Institution: Imperial College London

Unit of Assessment: 13B Metallurgy and Materials

Title of case study: Specification of Bioglass® as a cell stimulating synthetic bone graft and the active agent in Sensodyne Repair and Protect toothpaste

1. Summary of the impact

NovaBone® (NovaBone Products LLC) is a synthetic bone graft. It is a **Bioglass®** (a specific composition of bioactive glass) powder that orthopaedic surgeons use to regenerate (heal) bone defects (holes in bone). Research by Larry Hench, Julia Polak and their student Ioannis Xynos, that was published in 2001, showed that the dissolution products of the glass particles stimulated bone cells to produce new bone. This gave NovaBone a competitive edge over all other synthetic bone grafts at the time. Due to the data, NovaBone coined the term Osteostimulation, which describes this property. The Federal Drug Agency in the USA (FDA) allowed the claim, which led to a 20% increase in sales for NovaBone.

GlaxoSmithKline (GSK) released a new toothpaste in 2011, ***Sensodyne Repair and Protect*** and in the first 16 weeks attracted a 2.7% (£10M) market share. The active ingredient is Bioglass (NovaMin®). The fundamental research was carried out in the Department beginning with the work of Larry Hench and Julian Jones in 1999. They reported the effect of glass particle size on active ion release. 57% of people suffer from hypersensitivity (tooth pain) caused by fluid flow into exposed tubules in dentin that lead to nerve endings. When teeth are brushed with toothpaste containing NovaMin® , the particles bind to the dentine, where they dissolve and produce mineral with similar composition to enamel, which occludes the tubules. GSK developed a new toothpaste based on this research – *Sensodyne Repair and Protect*. *Sensodyne* delivered remarkable growth of 14% driven largely by the successful rollout of *Sensodyne Repair and Protect*.

2. Underpinning research

Larry Hench was Professor in the Department of Materials at Imperial from 1996-2005. His work at Imperial focused on understanding the mechanisms behind why Bioglass® performed better in animal experiments than other bioceramics. Bioglass® was known to bond to bone faster than other materials and to stimulate more rapid bone growth. Dr Julian Jones, now a Reader in the Department of Materials, carried out his PhD with Hench and was instrumental in carrying out key experiments.

Cell Culture studies: Hench's cell culture studies, carried out by his student Ioannis Xynos (co-supervised by Professor Dame Julia Polak of the Faculty of Medicine and co-director, with Hench, of the Tissue Engineering and Regerative Medecine centre at Imperial) found that the dissolution products of the glass, stimulated bone cells at the genetic level, causing the cells to produce bone matrix [1]. For example the study showed that expression of insulin-like growth factor II (IGF-II) increased by more than three-fold in the presence of the dissolution products of the glass. IGF is the most abundant growth factor in bone and induces osteoblast proliferation [1]. Extracellular matrix secretion was also increased, which mineralised without addition of supplements. Importantly, a beneficial response was dependent on the dose of ions to which the cells were exposed. Work reported in 2009 by Olga Tsigkou (PDRA), Dr Julian Jones and Professor Molly Stevens (all Department of Materials) later found that the optimal concentration of soluble silica to be 15-20 $\mu g ml^{-1}$ promoted the highest metabolic activity [5]. The work showed that the beneficial properties of Bioglass were due not only to its ability to bond to bone but also due to the dissolution products stimulating bone cells [1, 5]. The dissolution products caused biomineralisation (biological mineral formation) without any addition growth factors and without a bioactive glass substrate [5]. Hench termed the behaviour "Osteostimulation", which was coined and used by NovaBone

Products to describe the advantage Bioglass had over its competitors.

The result that the dissolution ions were stimulating cellular activity seeded the idea that if particles were introduced into toothpaste and dissolved in the mouth, natural repair of enamel may occur through biomineralisation of the dentine (formation of biological hydroxyapatite that is very similar to the mineral in dentine). It was then important to determine the optimal particle size and dose of particles that should be used.

Particle size: Further understanding of how particle size and doseage (mass/solution volume) influenced natural enamel repair, was needed. Jones and Hench produced data on how glass composition, particle size, specific surface area [2,4] and dosage [3] affected pH rise, dissolution profiles and mineral formation, which were critical to optimisation and commercialisation of the toothpaste. For example, Bioglass particles with particle sizes less than 5 µm were found to nucleate hydroxycarbonate apatite (HCA, the mineral component of enamel and dentine) within 22 hours in simulated body fluid when 2 mg/ml or less was used, but when higher concentrations were used, calcium carbonate formed instead [3]. The work showed that the smallest particles could be made with high-surface area and a narrow size distribution [2] and the fine particles dissolved and formed mineral (hydroxyapatite) fastest [4]. Studies in physiological solutions showed that using too high a concentration of the < 5 µm particles in a fixed volume, could change the reaction of the glass, forming calcium carbonate instead of the enamel-like hydroxyapatite [3]. As a result the toothpaste contains the < 5 µm particles of Bioglass at a concentration of 7.5%.

3. References to the research

* References that best indicate quality of underpinning research.

1. *Xynos, I.D., Edgar, A.J., Buttery, L.D.K., Hench, L.L., Polak, J.M. “Gene-expression profiling of human osteoblasts following treatment with the ionic products of Bioglass® 45S5 dissolution”, *Journal of Biomedical Materials Research* 2001: 55: 151-157. DOI: 10.1002/1097-4636(200105)55:2<151::AID-JBM 1001>3.0.CO;2-D

2. Sepulveda, P., Jones J.R., Hench L.L. “Characterisation of melt-derived 45S5 and sol-gel derived 58S bioactive glasses”, *Journal of Biomedical Materials Research*, 2001; 58: 734-740. DOI: 10.1002/jbm.10026

3. *Jones J.R., Sepulveda, P., Hench L.L. “Dose-dependent behaviour of bioactive glass dissolution”, *Journal of Biomedical Materials Research*, 2001: 58: 720-726. DOI: 10.1002/jbm.10053

4. *Sepulveda, P., Jones J.R., Hench L.L. “In vitro dissolution of melt-derived 45S5 and sol-gel derived 58S bioactive glasses”, *Journal of Biomedical Materials Research*, 2002: 61: 301-311. DOI: 10.1002/jbm.10207.

5. Tsigkou, O., Jones, J.R., Polak, J.M., Stevens, M.M. “Differentiation of fetal osteoblasts and formation of mineralized bone nodules by 45S5 Bioglass® conditioned medium in the absence of osteogenic supplements”, *Biomaterials*, 2009: 30: 3542-3550. DOI: 10.1016/j.biomaterials.2009.03.019

4. Details of the impact

- **Gene stimulation (Osteostimulation)**: The fact that critical concentrations of dissolution products stimulated bone cells to produce more bone matrix. This led to use of the term “Osteostimulation” by NovaBone Products, which described to surgeons how NovaBone® performed better than its competitors, leading to a 20% increase in sales.

The Vice President Research & Development at NovaBone Products LLC states:

"*…the work conducted by Dr Larry Hench and yourself, in collaboration with Professor Dame Julia Polak, carried out from 1998-2002…, enabled NovaBone Products to provide scientific data to the FDA to support claims of "Osteostimulation" for our products. More specifically, the studies conducted at the Imperial College London were essential to the development and definition of the concept of Osteostimulation which is now understood among orthopaedic surgeons and researchers as the activation of the genes responsible for osteoblast differentiation and proliferation. In addition, the Osteostimulation studies that you have conducted provided NovaBone with an important marketing advantage over our competitors that claim their products to be osteoconductive. This advantage has allowed NovaBone to increase sales by more than 20% since the claim of Osteostimulation was allowed by the FDA. As you may be aware, NovaBone is available in more than 80 countries and has been used in more than 1 million patients worldwide with significant growth expected to continue well into the foreseeable future."* [D]

NovaBone is a company with $15M in revenue and more than 30 employees.

- **Biomineralisation:** The fact that dissolution products within a material stimulated biomineralisation led David Greenspan, who was previously Hench's PhD student, to develop a toothpaste containing bioactive glass particles to treat hypersensitivity. The product was named NovaMin®.

David Greenspan, Vice-President for Research at US Biomaterials and then at NovaMin Technology Inc. states:

"The research that we funded at Imperial focused on materials characterization (dissolution and bioactivity) and cellular response. A key aim was to determine mechanisms behind why bioactive glass was performing so well in vivo in terms of rate of bone bonding. Collaborations between Larry Hench and Professor Dame Julia Polak led to in vitro studies (e.g. J Biomed Mater Res 2001.55: 151-157) that revealed that the dissolution products of the bioactive glass stimulated cells at the genetic level. Glass characterization studies that we funded focused on understanding how bioactive glass type (sol-gel v melt-derived), particle size, specific surface area and dissolution media type affected the rate of dissolution and apatite formation (J Biomed Mater Res B, 2001,58B:734-740 and J Biomed Mater Res A 2002:61A: 301-311)."

"The study of how the dose (concentration) of bioactive glass affected its dissolution and bioactivity (J Biomed Mater Res B 20A58P.72A-726) was also important work. These data, along with other studies that we conducted, contributed to our confidence that relatively small particles used in NovaMin would be appropriate, and that we could achieve an effective loading of NovaMin in the toothpaste. Novamin Technology, Inc. was acquired by GlaxoSmithKline in December 2009 for $135 million" [E].

- **Clinical studies** show brushing with toothpaste containing NovaMin® can: reverse early tooth decay; eliminate hot and cold sensitivity and kill more bacteria that cause gum disease than standard toothpaste. **GSK** acquired NovaMin® in 2009 for **$135M**. *Sensodyne Repair and Protect* was launched in 2011 in over 20 countries including most of the EU.

- ***Sensodyne Repair and Protect*** has, since its launch in 2011, been purchased by almost 1.5m UK households and is worth £10m in the UK market alone [A]. It has achieved 2.7% share of the total toothpaste market and became the number one toothpaste launch in 2011 based on the first 16 weeks of sales. *Sensodyne Repair and Protect* has won Product of the Year 2012 in the Toothpaste category and numerous packaging awards including The Grocer Gramia Awards 2011, Packaging of the Year, [A] and won Product of the Year in 2013 [B]. Sensodyne bucks the trend in consumer products as a GSK press release indicates… "*However, toothpaste performance was particularly strong in the quarter: Sensodyne delivered double digit growth (+14%) driven largely by the successful rollout of Sensodyne Repair and Protect."* This contributed to a consumer healthcare turnover of £1.277Bn in Q2 2011 of which oral Healthcare comprised £425M. NovaMin® achieved considerable recognition prior to acquisition by GSK [C].

5. Sources to corroborate the impact

A. Sensodyne Repair and Protect: http://www.talkingretail.com/products/productnews/glaxosmithkline-introduces-two-new-toothpastes
(Archived at https://www.imperial.ac.uk/ref/webarchive/7kf*)*

B. Sensodyne Repair and Protect wins Product of the Year 2013, which is voted for by consumers: http://www.talkingretail.com/products/product-news/sensodyne-announces-toothpaste-product-of-the-year-2013-win
(Archived at https://www.imperial.ac.uk/ref/webarchive/8kf*)*

C. NovaMin is calcium sodium phosphosilicate (bioactive glass) http://en.wikipedia.org/wiki/NovaMin
(Archived at https://www.imperial.ac.uk/ref/webarchive/9kf*)*

D. Letter from Vice President of Research and Development NovaBone Product LLC confirming that the work carried out at Imperial led directly to FDA approval

E. Letter from Vice President for Research of NovaMin Technologies when NovaMin was launched confirming that the work done at Imperial contributed to its development.