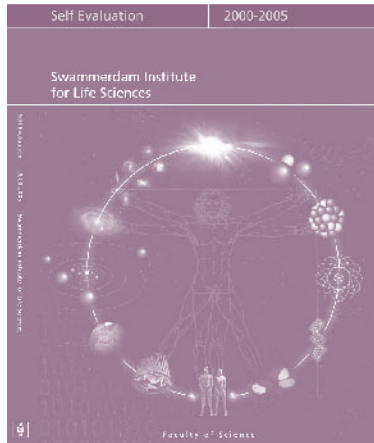


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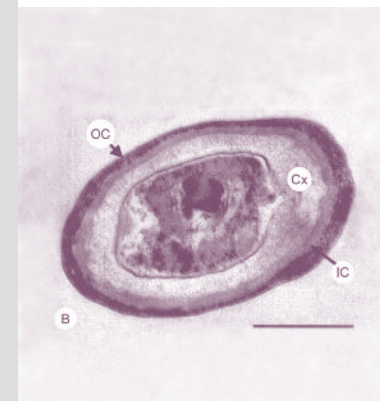


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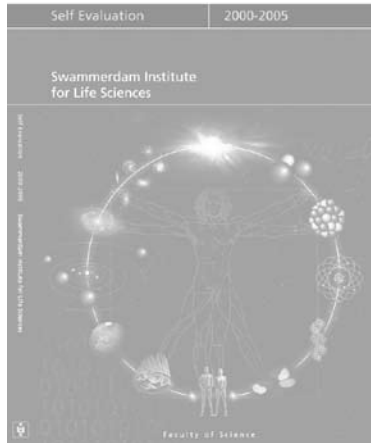


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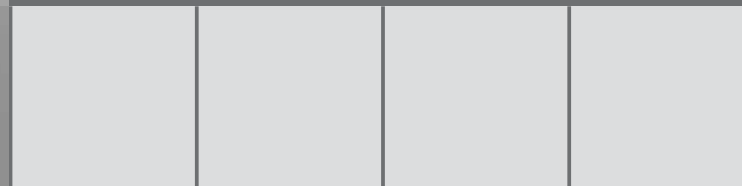
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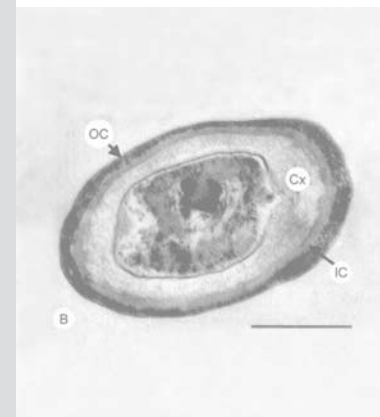


Annual Report 2006



FACULTY OF SCIENCE

UNIVERSITEIT VAN AMSTERDAM



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The Swammerdam Institute in 2006

Introduction

The Swammerdam Institute for Life Sciences (SILS) is one of the ten research institutes of the Faculty of Science of the Universiteit van Amsterdam. For the first time since its creation in 2000, the institute has been evaluated by an external (international) evaluation committee. In the eyes of the committee, the prospects of SILS are very good. It foresees a bright outlook for life sciences in Amsterdam, and it sees SILS playing an instrumental role in it. This is supported by the bibliometric study of SILS over the period 1995 – 2005, indicating an above average research potential of the current SILS researchers.

The committee also indicated some points for improvement. Most of the research groupings are relatively small, which can make it hard to be internationally competitive. Collaborations are therefore seen as an important part of SILS portfolio for the future. It also pointed out the delicate balance between research and teaching; for SILS the teaching load is heavy and could be impacting the productivity of the various groups.

In order to further strengthen SILS' position in research, these and other recommendations from the committee are currently being discussed within the institute, and will lead to the creation of a revised strategic plan for the years 2007-2011.

New and exciting developments have been taking place in 2006 that further solidify the position of SILS.

The ongoing activities regarding the collaboration of the UvA (SILS) with neighbouring institutes AMOLF (Institute for Atomic and Molecular Physics), CWI (Centrum voor Wiskunde en Informatica) and with the Vrije Universiteit in the area of Systems Biology, have resulted in the signing of an agreement to form the Netherlands Institute for Systems Biology (NISB). The NISB focuses on the integrated functioning of metabolic, signal-transduction and genetic networks in combination with systems that drive the generation of shape and force in living cells.

Regarding the research facilities, a new, state-of-the-art green house complex has been completed in the first half of 2006. Final plans for a new building for the entire Faculty of Science have been completed, and we are awaiting to finally co-locate all SILS research groups in the same building in the next few years.

1. Preface by the director

In 2006 our financial position appears to have stabilised. We are still awaiting the final figures, due to changes within the financial systems within the university, and the changing allocation of funds for research and education. The institute will continue its' extremely careful financial management and will make clear choices on what we will and will not undertake. The apparent lack of flexibility has also been identified by the external evaluation committee. In line with its recommendation we will also in the coming years strive to fund new initiatives.

Highlights

- Prof.dr J. Hugenholtz, affiliated to NIZO Food Research, the Wageningen Centre for Food Science (WCSF) and the Kluyver Centre for Genomics of Industrial Fermentations (KCGIF), was appointed as honorary professor in Industrial Microbial Physiology in May 2006.
- Both dr J. Teixeira de Mattos and prof.dr J. Hugenholtz have obtained a transnational SysMo grant. This allows the Molecular Microbial Physiology group of prof.dr K. Hellingwerf to initiate two new systems biology projects (1) on regulation of respiration in *Escherichia coli* and (2) on growth and product formation in lactic acid bacteria.
- At the end of 2006, prof.dr J. Wells was appointed as a Senior Scientist within the Wageningen Center for Food Sciences (WCFS) and he will participate in a new project concerning intestinal homeostasis.
- dr P.J. Verschure received the Feulgen Prize of the Society for Histochemistry.
- An EU TMR-grant was awarded to prof.dr Th. Gadella in collaboration with 7 other European groups working on Nod factor signalling.
- Dr C. Testerink was awarded a VIDI for the project titled: Modulation of protein kinase function by the lipid second messenger phosphatidic acid.
- Dr R. Mirabella was awarded a VENI for the project titled: C6 volatiles: a new class of signal molecules in plants.
- A grant from the Foundation for Technology & Science (STW) was awarded to the group of prof.dr C. Pennartz, for the development and application of miniaturized equipment for ensemble recordings in mouse models of brain disease.
- The group of prof.dr W. Wadman will participate in a large research program (TTI Pharma) on the role of the endocannabinoid receptor. This program will continue our collaboration with Solvay Pharmaceuticals, the leading industrial partner in the program.
- Prof.dr M. Joëls was the main applicant of a EUROCORES on "Stress and Mental Health", which was approved by the ESF. In addition, prof.dr M. Joëls received an HFSP programme grant.

- Prof.dr A. Smilde was the Eastern Analytical Symposium 2006 Award Recipient for Achievements in Chemometrics.
- The group of dr. Timo Breit was involved in the installation of an e-BioScience Laboratory (e-BioLab) designed for the interpretation of the results of (computational) -omics experiments using a.o. visualisation on a high resolution video wall. The e-BioLab will enable multidisciplinary co-operation and is an initiative of SILS, IvI, SARA, NBIC and NIKHEF in the framework of the Virtual Lab for e-science project.

With respect to education and training, we have observed yet another increase in Bachelor students: Psychobiology attracted 136 students (108 in 2005), Biomedical Sciences attracted 140 students (123 in 2005). The institute has trained and educated students to a total of around 1700 in the Life Sciences Bachelors & Masters. Moreover, we have seen 17 PhD students successfully defend their thesis in 2006. The further increase in education-related activities is welcomed, but also forces the institute to carefully balance the needs (and related finances) for research AND education.

Future

In 2007 the recommendations of the external evaluation committee will be translated into a new strategic plan 2007-2011. We are entering a period in which considerable investments have been announced for areas in which our researchers are involved (e.g. cognition, neuro-informatics, systems biology). This creates new opportunities to further strengthen our research position. Overall, we are facing an exciting, yet challenging future for the Life Sciences, in which SILS can and will play an important role.

Life Sciences Research: Build on our Strengths

Introduction

The Swammerdam Institute is bringing together more than 200 researchers with knowledge from many areas of science, amongst others: biology, (bio)chemistry, (bio)physics, medicine and data analysis- and information technology. In these areas research is carried out at the molecular, cellular, and organismal level. Integrating the knowledge from different areas is essential to reach our final goal: understanding life processes in organisms and cells. Bioinformatics and data analysis are essential in this process and, Systems Biology is increasingly becoming a focal point of attention.

In the institute research is carried out within four clusters: 'The Living Cell', 'Plants and Health', 'SILS Center for NeuroScience' and 'Life Science Technologies'. The first three clusters study processes that take place within and between cells, such as signal transduction, growth and cell division and the structure of chromatin. Between these research themes many interactions take place ranging from the use of common methods to research collaborations. The fourth cluster, Life Science Technologies, applies advanced technologies to fundamental biological research and carries out technology development, keeping the SILS researchers at the forefront of Science. Life Science Technologies has extensive collaborations with other research groups within and outside SILS. A great amount of technologies and relating expertise has been build up, and genomics and advanced microscopy facilities have been created for the benefit of all research groups at the Swammerdam Institute.

The institute studies a number of central themes on an institute wide level. These are for instance gene expression, the structure of DNA molecules and chromatin, protein - protein interactions, protein structure – function relations and signal transduction processes, as these take place in man, animal, plant and micro-organism. Within the institute this leads to exchange of information and extension of research over the borders of different disciplines. Crossing the borders between the different research topics within the institute and via interactions with strategic research partners, important and unique discoveries are made that lead to the discovery of life's secrets and to applications that improve the quality of life.

Research Output

Clusters	PhD Theses	Academic Publications	Patents
The Living Cell	5	69	3
Plants and Health	5	20	0
SILS Center for NeuroScience	5	60	0
Life Science Technologies	2	28	0
Total	17	177	3

Research Input

Clusters	FS1*	FS2**	FS3°	Total
The Living Cell	19.9	13.2	14.9	48.0
Plants and Health	10.0	5.3	5.5	20.8
SILS Center for NeuroScience	14.5	4.2	6.3	25.0
Life Science Technologies	7.6	2.3	16.4	26.3
Total	52.0	25.0	43.1	120.1

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Research input in full time equivalent

The research input of the academic staff per full time equivalent has been calculated making use of the following parameters:

Full Professors:	0.5 fte research
Assistant and Associate Professors:	0.5 fte research
Postdoctoral Fellows:	0.9 fte research
PhD Students:	0.75 fte research
Research Technicians:	1.0 fte research

Research groups within the Swammerdam Institute for Life Sciences**The Living Cell**

Molecular Microbial Physiology	Prof.dr K.J. Hellingwerf
Molecular Biology and Microbial Food Safety	Prof.dr S. Brul
Cellular Microbiology	Prof.dr J.M. Wells
Structure and Functional Organisation of the Cell Nucleus	Prof.dr R. van Driel
Epigenetic Regulation of Gene Expression	Prof.dr A.P. Otte
Molecular Cytology	Prof.dr Th.W.J. Gadella

Plants and Health

Plant Physiology	Prof.dr M.A. Haring
Plant-Pathogen Interaction	Prof.dr B.J.C. Cornelissen

SILS Center for NeuroScience

Animal Physiology and Cognitive Neuroscience	Prof.dr C.M.A. Pennartz
Cellular and Systems Neurobiology	Prof.dr W.J. Wadman
Hormonal Regulation of Signal Transduction in the Brain	Prof.dr M. Joëls

Life Science Technologies

Mass Spectrometry of Biomacromolecules	Prof.dr C.G. de Koster
BioSystems Data Analysis	Prof.dr A.K. Smilde
Micro Array Department and Integrated Bioinformatics Unit	dr T.M. Breit
Centre for Advanced Microscopy	dr E.M.M. Manders, prof.dr Th.W.J. Gadella

Research Clusters

The Living Cell

Cells, the basic units of higher organisms and the competing individuals in microbiology, are the central topic of study of 'The Living Cell'. This cluster focuses on the chain of events all the way from modulation of gene expression, e.g. by signals coming from the environment, up to the resulting phenotype elicited by such signals. This process is studied in (cells of) micro-organisms, animals and plants, most often to resolve basic scientific issues, but also in a more applied context, in particular aiming to improve food and health. The mission of the cluster 'The Living Cell' is to understand life, in particular in its simplest form of a living cell, all the way from the molecular level, upwards via the complex biochemical and genetic networks that it encompasses, to the individual organism that can be successful in the struggle for survival. The unique information that this approach provides, the possibility of linking this information with metabolomics and proteomics data, combined with the computational simulation of the processes under study, is leading to a shift in paradigm, often referred to as 'Systems Biology'. 'The Living Cell' is uniquely positioned to play a key role in this development.

Six chairs contribute to the research cluster 'The Living Cell': 'Molecular Microbial Physiology', 'Molecular Biology and Microbial Food Safety', 'Cellular Microbiology', 'Molecular Cytology', 'Epigenetic Regulation of Gene Expression', and 'Structural and Functional Organization of the Cell Nucleus'.



Molecular Microbial Physiology

Chairholder: Prof.dr K.J. Hellingwerf

Jeroen Hugenholtz	Professor
Joost Teixeira de Mattos	Associate Professor

Introduction

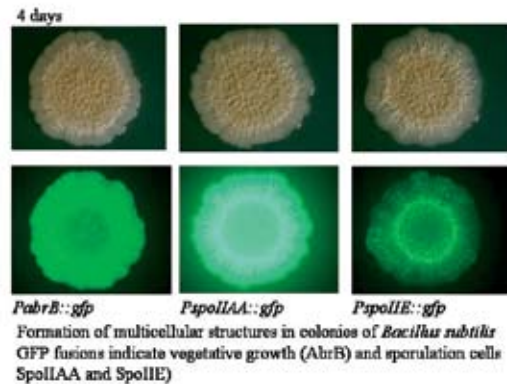
The general aim of our research team is to discover the properties that allow living (microbial) cells to catalyze a large array of concurrent chemical fluxes and information flows. From these processes and in particular their mutual interactions 'life', with its typical characteristics as: adaptation to the environment, reproduction and evolution, has emerged. Micro-organisms are particularly successful in this respect as can be concluded from the fact that they inhabit even the most extreme and variable ecosystems known to exist on this earth (and possibly even beyond), they can grow at very high rates, and can even adapt/evolve genetically.

Our work focuses on various aspects of this process, like (i) the details of intra-molecular signal-generation in (photo) receptor proteins, (ii) signal transfer between subsequent components in a signal transduction chain, (iii) the regulatory function of modulated gene expression, and (iv) the functional integration of these processes in the physiology of a range of micro-organisms, relevant for food and health, etc. By combining theoretical (*i.e.* computational) and experimental approaches, insight is obtained into basic principles that underlie functional interactions in (information) flux-carrying macromolecular networks, and accordingly into a **biochemical system** that sustains microbial (*i.e.* cellular) **life**.

Research Highlights

Until recently, light-sensing in micro-organisms was only studied in phototrophic organisms. We have now clearly demonstrated light-sensing responses also in the chemotrophs *Escherichia coli*, *Bacillus subtilis* and *Idiomarina loihiensis*. These organisms have been shown to contain the blue-light photoreceptor proteins YcgF, YtvA and PYP, respectively. Especially the findings in *E. coli* and *B. subtilis* are of interest, since these are generally considered to be model organisms for Gram-negative and Gram-positive bacteria, respectively.

It was shown that the general stress response in *B. subtilis* is modulated by blue light via the LOV domain of YtvA. Besides this, a completely new light-effect, **elicited by red light**, was found in this organism. The presence of light was shown to inhibit biofilm formation in *E. coli* (with the involvement of YcgF) and in *I. loihensis*. The involvement of light-receptors in the formation of biofilms is of specific interest, because it has become clear that in Nature, cells often live in these “multi-cellular” structures, which increases their antibiotic resistance considerably. Whereas a lot of progress has been made in understanding the cellular changes that occur when an organism switches from a planktonic life style to a biofilm, not much is known about perception of the signals that can trigger this switch. The new photoreceptors discovered in our group may turn out to be a very convenient tool to further characterize these latter processes.



Yeast cells have been grown under conditions of defined and controlled low oxygen availability. Quantitative analysis revealed that there is a micro-aerobic range of growth conditions that results in yeast cells that are vastly different from both fully aerobically and anaerobically grown cells, with respect to: their the transcriptome and proteome profile, the functioning of their energy conservation machinery and their general physiological state. The notable differences in efficiency of energy conservation suggest the existence of an efficient uncoupling mechanism in *Saccharomyces cerevisiae* unknown hitherto. In *E. coli* we have developed a method to measure all quinone components (i.e. the oxidized and reduced form of UQ, DMQ and MQ) under physiologically well-defined conditions. Regulation of the redox state of these components is more complex than predicted by current theories.

Other Highlights

- Prof.dr. J. Hugenholtz, affiliated to NIZO Food Research, the Wageningen Centre for Food Science (WCSF) and the Kluyver Centre for Genomics of Industrial Fermentations (KCGIF), was appointed as honorary professor in Industrial Microbial Physiology in May 2006.
- Prof.dr K. Hellingwerf organized the ESF/EMBO sponsored meeting on “Microbial systems- and synthetic biology” in October 2006, in San Feliu, Spain.
- Dr. J. Teixeira de Mattos was elected as secretary of the scientific committee of the 13th European Congress on Biotechnology 2007 (European Federation of Biotechnology, Barcelona, Spain) and as member of the organizing committee of this meeting.

Future Prospects

- Work in the photobiology and molecular physiology projects will be continued to resolve the molecular mechanisms of the new processes discovered (*i.e.* photoreception in RsbP and uncoupling in yeast mitochondria).
- The photobiology project will be extended to include more explicitly aspects of systems biology, through mathematical modelling in which photocycle characteristics of YtvA and AppA will be integrated into a model describing the cellular (stress) response.
- Both dr Teixeira de Mattos and prof.dr Hugenholtz have obtained a transnational SysMo grant. This allows the group to initiate two new systems biology projects on (1) regulation of respiration in *Escherichia coli* and (2) on growth and product formation in lactic acid bacteria.



Molecular Biology and Microbial Food Safety

Chairholder: Prof.dr S. Brul

Frans Klis Associate Professor (Senior Scientist)
 Hans van der Spek Assistant Professor
 Gertien Smits Assistant Professor

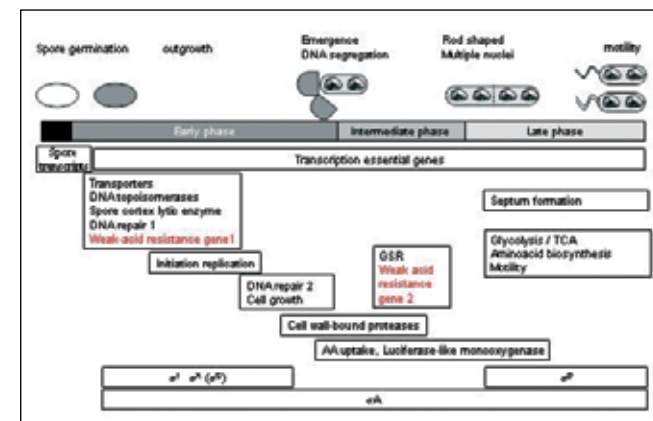
Introduction

Our group aims at understanding the behaviour of (micro)organisms in relation to their food or pharma related environment using approaches ranging from classical molecular biology and biochemistry to state of the art functional genomics and systems-biology. The tool kit we apply includes genome-wide micro-array analysis, proteomics, various advanced microscopy techniques and microbial physiology using controlled cell culturing systems such as fermentors and chemostats. We have major contacts and contracts with the food and pharma industry focusing on the application of our research in practical settings. Results are as much as possible quantified and analysed using a number of modelling tools. The areas of interest cover: (1) The interaction of fungal cells, in particular bakers' yeast (*Saccharomyces cerevisiae*) with environments often encountered in the food manufacturing industry and *Candida* species with medically relevant biotic and abiotic surfaces. The prime focus is on both thermal and weak-organic acid stress response and resistance development as well as on the analysis of the behaviour of cells in biofilms. In our experimental set-up we focus on analysing and subsequently being able to interfere with stress cross-tolerance mechanisms. Specifically in *Candida* we focus on the cell wall proteome and cell wall assembly enzymes and their regulation in the context of trying to identify novel antifungal targets. (2) The second area of interest covers the behaviour of bacterial spore-formers (mainly *Bacillus subtilis* and *Bacillus cereus*, a close relative of *Bacillus anthracis*). These are organisms of prime-importance to the food industry. Their occurrence necessitates the application of harsh food preservation processes such as high thermal treatments. The mechanistic basis of sporulation initiation, the occurrence of extremely high thermal resistance of bacterial spores (e.g. resistance to various minutes at 121°C), as well as molecular mechanisms involved in the early phases of spore germination are still far from understood. We focus, in a long-standing collaborative effort with the Microbiology group, TNO Quality of Life and the food industry, on all three areas of research. Additionally we study the mechanisms involved in stress resistance of vegetative cells and germinating

spores against weak-organic acid preservatives. The data provide targets for inhibition of unwanted microbial growth. (3) Finally, we focus on models for host physiology and host-microbe interactions. In collaboration with the virology department of AMC, *C. elegans* and eukaryotic cell cultures are used to study the adverse effects of antiretroviral compounds on host cells. Furthermore, we focus on the study of pathogenic yeast (see also 1) and, together with the Cellular Microbiology group of prof.dr Jerry Wells, on bacterial vegetative pathogens. Our prime area of research is the modulation by these micro-organisms of epithelial cell barrier functions.

Research Highlights

We continued development of a tool to predict spore survival upon thermal treatment (see Keijser, 2006). A full description of the germination-specific gene-expression profile was generated (Keijser et al. submitted; see picture). Inactivation of germination specific genes showed that the process is most likely governed by redundant systems that get specific functions during germination of thermally damaged spores or upon germination under stress. Finally, our studies of stress response in *B. subtilis* towards the classical preservative sorbic acid identified 3 genes that upon inactivation led to sorbic acid hypersensitivity. This discovery was patented with Unilever (ter Beek et al., 2006). Close inspection of the gene-expression profile of germinating spores showed that two of three genes are expressed (transiently) during spore germination under optimal conditions.



A systems overview of gene expression during spore-germination.

In our studies on (spoilage and medically relevant) yeasts we developed new analytical tools based on t-statistics for the analysis of genomic expression and fitness profiles. In *S. cerevisiae* we identified that membrane remodelling is most importantly involved in resistance against the natural antimicrobial compound chitosan (Zakrzewska, Euk. Cell, in press). Studies on the cell wall of *C. albicans* have shown the importance of changes in its cell wall protein structure for virulence (de Groot et al., 2006). We leveraged this tool in collaborative studies of various other fungal cell wall proteomes such as *Schizosaccharomyces pombe*, *Aspergillus niger* and *Phytophthora ramorum*. Also, we have made significant progress in *in-vivo* measurement of intracellular pH in yeasts. We are now able to assess this parameter in the cytosol and the mitochondrial matrix. The data will be incorporated in cellular (mathematical) models of biochemical events during stress with weak acids, heat and oxidative agents. Finally, we have performed genome-wide deletion studies on yeast stress tolerance acquisition in collaboration with prof.dr Steve Oliver of the University of Manchester. (3) We succeeded in quantifying the toxic effects of anti-retroviral drugs with a mitochondria specific qPCR assay in *C. elegans*.

Other Highlights

- S. Brul was awarded a Distinguished Research Fellowship of the University of Tasmania in Australia. In that framework he will visit the University in June 2007, lecture and organise a Workshop with local Faculty.
- Furthermore, he received a Unilever grant and authors award.
- The joint fungal expertise of our department (Dr. Frans Klis, senior researcher) and the department for Mass Spectrometry of Biomacromolecules with post-doctoral fellow Dr. Piet de Groot attracted the attention of the dental faculty (ACTA). They consulted us in the framework of their study on the involvement of *Candida* in oral disease during the ageing process. In particular the research aims at studying mixed oral bacteria *Candida* biofilms. A (joint ACTA-SILS) VIDI-grant proposal has been submitted on this topic by Piet de Groot.
- At the major international biannual Food Microbiology meeting FoodMicro 2006 in Bologna with near to 1000 participants three of the abstract submissions of the group were selected for an oral presentation.
- Finally, Dr. Frans Klis was a member of the scientific advisory board of the Priority Program of the Deutsche Forschungs Gemeinschaft 'Colonisation and infection by human pathogenic fungi'.

Future Prospects

- In *Bacillus* we will expand our studies of weak-acid stress response both in vegetative cells and germinating spores beyond sorbic acid and also we will start assessing stress cross-resistance and sensitivity of strains in which the levels of expression of putative mediator genes are modulated. Our studies on spore germination will include a molecular physiology assessment of effects of thermal stress on germination frequency and lag-time.
- For the yeast work we aim at linking cellular cytosol and pH reference data to molecular data on genome-wide expression during stress exposure. For both acid and thermal stress, biochemical data will be put in mathematical models of cellular stress physiology. Phenotypic profiling data in *S. cerevisiae* on cellular cross-tolerance mechanisms will be analysed to uncouple growth-rate related phenomena to specific stress related phenomena.
- In *C. albicans* we will continue our work together with the department of Klinical Proteomics of prof.dr Chris de Koster and ACTA. We will study biofilm formation on substrates mimicking mucosal surfaces, biofilm formation under polymicrobial conditions and we aim at the identification of cell wall assembly enzymes.
- The study of retroviral drug toxicity in *C. elegans* and cultured human cells will be reinforced with a starting PhD student. He will extend the observations on the effects of such compounds on mitochondrial numbers to assessing their impact on mitochondrial function. We will perform studies both in *C. elegans* and cultured epithelial cells.

Cellular Microbiology

Chairholder: Prof.dr J.M. Wells

Introduction

The aim of the Cellular Microbiology research group headed by Prof.dr Wells is to investigate the interactions between microbes and humans and to ultimately translate this research into new strategies for combating or preventing diseases. In previous collaborations the group has identified two-component signalling systems that are essential for *Streptococcus pneumoniae* to survive and that cause infection in the host. We are now aiming to explore their role and mechanism of action. Of particular interest are gene products that are potentially useful as targets for novel antibacterials, anti-infectives or vaccines. In collaboration with TNO we are investigating interactions of commensal and probiotic bacteria with the innate immune system of the host. Dendritic cells are of major interest as they are abundant at mucosal sites where they perform a crucial role in regulating tolerance and inflammation. Research on these topics could have important implications for the therapy or prevention of infectious diseases, inflammatory bowel disease, allergy and autoimmune disorders.

Research Highlights

Research on a Senter/CDTI -funded project involving industrial and academic partners from Spain and The Netherlands began this year. The research is aimed at understanding the role of an essential signalling system and its mechanism of action in *Streptococcus pneumoniae* and other drug-resistant Gram-positive pathogens. Collaborative research on the structure of these proteins is also underway in order to facilitate the discovery and development of chemical inhibitors of this vital regulatory pathway.

Research initiated in the group leaders former laboratory on the development of an intranasally administered vaccine against *Streptococcus pneumoniae* (pneumococcus) was published. Here, the harmless milk bacterium *Lactococcus lactis*, intracellularly producing the pneumococcal surface protein A (PspA) was evaluated as a mucosally delivered vaccine. Economical and effective vaccines against pneumococcus are needed for implementation in poorer countries where this pathogen is reported to cause around 1 million infant deaths p.a. Given the success obtained with this experimental vaccine and the safety profile of *L. lactis* there is considerable potential to develop a pneumococcal vaccine for use in

humans and to broaden this approach to combat other major pathogens.

Other Highlights

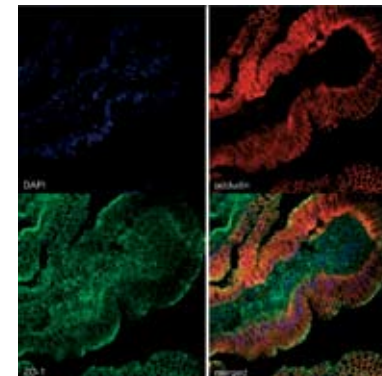
At the end of 2006, Prof.dr Wells was appointed as a Senior Scientist within the Wageningen Center for Food Sciences (WCFS) and he will participate in a new project concerning intestinal homeostasis.

Prof.dr Wells is a member of the Scientific Organizing Committee of the forthcoming *Campylobacter* and *Helicobacter* Research Organisation (CHRO International Congress to be held in The Netherlands Sept 2007), and he was a Workshop Panel Member and Chairperson at the European Mucosal Immunology Group Conference, Prague October, 2006.

Prof.dr Wells was invited speaker and keynote speaker at several meetings, for instance the ESF-EMBO Joint Symposium on Bacterial Networks and Systems Biology in Spain, and the Food Micro 2006 Congress in Italy.

Future Prospects

This year research will continue on elucidating the function and mechanism of the essential signalling system YycFG in the major human pathogen *Streptococcus pneumoniae*. Additionally a new TI-Pharma-funded project involving a large national consortium will start. This project is concerned with the exploiting Toll-like receptors for drug discovery.



Structure and Functional Organisation of the Cell Nucleus

Chairholder: Prof.dr R. van Driel

Paul Fransz	Assistant Professor
Maike Stam	Assistant Professor
Pernette Verschure	Assistant Professor

Introduction

The one-dimensional structure of the genome of an increasing number of eukaryotes is being fully sequenced. A major challenge is to understand how it functions in terms of orchestration of expression of the many thousands of genes it encodes. Gene control in eukaryotes is conducted at three hierarchical levels. One is that of the individual gene, involving cis- and trans-acting factors, such as enhancers, promoters and transcription factors. Information at the second level is stored as posttranslational modifications of histones, incorporation of histone variants and DNA methylation patterns. The third level is the compartmentalisation of the interphase cell nucleus. Gene regulation at this last level immediately relates to the folding of the chromatin fibre in the nucleus.

Our aim is to unravel epigenetic mechanisms that employ the functional compartmentalization of the interphase nucleus and related higher order chromatin structure. Epigenetic systems are essential for among others stable cell differentiation and have been found deregulated in various diseases. We concentrate on the dynamic structure of chromatin and the behaviour of the nuclear machineries involved in gene transcription, gene silencing and DNA repair. We combine structural studies, often on living cells, with molecular biological, biochemical and other molecular approaches. It is our ambition to be among the first to develop quantitative and predictive models of regulatory epigenetic networks that can guide experimental approaches.

Research Highlights

- In the past year we obtained new insights into the epigenetic mechanism that controls paramutation in maize. Application of the 3C-technology, in combination with chromatin immunoprecipitation (ChIP), has shown that physical interactions occur between specific genomic regulatory elements that are 100 kb apart. In part correlated with these interactions, a striking

developmental choreography of histone modifications and histone positioning is observed at these regulatory elements. This integrated approach may now be extended to unravel *in trans* gene regulatory interactions, i.e. between regulatory elements located on different chromosomes.

- Microscopical investigations on heterochromatic chromocenters in *Arabidopsis* cells revealed a fascinating organization of subdomains of epigenetically modified chromatin and of individual repeat classes. Results support our view of a sequential process of chromatin compaction.
- In the EU-EpiVector project we have successfully set up a genetically stable episomal system to visualise episomes in the nucleus of living cells and manipulate its activity at the epigenetic level. This system is being used to explore structure-function relationships in the interphase nucleus and develop novel vectors for gene therapy.
- Based on the VIDI-2003 project, which is focussed on controlled changes in epigenetic gene regulation and chromatin structure, we are developing a patent application on the newly developed system in mammalian cells.
- In the Huntington (Htt) project we explore the causal relationships between expression of the mutated Htt protein, formation of aggregates in the nucleus, cell death-survival, changes in histone modifications and gene expression in a cell model system.
- In cooperation with our group, prof.dr Reinhart Heinrich (Berlin; who tragically died October 2006) and Dr Frank Bruggeman (Manchester, Amsterdam) have explored the behaviour of gene networks that are controlled at the single gene and the epigenetic level. Based on these preliminary studies we started to develop a new research line combining measurements on natural and engineered gene networks in cultured cells in combination with predictive mathematical modelling.

Other Highlights

Dr P.J. Verschure received the Feulgen Prize of the Society for Histochemistry.

Dr P.F. Fransz is a member of the organising committee of the 16th International Chromosome Conference, Amsterdam, 2007.

R. van Driel is member of the advisory and site visiting board of various systems biology programs in Europe: the systems biology initiative of the European Science Foundation, the EU EraNet program ERASysBio, the German ForSys and HepatoSys programs, and the Irish national SFI CSET Systems Biology program.

Future Prospects

In the forthcoming year we will make the next steps in starting up a new research line focusing on a systems biology approach of analysing multi-level regulated gene networks. This will involve one PhD student. In addition two collaborative grant applications will be submitted. The work on the dynamic behaviour of heterochromatin in *Arabidopsis* (thesis Dr Tessadori) will be continued by using this system for analysis of the molecular mechanisms that control reversible heterochromatin disassembly. Here we will take full advantage of the genetic, cell biological and biochemical potential of this plant system. Attempts to transfer the paramutation system from maize to *Arabidopsis* will be continued. At the same time we intend to broaden the paramutation research line towards *in trans* interactions in general between loci in plants and in cultured mammalian cells. The epivector system developed in 2006 will be exploited to analyse in detail the chromatin state dependant behaviour of epivector chromatin *in vivo* and analyse the mechanism of the highly reliable equal distribution of the episomes during mitosis. Finally, an extra effort will be made to develop the *in vivo* chromatin structure/gene expression system designed by Dr Verschure. Closely related to these *in vivo* approaches is the ongoing work on DNA repair and the derived system on the analysis of the assembly of the transcription initiation complex. The newly developed research on Huntington's disease will be continued in cooperation with the Breit lab.



Epigenetic Regulation of Gene Expression

Chairholder: Prof.dr A.P. Otte

David Satijn Assistant Professor

Introduction

It is our long term aim to understand epigenetic regulation of gene expression in terms of cell differentiation and human disease. Research is focused on unravelling the function of multiprotein complexes, such as the repressing Polycomb group (PcG) proteins. PcG proteins form multimeric protein complexes that are part of a cellular memory system that is responsible for the inheritance of gene activity to progeny cells. The action of PcG complexes is delimited by the presence of genomic elements, STAR elements, which counteract PcG mediated repression. The dynamic interplay between these two, functionally antagonistic, systems is studied. We further study the implications of de-regulated expression of components of these gene regulation systems on both the activity of genes and on directing cells towards pathological states.

Our main expertise lies in:

- (i) The utilization of a unique anti-PcG antibody panel that we developed over the years. The panel is used by us to unravel the composition and dynamic behaviour of PcG complexes, particularly in the context of human cancers, as well the analyzing genetic target loci of PcG complexes.
- (ii) The employment of STAR elements to increase the predictability, expression levels and stability of therapeutic proteins in mammalian cells. Our knowledge of epigenetic gene regulation has important biotechnological and commercial implications.

Research Highlights

We developed a novel, very stringent selection system for the establishment of mammalian cell lines that produce therapeutic proteins. This allows us to screen ~ ten-fold fewer colonies than usual to obtain a high-producer cell line. In addition average protein expression levels are at least ten-fold higher than when traditional selection systems are employed.

We have started to analyze the chromatin structure of STAR elements, using CHromatin ImmunoPrecipitation assays. We found that a stably incorporated

reporter gene when flanked by STAR elements has a much higher histone acetylation status than a non-protected reporter gene, nicely correlating with higher gene expression levels. Furthermore, around the promoter of the reporter gene that is non-protected by STAR elements, higher levels of Polycomb group proteins are found in comparison with STAR-protected promoters. These results provide molecular mechanistic insight in the action of STAR elements.

Other Highlights

Through Crucell, four novel STAR technology licenses were sold to leading biotechnology companies, such as Genzyme and Novartis. In 2006 more than 10 patents were awarded concerning STAR technology.

Future Prospects

In the coming year we focus on further understanding the relation between PcG proteins and STAR elements. Therefore, we will extend our analysis of the chromatin structure of STAR elements and STAR element-protected reporter genes. In addition, we will analyze and implement novel, cellular promoters that convey even higher protein expression levels than currently used viral promoters. Finally, we want to utilize epigenetic regulatory tools to develop novel expression systems in which protein expression, growth rates of the cells and secretion of the proteins can be coordinately modulated to achieve an optimal expression platform for therapeutic proteins. As such we aim to investigate and modulate in a comprehensive way

- (i) The role of STAR elements in expression and stability of protein expression;
- (ii) An inverse relationship between cell growth and protein expression levels;
- (iii) Secretion of proteins.



Molecular Cytology

Chairholder: Prof.dr Th.W.J. Gadella

Michiel Müller	Associate Professor
Tanneke den Blaauwen	Assistant Professor
Joachim Goedhart	Assistant Professor
Erik Manders	Assistant Professor

Introduction

Molecular Cytology is the study of the dynamic architecture of living cells. Our central theme is 'Self-organization and signalling in living cells'. Self-organization is the intrinsic property of matter to organize itself in a (dynamic) structure, whereas signalling implies the activity of gene-products to control a local activity which can alter the local cellular architecture (e.g. driving morphogenesis). In order to achieve a certain 3D architecture in cells, these two important mechanisms work in concert. At Molecular Cytology both mechanisms are studied with emphasis on membrane-related architecture of living cells using advanced microscopy tools. The main research areas are:

- 1) Spatial organization of sub-cellular signalling (group leader prof.dr Th.W.J. Gadella and dr J. Goedhart). We want to understand how cells can achieve and maintain a local signal in order to drive morphogenesis, to define new cytoskeletal anchorage or vesicle-docking sites. We focus on signal flow across and in the plane of the membrane of living mammalian cells starting from histamine/P2Y receptors, G- α Q to PLC activation triggering downstream calcium and kinase signalling.
- 2) Molecular mechanism of bacterial proliferation (group leader dr T. den Blaauwen). Two dynamic self-assembling membrane-bound protein complexes (hyperstructures) are involved in the elongation and division of the bacterial cell. The complexes extend the lateral cell envelope and produce complete new cell poles. The actin homologue MreB and the tubulin homologue FtsZ recruit these complexes, respectively. The identity, function and dynamics of the proteins in these complexes are studied.
- 3) Self organisation in complex (biological) systems (group leader dr M. Müller). We aim to understand the self-organizational properties of biomembranes in functional domains crucial in cellular signalling. We also study the mechanism of lipid droplet formation and breakdown, and aim to find cell morphological parameters linked to the (mal)function of lipid droplets, with implications for

diabetes and atherosclerosis. To this end we apply and develop quantitative microscopy reporting on the chemical composition and physical state. These research themes heavily depend on advanced microscopy technology organized within the Centre for Advanced Microscopy (CAM, 2004). The goal of CAM is to boost Life Sciences research using and developing (optical) microscopy techniques. Current most prominent developments are Coherent Anti-Stokes Raman (CARS) Microscopy (dr Müller), Third-Harmonic Generation (THG) Microscopy (dr Müller), Controlled Light Exposure Microscopy (CLEM) (dr Manders) and Spinning disk & Total Internal Reflection (TIR)- Fluorescence Lifetime Imaging Microscopy (FLIM) (prof.dr Gadella).

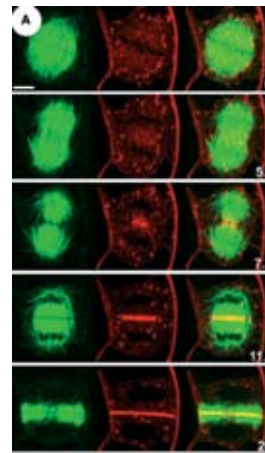


Figure 1. Endocytosis of cell surface material mediates cell plate formation during plant cell cytokinesis. In contrast to a 40 year old dogma and text book knowledge stating that the new cell wall separating two daughter cells during plant cell division is synthesized from Golgi vesicles, we show that cell surface material is used to form this structure. The picture shows the endocytic cell surface marker FM4-64 (red) labeling the cell plate from initiation until completion. Microtubules (green) (MAP-GFP) are forming the phragmoplast around it, time is given in minutes.



Figure 2. Prototypes of the CLEM unit, the essential part of the CLEM microscope.

Left: three experimental CLEM units; right: the commercial CLEM unit built by Nikon

Research Highlights

- We demonstrated that for plant cell division, cell surface material is (re-)used to build the cell plate separating the daughter cells (Dhonukshe et al (2006), Dev. Cell 10, 137-150). These results highlight a novel endocytosis pathway contributing to cell plate growth and break the 40 year old (textbook) dogma of Golgi delivery and complete de novo synthesis of this new plasma membrane.

- We have developed a new microscope technology (CLEM; Controlled Light Exposure Microscopy) that strongly reduces phototoxicity and photobleaching (Hoebe et al (2007), Nature Biotechnology). This technology is now applied in several collaborative research projects. The CLEM project is a collaboration between the Centre for Advanced Microscopy (SILS) and the AMC.
- We have developed the experimental and numerical procedures that permit for the first time to obtain quantitative compositional and physical state specific information from multiplex CARS microscopy images, without *a priori* knowledge of the vibrational spectrum (E.M. Vartiainen et al. (2006), Opt. Expr. 14(8), 3622-3630; H.A. Rinia et al. (2006), J. Biomed. Opt 11(5), 050502-1-050502-3).

Other Highlights

- An EU TMR-grant was awarded to prof.dr Gadella in collaboration with 7 other European groups working on Nod factor signalling.
- The patented CLEM technology, invented by dr Manders, has been licenced out to Nikon Japan and is commercially available from August 2006.
- Best poster of the conference award: Svetlana Alexeeva, Gert-Jan Kremers, Dorus Gadella, and Tanneke den Blaauwen. Title: To FRET or not to FRET? Measuring protein-protein interactions during cell division in *E. coli*. Gordon Research Conference on Single molecule approaches in Biology (June 18-23) USA.

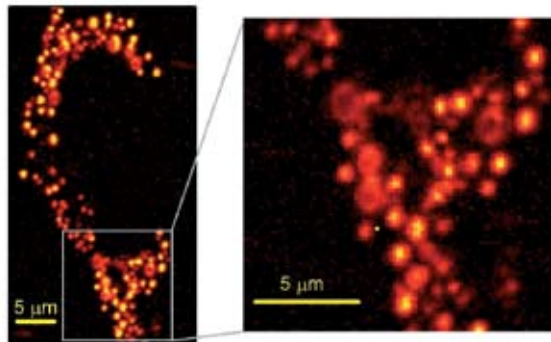


Figure 3. (a) THG optical section of LDs in a HeLa cell, incubated overnight with oleic acid complexed to Bovine Serum Albumin. (b) High resolution THG image of the area indicated in (a).

Future Prospects

- We aim to publish the first FRET-system reporting on Galfa-Q activation. Galfa-Q is a major signalling node between phospholipid signalling and various

- 7 membrane-spanning receptors in mammalian cells.
- We will further improve the CLEM technology and further reduce phototoxicity, a limiting factor for many of live-cell imaging experiments.
- We aim to realize portable endoscopic THG microscopy of lipid droplets, as well as to report for the first time on cell type and cell location dependent lipid droplet chemical composition and morphology.
- We aim to publish the first paper that describes a reliable FRET-system to study the interaction of rare proteins in bacteria.
- We aim to publish that MreB is not involved in DNA segregation in contrast to numerous publications that state the reverse. We also aim to publish that MreBCD/MraY and MurG are part of the elongation protein complex.

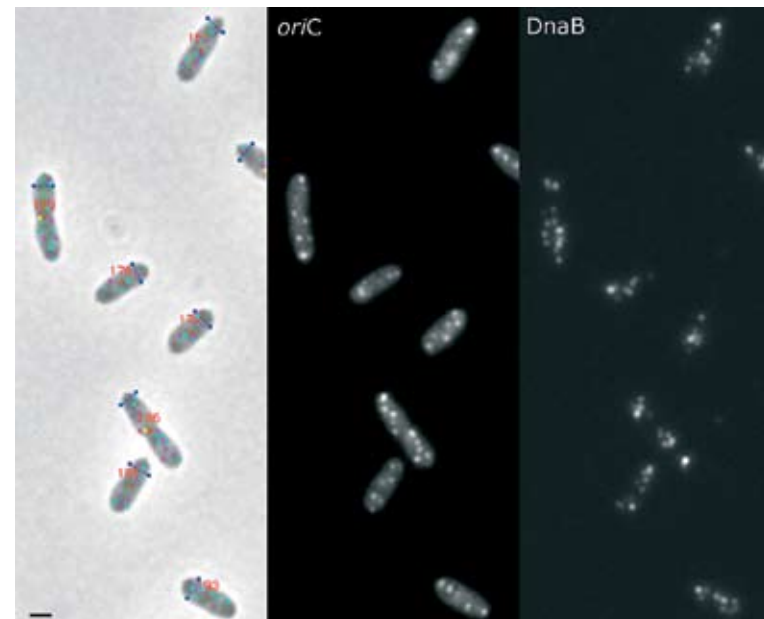


Figure 4. Co-labeling of *oriC*-region and DnaB. Left image shows the phase contrast image of the cells, their length and diameter as determined by the Object Image program (*cf.* Experimental Procedures). The purple dots show the manually determined position of *oriC*-regions and the cyan dots show the manually determined position of DnaB. Middle image shows the *oriC* region positions (*lacO* cassette bound by GFP-LacI⁹) and the far right image shows the labeling with the pAb against DnaB and secondary antibodies conjugated to Oregon Green. The bar equals 1 mm.

Research Clusters

Plants and Health

Plants are the world's primary source for food and feed, for raw materials for industry, and they provide the oxygen we breathe. Although the health of plants is constantly challenged in both natural and agronomic ecosystems, plants can master most challenges. The Swammerdam Institute for Life Sciences is aiming to unravel the molecular mechanisms of resistance against pathogens and insects, and to study the cellular signal transduction pathways controlling stress responses in general. Knowledge of the genetics and biochemistry of these processes can be translated into improvement of agricultural crops and plant protection schemes.

Two chairs contribute to the research cluster 'Plants and Health': 'Plant Physiology' and 'Plant-pathogen Interaction', while the chairs "Molecular Cytology" and "Nuclear organization" study related topics on plant model systems



Plant Physiology

Chairholder: Prof.dr M.A. Haring

Rob Schuurink	Assistant Professor
Teun Munnik	Associate Professor

Introduction

We are studying two signal transduction cascades that help plants cope with biological and environmental stress conditions: phospholipid-based cellular signalling and volatile-based external communication.

The main character in the first pathway is the lipid second messenger, phosphatidic acid (PA), which is produced via activation of phospholipase D (PLD) or indirectly, via the combined action of phospholipase C (PLC) and diacylglycerol kinase (DGK). By manipulating the activity of individual PLC, DGK and PLD genes in tomato and *Arabidopsis* plants, we aim to elucidate their role in plant stress signalling and development. How PA exerts its effects is still unknown, mainly due to the lack of characterized target proteins. We identified several protein kinases that directly and specifically bind PA, including CTR1, a key regulator of the signalling pathway controlled by the stress hormone ethylene.

In our second theme, we study the biosynthesis and regulation of volatile benzenoids. We have started to focus on benzoic acid synthesis in our model system *Petunia hybrida* W115 (Mitchell). We have identified, through microarray analyses, the genes that putatively encode the enzymes that shorten the C3 side chain in phenylpropanoids to the C1 side chain in benzenoids. We have also identified an ABC-transporter of which the expression strongly correlates with benzenoid production and we are using an RNAi approach to identify its function *in planta*. Furthermore, we use *Arabidopsis* to study responses of plants to the wound-induced C6-volatile E-2-hexenal. Through a genetic approach we have discovered that γ -amino-butyric acid (GABA) plays an important role in transducing the perception of E-2-hexenal. Finally, we use tomato as a model system to study the regulation of terpenoid biosynthesis and to determine which terpenoids are important in attracting and repelling insects. Our goal is to engineer the synthesis of these terpenoids in cultivated tomatoes.

Research Highlights

Analysis of a collection of tomato and *Arabidopsis* transgenics revealed special features of individual phospholipase genes in these plant species. In tomato we discovered that LePLD β 1 responds to elicitor treatment and that RNAi cell lines that no longer express this gene has reduced xylanase-induced PLD activity and respond with a disproportionate oxidative burst. This links LePLD β 1 to plant-pathogen interactions. The *Arabidopsis* *AtPLD α 1* and *AtPLD δ 1* genes were found to be involved in the wounding response and salt tolerance. Knock-out lines for these genes were impaired in their PA response upon wounding, with the severest effect in the *AtPLD α 1* and *AtPLD δ 1* double knock-out. This double mutant appeared to be highly sensitive to NaCl (150mM) in the growth medium.



Preliminary results indicate that an *Arabidopsis* diacylglycerol kinase knock-out line also is more sensitive to salt treatment, while a phospholipase C mutant displays an aberrant root phenotype upon salt treatment. In addition, we have obtained an *Arabidopsis* diacylglycerol kinase knock-out line that appears to be more sensitive to pathogen infection and several DGK and PLC knock-out lines that give impaired PA accumulation upon cold-treatment. With regard to the molecular mechanism of PA we further investigated PA-binding proteins. Characterization of the Raf-like protein kinase CTR1 revealed a novel PA-binding region at the C-terminus of the protein kinase domain. Binding of

PA was found to inhibit its kinase activity *in vitro*. In collaboration with Prof.dr. Dorus Gadella (SILS, Molecular Cytology) we have developed GFP biosensors that allow the visualization of specific species of phospholipids.

In collaboration with dr Michiel Müller (SILS, Molecular Cytology) we have described the hydrodynamics and cell volume oscillations in the pollen tube apical region of *Nicotiana tabacum* pollen. This has resulted in a new model that proposes that these are integral components of the biomechanics of pollen tube growth.

We have now firmly established a role for GABA as a signal for *E*-2-hexenal responses in *Arabidopsis*. GABA synthesis is highly regulated through a Ca²⁺-Calmodulin regulated glutamate decarboxylase and GABA levels increase upon *E*-2-hexenal treatment. Moreover, the hexenal-response mutant *her1* accumulates more GABA and by manipulating GABA levels the mutant becomes even more resistant to *E*-2-hexenal, indicating that GABA indeed acts as a signal molecule. With regard to terpenoid synthesis, we have shown that jasmonic acid induces only the transcription of linalool synthase in trichomes while at the same time inducing the direct defence responses in the other tissues of the leaf and stem. Thus JA-responses are highly regulated through a different set of transcription factors in the trichomes. Finally, the role of geranyldiphosphate synthase in producing precursors for gibberellin biosynthesis has been now confirmed in *Arabidopsis*.

Other Highlights

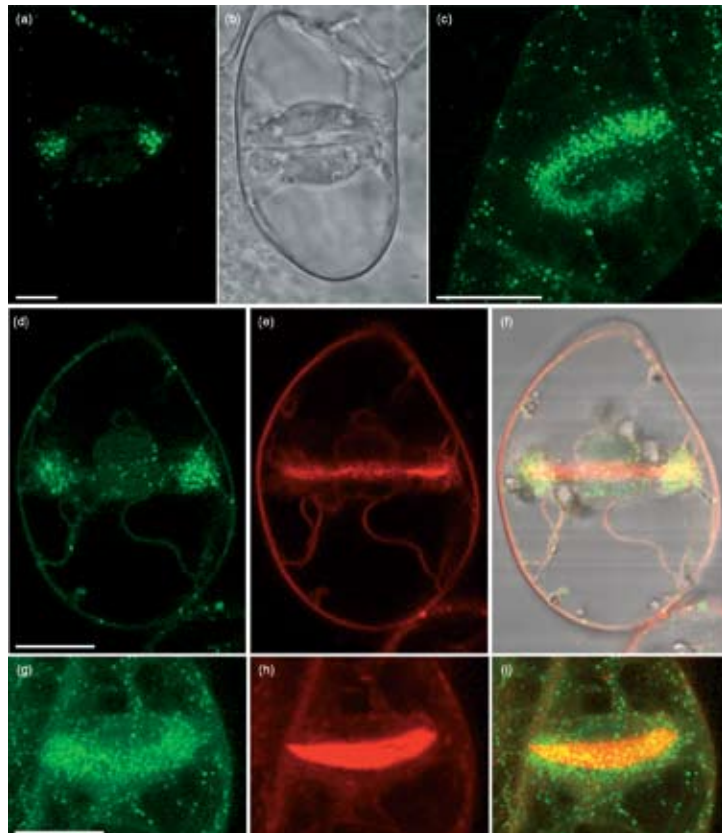
VIDI dr Christa Testerink: Modulation of protein kinase function by the lipid second messenger phosphatidic acid

VENI dr Rosanna Mirabella: C6 volatiles: a new class of signal molecules in plants

Future Prospects

The collection of *Arabidopsis* knock-outs in phospholipid biosynthesis that have a distinct phenotype with regard to salt or pathogen tolerance will be investigated in more detail. Double and triple knock-outs will be made to enhance the phenotypic effects discovered so far. Introduction of biosensors into these lines and development of PA-biosensors will allow us to study the subcellular changes in distinct phospholipids pools and link these to physiological processes like salt stress. Both the molecular basis of PA-binding of the protein kinase CTR1 as well as the *in vivo* consequences will be studied. We aim to elucidate the 3-D structure of the kinase domain of *Arabidopsis* CTR1 in the presence of PA and identify the critical residues in this PA-binding site. Localization of CTR1 in response

to PA *in vivo* will be studied using a GFP fusion of the CTR1 PA-binding domain. Our collection of PLC, PLD and DGK mutants will be screened for ethylene-response phenotypes. Now that we have *Arabidopsis* lines available that are incapable of sensing or producing E-2-hexenal, we can investigate the role of E-2-hexenal as signalling molecule in priming defence responses. T-DNA insertion mutants of E-2-hexenal or GABA-inducible genes will be obtained to investigate their role in transducing C-6 volatile signals. Furthermore, we will start to engineer the production of terpenoids in tomato trichomes. Finally, we will use promoter-reporter constructs to determine the *cis*-regulatory elements that determine ODO1 expression and translate our findings from the petunia flower model to the tomato fruit model.



Plant-pathogen Interaction

Chairholder: Prof.dr B.J.C. Cornelissen

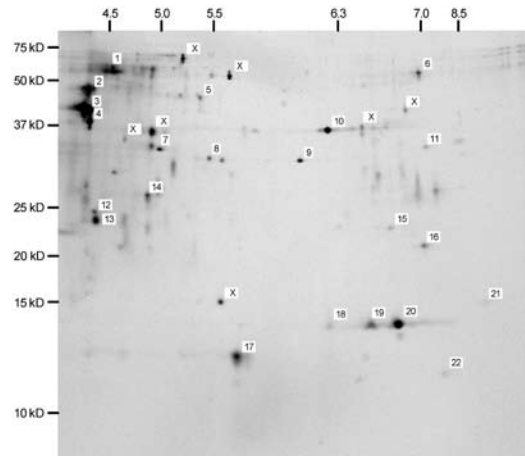
Frank Takken Assistant Professor
Martijn Rep Assistant Professor

Introduction

Plant-pathogen interactions culminate either in colonisation of the plant, causing disease symptoms, or in a resistance response of the plant preventing pathogen ingress. In the latter case one speaks of resistance, in the former of susceptibility of the plant. For in depth research on the molecular basis of susceptibility and resistance we focus on interactions between soil borne pathogens and their hosts, using the interactions of the fungus *Fusarium oxysporum* and the root knot nematode *Meloidogyne incognita* with tomato (*Solanum esculentum*) as models. For some aspects, the model plant *Arabidopsis thaliana* is included. Our specific interest is focussed on basal and induced defence mechanisms of the host and on virulence and avirulence factors of the pathogen.

Disease resistance of tomato to races of *F. oxysporum* producing avirulence factor 2 (Avr2), is mediated by the R (Resistance) protein I-2, whereas resistance against *M. incognita* requires the R protein Mi-1.2. Our working hypothesis is that upon recognition of a matching avirulence factor, an R protein changes conformation. This allows the R protein to form a multimeric protein complex, or activate a pre-existing protein complex, that subsequently activates a defence signalling cascade. The ability of a pathogen to infect and colonise its host depends on 'general' pathogenicity genes as well as on specific, secreted 'effector' proteins. Secreted proteins can also be 'avirulence factors' when they are recognized in the host plant by a matching resistance gene, thereby triggering disease resistance.

Our research aims at 1) the identification and dissection of the protein complex (-es) involved in I-2 and Mi-1.2 mediated resistance, the functional analysis of individual complex-components and regulation of the downstream signalling components; and 2) uncovering the role of pathogenicity genes and effector proteins (including avirulence factors) of *F. oxysporum* and identification of their targets in tomato.



Research Highlights

The generation of mutants of *F. oxysporum* with insertional mutagenesis was finalized with over 10,000 transformants obtained. All have been tested in bioassays and around 100 pathogenicity mutants were identified. The product of one gene identified from this screen ('5G2') was localized to the nucleus. The *frp1* mutant obtained in an earlier screen was shown to have defects in expression of genes required for root colonization.

The *F. oxysporum* SIX1 and SIX2 genes, encoding *in planta* secreted proteins, were shown to be highly specific for the tomato wilt form of this fungus and may have been subject to horizontal gene transfer. These and six additional genes for *in planta* secreted proteins are located on the same small chromosome.

VIGS (Virus Induced Gene Silencing) experiments in tomato revealed a role for the I-2 interacting proteins KLC, Formin and TRAX in disease resistance to *Cladosporium fulvum*. Full length cDNA's for these proteins were isolated and functional analysis was initiated.

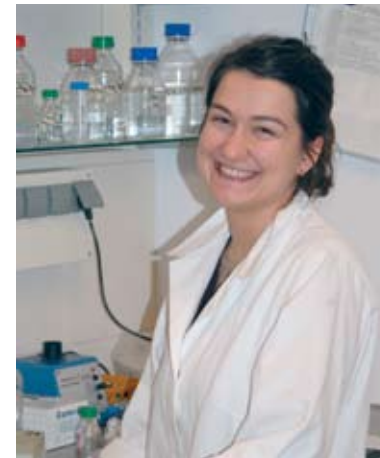
Expression studies of the genes for three isoforms of SUMO (small ubiquitin-like modifier) in *Arabidopsis* using fusions of the sumo promoters with the GUS reporter gene revealed distinct expression patterns for the three isoforms. Together with the opposite phenotypes (such as early flowering, growth phenotypes etc) caused by (over)expression of the various SUMO isoforms and derived mutants, this observation suggests different functions for the different SUMO proteins *in planta*.

Future Prospects

All ~100 pathogenicity mutants of *F. oxysporum* will be analyzed in detail (number of insertions, gene identification, phenotypes). The analysis of nutritional, gene regulatory and root colonization defects of the *frp1* mutant will be finalized. The *F. oxysporum* chromosome containing at least 8 genes for *in planta* secreted will be analysed in detail in collaboration with the Broad Institute (U.S.). Analysis of transcriptional regulation of the SIX1 gene and processing of the Six1 protein will be finalized. The function of several newly discovered SIX genes, including a candidate avirulence gene (SIX4) will be studied through gene disruption and complementation. The function of the tomato xylem sap protein Xsp10 will be studied in relation to resistance and susceptibility to *Fusarium* infection.

The function of previously identified I-2 interacting proteins (especially formin and KLC) will be studied in relation to disease resistance mediated by I-2, Rx and Mi-1. Our nucleotide binding studies will be extended to Rx and Mi-1 and the role of regulatory N- and C-terminal domains on ATPase activity analysed. Related to this, the intramolecular interaction patterns of Rx and Mi-1 in relation to the nucleotide binding state will be examined.

Transgenic *Arabidopsis* lines expressing (mutant) SUMO proteins will be analysed for altered resistance/susceptibility phenotypes to *Fusarium* and *Pseudomonas syringae*. Using tagged SUMO proteins we aim to identify *in vivo* SUMO substrates.



Research Clusters

SILS – Center for NeuroScience

The human brain might well be the most complex control system on earth. It consists of billions of nerve cells that are connected to each other in circuits of dazzling complexity. Moreover each individual nerve cell is capable of processing information that it receives from thousands of companions, finally resulting in a very complex and precisely fine-tuned response pattern. At the Swammerdam Institute for Life Sciences the brain is studied at the level of the molecule, the cell, the network and the organism. Although still many questions are unanswered about the structure of the nerve cell, and the way transmission of signals takes place, the real challenge is to bridge the gap between the various levels of integration. In particular, real breakthroughs are expected at the level of networks. How are they organized, and how can they be influenced? Various electrophysiological techniques help the researchers of the institute to answer these questions by allowing them to observe individual nerve cells and groups of nerve cells in specific parts of the brains. Such techniques will provide insight in processes taking place during learning, but also in diseases like epilepsy and in responses to stress.

Three chairs contribute to the research cluster 'SILS Center for NeuroScience': 'Animal Physiology and Cognitive Neuroscience', 'Cellular and Systems Neurobiology' and 'Hormonal Regulation of Signal Transduction in the Brain'.



Animal Physiology and Cognitive Neuroscience

Chairholder: Prof.dr C.M.A. Pennartz

Wim Ghijsen	Assistant Professor
Francesco Battaglia	Assistant Professor
Sander Daselaar	Assistant Professor

Introduction

The group's global research aim is to elucidate how neuronal networks distributed across the prefrontal cortex, temporal cortex and striatum cooperate in a number of cognitive processes, including learning and memory consolidation, attention and sensory integration. This aim is pursued using a variety of techniques and at various aggregate levels, ranging from the sub-cellular to macroscopic and behavioural domain. Nonetheless, most of the research focuses on the level of systems physiology. General research topics include:

- The short-term consolidation of memorized information of recent experiences. A very promising candidate mechanism for mediating this process is spontaneous "off-line" reactivation of stored information. After an initial experience which is marked by highly specific firing patterns in brain structures involved in memory, a replay of these firing patterns can be observed, with preservation of temporally specific features such as the order in which brain cells fire. In particular, we pursue the relevance of this phenomenon for memory consolidation, and how the replay is being orchestrated amongst different brain areas, such as the hippocampus and nucleus accumbens. Technically, this project is carried out in animals by performing ensemble recordings using 'tetrode arrays', and in humans by fMRI (functional magnetic resonance imaging) and TMS (transcranial magnetic stimulation) techniques.
- The neural basis of reinforcement learning and changes in motivation and attention. In two electrophysiological projects, we study how neuronal groups in a frontal brain structure engage in the formation of representations of reward, and how networks of cells collectively learn to generate predictions about upcoming rewards, based on sensory cues that precede reward delivery. We also investigate which neurotransmitters and receptors influence the formation of neural representations of reward predictions. Technically, we

use ensemble recordings in combination with local *in vivo* pharmacology to probe these mechanisms. In addition, neural correlates of attention and flexible shifting of focal attention are being studied with ensemble recording techniques.

- An important goal in studying the motivational basis of action selection is to understand how the output of the ventral striatum to motor structures is constructed and regulated. The interaction between striatal output neurons (spiny project neurons) is an important determinant of this regulation of output and involves the release of amino acid and neuropeptide transmitters. Using brain slices of the striatum and patch-clamp techniques we will investigate how variation in presynaptic stimulation patterns leads to differentiation in release between amino acids and neuropeptides, and how these different transmitters contribute to mutual interactions such as lateral inhibition between neurons. Sub-cellular mechanisms are investigated by measuring effects of presynaptic neuropeptide receptor activation / inactivation on fast (~milliseconds) amino acid release in purified nerve terminals. In addition, adaptation of the differential transmitter release upon drug addiction will be subject of study. This research helps to understand how synaptic plasticity contributes to maladaptive changes occurring in the brain as a consequence of drug abuse.
- The investigation of interrelationships between genes, learning and memory capacities as measured in behaviour, and the systems physiology which forms the interface between gene expression and overt behaviour. These interrelationships are being studied in the context of learning and memory capacity, spatial navigation and behavioural impulsivity in genetically varying, recombinant mouse strains and targeted knockout mice.
- Finally, an important general aim has become to support all of the above-mentioned disciplines by advanced methods of Computational Neuroscience. Furthermore, translational research is conducted by converting principles discovered in animal experiments to new studies on human brain (e.g. in fMRI methodology).

Research Highlights

- Joint ensemble recordings have been made from two brain structures simultaneously. These recordings are being made in a study on replay, which can be observed when rats go to sleep and rest after an intensive period of

reward-seeking behaviour. We found that two connected brain structures, the hippocampus and the nucleus accumbens, reactivate coherently (i.e., together in time) during off-line processing. Moreover, the data indicate that reward-related information is being replayed in the nucleus accumbens, which means that emotionally valuable information is spontaneously retrieved during sleep and other stages important for memory consolidation.



- In examining the neural basis of reinforcement learning, we found that the rat orbitofrontal cortex encodes information about the reward magnitude an animal expects after having perceived an olfactory cue associated with the reward. In addition, we validated two types of 'combidrive', i.e. an instrument for combining stable ensemble recordings with local, intracranial drug applications. Using this novel instrument, we studied the role of NMDA receptors in prefrontal excitability and discovered patterns of oscillatory activity to which spikes is phase-locked. Finally, a first series of recording studies on rats engaged in attentional switching were conducted.
- The role of neurotransmitter transporters in presynaptic cross-talk was investigated by measuring the effect of the GABA transporter substrate Gamma-Vinyl-GABA on glutamate and GABA release from purified hippocampal nerve terminals. In addition to a fast, elevation of Ca²⁺-channel dependent GABA release, a slower GABAB-receptor mediated inhibition of both GABA and glutamate release was found, indicating GABA transporter regulated presynaptic cross-talk of GABA-ergic nerve terminals with neighbouring GABA-ergic and glutamatergic synapses via GABAB-receptors.

- Novel instrumentation was developed for performing multi-tetrode recordings in freely moving, task performing mice. This technique was successfully applied in the mouse hippocampus, entorhinal cortex and prefrontal cortex. Behavioural screening of several tens of recombinant-inbred mouse lines was performed to identify hereditary components in learning and memory disorders with high degrees of chromosomal linkage.
- We finished data collection for our first fMRI experiment. The aim of the experiment is to establish whether reactivation processes in the human brain can be detected in a way that is analogous to the results found in animals. The fMRI paradigm involves a training session on a visuomotor task flanked by two rest periods, which will allow the assessment of reactivation. The training session is followed by a retest in the scanner 7 hours later on the same day. During this period, learning “consolidates”, leading to an improvement in performance on the retest without additional training, a phenomenon known as “off-line learning”. Data analysis is currently being carried out with the intent to link reactivation of training-related activity during rest to subsequent “off-line learning”. A follow-up fMRI experiment has also been started using an auditory learning task and MRI-compatible headphones. Finally, we aim to disrupt off-line learning and memory consolidation by transcranial magnetic stimulation in humans, and by electrical intervention of hippocampal processing in rats. Initiation of further forms of translational research will be pursued.
- In external collaborations, we have developed a model for the formation and dynamics of entorhinal grid cells in rodents, and we characterized the neural activity in the monkey amygdala in response to emotionally significant stimuli.

Other Highlights

The group developed a miniaturized, multi-channel recording system with wireless data transmission: new and versatile instrumentation for cognitive and physiological research in freely moving animals.

A grant from the Foundation for Technology & Science (STW) was awarded, for the development and application of miniaturized equipment for ensemble recordings in mouse models of brain disease

Two publications were listed in the Faculty of 1000 Biology evaluations:

- a) Daselaar SM, Fleck MS, Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *Journal of Neurophysiology* 2006; 96: 1902-11. *F1000 factor 6*.
- b) Daselaar SM, Fleck MS, Dobbins IG, Madden DJ, Cabeza R. Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. *Cerebral Cortex* 2006; 16: 1771-82. *F1000 factor 6*.

Future Prospects

- To establish whether, after a learning task in an fMRI scanner, reactivation processes in the human brain can be detected in a way that is analogous to the results found in animals. Furthermore, we aim to disrupt off-line learning and memory consolidation by transcranial magnetic stimulation in humans, and by electrical intervention of hippocampal processing in rats. Initiation of further forms of translational research will be pursued.
- We aim to integrate electrophysiological and neurochemical approaches more strongly than was hitherto feasible, first by giving the research projects combining ensemble recordings and drug application by microdialysis a strong push ahead, and second by extending our investigations of intra-striatal synaptic communication by new patch-clamp experiments and synaptosome studies using a newly developed instrument to measure transmitter release with a high time resolution.
- A 2-photon imaging setup has been built up to visualize the morphology and neural activity of neurons in the living mouse brain. Consequences of associative learning and multimodal interactions in the population dynamics of sensory neurons in the rat neocortex will be studied by bulk labeling of neurons with Calcium-indicator dyes *in vivo*.
- To complete the ensemble recording studies on attention in rats, and describe on the basis of these results the neural correlates of attentional switching and the level of neural assemblies. Furthermore, the role of NMDA receptors in mediating the formation of reward-expectancy correlates will be elucidated, as well as the hitherto unknown origin of the oscillatory activity observed in orbitofrontal cortex.

- Continued behavioural screening is expected to raise indications for chromosomal linkage sites of aberrant learning in mice. Ensemble recordings from mouse brain should yield indications about the neural mechanisms of spatial memory, self-localization, impulsive decision making and neural coding of information about delay and magnitude of reward. Recordings from genetically modified mice will be initiated (e.g. local NMDA receptor knockout).
- The scope of Computational Neuroscience activities will be expanded to support new experiments and analyses in ensemble recordings, fMRI and TMS research and simulations of multimodal neuronal networks.



Cellular and Systems Neurobiology

Chairholder: Prof.dr W.J. Wadman

Hans van Hooft	Assistant Professor
Jan Gorter	Assistant Professor
Taco Werkman	Assistant Professor

Introduction

Excitability is the most prominent property of the nervous system and its components. How ion-channels are organized and quantitatively balanced in the neuronal membrane, how they lead to neuron specific firing patterns and how these can be modulated at different time scales (plasticity) belong to the most exciting problems in neuroscience that can now be solved in a multidisciplinary approach. Neurons communicate with each other through a variety of synapses. To provide minimal functionality neurons need to be combined in small circuits. We have organized our research around a few well defined topics in the realm of neuronal excitability. Our core approach is a functional electrophysiological one (from patch-clamping to *in vivo*). State-of-the-art optical techniques (Ca-imaging, Voltage Sensitive Dyes) and various multi-contact electrode recordings allow the analysis of population activity. When needed, collaborations provide anatomical, immunohistochemical, molecular, genetic and behavioural expertise.

The first of our three major research lines studies the fundamental properties of the 5-HT₃ receptor and tries to understand its functional role in local circuits and development. Molecular techniques produced mice in which the 5HT₃ receptor expressing neurons are labelled with GFP and can be studied efficiently. This has opened a wide range of possibilities to investigate the role of this receptor in functionally connected neurons and also its highly specific role in cortical column formation.

The second research line studies epilepsy e.g. seizure generation, epileptogenesis (micro-array technology) and pharmacoresistance. The latter topic we approach from two sides: a) (non-) penetration of drugs via the blood-brain-barrier and b) modification of drug targets, mainly sodium channels. These studies are of high clinical relevance and we strengthen them through a side appointment at the Academic Hospital in Ghent and intense collaboration with SEIN in Heemstede. The therapeutic potential of deep brain stimulation is investigated in patients and

in animal models. Technical realization is supported by collaboration with Philips Medical Systems.

The third research line concentrates on specific pharmacological modulation of neuronal circuits. One of the aims is to improve the specificity of drugs that are used against schizophrenia. In collaboration with Solvay Pharmaceuticals we study differential modulation of the firing pattern of dopaminergic neurons in the Substantia Nigra and the Ventral Tegmental Area of the rat. In addition, we support the activities of a spin-off company named Sensocom.

Most of our experiments are supported by computer modelling, focusing on single cell excitability in relation to the direct chemical surrounding of the neuron as well as on the adaptive strategies for excitability that optimize the working range of active neurons. In the latter case we try to extrapolate the consequences of single cell strategies to larger neuronal networks. The combination of theoretical and experimental work has proven to be very fruitful in the scientific setting of SILS and the FNWI.

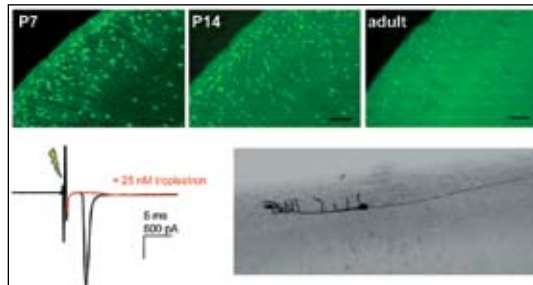


Fig 1: GFP labelled interneurons in cortical slices from animals of 1 week, 2 weeks and adult. Lower panel gives the (5HT3 specific) synaptic serotonin response of a Cajal-Retzius cell, illustrated in the panel to the right.

Research Highlights

The studies on homeostatic scaling of neuronal excitability as modulated by synaptic activity were finished with the publication of a series of papers and a modelling study that resulted in the promotion of dr. Michiel Remme. We started a new collaboration with prof.dr.Tallie Baram from the University of Irvine California in order to elucidate the underlying molecular mechanisms of Ih homeostatic regulation.

The investigation of the interactions between serotonin and dopamine / GABA in the Substantia Nigra and Ventral Tegmental Area was completed. We hypothesize

that the various serotonin, dopamine and GABAB receptors have to some extent a private G-protein pool which allow an intricate convergence of their activity on the GIRK channel and on the regulation of firing activity. This could explain the difference in response of VTA and SN on typical and atypical anti-psychotics. We have applied for several forms of new funding in order to pursue this highly interesting research line.

Mice that have been generated in collaboration with prof. Monyer in Heidelberg and in which Green Fluorescent Proteins visualize the neurons that contain the 5-HT-3 receptor are used to study the functional role of this receptor in the brain. We have quantified the calcium permeability of the ion channel that is mediated by 5HT3 and continued the investigation of its contribution to development of functional columns in the cortex. It has now been established that Cajal Retzius cells receive a dominant serotonin input via this receptor in particularly in early life. Manipulating this signal pathway has a strong effect on the morphology of cortical pyramidal neurons.

The study on the interaction of various inputs on subiculum neurons in the hippocampal region was completed and submitted for publication. It proved the usefulness of the V(oltage) S(ensitive) D(ye) technique for the analysis of spatial/temporal integration of neuronal signals in the *in-vitro* slice. This permits us to analyze network activity from a different perspective. The studies have been continued by analyzing the spatial organization of theta rhythm in a combined hippocampus-entorhinal cortex slice. Special attention was given to human slice preparations that became available due to epilepsy surgery in the Vrije Universiteit (prof.dr.M.Witter) and in which we investigated spontaneous seizure-like activity and its response to anti-epileptic drugs.

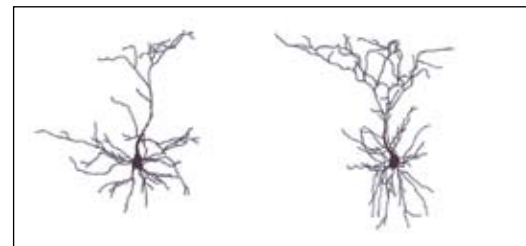


Fig 2: Morphology of typical cortical neurons that developed under normal conditions (right panel) or in the absence of serotonergic innervation (left neuron). The latter one has restricted morphology

The micro array study on gene expression in different brain regions (CA3, Entorhinal Cortex and Cerebellum) during the prominent phase of epileptogenesis in a rat model of Temporal Lobe Epilepsy (1 day to 3 month after status) was completed and published. It has given us a huge data base of interesting biological “processes” that are affected by epileptogenesis. We will use them as new leads in the investigation of epileptogenesis. The first process that is now under investigation is inflammation. This research line also studies the regulation of the blood brain barrier, where we found that multi-drug-transporter proteins are up-regulated during epileptogenesis. This could explain why in some cases pharmacoresistance develops, as it implies that drugs like phenytoin are strongly extruded from the brain under these conditions. Further studies will have to show, whether this is a universal mechanism or whether large differences exist between anti-epileptic drugs.

The studies on the use of deep brain stimulation have been continued on patients as well as in experimental animals. In the latter a modulating effect of continuous background stimulation in the hippocampus with 130 Hz could be demonstrated on several parameters of evoked seizures during kindling. Moreover 130 Hz stimulation seems to be more effective than low frequency stimulation. A first trial with 10 pharmacoresistant patients was also successfully completed and published. It demonstrates the potential of DBS for epilepsy treatment. A new alliance with Philips Eindhoven was started to realize practical application and fundamental support for DBS.

The theoretical studies on scaling of neuronal excitability using a combination of I_h and I_A were finished. Analytical as well as computational analysis demonstrated that such a system of regulation can work and has several advantages over other described ways of regulation. In addition we investigated whether such a scaling mechanism could interfere with learning rules that employ Spike Time Dependent Plasticity in order to implement learning and pattern recognition. We conclude that such interaction are insignificant, which implies that excitability scaling with intrinsic potassium channels could be a reality. We also investigated the consequences of scaling in a neuronal network that contains excitatory and inhibitory neurons. The studies that investigated the role of the extracellular space and neuron-glia interactions in seizure generation were completed.

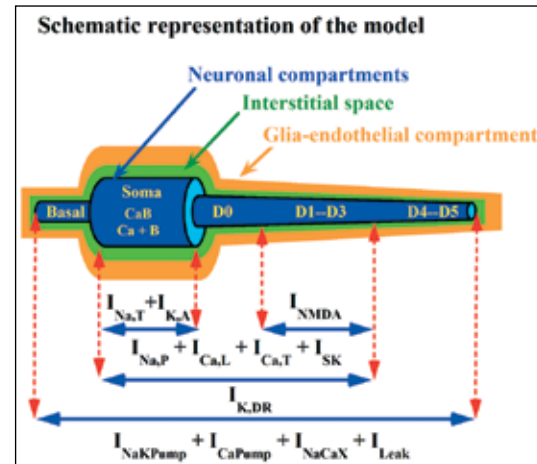


Fig 3: Schematic overview of a computational model of a branched neuron that interacts with a glia surrounding compartment through an extracellular space of restricted dimensions.

Other Highlights

A new research grant from ALW (dr. Hans van Hooft) was obtained that will allow to intensify the research on the 5HT3 receptor.

A new NEF grant was obtained that will allow studying the role of inflammation in epileptogenesis.

Two new collaborators were hired on positions made available from NEF for epilepsy research. A post-doc will investigate seizure generation, while a PhD student (AIO) will continue the work on sodium channel modulation.

The collaboration with Philips Research was finalized and projects (three PhD students {AIO's}) are being started in Eindhoven and in Amsterdam.

Our group will participate in a large research program on the role of the endocannabinoid receptor. This program will continue our collaboration with Solvay Pharmaceuticals, the leading industrial partner in the program.

Our group participates in an international attempt to investigate and compare 3 different animal models of temporal lobe epilepsy. Two labs for each model will generate epileptic animals and a centralized analysis using micro arrays to quantify gene expression in the Dentate Gyrus will be undertaken. This effort

should tell us which processes all models have in common and how large inter-lab and inter-model variation is.

The spin-off company Sensocom was provided with a state-of-the-art set up in which depth EEG signals from several relevant brain regions can be quantified under strict behavioural conditions.

Future Prospects

In 2007 several new projects will start as soon as new collaborators have been recruited. Our main mission will be the control and organization of excitability under basic and pathological conditions. We concentrate on our three main research lines:

1) Functional role of 5HT₃ receptors in development and under adult conditions. The mice with GFP-labeled 5HT₃ receptors will be used to further elucidate cell type specific properties of neurons that contain this receptor (focus on Cajal Retzius cells and on cortical pyramidal neuron morphology). Our VSD and calcium imaging expertise will be extremely useful.

2) We will substantiate the hypotheses that were formulated to explain pharmacoresistance on the basis of (local) modulation of the permeability of the blood brain barrier and we will investigate the possibilities for using multi-drug transporter proteins regulators in the control of epilepsy / epileptogenesis. The leads that have come out of the micro-array experiments on epileptogenesis will be followed up and we will investigate the role of inflammation in epileptogenesis. We will also continue the investigations into the potential use of Deep Brain Stimulation as an alternative treatment against epilepsy. We have created new possibilities to link it with the clinic. The epilepsy research line will be merged with the one on intrinsic scaling of excitability.

3) The continuation of our collaboration with Solvay Pharmaceuticals will take place within the framework of TIPharma and will concentrate on the role of eCB receptors in specific behavioural conditions. We will seek new funding for the project that studies interaction between serotonin and dopamine which formed our hypothesis for different responses from SN / VTA.

In addition the following points will also merit attention:
We will further strengthen and integrate the use of optical techniques for

the recording of membrane voltages and employ it to investigate the spatial properties of oscillatory behaviour in hippocampal-EC brain slices as well.

The computer modelling studies on excitability scaling and seizure generation will be completed and new lines that support e.g. deep brain stimulation will need to be formulated. Financing will be needed, probably with the new Dutch frameworks for NeuroInformatics, Cognition or Systems Biology.



Hormonal Regulation of Signal Transduction in the Brain

Chairholder: Prof.dr M. Joëls

Paul Lucassen Associate Professor
Harm Krugers Assistant Professor
Henk Karst Researcher

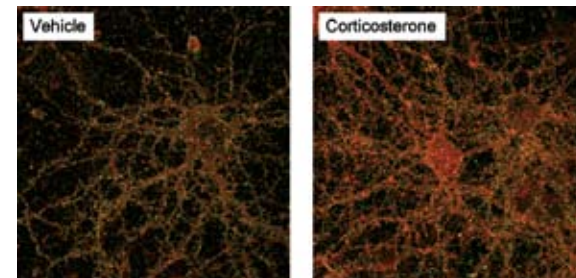
Introduction

The main aim of our research is to delineate how stress hormones affect the function of rodent brain cells and how this can explain behavioural adaptation. The emphasis of our research is on the cellular processes that are altered by stress hormones like corticosterone. To investigate this we use electrophysiological recording techniques, mostly *in vitro*. In collaboration with others this is combined with methods that monitor gene expression patterns. The latter is highly relevant, as corticosteroid hormones act via their nuclear receptors as regulators of transcriptional activity. Recently, however, we discovered that corticosteroid hormones also change neuronal function in a rapid non-genomic manner. It is the combined rapid (non-genomic) and delayed (genomic) pathways which make corticosteroid hormones such powerful tools to change brain function over a prolonged period of time after stress. In addition to examining neuronal cell function and the underlying molecular mechanism, we also investigate the effect of stress on the morphology of brain cells. The theories that come forward from the experimental work in animals are tested also in the human brain, in collaboration with other research labs.

While most of the research focuses on the effect of a single exposure to stress, we are also interested in long-term consequences of stress. One series of investigations therefore specifically examined how repetitive stress during adulthood can change brain function, neurogenesis and the shape of neurons for a prolonged period of time. Another research line is dedicated to the long-term consequences of stressful situations early in life. The latter can pertain to maternal deprivation of neonatal rat pups; however, we are also interested in extremes within the natural variation of maternal care.

A separate research line concerns the role of structural proteins and cell cycle factors in neurodegenerative diseases, like Alzheimer's disease. Here we use experimental animal models for neurodegenerative diseases (usually genetically

modified mutants) and examine changes in neurogenesis, morphology, electrical properties and behaviour at various ages.



Corticosterone promotes GluR2 trafficking to the membrane. Corticosterone applied to primary hippocampal cultures for 3 hours enhances expression of GluR2 subunits (red label) in the membrane (right panel) in comparison to vehicle treated cells (left panel). Membrane expression of GluR1 subunits remains unaltered after application of corticosterone (green label). Experiments were performed together with Casper Hoogenraad (Erasmus University Rotterdam).

Research Highlights

Over the past year we have studied the rapid non-genomic effects of corticosterone in more detail. On the one hand we examined the intracellular signalling pathway. We observed that the previously described rapid effect of corticosterone on glutamate release probability is most likely mediated by mineralocorticoid receptors inserted into the presynaptic membrane. Via these receptors corticosterone activates the ERK pathway, which then results in fusion of vesicles with the presynaptic membrane. In addition to these presynaptic pathways, corticosterone can also change a particular K-conductance, via a postsynaptic non-genomic pathway.

On the other hand we examined the importance of non-genomic effects for the interaction of corticosterone with other stress hormone systems in brain. We observed that corticosterone (non-genomically) acts in the same direction as noradrenaline when the two hormones are present at the same time. However, when genomic actions of corticosterone are allowed to develop, the hormone completely suppresses the effect of noradrenaline. This has led to the hypothesis that stress hormones like corticosterone and noradrenaline in concert strengthen synaptic contacts shortly after the stress and thus help to encode the information.

The subsequent delayed effect of corticosterone makes it very hard for new information to change synaptic contacts, which helps to preserve the original message.

Other Highlights

Members of the group organized 3 SILS-CNS Masterclasses (March 2nd, September 26th, December 11th); a symposium in the Biological Centre Haren; an international workshop on Stress, Plasticity and Memory (Nervi, Italy); a symposium during the 5th FENS Forum Meeting in Vienna; several symposia during the 5th ENP Meeting (Doorwerth); Marian Joëls served as Vice-Chairman of the FENS Forum 2010 Local Organizing Committee.

Paul Lucassen received a grant from the HersenStichting Nederland; Marian Joëls received an HFSP programme grant.

Marian Joëls was the main applicant of a EUROCORES on “Stress and Mental Health”, which was approved by the ESF.

Members of the group served as referee for many international journals (including the top-tier journals) and funding agencies; Marian Joëls was elected on the Editorial Board of Neural Plasticity.

Marian Joëls served on the Board of the KNAW Science Division; the Board of the Division Earth and Life Sciences ALW/NWO; acted as chairman of the National Initiative Brain & Cognition; as Departmental Head Earth and Life Sciences UvA; and was elected as chairman of the Dutch Neurofederation.

Future Prospects

For the upcoming year we have the following aims:
We aim to better understand the mechanism and physiological importance of the rapid non-genomic corticosteroid effects.

We will examine the rapid and delayed interactions between corticosteroids and other stress hormone systems, in the hippocampus as well as other areas. This will be done both with electrophysiological techniques in rodent tissue and in the human brain using fMRI approaches.

With respect to the delayed corticosteroid effects, we will investigate the ways in which stress hormones affect the glutamatergic signalling in the hippocampus and the consequences of these effects for behaviour. We will furthermore study the mechanism underlying delayed effects of corticosteroid hormones on cellular morphology in brain.

We will examine the long-term consequences of maternal care and maternal deprivation for the physiology, morphology and proliferation in various hippocampal areas.

Mutant mouse models for Alzheimer’s Disease or Frontotemporal Dementia will be tested for cell cycle, morphology and functional properties in the hippocampus.



Research Clusters

Life Science Technologies

The Swammerdams' Life Science Technologies Cluster carries out fundamental biological research and makes a wide range of techniques available to the SILS researchers. Advanced microscopy enables us to bridge the gap between the level of single molecules and the level of aggregates of molecules in single/multiple cells, and to make the life processes visible in time (4D imaging). The institute works with the newest modes of advanced optical microscopy, for instance FRET-microscopy, enabling the measurement of distances between molecules in a range of one to eight nanometres in intact living cells.

Micro-array technology simultaneously analyses all genes of a particular organism, in a particular cell type or under specific growth or stress conditions or other internal or external stimuli. The Micro-Array Department (MAD), a semi commercial facility, produces micro-arrays for the spotted-array technology platform, for example for the genes of man, mouse, yeast, tomato, petunia plants, etc. and makes GeneChips from Affymetrix available. The MAD is accessible to all academic, as well as industrial research groups, and can be found on the internet at www.microarray.nl. The large stream of data, produced by micro array technology, needs to be processed and analysed by means of bioinformatics, for which a bioinformatics support group has been established.

Mass spectrometry is essential to characterize proteins and to analyze the relationship between the structure and function of a protein (proteomics). Mass spectrometry is a key technology at SILS in which we have a long history and substantial expertise. An important part of the research involves the identification, quantification and functional characterization of proteins. Bioinformatics also plays an important role in this by efficiently analysing the data streams. Bioinformatics and data analysis are essential to collect, compare and integrate all available data, and to present them to the researchers in a way that the information is summarised and visualises the underlying biological processes.

Three chairs and one department contribute to the research cluster 'Life Science Technologies': 'Mass Spectrometry of Biomacromolecules', 'Micro Array Department and Integrative Bioinformatics Unit', 'Biosystems Data Analysis' and 'Molecular Cytology'.

Mass Spectrometry of Biomacromolecules

Chairholder: Prof.dr C.G. de Koster

Luitzen de Jong Associate Professor

Leo de Koning Assistant Professor

Introduction

Future progress in the life sciences will heavily depend on the integration of chemistry, physics, mathematics, (bio)informatics and biology. Our group combines mass spectrometry with biomolecular and organic chemistry. We focus on four research themes that are carried out in close collaboration with other groups within and beyond the Swammerdam Institute for Life Sciences, i.e., (i) systematic analysis of protein-protein interactions, (ii) post-transcriptional regulation of gene expression, (iii) host-fungal pathogen interactions and (iv) identification of biomarkers to discriminate between healthy and diseased state. We are developing innovative, mass spectrometry-based experimental approaches that are designed for these research areas, but which are also more widely applicable.

Research Highlights

Chemical crosslinking is used to identify nearest neighbours in protein complexes, while identifying crosslinked amino acids residues is a powerful method to validate models of the 3-D structure of proteins. Mapping of cross-links in proteolytic digests of large protein complexes requires cleavable cross-linkers that enable isolation of the cleavage products with preservation of information about connection. We discovered an amine-specific cross-linker, bis(succinimidyl)-3-azidomethyl glutarate (BAMG), that fulfils these requirements. Two parallel reaction pathways are induced by tris(carboxyethyl)-phosphine (TCEP) in cross-linked peptides from BAMG-treated cytochrome c. One pathway leads to cleavage in a fraction of the cross-linked species and in the other pathway the azido group of BAMG is reduced to an amino group without cleavage. Cross-linked peptides and peptides modified by BAMG without actual cross-linking yield distinct sets of TCEP-induced reaction products that can be isolated by reverse-phase diagonal chromatography and identified by mass spectrometry to reveal the identity of parent compounds. The ease by which cross-link-derived reaction products can be isolated and identified opens avenues

for mapping cross-links in complex biological assemblies and mixtures of protein complexes.



Future Prospects

Focal points in our MS research program are as mentioned above i) systematic analysis of protein-protein interactions, ii) post-transcriptional regulation of gene expression, iii) host-fungal pathogen interactions and iv) biomarker identification.

i) In our projects where characterization of protein-protein complexes plays an important role we will move towards functional characterization of larger assemblies using our new cross-linkers. For this purpose novel and innovative cross-linkers will be further developed and improved in close collaboration with organic chemists (J. van Maarseveen, HIMS) to enhance quantitative, selective and sensitive detection of protein assemblies in complex biomatrices. In collaboration with others several complexes will be structurally characterized, *id est* the divisome and subcomplexes thereof from *E.coli* (Dr T. den Blaauwen), the HGF/SF – MET complex (with Dr E Gherardi, MRCC, Cambridge, UK) and the yeast exosome (with Dr D. Tollervy, WTCCB, Edinburgh, UK).

ii) In collaboration with Prof.dr K.J. Hellingwerf and dr M.J. Teixeira de Mattos we will aim at unraveling the regulatory circuit underlying the transition of aerobic to (semi)-anaerobic metabolism in *E. coli*. Cultures of *E. coli* will be pulse labeled with AZHAL before, during and after the transition from aerobic to anaerobic metabolism. Within the scope of IOP Vertical Genomics we will quantitatively map glycolytic enzymes and compare data with mRNA concentration to unravel new post-transcriptional control mechanisms for regulation of glycolysis.

iii) The MS group will further explore the question how mass spectrometry in combination with novel purification strategies and bioinformatics tools can provide detailed quantitative structural and functional information about cell wall proteins of *Candida albicans* and *Saccharomyces* spec. With the group of Prof.dr S. Brul we will aim at characterization of the spore proteome to gain insight into the development of *Bacillus subtilis* spores. We will continue the collaborations with the groups of the SILS-plant cluster.

iv) In the framework of our collaborative clinical proteomics research with the AMC, biomarker identification is an important research theme. We will focus on identification of diagnostic and prognostic markers for ovarian cancer in collaboration with Dr M.R Buist (AMC), for idiopathic nephrotic syndrome with Dr. J. Aten (AMC) and within SILS-LST with the Biosystems Data Analysis group of Prof.dr A. Smilde. Together with the group of Prof.dr J. Aerts (AMC) further research is planned for the identification of biomarkers for Gaucher and Fabry disease.



Biosystems Data Analysis

Chairholder: Prof.dr A.K. Smilde

Huub Hoefsloot Associate Professor
Johan Westerhuis Assistant Professor

Introduction

The general aim of our research is developing and validating methods for summarizing and visualizing complex biological data.

Research Highlights

A key question in omics data analysis is whether the results of a data analysis can be trusted (this is called validation in our jargon). A validation method has been developed for a commonly used metabolomics data analysis method (ASCA). Moreover, an existing validation method in metabolomics – cross-validation – has shortcomings, which have been investigated and reported.

In clinical proteomics, a key question is to find reliable biomarkers for a given disease. A biomarker selection and validation method has been developed which showed good results. In many cases, clinical biomarker discovery is based on disease classification methods. In a national collaboration (with seven other groups) a strategy for finding and validating the best classification method for a given problem has been established.



Other Highlights

Prof.dr A. Smilde was the Eastern Analytical Symposium 2006 Award Recipient for Achievements in Chemometrics, Nov 2006, NJ, USA.

Future Prospects

In the coming year we will be:

- 1) Developing a method for analyzing dynamic metabolomic data: modelling differences in hormone dynamics of control and narcoleptic patients.
- 2) Developing methods for incorporating *a priori* biological information in metabolomics data analysis tools: generating more realistic models.
- 3) Developing methods for identifying time-course patterns in clinical proteomics data: tracking the efficacy of treatments.



Micro Array Department and Integrative Bioinformatics Unit

Group leader: Dr T.M. Breit

Floyd Wittink	Project management “wet-lab”
Mattijs Jonker	Project management “dry-lab”
Jenny Batson	Project Administration
Marco Roos	Senior Researcher IBU
Han Rauwerda	Senior Researcher IBU

Introduction

MicroArray Department (MAD): Microarray technology has become a well-established tool in the analysis of genome-wide gene expression studies. The ultimate goal of a microarray experiment is simultaneous examination of the expression of all genes of a specific organism, in a cell type in a specific growth or stress condition, to unravel complex cellular mechanisms or identify and use biomarkers. Transcriptomics biomarkers are genes whose expression profile can be used for diagnostic purposes or to monitor and predict cellular processes. Another purpose is to examine the DNA of tissues or individuals for mutations that can be related to complex diseases like cancer or diabetes. Because microarray experiments produce a vast amount of data, extensive bioinformatics infrastructure, methods and expertise are needed to cope with these data effectively. Microarray bioinformatics comprise data-handling (storage and exchange), data-preprocessing (normalization and validation), and data-analysis (clustering, biomarker selection, etc.). The MAD consists of a microarray technology section (Wet-lab) with 3 specialists, a microarray data-analysis section (Dry-lab) with 5 bioinformaticians, and management with 2 staff members. The MAD operates as a technology and bioinformatics core facility for UvA scientists, as well as service provider for external academic and industrial customers. The MAD is an official Affymetrix Service Provider and is in the process of becoming a certified Agilent Service Provider.

Integrative Bioinformatics Unit (IBU): To be able to perform true analyses of transcriptomics data, these data must be combined with other biological -omics data. The bioinformatics research group consists of ~10 staff members with expertise in experimental biology, bioinformatics, informatics, statistics, plus mathematics, and combines multidisciplinary life sciences research with bioinformatics research in a collaborative setting, with a strong focus on

transcriptomics. IBU's main research efforts are: i) domain interaction with the aim to extend the possibilities for computer-assisted experimental biology research by building an actual e-BioScience laboratory (e-BioLab) with a virtual lab e-bioscience problem solving environment; ii) domain modelling with the aim to enable biological problem-solving and phenomenon-discovery via data integration and computational experiments. To this end, IBU participates in three nationwide projects: “BioRange”, a nationwide bioinformatics research project; “BioAssist”, a national bioinformatics support programme and “Virtual Lab for e-Science (VL-e)”, the Dutch e-science project in the field of ICT infrastructure and methods.

Research Highlights

The most important achievements of the MAD during 2006:

- Installation of support-bioinformatics Dry-lab with staff, microarray data-analysis methods and infrastructure.
- As official Affymetrix Service provider, the MAD has introduced and validated SNP analyses.
- Started procedure to become a certified Agilent Service Provider.
- Started development of microRNA array, universal array and combination array.
- Ongoing acquisition of new industrial and academic clients, many new projects.
- Organized a nation-wide jubilee microarray competition for life sciences researchers.
- Execution of projects and start of research initiatives with SILS groups (van Driel, Brul, Crielaard, Wadman).
- Execution of projects and start of research initiatives with AMC groups (Versteeg, van Kampen)
- Execution of strategic collaboration with the RIVM on p53 research.
- Start of strategic collaboration with UMC on medical microbiology.
- Construction of an e-BioScience Laboratory (eBioLab) with a VL problem-solving environment.
- First software applications running: R on Grid and SigWin-finder workflow tool
- Partner in initiation of virtual e-BioScience institute.
- First integrative experiments with semantic web-technology.
- First research articles accepted.

Other Highlights

Dr T.M. Breit is a permanent member of the National Advisory Committee as well as the Management Team of the Netherlands BioInformatics Centre (NBIC).

Dr T.M. Breit became a member of the NGI Horizon program committee.

Dr S. Marshall is Advisory Committee Representative for the UvA in the world wide web consortium (W3C); Semantic Web Health Care and Life Sciences Interest Group.

Future Prospects

The challenges for 2007 are to:

MAD Technology;

- implement a bead based microarray technology platform.
- develop, test, evaluate and implement relevant microarray technology implementations such as: microRNA, universal, combination and protein arrays.

MAD Bioinformatics;

- test, evaluate and implement relevant bioinformatics methods, tools and infrastructure such as advanced biomarker selection, data preprocessing and analysis.
- extend our current life sciences research programs on gene-expression regulation, food-safety and toxicogenomics by focused research.

MAD Research;

- develop a problem solving environment for the complete chain of microarray data analysis.
- perform true integrative bioinformatics computational experimentation.
- further develop the actual e-BioLab.
- develop an information resource model within the Huntington use case.



SILS and society

Introduction

The Swammerdam Institute for Life Sciences is active in the study of life processes that create and determine a living organism. Life Sciences are developing rapidly, and the developments in life sciences continue to have a huge societal impact, for instance in the areas of nutrition, medicine, and industrial applications. The Swammerdam Institute carries out fundamental research, with attention for applied oriented research. This is illustrated for instance by our collaborations with several companies and TNO.

Communication with the public

Next to training scientists, and making them aware of the need for societal communication, scientists from the institute directly engage in communication with the public. One form this takes is by participating in the beta-festivals the faculty collaborates in, and in the open day at the Science Park. At the open day the people of Amsterdam, and especially the Watergraafsmeer are invited to see what research is carried out at the sciencepark.

NEMO, the children's science centre and the Universiteit van Amsterdam collaborate in organising the "Wake Up!" children's lecture series. Dr Gertien Smits, microbiologist of the Swammerdam Institute has given a lecture with the title "Can you eat bacteria?" (*Kun je bacteriën eten?*) in this lecture series on March 12, 2006. In this lecture she explained the children that bacteria are present everywhere, and that, together with our food we eat many bacteria. However, inside our body we already have millions of bacteria that help us to digest our food. Most of the time these bacteria make sure that if we accidentally eat bad bacteria, they don't take over and make us ill.

Collaboration with industry

Contacts with industry are very important for the Swammerdam Institute. Therefore we stimulate our staff when they are asked as advisors by industry. A few examples: Dr Frans Klis advises DSM (Delft), Prof.dr Klaas Hellingwerf advises Purac Biochem on the bioinformatics of a lactic acid bacterium. Dr.

Joost Teixeira de Mattos is external adviser of Heineken-Zoeterwoude and DSM-Delft. Prof.dr Michel Haring advises Rijk Zwaan Breeding, prof.dr Arie Otte collaborates with and advises Crucell and prof.dr Stanley Brul has several collaborations with Unilever. Prof.dr Wytse Wadman, in the area of neurobiology collaborates with Solvay Pharmaceuticals and Philips and has a strong link with the clinical through a side appointment in the Academic Hospital Ghent. Prof.dr Ben Cornelissen advises Arcadis in the area of Dutch Elm disease (“Dutch Trig”).

Our commitment to collaborating with industry is also shown in our projects with shared grant applications, for instance prof.dr Michel Haring and dr Rob Schuurink collaborate with Keygene, and have expanded this collaboration by a successful STW application. The longstanding collaboration of prof.dr Wytse Wadman with Solvay Pharmaceuticals is built on by shared participation in a TTI Pharma project. Prof.dr Age Smilde and dr Huub Hoefsloot collaborate with Unilever and other (academical) partners in an EU Transfer of Knowledge project.

Innovation

Innovative results are protected in patent applications, to ensure full societal use of important findings. The institute participates in the Technopartner funded collaboration I Am Starter, in which the UvA and the AMC collaborate with the Vrije Universiteit and its academic Medical Centre (VUMC).



4. Management

Finance, Personnel and Infrastructure

Finance

Due to the introduction of new financial systems at the UvA, the financial results for 2006 will be shown either in a separate addendum to this annual report, or in the report for 2007.

Revenues and costs for previous years*

	2005	2004	2003	2002	2001
university funding	7577	8987	7364	6131	5838
external funding	4515	6167	4474	3883	3852
total revenues	12092	15154	11838	10014	9690
personnel costs	9122	9626	8919	7465	7096
equipment	803	1775	998	782	600
bench fees	2729	3214	2312	1668	1636
total costs	11851	14614	12229	9915	9332
result	241	540	-391	99	358

* All amounts are given in K Euro.

In this table –starting from 2004–external funding is considered to be 2nd and 3rd funding source only.

Funding

The funding results for 2006 will be shown either in a separate addendum to this annual report, or in the report for 2007.

The funding system of Netherlands universities distinguishes three different kinds of funding sources. These funding sources are numbered one to three. Resources originating from the Netherlands government and directly given to the university are referred to as the first funding source. External funding is divided into funding originating from the Netherlands Organization for Scientific Research (second funding source) and money originating from all other resources such as EU and contract research (third funding source).

Income and costs in the 1st funding source, in k€, for the years 2003-2005.

	2005	2004	2003
Revenues	7577	8987	7793
Costs	7357	8902	8291
Result	220	85	-498

Income and costs in the 2nd funding stream, in k€, for the years 2003-2005.

	2005	2004	2003
Revenues	2160	2303	2279
Costs	2160	2303	2279
Result	0	0	0

Income and costs in the 3rd funding stream, in k€, for the years 2003-2005.

	2005	2004	2003
Revenues	2355	3864	1766
Costs	2334	3409	1659
Result	21	455	107

Financial reserves of the Swammerdam Institute for Life Sciences

As stated before, the institute's resources can be divided into university funding and external funding. In a similar way the financial reserves of the institute can be discerned by their origin. Profits or losses that are made on externally funded projects increase or decrease the reserves of the 3rd funding stream. Because most groups have externally funded projects they also possess a certain amount of these reserves. They can spend money from these reserves if additional resources are lacking but required for continuation of their research. Results from university funded activities of the institute increase (or decrease) the 1st funding stream reserves. Because the resources of the 1st funding stream are spent by the management these reserves can be considered to belong to the management. It must be stated that the management is responsible for the entire financial reserves at all times.

Reserves for the Swammerdam Institute, in k€, for the years 2005-2006

	01-01-06	01-01-05
Reserves (1st funding stream)	558	233
Reserves (3rd funding stream)	1005	1089
Total financial reserves	1563	1322

Private and Public Partnerships

The Swammerdam Institute actively establishes collaborations with industry. Universities play a role of increasing importance in creating innovations, either directly by establishing spin-off companies, or indirectly by making its results publicly available. The life sciences results from the Swammerdam Institute can for instance be used in the areas of medicine development, food development and food safety, and environmental processes. In order to protect its intellectual properties the Swammerdam Institute follows an active patenting policy. In most cases our IP forms the basis for collaborations with industrial partners.

To achieve our aims, the Institute seeks further partnerships with industry. These collaborations can have different forms like consultancies for industrial R&D organizations, transfer of biological materials, patent licensing, sponsored research and services using advanced techniques. In some cases we consider and set up spin-off companies. In the collaborations with industry the institute aims to establish long lasting relations with partners all around the world that are based on confidence and mutual respect, and in which benefits, both technological / scientific and financial are mutually shared. Upon request a brochure of the institute and a description of our research portfolio can be send. For further information please contact: sande@science.uva.nl.

Personnel

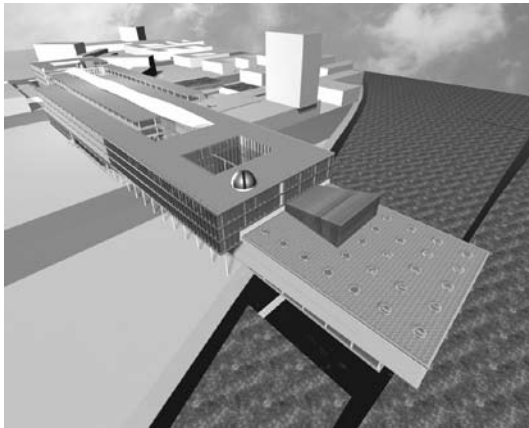
The university aims at a more equal division of males and females in the staff at all levels. At the level of PhD students and post doctoral fellows we have roughly an equal division. At the level of assistant professor, associate professor and professor however, the majority of staff is male. In application procedures for new staff the Swammerdam Institute for Life Sciences actively looks for female staff at these levels.

Age-wise our staff is spread over the full range from starting PhD, to people who

are (close to) retiring. In recent years a lot of young people have been appointed, bringing new ideas and enthusiasm. We also feel it is very valuable to keep the experience and network of retiring staff accessible. Therefore we keep the connections, and use our retiring staff in advisory roles.

Infrastructure

The Swammerdam Institute for Life Sciences is divided over two locations and looking forward to completion of the new planned building of the faculty in 2008/2009. The new green house complex was ready for use in the spring of 2006.



Evaluation of the Swammerdam Institute for Life Sciences

Composition of the SILS Scientific Advisory Board

Chairman: Dr N.C.M. Laane
DSM Food Specialties

Prof.dr P. de Wit
Laboratory of Phytopathology
Wageningen University

Prof.dr J.P. Armitage
Department of Biochemistry
University of Oxford

Prof.dr J. Garthwaite
Wolfson Institute for Biomedical Research
University College London

Prof.dr C. Cremer
Interdisciplinary Center for Scientific Computing
Ruprecht-Karls-University

Evaluation in 2006

On Thursday 20 and Friday 21 April the third meeting of the Scientific Advisory Board (SAB) of the Swammerdam Institute for Life Sciences took place. The SAB members were asked to advise the dean of the Faculty of Science and the director of SILS on the quality of the SILS' research and research groups, in preparation for an external research evaluation. In a concluding session at the end of the second day the SAB and the director of SILS briefly discussed the main subjects that had caught the attention of the Board. The SAB feels two day visits every two years are the best way to evaluate SILS.

The SAB felt very pleased with the research at the Swammerdam Institute. The morale of the groups is considered to be very good, and the staff is felt to be enthusiastic and professional in their research. This includes the PhDs and the postdocs the SAB has met.

5. Scientific Advisory Board

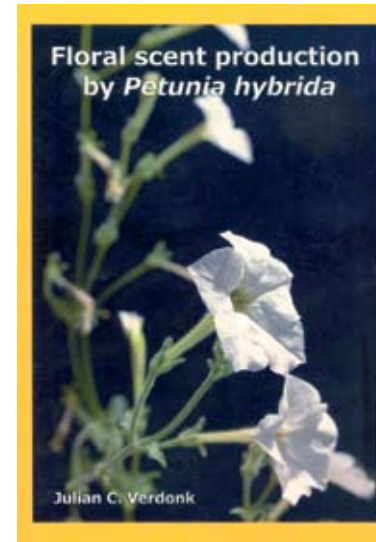
The general level of the research is very good (“pretty outstanding international level research”), and when science moves forward, in an active manner so do the researchers at SILS. The SAB recommends SILS to make a strategic plan.

The SAB, as in the previous two evaluations, stresses their appreciation for internal interactions, and encourages the SILS management to stimulate these, and to stimulate joint publications. The SAB is of the opinion that some excellent interactions exist around the technology groups. The SAB feels the attention given to Systems Biology is very positive, and thinks it can help to further stimulate internal interactions. The SAB feels Systems Biology at SILS should be open for all groups to participate in.

The SAB feels it currently cannot give much advice on Organisation and Finances, because the program concentrated on scientific matters. The committee members feel they would like to spend some time during the next visit on organizational matters, to be able to give advice again on these aspects. The SAB noted a very good level of personal grants with the staff of SILS, and feels this is well above the average in the Netherlands. The SAB commends SILS on this, and considers it a mark of good quality.

The SAB feels National and International collaborations are essential for a research institute, and recommends SILS to keep investing efforts in maintaining and expanding its external collaborations. The SAB feels the number of collaborations SILS has is very good.

The SAB is of the opinion it is very important to different disciplines, and has recommended SILS (also during its previous evaluations) to keep links with (bio)-chemistry, (bio)-physics and mathematics. The SAB realized the difficulty this can give because of the organizational and financial structure of the university, and the restraints this can give. The SAB welcomes the discussions that are being held in the framework of Systems Biology, and hopes this will strengthen SILS in these areas. Close interactions are needed between biology and mathematicians, and both kinds of scientists must be encouraged to be open minded.



6. Assessment of Research Quality

Peer Review: outcome at the Institute Level

The Peer Committee

Prof.dr P.R. Cook (University of Oxford);
Prof.dr W.P.M. Hoekstra (University Utrecht, Royal Academy of Arts and Sciences, Chair);
Prof.dr J.G.R. Jefferys (University of Birmingham);
Prof.dr D.B. Kell (University of Manchester);
Prof.dr D. Scheel (Leibnitz Institute of Plant Biochemistry).
Drs Klaas Deen acted as secretary.

The Swammerdam Institute was assessed at the level of the research institute and its programmes. The assessment is based on a thorough self evaluation report by the institute and on interviews which the peer committee had with the management of the faculty, the director of the institute and the program leaders. Next to these the committee received a bibliometric study of the output from the institute.

In their assessment the committee evaluated the past performance and whenever possible gave comments towards the future of the institute.

The committee followed the instructions of the Standard Evaluation Protocol (SEP) in a strict way. With regard to the research programmes, the committee had given ratings for the 'Quality', 'Productivity', 'Relevance' and 'Prospects'. The part of the report on the evaluation of the institute is represented below.

Evaluation of the institute

Quality:	4
Productivity:	3/4
Relevance:	4/5
Prospects:	4

Quality

The Swammerdam Institute for Life Sciences (SILS) started in 2000 as a result of implementing within the Science faculty a new model for organising research. SILS is organised in four clusters, each encompassing a number of research groups. Although the clusters are certainly helpful for the organisation of the research, they are not the cornerstones of the institute. The very informative self evaluation and the open discussions with the group leaders during the site visit revealed that the various research groups and expertise centres are the real cornerstones of SILS. Although the committee met some group leaders with a slight reservation towards SILS as an appropriate umbrella for their research and their ambitions, it should be stressed that SILS is seen by the research leaders in general as a useful organisation within the faculty to cope with the opportunities and the threats for the life sciences.

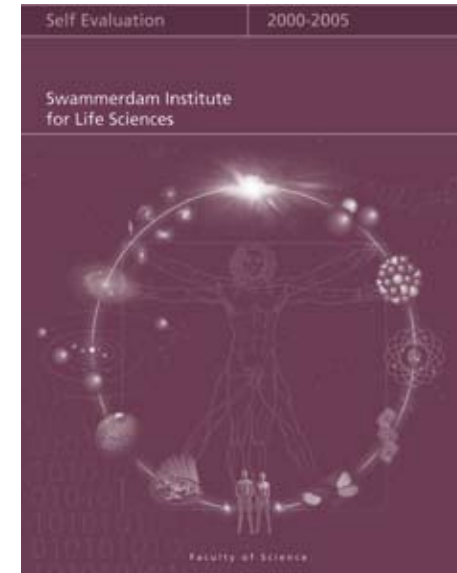
Within SILS, research groups and expertise centres of high quality are brought together. There are many groups with a very sound conceptual view on fundamental as well as on applied science. The concept of system biology is illustrative in this respect. The quality of the research is also shown by the fact that SILS is very successful in finding research funds, and especially the many prestigious personal grants are worth mentioning. Moreover, SILS is operating in a surrounding (AMOLF, CWI, AMC, NIN) that offers many opportunities for fruitful co-operations. There is a bright outlook for life sciences in Amsterdam and SILS could be very instrumental to realise this. However, the committee has noticed that most of the research groupings are comparatively small, and this can make it hard to be internationally competitive. Collaborations are therefore seen as an important part of the SILS portfolio for the future.

Productivity

The quality of the output is high, which was also confirmed by the extensive bibliometric analysis.

Many SILS groups reach with their papers frequently top journals. However, the productivity is open for improvement. Although in general the productivity is good to very good, it is quantitatively not up to the international standard. An explanation for this could be, as indicated by many group leaders, the heavy (and unevenly spread) teaching load they experience. Although the committee tends to accept this explanation, it is very remarkable that hardly any one could give an insight as to the factual teaching load. The committee wants to stipulate that

in order to act as a reputable research institute within a university that is proud to be acknowledged as research-university, the balance between research and teaching is delicate. Fact is that a nominal teaching time of 0.5 is vastly in excess of that of its international competitors.



Relevance

The relevance of SILS as an institute where forefront research in life sciences is performed and where many efforts are done to stimulate public engagement with science is very good.

Prospects

The prospects for SILS are very good, although not unconditional.

The present director of SILS was appointed in 2005. He has no personal research group, but brings in managerial expertise in academic organisations. It is too early to evaluate his performance, but extensive talks during the site visit taught the committee that the director is well aware of the strengths and the weaknesses of

the institute as well as of the opportunities and threats facing it. He clearly shows dedication and ambition to lead SILS, mainly by supporting the group leaders - respecting their authentic academic responsibilities - and by creating a more transparent and coherent organisation.

SILS is advised regularly by a Scientific Advisory Board (SAB). The SAB reports reveal that the SAB advises are very instrumental for SILS. In retrospect it would have been nice if the committee during the site visit had an opportunity to interview the chairman of the SAB.

The committee has spoken with a delegation from PhD students and post docs. There the committee noticed that SILS has not yet succeeded to become visible as a coherent institute for these groups. Although the location of the institute at two different places certainly is a problem, the main problem seems that not enough is done to bridge the gaps between the various clusters. Especially the Silly talks were blamed for not being very communicative. The committee strongly feels that SILS should look for more effective tools to inform young scientists about what is going on in SILS. This could be very helpful for creating corporate identity and could, even more importantly, serve as a vital aspect in the training of future researchers. Regular seminar lectures, master classes, SILS symposia etc. could, and in fact should, be organised SILS wide. There is no need to wait till the new housing is effective.



As a consequence of modern biology, data handling and modelling are very important. Within SILS there is a very active group dealing with these aspects, but there is a need for more. The committee believes it is not realistic to expect that the BDA, with a part time group leader, is able to fulfil all the needs.

Although there seem to be a lot of ideas about e-Bioscience, the committee could not find a clear and coherent vision in this respect. The committee feels that the problem of proper data handling and adequate modelling within SILS should be a main point for the future strategy.

A main point for the future strategy is also the focus of the institute. Some groups feel that they heavily depend on external funding. To find more sources, they tend to expand their research in many different lines. This may cause lack of focus. The committee advises SILS to develop a strategy where the groups focus their research mainly on the areas where SILS members are unique and really competitive.

Another concern with regard to the funding deals with lack of flexibility. As it is now there is hardly seed money in SILS for an adequate and proactive strategic policy. The committee believes it should be worthwhile to strive for more seed money at the level of the institute.

Last but not least, SILS is very depending on highly advanced equipment. The committee met all over SILS great concern that it might be very difficult to keep up with the very expensive equipment development. This is indeed also in the view of the committee a point of great concern. Biology is Big Science now and universities and funding agencies need to recognize this.

Appendix 1a

Molecular Microbial Physiology

Chairholder: Prof.dr K.J. Hellingwerf

Research Results in Numbers

Peer reviewed publications	16
Non-peer reviewed publications	0
PhD Theses	0
Patent applications	0

Staff

Klaas Hellingwerf

Jeroen Hugenholtz

Joost Teixeira de Mattos

(Research input in fte during 2006)

Chairholder

Honorary Professor (bijzonder hoogleraar)

Associate Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	0.6	0	0	0.6
Research Fellow	0.9	0.9	0.35	2.2
PhD Student	0	1.5	1.5	3
Technician	0.6	0	0.5	1.1
Total	2.6	2.4	2.4	7.4

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4/5
Productivity:	4
Relevance:	5
Prospects:	4

Publications

Key Publications

Yeremenko, S., Stokkum, I.H.M. van, Moffat, K., & Hellingwerf, K.J. (2006). Influence of the crystalline state on photoinduced dynamics of photoactive yellow protein studied by ultraviolet-visible transient absorption spectroscopy. *Biophys.J.*, 90(11), 4224-4235.

Avila-Perez, M., Hellingwerf, K.J., & Kort, R. (2006). Blue light activates the sigmaB-dependent stress response of *Bacillus subtilis* via YtvA. *J.Bacteriol.*, 188(17), 6411-6414.

Academic publications (refereed)

Albracht, S.P.J., Roseboom, W., & Hatchikian, E.C. (2006). The active site of the [FeFe]-hydrogenase from *D.desulfuricans*. I. Light sensitivity and magnetic hyperfine interactions as observed by electron paramagnetic resonance. *J.Biol. Inorg. Chem.*, 11, 88-101.

Avila-Perez, M., Hellingwerf, K.J., & Kort, R. (2006). Blue light activates the sigmaB-dependent stress response of *Bacillus subtilis* via YtvA. *J.Bacteriol.*, 188(17), 6411-6414.

Bekker, M., Teixeira De Mattos, M.J., & Hellingwerf, K.J. (2006). On the role of Two-component regulation systems in bacterial physiology. *Science Progress*, 89(3/4), 213-242.

Deutscher, J., Francke, C., & Postma, P.W. (2006). How phosphotransferase system-related protein phosphorylation regulates carbohydrate metabolism in bacteria. *Microbiol.Mol.Biol.Reviews*, 70(4), 939-1031.

Grinstead, J.S., Avila-Perez, M., Hellingwerf, K.J., Boelens, R., & Kaptein, R. (2006). Light-induced flipping of a conserved glutamine sidechain and its orientation in the AppA BLUF domain. *J.Am.Chem.Soc.*, 128(47), 15066-15067.

Grinstead, J.S., Hsu, S.-T.D., Laan, W.W.J., Bonvin, A.M.J.J., Hellingwerf, K.J., Boelens, H.F.M., & Kaptein, R. (2006). The solution structure of the AppA BLUF domain: Insight into the mechanism of light-induced signaling. *ChemBioChem*, 7, 187-193.

Hazra, P., Inoue, K., Laan, W.W.J., Hellingwerf, K.J., & Terazima, M. (2006). Tetramer formation kinetics in the signalling state of AppA monitored by time-resolved diffusion. *Biophys.J.*, 91(2), 654-661.

Laan, W.W.J., Gauden, M., Yeremenko, S., Grondelle, R. van, Kennis, J.T.M., &

Hellingwerf, K.J. (2006). On the mechanism of activation of the BLUF domain of AppA. *Biochemistry*, 45, 51-60.

Linden, H.P. van der, Burgdorf, T., De Lacey, A.L., Buhrke, T., Scholte, M., Fernandez, V.M., Friedrich, B., & Albracht, S.P.J. (2006). An improved purification procedure for the soluble [NiFe]-hydrogenase of *R.eutropha*: new insights into its (in)stability and spectroscopic properties. *J.Biol.Inorg.Chem.*, 11, 247-260.

Roseboom, W., De Lacey, A.L., Fernandez, V.M., Hatchikian, E.C., & Albracht, S.P.J. (2006). The active site of the [FeFe]-hydrogenase from *D. desulfuricans*. II. Redox properties, light sensitivity and CO-ligand exchange as observed by infrared spectroscopy. *J.Biol.Inorg.Chem.*, 11, 102-118.

Stokkum, I.H.M. van, Gobets, B., Gensch, T., Mourik, M., Hellingwerf, K.J., Grondelle, R. van, & Kennis, J.T.M. (2006). (Sub)-picosecond spectral evolution of fluorescence in photoactive proteins studied with a synchroscan streak camera system. *Photochem.Photobiol.*, 82(2), 380-388.

Veening, J.W., Kuipers, O.P., Brul, S., Hellingwerf, K.J., & Kort, R. (2006). Effects of phosphorelay perturbations on architecture, sporulation, and spore resistance in biofilms of *Bacillus subtilis*. *J.Bacteriol.*, 188, 3099-3109.

Vengris, M., Larsen, D.S., Horst, M.A. van der, Larsen, O.F., Hellingwerf, K.J., & Grondelle, R. van (2006). Ultrafast dynamics of isolated model photoactive yellow protein chromophores: "Chemical perturbation theory" in the laboratory. *J.Phys.Chem.B.*, 109(9), 4197-4208.

Visser, W.F., Roermund, C.W.T. van, Hellingwerf, K.J., Waterham, H.R., & Wanders, R.J.A. (2006). First identification of a 2-ketoglutarate/isocitrate transport system in mammalian peroxisomes and its characterization. *Biochem. Biophys.Res. Commun.*, 348(4), 1224-1231.

Wilderen, L.J. van, Horst, M.A. van der, Stokkum, I.H.M. van, Hellingwerf, K.J., Grondelle, R. van, & Groot, M.L. (2006). Ultrafast infrared spectroscopy reveals a key step for successful entry into the photocycle for photoactive yellow protein. *Proc.Natl.Acad.Sci.USA*, 103(41), 15050-15055.

Yeremenko, S., Stokkum, I.H.M. van, Moffat, K., & Hellingwerf, K.J. (2006). Influence of the crystalline state on photoinduced dynamics of photoactive yellow protein studied by ultraviolet-visible transient absorption spectroscopy. *Biophys.J.*, 90(11), 4224-4235.

Invited Lectures

Crielaard, W. (2006, oktober 10). *Multispecies biofilm communities in the oral cavity*. Wageningen, Wageningen Center for Food Sciences.

Crielaard, W. (2006, april 10). *Response of Streptococcus mutans towards*

environmental stress and interaction of Streptococcus mutans with Veillonella parvula grown in dual species biofilm. Papendal, Wet.Voorjaarsvergadering NVVM/NVvM.

Hellingwerf, K.J. (2006, maart 15). *Systems microbiology.* Amsterdam, Sils research day.

Hellingwerf, K.J. (2006, april 11). *Effects of phosphorelay perturbations (and light?) on architecture, sporulation and spore resistance in biofilms of Bacillus subtilis.* Papendal, Annual NVvM meeting.

Hellingwerf, K.J., & Avila-Perez, M. (2006, mei 01). *On the biological function of YtvA from B.subtilis.* Il Ciocco, Italy, Gordon Res.Conf.on Photosensory Receptors & Signal Transduction

Hellingwerf, K.J. (2006, mei 11). *Transient functional unfolding of photoactive yellow protein (PYP).* Bedlewo, Poland, Workshop Polish Acad.of Sciences on the Structure and Function of Biomolecules II.

Hellingwerf, K.J. (2006, juni 04). *Signal generation in photoactive yellow protein (PYP).* Hyogo, Japan, 12th Int.Conference on Retinal Proteins.

Hellingwerf, K.J. (2006, oktober 05). *Systems microbiology.* Amsterdam, SILS Research Disc. on Systems Biology.

Hellingwerf, K.J. (2006, oktober 14). *From structural- and systems biology to 'synthetic' biology.* San Feliu, Spain, ESF-EMBO Symp. "Bacterial networks"-Joining the strengths of structural-and systems biology to reach 'synthetic' biology.

Hellingwerf, K.J. (2006, oktober 27). *On signal transduction networks, biofilm formation and sporulation in Bacillus subtilis.* Amsterdam, Autumn meeting MMP Section of NVvM.

Hellingwerf, K.J. (2006, november 10). *Photo-signaling.* Wageningen, Capita selecta "Structure & Dynamics of biomolecules in vivo and in vitro, Wageningen University.

Hellingwerf, K.J. (2006, november 21). *Signal transduction, biofilm formation and sporulation in Bacillus subtilis.* Vlaardingen, Progress report Unilever Research.

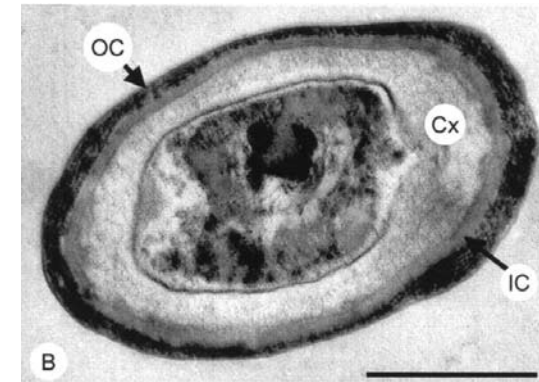
Hellingwerf, K.J. (2006, december 14). *Signal transduction networks, biofilm formation and sporulation in Bacillus subtilis.* Rosario, Argentina, Lecture Universidad de Rosario, Inst. de Biol.Mol. y Cellular de Rosario.

Hellingwerf, K.J. (2005, december 19). *The mechanism of photo-activation of Photoactive Yellow Protein.* Honolulu, USA, Pacifichem.

Teixeira De Mattos, M.J. (2006, maart 19). *On the redox state and size of the quinone pool in Escherichia coli.* Tomar, Portugal, Meeting on Microbial Respiratory Chains.

Teixeira de Mattos, M.J. (2006, april 11). *Modelling the heat response of*

Saccharomyces cerevisiae. Papendal, Voorjaarsvergadering Ned.Ver. Microbiologie



Appendix 1b

Molecular Biology and Microbial Safety

Chairholder: Prof.dr S. Brul

Research Results in Numbers

Peer reviewed publications	11
Non-peer reviewed publications	1
PhD Theses	0
Patent applications	2

Staff	(Research input in fte during 2006)
Stanley Brul	Chairholder
Hans van der Spek	Assistant Professor
Gertien Smits	Assistant Professor
Frans Klis	Associate Professor (senior researcher)

Position	FS1*	FS2**	FS3°	Total
Chairholder	0	0	0.3	0.3
Associate/Assistant professor	0.5	0.5	0	1.0
Research Fellow	0	1.5	0.2	1.7
PhD Student	0.4	0	2.3	2.7
Technician	3.3	0	0.3	3.6
Total	4.2	2.0	3.1	9.3

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	3/4
Productivity:	3
Relevance:	4
Prospects:	2/3

Publications

Key Publications

Brul, S., Schuren, F., Montijn, R., Keijser, B.J.F., Spek, H. van der, & Oomes, S.J.C.M. (2006). The impact of functional genomics on microbiological food quality and safety. *Int. J. Food Microbiol.* 112, 195-199.

Smits, G.J. Schenkman, L.R., Ende, H. van den, Brul, S., Pringle, J.R. & Klis, F.M. 2006. Role of cell-cycle regulated expression in the localized incorporation of cell-wall proteins in yeast., *Mol. Cell. Biol.* 17, 3267-3280.

Klis, F.M., Boorsma, A., & Groot, P.W. de (2006). Cell wall construction in *Saccharomyces cerevisiae* *Yeast* 23, 185-202.

Patent applications

Beek, A.S. ter, Brul, S., & Vaart, M van (19-12-2006). Screening method for the identification of a preservative.

Keijser, B.J.F. (2006). Control of preservation by biomarkers. no EP 05077246.6.

Academic publications (refereed)

Albrecht, A., Felk, A, Pichova, I, Naglik, J.R., Schaller, M., Groot, P.W.J. de, Maccallum, D., Odds, F.C., Schafer, W., Klis, F.M., Monod, M, & Hube, B. (2006). Glycosylphosphatidylinositol-anchored proteases of *Candida albicans* target proteins necessary for both cellular processes and host-pathogen interactions. *J.Biol.Chem.*, 281(2), 688-694.

Brul, S., Schuren, F., Montijn, R., Keijser, B.J.F., Spek, H. van der, & Oomes, S.J.C.M. (2006). The impact of functional genomics on microbiological food. *Int.J.Food Microbiol.*, 112, 195-199.

Meijer, H.J., Vondervoort, P.J. van, Yin, Q., Koster, C.G. de, Klis, F.M., Govers, F., & Groot, P.W.J. de (2006). Identification of cell wall-associated proteins from *Phytophthora ramorum*. *Mol.Plant Microbe Interact.*, 19(12), 1348-1358.

Pardini, G., Groot, P.W.J. de, Coste, A.T., Karababa, M., Klis, F.M., Koster, C.G. de, & Sanglard, D. (2006). The CRH family coding for cell wall glycosylphosphatidylinositol proteins with a predicted transglycosidase domain affects cell wall organization and virulence of *Candida albicans*. *J.Biol. Chem.*, 281(52), 40399-40411.

Ram, A.F.J., & Klis, F.M. (2006). Identification of fungal cell wall mutants

- using susceptibility assays based on Calcofluor white and Congo red. *Nature protocols*, 5, 2253-2256.
- Grün, C.H., Dekker, N., Nieuwland, A.A., Klis, F.M., Kamerling, J.P., Vliegthart, J.F.G., & Hochstenbach, F. (2006). Mechanism of action of the endo-(1--3)-alpha-glucanase MutAp from the mycoparasitic fungus *Trichoderma harzianum*. *FEBS lett.*, 580(16), 3780-3786.
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- Klis, F.M., & Groot, P.W.J. de (2006). Trends and highlights in Candida research. *FEMS Yeast Res.*, 6(4), 667-668.
- Smits, G.J., Schenkman, L.R., Brul, S., Pringle, J.R., & Klis, F.M. (2006). Role of cell-cycle regulated expression in the localized incorporation of cell wall proteins in yeast. *Mol.Biol.Cell*, 17(7), 3267-3280.
- Veening, J.W., Kuipers, O.P., Brul, S., Hellingwerf, K.J., & Kort, R. (2006). Effects of phosphorelay perturbations on architecture, sporulation and spore resistance in biofilms of *Bacillus subtilis*. *J.Bacteriol.*, 188(8), 3099-3109.
- Verstrepen, K.J., & Klis, F.M. (2006). Flocculation, adhesion and biofilm formation in yeasts. *Mol.Microbiol.*, 60(1), 5-15.

Book Chapter

- Brul, S., Spek, H. van der, Keijser, B.J.F., Schuren, F., Oomes, S.J.C.M., & Montijn, R.C. (2006). Functional genomics for optimal microbiological stability of processed food products. In *High pressure processing of foods* (pp. 190-250). Ames, USA: Blackwell.

Invited lectures

- Beek, A.S. ter (2006, augustus 29). *Mild treatment of Bacillus subtilis with the food preservative sorbic acid induces a stringent-type response, but not the general stress response of sporulation*. Bologna, Italy, Congress Food Micro.
- Brul, S. (2006, april 01). *Detection, characterization and process survival of Bacillus spores in the food industry*. Papendal, Annual Meeting Dutch Soc.for Microbiology.
- Brul, S. (2006, juni 12). *Dealing with Bacillus spores in the food industry for improved quality*. Budapest, Hungary, SAFE-Congress.
- Brul, S. (2006, juni 26). *Molecular tools to establish the effectiveness of thermal preservations; where did we start from?* Orlando, USA, IFT.
- Brul, S. (2006, augustus 29). *Dealing with bacterial spores in food processing: detection, identification, survival and process damage repair mode-of-action*.

Bologna, Italy, Congress Food Micro.

Klis, F.M. (2006, augustus 31). *Extraction techniques for fungal cell surface proteins*. Heidelberg, 3rd Int.Conf.on Mol.Mechanisms of Fungal cell wall biogenesis.

Shen, T. (2006, augustus 29). *A flow cytometry study of freeze-thaw and high pressure-low temperature induced damage to Bacillus subtilis cells in the ice I-III domain*. Bologna, Italy, Congress Food Micro.



Appendix 1c

Cellular Microbiology

Chairholder: Prof.dr J. Wells

Research Results in Numbers

Peer reviewed publications	3
Non-peer reviewed publications	0
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2006)
Jerry Wells Chairholder

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.25	0	0	0.25
Associate/Assistant professor	0	0	0	0
Research Fellow	0	0	2.3	2.3
PhD Student	0	0	0	0
Technician	0	0	0	0
Total	0.25	0	0.23	2.6

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Publications

Key Publications

Lioy, V.S., Martin, M.T., Camaccho, A.G., Lurz, R., Antelmann, H., Hecker, M., Hitchin, E., Ridge, Y., & Wells, J.M. (2006). pSM19035-encoded zeta toxin induces stasis followed by death in a subpopulation of cells. *Microbiology*, 152, 2365-2379.

Pin, C., Reuter, M., Pearson, B., Friis, L.M., Overweg, K., Baranyi, J., & Wells, J.M. (2006). Comparison of different approaches for comparative genetic analysis using microarray hybridizations. *Applied Microbiol.and Biotechn.*, 72, 852-859.

Pusch, O., Kalyanaraman, R., Tucker, L.D., Wells, J.M., Ramratnam, B., & Boden, D. (2006). An anti-HIV microbicide engineered in commensal bacteria: secretion of HIV-1 fusion inhibitors by lactobacilli. *AIDS*, 20, 1917-1922.

Academic publications (refereed)

Lioy, V.S., Martin, M.T., Camaccho, A.G., Lurz, R., Antelmann, H., Hecker, M., Hitchin, E., Ridge, Y., & Wells, J.M. (2006). pSM19035-encoded zeta toxin induces stasis followed by death in a subpopulation of cells. *Microbiology*, 152, 2365-2379.

Pin, C., Reuter, M., Pearson, B., Friis, L.M., Overweg, K., Baranyi, J., & Wells, J.M. (2006). Comparison of different approaches for comparative genetic analysis using microarray hybridizations. *Applied Microbiol.and Biotechn.*, 72, 852-859.

Pusch, O., Kalyanaraman, R., Tucker, L.D., Wells, J.M., Ramratnam, B., & Boden, D. (2006). An anti-HIV microbicide engineered in commensal bacteria: secretion of HIV-1 fusion inhibitors by lactobacilli. *AIDS*, 20, 1917-1922

Invited lectures

Wells, J.M. (2006, september 01). *Host microbe interactions and intestinal health*. Bologna, Italy, Food Micro Congress.

Wells, J.M. (2006, oktober 14). *Function of the YycF two-component system in Streptococcus pneumoniae and opportunities for drug discovery*. Sant Feliu de Guixols, Spain, ESF-EMBO Joint Symp. on Bacterial Networks and Systems Biology.

Wells, J.M. (2006, november 01). *Host-microbe interactions in the intestine and inflammatory bowel disease*. Utrecht, Translational Medicine Symposium, University of Utrecht

Wells, J.M. (2006, november 01). *Functional Foods: from markets to mechanisms*. Wageningen, Dutch Soc.for Microbiol.Symposium on Functional Foods.

Wells, J.M. (2006, december 11). *Host microbe interactions and intestinal health*. Wageningen, Food Summit, Wageningen Center for Food Sciences.



Appendix 1d

Structure and Functional Organisation of the Cell Nucleus

Chairholder: Prof.dr R. van Driel

Research Results in Numbers

Peer reviewed publications	11
Non-peer reviewed publications	0
PhD Theses	2
Patent applications	0

Staff

	(Research input in fte during 2006)
Roel van Driel	Chairholder
Philippe Bastiaens	Professor (bijzonder hoogleraar)
Johan Braeckman	Professor (bijzonder hoogleraar)
Paul Fransz	Assistant Professor
Maike Stam	Assistant Professor
Pernette Verschure	Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	0.75	0.75	0	1.5
Research Fellow	0	0	2.5	2.5
PhD Student	0.75	2.25	0.75	3.75
Technician	1.5	0.3	1	2.8
Total	3.5	3.3	4.3	11.1

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4/5
Productivity:	3
Relevance:	5
Prospects:	5

Publications

Key Publications

Fransz, P., Hoopen, R. ten, & Tessadori, F. (2006). Composition and formation of heterochromatin in *Arabidopsis thaliana*. *Chromosome Res.* 14:71-82.

Verschure, P.J. (2006). Chromosome organization and gene control: it is difficult to see the picture when you are inside the frame. *J Cell Biochem.* 99:23-34.

Zotter, A., Luijsterburg, M.S., Warmerdam, D.O., Ibrahim, S., Nigg, A., Cappellen, W.A., Hoeijmakers, J.H.J. van, Driel, R. van, Vermeulen, W., & Houtsmuller, A.B. (2006). Recruitment of the Nucleotide Excision Repair Endonuclease XPG to Sites of UV-induced DNA Damage Depends on Functional TFIIH. *Mol. Cell. Biol.* 26:8868-8879.

PhD Theses

Tessadori, F. (2006, september 15). *Plasticity of heterochromatin in Arabidopsis*. UvA Universiteit van Amsterdam (139 pag.). Prom./coprom.: Prof.dr R. van Driel, & P.F. Fransz.

Greil, F.A. (2006, november 23). *Heterochromatin composition and function in Drosophila*. UvA Universiteit van Amsterdam (146 pag.) (Amsterdam). Prom./coprom.: Prof.dr R. van Driel, & dr B. van Steensel.

Academic publications (refereed)

Brink, M.C., Velden, Y. van der, Leeuw, W. de, Mateos Langerak, J., Belmont, A.S., Driel, R. van, & Verschure, P.J. (2006). Truncated HP1 lacking a functional chromodomain induces heterochromatinization upon *in vivo* targeting. *Histochem Cell Biol.* 125, 53-61.

Fransz, P.F., Hoopen, R. ten, & Tessadori, F. (2006). Composition and formation of heterochromatin in *Arabidopsis thaliana*. *Chromosome Res.*, 14, 71-82.

Gladilin, E., Goetze, S., Langerak, J.M., Driel, R. van, Eils, R., & Rohr, K. (2006). Topological analysis of 3D cell nuclei using finite element template-based spherical mapping. *Proc. SPIE*, 6144, 1557-1566.

Leeuw, W. de, Verschure, P.J., & Liere, R. van (2006). Visualization and analysis of large data collections: a case study applied to confocal microscopy data. *IEEE Transactions on visualization and computer graphics*, 12 (5).

Luijsterburg, S.M., Noom, M., Wuite, G.J., & Dame, R.T. (2006). The

architectural role of nucleoid-associated proteins in the organization of bacterial chromatin: A molecular perspective. *J. Struct. Biol.*, 156, 262-272.

Lysak, M., Fransz, P.F., & Schubert, I. (2006). Cytogenetic Analyses of *Arabidopsis*. *Methods in Molecular Biology*, 323, 173-186.

Mylne, J.S., Barrett, L., Tessadori, F., Mesnage, S., Johnson, L., Bernatavichute, Y.V., Jacobsen, S.E., Fransz, P.F., & Dean, C. (2006). LHP1, the *Arabidopsis* homologue of heterochromatin protein1 is required for epigenetic silencing of FLC. *Proc. Natl. Acad. Sci. U. S. A.*, 103, 5012-5017.

Verschure, P.J. (2006). Chromosome organization and gene control: It is difficult to see the picture when you are inside the frame. *J. Cell. Biochem.*, 99, 23-34.

Verschure, P.J., Visser, A.E., & Rots, M.G. (2006). Step out of the groove: epigenetic gene control systems and engineered transcription factors. *Adv. Genet.*, 56, 163-204.

Visser, A.E., Verschure, P.J., Gommans, W.M., Haisma, H.J., & Rots, M.G. (2006). Step into the groove: engineered transcription factors as modulators of gene expression. *Adv. Genet.*, 56, 131-161.

Zotter, A., Luijsterburg, S.M., Warmerdam, D.O., Ibrahim, S., Nigg, A.L., Cappellen, W.A. van, Hoeijmakers, J.H.J., Driel, R. van, Vermeulen, W., & Houtsmuller, A. (2006). Recruitment of the nucleotide excision repair endonuclease XPG to sites of UV-induced DNA damage depends on functional TFIIH. *Mol. Cell. Biol.*, 26, 8868-8879.

Invited lectures

Driel, R. van (2006, maart 10). *Where do we go in the nucleus...?* Kerkrade, the Netherlands, Retraite Genetica.

Driel, R. van (2006, mei 05). *Relationship between the 1D organisation of the human genome and its 3D structure in the cell nucleus*. Prague, Czech republic, EMBO workshop on Nuclear organization.

Driel, R. van (2006, juli 13). *Quantitative and predictive modeling of in vivo chromatin-associated processes: the DNA repair case*. Heidelberg, Germany, Conference on systems biology of the mammalian cell.

Driel, R. van (2006, juli 25). *Relationship between the 1D organisation of the human genome and 3D chromatin structure in the cell nucleus*. Munich, Germany, Seminar University Munich.

Driel, R. van (2006, augustus 16). *Principles of 3D human genome structure*. Brno, Czech Republic, 3DGENOME Meeting.

Driel, R. van (2006, oktober 14). *Systems biology of the eukaryotic genome function*. Gosau, Austria, EMBO Workshop on Systems Biology meets chromatin function.

Appendix 1e

Epigenetic Regulation of Gene Expression

Chairholder: Prof.dr A.P. Otte

Research Results in Numbers

Peer reviewed publications	8
Non-peer reviewed publications	0
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2006)

Arie Otte	Chairholder
David Satijn	Assistant Professor

Position	FS1*	FS2**	FS3°	FS4°°	Total
Chairholder	0.4	0	0	0	0.4
Associate/Assistant professor	0.23	0	0	0	0.23
Research Fellow	0.3	0	1.6	0.9	2.8
PhD Student	0.75	0	0	0	0.75
Technician	1.7	0	0	3.1	4.8
Total	3.4	0	1.6	4.0	9

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding, °° FS4 = employed in a collaboration with Crucell

Result research evaluation 2006 according to VSNU protocol

Quality:	4
Productivity:	4/5
Relevance:	5
Prospects:	3/4

- Driel, R. van (2006, november 06). *A paradigm shift in Life Sciences systems biology hype, hope or necessity...*? Venlo, the Netherlands, WCFS Meeting.
- Driel, R. van (2006, december 14). *3D folding of the human genome in the interphase nucleus*. University of Heidelberg, Germany, seminar.
- Fransz, P.F. (2006, april 03). *A light switch for chromatin remodelling*. Lunteren, The Netherlands, EPS Symposium.
- Fransz, P.F. (2006, april 21). *Heterochromatin variation in Arabidopsis*. Amsterdam, The Netherlands, Seminar Free University.
- Fransz, P.F. (2006, september 19). *Genome Plasticity: How flexible is the organization of eukaryotic chromosomes?* Wageningen, the Netherlands, EPS.
- Stam, M. (2006, december 13). *b1 paramutation: DNA methylation, chromatin structure & long range in cis interactions*. Chandler Laboratory, Tuscon (AZ), USA, seminar.
- Verschure, P.J. (2006, september 07). *Functional chromosome organization in the interphase nucleus: Epigenetic gene control*. Stresa, Italy, Feulgen Prize awarding, 48th Symposium of the Society for Histochemistry.
- Verschure, P.J. (2006, oktober 02). *Functional chromosome organization in the interphase nucleus: Epigenetic gene control*. Krakow, Poland, Symposium "Hot topics in Eukaryotic Transcription", Jagiellonian University.
- Verschure, P.J. (2006, december 22). *Chromosome organization and epigenetic gene control systems*. Groningen, the Netherlands, Symposium Towards gene-specific chromatin remodeling.

Other results

Verschure, P.J. (2006). Functional chromosome organization in the interphase nucleus: Epigenetic gene control. Feulgen Prize of the Society for Histochemistry: Stresa, Italy (2006, september 07).



Publications

Key Publications

Boyer, L.A., Plath, K., Zeitlinger, J., Brambrink, T., Medeiros, L.A., Lee, T.I., Levine, S.S., Wernig, M., Tajonar, A., Ray, M.K., Bell, G.W., Otte, A.P., Vidal, M., Gifford, D.K., Young, R.A., & Jaenisch, R. (2006). Polycomb complexes repress developmental regulators in murine embryonic stem cells. *Nature* 441, 349-353.

Van Blokland, H.J.M., Kwaks, T.H.J., Sewalt, R.G.A.B., Verhees, J.A., Klaren, V.N.A. Siersma, T.K., Korse, J.W.M., Teunissen, N.C., Botschuijver, S., Van Mer, C., Man, S.Y., & Otte, A.P. (2006). A novel, high stringency selection system allows screening of few clones for high protein expression. *J Biotechnology*. Epub 2006 Oct 10.

Academic publications (refereed)

Bachmann, I.M., Halvorsen, O.J., Collett, K., Stefansson, I.M., Straume, O., Haukaas, S.A., Salvesen, H.B., Otte, A.P., & Akslen, L.A. (2006). EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *J Clin Oncol*, 24, 268-273.

Boyer, L.A., Plath, K., Zeitlinger, J., Brambrink, T., Medeiros, L.A., Lee, T.I., Levine, S.S., Wernig, M., Tajonar, A., Ray, M.K., Bell, G.W., Otte, A.P., Vidal, M., Gifford, D.K., Young, R.A., & Jaenisch, R. (2006). Polycomb complexes repress developmental regulators in murine embryonic stem cells. *Nature*, 441, 349-353.

Collett, K., Eide, G.E., Arnes, J., Stefansson, I.M., Eide, J., Braaten, A., Aas, T., Otte, A.P., & Akslen, L.A. (2006). Expression of enhancer of zeste homologue 2 is significantly associated with increased tumor cell proliferation and is a marker of aggressive breast cancer. *Clin Cancer Res*, 12, 1168-1174.

Fujimura, Y., Isono, K., Vidal, M., Endoh, M., Kajita, H., Mizutani-Koseki, Y., Takihara, Y., Lohuizen, M. van, Otte, A.P., Jenuwein, T., Deschamps, J., & Koseki, H. (2006). Distinct roles of Polycomb group gene products in transcriptionally repressed and active domains of Hoxb8. *Development*, 133, 2371-2381.

Kalantry, S., Mills, K.C., Yee, D., Otte, A.P., Panning, B., & Magnuson, T. (2006). The Polycomb group protein Eed protects the inactive X-chromosome from differentiation-induced reactivation. *Nat Cell Biol*, 8, 195-202.

Kwaks, T.H.J., & Otte, A.P. (2006). Employing epigenetics to augment the expression of therapeutic proteins in mammalian cells. *Trends Biotechnol.*, 24(3), 137-142.

Lee, T.I., Jenner, R.G., Boyer, L.A., Guenther, M.G., Levine, S.S., Kumar, R.M., Chevalier, B., Johnstone, S.E., Cole, M.F., Isono, K., Koseki, H., Fuchikami, T., Abe, K., Murray, H.L., Zucker, J.P., Yuan, B., Bell, G.W., Herbolsheimer, E., Hannett, N.M., Sun, K., Odom, D.T., Otte, A.P., Volkert, T.L., Bartel, D.P., Melton, D.A., Gifford, D.K., Jaenisch, R., & Young, R.A. (2006). Control of developmental regulators by Polycomb in human embryonic stem cells. *Cell*, 125, 301-313.

Van Blokland, H.J.M., Kwaks, T.H.J., Sewalt, R.G.A.B., Verhees, J.A., Klaren, V.N.A. Siersma, T.K., Korse, J.W.M., Teunissen, N.C., Botschuijver, S., Van Mer, C., Man, S.Y., and Otte, A.P. 2006. A novel, high stringency selection system allows screening of few clones for high protein expression. *J Biotechnology*. Epub 2006 Oct 10.



Appendix 1f

Molecular Cytology

Chairholder: Prof.dr Th.W.J. Gadella

Research Results in Numbers

Peer reviewed publications	20
Non-peer reviewed publications	3
PhD Theses	3
Patent applications	1

Staff	(Research input in fte during 2006)
Dorus Gadella	Chairholder
Nanne Nanninga	Emeritus Professor
Fred Brakenhoff	Emeritus Professor
Conrad Woldringh	Associate Professor (senior researcher)
Michiel Müller	Associate Professor
Erik Manders	Assistant Professor
Tanneke den Blaauwen	Assistant Professor
Joachim Goedhart	Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	1	1	0	2
Research Fellow	0	3	3.2	6.4
PhD Student	0.8	1.5	0.1	2.4
Technician	3.6	0	0	3.6
Total	5.9	5.5	3.3	14.9

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4
Productivity:	3
Relevance:	5
Prospects:	5

Publications

Key Publications

Dhonukshe, P., Baluška, F., Schlicht, M., Hlavacka, A., Šamaj, J., Friml, J., & Gadella Jr., T.W.J. (2006). Endocytosis of cell surface material mediates cell plate formation during plant cytokinesis. *Dev. Cell* 10: 137-150. (IF14.6)

Blaauwen, T. den, Aarsman, M.E.G., Wheeler, L., & Nanninga, N. (2006). Pre-replication assembly of *E.coli* replisome components. *Mol. Microbiol.*, 62, 695-708. (IF 6.2)

Patent Applications

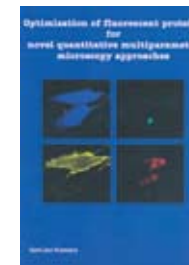
Manders, E.M.M. (16-05-2003). Method and apparatus for shaping an image of an object. no US 2006/0120065.

PhD Theses

Kremers, G.J. (2006, oktober 25). *Optimization of fluorescent proteins for novel quantitative multiparameter microscopy approaches*. UvA Universiteit van Amsterdam (157 pag.). Prom./coprom.: prof.dr. Th.W.J. Gadella, & dr. ir. J. Goedhart.

Vermeer, J.E.M. (2006, juni 15). *Visualisation of polyphosphoinositide dynamics in living plant cells*. UvA Universiteit van Amsterdam (177 pag.). Prom./coprom.: prof.dr. Th.W.J. Gadella, & dr. T. Munnik.

Vinkenvleugel, T.M.F. (2006, maart 10). *Timing of FtsQ midcell localisation and its interaction with other cell division proteins*. UvA Universiteit van Amsterdam (166 pag.). Prom./coprom.: prof.dr N. Nanninga, & dr T. den Blaauwen.



Academic publications (refereed)

- Adjobo Hermans, M.J.W., Goedhart, J., & Gadella, Th.W.J. (2006). Plant G- Protein heterotrimers require dual lipidation motifs of Galpha and Ggamma and do not dissociate upon activation. *J Cell Sci*, 119, 5087-5097.
- Amir, W., Planchon, T.A., Durfee, C.G., Squier, J., Gabolde, P., Trebino, R., & Müller, M. (2006). Simultaneous visualization of spatial and chromatic aberrations by two-dimensional Fourier transform spectral interferometry. *Opt. Lett.*, 31, 2927-2929.
- Bertsche, U., Kast, T., Wolf, B., Fraipont, C., Aarsman, M.E.G., Kannenberg, K., Rechenberg, M. von, Nguyen-Distèche, M., Blaauwen, T. den, Höltje, J-V., & Vollmer, W. (2006). Interaction between two murein (peptidoglycan) synthases, PBP3 and PBP1B, in *Escherichia coli*. *Mol. Microbiol.*, 61, 675-690.
- Blaauwen, T. den, Aarsman, M.E.G., Wheeler, L., & Nanninga, N. (2006). Pre-replication assembly of *E.coli* replisome components. *Mol. Microbiol.*, 62, 695-708.
- Dhonukshe, P.B., Bargmann, B.O.R., & Gadella, Th.W.J. (2006). Arabidopsis Tubulin Folding Cofactor B interacts with alpa tubulin *in vivo*. *Plant Cell Physiol.*, 47, 1406-1411.
- Dhonukshe, P.B., Vischer, N.O.E., & Gadella, Th.W.J. (2006). Contribution of microtubule growth polarity and flux to spindle assembly and functioning in plant cells. *J. Cell Sci.*, 119, 3193-3205.
- Dhonukshe, P.B., Baluska, F., Schlicht, M., Hlavacka, A., Samaj, J., Friml, J., & Gadella, Th.W.J. (2006). Endocytosis of cell surface material mediates cell plate formation during plant cytokinesis. *Dev Cell*, 10, 137-150.
- Kantardzhieva, A., Alexeeva, S.V., Versteeg, I., & Wijnholds, J. (2006). MPP3 is recruited to the MPP5 protein scaffold at the retinal outer limiting membrane. *FEBS J.*, 273, 1152-1165.
- Kremers, G.J., Goedhart, J., Munster, E.B. van, & Gadella, Th.W.J. (2006). Cyan and yellow super fluorescent proteins with improved brightness, protein folding, and FRET Forster radius. *Biochemistry*, 45, 6570-6580.
- Pillai, R.S., Brakenhoff, G.J., & Müller, M. (2006). Analysis of the influence of spherical aberration from focusing through a dielectric slab in quantitative nonlinear optical susceptibility measurements using third-harmonic generation. *Optics Express*, 14(1), 260-269.
- Pillai, R.S., Brakenhoff, G.J., & Müller, M. (2006). Anomalous behavior in the third harmonic generation z response through dispersion induced shape changes and matching X(3). *Appl. Phys. Lett.*, 89(11), 111123-1-111123-3.
- Pillai, R.S., Oh-e, M., Yokoyama, H., Brakenhoff, G.J., & Müller, M. (2006). Imaging colloidal particle induced topological defects in a nematic liquid crystal using third harmonic generation microscopy. *Optics Express*, 14(26), 12976-12983.
- Rinia, H.A., Bonn, M., & Müller, M. (2006). Quantitative multiplex CARS spectroscopy in congested spectral regions. *J. Phys. Chem. B*, 110, 4472-4479.
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- Vermeer, J.E.M., Leeuwen, W. van, Tobena Santamaria, R., Laxalt, A.M., Jones, D.R., Divecha, N., Gadella, Th.W.J., & Munnik, T. (2006). Visualization of PtdIns(3)P dynamics in living plant cells. *Plant J.*, 47, 687-700.
- Wurpel, G.W.H., & Müller, M. (2006). Water confined by lipid bilayers: A multiplex CARS study. *Chem. Phys. Lett.*, 425(4-6), 336-341.
- Zaritsky, A., Woldringh, C.L., Einav, M., & Alexeeva, S.V. (2006). Use of thymine limitation and thymine starvation to study bacterial physiology and cytology. *J. Bacteriol.*, 188, 1667-1679.
- Zonia, L.E., Müller, M., & Munnik, T. (2006). Hydrodynamics and Cell Volume Oscillations in the Pollen Tube Apical Region are Integral Components of the Biomechanics of *Nicotiana tabacum* Pollen Tube Growth. *Cell Biochem. Bioph.*, 46(3), 209-232.

Book chapters

- Manders, E.M.M., Soll, D.R., Terasaki, M., & Dailey, M.E. (2006). Confocal microscopy of living cells. In J. Pawley (Ed.), *Handbook of confocal microscopy, third edition*. New York, USA: Springer Science and Business Media.
- Rinia, H.A., Wurpel, G.W.H., & Müller, M. (2006). Measuring molecular order and orientation using CARS microscopy. In A. Dopico (Ed.), *Protocols in Biophysics to Study Membrane Lipids*. Totowa, NY, USA: Humana Press Inc..
- Rinia, H.A., Wurpel, G.W.H., & Müller, M. (2006). Visualization and characterization of domains in model membranes. In A. Ottova-Tien (Ed.), *Advances in Planar Lipid Bilayers and Liposomes 3* (pp. 85-123). Elsevier.

Invited lectures

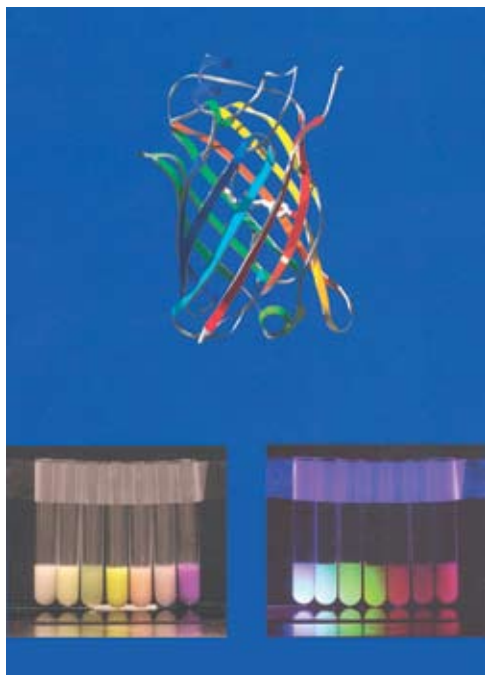
- Amir, W., Gabolde, P., Müller, M., Durfee, C.G., & Squier, J. (2006, mei 21). *Simultaneous visualization of spatial and chromatic aberrations by 2D Spectral Interferometry*. Long Beach, Ca. USA, CLEO/QUELS.
- Blaauwen, T. den, & Alexeeva, S.V. (2006, mei 03). *Time resolved cell division protein interaction by Fluorescence Resonance Energy transfer*. Brussel, Belgie, P5 Network (COBRA, PREVIS, EUR-INTAFAR, PNEUMOPEN, GRACE) pneumococ workshop.
- Blaauwen, T. den (2006, juni 13). *FRET to study protein interactions/What on earth is the Z-ring doing?* Luik, Belgie, EU-INTAFAR meeting.
- Blaauwen, T. den, & Karzmarek, A. (2006, augustus 23). *Is MreB involved in DNA segregation in Escherichia coli?* Copenhagen, Denmark, EMBO workshop.
- Blaauwen, T. den (2006, oktober 13). *Antibiotic resistance: a dead end or a challenge?* Lisbon, Portugal, Medical Chemistry in the 21st century 2006.
- Gadella, Th.W.J., Formiggini, F., Vermeer, J.E.M., Goedhart, J., Kremers, G.J., Munster, E.B. van, Mulder, A.B., Bono, J.-J., & Cullimore, J. (2006, januari 23). *Fluorescence imaging of Nod factor (-receptor) localization and interactions*. Toulouse, France, ANR meeting, CNRS-INRA.
- Gadella, Th.W.J. (2006, maart 23). *FLIM-GFP applications*. Amsterdam, the Netherlands, FRET-FLIM symposium with Lambert Instruments.
- Gadella, Th.W.J. (2006, mei 11). *Cellular fluorescence imaging: FRET, FRAP, FLIM, GFP*. LUMC, Leiden, the Netherlands, EMIL advanced course.
- Gadella, Th.W.J., Goedhart, J., Adjobo Hermans, M.J.W., Vischer, N.O.E., Kremers, G.J., Munster, E.B. van, Schleiffenbaum, A., Schultz, C., & Dhonukshe, P.B. (2006, juni 01). *In vivo dynamics of spindle microtubules and signalling across the membrane*. Ofir, Portugal, ELMC conference.
- Gadella, Th.W.J. (2006, juni 21). *Multiparameter in vivo imaging of cellular signalling*. Wageningen, the Netherlands, EPS summerschool.
- Gadella, Th.W.J. (2006, augustus 14). *Multimode Fluorescence Lifetime Imaging Microscopy (FLIM)*. Buenos Aires, Argentina, EMBO advanced course.
- Gadella, Th.W.J. (2006, september 04). *Multimode Fluorescence Lifetime Imaging Microscopy (FLIM)*. Heidelberg, Germany, Molecular Imaging advanced course.
- Gadella, Th.W.J. (2006, november 21). *FRET-microscopy*. Rotterdam, the Netherlands, OIC advanced course.
- Goedhart, J., Adjobo Hermans, M.J.W., Kremers, G.J., & Gadella, Th.W.J. (2006, januari 13). *Multiparameter imaging of signal transduction across the plasma membrane*. Enschede, the Netherlands, seminar, invited by prof. Subramaniam.
- Goedhart, J., Adjobo Hermans, M.J.W., Kremers, G.J., & Gadella, Th.W.J. (2006, januari 20). *Fluorescence microscopy of sub-cellular signalling*. Institute for Cancer Research, London, UK, Meeting with industry associated with FP6 IP molecular Imaging.
- Goedhart, J., Adjobo Hermans, M.J.W., Kremers, G.J., & Gadella, Th.W.J. (2006, juni 16). *Multiparameter and nanoscale imaging of signalling across the plasma membrane in single living cells*. Amsterdam, the Netherlands, Antoni van Leeuwenhoek symposium.
- Goedhart, J., Adjobo Hermans, M.J.W., Kremers, G.J., & Gadella, Th.W.J. (2006, augustus 14). *Multiparameter and nanoscale imaging of signalling across the plasma membrane in single living cells*. Buenos Aires, Argentina, EMBO advanced course.
- Goedhart, J. (2006, september 04). *Multiparameter imaging of cell signalling*. Heidelberg, Germany, EMBL summer school on MOLECULAR IMAGING.
- Goedhart, J., Adjobo Hermans, M.J.W., Kremers, G.J., & Gadella, Th.W.J. (2006, september 19). *Multiparameter imaging of signalling across the plasma membrane*. London, U.K., Probing the Cancer Cell: New Frontiers in Biological Imaging Meeting.
- Lange, M.J.L. de, Bonn, M., & Müller, M. (2006, oktober 09). *Determining phase boundaries in binary DPPC/Cholesterol mixtures*. Lunteren, the Netherlands, Annual Dutch meeting on Molecular and Cellular Biophysics.
- Manders, E.M.M. (2006, juni 16). *Dealing with phototoxicity in live-cell microscopy*. Amsterdam, Netherlands, Symposium: In the footsteps of Antoni van Leeuwenhoek.
- Manders, E.M.M. (2006, juli 15). *Dealing with phototoxicity in live-cell microscopy*. Berlin, Germany, Intern. symposium: Optical Analysis of Biomolecular Machines.
- Manders, E.M.M. (2006, oktober 02). *Dealing with phototoxicity in live-cell microscopy*. Krakow, Poland, Symposium: Hot Topics in Eucaryotic Transcription.
- Manders, E.M.M. (2006, oktober 25). *Dealing with phototoxicity in live-cell microscopy*. Badhoevedorp, Netherlands, Confocal workshop Nikon.
- Manders, E.M.M. (2006, november 23). *Dealing with phototoxicity in live-cell microscopy*. Rotterdam, Netherlands, Advanced course in Microscopy.
- Müller, M. (2006, mei 25). *Quantitative multiplex CARS micro-/spectroscopy in congested spectral regions*. Whistler, Canada, Coherent Optical Technologies and Applications.
- Rinia, H.A., Bonn, M., Schaffer, C.B., & Müller, M. (2006, oktober 10). *Quantitative measurement of the oxygenation state of Hemoglobin using CARS*. Lunteren, the Netherlands, Annual Dutch meeting on Molecular and

Cellular Biophysics.

Sovago, M., Smits, M., Worpel, G.W.H., Bonn, M., & Müller, M. (2006, oktober 10). *A molecular view of cation-lipid interactions*. Lunteren, the Netherlands, Annual Dutch meeting on Molecular and Cellular Biophysics.

Vartiainen, E.M., Rinia, H.A., Bonn, M., & Müller, M. (2006, maart 09). *Extraction of weak Raman lineshapes from CARS spectra*. Helsinki, Finland, Annual Meeting of the Finnish Physical Society.

Vermeer, J.E.M., Goedhart, J., Munnik, T., & Gadella, Th.W.J. (2006, maart 07). *Polyphosphoinositide dynamics in living plant cells visualized by lipid biosensors*. Lunteren, the Netherlands, NWO-CW Meeting, Lipid and Biomembranes.



Appendix 1g

Plant Physiology

Chairholder: Prof.dr M.A. Haring

Research Results in Numbers

Peer reviewed publications	14
Non-peer reviewed publications	2
PhD Theses	5
Patent applications	0

Staff (Research input in fte during 2006)

Michel Haring	Chairholder
Teun Munnik	Associate Professor
Rob Schuurink	Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	0.5	0.33	0	0.83
Research Fellow	0.75	2.0	2.3	5.1
PhD Student	1.1	0.75	0	1.9
Technician	2.6	0	0	2.6
Total	5.5	3.1	2.3	9.9

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4
Productivity:	3
Relevance:	4
Prospects:	4

Publications

Key Publications

Vermeer, J.E.M., Leeuwen, W. van, Tobena Santamaria, R., Laxalt, A.M., Jones, D.R., Divecha, N., Gadella, Th.W.J., & Munnik, T. (2006). Visualization of PtdIns(3)P dynamics in living plant cells. *Plant J.*, 47, 687-700.

Schuurink, R.C., Haring, M.A., & Clark, D.G. (2006). Regulation of volatile benzenoid biosynthesis in petunia flowers. *Trends Plant Sci.*, 11, 20-25.

PhD Theses

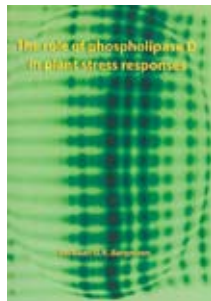
Ament, K. (2006, april 28). *Tomato defense responses induced by spider mites*. UvA Universiteit van Amsterdam (120 pag.). Prom./coprom.: prof. dr. M.A. Haring, & dr.ir. R.C. Schuurink.

Bargmann, B.O.R. (2006, december 12). *The role of phospholipase D in plant stress responses*. UvA Universiteit van Amsterdam (111 pag.). Prom./coprom.: prof. dr. M.A. Haring, & dr. T. Munnik.

Duyvesteyn, R.G.E. (2006, januari 12). *Pathogenicity of Fusarium oxysporum f.sp. lycopersici. Isolation and characterization of genes in the infection proces*. UvA Universiteit van Amsterdam (119 pag.). Prom./coprom.: prof.dr B.J.C. Cornelissen, & prof. dr. M.A. Haring.

Kant, M. (2006, juni 27). *The consequences of herbivore variability for direct and indirect defenses of plants*. UvA Universiteit van Amsterdam (192 pag.). Prom./coprom.: prof. dr. M.A. Haring, prof. dr. M.W. Sabelis, & dr.ir. R.C. Schuurink.

Verdonk, J.C. (2006, maart 14). *Floral scent production by Petunia hybrida*. UvA Universiteit van Amsterdam (120 pag.). Prom./coprom.: prof. dr. M.A. Haring, prof. dr. A.J. van Tunen, & dr.ir. R.C. Schuurink.



Academic publications (refereed)

Ament, K., Schie, C.C.N. van, Bouwmeester, H.J., Haring, M.A., & Schuurink, R.C. (2006). Induction of a leaf specific geranylgeranyl pyrophosphate synthase and emission of (E,E)-4,8,12-trimethyltrideca-1,3,7,11-tetraene in tomato are dependent on both jasmonic acid and salicylic acid signaling pathways. *Planta*, 224, 1197-1208.

Arrighi, J.F., Barre, A., Ben Amor, B., Bersoult, A., Soriano, L.C., Mirabella, R., de Carvalho-Niebel, F., Journet, E.P., Gherardi, M., Huguet, T., Geurts, R., Denarie, J., Rouge, P., & Gough, C. (2006). The Medicago truncatula lysine motif-receptor-like kinase gene family includes NFP and new nodule-expressed genes. *Plant Physiol.*, 142, 265-279.

Bargmann, B.O.R., Laxalt, A.M., Riet, B. ter, Schouten, E., Leeuwen, E. van, Dekker, H.L., Koster, C.G. de, Haring, M., & Munnik, T. (2006). LePLDb1 activation and re-localization in suspension-cultured tomato cells treated with xylanase. *Plant J.*, 45, 358-368.

Bargmann, B.O.R., & Munnik, T. (2006). The role of phospholipase D in plant stress responses. *Current Opinion in Plant Biology*, 9, 515-522.

Cock Buning, M. de, Lammerts van Bueren, E.T., Haring, M.A., Vriend, M.G.A., & Struik, P.C. (2006). 'Cisgenic' as a product designation. *Nat. Biotechnol.*, 24, 1329-1331.

Dhonukshe, P.B., Bargmann, B.O.R., & Gadella, Th.W.J. (2006). *Arabidopsis* Tubulin Folding Cofactor B interacts with alpha tubulin *in vivo*. *Plant Cell Physiol*, 47, 1406-1411.

Ramos-Diaz, A., Brito-Argaez, L., Munnik, T., & Hernandez-Sotomayor, S.M. (2006). Aluminum inhibits phosphatidic acid formation by blocking the phospholipase C pathway. *Planta*, 225(2), 393-401.

Schie, C.C.N. van, Haring, M.A., & Schuurink, R.C. (2006). Regulation of terpenoid and benzenoid production in flowers. *Current Opinion in Plant Biology*, 9, 203-208.

Schooten, B. van, Testerink, C.S., & Munnik, T. (2006). Signalling diacylglycerol pyrophosphate, a new phosphatidic acid metabolite. *Biochim Biophys Acta*, 1761, 151-159.

Schuurink, R.C., Haring, M.A., & Clark, D.G. (2006). Regulation of volatile benzenoid biosynthesis in petunia flowers. *Trends Plant Sci.*, 11(January 1), 20-25.

Tameling, W.I.L., Vossen, J.H., Albrecht, M., Lengauer, T., Berden, J.A., Haring, M.A., Cornelissen, B.J.C., & Takken, F.L.W. (2006). Mutations in the NB-ARC domain of I-2 that impair ATP hydrolysis cause autoactivation. *Plant Physiol.*, 140, 1233-1245.

- Vermeer, J.E.M., Leeuwen, W. van, Tobena Santamaria, R., Laxalt, A.M., Jones, D.R., Divecha, N., Gadella, Th.W.J., & Munnik, T. (2006). Visualization of PtdIns(3)P dynamics in living plant cells. *Plant J.*, 47, 687-700.
- Zonia, L.E., & Munnik, T. (2006). Cracking the green paradigm: Functional coding of phosphoinositide signals in plant stress responses. *Subcell Biochem*, 39, 207-237.
- Zonia, L.E., Müller, M., & Munnik, T. (2006). Hydrodynamics and Cell Volume Oscillations in the Pollen Tube Apical Region are Integral Components of the Biomechanics of *Nicotiana tabacum* Pollen Tube Growth. *Cell Biochem Bioph*, 46(3), 209-232.

Book chapters

- Sabelis, M.W., Takabayashi, J., Janssen, A., Kant, M., Wijk, M. van, Sznajder, B.A., Aratchige, N.S., Lesna, I.K.A., Belliure, B., & Schuurink, R.C. (2006). Ecology meets plant physiology: Herbivore-induced plant responses and their indirect effects on arthropod communities. In T. Ohgushi, T.P. Craig, & P.W. Price (Eds.), *Indirect Interaction Webs: Nontrophic Linkages through Induced Plant Traits*, ed (pp. 188-217-chapter 9). Cambridge, UK: Cambridge University Press.
- Verdonk, J.C., Haring, M.A., Tunen, A.J. van, & Schuurink, R.C. (2006). Targeted Transcriptomics to Elucidate the Regulation of Benzenoid Synthesis in *Petunia hybrida*. In J.A. Teixeira da Silva (Ed.), *Floriculture, Ornamental and Plant Biotechnology: Advances and Topical Issues* (1st Edition, Volume 1) (pp. 326 t/m338-chapter 38). Global Science Books, Ltd.

Invited lectures

- Bargmann, B.O.R. (2006, maart 06). *Phosphatidic acid- Message from the dead*. Lunteren, the Netherlands, NWO-CW Meeting, Lipid and Biomembranes.
- Haring, M.A. (2006, februari 08). *Hybridzucht, CMS-Sorten und Protoplastenfusion*. Plankstetten, Germany, Ökumenischer Gemüsebau-Tag.
- Haring, M.A. (2006, februari 09). *Von Hybridzucht, CMS-Sorten und Protoplastenfusion bis Gentechnik*. Bad Vilbel, Germany, Demeter Seminar Dottenfelderhof.
- Haring, M.A. (2006, april 19). *Regulation of floral scent production as part of the pollination syndrome of Petunia*. Almeria, Spain, Jornadas Polinizacion en plantas Hortícolas.
- Haring, M.A. (2006, april 25). "Omics"-tools in ecological research. Wageningen University, Netherlands, Workshop on Plant-Insect Interactions: From

Molecular Biology to Ecology.

- Haring, M.A., Verdonk, J.C., Moerkercke, A.N.A.I. van, & Schuurink, R.C. (2006, juli 27). *Regulation of floral scent biosynthesis*. Madison (WI), USA, 2nd Solanaceae Genome Workshop.
- Haring, M.A. (2006, september 25). *Hybridzucht und DNA Marker*. Dachau, Germany, Sortentag Bioland/Demeter.
- Haring, M.A. (2006, oktober 05). *Moderne technieken in de plantenveredeling*. Wageningen University, the Netherlands, Studiekring Biologische Landbouw.
- Haring, M.A. (2006, oktober 21). *Hoe kunnen planten ruiken?* Amsterdam, the Netherlands, Open Dag Science Park.
- Munnik, T. (2006, februari 02). *How do lipids signal?* Amsterdam, the Netherlands, Experimental Plant Sciences (EPS) Symposium: Intracellular signaling.
- Munnik, T. (2006, mei 19). *Order and disorder in plant lipid signalling*. Utrecht, the Netherlands, Symposium: Order and Disorder(s) of Cell Lipids.
- Munnik, T. (2006, juli 01). *Lipid signalling in plants*. Santa Maria Imbaro, Italy, Concorzio Mario Negri Sud (CMNC).
- Munnik, T. (2006, september 03). *Water stress signalling*. Oxford, UK, Gordon Research Conference in Salt & Water Stress in Plants.
- Schuurink, R.C. (2006, januari 25). *Mapping hexenal-response mutants with microarrays*. Jena, Germany, Max Planck Institute.
- Schuurink, R.C. (2006, juni 13). *Biosynthesis, regulation and role of volatiles in plants*. Fijnaart, the Netherlands, Rijk Zwaan.
- Schuurink, R.C. (2006, juni 28). *Flavor volatile emission in Amsterdam; sense and sensibility*. Universiteit van Amsterdam, the Netherlands, Amsterdam Platform for Plant Science.
- Schuurink, R.C. (2006, november 02). *A genetic approach to E-2-hexenal responses in Arabidopsis*. Lausanne, Switzerland, University of Lausanne.
- Schuurink, R.C. (2006, december 21). *A genetic approach to E-2-hexenal responses in Arabidopsis*. Göttingen, Germany, University of Göttingen.
- Vermeer, J.E.M., Goedhart, J., Munnik, T., & Gadella, Th.W.J. (2006, maart 07). *Polyphosphoinositide dynamics in living plant cells visualized by lipid biosensors*. Lunteren, the Netherlands, NWO-CW Meeting, Lipid and Biomembranes.
- Vermeer, J.E.M., & Munnik, T. (2006, juli 17). *Visualizing phosphoinositides in living plant cells*. Lyon, France, 15th FESPB.
- Zonia, L.E. (2006, april 03). *Biomechanics of pollen tube growth: Old theories and new hypotheses*. Lunteren, the Netherlands, NWO-ALW Experimental Plant Biology Meeting.

Appendix 1h

Plant-pathogen Interaction

Chairholder: Prof.dr B.J.C. Cornelissen

Research Results in Numbers

Peer reviewed publications	6
Non-peer reviewed publications	3
PhD Theses	1
Patent applications	0

Staff (Research input in fte during 2006)

Ben Cornelissen	Chairholder
Frank Takken	Assistant Professor
Martijn Rep	Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.1	0	0	0.1
Associate/Assistant professor	0.5	0.5	0	1
Research Fellow	0.5	0.9	1.8	3.2
PhD Student	1.7	0.8	0.4	2.9
Technician	1.7	0	1	2.7
Total	4.5	2.2	3.2	10.9

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4
Productivity:	3
Relevance:	4
Prospects:	3/4

Publications

Key Publications

Tameling W.I.L., Vossen J.H., Albrecht M., Lengauer T., Berden J.A., Haring M.A., Cornelissen B.J.C., Takken F.L.W. (2006) Mutations in the NB-ARC domain of I-2 that impair ATP hydrolysis cause autoactivation. *Plant Physiol.* 140: 1233-1245.

Takken F.L.W., Albrecht M., Tameling W.I.L. (2006) Resistance proteins: molecular switches of plant defence. *Curr. Opin. Plant Biol.* 9: 383-390.

PhD Theses

Duyvesteijn, R.G.E. (2006, januari 12). *Pathogenicity of Fusarium oxysporum f.sp. lycopersici. Isolation and characterization of genes in the infection proces.* UvA Universiteit van Amsterdam (119 pag.). Prom./coprom.: prof.dr B.J.C. Cornelissen, & prof. dr. M.A. Haring.

Academic publications (refereed)

Albrecht, M., & Takken, F.L.W. (2006). Update on the domain architectures of NLRs and R proteins. *Biochemical and Biophysical Research Communications*, 339, 459-462.

Gabriels, S.H.E.J., Takken, F.L.W., Vossen, J.H., Jong, C.F. de, Liu, Q., Turk, S.C.H.J., Wachowski, L.K., Peters, J., Witsenboer, H.M.A., Wit, P.J.G.M. de, & Joosten, M.H.A.J. (2006). cDNA-AFLP combined with functional analysis reveals novel genes involved in the hypersensitive response. *Mol. Plant-Microbe Interact.*, 19, 567-576.

Loon, L.C. van, Rep, M., & Pieterse, C. (2006). Significance of inducible defense-related proteins in infected plants. *Annu. Rev. Phytopathology*, 44, 7.1-7.28.

Rep, M., Duyvesteijn, R.G.E., Gale, L., Usgaard, T., Cornelissen, B.J.C., Ma, L.J., & Ward, T.J. (2006). The presence of GC-AG introns in *N. crassa* and other euscomycetes determined from analyses of complete genomes: implications for automated gene prediction. *GENOMICS*, 87, 338-347.

Takken, F.L.W., Albrecht, M., & Tameling, W.I.L. (2006). Resistance proteins: molecular switches of plant defence. *Curr. Opin. Plant Biol.*, 9, 383-390.

Tameling, W.I.L., Vossen, J.H., Albrecht, M., Lengauer, T., Berden, J.A., Haring, M.A., Cornelissen, B.J.C., & Takken, F.L.W. (2006). Mutations in the NB-ARC domain of I-2 that impair ATP hydrolysis cause autoactivation. *Plant Physiol.*, 140, 1233-1245.

Book chapters

- Kehr, J., & Rep, M. (2006). Protein extraction from xylem and phloem sap Plant Proteomics: Methods and Protocols. In V. Mechin, C. Damerval, M. Zivy, & H. Thiellement (Eds.), *Methods in Molecular Biology* (355) (pp. 27-36). Humana press.
- Rep, M., Does, H.C. van der, Meijer, M., Houterman, P.M., Dekker, H.L., Speijer, D., Koster, C.G. de, & Cornelissen, B.J.C. (2006). Secrets of xylem colonization- The xylem sap proteome of tomato infected with *Fusarium oxysporum* IS-MPM1. In C.. Quinto, S. Lopes-Lara Sanchez, & O. Geiger (Eds.), *Biology of Plant-Microbe Interactions* Vol. 5, 597-601.
- Takken, F.L.W., Tameling, W.I.L., Vossen, J.H., Albrecht, M., Berden, J.A., Ooijen, G. van, & Cornelissen, B.J.C. (2006). The NB-ARC domain of R proteins acts as a molecular switch regulating plant innate immunity. In Quinto, C. López-Lara Sánchez, S & Geiger, O. (Eds.), *Biology of Plant-Microbe Interactions* Vol. 5, p 225-230.

Invited lectures

- Rep, M. (2006, juni 06). *Virulence of Fusarium Oxysporum: host-and cultivar specificity*. Dijon, France, workshop Fusarium oxysporum.
- Rep, M. (2006, augustus 20). *The mixed the proteome of Fusarium oxysporum-infected tomato xylem vessels*. Cairns, Australia, Eighth International Mycological Congress.
- Takken, F.L.W. (2006, februari 02). *Innate immune receptors in plants and animals; do analogous modules have comparable functions?* UvA, Amsterdam, The Netherlands, EPS Symposium Intracellular signalling.
- Takken, F.L.W., Tameling, W.I.L., Albrecht, M., Ooijen, G. van, Vroomen, M.J. de, Vries, K.J. de, & Cornelissen, B.J.C. (2006, augustus 13). *R proteins, molecular switches of plant defence*. Copenhagen, Denmark, 8th Conference of the European Foundation for Plant Pathology & British Society of Plant Pathology Presidential Meeting.
- Takken, F.L.W. (2006, november 27). *The NB-ARC domain: an NTP-hydrolysing molecular switch*. New York, USA, Comparative Biology of Innate Immune Systems.

Appendix 1i**Animal Physiology and Cognitive Neuroscience***Chairholder:* Prof.dr C.M.A. Pennartz**Research Results in Numbers**

Peer reviewed publications	13
Non-peer reviewed publications	1
PhD Theses	1
Patent applications	0

Staff

Cyriel Pennartz	Chairholder
Guilen Fernandez	Honorary Professor (bijzonder hoogleraar)
Bruce McNaughton	Honorary SILS-CNS Professor (bijzonder hoogleraar)
Wim Ghijsen	Assistant Professor
Sander Daselaar	Assistant Professor
Francesco Battaglia	Assistant Professor

(Research input in fte during 2006)

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	1.5	0	0	1.5
Research Fellow	0	0.23	0.9	1.1
PhD Student	2.4	0.75	0.96	4.1
Technician	1.6	0	0	1.6
Total	6.0	1.0	1.9	8.9

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4
Productivity:	3/4
Relevance:	4
Prospects:	4

Publications

Key Publications

Lansink, C.S., Bakker, M., Buster, W., Lankelma, J., van der Blom, R., Westdorp, R., Joosten, N.J.M.A., McNaughton, B.L., & Pennartz, C.M.A. (2006) A split microdrive for simultaneous multi-electrode recordings from two brain areas in awake small animals. *J. Neurosci. Meth.* [Epub ahead of print].

McNaughton, B.L., Battaglia, F.P., Jensen, O., Moser, E.I., & Moser, M.B. (2006) Path-integration and the neural basis of the 'cognitive map' *Nature Reviews Neuroscience* 7: 663-678.

Ghijsen, W.E.J.M., Zuiderwijk, M., & Lopes da Silva, F.H. (2006) Electrically evoked GABA release in rat hippocampus CA1 region and its changes during kindling epileptogenesis. *Brain Research* 69-76.

PhD Theses

Nordquist, R.E. (2006, maart 09). *Corticostriatal systems and learning: changes induced by drug sensitization*. VU. Prom./coprom.: prof. dr. C.M.A. Pennartz.

Academic publications (refereed)

Daselaar, S.M., Fleck, M.S., Dobbins, I.G., Madden, D.J., & Cabeza, R. (2006). Effects of Healthy Aging on Hippocampal and Rhinal Memory Functions: An Event-Related fMRI Study. *Cerebral Cortex*, 1-12.

Daselaar, S.M., Fleck, M.S., Prince, S.E., & Cabeza, R. (2006). The medial temporal lobe distinguishes old from new independently of consciousness. *J. Neurosci.*, 26(21), 5838-5839.

Daselaar, S.M., Fleck, M.S., & Cabeza, R. (2006). Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J. Neurophysiol.*, 96, 1902-1911.

Dennis, N.A., Daselaar, S.M., & Cabeza, R. (2006). Effects of aging on transient and sustained successful memory encoding activity. *Neurobiol. Aging*.

Fleck, M.S., Daselaar, S.M., Dobbins, I.G., & Cabeza, R. (2006). Role of prefrontal and anterior cingulate regions in decision-making processes shared by memory and nonmemory tasks. *Cerebral Cortex*, 16, 1623-1630.

Ghijsen, W.E.J.M., Zuiderwijk, M., & Lopes da Silva, F.H. (2006). Electrically evoked GABA release in rat hippocampus CA1 region and its changes during

kindling epileptogenesis. *Brain Research*, 69-76.

Gorter, J.A., Vliet, E.A. van, Rauwerda, H., Breit, T.M., Stad, R., Schaik, L. van, Vreugdenhil, E., Redeker, S., Hendriksen, E., Aronica, E., Lopes da Silva, F.H., & Wadman, W.J. (2006). Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and entorhinal cortex during epileptogenesis in the rat *J. Epilepsia*.

Gorter, J.A., Vliet, E.A. van, Aronica, E., Breit, T.M., Rauwerda, J., Lopes da Silva, F.H., & Wadman, W.J. (2006). Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. *Journal of Neuroscience*, 26(43), 11083-11110.

Gothard, K.M., Battaglia, F.P., Erickson, C.A., Spitler, K.M. & Amaral, D.G. (2006) Neural Responses to Facial Expression and Face Identity in the Monkey Amygdala. *J Neurophysiol.* Nov 8; [Epub ahead of print].

Kalenscher, T., Ohmann, T., Windmann, S., Freund, N., & Gunturkun, O (2006). Single forebrain neurons represent interval timing and reward amount during response scheduling. *Eur. J. Neurosci.*, 24, 2923-2931.

Kalenscher, T., Ohmann, T., & Gunturkun, O (2006). The neuroscience of impulsive and self-controlled decisions. *Int. J. Psychophysiol.*, 62, 203-211.

McNaughton, B.L., Battaglia, F.P., Jensen, O., Moser, E.I., & Moser, M.B (2006). Path integration and the neural basis of the 'cognitive map'. *Nature Reviews Neuroscience*, 7, 663-678.

Oldenziel, W.H., van der Zeyden, M., Dijkstra, G., Ghijsen, W.E., Karst, H., Cremers, T.I. & Westerink B.H. (2006) Monitoring extracellular glutamate in hippocampal slices with a microsensor. *J Neurosci Methods*. Sep 15, [Epub ahead of print].

Book chapters

Daselaar, S.M., Browndyke, J., & Cabeza, R. (2006). Functional neuroimaging of cognitive aging. In Kingstone.A. Cabeza R (Ed.), *Handbook of functional neuroimaging of cognition*. Massachusetts: MIT Press.

Invited lectures

Battaglia, F.P. (2006, july 11). *Mathematical aspects of brain functions. Compositionality and Synchronization*. Rome, workshop at the Accademia dei Lincei.

Daselaar, S., (2006, Oct). *The neural correlates of memory formation, consolidation, and recollection: a functional MRI investigation* Seminar at the Amsterdam Academical Medical Centre, Dept of Radiology.

Appendix 1j

Cellular and Systems Neurobiology

Chairholder: Prof.dr W.J. Wadman

Research Results in Numbers

Peer reviewed publications	31
Non-peer reviewed publications	0
PhD Theses	2
Patent applications	0

Staff

Wytse Wadman
 Fernando Lopes da Silva
 Chris Kruse
 Rob Aalberse
 Hans van Hooft
 Jan Gorter
 Taco Werkman

(Research input in fte during 2006)

Chairholder
 Emeritus Professor
 Honorary Professor (bijzonder hoogleraar)
 Honorary Professor (bijzonder hoogleraar)
 Assistant Professor
 Assistant Professor
 Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	1	0	0.5	1.5
Research Fellow	0.45	0.8	0.23	1.5
PhD Student	0.44	0	0.75	1.2
Technician	0.5	0	1	1.5
Total	2.9	0.8	2.5	6.2

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality: 4/5
 Productivity: 4
 Relevance: 4/5
 Prospects: 4

- Kalenscher, T. (2006,). *A bird in the hand is worth two in the future, or the role of the avian prefrontal cortex in decision making*. Amsterdam, presentation on invitation by A. Heimerl at the NIN.
- Kalenscher, T. (2006, july 12). *A bird in the hand is worth two in the future, or the role of the avian prefrontal cortex in decision making*. Dortmund, Germany, presentation on invitation by Patrick Gajewski.
- Kalenscher, T., Windmann, S., & Pennartz, C.M.A. (2006, oktober 17). *Intertemporal decisions are economically irrational: A neuroeconomical account*. Atlanta USA, Posterpresentation at the meeting of the society for neuroscience SfN.
- Lansink, C. (2006, june). *Replay of reward-related information in the rat ventral striatum*. EndoNeuroPsycho Meeting of the Netherlands Federation for Neuroscience, Doorwerth.
- Pennartz, C.M.A. (2006, march 22). *Tetrode recordings in freely behaving mice and the behavioral screening of recombinant inbred mouse strains for detection of learning abnormalities*. Noordwijk, NeuroBSIK symposium.
- Pennartz, C.M.A. (2006, june 07). *Functions of oscillatory activity and neural synchrony in information processing*. Doorwerth, EndoNeuroPsycho Meeting of the Netherlands Federation for Neuroscience.
- Pennartz, C.M.A. (2006, june 20). *Networks for associative memory: from models to experiments*. Amsterdam, presentation on invitation by the Vrije Universiteit in Amsterdam.
- Ghijsen, W.E.J.M. (2006, oktober 03). *Sense and nonsense of genetic predisposition for depression*. Amsterdam, lecture in the Disciplinary Honours Lecture series of the UvA.

Other results

Pennartz, C.M.A. (2006). Development of a miniaturized, multi-channel recording system with wireless data transmission: new and versatile instrumentation for cognitive and physiological research in freely moving animals. Grant from the Foundation for Technology & Science (STW), Principal Applicant.: Utrecht.

Organizer of Symposium "Sleep and rest: the role of off-line processing in cognition" at the National Dutch Meeting for Endocrinology, Neuroscience and Psychology (June 2006).

Publications

Key Publications

- Gorter, J.A., Vliet, E.A. van, Aronica, E., Breit, T.M., Rauwerda, J., Lopes da Silva, F.H., & Wadman, W.J. (2006). Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. *J. Neurosci.*, 26(43), 11083-11110.
- Kager, J., Wadman, W.J., & Somjen, G.G. (2006). Seizure-like afterdischarges simulated in a model neuron. *Journal Comput Neurosci.* epub10.1007/s10827-006-0001-y.
- Vliet E.A. van, da Costa Araújo S, Redeker S, Aronica EA, Gorter JA. (2006). Long-lasting increased permeability of the blood-brain barrier during progression of epilepsy. *Brain*: Epub 2006 Nov 22.
- Welie, I. van, Remme, M.W.H., Hooft, J.A. van, & Wadman, W.J. (2006). Different levels of Ih determine distinct temporal integration in bursting and regular-spiking neurons in rat subiculum. *Journal of Physiology*, 203-214.
- Werkman, T.R., Glennon, J.C., Wadman, W.J., & McCreary, A.C. (2006). Dopamine receptor pharmacology: interactions with serotonin receptors and significance for the aetiology and treatment of schizophrenia. *CNS & neurological disorders drug targets*, 5(1), 3-23.

PhD Theses

- Olijslagers, J.E. (2006, januari 26). *Serotonergic modulation of dopamine and GABA inputs to A9 and A10 dopamine neurons and its role in antipsychotic drug efficacy*. UvA Universiteit van Amsterdam (160 pag.) (Amsterdam). Prom./coprom.: prof.dr W.J. Wadman, prof.dr C.G. Kruse, & dr T.R. Werkman.
- Remme, M.W.H. (2006, mei 30). *Scaling of excitability in neurons and networks*. UvA Universiteit van Amsterdam (144 pag.) (Wageningen: Ponsen & Looyen b.v.). Prom./coprom.: prof.dr W.J. Wadman.



Academic publications (refereed)

- Aronica, E., Boer, K., Redeker, S., Spliet, W. G., van Rijen, P. C., Troost, D. & Gorter, J. A. (2006) Differential expression patterns of chloride transporters, Na⁽⁺⁾-K⁽⁺⁾-2Cl⁽⁻⁾-cotransporter and K⁽⁺⁾-Cl⁽⁻⁾-cotransporter, in epilepsy-associated malformations of cortical development. *Neuroscience*, Epub.
- Alpherts, W.C., Vermeulen, J., van Rijen, P.C., Lopes da Silva, F.H., van Veelen, C.W. (2006) Dutch Collaborative Epilepsy Surgery Program. Verbal memory decline after temporal epilepsy surgery? A 6-year multiple assessments follow-up study. *Neurology*, 67(4), 626-31.
- Chameau, P.J.P., & Hooft, J.A. van (2006). Serotonin 5-HT(3) receptors in the central nervous system. *Cell Tissue Res.*, 326(2), 573-581.
- Dedeurwaerdere, S, Vonck, K, Herdt, V de, Waterschoot, L., Smedt, T, Raedt, R, Wyckhuys, T, Legros, B., Hese, P. van, Laere, K., Delbeke, J., Wadman, W.J., & Boon, P. (2006). Neuromodulation with levetiracetam and vagus nerve stimulation in experimental animal models of epilepsy. *Acta Neurol. Belg.*, 106(2), 91-97.
- Goncalves, S.I., de Munck, J.C., Pouwels, P.J., Schoonhoven, R., Kuijter, J.P., Maurits, N.M., Hoogduin, J.M., Van Someren, E.J., Heethaar, R.M., Lopes da Silva, F.H.. (2006) Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: inter-subject variability. *Neuroimage*. 2006 30(1), 203-13.
- Gorter, J.A., Vliet, E.A. van, Rauwerda, H., Breit, T.M., Stad, R., Schaik, L., Vreugdenhil, E., Redeker, S, Hendriksen, E., Aronica, E., Lopes da Silva, F.H., & Wadman, W.J. (2006). Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and entorhinal cortex during epileptogenesis in the rat *Journal. Epilepsia*.
- Gorter, J.A., Vliet, E.A. van, Aronica, E., Breit, T.M., Rauwerda, J., Lopes da Silva, F.H., & Wadman, W.J. (2006). Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. *J. Neurosci.*, 26(43), 11083-11110.
- Hirsch, E., Andermann, F., Chauvel, P., Engel, J., Lopes da Silva, F., Luders, H. (2006) Generalized Seizures: From clinical phenomenology to underlying systems and networks, *Progress in Epilepsy Disorders*, John Libbey Eurotext
- Kager, J., Wadman, W.J., & Somjen, G.G. (2006). Seizure-like afterdischarges simulated in a model neuron. *Journal Comput Neurosci.* epub10.1007/s10827-006-0001-y
- Lopes da Silva, F.H. (2006) Event-related neural activities: what about phase? *Prog Brain Res.* 159, 3-17.
- Olijslagers, J.E., Werkman, T.R., McCreary, A.C., Kruse, C.G., & Wadman, W.J. (2006). Modulation of Midbrain Dopamine Neurotransmission by Serotonin,

- a Versatile Interaction Between Neurotransmitters and Significance for Antipsychotic Drug Action. *Current Neuropharmacology*, 4, 59-68.
- Ozbas-Gerceker, F., Redeker, S., Boer, K., Ozguc, M., Saygi, S., Dalkara, T., Soylemezoglu, F., Akalan, N., Baayen, J.C., Gorter, J.A., & Aronica, E. (2006). Serial analysis of gene expression in the hippocampus of patients with mesial temporal lobe epilepsy. *Neuroscience*, 138(2), 457-474.
- Suffczynski, P., Lopes da Silva, F.H., Parra, J., Velis, D.N., Bouwman, B.M., van Rijn, C.M., van Hese, P., Boon, P., Khosravani, H., Derchansky, M., Carlen, P. & Kalitzin, S. (2006) Dynamics of epileptic phenomena determined from statistics of ictal transitions. *IEEE Trans Biomed Eng.* 2006 3(3), 524-32.
- Pfurtscheller, G., Brunner, C., Schlogl, A. & Lopes da Silva, F.H. (2006) Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks. *Neuroimage*. 31(1), 153-9.
- Stefan, H., Lopes da Silva, F.H., Loscher, W., Schmidt, D., Perucca, E., Brodie, M.J., Boon, P.A., Theodore, W.H. & Moshe, S.L. (2006) Epileptogenesis and rational therapeutic strategies. *Acta Neurol Scand.* 113(3), 139-55.
- Sun, G.C., Werkman, T.R., & Wadman, W.J. (2006). Kinetic changes and modulation by carbamazepine on voltage-gated sodium channels in rat CA1 neurons after epilepsy. *Acta Pharmacologica Sinica*, 27(12), 1537-1546.
- Sun, G.C., Werkman T.R., Battefeld A., Clare J.J. & Wadman W.J. (2006). Carbamazepine and Topiramate modulation of transient and persistent sodium currents studied in HEK293 cells expressing the Na_v1.3 α -subunit. *Epilepsia*
- Theuvenet PJ, van Dijk BW, Peters MJ, van Ree JM, Lopes da Silva FL, Chen AC. (2006) Cortical characterization and inter-dipole distance between unilateral median versus ulnar nerve stimulation of both hands in MEG. *Brain Topogr.* 2006, 19(1-2), 29-42.
- Vliet, E.A. van, & Gorter, J.A. (2006). De rol van multidrug transporters in farmacoresistente epilepsie. *Epilepsie, periodiek voor professionals*, 4(4), 10-12.
- Vliet, E.A. van, Schaik, R. van, Edelbroek, P.M., Redeker, A.M.J., Aronica, E.M.A., Wadman, W.J., Marchi, N. De, Vezzani, A., & Gorter, J.A. (2006). Inhibition of the multidrug transporter P-glycoprotein improves seizure control in phenytoin-treated chronic epileptic rats. *Epilepsia*, 47(4), 672-680.
- Vliet E.A. van, da Costa Araújo S, Redeker S, Aronica EA, Gorter JA. (2006). Long-lasting increased permeability of the blood-brain barrier during progression of epilepsy. *Brain*: Epub 2006 Nov 22.
- Welie, I. van, Hooft, J.A. van, & Wadman, W.J. (2006). Background activity regulates excitability of rat hippocampal CA1 pyramidal neurons by adaptation of a K⁺ conductance. *J Neurophysiol.*, 95(3), 2007-2012.
- Welie, I. van, Remme, M.W.H., Hooft, J.A. van, & Wadman, W.J. (2006). Different levels of I_h determine distinct temporal integration in bursting and regular-spiking neurons in rat subiculum. *Journal of Physiology*, 203-214.
- Werkman, T.R., Glennon, J.C., Wadman, W.J., & McCreary, A.C. (2006). Dopamine receptor pharmacology: interactions with serotonin receptors and significance for the aetiology and treatment of schizophrenia. *CNS & neurological disorders drug targets*, 5(1), 3-23.
- Westerink, R.H. (2006). Dopaminergic Neurotransmission. *CNS & neurological disorders drug targets*, 5(1), 1-3.
- Westerink, R.H. (2006). Targeting exocytosis: ins and outs of the modulation of quantal dopamine release. *CNS & neurological disorders drug targets*, 5(1):57-77.
- Westerink, R.H., Rook, M.B., Beekwilder, J.P., & Wadman, W.J. (2006). Dual role of calbindin-D in vesicular catecholamine release from mouse chromaffin cells. *Journal of Neurochemistry*, 99(2), 628-640.
- Wijk, M. van, Wadman, W.J., & Sabelis, M.W. (2006). Morphology of the olfactory system in the predatory mite Phytoseiulus Persimilis. *Exp. Appl. Acarol*, 40(3), 217-229.
- Wijk, M. van, Wadman, W.J., & Sabelis, M.W. (2006). Gross morphology of the central nervous system of a phytoseiid mite. *Exp Appl Acarol.* 40(3-4), 205-16.
- Witter, M., Kloosterman, F., Lopes da Silva, F.H., French, S. (2006) The Subiculum: the End of the Trisynaptic Pathway or the Heart of the Hippocampal Formation? In: The Subiculum comes of age Liset Menendez de la Prida, Susan Totterdell, John Gigg, and Richard Miles (Eds), *Hippocampus* 16, 916-923.
- Wyckhuys, T., Smedt, T. de, Claey, P., Raedt, R., Waterschoot, L., Vonck, K., van den Broecke, C., Mabilde, C., Leybaert, L., Wadman, W.J. & Boon, P. (2006) High Frequency Deep Brain Stimulation in the Hippocampus modifies seizure characteristics in kindled rats. *Epilepsia*.

Invited lectures

- Lopes da Silva, F.H. (2006, Feb 17), Workshop on Generalized Seizures: *from clinical phenomenology to underlying systems and networks*, Rome
- Wadman, W.J. (2006, Feb 28). *Homeostatic scaling of excitability in neurons: experiments and theory*. MPI, Tubingen, Duitsland
- Wadman, W.J. (2006, mar 06). *Functional deep brain stimulation for the control of epilepsy*. EWBR, Villard, Switzerland.
- Wadman, W.J. (2006, mar 15). *What does my research mean for Systems Biology?* Arena, Amsterdam SILS Research Day.
- Wadman, W.J. (2006, Apr 04). *Functional Deep Brain Stimulation for epilepsy control?* SILS-CNS, Amsterdam.

- Vliet, E.A. van (2006, Apr 10). *Permeability of the blood brain barrier during progression of epilepsy*. Heemstede, voordracht bij de wetenschappelijke raad van het SEIN in Heemstede.
- Wadman, W.J. (2006, Apr 11). *Redistribution of LVA Activated Currents in Dendrites of CA1 Pyramidal Cells* Dept of Neurology, Ghent, Belgie.
- Wadman, W.J. (2006, Apr 20). *Ionic channels in epilepsy: basic mechanisms and targets for treatment* ONWA Course on Epilepsy, Amsterdam.
- Lopes da Silva, F.H. (2006 Apr. 20), *Neurobiology of Epileptogenesis: the TLE syndrome*, EUREPA Spring Course, Lamego.
- Lopes da Silva, F.H. (2006, Apr 26) *Les signaux du cerveau*, Fondation Gulbenkian, Paris.
- Vliet, E.A. van (2006, juni 07). *Inhibition of multidrug transporters improves seizure control in an experimental model of temporal lobe epilepsy*. Doorwerth, lezing bij de Endo-neuro-psychometing.
- Vliet, E.A. van (2006, juni 08). *Blood brain barrier permeability during epileptogenesis*. Amsterdam, voordracht van de Master Class samen met Tally Baram.
- Remme, M. (2006, june 8) *Homeostatic scaling of excitability in neurons and networks*. Amsterdam, voordracht van de Master Class samen met Tally Baram.
- Wadman, W.J. (2006, July 04). *Basic mechanism of Deep Brain Stimulation: what is really known?* Helsinki, lezing bij het 7th European Congress on Epileptology, Helsinki, Finland.
- Wadman, W.J. (2006, Sept.05). *EM-velden en het brein*. Gemeenteraad Amsterdam, Amsterdam.
- Wadman, W.J. (2006, Sept.07). *From neuronal membrane to neuronal network*. SILS Systems Biology Lectures, Amsterdam.
- Vliet, E.A. van (2006, juli 05). *Long-lasting increased permeability of the blood-brain barrier during progression of epilepsy*. Helsinki, lezing bij het 7th European Congress on Epileptology, Helsinki, Finland.
- Gorter, J.A. (2006, july 06) *Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and temporal lobe during epileptogenesis in the rat*. 7th European Congress on Epileptology.
- Werkman, T.R. (2006, july 12). *Electrophysiology at the cellular and network level: assessment of the effect of endocannabinoids alone and in behavioural paradigms*. Weesp, lezing bij Top Institute Pharma" (TIP) bijeenkomst bij het bedrijf Solvay Pharmaceuticals.
- Wadman, W.J. (2006, Nov 02). *Basics in NeuroScience*. Philips Research, Eindhoven.
- Wadman, W.J. (2006, Nov 08). *Ion channels and excitability*. Philips Research, Eindhoven.
- Wadman, W.J. (2006, Nov 11). *Acute modulation of unit firing by deep brain stimulation in the human hippocampus*. Neuro Belgium, Brussel, Belgie
- Wadman, W.J. (2006, Nov 23). *Neuronal Networks and signal Integration*. Philips Research, Eindhoven.
- Vliet, E.A. van (2006, november 25). *Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy*. Zeist, 13th PhD Annual Meeting van de ONWA.
- Werkman, T.R. (2006, Nov 29). *Deep brain stimulation: application in Parkinson.s disease*. Philips Research, Eindhoven.
- Gorter, J.A. (2006, dec 08) *Complement activation in experimental and human temporal lobe epilepsy*. Proceedings of the American Epilepsy Society San Diego.
- Gorter, J.A. (2006, dec 22) *Epilepsy research in animal models*. Utrecht SWO meeting.

Other results

- Vliet, E.A. van (2006). Long-lasting increased permeability of the blood-brain barrier during progression of epilepsy. Uitreiking van Young Investigator Award tijdens het 7th European Congress on Epileptology, Helsinki, Finland (2006, juli 05).
- Vliet, E.A. van (2006). Oral presentation award. 13th PhD Annual Meeting van de ONWA: Zeist.



Appendix 1k

Hormonal Regulation of Signal Transduction in the Brain

Chairholder: Prof.dr M. Joëls

Research Results in Numbers

Peer reviewed publications	16
Non-peer reviewed publications	0
PhD Theses	2
Patent applications	0

Staff	(Research input in fte during 2006)
Marian Joëls	Chairholder
Jannie Borst	Honorary Professor (bijzonder hoogleraar)
Melly Oitzl	Honorary Professor (bijzonder hoogleraar)
Paul Lucassen	Assistant Professor
Harm Krugers	Assistant Professor
Henk Karst	Researcher

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	1	0	0	1
Research Fellow/Researcher	1	0.9	0	1.9
PhD Student	1.5	1.5	0.9	3.9
Technician	1.6	0	1	2.6
Total	5.6	2.4	1.9	9.9

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4/5
Productivity:	3/4
Relevance:	4/5
Prospects:	4/5

Publications

Key Publications

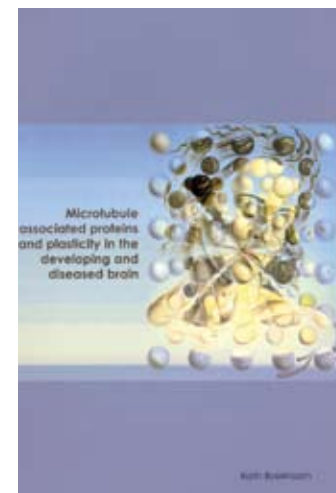
Boekhoorn, K., Terwel, D., Biemans, B., Borghgraef, P., Wiegert, O., Ramakers, G.J., Vos, K. de, Krugers, H., Tomiyama, T., Mori, H., Joëls, M., Leuven, .F, van & Lucassen, P.J. (2006). Improved long-term potentiation and memory in young tau-P301L transgenic mice before onset of hyperphosphorylation and tauopathy. *J Neurosci.*, 26(13):3514-3523.

Joëls, M., Pu, Z., Wiegert, O., Oitzl, M.S., & Krugers, H.J.. (2006). Learning under stress: how does it work? *Trends Cogn Sci.*, 10(4):152-158.

PhD Theses

Alfarez, D.N. (2006, maart 03). *The effects of stress and corticosterone on synaptic plasticity and neuronal morphology in the rodent hippocampus*. UvA Universiteit van Amsterdam (130 pag.) (Utrecht: DPP). Prom./coprom.: prof. dr M. Joels, & dr. H. Krugers.

Boekhoorn, K. (2006, september 26). *Microtubules associated proteins and plasticity in the developing and diseased brain*. UvA Universiteit van Amsterdam (236 pag.). Prom./coprom.: prof.dr M. Joels, & dr P.J. Lucassen.



Academic publications (refereed)

- Alfarez, D.N., Wiegert, O., & Krugers, H. (2006). Stress, corticosteroid hormones and hippocampal synaptic function. *CNS & neurological disorders drug targets*, 5(5), 521-529.
- Boekhoorn, K., Terwel, D., Biemans, B., Borghgraef, P., Wiegert, O., Ramakers, G.J.A., Vos, K. de, Krugers, H., Tomiyama, T., Mori, H., Joels, M., Leuven, F. van, & Lucassen, P.J. (2006). Improved long-term potentiation and memory in young tau-P301L transgenic mice before onset of hyperphosphorylation and tauopathy. *J. Neurosci.*, 26(13), 3514-3523.
- Boekhoorn, K., Joels, M., & Lucassen, P.J. (2006). Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the presenile Alzheimer hippocampus. *Neurobiology of Diseases*, 24, 1-14.
- Gemert, N.G. van, Meijer, O.C., Morsink, M.C., & Joels, M. (2006). Effect of brief corticosterone administration on SGK1 and RGS4 mRNA expression in rat hippocampus. *Stress*, 9(3), 165-170.
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- Lucassen, P.J., Heine, V.M., Beek, E. van der, Wiegant, V., Kloet, E.R. de, Joels, M., Fuchs, E., Swaab, D.F., & Czeh, B. (2006). Stress, Depression and Hippocampal Apoptosis. *CNS & neurological disorders drug targets*, 5(5), 531-546.
- Mayer, J., Klumpers, L., Maslam, S., Kloet, E.R. de, Joels, M., & Lucassen, P.J. (2006). Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the corticosterone-induced reduction of adult

- hippocampal neurogenesis. *J Neuroendocrinol*, 18, 1-3.
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- Wiegert, O., Joels, M., & Krugers, H. (2006). Timing is essential for rapid effects of corticosterone on synaptic potentiation in the mouse hippocampus. *Learning & Memory*, 13, 110-113.

Invited lectures

- Joels, M. (2006, maart 24). *Learning under stress: Emerging from a jumble*. Nijmegen, voordracht geven bij het FC Donders Institute, gast van Prof. Hagoort.
- Joels, M. (2006, maart 29). *Rapid and slow modulation of hippocampal synaptic potentials by corticosteroid hormones*. Lausanne, Zwitserland, voordracht bij EPFL op uitnodiging van Prof.dr. C.Sandi.
- Joels, M. (2006, juni 01). *Genomic and non genomic actions of corticosteroids*. Oegstgeest, voordracht geven bij 7th Tausk workshop.
- Joels, M. (2006, juni 07). *Corticosteroid as a two-staged rocket*. Doorwerth, voordracht geven bij de 5th ENP meeting.
- Joels, M. (2006, juli 12). *Effect of chronic stress on neurogenesis and physiology in rat: Normalization by GR antagonists?* Chicago, USA, voordracht geven bij 26th CINP.
- Joels, M. (2006, juli 13). *After chronic stress: Living with a different brain*. Chicago, USA, voordracht geven op uitnodiging van Prof.dr. R. Cohen van de University of Illinois.
- Joels, M. (2006, juli 14). *Stress and Learning: A Matter of Timing*. Chicago, USA, voordracht geven op uitnodiging van : Prof.dr. J. Disterhoft van de Northwestern University.
- Joels, M. (2006, augustus 26). *One hormone, one receptor, two effects: Genomic and non-genomic actions via the mineralocorticoid receptor*. Leiden, voordracht geven bij de 37th ISPNE Meeting.

- Joels, M. (2006, augustus 28). *Stress-induced changes in hippocampal function*. Amsterdam, voordracht geven bij KNAW Colloquium on PTSD.
- Joels, M. (2006, oktober 17). *Effects of Corticosteroids on Hippocampal Excitability: From Minutes to Hours*. Atlanta, USA, voordracht gegeven bij de Society for Neuroscience Meeting.
- Joels, M. (2006, december 08). *Stress en Leren: Hoe werkt het?* Amsterdam, voordracht gegeven bij het Committee Cognition, KNAW.
- Krugers, H. (2006, januari 24). *Corticosteroid modulation of hippocampal synaptic efficacy: receptors on the move?* Academic Medical Center, University of Amsterdam, voordracht op uitnodiging.
- Krugers, H. (2006, februari 27). *The yin and yang of corticosteroid hormones: modulation of learning and memory and synaptic efficacy*. Groningen, BCN lecture Dept Biological Psychiatry, RU Groningen.
- Krugers, H. (2006, april 10). *Corticosteroid hormones and synaptic efficacy: good guys or bad guys?* Nijmegen, voordracht geven op uitnodiging.
- Krugers, H. (2006, mei 23). *Traumatische herinneringen in een reageerbuis*. Amsterdam, voordracht geven bij Bessensap 2006, georganiseerd door NEMO.
- Krugers, H. (2009, september 29). *Corticosteroid modulation of AMPA receptor localization*. Haren, voordracht geven op uitnodiging van het Biological Centre of the University of Groningen.
- Lucassen, P.J. (2006, januari 16). *Neurogenesis and stem cells in the adult brain*. Groningen, lezing bij Department of Medical Physiology, University Medical Centre Groningen.
- Lucassen, P.J. (2006, januari 20). *Alzheimer's disease; the state-of-affairs*. Lunteren, NIBI meeting on The Biology of Memory.
- Lucassen, P.J. (2006, mei 19). *Doublecortin-like, a novel microtubule associated protein expressed in radial glia is crucial for neuronal precursor division and radial process stability during early corticogenesis*. Doorwerth, Neuronal Developmental Disorders meeting.
- Lucassen, P.J. (2006, juni 26). *Structural plasticity in relation to stress and depression*. Bristol England, lezing bij The University of Bristol, United Kingdom.
- Lucassen, P.J. (2006, juli 09). *Structural hippocampal plasticity in relation to stress and depression*. Wenen Oostenrijk, FENS meeting.
- Lucassen, P.J. (2006, september 04). *Structural plasticity and adult neurogenesis in relation to stress and dementia*. Chiemfausee, Duitsland, the Route 28 Summit in Neurobiology.
- Lucassen, P.J. (2006, september 27). *Increases in LTP and learning but not neurogenesis in young P301L tau mutant mice*. Leiden, ISPNE meeting.
- Lucassen, P.J. (2006, september 29). *Structural plasticity in the adult brain in relation to stress and disease*. Groningen, lezing bij Department of Molecular Neurobiology University of Groningen.
- Lucassen, P.J. (2006, oktober 11). *Doublecortin-like; a novel microtubule associated protein involved in mitotic spindle and radial fiber stability*. Groningen, lezing bij Stem Cell Cluster Groningen, Groningen University.
- Lucassen, P.J. (2006, november 01). *Changes in neurogenesis and hippocampal function in tau transgenic mice*. Berlijn, Duitsland, lezing geven op uitnodiging van Dr. Kempermann bij het Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch, Germany.
- Lucassen, P.J. (2006, november 01). *Doublecortin-like; a microtubule associated protein involved in mitotic spindle and radial fiber stability of radial glia cells during early cortical development*. Berlijn Duitsland, Invited lecture at the Max Delbruck Centre for Molecular Medicine Dr. G. Kempermann.
- Lucassen, P.J. (2006, november 01). *Structural plasticity in the adult brain in relation to stress and disease*. Berlijn, Duitsland, lezing geven op uitnodiging van Prof. Heuser bij de Klinik und Hochschulambulanz für Psychiatrie und Psychotherapie, Charite Campus Benjamin Franklin, University Berlin.



Appendix 11

Mass Spectrometry of Biomacromolecules

Chairholder: Prof.dr C.G. de Koster

Research Results in Numbers

Peer reviewed publications	8
Non-peer reviewed publications	0
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2006)

Chris de Koster	Chairholder
Jaap Boon	Honorary Professor (bijzonder hoogleraar)
Frank Laukien	Honorary Professor (bijzonder hoogleraar)
Piet Kistemaker	Honorary Professor (bijzonder hoogleraar)
Luitzen de Jong	Associate Professor
Leo de Koning	Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.5	0	0	0.5
Associate/Assistant professor	1	0	0	1
Research Fellow	0.3	0	0.9	1.2
PhD Student	0.75	0.62	1.5	2.9
Technician	3	0	0	3
Total	5.6	0.62	2.4	8.6

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4
Productivity:	3/4
Relevance:	5
Prospects:	4

Publications

Key Publication

Koning, L.J. de, Kasper, P.T., Back, J.W., Nessen, M.A., Vanrobaeys, F., Beeumen, J. van, Gherardi, E., Koster, C.G. de, & Jong L. de. (2006). Computer-assisted mass spectrometric analysis of naturally occurring and artificially introduced cross-links in proteins and protein complexes. *FEBS J.*, 2, 273, 281-291.

Academic publications (refereed)

- Bargmann, B.O.R., Laxalt, A.M., Riet, B. ter, Schouten, E., Leeuwen, E. van, Dekker, H.L., Koster, C.G. de, Haring, M., & Munnik, T. (2006). LePLDb1 activation and re-localization in suspension-cultured tomato cells treated with xylanase. *Plant J.*, 45, 358-368.
- Breemen, M.J. van, Bleijlevens, B., Koster, C.G. de, & Aerts, J.M.F.G. (2006). Limitations in quantification of the biomarker CCL18 in Gaucher disease blood samples by surface-enhanced laser desorption/ionization time-of-flight mass spectrometry. *Biochim. Biophys. Acta*, 1764, 1626-1632.
- Koblenz, T.S., Dekker, H.L., Koster, C.G. de, Leeuwen, P.W.N.M. van, & Reek, J.N.H. (2006). Bisphosphine based heterocapsules for the encapsulation of transition metals. *Chem. Commun. (Camb.)*, 28, 1700-1702.
- Koning, L.J. de, Kasper, P.T., Back, J.W., Nessen, M., Vanrobaeys, F., Beeumen, J.J. van, Gherardi, E., Koster, C.G. de, & Jong, L. de (2006). Computer-assisted mass spectrometric analysis of naturally occurring and artificially introduced cross-links in proteins and protein complexes. *FEBS J.*, 273, 281-291.
- Maarseveen, J.H. van, Reek, J.N.H., & Back, J.W. (2006). Transition-metal catalysis as a tool for the covalent labeling of proteins. *Angew. Chem. Int. Edit.*, 45, 1841-1843.
- Maarseveen, J.H. van, Reek, J.N.H., & Back, J.W. (2006). Transition-metal catalysis as a tool for the covalent labeling of proteins. *Angew. Chemie*, 45, 1841-1843.
- Meijer, H.J., Vondervoort, P.J. van, Yin, Q., Koster, C.G. de, Klis, F.M., Govers, F., & Groot, P.W.J. de (2006). Identification of cell wall-associated proteins from *Phytophthora ramorum*. *Mol. Plant Microbe Interact.*, 19(12), 1348-1358.
- Pardini, G., Groot, P.W.J. de, Coste, A.T., Karababa, M., Klis, F.M., Koster, C.G. de, & Sanglard, D. (2006). The CRH family coding for cell wall glycosylphosphatidylinositol proteins with a predicted transglycosidase domain affects cell wall organization and virulence of *Candida albicans*. *J. Biol. Chem.*, 281(52), 40399-40411.

Invited lectures

- Koster, C.G. de (2006, februari 08). *Interactomics: a diagonal chromatographic approach*. York, 9th Intern.Symposium on Hyphenated Techniques in Chromatography and Hyphenated Chromatographic Analyzers.
- Koster, C.G. de (2006, mei 08). *The impact of data analysis on SELDI identification of novel clinical biomarkers for Gaucher disease*. Munster, 7th Proteomics Information Exchange Meeting.
- Koster, C.G. de (2006, mei 18). *Mass spectrometry as an indispensable tool for characterization of protein tertiary and quaternary structure*. Gent, Colloquium Universiteit van Gent.

**Appendix 1m****Biosystems Data Analysis**

Chairholder: Prof.dr A.K. Smilde

Research Results in Numbers

Peer reviewed publications	15
Non-peer reviewed publications	0
PhD Theses	2
Patent applications	0

Staff (Research input in fte during 2006)

Age Smilde	Chairholder
Huib Hoefsloot	Associate Professor
Johan Westerhuis	Assistant Professor

Position	FS1*	FS2**	FS3°	Total
Chairholder	0.25	0	0	0.25
Associate/Assistant professor	1	0	0	1
Research Fellow	0	0	0.7	0.7
PhD Student	0.6	0.75	3	4.4
Technician	0.13	0	0	0.13
Total	2	0.8	3.7	6.5

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

Result research evaluation 2006 according to VSNU protocol

Quality:	4/5
Productivity:	5
Relevance:	4
Prospects:	4

Publications

Key Publications

Rubingh, C.M., Bijlsma, S., Derks, E.P.P.A., Bobeldijk, I., Verheij, E.R., Kochhar, S., Smilde, A.K. (2006). Assessing the performance of statistical validation tools for megavariate metabolomics data, *Metabolomics*, 2(2), 53-61.

Berg, R.A. van den, Hoefsloot H.C.J., Westerhuis, J.A., Smilde, A.K., Werf, M.J. van der (2006) Centering, scaling and transformations: improving the biological information content of metabolomics data. *BMC Genomics*, 7, 142.

PhD Theses

Tomasi, G. (2006, Mai 30). *Practical and computational aspects in chemometric data analysis*. Royal Veterinary and Agricultural University (Frederiksberg, Denmark: Royal Vet.and Agricultural Univ. Frederiksberg, Denmark). Prom./coprom.: R. Bro, & prof. dr. A.K. Smilde.

Backer, J.A., (2006, Mai 9) *Bridging time and length scales in dissipative particle dynamics*. Universiteit van Amsterdam. Prom/Coprom.: prof.dr P. Iedema & dr H. Hoefsloot.

Academic publications (refereed)

Berg van den, R.A., Hoefsloot, H.C.J., Westerhuis, J.A., Smilde, A.K., & Werf, M.J. van der (2006). Centering, scaling and transformations: improving the biological information content of metabolomics data. *BMC Genomics*, 7, 142.

Hageman, J.A., Berg, R.A. van den, Westerhuis, J.A., Hoefsloot, H.C.J., & Smilde, A.K. (2006). Bagged K-means clustering of metabolome data. *Crit.Rev. in Anal.Chem.*, 36(3-4), 210-220.

Hageman, J.A., Westerhuis, J.A., Fruehauf, H.-W., & Rothenberg, G. (2006). Design and assembly of virtual homogeneous catalyst libraries - towards in silico catalyst optimisation. *Adv. Synth. Catal.*, 348(3), 361-369.

Huub C.J. Hoefsloot, Johan A. Westerhuis & Age K. Smilde, Maximum Likelihood Scaling (MALS), *Journal of Chemometrics* 2006; 20:120-127.

Iedema, P.D., & Hoefsloot, H.C.J. (2006). Conditional Monte Carlo sampling to find branching architectures of polymers from radical polymerizations with transfer to polymer. *Macromolecules*, 39(8), 3081-3088.

Jansen, B., Nierop, K.G.J., Hageman, J.A., Cleef, A.M., & Verstraten, J.M. (2006). The straight-chain lipid biomarker composition of plant species responsible

for the dominant biomass production along two altitudinal transects in the Ecuadorian Andes. *Org. Geochem.*, 37(10), 1514-1526.

Nierop, K.G.J., Jansen, B., Hageman, J.A., & Verstraten, J.M. (2006). The complementarity of extractable and ester-bound lipids in a soil profile under pine. *Plant Soil*, 286(1-2), 269-285.

Ramaker, H.J., Sprang, E.N.M. van, Westerhuis, J.A., Gurden, S.P., Meulen, F.H. van der, & Smilde, A.K. (2006). Performance assessment and improvement of control charts for statistical batch process monitoring. *Statistica Neerlandica*, 60(3), 339-360.

Ramaker, H.J., Sprang, E.N.M. van, Westerhuis, J.A., & Smilde, A.K. (2006). Single channel event (SCE) for managing sensor failures in MSPC. *Computers & Chemical Engineering*, 30, 961-969.

Rothenberg, G., Hageman, J.A., Clerc, F.A., Fruhauf, H.W., & Westerhuis, J.A. (2006). How to find the best homogeneous catalyst. *Chemical Industries CRC (Catal.Org.React.)*, 115, 261-270.

Rubingh, C.M., Bijlsma, S., Derks, E.P.P.A., Bobeldijk, I., Verheij, E.R., Kochhar, S., & Smilde, A.K. (2006). Assessing the performance of statistical validation tools for megavariate metabolomics data. *Metabolomics*, 2(2), 53-61.

Skibsted, E., Boelens, H.F.M., Westerhuis, J.A., Witte, D.T., & Smilde, A.K. (2006). Simple assessment of homogeneity in pharmaceutical mixing processes using a near-infrared reflectance probe and control charts. *J.Pharmaceutical and Biomed.Analysis*, 41, 26-35.

Skibsted, E., Westerhuis, J.A., Smilde, A.K., & Witte, D.T. (2006). Theoretical framework for real time release of pharmaceutical products. *NIR News*, 17, 4-6.

Stanimirovic, O., Hoefsloot, H.C.J., Bokx, P. de, & Smilde, A.K. (2006). Linking PCA and time derivatives of dynamic systems, *Journal of Chemometrics*, 20, 43-53.

Visser, D.C., Hoefsloot, H.C.J., & Iedema, P.D. (2006). Modelling multi-viscosity systems with dissipative particle dynamics. *J. Computational Physics*, 214(2), 491-504.

Invited lectures

Hageman, J.A. (2006, mei 31). *Discussion of: Analysis and interpretation of correlations in metabolomics data*. Veldhoven, 4th Intern.Chemometrics Research Meeting.

Hoefsloot, H.C.J. (2006, juni 14). *Data analysis for -omics experiments*. Heteren, NIOO.

Smilde, A.K. (2006, april 07). *Biomarker discovery in metabolomics and*

Appendix 1n

Micro Array Department and Integrative Bioinformatics Unit

Group Leader: Dr T.M. Breit

Research Results in Numbers

Peer reviewed publications	6
Non-peer reviewed publications	2
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2006)

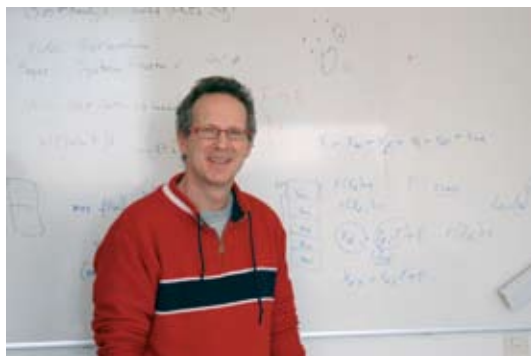
Timo Breit	Group Leader
Floyd Wittink	Project management “wet-lab”
Mattijs Jonker	Project management “dry-lab”
Jenny Batson	Project Administration
Marco Roos	Senior Researcher IBU
Han Rauwerda	Senior Researcher IBU

Position	FS1*	FS2**	FS3°	Total
Group Leader	0	0	0.5	0.5
Associate/Assistant professor	0	0.9	0.9	1.8
Research Fellow	0	0	1.5	1.5
PhD Student	0	0	0.75	0.75
Technician	0	0	3	3
Bioinformatics staff	0	0	3.6	3.6
Total	0	0.9	10.3	11.2

* FS1 = University Funding, ** FS2 = External funding, governmental grants

° FS3 = External funding, e.g. EU grants, commercial funding

- proteomics*. Eindhoven, Philips Natlab.
- Smilde, A.K. (2006, april 08). *Deconvolution and preprocessing of hyphenated metabolomics data*. Boston, USA, Metabolomics Society Meeting.
- Smilde, A.K. (2006, april 09). *Analyzing complex metabolomics data*. Reading, UK, Plant Metabolomics Conference.
- Smilde, A.K. (2006, mei 18). *Statistical challenges in biomarker discovery*. Amsterdam, Biomarker Discovery by Mass Spectrometry Conference.
- Smilde, A.K. (2006, september 13). *Dynamic medicinal metabolomics*. Dalian, China, Xiangshan Scientific Forum: Medicinal Metabonomics.
- Smilde, A.K. (2006, september 18). *Modern process chemometrics*. Wroclaw, Poland, ENBIS-6.
- Smilde, A.K. (2006, november 12). *Omics data analysis as a tool for systems biology discovery*. Somerset NJ, USA, Eastern Analytical Symposium.
- Westerhuis, J.A. (2006, november 29). *Statistical validation of metabolic differences*. Wageningen, Workshop Bioinformatics for metabolomics.
- Westerhuis, J.A. (2006, november 30). *Multiway analysis*. Nijmegen, Brugcollege IMM Radboud University Nijmegen.



Publications

Key Publications

Rauwerda, H., Roos, M., Hertzberger, B.O., & Breit, T.M. (2006). The promise of a virtual lab in drug discovery. *Drug Discov Today*, Mar;11(5-6), 228-36. Review.

Gorter, J.A., Vliet, E.A. van, Aronica, E., Breit, T.M., Rauwerda, H., Lopes da Silva, F.H., & Wadman W.J. (2006) Potential new anti-epileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. *J Neurosci.*, Oct 25;26(43), 11083-110.

Academic publications (refereed)

Baken, K.A., Pennings, J.L.A., Breit, T.M., Vries, A. de, Steeg, H.D. van, & Loveren, H. van (2006). Gene expression profiling of bis(tri-n-butyltin) oxide (TBTO) induced immunotoxicity in mice and rats. *Journal of Immunotoxicology*.

Gorter, J.A., Vliet, E.A. van, Rauwerda, H., Breit, T.M., Stad, R., Schaik, L. van, Vreugdenhil, E., Redeker, S., Hendriksen, E., Aronica, E., Lopes da Silva, F.H., & Wadman, W.J. (2006). Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and entorhinal cortex during epileptogenesis in the rat. *Journal. Epilepsia*.

Gorter, J.A., Vliet, E.A. van, Aronica, E., Breit, T.M., Rauwerda, J., Lopes da Silva, F.H., & Wadman, W.J. (2006). Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. *J. Neurosci.*, 26(43), 11083-11110.

Kooter, I.M., Pennings, J., Fokkens, P., Leseman, D., Boere, J., Gerlofs, M., Cassee, F., Schalk, J.A., Orzechowski, T., Schaap, M., Breit, T.M., Dormans, J., Oostrum, C. van, Vries, A. de, & Steeg, H. van (2006). Ozone induces clear cellular and molecular responses in the mouse lung independently of the transcription-coupled repair status. *J Appl Physiol*, Nov.(9).

Pronk, T.E., Pimentel, A.D., Roos, M., & Breit, T.M. (2006). Taking the example of computer systems engineering for the analysis of biological cell systems. *Bio Systems*.

Rauwerda, H., Roos, M., Hertzberger, L.O., & Breit, T.M. (2006). The promise of a virtual lab in drug discovery. *Drug Discov Today*, Mar;11(5-6), 228-236.

Book chapters

Inda, M.A., Belloum, A.S.Z., Roos, M., Vasunin, D., Laat, C.T.A.M. de, Hertzberger, L.O., & Breit, T.M. (2006). Interactive Workflows in a Virtual Laboratory for e-Bioscience: the SigWin-Detector Tool for Gene Expression Analysis. In *Proceedings of the second IEEE International Conference on e-Science and Grid Computing* (pp. 19). Amsterdam: e-Science.

Marshall, S., Post, L.J.G., Roos, M., & Breit, T.M. (2006). Using semantic web tools to integrate experimental measurement data on our own terms. In R. Meersman, Z. Tari, & P. Herrero (Eds.), *Proceedings of International Workshop on Knowledge Systems in Bioinformatics (KSiNBIT'06)* (OTM, LNCS4277) (pp. 679-688). Montpellier, France: Springer.



Appendix 2

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Manager Research and Acquisition: Dr Karin van de Sande

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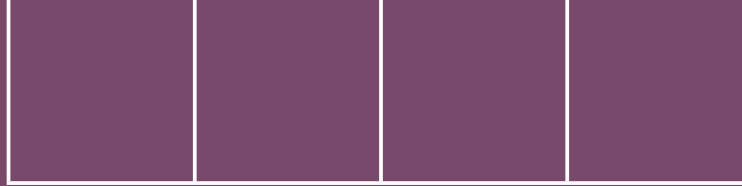
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