellent fusion rate – at 12 months, CT scans suggest close to 100% fusion (1 out of 150 failed), whereas for other SBGs it would be 80-92%" [5.3].

In addition, the use of Inductigraft™/AltaPore™ reduces the need for anaesthesia and thus reduces surgical risks to the patient as they no longer require autograft bone (from the iliac crest). The operative procedure is shorter as a result, so patients are anaesthetised for a reduced length of time.

This has significant benefits for patient outcomes and quality of life. In clinical trials, at 12 months post-surgery, researchers observed clinically significant decreases in disability in patients. Patients also reported reductions in pain and an improved quality-of-life post-surgery. In more than half of the patients, motor and sensory functions, reflexes, straight leg raises and femoral stretches were maintained or improved [5.4]. Additionally, in contrast to growth factor-based treatments, Inductigraft™/AltaPore™ is not contraindicated in people who are skeletally immature and therefore enables successful treatment of children and adolescents [5.3].

Improved health economics [5.3]

- Use of autograft involves two surgeries (harvesting of the bone followed by implantation).
  - ⇒ The operation itself is prolonged.
  - ⇒ Autograft harvesting procedures routinely experience 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.
  - ⇒ 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 metal supports.

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

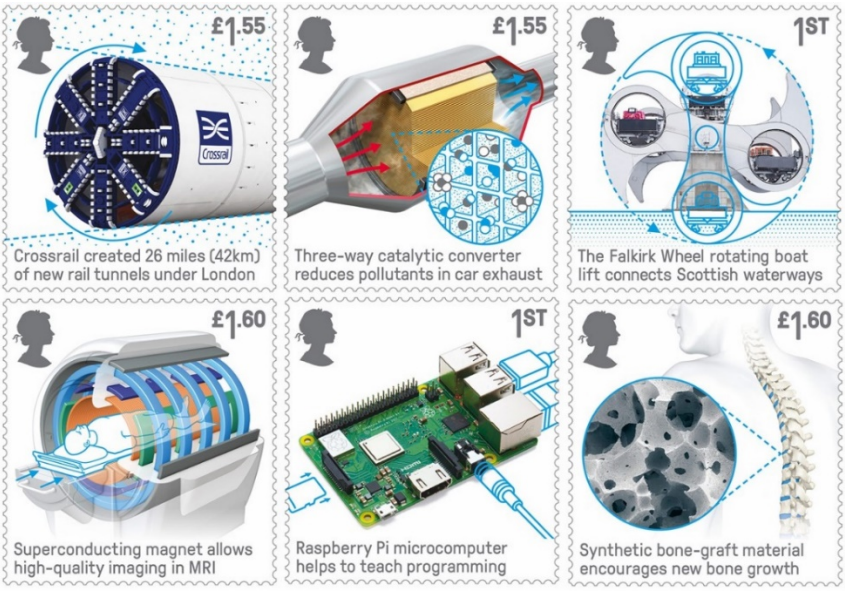
Baxter vs Autograft and Growth Factor Therapy
Reduced material and procedure costs • **–GBP400-600*/operation** compared to autograft-based procedures • **–GBP3,000-6,000*/operation** compared to growth factor therapy procedures
Reduced surgery time • 20% compared to autograft-based procedures (3 hours on average) **– GBP800/operation**
Reduced recovery time • Patients are released from hospital 2-3 days earlier compared to autograft-based procedures **–GBP700/operation (GBP210**/day)**
Reduced complications • 21% less complications compared to autograft-based procedures **– GBP5,000/operation** • Potential for complication in 50% of the cases of growth factor therapy procedures
Estimated savings*** • **GBP21,000,000/year** when compared to autograft-based procedures • **GBP50,000,000/year** when compared to growth factor-based procedures

*Converted from USD600-800 and USD4,000-8,000 respectively from XE.com, 22/01/2021.
**Converted from USD280 on XE.com, 18/08/2020.
***Based on approximately 24,000 procedures per year using Baxter products.

Recognising a British engineering achievement with wide-ranging benefits for society

Inductigraft™ is widely used in orthopaedic surgery, improving health outcomes for patients, saving healthcare costs, and providing substantial returns in revenue. As such, it has been widely recognised in academia and beyond as an example of best practice in the successful transfer of research knowledge into new health technology, with clear benefits for patients, healthcare providers and society.

In 2019, Inductigraft™ was selected as one of only seven innovations to be presented on Royal Mail Stamps celebrating British engineering achievements over the past 50 years (see below) [5.7].



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

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

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

[5.4] 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, 28,* 1733-1742. https://doi.org/10.1007/s00586-019-05926-1

[5.5] Mokawem, M., Katzouraki, G., Harman, C.L. & Lee, R. (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

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

[5.7] 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. Accessed 17 February 2021.