ANNUAL RESEARCH REPORT 2015
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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 2015 is presented in Table 1. We are pleased to note that the output in 2015 was high. The number of publications in refereed scientific journals and the IF-sum have considerably increased during the last years. In 2015 the highest number of scientific publications and a very high impact factor sum was accomplished. In 2015 a total of 15 PhD theses were published and defended.

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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. ACTA research on oral regenerative medicine is 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. Also on behalf of the Board of the Vrije Universiteit Amsterdam, the Board of the University of Amsterdam has appointed as members of the assessment committee:

Hans Marchen den Boer (Cavex Holland B.V.), Christopher McCulloch (University of Toronto), Jukka Meurman, chair (University of Helsinki), Mutlu Özcan (University of Zürich), William Wade (Queen Mary University of London). Jan Heijn (BetaText, Bergen NH) served as secretary of the assessment committee.

The two research programmes 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. to further strengthen the research at ACTA. For more details about this evaluation we refer to the assessment report of the committee.

**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 2003-2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
</tr>
<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 2015 15 dissertations were accomplished.

*PhD performance.* The percentage of PhD students that finished their thesis averages at 90% 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 shows a slightly increasing number over the last 20 years, despite a relatively stable input in fte of scientific personnel. The average quality of the publications has significantly improved over the 20-year period, as indicated by the increase of the impact factor sum (Figure 1). In 2015 the highest number of 286 refereed publications and a very high IF sum were obtained.

*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 2015 was 175.

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

![Graph showing impact factor sum and other metrics](image-url)

- **notable events in 2015**

*Publications in high ranking journals.* Outstanding contributions for the year 2015 were publications in high ranking biomedical journals, i.e. Lancet Infectious Diseases (impact factor 22.4), JAMA Psychiatry (impact factor 12.1), Clinical Infectious Diseases (impact factor 8.8), and Clinical Cancer Research (impact factor 8.7). ACTA scientists also published many papers in the top 10% journals in dentistry, i.e. 34 papers in the 6 journals with the highest impact factor in this field, among which 6 in the Journal of Dental Research.

*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 286 scientific papers in refereed journals, of which 267 in journals with an impact factor (SCI journals). 51% of these 267 papers appeared in journals belonging to the field “Dentistry, Oral Surgery and Medicine”. 24% of all publications were in the top 10% of the journals, 47% in the top 25% and 78% 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 2015 a total of 20 awards were received by ACTA scientists for their achievements. For more details we refer to the description of the two research programs.

Grants. As in previous years ACTA scientists obtained several important grants. An example of a successful grant is the participation of ACTA in the nationally funded and oriented Top Institute Food and Nutrition (TIFN) in 2011, where a new 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 ACTA and with the Netherlands Organization for Applied Scientific Research (TNO). Another example is the large EU-MUNDUS project: MOVE-AGE, in which ACTA participates. At this moment two ACTA PhD students are funded by this EU-project. In 2013 a large Marie Curie ITN EU project was granted by the EU. This project, named Euroclast, 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.

<table>
<thead>
<tr>
<th>Table 2. Percentage of publications in different quartiles of dentistry and non-dental journals in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>dentistry journals</strong></td>
</tr>
<tr>
<td><strong>numbers</strong></td>
</tr>
<tr>
<td>top 10%</td>
</tr>
<tr>
<td>Quartile 1</td>
</tr>
<tr>
<td>Quartile 2</td>
</tr>
<tr>
<td>Quartile 3</td>
</tr>
<tr>
<td>Quartile 4</td>
</tr>
<tr>
<td>total</td>
</tr>
</tbody>
</table>

- assessment at the program level
When the research at the program level is considered, both programs perform over the last years in general equally well in terms of parameters like input and output (personnel, PhD students, publications, dissertations etc). In 2015 the OII 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, the 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>9</td>
<td>161 (66)</td>
<td>22</td>
<td>118</td>
<td>11</td>
<td>451</td>
<td>20,00</td>
<td>0,70</td>
<td>11,25</td>
<td>31,95</td>
</tr>
<tr>
<td>ORM</td>
<td>5</td>
<td>140 (83)</td>
<td>10</td>
<td>63</td>
<td>-</td>
<td>315</td>
<td>18,60</td>
<td>4,25</td>
<td>16,00</td>
<td>38,85</td>
</tr>
<tr>
<td>OWI</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>0,85</td>
<td>0,85</td>
</tr>
<tr>
<td>ACTA*</td>
<td>13</td>
<td>286 (161)</td>
<td>9</td>
<td>175</td>
<td>11</td>
<td>745</td>
<td>38,60</td>
<td>4,95</td>
<td>28,10</td>
<td>71,65</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 2015 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>14,75</td>
<td>0,20</td>
<td>5,40</td>
<td>5,25</td>
<td>0,50</td>
<td>5,85</td>
<td>31,95</td>
</tr>
<tr>
<td>ORM</td>
<td>11,10</td>
<td>1,65</td>
<td>9,95</td>
<td>7,50</td>
<td>2,60</td>
<td>6,05</td>
<td>38,85</td>
</tr>
<tr>
<td>OWI</td>
<td>-</td>
<td>-</td>
<td>0,10</td>
<td>-</td>
<td>-</td>
<td>0,75</td>
<td>0,85</td>
</tr>
<tr>
<td>Total</td>
<td>25,85</td>
<td>1,85</td>
<td>15,55</td>
<td>12,75</td>
<td>3,10</td>
<td>12,45</td>
<td>71,65</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
main areas of interest contributes to improved prevention, diagnosis and treatment of relevant patient groups. 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 (86 international functions), as members of editorial boards of scientific journals (78) and in being leading in ‘wetenschappelijke verenigingen’ 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 practising 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 175 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 2015 ACTA researchers have again contributed actively in internationally held meetings, workshops and symposiums, both as organizers and participants. A total of 124 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 16 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 k€ 877 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 k€ 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 k€ 517, and the total amount of research contracts (3rd source) was k€ 2241.

- **personnel**
  The directorate of the institute comprises:
  
<table>
<thead>
<tr>
<th>Position</th>
<th>FTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>prof.dr. A.J. Feilzer, dean and director of research ad interim</td>
<td>p.m.</td>
</tr>
<tr>
<td>dr. T.J.M. van Steenbergen, co-ordinator of research</td>
<td>0.55 fte</td>
</tr>
<tr>
<td>mrs. F.M. Meijer, secretary</td>
<td>0.60 fte</td>
</tr>
<tr>
<td>dr. J.A.M. Korfage, research technician (started June 2014)</td>
<td>0.15 fte</td>
</tr>
</tbody>
</table>

  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 no research master training, the AGSD is at the moment limited to the PhD program.

- PhD student appointments
In Figure 2 the number of new PhD students at ACTA is shown in the years 1990 to 2015. Over the years, about 23% of all PhD students had a foreign nationality, about half of them from Europe, the rest from other continents. A mean number of about 9 new PhD students were appointed per year. Due to budget restrictions only 8 new PhD students could be appointed in 2015. About 40% of the PhD students have a dental background (see Table 5). Of all PhD students about 70% is female. The research institute has started a procedure for allocation new PhD positions for the two main research themes. This procedure resulted in 4 grants for new PhD projects in 2015. Two PhD-students started their project within 2015, the other two will begin in 2016.

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

![Figure 2: Numbers of new ACTA PhD students from the Netherlands and other countries](image)

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></td>
<td>Dutch</td>
<td>other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OII</td>
<td>36</td>
<td>13</td>
<td>10</td>
<td>3</td>
<td>6</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>ORM</td>
<td>25</td>
<td>22</td>
<td>15</td>
<td>-</td>
<td>8</td>
<td>4</td>
<td>74</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>63</td>
<td>36</td>
<td>21</td>
<td>3</td>
<td>14</td>
<td>12</td>
<td>153</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: “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 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 external review committee evaluated the PhD programme 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 eight full professors who were active in 2015 will retire, thus giving the opportunity to appoint highly qualified researchers with a focus on one of the two programmes. Due to budget restrictions the number of persons involved in research on university budget (1st source) had to be reduced slightly, despite the fact that both research priority areas receive a substantial grant from the UvA. Fortunately, the fte scientific personnel on grants (in particular 3rd source) increased.

- **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 has started a procedure for the allocation of new PhD positions for high quality projects which focus at the integration of fundamental and clinical science. This strategy will be continued further, concentrating on the two main research programmes.
  According to the PhD regulations of both universities the course programme will be 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.

**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

Program Leaders

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E.C.I. Veerman
G.H.W. Verrips
I. van der Waal
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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) focuses 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 health of the mouth 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 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

- Several novel machine learning and bioinformatics approaches to tackle “big data”-problems and to extract useful information from large data-sets were implemented. We developed “NGS-eval” a next generation sequencing error analysis and novel sequence variant detection tool, and used co-regularized spectral clustering to get insights in how oral microbial network function.

- The molecular biology of oral microorganisms as well as model systems for several oral infections and in vitro analyses of health promoting microbial activity were further studied, developed and exploited. It was shown that supplementation with arginine serves a health-promoting function; it enhances oral microcosm resilience towards acidification and suppresses outgrowth of the opportunistic pathogen Candida. Arginine facilitates stability of oral microbial communities and prevents them from becoming cariogenic.

- Also other preventive strategies were studied in model systems; a novel tea polyphenol-modified calcium phosphate nanoparticle and its remineralization potential were studied and importantly it was shown that biofilm layers affect the treatment outcomes of NaF and Nano-hydroxyapatite.

- We were able to get a better understanding of how (in vitro) phenotypic differentiation towards commensal and pathogenic oral biofilms progresses and showed in mixed biofilms that the pathogen Enterococcus faecalis benefits from a calcium hydroxide challenge. These insights were translated to treatment protocols and we were able to show that a modified salt solution prevents regrowth in dental root canals and can eliminate persistent bacteria. We obtained a better insight in the mechanisms of fluoride-resistance in oral pathogens by functional genome analyses of Streptococcus mutans and showed that, in vitro Streptococcus oligofermentans can inhibits Streptococcus mutans both neutral pH and cariogenic conditions.

- We showed that systemic Staphylococcus aureus infections are mediated by Candida albicans hyphal invasion of mucosal tissue.

- During the past couple of years, we have studied the role of tooth-associated fibroblasts in the formation of osteoclasts. These cells were cultured from teeth from healthy subjects and from periodontitis patients, either or not after infections with periodontal pathogens. We have summarized the role of periodontal ligament fibroblasts in osteoclast formation.
• Monocytes that enter the periodontium have to make the decision whether they differentiate toward macrophages – beneficial for clearing an infection – or towards osteoclasts, the bone-degrading cells that are mobilized during periodontitis. We described that under defined circumstances, osteoclastogenesis insensitivity can be induced, that is overcome in the presence and on bone surfaces.
• A recurrent problem in dental practice is peri-implantitis, an inflammatory condition that causes implant loosening. Knowledge on the characteristics of multinucleated giant cells, the cell type that surrounds implants is needed in order to be able to interfere with this process. It turned out that multinucleated giant cells are capable to lyse calcium-phosphate.
• Virtual teeth with and without tooth pathology have been developed for use in a virtual learning environment in dental education to evaluate the appearance of these virtual teeth for use in dental education and to compare them with contemporary educational models, such as plastic teeth and extracted human teeth. The results show that the appearance of the virtual teeth was considered more realistic than the appearance of the plastic teeth. The expectation is that the learning opportunities of the virtual teeth are better than of the plastic teeth.

Clinical studies
• The oral (microbial) ecology of the healthy oral cavity as well as several oral diseases and preventive strategies were studied by combining expert clinical evaluations and next-generation-sequencing microbial profiling techniques. We determined the long-term effect of antibiotic administration on the human normal oral and intestinal microbiota and found that the same exposure leads to two radically different responses in these human ecosystems. The oral ecosystem is remarkably resilient, whereas there are long-term (sometimes up to a year) microbial shifts in the gut.
• We established the inter-individual variation, correlations, and sex-related differences in the salivary biochemistry of young healthy adults.
• In a randomized controlled clinical trial, the effect of fixed orthodontic appliances and fluoride mouthwash on the oral microbiome of adolescents was studied. We concluded that, when provided proper oral hygiene is maintained, changes in the oral microbiome composition resulting from orthodontic treatment are minimal and do not negatively affect oral health. We fine-tuned our methodologies by evaluating the effect of propidium monoazide treatment on the measured bacterial composition of clinical samples (after the use of a mouthwash).
• We also studied the methicillin-resistant Staphylococcus aureus carriage rate among Italian dental students.
• Multi-disciplinary studies within Top Institute Food and Nutrition (TIFN studies) were performed in 2014 and 2015. These showed among 268 systemically healthy young adults interindividual variations, correlations, and sex-related differences in the salivary biochemistry. In addition, correlations between two different methods to score gingival bleeding and the relationship with dental plaque were evaluated. Probing to the bottom of the gingival pockets resulted in significantly more bleeding than running a probe along the gingival margin; this knowledge is important for future clinical trials for which now robust data is available to make the right choice for bleeding indexes.
• For and based on the different consensus meetings invited by the National Center for Dental Hygiene Research & Practice, the International Academy of Periodontology and the European Federation of Periodontology papers were written regarding using the best evidence to enhance dental hygiene decision making. Meta reviews for plaque control-home remedies practiced in developing countries, efficacy of homecare regimens for mechanical tooth cleaning in general and inter-dental tooth cleaning for plaque removal in managing gingivitis were conducted. In this line also mouthwashes were evaluated; the results of which were translated into patient brochures.
• Several papers based on clinical trials and systematic reviews were published in the scope of prevention of gingival and periodontal and peri-implant diseases. These include, the effect of CPC mouthrinses, CHX gels/mouthrinses, SLS containing dentifrices and the influence of mechanical instruments on the biocompatibility of titanium dental implants surfaces.
• We continued our collaborations with the Bandung University in various projects. In one study we tested vitamin C/calcium threonate/citrus flavonoids supplementations in a cohort of well documented periodontally diseased tea plantation workers. The results showed reductions of CRP, HbA1c and after such supplementation, indicating that a healthy diet may be helpful in fortifying host responses to with stand progression of periodontal disease.
• Several projects were related to the link between periodontitis and systemic diseases, (cardiovascular diseases and diabetes). To better understand why there is a lack of interdisciplinary care for patients, we
collaborated with the Slotervaart Hospital, and found that there is a great lack of unconscious willingness to exchange patient data between dentists and internists. Each professional is too much focused within their own professional world, but patients could much more benefit from proper interdisciplinary exchange for better oral and metabolic health. Using the ACTA Axium database year a study was initiated to establish the association between periodontitis and cardiovascular diseases in the Netherlands.

- There was a continuation of genetic studies in periodontitis: based on pleitropy we found the gene PLASMINOGEN to be associated with both CVD and periodontitis. In a functional study it was shown that certain genotypes for the ANRIL gene were associated with blood plasma levels of CRP. The implications are not clear but give more weight to the associations of periodontist and CVD.

- Previous mathematical modeling of periodontitis, was in this report year continued with modeling of peri-implantitis. Also for peri-implantitis it can be concluded that this is a complex condition with non-linear characteristics.

- Seven research projects of the section Social Dentistry have been conducted of which three concern intensive international collaborative projects.

- Existing extensive network of national and international cooperation in research has been expanded in 2015. Three foreign guest workers were welcomed: England (48 months), Brazil (12 months) and China (24 months).

- The project Research Agenda Oral health was launched in 2015. This project is focused on designing a national research agenda through collaboration with practitioners in the oral health and dental care field.

- In 2015 the ORA-STEM/H-OME study was started, with the goal 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. In total 50 autologous and allogeneic stem cell transplant patients are now being followed for a period of 12-18 months after stem cell transplantations.

- Systemic diseases and their treatment could lead to consequences for conditions in oral region and vice versa. An user friendly clinical quality tool for the dental professional has been developed and tested, in which data from relevant literature regarding systemic diseases and their oral manifestations can be disclosed. The tool has been validated.

- A clinical guideline on the need for antibiotic prophylaxis during dental treatment in patients having orthopedic implants has been developed; this will be a concerted action with dental associations and orthopedic associations.

- Patient centered adverse events to cancer treatment were studied in a multicenter design including sepsis, graft versus host disease and stomatitis. The first-line topical treatment for oral mucosal cGVHD was predominantly steroids (91.7 %), and the second preferred treatment was tacrolimus (41.7 %). The preferred treatment for hyposalivation was pilocarpine (41.7 %). The recommended frequency of oral cancer screening varied; half of the providers suggest a follow-up every 6 months.

- The epidemiology of head and neck squamous cell carcinoma in The Netherlands during the era of HPV-related oropharyngeal squamous cell carcinoma was evaluated. The study does not appear to support that HPV is the main contributor to a rising incidence of OPSCC as the effects of changes in smoking and alcohol use cannot be discounted.

- Sepsis in head and neck cancer patients treated with chemotherapy and radiation was studied in the literature and a consensus meeting. The paper contains seven clusters of statements about the clinical definition and management of infections and sepsis in head and neck cancer patients, which had a consensus. Furthermore, it offers a review of recent literature in these topics.

- Clinical studies investigating optimal root canal fillings and techniques are ongoing. Significantly less porosity was observed in root canals filled with the single cone technique compared to lateral compaction. Root fillings made by a single-cone technique with epoxy or methacrylate-based sealers were as effective in sealing the root canal as a cold lateral technique with epoxy sealers. The bond strength of calcium silicate cements in root canals is differentially influenced by the irrigation protocol and time. Disinfection of the infected root canal system is a crucial step in root canal treatments. Different aspects of irrigation with hypochlorite have been investigated in order to improve the cleaning of the root canal. A dissertation on this subject was successfully defended. As a result of this study an innovative irrigation solution was patented. This will be subject for future research.

- Continuing our program on family functioning and dental caries we further investigated the role of the family factors determining the amount of dental caries of children. Better organization of the family, positive involvement, encouragement were positively related to better oral health but the relationship between coercion and dental caries was inverse. The expectation that overweight and caries would be
related as both may be determined by an inadequate diet was not confirmed. The findings strongly suggest that preventive programs addressing family functioning may contribute to effective dissemination of the preventive message to prevent dental caries.

- In an in situ study it was shown that hesperidin significantly protects the dentin collagen matrix against degradation.
- Early detection of caries is important for prevention of large lesions and possibilities to restore with non-invasive manners. Unfortunately, two fluorescence-based intraoral devices (Soprolife and Diagnodent) did not contribute to a better detection of early carious lesions, than conventional inspection.
- Based on a relative simple and reproducible histological feature, adenoid cystic carcinomas of the salivary glands can be identified with a relatively poor prognosis.
- Based on miRNA profiling in saliva, benign and malignant tumors of the salivary glands can be identified.
- A prognostic model for patients with head-and-neck squamous cell carcinoma was validated, by which, based upon HPV status, co-morbidity and nodal status groups with relatively favorable, intermediate and poor prognosis are identified.

### Academic personnel in 2015 and 2016

**Research staff ACTA – OII (Oral Infections and Inflammation)**

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### Senior lecturers

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### Other lecturers and tenured research staff

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### Total tenured staff

Total: 17.80

### Non tenured staff

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### PhD students

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**Total non tenured staff** 14,15 18,55

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**Total 2nd funding** 0,70 0,65 2

**Total 3rd funding** 11,25 13,85 3

**Total research staff** 31,95 35,80

### Output

#### Dissertations


Scientific publications (refereed)
Chan, A., Cameron, M.C., Garden, B., Boers-Doets, C.B., Schindler, K., Epstein, J.B., Choi, J., Beamer, L., Roeland, E., Russi, E.G., Bensadoun, R.J., Teo, Y.L., Chan, R.J., Shih, V., Bryce, J., Raber-Durlacher, J., Gerber,


microvascular free flap reconstruction. Medicina Oral Patologia Oral y Cirugia Bucal, 20 (6), e744-e750. doi: 10.4317/medoral.20657


Scientific publications (non-refereed)


**Professional publications**


Publications for the general public

Patents

Grants: current projects with external funding
Bolscher, J.G.M. (2015). Co-investigator of research project on 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).
Crielaard, W. 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, Jiya Li. Collaborators: ACTA, the Netherlands; Saarland University, Germany (2014, November 01, 2016, November 01).
Research, Cargill, GlaxoSmithKline, TNO, WUR & ACTA (total investment 5.2 M€): (2012, January 01 - 2016, January 01).


Ten Cate, J.M., Crielaard, W., de Soet, J.J., van Loveren, C., van der Veen, M.H. & Volgenant, C.M.C. (2015). Seeing is believing. STW project; granted € 500.000: (2010, October 01 - 2016, October 01).

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**Indicators of Esteem**

**Scientific awards/honours**


**Memberships editorial board**

Aartman, I.H.A.: European Journal of Dental Education.

Bloemena, E.: ISRN Gastroenterology.
Organization of (inter)national scientific congresses and symposia


Invited speakers at (inter)national scientific congresses or symposia


De Vries, T.J. (2015, November 30). ACVR1 mutant periodontal ligament fibroblasts and their role in osteogenesis and osteoclastogenesis. Leiden, the Netherlands, International Lorentz Workshop.


Krom, B.P. (2015, November 01). 6e. Fungi in the oral cavity. Colgate Young expert workshop on biofilm models in oral health and disease. ACTA, Amsterdam, the Netherlands.


Loos, B.G. (2015, March 27). Een gezonde mond is goed voor de cardiovasculaire patiënt. Soestduinen, the Netherlands, Voorjaarscongres Vereniging van Orthodontisten,


Loos, B.G. (2015, October 14). Immunobiology of the healthy periodontium. Antalya, Turkey, Symposium Resilience: a new oral health concept beyond the absence of disease, the 47th Meeting Continental European Divison (CED, 6e International Association for Dental Research (IADR).

Loos, B.G. (2015, June 03). Key factors in the aetiology of peri-implantitis. London, United Kingdom, European Federation of Periodontology (EFP), EuroPerio VIII.
Loos, B.G. (2015, August 29). Oral disease and the need for public health approaches. Shanghai, China, Better gum health, better oral health, Philips Sonicare Advisory Board Meeting on China consensus on gingival health review meeting.

Loos, B.G. (2015, March 21). Oral infections are risk factors for general health. School of Dental Medicine University of Zagreb, Croatia, 1st International Congress.


Van der Veen, M.H. (2015, October 01). 6e. From plaque to biofilm. Colgate Young expert workshop on biofilm models in oral health and disease. ACTA, Amsterdam, the Netherlands.


Van der Waal, I. (2015, October 22). Odontogenic cysts; an overview with emphasis on the histological aspects. Gent, Belgium, Belgische Pathologen Week.


Zaura, E. (2015, November 01). The role of the microbiome in health. ACTA, Amsterdam, the Netherlands, Colgate Young expert workshop on Biofilm models in oral health and disease.

Other (inter)national scientific functions
Brand, H.S.: President-Elect - Salivary Research Group, International Association of Dental Research (IADR).
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.
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.
De Soet, J.J.: Treasurer - Stichting Orale Biologie.
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.
Laine, M.L.: Member - Decentralized selection of dentals students committee ACTA.
Laine, M.L.: Member - Doctoral Education Committee ACTA (DECA).
Laine, M.L.: Corresponding member - Finnish Dental Society Appolonia.
Laine, M.L.: Member - MSc-Peridontology exam commission, C. Delatola, ACTA.
Laine, M.L.: Member - Structure committee section Periodontology ACTA.
Loos, B.G.: Member scientific committee - 47th Meeting Continental European Division (CED), International Association for Dental Research (IADR), October 14-17, Antalya, Turkey.
Loos, B.G.: Board member - International Association for Dental Research (IADR), Continental European Division (CED).
Loos, B.G.: Opponent - PhD thesis: Periodontitis and rheumatoid arthritis; a search for causality and role of Porphyromonas gingivalis. M. de Smit, Faculty of Medicine, Dept. of Dentistry and Oral Care, Rijksuniversiteit Groningen, the Netherlands, 4 November 2015.
Loos, B.G.: Member - IADR Young Investigator Awards Committee.
Loos, B.G.: Board member Society for the Advancement of Natural Sciences, Medicine and Surgery, University of Amsterdam, the Netherlands.
Slot, D.E.: Member - Global Dental Hygiene Advisory board.
Slot, D.E.: Member lustrum commissie 2016 - Nederlandse Vereniging voor Parodontologie (NVvP).
Slot, D.E.: Member commissie richtlijn parodontale behandeling in de algemene praktijk - Nederlandse Vereniging voor Parodontologie (NVvP).
Slot, D.E.: Member congres commissie - Nederlandse Vereniging voor Parodontologie (NVvP).
Van der Veen, M.H.: Honorary lecturer - University of Liverpool, UK.
Van der Veen, M.H.: Secretary general - European Organization for Caries Research (ORCA).
Van der Waal, I.: Peer reviewer - Cancer Research UK; Peer review request on A phase III randomised trial of Lugol's Iodine in surgical management of epithelial dysplasia in the oral cavity and oropharynx.
Van der Waal, S.V.: Member scientific committee - Nederlandse Vereniging voor Endodontologie (NVvE).
Van der Weijden, G.A.: Member - Benoemingscommissie KIMO.
Van der Weijden, G.A.: Board member - Nederlandse Vereniging voor Parodontologie (NVvP).
Van der Weijden, G.A.: Member stuurgroep 2, kamer mondzorg - NMT & ACTA.
Van der Weijden, G.A.: Chairman commissie richtlijn Peri-Implantitis - NVOI/NVvP.
Van Diermen, D.E.: Chair - Special Interest Group Medically Complex Patients, Association Dental Education Europe, since August 2014.
Van Loveren, C.: Member advisory board - Sugar Bureau UK.
Van Loveren, C.: Member advisory board - Tooth Friendly Society.
Zaura, E.: Visiting professor - Oral Microbiology and Preventive Dentistry, Faculty of Medicine, University of Latvia, Riga, Latvia.

Supervisor of an external PhD student

Collaborations
- ACHMEA BV NL, B Egberts, EU H2020 ADVOCATE project partner.
- Aridhia Informatics Ltd UK, R. Bryce, K. O’Hanlon, EU H2020 ADVOCATE project partner.
- Ben Gurion University of the Negev, Beer Sheva, Israel, Dr. M. Meijler.
- Brigham and Womens’s Hospital, Harvard University, Boston. MA, USA Professor S.T. Sonis and Dr. N.S. Treister.
- Carolinas Medical Center, Dept. of Oral Medicine, Michael Brennan.
- Catharina Ziekenhuis, Eindhoven, the Netherlands. Department of Oral and Maxillofacial Surgery: Pijpe J.
- Cedars-Sinai Medical Center, Los Angeles, CA, Professor J.B. Epstein.
- Center for Advanced Research in Public Health, Valencia, Spain, Dr. Alex Mira.
- Centre for Integrative Bioinformatics (IBIVU), VU Amsterdam, Prof. J. Heringa, Dr. S. Abeln.
- Cipto Mangukusumo Hospital, Jakarta, Republic of Indonesia.
- DeCare Dental Insurance Ireland IE, M Walsh, EU H2020 ADVOCATE project partner.
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- Department of Laboratory Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden.
- Department of Microbial Diseases, UCL Eastman Dental Institute, London, United Kingdom.
- Department of Otorhinolaryngology, VUmc
- Department of Pathology, VUmc
- Department of Periodontology, Endodontology and Cariology, University of Basel, Basel, Switzerland.
- Division of Otolaryngology and Head and Neck Surgery, City of Hope, Duarte, CA, USA, Joel B Epstein.
- Faculty of Archeology, Leiden University, Drs. K.A. Ziesemer, prof.dr. Corinne Hofman.
- Genetics and Genomic Medicine Programme, UCL Institute of Child Health, London, United Kingdom.
- Glasgow Dental School, School of Medicine, College of Medicine, Veterinary and Life Sciences, University of Glasgow, United Kingdom.
- Harvard University Brigham and Women’s Hospital, Boston MA, USA Dept. of Oral Medicine Stephen Sonis.
- Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy, Paolo Bossi.
- Helperby Therapeutics Limited, London, United Kingdom.
- Keele University, UK, Neal Maskrey, EU H2020 ADVOCATE project partner.
- Kindertandheelkundepraktijk Bambodino, Rotterdam, the Netherlands, Gambon DL.
- Kobenhavns Universitet DK, Dental School, Prof L. Cristensen, EU H2020 ADVOCATE project partner.
- Malmö University, Sweden, Faculty of Health and Society, Biomedical Sciences: Sotres J. Faculty of Odontology, Prosthetic Dentistry: Lindh L, Arnebrandt T.
- Massachusetts General Hospital/Harvard University, Dept. of OMFS.
- Molecular Cell Physiology, FALW, VU, Dr. Wilfred Röling.
- National Institutes of Health Washington DC.
- NHS England UK, C Bridgeman, EU H2020 ADVOCATE project partner.
- Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands. Department of Oral and Maxillofacial Surgery: Gilijamse M.
- Radboud UMC, Radboud University Nijmegen, Professor N.M.A. Blijlevens and Professor M.C.D.N.J.M. Huysmans.
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- Research Group Microbiology and Systems Biology, TNO Earth, Life and Social Sciences, Zeist, The Netherlands.
- School of Stomatology, Sun Yat Sen University, Guangzhou, China, Prof. Wei X.
- Semmelweis Egyetem Hu, Dental School, Prof M Madlena, EU H2020 ADVOCATE project partner.
- SpectrumK GmbH DE, J Bentz, EU H2020 ADVOCATE project partner.
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- Universitat International Catalunya, Barcelona, Spain.
- Universiteit Zurich, MKG.
- University College Cork, National University Of Ireland, CORK IE, Dental School, Prof N Woods, EU H2020 ADVOCATE project partner.
- University Of Leeds, UK, Dental school, Prof H Whelton, Prof G Douglas, EU H2020 ADVOCATE project partner.
- University of Maryland Dental School, Baltimore, USA, Dr. M.A. Jabra-Rizk.
- University of Nagasaki, Japan, Dr. Y. Iijima.
- University of Washington Medical Center, Seattle. Dept. of OMSF.
- VU University Medical Center, Amsterdam, the Netherlands, Department of Oral and Maxillofacial Surgery/Oral Pathology: Baart JA, Ruslin M, Wolff J, Boffano P, Forouzanfar T, Karagözoglu KH.
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- Catharina Ziekenhuis, Eindhoven, the Netherlands, Department of Oral and Maxillofacial Surgery: Pijpe J.
- Clinic for Carolinas Health Care System Charlotte, North Carolina, USA Professor Michael Brennan
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- College of Dentistry, New York University, USA, Richard Niederman
- Common Wealth University, Virginia, Prof.dr. H.A. Schenkein
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- Department of Paediatric Dentistry, Faculty of Dentistry, Near East University, Nicosia, Cyprus.
- Department of Periodontics, School of Dentistry, University of Missouri-Kansas City, USA, Charles Cobb
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- Erasmus Medisch Centrum, Dr. M. van Zelm
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- Health Science Research Center, Indiana University-Purdue University, Fort Wayne, IN, USA, Mark Putt
- Interleukin Genetics, USA: Prof.dr. K. Kornman
- J. Sotres, L. Lindh, T. Arnebrant. Biomedical Sciences, Faculty of Health and Society, Malmö University, Malmö, Sweden.
- Khon Kaen University, Thailand, Dept. of Oral Diagnosis. P. Chiayarit, and S. Taweewachaisupapong.
- Kindertandheelkundepraktijk Bambodino, Rotterdam, the Netherlands, Gambon DL.
- M. Zourob. Department of Chemistry, Alfaisal University, Al Zahrawi Street, Al Maather, Al Takhaussusi Road, Riyadh 11533, Kingdom of Saudi Arabia.
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- Oral Diagnostic Sciences University of Adelaide, Adelaide Australia Professor Richard Logan
- Prof.dr. Yvette van Kooyk. Dept. Molecular Cell Biology and Immunology, VU Medical Center.
- Radboud University Medical Center Prof.dr. W.H. van Palenstein Helderman and Prof.dr Nicole Blijlevens
- T. van Werven. Department of Farm Animal Health, Faculty of Veterinary Medicine, Utrecht University, Utrecht, 3584 CL, the Netherlands; University Farm Animal Practice, 3481 LZ Harmelen, the Netherlands.
- The Netherlands Organization for Applied Scientific Research (TNO), Zeist, the Netherlands MSB Group: Imangaliyev S, Tsivtsivadse E.
- Tigran, Malmö, Sweden, U. Lundgren
- TNO, Zeist, Dr. E. Tsivtsivadze and Prof.dr.ir. B.J.F. Keijser, Preventive dentistry, ACTA-TNO Zeist
- Université François Rabelais, France, Pathologies Respiratoires: protéolyse et aérosolthérapie, F. Lecaille.
- 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 Amsterdam, Core facility Cellular Imaging / LCAM-AMC. J. Stap.
- University of Bandung, Indonesia, Amaliya
- University of Bonn, Dept. of Periodontology, Prof.dr. S. Jepsen
- University of Cairo, Oral Medicine and Periodontology Department- Faculty of Dentistry- Egypt Karim M. Fawzy El-Sayed
- University of California Los Angeles, USA, School of Dentistry and Dental Research Institute. D.T.W. Wong.
- University of Gothenburg Sweden Professor Inger von Bültzingslöwen
- University of Kiel, Germany, Dept. of Gastro-Enterology, 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 Wageningen, The Netherlands, Dr. S. Boesveldt
Current PhD projects


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 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 on 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.

I. Societal relevance for the dental professional in the Netherlands

Courses organized for Dutch dental and medical professionals


**Brand, H.S.** Acute Medical Situations in the dental office. 4 September 2015. Post graduate school, ACTA, Amsterdam.

**Brand, H.S.** Acute Medische Situaties in de Tandartspraktijk. 6 November 2015. PAOT-cursus, Maastricht.

**Brand, H.S.** Acute Medical Situations in the dental office. 2 December 2015. Department of orthodontics, ACTA, Amsterdam.

**Teeuw, W.J.** Verwijzersavond. Moderator. Periodontic Clinic, ACTA, Amsterdam, the Netherlands, 14 October 2015.

**Van der Waal, I.** Mondpathologie. Een nascholingscursus voor KNO-artsen en dermatologen. Amsterdam, 6 February 2015.


**Van der Waal, I. & Schulten, E.A.J.M.** Nascholingscursus voor kaakchirurgen en pathologen. 3 en 4 September 2015, Amsterdam.


**Van Strijp, A.J.P.** Wortelcariës en droge mond.QP Mondhygiëne; QP dag Mondzorg voor ouderen, 6 March.


Lectures given during courses for Dutch dental and medical professionals

A large number of lectures were given during courses for dentists, medical specialists and oral hygienists in the Netherlands by the following scientists:

**Bizzarro, S.** Diabetes mellitus en mondgezondheid Iqual. KNMT, Arnhem, the Netherlands, 11 November 2015, Gilze, the Netherlands, 2 November 2015, Zwolle, the Netherlands, 29 October 2015.

**Bloemena, E.** Cyto- en histopathologie van speekselkliertumoren; Mond- en Kaakziekten: een nascholingscursus voor kaakhirurgen en pathologen, 4-9-15, Trippenhuis, Amsterdam


**Crielaa rdd, W.** (13 & 20 June). Hygiëne en infectiepreventie: constant voortschrijdende inzichten. QP voor tandartsen.


**De Soet, J.J.** (29 May). Infectiepreventie richtlijnen binnen de mondzorgpraktijk; boeien of boeiend? QP voor mondhygiënisten.


**De Visscher, J.G.A.M.** Herkennen van relevante afwijkingen in en rond de mond. Tandartsen en mondhygiënisten. 11 December 2015, Amsterdam


**Krom, B.** (29 May). Biofilms in tandheelkunde; vriend en vijand! QP voor mondhygiënisten.

**Krom, B.** (13 & 20 June). Biofilms in tandheelkunde; vriend en vijand! QP voor tandartsen.

**Laheij, A.M.G.A.** (29 May). Voorkomen van kruisbesmetting door het juist indelen en reinigen/desinfecteren van de praktijkruimtes. QP voor mondhygiënisten.


**Loos, B.G.** Parodontologie – Implantaat verlies – Peri-implantitis Masterclass Implantology, ACTA Dental Education, Amsterdam, the Netherlands, 15 April 2015.

**Loos, B.G.** Een gezonde mond is goed voor de cardiovasculaire patiënt, NVvP-Philips Symposium De link tussen algemene gezondheid en parodontitis, Rijksmuseum, Amsterdam, the Netherlands, 13 March 2015.

**Loos, B.G.** Een gezonde mond in een gezond lichaam. Rotterdamse Tandartsen Vereniging, Rotterdam, the Netherlands, 16 November 2015.

**Rademacher, W.M.H.** Veilig werken in de tandheelkunde praktijk. QP, 28-01-15.


**Teeuw, W.J.** Mondzondheid & Diabetes mellitus. Regionale Organisatie Huisartsen Amsterdam, the Netherlands, 19 August 2015, 3 and 13 September 2015.
Organization of congresses and symposia for professionals in the Netherlands


Invited speakers at professional congresses or symposia in the Netherlands

Bizzarro, S. (2015, November 27). Het effect van de behandeling van parodontitis zonder en met antibiotica; nieuwe inzichten. Ede, the Netherlands, NVvP congres Up to date, Cinemec.


Danser, M.M. (2015, February 06). Microbiologie wat weten we en wat kunnen we ermee? Amsterdam, the Netherlands, ANT congress.


Teeuw, W.J. (2015, November 18). Diabetes en mondgezondheid. Hilversum, the Netherlands, Webinar KNMT.
Van der Weijden, G.A. (2015, March 06). De kracht en zwakte van het parodontium. Amsterdam, the Netherlands, Paro 2015, RAI.

Professional functions in the Netherlands

Bloemena, E.: Chair - Comité Bij- en Nascholing NVVP.
Bloemena, E.: Member - Committee Kwaliteit en Beroepsuitoefening NVVP.
Bloemena, E.: Member - Committee richtlijn Hoofd Hals Kanker.
Bloemena, E.: Board member - NVVP.
Bloemena, E.: Chair - Wetenschappelijke Raad PALGRA.
Brand, H.S.: Member - Ondernemingsraad ACTA, start: 1 July.
De Soet, J.J.: Lid - KNMT commissie Richtlijn infectiepreventie voor mondzorgpraktijken, KNMT Nieuwegein.
Gorter, R.C.: Vervangend lid Algemene Interfacultaire Ethische Commissie - UvA.
Laheij, A.M.G.A.: Lid KNMT Commissie OnderzoeksBegeleiding - KNMT Nieuwegein.
Rosema, N.A.M.: Lid beoordelingscommissie KRM - Kwaliteitsregister Mondhygiënisten, Nieuwegein, the Netherlands.
Rozema, F.R.: Member - Ad Hoc Committee, Toewijzingopleidingscapaciteit MKA, NVMKA.
Rozema, F.R.: Chair - Consilium Chirurgicum Oris.
Van Bruchem-Laheij, A.M.G.A.: Member - Commissie onderzoeksbegeleiding KNMT.
Van Bruchem-Laheij, A.M.G.A.: Member - Commissie Richtlijn infectiepreventie voor mondzorgpraktijken KNMT.
Van der Heijden, G.J.M.G.: Visiting Fellowship - NYU.
Van der Weijden, G.A. & Slot, D.E.: Redactie - Folder mondspoelmiddelen NVvP.
Volgenant, C.M.C.: Lid - KNMT commissie Richtlijn infectiepreventie voor mondzorgpraktijken, KNMT Nieuwegein.

II. Societal relevance for the dental professional internationally

Professional functions internationally

Brand, H.S.: Co-opted member - Association of Basic Science Teachers in Dentistry.
Brand, H.S.: President-Elect - Salivary Research Group, International Association of Dental Research (IADR).


Elkerbout, T.A.: Member - Dental project in orphanages, Jinotepe, Nicaragua, 16-20 November.


Raber-Durlacher, J.E.: Active member - EORTC Quality of Life Group.

Raber-Durlacher, J.E.: Leadership - Mucositis Study Group MASSC/ISOO.

Rozema, F.R.: Chair - IT advisory committee IAOMS.

Van der Heijden, G.J.M.G.: Visiting fellowship NYU.

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


Invited speakers at international professional congresses or symposia


Slot, D.E. (2015, November 07). Dental implants; how should they be cleaned by the DCP and their owner? Sydney, Australia, DHAA.


III. Contacts with the general public

Interactions with the press and the general public


Van der Veen, M.H. (2015). Poetslessen Hou je mond gezond i.s.m. het ivoren kruis op 20 basisscholen.


Inaugural lectures professorship


Impact of the research on the general public or professionals


Oral and Maxillofacial Surgery AMC. Three standards have been drawn up for the Dutch association for Oral and Maxillofacial Surgery (Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie, NVMKA).

Oral and Maxillofacial Surgery VUmc. The guidelines for diagnosis and treatment of patients have been adopted by the Dutch association for Oral and Maxillofacial Surgery (Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie, NVMKA).

Preventive Dentistry. Patients referred to the cariology clinic by their dentist are seen and advised.
Oral Regenerative Medicine

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E.A.J.M. Schulten  P.F. van der Stelt  D.B. Tuinzing

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 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 main objectives of ORM-related research are the degenerating/degenerated oral tissues and an improved ability to replace or regenerate these tissues, thereby restoring oral function and thus 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

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 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.
A project focused 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 one-off implants for the specific bone volume in the individual patient.

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 being harmless are now found to evoke an immunological response. Since the use of implant material 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 e.g. 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 sensitization of the host. Systemic effects are largely not yet investigated but do include allergic skin rash. It is of utmost importance to develop safe biomaterials and implants for oral regenerative medicine. For this topic scientists with different background join 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 questionable adverse events to dental materials. Currently the skin patch 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 as 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 tissues wished for, such as bone and cartilage. Insight in the interaction between implanted material either being of biological non-biological origin and the surrounding tissues is of crucial importance for the understanding how the host 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 in contrast to skin heals rapidly and with almost scar free healing. 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 is 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 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 secondary cause of this bone loss is infection. The primary cause of peri-implant bone loss can be overloading, immunological response to the implant material.

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). Six 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.
- Additive manufacturing is the process of joining materials to create objects from digital 3-dimensional (3D) model data, which is a promising technology in oral and maxillofacial surgery. We reviewed two of the current and emerging modalities for reconstruction of oral and maxillofacial bone defects, namely human maxillary sinus floor elevation as a valid model to test bone tissue engineering approaches enabling the application of 1-step surgical procedures and seeding of Good Manufacturing Practice-level adipose stem cells on computer-aided manufactured scaffolds to reconstruct large bone defects in a 2-step surgical procedure, in which cells are expanded ex vivo and seeded on resorbable scaffolds before implantation. The potential of tissue engineered constructs designed for the repair of large oral and maxillofacial bone defects in load-bearing situations in a 1-step surgical procedure combining these 2 innovative approaches is particularly emphasized.
- Polypyrrole (PPy) is a conducting polymer that enables controlled drug release upon electrical stimulation. We characterized the biocompatibility of PPy with human primary osteoblasts, and the effect of dopants. Conducting polymers doped with dodecylbenzenesulfonate are well tolerated by osteoblasts. Our results could provide a basis for the development of novel orthopaedic or dental implants with controlled release of antibiotics and pharmaceuticals that fight infections or focally enhance bone formation in a tightly controlled manner.
- Biomimetic coatings to increase endothelialisation 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 antithrombotic additives, such a nitric oxide donors, to a stable protein coating might lead to successful endothelialisation of a material’s surface. We showed that sodium nitrite-collagen conjugate coating with 25-50 μM sodium nitrite on silicone tubes increases the number of endothelial cells attached and inhibits platelet adhesion suggesting that this coating is highly promising for use in blood-contacting parts of biomedical devices.
- Surface modification by functional groups promotes endothelialisation in biohybrid artificial lungs, but whether it affects endothelial cell stability under fluid shear stress, and the release of anti-thrombotic factors, e.g. nitric oxide (NO), is unknown. We found that silicone-surface modification of blood-contacting parts of artificial lungs with carboxyl and amine, but not peroxide-groups followed by collagen immobilization allows the formation of a stable functional endothelial cell layer. Amine-group-modification seems undesirable since it affected silicone’s physical properties.
• Two of the current and emerging modalities for reconstruction of oral and maxillofacial bone defects were investigated, namely human maxillary sinus floor elevation as a valid model to test bone tissue-engineering approaches enabling the application of 1-step surgical procedures and seeding of Good Manufacturing Practice-level adipose stem cells on computer-aided manufactured scaffolds to reconstruct large bone defects in a 2-step surgical procedure, in which cells are expanded ex vivo and seeded on resorbable scaffolds before implantation. Furthermore, imaging-guided tissue-engineering technologies to predetermine the surgical location and to facilitate the manufacturing of custom-made implants that meet the specific patient's demands were discussed. The potential of tissue-engineered constructs designed for the repair of large oral and maxillofacial bone defects in load-bearing situations in a 1-step surgical procedure combining these 2 innovative approaches was particularly emphasized.

• The indications, results and complications of patients with cranio and maxillofacial defects treated with porous polyethylene (Medpor®) implants were investigated. The main reason for implant surgery was post-traumatic functional impairment. Most implants were placed at the mandibular angle and the orbital floor. Unsatisfactory appearance scored the highest in postoperative complications (10.1%) followed by infection rate (7.2%).

• In a multi-disciplinary team a customizable ear model was developed for 3D printing of ear implants. The results demonstrated that the parametric standard model could be used as a feasible method to generate custom implants based on existing ear images.

3D printing and biomimetic coating - CAD/CAM

• A study on the precision of intraoral scanners using different software packages and different clinical parameters used in operative dentistry showed that the are several clinical circumstances that influence the clinical outcome.

• Two studies on the adoption of digital technologies by dental practitioners in the Netherlands showed that there are many barriers to overcome before digital technologies will be accepted for use in the general dental practice. These factors are based on the individual dentists interest, trust in digital systems, behaviour of colleagues and friends, as well as economic factors.

• A series of CAD/CAM materials were investigated with the focus on the influence of restoration thickness, strength of the total restoration.

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

Tissue response of the host

• Experimental studies on the release of nickel and palladium from dental appliances and clinical studies on potential side effects of this type of appliances.

• A study on the use of CBCT scanners for the transfer accuracy of guided surgery systems in dental implant surgery showed that different systems have different levels of accuracy and that when trusting on surgical guides when following an non-invasive flapless protocol one has to be aware of these limitations. We are now focussing our attention to various possible calibration approaches.

• A novel immune competent gingiva equivalent model (reconstructed gingiva epithelium with integrated Langerhans Cells on a fibroblast populated lamina propria) has been developed to investigate inflammatory responses caused by contact sensitizers and irritants including medical device metals in vitro. It was found that initial innate tissue and dendritic cells responses to chemicals are clearly very different to those occurring in skin.

• Our epidermal equivalent assay for identifying and labelling sensitizers is undergoing world-wide validation in an international multi-centre study.

• A number of in vitro assays developed to identify sensitizers from non-sensitizers have been used to investigate potential adverse effects of metals and leachables released from dental implants.

Biological response to loading

• Research on the use of 4 reduced diameter implants (1.8-2.4 mm) supporting an over denture in the lower jaw showed encouraging results when evaluating patients quality of life. The results are comparable to more invasive approaches with normal diameter implants leading to more predictable treatment options for patients with limited bone volume.

• Aging reduces bone mass as well as the anabolic response of bone to mechanical stimuli, resulting in osteopenia. Endoplasmic reticulum (ER) stress impairs the response of myogenic cells to anabolic stimuli, and is involved in sarcopenia, but whether ER stress also contributes to osteopenia is unknown. We found
that the expression of several ER stress markers was higher in osteocytes from bones of old compared to adult mice. Since ER stress altered the response of osteocytes to mechanical loading, it could be a novel factor contributing to osteopenia. Anabolic resistance reflects the inability of skeletal muscle to maintain protein mass by appropriate stimulation of protein synthesis. We hypothesized that ER stress contributes to anabolic resistance in skeletal muscle with aging, but we found that ER stress is probably not involved in anabolic resistance in skeletal muscle with aging.

- Insulin-like growth factor 1 (IGF-1) and interleukin 6 (IL-6) play an important role in the adaptation of both muscle and bone to mechanical stimuli. We have provided an overview of the functions of IL-6 and IGF-1 in bone and muscle metabolism, and the intracellular pathways that are well known to mediate these functions.

- Generalized osteoporosis is common in patients with inflammatory diseases, possibly because of circulating inflammatory factors that affect osteoblast and osteoclast formation and activity. We found that CXCL8 and CCL20 did not decrease osteoblast proliferation or gene expression of matrix proteins. CXCL8 and CCL20 did not directly affect osteoclastogenesis. However, CXCL8 and CCL20 enhanced osteoblast-mediated osteoclastogenesis, partly via IL-6 production, suggesting that CXCL8 and CCL20 may contribute to osteoporosis in rheumatoid arthritis by affecting bone cell communication.

- Multiple factors contribute to bone loss in inflammatory diseases such as rheumatoid arthritis (RA), but circulating factors and immobilization play a crucial role. Mechanical loading prevents bone loss in the general population, but the effects of mechanical loading in patients with RA are less clear. We found that RA serum containing inflammatory factors, did not alter the intrinsic capacity of osteocytes to sense mechanical stimuli, but upregulated osteocyte-to-osteoclast communication. Mechanical loading nullified this upregulation, suggesting that mechanical stimuli could contribute to the prevention of osteoporosis in inflammatory disease.

- There is considerable variation in the shape of osteocyte lacunae, which is likely to influence the function of osteocytes as the professional mechanosensors of bone. We have discussed how mechanical loading could affect the shape of osteocyte lacunae, and how the shape of osteocytes could influence their mechanosensation. Altered lacunar morphology has been associated with bone pathology. It is important to know whether osteocyte shape is part of the etiology.

- Adaptation of bone to mechanical stresses normally produces a bone architecture that combines a proper resistance against failure with a minimal use of material. This adaptive response is governed by mechanosensitive osteocytes. We have discussed current insights on how osteocytes perceive mechanical stimuli placed on whole bones. Particular emphasis is placed on the role of estrogen in signaling pathway activation by mechanical stimuli, and on computer simulation with cell biology to unravel biological processes contributing to bone strength.

Response of oral mucosa to injury

- Tissue engineered skin and mucosa equivalents have been established from TERT immortalized cell lines and validated against the primary cell counterparts. The models consist of reconstructed epithelium on a fibroblast populated dermis or lamina propria. Inflammatory responses during wound healing and scar formation were investigated. Preliminary experiments have been performed to introduce oral healthy and pathogenic biofilm onto these organotypic mucosa equivalents.

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

Pain, trauma and dysfunction

- The long-term research line on the management of orofacial pain and temporomandibular disorders results in a continuous number of scientific papers on this topic. Among these studies, a large-scale epidemiological study was published with prevalence data of temporomandibular pain in the Dutch population. Research of the heritability of temporomandibular disorders showed that genetic factors are partly responsible for the development of temporomandibular pain.

- Studies on the recognition of pain in persons with impaired cognition (like people with dementia or Down syndrome) are ongoing. For example, an international roadmap was published sketching the development of a multidisciplinary pain observation tool.

- In a series of experimental and clinical studies, a positive association between mastication and cognition was found. These results may have important consequences for daily care of elderly persons.

- Several studies on bruxism have contributed to an improved insight into the pathophysiology, diagnosis, consequences, and management of sleep bruxism.
A series of articles describes the outcomes of studies on various aspects of tooth wear. For example, a longitudinal study showed that a recently developed tooth wear grading scale is sensitive enough to monitor the progress of tooth wear over time.

Ongoing studies on the different types of cartilage in the temporomandibular joint aim to explain the clinical observation that condylar cartilage is more vulnerable for remodelling than the cartilage of the disc and fossa. The role of mechanical loading in this process is being studied as well.

A review of published studies of the last 30 years on traumatology showed that in American, African and Asian studies road traffic crashes were the predominant cause. In European studies the aetiology varied, with assaults and road traffic crashes being the most important factors. In Oceania assaults were the most important.

We found that measurements of the height of the ramus on orthopantomographic (OPT) images cannot be relied on as an absolute indication for surgical intervention in patients with mandibular condyle fracture.

### Academic personnel in 2015 and 2016

#### Research staff ACTA – ORM Oral Regenerative Medicine

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 | Zamani, dds. Y. | pm | pm | guest
 | Zande, MSc. M.M. van der | 0,30 | 0,30 | 1
Total non tenured staff | | | | 28,40 25,40
Total 1st funding | | | | 18,60 18,65 1
Total 2nd funding | | | | 4,25 2,60 2
Total 3rd funding | | | | 16,00 14,80 3
Total research staff | | | | 38,85 36,05

Output

Dissertations


Scientific publications (refereed)


71


Scientific publications (non refereed)


Annual Research Report 2015


Professional publications


Patents

Grants: current projects with external funding


Scherder, E.J.A. & Lobbezoo, F. (2015). 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,--; NutsOHRA, RCOAK, SBOH, Henriëtte Hofje as sources for the funding of three PhD projects (NutsOHRA €150.000,--; RCOAK €160.000,--; Henriëtte Hofje €40.000,--; Alzheimer Nederland €30.000,--; total = €380.000,--; (2012, January 01 - 2017, December 31).

Scherder, E.J.A. & Lobbezoo, F. (2015). Pijn bij volwassenen met een verstandelijke beperking. F. Lobbezoo responsible for the dental part of this project which equals approx. 1/4 of the total amount granted €3.750,--; NutsOHRA, Fonds Verstandelijk Beperkten and Innovatiefonds as sources of funding for one PhD project (NutsOHRA, €150.000,--; Fonds Verstandelijk Gehandicapten €15.000,--; Innovatiefonds €50.000,--; Total €215.000,--; (2010, January 01 - 2015, December 31).


Indicators of Esteem

Editorship book


Memberships editorial board

Aarab, G.: Journal of Dental Sleep Medicine.
Bakker, A.D.: Odontology.
Everts, V.: The Open Bone Journal.
Everts, V.: The Open Enzyme Inhibition Journal.
Feilzer, A.J.: Odontology.
Forouzanfar, T.: Journal of Surgical Case Reports.
Forouzanfar, T.: Triple R.
Goené, R.J.: Journal of Implant and Reconstructive Dentistry.
Lobbezoo, F.: Journal of Craniodental Function.
Lobbezoo, F.: Journal of Dental Sleep Medicine.
Van Calcar, N.P.: DeTandartspraktijk.
Scientific awards/honours


Organization of (international) scientific congresses and symposia


Invited speakers at (inter)national congresses or symposia


Gibbs, S. (2015, November 07). Understanding the mechanistic differences between sensitization and irritation with the aid of tissue engineered skin models. Natal, Brazil, Congress of Toxicology for Developing Countries.


Koutris, M. (2015, June 05). Pijn, neurofysiologie, hoofdpijn, neuropathie, etc. Amsterdam, the Netherlands, Endo Leergang 2014-2015, ACTA.


Koutris, M. (2015, September 26). Sleep and orofacial pain. Amsterdam, the Netherlands, Closed Meeting of the EACD.


Lobbezoo, F. (2015, April 17). Defining and grading of sleep bruxism. Amsterdam, the Netherlands, Academic Advisory Board Meeting Grindcare/Sunstar.

Lobbezoo, F. (2015, September 25). Dental Sleep Medicine – Overview. Amsterdam, the Netherlands, EACD.


Visscher, C.M. (2015, September 25). Diagnostics of temporomandibular disorders. Amsterdam, the Netherlands, Closed meeting EACD.

Wetselaar, P. (2015, September 26). Sleep disorders and their associations with tooth wear. Amsterdam, the Netherlands, Closed Meeting EACD.


Other (inter)national scientific functions

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

Bakker, A.D.: Reviewer project proposal - Croatian Science Foundation.

Bakker, A.D.: Board member - Dutch Society for Calcium and Bone Metabolism.

Bakker, A.D.: Chair training committee - European Calcified Tissue Society.

Bakker, A.D.: Chair new investigators committee - European Calcified Tissue Society.

Bakker, A.D.: Co-chair new investigator committee - European Calcified Tissue Society.

Bakker, A.D.: Board member - European Calcified Tissue Society.

Bakker, A.D.: Reviewer - FWO grant applications, Belgium.

Bakker, A.D.: Member scientific program committee - Herbert Fleisch workshop II.


Everts, V.: Visiting professor - Chulalongkorn University, Bangkok,

Everts, V.: Member and principal investigator - NIRM.

Gibbs, S.: Member - European Research Group for Experimental Contact Dermatitis (ERGECED).

Gibbs, S.: Reviewer - Gingerelll Alfred Research Austria.

Gibbs, S.: Member and principal investigator - NIRM.

Gibbs, S.: Jury member - Project NC3Rs, London, UK.

Gibbs, S.: Jury member - Project STW.

Gibbs, S.: Reviewer - ZonMW.
Klein-Nulend, J.:  

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.:  
Member research assessment committee - Group Biomedical Sciences (Dept. Oral Health Sciences and Dept. Development and Regeneration), KU Leuven, Belgium.

Klein-Nulend, J.:  
Outer board member - Irish Research Council Postdoctoral International Assessment 2015 (Fellowships in Science, Engineering and Technology), Royal Irish Academy.

Klein-Nulend, J.:  
Founding member - Micro-mechanical Tissue Repair Society.

Klein-Nulend, J.:  
VICI-Assessment committee member - Organisation for Scientific Research (NWO). Domain: Life Sciences, Utrecht, the Netherlands.

Klein-Nulend, J.:  
External professor - San Carlos University, Dept. Physics, Cebu City, Philippines.

Koutris, M.:  
Chair research committee - European Academy of Craniomandibular Disorders (EACD), since 2011.

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.

Lobbezoo, F.:  

Lobbezoo, F.:  
Senior member - Society of Oral Physiology (Store Kro Club), since 2015.

Lobbezoo, F.:  
NYU Visiting Guest Faculty Recipient 2014-2015 - College of Dentistry, New York University, New York, NY, USA.

Sanderink, G.C.H.:  
Chairman - Trust Fund International Association of DentoMaxilloFacial Radiology.

Schulten, E.A.J.M.:  
Fellow - International Team for Implantology (ITI), Basel, Switzerland.

Tahmaseb, A.:  
Member - EAO consensus meeting Pfafficon Switzerland 14-02-2015.

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

Van Loon, J.J.W.A.:  

Van Loon, J.J.W.A.:  
Vote-selected member - Governing board member, American Society for Gravitational and Space Biology (ASGSB), period 2015-2018.

Van Loon, J.J.W.A.:  
External examiner - Limerick Institute of Technology. MSc. thesis from Adam Shinner: Microgravity induced phytohormones.

Wismeijer, D.:  
Member - EAO consensus meeting Pfafficon Switzerland 14-02-2015.

Zandieh Doulabi, B.:  
Visiting professor - Research Center for New Technologies in Life Sciences Engineering, University of Tehran, Iran.

Zandieh Doulabi, B.:  
Head Department Regenerative Medicine - Research Centre for New Technologies in Life Science Engineering, University of Tehran, Iran.

**Supervisor of an external PhD student**


**Wolff, J.** Supervisor of external PhD student Juha Koivisto with thesis: The application and performance of MOSFET radiation dosimeters - University of Tampere, University of Helsinki, Finland, 16 October 2015.
Collaborations

- Amsterdam University of Applied Sciences, prof. dr. R. Engelbert, Amsterdam, the Netherlands.
- Centre of Oral Rehabilitation, Norrköping, Sweden, Department of Orofacial Pain and Jaw Function, Faculty of Odontology, Malmö University, Sweden, Scandinavian Center for Orofacial Neurosciences, dr. P Larsson.
- Chulalongkorn University, Bangkok, Thailand, P. Pavasant.
- Cipto Mangukusumo Hospital, Jakarta, Republic of Indonesia.
- Department of Oral and Maxillofacial Surgery, University of Torino, Italy.
- Department of Orthopedics, VUmc.
- Department of Radiology, University of Helsinki, Finland.
- Ege University, Faculty of Medicine, Center for Brain Research & Department of Physiology, prof.dr. K. Türker, Bornova, Izmir, Turkey.
- Massachusetts General Hospital/Harvard University, Dept. of OMFS.
- National Institutes of Health Washington DC.
- Radboud umc, IQ-healthcare, prof.dr. R. Nijhuis, Nijmegen, the Netherlands.
- Slotervaart General Hospital, Department of Clinical Neurophysiology and Brain Mapping Laboratory, dr. H.L. Hamburger, Amsterdam, the Netherlands.
- 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 A. Schuller, Leiden, the Netherlands.
- Universitat International Catalunya, Barcelona, Spain.
- Universiteit Zurich, MKG.
- University at Buffalo, Department of Oral Diagnostic Sciences, dr. R. Ohrbach, Buffalo (NY), USA.
- University Estadual Paulista (UNESP), Department of Dental Materials and Prosthodontics, prof.dr. Daniela Aparecida de Godoi Gonçalves and prof.dr. Cinara M. Camparis, Araraquara School of Dentistry, Araraquara, Brazil.
- University Medical Center (UMC) Utrecht and Radboudumc, IQ-healthcare, dr. CM Speksnijder, Nijmegen, the Netherlands.
- University of Aarhus, Department of Orofacial Pain and Jaw Function, prof. dr. Peter Svensson, Aarhus, Denmark.
- University of Helsinki, Department of Stomatognathic Physiology & Prosthetic Dentistry, dr. J. Ahlberg, Helsinki, Finland.
- University of Minnesota, Department of Diagnostic and Biological Sciences and Division of Epidemiology and Community Health, Minneapolis, Minnesota, USA, dr. Mike T John.
- University of Montreal. Faculty of Dentistry, prof.dr. Gilles Lavigne, Montreal, PQ, Canada.
- University of Padova, TMD Clinic, prof. dr. D. Manfredini, Padova, Italy.
- 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 Tokushima, E. Tanaka.
- University of Umea, Faculty of Medicine, department of Clinical Oral Physiology, prof. dr. A. Wännman, Umea, Sweden.
- University of Washington Medical Center, Seattle. Dept. of OMSF.
- 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.

Current PhD projects


Tio, start: 2012.


Societal impact

The societal impact of the programme is evident by, among others, the impact on patient care, interactions with the industry and other non-university groups, the impact on professionals, and relevant (inter-)national functions. The research program also contributes to the post-graduate training programs.

The research on overloading and pain of the musculoskeletal structures of the masticatory system has direct impact on the quality of diagnostic procedures and of patient care, and extends its influence towards an improvement of the (oral-) health-related quality of life. The implications of this research are not only important for general orofacial pain patient groups, but also for more vulnerable populations like those suffering from dementias and otherwise impaired cognitive abilities.

An ambitious future goal of the program is to improve health care and treatment of patients with juvenile idiopathic arthritis. Diagnosis of arthritis of the jaw joint is commonly missed by clinicians, eventually possibly leading to progressive pain and malfunctioning of the joint. Research started in 2012 is focused on learning the biological parameters of the three types of cartilage present in the jaw joint. Inflammation will be mimicked in vitro and it will be determined whether mechanical loading will lead to a decreased inflammation. Special focus is on orthodontic patients with cranio-facial deformities and/or related malocclusions. A program of quality of life related to this topic is carried out.

During the last couple of years it became clear that implanted materials like metals can have adverse effects like inflammation, irritation, allergy. The local and systemic effects of leachables from dental implants is now an important issue of investigation. The safety assessment (hazard identification) resulting from an improved understanding how dental implants influence the local and systemic environment will have an enormous impact on the society.

The development of physiologically relevant human models to replace or reduce the use of animals (3Rs) to investigate oral wound healing, healthy and pathogenic biofilm and adverse effects of dental materials has a huge societal and political impact in Europe.

The societal impact of the research on oral and maxillofacial radiology is focused on the improvement of diagnostic imaging procedures. This relates to not only technical parameters, but also other factors that influence the diagnostic performance of radio-diagnostic procedures, such as the effect of viewing conditions and observer characteristics. Part of the activities includes continuing education courses on the safe use of radiation in dental practice and application of digital imaging in dentistry.

Enamel fluorosis is an increasing aesthetic problem in several countries. The project on mechanism of enamel fluorosis adds to our understanding how these defects develop which will help to prevent these defects in future. The results of our research on bone adaptation and regeneration will offer multiple opportunities for the development of new therapeutic agents to prevent (inflammation-associated) unwanted clinical bone loss, thereby preventing among others mobility loss with aging.

The design of dental implants differs between brands and indication areas. On the other hand de design van also have an influence on the reaction of bone and soft tissue surrounding the dental implant. Research in this area can help develop redesign the implant abutment interface but also influence the success of the present generation of implants.

Research looking at a minimal invasive approach in the treatment of patients with over dentures using reduced diameter implants (1.8-2.4 mm in diameter) shows us that this approach opens new doors for the treatment of those patients that due to medical conditions or lack of bone volume were exempted from treatment.

After years of in vitro study on calcium Phosphate and absorbed BMPs in bone regeneration an ZonMw grant has been gained with which together with industry it is now possible to take the final step and fine tune the product to take it to the clinic. The research is now focussed on getting the CE registration for this product making it one of the first bioactive bone regenerative products allowed to be used in patient treatment.

3D printing crown and bridge work in composite resins or ceramic materials is a future approach on the production of prosthetics in dentistry. Together with industry we are involved with the devolvement of both 3D printing processes.

A novel approach in tooth replacement with dental implants is individually designing the implant based on the CBCT scan and the milling or printing it. The tooth root is then extracted and the individual implant is inserted into the alveolus. This approach is also part of a patent that ORM has acquired in which the individualisation of dental implant design tailored to the individual patient which is then printed in either titanium or a ceramic material including the individual drill guide and tooling. Using this approach there are a lot less limitations in shape or form of dental implants.
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


Berkhout, W.E.R. - Stralingshygiënisch Gekwalificeerd Beroepsbeoefenaar mbt CBCT, March; 11-26 June; 1-16 October.

Berkhout, W.E.R. Stralingshygiënisch Gekwalificeerd Beroepsbeoefenaar mbt CBCT, variant MKA, 5-19 June; 26 November; 4 December.

De Lange, J. QP MKA-chirurgie, Utrecht: 31/1 and 14/2.

De Lange, J. QP Edentate patiënt, Amsterdam: 28/11 and 12/12.


Dubois, L. MKA 3D dag, 12 December, 2015.


Wetselaar P. Organisatie en moderatie Quality Practice-assistenten Update dag, Utrecht, November 13, 2015


Lectures given during courses for Dutch dental and medical professionals

Aarab G. TMD-pijn: de rol van de mondhygiënist. QP Mondhygiëne, Amsterdam, the Netherlands, November 21, 2015.

Aarab, G. Een snurker in de stoel. QP Assistenten Update dag, Utrecht, the Netherlands, November 13, 2015.


Baart, J.A. Lokale anesthesie voor assisterenden VUmc/ACTA Amsterdam, 24-09-2015.


Baart, J.A. Tandletsel, Bussum, 30-10-2015.


Baart, J.A. Symptomen en syndromen, orthodontisten in opleiding. ACTA, 09-12-2015.


Baart, J.A. Pijn in het gebruik van pijnstillers. Nijmegen, the Netherlands, UMC Radboud PAOT. April 10, 2015


De Lange, J. Derde molaren en apexresecties; Indicatiestelling en behandeluitkomsten. Quality Practice Jaarbeurs Utrecht 31/1 and 14/2.


De Lange, J. Reconstructie van de edentate bovenkaak. Quality Practice, ACTA Amsterdam 28/11 and 12/12.

De Lange, J. Geïmpacteerde elementen; evidence based management? Voorjaarsvergadering NvVO 27/3.


Dubois, L. Innovaties in de traumatologie, VMTI studentencongres, ACTA Amsterdam, 12 June 2015.

Dubois, L. Traumatologie: face first!, Assistentendag St. Antonius ziekenhuis, Nieuwegein, 9 October 2015.

Dubois, L. NOMA, parodontitis extravaganza, NVMKA, Amersfoort, 6 November 2015.

Dubois, L. Computer assisted surgery, 3D dag, MKA 3D dag, AMC Amsterdam, 12 December.

Dubois, L. Intra-operatieve navigatie, MKA 3D dag, AMC Amsterdam, 12 December.

Dubois, L. Workshop navigatie, MKA 3D dag, AMC Amsterdam, 12 December.

Koutris M. Workshop Verschillende soorten orofaciale pijn, QP Assistenten Updatedag, Utrecht, the Netherlands, November 13, 2015.

Koutris M. Neuropathische pijn, QP Mondhygiëne, Amsterdam, the Netherlands, November 21, 2015.

Lobbezoo F. Wat is pijn? QP Mondhygiëne themadag Pijn: van bron tot brein, Amsterdam, November 21, 2015.


Rollman, A. Fysiotherapie in de tandheelkunde. QP Assistenten Update dag, ADE, Utrecht, the Netherlands, November 13, 2015.


Tahmaseb, A. Creating the virtual patient: how to integrate facial, optical and radiological imaging components. Amsterdam, the Netherlands, ADE course The edentulous patient, 26 September 2015.

Tahmaseb, A. ITI Cadaver Course, Rotterdam, the Netherlands, 21 January 2015.


Van Daelen, A.C.L. Person to person, klinische cursus implantologie chirurgie en prothetiek (live surgery), Tendens tandartsen, Amsterdam, samen met R. Goené. 24 January 2015.

Van Daelen, A.C.L. Person to person, klinische cursus implantologie chirurgie en prothetiek (live surgery), Tendens tandartsen, Amsterdam, samen met R. Goené. 21 March 2015.

Van Daelen, A.C.L. De bovenbouw, cursus NVOI, Haarlem samen met R. Goené en H. Meijer. 18 June 2015

Van Daelen, A.C.L. Person to person, klinische cursus implantologie chirurgie en prothetiek (live surgery), Tendens tandartsen, Amsterdam, samen met R. Goené. 20 June 2015.


Van Daelen, A.C.L. Person to person, klinische cursus implantologie chirurgie en prothetiek (live surgery), Tendens tandartsen, Amsterdam, samen met R. Goené. 28 November 2015.

Van Daelen, A.C.L. Hands-on cursus, Delft: Immediat tandvervanging in de esthetische zone. 2 December 2015.


Van Loon, J.J.W.A. Sensing changes of the gravitational load (from cells to organisms and beyond): Technical and physiological aspects of plant life in space. Amsterdam, the Netherlands, VU, college@Extreme Biology course. November 27, 2015.

Visscher, CM. Mondgewoonten – is dat erg? QP Mondhygiëne, Amsterdam, the Netherlands, June 27, 2015.

Visscher CM. Hoofdpijn. QP Mondhygiëne, Amsterdam, the Netherlands, November 21, 2015.


Wismeijer, D. QP lezing Periimplantitis A surgical approach, 6 March 2015.


Wismeijer, D. Toekomstverwachtingen in de orale implantologie. QP dag Een implantaat de oplossing voor elk diasteem? 21 March 2015.


Wismeijer, D. Game Changers in de Tandheelkunde. KNMT studenten congres, 2 October 2015.

Wismeijer, D. Niet meer weg te denken 3D/Bot. KVPA Lustrum congress It’s showtime!, 16 October 2015.

Wismeijer, D. Implantaten en de edentate patiënt. ADE course The edentulous patient, 12-13 November 2015.

Organization of congresses and symposia for professionals in the Netherlands


Invited speakers at professional congresses or symposia in the Netherlands


Aarab, G. (2015, December 11). Associaties van bruxisme met slaapapneu en andere slaapstoornissen. Ermelo, the Netherlands, Jaarcongres NVGPT.


Lobbezoo, F. (2015, March 18). DC/TMD expandend. Amsterdam, the Netherlands, Sectie Tandarts-Gnatholoog, NVGPT.


Schulten, E.A.J.M. (2015, June 12). De geatrofieerde edentate kaak: nog niet het einde. Amsterdam, the Netherlands, Symposium voor Tandprothetici i.s.m. Straumann Nederland. ACTA.


Vischer, C.M. (2015, November 07). 1. Inleiding TMD diagnostiek. 2. Workshop Diagnostiek. 3. Workshop Oefentherapie. Amsterdam, the Netherlands, Symposium TMD-doedag voor fysiotherapeuten, ADE.


Professional functions in the Netherlands

Baart, J.A.: 
Member redactieraad - Geneesmiddelenbulletin.

Baart, J.A.: 
Board member - Nederlandse Vereniging van Tandartsen.

Baart, J.A.: 
Chair - WTA.

Becking, A.G.: 
Lid - Centrale Opleidingscommissie, Kennemer Gasthuis, Haarlem.

Becking, A.G.: 
Lid - Commissie onderzoek en aanbeveling NVMKA.

Becking, A.G.: 
Lid - Concilium Chirurgicum Oris (CCO).

Becking, A.G.: 
Lid - Implementatie commissie competentietijgericht opleiden MKA, Nederlandse Vereniging voor Mondzieken, Kaak- en Aangezichtschirurgie (NVMKA).

Becking, A.G.: 
Voorzitter - Maatschap MKA Kennemerland.

Becking, A.G.: 
Medisch manager - MKA, Kennemer Gasthuis, Haarlem.

Becking, A.G.: 
Opleider - Perifere deelopleiding MKA, Kennemer Gasthuis, Haarlem.

Berkhout, W.E.R.: 
Member - Collège van Opleiders Stralingsopleidingen 2013-.

Berkhout, W.E.R.: 
Advisor - KNMT inzake praktijkrichtlijn Radiologie 2015-.

Berkhout, W.E.R.: 
Member - Raad van Commissarissen Nederlands Tijdschrift voor Tandheelkunde 2013-.

Berkhout, W.E.R.: 
Coördinerend stralingsdeskundige - VU ACTA Amsterdam 2013-.

De Lange, J.: 
Lid - Capaciteitsorgaan.

De Lange, J.: 
Lid - COK.

De Lange, J.: 
Lid - Concilium Chirurgicum Oris (CCO).

De Lange, J.: 
Voorzitter - CTS.

De Lange, J.: 
Bestuurslid (inkomend voorzitter) - NVMKA.

Disse, M.A.: 
Dutch representative (member) - Efosa.

Disse, M.A.: 
Member - The Amsterdam Cleft Lip and Palate team, location VUmc/ACTA.

Dubois, L.: 
Secretaris - Bridge the Gap Foundation.

Dubois, L.: 
Lid - Protocollen aangezichtsletsel NVMA.

Dubois, L.: 
Lid - Richtlijncommissie spoedoperaties, Nederlandse Vereniging voor Heelkunde en Kwaliteitsinstituut Medisch Specialisten.

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.

Lobbezoo, F.: 
Plaatsvervangend lid - Universitaire Onderzoekscommissie (UOC), Universiteit van Amsterdam, since 2013.

Prahl, C.: 
Board member - Stichting ter bevordering van de orthodontie.

Van Daelen, A.C.L.: 
Mondonderzoeker - Centrale klachtencommissie KNMT.

Van Daelen, A.C.L.: 
Member visitatiecommissie tandarts-implantoloog - NVOI.

Van Daelen, A.C.L.: 
Member opleidingscommissie - NVVRT (opleiding Restauratief tandarts).

Van der Kaaij, N.C.W.: 
Member - Schisisteam Erasmus MC Sophia kinderziekenhuis.

Van der Stelt, P.F.: 
Director - Nederlands Tijdschrift voor Tandheelkunde BV, Houten 2005-.
Van der Stelt, P.F.: Chair - Stichting Bevordering Tandheelkundige Kennis, Houten 2005-.
Wismeijer, D.: Visitaator - NVOI praktijk visitaties herregistratie.

II. Societal relevance for the dental professional internationally

Professional functions internationally
Becking, A.G.: Visiting surgeon - CIPTO Mangukusomo Hospital, Jakarta, Indonesia.
Becking, A.G.: Visiting Professor - Universitat International Catalunya, Spain.
De Lange, J.: Faculty member - AOCMF.
De Lange, J.: Faculty member - SORG.
Wismeijer, D.: Board member responsible for training and education - International Team for Implantology (ITI).
Wismeijer, D.: Chair - Training and Education committee International Team for Implantology (ITI).

Invited speakers at international professional congresses or symposia
Becking, A.G. (2015, October 26). Computer-assisted planning and surgery, the basics. Melbourne, Australia, SORG pre-conference course on Patients specific solutions, ICAMS.
De Lange, J. (2015, September 26). Bimaxillary protrusion osteotomy for treatment of obstructive sleep-apnea. Amsterdam, the Netherlands, EACD, ACTA.
Dubois, L. (2015, October 26). New technological developments to raise the predictability of orbital reconstruction. Melbourne, Australia, SORG preconference course ICAMS.
III. Contacts with the general public

Interactions with the press and the general public


Inaugural lectures


Impact of the research on the general public or professionals

Oral and Maxillofacial Surgery VUmc. The guidelines for diagnosis and treatment of patients have been adopted by the Dutch association for Oral and Maxillofacial Surgery (Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie, NVMKA).


Van der Stelt, P.F. Lead-author Praktijkrichtlijn Tandheelkundige Radiologie, KNMT.


Functions in public committees


Hoogeveen, R.C.: Chair - ANVS, werkgroep herziening Eindtermen stralingshygiëne tandheelkunde en CBCT April-December.
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 within the curriculum, research on new teaching methods, such as the Objective Structured Clinical Examination (OSCE), development and evaluation of a computer aided digital teaching system creating a virtual learning environment including the application of haptics (the Simodont Dental Trainer), the development of virtual teeth and jaws and comparison with biomedical education elsewhere in Europe.

The input of academic personnel is limited to staff of the educational institute, and to some members of the various departments. The research should not be considered as a separate programme; however it is intended that this research will increase in the coming years.

Results
In 2015 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 in a dental trainer is essential for good performance. Also the availability of sound seemed to have a positive effect on the appreciation and performance of students though further research is needed to confirm this. 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. Inter and intra observer reliability in reality as well as virtual reality are rather poor, further research aims to find ways to improve the reliability of assessments.

Academic personnel in 2015 and 2016

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>fte 2015</th>
<th>plan 2016</th>
<th>funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff members education institute</td>
<td>Vervoorn, dr. J.M.</td>
<td>0,10</td>
<td>0,10</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Wesselink, prof.dr. P.R.</td>
<td>pm</td>
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Output
Scientific publications (refereed)

Professional publications

Indicators of Esteem

Grants: current projects with external funding

Memberships editorial board
Gorter, R.C.: European Journal of Dental Education.

Invited speakers at (inter)national congresses or symposia
Vervoorn, J.M. (2015, August 11). Benefits of virtual training for all stakeholders in the educational process. Kuta, Indonesia, South East Asia Association for Dental Education (SEAADE) 11-14 August.

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.
Vervoorn, J.M.: Chair - Simodont Users Meeting.

Collaborations
- MOOG inc. Development of the Simodont dental trainer.
- 3M – Development of real scans into virtual reality application.
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. This involves in particular the research on a computer aided digital learning environment (the Simodont dental trainer).

I. Societal relevance for the dental professional in the Netherlands
Courses organized for Dutch dental and medical professionals

Invited speakers at “professional” congresses or symposia in the Netherlands
Bakker, D.R. (2015, March 18). The ACTA experience, how ACTA uses the Simodont. Alkmaar, the Netherlands, DSSH.

Professional functions in the Netherlands
Gorter, R.C.: Vervangend lid Algemene Interfacultaire Ethische Commissie - UvA.

II. Societal relevance for the dental professional internationally
Professional functions internationally
Serrano, C.: Assistent professor - Dentistry School - Universidad de Concepcion Chile.
## Appendix 2015

List of SCI journals, their impact factors and the number of ACTA publications in 2015 in each journal.

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