Institution: Queen Mary University of London (QMUL)

Unit of Assessment: 15 (General Engineering)

Title of case study: Fixing Fractures Fast*:* ***ApaTech™*** – Development of Synthetic Bone Grafts with Improved Efficacy and Reliability

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

Seminal materials research at QMUL and its technological transfer via the QMUL spin-out ApaTech™, has led to the development of a range of cost-effective synthetic bone graft (SBG) products (ApaPore™, Actifuse™ and Inductigraft™), which safely and effectively stimulate rapid bone healing and are more reliable than previous autograft procedures. The successful use of the ApaTech™ range of products has delivered impact on health and welfare by reducing post-operative infection risks and improving recovery rates. To date, ApaTech™ products have been used to treat over 370,000 patients in over 30 countries. In 2010, ApaTech™ had 4% of the US SBG market, a $20 million annual turnover, employed 160 people in nine countries, and was sold to Baxter International for £220 million. By 2012, ApaTech™ products had attained a 10% share of the global SBG market (treating 125,000 patients per annum), estimated to be around $510 million. Other impacts include altering surgical clinical practice away from the use of autograft.

2. Underpinning research (indicative maximum 500 words)

Synthetic bone grafts (SBG) are highly porous materials (>60% porous) usually consisting of a ceramic with a calcium-phosphate-based chemistry and open foam-like porous structure, which mimics cancellous 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 SBG 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.

Pioneering biomaterials research at QMUL between 1993 and 2001, initially led by Prof Bonfield and Prof Best (both at QMUL until 1999) and subsequently by Dr Hing (at QMUL 1991 to present), focussed on two lines of basic research. First, to study how minor fluctuations in SBG chemistry can either enhance or impair bone healing and second, the investigation of the sensitivity of bone regeneration to the exact structural characteristics of the porous ceramic foam. The impact of this research was secured with a progressive policy of protecting intellectual property (IP), which enabled the translation of these research findings into clinical practice through the foundation of ApaTech™ in 2001, a QMUL spin-out company designed to commercialise a series of novel bioactive SBGs. ApaTech's™ other founding scientists were postdocs within the group at QMUL, including Prof Gibson (now at Aberdeen) who contributed much of the chemistry-based IP.

IP was based around two central patents relating to the importance of reliable control of both graft chemistry and pore structure. Consultation with leading orthopaedic surgeons highlighted a demand for SBGs that could "wick" blood, therefore making them easier to handle in the operating theatre. To achieve structures with independently controllable macro- and strut-porosity, a novel production route was developed and patented for the manufacture of hierarchical (multi-scale) pore structures based on the concept of particle stabilized slip foaming [1]. This technology facilitated investigation of the response of bone healing to porosity characteristics, demonstrating that SBG structures should be as porous as possible, retaining sufficient strength only to withstand surgical handling – with higher porosity permitting faster cellular colonisation, revascularisation and bone repair. In addition, higher porosity structures also had lower stiffness, supporting larger volumes of bone regeneration through bones' mechano-sensitivity. Increasing strut-porosity was also shown to further accelerate the healing process and maintain regenerated bone health in the long-term, through additional increase in structural permeability and reduction in stiffness [3]. These findings were unique because they were contrary to the established thinking of surgeons and bioengineers at the time, who generally thought that bone grafts should be strong.

This research led to the launch of ApaPore™ in 2001, a hydroxyapatite SBG available in three porosity grades (60%, 70% and 80%). Concurrently, research continued at QMUL focused on

mimicking bone-mineral chemistry though the development of novel patentable routes for the controlled synthesis of hydroxyapatite (HA), to produce phase pure stoichiometric and substituted apatites [2]. This work facilitated rigorous investigations into the biological response to the chemical characteristics of the material. These studies established that controlled levels of ionic substitution had a positive impact on bone healing, whereas <5% deviations from phase purity had a significant negative impact on bone healing, resulting in revision of the ISO standard for HA. Particular interest was focused on silicate-substituted hydroxyapatite (SA) as a result of an earlier independent work suggesting that silicate was essential for early bone development. An optimal level of 0.8wt% was established [4] leading to the launch of Actifuse™ in 2005, a silicate-substituted SBG with 80% porosity that was subsequently developed into the Actifuse-ABX™ and Actifuse-Shape™ formats released to market in 2008 and 2009.

At the outset of this research, Dr Hing developed the novel production route for hierarchical porosity and ran initial investigations into biological response to SBG structure and chemistry. From 2000, Dr Hing led the research at QMUL to investigate the optimal level of silicate addition and the mechanisms of action behind chemical mediation of bioactivity. This 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 [5]. More significantly, recent work has demonstrated that further optimisation of strut porosity in SBG enables a synthetic graft to stimulate stem cells to differentiate into bone forming cells facilitating yet faster, more reliable bone regeneration [6], particularly important in the treatment of patients with impaired bone biology, multi-level spinal fusions or complicated trauma injuries, resulting in the launch of Inductigraft™ by Baxter International in 2013, the first commercially available SBG with proven osteoinductivity.

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

1. Hing K.A., Bonfield W. (1999) “Foamed Ceramics” International Patent, WO 00/20353
2. Gibson, I. R., Best, S. M. and Bonfield, W. (1999), ‘Chemical characterization of silicon-substituted hydroxyapatite’. *J. Biomed. Mater. Res.*, 44: 422–428.
3. Hing K.A, Annaz B, Saeed S, Revell P.A, Buckland T. (2005) ‘Microporosity Enhances Bioactivity of Synthetic Bone Graft Substitutes’ *J. Maters Sci: Materials in Medicine*, 16(5), 467-475
4. Hing K.A, Revell PA, 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(29), 5014-26.
5. 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.
6. Chan, O., M.J. Coathup, A. Nesbitt, C.Y. Ho, K.A. Hing, T. Buckland, C. Campion, and G.W. Blunn, ‘The effects of microporosity on osteoinduction of calcium phosphate bone graft substitute biomaterials’. *Acta Biomaterialia*, 2012. 8(7): p. 2788-2794.

Research Grant/Contract Funding: £555,000 (since 2008), £1,140,000 (since 1999)

Venture Capital/Company Sale Funding: Total acquired is in the region of £256,000,000

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

This seminal research and its successful technological transfer via the spin-out ApaTech™ has delivered products that have achieved very significant impact with major global reach from 2008 onwards. The successful use of the ApaPore™, Actifuse™ (and most recently Inductigraft™) series of products has delivered impact on health and welfare for over 370,000 patients in over 30 countries. By 2012, the ApaTech™ products had attained a 10% share of the global SBG market, estimated to be around US$510 million, demonstrating major economic and commercial impact.

New safe, reliable and high-performance SBGs

In response to the demand for safe reliable SBGs the ApaPore™, Actifuse™ and Inductigraft™ produced by ApaTech™ and based on QMUL research have delivered significant health and

economic impact by outperforming many of the SBGs previously available for use in bone defect, joint revision, trauma or spinal surgery. Significantly Actifuse™ has been clinically demonstrated to be equivalent to the 'gold standard' autograft in highly challenging applications such as posterior lumbar fusion spinal surgery, where its use resulted in 76.5% fusion rates at 24 months, while clinical outcomes established significant pain improvement as compared with other SBGs [Section 5, source 1]. Moreover, when used alone, fusion rates as high as 90% at 12 months have been reported and equivalence in performance has even been established between Actifuse™ and rhBMP-2 based growth factor treatments (e.g. Infuse™) [Section 5, sources 2,3]. Furthermore, the development of Inductigraft™, a synthetic bone graft with proven ability to stimulate stem cells, has the potential to be even more reliable and rapidly support bone regeneration with both improved safety and cost effectiveness compared to treatment with autograft or growth factors.

Enhancing patient well-being

In terms of patient outcomes, the use of Actifuse™ and Inductigraft™, as more effective and/or reliable SBGs, has a dual impact on patient well-being. First, the patient is not subjected to a second operative procedure to remove autograft bone from the iliac crest, a procedure which increases the chances of infection (there being two operative sites rather than one) and results in post-operative pain at the graft donor site in up to 38% of patients and reported to last for two years or longer in up to 18% of patients (4,600 annually in the UK). Second, a patient treated with Actifuse™ which has equivalent performance to autograft, has a greater chance of avoiding reoperation or revision surgery, due to increased reliability. Further, patients are typically released from hospital two to three days earlier, impacting positively on both the patient's quality of life and that of their family, friends and work colleagues. Given that 38% of the 80,000 bone grafting procedures performed in the UK in 2012 used autograft, adoption of Actifuse™ or Inductigraft™ could positively affect 30,000 patients on an annual basis in the UK alone.

Improving health economics

From the perspective of heath economics use of Actifuse™ or Inductigraft™ rather than autograft has an immediate impact through reduction in both theatre time and hospital stay. Using a typical fusion procedure in the UK as an example, use of Actifuse™ typically reduces surgery time by 40 minutes saving an estimated £800 per operation (where a fusion procedure costs between £7,000-£10,000). Patients not subjected to donor surgery are usually released from hospital two to three days earlier saving £225 per day. Considering just these two factors results in a potential saving to healthcare budgets of £45 million per annum in the UK alone [Section 5, source 4]. Furthermore, health economics also benefit from a procedure with reduced infection risks and equivalent (to autograft) or increased (to non-optimised SBGs) success rates. About 5% of spinal cases require revision surgery and surgeons are beginning to report lower revision rates with use of Actifuse™ (where revision surgery costs £4,000-£6,000 in the UK). When considering the benefits of Actifuse™ or Inductigraft™ vs treatment with rhBMP-2 based growth factor treatments (e.g. Infuse™), aside from the concerns regarding the safety and efficacy, a benefit to healthcare economics results from the significantly reduced average product costs of Actifuse™ (£650) and Inductigraft™ (£970), which are typically £2,500 for growth factor treatments (e.g. Infuse™).

Changing surgical practice: impressive take up of ApaTech products

The reach of the research in terms of numbers of patients treated and rising surgeon awareness of the importance of SBG performance to surgical outcomes and benefits to using optimised SBGs is demonstrated by the impressive rate of ApaTech™ market penetration. In 2009 ApaTech™ had a five-year sales growth rate of 8.3% (Deloitte: Europe, Middle East and Africa report) resulting in the sale of ApaTech™ to Baxter International in 2010. At this point ApaTech™ had 4% of the US SBG market, an annual revenue of $20 million, a quarterly growth rate of 20%, employed 160 people in nine countries (including 84 people who continue to be employed at the manufacturing facility in Elstree, UK) and had treated >120,000 patients worldwide. The ApaTech™ range of products were regularly used by 680 surgeons in the USA with a net surgeon uptake of 15 surgeons per month. By 2012, the ApaTech™ share of the SBG market had doubled to 9.6% in the US (~20,000 procedures annually), increased to 12% in the UK (2,400 procedures annually) and 10% globally [Section 5, source 4] equating to world-wide treatment rates of 125,000 patients annually. To date in excess of 370,000 patients in over 30 countries have been treated with ApaTech™ products.

Within London (including the Royal National Orthopaedic Hospital and the National Hospital for Neurology and Neurosurgery) Actifuse™ is used in 20-25% of spinal cases that use an SBG. This reach should increase given that the global bone grafting market is predicted to increase at an annual rate of 4% [Section 5, source 4], and surgeon awareness of the economic and healthcare benefits of using the ApaTech™ range of products will continue to grow following publication of key clinical papers [Section 5, sources 1-3].

Recognition of research impact and stimulating public interest

This research and its successful technological transfer has also been recognised through a number of prestigious awards to the founding scientists Bonfield, Best and Hing for their outstanding contribution to the field, including awards from the Royal Academy of Engineering; the Royal Society of Armourers and Brasiers; the Institute of Materials, Minerals and Mining; and the UK, European and Japanese Societies for Biomaterials. The importance of this research to society was also recently demonstrated by a piece featuring Dr Hing on the development and use of Actifuse™ bone grafts during an episode of 'Bang Goes the Theory' (Broadcast, BBC1 7.30pm Mon, 4 Mar 2013 and BBC2, 7.00pm Tue, 5 Mar 2013) with an audience of 4 million [Section 5, sources 5-6]. More recently, the research was the focus of a short film produced as part of a series of films showcasing QMUL research available to the public via the QMUL YouTube channel as part of the College's on-going commitment to knowledge dissemination and pubic engagement.

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

1. Jenis, Louis G.; Banco, R J. (2010) Efficacy of Silicate-Substituted Calcium Phosphate Ceramic in Posterolateral Instrumented Lumbar Fusion Spine. 35(20):E1058-E1063.
2. Nagineni Vamsi V; James A.R., Alimi , M., Hofstetter C., Shin B.J., Njoku I., Tsiouris A.J, Härtl R. (2012) Silicate-Substituted Calcium Phosphate Ceramic Bone Graft Replacement for Spinal Fusion Procedures Spine 37: E1264 – E1272
3. Pimenta, Luiz; Marchi, L; Oliveira, L; Coutinho, E; Amaral, R (2013) A Prospective, Randomized, Controlled Trial Comparing Radiographic and Clinical Outcomes between Stand-Alone Lateral Interbody Lumbar Fusion with either Silicate Calcium Phosphate or rh-BMP2 J Neurological Surgery A (74) 343-350
4. World Wide, US, EU and UK Bone replacement Markets. SmartTrak.net August 2013, BiomedGPS, LLC, USA
5. Episode of 'Bang Goes the Theory' BBC 1 featuring QMUL's bone graft research: www.sems.qmul.ac.uk/videos/4c1fa420fb48f875c6ae07b964463e82
6. www.attentional.com/screenwatch/viewings/wk-monday-4th-sunday-10th-march-2013
7. Manufacturing Director, ApaTech. Aspect corroborated: Product innovation: Origin of ApaPore™, Actifuse™ and Inductigraft™ BGS apatite synthesis and BGS manufacturing technologies.
8. Associate Director Research and Development, Innovation and Technical Alliances, ApaTech. Aspect corroborated: Product innovation: Design/specification of ApaPore™, Actifuse™ and Inductigraft™ BGS structure and chemistry. Underpinning technology: Elucidation of the mechanisms of action behind enhanced bioactivity of ApaTech™ SBGs. Product reach: Market penetration, impact on health economics and patient outcomes.
9. Consultant Spinal Orthopaedic Surgeon, Royal National Orthopaedic Hospital NHS Trust. Aspect corroborated: Product reach: Changing surgeon practice by raising awareness and standards of care, delivering significant improvement to patient experience and healthcare economics.
10. Collaborator, pre-clinical trials, Director Institute of Orthopaedics and Musculo-Skeletal Science, UCL. Aspect corroborated: Product innovation: Inductigraft™ first calcium-phosphate based SBG in class with proven osteoinductivity. Efficacy of ApaTech™ SBGs in models of spine fusion.
11. Former Director of the IRC, founding scientist. Aspect corroborated: Enabling environment: Supportive nature of QML with respect to facilitating patent protection of IP and spin out of ApaTech via VC funding.