


ABSTRACT BOOK

BIOLOGY CROSSROADS

7th International Symposium

CROSSROADS IN BIOLOGY

March 28 - 29, 2019

Cologne, Germany

7th International Symposium

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March 28 – 29, 2019
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WELCOME TO CROSSROADS IN BIOLOGY 2019!

Dear friends, dear students, dear colleagues,

we are happy to welcome you to the 7th Crossroads in Biology Symposium (CiB 2019) taking place from March 28 to 29, 2019 in Cologne, Germany.

The objective of this - more or less - biannual meeting is to bring together students and scientists from different academic levels and backgrounds. As the main goal is to foster strong interactions between students, postdocs, junior group leaders and internationally leading scientists, we cordially invite you to actively participate in this scientific “crossroad”. In a joint effort, we prepared a program that we believe will represent exciting state-of-the-art research and provide room for discussion in a multidisciplinary forum.

The CiB 2019 will cover the following topics:
Mitochondrial Biology, Regulation of Gene Expression, Cell Death & Disease and Drug Development.

This year, we are honored to host Prof. Werner Kühlbrandt, director of the Max Planck Institute of Biophysics in Frankfurt, as the keynote speaker of CiB 2019. Werner Kühlbrandt is a member of EMBO and the German National Academy of Science Leopoldina as well as various editorial boards, and his department focuses on deciphering the structure and function of membrane proteins and their complexes. By employing state-of-the-art techniques such as CryoEM and CryoET, his group has contributed immensely to the number of determined structures of membrane protein assemblies.

We are looking forward to fruitful discussions during the talks of our 13 renowned speakers and presentations of 26 posters. Finally, we wish all participants a not only scientifically, but also personally inspiring and memorable stay in Cologne!

Sincerely,
Your CiB Organizing Committee

Mihaela Bozukova, Kai Fiedler, Jennifer Gerbracht, Dieu Hien Ho, Chih-hsuan Hsin, Yvonne Lasarzewski, Hong Nhung Nguyen, Fabian Schorn, Britta Thewes, Julia Tschirka, Paul Werthenbach

CONFERENCE INFORMATION

VENUE
MTI building (Access via the CECAD building)
Medical Faculty (Building 44b)
University of Cologne
Joseph-Stelzmann-Str. 9
D-50931 Cologne

GENERAL INFORMATION
Please wear your name badge at all times during the symposium to simplify social interaction. Please indicate upon registration if you would like to receive a Certificate of Attendance. A digital certificate will be sent to you via e-mail a few days after the symposium. The venue has a cloak room available for participants to hang their jackets.

WiFi
Internet access via WLAN is free of charge in the MTI building at the SSID “eduroam”. For participants without eduroam access, please find a WLAN code in your bag for guest internet access of the University Hospital Cologne. This account is valid throughout the whole conference area and duration.

PRESENTATIONS
Presentations take place in the MTI main lecture hall. Please enter through the designated backstage doors when presentations have started in order not to disturb the speakers.

POSTER SESSION
The posters have to be set up until 14.30 p.m. on Thursday, March 28 and will be removed by us in the evening. The session itself will take place at 4.45 pm with an open end. Please find the number of your poster in this booklet and use the corresponding poster stand. Please use the mounting material provided by the organizers. The number will serve as an identification mark for our poster committee of selected junior group leaders to appoint the three most outstanding posters. All registered participants presenting a poster are eligible for the prize and must be available to present their poster to the jury. The poster prize awardees will be announced on Friday, March 29.

MEALS AND BEVERAGES

Thursday lunch (sandwiches, pretzels) will be provided by Kamps bakery and Friday lunch by the caterer Odenkirchen. Thursday's *Meet the Speakers* lunch will take place in a separate area. We tried to consider dietary restrictions that have been indicated in the registration forms.

TRAM AND BUS

Tram stations near the MTI lecture hall are 'Lindenburg/Universitätskliniken' for tram line 9 and 'Gleueler Str./Gürtel' for tram line 13. Line 9 with direction 'Königsforst' passes tram stop 'Neumarkt' from where you can switch to lines 16 or 18 to reach Cologne central station. Line 13 with direction 'Holweide' passes tram stop 'Venloer Str./Gürtel' where you can go to Ehrenfeld railway station.
The next bus stop is 'Lindenthal Geibelstr.' for bus line 146 with direction 'Neumarkt' driving to the city center passing 'Rudolfplatz' and 'Neumarkt'.

TAXI INFORMATION

Taxi Ruf Köln	0049-221-2882
Taxiunternehmen Affeldt	0049-221-99555615
Taxi17	0049-221-170000
TaxiKöln	0049-221-50070000

INSURANCE

The organizers are not liable for loss or damage of items of the wardrobe. For speakers and people who have travelled with luggage, a storage room will be available that will be locked. For this, please inquire the responsible person at the registration desk

PRIVACY PROTECTION STATEMENT (Datenschutz)

Please be aware that we will take photos and/or make films during the symposium that might be used to report about this event and for other non-commercial purposes (website, press release, print products, social media). If you disagree, please contact the photographers and/or filmmakers directly during the symposium.

We would like to thank to all our sponsors ...

... and supporters!

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09:15 - 09:30	**Opening remarks**

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10:00 - 10:30	**Jodi Nunnari** *University of California, USA* Mitochondrial Behavior
10:30 - 11:00	**Walter Neupert** *Max Planck Institute of Biochemistry, Germany* Molecular mechanisms of mitochondrial homeostasis
11:00 - 11:30	*Coffee break*
11:30 - 12:30	**Keynote Lecture** **Werner Kühlbrandt** *Max Planck Institute of Biophysics, Germany* Mechanistic insights from high-resolution cryoEM structures of ATP synthases
12:30	**Meet the Speakers***/ Lunch break*

Session II: Regulation of Gene Expression

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15:00 - 15:30	**Karsten Rippe** *University of Heidelberg, Germany* Linking aberrant chromatin features in leukemia to deregulated gene expression
15:30 - 16:00	*Coffee break*
16:00 - 16:30	**Steve Horvath** *University of California LA, USA* New Epigenetic Clocks
16:45 - 18:00	**Poster session**
18:00	**Welcome party**

FRIDAY 29 MARCH 2019

Session III: Cell Death & Disease

09:30 - 10:00	**Wendy Wei-Lynn Wong** *University of Zürich, Switzerland* Inhibitors of Apoptosis proteins in disease and inflammation
10:00 - 10:30	**Seamus Martin** *Trinity College Dublin, Ireland* Cell Stress and Inflammation
10:30 - 11:00	*Coffee break*
11:00 - 11:30	**Ivan Đikić** *Goethe University Frankfurt, Germany* Ubiquitination and Autophagy Networks in Health and Disease
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13:15	**Poster prize**

Session IV: Drug Development

13:30 - 14:00	**Zubida Al-Majdoub** *University of Manchester, UK* Global and Targeted Proteomics for Quantification of Human Blood-Brain Barrier Transporters in Health and in Dementia
14:00 - 14:30	**Mark Brönstrup** *Helmholtz Center for Infection Research, Germany* Metabolome-based studies on bacterial pathogens, antibiotics and their interplay
14:30 - 14:45	*Short coffee break*
14:45 - 15:15	**Jana Haase** *University of Dublin, Ireland* Molecular mechanisms of inflammation-induced depression – is anything “SERTain”?
15:30	**Closing remarks**

SPEAKERS

Werner Kühlbrandt
Max Planck Institute of Biophysics, Germany

Keynote lecture
11:30 a.m.
Thu, March 28

Werner Kühlbrandt studied chemistry and crystallography at the Free University Berlin, and biochemistry and biophysics at King's College London. He did his PhD with Nigel Unwin at the MRC Laboratory of Molecular Biology in Cambridge, UK, investigating the structure of two dimensional ribosome crystals by electron microscopy. He turned to structural studies of membrane proteins as a postdoc, first at the ETH Zürich, and then at Imperial College London. After a short stay at UC Berkeley, CA, he became a group leader at the EMBL Heidelberg in 1988. Since 1997 he is a director at the Max Planck Institute of Biophysics in Frankfurt, Germany, where his department of Structural Biology studies the structure and mechanisms of membrane proteins by X-ray and electron crystallography, single-particle cryo-EM, electron tomography and biophysical methods.

Mechanistic insights from high-resolution cryoEM structures of ATP synthases

With the ongoing resolution revolution in electron cryo-microscopy (cryoEM), large and dynamic membrane protein complexes have become accessible to high-resolution structural studies. We have used single-particle cryoEM to determine the structure of the complete, monomeric ATP synthase (cF_1F_o) from spinach chloroplasts at up to 2.9 Å, and of the dimeric mitochondrial F_1F_o ATP synthase (mtF_1F_o) from the green alga Polytomella at around 2.7 Å resolution. Bound nucleotides with their coordinating Mg ions and water molecules are resolved in cF_1. The two-domain subunit δ of cF_1F_o (OSCP in mitochondria) joins the three α-subunits of the F_1 head to the peripheral stalk in three different ways. Three resolved rotary states of cF_1F_o indicate that the peripheral stalk flexes to store torsional energy, whereas subunit γ of the central stalk works as a rigid body. In both mitochondria and chloroplasts, subunit a in the membrane-embedded F_o motor forms two aqueous channels to conduct protons to and from the protonation sites on the c-ring rotor that powers ATP generation. The channels and the polar and charged sidechains that define them in the hydrophobic membrane interior are conserved over an evolutionary distance of around 1.5 billion years. The F_o motor assembly with its hairpin of long, membrane-embedded subunit a helices adapts equally well to the 10-subunit c-ring of mtF_1F_o and the 14-subunit c-ring of cF_1F_o. Electron cryo-tomography of chloroplast thylakoids indicated that cF_1F_o is always monomeric, whereas all mtF_1F_o dimers form rows that impose high local membrane curvature on the inner membrane. When reconstituted into proteoliposomes, yeast and Polytomella ATP synthase dimers assemble into rows spontaneously, inducing high local membrane curvature as in mitochondria.

Notes

Alexey Amunts
University of Stockholm, Sweden

Session I: Mitochondrial Biology
9:30 a.m.
Thu, March 28

Our research group investigates the fundamental question of how proteins are synthesized, folded and assembled into functional multicomponent membrane complexes that drive the cellular energy production. To dissect the mechanism and dynamics of translation, membrane insertion and bioenergetics in mitochondria and chloroplast, we use cryo-EM.

Crossroads in mitochondrial Biology

Our group determined cryo-EM structures of the human mitoribosome with mRNA, tRNAs and translation activators in 8 different functional states, as well as its assembly intermediates. We also determined the complete atomic model of a mitochondrial ATP synthase and unusual type of a plant Photosystem I.

These studies showed that macromolecular machineries in organelles have adopted intricate compositions and unique tasks, adding incredible complexity to the records. The achieved understanding of the architecture of these specialized systems provides now a framework to study even more sophisticated questions regarding the assembly and evolution mechanisms of the critical bioenergetic membranes that fuel life.

Notes

Jodi Nunnari

University of California Davis, USA

Session I: Mitochondrial Biology

10:00 a.m.

Thu, March 28

Jodi Nunnari is a pioneer in the field of mitochondrial biology. She was the first to describe the organelle as a dynamic network in homeostatic balance and decipher the mechanisms of the machines responsible for mitochondrial division and fusion. Nunnari was born and raised in Cleveland, Ohio, and studied chemistry at the College of Wooster before attaining a Ph.D. in pharmacology fromVanderbilt University. She was a postdoctoral fellow with Peter Walter at the University of California, San Francisco and joined the faculty at the University of California, Davis in The College of Biological Science in The Department of Molecular and Cellular Biology in 1996. Nunnari was named Editor-in-Chief of The Journal of Cell Biology in 2015, becoming the first woman to serve in this position. She is a member of the the American Society for Cell Biology, and served as the Society's president in 2018. In 2017, Nunnari was elected as a member of the National Academy of Sciences.

Mitochondrial Behavior

The focus of my group is to uncover the biology and roles of mitochondria in cellular homeostasis. Mitochondria perform fundamental functions in eukaryotic cells, including ATP production via respiration and cellular ion and phospholipid homeostasis. They also serve as platforms to integrate signaling pathways such as cell death and innate immunity. Work in my lab has established that mitochondrial functions are tightly linked to mitochondrial form and behavior, controlled by separate, but somehow coordinated machines that control mitochondrial dynamics, positioning, motility and mitochondrial DNA transmission. We have also addressed the fundamental question of how mitochondrial membranes are sub-compartmentalized to reveal the basis of the complex internal architecture of the organelle. More recently our work has implicated the endoplasmic reticulum (ER) as an integral and pervasive player in the regulation of mitochondrial form and function, which exerts its role through intimate contacts with mitochondria and other organelles, such as the lysosome. In this proposal, we explore the fundamental roles and modes of action of ER-mitochondria contact sites. By addressing the fundamental mechanisms governing mitochondrial behavior, we will illuminate how they contribute to pathogenesis.

Notes

Jan Riemer
University of Cologne, Germany

Session I: Mitochondrial Biology
10:30 a.m.
Thu, March 28

Jan Riemer studied biochemistry at the University of Tübingen, Germany. He obtained his PhD at the ETH Zurich, Switzerland, and the University of Copenhagen, Denmark, with Lars Ellgaard and Ari Helenius. After a PostDoc at the University of Copenhagen, Riemer first became a senior scientist and later an independent group leader and junior professor, both at TU Kaiserslautern, Germany. Since 2015, Riemer is a professor for Biochemistry at the University of Cologne, Germany. His lab focuses on redox regulation, oxidative folding and the regulation of mitochondrial protein import.

Cytosolic Regulation of Mitochondrial Biogenesis

(Kindly substitutes for Walter Neupert)

Notes

Stefan Ameres
Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Austria

Session II: Regulation of Gene Expression
14:30 p.m.
Thu, March 28

Stefan L. Ameres earned his Master's degree in Biology at the Friedrich-Alexander University Erlangen-Nuremberg (Germany), and his PhD degree at the University of Vienna (Austria). In his award-winning PhD thesis, he reported the first in-depth enzymatic characterization of the human RNA interference effector complex. After his postdoctoral studies at the University of Massachusetts Medical School (Worcester, MA, USA), he joined IMBA as a group leader in 2012. For his innovative studies on fundamental biological mechanisms of gene regulation, Stefan Ameres received several awards, including the Houska Award and the Research Award for Young Scientists (Austrian Assoc. for Genetics and Genetechnology), and he obtained a Starting and Proof-of-Concept grant from the European Research Council (ERC) and a START grant from the Austrian Science Fund (FWF). He is member of the EMBO Young Investigator Program and the Austrian Academy of Sciences (Young Academy).

Mechanism and Biology of RNA Silencing (EMBO Young Investigator Lecture)

Notes

Karsten Rippe
German Cancer Research Center (DKFZ) and Bioquant, Division of Chromatin Networks, Germany

Session II: Regulation of Gene Expression

15:00 p.m.

Thu, March 28

Linking aberrant chromatin features in leukemia to deregulated gene expression

It is now well established that ‘active’ or ‘repressive’ chromatin states with distinct histone modifications and DNA methylation marks are tightly linked to cell type specific gene expression patterns. In cancer cells the underlying networks are frequently deregulated. However, linking the resulting aberrant chromatin features to the pathophenotype is challenging. We are dissecting deregulated epigenetic signaling in primary tumor cells from patients with leukemia to address this question. It is discussed howcancer specific chromatin patterns can be exploited for novel patient stratification schemes and linked to deregulated transcription and signaling pathways.

Notes

Steve Horvath

Human Genetics and Biostatistics David Geffen School of Medicine, University of California, Los Angeles, USA

Session II: Regulation of Gene Expression

16:00 p.m.

Thu, March 28

Dr. Horvath's research lies at the intersection of aging research, epidemiology, chronic diseases, epigenetics, genetics, and systems biology. He works on all aspects of biomarker development with a particular focus on genomic biomarkers of aging. He developed a highly accurate multi-tissue biomarker of aging known as the epigenetic clock. Dr Horvath developed systems biologic approaches such as weighted gene co-expression network analysis which lend themselves for integrating gene genomic data sets. These methods have been used for a broad spectrum of age related diseases including neurodegenerative diseases, cancer, cardiovascular disease. Dr. Horvath received a Ph.D. in Mathematics from the University of North Carolina, Chapel Hill in 1995 and a Doctorate of Science in Biostatistics from the Harvard School of Public Health in 2000.

New Epigenetic Clocks

DNA methylation based biomarkers of aging known as collectively as "epigenetic clock" can be used to measure the age of any human or chimpanzee tissue, cell type, or fluid that contains DNA. DNA methylation age captures aspects of biological age. The skin & blood clock (based on 391 CpGs) is tailor-made for human fibroblasts, keratinocytes, buccal cells, endothelial cells, lymphoblastoid cells, skin, blood, and saliva samples. Gestational age correlates with DNAm age in cord blood. When used on fibroblasts from Hutchinson Gilford Progeria Syndrome patients, this age estimator (referred to as the skin & blood clock) uncovered an epigenetic age acceleration with a magnitude that is below the sensitivity levels of other DNAm-based biomarkers. Arguably the strongest predictor of lifespan, DNAm GrimAge, is a composite biomarker based on seven DNAm surrogates of plasma protein levels and a DNAm-based estimator of smoking pack-years. Using large-scale validation data from thousands of individuals, we demonstrated that DNAm GrimAge stands out among existing epigenetic clocks in terms of its predictive ability for time-to-death (P=2.0E-75), time-to-coronary heart disease (P=6.2E-24), time-to-cancer (P=1.3E-12), its strong relationship with computed tomography for fatty liver/excess visceral fat, and age-at-menopause (P=1.6E-12). Overall, these epigenetic biomarkers are expected to find many applications including human anti-aging studies.

Notes

Wendy Wei-Lynn Wong
University of Zurich, Switzerland

Session III: Cell Death & Disease
9:30 a.m.
Fri, March 29

Our laboratory investigates how cell death proteins may regulate signaling downstream of TNFR2 in different stromal and immune compartments. In particular, we investigate the effect of targeting cell death proteins will have in tumor extravasation, endothelial cell permeability and immune cell differentiation and function. We anticipate the molecular understanding of how and when cell death proteins directly regulate inflammation will lead to novel targets in reducing acute or chronic inflammation.

Inhibitors of Apoptosis proteins in disease and inflammation

Recent data suggests that LPS stimulation can trigger inflammasome activation through a TNFR2/TNF/TNFR1 mediated loop in xiap-/- macrophages. Yet, the direct role TNFR2-specific activation plays in the absence of XIAP is unknown. We found TNFR2-specific activation lead to cell death in xiap-/- myeloid cells, particularly in the absence the RING domain. RIPK1/TAK1 kinase activity downstream of TNFR2 resulted in a TNF/TNFR1 cell death independent of necroptosis. TNFR2-specific activation lead to a similar inflammatory NF-kB driven transcriptional profile as TNFR1 activation with the exception of up-regulation of NLRP3 and caspase-11. Activation and up-regulation of the canonical inflammasome was mediated by RIPK1 kinase activity and ROS production. While both RIPK1 kinase activity and ROS production reduced cell death as well as release of IL-1β, the release of IL-18 was not reduced to basal levels. This study supports, targeting TNFR2 specifically toreduce IL-18 release in XIAP deficient (XLP-2) patients.

Notes

Seamus Martin

Trinity College Dublin, Ireland

Session III: Cell Death & Disease

10:00 a.m.

Fri, March 29

Cell Stress and Inflammation

Seamus Martin is the Smurfit Chair of Molecular Genetics (since 1999) at The Smurfit Institute of Genetics, Trinity College Dublin, Ireland. He is a PhD graduate of the National University of Ireland and was a post-doc with Ivan Roitt at University College London, and then with Doug Green at La Jolla, California. His lab is interested in the interplay between signals for cell death and inflammation. We are currently interested in how IL-1 family cytokines become processed, activated and released and the role of the latter cytokines as canonical DAMPs. We are also interested in when and how Fas and TRAIL promote inflammation and how cell stress-induced inflammation is initiated. Seamus was elected to The Royal Irish Academy of Sciences in 2006, to the European Molecular Biology Organization (EMBO) in 2009 and served as President of the European Cell Death Organization (ECDO) from 2016-2018. He is an author of the 11th, 12th and 13th Editions of 'Essential Immunology'and is Editor-in-Chief of The FEBS Journal (since 2014).

Notes

Ivan Đikić

Goethe University Frankfurt, Germany

Session III: Cell Death & Disease
11:00 a.m.
Fri, March 29

Ivan explores molecular mechanisms of cellular signalling, which have a high relevance to human diseases such as cancer, neurodegenerative disorders and inflammation. Early on, he started to focus on ubiquitin to understand how this modification regulates a large variety of physiological and pathophysiological processes. He established a novel concept of ubiquitin signal recognition by specialized domains serving as ubiquitin receptors. His group demonstrated how multiple monoubiquitination controls EGFR endocytosis and cloned several ubiquitin receptors, which regulate DNA repair, inflammation, cancer, infection and proteasomal degradation. In addition, his team has revealed the functions of linear ubiquitin chains in promoting the NF-kB pathway, thereby impacting on pathogen defenses and other immune responses. Recently, he described the chemistry of a novel type of ubiquitination that is utilized by the bacterial pathogen Legionella to control multiple cellular processes. One of his current major interests lies in selective autophagy, which is essential for the clearance of protein aggregates, pathogens and damaged organelles from the cell. His team has provided important mechanistic insight in the regulatory networks and the structures controlling mitophagy, xenophagy and ER-phagy, shaping host-pathogen interactions and

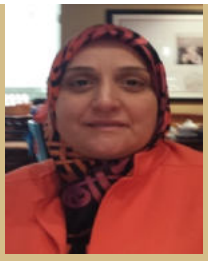
Endoplasmic reticulum turnover via selective autophagy

The endoplasmic reticulum (ER) is the largest intracellular endomembrane system enabling synthesis and transport of cellular components. Constant ER turnover is needed to meet different cellular requirements and autophagy plays an important role in this process. In mammalian cells the ER is degraded via a selective autophagy pathway (called ER-phagy), mediated by specific ER-resident proteins that interacts with LC3, via conserved LC3-interacting region (LIR). Reticulon-type protein FAM134B is responsible for the turnover of ER sheets as its overexpression stimulates ER fragmentation and delivery to lysosomes via the autophagy pathway. Conversely, blockade of autophagy or depletion of FAM134B triggers a marked increase in the ER volume. Mutations of FAM134B in humans are unable to act as ER-phagy receptors and cause sensory neurodegeneration. We have recently identified full length reticulon 3 (RTN3) as a specific receptor for the degradation of ER tubules. The major questions we are exploring at the moment deal with the action of reticulone domains in banding the membranes and the regulatory mechanisms of a family of co-receptors that assist FAM134B or RTN3 proteins in selecting the appropriate cargoes during the ER-phagy process. Taken together, ER-phagy possesses the potential to remodel or rebalance the entire ER network and – given the physical and functional connection of ER to other organelles inside the cell – ER-

impacting on the development of neurodegenerative diseases like ALS.

phagy might also impact the function of other organelles as well.

Notes



Zubida Al-Majdoub
University of Manchester, UK

Session IV: Drug Development
13:30 p.m.
Fri, March 29

Zubida Al-Majdoub has performed her undergraduate studies in Tripoli University, Libya and worked there as Teaching Assistant. She has completed her MPhil in Medicinal Chemistry from School of Pharmacy, University of Manchester, followed by a PhD in Quantitative Proteomics under the supervision of Professor Simon Gaskell and Dr. Jill Barber.

Today she is a Research Associate in the group of Professor Amin Rostami-Hodjegan in Division of Pharmacy & Optometryat at the University of Manchester. Her research work focus is global and targeted proteomics for quantification of human transporters.

Global and Targeted Proteomics for Quantification of Human Blood-Brain Barrier Transporters in Health and in Dementia

The blood-brain-barrier (BBB) remains a focal point of interest for many scientists who are working on approaches to deliver various therapeutic agents into the brain. Alterations to BBB proteins can lead to changes in brain function affecting the susceptibility of the CNS to exposure to xenobiotics in the systemic circulation. Zubida's research focused on the quantification of transporters, enzymes and other proteins at BBB and measurement protein content of the microvascular fraction to populate PBPK model predicting drug disposition and the potential differences in health and disease.

Notes

Mark Brönstrup
Helmholtz Center for Infection Research, Germany

Session IV: Drug Development
14:00 p.m.
Fri, March 29

Mark did his doctoral thesis in Organometallic Chemistry in the Gas Phase (with Prof. Dr. Drs. h.c. Helmut Schwarz) at the TU Berlin. He later became laboratory head for mass spectrometry at the Aventis Department of Chemistry in Frankfurt. Since 2014 Mark is Head of Department for Chemical Biology at the Helmholtz Centre for Infection Research, Braunschweig, and W3 professor at Leibniz University of Hannover. His research interests are the antibacterial and antiviral drug discovery with a focus on natural product-derived lead optimization as well as antibacterial drug conjugates. Moreover, he leads mode of action studies through metabonomics, intracellular drug quantification, peptide arrays, chemical pulldown experiments, pattern matching techniques (imaging, impedance measurements), including analytical method development.

Induction and quantification of drug uptake into Gram-negative bacteria

Infections caused by pathogenic bacteria represent a major health threat that is expected to rise further in the future. The need for novel antibiotics is currently not met by R&D efforts, in particular in the area of infections caused by Gram-negative bacteria. A main scientific hurdle is the lack of understanding how to assure a sufficient translocation of bioactive molecules across the Gram-negative cell wall.

A lead finding strategy with proven track record focuses on natural products from microorganisms that have solved the penetration problem in an evolutionary process. The cystobactamids, gyrase inhibitors isolated from Cystobacter sp., represent a novel lead series with an unusual structure composed of PABA oligomers and potent, broad spectrum activity against Gram negative bacteria. We will report three modular synthesis to cystobactamid analogs, and their application to generate (i) probes for cellular biology research and (ii) analogs with improved antibacterial properties and in vivoefficacy.

In an alternative lead finding strategy, our efforts to induce an active transport of small molecules into Gram negative bacteria will be presented. We report the design, synthesis and characterization of a series of theranostics agents based on 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid amide (DOTAM) derivatives,[4] comprising siderophores that are internalized into Gram negative bacteria, inhibit bacterial growth and demonstrate efficacy to visualize bacterial infections in mice by optical imaging in vivo. In addition, three orthogonal approaches (growth recovery, FAP, fractionation coupled to LC/MS/MS) to quantify the intracellular accumulation of such conjugates will be presented.

Notes

Jana Haase
University of Dublin, Ireland

Session IV: Drug Development
14:45 p.m.
Fri, March 29

Jana Haase obtained her PhD from the Max-Planck-Institute for Molecular Genetics and the Free University Berlin. Following a period of postdoctoral research at Trinity College Dublin, she took up her current position at University College Dublin in 2003. The main theme in her research group is the regulation of neurotransmitter systems under physiological and pathological conditions, with a particular focus on the serotonergic system and its relevance to mood disorders as well as the mechanism of action of antidepressant drugs and psychostimulants. Over the past few years the group has been studying various aspects of serotonin transporter (SERT) regulation, including protein-lipid and protein-protein interactions. More recently, the main focus of her research has been the regulation of SERT in response to immune system activation, using both in vitro and in vivo approaches, including animal models relevant to human disease.

Molecular mechanisms of inflammation-induced depression – is anything "SERTain"?

The serotonin transporter (SERT) facilitates high affinity reuptake of the neurotransmitter serotonin from the extracellular fluid and dysregulation of transporter function has been implicated in a range of mood disorders including depression. Over the past few years, a number of studies have linked immune system activation to depression as well as to altered serotonin transporter activity. Advancing previous studies which focussed on acute effects of immune system activation, we used collagen-induced arthritis (CIA) in mice as a model of chronic inflammatory disease, to investigate the effect of prolonged inflammation on brain SERT function and behaviour. We found that CIA mice display anhedonia, a core depression-like behaviour. Moreover, behavioural symptoms are temporally correlated with a region-specific upregulation of SERT activity in the hippocampus which occurs at a post-translational level and is independent of SERT trafficking. Further analysis shows that tumour necrosis factor (TNF) αand its receptor (TNFR1) were specifically upregulated in the hippocampus of CIA mice, indicating altered TNFα signalling in this brain region. Anti-TNFα treatment using etanercept not only diminished joint inflammation, but also prevented the development of depression-like behaviour and the upregulation of SERT activity in the hippocampus, suggesting a key role for TNFα signalling in brain function regulation in this disease model. Current investigations in our lab are focused on understanding molecular determinants of sex differences in behavioural and neurochemical phenotypes in CIA mice. In summary, our study provides novel insight into molecular mechanisms underlying comorbid depression in chronic inflammatory diseases.

Notes

POSTER ABSTRACTS

1 Differential contribution of Tau isoforms to neuronal plasticity in health and disease

Bachmann, S.[1,2], Bell, M.[1,2] and Zempel, H.[1,2]

[1] *Center for Molecular Medicine Cologne,*
[2] *Institute of Human Genetics, University Hospital Cologne*

Over 50 years of research have provided insights into the pathology of neurodegenerative diseases, like Alzheimer Disease and Frontotemporal Dementia. One hallmark of these diseases is the accumulation of hyperphosphorylated tau in the somatodendritic compartment of neurons. Tau is crucial to maintain neuronal function, as it is involved in processes like neuronal differentiation and synapse formation. Recent results suggest differential roles for the six human brain-specific isoforms in synaptic functions and in tau-mediated neurotoxicity. In addition, the isoforms vary in their intracellular distribution and in their expression between distinct brain regions. To investigate the differential role of the isoforms to neuronal dysfunction, this project will characterize the isoforms in regard to their function in microtubule stability, spine formation and mediation of neuronal dysfunction in suitable model systems, such as human neurons derived from induced pluripotent stem cells. Furthermore, the influence of tau on neuronal subtypes and their susceptibility to tau toxicity will be investigated with state-of-the-art genetic and cell biological methods. Expected results will provide a major understanding of basic biological functions of tau isoforms in health and disease and identify potential therapeutic targets for the treatment of Alzheimer Disease and related Tauopathies.

2 CLEC3A: A Cartilage-specific Bacterial Killer

Dzemal Elezagic

Septic arthritis is a severe inflammatory disease of cartilage which leads to rapid joint destruction. A major risk factor for septic arthritis is arthroplasty. Arthroplasties are commonly performed procedures and up to 2% of them are estimated to result in septic arthritis. An important factor contributing to the severity of the disease is cartilage's limited cellular immune response. The expression of ubiquitous antimicrobial peptides (AMPs) in cartilage has been described to be an alternative immune response. However, AMPs specifically expressed in cartilage have so far not been identified. The cartilage-specific C-type lectin domain family 3 member A (CLEC3A) exhibits structural similarities to AMPs and is highly susceptible to proteolytic cleavage. We detected fragmentation of CLEC3A in human cartilage and proteolytic cleavage of the protein after incubation with P.aeruginosa culture supernatants. This prompted us to investigate the antimicrobial activity of CLEC3A. Peptides of CLEC3A indeed lead to killing of Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus, the most common septic arthritis-causing pathogen. Furthermore, the peptides permeabilized bacterial membranes and bound lipopolysaccharide on membranes of Gram-negative bacteria. In an attempt to address the problem of arthroplasty-associated infections, we coated chimeric CLEC3A-peptides on titanium, a common joint prostheses material. Bacterial adhesion was significantly reduced by coating the titanium substrates with CLEC3A-peptides. Moreover, microbicidal concentrations of CLEC3A peptides showed no cytotoxicity against primary human chondrocytes. Taken together, we here for the first time identify cartilage-specific AMPs, shed light on their mechanism of action and assess their potential application in the prevention and treatment of cartilage infection.

3 Is there a clinical relevance of T- and B-cell activity for cognition and behavior in epilepsy patients with evident or suggested limbic encephalitis?

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Cognitive and behavioral impairments are major symptoms of limbic encephalitis. They are relevant for the diagnosis of LE and for the monitoring of the disease and its treatment. LE can be grossly differentiated into forms with autoantibodies against cell surface antigens and intracellular antigens. A still open question is that of the role of T-cell and B-cell activity in regard to cognitive impairment. 136 patients with late and recent onset temporal lobe epilepsies of possible autoimmune etiology were analyzed in regard to memory, executive functions, and depression in relation to the presence or absence of known and non-specific antibodies and in regard to T- and B-cell activity as assessed by flow cytometry (FACS, peripheral blood and CSF). All patients were tested in regard to executive functions (EpiTrack), memory (verbal VLMT and figural DCS-R), and depression (BDI-I). Data were analyzed by means of a stepwise hierarchical regression analysis taking demographic, clinical, antibodies, and T- and B-cell activity from FACS analysis as potential predictors. 43% of the patients were completely antibody negative, 13% were GAD65, 18% oncological, 4% VGKC/NMDA-R, and 22% non-specifically antibody positive. Apart from the fact that more males than females were in the GAD65 and non-specifically positive group, the groups did not differ in regard to demographic or disease parameters. CD4+ T cells were more prominent in GAD and oncological positive patients, CD8+ T cells in the GAD and non-specific group. Multiple regression analysis indicated a role of education, antiepileptic drug load, amygdala and/or hippocampal pathology, and CD4+ T cells in CSF in verbal memory and executive functions. Depression and figural memory were not related to FACS results. The results thus demonstrate a significant impact of T-cell activity on verbal memory and executive functions in patients with evident and suggested limbic encephalitis

4 Role of endothelial cell death in sepsis progression

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Endothelial dysfunction plays a key role in sepsis progression from systemic inflammatory response syndrome (SIRS) to septic shock and eventually leading to death due to multiple organ failure. Compromised endothelial functions due to shedding of endothelial glycocalyx, loss of thromboresistance, and deregulated endothelium-dependent vasotone regulation as well as sustained endothelial activation are widely discussed as the causes of sepsis progression. However, the role of endothelial cell death and their cell death regulators involved during sepsis are unclear. Here we have studied the programmed cell death (PCD) pathways that are involved in EC death and its impact on sepsis progression. In our study, we have identified that ECs majorly undergo necroptosis during LPS-induced severe sepsis in lungs. Higher degree of necroptosis was found in severely hypothermic and hypotensive mice. In vitro, we found increased necroptosis in LPS treated ECs, upon siRNA mediated knockdown of a key death regulator TGF beta activated kinase 1 (TAK1) compared to LPS-treated control groups. Hence, we studied sepsis progression in endothelial specific TAK1 deleted (Tie2CreERT2;TAK1fl/fl) mice (TAK1ECKO). TAK1ECKO mice showed accelerated sepsis progression due altered cytokine profile and acute respiratory distress syndrome (ARDS). This accelerated progression of sepsis however was rescued in endothelial-specific double knockout of TAK1 and Receptor interacting protein kinase 3 (RIPK3), which is an integral component of the necrosome complex. Our data indicates increased endothelial necroptosis contributes to sustained inflammatory activation and alters cytokine profile which can accelerate sepsis progression and mortality. Biomarkers of endothelial necroptosis thus could have prognostic potential.

5 Mechanism of UHRF1 intracellular regulation by TIP60

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UHRF1 (Ubiquitin-like containing PHD and RING finger domains 1) and TIP60 (Tat-interacting protein of 60 kDa) are believed to be present in the same epigenetic complex and together they take part in variety of activities like DNA methylation, chromatin remodeling, cell cycle and DNA damage repair [1]. UHRF1 has high expression levels in many cancers and it promotes cellular proliferation [2]. TIP60 belongs to MYST family and maintains the genomic stability and suppresses tumorigenesis [1]. The aim of this study was to investigate the relationship between UHRF1 and TIP60 proteins. Our results showed that UHRF1 directly interacts with the MYST domain of TIP60 and increasing the levels of TIP60 leads to down regulation of UHRF1 and DNMT1 in cancer cells [1]. We also observed that higher levels of TIP60 decreases the association of UHRF1 with USP7 (ubiquitin-specific peptidase 7) and promotes degradation of UHRF1by proteasomal pathway. This suggests a regulatory role of TIP60 in maintaining an optimal level of UHRF1in normal cells which can be explored later to target high levels of UHRF1 in tumors for anticancer therapy.

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6 Loss of genomic integrity by lysosphingolipid imbalance drives ageing in the heart

Yao Wenjie

Loss of genomic integrity induced by lysosphingolipid imbalance drives ageing in the heart Cardiac dysfunctions dramatically increase with age. Revealing a currently unknown contributor to cardiac ageing, we report the age-dependent, cardiac-specific accumulation of the lysosphingolipid sphinganine (dihydrosphingosine, DHS) as an evolutionarily conserved hallmark of the aged vertebrate heart. Mechanistically, the DHS-derivative sphinganine-1-phosphate (DHS1P) directly inhibits HDAC1, causing an aberrant elevation in histone acetylation and transcription levels, leading to DNA damage. Accordingly, the pharmacological interventions preventing (a) the accumulation of DHS1P using SPHK2 inhibitors; (b) the aberrant increase in histone acetylation using histone acetyltransferase (HAT) inhibitors; (c) the DHS1P-dependent increase in transcription using an RNA polymerase II inhibitor, blocks DHS-induced DNA damage in human cardiomyocytes. Importantly, an increase in DHS levels in the hearts of healthy young adult mice leads to an impairment in cardiac functionality indicated by a significant reduction in left ventricular fractional shortening and ejection fraction, mimicking the functional deterioration of aged hearts. These molecular and functional defects can be partially prevented in vivo using HAT inhibitors. Together, we report an evolutionarily conserved mechanism by which increased DHS levels drive the decline in cardiac health.

7 Cellular changes during diapause in Daphnia resting embryos

Luxi Chen

Diapause is a form of dormancy, predetermined by the genotype allowing animals to overcome harsh environmental conditions. During the phase of apparent death, development, growth and metabolic activity are depressed until distinctive environmental cues signal favorable living conditions. Metabolic depression during diapause is quite challenging for cells, as they must maintain their viability at reduced energy flows. However, the mechanisms that control halted development during diapause have not been thoroughly described. We investigated diapause related changes on the cellular level in diapausing and non-diapausing Daphnia magna embryos. Using (immuno-)fluorescent labeling, we observed the expressions of cell cycle associated proteins, nucleolar proteins, cytoskeletal proteins, and histone proteins. We also quantified the expression patterns of associated genes with the help of qPCR. We found that, the cytoskeleton is gradually reduced to a minimum, rendering diapausing cells compact and condensed. Accompanied by a downregulation of the proliferating cell nuclear antigen (PCNA), the mitotic activity is brought to a halt during diapause. We speculate that the expressions of modified histone proteins points to a decline in DNA transcription during diapause. At the same time, we observe that the diapausing cells still maintain their nucleoli, which may indicate ongoing RNA translation. In this context we found high levels of 18S mRNA and the nucleolar protein fibrillarin in diapausing cells. Our results suggest that cells in diapause have evolved some unique strategies that allow long-term suspended animation maintaining the capacity of resurrection.

8 Transcriptomics suggest that photosymbiont recognition in cnidarians and sacoglossans depends on pattern recognition receptors (PRRs)

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Among metazoans, many phyla are able to associate with photosynthetic organisms and are thus benefiting passively from photosynthesis. In sea slugs (Gastropoda), the animal host either forms a symbiosis with unicellular algae, usually Symbiodinium (Nudibranchia-Dinoflagellates), or retains only the chloroplasts of its food resource (Sacoglossa) - a process known as functional kleptoplasty. The cellular and molecular mechanisms behind the establishment and the maintenance of the symbiosis and chloroplast retention remain largely unknown in these mollusks. In cnidarians, however, it is commonly accepted that proteins involved in immune response, known as pattern recognition receptors (PRRs), such as scavenger receptors and thrombospondins, are involved in the recognition of the symbiont, and hence, in the establishment of the symbiosis. For the sacoglossan sea slug Elysia chlorotica, the role of PRRs in chloroplasts incorporation has been recently suggested, but detailed analyses for this species and other sea slugs information on PRRs are absent. We studied the gene expression profiles of three Sacoglossan species Elysia cornigera, Elysia timida (both starving), and Elysia chlorotica (feeding) and compared them to the gene expression in cnidarians that were introduced to Symbiodinium after a bleaching event. Our results show that the general expression profile among the different taxa and conditions are similar, but the expression of specific PRRs differs. These findings contribute to understanding the genomic basis involved in the establishment of the photosymbiosis in cnidarians and the chloroplast retention in sacoglossans.

9 yylncT Defines a Class of Divergently Transcribed lncRNAs and Safeguards the T-mediated Mesodermal Commitment of Human PSCs

Stefan Frank, Gaurav Ahuja, Deniz Bartsch, Nicole Russ, Wenjie Yao, Vijay Suresh Akhade, Yulia Kargapolova, Theodore Georgomanolis, Jan-Erik Messling, Marie Gramm, Lilija Brant, Rizwan Rehimi, Natalia Emilse Vargas, Alina Kuroczik, Tsun-PoYang, Raja Ghazanfar Ali Sahito, Julia Franzen, Juergen Hescheler, Agapios Sachinidis, Martin Peifer, Alvaro Rada-Iglesias, Meena Kanduri, Ivan G. Costa, Chandrasekhar Kanduri, Argyris Papantonis, Leo Kurian

Human protein-coding genes are often accompanied by divergently transcribed non-coding RNAs whose functions, especially in cell-fate decisions, are poorly understood. Using an hESC-based cardiac differentiation model, we define a class of divergent lncRNAs, termed yin yang lncRNAs (yylncRNAs), that mirror the cell-type-specific expression pattern of their protein-coding counterparts. yylncRNAs are preferentially encoded from the genomic loci of key developmental cell fate regulators. Most yylncRNAs are spliced polyadenylated transcripts showing comparable expression patterns in vivo in mouse and in human embryos. Signifying their developmental function, the key mesoderm specifier BRACHYURY (T) is accompanied by yylncT, which localizes to the active T locus during mesoderm commitment. yylncT binds the de novo DNA methyltransferase DNMT3B, and its transcript is required for activation of the T locus, with yylncT depletion specifically abolishing mesodermal commitment. Collectively, we report a lncRNA-mediated regulatory layer safeguarding embryonic cell fate transitions.

10 DNA uptake during bacterial transformation – testing predictions of a translocation ratchet model

Sebastian Kraus and Berenike Maier

Institute for Biological Physics

Transformation is a wide spread and conserved mechanism of horizontal gene transfer. The inheritable integration of extracellular DNA into the genome contributes to bacterial evolution and the spread of antibiotic resistance. Neisseria gonorrhoeae is naturally competent for transformation. We investigate the molecular mechanism driving DNA uptake from the environment into the periplasm. Previously our group showed using single molecule assays with laser tweezers, that the velocity-force relation of periplasmic DNA uptake is in a good agreement with a translocation ratchet model. Therein, movement of DNA within the membrane pore is driven by Brownian motion. The binding energy of the ComE chaperones to DNA drive DNA movement into the periplasm. To test whether the model fits a broad range of binding constants, we inserted point mutations into the comE sequence. DNA uptake events were recorded for comE overexpressing (OE) strain and mutation R71A but not for mutation K63A. We found that comE (OE) and R71A had no effect on transformation efficiencies compared to WT, whereas K63A showed transformation efficiencies comparable to ΔcomE1234. DNA uptake assays with fluorescently labeled DNA showed four times higher fluorescence intensities (FI) of comE OE related to WT and R71A. K63A FI was comparable to ΔcomE1234, in agreement with single molecule assays. Currently, we are characterizing the effects of the mutations on force generation by the translocation ratchet motor using optical tweezers.

11

Matheus Sanita Lima

Organelle genomes are the most sequenced type of chromosome, given their relative compactness and importance on fields like forensics, medicine and molecular evolution. Next generation sequencing (NGS) has been generating unprecedented amounts of genomic and transcriptomic data that are shaping the organelle genomics research. However, most of the RNA sequencing (RNA-seq) data is still used only for the study of cell nucleus, being the organelle reads even discarded in such investigations. Here, we used this untapped data source to investigate the transcription of organelle genomes in plastid-bearing protists. We mapped the transcriptomes over the genomes of 118 protist species to verify the utility of RNA-seq data in unravelling the organelle genome transcription architecture.

12 Gene transfer between bacterial subspecies causes fitness changes

Isabel Rathmann, Mona Förster, Jeffrey Power, Viera Kovacova, Michael Lässig, Berenike Maier

University of Cologne, Institute for Biological Physics

Horizontal gene transfer is an important driving force behind bacterial evolution and adaptation to ecological niches. Bacillus subtilis can take up extracellular DNA when it reaches the state of competence. How gene transfer between subspecies conveys specific fitness costs and gains is a subject of ongoing research. Here, we perform parallel evolution experiments by transferring DNA from Bacillus subtilis W23 to Bacillus subtilis 168, where donor and recipient have a sequence identity of 92.4% for 90% of the genomes. Through whole-genome sequencing, we detect orthologous replacements up to 20% of the genome after 20 evolutionary cycles with an average detected rate of 0.35% h^-1. We find that the mobile element ICEBs1 is deleted from the auxiliary genome of the recipient in all replicates. Insertions from the auxiliary genome of W23 are detected as well as de novo mutations. By performing fitness assays, we find that the evolved strains increase their fitness in the exponential phase, even though selection is absent from the experiment. Here, further time-resolved fitness experiments may elucidate the complex interplay between gene transfer and fitness effect.

13 POLG-related disorders: From a neuronal model system to therapeutical approaches.

Michael Bell, Sarah Bachmann, and Hans Zempel

The poster provides a literature based overview about the causes, pathomechanisms as well as neuropathological manifestations of disorders that are related to mutations in the POLG gene, e.g. the Alpers-Huttenlocher-Syndrome and related phenotypes. The goal of future research will include to establish a neuronal model system carrying specific point mutations, which are highly abundant in patients, in order to apply and improve potential therapeutical treatments.

14 Involvement of mitochondrial bioenergetics in the pathogenesis of hepatic encephalopathy

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Hepatic encephalopathy (HE) is a neuropsychiatric disorder resulting from various forms of liver dysfunction. Ammonia is accumulating in the blood stream as it cannot be detoxified in the damaged liver. It can pass the blood-brain barrier leading to neurological disturbances ranging from confusion to hepatic coma. The only curative treatment option is liver transplantation. A main role for HE pathogenesis is ascribed to impaired function of astrocytes serving as housekeepers for neurons.
Ammonia is known to cause fragmentation of the mitochondrial network and to result in disturbances of energy metabolism. However, the exact mechanisms and attribution to neuronal dysfunction remains largely unknown.
Our cell culture system employs MOG-G-CCM (astrocytoma) as well as primary rat astrocytes treated with 5 mM NH_4Cl to address the influence of ammonia on mitochondrial dysfunction. We show that high ammonia leads to a drastic reduction of mitochondrial respiration as well as glycolysis. Furthermore, we find significant changes in the metabolome of ammonia-treated cells, in particular an increase of certain amino acids after 24 or 48 h of treatment. Additionally, we show an impairment of the TCA-cycle upon excess of ammonia which is further supported by metabolomic tracing of isotopic labelled $^{15}NH_4Cl$.
Overall, our data support the hypothesis that excess ammonia rapidly interferes with the TCA-cycle and thereby mitochondrial respiration is impaired downstream. In the future, we hope to exploit these novel insights for developing strategies for HE therapy.

15 Characterization of C12orf65, a member of the mitochondria translation release factor family

Ana-Madalina Ion

Human mitochondria have their own DNA, which encodes 13 proteins. Only two of the three universally-conserved stop codons are used to terminate these open reading frames, UAA and UAG, as UGA encodes for tryptophan. Translation release factors ensure that when the ribosome encounters a stop codon, the synthesised polypeptide is released from the tRNA at the P-site. Four putative translation termination factors have been identified in human mitochondria: mtRF1, mtRF1a, C12orf65 and ICT1. Only mtRF1a has been proven to decode both stop codons UAA and UAG. The full function of the others remains elusive. The aim of my project is to unveil the role of C12orf65 by identifying the proteins it interacts with. This will be achieved using proximity labelling via a promiscuous biotin-ligase biotin ligase (BioID). A HEK293 cell line has been generated that can inducibly overexpress C12orf65-BioID2-HA fusion protein. Proteins that interact with C12orf65 will then be identified by mass-spectrometry. Thus far, I have five HEK293 cell lines, all of which show that the fusion protein partitions to the mitochondrial matrix. Having identified the clone that has the highest expression of the fusion protein in mitochondria with negligible levels and lowest in the cytosol, this will be used this clone for biotinylation experiments, mitochondria isolation and identification of C12orf65 interactor proteins by mass-spectrometry. The interaction with the identified proteins will be validated and may inform on the role of C12orf65 in mitochondrial translation.

16

Gomez-Duran Aurora

Maternally inherited polymorphic variants of mitochondrial DNA (mtDNA) alter the risk of developing common late-onset human diseases, but the underlying mechanisms are not understood. By using a collection of cell lines of carrying several variants in the mtDNA, we show that mTORC1 is a key mediator between the mitochondrion and cell nucleus in response to subtle differences in the mtDNA sequence. mTORC1 inhibition and activation, evidenced its compensatory role on a myriad of functions including mitochondrial morphology, functionality and biogenesis, metabolism rewiring, cell growth and maintenance of cytoplasmic reactive oxygen species levels (ROS) that were abolished by mild inhibition of CIII activity. Our findings provide a new mechanism linking mtDNA variation with cancer and neurodegenerative disease that does not directly involve oxidative phosphorylation. However, although manipulating mTORC1 may have therapeutic benefits, it will disrupt mitochondrial homeostasis in genetically defined groups with potentially adverse effects.

17 Membrane phospholipids regulate protease activity in mitochondria

Yohsuke Ohba, Thomas MacVicar, and Thomas Langer

Mitochondria are dynamic organelles involved in a variety of cellular processes, such as energy production via oxidative phosphorylation and the ATP biosynthesis, which is essential for cell viability. The mitochondrial function requires a coordinated supply of proteins and phospholipids. Phospholipid composition, transport and membrane allocation are essential for mitochondrial protein function and homeostasis. Mitochondria have a unique membrane phospholipid composition and most of the mitochondrial phospholipids come from outside of mitochondria, but it is unclear how they are incorporated and maintained. We focus on one of the lipid transfer proteins in mitochondria celled PRELID3B and found that PRELID3B transfers phosphatidylserine and maintains the amount of phosphatidylethanolamine (PE) in mitochondria. We also found that PRELID3B is degraded by mitochondrial protease YME1L, which is on the inner mitochondrial membrane, and the protein amount of PRELID3B, regulated by YME1L, determines the mitochondrial PE level. Interestingly, the YME1L mediated proteolysis is increased in PRELID3B KO cells, and that is caused by the reduced amount of PE in mitochondria. About physiological relevance, we find a certain situation that mitochondrial PE is decreased and the protease is active. We would also like to discuss this point.

18 The role of metabolic regulation in protein turnover

Sonia Ravanelli

Many evidences indicate strong interconnection between ubiquitin/proteasome system (UPS) and mitochondrial stress-related pathways, however, many questions remain unanswered. Our group observed that defects in mitochondrion-related genes or treatment with mitochondrial stressors induce a decrease of proteolytic pathways in C. elegans as well as in mammalian cells. We recently observed in C. elegans that defects in some specific metabolic reactions lead to UPS downregulation independently of the mitochondrial unfolded protein response (UPRmt). Interestingly, the observed proteolysis downregulation does not affect the entire proteome but it seems rather specific for a subset of proteins. Preliminary results from genetic interaction studies in C. elegans suggest that intermediate metabolites produced in the branched chained amino acid (BCAA) catabolism could possibly act as signaling molecules to trigger the UPS regulation. By analyzing the possible involvement of transcription factors known to be involved in different types of stress responses, only skn-1/Nrf emerged to be important for the observed UPS downregulation. Due to its known involvement in oxidative stress response, metabolic adaptation and transcriptional regulation of proteasome subunit, skn-1/Nrf is a promising candidate to be a key player in this putative stress response. Our plan is to further investigate the mechanisms underlying the UPS regulation in response to specific metabolic changes and the possibility that this would represent a protective response to maintain homeostasis.

19 Loss of the mitochondrial i-AAA protease YME1L leads to ocular dysfunction and spinal axonopathy

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Disturbances in the morphology and function of mitochondria cause neurological diseases, which can affect the central and peripheral nervous system. The i-AAA protease YME1L ensures mitochondrial proteostasis and regulates mitochondrial dynamics by processing of the dynamin-like GTPase OPA1. Mutations in YME1L cause a multi-systemic mitochondriopathy associated with neurological dysfunction and mitochondrial fragmentation but pathogenic mechanisms remained enigmatic. Here, we report on striking cell-type specific defects in mice lacking YME1L in the nervous system. YME1L-deficient mice manifest ocular dysfunction with microphthalmia and cataracts and develop deficiencies in locomotor activity due to specific degeneration of spinal cord axons, which relay proprioceptive signals from the hind limbs to the cerebellum. Mitochondrial fragmentation occurs throughout the nervous system and does not correlate with the degenerative phenotype. Deletion of Oma1 restores tubular mitochondria but deteriorates axonal degeneration in the absence of YME1L, demonstrating that impaired mitochondrial proteostasis rather than mitochondrial fragmentation cause the observed neurological defects.

20 Effect of the phosphodiesterase 5 inhibitor sildenafil on skeletal muscle ischaemia-reperfusion

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Background: Lower-limb ischemia reperfusion (IR) is very frequent and associated with significant morbidity and mortality. Involving muscle mitochondrial dysfunction and oxidative stress, such public health issue still needs more efficient therapeutic approaches. Phosphodiesterase5 inhibitors demonstrated antioxidant and beneficial effects in several organs submitted to IR.
Methods: To test whether the phosphodiesterase 5 inhibitor Sildenafil reduce muscle injury in mice submitted to hindlimb IR, 18 mice were randomized to IR (2h unilateral tourniquet application followed by 2h reperfusion) or IR + Sildenafil (1mg/kg i.p 30 minutes before ischemia). Maximal oxidative capacity (VMax) and relative contribution of the mitochondrial respiratory chain complexes II, III, IV (VSucc) and IV (VTMPD/Asc), together with calcium retention capacity (CRC) a marker of apoptosis, and tissue reactive oxygen species (ROS) production using respectively high resolution respirometry, spectrophotometry and electronic paramagnetic resonance, were determined in gastrocnemius muscles from both hindlimbs.
Results: Compared to the non-ischemic hindlimb, IR significantly reduced mitochondrial VMax (from 11.79 ± 1.74 to 4.65 ± 1.11 pmol/(s*mg ww); $p < 0.05$ -50.2±16.3%), IR also decreased the CRC (from 2.33 ± 0.41 to 0.84 ± 0.18 µmol/mg dw); $P < 0.05$; -61.1± 6.7%). These alterations were not corrected by Sildenafil, although it tended to decrease ROS production (64.3 ± 31.9 vs 21.9 ± 16.6 %; $p = 0.08$) in control and treated mice, respectively.
Conclusions: lower limb IR impairs skeletal muscle mitochondrial function and increases oxidative stress. Despite tending to reduce ROS production, Sildenafil did not show protective effects on muscle mitochondrial functions.

21 The protein quality control system and Vms1 are involved in the cellular response to increased mitochondrial protein damage caused by advanced glycation endproducts

Johanna Zemva, Claus Rodemer, Thomas Fleming, Sylvia Kaden, Hermann-Josef Gröne, Peter P. Nawroth, Jens Tyedmers

Question: Advanced glycation endproducts (AGEs) result from the reaction of carbonyls with proteins, lipids and DNA. AGEs are known to be increased in patients with diabetes and seem to play a pivotal role in the development of late complications. Methylglyoxal (MG) is a highly reactive dicarbonyl that is formed non-enzymatically during glycolysis. It preferably binds to arginine residues, leading to the accumulation of hydroimidazolone (MG-H1). The cellular effects of MG-H1 are poorly understood. We questioned (i) which molecular pathways handle increased MG-H1 formation and (ii) where accumulates MG-H1 intracellularly.
Methods: High throughput techniques in yeast were used to identify genes that are involved in MG-stress. These genes were further validated in mouse endothelial cells (MECs). In MECs, localization of MG-H1 formation (both endogenous and after MG-treatment) was analyzed using immunofluorescence (IF) and electron microscopy (EM).
Results: In yeast, RNASeq analysis after MG-treatment revealed a strong induction of the protein quality control system including the inducible Hsp70s. Accordingly, loss of Hsp70 and also Vms1 decreased MG-tolerance in yeast. To further validate these data in the mammalian system, MECs were treated with Hsp70 and Vms1 siRNA, which rendered the cells more vulnerable to MG. Using IF and EM in endothelial cells, we found that MG-H1 accumulates at the site of mitochondria under basal conditions and that mitochondrial MG-H1 accumulation is aggravated under MG-stress.
Conclusion: Different components of the protein quality control are needed to handle AGE-induced proteotoxicity. Both, Hsp70 and Vms1, could play a central role in preserving mitochondrial function in diabetes.

22 Retinoic acid-induced calvarial fragmentation requires concerted interactions between osteoblasts, osteoclasts, and chondrocytes

B. Geidner, S. Jeradi, H.-M. Pogoda, M. Hammerschmidt

Exposure to Retinoic acid (RA) above physiological levels has been associated with increased bone fragility in humans. Accordingly, elevated RA levels caused by a loss-of-function mutation in the CYP26B1 gene expressing a RA-metabolizing enzyme lead to fragmentation of calvaria in human fetuses. However, it remains unclear which cell populations primarily mediate the described bone fragility and/or bone depletion phenotype caused by elevated RA levels. In this study, we employ the zebrafish as a model to further investigate the effects of RA in bone formation, remodeling, and maintenance. Previously, we showed that ectopic RA induces increased bone resorption by osteoclasts, causing the aforementioned calvarial fragmentation. Additionally, we revealed that RA fails to induce calvarial fragmentation in the absence of osteoclasts or osteoblasts. Surprisingly, recent results from our laboratory indicate that RA also fails to induce calvarial fragmentation upon depletion of chondrocytes from the epiphyseal bar located immediately beneath the areas of the observed calvarial bone resorption. Thus, our findings indicate that RA-induced calvarial fragmentation requires the involvement of three different cell populations, namely osteoblasts, osteoclasts, and chondrocytes. However, whether these three cell populations either respond directly, indirectly, or even act independently from RA in that functional context still needs to be identified. In order to determine which of these three populations directly respond to RA, we are establishing transgenic lines expressing a floxed and heat-shock inducible dominant negative RA receptor, as well as cell-type specific cre lines. These will enable us to block RA signaling specifically in one of those three distinct cell populations via a binary transgenic approach, thereby allowing the identification of the direct RA target involved in bone fragmentation.

23 High-throughput screening of compounds inhibiting Glutamylases

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Glutamylation is a post-translational modification (PTM) that results in the addition of secondary glutamate side chains in an ATP dependent reaction. This PTM is carried out by Tubulin Tyrosine Ligase Like enzymes (TTLLs). Important substrates of these enzymes are α- and β- Tubulins which together form heterodimers that are the building blocks of Microtubules (MTs). The extent of glutamylation dictates the interaction of MTs with its interacting partners hence is important in regulating MT behavior and function. The ratio of stable and dynamic microtubules is critical for neuronal function. Interestingly, not only MTs with reduced stability have been found in association with classical neurodegenerative diseases (eg. ADs, PDs, ALS) but also hyperstable MTs seem to be associated with inherited neurological diseases associated with secondary neurodegenerative processes (i.e. Hereditary Spastic Paraplegia). In essence, there seems to be a difference in MT stability depending on the clinical condition. The objective of this project is to identify small molecules that selectively inhibit the glutamylation activity of TTLLs. These inhibitors will be used as chemical tools to study the role of this PTM in regulating MT behavior and to develop a deeper understanding of the molecular mechanisms that are targeted by such inhibitors. Identified substances can also serve as future drug precursors. In order to identify TTLL inhibitors, high throughput screen (HTS) of small molecule library consisting of over 60,000 compounds was conducted for which a primary assay was developed, miniaturized and adapted to screening robotics. The hits hence obtained will be verified by secondary assays. This is the first HTS campaign for TTLLs. With this study we provide evidences to prove “druggability” of this class of enzymes.

24 A Physiologically-Based Pharmacokinetic Model of Voriconazole

Xia Li, Sebastian Frechen, Daniel Moj, Max Taubert, Chih-hsuan Hsin, Gerd Mikus, Thorsten Lehr, Uwe Fuhr

Objective: Voriconazole, a first-line anti-fungal therapy, exhibits non-linear pharmacokinetics together with large inter-individual variability but has a narrow therapeutic range. We aim to investigate the metabolism of voriconazole to better understand dose- and time-dependent alterations in the pharmacokinetics of the drug and to provide the model basis for safe and effective use according to CYP2C19 genotype.
Methods: In vitro assays were conducted to assess mechanism-based inactivation (MBI) of CYP3A4 by voriconazole. These results were combined with 93 published concentration-time curves of voriconazole from clinical trials to develop a whole-body physiologically-based pharmacokinetic (PBPK) model for healthy volunteers. The model was evaluated with the predicted/observed ratio of AUC and Cmax, geometric mean fold error, as well as the comparison of predicted with observed concentration-time curves from virtual studies over the full range of voriconazole administration dosage regimen (including intravenous and oral, dosing from 1.5 to 6 mg/kg and from 50 to 400 mg). Subsequently, the voriconazole model was coupled with independently developed CYP3A4 substrate models (midazolam and alfentanil) to assess the validity of the model to describe the inhibitory effects of voriconazole on CYP3A4.
Results: The IC50 shift assay showed that voriconazole has a MBI on CYP3A4 with a 16-fold difference in the absence and presence of NADPH. The inactivation kinetic assay provided a K_(I) of 9.33 (95% confidence interval: 2.56 to 34.0) μM, supporting the integration of MBI model into the PBPK model. PBPK model verification demonstrated good performance of the model, with 82% of predicted/observed AUC ratios and all Cmax ratios from 28 test datasets being within a 2-fold range. For those studies reporting CYP2C19 genotype, 88% of AUC ratios and 95% of Cmax ratios were inside the 2-fold range of 41 test profiles. For the effect of voriconazole on midazolam and alfentanil, the predicted/observed AUC change for these CYP3A4 substrates by voriconazole ranged from 1.01 to 1.36, indicating that CYP3A4 inhibition was appropriately incorporated into the voriconazole model.
Conclusions: Both the in vitro assay and model-based simulations confirmed the MBI of CYP3A4 by voriconazole as a pivotal characteristic of the drug's pharmacokinetics. The PBPK model developed here could support individual dose adjustment of voriconazole, also according to genetic polymorphisms of CYP2C19, and DDI risk management.

25 Yeast overexpression screen for cellular components restoring plasma membrane trafficking of human kidney anion exchanger 1

Xiaobing Li

Human kidney anion exchanger 1 (kAE1) represents a bicarbonate transporter in the basolateral membrane of renal epithelial cells that participates in the fine-tuning of acid-base homeostasis by mediating electroneutral Cl-/HCO3- exchange. Several autosomal mutations in the kAE1 encoding gene (SLC4A1) can cause clinical disorders known as distal renal tubular acidosis (dRTA) which are linked to kAE1 mis-folding, ER/Golgi retention, and/or premature degradation. Despite that some proteins involved in kAE1 trafficking could be identified, the precise mechanism(s) resulting in dRTA still remain unclear. Since wild-type kAE1 could be successfully expressed in yeast and partially colocalizes in the plasma membrane, we are going to use yeast as experimental model system to identify proteins which affect intracellular kAE1 trafficking to the plasma membrane and/or its turnover which is vital for proper kidney function. By using a yeast ORF expression library (~ 6,000 ORFs), we will initially establish a Western- and FACS-based screening approach in S. cerevisiae to test which yeast proteins, when overexpressed, modulate the cellular expression and plasma membrane localization of kAE1. To date, we finished a FLAG-tagged kAE1 expression construct which was successfully integrated into yeast genome by homologous recombination and confirmed its in vivo expression and localization by western analyses and immunofluorescence microscopy. In further experiments, we want to analyze the cellular proteins that have been identified in the ORF screen to understand how these proteins are capable to increase and/or restore plasma membrane transport of wild-type kAE1 as well as clinically relevant kAE1 mutant variants.

26 Molecular signatures during the ageing of mouse liver

Chrysa Nikopoulou

During ageing the ability of the organism to maintain homeostasis decreases, adaptability to stress signals diminishes, functional and structural properties of tissues deteriorate, resulting in morbidity and mortality. The liver, unlike the other organs, retains the ability to regenerate with older age and does not exhibit well-documented functional changes. Nevertheless, hepatocytes, the main cellular population of the liver, proliferate later and in smaller percentage in old liver during regeneration. In order to delineate the molecular mechanisms that drive transcriptional changes during the ageing of liver cells, we have established a protocol to create liver 3D organoids by utilizing liver adult stem cells from young and old mice. These organoids are comprised of a heterogeneous cell population of stem and epithelial cells that create an environment, which recapitulates basic liver functions, and thus can prove informative in terms of qualitative and quantitative potency of adult stem cells to regenerate. We are aiming to get deeper insight in the cellular composition based on the gene expression profile of liver organoids during ageing and compare it to the respective mouse liver tissue by utilizing cell sorting, single-nucleus and bulk RNA sequencing.

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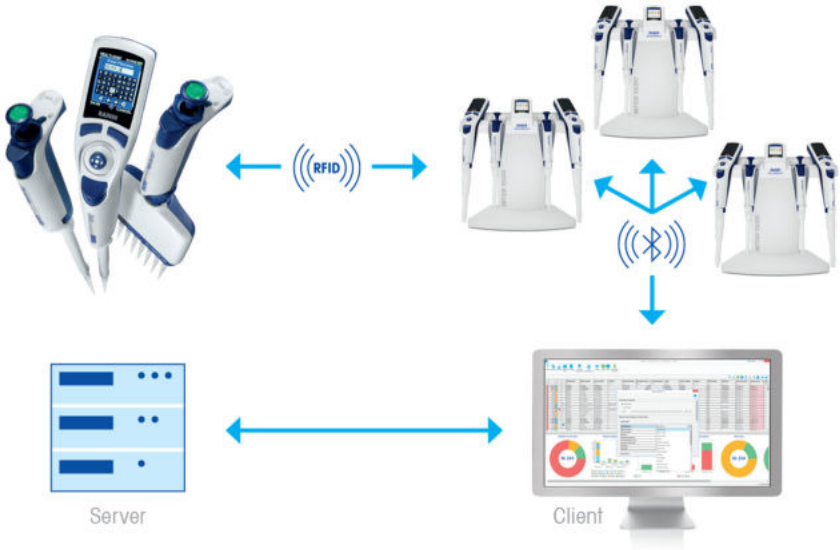

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Rick Scavetta, PhD, has been working as an independent Data Science trainer for the past 7 years (since 2012).

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Operating as "Scavetta Academy", Rick has a close and recurring presence at primary research institutes all over Germany, including many Max Planck Institutes and Excellence Clusters, covering research fields from molecular genetics, primatology, Earth sciences, marine biology and behavioural psychology.

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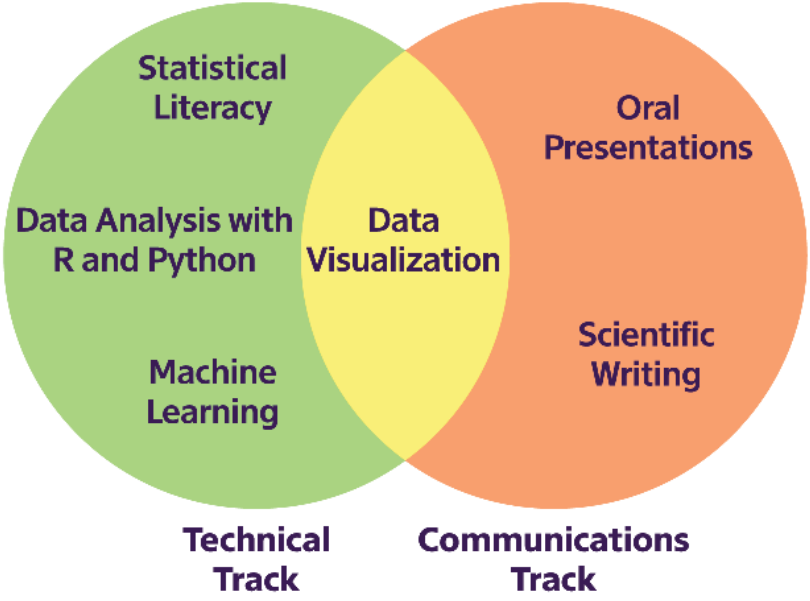

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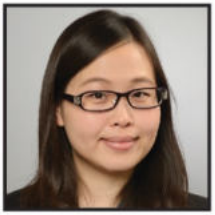

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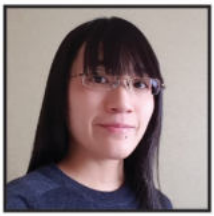

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Photo by Katharina Link (Max Planck Institute for Biology of Ageing, Cologne)

Back row (left to right): Mihaela Bozukova, Dieu Hien Ho, Yvonne Lasarzewski, Britta Thewes, Jennifer Gerbracht, Paul Werthenbach
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