ANNUAL
RESEARCH
REPORT 2008

Academic
Centre for Dentistry
Amsterdam
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INTRODUCTION

The annual report starts with chapters containing the annual survey of the director, and overviews of the scientific activities. As in preceding years the scientific performance is thereafter presented for each programme per department. Detailed information is given of dissertations, publications in journals indexed in the database of the Institute of Scientific Information, other scientific publications, professional publications, indicators of esteem and collaborations.

Some issues for 2008 are specifically mentioned in this report. These include the external assessment of the research by an international peer review committee, the reorganisation of the organisational structure in ACTA, reductions in the budget for research, and the determination of two main research themes on which the research of ACTA will be focussed.

An overview of the output is presented on page 11. This table summarises for each department and section the number of publications that have appeared in 2008 in SCI-journals, the number of other scientific publications, and the number of professional publications. Data on abstracts and on popularising publications are not included in this report. Also the personnel involved in full time equivalent (fte) and the impact factor-sum (IF-sum) are included in this table. The IF-sum was calculated for each department by adding together the impact factor values of all 2008 publications according to the principle listed in the footnotes of the table. We are pleased to note that the output in 2008 was high: the number of publications in SCI indexed journals and the IF-sum were substantially higher that in any of the previous years of the research institute.

Research Institute ACTA
prof.dr. V. Everts director of research
dr. T.J.M. van Steenbergen co-ordinator of research

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REPORT OF THE DIRECTOR

The Research Institute ACTA

- **mission statement**
  Dental research at ACTA focuses on the study of health and diseases of the tissues in and around the oral cavity. Beside infectious diseases like dental caries and periodontal inflammatory processes, attention is paid to the development, function and regenerative capacities of the hard tissues in general, dysfunction of the masticatory system and diseases of salivary glands and oral mucosa. It is the general aim to improve strategies for diagnosis and prevention of diseases and functional repair of the affected tissues in and around the oral cavity. In our attempts to fulfil this mission special care is taken to establish:
  - integration of basic disciplines with the clinical fields
  - education and further academic training of PhD-students
  - promotion and improvement of the quality of the research in ACTA with special attention to the translation of the results into applications in clinical dentistry. To this end there is a vivid interaction with professional dental organisations and industries.

- **positioning of the research institute**
  The Research Institute ACTA is the only institute for research of the Academic Centre for Dentistry Amsterdam (ACTA). ACTA comprises the combined Faculties of Dentistry of the University of Amsterdam and the VU University Amsterdam. National cooperation is organized in the Netherlands Institute of Dental Sciences (Interuniversitaire Onderzoekschool Tandheelkunde, IOT). In 2008 two main research themes were chosen, on which research will be focused. These main themes are formed around scientifically strong groups and address relevant clinical topics. The first theme is "Oral infections and immunity"; this theme focuses on the etiology, prevention and therapy of caries, periodontal and endodontal infections. The second theme is "Bioengineering, reconstruction and function repair of teeth and bone". This theme focuses on the biological process of adaptation and repair of bone and periodontium, and on biocompatibility of dental materials.

- **description of output, leading scientific journals in the field**
  The research has a relatively broad focus and deals with questions originating from clinical dental practice. Within the overall research programme there are large variations in the approaches taken, ranging from basic medical-biological to clinically applied. This is reflected in the type of journals where ACTA researchers publish. Some groups primarily present their findings in journals read in the dental research community, while others also aim for the general medical-biological literature.

Evaluation of the research program

- **external evaluation**
  In 2008 an external evaluation of dental research in the Netherlands was completed according to the new Standard Evaluation Protocol designed by the VSNU. A four day site visit was included in this evaluation. In general, the evaluation committee considered the quality, production, relevance and academic reputation of dental research at ACTA as very good. The committee has given several recommendations for future research planning. Based on this report, the director of the research institute has conceived several intentions to further strengthen the research at ACTA. For more details about this evaluation we refer to the assessment report of the committee.

- **long time performance**
  The performance of the research institute and its member groups is evaluated over a longer period (see Table 1). These data show that the number of dissertations per year has fluctuated between 6 and 20. This reflects variations in external collaborations (such as non-ACTA employees receiving a PhD from our universities) and - in particular - tenure staff members
finishing their PhD. The current figure of about 13 dissertations reflects the number of PhD students 'employed'. The percentage of PhD students that finished their thesis averages at 90% over the last 15 years, and the mean time between start of employment and defending the thesis is 4.6 years. This figure is corrected for the 0.6 to 0.8 fte employment of several PhD students and for long leave of absence (e.g. illness) of some PhD students.

The main attention in the research assessment at the individual and department level is given to international publications in journals with a peer review referee system and an impact factor (SCI publications). This category shows a slightly increasing number over the last 15 years, despite a roughly stable input in fte scientific personnel. The average quality of the publications has significantly improved over that 15-year period, as judged by the continuous increase of the impact factor sum (see figure 4). In 2008 the highest number of SCI indexed publications and the highest IF sum was obtained.

**remarkable events in 2008**
Outstanding contributions for the year 2008 that we like to mention are publications in high quality biomedical journals (i.e. Journal of Clinical Investigation, Journal of the National Cancer Institute, Hepatology, Journal of Cellular and Molecular Medicine, Arthritis and Rheumatism Research, Faseb Journal, and Biomaterials, all journals with an impact factor higher than 6), and four publications in the Journal of Dental Research, which is considered the most prestigious dental journal with the highest impact factor in the category.

In addition to the output indicators given, the percentage of papers in high impact journals in the field gives valuable information. ACTA published in total 176 scientific papers in journals with an impact factor (SCI journals). 64% of these papers appeared in journals belonging to the field “Dentistry, Oral Surgery and Medicine”. 31% of these publications were in the top 25% of the journals and 62% in the top 50%. This means that a relatively large number of publications were published in the top journals in the field.

On a personal level a considerable number of ACTA employees rank in the top of the dental and biomedical research community, as determined by the various indicators of esteem. In 2008 a total of 17 awards were received by ACTA scientists for their achievements.

**assessment at the department level**
When the research at the department or section level is considered it is clear that some groups perform very well throughout the years and are stable in terms of input and output parameters (personnel, PhD students, publications, dissertations etc). In the evaluation report of dental research in the Netherlands which was performed in 2008 these groups received ratings between 4 and 5 (on a 5 point scale). Programmes that have got excellent ratings in 2008 include those from the sections Cariology/Experimental Preventive Dentistry, Oral Biochemistry, Oral Cell Biology, and Social Dentistry.

Societal impact

**congresses attended and organized**
In 2008 ACTA researchers have again contributed actively in internationally held meetings, workshops and symposia, both as organisers and participants. A total of 115 lectures were given as ‘invited speaker’ at international congresses and symposia. In addition a large number of presentations were given at international congresses after selection on submission of abstracts and during congresses and symposia for a Dutch audience. Due to this large number, congress abstracts are not listed in this annual report. A total of 18 international meetings were organised by members of one of the departments of ACTA.

**societal impact**
The prime societal value of a strong research programme is obviously its effect on the quality of the teaching given at ACTA, both for undergraduate students, graduate students, students participating in the post-initial specialist courses, and for PhD students. New findings and concepts are included in the curriculum at ACTA, but also presented to dental practitioners at
frequently held education activities, e.g. ACTA Quality Practice. The Research Institute participates in the ACTA curriculum by offering scientific training to all ACTA dental students. ACTA employees take an active role as Executives in international scientific organisations (63 international functions), as members of the editorial boards of international scientific journals (69) and in being leading in 'wetenschappelijke verenigingen' of researchers and dental practitioners in the Netherlands. Furthermore, the societal impact is evident form the organisation of symposia and congresses in the Netherlands, presentations for dentists, medical specialists and patient groups, memberships of advisory councils, and frequent contacts with the industry. In addition many scientists are also working as dentists in specialized clinics at ACTA or in the Amsterdam region. Obviously the societal impact of their activities, individually as clinically active professionals and leading among their peers, should be acknowledged. This is also evident from the relatively large number of 109 professional publications. Several ACTA researchers also wrote a considerable number of popularising publications, the details of which are not included in this scientific report. Each year several research findings are being highlightened in the general press. An example for 2008 is the finding that specific salivary peptides promote wound healing.

Management

• finances
The overall budget of the research institute is divided into a part controlled directly by the directorate and another part that is allocated to the departments. The institute budget (senso stricto) is used for the management of the institute, the salaries of the PhD students and post doctoral employees, for travel allowances for these two groups and for the organization of courses and the annual two day research meeting. Details of the finances of the Institute are given in Table 3. The research budgets for the departments are distributed with a model based on several indicators. For 2008 an allocation model was used, based on several parameters, such as external peer review, bibliometric data over the last 5 years, education, PhD theses and external funding. In addition, standard bench fees are issued for the various categories of researchers (staff, post-docs, PhD students, technicians and other supporting OBP staff).

In 2008 an extensive reorganisation was performed within ACTA. Part of this reorganisation was a substantial reduction in the research budgets, both for PhD students and for the research programmes of most departments. This reduction will be executed for the largest part in the budget restrictions in 2009.

• personnel
The directorate of the institute comprises:
prof.dr. V. Everts, director of research 0.4 fte
dr. T.J.M. van Steenbergen, co-ordinator of research 0.5 fte
mrs. F.M. Meijer, secretary 0.6 fte

The activities of the Research Institute directorate consist of organising the 2-monthly aio-refereeremiddagen, the screening of new research projects, the day-to-day interaction with graduate students on practical matters regarding their position, compiling the annual research report, the planning of graduate courses, allocating budgets for research to the departments, controlling the institutes budget and dealing with general correspondence on research issues with UvA, VU etc.

PhD students

• PhD student appointments
All vacancies for PhD positions have been filled in 2008. In Figure 1 the number of new PhD students at ACTA is shown in the years 1990 to 2008. Over the years, about 23% of all PhD students had a foreign nationality, about half of them from Europe, the rest from other
continents. A mean of 9 new PhD students was appointed each year. However, due to budget restrictions only 2 new PhD students could be appointed in 2008. About half of all PhD students have a dental background (see Table 5). Of all PhD students about 50 % is female. The research institute has started a procedure for allocation new PhD positions for high quality projects directed at the integration of basic and clinical science. In 2008 two grants for this open competition were awarded. This open competition will be continued in the coming years.

Figure 1. Numbers of new ACTA PhD students from the Netherlands and other countries

- **PhD Courses**
  
  The following courses were organised for PhD students: "Dentistry for non-dentist PhD students", "Writing and Presenting in English", "Methodology and Statistics", "Introduction in SPSS" and "Oral Biology". Dentistry is a multidisciplinary science and the background of the PhD students of the IOT is diverse. Therefore, most PhD students follow external courses on specific research areas, given by experienced lecturers of research schools in other disciplines.

- **PhD thesis duration and completion rate**
  
  Attention has been paid to the problems related to the social security benefits of PhD students and the time that PhD students need to finish their thesis. The mean time of 4.6 years between start and defence of the thesis within ACTA is slightly lower than the mean duration of PhD theses in research schools in the Netherlands of 5.1 years (see the report "Rendement en duur van promoties in de Nederlandse onderzoekscholen", Oost en Sonneveld, 2004). In addition, the mean duration of preparing a thesis has shown a declining tendency over the years (Figure 2). Over the last 18 years, about 90 % of all PhD students in ACTA completed their thesis (Figure 3). This high percentage is substantially larger that the mean percentage of 75 % of PhD students who finish their thesis in Dutch research schools according to the report by Oost en Sonneveld mentioned above.
  
  The external review committee noted that they were impressed by the organisation and practice of PhD training and supervision at ACTA. They concluded that it is a well organised programme, with a remarkably high dissertation rate.
Figure 2. Mean duration of completing the thesis of ACTA PhD students related to the year of entry

Figure 3. Percentage of ACTA PhD students finishing their thesis related to the year of entry
Points of attention

- HRM and Retirement
The research staff at ACTA has been comparatively young in the last decades. This was the result of the merging of the dental schools in the mid 1980's. Now we are approaching a situation where heads of departments and senior scientists are retiring. In 2008 ACTA has written a plan for future appointments of full professors.

- new building planned for 2010
The new ACTA building located at the VU campus will bring together groups that are currently spread out over the city at four different locations. Optimal research facilities at the new ACTA building are planned to encourage collaboration between the research groups that require laboratory facilities. The increased number of scientists at one location will also facilitate to jointly take initiatives, such as in molecular aspects of dental research.

- Future developments
Within the Netherlands, graduate schools will be formed at a local level to integrate research training both for students in the Master phase and for PhD students. In 2007 the responsibility for PhD training at ACTA was transferred from the IOT to the ACTA Research Institute. In 2009 a new graduate school will be installed at ACTA in which the PhD training will be organised. The research at ACTA has always been characterized by a wide range of different topics that covered most dental disciplines. The policy for the nearby future is on one hand to maintain all good performing research programmes, but on the other hand to focus more on specific research areas with an excellent performance. Larger research groups with a good potential could focus on biofilms and oral infections (including groups such as Cariology, Periodontology, Oral Microbiology and Oral Biochemistry), and on bioengineering and reconstruction of bone and teeth (including groups such as Oral Cell Biology, Oral Function, Oral Implantology, Periodontology, Dental Material Sciences and Functional Anatomy). For the later focus area, close collaboration exists in the research institute MOVE; a collaboration between ACTA, the VU University Medical Center and the faculty of Movement Sciences at the VU University Amsterdam. In 2008 and coming years the research budget from the 1st source (University budget) will be seriously diminished due to budget restrictions. It will be a big challenge to compete for 2nd and 3rd source grants and to maintain or improve the high output that ACTA has produced in the past.

Conclusion
The analysis of the various parameters of performance shows that the research at ACTA is in a stable and - in most areas - increasingly improving state. However, due to budget restrictions, future performance may be at stake.
Table 1. Comparison of research indicators

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Footnotes:
SCI = number of scientific papers in journals indexed in the database of the Institute of Scientific Information (ISI).
wp1 = academic personnel funded by 1st source in fte
wp2 = academic personnel funded by 2nd source in fte
wp3 = academic personnel funded by 3rd source in fte

Figure 4. Impact factor sum of ACTA publications, total scientific publications in journals indexed in the science citation index (SCI publications) and total scientific personnel in fte.
Table 2. Summary of the number of publications, impact factor sum and academic personnel in fte (year 2008)

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This table summarises the number of publications that have appeared in 2006 in SCI-journals, the number of other scientific publications, and the number of professional publications. Also the personnel involved in full time equivalent (fte) and the impact factor-sum (IF-sum) are included in this table. The IF-sum was calculated for each department by adding together the impact factor values of all 2006 publications according to the principle listed in the footnotes of the table. In this report no information is given on abstracts and on popularising publications.

Footnotes:
- **Dis** = number of dissertations.
- **SCI** = number of scientific papers in journals indexed in the database of the Institute of Scientific Information (ISI). Between parentheses is the number of first authors belonging to the department in question.
- **OSP** = other scientific publications (international, refereed)
- **PP** = professional publications
- **IF** = sum of impact factors as indexed by ISI. For publications with first author belonging to the department in question, 100% of the impact factor value is awarded to the department, for publications with the last author belonging to the department, 75% is awarded, and for co-authors 50% (only one co-author per department).
- **wp1** = academic personnel funded by 1st source in fte
- **wp2** = academic personnel funded by 2nd source in fte
- **wp3** = academic personnel funded by 3rd source in fte
- **wp tot** = all academic personnel
- **CEP** = Department of Cariology Endodontology Pedodontology
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* ACTA = the total number of dissertations and papers reflects the total for ACTA; if a dissertation or paper was a product of more than one section they were counted only once

** ACTA IF=the total impact factor sum of all ACTA publications, and not a summation of the data from each department
Table 3. Finances ACTA Research Institute 2008

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Note, this table is given in Dutch to avoid confusion in terminology.
Table 4:

fte of staff and PhD students (see Table 2) by type of position

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*We note that a substantial amount of people employed by university funding (1st) are in fact employed by money earned from industrial funding (3rd)*

CEP = Department of Cariology Endodontology Pedodontology
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Department of Cariology Endodontology Pedodontology

Diseases of the Dental Tissues and their Prevention

Program leader

Prof.dr. J.M. ten Cate
Department of Cariology Endodontology Pedodontology
ACTA, Louwesweg 1
1066 EA Amsterdam
Tel: +31-20-5188440
E-mail: JM.ten.Cate@acta.nl

Full professors

J.M. ten Cate  C. van Loveren  W. Crielaard  P.R. Wesselink

Research objectives

The research program of the Department of Cariology Endodontology Pedodontology covers physico-chemical, biochemical, microbiological and clinical aspects of enamel, dentin and root caries and infection of the root canal. These aspects are studied by means of various intra-oral and in vitro models which simulate the natural processes in the oral environment and which are designed to evaluate the effects of preventive measures and restorative materials and procedures, thereby covering the field of research from the molecular level up to in situ studies.

The formation, structure and properties of biofilms on hard tissue surfaces are studied extensively. The action of anticariogenic and antimicrobial agents are studied in the Constant Depth Film Fermenter (CDFF) and in a microtiter biofilm model.

Fluoride that, at present, is still the most effective caries-preventive agent is subject for further study. A better understanding of its mode of action, also on the molecular level towards microbial metabolism, as well as its possible side-effects (fluorosis and the induction of a fluoride-resistant oral microflora) will help to improve formulations and the development of fluoride-releasing devices and restorative materials.

In addition to fluoride, antimicrobials have come into focus as caries preventive agents. The efficacy alone or in combination with fluoride is still unknown and application protocols are not yet based on a critical evaluation of experimental and clinical results. The successes of antimicrobials in caries prevention are still limited.

The prevention of bacterial penetration in the root dentinal tubules and the root canal by a proper seal of the restoration is of major importance for the life expectancy of teeth. Modified disinfection methods of the root canal are studied. New filling methods and contemporary adhesive systems are tested in in vitro leakage models and in clinical studies.

Better treatment concepts (preventive as well as conservative and in relation to behaviour management) of dental caries in children are studied. Treatment concepts like ART (Atraumatic Restorative Treatment), the influence of total rehabilitation of the children’s dentition on general and oral health, consequences of restorative treatment on the child’s coping and anxiety are under investigation.
Results

Section Experimental preventive dentistry

A good definition of commensal microflora and an understanding of its relation to health are essential in preventing and combating disease. In the past year efforts were targeted to obtain such a definition in molecular detail. First of all in a pyrosequencing analysis of the oral microflora of healthy adults we obtained a radically new insight into the diversity of human oral microflora, which, with an estimated number of 20,000 phylotypes, is considerably higher than previously reported. Furthermore we studied the effects of a probiotic *Lactobacillus* on the compositional stability of oral microbial communities and found that, although not able to form a monospecies biofilm, *L. salivarius* established itself into the oral community if inoculated simultaneously with the microcosm and was able to change the community profiles of these microcosms. A novel method to study the dynamics of the oral microflora, Multiplex Ligation-dependent Probe Amplification, was successfully developed and applied. Specific species-species interactions were investigated between *Candida albicans* and either *Candida glabrata* or *Streptococcus mutans* in biofilms grown on various surfaces, with or without saliva. Confocal laser scanning microscopy was used to characterize biofilms and to quantify the number of hyphae in each condition tested. We showed that glucose and the presence of *S. mutans* suppressed *C. albicans* hyphal formation and could conclude that *Candida* biofilms are significantly affected by saliva, substratum type and by the presence of other micro-organisms. Molecular details of specific bacterial virulence factors were studied in *Porphyromonas gingivalis*.

We explored the genetic background of capsule biosynthesis in a representative group of K1 serotype *P. gingivalis* strains and showed that the capsular polysaccharide locus of *P. gingivalis* is conserved but varies slightly among K1 strains. This allowed is to design a new K1-specific PCR-based serotyping assay which showed to be much faster than double immunodiffusion and could detect K1 strains in a very selective and sensitive way.

In *Streptococcus mutans* we identified a polysaccharide deacetylase that shows homology to the catalytic domains of peptidoglycan deacetylases from *Streptococcus pneumoniae* and *Listeria monocytogenes*, both of which are involved in the bacterial defense mechanism against human mucosal lysozyme. *S. mutans* cells in which we deleted the pgdA gene displayed a different colony texture and a slightly increased cell surface hydrophobicity and yet did not become hypersensitive to lysozyme as shown previously for *S. pneumoniae*. To understand this apparent lack of activity, the high-resolution X-ray structure of *S. mutans* PgD was determined; it showed the typical carbohydrate esterase 4 fold, with metal bound in a His-His-Asp triad. The protein exhibited metaldependent de-N-acetylase activity toward a hexamer of N-acetylglucosamine. No activity was observed toward shorter chitooligosaccharides or a synthetic peptidoglycan tetrasaccharide. In agreement with the lysozyme data this would suggest that *S. mutans* PgdA does not act on peptidoglycan but on an as-yet-unidentified polysaccharide within the bacterial cell surface. Strikingly, the pgdA-knockout strain showed a significant increase in aggregation/agglutination by salivary agglutinin, in agreement with this gene acting as a deacetylase of a cell surface glycan.

Section Clinical Cariology

Clinical aspects of prevention focused on optimization of frequency of fluoride use. In an in situ experiment is was found that increasing the frequency of the number of daily applications from 2 to 3 gave further protection against dentin caries but not against enamel caries.

For dentin, the additional fluoride application resulted in significantly more structurally bound fluoride compared to the control group.

In an in situ experiment the efficacy of chlorhexidine in preventing dentin and enamel demineralization was studied. It was shown that the clinical use of 0.2% chlorhexidine mouthrinse did not protect enamel nor dentin against demineralization. Furthermore, no differences in acid production of plaque samples obtained from the chlorhexidine-treated and control groups were observed. This result was also found for plaque samples originating from natural tooth surfaces.
Section Endodontology

Our endodontic group performed together with a dental school in São Paulo a joined research in which it appeared that C-reactive protein (CRP) levels in dog serum increase significantly during the development of apical periodontitis (AP). During 6 months post-root canal treatment, the CRP concentration decreased significantly. Also the accuracy of two imaging methods in diagnosing AP in dogs was evaluated using histopathology as gold standard. Cone beam computed tomography (CBCT) detected significantly more periapical lesions than periapical radiography (PR). In laboratory studies, CBCT and optical coherence tomography accurately diagnosed vertical root fractures whereas PR did not. Furthermore, it appeared on extracted teeth that certain rotary file and root filling techniques created fractures, craze lines and incomplete cracks in root dentin. Two different leakage models were used to assess fluid transport through the same filled roots by measuring either movement of an air bubble or concentration of glucose; the results of two models were found comparable. However, glucose reacted with some materials therefore not always being suitable as a tracer in leakage studies.

In the irrigation studies this year, the first ideas were formulated for the physical explanation of the sonic, ultrasonic and laser activated canal irrigation. Furthermore, (preliminary) studies on the improvement of the ultrasonic activated irrigation were done by reinforcing the irrigant (addition of micro particles) and pulsation of the ultrasound. Two joined (ACTA & TU Twente) articles (dental-fluid dynamics) were submitted on the sonic and laser activated irrigation.

Section Paediatric dentistry

Paediatric dentistry mainly focusses on child related aspects in the treatment of young patients. The 2008 results concentrate on the relation between dental caries, its treatment and the consequences for a child’s general health. Several articles and a thesis have been produced on the subject giving way to the understanding that full treatment, including not only curative but also preventive measures, is to be preferred above an approach of just prevention or restoration and/or extraction. Dental treatment seems to have no influence on the body growth. The clinical trials of the section support the paradigm that restoration and the development of dental anxiety seem to be mutually exclusive: pain related experiences cause an increased pain sensitivity during sequential treatments. Since the avoidance of treatment has comparable negative consequences the results attribute to the complex nature of managing restorative dentistry in children.
### Academic personnel in 2008 and 2009

#### Research staff ACTA - CE (in full time equivalents)

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Annual Research Report 2008

Dissertations


Publications in journals indexed in SCI


Other scientific publications (international, refereed)


Professional publications


External reports


Indicators of Esteem

Grants: current projects with external funding


Cate, J.M. ten. Centraal onderzoeksfonds UvA 4 jaar, €60.000,- per jaar (2007-2010)

Cate, J.M. ten. Academy professor Royal Academy of Arts and Sciences (KNAW), total €1.000.000,-, period 2008-2013.

Crielaard, W. KNAW/CAS (Chinese Academy of Sciences). Grant in the “China Exchange Programme”: travel grant for lectures in Beijing, Guangzhou and Hong Kong.


Exterkate, R.A.M. & Cate, J.M. ten. Development and evaluation of relevant dental in vitro biofilm models for the screening of new active compounds. GABA, Münchenstein, Switzerland; October 2007 – October 2010, € 150,000,-.

Loveren, C. van, Strijp, A.J.P. van & Laheij, A.M.G.A. Remineralization of enamel and dentine lesions with two different oral hygiene protocols. GABA, Münchenstein, Switzerland; November 2007 – July 2008, €58,000,-.

Elfrink, M.E.C. Developmental disturbances in deciduous teeth. €30.000,- for research.

Metska, M. & Özok, A.R. Grant European Society of Endodontology Research €10,000,-.


Wesselink, P.R. et al. Ministry OCW €850 000,-. Simodont project for three years (one third of this amount each year).


Zaura, E., Cate, J.M. ten & Crielaard, W. The Oral Cavity Chip. TNO / ACTA, Ministry of Economic affairs, Industry Phase 1, approx 400 k€, 50 % industry 50 % ministry of Economic affairs. Start: 2006-2010.

Membership of international editorial boards

Amerongen, W.E.: BRAZILIAN J PED DENT
Cate, J.M. ten: EUR J ORAL SCI
Cate, J.M. ten: INT J DENT
Cate, J.M. ten: J ORAL MICROBIOL
Cate, J.M. ten: ODONTOLOGY
Loveren, C. van: INT J DENT HYG
Peters, L.B.: INT ENDOD J
Sluis, L.W.M. van der: ENDOdontic PRACTICE
Wesselink, P.R.: DEUTSCHE ZAHNÄRZTLICHE ZEITSCHR
Wesselink, P.R.: ENDOdontic PRACTICE
Wesselink, P.R.: ENDOdontIE
Wesselink, P.R.: INT ENDOD J
Wu, M.K.: INT ENDOD J

Organisation of international congresses or symposia


Invited speakers at international congresses or symposia

Cate, J.M. ten (2008, October 29). Autoinducer2 in biofilms. Oslo, Norway, University of Oslo symposium.
Cate, J.M. ten (2008, October 09). Biofilms, a different way to look at dental plaque. Manilla, Philippines, SEA Division IADR.
Cate, J.M. ten (2008, December 01). Biofilms, a new way to look at dental plaque. Seoul, Korea, KADR annual meeting.
Cate, J.M. ten (2008, November 04). Caries prevention, more than fluoride? Hong Kong, China, University symposium.
Cate, J.M. ten (2008, June 06). New developments in de- and remineralization. onbekend, Unilever Discovery Workshop.
Cate, J.M. ten (2008, November 29). The future of dentistry and IADR. Nagoya, Japan, JADR meeting.
Cate, J.M. ten (2008, January 10). The need for effective caries antibacterial approaches. Vina del Mar, Chile, ICNARA congress.
Cate, J.M. ten (2008, July 02). Why another meeting. Toronto, Canada, IADR global meeting.


Sluis, L.W.M. van der (2008, June 13). Endodontic irrigation. La Baule, France, Congress international SFE.


Wesselink, P.R. (2008, April 09). Consequences and strategies to deal with residual post-treatment root canal infection. Vancouver, Canada, Pre-congress course annual meeting American Association of Endodontics (AAE).


Scientific awards/honours


Other international functions

Amerongen, W.E. van: Council member. EAPD.

Cate, J.M. ten: Immediate past president. Central European Division of the International Association for Dental Research.

Cate, J.M. ten: Management committee. European Research Group Oral Biology (ERGOB).

Cate, J.M. ten: President. IADR Board of directors.

Cate, J.M. ten: Honorary professor. Universidad Peruana Cayetano Heredia, Lima, Peru.

Cate, J.M. ten: Honorary professor. University of Hong Kong.

Cate, J.M. ten: Facultetsopponenten. (N. Ahmed), University of Oslo.

Loveren, C. van: Vice President. European Organization for Caries Research (ORCA).

Veen, M.H. van der: Secretary/Treasurer. Diagnostic Sciences Group IADR.

Veen, M.H. van der: Member advisory board. ORCA.


Wu, M.K.: Guest Professor. Peking University School of Stomatology.

Collaborations

- AMC Research Landsteiner Laboratory, Academic Medical Center.
- AMC, Department of Biomedical Opticals, Amsterdam, the Netherlands.
- AMC, Department of Electron Microscopy, Amsterdam, the Netherlands.
- Erasmus MC, Rotterdam- Dept. of Biomedical Engineering.
- Erasmus MC, Rotterdam, Optical Coherence Tomography.
- Federal University of Paraiba, Joao Pessoa, Brasil.
- Gaba International Ltd., Therwil, Switzerland.
- Inspektor Research Systems BV, Amsterdam, the Netherlands.
Current PhD projects


Department of Oral Function

Oral Function and Oral Rehabilitation

Program leader

Prof.dr.ir. M. Naeije
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Tel: +31-20-5188423
E-mail: M.Naeije@acta.nl

Full professors

M. Naeije  F. Lobbezoo  D. Wismeijer

Research objectives

The general mission of the programme is to improve the dentist’s knowledge of the normal and the disturbed movement functions of the human masticatory system, the factors that influence these functions, and the treatment modalities that preserve or restore the patient’s function. The present research programme comprises two major research domains, Oral Kinesiology and Oral Implantology and Prosthetic Dentistry.

Results

Oral Kinesiology

Influence of (experimental) orofacial pain upon the sensorimotor control of the human masticatory system:

In a collaborative study with the department of Oral Maxillofacial Surgery, Prosthodontics, and Special Dental Care of the University of Utrecht (dr. A. van der Bilt) the influence of exercise-induced muscle pain and fatigue on the stiffness of the human masticatory system and on the amplitude of the jaw-stretch reflex were studied. Preliminary results indicate that stiffness and reflex amplitude behave differently after exercise; the stiffness decreases and the reflex amplitude increases. These results shed doubt on the often quoted interpretation of the increase in reflex amplitude as being indicative for an increase in stiffness of the system. In another collaborative study with the Discipline of Physiology of the University of Adelaide, Australia (prof.dr. K.S. Turker), it was found that exteroceptive jaw reflexes, elicited by electrical lip stimulation, are ‘gated’ during simulated mastication (i.e., they become progressively smaller when the teeth are moving towards occlusion) when the stimuli are mildly painful. Conversely, moderately painful stimuli yield progressively stronger reflex responses during mouth closing.

Pathophysiology, diagnosis and treatment modalities of chronic temporomandibular disorders (TMD):

A longitudinal questionnaire study to psychosocial factors related to the development of treatment need in orofacial pain patients is being performed. Patients with a demand of treatment are recruited in collaboration with the Dutch Centers for Special Dental Care, while
persons with orofacial pain, but without a demand of treatment are recruited from a random sample of the Dutch population. Preliminary analyses indicate that, besides the level of pain, especially the psychological factors "anxiety of movement" and "external pain control" is related to treatment demand. Another questionnaire study showed that the ethnic background of TMD patients in The Netherlands is associated with psychological factors, regardless of socioeconomic status, but not with TMD pain complaints and oral parafunctions. Questionnaires are also being developed to measure the patient specific complaints and the patient’s fear of movement.

Pathophysiology, diagnosis and treatment modalities of (sleep-related) oral movement disorders: A scale was developed for occlusal and non-occlusal tooth wear grading. The scale was shown to be reliable, especially for the clinical (chair-side) grading of occlusal surfaces. An ongoing study will assess this scale’s ability to validly discriminate between erosion and attrition as the main cause of the observed tooth wear. In a large-scale questionnaire study (a collaborative study with dr J. Ahlberg of the University of Helsinki), it was shown that frequent bruxers are more than two times more likely to report severe stress and had more than three times more likely anxiety than non-or-mild bruxers. In the follow-up part of the randomized clinical trial (RCT), performed in collaboration with the Slotervaart General Hospital, to the efficacy of two types of treatment modalities for obstructive sleep apnea (OSA), it was found that both continuous airway pressure and the mandibular advancement device remained effective after one year of usage. Importantly, there was a significant reduction in excessive daytime sleepiness with both treatment modalities. A retrospective assessment of part of the RCT data revealed that increasing the jaw gape with an intra-oral device yields an aggravation of a pre-existing OSA. This finding has important implications for the clinic, where such devices are commonly made for a variety of conditions while the presence of a possible OSA is not always known, neither to the dentist nor to the patient.

The development, diagnosis and treatment of internal derangements of the temporomandibular joint:
In a kinematic, 2-year follow-up study to the natural course of an anterior disc displacement with reduction (ADDR) in clinical cases (ADDR with intermittent locking) and in community cases (ADDR without functional problems), preliminary results have shown that at the 1-year follow-up, the ADDR’s in the community cases had all remained stable over time. However, in about 40% of the clinical cases, there was a shift towards a later reduction of the displaced disc on opening or the disc did not reduce at all anymore. In an experiment with a 1-hour intense gum chewing exercise it was shown that the ADDR’s in the community cases did not respond to this exercise, whereas the ADDR’s in about 40% of the clinical cases showed a temporary shift to a later disc reduction on opening or showed a temporary loss of reduction.

Fig: Example of the superimposed sagittal opening and closing movement traces of the kinematic center of a joint with an ADDR. Interferences in the movement traces (see arrows) coincide with the reduction (opening click) and the dislocation of the disc (closing click). Opening traces are in black; closing traces are in grey.

Oral Implantology and Prosthetic Dentistry
Incorporation of proteins in biomimetic coatings (dr. Y. Liu):
A slow release of BMP’s (bone morphogenetic proteins) from the implant coatings is thought to have a stimulating effect on bone growth. Besides oral implants, bone filling osseoconductive materials and membranes have also been coated and have become integrated in the department’s research projects.
As part of a new experimental dental-implant model for the in-vivo testing of functionalized surfaces within unfavourable bony environments, thirty-four goats were implanted with 4 implants per animal (in collaboration with Bern and Inner Mongolia Agriculture University China). All animals have been sacrificed and the histological analysis has been evaluated. The results are in the write up stage.

Ca/P ratio influences biomimetic coatings formation on implants and bone fillers. Three different kinds of coating materials for titanium, zirconia, Bio-Osis, bioceramics and membranes were developed.

In a Sinus lift model (clinical trial) 8 patients have been treated with Bio-Oss functionalized with BMP-2 and the histology has been analysed. The results are in the writeup stage.

The use of tissue expanders to expand the mucosa in area’s where bone augmentation is the indicated treatment. 12 goats have been treated and slaughtered, histology has been carried out and the material has been evaluated. The first report is in the write up phase.

Osteoclast-controlled protein release from calcium-phosphate-based bone-substitute materials: A biomimetic coating technique. This project in collaboration with Frank Klenke, Clinical Research Department, University of Bern Switzerland is coming to an end. We expect to present the PhD thesis before the end of 2009.

Evaluation of patient treatment where oral implants are incorporated (prof.dr. D. Wismeijer): A. Tahmaseb. The MEC approval has been given for the project: Pre-surgical CAD/CAM Planning and Fabricating Surgical Guide and Superstructure on Dental Implants In Order To Restore the Fully Edentulous Mandible/Maxilla. A total of 35 patients has been treated. The in vitro stress and misfit analysis has been carried out. It seems that the misfit of the CAD CAM planned and fabricated superstructure is less than that which can be acquired using the convention impression technique. The results are in the write up phase and the first article has been accepted.

BIOS-2. The Breda Implant overdenture study. An evaluation after 8 years. This project has run since 1992. This year the variables concerning the hard and soft peri-implant tissues 8 years after the initial treatment have been evaluated. In cooperation with the department of oral microbiology we are also looking at genetic factors related to bone loss and smoking. The microbiology has been evaluated. The DNA analysis has been carried out. All OPT’s have been evaluated with the radiology department. The statistical analysis is now being carried out. The write up of the clinical results is in progress. This project has been rather slow but has been picked up again by GT Stoker who is back in the department for 0.2 Fte.

A multi centre randomized controlled clinical trial comparing conventional loading of an overdenture on two implants with a bar to immediate loading of an overdenture on two implants with a bar. Patient treatment started in February 2007 and up till now 95% of the patients have been incorporated in both centers. The PhD student that was to evaluate the project resigned due to inadequate salary conditions. The project is now being carried by one of the OI master students together with the ITI clinical scholar. The first article has been submitted for publication.

Implants supporting free end saddles. A multi center clinical trial. All the patients have been treated and the 6 month evaluation has been carried out. In 2007 the second patient evaluation has taken place. The third evaluation was carries out in 2008. The material is now being analysed in the Dunedin Dental School (NZ).

A new project which is being carried out in our department together with the department of experimental Dermatology of the VUMC (dr. Susan Gibbs) is "Developing an autologous full thickness graft which can be used in the oral cavity. A.P. Vriens (Tio). The first publication: Comparison of autologous full thickness gingiva and skin substitutes for wound healing has been accepted.
### Academic personnel in 2008 and 2009

#### Research staff ACTA - CD (in full time equivalents)

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#### Dissertations


#### Publications in journals indexed in SCI


Other scientific publications


Professional publications


Indicators of Esteem

Grants: current projects with external funding

Liu, Y. & Wismeijer, D. Koninklijke Nederlandse Akademie van Wetenschappen (KNAW). Samenwerkings-project 08CDP043, 2008 (€69,690,-) for three years.

Liu, Y. & Wismeijer, D. ITI Foundation, Basel, Switzerland. In vivo degradability and osteoconductivity of calcium phosphate coatings with different crystalline properties. Sum awarded: 193,000 CHF.

Wismeijer, D. Straumann AG Switzerland. Immediate loading of two implants connected by a bar and an overdenture. A RCT comparing immediate loading with conventional loading. €140,000,-.

Wismeijer, D. & Tahmaseb, A. Straumann AG Switzerland. Evaluation of the EXE plan CAD/CAM system, €200,000,-.

Membership of international editorial boards

Lobbezoo, F.: J ORAL REHABIL
Naeije, M.: J ORAL REHABIL

Organization of international congresses or symposia


Invited speakers at international congresses or symposia


Other international functions

Liu, Y.: Honorary professor, April 2006. Hospital of Stomatology, Dental School of ZheJiang University, Huangzhou, China.

Liu, Y.: Scientific advisor. Maxillofacial surgery department, University of Bern, Bern, Switzerland.

Lobbezoo, F.: Member of the Research Committee. European Academy of Craniofacial Disorders (EACD).


Wismeijer, D.: Member. Education Committee of the ITI (CH).

Collaborations

Oral Kinesiology:
- Slotervaart General Hospital, Department of Clinical Neurophysiology and Brain Mapping Laboratory, dr. H.L. Hamburger, Amsterdam, the Netherlands.
- University of Utrecht, Department of Oral Maxillofacial Surgery, Prosthodontics, and Special Dental Care, dr. A. van der Bilt, Utrecht, the Netherlands.
- Vrije Universiteit, Department of Clinical Neuropsychology, prof.dr. E.J.A. Scherder, Amsterdam, the Netherlands.
- Université de Montréal, Faculté de médecine dentaire, Departement de santé buccale, prof.dr. G.J. Lavigne, Montréal, Quebec, Canada.
- University of Halle Dental School, dr. M. John, Halle, Germany.
- University at Buffalo, Department of Oral Diagnostic Sciences, dr. R. Ohrbach, Buffalo (NY), USA.
- University of Aalborg, Center for Sensory-Motor Interaction, Orofacial Pain Laboratory, prof.dr. P. Svensson, Aalborg, Denmark.
- University of Dundee, the Dental School, prof.dr. S.W. Cadden & dr. P. Maillou, Dundee, Scotland, United Kingdom.
- Ege University, Faculty of Medicine, Center for Brain Research & Department of Physiology, prof.dr. K. Türker, Bornova, Izmir, Turkey.
- Catholic University of Leuven, Department of Stomatognathic Physiology, prof.dr. A. De Laat, Leuven, Belgium.
- University of Malmö, Department of Stomatognathic Physiology, prof.dr. M. Nilner, Malmö, Sweden.
- University of Naples “Frederico II”, Department of Orthodontics, prof.dr. A. Michelotti, Naples, Italy.
- University of Helsinki, Department of Stomatognathic Physiology & Prosthetic Dentistry, dr. J. Ahlberg, Helsinki, Finland.
- University of Padova, TMD Clinic, dr. D. Manfredini, Padova, Italy.
- Nederlandse Vereniging van Hoofdpijnpatienten, dr. M. van den Berg, Amersfoort, Nederland.
Oral Implantology and Prosthetic Dentistry:
- Inner Mongolia Agriculture University, Huhehot, China.
- Department of Nuclear Medicine and School of Dentistry, University of Nijmegen, the Netherlands: (dr. Otto Bormen and prof.dr. J.A. Jansen)
- Department of Prosthetic Dentistry of the University of Dunedin Dental School (Alan Payne)
- Department of MFP and Special Dental Care of the AMPHIA teaching hospital Breda (NL).
- Department of Oral and maxillofacial Surgery of the AMPHIA teaching hospital Breda (NL).
- Hospital of Stomatology, Dental School of Zhejiang University, Huangzhou, China.
- Clinic Research Department (dkf), University of Bern, Bern, Switzerland.
- University of Utrecht, Department of Oral Maxillofacial Surgery, Prosthodontics, and Special Dental Care, dr. M.C. Cune, Utrecht, the Netherlands.

Current PhD projects

Department of Periodontology

Biology, Physiology and Pathophysiology of the Periodontium

Program leader

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E-mail: U.vd.Velden@acta.nl

Full professors

U. van der Velden  W. Beertsen  B.G. Loos

Research objectives

Periodontitis is a destructive inflammatory disease of the supporting tissues of the teeth. It is caused by bacteria and affects a substantial part of the human population. Over the age of 45 years it is a major cause for tooth loss. This research program is devoted to clarify the individual differences in susceptibility to periodontitis and to investigate the mechanisms involved in periodontal breakdown and repair/regeneration. In addition the evaluation of the efficacy of new preventive and therapeutic measures is part of the program.

The following questions are addressed:
1. Susceptibility to periodontitis and systemic effects:
   - Which are the bacterial and host factors involved?
   - To what extent are hereditary factors important?
   - What are the systemic effects of periodontitis?
2. Degradation and regeneration:
   - How is the extracellular matrix of the periodontium degraded?
   - What mechanisms are responsible for tissue homeostasis?
3. Prevention and treatment of periodontitis:
   - Which are the most effective measures to prevent and control dental plaque?

Results

Periodontitis is a complex disease because of its multifactorial etiology (bacteria, genetics and life style factors). A limited number of family studies suggested that periodontitis aggregates in families. Although family studies might give a first impression of familial aggregation, they can not distinguish between the influence of genetic and shared environmental effects as an explanation for the familial clustering of periodontitis. In this respect twin studies are especially useful. For chronic periodontitis relatively few twin studies have been carried out, but the results suggest a substantial role of genetic factors in the etiology. However these studies have limitations because they were not based on selected periodontitis patients. Therefore a twin study was initiated to assess, in monozygotic (MZ) and dizygotic (DZ) twin pairs selected on the basis of one sib of a twin pair suffering from moderate to severe chronic adult periodontitis, the contribution of genetics, life style factors and periodontal pathogens to the clinical phenotype of
the disease. The results showed that both MZ and DZ twins were discordant regarding attachment loss and bone loss. The discordance was greater in DZ compared to MZ twins. In MZ twins the discordance could not be explained by education, smoking, body mass index and periodontal pathogens. Therefore, the factors that play an important role in the development of chronic adult periodontitis are yet to be determined.

Regarding gaining further insight in genetic factors for the susceptibility of periodontitis we are following two strategies: 1) candidate gene approach; 2) genome wide search. The first approach has been carried out in previous years in our own institution on the basis of INFOBIOMED on patients with chronic periodontitis. With data in the Periodontitis Data Warehouse (PDWH) (INFOBIOMED), final data analysis was carried out to model genetic factors in conjunction with bacterial and lifestyle factors. The final results should be ready for publication in 2009. The candidate gene approach has also been extended to material in the biobank from the European Genetics Consortium (EPG), of which we are one of three founding partners. Genetic epidemiology with the candidate gene approach was applied to the 600 patients with aggressive periodontitis (AgP) and 800 controls that are part of EPG. We have tested IL-1 and NOD-1 gene polymorphisms. For both candidate genes no relation with AgP was found. IL-6 gene polymorphisms are now in a final stage of analysis. Furthermore, a chromosomal locus associated with cardiovascular disease was used as candidate region in relation to AgP; here we found a relationship, suggesting that perhaps cardiovascular disease and periodontitis may have at least one common genetic risk factor. The second approach (genome wide search) has been applied on 200 cases; we have identified the B-defensin gene as a genetic risk factor for AgP; this was replicated in the remainder of AgP patients and also in our chronic periodontitis cohort. We are currently still expanding our biobank of AgP patients; a new genome wide search is planned with newly developed gene chips, containing 1 million gene polymorphisms dispersed over the total genome. The Institute for Clinical Molecular Biology from the Medical Center University of Kiel (P.I. prof. S. Schreiber) is financing these efforts.

The systemic effects of periodontitis are still being investigated. A pro-coagulant state in periodontitis may also be related to activated platelets. We have demonstrated for the first time that blood platelets in periodontitis are present in vivo in an activated form. Moreover, specifically P. gingivalis and A. actinomycetemcomitans can activate blood platelets ex vivo. We will continue this work by further studying the role of platelets in periodontal disease and health. The systemic effects of periodontitis will further be studied: we have initiated an ambitious intervention study, where we apply various antimicrobial regimens in conjunction with traditional scaling and rootplanning. The effects of therapy on acute phase proteins, white blood cells and pro-coagulant state will be investigated.

Infantile malignant osteopetrosis is a fatal disease characterised by non-functional osteoclasts. The only treatment is hematopoietic stem cell transfer which restores the pool of active osteoclasts. In collaboration with the Department of Molecular Medicine and Gene Therapy, Lund University, Sweden, we investigated in a mouse model for infantile malignant osteopetrosis whether autologous cells could cure the disease. Autologous stem cells were injected in mutant mice which had not been irradiated and gave rise to functional osteoclasts. Remarkably, these mice survived. Bone marrow cavities were formed and in vitro assays confirmed that the transplanted cells gave rise to functional, bone resorbing osteoclasts.

In collaboration with the Department of Oral Cell Biology, we aimed to unravel the regulatory role of osteocytes in the formation of osteoclasts. In parallel with their typical response to pulsating fluid flow, which mimics mechanical loading as it appears in vivo, especially osteocytes and not periosteal fibroblasts or osteoblasts influenced osteoclast formation and bone resorption by secreting soluble factors. Studies on the prevention and treatment of periodontal diseases concentrate on the efficacy of electric/manual toothbrushes, dentifrices, mouth rinses and antibiotics. Our results have shown that there was no statistically significant difference in resolving experimental gingivitis between two manual toothbrushes. A dentifrice containing liquorice and curcuma extracts did not contribute to mechanical plaque removal during manual toothbrushing nor did it prevent the onset of gingivitis. It seemed that the mechanical action provided by the toothbrush was the main factor in the plaque-removing process. Furthermore, we found that 0.07% CPC mouthwash and 0.1% hexetidine mouthwash were both superior to a 0.0% CPC-placebo mouthwash in a 3-day "de novo" plaque formation model. In addition we showed that no statistically significant differences could be observed testing three prototype electric toothbrush brushheads compared to the regular brushhead.
Academic personnel in 2008 and 2009

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Dissertations


Publications in journals indexed in SCI


Professional publications


External reports


Indicators of Esteem

Grants: current projects with external funding

Loos B.G. The need for periodontal therapy in the prevention of systemic diseases (2008). A grant supplied by CVZ, the Netherlands. Total €80,000,-.


Membership of international editorial boards

Beertsen, W.: EUR J ORAL SCI
Loos, B.G.: J CLIN PERIODONTOL
Loos, B.G.: J DENT RES
Loos, B.G.: ORAL HEALTH PREV DENT
Velden, U. van der: J CLIN PERIODONTOL
Weijden, G.A. van der: INT J DENT HYG

Scientific awards/honours


Invited speakers at international congresses or symposia


Other international functions

Loos, B.G.: External examiner MSc. EFP Graduate programs in periodontology.
Loos, B.G.: Member publications committee Functie bij : International/American Association of Dental Research (IADR/AADR).
Velden, U. van der: External examiner MSc. EFP Graduate programs in periodontology.
Velden, U. van der: Board Member. European Federation of Periodontology.
Velden, U. van der: Chairman post graduate education committee. European Federation of Periodontology.
Vries, T.J, de: External examiner MSc thesis. EFP Graduate programs in periodontology.
Collaborations

- Universiteit van Amsterdam, Celbiologie & Histologie (prof.dr. C.J.F. van Noorden), Amsterdam, NL
- Universiteit van Amsterdam, Klinische Chemie (prof.dr. A. Sturk & dr. R. Nieuwland), Amsterdam, NL
- Department of Molecular Medicine and Gene Therapy, Lund University, Lund, Sweden, (dr. J. Richter)
- University of Sheffield (dr. D. Buttle), Sheffield, United Kingdom
- Celltech (dr. A. Docherty), London, United Kingdom
- Padjadjaran University, Dept. of Periodontology (dr. S. Lambri), Bandung, Indonesia
- Unilever Research (dr. D.J. Page), Port Sunlight, United Kingdom
- Ludwig Boltzmann Institut fur Osteologie (prof.dr. P. Fratzl) Vienna, Austria
- Universität Kiel (dr. P. Saftig) Kiel, Germany
- Braun Oral Research (dr. P. Warren) Baltimore, USA
- University of Kiel, Dept. of Gastro-Enterology (prof.dr. S. Schreiber), Germany
- University of Bonn, Dept. of Periodontology (prof.dr. S. Jepsen), Germany
- University of Oslo, Dept. of Oral Biology (dr. K. Schenck), Norway

Current PhD projects


Section: Oral Cell Biology

Bioengineering of Bone and Periodontium

Program leader

Prof. dr. V. Everts
Oral Cell Biology
ACTA
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tel: 31-20-4448661
e-mail: v.everts@VUmc.nl

Full professors

V. Everts  J. Klein Nulend  R.A. Bank

Research objectives

The program “Bioengineering of Bone and Periodontium” of the Department of Oral Cell Biology studies the biological processes of functional adaptation and guided regeneration of bone and periodontium. Research focuses on fundamental aspects of mechanotransduction, and tissue engineering of bone, cartilage, and periodontium. The results are used in more applied research towards repair and regeneration of jaw bone and periodontium, and prevention/treatment of infections around implants.

Mechanical stress is capable of modulating the activity of osteoblasts and osteoclasts, which are orchestrated in their activity by the mechanosensitive osteocytes, and the activity of periodontal fibroblasts, which mediate adaptation of the tissue to a changing force regime. To clarify the cell biological processes of mechanical adaptation, in vitro experiments are performed in which the reaction of bone and connective tissue cells to mechanical stress is studied in cell and organ culture, and at the single cell level. The results are verified in studies of bone under weightlessness conditions during space flight, and in disuse osteoporosis. Bone growth factors are locally produced growth factors, which can be used for clinical regeneration of bone and cartilage. They are involved in fracture repair and in the regulation of normal bone growth, but they also play a role in pattern formation of the dentition and the skeleton in the early embryonic phase. Their role in regeneration of bone and periodontium is studied using cell and animal experiments.

The tissue engineering part of the research is focused around (1) the synthesis, deposition, and degradation of the collagen network in bone and cartilage, (2) the use of adipose tissue-derived mesenchymal stem cells in combination with injectable scaffolds (hydrogels) or resorbable scaffolds and growth factors for tissue engineering of a.o. jaw bone augmentation by sinus floor elevation and the intervertebral disc, and (3) the role of mechanical factors in stem cell differentiation.
Results

Regeneration of bone and periodontium

A model aimed to reconstruct a periodontium became operational. The model consists of a narrow space located between an artificial root and bone substitute, filled with a collagen gel in which human periodontal ligament cells are seeded. The PDL cells were subjected to various loading regimes in axial direction mimicking mastication. The cells responded differently depending on the loading magnitude. Low and moderate loading regimes changed expression of signaling molecules whereas high loading increased the expression of collagen type I, the principal matrix protein of the ligament. The data show that PDL cells react differently when loaded at different magnitudes.

The anion exchanger Ae2 is a membrane protein of many cell types involved in intracellular pH handling. We detected Ae2 in maturation stage ameloblasts. The enamel of mice in which Ae2 was partially inactivated failed to fully mature and resulted in formation of softer enamel that was quickly eroded after eruption. The data show that pH regulation by ameloblasts is crucial for their function, i.e. producing a layer of hard enamel.

Uremia in young rats severely affects jaw bone development and disrupts formation of enamel and dentin. In an attempt to improve enamel quality in these rats the animals were put on a regime of fluoride in drinking water. Fluoride however aggravated the uremic effects on development of enamel. Therefore systemic use of fluoride should be discouraged in young children with renal problems.

Distraction osteogenesis is a technique to augment bone tissue by gradual distracting two bone ends. In the gap between the bone ends new bone will form. The technique is currently applied to augment bone in the human mandible before placing implants. Ultrasound is believed to stimulate bone formation. In collaboration with the Dept of Maxillofacial Surgery in Groningen patients who had undergone vertical distraction osteogenesis of the mandible were exposed to ultrasound. Ultrasound, however, did not accelerate bone healing during distraction osteogenesis.

In collaboration with a group in Sweden we have shown that osteopetrosis in mice can be cured by wild-type hematopoietic stem cells. These cells were injected in non-irradiated mice and gave rise to the formation of bone marrow cavities in long bones and calvaria. Injecting stem cells resulted in the formation of actively resorbing osteoclasts and reversed lethally progressive osteopetrosis in the oc/oc mice. In vitro, bone resorption was associated with osteoclasts containing wild-type nuclei. These findings demonstrate that irradiation of non-functional bone marrow is not required prior to hematopoietic stem cell therapy as a cure for osteopetrosis.

Src is highly expressed in osteoclasts. Therefore drugs like AZD0530, designed to inhibit Src activity, could selectively interfere with osteoclast activity in diseases with excessive bone loss, such as periodontitis. We explored the effects of AZD0530 on human osteoclast differentiation and activity. Its effect on formation and activity of human osteoclasts in vitro was determined in co-cultures of human osteoblasts and peripheral blood mononuclear cells. AZD0530 was most effective in inhibiting osteoclast-like cell formation when present at the onset of osteoclastogenesis, suggesting that Src activity is important during the initial phase of osteoclast formation. Formation of active, phosphorylated c-Src, which was highly present in osteoclast-like cells in co-cultures and in PBMC monocultures, was significantly reduced by AZD0530. Furthermore it reversibly prevented osteoclast precursor migration from the osteoblast layer to the bone surface and subsequent formation of actin rings and resorption pits. These data suggest that Src is pivotal for the formation and activity of human osteoclasts, probably through its effect on distribution of the actin microfilament system.

Adipose tissue-derived mesenchymal stem cells (AT-MSCs) constitute a promising tool for tissue engineering approaches targeting skeletal defects. For bone tissue engineering, it is important that MSCs differentiate into osteoblasts. Polyamines, which are organic cations involved in cell proliferation and differentiation, have been implicated in bone growth and development. We found that the polyamine spermine regulates the differentiation of AT-MSCs along the osteogenic lineage. Therefore polyamines may constitute a promising tool for bone tissue engineering approaches using AT-MSCs.

Considerable effort has been put on the characterization of the collagen network of the different cartilage tissues (articular cartilage, meniscus, annulus fibrosus, nucleus pulposus) and the phenotypic behavior of these cells (as chondrocytes and as chondrons) cultured for weeks in alginate beads. Furthermore, a start has been made in characterizing recently described collagen-binding receptors (DDR2, Endo180) on chondrocytes and stem cells. In addition, stem cells have been co-cultured with nucleus pulposus cells in collagen hydrogels to promote chondrogenic
differentiation. Finally, adhesion experiments have been carried out on caprolactone with cells derived from human adipose tissue.

**Mechanical adaptation and regeneration**

Bone has the capacity to alter its mass and structure to its mechanical environment. Osteocytes are generally thought to be the professional mechanosensors of bone. A strain-derived fluid flow through the lacuno-canicular porosity seems to mechanically activate them, resulting in the production of signalling molecules such as nitric oxide (NO), which inhibits osteocyte apoptosis and alters osteoblast and osteoclast activity thereby preventing bone loss. Bone unloading results in osteocyte apoptosis, which attracts osteoclasts leading to bone loss. We have shown that mechanical loading by pulsating fluid flow inhibits apoptosis via alterations in Bcl-2 and caspase-3 gene expression, which is at least partly regulated by NO.

External mechanical forces on cells are known to influence cytoskeletal structure and thus cell shape. Mechanical loading in long bones is unidirectional along their axes, whereas the calvariae are loaded at much lower amplitudes in radial and/or tangential directions. We hypothesized that if osteocytes can indeed sense matrix strains directly via their cytoskeleton, the 3D shape and the long axes of osteocytes in fibulae and calvariae will bear alignment to the different mechanical loading patterns in the two types of bone. We used nano-CT and confocal microscopy to demonstrate significant differences in 3D morphology and the alignment of osteocytes in unidirectionally loaded mouse fibulae and multidirectionally loaded calvariae. This suggests a possible role of osteocytes in direct mechanosensing of matrix strains and adaptation of their 3D morphology to mechanical loading for efficient mechanosensing. The relatively spherical morphology of calvarial osteocytes suggests that these cells are more mechano-sensitive than fibular osteocytes, which provides a possible explanation of efficient physiological load bearing for the maintenance of calvarial bone despite its condition of relative mechanical disuse.

External mechanical loading on mammalian cells results in surface integrin-mediated elongation of cytoskeletal stress fibers in the direction of principle strains. Paxillin is an integral part of the focal adhesions and is known to localise to the mechanosensing region of the cell. We found that the external mechanical loading pattern determines the orientation of the actin-cytoskeleton in the osteocyte cell bodies in situ, and that the focal adhesions likely mediate direct mechanosensation of matrix strains by the osteocyte cell bodies. This provides direct evidence to a plausible new mechanism of mechanosensation of matrix strains via the osteocyte cell bodies in bone.
### Academic personnel in 2008 and 2009

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#### Dissertations


Academic Centre for Dentistry Amsterdam


Publications in journals indexed in SCI


Other scientific publications (international, refereed)


Professional publications


External reports


Indicators of Esteem

Grants: current projects with external funding


Bronckers, A.L.J.J. Grant SRON ‘Osteoclast formation under microgravity and hypergravity. (June 2009-January 2011). Postdoc, 1.5 years and bench fee (total amount k€150).


Everts, V. Grant to Renata Neves, Brazilian PhD student awarded a scholarship from the CAPES Foundation, a federal agency under the Ministry of Education of Brazil, to develop part of her PhD research as a special student at Academic Centre of Dentistry Amsterdam (ACTA), under supervision of V. Everts and R.A. Bank (November 2007-May 2008).


Membership of international editorial boards

Bronckers, A.L.J.J.: ODONTOLOGY
Everts, V.: INT J DENT.
Everts, V.: OPEN BONE J.
Everts, V.: OPEN ENZYME INHIB J.
Klein Nulend, J.: J MUSCULOSKELETAL RES
Klein Nulend, J.: OPEN BION J
Klein Nulend, J.: OPEN NITRIC OXIDE J
Klein Nulend, J.: OPEN TISSUE ENG REG MED J
Loon, J.J.W.A. van: BIOL SCI SPACE
Loon, J.J.W.A. van: MICROGRAVITY SCI TEC
Lyaruu, D.M.: CONNECT TISSUE RES

Scientific awards/honours


Organisation of international congresses or symposia


Invited speakers at international congresses or symposia


Other international functions

Loon, J.J.W.A. van: President. European Low Gravity Research Association, ELGRA.
Loon, J.J.W.A. van: Member evaluation board. ESA Fly-your-thesis student program for parabolic flight campaign.

Collaborations

- City University of New York, Dept. Mechanical Engineering (prof.dr.ir. S.C. Cowin), New York, NY, USA.
- Erasmus University Rotterdam, Dept. Orthopaedics (prof.dr.ir. H. Weinans), Rotterdam, NL.
- Eindhoven University of Technology, Dept. Biomedical Engineering (prof.dr.ir. R. Huiskes), Eindhoven, NL.
- Hospital Hilversum, Dept. Orthopaedics (dr. G.H.R. Albers), Hilversum, NL.
- Keele University, Centre for Science and Technology in Medicine (prof.dr. A. El Haj), Stoke-on-Trent, UK.
- Brown Medical School/Rhode Island Hospital, Dept. Orthopaedics, Providence, RI, USA (dr. Q. Chen).
- Spaarne Hospital Heemstede, Dept. Orthopaedics (dr. P.A. Nolte), Heemstede, NL.
- University of Aberdeen Medical School, Dept. Medicine and Therapeutics (dr. M.H. Helfrich), Aberdeen, Scotland.
- Utrecht University Medical Center, Dept. Orthopaedic Surgery (dr. W.J.A. Dhert), Utrecht, NL.
- VUmc, Dept. Endocrinology (prof.dr. P. Lips), Amsterdam, NL.
- VUmc, Dept. Clinical Physics and Engineering (dr.ir. Th.H. Smit, dr. R. Breuls), Amsterdam, NL.
- VUmc, Dept. Haematology (dr. G.J. Schuurhuis), Amsterdam, NL.
- VUmc, Dept. Plastic Surgery (prof.dr. M. Ritt), Amsterdam, NL.
- Göttingen University, Dept Biophysics (prof.dr. C.F. Schmidt), Göttingen, Germany
- VUmc, Dept. Theoretical Physics (prof.dr. F.C. Mackintosh), Amsterdam, NL.
- Radboud University Nijmegen Medical Centre, NL, Dept. Orthodontics and Oral Biology (prof.dr. A.M. Kuipers-Jagtman, dr. J.C. Maltha, dr. R. van ’t Hoff)
- TNO/VUmc (prof.dr. R.A. Bank), Leiden/Amsterdam, NL.
- Kyoto University, Dept Mechanical Engineering and Science (prof.dr.ir T. Adachi, dr. M. Tanaka), Kyoto, Japan.
- AMOLF, Biological Soft Matter Group (dr. G. Koenderink), Amsterdam, NL.
- Harvard University, Boston, MA, USA (dr. R. Krishnan).
- Radboud University Nijmegen Medical Centre, NL, Dept Orthodontics and Oral Biology (prof.dr. A.M. Kuipers-Jagtman, dr. J.C. Maltha, dr. R. van ’t Hoff)
- Radboud University Nijmegen Medical Centre, Dept. of Biomaterials (prof.dr. J. Jansen and dr. X.F. Walboomers)
- University of Groningen, Dept. Oromaxillofacial Surgery (dr. J. Schortinghuis)
- Univ. Madrid, Spain, prof.j. Medina.
- Univ Oulu Finland: dr. S. Kellokumpu
- Univ. Madrid, Spain, prof. R. Marco.
- Univ. Madrid, Spain, prof. Medina.
- Univ. Milan, Italy, prof. S. Bradamante.
- Techn. Univ. Eindhoven, prof. M. Rauterberg
- Centrum voor Constructie en Mechatronics, CCM, Nuenen, the Netherlands
- Dutch Space, Leiden, the Netherlands
- Univ. Utrecht, Prof. J. Boonstra.
- Univ. Nijmegen, HMFJ, J.C. Maan, P. Christianen.
- Univ. Groningen, dr. H. Harmsen
- Univ. of Connecticut, USA, M. Musgrave
- VU Amsterdam, Fact. Physics, D. Iannuzzi
- Univ. Nijmegen, prof. E. Roubos, dr. B. Jenks
Current PhD projects


Section: Oral Microbiology

Microbiological Aspects of Oral Infections

Program leader

Prof.dr. W. Crielaard
Oral Microbiology
ACTA
Van der Boechorststraat 7
1081 BT Amsterdam
Tel: +31-20-444 8679
E-mail: W.Crielaard@acta.nl

Full professors

W. Crielaard  A.J. van Winkelhoff

Research objectives

Oral infections are caused by interaction of the host and the bacterial biofilm. Therefore, host-parasite interactions are a major part of the research aims of the section. The interaction is studied by microbiological analysis of oral biofilms in different oral infectious diseases: periodontitis, peri-implantitis, caries and mucositis. Susceptibility for periodontal destruction and abscess formation due to caries is studied by identifying gene polymorphisms in innate immunity genes in patients and controls using the candidate gene approach. In this way, the relationship between genetic features of the host and the microflora is studied.

Interactions between the periodontal pathogen Porphyromonas gingivalis and human oral fibroblasts are studied and by using mutant strains of P. gingivalis the role of specific virulence factors is studied. One research objective is to study the role of encapsulation and K antigens in the virulence of P. gingivalis. The study of the genetic basis of the different K antigens of this pathogen is currently under investigation.

Spread of periodontal pathogens within isolated populations and transmission between spouses and siblings, is of current scientific interest. Transmission patterns of different bacterial species is investigated. This is of paramount importance to understand spread of primary (Aggregatibacter actinomycetemcomitans and P. gingivalis) pathogens and commensal species (Tannerella forsythia).

Results

Molecular diagnostic tools for determining microbial risk factors for periodontal disease, peri-implantitis, mucositis and caries have been further developed and implemented. These techniques have shown great sensitivity and have been implemented in the routine diagnostics of oral infections. For further improvement of detection of microorganisms, specific microbial virulence factors and host genetic factors, new approaches are in development.

A. actinomycetemcomitans is studied for diagnostic purposes. A. actinomycetemcomitans (Aa) can be cultivated or detected by (real-time) PCR. It is found that most (90%) of the serotype e strains do not react in the Real-Time PCR. The prevalence of the serotype e varies between 1,3% in the
Netherlands to 8.2% in Indonesia of all Aa strains. AFLP analysis showed a clonal distribution of this group which includes references strains from various geographical origins. 16S rRNA sequencing confirmed the AFLP findings. DNA-DNA homology analysis yields a homology almost 70% and is on the borderline of a distinct species (collaboration with dr. S. van Trappen en prof.dr. P. de Vos, Ghent University, Belgium).

Transmission of the periodontal pathogen T. forsythia (Tf) has been studied between humans (in Indonesia) and between humans and domestic cats (collaboration with dr. H. Booij-Vrieling, University of Utrecht) by using AFLP analyses. In the Indonesian study, we failed to proof transmission of Tf between spouses or siblings. Identical AFLP-genotypes were scarcely found and only in non-related subjects. 8.3% harboured more than one genotype Tf. From a study on 48 Dutch domestic young cats (<2 yr old) and their owners no identical strains were found. However, in a group of 6 couples of older cats (>5 yrs old) and their owners, one identical strain was isolated. The large number of genotypes suggest an environmental source of Tf.

In relation to the genetic background of periodontal diseases the candidate gene approach has been developed. Within the INFOBIOMED EU project built data warehouse has been extended and records have been analyzed by data mining techniques in collaboration with bioinformatics (prof.dr. V. Moustakis, Heraklion). Using tagging SNP’s in a large population of patients (N = 805 cases and 1.415 controls) an association was found between chronic periodontitis and a SNP in an innate immunity gene (in collaboration with dr. A. Scheafer, Kiel).

Candidate gene polymorphisms have also been studied in association with peri-implant infections. CD14-260 polymorphism that previously has been associated with periodontitis did not show any association with peri-implantitis (in collaboration with prof.dr. S. Renvert, Kristianstad). The CD14-260 C>T polymorphism was studied in a Surinam child population in relationship to formation of abscesses or fistulae. It was found that abscess or fistulae formation was significantly inhibited in children with the CD14-260 T.T genotype.

Healthy gingiva- (GF) and periodontal ligament (PDLF) fibroblasts respond to P. gingivalis by expressing the pro-inflammatory cytokines interleukin (IL)-1, IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), RANTES (regulated upon activation, normal T-cell expressed and secreted), and macrophage-colony stimulating factor (M-CSF). In GF but not PDLF, expression of OPG was decreased. Also, from each individual, either GF or PDLF responded stronger to P. gingivalis.

The cytokines produced by GF and PDLF can also play a role in osteoclast formation. Indeed, conditioned medium from infected GF stimulated osteoclast formation in vitro, but inhibited RANKL and M-CSF induced osteoclast formation. Moreover, encapsulated P. gingivalis were less able to induce an inflammatory response and effect osteoclast formation, than non-encapsulated P. gingivalis. Currently oral fibroblasts from periodontitis patients and healthy persons are being collected to investigate if they respond differently to P. gingivalis.

Using an isogenic mutant first evidence was found that the capsular polysaccharide of P. gingivalis reduces the immune response of human gingival fibroblasts. The construction of this capsule mutant opens doors to study the host-microbe interaction on a molecular level. Another mutant construction strategy was shown to be successful in knocking out 12 capsule biosynthesis related genes of P. gingivalis. Studies on microarray analyses of different capsular types of P. gingivalis were initiated.

Studies on mucositis in patients with bone marrow transplanted where continued and results indicate an association between Candida colonisation and mucositis.
Academic personnel in 2008 and 2009

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Publications in journals indexed in SCI


Other scientific publications


Professional publications


Indicators of Esteem

Grants: current projects with external funding

KNAW/CAS (Chinese Academy of Sciences) Grant in the "China Exchange Programme": travel grant for lectures in Beijing, Guangzhou and Hong Kong.

Membership of international editorial boards

Winkelhoff, A.J. van: CLIN ORAL IMPLAN RES
Winkelhoff, A.J. van: EVID DENT PRACT
Winkelhoff, A.J. van: J CLIN PERIODONTOL
Winkelhoff, A.J. van: J PERIODONTAL RES
Winkelhoff, A.J. van: J PERIODONTOL

Invited speakers at international congresses or symposia

Soet, J.J. de (2008, November 24). Dental caries and genetics. Sao Paulo, Brazil, Dental School post academic program Faculdade de Odontologia da Universidade.
Winkelhoff, A.J. van (2008, March 07). Drugs against bugs. Frankfurt, Germany, ARPA.

Scientific awards/honours

Organization of international congresses or symposia


Other international functions

Soet, J.J. de: Secretary General. ORCA (European Organisation of Caries Research).
Winkelhoff, A.J. van: Member scientific committee. European Federation of Periodontology.
Winkelhoff, A.J. van: Visiting professor. University of London, Eastman Dental Hospital, Department of Periodontology.

Collaborations

- University of Oslo, Dept. of Microbiology, prof.dr. l. Olson, Oslo, Norway
- University of Gothenburg, Dept. of Oral Microbiology, prof.dr. G. Dahlén, Gothenburg, Sweden
- University College of London, Queen Mary’s School of Medicine and Dentistry, prof.dr. M. Curtis, London, UK
- Department of Medical Microbiology and Infection prevention, VU University Medical Center, prof.dr. C.M.J.E. Vandenbroucke-Graauls, Amsterdam, the Netherlands
- Laboratory of Immunogenetics, VU University Medical Center, prof.dr. A.S. Peña, Amsterdam, the Netherlands
- Department of Oral and Maxillofacial Surgery and Maxillofacial Prosthetics, University of Groningen, prof.dr. B. Stegenga, Groningen, the Netherlands.
- Department of MicroArrayFacility, dr. T. Breit, Universiteit van Amsterdam, the Netherlands
- Faculty of Veterinary Medicine, dr. H. Booj-Vrielings, University of Utrecht, the Netherlands
- Department of Health Sciences, Kristianstad University, prof.dr. S. Renvert, Kristianstad, Sweden
- Department of Informatics, VU University Medical Center, Amsterdam, the Netherlands
- Department of Dentistry and Oral Hygiene and Department of Biomedical Engineering. Faculty of Medical sciences, University of Groningen, Groningen, the Netherlands. prof.dr. M.C.D.N.J.M. Huysmans.
- Division of Biological Chemistry and Drug Discovery, School of Life Sciences, University of Dundee, Dundee, UK.
- Department of Medical Microbiology and National Reference Center for Systemic Mycoses, University Medical Center Göttingen, Göttingen, Germany.
- Department of Molecular Cell Physiology, VU University Amsterdam, the Netherlands.
- MRC-Holland BV, Amsterdam, the Netherlands.
- TNO Quality of Life, Business Unit Food and Biotechnology Innovations, Microbial Genomics Group, Zeist, the Netherlands.
- Josephine Bay Paul Center, Marine Biological Laboratory, Woods Hole, MA, USA.
- Department of Molecular Microbial Physiology, Swammerdam Institute for Life Sciences, Faculty of Science, Universiteit van Amsterdam, Amsterdam, the Netherlands.
- Department of Pediatric and Social Dentistry, São Paulo State University (UNESP), Araçatuba, Brazil.
- Department of Prosthodontics and Periodontology, Dental School of Piracicaba, State University of Campinas, SP, Brazil.
- Centre for Advanced Microscopy, Section of Molecular Cytology, Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, the Netherlands.
- Microarray Department & Integrative Bioinformatics Unit, Faculty of Science, University of Amsterdam, Amsterdam, the Netherlands.
- Institute of Computer Science, FORTH Vassilika Vouton, Heraklion, Greece, prof.dr. V. Moustakis.
- University of Kiel, Institute for Clinical Molecular Biology, Kiel, Germany, dr. A. Scheafer.
- Laboral Diagnostics CV, Houten, the Netherlands.

Current PhD projects


Department of Oral and Maxillofacial Surgery / Oral Pathology

Oral and maxillofacial disorders: diagnosis and treatment

Program leader

Prof.dr. I. van der Waal
Department of Oral and Maxillofacial Surgery/Oral Pathology
ACTA
VU Medical Center
P.O. Box 7057
1007 MB Amsterdam
Tel: +31-20- 444 1023
E-mail: i.vanderwaal@vumc.nl

Full professors

Research objectives

The research of the Department of Oral and Maxillofacial Surgery/Oral Pathology consists of eight main areas of interest, being:
1. Early diagnosis of oral cancer and precancer, including cancer of the salivary glands.
2. Surgical orthopedics of the maxillofacial skeleton.
3. Maxillofacial implantology and reconstructive preprosthetic surgery.
4. Inflammatory and inflammatory-like diseases of the oral and perioral structures, including the jaw bones and the lymph nodes of the neck.
5. The effects of chemotherapy and bisphosphonates on the oral microcirculation and the possible role in the development of osteonecrosis of the jaw.
6. Evaluation of the effect of anticoagulant medication on blood loss during and after dentoalveolar surgery (the BLACK study).
8. The relationship between anxiety, pain and third molar extractions.

A substantial percentage of oral cancer is preceded by so-called precursor lesions, particularly leukoplakia. Intervention in the precursor stage may prevent the development of frank malignancy. The ongoing intervention study of oral leukoplakia is being continued both in a retrospective and prospective manner. Amongst others, the prognostic value of the DNA content is examined with regard to the predictive value of malignant transformation. There is a close collaboration with both the General Pathology Department and the ENT - Department of the VU University Medical Center (VUMc) in Amsterdam, both being related to the VUMc-Institute for Cancer and Immunology (V-ICI).

Salivary gland tumours are a very heterogeneous group of tumours, with more than 40 subtypes recognised in the most recent WHO classification. Classification is based solely on histopathology. Sometimes, correct classification and prediction of biological behaviour is difficult. Therefore, our studies aim to better characterize these tumours at the genomic and
protein level. There is a close collaboration with the General Pathology Department, related to the VUmc-Institute for Cancer and Immunology (V-ICI), and with the Department of Oral Biochemistry of ACTA.

The research on surgical orthopedics is focused on maxillofacial function and healing capacity after treatment of acquired and congenital jaw deformities. Attention is focused on the indications/contraindications and preventive measures in surgical-orthodontic treatment of dentofacial deformities. In addition, the dynamics of the surrounding tissues after corrective surgery of maxillofacial bones is studied, e.g. the musculature and the temporal mandibular joint. In these studies there is a close collaboration with the department of Orthodontics.

The research on maxillofacial implantology and reconstructive preprosthetic surgery deals primarily with bone and bone-substitutes in maxillofacial implantology. Research includes a number of investigations on the maxillary sinus floor elevation model, where bone grafts and bone substitutes are investigated. Apart from that, the patient material in general and of post-oncological patients in particular forms a valuable source for research. In the studies mentioned before there is a close collaboration with the department of Oral Cell Biology of ACTA, the department of Endocrinology of the VUmc and the departments of Oral and Maxillofacial Surgery at the Rijnland Hospital, Leiderdorp and the St Antonius Hospital, Nieuwegein. The research on surgical orthodontics and on maxillofacial implantology is included in the recently established Research Institute MOVE of the VUmc.

Two new implantology research programs started in 2008 at the AMC location: 1) the clinical usefulness of Implant Stability Quotient (ISQ) measurements in implant stability and osseointegration, and 2) the effect of different fixation techniques on the bone quality in buccal onlay bone grafting.

Giant cell granuloma of the jaw bone is a rare, but sometimes aggressive disease. The research is focused on the possible value of the use of calcitonin or interferon, particularly in aggressive or recurrent giant cell granulomas. As an immunologic spin-off of the CHIMED study (study on the treatment of non-tuberculous mycobacterial lymphadenitis in children, comparing surgical versus medical treatment) 22 single nucleotide polymorphisms (SNPs) in a CHIMED patient cohort were analyzed to screen for the most common mutation (818del4 in IFNGR1) that leads to Mendelian Susceptibility to Mycobacterial Disease (MSMD). In another spin-off a new mycobacterial species Mycobacterium manteni was discovered.

Bisphosphonates are commonly prescribed for treatment and prevention of osteoporosis, and they are also used in combination with chemotherapy and radiotherapy to treat cancers that are metastatic to bone. Recent publications describe a condition, known as osteonecrosis of the jaw, in which patients receiving bisphosphonates while undergoing chemotherapy develop avascular necrosis of the jaw either spontaneously, due to oral trauma or following dental extraction. The aim of this study is to elucidate the effects of chemotherapy and bisphosphonates on the oral microcirculation of breast cancer and multiple myeloma patients. Furthermore, the effects of cytotoxic chemotherapy on the microvasculature, morphology and capillary density of the oral mucosa are evaluated. This research program is conducted in collaboration with the Departments of Internal Medicine, Division of Hematology and Oncology, Translational Physiology and Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam.

The aim of the study on anticoagulant medication is to evaluate the effect of low dose regimes of aspirin, as well as the effect of ticlopidine and clopidogrel, on bleeding in patients undergoing oral surgical procedures. This research program is performed in close collaboration with the Department of Internal Medicine, Vascular Medicine, Academic Medical Center Amsterdam.

The aim of the study on evidence-based guideline development on the management of invasive dental procedures in patients using antithrombotic medication is to assess the best available evidence on the risks and benefits of withholding or continuing antithrombotic medication during invasive dental procedures, assess the current practice by dentist, general practitioners, and oral surgeons, and to develop a multidisciplinary practice guideline on this topic. This research program is carried out in close collaboration with the department of Social Dentistry and Behavioural Sciences, ACTA.

The research on anxiety and third molar surgery investigates the relation between anxiety sensitivity, dental anxiety, expected pain and experienced pain following third molar surgery. This research program is conducted in collaboration with the department of Social Dentistry and Behavioural Sciences, ACTA.
Results

The study on early diagnosis of oral cancer, including the salivary glands, is ongoing. A thesis on oral melanoma has been completed in 2008. The project on the possible value of markers for the diagnosis and prognosis of salivary gland tumours has been focused until now on adenoid cystic carcinoma and myoepithelioma, but will be expanded to other tumour types.

The project on the possible value of markers for the diagnosis and prognosis of salivary gland tumours has been focused on tumours with myoepithelial differentiation, i.e. adenoid cystic carcinoma and (malignant) myoepithelioma. The results are summarized in a thesis, based on five manuscripts accepted in peer-reviewed papers. These studies are now expanded to tumour types with mucinous differentiation.

The group on surgical orthopedics of the maxillofacial skeleton has been making steadily progress, focusing on condylar hyperplasia and on the use of imaging techniques on soft tissue changes after orthognatic surgery.

The randomized study on the removal of asymptomatic lower wisdom teeth has been finished. A manuscript has been submitted.

Several multi-centre studies are running concerning new implant surfaces and new implant designs. In the line of bone and bone substitute research in the sinus floor elevation model, there are several studies running. The most recent study is on the clinical and histological results on SBC (Straumann Bone Ceramic) in sinus floor elevation. Early clinical and histological results are promising.

The studies on inflammatory and inflammatory-like diseases of the oral and peri-oral structures, including the jaw bones and the lymph nodes of the neck, have been running well. Two manuscripts on the CHIMED study spin-offs are now under editorial review.

In the study on the effects of chemotherapy on the oral microcirculation the animal protocol has been approved by the DEC. The first experiments have been performed and the first articles have been submitted in 2008.

In the project on the evidence-based guideline development a questionnaire study has started in collaboration with the NMT (Dutch Dental Association). Results are expected in January 2009. A study that evaluated the quality of existing guidelines from the USA and UK has been performed and an article has been submitted.

In the study on dental anxiety, quality of life and third molar surgery, one manuscript has been published in 2008 while another has been accepted for publication.
### Academic personnel in 2008 and 2009

#### Research staff ACTA - MZ (in full time equivalents)

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#### Dissertations


Publications in journals indexed in SCI


Academic Centre for Dentistry Amsterdam


Other scientific publications (international, refereed)


Elsevier.


Professional publications


**Indicators of Esteem**

**Grants: current projects with external funding**

Bruggenkat, C.M. ten. SBC (Straumann Bone Ceramic) bone substitute for sinus floor elevation (2005-2008) Straumann; € 52.000,-

Membership of international editorial boards

Becking, A.G.: ORTHOD CRANIOFAC RES
Bruggenkate, C.M. ten: CLIN ORAL IMPLAN RES
Goené, R.J.: EUR J ORAL IMPLANTOL
Lindeboom, J.A.H.: EUR J ORAL IMPLANTOL
Tuinzing, D.B.: PADIADJARAN J DENT
Waal, I. van der: ACTA STOMATOLOGICA CROATICA
Waal, I. van der: EUR J CANCER
Waal, I. van der: J DENT UNIV SAO PAOLO
Waal, I. van der: J STOMATOL INVEST
Waal, I. van der: MEDICINA ORAL
Waal, I. van der: MINERVA STOMATOL
Waal, I. van der: ORAL HEALTH PREV DENT
Waal, I. van der: ORAL MAXIL SURG
Waal, I. van der: ORAL ONCOLOGY
Waal, I. van der: PADIADJARAN J DENT

Invited speakers at international congresses or symposia

Brand, H.S. (2008, May 15). Xerostomia and thirst are predictors for survival of hemodialysis patients. Egmond aan Zee, the Netherlands, 8th European Symposium on Saliva.
Bruggenkate, C.M. ten (2008, January 10). History of the ITI. Brussels, Belgium, Foundations meeting Belgium ITI.
Bruggenkate, C.M. ten (2008, October 03). Krumelchen. Freiburg, Germany, Krekeler Memorial symposium.

Organization of international congresses and symposia


Scientific awards/honours


Other international functions

Becking, A.G.: Member scientific committee. European Association Craniomaxillofacial Surgery
Becking, A.G.: Member. ITI.
Becking, A.G.: Member. Strasbourg Osteosynthesis Research Group
Bruggenkate, C.M. ten: Board member. Internal Team Implantology Basel, Switzerland
Bruggenkate, C.M. ten: Delegate. ITI Finland
Bruggenkate, C.M. ten: Member expert pool. ITI/Straumann
Bruggenkate, C.M. ten: Register of external evaluation experts. Hellenic Quality Assurance Agency for Higher Education (HQAA)
Waal, I. van der: Chairman development committee. ITI Straumann
Waal, I. van der: Expert for the UICC. Telepathology Consultation Center for odontogenic tissue. International Union Against Cancer (UICC)
Waal, I. van der: Member scientific committee. STOMA
Collaborations

- Biofarmind, The Hague, the Netherlands
- Crucell, Leiden, The Netherlands
- Institut für Anatomie, Zentrum für Experimentelle Medizin, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
- Leids Universitair Medisch Centrum, afdeling mondziekten en kaakchirurgie, Leiden
- Netherlands Cancer Institute, Amsterdam, The Netherlands
- Sint Antonius Ziekenhuis, afdeling dermatologie, Nieuwegein
- Swammerdam Institute for Life Sciences, University of Amsterdam, Amsterdam, The Netherlands
- Universitair Medisch Centrum Utrecht, afdeling Neurologie
- University of Parma, Unit of Oral Pathology and Medicine, Section of Odontostomatologia, Department of EMT, Dental Ophthalmological, and Cervicofacial Sciences, Parma, Italy
- VUMc, afdeling Heelkunde, sectie Vaatchirurgie, Amsterdam
- VUMc, afdeling Nucleare Geneeskunde en PET research, Amsterdam
- VUMc, afdeling Neurologie, Amsterdam
- VUMc, Department of Clinical Epidemiology and Biostatistics, Amsterdam
- VUMc, Department of Clinical Genetics
- VUMc, Department of Endocrinology, Amsterdam
- VUMc, Department of Otolaryngology/Head and Neck Surgery, Amsterdam
- VUMc, Department of Pathology, Amsterdam
- VUMc, EMGO-instituut, Onderzoeksgroep Huisartsengeneeskunde, Amsterdam

Current PhD projects


Section: Oral and Maxillofacial Radiology

Diagnostic Imaging of the Tissues in the Maxillo-facial Complex

a. Computer aided analysis of digital radiographic images
b. Three dimensional visualization of radiographic information

Program leader

Prof. dr. P.F. van der Stelt
Oral and Maxillofacial Radiology
ACTA, Louwesweg 1
1066 EA Amsterdam
Tel: +31-20-5188 262
E-mail: P.vd.Stelt@acta.nl

Full professor

P.F. van der Stelt

Research objectives

The research of the Department of Oral and Maxillofacial Radiology is focused on the development and improvement of diagnostic methods for the visualization of normal and abnormal structures in the maxillofacial complex. This is realized from different perspectives including both fundamental and applied (clinical) components:

The application of advanced digital image processing procedures enables the recognition of specific features in radiographic images of normal and abnormal structures being characteristic for the condition of these structures. Typically, these features are either used for the quantitative assessment of tissue characteristics (density, homogeneity, etc.) or they add a new dimension to the description of the (patho) physiology of the tissue structures under investigation. Commonly the order of magnitude of this description is between the microscopic (micro; e.g., connectivity, density) and the anatomic (macro; e.g., texture, entropy) level.

2. Three dimensional visualization of radiographic information.
An important aspect of the research objectives is the visualization of radiographic image data into 3D-space. The purpose of 3D imaging is to overcome the inherent drawbacks of projection radiography, such as the lack of information about the third dimension. We try to achieve this goal by the use of specific 3D reconstruction techniques called Local CT and Cone Beam CT, which results in a much lower dose and a higher resolution than conventional CT. This makes the technique a better choice for many common dental diagnostic tasks than conventional CT.
Results

Computer aided analysis of digital radiographic images.
Our contribution to the Osteodent project (see annual report 2006) was focused on the quantitative analysis of the radiographic trabecular pattern on intra-oral radiographs and panoramic radiographs. We were able to demonstrate that quantitative analysis of the radiographic trabecular pattern is able to predict between 70 and 80% of the osteoporotic subjects. Several papers were published in 2007 and 2008. The large database of images and clinical parameters is further explored and several publications are in progress.

Another implementation of computer aided analysis of digital images is the quantitative assessment and colour coded visualisation of bone quality around implants. A large study is in progress based on the analysis of longitudinal data of panoramic images of implant patients. The amount of bone loss and percentage of implants that are failing is correlated with several social and clinical parameters of these patients. The first results will be available and published in 2009.

Three dimensional visualization of radiographic information
Several studies based on CBCT data sets, both clinical and fundamental, are on the way. The CBCT facilitates many opportunities for collaboration with other dental disciplines, such as orthodontics (interactive location of cephalometric points in 3D), CMD-treatment (TMJ disorders), Implantology (templates for guided surgery based on series of axial slices and 3D reconstructions), oral surgery (impacted third molars) and endodontology (number of root canals; vertical root fractures). The first publications of the endo-studies were accepted.

The work on virtual 3D data using a 3D wand, shutter glasses and mini LCD screens with left and right perspective are making progress. One dissertation was published based on this study. Lack of time keeps the progress at a slow pace, but nevertheless some new developments were achieved. The purpose of these studies is to develop the optimum system for the display of 3D information in a clinical environment.

Within the framework of 3D reconstruction and volume rendering we contributed to the Simodont project. The feasibility of 3D volume rendering of objects to be used in a virtual learning environment was shown. The virtual learning environment consists of a haptic device with realistic 3D feedback to train students in cavity preparations on simulated teeth.
Academic personnel in 2008 and 2009

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Publications in journals indexed in SCI


Professional publications

Indicators of Esteem

Membership of international editorial boards

Mileman, P.A.: DENTOMAXILLOFACIAL RAD
Sanderink, G.C.H.: DENTOMAXILLOFACIAL RAD
Sanderink, G.C.H.: ORAL RADIOL
Stelt, P.F. van der: CLIN ORAL IMPLAN RES
Stelt, P.F. van der: DENTOMAXILLOFACIAL RAD
Stelt, P.F. van der: EUR J DENT
Stelt, P.F. van der: ODONTOLOGY
Stelt, P.F. van der: ORAL SURG ORAL MED

Invited speakers at international congresses or symposia


Other international functions


Organization of international congresses or symposia

Collaborations

- Prof. R. Jacobs, Imaging Sciences, Katholieke Universiteit Leuven, Belgium
- Prof. S.M. Dunn, Rutgers University Dept. of Biomedical Engineering, Piscataway NJ, USA.

Current PhD projects


Section: Orthodontics

Craniofacial development, psychosocial aspects and biomaterials in orthodontics

Program leader

Prof. dr. H. van Beek
Orthodontics
ACTA, Louwesweg 1
1066 EA Amsterdam
Tel: +31-20-5188 415
E-mail: H.v.Beek@acta.nl

Full professors

H. van Beek
A. Zentner

Research objectives

The research activities at the Department of Orthodontics focus on basic and clinical research in orthodontics and related disciplines. Three main themes exist:
1. Basic and clinical description of environmentally and genetically induced aberrations of facial form.
2. To determine the impact of Orthodontics on the quality of life.
3. To optimize orthodontic material properties and procedures for clinical use.

Results

The research activities at the Department of Orthodontics focus on basic and clinical research in orthodontics and related disciplines, and the following directions were pursued in the year 2008.
1. Growth and growth regulation during normal and abnormal craniofacial development. A number of projects were carried out within this larger theme, which for a long time has been the department’s major research field. Strong collaboration links have been established with the Section of Functional Anatomy ACTA. Animal experimental set-ups with soft diet elucidate the function-morphology interrelation with regard to facial form and function.
2. Orthodontics and quality of life. This research theme has now been expanded and new projects have been started on the basis of previous work. In particular collaborative work with the section of Social Dentistry has been intensified.
3. Biomaterials. Studies were carried out in collaboration with the section of Dental Material Sciences ACTA. Bond strength and setting characteristics of glass ionomer cements and fatigue fracture of orthodontic arch wires were investigated.
### Academic personnel in 2008 and 2009

#### Research staff ACTA - OR (in full time equivalents)

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#### Total 1st funding

| total 1st funding | 2,80 | 2,35 | 1       |

#### Total guests

| total guests       | --   | 0,05 | guest   |

#### Total research staff

| Total research staff | 2,80 | 2,40 |

### Dissertations


### Publications in journals indexed in SCI


Other scientific publications (international, refereed)


Professional publications


Indicators of Esteem

Membership of international editorial boards

Zentner, A.: EUR J ORTHODONT
Zentner, A.: J DENT BIOMECH
Zentner, A.: J OROFAC ORTHOPED
Zentner, A.: ORTHODONTIA
Invited speakers at international congresses or symposia

Beek, H. van (2008, March 01). Simple solutions for difficult problems with the Van Beek appliance. Theory and practice, tricks and pitfalls in headgear-activator therapy; Vertical control in dentofacial orthopedics. Kitzbühel, Austria, Precongress 1 day course meeting.

Other international functions

Beek, H. van: Examiner postgraduate programme in orthodontics. University of Gent, Belgium.
Winter, F.R. de: Chairman quality committee. Federation of Orthodontic Specialists Associations, EFOSA.
Zentner, A.: Member expert committee. German Orthodontic Society (DGKFO) on benefits and Effects of Orthodontic Treatment.

Current PhD projects

Section: Social Dentistry and Behavioural Sciences

Oral Health-related Well-being and Behaviour

Program leader

Prof.dr. J. Hoogstraten
Social Dentistry and Behavioural Sciences
ACTA, Louwesweg 1
1066 EA Amsterdam
Tel: +31-20-5188 247/246
Fax: +31-20-5188 233
E-mail: J.Hoogstraten@acta.nl

Full professors

J. Hoogstraten  A. de Jongh  G.H.W. Verrips

Research objectives

In line with recent developments within the section and ACTA, concerning both staff-composition and research reorientation, and stimulated by the very good/excellent rating of the section’s research efforts received from the International Review Committee, research is now focused on Oral Health-related Well-being and Behaviour, of both patients and general dental practitioners and their staff. Three general objectives are guiding the section’s research efforts now: one, to monitor and improve the oral health of the Dutch population and to increase patients’ quality of life and satisfaction and the public trust in dentistry; two, to assess the determinants and general consequences of occupational stress and well-being of general dental practitioners and their staff; three, to study dental anxiety and pain, two major barriers to seek and maintain dental care, of both adult and child-patients, from a multidimensional perspective and with the help of psychologists, dentists, and double-trained staff-members.

Results

Research findings suggest that oral health, general health and quality of life (Q of L) have different determinants. At least in a healthy population oral and general health appear to be unrelated.

The most well-known instrument to assess oral health-related Q of L is the OHIP (Oral Health Impact Profile). It was shown that this measure is susceptible to order effects which implicate possible bias of results. Testing Locker’s hierarchical model, which in theory underlies the OHIP, results demonstrated the empirical tenability of this model. But for the Child version of the OHIP (COHIP) it appeared that the alleged structure of five subscales could not be demonstrated. Further validation is suggested and it seems advisable to revise and adapt the subscales and use them separately since they are strongly correlated.

We may add that for specific subgroups within the child and adult population the concept Q of L also proved useful: extremely low birth weight adolescents, children with craniofacial conditions, children undergoing general anaesthesia and highly anxious child and adult patients.
Research findings once more underline the importance of pain-free treatments and awareness of patients’ individual predisposition to anxiety to reduce the risk of iatrogenic psychological harm. In order to reduce or prevent psychological harm of wisdom teeth removal it was suggested to give patients’ an intensive separate consultation before extraction. Anxious dental patients with a negative experience regarding dental injections, moreover, may feel elevated levels of pain leading to negative expectations for the future. Likewise, dissipative emotional and interceptive reactions during dental treatment have the greatest potential risk of precipitating pathological forms of dental anxiety. Level of dental anxiety was found to be an important factor in the response of children to a local anaesthesia injection and for children having a choking phobia EMDR-treatment seems effective. The anxiety-provoking capacity of 67 stimuli characteristics of the dental setting were assessed and the Level of Exposure-Dental Experiences Questionnaire was developed and psychometrically analyzed using five different samples. Result are promising. It was also shown that invasive stimuli (e.g. surgical procedures) are rated as the most anxiety provoking.

It was confirmed once more that the Maslach Burnout Inventory (MBI) is a suitable instrument for use among dentists. Given the clear increase in burnout risk found, this topic should remain under investigation in dentistry. Findings indicate, in a longitudinal study among dentists, that out of the three MBI-dimensions, emotional exhaustion precedes depersonalisation which in turn precedes personal accomplishment, and that positive job resources most valued are ‘Immediate results / Aesthetics’ and that, ‘Idealism / Pride’ and ‘Patient care’ showed most predictive value with regard to engagement among dentists. As for prevention of burnout it appeared, using first and fifth year scores of cohorts of fifth year dental students from five European dental schools, that dental students show a negative development with regard to Emotional Exhaustion and psychological distress. It is recommended that dental faculties focus on prevention and intervention of stress among their undergraduates. As usual our collaborative research with other ACTA sections were also productive. We refer to the research output of the departments of Orthodontics, Cariology, Endodontology, Pedodontology, Oral and Maxillofacial Surgery and Periodontology.
Academic personnel in 2008 and 2009

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| non-tenured staff            | Bos, dr. A.                    | 0.20     | --        | 1       |
| PhD students                 | Edeler jr. MA., drs. H.A.      | 0.40     | 0.05      | 1       |
|                              | Kieffer, drs. J.M.             | 0.70     | 0.70      | 1       |
|                              | Klaassen, drs. M.A.            | 0.20     | 0.20      | 1       |
|                              | Oosterink-Wubbe, drs. F.M.D.   | 0.40     | 0.20      | 1       |
|                              | Vermaire, drs. J.H.            | 0.20     | 0.20      | 3       |

Total non tenured staff       |                                | **2.10** | **1.35**  |

total 1st funding            |                                | 4.20     | 3.15      | 1       |
total 3rd funding            |                                | 0.20     | 0.20      | 3       |
Total research staff          |                                | **4.40** | **3.35**  |

Dissertations


Publications in journals indexed in SCI


Other scientific publications (international, refereed)


Professional publications


External reports


Indicators of Esteem

Grants: current projects with external funding

Gorter, R.C. Dental health services research unit. A work-related stress audit in general dental practice: The psychological health of dental health professionals working in the Western Health and Social Services Board (WHSSB), Dundee, UK. External funding 2007 – 2008: €13562.50. –

Poorterman, J.H.G. Tandheelkundige verzorging volwassen ziekenfondsverzekerden, 2007-2008. In order of College voor Zorgverzekeringen; €146.000. –


Membership of international editorial boards

Gorter, R.C.: EUR J DENT EDUC

Scientific awards/honours

Collaborations

- H. Buchanan & N. Coulson, Health Psychology, Institute of Work Health & Organisations, Faculty of Social Sciences, Law and Education, University of Nottingham, UK, Fear of dental pain, Cochrane review group (psychological interventions and dental surgery), third molar surgery in relation to anxiety and pain.
- Prof. P. Coulthard, dept. of Oral and Maxillofacial Surgery, School of dentistry, Manchester, Cochrane review group (analgesics and third molar extraction).

Current PhD projects


Section: Dental Material Sciences

Dental Restorations

Program leader

Prof.dr. A.J. Feilzer
Dental Material Sciences
ACTA, Louwesweg 1
1066 EA Amsterdam
Tel: +31-20-5188335
E-mail: A.Feilzer@acta.nl

Full professors

A.J. Feilzer  J.M. van der Zel

Research objectives

The general objective of this program is to predict and improve the clinical performance of dental restorative materials covering the complete range of materials involved in the procedures of creating restorations with direct or indirect techniques. Composition, structure and fabrication of the materials as well as their handling and application techniques are studied in vitro as well as in vivo. The increasing trend to replace the difficult and costly manual procedures by automated procedures with information technology is being studied on its merits. In particular the possible advantages of the automated production of indirect restorations by CAD/CAM technology are evaluated. The physical properties and quality of restorations, as well as the esthetic properties, influenced by digital color measurement and reproduction, are subject of our attention. CAD/CAM technology offers the possibility to use new strong ceramic materials as a base for all-ceramic restorations. Mainly the research into Y-TZP zirconia indicates that its excellent physical properties make it an alternative for metal alloys in stress-bearing substructures.

Apart from basic scientific research, a substantial part of the research involves the development of laboratory experiments and equipment that simulate the clinical conditions as closely as possible, ultimately to be used as standard quality control tests (so-called accelerated tests). Examples of such equipment are the 'ACTA-wear machine', the 'ACTA-tensilometer' and the 'ACTA-fatigue device'.

Since 2002 the research area of the section includes clinical research on dental materials. For instance a study into the performance of indirectly made resin composite crown restorations has been started. In 2003 in the department clinic a start was made with special consulting hours where patients with suspected health effects, related to metals used in dental restorative materials, can be referred to. This project has developed both clinically and on basic science aspects quite well.

More specifically, the following aspects were investigated:
1. The effect of various agents on the morphology of dentin surfaces and the consequence on the quality of the bond with restorative materials.
2. The effect of test set up design on the results of the (micro and macro) tensile bond strength tests.
3. The operator independent determination of optical properties of resin-based composites and ceramics in relation to composition and the effect of aging on color.
4. The effect of the design of core build-up constructions on the resistance to premature failure during fatiguing.
5. The effect of water sorption of adhesives and resin cements on the adhesion to ceramics and the occurrence of fractures in ceramic crowns and inlays.
6. The effect of fatigue loading on the cohesive and adhesive properties of bonded restorations.
8. The effect of fatigue loading on phase changes in zirconia.
9. The effect of restorations under stressed conditions studied by three-dimensional finite elemental analysis (3D FEA).
10. The effect of surface defects on the strength of ceramics.
11. The thermal compatibility of dental ceramic systems.
12. The effect of design parameters on the survival rate of adhesive bridges.
13. The applicability of glass ionomer cement for orthodontic purposes.
14. The effects on general health of metal based restorative materials.

Results

Substantial progress has been made in revealing the mechanisms that play a role in the stress distribution in specimens exposed to tensile stresses in bond strength tests. For this research FEA was used to demonstrate the stress distributions in test specimens in more detail. It was shown that specimen size and shape had a significant influence on the bond strength. Based on this knowledge new studies towards the bonding properties, strength and design properties were started. Special attention was paid to (i) core build-up and post systems, (ii) orthodontic bracket systems, and (iii) cantilevered teeth and (pre)molars. Furthermore, fracture toughness and fatigue of model systems were investigated. Various experimental and new commercial versions of low shrinking restorative monomer systems were tested in our department.

The development of ‘smart’ ceramics such as Y-TPZ-Zirconia is of main interest as a strong base for full ceramic restorations that might replace the use of metallic materials in restorative dentistry. In applied science nano-technology is an example of a field of increasing interest, which has been introduced in dentistry. The CAD/CAM-technology in dentistry has reached a stage that can compete with all manual restorative methods. This fast-growing technique becomes a main area of interest in the field of quality assessment. A new technique in CAD/CAM is the rapid fabrication technique, which opens new opportunities for homemade indirect ceramic restorations and introduction of new ceramic materials.

Color measurements and automated color reproduction with the aid of CAD/CAM are of great scientific and commercial interest. A number of color measurement devices has been tested and their clinical performance has been evaluated. A significant relation of the color of different segments of teeth was demonstrated, which can be used to reconstruct the tooth color of missing parts of the tooth.

In 2003 a start was made to develop a laboratory test to determine the composition of metal alloys used intra-orally for indirect restorations. This test is of main interest, as only traces of the metals need to be collected in situ to be analyzed on allergenic substances. Because of the medical aspects involved, cooperation has been sought with the departments of clinical immunology, pathology and dermatology of the academic hospital (VUmc). Clinically, more than a 500 patients with suspected health effects on dental materials were evaluated, while with a modified lymphocyte transformation test immunologic reactions of the T-lymphocytes on the composing metals of their dental restorations was screened. The incidence of metal-ion release by the use of metallic restorative materials is a topic of main interest. However, in spite of an extensive amount of literature, there is a lack of overview on the dental consequences of these effects.
Academic personnel in 2008 and 2009

<table>
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Dissertations


Publications in journals indexed in SCI


External reports


Indicators of Esteem

Grants: current projects with external funding

Signum-NECO follow study.

Membership of international editorial boards

Feilzer, A.J.: AM J DENT
Feilzer, A.J.: ODONTOLOGY
Zel, J.M. van der: DIGITAL DENT J

Organization of international congresses or symposia

Invited speakers at international congresses or symposia


Other international functions


Zel, J.M. van der.: Chairman. ISO/TC106 ad hoc committee for standardization of dental CAD/CAM systems.

Collaborations

- Elephant Industries, Hoorn, the Netherlands
- Degudent GmbH, Hanau
- Heraeus Kulzer GmbH, Wehrheim
- 3M-ESPE, Zoeterwoude
- Cavex Holland B.V., Haarlem
- Melisa.org, (prof.dr. V. Stejskal), Stockholm, Sweden.
- Laborcentrum Bremen, dr. E. Valentine-Thon, PhD
- Department of Dermatology, Albert Schweitzer Ziekenhuis, (dr. R. Laeijendekker)
- Department of Pathology, VU medical center, (prof.dr. R.J. Scheper)
- VU medical center, Laboratory of Clinical Immunology, (dr. M. van Blomberg)
- Department of Dermatology, VU medical center, (dr. Th. Rustemeyer)
- UMC Groningen, Conservative dentistry (prof.dr. M.C.D.N.J.M. Huysmans; prof.dr. M. Özcan)
- Department of Prosthetic Dentistry and Biomaterials research, Institute of Dentistry, University of Turku, Turku, Finland (prof.dr. P. Vallittu)
- University of Tanta
- University of Alexandria
- University of Cairo
- Universität Regensburg, (prof.dr. M. Behr)

Current PhD projects


Section: Functional Anatomy

Oral Function and Oral Rehabilitation: Functional Anatomy

Program leader

Dr. ir. J.H. Koolstra  
Functional Anatomy  
ACTA  
Meibergdreef 15  
1105 AZ Amsterdam  
Tel: +31-20-5665 370  
E-mail: j.h.koolstra@amc.uva.nl

Research objectives

The research program deals with the general question of how histological, anatomical, (neuro-)physiological and mechanical properties of the jaw muscles, jaws and jaw joints affect the development, maintenance and degradation of form and function of the masticatory system. The mission is to obtain fundamental knowledge to enable prevention of oral dysfunction and recovery of pathologic structure and function in the masticatory system.

The research is concentrated at the following three themes:

1) Unraveling of the mechanisms of bone adaptation to its mechanical function with emphasis to (1) architecture, structure and mechanical loading, (2) tensions and deformations at the tissue and cellular level and (3) the response of bone cells to tensions and deformations controlling growth and adaptation.

2) Testing of hypotheses regarding bone adaptation by analysis of the effects of experimentally altered loading on shape and structure of bone using animal models.

3) Application of biomechanical models in clinical situations to predict risks of aberrant loading patterns and loss of tissue in relation to muscle atrophy, loss of dental elements, jaw joint dysfunction, oral implants, orthodontic treatment and oral surgery.

Results

The different components of the masticatory system are loaded by forces and torques as a result of muscle activation. The myosin heavy chain composition, which is indicative for the muscle’s physiological properties and herewith its possibilities to apply dynamic loads, has been demonstrated to adapt to its functional requirements. The mechanism of this adaptation is subject to study and preliminary results indicate that muscle fibers do not change in an all-or-not fashion but show adaptational changes that propagate along them. Translated to the effects on bone loading it was found that at sites where jaw closing muscles are attached, the mineralization is relatively low, indicating more active bone remodelling than, for instance, where jaw opening muscles are attached. Experiments to analyse this relationship more directly by chronic stimulation of relevant muscles or simultaneous measurement of bone strain and activity of adjacent muscles are in preparation. A novel method to obtain jaw muscle activity and concomitant mandibular bone strain in free moving rabbits has been implemented successfully. Strong correlations between periods of masseter muscle activity and periods of mandibular
deformations were demonstrated. Study of the relationships between the estimated muscle forces and registered strain amplitudes and directions is in progress.

In order to gain insight in the adaptive processes that take place during normal and abnormal bone remodelling the bone’s structural and mechanical properties have been analysed during prenatal and postnatal development as well as in the adult stage. In trabecular prenatal and newborn bone tissue a characteristic distribution of mineralization was found, being higher in the cores than at the surface of trabecular elements. Similar results have been obtained in the adult mandibular condyle. This suggests that trabeculae are stiffer in their cores and more compliant at their surface. This was confirmed by nanoindentation. Using large scale Finite Element Analysis of complete adult human mandibular condyles it was found that the mechanical consequences for the bone structure as a whole bone can be dramatic. It gives the bone much more compliance than would be the case when all the bone tissue would have had the same stiffness. Furthermore, it gives the bone strength along the directions of habitual loading and compliance in other directions. Similar results were found in postnatal bone indicating that the underlying mechanism is maintained during bone remodelling processes during growth and adaptation of healthy condylar bone. The alveolar bone quality in the maxilla and mandible have been analysed in relation to differences of success for application of dental implants. Preliminary results indicated that in the elderly but dentate maxilla the mineralization of the alveolar bone is less than in the mandible.

A start has been made to understand the aetiology of internal derangements of the temporomandibular joint. As hypermobility of this joint is suspected to be one of the milder forms of internal derangement that eventually may lead to failure, a (in perspective patient specific) dynamic biomechanical model has been developed to study aberrant muscle activation in combination with such a joint as a possible cause for the development of dysfunction. Applying this model to normal morphology and muscle activation it was predicted that, in contrast to the general opinion, the temporomandibular joint has to withstand larger loads during unloaded jaw-opening movements than during unloaded closing. Osteoarthrosis (OA) of the temporomandibular joint is considered one of the most severe types of joint disease. As the material properties and architecture of both the articular cartilage and the subchondral bone have been found to change with the severity of OA, a start has been made to analyse these properties with microCT in combination with biomechanical modelling. To visualize the cartilaginous structures a method for contrast enhancement was contrived. A number of pilots have appeared successful. Preliminary results indicate that herewith also the concentration of proteoglycans can be assessed. As this concentration gives an indication how much the tissue is able to attract water, it also gives an indication how well it will be able to withstand compressive loads and what its consequences are for loading (and herewith adaptation) of the subchondral bone.

Although the program’s main focus remains the fundamental understanding of the relationship between form and function in the masticatory system, the relevant knowledge has reached such a level that extrapolation to clinical relevant questions becomes feasible. To that purpose the current projects aim to provide knowledge at the tissue- and organ level to predict tissue loading, its changes due to adaptation, and its consequences that can be applied to clinical problems regarding, for instance, oral implants, orthodontic treatment, osteoarthrosis and oral dysfunction.
## Academic personnel in 2008 and 2009

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* We regret to mention that prof. Van Eijden has passed away early 2007.

## Publications in journals indexed in SCI


Other scientific publications


Indicators of Esteem

Grants: current projects with external funding


Invited speakers at international congresses or symposia


Membership of international editorial board

Koolstra, J.H.: J DENT BIOMECH.

Other international functions

Koolstra, J.H.: Member international scientific committee. 16th Congress European Society of Biomechanics, July 6th-9th, Lucerne, Switzerland.

Collaborations

- Eindhoven University of Technology, Department of Materials Technology (prof.dr.ir. J.M.J. den Toonder), Eindhoven, the Netherlands
- Hiroshima University, Department of Orthodontics (dr. N. Kawai), Hiroshima, Japan
- University of Tokushima, Department of Orthodontics and Dentofacial Orthopedics (prof. E. Tanaka), Tokushima, Japan.
- Kyushu University, Department of Oral and Maxillofacial Radiology (dr. T.K. Goto), Fukuoka, Japan.
- University of Naples, Department of Orthodontics (I. Cioffi, dr. M. Farella), Naples, Italy.
- The Fourth Military Medical University, Department of General Dentistry (prof. Y. Chen), Xi’an, China.
- AMC, Department of Orthopedics (dr. L. Blankevoort.)
- NKI-AVL, UvA, Division of Immunology (dr. J. Borst).
Current PhD projects


Section: Oral Biochemistry

Protective Functions of Saliva for the Oral Cavity

Program leader

Prof.dr. E.C.I. Veerman
Oral Biochemistry
ACTA
Van der Boechorststraat 7
1081 BT Amsterdam
Tel: +31-20-444 8675
E-mail: eci.veerman@VUmc.nl

Full professors

E.C.I. Veerman
A. van Nieuw Amerongen

Research objectives

Without saliva all oral tissues will be affected by exogenous factors as microorganisms and aggressive nutritional components. Saliva apparently protects oral surface tissues against harmful attacks. The primary aim of the research of the Department of Oral Biochemistry is to analyse the contribution of the individual salivary components, particularly of the (glyco) proteins to maintain oral tissues healthy, also in relation to microbiological aspects of oral infections. The research is focussed on answering the following questions:

1. What are the biological functions of the salivary (glyco) proteins and subsequently what is the biological significance of the variation in glandular (glyco) proteins from the submandibular, sublingual and parotid glands?
2. What is the biological significance of the whole set of salivary proteinase inhibitors, particularly the specific salivary cystatins? Are they involved in the regulation of oral inflammatory processes? What is the relation between immuno-neuro-regulatory processes in the periodontium and mucosa and the expression of inhibitory proteins in the salivary glands?
3. Can synthetic peptide analogues of histatins be applied as broad spectrum antibiotics, particularly to Candida albicans and other oral pathogens? In future such peptides might be useful in newly developed saliva substitutes.
4. The effect of conditions known for their potential to impair oral health (such as the use of medical drugs, systemic diseases and psychological stress) on the quality of saliva.
5. Influence of saliva on the interaction of oral microrganisms with oral epithelial cells.

Results

Properties and working mechanism of antimicrobial peptides

In salivary lactoferrin a second antimicrobial domain (designated lactoferrampin), has been identified. In the native molecule the lactoferrampin domain is situated in close proximity to another antimicrobial domain, lactoferricin. To investigate whether these sequences together form a functional unit, we have designed a chimeric peptide in which the spatial orientation of two antimicrobial domains of lactoferrin is mimicked as confirmed by NMR structural analysis (in collaboration with dr. H. Vogel, Univ. of Calgary, Canada). This chimera exhibits enhanced antimicrobial activity against both yeasts and a variety of Gram-positive and Gram-negative
Annual Research Report 2008

bacteria compared to the individual peptides. The interaction of the chimera with model membranes is currently further investigated using several biophysical methods including Differential Scanning Calorimetry, Circular dichroism and NMR analysis (in collaboration with dr. M. Bastos, Univ. Porto, Portugal and dr. H. Vogel, Univ. of Calgary, Canada).

In ongoing collaborative studies with a number of research institutes the efficacy is explored of antimicrobial peptides against several notorious multidrug-resistant bacteria, e.g. *Vibrio haemolyticus*, *Vibrio cholerae* (University of Culiacán Sinaloa, Mexico), *Microbacterium tuberculosis*, *Helicobacter pylori*, *Pseudomonas aeruginosa* (Dept. of Medical Microbiology, VUmc), *Burkholderia pseudomallei*, (Dept. of Oral Diagnosis and Tropical Diseases, University of Khon Kaen, Thailand).

Saliva as diagnostic fluid

Currently, we explore the potential of saliva as diagnostic fluid for monitoring various diseases. One of the diseases which potentially can be diagnosed using saliva is Idiopathic Nephropathy (IgAN). This disease is caused by deposition in the kidney of aberrantly glycosylated IgA. We have developed compounds to facilitate detection of aberrantly glycosylated IgA molecules in patient saliva. In collaboration with dr. I. van Die, Dept. of Molecular Cellbiology and Immunology, VUmc, Amsterdam this line of investigation will be continued.

Saliva, epithelia and microorganisms

This line of research is focussed on the role of saliva in protection and maintenance of oral epithelia. It was already found that in particular parotid saliva enhances the *in vitro* wound closure of epithelial cells. We now have identified the active agent as members of the histatin family, which thus far had been implicated in the protection against microorganism. Their effects on epithelial cells occurs after binding to a membrane receptor, resulting in enhanced cell migration. Future research will focus on identification of the minimal active domain and identification of the cellular receptor and signalling pathways. Furthermore the influence of oral microorganisms on the wound-closing effects will be studied, in the absence and presence of salivary components such as LL-37, defensins, histatins, lactoferrin and lactoferrin-derived peptides.

Interactions of salivary agglutinin with microorganisms, its role in innate immunity

A large number of bacteria has been tested for binding of salivary agglutinin (SAG) and a peptide representing the binding site of SAG. There was a good correlation between binding to the parent SAG molecule and the peptide for different bacterial species, suggesting that this peptide domain is responsible for the broad-binding properties of SAG. To explain the broad spectrum bacteria binding properties of SAG several conserved bacterial cell surface components were tested for binding to SAG. SAG bound to the cell wall component peptidoglycan. The peptide backbone of peptidoglycan was responsible for this binding. In collaboration with dr K. Hartshorn (New York) was shown that salivary agglutinin could bind influenza A viruses and enhances the uptake of influenza virus by neutrophils. SAG also bound to *C. albicans* that were in the logarithmic growth phase but much less to *C. albicans* in the stationary growth phase. Binding of salivary components to *C. albicans* inhibited hyphen formation, which is considered to be the more infectious form. Future research will focus on other salivary components which induce the yeast-like growth form and the *C. albicans* component that is responsible for binding of SAG in the logarithmic growth phase.

Impact of systemic diseases on saliva

This line of research, which examines the impact of systemic diseases on the composition and properties of saliva, focuses on patients with kidney disease (prof.dr. P.M. ter Wee, VUmc), patients with gastrointestinal diseases (dr. A.A. van Bodegraven, VUmc), and patients receiving stem-cell transplantation for malignant diseases (dr. J. Raber-Durlacher, LUMC). Results indicate that the level of xerostomia is associated with the severity of the systemic disease.

Diagnosis and treatment of saliva-related oral problems

Since May 2007 dr. C.P. Bots, dentist, has joined the saliva clinic at ACTA, which guides patients suffering from saliva-related problems. More than 150 patients have been diagnosed and provided with advice. In addition, patient oriented research has been undertaken to evaluate the efficacy of oral moisturizing gels for the alleviation of xerostomia. In another project it was investigated whether the level of oral dryness can be estimated by judging the appearance of the tongue.
Academic personnel in 2008 and 2009

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Publications in journals indexed in SCI


Other scientific publications (international, refereed)


Professional publications


Patents


Indicators of Esteem

Grants: current projects with external funding

Bolscher, J.G.M. (2006-2010). Grant from Thailand government. Co-investigator of research project: "Antimicrobial peptides against Burkholderia pseudomallei", covering: PhD-student, visits to foreign research labs and visits of co-investigator to Khon Kaen University. Principal Investigator: prof.dr. Suwimol Taiwetchaisupapong, Department of Oral Diagnosis, Khon Kaen University, Thailand. Co-Investigators: dr. Surasakdi Wongratanacheewin, Melioidosis Research Center, and Department of Microbiology, Faculty of Medicine, Khon Kaen University, Thailand.


Organization of international congresses or symposia


Invited speakers at international congresses or symposia

Brand, H.S. (2008, May 15). Xerostomia and thirst are predictors for survival of hemodialysis patients. Egmond aan Zee, the Netherlands, 8th European Symposium on Saliva.

Scientific awards/honours


Other international functions


Collaborations

- VUmc, Dept. of Medical Microbiology (prof.dr. C.M.J.E Vandenbroucke-Grauls, dr. B. Appelmelk).
- VUmc, Dept. of Molecular Cell Biology and Immunogenetics, section Immunomodulation (prof.dr Y. van Kooyk, dr. T.B.H. Geijtenbeek).
- VUmc, Dept. of Molecular Cell Biology and Immunogenetics, section Glycoimmunology (dr. I van Die).
- VUmc, Dept. of Molecular Cell Biology and Immunogenetics, section Dermatology (dr. S. Gibbs, prof.dr. R. Schepers).
- Universiteit van Amsterdam, AMC, Dept. of Cell Biology and Histology (dr. J. van Marle).
- Universiteit van Amsterdam, AMC, Dept. of Human Retrovirology (prof.dr. B. Berkhout).
- TNO Defence, Security and Safety (dr. F.J. Bikker).
- University of Chile, Santiago, Institute of Biomedical Sciences (prof.dr. M. González).
- University of Madrid, Centro di Investigaciones Biologicas (prof.dr. L. Rivas).
- University of Oporto, Portugal, Dept of Chemistry (dr. M. Bastos).
- UAIS, Faculty of Medicine, Hospital Pediatrico de Sinaloa, Mexico (dr. Nidia León SicaIaos).
- Khon Kaen University, Thailand, Dept of Oral Diagnosis (dr. S. Taweechaisupapong).
- University of Chiang Mai, Thailand, Dept. of Odontology and Oral Pathology (dr. S. Krishanaprakornkit).
- Mahidol University, Bangkok, Thailand, Faculty of Science and Faculty of Tropical Medicine (prof.dr. S. Sirisinha and dr. N. Chantratita).
- University of Aquila (Italy), Dept. of Biomedical Sciences and Technology (dr. A. Bozzi).
- Deutsche Krebsforschungszentrum Division of Molecular Genome Analysis, Heidelberg (dr. C. End).
- University of Calgary, Calgary, Canada. Dept. of Biological Sciences (prof.dr. H.J. Vogel).
- The Hebrew University, Hadassah School of Dental Medicine, Department of Pediatric Dentistry, Jerusalem, Israel (dr. E. Davidovich).
- National University of Ireland, Galway, Department of Chemistry (dr. N. Karlsson).
- Sanguin, Departments of Immunopathology (dr. D. Wouters) and Blood Cell Research (prof.dr. T. van den Berg).

Current PhD projects


Appendix

List of SCI journals, their impact factors and the number of ACTA publications in 2008 in each journal

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