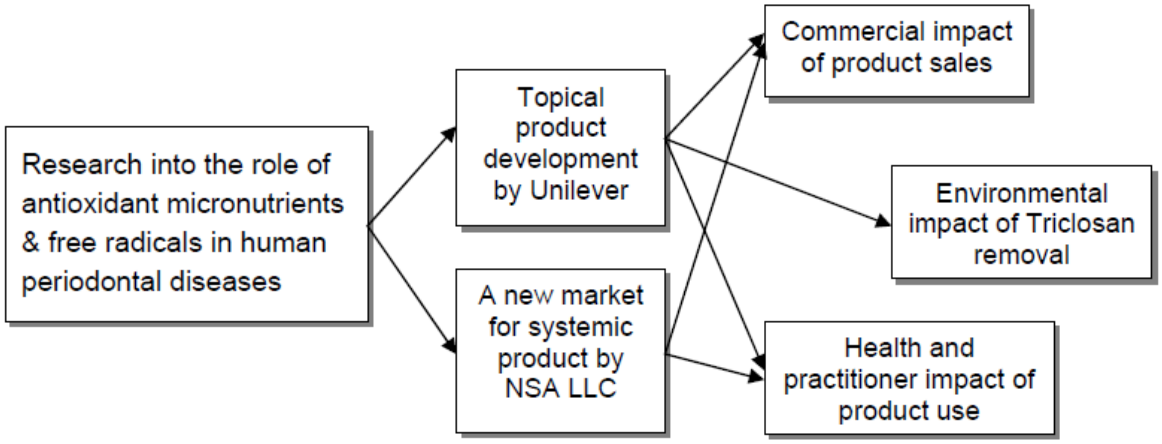
Institution: The University of Birmingham

Unit of Assessment: 3

Title of case study: Commercial products for improved oral health based upon novel antioxidant micronutrient approaches delivered via toothpastes and food capsules

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

Pioneering basic research into the role of oxygen free-radical damage and antioxidant micro-nutrient protection in human periodontal diseases by the Periodontal Research Group in Birmingham has led to the development and marketing of novel toothpaste formulations and new applications for other nutrient products in collaboration with global consumer healthcare companies. This work has changed thinking in the field and has had significant **commercial impact** in terms of changing business R&D and marketing strategies**.** Resultant technologies have demonstrated reductions in gingivitis and periodontitis with associated **social, economic and health impacts**. In addition, our research is enabling Triclosan, an antibacterial compound used widely in soaps, detergents, mouthwashes and toothpastes, to be replaced with more environmentally-friendly, natural and equally efficacious agents.



2. Underpinning research (indicative maximum 500 words)

Periodontitis is a severe form of gum disease (periodontal disease) and the most common chronic inflammatory disease of humans, affecting 50% of adults globally. Whilst it is initiated by the accumulation of a bacterial plaque biofilm at and below the gum margin, 80% of the resultant tissue damage is caused by an exaggerated host immune response to the plaque biofilm. Whilst plaque removal by tooth brushing is key to prevention and treatment, therapeutic outcomes are limited and methods of modulating the hosts' immune response are needed. Not only is periodontitis a major cause of tooth loss worldwide it is also a significant independent risk factor for atherogenic cardiovascular disease and diabetes, due to bacterial entry into the bloodstream and the resultant acute-phase response and oxidative stress that ensues.

The Periodontal Research Group led by Professor Iain Chapple and Dr John Matthews (Reader; 1993-current) and involving Drs Melissa Grant (Former Research Fellow, Lecturer; 2011-current) and Michael Milward (Senior Lecturer; 2005-current) has pioneered research into antioxidant and free radical biology and its impact on chronic inflammatory diseases (particularly periodontal diseases) since 1996. Antioxidant micronutrients are natural dietary compounds that protect the body's cells and tissues from excessive release of damaging oxygen radicals, preventing oxidative stress and therefore the generation of destructive inflammation that characterises periodontitis. They act at atomic and molecular levels via cell signalling cascades. Our work in this field began with the development of an enhanced chemiluminescence assay to measure small molecule total antioxidant capacity in biological fluids and tissues (1) and led to the elucidation of reduced glutathione (GSH) as the key antioxidant at exposed epithelial surfaces, which was deficient in both periodontal and lung disease (2, 3).

A hypothesis that GSH was key in regulating inflammation via NFκB modulation within mucosal tissues was proposed by us in 1996 (Chapple *et* al *J Clin Molec Pathol* 1996:49;M247-55; 2nd most read paper in journal/year) and 1997 (Chapple *et al J Clin Perio* 1997:24;287-96: 189

citations), identifying NFκB antagonists as potential therapeutic targets. This thesis has since been proven (3) and several therapeutic strategies using GSH have been adopted in medicine for inflammatory disease management. In addition, targeting the NFκB pathway using natural and pharmacological approaches has become a major focus in the development of anti-inflammatory therapies in general. Our approach aims to facilitate GSH preservation by boosting tissue antioxidant status through either topical application in toothpastes or systemic application via a parenteral route using micronutrient capsules, and to stimulate GSH synthesis by activation of the anti-inflammatory transcription factor Nrf2 [Nuclear factor (erythroid-derived 2)-like 2] (3).

Large scale epidemiological studies (4) and case-control studies (2004) confirmed antioxidant micronutrient deficiency in periodontitis and an intervention study (Chapple *et al J Clin Perio* 2007:34; 103-10) demonstrated that resolving periodontal inflammation led to antioxidant recovery. In parallel with work on antioxidant biology, studies investigating the origins of oxidative stress in peripheral blood neutrophils from periodontitis patients (3,5,6) demonstrated these cells as being dysregulated in periodontitis patients and identified mechanisms, which have subsequently formed a target for novel toothpaste formulations (3,6). Studies on oral epithelial cells also demonstrated that NFκB modulation was possible using micronutritional approaches (7). This, alongside work on neutrophil biology, led to translational studies aimed at developing local and systemic approaches for modulating periodontal inflammation in collaboration with industry, leading to product development (3,5,6).

This research has resulted in keynote lectures/symposia at the International Association for Dental Research (2005, 2009, 2011, 2012); the British Society for Oral and Dental Research (2004, 2013); the European Federation of Periodontology (2003, 2006, 2009, 2012); American Nutraceutical Association (2010); Royal Society of Medicine (2010); and several awards: Australian Dental Association Eminent Lectureship 2010; The Charles Tomes Medal and Lecture, The Royal College of Surgeons England 2010; International lectures for national periodontal societies in Germany, Belgium, Switzerland, Holland, Denmark, Spain, Mexico, Greece (2010-2013). The lectures have focussed on how we have improved understanding of the oxidative stress process and its impact in periodontitis and as a result, reported novel therapeutic approaches.

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

1. Chapple ILC, Mason GM, Matthews JB e*t al*. Enhanced chemiluminescent assay for measuring the total antioxidant capacity of serum, saliva and crevicular fluid. Ann Clin Biochem. 1997: 34;412-421. doi: 10.1177/000456329703400413.
2. Chapple ILC, Brock G, Eftimiadi C, *et al.* Glutathione in gingival crevicular fluid and its relation to local antioxidant capacity in periodontal health and disease. Mol Path, 2002:78,55,367-373. doi:10.1136/mp.55.6.367.
3. Dias HK, Chapple ILC, Milward MR *et al*. Sulforaphane restores cellular glutathione level and reduces chronic periodontitis neutrophil hyperactivity *in vitro*. PLoS ONE. 2013:8(6):e66407. doi:10.1371/journal.pone.0066407.
4. Chapple ILC, Milward M, Dietrich T. The prevalence of inflammatory periodontitis is negatively associated with serum antioxidant concentrations J Nutr. 2007:137;657-64.
5. Matthews JB, Wright H, Roberts A *et al*. Hyperactivity and reactivity of peripheral blood neutrophils in chronic periodontitis. Clin Exp Immunol, 2007:147;255-64. doi: 10.1111/j.1365-2249.2006.03276.x.
6. Chapple ILC, Matthews JB, Wright HJ *et al*. Ascorbate and α-tocopherol differentially modulate reactive oxygen species generation by neutrophils in response to FcγR and TLR agonists. Innate Immunity 2013:19;15-9. doi: 10.1177/1753425912455207.
7. Milward MR, Chapple ILC, Grant MM *et al*. The action of a natural antioxidant on periodontal pathogen stimulated oral keratinocytes. Innate Immunity 2013:19;140-51. doi: 10.1177/1753425912454761.

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

A. <u>Commercial Impact</u>

Topical product development by Unilever

With more than 50% of the adult UK population affected by periodontal disease, the cost to the UK economy alone was estimated at £2.78-billion in 2008 (ATP Consulting 2008). As such, novel

treatment modalities for modulating periodontal inflammation represent an enormous market for healthcare companies. Unilever, a global consumer healthcare company, has invested several million GBP in research & development (R&D) activities (£1.5-million directly to the University of Birmingham's Periodontal Research Group) based on our investigator-led collaborative proposals. Our work has defined mechanisms by which oxidative stress drives inflammation in different model systems and we subsequently developed a Platform Evaluation Capability (PEC1 & PEC2 programs) to enable the high-throughput screening of natural micronutrients for anti-inflammatory properties (e1, e2, e3). We have investigated the highest-performing new actives in our model systems and elucidated their mechanisms of action. This research has resulted in the development of a new health product concept of micronutritional approaches for modulating inflammation, its introduction to a global market, and further development of combined actives to secure intellectual property and patents. Staff across Unilever's R&D centres are actively involved in exploiting the data from ongoing studies, with the novel insights and science being used in the identification of new technologies and next-generation market innovations.

A new clinical intervention has been developed from basic research in collaboration with Unilever PLC (70% Birmingham), which has transformed traditional approaches to combating gingivitis and periodontitis, and is delivered topically through a toothpaste formulation.

1. Proof-of-principle phase-1 product was developed and taken to market in 2008 in a low profile approach to assess market uptake and introduce a new therapeutic concept based upon oral tissue nourishment (Unilever NutriActiv toothpaste - e1). This was launched in many of the key and largest European oral care markets, including France, Italy, Greece and central Europe (e2).
2. Pivotal phase-2 studies have been run with a product that employs a combination of 3 micro-nutrients and a key clinical study is currently underway with our group (May-Nov 2013), with a view to a new product launch in 2014/15. The study outcomes are commercially sensitive but will be published as a journal supplement for claims support, similar to that under (e1).

Systemic product application and new market development by NSA LLC

The application of an existing nutritional intervention has also been expanded to a new global market through an investigator-led Randomised Controlled Trial (2012), the first of its kind in oral care research. Based upon our ideas and research, National Safety Associates (NSA LLC, Memphis), a US-based company who make a product known as "JuicePlus®", has funded 3 investigator-led studies. The studies are aimed at elucidating the clinical benefits of JuicePlus®, a phytonutrient dietary intervention (in capsule form), as an adjunct to periodontal therapy (*clinicaltrials.gov* NCT00952536), as a mono-therapy (multi-centre, 3-country study underway - *clinicaltrials.gov* NCT01229631) and also as an approach for reducing post-operative morbidity and improving healing following wisdom tooth surgery (*clinicaltrials.gov* NCT01145820).

Successful outcomes from the first study are already published, creating a new use for the product and a new market (oral healthcare) for the company. This has opened up an entirely novel and substantial business opportunity for NSA (e3) with data from the first study being disseminated globally via the literature, and in academic and business conferences in the USA, Europe and the UK. This has assisted NSA in the planning and marketing of their global business, which generates over US$350-million in sales annually (>0.5-million customers in the USA alone) across more than 20 countries around the world, providing global reach for such oral health benefits (e3).

Wider market recognition and adoption within healthcare industry

Johnson and Johnson (J&J) have now recently engaged our group in analyzing, using our in-house assays, the antioxidant capacity of their mouthrinse formulations (January 2012 - current), and are planning product revisions and developments based on these outcomes (e3). This research has highlighted to J&J the significant potential of mouthrinses in contributing to oral health through previously unexplored properties. Consequently, J&J have invested, to-date, in excess of £100k in support of R&D activities in this area in partnership with us.

B. Health and Practitioner Impacts

Our research on antioxidant micronutrients and their demonstrable modulation of innate immune

responses has contributed to an entirely new therapeutic field in Dentistry and has been recognized globally. Several countries, consortia of countries through European and International academic associations, and European bodies have engaged in symposia, workshops and have published consensus statements from expert groups on the importance of nutritional advice for periodontal care (e.g. 7th European Workshop on Periodontology 2010 (e4), the leading influence in the discipline in Europe and now the world). This document highlights the need to engage patients in practice with nutritional advice in the management of their periodontal disease.

Our paper in *J Clin Perio* (e5) demonstrated periodontal health benefits from micronutrient capsules and was immediately identified by the editor of the top impact factor dental journal in the world for a pubcast, and made 'open access', in order to facilitate public and practitioner dissemination. The message has also reached the world's Integrative Medicine community, by a published interview on the paper in a US-based journal, invited within 21-days of the paper's release (e6). Nationally, industry-funded road-shows have disseminated these findings (2011-2012) to dental care professionals (over 2000 delegates across 10 UK venues), and stimulated substantial interest, with evidence of changes in practice, provided by feedback from practitioner delegates (e7). A chapter by Chapple and Grant was also commissioned in a new textbook *Food constituents and oral health (*Woodhead Publishing LTD., Chapter 11, ISBN:978-1-84569-153-0) which is targeted at educating practitioners in these new adjunctive treatment modalities. Our micronutrient results have also been cascaded to the global integrative medicine community (e8).

C. Environmental Impact

Our novel toothpaste actives, developed in collaboration with Unilever, provide a viable alternative to the use of Triclosan, a chlorinated aromatic antibacterial compound used widely in soaps, detergents, mouthwashes and toothpastes. Triclosan is toxic to aquatic bacteria at levels found in the environment and inhibits photosynthesis in key algae responsible for a large part of the photosynthesis which occurs on earth. To be able to replace Triclosan with natural active ingredients that provide equivalence in clinical efficacy, without adverse effects upon the environment, is a longer-term goal for companies such as Unilever. While this will depend on local product affordability in different countries in the short term, our phase 2 data now provides proof of principle that this is an achievable goal using micronutrient approaches and longer-term this will likely lower the costs of oral healthcare products, targeting universal affordability (e2, e3).

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

e1. An entire supplement of the International Dental Journal, sponsored by Unilever, was devoted to healthcare benefits from the administration of micronutrients within a toothpaste formulation. International Dent Journal 2007: 57; S2; 117-149. Available upon request.
e2. Unilever letter outlining impact on strategic direction of oral care business, market reach of Unilever, sales data on NutiActiv, expected sales data on phase-2 formulation.
e3. Confirmation that services and policies of 3 major multi-national companies have been influenced and driven by our research in this field, specifically Unilever, NSA and J&J. Impact upon national societies and professional opinion is evidenced by invited lectures.
e4. The European Federation of Periodontology have also published via open access a keynote review paper and consensus report for the profession and public (J Clin Periodontol 2011:38;suppl 11:114-118. doi: 10.1111/j.1600-051X.2010.01675.x; J Clin Periodontol 2011: 38; suppl 11: 142-158. doi: 10.1111/j.1600-051X.2010.01663.x.).
e5. Chapple ILC, Milward MR, Ling-Mountford N, Weston P, Carter K, Askey K, Dallal GE, De Spirt S, Sies H, Patel D and Matthews JB. (2012), Adjunctive daily supplementation with encapsulated fruit, vegetable and berry juice powder concentrates and clinical periodontal outcomes: a double-blind RCT. J of Clin Periodontol, 39: 62–72. doi: 10.1111/j.1600-051X.2011.01793.x. Only open access paper in volume.
e6. Record of interview with US-based Integrative Medicine journal (www.vitasearch.com).
e7. Letter from AB Communications confirming feedback from P&G lecture series 2011-12.
e8. Evidence of clinical benefit also from presentations at Experimental Biology (Anaheim 24th March 2010); The American Nutraceutical Academy (ANA) (Pheonix 2010, 25th March 2010); The ANA (Palm Beach California 24th April 2011); The European Congress on Integrative Medicine (ENA - Berlin – 4th December 2010).