Institution: University of Leeds

Unit of Assessment: 3

Title of case study: Improved oral healthcare using biomimetic peptide technology

Period when the underpinning research was undertaken: Work began in the School of Chemistry in 1997 and in the School of Dentistry in 1998. Work ended in the School of Chemistry in 2013 with Amalia Aggeli's departure from Leeds. Work continued throughout to date in the School of Dentistry.

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:
Jennifer Kirkham	PI, Professor and Head of Oral Biology	1980-2019
Amalia Aggeli	Lecturer/Associate Professor	1998-2013
Robert Davies	PDRA/Lecturer	2003-present
Julie Burke	Clinical Lecturer Hon Consultant	2011-2015
Sushmita Saha	PDRA	2004-2015
Steven Brookes	Lecturer/Senior Lecturer	1995-2019
Sarah Harris	Lecturer/Associate Professor	2004-present
Xuebin Yang	Lecturer/Associate Professor	2004-present

Period when the claimed impact occurred: 2013-present

Is this case study continued from a case study submitted in 2014? Y

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

Direct treatment costs due to dental diseases worldwide are estimated to be USD297,670,000,000. Untreated tooth decay is the most common disease worldwide, with a 35.8% prevalence in western Europe. Following the successful spin-out of Leeds' "Filling without Drilling" patent-protected self-assembling peptide (SAP) technology for treatment of early decay (pre-2014), several new SAP products are now available for treating tooth sensitivity and tooth erosion and maintaining dental health. The Swiss company (Credentis AG), formed to market Leeds' technology within Europe, has won two major awards and is introducing a new product treating periodontal ("gum") disease, the sixth most common of all diseases. In 2017, the rights to the early caries lesion SAP treatment were assigned to a major transnational company, now delivering to a global market, including the US. In Late 2020 Credentis AG was acquired by Swiss dental company vVardis and is now a research and development arm of that parent company.

2. Underpinning research (indicative maximum 500 words)

Self-assembling peptides (SAPs) are synthetic oligomeric moieties of naturally occurring amino acids. Unassembled they exist as non-Newtonian fluids. By manipulating intramolecular non-covalent forces, the formation of fibrillar structures dominate, which provide a templated heterogeneous nucleation site for hydroxyapatite. SAP biomimetic regenerative technology for applications in oral healthcare developed out of multi-disciplinary research at Leeds. This work was

led by **Aggeli** (formerly Royal Society University Research Fellow in the School of Chemistry at Leeds, then Lecturer until 2014) and **Jennifer Kirkham** (Professor of Oral Biology, School of Dentistry (SoD), University of Leeds until 2019). **Robert Davies** (Research Fellow in the School of Chemistry, 2009-2012, Research Fellow in the SoD, 2012-2019, now Lecturer in the SoD) further developed SAPs for new applications and leads the work going forward.

Supported by EPSRC and the Wellcome Trust, **Aggeli** described the driving principles governing the spontaneous self-assembly of β-sheet forming peptides into fibrillar scaffold structures **[1]**. This included the ability to design in responsiveness to specific external triggers in order to control the assembly process. Funded by EPSRC and industry, further characterisation of peptide physico-chemical characteristics has been taken forward by **Davies** to inform further rational design and elucidate mechanism **[2]**.

Kirkham's group utilised enamel development as a paradigm for understanding the way in which extracellular matrix proteins control crystal nucleation, deposition and tissue architecture in mammalian biomineralisation. This was based upon the hypothesis that domains of negative charge on extracellular matrix proteins (themselves self-assembling) were responsible for crystal nucleation during enamel biomineralisation **[3]**. The work was funded through **Kirkham's** Wellcome Trust programme (associated Wellcome Trust, Biotechnology and Biological Sciences Research Council (BBSRC) project grants, and EPSRC collaborative and Proof of Concept awards from 1998 to date).

Kirkham and **Aggeli** used knowledge gained from an understanding of the way in which mineralised tissues form, combined with an understanding of the drivers behind peptide self-assembly, to address unmet clinical challenges in mineralised tissue repair and regeneration. The Leeds researchers designed peptides that would be unassembled (monomeric) at pH values >7.5, providing a low viscosity, injectable fluid that would spontaneously assemble to form a 3D fibrillar scaffold under physiological conditions. In addition, peptides were developed to provide, via their amino acid side chains, domains of negative charge once assembled. The resulting 3D structures therefore mirror biological macromolecules found in extracellular matrices of the mammalian skeleton.

Translational, collaborative research between the two groups was funded by an EPSRC CASE (Cooperative Awards in Science & Technology) award, a Leeds Teaching Hospitals Trust research award and the Leeds Wellcome-EPSRC Centre of Excellence in Medical Engineering: "WELMEC"). This research went on to test the hypotheses that rationally designed self-assembling synthetic peptides could nucleate mineral crystals *in vitro* and *in situ* within artificial decay lesions in human teeth **[4]**.

Taking this information together, a proof of concept clinical trial (with Prof PA Brunton, formerly Professor of Restorative Dentistry, Leeds, now PVC, Otago, NZ) was carried out in Leeds, applying one of the peptides (P_{11}-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, confirmed in case studies in general dental practice. One application reduced lesion size and shifted progression of lesion from 'arrested/progressing' to 'remineralising' **[5]**.

By comparing a range of related but differenced peptides, the Leeds researchers were able to identify the most important design criteria favouring mineral nucleation and promotion of crystal growth. Work funded by EPSRC-Credentis AG and carried out by **Kirkham** and **Aggeli** compared the efficacy of these rationally designed peptides in repair of caries lesions and showed that P_{11}-4 remained the best performing candidate.

International collaboration between Leeds and University of Campinas Brazil has also demonstrated the viability of P_{11}-4 as a treatment for demineralised dentine and potential application for increasing bond strength in etch and rinse adhesive systems.

Work funded by Geistlich Biomaterials (Switzerland) and carried out in **Kirkham's** labs in

collaboration with **Dr Julie Burke** (Lecturer in Oral Surgery at Leeds, now Associate Professor in Oral Surgery in Edinburgh) and **Dr Xuebin Yang** (Associate Professor in Oral Biology at Leeds) demonstrated the ability of P_{11}-4 to promote bone regeneration and repair in a critical defect model *in vivo*. The group also carried out *in silico* modelling of the mode of action of P_{11}-4 (with **Dr Sarah Harris**, School of Physics at Leeds) that illustrated the molecular action of P_{11}-4 in nucleating mineral crystals in its assembled (but not monomeric) state **[6]**. These data led to proof of concept work to determine the effect of application of P_{11}-4 on periodontal repair (regenerating the tooth supporting tissues including the bone of jaw and the periodontal ligament). The data showed unequivocally that P_{11}-4 promotes periodontal healing and repair **[7]**.

In 2018, a grant was awarded by the University of Leeds' Medical Technologies Innovation and Knowledge Centre (funded by EPSRC and BBSRC) to **Davies**, Deirdre Devine and **Kirkham**, School of Dentistry, Leeds to provide proof of concept data demonstrating that SAPs can be used as drug delivery vehicles for the control of periodontal pathogens (ongoing study).

The research programme illustrates how a multi-disciplinary team of clinicians, chemists and life scientists were able to draw upon the physico-chemical principles of peptide assembly behaviour and mineral nucleation ability to design biomimetic materials to recapitulate skeletal tissue development and so effect regeneration and repair across a range of oral healthcare challenges.

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

[1] Aggeli A, Bell M, Carrick LM, Fishwick CWG, Harding R, Mawer PJ, Radford SE, Strong AE, Boden N. pH as a trigger of peptide β-sheet self-assembly and reversible switching between nematic and isotropic phases. J Am Chem Soc. 2003; 125(32):9619-28. doi: 10.1021/ja021047i
[2] Davies RPW, Liu B, Maude S, Carrick LM, Nyrkova I, McLeish, TC, Harris SA. Peptide strand length controls the energetics of self-assembly and morphology of β-sheet fibrils. Peptide Science. 2018; 110:e23073. doi:10.1002/bip.2307312
[3] Kirkham J, Zhang J, Wallwork ML, Smith DA, **Brookes SJ**, Shore RC, Wood SR, Robinson C. Evidence for charge domains on developing enamel crystal surfaces. J Dent Res. 2000; 79(12):1943-7. doi: 10.1177/00220345000790120401
[4] Kirkham J, Firth A, Vernals D, Boden N, Robinson C, Shore RC, **Brookes SJ**, **Aggeli A**. Self-assembling peptide scaffolds promote enamel remineralization. J Dent Res. 2007; 86(5):426-30. doi: 10.1177/154405910708600507
[5] Brunton PA, **Davies RWP**, **Burke JL**, Smith A, **Aggeli A**, **Brookes SJ**, Neeser R, Bröseler F, Tietmann C, **Kirkham J**. Treatment of early caries lesions using biomimetic self-assembling peptides – a clinical safety trial. Br Dent J. 2013; 215(4):E6. doi: 10.1038/sj.bdj.2013.741
[6] Saha S, Yang X, Wijayathungab N, Harris S, Feichtinger G, **Davies RPW**, **Kirkham J**. A biomimetic self-assembling peptide promotes bone regeneration in vivo: a rat cranial defect study. Bone. 2019;127:602-611. doi: 10.1016/j.bone.2019.06.020
[7] El-Sayed B, **Davies RPWD**, El-Zehery R, Ibrahim FM, Grawish E, **Kirkham J**, El-Gendy R. An in-vivo intraoral defect model for assessing the use of P11-4 self-assembling peptide in periodontal regeneration. Front. Bioeng. Biotechnol. 2020; 8:559494. doi: 10.3389/fbioe.2020.559494

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

Context: Untreated tooth decay in adults is the most common disease across the globe with an estimated 3 billion people affected **[A]**, yet the principles of treatment for dental decay have remained unchanged and inherently sub-optimal for almost 100 years. The earliest sign of tooth decay is the "white spot" lesion, visible to the clinician on the tooth surface. There is no consensus view as to how this should be treated. Clinicians have three choices: 1) monitor the lesion to determine whether or not it is getting bigger, then excavate and fill; 2) apply fluoride treatments, then proceed as in (1) or 3) place a small restoration. Ultimately all restorations will fail and need to be replaced by larger fillings **[B]**. Treatment currently costs the UK GBP2,000,000,000 each year within the NHS alone **[C]**, driving oral health inequalities. 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. Furthermore, restorative procedures produce aerosols, which provide a vehicle for droplet-spread diseases such as SARS and Covid-19.

Periodontal disease is the sixth most common disease worldwide **[A]** and the most common cause of tooth loss in the ageing population. Taken together, the cost of oral healthcare in Western Europe is USD101,970,000,000 **[E]**.

Leeds' SAP technology provides a simple, aerosol free, cost effective alternative to current treatments (costing less than a third of the most simple conventional filling **[D]**), allowing the clinician to heal, rather than repair, dental decay.

At REF2014: Leeds' SAP patented technology had been licensed to a Swiss spin out company that the University of Leeds holds equity in, called Credentis AG. Following first-in-man clinical trials at Leeds, Credentis obtained a CE label to market the technology, trademarked as "Curolox", as a Class II medical device throughout Europe and Switzerland. The first product in the range, "Curodont Repair" was in early clinical use treating patients in continental Europe and Switzerland as a professionally applied product. A second product, Curodont Protect, had just been launched and a third, Curodont D'Senz had been formulated.

Since REF2014:

New products/ new clinical interventions have significantly increased the reach of this technology, resulting in:

1. Over-the-counter (OTC) products with SAP P_{11}-4 being made widely available:
   i) a new treatment for tooth sensitivity ("Curodont D'Senz"), produced by Credentis AG. Now in use in the EU and Switzerland **[F]**.
   ii) a classic toothpaste ("Candida Protect Professional", produced by Mibelle AG (subsidiary of Migros) upon a licence to Credentis Mainly available in Switzerland **[F]**.
   iii) a specialised toothpaste ("Emofluor Twin Care" from Dr Wild & Co), produced by Dr Wild & Co upon a license from Credentis. Available in the EU and Switzerland **[F]**.
   iv) intensive protection gel against caries and erosion ("Curodont Protect"), produced by Credentis AG, Now available in the EU and Switzerland **[F]**.
   v) a consumer product portfolio "Curodont for Sensitive Teeth", produced by Credentis AG has been launched Direct-to-Consumer. The portfolio contains novel products such as chewing gums and chewie's as well as classic formats such as toothpastes **[F]**.

   All OTC products include SAP P_{11}-4 at effective levels. Candida Protect Professional with SAP P_{11}-4 (Curolox) is the top of the line toothpaste of the Candida portfolio. Produced by Migros, the Swiss market leader for toothpaste following a new licence deal, the toothpaste sells around 250,000 units per year. Migros has a large market share in Switzerland and is one of the leading toothpaste brands in the country.

2. Curodont Repair Fluoride Plus being launched in the US in 2019, following a distribution deal with Straumann AG for the US market.

3. All products containing SAP P_{11}-4 being regulated as oral care products under US Food and Drug Administration Regulation 21 CFR 355 (the so-called fluoride monograph). Formal regulatory approval or clearance is not necessary, but listing within the National Drug Code database is required.

4. The non-exclusive rights to distribute Curadont Repair being given to Straumann AG **[G]** in 2017, a large international oral healthcare company and the market leader in dental implants and periodontal regeneration. Straumann is now selling Curadont Repair in key global markets, including the US [**I**]. Additional indications of products with SAP P_{11}-4 are under negotiation.

Impacts on commerce:

5. Credentis AG was awarded the Swiss Excellence award (for a new product containing P_{11}-4 introduced to the market place) in 2015, following their receipt of the Swiss technology award in 2013 **[F,H]**.

6. An entirely new clinical application for the peptide technology has been illustrated by the Leeds researchers in regenerating the periodontium. Credentis AG is now proposing to expand into this new market **[F]**.

7. Credentis AG was acquired by Swiss dental company vVardis and is now a research and development arm of that parent company **[F]**.

Investment by overseas industry:

8. Credentis has invested GBP500,000 in a co-development project with Leeds School of Dentistry **[H]**, in-kind investment in a proof of concept study.

The initial invention and Intellectual Property (IP) protection has enabled further pathway activities since REF2014 allowing for commercial exploitation:

9. A new patent using the technology for tooth whitening has been published by Credentis, who are seeking to market this new whitening product in the near future **[F]**.

10. Five new patents have been published as continuation in part (CIPs) in the US by the University of Leeds team, strengthening the IP position within the US and offering other peptides for development **[I]**.

11. Over 200 publications on SAP P_{11}-4, including six randomised clinical trials on Curodont Repair – published across the international scientific community all showing superiority over fluoride varnish or other caries-arresting medicaments.

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

[A] James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392(10159):1789-1858. doi: 10.1016/S0140-6736(18)32279-7
[B] Chadwick BL, Dummer MH, Dunstan F, et al. The longevity of dental restorations: A systematic review. NHS Centre for Reviews and Dissemination, University of York, York. 2001
[C] Dentistry in England: A National Audit Office memorandum to support a Health and Social Care Committee Enquiry. The Stationery Office, London. 2020
[D] Band 2 treatment (including fillings): GBP62.10, NHS Dental Charges 2020.
Curodont Repair, Curodont Protect and Curodont D'Senz RRP EUR19.99.
[E] Righolt AJ, Jevdjevic M, Marcenes W, Listl S (2018) Global-, Regional-, and Country-Level Economic Impacts of Dental Diseases in 2015. J Dent Res. 2018;97(5):501-507. doi: 10.1177/0022034517750572
[F] Portfolio of evidences provided by Credentis to illustrate their product range
[G] Straumann product launch
[H] Credentis website: http://www.credentis.com/en/ www.curodont.com
[I] Leeds self-assembling peptides patent portfolio supplied by University of Leeds' Research and Innovation Service