Institution: The University of Birmingham

Unit of Assessment: UOA3 - Dentistry

Title of case study: Development of periodontal disease predictive technologies and their commercialisation by two SME's and three multi-nationals

1. Summary of the impact (indicative maximum 100 words)
Our biomarker research and underpinning technologies have **commercially impacted** upon the global R&D strategies of Unilever, Philips and Mars, realising new market areas for them, resulting in several million GBP invested in related R&D as well as "claim support" for products both in development and already available on shelves. Unilever have adopted biomarker outcomes as endpoints in clinical trials of new products, and Philips and Mars are developing with us saliva-based near-patient diagnostic tests for the human and small animal markets. We have also spun out two SME's: A) <u>Oral Health Innovations</u> (OHI) Ltd has developed online risk and disease analysis software for oral conditions, which was piloted, adopted and launched by Denplan, the UKs largest dental capitation plan operator (accessing 6500 dentists and 1.8 million patients), at the 2013 annual British Dental Association conference; and B) <u>GFC Diagnostics</u> makes SmokeScreen™ a non-invasive, sensitive and objective saliva test developed from our biomarker research at Birmingham University. Both technologies have already provided demonstrable **social** and **commercial impact** and given their uptake to date, will also deliver **economic, environmental** and **health impacts**.

2. Underpinning research (indicative maximum 500 words)
Inflammatory periodontitis is a complex disease affecting 50% of adults globally. It costs the UK economy £2.78-billion (ATP Consulting 2008) and also impacts negatively upon general health. Severe disease is independently associated with all-cause mortality; poor glucose control and cardio-renal outcomes in diabetes and atherogenic vascular disease (www.perioworkshop.org). While periodontal therapy improves diabetes control and outcomes, periodontitis is a silent disease - often diagnosed late when the destructive changes are irreversible. Diagnostically accurate biomarkers are therefore needed to facilitate screening in primary dental and medical practices.
Research at the University of Birmingham over the past 15 years has pioneered the development of a range of methods to predict periodontal risk and the presence of disease (1). We have developed and evaluated assays for biomarkers of periodontitis and associated systemic inflammatory diseases and their risk factors (1-7). This work has been led by Professor Iain Chapple (Professor of Periodontolgy) and Dr John Matthews (Reader in Oral Immunology), and involved Dr Melissa Grant (Lecturer in Oral Biology), Dr Michael Milward (Senior Lecturer), Dr Graham Cope (Honorary Senior Research Fellow) and Dr Mike Busby (Honorary Lecturer).
Our work is focussed in 4 main areas:
A) **Assay Development**: studies into disease processes for disease prediction and early diagnosis B) **Biomarker Discovery**: for prediction of disease development, presence and progression. C) **Biomarker Utility**: in near patient diagnostic tests and evaluation of novel oral product efficacy. D) **Development of near-patient Biofeedback Tools**: for risk assessment and disease scoring to support behaviour change through immediate personalised biofeedback to patients. We began by exploring the biochemical composition of a fluid exudate from gingiva (gums), gingival crevicular fluid (GCF), which led to the development of several measurement methodologies and assays (2,3,6,7), enabling exploration of disease mechanisms and novel therapies. Development of early prognostic/diagnostic tests and treatment outcome measures required the establishment of highly sensitive assays capable of quantifying sub-attomole levels of biomarkers in nano-litre volumes of GCF. Several chemiluminescence assays for GCF analysis were developed from first principles (3,4) and applied to the study of disease processes. GCF biomarkers have subsequently been shown to be valid and superior discriminators of gingival and periodontal disease/health and have been adopted as outcome measures for clinical trials of novel oral healthcare products (5). Our total antioxidant capacity assay (4) was the first to identify oxidative stress and antioxidant deficiency in periodontitis (locally & systemically) and led to a new research era in micro-nutritional approaches to managing periodontal diseases.
Whilst GCF biomarker analysis has now become accepted in clinical trials of novel oral care products, it does not lend itself to near patient testing. Hence, our expertise targeted the analysis of

saliva as a diagnostic fluid using novel methods of saliva collection and delivery to analytical devices. Using saliva chemistry, we developed a near-patient test (2) for nicotine/cotinine using our patented technology and demonstrated its' efficacy in smoking cessation in a randomised controlled trial in primary dental care practice, where it led to 23% quit rates versus 7% for standard smoking cessation programs (BMJ doi: 10.1136/bmj.38621.4639 00.7C).

More recently, through industry funding, we have pioneered the development of quantitative "non-presumptive" FT-ICR-MS/MS proteomics in novel biomarker discovery in GCF and saliva for human periodontal diagnosis (£400,000 grant from Philips), and gingivitis mapping (£500,000 grant from Unilever). Over 1000 proteins have been identified quantitatively, including several proteins with previously unknown biological activity in the mouth (6). Patent applications have been filed as joint inventions on novel proteins that discriminate oral health and disease.

Parallel studies in dogs have begun (£156,000 grant from Mars) with a view to developing handheld diagnostic testing devices for periodontitis in dental, medical and veterinary practices. A unique collaboration has recently been brokered with two large multi-nationals (Philips & Mars) whereby we are investigating the parallels between human and dog oral proteomes. This is with a view to translating discoveries from unique longitudinal studies of periodontitis in dogs to the human condition and also to develop biomarker panels for near-patient diagnosis in both species. Philips has existing handheld immunoassay technology, to which the discoveries can be adapted, facilitating use within non-dental environments.

Given recent evidence indicating periodontitis as a risk factor for rheumatoid arthritis (RA) (de Pablo, Chapple et al 2009, *Nature Rev Rheumatol;* doi:10.1038/nrrheum.2009.28) we have gone on to develop methods to identify citrullinated proteins in saliva, as early prognostic biomarkers of seropositive RA and we are working with Philips on their further exploitation (7). Patents have been filed as joint inventions.

Complementary work on risk factors for periodontal disease has led to the development and evaluation of near-patient feedback tools to help with behaviour change (1). This is being taken forward by Oral Health Innovations ltd (OHI), a University spinout company formed in 2008.

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

1. Busby M, Chapple EC, Matthews R, Chapple ILC (2013). Practitioner evaluation of a novel online integrated oral health and risk assessment tool: a practice pilot. Br Dental J: 215: 115-120. doi: 10.1038/sj.bdj.2013.738
2. Cope G, Nayyar P, Holder R, Brock G, Chapple ILC (2000). Near-patient test for nicotine and its metabolites in saliva to assess smoking habit. Ann Clin Biochem 37: 666-673. doi: 10.1258/0004563001899717.
3. Chapple ILC, Matthews JB, Thorpe GHG *et al* (1993). A new ultrasensitive chemiluminescent assay for the site-specific quantification of alkaline phosphatase in gingival crevicular fluid. J Periodont Res 28: 266-273. doi: 10.1111/j.1600-0765.1993.tb02093.x
4. Chapple ILC, Mason GM, Matthews JB *et al* (1997). Enhanced chemiluminescent assay for measuring the total antioxidant capacity of serum, saliva and crevicular fluid. Ann Clin Biochem 34:412-421. doi: 10.1177/000456329703400413.
5. Scott A, Milward, MR, Linden GJ *et al*. (2012) Mapping biological to clinical phenotypes during the development (21 days) and resolution (21 days) of experimental gingivitis. J Clin Periodont 39: 123-131. doi: 10.1111/j.1600-051X.2011.01825.x
6. Grant MM, Creese A, Barr G *et al* (2010). Proteomic analysis of a non-invasive human model of acute inflammation and its resolution: the 21 day gingivitis model. J Proteome Research 9: 4732-4744. doi: 10.1021/pr100446f.
7. Creese A, Grant MM, Chapple ILC, Cooper HJ (2011). On-line liquid chromatography neutral loss-triggered electron transfer dissociation mass spectrometry for the targeted analysis of citrullinated peptides. Analytical Methods 3: 259-266. doi: 10.1039/C0AY00414F.

Grants:

Prof T Dietrich (Coordinator), Prof I Chapple, Prof P Cooper, Dr P de Pablo. *Rheumatoid Arthritis and Periodontal Inflammatory Disease (RAPID).* European Commission Marie-Curie ITN, €4.3M. 01/04/2012-31/3/2016.

Prof R Stockley, Prof I Chapple, Prof T Dietrich, E Sapey. *TRIGGER: King of hearts, joints and lungs; periodontal pathogens as etiologic factor in RA, CVD & COPD & their impact on treatment*

strategies, European Commission Collaborative Project, £369K to Birmingham. 1/4/2013-31/3/2017.

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

This research has generated substantial **commercial impact** via additional investment of several £-millions in R&D by 3 major companies since 2008, and is driving these organisations in developing and evaluating new/improved oral care products (e1). It has also led to the formation of two UK spinout companies: 1) to design and successfully market an innovative online biofeedback technology into high street dental practices; 2) to design and market a low cost near patient test for cotinine in saliva used in smoking cessation and identification of exposure.

Influence on R&D investment by multinationals

Building on this research and his related expertise, Chapple and his team have collaborated with Unilever, Philips and Mars, helping them create new business areas which has led to their related investment in R&D (e1). Over 30 scientific employees are now involved in this work within these companies and many more marketing staff. For Mars, 100 million pet dogs are potentially affected globally, with the impact being the ability to diagnose canine periodontitis and also evaluate novel oral care products without the need for general anaesthesia. For Philips the potential application and market is 50% of the developed world human population who are at risk of periodontitis.

Unilever: As a result of our proteomics work, Unilever has now adopted several novel biomarkers as key measures of product efficacy assessment in clinical trials of oral care products. This is helping them to evaluate product efficacy and to identify and develop future innovative therapies. Our proteomics studies have also led to a greater understanding of the biological processes within the gingival tissues in health and disease. This understanding is impacting upon Unilever's R&D and driving their development of novel oral healthcare products (e1). The importance of our work is evidenced by £800K of funding received from Unilever during the REF period, and has led to Chapple serving Unilever's 6-person global advisory board on business strategy for 15 years. Indeed **health impacts** have already been realized as our research has underpinned claim support for new toothpastes from Unilever PLC, sold to customers worldwide.

Philips: Our work has led to an entirely new R&D arm at Philips (global) to identify saliva biomarkers to discriminate, for the first time, periodontal health and disease (e1,e2). We have also generated assays for, and identified, citrullinated proteins within saliva, which are now being developed as early diagnostic tests for seropositive rheumatoid arthritis (e3). Inventions and patents have been filed with Philips (e2,e3), underpinning **health and commercial impacts** at a global level. Philips will adapt findings to existing hand-held saliva testing devices for periodontal diagnosis in humans in non-dental as well as dental environments, providing commercial sales. The health impact will be to enable objective early diagnosis of periodontitis in patients in dental practice which is currently a neglected area. This approach will also allow periodontal screening in medical practice for patients with other medical conditions associated with periodontitis, such as diabetes and cardiovascular disease.

Mars: Mars Petcare UK also participate in a tripartite collaboration with Philips and the University of Birmingham to develop handheld saliva diagnostic tests for veterinary practice, eliminating the need to anaesthetise dogs to diagnose gum disease, and helping to develop novel pet foods.

Impact on practitioners

This successful research portfolio has stimulated a multi-disciplinary saliva biobank for biomarker discovery in Renal, Rheumatology, Respiratory and Diabetes Medicine, at Birmingham's Inflammation Research Facility (IRF), supported by collaborative research grants (see section 3). Over 800 saliva samples are biobanked and 1000's more are planned. The benefits of the saliva diagnostic program have convinced the local medical research community to collect saliva from all chronic disease patient cohorts.

Development and commercialisation of a near patient test for nicotine in saliva

Our research has underpinned the development and commercialisation of a product used to test for nicotine metabolites in saliva. This was originally developed to promote smoking cessation using personalised biofeedback, but has more recently been employed to confirm the presence or absence of recent nicotine inhalation (e4). This was one of the first patented saliva near-patient

diagnostics (e5) and subsequently led this field. The trademarked product, "Saliva SmokeScreen" was commercialized by a UK-based SME, GFC Diagnostics as a spin out of the University of Birmingham (2007), to promote and develop near-patient test products. At December 2012 the SME had grown to five employees and sold 6,500 Saliva SmokeScreen tests to five major customers across three countries, where low-cost near-patient tests are essential (e1).

Saliva SmokeScreen enables dentists to increase smoking cessation among their patients by providing immediate personalized biofeedback of test results. The test has also been shown to be able to identify users of smokeless tobacco, such as betel quid, which causes oral cancer. A recent study indicated that Saliva SmokeScreen was a viable alternative to more expensive ELISA-based technologies making it ideally suited for future application (e6). Regular media impact of the application of Saliva SmokeScreen includes coverage by the BBC (e7).

Development and commercialisation of an online oral health risk assessment tool

Oral Health Innovations Ltd (OHI) is a University spinout company (Chapple) with the sole UK and Ireland license for the risk and disease assessment software "Previser.co.uk". It was established in 2008 to develop a practical and evidence-based tool to facilitate individualised patient biofeedback to drive health behaviour change. OHI has developed (2008-2013) a bespoke comprehensive oral health risk, disease and patient-perception tool – DEPPA – for the UK's largest dental capitation plan operator "Denplan", accessing 6500 dentists and 1.8-million patients (e1). DEPPA was piloted in December 2012 by 25 Denplan Excel practices on over 650 patients. The pilot demonstrated strong endorsement for the novel online system, with mean satisfaction scores in all domains exceeding 85% (1). The Editor-in-Chief of the British Dental Journal referred to the system as "truly field changing" since it links outcomes to patient capitation fee banding, incentivising patients to take greater control of their own oral health. The Department of Health has subsequently embarked on a capitation NHS pilot dental system, on which Chapple has advised.

Denplan launched DEPPA to the media and profession at the BDA conference 26th April 2013 in London, where Chapple spoke about the system and underpinning philosophy. Dedicated Denplan training courses with the new system commenced in 2013 with 1000 Excel dentists having access to the system and 200 actively using it within the first 3-months of its launch (e1).

OHI donate profits to research charities, (£10K committed to the UK Oral & Dental Research Trust in 2013) providing oral healthcare **sector impact** underpinning future R&D.

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

e1 Confidential testimonial from the Director of Oral Care Discovery, Unilever R&D. Testimonials from: the Principal Scientist/Director/Consumer & Dental Affairs, Philips Research; the Chief Dental Officer, Denplan Ltd; the Managing Director, OHI Ltd;.the Technical Director, GFC Diagnostics Ltd.

e2 Analysis of Saliva Proteome for Biomarkers of Gingivitis & Periodontitis using FT-ICR-MS/MS (US patent application PCT/IB2013/058431). Inventors: I Chapple, A Creese, H Cooper (filed 10-09-2013)

e3 System & Method for Estimating Susceptibility to a Medical Condition (US patent application PCT/IB2013/058342). Inventors: I Chapple, A Creese, H Cooper (filed 06-09-2013).

e4 Spanou C, Simpson A, Hood K, et al (2010) Preventing disease via opportunistic, rapid engagement by primary care teams using behaviour change counselling (PRE-EMPT): protocol for general practice-based cluster randomised trial. BMC Fam Prac 11: Art. 11. doi: 10.1186/1471-2296-11-69.

e5 Cope G, Bunce R, Gibbons J. *Method of assaying.* Worldwide patent: WO 93/09431 (13.05.1993)

e6 An evaluation of a rapid semi-quantitative saliva test for cotinine and other nicotinic metabolites to identify and monitor the use of smokeless tobacco: A pilot study, Dr Asiya Kaiser Leena Sankla, Dr Graham Cope and Professor Iain Chapple, UKNSCC, 18/6/2012. http://www.uknscc.org/uknscc2012_presentation_151.php

e7 http://news.bbc.co.uk/local/oxford/hi/front_page/newsid_8434000/8434733.stm