Institution: Queen Mary University of London (QMUL)

Unit of Assessment: B15 (General Engineering)

Title of case study:

A new concept in bone regeneration: Instructive Bone Graft AttraX™ – Progentix Orthobiology BV

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

Research by Professor Joost de Bruijn and team at QMUL from 2004 was critical to demonstrating the efficacy and commercial viability of a novel Instructive Bone Graft (IBG) product, AttraX™. The technology, commercialised via the spin-out business Progentix Orthobiology BV (founded in 2007) was sufficiently mature by 2008 to attract series A investment of €1 million series A financing by BioGeneration Ventures. The development of AttraX™ has led to a trade sale totalling up to US$ 80 million to the global top 5 spine company NuVasive Inc. in 2009. In 2011 an exclusive distribution deal with a global top 3 dental company was signed for use of the technology in the field of dentistry and craniomaxillofacial surgery. After regulatory approval of AttraX™ in Europe (CE mark), the product was commercialised in 2011 and has been used successfully in more than eleven thousand patients (as of 2013Q3) with global reach (including EU, US, Australia, New Zealand and Brazil). Within 1 year of commercialisation, a 1.1% share of the estimated US$2 billion global spinal bone graft market has been achieved. This research has seen an economical benefit in terms of newly formed jobs from 2 FTE in 2008 to 25 FTE in 2013 at Progentix Orthobiology BV.

2. Underpinning research (indicative maximum 500 words)

Until the early 1990's synthetic bone replacement materials were solely used as scaffolds to guide bone growth along their surface (osteoconduction). Due to their limited bone repair potential, they could only be used to fill small bone defects. For the treatment of larger, clinically relevant bone defects, materials with bone inducing properties (osteoinduction) are required. Although the only option available to surgeons was the use of patient-own bone tissue harvested from other locations in the body (with associated complications) or the use of expensive drug-based therapies.

From the mid-1990's onward Prof de Bruijn has been conducting research aimed at developing synthetic bone replacement materials that have bone-inducing properties, termed Instructive Bone Graft (IBG). The successful translation of such materials delivers significant clinical impact by providing a complication free alternative to conventional therapies. In 2004 Prof de Bruijn accepted a full-time position at QMUL, as Chair of Biomaterials, and he also established the company Xpand Biotechnology BV[1] through a government start-up grant via the University of Twente, the Netherlands. A research partnership between Xpand Biotechnology BV and QMUL was established with the company funding two research positions at QMUL in 2004 that focussed on development of novel IBG products, with a further position funded by QMUL.

The research on IBGs focussed on understanding and unravelling the process of material-induced bone formation. Prof de Bruijn and team showed that inflammation plays a role in ectopic bone formation (i.e. bone induction), facilitated by surface microstructured materials. They further showed that calcium phosphate materials with a specific submicron grain size and microporosity induce bone formation and lead to clinically relevant bone healing in defects that otherwise do not heal [1,2]. The involvement of macrophages in the earliest inflammatory phase was shown to play a role in mesenchymal stem cell homing and osteogenic differentiation when grown on these microstructured materials [3]. The research at QMUL was extended to demonstrate that the IBG technologies are at least equivalent in bone regeneration to the gold standard autologous (patient-own) bone and drug-based therapies (human recombinant bone morphogenetic protein 2 – rhBMP2), thereby demonstrating the clinical and commercial viability of the research [4-6].

Due to upcoming Series A financing (€1 million funding by BioGeneration Ventures in 2008), Progentix Orthobiology BV was founded in 2007 with Prof de Bruijn as founder and CEO to commercialise the IBG technology. Further, the successful outcomes of the IBG studies led Prof de

Bruijn to reduce his commitment at QMUL to 0.2 FTE and focus more on the growth of Progentix Orthobiology BV. Preclinical efficacy studies have shown that the IBG technology is excellent for use in spinal fusion, which represents about 50% of the US$5 billion bone graft market. A 100% spinal fusion was obtained after 3 months of implantation compared to at least 6 or 12 months for other competitive synthetic bone replacement materials and technologies. Clinical safety studies in patients with palatal cleft defects showed that the IBGs are fully resorbed and replaced by bone tissue after 12 months of implantation. Eventually, the QMUL research formed the basis of not only VC funding but also of the US$80 million trade sale of Progentix Orthobiology BV to NuVasive Inc. and the signing of an exclusive distribution deal with a global top 3 dental company.

[1] Progentix BV until 2007 – note that Progentix Orthobiology BV, established in 2007, is an entirely separate company

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

1. Yuan H, van Blitterswijk CA, de Groot K, de Bruijn JD. A comparison of bone formation in biphasic calcium phosphate (BCP) and hydroxyapatite (HA) implanted in muscle and bone of dogs at different time periods. *J Biomed. Mater Res A*. 78(1):139-147 (2006).
2. Yuan H, van Blitterswijk CA, de Groot K, de Bruijn JD. Cross-species Comparison of Ectopic Bone Formation in Biphasic Calcium Phosphate (BCP) and Hydroxyapatite (HA) Scaffolds. Tissue Engineering 12(6):1607-1615 (2006).
3. Eniwumide, JO, Yuan, H; Cartmell, SH; Meijer, GJ; de Bruijn, JD. Ectopic bone formation in bone marrow stem cell seeded calcium phosphate scaffolds as compared to autograft and (cell seeded) allograft. European Cells & Materials 14:30-38 (2007).
4. Yuan H, Fernandes H, Habibovic P, de Boer J, Barradas AM, de Ruiter A, Walsh WR, van Blitterswijk CA, de Bruijn JD, Osteoinductive ceramics as a synthetic alternative to autologous bone grafting, Proc Natl Acad Sci U S A. 107(31):13614-13619 (2010).
5. Yuan H, Fernandes H, Habibovic P, de Boer J, Barradas AM, de Ruiter A, Walsh WR, van Blitterswijk CA, de Bruijn JD, 'Smart' biomaterials and osteoinductivity, Nat Rev Rheumatol, 7(4)-c1 (2011).
6. Barbieri D, Yuan H, de Groot F, Walsh WR, de Bruijn JD, Influence of Different Polymeric Gels on the Ectopic Bone Forming Ability of an Osteoinductive Biphasic Calcium Phosphate Ceramic, Acta Biomater. 7(5):2007-2014 (2011).

Funding:

- €1 million series A financing to Progentix Orthobiology BV by BioGeneration Ventures (2008).
- US$80 million deal with NuVasive Inc. to acquire all stock of Progentix Orthobiology based on reaching certain milestones (2009).
- Several Dutch and EU grants to Progentix for developing the osteoinductive ceramics technology, amounting to more than €5 million in the past 8 years.

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

Research conducted by Prof deBruijn (QMUL from 2004 onwards) has been critical to the success of a start-up business Progentix Orthobiology BV (founded in 2007) and its revolutionary new IBG product AttraX™. Significant impact has been generated from 2008 onwards. Economic impact includes venture capital funding (2008 - €1 million from BioGeneration Ventures - Section 5, source 2) and commercial deals with the leading global spinal surgery device company NuVasive Inc (2009 – up to US$80 million trade sale - Section 5, source 3) and a dental (2011) market leader to market AttraX™ and other related products. Since 2011 AttraX™ has been used successfully in more than eleven thousand patients (as of 2013Q3) with global reach demonstrating impact on health and welfare. Within 1 year of commercialisation, a 1.1% share of the estimated US$2 billion global spinal bone graft market had been achieved. This research has seen an economical benefit in terms of new jobs at Progentix Orthobiology BV with an increase in staff from 2 FTE in 2008 to 25 FTE in 2013.

Improved Instructive Bone Graft AttraX™ – impacting unmet clinical and commercial need

There is an unmet clinical and commercial need for a product with the same effectiveness as the

gold standard autograft but without its disadvantages. Current alternatives to autograft have major drawbacks such as immune reactions, disease transfer, regulatory constraints, limited efficacy and high costs. AttraX™, developed with QMUL underpinning research and marketed under an agreement worth up to US$80 million from NuVasive Inc., delivers impact on the unmet clinical and commercial need as its bone regeneration potential is in line with that of the clinical gold standard autograft and bone growth factor rhBMP2 Infuse™ (annual sales totaling US$1 billion) and superior to other synthetic biomaterials [Section 5, sources 4,5]. Further it is more cost-effective than Infuse™. AttraX™ is targeted at the US$5 billion global orthopaedic bone graft market as a substitute of autologous bone, initially impacting the US$2 billion spinal market, representing approx. 1 million procedures per annum [Section 5, source 6]. Since the introduction to market of AttraX™ at the end of 2011, more than eleven thousand patients have been treated (as of 2013Q3) spread across the world (including EU, US, Australia, New Zealand and Brazil). Within 1 year of commercialisation, AttraX™ had attained rapid market penetration equivalent to 1.1% share of the estimated US$2 billion global spinal bone graft market [Section 5, sources 7,8]. The approval of a putty formulation in the US in 2014 will allow full scale rollout in the home-market of NuVasive and should lead to a 10% market share within 2 years with a potential to grow to >25% in the coming 5-8 years.

Delivering health impact to patients

AttraX™ has delivered significant benefit to over 11,000 patients who have received the product since it was introduced in 2011. The impact relates firstly to benefit to patients compared to the autograft gold-standard procedure where bone taken from one area of the patient and placed at the defect site resulting in two operative sites. AttraX™ delivers similar performance to autograft but without the disadvantages, which include significant post-operative pain at the graft donor site in over 30% of patients, which can last for 2 years or more in some patients. Treatment with AttraX™ further reduces the risk of revision surgery as the synthetic product has greater reliability compared to living autograft. The simpler and quicker AttraX™ operative procedure ensures more rapid recovery, with less time in hospital and a more rapid return to full activity and work for patients, when compared to autograft. There are also potential safety benefits to patients when compared to the rhBMP2 growth factor product Infuse™, with current concerns over significant side effects of Infuse™ reported.

Delivering economic/commercial impact and changing clinical practice

The development of AttraX™ has already generated major economic and commercial impact, summarised as follows:

- Supporting the establishment of a company, Progentix Orthobiology BV to commercialise the product.
- Attracting significant venture capital investment for the development.
- Securing a trade sale worth up to US$80 million from NuVasive to obtained exclusive worldwide distribution rights for spinal treatment.
- Securing an exclusive distribution deal with a global top 3 dental company for use of the technology in the field of dentistry and craniomaxillofacial surgery.
- Generating new jobs, with Progentix Orthobiology BV employing 25 FTE staff in 2013, compared to 2 FTE in 2008.

In health economics terms the use of AttraX™ delivers significant savings compared to autograft or Infuse™ as follows. Compared to the clinical gold standard autograft, AttraX™ delivers:

- A reduction in length of the operation compared to autograft, estimated at approximately 40 minutes, resulting in a saving of approximately £800 per operation.
- Reduced post-operative hospital stay, typically 2-3 days less with a saving cost of approx. £225 per day.
- Reduced post-operative complications, and revision surgery, which costs approx. £5,000.

The product cost for AttraX™ (approx. US$1,500 for one spinal level) is considerably lower than other products with similar reported efficacy, such as Infuse™ (US$4,000) or Osteocel (allograft plus stem cells - US$3,500).

The commercial partnership between Progentix Orthobiology BV and NuVasive Inc is being used

to impact clinical practice as a synthetic bone graft is now available that is as effective as the gold standard autologous bone graft and more cost-effective and safe than the growth factor rhBMP2 (Infuse™). The recent agreement with a global top 3 dental company for use of the technology in the field of dentistry and craniomaxillofacial surgery will impact practice within these clinical specialisms that relate to more than 1.5 million procedures annually.

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

1. www.progentix.com
2. http://www.investegate.co.uk/article.aspx?id=20080122075500NT248. Aspect corroborated: €1 million series A financing to Progentix Orthobiology BV by BioGeneration Ventures.
3. http://www.progentix.com/Progentix_NUVA_Release_FINAL_adj.pdf. Aspect corroborated: US$80 million deal with NuVasive Inc. to acquire all stock of Progentix Orthobiology based on reaching certain milestones (2009).
4. Yuan H, Fernandes H, Habibovic P, de Boer J, Barradas AM, de Ruiter A, Walsh WR, van Blitterswijk CA, de Bruijn JD, Osteoinductive ceramics as a synthetic alternative to autologous bone grafting, Proc Natl Acad Sci U S A. 107(31):13614-13619 (2010), PMID: 20643969
5. Yuan H, Fernandes H, Habibovic P, de Boer J, Barradas AM, de Ruiter A, Walsh WR, van Blitterswijk CA, de Bruijn JD, 'Smart' biomaterials and osteoinductivity, Nat Rev Rheumatol, 7(4)-c1 (2011) doi:10.1038/nrrheum, PMID: 21584973
6. World Wide, US, EU and UK Bone replacement Markets. SmartTrak.net August 2013, BiomedGPS, LLC, USA
7. Professor of Tissue Regeneration, MIRA Institute, Twente University, The Netherlands. Aspect corroborated: Improved Instructive Bone Graft AttraX™ – impacting unmet clinical and commercial need. Delivering health impact to patients. Delivering economic/commercial impact and changing clinical practice.
8. Chairman of the Board, Progentix Orthobiology BV, BioGeneration Ventures, The Netherlands. Aspect corroborated: Improved Instructive Bone Graft AttraX™ – impacting unmet clinical and commercial need. Delivering health impact to patients. Delivering economic/commercial impact and changing clinical practice.