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INTRODUCTION

ACTA is the combined Faculty of Dentistry of the University of Amsterdam (UvA) and the VU University Amsterdam. ACTA has a unique position in the Netherlands, being a combined faculty of two universities since 1984. The boards of both the University of Amsterdam and the Vrije Universiteit Amsterdam share the responsibility for the research at ACTA. Research at ACTA is organized in the ACTA Dental Research Institute.

The annual report starts with chapters containing the annual survey of the dean, and overviews of the scientific activities. As in preceding years the scientific performance is subsequently presented for each programme. Detailed information is given of dissertations, scientific publications in refereed journals, other scientific publications, professional publications, indicators of esteem, collaborations and societal impact.

In 2014 an international review committee evaluated the two research programs of ACTA. Both programmes Oral Infections and Inflammation and Oral Regenerative Medicine received a very good to excellent rating.

An overview of the scientific output in 2016 is presented in Table 1. During the last decade, the output has increased considerable. The number of scientific publications and the impact factor sum remained high in 2016. The number of PhD theses continued to increase and an all time high number of 25 PhD theses were published and defended in 2016.

Research Institute ACTA

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REPORT OF THE DEAN

The Research Institute ACTA

- mission statement
Dental research at ACTA focuses on the study of health and diseases of essentially all tissues of the oral cavity, the masticatory system and of oral fluids. Besides infectious diseases like dental caries, periodontal and periapical inflammatory processes, and inflammatory processes around dental implants, attention is paid to the development, function and regenerative capacities of the hard tissues, pain and dysfunction of the masticatory system, and diseases of salivary glands and oral mucosa. It is the general aim to improve strategies for diagnosis, treatment indication and treatment planning as well as prevention of diseases, functional repair of the affected tissues in and around the oral cavity and evaluation of therapies developed to treat patients. Moreover, we aim to gain insight in the aetiology and pathology as well as the risk factors involved in these diseases. In our attempts to fulfil this mission we aim to establish:
- integration of the clinical sciences with fundamental disciplines
- education and further academic training of post-graduate and PhD-students
- knowledge transfer 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 organizations and industries.

- positioning of the research institute
National position. ACTA comprises the combined Faculties of Dentistry of the University of Amsterdam and the Vrije Universiteit Amsterdam. The ACTA Research Institute is the only institute for research of the faculty.
Research programs. From 2011, ACTA research has been organized into the two research programmes (see below). Next to these two major programmes, some limited other research is performed, which is mainly education-related.
The programme Oral Infections and Inflammation (OII) focuses on (i) the aetiology, prevention and therapy of oral infections such as caries, periodontal and endodontic infections, on (ii) oral inflammatory processes, protective functions of saliva, oral cancer and on (iii) the definition of a normal, healthy oral cavity including psychosocial factors.
The programme Oral Regenerative Medicine (ORM) focuses on (i) the biological process of adaptation and repair of teeth, bone, mucosa and periodontium, on (ii) the biocompatibility of dental materials, and on (iii) regenerating damaged oral tissue by means of stem cell therapy and/or tissue engineering techniques, taking into account the mechanical threats of the masticatory system. Untill December 31st 2016, ACTA research on oral regenerative medicine was also included in the interfaculty MOVE Research Institute Amsterdam, a collaboration between the faculty of Behavioural and Movement Sciences, the VU University Medical Centre (VUmc) and ACTA.

- description of output, leading scientific journals in the field
Within both research programmes considerable differences exist in the approaches used; yet, both range from fundamental medical-biological to clinical-applied science. This is reflected by the type of scientific journals in which 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
SEP external evaluation. In 2014 an external evaluation of dental research of ACTA was completed according to the Standard Evaluation Protocol designed by the VSNU.
The two research programs of ACTA, Oral Infections and Inflammation and Oral Regenerative Medicine were evaluated separately with respect to quality of the research, relevance to society and viability.
The committee concluded about the program Oral Infections and Inflammation: The quality of research in this programme was considered excellent. Many strong publications from the OII group have had a considerable impact in the field of dental research and have influenced opinion development on these topics in the broader scientific community. The relevance of the group’s research to society was considered to be very good. Collectively the future of the programme was considered to be very good.
The committee concluded about the program Oral Regenerative Medicine: Because of the future trajectory and promise provided in particular by the increased integration of cell biology approaches into scaffold
development and prosthodontics/implantology research, the research quality of the ORM programme was
considered to be excellent. The ORM programme’s impact on society is considered to be very good. While
there are some structural organizational issues that need to be resolved to ensure further integration,
research success and ongoing productivity, the group’s viability is considered to be very good.
The committee gave a number of valuable recommendations that will be elaborated in the next years.

In spring 2017, an external evaluation of both Research Priority Grants of the University of Amsterdam will
be performed.

Citation analysis. In 2013, the CWTS in Leiden has performed a bibliometric analysis of the ACTA scientific
publications over the years 2001-2011. One of the goals of this study was to identify possible benchmarks.
These benchmark candidates were investigated in more detail and compared with the performance of ACTA.
The conclusions of this study are as follows:

In this study we developed and applied a method to identify benchmark candidates for institutes with a non-
mainstream research profile. These benchmarks are used to position the performance of ACTA. The outcome
of this study shows an important role of ACTA in terms of output. ACTA has published an impressive amount
of papers during the period studied (1,142 papers). Also the amount of number of citations received is very high
(4,667) as well as the number of publications in the top 10% most highly cited (P_top10). It should be noted,
however, that the latter two are size-dependent: the more you publish, the more citations you will receive. If
we look at the impact (MNCS and PP_top10, citations per publication normalized by field), ACTA is among the
middle group. Still the impact is well above world average (10%).

Summary of research output and input

<table>
<thead>
<tr>
<th>Table 1. Comparison of research indicators 2004-2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Dissertations</td>
</tr>
<tr>
<td>Refereed publications</td>
</tr>
<tr>
<td>First author from ACTA</td>
</tr>
<tr>
<td>Other scientific publications</td>
</tr>
<tr>
<td>Professional publications</td>
</tr>
<tr>
<td>Publications for general public</td>
</tr>
<tr>
<td>Impact factor sum</td>
</tr>
<tr>
<td>Personnel WP 1</td>
</tr>
<tr>
<td>WP2</td>
</tr>
<tr>
<td>WP3</td>
</tr>
<tr>
<td>Guests</td>
</tr>
<tr>
<td>Total personnel</td>
</tr>
</tbody>
</table>

wp1 academic personnel funded by 1st source in fte; this includes direct funding by the university
wp2 academic personnel funded by 2nd source in fte; this includes research grants obtained in national
competition from NWO, STW and KNAW
wp3 academic personnel funded by 3rd source in fte; this includes research contracts for specific projects
obtained from external organizations, such as industry, governmental ministries, European Commission and
charity organizations

• long time performance

Dissertations (PhD theses). The performance of the research institute over a longer period is shown in Table 1.
These data show that the number of dissertations per year has fluctuated between 6 and 18. This reflects
variations in external collaborations, such as non-ACTA employees receiving a PhD from our universities and
tenure staff members finishing their PhD. In 2016, 25 dissertations were accomplished.
PhD performance. The percentage of PhD students that finished their thesis averages 92% over the last 20 years, and the mean time period 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. maternity and illness) of some PhD students.

Scientific publications. The main attention in the research assessment at the individual and program level is given to publications in scientific journals with a peer review referee system. This category has increased considerable since the turn of the century, and resulted in a stable high output since 2013. In 2016, again a high number of 272 refereed publications was obtained. The majority of these publications were published as open access (Gold/Hybrid 29%, Green 32%). The average quality of the publications has also improved during the last two decades, as indicated by the concominant increase of the impact factor sum (Figure 1).

Professional publications. ACTA scientists are very active in communicating their research findings not only to the scientific community, but also to professionals. The number of professional publications in 2016 was 131.

Figure 1. Impact factor sum of ACTA publications, scientific publications in refereed journals, professional publications and total scientific personnel in fte.

- notable events in 2016

Publications in high ranking journals. Outstanding contributions for the year 2016 were publications in high ranking biomedical journals, i.e. Trends in Biotechnology (impact factor 12.1), Proceedings of the National Academy of Sciences of the United States of America (impact factor 9.4), Oncogene (impact factor 7.9), and Schizophrenia Bulletin (impact factor 7.6). ACTA scientists also published 16 papers in the top 10% journals in dentistry.

Impact factors. 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 272 scientific papers in refereed journals, of which 253 in journals with an impact factor (SCI journals). 41% of these 253 papers appeared in journals belonging to the field Dentistry, Oral Surgery and Medicine. 15% of all publications were in the top 10% of the journals, 42% in the top 25% and 80% in the top 50% (Table 2). This means that, as in previous years, a relatively large number of publications were published in the top journals in the field, both in dental and in non-dental journals.
Indicators of esteem. On a personal level a number of ACTA employees rank in the top of the international dental community, as determined by the various indicators of esteem, such as editorships, invited lectures, and congresses organized. In 2016 a total of 9 awards were received by ACTA scientists for their achievements. For more details we refer to the description of the two research programs.

Grants. In 2016, the successful participation of ACTA in the nationally funded and oriented Top Institute Food and Nutrition (TIFN) was completed. In the TIFN theme ‘Oral Health’, which started in 2011, world players in the oral care industry, the chewing gum industry, flavour industry, food industry and (oral) care appliances industry collaborated with ACTA and with the Netherlands Organization for Applied Scientific Research (TNO). At this moment two ACTA PhD students are funded by the large EU-MUNDUS project MOVE-AGE. In 2013 the large Marie Curie ITN EU project Euroclast was granted by the EU. This project is coordinated by ACTA and involves participation of seven academies and two industrial partners and a total of 11 PhD students. In 2015, the EU Horizon 2020 Research Program awarded 6 million Euro’s for the project ADVOCATE – Adding value to oral care. A grant was obtained in collaboration with the Radboud University Nijmegen from the Dutch Cancer Society to explore oral complications in cancer patients (KWF-HOME). The Netherlands Organisation for Health Research and Development (ZonMw) granted a project for the development of biomimetic bone substitutes (BIOBONE).

Table 2. Percentage of publications in different quartiles of dentistry and non-dental journals in 2016

<table>
<thead>
<tr>
<th></th>
<th>dentistry journals</th>
<th>non-dental journals</th>
<th>all journals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>numbers</td>
<td>percentage</td>
<td>numbers</td>
</tr>
<tr>
<td>top 10%</td>
<td>16</td>
<td>15 %</td>
<td>23</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>30</td>
<td>29 %</td>
<td>78</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>39</td>
<td>38 %</td>
<td>55</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>24</td>
<td>23 %</td>
<td>15</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>11</td>
<td>11 %</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>104</td>
<td>100 %</td>
<td>149</td>
</tr>
</tbody>
</table>

- assessment at the program level

In general, both research programs have performed comparable in terms of parameters like input and output during the past (personnel, PhD students, publications, dissertations etc). In 2016 the output of the OII programme was higher than the ORM programme, in particular with respect to professional publications, see Table 3. Other research (OWI), not related to the two programs, is limited both in terms of input (personnel and budget), and of output. Despite the very limited financial input by ACTA, this education related research is considered valuable.
Table 3. Summary of the number of publications, impact factor sum and academic personnel in fte

<table>
<thead>
<tr>
<th>Program</th>
<th>Dis</th>
<th>Ref publ</th>
<th>OSP</th>
<th>PP</th>
<th>PGP</th>
<th>IF</th>
<th>wp1</th>
<th>wp2</th>
<th>wp3</th>
<th>wp tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>OII</td>
<td>15</td>
<td>149 (65)</td>
<td>16</td>
<td>95</td>
<td>3</td>
<td>426</td>
<td>24,85</td>
<td>0,50</td>
<td>12,20</td>
<td>37,55</td>
</tr>
<tr>
<td>ORM</td>
<td>15</td>
<td>135 (63)</td>
<td>6</td>
<td>59</td>
<td>-</td>
<td>368</td>
<td>20,75</td>
<td>3,40</td>
<td>15,60</td>
<td>39,00</td>
</tr>
<tr>
<td>OWI</td>
<td>-</td>
<td>1 (1)</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td>0,30</td>
<td>-</td>
<td>0,25</td>
<td>0,55</td>
</tr>
<tr>
<td>ACTA*</td>
<td>25</td>
<td>272(140)</td>
<td>22</td>
<td>131</td>
<td>3</td>
<td>686</td>
<td>45,90</td>
<td>3,90</td>
<td>3,90</td>
<td>28,05</td>
</tr>
</tbody>
</table>

This table summarises the number of scientific publications in refereed 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 program by adding together the impact factor values of all 2016 publications.

- Dis = number of dissertations
- Ref publ = number of scientific papers in refereed journals. Between parentheses is the number of first authors belonging to the program in question
- OSP = other scientific publications (international, refereed)
- PP = professional publications
- PGP = publications for the general public
- IF = sum of impact factors as indexed by 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
- wp tot = all academic personnel in fte
- OII = Oral Infections and Inflammation
- ORM = Oral Regenerative Medicine
- OWI = Education Institute and other research
* ACTA = the total number of dissertations and papers reflects the total for ACTA; a dissertation or paper was counted only once; the total impact factor sum is not a summation of the data from each program

Table 4: fte of staff and PhD students (see table 2) by type of position

<table>
<thead>
<tr>
<th>Program</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OII</td>
<td>17,40</td>
<td>0,20</td>
<td>7,20</td>
<td>7,45</td>
<td>0,30</td>
<td>5,00</td>
<td>37,55</td>
</tr>
<tr>
<td>ORM</td>
<td>12,75</td>
<td>1,10</td>
<td>5,20</td>
<td>8,00</td>
<td>2,30</td>
<td>10,40</td>
<td>39,00</td>
</tr>
<tr>
<td>OWI</td>
<td>0,10</td>
<td>-</td>
<td>0,10</td>
<td>0,20</td>
<td>-</td>
<td>0,75</td>
<td>0,55</td>
</tr>
<tr>
<td>Total</td>
<td>30,25</td>
<td>1,30</td>
<td>12,50</td>
<td>15,65</td>
<td>2,60</td>
<td>15,65</td>
<td>77,10</td>
</tr>
</tbody>
</table>

OII = Oral Infections and Inflammation
ORM = Oral Regenerative Medicine
OWI = Education Institute and other Research

Societal impact

- impact on teaching and dental care

The prime societal values of a strong research program in a dental discipline are the effect on teaching and on dental care. The research improves the quality of 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 are also presented to dental practitioners at frequently held education activities, e.g. Quality Practice. The Research Institute participates in the ACTA curriculum by offering scientific training to all ACTA dental students. The societal impact of the research of ACTA is also focussed on the influence on patient care, both within ACTA and externally. Research on different
The high number of professional publications contributes to this societal impact. In this annual report the societal impact of each research program is described in more detail in the respective chapters.

- **functions in the scientific and professional community**
  ACTA employees take an active role as executives in international scientific organizations (87 international functions), as members of editorial boards of scientific journals (61) and in being leading in ‘wissenschaftliche Verenignungen’ of researchers and dental practitioners in the Netherlands. Furthermore, the societal impact is evident from the organization of symposia and conferences in the Netherlands and abroad, presentations for dentists, medical specialists and patient groups, memberships of advisory councils, and frequent contacts with the industry. In addition many scientists are also practicing 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. The societal impact is also evident from the relatively large number of 131 professional publications. Some ACTA researchers also wrote popularising publications aimed at a more general audience. Several research findings were high lightened in the general press.

- **invited lectures and congresses organized**
  In 2016 ACTA researchers have again contributed actively in internationally held meetings, workshops and symposiums, both as organizers and participants. A total of 105 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 or international audience. Due to this large number, congress abstracts are not listed in this annual report. A total of 18 international meetings were organized by ACTA scientists.

**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) of €817 is used for the management of the institute, salaries of PhD students, for travel allowances of PhD students, for the organization of courses for PhD students and for printing PhD theses.
  The research budgets for the departments (in total being €3298) are distributed based on a model containing 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 PhD students appointed by the research institute.
  In addition to the university budget (1st source) ACTA scientists were involved in many research projects with external funding. The total amount of research grants (2nd source) was €215, and the total amount of research contracts (3rd source) was €2053.

- **personnel**
  The directorate of the institute comprises:
  - prof.dr. A.J. Feilzer, dean and director of research ad interim p.m.
  - dr. T.J.M. van Steenbergen, co-ordinator of research 0.55 fte
  - dr. H.S. Brand, co-ordinator of research (started May 2016) 0.40 fte
  - mrs. F.M. Meijer, secretary 0.60 fte
  - dr. J.A.M. Korfage, research technician 0.15 fte

  The activities of the research institute directorate consist of organizing scientific meetings with presentations of PhD students, 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

The ACTA PhD training program is organized in the ACTA Graduate School of Dentistry (AGSD). As ACTA has currently no research master training, the AGSD is limited to the PhD program.

- PhD student appointments

In Figure 2, the number of new PhD students at ACTA is shown from the years 1991 to 2016. 26% of the current PhD students has a foreign nationality. In 2016, 9 new PhD students were appointed by ACTA which is similar to the long-term average number. Three of these students have been appointed by the research institute. More than half of all PhD students have a dental background (see Table 5). Of all PhD students about 70% is female.

Figure 2. Numbers of new ACTA PhD students from the Netherlands and other countries

![Graph showing numbers of new ACTA PhD students from the Netherlands and other countries]

Table 5: PhD students by type of undergraduate training

<table>
<thead>
<tr>
<th>program</th>
<th>dentistry</th>
<th>dentistry</th>
<th>biology / chemistry</th>
<th>psychology</th>
<th>medicine</th>
<th>other</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OII</td>
<td>31</td>
<td>19</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>ORM</td>
<td>22</td>
<td>26</td>
<td>16</td>
<td>1</td>
<td>14</td>
<td>4</td>
<td>83</td>
</tr>
<tr>
<td>OWI</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>45</td>
<td>26</td>
<td>6</td>
<td>23</td>
<td>16</td>
<td>171</td>
</tr>
</tbody>
</table>

OII = Oral Infections and Inflammation
ORM = Oral Regenerative Medicine
OWI = Education Institute and other research
PhD Courses
The following courses are organized for PhD students: Scientific Integrity, Dentistry for non-dentist PhD students, Writing and Presenting in English, Methodology and Statistics and Oral Biology. Dentistry is a multidisciplinary science and the background of the PhD students of ACTA is diverse. Therefore, most PhD students also follow external courses on specific research areas, organized by 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 between start of the PhD project and the defence of the thesis within ACTA amounts 4.6 years.

Figure 3. Mean duration of completing the thesis of ACTA PhD students related to the year of entry

Over the last 20 years, about 90% of all PhD students in ACTA completed their thesis (Figure 4). The PhD programma was evaluated by an external review committee in 2014. They concluded: Following queries about the infrastructure and core facilities, there was strong and unanimous agreement on the effectiveness of the ACTA programme to provide excellent PhD training. The students indicated that their programmes were well-organized and were well-supported to enable fulfilment of their research goals.
Points of attention

HRM and retirement
In the coming years several full professors who were active in 2016 will retire, thus giving the opportunity to appoint highly qualified researchers with a focus on one of the two programmes. The number of persons involved in research on university budget (1st source) increased compared to 2015, while the fte scientific personnel on grants (in particular 3rd source) showed a slight decrease.

PhD training
The duration of the PhD programme is, like elsewhere in The Netherlands, in general 4 years full time. PhD students with an employee status are generally employed for 4 years full time or for 5 years during 4 days a week. PhD students funded by EU grants are appointed for 3 years. Recently, it has been decided that future PhD students funded by ACTA will also be appointed for 3 years.

The research institute will continue its strategy, concentrating on the two main research programmes. New PhD positions will be reserved for high quality projects which focus at the integration of fundamental and clinical science.

According to the PhD regulations of both universities the course programme has been formalized with 30 ECTS points and examinations. The integration between the PhD training programme and the post-graduate clinical training programmes for dental specializations, which is limited now to the courses on statistics and oral biology, will be intensified. Following a course on Scientific Integrity is obligatory for all PhD-students.

Conclusion
The research at ACTA has always been characterized by a wide range of different topics that covered most dental disciplines. The present policy is to focus on the two specific research areas with an excellent performance.

The analysis of the various parameters of performance shows that the research at ACTA is, despite of budget restrictions, increasingly improving. Future performance will be dependent among others from the success in obtaining 2nd and 3rd source grants.
Oral Infections and Inflammation

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Full professors

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B.J.F. Keijser
J. de Lange
C. van Loveren
F. R. Rozema
E. A. J. M. Schulten
L. E. Smeele
E. C. I. Veerman
G. H. W. Verrrips
I. van der Waal
G. A. van der Weijden
Introduction

Oral Infections and Inflammation

The oral cavity is one of the most infected parts of man. We hardly understand why most people are completely healthy with at least a thousand different species of microorganisms in billions of numbers present in the mouth, while other individuals develop oral infectious diseases, chronic inflammatory processes and other pathologies, including oral cancers. The central research theme “Oral Infections and Inflammation” (OII) focusses on the pathophysiology, epidemiology and (psycho)social aspects of oral infections and inflammation and prevention and treatment of those, as well as defining and understanding the healthy oral cavity as a complex ecosystem, with applications far beyond the mouth alone. The four topics in this program interact with each other and can be depicted in the schematic diagram below.

Research theme Oral Infections and Inflammation

![Diagram of Research theme Oral Infections and Inflammation]

Research objectives

1) The healthy oral cavity and good systemic health.

Oral health is an essential part of the general health of each person during his or her life. Poor oral health, oral infections and inflammation, oral cancer and other oral pathology, can lead to major health risks and might affect the progression of cardiovascular diseases, diabetes, cancer and cancer dissemination, systemic chronic and acute infections and vital organ failure. Poor oral health leads to a lower quality of life and economic hardship. In collaboration with several industrial partners, the Netherlands Organization for Applied Scientific Research (TNO) and the Top Institute of Food and Nutrition (TIFN), we work on defining normal oral health using a molecular biology approach (-omics). At the same time, we investigate the systemic effects of oral infectious processes in relation to atherosclerotic cardiovascular disease and diabetes, both by literature review and with an intervention trial (focus is mainly on changes in the microbiome and in biomarkers of the named systemic diseases).

2) Innate immunity (cells/saliva), and susceptibility for caries and periodontal diseases.

Studies into the role of saliva and innate immune cells (oral PMN) in the maintenance of oral health have a prominent place. Several salivary proteins have strong antimicrobial capabilities and have important proteinase inhibitory actions. Synthetic peptide analogues of salivary histatins are tested as broad spectrum antibiotics. The influence of saliva on the interaction of oral microorganisms with oral epithelial cells and the in vitro wound healing capacities of salivary components are also being investigated. We find PMN in rinsing samples and they have antimicrobial functionality and are thought to have an essential role in maintaining oral health. For periodontal diseases, we collaborate in a self-supported European consortium to identify genetic variations, and we model periodontal disease as a complex system (environmental, life style factors, systemic factors, randomness).
3) Epidemiology and pathophysiology of oral cancer.
Forms of oral cancer, precursor lesions of oral cancer, particularly leukoplakia, and salivary tumours are studied. Amongst others, the prognostic value of molecular markers is examined with regard to the malignant transformation of leukoplakia, and the role of the human papilloma virus (HPV) has been studied. Poor oral health with its concomitant increase in the oral bacterial load, can predispose for oral cancer. Oral infections are independently associated with oral (pre)cancers. Therefore, not only the traditional risk factors smoking and alcohol usage play a role in oral cancer, but also oral bacteria, yeast and virus. Laboratory and clinical studies are ongoing. Intervention in the precursor lesions of oral cancer, particularly leukoplakia, may prevent the development of frank malignancies. Also other odontogenic tumours are studied, with emphasis on ameloblastomas and keratocystic odontogenic tumours. Characterization is also included of salivary gland tumours at the genomic and protein level.

4) Prevention and therapy of oral infections and inflammation.
The knowledge that oral infections may have systemic effects, provides a fundamental basis for new cost-effective prevention programs as well as economic and social spin-off product-innovations in the food and oral care products and dental restorative materials. The dental and medical profession is (re)educated with new knowledge on the fundamentals of normal oral health and the risks of having chronic oral inflammatory processes. The formation, structure and properties of oral and dental biofilms are studied, also in relation to tooth and implant structures. In addition, new antimicrobials and peptides have come into focus as caries and periodontitis preventive agents. Studies into the most effective clinical measures to prevent inflammation of the gingiva and mucosa and to control oral health are being conducted, including substantial efforts to reach clinical standards for evidence based dentistry. Part of successful prevention measures is to improve and to maintain the well-being of both regular dental patients and subgroups of patients suffering from (extreme forms of) anxiety or (anticipated) pain or from physical/mental handicaps.

The researchers within the theme Oral Infections and Inflammation have an international prominence in the field of oral health and have acquired a global leadership role in the emerging field of complex ecosystems such as the oral cavity; thus understanding of oral infections, inflammatory processes, oral cancer and the definition of a normal, healthy oral cavity including psychosocial factors. We have been awarded a grant from the University of Amsterdam (UvA) (starting date 1-1-2011) and we demonstrated the multiplier effect (both on the academic as well as the economic aspects) by participating in the Top Institute of Food and Nutrition (TIFN) (contract signed December 2011, first year research in 2012, ending date December 2016).

Results obtained
Preclinical studies
- In an in vitro study on the anti-erosive effects of phytosphingosine (PHS) it was shown that PHS significantly reduced tissue loss. Toothpastes containing Sn2+ and F ions were significantly more effective compared to PHS.
- Diffusion of antimicrobials in multispecies biofilms were evaluated in a new biofilm model.
- In order to evaluate the ability of dental materials to prevent and to arrest caries lesions in approximal surfaces in contact with occlusoproximal restorations, a systematic review and meta analysis was carried out. The results showed that in laboratory studies, GIC shows better ability to arrest caries lesions in approximal adjacent surfaces, but this ability was not confirmed in longitudinal clinical trials.
- We previously established that osteoclasts can be cultured from three distinct mouse bone marrow precursor sets: early blasts, myeloid blasts and monocytes. Now their susceptibility to inflammatory cytokine IL-1beta was established. It was shown that the less differentiated lineages early blast and myeloid blasts responded by increased osteoclast formation and that monocytes were relatively indifferent. Early blasts showed higher proliferation, myeloid blasts responded by enhanced and earlier fusion of precursors.
- Inflammatory cytokines such as TNF-alpha accumulate in the inflamed periodontium, leading to osteoclast activation and periodontal bone loss. In an attempt to isolate possible players in this process, osteoclast formation by periodontal ligament fibroblasts and peripheral blood, containing osteoclast precursors were incubated with infliximab, a widely-used TNF-blocker. Infliximab potently blocked the formation of cell clusters preceding osteoclast formation as well as the formation of osteoclasts.
• It has previously been established that different categories of monocytes, the classical, intermediate and non-classical monocytes, can give rise to osteoclasts. Inflammatory cytokines, such as IL-17, a key-player in periodontitis, may further activate osteoclast precursors. Especially intermediate monocyte-derived osteoclasts were more active in the presence of IL-17.

• For Workpackage 5 Field Studies of the ADVOCATE project, which is funded through the EU Horizon 2020 program, strong collaborative workstreams in Germany, Denmark and the Netherlands have been build together with project partners and general dental practitioners.

• The project Research Agenda Oral health aims at establishing a national oral health outcomes research agenda. The long list of topics as suggested by general dental and oral health care practitioners has become available. Topics of this list will be prioritized by dentists and oral health care practitioners.

• We have characterized the immunomodulatory and anti-inflammatory activities of chicken cathelicidin-2 derived peptides in vitro.

• The anti-erosive effects of PHS were established in a pH cycle model.

• The use of magnetic beads for optimization of bead-based diagnostic tests has been evaluated.

• It was found that PAI-2/SerpinB2 inhibits the proteolytic activity in a P. gingivalis-dominated multispecies bacterial consortium.

• We developed Valine-Leucine-Lysine containing peptides. After proteolysis by bacterial enzymes, these are incorporated in the bacterial cell wall.

• We have developed novel synthetic sortase A substrates that are incorporated with high efficacy into the S. aureus cell wall.

• We continued to study the inflammation-driven process of osteoclastogogenesis, from monocytes to pre-osteoclasts, to osteoclast and multinucleated giant cells; this is the field of osteoimmunology and was carried out as preclinical studies in mice or with ex vivo materials. Various sources of bone-samples showed a differential capability for osteoclast generation and functionality. The role of periodontal ligament cells in inflamed situations or normal situations was investigated, again by ex vivo cell cultures or mouse models.

• A novel compound to maintain a healthy oral plaque ecology in vitro was discovered and characterized.

• It was shown that nitrate and the origin of saliva influence the composition and short chain fatty acid production of oral microcosms.

• We explored a new algorithm, metaModules, which identifies key functional subnetworks in microbiome-related diseases.

• We studied and characterized the red and green fluorescence from oral biofilms.

• A systematic review and meta-analysis on the prevalence and nature of fungi in root canal infections was compiled.

• It was shown that a single nucleotide change in the promoter mutp enhances fluoride resistance of Streptococcus mutans.

• Epithelial cell detachment by Porphyromonas gingivalis biofilm and planktonic cultures was characterized.

• It was shown that in mixed biofilms Enterococcus faecalis benefits from a calcium hydroxide challenge and culturing.

• A systematic review with meta-analysis on psychosocial correlates of oral hygiene behaviour in people aged 9 to 19 was compiled.

• We showed interspecies interactions between Clostridium difficile and Candida albicans.

• A study on Candida albicans in multispecies oral communities was showed that Candida albicans in oral biofilms could prevent caries.

• A study on fine-tuning covalent inhibition of bacterial quorum sensing was performed.

• Antibiotic resistance testing and host interactions were performed in Staphylococcus-Candida interaction models.

• New in vitro models for Candida biofilm development were explored.

• A study on failed bonded interfaces submitted to microcosm biofilm caries development was carried out.

• Candida albicans metabolism and biofilm heterogeneity were studied by transcriptome mapping.

Clinical studies

• The early detection of periapical lesions with color power Doppler was investigated.

• Methods of teaching undergraduate students to perform root canal treatment as well as virtual learning environments and its effects on the performance and satisfaction of dental students were studied.
• 3-years results showed that the survival rate of the approximal ART restorations is positively influenced by the bilayer technique, and the application of nanofilled coating increases the longevity of the conventional approximal ART restorations.

• A study aiming to investigate the influence of parental presence during dental treatment on children’s behaviour and perception was carried out. The results showed that the only significant finding lay in the antithesis of how children perceived their last treatment session and how the dentist rated children’s behaviour regarding parental presence. Parents’ scores of their child’s behaviour were unrelated to parental presence.

• A multicenter, cross-sectional study was carried out to evaluate the associated factors for developing early childhood caries (ECC) and Severe-ECC (S-ECC) in a group of children aged 24-71 months in Turkey. The results showed a significant difference between the children with caries and caries-free associated with the brushing initiation age started before or after 18 months.

• The composition of immune infiltrate in head and neck squamous cell carcinoma is related to tumor outcome.

• The presence of viral antigens in HPV-related oropharyngeal tumors might serve as targets for immunotherapy.

• Mucoepidermoid carcinoma of the salivary gland has aberrant expression of mucins and carbohydrates.

• Since 2015 the ORA-STEM/H-OME study is running. The goal is to determine the relationship between several oral complications (like oral mucositis and oral graft-versus-host disease), oral health (caries and periodontitis) and biological determinants like the oral microbiome and proteome in stem cell transplant patients.

• We found that sialendoscopy of the major salivary glands improved both the objective (salivary flow rate) and subjective oral dryness in patients with Sjögrens syndrome.

• We performed an inventory of the oro-dental manifestations of Crohn’s disease.

• We have shown that physical exercise increases salivary viscosity caused by an increase in MUC5B secretion in saliva.

• We have shown that salivary agglutinin is the most important complement-stimulating component of saliva.

• Several papers based on clinical trials and systematic reviews were published on the topic of prevention and treatment of periodontal diseases and periimplantitis. Such as the added effect of a chemotherapeutic cooling solution in an ultrasonic device or the added effect of lasers and the effect of systemic antibiotics and local disinfection, all adjunctive to scaling and root planning (SCRP). The outcome of SCRP is better explained by the pre-operative periodontal microbiome than the prescription of systemic antibiotics. The efficacy of powered tooth brushing following a single brushing exercise, the efficacy of brushing with and without a dentifrice, CHX mouth rinses and SLS containing dentifrices, the incidence of complications associated with lip and/or tongue piercings and the effect of water on morning bad breath. A clinical study was prepared and performed comparing interdental brushes and the waterflosser on gingival bleeding and gingival abrasions.

• Several projects were related to the link between periodontitis and systemic diseases, (cardiovascular diseases and diabetes). Using the ACTA Axium database a study was published that reported on the association between periodontitis and cardiovascular diseases in the Netherlands. The difficulty to interpret the association of periodontitis with various co-morbidities has been discussed in a Letter. Arterial stiffness was found to be associated with periodontitis. We proposed plausible mechanisms how to explain the associations of periodontitis with various diseases.

• The research in the department of periodontology also focused on peripheral and oral polymorphonuclear leukocytes (oPMN) and various salivary peptides in maintaining oral health. We reviewed their role and used oral rinses to study numbers and function of oPMN in young adults, edentulous dental patients and periodontitis patients. The results show that oPMN are end stage cells, but yet very capable to phagocytize and digest oral bacteria, and to produce reactive oxygen species, proving their role in the maintenance of oral health.

• We studied the microbiomes associated with equine periodontitis and equine oral health.

• We showed that microbial profiles at baseline and not the use of antibiotics determine the clinical outcome of the treatment of chronic periodontitis.

• A study of the variation in the salivary peptide profiles of young healthy adults was performed.

• A cohort study on the dynamics of red fluorescent dental plaque during experimental gingivitis revealed three subpopulations in young healthy adults.
The effect of parental presence on the child’s perception and co-operation during dental treatment was studied.

A cross-sectional study on the comparison of red autofluorescing plaque and disclosed plaque was performed.

### Academic personnel in 2016

#### Research staff ACTA – OII Oral Infections and Inflammation

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Academic Centre for Dentistry Amsterdam

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**Total non tenured staff** 19,20

**Total 1st funding** 24,85 1

**Total 2nd funding** 0,50 2

**Total 3rd funding** 12,20 3

**Total research staff** 37,55

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## Output

### Dissertations


Scientific publications (refereed)


periodontitis: a randomized clinical trial. Lasers in Medical Science, vol 31, no. 2, pp. 343-353. DOI: 10.1007/s10103-016-1868-0


Loos, B.G. (2016). Severe periodontitis may result in higher numbers of oral polymorphonuclear (oPMN) leukocytes in oral rinse samples The Journal of Evidence-Based Dental Practice, vol 16, no. 1, pp. 73-74.


Sprangers, S., Schoenmaker, T., Cao, Y., Everts, V. & de Vries, T.J. (2016). Different blood-borne human osteoclast precursors respond in distinct ways to IL-17A Journal of Cellular Physiology, vol 231, no. 6, pp. 1249-1260. DOI: 10.1002/jcp.25220


**Other scientific publications**


Professional publications


Publications for the general public


Grants: current projects with external funding

Bloemena, E. Optimizing access to personalized cancer therapy in The Netherlands; from tissue to therapy. ZonMW call Personalized treatment 2015, participant (2015, January 01 - 2016, December 31).

Bolscher, J.G.M. Co-investigator of research project: Starvation response, biofilm formation and drug tolerance in Burkholderia pseudomallei, granted by the Thailand Research Fund through the Royal Golden Jubilee Ph.D. Program (Grant no. PHD/0351/2551) during 6 years (2010-2016). Granted total 1,555,000 Thai baht; covering PhD-student MSc. A. Chitchanok visits to ACTA and visits of co-investigator to Khon Kaen University. Principal Investigator: prof.dr. S. Taweechaisupapong, Faculty of Dentistry, Department of Oral Diagnosis, Khon Kaen University, Thailand (2010, January 01 - 2016, December 31).


Crieldaard, W. (collaborator) Collaboration research on anti-caries biomaterials containing nanoparticles International Science and Technology Cooperation Program of China (2014DFE30180). Granted 1.22 million RMB. Principal investigators: Xuedong Zhou (PI), Lei Cheng, Jiyao Li. Collaborators: ACTA, the Netherlands; Saarland University, Germany (2014, November 01, 2016, November 01).


Crielaard, W. & Krom, B.P. Studying dynamics in complex microbial biofilms. NWO Middelgroot, granted €164.000: (2013, January 01 - 2017, January 01).


Krom, B.P., Brandt, B.W. & Exterkate, R.A.M. Plaque on white spots is different compared to plaque on dental enamel. GlaxoSmithKline, granted 15.000 euro: (2015, January 01 – 2016, December 31).


Ten Cate, J.M., Crielaard, W., de Soet, J.J., van Loveren, C., van der Veen, M.H. & Volgenant, C.M.C. Seeing is believing. STW project; granted € 500.000: (2010, October 01 - 2016, October 01).


Wang, T. TOPPER project: Treatment of periodontal disease, prosthodontics evaluated by oral radiology. PhD program during 4 years, financially supported by Grant China Scholarship Council (CSC), granted €57.600,00: (2016, September 01 - 2020, November 01).


Indicators of Esteem

Scientific awards/honours


Zemouri, C. (May 9-12, 2016). The International Union against Sexually Transmitted Infections (IUSTI): 17th IUSTI world congress Marrakesh; Marrakesh, Morocco.

Memberships editorial board

Aartman, I.H.A.: European Journal of Dental Education.
Bloemena, E.: ISRN Gastroenterology.
Brand, H.S.: Nederlands Tijdschrift voor Tandheelkunde.
Crielaard, W.: Critical Reviews in Microbiology.
Gorter, R.C.: European Journal of Dental Education.
Krom, B.P.: Odontology.
Krom, B.P.: Critical Reviews in Microbiology.
Krom, B.P.: Scientific Reports.
Laine, M.L.: Current Oral Health Reports.
Laine, M.L.: Finnish Dental Society Apollonia
Loos, B.G.: Journal of Dental Research
Özen, B.: Biomed Research International (SCI-Expanded), Special Issue Biomaterials for Dental Applications, Hindawi Publishing Group.
Özen, B.: Makara Journal of Health Research (MJHR) (Emerging Sources Citation Index), International Advisory Editorial Board member
Özen, B.: American Journal of Medical Sciences and Medicine, Science and Education Publishing
Özen, B.: Journal of International Dental and Medical Research, Ectodermal Displasia Group
Özen, B.: EC Dental Science, Ecronicon.
Zaura, E.: Caries Research.

Organization of (inter)national scientific congresses and symposia
Bikker, F.J. (May 18-20, 2016). Atlant Conference. Innate host defence and infections, from basic science to applications. Utrecht, the Netherlands.
Brand, H.S. (April 7-8, 2016). 7th Meeting of the Association of Basic Science Teachers in Dentistry, Amsterdam.
Crielaard, W. & Loos, B.G. (September 20–23, 2016). Organizing committee. Symposium: The healthy oral ecosystem is resilient to common challenges, International Association of Dental Research (IADR)/Pan European Region (PER), Jerusalem, Israel.

Invited speakers at (inter)national scientific congresses or symposia
Bloemena, E. (April 8-9, 2016). Pathology of sentinel node biopsy in the SENT trial. 7th Meeting on Sentinel Node Biopsy in head and neck cancer, Rome, Italy.


Loos, B.G. (October 11, 2016). Oral infections and inflammation affect the cardiovascular system and the hematocrit. Invited lecture at the program: Good Oral Health and (top)sports, a double achievement! Scientific meeting Foundation Education in the Sportsmedicine, Bilthoven, the Netherlands.

Loos, B.G. (September 20-22, 2016). Normal host immune factors in the healthy oral cavity and resistance to perturbation. Symposium The healthy oral eco-system is resilient to common challenges, during the International Association of Dental Research (IADR)/Pan European Region (PER), Jerusalem, Israel.

Loos, B.G. (August 24, 2016). Periodontitis and atherosclerotic cardiovascular disease. School of Dental Medicine, Hong Kong University, Hong Kong.


Rosema, N.A.M. (June 22, 2016.) Tandenpoetsen anno 2016, wetenschapsdag, CTM-Groningen, the Netherlands.


Van der Waal, I. (September 16, 2016). Leukoplakia; to treat or no tot treat. EAOM, Torino, Italy.


**Other (inter)national scientific functions**

**Bolscher, J.G.M.:** Advisory Board Chiang Mai University Journal of Natural Sciences, 2013-

**Brand, H.S.:** President-Elect Salivary Research Group, International Association of Dental Research (IADR).

**Crielaard, W.:** Co-chair of the ILSI Functional Food Taskforce Oral and Systemic Health.

**Crielaard, W.:** Board member Oral Microbiology and Immunology Group, British Society for Oral and and Dental Research.

**Crielaard, W.:** Visiting professor Oral BioSciences, Hong Kong University, Hong Kong, China.

**Crielaard, W.:** Visiting professor Oral Microbiology School of Stomatology, Sun Yat Sen University, Guangzhou, China.

**Crielaard, W.:** Member of the Thesis Advisory Committee Preethi Prajod; Faculty of Dentistry, National University of Singapore.

**Deng, D.M.:** Coordinator International Summer camp for ACTA students, Chengdu, Sichuan, China July 3-17.

**Deng, D.M.:** Guest professor Oral Microbiology, School of Stomatology, Sun Yat Sen University, Guangzhou, China.

**Deng, D.M.:** Chair of PhD defense committees West China College of Stomatology, Sichuan University, Chengdu, China.

**De Soet, J.J.:** Member working group to develop new guidelines for Infection Prevention in dentistry for the NMT Nederlandse Vereniging voor Medische Microbiologie.

**De Soet, J.J.:** Treasurer Stichting Orale Biologie.

**Gorter, R.C.:** Executive committee Association for Dental Education in Europe (ADEE), since 2013.

**Gorter, R.C.:** Executive committee Platform for Better Oral Health in Europe.

**Krom, B.P.:** Member of the Thesis Defense Committee Marian Van Kerckhoven, Laboratory of Microbiology, Parasitology and Hygiene, Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Belgium. PhD defense: April 2017.

**Krom, B.P.:** Member of the Thesis Advisory Committee Devon Allison, Baltimore, Department of Microbial Pathogenesis, Dental School, University of Maryland, USA. PhD defense: May 2017.

**Laheij, A.M.G.A.:** Member working group to develop new guidelines for Infection Prevention in dentistry for the NMT - Nederlandse Vereniging voor Medische Microbiologie. September 2013-2015.

**Loos, B.G.:** Member IADR Distinguished Scientist Award Committee (2016-2017).

**Loos, B.G.:** Member Continental European Division (CED) of IADR Research Prizes and Travel Grant Awards Committee (2007-current).


**Loos, B.G.:** Member Organizing Committee, EFP EuroPerio9, 2018, Amsterdam, the Netherlands.

**Loos, B.G.:** Member IADR Young Investigator Awards Committee (2014-2017).

Loos, B.G.: Councillor to the Board of the CED (Continental European Division) of the International Association of Dental Research (IADR) and CED representative to the PER (Pan European Region) of the IADR. (2013-2016).

Loos, B.G.: Member committee annual Meridol Research Prize, German Society of Periodontology (DGP), Germany. (2005-current).

Loos, B.G.: Project leader European Periodontal Genetics (EPG) taskforce; a multicenter research project Genetics of periodontitis, a collaboration of University of Kiel, Germany, University of Oslo, Norway and ACTA, the Netherlands. (2001-current).

Shemesh, H.: Member Scientific committee of the Dutch Association of Endodontology (NVe).

Van der Veen, M.H.: Honorary lecturer University of Liverpool, UK.

Van der Veen, M.H.: Invited expert and member of working group 3 of EFP-ORCA joined workshop The boundaries between caries and periodontal diseases.

Van der Velden, U.: Board member Education Committee of the European Federation of Periodontology.

Van der Velden, U.: Chair Lustrumcongres Nederlandse Vereniging voor Parodontologie (NVvP) 15 April 2016, Hoorn, the Netherlands.

Van der Waal, S.V.: Member scientific committee Nederlandse Vereniging voor Endodontologie (NVe).

Van Loveren, C.: Member advisory board Sugar Bureau UK.

Van Loveren, C.: Member advisory board Tooth Friendly Society.


Volgenant, C.M.C.: Member working group to develop new guidelines for Infection Prevention in dentistry for the NMT Nederlandse Vereniging voor Medische Microbiologie.

Zaura, E.: Visiting professor Oral Microbiology and Preventive Dentistry, Faculty of Medicine, University of Latvia, Riga, Latvia.

Zaura, E.: Invited expert and member of working group 1 of EFP-ORCA joined workshop The boundaries between caries and periodontal diseases.

Zaura, E.: Elected member of CED-IADR board, since September 2016.

Supervisor of an external PhD student


Collaborations
- Ben Gurion University of the Negev, Beer Sheva, Israel, dr. M. Meijler.
- BENECOMO, Flemish Netherlands Geriatric Oral Research Group and Zorgaccent, Amersfoort, the Netherlands, dr. G.J. van der Putten.
- Clinic for Carolinas Health Care System Charlotte, North Carolina, USA Professor Michael Brennan.
- College of Dentistry, New York University, USA, Richard Niederman.
- Common Wealth University, Virginia, prof.dr. H.A. Schenkein.
- Center for Advanced Research in Public Health, Valencia, Spain, dr. Alex Mira.
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- Department of Otorhinolaryngology, VUMc.
- Department of Pathology, VUMc.
- Department of Pedodontontology, dr. B. Özen, Istanbul Kemerburgaz University, Istanbul, Turkey.
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- Diseases and Immunology, Utrecht University, 3584 CL Utrecht, the Netherlands. prof.dr. H.P. Haagsman.
- Division of Cariology and Endodontology, prof.dr. I. Krejci, University of Geneva, Switzerland.
- Division of Molecular Host Defence, Faculty of Veterinary Medicine, Department of Infectious.
- Department of Conservative Dentistry, University Medical Center Groningen, the Netherlands (dr. L.W.M. van der Sluis).
- Department of Dentistry, Aarhus University- dr. Lisselotte Kirkevang.
- Department of Endodontontology, Dental School, Aristotle University of Thessaloniki, Greece (prof. T. Lambrianidis).
- Department of Periodontics, School of Dentistry, University of Missouri-Kansas City, USA, Charles Cobb.
- Division of Endodontics, Department of Dental Medicine, Karolinska Institutet, Sweden (dr. L.E. Chavez de Paz).
- Erasmus Medisch Centrum, dr. M. van Zelm.
- Faculty of Archaeology, Leiden University, drs. K.A. Ziesemer, prof.dr. Corinne Hofman.
- Genetics and Genomic Medicine Programme, UCL Institute of Child Health, London, United Kingdom.
- Health Science Research Center, Indiana University-Purdue University, Fort Wayne, IN, USA, Mark Putt.
- Helperby Therapeutics Limited, London, United Kingdom.
- Interleukin Genetics, USA: prof.dr. K. Kornman.
- Kindertandheelkundepraktijk Bamboodino, Rotterdam, the Netherlands, dr. D.L. Gambon.
- Khon Kaen University, Thailand, Dept of Oral Diagnosis, prof.dr. S. Taweechaisupapong, dr. S. Kanthawong and dr. C. Anutrakunchai.
- Mesoscale Chemical Systems, Faculty of Science and Technology, University of Twente, the Netherlands (dr. D. Fernandez Rivas).
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- Oral Diagnostic Sciences University of Adelaide, Adelaide, Australia, Professor Richard Logan.
- Physics of Fluids group, Faculty of Science and Technology, University of Twente, the Netherlands (dr. B. Verhaagen, prof. M. Versluis).
- Radboud University Medical Center prof.dr. W.H. van Palenstein Helderman and prof.dr. Nicole Blijlevens.
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- School of Stomatology, Sun Yat Sen University, Guangzhou, China, prof. X. Wei.
- Temple University Philadelphia, Kornberg Dental School, United States.
- The Netherlands Organization for Applied Scientific Research (TNO), Zeist, the Netherlands.
- The Swammerdam Institute for Life Sciences, UvA, Amsterdam, dr. Joost Teixeira de Matos.
- TNO, Zeist, dr. E. Tsivtsivadze and prof.dr. B. Keijser, Preventive Dentistry, ACTA-TNO, Zeist.
- UCLA, School of Dentistry, Los Angeles CA. Wong, D.T.W.
- University of Amsterdam, Core facility Cellular Imaging / LCAM-AMC. J. Stap.
- University of Maryland Dental School, Baltimore, USA, dr. M.A. Jabra-Rizk.
- University of Nagasaki, Japan, dr. Y. Iijima.
- University of Phayao, Thailand, School of Medical Science, dr. A. Puknun.
- Uniklinikum Schleswig-Holstein-Campus, Kiel, Germany, Clinic for Conservative Dentistry and Periodontology, Christof Doerfer and Karim M. Fawzy El-Sayed.
- Universiteit van Amsterdam, AMC, Dept. of Clinical Chemistry.
- Universiteit van Groningen, Dept. of Periodontology.
- University Federico II, Naples, Italy. Department of Periodontology, Andrea Blasi.
- University of Bandung, Indonesia, Amaliya.
- University of Bonn, Dept. of Periodontology, prof.dr. S. Jepsen.
- University of Cagliari, Italy, prof. E. Cotti.
- University of Cairo, Oral Medicine and Periodontology Department- Faculty of Dentistry- Egypt, Karim M. Fawzy El-Sayed.
- University of Gothenburg Sweden Professor Inger von Bültzingslöwen.
- University of Kiel, Germany, Dept. of Gastro-Enteroology, prof.dr. S. Schreiber.
- University of Kiel, Germany, Institute for Clinical Molecular Biology, dr. A. Scheafer.
- University of Kristianstad, Sweden, prof.dr. S. Renvert.
- University of Madrid, Spain, prof.dr. M. Sanz.
- University of Malaya, Malaysia, Faculty of Dentistry, dr. Rathna Devi Vaithilingam.
- University of Milan, Italy, Unit of Periodontology, Giulio Rasperini.
- University of Patras, Greece, prof.dr. T. Bountis.
- University of Rome, Italy, prof. dr. Pilloni.
- University of Toronto, Dept. of Endodontics dr. Anil Kishen.
- University of Wageningen, the Netherlands, dr. S. Boesveldt.
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- West China School of Stomatology, Sichuan University, China, prof. J. Li, dr. L. Cheng.

**Current PhD projects**


**Cao Y.** Different osteoclasts and their response to cytokines. Supervisor: prof.dr. V. Everts, co-supervisor: dr.ir. T.J. de Vries, start 2014.


Societal impact

Oral infections and oral cancer have a substantial impact on the society. Oral infectious diseases are the most frequent infections in the western society and have important consequences, both medically and economically. Head and neck squamous cell carcinomas (HNSCC) and specifically oral squamous cell carcinomas (OSCC) are the most prevalent forms of head and neck cancer. The general aim of the program is to understand the normal healthy oral cavity and to understand links with general health, to study oral innate immunity and susceptibility to caries and periodontal diseases, to study prevention and treatment options for the oral infectious and inflammatory processes and to study the epidemiology and pathogenesis of oral cancers, in particular in relation to good/poor oral health. In addition, attention is paid to social and psychological aspects of dental treatment, such as dental anxiety.

Through education, a new generation of dentists and researchers in the Netherlands, Europe and the world are trained to implement a radical shift from mechanistically and (invasive) treatment oriented professionals to 21st century oral physicians focused on diagnosis and prevention of dental and of oral infections and maintenance of the quality of life. Over the last 5 years it has become increasingly clear that oral infections are having negative impact on cardiovascular health, diabetic status and quality of life. The researchers in this theme focus on this aspect.

The members of our priority area have had a relative large number of invitations to give lectures at dental congresses, and to educate the dental profession on fundamental understanding of oral health. Moreover, we experienced increased interest from newspapers, magazines and radio programs in the above subjects, in which we participated. The link oral health - general health is actively communicated by the researchers. Important for the dental profession and the general public, is the substantial number of published and accessible systematic reviews (and meta-analyses) on the various modes of prevention and oral hygiene measures. These contribute to clinical protocols for the dental profession and form the basis for evidence based dentistry.

Ongoing clinical research on oral and head/neck cancer contributes to improved prevention, diagnosis and treatment of relevant patient groups. New plans are developed to bring together knowledge on oral microbiomes and salivary innate immune peptides with oral cancer diagnosis and pathophysiology. The program has strong links with all players in the oral care industry; this not only results in contract research, but also in industrial co-funding of grants (STW) and has led to participation of ACTA in the Top Institute Food
and Nutrition (TIFN), where the theme Oral Health has been initiated. In this theme, world players in the oral care industry, the chewing gum industry, flavour industry, food industry and (oral) care appliances industry collaborate with the University of Wageningen, TNO and ACTA.

The societal impact of the research is evident from the impact on patient care and public dental health, and from collaborations with the industry, as is shown by for instance the grants obtained and the external reports. The societal impact of the clinical research contributes to improved prevention, diagnosis and treatment of relevant patient groups. The societal impact is evident from the items listed below. The societal impact of the clinical research on oral and maxillofacial surgery is focussed on the influence on patient care, both within the department and externally. Research contributes to improved treatment of relevant patient groups.

I. Societal relevance for the dental professional in the Netherlands

Courses organized for Dutch dental and medical professionals

Lectures given during courses for Dutch dental and medical professionals
De Soet, J.J. (April 13 & 19, 2016). IQual/Preventietour KNMT: Herziene richtlijn infectiepreventie, wat is echt nieuw?
Laheij, A.M.G.A. (April 18 & 20, 2016). IQual/Preventietour KNMT: Herziene richtlijn infectiepreventie, wat is echt nieuw?

Laine, M.L. (February 19, 2016). Organisatie van Nederlands Tandprothetici (ONT), Nazorg bij implantaten, Microbiologie van parodontale en peri-implantaire ontstekingen, Amsterdam, the Netherlands.


Loos, B.G. (April 9, 2016). De link tussen parodontale ontstekingen, diabetes en hart, ACTA-QP THK 4, Nascholingscongres Tandheelkunde over grenzen, Utrecht, the Netherlands.

Loos, B.G. (April 23 & September 10, 2016). Parodontologie ACTA BIG re-registration course, Amsterdam, the Netherlands.


Rosema, N.A.M. (November 4, 2016). Dagvoorzitter, Congres, NVAMK Uit de hoge hoed, Stadion Galgenwaard Utrecht, the Netherlands.


Teeuw, W.J. (September 16, 2016). Does periodontal treatment really contribute to metabolic health? 25th-anniversary of the MSc-program Periodontology ACTA, Amsterdam, the Netherlands.


Van der Waal, S.V. (December 9, 2016). ACTA Dental Education Endodontische leergang, Amsterdam.


Organization of congresses and symposia for professionals in the Netherlands

Invited speakers at professional congresses or symposia in the Netherlands


Professional functions in the Netherlands

Bloemena, E.: Voorzitter Wetenschappelijke Raad PALGA.
Bloemena, E.: Bestuurslid Nederlandse Vereniging Voor Pathologie.
Bloemena, E.: Voorzitter Cie Bij- en Nascholing NVVP.
Bloemena, E.: Lid Richtlijn cie Hoofd-hals tumoren.
Brand, H.S.: Lid ondernemingsraad ACTA.
Danser, M.M.: Chair Nederlandse Vereniging voor Parodontologie (NVvP).
De Soet, J.J.: Lid KNMT commissie Richtlijn infectiepreventie voor mondzorgpraktijken, KNMT Nieuwegein.
Laheij, A.M.G.A.: Lid KNMT Commissie OnderzoeksBegeleiding, KNMT, Nieuwegein.
Laine, M.L.: Member Doctoral Education Committee ACTA (DECA).
Laine, M.L.: Member Benoemingscommissie leerstoel Parodontologie, in het bijzonder de preventie en therapie van parodontale aandoeningen, dr. G.A. van der Weijden, section Periodontology, ACTA.
Laine, M.L.: Member Structure committee of section Periodontology, ACTA.
Laine, M.L.: Member Decentralized selection of dental students committee, ACTA.
Schreuder, W.H.: Lid PAOK commissie NVMKA.
Smeeele, L.E.: Voorzitter auditcommissie Nederlandse Werkgroep Hoofd HalsTumoren.
Smeeele, L.E.: Lid Commissie Oncologie, Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie.
Smeeele, L.E.: Voorzitter DNHA (Dutch Head and Neck Audit).
II. Societal relevance for the dental professional internationally

Professional functions internationally
Brand, H.S.: Co-opted member Association of Basic Science Teachers in Dentistry.

Invited speakers at international professional congresses or symposia
Volgenant, C.M.C. (October 22, 2016). What is oral health? Colgate Talks (online conference), Basel (CH).

III. Contacts with the general public

Interactions with the press and the general public
Rosema, N.A.M. (December 4, 2016). Wat is de definitie van een gezonde mond? Artikel Factaal.
Rosema, N.A.M. (June 1, 2016). Interview Martijn Rosema. Artikel Stand-by.
Teeuw, W.J. (November 8, 2016). Ernstige parodontitis moet je interdisciplinair behandelen. Interview Nederlands Tandartsenblad 71 (18); 8. http://ntdbitaal.nl/content/%E2%80%9CErnstige-parodontitis-moet-je-interdisciplinair-behandelen%E2%80%9D-
Impact of the research on the general public or professionals

Patients referred to the cariology clinic by their dentist are seen and advised.


Volgenant, C.M.C & de Soet, J.J. Project Mondgezondheid bij bewoner op Sal, Kaapverdië, met een sociale achterstand. Project in samenwerking met de lokale overheid om mondgezondheid in kaart te brengen.
Oral Regenerative Medicine

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Introduction
The human masticatory system has several important functions that determine an individual’s general health and well-being, like biting, chewing, swallowing, talking, laughing, and yawning. Sometimes, patients are confronted with problems in performing these functions. This may have various causes. On the one hand, chemical and bacteriological factors may hamper a healthy functioning of the masticatory system by causing infection and inflammation. On the other hand, mechanical overloading as well as underloading or disuse of
the constituent structures of the masticatory system (viz., teeth, bone, cartilage, muscles, and joints) may yield functional oromandibular impairments. Importantly, trauma or disease may result in damaged tissues which in turn result in functional oromandibular impairments. The research of ACTA’s research program “Oral Regenerative Medicine” (ORM) focuses on regenerating damaged oral tissue by means of guided tissue regeneration, stem cell therapy or tissue engineering techniques, taking into account the mechanical threats for the masticatory system and inflammatory reactions involved in tissue repair. Relevant clinical problems are used to guide the research aimed at developing novel solutions for these clinical problems. Groups that are involved in ORM-ACTA are Oral Kinesiology (OKI), Oral Implantology and Prosthodontics (IMP), Dental Materials Sciences (DMS), Oral Cell Biology and Functional Anatomy (OCB/FA), Oral Radiology (ORA), Orthodontics (ORT), and Oral and Maxillofacial Surgery (OMS), both of the Academic Medical Center (AMC) and of the VU University Medical Center (VUmc).

The Interfaculty MOVE Research Institute Amsterdam has chosen “Regenerative Medicine” as one of its domains (i.e., a collaboration of researchers within the VU campus on a key topic). Likewise, ORM has been formulated as one of the two priority areas (“zwaartepunt”) of ACTA. As implied above, a healthy oral system is characterized not only by the absence of infection and/or inflammation of dental and periodontal tissues, but also by a healthy musculoskeletal system and oral mucosa. Musculoskeletal tissues (i.e., bone, cartilage, muscles, and joints) and mucosa (epithelium and underling connective tissue) can be damaged or even destroyed by, for example, mechanical overloading, disuse, disease or trauma. In case of tissue loss, the replacement or regeneration of degenerating/degenerated cells, tissues, or organs is needed to restore or establish normal function. ORM studies these processes both at a fundamental and translational level in multidisciplinary settings, in which dentistry/oral medicine closely collaborates with medical disciplines like orthopaedics, neurology and dermatology/plastic surgery, both within and outside The Netherlands.

The objective of the ORM research is to investigate degenerating oral tissues in order to develop novel therapeutic strategies to replace or regenerate these tissues, thereby restoring oral function and thus improving oral health-related quality of life. The ultimate goal of oral regenerative medicine is to regenerate parts of the masticatory system, e.g. teeth, jaw bone and/or mucosa. Since this dot on the horizon is far away, we now concentrate on:

A. Regeneration of jaw bone and oral mucosa.
B. Local tissue and systemic (immune) response of the host to implant materials and restoratives.
C. Implementing new technologies in the repair and restoration of oral and maxillofacial structures.
D. Gaining in-depth knowledge of non-infectious diseases of the masticatory system.

Research objectives

A. Regeneration of jaw bone and oral mucosa

Stem cells and smart substrates

Adipose tissue derived stem cells have been used to heal bone defects in human jaws. The application of these cells proved to result in an improved healing of the bone defects. In the coming period this will be further explored making use of different types of biological and non-biological substrates (see B ). After we successfully determined the safety and efficacy of adipose stem cells together with a bone substitute material for bone regeneration in a clinical phase 1 study, we will continue to use maxillary sinus floor elevation as a valid model to test bone tissue engineering approaches.

3D printing and biomimetic coating - CAD/CAM

For the repair of bone defects autologous bone is considered as the gold standard. However, the harvesting and transplantation of autologous bone is often associated with morbidity and pain at the donor site. Using bone tissue engineering technology we have developed a biomimetic octocalcium phosphate seeded with BMP-2 that in animal studies has proven to be osteoinductive, biocompatible and biodegradable. By making use of 3D bioprinters and the biomimetic coating developed in this research program, scaffolds containing (stem) cells and proteins will be constructed that can be implanted. The biomimetic coating involves the use of different growth factors that modulate cell behaviour and activity. By combining these different modalities it will be possible to finely tune tissue formation at sites wished for.

Computer Aided Design/Computer Aided Manufacturing (CAD/CAM) of tooth replacement, crown and bridgework and guided implant placement devices used to insert both tooth root implants as well as implants used to substitute bone loss based on CBCT scans combined with planning and designing software are also...
being developed in this research program. In a joint project with industry the technology used to 3D print composite, PMMA and ceramics in crown and bridgework is being refined and a clinical trial has been initiated. A project focussed on the milling / printing of full tooth implants has shown that we can print teeth in titanium and zirconium within the same dimensions as the tooth scanned with CBCT. This technology makes it possible to design and fabricate implants for the specific bone volume in the individual patient. In-vitro research is being carried out to analyse the behaviour of cells of the oral mucosa around these printed implant materials.

B. Tissue response of the host to implant materials and restoratives

**Tissue response of the host**

Tissue lost after trauma or surgical intervention should be replaced or, most preferably, regenerate. In this part of the programme regeneration is induced by making use of a wide variety of scaffold materials, different cell types (e.g. stem cells) and a variety of growth factors and cytokines. The collaboration between clinical and non-clinical scientists from different departments and backgrounds (dental material sciences, implantology, oral cell biology) ensures a multi-disciplinary approach. It becomes more and more clear that implant materials, long thought as being harmless, may evoke an immunological response. Since the use of implant materials increases tremendously; knowledge about the response of these materials is of crucial importance. Whereas in the majority of cases, implants remain inert in the host, in some cases adverse events are observed. Host responses can include bioreabsorption (breakdown) of the implant material resulting in leachables, entering the surrounding tissue and systemic circulation. The local tissue effects include an inflammatory response leading to adjacent mucosa and bone degradation, irritation to the surrounding tissues and/or sensitization of the host. Systemic effects are largely not investigated yet but do include allergic skin rash. It is of utmost importance to develop safe biomaterials and implants for oral regenerative medicine. Scientists with different background have joined forces in order to tackle these issues. Two approaches to this research line are investigated:

1) Safety assessment of dental implants. For this the Adverse Outcome Pathway (AOP) approach is used to investigate potential inflammatory responses in full compliance with the 3Rs. Toxicity, irritation and sensitization are the focus. Both organotypic in vitro tissue engineered oral mucosa and bone constructs are used as healthy and disease models with integrated immune cells (e.g. Langerhans Cells) as well as traditional cell cultures.

2) Improved diagnostic testing of adverse events attributed to dental materials. Currently the skin patch test is used to identify an allergic response of the individual to a dental implant. Due to differences in skin and oral immunity as well as cutaneous penetration, often false negatives are diagnosed. Improved patch testing methods, (e.g use of microneedles and different salts) as well as in vitro lymphocyte proliferation and cytokine tests are being investigated a alternatives.

**Biological response to loading**

The maintenance and survival of tissues like bone and cartilage largely depend on mechanical loading exerted upon these tissues. The different cell types that harbour these tissues are mechanosensitive and respond to mechanical loading. Also the stiffness of the substrate the cells live on, has profound effects on their metabolic activities. A combination of substrate stiffness and mechanical loading will make it possible to direct the cells in such a way that they generate the required tissues, such as bone and cartilage. Insight in the interaction between the implanted material either being of biological or non-biological origin and the surrounding tissues is of crucial importance for the understanding how the host will respond to the implanted material. Special attention is paid to the response of the tissue under conditions of mechanical loading or unloading.

**Response of oral mucosa to injury**

Oral mucosa heals rapidly and is almost scar free in contrast to skin. With the aid of physiologically relevant tissue engineered oral mucosa and skin constructs, mechanisms of healing are compared in vitro. In particular, differences in proliferation, migration and differentiation of the epithelium and the deposition of extracellular matrix by (myo-)fibroblasts are investigated. Trafficking of immune cells involved in determining the quality of scar formation is the focus as well as the impact of the environment e.g. air versus saliva. In addition to saliva, the role of the oral microbiome (oral healthy and pathogenic biofilm) is investigated with regards to oral mucosa homeostasis and wound healing. Once normal healing mechanisms are established, the models can be used to investigate i) medical devices (implants) safety and soft tissue attachement and ii) the mode of action of novel therapeutic compounds in vitro.
C. Gaining in depth knowledge of non-infectious diseases of the masticatory system.

**Pain, trauma and dysfunction**

Overloading of the constituent tissues of the masticatory system, notably cartilage, bone, muscle tissue, periodontal tissues, and hard dental tissues due to bruxism (i.e., tooth grinding and clenching) and adverse oral habits (e.g., nail biting and excessive gum chewing) may lead to pain and dysfunction of the chewing apparatus. In turn, such conditions may yield risks for the individual’s general health and cognitive abilities. A threat to the success of dental implants is peri-implant disease which is characterized by bone loss around the individual implants. The primary cause of peri-implant bone loss can be overloading, immunological response to the implant material. The secondary cause of this bone loss is infection.

Within the framework of ORM, the causes, consequences, and management of pain, trauma and dysfunction of the masticatory system are studied in multiple international and multidisciplinary settings.

The following items are studied:
- diagnosis, epidemiology, pathophysiology, and management of bruxism, obstructive sleep apnea, and orofacial pain.
- relationship between mastication and cognition in elderly institutionalized persons with different types of dementia
- surgical treatment strategies for orthognatic defects
- incidence and treatment of maxillofacial trauma
- peri-implantitis

**Results obtained**

**A. Regeneration of jaw bone and oral mucosa**

**Stem cells and smart substrates**

- Biomimetic calcium phosphate coating can be a carrier for bone morphogenetic protein (BMP). Additional studies were published in which the release was investigated of bone morphogenetic protein (BMP) incorporated into calcium phosphate as a carrier. This technology known as biomimetic coating has been the basis for research at ACTA during the last 8 years. It has been shown to be an effective bone substitute in critical size defects promoting osteogenesis and enhancing bone growth. A PhD study that was defended this year has shown the value of this material in the regeneration of critical sized bone defects. This study also showed that when hydroxypropyltrimethylammonium chloride chitosan was incorporated into the calcium phosphate coating, next to osteogenic properties it also showed antimicrobial properties conferring this material a promising application in infected bone defects.

- Tissue-engineered constructs need to become quickly vascularized in order to ensure graft take. One way of achieving this is to incorporate endothelial cells (EC) into the construct. The adipose tissue stromal vascular fraction (adipose-SVF) might provide an alternative source for endothelial cells as adipose tissue can easily be obtained by liposuction. Therefore we extensively characterized endothelial cells from adipose tissue (adipose-EC) and compare them with endothelial cells from dermis (dermal-EC) with respect to purity, surface marker expression, proliferation, migration, cytokine secretion and sprouting. Similar characteristics of adipose-EC compared to their dermal-derived counterpart were found making them an excellent source for tissue engineering purposes, since they are readily available, and easily isolated and multiplied.

- In patients undergoing maxillary sinus floor elevation (MSFE) for dental implant placement, bone substitutes are currently evaluated as alternatives for autologous bone. However, bone substitutes have only osteoconductive properties and lack osteoinductive potential. We performed the first-in-human study using freshly isolated, autologous adipose stem cell preparations (the stromal vascular fraction (SVF) of adipose tissue) applied in a one-step surgical procedure with calcium phosphate ceramics (CaP) to increase maxillary bone height for dental implantations. Ten patients received CaP plus SVF on one side, whereas bilaterally treated patients (6 of 10) received CaP only on the opposite side. This allowed intrapatient evaluation of the potential added value of SVF supplementation, assessed in biopsies obtained after 6 months. Feasibility, safety, and potential efficacy of SVF for bone regeneration were demonstrated, showing high potential for this novel concept.

- Stability and antithrombotic functionality of endothelial cells on silicone hollow fibers (SiHFs) are critical in the development of biohybrid artificial lungs. We found that flow preconditioning of endothelial cells on collagen-immobilized SiHFs enhanced cell retention and antithrombotic function, which could significantly improve current biohybrid artificial lungs.
Biomimetic coatings to increase endothelialization of blood-contacting materials in biomedical devices are promising to improve the biocompatibility of these devices. Although a stable extracellular matrix protein coating on a biomaterial’s surface is a prerequisite for endothelial cell attachment, it also stimulates platelet adhesion. Therefore, antithrombic additives, such as nitric oxide donors, to a stable protein coating might lead to successful endothelialization of a material’s surface. Our data showed that sodium nitrite-collagen coating with 25-50 μM sodium nitrite on silicone tubes increases the number of endothelial cells attached and inhibits platelet adhesion suggest that this coating is highly promising for use in blood-contacting parts of biomedical devices.

Biocompatibility of artificial lungs can be improved by endothelialization of hollow fibers. Bioavailability of growth-inducing and anti-thrombotic agents on the hollow fiber-blood interface inhibits thrombosis. We found that nanoliposomal anti-thrombotic sodium nitrite-nanoliposomal growth-inducing growth hormone-collagen conjugate coatings promote endothelialization of silicone hollow fibers in biohybrid artificial lungs.

For bone tissue engineering synthetic biphasic calcium phosphate (BCP) with a hydroxyapatite-β-tricalcium phosphate (HA/β-TCP) ratio of 60/40 (BCP60/40) is successfully clinically applied, but the high percentage of HA may hamper efficient scaffold remodeling. With BCP with a lower (HA/β-TCP) ratio (BCP20/80) is more desirable is still unclear. Vascular development is needed before osteogenesis can occur. We found that BCP20/80-based composites showed enhanced osteogenic and vasculogenic differentiation potential compared to BCP60/40-based composites in vitro, suggesting that BCP20/80-based composites might be more promising for in vivo bone augmentation than BCP60/40-based composites.

3D printing and biomimetic coating - CAD/CAM, dental implants

- A study on the precision of intraoral scanners using different software packages and different clinical parameters used in operative dentistry showed that there are several clinical circumstances that influence the clinical outcome. We have also shown that the combination of STL files and DICOM files when creating a digital planning environment in software to create drill guides and FDP’s for patient treatment has limitations. We see that VOXEL size in the DICOM file as well as scattering of metallic objects in the mouth (fillings, FDP’s etc) make it difficult and in some cases even impossible to match these files. We are now looking into technologies to make this matching process more predictable. Two articles on this subject was published this years.

- Additive manufacturing is the process of building objects layer by layer by joining materials base on digital 3-dimensional (3D) model data. When using this technology in printing FDP’s (crown and bridge work) for dental use it is important that the materials used to print and the machines themselves are calibrated to optimise the fit of the restorations. Apart from that, the build direction also plays a role. We have managed to optimise the build angle of 3D printed resin based dental restorations so that they now are ready for clinical use. This year we were the first clinic in the world to 3D print a crown on a dental implant and insert this into a patients mouth.

- Dental implants are generic in shape and size. This means that the implants dictate the shape and size of the bone defect in which they are to be inserted. Often this means that the bone has to be augmented to allow the implant to fit. Using CAD and 3D printing technologies we are now able to design dental implants in any dimension and shape to fit the bone instead of augmenting the bone to fit the implant. Implants have been printed in ceramics and titanium, and analysed for the dimensional stability and congruence to the CAD files showing promising results.

- The same technology has been used to fine tune the autotransplantation of teeth. STL files to be transplanted teeth have been drawn from DICOM data from CBCT scans. Replicas of these teeth have been printed together with drills and osteotomes in titanium. After extraction of the hopeless or irrational to treat tooth the alveolus is shaped by using the drills and the osteotome to create a neo alveolus. The to be transplanted teeth are then extracted and transplanted to the neo alveolus. Our research shows that the fit is immediate, the periodontium of the to be transplanted teeth is hardly distorted and the ingrowth of the natural tooth is more predictable.

- The diameters of dental implants generally vary between 3.0 and 6.0 mm. We have carried out a study looking at dental implants with a diameter varying between 1.8 and 2.4 mm supporting overdentures in edentulous patients. We have shown that these implants show at least in the short term predictable results comparable to regular diameter implants.

- Two solitary dental implants in the maxilla with dalla bona attachments is an treatment approach that has not yet been reported on in the literature. We have an RCT running in the department where we have...
reported on the 1 year follow-up results in an article. These are a little less positive than when using 4 interconnected implants.

- The fatigue properties of the dental CAD-CAM materials zirconia and lithium disilicate with respect to their manufacturing procedures.

B. Tissue response of the host to implant materials and restoratives

Tissue response of the host

- The gold standard for the diagnosis of allergic hypersensitivity is skin testing. However, this has only been validated for epidermal antigen contact. For several metals, patch testing gives unreliable results. The current alternative to metal allergy patch-testing is the in vitro lymphocyte proliferation test (LTT) using [3H] thymidine. This method is promising but requires handling of radioactive material and has a low predictive value. Therefore the aim of this ongoing research is to develop a radioactive free LTT by using carboxyfluorescein succinimidyl ester (CFSE) and to evaluate the influence of human pooled serum (HPS) versus autologous serum, on the sensitivity of the LTT to nickel (NiSO4) and titanium salts. Peripheral blood mononuclear cells derived from nickel and titanium allergic patients and healthy controls are being used in this clinical study.

- We have studied the clinical consequences when changing the position of the implant-abutment interface where restoring dental implants with an abutment en FDP’s. A PhD thesis showed that if the implant abutment interface is at bone level more bone loss can be seen on the X-rays. We also learned that if the mucosal thickness surrounding bone level implants is 2 mm or more there is statistically significantly less crestal bone loss when compared to bone level implants placed in less than 2 mm of initial mucosa thickness. This has implications when indicating either bone level or tissue level implants in partially edentulous patients.

- Novel immune competent gingiva and skin equivalent models (GE-LC; SE-LC) (reconstructed gingiva epithelium with integrated MUTZ-3 derived Langerhans Cells on a fibroblast populated lamina propria) were used to compare LC activation and migration from oral versus skin epithelium. Topical exposure to sub-toxic concentrations of contact sensitizers resulted in LC migration out of the epithelia. Neutralizing antibody to CXCL12 blocked allergen-induced LC migration in SE-LC but not in GE-LC. Also, gingival fibroblasts secreted very low amounts of CXCL12 compared to skin fibroblasts even when stimulated with rhTNFα or rhIL-1α.

- In gingiva, upon allergen exposure, MUTZ-3 LC migrate in a CXCL12 independent manner from the epithelium-to-lamina propria in contrast to the CXCL12 dependent manner found in skin. In both gingiva and skin, LC within the lamina propria were found to be mature becoming CD1a- CD83+. These physiologically relevant in vitro models, which not only are human but which also resemble specific tissues, may aid in the identification of factors regulating immune stimulation which in turn will aid the development of therapeutic interventions for allergy and inflammation, anti-cancer vaccines as well as improving diagnostics for skin and oral allergy.

- Two studies showed toxic and immunological responses of palladium and nickel which were investigated because of their potential adverse effects from dental implants.

Biological response to loading

- Insulin-like growth factor-1 (IGF-1) is anabolic for muscle by enhancing the rate of mRNA translation via activation of AKT and subsequent activation of the mammalian target of rapamycin complex 1 (mTOR), thereby increasing cellular protein production. IGF-1 is also anabolic for bone, but whether the mTOR pathway plays a role in the rate of bone matrix protein production by osteoblasts is unknown. We have shown that IGF-1 and pulsating fluid flow activate mTOR, thereby stimulating the rate of mRNA translation in osteoblasts. The known anabolic effect of mechanical loading and IGF-1 on bone may thus be partly explained by mTOR-mediated enhanced protein synthesis in osteoblasts.

- Bone remodeling can be disturbed in active rheumatoid arthritis (RA), possibly as a result of elevated levels of circulating inflammatory cytokines. Osteocyte-specific proteins and cytokines play a vital role in bone remodeling by orchestrating bone formation and/or bone resorption. We found that gene expression of human osteocyte-specific proteins and cytokines was affected by RA-serum, and exogenous recombinant cytokines treatments suggesting that osteocytes could provide a new target to prevent systemic inflammation-induced bone loss in RA.

- Delayed fracture healing is frequently experienced in patients with systemic inflammation such as during rheumatoid arthritis (RA). The reasons for this are diverse, but could also be caused by inflammatory
cytokines and/or growth factors in serum from patients with active disease. We found that sera from patients with active RA negatively affect differentiation of osteochondrogenic precursors, and as a consequence may contribute to delayed fracture healing in these patients.

- **During the initial stages of bone repair**, proinflammatory cytokines are released within the injury site, quickly followed by a shift to anti-inflammatory cytokines. The effect of pro- and anti-inflammatory cytokines on osteogenic differentiation of mesenchymal stem cells is controversial. We found that all cytokines studied have both enhancing and reducing effects on osteogenic differentiation of human adipose stem cells (hASCs), even when applied for 72 h only. Some cytokines, specifically IL-6, may be suitable to induce osteogenic differentiation of mesenchymal stem cells as a strategy for enhancing bone repair.

- **The metabolite 1,25-dihydroxyvitamin D (1,25(OH)₂D) is synthesized from its precursor 25-hydroxyvitamin D (25(OH)D) by human osteoblasts leading to stimulation of osteoblast differentiation in an autocrine or paracrine way. Osteoblast differentiation is also stimulated by mechanical loading through activation of various responses in bone cells such as nitric oxide signaling. We found that 1,25(OH)₂D₃ and mechanical loading, both stimuli of the differentiation of osteoblasts, interact at the cellular level.**

**Response of oral mucosa to injury**

- **Tissue engineered oral mucosa equivalents constructed from TERT immortalized cells (OME) (reconstructed epithelium on a fibroblast populated lamina propria) were used to investigate inflammatory responses during wound healing. After introduction of a full thickness wound, OME showed an immediate inflammatory response (IL-6, CCL2 and CXCL8) followed by complete re-epithelialization. Seven days after wounding, tissue integrity, metabolic activity and cytokine levels had returned to pre-wounded state. This organotypic model will provide a valuable tool to investigate oral mucosa biology and can also be used as an animal alternative for drug targeting, investigating soft tissue attachment to implants, microbial biofilm studies and testing new therapeutics. Oral wounds heal faster and with better scar quality than skin wounds. Deep skin wounds where adipose tissue is exposed, have a greater risk of forming hypertrophic scars. Differences in wound healing and final scar quality might be related to differences in mesenchymal stromal cells (MSC) and their ability to respond to intrinsic (autocrine) and extrinsic signals, such as human salivary histatin. It was found that, compared to skin derived MSC, gingiva MSC showed greater proliferation and migration capacity, and less matrix contraction in full thickness tissue equivalents, which may partly explain the superior oral wound healing. Epidermal keratinocytes were required for enhanced adipose MSC matrix contraction and alpha smooth muscle actin expression, and may therefore contribute to adverse scarring in deep cutaneous wounds. Histatin enhanced migration without influencing proliferation or matrix contraction in all three MSC, indicating that salivary peptides may have a beneficial effect on wound closure in general. Understanding the mechanisms responsible for the superior oral wound healing will aid us to develop advanced strategies for optimal skin regeneration, wound healing and scar formation.**

- **Chronic ulcers represent a major health burden in our society. Protein based therapies fail in part due to proteolytic activity in the chronic wound bed. In this study, the stability of saliva derived histatins within the chronic wound environment was investigated. Chronic wound extracts were isolated from non-healing ulcers in this in vitro study. Incubation with chronic wound extracts resulted in serious breakdown of Hst1 and Hst2 (~50% in 8h) and to lesser extent cyclic Hst1 and the minimal active domain of Hst1 (~20% in 8h). However, an initial 8-hour pulse of histatins during a 96-hour study period was sufficient to stimulate fibroblast migration equally well as a continuous 96-hour exposure, indicating that, despite being susceptible to proteolytic breakdown, they may possibly be used as novel bioactive therapeutics, exerting their activity for up to four days after a single exposure.**

**Gaining in depth knowledge of non-infectious diseases of the masticatory system.**

**Pain, trauma and dysfunction**

- In a series of studies, we have demonstrated that 3D reconstructions of Cone-beam CTs of the upper airway can be performed reliable. In addition, based on a systematic review of the literature, the smallest cross-sectional area of the upper airway was found to be the most important anatomical characteristic to explain the pathophysiology of obstructive sleep apnea (OSA). Finally, the discipline “Dental Sleep Medicine” was redefined as to include other sleep disorders that affect (or are affected by) dentistry apart from OSA.

- A study amongst adolescents in Israel showed that both sleep bruxism and awake bruxism are prevalent conditions, equally in both genders.
• An extensive tooth wear evaluation system (TWES) was introduced. Using part of that system, it was shown that tooth wear can be assessed reliably on dental casts as well as on intra-oral photographs. Finally, a population study demonstrated that tooth wear is a prevalent condition in The Netherlands, and that the condition has gotten increasingly severe over the past ten years.

• Studies on orofacial pain in intellectually disabled or non-verbal individuals revealed that 1. pictograms are helpful to assess both pain intensity and pain quality in adults with Down Syndrome; 2. The MOBID orofacial pain scale is not useful (not reliable) for pain assessment in people with severe dementia; and 3. The OPS-NVI yields promising results for the assessment of orofacial pain during eating of elderly with dementia.

• Using the 3Q-TMD, a large-scale population study on the prevalence of temporomandibular disorders (TMD) was published, showing increasing symptoms during adolescence, a peak in middle age, and a gradual decrease thereafter – the more so in women as compared to men. The validity of the 3Q-TMD was demonstrated against the international gold-standard system DC/TMD. For the latter system, recommendations were formulated for its future usage in research and in clinical settings. Finally, the experience of TMD pain was found to be strongly associated with depression. Using computer models, it was shown that jaw-muscle relaxation and laterotrusive movements are useful strategies to resolve open locks of the temporomandibular joint.

### Academic personnel in 2016

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**Total research staff**: 39.00

## Output

### Dissertations


Scientific publications (refereed)


through exosomal transfer of 5pppRNA. Proceedings of the National Academy of Sciences of the United States of America, vol 113, no. 5, pp. E587-E596. DOI: 10.1073/pnas.1518130113


Sprangers, S., Schoenmaker, T., Cao, Y., Everts, V. & de Vries, T.J. (2016). Different blood-borne human osteoclast precursors respond in distinct ways to IL-17A. Journal of Cellular Physiology, vol 231, no. 6, pp. 1249-1260. DOI: 10.1002/jcp.25220


Other scientific publications


Professional publications


Gibbs, S. Bijna zoals een echte huid. LinkedIn-ZonMw Showcase Translational Research: from bench to bedside. (2016). Web publication/site, LinkedIn-ZonMw, Nederland.


Scholtanus, J.D. (2016). Hora est 2. Is door amalgaam verkleurd dentine een geschikt substraat voor hechting van composiet? Nederlands Tijdschrift voor Tandheelkunde, vol 123, no. 6, pp. 313. DOI: 10.5177/ntvt.2016.06.16152

Grants: current projects with external funding


Chen, H. Use of Cone Beam Computerized Tomograph (CBCT) for the diagnosis of obstructive sleep apnea. PhD project financially supported by Grant China Scholarship Council (CSC), granted €26.700.000: (2013, October 01 - 2017, October 01).

De Lange, J. Ongoing research in OSA. 4Dental project, granted €30.000: (2016, January 01 - 2016, December 31).


De Oliveira Gamba, T. Association of two craniometric methods for sexual prediction in CBCT scans. One year scholarship in the context of doctoral research of Mr. De Oliveira Gamba, financially supported by the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES; Process: 2017, October 01).

Everts, V., van Lenthe, G.H., Koolstra, J.H. & Lobbezoo, F. Biomechanical changes in articulation of the jaw joint due to aging. EU MOVE project. Granted 3 years full time: (2014, October 01 - 2017, October 01).


Forouzanfar, T. Klinische validatie van SPG-stimulatie in chronische clusterhoofdpijnpatiënten met het ATI-neurostimulatiesysteem. Innovatiefonds zorgverzekeraars, granted € 300.000,: (2013, December 01 - 2016, December 01).


Scherder, E.J.A. & Lobbezoo, F. Diagnostiek en behandeling van pijn bij mensen met een dementia die thuis wonen of in het verpleeghuis zijn opgenomen. F. Lobbezoo responsible for the dental part of this project which equals approx. 1/3 of the total amount granted €126.667, (2016, January 01 – December 31).
Van Eijnatten, M. Artificial intelligence in medical 3D printing, Young eScientist of the year award 2016, granted €50.000,- (of which € 40.000,- in kind in the form of an eScience engineer). (2016, January 01 - 2016, December 31).
Van Eijnatten, M. Improving the accuracy of CBCT technology for applications in medical 3D printing. Planmeca Oy Finland, granted €64.796,- (2016, January 01 - 2016, December 31).
Wang, T. TOPPER project: Treatment of periodontal disease, prosthodontics evaluated by oral radiology. PhD program during 4 years, financially supported by Grant China Scholarship Council (CSC), granted €57.600,00: (2016, September 01 - 2020, November 01).
Wismeijer, D. Evaluating CAD CAM zirconium implant crowns. ITI Grant (together with Chris Evans (Sydney, AUS), granted €30.000, (2015, January 01- 2016, December 31).
Wismeijer, D. 3D printed restorations on dental implants. A clinical trial. TKI funding, granted €97.865, and €80.000, (2015, January 01- 2016, December 31).
Wolff, J.E.H. & Forouzanfar, T. 3D-technology. DSM Grant, granted 0,4 fte Phd student, Geleen, the Netherlands (2015, January 01 - 2016, December 31).
Indicators of Esteem

Editorship book

Memberships editorial board
Aarab, G.: Journal of Dental Sleep Medicine.
Bakker, A.D.: Odontology.
De Vries, N.: The Open Otorhinolaryngology Journal (TOOTOR).
Lobbezoo, F.: Journal of Craniofacial Function.
Lobbezoo, F.: Journal of Dental Sleep Medicine.
Van der Stelt, P.F.: Clinical Oral Implants Research.
Van der Stelt, P.F.: Dentomaxillofacial Radiology.
Van der Stelt, P.F.: Journal of Dentistry Shiraz University of Medical Sciences.
Van der Stelt, P.F.: Odontology.

Scientific awards/honours
Chen, H. (June 18, 2016). EADMFR Research award 2nd prize for best oral presentation: Reliability and accuracy of imaging software for three-dimensional analysis of the upper airway on cone beam CT. European Academy for DentoMaxilloFacial Radiology, Cardiff, UK.
Fazaeli, S. (January 8, 2016). Bolk prijs, Nederlandse Anatomien Vereniging, Lunteren, the Netherlands.


Organized scientific congresses and symposia

Bakker, A.D. (May 2–5, 2016). Organizer. ECTS PhD training course, Oxford UK.

Bakker, A.D. (November 8 – 9, 2016). Organizer. 26e Najaarsvergadering Nederlandse Vereniging voor Calcium en Botstofwisseling, Zeist, NL.


De Vries, N. (May 20, 2016). Organizing committee of innovation in the treatment of OSA. Amsterdam, the Netherlands.


Forouzanfar, T. (October 20–21, 2016). Organizer. 3D Printing in Healthcare Conference, Amsterdam, the Netherlands.


Tahmaseb, A. (April 15-16, 2016). Chair and member of the scientific organization committee. ITI Congress Benelux, Expecting the unexpected: We tried everything but still. Maastricht, the Netherlands.


Wismeijer, D. (April 15-16, 2016). Member of the scientific organization committee. ITI Congress Benelux, Expecting the unexpected: We tried everything but still. Maastricht, the Netherlands.

Invited speakers at (inter)national congresses or symposia


Forouzanfar, T. (October 8, 2016). Phase I/II trial of SVF for maxillary sinus floor one augmentation. CELLS / Musculoskeletal conference, Amsterdam, the Netherlands.

Annual Research Report 2016


Gibbs, S. (September 14, 2016). Focus on innovative skin models for safety testing. Liverpool University.


Hoeckema, A. (May 20, 2016). Bimaxillary osteotomy; only for severe OSAS? Symposium OSA Revisited, Amsterdam, the Netherlands.


Lobbezoo, F. (June 3-4, 2016). 1. Bruxism diagnosis and etiology. 2. Bruxism management and clinical consequences. 2nd Congresso Nazionale GSID Let’s chew on bruxism, Marina di Carrara, Italy.


Schulten, E.A.J.M. (March 18, 2016). Edentulous patients. Symposium VUmc, Straumann, Uden, NL.

Schulten, E.A.J.M. (September 13, 2016). Edentulous patients, Symposium VUmc Straumann Zwolle, NL.

Tahmaseb, A. (April 15-16, 2016). So now we have a guideline and then what? ITI Congress Benelux, Expecting the unexpected: We tried everything but still. Maastricht, the Netherlands.


Tahmaseb, A. (November 12-14, 2016). Small diameter implants. Straumann platinum congress, South Carolina, USA.


Thymi, M. (December 1, 2016). Associations between sleep bruxism and (peri-)implant complications. Update of an ongoing follow-up study. Academic Advisory Board Meeting Grindcare/Sunstar, Amsterdam, the Netherlands.


Van Loon, J.J.W.A. (November 24, 2016). Sensing changes of the gravitational load (from cells to organisms and beyond). VU-University, master course Extreme Biology, Amsterdam, NL.


Wismeijer, D. (March 10, 2016). Digital workflow in dentistry, Where are we and where are we going. Keynote speaker. 33rd Interdisciplinary Dental Conference Rasmushof, KitzBuhl.

Wismeijer, D. (April 15-16, 2016). So now we have a guideline and then what? ITI Congress Benelux, Expecting the unexpected: We tried everything but still. Maastricht, the Netherlands.


Wolff, J.E.H. (March 18, 2016). Edentulous patients. Symposium VUmc, Straumann, Uden, NL.


Wolff, J.E.H. (September 13, 2016). Edentulous patients, Symposium VUmc Straumann Zwolle, NL.


Other (inter)national scientific functions

Aarab, G.: Member research committee American Academy of Dental Sleep Medicine (AADSM), since 2012.

Aarab, G.: Member research committee Dutch Society of Dental Sleep Medicine (NVTS), since 2012.
Baggen, J.H.M.: Member research committee, Nederlandse Vereniging Tandheelkundige Slaapgeneeskunde (NVTS), since 2016
Bakker, A.D.: Secretary Dutch Society for Calcium and Bone Metabolism.
Bakker, A.D.: Leader Education committee European Calcified Tissue Society (ECTS).
Bakker, A.D.: Board member European Calcified Tissue Society (ECTS).
De Vries N.: Member of the Medische Advies Raad ApneuVereniging, since 2012.
De Vries N.: Member of the Medical Advisory Board NightBalance, since 2014.
De Vries N.: Member of the Medical Advisory Board Recent, since 2013.
De Vries N.: Consultant for Philips Health care, since 2014.
De Vries N.: Consultant for Olympus, since 2014.
De Vries N.: Consultant for AE Mann Foundation, since 2016.
Gibbs, S.: Member European Research Group for Experimental Contact Dermatitis (ERGEC).
Gibbs, S.: Directory board member MOVE Research Institute & VU University, Amsterdam, the Netherlands.
Gibbs, S.: Project jury member NC3Rs, London, UK.
Hoekema, A.: President Nederlandse Vereniging voor Tandheelkundige Slaapgeneeskunde (NVTS), since 2008.
Hoekema, A.: Member research committee, American Academy for Dental Sleep Medicine (AADSM), since 2009.
Hoekema, A.: Member steering committee, Oral Appliance Network for Global Effectiveness (ORANGE Registry), since 2012.
Hoekema, A.: Member steering committee, OSAS richtlijn, Kennisinstituut Medisch specialisten, Utrecht, the Netherlands, since 2015.
Klein-Nulend, J.: Member scientific board Department of Regenerative Medicine, Research Centre for New Technologies in Life Science Engineering, University of Tehran, Iran.
Klein-Nulend, J.: External professor San Carlos University, Dept. of Physics, Cebu City, Philippines.
Klein-Nulend, J.: Outer board member Irish Research Council Postdoctoral International Assessment 2015 (Fellowships in Science, Engineering and Technology), Royal Irish Academy.
Kramer, G.J.C.: Voorzitter Wetenschap- en accreditatiecommissie NVvO.
Kuitert, R.B.: Lid Richtlijncommissie NVvO.
Lobbezoo, F.: Senior member Society of Oral Physiology (Store Kro Club), since 2015.
Lobbezoo, F.: Chair Nederlandsch Tandheelkundig Genootschap (NTG) [Dutch Dental Society], since 2016.
Prahl, C.: Lid bestuur NVOS.
Van Loon, J.J.W.A.: User committee member for STW-project A lab-on-a-chip device to screen for the effect of mechanical signals on cells from dr.ir. Jeroen Rouwkema, Twente University, Enschede, NL.

Van Westing, K.: Lid richtlijncommissie NVvO.
Wismeijer, D.: Visiting professor of the University of Belgrado Dental School.
Wu, G.: Visiting professor in Guangzhou Medical University, China.
Wu, G.: Visiting professor in Wenzhou Medical University, China.

**Supervisor of an external PhD student**


**Collaborations**

- A. Gefen, Tel Aviv University, Israel. E. Corsini, Università degli Studi di Milano, Milan, Italy.
- AMC, dr. P. Kloen (Dept Orthopaed Traumatol), Non-unions.
- Amsterdam University of Applied Sciences, prof.dr. R. Engelbert, Amsterdam, the Netherlands.
- Ankara University, Department of Dentomaxillofacial Radiology, Faculty of Dentistry, Ankara, Turkey. Prof. K. Kamburoglu.
- Department of Oral and Maxillofacial Surgery, University of Torino, Italy.
- Department of Orthopedics, VUmc.
- Department of Radiology, University of Helsinki, Finland.
- E. Roggen, 3Rs Management and Consultancy, Denmark.
- Ege University, Faculty of Medicine, Center for Brain Research & Department of Physiology, prof.dr. K. Türker, Bornova, Izmir, Turkey.
- Hacettepe University, Department of Dentomaxillofacial Radiology, Faculty of Dentistry, Ankara, Turkey. Prof. N. Avcu.
- Harvard University, Boston, MA, USA, dr. Ramaswami Krishnan (Dept. of Mechanical Engineering): Osteocyte mechanosensing.
- Katholieke Universiteit Leuven, Leuven, Belgium, prof.dr. Frank P. Luyten (Dept. of Rheumatology, Skeletal Biology & Engineering Research Center, Prometheus, Division of Tissue Engineering): Systemic inflammation and generalized osteoporosis.
- Kyushu University, Kyushu, Japan, prof.dr. Daisuke Mizuno (Dept. of Physics): Macro and microrheology of stem cells.
- Leiden University Medical Center (LUMC), Department of Public Health and Primary Care (PHEG), prof.dr. W.P. Achterberg, Leiden, Netherlands.
- New York University Dental College, prof.dr. K.G. Raphael, New York, NY, USA.
- Newcastle University, Centre for Oral Health Research & Institute of Health and Society, Newcastle-upon-Tyne Hospitals’ NHS Foundation Trust, dr. J. Durham, Newcastle-upon-Tyne, UK.
- Okayama University, Okayama, Japan, prof.dr. Hiroshi Kamioka (Dept. of Orthodontics): Osteocyte imaging and mechanosensing.
- R. Monge, BeOnChip Spain (Eurostars).
- Radboudumc, IQ-healthcare, prof.dr. R. Nijhuis, Nijmegen, the Netherlands.
- San Carlos University, Cebu City, Philippines, prof.dr. Rommel G. Bacabac, (Dept. of Physics, Biomedical Physics Group): Biophysics bone adaptation and regeneration.
- School of interdisciplinary dentistry, Vienna medical faculty, Austria.
- Shandong University, Department of Orthodontics, Faculty of Dentistry, Jinan, China, prof. Jing Guo.
- Slotervaart General Hospital, Department of Clinical Neurophysiology and Brain Mapping Laboratory, dr. H.L. Hamburger, Amsterdam, the Netherlands.
- Spaarne Hospital Hoofddorp, dr. Peter A. Nolte (Dept Orthopaedics): Low intensity pulsed ultrasound/micromechanical stimulation of bone.
- State University of Campinas, Piracicaba Dental School, Piracicaba, Brazil, prof. M. Lima de Oliveira and prof. S.M. Almeida Boscolo.
- TNO Life Style - Behavioral and Societal Sciences, dr. E. Vermaire and dr. A. Schuller, Leiden, the Netherlands.
- University at Buffalo, Department of Oral Diagnostic Sciences, dr. R. Ohrbach, Buffalo (NY), USA.
- University College of Dentistry, Department of Biomedical Sciences, dr. E. Schneiderman, Dallas, Texas, United States of America.
- University Estadual Paulista (UNESP), Department of Dental Materials and Prosthodontics, prof.dr. Daniela Aparecida de Godoi Gonçalves, Araraquara School of Dentistry, Araraquara, Brazil.
- University Medical Center (UMC) Utrecht, dr. CM Speksnijder, Utrecht, the Netherlands.
- University of Aarhus, School of Oralfacial Pain and Jaw Function, prof.dr. Peter Svensson, Aarhus, Denmark.
- University of Adelaide, School of Dentistry, prof.dr. G.C. Townsend, Adelaide, Australia.
- University of Antwerp, Faculty of Medicine and Health Sciences, Department of Rehabilitation Sciences and Physiotherapy, dr. Willem de Hertogh, Antwerp, Belgium.
- University of Athens, Orofacial Pain Clinic, Dental School, National and Kapodistrian, dr. Michail Tzakis, Emeritus prof. Vron Droukas, Athens, Greece.
- University of Gothenburg, Institute of Odontology, Department of Behavioral and Community Dentistry, Sweden., dr. M. Hakeberg & dr. G. Jonasson.
- University of Helsinki, Department of Stomatognathic Physiology & Prosthetic Dentistry, dr. J. Ahlberg, Helsinki, Finland.
- University of Linjöping, Linjöping, Sweden, dr. Anna Fahlgren (Dept Orthopaedics): Bone implant loosening.
- University of Linjöping, Linjöping, Sweden, dr. Edwin de Jager (Biosensors and Bioelectronics Centre): Osteocyte mechanotransduction and polymer microactuators.
- University of Montreal. Faculty of Dentistry, prof.dr. Gilles Lavigne, Montreal, PQ, Canada.
- University of Naples Federico II, Department of Neurosciences, Reproductive and Oral Sciences, Section of Orthodontics and Temporomandibular Disorders, prof.dr. A. Michelotti, Naples, Italy.
- University of Padova, TMD Clinic, prof.dr. D. Manfredini, Padova, Italy.
- University of Tehran, Tehran, Iran: prof.dr. Ghassem Amoabediny (Research Center for New Technologies in Life Science Engineering / Biochemical, Biomedical, and Nanobio Engineering): Tissue engineering.
- University of Tel Aviv, Department of Oral Rehabilitation, The Maurice and Gabriela Goldschleger School of Dental Medicine, prof.dr. Efraim Winocur, Tel Aviv, Israel.
- University of Umea, Faculty of Medicine, Department of Clinical Oral Physiology, prof.dr. A. Wännman, Umea, Sweden.
- Vrije Universiteit, Department of Clinical Neuropsychology, prof.dr. E.J.A. Scherder, Amsterdam, the Netherlands.
- Vrije Universiteit, Nederlands Tweelingen Register (NTR), prof.dr. D.I. Boomsma, Amsterdam, the Netherlands.
- VU University Medical Center Amsterdam, Department of General Practice & Elderly Care Medicine, prof.dr. C.M.P.M. Hertogh, Amsterdam, the Netherlands.
- VU University Medical Centre Amsterdam, Department of Anesthesiology, EMGO+ Institute for Health and Care Research, prof.dr. R.S. Perez, Amsterdam, the Netherlands.
- VUmc, dr. Marco N. Helder (Dept. of Oral & Maxillofacial Surgery), Basic science and clinical application of adipose stem cells.
- VUmc, dr. N. Bravenboer (Dept. of Clin Chem), Systemic inflammation, bone adaptation and regeneration.
- VUmc, prof.dr. Willem F. Lems (Rheumatology), Systemic inflammation and bone biology.

Current PhD projects


Societal impact
The societal impact of the scientific merits of the section of Oral Kinesiology is expressed by the various post-academical courses organized and large amount of lectures provided for professionals. Besides courses for dentists, also courses for other professionals in the field of orofacial pain have been organized, such as for mouth hygienists, physical therapists and dental assistants. In addition, on a regular basis, the expertise as developed in the section of Oral Kinesiology receives attention from the media. The societal impact of the clinical research on oral and maxillofacial surgery is focussed on the influence on patient care, both within the department and externally. Research contributes to improved treatment of relevant patient groups.

I. Societal relevance for the dental professional in the Netherlands

Courses organized for Dutch dental and medical professionals


Aarab, G. & Wetselaar, P. (May 12, 2016). Organisation of a TMD-course for orthodontists and oral-maxillofacial surgeons (AMC and VUmc) i.o., Amsterdam, the Netherlands.


De Lange, J. (October 7-10, 2016). Cursus Slaap en OSAS voor tandartsen, ACTA, ADE.
Hoogeveen, R.C. (29 January; 14 October-4 November 2016). Stralingshygiënisch Gekwalificeerd Beroepsbeoefenaar mbt CBCT.
Hoogeveen, R.C. (5-19 February; 3-24 June; 25 November-9 December 2016). Stralingshygiënisch Gekwalificeerd Beroepsbeoefenaar mbt CBCT, variant MKA.
Stroy, L.P.P. (November 28, 2016). Dento-alveolaire cursus voor de ACTA Dental Education BV.
Tahmaseb, A. (2016). Cadaver Course on anatomy for the ITI. Rotterdam University.

Lectures given during courses for Dutch dental and medical professionals


Dubois, L. (April 9, 2016). De blinde vlek. ACTA Quality Practice: thema Medisch Tandheelkundige Interactie, Jaarbeurs, Utrecht.

Dubois, L. (June 7, 2016). Maxillofacial Traumatology. The ABC’s of Trauma, AMC.

Dubois, L. (June 24, 2016). 1. Tandletsel in de praktijk, de dilema’s. 2. Trauma van klein tot groot. ACTA QP Mondhygiëne, Jaarbeurs, Utrecht.


Hoogeveen, R.C. (May 21 & 28, 2016). Tandheelkundige Cone Beam CT en stralingsrisico’s, objectief, relatief en subjectief beschouwd, ACTA QP.

Hoogeveen, R.C. (May 21 & 28, 2016). Interactieve presentatie Orthodontische Radiologie, Workshop ACTA QP.


Kuijs, R.H. (June 4 & 18, 2016). Gebitslrijtage, to treat or not to treat, what are the questions. ACTA Quality practice, Amsterdam.


Van Loon, J.J.W.A. (April 15, 2016). Gravity related experimentation in space and on ground, master course Medische Natuurwetenschappen, VU-University, Amsterdam, NL.


Wismeijer, D., Tahmaseb, A. & Hassan, B. (2016). Course and lectures on Oral Anatomy (Masterclass Implantology), runs the whole year, ACTA DE.


Organization of congresses and symposia for professionals in the Netherlands


De Lange, J. (March 9, 2016). Organization AB profylaxe, klinische avond ACTA.

De Lange, J. (November 11, 2016). Organization NMT/AVL/AMC Oncologie, klinische avond ACTA.


De Lange, J. (December 7, 2016). Organization Innovaties in de tandheelkunde, klinische avond ACTA.
Invited speakers at professional congresses or symposia in the Netherlands


Visscher, C.M. (November 11, 2016). TMD and atypical facial pain. Interdisciplinary pain symposium: Pain in the Head and Neck Area, Utrecht, the Netherlands,


Wismeijer, D. (June 3, 2016). De bal is rond en aan het rollen. VIT: Implantologie is topsport, Maastricht, the Netherlands.


Professional functions in the Netherlands

Baart, J.A.: Lid Bestuur NWVT.
Baart, J.A.: Voorzitter WTA cie NWVT.
Baart, J.A.: Voorzitter WTA leesie (Hamers Duyvynszprijs).
Becking, A.G.: Lid Commissie onderzoek en aanbeveling, NVMKA.
Becking, A.G.: Lid Concilium Chirurgicum Oris.
Becking, A.G.: Lid Stipendium commissie BOOA research grant, NVMKA.
Berkhout, W.E.R.: Member College van Opleiders Stralingsopleidingen 2013.-
Berkhout, W.E.R.: Lid Stipendium commissie BOOA research grant, NVMKA.
De Lange, J.: Bestuurslid (inkomend voorzitter) NVMKA.
De Lange, J.: Voorzitter CTS.
De Lange, J.: Lid Capaciteitsorgaan.
De Lange, J.: Lid Consilium Chirurgicum Oris (CCO).
De Lange, J.: Lid COK.
De Lange, J.: Lid CKC KNMT.
De Lange, J.: Redactielid Quality Practice.
Disse, M.A.: Vice-president RTS.
Disse, M.A.: Dutch representative (member) Efosa.
Disse, M.A.: Member; The Amsterdam Cleft Lip and Palate team, location VUMc/ACTA.
Dubois, L.: Chef de kliniek WPM.
Dubois, L.: Lid Expertise team divisie chirurgie.
Dubois, L.: Lid Richtlijn spoedoperaties kwaliteitsinstituut medisch specialisten (NVH).
Dubois, L.: Secretaris Stichting Bridge the Gap, NOMA en schisis team.
Dubois, L.: Lid Coördinatie Commissie Traumatologie AMC.
Kramer, G.J.C.: Member Schisisteam MCA Alkmaar.
Kramer, G.J.C.: Chair/secretary Special Interest group ortodontics NVSCA.
Kuitert, R.B.: Member Centraal College.
Kuitert, R.B.: Member Concilium Orthodonticum.
Kuitert, R.B.: Member European Teachers’ Forum.
Kuitert, R.B.: Member Nebeop/visiting assessment committee.
Lobbezoo, F.: Chair Curatorium Bijzondere Leerstoel Angst- en Gedragsstoornissen in de Tandheelkundige Praktijk, since 2014.
Lobbezoo, F.: Chair Curatorium Bijzondere Leerstoel Kwaliteit van Mondzorg, since 2015.
Lobbezoo, F.: Chair Curatorium Bijzondere Leerstoel Mondgezondheid en Kwaliteit van Leven, since 2015.
Lobbezoo, F.: Member Interim Management Team, MOVE Research Institute, Amsterdam.
Nijkamp, P.: Member Schisisteam, Den Haag-Leiden.
Nijkamp, P.: Consultant orthodontist CBT afdeling MKA-chirurgie LUMC.
II. Societal relevance for the dental professional internationally

Professional functions internationally

Becking, A.G.:
- President SORG (Strasbourg Osteosynthesis Research Group).
- Visiting professor Universitat International Catalunya, Barcelona, Spain.

De Lange, J.:
- Faculty member and chairman SORG Trauma section.

De Lange, J.:
- Faculty member AOCMF.

Dubois, L.:
- Member SORG Trauma section.

Dubois, L.:
- Member KLS Martin expertise group Osteosynthesis.

Gimenez Gonzalez, B.:
- Board member Spanish Society of Aesthetic and Prosthetic dentistry (SEPES).

Koutris, M.:
- Board member Greek Society of Orofacial Pain, since 2014.

Koutris, M.:
- Member RDC-TMD Consortium, Calibration Committee, since 2014.

Koutris, M.:
- Member RDC-TMD Consortium, Governance Committee, since 2015.

Visscher, C.M.:
- Board member Physical Therapy Board of Craniofacial and Cervical Therapeutics (PTBCCT), USA, since 2003.

Wismeijer, D.:
- Board Member ITI.

Wismeijer, D.:
- Board Member Digital Dentistry Society (DDS).

Wismeijer, D.:
- Chairman ITI Education Committee.

Wismeijer, D.:
- Examiner Royal College of Surgeons of Edinburgh.

Wismeijer, D.:
- Member Scientific Advisory Board (SAB) International Association of Digital Dentistry (IADD).

Organization of international congresses and symposia for (health care) professionals

Gimenez Gonzalez, B. (February 6-7, 2016). Young president Young Values SEPES in charge of the Valores, SEPES SYMPOSIUM, Madrid, Spain.

Gimenez Gonzalez, B. (July 8-10, 2016). Coordinating and moderating Campus SEPES (Consensus Meeting), Vitoria, Spain.


Invited speakers at international professional congresses or symposia

Aarab, G. [June 9-10, 2016]. 1. The associations between sleep bruxism and OSA. 2. Titration, where to start? AADSM meeting, Denver, VS.


Aarab, G. [November 26, 2016]. 1. Temporomandibular side-effects of oral appliance therapy in obstructive sleep apnea. 2. The clinical aspects of oral appliance therapy in obstructive sleep apnea. DGFDT meeting, Bad Homburg, Germany.


Becking, A.G. [October 1, 2016]. Conventional planning in orthognathic Surgery, SORG course on planning and pitfalls in Orthognathic Surgery, Liverpool, UK.


De Lange, J. [July 7-9, 2016]. 1. Osteosynthesis techniques in the mandible, principles and definitions. 2. Treatment of isolated central and centro-lateral (Le fort type) fractures, buttress stabilization. 3. Zygomatic fractures. AO basic course, Chandigarh, India.


De Vries, N. [2016]. Obstructive Sleep Apnea Surgery Course with hands on Cadaver, 3-day Muscat, Oman.

De Vries, N. [2016]. Surgically Oriented Hands-On Workshop, 3-day OSAS Surgery International Course, Orlando, Florida.

Dubois, L. [January 28, 2016]. 1. Indications and timing of orbital reconstruction. 2. Approaches from above. 3. 3d Planning in orbital surgery AO CMF Course Advances on the Orbit, Rotterdam.


Liu, Y. (November 18-20, 2016). Development and pre-clinic studies of Biobone. Symposium in biomimetics, School of Materials Science and Engineering, National Engineering Research Center for Tissue Reconstruction, South China University of Technology, Guangzhou, China.


Raber-Durlacher, J.E. (November 8-9, 2016). Low level laser therapy for the management of oral cGHVD. German, Austrian, Swiss GVHD Working Group, Basel, Switzerland.


Teng, F. (September 29 - October 1, 2016). Modification of implant necks to enhance attachment between implants and peri-implant soft issue: an experimental study in beagle dogs. European Association for Osseointegration (EAO), Paris, France.

Teng, F. (October 18-21, 2016). In-vitro evaluation of biomimetic incorporation and release kinetics of BMP2 on functionalized Bio-Oss® Block. Travel Scholarship Bioceramics 28, Charlotte, North Carolina, USA.

Teng, F. (October 21, 2016). Development and preclinical studies of Biobone - BMP2 with xenogenic bone replacement material. Freiburg University, Germany.


III. Contacts with the general public

Interactions with the press and the general public


Impact of the research on the general public or professionals

Oral Implantology: Digital technologies in dentistry make the dental workflow more precise and dental treatment can be realized a lot quicker and possibly cheaper. This means that the dental treatment will have less impact on the patient's everyday life. One of the milestones we have reached in 2016 is the first 3D printed crown on a dental implant that was placed in a patient. The total material costs of this crown was 30 euro cents.

Van der Stelt, P.F. (October 12, 2016). Overleg over vernieuwing Besluit basisveiligheidsnormen stralingsbescherming namens KNMT bij VWS, Den Haag.
Education related research, including other research

Research on Dental Education
Associate dean of educational research and development
Dr. J.M. Vervoorn
Education Institute
ACTA, Gustav Mahlerlaan 3004
1081 LA Amsterdam
Tel: +31-20-5980438
E-mail: J.Vervoorn@acta.nl

Research objectives
In the ACTA faculty of Dentistry research is performed on several aspects of education in dentistry. This includes research on the evaluation of courses and performance of students within the curriculum, research on new teaching methods, development and evaluation of a computer aided digital teaching system creating a virtual learning environment including the application of haptics (the Simodont Dental Trainer). Also some projects are carried out on assessment of the safety of the learning environment and the effect of interventions.
The input of academic personnel is limited to staff of the educational institute, and to some members of the various departments. The research is not considered as a separate programme; however it is intended that this research will increase in the coming years.

Results
In 2016 again several experiments have been carried out with respect to choices in the development of the virtual dental trainer. It appeared that availability of force feedback (FFB) in a dental trainer is essential for good performance but some variance in FFB is acceptable for learning. Data on inter and intra observer reliability of assessment showed that including calibration in the workflow of an assessment procedure improved the reliability of the assessments till a certain extend, after that calibration did not further affect the interreliability. Students that were able to perform well in reality are also able to perform in VR; a longer learning curve in Reality does not seem to result in a longer learning curve in VR. Giving students freedom to decide on their testing moment for Manual Dexterity provides better result on these tests than when the test date is fixed by the school.

Academic personnel in 2016

<table>
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<th>Position</th>
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<td>Vervoorn, dr. J.M.</td>
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<td>Wesselink, prof.dr. P.R.</td>
<td>pm</td>
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<td>Serrano Petrillo, dds. C.M.</td>
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Output

Scientific publications (refereed)


Professional publications


Indicators of Esteem

Scientific awards


Memberships editorial board

Gorter, R.C.: European Journal of Dental Education.

Invited speakers at (inter)national congresses or symposia


Other (inter)national scientific functions

Gorter, R.C.: Executive board member Association for Dental Education in Europe (ADEE), since 2013.

Gorter, R.C.: Member Platform for better oral health in Europe.

Serrano Petrillo, C.M.: Chair Special Interest Group: Transition to Clinical Training in Dentistry.

Vervoorn, J.M.: Chair Simodont Forum ADEA/ADEE.


Wesselink, P.R.: Chair special interest group ADEE: Virtual reality in dental education, since 2009.

Current PhD projects


Societal impact
The societal impact of the research and development is focused on the effect of learning behaviour on learning outcomes and on the implementation of new technologies in education. Also developments have an increased focus on improving safety of the learning experience. This involves in particular the developments of virtual exercise on a digital impression of the patient in advance of the actual clinical procedure using a computer aided digital learning environment (the Simodont dental trainer).

I. Societal relevance for the dental professional in the Netherlands

Interactions and collaborations with the industry and other non-university groups
MOOG inc. Development of the Simodont dental trainer.
3M – Development of real scans into virtual reality application.

Courses organized for Dutch dental and medical professionals
Wesselink, P.R. & Vervoorn, J.M. (June 5-6, 2016). Quality Assurance in Clinical Dental Training, Poznam, Poland.

Professional functions in the Netherlands
Gorter, R.C.: Vervangend lid Algemene Interfacultaire Ethische Commissie UvA.
Vervoorn, J.M.: Chair Simodont Users Meetings.

II. Societal relevance for the dental professional internationally

Professional functions internationally
## List of SCI journals, their impact factors and the number of ACTA publications in 2016 in each journal

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