Institution: Queen Mary University of London

Unit of Assessment: 12

Title of case study: AttraX™: Development of a synthetic bone graft to treat bone defects

Period when the underpinning research was undertaken: 2004 – 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:**
JD de Bruijn	Professor of Biomaterials	2004-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)

AttraX™ is a synthetic bone graft used to treat bone defects. It delivers the same effectiveness as the gold standard autograft (patient's own bone) but without the disadvantages such as post-operative pain and risk of revision surgery. AttraX was commercialised by the spin out company Progentix Orthobiology BV in 2007, based on research by Queen Mary's Prof. de Bruijn. It was sold to one of the top 3 global spine companies, NuVasive Inc. It is estimated that AttraX is used in 20,000 procedures per year (compared to 11,000 in 2014), including in the EU, US, Australia, New Zealand and Brazil. AttraX costs approximately USD1,500 per surgery, which is considerably lower than other products with similar reported efficacy. Due to reduced surgery times and post-operative complications and shorter hospital stays, the use of AttraX instead of autografts saves USD26,000,000 per year.

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. The only option available to surgeons was the use of patient-own bone tissue (autograft) harvested from other locations in the body (with associated complications) or the use of expensive drug-based therapies. These have major drawbacks such as immune reactions, disease transfer, regulatory constraints, limited efficacy and high costs. Thus, there was an unmet clinical need for a product with the same effectiveness as the gold-standard autograft but without its disadvantages. From the mid-1990's, Prof de Bruijn has been conducting research aimed at developing synthetic bone replacement materials that have bone-inducing properties, termed Instructive Bone Grafts (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 Queen Mary, as Chair of Biomaterials. He also established Progentix Orthobiology BV, as founder and CEO, to commercialise the IBG technology through a government start-up grant via the University of Twente, the Netherlands. A research partnership was established with the company funding researchers at Queen Mary in 2004, which eventually led to the development of a novel IBG product, AttraX™. The research focused on understanding and unravelling the process of material-induced bone formation. Prof de Bruijn and his team showed that inflammation plays a role in bone induction, facilitated by surface microstructured materials. They further showed that calcium phosphate materials with a specific surface topography induce bone formation and lead to clinically relevant bone healing in defects that otherwise do not heal [3.1, 3.2]. 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 [3.3]. The research was extended to demonstrate that AttraX was at least equivalent in bone regeneration to the gold standard autologous (patient-own) bone and drug-based therapies such as growth factor therapy, thereby demonstrating the clinical and commercial viability of AttraX [3.4-3.6].

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

[3.1] Yuan H, van Blitterswijk CA, de Groot K, de Bruijn JD (2006). 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. https://doi.org/10.1002/jbm.a.30707

[3.2] Yuan H, van Blitterswijk CA, de Groot K, de Bruijn JD (2006). Cross-species Comparison of Ectopic Bone Formation in Biphasic Calcium Phosphate (BCP) and Hydroxyapatite (HA) Scaffolds. *Tissue Engineering, 12(6),*1607-1615. https://doi.org/10.1089/ten.2006.12.1607

[3.3] Eniwumide, JO, Yuan, H; Cartmell, SH; Meijer, GJ; de Bruijn, JD (2007). 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. https://doi.org/10.22203/ecm.v014a03

[3.4] Yuan H, Fernandes H, Habibovic P, de Boer J, Barradas AM, de Ruiter A, Walsh WR, van Blitterswijk CA, de Bruijn JD (2010). Osteoinductive ceramics as a synthetic alternative to autologous bone grafting. *Proc Natl Acad Sci U S A, 107(31)*, 13614-13619. https://doi.org/10.1073/pnas.1003600107

[3.5] Barbieri D, Yuan H, de Groot F, Walsh WR, de Bruijn JD (2011). Influence of Different Polymeric Gels on the Ectopic Bone Forming Ability of an Osteoinductive Biphasic Calcium Phosphate Ceramic. *Acta Biomater, 7(5)*, 2007-2014. https://doi.org/10.1016/j.actbio.2011.01.017

[3.6] R. Duan, L.A. van Dijk, D. Barbieri, F. de Groot, H. Yuan and J.D. de Bruijn (2019). Accelerated bone formation by biphasic calcium phosphate with a novel sub-micron surface topography. *Eur Cell Mater, 28(37),* 60-73. https://doi.org/10.22203/ecm.v037a05

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

AttraX™ [5.1] was commercialised by the spin out company Progentix Orthobiology BV in 2007, based on research led by Queen Mary's Prof. de Bruijn. In 2009, 40% of the company was sold to one of the top 3 global spine companies, NuVasive Inc. with the sale finalised in 2018 [5.2]. AttraX received regulatory approval in Europe (CE mark) in 2011 and USA (510(k) clearance) in 2015 [5.4].

AttraX addresses an unmet clinical need

AttraX delivers on an unmet clinical need, as its bone regeneration potential is in line with that of the clinical gold standards, autograft and growth factor therapy, but without the disadvantages:

- Treatment with AttraX reduces the risk of revision surgery as the synthetic product has greater reliability compared to living autograft;
- There is also a reduced need for anaesthesia. Some surgical procedures would not require general anaesthesia but the need to obtain autologous bone (from the iliac crest) makes anaesthesia mandatory, increasing surgical risks for the patient;
- 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 growth factor therapy, with current concerns over significant side effects reported.

AttraX has also been shown to have superior performance in inducing bone regeneration to other synthetic biomaterials, as shown in Figure 1 [5.5].

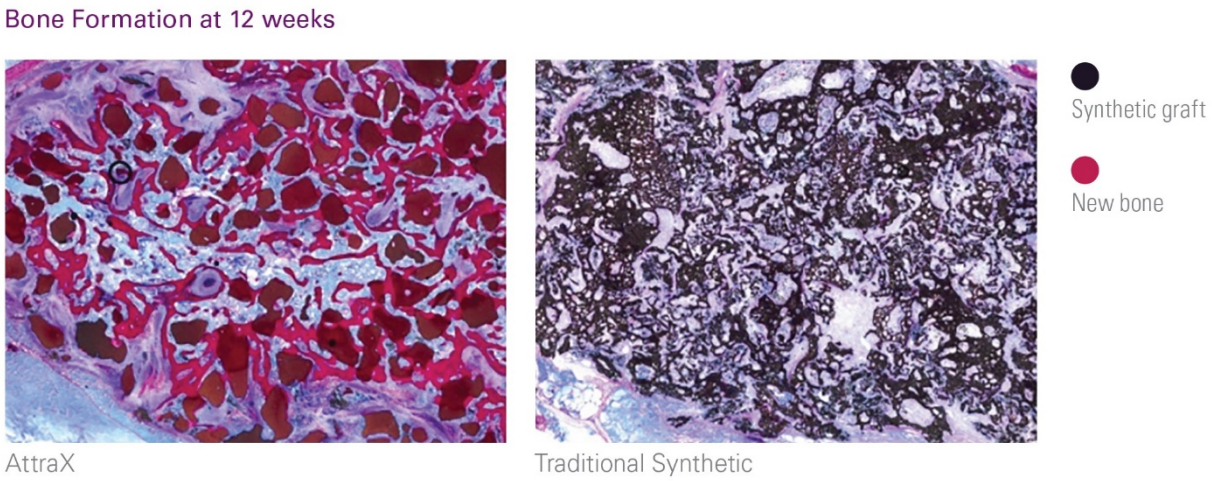

Figure 1: Comparison of bone formation at 12 weeks between Left: AttraX and Right: traditional synthetic materials. Reprinted from *AttraX® Portfolio*, NuVasive Inc 2018. Copyright by NuVasive, Inc.

There are two main formats of the AttraX material available [5.5]:

1. A putty containing the core technology as granules with a mouldable wax;
2. A scaffold product containing bovine collagen plus granules.

The products have similar performance characteristics but provide options for surgeons who have different preferences.

It is estimated that AttraX™ is used in 20,000 procedures per year (compared to 11,000 in 2014), globally [5.5].

AttraX improves health economics

The use of AttraX delivers significant savings compared to autograft or growth factor therapy, as detailed in the table below [5.5], due to:

- A lower product cost
- Reduced operation times compared to autograft
- Reduced post-operative hospital stays
- Reduced post-operative complications and need for revision surgery

Item	AttraX™	Autograft	Growth factor therapy
Material cost /procedure (USD)	1,500	N/A	3,500-4,000
Operation time	40 minutes lower than autograft	+USD1,000/operation	
Recovery time	2-3 days less than autograft	+USD840/operation	
Complications	21% less complications than autograft	+USD6,000/operation	Potential for complications in 50% of cases

Thus, AttraX™ is estimated to save (per year):

- USD26,000,000 per year when compared to autograft-based procedures
- USD60,000,000 per year when compared to growth factor-based procedures

Figure 2: Picture of Attrax® Scaffold. Reprinted from NuVasive Inc 2018. Copyright [2018] by NuVasive, Inc.

The Queen Mary developed IBG, AttraX, fills a major gap in the bone replacement materials market. AttraX has the same effectiveness as the gold standard autograft and improved health economics, but mitigates its disadvantages such as 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, immune reactions, disease transfer and regulatory constraints.

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

[5.1] NuVasive, Inc (2018). *AttraX Portfolio*. https://www.nuvasive.com/wp-content/uploads/2019/08/AttraX-Overview-Brochure.pdf

[5.2] NuVasive, Inc. (2018). 2018 Annual Report (pp. 104). https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwiKjJLG78_uAhV3UhUIHTLFBbcQFjABegQIAhAC&url=http%3A%2F%2Fir.nuvasive.com%2Fstatic-files%2F747617c5-1824-4d52-89b6-88a2d56399f3&usg=AOvVaw0p_-spoxSYZ5QQE0Numo62

[5.3] Science Business. (2009). Progentix Orthobiology secures $15M from commercialisation partner. https://sciencebusiness.net/news/69788/Progentix-Orthobiology-secures-%2415M-from-commercialisation-partner. 29 Jan 2021.

[5.4] US Food and Drug Administration (23 January 2013). *Traditional 510(k) Premarket Notification* (K151584– AttraX Putty)

[5.5] Fresh Perspective (2020). *Impact Case Study: Synthetic Bone Grafts - Progentix™*

[5.6] EV Wezel. Chairman of Borad of Directors. Progentix Orthobiology BV (testimonial letter, 10 March 2019). [Corroborator 1]