Advancing the prevention, diagnosis, treatment and management of oral diseases.

Annual Report 2012-2013
The **Oral Health CRC** seeks to reduce the economic and social burden of oral diseases on Australians.

We bring together world-class scientific and clinical research teams with Australian manufacturers and established global marketers and distributors.

We commenced operation in January 2010 and our work continues the research undertaken by our predecessor, the CRC for Oral Health Science. We are funded through the Australian Government’s Cooperative Research Centres program and the contributions of our Participants.

The challenge

Oral diseases are among the most prevalent diseases in the Australian community. Almost 60% of 14-year-olds in Australia have had decay in their permanent teeth. More than one in five Australian adults over the age of 65 have lost all their natural teeth, leaving them vulnerable to further health problems. More than 60,000 Australians a year are hospitalised for preventable oral health conditions.

Oral diseases include dental decay (caries), periodontal disease (disease of the gum tissue) and oral cancer.

The cost to the Australian economy of oral diseases is $8.4 billion a year (Australian Institute of Health and Welfare).

A growing body of evidence links oral disease to other health conditions including diabetes, cardiovascular diseases, kidney disease, respiratory diseases, inflammatory diseases and some cancers.
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OVERVIEW 2012 - 2013
RESEARCH PROGRESS

RESEARCH PROGRAMS

PROGRAM 1

Oral and Systemic Diseases

Researching the prevalence of oral diseases and the links between oral health and systemic diseases including diabetes, heart disease, kidney disease and certain cancers.

Oral diseases epidemiology
Expanding understanding of oral disease in our community with particular focus on ‘at risk’ population groups, including children, older people and rural populations.

Oral and systemic diseases epidemiology
Large-scale studies investigating biological links between oral disease and systemic diseases including diabetes, cardiovascular diseases and kidney disease.

Microbiome and biomarkers
Identifying microbiological and molecular biomarkers of oral diseases and of systemic diseases.

PROGRAM 2

Prevention and Early Diagnosis

Improving our capacity to prevent and diagnose oral disease through the development of novel preventive products, diagnostic tools and oral health promotion approaches.

Development of diagnostics
Researching and developing chairside diagnostic tools for the early identification of periodontal disease and dental caries.

Novel preventive products
Developing new over-the-counter preventive products including saliva substitutes, mouthwashes and varnishes that prevent dental caries and periodontal disease.

Functional foods and beverages
Investigating the addition of ‘tooth friendly’ properties in foods and beverages to minimise enamel erosion and prevent dental caries.

Optimisation of nutraceutical development
Continuous improvement of the production processes for CPP-ACP (RECALDENT™).

Oral health promotion
Developing and trialling new approaches to promoting oral health, with a particular focus on ‘at risk’ groups including children, the elderly, people living with mental illness and rural populations.

PROJECTS

Oral diseases epidemiology
Data has been obtained and analysis has commenced on a study of preventable dental hospitalisations of Victorian children over a 10-year period to 2012. Hospitalisations for dental conditions are the largest cause of preventable hospitalisations for Victorians under 20 years of age.

Screening of 11,247 plasma samples has commenced as part of a collaboration with the Baker IDI Heart and Diabetes Institute that is examining associations between periodontal disease and diabetes and heart disease.

Platform technologies have been developed and clinical investigations to identify microbiomic and molecular biomarkers indicative of the onset of oral diseases have commenced.

PROJECTS HIGHLIGHTS

Data has been obtained and analysis has commenced on a study of preventable dental hospitalisations of Victorian children over a 10-year period to 2012. Hospitalisations for dental conditions are the largest cause of preventable hospitalisations for Victorians under 20 years of age.

Screening of 11,247 plasma samples has commenced as part of a collaboration with the Baker IDI Heart and Diabetes Institute that is examining associations between periodontal disease and diabetes and heart disease.

Platform technologies have been developed and clinical investigations to identify microbiomic and molecular biomarkers indicative of the onset of oral diseases have commenced.

Prototype successfully developed and trialled for a chairside diagnostic to detect the pathogen Porphyromonas gingivalis in patients’ saliva and indicate risk of periodontal disease.

Two years since its commercial release by GC Corporation, the fluoride varnish MI Varnish™ is the eighth highest selling tooth varnish in the USA. Varnishes are used by dental professionals to protect against demineralisation and tooth sensitivity. Using Oral Health CRC research, MI Varnish™ is enhanced with CPP-ACP (RECALDENT™) and has been shown to inhibit enamel demineralisation to a greater extent than conventional varnishes.

Prototype of a new saliva substitute with tooth remineralising properties was successfully trialled with cancer patients to measure patient acceptance (people receiving cancer treatment frequently experience reduced salivary flow compromising their oral health).

An intervention to promote oral health among people living with mental illness was developed following a needs analysis. Training is now being carried out with mental health workers around Victoria.

For more information see page 23

For more information see page 27
<table>
<thead>
<tr>
<th>RESEARCH PROGRAMS</th>
<th>PROJECTS</th>
<th>HIGHLIGHTS</th>
</tr>
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<tr>
<td><strong>PROGRAM 3</strong></td>
<td><strong>Novel therapeutics and dental professional products</strong>&lt;br&gt;Researching novel therapeutics for the early treatment of periodontal disease which can currently only be treated once symptoms become clinically visible.</td>
<td>&gt; Completed a prototype of a vaccine formulation against Porphyromonas gingivalis (the keystone pathogen associated with periodontitis). The prototype vaccine can now progress to a Phase 1 Clinical Trial.</td>
</tr>
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<td><strong>Intervention and Management</strong>&lt;br&gt;Developing and trialling novel therapeutics, dental professional products and new models of care to treat oral diseases.</td>
<td><strong>Minimal intervention dentistry</strong>&lt;br&gt;Assessing the clinical and cost effectiveness of new minimal intervention dentistry techniques that promote prevention and non-invasive management of oral disease.</td>
<td>&gt; A novel topical therapeutic gel for the treatment of periodontitis has performed well in several assays and will be further refined in the coming year.</td>
</tr>
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<td><strong>Dental workforce</strong>&lt;br&gt;Investigating new models of care for meeting the oral health needs of the Australian community.</td>
<td>&gt; Successfully completed a ‘proof of concept’ study into the use of tele-dentistry technology including video conferencing and intraoral cameras and commenced preparations to field test the technology in rural nursing homes.</td>
</tr>
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<td></td>
<td><strong>Dental practice-based research network (eviDent)</strong>&lt;br&gt;A consortium of dental care providers established by the Oral Health CRC and the Australian Dental Association (Vic) committed to advancing evidence-based dental care.</td>
<td>&gt; Completed data collection for a large-scale study investigating factors in the success or failure of 8,000 dental implants in 4,128 patients. This project is being conducted by the eviDent dental practice-based research network.</td>
</tr>
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<td><strong>PROGRAM 4</strong></td>
<td><strong>Novel biomaterials and implants</strong>&lt;br&gt;Researching and developing new biomaterials that interact with the biological system of the mouth to assist tooth restoration.</td>
<td>&gt; Oral Health CRC participant GC Corporation launched its Fuji VII-EP (Enhanced Protection) glass ionomer cement in the USA and New Zealand in October 2011. Developed through the Oral Health CRC, continuing testing is demonstrating superior demineralisation protection and antimicrobial activity when compared to a glass ionomer cement without CPP-ACP (RECALDENT™).</td>
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<tr>
<td><strong>Reconstruction and Regeneration</strong>&lt;br&gt;Developing innovative biocompatible dental materials and technologies to strengthen and reconstruct tooth and periodontal tissues.</td>
<td><strong>Tissue engineering and regeneration</strong>&lt;br&gt;Investigating the use of new technologies to repair and regenerate bone and gum tissue.</td>
<td>&gt; An initial study into tissue grafting techniques following implant surgery was completed and will lead to further research into healing outcomes for patients following dental implants.</td>
</tr>
</tbody>
</table>

For more information see page 33

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Outcomes of Major Performance Review

“The CRC is delivering a comprehensive and broad portfolio of translational research that has the potential to further generate significant economic and social benefits.”

The Oral Health CRC’s Major Performance Review was held in April 2013. The review concluded that the productivity and quality of research that is being conducted by the Centre is leading edge and well recognised internationally. It found that the CRC is delivering a comprehensive and broad portfolio of translational research that has the potential to further generate significant economic and social benefits and reduce the impact of oral health disease and disorders both in Australia and worldwide.

Although the CRC is funded to operate for another five years, the review panel recommended that greater attention now be given to transition planning for the Centre’s activities. To this end, the CRC has developed a scoping paper that considers possible planning scenarios including the establishment of an Oral Health Institute within the University of Melbourne.
## Intellectual Property

At the conclusion of 2012-13 the Oral Health CRC held a number of key pieces of patented intellectual property.

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<td>Relates to a method of diagnosing malignant or premalignant lesions, particularly lesions in the oral cavity such as oral squamous cell carcinoma.</td>
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* Denotes patent applications that are subject to an option to license to CSL Limited and Sanofi Pasteur Inc.
@ Denotes patent applications that are licensed to Cadbury Enterprises Pte Ltd
# Denotes patent application being evaluated by industry party.
### Awards

Staff and students in the Oral Health CRC were recognised with a total of 11 awards in the 2012-13 year.

<table>
<thead>
<tr>
<th>Award Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Geoff Adams</td>
<td>Journal of Dental Researcher Reviewer Appreciation for Exemplary Service Awards, International Association for Dental Research</td>
</tr>
<tr>
<td>Dr Nathan Cochrane</td>
<td>Basil Glover Bibby Award for Excellence in Cariology Research, International Association for Dental Research</td>
</tr>
<tr>
<td>Dr Nathan Cochrane</td>
<td>Young Professional of the Year, Board of Professions Australia</td>
</tr>
<tr>
<td>Dr Nathan Cochrane</td>
<td>WM and AV Eggleston Trust Excellence in Teaching Award</td>
</tr>
<tr>
<td>Ms Hasnah Said Gulam Khan</td>
<td>International Association for Dental Research divisional prize</td>
</tr>
<tr>
<td>Mr Thomas Lo</td>
<td>National Elsdon Storey Research award for the Most Meritorious Research, Australian Society of Orthodontists.</td>
</tr>
<tr>
<td>Associate Professor Julie Satur</td>
<td>Public Oral Healthcare Award, Dental Health Services Victoria</td>
</tr>
<tr>
<td>Dr Kheng Tan</td>
<td>International Association of Dental Research (ANZ) Early Career Research Travel Grant</td>
</tr>
<tr>
<td>eviDent project team</td>
<td>Australian Dental Association Annual Award</td>
</tr>
<tr>
<td>eviDent project team</td>
<td>International Association of Dental Research Colgate Community-Based Research Award for Dental Caries Prevention in 2011</td>
</tr>
<tr>
<td>eviDent project team</td>
<td>Best practice-based research poster, International Association of Dental Research, Seattle Conference March 2013</td>
</tr>
</tbody>
</table>
The governance structure of the Oral Health CRC consists of the Governing Board, the Chief Executive Officer and the Deputy Chief Executive Officer. The Governing Board meets quarterly to provide strategic direction and oversight, as well as managing risk and providing audit oversight.

The Board is representative of the Participants in the CRC and also reflects a skills-based selection strategy.

Board members:

Chairman (Independent):
The Hon Dr Michael Wooldridge  
BSc, MMBS, MBA

Directors:

Melbourne Laureate Professor  
Eric Reynolds AO  
PhD Medical Science (University of Melbourne), BSc Hons (University of Melbourne), FICD, FTSE, FRACDS  
Chief Executive Officer,  
Oral Health CRC  
Head, Melbourne Dental School,  
University of Melbourne

Dr Charles Day  
(resigned 25 Sept 2013)  
BA (University of Melbourne),  
BE (Hons) (University of Melbourne),  
DPhil (Oxon), GAICD  
University of Melbourne Commercial Ltd

Dr Mark Hargreaves  
(appointed 25 Sept 2013)  
BSc (Hons) (University of Melbourne,  
MA (Ball State University, USA),  
PhD (University of Melbourne),  
Professor Physiology, University of Melbourne,  
Pro Vice Chancellor (Research Partnerships), University of Melbourne

Mr Chern Chou Yeow  
BSc (University of British Columbia)  
Recaldent™ Business Development Manager  
Cadbury Enterprises Pte Ltd

Dr Neil Hewson  
BSc Hons (Monash University), BDSc (Melbourne University), LDS (Vic), FADI,  
FICD, FPDA  
Independent Director

Mr Peter Hobman  
(resigned 27 May 2013)  
B Tech Biotech Hons (Massey University)  
General Manager, Business Development, Strategy and Corporate Development  
Murray Goulburn Co Op Ltd

Dr Andrew Nash  
PhD Immunology (University of Melbourne),  
BSc (Hons) (University of Melbourne)  
Director of Research, CSL Limited  
Honorary Associate Professor,  
Bio21 Institute at the University of Melbourne

Mr Satoshi Tosaki  
BChem (Shizuoka University)  
General Manager, Products Management Department  
GC Corporation (Japan)

Mr Stephen Haynes  
Managing Director  
GC Australasia Dental Pty Ltd  
Alternate for Mr Satoshi Tosaki
Dr Jason Coonan  
(Alternate Director for Prof Mark Hargreaves appointed 25 Sept 2013)  
BSc Hons (La Trobe University), PhD (University of Melbourne) M IP Law (University of Melbourne), FiPTA, GAICD University of Melbourne Commercial Ltd

Secretary to the Governing Board:

Ms Gilda Pekin  
BEc, FCPA, LLB, CTA, MAICD, ICSA, GIA  
Deputy CEO/Business and Commercial Manager, Oral Health CRC  
Management team

Audit and Risk Committee

Members:

The Hon Dr Michael Wooldridge, Melbourne Laureate Professor Eric Reynolds, Dr Neil Hewson.

Committee Secretary:

Ms Gilda Pekin

The committee meets four times a year.

Management team

Melbourne Laureate Professor Eric Reynolds AO is Chief Executive Officer of the Oral Health CRC, and is the Scientific Leader and Research Director of the Oral Health CRC’s research program.

Ms Gilda Pekin is the Deputy CEO and Business/Commercial manager.

Reporting to the Deputy CEO are the Finance Manager Ms Eva Roden (CPA), Communications Manager (Ms Genevieve Costigan resigned in July 2013 and will be replaced in 2013), and Office Manager Ms Pamela Spencer-Gardner.

Two committees oversee key outputs from Oral Health CRC staff and students: the Education Committee assesses student projects and responsibilities; the Publications Committee reviews journal papers, presentations and reports produced by the CRC to ensure intellectual property is protected and academic integrity is maintained.

Melbourne Laureate Professor Eric Reynolds AO receives Distinguished Scientist Award from the International Association for Dental Research.
Participants

The Oral Health CRC is established as an unincorporated joint venture by way of a Participants Agreement.

Under the Participants Agreement, participants can be classified as either ‘Centre’ Participants or ‘Project’ Participants. Under the Commonwealth Funding Agreement, participants are classified as either ‘Essential’ Participants or ‘Other’ Participants.

The Participants Agreement is between the Centre Participants and allows for them to manage, govern and otherwise participate in the CRC.

The Centre Participants have also established Oral Health CRC Ltd, a public company limited by guarantee, to act as the management company for the Centre and receive Commonwealth Funding on behalf of the joint venture parties under the CRC Management Agreement. Oral Health CRC Ltd is also the exclusive agent of the Centre Participants for the purposes of entering into Project Participants agreements.
Funding
The Oral Health CRC was funded in 2009 under Round 11 in the Commonwealth Cooperative Research Centres Program. Participants in the Oral Health CRC were awarded up to $31.6m over 8.5 years under the Commonwealth Funding Agreement. The Centre commenced operations from 1 January 2010 by way of a grant from the Commonwealth Government together with cash and in-kind contributions from the Participants.

In 2012-13 total funding amounted to $29 million, including $23.6 million in in-kind contributions from Participants.

Funding 2012-13:

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>Commonwealth Funding Agreement</td>
<td>$3,520,000</td>
</tr>
<tr>
<td>Value of Participants’ staff in-kind contributions</td>
<td>$19,210,000</td>
</tr>
<tr>
<td>Participants’ non-staff in-kind contributions</td>
<td>$4,412,531</td>
</tr>
<tr>
<td>Participants’ cash contributions</td>
<td>$1,893,464</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$29,035,995</strong></td>
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</table>
**Intellectual Property and Commercialisation**

**IP management process**

The Oral Health CRC adheres to the National Principals of IP Management for Publicly Funded Research. Our Participants Agreement provides individual participants with rights to commercialise Centre IP that falls within clearly defined IP fields. The Centre also has a Commercialisation Plan that describes the policies relating to ownership, protection and exploitation of IP. The Participants Agreement provides defined and agreed fields within which parties have rights to IP and the Commercialisation Plan defines how those rights will be managed.

CRC Executive Management together with well-trained and commercially-focused researchers readily identify new IP within defined fields, instigate protection of the IP, and bring it to the attention of commercial parties in accordance with the Participants Agreement and the Commercialisation Plan. Once the commercial party has expressed an interest in the IP, it is expected that licensing and royalty arrangements can be negotiated.

If the commercial party does not express interest in adopting the IP, it is available to be considered for utilisation more widely.

**Option to license P. gingivalis IP in periodontal research project**

The research collaboration into the treatment of chronic periodontal disease between The University of Melbourne, CSL Limited and Sanofi Pasteur Inc continues to move ahead successfully. Research is now focused on the development of two products – a vaccine and a topical therapeutic gel. It is envisaged that these two products used in an integrated treatment regime would provide initial treatment and then long-term protection from chronic periodontitis. This novel treatment approach has been patented by the CRC.

The CRC’s commercial agent, Oral Health Australia Pty Ltd, has entered into a Commercialisation Agreement with CSL Limited and CSL Limited has entered into a back-to-back arrangement with Sanofi Pasteur Inc. The Agreement provides for two separate options to license the Centre IP known as the P. gingivalis IP (see the table below). During the option term, all matters relating to patenting and other protection strategies of the patent families subject to option are to be addressed by Oral Health Australia Pty Ltd and CSL Limited by consensus with input from Sanofi Pasteur Inc for some critical decisions.

CSL Limited provides qualified in-house patent attorneys to the Centre to manage the prosecution of patents and project management assistance.

This arrangement leverages the potential of existing IP and provides clarity in relation to responsibilities concerning the management of IP. It also allows for expert input into decisions concerning complex IP and commercial patenting strategies. When options are exercised, management of the IP will fall to CSL Limited with input from Sanofi Pasteur Inc.

The Sanofi Pasteur Inc research team located in Lyon, France is now involved in the vaccine development while the topical therapeutic research is being conducted by the Sanofi team in Boston, USA. The Agreement also provides for strategic oversight of the research and project IP by a Joint Strategic Management Committee comprised of representatives from Oral Health Australia Pty Ltd, CSL Limited and Sanofi Pasteur Inc. The day to day research collaboration between the Melbourne Dental School and CSL Limited in Melbourne and Sanofi Pasteur Inc in Lyon and Boston is managed by a Joint Research Committee. With the challenge of distance and international time zones, regular teleconferences and scheduled face to face meetings of the Joint Research Committee are integral to the success of the collaboration.
**Key IP held by the Oral Health CRC**

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Products

Research carried out within the Oral Health CRC has led to two commercially available products within the life of this current CRC. These two products join a series of products commercialised under the previous CRC (the CRC for Oral Health Science).

MI Varnish™

MI Varnish™ is a fluoride varnish used by dentists to protect teeth against demineralisation and tooth sensitivity. Utilising CRC research, the fluoride varnish is enhanced with CPP-ACP (RECALDENT™) which releases calcium and phosphate ions into the tooth. Research has shown that this enhanced formulation inhibits enamel demineralisation to a greater extent than conventional varnishes.

OH-CRC participant GC Corporation commercially released MI Varnish™ in the USA in February 2012 and it has quickly become the 8th largest selling varnish in a competitive market of 27 comparative products. Researchers in the CRC continue to test the varnish’s efficacy and protective properties.

Fuji VII-EP (Extra Protection) glass ionomer cement

Fuji VII-EP (Extra Protection) is a new glass ionomer cement (GIC) that has been developed through the Oral Health CRC and has been commercialised by GC Corporation. The GIC contains fluoride and CPP-ACP (RECALDENT™) and has been shown to protect adjacent tooth tissue from demineralisation. This novel GIC has been launched in the USA and New Zealand. It is used by oral health professionals on exposed root surfaces to protect against demineralisation and tooth sensitivity.

Intellectual Property and Commercialisation (cont.)
Education and Training

The Oral Health CRC has attracted outstanding students and fosters a culture of engagement and mentoring among students, between academics and students, and between industry parties and students.

**Students**

A total of 34 students completed their studies during the 2012-13 year, taking the total number of student completions at the CRC to 50 since 2010. Over the course of the CRC, there have now been a total of 123 student commencements, including 46 PhD students. A total of 69 students are currently continuing their studies.

<table>
<thead>
<tr>
<th>Total student commencements</th>
<th>PhD</th>
<th>Doctor of Clinical Dentistry</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program 1: Oral and Systemic Diseases</td>
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<td>7</td>
<td>0</td>
<td>14</td>
</tr>
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<td>2</td>
<td>33</td>
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<td>17</td>
<td>17</td>
<td>9</td>
<td>43</td>
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<td>5</td>
<td>26</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>64</td>
<td>13</td>
<td>123</td>
</tr>
</tbody>
</table>
Continuing Professional Development (CPD)

The Oral Health CRC supports the Professional Development (CPD) program that is available to dental professionals around Australia. The CPD program offered 31 days of CPD programs during the year that were attended by more than 525 oral health professionals. The 22 courses offered are run under an agreement between the Oral Health CRC, the University of Melbourne Dental School and the Australian Dental Association Victorian Branch.

The CPD courses are designed to bring the latest clinical and scientific information to oral health providers. During 2012-13, all CPD courses were fully subscribed with many having waiting lists.

Visitor-in-residence program

During the 2012-13 year a new visitor-in-residence program was established with the Board allocating funds in the annual budget to support visiting experts to share their knowledge with students and staff. The first invitee was Professor Richard Darveau, Adjunct Professor of Microbiology and Professor of Periodontics from the University of Washington, USA, who visited the CRC in November 2013. His series of lectures and workshops discussed the innate host response to microbial colonisation and infection – a field of particular interest in understanding the development of periodontal disease.
Communication and Engagement

The Oral Health CRC is committed to communicating the findings and significance of its work to the wider community, and to engaging with the oral health and scientific communities to ensure our work continues to be relevant and at the forefront of international research.

Community
The Oral Health CRC continues to identify opportunities to inform the community of its work and to share its knowledge and understanding of oral health. CRC staff were the subject of a total of 31 media stories and interviews during 2012-13. Our website is visited by close to 3,000 people a month, the largest number of visitors coming from Australia closely followed by the USA, India, United Kingdom, New Zealand, Canada, Singapore, Japan and Iran. The top search phrases used to find our website are Tooth Mousse, Tooth Mousse Plus, Oral Health CRC, Recaldent™ and Oral Cancer.

Oral health professionals
We work closely with professional bodies and public and private dental providers.

Our annual CRC symposium is offered free to oral health professionals around Australia and brings together researchers and practitioners to discuss timely topics. We partner with the University of Melbourne and the Australian Dental Association (Vic) to deliver a well-subscribed Continuing Professional Development program to oral health professionals around Australia.

With the Australian Dental Association we have also established Australia’s first oral health practice-based research network, eviDent. This network is identifying research needs and bringing together oral health practitioners and CRC researchers to collaborate on practice-based research projects. The eviDent network maintains the CRC’s knowledge of current dental practices at the same time as developing the capacity of the oral health workforce to produce and use research findings.
**Scientific community**

The Oral Health CRC is an active participant in the international dental and microbiology research communities. During 2012-13 staff and students from the Centre gave 51 presentations at scientific conferences, presented 28 conference posters, and published 91 journal articles.

The Centre encourages and supports external scientific visitors who can contribute to the depth of the scientific research program and contribute to the collegiate, teaching and scientific activities of the Centre. Visitors during 2012-13 included:

- **Dr William Giannobile**, the Editor of the Journal of Dental Research, August 2012
- **Dr Vincent Meuric**, Clinical Teaching Fellow in Periodontology and Lecturer, Dental School, University of Rennes I, France, 1 October 2011 to 30 September 2012
- **Prof Chris van Weel**, Department of Primary and Community Care, Radboud University Medical Centre, Nijmegen, The Netherlands, October 2012
- **Dr Sebastian Baumgaertel**, Department of Orthodontics, School of Dental Medicine, Case Western Reserve University, Cleveland, Ohio, 31 May 2012 to 30 May 2013
- **Dr Maria Bazzocchi**, University of Bologna, Italy, 1 August 2012 to 31 October 2012
- **Dr Sameera Asipath Edirisooriya**, Faculty of Dental Science, University of Peradeniya, Sri Lanka, 1 March 2013 to 28 February 2014
- **Dr Hamidreza Poureslami**, Department of Pediatric Dentistry, Dental School, Kerman University of Medical Science, Kerman, Iran - 5 March 2013 to 10 April 2013
Oral and Systemic Diseases

Researching the prevalence of oral diseases and the links between oral health and systemic diseases including diabetes, heart disease, kidney disease and certain cancers.

Program 1 consists of three major projects:

- Oral diseases epidemiology
- Oral and systemic diseases epidemiology
- Microbiome and biomarkers

Project managers:

- Associate Professor Rodrigo Mariño
- Mr Geoff Adams
- Professor Dick Wettenhall
- Associate Professor Stuart Dashper

Oral diseases epidemiology

In 2012-13 activities in this project have particularly focused on preventable dental hospitalisations.

Data have been obtained and are currently being analysed for the study ‘Preventable Dental Hospitalisations (PDH) of Victorian Children, 2001/02 - 2011/12’. These dental hospitalisations are the highest cause of all preventable hospitalisation for Victorians under 20 years of age. They are costly to families and to the health system. The distribution and determinants of PDH are being studied and options for prevention identified.

Presentations were made at the IADR General Session in Brazil in June 2012, the Australian Centre for Population Oral Health (ARCPOH) Fluoridation Consensus Conference in Adelaide in August 2012, the Public Health Congress in Adelaide in September 2012 and the National Oral Health Promotion Plan Workshop in Canberra in February 2013. The article ‘Building the links between surveillance, research, and policy and practice’ was published in the journal, Community Dentistry and Oral Epidemiology.

A chapter has also been written for the book Promoting Children’s Oral Health - Theory and Practice that is now in press.

Oral and systemic diseases epidemiology

Over the last two decades there has been a growing understanding of the importance of oral health to people’s general health. Periodontitis is a chronic inflammatory disease associated with specific bacteria in a biofilm that destroys the connective tissue and bone supporting the teeth and can lead to tooth loss.
Emerging epidemiological evidence also suggests associations between periodontitis and various systemic diseases, including cardiovascular disease, diabetes, chronic kidney disease, metabolic syndrome, obesity, rheumatoid arthritis, respiratory diseases, preterm and low-weight births, certain cancers, and Alzheimer’s disease.

This is supported by basic research into the mechanisms involved in these associations. Studies have also shown considerable comorbidity with cardiovascular disease, diabetes and chronic kidney disease. These diseases share with periodontal disease common modifiable risk factors such as tobacco smoking, obesity, physical inactivity, poor diet, high blood pressure and stress.

The Oral Health CRC is continuing to collaborate with the Baker IDI Heart and Diabetes Institute to investigate the possible relationships between diabetes, heart disease and kidney disease with periodontal disease. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab), conducted by the Baker IDI Heart and Diabetes Institute, is the largest Australian longitudinal population-based study examining the natural history of diabetes, pre-diabetes, heart disease and kidney disease. The cohort consists of 11,247 participants who were recruited in 1999 to 2000 and was the first national diabetes prevalence study to be conducted in Australia.

Serum, plasma and saliva antibody responses have been used to diagnose periodontitis, estimate its activity, classification and prognosis, and the success of treatment. Researchers at the Oral Health CRC, and others, have shown that increasing levels of serum antibodies specific for the bacterium P. gingivalis correlate with increasing severity of chronic periodontitis. Furthermore, only chronic periodontitis patients were found to have a P. gingivalis-specific antibody response, indicating that antibody responses to periodontal bacteria are possible biomarkers for chronic periodontitis patients.

Through the Baker IDI the Oral Health CRC has access to the plasma samples collected at the initial AusDiab survey in 1999 to 2000. The baseline AusDiab survey plasma samples are now being screened at the Oral Health CRC for antibodies to the periodontal pathogens. A high throughput ELISA assay pipeline consisting of a Perkin Elmer robotic system (MultiProbe II plus) and plate reader (Victor 3) has been established. The results from the ELISA assays will be combined with demographic and epidemiological risk factor information to study the associations between diabetes, heart disease and chronic kidney disease with periodontal disease.

We have recently established a new research collaboration with the Australian Red Cross Blood Service and the ANZ Intensive Care Research Centre of the Department of Epidemiology and Preventive Medicine at Monash University. With these collaborators the Oral Health CRC is investigating possible associations between the presence of periodontal disease in blood donors and adverse events in patients receiving blood transfusions. Red blood cell (RBC) transfusions are a common lifesaving therapy for patients hospitalised in intensive care units (ICU), with up to 45% of patients receiving at least one RBC transfusion during their ICU stay. However, RBC transfusions have been independently associated with occurrence of adverse events in critically ill patients, with the reasons for this association currently unknown. There is a need to improve the understanding of the association between RBC transfusion and the occurrence of adverse events. Chronic periodontitis may be a relevant disease for transfusion recipients as it is caused by overgrowth of various subgingival plaque bacterial species, particularly P. gingivalis, and can result in asymptomatic bacteraemia. Chronic periodontitis is not screened in blood donors and P. gingivalis is not readily detectable by routine bacterial screening tests.
Microbiome and biomarkers

This project aims to obtain information on the microbiological and molecular biomarkers of oral and systemic diseases such as periodontitis. By identifying molecules which are associated with disease, Oral Health CRC researchers plan to develop a multiplex diagnostic test that will provide early detection and better treatment of diseases.

A major problem in the management of periodontitis is the difficulty of early detection of the disease. Currently, periodontitis is diagnosed retrospectively by clinical observation of tissue damage. The ability to predict imminent disease progression would allow for targeted preventive therapy. Given the seriousness of chronic periodontitis as a major public health problem, there is an urgent need for advancing diagnostic technology. The recent revolution in genomics and the associated development of analytical technologies for disease biomarker discovery, particularly immunodiagnostic and nucleic acid-based microarrays, mass spectrometry (MS) and nuclear magnetic resonance spectrometry (NMR), have created new opportunities for the development of high specificity and high sensitivity diagnostic assays with considerable potential for the early detection of diseases.

We have developed platform technologies for the identification of microbiomic and molecular biomarkers indicative or predictive of the early onset of disease and will evaluate the candidate biomarkers in a clinical investigation designed to compare healthy and diseased subjects and to follow disease progression in patients with established periodontitis. Chronic periodontitis has a polymicrobial biofilm aetiology and interactions between key bacterial species are strongly implicated as contributing to disease progression. Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia have all been implicated as playing roles in disease progression. P. gingivalis cell-surface-located protease/adhesins, the gingipains, have been suggested to be involved in its interactions with several other bacterial species. Little is known of T. denticola factors important for polymicrobial biofilm formation. The aims of this section of the study were to determine polymicrobial biofilm formation by P. gingivalis, T. denticola and T. forsythia, as well as the role of P. gingivalis gingipains in biofilm formation by using a gingipain null triple mutant and the role of T. denticola motility using a flagellar mutant. To determine homotypic and polymicrobial biofilm formation a flow cell system was employed and the biofilms imaged and quantified by fluorescent in situ hybridization using DNA species-specific probes and confocal scanning laser microscopy imaging. Of the three species, only P. gingivalis and T. denticola formed mature, homotypic biofilms, and a strong synergy was observed between P. gingivalis and T. denticola in polymicrobial biofilm formation. This synergy was demonstrated by significant increases in biovolume, average biofilm thickness and maximum biofilm thickness of both species. In addition there was a morphological change of T. denticola in polymicrobial biofilms when compared with homotypic biofilms, suggesting reduced motility in homotypic biofilms. The T. denticola nonmotile mutant formed structurally different polymicrobial biofilms with P. gingivalis that lacked the defined intracolonial channels of the wild-type biofilms. This study has identified novel mechanisms and molecular targets that could be used to prevent the development of pathogenic subgingival plaque and this may be useful in the treatment and prevention of periodontal diseases.

In addition to the polymicrobial nature of disease there is strong evidence for variation in virulence amongst P. gingivalis strains. To identify gene products that are associated with virulence we have sequenced the genomes of a number of P. gingivalis strains and closely related species using our in-house nextGen sequencing technology. Using these data we will define the core genome and pangenome of P. gingivalis which will enable a much better understanding of how this bacterium survives in the oral cavity and causes tissue damage. The variation in cell surface proteins across the strains is also being determined, which is essential for the detection technologies used in the diagnostic kits that are being developed in the Oral Health CRC.
Prevention and Early Diagnosis

Improving our capacity to prevent and diagnose oral disease through the development of novel preventive products, diagnostic tools and oral health promotion approaches.

Program 2 consists of five projects:

- Development of diagnostics
- Novel preventive products
- Functional foods and beverages
- Optimisation of nutraceutical development
- Oral health promotion

Project managers:

- Dr Nathan Cochrane
- Associate Professor Stuart Dashper
- Associate Professor Mathew Hopcraft
- Professor David Manton
- Associate Professor Rodrigo Marino
- Associate Professor Neil O’Brien-Simpson
- Associate Professor Julie Satur
- Dr Brent Ward

Development of diagnostics

Chairside diagnostic for periodontitis

Following an extensive research program we have this year been successful in producing a prototype chairside diagnostic for the detection of the periodontal pathogen Porphyromonas gingivalis in patients’ saliva. The prototype has been developed with industry participant GC Corporation, using monoclonal antibodies produced by CSL Limited, also a CRC industry participant.

This research utilises intellectual property developed by the Oral Health CRC and the chairside diagnostic has the potential to determine the risk for patients of periodontal breakdown, which is linked to increasing P. gingivalis cell numbers. The diagnostic may also have use as a diagnostic for implant failure due to the close association between increases in P. gingivalis cell numbers in saliva and implant failure. By using this diagnostic dentists will be able to use an evidence-based dentistry approach in providing treatment at a stage where minimal intervention/treatment halts the progression of disease rather than waiting for visible signs of disease as the point to start treatment.
Our approach, based on monoclonal antibodies directed to a specific protein of the periodontal pathogen P. gingivalis, has resulted in the development of a diagnostic kit that is based on the proven design of the chairside diagnostic for dental caries that detects Streptococcus mutans. We have validated these kits to have a detection threshold that will determine disease at an early stage that is undetectable clinically. We have also tested this P. gingivalis saliva test kit on 50 periodontal patients and 50 periodontally healthy controls with the majority of patients testing positive for the bacteria. We have cross-referenced the results of the kit with the highly sensitive laboratory-based method quantitative PCR.

We found that the kit was as sensitive as the qPCR assay and that the kit has very high specificity and sensitivity. We are now moving to a new phase of testing of the P. gingivalis saliva detection kit which is aimed at investigating re-occurrence of disease and whether the kit can be used as a predictive measure of disease progression.

**Novel preventive products**

**Topical remineralisation products**

Fluoride varnishes were developed for professional application to deliver fluoride into the oral environment and inhibit demineralisation and promote remineralisation. The Oral Health CRC sought to improve the efficacy of a fluoride varnish by developing a varnish that also releases calcium and phosphate ions to improve remineralisation.

This research has now been commercialised as MI Varnish™ which is produced by Oral Health CRC participant GC Corporation. The product was commercially released in February 2012 and is now the eighth largest selling varnish in the USA.

The CRC is also testing a number of prototype professional tooth crèmes containing CPP-ACP (RECALDENT™). These have been developed and are being assessed by the CRC. Laboratory testing has shown that these paste formulations are promising. An in situ study is currently underway exploring the effectiveness of a variety of novel toothpastes and crèmes to regress early tooth decay.

**Saliva substitute**

Saliva plays a crucial role in maintaining the health of the oral tissues. Evidence indicates that rates of hyposalivation (lack of saliva) are increasing as the population ages and people are increasingly medicated. The majority of saliva substitutes seek to relieve oral dryness but do not replace the many functions of saliva. One of the aims of this project is to develop a superior saliva substitute that mimics the functions of natural saliva.

A prototype saliva biomimetic has been produced by GC Corporation in collaboration with the Oral Health CRC. This saliva substitute contains bioactive ingredients from milk that mimic the function of two central proteins in saliva - Mucins and Statherin.

The milk peptides added to this prototype product stabilise calcium and phosphate and thereby inhibit demineralisation, promote remineralisation and lubricate the soft and hard tissues in the mouth for improved oral comfort.

This prototype saliva biomimetic has been tested in a clinical patient acceptance trial at the Peter MacCallum Cancer Centre. Feedback from participants was positive. This saliva biomimetic has significant potential to improve the quality of life for people suffering from hyposalivation. It will work to inhibit demineralisation, promote remineralisation, lubricate the mouth and potentially inhibit oral biofilms. This has the potential to reduce the quantity of dental treatment that patients are likely to need which also has significant cost benefits for the community.

**Dry mouth products**

The oral cavity provides bacteria with a range of hard and soft tissue surfaces to attach to and a variety of distinctly different microhabitats. The unique, non-shedding hard surfaces of teeth, in particular, allow for the accretion of the thick, complex, structured polymicrobial biofilms known as dental plaque.

The stability of oral microbial biofilms involves dynamic balances of a range of synergistic and antagonistic interactions among species and their environment. Minor adjustments in the oral environment can affect these natural balances potentially leading to shifts in the ecology and changes in the species composition of oral microbial biofilms.
These changes in species composition can lead to the development of a more pathogenic plaque if opportunistic species, such as Streptococcus mutans, Streptococcus sobrinus and Lactobacillus casei, become dominant in the microbial community.

Growth as a biofilm affords many advantages to bacteria. Most importantly in the oral cavity, the failure of the bacterium to attach and grow as a biofilm will result in its clearance. Biofilms also provide a level of protection against antimicrobial agents, which is achieved by a number of processes including: the slowing of penetration of some antimicrobial agents into the biofilm matrix; the slowing of the growth rate of bacteria in the deeper layers of the biofilm; and the binding of some antimicrobial agents to extracellular polymers thereby reducing their effective concentration.

Development of biofilm disruptive agents that do not have direct antibacterial activity can provide another strategy for plaque control singly or in combination with antimicrobial agents. This technology has special application for the treatment of patients with reduced salivary flow as incorporation of antiplaque agents into dry mouth products could augment the antiplaque activity of natural saliva. In this study we have shown the antibiofilm activity of CPP-ACP (RECALDENT™) and further characterised the antibiofilm activity of κ-casein glycopeptides.

A single 10 minute treatment with 1% CPP-ACP (RECALDENT™) resulted in a 60% decrease in biofilm biomass and thickness of established S. mutans biofilms grown in vitro. This effect was not due to the peptide component of CPP-ACP alone as the addition of 0.5% CPP, without the ACP, had no significant effects on the biofilm. From these results it appears that CPP-ACP could have an antiplaque effect in vivo.

Caseinomacropieceptide (CMP), the variably phosphorylated and glycosylated forms of the bovine milk protein fragment κ-casein(106-169), are produced during cheese production and have been shown to have a range of bioactivities. The objective of the study was to determine the ability of the glycosylated forms of κ-casein (106-169) (κ-casein glycopeptides, KCG) to disrupt S. mutans biofilms grown in flow cells. Confocal laser scanning microscopy (CLSM) was used to monitor the effect of KCG on S. mutans biofilms. CLSM analysis of 16 h S. mutans biofilms showed that a single application of 2.4 mg/ml KCG reduced total biofilm biovolume and average biofilm thickness by 54%. A combination of 2.4 mg/ml KCG and 20 mM ZnCl2 (KCGZn) caused a more significant disruption of the biofilms reducing total biofilm biovolume by 78% and average biofilm thickness by 81%.

**Polymicrobial biofilm caries model**

Over 1,000 bacterial taxa at the species level have been detected in the various habitats of the human oral cavity. Unlike classic infectious diseases involving a single organism, dental caries involves changes in the abundances of the various bacteria that make up the supragingival plaque component of the oral microbiota. The aim of this study was to develop an in vitro model of dental caries initiation using a six species polymicrobial biofilm that could assess microbiological changes leading to measurable changes in enamel mineralisation. A constant-depth film fermentor (CDFF) was used to culture a model supragingival plaque community composed of Streptococcus sanguinis, Streptococcus mutans, Actinomyces naeslundii, Veillonella parvula, Lactobacillus casei, and Fusobacterium nucleatum. The fermentor consisted of a rotor containing 15 removable polytetrafluoroethylene pans with each pan holding three plugs composed of an enamel block as substratum for the biofilm. The CDFF was maintained at 37°C under an anaerobic atmosphere and fed with an Artificial Saliva Medium (ASM) at a constant flow rate of 10 mL/h. In order to mimic in vivo bacterial growth conditions in the oral cavity with food intake and to provide a cariogenic challenge, a 1% (w/v) sucrose solution in ASM was pumped into the CDFF eight times a day at two hourly intervals.

The CDFF was sampled on days 5, 8 and 14 after inoculation. Bacterial biofilm species composition was determined by quantitative real-time PCR using species-specific primers. Enamel lesion development and mineral content of the enamel substratum was determined after sectioning by transverse microradiography and microdensitometry.
qPCR of the starting inoculum confirmed that high numbers of all six species were initially present. Polymicrobial biofilms established rapidly on the enamel substratum of the CDFF. The biofilms were dominated by the acidogenic and aciduric species S. mutans and L. casei although all species were detected at all time points. Enamel subsurface lesion depth increased from 40 ± 8 at day 5 to 112 ± 16 μm at day 14. The rapid development of enamel subsurface lesions and demineralization and the high levels of S. mutans and L. casei demonstrate a high cariogenic challenge which can be modified appropriately by adjusting the timing of sucrose additions. This model will be used for the screening of novel anticariogenic compounds.

Optimisation of nutraceutical development

A major focus of this project is to investigate strategies that will lead to continued optimisation of the current CPP-ACP (RECALDENT™) production processes at the Victorian production plant in Scoresby. The project also aims to develop new improved production processes that may enable more significant improvements to be made to the operation of the plant, be it higher yields and/or reduced production costs.

Two sports drinks containing high levels of calcium were found to have low erosion potential however they were also found to be unpalatable. This confirms that many sports drinks have erosive potential and that currently modified beverages are not ideally formulated. This indicates an excellent opportunity for developing sports beverages with a low erosive potential and that remain palatable.

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Functional foods and beverages

Researchers in this project are investigating the potential of producing over-the-counter functional foods and beverages that benefit teeth by minimising erosion potential, and assisting in preventing dental caries. It is envisaged that these products could include sports drinks and chewing gum.

Oral health surveys are identifying an increase in the number of children showing signs of dental erosion, and this increasing prevalence has been linked to the growing consumption of acidic beverages, in particular, sports drinks.

In our initial study we have tested a range of purchased sports beverages in an in vitro erosion assay. This showed that the majority of sports beverages had erosive potential.

In 2010-11 the Oral Health CRC conducted a detailed mass balance trial on various in-line samples collected at different stages of the production process at Scoresby. In mid 2012 a more extensive and detailed series of production trials was undertaken at Scoresby, with over 250 individual samples taken from five different trial runs. The data that were collected from the analyses of these in-line samples has provided a comprehensive picture of the current RECALDENT™ production process. This has provided valuable baseline data of the process, and will enable detailed comparisons to be made on yield and purity with the data collected in the other trials where various modifications of the current process are trialled.

Oral health promotion

Mental health and oral health

Due to a number of factors, people with mental health issues experience higher rates of oral disease than the wider community. The Oral Health CRC has partnered with NEAMI, a non-government mental health organisation that provides support services for people with severe mental illness, to find ways to better address the oral health needs of people living with mental illness. A needs analysis was completed during 2011 and reported back to NEAMI. During 2012 developmental work on interventions was undertaken; a systematic review of literature was completed; and a single question to assess the oral health status of NEAMI’s clients was developed to be included in their health assessment tool.
Supporting resources, including a decision tree, have been developed to assist support staff to provide oral health advice to their clients.

The Oral Health CRC has recruited a research student who is conducting oral health information sessions across Victoria in conjunction with a NEAMI health promotion officer. Oral Health CRC Participant Colgate has provided oral health care support packages. The project will be evaluated to determine its effectiveness as an appropriate oral health intervention for this high risk group.

**Colgate Chair of Population Oral Health**

Included under the CRC’s Oral Health Promotion program is Colgate’s support for the Colgate Chair of Population Oral Health in the Melbourne Dental School. This position, currently held by Professor Mike Morgan, plays a significant role in promoting the importance of oral health to overall health, providing expert advice to governments and to health promotion organisations.

**Innovation in delivery of oral health promotion**

The Multimedia Web Enhancement Oral Health Promotion Program for Older Adults is a study exploring the ways in which the oral health care system can address the difficulties, problems and challenges of delivering the best oral health information to older people. The study was made possible with funding from BUPA, and examined the application of a community-based, web-enhanced model to empower older people to manage their oral health needs.

Forty-seven active, independent-living older adults participated in this evaluation. After the intervention participants responded with higher levels of achievement than before participating in this web-based oral health program. Participants showed statistically significant improvements in oral health attitudes (4.2 vs. 4.8; p<0.05), knowledge (18.4 vs. 23.3; p<0.001), and self-efficacy (84.6 vs. 89.4; p<0.02), as well as, self-reported oral hygiene practices (i.e., frequency of use of dental floss) (p<0.05). Thus, the e-ORHIS approach was successful in improving oral health knowledge, attitudes and self-efficacy, and represents a helpful approach for the design of oral health interventions for older adults. Further evaluation with a larger sample is required to test the long-term impact, including the economic impact, of the e-ORHIS approach.
Intervention and Management

Developing and trialling novel therapeutics, dental professional products and new models of care to treat oral diseases.

Program 3 consists of four major projects:

- Novel therapeutics and dental professional products
- Minimal intervention dentistry
- Dental workforce
- Dental practice-based research network

Project Managers:

- Dr Denise Bailey
- Dr Nathan Cochrane
- Associate Professor Stuart Dashper
- Professor John Hamilton
- Associate Professor Rodrigo Mariño
- Associate Professor Neil O’Brien-Simpson
- Professor Robert Pike
- Professor Laurie Walsh

Novel therapeutics and dental professional products

Periodontitis vaccine

Chronic periodontitis is a major public health problem and affects one in four adults, with the risk increasing with age. Research in this program is seeking to develop a vaccine that can be used to treat patients with chronic periodontitis and also to prevent disease onset in those at risk of developing periodontitis.

Approximately 20-30% of Australian adults have some degree of periodontitis. The disease is characterised by the destruction of the soft tissue and bone that supports teeth. At present, periodontitis can only be detected once damage has occurred, and it is costly and time-consuming to treat and maintain periodontal health. There is also growing evidence linking periodontal disease with systemic diseases such as cancer, cardiovascular disease and diabetes.

Researchers at the Oral Health CRC are working on a vaccine to treat periodontitis, and are also investigating links between periodontal disease bacteria and chronic inflammation.

Research on the development of a vaccine is now well advanced. Three bacterial species have been closely associated with chronic periodontitis: *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*. Of these, *P. gingivalis* has been most strongly associated with disease severity. Hence our initial focus has been on *P. gingivalis* which has been described as a keystone pathogen.
By vaccinating against this bacterium we anticipate that disease may be prevented. As well as targeting this keystone pathogen, we have also continued research into developing a vaccine for the two other pathogens, T. denticola and T. forsythia, to potentially provide enhanced protection with a multi-species vaccine.

**Oxantel**

Chronic periodontitis is an inflammatory disease of the supporting tissue of the teeth associated with specific bacteria. With the exception of the spirochaete T. denticola, these species are Gram-negative, proteolytic, anaerobic bacteria that include P. gingivalis, T. forsythia and A. actinomycetemcomitans, all of which rely on complex anaerobic respiration of amino acids for survival and proliferation. These species largely exist as part of a polymicrobial biofilm accreted to the surface of the tooth root. Bacteria growing in biofilms are more resistant to antimicrobial agents and host immune responses than their planktonic counterparts and as such biofilm-related diseases can be persistent and hard to resolve.

We have shown that the anthelmintic drug Oxantel directly inhibits P. gingivalis fumarate reductase activity, inhibits planktonic growth and inhibits P. gingivalis homotypic biofilm formation at subminimal inhibitory concentrations. Oxantel also inhibits T. forsythia and A. actinomycetemcomitans growth and biofilm formation but has no effect on the growth of T. denticola. It is not surprising that Oxantel does not inhibit T. denticola growth as bioinformatic analysis indicates that the genome of this spirochaete does not encode a fumarate reductase (Frd) gene. Transcriptomic analysis showed that Oxantel treatment caused the upregulation of 22 P. gingivalis gene products. All of these genes are part of a regulon controlled by haem availability.

There was no large scale change in the expression of genes encoding metabolic enzymes indicating that P. gingivalis is unable to overcome Frd inhibition. Oxantel disrupted the development of pathogenic polymicrobial biofilms composed of P. gingivalis, T. forsythia and T. denticola in a concentration-dependent manner. In these biofilms all three species were inhibited to a similar degree demonstrating the synergistic nature of biofilm formation by these species and the dependence of T. denticola on the other two species. Data collected so far indicates that Oxantel may have potential as a treatment for periodontitis.

**Gingipain antagonists**

Researchers in this project have been investigating the role of cysteine proteases from the major bacterial pathogen involved in periodontal disease, P. gingivalis, in eliciting the inflammation that is central to the condition. The active sites of the enzymes have been characterised in fine detail to allow the development of specific inhibitors that may allow us to treat the condition. We have characterised the enzymes using specific libraries of compounds and the information gained led to the design of a number of potential lead compounds. Testing of these against host proteases, which we want to avoid targeting as it will lead to toxicity effects, showed that some host enzymes were targeted to some extent by the inhibitors developed. More recently, we have mapped the preferences of the bacterial enzymes for so-called ‘unnatural’ amino acids. Since there are many more unnatural amino acids than natural ones, the resulting libraries of compounds are enlarged and our chances of identifying molecules specific to the bacterial enzymes are enhanced. We are now developing lead molecules again for testing.

We have also been investigating the role of a host receptor, PAR-2, in the development of periodontal disease. Previous work revealed that the receptor was crucial to the bone destruction associated with the disease and indicated that T-cells from the immune system might be involved. Work to further validate these data suggests that PAR-2 on T-cells is indeed associated with disease progression. Antagonists of this receptor are being used in disease models to validate their potential as a target for treatment of the disease.

The P. gingivalis cell-surface cysteine proteinases, the Arg-specific proteinases (RgpA, RgpB) and the Lys-specific proteinase (Kgp), which are known as gingipains, have been implicated as major virulence factors. All three gingipain precursors contain a propeptide of around 200 amino acids in length that is removed during maturation. The aim of this study was to characterise the inhibitory potential of the Kgp and RgpB propeptides against the mature cognate enzymes.
Mature Kgp was obtained from *P. gingivalis* mutant ECR368, which produces a recombinant Kgp with an ABM1 motif deleted from the catalytic domain (rKgp) that enables the otherwise membrane bound enzyme to dissociate from adhesins and be released.

Mature RgpB was obtained from *P. gingivalis* HG66. Recombinant propeptides of Kgp and RgpB were produced in *Escherichia coli* and purified using nickel-affinity chromatography. The RgpB propeptide displayed non-competitive inhibition kinetics with a Ki 12 nM. Both propeptides exhibited selectivity towards their cognate proteinase. The specificity of both propeptides was demonstrated by their inability to inhibit caspase-3, a closely related cysteine protease, and papain that also has a relatively long propeptide. Both propeptides at 100 mg/L caused a 50% reduction of *P. gingivalis* growth in a protein-based medium.

In summary, this study demonstrates that gingipain propeptides are capable of inhibiting their mature cognate proteinases and may have utility in the treatment or prevention of *P. gingivalis*-related disease.

**Minimal intervention dentistry**

Minimal intervention dentistry is a relatively new approach to managing dental caries that focuses on promoting prevention and on the use of non-invasive methods to manage disease itself, rather than managing symptoms. The approach combines remineralising treatments with standard dental practices, and works with patients to encourage and enable greater self- and home-care. An impediment to the wider uptake of the minimal intervention approach is its perceived costliness due to it requiring more patient visits than current models of care. This research project has designed and is implementing a clinical trial titled ‘Assessing the cost effectiveness of implementing a minimal intervention dentistry approach for adolescent public patients at high risk for dental caries.’ This is a collaborative project between the Oral Health CRC, Dental Health Services Victoria and Health Economics at Deakin University. The aim of the study is to determine whether a minimal intervention dentistry approach is cost effective compared with current models of care in achieving positive oral health outcomes for this population group. The study protocol has been developed; it will be a 24-month cluster-randomized longitudinal clinical trial. Twelve community dental clinics will be recruited. Six clinics will be randomly assigned to the test intervention and the other six to the control. The plan is to recruit 42 participants per clinic, or in total 504 patients. At baseline subjects will be screened to determine their oral health, caries experience and attitudes towards changing their oral health. The control group will be reviewed twice at 12 and 24 months whereas the intervention group will be reviewed at 3, 6, 12, 18 and 24 months.

Participants will have their oral health assessed at each review visit and bitewing radiographs as required. The control group will receive current practice standard of care. The intervention group will receive the minimal intervention approach where the focus will be on prevention and early intervention to control the disease, remineralisation and monitoring of non-cavitated lesions, conservative restoration of more advanced disease and the repair of restorations rather than replacement.
Ultimately, an economic appraisal of these two models of treatment will be performed to determine which approach is more cost effective. Other outcomes of this study will be qualitative data about the acceptance of the minimal intervention dentistry approach by patients and clinicians and whether a better oral health outcome is achieved by the use of the new approach. The protocol for this clinical study has been developed. Funding has been secured and ethics approval obtained.

**Dental workforce**

Studies within this project are aiming to better understand the profile of Australian and New Zealand oral health profession students. Data were collected from Bachelor of Oral Health students (BOH) in Australia and New Zealand to provide a description of the socio-demographic profile of BOH students in Australian and New Zealand dental schools. Additionally, it aimed to describe their career decisions, preferences, influences and choices. The study indicated an overall different BOH student profile compared to Bachelor of Dentistry students. Another study looked at the stress levels and health promoting attributes of dental students.

While face-to-face patient examinations are regarded as the most accurate method of correct oral health diagnosis, in rural and regional Australia there are major oral health workforce shortages that make face-to-face examinations difficult. Also in Victorian nursing homes, only 11 percent of residents have seen a dentist in the past 12 months.

We carried out a pilot study (proof of concept) to test the feasibility and reliability of using video conferencing and intraoral cameras at remote facilities for screening of patients for oral diseases and for the development of treatment plans in real-time compared with traditional face-to-face oral examinations. Results indicate that the proposed tele-dentistry approach for oral health screening using an intraoral camera was feasible and reliable as an alternative to traditional oral health examination. Patients expressed high levels of satisfaction with the tele-dentistry service.

The second stage of this project involves the field-testing of tele-dentistry technology at two nursing homes. In this test tele-dentistry assistants will assist in the virtual dental examination, with the dentist located off-site. Another field test of this tele-dentistry approach will target children and adolescents living in rural and remote locations. The approach will utilise trained oral and non-oral health professional assistants to take video images and upload them for review and treatment planning by an off-site paediatric consultant, and arrange for specialist dental services as required. The assessments/consultations will be conducted in three specific specialist areas: (i) palate and cleft lip and palate, (ii) dental trauma and support for the management of oro-facial trauma in rural, remote or isolated practices and (iii) orthodontics - malocclusions remaining untreated due to the lack or restricted access to services.

Dental practice-based research network (evident)

The eviDent dental practice-based research network is a consortium of dental care providers committed to advancing the knowledge of dental practice and ways to improve it. It is an initiative of the Oral Health CRC and the Australian Dental Association Victorian Branch.

The network aims to encourage relationships between practitioners and academic researchers. By building research capacity to produce and use evidence, eviDent facilitates and supports dental practices to produce and disseminate evidence that can be translated into practice and inform policy. The eviDent committee considers project proposals submitted by its dental practitioner and academic members.

Recruitment for the eviDent dental practice-based research network (DPBRN) is on track, with 12 academic investigators, 39 practitioner investigators and six research collaborators recruited to the network. Currently, eviDent has four projects close to completion: (i) an evaluation of eviDent, (ii) a five year retrospective assay of implant complications, (iii) management of molar-incisor hypomineralisation and (iv) the PREVENT study.

An evaluation of eviDent (which specifically looked at the perceived benefits and burdens of participation in eviDent) is completed. A manuscript is being prepared.
The implant study collected data from 34 practitioners, 4,128 patients and from over 8,000 implants. The data set has been cleaned, has undergone preliminary analysis and is now being investigated further with the help of three post-graduate students.

The molar-incisor hypomineralisation study has completed data collection and is undergoing final analysis.

The eviDent Chief Investigators also received the US $75,000 inaugural Colgate/IADR Community-based research award for caries prevention for an interdisciplinary project between eviDent and VicReN (the Victorian PBRN for medical GPs) which has submitted its final report.

New eviDent projects underway include a Children’s Dental Program to assess the value of school dental screening and diagnosis and treatment and maintenance of periodontal patients by general dentists.

Further eviDent project proposals recently approved by the DPBRN Committee are (i) the investigation of the longevity of anterior resin bonded bridges and (ii) the identification of unrecognised diabetes and pre-diabetes in a dental setting.

Strong links have been established with PEARL DPBRN based in New York, USA and a second US-based DPBRN, Northwest PRECEDENT, with an exchange of protocols that will lead to joint multi-centre studies. Additionally, a joint project is planned with Columbia University, New York, USA.
Reconstruction and Regeneration

Developing innovative biocompatible dental materials and technologies to strengthen and reconstruct tooth and periodontal tissues.

Program 4 consists of two research projects:
> Novel biomaterials and implants
> Reconstruction and regeneration

Project managers:
> Professor Ivan Darby
> Professor John Hamilton
> Associate Professor Joseph Palamara
> Associate Professor Roy Judge

Novel biomaterials and implants

Enhanced glass ionomer cement

Biomaterials are materials that interact with biological systems. Researchers in this program are investigating new biomaterials that can be used to improve tooth restoration.

The first commercial outcome of research in this program was achieved in October 2011 with the release onto the US and New Zealand markets of a new product, FujiVI-EP (Enhanced Protection), a functional glass ionomer cement, by Oral Health CRC participant GC Corporation. Glass ionomer cements (GICs) are used by oral health professionals on exposed root surfaces to protect against demineralisation and tooth sensitivity. Researchers in the Oral Health CRC sought to develop an improved and functional GIC capable of remineralising surrounding areas of tooth enamel.

An initial study provided information on the amount of calcium, phosphate and fluoride that is released from a prototype GIC containing 3% CPP-ACP (RECALDENT™) in comparison to a commercial GIC not containing CPP-ACP (FujiVII). The GICs were exposed in different acidic media and pH for different periods of time and a comparison of the release of these ions was made.

The study established the benefits of including 3% CPP-ACP into the GIC Fuji VII (manufactured by the CRC industry participant GC Corporation) by investigating the calcium, phosphate and fluoride ion release and the microhardness of the material after it had been subjected to acidic and neutral environments over one, two and three days.
Tests to induce ion release from the GIC were done at neutral pH 7.0 (to mimic saliva which normally varies between pH 6.2 to 7.4) and in three acidic environments; (1) citric acid from food acids additives at pH 5.0; (2) lactic acid from product of bacterial flora in the mouth at pH 5.0 and (3) hydrochloric acid used to mimic gastric reflux from the stomach at pH 2.0. A constant ionic strength of 0.05M (consistent with saliva) was chosen.

A drop in hardness and increase in ion release was observed during acid exposure compared to a neutral environment. The calcium and phosphate ion release was significantly greater for the GIC containing 3% CPP-ACP than the GIC without CPP-ACP but no significant difference was found for the fluoride ion release. These results indicate that the GIC with 3% CPP-ACP was superior to the normal GIC.

A pilot study has now been undertaken to investigate if the GIC could be recharged with calcium, phosphate and fluoride ions lost during demineralisation, and if the surface hardness could be restored. Samples were pre-treated for 24 hours in hydrochloric acid and water (control) for ion release and hardness loss. These samples were then placed in three treatment solutions namely; CPP-ACFP solution at pH 5.5 and 7.0 and Tooth Mousse Plus (commercial crème) and analysed for ion up-take and gain in hardness. All solutions produced a gain in hardness.

Protocol and solutions for treatment have now been established for the next part of the study. This will involve a three-day study with initial acid challenge and pre-treatment every 12 hours and detection of mass loss, hardness and chemical (ion) analysis.

A second part of this project is investigating the antimicrobial activity of the FujiVII-EP GIC (containing RECALDENT™) and its capacity to prevent the emergence of secondary caries at the margins of a restoration. Researchers compared Streptococcus mutans biofilm formation after 16 hours of growth on FujiVII GIC with FujiVII-EP. Incorporation of 3% CPP-ACP (RECALDENT™) into Fuji VII GIC (FujiVII-EP) resulted in large reductions in the biovolume, average thickness and maximum thickness of S. mutans biofilms that formed on the surface of this material compared with FujiVII GIC without CPP-ACP. The surface area of the material that was colonised by the bacterium also decreased markedly when 3% CPP-ACP was incorporated into the material.

FujiVII EP containing 3% RECALDENT™ was able to reduce the total biofilm biovolume by 66%, average biofilm thickness by 74% and maximum thickness by 40% compared with FujiVII GIC without RECALDENT™. It acts by reducing the ability of S. mutans to colonise the surface of the GIC. The biofilms formed on Fuji VII GIC with RECALDENT™ are less protected and potentially more susceptible to antimicrobial agents, as demonstrated by an increase in the Surface Area: Biovolume Ratio of 61%.

A study has been completed on the healing of Bio-Oss grafted marginal gaps following implant surgery, investigating the effect of submerged vs. non-submerged healing. The study found there to be very little difference in histomorphometric healing outcomes as well as modeling of the facial bone between submerged and non-submerged protocols. The study provides a basis for further investigation of healing processes following implant surgery.

Evaluation of the fit of CAD/CAM abutments

A study comparing the fit of computer-aided design/computer assisted manufacture (CAD/CAM) abutments provided by a single system with proprietary prefabricated abutments on various implant systems has been completed.

Titanium CAD/CAM abutments were compared with prefabricated abutments on five different implant types. The samples were embedded in epoxy resin, sectioned longitudinally, and polished. Scanning electron microscopy was used to measure the gap between the implants and abutments at the connecting flanges and internal features. Independent tests were used to compare data.
A mean difference of 1.86 μm between the gold synOcta and CAD/CAM abutments on the Straumann Standard Plus implant was observed to be statistically significant (P = .002).

Less than 0.4 μm of difference was found between the CAD/CAM and prefabricated abutments for the remaining implant types, and statistical significance was not observed. Mean differences of 34.4 μm (gold) and 44.7 μm (titanium) were observed between the CAD/CAM and prefabricated abutments on the Straumann Standard Plus implants, which were statistically significant (P < .001). A mean difference of 15 μm was also observed between the CAD/CAM and prefabricated abutment on the NobelReplace implant, which was statistically significant (P = .026). All other groups had less than 4 μm of difference, and statistical significance was not observed.

The CAD/CAM abutments appeared to have a comparable fit with prefabricated abutments for most of the systems evaluated. Design differences between the abutment connections for both Straumann implants were observed that affected the fit of internal components of the implant-abutment connections.

**Fracture resistance of titanium and zirconia abutments**

Little information comparing the fracture resistance of internal connection titanium and zirconia abutments exists to validate their use intraorally.

The purpose of this in vitro study was to determine the fracture resistance of internal connection titanium and zirconia abutments by simulating cyclic masticatory loads.

Twenty-two specimens simulating implant-supported anterior single crowns were randomly divided into two equal test groups: Group T with titanium abutments and Group Z with zirconia abutments. Abutments were attached to dental implants mounted in acrylic resin, and computer-aided design/computer-aided manufacturing (CAD/CAM) crowns were fabricated. Masticatory function was simulated by using cyclic loading in a stepped fatigue loading protocol until failure. Failed specimens were then analysed by using scanning electron microscopy (SEM) and fractographic analysis. The load (N) and the number of cycles at which fracture occurred were collected and statistically analysed by using a 2-sample test (α=.05).

The titanium abutment group fractured at a mean (SD) load of 270 (56.7) N and a mean (SD) number of 81,935 (27,929) cycles. The zirconia abutment group fractured at a mean (SD) load of 140 (24.6) N and a mean (SD) number of 26,296 (9,200) cycles. The differences between the groups were statistically significant for mean load and number of cycles (P<.001). For the titanium abutment specimens, multiple modes of failure occurred. The mode of failure of the zirconia abutments was fracture at the apical portion of the abutment without damage or plastic deformation of the abutment screw or implant.

Within the limitations of this in vitro study, 1-piece zirconia abutments exhibited a significantly lower fracture resistance than titanium abutments.

The mode of failure is specific to the abutment material and design, with the zirconia abutment fracturing before the retentive abutment screw.

**Diamond as a scaffold for bone growth**

Diamond is an attractive material for biomedical implants. In this work, its capacity as a bone scaffold was investigated. It is well established that the bioactivity of a material can be evaluated by examining its capacity to form apatite-like calcium phosphate phases on its surface when exposed to simulated body fluid. Accordingly, polycrystalline diamond (PCD) and ultrananocrystalline diamond (UNCD) deposited by microwave plasma chemical vapour deposition were exposed to simulated body fluid and assessed for apatite growth when compared to the bulk silicon. Scanning electron microscopy and X-ray photoelectron spectroscopy showed that both UNCD and PCD are capable of acting as a bone scaffold. The composition of deposited apatite suggests that UNCD and PCD are suitable for in vivo implantation with UNCD possibly favoured in applications where rapid osseointegration is essential.
Glossary of terms

ADA Australian Dental Association Inc

ADAVB Australian Dental Association Victorian Branch

ADRF Australian Dental Research Foundation

caries tooth decay

CDFF constant-depth film fermentor

CPP-ACP (casein phosphopeptide-amorphous calcium phosphate) The peptide complex derived from cows’ milk which has been shown to replace minerals lost in the tooth decay process (marketed as Recaldent™)

CRC Cooperative Research Centre

OH-CRC Oral Health CRC

demineralisation the weakening of tooth structure through the loss of minerals

dental plaque a biofilm of bacteria that builds up on teeth and can lead to dental caries or periodontitis if not removed regularly

DPBRN Dental Practice Based Research Network
dentine The part of the tooth beneath the enamel and surrounding the pulp chamber and root canals

DHSV Dental Health Services Victoria

GIC Glass Ionomer Cement

gingival crevicular fluid the fluid in the periodontal pockets around teeth

in-situ studies studies conducted on samples of human tissue that have been placed in another human, situated near the natural tissue

in-vitro studies studies conducted outside the human body or other living organisms

ISO International Organisation for Standardisation

IP intellectual property

MSBS microshear bond strength

NH&MRC National Health and Medical Research Council

NIH National Institute of Health (United States of America)
nutraceutical a substance that is a food or part of a food which provides health or medical benefits

periodontal disease disease that affects the supporting structure of the tooth

periodontitis advanced peridontal disease characterised by inflammation/infection, discomfort in the gums and loosening of the teeth

RECALDENT™ an anticariogenic technology containing CPP-ACP

remineralisation the strengthening of tooth structure by incorporation of calcium, phosphate and/or fluoride

sub-gingival plaque plaque from below the gum line
Participants

Universities

THE UNIVERSITY OF MELBOURNE

MONASH University

THE UNIVERSITY OF QUEENSLAND

Industry Participants

kraft foods

Colgate

MURRAY GOUldbURN

GC

CSL

Established and supported under the Australian Government’s Cooperative Research Centre program.