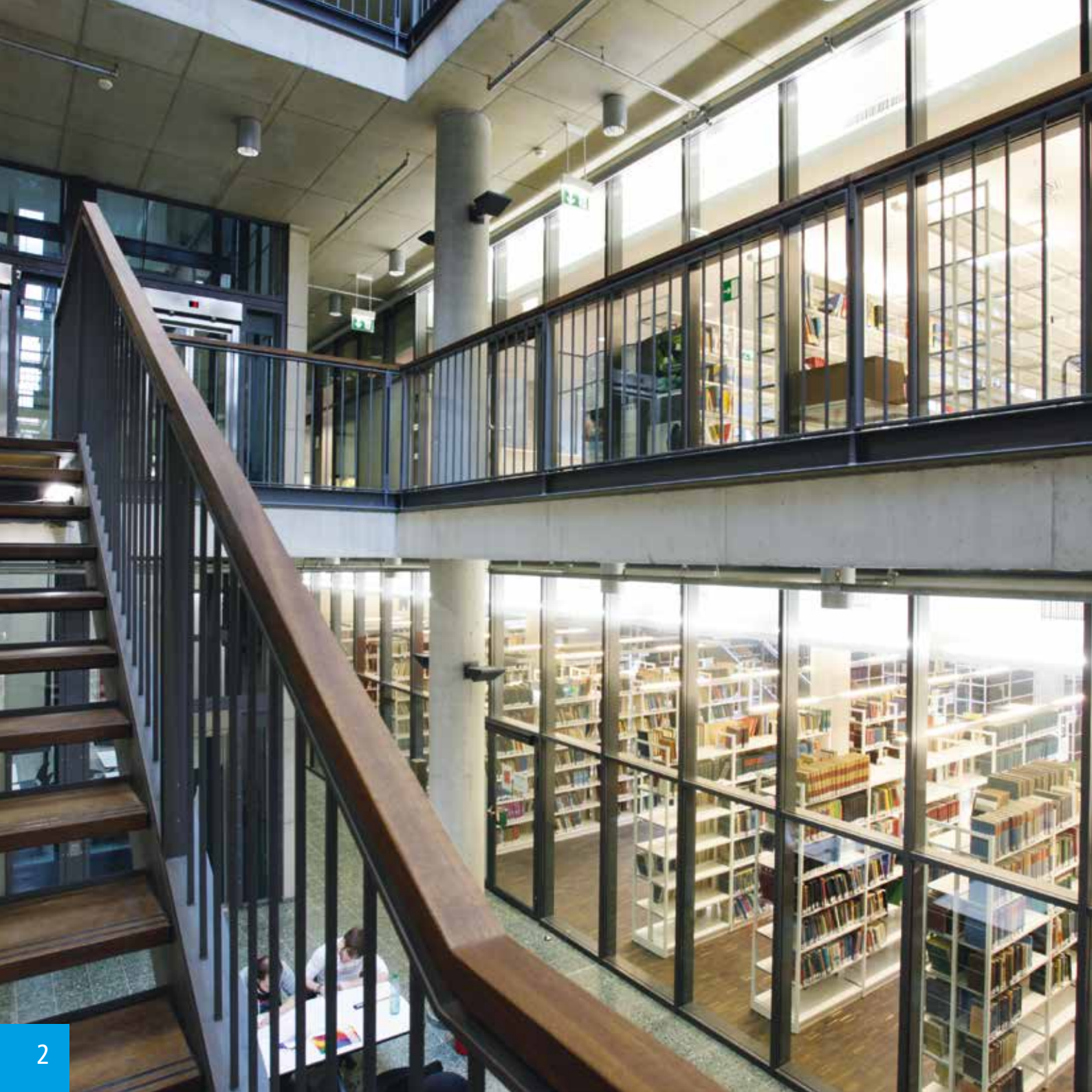
Department of Biology

At a glance



UNIVERSITY OF COLOGNE
FACULTY OF MATHEMATICS
AND NATURAL SCIENCES
DEPARTMENT OF BIOLOGY

University of Cologne



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INTRODUCTION

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Foreword

In April 2015, the "Fachgruppe Biologie" was restructured into the "Department of Biology" within the Faculty of Mathematics and Natural Sciences at the University of Cologne. It now comprises three institutes with 37 professorships; the Botanical Institute, the Institute for Genetics and the Institute for Zoology.

This brochure aims to present ongoing activities in the Department of Biology. It provides an overview of projects being pursued by individual research groups within the institutes, including several Independent Junior Research Groups. Many research group leaders are members of prominent research associations such as Collaborative Research Centres funded by the German Research Foundation (DFG) and some are affiliated to the Center for Molecular Medicine Cologne (CMMC) and the Cologne Center for Genomics (CCG). The Department of Biology also hosts the two DFG-funded Clusters of Excellence at the University of Cologne; the Cologne Cluster of Excellence in Cellular Stress Responses in Aging-Associated Diseases (CECAD) and the Cluster of Excellence in Plant Sciences (CEPLAS). The respective visions of both Clusters are briefly presented, and the new professors recruited during the 2012–2017 funding period introduce themselves. As research infrastructure, the Department of Biology houses two technology platforms; the Cologne Biocenter Imaging Facility and the Biocenter Mass-Spectrometry Platform. Both of these facilities can be accessed by research groups from the Department of Biology, and also by external users.

The study program of the Department of Biology includes the Bachelor of Biology degree and the English-speaking master's program in Biological Sciences. These courses provide students with specialized training that aligns with the research priorities of the department. In addition, interdisciplinary master's degree programs in Environmental Sciences (IMES) and Neuroscience are offered. The department also offers two teaching degrees; a Bachelor of Arts and a Master's of Education, which train graduates to teach biology at grammar and comprehensive schools. Furthermore, the department offers a "fast-track" master's/doctorate program, affiliated with the Graduate School for Biological Sciences (GSfBS). The GSfBS was established in 2006 as the first graduate school at the University of Cologne, offering specialized training and support for all doctoral students and serving as an umbrella that oversees the various other structured Ph.D. programs in biosciences.

As you will see, the Department of Biology provides an excellent environment to address some of the most challenging questions in modern biology. Interdisciplinary project ideas can be discussed at the recently established "Biocenter Friday" – an informal get-together of all PIs and postdoctoral researchers at the Department of Biology.

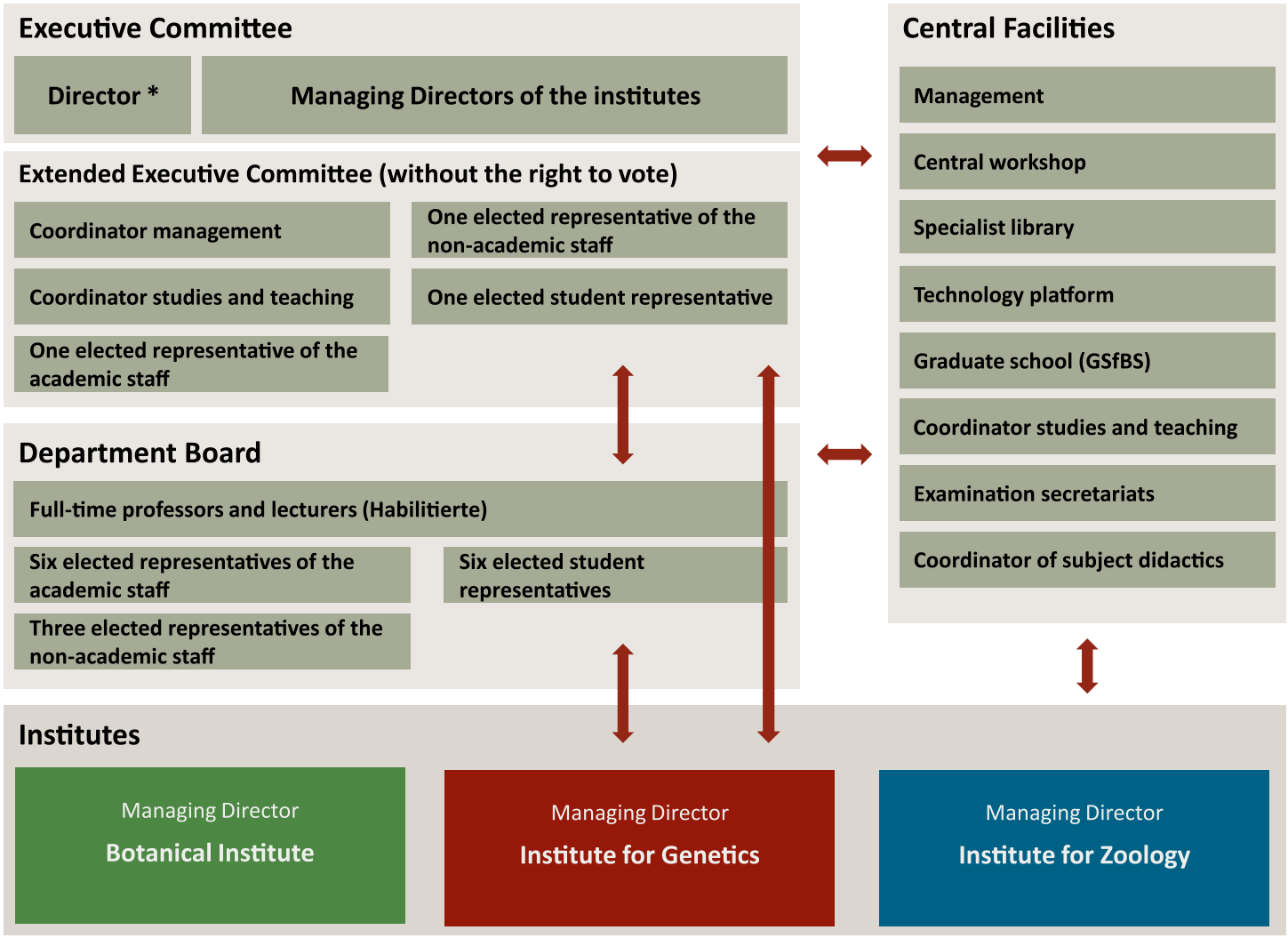
We hope that you will enjoy reading about our science and more in the following pages.

Prof. Dr. Ulf-Ingo Flügge
Director

ORGANIZATION

The core of the Department of Biology is represented by the three institutes and includes embedded central facilities. The department is headed by a director who is elected by the Department Board and represents all university groups. The Department Board meets at least twice per semester and works on statements and recommendations for topics decided by the faculty. The Executive Committee, consisting of the Department Director and the three directors of the institutes, is responsible for the management of the department and administrative matters. It also takes decisions on how the budget given by the Ministry for School and Further Education in North Rhine-Westphalia is spent.

The central facilities were established under the umbrella of the department to strengthen its structure. The management coordinator supports the Department Director with all necessary information and prepares the Executive Committee and Department board meetings. The central workshop provides comprehensive support to members of the department for the development and maintenance of operational equipment in research and teaching. The coordinator for studies and teaching manages the Bachelor and Master programs, which were established in 2005/6. Furthermore, there are eight different Ph.D. programs running in, or associated with, the Department of Biology, providing high-quality education for young scientists.



*elected by the Department Board

COOPERATIONS

The Department of Biology strongly cooperates with the Institute for Biochemistry, which is an associated member of the Department of Biology. It is also closely linked to (i) the Center for Molecular Medicine Cologne (CMMC), representing a multi-disciplinary center within the Faculty of Medicine and the Faculty of Mathematics and Natural Sciences and pursuing disease-oriented research, and to (ii) the Cologne Center for Genomics (CCG), which is also an inter-faculty center established for large-scale technologies in genomics (Prof. Michael Nothnagel, Prof. Peter Nürnberg). The CCG provides support for e.g., next-generation sequencing, gene mapping, expression profiling etc. Within the framework of the two Clusters of Excellence CECAD and CEPLAS, a close cooperation was established with the Cologne University Hospital, the Max Planck Institutes for Biology of Ageing and for Metabolism Research (headed by Jens Brüning, a former Professor at the Institute for Genetics) and the Center for Neurodegenerative Diseases (DZNE), and the University of Düsseldorf, the Max Planck Institute for Plant Breeding Research (MPIPZ Cologne) and the Forschungszentrum Jülich, respectively.
The Faculty of Mathematics and Natural Sciences together with the Department of Biology intend to establish a focus on Computational Biology at the University of Cologne. To strengthen this area of research and teaching, the University of Cologne and the Max Planck Institute for Plant Breeding Research have jointly established a Jeff Schell endowment professorship, which is occupied by Prof. Achim Tresch. Prof. Tresch is working in the field of transcriptomics, regulatory networks, and epigenomics and develops new statistical models that are capable of dealing with vast amounts of heterogeneous data. Activities in computational sciences are linked to the Sybacol (Systems Biology of Ageing Cologne) consortium. This initiative merges the work of life scientists involved in aging research with that of theoretical physicists, mathematicians and bioinformaticians at the Faculties of the Natural Sciences and Medicine and at the Max Planck Institute for Biology of Ageing. The work of Prof. Andreas Beyer focuses on the integration of functional genetics with interactome data in order to understand the functioning of cellular systems.

The field of Computational Biology is furthermore enriched by a close cooperation with the Research Center Jülich: PD Dr. Silvia Gruhn uses mathematical models to investigate how rhythmic motor activity in the nervous system is generated, and in particular, which neural mechanisms underlie animal locomotion and movement control.

Taken together, the Department of Biology represents an internationally cooperating research focus in the field of molecular life sciences, which is also reflected in four Collaborative Research Centres (CRC 635, 670, 680 und 829).

TEACHING & EDUCATION

In biology, about 240 students start the Bachelor of Science course and 80 students the Master of Science course each year. In addition, the Department also conducts the teaching degree in biology at grammar and comprehensive schools (since winter 2011/12, the Bachelor of Arts and since winter 2014/15, the Master of Education). The Master's program in "Biological Sciences" held in English, started in winter 2005/6 and allows a specialization in one or more of the seven research priorities of the Department. The B.Sc. and the M.Sc. programs were accredited in May 2009 and currently participate in the University of Cologne´s model accreditation. The courses offered in Biology are complemented by interdisciplinary master's degree programs in Environmental Sciences (IMES) and Neuroscience. A "fast-track" master's/doctoral program for excellent students is supported by the Master's program and the Graduate School for Biological Sciences (GSfBS). The GSfBS was established in 2006 and is a registered study course since 2008. Currently, 330 out of the 490 doctoral candidates in biology are enrolled in the GSfBS, with 40% being international and 60% female. Centered on the functional analysis of biological processes, the scientific base of the program is broad, providing students with opportunities for training in fields ranging from ecology and evolution to molecular genetics or physiology, and including all of the major microbial, plant and animal model systems. The doctoral program reflects the increasing importance of interdisciplinary research and provides comprehensive training for scientific, methodological and transferable skills. Each doctoral candidate is guided by an individual thesis committee, allowing the completion of a demanding research project in the shortest possible time. Group identity is fostered by soft-skills courses, retreats and events such as student-organized conferences, career days, company visits, Ph.D. days, alumni days etc. The GSfBS serves as an umbrella structure for all doctoral candidates in biology striving for a Dr. rer. nat. degree and for currently seven specified structured graduate programs: The Research Training Group-Neural Circuit Analysis (RTG-NCA), the International Max Planck Research School 'Molecular Plant Sciences' (IMPRS), the Ph.D. program in Pharmacology and Experimental Therapeutics, the Cologne Graduate School of Ageing Research, the ITN CodeAge, the Marie Curie Action 7th Framework Programme and the Excellence cluster CEPLAS Graduate School.

Scientists at the Botanical Institute use state-of-the-art molecular techniques to address current challenges in plant sciences, covering cell und developmental biology, molecular physiology, the evolution of plants and responses of plants to the biotic and abiotic environment. Organisms currently studied include *Arabidopsis thaliana*, its alpine relative *Arabis alpina*, *Lotus*, maize, barley, potato, sugar beet, mosses and algae. Our institute is instrumental in the Cluster of Excellence in Plant Sciences (CEPLAS see p. 92), a joint research program of the Universities of Cologne and Düsseldorf, the Max Planck Institute for Plant Breeding Research and the Forschungszentrum Jülich. Basic research in CEPLAS is dedicated to developing new paradigms for crop improvement through the exploitation of natural variation, biodiversity and synthetic biology. CEPLAS holds a unique position within the German Excellence Initiative as the only cluster focusing exclusively on plant science. Through CEPLAS funding, four new professorships were established at the Botanical Institute in 2014. The Botanical Institute is also internationally known for its Culture Collection of Algae (CCAC) which harbors more than 4,000 strains of microalgae from around the world. Our faculty is embedded within extensive collaborations with other renowned institutions world-wide. These activities have made Cologne an internationally highly recognized center for Molecular Plant Sciences.

At the Botanical Institute, students and scientists acquire the necessary high-end skills to be successful in the fields of plant biology, molecular biology and biochemistry. Two international graduate schools, which are jointly organized by the Max Planck Institute for Plant Breeding Research and the University of Düsseldorf (IMPRS; CEPLAS Graduate School), offer three-year structured Ph.D. programs in Molecular Plant Sciences. These schools combine cutting-edge research with an interdisciplinary training program in scientific and career-relevant skills. In the frame of CEPLAS, our faculty participates in the new B.Sc. program in Quantitative Biology. This program aims to train a new generation of scientists at the interface between biology, computational sciences, mathematics and statistics.

RESEARCH

Botanical Institute

Plant–Microflora Interactions in Changing Environments

DOWN TO THE ROOTS FULL OF SECRETS AND MYSTERY

Marcel Bucher

Botanical Institute

Plants exhibit great phenotypic plasticity in interactions with their biotic and abiotic environment. The association between plants and their endophytic microflora is a complex trait, involving reciprocal adaptation between interacting partners. The research group analyses the genetic and mechanistic basis underlying symbioses with beneficial soil fungi, with a special emphasis on (i) the arbuscular mycorrhizal symbiosis and (ii) the root-associated fungal microflora and how endophytic fungi affect plant growth and fitness. We study the legume *Lotus japonicus*, closely related species of the mustard family (Brassicaceae), and maize.

Virtually all roots host a microbial community that is a key determinant of plant health and productivity. This microbiome covers a

MAIN AREAS OF RESEARCH

Transcriptional and post-transcriptional control of symbiosis development and function in mycorrhizae

❊

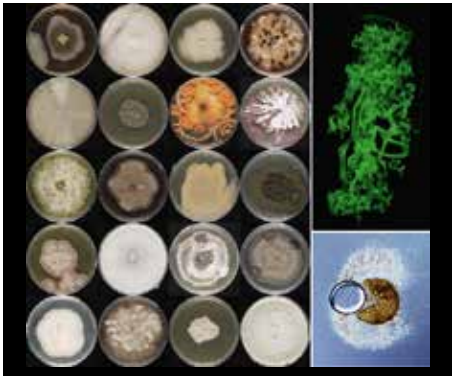
Cooperative cis*-regulation of nutrient uptake in root–fungus interactions*

❊

Structure and function of root-associated fungal communities using culture-based and culture-independent approaches

❊

Bioengineering of the root–soil interface



Top left: Scientific collage of Petri dishes with agar and diverse fungi collected from plant roots. These fungi originate from our Collection of Root Associated Fungi (CORFU) with currently 600 isolates.
Top right: Fluorescent fungal arbuscule colonizing a root cell of *Lotus japonicus*. This unit is called the symbiosome and is the site where reciprocal exchange of nutrients and metabolites between the plant and symbiotic fungus takes place.
Bottom right: Crushed spore of an arbuscular mycorrhizal fungus with its lipid content released. The images to the right were taken using a laser-scanning confocal (top) and a DIC optical (bottom) microscope.

KölnTourismus_GmbH_Axel Schulten

large spectrum of different taxa and protects plants from nutrient and water deprivation and pathogen attack. A tangible proof of the importance of root–microflora interactions are the arbuscular mycorrhizal (AM) fungi. In AM symbiosis, the host plant derives mainly phosphorus from the fungus, which in turn, benefits from plant-based photosynthetic carbohydrates. The genetic architecture underlying the mycorrhizal phosphate uptake pathway is therefore at the core of our research interests. *Lotus japonicus* and maize mutants affected in central components of mycorrhizal symbiosis are investigated using molecular physiological, genetic and biochemical tools. We currently investigate the formation of specific heterocomplexes of transcription factors that promote mycorrhiza-specific responses, and the mechanisms that dictate complex formation.

Moreover, we elucidate the composition and function of the root fungal microbiome of mycorrhizal and non-mycorrhizal plant species in nature and under controlled conditions using molecular fingerprinting methods and next-generation sequencing in combination with culture-dependent and -independent techniques. Here, we are mainly interested in how plants select microbes from soil for their own benefit and how abiotic and biotic parameters modulate this selection.

Our work hopefully contributes to the breeding of better crops for a sustainable agriculture and global food security.

Publications

Drissner D, Kunze G, Callewaert N, Gehrig P, Tamasloukht M, Boller T, Felix G, Amrhein N, and Bucher M (2007). Lyso-phosphatidylcholine is a signal in the arbuscular mycorrhizal symbiosis. Science 318: 265-268.

Lota F, Wegmüller S, Buer B, Sato S, Bräutigam A, Hanf B and Bucher M (2013). The *cis*-acting CTTC-P1BS module is indicative for gene function of *LjVTI12*, a Qb-SNARE protein gene that is required for arbuscule formation in *Lotus japonicus.* Plant J. 74: 280-293.

Rausch C, Daram P, Brunner S, Jansa J, Laloi M, Leggewie G, Amrhein N and Bucher M (2001). A phosphate transporter expressed in arbuscule-containing cells in potato. Nature 414: 462-470.

Willmann M, Gerlach N, Buer B, Polatajko A, Nagy R, Koebke E, Jansa J, Flisch R, and Bucher M (2013). Mycorrhizal phosphate uptake pathway in maize: Vital for growth and cob development on nutrient poor agricultural and greenhouse soils. Front. Plant Sci. 4: 533. doi: 10.3389/fpls.2013.00533.

Xue L, Cui H, Buer B, Vijayakumar V, Delaux P-M, Junkermann S, and Bucher M (2015). Network of GRAS transcription factors involved in the control of arbuscule development in *Lotus japonicus*. Plant Physiol. 167: 854-871.

Plant Molecular Physiology

CHLOROPLASTS ARE SENSORS AND TARGETS FOR METABOLIC ACCLIMATION PROCESSES

Ulf-Ingo Flügge

Botanical Institute

Plastids are organelles that harbor photosynthesis-related processes and numerous anabolic pathways, such as the synthesis of amino acids, fatty acids, starch, isoprenoid-derived pigments, and certain hormones. Plastidial metabolism is linked to the requirements of the whole plant by extensive transport across the plastid envelope. Our aim is to elucidate the multifaceted functions of plastidial phosphate translocators (PT) in plant performance and development. The PT family comprises four classes of antiporters that exchange inorganic phosphate against phosphorylated intermediates, such as triose phosphates (TPT), phosphoenolpyruvate (PPT), glucose 6-phosphate (GPT), and pentose phosphates (XPT). Mutant and transgenic approaches in the model plant *Arabidopsis thaliana* have already underlined the essential role of PT family members. Future work will focus on their involvement in development and signaling, including chloroplast-to-nucleus (retrograde) signaling that orchestrates organelle and cell development, as well as metabolism in response to abiotic stresses.

MAIN AREAS OF RESEARCH

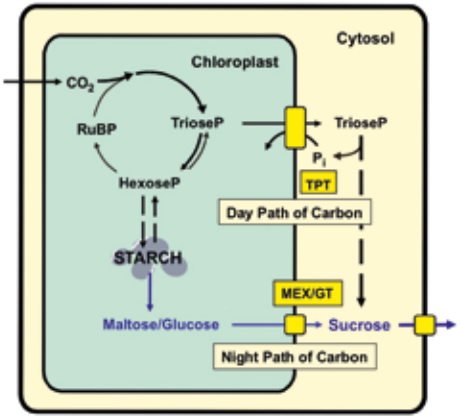
Transporters in plastids and plant performance

❊

Source–sink relationships

❊

Plant secondary metabolites in microbiota interactions



The chloroplast triose phosphate/phosphate translocator (TPT) represents the major path for fixed carbon during photosynthesis, whereas at night, photoassimilated carbon is exported as maltose and glucose deriving from transitory starch breakdown. In both cases, sucrose is formed and allocated to heterotrophic tissues as a source of carbon and energy. MEX, maltose exporter; GT, glucose translocator.

Photoassimilates produced in green leaves, the source tissue, have to be allocated to non-green sink tissues, where they can be used for metabolism or stored, e.g. as sugars, starch or fatty acids. We could recently demonstrate that the simultaneous genetic modification of both source and sink organs led to a doubling of tuber starch in potato. With the support of the Bill & Melinda Gates foundation, such "pull–push" approaches are now being exploited to enhance the starch content in cassava, a major staple food in tropical and subtropical regions.

Within the CEPLAS Excellence Cluster, we aim to identify and functionally analyze plant secondary metabolites and biosynthetic pathways that are decisive for the communication of plants with the root endophyte community, reversely triggering particular plant metabolite profiles. Specific attention is given to the role of glucosinolates, which serve as potential signaling compounds in plant–environment interactions. One aim is to identify metabolic regulons that determine the diversity of phytochemicals in plant–endophyte interactions. The molecular assembly of compatible genetic elements in "synthetic microbes" and "synthetic plants" will have a significant impact on developing next-generation agricultural products and might also lead to biotechnological innovations.

Publications

Jung, B., Ludewig, F., Schulz, A., Meißner, G., Wöstefeld, N., Flügge, U.I., Pommerrenig, B., Wirsching, P., Sauer, N., Koch, W., Sommer, F., Mühlhaus, T., Schroda, M., Cuin, T.A., Graus, D., Marten, I., Hedrich, R., Neuhaus, H.E. (2015). Identification of the transporter responsible for sucrose accumulation in sugar beet taproots. Nat. Plants 1. doi:10.1038/nplants.2014.1.

Häusler, R.E., Heinrichs, L., Schmitz, J., Flügge, U.I. (2014). How sugars might coordinate chloroplast and nuclear gene expression during acclimation to high light intensities. Mol. Plant 7: 1121-1137.

Ludewig, F., Flügge, U.I. (2013). Role of metabolite transporters in source-sink carbon allocation. Front. Plant Sci. 4: 231.

Jonik, C., Sonnewald, U., Hajirezaei, M.R., Flügge, U.I., Ludewig, F. (2012). Simultaneous boosting of source and sink capacities doubles tuber starch yield of potato plants. Plant Biotech. J. 10: 1088-1098.

Gigolashvili, T., Geier, M., Ashykhmina, N., Frerigmann, H., Wulfert, S., Mugford, S.G., Kopriva, S., Haferkamp, I., Flügge, U.I. (2012). Much more than a thylakoid ADP/ATP carrier – enlightening a role of TAAC in plastidic phosphoadenosine 5´-phosphosulfate (PAPS) supply to the cytosol. Plant Cell 24: 4187-4204.

Molecular Responses of Plants to the Light Environment

Ute Höcker

Botanical Institute

Sunlight is the primary source of energy for plants. Therefore, plants have evolved a variety of mechanisms to adapt growth and development to the ambient light conditions, with the aim to optimize growth – and ultimately – seed production in a competitive environment. We are interested in identifying and understanding the genes and proteins that underlie these adaptive developmental responses to light. To this end, we are mostly using the model species *Arabidopsis thaliana* and a combination of genetic, molecular and biochemical approaches.

Plants perceive light conditions through a number of photoreceptors that initiate a signaling cascade and result in vast changes in gene expression. Our research

MAIN AREAS OF RESEARCH

Protein ubiquitination in light signal transduction

❊

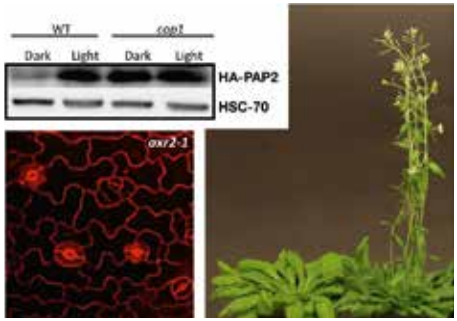
Light-controlled plant development

❊

Evolution of light signaling components

❊

Light–auxin crosstalk in the differentiation of stomata



Glimpse into research on light responses: molecular biology, a leaf surface and *Arabidopsis* plants

focuses on the proteins involved in the light signaling cascade. In particular, we analyze an E3 ubiquitin ligase (COP1/SPA complex) that controls the degradation of transcription factors during light signal transduction. Here, we focus on the regulation of COP1 activity by SPA proteins and light.

We also investigate the evolution of the COP1/SPA complex. Although the *COP1* gene also exists in humans, where it controls processes such as cell division and possibly tumor suppression, *SPA* genes are specific to plants. By analyzing COP1 and SPA function in the early land plant *Physcomitrella patens* (a moss), we aim to understand why *SPA* genes evolved in the green lineage.

Light conditions initiate a large number of adaptive responses. Examples are an increased stem elongation in shady conditions, more stomata and a thickening of leaves in the light, and the regulation of flowering time by day length. To understand how a common set of photoreceptors can induce such diverse responses throughout plant development, we analyze the functions of transcription factors in light signaling. Moreover, we investigate the crosstalk between light and the hormone auxin in stomata differentiation and shade avoidance.

Publications

Balcerowicz M., Ranjan A., Rupprecht L., Fiene G., Hoecker U. (2014). Auxin represses stomatal development in dark-grown seedlings via Aux/IAA proteins. Development 141: 3165-3176.

Maier, A., Schrader, A., Kokkelink, L., Falke, C., Welter, B., Iniesto, E., Rubio, V., Uhrig, J.F., Hülskamp, M. and Hoecker, U. (2013). Light and the E3 ubiquitin ligase COP1/SPA control the protein stability of the MYB transcription factors PAP1 and PAP2 involved in anthocyanin accumulation in Arabidopsis. Plant J. 74: 638-651.

Rolauffs, S., Fackendahl, P., Sahm, J., Fiene, G. and Hoecker, U. (2012). Arabidopsis *COP1* and *SPA* genes are essential for plant elongation but not for acceleration of flowering time in response to a low red light to far-red light ratio. Plant Physiol. 160: 2015-2027.

Ranjan, A., Fiene, G., Fackendahl, P. and Hoecker, U. (2011). The Arabidopsis repressor of light signaling SPA1 acts in the phloem to regulate seedling deetiolation, leaf expansion and flowering time. Development 138: 1851-1862.

Balcerowicz, M.*, Fittinghoff, K.*, Wirthmueller, L., Maier, A., Fackendahl, P., Fiene, G., Koncz C. and Hoecker, U. (2011). Light-exposure of Arabidopsis seedlings causes rapid de-stabilization as well as selective post-translational inactivation of the repressor of photomorphogenesis SPA2. Plant J. 65: 712-723. *joint first authorship

Arabidopsis Epidermal Cells as a Model to Study Intracellular Communication and Cell Morphogenesis

GLAUBE AN DAS BESTE IN JEDEM

Martin Hülskamp

Botanical Institute

Transmission Electron Micrograph of an *Arabidopsis thaliana* leaf with regularly spaced trichomes.

MAIN AREAS OF RESEARCH

Epidermal patterning in shoot and root

❊

Evolution of TTG1-dependent adaptive traits

❊

Molecular function of the BEACH-domain protein SPIRRIG

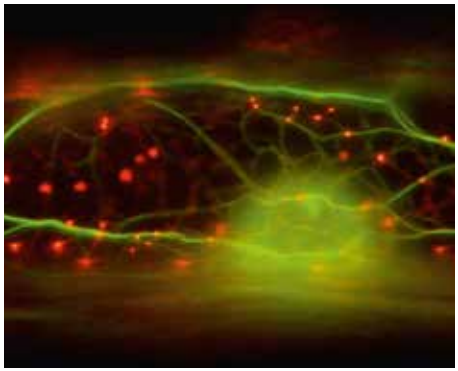
Epidermal cells and in particular trichome cells in *Arabidopsis thaliana* are excellent model systems to study cellular interactions and the regulation of cell morphogenesis at a functional level. We are currently focusing on three research areas.

1) The regular distribution of trichomes in the leaf epidermis is governed by a group of evolutionarily conserved transcription factors that mediate the cellular interaction through the movement of proteins between cells. We are developing models to explain the underlying molecular mechanism.

2) Five adaptive traits including trichome and root hair formation, anthocyanin, proanthocyanin and seed-coat mucilage production are regulated by a common pathway. We study its micro- and

macroevolution by genome-wide association mapping and genetic analysis, respectively, in *Arabis alpina*.

3) BEACH-domain proteins are evolutionarily conserved and function in membrane dynamics. We are exploring the molecular function of the BEACH-domain protein SPIRRIG in endomembrane trafficking and in the regulation of RNA stability in RNA processing bodies.



Sub-cellular spatial distribution of actin (labeled with talin:GFP, shown in green) and plus ends of microtubules (labeled by EB1-RFP, shown in red).

Publications

Pesch P., Dartan B., Birkenbihl R., Somssich I.E. and Hülskamp M. (2014). *Arabidopsis* TTG2 regulates *TRY* expression through enhancement of the activator complex triggered activation. Plant Cell 10: 4067-4083.

Pesch M., Schultheiß I., Digiuni S., Uhrig J.F., Hülskamp M. (2013) Mutual control of intracellular localisation of the patterning protein AtMYC1, GL1 and TRY/CPC in *Arabidopsis*. Development 140: 3456-3467.

Balkunde R., Bouyer D., Hülskamp M. (2011). Nuclear trapping by GL3 controls intercellular transport and redistribution of TTG1 protein in *Arabidopsis*. Development 138: 5039-5048.

Bouyer D., Geier F., Kragler F., Schnittger A., Pesch M., Wester K., Balkunde R., Timmer J., Fleck C., Hülskamp M. (2008). Two-dimensional patterning by a trapping/depletion mechanism: the role of TTG1 and GL3 in *Arabidopsis* trichome formation. PLoS Biol. 6: e141.

Kirik, V., Schrader A., Uhrig J.F. and Hülskamp M. (2007). *MIDGET* unravels functions of the *Arabidopsis* topoisomerase VI complex in DNA endoreduplication, chromatin condensation, and transcriptional silencing. Plant Cell 19: 100-110.

The Molecular Basis of Plant Adaptation: Linking Molecular Biology, Population Genetics and Ecology

NOTHING IN EVOLUTION MAKES SENSE
EXCEPT IN THE LIGHT OF BIOLOGY

Juliette de Meaux

Botanical Institute

"Nothing in evolution makes sense except in the light of biology". With this maxim, I reverse the famous quote of Dobzhansky, one of the founders of modern evolutionary biology, who once wrote "nothing in biology makes sense except in the light of evolution". Random mutations and genetic drift play a major role in the evolution of complex organisms, yet key modifications have taken place that have allowed species to thrive in their native environment by optimizing existing molecular functions to their novel ecological role. It is the goal of my research to unravel the molecular underpinnings of adaptive evolution in plant systems. In other terms, we aim to dissect the molecular mechanisms of Darwinian evolution in complex natural systems.

MAIN AREAS OF RESEARCH

Adaptive evolution in Arabidopsis *species*

❊

New methods to detect molecular systems targeted by natural selection

❊

Population genomics in native ecological systems

We work with the weedy annual and model plant species *Arabidopsis thaliana* and its close relatives *A. lyrata* and *A. halleri*. Over the years, our group has worked to understand how genes that control adaptively relevant functions evolved in *A. thaliana*. We have worked on genes controlling ecologically important traits such as flagellin perception or seed physiology and have characterized their evolution within and between species. This work highlighted the role of major QTLs

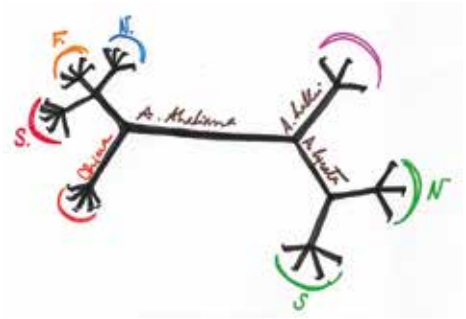


Fig. 1

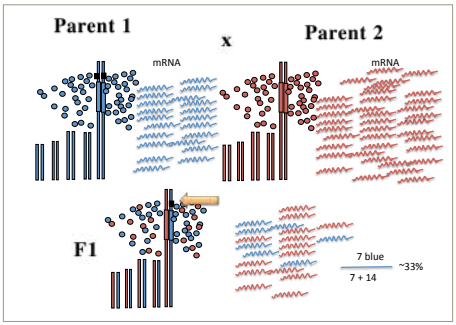


Fig. 2

Fig 1: We study functional molecular evolution in *Arabidopsis thaliana* and its two sister species in the *Arabidopsis* genus, *A. lyrata* and *A. halleri*. Studying molecular changes in an explicit phylogeographic or phylogenetic context allows the molecular changes specific to each branch to be distinguished. This facilitates the detection of the footprints left by natural selection.

Fig 2: One of the types of molecular changes we monitor are *cis*-regulatory mutations that are active in specific stress conditions. The gene expression level in each parent is controlled by the joint action of *cis*-acting regions (promoters upstream of the transcribed region) and *trans*-acting factors (i.e., transcription factors, microRNAs etc., represented by circles). Allele-specific expression in F1 individuals, i.e. offpsring of the two parental genotypes, is controlled by *cis*-acting differences. In this example, the analysis of allele-specific expression in the F1 shows that the blue parent expresses the target gene at a lower level, partly because the *cis*-acting region of the blue parent is weaker. Since the advent of next-generation sequencing methodologies, this approach can be applied to all transcripts in the genome.

but also revealed that the link between molecular change and fitness in the field is complex and can depend on the evolution of other traits.

Large-effect mutations or QTLs never recapitulate on their own the whole of the genetic changes that enabled adaptation in a given species and a given environment. Mutations of smaller effect are also necessary to approach closely the fitness optimum. When examined collectively and not as singular events such as adaptive QTLs, they form a population of mutations that accumulate in a given molecular system or pathway. Their distribution may thus reveal the target(s) of polygenic forms of adaptation. Our laboratory has designed and developed approaches in plants to ascertain the genomic distribution of all mutations that alter gene *cis*-regulation in a given environment. We will use and expand this approach over the coming years to map the distribution of *cis*-acting mutations within and between species throughout the functional landscape of *Arabidopsis* plants.

Publications

Hu JY, Zhou Y, He F, Dong X, Liu LY, Coupland G, Turck F and de Meaux J (2014). *MIR824*-regulated *AGAMOUS-LIKE*-16 contributes to flowering-time repression in *Arabidopsis thaliana*. Plant Cell 26: 2024-2037.

He F, Zhang X, Hu J, Turck F, Dong X, Goebel U, Borevitz J and de Meaux J (2012). Genome-wide analysis of *cis*-regulatory divergence between species in the *Arabidopsis* genus. Mol. Biol. Evol. 29: 3385-3395.

Kronholm I, Picó FX, Alonso-Blanco C, Goudet J and de Meaux J (2012). Genetic basis of adaptation in *Arabidopsis thaliana*: local adaptation at the seed dormancy QTL *DOG1*. Evolution 66: 2287–2302.

Vetter MM, Reymond M, Kronholm I, Bergelson J, Robatzek S and de Meaux J (2012). Evolution of flagellin perception in *Arabidopsis thaliana* and its relatives. Mol. Biol. Evol. 29: 1655-1667.

He F, Zhang X, Hu JY, Turck F, Dong X, Goebel U, Borevitz J and de Meaux J (2011). Widespread interspecific divergence in *cis*-regulation of transposable elements in the *Arabidopsis* genus. Mol. Biol. Evol. 29: 1081-1091.

Microalgal Research: Evolution, Diversity, Biotechnology

IT'S BETTER TO BURN OUT
THAN IT IS TO RUST

(NEIL YOUNG, RUST NEVER SLEEPS, 1979)

Michael Melkonian

Botanical Institute

Microalgae are photosynthetic microorganisms responsible for about half of global carbon dioxide fixation and thus, play a pivotal role as primary producers in the world's ecosystems. During evolution, they formed the oxygen atmosphere, and evolved into the land plant flora that changed the face of the Earth. Despite their importance, little is still known about their diversity and how the major evolutionary transitions in which algae participated came about. It is estimated that 90% of the biodiversity of algae is still unexplored, in addition to their potential for solving global environmental problems, such as the shortage of food, energy and phosphorus.

Our research aims to enhance knowledge of microalgae to address fundamental questions about their origin and evolution, and their use in biotechnology and environmental biotechnology. The current emphasis of our research is in two main areas: (1) Biodiversity, systematics, and evolution of microalgae and their photosynthetic organelles; (2) applications in biotechnology and environmental biotechnology using microalgae immobilized on Twin-Layers.

MAIN AREAS OF RESEARCH

Biodiversity, phylogeny, systematics, and evolution of microalgae and their photosynthetic organelles

❊

Application of microalgae in biotechnology and environmental biotechnology using Twin-Layers

Cell division in the desmid *Micrasterias furcata* (strain CCAC 4581).

Inset: The mucilage-secreting desmid *Cosmarium pachydermum* (strain CCAC 2872) grown on Twin-Layers for biotechnological applications.

The group relies on the Culture Collection of Algae at the University of Cologne (CCAC; http://www.ccac.uni-koeln.de/), a public repository of ~4,000 living microalgal strains and one of the largest such collections worldwide, to provide

strains for research and teaching. We are particularly interested in the major evolutionary transitions in which algae were involved, such as the origin of photosynthesis in eukaryotes, the diversification of the major lineages of microalgae, the delineation of species, and the transition to land. The group uses transcriptomic and genomic approaches to address these questions, but also aims to enhance knowledge about the unknown diversity of microalgae by describing novel taxa at all taxonomic levels. Our research is curiosity- rather than hypothesis-driven.

Applications in biotechnology involve pigments, polyunsaturated fatty acids and polysaccharides; applications in environmental biotechnology address nutrient and toxin removal from wastewater and the use of microalgae as biofertilizers.

Publications

Shi, J., Podola, B., Melkonian, M. (2014). Application of a prototype-scale Twin-Layer photobioreactor for effective N and P removal from different process stages of municipal wastewater by immobilized microalgae. Bioresource Technol. 154: 260-266. doi:10.1016/j.biortech.2013.11.100.

Sayou C., Monniaux M., Nanao M.H. Moyroud E., Brockington S. F.,Thévenon E., Chahtane H., Warthmann N., Melkonian M., Zhang Y., Wong G. K.-S., Weigel D, Parcy F., Dumas R. (2014). A promiscuous intermediate underlies the evolution of LEAFY DNA binding specificity. Science 343: 645-648. doi:10.1126/science.1248229.

Klapoetke, N.C., Murata, Y., Kim, S.S., Pulver, S.R., Birdsey-Benson, A., Cho, Y.K., Morimoto, T.K., Chuong, A.S., Carpenter, E.J., Tian, Z., Wang, J., Xie, Y., Yan, Z., Zhang, Y., Chow, B.Y., Surek, B., Melkonian, M., Jayaraman, V., Constantine-Paton, M., Wong, Gane K.-S., Boyden, E.S. (2014). Independent optical excitation of distinct neural populations. Nat. Methods 11: 338-346. doi:10.1038/nmeth.2836.

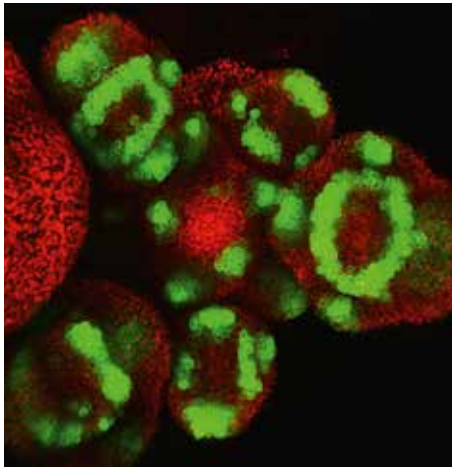
Li, F.-W., Villarreal, J.C., Kelly, S., Rothfels, C.J., Melkonian, M., Frangedakis, E., Ruhsam, M., Sigel, E.M., Der, J.P., Pittermann, J., Burge, D.O., Pokorny, L., Larsson, A., Chen, T., Weststrand, S., Thomas, P., Carpenter, E., Zhang, Y., Tian, Z., Chen, L., Yan, Z., Zhu, Y., Sun, X., Wang, J., Stevenson, D.W., Crandall-Stotler, B.J., Shaw, A.J., Deyholos, M.K., Soltis, D.E., Graham, S.W., Windham, M.D., Langdale, J.A., Wong, G.K.-S., Mathews, S., Pryer K.M. (2014). Horizontal transfer of an adaptive chimeric photoreceptor from bryophytes to ferns. Proc. Natl. Acad. Sci. USA 111: 6672-6677. doi:10.1073/pnas.1319929111.

Wickett, N.J., Mirarab, S., Nguyen, N., Warnow, T., Carpenter, E., Matasci, N., Ayyampalayam, S., Barker, M.S., Burleigh, J.G., Gitzendanner, M. a., Ruhfel, B.R., Wafula, E., Der, J.P., Graham, S.W., Mathews, S., Melkonian, M., Soltis, D.E., Soltis, P.S., Miles, N.W., Rothfels, C.J., Pokorny, L., Shaw, a. J., DeGironimo, L., Stevenson, D.W., Surek, B., Villarreal, J.C., Roure, B., Philippe, H., dePamphilis, C.W., Chen, T., Deyholos, M.K., Baucom, R.S., Kutchan, T.M., Augustin, M.M., Wang, J., Zhang, Y., Tian, Z., Yan, Z., Wu, X., Sun, X., Wong, G.K.-S., Leebens-Mack, J., (2014). Phylotranscriptomic analysis of the origin and early diversification of land plants. Proc. Natl. Acad. Sci. USA 111: 4859-4868. doi: 10.1073/pnas.1323926111.

Plant Development – From Stem-Cell Niches to Lateral Organ Founder Cells

Wolfgang Werr

Botanical Institute | Institute for Zoology



Lateral organ initiation in the *Arabidopsis* inflorescence shoot

MAIN AREAS OF RESEARCH

Evolution of plant stem-cell niches

❄

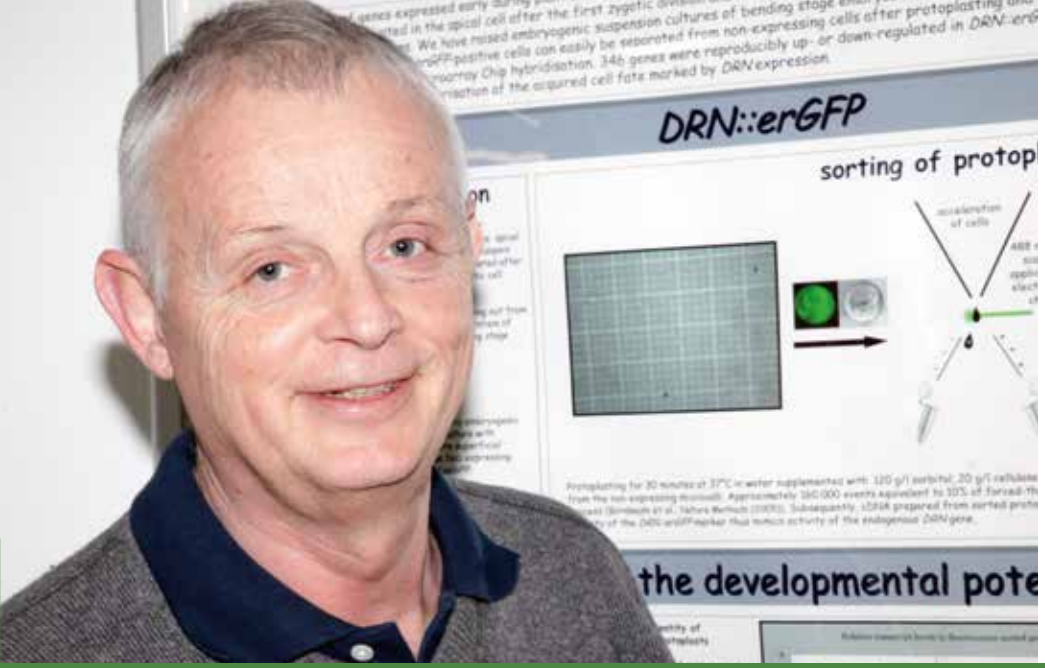
Shoot meristem function

❄

Specification of lateral organ founder cells

Postembryonic growth of plants depends on the function of meristems – highly organized groups of cells established during embryogenesis. Their long-term preservation throughout the plant life cycle relates to the maintenance of stem-cell niches, which provide pluripotent cells for differentiation, organ formation and growth. The shoot apical meristem (SAM) gives rise to the aerial plant body and in higher plants, is organized into a central stem-cell zone and a peripheral zone, where cells are prone to differentiation and founder cells for lateral organs are recruited in a species-specific phyllotaxy.

Using available plant genome sequences and PCR-based approaches, we asked for the evolution of homeodomain



transcription factors, which promote stem cell identity and are encoded within the *WUSCHEL-related homeobox* or *WOX* gene family. Phylogenetic reconstructions revealed that stem-cell-promoting members are absent in basal clades of the green tree of life, but were amplified and associated with specific stem-cell niches in a common ancestor of gymno- and angiosperms. Plesiomorphies in the *WOX* family apparently relate to changes in growth and architecture, which underlie the diversity of seed plants. Evolutionary signatures in the WOX DNA-binding homeodomains are currently addressed from a crystallographic, theoretical and functional perspective.

A second research area addresses the initiation of new lateral organs in the *Arabidopsis thaliana* SAM, starting in close proximity to the stem-cell population. Transcription of the *DORNRÖSCHEN-LIKE* (*DRNL*) gene prepatterns the number and position of founder cells and accompanies the onset of morphogenesis. Analysis of the *DRNL* promoter revealed the integration of an auxin response, but that floral meristem founder cells do not coincide with the position of auxin response maxima and locate more peripherally. The molecular basis of the underlying signal and the founder-cell transcriptome are currently under investigation.

Publications

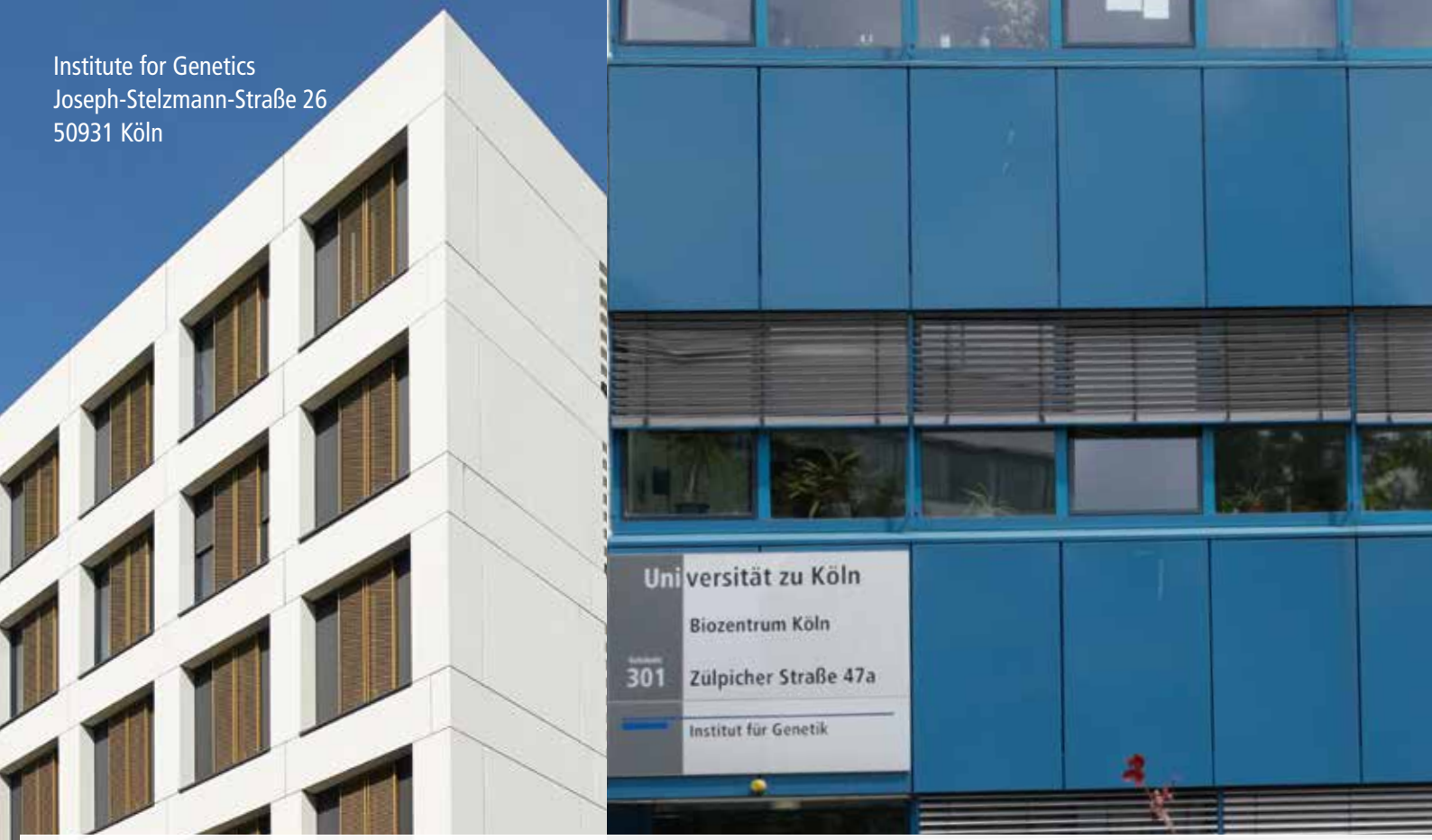
Chandler JW & Werr W (2014). Arabidopsis floral phytomer development: auxin response relative to biphasic modes of organ initiation. J. Exp. Bot. 65: 3097-3110.

Sakakibara K, Reisewitz P, Aoyama T, Friedrich T, Ando S, Sato Y, Tamada Y, Nishiyama T, Hiwatashi Y, Kurata T, Ishikawa M, Deguchi H, Rensing SA, Werr W, Murata T, Hasebe M, Laux T (2014). WOX13-like genes are required for reprogramming of leaf and protoplast cells into stem cells in the moss *Physcomitrella patens*. Development 141: 1660-1670.

Nardmann J & Werr W (2013). Symplesiomorphies in the *WUSCHEL* clade suggest that the last common ancestor of seed plants contained at least four independent stem cell niches. New Phytol. 199: 1081-1092.

Chandler JW, Jacobs B, Cole M, Comelli P & Werr W (2011). *DORNRÖSCHEN-LIKE* expression marks *Arabidopsis* floral organ founder cells and precedes auxin response maxima. Plant Mol. Biol. 76: 171-185.

Chandler JW, Cole M, Jacobs B, Comelli P, Werr W (2011). Genetic integration of DORNRÖSCHEN and DORNRÖSCHEN-LIKE reveals hierarchical interactions in auxin signalling and patterning of the *Arabidopsis* apical embryo. Plant Mol. Biol. 75: 223-236.



Institute for Genetics
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50931 Köln

The Institute for Genetics, founded in 1962 by Max Delbrück, currently includes twelve professorships and several independent research groups that promote excellence in research and teaching in the fields of genetics and molecular cell biology. Teaching activities include the Bachelor and Master of Science curricula in the Biological Sciences and in Biochemistry, as well as the training of Ph.D. students within structured programs and by individual supervision. Research at the Institute for Genetics covers a broad spectrum of issues in molecular and computational biology. Molecular mechanisms controlling cellular homeostasis at all levels are studied through mouse models and other model organisms, complemented by evolutionary and computational approaches. In collaboration with colleagues from the Medical Faculty, researchers from the Institute for Genetics founded the Cologne Excellence Cluster on Cellular Stress Responses in Aging Associated Diseases (CECAD, see p. 88). The Institute for Genetics has a strong tradition of shared infrastructure, central service units, and a flexible space concept, which allows young researchers to build their independent groups within an excellent international research environment. This successful concept has been implemented both at the main institute building located within the Biocenter, and at the recently opened CECAD research center.

RESEARCH

Institute for Genetics

Selective Protein Degradation: Mechanisms, Regulation, and Roles in Protein Quality Control or Cellular Regulation

THERE IS INFINITE ROOM
FOR CURIOSITY IN A TINY CELL

Jürgen Dohmen

Institute for Genetics

Cellular homeostasis involves the removal of damaged proteins and the control of protein levels according to physiological or developmental cellular states. A decline in the quality of these mechanisms is part of the aging process. In eukaryotic cells, the ubiquitin/proteasome system (UPS) is the main system for selective protein degradation and malfunctions in this system are linked to many human diseases. On the other hand, drugs that target UPS enzymes are used or developed for disease treatment. In the UPS, proteins are covalently marked by the attachment of ubiquitin or ubiquitin chains. The latter are recognized as degradation signals by a very large protease complex, the proteasome.

MAIN AREAS OF RESEARCH

Roles of dedicated chaperones in proteosome assembly

❊

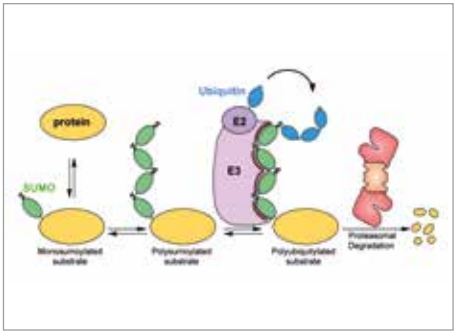
Mechanisms and functions of ubiquitin-dependent and -independent protein degradation

❊

Proteolytic control of small ubiquitin-related modifier (SUMO) conjugates

❊

Co- and post-translational mechanisms controlling cellular polyamine homeostasis



SUMO-mediated proteolytic targeting.

Using yeast and human cells, the group investigates how dedicated chaperones control the assembly of this complex, and how substrates are selected and targeted for degradation by the proteasome. We also investigate how molecular chaperones, which are usually involved in protein folding, redirect folding-deficient proteins to the ubiquitylation machinery. Another project studies how SUMO, a ubiquitin-related protein modifier with essential functions, controls proteins and how conjugation or deconjugation of this modifier is regulated in cells. A group of ubiquitin ligases was discovered and is studied, which recognizes proteins marked with SUMO chains and targets them for degradation by the proteasome. Another research area concerns polyamines, which are essential organic polycations, whose synthesis from amino acid precursors is subject to intricate homeostatic feedback control. Cancer cells have an increased demand for polyamines. A critical enzyme in polyamine biosynthesis is ornithine decarboxylase (ODC), which is controlled by a protein called ODC antizyme (OAZ). OAZ levels are regulated co-translationally and post-translationally by polyamines. Work of the group identified OAZ itself as the sensor in this system. Binding of polyamines to OAZ stimulates completion of its synthesis by ribosomes and inhibits its degradation by the proteasome.

Publications

Kock, M. Nunes, M.M., Hemann, M., Kube, S., Dohmen, R.J., Herzog, F., Ramos, P.C., and Wendler, P. (2015). Proteasome assembly from 15S precursors involves major conformational changes and recycling of the Pba1-Pba2 chaperone. Nat. Commun. 6: 6123. doi: 10.1038/ncomms7123.

Sriramachandran, A.M., and Dohmen, R.J. (2014). SUMO-targeted ubiquitin ligases. Biochim. Biophys. Acta 1843: 75-85.

Gowda, N.K.C, Kandasamy, G., Froehlich, M.S., Dohmen, R.J., and Andréasson, C. (2013). Hsp70 nucleotide exchange factor Fes1 is essential for ubiquitin-dependent degradation of misfolded cytosolic proteins. Proc. Natl. Acad. Sci. USA 110: 5975-5980.

Dohmen, R.J., and Scheffner, M. (Eds.) (2012). Ubiquitin Family Modifiers and the proteasome: Reviews and Protocols. Springer Protocols: Meth. Mol. Biol., Volume 832.

Kurian, L., Palanimurugan, R., Gödderz, D., and Dohmen R.J. (2011). Polyamine sensing by nascent ornithine decarboxylase antizyme stimulates decoding of its mRNA. Nature 477: 490-494.

An Evolutionary Approach to Cellular Proteostasis Regulation

MAKING SENSE OF PROTEIN FUNCTION IN THE LIGHT OF EVOLUTION

Kay Hofmann

Institute for Genetics

The human genome contains about 25,000 protein-coding genes, which give rise to about 50,000 different functional proteins. Only a small fraction of these has been studied experimentally, and the number of proteins considered as 'well understood' is even smaller. Thus, even 10 years after the 'decoding' of the human genome, we are still far from understanding what our genes are all about.

In our group, we try to address the gene/protein function problem using both bioinformatic and experimental methods. In particular, we make use of the fact that most eukaryotic proteins are not monolithic structures, but rather have a modular architecture consisting of multiple building blocks. Most of these blocks have a specific unit functionality,

MAIN AREAS OF RESEARCH

Recognition domains for ubiquitin-like modifiers

❄

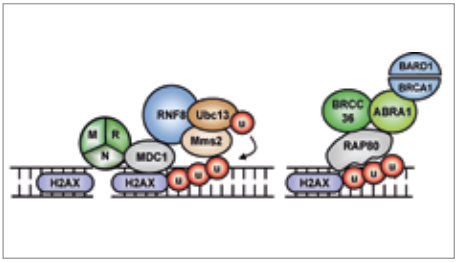
Sumo-targeted ubiquitin ligases

❄

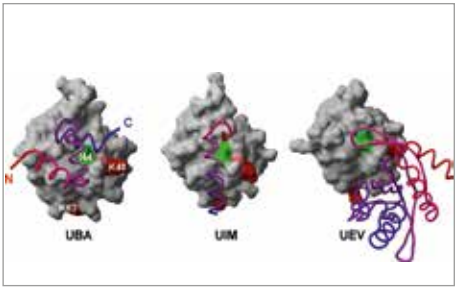
Evolution of innate immunity pathways

❄

Bioinformatic prediction of protein function



Ubiquitination regulates DNA-repair pathways.



Ubiquitin recognition domains.

and the combination of these so-called 'functional domains' determines the function of the whole protein. Over the course of evolution, the functional modules have been re-used, duplicated, mutated, deleted, reassorted, or any combination thereof. The reconstruction of the evolutionary history of a domain type yields important insights into the domain's function, its binding partners, and other important issues.

A particular focus of our group is the analysis of protein components that mediate or regulate intracellular protein degradation pathways. Proteostasis mechanisms employing the ubiquitin–proteasome system or selective autophagy are crucially important for the cell; errors in these processes are causally involved in diseases such as cancer, Alzheimer's, Parkinson's, and many others. At the same time, proteostasis is regulated by a highly complex network of >1,000 interacting components, only a few of which are sufficiently understood at the molecular level. The fact that most of these regulatory proteins have a highly modular architecture makes them excellent subjects for studies in protein evolution.

Publications

Kajava AV, Klopffleisch K, Chen S, Hofmann K (2014). Evolutionary link between metazoan RHIM motif and prion-forming domain of fungal heterokaryon incompatibility factor Het-s/Het-S. Sci. Rep. 4: 7436.

Keusekotten K, Elliot PR, Glockner L, Fiil BK, Damgaard RB, Kulathu Y, et al. (2013). OTULIN Antagonizes LUBAC Signaling by Specifically Hydrolyzing Met1-Linked Polyubiquitin. Cell 153: 1312-1326.

Vogt B, Hofmann K (2012). Bioinformatical Detection of Recognition Factors for Ubiquitin and SUMO. Meth. Mol. Biol. 832: 249-261.

Kraft C, Peter M, Hofmann K (2010). Selective autophagy: ubiquitin-mediated recognition and beyond. Nat. Cell Biol. 12: 836-841.

Hofmann K (2009). Ubiquitin-binding domains and their role in the DNA damage response. DNA Repair 8: 544-556.

Proteostasis in Development and Aging

YOU HAVE EVOLVED FROM WORM TO MAN,
BUT MUCH WITHIN YOU IS STILL WORM

Thorsten Hoppe

Institute for Genetics

Cellular differentiation, developmental processes and environmental factors challenge the integrity of the proteome in every eukaryotic cell. The maintenance of protein homeostasis, or proteostasis, involves the degradation of misfolded and damaged proteins, and is essential for cellular function, organismal growth, and ultimately, viability. Sustaining protein quality control (PQC) is not only a long-term challenge for individual cells but also for entire organisms, since damaged proteins accumulate with stress and aging. It is commonly thought that the age-related impairment of PQC affects general proteostasis networks, causing enhanced aggregation of misfolded proteins that can be toxic for cells and shortens organismal lifespan. Not all tissues are equally

MAIN AREAS OF RESEARCH

Cellular control of protein homeostasis (proteostasis)

❄

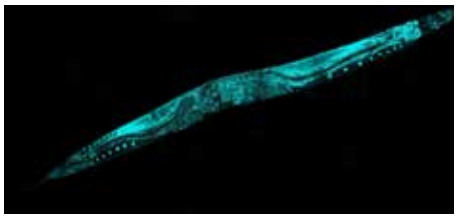
Systemic regulation of proteostasis networks

❄

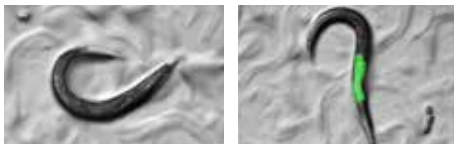
Role of proteolytic pathways in stress response and aging

❄

Protein aggregation diseases and neurodegeneration



We take advantage of the powerful genetic model *Caenorhabditis elegans*, which allows tissue-specific differences in aging-relevant proteostasis pathways to be addressed.



Expression of green fluorescent protein (GFP)-based substrates allows the rapid quantification of protein turnover in different tissues of *C. elegans*. The left panel shows a mutant worm with defects in proteolysis and substrate stabilization.

susceptible to the toxicity of protein aggregates, suggesting tissue-specific differences in proteostasis pathways. In humans, aberrant protein aggregation is often associated with neurodegeneration in age-dependent disorders such as Alzheimer's and Parkinson's diseases.

The ubiquitin/proteasome system (UPS) is a major proteolytic route, which functions in a cellular network that helps to maintain the proteome during stress and aging. The degradation of damaged proteins is mediated by the 26S proteasome upon attachment of ubiquitin (Ub) proteins (ubiquitylation). Another proteolytic system that supports protein homeostasis (proteostasis) is the autophagy–lysosome pathway that degrades proteins inside activated autophagosomes. An age-related impairment of either of these systems causes enhanced protein aggregation and affects lifespan, suggesting functional overlap and cooperation between UPS and autophagy in stress and aging. Despite the progress made in searching for key substrates that are destined for degradation, the major challenge in the field is to understand how these proteolytic systems are mechanistically coordinated to overcome age-related proteotoxicity. The ultimate goal of our research is to assemble a global picture of stress-induced proteolytic networks that are critical for the aging of multicellular organisms. We address tissue-specific regulation of protein degradation pathways using the powerful genetic model of *Caenorhabditis elegans*.

Publications

Segref A., Kevei E., Pokrzywa W., Schmeisser K., Mansfeld J., Livnat-Levanon N., Ensenauer R., Glickman M.H., Ristow M., Hoppe T. (2014). Pathogenesis of human mitochondrial diseases is modulated by reduced activity of the ubiquitin/proteasome system. Cell Metab. 19: 642-652.

Ermolaeva M.A., Segref A., Dakhovnik A., Ou H.L., Schneider J.I., Utermöhlen O., Hoppe T., Schumacher B. (2013). DNA damage in germ cells induces an innate immune response that triggers systemic stress resistance. Nature 501: 416-420.

Gazda, L., Pokrzywa, W., Hellerschmied, D., Löwe, T., Forné, I., Mueller-Planitz, F., Hoppe, T.*, Clausen, T. (2013). The myosin chaperone UNC-45 is organized in tandem modules to support myofilament formation in *C. elegans*. Cell 152: 183-195. *Co-senior author

Franz A., Orth M., Pirson P.A., Sonneville R., Blow J.J., Gartner A., Stemmann O., Hoppe T. (2011). CDC-48/p97 coordinates CDT-1 degradation with GINS chromatin dissociation to ensure faithful DNA replication. Mol. Cell 44: 85-96.

Kuhlbrodt K., Janiesch P.C., Kevei E., Segref A., Barikbin R., and Hoppe T. (2011). The Machado-Joseph disease deubiquitylase ATX-3 couples longevity and proteostasis. Nat. Cell Biol. 13: 273-281.

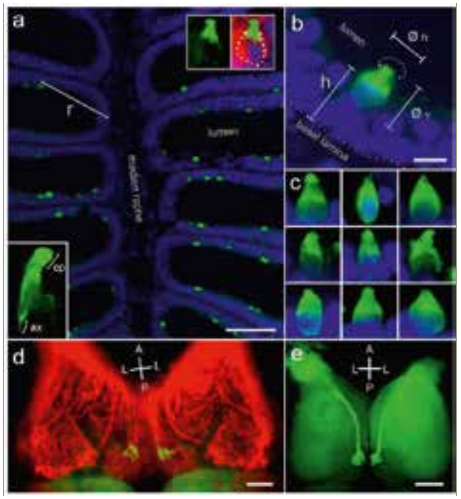
Sensation, Perception and Behavior in Vertebrate Olfaction

Sigrun Korsching

Institute for Genetics

Smell is an ancient and complex sense that is essential for food detection, prey and predator recognition, reproduction and other intraspecies communication. Tens of thousands of different chemicals can be detected and distinguished by the olfactory system. Several olfactory receptor gene families, both small and large, contribute to the detection of odors. The basic logic of olfactory perception involves labeled line (one receptor – one odor – one behavior) as well as combinatorial coding (one receptor – several odors and one odor – several receptors). Monogenic expression and axonal convergence serve to generate a receptotopic map in the olfactory bulb.

To understand the perception of odors, it is essential to identify the various receptor repertoires, reveal the ligand spectra of individual olfactory receptors, analyse the modification of the odor response by the circuitry of the olfactory bulb and higher brain centers, and examine the generation of behavior by these neural circuits. We mostly employ the vertebrate zebrafish model system to study these questions, using an array of molecular biological, genetic, physiological and behavioral methods.



Novel population of olfactory sensory neurons, named kappe in the zebrafish olfactory epithelium. (a) Go-ir (green) is seen in a sparse population of pear-shaped cells in horizontal sections of the olfactory epithelium. (b) At higher magnification, the apical position of Go-ir-positive cells (green) is clearly visible. (c) Nine Go-ir-positive cells show the typical range of morphologies for these neurons. (d) Whole-mount image of the adult zebrafish olfactory bulb, dorsal view. Zns2 labels all glomeruli, whereas Go-ir labels a single medial glomerulus (yellow). (e) Horizontal vibrotome cross-section (100 mm) reveals the extremely dorsal position of the Go-immunoreactive glomerulus in each olfactory bulb. A single, thick axon bundle is seen entering the glomerulus.

MAIN AREAS OF RESEARCH

Evolution of olfactory receptor gene families

❄

Deorphanization of olfactory receptors

❄

Delineation of olfactory neuronal circuits

❄

Characterization of odor-evoked behavior

Publications

Saraiva, L.R., Ahuja, G., Ivandic, I., Syed, A.S., Marioni, J.C., Korsching, S.I.*, Logan, D.W. (2015). Molecular and neuronal homology between the olfactory systems of zebrafish and mouse. Sci. Rep. 5: 11487. doi 10.1038/srep11487.
*Co-senior author

Syed, A.S. & Korsching, S.I. (2014). Positive Darwinian selection in the singularly large taste receptor gene family of an ‚ancient' fish, *Latimeria chalumnae*. BMC Genomics 15: 650. doi: 10.1186/1471-2164-15-650.

Behrens, M., Korsching, S.I. & Meyerhof, W. (2014). Tuning properties of avian and frog bitter taste receptors dynamically fit gene repertoire sizes. Mol. Biol. Evol. 31: 3216-3227. doi: 10.1093/molbev/msu254.

Syed, A.S., Sansone, A., Nadler, W., Manzini, I. & Korsching, S.I. (2013). Ancestral amphibian v2rs are expressed in the main olfactory epithelium. Proc. Natl. Acad. Sci. USA 110: 7714-7719. doi: 10.1073/pnas.1302088110.

Hussain, A. et al. (2013). High-affinity olfactory receptor for the death-associated odor cadaverine. Proc. Natl. Acad. Sci. USA 110: 19579-19584. doi: 10.1073/pnas.1318596110.

Mitochondrial Proteases in Cellular Regulation, Aging and Disease

Thomas Langer

Institute for Genetics

Mitochondria are dynamic cell organelles with essential catabolic and anabolic functions and critical roles in cell death pathways. Mitochondrial dysfunction contributes to aging and acts causally in the pathogenesis of many neurodegenerative disorders. The group analyses the conserved proteolytic system of these organelles, which ensures the quality control of mitochondrial proteins and regulates key steps during mitochondrial biogenesis. Using tissue-specific knockout mice, and cultured cells and *Saccharomyces cerevisiae* as model systems, the group analyses the function of conserved mitochondrial proteases on the molecular level and in a physiological context, aiming at a detailed understanding of the pathogenic

MAIN AREAS OF RESEARCH

Proteolytic control of mitochondrial dynamics and membrane biogenesis

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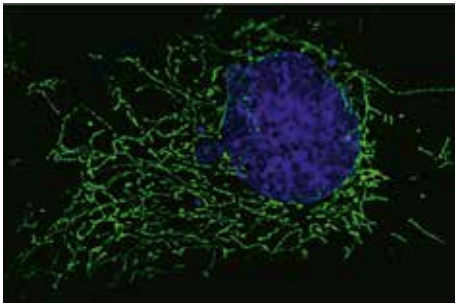
Mitochondrial phospholipid trafficking and metabolism

❊

Mitochondrial quality control

❊

Pathogenesis of neurodegenerative disorders and cardiomyopathies associated with mitochondrial proteases



The mitochondrial network in mouse embryonic fibroblasts expressing a mitochondrially targeted GFP variant (green). The nucleus was stained with DAPI (blue).

mechanisms of neurodegenerative and cardiac diseases associated with mutations in these proteases.

Mitochondria form a highly interconnected tubular network, which changes shape in response to physiological demands and stress, and serve as signaling hubs that direct multiple cellular communication processes. Proteases in the mitochondrial inner membrane control balanced fusion and fission events and their adaption to stress. They trigger stress-induced mitochondrial fragmentation, facilitating the autophagic removal of damaged mitochondria and cell death. Inhibition of this pathway prevents stress-induced cardiomyopathies and delays the onset of neurodegenerative disorders in various mouse models. Moreover, mitochondrial proteases regulate cellular signaling cascades and critical steps during the biogenesis of mitochondria. These include the biogenesis of mitochondrial proteins and phospholipids as well as the trafficking of phospholipids between mitochondrial membranes by specific lipid-transfer proteins. The activity of many mitochondrial proteases depends on the specific membrane environment. Scaffold proteins that define membrane domains with characteristic protein and lipid compositions are another focus of research of the group.

Publications

Lopez-Otin, C., Quiros, P., and Langer, T. (2015). New Roles of Mitochondrial Proteases in Health, Aging and Disease. Nature Rev. Mol. Cell Biol. 16: 345-359.

Anand, R., Wai, T., Baker, M.J., Kladt, N., Schauss, A.C., Rugarli, E., and Langer, T. (2014). The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. J. Cell Biol. 204: 919-929. doi: 10.1083/jcb.201308006.

Baker, M.J., Lampe, P., Stojanovski, D., Korwitz, A., Anand, R., Tatsuta, T., and Langer, T. (2014). Stress-induced OMA1 activation and autocatalytic turnover regulates OPA1-dependent mitochondrial dynamics. EMBO J. 33: 578-593. doi: 10.1002/embj. 201386474.

Merkwirth, C., Martinelli, P., Korwitz, A., Morbin, M., Brönnecke, H.S., Jordan, S.D., Rugarli, E.I., and Langer, T. (2012). Loss of prohibitin membrane scaffolds impairs mitochondrial architecture and leads to Tau hyperphosphorylation and neurodegeneration. PLoS Genet. 8: e1003021. doi: 10.1371/journal. pgen.1003021.

Connerth, M., Tatsuta, T., Haag, M., Klecker, T., Westermann, B., and Langer, T. (2012). Intramitochondrial transport of phosphatidic acid in yeast by a lipid transfer protein. Science 338: 815-818.

Cell Shape and Morphogenesis: Sub-Cellular and Supra-Cellular Mechanisms

Maria Leptin

Institute for Genetics

The shape of a developing organism is generated by the activities of its constituent cells: growth, proliferation, movements and shape changes. We are particularly interested in shape changes. One study concerns an extremely complex single cell; the terminal cell of the *Drosophila* tracheal system, which is highly branched and carries air to tissues through an intracellular tube bounded by a plasma membrane. During its rapid growth, the cell faces the task of synthesizing large amounts of membrane and sorting it correctly to defined domains. Extensive reorganization of the secretory organelles precedes membrane growth. We study how the cytoskeleton, small GTPases and polarity determinants direct the process, and how membrane trafficking processes contribute to building the tube.

MAIN AREAS OF RESEARCH

Membrane trafficking in building an intracellular air transportation system

❊

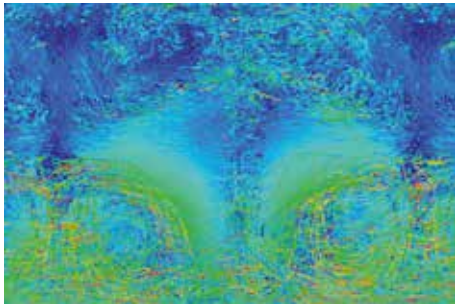
Transcriptional control of morphogenesis

❊

Whole-organism coordination of force generation in shaping tissues

❊

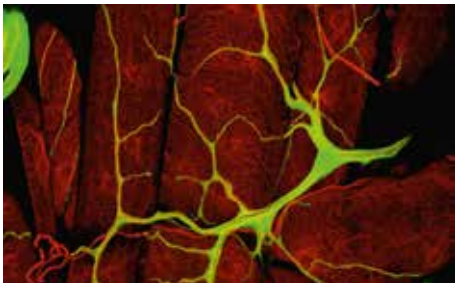
Innate immune mechanisms in the zebrafish



A flat projection of the entire surface of a *Drosophila* embryo in which the position and speed of 6,000 cells is followed over a 45-minute period. The head of the embryo is at the top; the center of the image is the ventral midline towards which the lateral cells are moving.

In another project, we investigate how the forces generated by individual cells in the early *Drosophila* embryo are integrated within the supracellular organisation of the whole organism to give the tissue its final shape. To understand force integration across many cell populations, we use simultaneous time-lapse imaging of multiple-angle views of the gastrulating embryo. We measure the specific shape changes in all the cells of the embryo, as well as the speed and direction of their movements. Genetic and mechanical manipulations reveal the underlying control circuits.

Part of the lab works on a different topic – innate immune responses, using the zebrafish as a model system. The innate immune system provides rapid defense against pathogens and also deals with non-pathogenic stresses. Fish model systems allow the *in vivo* observation of physiological processes. Specifically, we observe pathogens and the cells that attack them. We use genetically and chemically engineered *in vivo* fluorescent reporters to assay immune and stress responses in real time and at high spatial and temporal resolution as the cells of the fish encounter pathogens and stress signals.



A tracheal cell (green) innervating the larval muscles (tubulin stained in red) to provide them with air.

Publications

JayaNandanan N, Mathew R and Leptin M (2014). Guidance of subcellular tubulogenesis by actin under the control of a synaptotagmin- like protein and Moesin. Nat. Comm. 5: 3036.

Rembold M, Ciglar L, Yáñez-Cuna JO, Zinzen RP, Girardot C, Jain A, Welte MA, Stark A, Leptin M, Furlong EE (2014). A conserved role for Snail as a potentiator of active transcription. Genes Dev. 28: 167-181.

Banerjee, S & Leptin, M (2014). Systemic response to UV involves induction of leukocytic IL-1beta and inflammation in zebrafish. J. Immun. 193: 1408-1415.

Sigurbjörnsdóttir S, Mathew R, Leptin M (2014). Molecular mechanisms of de novo lumen formation. Nature Rev. Mol. Cell Biol. 15: 665-676.

Rauzi M, Hočevar Brezavšček A, Ziherl P, Leptin M (2013).Physical models of mesoderm invagination in *Drosophila* embryo. Biophys. J. 105: 3-10.

Inflammatory and Cell Death Signaling in Disease Pathogenesis

Manolis Pasparakis

Institute for Genetics

Healthy tissue homeostasis is maintained by balanced interactions between epithelial, stromal and immune cells and the commensal microbes that normally reside on the surface of our barrier tissues such as the gut and the skin. Disruption of tissue homeostasis can cause chronic inflammatory diseases and in some cases, also cancer. Our group studies the mechanisms that regulate immune responses, with a particular interest in identifying molecules and pathways that contribute to the pathogenesis of chronic inflammatory diseases. We use genetic mouse models to dissect the functions of specific genes and pathways that regulate inflammation and are responsible for causing disease. The study of the role of the IKK/NF-κB pathway, as well as of molecules

MAIN AREAS OF RESEARCH

Role of IKK/NF-κB signalling in disease pathogenesis

❊

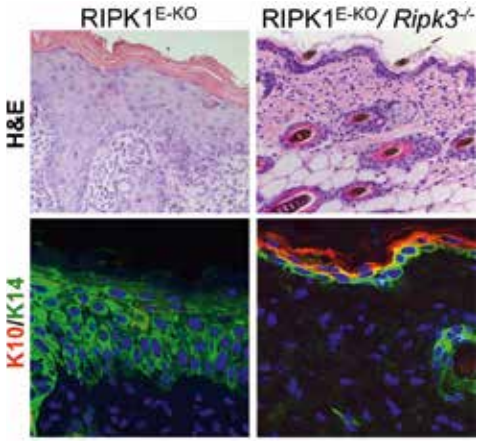
Mechanisms regulating apoptosis and necroptosis

❊

Role of epithelial cell death in tissue homeostasis and inflammation

❊

Role of inflammation in cancer



Keratinocyte-specific knockout of RIPK1 causes RIPK3-dependent necroptosis and skin inflammation.

participating in pro-inflammatory and death-inducing signaling cascades downstream of TNF receptors, constitutes a main focus of our work.

Our recent studies contributed to the identification of new mechanisms that regulate tissue homeostasis and inflammation in epithelial tissues. Our experiments showed that death of epithelial cells triggers severe chronic inflammation in barrier tissues such as the gut and the skin. In particular, our results revealed that necroptosis, a newly identified pathway or regulated necrotic cell death of intestinal epithelial cells triggered severe colon inflammation that resembles human colitis. In addition, our experiments showed that necroptosis of epidermal keratinocytes also triggered severe skin inflammation. Furthermore, our most recent studies revealed novel kinase-dependent and scaffolding functions of RIP kinase 1, a protein with a central role in TNF receptor 1 signaling, which is important for the regulation of epithelial cell survival and the maintenance of immune homeostasis in barrier tissues. These findings suggest that molecules controlling inflammatory and cell death signaling cascades in epithelial cells play central roles in the regulation of tissue homeostasis and inflammation. Since these pathways are conserved between mice and humans, our results suggest that similar mechanisms might contribute to the pathogenesis of human inflammatory diseases.

Publications

Dannappel M, Vlantis K, Kumari S, Polykratis A, Kim C, Wachsmuth L, Eftychi C, Lin J, Corona T, Hermance N, Zelic M, Kirsch P, Basic M, Bleich A, Kelliher M, Pasparakis M (2014). RIPK1 maintains epithelial homeostasis by inhibiting apoptosis and necroptosis. Nature 513: 90-94.

Bonnet MC, Preukschat D, Welz PS, van Loo G, Ermolaeva MA, Bloch W, Haase I, Pasparakis M (2011). The adaptor protein FADD protects epidermal keratinocytes from necroptosis in vivo and prevents skin inflammation. Immunity 35: 572-582.

Welz PS, Wullaert A, Vlantis K, Kondylis V, Fernandez-Majada V, Ermolaeva M, Kirsch P, Sterner-Kock A, van Loo G, Pasparakis M (2011). FADD prevents RIP3-mediated epithelial cell necrosis and chronic intestinal inflammation. Nature 477: 330-334.

Luedde T, Beraza N, Kotsikoris V, van Loo G, Nenci A, De Vos R, Roskams T, Trautwein C, Pasparakis M (2007). Deletion of NEMO/IKKgamma in liver parenchymal cells causes steatohepatitis and hepatocellular carcinoma. Cancer Cell 11: 119-132.

Nenci A, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, Huth M, Nikolaev A, Neufert C, Madison B, Gumucio D, Neurath MF, Pasparakis M (2007). Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature 446: 557-561.

Mitochondrial Dysfunction and Mechanisms of Axonal Degeneration

Elena Rugarli

Institute for Genetics

In an adult human individual, axons can reach the remarkable length of 1 meter and contain more than 99% of the cell cytoplasm. Survival of axons depends on efficient trafficking of organelles, cytoskeletal components and lipid constituents synthesized in the cell body. The goal of our research is to understand the pathogenic mechanisms underlying axonal degeneration, a chronic process that plays an important role in several neurodegenerative diseases. We have a special interest in unraveling how mitochondrial dysfunction contributes to this process. Neuronal survival, in fact, critically depends on the integrity and functionality of mitochondria. A hierarchical system of control mechanisms protects mitochondria against stress,

MAIN AREAS OF RESEARCH

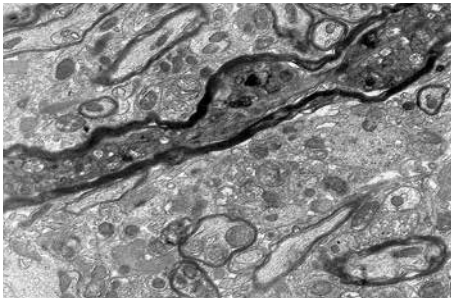
Unraveling the pathogenesis of hereditary spastic paraplegia

❄

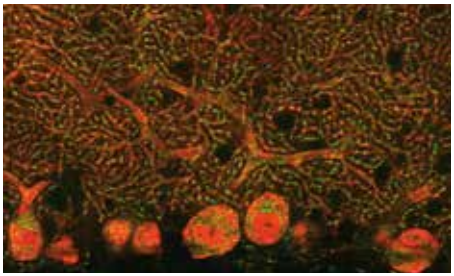
The role of mitochondrial dysfunction in neurodegeneration

❄

Mechanisms that regulate mitochondrial biogenesis



A degenerating axon in the spinal cord of paraplegin knock-out mice, a model for hereditary spastic paraplegia.



Mitochondrial distribution in dendrites of Purkinje cells in the cerebellum.

monitors mitochondrial damage and ensures the selective removal of dysfunctional mitochondrial proteins or organelles. This quality control system fails in an increasing number of neurodegenerative disorders, which include Parkinson's disease, spinocerebellar ataxia, spastic paraplegia and peripheral neuropathies. We are investigating the pathogenesis of neurodegenerative diseases caused by mutations in paraplegin or AFG3L2, the subunits of the mitochondrial m-AAA protease. In addition, we are interested in studying how defects in mitochondrial distribution, transport, turnover, and biogenesis affect the survival of different cells in the brain.

We also study the functions of genes involved in hereditary spastic paraplegia (HSP), an adult-onset genetic disorder, characterized by progressive weakness and spasticity of the lower limbs and due to the retrograde degeneration of the longest axons of the central nervous system, which compose the corticospinal tracts. We combine cell-biological approaches and the development of animal models to study the functions of different HSP genes involved in mitochondrial quality control, microtubule dynamics, and lipid metabolism. Our aim is to shed light on the pathogenesis of HSP and to identify common disrupted pathways that are amenable to therapy.

Publications

Gao J., Schatton D., Martinelli P., Hansen H., Pla-Martin D., Barth E., Becker C., Altmueller J., Frommolt P., Sardiello M., Rugarli E.I. (2014). CLUH regulates mitochondrial biogenesis by binding mRNAs of nuclear-encoded mitochondrial proteins. J. Cell Biol. 207: 213-223.

Kondadi, A.K., Wang, S., Montagner, S., Kladt, N., Korwitz, A., Martinelli, P., Herholz, D., Baker, M.J., Schauss, A.C., Langer, T. and Rugarli, E.I. (2014). Loss of the m-AAA protease subunit AFG3L2 causes mitochondrial transport defects and tau hyperphosphorylation. EMBO J. 33: 1011-1026.

Anand, R., Wai, T., Baker, M.J., Kladt, N., Schauss, A.C., Rugarli, E. and Langer, T. (2014). The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. J. Cell Biol. 204: 919-929.

Merkwirth, C., Martinelli, P., Korwitz, A., Morbin, M., Bronneke, H.S., Jordan, S.D., Rugarli, E.I. and Langer, T. (2012). Loss of prohibitin membrane scaffolds impairs mitochondrial architecture and leads to tau hyperphosphorylation and neurodegeneration. PLoS Genet. 8: e1003021.

Almajan, E.R., Richter, R., Paeger, L., Martinelli, P., Barth, E., Decker, T., Larsson, N.G., Kloppenburg, P., Langer, T. and Rugarli, E.I. (2012). AFG3L2 supports mitochondrial protein synthesis and Purkinje cell survival. J. Clin. Invest. 122: 4048-4058.

Regulatory Interactions in the Adaptation of Bacteria

Karin Schnetz

Institute for Genetics

A common regulatory principle in *Escherichia coli* and *Salmonella enterica*, as well as other enterobacterial species, is the silencing of a significant part of the genome by the abundant nucleoid-associated protein, HNS. Silencing and its gene-specific reversal in response to a variety of signals encountered in the environment is an important regulatory mechanism that these commensal and pathogenic bacteria employ to adapt in their natural habitat. The adaptation commonly involves sensing and transmission of the signal(s) by regulatory networks that trigger rapid and specific changes in the gene expression profile. The specificity of such responses is often achieved by the combined action of nucleoid-associated proteins (NAP) such as HNS, RNA polymerase co-factors, and global and specific regulators that operate

MAIN AREAS OF RESEARCH

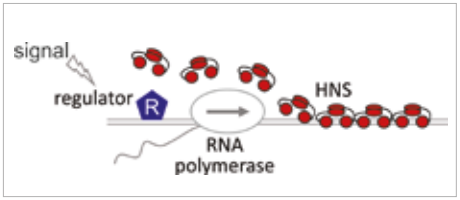
LeuO, a global antagonist of transcriptional silencing by HNS

❄

The signaling response regulator RcsB, a regulatory hub

❄

Interference of transcription and silencing by HNS



The abundant nucleoid-associated silencer protein HNS represses transcription by the formation of extended nucleoprotein complexes. HNS repression is relieved locus-specifically by transcription factors (regulator) in response to signal(s) (arrow). Furthermore, the elongating RNA polymerase (RNA-P) can displace HNS and relieve repression above a threshold transcription rate, thus resulting in signal amplification.

together at the transcriptional to post-transcriptional level of control. We study molecular mechanisms that specifically operate in overcoming silencing by HNS.

One aspect that we study concerns the antagonism of HNS-mediated transcriptional silencing by transcription factors of global regulatory function and the characterization of the signaling pathway involved. In particular, we address the function and modulation of activity of LeuO, a protein that is essential for *Salmonella* pathogenicity, YjjQ, an inhibitor of motility in *E. coli*, as well as the signal response regulator RcsB and its auxiliary proteins that are important in a variety of responses to membrane stress and other environmental cues.

Another aspect that we study relates to silencing by HNS and the dynamic bacterial genome organization. Silencing by HNS is mediated by the formation of extended nucleoprotein complexes that renders the DNA inaccessible. These nucleoprotein complexes need to be highly dynamic, as in bacteria, genome replication and segregation as well as transcription all occur at the same time. In particular, we study the interference of transcription by RNA polymerase across nucleoprotein complexes formed by HNS.

Publications

Kavalchuk, K., Madhusudan, S., and Schnetz, K. (2012). RNase III initiates rapid degradation of *proU* mRNA upon hypo-osmotic stress in *Escherichia coli*. RNA Biol. 9: 98-109.

Salscheider, S.L., Jahn, A., and Schnetz, K. (2014). Transcriptional regulation by BglJ–RcsB, a pleiotropic heteromeric activator in *Escherichia coli*. Nucl. Acids Res. 42: 2999-3008.

Sankar, S.T., Neelakanta, G., Sangal, V., Plum, G., Achtman, M., and Schnetz, K. (2009). Fate of the H-NS repressed *bgl* operon in evolution of *Escherichia coli.* PLoS Genet. 5: journal.pgen.1000405.

Stratmann, T., Pul, Ü., Wurm, R., Wagner, R., and Schnetz, K. (2012). RcsB-BglJ activates the *Escherichia coli leuO* gene, encoding an H-NS antagonist and pleiotropic regulator of virulence determinants. Mol. Microbiol. 83: 1109-1123.

Westra, E.R., Pul, U., Heidrich, N., Jore, M.M., Lundgren, M., Stratmann, T., Wurm, R., Raine, A., Mescher, M., Van, H.L., et al. (2010). H-NS-mediated repression of CRISPR-based immunity in *Escherichia coli* K12 can be relieved by the transcription activator LeuO. Mol. Microbiol. 77: 1380-1393.

Stress Signaling in Development and Disease

STRESS IS AN INEVITABLE PART OF OUR LIFE. THE ABILITY OF AN ORGANISM TO COPE WITH STRESSES IS FUNDAMENTAL TO ITS PROPER DEVELOPMENT AND SURVIVAL. STUDYING THE MOLECULAR MECHANISMS THAT ORCHESTRATE STRESS RESPONSES IS CRUCIAL FOR UNDERSTANDING DISEASES AND AGING.

Mirka Uhlirova

Institute for Genetics

Elaborate signaling and regulatory networks have evolved to govern the development and maintenance of multicellular organisms. Our lab is interested in understanding how signaling pathways cooperate to ensure homeostasis at the cellular, tissue and whole-body level during normal development and under stress conditions. We investigate how defects in these systems cause developmental anomalies, accelerate aging and contribute to disease states. We study mechanisms that underlie signaling specificity so that diverse signals are interpreted properly and are translated into sensible and biologically meaningful responses. We take advantage of the powerful genetic model of *Drosophila melanogaster* that facilitates both gene discovery and *in vivo* analysis of gene function. To gain mechanistic insights into the relationship between pathways and their components, we combine genetics with cell and molecular biology techniques, biochemistry, and genomic approaches. Our current research projects attempt to dissect the role of stress signaling pathways and downstream transcription factors (TFs) in the regulation of growth, proliferation, cell death and cell migration. Although these processes are elaborately controlled spatially and temporally during tissue morphogenesis, their deregulation promotes malignant transformation and cancer. We concentrate on the functional characterization of individual TFs and TF networks downstream of stress-activated MAPK kinase signaling in the process of *Drosophila* abdominal morphogenesis, tissue regeneration and wound healing, as well as tumorigenesis in the established *Drosophila* epithelial tumor model. Furthermore, we explore a link between cellular stress induced by aberrant pre-mRNA splicing, cancer development, and neurodegeneration.

MAIN AREAS OF RESEARCH

Role of stress signaling in homeostasis and cancer

❊

Stress signaling in tissue morphogenesis

❊

Transcription factor networks and signaling specificity

❊

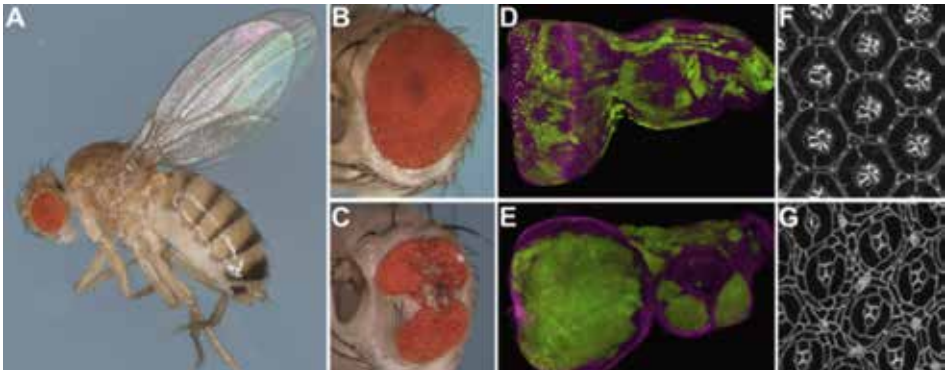
Pre-mRNA splicing, stress and disease

A) Bright-field image of a fruit fly, *Drosophila melanogaster.*

B, C) Bright-field images of adult *Drosophila* eyes in which wild-type (B) or mutant clones (C) were induced using the MARCM technique. The presence of mutant clones interferes with normal eye development, resulting in ommatidia elimination and differentiation defects.

D, E) Confocal micrographs of the *Drosophila* eye imaginal disc epithelium carrying GFP-marked (green) control (D) or tumor clones (E). Disc morphology and cell outlines are visualized with antibodies against Fasciclin III (magenta).

F, G) Confocal micrographs of wild type and mutant *Drosophila* pupal eye imaginal discs. Cell outlines are visualized with antibodies against DE-cadherin. In contrast to the regular hexagonal pattern of wild type ommatidia, in which photoreceptors, primary, secondary and tertiary pigment cells and bristles can be distinguished, the mutant ommatidia are not properly rearranged and contain surplus interommatidial cells that failed to be eliminated.



Publications

Claudius AK, Romani P, Lamkemeyer T, Jindra M, Uhlirova M (2014). Unexpected role of the steroid-deficiency protein ecdysoneless in pre-mRNA splicing. PLoS Genet. 10: e1004287.

Külshammer E, Uhlirova M (2013). The actin cross-linker Filamin/Cheerio mediates tumor malignancy downstream of JNK signaling. J. Cell Sci. 126: 927-938.

Rynes J, Donohoe CD, Frommolt P, Brodesser S, Jindra M, Uhlirova M (2012). Activating Transcription Factor 3 Regulates Immune and Metabolic Homeostasis. Mol. Cell Biol. 32: 3949-3962.

Sekyrova P, Bohmann D, Jindra M, Uhlirova M (2010). Interaction between *Drosophila* bZIP proteins Atf3 and Jun prevents replacement of epithelial cells during metamorphosis. Development 137: 141-150.

Wang Q, Uhlirova M, Bohmann D (2010). Spatial Restriction of FGF Signaling by a Matrix Metalloprotease Controls Branching Morphogenesis. Dev. Cell 18: 157-164.

Population Genetics and Bioinformatics

Thomas Wiehe

Institute for Genetics

Forces operating at different time scales are involved in the process of molecular evolution and are uncovered by a comparative approach directed to intraspecies and interspecies levels. Data analysis in both fields needs powerful bioinformatic algorithms. Our research interests are focused on the causes and consequences of molecular evolution. We pursue a micro- as well as macro-evolutionary approach, based on mathematical modeling, statistic and bioinformatic data analysis, to address questions about the type and tempo of evolutionary innovations.

MAIN AREAS OF RESEARCH

Theoretical population genetics

❄

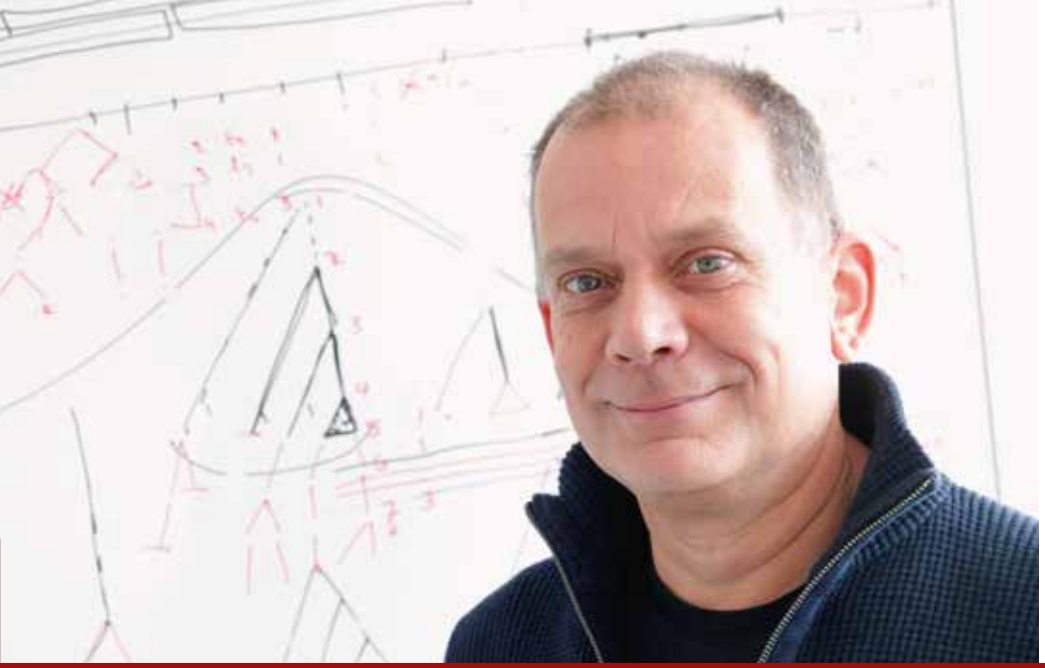
Comparative and evolutionary genomics

❄

Shared concepts in genomics and linguistics

Theoretical Population Genetics

We have a long-standing interest in the evolutionary dynamics of gene–gene interactions and the interplay of recombination and natural selection. In particular, we study molecular mechanisms of fast adaptation in immune system genes in Zebrafish and 'genetic hitchhiking' of epistatically interacting genes in *Drosophila* and humans.



Comparative and evolutionary genomics

Inter-specific comparisons involve drastically different time-scales, when functionally constrained genes are maintained over hundreds of million years.

We aim to quantify gene gain and loss over macro-evolutionary time and to pinpoint the evolutionary innovations in the gene pool at significant nodes in the tree of life, for instance, the common ancestor of bilateria.

Analogies in genetics and linguistics

Genetic and linguistic texts have many features in common and are accessible to computational analysis. In one of our projects, we investigate how the context of syntactic units influences and determines linguistic meaning or genetic function.

Publications

Heger P., Wiehe T. (2014). New tools in the box: An evolutionary synopsis on chromatin insulators. Trends Genet. 30: 161-171.

Disanto F., Wiehe T. (2014). On the sub-permutations of pattern avoiding permutations. Discrete Math. 337: 127.

Li H., Wiehe T. (2013). Coalescent tree imbalance and a simple test for selective sweeps based on microsatellite variation. PloS Comput. Biol. 9: e1003060.

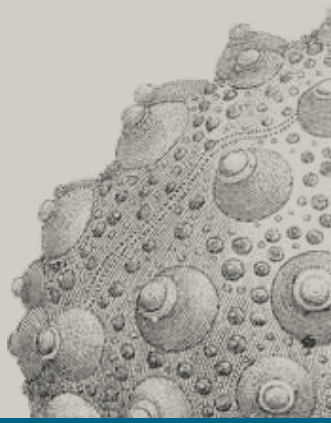
Heger P., Marin B., Bartkuhn M., Schierenberg E., Wiehe T. (2012). The chromatin insulator CTCF and the emergence of metazoen diversity. Proc. Natl. Acat. Sci. USA 109: 17507-17512.

Haubold B., Pfaffelhuber P., Domazet-Loso D. and Wiehe T. (2009). Estimating mutation distances from unaligned genomes J. Comput. Biol. 16: 1487-1500.

The Institute for Zoology is a multidisciplinary academic research and teaching institution that addresses biological phenomena at levels ranging from genes, molecules and cells to entire organisms, populations and ecosystems. We work on multiple animal models, applying a combination of experimental and theoretical approaches.

Organismal research spans the entire tree of life from protists to vertebrates. The research can be grouped into three main research themes: Ecology and Evolution, Developmental Biology, and Neuroscience. Research links and collaborations, however, occur between researchers across the entire institute – providing opportunities for tackling research problems in novel and flexible ways. One of the main drivers for our research is the fascination of studying how animals function and how their outstanding capabilities develop and evolved, with a specific focus on the central nervous system. Within the frame of collaborative research centres, excellence clusters and other BMBF-, DFG-, EU-, NIH- and NSF-funded consortia, members of our institute have extensive research collaborations worldwide. In addition, we offer a range of state-of-the-art research facilities and equipment, and a shared set of high-quality biology teaching laboratories.

RESEARCH



Institute for Zoology

Food-Web Ecology of Marine, Freshwater and Terrestrial Systems

Hartmut Arndt

Institute for Zoology

Understanding the functioning of food webs is prerequisite for the analysis of fluxes of materials and energy on our planet. The global biodiversity crisis concerns not only the unprecedented loss of species within communities, but also related consequences of ecosystem functions mediated by food webs. Food-web ecology considers the structure and dynamics of species trophic interactions, species diversity, their distribution and abundance. Since we are interested in the generality of concepts, our studies comprise deep-sea food webs, as well as running water, lake and desert systems in different regions of the world. Making use of current developments of molecular biology, electron and light microscopy, we use microbial food webs as model systems. Using continuous

MAIN AREAS OF RESEARCH

Functioning and diversity of microbial food webs in diverse ecosystems ranging from the deep sea, to freshwater and desert systems

❊

Molecular ecology, evolution and phylogeny of protists

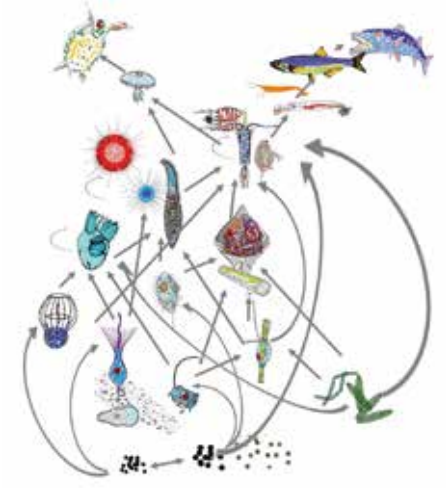
❊

Nonlinear dynamics of ecological systems using microbes as model organisms

❊

Ecology of freshwater fish: Migration and role as top predators in aquatic food webs

Ecological Rhine Station Cologne



Food web

cultures, we study theoretical ecology concepts of nonlinear dynamics of food-web interactions and the consequences of potentially occurring chaos and stable limit cycles. As the size structure of food webs is a consequence of long-term evolution, we try to understand evolutionary and ecological processes that govern this process and focus on the evolution of multicellularity from ancestral choanoflagellate protists. Our food-web studies are complemented by investigations into top-down effects, using fish as a model group. Thus, our main interests are life-history strategies, trophic polymorphism and behavior, and the biology of migrating fish. Current massive invasions of species, especially into the Rhine river system, require a mechanistic understanding of how biodiversity is related to ecosystem functioning that is necessary for estimating the impacts of species loss and invasions.

Transferring laboratory studies to the field is indispensable for ecological research. Intensive experimental field studies are carried out at the Ecological Rhine Station floating on the River Rhine. This enables direct observations of organisms in the flow of water with the aid of microscopes equipped with flow channels in the river laboratory. Fish ecology is the main focus in the Field Station of the Zoological Institute in Rees-Grietherbusch 120 km north of Cologne, on the flood plain of the River Rhine. Moreover, applied issues of rehabilitation of fish species and ecosystem management play an important role. Both stations combine basic research and the education of students.

Publications

Becks L, Arndt H (2013). Different types of synchrony in chaotic and cyclic communities. Nat. Commun. 4: 1359. doi: 10.1038.

Brabender M, Domonell A, Kiss AK, Nitsche F, Arndt H (2012). Phylogenetic and morphological diversity of novel soil cercomonad species with a description of two new genera (Nucleocercomonas and Metabolomonas). Protist 163: 495-528.

Magnhagen C, Hellström G, Borcherding J, Heynen M (2012). Boldness in two perch populations – long-term differences and the effect of predation pressure. J. Anim. Ecol. 81: 1311-1318.

Borcherding J, Beeck P, DeAngelis DL, Scharf WR (2010). Match or mismatch: the influence of phenology on size-dependent life history and divergence in population structure. J. Anim. Ecol. 79: 1101-1112.

Becks L, Hilker F, Malchow H, Jürgens K, Arndt H (2005). Experimental demonstration of chaos in a microbial food web. Nature 435: 1226-1229.

Terrestrial Ecology: from Microbes to Vertebrates

Michael Bonkowski

Institute for Zoology

The main research activities of our group focus on the function and fertility of soils. Soils host the greatest diversity of organisms found on our planet. We apply high-throughput sequencing to characterize the microbial communities in soil and those associated with plants. Our special interest relates to rhizosphere microbial interactions. By focusing on predator–prey interactions in the plant rhizosphere, we have shown that protist predators affect the turnover, community composition and function of rhizosphere bacteria, with significant feedback effects on the hormonal balance in plants, root architecture and the plants' nutrient uptake efficiency. Bacteria and protists strongly interact with mycorrhizal fungi. These effects have been shown to cascade

MAIN AREAS OF RESEARCH

Ecology and biodiversity of soil ecosystems

❊

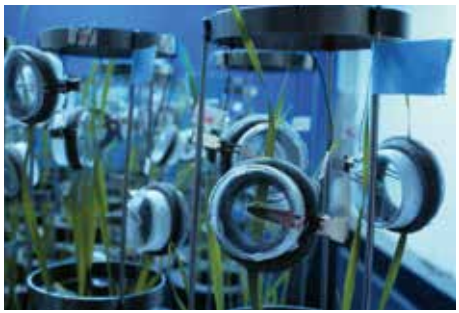
Plant–microbe interactions

❊

Island biogeography

❊

Ecology, taxonomy and evolution of the herpetofauna in Southeast Asia



Experiment investigating how plant microbial symbionts reduce aphid infection of barley.

Field research in Vietnam.

over several trophic levels and affect the performance of aboveground herbivores.

More recently, mechanisms of community assembly became a major a focus of our research. On lake islands, we found a clear species–area relationship. Natural enrichments with stable isotopes, such as ^{15}N signatures of arthropod predators, indicate their trophic positions, whereas their ^{13}C signatures show the degree of prey subsidy from aquatic systems, and variations in isotope signatures indicate niche breadth. Comparing isotope signatures across trophic levels gives detailed information on food chain length, as well as on changes in horizontal niche breadth, due to competitive processes with changing island size. We collaborate intensively with Cologne Zoo and the Institute of Ecology and Biological Resources (IEBR, Hanoi) on community assembly of reptiles and amphibia in the tropical rain forests of Vietnam and Laos. This research investigates adaptive radiation, especially patterns of geographic genetic differentiation and attributes of the ecology and life history of reptiles. We are particularly interested in placing this work in the context of ecosystem-level consequences of biodiversity loss due to factors such as habitat degradation and destruction, and to shifts in tolerances to changing temperatures expected by Global Change.

Collembola are common fungal feeders in soil.

Publications

Bradford MA, Wood SA, Bardgett RD, Black HIJ, Bonkowski M, Eggers T, Grayston SJ, Kandeler E, Manning P, Setälä H, Jones TH (2014). Discontinuity in the responses of ecosystem processes and multifunctionality to altered soil community composition. Proc. Natl. Acad. Sci. USA 111: 14478-14483.

van Schingen M, Pham CT, Thi HA, Bernardes M, Hecht V, Nguyen TQ, Bonkowski M, Ziegler T (2014). Current status of the Crocodile Lizard *Shinisaurus crocodilurus* Ahl, 1930 in Vietnam with implications for conservation measures. Revue Suisse de Zoologie 121: 425-439.

Koller R, Rodriguez A, Robin Ch, Scheu S, Bonkowski M (2013). Protozoa enhance foraging efficiency of arbuscular mycorrhizal fungi for mineral nitrogen from organic matter in soil to the benefit of host plants. New Phytol. 199: 203-211.

Bonkowski M, Villenave C, Griffiths BS (2009). Rhizosphere fauna: the functional and structural diversity of intimate interactions of soil fauna with plant roots. Plant Soil 321: 213-233.

Bradford MA, Jones TH, Bardgett RD, Black H, Boag B, Bonkowski M, Cook R, Eggers T, Gange AC, Grayston SJ, Kandeler E, McCaig AE, Newington JE, Prosser J, Setälä H, Staddon PL, Tordoff GM, Tscherko D, Lawton JH (2002). Impacts of soil faunal community composition on model grassland ecosystems. Science 298: 615-618.

Neural Control of Locomotion

Ansgar Büschges

Institute for Zoology

Across the animal kingdom, locomotion is a common element in a variety of behaviors that are essential for survival, such as foraging, escape or the search for a partner. We are interested in understanding its neural control. We study the neural basis of locomotion in invertebrates and vertebrates, i.e., walking in insects and swimming in fish and agnaths. Laboratory animals for the investigation of walking are mainly Phasmids (stick insects), and recently, also *Drosophila* (fruit fly).

The generation of a functional motor output in vertebrates and invertebrates results from the interaction of descending signals from the brain, the output from central pattern-generating networks located in the spinal cord or ventral nerve cord, feedback from sensory neurons concerning movements and forces generated in

MAIN AREAS OF RESEARCH

Electrophysiological properties and synaptic interactions of neurons that contribute to the generation of locomotor activity

❊

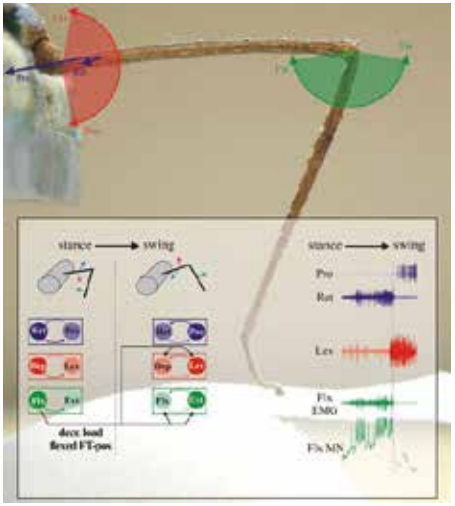
Cellular and network properties that allow for motor flexibility to meet different behavioral demands.

❊

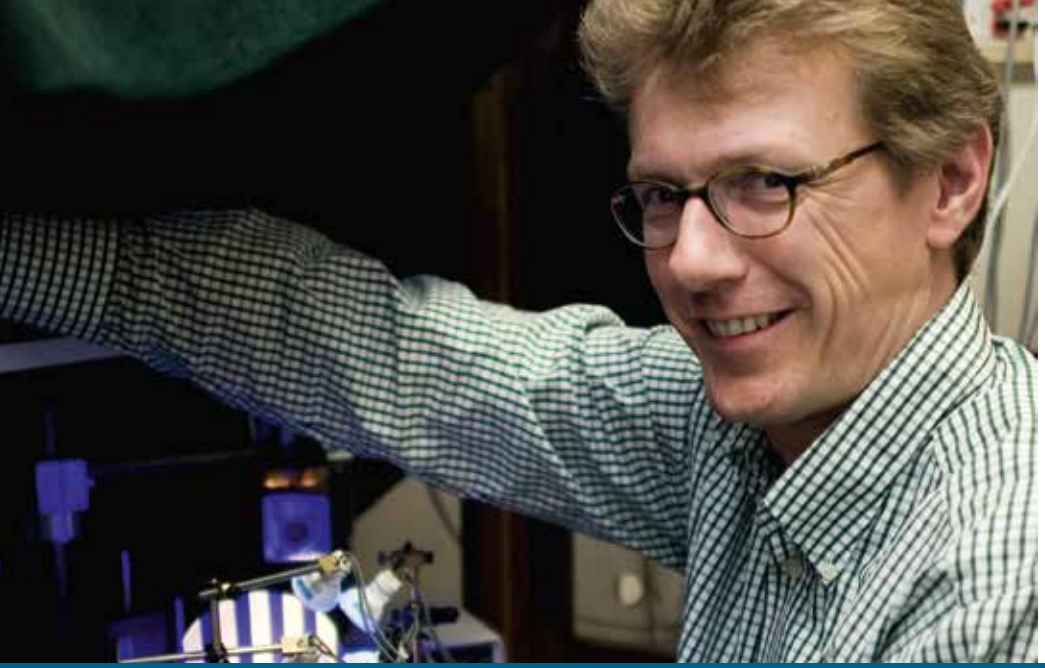
Identification and role of descending signals in the control of task-specific local information processing.

❊

Neural mechanisms and pathways governing inter-leg coordination



Generation of Leg Stepping in an Insect.
Background: Close-up of a stick insect middle leg with a representation of the three main leg joints.
Inset right: Recording of the activity of leg motoneurons and muscles during stepping at the transition from stance to swing.
Inset left: Conceptual scheme depicting the influence of reduced leg loading on the central pattern-generating networks that control the motoractivity of the thorax-coxa and the coxa-trochanter joints underlying the transition from stance to swing motor output.



the locomotor organs, and coordinating signals from neighboring segments or appendages. To date, most of the explicit neural mechanisms of interaction are still imprecisely understood. In order to better understand the importance of our findings for the action of motor networks on a more abstract level, we cooperate with mathematicians who are interested in developing computer models of neural networks for locomotion. We also cooperate with engineers, who develop legged robots. These colleagues are interested in finding the neurobiological solutions to movement control in order to improve the control mechanisms of their walking machines.

In our research, we investigate the mechanisms underlying the generation of locomotor behavior, from the analysis of movement kinematics down to the analysis of cellular properties. We employ a variety of techniques, often simultaneously, to record from and stimulate neurons in the central nervous system (CNS), sense organs and muscles, and to monitor their behavior. Techniques include the high-speed video analysis of movements, electromyograhic recordings and force measurements of muscle contractions, *en passant* recordings from motor nerves, sharp-electrode and patch-clamp recordings from neurons, immunocytochemistry and confocal microscopy. It is the simple organization of the stick insect and the fruit fly that particularly allows us to apply most of these techniques to intact or partially intact animals that exhibit locomotion or leg movements.

Publications

Berg, E., Hooper, S.L., Schmidt J., Büschges, A. (2015). A Leg-Local Neural Mechanism Mediates the Decision to Search in Stick Insects. Curr. Biol. 25: 2012-2017.

Buschmann, T., Ewald A., von Twickel, A. and Büschges, A. (2015). Controlling Legs for Locomotion - Insights from Robotics and Neurobiology. Bioinspir. Biomim. 10: 041001.

Hooper, S.L., Guschlbauer, C., Blümel, M., and Büschges, A. (2009). Neural Control of Unloaded Leg Posture and of Leg Swing in Stick Insect, Cockroach, and Mouse Differs from That in Larger Animals. J. Neurosci. 29: 4109-4119.

von Uckermann, G., Büschges, A. (2009). Premotor Interneurons in the Local Control of Stepping Motor Output for the Stick Insect Single Middle Leg. J. Neurophysiol. 102: 1956-1975.

Wosnitza, A., Bockemühl, T., Dübbert, M., Scholz, H. and Büschges, A. (2013). Inter-leg Coordination in the Control of Walking speed in *Drosophila*. J. Exp. Biol. 216: 480-491.

Chemical Ecology in Marine and Freshwater Systems

Eric von Elert

Institute for Zoology

Chemical ecology in freshwater systems

Chemically mediated interactions are of pivotal importance in freshwater and marine ecosystems. At the interface of primary producers and herbivores, chemically mediated food-finding and adaptations to dietary toxins and inhibitors are of key interest. The group analyzes processes of food-finding and the evolutionary adaptation of herbivores to toxins and to the detoxification of these toxins and inhibitors in lab experiments and at the scale of natural populations. We have shown that volatile organic compounds from primary producers are used for food-finding by aquatic invertebrates, and are investigating how ocean acidification affects this signaling in a marine context.

MAIN AREAS OF RESEARCH

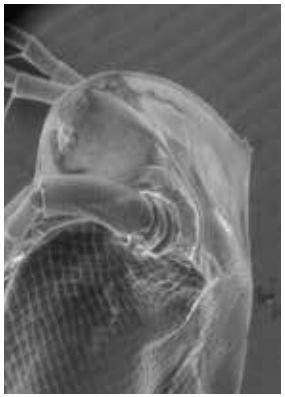
Algae–herbivore interactions

❊

Inducible defenses in zooplankton

❊

Cyanobacterial toxins and Daphnia



Daphnia pulex with neckteeth induced by chemical signals released by its predator larvae of *Chaoborus* sp.

Lymnaea stagnalis, an aquatic snail that uses volatile organic compounds to find food.

Cyanobacteria are known for their variety of secondary metabolites and for their low food quality for *Daphnia* and are predicted to become more abundant due to global warming. Here, the group focuses on the effects of protease inhibitors (PIs) and microcystins of cyanobacteria on *Daphnia*. *Daphnia* respond to PIs by changes in the expression of protease genes and by local adaptation of populations. Currently, we study the molecular basis of this evolutionary adaptation, and we use LC-MS and transcriptomics to understand how microcystins are taken up, excreted, and how they affect gene expression in *Daphnia*.

Another important type of chemically mediated interactions are defenses in prey that are induced by chemical signals released from the predator (kairomones). Such inducible defenses strongly affect trophic interactions and population fluctuations. Here, the focus is on changes in the life-history, morphology and behaviour of *Daphnia* in response to infochemicals released from predators such as fish, and larvae of the midge, *Chaoborus* sp. Using LC-MS and bioassay-guided fractionation, we aim to identify the chemical nature of these kairomones, and we work on deciphering the molecular basis of these inducible defences using proteomics and qPCR of target genes in *Daphnia*.

We approach these issues using analytical techniques such as HPLC, UPLC-MS, GC and GC-MS and molecular techniques including PCR, qPCR, transcriptomics and proteomics.

Publications

Schwarzenberger, A., Sadler, T., Motameny, S., Ben-Khalifa, K., Frommolt, P., Altmüller, J., Konrad, K. & Von Elert, E. (2014). Deciphering the genetic basis of microcystin tolerance. BMC Genomics 15: 776. doi: 10.1186/1471-2164-15-776.

Moelzner, J. & Fink, P. (2014). The smell of good food: volatile infochemicals as resource quality indicators. J. Anim. Ecol. 83: 1007-1014. doi: 10.1111/1365-2656.12220.

Effertz, C. & Von Elert, E. (2014). Light intensity controls anti-predator defences in *Daphnia*: the suppression of life-history changes. Proc. Biol. Sci. 281: 20133250. doi: 10.1098/rspb.2013.3250.

Sadler, T. & Von Elert, E. (2014). Dietary exposure of Daphnia to microcystins: No in vivo relevance of biotransformation. Aquat. Toxicol. 150: 73-82. doi: 10.1016/j.aquatox.2014.02.017.

Pajk, F., Von Elert, E. & Fink, P. (2012). Interaction of changes in food quality and temperature reveals maternal effects on fitness parameters of a keystone aquatic herbivore. Limnol. Oceanogr. 57: 281-292. doi: 10.4319/lo.2012.57.1.0281.

Zebrafish as a Model for Human Development and Disease

LET'S SEE WHAT FISH MODELS WITH THEIR COMPLEMENTARY METHODOLOGICAL STRENGTHS CAN TELL US ABOUT HUMAN DEVELOPMENT AND DISEASE

Matthias Hammerschmidt

Institute for Zoology

Our research focuses on different aspects of zebrafish development and disease, using forward genetics, reverse genetics (CRISPR/Cas), and transgenesis for loss- and gain-of-function analyses. Whereas previous work was concerned with the earliest embryonic development (dorsoventral patterning, gastrulation), we now study later developmental processes with a higher biomedical relevance.

We analyze various genes that are required for the proper epithelial integrity of the epidermis, and for proper epidermal–dermal junctioning. Some of these genes are also involved in fetal skin development in humans, and in carcinoma formation during adulthood. To unravel the relevant pathways involved, and to elaborate potential therapies, we screen for small compounds that alleviate both the developmental and carcinogenic effects. In addition, we study different aspects of cutaneous wound healing, which in contrast to in humans, is very rapid and scar-free in zebrafish. For one of the identified essential epidermal–dermal junction genes, which encodes the extracellular matrix protein Hmcn, we have also generated knockout mice.

MAIN AREAS OF RESEARCH

Skin development, cutaneous wound healing and squamous cell carcinoma formation

❊

Bone development and homeostasis, with particular focus on the role of retinoic acid

❊

Neuroendocrine control of energy homeostasis

❊

Extracellular matrix proteins in muscle and myotendinous junctions of zebrafish and mouse

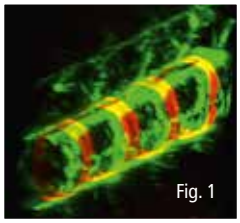


Fig. 1: Confocal image of sclerotomal cells (osteoblast precursors; green) surrounding the ossified central bodies (red) of the developing vertebral column of a zebrafish larva.

Fig. 2: Confocal image of hypothalamic axons (green) innervating the anterior pituitary gland (purple) of a zebrafish larva.

Similar to the zebrafish mutants, these mice display additional defects in muscular and muscle-tendon junction integrity, leading to a particular type of muscular atropy.

Another project deals with bone development and homeostasis. We could show that loss-of-function mutations in the retinoic acid (RA)-metabolizing enzyme CYP26B1 (and thus gain of RA signaling) in both zebrafish and humans leads to craniosynostosis (premature fusion of calvarial plates of the skull), due to premature osteoblast-to-osteocyte transitioning. Currently, we are analysing further traits of the mutant phenotypes, including the vertebral column and crosstalk with other signaling pathways.

Finally, as part of CECAD, we have established zebrafish models to analyze the neural circuits within the hypothalamus of the brain and towards the pituitary gland to study the neuroendocrine system in the control of energy homeostasis. As in humans, interference with this system can lead to obesity and increased body sizes on one hand, or to anorexia and decreased body sizes on the other.

Publications

Fischer, B., Metzger, M., Richardson, R., Knyphausen, P., Ramezani, T., Franzen, R., Schmelzer, E., Bloch, W., Carney, T.J. and Hammerschmidt, M. (2014). p53 and TAp63 promote keratinocyte proliferation and differentiation in breeding tubercles of the zebrafish. PLoS Genet. 10: e1004048.

Miyares, R.L., Stein, C., Renisch, B., Anderson, J.L., Hammerschmidt, M.* and Farber, S.A.* (2013). Long-chain Acyl-CoA syntehtase regulates Smad activity and dorsoventral patterning in the zebrafish embryo. Dev. Cell 27: 635-647. *joint corresponding authors

Richardson, R., Slanchev, K., Kraus, C., Knyphausen, P., Eming, S. and Hammerschmidt, M. (2013). Adult zebrafish as a model for cutaneous wound-healing research. J. Invest. Dermatol. 133: 1655-1665.

Laue, K., Pogoda, H.-M., Daniel P.B., van Haeringen A., Alanay Y., von Ameln S., Rachwalski M., Morgan T., Gray M.J., Breuning M.H., Sawyer G.M., Sutherland-Smith A.J., Nikkels P.G., Kubisch C., Bloch W., Wollnik B., Hammerschmidt, M.*, Roberston, S.P.* (2011). Craniosynostosis and multiple skeletal anomalies in humans and zebrafish result from a defect in the localized degradation of retinoic acid. Am. J. Hum. Genet. 89: 595-606. * joint corresponding authors

Carney, T.J., Feitosa, N., Sonntag, C., Slanchev, K., Kluger, J., Kiyozumi, D., Gebauer, J., Talbot, J., Kimmel, C.B., Sekiguchi, K., Wagener, R., Schwarz, R., Ingham, P.I. and Hammerschmidt, M. (2010). Genetic analysis of fin development in zebrafish identifies Furin and Hemicentin1 as potential novel Fraser Syndrome disease genes. PLoS Genet. 6: e1000907.

Cellular and Molecular Mechanisms of Neuromodulation

Peter Kloppenburg

Institute for Zoology

To survive, an animal must be able to adjust its behavior to changes in the environment. Accordingly, the neuronal circuits that control and drive behavior have to modify their functional properties. How plasticity of nervous systems is regulated at the cellular and molecular level on short time scales and during the lifespan is a central question. We are especially interested in the biophysical mechanisms that determine neuronal excitability and synaptic plasticity. The aim is to understand how the modulation of intrinsic and synaptic properties of single neurons (or groups of neurons) regulate the function of complex neuronal systems and ultimately control behavior.

In this context, an important area of research in our laboratory is the physiological compartmentalization of neurons and its consequences for the function of neural networks. In intact nervous systems, several neuromodulators often converge on a single neuron. The intracellular signaling pathways for many neuromodulators are known from the receptor to the ion channel. However, the interaction of

MAIN AREAS OF RESEARCH

Neuromodulation

❊

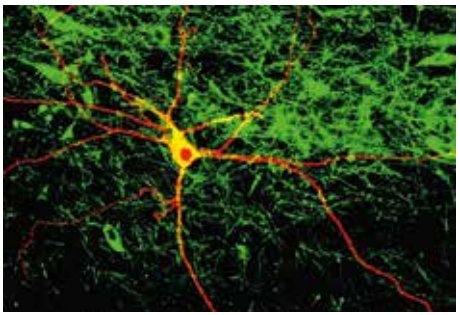
Neuron type-specific electrophysiological properties

❊

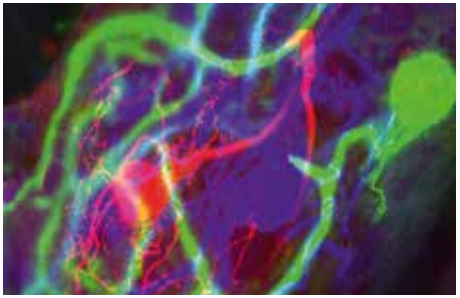
Synaptic transmission

❊

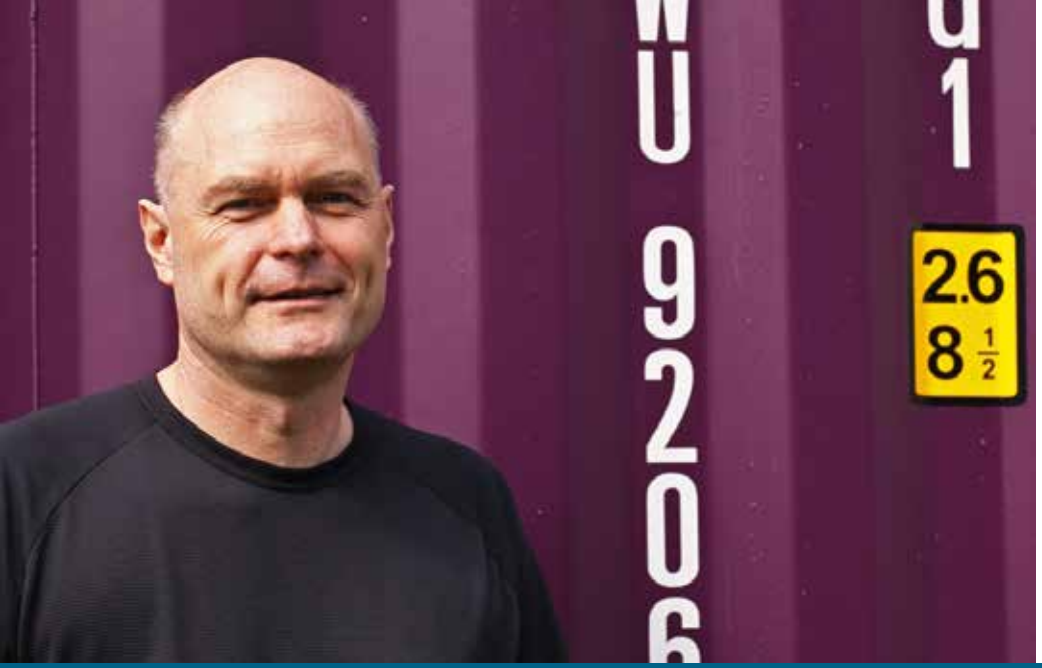
Intracellular Ca^{2+} handling



Dopaminergic midbrain neuron.



Three labeled neurons of a central pattern-generating neuronal circuit (stomatogastric ganglion).



different intracellular signaling pathways is not known in detail. It remains to be clarified, whether and how biochemically similar signaling pathways interact with each other, or whether they are spatially separated. Such localization or restriction of specific signaling pathways into specific functional microdomains becomes increasingly clear from biochemical and immunhistochemical studies. Clearly, functional compartmentalization has significant consequences for neuronal information processing, but this is physiologically not well demonstrated or understood yet.

To achieve these goals, the laboratory is using electrophysiological and optical recordings to obtain detailed knowledge of the physiological and computational consequences of cellular compartmentalization. Optical imaging techniques with high spatial and temporal resolution deep within living tissue, together with new fluorescence indicators for different cellular parameters, are well suited to address these questions directly.

Publications

Warren B, Kloppenburg P (2014). Rapid and slow chemical synaptic interactions of cholinergic projection neurons and GABAergic local interneurons in the antennal lobe. J. Neurosci. 34: 13039-13046. doi: 10.1523/JNEUROSCI.0765-14.2014.

Vogt MC, Paeger L, Hess S, Steculorum SM, Awazawa M, Hampel B, Neupert S, Nicholls HT, Mauer J, Hausen AC, Predel R, Kloppenburg P, Horvath TL, Brüning JC (2014). Neonatal insulin action impairs hypothalamic neurocircuit formation in response to maternal high-fat feeding. Cell 156: 495-509. doi: 10.1016/j.cell.2014.01.008.

Hess ME, Hess S, Meyer KD, Verhagen LA, Koch L, Brönneke HS, Dietrich MO, Jordan SD, Saletore Y, Elemento O, Belgardt BF, Franz T, Horvath TL, Rüther U, Jaffrey SR, Kloppenburg P, Brüning JC (2013). The fat mass and obesity associated gene (*Fto*) regulates activity of the dopaminergic midbrain circuitry. Nat. Neurosci. 16: 1042-1048. doi: 10.1038/nn.3449.

Fusca D, Husch A, Baumann A, Kloppenburg P (2013). Choline acetyltransferase-like immunoreactivity in a physiologically distinct subtype of olfactory nonspiking local interneurons in the cockroach (*Periplaneta americana*). J. Comp. Neurol. 521: 3556-3569. doi: 10.1002/cne.23371.

Klöckener T, Hess S, Belgardt BF, Paeger L, Verhagen LA, Husch A, Sohn JW, Hampel B, Dhillon H, Zigman JM, Lowell BB, Williams KW, Elmquist JK, Horvath TL, Kloppenburg P, Brüning JC (2011). High-fat feeding promotes obesity via insulin receptor/PI3K-dependent inhibition of SF-1 VMH neurons. Nat. Neurosci. 14: 911-918. doi: 10.1038/nn.2847.

Theory of Information Processing in Nervous Systems

FUNDAMENTAL INSIGHTS INTO NERVOUS SYSTEM FUNCTION REQUIRE A MULTIDISCIPLINARY APPROACH

Martin Paul Nawrot

Institute for Zoology

How do neurons in the brain concert their activity in order to rapidly process sensory information and to form correct decisions? How is information stored and retrieved in a neural network? Could principles of neural computation be useful for technological solutions? In the Computational Systems Neuroscience group, we investigate information processing in the nervous systems of different animal models. In an interdisciplinary team, we combine theoretical and experimental approaches with the ultimate goal of formulating valid theories and testable model hypotheses.

A major focus of our research is placed on the neuronal processes underlying sensation, memory formation, and decisions in insects. Insects are equipped with highly evolved sensory systems;

MAIN AREAS OF RESEARCH

Neural Coding: Reliable and efficient information processing in the noisy brain

❊

Neural Plasticity: Learning, memory formation, and decision-making in insects

❊

Neuromorphic Computing: brain-like computation with in silico *neural networks*

❊

NeuroRobotics: insect-inspired artificial minibrains for autonomous agents

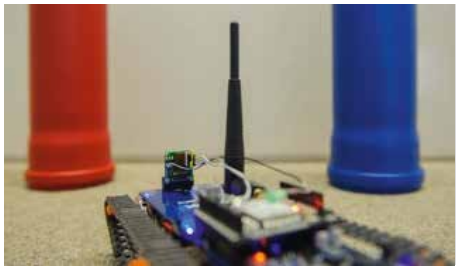


Fig. 1: NeuroRover: A robotic platform controlled by a spiking neural network simulation.

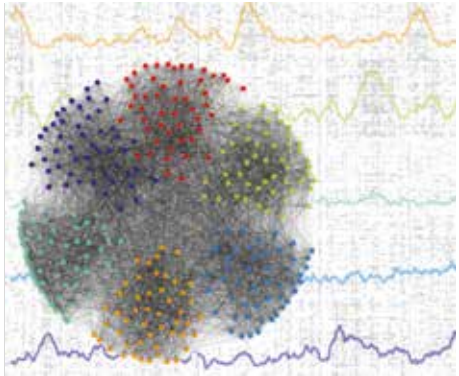


Fig. 2: Simulation of a cortical neural network of excitatory and inhibitory neurons with six excitatory neuron clusters (foreground) and their activity profiles over time (background).

they express complex context-dependent behavior, show fundamental learning abilities, and share many fundamental neuronal processing mechanisms with higher animals. However, insects have very limited neuronal resources – in the order of 100,000 (flies) to 1 million (bees and ants) neurons. Thus, insects are of particular interest for studying efficient coding strategies and are ideally suited for the simulation of biologically realistic brain models.

The insect repertoire of goal-directed behavior is still beyond the capabilities of today's artificial systems. In the field of Neurorobotics, we test insect-inspired neural network models for the control of autonomous robots. The robotic platform provides an embodiment for the simulated nervous system, which in turn, makes the robot sense, learn, and interact with its environment.

One step further, we use our models to explore the potential of Neuromorphic Computing, an emerging technology where 'artificial minibrains' can be realized on dedicated microchips that physically implement a network of neurons and synapses. Parallel processing, distributed memory, and high energy efficiency are promising features of neuromorphic computing that could become useful for intelligent systems and autonomous robots.

Publications

Pamir E, Szyszka P, Scheiner R, Nawrot MP (2014). Rapid learning dynamics in individual honeybees during classical conditioning. Front. Behav. Neurosci. 8: 313.

Schmuker M, Pfeil T, Nawrot MP (2014). A neuromorphic network for generic multivariate data classification. Proc. Natl. Acad. Sci. USA 111: 2081-2086.

Farkhooi F, Froese A, Müller E, Menzel R, Nawrot MP (2013). Cellular adaptation facilitates sparse and reliable coding in sensory pathways. PLoS Comput. Biol. 9: e1003251.

Rickert J, Riehle A, Aertsen A, Rotter S, Nawrot MP (2009). Dynamic encoding of movement direction in motor cortical neurons. J. Neurosci. 29: 13870-13882.

Krofczik S, Menzel R, Nawrot MP (2009). Rapid odor processing in the honeybee antennal lobe network. Front. Computat. Neurosci. 2: 9.

Reinhard Predel

Institute for Zoology

Cell-to-cell communication is of ancient origin and is a prerequisite for survival in a dynamic environment. The structurally and probably also functionally most variable type of messenger molecules within the the central nervous system (CNS) are neuropeptides. Single organisms can contain more than 50 neuropeptide genes, which give rise to hundreds of different neuropeptides that act on a similarly diverse array of mostly G protein–coupled receptors. Therefore, a single neuropeptide can act as a transmitter or neuromodulator within the CNS, but can also be released as a neurohormone into the circulation system where it often fulfills pleiotropic functions that can change during development. The situation becomes even more complex when considering processes such as the

MAIN AREAS OF RESEARCH

Evolution of neuroendocrine systems in arthropods

❊

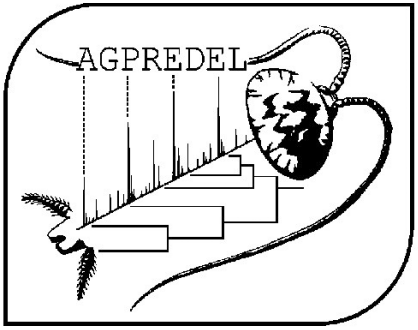
Development and utilization of methods for the mass-spectrometry-based peptide profiling of identified tissue samples or neurons from single specimens

❊

Development of simple methods for the typology of insect populations and scorpions using mass fingerprints

❊

Phylogeny of insects with a focus on the recently described Mantophasmatodea (Insecta)



differential expression of neuropeptide genes, differential processing of neuropeptide precursors, and the cell-specific post-translational modifications of neuropeptides.

We are interested in the evolution of these peptidergic signaling systems; the emphasis is on neuropeptides from the nervous system of invertebrates. The main topics are the development and utilization of methods for mass-spectrometry-based peptide profiling in identified neurons from the CNS and the analysis of the dynamics of cell-to-cell communication. We also develop methods for the typology of arthropod populations using taxon-specific neuropeptide patterns, which enable the separation of closely related taxa, but also the recognition of hybrid patterns and phylogenetic relationships. These methods are currently used to analyze relationships within the newly described insect order Mantophasmatodea, as well as the variability of scorpion toxins. Sample preparation is generally performed in the field and the mass-spectrometry analyses that we have developed for such purposes are fast and straightforward.

Publications

Neupert S, Fusca D, Schachtner J, Kloppenburg P, Predel R (2012). Toward a single-cell-based analysis of neuropeptide expression in *Periplaneta americana* antennal lobe neurons. J. Comp. Neurol. 520: 694-716.

Predel R, Neupert S, Huetteroth W, Kahnt J, Waidelich D, Roth S (2012). Peptidomics-based phylogeny and biogeography of *Mantophasmatodea* (Hexapoda). Syst. Biol. 61: 609-629.

Nasonia Genome Sequencing Consortium (2010). Functional and evolutionary insights from the genomes of three parasitoid *Nasonia* species. Science 327: 343-348.

Neupert S, Johard HAD, Nässel DR, Predel R (2007). Single cell peptidomics of *Drosophila melanogaster* neurons identified by Gal4-driven fluorescence. Anal. Chem. 79: 3690-3694.

Predel R, Neupert S (2007). Social behavior and the evolution of neuropeptide genes: lessons from the honeybee genome. BioEssays 29: 416-421.

The Evolution of Axis Formation and Gastrulation in Insects

Siegfried Roth

Institute for Zoology

Research from recent decades has revealed that many developmental and cellular processes show a striking degree of conservation throughout the animal kingdom from jellyfish to mammals. Findings from invertebrate model systems such as the fruit fly, *Drosophila melanogaster,* can often be directly transferred to vertebrates including humans. However, how can the striking diversity of body plans be reconciled with the existence of highly conserved developmental mechanisms? To address this question, we study the evolution of developmental mechanisms. Our focus is dorsoventral (DV) axis formation, which has been extensively studied in the fruit fly *Drosophila* and encompasses one of the best-known gene regulatory networks (GNR).

MAIN AREAS OF RESEARCH

Evolution of cell–cell communication and gene regulation in insects

❊

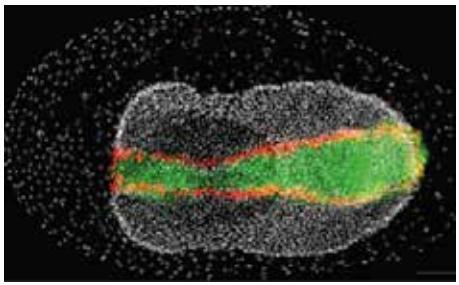
Mechanisms of self-regulatory patterning and scaling

❊

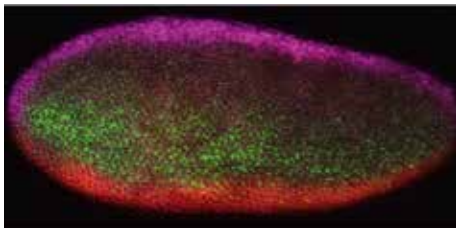
Evolution of morphogenetic processes

❊

The influence of ecology on the evolution of development



Gastrulation in the beetle *Tribolium.*



Distinct regions of gene expression along the dorsoventral axis in the embryo of the wasp *Nasonia vitripennis.*

In *Drosophila*, the DV axis is mostly patterned by a gradient of Toll signaling, a pathway that is not known for a patterning role in other animals, but rather for a highly conserved function in innate immunity. In contrast, the DV axis of other animals is established by a bone morphogenetic protein (BMP) signaling gradient, which in *Drosophila* has a more limited Toll-dependent function. In recent years, our lab has shown that BMP signaling progressively replaces Toll signaling in insects, which are members of more basal branches of the phylogenetic tree, similar to beetles, wasps and bugs. This work relates the derived mode of DV patterning in *Drosophila* to the more ancestral BMP-based mode found in other animals.

Interestingly, the greater influence of BMP signaling in basally branching insects is frequently linked to a high degree of pattern regulation not observed in *Drosophila*. For example, such insects can form two or more embryos within one egg. We are studying the molecular mechanism underlying this fascinating phenomenon and try to correlate the degree of pattern regulation with life-history traits. We also analyze Toll-based innate immunity in basal insects, as we assume that the patterning function of Toll was recruited from an ancestral function of Toll in protecting insect eggs against pathogens. These projects provide an ecological perspective to the evolution of development.

Publications

Özüak O, Buchta T, Roth S, Lynch JA (2014). Dorsoventral polarity of the *Nasonia* embryo primarily relies on a BMP gradient formed without input from Toll. Curr. Biol. 24: 2393-2398.

Lynch JA, Roth S (2011). The evolution of dorsal-ventral patterning mechanisms in insects. Genes Dev. 25: 107-118.

Lynch JA, Peel AD, Drechsler A, Averof M, Roth S (2010) EGF signaling and the origin of axial polarity among the insects. Curr. Biol. 20: 1042-1047.

Nunes da Fonseca R, von Levetzow C, Kalscheuer P, Basal A, van der Zee M, Roth S (2008). Self-regulatory circuits in dorsoventral axis formation of the short-germ beetle *Tribolium castaneum*. Dev. Cell 14: 605-615.

van der Zee M, Stockhammer O, von Levetzow C, Nunes da Fonseca R, Roth S (2006). Sog/Chordin is required for ventral-to-dorsal Dpp/BMP transport and head formation in a short germ insect. Proc. Natl. Acad. Sci. USA 103: 16307-16312.

Genes and Mechanisms Associated with Addiction

Henrike Scholz

Institute for Zoology

Alcohol abuse and dependence are extremely prevalent diseases that produce major health and social problems. Alcohol dependence is a complex behavior with a clear genetic component involving multiple genes. To understand cellular mechanisms and to identify neuronal networks underlying behaviors that are associated with addiction, our group uses the genetic model organism *Drosophila melanogaster*. On the cellular level, we are investigating how cellular stressors such as ethanol change neuronal plasticity. We identify neurons that are parts of a network that mediates behavior. Since addictive behaviors are complex, we dissect complex behaviors into different elements and ask how relevant these aspects are to the development of addictive behaviors.

MAIN AREAS OF RESEARCH

Determine how cellular stress changes neuronal plasticity and in turn, behavior

❊

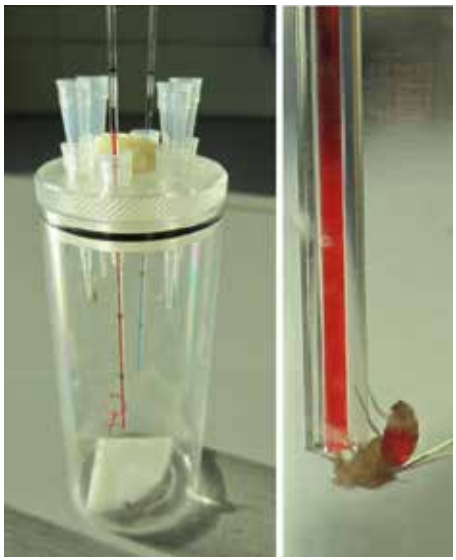
Identify modulatory mechanisms and networks contributing to behavior

❊

Unravel mechanisms of dysregulation of normal behavior

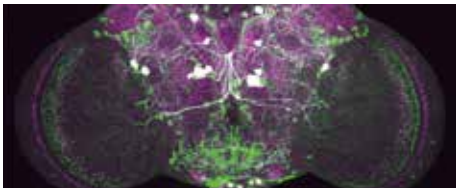
❊

Validate candidate genes associated with alcoholism in humans



The capillary feeder is one of the assays used in the laboratory to measure behavior in the fruit fly *Drosophila melanogaster*. The capillaries are filled with different colored solutions, in this case, blue and red. A fly – although relatively small – drinks measurable amounts of ethanol containing red-colored sucrose solution.

We have established *Drosophila melanogaster* as a genetic model system to analyze ethanol tolerance, a behavior associated with alcohol dependence. We change gene and neuronal network function by using molecular genetic, genetic and optogenetic methods, and analyze the consequences of these changes on behaviors that are associated with addiction, for example, alcohol tolerance and alcohol preference. Through detailed analyses of genetic mutants, we have determined that at least two different mechanisms contribute to tolerance; one acting at the level of a neuronal circuit to modulate brain function in response to ethanol, and the other acting at the cellular level as a cellular stress response, perhaps to protect the central nervous system (CNS) from ethanol-induced damage. A major short-term goal is to determine the molecular and cellular mechanisms by which these two pathways contribute to the neuronal adaptations underlying ethanol tolerance. In addition, we validate candidate genes that are implicated in alcoholism in humans. This analysis aims to open up new targets for drug treatment.



Brain of *Drosophila melanogaster*

Cellular studies of serotonergic neurons (magenta) expressed with GFP-tagged transgenes (green) are used to measure the effect of ethanol and stress on the single-cell level.

Publications

Juraeva D.*, Treutlein J.*, Scholz H.*, Frank J., Degenhardt F., Cichon S., Ridinger M., Mattheisen M., Witt S.H., Lang M., Sommer W., Hoffmann P., Herms S., Wodarz N., Soyka M., Zill P., Maier W., Mössner R., Gaebel W., Dahmen N., Scherbaum N., Schmäl C., Steffens M., Lucae S., Ising M., Müller-Myhsok B., Nöthen M.M., Mann K., Kiefer F., Spanagel R.*, Brors B.*, Rietschel M.* (2015). *XRCC5* as a Risk Gene for Alcohol Use Disorder: Evidence from a GWAS Gene-Set Based Analysis and a Functional Genetic Study in *Drosophila* and Humans. Neuropsychopharmacology 40: 361-371.

Scheiner R., Steinbach A., Strudthoff N., Scholz H. (2014). Octopamine indirectly affects proboscis extension response habituation in *Drosophila melanogaster* by controlling sucrose responsiveness. J. Insect Physiol. 69: 107-117.

Schneider A., Ruppert M., Hendrich O., Giang T., Vollbach M., Ogueta, M., Hampel, S., Büschges, A. and Scholz, H. (2012). Neuronal basis of innate olfactory attraction to ethanol in Drosophila. PLoS One 7: e52007.

Ogueta M., Cibik O., Eltrop R., Schneider A. and Scholz H. (2010). The influence of Adh function on ethanol preference and tolerance in adult *Drosophila melanogaster*. Chem. Senses. 35: 813-822.

Scholz H., Franz M., Heberlein U. (2005). The hangover gene defines a stress pathway required for ethanol tolerance development. Nature 436: 845-847.

Wolfgang Walkowiak

Institute for Zoology

Auditory communication has developed independently several times in the animal kingdom. Anuran amphibians are the most primitive tetrapods, which use airborne sound. Acoustic signals play an important role in controlling behavior, as well as autonomic nervous functions in this group of vertebrates. Using frogs and toads as model organisms, our studies are intended to understand the neural basis of acoustic communication. This comprises analysis of the auditory pathway, as well as sound generation mechanisms, which are closely related to the respiratory system. Particular emphasis is put on the evaluation of audio-vocal integration at brainstem levels. Audio-motor interaction in turn, is intensely controlled by the endocrine

MAIN AREAS OF RESEARCH

Analysis of the auditory system

❊

Neural basis of sound generation

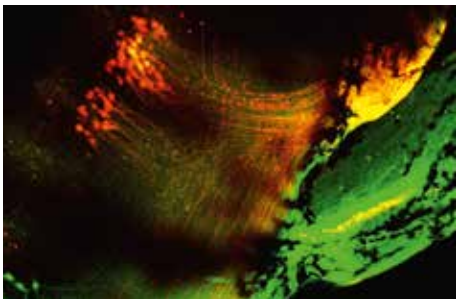
❊

Neural basis of sensory motor integration

❊

Basal ganglia and behavioral control

Bombina orientalis



Motorneurons backfill

system, especially sex steroids, and different di- and telencephalic structures – in particular, the limbic system and basal ganglia.

Recent anatomical studies have shown that the basal ganglia circuitry is highly conserved among all classes of vertebrates. In mammals, basal ganglia are involved in motor control, as well as action selection and emotional and cognitive functions. In order to elucidate the basic functions of this system, we have extended our research to lampreys, the phylogenetically oldest vertebrate group.

The analysis is conducted from the behavioral down to the single neuron level using different behavioral approaches, as well as neuroanatomical (immunohistology, hodology) and neurophysiological (intra- and extracellular recordings, patch-clamp) techniques.

Publications

Endepols, H., Roden, K.,Luksch, H., Dicke, U., Walkowiak, W. (2004). Dorsal striatopallidal system in anurans. J. Comp. Neurol. 468: 299-310.

Endepols, H., Schul, J., Gerhardt, H.C., Walkowiak, W. (2004). 6-hydroxydopamine lesions in anuran amphibians: a new model system for Parkinson's disease? J. Neurobiol. 60: 395-410.

Endepols, H., Helmbold, F., Walkowiak, W. (2007). GABAergic projection neurons in the basal ganglia of the green tree frog (*Hyla cinerea*). Brain Res. 1138: 76-85.

Walkowiak, W. (2007). Call production and neural basis of vocalization. In: Hearing and sound communication in amphibians. Springer Handbook of Auditory Research, Vol. 28, P.M. Narins, A.S. Feng, R.R. Fay, A.N. Popper, eds., Springer, pp. 87-112.

Maier, S., Walkowiak, W., Luksch, H., Endepols, H. (2010). An indirect basal ganglia pathway in anuran amphibians? J. Chem. Neuroanat. 40: 21-35.

JUNIOR RESEARCH GROUPS / EMMY NOETHER RESEARCH GROUPS

Quality Control of Mammalian Gene Expression

Niels Gehring

Junior Research Group

Gene expression is the process that converts our genetic information into the functional macromolecules of life – RNA and protein. Since gene expression is a fundamental process in all living organisms, diverse molecular mechanisms have evolved to detect errors and thereby ensure the accuracy of gene expression. Messenger RNAs (mRNAs) convey the blueprints of all proteins from the DNA to the protein biosynthesis machinery. Therefore, mRNAs execute an essential function during gene expression.

Our group works on nonsense-mediated mRNA decay (NMD), a cellular quality control mechanism, which detects mutated messenger RNAs. NMD prevents the production of C-terminally truncated

MAIN AREAS OF RESEARCH

Mechanism of mammalian nonsense-mediated mRNA decay (NMD)

❊

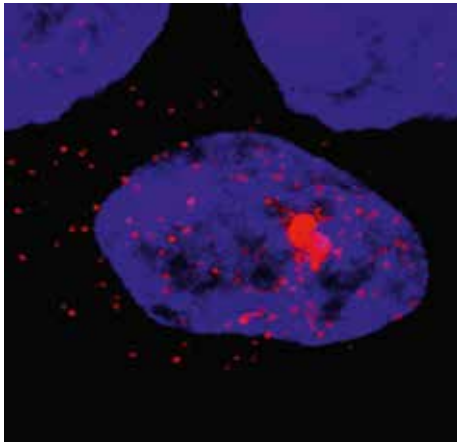
Regulation of messenger RNA turnover

❊

Assembly and function of RNA-binding protein complexes

❊

Processing of messenger RNAs



Expression of beta-globin mRNA (red) within a cultured human cell.

proteins, whose expression might be harmful to the cell. The activity of the NMD machinery limits the expression of disease-causing mutations and thereby influences the clinical symptoms of many inherited disorders. We use cultured human cells to analyze the mechanism that enables cells to discriminate between normal and erroneous mRNAs.

During its life, a mRNA molecule is processed, edited and transported from the cell nucleus to the cytoplasm. All these steps are controlled by distinct sets of trans-acting factors (mainly proteins but also other RNAs), to form so-called mRNPs. The composition of mRNPs determines the fate of any given mRNA and is thus an important denominator of gene regulation. Mutations in many mRNA-binding proteins cause Mendelian diseases, particularly of the central nervous system. This suggests that the improper formation of mRNPs might be a key event during the occurrence of neuro-developmental disorders. In our group, we study the characteristics of different mRNA-binding proteins and their dynamic interactions and cellular functions are our main research interest.

Publications

Boehm V, Haberman N, Ottens F, Ule J, Gehring NH (2014). 3' UTR length and messenger ribonucleoprotein composition determine endocleavage efficiencies at termination codons. Cell Rep. 9: 555-568. doi: 10.1016/j.celrep.2014.09.012.

Fatscher T, Boehm V, Weiche B, Gehring NH (2014). The interaction of cytoplasmic poly(A)-binding protein with eukaryotic initiation factor 4G suppresses nonsense-mediated mRNA decay. RNA 20: 1579-1592. doi:10.1261/rna.044933.114.

Burgute BD, Peche VS, Steckelberg AL, Glöckner G, Gaßen B, Gehring NH, Noegel AA (2014). NKAP is a novel RS-related protein that interacts with RNA and RNA binding proteins. Nucl. Acids Res. 42: 3177-3193. doi: 10.1093/nar/gkt1311.

Singh KK, Wachsmuth L, Kulozik AE, Gehring NH (2013). Two mammalian MAGOH genes contribute to exon junction complex composition and nonsense-mediated decay. RNA Biol. 10: 1291-1298. doi: 10.4161/rna.25827.

Steckelberg AL, Boehm V, Gromadzka AM, Gehring NH (2012). CWC22 connects pre-mRNA splicing and exon junction complex assembly. Cell Rep. 2: 454-461. doi: 0.1016/j.celrep.2012.08.017.

Post-Translational Lysine Acetylation as a Regulator of Protein Function in Health and Disease

LIFE SCIENCE MEANS TO DISCOVER
THE UNKNOWN DRIVEN BY THE
FASCINATION OF LIFE

Michael Lammers

Emmy Noether Research Group

The human genome contains approximately 20,000 genes, many of which encode proteins. At first glance, this is a rather low number considering a complex organism such as the human body; however, the complexity of the proteome is extensively enlarged by processes such as alternative splicing and post-translational modifications. Recently, a post-translational modification known for a long time to modify histones and regulate gene expression, namely lysine acetylation, has been shown to be far more widespread than originally expected. In fact, through the progress in quantitative proteomics, it turned out to be highly conserved from bacteria to man, and is present in all cellular compartments and in proteins that cover all essential cellular functions.

MAIN AREAS OF RESEARCH

Regulation of protein function by post-translational lysine acetylation

❊

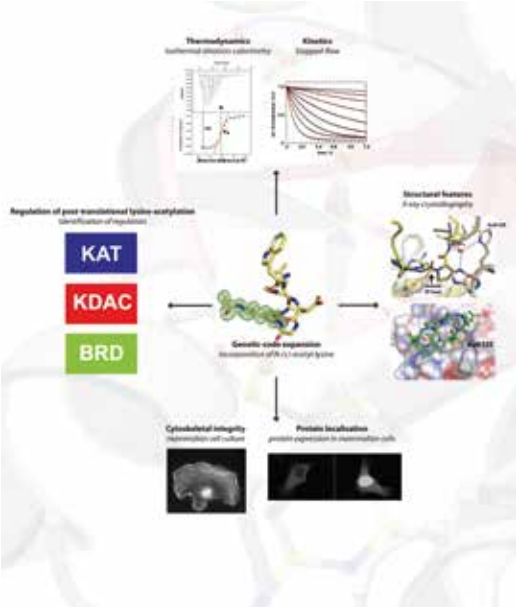
Deacetylation and acetylation by KDACs and KATs

❊

Regulation of the cytoskeleton by RhoGNBPs

❊

Using the genetic-code expansion to study protein function



Post-translational lysine acetylation is a fundamental regulator of protein function.

The acetylation level of proteins is precisely defined by the cellular metabolic, physiological, and cell-cycle state through the activities of lysine acetyltransferases (KATs), lysine deacetylases (KDACs) and even by site-specific non-enzymatic acetylation.

A dysfunction in the acetylation/deacetylation machinery is tightly connected to cellular disorders, as the overall acetylation pattern was found to be altered in several tumor types and furthermore, shows a strong variation during aging. In our group, we study how lysine acetylation regulates protein function, using a combined synthetic biological, cell biological and biophysical approach, including X-ray crystallography. Of central importance, we use a synthetically evolved acetyl-lysyl-tRNA/$tRNA_{CUA}$ pair from *Methanosarcina barkeri* to site-specifically incorporate acetyl-L-lysine into proteins. Using this genetic-code expansion concept allows us to study the impact of lysine acetylation on natively folded and quantitatively modified proteins. An important aspect of our research is to unravel how lysine acetylation is regulated dynamically by KDACs and KATs. This allows us to distinguish biologically relevant from non-relevant sites. Furthermore, as a therapeutic approach, it will enable us in the long run to develop more specific compounds with fewer off-target effects tackling the lysine acetylation machinery.

Publications

de Boor, S., Knyphausen, P., Kuhlmann, N., Wroblowski, S., Brenig, J., Scislowski, L., Baldus, L., Nolte, H., Krüger, M., and Lammers, M. (2015) The small GTP-binding protein Ran is regulated by post-translational lysine acetylation; PNAS 112, E3679–E3688.

Brenig, J., de Boor, S., Knyphausen, P., Kuhlmann, N., Wroblowski, S., Baldus, L., Scislowski, L., Artz, O., Trauschies, P., Baumann, U., Neundorf, I., and Lammers, M. (2015) .Structural and biochemical basis of the inhibitory effect of liprin-α3 on mDia1 function; J. Biol. Chem. 290, 14314–14327.

Lammers, M., Neumann, H., Chin, J. and James, L. (2010). Acetylation regulates Cyclophilin A catalysis, immunosuppression and HIV isomerization. Nat. Chem. Biol. 6: 331-337.

Lammers, M., Meyer, S., Kühlmann, D. and Wittinghofer, A. (2008). Specificity of Interactions between mDia Isoforms and Rho Proteins. J. Biol. Chem. 283: 35236-35246.

Rose, R.*, Weyand, M.*, Lammers, M.*, Ishizaki, T., Ahmadian. M.R. and Wittinghofer, A. (2005). Structural and mechanistic insights into the interaction between Rho and mammalian Dia. Nature 435: 513-518. *joint first authorship

Evolution of Epithelial Morphogenesis

Kristen Panfilio

Emmy Noether Research Group

Successful embryonic development requires the correct three-dimensional form and arrangement of tissues. A unique feature of insect eggs is that they develop two extraembryonic (EE) epithelia, which provide physiological and mechanical protection to the embryo. We are examining the morphogenesis – the changing tissue organization and form – of these epithelial tissues as they first envelop and later withdraw from the embryo, using developmental genetic, evolutionary, and bioinformatic approaches. To do so even more effectively, we are also developing new transgenic resources to further our work.

MAIN AREAS OF RESEARCH

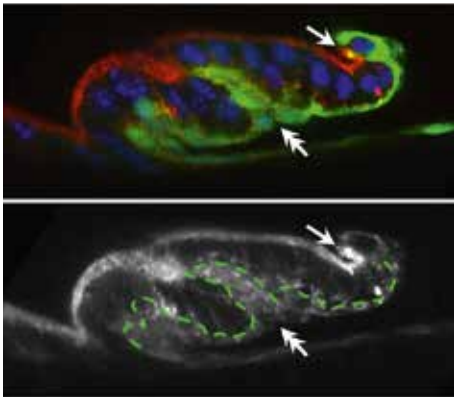
Evolution of development

❊

Live imaging of embryonic morphogenesiss

❊

Transcriptional regulation and molecular evolution



A folding, bilayered sheet of the extraembryonic tissues, with the outer tissue labeled in green with GFP, and red showing strong contraction of the cytoskeleton in the inner tissue.

Our main aim is to understand how the extraembryonic epithelia achieve the correct three-dimensional form and topography in relation to the embryo proper, and how this is coordinated over time as a succession of rearrangements occur. Genetic and live-imaging analyses provide insight into essential aspects of animal tissue development generally and of insects in particular.

Furthermore, the EE epithelia have evolved within the insects. By taking a comparative approach across species, we are examining the degree to which these morphogenetic events have been conserved, or not, during insect evolution. We conduct functional investigations in two species with distinct EE arrangements: the milkweed bug (*Oncopeltus fasciatus*) and the red flour beetle (*Tribolium castaneum*). Comparative analyses help to clarify how changes in molecular regulation and tissue organization have occurred during evolution. We focus on key transcription factors, including differential expression of downstream target genes, as well as on selected enhancer regions that control EE expression.

Publications

Koelzer, S., Kölsch, Y., and Panfilio, K.A. (2014). Visualizing late insect embryogenesis: Extraembryonic and mesodermal enhancer trap expression in the beetle *Tribolium castaneum*. PLoS ONE 9: e103967.

Panfilio, K.A., Oberhofer, G., and Roth, S. (2013). High plasticity in epithelial morphogenesis during insect dorsal closure. Biol. Open 2: 1108-1118.

Panfilio, K.A., and Roth, S. (2010). Epithelial reorganization events during late extraembryonic development in a hemimetabolous insect. Dev. Biol. 340: 100-115.

Panfilio, K.A. (2008). Extraembryonic development in insects and the acrobatics of blastokinesis. Dev. Biol. 313: 471-491.

Panfilio, K.A., Liu, P.Z., Akam, M., and Kaufman, T.C. (2006). Oncopeltus fasciatus zen is essential for serosal tissue function in katatrepsis. Dev. Biol. 292: 226-243.

Dynamics of Neuronal Circuits

Carmen Wellmann

Emmy Noether Research Group

Two fundamental goals of neuroscience are to explain, in terms of the organization of their cellular components, how nervous systems work and how they generate overt behavior. Our progress toward these goals has often come from thorough study of specific nervous systems, selected because their orderly cellular organization and favorable anatomy allow us to perform critical and repeatable experiments, or because under experimental conditions, they continue to express behaviorally related activity. Cellular explanations of properties of particular systems have led to insights and general principles that apply across phyla. One class of behaviors for which we have outlines of cellular explanations, is locomotion.

MAIN AREAS OF RESEARCH

Neural control of locomotion

❊

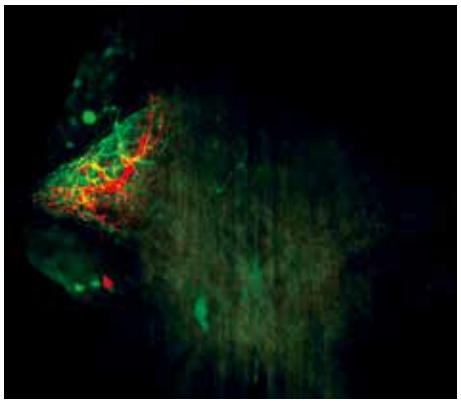
Coordination of neuronal networks

❊

Cellular properties of neurons and neuronal networks

❊

Synaptic interactions



Intracellular fill of two identified nonspiking interneurons with fluorescent dyes.

To understand the coordination of neuronal circuits, I study a locomotor system in crayfish – the swimmeret system. Four pairs of swimmerets beat rhythmically when the animals swim forward. Their

central nervous system consists of a chain of four distributed ganglia, which innervate each segment separately. Independently, it produces the rhythmic motor pattern that drives the swimmeret movement in the intact animal, as well as in the isolated nerve-cord preparation.

Each limb in each segment is driven by its own neuronal network consisting of five interneurons. The connections between these neurons are sufficient to produce rhythmic activity. A coordinating network spanning the four neuronal networks coordinates their activity pattern. I study the specific interaction between neurons, their particular properties, and how these two aspects contribute to the coordination of neuronal networks. The small number of neurons in this system of coupled networks helps us to analyze them in detail. We study these neurons with a range of different electrophysiological methods. The results from these experiments will help others to propose hypotheses for the function and coordination of complex networks.

Crayfish, *Pacifastacus leniusculus*

Publications

Seichter H.A., F. Blumenthal & C.R. Smarandache-Wellmann (2014). The swimmeret system of crayfish: A practical guide for the dissection of the nerve cord and extracellular recordings of the motor pattern. J. Vis. Exp. 93: e52109-e52109.

Mulloney B., C.R. Smarandache-Wellmann, C. Weller, W.M. Hall & R. DiCaprio (2014). Proprioceptive modulation of coordination of segmentally-distributed microcircuits. J. Neurophysiol. 112: 2799-2809.

Smarandache-Wellmann C.R. & S. Graetsch (2014). Mechanisms of coordination in distributed neural circuits: Encoding coordinating information J. Neurosci. 34: 5627-5639.

Smarandache-Wellmann C.R, C.R. Weller & B. Mulloney (2014). Mechanisms of coordination in distributed neural circuits: Decoding and integration of coordinating information J. Neurosci. 34: 793-803.

Smarandache-Wellmann C.R, C. Weller, T.M Wright Jr. & B. Mulloney (2013). Five types of non-spiking interneurons in the local pattern-generating circuits of the crayfish swimmeret system J. Neurophysiol. 110: 344-357.

EXCELLENCE INITIATIVE

CECAD'S VISION:

Exploring the Aging Process

CECAD is a joint initiative of the University of Cologne, the Cologne University Hospital, the Max Planck Institutes for Metabolism Research and for Biology of Ageing, and the Center for Neurodegenerative Diseases (DZNE). CECAD's vision is to unravel the full range of causes underlying aging-associated diseases and to translate the findings into new treatments. More than 400 international scientists are working to make this vision become real. Since November 2007, the CECAD Excellence Cluster has received public funding from the federal and state governments as part of the Excellence Initiative through the German Research Foundation (DFG). Following a successful initial funding period, CECAD received a positive evaluation and entered its second funding period in November 2012 that will last until October 2017. Scientists are unraveling the aging process in six research areas:

Mitochondrial Dysfunction in Aging and Neurodegeneration

Mitochondria are the powerhouses of the cell, keeping them supplied with energy. The activity of mitochondria decreases during aging and defects in mitochondria trigger age-associated diseases including neurodegeneration. Research Area A explores the quality control mechanisms that maintain the integrity of mitochondrial processes, and how the disruption of these mechanisms contributes to diseases.

Proteostasis in Aging-Associated Diseases

Cellular differentiation, developmental processes and environmental factors challenge the integrity of the proteome in every eukaryotic cell. The maintenance of protein homeostasis, or proteostasis, involves the repair and degradation of damaged proteins and is essential for human health. It is commonly thought that the age-related impairment of protein quality control affects general proteostasis networks and is involved in age-related pathologies.

DNA Damage Responses in Aging-Associated Diseases

The genome in each cell of the human body is constantly under attack. Over a lifetime, DNA damage accumulates and drives the aging process and causes age-related diseases, including cancer. Investigators in research area C focus on understanding how DNA repair systems remove the damage and how cells and tissues counteract the detrimental consequences of genome damage.

Membrane Senescence and Lipid-Associated Signals

Cell membranes are integral to our cells and contain enzymes, receptors and ion channels. The composition of their building blocks (lipids) changes over the course of a lifetime. Changes in lipid metabolism play an important role in aging-associated diseases such as hair loss, muscle weakness and obesity. Scientists in Research Area D investigate why the lipid composition of the cells alters over time and the mechanisms that promote aging-associated diseases.

Inflammation in Aging-Associated Diseases

When the immune system is not properly regulated, it can cause chronic inflammatory reactions. Prolonged inflammation can trigger aging-associated diseases such as cancer, chronic wounds, and type 2 diabetes. Research Area E focuses on the different phenomena associated with inflammation, such as the role of chronic inflammation in tissue and aging, or the link between inflammation and carcinogenesis.

Metabolic Signaling in Aging, Diabetes and Obesity

Nutrient intake and energy expenditure are controlled by a variety of metabolic and neuronal signaling pathways. Imbalances here can result in diseases such as obesity and type 2 diabetes. The energy-regulating signaling pathways also influence development, growth and the aging process.

Scientists in Research Area F work to identify the signaling cascades involved in regulating energy metabolism and explore how their findings might contribute to a longer, healthier life in old age.

In the frame of the second funding period, one new CECAD professor, Professor Dr. Marcus Krüger, was recently recruited.

www.cecad.uni-koeln.de

THE FOLLOWING SCIENTISTS OF THE DEPARTMENT OF BIOLOGY BELONG TO CECAD:

Prof. Hammerschmidt	Institute for Zoology	See page 60
Prof. Hoppe	Institute for Genetics	See page 32
Prof. Kloppenburg	Institute for Zoology	See page 62
Prof. Krüger	Institute for Genetics	See page 91
Prof. Langer	Institute for Genetics	See page 36
Prof. Pasparakis	Institute for Genetics	See page 40
Prof. Rugarli	Institute for Genetics	See page 42
Prof. Uhlirova	Institute for Genetics	See page 46
Prof. Schwarz	Institute for Biochemistry	
Prof. Schumacher	Medical Faculty / Institute for Genetics	
Prof. Trifunovic	Medical Faculty / Institute for Genetics	

In addition, CECAD hosts Independent Junior Research Groups.

Prof. Marcus Krüger

Quantitative Proteomics

Our research:

The proteome – the whole set of proteins in a cell – cannot be deduced entirely from the genome. For example, post-translational modifications (PTMs) are important for the dynamic regulation of protein activity, translocation, and stability. Moreover, PTMs are critical for signaling pathways and the deregulation of modifying enzymes often leads to diseases, such as cancer and type 2 diabetes mellitus.

My research group is applying large-scale quantitative proteomics to investigate signal transduction pathways in various mouse models.

Our goals:

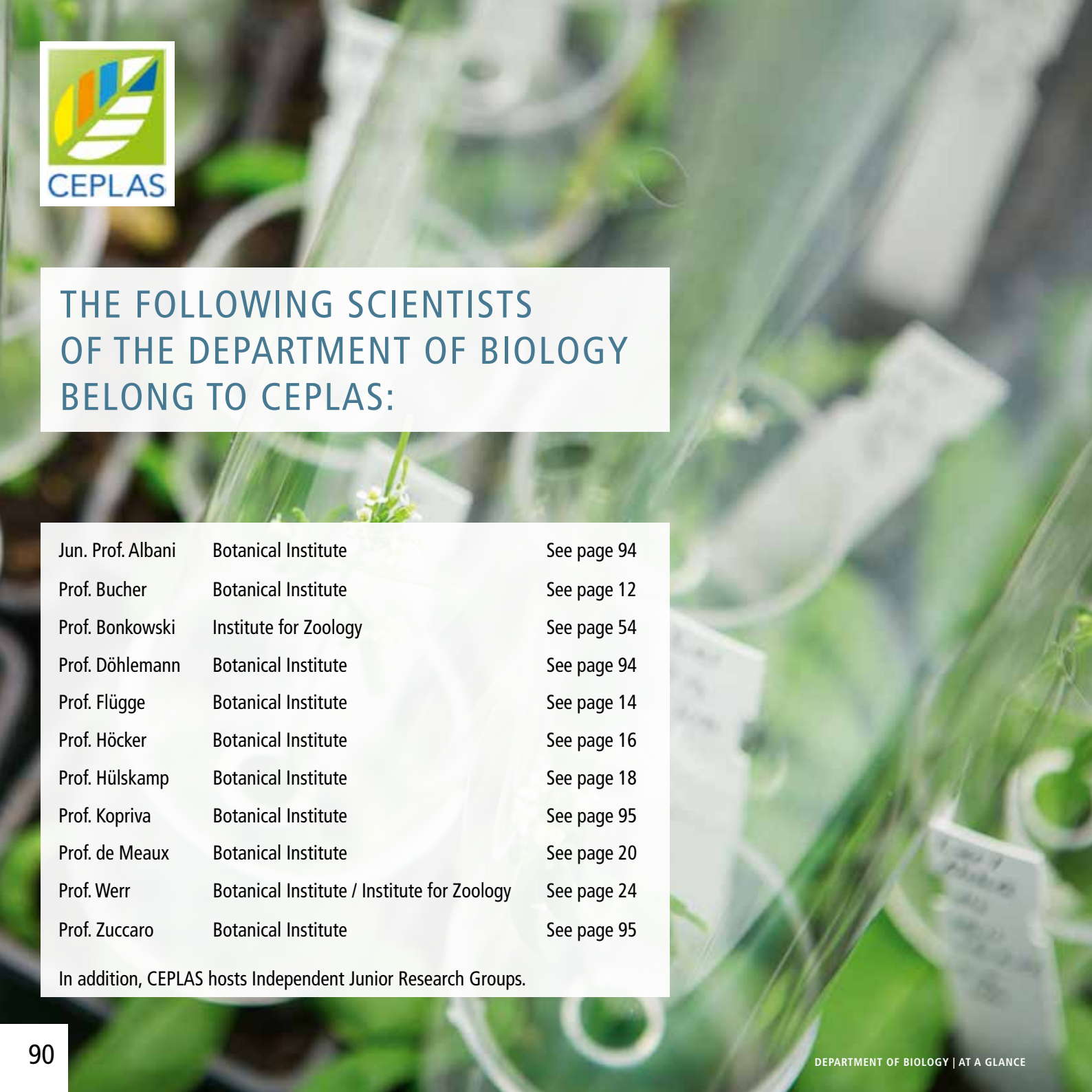
The group is aiming to identify protein and PTM profiles in living model organisms with relevance to human disease. With the long-term goal of developing new treatment methods, we intend to use the profiles as targets for new therapeutic agents. In the personalized medicine of the future, unbiased proteome analysis will be employed in addition to genome-wide strategies for the individual treatment of human patients.

Our successes:

The Krüger group is involved in transferring SILAC technology to various model organisms, including worms, zebrafish, and rodents. This allows us to determine protein concentrations and protein turnover in living animals using mass-spectrometry (LC-MS/MS).

Our methods/techniques:

The Krüger laboratory uses SILAC labeling of model organisms to quantify proteins and regulatory PTMs accurately. The group uses the enrichment of PTMs, such as phosphorylation and acetylation, via affinity- and antibody-based methods.



THE FOLLOWING SCIENTISTS OF THE DEPARTMENT OF BIOLOGY BELONG TO CEPLAS:

Jun. Prof. Albani	Botanical Institute	See page 94
Prof. Bucher	Botanical Institute	See page 12
Prof. Bonkowski	Institute for Zoology	See page 54
Prof. Döhlemann	Botanical Institute	See page 94
Prof. Flügge	Botanical Institute	See page 14
Prof. Höcker	Botanical Institute	See page 16
Prof. Hülskamp	Botanical Institute	See page 18
Prof. Kopriva	Botanical Institute	See page 95
Prof. de Meaux	Botanical Institute	See page 20
Prof. Werr	Botanical Institute / Institute for Zoology	See page 24
Prof. Zuccaro	Botanical Institute	See page 95

In addition, CEPLAS hosts Independent Junior Research Groups.

CEPLAS

The Cluster of Excellence in Plant Sciences – from complex traits towards synthetic modules (CEPLAS) is developing innovative strategies for sustainable plant cultivation. The cluster is working with internationally renowned scientists from the Universities of Cologne and Düsseldorf, the Max Planck Institute for Plant Breeding Research, and the Forschungszentrum Jülich.

Since November 2013, CEPLAS is funded by the DFG in the context of the Excellence Initiative for five years and as a Center of Excellence within the framework of the University of Cologne Institutional Strategy.
As part of CEPLAS, four new professorships (including a junior professorship hosted at the Max Planck Institute for Plant Breeding Research) were established within the Department of Biology at the Botanical Institute.

Plants are the basis of all human life. They provide food and feed, medical drugs, as well as raw materials for construction, clothing, and for energy production. However, global change, in particular altered precipitation and temperature patterns, is challenging the sustained production of crops and thus, the agronomic base of human civilization. Simultaneously, arable land is becoming scarce due to increased erosion and population pressure. A growing population and altered consumption patterns demand increased crop production for food, feed, and (bio)fuels. Meeting this demand will require innovative strategies for crop improvement that aim to enhance yield, without compromising increases in the use of water, nutrients, and soil, or diminished resistance to pests. The scientists at CEPLAS are therefore working on a fundamental understanding of the mechanisms of plant adaptation and are researching resource-efficient plant growth.

In this context, CEPLAS aims to achieve a fundamental understanding of the genetic mechanisms that enable plants to adapt to adverse environmental conditions and constraints. The research strategy of CEPLAS – from complex traits towards synthetic modules – builds on comparative evolutionary genomic analyses of complex traits in a phylogenetic framework. The genetic architecture and regulatory networks underlying complex traits will be uncovered through genomic and genetic comparisons of related species that differ in these traits. This knowledge provides the foundation for dissecting the gene networks into their modules and understanding their design principles with the help of quantitative models. Based on these findings, the re-design and re-synthesis of advantageous traits will become possible, to engineer plants harboring synthetic modules of these traits.

Specifically, CEPLAS researchers investigate the mechanistic basis and genetic architecture of four complex traits that have a crucial impact on adaption to limited resources and are therefore of outstanding importance in designing and breeding the crops of the future:

- Annual and perennial life strategies
- Photosynthetic carbon conversion efficiency
- Composition and function of the plant microbiome
- Metabolic interactions between plants and microbes

During the 2012–2017 funding period, four new CEPLAS professors were recruited (see p. 94/95).

www.ceplas.eu

Jun. Prof. Maria Albani

Molecular Systematics

My research focuses on understanding the molecular mechanisms that regulate the perennial growth habit in *Arabis alpina*. My group is interested in studying the contribution of axillary and lateral meristems in the perennial life cycle of *A. alpina*. We employ forward and reverse genetic approaches to understand the role of genes that regulate perennial-specific traits and that contribute to the perennial life strategy. My group has a strong background in the physiology of perennial traits in *A. alpin*a, the regulation of flowering time and its contribution to the perennial life cycle. We are now starting to investigate the role of lateral meristems in perennial traits and potential links with flowering behavior. I previously identified the *perpetual flowering 1* (*pep1*) mutant in *A. alpina* that flowers without vernalization and has disturbed perennial traits. I demonstrated that PEP1 is the *A. alpina* orthologue of the floral repressor FLOWERING LOCUS C (FLC), suggesting that PEP1 in *A. alpina* regulates flowering but also perennial traits. The *pep1* mutants are still perennial, suggesting that there are additional mechanisms that contribute to the perennial growth habit. In my grant (DFG – temporary Positions for Principal Investigators), I performed enhancer and suppressor mutagenesis screens of the *pep1* mutant. The isolation and characterization of the causal mutations will be continued in the frame of CEPLAS. In addition, the role of vascular cambium in the perennial life cycle and its contribution to perennial-specific traits such as adventitious root formation will be studied.

Prof. Gunther Döhlemann

Terrestrial Microbiology

Our research aims to identify and understand molecular mechanisms of microbe–plant interactions. The focus is on effector proteins of biotrophic microbes, which suppress host immunity and plant metabolism.

The basidiomycete fungi *Ustilago maydis* and *Ustilago hordei* parasitize their respective host plants maize and barley to cause smut disease. The pathogens establish biotrophic interactions, in which infected plant cells stay alive throughout the entire disease cycle. Whereas *U. hordei* infections are systemic and symptoms are only produced in the inflorescences, plant tumors induced by *U. maydis* can appear in basically all aerial parts of the maize plant. In *U. maydis*-infected maize plants, metabolism is reprogrammed and carbohydrate fluxes are redirected towards the infected tissue, in which massive proliferation of fungal hyphae occurs. Our research focuses on the mechanisms biotrophic pathogens use to establish in the host tissue. Specifically, we are investigating (i) how fungal effector proteins suppress host immunity and (ii) which host factors are required to establish compatibility.

Within CEPLAS, we are interested to (i) study the role of plant cysteine proteases in immunity and how they are modulated by microbial effectors and (ii) elucidate how organ-specific factors of both plant and colonizing microbe contribute to interaction outcomes.

Prof. Stanislav Kopriva
Plant Biochemistry

My research focuses on dissection of the molecular mechanisms of the regulation of sulfur metabolism, using a combination of biochemical, genetic and physiological approaches and exploiting natural variation.

My long-term goal is to understand how plants control the uptake and utilization of key mineral nutrients, using a combination of biochemical, genetic and physiological approaches. We showed by metabolic flux analysis that the enzyme adenosine 5´-phosphosulfate reductase is key for the control of sulfate assimilation, and identified numerous transcription factors that control the regulation of the corresponding genes. We are exploiting natural variation in *Arabidopsis* to dissect the control of sulfur metabolism.

Within CEPLAS, I will apply my expertise in metabolic flux analysis and genome-wide association mapping to address the interaction of rhizobacteria with plants and their contribution to plant nutrition. In addition, I aim to tackle the intriguing question of the cell-specific localization of nitrate and sulfate metabolism in C_4 plants.

Prof. Alga Zuccaro
Microbial Ecological Genetics

Currently, my research focuses on the mechanisms that enable symbiotic fungi to colonize plants successfully and on the processes accounting for variations in host preferences and fungal lifestyles, especially in mutualistic root endophytes. With respect to insights into how symbiotic fungi establish themselves in metabolically active root cells and how the plants are reprogrammed for enhanced performance, my group routinely uses integrated approaches that rely on the combination of reverse genetics, transcriptomics, cell biology, biochemistry and comparative genomics. We propose to analyze the genetics and cell biology of the root endophyte *Piriformospora indica*, and the closely related orchid mycorrhizal fungus *Sebacina vermiferain*, their symbioses with the model plants barley (monocot) and *Arabidopsis* (dicot) and to understand the evolutionary mechanisms involved in the establishment of biotrophy. Our primary interest is to find answers to the following questions:

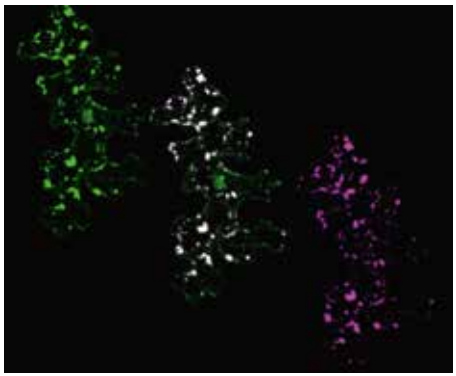
1. Which mechanisms allow root endophytes to suppress host defense in a wide range of unrelated plants? Do *P. indica* and *S. vermifera* use effector-like molecules in the form of small secreted proteins to manipulate different host plants and/or do they use other mechanisms, such as shielding themselves in place?
2. Which signals mediate the switch from the biotrophic to the cell-death-associated phase? And is this latter phase actively triggered by the fungus?
3. What are the basic events involved in the transition from saprotrophic to symbiotic lifestyles?

Imaging Platform Mass Spectrometry

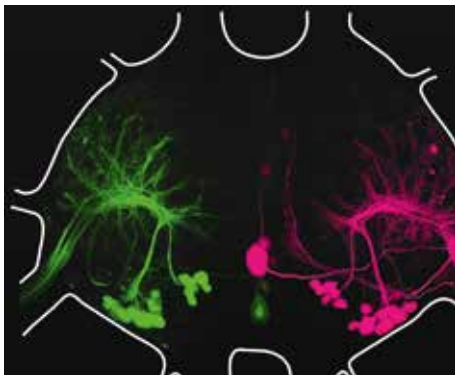
TECHNOLOGY PLATFORMS

Imaging Platform

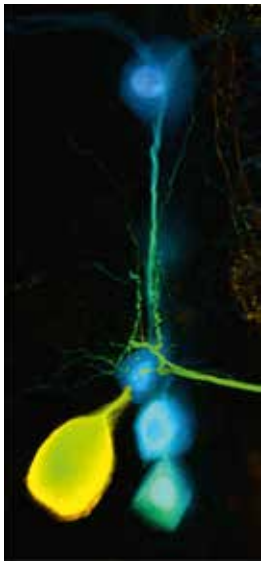
The imaging platform provides access and core competence to various fluorescence and electron microscopy techniques. After an introduction to the microscope of choice, the users have access to the platform and are encouraged to use it independently. The platform is located in the basement of the Biocenter. In addition to the microscopes, it offers space and equipment for specimen preparation, including a tissue-culture room with a clean-bench, CO_2 incubators and high-end dissecting microscopes. For image analysis, workstations are available. Booking of the appliances is facilitated through an on-campus booking system.



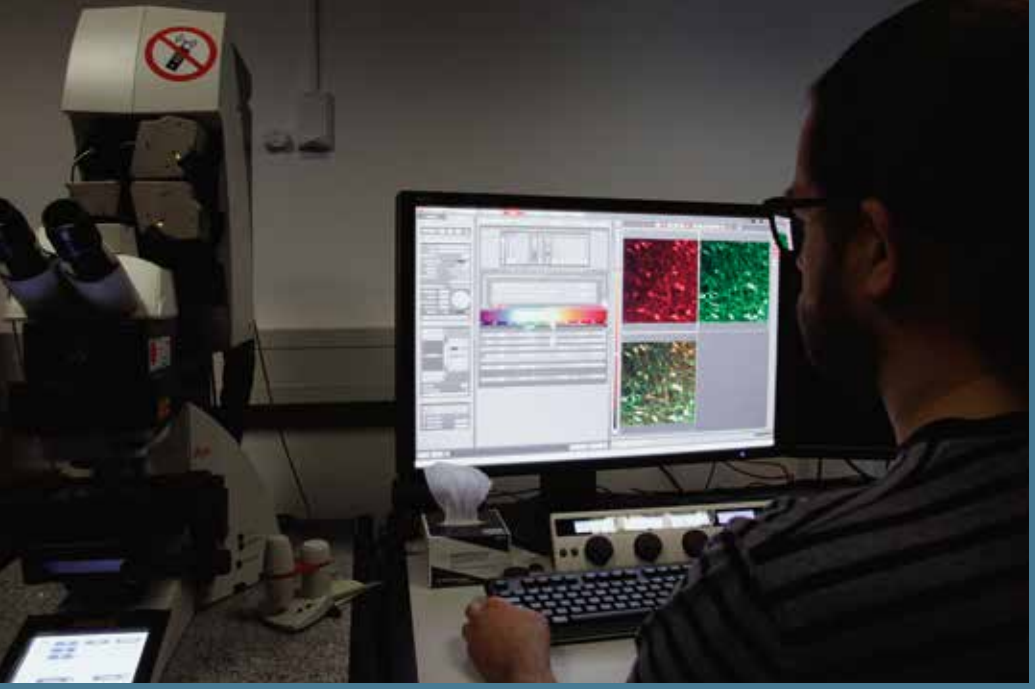
Co-localization of the endosome markers YFP-Lip5 (green) and VPS60.1-mCHERRY (red) in transiently transformed *Arabidopsis thaliana* epidermis cells.



Retrogradely labeled motor nerves in the mesothoracic ganglion of the stick insect.



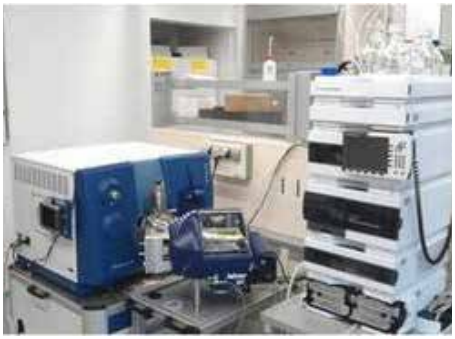
Depth-coded detail from retrogradely labeled neurons.



The following microscopes and facilities are currently available:

- Delta Vision RT
  (Restoration Imaging System)
- Leica TCS SP8
  (Laser Scanning Microscope)
- Olympus BX61
  (Wide Field Fluorescent Microscope)
- Zeiss LSM 510 Meta
  (Laser Scanning Microscope)
- FEI Quanta 250 FEG
  (Electron Scanning Microscope)
- Workstations for image analysis
- Tissue-culture lab for sample preparation

Biocenter Mass-Spectrometry Platform



The Biocenter Mass-Spectrometry Platform is a shared instrument facility with the aim to make mass spectrometry accessible to all interested researchers at the Cologne Biocenter and the Faculty of Mathematics and Natural Sciences.
We have instrumentation and expertise in multiple ionization techniques, including electrospray ionization (ESI), matrix-assisted laser desorption/ionization (MALDI) and (ICP). The combination with different analysis techniques such as time of flight (TOF), quadrupole, linear trap and orbitrap, allow a wide range of molecular structures to be investigated. The ESI instruments are equipped with LC or nano-LC, for sensitivity and chromatographic performance.

Currently, the platform consists of the following instruments:

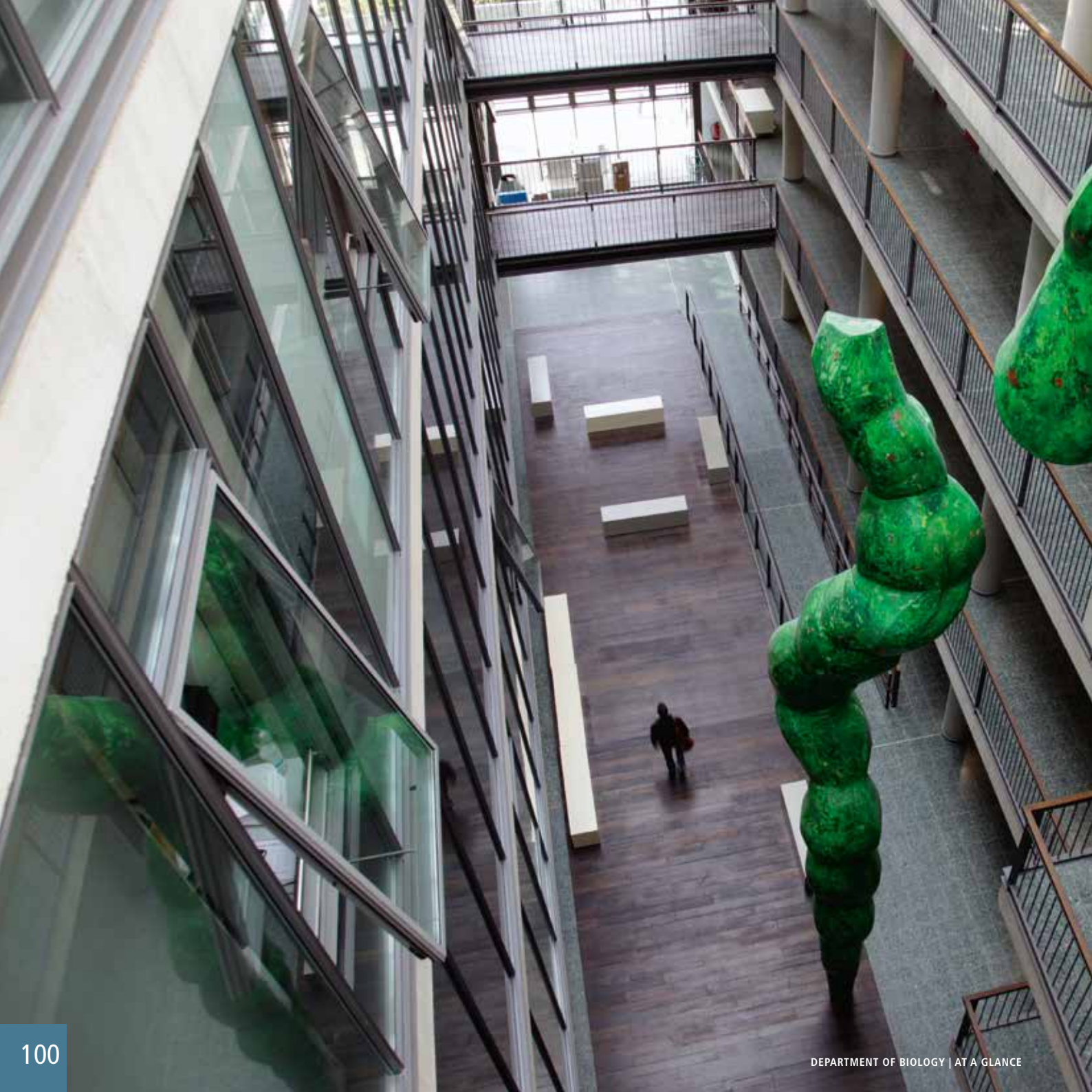
- Q Exactive (Thermo Scientific), an Orbitrap-based LC-MS system, provided by Prof. von Elert
- Maxis 4G (Bruker), an ESI-QqTOF system, provided by Prof. Bucher
- Qtrap 5500 (AB Sciex), a triple quadrupol linear ion trap system, provided by Prof. Bucher
- Ultraflextreme (Bruker), a MALDI-TOF instrument, provided by Prof. Predel
- Voyager (ABsciex), a MALDI-TOF instrument, provided by Prof. Predel
- Agilent 7700 (Agilent), an ICP mass spectrometer, provided by Prof. Bucher

With this variety of instrumentation, we are able to analyze a broad range of sample types and to use the best match between sample and mass spectrometer. The high-resolution mass spectrometers are designed for accurate mass measurement to confirm molecular formulae, to elucidate molecular structures or to identify unknown compounds (MS/MS mode). We also provide high-throughput quantification of small molecules.

The facility focuses on serving the needs of investigators at the Biocenter but we are also open to serve needs from outside the Biocenter and the University. If you are planning to submit samples or have questions regarding mass spectrometric analysis, please contact us.

The Biocenter MS platform is member of the DFG-accredited Core facilities in Germany and is supported by the Center of Excellence on Plant Sciences (CEPLAS).

http://www.biologie.uni-koeln.de/massenspektrometrie.html



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