## 1. Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Preface</td>
<td>6</td>
</tr>
<tr>
<td>3. Description of AIMMS</td>
<td>7</td>
</tr>
<tr>
<td>3.1 Background</td>
<td>7</td>
</tr>
<tr>
<td>3.2 Mission</td>
<td>7</td>
</tr>
<tr>
<td>3.3 Aims and objectives</td>
<td>7</td>
</tr>
<tr>
<td>4. Structure of AIMMS</td>
<td>8</td>
</tr>
<tr>
<td>4.1 Research groups and related institutes</td>
<td>8</td>
</tr>
<tr>
<td>4.2 Research programmes and interactions</td>
<td>8</td>
</tr>
<tr>
<td>4.3 AIMMS activities</td>
<td>8</td>
</tr>
<tr>
<td>4.4 Key facilities and infrastructure</td>
<td>10</td>
</tr>
<tr>
<td>4.5 Management and governance</td>
<td>10</td>
</tr>
<tr>
<td>5. SWOT</td>
<td>12</td>
</tr>
<tr>
<td>6. News</td>
<td>13</td>
</tr>
<tr>
<td>7. International collaboration and funding</td>
<td>14</td>
</tr>
<tr>
<td>8. Input of AIMMS</td>
<td>15</td>
</tr>
<tr>
<td>9. Output of AIMMS</td>
<td>17</td>
</tr>
<tr>
<td>9.1 Scientific output &amp; quality</td>
<td>18</td>
</tr>
<tr>
<td>9.2 Indicators of esteem</td>
<td>20</td>
</tr>
<tr>
<td>9.3 Societal impact</td>
<td>22</td>
</tr>
<tr>
<td>10. Education &amp; Training</td>
<td>25</td>
</tr>
<tr>
<td>10.2 PhD Projects bridging sections</td>
<td>26</td>
</tr>
<tr>
<td>12. Appendices</td>
<td>27</td>
</tr>
<tr>
<td>12.1 Output AIMMS 2012</td>
<td>28</td>
</tr>
<tr>
<td>12.1.1 Theses</td>
<td>29</td>
</tr>
<tr>
<td>12.1.2 Scientific papers, refereed</td>
<td>30</td>
</tr>
<tr>
<td>12.1.3 Books</td>
<td>31</td>
</tr>
<tr>
<td>12.1.4 Book chapters</td>
<td>32</td>
</tr>
<tr>
<td>12.1.1 Theses</td>
<td>33</td>
</tr>
<tr>
<td>12.2 Input AIMMS 2012</td>
<td>34</td>
</tr>
<tr>
<td>12.3 Collaborations AIMMS</td>
<td>35</td>
</tr>
<tr>
<td>12.3.1 Academic collaborations</td>
<td>36</td>
</tr>
<tr>
<td>12.3.2 non-Academic collaborations</td>
<td>37</td>
</tr>
<tr>
<td>12.4 Valorisation</td>
<td>38</td>
</tr>
<tr>
<td>12.5 AIMMS Seminars and Lectures</td>
<td>39</td>
</tr>
</tbody>
</table>
It is my pleasure to present to you the second Annual Report of AIMMS, the Amsterdam Institute of Molecules, Medicines and Systems. This Annual Report first provides a brief overview of the mission, the structure and organization of the institute as well as an overview of its research programmes and research staff. The report also summarizes the input and output data of the institute as a whole and of separate research programmes.

The last decade has witnessed major breakthroughs in the fields of molecular, cellular and systems biology, but also in related enabling technologies. These innovations fuel a general excitement that a 'molecular up to systems' understanding of health and disease is within our reach.

This has lead to establishment of AIMMS, at April 1st 2010, in which fifteen of the best research groups in pharmaceutical, life, computational life and molecular sciences at the VU Campus joined forces.

By integrating these scientific disciplines, AIMMS focuses at the elucidation of molecular mechanisms of diseases and the development of novel and safer drugs, therapeutics (e.g. proteins, antibodies and other biologics) and diagnostics (e.g. molecular and translational biomarkers).

Since the start of AIMMS, much effort has been invested in structuring the institute and creating a scientific environment in which interactions between research groups from the constituting faculties (Exact and Earth & Life Sciences, resp. FEW and FAW) can interact and optimally exploit new opportunities for synergy. To stimulate this process, for example competitive grants for seven ‘AIMMS-bridging’ PhD-projects and MSc-students grants were initiated. Moreover, in 2012 significant investments were planned in new, common Chemical Biology facilities.

The number of theses and publications in high impact journals has risen again in 2012. And the external, i.e. non-university funding of AIMMS was consistently high at 8.0 M€, which is significantly higher than in 2010.

Obviously, the success of a research institute is very much dependent on the quality, the ambitions and the successes of its students, postdocs, staff and other co-workers. It is thanks to them all, that we can present to you this AIMMS Annual Report.

On behalf of the students, postdocs, staff and Management Team of AIMMS,

Prof. dr. Nico P.E. Vermeulen (Director)

2. Preface

Word from the director

Interestingly, in 2012 the Nobel price for Chemistry was provided to two American scientists, R. Lefkowitz and B. Kobilka, for their research on GPCRs, i.e. G-protein coupled receptors, receptors constituting a major target for drug discovery and development, and a core area of research of AIMMS.

Since the start of AIMMS, much effort has been invested in structuring the institute and creating a scientific environment in which interactions between research groups from the constituting faculties (Exact and Earth & Life Sciences, resp. FEW and FAW) can interact and optimally exploit new opportunities for synergy. To stimulate this process, for example competitive grants for seven ‘AIMMS-bridging’ PhD-projects and MSc-students grants were initiated. Moreover, in 2012 significant investments were planned in new, common Chemical Biology facilities.

The number of theses and publications in high impact journals has risen again in 2012. And the external, i.e. non-university funding of AIMMS was consistently high at 8.0 M€, which is significantly higher than in 2010.

Obviously, the success of a research institute is very much dependent on the quality, the ambitions and the successes of its students, postdocs, staff and other co-workers. It is thanks to them all, that we can present to you this AIMMS Annual Report.

On behalf of the students, postdocs, staff and Management Team of AIMMS,

Prof. dr. Nico P.E. Vermeulen (Director)

3. Description of AIMMS

3.1 Background

Today there is still an unmet societal need, and enormous scientific challenge, for innovative development of new drugs and therapeutic and diagnostic strategies. As a matter of fact, even with relatively well known diseases, current therapies are effective in only 40% of patient populations, while other diseases still lack effective therapies. The most successful organizations in health will be those that focus on a better understanding of the molecular mechanisms and the patho-physiology of diseases. This requires basic and integrated research from molecules up to the systems level. The research process should thus tackle both the biology and chemistry of disease mechanisms, targets and metabolic pathways in an integrated fashion.

The last decade has witnessed important breakthroughs in the fields of molecular and cellular biology, designer synthesis and chemical space, bio-analytical technologies and approaches, and in the understanding of the biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of the biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines. Combined with new perspectives to integrate and understand biological systems with the understanding of biological fate and effects of medicines.

3.2 Mission

The mission of AIMMS is to conduct excellent, basic molecular life sciences aiming at fundamental breakthroughs in translational molecular medicine, drawing on the integrated study of biological processes and systems that will lead to new drugs, diagnostics and treatments.

3.3 Aims and objectives

In accordance with its mission, AIMMS is contributing to the fundamental understanding of:

- Molecular and biochemical processes, i.e. from molecule to system;
- Discovery and validation of new targets and diagnostics (e.g., translational biomarkers and diagnostic tools) and molecular mechanisms of diseases.

AFS

The two Science faculties of VU (i.e. Exact and Earth & Life Science faculties) and the Science faculty of the UVA have decided to merge into one new faculty, the Amsterdam Faculty of Sciences (AFS). The preparations for the AFS started in 2012 and should lead to one, major new Amsterdam Faculty of Sciences (AFS) in 2015. AIMMS will be an integral part of the AFS.
4. Structure of AIMMS

4.1 Research groups and related institutes

In 2012, fifteen research groups from the FEW-Department of Chemistry & Pharmaceutical Sciences (CPS; Faculty of Sciences), the FALW-Department of Molecular Cell Biology (MCB, Faculty of Earth & Life Sciences) and the Institute for Integrative Bio-Informatics (IBI-VU, Department of Informatics) constituted AIMMS. The AIMMS research groups represent different key-scientific disciplines, namely Pharmaceutical - , Life -, Computational Life - and Molecular Sciences (Figure 4.1).

4.2 Research programmes and interactions

The research in AIMMS focuses on the fundamental understanding of biological processes from molecules up to systems. AIMMS integrates top-level chemical, biological, pharmaceutical, systems biology and related medical sciences at VU University. The research activities of AIMMS can be clustered around three inter-related main research programmes (see also Figure 4.2).

a) Molecular mechanisms of biological processes

This programme comprises research aiming at in-depth understanding of the molecules and biological processes relevant to life (in health and disease). Moreover, it includes more specifically disease target identification and validation by combined molecular and network-based research.

b) Design and characterization of molecules and medicines

Research towards the discovery, design, synthesis, analysis and characterization of novel drug and therapeutic candidates, typically being small organic molecules, peptides, proteins, antibodies and other biologics. This includes the disposition, safety and pharmacological effects of the drug and therapeutic candidates.

c) Biomarkers and diagnostics

This AIMMS research programme comprises the discovery of appropriate translational biomarkers and corresponding in vitro and in vivo molecular diagnostic tools to facilitate the elucidation of molecular mechanisms of selected diseases and dedicated (novel) drug and therapeutic candidates.

4.3 AIMMS Activities

Since the start of AIMMS in April 2010, the management team has arranged multiple activities to create a top-scientific environment and synergy through interactions between its scientists, e.g. by a) an Annual AIMMS Meeting, b) a competition for AIMMS grants for Bridging PhD-projects, c) small AIMMS grants for common MSc-projects, and d) AIMMS seminar- and lectures series.

a) The second AIMMS Annual Meeting at April 4th 2012.

Around 120 persons attended this day: PhD students, MSc students, postdocs and professors! Apart from lectures of external scientists (prof. Frans Russel/ Nijmegen dr. Carsten Hoffman/Würzburg, and dr. Eefjan Breukink/Utrecht) and final keynote speaker of the day was prof. Gijs Wuite/VU-Physics. Moreover, young AIMMS talent was selected (and awarded) in a PhD-oral communication competition and a lively and large poster session.

b) Competitive AIMMS grants for Bridging PhD-projects

In 2011 it was decided to actively stimulate mutual interactions between AIMMS research groups. Thus six competitive ‘bridging PhD-projects were selected which groups from the two faculties were involved (Table 10.2). Project selection was primarily based on external peer review to ensure scientific excellence, but complemented by strategic considerations. The funding was based on a 50% matching by the research groups, thus allowing more projects and ensuring full commitment to the projects. A seventh project was complementary funded by four research groups in order to optimize interaction and synergy between experimental and systems biology approaches in the pathophysiology of tumorigenesis. See section 10.2 for more details.

c) Small research grants

With small grants bridging MSc projects are stimulated and pre-work can be done for external fund raising.

d) AIMMS Seminar and Lectures

Research themes, progress and ideas are shared amongst AIMMS group members through bi-weekly seminars. These seminars are well visited and mostly two speakers present and discuss work of their group to the whole of AIMMS. AIMMS further supports Lectures from external guests and visitors (see Appendix 12.5).
4.4 Key-facilities and infrastructure

The focus of AIMMS is on top-quality basic and application-directed molecular life sciences research. State-of-the-art research facilities and technologies are indispensable for that purpose. Investments in the context of ongoing and new, externally granted projects have led to significant improvement of the research infrastructure in the key areas of AIMMS research. Figure 4.3 provides an overview of several of the research facilities and platforms. Examples of newly acquired grants for research facilities:

- Dr. L. Visschers et al: Amsterdam Laboratory for Computational Chemistry (350k €euro), SNS-Sector plan, NWO-Basis equipment (2011-2012). Four AIMMS sections involved.
- Medicinal Chemistry and Molecular Toxicology invested in 2011-2012 in an auto-ITC (250k €euro) which is an automated high-throughput ITC-instrument to investigate energy changes upon protein-ligand binding.
- In 2012, the Chemical Biology facilities of AIMMS have been upgraded and extended by substantial investments by AIMMS and several AIMMS research groups (100k €euro each). The combined investments in robotics and a multilabel reader enables automated pipetting on both 96 and 384 wells scale as well as multiple types of screening assays with multiple types of read-out (e.g. fluorescence, absorbance, luminescence, etc.). In 2013, the Chemical Biology Platform will become operational, with technical support financed by AIMMS, DDC, Medicinal Chemistry and Target & Systems Biochemistry. A web-based registration site is under construction. With these investments, AIMMS will improve the capacity and synergy within the institute and, importantly, facilitate collaborations with others, e.g. at VUmc, thus potentially leading to new research and grant opportunities.
- In 2012, AIMMS also continued investing in necessary workhorse equipment: for example, a new ultracentrifuge has been jointly bought by several AIMMS groups (5 groups involved, 80k €euro). The perspective of the new research building OJ2 stimulates stimulates AIMMS groups sharing equipment right now.

4.5 Management and governance

The management team consists of the scientific director (Professor Nico P.E. Vermeulen) and a managing director (Jacqueline E. van Muijlwijk-Koezen) and three programme managers who are opinion leaders and heads of the departments involved (Professor Holger Lill, Professor Romano V.A. Orru, and Professor Bas Teusink).

The scientific director and managing The scientific director (SD) and managing director (MD) are responsible for day-to-day management. The management team (MT) meets on a bi-weekly basis and takes amongst others responsibility for:
- Preparation of long-term and annual policy plans;
- Preparation of annual reports and standard protocol evaluations;
- Approval of research projects to be undertaken at the Institute;
- Deciding on further approval for projects that fail to meet the quality parameters.
- Developing strategies for identification of existing and new scientific talent, e.g. stimulate more effective grant applications;
- Developing more structured and more effective valorization strategies;
- Interactions with the Supervisory Board on short and long term developments and strategies.
- Interactions with the External Scientific Advisory Committee, e.g. for quality and longer term strategic issues.

In 2012, the MT has updated an ‘AIMMS Visions’ document in which the current outcome of three Taskforces on ‘Platforms and Key-facilities’, possible ‘crystallisation themes for research’, collaboration with other VU/VUmc IOZIs, and the new opportunities following integral housing of all AIMMS groups in the new OJ2 building at the VU Campus (planned for 2015) are indicated. This document is the basis for strategic discussions within AIMMS, for the MidTerm Review in 2013 and for new future directions.

Figure 4.3 AIMMS key facilities

Figure 4.4 Governance and management structure of AIMMS

Young talent

Around 120 persons attended this Annual Meeting. IC 159 was filled with PhD-students, MSc-students, post-docs and staff. They listened to excellent presentations of three external keynote lectures in the morning (Prof. Russel Nijmegen, Dr. Hoffman Wurzburg and Dr. Breukink, Utrecht) and the final end-of-the-day keynote speaker: Prof. Waite, FEW-Physics).

Next to the poster competition, with 35 posters, there was a PhD competition for oral contributions. Each of the 15 Chairs of AIMMS were asked to pose one PhD-student and six were ultimately selected by the AIMMS Management Team to present their results. The audience scored via iPads the six candidates and the result appeared to be so close that (exceptionally) two winners were identified: Jan Simon Boerma (Molecular Toxicology) and Ingeborg Petterson (BioMolecular Spectroscopy). Poster award winners were: Chinde Jansen (Medicinal Chemistry), Sabrina de Munnek (Target and Systems Biochemistry) and Johan van Heerden (Systems Bioinformatics).
5. SWOT Analysis

In order to further improve the performance of AIMMS as a research institute, a SWOT analysis has been made. It summarizes current strengths, opportunities, weaknesses and threats.

**Strengths**
- Vertical and horizontal integration of multiple scientific disciplines on the VU campus, i.e. Life, Pharmaceutical, Computational Life and Molecular Sciences, in one institute
- Coverage of scientific disciplines at molecular, cellular and translational stages of the development of novel drugs, therapeutics (incl. biologics) and molecular diagnostics, thus adding significant value to high-impact scientific and social topics
- Strong position within FEW and FALW and strong links with other organizations/institutes, both at and outside the VU Campus. This is promoting a dynamic research environment
- Excellent research facilities and several platforms
- Strong and well organized PhD-programme, partly in collaboration with related Research institutes (e.g. LACDR, HRSMC, etc)

**Opportunities**
- Altering R&D strategies in Life Sciences and Pharma industry offer new opportunities for academia-industry collaborations
- Realization of strategic alliance (s) and collaborations with VUMC, based on outcomes of taskforces
- Potentially strong position in H2LS-VU can be substantiated, both in research and in education
- Unique and leading position in research oriented MSc-programmes
- Room for improving European funding, both for research and for educational activities
- Relocation to the planned new Q2 building offers new opportunities to exploit intra-AIMMS collaborations and centralization of technology platforms

**Weaknesses**
- Innovation and valorization strategies for AIMMS are still to be developed. Currently primarily based on individual groups and group leaders
- Scouting and stimulation of scientific talent can be improved
- Uncertainties about (reducing) internal budgets
- Uncertainties related to reorganization of VU governance
- IQ2s have no formal nor integral control over finances.

**Threats**
- Uncertainties about (reducing) internal budgets
- Uncertainties related to reorganization of VU governance
- IQ2s have no formal nor integral control over finances.

6. News

Only a selection of AIMMS news in 2012 is provided. Grants and Awards are described in section 9.2. A complete list of AIMMS news items can be found on www.aimms.vu.nl.

**Bio-Computational Chemistry**

Matthias Bickelhaupt was appointed as extraordinary professor in Theoretical Organic Chemistry at the Institute of Molecular and Materials, Radboud University Nijmegen. He will join the Theoretical Chemistry research group of professor Gerrit Groenenboom and model complex molecular systems and materials.

The rectors of the VU University (VU) Amsterdam and the Universitat de Girona (UdG) have signed an agreement regarding the organization of joint doctoral activities in the area of Computational and Theoretical Chemistry that lead to a double degree: successful candidates obtain both a PhD at VU University and a PhD at UdG in Girona. The groups of the VU and UdG in Theoretical and Computational Chemistry have been collaborating for almost 20 years and they have now more than 50 papers published together that have been cited more than 800 times. In addition, there have been numerous exchanges of PhD students, postdocs, and permanent staff between the two groups. At this moment, the two groups are involved in a European IRSES project with the University of Guanajuato (Mexico) and this year they have applied together with other European groups for an International Thematic Network of the ERC.

**Bio-Organic Chemistry**

CHEM21: A 26.4 million Euro IMI-JU programme on “green pharmacy”. Traditional synthetic routes and methods no longer meet the current standards set to sustainable large scale production of complex medicinal compounds. This consortium develops and explores environmentally benign, chemical manufacturing methods for medicines, which are both energy and atom efficient and minimize the production of waste and spare resources.

**European Lead Factory**

ELF: A 196 million Euro IMI-JU programme on early drug discovery. The European Lead Factory is a novel pan-European platform for innovative drug discovery, with 30 partners from big Pharma, SMEs and academia.

**Structural Biology**

The FDA’s Anti-Infective Drugs Advisory Committee voted unanimously that bedaquiline is effective and recommended accelerated approval of the drug for the treatment of multidrug-resistant Mycobacterium tuberculosis. This diarylquinoline as a tuberculosis drug has been developed in collaboration with Dirk Bald and co-workers from the division of Structural Biology and is patented by Jansen Pharmaceutica (Johnson&Johnson).

**Synthetic Chemistry**

Chris Slootweg is in 2012-2013 visiting professor at Université Paul Sabatier, Toulouse, France. He is exploring his interests in main-group chemistry and organometallic chemistry with the aim of developing novel building blocks for the creation of functional materials and designed catalyst structures for sustainable chemistry.
7. International collaboration and funding

The interdisciplinary research represented in AIMMS provides a highly competitive environment. AIMMS positions its research carefully within internationally recognized networks, to make its research partners attractive. In this way our research groups are attractive partners in European consortia and proved successful in the last year in joining big EU-funding schemes.

At the on-set of AIMMS initiatives of the participating research groups were actively promoted to acquire EC-funded projects e.g. by EU-proposal training for senior scientists and by hiring professional support for the preparation of proposals. This has led to significant funding in 2012. Last year Molecular Toxicology, Medicinal Chemistry as well as Bio-organic Chemistry were successful in three different IMI-JU funded public-private consortia (MIP-DLI, 3SM, KIDD, 20M€ and CHEM21, 26 M€). In these IMI-programmes more then ten big Pharma companies and a range of SMEs and academic partners in Europe join forces. On top of that Bio-organic chemistry was successful in the largest pan-European public private partnership, ELF (196 M€), funded by IMI-JU on early drug discovery (see the highlight). Previously, Molecular Toxicology got two other IMI-JU projects funded.

Obviously, European funding is increasingly important for research in the fields of AIMMS. For that reason, in 2012 AIMMS has also been very active in creating and joining consortia for research applications in domains of Marie Curie ITNs, the last KP7 programme and IMI-JU calls. Moreover, AIMMS is preparing strategically for future applications in the context of the different Priorities in Horizon 2020.

On a National level, Biomolecular Analysis obtained major funding from TA-COAST (SPRING) and STW (HT-EDA), while Synthetic Chemistry received a NWO-TOP grant (for the 3rd time). Bio-computational Chemistry obtained two ASPASIA grants from now.

In appendix 12.3 the collaborations with academic groups and non-academic groups are listed.

EU - highlight - ELF

The European Lead Factory (ELF) is a novel pan-European platform for innovative drug discovery. This partnership, an international consortium of 30 partners, is the first of its kind. Six big Pharma companies (Bayer, J&J, Sanofi, UCB, Astra-Zeneca, Merck) join forces with a range of SMEs (e.g. Mercachem, Syncom, Edehis, Synapha, Taros etc) and academia. The ELF creates unprecedented opportunities for the discovery of new medicines by providing public partners with an industry-like discovery platform to translate cutting-edge academic research into high-quality drug lead molecules on a scale and speed that was not possible previously. The international consortium European Lead Factory receives a €196 million grant from the Innovative Medicines Initiative to enhance early drug discovery and address the ever-increasing need for innovative therapeutics to tackle unmet medical needs.

AIMMS is prominently represented in the ELF by Bio-organic Chemistry who will deliver diverse libraries of heterocycles and other natural product-like fragments with rather complex architectures to the consortium. These libraries are crucial to feed the biological activity screening process in early drug discovery.

8. Input of AIMMS

The university-based funding (1GS) is complemented by external support from non-profit (2GS), industry (3GS) and EU (4GS) funds. The aggregated external funding (2GS + 3GS + 4GS) has grown significantly from 2010 to 2012 (i.e. from 6.3 to 8.0 M€, Table 8.1).

The total research staff of AIMMS at the end of 2012 added up to 94 ‘research fte’, calculated according to the ‘definite- afspraken wetenschappelijk onderzoek’, april 2010, VSNU. Furthermore the VSNU standards for the different categories of research personnel (HOOP-gebieden) have been used to calculate the research effort (Table 8.2 green).

In Appendix 12.2 the detailed list of employees (research fte) in each job category and type of funding is depicted. Table 8.2 summarizes the total research fte in a breakdown per type of funding. Approximately 65% of the research fte’s of AIMMS in 2012 were externally funded.

Table 8.1 Acquisition of AIMMS per type of funding

<table>
<thead>
<tr>
<th>Type of Funding</th>
<th>2008* (€)</th>
<th>2010 (€)</th>
<th>2011 (€)</th>
<th>2012 (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>non profit support (2GS)</td>
<td>2,909,894</td>
<td>2,823,694</td>
<td>2,327,259</td>
<td></td>
</tr>
<tr>
<td>support from industry (3GS)**</td>
<td>1,894,279</td>
<td>3,522,538</td>
<td>2,821,554</td>
<td></td>
</tr>
<tr>
<td>EU projects (4GS)**</td>
<td>1,540,604</td>
<td>2,134,401</td>
<td>2,795,546</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>5,500,000</td>
<td>6,344,778</td>
<td>8,480,632</td>
<td>7,944,358</td>
</tr>
</tbody>
</table>

* 2008, benchmark as described in business plan AIMMS
** The Faculty of Sciences discriminates between non-personal EU projects and funding by industry, whereas the Faculty of Earth & Life Sciences counts both types of financial support as 3GS. The latter amount has been divided equally over 3- and 4GS and total amounts for the whole institute are depicted.
9. Output of AIMMS

9.1 Scientific output & quality

All research results generated within AIMMS, including those from collaborative EU- and industry projects, are published in the international scientific peer reviewed literature.

Next to that many groups publish in monographs, deliver chapters in relevant scientific books and, if appropriate, in public media.

Further, dissemination of important findings in the patents is highly stimulated. It is the ambition of AIMMS to increase both the quality and the quantity of the scientific publications by setting a standard of two publications per investigator per year in an international journal with an impact factor in the top 20% of his/her scientific domain.

Moreover, the number of PhD-students should increase up to an average of two per Principle Investigator.

Table 8.2 Research fte per type of funding for research AIMMS

<table>
<thead>
<tr>
<th>fte per type of funding for research AIMMS</th>
<th>2009*</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>direct funding (1GS)</td>
<td>38.00</td>
<td>55.05</td>
<td>51.94</td>
<td>37.14</td>
</tr>
<tr>
<td>non profit support (2GS)</td>
<td>52.56</td>
<td>29.89</td>
<td>29.43</td>
<td>29.06</td>
</tr>
<tr>
<td>support from industry (3GS) + EU projects (4GS)</td>
<td>52.92</td>
<td>34.58</td>
<td>30.35</td>
<td>27.52</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>143</td>
<td>120</td>
<td>112</td>
<td>94</td>
</tr>
</tbody>
</table>

* july 2009, bench mark as described in business plan AIMMS

Table 8.3 Total number of PhD students of AIMMS

<table>
<thead>
<tr>
<th>PhD students real fte*</th>
<th>2009 **</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>90</td>
<td>67</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>Started</td>
<td>-</td>
<td>12</td>
<td>16</td>
<td>19</td>
</tr>
</tbody>
</table>

* Total number of PhD students: both according to SEP and scholarship - PhD students
** july 2009, bench mark as described in business plan AIMMS

9. Output of AIMMS

9.1 Scientific output & quality

All research results generated within AIMMS, including those from collaborative EU- and industry projects, are published in the international scientific peer reviewed literature.

Next to that many groups publish in monographs, deliver chapters in relevant scientific books and, if appropriate, in public media.

Further, dissemination of important findings in the patents is highly stimulated. It is the ambition of AIMMS to increase both the quality and the quantity of the scientific publications by setting a standard of two publications per investigator per year in an international journal with an impact factor in the top 20% of his/her scientific domain.

Furthermore, the number of PhD-students should increase up to an average of two per Principle Investigator.

Table 9.1 Scientific output of AIMMS

<table>
<thead>
<tr>
<th>Scientific output AIMMS *</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theses</td>
<td>15</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Scientific papers, refereed</td>
<td>211</td>
<td>219</td>
<td>253</td>
</tr>
<tr>
<td>Books</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Book chapters</td>
<td>13</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>240</td>
<td>271</td>
<td>279</td>
</tr>
</tbody>
</table>

* Scientific papers, non refereed, and conference proceedings are not included
A pilot grant from Vertex Pharmaceuticals, San Diego, for the upscaling of a cellular metabolite production system based on E. Coli expressed with Cytochrome P450 BM3 mutants.

**Synthetic Chemistry**

NWO – TOP grant Organophosphorus Chemistry – Novel Approaches to Advance and Preserve

EU Marie Curie International Training Network: Sustainable Phosphorus Chemistry (Coordinator)

**Systems Bioinformatics**

EU Marie Curie International Training Network’NORA:Nitrous Oxide Research Alliance training network”

EU Marie Curie International Training Network: – Advanced Multidisciplinary Training in Molecular Bacteriology (AMBER)

NWO Vidi grant – Frank Bruggeman “how individual bacteria can adapt to changing conditions”.

**Theoretical Chemistry**

NWO-VENI grant - Klaas Giesbertz “Time-dependent one-body reduced density matrix functional theory for strong electron correlations”.

**Integrative bio-informatics**

NWO Open Competition grant “Engineering Executable Models of Biological Networks”

EW Vrije Competitie”Finding conserved active modules: application to Th17 differentiation”

EU Marie Curie Initial Training Networks (ITN): “PROVADIS: PROtein VARIability Dissemination”

**Medicinal Chemistry**

EU COST ACTION grant K4DD “Kinetics for Drug Discovery”.

EU COST ACTION grant GLiSTEN to set up a European research network to study G Protein-Coupled Receptors.

**Molecular Toxicology**

NWO-JU-3 Prediction of Drug-Induced Liver Injury: Mechanism-Based Integrated Systems for the prediction of drug-induced liver injury.

NWO-Bazis grant ‘Amsterdam Laboratory for Computational Chemistry’. Molecular Toxicology was one of five co-applicants.

**Patent applications**

**Biomolecular Analysis:**

Patent on GC Fractionation (Jeroen Kool and Ferry Heus): Process to separate compounds starting from mixtures. # N2009010, 15 juni 2012.

**Bioorganic Chemistry**


These two patent applications describe the translation of our fundamental MCR-based synthetic methodologies to the production of a highly complex drug and its analogs, thus protecting our IP. Further, an exclusive license agreement was set-up with a pharma-company, who now has requested coverage for a wide range of countries, underlining their commitment to the commercialization of the process. The 1st milestone payment is received and the 2nd is expected soon.

**Awards**

**Bio-Computational Chemistry**

Célia Fonseca Guerra received a NWO Aspasia grant: “Anticancer Drugs and Artificial Supramolecular Aggregates: Rational Design through Condensed-Phase Computations”

Gabor Paragi received a Marie Curie fellowship: “Introducing stacking and halogen bonding effects into ligand-target interaction energy calculations”.

Matthias Bickelhaupt was appointed Member Management Committee COST Action CM1105: Functional metal complexes that bind to biomolecules and COST Action 1005: Supramolecular Chemistry in Water.

Sarah Harris, Laura Orian, Gabor Paragi and Jordi Poater received HPC-Europa2 fellowships.

**Bioorganic Chemistry**

Romano Orru received the Gold Badge for contribution to World Science and Int'l Scientific Collaborations of the International Science Partnership Foundation, Ukraine

**Medicinal Chemistry**

Chris de Graaf has been designated as meritorious runner up of the 2012 EFMC Prize for a Young Medicinal Chemist in Academia.

Albert Kooistra won the international Design a Molecule competition 2012 organized by the software company Cresset.

**Molecular Toxicology**

Jan Simon Boerman received the Best Oral Communication Award at the 2012 AIMMS Annual meeting (April 2012), with: ‘Novel strategies for drug-protein adduct formation and identification’.

Jelle Reinen received the 2012 Perkin Elmer Presentation Award in Medicinal Chemistry for his presentation on Screening and employment of bacterial cytochrome P450 BM3 mutants for biocatalytic production of drug metabolites’. (FIGON, Dutch Medicines Days, October 2012).

Galwin Vredenburg received the Best Oral Communication Award at the LACDR Spring Meeting 2012 and at

* poster awards not listed - see www.aimms.vu.nl
the national PhD-Students Competition at the FIGON Dutch Medicines Days, Lunteren, October 2012, with a presentation on ‘Reconstitution of Clozapine metabolism in yeast’.

9.3 Societal Impact

Congresses organized

Genetics:

Medicinal Chemistry:

Molecular Toxicology:

Synthetic Chemistry:
K. Lammertsma, A. Ehlers and C. Slootweg: 19th International Conference on Phosphorus Chemistry (ICPC 2012), July 8-12, Rotterdam (chairman) and K. Lammertmsa: EU COST Action CM0802 Phosphorus Sciences Network - PhoSciNet (22 countries, > 70 groups; vice chairman).

Systems Bio-informatics & Molecular Cell Physiology:
D. Bellomo, F. Cremazy, European iGEM Jamboree, October 5-7th, VU University Amsterdam, The Netherlands.

Integrative Bio-informatics:

Editorial Boards

Below just a few editorial boards of AIMMS members are listed:

Bio-Computational Chemistry
Matthias Bickelhaupt, member editorial boards Journal of Computational Chemistry (Wiley), Physical Chemistry Chemical Physics (Royal Society of Chemistry) and ChemistryOpen (Wiley-VCH)

BioMolecular Analysis
Henk Lingeman, Editor of Chromatographia

BioOrganic Chemistry
Romano Orru is member of the editorial board of Current Organic Chemistry
Romano Orru is member of the board of the Royal Dutch Society of Chemistry, Section of Organic Chemistry, member of the advisory board of the C2W-magazine and member of board of the NWO-studygroup Design & Synthesis

Integrative bio-informatics

Molecular Toxicology
Prof N.P.E. Vermeulen, editor of Environmental Toxicology & Pharmacology (1997- ) and associate editor of Biomarkers (1996-2005), Current Drug Metabolism (2007 -) and Drug Metabolism Letters (2007 -). He is a member of the Editorial boards of: Biochemical Pharmacology, J Biomedical & Environmental Sciences, Chemistry & Biodiversity, Chemico-Biological Interactions, Chemical Research in Toxicology, Chirality, Drug Metabolism Reviews, Expert Opinions on Drug Metabolism & Toxicology, Toxicology and Xenobiotica.

Dr. J.N.M. Commandeur is member of Editorial board of Toxicology Letters. He was invited as editor-in-chief for Current Toxicology Reports (Elsevier USA).

Synthetic Chemistry
K. Lammertmsa, member of the editorial boards of Organometallics (ACS), Beilstein Journal of Organic Chemistry (Open Access) and Editorial Board of Heteroatom Chemistry (Wiley).

K. Lammertmsa, member of the Steering Group Chemistry of the Dutch Top Sector Chemistry (Regiegroep Chemie), the Chemistry Board of NWO (lid Gebiedsbestuur NWO/CW), the Dutch Materials Scarcity Platform and Member of the Chemistry and Society section of the KNCV (think tank).

Other
AIMMS
Prof. Magnus Ingelman-Sundberg, Karolinska Institute Stockholm, was in April 2012 appointed as Professor Nauta Chair 2012, provided a Workshop and a public Lecture about ‘Pharmacogenomics in Drug Efficacy and Safety’. The press release received significant attention in the press and on the internet. Amongst others he was interviewed by Nefarma.

The iGEM team Amsterdam won the golden medal with the Cellular Logbook project. Ernst Bank, Maarten Slagter, Glenn Groenevvegen, Maarten Reijnders, Tania Quirin en Matias Mendeville, master students from AIMMS and SILS (UVa) developed a cellular epigenetic based memory module. They gave a presentation about their achievements in an AIMMS seminar (appendix 12.5).

Medicinal Chemistry

Maikel Wijtmans and Jeroen Kool (BioMolecular Analysis) designed and synthesized derivatisation reagents for biomarker discovery that have been made commercially available by Axon Medchem.

Integrative bio-informatics
Jaap Heringa, Scientific Director Netherlands Bioinformatics Centre (NBIC) and member Scientific Advisory Board of the Swedish national Bioinformatics Infrastructure for Life Sciences (BILS), Sweden and appointment as national representative for EU ESFRI project ELIXIR.

Molecular Toxicology
The press release ‘Genesimmedele te ontwikkelen met bacterieel enzym’, preceeding the defence of the PhD-thesis of dr. Vanina Rea received significant attention in the press and on the internet.

The press release ‘New computer techniques speed up drug research’ from CWI, the Centrum voor Wiskunde & Informatica (prof. Gunnar Klau et al., e.g. Dr. Daan Geerke) received significant attention in the press and on the internet.
10. Education & Training

Besides being strongly involved in BSc programmes of the faculties of Exact and Life & Earth Sciences (FEW and FAULW), AIMMS groups play a major role in a range of established and accredited MSc- and PhD-education programmes within FEW and FAULW. Moreover, AIMMS participates in several graduate- and top-research schools such as LACDR (Leiden Amsterdam Center for Drug Research), HRSMC (Holland Research School of Molecular Chemistry), ACM (Amsterdam Center for Multiscale Modelling), NRSCC (Netherlands Research School Coordination Catalysis) and NSB (National Institute for System Biology). 70 PhD students and 48 PostDocs were trained within AIMMS in 2012. Moreover, AIMMS participates in several graduate and top research schools such as LACDR (Leiden Amsterdam Center for Drug Research), HRSMC (Holland Research School of Molecular Chemistry), ACM (Amsterdam Center for Multiscale Modelling), NRSCC (Netherlands Research School Coordination Catalysis) and NSB (National Institute for System Biology). 70 PhD students and 48 PostDocs were trained within AIMMS in 2012.

Best European programme

Out of hundreds of Study programmes, AtoSiM (Atomic Scale Modelling of Physical, Chemical and Biomolecular Systems) has been once again considered one of the best European Master programmes and the EU has granted “Erasmus Mundus scholarships” for another round of 5 years from 2012 onwards. AtoSiM 2.0 is a highly integrated two year Erasmus Mundus master jointly operated by Ecole Normale Supérieure in Lyon, University La Sapienza in Rome, UvA and VU University Amsterdam (http://www.erasuslimmundus-atosim.cecam.org/).

Cancer Research

Biomolecular Sciences and Bioinformatics / Systems Biology are also involved in the international

Workshop petrinetworks as a part of the AIMMS Post-graduate course ‘Systems and Network Approaches in Human Life Science’

Table 10.1 Total number of AIMMS’ Master students

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bio-Informatics</td>
<td>22</td>
<td>27</td>
<td>26</td>
<td>42</td>
</tr>
<tr>
<td>Bio Molecular Sciences</td>
<td>88</td>
<td>104</td>
<td>141</td>
<td>142</td>
</tr>
<tr>
<td>Chemistry</td>
<td>61</td>
<td>60</td>
<td>86</td>
<td>102</td>
</tr>
<tr>
<td>Drug Discovery &amp; Safety</td>
<td>36</td>
<td>50</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Medical Natural Sciences</td>
<td>43</td>
<td>37</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>TOTAL</td>
<td>250</td>
<td>278</td>
<td>342</td>
<td>388</td>
</tr>
</tbody>
</table>

International PhD-courses are offered within the frameworks of LACDR, HRSMC, NRSCC, and TIPharma. The same holds true for high quality Summer Schools for PhD-students from national and international organizations (e.g. HRSMC-IRTG, IMI SafeSci-MET and ULLA (see highlight)). AIMMS groups are currently coordinator of several of these programmes (e.g. Marinwil, IRTG, IMI SafeSci-MET).
EU-PEOPLE grant proposals

In order to strengthen these international collaborations and create valuable training networks for our young talents, we proposed with three ULLA-partners a training programme for PhD students leading to 45 Joint Doctorates in the field of Antibiotics. However, whereas the proposal “CICKS: Combating Infections by Collaboration, Knowledge and Science” did pass the Erasmus Mundus Joint Doctorates (EMJD) thresholds, it was not granted. At a smaller scale AIMMS joint forces on bio-informatics (PROVADIS: Proteolytic Variability Detection; 2 AIMMS sections involved), on drug metabolism and disposition (ARIADME: Analytical Research in Absorption, Distribution, Metabolism and Elimination; 2 AIMMS sections involved), sustainability (SusPhos : Sustainable Phosphorus Metabolism and Elimination; 2 AIMMS sections involved), on nitrous oxide emissions (NORA: Nitrous Oxide Research Alliance training Network, coordinated by Chris Slootweg (Synthetic Bacteriology; 1 AIMMS section involved)) and international (e.g. Marie-Curie fellowships, ERC-grants) level. Successful competition in these prestigious grant programmes will be an important instrument in personal career developments and in tenure tracks. In 2012, 1 Veni project started, and 1 Veni and 1 Vidi have been granted to AIMMS researchers.

Multidisciplinary environment

AIMMS PhD-students and PostDocs have diverse backgrounds and come to work in the multidisciplinary programmes had reached thresholds but three of them were not granted. Of these, ARIADME and INSIGHT will be resubmitted in 2013. SusPhos was successful and this International Training Network, coordinated by Chris Slootweg (Synthetic Bacteriology) started in 2012.

One to one

On a one-to-one scale, in 2012 we extended our Double and Joint Degrees Programmes. The collaboration with the School of Pharmaceutical Sciences, University of Copenhagen was enlarged with the start of 2 additional PhD projects and a new Agreement has been signed with the University of Girona. The main objectives are to support and promote the joint supervision of doctoral theses, to improve the quality development of the two program lines of research and training activities, and to reinforce the international character of both doctoral programs. The first PhD students are expected to enroll in 2013.

Investment in quality

To increase the quality of its research programmes and also to offer ambitious PostDocs career opportunities in AIMMS-related fields, AIMMS promotes itself extensively as an attractice host-institute for PostDocs. Moreover, it actively stimulates and coaches talented PostDocs to compete for personal grant programs at the national (e.g. NWO Vernieuwingsimpuls Veni-, Vidi- and Vici-programmes) and international (e.g. Marie-Curie fellowships, ERC-grants) level. Successful competition in these prestigious grant programmes will be an important instrument in personal career developments and in tenure tracks. In 2012, 1 Veni project started, and 1 Veni and 1 Vidi have been granted to AIMMS researchers.

Evaluation AIMMS post-graduate courses

18 respondents (of 32 participants) scored the AIMMS Post-graduate course with 4-4.5 on quality, organization and balance between lectures, workshops and industrial contributions.

Some citations “Best course I have been to in my 3 years as a PhD 2”, “I liked that much of the info was based on practical examples”.

10.2 PhD Projects bridging sections

In 2010 seven competitive ‘bridging’ PhD-projects were selected in which groups from the two faculties were involved to stimulate mutual interaction. Project selection was primarily based on external peer review to ensure scientific excellence, but complemented by strategic considerations. The funding was based on a 50% matching by the research environment of AIMMS. This creates a need for relatively broad courses on different disciplines. Learning about other disciplines and more understanding of each other’s work will open eyes for possible linkages with own research and will give new opportunities for cooperation. Other perspectives, new approaches will sometimes just give that special break-through.

AIMMS Post-graduate schools

To fill this need, we started the AIMMS post-graduate school with different courses. The aim is to organize 2 post-graduate courses per year within a 3-year cycle, giving 6 different courses

<table>
<thead>
<tr>
<th>project no</th>
<th>PI’s</th>
<th>AIMMS Sections</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 001 - 201</td>
<td>de Boer - Tiedeus</td>
<td>Structural Biology / Target and Systems Biochemistry</td>
<td>GPCR-mediated oncogenic signaling, targeting 14-3-3 as mediators of apoptotic/proliferative switching</td>
</tr>
<tr>
<td>10 - 001 - 202</td>
<td>Esch-Luurink</td>
<td>Medical Chemistry / Molecular Microbiology</td>
<td>Spider in the web: multiple interactions of the essential cell division protein FtsQ as novel targets for antibiotic intervention</td>
</tr>
<tr>
<td>10 - 001 - 203</td>
<td>Kool-AB Smit</td>
<td>Biomolecular Analysis / Molecular Neurobiology</td>
<td>Identification of novel bioactive substances on brain receptors</td>
</tr>
<tr>
<td>10 - 001 - 204</td>
<td>Kooten-Vos</td>
<td>Genetics / Molecular Toxicology</td>
<td>Drug-induced genome instability: translation from yeast to human</td>
</tr>
<tr>
<td>10 - 001 - 205</td>
<td>Ruiters-van Spanning</td>
<td>Bioregionic Synthesis / Molecular Cell Physiology</td>
<td>Autonominic: chemo-enzymatic synthesis and molecular probing of respiratory NADH-dehydrogenases</td>
</tr>
<tr>
<td>10 - 001 - 206</td>
<td>Gera-Tauwink</td>
<td>Biomolecular Analysis / System Bioinformatics</td>
<td>The network pathophysiology of tumorigenesis: a systems biology approach (I)</td>
</tr>
<tr>
<td>10 - 001 - 207</td>
<td>Bruggeman-MJ Smit</td>
<td>Molecular Cell Physiology / Target and Systems Biochemistry</td>
<td>The network pathophysiology of tumorigenesis: a systems biology approach (II)</td>
</tr>
</tbody>
</table>
Adapted from Slinger et al. 2010

activates STAT3 via autocrine stimulation initiated by inducing IL-6 production via in tumor tissues1. HCMV is generally DNA, mRNA and/or viral proteins constitute a large family of receptor on the cell membrane. G protein-coupled receptors (GPCRs) constitute a large family of receptor proteins involved in a wide variety of physiological processes such as sight, smell, behaviour, immune system regulation and homeostasis. The HCMV virus encodes four GPCRs namely US27, US28, UL33 and UL78. In recent years, research by our group has demonstrated that US28 is able to constitutively activate various intracellular pathways such as JAK/STAT3, NFAT, NF-κB1 and β-catenin leading to inflammation and proliferation. To understand the mechanism behind US28 mediated signal transduction, we aim to characterize the US28 signalosome; all intracellular components that interact with US28 and enable US28 mediated signal transduction. A first step in identification of components of the US28 signalosome has been made by immunoprecipitation of components of the US28 signalosome; all intracellular proteins interact with each other in a concerted mechanism. These proteins are recruited to the division site in a hierarchical order [1]. The protein FtsQ seems to play a central role in this process, having interactions with many other cell division proteins. Interactions with FtsK, FtsB and FtsL are indispensable, and interference with any of these protein interactions causes severe cell division defects and inhibition of bacterial growth. FtsQ is a bitopic membrane protein, consisting of a short N-terminal transmembrane segment (residues 25-50) and a C-terminal periplasmic domain (residues 50-276). The periplasmic domain of FtsQ seems to be responsible for most essential interactions of this protein. The periplasm is relatively accessible for small-molecules (e.g. synthetic drugs). Another positive characteristic of this potential target is that FtsQ has a low cellular abundance (25-50 copies per cell). Finally, in 2008 the crystal structure of the periplasmic domain of FtsQ was resolved [2]. Altogether, this makes FtsQ an attractive drug target.

During the final stage of cell division, a set of at least 10 essential proteins interact with each other in a concerted mechanism. These proteins are recruited to the division site in a hierarchical order [1]. The protein FtsQ seems to play a central role in this process, having interactions with many other cell division proteins. Interactions with FtsK, FtsB and FtsL are indispensable, and interference with any of these protein interactions causes severe cell division defects and inhibition of bacterial growth. FtsQ is a bitopic membrane protein, consisting of a short N-terminal transmembrane segment (residues 25-50) and a C-terminal periplasmic domain (residues 50-276). The periplasmic domain of FtsQ seems to be responsible for most essential interactions of this protein. The periplasm is relatively accessible for small-molecules (e.g. synthetic drugs). Another positive characteristic of this potential target is that FtsQ has a low cellular abundance (25-50 copies per cell). Finally, in 2008 the crystal structure of the periplasmic domain of FtsQ was resolved [2]. Altogether, this makes FtsQ an attractive drug target.

The aim of this project is twofold: First, the interactions of FtsQ with other cell division proteins will be characterized in detail. Several biochemical techniques will be used to verify the protein interactions of FtsQ on both the protein level (identification of interaction partners) and the residue level (identification of binding interfaces). Second, novel classes of small-molecule inhibitors of these protein-protein interactions will be discovered and explored. A fragment-based drug discovery (FBDD) approach will be used to screen for hit compounds and optimization of these compounds to candidate antibacterials. Thus far, we have succeeded in expressing the periplasmic domains of FtsQ, FtsB and FtsL in E.coli and we are able to purify large amounts of FtsQ and FtsQ in complex with FtsB and FtsL. We are now studying the interactions between these proteins and the character of the complex. This AIMMS project takes place at the departments of Molecular Microbiology and Medicinal Chemistry. The tight cooperation between the departments results in an efficient research platform with a large network and many opportunities for national and international collaborations.

I am a second-year PhD student working on the AIMMS PhD project “Identification of novel bioactive substances on brain receptors”. I am from Hungary, and I obtained my master degree in Pharmacy at the University of Debrecen. My PhD project is a multidisciplinary project that bridges the Division of BioMolecular Analysis and the Department of Molecular and Cellular Neurobiology. Working on a project that bridges two departments is an excellent opportunity to gain experience in different research fields.

My first goal is to develop a hyphenated screening technology in which on-line cellular profiling, i.e. in a continuous-flow analysis format will be coupled post-column to a liquid chromatographic HPLC separation system with parallel mass spectrometric (MS) analysis in order to correlate bioactivity to identity. The functional response of ion channels and GPCRs will be determined with cellular calcium flux assays and/or assays using membrane-potential-sensitive dyes. For the separation of snake and cone snail venoms, a nano-high-performance liquid chromatography system will be coupled with an accurate mass spectrometer.


With the on-line screening technology developed, I will analyze relevant Elapidae snake and cone snail toxins for activity and affinity towards expressed subtype-specific nicotinic Acetylcholine Receptors (a family of ion channels) in order to identify new selective modifiers. The results obtained will hopefully not only deliver novel lead compounds for pharmaceutical development, but will also deliver specific tools for biochemical/pharmacological studies on ion channels. Selective modifiers, for example, could potentially be new pharmaceutical lead molecules for the treatment of ion-channel related diseases, e.g. epilepsy and migraine.

The second type of natural source that will be used in this project is brain tissue, at present still probably containing unarrived and/or hidden bioactive molecules. The purpose is to discover unknown endogenous ligands that are involved in brain functioning and brain related diseases. To achieve this, brain homogenates will be fractionated and screened for bioactivity with the cellular on-line screening technology. Screening of brain tissues will aid in understanding the functioning of ion channels in the brain, and in identifying their corresponding ligands.

Genomic instability is implicated in various pathological disorders and in humans it is associated with premature aging, neurological diseases, predisposition to various types of cancer and with inherited diseases. Also, DNA-damage can lead to chromosomal instability and aneuploidy. This AIMMS project is bridging two departments: molecular toxicology (FEW) and genetics (FAWL). We are using yeast as a model to investigate drug-induced molecular biological processes that are involved in maintenance of genomic stability and to identify novel genes that play role in conferring resistance and sensitivity to certain drugs. Evolutionary conserved genes will later be studied in human cells.

Some drugs show idiosyncratic drug reactions that are often related to cytochrome P450 generated chemically reactive intermediates, which can bind cellular targets like DNA and proteins. In case of acetaminophen, it is not acetaminophen itself but its active metabolite NAPQI that causes the damage, although only 1% of acetaminophen is converted to NAPQI in liver cells. In yeast, lacking drug-metabolizing P450s, acetaminophen toxicity was also observed at high concentrations, but no active metabolites could be detected. This makes yeast a very suitable model organism to study aspects of acetaminophen toxicity, which are not related to its active metabolite NAPQI.

In a genome-wide loss-of-function screen, which was performed in collaboration with Dr. Fred van Leeuwen (AvL-NKI, Amsterdam), we identified gene deletion strains, which are resistant to acetaminophen-induced growth arrest. Surprisingly, two of these genes are involved in post-replicative DNA repair, a process highly conserved between yeast and humans. We focus our research on the role of these genes in maintaining the genomic stability in the presence of drugs.

Yeast cells can undergo genomic adaptation such as aneuploidy in order to become resistant for various stress conditions. Gain of an extra chromosome can alter expression profiles of different genes, and by doing so, provide suitable conditions for increased resistance.

In a recent publication (Chen et al. Nature 2012) it was shown that yeast became resistant to an Hsp90 inhibitor, radicicol, by gaining an extra copy of chromosome XV. We would like to determine if acetaminophen resistance is achieved by means of aneuploidy and, if so, which chromosomes are involved. We will use techniques such as FACS, deep sequencing and qPCR to determine drug-induced genetic changes.

Furthermore, we also investigate other aspects of the growth arrest such as drug-induced nutrient starvation. We found that overexpression of a high affinity amino acid permease is also conferring resistance to acetaminophen and that acetaminophen is causing its ubiquilination and degradation.

Growth arrest by acetaminophen is achieved by cell cycle defects, whereby the normal budding process is affected. Arrested cells exhibit a multiple budding phenotype indicating that bud site selection and possibly chromosome segregation is deregulated. In deletion strains, lacking genes involved in DNA repair, growth arrest is bypassed, indicating a possible role as tumor suppressor.
Complex I (NADH dehydrogenase) plays a central role in cellular energetics by coupling electron transfer between NADH and quinone to proton translocation across the inner mitochondrial membrane. However, the flavin site of mitochondrial Complex I is also a major source of reactive oxygen species (ROS) and it appears that tumour cells are closer to excessive ROS generation than healthy cells due to a more negative redox potential of the NADH/H⁺ couple. Therefore, Complex I is an interesting potential of the NAD(H) couple.

The most potent among the many structurally diverse inhibitors of Complex I are the Annonaceous acetogenins, a large class of polyketide natural products isolated from the Annonaceae family of flowering plants. The typical structure of these compounds includes a (S)-5-methylbutenolide ring substituted at the 3-position with a long linear aliphatic chain incorporating mostly methylbutenolide ring substituted compounds includes a (S)-5-methylbutenolide ring substituted compounds. Simultaneously, the (S)-5-methylbutenolide ring (15) fused to a long alkyl chain, which is present in nearly all acetogenins, was successfully synthesized under mild conditions from cheap and natural materials.

Isolated acetogenins 1-6 with distinctive bis-THF ring systems that exhibit biological activity accompanied by the interesting synthetic targets 7-9 containing bis-THF-bis-epoxide systems with C2-symmetry.

The goal of this project is to synthesize and characterize analogues of the most active acetogenins 1-6. As depicted in fig. 2, these acetogenins include adjacent bis-THF ring systems, which play a major role in binding to Complex I. For an efficient synthetic strategy it is important to recognize the pseudo symmetry of these ring systems. Therefore it was proposed that C2-symmetric bis-THF-bis-epoxides 7-9 could be interesting intermediates for the synthesis of acetogenins and analogs.

We envision that these bis-THF-bis-epoxides 7-9 can be synthesized stereoselectively from epoxide scaffolds (10-14) by biocatalyzed hydrolysis, which was carried out using a broad range of biocatalysts from various microbial sources. Currently the hydrolysis products are analyzed to determine enantiomeric ratios, so that follow-up chemistry can be done to obtain the fused bis-THF core of annonaceous acetogenins.

The most potent among the many structurally diverse inhibitors of Complex I are the Annonaceous acetogenins, a large class of polyketide natural products isolated from the Annonaceae family of flowering plants. The typical structure of these compounds includes a (S)-5-methylbutenolide ring substituted at the 3-position with a long linear aliphatic chain incorporating mostly methylbutenolide ring substituted compounds. Simultaneously, the (S)-5-methylbutenolide ring (15) fused to a long alkyl chain, which is present in nearly all acetogenins, was successfully synthesized under mild conditions from cheap and natural materials.

The most potent among the many structurally diverse inhibitors of Complex I are the Annonaceous acetogenins, a large class of polyketide natural products isolated from the Annonaceae family of flowering plants. The typical structure of these compounds includes a (S)-5-methylbutenolide ring substituted at the 3-position with a long linear aliphatic chain incorporating mostly methylbutenolide ring substituted compounds. Simultaneously, the (S)-5-methylbutenolide ring (15) fused to a long alkyl chain, which is present in nearly all acetogenins, was successfully synthesized under mild conditions from cheap and natural materials.

The most potent among the many structurally diverse inhibitors of Complex I are the Annonaceous acetogenins, a large class of polyketide natural products isolated from the Annonaceae family of flowering plants. The typical structure of these compounds includes a (S)-5-methylbutenolide ring substituted at the 3-position with a long linear aliphatic chain incorporating mostly methylbutenolide ring substituted compounds. Simultaneously, the (S)-5-methylbutenolide ring (15) fused to a long alkyl chain, which is present in nearly all acetogenins, was successfully synthesized under mild conditions from cheap and natural materials.

The most potent among the many structurally diverse inhibitors of Complex I are the Annonaceous acetogenins, a large class of polyketide natural products isolated from the Annonaceae family of flowering plants. The typical structure of these compounds includes a (S)-5-methylbutenolide ring substituted at the 3-position with a long linear aliphatic chain incorporating mostly methylbutenolide ring substituted compounds. Simultaneously, the (S)-5-methylbutenolide ring (15) fused to a long alkyl chain, which is present in nearly all acetogenins, was successfully synthesized under mild conditions from cheap and natural materials.
Azra Mujic - Delic

The network pathophysiology of tumorigenesis: a systems biology approach

Molecular Cell Physiology / Target & Systems Biochemistry

My PhD project bridges the research groups of Target and Systems Biochemistry, Systems Bioinformatics, Molecular Cell Physiology and Biomolecular Analysis. The main focus is on interactions between signal transduction and metabolism in cancer, specifically the role of G-protein coupled receptors (GPCRs).

We know that in cancer cells signaling transduction is disturbed by over-expression of oncogenes and silencing of tumor-suppressor genes. Moreover, in order to sustain their highly proliferative nature, cancer cells tend to undergo a metabolic switch (also known as the Warburg effect) where they take up more glucose and glutamine and produce lactate.

So far, research has been very field specific, not looking much into the interaction between signaling proteins and metabolic proteins. However, in the past years it has become clear that signaling proteins affect metabolism and vice-versa. In this project we aim to bring the two fields together by experimental as well as modeling approaches to shed some light on the bigger picture, that is why are cancer cells the way they are and how can we tackle them.

The team includes three PhD students, with various backgrounds. My contribution to the project is mainly cell culture and performance of several types of assays to look at signaling and metabolism changes when cells are exposed to either expression of certain proteins or treatment with (possible) drugs. The other two students are focused on modeling of signaling and metabolic networks and on developing an analytical method for detection of metabolites.

Working in such a team is very interesting and challenging. Meeting each other often and discussing results is very important. Even though you cannot be an expert in all the aspects of this project, you need to understand the basics and be able to exchange your findings.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.

As a PhD student in a multidisciplinary team you get a chance to broaden your knowledge and learn new techniques. For instance, we also collaborate with the Department of Systems Biology of MD Anderson Cancer Center in Houston (Texas, USA). I got the opportunity to visit Houston and work in their lab for 2 months. It was an amazing experience in which I learned many new lab techniques. At this moment, the project is up and running. I am also setting up some techniques that are new for me and my lab which will be of great use in the future.
**Biocomputational Chemistry**

**Matthias Bickelhaupt**

**Research Profile**

Life sciences and sustainability are the context in which research programs are developed in the AIMS division of Bio-Computational Chemistry. Our staff consists of Matthias Bickelhaupt (professor of theoretical organic chemistry and biocatalysis) and Célia Fonseca Guerra (assistant professor of biocomputational chemistry) and 10-15 MSc, PhD, PD and visiting scientists.

**Theories and methods**

We are interested in developing chemical theories and methods for rationally designing molecules, nano-structures and materials as well as chemical processes toward chemical warfare.

**Research highlight**

As a PhD candidate in the group of Prof. Matthias Bickelhaupt, I work on several topics, one of which is a comparison of the halogen-bonding mechanism with the hydrogen-bonding mechanism. While hydrogen bonds are among the most well-known supramolecular interactions, halogen bonds are not so widely known, let alone understood.

Typically, hydrogen bonds are explained by an electrostatic attraction between an electronegative atom and the partial positive charge of a hydrogen atom connected to a second electronegative atom.

Previously it was shown that the electrostatic picture is only a small part of the hydrogen-bonding mechanism, and that there is also significant covalent character. This covalent character arises from charge transfer, as was very clearly shown in the σ*D–X orbital of halogen bonds. An important new research line in connection with the latter project is the development of anticancer drugs that are based on the stabilization of G-DNA domains. But many more research lines are under preparation or lifting off, ranging from astrochemistry, via solar cells to the detoxification of agents for chemical warfare.

**Key Publications**


**NWO - Aspasia Grant**

Célia Fonseca Guerra received an NWO Aspasia grant for the project ‘Anticancer Drugs and Artificial Supramolecular Aggregates: Rational Design through Condensed-Phase Computations’.

**Anticancer drugs**

An important new research line in connection with the latter project is the development of anticancer drugs that are based on the stabilization of G-DNA domains. But many more research lines are under preparation or lifting off, ranging from astrochemistry, via solar cells to the detoxification of agents for chemical warfare.

---

**Lando Wolters**

**Halogen bonds and hydrogen bonds: from small model systems to biochemistry**

**Research highlight**

As a PhD candidate in the group of Prof. Matthias Bickelhaupt, I work on several topics, one of which is a comparison of the halogen-bonding mechanism with the hydrogen-bonding mechanism. While hydrogen bonds are among the most well-known supramolecular interactions, halogen bonds are not so widely known, let alone understood.

Typically, hydrogen bonds are explained by an electrostatic attraction between an electronegative atom and the partial positive charge of a hydrogen atom connected to a second electronegative atom.

Previously it was shown that the electrostatic picture is only a small part of the hydrogen-bonding mechanism, and that there is also significant covalent character. This covalent character arises from charge transfer, as was very clearly shown in the σ*D–X orbital.

In my work, I have performed detailed bonding analyses of the halogen bonds in DX–A– complexes and compared them with analogous hydrogen bonds in DH–A– complexes (with D, X, A = F, Cl, Br, I). The results, published in ChemistryOpen 2012, 1, 96, show that halogen bonds also have a significant covalent component, that arises from charge transfer from the A– lone pair into the σ*D–X orbital (schematically shown below; MO diagrams on the right).

Interestingly, halogen bonds can have even more covalent character (up to 97% of the total bonding interactions!). Our vast series of detailed results reveal several trends, for both hydrogen and halogen bonds, that can only be explained when the covalent character of these interactions is taken into account.

In a research project of Dr. Célia Fonseca Guerra, we have extended and continued the study of these halogen bonds to the Watson-Crick AT and GC base pairs, in which the hydrogen bonds are replaced with halogen bonds. The same trends as for the small model systems were found, with covalency accounting for roughly a third of the total bonding interactions.
Biomolecular Analysis

Wilfried Niessen

Mission

The Division of BioMolecular Analysis (BMA) has the ambition to be a leading research group in the development of innovative analytical technologies for drug discovery and other life-science oriented areas. Our research projects are characterized by a common theme: combining traditional analytical techniques and instrumentation, mainly LC-MS, with methodologies from adjacent disciplines such as biochemistry, medicinal chemistry, or physical chemistry, in order to significantly enhance the information content of the analytical concepts developed. As such, we aim to discover novel, hitherto unknown bioactive compounds and/or perform target bioanalysis of known analytes at trace concentrations in complex biological matrices.

Combining analytical separation technologies with bioassays and parallel mass spectrometry, the so-called high-resolution screening (HRS) approach, enabling the simultaneous biological and chemical characterization of components in (complex) mixtures. At present, our research in this area mainly focuses on (1) the establishment of a versatile platform for the rapid discovery of novel active metabolites that might serve as starting point for further lead optimization, and (2) miniaturization of bioassays to apply these in sample-limited applications. Nano-separation coupled to a chip-based bioassay and parallel mass spectrometry is developed to search for bioactive peptides in snake venoms against acetylcholine binding protein (AChBP). Snake venoms often are complex mixtures of peptides with different functions. In the course of this project, a wide variety of snake venoms have been screened for bioactivities. Various peptides were found to be bioactive, not only known neurotoxins, but also peptides known to be cardioactive. Even unknown peptides were identified as bioactive against AChBP. This research is now extended to include other receptor proteins and to further identify the individual toxins found.

Molecular Interaction screening technologies

On-line (bio)active metabolite discovery

BMA has a long track record on the development of on-line technologies, combining analytical separation technologies with bioassays and parallel mass spectrometry, the so-called high-resolution screening (HRS) approach, enabling the simultaneous biological and chemical characterization of components in (complex) mixtures. At present, our research in this area mainly focuses on (1) the establishment of a versatile platform for the rapid discovery of novel active metabolites that might serve as starting point for further lead optimization, and (2) miniaturization of bioassays to apply these in sample-limited applications. Nano-separation coupled to a chip-based bioassay and parallel mass spectrometry is developed to search for bioactive peptides in snake venoms against acetylcholine binding protein (AChBP). Snake venoms often are complex mixtures of peptides with different functions. In the course of this project, a wide variety of snake venoms have been screened for bioactivities. Various peptides were found to be bioactive, not only known neurotoxins, but also peptides known to be cardioactive. Even unknown peptides were identified as bioactive against AChBP. This research is now extended to include other receptor proteins and to further identify the individual toxins found.

Ten different peptide ligands towards acetylcholine binding protein (AChBP) were detected in the snake venom of Jameson’s mamba (Dendroaspis jamesoni kaimosae), only four of which have been previously described. The picture shows negative peaks in the (lowest) bioactivity chromatogram, indicating bioactivity and a series of extracted-ion chromatograms corresponding to the most abundant ion observed in simultaneous LC–MS analysis of the snake venom. This information assists in establishing the identity of the bioactive peptides (Figure from F.A.H. Heus et al., Toxicol, 61 (2013) 112-124)

At-line nano-fractionation to microtiter plate assays

As not all bioassays are readily convertible into an on-line format, what is certainly true for cellular assays, we also developed post-column high-resolution nano-fractionation tools that allow us to subsequently perform a bioassay in 384- or 1536-well microtiter plates. In practice, the effluent of an LC separation is split between an MS to provide identity information and an in-house developed nano-fractionation device which puts the chromatogram in 1-5 s fractions onto the microtiter plate. The microtiter plate is then subjected to a conventional bioassay using a plate reader reader.

Following early developments where known on-line systems were converted in-at-line approaches, more challenging bioassays were investigated, e.g., metabolic profiling of small-molecule ligands towards histamine H4 and chermokine G-protein coupled receptors (GPCRs), This research is being expanded to the analysis of protein biochemicals. The same platform is also being investigated as an advanced tool in effect-directed analysis, as performed in environmental analysis, and developments involving implementation of surface plasmon resonance (SPR) are underway.

Trace bioanalysis technologies

Target protein analysis

The main effort in this area was related to the detection and semi-quantitative analysis of a drug-protein adduct, involving NAPQI (a reactive metabolite of acetaminophen) and albumin, in mouse serum. Via a complex, multi-step sample pre-treatment, the mouse serum albumin was isolated from the mouse serum, digested into peptides and analysed by LC–MS–MS.

Differences in mass and fragmentation spectra of the adducted and the non-adducted peptides enabled the selective detection of the adduct. About 0.2% of the mouse serum albumin of a mouse administered with acetaminophen was adducted.

Targeted metabolomics and biomarker analysis

New developments in this research area are the development of quantitative analytical methodology involving both LC–MS and GC–MS for the determination of a long list of relevant small-molecule metabolites in cellular systems, including amino acids, a variety of low-molecular-weight organic acids, and glycolytic intermediates.

Part of this research is done within an AIMMS project directed at a systems approach towards tumorigenesis (Warburg effect) with Divisions of Systems Bioinformatics and Target and Systems Biochemistry as well as other cellular systems.

Another part of the research, especially involving analyte derivatization strategies prior to LC–MS, is directed at urinary metabolites within clinical research. In collaboration with the Division of Medicinal Chemistry, we developed chemoselective tags for biomarker analysis using LC–MS. In this respect, a comparison of six different column chemistries for the comprehensive metabolic profiling of urine samples was performed, leading to preferrence for diol-HILIC columns, which have not yet been widely applied.

Future

From 2013 onwards, the research profile of the division will be broadened and include additional focus areas, as two new professors start.

New areas are related to intact protein analysis, glycemics and applications of capillary electromigration technologies.
Innovative Analytical Methodologies for Biopharmaceuticals

Marija Mladic

Innovative Analytical Methodologies for Biopharmaceuticals with parallel mass spectrometric bioaffinity/bioactivity assessment of on novel analytical methodologies such as pharmacy in the first place.

to study a multidisciplinary character, since I have a wide range at the same time to link them into two completely different fields and to gain knowledge and expertise in chemistry and pharmacology. The project academic and 5 industrial partners.

Medicinal Chemistry. I am working and Target and System Biochemistry/Divisions of BioMolecular Analysis pharmacology. In September 2011, I worked in a community and hospital and MS analysis.

Correlation between structure identity and bioaffinity is enabled by the parallel bioaffinity analysis using a radioligand binding assay. This first study follows by the relevant bioassay in conventional microtiter plates.

Due to the complex structures and physicochemical parameters of biomolecules in general, the analysis of protein drugs is a very challenging field of drug analytics. Therefore, my first goal was to demonstrate successful use of the methodology for bioaffinity assessment of metabolic mixtures of small ligands towards CXCR3 receptor. Therefore, my first goal was to demonstrate successful use of the methodology for bioaffinity assessment of metabolic mixtures of small ligands towards CXCR3 receptor. The methodology is based on parallel LC separation with MS identification of the metabolic mixtures and parallel mass spectrometric identification after liquid chromatography separation. The final idea of the project is to enable efficient analysis of bioactive CXCR3 ligands in complex mixtures, such as those derived from mutated or digested chemokines.

Bioaffinity/bioactivity assessment is performed in an innovative ‘at-line’ approach. It implies post-column high-resolution nano-fractionation followed by the relevant bioassay in conventional microtiter plates.

My research within the STW project on novel analytical methodologies for biopharmaceuticals is mainly focused on chemokine receptors with CXC motives. The aim of this project is to develop analytical methodologies that will allow bioaffinity/bioactivity assessment of protein drugs based on CXCR ligands with parallel mass spectrometric analysis of a metabolic mixture of NBI-74230, a small molecule ligand towards the CXCR3 receptor. Chemical structure of the parent compound with the MS2 fragmentation scheme is inserted in the figure. I. Reconstructed bioaffinity chromatograms after LC separation and nanofractionation of the metabolic mixture after duplicate injections at two different concentrations corresponding to 20 μM and 100 μM pre-incubation concentration of the parent compound. II. LC-MS traces depicted as extracted ion currents (EICs) of parent compound (black trace) and formed metabolites (red, blue, green and yellow traces). Correlation between structure identity and bioaffinity is enabled by the parallel bioaffinity and MS analysis.

Bio-organic Chemistry

Romano Orru

Research profile

We focus on efficient synthetic methodology employing one-pot processes. The methodology is applied to the diversity-oriented synthesis (DOS) of small focused libraries of fine-chemicals with a high added value, like building blocks for medicines or ligands for catalysis. We use multi-component reactions (MCRs), which combine multiple simple reagents to form a single product allowing molecular complexity and diversity to be created by formation of several covalent bonds in one-pot transformations. Our reactions proceed with high atom and step economy minimizing the number of functional group manipulations towards a given complex molecular target and avoiding the use of protective groups.

Since entering the field (see Synth 2003, 1471, cited > 500 times) the Orru-group has developed important novel entries in the emerging, highly competitive area of multi-component reactions (MCRs) and strategies for Diversity Oriented Synthesis. The approach, using simple starting materials to generate highly diverse libraries of functionalized small molecules in a single step, is not only very efficient, versatile, and environmentally friendly, but importantly provides rapid access to key compounds for fine chemicals with high added value, like small molecular probes for chemical biology research, building blocks for medicines or ligands for catalysis.

Both mechanistic aspects, stereochemistry using biocatalysis, optimization towards robust procedures and synthetic utility are studied in-depth in mainly externally funded projects and our chemistry proved already successful for the synthesis of potentially biologically active molecules (antitumor, antibiotics, hepatitis C) as well as ligands relevant to catalysis (N-heterocyclic carbene complexes, organocatalysts). A highlight of our research is a spectacular and unprecedented eight-component reaction, reported as Hot Paper in Angewandte Chemie (Int. Ed. 2009, 48, S585-S589) and highlighted in Nature. As a result, we receive growing recognition and are now one of the leading players in the field of multicomponent chemistry and diversity oriented synthesis.

Biocatalysis

A new line of research involves the use of biocatalysis in one-pot MCR-based syntheses. The stereoselectivity of many biocatalysts excellently complements the chemoselectivity of MCRs. Many MCRs can be performed in aqueous media and are thus in principle compatible with biocatalysis. The key objective of our research efforts in this programme is to explore and develop one-pot processes that combine (i) MCR methodology and (ii) biocatalysis. The PhD-projects focus on novel atom- and step efficient syntheses of APIs and pharmacologically relevant heterocycles. We employ products delivered from biocatalysis in our MCR-platform reactions. For example enantio- and/or diastereoselectively pure aldehydes or amines that are obtained in this way are valuable inputs for several MCRs developed in our group.

This strategy results in highly efficient combination of e.g. MAO-N-catalyzed desymmetrization (in coin with Turner) of cyclic meso-amines with L-glu-type 3CRs. This procedure is characterized by mild conditions, simple experimental procedures, excellent yields, dr. and ee values. This methodology proves applicable to a wide variety of 3,4-cis-substituted 1-pyrrolines and therefore of considerable synthetic value in the construction of arrays of other N-substituted 3CRs, substrates of prolyl peptides, for example, to access Wnemmers-type organocatalysts and for the synthesis of novel hepatitis C drugs (telaprevir, boceprevir etc.)

Key Publications


Gulevich, AV; Zhdkano, AG; Orru, RVA; Nenadjenko, VG. Chem Rev. 2010, 110, 5235. “N-heterocyclic Carbenes: Synthesis, Reactivity, and Application”.


Analysis of a metabolic mixture of NBI-74230, a small molecule ligand towards the CXCR3 receptor. Chemical structure of the parent compound with the MS2 fragmentation scheme is inserted in the figure. I. Reconstructed bioaffinity chromatograms after LC separation and nanofractionation of the metabolic mixture after duplicate injections at two different concentrations corresponding to 20 μM and 100 μM pre-incubation concentration of the parent compound. II. LC-MS traces depicted as extracted ion currents (EICs) of parent compound (black trace) and formed metabolites (red, blue, green and yellow traces). Correlation between structure identity and bioaffinity is enabled by the parallel bioaffinity and MS analysis.

2. granted IMI-JU programmes

1. CHEM21: A 26.4 million Euro IMI-JU programme on "green pharmacy".
2. ELF: A 196 million Euro "green pharmacy".
3. 2.4 billion Euro CHEMThomas: A 26.4 million Euro project.
5. ATOMES: A 2.5 billion Euro project.
6. 5859) and highlighted in Nature. As a result, we receive growing recognition and are now one of the leading players in the field of multicomponent chemistry and diversity oriented synthesis.

Romano Orru


Gulevich, AV; Zhdkano, AG; Orru, RVA; Nenadjenko, VG. Chem Rev. 2010, 110, 5235. “N-heterocyclic Carbenes: Synthesis, Reactivity, and Application”.

**Research Highlight**

Molecular probing of respiratory NADH-Dehydrogenases

The new line of research using biocatalysis and MCRs has also resulted in a ALMIS-funded project on Molecular Probing of Respiratory NADH-Dehydrogenases (PI: Eelco Ruijter; with Rob v Spanning and Hans Westerhof).

**Background:** Complex I (NADH dehydrogenase) plays a central role in cellular energetic by coupling electron transfer between NADH and quinone to proton translocation across the inner mitochondrial membrane. However, the flavin site (FMN) of mitochondrial Complex I is also a major source of reactive oxygen species (ROS) and it appears that tumour cells are closer to excessive ROS generation than healthy cells due to a more negative redox potential of the NAD(H) couple induced by the "Warburg effect." Therefore, Complex I is an interesting target for differential drug design.

**Objectives, Challenges, Approach and Impact:** Although the crystal structure of the peripheral arm of Complex I was resolved recently, the relationship between function (dysfunction, ROS production?) and structure remains elusive. The most intriguing processes occur in the poorly characterized membrane-embedded domain, in which the exact localization and number of quinone (1a and 1b) binding site(s) are yet to be determined. The most potent inhibitors of Complex I are the annonaceous acetogenins (2) natural products from Annonaceae flowering plants. Binding of acetogenins to Complex I inhibits electron transfer to ubiquinone, thus interfering with cellular respiration and the production of ATP. Moreover, ROS production has been observed when acetogenin rolinnastatin was added to bovine heart submitochondrial membrane fragments. A shift in balance from respiration to ROS production may account for the antitumor cell specificity of acetogenins. The butenolide ring (8) in acetogenins can undergo one-electron reduction, leading to a stabilized radical species contributing to additional ROS production.

Diversity & Biology oriented synthetic methodologies are used to access libraries of functional molecular probes for the systems biology studies. Our overall aim is to unravel the molecular mechanism controlling the relative rates of transfer of electrons to ubiquinone and to oxygen (creating ROS) by Complex I. On the basis of our findings pharmaceutical industry may reconsider acetogenins as cancer therapeutics and develop these compounds into an arsenal of drugs against multifactorial diseases.

**Progress:** Epoxide scaffolds (3-7) have been synthesized for enzymatic hydrolysis, which was carried out using a broad range of epoxide hydrolases, biocatalysts from various microbial sources (in collaboration with prof Faber, Univ Graz, Austra). Numerous biocatalysts showed good activity in producing the desired hydrolased products. Currently the stereoselectivity is determined after which the most selective epoxide hydrolases will be employed for the follow-up chemistry to synthesize the fused bio-THF core of annonaceous acetogenins.

Simultaneously, the alkyl fused butenolide ring (8), which is present in nearly all acetogenins, was successfully synthesized under mild conditions from cheap and natural materials. Biological screening is currently set-up for these probes to determine if ROS-production indeed plays a significant role in the bio-activity mode of action of these type of compounds.

**Genetics**

**Mission**

Research in the Section Genetics aims at understanding the molecular (epi)genetic mechanisms that control the development of complex multicellular organisms from a single cell. Special emphasis is on how alterations in the genetic mechanisms lead during evolution to the enormous diversity of morphologies that is seen today in the animal and plant kingdom. Such knowledge is not only of academic relevance but also essential to "translate" results obtained with model organisms, to species that are of medical and/or agricultural relevance.

**Genetic control of flower development**

1. **Specification of inflorescence architecture**

Evolution generated animal and plant species with an amazing morphological variation by mutation and selection. One of the big challenges in evolutionary developmental biology ("evo-devo") is to unravel the molecular basis of this diversity, which genes were altered, and how that affected gene function and morphology. Flowering plants (Angiospermae) offer excellent possibilities to address these fundamental questions, because they evolved highly divergent body architectures in a relative short period (100 MY), and a decent set of species is amenable to genetic analysis (forward genetics, transgenesis etc).

We previously showed that the floral identity of a meristem is defined by a transcription factor, known as LEAFY in Arabidopsis or ALF in petunia, which needs to be posttranslationally activated by an SCF-type ubiquitin ligase containing the F-box protein known as Unusual Floral Organs (UFO) or Double

**Top(DOT) and that alterations in the spatio-temporal expression patterns of these two meristem identity genes were key-factors in the divergence of flowering time and inflorescence architecture between species. We found that the divergent expression patterns of UFO and DOT result from alterations in their promoters. To unveil how these promoters diverged we mapped cis-regulatory elements in DOT and are now identifying the corresponding transacting factors. Similar studies are underway to unravel how promoter EVAGREEN, encoding a homeodomain transcription factor, evolved from a ancestral paralogs needed to maintain meristem stem cell niches into a gene that is specifically required for cymose inflorescences. In this way we attempt to understand the functional implications and the molecular mechanisms underlying the "rewiring" of gene regulatory networks during evolution.

2. **Basic cellular processes associated with the pigmentation of flowers**

The regulation of the pH in various endomembrane compartments is crucial for the intracellular transport of small molecules, and the trafficking of proteins and vesicles. Mutations that inactivate the proton pumps that acidify such compartment are lethal in animals and plants, which underlines their importance for life but also hampers the identifications of additional factors via mutants. However, flower color mutants are a fortunate exception to this rule. We found that petunia ph mutants, identified for a blue flower color, fail to hyperacidify the vacuoles in petal cells. Via these mutants we discovered a novel proton-pumping complex, consisting of two distinct P-ATPase transporters (PH1 and PH5), which is necessary and sufficient to hyperacidify vacuoles. We are now investigating how the tonoplast-based H+-ATPase PH5 diverged from paralogous in the plasma membrane with regard to its intracellular localization and regulation via the interacting P3B-ATPase PH1.

While studying these P-ATPase pumps we discovered a novel pathway by which proteins and membrane vesicles traffic to the vacuole in petal cells via a new intermediate "organelle" that we dubbed vacuolino. Exploitingflower color mutants we identified transcription factors (PH3, PH4, AN1, AN11) that are necessary for the formation of
“vacuolinos” and one target gene (PH1) that is required for their fusion with the central vacuole. We have now initiated studies to (i) identify the complete set of target genes of these transcription factors and (ii) to establish for individual target genes whether they are necessary for the formation or fusion of vacuolinos.

3. Epigenetics
Switching genes on and off requires a series of molecular steps that ultimately result in post-transcriptional modification of histones and structural chromatin changes. DNA methylation is another epigenetic control mechanism, which usually is associated with gene inactivation, and believed to be more stable.

An interesting question is whether there are genomic regions of which the methylation is almost as dynamic as the histone modifications. The presence of de novo methyltransferases, DNA-demethylases, and in mammals, the Ten Eleven Translocation (TET) enzymes, which convert methyl-C to hydroxymethyl-C, suggest that DNA methylation could be much more variable than anticipated. We are looking into these dynamics in plants by monitoring the expression of DFR in petunia, one of the floral pigmentation genes, which varies in methylation level between varieties and in expression level. Apart from a small region close to that the transcription start site, the S’ flanking region is severely methylated and yet the gene is expressed in flowers. In other varieties, the promoter region is even more methylated and inactive, giving rise to white flowers. To monitor the dynamic effects of methylation further we have identified several demethylases (Demeter and Demeter-like (DML)) in petunia. These enzymes demethylate DNA by Base Excision Repair (BER) but how these enzymes are targeted to specific genomic regions is poorly understood. A series of transgenic plants containing various types of silencing constructs was generated with the aim to down-regulate either the entire DME-DML silmethylase family or specific members. Thus far, the phenotype of all transgenics is indistinguishable from wild-type, suggesting that if methylation levels at certain loci are indeed increased, the biological effects are quite subtle. We are currently examining if the perception of methylated Cs in the DME-DML silenced plants is higher than in WT, and if so, which genomic loci are affected.

Cervical cancer cells - Cervical cancer is the second most common cancer in women worldwide and is linked to infection with certain types of the Human Papilloma Virus (HPV) family. The proteins encoded by the E6 and E7 genes of high-risk HPV play a crucial role in cervical carcinogenesis. Together with dr. Steinbergen (VUMc) we previously showed that in HPV-infected keratinocytes and HPV-positive cancer cells, the reactivated hTERT promoter and its promoter are severely methylated. An unexpected finding as in most cases methylated promoters are inactive. The role of the E6 and E7 proteins in hTERT reactivation and its increased promoter methylation was examined by transfecting primary keratinocytes with E6- and E7-expressing constructs. Cells with high-risk HPV versions of the E6 and E7 became immortal, showed hTERT reactivation and a slight increase in hTERT promoter methylation over time. These results suggest that hTERT reactivation by E6 - E7 does not require certain promoter sequences to first become methylated. Methylation seems to follow reactivation. One of the possibilities that will be examined is that during cell culturing, stably hTERT-expressing cells have a selective advantage and that increased promoter methylation contributes to this stability.

Integrative Bioinformatics

Jaap Heringa

Mission
The research mission of the Center for Integrative Bioinformatics (IBIVU) is building understanding of genome-wide systemic behavior of cells at all network layers. This is done by developing computational analysis and modelling methods to mine and understand data coming from high-throughput measurements. Integrating such information may involve various layers of genomics data: from DNA sequence data via molecules and cells to patients. The approach also links experimental design and computational analysis.

Key publications

Highlight
Gunnar Klau appointed as extraordinary professor of Bioinformatics and Operations Research

Formal cellular modelling strategies using Petri-Nets

We have further developed our modelling system based upon Petri nets. Given the expressiveness of the modelling framework, it needs relatively little computation power, thereby bringing modelling of real-life biological systems within reach. Together with the group of Prof. Martine Smir (AIMMS) we are modelling the canonical Wnt/β catenin pathway, and some further relevant impiing pathways, leading to a rationalization of various experimental results. One of the main goals of the project is to unravel the role of this network in colon-cancer.

Biological sequence / network comparison and alignment
Our longstanding activity in sequence alignment has focused on motif-based alignment over the years. We have generated a method to extract motifs from multiply aligned protein sequences, and have applied the technique in conjunction with protein secondary structure prediction methodology to delineate a general secretion motif for proteins targeted by the mycobacterial type VII secretion pathway. We are now also combining Chip-seq data and Transcription Factor motif information to optimize the alignment and recognition of transcription factor binding sites (TFBS) within DNA sequence data.

To adequately model complex behavior of biological systems one needs to take interactions into account. These interactions are captured by various types of biological networks such as metabolic, gene-regulatory, signal transduction, and protein-protein interaction (PPI) networks. Recent advances in biological networks have resulted in large amounts of network data, such that appropriate analysis methods are now sorely needed, particularly in the field of comparative network analysis. Here, one wants to detect commonalities between biological networks from different systems or species, or derived from different conditions. Beyond traditional comparison of single entities such as protein or DNA sequences, topology-aware comparison methods identify whole functionally conserved network components and thus improve the transfer of functional annotations and the generation, investigation, and validation of mechanistic hypotheses.

We have further developed the NATALIEWEB web server for accurate topology-aware protein-protein interaction (PPI) network alignment and now able to produce high-quality alignments between large PPI networks. It provides an interface to a recently introduced general network alignment method coined NATALIE, which is fast and robust and can flexibly deal with various scoring schemes taking both node-to-node correspondences and network topologies into account. Application of network alignment is widespread, and ranges from direct application such as cross-species comparison of the Wnt growth pathway to more indirect applications such as predicting protein-protein interactions based on parallel evolutionary signals, captured by phylogenetic trees cast as networks.
The Centre for Translational Molecular Medicine (CTMM) Translational Research IT (TraIT) project aims to develop a longlasting IT infrastructure for the Dutch Medical Centres (UMCs) that will facilitate the collection, storage, analysis, archiving and securing of the data generated in CTMM research projects, thereby linking clinical data with high throughput experiments. We are involved in guiding and supervising the process of storing, analysis and integrating molecular profiling data from techniques such as mass spectrometry, microarrays and next generation sequencing.

TraIT’s WPS addresses the infrastructure of TraIT, which should enable multi-level collaboration and data sharing for translational research within The Netherlands, starting with the CTMM projects. The infrastructure should enable data interoperability, integration and data sharing across the four data-capturing work packages. Initially a syntactic approach to integration has been explored, but we are initiating a collaboration between various VU computer science groups (e.g. van Harmelen, Bal and Fokkink), the IBIVU group and the VUMC to implement a semantic approach for data storage, interoperability and reasoning. The project will be largely based upon the Resource Description Framework (RDF) triple store, while we are developing new technology for -omics and bioinformatics related data querying, and automated model generation.

Network or using a number of networks in comparison.

Protein interaction and denaturation

An important research theme in the group is protein bioinformatics, ranging from sequence alignment and alignment-based analysis tools, via secondary structure and protein interaction prediction, to protein tertiary and quaternary structure prediction.

Predicting interface residues using orthology/paralogy relationships

Multiple sequence alignment (MSA) is one of the most important tools for gleaning structural and functional knowledge from homologous sequence information. We have used our MSA tool Praline and the Sequence Harmony method, for prediction function-specificity residues, for predicting protein-protein interaction (PPI) interface residues, based on alignment information including orthologous and paralogous sequences. Interaction prediction is based upon the following: If a protein A interacts with a protein B, then protein A’ do interacts with a protein B, then upon the following: If a protein resided on a number of networks in comparison.

sequence data, suggesting a number of residues putatively associated with disease progression. In the last year we have also compiled a database of homodimers and hetero-dimers to get more detailed insight in the type of amino acid mutations that induce or inhibit protein-protein interaction. We are further integrating correlated (or compensating) mutations to enhance the sensitivity of our PPI predictions.

Modelling the effective interaction between proteins

To assess if two proteins will interact under physiological conditions, information on the interactions energy from binding is needed. Statistical learning techniques, such as docking, for predicting protein-protein interactions cannot quantitatively estimate binding free energies. Full atomistic molecular simulation methods do have this potential, but are completely unfeasible for large-scale applications in terms of computational cost required. We investigated whether applying coarsegrained molecular dynamics simulations, is a viable alternative.

To this end we constructed a simulation tool for coarse-grained atomic prediction of protein-protein interfaces, based on applying a coarse-grained molecular model and reducing the system size to the minimum. We use the MARTINI force field, which lumps four heavy molecules/ segments per bead, for coarse-graining, and by simulating only the relevant part of the molecular system, the ‘PPI box’, we are able to reduce computation times drastically relative to full-molecule simulations. Using the system, we calculated the free energy barrier with respect to the bound state based on molecular dynamics simulations using both a full atomistic and a coarse-grained force field for the TCR-pMHC complex and the MP1-p14 scaffolding complex. We found that the binding free energies energy barriers from the coarse-grained simulations are at least as accurate as those from the full atomistic ones, while achieving a speedup of over 500-fold. We also observed that extensive sampling is extremely important for obtaining accurate free energy barriers, which is only within reach for the coarse-grained models. We further showed that the coarse-grained model preserves biological relevance of the interactions: i) we observe a strong correlation between evolutionary likelihood of mutations and the impact on the binding free energy barrier with respect to the bound state; and ii) we confirm the dominant role of the interface in the interaction. Our overall conclusion is that coarse-grained molecular simulations can realistically be used for the accurate prediction of protein-protein binding affinities interaction strength.

Modelling structural differences between the cold and the heat denatured state

The hydrophobic effect is the biggest factor in the stability of proteins. The water molecules and hydrophobic interactions also give rise to curiously temperature dependent behaviour: some proteins do not only unfold at high temperatures, but also at low temperatures (cold denaturation). We developed a simple model that reproduces both heat and cold denaturation. We obtain an absorption state that is much more compact than the heat denatured state, as has been observed experimentally. Moreover, we can reproduce the very characteristic heat capacity curves for protein folding. With our simple model, we can relate the slope of the curves on either side of the folding transition to the amount of exposed hydrophobic amino acids. This latter result gives a handle on interpreting Differential Scanning Calorimetry (DSC) data from high throughput analysis.

Next-generation sequencing (NGS) and oral health

Together with ACTA we have started a meta-genomics project based upon NGS data generation. Using various mock datasets, we have analysed the behaviour of common pre-processing and downstream tools that are used within this area of research. The main objective of the project is to develop bioinformatics technology that is able to delineate bacterial strains and species in the oral cavity with minimal error. In the long run we want to be able to relate bacterial compositions to oral disease in patients.
Medicinal Chemistry

Rob Leurs

Research profile

A decade after the unraveling of the human genome, a wealth of biological data has become available. This data explosion offers chemistry-related disciplines huge opportunities to convert this knowledge into relevant benefits for society, by, e.g., translating biological understanding into effective medicines and biomarkers. With its high interdisciplinary nature Medicinal Chemistry acts on the interface of biology and chemistry, combining fundamental expertise in synthetic organic chemistry, computational chemistry, cheminformatics, biochemistry and structural biology. The mission of VU Medicinal Chemistry (MC) is to understand ligand-protein interaction at the molecular detail, and to use this knowledge for the computational design and synthesis of new bioactive molecules. With these core activities MC aims to be a pivotal player in interdisciplinary scientific networks with a focus on two complementary themes, G Protein Coupled Receptor proteins (GPCRs) and Fragment-Based Drug Design (FBDD).

Molecular interactions scrutinized: Fragment-Based Drug Design

This research is dedicated to a better understanding of molecular interactions between a biologically active compound and its protein target. We are among the very first academic groups to have set up a Fragment-Based Drug Design (FBDD) platform and are recognized as one of the leading players. FBDD is emerging as a very successful approach as the focus on small interact- ing molecules simplifies many studies that are too complicated to handle with bigger, drug-like molecules. For example, in silico modelling and understanding of the binding kinetics (k_on and k_off) and thermodynamics of ligand-protein interaction are more reliable by limiting ligand size and interaction features, allowing careful analysis and validation of crucial interaction types. Next to studying our proprietary targets, FBDD also allows the group to participate in a variety of collaborations as probing a panel of different drug targets contributes to a better scientific understanding of ligand-protein binding. These studies also result in valuable hit compounds for the protein targets of our collaborators. Next to protein-protein interactions, ligand-gated ion channels, GPCRs (see below), kinases and PDEs are being studied. The latter project targets parasites. Trypanosoma brucei PDEs, validated targets to treat the neglected disease Human African trypanosomiasis (HAT). The studies that are led by our group are financed by TI Pharma and carried out by a consortium that also includes academic partners (e.g., Utrecht U, the Royal Tropical Institute) and large companies (e.g., Nycomed, Takeda, DND, IOTA Pharmaceuticals and Mercachem). Using fragment merging and fragment growing approaches, new compounds that inhibit this parasite enzyme have been identified. The therapeutic potential of the resulting compounds is currently being optimized.

In another FBDD program that is part of the highly successful EU FP7 Health project Neurocypres (coordinated by Prof. Guus Smit from the AIMMS Neurobiology department) the Medicinal Chemistry Division, together with University of Vienna and the Medical University of Vienna have gained new insights into the molecular basis of the GABA receptors. Three-dimensional models of these ion channels were constructed and validated using virtual screening approaches. The results were presented at Nature Chemical Biology. These studies also identified new binding fragments that are interesting starting points for developing new drugs against epilepsy, anxiety and sleep disorders.

**GPCRs: from delineation of ligand binding sites to new potent GPCR ligands**

GPCRs are one of the very important protein families in current and (in our opinion) future drug discovery. Ratio- nal drug design approaches on GPCR proteins remain one of our most important challenges. New concepts in GPCR pharmacology (e.g. receptor allosteric modulation, target residence time, GPCR heterodimerization) are crucial for future GPCR target discovery efforts and effective chemical exploitation of GPCR modulation. Effectively employing the state of the art approaches in GPCR Biochemistry, Structural Biology, Computational Chemistry and Structure-Based Drug Design (SBDD), MC is focusing on a diverse set of GPCR proteins, with main emphasis on the family of histamine and chemokine receptors. In the last years, considerable progress has been made in implementing emerging and hugely important molecular pharmacology concepts in the existing GPCR projects. Thus, the new concept of ligand-biased signaling, i.e., the discovery that GPCRs signal not only via G-proteins but also via other pathways such as mediated by β-arrestins, has been thoroughly explored for histamine H4 receptors. In collaboration with Novartis, it was shown that small structural changes in the agonist ligands result in diverse intrinsic activities for the different signaling pathways. These findings have immense implications for histamine H4 receptor drug development programs. Biocomputational approaches in combination with the design and synthesis of new ligands have resulted in molecular models that improve our understanding of ligand binding, especially when combined with the emerging structural information that is currently being generated by the scientific community (resulting amongst others in the Nobel prize for chemistry 2012). Next to ligand-biased signaling, the group is also implementing the concept of binding kinetics successfully into the histamine H4 receptor drug development program. Linking binding kinetics with structural understanding of ligand-protein interaction and clinical efficacy will be further explored in a recently funded IMI project (K4DID) with a strong consortium of European partners. Similar progress is being made on other GPCR targets, including histamine H1 receptor and chemokine receptors.

For the latter class, the group has now developed unique non-peptidomimetic small-molecule ligands that act as agonists for the chemokine receptor CXCR3. These compounds are part of a biaxial class in which efficacy can be modulated by intriguingly subtle changes in structure (figure below). The full agonists are very important chemical tools for the detailed assessment of receptor activation and for studying downstream CXCR3 signaling.

**CXCR3 activity curves of selected biaxial compounds, displaying the effect of an increasing halogen size and of moving a bromine atom. (above) An electrostatic potential visualisation of the biaxial part of the ortho-iodo CXCR3 agonist shows the possibility for halogen-bonding**

**Key Publications**


Chimed Jansen & Kristina Orrling
Designer drugs against African sleeping sickness

African sleeping sickness, a neglected disease
In the Division Medicinal Chemistry of AIMMS Chimed Jansen and Kris-
tina Orrling have discovered new molecules which could prove to be
stepping stones on the way to a new treatment for African sleeping sick-
ness
African sleeping sickness is the result of infection by the single celled
parasite, Trypanosoma brucei, follow-
ing a bite from an infected tsetse fly.
This parasite infects livestock which
form a natural reservoir from which
it spreads to thousands of people
across sub-Saharan Africa each year.
The initial symptoms are flu-like and
may be easily missed. However, if left
untreated the disease will eventually
progress and is inevitably fatal.
Current treatment options are effect-
tive for now, yet the side effects they
cause may result in the deaths of up
to 5% of patients. Hence finding new
treatment options is a priority for
drug researchers involved in the
field of so-called neglected diseases

Finding selective compounds using computer simulations
Chimed Jansen has developed computer models to predict the interactions
and binding orientations of millions
of molecules in the first crystal structure
of the TspPDEB1 enzyme, a potential
drug target to kill the Trypanosoma para-
site that causes African sleeping sickness.
Chimed explains: “We developed a com-
puter protocol that places small molecules
into the substrate binding pocket of the 3D
computer model of the protein. The quality
of the fit was determined and those small
molecules which appeared to fit into sub-
strate pocket of the protein best were se-
lected for purchase.” The 29 selected mol-
ecules were subsequently tested on the
actual protein in a Nycomed laboratory
in Konstanz and six of the molecules were
selected for purchase.

Kristina and Chimed have designed and synthesized new molecules that kill the sleeping
sickness parasite Trypanosoma brucei. To guide the design of the new substances, the VU
scientists created 3D models of the enzyme interacting with the research molecules, e.g.
(a) the design starting point rolipram and the (b) the most active anti-parasite molecule

Adaptive Differential Network-based Drug Design (ADNDD) and T.bruc
ei
With the progression of genome sequencing it has also become clear that
although two human individuals are identical to 99.9 % of their
genome sequence, they still differ in
any molecular pathway or network
of importance. With systems biology
it has become clear that the flux
through or signal transduction by intracellular pathways, is not
determined by a simple ‘rate-
limiting’ step and that which of the
molecular components determine
functions most, cannot be deduced
in any simple manner: thorough
experimental or computational
analysis is required.

Adaptive Differential Network-based Drug Design (ADNDD) and T.bruc
ei
With the progression of genome sequencing it has also become clear that
although two human individuals are identical to 99.9 % of their
genome sequence, they still differ in
any molecular pathway or network
of importance. With systems biology
it has become clear that the flux
through or signal transduction by intracellular pathways, is not
determined by a simple ‘rate-
limiting’ step and that which of the
molecular components determine
functions most, cannot be deduced
in any simple manner: thorough
experimental or computational
analysis is required.

Our group has contributed to the
above insights and postulated that
most remaining large diseases (e.g.
diabetes, cardiovascular, cancer) are
systems biology diseases and should be
approached accordingly.

We identified the glucose importer as
the best drug target. We compared this
target between T. brucei and a relevant
host tissue (human erythrocytes) and
developed differential network-based
drug target identification, which led
to a confirmation that the glucose
transporter should be the first target
to go for.

We developed an approach to deal with
a complication that is usually not
considered in drug targeting, i.e. that
the objects of study may well be ‘moving
targets’: gene expression may change in
the target cell upon application of the
drug inhibiting the target. We examined
alterations in the expression of the genes
encoding the glucose transporters in
T. brucei upon incubation of inhibitors
of glucose transport and found that
the expression of the relevant glucose
transporter decreased rather than
increased with added inhibitor.

We could explain this in terms of the
life cycle of T. brucei, particularly the
phenomenon that when entering its
host tissue (the Tse tse fly) the
organism is confronted with a lack of
glucose substrate.

Multiscale modelling and new facilities for model integration
Medicinal drugs have to work at the level
The complexity of the biological systems is distributed. This has led us to develop a new systems hypothesis vis-a-vis the origin of the Warburg phenotype, which is now being developed towards testing.

We performed a detailed control analysis in view of experimental information and our modern systems biology methodologies: The control of the Warburg phenomena is distributed. This has led us to develop a new hypothesis that probably recognizes the origin of the Warburg phenotype, which is now being developed towards testing.

We have been active in the standardization of models (through JWS, Joeny Snoeij), systems biology workflows to come to terms with this complexity. The one in which activities of various research groups worldwide are integrated depends critically on the communication not only between the research groups but even more so between the mathematical or data models they make.

We recognized an entirely different limitation: it is impossible that single research groups understand the biology and the mathematics required to model a system that reaches from molecule to whole patient.

We have developed a web-based facility that enables the integration of various models, ranging from various types of PK models, various types of PD models and molecular systems biology models.

Standards

The complexity of the biological systems that AIMMS targets is horrific. The systems biology group develops various methodologies of their macromolecular targets. At the same time, the disease they need to battle affects a substantial part of the body as a whole and thereby networks of hundreds of different types of molecule. The problem most quoted as limiting the understanding of multi-scale phenomena is that of stiffness of the corresponding differential equations in time.

We can recognize an entirely different limitation: it is impossible that single research groups understand both the biology and the mathematics required to model a system that reaches from molecule to whole patient.

We have developed a web-based facility that enables the integration of various models, ranging from various types of PK models, various types of PD models and molecular systems biology models.
still efficiently secreted to the cell surface. Based on this technology we are currently developing live vaccines that display multiple antigens at their cell surface in high densities. Finally, we are studying the substrate specificity of the TPS system in the important pathogen Neisseria meningitidis, which contains several of these secretion systems required for signal transduction.

Functioning of inner membrane proteins

Inner membrane proteins play an important role in the functioning of the bacterial cell envelope, including energy metabolism, cell division and signal transduction. For cell division a large multisubunit complex, also known as divisome, is formed at the center of the cell. The assembly of this complex follows a strict hierarchy and is tightly regulated. The main function of the divisome is contraction of the membrane and septum formation.

In our section, we are studying the role of FtsQ in divisome formation and cell division. FtsQ is an inner membrane protein with a large periplasmic domain. Because FtsQ performs an essential function in the assembly of the divisome, but is present in small quantities, the hypothesis is that this protein could be an interesting target for the development of antibacterial compounds.

A second project in this theme is signal transduction. Signal transduction is important for bacteria to mount an appropriate intracellular response upon sensing specific extracellular signals.

In our group, we study the process called cell surface signaling, in which a signal is sensed by an outer membrane receptor, transduced via an anti-sigma factor in the inner membrane and finally results in activation of an alternative sigma factor in the cytoplasm. We are analyzing the different cell surface signaling systems of the human pathogen Pseudomonas aeruginosa and determining how the signal is exactly transduced across the inner membrane. Our results indicate that a specific proteolytic cascade is required for signal transduction.

Protein secretion in pathogenic Mycobacteria

The important human pathogen Mycobacterium tuberculosis does not belong to the Gram-negative bacteria. Yet, if these bacteria are studied using electron microscopy, they have a similar cell envelope profile. Biochemical analysis showed that the mycobacterial cell envelope contains, in addition to a normal inner membrane, an outer membrane composed of very large and unique lipids called mycolic acids that are intercalated with other unusual (glycol)lipids. The presence of this second membrane implies that mycobacteria also must have a specialized secretion pathway. Recently such a secretion system has been identified and designated type VII secretion. Interestingly, pathogenic mycobacteria have up to five different type VII secretion systems. A considerable body of work has now demonstrated that some of these secretion systems transport important virulence factors that are crucial for mycobacterial survival inside the host. In our group, we study different aspects of the type VII secretion systems. The first aspect covers the working of this secretion machinery. We have identified different substrates for these secretion systems, but how are these substrates recognized?

In addition, we are in the process of isolating and characterizing the membrane complex of type VII secretion systems. A different aspect is the effect of protein secretion on virulence. What is the function of the secreted proteins and how do they interact with the host? Finally, we will use the information on this secretion system to improve the current tuberculosis vaccine strain M. bovis BCG and identify new compounds that block this persistent pathogen.

Autotransporters

Mycobacterial genomes contain up to five loci encoding type VII secretion systems, named ESX-1 to ESX-5. A number of different substrates have been identified that are secreted via these different secretion systems. Interestingly, these substrates seem to be secreted as folded heterodimers and they lack classical secretion signals.

Thus far the mechanism of substrate recognition is not well understood. We have now shown that our model ESX-5 substrates, PE25/PPE41, are targeted to their secretion system by a signal located in the C terminus of PE25. Site-directed mutagenesis of residues within this C terminus resulted in the identification of a highly conserved motif, i.e., YxxxD/E, which is required for secretion. Both the nature of the two conserved residues and the distance between these residues were crucial for secretion.

Subsequently, we performed similar experiments for the ESX-1 pathway. Surprisingly, ESX-1 substrates contained a C-terminal signal functionally equivalent to that of the ESX-5 substrates. Exchange of the C-terminal secretion signals between the different substrates restored secretion, but each protein remained secreted via its own ESX secretion system.

This results indicates that an additional signal provides system specificity. Therefore, our data show that the YxxxD/E motif is a general secretion signal that is present in all known mycobacterial T7S substrates or substrate complexes. Finally, we used this information to develop a search pattern for novel type VII secretion substrates.

This pattern used the YxxxD/E motif and the information that this motif is found approximately at position 80–95, in a flexible region that follows a typical helix-turn-helix structure.

Using this search pattern a number of secreted proteins with unknown secretion route were identified, indicating that indeed our search pattern can be used to predict unknown substrates.

Research Highlight

General secretion signal for the mycobacterial type VII secretion pathway

Sequence logo based on an alignment of all known mycobacterial type VII secretion substrates, only the region surrounding the identified YxxxD/E motif is shown.

Sequence logo based on an alignment of all known mycobacterial type VII secretion substrates, only the region surrounding the identified YxxxD/E motif is shown.

Sequence logo based on an alignment of all known mycobacterial type VII secretion substrates, only the region surrounding the identified YxxxD/E motif is shown.
The synapse proteome as entry point for drug discovery

The department of Molecular and Cellular Neurobiology (MCN) aims at understanding the molecular mechanisms of synaptic function and plasticity. Synapses form the points of contact between nerve cells in the brain and with muscle cells in the body. Synapses contain approximately 2000 proteins, which are crucially involved in neurotransmitter release and modulate presynaptic transmitter release. The role of synaptic proteins after knockdown or by over-expression is required to address gene/protein function at an appropriate in-depth level that is decisive for further drug screening or therapy design.

Defining potential targets

Molecular and Cellular Neurobiology uses proteomics technology to identify and quantify proteins in the synapse of animal models of disease or in human patient postmortem brain. In particular, much effort is directed to the understanding of protein complexes and how these may be important as ‘signalling machines.’

Currently we address the function of these proteins and aim to establish their contact site with the receptor. Obviously, the latter may form new entry points for compounds that affect AMPA-receptor function in a subtle way.

Dissecting the role of proteins in the synapse

In principle, proteomics analyses identify many potentially important proteins. Many of these have still unknown functions. In recent years MCN has developed automated high content microscopy at confocal resolution to assess the role of synaptic proteins after knockdown or by over-expression.

Obviously, synaptic protein function requires detailed analyses, including electrophysiology, intervention strategies both in vitro and in vivo, and the analysis of animal behavior. This pipeline of experimental analysis is required to address gene/protein function at an appropriate in-depth level that is decisive for further drug screening or therapy design.

Key publications


Molecular Toxicology
Nico Vermeulen

Mission
Our mission is to develop novel and innovative concepts concerning drug disposition and drug safety (~ ADME-Tox). Integration of advanced computational and experimental approaches is key, while the focus is on molecular mechanisms of bioactivation, bioactivation and adverse drug reactions. Our research involves Phase I enzymes, e.g. Cytochromes P450 (CYPs), Phase II enzymes, e.g. Glutathione S-transferases (GSTs), and other selected drug targets, in three strongly inter-related research lines:

1. Computational and biophysical approaches and tools to study proteins in simulation, and consequent development of innovative concepts concerning drug disposition and drug safety (~ DSM Innovative Synthesis).
2. Cells as primary hepatocytes, cell lines (HepG2, HepaRG) and stem-cell derived induced hepatocytes (iHep).
3. Molecular dynamics (MD)-based methods, ligand-affinities and selectivities are predicted and experimental results are rationalized. Recent awareness that protein-kinase plasticity plays a crucial role in CYP activities lends urgency to take ‘induced fit’ effects and protein dynamics into account in a more efficient manner. In a Horizon Valorisation project, earlier plasticity models have been extended to the prediction of binding modes to bio-catalytically active P450 BM3 mutants. This has led to a joint contribution to RECOMB (~ Gunnar Klau, CWL, and Alan Mark, Queensland).

Bioactivation

Reactive metabolites and adverse drug reactions

Drug metabolising enzymes play a very important role in the elimination of drugs from the body and to a large extent determine bioavailability and pharmacokinetics of drugs. They are several enzyme families display genetic polymorphisms due to mutations, frame shifts, gene deletions or gene duplications, sometimes large inter-individual variations in pharmacokinetics occur which lead to adverse drug reactions (ADRs) in part of the patient population. ADRs may result from unanticipated high plasma concentrations of the parent compound, leading to off-target pharmacological effects, or from the formation of high levels of active and/or protein-reactive drug metabolites. Our research focuses on the identification of the specific enzymes involved in the formation and inactivation of (re-)active metabolites of drugs in order to evaluate whether combinations of genetic polymorphisms at the level of Cytochromes P450 (CYPs), Phase II enzymes, e.g. Glutathione S-transferases (GSTs) and NADPH quinone oxidoreductase (NQO1) might determine individual susceptibility to rare, idiosyncratic liver injury or agranulocytosis. In a TI-Pharma project (‘Translational biomarkers of ADRs; S. Dragovic and J-S Boerma), we have shown that genetically determined GSTs, e.g. M1-1 and P-1-1, play an important role in the inactivation of reactive metabolites of Clozapine and Diclofenac. Interestingly, the GSTs displayed a strong regioslectivity in conjugation of the reactive intermediates to GSH when compared to the direct chemical reaction to GSH.

Therefore urinary excretion of the corresponding mercapturic acids will not only reflect internal exposure to reactive metabolic products but also discriminate between chemical vs. enzymatic toxicity. For both Clozapine and Diclofenac, we showed that human CYPs contribute differentially to their bioactivation. In collaboration with the Karolinska Institute (M. Ingelman-Sundberg) we demonstrated, in a bank of 100 human liver samples, an 8-fold inter-individual variability of bioactivation of Clozapine due to variability in CYP3A4. Therefore high CYP3A4-activity in combination with a deficiency in GSTM1 is likely a risk factor for hepatotoxicity of Clozapine. By genotyping patients treated with Clozapine, we also observed a higher frequency of null-genotypes of GSTM1 and T1 in patients with agranulocytosis when compared to patients without ADR, suggesting that GST deficiency is also a risk factor for agranulocytosis. We also developed novel LC-MS-based methodologies to characterise the selectivity of protein modifications by reactive metabolites. Using GST P1-1 as a target binding protein, we have shown that reactive intermediates for hepatotoxic drugs, such as Diclofenac, Clozapine, Troglitazone and Acetylsalicylic acid, react selectively with specific cysteine-residues probably due to differences in microenvironment and accessibility of protein thiols. In case of Diclofenac, protein-modifications resulting from three different reactive intermediates were observed. By comparing the profile of protein-adducts to that of GSH, in the context of two iHep projects, we showed that the reactivity of protein-thiols can be quite distinct from GSH-thiol.

In a novel IMI-JU project, entitled ‘MIP-DiLL’, we will extend the studies on the role of genetic polymorphisms of biotransformation enzymes and reactive drug metabolites in drug-induced liver injury (DILI) by using different in vitro hepatotoxicity models, such as primary hepatocytes cell lines (HepG2, HepaRG) and stem-cell derived hepatocytes.

Key Publications


Overall strategy to generate chemically reactive drug metabolites and to characterise their nucleophilic selectivity towards biologically relevant protein targets. Covalent binding of reactive metabolites (RMs) to proteins is considered to be one of the important mechanisms by which drugs cause tissue damage. (J.S. Boerma et al., Chem. Res. Tox.)
In collaboration with AMC (Mahdi Motazacker, Experimental Vascular Medicine), the structural impact was elucidated of a rare protein mutation as observed in a family with early cardiovascular disease (Ruben Vosmeer)

**Cellular toxicity**

The baker’s yeast S. cerevisiae has been further used as simple eukaryotic model organism to reconstitute the interplay between bioactivation and bioinactivation of drugs using human and human-like enzyme expression. Galvin Vredenburg has shown that Clozapine metabolism by P450 BM3 increased toxicity in yeast. Co-expression with GSTs resulted in non-enzymatically formed GSH-conjugates.

The metabolic profiles in the cells mimicked the isofrom-specific previously observed using purified enzymes. Why only one GST-isoform is successful in protecting yeast cells against reactive metabolites of Clozapine remains elusive, but perhaps hints at a role for particular Clozapine-GSH conjugates. The stable N-desmethyl-Clozapine was equally toxic as its parent compound, whereas exposure of cells to reactive metabolites of Clozapine induces degradation of the permease. Overexpression of a Ubiquitin protease also rescues, possibly by reversing the process of permease internalization and degradation. Growth arrest by Acetaminophen is accompanied by cell cycle defects, whereby the normal budding process is disturbed and chiasmosome segregation might be deregulated. In particular gene deletion strains, lacking genes DNA repair, growth arrest is bypassed, indicating a possible role as tumor suppressor.

Furthermore, we have started to work with mammalian tissue culture (Shakie Nevward) and generated stably transformed HEK293 cells with inducible human and murine GST. We expressed and purified recombinant NQO1 using E. coli and showed that the yield of trapped NAPQI-SG is indeed significantly reduced. These findings further underscore the importance of polymorphic GSTs and of Quinone reductases in protecting against drug bioactivation in a cellular context and the need to further evaluate this to understand idiosyncratic drug toxicity.

The AIMMS PhD project (Angelina Husseinovic) is investigating the role of Actemaminophen in growth arrest in yeast. We have identified in a multicyclop suppressor screen genes that rescue the cells from growth arrest. Overexpression of an amino acid permease is crucial for suppression, although exposure of cells to actemaminophen induces degradation of the permease. Overexpression of a Ubiquitin protease also rescues, possibly by reversing the process of permease internalization and degradation. Growth arrest by Acetaminophen is accompanied by cell cycle defects, whereby the normal budding process is disturbed and chiasmosome segregation might be deregulated. In particular gene deletion strains, lacking genes DNA repair, growth arrest is bypassed, indicating a possible role as tumor suppressor.

The AIMMS PhD project (Angelina Husseinovic) is investigating the role of Actemaminophen in growth arrest in yeast. We have identified in a multicyclop suppressor screen genes that rescue the cells from growth arrest. Overexpression of an amino acid permease is crucial for suppression, although exposure of cells to actemaminophen induces degradation of the permease. Overexpression of a Ubiquitin protease also rescues, possibly by reversing the process of permease internalization and degradation. Growth arrest by Acetaminophen is accompanied by cell cycle defects, whereby the normal budding process is disturbed and chiasmosome segregation might be deregulated. In particular gene deletion strains, lacking genes DNA repair, growth arrest is bypassed, indicating a possible role as tumor suppressor.

**Structural Biology**

**Holger Lill**

**Highlights**

- Early 2012, a patent entitled ‘P450 BM3 mutants and their use for regio- and stereoselective hydroxylation of alpha-ionone’ (investigators: Harini Venkataraman, Jan Commandeur and Nico Vermeulen; IBO5-ACS project) was filed, in cooperation with DSM IP Assets B.V.

- Upon our proposal, prof. Magnus Ingelman-Sundberg (Karolinska Institute, Sweden) was appointed ‘2012 Nauta Professor’. Amongst others he provided a very successful one-week course on ‘Epigenomic and genomic variation and mechanisms in drug efficacy and drug toxicity’.

**Mission**

The research of the section Structural Biology within AIMMS is directed at elucidation of biomolecular interactions, a fundamental principle in Life Science. This comprises interactions between individual proteins, whole-cell interac-tomics of key proteins in cellular metabolism and signalling, as well as interactions between proteins and small-molecule effectors. Research lines presently pursued include investment of energy metabolism in pathogenic bacteria, of the role of 14-3-3 proteins in tumor cell biology and the interaction of proteins involved with novel small-molecule compounds as potential drug candidates.

**1. Respiratory ATP synthesis – the new generation of (myco-)bacterial drug targets**

Tuberculosis causes approximately 2 million deaths per year and an estimated 1/3 of the world population harbors Mycobacterium tuberculosis in a dormant or latent form. Infections with multidrug-resistant and extensively drug-resistant mycobacterial strains as well as co-infection with HIV pose a global health challenge. To counteract development of drug-resistant strains and to shorten tuberculosis treatment the discovery of new drugs, validation of new target proteins, and understanding of drug/target interactions are essential.

In February 2012, Molecular Toxicology started with its 3rd IMI-JU project, entitled: ‘Prediction of Drug-Induced Liver Injury Mechanism-Based Integrated Systems for the prediction of drug-induced liver injury’ (Acronym: MIP-DILI; 35 M€, www.mip-dili.eu). It allowed Molecular Toxicology to appoint three PhD-students and one post-doc.

In 2012, Molecular Toxicology invested very significantly in novel equipment: a fully automated Agilent UPLC 1260 - 6200 Accurate-Mass TOF LC/MS, and in collaboration with Medicinal Chemistry, a automated MicroCal-Auto-ITC-200 instrument.

Energy metabolism has emerged as a new target-pathway for development of new anti-tubercular drugs (see Figure). Previously, in collaboration with Tibotec/GSK we validated ATP synthase as target of the diarylquinolines, a new, promising class of anti-tuberculosis drugs. We also showed that diarylquinoline lead compound bequidoline is highly selective with no significant effect on human ATP synthesis. In december 2012 the American Food and Drug Administration (FDA) has granted accelerated approval to bedaquiline for treatment of multidrug-resistant tuberculosis, making it the first new anti-tuberculosis drug approved in over 40 years.

The potency of presently known diarylquinolines is restricted to mycobacteria, with little or no effect on the growth of other Gram-positive or on Gram-negative bacteria. For a new set of compounds from this class, inhibited growth of key Gram-positive pathogens, was confirmed in combination with ATP synthase, revealing that ATP synthase in non-mycobacterial pathogens can be a promising drug target (Balemans et al. 2012). We also examined the issue of bacterial metabolic resting states observed for a variety of pathogenic bacteria, which display low susceptibility for most antibacterials. Based on our work with replicating and dormant mycobacteria we present examples of how bacterial metabolic states may be controlled, target pathways may be validated and screening on metabolically resting bacteria can be designed. A deeper understanding of bacterial metabolic states may provide valuable input for the design of efficient screening approaches in the discovery of new antibacterial agents (Bale & Kouil 2012).

Strong synergy has been found in mouse models for combinations of drugs either known or postulated to target energy metabolism, such as diarylquinolines, pyrazinamide and clofazimine (Fig. 1). Previously, we reported that pyrazinamide, the active form of pyrazinamide, decreased the proton motive force and respiratory ATP synthesis rates and cellular ATP levels in Mycobacterium bovis BCG (Lu et al. 2011). Extending this research line, we investigated synergy between inhibitors of energy metabolism in vitro settings, shedding light on the molecular basis of the observed synergy (manuscript submitted).

**2. Estrogen Receptor alpha as target for Fusicoccin and 14-3-3 proteins.**

Protein-protein interactions involving 14-3-3 proteins form the basis of many regulatory processes in living cells. Not surprisingly, changes in the expression, activity, and interaction of 14-3-3 proteins underlie a range of human diseases; e.g. cancer, Alzheimer’s disease, and bovine spongiform encephalopathy (BSE).

The discovery of a small ligand that modulates 14-3-3/target protein interactions offers an attractive...

3. Protein folding and translocation

Proteins are linear polymers of amino acids that need to fold into well-defined three-dimensional conformations to gain specific functions. Misfolded proteins have a high propensity to form aggregates, which are considered causative agents for numerous severe diseases, including Alzheimer’s and Parkinson’s disease and diabetes. Protein folding is thus crucial for all organisms. It is equally important that proteins localize correctly, in the right membrane or sub-cellular compartment. Folding and localization of newly synthesized proteins are two inter-dependent processes that we study using advanced spectroscopic and microscopic tools. We study the folding of the protein flavodoxin, using fluorescence and nuclear magnetic resonance spectroscopy. Flavodoxin is a bacterial reduct protein that transfers electrons via a non-covalently bound flavin mononucleotide (FMN) cofactor. Previously, we showed that denatured apoflavodoxin (i.e., flavodoxin without its cofactor) first forms a rather stable but misfolded intermediate, before it folds to the native state via a second, more native-like but unstable intermediate (Bollen et al. Biochemistry 2004; Bollen et al. PNAS 2006). The last step in flavodoxin folding is FMN binding to native apoflavodoxin (Bollen et al. JBC 2000). Recently, we showed that flavodoxin binds its FMN cofactor extremely tightly (picomolar affinity), and that this tight binding is mediated by many amino acid residues throughout the protein structure (Bollen et al. Nat Commun 2012; see research highlight). In the future we aim to study the folding of flavodoxin while it is synthesized on the ribosome. Gram-negative bacteria consist of two aqueous compartments: the cytoplasm and the periplasm. All proteins are synthesized in the cytoplasm, but many need to be translocated across the cytoplasmic membrane into the periplasm. This task is performed by two independent systems: the Sec and the Tat system. The Sec system translocates unfolded proteins through a narrow pore in the membrane, whereas the Tat system exclusively translocates folded proteins. We investigate the Tat system, in particular its structure, its mechanism, how it senses the foldedness of the proteins that are translocated. Recently, we deciphered how pathway-specific chaperones recognize their cognate substrate protein (Shanmugham et al. Plos One 2012). Numerous proteins require cofactors to be active. Computer simulations suggest that cooperative interaction networks achieve optimal cofactor binding. In this paper, we experimentally identified residues that are crucial for stabilizing these networks and thus for cofactor binding. This paper provides new insights into cofactor-binding interactions. First, we used a well-established titration procedure to determine the dissociation constant of flavodoxin. After each titration step, part of the free FMN binds rapidly to apoflavodoxin, causing the associated FMN fluorescence to be quenched nearly instantaneously to low level. We found that the Kd for FMN dissociation from flavodoxin is 3.51×10–10 M, consistent with previous reports for various flavodoxins. This study reveals for the first time that the titration procedure underestimates the KD-value of cofactor-bound proteins, because after this initial quenching extremely slow conformational events happen. Reconstituted holo-protein relaxes with a time constant of ~5 days to a state that binds the flavin cofactor about two orders of magnitude better than freshly formed flavodoxin. Nuclear magnetic resonance (NMR) spectroscopy revealed that many residues are involved in this relaxation process (Figure above). Several backbone amide cross-peaks shift with a time constant similar to the one observed by fluorescence. Relaxed flavodoxin is characterized by virtually no fluorescence of bound FMN and has a Kd of 3.82×10–12 M. Thus, tightening of FMN binding leads to an energetically highly favorable protein state with picomolar-binding affinity. Finally, we used NMR-detected hydrogen-deuterium exchange to identify residues that are responsible for this tight binding, and found that many residues throughout the 3D structure of flavodoxin form a network that stabilizes the cofactor-bound state of the protein (Figure left)

Key Publications

3. Protein folding and translocation

Proteins are linear polymers of amino acids that need to fold into well-defined three-dimensional conformations to gain specific functions. Misfolded proteins have a high propensity to form aggregates, which are considered causative agents for numerous severe diseases, including Alzheimer’s and Parkinson’s disease and diabetes. Protein folding is thus crucial for all organisms. It is equally important that proteins localize correctly, in the right membrane or sub-cellular compartment. Folding and localization of newly synthesized proteins are two inter-dependent processes that we study using advanced spectroscopic and microscopic tools. We study the folding of the protein flavodoxin, using fluorescence and nuclear magnetic resonance spectroscopy. Flavodoxin is a bacterial reduct protein that transfers electrons via a non-covalently bound flavin mononucleotide (FMN) cofactor. Previously, we showed that denatured apoflavodoxin (i.e., flavodoxin without its cofactor) first forms a rather stable but misfolded intermediate, before it folds to the native state via a second, more native-like but unstable intermediate (Bollen et al. Biochemistry 2004; Bollen et al. PNAS 2006). The last step in flavodoxin folding is FMN binding to native apoflavodoxin (Bollen et al. JBC 2000). Recently, we showed that flavodoxin binds its FMN cofactor extremely tightly (picomolar affinity), and that this tight binding is mediated by many amino acid residues throughout the protein structure (Bollen et al. Nat Commun 2012; see research highlight). In the future we aim to study the folding of flavodoxin while it is synthesized on the ribosome. Gram-negative bacteria consist of two aqueous compartments: the cytoplasm and the periplasm. All proteins are synthesized in the cytoplasm, but many need to be translocated across the cytoplasmic membrane into the periplasm. This task is performed by two independent systems: the Sec and the Tat system. The Sec system translocates unfolded proteins through a narrow pore in the membrane, whereas the Tat system exclusively translocates folded proteins. We investigate the Tat system, in particular its structure, its mechanism, how it senses the foldedness of the proteins that are translocated. Recently, we deciphered how pathway-specific chaperones recognize their cognate substrate protein (Shanmugham et al. Plos One 2012). Numerous proteins require cofactors to be active. Computer simulations suggest that cooperative interaction networks achieve optimal cofactor binding. In this paper, we experimentally identified residues that are crucial for stabilizing these networks and thus for cofactor binding. This paper provides new insights into cofactor-binding interactions. First, we used a well-established titration procedure to determine the dissociation constant of flavodoxin. After each titration step, part of the free FMN binds rapidly to apoflavodoxin, causing the associated FMN fluorescence to be quenched nearly instantaneously to low level. We found that the Kd for FMN dissociation from flavodoxin is 3.51×10–10 M, consistent with previous reports for various flavodoxins. This study reveals for the first time that the titration procedure underestimates the KD-value of cofactor-bound proteins, because after this initial quenching extremely slow conformational events happen. Reconstituted holo-protein relaxes with a time constant of ~5 days to a state that binds the flavin cofactor about two orders of magnitude better than freshly formed flavodoxin. Nuclear magnetic resonance (NMR) spectroscopy revealed that many residues are involved in this relaxation process (Figure above). Several backbone amide cross-peaks shift with a time constant similar to the one observed by fluorescence. Relaxed flavodoxin is characterized by virtually no fluorescence of bound FMN and has a Kd of 3.82×10–12 M. Thus, tightening of FMN binding leads to an energetically highly favorable protein state with picomolar-binding affinity. Finally, we used NMR-detected hydrogen-deuterium exchange to identify residues that are responsible for this tight binding, and found that many residues throughout the 3D structure of flavodoxin form a network that stabilizes the cofactor-bound state of the protein (Figure left)
Synthetic Chemistry

Koop Lammertsma

Sustainability of the element phosphorus is at the heart of the research of the Organic Chemistry division of AIMMS. Phosphorus is an essential element in the life cycle that will become scarce within this century at the current rate of consumption of the world’s reserves. With the combined use of new synthetic methodologies and high-level theoretical modeling, new vistas are explored for the eco-friendly synthesis, smart use, recycling, and exploitation of phosphorus-based processes and materials. This is to lead to novel reagents, tailor-made building blocks, new compound classes, catalysts, ligands, and (opto)metallic chemistry.

Our staff consists of Koop Lammertsma (professor of organic and organometallic chemistry), Chris Sooltweg (assistant professor of main group and organometallic chemistry), Andreas Ehlers (assistant professor of transition metal and computational chemistry), and 10-15 MSc, PhD, and PDs. The number of participating scientists will grow as a result of the recently awarded research grants.

TOP Grant
Koop Lammertsma received his third NWO – TOP grant (780 k€) with the proposal entitled Organophosphorus Chemistry – Novel Approaches to Advance and Preserve

Key Publications


Systems Bio-informatics

Bas Teusink

Mission
The mission of the Systems Bioinformatics group is to advance science, medicine and biotechnology, through the understanding of the physiology of unicellular organisms in terms of design principles of the underlying biological networks. Design principles are a set of rules that link systems specifications (the design) to the physiological effect in real biological systems (the “how”). Optimal designs are characterized by design and parameter constraints acting on it to biological implementations (“designs”). Most biological functions emerge from the interactions of biological components, either intracellular ones or with cells as components. We study this emergence, and its chance and necessity.

The Systems Bioinformatics group combines experimental, modeling and theoretical approaches to study cellular physiology, with an emphasis on metabolic networks. We want to understand the working of regulatory mechanisms (the “how”), but also their design principles (the “why”). Rather than being strictly academic, this has far-reaching consequences for applications in biology. Design principles provide rules that allow generalization and translation of understanding from one organism or component to another. One example is the (bacterial) Crabtree effect in microbes and yeasts: this is a shift in strategy from respiration to fermentation under conditions of nutrient excess. The same shift is observed in many tumor cells, where the effect is known as the Warburg effect. By studying the design principles of such metabolic shifts in a simple organism, the lactic acid bacterium Lactococcus lactis, we aim to provide a rationale for the cancer case as well. With AIMMS, we now collaborate with experts in cancer signaling (prof M Smit) to combine our expertise in metabolism and modelling with their expertise in metabolic networks (“roadmaps”) of any organism based on its genome. Through constraint-based modeling we animate such networks and produce hypotheses about fluxes (“traffic”). Such techniques are now well established for single-cell cultures and allow (i) integration ofomics data sets at genome-scale: such models provide knowledge-based mappings between biological components allowing advanced integrative bioinformatics; (ii) prediction of optimal yields and pathways potentially limiting that yield (used for process design); (iii) prediction of drug targets (in the case of pathogens).

We apply these techniques in a number of projects, e.g. to improve vaccine production through medium optimisation or improve photosynthetic cyanobacteria to produce biosolar-based biofuels. A number of projects provide improved methods and tools for constraint-based modeling and method development in the direction of microbial consortia. The latter is extremely relevant for the ecology of soil, oral and intestinal microbiota. We have developed powerful and user-friendly software for genome-scale metabolic modeling, model development and standardisation. We developed a worldwide standard for defining such models in Systems Biology Markup Language (SBML level 3).
Detailed kinetic models

Another approach we use is that of detailed kinetic models of yeast glycolysis, published in 2000 (Teusink Eur J Biochem 2000), to solve a 30-year old biological question that could not be solved by traditional molecular biology. We are currently, through collaborations within AIMMS, trying to bring such quantitative standards to the field of mammalian cell cultures.

In 2012 we have updated a detailed kinetic model of yeast glycolysis, published in 2000 (Teusink Eur J Biochem 2000), to solve a 30-year old biological question that could not be solved by traditional molecular biology. We are currently, through collaborations within AIMMS, trying to bring such quantitative standards to the field of mammalian cell cultures.

Cost-benefit analysis

In the last research line, we aim to understand the why of biological regulation as the result of a cost-benefit analysis. Providing a specific proxy for fitness, e.g. growth rate, and constraints that give rise to trade-offs, we develop theory and models that allow us to predict how such constraints or selective conditions shape regulatory strategies. For example, using growth rate optimisation under limited resources (defining protein cost), we can show that the known regulatory network that regulates ribosome biosynthesis in E. coli is able to robustly fine-tune the ribosomal content as a function of the growth rate. In collaboration with VU mathematicians (Joost Lunshof en Bob Planque) we have now developed a method to compute the optimal gene expression at a genome-scale, something that was impossible computationally before.

Experimentally, we back up model predictions by laboratory evolution experiments, allowing cells to adapt to the conditions (and reach the optimal state that we predict). These experiments include serial dilutions in batch growth, chemostat and auxostat cultivations, and a newly developed protocol to select for cell number (yield). One of the limitations of our current approaches is that it has focused mainly on constant conditions and on whole populations. We are currently extending these approaches towards dynamic environments (Veni-project by dr Filippe Santos started March 2012) and towards the role of population heterogeneity in adaptive evolution (focus of a Vidi proposal by dr Frank Bruggeman, started October 2012).

Key Publications


A successful collaboration between mathematicians and systems biologists simplifies metabolic engineering problems

In metabolic engineering applications, such as biofuel production, metabolic networks are engineered for enhanced product formation. The maximal product yield that can be attained by a metabolic network can be predicted from a so-called stoichiometric model of an organism, using a computational method called flux balance analysis. Such a model incorporates all the metabolic reactions of the organism, which easily involves hundreds to thousands of reactions. Such models are being developed within the research group of Prof Dr Bas Teusink. The states of optimal metabolism of those metabolic networks are characterized by a so-called solution space. This solution space is bounded by thousands to millions of so-called vertices, which are each optimal flux distributions and together give rise to all alternative, optimal solutions. Those solution spaces are huge, high-dimensional spaces, which are hard to envision, navigate and comprehend in biochemical terms.

With the help of two mathematicians, Dr Steven Kelk (ex-CWI) and Prof Dr Leen Stougie (VU & CWI), the systems biologists Dr Brett Olivier (VU) and Prof Dr Frank Bruggeman (VU), recently discovered how the underlying structure of solution spaces of metabolic networks in states of optimal activity results from a combinatorial explosion of independent activities of metabolic subnetworks. They developed a computational method to decompose the solution space into a handful of small metabolic networks that independently attain alternative flux states, each in agreement with the maximal yield of the biotechnological product. This method enables the navigation of optimal solution spaces of metabolic networks by biotechnologists in terms of simple metabolic network diagrams and simplifies metabolic engineering.

**Target and Systems Biochemistry**

**Martine Smit**

**Mission**
The Target and Systems Biochemistry group has the mission to understand how ligand-protein interaction at the molecular level enables the cell to translate external signals into cellular responses.

Our research focuses on GPCRs, belonging to the family of histamine and chemokine receptors, playing a role in inflammatory, CNS related disorders and/or cancer. We are studying the chemokine receptors, with particular interest in the CXCR receptors and chemokine receptors expressed by herpesviruses (HCMV, KSIV, EBV). In addition, research focuses on the histamine H1 and new H4 receptor. Target and Systems Biochemistry focuses on the biochemical and molecular pharmacology of its GPCR targets to assist the discovery of new chemical entities with improved GPCR interaction with promising pharmacological properties. Molecular mechanism of novel GPCR properties, including constitutive protein activity, allosteric modulation, biased signaling and dimerization are being thoroughly investigated. This work is done in close collaboration with the AIMMS group Medicinal Chemistry, forming the Division of Medicinal Chemistry in the Department of Chemistry and Pharmaceutical Sciences.

**GPCR heterodimerization**

Both histamine (H1 and H4 receptors) and (viral) chemokine receptors function as oligomers, for which functional consequences of heterodimerization (BRET/FRET based) are being assessed. Heteromerization of CXCR3 and CXCR4 resulted in the cross-inhibition of chemokines by agonists – but not antagonists – that bind to the other receptor. Interestingly, however, β-arrestin-2 recruitment to CXCR3-CXCR4 was synergistically increased by co-stimulation with CXCR3 and CXCR4 chemokines (Watts et al 2012a, publ.3).

**Biased signaling**

It has become apparent that GPCRs, including histamine and chemokine receptors do not only activate G proteins but might also activate non-G protein signaling pathways. Hence, assessment of multiple intracellular signaling events is required to fully GPCR ligand- and efficacy. Label-free impedance measurements of CXCR3-expressing cells were analyzed in combination with G protein-dependent CRE reporter gene activity and β-arrestin2 recruitment in response to stimulation with chemokines and synthetic small molecule agonists. Differences in response kinetics between chemokines and the synthetic small molecule agonists were observed. Moreover, CXCL9 was identified as a fully G protein-biased chemokine (Watts et al 2012b, publ.4). After the discovery that a well-known reference antagonist of the histamine H4R was surprisingly identified as partially active in a β-arrestin2 recruitment assay, we evaluated the signaling of different H4R compound classes. Compounds were tested in a G protein activation and β-arrestin2 recruitment assay. Subsequent comparison of compound efficacies in both pathways allowed us to identify both G protein and β-arrestin2 biased ligands for the H4R (Nijmeijer et al 2012, publ. 5, fig. 1). These biased H4R ligands are important pharmacological tools to unravel the role of G protein versus β-arrestin signaling in H4R (patho-)physiology. Selective targeting of GPCR signaling pathways with biased ligands may offer new therapeutic opportunities.

**HCMV encoded GPCRs**

Previously, we had demonstrated that human cytomegalovirus (HCMV)-encoded receptor proteins US28 and UL33 act as functional and constitutively active GPCRs. Recently, we showed that the viral chemokine receptor US28 displays oncogenic signaling properties, promoting tumorigenesis via activation of the IL-6/STAT3 axis and is expressed in glioblastoma. Based on these results US28 was put forward as one of the key players in glioblastoma (publ. 2, see highlight). Transgenic mice expressing US28 show enhanced inflammation and tumor formation in the intestine, associated with increased activation of the β-catenin signaling network. US28 activates the β-catenin pathway in a non conventional manner (publ. 1). Currently, we are using a Systems Biology approach to further dissect and understand how these viral receptors hijack cellular signalling networks to contribute to tumorigenesis. By taking an integrative approach involving both the iterative development of innovative modeling approaches (other AIMMS research groups Systems bioinformatics [Ruppertman/Teusink/Westhoff] and Integrative Bioinformatics [Heringa/Feenstra]) and experimental work, we aim to unravel the mechanistic complexity of GPCR mediated signaling.

**Key Publications**

in glioma, the role of HCMV in the pathology of gliomas was discussed. Based on the available scientific data, consensus was reached about the importance of HCMV in glioma and directions for future research to understand viral oncomodulation and therapeutic targeting were defined (Dziurzynski et al Neuro Oncology 2012). Interestingly, US28, together with a few other viral target proteins, was designated a prime drug target for future therapeutic strategies towards glioma.

Oncomodulatory properties of viral chemokine receptor US28 mediated by a novel activation mechanism of TCF-LFP transcriptional regulators.

Expression of US28 in NIH-3T3 cells induces a pro-angiogenic and transformed phenotype by up-regulating the expression of vascular endothelial growth factor (VEGF). US28-expressing cells promote tumorigenesis when injected into nude mice (Mausang et al, PNAS 2006). Microarray studies reveal differential expression of genes involved in oncogenic signaling. In particular, the expression of cyclooxygenase-2 (COX-2), a major determinant in inflammatory diseases and in several forms of cancer, is highly upregulated (Mausang/Langemeyer et al, Cancer research 2009). We have shown that US28 activates various inflammatory and proliferative signalling pathways. Via constitutive activation of NFkB, the IL6/STAT3 axis is implemented in a positive feed forward loop (Slinger et al., 2009). We have shown that US28 activates various inflammatory and proliferative signalling pathways. Via constitutive activation of NFkB, the IL6/STAT3 axis is implemented in a positive feed forward loop (Slinger et read more on the previous page)

HCMV IEA, US28, and STAT3 phosphorylation in primary glioblastoma specimens. Representative immunohistochemical stainings are shown. (A) Presence of US28 (brown), (B) Presence of phospho-STAT3 (brown), (C) Presence of HCMV IEA (brown), (D) Presence of SMC α-actin (brown). Adapted from Slinger et al., 2010.

The research highlighted consensus on the role of HCMV and viral GPCR US28 in glioblastoma.

Research highlight

Consensus on the role of HCMV and viral GPCR US28 in glioblastoma

Herpesviruses express GPCRs, homologous to the human chemokine receptor family members. These viruses are widespread pathogens, which establish a lifelong latent and persistent infection. In immune-competent hosts, infection is often asymptomatic, while reactivation can lead to serious pathological conditions. These viral GPCRs (vGPCRs) play multifaceted roles in viral pathology. By acting as chemokine sinks, the vGPCRs enable immune evasion and establishment of latent infection. Moreover, these receptors proteins enable constitutive activation of various G-protein mediated signaling pathways. By rewiring cellular signaling networks in the infected host cells, the vGPCRs mediate proliferative, pro-angiogenic and anti-apoptotic responses in the infected host cells.

The Human Cytomegalovirus (HCMV) encodes two GPCRs (US28, UL33) that display constitutive activation which is correlated to increased proliferation, pro-angiogenic and anti-apoptotic responses of transfected cells. In previous years, these US28 have been shown to mediate oncomodulatory effects in transfected and HCMV-infected cells. These observations have been extended to the analysis of clinical samples in which the vGPCR could be correlated to aggressiveness of glioblastoma (Slinger et al Sci Signal 3, 2010). Furthermore, in vivo data using transgenic mice correlates US28 expression to colon cancer (Bongers et al J Clin Invest 2010).

In a special symposium attended by neurosurgeons, oncologists and virologists on the role of HCMV in glioma, the role of HCMV in the pathology of gliomas was discussed. Based on the available scientific data, consensus was reached about the importance of HCMV in glioma and directions for future research to understand viral oncomodulation and therapeutic targeting were defined (Dziurzynski et al Neuro Oncology 2012). Interestingly, US28, together with a few other viral target proteins, was designated a prime drug target for future therapeutic strategies towards glioma.

Oncomodulatory properties of viral chemokine receptor US28 mediated by a novel activation mechanism of TCF-LFP transcriptional regulators.

Expression of US28 in NIH-3T3 cells induces a pro-angiogenic and transformed phenotype by up-regulating the expression of vascular endothelial growth factor (VEGF). US28-expressing cells promote tumorigenesis when injected into nude mice (Mausang et al, PNAS 2006). Microarray studies reveal differential expression of genes involved in oncogenic signaling. In particular, the expression of cyclooxygenase-2 (COX-2), a major determinant in inflammatory diseases and in several forms of cancer, is highly upregulated (Mausang/Langemeyer et al, Cancer research 2009). We have shown that US28 activates various inflammatory and proliferative signalling pathways. Via constitutive activation of NFkB, the IL6/STAT3 axis is implemented in a positive feed forward loop (Slinger et...
Faster and more reliable DFT methods (Mirko Franchini, Alexey Yakovlev)

This line of research is done largely at the SCM company and is directed towards faster and more reliable DFT methods. One aspect concerns the adaptation of core algorithms used in the ADF program to the emerging massively parallel computers. While it has always been common practice for theoretical chemists to closely follow trends in computational science to increase the size of systems that can be modeled, we now see a change of paradigm in which existing parallelizations that scale up to a few tens or a hundred cores will no longer be able to saturate the full power of new supercomputers that will consist of many thousands of computer cores. Similarly they are not able to employ the relatively cheap computer resources offered by graphical processor units (GPUs). In NCF and NVIDIA sponsored projects we developed new algorithms that target this new class of hardware and open up for much larger scale calculations than were possible at the current hardware. We are now working on utilizing the ADF-DFT approach as the engine in an ab initio molecular dynamics approach. Another collaboration with SCM concerns improvements of the accuracy and reliability of current algorithms by reinvestigating numerical integration and density fitting approaches. These were initially developed to provide precise energetics for single points on the molecular potential energy surface while they are nowadays used to compute a wealth of molecular properties and to study the energetics for a wide range of points on the surface (e.g. to find and analyze transition states, or to allow for thermodynamical averaging). We have defined new algorithms that give much improved stability in numerically difficult situations.

Applications

All of the group members involved in the development work outlined above are also involved in collaborations with experimental groups inside and outside the VUA. We will only mention collaborations with the VUA here. Recent collaborations on photochemistry and photophysics concern study of the fluorescence properties of flavonoids (collaboration with Arise), study on the mechanism of chlorophyll formation (collaboration with Groot). In the context of protein densities we collaborate with medicinal chemistry group to investigate application in virtual screening workflows.

Key Publications


12. Appendices

12.1 Output AIMMS 2012

12.1.1 Theses


12.1.2 Scientific Papers, refereed


Boele, J., Olivier, B.G. & Teusink, B. (2012). FAME, the flux analysis and modelling environment. BMC Systems Biology, 6(8).


Bioanalytical Chemistry, 403, 367-375.


Synapse associated protein 102 (SAP102) binds the C-terminal part of the scaffolding protein neurobeachin. PLoS ONE, 7(6).


12.1.3 Books


12.1.4 Book Chapters


### 12.2 Input AIMMS 201

<table>
<thead>
<tr>
<th>name</th>
<th>fte</th>
<th>research fte</th>
<th>function **</th>
<th>department</th>
<th>type of funding ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abeln, S.</td>
<td>0.80</td>
<td>0.4</td>
<td>assist prof</td>
<td>Inf</td>
<td>2</td>
</tr>
<tr>
<td>Amstalden - van Hove, E.R.</td>
<td>0.90</td>
<td>0.81</td>
<td>postdoc</td>
<td>CPS</td>
<td>2</td>
</tr>
<tr>
<td>Andaloussi, M.</td>
<td>0.50</td>
<td>0.45</td>
<td>postdoc</td>
<td>CPS</td>
<td>2</td>
</tr>
<tr>
<td>Augustijn, K.D.</td>
<td>0.62</td>
<td>0.56</td>
<td>postdoc</td>
<td>CPS</td>
<td>3</td>
</tr>
<tr>
<td>Bachmann, H.</td>
<td>0.56</td>
<td>0.5</td>
<td>postdoc</td>
<td>MCB</td>
<td>2</td>
</tr>
<tr>
<td>Bailey, D.S.</td>
<td>0.50</td>
<td>0.45</td>
<td>postdoc</td>
<td>CPS</td>
<td>3</td>
</tr>
<tr>
<td>Bakker, B.M.</td>
<td>0.10</td>
<td>0.05</td>
<td>ass prof</td>
<td>MCB</td>
<td>1</td>
</tr>
<tr>
<td>Bald, D.</td>
<td>0.80</td>
<td>0.4</td>
<td>assist prof</td>
<td>MCB</td>
<td>1</td>
</tr>
<tr>
<td>Bastiaansen, KCJT</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>MCB</td>
<td>2</td>
</tr>
<tr>
<td>Bavono, P.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>Inf</td>
<td>3</td>
</tr>
<tr>
<td>Beer, S.B.A., de</td>
<td>0.59</td>
<td>0.44</td>
<td>PhD student</td>
<td>CPS</td>
<td>1</td>
</tr>
<tr>
<td>Bellomo, D.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB</td>
<td>2</td>
</tr>
<tr>
<td>Berg van Saparoea, HB</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB</td>
<td>3</td>
</tr>
<tr>
<td>Bickelhaupt, F.M.</td>
<td>1.00</td>
<td>0.5</td>
<td>prof</td>
<td>CPS</td>
<td>1</td>
</tr>
<tr>
<td>Bitter, W.</td>
<td>0.25</td>
<td>0.5</td>
<td>prof</td>
<td>MCB</td>
<td>1</td>
</tr>
<tr>
<td>Blaazer, A.R.</td>
<td>0.15</td>
<td>0.11</td>
<td>PhD student</td>
<td>CPS</td>
<td>3</td>
</tr>
<tr>
<td>Blankervoort, RK</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>MCB</td>
<td>2</td>
</tr>
<tr>
<td>Boele, J.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>Inf</td>
<td>1</td>
</tr>
<tr>
<td>Boer, A.H., de</td>
<td>0.80</td>
<td>0.4</td>
<td>ass prof</td>
<td>MCB</td>
<td>1</td>
</tr>
<tr>
<td>Boerma, J.S.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS</td>
<td>3</td>
</tr>
<tr>
<td>Bonzanni, N.</td>
<td>0.88</td>
<td>0.79</td>
<td>postdoc</td>
<td>Inf</td>
<td>1</td>
</tr>
<tr>
<td>Boogerd, F.C.</td>
<td>0.80</td>
<td>0.4</td>
<td>assist prof</td>
<td>MCB</td>
<td>1</td>
</tr>
<tr>
<td>Boon, L.J.P, van der</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS</td>
<td>2</td>
</tr>
<tr>
<td>Borger, J.E.</td>
<td>0.04</td>
<td>0.03</td>
<td>PhD student</td>
<td>CPS</td>
<td>2</td>
</tr>
<tr>
<td>Boudriesz, E.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>MCB</td>
<td>3</td>
</tr>
<tr>
<td>Bosma, R.</td>
<td>0.12</td>
<td>0.11</td>
<td>postdoc</td>
<td>CPS</td>
<td>1</td>
</tr>
<tr>
<td>Bosma, R.</td>
<td>0.08</td>
<td>0.0718</td>
<td>postdoc</td>
<td>CPS</td>
<td>2</td>
</tr>
<tr>
<td>Branco dos Santos, F</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB</td>
<td>2</td>
</tr>
<tr>
<td>Braver, M.W., den</td>
<td>0.59</td>
<td>0.44</td>
<td>PhD student</td>
<td>CPS</td>
<td>3</td>
</tr>
<tr>
<td>Bruggeman, FJ</td>
<td>0.50</td>
<td>0.25</td>
<td>ass prof</td>
<td>MCB</td>
<td>1</td>
</tr>
<tr>
<td>Bruggeman, FJ</td>
<td>0.50</td>
<td>0.25</td>
<td>ass prof</td>
<td>MCB</td>
<td>2</td>
</tr>
</tbody>
</table>

* Research effort in fte as described by the VSNU. See Chapter 8. Input
** postdocs by definition SEP; non-tenured staff; UFO functions ‘onderzoeker 1 - 4’
*** Definitions as stated in SEP 2009-2015: 1 = Direct funding; 2 = Research grants; 3 = Contract Research + EU funding
<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Department</th>
<th>Years</th>
<th>10-year Impact Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capoferri, L.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Cioc, R.C.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Commandeur, J.N.M.</td>
<td>ass prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Cremazy, F.G.E.</td>
<td>postdoc</td>
<td>MCB</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Della Pina, S</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Dijk, E., van</td>
<td>PhD student</td>
<td>Inf</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Dragovic, S.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Dragovic, S.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Edink, E.S.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Ehlers, A.W.</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Esch, I.J.P., de</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Esch, I.J.P., de</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Falck, D.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Feenstra, K.A.</td>
<td>assist prof</td>
<td>Inf</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Fidalgo de Almeida, P.M.</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Fonseca Guerra, C.</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Geerke, D.P.</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Giera, M.A.</td>
<td>postdoc</td>
<td>MCB</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Giersbartz, K.J.H.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Glas, M.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Gori Giorgi, P.</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Graaf, C., de</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Graaff, C., de</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Grinsven, K.W.A., van</td>
<td>postdoc</td>
<td>MCB</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Gritsenko, O.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Haaksema, E.J.J.</td>
<td>prof</td>
<td>CPS</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Hanemaaijer, M.J.</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Heerden, J.H., van</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Heijden, G., van der</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Heringa, J.</td>
<td>prof</td>
<td>MCB</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Heringa, J.</td>
<td>prof</td>
<td>Inf</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>Heshmat, M.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Hettling, J.</td>
<td>PhD student</td>
<td>Inf</td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Hettling, J.</td>
<td>postdoc</td>
<td>Inf</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Hettling, J.</td>
<td>postdoc</td>
<td>Inf</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Heus, F.A.M.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Hooijen, S.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Hooijschuur, J.H.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Huseinovic, A.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Jaarsma, R.</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Jacobsen, A.</td>
<td>PhD student</td>
<td>Inf</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Jansen, C.J.W.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Janssen, G.V.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Janssen, M.H.M.</td>
<td>prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Jong, WSP</td>
<td>postdoc</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Jonkens, L.W.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Kahraman, P</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Karssen, C.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Karssen, C.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Kazaryan, A.K.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Khandelwal, R.A.</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Kiewisch, K.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Klau, G.W.</td>
<td>prof</td>
<td>Inf</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>Kleeff, P.J.M., van</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Koes, RE</td>
<td>prof</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Kooistra, A.J.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Kool, J.</td>
<td>assist prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Kooeter, JM</td>
<td>assist prof</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Kort, R.</td>
<td>prof</td>
<td>MCB</td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Krab, K.</td>
<td>ass prof</td>
<td>MCB</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>Kruthof, A.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Krumpochova, P.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Kuhne, S.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Kuhne, S.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Lakayan, D.</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Lammertsma, K.</td>
<td>prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Lehmann, C.S.</td>
<td>PhD student</td>
<td>MCB</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Lehmann, C.S.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Leurs, R.</td>
<td>prof</td>
<td>CPS</td>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td>Leurs, R.</td>
<td>prof</td>
<td>CPS</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Lill, H.</td>
<td>prof</td>
<td>MCB</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Linden, O.P.J., van</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Linden, O.P.J., van</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Lingeman, H.</td>
<td>ass prof</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Lint, M.J., van</td>
<td>PhD student</td>
<td>CPS</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Luirink, S.</td>
<td>ass prof</td>
<td>MCB</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Malet Giralt, F.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Maussang Detaille, D.A.B.</td>
<td>postdoc</td>
<td>CPS</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Name</td>
<td>Percentage</td>
<td>BaseScore</td>
<td>Position</td>
<td>Institute</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>May, A.</td>
<td>0.53</td>
<td>0.4</td>
<td>PhD student</td>
<td>Inf 1</td>
</tr>
<tr>
<td>McCormack - Venhorst, J.</td>
<td>0.18</td>
<td>0.16</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Meer, R. van</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Meer, T.K., van der</td>
<td>0.17</td>
<td>0.15</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Mentel, L.M.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Millo, D.</td>
<td>0.69</td>
<td>0.62</td>
<td>postdoc</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Mirtschink, A.P.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Mladic, M.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Molenaar, D.</td>
<td>1.00</td>
<td>0.5</td>
<td>postdoc</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Mone, M.J.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Mone, M.J.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Mujic - Delic, A.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Mulder, J.R.</td>
<td>1.01</td>
<td>0.76</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Munnik, S.M., de</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Nicu, V.P.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Niessen, W.M.A.</td>
<td>0.40</td>
<td>0.2</td>
<td>prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Niijmeijer, S.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Niraghatam, B.R.</td>
<td>0.62</td>
<td>0.56</td>
<td>postdoc</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Oliveira Lebre Direito, M.S.</td>
<td>0.23</td>
<td>0.17</td>
<td>PhD student</td>
<td>MCB 2</td>
</tr>
<tr>
<td>Olivier, B.G.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB 2</td>
</tr>
<tr>
<td>Orrling, K.M.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Ornu, R.V.A.</td>
<td>1.00</td>
<td>0.5</td>
<td>prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Otvos, R.A.</td>
<td>0.92</td>
<td>0.69</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Ozturk, P.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Pelgrom, A.J.E.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Petterson, L.J.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Pool, R.</td>
<td>0.17</td>
<td>0.15</td>
<td>postdoc</td>
<td>Inf 1</td>
</tr>
<tr>
<td>Pop, O.I.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Quattrociocchio, FM</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Rabbers, L.</td>
<td>0.21</td>
<td>0.19</td>
<td>postdoc</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Rafee Fanood, M.M.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Rea, V.</td>
<td>0.16</td>
<td>0.12</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Reinjen, J.</td>
<td>0.50</td>
<td>0.45</td>
<td>postdoc</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Reinjen, J.</td>
<td>0.50</td>
<td>0.45</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Roling, W.F.M.</td>
<td>0.80</td>
<td>0.4</td>
<td>ass prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Rombouts, J.A.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Rong, M.K.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Roth, S.</td>
<td>0.83</td>
<td>0.75</td>
<td>postdoc</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Roumen, L.</td>
<td>1.00</td>
<td>0.9</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Ruijter, E.</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Schat, H</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Schmitz, J.P.J.</td>
<td>0.26</td>
<td>0.23</td>
<td>postdoc</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Schooten, D.J.</td>
<td>0.16</td>
<td>0.12</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Schooten, D.J.</td>
<td>0.83</td>
<td>0.75</td>
<td>postdoc</td>
<td>MCB 3</td>
</tr>
<tr>
<td>Schwabe, A</td>
<td>1.00</td>
<td>0.75</td>
<td>postdoc</td>
<td>MCB 2</td>
</tr>
<tr>
<td>Sewradj, S.P.</td>
<td>0.59</td>
<td>0.44</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Shanmugham, A.</td>
<td>0.90</td>
<td>0.81</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Siderius, M.H.</td>
<td>0.80</td>
<td>0.4</td>
<td>assist prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Sietsma, A</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>MCB 2</td>
</tr>
<tr>
<td>Slootweg, J.C.</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Smit, M.J.</td>
<td>0.90</td>
<td>0.45</td>
<td>prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Snoep, J.L.</td>
<td>0.20</td>
<td>0.1</td>
<td>prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Souer, E/J</td>
<td>0.90</td>
<td>0.45</td>
<td>assist prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Spanning, R.J.M., van</td>
<td>0.80</td>
<td>0.4</td>
<td>assist prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Switziar, L.</td>
<td>0.32</td>
<td>0.24</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Taymaez, H.</td>
<td>0.79</td>
<td>0.71</td>
<td>postdoc</td>
<td>Inf 3</td>
</tr>
<tr>
<td>Tecmer, P.</td>
<td>0.49</td>
<td>0.37</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Teusink, B</td>
<td>0.80</td>
<td>0.4</td>
<td>prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Teusink, B.</td>
<td>0.20</td>
<td>0.1</td>
<td>prof</td>
<td>Inf 1</td>
</tr>
<tr>
<td>Ulsen, JP</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Vargas Lopez, R.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>MCB 1</td>
</tr>
<tr>
<td>Venkataraman, H.</td>
<td>0.49</td>
<td>0.37</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Venkataraman, H.</td>
<td>0.49</td>
<td>0.37</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Verheij, M.H.P.</td>
<td>0.25</td>
<td>0.19</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Verheij, M.H.P.</td>
<td>0.46</td>
<td>0.41</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Verkaar, F.</td>
<td>0.67</td>
<td>0.6</td>
<td>postdoc</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Verkaar, F.</td>
<td>0.33</td>
<td>0.3</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Vermeulen, N.P.E.</td>
<td>0.50</td>
<td>0.25</td>
<td>prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Vidami - Negoeescu, E.C.</td>
<td>0.41</td>
<td>0.31</td>
<td>PhD student</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Vischer, H.F.</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Visscher, L.</td>
<td>1.00</td>
<td>0.5</td>
<td>prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Vlaar, T.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 2</td>
</tr>
<tr>
<td>Vos, J.C.</td>
<td>1.00</td>
<td>0.5</td>
<td>assist prof</td>
<td>CPS 1</td>
</tr>
<tr>
<td>Vredenburg, G.</td>
<td>1.00</td>
<td>0.75</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Wassenaar, T.A.</td>
<td>0.09</td>
<td>0.08</td>
<td>postdoc</td>
<td>CPS 3</td>
</tr>
<tr>
<td>Watts, A.O.</td>
<td>0.16</td>
<td>0.12</td>
<td>PhD student</td>
<td>CPS 3</td>
</tr>
</tbody>
</table>
### 12.3 Collaborations AIMMS

#### 12.3.1 Academic Collaborations (national and international)

**2010-2013**

<table>
<thead>
<tr>
<th>AIMMS section</th>
<th>Collaborators</th>
<th>Name (Institute)</th>
<th>Type*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocomputational Chemistry</td>
<td>Prof. Dr. B. Lippert (bioinorganic chemistry)</td>
<td>TU Dortmund, Germany: supported by Max Planck-Gesellschaft</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dr. R. A. Layfield (inorganic chemistry)</td>
<td>University of Manchester, UK</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. G. Frenking (inorganic, organometallic and catalytic computational chemistry)</td>
<td>Philipps-Universität Marburg, Germany</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. M. Solà, Universitat de Girona, Spain: supported by European Union (TMR and HPC Europa programs) and Deutscher Akademischer Austauschdienst (DAAD)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. S. Simon, Universitut de Girona, Spain: supported by European Union HPC Europa program (2006-present)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. M. J. Ramos, Universidade do Porto, Portugal: supported by Portuguese Science Foundation (FCT)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. F. Wang, Swinburne University, Australia.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. J. K. Nagle (inorganic chemistry)</td>
<td>Bowdoin College, Brunswick, Maine, USA</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. M. Remko, Bratislava: supported by European Union HPC Europa program</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. L. Orian, University of Padova, Italy: supported by European Union HPC Europa program</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. G. Barone, University of Palermo, Italy: supported by European Union HPC Europa program</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. G. Paragi, University of Seget, Hungary: supported by European Union HPC Europa program</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. U. Radius, Universität Würzburg, Germany: supported by European Union HPC Europa program</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. M. Palusiak, University of Lodz, Poland: supported by European Union HPC Europa program</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. A. Kovacs (inorganic chemistry), Budapest University of Technology and Economics, Hungary: supported by Royal Netherlands Academy of Sciences (KNAW) and Hungarian Academy of Sciences</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. V. Syrovetsky, Academy of Sciences of the Czech Republic, Prague, Czech Republic</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. J. Sponer, Academy of Sciences of the Czech Republic, Brno, Czech Republic</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. M. Swart, ICREA and University of Girona, Spain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. G. Merino (theoretical chemistry), University of Guanajuato, Mexico</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. S. E. Galembeck (theoretical chemistry), Universidade de São Paulo, Brazil</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. F. Cossio (theoretical organic chemistry), University of San Sebastian, Spain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(supported by Spanish Consolider-Ingenio 2010)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr. I. Fernández (theoretical organic chemistry), Universidad Complutense, Madrid, Spain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. W. D. Allen (theoretical chemistry), University of Georgia, Athens, Georgia, USA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. F. DeProft (theoretical chemistry), Vrije Universiteit Brussel, Belgium</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. S. Grimme, Universität Münster, Germany (supported by IRTG: DFG + NWO)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. J. Müller, Universität Münster, Germany (supported by IRTG: DFG + NWO)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. W. Leitner, RWTH Aachen, Germany</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. Y. Ren, Sichuan University, Chengdu, China.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. A. Riera, Institute for Research in Biomedicine, Barcelona, Spain.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. S. Wijmenga, Radboud Universiteit Nijmegen, The Netherlands</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. J. H. Reek, Universiteit van Amsterdam, The Netherlands (supported by NRSC-C)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. L. D. A. Siebbeles, Technische Universiteit Delft, The Netherlands</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prof. Dr. V. J. Linnartz, Leiden Universiteit, The Netherlands</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* 1 = joint publications, 2 = PhD project, 3 = joint research, 4 = sharing datasets or software, 5 = consultancy, 6 = other
Academic collaborations AIMMS continued

Biomolecular Analysis
- Dr. Gestur Vidarsson, Prof. Ellen van der Schoot (Sanquin) 4
- Christien Dijkstra, Yvette van Kooyk, Irma van Die, Anton Horrevoets (Molecular Cell Biology and Immunology) (VUMc) 4
- Dr. Perez (Anesthesiology) 3, 4
- Prof. Polman (Neurology) 6
- Prof. Kraal (Molecular Cell Biology and Immunology) (VUMc) 6
- Prof. d. r. d. M. Richardson (UL, Institute of Biology) 3, 4
- Prof. d. r. Lewis (Mol. Bioscience, Univ. Queensland, Australia) 3, 4
- Prof. d. M. d. K i n i (Department of Biological Science at the National University of Singapore) 4, 6
- Prof. d. r. d. W. F. Nielen (WUR & RIKILT) 4
- Prof. d. r. d. A. Kerentens (IMM-KUN,NMR) 1, 3
- Prof. d. s. W i j n e n g a (IMM-KUN op gebied van NMR) 3
- Prof. d. r. d. R. H. Pieters (UU-IRAS) 1, 3
- Prof. d. r. B i s c h o f f (RUG – Anal Biochem) 3
- Prof. d. J. d. d e J o r g (UU – Biomolecular Analysis) 4
- Prof. d. r. d. J. d. d e B o e r (IVM-VU) 4

Bio-Organic Chemistry
- Dr. Van Wamel (antibiotics/resistance- Erasmus Medical Center) 1 or 3
- Prof. Breukink (antimicrobial resistance-UU) 1 or 3
- Prof. Braakenhoff (cancer/anti-tumor- VUMc) 1 or 3
- Dr. Windhorst/Dr. Vugts (fundamental radiochemistry, RNC-VUmc) 1 or 3

Molecular Microbiology
- Prof. d. W. d. e. G i e r (Stockholm University) 1
- Prof. G. Von Heijne (Stockholm University) 1
- Prof. d. d. P. G. e n e v a u x (CNRS, Toulouse) 1
- Prof. d. S. d. H i g h (Univ. Manchester) 1
- Prof. J. L o ê w e (Univ. of Cambridge) 3
- Prof. J. B e c k w i t h (Harvard Med. School) 1
- Prof. J. T a r m e (Yokohama Univ) 1
- Prof. S. W a g n e r (Univ. Tubingen) 1
- Dr. E. M. d. M. e. A g g e r (Univ. of Cambridge) 1
- Prof. G. R i m m e l z w a a n (Erasmus MC, Rotterdam) 3
- Dr. A. d. d. V a n d e r E n d e (AMC, Amsterdam) 3
- Prof. S. B h u s h a n (RVC, Würzburg) 3
- Dr. T. D e n B l a a u w e n, Prof. L. H a m o n e u (Univ. Dutch, Microbiology) 1
- Prof. J. T a m m e s d. A. d. C. d. V u s t (AMC, Amsterdam) 1
- Prof. E. P e t e r m a n, Prof. G. W. d. W a g e r (VU Physic) 2, 3
- Prof. A. B. d. S m i t (VU Neurobiology) 1
- Dr. M. d. d. J o n g e (Radboud Univ. Nijmegen) 3
- Dr. A. A b d a l l a h K A U S T, Saudi Arabia) 1
- Dr. I. d. d. d. E s c h (VU, Medicinal Chemistry) 2, 3
- Prof. M. d. d. G o t e r o m (AMOLF, Amsterdam) 3
- Dr. J. d. d. H a a n (VUMC, Cell Biology) 3
- Dr. J. G a r a l e p p o (Univ. of Cambridge) 3
- Prof. J. T o m m a s s e n (Univ. Utrecht) 1
- Prof. P. G. d. S. G. d. G a l e p o n (Univ. of Cambridge) 1
- Dr. M. d. d. B. d. L a n d s t e i n e r L a b (AMC, UvA) 1
- Prof. H. V e r h e u l (VUmc) 3, 4

Integrative Bioinformatics
- Prof. d. G. M. d. M. d. J e m e r (VUMc, Dir. CTMM/Trait) 4
- Dr. R. F. a. d. T. d. G. i. d. T (VUMC/CCA, WP leader CTMM/Trait) 4
- Dr. C. J. i. m. e n z e r (VUMC/CCA, WP leader CTMM/Trait) 4
- Dr. J. B e l e n b e l (VUMC, CTMM/Trait) 4
- Dr. E. P. e. d. T. J. d. M. d. L. d. G. (VUMC, Cell Biology) 4
- Dr. C. G. d. L a r s e n (AMOLF, Amsterdam) 4
- Dr. C. d. G. d. L e c l e r c (AMOLF, Amsterdam) 4
- Dr. E. P. e. d. T. d. G. i. d. T (VUMC, Cell Biology) 4
- Dr. C. G. d. L a r s e n (AMOLF, Amsterdam) 4

* 1 = joint publications, 2 = PhD project, 3 = joint research, 4 = sharing datasets or software, 5 = consultancy, 6 = other
### Academic collaborations AIMMS continued

#### Molecular Neurobiology
- Prof. Dr R. Leurs (VU) 1, 3
- Dr I. De Esch (VU) 1, 3
- Dr. J. Kool (VU) 1, 2
- Prof. Dr C. Ullens (KULeuven) 1, 3
- Prof. Dr. D. Choquet (Inserm Bordeaux) 1, 3

#### Molecular Toxicology
- Prof. G. Peters, dr. N. Franke/I. Cloos (VUmc, allen CCA/V-ICI) 1
- dr. S. Heukelom (VUmc, Radiotherapie) 1
- dr. F. van Leeuwen; dr. M. Motazacker (AMC, Vascular Medicine) 1

#### Structural Biology
- R. van Spanning, VU MCF 3
- Prof. E. Peterman, VU Physics 1, 2, 3
- Prof. F. Bruggerman, Prof. B. Teusink, VU MCF 1
- Dr. C. Ottmann (TUE) 3
- Prof. R. van Spanning, VU MCF 3
- Prof. E. Peterman, VU Physics 1, 2, 3
- Prof. F. Bruggerman, Prof. B. Teusink, VU MCF 1
- Dr. C. Ottmann (TUE) 3

#### Synthetic Chemistry
- Dr. G. Rothenberg (catalysis, UvA) 3
- Prof. F.M. Bickelhaupt (biosolar cells, VU) 2
- Prof. R.V.A. Orru (organic catalysis, NRSCC, VU) 2
- Prof. B. de Bruin (Organometallics, UvA) 1
- Prof. H. Lill (Synthesis, VU) 3
- Prof. W. Uhl (inorganic synthesis, Univ. of Münster, DE) 1

#### Target and Systems Biochemistry
- Prof. Guus van Dongen (VUmc) 1
- Dr. Connie Jimenez (VUmc) 3
- Prof. Dijkstra et al (potential collaborators: de Vries, Mebius) (VUmc) 3
- Dr. Cees Tensen (LUMC) 1
- Dr. J. Thole (TBVI, Lelystad) 6
- Dr. S. Bashiri (Xbrane Bioscience, Stockholm) 5

#### Molecular Microbiology
- Prof. P. Willemse (CVI Leiden) 6
- Dr. P. Van der Ley (Mackey Group, Münster) 6
- Dr. T. Würdinger (VUmc) 3
- Dr. T. Würdinger (VUmc) 3

#### Integrative Bio-informatics
- Dr. Henk Obbink, Dr. Wim van der Linden (Philips, CTMM/TraIT) 1
- Kees van Bochove (The Hyve, CTMM/TraIT) 3
- Jos Lunenberg, Dr. Bas Tolhuis (Genalice, CTMM/TraIT) 1

#### Medicinal Chemistry
- Prof. Titia Sixma (NKI) 1
- Dr. Ype Elgersma (EUR) 3
- Dr. Henk Schallig (KIT) 1
- Dr. Ype Elgersma (EUR) 3
- Dr. Henk Schallig (KIT) 1

#### Molecular Cell Physiology
- EUR: Hans van Leeuwen 1

#### Bioinformatics
- Dr. Henk Obbink, Dr. Wim van der Linden (Philips, CTMM/TraIT) 1
- Kees van Bochove (The Hyve, CTMM/TraIT) 3
- Jos Lunenberg, Dr. Bas Tolhuis (Genalice, CTMM/TraIT) 1

#### Molecular Cell Physiology
- EUR: Hans van Leeuwen 1

#### Biomolecular Analysis
- Dr. Hub Ovas (NKI) 3
- Dr. J. Wieling (QPS) 1

#### Bio-Organo-Chemistry
- Dr. Ovaas, (compound screening, NKI) 3
- Dr Orsel (biorenewables, CSM) 3
- Prof. v. Soolingen (tuberculose reference lab, RIVM) 1
- Dr Leemhuis (compound libraries, Mercachem) 1
- Dr v Helden (Screening, Oss Screening-Pivot Park) 1
- Dr Piet/Tjihuis (heterocycle synthesis, Speci) 1
- Dr Rijnders (screening, Tri-Pharma) 1
- Dr Benigni (process-scale-up, CHEMO-group, Chemessemitia, I) 1
- Dr Hueser (libraries and screening, Bayer) 1
- Dr Tzalis (libraries, Taros) 1
- Dr Tsallis (libraries, Taros) 1
- Dr Otsomaa (sustainable manufacturing, Orion Pharma) 1
- Dr Lagouardat (green pharmacy, Sanofi) 1
- Dr Barry (green Pharmacy, Reaxa) 1
- Dr Tzalis (libraries, Taros) 1
- Dr Tzalis (libraries, Taros) 1
- Dr Dolan (libraries, GSK) 1
- Dr Dolan (libraries, GSK) 1

#### Biochemical Analysis
- • Dr. Huib Ovas (NKI) 3
- • Dr. J. Wieling (QPS) 1

#### Non-academic Collaborations (national and international)

<table>
<thead>
<tr>
<th>AIMMS Section</th>
<th>Collaborators Name (Institute)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocomputational Chemistry</td>
<td>• Blum Scientific, München, Germany</td>
<td>3, 5</td>
</tr>
<tr>
<td>Biomolecular Analysis</td>
<td>• Dr. Huib Ovas (NKI)</td>
<td>3</td>
</tr>
<tr>
<td>• Dr. J. Wieling (QPS)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bio-Organo-Chemistry</td>
<td>• Dr. Ovaas, (compound screening, NKI)</td>
<td>3</td>
</tr>
<tr>
<td>• Dr Orsel (biorenewables, CSM)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>• Prof. v. Soolingen (tuberculose reference lab, RIVM)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Leemhuis (compound libraries, Mercachem)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr v Helden (Screening, Oss Screening-Pivot Park)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Piet/Tjihuis (heterocycle synthesis, Speci)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Rijnders (screening, Tri-Pharma)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Benigni (process-scale-up, CHEMO-group, Chemessemitia, I)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Hueser (libraries and screening, Bayer)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Tzalis (libraries, Taros)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Otsomaa (sustainable manufacturing, Orion Pharma)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Lagouardat (green pharmacy, Sanofi)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Barry (green Pharmacy, Reaxa)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Tzalis (libraries, Taros)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Tzalis (libraries, Taros)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>• Dr Dolan (libraries, GSK)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Integrative Bio-informatics</td>
<td>• Dr. Henk Obbink, Dr. Wim van der Linden (Philips, CTMM/TraIT)</td>
<td>1</td>
</tr>
<tr>
<td>• Kees van Bochove (The Hyve, CTMM/TraIT)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>• Jos Lunenberg, Dr. Bas Tolhuis (Genalice, CTMM/TraIT)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medicinal Chemistry</td>
<td>• Prof. Titia Sixma (NKI)</td>
<td>1</td>
</tr>
<tr>
<td>• Dr. Ype Elgersma (EUR)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>• Dr. Henk Schallig (KIT)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Molecular Cell Physiology</td>
<td>• EUR: Hans van Leeuwen 1</td>
<td></td>
</tr>
<tr>
<td>Molecular Chemistry</td>
<td>• Dr. P. Willemsen (CVL Leiden) 6</td>
<td></td>
</tr>
<tr>
<td>• Dr. P Van der Ley (InTravac, Bithoven) 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prof. T. Sixma (NKI, Amsterdam) 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dr. J. Thole (TBVI, Leiden) 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dr. S. Bashiri (Xbrane Bioscience, Stockholm) 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dr. A. Omrani (Ibara Bioscience, Stockholm) 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Prof. P. Hermans (Crucell, Leiden) 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1 = joint publications, 2 = PhD project, 3 = joint research, 4 = sharing datasets or software, 5 = consultancy, 6 = other
12.4 Valorisation activities

Projects 2007 – 2012 with industrial involvement

<table>
<thead>
<tr>
<th>AIMMS Section</th>
<th>Research topic</th>
<th>Funding source</th>
<th>Company involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocomputational Chemistry</td>
<td>Spin-off company Scientific Computing &amp; Modeling NV, Amsterdam, Netherlands</td>
<td>SCM</td>
<td>Wacker Chemie</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wacker Chemie</td>
</tr>
<tr>
<td>Biomolecular Analysis</td>
<td>Metabolic stability assessment as new tool in the Hit-to-Lead selection process and the generation of new lead compound libraries</td>
<td>Ti-Pharma</td>
<td>MS, Xendo Laboratories</td>
</tr>
<tr>
<td></td>
<td>Towards novel translational safety biomarkers for adverse drug toxicity</td>
<td>Ti-Pharma</td>
<td>MSD, PepScan, Abbott, PamGene, BDS, Galapagos, NOTOX</td>
</tr>
<tr>
<td></td>
<td>Innovative Analytical Methodologies for Biopharmaceuticals</td>
<td>STW</td>
<td>Spark Holland, Tosoh Biosciences, PRA International, MSD, Beckman Coulter, BioNavis, Heineken Supply Chain, RIKILT, Technex, Synthion, EuroProxima, Stichting Waterproof</td>
</tr>
<tr>
<td></td>
<td>Enhanced bioresolution and miniaturization of Surface Plasmon Resonance optical sensing</td>
<td>TA-Coast</td>
<td>Het Waterlaboratorium, Stichting WaterNet, Vitens, STOWA, Omegam Laboratory, Tijkswaterstaat, Grontmij Nederland, KWR, Spark Holland, RIWA Maas</td>
</tr>
<tr>
<td></td>
<td>High-Throughput Effect-Directed Analysis: a novel platform for rapid and sensitive identification of toxic compounds in the aquatic environment</td>
<td>STW</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
<td></td>
<td>Development of glycomics technology</td>
<td>Ludger Ltd.</td>
<td>CHEMO-group, Chemessentia, GSK, J&amp;J, Orion, Bayer, Sanofi, Evolva, Pfizer</td>
</tr>
<tr>
<td></td>
<td>Glycosylation analysis of biologicals</td>
<td>Synthion b.v.</td>
<td>Sudlow, Mercachem, Edelris, Sygnature, Taros, Astra, Lundbeck, UCB, Bayer, J&amp;J, Merck, Sanofi</td>
</tr>
<tr>
<td></td>
<td>New MS interfacing techniques</td>
<td>BeckmanCoulter</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
<td></td>
<td>Improved analysis of therapeutic peptides and proteins</td>
<td>IWT</td>
<td>Janssen Pharmaceutica</td>
</tr>
<tr>
<td>Bio-organic Synthesis</td>
<td>Hepatitis C</td>
<td>NWO</td>
<td>CHEMO-group, Chemessentia, GSK, J&amp;J, Orion, Bayer, Sanofi, Evolva, Pfizer</td>
</tr>
<tr>
<td></td>
<td>Green Pharmacy</td>
<td>EU IMI-JU (CHEM21)</td>
<td>Syncom, Mercachem, Edelris, Sygnature, Taros, Astra, Lundbeck, UCB, Bayer, J&amp;J, Merck, Sanofi</td>
</tr>
<tr>
<td></td>
<td>Early drug discovery platform</td>
<td>EU IMI-JU (Lead Factory)</td>
<td></td>
</tr>
<tr>
<td>Integrative Bioinformatics</td>
<td>Data integration for translational medicine</td>
<td>CTMM/TraIT</td>
<td>Genalice, Philips, The Hyve</td>
</tr>
<tr>
<td>Molecular Cell Physiology</td>
<td>• Serotonin receptor ligands</td>
<td>• EU FP7 Beactica</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Novel neuropharmaceutical drugs</td>
<td>• FES Synaptologies, Noldus Saromics, IOTA, Kinasedetect</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Histamine H4 ligands</td>
<td>• EU FP7 Beactica</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Computation &amp; drug design</td>
<td>• Boehinger Ingelheim Boehinger Ingelheim</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Kinase inhibitor</td>
<td>• Boehinger Ingelheim</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Histamine H1-H4 ligands</td>
<td>• STW Zoobio, Pamgene</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• African Sleeping Sickness</td>
<td>• NGI Griffin Discoveries</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Ligand-gated ion channels</td>
<td>• Ti Pharma Takeda, IOTA, Mercachem</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Kinetics for Drug Discovery</td>
<td>• Ti Pharma MSD, Abbott StewArt Zoobio, Pamgene, Sanofi-Aventis, Sierra, Heptares</td>
<td></td>
</tr>
<tr>
<td>Molecular Microbiology</td>
<td>• Systems Biology</td>
<td>• Systems Biology</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Protein production</td>
<td>• Pfizer Pfizer</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Synthetic Polymer production</td>
<td>• PP7 Fujifilm</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• PCR</td>
<td>• STW Various biotech MRC-Holland</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Systems Biology</td>
<td>• Unilever Unilever</td>
<td></td>
</tr>
<tr>
<td>Molecular Neurobiology</td>
<td>• Integrative Systems Biology</td>
<td>• AstraZeneca AstraZeneca</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Systems Biology</td>
<td>• Pfizer Pfizer</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Protein production</td>
<td>• BRC/BBSRC NOLDUS, DeltaPhenomics</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Synthetic Polymer production</td>
<td>• FES Danone</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• PCR</td>
<td>• STW Various biotech</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Systems Biology</td>
<td>• Unilever Unilever</td>
<td></td>
</tr>
<tr>
<td>Molecular Toxicology</td>
<td>• Vaccine Development</td>
<td>• STW Alberta Bioscience</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Vaccine Development</td>
<td>• Vinnova Alberta Bioscience</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Vaccine Development</td>
<td>• FFS Alberta Bioscience</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td>• Development Antibiotics</td>
<td>• FP7 Various biotech</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• SYLICS BV, Beactica</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• EU FP7 Noldus, DeltaPhenomics</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• Danone Danone/ Nutricia</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• STW Alberta Bioscience</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• Unilever Unilever</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• Vertex Pharmaceuticals Vertex Pharmaceuticals</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• BASF &amp; Abbott BASF &amp; Abbott</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• IMI-JU 12 EFPIA partners + SMEs</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• IMI-JU 14 EFPIA partners + SMEs</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• IMI-JU 14 EFPIA partners</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• NWO/ACTS-IBOS (2 projects) BASF &amp; Abbott</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• MDI-BLLE: prediction drug-induced liver injury 12 EFPIA partners + SMEs</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• eTOX: In silico prediction of drug safety 14 EFPIA partners + SMEs</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• SafeSciMET: modular education &amp; training programme for medicines safety sciences 14 EFPIA partners + SMEs</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• Cytochrome P450 BM3 mutants as novel biocatalysts MSD, Syncom, DSM, Isobionics, XenoPharm Systems, University of Twente, Unilever, Sysmex, and other partners</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• Metabolic stability/Lead finding and optimization MSD, Syncom, DSM, Isobionics, XenoPharm Systems, University of Twente, Unilever, Sysmex, and other partners</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
<td>• Translational safety biomarkers for adverse drug reaction MSD, Abbott, Galapagos, Notus, Pepscan, Pamgene, Biodetection Systems, University of Twente, Unilever, Sysmex, and other partners</td>
<td></td>
</tr>
</tbody>
</table>

**Structural Biology**
- Antibacterial targeting bioenergetics against drug-resistant bacteria.
- From FLIM to FLIN (EU Marie Curie)
- Development and application of new fluorescene microscopy techniques

**Synthetic Chemistry**
- Ligand screening
- Reduction of phosphine oxides
- GSK Vaccins
- GSK Vaccins

**System Bioinformatics**
- Model-based optimisation of vaccine production
- Heterogeneity in populations of bacteria
- Selection of high-performance strains
- STW
- DSM, Purac, CSK, Friesland-Campina CSK

**Target and Systems Biology**
- Nanobodies targeting viral GPCRs
- STW
- MSD, Abbott
- MSD, Danone Vertex Pharmaceuticals
- MSD, BeckmanCoulter, Spark, Tosoh, PRA, Bionavis

**Molecular Cell Physiology**
- Serotonin receptor ligands
- EU FP7 Beactica

**Molecular Microbiology**
- Systems Biology
- Protein production
- Synthetic Polymer production
- PCR
- Systems Biology

**Molecular Neurobiology**
- Integrative Systems Biology
- AstraZeneca

**Molecular Toxicology**
- Vaccine Development
- Vaccine Development
- Vaccine Development
- Development Antibiotics
- STW Alberta Bioscience
- Vinnova Alberta Bioscience
- FFS Alberta Bioscience
- SYLICS BV, Beactica
- EU FP7 Noldus, DeltaPhenomics
- Danone Danone/ Nutricia
- Vertex Pharmaceuticals
- BASF & Abbott BASF & Abbott
- IMI-JU 12 EFPIA partners + SMEs
- IMI-JU 14 EFPIA partners + SMEs
- IMI-JU 14 EFPIA partners
- NWO/ACTS-IBOS 2 projects BASF & Abbott
- MDI-BLLE: prediction drug-induced liver injury 12 EFPIA partners + SMEs
- eTOX: In silico prediction of drug safety 14 EFPIA partners + SMEs
- SafeSciMET: modular education & training programme for medicines safety sciences 14 EFPIA partners + SMEs
- Cytochrome P450 BM3 mutants as novel biocatalysts MSD, Syncom, DSM, Isobionics, XenoPharm Systems, University of Twente, Unilever, Sysmex, and other partners
- Metabolic stability/Lead finding and optimization MSD, Syncom, DSM, Isobionics, XenoPharm Systems, University of Twente, Unilever, Sysmex, and other partners
- Translational safety biomarkers for adverse drug reaction MSD, Abbott, Galapagos, Notus, Pepscan, Pamgene, Biodetection Systems, University of Twente, Unilever, Sysmex, and other partners
## 12.5 AIMMS Seminars and Lectures

### 2012

<table>
<thead>
<tr>
<th>Date</th>
<th>Speaker</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 9th</td>
<td>Dirk Bald (Structural Biology)</td>
<td>'Bacterial energy metabolism and new antibiotics'</td>
</tr>
<tr>
<td></td>
<td>Hester Zijlstra (Bio-computational Chemistry)</td>
<td>'Natural and Artificial DNA Quadruplexes - Intrinsic Stacking Preferences versus Constraints of the Backbone'</td>
</tr>
<tr>
<td>Jan 23rd</td>
<td>Ana Sauri Peris (Molecular Microbiology)</td>
<td>'Autotransporters in bacteria: virulence factors that can be useful'</td>
</tr>
<tr>
<td></td>
<td>Karin Kiewisch (Theoretical Chemistry)</td>
<td>'Electron densities of proteins from subsystem density functional theory'</td>
</tr>
<tr>
<td>Feb 6th</td>
<td>Felipe Santos (Systems Bioinformatics)</td>
<td>'Understanding evolution strategies of microorganisms'</td>
</tr>
<tr>
<td></td>
<td>Harini Venkataraman (Molecular Toxicology)</td>
<td>'Engineering cytochrome P450 BM3 for regio- and stereoselective hydroxylation'</td>
</tr>
<tr>
<td>Feb 20th</td>
<td>AIMMS Lecture Lynne Kamerlin (Department of Cell and Molecular Biology, Uppsala University)</td>
<td>'Protein evolution: randomized or targeted?'</td>
</tr>
<tr>
<td>Feb 23rd</td>
<td>AIMMS Lecture Prof.dr.ir. M.W. Fraaije (Molecular Enzymology group, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen)</td>
<td>'Discovery and (re)design of oxidative biocatalysts'</td>
</tr>
<tr>
<td>March 5th</td>
<td>Bart van den Berg (Molecular Microbiology)</td>
<td>'Spider in the web: multiple interactions of the essential cell division protein FtsQ as novel targets for antibiotic intervention'</td>
</tr>
<tr>
<td></td>
<td>Angelina Huseinovic (Molecular Toxicology &amp; Genetics)</td>
<td>'Drug-induced genome instability: translation from yeast to human'</td>
</tr>
<tr>
<td>March 15th</td>
<td>AIMMS Lecture Dr. Sarah Trimpin (Department of Chemistry, Wayne State University, Detroit, Michigan, USA)</td>
<td>'Advances in ion formation for use in mass spectrometry: LSI, MALDI and SAIL'</td>
</tr>
<tr>
<td>March 19th</td>
<td>AIMMS Lecture Prof. Andrew L. Hopkins DPhil FRSC FSB (Director of SULSA, SULSA Research Professor of Translational Biology, Chair of medicinal Informatics, College of Life Sciences, University of Dundee, UK)</td>
<td>'Network pharmacology in drug design'</td>
</tr>
<tr>
<td>April 2nd</td>
<td>Annual Meeting Keynote lecture Prof. dr. Frans Russel (Radboud University Nijmegen Medical Centre)</td>
<td>'Ins and outs of membrane transporters in drug disposition and safety'</td>
</tr>
<tr>
<td></td>
<td>Keynote lecture dr. Carsten Hoffman (Institut für Pharmakologie, Universität Würzburg)</td>
<td>'GPCR based FRET-probes to investigate drug efficacy and receptor activation in live cells'</td>
</tr>
<tr>
<td></td>
<td>Keynote lecture dr. Efkan Breukink (Utrecht University)</td>
<td>'The bacterial cell wall synthesis machinery, an old target with lots of opportunities left'</td>
</tr>
<tr>
<td></td>
<td>PhD competition Ingeborg Petterson (Bio-Analytical Spectroscopy/BioMolecular Spectroscopy)</td>
<td>'Time-resolved Raman spectroscopy for depth measurements through non-transparent materials'</td>
</tr>
<tr>
<td></td>
<td>PhD competition Nicola Bonzanni (Integrative Bioinformatics)</td>
<td>'Formal modelling strategies in single and multi-cellular differentiation'</td>
</tr>
<tr>
<td></td>
<td>PhD competition Mojgan Heshmat (Bio-Computational Chemistry &amp; Theoretical Chemistry)</td>
<td>'Theoretical Studies on VCD spectroscopy with applications in Medicinal Chemistry'</td>
</tr>
</tbody>
</table>
PhD competition Zora Soprova (Molecular Microbiology) - ‘Autotransporters: how virulence factors can be useful’

PhD competition Sanne Bouwman (Bio-Organic Chemistry) - ‘Diversity-oriented synthesis of Uridyl peptide antibiotics using multi-component reactions’

PhD competition Jan Simon Boerma (Molecular Toxicology) - ‘Novel strategies for drug-protein adduct formation and identification’

Keynote lecture Prof. Dr. Gijs J.L. Wuite (VU University Amsterdam) - ‘Unraveling the dynamics of repair-protein binding to DNA, one molecule at a time’

April 16th
AIMMS Lecture Wilfried Niessen (interim head Biomolecular Analysis and Spectroscopy, director Hyphen MassSpec) - ‘Fragmentation of even-electron ions in tandem mass spectrometry, a tutorial. Tools to elucidate fragment-ion identity’

April 17th
AIMMS Lecture Uwe Bornscheue (University of Greifswald, Germany) - ‘In silico discovery and application of transaminases in organic synthesis’

May 7th
AIMMS Lecture Antoine van Kampen (IBIVU - lecture series “Bioinformatics for Translational Medicine”) - ‘Exome sequencing’

May 14th
AIMMS Lecture Oren Tzfadia, Ph.D. (Weizmann Institute of Science, Israel) - ‘A systems biology framework for studying metabolic pathways’

May 21st
Alexandra Pelgrom (Target and Systems Biology & Structural Biology) - ‘GPCR-mediated oncogenic signaling, targeting 14-3-3 as mediators of apoptotic/proliferative switching’

Azra Delic (Molecular Cell Physiology & Target and Systems Biology) - ‘The network pathophysiology of tumorigenesis: a systems biology approach’

June 11th
Keynote lecture in AIMMS post-graduate course prof. dr. Matthias Heineman (Molecular Systems Biology, RUGroningen) - ‘Towards a quantitative understanding of dynamic metabolic systems’

June 12th
Keynote lecture in AIMMS post-graduate course Ursula Klingmueller (German Cancer Research Institute) – ‘Systems Biology of Signal Transduction’

Sept 10th
Kristina Orrling (Medicinal Chemistry) – ‘Jointly Changing the Future for Human African Sleeping Sickness – PDE Inhibitors as Trypanocidals’

Oct 8th
AIMMS Lecture Dr. Ryan Mccleary (National University of Singapore) – ‘Toxins in snake venom’

Oct 11th
Lecture Prof. Dr. Christiaan Leeuwenburgh (University of Florida, Institute on Aging, Department of Aging and Geriatric Research, College of Medicine, Chief Division of Biology of Aging) - ‘Mitochondria and autophagy play a central role in aging and disease’

Oct 22nd
AIMMS Lecture Prof. Dr. Ron M.A. Heeren (FOM-AMOLF Amsterdam) - ‘Unraveling molecular complexity on biological surfaces with imaging mass spectrometry’

Nov 5th
AIMMS Lecture Dr. Erwin den Blaauwen (UvA) - ‘Studying bacterial cell division and inhibition; FtsZ as a case study of target driven development of antibiotics’

Nov 14th
AIMMS Lecture prof. dr. Alan E. Mark (University of Queensland, Australia) - ‘Peptides and proteins in action’

Nov 19th
Joost Boele (Systems Bio-Informatics) - ‘PAPD5 mediates isomiR-specific adenylation of oncomiR miR-21 to induce its degradation’

Michiel den Braver (Molecular Toxicology) ‘IMI MIP-DILI: IdioSyncratic Drug-Induced Liver Injury’

Dec 3rd
AIMMS Lecture Prof. dr. Sassha Ott (Department of Photochemistry and Molecular Science, Uppsala University, Sweden) - ‘Artificial Photosynthesis - Hydrogen from Enzyme Active Site Models’

Dec 3rd
AIMMS Lecture Prof. dr. Leon Reubsaet (Bioanalytics@UiO, Oslo) - ‘Immuno-MS as valuable tool in robust biomarker determination. How to quantify diagnostic proteins at ultra low levels in biological samples?’

Dec 4th
AIMMS Lecture Prof. Dr. Christian Mueller (Institute for Chemistry and BioChemistry, Inorganic Chemistry, Free University Berlin, Germany) - ‘Chelating Phosphinines - New Perspectives in the Field of Aromatic Phosphorus Heterocycles’