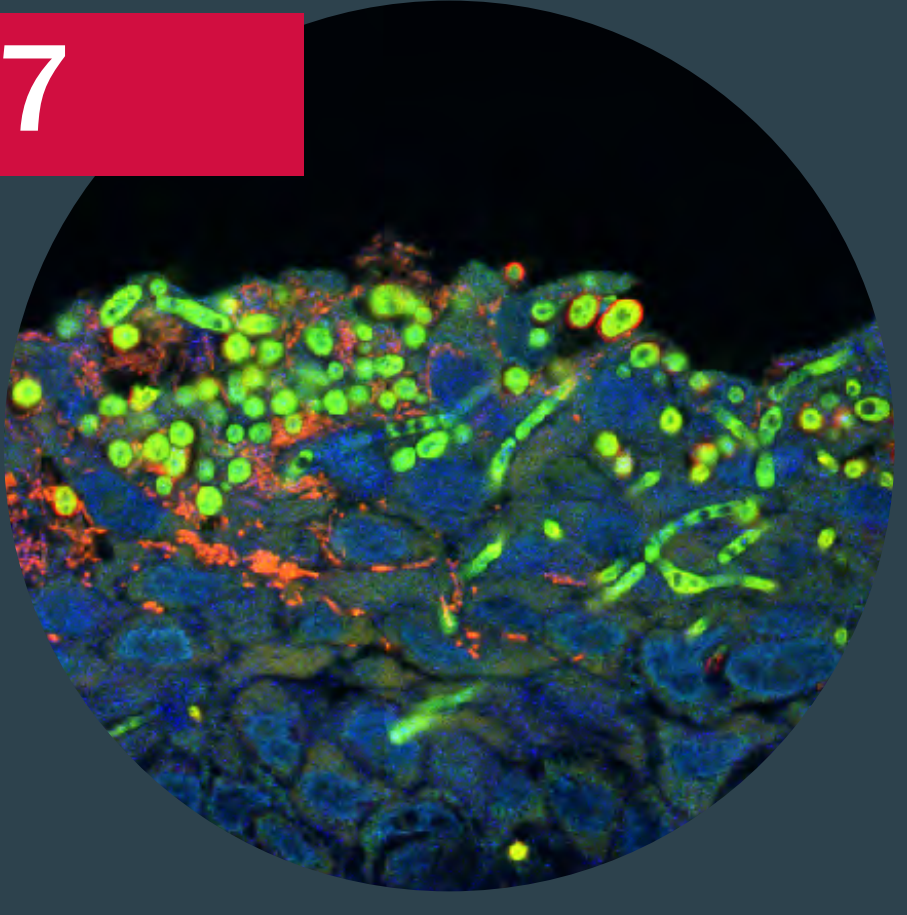
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

School of Dentistry
Ysgol Deintyddiaeth

ANNUAL RESEARCH REPORT

for 2017



Contents

Cover image: In vitro model of Candida invasion. Infection of 3D human oral mucosal tissue model with a mixed species biofilm of Candida albicans and select oral bacteria recapituiates events that lead to pathogenesis and results in aggressive fungal invasion. Confocal microcope image of tissue model following staining of epithelial cells with Hoechst 33342 dye (nuclei, blue) and a fluorescently labelled pan-cytokeratin antibody (cytoplasm, green), bacteria with a universal-bacterial peptide nucleic acid (PNA) probe (red), and C. albicans using a Yeast Traffic Light PNA probe (AdvanDX, bright green). Courtesy of Morse and Wiliams, School of Dentistry, Cardiff University.

Foreword

Professor Daniel Aeschlimann
Director of Research

It is with great pleasure that I introduce this inaugural issue of the Cardiff University School of Dentistry Annual Research Report, after becoming Director of Research for the School last year. This report outlines the emphasis and important discoveries of our research programmes in 2017. It highlights the breadth and depth of the research conducted in our School but enabled through an extensive network of national and international partners and collaborators.

Research in the School embraces a wide range of topics, and organisationally, is conducted in focused groupings. These are clustered into two major interacting themes, essentially constituting the biomedical sciences and public health-related research, which share some of their technical capabilities. The emphasis of our research is on addressing key questions relevant to dentistry and oral health, but with a focus on fundamental topics including microbiology, cell biology, genetics, structural biology, bioinformatics, behavioural science and other aspects of biology. Through this focus on the general principles underlying complex biological systems and their dynamic interactions, our research programmes reach beyond the speciality and impact on many different aspects of clinical medicine. This is highlighted by the successes in translating research such as the clinical role-out of a warning sensor for catheter blocking developed in the School by Mark Waters' and David Williams' group.

Among the notable publications for this period were a study published in *Nature Communications* by David Thomas and colleagues on the lipid modifying enzyme mcr-1 that confers antibiotic resistance, which provided support for the paradigm of antibiotic resistance coming at a cost to fitness; a study by Konrad Beck and colleagues in *Biochemical Journal* demonstrating a critical role of phospholipase C zeta, and specifically its C2 domain, in evoking intracellular calcium oscillations that are essential for the initiation of egg activation during mammalian fertilisation; and a study published in *Human Molecular Genetics* from my group and collaborators on the mechanism by which mutations in the gene encoding the enzyme transglutaminase 6 cause spinocerebellar ataxia. Outcomes from several major clinical trials were reported including the 'Designed to smile' programme in *Health Technology Assessment*, and an alcohol-related violence intervention based around operational change in licensed premises published in *Addiction*.

It is immensely pleasing to see key discoveries being recognized with awards. A stand-out success this year was the Cardiff University Innovation and Impact award to the Advanced Therapies Group headed by David Thomas for their role in the development of an alginate-based drug for cystic fibrosis and other biofilm-mediated multi-drug resistant infections, in collaboration with an international consortium. Among the many well deserved successes of our junior researchers, Daniel Morse's Senior Colgate Prize at the British Society for Oral and Dental Research conference in Plymouth for his work on virulence of mixed species biofilms has been a particular highlight.

A big thank you goes to Jonathan Shepherd who retired at the end of 2017 for his leadership in the School and in research over many years. His contributions leave a lasting legacy, and a group, now headed by Simon Moore, that is going from strength to strength.

Finally, looking to 2018 and beyond, it is important that we do not remain idle but adapt to the changing environment, embrace new developments and expand our capacity and reach through broadening our collaboration across classical technical disciplines even further. It was pleasing to see that a number of us are involved with the newly established Materials, CURE-Infection and Nanosome Research Networks, a University initiative that fosters collaboration and capacity building in newly emerging areas of science. Involvement at early stages at the forefront of development is critical to drive our research forward. Biomedical research has entered an era where mathematics and bioinformatics, as well as the capacity to generate and analyse large data sets, play an increasingly essential role in driving progress and the School has successfully embraced this as can be seen within the Orthodontic and 3D imaging group. It is equally critical that we are developing the next generation of scientists and clinician-scientists, the granting of a Young Investigator award by the Medical Research Council to Elaine Ferguson is a notable achievement. Given these successes and strategic investments we should be in an excellent position to grow our research base even further.

Professor Alastair J Sloan
Head of School

I am delighted to introduce the Annual Research Report for 2017 from Cardiff University School of Dentistry. Much has been achieved by academic research staff and students in the School over the last year and this report provides an opportunity to showcase a sample of these and provide information regarding activity from the School's research groups. The School of Dentistry engages in world leading translational research which aligns with Welsh and UK government policy of integrating health and social care. We work with collaborators and partners across the globe to undertake truly interdisciplinary studies and I hope you enjoy reading the report and learning about the research activity of the School.

Our **World-Leading Research** has **impact**

The School of Dentistry is involved in world-leading research programs aimed at improving human health and welfare. Our research directly influences public policy and clinical practice in a number of key areas, and generates health, socio-economic and commercial impacts.

www.cardiff.ac.uk/dentistry/research/impact-and-translational-research

Our research is built on partnerships with national bodies and Government, and some of the World's leading organisations, as well as interdisciplinary collaboration across our institution and with other universities, and contribute to major projects. As a result, our research has a wide reach and makes a real difference to people's lives.

Case study 1: OligoG for the treatment of cystic fibrosis

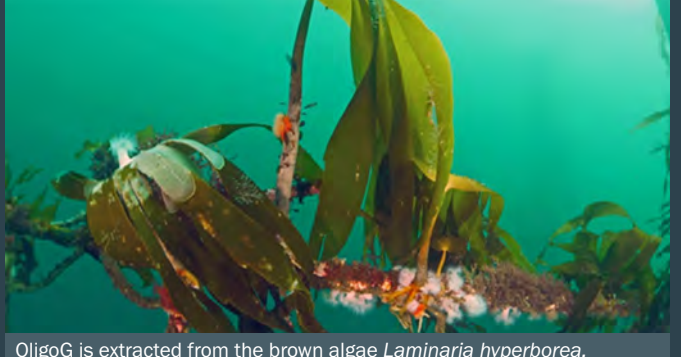
A collaborative project between the Advanced Therapies Group (ATG), Norwegian biopharmaceutical company AlgiPharma AS and Cardiff and Vale University Health Board won Cardiff University's Medical Innovation Award in 2017.

The team, led by Professor David Thomas, discovered that alginates extracted from seaweed could combat multi-drug resistant infections by disrupting the formation of microbial biofilms and increasing bacterial susceptibility to antibiotics.

Using our research about how the alginate works, AlgiPharma developed a new inhalation therapy for cystic fibrosis that has completed five clinical trials and demonstrated an excellent safety record. A new dose optimisation clinical trial, supported by the European research framework programme Horizon 2020, is expected to begin in September 2018. OligoG received an FDA Orphan Drug Designation in February 2016, for the treatment of cystic fibrosis, meaning that the process of gaining marketing approval in the US and EU is expected to be faster and easier than a conventional drug and the commercial benefits will emerge quickly. OligoG has featured on the Cystic Fibrosis Foundation (CFF) drug development pipeline since 2016, which is an interactive tool for clinicians and patients to follow the progress of potential CF treatments through the different phases of clinical research.

www.cardiff.ac.uk/research/explore/research-units/advanced-therapies-group

Bacteria isolated on blood agar



OligoG is extracted from the brown algae *Laminaria hyperborea.*

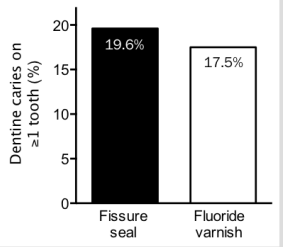
The ATG receiving their Innovation and Impact award.

Case study 2: Designed to Smile

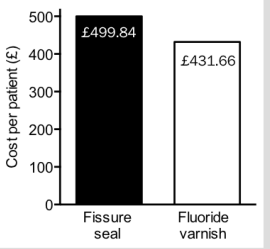
Professor Ivor Chestnutt and the Dental Public Health Unit have provided invaluable evidence of cost-effectiveness for NHS dental services, such as the 'Designed to Smile' (D2S) Programme in Wales, which is an oral health improvement programme targeted at children living in deprived communities with a focus on in-school toothbrushing. The results of this research were published in 2017, showing that the prevalence of dental caries in five year-olds has fallen by 12% since the D2S Programme was launched in 2008. As a direct result of our evaluation, Welsh Government decided to continue funding the programme, and in March 2017, they announced that the D2S programme would be re-focused to target children under five, given the evidence of earlier onset of tooth decay demonstrated in our research.

The team's paper evaluating the relative clinical and cost effectiveness of fissure sealant and fluoride varnish was among the top 10 most-read articles in the Journal of Dental Research in 2017. This report demonstrated that fluoride varnish was equally effective at decay prevention, but cheaper than fissure sealants, ultimately leading to the discontinuation of sealant provision as part of the D2S Programme.

www.cardiff.ac.uk/research/explore/research-units/dental-public-health-unit



The proportion of children who developed dentine caries on at least 1 first permanent molar at 36 months was broadly similar.



The overall per-patient cost saving of fluoride varnish was £68.13 (95% CI £5.63 to £130.63; $p = 0.033$).

Other highlights of our influential research:

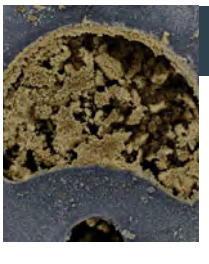
Our researchers made significant progress this year in a wide range of areas.

Reducing Violent Crime:

The Cardiff Model for Violence Prevention continues to be implemented across the UK, and has also been adopted in other cities around the world, including in the Netherlands, United States, Australia and South Africa.

Diagnosis of gluten-related neurological dysfunction:

Professor Aeschlimann's team linked development of autoantibodies to transglutaminase 6 with immune-mediated ataxia. This led to the recognition of neurological presentations of gluten sensitivity by clinicians, and development of an assay for these autoantibodies, detection of which is now being implemented in clinical diagnosis.



Early warning of cathether blockage:

An early warning sensor for catheter blockage, developed by Professors Mark Waters and David Stickler, has been licensed to MBi Wales Ltd and CE marked as a class 1 sterile device. A commercial feasibility agreement has been reached with a global urostomy company to incorporate the sensor into their leg bags and urine meters, with predicted sales of 1-2 million units.

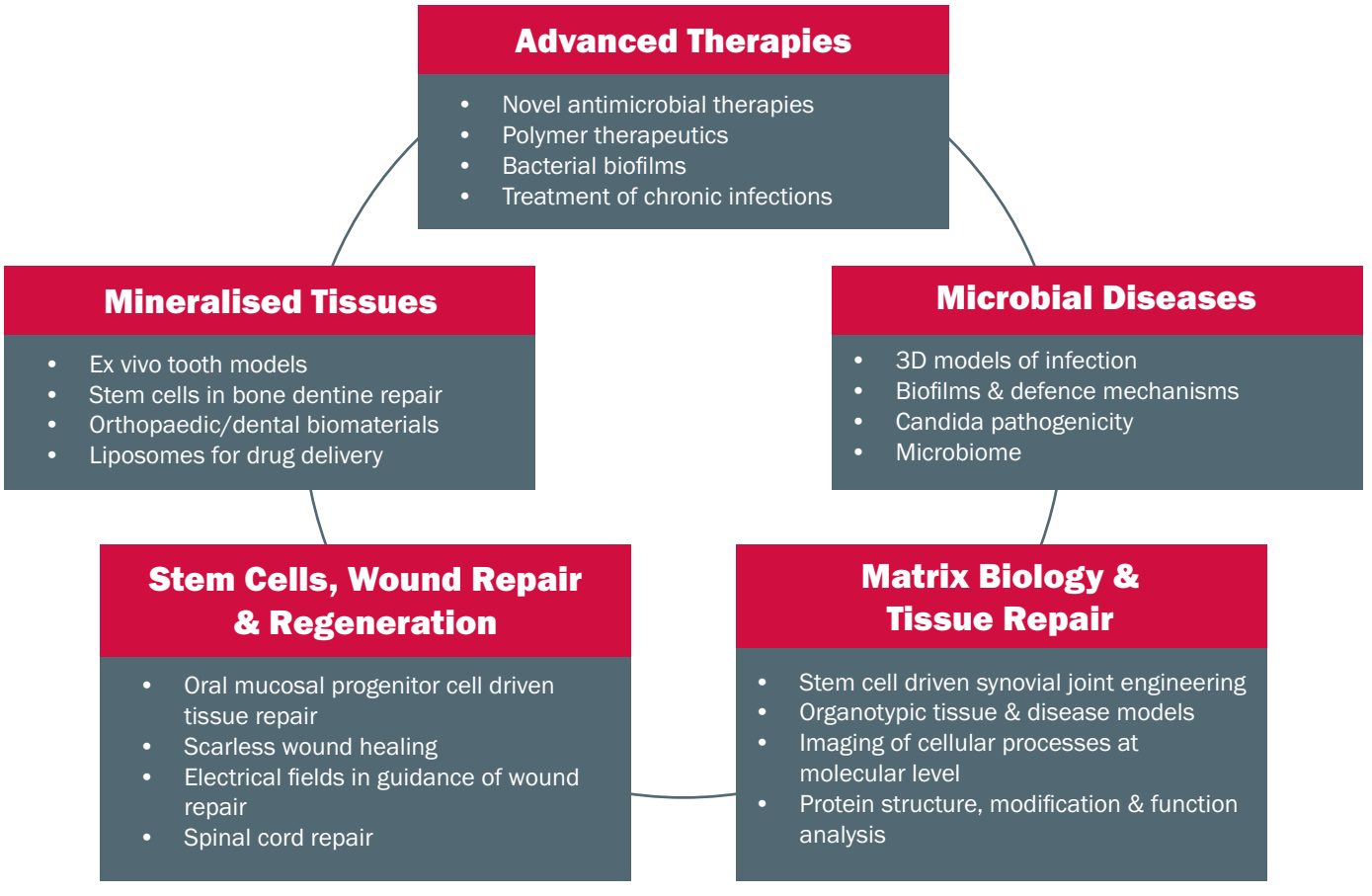
Improving public services:

An evaluation of orthodontic service provision in Wales, following on from a review in 2010 by Professor Richmond, confirmed that the implementation of the recommendations made at the time to Welsh Government, local health boards and orthodontic providers made the service considerably more efficient and cost-effective.

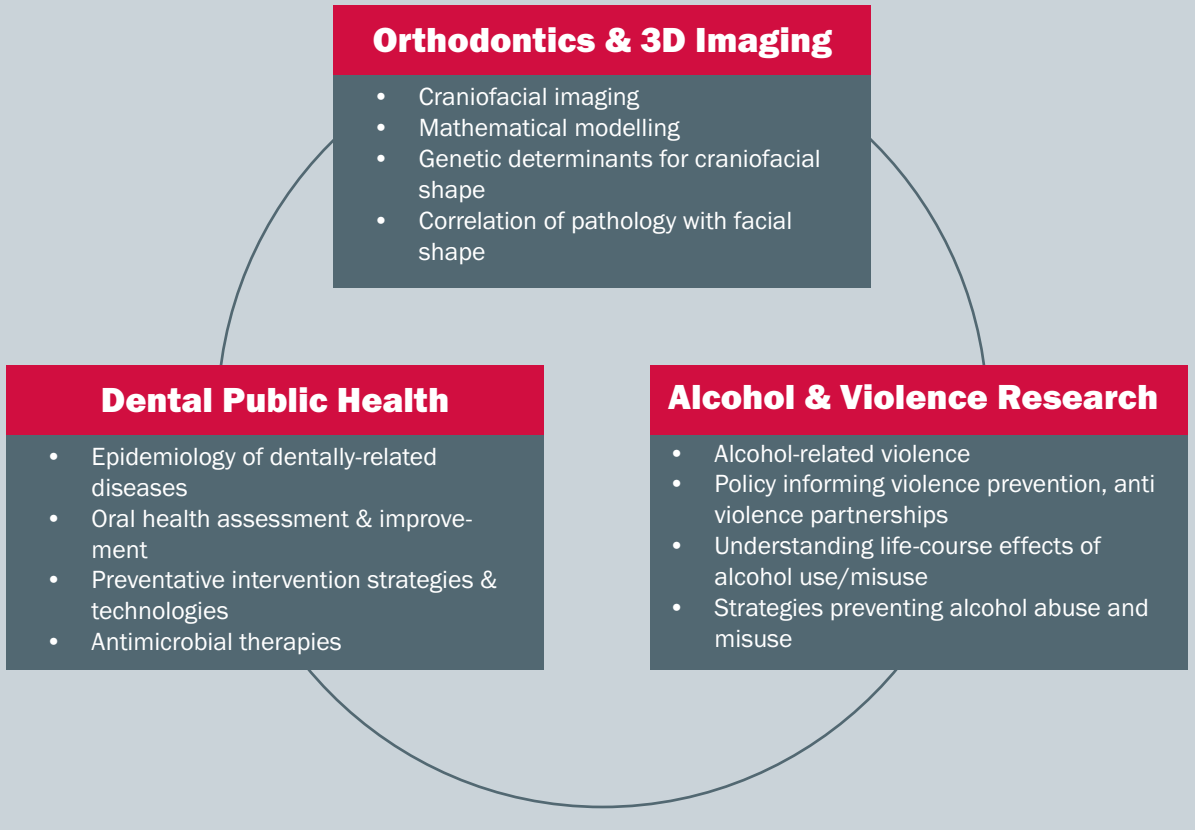
Further details at: www.cardiff.ac.uk/dentistry/research/impact-and-translational-research

Research **summary**

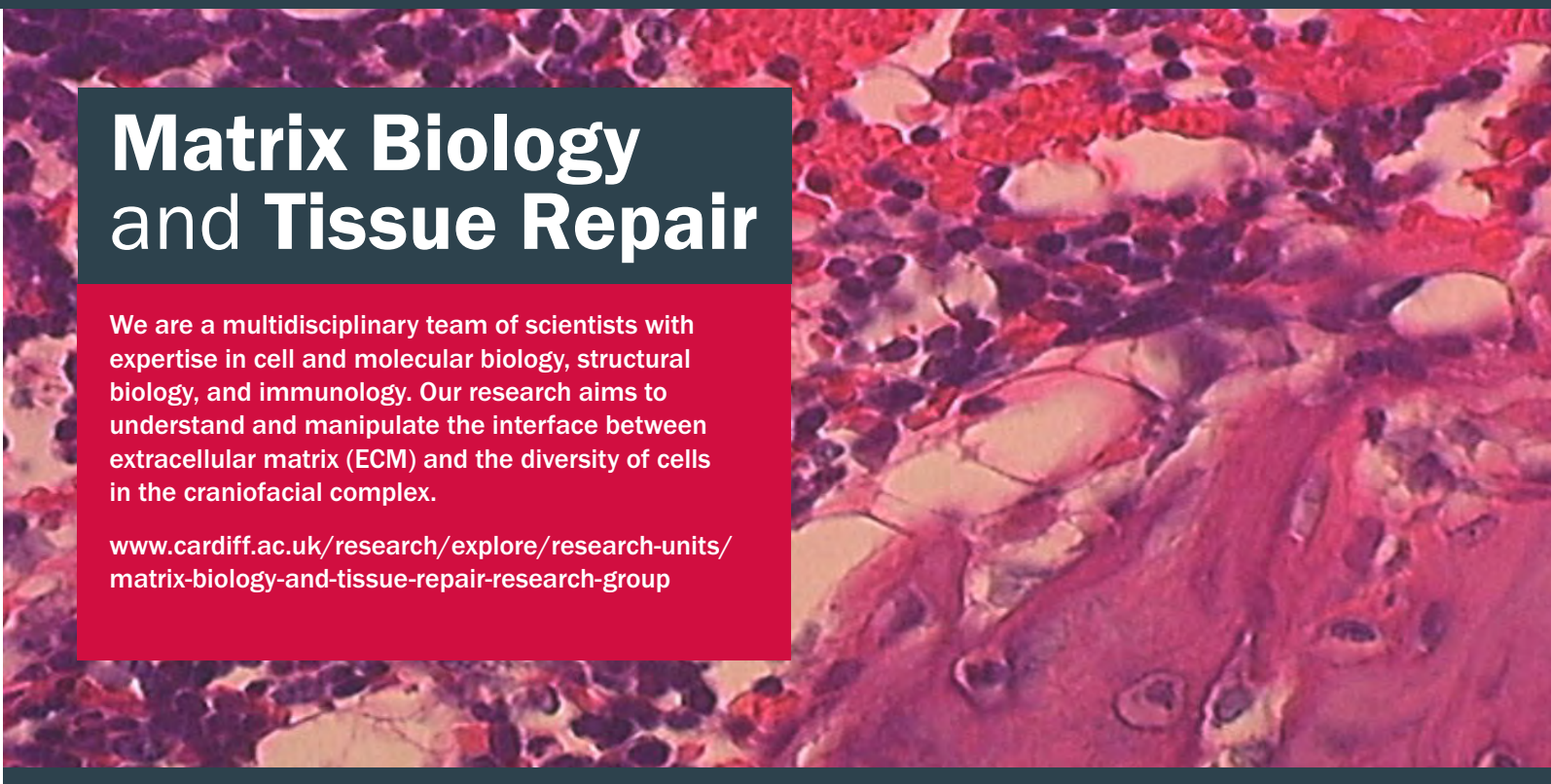
Core competencies in Oral and Biomedical Sciences:



Core competencies in Applied Clinical Research and Public Health:



Matrix Biology and Tissue Repair



We are a multidisciplinary team of scientists with expertise in cell and molecular biology, structural biology, and immunology. Our research aims to understand and manipulate the interface between extracellular matrix (ECM) and the diversity of cells in the craniofacial complex.

www.cardiff.ac.uk/research/explore/research-units/matrix-biology-and-tissue-repair-research-group

Our goals are:

- To elucidate and counteract pathological processes leading to tissue destruction in inflammation, cancer and ageing
- To create functional tissue through application of life science principles.

The ECM and its interaction with various cells are critically important to regulate inflammation, repair/regenerative processes and invasive cancers. Connective tissue cells control migration, survival and proliferation of endothelial and epithelial cells as well as recruitment and activation of antigen presenting cells that orchestrate the inflammatory response. Altered connective tissue cell responses are associated with many diseases, either because of direct involvement in the etiology or because of the fibrosis that accompanies the tissue damage. Experimental models have been established within the group to decipher cellular interactions regulating distinct aspects of the repair and disease process. These relate to inflammation, angiogenesis, re-epithelialisation, cancer stromal cell interactions and ECM changes occurring with ageing. The emphasis is to gain a molecular understanding of the role of post-translational modifications of proteins in organ system function, and how aberrant protein modifications or proteolysis contributes to pathogenesis.

Highlights of 2017:

- A step towards understanding how TGM6 gene mutations cause spinocerebellar ataxia (SCA-35): Cellular toxicity of mutants is associated with failure in nuclear localization whereby mutant transglutaminase 6 has a dominant negative effect on the wildtype enzyme due to complex formation (Tripathy et al., 2017. Hum Mol Genet 26: 3749-62).
- Serological testing for transglutaminase 6 autoantibodies has been implemented in clinical diagnostic service.
  zedira.com/Celiac-disease-products
- Collaborative work with the groups of Drs F.A. Lai and M. Nomikos has shown that mutations in the enzyme phospholipase C zeta can cause infertility in men; as highlighted by a Biochemical Society press release, this discovery could enable earlier sperm diagnosis and treatment.
  www.portlandpresspublishing.com/sites/default/files/BiochemJ-Male%20infertility.pdf
- Development of a novel approach to investigate dynamic changes in cell surface topography: This new methodology demonstrated that rapid changes in the micro-ridges on the cell surface of neutrophils are needed for neutrophil shape changes, such as during phagocytosis and spreading. (Al Jumaa et al., 2017. Sci Rep 7: 9790).

Linked Research Centres:

Professor Aeschlimann is a founding member of the Arthritis Research UK Centre of Excellence for Biomechanics and Bioengineering, where he is the lead for the osteoarthritis biomarker development programme. Organotypic in vitro human cartilage osteoarthritis models were developed and employed in biomarker discovery.

www.cardiff.ac.uk/arthritis-biomechanics-bioengineering-centre/

He is also a founding member of the Sheffield Institute of Gluten-Related Disorders (SIGReD), which brings together interdisciplinary experts to develop new strategies for effective diagnosis of gluten-related disorders. The work here focuses on the gut-brain axis of the immune system and how this links to autoimmune ataxia.

www.sheffield.ac.uk/news/nr/gluten-related-diseases-1.259247

Key project summary:

Unconventional protein secretion in innate immunity, a new link between transglutaminase 2 and disease processes:

Adamczyk et al., 2015. J Cell Sci 128:4615-28;
Aeschlimann and Knäuper, 2017. Amino acids 49: 453-60.

Background: Transglutaminase (TG) 2 is an enzyme that modifies proteins through deamidation, transamidation or esterification of glutamine residues. It has a predominant role in the cell stress response, and its stabilization of extracellular protein assemblies has a pivotal function in tissue repair. However, aberrant TG2 activity has been shown to be a driver of fibrosis as well as autoimmunity. TG2 is released from cells via an unknown unconventional secretion pathway, and this mechanism controls extracellular activity linked to disease processes.

Discovery: Purinergic (P2X) receptors are ion channels with important roles in innate immunity. Extracellular ATP secreted through membrane channels / vesicles following cell stimulation or released from compromised cells can trigger their activation and depending on circumstances, is enforced by further ATP release from innate immune cells.

Within this context, P2X7 receptor (P2X7R) activation acts as a danger signal amplification system within the local milieu through paracrine signalling. We have shown that rapid active export of TG2 is linked to activation of P2X7R, and that through co-secretion of thioredoxin-1, this mechanism controls extracellular levels of active enzyme. Thioredoxin-1, an oxidoreductase enzyme with a function in β-defensin activation in myeloid cells, prevents inactivation of TG2 which would otherwise readily occur in the oxidative extracellular environment.

To gain an understanding, at the molecular level, of how P2X7R activation couples to downstream events including TG2 externalization and inflammatory cytokine release, we investigated the potential receptor-linked effector pathways (Fig 1). Our results do not support packaging of TG2 within vesicles for release but identified receptor membrane pore

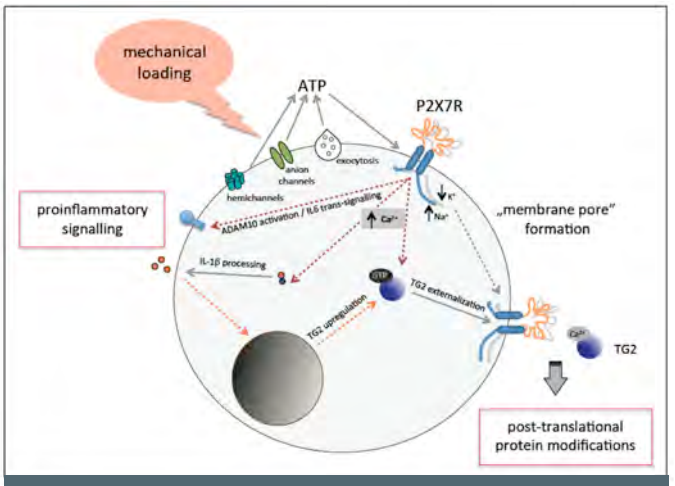


Fig 2. Schematic outlining how aberrant joint loading-induced release of ATP drives inflammatory signaling and TG2 upregulation and externalization/activation, a process that ultimately drives bone and cartilage pathology in joint disease.

formation as essential. Furthermore, P2X7R triggered membrane pore activity directly correlated with TG2 export in various mutant receptors. P2X7R is integral to the NLRP3 inflammasome pathway in myeloid cells that can also be triggered by caspase 4/5-mediated pyroptosis with associated gasdermin D pore formation.

However, our data shows that TG2 externalisation occurs in the absence of cell death (either pyroptosis or apoptosis) and can occur without inflammasome assembly, although a partial mechanistic overlap is indicated by inflammasome-activation leading to TG2 processing prior to export.

Importance: Our results show that purinergic signaling controls TG2 externalization via a novel mechanism for protein export. Other proteins undergoing alternative secretion, many of which are potent biological signals, may share this pathway with TG2 and hence understanding the regulatory mechanism for this pathway is of central importance. Furthermore, this identifies a pathway that ties extracellular protein modifications into the danger signal-mediated innate immune response (Fig 2). These recent insights therefore offer new opportunities for therapeutic intervention in chronic inflammatory and autoimmune diseases such as arthritis and gluten sensitivity.

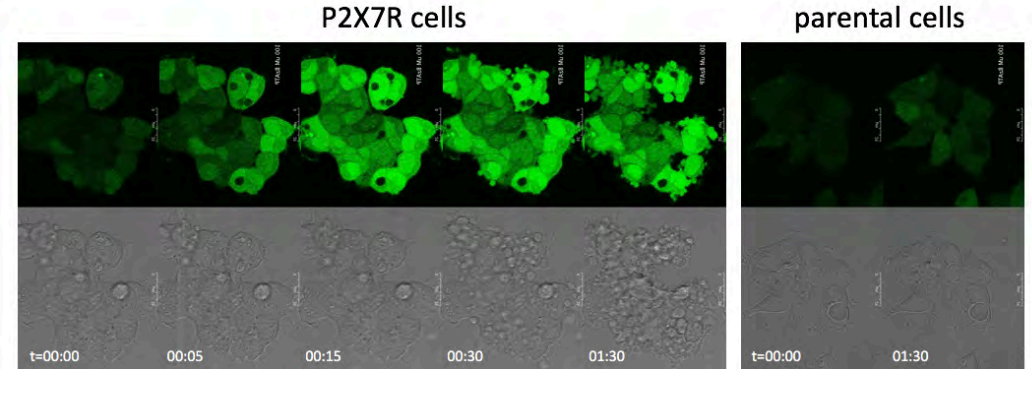


Fig 1. P2X7 receptor activation leads to rapid rise in intracellular Ca^{2+} and overt membrane changes. Parental or P2X7R expressing HEK293 cells were loaded with Ca^{2+} indicator Fluo-4 and then stimulated with the P2X7 receptor selective agonist BzATP. Changes in fluorescence (top) and cell morphology (phase contrast, bottom) were monitored over time (min:sec). Images represent an optical section captured by confocal microcopy.

Professor Daniel Aeschlimann

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MSc (Biochemistry, Biophysical Chemistry, Cell Biology and Molecular Genetics), 1990, Biocenter, University of Basel, Basel, Switzerland. PhD (Biochemistry), 1993, University of Basel, Basel, Switzerland. Fellowships from EMBO and Swiss National Science Foundation. Various academic positions in Switzerland, USA and UK. Since 2001, Professor of Biological Sciences, Cardiff University, UK. Head of Matrix Biology & Tissue Repair Research Unit and Director of Research for School of Dentistry.

The function of transglutaminases and protein crosslinking in physiological processes and also in disease has been a central theme of my research. Current research focuses on the role of transglutaminase enzymes in innate immunity and in the development of autoimmune disease in the context of gluten sensitivity and arthritis.

Key Publication:

Tripathy D, et al. (2017). Mutations in TGM6 induce the unfolded protein response in SCA35. Human Mol Genet 26: 3749-62.

Full list at: www.cardiff.ac.uk/people/view/39472-aeschlimann-daniel

Dr Konrad Beck

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Diploma in Physics, 1981 JWG University Frankfurt a. M., Germany. Ph.D. in Biology, 1984, MPI Biophysics, Frankfurt a. M., Germany. Habilitation in Biophysics, 1990, University Linz, Austria; various academic positions and fellowships in Basel, Switzerland; Linz, Austria; Portland OR, USA; Piscataway NJ, USA; Nagoya, Japan; Lyon, France; since 2004 Lecturer in Protein Biophysics, Cardiff University, U.K.

My main work relates to the structure, folding and assembly of multidomain proteins especially those of the extracellular matrix. Collaborations with the groups of F.A. Lai (School of Biosciences) and M. Nomikos (College of Medicine, Qatar University) focus on the effect of mutations in the cardiac calcium release channel (RyR2), phospholipase C zeta, and calmodulin. Work together with the groups of AK Sewell and DK Cole (School of Medicine) aims to determine the molecular mechanism of immunological escape by SL9, a well-known HIV epitope restricted by HLA-A2.

Key Publication:

Nomikos M, et al. 2017. Male infertility-linked point mutation reveals a vital binding role for the C2 domain of sperm PLCζ Biochem J. 474: 1003-1016.

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Dr Sharon Dewitt

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BSc (Pharmacology, University of Wales College of Medicine), PhD (Cell Biology & Immunology, Cardiff University), Wellcome Trust funded postdoctoral researcher (Cardiff University, 2003-2010), Cardiff Academic Fellow (Arthritis Research UK, 2010-2014), Lecturer (Cardiff University School of Dentistry, since 2014)

The focus of my research is to identify the early cellular events that occur in disease processes such as arthritis. These early events can then be exploited as indicators of disease to enable early diagnosis and treatment; or as a means of manipulation and modification of the disease process. Areas of expertise include Ca^{2+} imaging, confocal and single cell microscopy.

Key Publication:

Al Jumaa MA, et al 2017. Topographical interrogation of the living cell surface reveals its role in rapid cell shape changes during phagocytosis and spreading Sci Rep 7(1): 9790.

Full list at: www.cardiff.ac.uk/people/view/39492-dewitt-sharon

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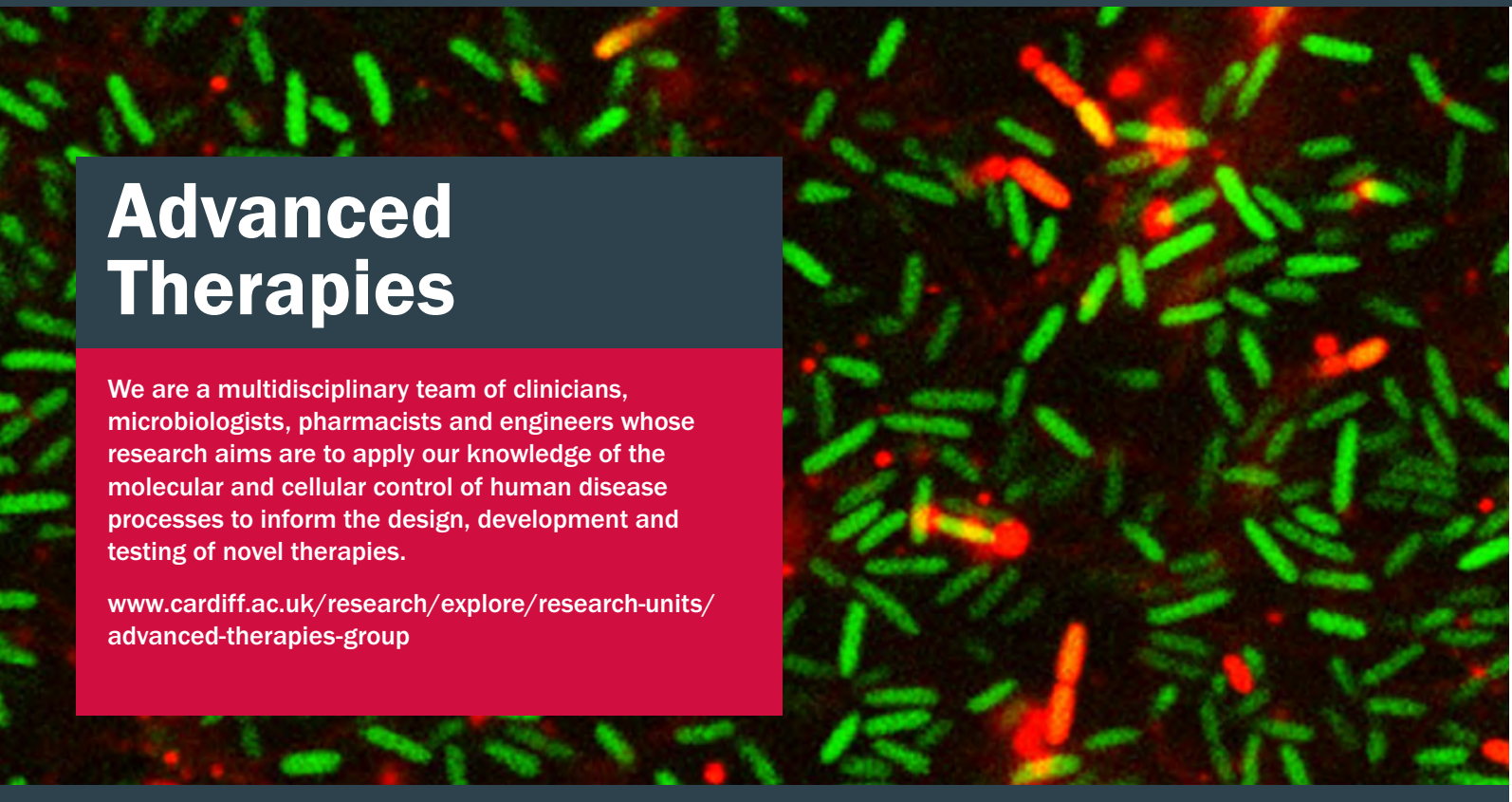
Diplom Chemistry (equivalent BSc, University of Bielefeld, Germany), Dr rer. nat. (equivalent PhD in Biochemistry, University of Bielefeld, Germany), 1993-1995 Wellcome Trust Travelling fellow (Strangeways Research, Cambridge), 1995-2000 Post-doctoral fellow (University of East Anglia, Norwich), 2001-2006 Lecturer (University of York, York), since 2006 Senior Lecturer (Cardiff University)

Major research interests in my group focus on the understanding of metalloproteinase function in the arthritic diseases and cancer. The groups main focus is to understand the role of metalloproteinases in cellular signalling at the molecular level and to design novel therapeutic regimens to combat arthritic disease and cancer as well as to discover biomarkers.

Key Publication:

Wanger, T. et al. 2015. Differential regulation of TROP2 release by PKC isoforms through vesicles and ADAM17. Cellular Signalling 27 (7): 1325-1335.

Full list at: www.cardiff.ac.uk/people/view/39462-knauper-vera



Advanced Therapies

We are a multidisciplinary team of clinicians, microbiologists, pharmacists and engineers whose research aims are to apply our knowledge of the molecular and cellular control of human disease processes to inform the design, development and testing of novel therapies.

www.cardiff.ac.uk/research/explore/research-units/advanced-therapies-group

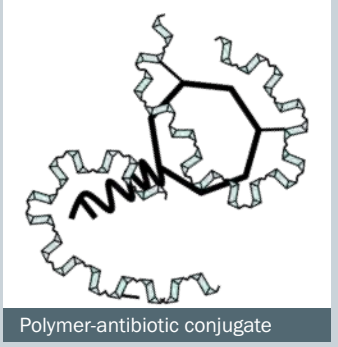
Working with our academic and industrial partners around the world, we are using our expertise in the design and delivery of novel therapeutic interventions, to target a range of, often life-threatening, infective and chronic inflammatory conditions including multi-drug resistance, cystic fibrosis, chronic skin wounds and peri-implantitis.

Our goals are:

- To translate our findings, from the laboratory to the clinic, to improve the treatment of patients
- To develop treatment strategies (both topical and intravenous) to improve current treatment efficacy/efficiency and inform the design of entirely novel polymer therapeutics
- To utilise the toolkit our experienced inter-disciplinary team has developed, to analyse anti-biofilm therapeutic interventions against bacterial biofilms and surfaces (at the cellular, protein and gene levels).

Highlights of 2017:

- Significant advances in understanding how our dextrin-colistin conjugates alter the cellular interactions of colistin and inhibit kidney damage.



Polymer-antibiotic conjugate

- Filing of 2 new patent applications with AlgiPharma AS, based on the first bifunctional polymer therapeutics, to complement our patent portfolio.
- Cardiff University Innovation and Impact Award for Medicine (see page 4 for details).

Linked Research Centres:

Dr Anne Tøndervik & Dr Havard Sletta, Biotechnology and Nanomedicine, SINFEF, Trondheim, Norway.
www.sintef.no/en/industry/biotech-and-nanomedicine

Prof. Tim Walsh & Dr Brad Spiller, Infection & Immunity, School of Medicine, Cardiff University.
www.cardiff.ac.uk/medicine/research/divisions/infection-and-immunity

Prof. Paul Lewis, School of Management, Swansea University.
www.swansea.ac.uk/som

Prof. Thorsten Wohland, Centre for Bio-Imaging Sciences, National University of Singapore, Singapore.
www.dbs.nus.edu.sg/lab/BFL/index.html

Prof. Mark Gumbleton, School of Pharmacy and Pharmaceutical Sciences, Cardiff University.
www.cardiff.ac.uk/pharmacy-pharmaceutical-sciences

Dr Niklaas Buurma, Physical Organic Chemistry, School of Chemistry, Cardiff University.
www.cardiff.ac.uk/study/postgraduate/research/programmes/area/physical-organic-chemistry

Dr Gary Chinga-Carrasco, Paper & Fibre Research Institute, Trondheim, Norway. **www.rise-pfi.no**

Prof. Peter Griffiths, Pharmaceutical, Chemical & Environmental Sciences, Faculty of Engineering & Science, Greenwich University.
www.gre.ac.uk/engsci/study/pharchemenv

Key project summary:

Developing a novel therapy to tackle life-threatening, drug-resistant bacterial infections.

Pritchard et al., 2017. Antimicrob Agents Chemother. 61:e00762-17.

Background: This research describes an alginate-based oligosaccharide nanomedicine, OligoG, developed as a mucolytic therapy for chronic respiratory disease. We demonstrated the ability of this agent to potentiate the effectiveness of selected antibiotics against multi-drug resistant bacterial biofilms. Our research programme involves defining its mechanism of action.

Discovery: *Pseudomonas aeruginosa* is an important human pathogen of patients with chronic lung infections such as cystic fibrosis, where it forms dense, 3-dimensional aggregates or microcolonies, which are more readily able to resist antimicrobial treatment than conventional biofilms. In Pritchard et al., (2017), we successfully modelled this in the laboratory, demonstrating the ability of OligoG to not only disrupt these microcolonies (Fig 1) but also potentiate the activity of colistin (the 'antibiotic of last resort') against these 'difficult-to-treat' bacteria. We have also shown mechanistically that these effects are achieved by modulation of acyl-homoserine lactones (e.g. 3-oxo-C12 AHL) via quorum sensing signaling pathways (Fig 2) via disruption of bacterial motility (Fig 3).

Importance: This work contributes to our understanding of how the prototypical therapy OligoG mediates biofilm/microcolony disruption, at the cellular and molecular level, showing how it disrupts, not only the ability of bacteria to form biofilms, but also the charged polymeric biofilm matrix. This study also proposes a mechanistic rationale for the previously-described anti-biofilm properties of this novel antimicrobial agent that is currently in human clinical trials.

Fig 3 Testing inhibition of bacterial motility using Motility Test Agar

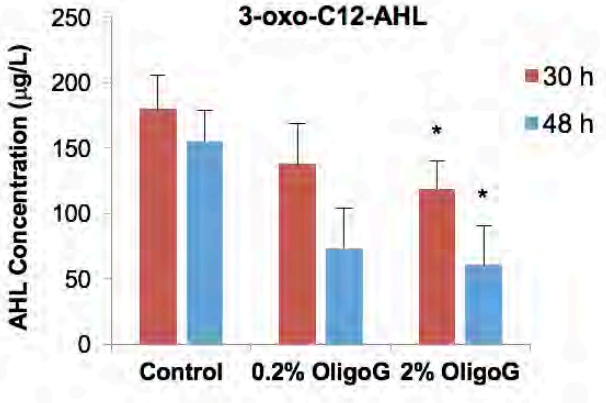


Fig 2. Effect of OligoG CF-5/20 on cell signaling molecules in vitro. High performance liquid chromatography mass spectrometry (LC-QQQ-MS) to quantify acyl homoserine lactone (AHL) production of *P. aeruginosa* PAO1 grown in MH and AS medium in a time course assay (30 and 48 h) showing the effect of OligoG CF-5/20 on 3-oxo C12-AHL (*p<0.05; n=3).

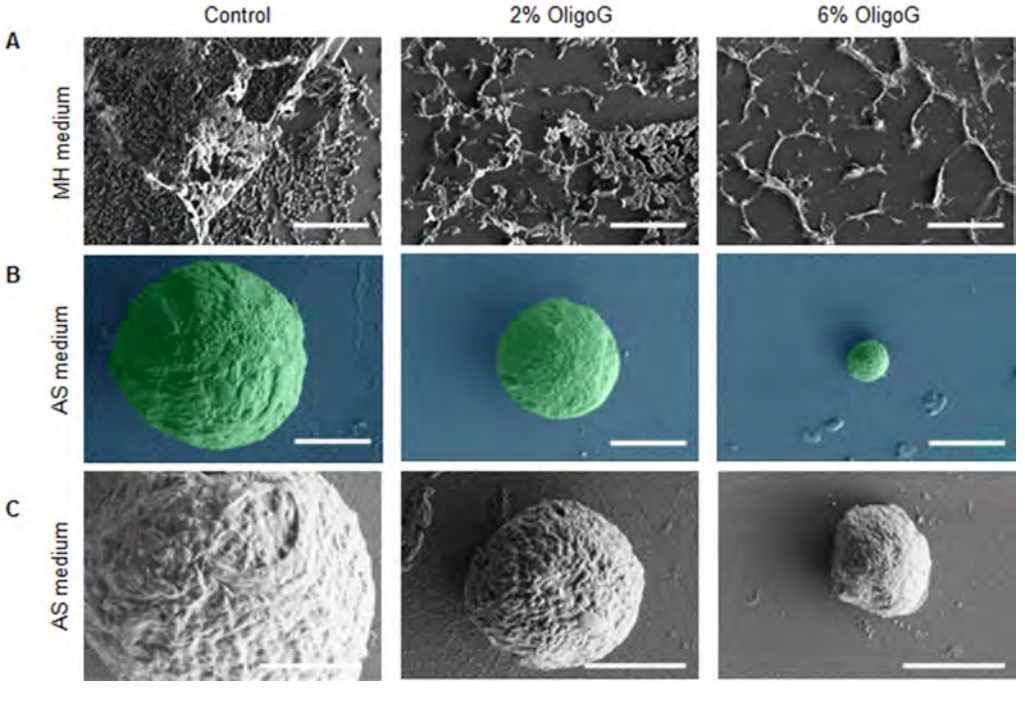


Fig 1. Biofilm formation assays showing biofilms of mucoid *P. aeruginosa* grown in Mueller-Hinton broth (MH) or artificial sputum medium (AS). Scanning electron microscopy images of *P. aeruginosa* (NH57388A) biofilms grown ±OligoG CF-5/20 for (A) 24 h in Mueller Hinton broth [scale bars, 10 µm]; (B) 48 h in artificial sputum medium ± OligoG cf-5/20, [scale bars, 5 µm]; (C) zoomed in images as in B [scale bars, 5 µm].

Professor David W Thomas

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A clinician with a background in studying the role of microbial biofilms in human disease states to improve their management and diagnosis, I lead the Advanced Therapies Group. I am a previous Wellcome Trust Clinical fellow (Bristol University) and currently Professor/ Hon. Consultant in Oral and Maxillofacial Surgery at the University Hospital of Wales.

Key Publication:

Yang Q, et al. 2017. Balancing mcr-1 expression and bacterial survival: a delicate equilibrium between essential cellular defence mechanisms.Nat Commun 8:2054.

Full list at: www.cardiff.ac.uk/people/view/39420-thomas-dave-w

Dr Katja E Hill

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With a background in microbial ecology and molecular biology, I am interested in the mechanisms of gene regulation and control in bacterial biofilms. My current research involves translation to clinical practice through the testing of novel compounds (from e.g. seaweed and the Australian rainforest) for the management of human chronic diseases such as cystic fibrosis and wound healing of 'difficult to treat' wounds, to characterise their antibacterial/anti-biofilm properties.

Key Publication:

Pritchard, M. et al. 2016. A new class of safe oligosaccharide polymer therapy to modify the mucus barrier of chronic respiratory disease. Mol Pharma 13(3), 863-872.

Full list at: www.cardiff.ac.uk/people/view/39529-hill-katja

Dr Elaine L Ferguson

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My translational research in polymer therapeutics focuses on optimising drug release by attachment of biodegradable polymers, to target proteins, peptides and drugs to sites of inflammation, thereby minimising toxicity, overcoming resistance and increasing bioavailability. Funded by an MRC New Investigator Research grant, I am currently investigating the accumulation and nephrotoxicity of dextrin-colistin conjugates and, in collaboration with AlgiPharma AS, investigating novel combinations of polymers and antibiotics.

Key Publication:

Roberts, J. et al. 2016. In vitro evaluation of the interaction of dextrin-colistin conjugates with bacterial lipopolysaccharide. Journal of Medicinal Chemistry 59(2), 647-654.

Full list at: www.cardiff.ac.uk/people/view/39401-ferguson-elaine

Dr Manon F Pritchard

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Following completion of my dental clinical foundation years and PhD in microbiology, I have successfully published a series of papers and been awarded several prizes in recognition of my work. I am currently developing therapeutic nanomedicines for the treatment of multi-drug resistant bacterial biofilm infections, utilising alginate oligomers and epoxy-tigliane molecules derived from seaweed and the rainforest, respectively. My research is consolidated by the successful translation of therapies into clinical trials.

Key Publication:

Pritchard MF et al. 2017. A low-molecular-weight alginate oligosaccharide disrupts Pseudomonal microcolony formation and enhances antibiotic effectiveness. Antimicrob Agents Chemother 61(9): e00762-17.

Full list at: www.cardiff.ac.uk/people/view/178890-pritchard-manon

Dr Lydia C Powell

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As an engineer, my research interests include characterising interactions between bacteria, novel therapeutics and surfaces, biofilm formation/disruption in both static and dynamic systems using Atomic Force Microscopy, Confocal Laser Scanning Microscopy, Scanning Electron Microscopy and zeta potential/sizing measurements. Recent projects include investigating biofilm formation on nanocellulose dressing materials, voice box prostheses, and use of the alginate oligomer, OligoG, as an inhaled therapy for cystic fibrosis.

Key Publication:

Powell LC, et al. 2016. An investigation of Pseudomonas aeruginosa biofilm growth on novel nanocellulose fibre dressings. Carbohydr Polym 137: 191-197.

Full list at: www.cardiff.ac.uk/people/view/182109-powell-lydia

Microbial Diseases

The Microbial Diseases Research Group has extensive research expertise across a wide range of oral and non-oral human infections. Significant focus is devoted to the pathogenesis and treatment of biofilm related infections, as well as how the host responds to these infections. To facilitate our multidisciplinary research, we have dedicated facilities and equipment for the study of biofilms, and we liaise closely with oral and medical microbiology laboratories, which enable access to clinical specimens for study and help in highlighting clinical problems where our research can be directed.

www.cardiff.ac.uk/research/explore/research-units/microbial-diseases-research-group

Our research aims are:

- To develop novel therapies to prevent and treat biofilm-mediated infections
- To investigate the complexity of biofilm communities and explore the interactions between microbial constituents
- To study host immune responses to infection, with the ultimate goal of developing diagnostics and immunotherapies

Historically, the role of microorganisms in human infection has involved research into single species organisms grown in liquid culture. However, in recent decades it has become evident that most infections are caused by multispecies biofilm communities attached to surfaces (Fig.1). Indeed it is now estimated that over 65% of all human infections have a biofilm origin. A good example of an infectious biofilm is dental plaque, which is responsible for the two most prevalent human infections, namely caries and periodontal disease. Biofilm research is not only important given the prevalence of such infections, but also because of their recalcitrance to removal from surfaces by physical and chemical approaches. Importantly, biofilms frequently have up to 1000-fold greater tolerance to administered antimicrobials and are therefore a major cause of antimicrobial resistance.

Linked Research Centres:

The research group is linked with the University Research Network: CURE-Infection (Cardiff University Antimicrobial Resistance and Infection Biology Network). CURE-Infection network addresses fundamental questions about infection biology - how pathogens are acquired, transmitted and evolve in an era of increasingly mobile human population, drug dependency and antimicrobial resistance. It aims to enhance research on the interlinked themes of antimicrobial resistance, antimicrobial discovery, and infection biology.

Highlights of 2017:

- **2017 Senior Colgate Prize - Daniel Morse.** 'Contribution of oral bacteria to Candida virulence and denture stomatitis'.

- **Oral And Dental Research Trust 2017 GSK Research Award - Josh Twigg.** 'Disinfection of denture-acrylic biofilms incorporating respiratory pathogens using pulsed microwave energy.'

Key project summary:

Development of an early warning sensor for predicting urinary catheter encrustation.

Malic S, et al. 2012 J Biomed Mater Res B Appl Biomater. 100(1):133-7.

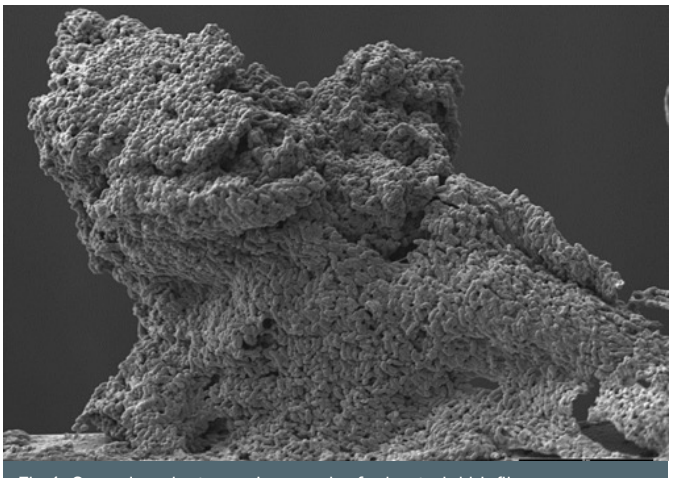

Fig 1. Scanning electron micrograph of a bacterial biofilm on an endotracheal tube

Background: Healthcare-associated infections (HCAIs) arise following patient contact with the healthcare system. Within Wales, a recent survey (2012) revealed a HCAI incidence of 4.4%, with urinary tract infections (UTIs) being the most prevalent (20.9%). Results showed that 50% of UTIs involved a urinary catheter. Catheter associated urinary tract infections (CAUTIs) occur in vulnerable patients and will increase patient morbidity and mortality, as well as healthcare costs. CAUTIs are often asymptomatic, and consequently, serious complications such as kidney infection, calculus formation and bacteraemia may arise without warning. Of particular concern is when crystalline biofilms develop that block the urinary catheter. Research to address this problem has been on-going through collaboration between the Microbial Diseases Research group and our industrial partner, MBi Wales Ltd.

Discovery: Several bacterial species can induce CAUTIs. One key bacterium is *Proteus mirabilis*. *Proteus mirabilis* are typically small (1 µm in length), rod shaped bacteria, but when they contact a catheter surface, develop into elongated (20-30 µm long) and highly motile cells. These 'swarmer cells' secrete a polysaccharide slime matrix, arrange themselves into rafts of parallel cells and move rapidly along the catheter. Co-ordinated expression of virulence genes occurs during swarmer-cell development, and studies have shown that during this process there is a 30-fold increase in the production of urease. Urease hydrolyses urea, with release of ammonia and elevation of urine pH. This increased pH of urine induces formation of crystalline magnesium and calcium salts responsible for encrustation and blockage of the catheter lumen (Fig 2). Up until recently, prediction of catheter encrustation has been highly problematic. However, our research has led to the development of an ammonia sensor constructed using a silicone base material that can be positioned in-line with the urinary catheter. The sensor detects ammonia and pH changes generated by the action of urease on urea, leading to a visible colour change.

Importance: Healthcare-associated infections (HCAIs) are defined as those that arise following patient contact with the healthcare system. These infections encompass not only those acquired by patients in hospitals, but also those arising from home healthcare and care within nursing homes. It is thought that nearly 10% of patients in the UK suffer from HCAIs. Of concern is that HCAIs often occur in individuals who are vulnerable or debilitated leading to increased patient morbidity and mortality, together with increased associated costs for health care providers. The importance of HCAIs is recognised worldwide, and within Wales, the Welsh Assembly Government first published its strategy for tackling HCAIs in 2004, with the key goal of reducing the incidence of HCAI in Wales.

The most prevalent of all HCAIs are CAUTIs, which globally account for up to 40% of all HCAI. The use of an indwelling urinary catheter is standard treatment for urine retention and incontinence within both hospital and nursing home settings. Worldwide, it is estimated that over 100 million urinary catheters are used with an associated incidence of CAUTIs exceeding 1 million. As a result of this high incidence, the associated financial costs are extensive, and in the USA alone, annual management of CAUTIs is thought to be of the order of $450 million. Given the fact that our society is an increasingly elderly one, it is likely that such costs will only increase in future years. Urinary catheter blockage caused by the crystalline biofilms of *P. mirabilis* are particularly problematic, since along with painful bladder distension, serious complications may occur including acute pyelonephritis, calculus formation, and bacteraemia. Until now, management of the problem has been to treat the problem after it has manifested. However, with the advent of this new sensor, clinicians will have the opportunity to predict and therefore manage conditions prior to clinical symptoms occurring.

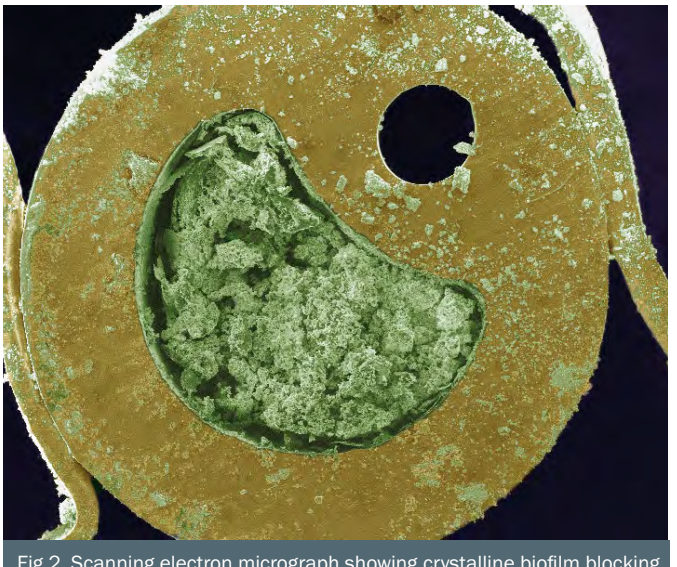

Fig 2. Scanning electron micrograph showing crystalline biofilm blocking the lumen of a urinary catheter.

Professor David W Williams

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Professor Williams (DW) is the Lead of the Oral and Biomedical Sciences research theme and is a principle investigator within the Microbial Diseases research group.

His research interests primarily focus on microbial biofilms and human infection. Over 65% of hospital infections have a biofilm origin and their treatment is highly problematic given their high resistance to antimicrobials. Unsurprisingly, biofilm research is highly important and timely given global concerns over the emergence of antimicrobial resistance. On-going projects are studying biofilms in ventilator-associated pneumonia, catheter associated urinary tract infection, and denture stomatitis. He has access to a dedicated biofilm research laboratory which houses a range of flow cells and bioreactors to enable biofilm study.

Key Publication:

Mariyaselvam, M. et al. 2017. Endotracheal tubes and fluid aspiration: An in vitro evaluation of new cuff technologies. BMC Anesthesiology, 17:36.

Full list at: www.cardiff.ac.uk/people/view/39506-williams-david

Professor Mike Lewis

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Professor Lewis (ML) is Professor of Oral Medicine in the School of Dentistry. He served as Dean of Dentistry and Head of the School of Dentistry (2010-2017). He is Director of the Clinical Board for Dentistry of Cardiff & Vale University Health Board. He holds an honorary NHS position as Consultant in Oral Medicine.

His research interests for more than 30 years have involved clinical and laboratory based aspects of orofacial bacterial, candidal and viral infections. ML has on-going research projects in the involvement of biofilms in ventilator-associated pneumonia and denture stomatitis (erythematous candidosis). In addition, he presently has active studies exploring the appropriate usage of antimicrobial agents in primary dental care practices within Wales and the antibiotic prescribing for treatment or prophylaxis of dental infections in the secondary care dental hospital in the UK.

Key Publication:

Marino P, et al. 2017. Community analysis of dental plaque and endotracheal tube biofilms from mechanically ventilated patients. J Crit Care 39: 149-155.

Full list at: www.cardiff.ac.uk/people/view/39465-lewis-michael

Professor Mark Waters

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Mark Waters is Professor of Biomaterials and a Director of MBI (Wales) Ltd, an R&D lead University spin-out company specializing in the formulation of custom silicone elastomers.

He has over 25 years' experience in the area of biomaterials and in particular in the development of novel silicone elastomeric materials. Recent research has focussed on the development of antimicrobial silicone materials and biosensors for detecting the early onset of bacterial infection. This work has led to a patented sensor which gives an early warning of impending urinary catheter blockage caused by the prevalence of urease producing bacteria in the bladder.

Key Publication:

Payne, T et al. 2015. The evaluation of new multi-material human soft tissue simulants for sports impact surrogates. J Mech Behav Biomed Mater 41:336-56.

Full list at: www.cardiff.ac.uk/people/view/183030-

Dr Xiao-Qing Wei

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Dr Xiao-Qing Wei is a Senior Lecturer. He has a Medical degree from the School of Medicine of Peking University in Beijing, China, and worked in Beijing Youan Hospital as a clinician. He subsequently received a PhD in Immunology from the University of Glasgow, UK, where he remained as a postdoctoral research fellow until moving to Cardiff in 2004.

Cytokines play a pivotal role in controlling the outcome of infectious and inflammatory diseases by regulation of host innate and adaptive immunity. My research has focused on understanding the role of some important pro-inflammatory cytokines, such as IL-18, IL-12, IL-23, IL-27 and a novel anti-inflammatory cytokine, IL-35, in the disease process in order to find practical ways to regulate host immune responses for disease treatment.

Key Publication:

Shi GN, et al. 2017. Enhanced antitumor immunity by targeting dendritic cells with tumor cell lysate-loaded chitosan nanoparticles vaccine. Biomaterials 113: 191-202.

Full list at: www.cardiff.ac.uk/people/view/39509-wei-xiao-qing

Dr Melanie Wilson

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BDS Queens University Belfast (QUB); BSc (Hons) Medical Microbiology, QUB; Fellowship in Dental Surgery, London; PhD University of Wales College of Medicine; Fellowship Royal College of Pathologists. MRC Clinical Fellowship; currently Senior Lecturer and Honorary Consultant in Oral Microbiology.

The main focus of my research has been the application of molecular methods to the study of complex microbial communities, including dental plaque, the chronic wound microbiota, bacteria associated with oral cancer and, more recently, the biofilms involved in community and ventilator associated pneumonia. Other research interests relate to antimicrobial resistance in orofacial infection, the antimicrobial and antibiofilm effects of probiotics and their products, and host pathogen interactions, for example the interaction of microaerophilic streptococci with extracellular matrix components and Candida species with host tissues.

Key Publication:

Sands, KM et al. 2017. Respiratory pathogen colonization of dental plaque, the lower airways, and endotracheal tube biofilms during mechanical ventilation. J Crit Care 37: 30-37.

Full list at: www.cardiff.ac.uk/people/view/39519-wilson-melanie

Mineralised Tissues

Our research is focused on understanding the biological processes involved in the repair and maintenance of the functional integrity of mineralised tissues and their response to injury and associated pathology. With research expertise in cell biology, matrix biology, biomaterial science and clinical dentistry, our goal is to use our knowledge and expertise to develop novel approaches for tissue repair and regeneration.

http://www.cardiff.ac.uk/research/explore/research-units/mineralised-tissue-group

Our goals are:

- Elucidation of mesenchymal stem cell biology; understanding their heterogeneous nature and harnessing their power for stimulating mineralised tissue formation (bone and dentine).
- Develop novel targeted technologies for the delivery of osseoinductive bioactives and anti-microbials to promote better repair of mineralised tissues.

The mineralised tissues of the oral cavity are important for both overall function and facial aesthetics. Central players in facilitating their repair process are mesenchymal stem cells (MSCs), which differentiate into either osteoblasts or odontoblast-like cells to synthesise bone or reparative dentine respectively. MSCs of dental pulp show great promise as a cell source not only for bone and dentine repair, but other tissues including nerves, muscle, cartilage, heart and liver.

Our research has advanced understanding regarding the heterogeneity of MSCs populations, which vary in terms of their proficiency to synthesise bone, dentine and other tissue types, informing on their utilisation in clinical therapy.

Moreover, repair is orchestrated by a variety of bioactive growth factors, which may be produced by MSCs. Additionally matrix proteins within dentine have also been established as potent stimulators of bone and dentine repair. These bioactive factor sources could be utilised to restore inefficient signalling where repair is compromised - as associated with conditions such as diabetes, osteoporosis and as a general consequence of aging.

In support of these studies, we have developed 3D organotypic culture models to provide high throughput model systems for simulating tissue repair processes and to address the 3Rs in this field of bioengineering

A significant feature of our research has been to consider the microbial burden within the oral cavity that leads dentine / pulp and bone supporting the teeth susceptible to pathological destruction and prevent successful repair. A key focus of our research is in the development of novel targeted delivery technologies for the elimination of such bacterial infections.

Highlights of 2017:

- Dentine matrix proteins can be successfully incorporated into targeted liposomal delivery systems at therapeutic levels to induce chemotactic dental pulp stem cell recruitment, upregulation of osteodentin gene expression and biomineralisation for reparative dentistry.
- We have established manufacturing methods at a commercial production scale for our patented liposomal antimicrobial bone cement technology and have extended the product's shelf-life by optimising freeze-drying protocols. This technology is now in the pre-clinical phase of testing for regulatory approval with an aim of getting the product into clinic over the next 5 years.

Linked Research Centres:

Professor Sloan, Professor Waddington and Dr Ayre are all members of Cardiff Institute for Tissue Engineering and Repair, the Cardiff University Nanosome network and associate members of the Arthritis Research UK Centre for Excellence for Biomechanics and Bioengineering.

Key project summary:

Liposomal delivery systems for antimicrobials and growth factors:

Melling, G.et al., 2018. J Tissue Eng Part A. In Press.
Nishio Ayre, W.et al., 2016.
J Biomed Mater Res B Appl Biomater 104(8):1510-1524.

Background: Liposomes are vesicles consisting of a bilayer of lipid molecules which enclose an aqueous space (Fig 1). Their use as drug carriers dates back to the early 1970s and they have since been widely used for the delivery of anti-cancer drugs, antimicrobials, chelating agents, steroids, vaccines, proteins and genetic material. This is owed to their biocompatibility, long circulation time, ability to encapsulate both hydrophilic and hydrophobic therapeutics and ability to be tailored in terms of size, charge and composition. Existing methods to deliver therapeutics from orthopaedic and dental materials are limited and often suffer from poor release characteristics, reduced mechanical properties and usually require high doses to achieve therapeutic effects. In particular, poor release characteristics when delivering antibiotics is of growing concern due to the increase in antibiotic resistance. Similarly effective delivery of growth factors is often hindered by lack of targeted release and biological degradation. Our current research therefore focuses on using liposomes to enhance local delivery of antibiotics and growth factors for dental and orthopaedic applications.

Discovery: We developed a novel, patented method of incorporating liposomes into polymethylmethacrylate bone cement. This technique resulted in significantly higher amounts of gentamicin sulphate antibiotic being released (22% compared to 9% for commercial cement) over a prolonged 60 day period. Of particular interest are the improvements this system had on fracture toughness and fatigue crack growth rates. Optimisation of the delivery system also revealed that positively charged liposomes further enhances the antimicrobial activity against clinical isolates of *Staphylococcus aureus*, bacteria often implicated in joint replacement failure.

The system was subsequently applied to dental restorative materials as previous research from our group highlighted inclusion of triclosan and chlorhexidine into glass ionomer cements negatively impacts on mechanical properties. Liposomes were able to overcome these limitations by

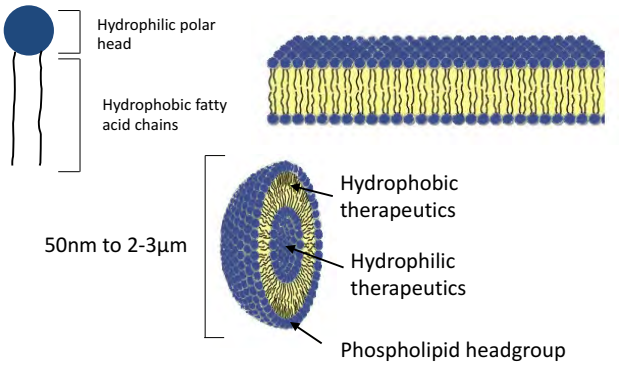

Fig 1. The amphiphilic nature of phospholipids allow it to naturally form bilayer structures and spherical vesicles (liposomes) for drug delivery purposes.

improving the drug-material interactions. Similar results were observed when attempting to deliver hydrophobic Triclosan from thermoset methylcellulose hydrogels. Interestingly, the hydrogel was unable to release Triclosan when incorporated as a powder, however, liposomes allowed long-term release to take place, with minimal impact on viscoelastic and setting properties. This was highlighted by increased antimicrobial activity against *S. anginosus* and *E. faecalis*, bacteria associated with pulpitis and root canal infections.

When investigating the osteogenic properties of different compositions of liposomes, it was found that treating human bone marrow stem cells with phosphatidylserine liposomes alone or in combination with BMP-2 significantly increased the expression of osteogenic markers at key time points (e.g. RUNX2, collagen type I, osteocalcin and alkaline phosphatase). It is thought that phosphatidylserine acts by upregulating endogenous TGF-β1 expression, which in turn increases BMP receptor localisation on the cell surface and therefore canonical signalling through SMAD 1/5/8 pathways. Encapsulating BMP-2 into liposomes also resulted in greater mineralized nodule formation. Similar studies encapsulating demineralised dentine matrix (DDM) highlighted that DDM liposomes promoted the upregulation of osteodentine markers (osteocalcin and RUNX2), mineralisation and chemotaxis when stimulating dental pulp stem cells (DPSCs)(Fig 2).

Importance: The use of liposomes has been shown to not only enhance the release and mechanical properties of biomaterials, but when specific lipids are employed, also induce a beneficial cellular response. This work highlights the potential for these delivery systems to prevent infections and improve the long-term success rates of dental and orthopaedic implants and procedures. This will ultimately help reduce implant revision rates, incurring cost savings for health services and enhancing patient quality of life.

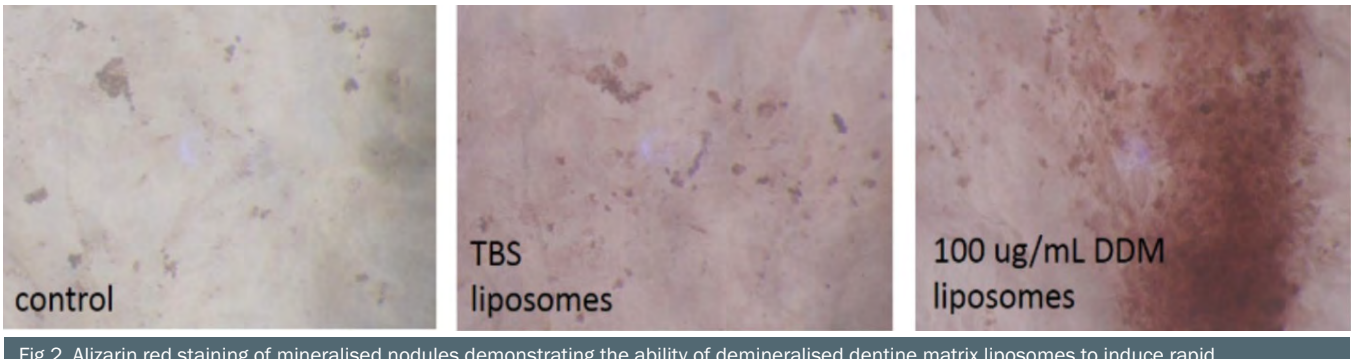

Fig 2. Alizarin red staining of mineralised nodules demonstrating the ability of demineralised dentine matrix liposomes to induce rapid differentiation and minerlisation of dental pulp stem cells. DDS, demineralised dentine matrix; TBS tris-buffered saline.

Professor Rachel Waddington

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PhD Faculty of Medicine, University of Liverpool 1988; BSc (Hons), Biochemistry, University of Birmingham 1984. Winner of Senior Colgate prize (1990) and the MINTIG Mineralised tissue Research Travel Award (1996), both awarded by the British Society for Dental and Oral Research. Currently non-clinical professor in Oral Biochemistry and Associate Director for Engagement, Enterprise and Innovation; co-lead of the Mineralised Tissue Research Group..

Professor Waddington has more than 30 years' experience of research in bone and dentine biology and the role of the extracellular matrix environment in driving repair processes.

Key Publication:

Avery, S. et al. 2017. Analysing the bioactive makeup of demineralised dentine matrix on bone marrow mesenchymal stem cells for enhanced bone repair. Eur Cell Mater 34: 1-14.

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Professor Alastair Sloan

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PhD, Cell Biology Faculty of Medicine & Dentistry, University of Birmingham (1997); BSc (Hons) Biomedical Sciences; University of Wales (1993); Postgrad. Cert. Teaching in Higher Education, University of Birmingham, (2002). Winner of International Association Dental Research Distinguished Scientist Young Investigators Award 2011; British Society Oral and Dental Research MINTIG Research Travel Award (1998). Visiting Professor, 4th Military Medical University, Xi'an, China and China Medical University, Shenyang, China. Currently non-clinical professor of Bone Biology & Tissue Engineering and Head of School of Dentistry; co-lead of the Mineralised Tissue Research Group.

Professor Sloan's research is multi-disciplinary and focussed on the repair and regeneration of mineralised tissues through study of the behaviour and therapeutic use of dental pulp stem cells, ex vivo organotypic culture models and to control infection within these tissues.

Key Publication:

Alraies, A. et al. 2017. Variation in human dental pulp stem cell ageing profiles reflect contrasting proliferative and regenerative capabilities. BMC Cell Biology 18: 12.

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Dr Wayne Nishio Ayre

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PhD, Mechanical Engineering, Cardiff University (2013); BEng Medical Engineering, Cardiff University (2009). Winner of The Worshipful Company of Engineers Mercia Award in Medical Engineering (2014); British Orthopaedic Research Society – International Travelling Fellowship (2016); Cardiff Institute of Tissue Engineering and Repair Young Investigator Award (2015); IADR-PER GSK-Mineralised tissue group prize (2014). Currently Lecturer in Biomaterials, School of Dentistry.

Dr Ayre's research interests is focused on the design, development and testing of medical devices and biomaterials. His particular areas of interest revolve around using lipid coatings and delivery systems to enhance osseointegration and prevent infections of orthopaedic implants and dental material combinations of polymers and antibiotics.

Key Publication:

Nishio Ayre, W. et al. 2016. A novel liposomal drug delivery system for PMMA bone cements. J Biomater Mater Res B Appl Biomataer. 104(8), 1510-1524.

Full list at: www.cardiff.ac.uk/people/view/142785-nishio-ayre-wayne

Dr Leili Sadaghiani

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DDS, Mashhad University-Iran, 1994; MSc (Restorative Dentistry/ Dental Materials) Manchester University, 1997; MFDS RCS (Eng), 2001; FDS (Rest Dent) RCS (Eng), 2010; PhD (Tissue Engineering) Cardiff University, 2015. Recipient of 3M ESPE / Oral and Dental Research Trust Dental Biomaterials Award (2008), Academy of Operative Dentistry Poster Prize (2010), & GSK-Mineralised Tissue Group prize at BSODR (2013). Currently Clinical Senior Lecturer/ Consultant in Restorative Dentistry.

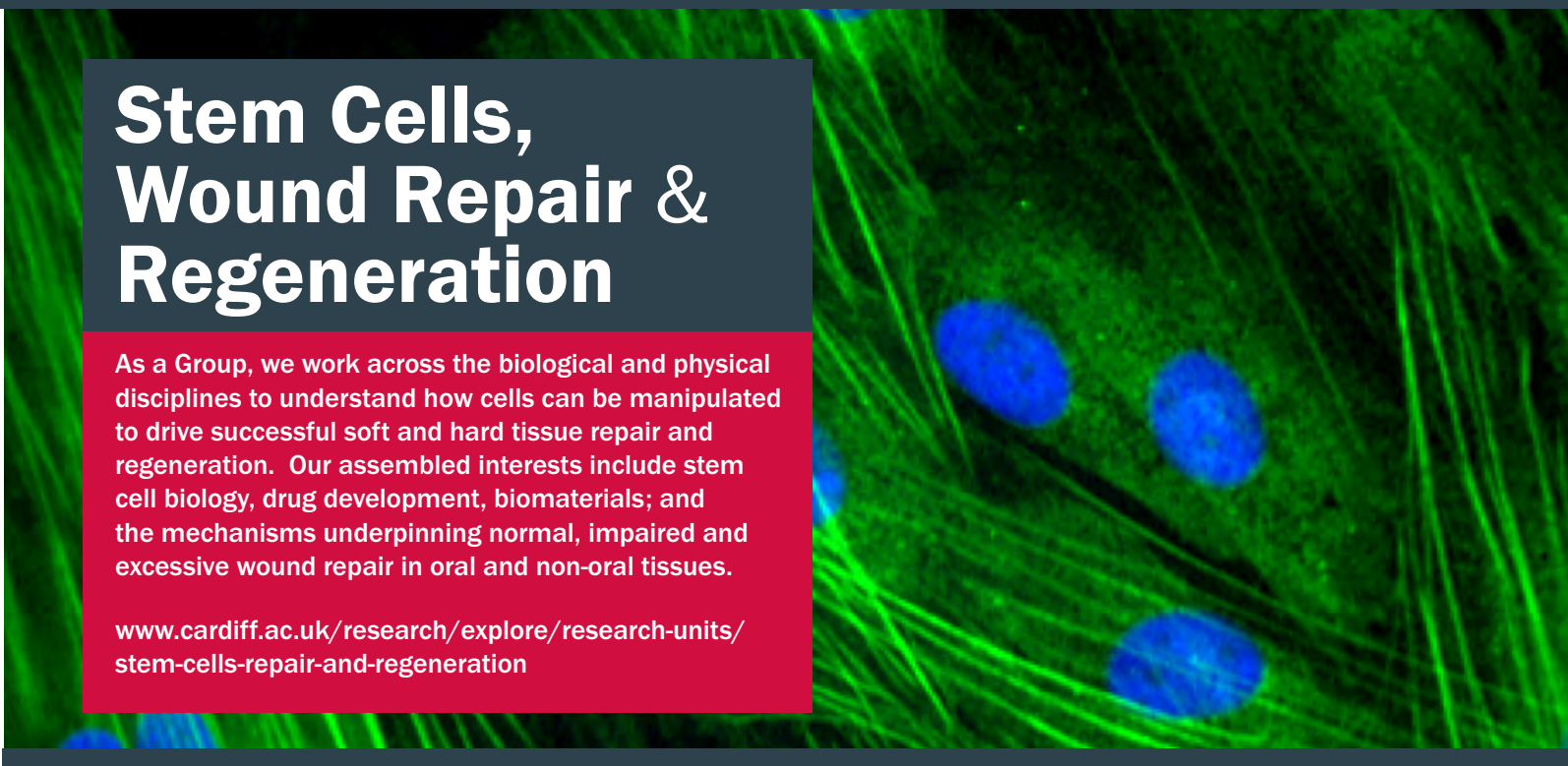
Dr Sadaghiani's research interest is in pulp biology, biological effects of dental materials, pulp stem cells and tissue engineering. Her research activity focuses on investigating the impact of dentine conditioning, application of dentine-derived growth factors, and enamel matrix proteins on inducing reparative dentinogenesis. Research is translational, and focused on vital pulp therapy.

Key Publication:

Sadaghiani, L et al. 2016. Growth factor liberation and DPSC response following dentine conditioning. J Dent Res 95(11):1298-307.

Full list at: www.cardiff.ac.uk/people/view/39423-sadaghiani-leili

Stem Cells, Wound Repair & Regeneration



As a Group, we work across the biological and physical disciplines to understand how cells can be manipulated to drive successful soft and hard tissue repair and regeneration. Our assembled interests include stem cell biology, drug development, biomaterials; and the mechanisms underpinning normal, impaired and excessive wound repair in oral and non-oral tissues.

www.cardiff.ac.uk/research/explore/research-units/stem-cells-repair-and-regeneration

Our goals are:

- To understand the mechanisms underlying the repair and regeneration of oral, dermal and neural tissues, during health and disease.
- To use this knowledge to develop stem cell, pharmaceutical, biomaterial, bioelectrical and other therapeutic strategies to promote wound repair in these and other tissues throughout the body.

Research within Stem Cells, Wound Repair & Regeneration aims to enhance our understanding of the cellular and molecular mechanisms regulating the repair and regeneration of oral, dermal and neural tissues during health and disease. We are particularly focussed on the basic cellular biology of oral- and neural-tissue derived, mesenchymal stromal cells, neural crest progenitor cells and induced pluripotent stem cells. As part of achieving impact on patient health and well-being, we are also focussed on the delivery and translational development of exogenous stem cells as clinical therapies for the treatment of acute and chronic diseases.

Other key areas of research utilise our knowledge of the mechanisms underpinning normal and aberrant wound healing processes to develop pharmaceutical, biomaterial, bioelectrical and other therapeutic approaches, which restore or enhance molecular signalling events and repair/regeneration responses in endogenous and exogenously-applied cells, leading to more successful wound healing outcomes.

Through these research initiatives, our objectives are to facilitate the advancement of novel and more effective treatments, which overcome the inadequacies surrounding existing wound repair therapies and drive improvements in the patient's quality of life.

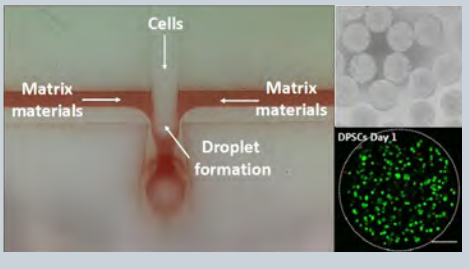
Linked Research Centres:

Professor Stephens and Dr Moseley are founding members of the Cardiff Institute for Tissue engineering and Repair (CITER), an internationally recognised centre of excellence in the field of tissue repair, regeneration and rehabilitation, focusing on interdisciplinary research, education and clinical practice:-

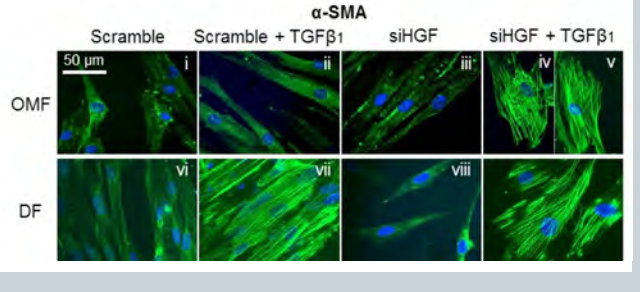
www.cardiff.ac.uk/cardiff-institute-tissue-engineering-repair

Highlights of 2017:

- Utilisation of micro-fluidic technology to quickly and effectively encapsulate dental pulp and neural stem cells within alginate-collagen microcapsules. Stem cells were able to retain their viability and neural differentiation capacity within such microcapsules both in vitro and ex vivo. This offers hope for 'protected' stem cell transplantation for the replacement of damaged tissue in several diseases, including spinal cord injury. (Hidalgo San Jose, L et al. 2018 Tissue Eng Part C methods, in press. TEC2017.0368 in press.)



- Establishment of the key roles which hepatocyte growth factor (HGF) isoforms (full-length, NK1 and NK2) play in mediating enhanced proliferative, migratory and non-scarring properties in oral mucosal fibroblasts (OMFs). Knockdown of HGF expression by siRNA or with transforming growth factor-β1 (TGF-β1), demonstrated that full-length HGF and NK1 isoforms principally mediate enhanced OMF wound healing responses, advocating their use as potential therapeutics for fibrotic conditions (Dally, J et al. 2017. Int j Moi Sci 18, 1843).



Key project summary:

Kindlin-1 regulates keratinocyte electrotaxis:

Zhang, G et al. 2016. Kindlin-1 regulates keratinocyte electrotaxis. J Invest Dermatol 136(11):2229-39.

Background: Kindler syndrome (KS) is an autosomal recessive blistering skin disease resulting from pathogenic mutations in FERMT1. This gene encodes kindlin-1, a focal adhesion protein involved in activation of the integrin family of extracellular matrix receptors. Most cases of KS show a marked reduction or complete absence of the kindlin-1 protein in keratinocytes, resulting in defective cell adhesion and migration. Electric fields (EF) also act as intrinsic regulators of adhesion and migration in the skin, but the molecular mechanisms by which this occurs are poorly understood.

Discovery: We found that keratinocytes derived from KS patients are unable to undergo electrotaxis (Fig. 1), and this defect is restored by overexpression of wild-type kindlin-1 but not a mutant carrying the W612A mutation that prevents kindlin-integrin binding (Fig. 2). Moreover, deletion of the pleckstrin homology domain of kindlin-1 also failed to rescue electrotaxis in KS cells, indicating that both integrin and lipid binding are required for this function. Kindlin-1 was also required for the maintenance of lamellipodial protrusions during electrotaxis via EF-activated β1-integrin. Indeed, inhibition of β1-integrins also leads to loss of electrotaxis in keratinocytes.

Importance: We describe a role for kindlin-1 in sustaining directional migration of keratinocytes in response to physiologic EFs, and demonstrate that the interaction of kindlin-1 with β1-integrins is important to maintain lamellipodia at the leading edge, which is necessary to achieve the full biological response of EF-mediated directional migration. Thus kindlin-1 may act to relay local signals, via PI-3-K, to fully activate β1-integrins to stabilize the newly formed lamellipodia in the direction of the applied EF. Studying the function of kindlin-1 in electrotaxis will not only improve our understanding of skin integrity in KS patients, but also the mechanisms of directional sensing and migration which are required for other biological processes such as embryonic development, inflammation and tumour cell metastasis.

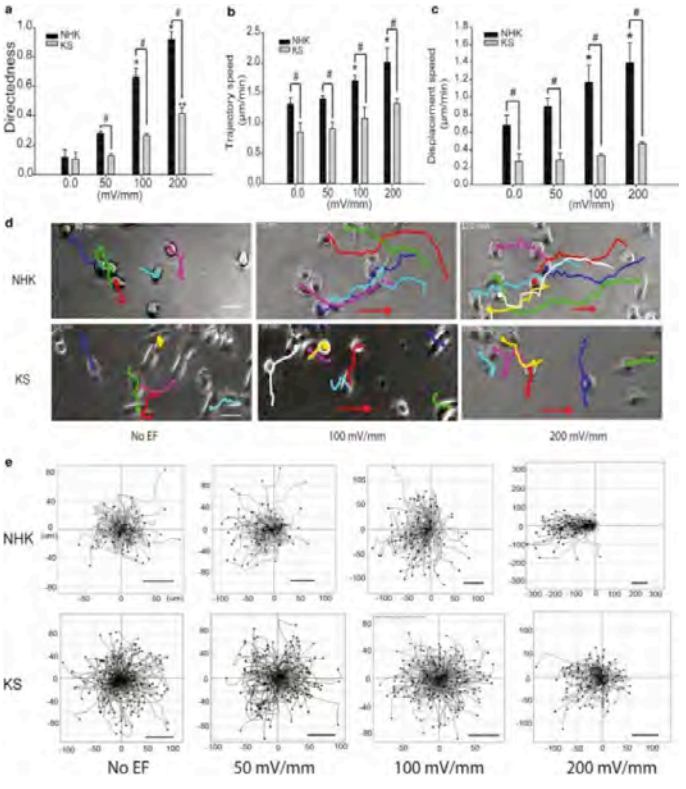


Fig 1. Electrotaxis is impaired in KS cells. (a-c) Graphs show: (a) migration directedness, (b) trajectory speed, and (c) displacement speed of normal human keratinocytes (NHK) and KS cells with EF-specified treatment from 2-hour movies. (d) Representative time-lapse images show movement of NHK (top panel) and KS (bottom panel) in response to indicated EF. The track lines indicate migration paths. (e) The cell migration trajectories of approximately 200 cells of NHK (top panel) and KS (bottom panel) in EF ranges from 0 to 200 mV/mm are presented with starting positioned at origin (0, 0).

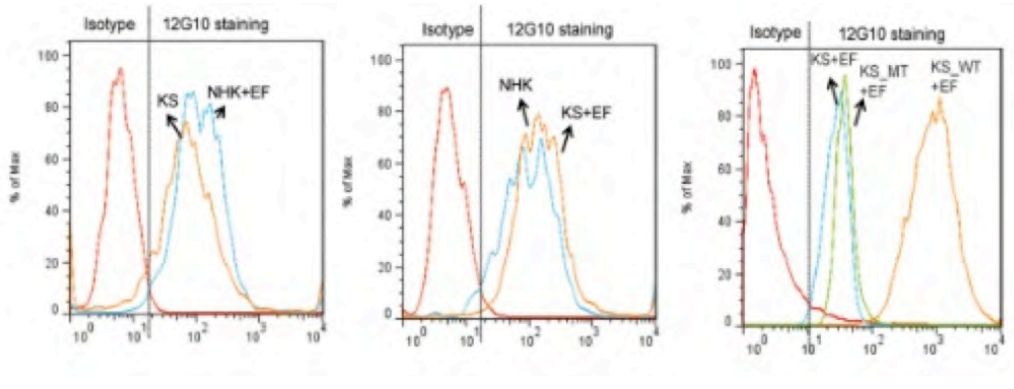


Fig 2. FACS shows an increase of peak fluorescence for active ζ1-integrin in (left) EF-treated NHK but not (middle) EF-treated KS cells; EF-treated KS_WT showed a much stronger fluorescent signal than (right) EF-treated KS and KS_MT cells. WT, wildtype; MT, mutant.

Professor Phil Stephens

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BSc (Hons) Biochemistry and Cell Biology, University of Leeds; PhD Biochemistry and Cell Biology, University of Leeds. Since 2008, Professor of Cell Biology, Cardiff University. Since 2013, Designated Individual HTA Research Licence, Cardiff University. Since 2015, Academic Lead for Cardiff University Biobank. Since 2016, Dean of International & Engagement, College of Biomedical and Life Sciences, Cardiff University. Since 2017, President of the European Tissue Repair Society (ETRS).

Research interests: Oral progenitor cell biology (lineage development/control, immunosuppression, bacterial suppression, tissue healing); dysfunctional (chronic skin wound) biology; development of in vitro systems to replace animals in experimentation; live cell imaging (in vitro and in vivo).

Key Publication:

Roper, JA, et al. (2015). Ultrasonic stimulation of mouse skin reverses the healing delays in diabetes and aging by activation of Rac1. J Invest Dermatol 135:2842-51.

Full list at: www.cardiff.ac.uk/people/view/39411-stephens-phil

Professor Bing Song

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MD, China Medical University, China (1995). PhD, School of Medical Sciences, University of Aberdeen, UK (2004). University Research Fellow, the Royal Society, UK (2005). Since 2009, Professor of Regenerative Medicine, Cardiff University. British Council Global Innovation Initiative award (2014). Since 2017, Director of International, School of Dentistry, Cardiff University.

Research interests: Electric signals regulated stem cell biology (migration, proliferation, differentiation); electric signals promoted neural regeneration and repair (spinal cord injury, Parkinson's disease); remyelination of regenerated neuron with oligodendrocyte progenitor cells; dental pulp stem cells based bioengineered nanoscaffold assisted tissue engineering; stem cell encapsulation; cornea and retina regeneration; electric signals regulated immunisation and wound repair.

Key Publication:

Zhang, G et al. 2016. Kindlin-1 regulates keratinocyte electrotaxis. J Invest Dermatol.136 (11): 2229-39.

Full list at: www.cardiff.ac.uk/people/view/39415-song-bing

Dr Ryan Moseley

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BSc (Hons) Biochemistry, Swansea University, 1991; PhD Oral Biochemistry, University of Wales College of Medicine, 1996. Since 2008, Director of the CITER MSc Programme in Tissue Engineering, Cardiff University. Since 2017, Reader in Tissue Repair, Cardiff University.

Research interests: Mechanisms underlying preferential (e.g. oral mucosa), normal (e.g. skin, bone) and impaired/abnormal tissue repair (e.g. chronic wound, diabetic bone) responses and fibrosis (keloid scars); development of cellular, biomaterial and pharmaceutical strategies for enhanced oral-dermal wound healing and reduced scarring; characterization and development of dental pulp stem cells (DPSCs) for clinical applications.

Key Publication:

McInnes RL, et al. (2014). Contrasting host immuno-inflammatory responses to bacterial challenge within venous and diabetic ulcers. Wound Rep Regen (2014), 22:58-69.

Full list at: www.cardiff.ac.uk/people/view/39455-moseley-ryan

Dental Public Health

Our research focuses on oral health improvement and ranges from clinical trials of preventive dental technologies to studies designed to further understanding of and actions to address oral health inequalities and the delivery of dental care.

www.cardiff.ac.uk/research/explore/research-units/dental-public-health-unit

Our goals are:

To undertake research from a population perspective which will:

- Inform dental health and care need in Wales and beyond
- Contribute to the evidence base for effective preventive dental care
- Change how dental care is delivered to maximise benefit for patients and public.

Whilst oral health has improved dramatically over the past three decades, dental caries (tooth decay) remains a significant public health problem. In common with most chronic health conditions, oral disease correlates closely with social and economic circumstances and inequalities in oral health pose a significant public health problem.

We are involved in a range of research projects which aim to enhance the evidence base for improving oral health and delivering dental care. While our work is based in Wales and we have a particular interest in oral health in the Principality, our collaborations and the outcome of our work is of relevance, locally, nationally and internationally.

We work closely with colleagues in Cardiff and Vale Local Health Board, Public Health Wales and the office of the Chief Dental Officer at Welsh Government. We contribute the oral health workpackage to the Health Care Research Wales funded Centre for Primary and Emergency Care Research (PRIME). We also host the Wales Oral Health Information Unit on behalf of Welsh Government and Public Health Wales.

Highlights of 2017:

- We completed one of the largest ever randomised controlled trials of a preventive dental intervention
- Our work on antibiotic prescribing won the Andy Anderson Memorial Prize at the Annual Meeting of the British Association for the Study of Community Dentistry
- The work that we carried out around toothbrushing in infants and toddlers has featured widely in the media www.bbc.co.uk/news/uk-wales-40827208
- At the International Association for Dental Research, held in San Francisco, California, we reported how the Welsh National Oral Health Improvement programme was working and had positively impacted on oral health.

Linked Research Centres:

Prof Chestnutt leads the dental and oral health work package in the Health and Care Research Wales funded Primary and Emergency Care Research Centre (PRIME) . This multidisciplinary Centre aims to improve the health and wellbeing of people in Wales and internationally through: conducting high quality research on topics of national policy priority which contributes to the evidence base in primary and emergency care; ensuring that research findings are translated into policy and practice.

www.primecentre.wales/

Within the Dental Public Health Unit, we host the Wales Oral Health Information Unit (WOHIU) , led by Maria Morgan. The unit provides independent professional advice, quality assurance, data cleaning, data verification, data analysis and a reporting service on behalf of the Welsh Government commissioned via Public Health Wales. The WOHIU and the Wales Dental Epidemiology Co-ordinator work with the Community Dental Services and the Welsh Government (through the Office of the Chief Dental Officer and the Health Statistics and Analysis Unit in the Statistics Directorate) to deliver the surveys.

www.cardiff.ac.uk/research/explore/research-units/welsh-oral-health-information-unit

Key project summary:

Seal or Varnish? A randomised controlled trial to determine the relative cost and effectiveness of pit and fissure sealant and fluoride varnish in preventing dental decay.

Chestnutt IG, et al. 2017. Health Technol Assess 2017;21(21) https://doi.org/10.3310/hta21210

Fissure Sealant

Fluoride Varnish

Background: Fissure sealants (FS) and fluoride varnish (FV) have been shown to be effective in preventing dental caries when tested against a no treatment control. However, the relative clinical and cost-effectiveness of these interventions is unknown.

Objective: To compare the clinical and cost effectiveness of FS and FV in preventing dental caries in first permanent molars (FPMs) in 6-7 year-olds and to determine their acceptability.

Design: A randomised controlled allocation-blinded clinical trial, with two parallel arms.

Setting: A targeted population programme using mobile dental clinics in schools located in areas of high social and economic deprivation in South Wales.

Participants: 1016 children were randomised 1:1 to receive either FS or FV.

Interventions: Resin-based fissure sealants were applied to caries-free FPMs and maintained at six monthly intervals. Fluoride varnish was applied at baseline and at six month intervals over the course of 3 years.

Main outcome measures: The proportion of children developing caries into dentine (D4-6MFT) on any one of up to four treated first permanent molars after 36 months. Assessors were blinded to treatment allocation. Economic measures established the costs and budget impact of FS and FV and the relative cost-effectiveness of these technologies. Qualitative interviews determined the acceptability of the interventions.

Results: At 36 months 835 (82%) children remained, 417 in the FS and 418 in the FV arms respectively. A smaller proportion of children who received FV (73[17.5%]) developed caries into dentine on a least one FPM compared with FS (82 [19.6%]) OR = 0.84 (CI 0.59 to 1.21) p = 0.35, a non-statistically significant difference between FS and FV treatments. The results were similar when the number of newly decayed teeth OR = 0.86 (CI 0.60 to 1.22) and tooth surfaces OR = 0.85 (CI 0.59 to 1.21) were examined. Trial fidelity was high, 95% received 5 or 6 of the 6 scheduled treatments. Between 74% and 93% of sealants (upper and lower teeth) were intact at 36 months. The costs of the two technologies showed small, but statistically significant differences between arms; NHS costs (including intervention costs) of FS vs. FV was £500 vs. £491) with a mean difference of £68.13 (95% CI 5.63-130.63, p= 0.033) in favour of FV. The budget impact analysis suggests there is a cost saving of £68.13 (95% CI 5.63-130.63, p= 0.033) per child treated, using FV compared with the application of FS over this time period. An acceptability score completed by the children immediately after treatment and subsequent interviews demonstrated both interventions were acceptable to the children. No adverse effects were reported.

Conclusions: In a community oral health programme utilising mobile dental clinics and targeted at children with high caries risk, twice yearly application of fluoride varnish resulted in caries prevention which is not significantly different from that obtained by applying and maintaining fissure sealants after 36 months. Fluoride varnish proved less expensive.

Funding details: This work was funded by the NIHR HTA programme Ref 08/08/104/04

Registration: EudraCT No: 2010-023476-23 ISRCTN ref: ISRCTN17029222

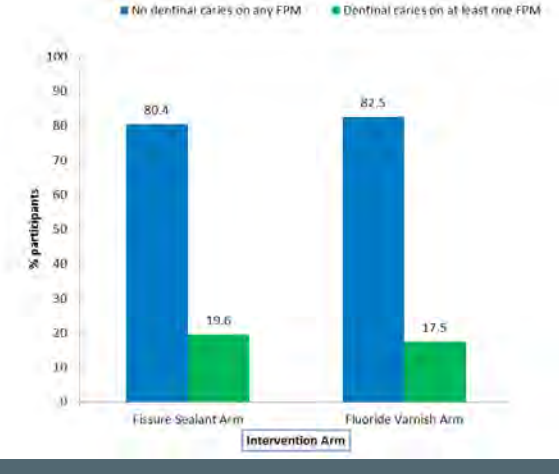
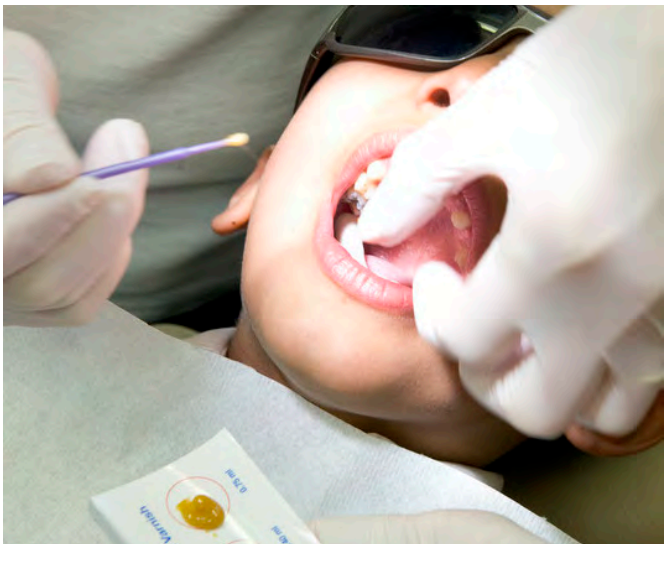


Figure The proportion of children with dentinal caries (D4-6MFT) on any FPM in the trial, at 36 months follow up by intervention arm.



Professor Ivor G Chestnutt

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Ivor Chestnutt is Professor in Dental Public Health at School of Dentistry, Honorary Consultant to Cardiff and Vale University Health Board and is registered as a Specialist in Dental Public Health. He is a graduate of the University of Edinburgh (BDS 1985) and received both his MPH (1995) and PhD (1992)degrees from the University of Glasgow. He holds Fellowships in dental surgery and dental public health from the Royal College of Surgeons of Edinburgh (1990 and 1998), the Royal College of Physicians and Surgeons of Glasgow (2003) and the Royal College of Surgeons, England(2002). Ivor is a Fellow of the Faculty of Public Health (2003) and a Fellow of the Higher Education Academy (2006). He is also the Clinical Director of the University Dental Hospital in Cardiff and is Director of Postgraduate studies in the School of Dentistry.

Professor Chestnutt's research interests include dental health services research, clinical trials of preventive dental products and dental epidemiology.

Key Publication:

Chestnutt IG, et al. 2017. Fissure seal or fluoride varnish? A randomised trial of relative effectiveness, J Dent Res 96 (7), 754-761.

Full list at: www.cardiff.ac.uk/people/view/39480-chestnutt-ivor

Maria Morgan

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Maria Morgan is a public health professional with academic and health service experience. She leads the work of the Welsh Oral Health Information Unit funded by Welsh Government, which involves evaluating Designed to Smile, the national child oral health promotion programme. She also contributes to public health research and education and works part-time as public health specialist for Public Health Wales.

Three main themes make up her research interests: public health nutrition, which continues early MPhil research; public health, both generic and dental, and dental epidemiology.

Key Publication:

Monaghan N. and Morgan M. 2017. What proportion of caries into dentine at age 5 is present at age 3? Community Dental Health 34, 93–96

Full list at: www.cardiff.ac.uk/people/view/39445-morgan-maria

Dr Anwen Cope

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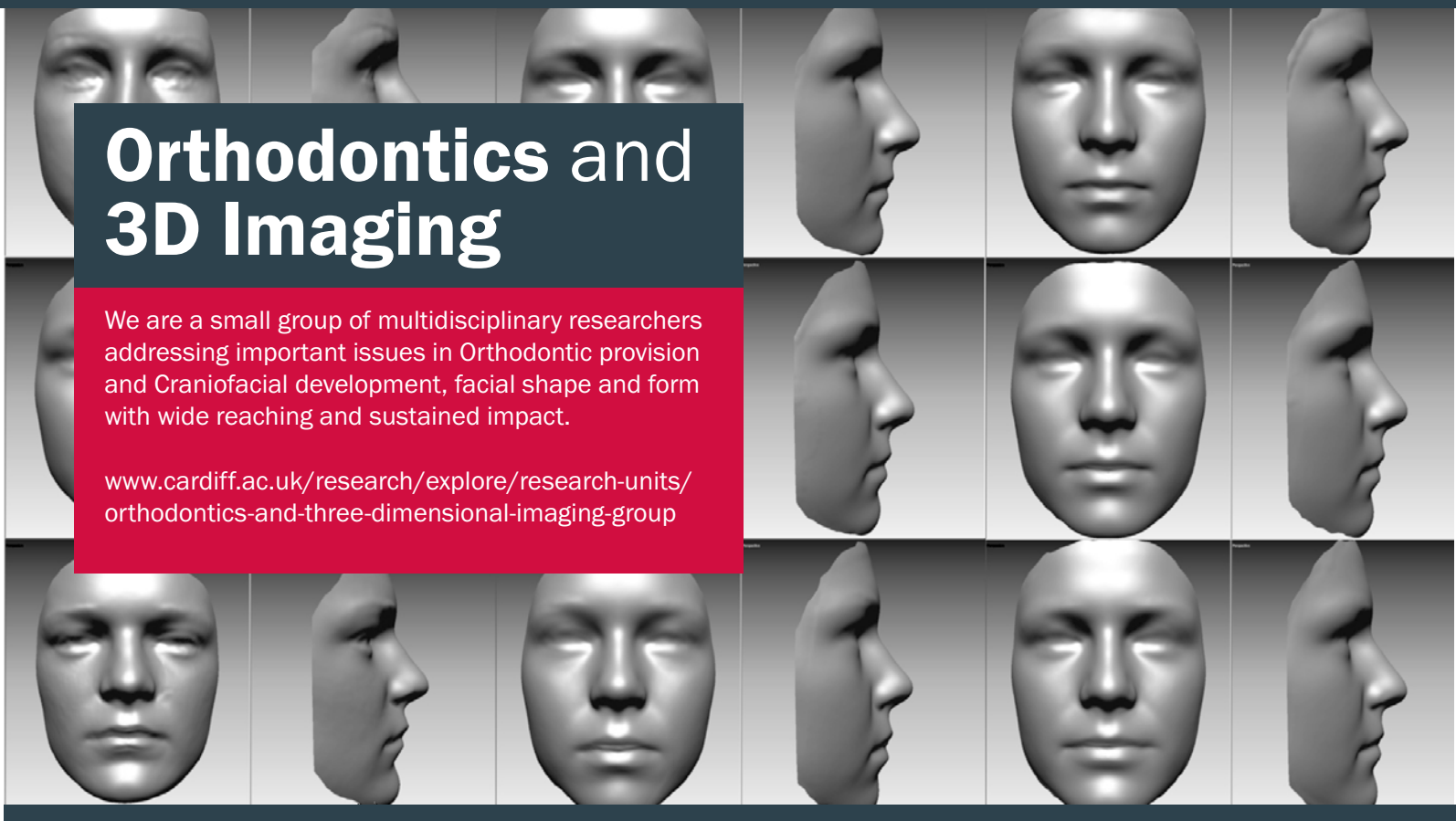
BDS, 2009, Cardiff University. PhD (Medicine), 2015, Cardiff University. MPH, 2018, Cardiff University. Currently holds a Health and Care Research Wales Clinical Research Time Award. Since 2015, an Honorary Clinical Lecturer in Dental Public Health in Applied Clinical Research and Public Health, School of Dentistry, Cardiff University, UK.

My research focuses on how antibiotics are used in the management of acute dental problems in primary care and factors influencing care-seeking behaviour during episodes of dental problems.

Key Publication:

Cope AL, et al. 2016 Antibiotic prescribing in UK general dental practice: a cross‐sectional study. Community Dent Oral Epidemiol 44: 145–153
Full list at: www.cardiff.ac.uk/people/view/337589-cope-anwen



Orthodontics and 3D Imaging

We are a small group of multidisciplinary researchers addressing important issues in Orthodontic provision and Craniofacial development, facial shape and form with wide reaching and sustained impact.

www.cardiff.ac.uk/research/explore/research-units/orthodontics-and-three-dimensional-imaging-group

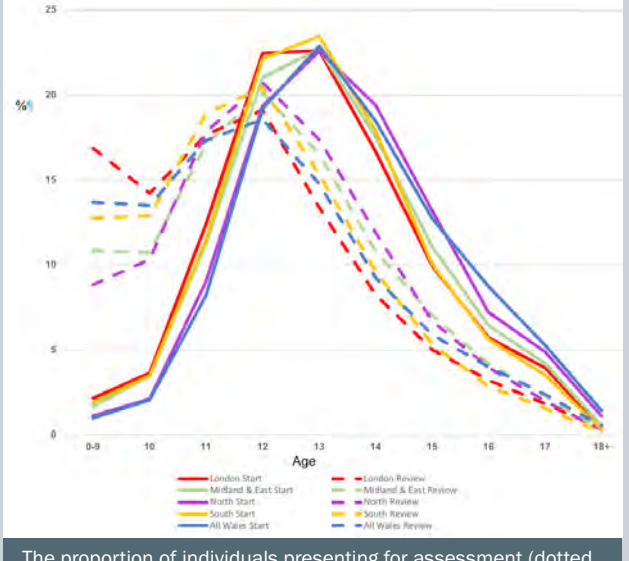
Our goals are:

- **Orthodontics**
  To improve the planning and delivery of the orthodontic services so that they are both cost-efficient and cost-effective.
- **3D imaging**
  To fully explain facial variation (biological make-up, anatomy, facial surface morphology and function) to inform a fully functioning biomechanical head model which is of value to improve healthcare interventions, improve wellbeing and quantify facial variation for face-wear, facial identification/forensics and computer interface industries

Highlights of 2017:

- **Orthodontic provision**
  A review of our 2008 recommendations for orthodontic provision was undertaken:
  gov.wales/topics/health/professionals/dental/orthodontics
  The number of orthodontic providers has been reduced from 133 to 82, also the number of assessments reduced by 10,694 leading to an increase (n=669) in the number of orthodontic treatments to a total of 9660 patients for a cost of £13,385,493. In short, the cost-efficiency of the orthodontic service has been greatly improved.

- **Waiting lists**
  A review into orthodontic waiting lists has highlighted wide variation in orthodontic practice record keeping, with some orthodontic practitioners having over capacity and others under capacity for treatment. We have recommended that waiting lists should be standardised throughout Wales and the information shared with Health Boards. Orthodontic treatments are undertaken at an older age in the North and Wales compared to other regions in England and Wales, prompting our recommendation that the waiting lists and the age of treatment starts should be monitored annually to track trends and improve efficiencies.



The proportion of individuals presenting for assessment (dotted line) and treatment (solid line) for the various regions in England and Wales. All treatments in England and Wales start within a 6 to 9-month period and assessments within a 12-month period.

Key project summary:

Genotype – phenotype association of the face

Djordjevic J, et al., 2016. PLoS One 11(9):e0162250;
Farnell D, et al. 2017. Commun Comput Inform Sci 723: 674-85;
Abbas H, et al., 2018. Comp Visual Media 4: 17;
Howe LJ, et al. 2018. bioRxiv, Cold Spring Harbor Laboratory 2018: 255901.

Background: Although human faces contain the same components, eyes, nose, lips, cheeks, forehead and chin, the relative position of these features as well as their individual shapes can vary widely. We have previously identified genetic and environment associations with facial features which will give rise to subtle facial variations.

Population variation

Discovery: We have explored the subtle facial differences in multilevel principal component analysis (mPCA) in 4 populations (Croatia, England, Finland, and Wales) and identified subtle patterns of facial shape, discriminating between the sexes and countries (Fig. 1).

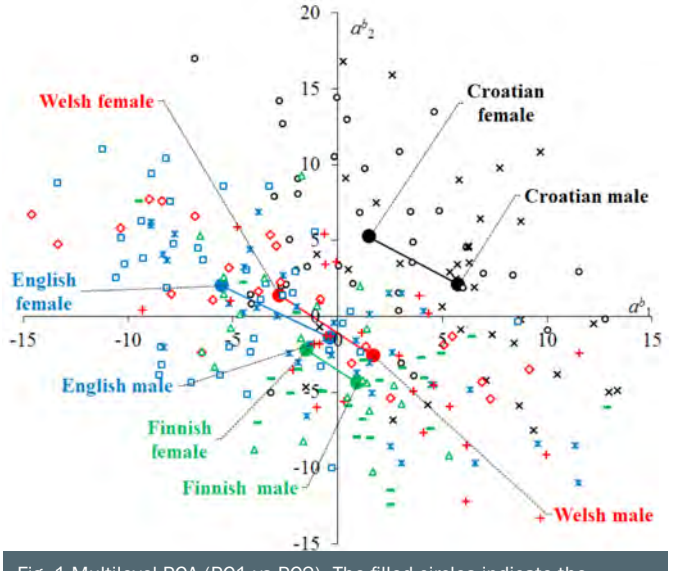


Fig. 1 Multilevel PCA (PC1 vs PC2). The filled circles indicate the centroids, whereby females and males from the same country are linked by a line following a similar trajectory.

The combination of the 3D facial features using geodesic distances provides a male/female classification accuracy of 89%. They also show that nose-related traits provide the most discriminative facial feature for sex classification, with the most discriminative features lying along the 3D face profile.

In a multicentre collaboration along with Bristol University we used bidirectional Mendelian randomization (MR) to test the hypothesis that genetic liability to non-syndromic cleft lip/palate (nsCL/P) is causally related to implicated facial phenotypes. We found strong evidence, using Polygenic Risk Scores (PRS) of genetic overlap between nsCL/P and philtrum width; a 1 standard deviation increase in nsCL/P PRS was associated with a 0.10 mm decrease in philtrum width (95% C.I. 0.054, 0.146; P = 0.00002).

Importance: The mPCA has the potential to discriminate subtle differences in population groups who have undergone different treatment modalities.

Genotype – phenotype associations

Discovery: With Bristol University, we were the first to identify the PAX3 gene association with the prominence of the nasal root and this has subsequently become a validation prerequisite for future Genome Wide Association Studies (GWAS) in this area. Genetic factors can explain more than 70% of the phenotypic facial variation in facial size, nose (width, prominence and height), lips prominence and inter-ocular distance. A few traits have shown potential dominant genetic influence: the prominence and height of the nose, the lower lip prominence in relation to the chin and upper lip philtrum length. Environmental contribution to facial variation seems to be the greatest for the mandibular ramus height and horizontal facial asymmetry.

In addition, we work closely with CUBRIC (Professor Derek Jones), Computer Science (Professors David Marshall and Paul Rosin) and Engineering (Dr Hanxing Zhu) in Cardiff University to determine facial muscle fibre orientation and develop active biomechanical models to simulate facial surgery (Fig. 2).

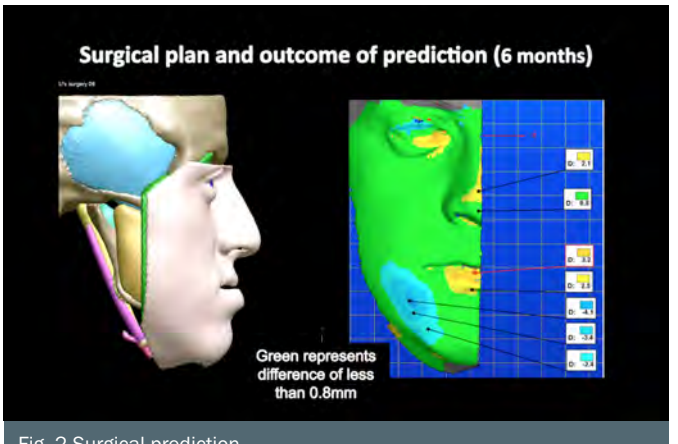


Fig. 2 Surgical prediction
hml.cardiff.ac.uk/Play/1617; https://itunes.apple.com/gb/book/3d-imaging/id974985609?mt=13

Importance: It is clear that some facial traits are dominant in families and tend to be passed on from one or both parents to their offspring. The heritability of father and offspring facial features are currently being explored further with Peter Claes in Leuven, Belgium funded by Cardiff / KU Leuven Universities collaborative initiatives. Understanding of genetic contributions to facial shape will ultimately allow us to develop better models for prediction of treatment outcome.

Professor Stephen Richmond

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BDS (1979), DOrth, RCS (1984), MScD (1984), FDS,RCS (Ed) (1985), CHT, RCS (1989), PhD (1990), FDS.

Research interests: Wide variety of research involving orthodontic provision, orthodontic treatment need and outcomes as well as the interface with many disciplines using 3D facial imaging.

Key Publication:

Richmond S. Review of the Orthodontic Services in Wales 2008-09 to 2015-16, Cardiff University 14th Dec 2016. (http://gov.wales/topics/health/professionals/dental/orthodontics/?lang=en).

Full list at: www.cardiff.ac.uk/people/view/39436-richmond-stephen

Dr Alexei Zhurov

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BSc Applied Maths, MIPT (1988), MSc Applied Maths, MIPT (1990) Dolgoprudny, Russia. PhD Applied Maths, IPM RAS, Moscow, Russia1995. 2001-present Research Officer, Biomechanics and 3D Imaging Applied Research and Public Health.

Research interests: Three-dimensional analysis of the human face contact biomechanics, biomechanics of soft tissues, FEM simulation. Theory of heat and mass transfer and chemical hydrodynamics. Nonlinear differential equations, exact solutions. Dynamical systems, computer algebra.

Key Publication:

Djordjevic J, et al. 2016 Genetic and Environmental Contributions to Facial Morphological Variation: A 3D Population- Based Twin Study. PLoS One. 1;11(9):e0162250.

Full list at: www.cardiff.ac.uk/people/view/39394-zhurov-alexei

Dr Damian Farnell

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BSc (Mathematical Physics) Departments of Mathematics and Physics, UMIST, 1991. PhD ("Integrable and Non-Integrable Quantum Arrays") Department of Mathematics, UMIST, 1994. Post-Doctoral Research Associate, Universities of Manchester, Leeds, Munich, and Cologne, 1996-2003, 2007-2011. Lecturer of Ophthalmic Imaging, St. Paul's Eye Unit, Royal Liverpool University Hospital Trust, University of Liverpool, 2003-2006. Senior Lecturer of Mathematics, Division of Mathematics and Statistics, University of South Wales, 2011-2014. Senior Lecturer of Medical Statistics, School of Dentistry, Cardiff University, since 2014.

Medical imaging and image processing, Pedagogy research, especially relating to mathematics and statistics teaching, Numerical biosimulation, Quantum magnetism, Quantum many-body theory.

Key Publication:

Farnell, DJJ, et al. 2017 Initial results of multilevel principal components analysis of facial shape. In Medical Image Understanding and Analysis 21st Annual Conference, Springer, Commun Comput Inform Sci 723: 674-685.

Full list at: www.cardiff.ac.uk/people/view/39526-farnell-damian

Alcohol and Violence

Through practical research on alcohol-related harms and violence, our leading academics, working in collaboration with external partners and organisations, have helped to understand, monitor and alleviate the causes of alcohol-related harms and violent behaviour.

www.cardiff.ac.uk/violence-research-group

Our goals are:

- To understand the causes and effects of alcohol misuse and violence and to produce real-world applications to prevent it;
- To evaluate alcohol-related harms and violence prevention initiatives, working with service providers - health agencies, social services, criminal justice agencies, local governments and third sector organisations;
- To evaluate the effectiveness of interventions designed to reduce the psychological, social and economic impacts of alcohol misuse and violence; and
- To translate effective innovations into local, national and international policy and practice.

The Alcohol and Violence Research Group draws on expertise from across Cardiff University. The strength and reputation of the group comes from its interdisciplinary research across the fields of psychiatry, public health, dentistry, criminal justice, police, psychology, materials science, computer science and economics; and its extensive record of innovation and contributions to policy and alcohol-related harms and violence prevention.

Linked Research Centres:

Professor Simon Moore is the Co-director of the Crime and Security Research Institute, which draws expertise from the Universities' Police Science Institute, the Alcohol and Violence Research Group, and the Data and Knowledge Engineering Group.

www.cardiff.ac.uk/crime-security-research-institute

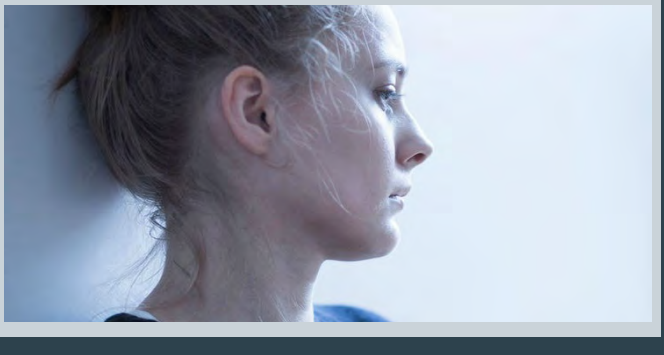
The Alcohol and Violence Research Group also works closely with DECIPHer, the Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement. DECIPHer has a particular focus on developing and evaluating multi-level interventions that will have an impact on the health and well-being of children and young people.

decipher.uk.net/

Highlights of 2017:

- A new study published in the Journal of Public Health has found that consuming more than one UK standard unit of alcohol per day is detrimental to cognitive performance, and is more pronounced in older populations.
- The concept and examples of Alcohol Intoxication Management Services and an outline of the services' evaluation project are published in the Emergency Medicine Journal and used in the discussion of the NHS England's plan to set up these services across England in 2018.
- The Academy of Medical Royal Colleges, the Chartered College of Teaching, and the College of Policing have signed and published an evidence 'Magna Carta', which declares that these institutions expect all members to take full account of evidence and evidence-informed guidance in their daily decisions and advice to individuals and organisations.
- A study which discovers that deprivation makes adolescent girls six times more likely to suffer violence-related injury than girls in affluent areas is published in the Journal of Public Health.

Page et al., 2017. J Public Health, in press (doi: 10.1093/pubmed/fdx073)



Key project summary:

Evaluating the Diversion of Alcohol-Related Attendances (EDARA): An Evaluation of Alcohol Intoxication Management Services (AIMS).

Irving, et al. 2017. Emerg Med J, in press 10.1136/emermed-2016-206451

Background: Urgent and emergency care services in the UK face a substantial burden from patients who are intoxicated by alcohol. Approximately 70% of attendances at Emergency Departments (EDs) are alcohol related at peak times. ED attendances for alcohol poisoning in England approximately doubled between 2008 and 2014. Alcohol-related attendances can cause the clinical environment to suffer, decrease physicians' productivity, and increase stress and frustration among staff which causes a detriment to care. Most cases of alcohol intoxication can be resolved without treatment or only require observation and simple supportive care. Patients may be managed more efficiently in lower-dependency settings. Alcohol Intoxication Management Services (AIMS) are designed to receive, treat, and monitor intoxicated patients who would normally use 999 ambulances and emergency department (Fig 1). The EDARA project evaluates the acceptability, effectiveness and cost effectiveness of AIMS, involving observations and interviews with key stakeholders, questionnaire surveys of people using AIMS and people using EDs (as they may benefit through reducing the number of drunk people in shared waiting areas), analysis of AIMS activity and outcomes, comparison of ambulance services and hospital key performance indicators.

Fig 1. Mobile AIMS unit

Results so far: Interviews with AIMS users revealed most perceived the staff and environment of AIMS to be appropriate for their level of need. Interviewees appeared to appreciate the special communication skills of staff in reassuring and managing individual patients and friends. Some AIMS users highlighted concerns around the timing and risk associated with patient discharges. Survey respondents indicated high levels of satisfaction across all aspects of care provided by AIMS. The majority preferred to be treated in the AIMS, compared to treatment elsewhere e.g. ED or going home. Overall AIMS offer an alternative to ED attendance that appear acceptable to users. However, there is marked variation in the services provided.

Importance: Simon Stevens, Head of NHS England, expressed his intention of setting up more AIMS in cities in England in 2018 and results of the evaluation project will help shape such plans.

Professor Simon C Moore

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Professor of Public Health Research, Director of Alcohol & Violence Research Group, Co-director of the Crime and Security Research Institute, publicly appointed by the Welsh Minister for Health as an advisor to the Welsh Government on matters relating to alcohol misuse and substance abuse.

The aim of my research is to translate basic-level, fundamental science and apply it to the real world in order to improve community safety and the health of our communities. My work is multi-disciplinary, crossing psychology, neuroscience, economics, medicine, public health and other disciplines and typically involves practitioners and policy makers. All projects have a clear impact pathway, whether that is to inform policy and practice directly or to seed further work such as an implementation trial. Methods include "big data" data linkage projects, randomised controlled trials, computer modelling and simulation and various other approaches.

Key Publication:

Irving, A.et al. 2017. Managing alcohol-related attendances in emergency care: can diversion to bespoke services lessen the burden? Emerg Med J 35(2), 79-82. (10.1136/emermed-2016-206451)

Full list at: www.cardiff.ac.uk/people/view/39454-moore-simon-c

Professor Jonathan Shepherd

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Professor of Oral and Maxillofacial Surgery. Honorary professor at Deakin University, Australia. Publicly appointed by the Home Secretary as the Academy of Medical Sciences member of the Home Office Science Council. Independent member of the UK Cabinet Office What Works Council. NHS representative on the Welsh Government's ministerial Violence against Women Advisory Board. Founder trustee of the Chartered College of Teaching.

My research on clinical decisions, community violence and the evidence ecosystem has made many contributions to clinical and public policy and to legislation. Prompted by my discoveries I led the development of a prototype community safety partnership which I continue to chair and which was used as a model in the 1998 Crime and Disorder Act which mandated the creation of such partnerships across Great Britain.

Key Publication:

Shepherd JP and Sumner SA, 2017. Policing and public health - Strategies for collaboration. JAMA 317(15): 1525-26

Full list at: www.cardiff.ac.uk/people/view/39410-shepherd-jonathan

Dr Vaseekaran Sivarajasingam

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Reader in Oral and Maxillofacial Surgery. Director of National Violence Surveillance Network of Emergency Departments in England and Wales. Core member of the Welsh Government, Emergency Care Data Set Implementation Group.

My research includes evaluations of public space CCTV and the measurement of injury from violence using Emergency Department (ED) records. This work demonstrates the reliability and validity of hospital data for this purpose. Stemming from this, I have studied violence using panel data relating to socioeconomic, injury and alcohol variables. I am the Director of the National Violence Surveillance Network (NVSN) of 117 EDs in England and Wales which has provided annual reports on trends in violence-related harm since 2000.

Key Publication:

Sivarajasingam, V.et al. 2017. Injury resulting from targeted violence: An emergency department perspective. Crim Behav Ment Health, in press (10.1002/cbm.2066)

Full list at: www.cardiff.ac.uk/people/view/39421-sivarajasingam-vaseekaran

PhD successes

Ana Mafalda Reis

Thesis Title:
Autoantibodies that drive extraintestinal manifestations of gluten-related disorders are developed in the gut

Supervisors:
Professor Daniel Aeschlimann,
Dr Xioa-Qing Wei

Summary:

Gluten sensitivity affects around 1% of the Western population, with ingestion of gluten initiating an autoimmune response in the small intestine of susceptible individuals (Celiac disease). However, gluten sensitivity can present with symptoms/ manifestations other than those related to bowel inflammation, including neurological deficits such as ataxia and neuropathy. Identification of such patients with a predisposition to develop neurological deficits is crucial to prevent irreversible damage to neural tissues.

One of the hallmarks of gluten-related disorders is a robust IgA autoantibody response to transglutaminase 2 (TG2) and other TG isozymes. One such isozyme, TG6, is predominantly expressed by a subset of neurons in the central nervous system and shares enzymatic properties of TG2 (autoantigen in Celiac disease) that have been implicated in pathogenesis. Previous studies also identified TG6 as the primary target of the immune response in patients with cerebellar ataxia due to gluten sensitivity, independent of intestinal involvement.

This project aimed to develop a mechanistic understanding of autoantibody development linked to extraintestinal disease-manifestation, and determine whether autoantibody development to TG6 occurs in conjunction with that to TG2, i.e. in the gut, or if it has an independent origin. Analysis of intestinal biopsies detected, for the first time, the presence of TG6-reactive B-cells and plasma cells in the intestinal mucosa of patients presenting with gluten-related disorders but not in unrelated disease controls. Additionally, innate immune cells were identified as a possible source of TG6 at the intestinal level.

These findings suggest that autoantibodies that drive the extraintestinal manifestations of gluten-related disorders are developed in the gut, lending further support for B cells/plasma cells in the small intestine being centre stage of pathogenesis.

Nor Azlida Binti Mohd Nor

Thesis Title:
The impact of a reduction in fluoride concentration in the Malaysian water supply on the prevalence of fluorosis and dental caries

Supervisors: Professor Ivor G Chestnutt, Professor Barbara Chadwick, Dr Damian Farnell

Summary:

Concerns over increasing levels of fluorosis as a consequence of water fluoridation have lead to a reduction in the concentration of fluoride in the public water supply in Malaysia from 0.7 ppm to 0.5ppm. This study investigated the consequences of this policy decision on the prevalence and severity of dental fluorosis and caries in children. This study involved life-long residents aged 9 and 12 year-olds in fluoridated and non-fluoridated areas in Malaysia (n=1155). In the fluoridated area, children aged 12 years and 9 years were exposed to 0.7 and 0.5 ppm respectively at the times when maxillary central incisors developed. Standardized photographs of maxillary central incisors were blind scored for fluorosis using Dean's criteria. Dental Caries was examined using ICDAS II criteria.

The prevalence of fluorosis (Dean's score≥2) among children in the fluoridated area (35.7%, 95% CI: 31.9%-39.6%) was significantly higher ($p<0.001$) than children in the non-fluoridated area (5.5%, 95% CI: 3.6%-7.4%). Of those in the fluoridated area, the prevalence of fluorosis decreased from 38.4% (95% CI: 33.1%-44.3%) for 12-year olds to 31.9% (95% CI: 27.6%-38.2%) for 9-year olds, although this difference was not statistically significant ($p=0.139$). The mean caries experience in the permanent dentition was significantly lower in the fluoridated area than the non-fluoridated area for both age groups ($p<0.05$). In the multivariate models, the difference of the differences of caries experience between fluoridated and non-fluoridated areas remained statistically significant. This suggests that caries preventive effect is still maintained at 0.5 ppm.

The findings demonstrate that the change in fluoride level from 0.7 to 0.5 ppm has reduced fluorosis and maintains a caries preventive effect.

PhD successes

Rhiannon Griffiths

Thesis Title:
Novel biomarkers for arthritis: The role of P2X7 receptor in transglutaminase 2 export and activation

Supervisors: Professor Daniel Aeschlimann, Professor Arwyn Jones

Summary:

Transglutaminase 2 (TG2)-mediated stabilization of extracellular protein assemblies has a pivotal function in tissue repair. TG2 modifies proteins in several ways, including transamidation, esterification and deamidation of target glutamine residues. There is evidence of increased expression and activity of TG2 in osteoarthritis, which could lead to generation of protein modifications, providing biological markers of disease. The mechanism of TG2 release by cells controls its extracellular activity and is unconventional and enigmatic. Our group has for the first time implicated P2X7 receptor activation in TG2 export [1]. P2X7R has several activation states; ATP stimulation causes ion channel opening, allowing membrane depolarization and Ca^{2+} entry into the cell. Prolonged stimulation leads to membrane pore activity, however the identity of this pore is unknown. A gain-of-function mutation in P2X7R expressed in HEK293 cells shows enhanced TG2 externalization from cells, correlating with increased pore activity, implicating P2X7R itself. Thioredoxin, a TG2 activator, is co-secreted. To confirm the physiological relevance of our findings in innate immune cells, human peripheral blood monocytes were differentiated into macrophages and P2X7R mediated TG2 export assessed. Our investigations into this process are starting to unravel a novel secretory pathway, which constitutes a novel therapeutic target for diseases driven by TG2.

Publication:

Adamczyk, M., Griffiths, R., Dewitt, S., Knäuper, V, and Aeschlimann, D. (2015). P2X7 receptor activation regulates rapid unconventional export of transglutaminase-2. J. Cell Sci. 128(24).

Daniel Morse

Thesis Title:
Denture acrylic biofilms: microbial composition, interaction and infection

Supervisors:
Professor David Williams, Dr Melanie Wilson, Dr Xiao-Qing Wei, Professor Michael Lewis

Summary:

Denture-associated stomatitis (DS) affects up to 60% of denture-wearers and is primarily attributed to the presence of the fungus Candida albicans in biofilms on the denture-fitting surface. The role of the resident oral bacteria toward this disease is unclear, therefore this research aimed to characterise the bacterial oral microbiome in patients with and without DS; and to evaluate the contribution of bacteria within mixed-species biofilms toward the virulence of C. albicans.

Co-culture of oral bacteria with C. albicans in mixed-species biofilms resulted in an enhancement of C. albicans virulence factors such as hyphal formation, and production of hydrolytic enzymes compared with C. albicans-only biofilms. These biofilms also led to increased tissue damage in an infection model, and substantial microbial invasion. The clinical study identified high similarities in the bacterial microbiomes of denture surfaces, but a decrease in the diversity in smokers with DS relative to non-smokers. A significant increase in the number of unique bacterial species was observed in samples of the tongue.

The in vitro modulating capacity of bacteria toward Candida virulence, and the observed species-level differences in bacteria between DS and non-DS patients highlight the need for consideration of the bacterial composition of oral biofilms in the pathogenesis of DS.

Publications:

Morse DJ, Wilson MJ, Wei X, Lewis MAO, Bradshaw DJ, Murdoch C, Williams DW (2018). Denture-associated biofilm infection in three-dimensional oral mucosal tissue models. J Med Microbiol 67(3): 364-75.

Cavalcanti YW, Morse DJ, da Silva WJ, Del-Bel-Cury AA, Wei X, Wilson M, Milward P, Lewis M, Bradshaw D, Williams DW (2015). Virulence and pathogenicity of Candida albicans is enhanced in biofilms containing oral bacteria. Biofouling 31(1): 27-38.

Helen Rogers

Thesis Title:
Candida and host cell interactions associated with colonisation and infection

Supervisors:
Professor David Williams, Dr Xiaoqing Wei

Summary:

Candida is recognised by host immune cells through pattern recognition receptors e.g. dectin-1. The immune cells produce cytokines to drive adaptive immune responses. The type of T-helper (Th) cell response that occurs is an important factor in whether candidal colonisation or clearance occurs.

The focus of this research was to employ in vivo and in vitro models to assess the immune response to Candida albicans. Increased pro-inflammatory Th17 and Th1 responses were evident in denture stomatitis patients based on cytokine profiles. In chronic hyperplastic candidosis (CHC) tissues, significantly higher levels of CD4+, IL-12A+, IL-17A+ and EBi3+ positive immune cells were detected by immunohistochemistry (IHC) compared to control tissues. This finding was indicative of an increased Th17 response in CHC. IHC detection of individual cytokine subunits in cells suggested both IL-35 and IL-12 were present, indicative of Treg and Th1 cell responses, respectively. Challenging a human monocyte cell line and human peripheral blood mononuclear cells with C. albicans resulted in IL-23 expression, indicative of a Th17 response.

Extrapolation of these findings to the host interaction with Candida requires additional clinical studies. This research does however indicate that host recognition of C. albicans leads to a predominantly pro-inflammatory Th17 response.

Publications:

Rogers H, Wei XQ, Lewis MAO, Patel V, Rees JS, Walker RV, Maggio B, Gupta A and Williams DW (2013). Immune response and candidal colonisation in denture associated stomatitis. J Clin Cell Immunol 4: 178.

Rogers H, Williams DW, Feng GJ, Lewis MAO, and Wei XQ (2013). Role of bacterial lipopolysaccharide in enhancing host immune response to Candida albicans. Clin Dev Immunol: 320168.

Wei XQ, Rogers H, Lewis MAO, and Williams DW (2011). The role of the IL-12 cytokine family in directing T cell responses in oral candidosis. Clin Dev Immunol: 697340.

Paola Marino

Thesis Title: Interaction of the Oral Microbiota with Respiratory Pathogens in Biofilms of Mechanically Ventilated Patient

Supervisors:
Professor David Williams, Professor Michael Lewis

Summary:

Mechanically ventilated (MV) patients are at risk of ventilator-associated pneumonia (VAP). During mechanical ventilation the mouth becomes colonised by respiratory pathogens (RP) and the endotracheal tube (ETT) facilitates leakage of oropharyngeal secretions to the lower airways, whilst also supporting a biofilm likely contributing to VAP. This research aimed to establish the relationship between oral microorganisms (OMs) and RP in colonisation of dental plaque and ETT biofilms and the evaluation of intervention strategies to limit RP colonisation.

The microbial composition of dental plaque, ETT biofilms, and non-directed bronchial lavages (NBLs) from MV patients was characterised by culture and molecular methods. RPs were frequently present at all these sites. OMs occurred in ETTs and NBLs. Isolates from these sites in a single patient also were molecularly determined to be the same strains. NGS showed no significant difference between dental plaque and ETT biofilm microbiomes.

In vitro biofilms revealed that OMs increased RP colonisation and associated gene expression. In in vivo studies, toothbrushes and foam swabs were found to be equally efficient at removing dental plaque and improving oral hygiene in MV patients. In vitro investigation found Chlorhexidine to be the most effective mouthwash in combatting biofilms, despite high tolerance by P. aeruginosa.

Publications:

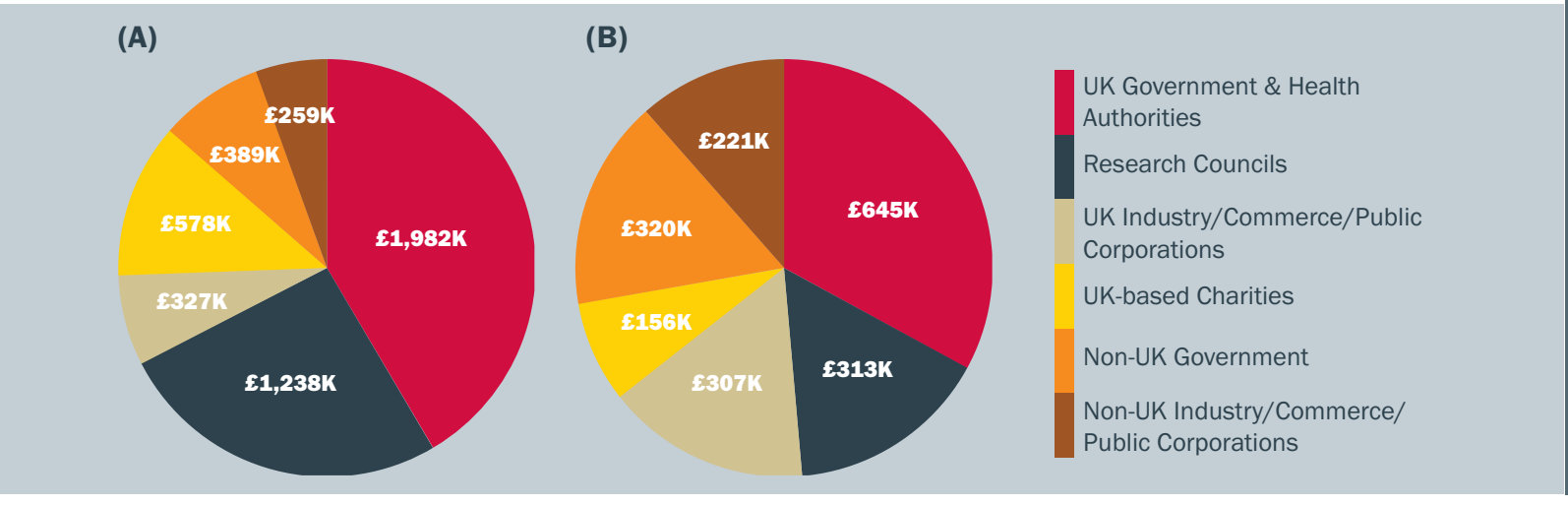
Marino PJ, Hannigan A, Haywood S, Cole JM, Palmer N, Emanuel C, Kinsella T, Lewis MA, Wise MP, Williams DW (2016). Comparison of foam swabs and toothbrushes as oral hygiene interventions in mechanically ventilated patients: a randomised split mouth study. BMJ Open Respir Res 3(1): e000150.

Marino PJ, Wise MP, Smith A, Marchesi JR, Riggio MP, Lewis MAO, Williams DW (2017). Community analysis of dental plaque and endotracheal tube biofilms from mechanically ventilated patients. J Crit Care 39: 149-155.

Research Funding

Overview of active grants

Our research groups were part of collaborative research awards with other Institutions totaling £4,775K (A) for the financial year 2016-17 (Aug-Jul), with £1,964K (B) being allocated to the School of Dentistry. Research funding for the financial year broken down per sector is given below.



Current major grants

List of substantial grants (≥500K) awarded since 2014 that involve our staff:

- Moore S (co-I) et al, Medical Research Council: "DECIPHer: Centre for the development and evaluation of complex interventions for Public Health improvement." £2,936K, 2014-18
- Moore S (PI) et al, Economic & Social Research Council: "Alcohol misuse: Electronic longitudinal alcohol study in communities (ELAStiC)." £978K, 2015-18
- Chestnutt I (co-I) et al, Welsh Government: "Wales Centre for Primary and Emergency Care." £2,700K, 2015-18
- Moore S (PI), Sivarajasingam V et al, The Secretary of State for Health: "An evaluation of alcohol treatment centres: Implications for service delivery, patient benefit and harm reduction" £740K, 2016-18
- Aeschlimann D (co-I) et al, Arthritis Research UK: "Arthritis Research UK Biomechanics & Bioengineering Centre." £2,000K, 2016-20
- Thomas, DW (co-I) et al, Norwegian Research Council/AlgiPharma AS: "Tailored OligoG in the treatment of chronic infectious biofilms." NOK 40,000K (£1,240K, Cardiff award), 2014-17
- Thomas DW (co-I), Hill KE (co-I) et al, Norwegian Research Council/ AlgiPharma AS: "Treatment of chronic infective disease with alginate oligomer-based formulations." NOK 48,000K (£394K, Cardiff award), 2015-18

New grants

New grants awarded to our staff in 2016/17 financial year (grants ≥50K per annum):

- Aeschlimann D (PI), Dewitt S, Knäuper V, Medical Research Council: "Converting targets into biomarker assays for osteoarthritis patient diagnosis and stratification." £50K, 2016-17
- Aeschlimann D (PI), Dewitt S et al, Life Science Research Network Wales: "A new angle to diagnosis and treatment of gluten related disorders." £50K, 2016-17
- Aeschlimann D (co-I) et al, NC3Rs: "Mechanical loading in disease (MeLoDi)." £100K, 2017
- Ferguson E, Medical Research Council: "Accumulation and nephrotoxicity of dextin-colistin conjugates." £407K, 2016-2020
- Moseley R (PI) et al, QBiotics Ltd: "Elucidation of the underlying mechanisms of action by which novel epoxy-tigliane pharmaceuticals promote preferential wound healing responses." £252K, 2016-18
- Moseley R (PI) et al, Medical Research Council: "Repurposing ingenol mebutate as a novel pharmaceutical therapy for dermal fibrosis." £50K, 2016-17
- Moseley R (PI) et al, Wellcome Trust: "Repurposing ingenol mebutate as a novel pharmaceutical therapy for dermal fibrosis." £50K, 2017-18
- Nishio Ayre W (PI), Sloan A, National Institute for Health Research: "Fluorophosphonate biofunctionalisation of biomaterials for orthopaedic applications." £129K, 2016-2018
- Nishio Ayre W (PI) et al, Welsh Government: "Optimisation and toxicity testing of the liposomal drug delivery system for orthopaedic bone cement." £74K, 2017-18
- Sloan A (co-I), Wilson M (co-I) et al, Welsh Government: "Towards the commercialisation of dual action mucoadhesive patches to treat periodontal disease." £74K, 2017-18
- Stephens P, Welsh Government Life Science Hub: "Oral progenitor cells to treat acute kidney injury." £75K, 2016-2017
- Thomas D (PI), Hill K, Powell L, Pritchard M, QBiotics Ltd: "Characterisation of novel therapeutics for the topical treatment of multi-drug resistant wound infections." £284K, 2016-18
- Thomas D (co-I), Powell L (co-I) et al, Welsh Government: "Development of novel BMA-sulfobetaine nanoparticle delivery system to treat chronic wound infections." £50K, 2017-18
- Waddington R, Knowlegde Transfer Partnership with Renishaw PLC: "To transfer and embed new knowledge to develop world-leading innovative manufacturing processes for medical and dental prostheses, using robust assays that identify the behaviour of implant surfaces." £212K, 2016-19
- Waddington R (PI), Nishio Ayre W, Sloan A, Philips GmBH: "Effect of hydrogen peroxide and 456 nm light on dental tissues." £61K, 2016-18

Guest seminar speakers

Andrews R. School of Medicine, Cardiff University, Cardiff, UK: *"Overview of Omics and next-generation sequencing: transcriptomics (RNAseq), epigenetics and chromatin structure (ChIPseq, RRBS), variant discovery (exomeseq)."*

Bradshaw D. GlaxoSmithKline, Weybridge, UK: *"Dental Research: An Industrial & Consumer Perspective."*

De Bank P. Department of Pharmacy and Pharmacology, University of Bath, Bath, UK: *"Bioactive matrices for tissue engineering and wound healing."*

Evans N. Bioengineering Science Research Group, University of Southampton, Southampton, UK: *"Nanoparticle delivery for bone repair."*

Genever P. Department of Biology, University of York, York, UK: *"Stem cells versus stromal cells: Disentangling MSC function."*

Huang J. School of Biomedical Sciences, University of Hong Kong, Hong Kong, China: *"Bacteria engineering to understand biological patterns and tumour targeting."*

Salmon P. Bruker MicroCT, Kontich, Belgium: *"Dental applications of microCT and the latest hardware and software developments."*

Sholugu N. Regenerative, Modular & Developmental Engineering Laboratory (REMODEL), The National University of Ireland, Galway, Ireland: *"Decellularisation of cell-synthesised matrices as a platform model across a range of clinical targets for drug screening purposes."*

Research Awards:

"Cardiff University Innovation and Impact Award for Medicine"	**"Cardiff Institute for Tissue Engineering and Repair, Annual Scientific Meeting, Best Oral Presentation"**	**"Cardiff Institute for Tissue Engineering and Repair, Annual Scientific Meeting 2017, Best Oral Presentation"**
Advanced Therapies Group, School of Dentistry	NG Morris	Elen Everett
"Future research leaders of Wales programme" Welsh Crucible	**"British Society for Oral and Dental Research, Senior Colgate Prize"**	**"Oral and Dental Research Trust Research Award"**
Wayne Ayre	Daniel Morse	Joshua Twigg
"Roger Anderson Poster Prize" The British Association for the Study of Community Dentistry (BASCD)	**"British Society for Oral and Dental Research, Unilever Poster Prize, commendation"**	**"ESE Wladimir Adlivankine Research Prize, European Society of Endodontology"**
Anwen Cope	Joshua Twigg	SS Virdee

"TC White Lecture Award" The Royal College of Physicians and Surgeons, Plymouth

Anwen Cope

Publications 2017

Adamczyk M (2017). Transglutaminase 2 in cartilage homeostasis: novel links with inflammatory osteoarthritis. Amino Acids 49(3): 625-633. doi: 10.1007/s00726-016-2305-1.

Adams R, Hamid L, Binney A, Claydon N, Farnell D, Griffiths B, and Thomas D (2017). A radiographic analysis of anatomical variation at the mandibular of intraoral bone harvesting. Oral Surg, in press doi: 10.1111/ors.12304.

Aeschlimann D, and Knäuper V (2017). P2X7 receptor-mediated TG2 externalization: a link to inflammatory arthritis? Amino Acids 49(3): 453-460. doi: 10.1007/s00726-016-2319-8.

Alemam AAH, Dummer PMH, and Farnell DJJ (2017). A Comparative Study of ProTaper Universal and ProTaper Next Used by Undergraduate Students to Prepare Root Canals. J Endod 43(8): 1364-1369. doi: 10.1016/j.joen.2017.03.038.

Aleksenko L, Tettey Y, Gyasi R, Obed S, Farnell DJJ, and Quaye IK (2017). Maternal demographic and placental risk factors in term low birth weight in Ghana. J Preg Child Health 4: 325. doi: 10.4172/2376-127X.1000325.

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Aresi G, Alfieri S, Lanz M, Marta E, and Moore S (2017). Development and validation of a multidimensional motivations to study abroad scale (MMSAS) among European credit mobility students. Int J Intercult Relat, in press. doi.org/10.1016/j.ijintrel.2017.10.004.

Avery SJ, Sadaghiani L, Sloan AJ, and Waddington RJ (2017). Analysing the bioactive makeup of demineralised dentine matrix on bone marrow mesenchymal stem cells for enhanced bone repair. Eur Cell Mater 34: 1-14. doi: 10.22203/eCM.v034a01.

Bakhtiar H, Mirzaei H, Bagheri MR, Fani N, Mashhadiabbas F, Baghaban Eslaminejad M, Sharifi D, Nekoofar MH, and Dummer P (2017). Histologic tissue response to furcation perforation repair using mineral trioxide aggregate or dental pulp stem cells loaded onto treated dentin matrix or tricalcium phosphate. Clin Oral Investig 21(5): 1579-1588. doi: 10.1007/s00784-016-1967-0.

Bibars ARM, Al-Hourani Z, Khader Y, and Waters M (2017). Effect of thixotropic agents as additives on the mechanical properties of maxillofacial silicone elastomers. J Prosthet Dent S0022-3913(17)30437-7, in press. doi: 10.1016/j.prosdent.2017.06.014.

Bishop FR, Li PHY, Zinke R, Darradi R, Richter J, Farnell DJJ, and Schulenburg J (2017). The spin-half XXZ antiferromagnet on the square lattice revisited: A high-order coupled cluster treatment. J Magn Magn Mater 428: 178–188. doi: 10.1016/j.jmmm.2016.11.043.

Bovay A, Zoete V, Dolton G, Bulek AM, Cole DK, Rizkallah PJ, Fuller A, Beck K, Michielin O, Speiser DE, Sewell AK, and Fuertes Marraco SA (2017). T cell Receptor Alpha Variable 12-2 bias in the immunodominant response to Yellow fever virus Eur J Immunol, in press. doi: 10.1002/eji.201747082.

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Chestnutt IG, Hutchings S, Playle R, Morgan-Trimmer S, Fitzsimmons D, Aawar N, Angel L, Derrick S, Drew C, Hoddell C, Hood K, Humphreys I, Kirby N, Lau TMM, Lisles C, Morgan MZ, Murphy S, Nuttall J, Onishchenko K, Phillips C, Pickles T, Scoble C, Townson J, Withers B, and Chadwick BL (2017). Seal or Varnish? A randomised controlled trial to determine the relative cost and effectiveness of pit and fissure sealant and fluoride varnish in preventing dental decay. Health Technol Assess 21(21): 1-256. doi: 10.3310/hta21210.

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Chuenjitwongsa S, Oliver RG, and Bullock AD (2017). Developing educators of European undergraduate dental students: Towards an agreed curriculum. Eur J Dent Educ, in press. doi: 10.1111/eje.12306.

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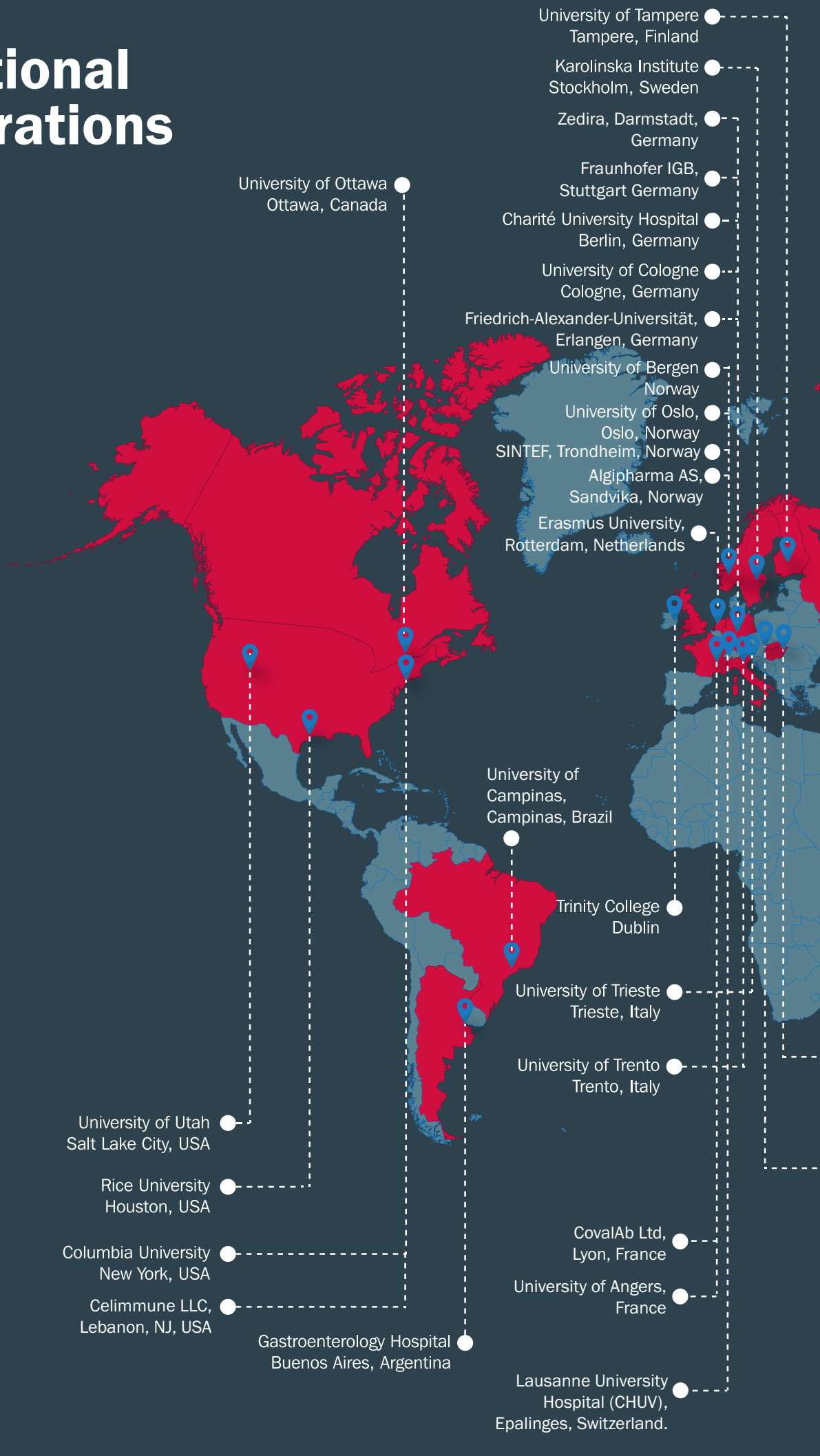
International Collaborations

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