

## **School of Clinical Dentistry**

**RA5a: Research Environment and Evidence of Esteem**

**Nov 2007**

## Overview

The School of Clinical Dentistry is a research-led institution that continues to be at the forefront of international dental research. We have sustained an upward trajectory for research quality and successes since the first RAE, and we achieved a "5" rating in 2001. Our achievements have been greatly enhanced by the strategic appointment of clinical and non-clinical scientists and by continued investment in our research infrastructure. We have **doubled the number of staff** returned from 16 in 2001 to 32 in 2007. New staff include **6 clinical professors, 2 clinical senior lecturers and 9 non-clinical scientists**. Since 2001 we have invested over £300,000 in research facilities and we are currently building a **new £5.5M research wing** to be opened in early 2008.

## Research environment

The School has well-equipped state-of-the-art research facilities that have been continuously improved since 2001 to accommodate our increased activity. We have dedicated facilities for cell and tissue culture, molecular biology, proteomics, time lapse microscopy, image analysis, electron microscopy, materials testing, microbiology and *in vivo* electrophysiology. There are central facilities for mass spectroscopy, DNA sequencing, monoclonal antibody production, flow and image cytometry and animal care. The School's facilities have been significantly enhanced since 2001 with investment of over £300,000 in redevelopment of research laboratories and equipment, mostly as a result of a successful **SRIF2 bid (£270,000) in 2004**. Currently the School is undergoing further development following a **SRIF3 award of £3.1M**. This is contributing to a **new research wing (total cost £5.5M)** incorporating over **660m<sup>2</sup>** of new research laboratories and offices for research staff and postgraduate students. The laboratories include new resources for cell culture and tissue engineering, cell and molecular biology, proteomics, neuroscience and advanced microscopy. Further support from HEFCE and DoH (£8.3M as a consequence of increased BDS numbers) has enabled an overall **£14M expansion and refurbishment programme** which will enhance clinical facilities for teaching and research within the existing Dental Hospital. This investment and continuing redevelopment will allow a marked expansion of research activity and the further development of a vibrant research-led culture.

## Research Capacity Building

Research capacity has been further enhanced recruitment of research active staff and increased research income. Since 2001 we have recruited **6 clinical professors** (Deery, Griffiths, Lennon, Robinson PG, Speight, Thornhill), **2 clinical senior lecturers** (Farthing, Yates) and **9 non-clinical scientists** (Andrew, Baker, Bingle, Crawford, Gibson, Miller, Murdoch, Stafford, Whawell) all of whom have strong research track records and are returned as research active. A particular achievement was the appointment of **Yates** (2006) who won a **HEFCE/UKCRC Senior Clinical Lectureship award**, the only such appointment in Dentistry in the UK.

The School supports four internal PhD studentships as well as having a small Research Fund to pump-prime new projects. Similar funds in the University can be bid for on a competitive basis each year. The Dental School has been awarded 9 University studentships in the assessment period. We also have Fee Scholarships for up to 5 home PhD students per year, encouraging staff to apply for studentships and enabling able young individuals to undertake research training.

## Research Strategy

Research is managed by the Dental School **Research Committee** which includes the four research group leaders and is chaired by the Research Dean (**Robinson PP** until 2005,

**Speight** from 2006), who also provides input to, and feedback from, the Faculty and University Research Committees. The Postgraduate Research Tutor and the School Dean also sit on the committee and there is representation from the Sheffield Teaching Hospitals NHS Trust to ensure a co-ordinated research strategy for the Dental School and Hospital. The Research Committee is responsible for overall research strategy, for allocation of internal research funds, for overseeing selection and monitoring of postgraduate students and for disseminating information to staff.

Our overall strategy for research is:

- to build on established strengths as identified by the four research groups
- to develop areas of research that are responsive to national and international priorities
- to develop collaborations with other internationally leading scientists and with industry

The School has developed strong links with other University departments. For example our Oral Biomaterials Group plays a leading role in the University **Centre for Biomaterials and Tissue Engineering** and also leads the University of Sheffield's participation in the DTI-funded **Healthcare Technologies Knowledge Transfer Network (Hatton)**, which is composed of a partnership of only six universities. The School is involved in a number of **EU-funded projects** (PI, **Hatton**) to a total value of **€9.8M (£6.6M) of which over £800,000** has come to the Dental School. The Dental Public Health Group are key partners in a number of major initiatives to investigate provision of dental services and quality of life issues, and are part of the **recent £1.2M Leverhulme Trust, "Changing Families, Changing Food"** research programme (PI Jackson, UoA 32). Several of our research students are jointly supervised by staff from these other departments, ensuring all necessary support, and fostering productive collaborations. We also have significant **international collaborations** including with Universities in USA, Brazil, Canada, Uganda, China, Germany, Italy and Japan.

We continue to develop **links with industry** and have a number of collaborations which provide opportunities for clinical exploitation of our research. For example, an on-going partnership with **GlaxoSmithKline**, (PI, **Boissonade**) has funded 11 projects including 3 CASE studentships and 5 project grants, and a recent **BBSRC/GSK industrial partnership award worth £359,000**. Total funding from this collaboration, including studentships is over **£930,000**, including over **£390,000 from MRC and BBSRC**. The Oral Neuroscience group has also developed new links with **Eli Lilly** and **Renovo** which will fund new areas of research and two PhD studentships.

## Research Students

The School currently hosts 41 PhD students (plus 11 writing up in year 4), twenty are home students, 4 EU and 19 overseas, the majority (30) are full time.

The School has a robust policy for the selection, monitoring and support of postgraduate research students and provides a vibrant and productive research training environment. This has been enhanced over recent years under the guidance of our Postgraduate Research Tutor (Douglas) who has recently been appointed **Sub-Dean for Postgraduate Affairs** in the Faculty of Medicine. In an **Independent Review of Research Supervision** (2006) the School received 13 commendations relating to areas of good practice and innovation.

All new PhD students are allocated two supervisors and an independent academic adviser who are responsible for providing guidance and direction to ensure successful completion. Student progress is assessed annually using oral and poster presentations, written assignments, and oral examinations. PhD students also receive extensive training in generic and transferable skills through the well-established University Research Training Programme

(RTP). Students can select from over 400 units and complete a minimum of 45 credits, equivalent to almost 4 weeks of training per year for 3 years. All students (and staff) are encouraged and supported to present their research at national and international meetings, and to enter research prize competitions, as success is a good marker of esteem. We have had a series of notable successes with over 30 prizes in the dental research field since 2001.

## Staffing Policy

Staffing strategy is based on our continuing determination to be research-led, whilst maintaining high-quality teaching for our undergraduate and postgraduate students. Recruitment of new staff is undertaken with particular reference to their ability to enhance our existing research groups. All staff are supported to develop their research and academic skills by a well structured University probationary programme.

The School pays particular attention to the career progression of staff by providing opportunities for professional development and training. The success of this strategy is evidenced by the **internal promotion of 6 staff to Chairs** (Boissonade, Douglas, Farthing, Hatton, Rodd, Rawlinson), **one to Reader** (Loescher,) **and two to Senior Lecturer** (Johnson, Gibson).

Eleven clinical staff are working for a PhD as part of a combined approach we have developed to provide an integrated clinical academic training pathway, funded either internally as lecturers or as extended SpR programmes.

Staff are appraised annually, as part of the University-wide Staff Review and Development Scheme (SRDS), and are guided towards their particular strengths permitting increased research time when it is needed. The HoD and research group leaders mentor all staff to ensure that they receive the highest level of support and encouragement. New lecturers undertake a period of probation during which they participate in the University *Certificate in Learning and Teaching* which includes training in research and supervisory skills. All academic staff are also encouraged to supervise postgraduate research students, and one of our strengths is the distribution of this activity across a majority of the staff submitted. New PhD supervisors are mentored by a more experienced colleague who shares the supervision.

## RESEARCH GROUPS

Our research is organised into interdisciplinary groups reflecting our philosophy that progress is derived most readily from a multidisciplinary approach and that research should not be constrained by the traditional boundaries of clinical disciplines. We continue to focus our research activity into areas of international excellence. Since 2001 we have increased our research groups from three to four. The new group '**Dental Public Health**' has been formed following the appointment in 2002 of a Professor in Dental Public Health (**Robinson PG**). Each group has a leader of international standing who is responsible for co-ordinating activities and implementing strategic decisions made by the School Research Committee. During the assessment period each group has obtained research income in excess of £1.0M.

Details of our research groups, including their aims and achievements are detailed below:

<b>A</b>	Oral Biomaterials
<b>B</b>	Oral Disease
<b>C</b>	Oral Neuroscience
<b>D</b>	Dental Public Health

## A ORAL BIOMATERIALS

**Group leader:** Professor Paul V Hatton

**Members:** Brook I, Crawford, Miller, Johnson, van Noort

**Background:** We have continued to develop the research themes reported in RAE 2001, in the areas of Biomaterials Science and Tissue Engineering. New recruitment has strengthened tissue engineering (**Crawford**) and implant biomaterials research (**Miller**). We currently have **3 research assistants, one technician and 15 PhD students**. The group remains highly interdisciplinary, well-supported by Research Council and European funding, and has extensive international collaborations with highly regarded research centres in **Zurich, Basel, Uppsala, Minho, Trento, Limerick, Kyoto, Siena, Nagasaki and Sao Paulo**.

**Aims:** The focus of the group is the study of biomaterials and biomaterials-related therapies for the treatment of disease and trauma related to the head, neck and mouth.

**Activities and Achievements:** During the assessment period, the group has been involved in research programmes with a total value **greater than £20.0M** of which almost **£1.50M** has come to the Dental School.

### ***Biomaterials Science***

There have been significant successes in advanced biomaterials science, custom implants for dentistry and surgery, dental technology and biocompatibility. Dental applications for nanotechnology is an emerging field with funding from EPSRC and new collaborative research projects with the Irish Republic. Major projects include:

1. **Novel glass-ionomer bone cements** (*EPSRC, Hatton, Brook, £105,000*). A major problem with dental glass-ionomer cements for bone repair is release of aluminium ions (Hatton 3). This project has demonstrated the potential of non-aluminium, iron-based ionomer glasses for the development of a new generation of bone cements.
2. **“NANOLAB” new nanorobotics technology for measurement and manipulation at the nanoscale.** (*EPSRC Basic Technology Programme, Hatton (PI, Inkson, Engineering Materials) £1.85M*) The role of the dental school is to develop applications for new nanoscale instrumentation. This research is scientifically and strategically important, it has increased our understanding of new clinically important nanocomposites and resulted in a recent UK Technology Strategy Board grant (*PI, Hatton, £500,000*)
3. **Nano-composites for load bearing applications and development of bioactive adhesive materials and bone regenerating allografts for skeletal applications.** (*Eire Government/EU Enterprise Ireland Technology Development grant, Brook, Farthing (Co-Investigators with University of Limerick) total awards £9,000 (2005) £200,000 (2006)*). Our expertise in biocompatibility assessment (e.g. Brook1-4) has led to a number of awards in this area. These projects investigate biological responses to nanostructured biomaterials to determine whether their safety is compromised, and to the development of improved devices for bone tissue repair, particularly in maxillofacial applications.
4. **Development of customised prostheses** (*DTI, van Noort, Brook, £64,500*). The development of custom implants is highly relevant to the challenges presented in maxillofacial surgery and the group have recognised expertise in bioceramics (Brook 2, Hatton 4, Johnson 2-3, Miller 2). This project has developed a viable method to fabricate

custom devices for bone repair in the face. This will also impact on the development of custom scaffolds for tissue engineering.

### ***Tissue Engineering***

This highly successful research theme is focused on the development of regenerative therapies for the skeletal system. It arose from strong EU collaborations and interaction with other groups in the University, particularly Chemistry and Engineering Materials. The area has been strengthened by the expertise provided by the appointment of **Crawford**. Our programme encompasses every aspect of tissue engineering including cell source and expansion, *in vitro* culture, and assessment of tissue constructs. Important clinical applications include facial reconstruction, especially in the nasal and ear area. The group is internationally recognised in skeletal tissue engineering. Major projects include:

5. **“SCAFCART”: Novel Bioresorbable Scaffolds and Culture Methods for Cartilage Tissue Engineering.** (EC FP5, Hatton, Brook, Crawford. Total value: €7.0M. Dental School award: £312,000). This key project pioneered the fabrication of layered, polymer-ceramic composite scaffolds with significant potential in anchoring constructs to bone tissue and set new standards for the biological quality of engineered tissues. (Crawford 1, 3). A PhD student on this project won the UK Society of Biomaterials e-poster prize.
6. **“SPIDERMAN” Development of novel spider protein derived implants and devices for orthopaedic surgery** (EC FP5, Hatton), Crawford (with Swedish University of Agricultural Sciences and 9 other partners). Total value €6.0M. Dental School award £251,071). We are widely recognised for expertise in scaffold evaluation (e.g. Crawford 4). This interdisciplinary research programme demonstrated the value of silk proteins for use in a range of medical applications as well as tissue engineering scaffolds. A PhD student on this project was awarded the British Society for Matrix Biology poster prize.
7. **Development of transgenic chondrocytes and human tissues for tissue engineering and therapeutic targeting** (BBSRC. Crawford, Hatton (with Barker (PI, UoA 4) Medical School), £125,575 (2005), £102,000 (2007)). We are one of only a few groups worldwide who have generated tissue engineered cartilage using transgenic chondrocytes.
8. **“EXPERTISSUES” Novel Therapeutic Strategies for Tissue Engineering of Bone and Cartilage Using Second Generation Biomimetic Scaffolds** (EC FP6 Hatton (PI), Brook, Crawford (with University of Minho, Portugal and 18 other partners). Total value €16,200,000. Dental School award £286,000). We have a pivotal role in this European network of excellence, leading one workpackage and contributing to technical programmes on scaffold fabrication, evaluation, and bioreactors. We have been able to produce novel bioglass-polymer composite scaffolds, evaluate new chitosan-starch scaffolds not available in the UK (Crawford 4), and characterise our own porous ceramic scaffolds with a leading international microCT groups (Ralph Muller, Zurich).
9. **Marie Curie Training Network** (EC FP6, Hatton (PI), Brook, Crawford. £286,000). Indirectly related to the Network of Excellence above, this project provides 2 research assistants for collaborative projects as well as opportunities for overseas researchers to undertake training in our laboratories.
10. **Electrospun Scaffolds** (BBSRC, Brook (with Ryan (PI), Chemistry, MacNeil, Engineering Materials) £450,000). Electrospinning offers the possibility of scaffolds with

unusual properties that resemble a synthetic extracellular matrix rather than a “traditional” cell support. This project connects the School to the polymer processing expertise in our Chemistry department.

11. **Tissue Engineering on Porous Bioceramic Scaffolds** (*EPSRC/Ceramisys CASE studentship, Hatton, Crawford. £76,000*). We have produced new ceramic scaffolds for bone tissue engineering.

In addition to these research projects we have also obtained funds to improve our infrastructure, including **Yorkshire Forward Regional Development Agency** funds (Hatton) of £72,000, and a **BBSRC Research Equipment Initiative** (confocal microscope, Brook & Hatton (with Haycock (PI), Engineering Materials), £357,457).

**Research strategy** over the next five years:

- Research into nanoscale composites for dental applications. There is evidence that nanostructured dental biomaterials offer superior properties (aesthetics, wear), yet further work is needed before such systems can influence the market and benefit patients.
- Custom implants, implant biomaterials, and scaffolds for tissue engineering. We will investigate fabrication methods for custom implants, including investigation of new ceramic biomaterials, and will promote the use of custom devices for repair of facial tissues.
- Improved biological quality for engineered tissues. We will investigate the factors that influence biological quality in tissue engineering, and in particular continue to improve our investigation of functional properties of engineered tissues.
- We plan to increase the amount of research undertaken in collaboration with industrial partners and directed towards new products and technologies for the medical device and healthcare technologies sectors.

## **B ORAL DISEASE**

**Group leader:** Professor Ian Douglas

**Members:** Bingle, Craig, Farthing, Griffiths, Murdoch, Rawlinson, Speight, Stafford, Thornhill, Walsh, Whawell.

**Background:** There have been several staff changes since the last RAE, which have resulted in an increased focus towards cellular interactions and immunity in disease. The group has been strengthened by the appointment of **four new clinical professors** (Speight, 2003, Farthing 2003, Thornhill, 2005, Griffiths, 2005) and **four non-clinical scientists** (Whawell, 2003, Bingle, 2005, Murdoch, 2006, Stafford, 2007). The group has **5 research assistants, 11 PhD students and 6 research technicians**. New staff have significantly enhanced research into integrins, chemokines, metastasis in oral cancer (Farthing, Murdoch, Speight, Whawell), cellular microbiology (Murdoch, Stafford), aspects of mucosal immunity (Bingle, Farthing, Thornhill), models of candidosis (Thornhill, Murdoch) and the genetic basis of pre-disposition to periodontitis (Griffiths). Members of the group have strong **collaborative links** with other departments in the University (Chemistry, Engineering Materials, Respiratory Medicine, Histopathology) and with other Universities nationally (Leeds, QMUL, UCL) and **Internationally (San Antonio, Harvard, Sao Paulo, Frankfurt, Beijing, Songkla)**

**Aims:** The group investigates the biology, diagnosis and prevention of oral diseases. Particular effort is focussed on identifying cellular and molecular mechanisms responsible for

oral mucosal diseases and infections, and on how this knowledge can be applied to improve diagnosis and treatment.

**Activities and Achievements:** During the last five years the group held **research grants with a combined total value of £1.25M** derived largely from medical charities, research councils and industry. The research strategy outlined in the last RAE has largely been achieved leading to significant publications and grant awards, 8 PhDs and 8 MPhils successfully completed. Staff who have left since the last RAE contributed to achievements including the first to develop a new index of enamel defects (**Brook AH**) and the formation of a spinout company (CellFactors) which developed human hypertrophic chondrocytes for bone repair (**Stringer**). Their departure has provided new opportunities to re-focus research whilst capitalising on the expertise left behind. Notable projects and their sources of funding include:

### **Oral mucosal immunity**

1. **Innate immunity.** PLUNCs are a family of novel proteins, which have structural similarity to lipopolysaccharide binding protein and are thought to be important in mucosal defence. They were discovered and sequenced in Sheffield by **Bingle** and coworkers (*Biochim Biophys Acta*; 2000,1493:363). A phylogenetic analysis has shown that PLUNCs are present in saliva and uniquely that different PLUNCs are expressed in different salivary glands (Bingle 1,2). Further studies are investigating the role of PLUNCs and other defence proteins (WAP) in innate immunity in the oral cavity (Bingle 3,4).
2. **Oral keratinocytes and mucosal immunity.** **Farthing** has shown that pro-inflammatory cytokines stimulate adrenomedullin production by keratinocytes resulting in increased adhesion molecule expression (Farthing 2,3,4). She showed that, unlike in gut and breast, lymphocytes expressing  $\alpha\epsilon\beta7$  do not bind to E-cadherin in the oral mucosa. Current work (*Sheffield Hospitals Charitable Trust; Farthing, £48,111, University PhD Studentship, Farthing, Whawell, £40,500*) in collaboration with the **Babraham Institute, Cambridge** (Kilshaw) aims to identify the oral ligand and define the role of  $\alpha\epsilon\beta7$  in oral epithelial-lymphocyte interactions. **Thornhill** (3,4) has studied mechanisms of keratinocyte activation in oral lichenoid reactions and has demonstrated the role of ICAM1 and certain cytokines.

### **Oral cancer**

3. **Role of integrins in oral cancer.** **Speight** led a group who identified the fundamental role of the  $\alpha v\beta6$  integrin in regulating epithelial cell invasion in oral cancer (Speight 1,2,3), which is now leading to new therapeutic interventions. Current work (*Yorkshire Cancer Research, Whawell, Speight, £80,000*) is investigating integrin-ADAM (A Disintegrin And Metalloproteinase) protein interactions in cancer cell invasion and malignant progression.
4. **Biomarkers for head and neck cancer** (*Mexican National Council for Science and Technology (CONACYT), PhD studentship, Speight. CAPES, Brazil Government Fellowship (to Vargas), Speight £17,500*) Minichromosome Maintenance Proteins are novel markers of cell cycle progression. We have shown them to be predictive of progression of oral dysplasia to malignancy and superior to conventional markers such as Ki-67. Using tissue microarray technology the group is studying large numbers of specimens to determine the true prognostic capability of these proteins. Other studies have shown that analysis of DNA ploidy can also predict malignant progression of oral dysplastic lesions. New funding has been obtained to conduct the first prospective

clinical trial to evaluate DNA ploidy analysis in oral cytology specimens. (*Sheffield Hospitals Charitable Trust; Speight, Craig, £65,000*)

5. **Oral cancer metastasis** (*PhD fellowships to Collier: Barts and the London, Joint Research Board, £65,000; CRUK, £21,000; RCS Edin, £43,000; all sponsored by Farthing. Pakistan Gov't PhD studentship, Farthing*). **Farthing's** group were the first to show that certain lymphocyte-derived chemokines can regulate oral epithelial cell behaviour, including migration and that these act through specific receptors not previously identified on epithelial cells. This work may have a major impact on our understanding of control of metastasis in oral cancer. A PhD student on this project (Collier) won the **BSDR Junior Colgate prize (2005)** and the **IADR Junior Hatton Award (2006)**.

**Murdoch** has shown that macrophages induce angiogenesis and tumour metastasis by a mechanism involving chemotaxis to angiopoietin 2 (Murdoch 1).

### ***Improving diagnosis/detection of infection***

6. **A new sensor for bacteria using binding or specific degradation of stimuli responsive polymers** (*EPSRC, Douglas (with Rimmer, Swanson (Chemistry), MacNeil (Engineering Materials), £614,480*). This project is the first to use unique "smart" polymers with tethered antibiotics that bind directly to bacteria or peptides that can be cleaved by bacterial proteases to detect bacteria or their products. Binding or modification results in conformational change of the polymer allowing detection by a fluorescent signal (NRET). This approach has numerous potential clinical applications, including early detection of wound infection as part of 'smart' wound dressings.
7. **Disposable protease sensor array for monitoring inflammation.** This group has characterised clinical parameters and gingival crevicular fluid constituents in periodontal disease (Rawlinson 1,2,3) and has developed a clinical biosensor for periodontal inflammation which will monitor three proteases in gingival crevicular fluid (*BBSRC Douglas, Rawlinson, (with Krause, QMUL) £89,839*). Certain profiles may be predictive of periodontal tissue breakdown.
8. **Diagnosis and management of periodontal disease.** **Griffiths** was recruited as an expert in this area and has studied the genetics and treatment of aggressive periodontal disease (Griffiths 1,3,4). Ongoing studies include a pivotal multicentre RCT to evaluate the effect of a single treatment of photodynamic disinfection in adults with chronic periodontal disease (*Ondine Research Laboratories. Griffiths, (with Suvan and Donos, UCL) £80,000*).

### ***Microbial-cell interactions***

9. **Candida-endothelial interactions under conditions of flow** (*NIH. Thornhill (with Lopez-Ribot, San Antonio), £170,000*). The group has developed an *in-vitro* model for studying candida-endothelial interactions under conditions of flow, and subsequent trans-endothelial migration. It is the first study to use flow conditions to mimic the tissue invasion that occurs during systemic candidosis. An engineered strain of *Candida albicans* is being employed in which morphogenesis and virulence can be controlled. This will lead to improved understanding of the pathogenesis of this serious infection and improved approaches to therapy.
10. **Host-microbial interactions.** The group have considerable expertise in the study of bacterial-cell interactions and other aspects of pathogenicity (Murdoch 2,3,4; Stafford 1,2,3,4; Whawell 4). Advances achieved include the identification of molecular mechanisms involved in streptococcal-platelet interactions (Douglas 1,2,4), which

increase our understanding of the pathogenesis of infective endocarditis. Recently the group has identified sub-populations of the periodontal pathogen *Porphyromonas gingivalis* that are highly invasive into epithelial cells and current work (*Thai Government PhD studentship, Douglas*) is using gene microarrays to identify the transcriptome that characterises this hyperinvasive phenotype.

**Research strategy** over the next five years:

- Develop *in vitro* models for studying at the cell and molecular level common oral diseases including oral cancer, oral lichen planus, recurrent aphthous stomatitis, and oral candidosis.
- Develop models to study mechanisms of oral cancer metastasis, including studies of interactions of tumour cells and endothelium under conditions of flow.
- Investigate the role of innate and immune-mediated host defence mechanisms in oral diseases and develop genetic epidemiological studies to investigate susceptibility.
- Investigate the role of integrins and chemokines in the behaviour and cellular interactions of oral epithelial cells and leukocytes.
- Investigate the diagnostic value of potential biomarkers of oral cancer.
- Develop biomimetic polymer vesicles for intracellular targeted delivery of genes, drugs and radioisotopes to head and neck cancer.
- Characterise the molecular events in oral bacterial-human cell interactions, including platelets and epithelial cells, with a view to understanding their impact on disease and the development of novel approaches for prevention.
- Investigate methods for improved diagnosis and treatment of periodontal diseases, and study aspects of disease progression.

## C ORAL NEUROSCIENCE

**Group Leader:** Professor Peter P Robinson

**Members:** Andrew, Atkins, Loescher, Boissonade, Rodd, Smith, Yates.

**Background:** This group has expanded, new expertise has been introduced, and substantial progress made toward the objectives described in RAE2001. Since 2001 we have recruited **Andrew**, an expert on whole animal neurophysiology and **Yates**, who was awarded a UKCRC/HEFCE Senior Clinical Lectureship. The group has **3 research technicians** and **3 post-doctoral research assistants** who provide support and expertise for specific methodologies. **Seven PhD students** are currently registered for higher research degrees. Thus, twenty one neuroscientists attend regular group meetings and provide an ideal milieu for critical scientific appraisal and advice. Excellent laboratory facilities are based in the Dental School and in recently refurbished laboratories in the Department of Biomedical Science (*in vivo* studies, electrophysiology) allowing opportunities for collaboration with colleagues from other departments. We have national collaborations at the Universities of Leeds and Bristol and strong **international collaborative** links with neuroscience groups in the **Karolinska Institute, Stockholm** and the **University of São Paulo, Brazil**. We also have strong links with several **industrial partners**; *GlaxoSmithKline* has provided a series of grants and studentships, *Pfizer* has supported two clinical studies, and *Renovo* has supported a new field of laboratory investigations (see details below).

**Aims:** The overall aim is to develop new methods of managing the pain or distressing sensory disturbances that result from disease or nerve injury. Our philosophy has been to undertake laboratory animal studies to understand basic mechanisms and to define principles of treatment which are then applied to the management of patients. Finally the outcome has been assessed in prospective quantitative clinical studies. This sequence is exemplified by our studies on the management of **patients with trigeminal nerve injuries**,

in which we are world leaders. Our ability to pursue this approach results from our base within a clinical school and from the combined expertise to undertake a full spectrum of laboratory projects. Clinically, we have developed a large referral base for patients with trigeminal nerve injuries, who travel to Sheffield from throughout the UK and from abroad. This provides unique opportunities to obtain patient material for laboratory evaluation and correlation with symptoms.

**Achievements:** Since 2001 **10 PhD students** and one MPhil have successfully completed. The group has held research grants with a **combined value of over £1.5M**. Specific projects with the sources of funding and outcomes include:

### **Trigeminal nerve injuries**

1. **Mechanisms of injury-induced pain.** (*Wellcome Trust. Loescher, Boissonade, Robinson, £42,055. Sir Jules Thorn Charitable Trust. Robinson, Loescher, Boissonade, £73,300 since 2001*). Using animal tissue and our unique archive of human lingual nerve specimens (obtained at the time of nerve repair), we have shown changes in expression of neuropeptides in damaged nerves (Robinson 1,2,3). With quantitative image analysis we were the first to demonstrate significantly higher levels of calcitonin gene-related peptide in patients with pain (Loescher 1), thereby revealing a potential therapeutic target. Electrophysiological studies demonstrated that neuropeptides applied either topically or by close-arterial injection to damaged axons could modulate abnormal neural activity (Loescher 4; **Unilever Poster Prize** awarded to Smith in 2003).
2. **Ultrastructural studies on human lingual nerve neuromas.** (*Action Medical Research, Robinson, Loescher, Boissonade, £92,500 since 2001*). This quantitative ultrastructural study revealed a series of morphological changes in damaged axons, including alterations in axonal size, myelin sheath thickness, and the extent of exposure and apposition of non-myelinated axons, which contribute to the development of sensory disorders after injury (Loescher 2; Robinson 4; **Unilever Poster Prize** awarded to Vora in 2002).

### **Enhancing nerve regeneration**

3. **The effect of scarring on axonal regeneration.** (*Wellcome Trust, Atkins, Boissonade, Loescher, Smith, Robinson, £173,243*). Following evaluation of the effects of neurotrophins on regeneration (Smith 1,2,3,4), we have assessed the role of scarring. In an initial proof-of-concept study using transgenic mice this innovative study provided the first clear evidence that scarring at a nerve repair site impeded regeneration and recovery. Subsequent evaluation of a range of potential scar-reducing agents (with Ferguson and *Renovo*, Manchester) has identified a potential therapeutic agent for enhancing regeneration in patients (Atkins 1,2; **Senior Colgate Prize** awarded to Atkins in 2005).

### **Central mechanisms of neuropathic pain.**

4. **Spinal mechanisms underlying chronic pain.** (*Wellcome Trust, Andrew, £108,952*). Building on his post-doctoral studies (Andrew 1,3,4) **Andrew** was recruited to bring *in vivo* electrophysiological expertise. This study is assessing quantitative physiological characteristics of lamina I spinoparabrachial neurones in different models of neuropathic pain. The goal is to identify specific classes of neurons in which the receptive properties change after a nerve injury, and could therefore account for behavioural signs of neuropathic pain.
5. **Mechanisms of central sensitization.** (*MRC Capacity-Building Studentship, Andrew, Robinson, £57,400*). This project was funded to increase the number of *in vivo* physiologists in the UK, an area of research that had been identified as being of strategic

importance to the national science base. The project will focus on whether distinct types of glutamate receptor sub-units or calcium channels are involved in nerve injury-induced sensitization of spinal nociceptive projection neurons.

### **Dental Pain**

6. **Mechanisms of human dental pain.** (*MRC/GlaxoSmithKline CASE studentship. Boissonade, Rodd, £60,000; University of Sheffield Studentship. Rodd, Boissonade, £25,000*). Immunocytochemistry and RTPCR were used to identify receptors in the human tooth pulp, and link changes in their expression to clinical symptoms. It provided the **first evidence** that changes in vanilloid- and PAR2-receptor expression were linked with the presence of pain, and that expression of vasoactive intestinal polypeptide is increased with caries, and may have a role in neuronal regeneration (Rodd, 1,2,3,4, Boissonade 1).

### **Pharmacology of trigeminal pain**

7. **Pharmacology of trigeminal inflammatory pain** (*GlaxoSmithKline, 8 project grants, to Boissonade, £382,217*). These projects have developed an animal model to study central changes that result from inflammation and stimulation of the dental pulp. This model can predict analgesic efficacy more accurately than other models (Boissonade 3) and we have used it to assess the potential analgesic efficacy of a variety of novel compounds.
8. **Pharmacological targets for trigeminal inflammatory and neuropathic pain.** (*BBSRC/GlaxoSmithKline CASE studentship, £53,000. MRC/GlaxoSmithKline CASE studentship. Boissonade, Loescher, Yates, Robinson, £68,000*). These studies investigated the role of specific sodium channels, vanilloid receptors, and a range of other regulators of neuronal excitability in models of inflammatory and neuropathic pain (Boissonade 2,4). The industrial link provided access to new pharmacological expertise and novel agents, and revealed a series of new potential therapeutic targets (Yates 2,3,4).
9. **Immediate-early gene expression and intracellular signalling in the trigeminal system.** (*BBSRC/GlaxoSmithKline Industrial Partnership Award. Boissonade, £359,000*). This project is investigating signalling molecules within stimulation-transcription pathways that are activated by prolonged neuronal activity and are relevant to mechanisms of synaptic plasticity. The project will examine these mechanisms using a variety of molecular markers to identify central changes that may be linked to the development of oro-facial pain.
10. **Clinical management of oro-facial pain and dental anxiety.** (*Pfizer. Loescher, Robinson, Yates, Smith, £16,000. GlaxoSmithKline, Boissonade, Yates, Robinson, £39,000*). The efficacy of the new membrane-stabilizing drug, Pregabalin, is being assessed in the management of patients with burning mouth syndrome, and with dental anxiety. With a view to future work we are also evaluating the intensity, variability and duration of dental pain associated with periapical inflammation.

### **Research strategy** over the next five years:

- Use laboratory and clinical studies to evaluate novel medical and surgical treatments for the management of oro-facial pain and nerve injury-induced sensory disorders.
- Evaluate and optimise the efficacy of scar-reducing agents in enhancing recovery after peripheral nerve injury.
- Characterize anatomically, physiologically and pharmacologically the ascending pain pathways that are of critical importance in underpinning the behavioural changes caused by tissue damage or inflammation.

- Further our understanding of inflammation-induced thermal hyperalgesia by correlating expression of a variety of transient receptor potential channels with patient responses to thermal testing and reported pain histories.
- Identify intracellular signalling pathways involved in central changes linked to the development of oro-facial pain.

## D DENTAL PUBLIC HEALTH

**Group Leader:** Professor Peter G Robinson

**Members:** Baker, Benson, Deery, Gibson, Lennon, Rodd, Speight.

**Background:** This group was formed in 2006 following new appointments in Dental Public Health (**Robinson PG** (2002), **Lennon** (2004)), Psychology (**Baker**, 2005), Sociology (**Gibson**, 2004) and Paediatric Dentistry (**Deery**, 2006). The group has effective collaborations with researchers in the UK and overseas (**Toronto, Uganda, Dublin**), with substantial grant income and an increase in research outputs. The group has **3 research assistants**, **10 PhD students** and has held 6 funded PhD studentships.

**Aims:** To use the theories and empirical traditions of Dental Public Health, Sociology and Psychology to improve the oral health of individuals and communities. The group works in three areas. **Oral health and quality of life** adopts a psychosocial approach to understand oral health from the patient's perspective, allowing more comprehensive evaluation of clinical interventions. Our **Children and Young People** programme extends the patient-centred approach by giving children an active voice in relation to their oral health. **Evaluation of health care** considers the costs and effects of interventions for evidence-based policy and decision-making at national, local and clinical levels.

**Activities and Achievements:** Total value of research grants awarded to group members during this assessment period is **over £1.1M**. Key projects include:

### ***Oral health and quality of life.***

1. **Testing a conceptual model of oral health: a structural equation modelling approach.** The use of health related quality of life data requires a sophisticated understanding of the relationship between clinical status and its impact on everyday life. This study (Baker 3) used novel statistical techniques on pooled data to test and confirm the validity of the dominant conceptual model of oral health used in dentistry.
2. **The determinants and consequences of oral health related quality of life.** The group has considerable expertise using quality of life measures and understanding the relationships between clinical status and quality of life (Baker 1,2: Gibson 1,2,4: Robinson 2,3). Current work includes a longitudinal study in children (*Malaysian Government PhD studentship. Robinson, Baker £60,000*) which is the first to use an underlying theoretical construct to explore these relationships in teenagers.
3. **Does undergoing orthodontic treatment affect the quality of life of adolescents?** (*British Orthodontic Society Foundation, Benson (with QMC, Manchester & KCL) £40,201*). This multicentre longitudinal study compares the quality of life of young people during and after orthodontic treatment with that of children not receiving treatment.

### ***Children and young people***

4. **Improving Somali health: an e-learning initiative for housebound Somali women.** (*The Health Foundation, Rodd, £84,000*) This project demonstrated the effectiveness of innovative participatory health education techniques in this high-disease, hard to reach population.
5. **Exploring Asian British experience of living with visible disfigurement.** (ESRC /Sheffield Health and Social Research Consortium CASE award, Baker, Gibson (with Thompson (Psychology), £50,000). Little attention has been given to the experience of children with disfigurement, still less so amongst minority groups. This research uses oral health as a case study in visible disfigurement.
6. **Behind the smile: Coping and self-esteem in children with dental and oro-facial differences** (*Sheffield Hospitals Charitable Trust. Rodd, Baker. £32,100*) This child centred project combines qualitative and quantitative methods to explore the impact of dental differences as children make the important transition from primary to secondary school.
7. **The Voice of the child in cleft lip and palate.** (*University of Sheffield, PhD studentship, Gibson, Rodd (with James (Sociology)). £40,500*). Despite the great strides in clinical care of children with cleft lip and palate, their experiences and wishes have not been formally considered in the condition's management. This study uses social research approaches novel in dentistry.
8. **Family impact of cleft lip and palate.** (*Sheffield Health and Social Research Consortium, Baker (with Stern, Willmot (NHS Trust) £15,633*). This study assesses family impact of cleft lip and palate, and the primary carer's levels of stress and adjustment.
9. **Changing families changing food. Socio-historical changes in food patterns in Bradford and Barnsley** (*The Leverhulme Trust. Gibson (with Jackson (PI), Smith, Ward (School of Health and Related Research) Dental School share £20,000*). This £1.2M multidisciplinary project focuses on the family through the medium of food. Using common risk factor approaches, the dental component considers the transmission of values through generations by collecting data from children and parents.

### **Evaluation**

10. **Cochrane systematic reviews.** The group have undertaken a number of internationally important systematic reviews. A review of **powered vs manual brushes** for oral health (Robinson 2) was widely cited in the national and international lay press and was the most frequent hit in the Cochrane library and Journal of Dentistry. Updates have been equally prominent. It has set new standards in trial design in this area. The findings of **Fluorides for the prevention of white spots on teeth during fixed brace treatment** (Benson 2) were cited and discussed in the Journal of Evidence Based Dentistry and the British Dental Journal abstract summaries.
11. **Training the dental team away from the hospital** (*NDWU, Brook AH, Robinson, £597,000*). This project developed and evaluated dental outreach training. Qualitative evaluations informed a randomised controlled trial showing that outreach increased students' treatment planning ability and confidence (Lennon 1; Robinson 4). This is the most robust evaluation of dental outreach to date. Its findings are reflected in national educational policy and have been used by other schools.
12. **Fluorides and oral health. Lennon** is a world-leading expert in fluoridation. His work has considered the optimal concentrations of fluoridated milk (Lennon 2) and has also shown its limited effectiveness at current doses compared to fluoridated water (Lennon

3). Currently he is working to optimise implementation of water fluoridation (*British Fluoridation Society, Lennon, £122,000*). In other studies, **Benson** has evaluated the clinical effectiveness of fluoridated bands in orthodontic treatment (Benson 1,2)

13. **Evaluation and cost-effectiveness of oral cancer screening.** (*NHS Health Technology Assessment Programme. Speight (with Moles, Downer (UCL), Palmer (York). £67,300*). This major programme used costing data, three systematic reviews and a bespoke computer-simulation model (Speight 4). Data showed that opportunistic screening in primary care may be cost-effective. Value of Perfect Information analyses identified suitable areas where research can be most effectively targeted. This work has informed national policy. The group (with Baker) are now evaluating factors which may affect case referral from primary to secondary care.

**Research strategy** over the next five years:

- Develop our understanding of the relationships between clinical factors and health-related quality of life and to explore what factors mediate these relationships.
- Continue to explore the extent to which quality of life is a dynamic concept.
- Consider the voice of the child when assessing oral health and planning and evaluating oral health services.
- Further evaluate personal, clinical and community-based oral healthcare interventions using complementary methods.

## EVIDENCE OF ESTEEM

### Honours and awards.

During the assessment period **Lennon** was awarded an **OBE** for services to dental health, **Robinson PP** was elected a Fellow of the Academy of Medical Sciences. **Speight** (2003) and **Robinson PP** (2005) presented the Charles Tomes Lecture of the Royal College of Surgeons, England. **Speight** (2003) and **Craig** (2004) were awarded FDS Edinburgh *ad hominem* and **Hatton** (2003) was awarded the Biocompatibles Endowed Prize of the UK Society for Biomaterials. In 2006 **Robinson PP** gave the prestigious Graham Embery Memorial Lecture at the BSDR/PEF.

### Research prizes.

Staff or their students have won **more than 30** national and international research prizes during the assessment period. These include:

American Ass Oral & Maxfac Radiology	2001	Poster Prize
RSM, Pathology Section	2001	Presidents prize
BSDR/Pan European Federation	2002	Unilever Poster Prize
IADR	2002	Colgate Research in Prevention award
International Ass for the Study of Pain	2002	Ronald Dubner prize
UK Society Biomaterials	2002	e-Poster Prize
BSDR	2003	Unilever Poster Prize
American Academy of Oral Medicine	2004	Robert Schattner Prize
Brit Society for Matrix Biology	2004	Poster Prize
BSDR	2004	Ivoclar Dent Mat Prize
IADR	2004	Colgate Research in Prevention Award
UK Society Biomaterials	2004	e-Poster Prize
BSDR	2005	Ivoclar Dent Mat Prize
BSDR	2005	Junior Colgate Prize
BSDR	2005	Senior Colgate Prize
BSDR	2006	Unilever Poster Prize
IADR	2006	Junior Hatton Award
IADR	2006	John Clarkson Fellowship
UK Society Biomaterials	2006	Poster Prize
UK Society Biomaterials	2006	Oral Prize
Journal of Orthodontics	2007	Scientific Paper of the Year (Maney prize)

### Service on National and International Bodies

School staff have major leadership roles in the dental profession and within their respective specialist societies, and have served on 40 national and international bodies. **Senior positions** are summarised in the table below:

Name	Organisation	Role
Benson	Clinical Orthodontic Collaboration	Secretary
Craig	British Association for Forensic Odontology	<b>President</b> (06 – 08)
Craig	BDA Health & Science Committee	<b>Chair</b> (00-03)
Douglas	BSDR, Oral Microbiology and Immunology Group	<b>Chair</b>
Farthing	BSDR, Management Committee	Ass Treasurer (05-)

Farthing	BSDR/MRC Dental Research Review	Member
Farthing	BSDR, Oral Pathology and Medicine Group	President (07)
Hatton	DTI global watch Mission to USA (2005)	Co-ordinator
Hatton	UK Society for Biomaterials	<b>President</b> (04 - )
Lennon	British Fluoridation Society	<b>Chair</b>
Robinson PG	BSDR, Management Committee	Editor (05 - )
Robinson PP	Association British Academic Oral & Maxillofacial Surgeons	<b>President</b> (05 - 07)
Robinson PP	Academy of Medical Sciences Sectional Committee	<b>Member</b>
Robinson PP	Academic Advisory Committee Oral & Maxillofacial Surgery	<b>Chair</b>
Rodd	British Society of Paediatric Dentistry, Teachers Group	Treasurer (03 - 05)
Speight	British Society for Oral & Maxillofacial Pathology	<b>President</b> (01 – 03)
Speight	BSDR, Awards Committee	<b>Chair</b> (07 - )
Speight	IADR, Hatton Committee	Member/ <b>Chair</b> (02)
Speight	IADR, Oral Medicine and Pathology Group	<b>President</b> (02 - 03)
Speight	International Association of Oral Pathologists	<b>President</b> (06 – 08)
van Noort	BSDR Dental Materials Group	<b>President</b> (01 - 05)
van Noort	UK Dental Materials Panel	<b>Chair</b>
Whawell	BSDR, Oral Pathology and Medicine group	Secretary

### Keynote and invited addresses to major national and international meetings

Staff have presented keynote and invited lectures at **50** national and **over 60** international meetings since 2001. Prestigious addresses at **international** meetings include

<b>2001</b>	Robinson PG	Quality in Health care	Nagasaki
	Speight	International Congress on Oral Cancer	The Hague
	Thornhill	International Congress on Oral Immunology	Lillihamer
	van Noort	European Dental Materials Conference	Glasgow
	van Noort	International Conference on Adhesive Dentistry	Berlin
<b>2002</b>	Craig	Singapore Dental Association	Singapore
	Farthing	International Association of Oral Pathologists	Singapore
	Lennon	Association for Dental Education in Europe	Ljubljana
	Speight	International Association of Oral Pathologists	Singapore
	van Noort	IADR/PEF, Symposium	Cardiff
<b>2003</b>	Brook	European Dental Materials Conference	Bergen
	Craig	European Ass Forensic Odontology	Switzerland
	Farthing	IADR, Symposium	Gothenberg
	Lennon	WHO workshop	Rome
	Lennon	WHO workshop	Cairo
	Thornhill	International Congress on HCV and Lichen Planus	Rome
<b>2004</b>	Craig	International Association of Oral Pathologists	Madrid
	Robinson PG	World Workshop on Oral Manifestations of HIV	Thailand
	Robinson PP	American & Canadian Pain Societies	Vancouver
	Speight	International Association of Oral Pathologists	Madrid
	Speight	Dean's Lecture, University California, SF	USA
	Speight	Maltese Dental Association	Malta
<b>2005</b>	Lennon	American Dental Association	Chicago
	Loescher	American & British Associations OMFS	Boston

	Hatton	Baltic Stem Cell Conference, University of Rostock	Germany
	Hatton	Associated Nanotechnology Congress, Rice University	USA
	Robinson PP	American & British Associations OMFS	Boston
	Robinson PP	French Dental Association	Paris
	Rodd	Australian Dental Association	Adelaide
	Rodd	Australasian Paediatric Dentistry Conference	Adelaide
	Speight	Asian Society Oral & Maxillofacial Pathology	Korea
	Speight	Ed & Herb Stein Chair Symposium, Univ Tel Aviv	Israel
	Speight	WHO Workshop on Oral Precancer	London
<b>2006</b>	Gibson	BSDR/PEF, Symposium	Dublin
	Hatton	International Sobre Art	Edinburgh
	Lennon	WHO workshop	Beijing
	Lennon	WHO/IADR workshop	Geneva
	Robinson PG	BSDR/PEF	Dublin
	Robinson PG	International Association for Dental Research	Brisbane
	Smith	American Ass Oral & Maxfac Surgeons	San Diego
	Speight	International Association of Oral Pathologists	Brisbane
	Thornhill	World Workshop in Oral Medicine	Puerto Rico
<b>2007</b>	Hatton	Finnish Society for Tissue Engineering	Tampere
	Hatton	European Medicines Agency (EMA)	Lisbon
	Rodd	International Association of Paediatric Dentistry	Hong Kong
	Speight	Centre of Excellence 'SuperDentist' development programme	Osaka
	Speight	European Congress of Pathology	Istanbul

### International research Collaborations

The School collaborates widely throughout the UK and overseas. There are current International research collaborations with over 20 universities including in USA, Canada, New Zealand, Brazil, Thailand, China, Uganda, Netherlands, Sweden, Germany, Italy.

### Editorial Activities

Staff sit on the editorial boards of **over 20 research journals** including Journal of Dental Research, Journal of Tissue Engineering & Regenerative Medicine, Journal of Dentistry and Journal of Medical Engineering and Technology. Staff are senior advisers to Oral Oncology and the British Dental Journal.

Five staff act as editors to major journals: Archives of Oral Biology (**Speight**), International Journal of Paediatric Dentistry (**Rodd**), International Journal of Forensic Odontostomatology (**Craig**), Journal of Orthodontics (**Benson**) and Oral Surgery (**Smith**).

Staff also regularly **referee papers** for over 40 national and international journals.

### Grant refereeing.

Staff have refereed grants from a wide range of prestigious grant-awarding bodies, including: MRC, Wellcome Trust, EPSRC, BBSRC, Action Medical Research, Cancer Research UK, NHS, Royal College of Surgeons, Welsh Office, British Heart Foundation, Irish Health Board.

### Examination of Overseas Research Degrees

Staff frequently examine research degrees throughout the UK, but as a measure of international esteem, a number of staff have examined research degrees for overseas universities: **Boissonade** (Queensland Australia), **Douglas** (Trinity College Dublin, Prince of Songkla University, Thailand), **Hatton** (University Twente, Netherlands), **Robinson PG** (Hong Kong, Toronto), **Speight** (Malta, Melbourne), **van Noort** (Turku, Finland, ACTA, Netherlands).

#### **Conferences organised.**

A number of staff have been involved in the organisation of research related national and international meetings including (those in bold were held in Sheffield): **British Society of Paediatric Dentistry** (Rodd, 2002), British Society for Oral and Maxillofacial Pathology (Speight, 2003), International Conference for Critical Health Psychology (Baker, 2005), International Association of Oral Pathologists (Speight, 2002, 2004, 2006, 2008), **British Association for Lung Research** (Bingle, 2006), **Association of British Academic Oral & Maxillofacial Surgeons** (Robinson PP, 2006), BSDR/Pan-European Federation (Douglas, Whawell, 2006; Robinson PG, Speight, 2008), IADR (Farthing, 2003). European Society for Biomaterials (Hatton, 2007).