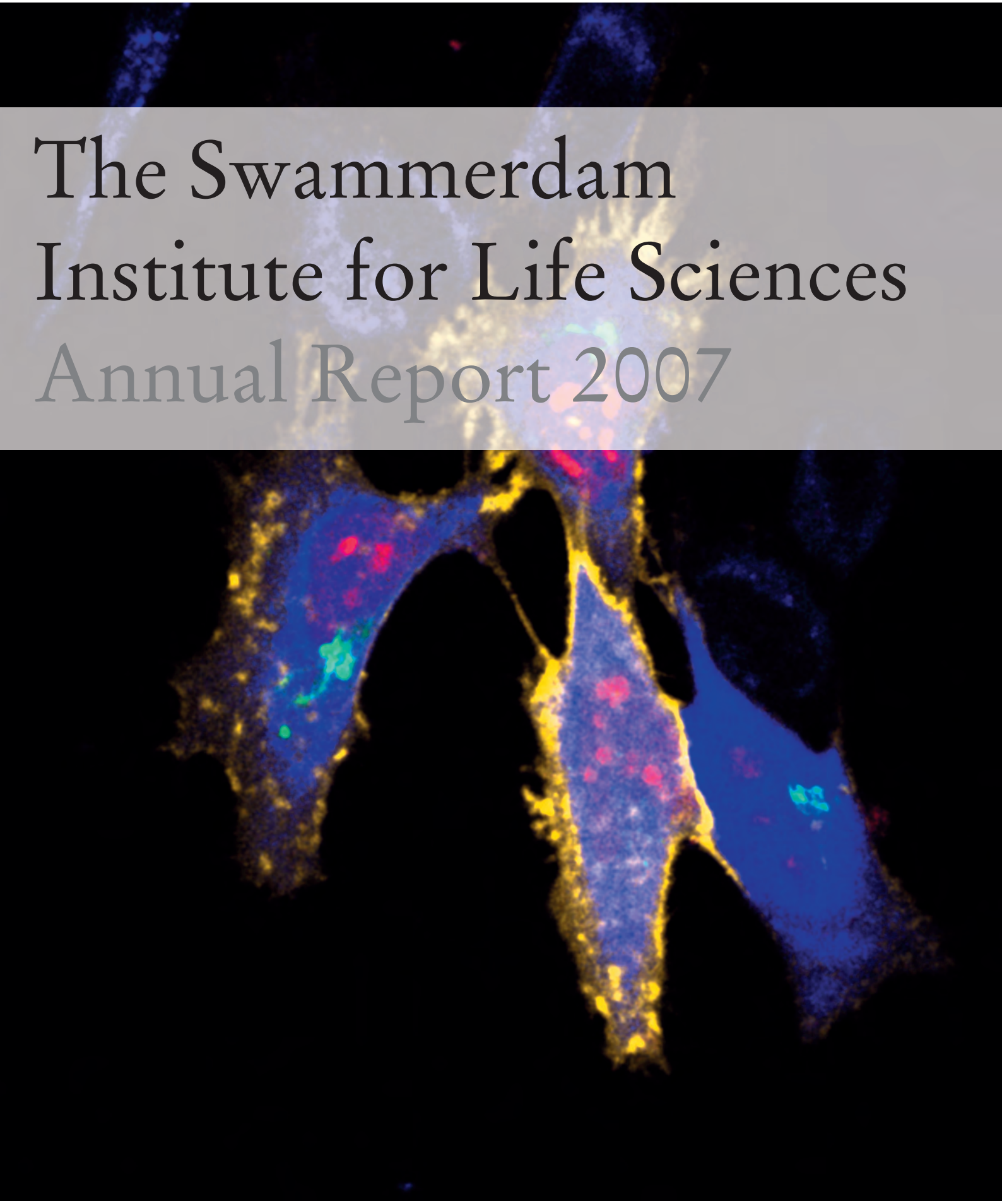
University of Amsterdam

The Swammerdam Institute for Life Sciences

Annual Report 2007



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UNIVERSITY OF AMSTERDAM

The Swammerdam Institute for Life Sciences

Annual Report 2007

Faculty of Science

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1. Preface by the director

The Swammerdam Institute for Life Sciences: developments in 2007

Introduction

The annual report 2007 represents an impressive summary of the excellent work performed by the various research groups within the Swammerdam Institute for Life Sciences.
A year ago the external review board concluded that the outlook for life sciences in the Amsterdam area, and thus also in SILS, is bright, but that continued successful international competition was dependent upon further enhancement of research collaborations. In 2007 such co-operations have indeed further been established and extended. I would mention here just two examples:
The Netherlands Institute for Systems Biology (NISB), established in December 2006, supported by various research groups within SILS, is starting to become a very fruitful 'playing ground', involving researchers from various disciplines and organizations (UvA/SILS, VU, AMOLF/FOM and CWI).
In the area of neuroscience, especially cognition, new activities within the Center for Cognitive Science Amsterdam (CSCA) have been initiated. On top of that, the Spinoza Center for Neuroimaging has been founded, supported by the UvA, VU/UMC, AMC and NIN (Netherlands Institute for Neuroscience) and the city of Amsterdam. The various parties are aiming to co-invest in fMRI-facilities which would lead to greatly extending the excisting co-operation within the Amsterdam area with regard to neuroscience.
All this all could not be done without the co-operative and pro-active attitude of many of our SILS-researchers in building and maintaining these and other new initiatives.
Such new co-operations might pose a potential threat to the structure and organization of the institute, but I'm convinced that by keeping state of the art technology at the heart of the institute, these initiatives will strengthen us as an institute.

Highlights

Prof.dr Joost Teixeira de Mattos was appointed as professor at SILS in 2007. He has been Secretary of the scientific committee of the 13th European Congress of Biotechnology, held in Barcelona, Spain, 16-19 September. He also was elected as the best lecturer 2007 by the students Biomedical Sciences of the University of Amsterdam.

Prof.dr Stanley Brul is Distinguished Research Scholar of the University of Tasmania, Australia, and Technology auditor of TNO Quality of Life, In 2007 he received the Unilever author award.

2007 saw the formal start at the MBMFS group of Dr. Benno ter Kuile with a research team of the Dutch Food Safety Authority.

Dr Pernette Verschure obtained an NWO Meervoud grant, concentrating on the development, quantitative analysis and modelling of small synthetic epigenetic networks in mammalian cells.
Dr Paul Fransz has organized, together with prof.dr H. Tanke and dr J. de Jong the 16th International Chromosome Conference, that took place from August 25 to 29 in Amsterdam.

Prof.dr Roel van Driel was appointed as (founding) scientific director of the Netherlands Institute for Systems Biology (NISB) in Amsterdam and of the Netherlands Consortium for Systems Biology (NCSB) program of the Netherlands Genomics Initiative (NGI).

Prof.dr Dorus Gadella was elected as president of the Netherlands Society for Microscopy.

Dr Christa was awarded a personal NOW Aspasia grant. The Centre for Biosystems Genomics, in which the Plant Pathology group of prof.dr Ben Cornelissen participates, has again been recognized as a centre of excellence in the Netherlands. This allows us to initiate new projects in 2008.

Members of the group of prof.dr Marian Joëls organized a Topschool for 15 MSc /PhD students with 5 international tutors (June 11-15). Dr Harm Krugers received a grant from the HersenStichting Nederland and a KNAW China exchange project grant; dr Henk Karst received an NWO-ALW grant in the open competition. Prof.dr Marian Joëls was elected on the Editorial Board of the new open access journal Frontiers in Behavioral Neuroscience. Prof.dr Marian Joëls was appointed Emil Kraepelin Professor of Psychiatry 2007, at the Max Planck Institute for Psychiatry.

The Micro Array Department and Integrative Bioinformatics Unit of dr Timo Breit has initiated strategic collaborations with several external research organisations: Laboratorium voor Toxicologie, Pathologie en Genetica (TOX), RIVM, (Bilthoven); Medical Microbiology, UMC (Utrecht); ACTA, VU-AMC (Amsterdam); Moleculaire Celbiologie, UL, (Leiden).

Prof.dr Antoine van Kampen, head of the AMC Bioinformatics Laboratory and Scientific Director of the Netherlands Bioinformatics Centre has been appointed as part time professor at SILS.

The “Synthetic Forager” - STREP EU grant was awarded within the 7th Framework Programme - ICT 217148 . Prof.dr Cyriel Pennartz is co-applicant for this grant.

Teaching

With respect to education, which is part of the tasks of the research institute within a research-university, the teaching load for our staff has further increased. Especially the Psychobiology and Biomedical Sciences bachelor tracks attract every year more students. A concise analysis of all teaching activities performed by SILS employees has been carried out, in order to understand the exact amount of time spent on teaching. The results indicate that our staff spent approximately 50% of their time on teaching. This amount has been characterized by the external evaluation board as being ‘vastly in excess of that of its international competitors’. In order to keep a sound balance between research and teaching, we aim in 2008 to acquire more funds to alleviate this.

2. Scientific Program

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', 'Plant Signalling', '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	86	6
Plant Signalling	1	19	2
SILS Center for NeuroScience	3	56	1
Life Science Technologies	0	33	0
Total	9	194	9

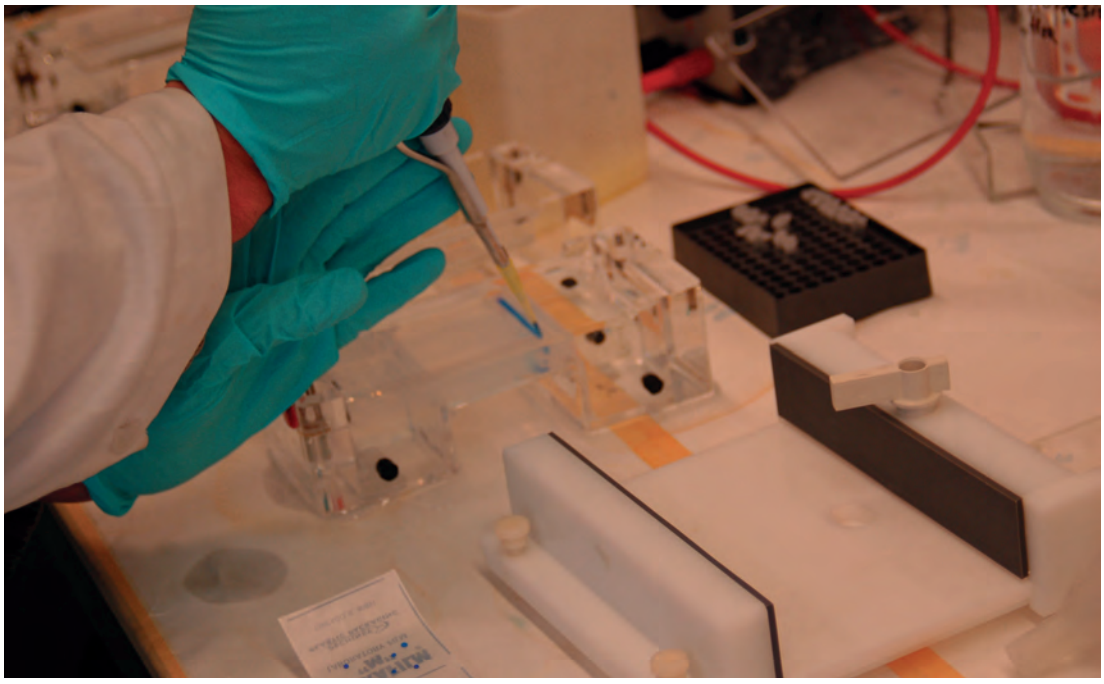
Research Input				
Clusters	FS1*	FS2**	FS3◊	Total
The Living Cell	20.3	11.3	15.2	46.8
Plant Signalling	9.9	6.6	5.7	22.2
SILS Center for NeuroScience	14.2	5.9	7.6	27.7
Life Science Technologies	8.9	1.8	13.3	24.0
Total	53.3	25.6	41.8	121.5

* 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
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

Plant Signalling

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 information that this approach provides, the possibility of linking this information with metabolomics and proteomics data, combined with modelling to start simulating the processes under study, is contributing to our approach of Systems Biology. 'The Living Cell' is uniquely positioned to play a key role in this development.

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

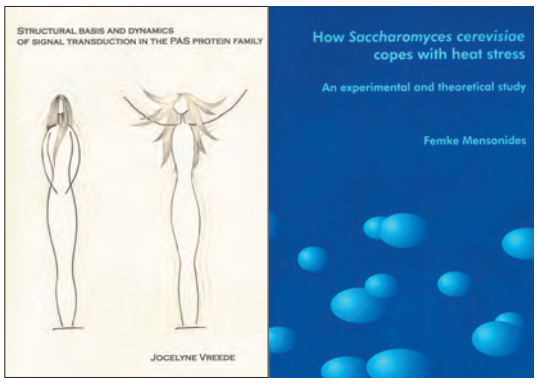
Molecular Microbial Physiology

Chairholder: Prof.dr K.J. Hellingwerf

Jeroen Hugenholtz	Professor
Joost Teixeira de Mattos	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. Microorganisms 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 *bio*chemical *system* that sustains microbial (i.e. cellular) *life*.



Research Highlights

- We have shown that the general stress response in *Bacillus subtilis* can be modulated by blue light via the LOV domain of YtvA and by red light via the PAS domain of the RsbP protein. Particularly the latter response is of interest because RsbP, which is able to bind tetrapyrrole derivatives, may represent an entire new family of photosensory receptors. YtvA activates the stress response sigma factor (σ^B) through a very complicated aggregate of signal transduction proteins, called the 'stressosome'. Through knock-out experiments the minimally required stressosome composition for light signaling through YtvA has been determined.

- For the BLUF domain of AppA it has been established that the trigger for structural change in this photoreceptor domain is a 180 degrees flip of a catalytic glutamine side chain. We have now convincingly demonstrated that this 'Q-flip' is initiated by transient neutral bi-radical formation between the flavin chromophore and a nearby tyrosine side chain. A nearby tryptophan competes with this tyrosine as the hydrogen atom donor to the flavin; 'H'-transfer from the latter, however, represents a biologically non-productive reaction channel.

- It has been established that the alternative cytochrome bd_2 oxidase in *Escherichia coli* does not contribute to the build-up of the proton motive force. Nevertheless, the electron flux through this enzyme may be significant, as inferred from its high activity in a mutant that lacks other terminal oxidases. The bd_2 oxidase has hitherto been considered of little physiological relevance, but is possibly a major device to uncouple respiration from energy conservation.

Other Highlights

Prof.dr Joost Teixeira de Mattos has been Secretary of the scientific committee of the 13th European Congress of Biotechnology, held in Barcelona, Spain, 16-19 September. He also was chair of the session on Biofilms of the Annual Meeting of the Netherlands Society for Microbiology. Prof.dr Joost Teixeira de Mattos contributed as a lecturer to the Advanced Course on Microbial Physiology of

the University of Delft, and he has been elected as the best lecturer 2007 by the students Biomedical Sciences of the University of Amsterdam.

Future Prospects

- Characterization of the newly identified tetrapyrrole-containing photoreceptor protein from *Bacillus subtilis* with respect to the nature of the chromophore bound *in vivo*, light-regulation of phosphatase activity, etc.
- Resolution of the role of the various stressosome components (i.e. RsbS -T, -R, and its homologues) in the initiation of the general stress response in *Bacillus subtilis*.
- Characterization of the physiology of *E. coli* strains with an altered content of the components of the respiratory chain, in particular the three alternative quinol oxidases.
- Extension of the hierarchical metabolic control analysis of glycolytic components in *Saccharomyces cerevisiae* in response to oxygen availability.

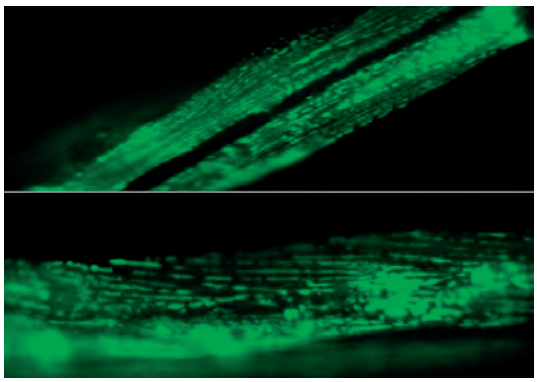
Molecular Biology and Microbial Food Safety

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 functional genomics and systems biology approaches. We are a member of the Netherlands Institute for Systems Biology (NISB). Our scientific approach is both focused on asking 'bottom-up' as well as 'top-down' systems biology questions. We use the model yeast *Saccharomyces cerevisiae* to develop genome-wide analysis concepts with a strong application potential towards food spoilage and medical fungi as well as food spoilage and pathogenic bacteria. The tools we apply include genome-wide micro-array analysis, proteomics, various advanced microscopy techniques and controlled cell culturing systems such as fermentors and chemostats. Results are as much as possible quantified and analysed using a number of modelling tools including in-house developed micro-array and functional data analysis software. Additionally we develop experimental models for the study of host-microbe interactions and physiology. We have major contacts and contracts with the food and pharma industry focussing on the application of our research in practical settings.



Research Highlights

- In 2007 we performed a 'systems' analysis of bacterial spore germination through the functional interpretation of the genome-wide expression profile of germinating spores (Keijser et al., 2007). A TNO patent based on joint research, on the prediction of spore germination as a function of the intactness of spore rRNA, was published.

- Concomitantly we finalized the analysis of the response of vegetative Bacilli against the common weak acid preservative sorbic acid and related compounds (Ter Beek et al., 2008). The data was used to underpin a Unilever patent based on joint research that aims at synergizing the activity of sorbic acid. A descriptive model that links spore germination functional modules and weak-acid response was made.

- For yeast we have also analyzed its response to lipophilic weak-acid stress using in situ pH measurement with pH sensitive pHluorin (see illustration). Methods were developed to functionally analyze cellular behaviour on a genome-wide level. The article by Zakrzewska *et al*. (2007) clearly illustrates the power of a genomic analysis of fungal stress physiology. By subjecting a genomic library of yeast deletion strains to selective stress conditions (fitness profiling) we are now also able to systematically identify cellular functions and pathways that are suitable targets for antifungal combination strategies. We have identified two major aspects of the yeast adaptive response. The first (Zakrzewska *et al*., submitted for publication) entails massive non-transcriptionally regulated cellular remodelling through vesicle-mediated transport routes, which is crucial for the adaptive response to almost any stress tested. The second comprises of a strong down-regulation of growth capacity through the decreased biosynthesis of ribosomes, and a concomitant increase in stress tolerance.

- Finally, in the field of analysing in a multicellular model stress response, we successfully expressed fluorescent proteins in mitochondria of muscle cells of *Caenorhabditis elegans* which gives us now a perfect tool to study mitochondrial morphology in cells exposed to toxic compounds such as antiviral agents (see illustration).

Other Highlights

Prof.dr Stanley Brul is Distinguished Research Scholar of the University of Tasmania, Australia, Technology auditor of TNO Quality of Life, Consultant for Unilever, Editor of Innovative Food Science and Emerging Technologies and Member of the Faculty of 1000. In 2007 he received the Unilever author award.

Dr Frans Klis is Editor of Eukaryotic Cell, FEMS Yeast Research and Yeast.

2007 saw the formal start at MBMFS of Dr. Benno ter Kuile with a research team of the Dutch Food Safety Authority.

Future Prospects

- In 2008 we will start within our bacterial group with an integration of the knowledge on weak-acid stress resistance and spore germination in *Bacillus subtilis*. A working hypothesis on the modules operative in spore germination has been proposed and will be the framework for these studies. We will use a promoter trap library to analyze thermal damage repair processes at the level of single germinating spores.

- Stress response research on antibiotic resistance acquisition was recently started in *Escherichia coli* and we expect in 2008 to focus on the establishment of the chemostat growth model to be able to study the process quantitatively.

- In our medical yeast research line we progress studies in quantitative proteomics of the fungal cell wall. Next in vitro models for mucosal infections by *Candida albicans* will be developed.

- The underpinning theoretical studies on microbial stress response analysis focuses on a genome wide analysis of the interaction between pH homeostasis and weak acid stress as well as on studying the causal relationship between growth rate and stress tolerance.

- Our model systems studies in *C. elegans* will focus on functional metabolic data to establish the worm as a valid model to study side effects of anti-HIV drugs on human metabolism as well as compounds to compensate these.

Structure and Functional Organisation of the Cell Nucleus

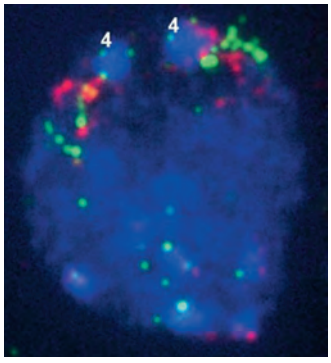
Chairholder: Prof.dr R. van Driel

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

Introduction

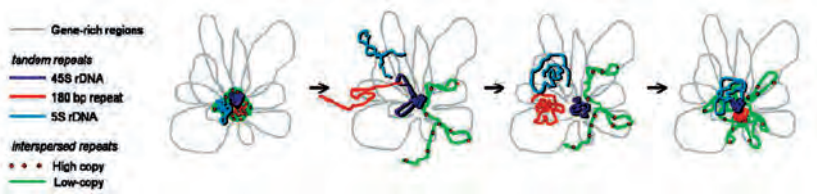
The one-dimensional structure of the genome of an increasing number of eukaryotes has been fully sequenced. A major challenge is to understand how it functions in terms of orchestration of expression of the many thousands of genes it encodes. Gene expression in eukaryotes is controlled at three hierarchical levels. One is that of individual genes, involving cis regulatory elements and trans-acting 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 is tightly associated with the folding of the chromatin fibre in the nucleus.

Our aim is to unravel gene regulatory mechanisms that combine these three control levels. We concentrate on the dynamic structure of chromatin and the behaviour of the nuclear machineries involved in gene activation and silencing and DNA repair. We combine structural studies, often on living cells, with molecular biological, biochemical and other methodologies and with predictive modelling. We approach regulatory systems in the genome as networks of molecular components that interact in time and space. It is our ambition to be among the first to develop quantitative and predictive models of regulatory epigenetic networks.



Research Highlights

- Considerable progress has been made with the development of an engineered small epigenetic system in mammalian cells and its analysis using a network analysis.
- In parallel, we started a thorough quantitative analysis of the behaviour of transcription factor networks that orchestrate genome-wide gene expression. Modelling approaches are in close cooperation with Dr Bruggeman (NISB).
- The work on functional 3D genome analysis resulted in a PhD thesis defended in 2007.
- The in-depth analysis of the epigenetic behaviour of the maize paramutation system, combining systematic analysis of chromatin-chromatin interactions (3C technique), histone modifications and local nucleosome density has been carried out, resulting in two PhD theses to be defended in 2008.
- Our ongoing *in vivo* analysis of the nucleotide excision DNA repair system has resulted in a comprehensive quantitative and predictive model of this complex process (cooperation with Dr Höfer, DKFZ, Heidelberg). This combined 'wet' and 'dry' approach gives new and deep understanding of the molecular choreography of chromatin-associated processes *in vivo*. The work results in a PhD thesis, to be defended in 2008.
- Work on artificial episomes that are stably present in mammalian cells unexpectedly showed that episomal genes behave remarkably similar to genomic loci with respect to epigenetic regulation and nuclear localization.
- Novel approaches have been developed to analyse the regulation of transitions in large-scale chromatin structure in Arabidopsis in terms of molecular networks, resulting in two grant applications.
- The research on epigenetic dysregulation in Huntington's disease resulted in a thorough screen of epigenetic properties during the onset of HD, using a combined experimental and computational approach.



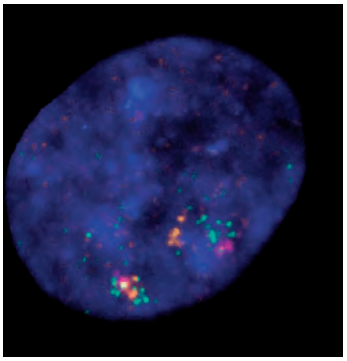
▲ Chromatin dynamics during Arabidopsis protoplast culture. Schematic representation of an interphase chromosome before and after protoplast formation, showing repeat regions (color) and gene-rich regions (gray). Chromosome 4 is shown, which has all major tandem repeats (180 bp, 45S rDNA and 5S rDNA). All repeat regions except 45S rDNA) become decondensed in protoplasts. From Tessadori et al. (2007) Plant J. 50:848-57

Other Highlights

Dr Pernette Verschure obtained an NWO Meervoud grant, concentrating on the development, quantitative analysis and modelling of small synthetic epigenetic networks in mammalian cells. Dr Pernette Verschure submitted a patent application on the synthetic epigenetic cell system has ('A method for regulating eukaryotic gene expression at the level of chromatin' (patent application P6007036EP).

Dr Paul Fransz has organized, together with prof.dr H. Tanke and dr J. de Jong the 16th International Chromosome Conference, that took place from 25 - 29 August in Amsterdam.

Prof.dr Roel van Driel obtained a FOM grant, as part of a large FOM program on DNA and chromatin. It builds on our expertise in the analysis of folding of the chromatin fibre in the mammalian interphase nucleus. Prof.dr Roel van Driel was appointed as (founding) scientific director of the Netherlands Institute for Systems Biology (NISB) in Amsterdam and of the Netherlands Consortium for Systems Biology (NCSB) program of the Netherlands Genomics Initiative (NGI).



Future Prospects

The year 2008 will mark the start of an important overall change in the approach of the Nuclear Organisation Group. We will concentrate and

coordinate our efforts on quantitative understanding of gene control systems in higher eukaryotes (plants and cultured mammalian cells), approaching them as molecular networks. Quantitative and predictive models will be a major guiding principle. This systems biology approach for gene regulation in eukaryotes builds on the expertise acquired in the past few years and is enhanced by the two grants obtained recently (see above). It will require a structural cooperation with physicists and bio-mathematicians, part of which is already in place: Frank Bruggeman (NISB), Thomas Höfer (DKFZ, Heidelberg) and Dieter Heermann (Heidelberg University).

Epigenetic Regulation of Gene Expression

Chairholder: Prof.dr A.P. Otte

John Verhees Assistant Professor (Since 07-07)

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 extensively analyzed the chromatin structure of STAR elements, using Chromatin Immuno-Precipitation 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, very well 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.

- Also, we found that a low level of RNA transcription originates from the STAR elements. The direction of transcription correlates with the optimal direction in which the STAR elements have to be placed to achieve higher gene expression levels.

- Finally, we developed a novel set of selection markers, based on their ability to restore the synthesis of essential metabolic components that normally lack from the cells. Application of these markers warrants a high degree of stability of gene expression over prolonged periods of time.

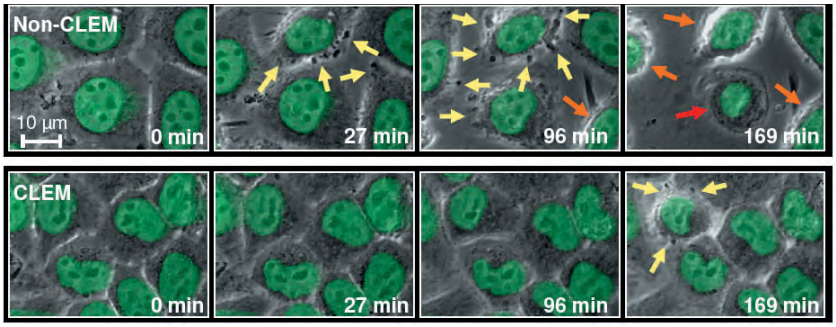
Future Prospects

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; 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

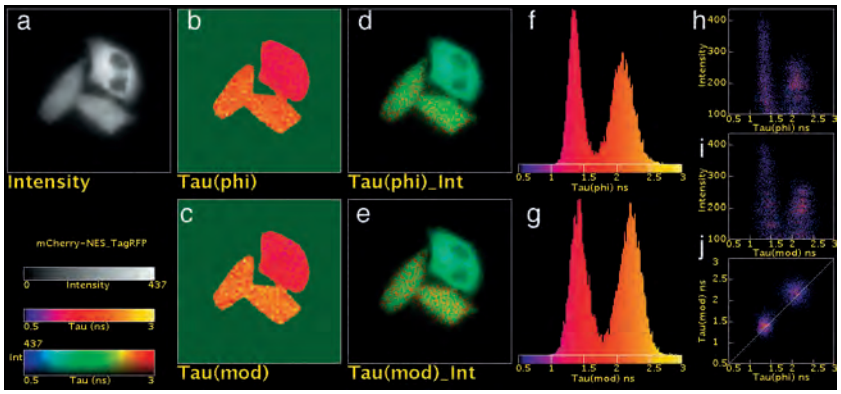


Introduction

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 Dorus Gadella & dr Joachim 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-alfaQ to PLC activation triggering downstream calcium and kinase signalling.
2) Molecular mechanisms of bacterial proliferation (group leader dr Tanneke 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. Michiel 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.



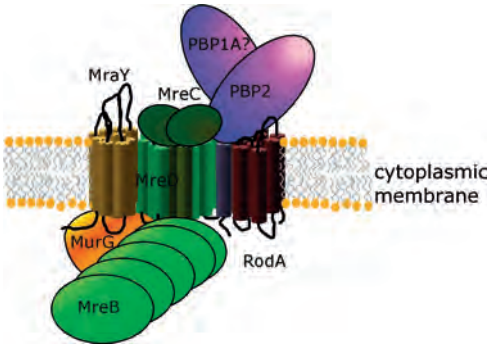
These research themes heavily depend on advanced microscopy technology organized within the Centre for Advanced Microscopy (CAM, 2004). The goal of CAM is to boost Life Sciences research using & developing (optical) microscopy techniques. Current most prominent developments are Coherent Anti-Stokes Raman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

Research Highlights

- The Controlled Light Exposure Microscopy (CLEM) technology for strong reduction of phototoxicity and photobleaching was published (Hoebe et al (2007), Nature Biotechnology).
- We have achieved for the first time imaging of cell type and cell location-dependent lipid droplet chemical composition and morphology in living cells using CARS microscopy (Rinia et al., submitted)
- We have made a FRET-based reporter system to monitor agonist-induced GalphaQ heterotrimer-activation in living mammalian cells. Using this reporter we elucidated for the first time that GalphaQ does not dissociate but undergoes a conformation change upon activation (Adjobo-Hermans et al, submitted)
- In contrast to what was generally believed, we show that MreB is not involved in genome segregation in *E. coli*, but that it is involved in the recruitment of a protein complex (elongase) that directs lateral cell envelope synthesis (Karzmarek et al., 2007). We also show that the peptidoglycan precursor synthases MraY and MurG are part of this complex (Mohammadi et al., 2007).

Other Highlights

- Dorus Gadella was elected as president of the Netherlands Society for Microscopy
- An EU SME-grant was awarded to Tanneke den Blaauwen in collaboration with 12 European groups working on the development of antibiotic screening assays and the development of new antibiotics that will inhibit bacterial cell division.



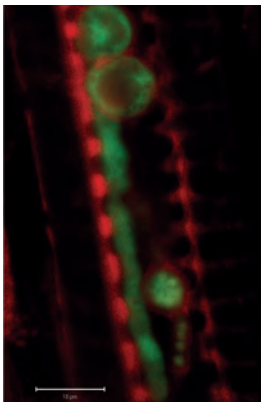
Future Prospects

- We aim to publish a novel FLIM-based screening method for selection of super fluorescent protein variants with the identification of the most efficient fluorescent protein variant ever described.
- We aim to publish about the mathematics behind CLEM and a major improvement of the confocal CLEM technology and we aim to make the first wide-field CLEM images.
- We aim to publish the first paper that describes a reliable FRET-system to study the interaction of rare proteins in bacteria. Furthermore we aim to deepen our understanding of the bacterial divisome and elongation complexes including the analysis of the GTP-binding pocket of FtsZ, a mutagenesis analysis and first crystal structure of FtsQ, the in situ labelling of peptidoglycan synthesis and the analysis of the localization of PBP5 in *E. coli.*
- We aim to publish a paper describing the characterization of p63RhoGEF (a novel novel effector of Galphaq) in single living cells. The dynamics of the interaction of p63RhoGEF with Galphaq will be examined as well.

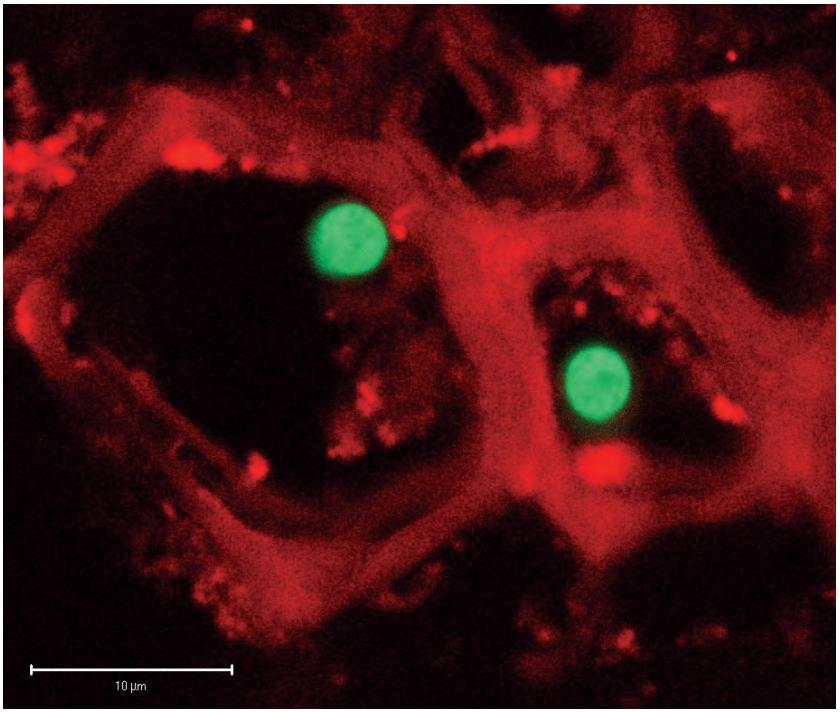
Research Clusters

Plant Signalling

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.



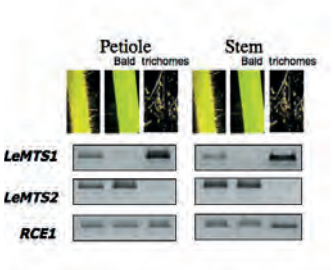
Two chairs contribute to the research cluster 'Plant Signalling': 'Plant Physiology' and 'Plant-pathogen Interactions', while the chairs "Molecular Cytology" and "Nuclear organization" study related topics on plant model systems



Plant Physiology

Chairholder: Prof.dr M.A. Haring

Rob Schuurink	Assistant Professor
Teun Munnik	Assistant Professor
Christa Testerink	Associate Professor

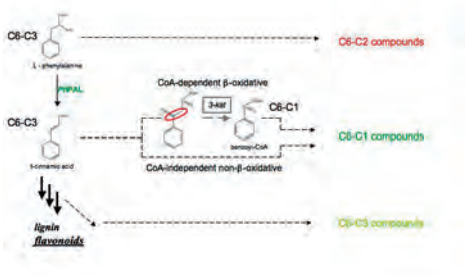


► Tomato Monoterpene synthase 1 (*LeMTS1*) is expressed in trichomes of petioles and stems. Expression was analyzed by RT-PCR. RUB1 conjugating enzyme (RCE1) was used as a constitutive control. MTS2 is not expressed in trichomes

Introduction

One of the topics in our group concerns the biosynthesis, regulation and biological role of volatiles. In the last decade *Petunia hybrida* has emerged as the model of choice to study volatile benzenoid and phenylpropanoid synthesis, emission and regulation. These volatiles are synthesized predominantly in the corolla limb and emission is highly regulated, with a circadian rhythm, during corolla development, pollination and senescence. With all the biochemical and molecular tools available much of our understanding of volatile benzenoid/phenylpropanoid has been obtained with Petunia. The knowledge obtained with this system is being applied to alter tomato fruit volatile production and thereby taste. In addition, we use tomato as a model system to study the role of terpenoids in its interaction with insects. We focus on terpene synthases expressed in trichomes and have identified several terpenoids that repel or attract whiteflies. Our aim is to engineer the production of these terpenoids. Finally, we use Arabidopsis for forward genetic screens to identify genes important in the response to the wound-induced C6-volatile *E*-2-hexenal. We also aim to identify genes that are specifically regulated by *E*-2-hexenal using a transcriptomics approach.

The second topic, phospholipid signaling is centered around 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 analyzing knockout lines of individual PLC, DGK and PLD genes in *Arabidopsis* plants, we aim to elucidate their role in plant stress signaling 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 signaling pathway controlled by the stress hormone ethylene. How phosphatidic acid modulates protein function and downstream plant responses, is a topic that will receive more attention in the coming years. Another goal of our research is to identify key information cascades that control pollen tube growth, and to understand how these networks link to the biomechanics that drive cell elongation. Our most recent work shows that transcellular hydrodynamic flux drives pollen tube growth and modulates the rates of exocytosis and endocytosis.



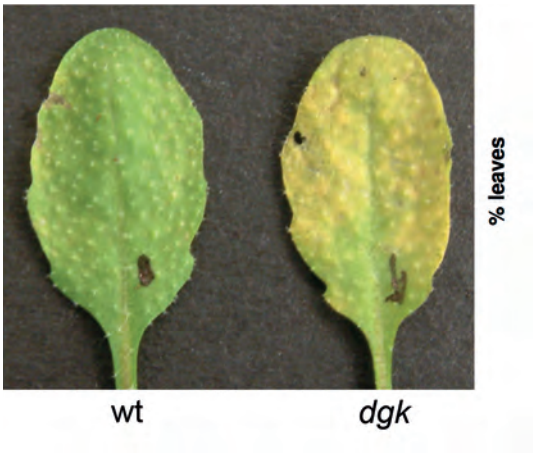
►► Schematic view of volatile benzenoid (C6-C1), C6-C2 and phenyl-propanoid (C6-C3) biosynthesis in Petunia petals. The benzenoid compounds are partly made via a (-oxidative pathway in which 3-keto-acylthiolase (3-kat) plays a crucial role.

Research Highlights

Since we established last year that (-aminobutyric acid (GABA) acts downstream of E-2-hexenal in Arabidopsis we have put much effort in determining which genes are specifically regulated by E-2-hexenal or GABA in collaboration with the MicroArrayDivision (MAD). We identified a set of genes that responds specifically to either GABA or hexenal. We also established that GABA plays an important role in the interaction with the bacterial pathogen *Pseudomonas syringae*. In Petunia we have identified a keto-acylthiolase that is putatively involved in shortening the C3-side chain to C1. Silencing of this gene indicates that this is indeed the case, with very interesting, unexpected fluxes to other volatile benzenoids/phenylpropanoids as a consequence. Moreover, we have identified an enhancer in the promoter of the transcription factor ODORANT1, which regulates genes in the shikimate pathway that provides the precursors for

phenylalanine production. We also use this knowledge to study the regulation of benzenoid/phenylpropanoid biosynthesis in tomato fruits. Using wild and cultivated tomatoes we determined that several terpenoids, produced by the trichomes play a role in repelling or attracting whiteflies. We are currently isolating the corresponding terpene synthase cDNAs using the Massive Parallel Sequence technology of 454 Life Sciences (GS-flex).

Earlier, we have provided evidence for the role of PA in plant defence using elicitor-challenged cell suspensions of tomato, parsley and alfalfa. Currently, we are addressing PA's role in the model system *Arabidopsis thaliana* by sertion lines of selected lipid signaling genes. One DGK gene was found to be required for full resistance against virulent *Pseudomonas* and *H. parasitica*, while two PLD genes were found to be involved in resistance against avirulent *Pseudomonas* strains. The DGK mutant is affected in PR1 gene expression, which seems to be independent of salicylic acid. Furthermore a PLC mutant with aberrant root architecture was found, suggesting a link with the phytohormone auxin. Preliminary results indicate that various DGKs and PLCs are involved in the plants PA response to cold, while 2 PLD mutants were found to be affected in their salt tolerance. In our search for targets of the signaling lipid PA several protein kinases were discovered that bind PA. These include two SNF-1 related protein kinases (SnRKs) implicated in osmotic stress, and the MAPKKK homologue CTR1, which is a negative regulator of ethylene signaling. CTR1 protein kinase activity was inhibited by low concentrations of PA *in vitro*. PA was also found to disturb the interaction of CTR1 with the ethylene receptor ETR1. Further analysis revealed a novel PA-binding site located at the C-terminus of the protein. The ability to specifically bind PA was localized to a 90 AA fragment that encompasses the activation loop (Testerink *et al*., 2007). In collaboration with the lab of Dorus Gadella (Molecular Cytology), we showed that YFP-$PH_{PLC\delta1}$ can be used as biosensor to visualize PtdIns(4,5)P_2 in tobacco BY-2 cells and Arabidopsis seedlings *in vivo*. This revealed an association of this biosensor with the newly formed cell membrane of a dividing plant cell.



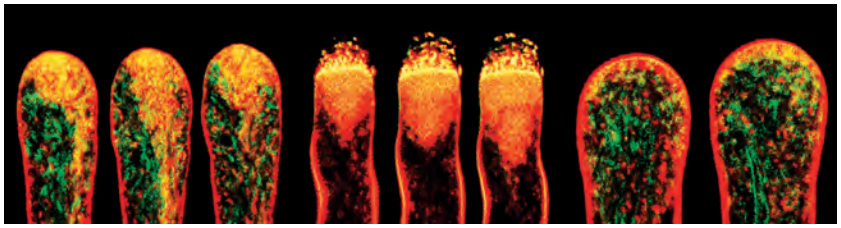
◄ Arabidopsis diacylglycerolkinase (dgk) knock-out mutant is compromised in basal disease resistance **Left.** Symptoms caused by pressure infiltration of leaves with *P. syringae pv maculicola (Psm)* 3 days after inoculation. **Right**. Distribution of disease severity classes of plants infected with *H. parasitica* Waco9. Classes represent the percentage of leaves with: I, no symptoms; II, trailing necrosis; III, <50% of leaf area covered with sporangia; IV, >50% of leaf area covered with sporangia, with additional chlorosis and leaf collapse. Data represent 280 leaves of 40 plants per genotype. Asterisk indicates statistically significant different frequency distribution of the disease severity classes compared to wild type (Chi-square test; α=0.05, n=280). Similar results were obtained in an independent experiment.

Other Highlights

- Top Institute Green Genetics grant for Robert Schuurink
- NWO Aspasia grant for Christa Testerink
- ECHO grant for Teun Munnik

Future Prospects

Now that we have established which terpenoids are important in tomato-whitefly interactions, we will clone the corresponding terpene synthase cDNAs, characterize them biochemically and overexpress them in trichomes of cultivated tomatoes. Furthermore, we will characterize two additional Arabidopsis mutants that are not responsive to *E*-2-hexenal and try to map the mutations. Finally, we will investigate the role of 3-ketoacylthiolase in β-oxidative benzenoid biosynthesis and determine the importance of the putative enhancer in the *ODORANT1* promoter via a transgenic approach. For more detailed visualization of lipid domains in the cell, we have constructed biosensors specific for PtdIns3P, PtdIns4P, PtdIns(4,5)P_2 and DAG, while those for PA are being developed. This will allow us to further characterize the role and dynamics of PA and phosphoinositides (PPIs) during plant development and stress responses. A functional genomics approach has been started to determine how subcellular phospholipid pools are being generated and maintained by screening T-DNA insertion mutants in lipid kinases, phosphatases and hydrolases. Currently, the functional significance of PA-binding for CTR1 and SnRK2 function is being studied *in vivo*.



▲ Time-lapse images of tobacco pollen tubes double-labelled with FM 1-43 (green) and FM 4-64 (red) to identify sites of endocytosis and exocytosis and visualize membrane trafficking patterns (Zonia and Munnik, 2008). The first 3 images are from a pollen tube undergoing normal growth. The next 3 images are from a pollen tube undergoing hypertonic stress, which stimulates endocytic membrane retrieval at the apex and inhibits exocytosis. The last 2 images are from a pollen tube undergoing hypotonic stress, which stimulates exocytosis and growth and attenuates endocytosis. Together with previous work (Zonia et al., 2006; Zonia & Munnik, 2007), these data reveal that transcellular hydrodynamic flux is a key integrator of pollen tube growth, providing a motive force for cell elongation and regulating the rates of membrane insertion (exocytosis) and retrieval (endocytosis).

Plant-pathogen Interactions

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

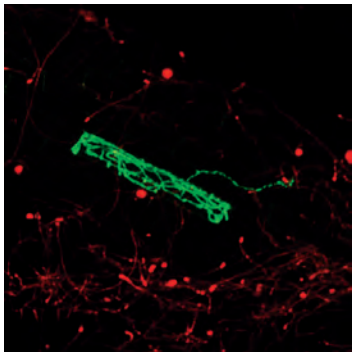
Frank Takken	Assistant Professor
Martijn Rep	Assistant Professor

Introduction

Plant-pathogen interactions result 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 R protein 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

- Two important breakthroughs related to *F. oxysporum* avirulence factors were achieved. One was the identification of Avirulence factor 1 (Avr1) as a secreted protein and the demonstration that it suppresses Resistance-gene mediated immunity. The second was the identification of Avirulence factor 2 (Avr2), also as a secreted protein, and the demonstration that it can trigger a resistance reaction in leaves when co-expressed with the matching resistance gene, I-2.

- *F. oxysporum* isolates that attack tomato were found to contain a unique 'tomato wilt' chromosome carrying most avirulence and effector genes encoding small proteins secreted during colonization. This chromosome was experimentally transferred to a non-pathogenic isolate, and this isolate thereby became a tomato pathogen. This phenomenon has never been reported before, and implies that horizontal gene transfer may be an important factor in the evolution of pathogenicity in fungi.

- Most resistance (R) proteins contain a nucleotide-binding domain, NB-ARC, which is also found in metazoan proteins Apaf-1 and CED-4. A highly conserved methionine-histidine-aspartate (MHD) motif is present at the carboxy-terminus of the NB-ARC. Extensive mutational analysis of I-2 and Mi-1 revealed an important regulatory role for the MHD. Based on a 3D model built on the Apaf-1 template structure we propose that the MHD motif fulfils the same function as the sensor II motif found in AAA+ proteins; coordination of the nucleotide and control of subdomain interactions. Subsequent co-expression of (mutant) Mi-1 subdomains revealed that the N and C-terminal domains can functionally trans-complement and form physical intramolecular interactions which allowed us to analyse the intramolecular dynamics of this protein.

- Overexpression of SUMO (small ubiquitin-like modifier) isoforms in Arabidopsis revealed distinct developmental phenotypes revealing non-redundant functions for the individual isoforms. Furthermore, overexpression of SUMO1 and 2, wildtype and conjugation deficient variants, was found to trigger constitutive plant defences thereby specifically linking SUMO1/2 to plant defence.

Other Highlights

The Centre for Biosystems Genomics, in which the Plant Pathology group participates, has again been recognized as a centre of excellence in the Netherlands. This allows us to initiate new projects in 2008.

Future Prospects

- Work on *F. oxysporum* pathogenicity will focus on transcriptional regulation of pathogenicity. The molecular function of '5G2', a probable transcription factor and additional candidate transcriptional regulator will be investigated regarding its' role in initiating a 'pathogenesis program' leading to root invasion.

- We will continue our investigation of the function of the currently identified small secreted proteins in host colonization by looking for interactions with host proteins.

- We will also continue our nucleotide binding studies on I-2, Rx and Mi-1, investigate the role of the regulatory N- and C-terminal domains on ATPase activity and relate nucleotide binding state to intra- and intermolecular interactions.

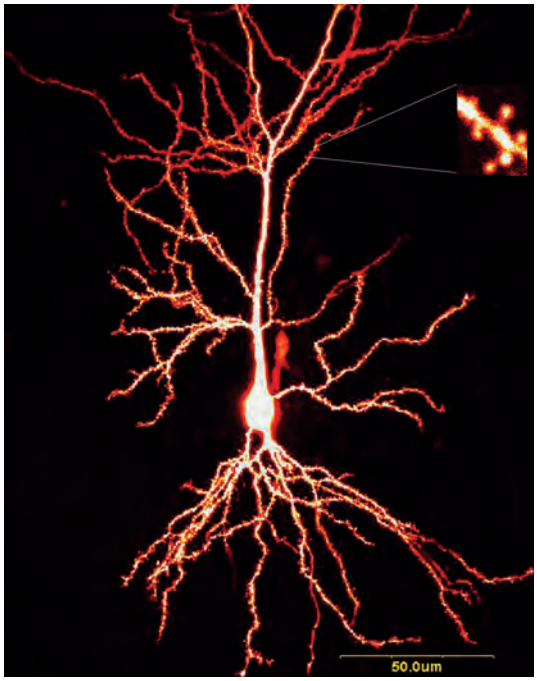
- Furthermore, the function of previously identified I-2 interacting proteins (especially formin, KLC, Trax and Hsp17) will be studied in relation to disease resistance mediated by I-2, Rx and Mi-1 in stably silenced transgenic

plants. A new aim is to elucidate the function of Avr2 and its role in I-2 mediated resistance.

- Transgenic Arabidopsis lines expressing (mutant) SUMO proteins will be used to identify *in vivo* SUMO substrates and to study how SUMO regulates plant defense.

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

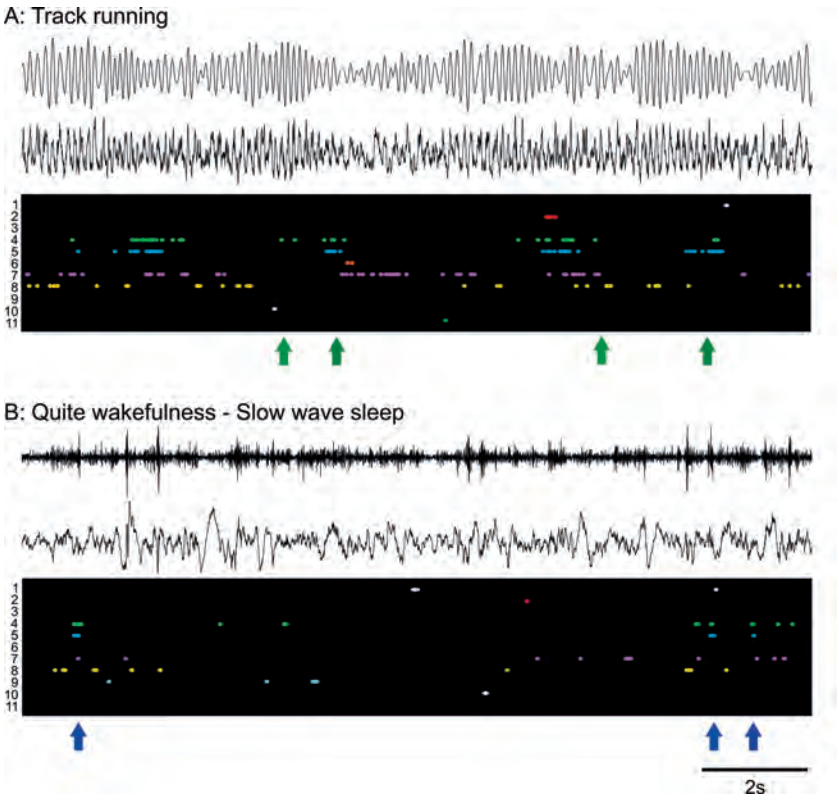
Wim Ghijsen	Assistant Professor
Francesco Battaglia	Assistant Professor
Sander Daselaar	Assistant Professor

Introduction

The global research aim of the APCN group is to elucidate how neuronal networks distributed across the prefrontal cortex, occipital and temporal cortex and ventral 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 subcellular to systems and behavioural levels. 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. In addition, fMRI and TMS are used to study how brain systems interact during encoding, storage and retrieval of information. Translational research from animal to humans (and back) is considered a general specialty of the group.



▲ As a rat was running on a triangle track foraging for sweet rewards (A) and during periods of rest and sleep (B) recordings of neuronal activity were made from two brain areas; i.e. the hippocampus and the ventral striatum. A: the upper two traces show the filtered (top) and raw (bottom) hippocampal EEG. During active behavior like running, the hippocampal EEG showed a regular pattern of oscillations in the theta band frequency (6-10 Hz). In a period of 15s, the rat crossed 4 reward sites (indicated with green arrows). Each row in the plot below the EEG traces represents a single ventral striatal neuron, its spikes being marked by specifically colored dots. Note the high variability in the firing patterns around each reward site arrival but also the positively correlated firing of neurons 4 and 5. B: The hippocampal local field potential during quite resting and slow wave sleep is dominated by large irregular activity interleaved with sharp wave-ripple complexes. Bottom and top traces represented raw and EEG traces. Note the concurrent firing of cell 4 and 5 at the time of a ripple (indicated by blue arrows).

- We are also studying the memory consolidation problem from theoretical and computational viewpoints. We are developing new computational models of memory consolidation and the formation of semantic memories, by making use of concepts from computational linguistics and Bayesian inference.

- Population coding 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. 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 at the mechanistic level. The interaction between striatal output involves the release of amino acid and neuropeptide transmitters. Using brain slices of the striatum and patch-clamp techniques we investigate how variation in presynaptic stimulation patterns leads to differentiation in release between amino acids and neuropeptides, and how these processes affect striatal output. Subcellular mechanisms will be investigated by measuring effects of presynaptic neuropeptide receptor activation/inactivation on fast (~milliseconds) amino acid release in purified nerve terminals.

- 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, e.g. regionally restricted NMDA receptor deletions in hippocampus.

- An important novel research aim is to investigate how neural assemblies in the brain cooperate to generate multimodal (multi-sensory) representations, and how sensory inputs from different modalities are combined to achieve such integrated representations. This goal is being pursued by 2-photon-imaging, fMRI and ensemble recording techniques.

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, we developed and validated technology to causally interfere with hippocampal EEG events (ripples) that are important for memory reactivation.

- In examining the neural basis of reinforcement learning and attention switching, we found that the rat orbitofrontal cortex encodes information about the reward probability an animal expects after having perceived an olfactory cue associated with the reward. Using a novel instrument, we also studied the role of NMDA receptors in the formation of reward-expectancy coding patterns and discovered patterns of oscillatory activity to which spikes is phase-locked. Finally, we studied the dynamics of medial prefrontal ensemble firing patterns when rats are exposed to attentional distracters and engage in attentional switching.

- A post-doc project was started in order to investigate the role of neuropeptides such as Dynorphin and Met-enkephalin in intrasynaptic communication inside the nucleus accumbens. For that purpose, synaptic transmission between interconnected medium-sized spiny neurons is being measured by dual whole-cell patch clamp electrophysiology monitoring inhibitory GABAergic postsynaptic currents and potentials upon presynaptic stimulation.

- 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 identified hereditary components in learning and memory disorders with high degrees of chromosomal linkage. A first series of recordings was successfully conducted in mice with hippocampal NMDA-receptor deletions. These mice performed a food-reward search task in a star-shaped maze, allowing to probe the allo- or egocentric strategies that animals may use for spatial navigation and foraging.

- We finished data analysis of two fMRI experiments. The first experiment investigated whether reactivation processes in the human brain can be detected in a way that is analogous to the results found in animals. Results showed that learning-related brain areas reactivated during rest after training, and the extent of reactivation was positively correlated with the degree of prior learning. At the same time, activity decreased in regions that are normally active during rest, and this change was also directly coupled with the extent of reactivation. The second experiment investigated a possible competition between learning and remembering. The fMRI study tested the hypothesis that remembering hinders learning when both processes happen within a brief period. The study yielded three findings. First, remembering old information was associated with impaired learning of new information. Second, this behavioural effect was coupled with suppression of learning-related activity in visual and medial temporal areas. Finally, we show that the mid-ventrolateral prefrontal cortex resolves the memory competition by allowing rapid switching between learning and remembering.

- We devised a computational model of memory consolidation, inspired by concepts from computational linguistics, in which semantic

memories are considered as neural traces that encoding relationships between items, expressed in tree-like graphs, and in which offline reactivation of recent memories acts as a trigger of Monte-Carlo-like training of the correspondent generative model.

- A 2-photon imaging setup has been built up to visualize the morphology and neural activity of neurons in the living mouse brain. The study of spatially ordered structure of neural assembly activity is now feasible *in vivo*.

Other Highlights

The "Synthetic Forager" - STREP EU grant was awarded within the 7th Framework Programme - ICT 217148 . Prof.dr Cyriel Pennartz is co-applicant for this grant, and was awarded about 570.000 euro.

The publication Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2007). Que PASA? The Posterior Anterior Shift in Aging. Cereb Cortex was listed in the Faculty of 1000 Medicine evaluations: *F1000 factor 6* ("Must Read").

Future Prospects

- 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 animal-human translational research will be pursued.

- The role of neuropeptides in intra-striatal synaptic communication will be investigated upon cocaine-induced behavioural sensitization.

- The *in vivo* 2-photon imaging technique, combined with bulk labelling of neurons with Calcium-indicator dyes *in vivo*, will permit us to study the consequences of associative learning and multimodal interactions in the population dynamics of sensory neurons in the rat neocortex

- 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).

- We aim to complete the ensemble recordings from mice with hippocampal NMDA-receptor deletions performing for the star-maze task. This project will also be the test-bed for the development of a wireless electrophysiology recording system, funded by a STW grant. New mutant mouse lines will be recorded to probe the molecular mechanisms governing hippocampal memory consolidation processes and spatial representation.

- We plan a new series of experiments investigating the interaction between the hippocampus and prefrontal cortex during sleep, by using Local Field Potential and Current Source Density Analysis methods.

- We plan to follow-up our recent fMRI experiments on memory formation & retrieval using transcranial magnetic stimulation, which allows us to temporarily disrupt the brain regions that were active in the fMRI experiments.

- The question of how neural assemblies in the brain cooperate to generate multi-sensory representations will be pursued using ensemble recording techniques applied to several neocortical and hippocampal recording areas simultaneously.

Cellular and Systems Neurobiology

Chairholder: Prof.dr W.J. Wadman

Hans van Hooft	Assistant Professor
Jan Gorter	Assistant Professor
Taco Werkman	Assistant Professor
Natalie Cappaert	Assistant Professor (Since 11/07)

Introduction

Excitability is still the most prominent property of the nervous system. 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 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, immuno histochemical, 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 labeled 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 the epilepsy center in Heemstede (SEIN). The therapeutic potential of deep brain stimulation is investigated in patients and in animal models.

The third research line concentrates on specific pharmacological modulation of neuronal circuits. A new line that focuses on the role of the endocannabinoids system has been started. We support the activities of a spin-off company Sensocom.

Most of our experiments are supported by computer modeling, 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.

Research Highlights

Within the research line on epilepsy projects, both dealing with potential sources of pharmaco resistance came to a successful finish this year. The long standing study that concentrated on the role of the sodium channel in epilepsy and in pharmacoresistance has completed an large study where the responses of different sodium channel subunit types to the standard collection of anti-epileptic drugs was investigated with state-of-the art patch clamp techniques. We observed considerable differences that open possibilities for therapeutic strategies. A new project subsidised by NEF has started to this aim. In a second project the role of the blood brain barrier, which under normal conditions forms an almost impassable barrier to the brain was investigated. Special proteins remove unwanted foreign objects that leak through the barrier and a lot of pharmaceuticals share this fate. However, in particularly during epilepsy, large leakage of the BBB may occur in particular during and after seizures. On the other hand such events also up regulate the protein with the barrier function. Erwin van Vliet carefully investigated this

delicate balance and also manipulated the proteins involved in order to understand their role. The challenge was also to find differences in transport into the brain for classical and new anti-epileptic drugs, which has potential therapeutic value. After successful defence of his thesis Erwin continued as a post-doc on this project.

The studies on homeostatic scaling of brain excitability were restarted with three new project lines: one that aims at revealing the molecular mechanisms behind the increase/decrease of HCN expression (in collaboration with prof. Tallie Baram in Irvine , CA) funded by NEF, one that aims at theoretical understanding on how such a mechanism can be incorporated in large networks without serious negative consequences for stability, learning and memory in such networks and one project that aims at applying this knowledge in therapeutic strategies in particular involving deep brain stimulation. The link with the clinic in Ghent proved to be very useful in this sense.

The use of Voltage Sensitive Dyes for parallel recording from large numbers of sites in (neuronal (slice) networks has finally surpassed the level of technical developments and a first study that proves its use as a technique to understand functional connectivity between larger brain structures was published. We predict that this technique will be incorporated in many other research projects as it is the best way investigate synchronization in large neuronal populations (epilepsy) as pilots show that it is quite possible to identify cortical columnar organization (5 HT3 project) and as it might be the best way to determine the spatial extend of functional stimulation.

Finally the series of studies that used modelling, mainly at the cellular level, to understand the generation of epileptic seizures, spreading depression and the role of ion homeostasis in these events, was completed and finished with theses defences. In a new project on computational modelling we will investigate how the cellular knowledge can best be expanded to understand network behaviour.

Other Highlights

Yaov Noam received the Unilever research prize for this experimental work.

Taco Werkman acquired and started a large research grant in the context of the Top Institute Pharma and in collaboration with Solvay Pharmaceuticals.

Hans van Hooft acquired an ALW grant to further investigate the role of the 5HT3 receptor in columnar cortical development.

Jan Gorter acquired a NEF grant to continue the studies on the role of inflammation in epileptogenesis.

Future Prospects

The almost complete renewal of the AIO crew in our group has lead to a considerable redefinition of the project lines, in light of current international developments. As all lines were very successful in acquiring external funding there was no reason to limit our efforts; the refocus on basic mechanisms of phenomena with strong clinical relevance (epileptogenesis, pharmaco resistance Deep Brain Stimulation, Cortical development, Cannabinoid modulation) will therefore be continued with fresh spirits. The fact that we are strongly supported by at least three industrial partners underscores the societal relevance of the questions we are dealing with.

Hormonal Regulation of Signal Transduction in the Brain

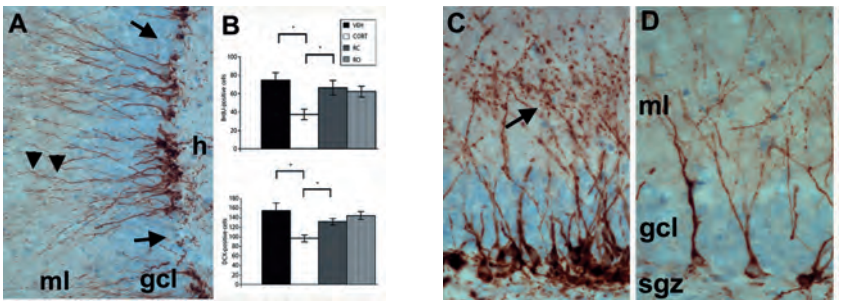
Chairholder: Prof.dr M. Joëls

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 and network processes that are altered by stress hormones like corticosterone, in interaction with other stress-released modulators such as noradrenaline. 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, changing 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 generation, morphology and turn-over 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 and the individual differences in susceptibility to adverse effects thereof. We particularly focus on 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 the natural variation of maternal care.
A separate research line concerns the role of structural plasticity 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.



▲ A) New neurons in the adult hippocampus as identified by Doublecortin (DCX) immunostaining. The presence of empty regions or "gaps" (arrows) where no DCX positive cells are found, is more frequent in stressed animals.
B) Quantification of BrdU- and DCX-positive cell numbers in the hippocampus of rats treated with vehicle (veh), corticosterone (cort) or corticosterone plus a blocker of the stress hormone receptor (RC), and with the blocker alone (RO). The significant reduction in both newborn cells after chronic stress or chronic corticosterone treatment is normalized by giving the blocker for the last 4 days (Mayer et al., 2006; Oomen et al., 2007).
C+D) Details of the different individual morphology of DCX-positive cells showing strong immunostaining of long and complex processes extending into the ml (arrow)(C), versus regions with less cells and often shorter and less complex dendritic extensions (D). In chronically stressed animals, the latter type is more prominent.

Research Highlights

We completed an extensive study showing that corticosterone rapidly and reversibly activates the ERK pathway in CA1 pyramidal neurons, via presynaptically located mineralocorticoid receptors. This enhances release probability of glutamate-containing vesicles. The hormone also activates ERK via postsynaptic mineralocorticoid receptors, thus reducing the A-current. Potentially both processes rapidly increase excitability of CA1 cells.

Rapid and delayed corticosteroid actions seen in the CA1 area cannot be generalized to other brain regions. For instance we found that delayed attenuation of the firing frequency of CA1 neurons by corticosterone (as earlier described) does not occur in basolateral amygdala neurons; rapid effects are also region-specific. This suggests that conditions which strongly activate the basolateral amygdala -i.e. emotionally arousing situations- may have longer-lasting consequences for brain function than more neutral conditions. In a collaborative study with the laboratories of Guillen Fernandez (RU) and of Anda van Stegeren (UvA) it was indeed found that emotionally arousing pictures are very well remembered by humans who are exposed to a strong stressor or a high dose of stress hormones just before or during the learning trial. The mechanism involved in stress-induced facilitation of memory formation seems to involve trafficking of glutamate receptor subunits. When studying stress effects on structural plasticity, we found that 21 days of chronic stress reduces the survival of adult-generated hippocampal neurons.

This could be normalized already by a 4 day treatment with a glucocorticoid receptor antagonist. These studies are now extended into the early life period.

Other Highlights

- Members of the group of prof.dr Marian Joëls organized a Topschool for 15 MSc /PhD students with 5 international tutors (June 11-15); an international workshop on Stress, Plasticity and Memory (Doorwerth); several symposia during the 6th ENP Meeting (Doorwerth).

- Dr Harm Krugers received a grant from the HersenStichting Nederland and a KNAW China exchange project grant;

- dr Henk Karst received an NWO-ALW grant in the open competition.

- Members of the group of prof.dr Marian Joëls served as referee for many international journals (including the top-tier journals) and funding agencies; prof.dr Marian Joëls was elected on the Editorial Board of the new open access journal Frontiers in Behavioral Neuroscience.

- Prof.dr 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 installed as chairman of the Dutch Neurofederation.
- Prof.dr Marian Joëls was appointed Emil Kraepelin Professor of Psychiatry 2007, at the Max Planck Institute for Psychiatry.

Future Prospects

In the upcoming period we will further explore the functional relevance of rapid non-genomic effects of corticosteroid hormones. On the one hand this will be examined in animal models. We hypothesize that i) nuclear mineralocorticoid receptors are tonically activated and that their actions are not much influenced by ultradian variations in hormone level; ii) glucocorticoid receptor activation quite closely follows the ultradian pulses, but that effects mediated via this receptor follow circadian rather than ultradian variations;
iii) that effects via membrane mineralocorticoid receptors are the only means for hippocampal CA1 neurons to functionally follow an ultradian pattern.

On the other hand we will examine the influence of non-genomic corticosteroid actions in the human brain. We will test the idea that elevated cortisol levels around the time of encoding promote memory processes, while elevations in hormone level taking place several hours before the encoding of information hamper subsequent memory formation.

A second question that will be approached in this year relates to early life events: Is the amount of maternal care that an individual pup receives from its mother a reliable predictor for hippocampal function later in life?

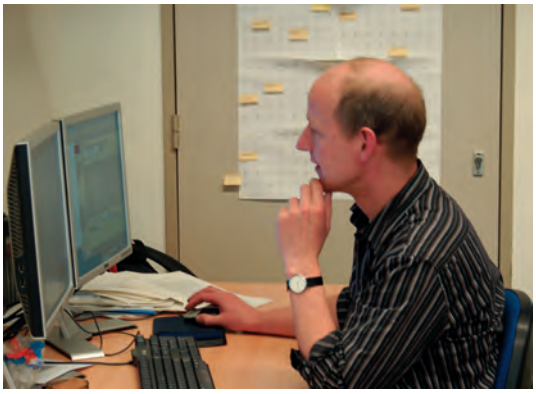
We will also address consequences of early life stress for adult hippocampal structure. We hypothesize that lasting changes are induced in adult proliferation rate and neurogenesis after maternal separation. Do such changes have functional implications for the circuit and can they be reversed by e.g. antidepressant drugs? We will further focus on a better understanding of the cell cycle changes in the Alzheimer hippocampus using transgenic mice and human brain tissue.

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. Bio-informatics 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 three research themes that are carried out in close collaboration with other groups within and beyond the Swammerdam Institute for Life Sciences (SILS) of the University of Amsterdam, i.e., (i) systematic analysis of protein-protein interactions, (ii) post-transcriptional regulation of gene expression, and (iii) host-fungal pathogen interactions. 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

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, and (iii) host-fungal pathogen interactions. In program (i) we will explore the use of BAMG to map protein-protein interactions in complex biomatrices. The development of accurate LC-FT-ICR-MS and novel software in our second research line opens new ways to study tertiary structure of multi-domain proteins and topology of protein complexes by identification of artificial isotopically labeled cross-links and/or natural cross-links such as disulfide bonds. Accurate mass mapping of the latter will give insight in intramolecular domain-domain interaction in heavily glycosylated fungal cell wall proteins that are not amendable to straightforward crystallization. In collaboration with the group of prof Sinz (Martin-Luther-Universität Halle-Wittenberg) we will structurally characterize conformational change of the peroxisome proliferator-activated receptor alpha (PPARα) complex upon ligand interaction by identification of isotopically labeled cross-links. With the Popolo group (Università degli Studi di Milano) we will study the structure and function of the X8 domain subfamily of cell wall β(1,3)-glucanases. (ii) In collaboration with Prof. dr Klaas Hellingwerf and Prof. dr Joost Teixera 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* have been pulse labeled with the proteogenic unnatural amino-acid azidohomoalanine (AZHAL) before, during and after the transition from aerobic to anaerobic metabolism. In the upcoming period we will develop selective and sensitive methods for sequestration, MS identification and quantification of AZHAL containing peptides in total *E. coli* cell lysates. Within the scope of IOP Vertical Genomics we will map quantitatively 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*, *Saccharomyces spec* and other fungi. We will continue the productive collaborations with the groups of the SILS-plant cluster.

Future Prospects

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protein interactions, (ii) post-transcriptional regulation of gene expression, and (iii) host-fungal pathogen interactions. In program (i) we will explore the use of BAMG to map protein-protein interactions in complex biomatrices. The development of accurate LC-FT-ICR-MS and novel software in our second research line opens new ways to study tertiary structure of multi-domain proteins and topology of protein complexes by identification of artificial isotopically labeled cross-links and/or natural cross-links such as disulfide bonds. Accurate mass mapping of the latter will give insight in intramolecular domain-domain interaction in heavily glycosylated fungal cell wall proteins that are not amendable to straightforward crystallization. In collaboration with the group of prof Sinz (Martin-Luther-Universität Halle-Wittenberg) we will structurally characterize conformational change of the peroxisome proliferator-activated receptor alpha (PPARα) complex upon ligand interaction by identification of isotopically labeled cross-links. With the Popolo group (Università degli Studi di Milano) we will study the structure and function of the X8 domain subfamily of cell wall β(1,3)-glucanases. (ii) In collaboration with Prof. dr Klaas Hellingwerf and Prof. dr Joost Teixera 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* have been pulse labeled with the proteogenic unnatural amino-acid azidohomoalanine (AZHAL) before, during and after the transition from aerobic to anaerobic metabolism. In the upcoming period we will develop selective and sensitive methods for sequestration, MS identification and quantification of AZHAL containing peptides in total *E. coli* cell lysates. Within the scope of IOP Vertical Genomics we will map quantitatively 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*, *Saccharomyces spec* and other fungi. We will continue the productive collaborations with the groups of the SILS-plant cluster.

Biosystems Data Analysis

Chairholder: Prof.dr A.K. Smilde

Huub Hoefsloot	Associate Professor
Johan Westerhuis	Assistant Professor
Antoine van Kampen	Professor (0.2 fte)

Introduction

General goal: Developing and validating methods for organizing, summarizing and visualizing complex biological data.

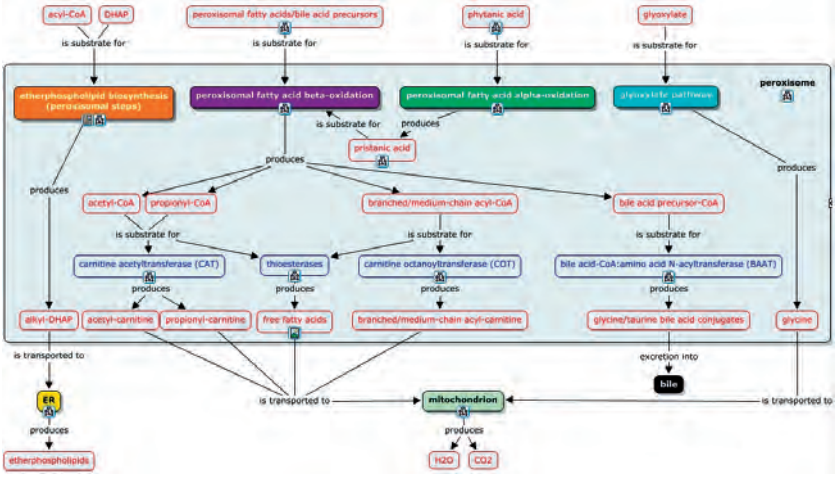
Specific: The research is divided in two closely related themes: biomedical bioinformatics and biostatistics for systems biology

Biomedical bioinformatics

Challenges in systems biology, biomedical research and e-bioscience include the organization, representation, integration and presentation of knowledge and experimental data. A knowledge base framework dedicated to the biomedical domain will provide mechanisms to address these challenges. The knowledge base framework uses an ontology based on the Web Ontology Language (OWL) to represent the data while graphical concept maps (Figure 1) are used to organize and present pieces of information to the researcher or clinician. The concept maps may describe systems at a multi-scale level (in time and space), which may provide input for data-driven and mechanistic models. The OWL ontology and concept maps provide the base to integrate experimental data, information from the public biological databases and results from modelling. The knowledge base frame work can be used to describe any specific domain (e.g., pathway, organelle, cell, organ, organism) and provides the user with overview and insight in this domain.

Biostatistics for systems biology

In systems biology an abundance of omics data is generated. These data have to be analyzed to infer properties of the biological system. These analyses are done by making models and fitting the data to the models. The estimated model parameters serve then as the vehicle for understanding the underlying phenomena of the system. The models used can



▲ Example of a concept map showing the four key peroxisomal pathways. Icons associated with specific concepts provide links to other concept maps or information resources.

range from purely data driven models (multiway component analysis and extensions) to mechanistic models (e.g. sets of differential equations) and combinations of those models; so called grey models. These grey models form the bridge between the two themes: biological a priori knowledge can be formalized in concept maps and thus incorporated into the grey models. Mostly, proteomics and metabolomics data are being analyzed. The biological application areas are very diverse: microbiology, nutrition, medical biology, toxicology and pharmacology.

Research Highlights

Biomedical bioinformatics

A first version of the knowledge base framework was implemented (Willemsen et al, in preparation) and used to describe the main peroxisomal metabolic pathways and related disorders (Komen et al, in preparation). We initiated the development of a knowledge base that provides a structured and comprehensive definition of the vascular endothelium-specific MAPK pathway in atherosclerosis and arteriogenesis. The peroxisome knowledge base can be accessed through *http://amc-app1.amc.sara.nl/Cmap_Knowledge_Browser/init.do.*

Biostatistics for systems biology

Two important contributions were made. The first one concerns validation tools. Such tools provide figures of merit for the reliability of the obtained results from a statistical analysis. Three papers were published on this topic in various journals with various applications (see key publication 1). Another important contribution is the publication of a show-case of the power of grey models to understand complex biological systems (see key publication 2).

Other Highlights

- Prof.dr Age Smilde holds a part-time position of program manager biostatistics at TNO Quality of Life (Zeist, The Netherlands).

Future Prospects

Biomedical bioinformatics

The OWL ontology underlying the information provided by the concept maps will be improved and extended. Moreover, we aim to integrate this broad ontology with other biomedical ontologies and vocabularies to further standardize the representation of information and experimental data. We will start the development of a 'knowledge editor' that must streamline the addition of concept maps to the database. Approaches will be developed to integrate the knowledge base with data-driven and mechanistic modelling to gain further insight in biological systems.

Biostatistics for systems biology

Multivariate discriminant methods for data with a complex underlying design will be developed by extending the ASCA method with a discriminant analysis option. A start will be made with the development of methods to combine systems theory approaches with biological knowledge to estimate the connectivity in a biological network. Multivariate data analysis methods disregard the knowledge already available of the system that is studied, but use abstract statistical parameters to focus the analysis. We want to make new data analysis methods that use the prior information already in the analysis of the data. This will adjust the focus towards the prior knowledge. Previously we used the experimental design, smoothness and transcription factor connection strength as prior information. Recently, biological information is being formalized in knowledge or concept maps. In the following years we will work in incorporation

of these concept maps in data analysis tools such that the interpretation of the data models will be improved considerably. Furthermore, we will work on the design of experiments in complex dynamic studies. How many individual are needed in each treatment group, how often, when and which compartment should be measured in order to obtain sufficient information of the treatment.

Micro Array Department and Integrative Bioinformatics Unit

Group leader: Dr. T.M. Breit

Floyd Wittink	Project management "wet-lab"
Martijs Jonker	Project management "dry-lab"
Jenny Batson	Project Administration
Marco Roos	Senior Researcher IBU
Han Rauwerda	Senior Researcher IBU

Introduction

Microarray technology is 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, during specific growth or stress conditions, 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. 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-IBU consist of i) a microarray technology section (Wet-lab) with ~5 specialists that provide transcriptomics service & support and perform microarray technology R&D; ii) a microarray data-analysis section (Dry-lab) with ~11 bioinformaticians that provide transcriptomics data analysis service & support and performs bioinformatics R&D; and iii) a management part with 2 staff members. Together, the MAD operates as a transcriptomics technology and bioinformatics expertise centre and core facility for UvA scientists, as well as 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.

The focus of the Wet-lab R&D is to improve the microarray technology for transcriptomics with a strong focus on sample size reduction. We aim to eventually analyze single cells by microarray technology. The focus of the Dry-lab is on the

methods, tools and infrastructure necessary to perform advanced transcriptomics data-analysis starting from array design until publication. Another important focal point for the whole group is design-for-experimentation. Performing well designed range finding experiments should elucidate the role of time and space in microarray transcriptomics experiments. To this end, MAD-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 Wet-lab started work on the Luminex system, which is a bead-based high-throughput transcriptomics analyses system. This work was started as a strategic collaboration with the Luminex Corp. It also developed a microarray protocol for single-embryo transcriptomics analysis on Zebra fish.

The Dry-lab has built an actual e-BioScience laboratory (e-BioLab) on the Virtual L for e-(Bio)Science problems that enables domain interaction with the aim to extend the possibilities for computer-assisted experimental biology research. The e-BioLab was officially opened December 13, 2007.

In addition the Dry-lab extended the MicroArray Problem Solving Environment with many automated elements for microarray data analysis and inter-pretation, like probe reannotation (Dai+ and OligoRap) and experiment check (HybQC). It has produced many (collaborative) research articles.

Other Highlights

The Micro Array Department and Integrative Bioinformatics Unit of dr Timo Breit has initiated strategic collaborations with several external research organisations: Laboratorium voor Toxicologie, Pathologie en Genetica (TOX), RIVM, (Bilthoven); Medical Microbiology, UMC (Utrecht); ACTA, VU-AMC (Amsterdam); Moleculaire Celbiologie, UL, (Leiden).

Future Prospects

- Perform a hallmark time-axis microarray experiment on Zebrafish.
- Establish range-finding protocols for Luminex system.
- Introduce the 500K Affymetrix SNP analysis.
- Extension of the MicroArray Problem Solving Environment for microarray data analysis and interpretation
- Set-up the basic infrastructure for prokaryote transcriptomics data handling.
- Develop methods, tools, and infrastructure to translate prokaryote high-throughput de-novo sequence information into microarray designs.
- Write > 15 (collaborative) research articles.

3. Societal Activities

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. Prof.dr Michel Haring, Professor in Plant Physiology of the Swammerdam Institute has given a lecture with the title "How do plants smell?" (*Hoe ruikt een plant?*) in this lecture series on April 22, 2007. In this lecture he explained the children that plants have a scent, and can notice scents given off by the plants that stand next to them. When plants are attacked (eaten by a cow, or by insects) they can give off extra signals, that other pants can sense, and that we can smell. These signals warn the other plants for danger, and they will produce molecules that give a bad taste. The cow will move away, to eat other plants. Plants also use scents to attract insects that they need to pollinate them.

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. 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

The integrated results for 2007 show an operating shortage of 309 k€ where a negative result of 423 k€ was budgeted. Compared with the budgeted result the financial performance of SILS was close to expected. However, the amount of -309 k€ gives a distorted view on the institute's financial performance because the financial system introduced in 2006 still delayed some transactions. This resulted in the integration of >300 k€ costs which should not have been included. A correction is expected in 2008.

Revenues and costs over 2007, compared with previous years							
	2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
University funding*	5838	6131	7364	8987	7577	13234	12795
External funding	3852	3883	4474	6167	4515	4701	4952
Total revenues	**9690**	**10014**	**11838**	**15154**	**12092**	**17935**	**17747**
Personnel costs	7096	7465	8919	9626	9122	12816	13918
Bench fees	2236	2450	3310	4989	2729	5362	4138
Total costs	**9332**	**9915**	**12229**	**14614**	**11851**	**18178**	**18056**
Result	**358**	**99**	**-391**	**540**	**241**	**-243**	**-309**

* All amounts are given in K Euro.

Figure: representation of revenues and costs of the Swammerdam Institute for Life Sciences, in k€, for the years 2001-2005.
In this table -starting from 2004-external funding is considered to be 2nd and 3rd funding source only.

Funding

The funding system of Dutch universities distinguishes three different kinds of funding resources. These are referred to as so called "funding sources" and are numbered one to three. Resources originating from the university itself 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).

	2003	**2004**	**2005**	**2006**	**2007**
Revenues	7793	8987	7577	13234	12795
Costs	8291	8902	7357	13580	13259
Result	**-498**	**85**	**220**	**-346**	**-464**

Figure 1: representation of income and costs in the 1st funding source, in k€, for the years 2003-2007.

	2003	2004	2005	2006	2007
Revenues	2279	2303	2160	2032	2299
Costs	2279	2303	2160	2048	2226
Result	0	0	0	-16	73

Figure 2: representation of income and costs in the 2nd funding source, in k€, for the years 2003-2007.

	2003	2004	2005	2006	2007
Revenues	1766	3864	2355	2669	2653
Costs	1659	3409	2334	2550	2571
Result	107	455	21	119	82

Figure 3: representation of income and costs in the 3rd funding source, in k€, for the years 2003-2007.

Figure 1 shows that in 2006, first funding source income and costs increased by almost 6000 k€ compared to 2005. This increase is the result of the introduction of a new university wide full-cost financial system. Essentially all kinds of costs that were not, or not completely, calculated in previous years (housing, ICT infrastructure, etc) were calculated to the institute as of 01-01-2006. Simultaneously budgets were increased.
This explains the difference in financial terms but does not give a good view on the effects on research and education capacity. Therefore, the slightly decreased number of employees is a better indicator.

Funding from the Dutch Organization for Scientific Research (2nd funding source) remains stable in the past years. Third funding source income slightly increased in the past years. The numbers of 2004 profited from two major incidental incomes explaining the decrease. The first incidental revenue in 2004 existed of 1045 k€ that SILS received for its role as coordinator of an EU program. This was transferred directly to other partners in this program. The second was a 404 k€ result of the successful sales of a spin-off company.

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-out 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 causes 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-out companies. In the collaborations with industry the institute looks for 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: g.p.c.m.vandesande@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

As stated in the last Annual Reports, the Swammerdam Institute for Life Sciences is divided over two locations and looking forward to completion of the new planned building of the faculty. The actual building process started with the construction of the greenhouse in 2004. This greenhouse has been taken into service in 2006. In the summer of 2007 the construction of the main buildings started. In the spring of 2009, the first part of the institute will move to this new location.

Appendix 1. Research Results

Appendix 1a

Molecular Microbial Physiology

Chairholder: Prof.dr K.J. Hellingwerf

Research Results in Numbers

Peer reviewed publications	17
Non-peer reviewed publications	3
PhD Theses	3
Patent applications	3

Staff (Research input in fte during 2007)

Klaas Hellingwerf	Chairholder
Jeroen Hugenholtz	Honorary Professor (bijzonder hoogleraar)
Joost Teixeira de Mattos	Professor

Position	FS1*	FS2**	FS3◊	Total
Chairholder/Professor	0.75	0	0	0.75
Associate/Assist. prof.	0.25	0	0	0.25
Research Fellow	0.9	1.7	0	2.6
PhD Student	0	0.9	2.0	2.9
Technician	0.8	0	0.6	1.4
Total	**2.7**	**2.6**	**2.6**	**7.9**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Gauden M, Grinstead JS, Laan W, van Stokkum IHM, Avila-Perez M, Boelens R, Kaptein R, van Grondelle R, Hellingwerf KJ and Kennis JTM (2007). On the Role of Aromatic Side Chains in the Photoactivation of BLUF Domains. *Biochemistry* 46: 7405-7415.

Brooijmans, R.J., Poolman, B., Schuurman-Wolters, G.K., de Vos, W.M., & Hugenholtz, J. (2007). Generation of a membrane potential by *Lactococcus lactis* through aerobic electron transport. *J. Bacteriol*. 189: 5203-5209

PhD Theses

Mensonides, F.I.C. (2007, May 16). *How Saccharomyces cerevisiae copes with heat stress. An experimental and theoretical study.* UvA Universiteit van Amsterdam (Amsterdam). Prom./coprom.: prof.dr. S. Brul, prof.dr. K.J. Hellingwerf & dr. M.J. Teixeira de Mattos.

Vreede, J. (2007, February 15). *Structural basis and dynamics of signal transduction in the pas protein family*. UvA Universiteit van Amsterdam (Amsterdam: PrintPartners Ipskamp). Prom./coprom.: prof.dr. K.J. Hellingwerf & prof.dr. W. Crielaard.

Zakrzewska, A.M. (2007, October 02). *Exploring plasma membrane stress response in Saccharomyces cerevisiae with functional genomics*. UvA Universiteit van Amsterdam (Warsaw: Printing House Zakrzewska Broth.). Prom./coprom.: prof.dr. S. Brul & prof.dr. K.J. Hellingwerf.

Patent applications

Brooijmans, R.J. & Hugenholtz, J. (01-12-2007). Heme (and vitamine K2) dependent nitrate reduction in *Lactobacillus plantarum*. no P6014245EP.

Hellingwerf, K.J. & Teixeira de Mattos, M.J. Light-driven CO2-reduction to organic compounds to serve as fuels or as industrial half products by an autotroph containing a fermentative gene cassette. no P6017380EP.

Wegkamp, A., Santos, F., Hugenholtz, J. & Smid, E.J.. Increased folate levels by fermenting melon juice. no P6016483EP.

Academic publications (refereed)

Alexandre, M.T.A., Arents, J.C., van Grondelle, R., Hellingwerf, K.J. & Kennis, J.T.M. (2007). A base-catalyzed mechanism for dark state recovery in the *Avena sativa* phototropin-1 LOV2 domain. *Biochemistry*, 46, 3129-3137.

Bekker, M., Kramer, G., Hartog, A.F., Koster, C.G. de, Hellingwerf, K.J. & Teixeira de Mattos, M.J. (2007). Changes in the redox state and composition of the quinone pool of *Escherichia coli* during aerobic batch-culture growth. *Microbiology*, 153, 1974-1980.

Bekker, M., Teixeira de Mattos, M.J. & Hellingwerf, K.J. (2007). The role of two-component regulation systems in the physiology of the bacterial cell. *Sci.Progress, 89*, 213-242.

Brooijmans, R.J., Poolman, B., Schuurman-Wolters, G.K., de Vos, W.M. & Hugenholtz, J. (2007). Generation of a membrane potential by *Lactococcus lactis* through aerobic electron transport. *J. Bacteriol.*, 189, 5203-5209.

Deng, D.M., Cate, J.M. ten & Crielaard, W. (2007). The adaptive response of *Streptococcus mutans* towards oral care products: Involvement of the C1pP serine protease. *Eur.J.Oral Sci.*, 115, 363-370.

Deng, D.M., Liu, M.J., ten Cate, J.M. & Crielaard, W. (2007). The VicRK system of *Streptococcus mutans* responds to oxidative stress. *Journal of Dental Research*, 86, 606-610.

Gauden, M, Grinstead, J.S., Laan, W.W.J., Stokkum, I.H.M. van, Avila-Perez, M., Boelens, R., Kaptein, R., Grondelle, R. van, Hellingwerf, K.J. & Kennis, J.T.M. (2007). On the role of aromatic side chains in the photoactivation of BLUF domains. *Biochemistry*, 46, 7405-7415.

Horst, M.A. van der, Arents, J.C., Kort, R. & Hellingwerf, K.J. (2007). Binding, tuning and mechanical function of the 4-hydroxy-cinnamic acid chromophore in photoactive yellow protein. *Photochem. Photobiol. Sci.*, 6, 571-579.

Horst, M.A. van der, Key, J. & Hellingwerf, K.J. (2007). Photosensing in chemotrophic, non-phototrophic bacteria: Let there be light sensing too. *Trends Microbiol., 15*(12), 554-562.

Ladero, V., Ramos, A., Wiersma, A., Goffin, P., Shanck, A., Kleerebezem, M., Hugenholtz, J., Smid, E.J. & Hols, P. (2007). High-level production of the low-calorie sugar sorbitol by *Lactobacillus plantarum* through metabolic engineering. *Appl. Environ. Microbiol., 73*, 1864-1872.

Loiseau, L., Gerez, C., Bekker, M., Ollagnier-de Choudens, S., Py, B., Sanakis, Y., Teixeira de Mattos, M.J., Fontecave, M. & Barras, F. (2007). ErpA, an iron sulfur (Fe S) protein of the A-type essential for respiratory metabolism in *E.coli*. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 13626-13631.

Majerus, T., Kottke, T., Laan, W.W.J., Hellingwerf, K.J. & Heberle, J. (2007). Signal relay within the blue-light receptor AppA traced by time-resolved FTIR spectroscopy. *ChemPhysChem., 8*, 1787-1789.

Rademaker, J.L., Herbet, H., Starrenburg, M.J., Naser, S.M., Gevers, D., Kelly, W.J., Hugenholtz, J., Swings, J. & van Hylckama Vlieg, J.E.T. (2007). Diversity analysis of dairy and non-dairy *Lactococcus*

lactis isolates, using a novel multilocus sequence analysis scheme and (GTG)5-PCR fingerprinting. *Appl. Environ. Microbiol.*, 73, 7128-7137.

Santos, F., Vera, J.L., Lamosa, P., de Valdez, G.F., De Vos, W.M., Santos, H., Sesma, F. & Hugenholtz, J. (2007). Pseudovitamin B12 is the corrinoid produced by *Lactobacillus reuteri* CRL1098 under anaerobic conditions. FEBS lett., 581, 4865-4870.

Wells-Bennik, M., Hugenholtz, J. & Olieman, K. (2007). Natuurlijke verrijking van gefermenteerde producten met vitamine K. *Voedingsmiddelen-technologie, 10*, 14-16.

Zhang, J., Fu, R.Y., Hugenholtz, J., LI, Y. & Chen, J. (2007). Glutathione protects *Lactococcus lactis* under acid stress. *Appl. Environ. Microbiol.*, 73, 5268-5275.

Book Chapter

Bouwman, J., van Eunen, K., Tuzun, I., Postmus, J., Canelas, A., van der Brink, J., Lindenbergh, P.A., Teixeira de Mattos, M.J., Smits, G.J., Brul, S., Hellingwerf, K.J., Westerhoff, H.V. & Bakker, B.M. (2007). Standardization and *in vivo*-like enzyme activity measurements in yeast. In M.G. Hicks & C. Kettner (Eds.), *Experimental Standard Conditions of Enzyme Characterizations* (Vol.2) (pp. 11-20). Frankfurt, Germany: Beilstein-Institut.

Hugenholtz, J. & van Hylckama Vlieg, J.E.T. (2007). Monitoring cheese ripening: new developments. In B.C. Weimer (Ed.), *Improving the flavour of cheese* (pp. 351-370). Cambridge, England: Woodhead Publ.Ltd..

Mensonides, F.I.C., Bakker, B., Brul, S., Hellingwerf, K.J. & Teixeira de Mattos, M.J. (2007). A kinetic model as a tool to understand the response of *Saccharomyces cerevisiae* to heat exposure. In S Brul, S. van Gerwen & M. Zwietering (Eds.), *Modelling microorganisms in Food* (pp. 228-249). Cambridge U.K.: Woodhead.

Invited Lectures

Hellingwerf, K.J. (2007, December 13). *On the photobiology of chemotrophic micro-organisms.* Nagoya, Japan, Lecture Nagoya University.

Hellingwerf, K.J. (2007, December 12). *On the use of ultra-fast spectroscopy to study the mechanism of photoreceptor activation.* Okazaki, Japan, Morino Lecture, Institute for Mol.Science.

Hellingwerf, K.J. (2007, December 11). *Photosensory proteins as vehicles to bridge computational biophysics and systems biology to initiate the field of synthetic biology.* Kyoto, Japan, Lecture University of Kyoto.

Hellingwerf, K.J. (2007, October 30). *Flavin-based photoreceptors: radically different.* Amsterdam, Discussion group on Computational Sciences, Dept. Chemistry, University of Amsterdam.

Hellingwerf, K.J. (2007, February 06). *Influence of the crystalline state on photo-induced dynamics of PYP, studied by UV/Vis transient absorption spectroscopy.* Grenoble, Switzerland, ESRF Workshop "Spectroscopy around Biological Crystallography".

Hellingwerf, K.J. (2007, November 26). *Photoreception as a tool in molecular cytology and systembiology.* Vilnius, Lithuania, Workshop New frontiers in biophysics.

Hellingwerf, K.J. (2007, May 02). *Photosensory proteins as vehicles to bridge computational biophysics and systems biology to initiate the field of synthetic biology.* Julych, Germany, Workshop "From computational biophysics to systems biology (CBSB07)".

Hellingwerf, K.J. (2007, May 14). *Photosensory proteins as vehicles to bridge computational biophysics and systems biology to initiate the field of synthetic biology: A key role for Bacillus subtilis.* Groningen, lecture Dept. of Molecular Genetics, University of Groningen.

Hellingwerf, K.J. (2007, May 22). *Photosensory proteins as vehicles to bridge computational biophysics and systems biology to initiate the field of synthetic biology: A key role for Bacillus subtilis.* Buenos Aires, Argentina, Lecture Dept. of Microbiology, University of Buenos Aires.

Hellingwerf, K.J. (2007, October 11). *Radical photobiology.* Leiden, University of Leiden.

Hellingwerf, K.J. (2006, July 26). *Structure-based drug design based on cyclic-di-GMP metabolism.* Parma, Italia, University of Parma: EU-consortium on Dev. of new anti-bacterials.

Hellingwerf, K.J. (2007, April 03). *Two-component systems as a target for the development of new anti-bacterials.* Amsterdam, Task-group meeting IUPAC.

Hugenholtz, J. (2007, May 21). *Comparative systems biology of lactic acid bacteria.* Heidelberg, Workshop at EML on Data Management.

Hugenholtz, J. (2007, May 17). *Metabolic engineering and functional genomics of lactic acid bacteria.* Beijing, China, Invited lecture at Inst. for Microbiology of the Chinese Academy of Sciences.

Hugenholtz, J. (2007, May 16). *Public private partnerships for innovation in food-processing.* Beijing, China, Sino-Dutch Food and Nutrition Seminar.

Hugenholtz, J. (2007, December 12). *Systems biology of lactic acid bacteria.* Wageningen, VLAG-course on Physiology of food-associated microorganisms.

Hugenholtz, J. (2007, June 13). *The role of arginine on the composition of the Lactococcus lactis population in cheese starters.* Papendal, NIZO Dairy Congress.

Hugenholtz, J. (2007, March 21). *Zero-growth of industrial microorganisms.* Orlando, USA, World Congress on Industrial Biotechnology and Bioprocessing.

Hugenholtz, J. (2007, July 15). *Zero-growth of industrial microorganisms.* Quebec, Canada, Congres Biochemical Engineering XV.

Appendix 1b

Molecular Biology and Microbial Safety

Chairholder: Prof.dr S. Brul

Research Results in Numbers

Peer reviewed publications	12
Non-peer reviewed publications	8
PhD Theses	2
Patent applications	3

Staff (Research input in fte during 2007)

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	0.3	0	0.1	0.4
Associate/Assist. prof.	1.0	0	0	1.0
Research Fellow	0	0.9	0	0.9
PhD Student	0.75	0	2.4	3.2
Technician	1.3	0	0	1.3
Total	3.4	0.9	2.5	6.8

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

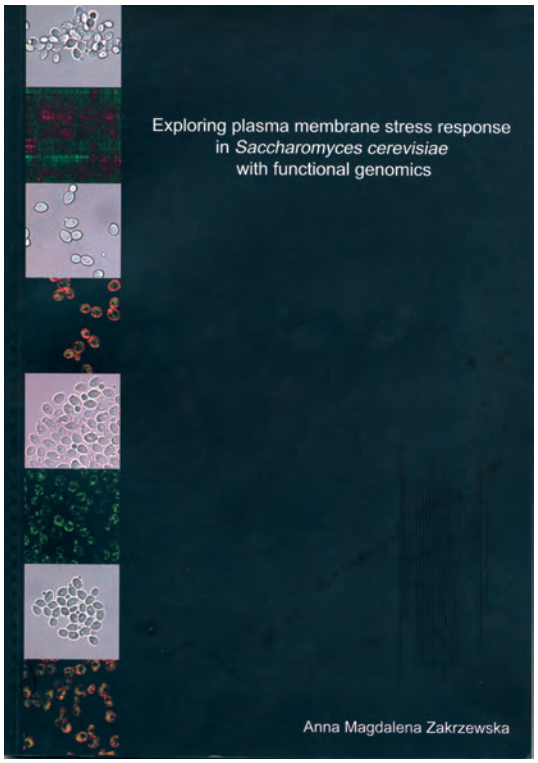
Keijser, B.J.F., ter Beek, A., Rauwerda, H., Schuren, F., Montijn, R., van der Spek, H. and Brul, S. (2007). Analysis of temporal gene expression during *Bacillus subtilis* spore germination and outgrowth. J. Bacteriol. 189, 3624-3634.

Zakrzewska, A., Boorsma, A., Delneru, D., Brul, S., Oliver, S.G. and Klis, F.M. (2007). Identification of cellular processes and pathways that protect yeast cells against the plasma membrane-perturbing compound chitosan. *Euk. Cell* 6, 600-608.

PhD Theses

Mensonides, F.I.C. (2007, May 16). *How Saccharomyces cerevisiae copes with heat stress. An experimental and theoretical study.* UvA Universiteit van Amsterdam (Amsterdam). Prom./coprom.: prof.dr. S. Brul, prof.dr. K.J. Hellingwerf & dr. M.J. Teixeira de Mattos.

Zakrzewska, A.M. (2007, October 02). *Exploring plasma membrane stress response in Saccharomyces cerevisiae with functional genomics.* UvA Universiteit van Amsterdam (Warsaw: Printing House Zakrzewska Broth.). Prom./coprom.: prof.dr. S. Brul & prof.dr. K.J. Hellingwerf, dr F.M. Klis.



Patent applications

Albers, R., Ledeboer, A.M. & Brul, S.. Edible product containing beneficial moulds and/or yeast. no WO/2007/031129.

Albers, W., Brul, S., Ledeboer, A.M. & Mayjer, W.M.. Edible product containing beneficial bacteria. no WO/2007/009568.

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

Academic publications (refereed)

Groot, P.W.J. de, Yin, Q., Weig, M., Sosinska, G.J., Klis, F.M. & Koster, C.G. de (2007). Mass spectrometric identification of covalently bound cell wall proteins from the fission yeast *Schizosaccharomyces pombe. Yeast, 4*(4), 267-278.

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Klis, F.M., Jong, M. de, Brul, S. & Groot, P.W.J. de (2007). Extraction of cell surface-associated proteins from living yeast cells. *Yeast, 24*(4), 253-258.

Klis, F.M., Groot, P.W.J. de & Brul, S. (2007). Identification, characterization, and phenotypic analysis of covalently linked cell wall proteins. *Methods Microbiol.*, 36, 36013-36018.

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a predicted transglycosidase domain affects cell wall organization and virulence of *Candida albicans. J. Biol. Chem., 281*(52), 40399-40411.

Pel, H.J., Winde, J.H. de, Archer, D.B., Dyer, P.S., Hofmann, G., Klis, F.M. & et al., . (2007). Genome sequencing and analysis of the versatile cell factory *Aspergillus niger* CBS 513.88. *Nat. Biotechnol., 2*, 221-231.

Urrutia, G., Arabas, K., Autio, K., Brul, S., Hendrickx, M., Kakolewski, A, Shen, T. & et al., . (2007). SAFE ICE: Low-temperature pressure processing of foods: Safety and quality aspects, process parameters and consumer acceptance. *J. Food Engineer., 83*, 293-315.

Yin, Q., Groot, P.W.J. de, Jong, L. de, Klis, F.M. & Koster, C.G. de (2007). Mass spectrometric quantitation of covalently bound cell wall proteins in *Saccharomyces cerevisiae. FEMS Yeast Res., 7*(6), 887-896.

Zakrzewska, A.M., Boorsma, A., Delneri, D., Brul, S., Oliver, S.G. & Klis, F.M. (2007). Cellular processes and pathways that protect *Saccharomyces cerevisiae* cells against the plasma membrane-perturbing compound chitosan. *Eukaryot.Cell, 6*(4), 600-608.

Book Chapter

Bouwman, J., van Eunen, K., Tuzun, I., Postmus, J., Canelas, A., van der Brink, J., Lindenbergh, P.A., Teixeira de Mattos, M.J., Smits, G.J., Brul, S., Hellingwerf, K.J., Westerhoff, H.V. & Bakker, B.M. (2007). Standardization and *in vivo*-like enzyme activity measurements in yeast. In M.G. Hicks & C. Kettner (Eds.), *Experimental Standard Conditions of Enzyme Characterizations* (Vol.2) (pp. 11-20). Frankfurt, Germany: Beilstein-Institut.

Brul, S., Spek, H. van der, Keijser, B.J.F., Schuren, F., Oomes, S.J.C.M. & Montijn, R.C. (2007). Functional genomics for optimal microbiological stability of processed food products. In C. Doona, P. Dunne & F.E. Feeherry (Eds.), *High Pressure Processing of Foods* (pp. 173-194). Ames, USA: Blackwell.

Brul, S. & Westerhoff, H.V. (2007). Systems biology and food science. In S. Brul, S van Gerwen & M Zwietering (Eds.), *Modelling microorganisms in Food* (pp. 250-288). Cambridge U.K.: Woodhead.

Groot, P.W.J. de, Brandt, B.W. & Klis, F.M. (2007). Cell wall biology of Candida. In Cristophe d'Enfert & Bernhard Hube (Eds.), *Candida comparative and functional genomics* (pp. 293-325). Caister Academic Press.

Klis, F.M. (2007). A molecular and genomic view of the fungal cell wall. In Richard J. Howard & Neil A.R. Gow (Eds.), *Biology of the fungal cell* (The mycota, 8). Berlin, Heidelberg, New York: Springer Verlag.

Klis, F.M., Groot, P.W.J. de & Brul, S. (2007). Identification, characterization, and phenotypic analysis of covalently linked cell wall proteins. In I. Stansfield & M. Stark (Eds.), *Methods in Microbiology* (pp. 281-301). Oxford, UK: Academic Press.

Mensonides, F.I.C., Bakker, B., Brul, S., Hellingwerf, K.J. & Teixeira de Mattos, M.J. (2007). A kinetic model as a tool to understand the response of *Saccharomyces cerevisiae* to heat exposure. In S Brul, S. van Gerwen & M. Zwietering (Eds.), *Modelling microorganisms in Food* (pp. 228-249). Cambridge U.K.: Woodhead.

Smelt, J.P.P.M. & Brul, S. (2007). Modelling lag-time in predictive microbiology with special reference to lag phase of bacterial spores. In S. Brul, S. van Gerwen & M. Zwietering (Eds.), *Modelling lag-time in predictive microbiology with special reference to lag phase of bacterial spores* (pp. 67-81). Cambridge U.K.: Woodhead.

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Brul, S., van Gerwen, S. & Zwietering, M. (Eds.). (2007). *Modelling microorganisms in Food.* Cambridge U.K.: Woodhead.

Brul, S. (Ed.). (2007). *Innovative Food Science and Emerging Techn.*

Brul, S. (Ed.). (2007). *Open Biotechnology Journal.*

Klis, F.M. (Ed.). (2007). *EUKARYOTIC CELL.*

Klis, F.M. (Ed.). (2007). *FEMS Yeast Res.*

Klis, F.M. (Ed.). (2007). *Yeast.*

Invited lectures

Brul, S. (2007, September 18). *Microbial systems biology; new frontiers open to predictive microbiology.* Athens, Greece, 5th International Congress on Predictive Microbiology of Foods.

Brul, S. (2007, June 01). *Strategic research in the Food Industry and contribution by the Food Safety Centre of Excellence.* Melbourne, Australia, Annual meeting of the Australian Inst. for Food Technology.

Brul, S. (2007, September 01). *Functional genomics to enhance the effectiveness of food preservatives; mode of action of sorbic acid, a case study.* Edinburgh, UK, Autumn meeting Soc. for Microbiology.

Brul, S. (2007, July 01). *Understanding microbial systems: the key to improving food safety and quality.* Tasmania, Australia, Distinguished Research Scholar Lecture.

Klis, F.M. (2007, March 11). *Cell wall polysaccharides of fungi and plants.* Biarritz, The first international Fungal/Plant cell wall meeting.

Klis, F.M. (2007, June 01). *Exploring the fungal cell wall proteome.* Graz, Graz University of Technology.

Klis, F.M. (2007, April 17). *Fungal cell surface proteins.* Papendal, Annual Meeting VVvM.

Klis, F.M. (2007, December 11). *Glycoproteomics of the fungal cell wall.* Osnabrueck, University of Osnabrueck.

Klis, F.M. (2007, May 24). *Molecular characterization of the fungal cell wall proteome.* Basel, Biozentrum, University of Basel.

Appendix 1c

Structure and Functional Organisation of the Cell Nucleus

Chairholder: Prof.dr R. van Driel

Research Results in Numbers

Peer reviewed publications	17
Non-peer reviewed publications	0
PhD Theses	1
Patent applications	0

Staff (Research input in fte during 2007)

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/Assist. prof.	1.0	0.5	0	1.5
Research Fellow	0.2	0.1	1.8	2.1
PhD Student	0.9	1.5	0.75	3.2
Technician	2.5	1.0	0.2	3.7
Total	**5.1**	**3.1**	**2.8**	**11.0**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Mateos-Langerak, J., M.C. Brink, M.S. Luijsterburg, I. van der Kraan, R. van Driel, and P.J. Verschure. (2007). Pericentromeric heterochromatin domains are maintained without accumulation of HP1. *Mol Biol Cell.* 18:1464-71.

Tessadori, F., R.K. Schulkes, R. van Driel, and P. Fransz. (2007). Light-regulated large-scale reorganization of chromatin during the floral transition in Arabidopsis. *Plant J.* 50:848-57.

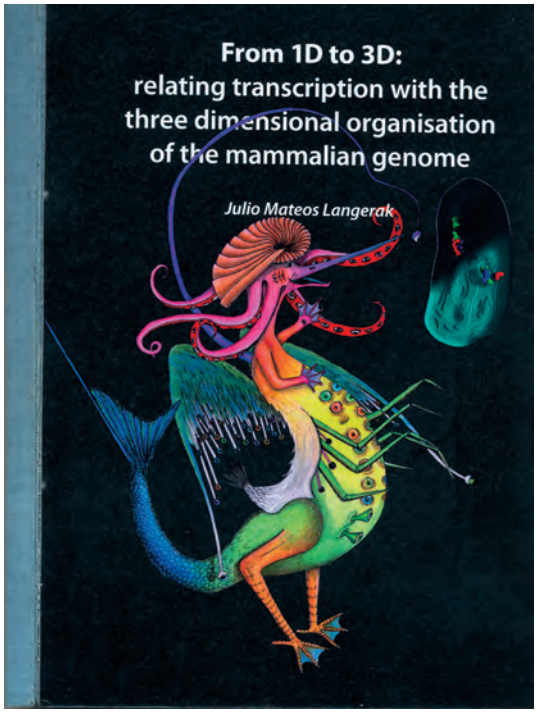
Goetze, S., J. Mateos-Langerak, H.J. Gierman, W. de Leeuw, O. Giromus, M.H. Indemans, J. Koster, V. Ondrej, R. Versteeg, and R. van Driel. (2007).

The three-dimensional structure of human interphase chromosomes is related to the transcriptome map. *Mol Cell Biol.* 27:4475-87.

Haring, M., S. Offermann, T. Danker, I. Horst, C. Peterhansel, and M. Stam. (2007). Chromatin immunoprecipitation: optimization, quantitative analysis and data normalization. *Plant Methods.* 3:11.

PhD Theses

Mateos Langerak, J. (2007, September 19). *From 1D to 3D: relating transcription with the tree dimensional organisation of the mammalian genome.* UvA Universiteit van Amsterdam (142 pag.) (Amsterdam). Prom./coprom.: Prof.dr R. van Driel.



Academic publications (refereed)

Bohn, M., Heermann, D.W. & Driel, R. van (2007). Random loop model for long polymers. *Phys. Rev. E, 76.*

Driel, R. van (2007). Chromatin is wonderful stuff. *SEMIN CELL DEV BIOL, 18*(5), 649-650.

Fakan, S. & Driel, R. van (2007). The perichromatin region: A functional compartment in the nucleus that determines large-scale chromatin folding. *SEMIN CELL DEV BIOL, 18*(5), 676-681.

Gierman, H.J., Indemans, M.H., Koster, J., Goetze, S., Seppen, J., Geerts, D., Driel, R. van & Versteeg, R. (2007). Domain-wide regulation of gene expression in the human genome. *GENOME RES, 17*(9), 1286-1295.

Gladilin, E., Goetze, S., Mateos Langerak, J., Driel, R. van, Rohr, K. & Eils, R. (2007). Stochastical analysis of finite point sampling of 3D chromatin fiber in interphase cell nuclei. *Proc. of BIRD*, 104-118.

Goetze, S., Mateos Langerak, J., Gierman, H.J., Leeuw, W. de, Giromus, O., Indemans, M.H., Koster, J., Ondrej, V., Versteeg, R. & Driel, R. van (2007). The three-dimensional structure of human interphase chromosomes is related to the transcriptome map. *MOL CELL BIOL, 27*(12), 4475-4487.

Goetze, S., Mateos Langerak, J. & Driel, R. van (2007). Three-dimensional genome organization in interphase and its relation to genome function. *SEMIN CELL DEV BIOL, 18*(5), 707-714.

Haring, M., Offermann, S., Danker, T., Horst, I., Peterhaensel, C. & Stam, M. (2007). Chromatin immunoprecipitation: optimization, quantitative analysis and data normalization. *Plant Methods, 3*(11).

Lindhout, B.I., Fransz, P.F., Tessadori, F., Meckel, T., Hooykaas, P.J. & Zaal, B.J. (2007). Live cell imaging of repetitive DNA sequences via GFP-tagged polydactyl zinc finger proteins. *NUCLEIC ACIDS RES, 35*(16), 1-9.

Luijsterburg, M.S., Goedhart, J., Moser, J., Kool, H., Geverts, B., Houtsmuller, A.B., Mullenders, L.H., Vermeulen, W. & Driel, R. van (2007). Dynamic *in vivo* interaction of DDB2 E3 ubiquitin ligase with UV-damaged DNA is independent of damage-recognition protein XPC. *J. Cell Sci., 120*(15), 2706-2716.

Mateos Langerak, J., Goetze, S., Leonhardt, H., Cremer, T., Driel, R. van & Lanctôt, C. (2007). Nuclear architecture: Is it important for genome function and can we prove it? *J CELL BIOCHEM, 102*(5), 1067-1075.

Mateos Langerak, J., Brink, M.C., Luijsterburg, M.S., Kraan, I. van der, Driel, R. van & Verschure, P.J. (2007). Pericentromeric heterochromatin domains are maintained without accumulation of HP1. *MOL BIOL CELL, 18*(4), 1464-1471.

Post, L.J.G., Roos, M., Marshall, S., Driel, R. van & Breit, T.M. (2007). A semantic web approach applied to integrative bioinformatics experimentation: a biological use case with genomics data. *BIOINFORMATICS, 23*(22), 3080-3087.

Royen, M.E. van, Cunha, S.M., Brink, M.C., Mattern, K.A., Nigg, A.L., Dubbink, H.J., Verschure, P.J., Trapman, J. & Houtsmuller, A.B. (2007). Compartmentalization of androgen receptor protein-protein interactions in living cells. *J CELL BIOL, 177*(1), 63-72.

Tessadori, F., Chupeau, M.C., Chupeau, Y., Knip, M., Germann, S., Driel, R. van, Fransz, P.F. & Gaudin, V. (2007). Large-scale dissociation and sequential reassembly of pericentric heterochromatin in dedifferentiated Arabidopsis cells. *J CELL SCI, 120*(7), 1200-1208.

Tessadori, F., Schulkes, R.K., Driel, R. van & Fransz, P.F. (2007). Light-regulated large-scale reorganization of chromatin during the floral transition in Arabidopsis. *Plant J*., 50(5), 848-857.

Vries, A.H. de, Krenn, B.E., Driel, R. van, Subramaniam, V. & Kanger, J.S. (2007). Direct observation of nanomechanical properties of chromatin in living cells. *Nano Letters, 7*(5), 1424-1427.

Invited lectures

Driel, R. van (2007, January 11). *Chromatin-associated processes in vivo: how does it work...?* University of Munich, Germany, seminar.

Driel, R. van (2007, July 17). *How to package two meters of DNA with tens of thousands of genes inside a microns-size cell nucleus and let it work for you.* TU Delft, the Netherlands, seminar.

Driel, R. van (2007, September 12). *In vivo assembly and action of the nucleotide excision repair complex*. Montpellier, France, EMBO conference.

Driel, R. van (2007, February 02). *Orchestration of expression of thousands of genes.* University of Munich, Germany, seminar.

Driel, R. van (2007, December 18). *Systems biology to combat metabolic syndrome.* Lisbon, Portugal, EuroBioForum Meeting.

Stam, M. (2007, March 09). *b1 paramutation: long-range in cis and trans interactions.* Vienna, Austria, GMI: invited by Ortrun Mittelsten Scheid.

Stam, M. (2007, May 14). *b1 paramutation: the heritable transfer of epigenetic information in trans.* Halle (Salle), Germany, International Meeting "Communication in Plants and their Response to the Environment".

Verschure, P.J. (2007, February 16). *Chromosome organization and epigenetic gene control systems.* Lisbon, Portugal, seminar: Institute of Molecular Medicine, Faculty of Medicine.

Verschure, P.J. (2007, August 27). *Chromosome organization and epigenetic gene control systems.* Amsterdam, the Netherlands, The 16th International Chromosome Conference.

Verschure, P.J. (2007, September 10). *Chromosome organization and epigenetic gene control systems.* Amsterdam, the Netherlands, The 6th Dutch chromatin meeting.

Verschure, P.J. (2007, February 15). *Functional chromosome organization in the interphase cell nucleus: Epigenetic gene control.* Lisbon, Portugal, Gulbenkian Institute, seminar.

Other results

Fransz, P.F. (2007). 16th International Chromosome Conference. organising committee: RAI Amsterdam, the Netherlands (2007, August 25 - 2007, August 29).

Appendix 1d

Epigenetic Regulation of Gene Expression

Chairholder: Prof.dr A.P. Otte

Research Results in Numbers

Peer reviewed publications	4
Non-peer reviewed publications	0
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2007)

Arie Otte	Chairholder
John Verhees	Assistant Professor

Position	FS1*	FS2**	FS3◊	FS4◊◊	Total
Chairholder	0.4	0	0	0	0.4
Associate/Ass. prof.	0.25	0	0	0	0.25
Research Fellow	0.9	0	2.6	0.8	4.3
PhD Student	0.75	0	0	0	0.75
Technician	2.2	0	0.8	0	3.0
Total	**4.5**	**0**	**3.4**	**0.8**	**8.7**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

◊◊FS4 = employed in a collaboration with Crucell

Publications

Key Publications

Otte, A.P. Kwaks, T.H.J., van Blokland, R.J.M., Sewalt, R.G.A.B., Verhees, J., Vincent N.A. Klaren, V.N.A., Siersma, T.K., Korse, H.W.M., Teunissen, N.C., Botschuijver, S., van Mer, C., and Man, S.Y. (2007). Various expression augmenting DNA elements benefit from STAR-Select, a novel high stringency selection system for protein expression. *Biotechn. Prog.,* 23, 801-807.

Van Galen, J.C., Muris, J.J., Oudejans, J.J., Vos, W., Giroth, C.P., Ossenkoppele, G.J., Otte, A.P., Raaphorst, F.M., Mayjer, C.J. (2007). Expression of the polycomb-group gene BMI1 is related to an unfavourable prognosis in primary nodal DLBCL. *J Clin Pathol*. 60,167-172.

Academic publications (refereed)

Blokland, H.J.M. van, 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., Mer, C. van, Man, S.Y. & Otte, A.P. (2007). A novel, high stringency selection system allows screening of few clones for high protein expression. *J BIOTECHNOL, 128*(2), 237-245.

Galen, J.C. van, Muris, J.J., Oudejans, J.J., Vos, W., Giroth, C.P., Ossenkoppele, G.J., Otte, A.P., Raaphorst, F.M. & Mayjer, C.J. (2007). Expression of the polycomb-group gene BMI1 is related to an unfavourable prognosis in primary nodal DLBCL. *J CLIN PATHOL, 60*(2), 167-172.

Leenders, G.J. van, Dukers, D., Hessels, D., Kieboom, S.W. van den, Hulsbergen, C.A., Witjes, J.A., Otte, A.P., Mayjer, C.J. & Raaphorst, F.M. (2007). Polycomb-Group Oncogenes EZH2, BMI1, and RING1 are overexpressed in Prostate Cancer with adverse pathologic and clinial features. *EUR UROL, 52*(2), 455-463.

Otte, A.P., Kwaks, T.H.J., Blokland, R.J. van, Sewalt, R.G.A.B., Verhees, J.A., Klaren, V.N.A., Siersma, T.K., Korse, H.W., Teunissen, N.C., Botschuijver, S., Mer, C. van & Man, S.Y. (2007). Various expression-augmenting DNA elements benefit from STAR-Select, a novel high stringency selection system for protein expression. *BIOTECHNOL PROGR, 23*(4), 801-807.

Appendix 1e

Molecular Cytology

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

Research Results in Numbers

Peer reviewed publications	20
Non-peer reviewed publications	5
PhD Theses	1
Patent applications	0

Staff (Research input in fte during 2007)

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/Assist. prof.	1.0	0.5	0	1.5
Research Fellow	1.1	3.9	2.1	7.1
PhD Student	0	0.25	1.0	1.25
Technician	2.0	0	0.8	2.8
Total	**4.6**	**4.7**	**3.9**	**13.2**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Hoebe, R.A., Oven, C.H. van, Gadella, Th.W.J., Dhonukshe, P.B., Noorden, C.J.F. van & Manders, E.M.M. (2007). Controlled light-exposure microscopy reduces photobleaching and phototoxicity in fluorescence live-cell imaging. *Nat. Biotechnol., 25*(2), 249-253.

Merzlyak, E.M., Goedhart, J., Shcherbo, D., Bulina, M.E., Shcheglov, A.S., Fradkov, A.F., Gaintzeva, A., Lukyanov, K.A., Lukyanov, S., Gadella, Th.W.J. & Chudakov, D.M. (2007). Bright monomeric red fluorescent protein with an extended fluorescence lifetime. *Nat. Methods, 4*(7), 555-557

PhD Theses

Läppchen, T. (2007, January 17). *Synthesis of GTP Analogues and Evaluation of their Effect on the Antibiotic Target FtsZ and its Eurkaryotic Homologue Tubulin.* UvA Universiteit van Amsterdam (167 pag.) (Amsterdam). Prom./coprom.: G.J. Koomen & dr T. den Blaauwen.

Sreedharan Pillai, R. (2007, February 27). *Third-harmonic generation from isotropic and anisotropic media using focused laser beams.* UvA Universiteit van Amsterdam (101 pag.) (Amsterdam: Universiteit van Amsterdam). Prom./coprom.: prof. dr G.J. Brakenhoff & dr. M. Müller.

Academic publications (refereed)

Goedhart, J., Vermeer, J.E.M., Adjobo-Hermans, M.J.W., Weeren, L. van & Gadella, Th.W.J. (2007). Sensitive Detection of p65 Homodimers Using Red-Shifted and Fluorescent Protein-Based FRET Couples. *PLoS ONE, 2*(10), e1011.

Hoebe, R.A., Oven, C.H. van, Gadella, Th.W.J., Dhonukshe, P.B., Noorden, C.J.F. van & Manders, E.M.M. (2007). Controlled light-exposure microscopy reduces photobleaching and phototoxicity in fluorescence live-cell imaging. *Nat. Biotechnol., 25*(2), 249-253.

Jong, W.S., Hagen-Jongman, C.M. ten, Blaauwen, T. den, Slotboom, J.D., Tame, J.R.H., Wickström, D., Gier, J.-W.L. de, Otto, B.R. & Luirink, J. (2007). Limited tolerance towards folded elements

during secretion of the autotransporter Hbp. *Mol. Microbiol., 63*(5), 1524-1536.

Karczmarek, A., Martinez-Arteaga Baselga, R., Alexeeva, S.V., Hansen, F.G., Vicente, M, Nanninga, N. & Blaauwen, T. den (2007). DNA and origin region segregation are not affected by the transition from rod to sphere after inhibition of *Escherichia coli* MreB by A22. *Mol. Microbiol., 65*(1), 51-63.

Kremers, G.J., Goedhart, J., Heuvel, D.J. van den, Gerritsen, H.C. & Gadella, Th.W.J. (2007). Improved green and blue fluorescent proteins for expression in bacteria and mammalian cells. *Biochemistry, 46*(12), 3775-3783.

Lange, M.J.L. de, Bonn, M. & Müller, M. (2007). Direct measurement of phase coexistence in DPPC/Cholesterol vesicles using Raman spectroscopy. *CHEM PHYS LIPIDS, 146*(2), 76-84.

Leeuwen, W. van, Vermeer, J.E.M., Gadella, Th.W.J. & Munnik, T. (2007). Visualization of phosphatidylinositol 4,5-bisphosphate in the plasma membrane of suspension-cultured tobacco BY-2 cells and whole Arabidopsis seedlings. *Plant J., 52*(6), 1014-1026.

Luijsterburg, M.S., Goedhart, J., Moser, J., Kool, H., Geverts, B., Houtsmuller, A.B., Mullenders, L.H., Vermeulen, W. & Driel, R. van (2007). Dynamic *in vivo* interaction of DDB2 E3 ubiquitin ligase with UV-damaged DNA is independent of damage-recognition protein XPC. *J. Cell Sci., 120*(15), 2706-2716.

Merzlyak, E.M., Goedhart, J., Shcherbo, D., Bulina, M.E., Shcheglov, A.S., Fradkov, A.F., Gaintzeva, A., Lukyanov, K.A., Lukyanov, S., Gadella, Th.W.J. & Chudakov, D.M. (2007). Bright monomeric red fluorescent protein with an extended fluorescence lifetime. *NAT METHODS, 4*(7), 555-557.

Mohammadi, T., Karczmarek, A., Crouvoisier, M., Bouhss, A., Mengin-Lecreulx, D. & Blaauwen, T. den (2007). The essential peptidoglycan glycosyltransferase MurG forms a complex with proteins involved in lateral envelope growth as well as with proteins involved in cell division in *Escherichia coli. Mol. Microbiol., 65*(4), 1106-1121.

Munster, E.B. van, Goedhart, J., Kremers, G.J., Manders, E.M.M. & Gadella, Th.W.J. (2007). Combination of a spinning disc confocal unit with frequency-domain fluorescence lifetime imaging microscopy. *Cytometry A.*, 71(4), 207-214.

Müller, M. & Zumbusch, A. (2007). Coherent anti-Stokes Raman Scattering Microscopy. *ChemPhysChem., 8*(15), 2156-2170.

Norris, V., Blaauwen, T. den, Cabin-Flaman, A., Doi, R.H., Harshey, R.M., Janniere, L., Jimenez-Sanchez, A., Jin, D., Levin, P.A., Mileykovskaya, E., Minsky, A., Saier, M. Jr. & Skarstad, K. (2007). Functional taxonomy of bacterial hyperstructures. *MICROBIOL MOL BIOL REV, 71*(1), 230-253.

Norris, V., Blaauwen, T. den, Doi, R.H., Harshey, R.M., Janniere, L., Jimenez-Sanchez, A., Jin, D.J., Levin, P.A., Mileykovskaya, E., Minsky, A., Misevic, G., Ripoll, C., Saier, M. Jr., Skarstad, K. & Thellier, M. (2007). Toward a hyperstructure taxonomy. *ANNU REV MICROBIOL, 61*, 309-329.

Rinia, H.A., Bonn, M., Müller, M. & Vartiainen, E.M. (2007). Quantitative CARS spectroscopy using the maximum entropy method: The main lipid phase transition. *ChemPhysChem, 8*(2), 279-287.

Scheffers, D.-J., Robichon, C., Haan, G.J., Blaauwen, T. den, Koningstein, G., Bloois, E. van, Beckwith, J. & Luirink, J. (2007). Contribution of the FtsQ transmembrane segment to localization to the cell division site. *J BACTERIOL, 189*(20), 7273-7280.

Smits, M., Sovago, M., Wurpel, G.W.H., Kim, D., Müller, M. & Bonn, M. (2007). Polarization-Resolved Broad-Bandwidth Sum-Frequency Generation Spectroscopy of Monolayer Relaxation. *J. Phys. Chem. C, 111*(25), 8878-8883.

Smits, M., Ghosh, A., Bredenbeck, J., Yamamoto, S., Müller, M. & Bonn, M. (2007). Ultrafast energy flow in model biological membranes. *New J. Phys., 9*(390).

Smits, M., Ghosh, A., Sterrer, M., Müller, M. & Bonn, M. (2007). Ultrafast vibrational energy transfer between surface and bulk water at the air-water interface. *Phys. Rev. Lett.,Mar 2*(98 (9)).

Sovago, M., Wurpel, G.W.H., Smits, M., Müller, M. & Bonn, M. (2007). Calcium-induced phospholipid ordering depends on surface pressure. *J. Am. Chem. Soc., 129*(36), 11079-11084.

Non-refereed publications

Müller, M., Rinia, H.A., Bonn, M., Vartiainen, E.M., Lisker, M. & Bel, A. (2007). Quantitative multiplex CARS spectroscopy in congested spectral regions. In A. Periasamy & P.T.C. So (Eds.), *Multiphoton Microscopy in the Biomedical Sciences VII Vol. 6442. SPIE.*

Pillai, R.S., Brakenhoff, G.J. & Müller, M. (2007). Third harmonic generation: anomalous behavior in the THG z-response and microscopy applications. In A. Periasamy & P.T.C. So (Eds.), *Multiphoton Microscopy in the Biomedical Sciences VII Vol. 6442. SPIE.*

Rinia, H.A., Burger, K.N.J., Bonn, M. & Müller, M. (2007). Multiplex coherent anti-Stokes Raman scattering microscopy on lipid droplets in HeLa cells. In T. Wilson & A. Periasamy (Eds.), *Confocal, Multiphoton, and Nonlinear Microscopic Imaging III Vol. 6630. SPIE.*

Verhoeven, G., Dogterom, M., Alexeeva, S.V. & Blaauwen, T. den (2007). Studying bacterial cell division using optical tweezers. In *Biophysical Society Annual Meeting Abstracts Issues Vol. Jan. 2007. Biophys. J.* (pp. 306A-360A).

Book chapters

Rinia, H.A., Wurpel, G.W.H. & Müller, M. (2007). Measuring molecular order and orientation using coherent anti-Stokes Raman scattering microscopy. In A.M. Dopico (Ed.), *Methods in Membrane Lipids* (pp. 45-61). Totowa (NJ), USA: Humana Press Inc., 2007.

Invited lectures

Blaauwen, T. den (2007, May 29). *Cell division protein FtsZ as new antibiotic target.* Amsterdam, the Netherlands, MC2.

Blaauwen, T. den (2007, April 02). *Fighting microbial resistance through development of new antimicrobial agents directed against new specific targets.* Amsterdam, the Netherlands, IUPAC project no 2005-037-01.

Blaauwen, T. den & Läppchen, T. (2007, April 04). *Inhibition studies of GTP analogues on the bacterial cytoskeletal FtsZ and its mammalian homologue tubulin.* Amsterdam, the Netherlands, IUPAC project no 2005-037-1.

Blaauwen, T. den (2007, July 04). *The bacterial morphogenetic protein complexes: elongase and divisome.* Warwick, UK, Bacterial Cell Wall Biosynthesis Network (BACWAN).

Blaauwen, T. den (2007, March 13). *The E. coli elongase and divisome.* Lyon, France, Final COBRA meeting and BIOVISION.

Blaauwen, T. den & Läppchen, T. (2007, January 11). *The effect of C8-substituted GTP analogues on FtsZ and is eucaryotic homologue Tubulin.* Autrans, France, 3th General Assembly EUR-INTAFAR.

Gadella, Th.W.J. (2007, October 23). *FRET-microscopy.* Erasmus University, Rotterdam, the Netherlands, OIC advanced course.

Gadella, Th.W.J. (2007, May 08). *FRET-microscopy.* Erasmus University, Rotterdam, the Netherlands, OIC advanced course.

Gadella, Th.W.J., Goedhart, J., Adjobo-Hermans, M.J.W., Kremers, G.J., Vermeer, J.E.M. & Weeren, L. van (2007, September 05). *Imaging heterotrimeric G-protein activity in plant and mammalian cells.* Köln, Germany, Plant Cell Biology Symposium, MPI für Züchtungsforschung.

Gadella, Th.W.J., Goedhart, J., Adjobo-Hermans, M.J.W., Kremers, G.J. & Weeren, L. van (2007, September 20). *Imaging signalling across the plasma membrane.* Wageningen University, the Netherlands, seminar.

Gadella, Th.W.J., Goedhart, J., Adjobo-Hermans, M.J.W., Kremers, G.J. & Weeren, L. van (2007, September 27). *Imaging spatiotemporal dynamics of signalling across the plasma membrane.* CWI, Amsterdam, the Netherlands, Spatial fluctuations in cell biology symposium.

Gadella, Th.W.J., Goedhart, J., Adjobo-Hermans, M.J.W., Kremers, G.J. & Weeren, L. van (2007, September 06). *Multimode microscopy of signalling across the plasma membrane (imaging the cancer cell).* Oxford, UK, RMS Cell Imaging Techniques Course, Oxford Brooke University.

Gadella, Th.W.J., Goedhart, J., Adjobo-Hermans, M.J.W., Kremers, G.J. & Weeren, L. van (2007, August 29). *Multiparameter imaging of signalling across the plasma membrane.* Prague, Czech Republic, DiMI/EMIL Summer School.

Gadella, Th.W.J., Goedhart, J., Adjobo-Hermans, M.J.W., Kremers, G.J. & Weeren, L. van (2007, June 16). *Multiparameter imaging of signalling across the plasma membrane.* Naples, Italy, 2nd International ESMI conference.

Gadella, Th.W.J., Goedhart, J. & Adjobo-Hermans, M.J.W. (2007, March 30). *Probing signalling on the nm scale with TIRF and FRET.* Heidelberg, Germany, Workshop EU on Molecular Imaging of Cellular Nanostructure, University of Heidelberg.

Karczmarek, A. & Blaauwen, T. den (2007, September 05). *Localization of PBP5 in Escherichia coli.* Nantes, France, EU-INTAFAR.

Manders, E.M.M. (2007, November 09). *Dealing with phototoxicity in live-cell microscopy.* Amsterdam, the Netherlands, NVBMB symposuim "Molecular and Cellular Imaging".

Manders, E.M.M. (2007, October 18). *Dealing with phototoxicity in live-cell microscopy.* Munich, Germany, Guest lecture at Institute of Stem Cell Research GSF.

Manders, E.M.M. (2007, October 25). *Dealing with phototoxicity in live-cell microscopy.* Goettingen, Germany, Guest lecture Max Planck Inst. for Biophysical Chemistry.

Manders, E.M.M. (2007, August 29). *Dealing with phototoxicity in live-cell microscopy.* Prague, Czech Republic, DiMI/EMIL Summer School on Molecular Imaging 2007.

Manders, E.M.M. (2007, June 17). *Dealing with phototoxicity in live-cell microscopy.* Prague, Czech Republic, 8th Multinational Congress on Microscopy (8MCM).

Manders, E.M.M. (2007, April 10). *Dealing with phototoxicity in live-cell microscopy.* Valencia, Spain, Focus on Microscopy 2007.

Manders, E.M.M. (2007, April 17). *Dealing with phototoxicity in live-cell microscopy.* York, UK, 7th Meeting of the European Light Microscopy Initiative (ELMI).

Manders, E.M.M. (2007, March 01). *Dealing with phototoxicity in live-cell microscopy.* Badhoevedorp, the Netherlands, Confocal workshop Nikon.

Müller, M., Rinia, H.A., Vartiainen, E.M. & Bonn, M. (2007, April 10). *Quantitative multiplex CARS micro/spectroscopy in congested spectral regions.* Valencia, Spain, seminar.

Müller, M., Rinia, H.A., Bonn, M., Vartiainen, E.M., Lisker, M. & Bel, A. (2007, January 22). *Quantitative multiplex CARS spectroscopy in congested spectral regions.* San Jose (CA), USA, seminar.

Appendix 1f

Plant Physiology

Chairholder: Prof.dr M.A. Haring

Research Results in Numbers

Peer reviewed publications	10
Non-peer reviewed publications	1
PhD Theses	1
Patent applications	2

Staff (Research input in fte during 2007)

Michel Haring	Chairholder
Teun Munnik	Associate Professor
Rob Schuurink	Assistant Professor

Position	FS1*	FS2**	FS3◊	Total
Chairholder	0.5	0	0	0.5
Associate/Assist. prof.	0.7	0.8	0	1.5
Research Fellow	0	2.9	1.7	4.6
PhD Student	1.1	1.2	0.75	3.1
Technician	1.5	0	0.6	2.1
Total	3.8	4.9	3.1	11.8

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

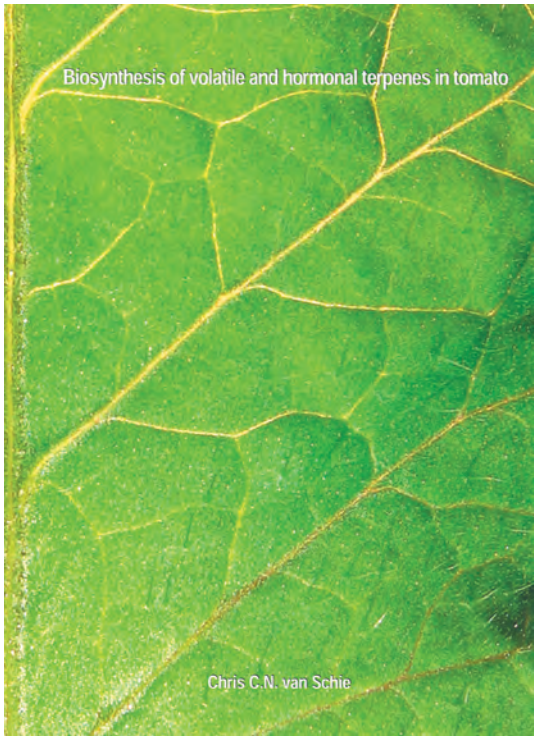
Key Publications

Schie, C.C.N. van, Ament, K., Schmidt, A., Lange, T. de, Haring, M.A. & Schuurink, R.C. (2007). Geranyl diphosphate synthase is required for biosynthesis of gibberellins. *Plant J., 52*, 752-762.

Testerink, C., Larsen, P.B., Does, D. van der, Himbergen, J.A.J. van & Munnik, T. (2007). Phosphatidic acid binds to and inhibits the activity of Arabidopsis CTR1. *J Exp. Bot. 58*, 3905-3914.

PhD Theses

Schie, C.C.N. van (2007, January 09). *Biosynthesis of volatile and hormonal terpenes in tomato.* UvA Universiteit van Amsterdam (156 pag.) (Amsterdam: Universiteit van Amsterdam). Prom./coprom.: prof.dr M.A. Haring & dr.ir R.C. Schuurink.



Patent Applications

Bleeker, P.M., Ament, K., Diergaarde, P.J., Both, M. de & Schuurink, R.C.. Plant volatiles. no PG014800.

Bleeker, P.M., Diergaarde, P.J., Haring, M.A., Schie, C.C.N. van, Schuurink, R.C. & Both, M. de. Trichome specific promoters. no P6018537.

Academic publications (refereed)

Goedhart, J., Vermeer, J.E.M., Adjobo-Hermans, M.J.W., Weeren, L. van & Gadella, Th.W.J. (2007). Sensitive Detection of p65 Homodimers Using Red-Shifted and Fluorescent Protein-Based FRET Couples. *PLoS ONE, 2*(10), e1011.

Kooijman, E.E., Tieleman, D.P., Testerink, C., Munnik, T., Rijkers, D.T., Burger, K.N. & Kruijff, B. de (2007). An electrostatic/hydrogen bond switch as the basis for the specific interaction of phosphatidic acid with proteins. *J BIOL CHEM, 282*(15), 11356-11364.

Leeuwen, W. van, Vermeer, J.E.M., Gadella, Th.W.J. & Munnik, T. (2007). Visualization of phosphatidylinositol 4,5-bisphosphate in the plasma membrane of suspension-cultured tobacco BY-2 cells and whole Arabidopsis seedlings. *Plant J., 52*(6), 1014-1026.

Ramoz-Diaz, A., Brito-Argaez, L., Munnik, T. & Hernandez-Sotomayor, S.M. (2007). Aluminum inhibits phosphatidic acid formation by blocking the phospholipase C pathway. *Planta, 225*(2), 393-401.

Rommens, C.M., Haring, M.A., Swords, K., Davies, H.V. & Belknap, W.R. (2007). The intragenic approach as a new extension to traditional plant breeding. *Trends Plant Sci., 12*(9), 397-403.

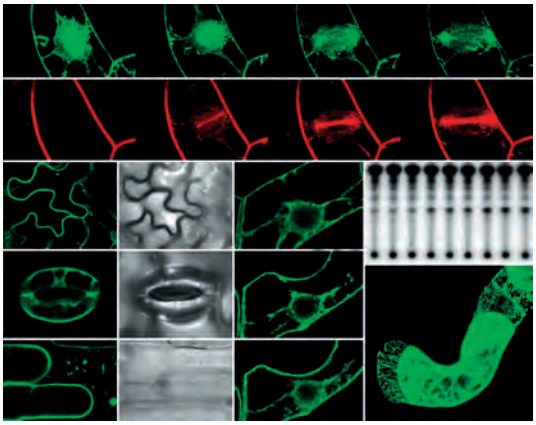
Schie, C.C.N. van, Ament, K., Schmidt, A., Lange, T. de, Haring, M.A. & Schuurink, R.C. (2007). Geranyl diphosphate synthase is required for biosynthesis of gibberellins. *Plant J., 52*(4), 752-762.

Schie, C.C.N. van, Haring, M.A. & Schuurink, R.C. (2007). Tomato linalool synthase is induced in trichomes by jasmonic acid. *Plant Mol. Biol., 64*(3), 251-263.

Schweighofer, A., Kazanaviciute, V., Scheikl, E., Teige, M., Doczi, R., Hirt, H., Schwanninger, M., Kant, M., Schuurink, R.C., Mauch, F., Buchala, A., Cardinale, F. & Meskiene, I. (2007). The PP2C-type phosphatase AP2C1, which negatively regulates MPK4 and MPK6, modulates innate immunity, jasmonic acid, and ethylene levels in Arabidopsis. *Plant Cell, 19*(7), 2213-2224.

Testerink, C., Larsen, P.B., Does, D. van der, Himbergen, J.A.J. van & Munnik, T. (2007). Phosphatidic acid binds to and inhibits the activity of Arabidopsis *CTR1. J EXP BOT, 58*(14), 3905-3914.

Zonia, L.E. & Munnik, T. (2007). Life under pressure: hydrostatic pressure in cell growth and function. *Trends Plant Sci., 12*(3), 90-97.



Non-refereed publications

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. (2007). 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.), Ecological Communities: Plant Mediation in Indirect Interaction Webs (pp. 188-217). Cambridge: Cambridge University Press.

Membership editorial board

Munnik, T. (Ed.). (2007). *Plant Signalling & Behavior.*

Munnik, T. (Ed.). (2007). *Planta.*

Invited lectures

Haring, M.A. (2007, June 06). *Analyzing plant scent: terpenoids and benzenoids.* Wageningen, the Netherlands, EPS international PhD course Metabolomics.

Haring, M.A. (2007, February 17). *Braucht die Ökologischen Landwirtschaft eine eigene Pflanzenzüchtung?* Nürnberg, Germany, BioFach.

Haring, M.A. (2007, November 20). *De nieuwe genetica: overerving van epigenetische eigenschappen.* Utrecht, the Netherlands, COGEM jaarvergadering.

Haring, M.A. (2007, December 03). *Gentechnik in der Landwirtschaft: wie und warum (nicht)?* Luxemburg, seminar Oikopolis.

Haring, M.A. (2007, April 22). *Hoe planten ruiken.* Science Museum Nemo, Amsterdam, the Netherlands, Nemo Kinderlezing.

Haring, M.A. (2007, December 03). *Moderne Pflanzenzüchtung: von der Zellfusion bis Gentechnik.* Luxemburg, seminar Oikopolis.

Haring, M.A. (2007, December 13). *Plant -Insect interactions.* Haren, Groningen, PhD course Research School Functional Ecology.

Haring, M.A. (2007, February 07). *Regulatory genes involved in the production of volatiles in tomato fruit.* Wageningen, the Netherlands, CBSG Summit.

Haring, M.A. (2007, December 10). *Züchtungstechniken im Gemüsebau: wo geht die Reise hin?* Bonn, Germany, seminar Bundesverband Deutscher Pflanzenzüchter.

Moerkercke, A.N.A.I. van (2007, October 30). *Functional analysis of the ODORANT1-promoter in Petunia flowers.* Amsterdam, the Netherlands, World Petunia Days.

Munnik, T. (2007, August 26). *Lipid Signalling in response to Stress.* Warsaw, Poland, Third meeting of the Polish Society of Plant Experimental Biology.

Munnik, T. (2007, July 22). *Lipid signals in plant defense.* Sorrento, Italy, XIII International Congress of the International Society for Molecular Plant-Microbes Interaction (IS-MPMI).

Munnik, T. (2007, October 09). *Lipidomics in Plant Cell Signalling.* Toulouse, France, 4th Lipidomics Meeting (GERLI).

Munnik, T. (2007, November 22). *Phospholipid signalling gets the green light.* Würzburg, Germany, seminar.

Munnik, T. (2007, April 02). *Phospholipid signalling in plants - 'Seeing is believing'.* York, UK, 3rd European Symposium on Plant Lipids.

Munnik, T. (2007, May 16). *Phospholipid-based signalling - 'seeing is believing'.* Strbske Pleso, Slovakia., 3rd International Symposium on Plant Neurobiology.

Munnik, T. (2007, October 11). *Plant phospholipid signalling.* Castanet-Tolosan, France, INRA-CNRS.

Munnik, T. (2007, December 10). *Visualizing Phospholipid-Based Signalling Events in Plant Cells.* Prague, Czech Republic, Academy of Sciences of the Czech Republic.

Schooten, B. van (2007, April 03). *Genetic evidence for the involvement of PA signalling in Arabidopsis disease resistance.* Lunteren, the Netherlands, EPS Research Day.

Schuurink, R.C. (2007, December 10). *E-2 hexenal signalling in Arabidopsis.* Les Diablerets, Switzerland, The Gordon Research Conferences: FLORAL & VEGETATIVE VOLATILES.

Schuurink, R.C. (2007, August 30). *Involvement of GPS in the biosynthesis of GAs and of GABA in the responsiveness to E-2-hexenal.* Jena, Germany, seminar: Max Planck Institute for Ecology.

Schuurink, R.C. (2007, June 29). *Plant volatiles: regulation of biosynthesis and role in signalling.* Ithaca, USA, seminar: Cornell University, Department of Plant Pathology.

Testerink, C. (2007, November 15). *Lipids sense the stress in plants.* Leiden, the Netherlands, IBL Symposium on Stress! Responses and Adaptations.

Appendix 1g

Plant-pathogen Interaction

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

Research Results in Numbers

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

Staff (Research input in fte during 2007)

Ben Cornelissen	Chairholder
Frank Takken	Assistant Professor
Martijn Rep	Assistant Professor

Position	FS1*	FS2**	FS3◊	Total
Chairholder	0.1	0	0	0.1
Associate/Assist. prof.	1.0	0	0	1.0
Research Fellow	0.9	0.9	0.9	2.7
PhD Student	1.3	0.75	0.75	2.8
Technician	2.8	0	0.9	3.7
Total	**6.1**	**1.7**	**2.6**	**10.4**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Houterman, P.M., Speijer, D., Dekker, H.L., de Koster, C.G., Cornelissen, B.J.C. and Rep. M. (2007). The mixed proteome of *Fusarium oxysporum*-infected tomato xylem vessels. *Mol. Plant Pathol.* 8: 215-221

van Ooijen, G., van den Burg, H.A., Cornelissen, B.J.C., and Takken, F.L.W. (2007). Structure and function of Resistance proteins in solanaceous plants. *Annu Rev Phytopath* 45, 43-72.

Academic publications (refereed)

Cuomo, C.A., Güldener, U., Xu, J.-R, Trail, F., Turgeon, B.G., Di Pietro, A., Walton, J.D., Ma, L.J., Baker, S.E., Rep, M., Adam, G., Antoniw, J., Baldwin, T., Calvo, S., Chang, Y.-, DeCaprio, D., Gale, L.R., Gnerre, S., Goswami, R.S., Hammond-Kosack, K., Harris, L.J., Hilburn, K., Kennell, J.C., Kroken, S., Magnuson, J.K., Mannhaupt, G., Mauceli, E., Mewes, H.-, Mitterbauer, R., Muehlbauer, G., Münsterkötter, M., Nelson, D., O'Donnell, K., Quellet, T., Qi, W., Quesneville, H., Roncero, M.I.G., Seong, K.-, Tetko, I.V., Urban, M., Waalwijk, C., Ward, T.J., Yao, J., Birren, B.W. & Kistler, H.C. (2007). The Fusarium graminearum genome reveals a link between localized polymorphism and pathogen specialization. *SCIENCE, 317*(5843), 1400-1402.

Does, H.C. van der & Rep, M. (2007). Virulence genes and the evolution of plant pathogenicity in fungi. *Mol. Plant-Microbe Interact., 20*, 1175-1182.

Gabriels, S.H.E.J., Vossen, J.H., Ekengren, S.K., Ooijen, G. van, Abd-El-Haliem, A.M., Berg, G.C.M. van den, Rainey, D.Y., Martin, G.B., Takken, F.L.W., Wit, P.J.G.M. de & Joosten, M.H.A.J. (2007). An NB-LRR protein required for HR signalling mediated by both extra- and intracellular resistance proteins. *Plant J.*, 50(1), 14-28.

Houterman, P.M., Speijer, D., Dekker, H.L., Koster, C.G. de, Cornelissen, B.J.C. & Rep, M. (2007). The mixed proteome of *Fusarium oxysporum*-infected tomato xylem vessels. *Molecular Plant Pathology, 8*, 215-221.

Ooijen, G. van, Burg, H.A. van den, Cornelissen, B.J.C. & Takken, F.L.W. (2007). Structure and function of Resistance proteins in solanaceous plants. *Annual Review of Phytopathology*, 45, 43-72.

Tameling, W.I.L. & Takken, F.L.W. (2007). Resistance proteins: scouts of the plant innate immune system. *European Journal of Plant Pathology. DOI: 10.1007/s10658-007-9187-8.*

Invited lectures

Lukasik, E., Cornelissen, B.J.C. & Takken, F.L.W. (2007, October 17). *Role of nucleotide binding for R protein function.* Lunteren, the Netherlands, Bioexploit Meeting.

Ooijen, G. van, Cornelissen, B.J.C. & Takken, F.L.W. (2007, January 01). *A role for the conserved MHD motif for R protein function.* Sorrento, Italy, XIIIth International Congress on Molecular Plant-Microbe Interactions.

Rep, M. (2007, September 12). *Fusarium oxysporum: from harmless root colonizer to hostspecific vascular wilt pathogen.* University of Bath, UK, BSPP Presidential Meeting 2007 (Attack and Defence in Plant Diseases).

Rep, M. (2007, November 27). *The evolution of host- and cultivar-specific virulence in Fusarium oxysporum.* Wellington, New Zealand, Joint NZMS-NZSMB Conference 2007.

Rep, M. (2007, April 02). *The mixed proteome of Fusarium oxysporum-infected tomato xylem vessels.* Lunteren, the Netherlands, ALW-discussion platform EPW.

Takken, F.L.W. (2007, July 12). *Host-Pathogen Interaction from Plants to Mammals -Distinct and Shared Pathways of Immune Defence.* University Hospital, Kiel, Germany, seminar: Inflammatory diseases of barrier organs.

Takken, F.L.W. (2007, December 07). *Molecular mechanisms regulating the activity of plant NB-LRR resistance proteins.* Zurich, Switzerland, seminar: Institute of Plant Biology.

Takken, F.L.W. (2007, November 20). *The NB-ARC domain of R proteins acts as a molecular switch regulating plant innate immunity.* LMU München, Germany, seminar: Max von Pettenkofer Institut.

Appendix 1h

Animal Physiology and Cognitive Neuroscience

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

Research Results in Numbers

Peer reviewed publications	23
Non-peer reviewed publications	0
PhD Theses	1
Patent applications	1

Staff (Research input in fte during 2007)

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

Position	FS1*	FS2**	FS3◊	Total
Chairholder	0.5	0	0	0.5
Associate/Assist. prof.	1.0	0.5	0	1.5
Research Fellow	0	0.9	1.2	2.1
PhD Student	2.6	2.2	0.75	5.6
Technician	0.6	0	0	0.6
Total	**4.7**	**3.6**	**2.0**	**10.3**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Van Duuren E, Nieto Escámez FA, Joosten RNJMA, Visser R, Mulder AB and Pennartz CMA (2007). Neural coding of reward magnitude in the orbitofrontal cortex of the rat during a five-odour olfactory discrimination task. *Learning and Memory* 14: 446-456.

Hoffman KL, Battaglia FP, Harris K, MacLean JN, Marshall L, Mehta MR. (2007). The upshot of up states in the neocortex: from slow oscillations to memory formation. *J. Neurosci.* 27: 11838-11841.

Kalenscher T and Pennartz CM. (2007). Is a bird in the hand worth two in the future? The neuroeconomics of intertemporal decision-making. Prog Neurobiol. Dec 7; [Epub ahead of print].

PhD Theses

Dongen, Y.C. (2007, November 14). *Direct and indirect communication between functionally different regions of the rat striatum.* Vrije Universiteit van Amsterdam. Prom./coprom.: prof. dr. C.M.A. Pennartz.

Patent

Pennartz, C.M.A., Battaglia, F.P., Manuputy, R. & Bakker, M. The Lantern: an ultra-lightweight microdrive for chronic ensemble recordings in freely moving mice using six independently movable tetrodes. no. 2AF75.

Academic publications (refereed)

Aronica, E., Boer, K. de, Vliet, E.A. van, Redeker, S., Baayen, J.C., Spliet, W.G.M., Rijen, P.C. van, Troost, D, Lopes da Silva, F.H., Wadman, W.J. & Gorter, J.A. (2007). Complement activation in experimental and human temporal lobe epilepsy. *Neurobiology of Diseases,* 26, 497-511.

Aronica, E., Boer, J. de, Becker, A., Redeker, S., Spliet, W.G., Rijen, P.C. van, Wittink, F., Breit, T.M., Wadman, W.J., Lopes da Silva, F.H., Troost, D & Gorter, J.A. (2008). Gene expression profile analysis of epilepsy-associated gangliogliomas. *Neuroscience, 151,* 272-292.

Bouwman, B.M., Suffczynski, P., Lopes da Silva, F.H., Maris, E. & Rijn, C.M. van (2007). GABAergic mechanisms in absence epilepsy: a computational model of absence epilepsy simulating spike and wave discharges after vigabatrin in WAG/Rij rats. *Eur. J. Neurosci., 25,* 2783-2790.

Daselaar, S.M., Rice, H.J, Greenberg, D.L., Cabeza, R., LaBar, K.S. & Rudin, Ch. (2008). The Spatiotemporal Dynamics of Autobiographical Memory: Neural Correlates of Recall, Emotional Intensity, and Reliving. *CEREB CORTEX,* 217-229.

Davis, S.W., Dennis, N.A., Daselaar, S.M., Fleck, M.S. & Cabeza, R. (2007). Que PASA? The Posterior Anterior Shift in Aging. *CEREBRAL CORTEX.*

Dennis, N.A., Daselaar, S.M. & Cabeza, R. (2007). Effects of aging on transient and sustained successful memory encoding activity. *Neurobiol. Aging, 28*, 1749-1758.

Duuren, E. van, Escamez, F.A.N., Joosten, R.N.J.M.A., Visser, R., Mulder, A.B. & Pennartz, C.M.A. (2007). Neural coding of reward magnitude in the orbitofrontal cortex of the rat during a five-odor olfactory discrimination task. *Learning & Memory, 14,* 446-456.

Duuren, E. van, Blom, R. van der, Joosten, R.N.J.M.A., Mulder, A.B., Pennartz, C.M.A. & Feenstra, M.G. (2007). Pharmacological manipulation of neuronal ensemble activity by reverse microdialysis in freely moving rats: a comparative study of the effects of tetrodotoxin, lidocaine, and muscimol. *The Journal of Pharmacology and experimental Therapeutics, 323*(1), 61-69.

Ghijsen, W.E.J.M., Zuiderwijk, M. & Lopes da Silva, F.H. (2007). 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, R. van, Vreugdenhil, E., Redeker, S., Hendriksen, E., Aronica, E., Lopes da Silva, F.H. & Wadman, W.J. (2007). Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and entorhinal cortex during epileptogenesis in the rat. *Epilepsia, 48,* 53-64.

Gothard, K.M., Battaglia, F.P., Erickson, C.A., Spitler, K.M. & Amaral, D.G. (2007). Neural responses to facial expression and face identity in the monkey amygdala. *J. Neurophysiol., 97,* 1671-1683.

Hoffman, K.L., Battaglia, F.P., Harris, K., MacLean, J.N., Marshall, L.. & Mehta, M.R. (2007). The upshot of up states in the neocortex: from slow oscillations to memory formation. *J. Neurosci., 27,* 11838-11841.

Kalenscher, T. (2007). Choosing is feeling - the cognitive neuroscience of decision making. *LANCET NEUROL, 6,* 26-27.

Kalenscher, T. (2007). Decision Making: Don't Risk a Delay. *Current Biology, 17,* R58-R61.

Kalitzin, S.N., Parra, J., Velis, D.N. & Lopes da Silva, F.H. (2007). Quantification of unidirectional nonlinear associations between multidimensional *signals. IEEE transactions on bio-medical engineering, 54,* 454-461.

Lansink, C.S., Bakker, M, Buster, W., Lankelma, J., Blom, R. van der, Westdorp, R., Joosten, R.N.J.M.A., Mc.Naughton, B.L. & Pennartz, C.M.A. (2007). A split microdrive for simultaneous multi-electrode recordings from two brain areas in awake small animals. *J. Neurosci. Methods, 162,* 129-138.

Munck, J.C. de, Goncalves, S.I., Huijboom, L., Kuijer, J.P., Pouwels, P.J., Heethaar, R.M. & Lopes da Silva, F.H. (2007). The hemodynamic response of the alpha rhythm: an EEG/fMRI study. *NEUROIMAGE, 15,* 1142-1151.

Nordquist, R.E., Voorn, P., Mooij-van Malsen, J.G. de, Joosten, R.N.J.M.A., Pennartz, C.M.A. & Vanderschuren, L.J.M.J. (2007). Augmented reinforcer value and accelerated habit formation after repeated amphetamine treatment. *Eur. Neuropsychopharmacol., 17,* 532-540.

Oldenziel, W.H., Zeyden, M. van der, Dijkstra, G., Ghijsen, W.E.J.M., Karst, H., Cremers, T.I. & Westerink, B.H. (2007). Monitoring extracellular glutamate in hippocampal slices with a microsensor. *J. Neurosci. Methods, 160,* 37-44.

Parra, J., Lopes da Silva, F.H., Stroink, H. & Kalitzin, S. (2007). Is colour modulation an independent factor in human visual photosensitivity? *BRAIN, 130,* 1679-1689.

Taverna, S., Canciani, B. & Pennartz, C.M.A. (2007). Membrane properties and synaptic connectivity of fast-spiking interneurons in rat ventral striatum. *Brain Research, 1152,* 49-56.

Tobler, Ph.N & Kalenscher, T. (2007). Awfully afraid? Dissociating decision- from motor- and sensory-related brain activation during perceptual choices. *J. Neurosci., 27,* 6081-6082.

Tolner, E.A., Frahm, C, Metzger, R., Gorter, J.A., Witte, O.W., Lopes da Silva, F.H. & Heinemann, U. (2007). Synaptic responses in superficial layers of medial entorhinal cortex from rats with kainate-induced epilepsy. *Neurobiology of Diseases, 26,* 419-438.

Invited lectures

Battaglia, F.P. (2007, May 09). *The prefrontal-hippocampal connection during decision making: evidences from neural ensemble recordings in rats.* Nijmegen, the Netherlands, Universiteit van Nijmegen.

Battaglia, F.P. (2007, November 05). *The upshot of upstates in the neocortex: from slow oscillations to memory formation.* San Diego USA, Minisymposium Neuroscience Congress

Kalenscher, T. (2007, June 06). *Ensemble recordings in freely moving mice in a reward devaluation task.* Doorwerth, the Netherlands, ENP Meeting.

Kalenscher, T. (2007, May 24). *Is a bird in the hand worth two in the future? Impulsivity, neuroeconomics and reward value representation in the brain.* Amsterdam, the Netherlands, ONWA Epos Course, AMC.

Kalenscher, T. (2007, November 15). *Is a bird in the hand worth two in the future? Intertemporal decisions in the brain.* Innsbruck, Austria, Inst. of economics and finance at the University Innsbruck.

Kalenscher, T. (2007, July 21). *Is a bird in the hand worth two in the future? Intertemporal decisions, self-control, and the avian 'prefrontal cortex'.* Leiden, the Netherlands, Meeting of the priority program Executive Functions'.

Kalenscher, T. (2007, April 13). *Is a bird in the hand worth two in the future? The role of the avian 'prefrontal cortex' in decision making.* Amsterdam, the Netherlands, Acacia.

Lopes da Silva, F.H. (2007, October 03). *A cortical focus of spike-and-wave discharges in a genetic model of absence epilepsy: is there any evidence besides electrophysiological?* Antalya, Turkey, Symposium on Idiopathic generalized epilepsies, developmental aspects; bridging basic science and clinical research.

Lopes da Silva, F.H. (2007, February 12). *Conceptualization of epileptogenic zone, ictus trigger zone, symptomatogenic zone and epileptogenic lesion.* São Paulo, Brazil, 1st Latin-American Summer School on Epilepsy.

Lopes da Silva, F.H. (2007, July 02). *Epilepsy as diseases of neuronal network dynamics. models and predictions.* Arrábida, Portugal, Workshop Ways of Complexity: life sciences.

Lopes da Silva, F.H. (2007, February 09). *Gene expression in the course of epileptogenesis.* São Paulo, Brazil, 1st Latin-American Summer School on Epilepsy.

Lopes da Silva, F.H. (2007, September 18). *Integrity in Biomedical Research: The Role of Education.* Lisabon, Portugal, World Conference on Research Integrity.

Lopes da Silva, F.H. (2007, May 17). *Neuronal basis of brain rhythms: from cortical ensembles to EEG signals.* Nijmegen, the Netherlands, Symposium Applied Neurophysiology.

Lopes da Silva, F.H. (2007, September 29). *Principles of interictal-ictal transitions and precursors of seizures.* Freiburg, Germany, Third International Workshop on Seizure Prediction in Epilepsy.

Lopes da Silva, F.H. (2007, August 23). *Statistical Challenges in Brain Structure and Dynamics.* Lisabon, Portugal, 56th Session International Statistical Institute.

Lopes da Silva, F.H. (2007, May 25). *The Hippocampal-entorhinal system: re-entrant circuits and oscillations.* Amsterdam, Farewell symposium Menno Witter.

Pennartz, C.M.A. (2007, December 19). *Learning to like places: memory formation in spatial and motivational systems.* Berlin, Germany, Freie Universität Berlin, Dept. Mol. Neurobiology.

Pennartz, C.M.A. (2007, May 21). *Neural networks for associative memory.* Amsterdam, the Netherlands, Dept. Experimental Neurophysiology, Vrije Universiteit Amsterdam.

Pennartz, C.M.A. (2007, March 30). *Population coding and memory formation in the brain.* Nijmegen, the Netherlands, Cognitive Science Center Amsterdam (CSCA) Lustrum Symposium.

Pennartz, C.M.A. (2007, April 18). *Population coding and memory formation in the brain´s reward system.* Nijmegen, the Netherlands, Dept. Biofysica, Radboud Universiteit. Nijmegen.

Pennartz, C.M.A. (2007, June 19). *Sleep, off-line processing and the brain´s reward system.* Athene, Greece, International Neuroscience Symposium,.

Pennartz, C.M.A. (2007, May 14). *Systems neurophysiology of Cognitive Control.* Amsterdam, the Netherlands, ONWA Epos Course, AMC.

Appendix 1i

Cellular and Systems Neurobiology

Chairholder: Prof.dr W.J. Wadman

Research Results in Numbers

Peer reviewed publications	17
Non-peer reviewed publications	1
PhD Theses	4
Patent applications	0

Staff (Research input in fte during 2007)

Wytse Wadman	Chairholder
Fernando Lopes da Silva	Emeritus Professor
Chris Kruse	Honorary Professor (bijzonder hoogleraar)
Rob Aalberse	Honorary Professor (bijzonder hoogleraar)
Hans van Hooft	Assistant Professor
Jan Gorter	Assistant Professor
Taco Werkman	Assistant Professor

Position	FS1*	FS2**	FS3◊	Total
Chairholder	0.5	0	0	0.5
Associate/Assist. prof.	1.1	0	0.5	1.6
Research Fellow	0	0.4	0.9	1.3
PhD Student	0.75	0	1.7	2.5
Technician	1.0	0	0.6	1.6
Total	**3.4**	**0.4**	**3.7**	**7.5**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Vliet, E.A. van, Costa Araujo, S. da, Redeker, S., Schaik, R. van, Aronica, E. & Gorter, J.A. (2007). Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. *BRAIN, 130*, 521-534.

Cappaert, N., Wadman, W.J. & Witter, M.P. (2007). Spatiotemporal analyses of interactions between entorhinal and CA1 projections to the subiculum in rat brain slices. *Hippocampus, 17*, 909-921.

Kager H, Wadman WJ, Somjen GG. Seizure-like afterdischarges simulated in a model neuron. *J Comput Neurosci*. 2007 22(2):105-28.

PhD Theses

Kager, J. (2007, May 23). *Neuronal ion homeostasis underlying graded persistent firing, epileptiform seizures and spreading depression. A computational study.* UvA Universiteit van Amsterdam (235 pag.) (Wageningen: Ponsen & Looijen b.v.). Prom./coprom.: prof.dr W.J. Wadman & G.G. Somjen.

Sun, G. (2007, October 16). *Subunit specific modulation of sodium channels by anti-epileptic drugs.* UvA Universiteit van Amsterdam (134 pag.) (Zutphen: Wohrmann Print). Prom./coprom.: prof.dr W.J. Wadman & dr T.R. Werkman.

Vliet, E.A. van (2007, November 16). *The role of the blood-brain barrier and multidrug transporters in pharmacoresistant epilepsy.* UvA Universiteit van Amsterdam (247 pag.) (Enschede: Ipskamp). Prom./coprom.: prof.dr W.J. Wadman & dr J.A. Gorter.

Wijk, M. van (2007, September 21). *Deciphering the code of herbivore-induced plant odours: the whole is different from the sum of its parts.* UvA Universiteit van Amsterdam (203 pag.) (Amsterdam). Prom./coprom.: prof.dr M.W. Sabelis & prof.dr W.J. Wadman.

(D8-1) (D9-1) (D10-1)

Academic publications (refereed)

Aronica, E., Boer, K. de, Vliet, E.A. van, Redeker, S., Baayen, J.C., Spliet, W.G.M., Rijen, P.C. van, Troost, D, Lopes da Silva, F.H., Wadman, W.J. & Gorter, J.A. (2007). Complement activation in experimental and human temporal lobe epilepsy. *Neurobiology of Diseases, 26*, 497-511.

Aronica, E., Boer, K., Redeker, S., Spliet, W.G., Rijen, P.C. van, Troost, D & Gorter, J.A. (2007). Differential expression patterns of chloride transporters, Na+-K+-2Cl—cotransporter and K+-Cl—cotransporter, in epilepsy-associated malformations of cortical development. *Neuroscience, 145*, 185-196.

Aronica, E., Boer, J. de, Becker, A., Redeker, S., Spliet, W.G., Rijen, P.C. van, Wittink, F., Breit, T.M., Wadman, W.J., Lopes da Silva, F.H., Troost, D & Gorter, J.A. (2008). Gene expression profile analysis of epilepsy-associated gangliogliomas. *Neuroscience, 151*, 272-292.

Aronica, E., Redeker, S., Boer, K., Spliet, W.G., Rijen, P.C. van & Gorter, J.A. (2007). Inhibitory networks in epilepsy-associated gangliogliomas and in the perilesional epileptic cortex. *Epilepsy Research, 74*, 33-44.

Aronica, E.M.A. & Gorter, J.A. (2007). Gene expression profile in temporal lobe epilepsy. *Neuroscientist, 13*, 100-108.

Boon, P., Vonck, K, Herdt, V de, Dycke, A. van, Goethals, M., Goossens, L., Zandijcke, M. van, Smedt, T. de, Dewaele, I., Achten, R., Wadman, W.J., Dewaele, F. & Roost, D. van (2007). Deep brain stimulation in patients with refractory temporal lobe epilepsy. *Epilepsia, 48*, 1551-1560.

Cappaert, N., Wadman, W.J. & Witter, M.P. (2007). Spatiotemporal analyses of interactions between entorhinal and CA1 projections to the subiculum in rat brain slices. *Hippocampus, 17*, 909-921.

Gorter, J.A., Vliet, E.A. van, Rauwerda, H., Breit, T.M., Stad, R., Schaik, R. van, Vreugdenhil, E., Redeker, S., Hendriksen, E., Aronica, E., Lopes da Silva, F.H. & Wadman, W.J. (2007). Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and entorhinal cortex during epileptogenesis in the rat. *Epilepsia, 48*, 53-64.

Gorter, J.A. (2007). Neurobiologische mechanismen van farmacoresistente epilepsie. *Epilepsie, periodiek voor professionals,* 6-9.

Gorter, J.A. & Aronica, E. (2007). Ontstekings-processen in experimentele en humane epilepsie. *Epilepsie, periodiek voor professionals*, 10-12.

Kager H, Wadman WJ, Somjen GG. Seizure-like afterdischarges simulated in a model neuron. *J Comput Neurosci. 2007 22*(2):105-28.

Noam Y & Baram TZ., Ps in the (channel) pod are not alike... *Epilepsy Curr. 2007 7*(5):136-7.

Raedt, R, Boon, P., Perssson, A., Alborn, A.M., Boterberg, T., Dycke, A. van, Linder, B., Smedt, T, Wadman, W.J., Ben-Menachem, E. & Erikson, P.S. (2007). Radiation of the Rat Brain Suppresses Seizure-Induced Neurogenesis and Transiently Enhances Excitability during Kindling Acquisition. *Epilepsia*, 1-12.

Sun, G., Werkman, T.R., Battefeld, A., Clare, J.J. & Wadman, W.J. (2007). Carbamazepine and topiramate modulation of transient and persistent sodium currents studied in HEK293 cells expressing the Na(v)1.3 alpha-subunit. *Epilepsia, 48*, 774-782.

Tolner, E.A., Frahm, C, Metzger, R., Gorter, J.A., Witte, O.W., Lopes da Silva, F.H. & Heinemann, U. (2007). Synaptic responses in superficial layers of medial entorhinal cortex from rats with kainate-induced epilepsy. *Neurobiology of Diseases, 26*, 419-438.

Vliet, E.A. van, Costa Araujo, S. da, Redeker, S., Schaik, R. van, Aronica, E. & Gorter, J.A. (2007). Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. *BRAIN, 130*, 521-534.

Vliet, E.A. van & Gorter, J.A. (2007). Complexities in the association of human blood brain barrier disruption with seizures: Importance of patient population and method of disruption. *BRAIN, 130*, e78.

Vliet, E.A. van, Schaik, R. van, Edelbroek, P.M., Voskuyl, R.A., Redeker, S., Aronica, E., Wadman, W.J. & Gorter, J.A. (2007). Region-Specific Overexpression of P-glycoprotein at the Blood-Brain Barrier Affects Brain Uptake of Phenytoin in Epileptic Rats. *The Journal of Pharmacology and experimental Therapeutics, 322*, 141-147.

Wyckhuys, T, Smedt, T. de, Claeys, P., Raedt, R, Waterschoot, L., Vonck, K, Broecke, C. van den, Mabilde, C., Leybaert, L., Wadman, W.J. & Boon, P. (2007). High frequency deep brain stimulation in the hippocampus modifies seizure characteristics in kindled rats. *Epilepsia, 48*, 1543-1550.

Non-refereed publications

Vliet, E.A. van (2007). Therapieresistentie: te strenge controle bij Checkpoint Charley? *Episcoop, 3*, 22-24.

Invited lectures

Gorter, J.A. (2007, July 06). *Molecular antiepileptogenic targets.* Braine-l'Alleud, Belgium, UCB Pharma Meeting.

Gorter, J.A. (2007, June 04). *Strategies to prevent epileptogenesis.* Heemstede, the Netherlands, SEIN.

Hooft Hans van, (2007, March 29). *Properties and function of the 5HT3 receptor*, RMI Utrecht, Department Pharmacology & Anatomy

Lopes da Silva, F.H. (2007, November 30). *Brain electric/magnetic dynamics: the concepts of phase and synchrony*. Paris, France, Workshop Brain Dynamics.

Vliet, E.A. van (2007, March 06). *Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy*. Amsterdam, AMC, Pathology Research Day.

Vliet, E.A. van (2007, July 06). *Pharmacoresistance in rats with chronic epilepsy*. Braine-l'Alleud, Belgium, UCB Pharma Meeting.

Vliet, E.A. van (2007, September 18). *The role of the blood-brain barrier in pharmacoresistant epilepsy*. Maastricht, Department of Psychiatry and Neuropsychology Universiteit van Maastricht.

Werkman, T. (2007, October 23): *Endocannabinoid effects at the cellular and network level of the prefrontal cortex*, Weesp, Top Institute Pharma Solvay Pharmaceuticals.

Wadman, W.J. (2007, December 5) *Evaluation and modulation of neuronal excitability in local epileptic circuits*. Bochum, department of neuroscience.

Wadman, W.J. (2007, May 12) *Neuro Mythes, Utrecht, symposium it is all in the brain*.

Wadman, W.J. (2007, June 6) *The role of sodium channels in pharmaco resistance*. Brussel, UCB pharma

Wadman, W.J. (2007, September 29) *Evaluation and modulation of neuronal excitability in local epileptic circuits*, Freiburg, Symposium on Seizure prediction

Wadman, W.J. (2007, November 22) *Denken met Hersenen, Amstelveen*, Academia Amstel

Wadman, W.J. (2007, December 21) *Physiological aspects of network plasticity and excitability*, Utrecht, SWO meeting

Appendix 1j

Hormonal Regulation of Signal Transduction in the Brain

Chairholder: Prof.dr M. Joëls

Research Results in Numbers

Peer reviewed publications	18
Non-peer reviewed publications	2
PhD Theses	1
Patent applications	0

Staff (Research input in fte during 2007)

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/Assist. prof.	1.0	0	0	1.0
Research Fellow/Researcher	0.9	0.9	0	1.8
PhD Student	1.4	1.0	1.2	3.6
Technician	2.3	0	0.7	3.0
Total	**6.1**	**1.9**	**1.9**	**9.9**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Sennvik K*, Boekhoorn K*, Lasrado R*, Terwel D, Verhaeghe S, Korr H, Schmitz C, Tomiyama T, Mori H, Krugers H, Joëls M, Ramakers GJ, Lucassen PJ, van Leuven F. (2007). Tau-4R suppresses proliferation and promotes neuronal differentiation in the hippocampus of tau knockin/knockout mice. FASEB J. 21: 2149-2161.

* equal contribution

Joëls M, Karst H, Krugers HJ, Lucassen PJ.(2007). Chronic stress: implications for neuronal morphology, function and neurogenesis. *Front Neuroendocrinol*. 28: 72-96.

PhD Theses

Morsink, M. (2006, July 26). *Glucocorticoid control of gene transcription in neural tissue.* Universiteit van Leiden. Prom./coprom.: Prof.dr R. De Kloet & prof.dr M. Joels.

Academic publications (refereed)

Chameau, P.J.P., Qin, Y.J., Smit, G. & Joels, M. (2007). Glucocorticoids specifically enhance L-type calcium current amplitude and affect calcium channel subunit expression in the mouse hippocampus. *J. Neurophysiol., 97*, 5-14.

Czeh, B. & Lucassen, P.J. (2007). What causes the hippocampal volume decrease in depression? : Are neurogenesis, glial changes and apoptosis implicated? *Eur Arch Psychiatry Clin Neurosci, 257*, 250-260.

Joels, M., Karst, H., Krugers, H. & Lucassen, P.J. (2007). Chronic stress: Implications for neuronal morphology, function and neurogenesis. *Frontiers in Neuroendocrinology, 28*, 72-96.

Joels, M. & Krugers, H. (2007). LTP after stress: up or down? *Neural Plasticity*, 1-6.

Joels, M. (2007). Role of corticosteroid hormones in the dentate gyrus. *PROG BRAIN RES, 163*, 355-370.

Karst, H. & Joels, M. (2007). Brief RU 38486 Treatment Normalizes the Effects of Chronic Stress on Calcium Currents in Rat Hippocampal CA1 Neurons. *NEUROPSYCHOPHARMACOL, 32*(8), 1830-1839.

Krugers, H., Linden, S. van der, Olst, E van, Alfarez, D.N., Maslam, S., Lucassen, P.J. & Joels, M. (2007). Dissociation between apoptosis, neurogenesis, and synaptic potentiation in the dentate gyrus of adrenalectomized rats. *Synapse, 61*(4), 221-230.

Kuhn, H.G., Cooper-Kuhn, C.M., Boekhoorn, K. & Lucassen, P.J. (2007). Changes in neurogenesis in dementia and Alzheimer mouse models: are they functionally relevant? *Eur Arch Psychiatry Clin Neurosci, 257*, 281-289.

Morsink, M.C., Gemert, N.G. van, Steenbergen, P.J., Joels, M., Kloet, E.R. de & Datson, N.A. (2007). Rapid glucocorticoid effects on the expression of hippocampal neurotransmission-related genes. *Brain Research, 1150*, 14-20.

Oldenziel, W.H., Zeyden, M. van der, Dijkstra, G., Ghijsen, W.E.J.M., Karst, H., Cremers, T.I. & Westerink, B.H. (2007). Monitoring extracellular glutamate in hippocampal slices with a microsensor. *J. Neurosci. Methods, 160*, 37-44.

Oomen, C.A., Mayer, J.L., Kloet, E.R. de, Joels, M. & Lucassen, P.J. (2007). Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. *Eur. J. Neurosci., 26*, 3395-3401.

Pu, Z., Krugers, H. & Joels, M. (2007). Corticosterone time-dependently modulates {beta}-adrenergic effects on long-term potentiation in the hippocampal dentate gyrus. *Learning & Memory, 14*, 359-367.

Sennvik, K., Boekhoorn, K., Lasrado, R., Terwel, D., Verhaeghe, S., Korr, H., Schmitz, C., Tomiyama, T., Mori, H., Krugers, H., Joels, M., Ramakers, G.J., Lucassen, P.J. & Leuven, F. van (2007). Tau-4R suppresses proliferation and promotes neuronal differentiation in the hippocampus of tau knockin/knockout mice. *The Faseb Journal, 21*, 2149-2161.

Sidiropoulou, K., Joels, M. & Poirazi, P. (2007). Modelling stress-induced adaptations in Ca++ dynamics. *NEUROCOMPUTING, 70*, 1640-1644.

Veenema, A.H., Kloet, E.R. de, Wilde, M.C. de, Roelofs, A.J., Kawata, M., Buwalda, B., Neumann, I.D., Koolhaas, J.M. & Lucassen, P.J. (2007). Differential effects of stress on adult hippocampal cell proliferation in low and high aggressive mice. *J. Neuroendocrinology, 19*, 489-498.

Verwer, R.W.H., Sluiter, A.A., Balesar, R.A., Baayen, J.C., Noske, D.P., Dirven, C.M., Wouda, J., Dam, A.M., Lucassen, P.J. & Swaab, D.F. (2007). Mature astrocytes in the adult human neocortex express the early neuronal marker doublecortin. *BRAIN, 130*, 3321-3335.

Vrede, van de Y., Fossier, P., Baux, G., Joels, M. & Chameau, P.J.P. (2007). Control of IsAHP in mouse hippocampus CA1 pyramidal neurons by RyR3-mediated calcium-induced calcium release. *Eur. J. Physiol., 455*, 297-308.

Vreugdenhil, E., Kolk, S.H., Boekhoorn, K., Fitzsimons, C.P., Schaaf, M, Schouten, Th., Sarabdjitsingh, A., Sibug, R. & Lucassen, P.J. (2007). Doublecortin-like, a microtubule-associated protein expressed in radial glia, is crucial for neuronal precursor division and radial process stability. *Eur. J. Neurosci., 25*, 635-648.

Book Chapters

Joels, M. & Karst, H. (2007). Corticosteroid effects on hippocampus. In Fink (Ed.), *Encyclopedia of Stress* (2) (pp. 321-326). Academic Press.

Joels, M. (2007). De slechte naam van stress. In *Spui Essay* (pp. 20-21). Amsterdam.

Invited lectures

Joels, M. (2007, February 15). *Leven met stress.* Amsterdam, the Netherlands, Academische club UvA.

Joels, M. (2007, November 28). *Brain Corticosteroid Effects: from minute to month, from rodent to man.* Munich, Germany, Emile Kraepelin Professorship.

Joels, M. (2007, April 19). *Corticosteroid actions in brain.* Busto Arsizio, Italy, European Working Group on Rett Syndrome.

Joels, M. (2007, April 18). *Corticosteroid actions in hippocampus: From minutes to hours.* Milan, Italy, University of Milan.

Joels, M. (2007, August 24). *Corticosterone in the hippocampus: a two-staged rocket.* Boedapest, Hungary, World Conference of Stress.

Joels, M. (2007, October 04). *Dual effects of mineralocorticoids on excitability of limbic neurons.* Munich, Germany, AGNP Meeting.

Joels, M. (2007, October 12). *Hippocampal function after chronic stress.* Vienna, Austria, 6th World Congress on Stress.

Joels, M. (,). *How stress affects hippocampal function.* Magdeburg, Germany, Univerity of Magdeburg.

Joels, M. (2007, October 11). *Is stress altijd slecht voor je hersenen?* Utrecht, the Netherlands Hersenpublieksdag.

Joels, M. (2007, August 02). *Mechanisms contributing to effects of stress hormones in brain.* Perth, Australia, Telethon Inst. Child Research.

Joels, M. (2007, July 17). *Mechanisms contributing to glucocorticoid effects on memory.* Melbourne, Australia, IBRO World Congress of Neuroscience.

Joels, M. (2007, March 29). *Meer beta-studenten?* Amsterdam, the Netherlands, UvA, FNWI Diesrede.

Joels, M. (2007, January 10). *Stress effects on hippocampal excitability: Influence of life history.* Edinburgh, UK, HFSP symposium.

Joels, M. (2007, March 30). *The importance of mineralocorticoid receptors in limbic brain areas.* Paris, France.

Karst, H. (2007, November 28). *Rapid nongenomic effects of corticosteroids.* Munich, Germany, Max Planck Institute for Psychiatry.

Krugers, H. (2007, February 23). *Cortisol en Depressie.* Groningen, the Netherlands, Farewell Symposium Prof dr Jaap Korf.

Krugers, H. (2007, November 28). *Glucocorticoid receptor activation promotes AMPA receptor trafficking and hippocampal learning.* Munich, Germay, Max Planck Institute for Psychiatry.

Krugers, H. (2007, October 05). *Hormonal control of molecular mechanisms involved in emotional memories.* Lausanne, Switzerland, EPFL.

Krugers, H. (2007, November 20). *Hormonal control of molecular mechanisms involved in learning and memory.* Maastricht, the Netherlands, University of Maastricht.

Krugers, H. (2007, June 08). *Hormonal control of molecular mechanisms involved in learning and memory.* Doorwerth, the Netherlands, 6th Dutch Endo-Neuro Meeting.

Krugers, H. (2007, May 24). *Hormonal control of molecular mechanisms involved in learning and memory.* Doorwerth, the Netherlands, IBANGS symposium.

Krugers, H. (2007, January 05). *Hormonal modulation of AMPA receptor function.* Amsterdam, the Netherlands, Universiteit van Amsterdam.

Lucassen, P.J. (2007, May 14). *Alzheimer mouse models; where have come from and are we there yet?* Bonn, Germany, International Meeting of the International Foundation Alzheimer Research in Bad Honnef.

Lucassen, P.J. (2007, December 04). *Cellular plasticity changes in relation to stress and dementia.* Göttingen, Germany, Department of Psychiatry, Göttingen University.

Lucassen, P.J. (2007, June 04). *Changes in neurogenesis in dementia; are they functionally relevant?* Groningen, the Netherlands, BCN International Stem Cell Symposium.

Lucassen, P.J. (2007, January 12). *Changes in neurogenesis in relation to dementia.* Berlin, Germany, NEURAD Kick off Symposium.

Lucassen, P.J. (2007, April 02). *Does depression damage the brain?* London, England, Conference on Depression: Causes in the Brain, Consequences on the Body. Inst. of Psychiatry, King's College London, Royal Society of Medicine.

Lucassen, P.J. (2007, May 21). *Increases in LTP and learning but not neurogenesis in young P301L tau mutant mice.* Doorwerth, the Netherlands, Symposium "Modelling neuro-degeneration: causes and consequences", of the 9th Annual Genes, Brain and Behavior Meeting - IBANGS 2007.

Lucassen, P.J. (2007, October 10). *Neurogenesis in neuropsychiatric disorders.* Vienna, Austria, Targeted Expert Meeting prior to the ECNP meeting in Vienna.

Lucassen, P.J. (2007, September 21). *Regulation of cellular plasticity by stress and dementia.* Göttingen, Germany, 1st NEURAD summer school.

Lucassen, P.J. (2007, November 28). *Structural plasticity and neurogenesis in relation to stress and depression.* Munich, Germany, Emile Kraepelin Professorship to Marian Joels at the Max Planck Inst. for Psychiatry.

Lucassen, P.J. (2007, October 10). *The role of neurogenesis in antidepressant action.* Vienna, Austria, invited discussant at the Targeted Expert Meeting preceding the ECNP stress meeting.

Appendix 1k

Mass Spectrometry of Biomacromolecules

Chairholder: Prof.dr C.G. de Koster

Research Results in Numbers

Peer reviewed publications	12
Non-peer reviewed publications	0
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2007)

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/Assist. prof.	0.9	0	0	0.9
Research Fellow	0.8	0	1.0	1.8
PhD Student	1.3	0.9	0.75	3.0
Technician	3.0	0	0	3.0
Total	**6.5**	**0.9**	**1.8**	**9.2**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publication

Yin QY, de Groot PW, de Jong L, Klis FM, De Koster CG. Mass spectrometric quantitation of covalently bound cell wall proteins in *Saccharomyces cerevisiae.* FEMS Yeast Res. 2007 Sept;7(6):887-96. *Epub* 2007 Jul 6.

Kasper PT, Back JW, Vitale M, Hartog AF, Roseboom W, de Koning LJ, van Maarseveen JH, Muijsers AO, de Koster CG, de Jong L. An aptly positioned azido group in the spacer of a protein cross-linker for facile mapping of lysines in close proximity. *Chembiochem*. 2007 Jul 23;8(11):1281-92.

Academic publications (refereed)

Pel, H.J., Winde, J.H. de, Archer, D.B., Dyer, P.S., Hofmann, G., Schaap, P.J. & Groot, P.W.J. de (2007). Genome sequencing and analysis of the versatile cell factory *Aspergillus niger* CBS 513.88. *Nat.Biotechnol., 2*, 221-231.

Bekker, M., Kramer, G., Hartog, A.F., Koster, C.G. de, Hellingwerf, K.J. & Teixeira de Mattos, M.J. (2007). Changes in the redox state and composition of the quinone pool of *Escherichia coli* during aerobic batch-culture growth. *Microbiology, 153*, 1974-1980.

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Hendriks, M.M.W.B., Smit, S., Akkermans, L.M.W., Reijmers, Th.H., Eilers, P.H.C., Hoefsloot, H.C.J., Rubingh, C.M., Koster, C.G. de, Aerts, J.M.F.G. & Smilde, A.K. (2007). How to distinguish healthy from diseased? Classification strategy for mass spectrometry based clinical proteomics. *PROTEOMICS, 7*(20), 3672-3680.

Houterman, P.M., Speijer, D., Dekker, H.L., Koster, C.G. de, Cornelissen, B.J.C. & Rep, M. (2007). The mixed proteome of *Fusarium oxysporum*-infected tomato xylem vessels. Molecular Plant Pathology, 8, 215-221.

Klis, F.M., Jong, M. de, Brul, S. & Groot, P.W.J. de (2007). Extraction of cell surface-associated proteins from living yeast cells. *Yeast, 4*, 253-258.

Mayjer, H.J., Vondervoort, P.J. van, Yin, Q., Koster, C.G. de, Govers, F. & Groot, P.W.J. de (2007). 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. (2007). 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.

Peters, R., Litvinov, V.M., Steeman, P., Dias, A.A., Mengerink, Y., Benthem, R. van, Koster, C.G. de, Wal, S. van der & Schoenmakers, P.J. (2007). Characterisation of UV-cured acrylate networks by means of hydrolysis followed by aqueous size-exclusion combined with reversed-phase chromatography. *J.Chromatography, 1156*(1-2), 111-123.

Smit, S., Breemen, M.J. van, Hoefsloot, H.C.J., Smilde, A.K., Aerts, J.M.F.G. & Koster, C.G. de (2007). Assessing the statistical validity of proteomics based biomarkers. *Anal. Chim. Acta, 592*, 210-217.

Yin, Q., Groot, P.W.J. de, Jong, L. de, Klis, F.M. & Koster, C.G. de (2007). Mass spectrometric quantitation of covalently bound cell wall proteins in *Saccharomyces cerevisiae. FEMS Yeast Res., 7*(6), 887-896.

Kasper, P.T., Back, J.W., Vitale, M., Hartog, A.F., Roseboom, W., Koning, L.J. de, Maarseveen, J.H. van, Muijsers, A.O., Koster, C.G. de & Jong, L. de (2007). An aptly positioned azido group in the spacer of a protein cross-linker for facile mapping of lysines in close proximity. *Chembiochem., 8*(11), 1281-1292.

Invited lectures

Koster, C.G. de (2007, May 07). *Mass spectrometric quantitation of covalently bound cell wall proteins in S.cerevisiae*. Munster, Germany, 8th Proteomics Inf.Exchange Meeting.

Koster, C.G. de (2007, January 31). *Proteome-wide high throughput quantification of yeast glycolytic proteins.* Amsterdam, Third Int.Symp. on Separation and Characterization of Nat. and Synthetic Macromolecules.

Appendix 1l

Biosystems Data Analysis

Chairholder: Prof.dr A. Smilde

Research Results in Numbers

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

Staff (Research input in fte during 2007)

Age Smilde	Chairholder
Antoine van Kampen	Professor
Huub Hoefsloot	Associate Professor
Johan Westerhuis	Assistant Professor

Position	FS1*	FS2**	FS3◊	Total
Chairholder	0.25	0	0	0.25
Professor	0	0	0.2	0.2
Associate/Assist. prof.	1.0	0	0	1.0
Research Fellow	0	0	0.9	0.9
PhD Student	0.6	0	1.9	2.5
Technician	0	0	0	0
Total	**1.9**	**0**	**3.0**	**4.9**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Smit, S., van Breemen, M.J., Hoefsloot, H.C. J., Smilde, A.K., Aerts, J.M.F.G.and de Koster; C.G. (2007). Assessing the statistical validity of proteomics based biomarkers, *Analytica Chimica Acta*, 592: 210-217.

Westerhuis JA, Derks EPPA, Hoefsloot HCJ, Smilde AK, Grey Component Analysis, *Journal of Chemometrics* 21(10-11) (2007) 474-485.

Academic publications (refereed)

Goodacre, D., Broadhurst, D., Smilde, A.K., Kristal, B.S., Baker, J.D., Beger, R. & Bessant, C. (2007). Proposed minimum reporting standards for data analysis in metabolomics. *Metabolomics, 3*, 231-241.

Hendriks, M.M.W.B., Smit, S., Akkermans, L.M.W., Reijmers, Th.H., Eilers, P.H.C., Hoefsloot, H.C.J., Rubingh, C.M., Koster, C.G. de, Aerts, J.M.F.G. & Smilde, A.K. (2007). How to distinguish healthy from diseased? Classification strategy for mass spectrometry based clinical proteomics. *PROTEOMICS, 7*(20), 3672-3680.

Hoefsloot, H.C.J., Westerhuis, J.A., Verouden, M.P.H. & Smilde, A.K. (2007). MALS. *J. Chemometr., 20*, 120-127.

Iedema, P.D., Wulkow, M. & Hoefsloot, H.C.J. (2007). Conditional Monte Carlo sampling to find branching architectures of polymers from radical polymerizations with transfer to polymer and recombination termination. *Polym., 48*, 1770-1784.

Kiers, H.A.L. & Smilde, A.K. (2007). A comparison of various methods for Multivariate Regression with highly collinear variables. *Statistical Methods and Applications, 16*, 193-228.

Kleemann, R., Verschuren, L., Erk, M.J. van, Nikolsky, Y., Cnubben, N.H.P., Verheij, E.R., Smilde, A.K. & Hendriks, H.F.J. (2007). Increased dietary cholesterol-induced atherosclerosis is associated with liver inflammation: Identification of novel regulatory pathways and transcriptional regulators involved in switch from metabolic adaptation to inflammatory state. *Genome Biology, 8*, R200.

Nueda, M.J., Conessa, A., Westerhuis, J.A., Hoefsloot, H.C.J., Smilde, A.K., Talon, M. & Ferrer, A. (2007). Vering gene expression patterns in time course microarray experiments by ANOVA-SCA. *BIOINFORMATICS, 23*, 1792-1800.

Rothenberg, G., Hageman, J.A., Clerc, F.A., Fruehauf, H.-W. & Westerhuis, J.A. (2007). How to find the best homogeneous catalyst. *Catalysis of Organic Reactions, 115*, 261-270.

Skibsted, E., Westerhuis, J.A., Smilde, A.K. & Witte, D.T. (2007). Examples of NIR based real time release in tablet manufacturing. *J.Pharmaceutical and Biomed.Analysis, 43*, 1297-1305.

Smit, S., Breemen, M.J. van, Hoefsloot, H.C.J., Smilde, A.K., Aerts, J.M.F.G. & Koster, C.G. de (2007). Assessing the statistical validity of proteomics based biomarkers. *Anal. Chim. Acta, 592,* 210-217.

Sprang, E.N.M. van, Streefland, M., Pol, L.A. van der, Beuvery, E.C., Ramaker, H.J. & Smilde, A.K. (2007). Manufacturing vaccines: an illustration of using PAT tools for controlling the cultivation of *Bordetella pertussis. Quality Engineering, 19*(4), 373-384.

Timmerman, M.E., Kiers, H.A.L. & Smilde, A.K. (2007). Estimating confidence intervals for principal component analysis: A comparison between the bootstrap and asymptotic results. *Br. J. Math. Stat. Psychol., 60*, 295-314.

Vis, D.J., Westerhuis, J.A., Smilde, A.K. & Greef, J. van der (2007). Statistical validation of megavariate effects in ASCA. *BMC BIOINFORMATICS, 8*, 322.

Westerhuis, J.A., Derks, E.P.P.A., Hoefsloot, H.C.J. & Smilde, A.K. (2007). Grey component analysis. *J. Chemometr., 21*(10-11), 474-485.

Westerhuis, J.A., Hageman, J.A., Fruhauf, H.W. & Rothenberg, G. (2007). Understanding ligand diversity. *Chimica Oggi, 25*, 28-32.

Damian, D., Oresic, M., Verheij, E.R., Meulman, J., Friedman, J., Adourian, A., Morel, N., Smilde, A.K. & Greef, J. van der (2007). Applications of a new subspace clustering algorithm (COSA) in medical systems biology. *Metabolomics, 3*(1), 69-77.

Membership editorial board

Smilde, A.K. (Ed.). (2007). *J. Chemometr.*

Westerhuis, J.A. (Ed.). (2007). *J. Chemometr.*

Invited lectures

Hoefsloot, H.C.J. (2007, September 04). *Statistical validation of biomarkers.* Amsterdam, NL, European Biomarkers Summit.

Smilde, A.K. (2007, September 05). *Emergence and causality in biological systems.* Aas, Norway, PLS07 Meeting.

Smilde, A.K. (2007, March 19). *Finding functional modules in metabolomics.* Geilo, Norway, Norwegian Chemometrics Society.

Smilde, A.K. (2007, May 08). *Megavariate analysis-of-variance.* Rolduc, NL, First IBS Channel Network Conference.

Smilde, A.K. (2007, June 11). *Metabolomics as an essential module in systems biology models.* Manchester, U.K., Third International Metabolomics Meeting.

Westerhuis, J.A. (2007, August 01). *Microbial metabolomics: Explorative analysis of complex data.* Azores, Portugal, ISBIS Conference.

Westerhuis, J.A. (2007, June 01). *Validation of metabolic differences and variable importance.* Manchester, U.K., Metabolomics Conference.

Appendix 1m

Micro Array Department and Integrative Bioinformatics Unit

Group Leader: Dr T.M. Breit

Research Results in Numbers

Peer reviewed publications	15
Non-peer reviewed publications	4
PhD Theses	0
Patent applications	0

Staff (Research input in fte during 2007)

Timo Breit	Group Leader
Floyd Wittink	Project management "wet-lab"
Mattijs Jonker	Project management "dry-lab"
Jenny Batson	Project Administration

Position	FS1*	FS2**	FS3◊	Total
Group Leader	0.5	0	0	0.5
Project Management	0	0.9	0.9	1.8
Technician	0	0	5.2	5.2
Bioinformatics staff	0	0	2.4	2.4
Total	**0.5**	**0.9**	**8.5**	**9.9**

* FS1 = University Funding

** FS2 = External funding, governmental grants

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

Publications

Key Publications

Bruins W, Bruning O, Jonker MJ, Zwart E, van der Hoeven T, Pennings JLA, Rauwerda H, de Vries A, Breit TM. (Accepted). Absence of Ser389 phosphorylation in p53 affects the basal gene-expression level of many p53-dependent genes and alters the biphasic response to UV exposure in MEFs. *MCB.*

Post LJG, Roos M, Marshall MS, van Driel R, Breit TM. (2007). The semantic web Approach applied to integrative bioinformatics experimentation: a biological use case with genomics data. *Bioinformatics 23*(22):3080-7.

Academic publications (refereed)

Aronica, E., Boer, J. de, Becker, A., Redeker, S., Spliet, W.G., Rijen, P.C. van, Wittink, F., Breit, T.M., Wadman, W.J., Lopes da Silva, F.H., Troost, D & Gorter, J.A. (2008). Gene expression profile analysis of epilepsy-associated gangliogliomas. *Neuroscience, 151*, 272-292.

Banus, H.A., Pennings, J.L.A., Vandebriel, R.J., Wester, P.W., Breit, T.M., Mooi, F.R., Hoebee, B. & Kimman, T.G. (2007). Lung response to *Bordetella pertussis* infection in mice identified by gene-expression profiling. *IMMUNOGENETICS, 59*(7), 555-564.

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Bruins, W., Bruning, O., Jonker, M.J., Swart, E., Hoeven, T. van der, Pennings, J.L.A., Rauwerda, H., Vries, A. & Breit, T.M. (2008). Absence of Ser389 phosphorylation in p53 affects the basal gene-expression level of many p53-dependent genes and alters the biphasic response to UV exposure in MEFs. *Mol. Cell. Biol..*

Bruins, W., Jonker, M.J., Bruning, O., Pennings, J.L.A., Schaap, M.M., Hoogervorst, E.M., Steeg, H. van, Breit, T.M. & Vries, A. (2007). Delayed Expression of Apoptotic and Cell Cycle Control Genes in Carcinogen-Exposed Bladders of Mice Lacking p53. S389 Phosphorylation. *CARCINOGENESIS, 28*(8), 1814-1823.

Gorter, J.A., Vliet, E.A. van, Rauwerda, H., Breit, T.M., Stad, R., Schaik, R. van, Vreugdenhil, E., Redeker, S., Hendriksen, E., Aronica, E., Lopes da Silva, F.H. & Wadman, W.J. (2007). Dynamic changes of proteases and protease inhibitors revealed by microarray analysis in CA3 and entorhinal cortex during epileptogenesis in the rat. *Epilepsia, 48*, 53-64.

Keijser, B.J.F., Beek, A.S. ter, Rauwerda, H., Schuren, F., Montijn, R., Spek, H. van der & Brul, S. (2007). Analysis of temporal gene expression during *Bacillus subtilis* spore germination and outgrowth. *J BACTERIOL, 189*(May, 9), 3624-3634.

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., Oostrom, C. van, Vries, A. de & Steeg, H. van (2007). Ozone induces clear cellular and molecular responses in the mouse lung independently of the transcription-coupled repair status. *J APPL PHYSIOL, 102*(3), 1185-1192.

Korkhov, V., Vasunin, D., Wibisono, A., Belloum, A., Inda, M.A., Roos, M. & Breit, T.M. (2007). Interactive dataflow driven workflow engine for Grid enabled resources Scientific Programming. *Journal of Scientific Programming, 15*(3), 173-188.

Post, L.J.G., Roos, M., Marshall, M.S., Driel, R. van & Breit, T.M. (2007). A semantic web approach applied to integrative bioinformatics experimentation: a biological use case with genomics data. *BIOINFORMATICS, 23*(22), 3080-3087.

Pronk, T.E., Pimentel, A.D., Roos, M. & Breit, T.M. (2007). Taking the example of computer systems engineering for the analysis of biological cell systems. *BIOSYSTEMS, 90*(3), 623-635.

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Pronk, T.E., Vink, E., Bosnacki, D. & Breit, T.M. (2007). Stochastic modeling of codon bias with PRISM. In I. Linden & C. Talcott (Eds.), *Proceedings of the 3rd international workshop on Methods and Tools for Coordinating, Distributed and Mobile Systems MTCoord 2007. Electronic Notes in Theoretical Computer Science.* Nicosia, Cyprus: Computer Science Department, University of Cyprus.

Rauwerda, H., Leeuw, W.C. de, Adriaanse, J., Bouwhuis, M., Vet, P. van der & Breit, T.M. (2007). The role of e-BioLabs in a life sciences collaborative working environment. In *Proceedings Conference e-Challenges*.

Ruttenberg, A., Clark, T., Bug, W., Samwald, M., Bodenreider, O., Chen, H., Doherty, D., Forsberg, K., Gao, Y., Kashyap, V., Kinoshita, J., Luciano, J., Marshall, M.S., Ogbuij, C., Rees, J., Stephens, S., Wong, G., Wu, E., Zaccagnini, D., HongserMayer, T., Neumann, E., Herman, I. & Cheung, K.H. (2007). Advancing Translational Research with the Semantic Web. *BMC BIOINFORMATICS, 8*(suppl.3).

Smit van Dixhoorn, M.G.A., Munir, R., Stad, R., Haan, M. de, Hoeven, T. van der, Rauwerda, H., Breit, T.M., Thallinger, G.G. & Wadee, A.A. (2007). Gene expression profiling of suppressor mechanisms in tuberculosis. *MOL IMMUNOL, 7*.

Vroling, A.B., Jonker, M.J., Breit, T.M., Fokkens, W.J. & Drunen, C.M. van (2007). Comparison of expression profiles induced by dust mite in airway epithelia reveals a common pathway. *J ALLERGY CLIN IMMUN*.

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Book chapters

Kashyap, V., Cheung, K.H., Doherty, D., Samwald, M., Marshall, M.S., Luciano, J., Stephens, S., Herman, I. & Hookway, R. (2007). An ontology based approach for data integration; An application in Biomedical Research. In J. Cardoso, M. Hepp & M. Lytras (Eds.), *Real-World Applications from Industry* (Semantic Web and Beyond, 6). Springer.

Appendix 2. Contact Details

Director: Dr H.D. Veldhuis

Manager Business and Finance: Dr C. Huijser

Manager Research and Aqcuisition: Dr K. van de Sande

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