The Hartmut Hoffmann-Berling International Graduate School of Molecular & Cellular Biology

HBIGS

Student Retreat 2013

- Munich -

Dear fellow HBIGS students,

Thanks for taking part in the 2013 retreat! We hope you have a great weekend with plenty of fascinating talks on cutting-edge science from Heidelberg, covering a wide range of disciplines. This retreat is not only meant for you to hear about what other PhD students are doing but also to get to know your colleagues personally. Take this unique chance to build up your network, exchange with the other HBIGS students, and establish friendships and collaborations.

Munich was chosen as this year's venue for its historical allure and cultural richness, so you're encouraged fully to take advantage of the opportunities built into the schedule to explore the area and experience some of what the Bavarian capital has to offer.

Enjoy your weekend, be inspired, network, and have a great time!

Your Student Speaker team,

Julianne, Patric and Julian

Upon coming to Germany, most students will already be familiar with Munich. It's the capital of the state of Bavaria, located on the River Isar north of the Alps. More than 1.4 million people live within city limits, making it the third largest city in Germany, behind Berlin and Hamburg.

Munich is also still remembered for hosting the 1972 Olympics and the Olympic Park – that at the time was an architectural masterstroke with its big "glass tents" – is now a landmark used for all kind of events.

The world-famous traditional Oktoberfest takes place every autumn at the Theresienwiese. All local Munich breweries (which dominate the ever-present beer culture) construct enormous tents at the fairgrounds, where you can listen to live-music, enjoy a Brathendl (grilled chicken) and of course, drink beer by the liter in the infamous Maßkrug.

One of the largest manufacturers of luxury cars, BMW (bayrische Motoren-Werke) maintains its headquarters in Munich and offers some interesting insights into car engineering at the fascinating BMW museum.

Also well known is the football team FC Bayern-München that is currently playing in the newly errected Allianz-Arena, which is the first stadium in the world that has the capacity to change its entire exterior color.

Inner city

At the center of the city is the Marienplatz—a large open square named after the Mariensäule, a Marian column in its centre—with the Old and the New Town Hall. Its tower contains the Rathaus-Glockenspiel. Three gates of the demolished medieval fortification have survived to this day—the Isartor in the east, the Sendlinger Tor in the south and the Karlstor in the west of the inner city. The Karlstor leads up to the Stachus, a grand square dominated by the Justizpalast (Palace of Justice) and a fountain.

The Peterskirche close to Marienplatz is the oldest church of the inner city. It was first built during the Romanesque period, and was the focus of the early monastic settlement in Munich before the city's official foundation in 1158. Nearby St. Peter the Gothic hall-church Heiliggeistkirche (The Church of the Holy Spirit) was converted to baroque style from 1724 onwards and looks down upon the Viktualienmarkt, the most popular market of Munich.

The Frauenkirche is the most famous building in the city centre and serves as the cathedral for the Archdiocese of Munich and Freising. The nearby Michaelskirche is the largest renaissance church north of the Alps, while the Theatinerkirche is a basilica in Italianate high baroque which had a major influence on Southern German baroque architecture. Its dome dominates

the Odeonsplatz. Other baroque churches in the inner city which are worth a detour are the Bürgersaalkirche, the Dreifaltigkeitskirche, the St. Anna Damenstiftskirche and St. Anna im Lehel, the first rococo church in Bavaria. The Asamkirche was endowed and built by the Brothers Asam, pioneering artists of the rococo period.

The large Residenz palace complex (begun in 1385) on the edge of Munich's Old Town ranks among Europe's most significant museums of interior decoration. Having undergone several extensions, it contains also the treasury and the splendid rococo Cuvilliés Theatre. Next door to the Residenz the neo-classical opera, the National Theatre was erected. Among the baroque and neoclassical mansions which still exist in Munich are the Palais Porcia, the Palais Preysing, the Palais Holnstein and the Prinz-Carl-Palais. All mansions are situated close to the Residenz, same as the Alte Hof, a medieval castle and first residence of the Wittelsbach dukes in Munich.

Close to the city center, there is a large green park called the "Englischer Garten“. It is larger than New York's Central Park and is one of the world’s largest urban public parks, contains a nudist area, jogging tracks and bridle-paths.

Munich also has two of the best universities in Germany, the Ludwigs-Maximilians-Universität (LMU) and the Technische Universität München (TU), which both also hold high rankings among the world's top universities.

Keynote Speaker:

Prof. Dr. Andreas Ladurner is Full Professor and Chair of Physiological Chemistry at the Ludwig Maximilians University of Munich. He holds a Ph.D. in Chemistry from the University of Cambridge and currently sits on the Advisory Boards of the University of Milan and Volition, Inc., Singapore. He has served as Editor of *Nature Structural and Molecular Biology* and *Epigenetics and Chromatin* journals and received numerous distinguished awards, including the Wellcome Trust International Prize, the Young Investigator Award from Schering Stiftung, the Outstanding Young Investigator Award from IAPSAP, and 1st Prize in the Young Italians Abroad program. He has conducted research at Glaxo SmithKline Pharmaceuticals, Cal Berkely as an HHMI Fellow, and EMBL in Heidelberg as a Group Leader before accepting the full professorship in Munich. Using many different model systems from yeast to human clinical samples and diverse methods ranging from crystallography to physiology, his research aims to characterize novel post-translational modifications regulating the dynamic assembly and remodeling of chromatin.

Schedule

Friday, 14th

Time	***Event***	***Chair***
13:14	Leaving Heidelberg	
17:00	Arrival at the hostel	
17:45-18:30	Keynote speaker, Prof. Dr. Andreas Ladurner	
18:30	Dinner at the hotel	
19:30-20:30	Talks: Genetics & Plant Biology ▪ Florian Huber ▪ Devanjali Dutta ▪ Sanja Curcin ▪ Christophe Gaillochet	Julianne
20:30-20:45	Dessert Break	
20:45-21:45	Talks: Parasitology & Structural Biology ▪ Julius Mulindwa ▪ Priyanka Fernandes ▪ Kartik Bane ▪ Julian Kellner	Julianne

Saturday, 15th

Time	***Event***	***Chair***
Until 10:00	Breakfast	
10:00-11:00	Talks: Cell Biology ▪ Vihang Ghalsasi ▪ Verena Müller ▪ Harsha Garadi Suresh ▪ Ewa Zatorska	Patric
11:00-11:15	Coffee Break	
11:15-12:15	Talks: Cell Biology ▪ Blanca Ana Iachia y Baca ▪ Rahul Kumar ▪ Andreas Matern ▪ Michael Lang	Patric

12:15-13:00	Lunch	
13:00-14:15	Talks: Neuroscience ▪ Slavil Peykov ▪ Catarina Luis ▪ Chen-Min Yeh ▪ Christoph Pille ▪ Patric Pelzer	Julian
14:15-14:30	Coffee Break	
14:30-15:45	Talks: Neuroscience ▪ Dimitri Hefter ▪ Yan Shi ▪ Ina Simeonova ▪ Ioana Goganau ▪ Julianne McCall	Julian
17:00	Brewery Tour meet at Marienplatz	

Sunday, 16th

Time	***Event***	
Until 10:00	Breakfast and clearing the rooms	
12:30	City Tour meet at Marienplatz	
16:20	Leaving Munich	
19:53	Arrive in Heidelberg	

Abstracts

GENETICS & GENOMICS

Florian Huber
Lab: Michael Knop, ZMBH

A genome-wide screen for gene dosage compensation in yeast

When the gene copy number in a cell's genome changes, cells may react by gene dosage compensation (GDC) in order to return protein amounts to wild-type levels. Until now, research on GDC has focused mainly on sex chromosomes or on how cells deal with acquired chromosomal aberrations. However, studies on GDC at the level of single genes are still largely absent. The aim of this study is to determine which genes are subject to GDC on a gene-by-gene basis in the yeast Saccharomyces cerevisiae. First, protein amounts and stabilities of a given gene of interest (GOI) will be compared between homozygous diploid strains (100% gene dosage) and hemizygous strains (50% gene dosage). This will be done by high content microscopy of a genome-wide library of proteins tagged with tandem fluorescent protein timers (tFTs) that allow the simultaneous measurement of protein amounts and stabilities in living cells. Genes showing evidence of compensation will then be further investigated to learn at which level from gene to protein GDC takes place and to identify potential regulators of GDC.

Devanjali Dutta
Lab: Bruce Edgar, ZMBH

Transcriptome profiling of Drosophila intestinal cell populations

The epithelial cell lining of the gastrointestinal tract in Drosophila melanogaster (Drosophila / fruit fly) is maintained by a continuous supply of cells, which arise by the differentiation of multipotent progenitors that originate from intestinal stem cells (Micchelli and Perrimon, 2005; Ohlstein and Spradling, 2007). Intestinal stem cells (ISCs) proliferate throughout the life of the adults, replacing themselves and generating transient cells called enteroblasts (EBs), which differentiate into enterocytes (ECs) or enteroendocrine cells (EEs). Transcription factor Escargot (esg) is a common marker for both ISCs and EBs. In addition to these cell types, the midgut region of the intestine is ensheathed by two layers of visceral muscle (VM)

cells and supplied with oxygen by the trachea. The proper regulation of intestinal stem cell maintenance, proliferation and differentiation is critical for maintaining gut homeostasis (Jiang and Edgar, 2009). As our understanding of stem cell development and function in vivo becomes more sophisticated, it has become important to profile the various intestinal cell types at the transcriptome level. Although expression studies have been performed on whole midguts of adult Drosophila (Buchon et al, 2009 ; Osman et al, 2012; Jiang and Edgar, 2011), cell type-specific transcriptome profiling of the Drosophila midgut cell types has not yet been undertaken. We present a protocol which can be useful for quantitative comparisons of gene expression across the different intestinal cell populations of the Drosophila midgut under physiological or any experimental condition of overexpression or knockdown.

PLANT BIOLOGY

Sanja Curcin
Lab: Thomas Rausch, COS

Glutathione boost with ectopic expression of bifunctional StGCL-GS enzyme in tobacco enhances host and non-host defense

Glutathione has been implicated to have important roles in different stress responses, including biotic stress. To assess the involvement of glutathione in response to pathogens, tobacco (Nicotiana tabacum L.) transgenic lines with overexpression of bifunctional GCL-GS enzyme from Streptococcus thermophilus for glutathione overproduction were used. The transgenic lines accumulated up to tenfold more glutathione than wild type and had strong increase in the expression of Pathogenesis-related protein (PR) genes of both NPR1-dependent and independent branches of salicylic acid (SA) pathway. When infected with host Pseudomonas syringae pv. tabaci pathogen, transgenic lines accumulated more SA and storage glucoside form (SAG), which led to hypersensitive response (HR)-like symptoms and reduction of chlorotic areas around the infection site. However, bacterial number in planta was only transiently reduced. Moreover, infection of tobacco lines with non-host pathogens of Pseudomonas syringae (pv. maculicola and syringae) showed strong reduction of bacterial number during the whole course of infection and formation of HR lesions.

Additionally, transgenic lines had more callose depositions in response to non-host pathogens. Taken together, our results suggest an important role of glutathione in tobacco defense against both host and non-host pathogens.

Gaillochet Christophe
Lab: Jan Lohmann, COS
Uncovering the regulatory network mediating HEC1 function in Arabidopsis shoot apical meristem

Plants generate their aboveground tissues post-embryonically through the activity of stem cell pools localized at the tip of the stem. Despite their significant importance in generating the whole plant body, our understanding of the molecular processes underlying stem cell activity remains elusive. We recently characterized HECATE1 gene (HEC1), member of the bHLH transcription factors family, which is involved in regulating stem cell behavior at the Shoot Apical Meristem (SAM). We are currently using imaging techniques to record dynamically HEC1 activity on stem cell homeostasis and on hormonal signaling. Furthermore, to uncover the regulatory network associated with this factor, we are also identifying HEC1 co-factors and the target genes mediating its activity by expression profiling and genome-wide binding studies.

PARASITOLOGY

Julius Mulindwa
Lab: Christine Clayton, ZMBH
An approach to determine the Transcriptome of T. b. rhodesiense from Sleeping Sickness Patients

T. b. rhodesiense is a human infective parasite responsible for the acute form of Sleeping Sickness and is mainly found in Eastern and Southern Africa. The disease is characterized by two stages: the early haemo-lymphatic stage and late meningo-encephalitic stage, which leads to death if untreated. Therefore, this study is aimed at analyzing the transcriptomes of clinical isolates of T. b. rhodesiense from patient peripheral blood (early stage) and cerebral spinal fluid (late stage), using high-throughput RNA

sequencing. However, given the low parasitaemia during active infection, a method was developed to specifically amplify the trypanosome RNA above the human cellular RNA background to a level sufficient for sequencing. Furthermore, using a rodent model, the optimal method was developed for isolating the parasites from body fluids with minimal effect on the transcriptome of the parasite. Human samples (blood and CSF) were subsequently collected for transcriptome analysis. Analysis of the differential gene expression of T. b. rhodesiense in the bloodstream and CSF will provide some insight into the human-trypanosome interaction, thus enabling the identification of diagnostic markers and possible targets for chemotherapy for Sleeping Sickness.

Priyanka Fernandes
Lab: Ann-Kristin Müller, Dept of Infectious Diseases

Functional characterisation of a novel Plasmodium antigen and its implications on malaria pathophysiology

Despite decades of research, malaria still remains one of the most poorly understood diseases. While the recent failure of the RTS, S pre-erythrocytic malaria subunit vaccine presents an interesting conundrum, it nevertheless insinuates a more complex host-parasite interaction than we imagined. For many years now, the liver phase of malaria has been the focus of research, primarily because of the large repertoire of protective immune responses that can be developed at this stage. Numerous experiments with irradiated or genetically attenuated parasites have substantiated the role of the liver in inducing sterile immunity and long-lasting protection. However, the fundamental mechanism of this protection is still elusive. In a previously unpublished study, liver stages of irradiated (RAS) and wild type parasites were compared which revealed differential expression of certain transcripts in RAS that were hypothesized to interact with the host's immune system. From them, certain transcripts were shortlisted based on in silico analysis for T cell epitopes, MHC/HLA binding affinities, domains and later validated by ELISPOT assays for IFN-γ responses from PBMCs of malaria-exposed and non-exposed donors. My PhD project centres on the functional characterisation of one of these identified antigens in the entire life cycle using the rodent system and the murine parasite strain Plasmodium berghei.

Kartik Bane
Lab: Friedrich Frischknecht, Dept of Infectious Diseases
Actin's dance : From the choreographer's eyes

Actin is the basis of movements in many organisms. Malarial parasites also have to move in the skin of vertebrate host to reach nearest blood vessel and in mid-gut of mosquito to reach the wall of mid-gut. Motility of malarial parasite is actin-myosin based. In stark contrast to eukaryotic or bacterial actin, malarial parasite's actin forms tiny filaments. The talk would be about how conventional strategies fail to detect actin filaments and proposal of novel strategy in visualizing these tiny filaments, consequently looking at actin dynamics in live cells of parasite.

Julian Kellner
Lab: Anton Meinhart, Max Planck Institute for Medical Research
Structural and Functional Characterization of the RNA helicase DDX1

In eukaryotes and archaea, tRNAs, the essential adapter molecules in translation, can contain intervening sequences such as introns. During their maturation, these tRNAs undergo splicing by an endonuclease complex, which removes the intron from the tRNA-precursor, thereby generating upstream 5’ and downstream 3’ exon halves (Abelson, Trotta, et al. 1998). Subsequently tRNA exon halves are joined in a ligase reaction (Filipowicz et al. 1983). In mammals and archea, direct ligation of the 2’,3’-cyclic phosphate of the upstream exon halve with the 5’-OH of the downstream exon halve is believed to constitute the major pathway (Englert et al. 2011). Recently RtcB in archaea and E. coli (Shuman 2011), the HSPC117 complex in mammals (Popow et al. 2011), respectively, has been identified to be the direct RNA 2’,3’-cyclic phosphate ligase.
Among other proteins, the HSPC117 ligase complex contains the DEAD-box helicase DDX1 (Drewett et al. 2001). DDX1 is unique among homologous helicases since it contains a hnRNP U like insertion motif in its RecA like consensus sequence (Godbout et al. 1994).The role of DDX1 during RNA ligation is enigmatic so far and we therefore set out to functionally and structurally characterize the molecular mechanism of DDX1 with a strong focus on its unique hnRNP U insertion motif.

CELL BIOLOGY

Vihang Ghalsasi
Lab: Victor Sourjik, ZMBH
Engineering bacterial chemotaxis for biosensory application

Chemotaxis is the migration of an organism towards or away from a certain compound. Bacterial chemotaxis is one of the most thoroughly studied model system of signal transduction. The system consists of chemoreceptors, which are transmembrane proteins involved in the sensing of compounds and other intracellular proteins involved in signal transduction. Due to its relative simplicity and modularity, chemotaxis pathway is amenable to manipulations. The proposed strategy herein is to exploit this plasticity and evolvability of the chemotaxis system to develop a synthetic system for sensing and clearance of biofilms. Biofilms are aggregates of bacteria embedded in a self-produced matrix. Living in a matrix protects the cells from desiccation and starvation and makes them exceptionally resistant to conventional methods of disinfection. Biofilms pose a severe threat in human diseases and in industrial settings. Thus it is essential to design a novel biofilm clearance system. The system consists of a killer strain that can sense the biofilms by sensing the compounds secreted by them and shows chemotaxis towards the biofilm. It carries a gene that codes for an anti-biofilm compound. The killer strain will synthesize the compound in response to the presence of the biofilm, which will eventually clear the biofilm.

Verena Müller
Lab: Victor Sourjik, ZMBH
Role of motility and chemotaxis in biofilm formation of Escherichia coli

Chemotaxis allows bacteria to sense and respond to environmental gradients and thereby to find conditions that are optimal for survival and growth. However, little is known about the importance of chemotaxis in the multicellular behavior of bacteria, such as biofilm formation. To better understand the role of motility and chemotaxis in Escherichia coli biofilms, we systematically analyzed the effect of chemotaxis gene knockouts on biofilm formation. We demonstrate that some, but not all, chemotaxis mutants are deficient in biofilm formation. While some of these effects

could be explained by the defects in motility, our results also imply a motility-independent function of chemotactic signaling in biofilm development. Because motility is known to be regulated via the second messenger cyclic-diguanosine-monophosphate (c-di-GMP), we also investigated the effects of c-di-GMP signaling on biofilm formation. The observed effects of c-di-GMP apparently depend on the type of the biofilm assay, but increased biofilm formation at the liquid-surface interface upon downregulation of c-di-GMP may be related to the increased motility.

Harsha Garadi Suresh
Lab: Bernd Bukau, ZMBH

Lipid biosynthetic enzymes reversibly co-cluster at ER- mitochondria encounter sites (ERMES) upon glucose starvation, providing a link to autophagy

We observed that upon prolonged glucose starvation of S.cerevisiae, ER and mitochondria form punctate structures that can rapidly regain their typical morphologies upon re-addition of glucose. Coinciding with these dramatic morphological changes we observed that fatty acid and phospholipid biosynthetic enzymes to be co-clustering at the punctate ER-mitochondrial encounter/contact sites (ERMES). A correlative lipidomics study indicates an increase in the cellular lipid levels upon onset of these enzyme clusters indicating that the enzymes co-sequester possibly for superior substrate channeling to efficiently and locally synthesize lipids. Interestingly, autophagic proteins co-localized with these enzyme clusters. We also observed that recruitment of autophagic factors to these sites is dependent on the formation of enzyme clusters at the ERMES. Importantly, induction of autophagy is one of the key responses of cells to starvation. Autophagy involves engulfment of portions of the cytoplasm by an isolation membrane forming the autophagosome, which subsequently fuse with the vacuole/lysosome resulting in the degradation of its contents. ER-mitochondria contact site is one of the debated sources of membrane for the autophagosome biogenesis. We are currently testing the role of these active enzyme sequestrations at ERMES for their possible involvement in membrane biogenesis that is required for autophagy.

Ewa Zatorska
Lab: Sabine Strahl, COS
Protein O-mannosylation in the context of protein translocation into the ER

O-mannosylation of proteins is an evolutionary conserved modification, which is crucial for development and growth of fungi, plants and animals. Initation of this process occurs at the endoplasmic reticulum (ER) and is mediated by complexes of membrane proteins of the O-mannosyltransferase (PMT) family. It was suggested that PMTs mannosylate proteins during their translocation into the ER, but a final proof is still missing. In Saccharomyces cerevisiae the major PMT complexes – heteromeric Pmt1/Pmt2 and homomeric Pmt4/Pmt4 complex – show different substrate specificity. Interesingly, in some cases they can act on the same protein, but on different domains. Here, we demonstrate that the major Pmt1/Pmt2 complex is directly associated with the translocon machinery. In addition, our data suggest that Pmt1 and Pmt2 play different roles within this complex.

Blanca Ana Iachia y Baca
Lab: Frauke Melchior, ZMBH
Interplay between sumoylation and prolyl cis/trans isomerization

Reversible protein modifications are important mechanisms for the regulation of cellular events. The posttranslational modification with SUMO is involved in many aspects of cellular life and is tightly regulated itself by phosphorylation/acetylation. Interestingly, many of the verified sumoylation sites in targets are lysine residues preceding proline, which may point to a new exciting possibility for regulation. Prolyl bonds in proteins have the potential to adopt two different conformations, trans or cis, and the slow interconversion between both conformers is accelerated by peptidyl prolyl cis/trans isomerases. Some members of this enzyme family are key regulators of phosphorylation/dephosphorylation events at proline directed phosphorylation sites. The aim of my project is to search for a similar interplay between sumoylation and prolyl cis/trans isomerization. For this, I started investigating the protein RanBP2 which intriguingly contains both SUMO E3 ligase activity and a cyclophilin domain (cyclophilins are a major family of prolyl isomerases). To identify a

functional role for the mostly uncharacterized cyclophilin domain in RanBP2 I searched for interaction partners by using pull downs with the recombinant cyclophilin domain followed by mass spectrometry. Verified interaction partners will be investigated concerning their connection to the SUMO pathway.

Rahul Kumar
Lab: Herbert Steinbeisser, Institute of Human Genetics
Xenopus Paraxial Protocadherin (PAPC) regulates Nemo like kinase (Nlk)

Canonical Wnt signaling regulates key developmental processes via β-Catenin stabilization and its complex formation with various transcription factors such as Tcf/Lef etc . Tcfs are also substrates of Nemo like kinase (Nlk) and via phosphorylation of these proteins, NLK regulates the Wnt/β-catenin signaling pathway. Little is known however which intracellular factors regulate Nlk activity in vivo. Here we show that in Xenopus embryos xNlk1 has germ layer specific activities, acting as an activator of Wnt signaling in ectoderm and as a repressor in mesoderm. Furthermore we found, that xNlk1 and xNlk2 possess non-redundant activities. In a yeast two Hybrid screen we have identified Paraxial protocaherin (PAPC) as binding partner for NLK1. Co-IP and Immunoflourescence confirmed the interaction between the intracellular domain of PAPC and xNlk1. Gain of function experiments in Xenopus embryos revealed that PAPC is able to antagonize NLK function in the Wnt signaling pathway. Our experiments demonstrate for the first time that NLK activity can be regulated by protocadherins. The mode of this inhibition is currently under investigation.

Andreas Matern
Lab: Matthias Mack, University of Applied Sciences Mannheim
FMN riboswitches as novel antimicrobial drug targets for flavin-analogs

FMN riboswitches (RFN elements) are promising targets for novel antimicrobial drugs. The genes coding for the enzymes, involved in the riboflavin biosynthesis in Streptomyces coelicolor and S. davawensis are grouped in an operon like cluster. Their expression is regulated by a FMN riboswitch, that can be blocked by FMN analogs (e.g. roseoflavin). This regulation of expression is a translational gene repression in which the ribosomal binding site (RBS) is made inaccessible throughout binding of

FMN to the secondary structure of the RFN aptamer. In the turn of validating cellular targets for novel antimicrobial drugs, FMN riboswitches are of great interest, since they are highly specific receptors for small compounds, as for example FMN and they are prone to its analogs based on e.g. roseoflavin. It was reported earlier, that roseoflavin inhibits growth of several Gram-positive bacteria, such as Bacillus subtilis and Micrococcus luteus (Sarcina luteus) and also potentially pathogenic bacteria as Staphylococcus aureus, Listeria Monocytogenes and Bacillus cereus.

Michael Lang
Lab: Matthias Mayer, ZMBH

Identification and characterization of the chaperone and co-chaperone partners of HSF1 involved in the Heat Shock cellular response

The induction of eukaryotic heat shock genes in response to an increase of temperature is mediated by the binding of a transcription factor to certain DNA sequences known as Heat Shock Elements. In human cells, this transcriptional activator is called Heat Shock Factor 1, or HSF1. In non-stressful conditions, HSF1 exists as an inactive monomer, bound to negative regulators that are believed to be heat shock chaperone proteins, forming a multi-chaperone complex. Upon heat shock, HSF1 is released from this complex, and trimerizes, hence strongly activating transcription of the heat shock genes. Increasing levels of Heat shock proteins in the cell result in the reassociation of the HSF1-Hsps complex, and reestablishment of the repressed state. In order to identify to chaperone partners of HSF1, SILAC experiments will be performed, and heavy amino-acid labeled culture will be submitted to a temperature stress. Lysis of the cells followed by immunoprecipitation will isolate HSF1, along with all the proteins interacting with it. Gel separation, coupled with mass spectrometry will then separate and quantify the different peptides. Identified partner proteins will be purified and binding to HSF1 will be analyzed biochemically and biophysically.

NEUROSCIENCE

Slavil Peykov
Lab: Gudrun Rappold, Institute of Human Genetics
Identification and functional characterization of *Shank2* in Schizophrenia

Many genes, that have been associated with neurodevelopmental and psychiatric diseases, encode for synaptic proteins. In our study I focused on the potential role of Shank2 in schizophrenia. Mutations in Shank2 are already associated with intellectual disability and autism. Different evidences for a genetic overlap in some key genes involved in these conditions and schizophrenia have been published in the literature last few years. More important the other two members of the Shank family, Shank1 and Shank3 have also been reported to contribute to schizophrenic phenotypes. In the light of this Shank2 gene becomes a logical candidate for having an association with schizophrenia. In order to test this hypothesis I performed a Sanger sequencing screening of all exons and exon-intron boundaries of the Shank2 neuronal isoform in a cohort of 177 trios and 304 singleton schizophrenia patients. After that I analyzed the functional impact of the 4 most promising identified missense mutations in overexpression and knockdown-rescue experiments in primary hippocampal neurons from rat with the major focus on morphological changes of the neurons.

Catarina Luis
Lab: Georg Köhr, Central Institute of Mental Health, Mannheim
Linking addiction-related behavior to synaptic efficacy in the Nucleus Accumbens

Drug addiction is a chronically relapsing disorder characterized by compulsive drug taking and seeking. Worldwide is estimated to affect 3.4 to 6.6 % of the adult population. Identifying the mechanisms underlying this disorder might result in therapeutic progress in treating this often, devastating disease. The Nucleus Accumbens (NAc), has been identified as a key brain region involved in processing reward and goal-directed behaviour. Plasticity in the NAc and its associated circuitry has been found to have an important role in many forms of reward-dependent learning. Drugs of abuse are thought to hijack this circuitry by its strong reinforcing effects.

Specifically, transition to addiction is associated with persistent impairment of long-term depression (LTD) in the NAc, which is specific to subjects that develop addictive behaviour. Nevertheless, a casual link between behavioural responses to abused drugs and synaptic plasticity changes in the NAc has yet to be uncovered. The present study aims to monitor cocaine-induced changes in synaptic strength in the NAc of awake rats by in vivo electrophysiology. A prolonged cocaine self-administration animal model, in which rats exhibit behaviours similar to the hallmarks of substance dependence in the DSM-IV diagnostic manual, will allow the study of electrophysiological changes during disease progression.

Chen-Min Yeh
Lab: Soojin Ryu, Max Planck Institute for Medical Research

The regulation of hypothalamic crh from cortisol under circadian cycles

Negative feedback mediated by glucocorticoids is one of the most prominent features of the hypothalamic-pituitary-adrenal (HPA) axis regulation. Corticotropin-releasing hormone (crh), the principle regulator of the HPA axis in the hypothalamic paraventricular nucleus (PVN) is the major target of the negative feedback. The suppression of PVN crh transcript by glucocorticoid was observed normally with a latency of days in vivo and whether there are fast responses under basal condition is still elusive. Here, using zebrafish larvae, we described the maturation of cortisol and crh mRNA patterns and addressed the negative regulation from cortisol to neurosecretory preoptic area (NPO) crh transcripts under the basal condition. While the daily variations of NPO crh transcript and cortisol negatively correlated with each other, both dampening cortisol level or interfering with its signaling did not perturb the basal fluctuation of NPO crh transcripts. In contrary, optogenetically increasing endogenous cortisol level acutely altered the fluctuation of NPO crh and suppressed the normal stress response. Furthermore, the fast change of crh transcripts induced by cortisol increase was detected on the level of mRNA but not heteronuclear RNA with a glucocorticoid receptor (GR)-dependent mechanism. Therefore, our data not only demonstrates how cortisol modulates NPO crh fluctuation under basal condition but also suggested that cortisol induces acute crh mRNA reduction through GR mediating mechanism.

Christoph Pille
Lab: Michael Brunner, Biochemistry Center Heidelberg
Characterization of the putative transcriptional regulator ASM-1 a potential new factor in the circadian clock of Neurospora crassa?

The circadian clock in Neurospora crassa consists of positive and negative feedback loops. Key players are the transcription factor White Collar Complex (WCC) its inhibitor FREQUENCY (FRQ). The WCC leads to expression of FRQ which in turn inhibits the transcriptional activity of the WCC. The WCC is binding at its recognition site GATG, which is also known as clock-box (cBox) and leads to the circadian expression of frq. The clock box in the promoter of frq is flanked by the sequence CGCTGC. A databank analysis found the transcription factors PHD1 and SOK2 from yeast binding to this sequence. The homologue protein in Neurospora is ASCOSPORE MATURATION-1 (ASM-1). ASM-1, PHD1 and SOK2 build together with StuA from Aspergillus nidulans and EFGTF-1 from Candida albicans a group of proteins, which share the same DNA binding motif called APSES-domain. These proteins are reported to play important role in the development of the fungi. An ASM-1 deficient fungus shows slower conidia formation. The proposed binding site at the frq promoter and its regulatory role in cell cycle and fungal development makes ASM-1 likely to be another part of the circadian clock in N. crassa.

Patric Pelzer
Lab: Thomas Kuner, Interdisciplinary Center for Neurosciences
Function of Cortico-Thalamo-Cortical Loops

The brain is divided into many functional units. The cortex the highest brain center communicates with the rest of the brain largely through the thalamus, the “distributing” unit of the brain. Albeit a rich reciprocal connectivity between the thalamus und the cortex, research focused mainly on the thalamo-cortical connectivity. However from an anatomical point of view the the cortico-thalamic connections outnumber these. The function of the cortico-thalamic connectivity and the forming loops are largely unknown.
Using channelrhodopsin, a heterologously expressed light-sensitive channel, as a tool to stimulate single synapses, I intend to:

1. investigate the synaptic transmission properties of the cortico-thalamic synapses,
2. characterize changes due to deletion of certain receptors,
3. and continue to describe subsequent implications for the animal in behavioral assays.

Dimitri Hefter
Lab: Andreas Draguhn, Institute of Physiology and Pathophysiology
Amyloid Precursor Protein and Hypoxia in the Mouse Hippocampal Slice

The Amyloid Precursor Protein (APP) is known for its pivotal role in the development of Alzheimer´s Disease (AD). Besides a variety of functions in the nervous system, APP, particularly its soluble extracellular fragment sAPP-alpha, was shown to interact with several cell survival pathways and protect against excitotoxic and hypoxic stress in cell cultures. Mice lacking APP show increased mortality rates after an induced stroke; however, it is difficult to differentiate between the possible causes of mortality e.g. decreased blood supply or increased neuronal death or inflammation in vivo. Therefore, we investigate the role of APP in hypoxia in hippocampal slice preparations, as the hippocampus is one of the first brain areas to suffer from hypoxia. This model allows us to study spontaneous neuronal network activity and evoked responses under controlled pharmacological and environmental conditions. If the hypothesis of an increased susceptibility to hypoxia in slices from APP-KO mice is confirmed genetic manipulations (e.g. aAPP-alpha Knock In) or pharmaceutical interventions (e. g. application of specific calcium channel blockers) can be performed to understand the underlying mechanisms and identify the downstream targets.

Yan Shi
Lab: Francesca Ciccolini , Interdisciplinary Center for Neurosciences
Regulation of neural stem cell activation by the nuclear orphan receptor Tlx

Neural stem cells (NSCs) in the adult mammalian brain continue to generate new neurons throughout the life span of the animal. This process of adult neurogenesis initiates with the activation and quiescent NSCs consequent entry into the cell cycle. The proliferation and differentiation of NSCs are

regulated by the integration of intrinsic and extrinsic signals, which change according to temporal and local cues. The molecular players underlying this regulation are largely unknown. Our group has developed an approach to separate NSCs and their differentiated precursors. By investigating the gene expression changes in the mouse lacking the expression of the nuclear orphan receptor Tlx, we have recently shown that Tlx is essential for modulating cell cycle entry of NSCs in the postnatal. The project will probe the genes that are specifically involved in NSC activation and differentiation in Tlx-/- mice.

Ina Simeonova
Armin Blesch, Center for Spinal Cord Injury

Induced pluripotent stem cells in the treatment of spinal cord injury

Spinal cord injury is characterized by massive degeneration of neural tissue and by the formation of cysts and cavities filled with liquid, cellular debris and inhibitory as well as inflammatory molecules. Tissue replacement might only be achieved by transplanting cells, reasonably neural stem/progenitors cells, which will fill the lesion site, differentiate into neural phenotypes, form a relay and promote regeneration and remyelination of host axons. In this context, embryonic stem cell (ESC)-homologue induced pluripotent stem cells (iPSCs) represent the best, ethically correct tool to obtain large amounts of NSCs in vitro for autologous transplantation. iPSC-derived NSCs were transplanted as neurospheres in a mouse model of SCI, resulting in their survival, differentiation, integration in the host circuitries and partial recovery of the animals. However, their differentiation could not be directed towards desired phenotypes. My main aim is to obtain from rat and human iPSCs a set of pre-patterned immature glia and neurons with defined spinal phenotypes and autologously transplant them in Fischer 344 rats after SCI in defined combinations, to identify the cell type that contributes to recovery the most. Pre-patterned spinal neurons are supposed to constitute the relay station that connects rostral and caudal axotomized neuronal projections.

Ioana Goganau
Armin Blesch, Center for Spinal Cord Injury
Electrical stimulation for axonal regeneration in spinal cord injury

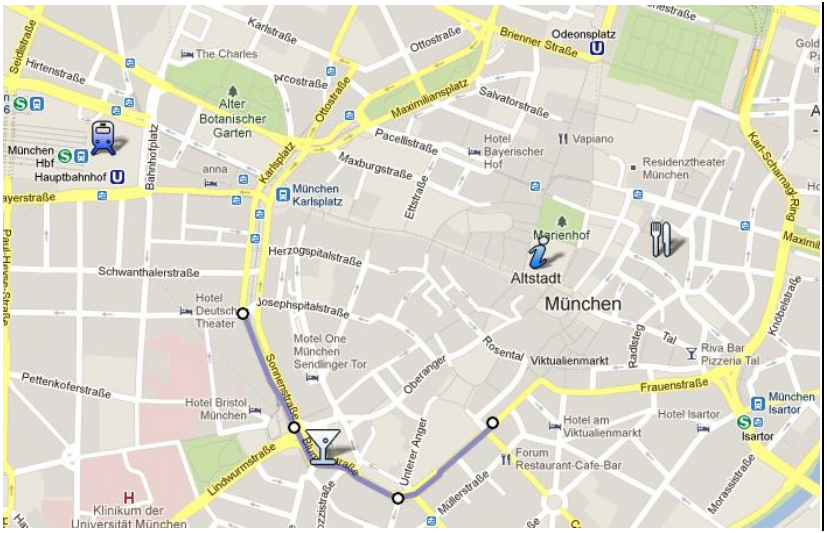
Electrical activity (EA) has multiple roles in cell migration, formation of neuronal circuits and survival in the developing nervous system. Several lines of evidence also suggest that EA of injured adult neurons plays a crucial role in activating signaling pathways and genes that, depending on the circumstances, can result in inhibition or stimulation of neuroregeneration. Methods to modify the EA could be particularly useful in spinal cord injury (SCI) since none of the existent or proposed experimental approaches to activate regenerative programs in injured neurons in SCI can be easily translated to a clinical setting while remaining fully effective. My aims are to identify the mechanisms underlying electrical activity-mediated structural changes and axonal growth, and at the same time to investigate the potential of activity-driven intrinsic pathways to increase neuronal regeneration for the treatment of central nervous system (CNS) disease or traumatic CNS injury. I therefore explore the most efficient stimulating approach to promote regeneration of sensory fibers in the spinal cord of rats, analyze the transcriptional and biochemical changes following such stimulation, and apply these protocols in a rat model of cervical SCI. Practical means, such as electrical stimulation and physical activity could be translated effectively to larger animal models and humans, and could be used in combinatorial treatments for axon regeneration to achieve functional recovery.

Julianne McCall
Armin Blesch, Center for Spinal Cord Injury
Transcriptional Regulation of Adult Mammalian Axonal Regeneration

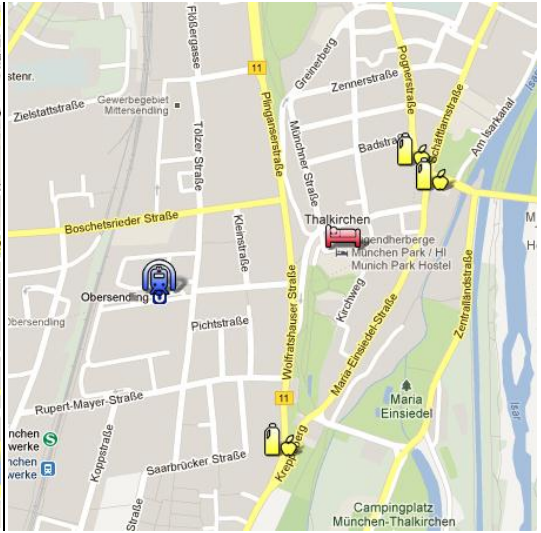
While there are numerous environmental factors that influence the effective or failed regenerative growth in the mammalian peripheral and central nervous systems, respectively, neuron-intrinsic growth programs significantly contribute to the success or failure of the repair. Dorsal root ganglion (DRG) neurons serve as a consistent model for studying the role of cell autonomous mechanisms upon injury.
Following a peripheral nerve crush lesion, DRG neurons initiate a genetic process that drives axonal regeneration to reinnervate appropriate targets.

Similar damage to the central branch of the same cell, however, fails to trigger any such cellular growth program and repair. However, if a peripheral conditioning lesion (CL) precedes an injury to the central branch, some growth is observed within the inhibitory environment of the CNS. The effect can be demonstrated in vitro, by an increase in neurite growth from dissociated and cultured DRG cells, and in vivo, by an increase in axon sprouting in the lesioned spinal cord. All evidence indicate that the CL effect is dependent upon transcription, and further data show that over 1,000 genes change expression level after a peripheral branch injury, compared to very few after a central branch lesion. Transcription factors likely play a major role in coordinating the abundant genetic changes, as recent microarray analyses suggest. To investigate mechanisms underlying the regenerative program activated by peripheral conditioning lesions, a recently optimized in vitro neurite growth assay in addition to electroporation transfection of candidate genes into primary neurons will be used as a screening tool.

Munich center



Around the hostel



Hostel: Jugendherberge München-Park
Miesingstraße 4, 81379 Munich

Grocery stores

Restaurant: Hofbräuhaus

Partytime!!!
these seems to be the street to go for a fun night out

Meet at the Marienplatz for both tours

Tram [U3] stop

Main train station

Train connection

Friday	Time	Platform	Train
Heidelberg Hbf	13:14	3	EC 219
Munich Hbf	16:11	3	
Munich Hbf	16:28		U7
Sendlinger Tor	16:30		
Sendlinger Tor	16:33		U3
Obersendling	16:42		
Sunday			
Munich Hbf	16:20	11 Süd	IC 1910
Heidelberg Hbf	19:53	12	

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Blanca Iachia
015207435966


Catarina Luis
017676855024


Christophe Gaillochet
017686784234


Devanjali Dutta
017664962434


Dimitri Hefter
015774622413


Florian Huber


Ina Simeonova
017663681513


Ioana Goganau
01744286459


Julius Mulindwa


Michael Lang
017620211698


Priyanka Fernandes
017671632690


Sanja Curcin
017634939948


Verena Müller


Vihang Ghalsasi
017671623990


Yan Shi
015776852732


Patric Pelzer
017622866960


Julian Kellner
017630754468


Julianne McCall
01626788534


Harsha Garadi Suresh


Chen-Min Yeh


Andreas Matern


Kartik Bane

Ewa Zatorska

Slavil Peykov

Christoph Pille

Rahul Kumar