Institution: University of Leeds

Unit of Assessment: Chemistry (UoA 8)

Title of case study 1:
"Filling without drilling": A new class of product for the treatment of early stage dental decay based on hydrogels of self-assembling peptide tapes

1. Summary of the impact

A new class of synthetic self-assembling peptides has been developed at Leeds into a product that allows the enamel in the dental cavities to be regenerated. The peptides assemble to form gels that have been shown to be promising biocompatible materials with applications in regenerative medicine, for example in the regeneration of bone. Credentis AG (Switzerland) was founded in January 2010 to commercialise the technology in the dental care domain. Its first product Curodont™ Repair - the first product of its kind in dental care – has completed first-in-man safety trials (also at Leeds); has received regulatory approval for clinical use in Switzerland, Europe and Australia; and was launched in Switzerland and Germany in Q1/2013. The product has tremendous promise because most adults suffer from dental caries which often go untreated because of patients' fear of the dental drill. A second product Curodont™ Protect, approved in April 2013 and regulated as a cosmetic, has been launched in 2013 for the treatment of dentin hypersensitivity. Credentis has established a UK base in Leeds and has engaged a UK company as distributor of its products from October 2013.

2. Underpinning research

This new regenerative therapy for the treatment of early enamel decay developed from an interdisciplinary, collaborative research programme at the University of Leeds led by **Aggeli** (School of Chemistry and Centre for Self-Organising Molecular Systems, SOMS/Centre for Molecular Nanoscience, CMNS) and Kirkham (Leeds Dental Institute).

The initial underpinning research formed part of a major programme on peptide self-assembly within the SOMS Centre at Leeds led by **Boden**. In 1995, Aggeli, then a PhD student in the School of Chemistry at Leeds supervised by Boden, described for the first time the ability of peptides to aggregate to form supramolecular nanotapes and gels (A. Aggeli, *Spectroscopic studies of self-assembling peptides in solution and in lipid bilayers,* PhD thesis, University of Leeds, 1995). Subsequently, supported by EPSRC, Aggeli and Boden, together with **Fishwick**, Radford (Faculty of Biological Sciences) and McLeish (School of Physics), established (between 1995 and 2003) the underlying principles required for peptide self-assembly into nanotapes and gels (1); a theoretical framework to explain the experimental behaviour of self-assembled peptides (2); and the principles to design in responsiveness to external triggers in order to control the assembly process (3). Under specific conditions, peptides undergo hierarchical self-assembly through formation of micrometer-long β-sheet "nanotapes", which stack in pairs to form ribbons, further assemble to form fibrils, and then entwine to form fibres. This assembly process is principally driven by intermolecular hydrogen bonding between peptide backbones, together with additional interactions between specific backbones, and offered the potential for a new generation of biomaterials with many different applications. This research was described in three seminal papers(1-3) in high-impact journals that have collectively accrued over 1100 citations.

Kirkham's group [funded from 1998 through Wellcome Trust programme and project grants (088908/Z/09/Z) and BBSRC (9709001; ABY08147; REI18424) equipment grants] utilised enamel development as a paradigm for understanding how extracellular matrix proteins control crystal nucleation, disposition and tissue architecture in mammalian biomineralisation. This research established the principles that underpin the control of crystal growth in developing enamel, leading to the hypothesis that domains of negative charge on extracellular matrix proteins were responsible for crystal nucleation during enamel biomineralisation (4).

Kirkham and Aggeli's collaboration since 2003 has used the knowledge of the structure-function relationships of self-assembling peptides and the mechanism of mineralised tissue formation to address clinical challenges in dental cavity healing. Peptides were selected that would be monomeric at pH >7.5, providing a low viscosity, injectible fluid that would spontaneously assemble to form a three-dimensional fibrillar scaffold under physiological conditions. In addition, the peptides were designed to provide, via their amino acid side chains, domains of negative

charge once assembled. The resulting three-dimensional structures were therefore designed to mimic the biological macromolecules found in extracellular matrices of the mammalian skeleton.

Applied collaborative research between the two groups [funded by an EPSRC CASE award, a Leeds Teaching Hospitals Trust research award, Leeds' EPSRC Medical Technologies Innovation Knowledge Centre (EP/I019103/1) and Geistlich Biomaterials, Switzerland] tested the hypotheses that rationally designed self assembling synthetic peptides could nucleate mineral crystals *in vitro* and *in situ* within artificial decay lesions in extracted human teeth and were both biocompatible and non-allergenic in animals (5). Taking this information together, a first-in-man clinical trial (National Research Ethics System project number 10/H1207/75) was carried out in 2010 (led by Brunton, Professor of Restorative Dentistry, Leeds) applying one of the peptides (P11-4) to early enamel decay lesions in patients. The results provided unequivocal evidence of efficacy following a single treatment of the lesions with the peptide material (6).

Key personnel

Centre for Self-Organising Molecular Systems/School of Chemistry
Amalia Aggeli (PhD student, 1992-1995; Royal Society Dorothy Hodgkin Fellow, 1997-2001; Royal Society University Research Fellow, 2001-9; Lecturer, 2009-)
Neville Boden (Lecturer 1966-81; Reader 1981-91; Professor 1991-2001; Research Professor 2001-2005; now retired)
Colin Fishwick (Lecturer 1985-1997, Senior Lecturer 1997-2006, Professor 2006-)
PhD students: Mark Bell (1995-2000); Lisa Carrick (1998-2002); Richard Harding (1993-1997); Peter Mawer (1997-2002); A Firth (2003-2008).

Leeds Dental Institute: Jen Kirkham (Lecturer then Senior Lecturer then Reader, 1980-; Professor of Oral Biology 1999-)

School of Physics: Tom McLeish (Professor of Polymer Physics, 1993-2008)

Faculty of Biological Sciences: Sheena Radford (Lecturer, 1995-8; Reader, 1998-2000; Professor of Structural Molecular Biology, 2000-)

3. References to the research

1) Aggeli, A, Bell, M, Boden, N, Keen, J, Knowles, PF, McLeish, TCB, Pitkeathly, M & Radford, SE., Responsive gels formed by the spontaneous self-assembly of peptides into polymeric β-sheet tapes, *Nature*, 1997, **386**, 259-262, (500 citations; Source: Scopus, 24/10/13) http://dx.doi.org/10.1038/386259a0
   The paper describes the detailed characterisation of organogel and hydrogel peptide tape-based materials.
2) Aggeli, A., Nyrkova, I., Bell, M., Harding, R., Carrick, L., McLeish, TCB, Semenov, A. & Boden, N., Hierarchical self-assembly of chiral rod-like molecules as a model for peptide beta-sheet tapes, ribbons, fibrils and fibres, *Proc. Natl. Acad.Sci. USA* 2001, **98**, 11857-11862 (462 citations; Source: Scopus, 24/10/13) http://dx.doi.org/10.1073/pnas.191250198
   The hierarchical route to self-assembly of peptide tapes was described, together with a theoretical framework for the self-assembly process.
3) Aggeli A, Bell M, Carrick LM, Fishwick CWG, Harding R, Mawer PJ, Radford SE, Strong AE, Boden N., pH as a trigger of peptide beta-sheet self-assembly and reversible switching between nematic and isotropic phases, *J. Am. Chem. Soc.* 2003, **125**, 9619-9628 (201 citations; Source: Scopus, 24/10/13) http://dx.doi.org/10.1021/ja021047i
   This paper describes pH-responsive peptides whose self assembly is controlled by a specific external trigger
4) Kirkham, J, Zhang, J, Wallwork, ML, Smith, DA, Brookes, SJ, Shore, RC, Wood, SR and Robinson, C., Evidence for Charge Domains on Developing Enamel Crystal Surfaces, *J. Dental Research*. 2000, **79**, 1943-1947 (38 citations; Source: Scopus, 24/10/13) http://dx.doi.org/10.1177/00220345000790120401
5) Kirkham, J., Firth, A, Vernals, D., Boden, N, Robinson, C., Shire, RC, Brookes, SJ and Aggeli, A, Self-assembling peptide scaffolds promote enamel remineralization, *J. Dental Research* 2007, **86**, 426-430 (59 citations; Source: Scopus, 24/10/13)

http://dx.doi.org/10.1177/154405910708600507
The paper presents for the first time the potential of peptide gels for the treatment of dental-caries like lesions.
6) Brunton, PA, Davies, RWP, Burke, JL, Smith, A, Aggeli, A., Brookes, SJ and Kirkham, J, Treatment of early caries lesions using biomimetic self assembling peptides, *British Dental Journal* 2013, **215**, E6. http://dx.doi.org/10.1038/sj.bdj.2013.741
The paper describes the results of the first-in-man safety trials.

All papers are in internationally-leading peer-reviewed journals and are hence ≥2*, but references 1-3 are particularly highlighted by the UoA to demonstrate the quality of the underpinning research.

4. Details of the impact

Context: Dental decay is the most common of all diseases (prevalence: ~10% of the population p.a. in the western world i.e. 100 million lesions p.a.), yet the principles of treatment have remained unchanged for almost 100 years (*J. Dent.* 2003, **31**, 395-405). Most adults worldwide suffer from dental caries (tooth decay), many of which go untreated because of patients' fear of the dental drill. The earliest sign of tooth decay is the "white spot" lesion, visible to the clinician on the tooth surface. There is no current consensus view regarding treatment, and clinicians have three choices: (a) to monitor the lesion, and then to excavate and fill; (b) to apply fluoride treatments, and then to proceed as in (a); and (c) to place a small restoration. Ultimately, all restorations fail and need to be replaced with larger fillings, and will eventually lead to tooth loss and replacement. Treatment currently costs the UK NHS *ca* £2bn pa (roughly half the budget for dental care; Office of the Government Auditor). Drilling is feared by many patients, inhibiting their attendance at the dentist and so precluding opportunities for early diagnosis and treatment of decay as well as diseases such as oral cancer. Leeds' self-assembling peptide technology provides a simple and cost-effective alternative to current treatments that avoids a subsequent need for larger fillings; this technology removes the clinician's dilemma of whether to treat decay, and removes the need for drilling and thus the fear of visiting the dentist.

Societal impact

Public interest was stimulated through promotional material from EPSRC; in a story featuring Prof. Kirkham on Channel 4 News; and in an article in the *Daily Mail* (A).

Economic impacts

A company was established ("Credentis AG", Switzerland; www.credentis.com) in January 2010, in which the University of Leeds is a major stakeholder, to exploit under license Leeds' IP on self-assembling peptides in the dental domain (B,C). **Jobs have been created** for highly-skilled researchers at both Credentis in Switzerland (2010, 0.5 FTEs; 2011, 2 FTEs; 2012, 3 FTEs; 2013, 4 FTEs) and at the University of Leeds (3 FTEs in 2013) (C). In its first two years of operation, the company has **raised external investment** of *ca* 4.75M Swiss francs (*ca* £3M) in three rounds (2010, 0.25M CHF; 2011, 2.5M CHF; 2013, 2.0M CHF) (C).

Leeds' IP has enabled the adoption of **disruptive technology** within dental care. The platform technology for self assembling peptide design developed in Leeds was patented (D, currently maintained), and underpins diverse applications including the design of biomimetic scaffolds in tissue engineering. Following Leeds research using self assembling peptide technology to treat decay lesions in extracted teeth, an applications patent was granted in 2009 (E) and is currently maintained. Subsequent Leeds research comparing the ability of different peptide designs to nucleate mineral crystals and to regenerate bone led to the filing of a patent in the US (F).

Credentis was recognised as one of the top 100 Swiss start-up companies in 2011, 2012 and 2013 (http://www.startup.ch/index.cfm?CFID=241786181&CFTOKEN=45081364&page=129572&profilesEntry=1) by a panel of start-up company experts in conjunction with Handelszeitung. In 2012, Credentis opened at UK office in Leeds, reflecting the continuing close collaboration with researchers in the University. Support for this collaborative research programme includes a new £1.2M award via the Leeds EPSRC Medical Technologies Innovation and Knowledge Centre (EP/I019103/1) to develop second-generation peptides for further dental applications to increase the Credentis product range (G). Leeds researchers (Aggeli, Kirkham) are developing new

technology and minimising commercial risk via the provision of access to a full and validated pipeline screening facility including (a) rational peptide design; (b) characterisation of self-assembly processes; (c) computational modelling; (d) theology testing; (e) screening for capacity to induce mineralisation; (f) cytotoxicity testing; (g) *in situ* (*ex vivo*) testing; (h) clinical trials; and (i) process development.

A new product (initially Curodont™, and now Curodont™ Repair (H)) containing peptide P11-4, based on patents of Leeds researchers, was granted its CE certificate in January 2012 (C) and has now entered the European market for clinical use as a class IIa medical device; the product has also been approved for clinical use in Australia, and Health Canada approval is pending. Large scale production of Curodont™ provides a fully GMP-compliant product (50,000 patient treatments in the first run) for which patient acceptability has been shown to be very high. Leeds researchers contributed to this outcome by conducting first in man safety trials for P11-4, demonstrating a clear clinical improvement over treatment of class 5 lesions with the peptide (6). The product has been launched in Germany and Switzerland in Q1/2013. Credentis has engaged a UK dental specialist company, Optident, who will distribute and supply the products within the UK market from October 2013 (I). A second product, Curodont™ Protect, was approved(H) in April 2013, is regulated as a cosmetic and has been launched in selected markets in 2013; here, the formulation of the peptide has been adapted for the treatment of dentin hypersensitivity and the prevention of tooth decay.

There has been significant **investment in research and development** of this peptide technology (including P11-4) by overseas industry. In addition to support from Credentis AG (G), a collaborative project with Geistlich Biomaterials (Switzerland) demonstrated that self-assembling peptides can promote highly efficient bone regeneration in an animal model.

Health impact

A new clinical intervention – a medical device for restoration of early enamel caries – has been developed, trialled in patients and a definite positive outcome demonstrated (6). Leeds researchers were involved in all stages of the product development from laboratory to chairside (C). The resulting marketed products launched in 2013 are seen by the profession to fill the previously unfilled gap between prevention and surgical intervention (J).

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

(A) For example: (a) “Tooth technology”, EPSRC Growth Story, May 2013; (b) Story on Channel 4 news, 22nd August 2011 (http://www.channel4.com/news/no-more-dental-drilling-and-filling; accessed 28.10.13); (c) *Daily Mail*, 22nd August 2011 (http://www.dailymail.co.uk/health/article-2029014/Painless-tooth-fillings-drilling-make-dentist-trips-irksome.html; accessed 28.10.13).

(B) License agreements between University of Leeds and Credentis, 06.01.2011 and 02.01.2013.

(C) Letters, Chief Executive Officer, Credentis, 2013, 13th June 2013 and 30th August 2013.

(D) Platform technology patent: “Beta Sheet Forming Peptides“; Proprietor : UoL, Inventors : N. Boden, A. Aggeli, T. C. B. McLeish, Priority Date: 28/3/1996, European Patent No: EP 0 759 933,B1, granted 08/05/2002 and being currently maintained.
The patent recognised at an early stage the potential applications of the new materials

(E) “Beta-sheet forming peptides and materials made thereof”, Proprietor: UoL, Inventors : N. Boden, A. Aggeli, E. Ingham, J. Kirkham, Priority Date: 17/07/2003, European Patent No: EP 1 523 494 B1, granted 23/12/2009 and being currently maintained.

(F) “Beta Sheet Tapes Ribbons in Tissue Engineering”, Assignee: UoL, Inventors: N. Boden, A. Aggeli, E. Ingham, J. Kirkham, US Patent No: US 7700721, granted 20/4/2010 and being currently maintained.

(G) Collaborative agreement with Credentis AG, 29th April 2013.

(H) “Curodont™ Repair and Curodont Protect™ for the treatment and prevention of tooth decay”, NIHR Horizon Scanning Centre, University of Birmingham, July 2013.

(I) Letter, Commercial Director, Optident Ltd., 24th September 2013.

(J) “Curolux Technology: Regenerative Cutting-Edge Technology”, brochure containing quotes from independent dental practitioners who have used Curodont™ Repair, 2013.