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Vorwort

Liebe Kolleginnen und Kollegen, liebe Gäste,
wir begrüßen Sie sehr herzlich zu unserem zehnten *Leipziger Research Festival of Life Sciences* der Universität Leipzig. Die jährliche wissenschaftliche Leistungsschau gibt allen jungen »Life Science« Wissenschaftlern und Ärzten aus der Universitätsregion die Möglichkeit, ihre neuesten Forschungsergebnisse in einer öffentlichen »Wissenschaftswerkstatt« zu präsentieren. Die hohe Zahl von Abstracteinsendungen unterstreicht die Attraktivität dieses weit über die Fächergrenzen reichenden wissenschaftlichen Kommunikationsforums. Der vorliegende Abstract-Band soll auch der interessierten Öffentlichkeit, der Politik und Industrieunternehmen dienen, die facettenreiche Aktivität und die Erfolge der Leipziger Wissenschaftslandschaft gerade im Bereich »Life Science« und der gesamten Medizin kennen zu lernen. Der Band ist mit Stichpunkten zur Forschungskompetenz und email-Verweisen zugleich ein wissenschaftliches »who is who«, um schnelle Problemlösungen durch Zusammenarbeit »next door« zu erleichtern.
Mit besonderer Wertschätzung des wissenschaftlichen Nachwuchses werden auch in diesem Jahr die besten Posterpräsentationen mit den renommierten Forschungspreisen des *Research Festivals Leipzig* ausgezeichnet.
Wir werden in diesem Jahr auch den kompetitiv eingeworbenen Forschungsverbünden in den Lebenswissenschaften an der Universität Leipzig einen besonderen Raum geben, um Vorhaben und Ergebnisse im Rahmen der Landesexzellenzinitiative und Leipziger Forschungszentrums für Zivilisationserkrankungen (LIFE), des Integrierten Forschungs- und Behandlungszentrums (IFB AdipositasErkrankungen), des Translationszentrums für Regenerative Medizin (TRM) und des Kompetenzzentrums für computerassistierte Chirurgie (ICCAS) zu präsentieren und zur Diskussion zu stellen.
Wir hoffen, dass unser Research Festival auch in seinem 10. Jahr seinen doppelten Zweck, die Präsentation eigener innovativer Forschungsergebnisse und Kontaktforum mit jungen und älteren Wissenschaftlern und Ärzten über Fach- und Hierarchiegrenzen hinaus, erfüllen wird. Das Research Festival begleitet und stärkt somit die zukunftsweisende Entwicklung des biomedizinischen und biotechnologischen Standorts der Universität Leipzig.
Für die engagierte Mitarbeit, ohne die dieses Festival nicht zustande gekommen wäre, danken wir allen Unterstützern sehr.

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POSTER 1

Investigation of tau splicing and phosphorylation in a mouse model

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TRM – Tissue Repair and Replacement
Tumor Targeting

Neuritic plaques and neurofibrillary tangles are the characteristics in Alzheimer's Disease (AD) brains. Neurofibrillary tangles consist of paired helical filaments (PHF), which are formed by abnormally hyperphosphorylated tau protein. Tau is encoded by a single gene composed of 16 exons. Human adult brain contains at least six isoforms formed by alternative splicing of exons E2, E3 and E10. Due to differential expression of all isoforms during development they are likely to have distinct physiological roles. In this study, a comprehensive comparison of the tau splicing patterns from different murine brain preparations was achieved utilizing immunoblots after two-dimensional gel electrophoresis. Thereby commercially available and newly generated isoform-specific monoclonal antibodies (mAb) and polyclonal serum (pAb) as well as phosphorylation-specific mAbs were applied. Murine brain homogenates were prepared using short post-mortem delays and a fast work-up in the presence or absence of phosphatase (PPase) inhibitors. Significant differences in the total tau pattern could be shown. Samples prepared in the presence of PPase inhibitors displayed additional spots in the acidic range of the pH-gradient. The complexity of the tau pattern was reduced by dephosphorylation and single isoforms could be allocated accordingly. Importantly, antibodies recognizing assumed AD-specific phosphorylation sites stained some murine tau spots on the immunoblots. Thus, this study offers valuable clues to the isoform pattern and phosphorylation degree of tau in a mouse model.

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POSTER 2

In vivo antibacterial activity of oncocin derivative Onc72 against Escherichia coli in a systemic septicaemia infection mouse model

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The incidence of serious infections by multi-drug resistant bacteria is still increasing and has triggered research in different areas, i.e. hygiene, microbiology, biochemistry and chemistry, to overcome such life-threatening diseases. Oncocin is a novel designer peptide that belongs to the family of proline-rich antimicrobial peptides, which we have developed to treat Gram-negative infections caused by Enterobacteriaceae (*E. coli* and *K. pneumoniae*) and non-fermenting species (*A. baumannii* and *P. aeruginosa*).
Here, we describe the *in vivo* efficacy and the target inhibition mode of novel oncocin derivatives with (i) superior antimicrobial activities, (ii) high serum stabilities, (iii) no hemolytic activity, (iv) no eukaryotic cell toxicity, and (v) fast bactericidal activity.
NMRI mice treated i.p. with a daily dose of 160 mg of Onc72 per kg body weight (BW), did not show toxic, behavioral, immunological, or histological abnormalities. Moreover, oncocin did not possess any cytotoxic activity or a modulatory effect on murine bone marrow-derived dendritic cells. The same mouse strain was used to establish a lethal peritoneal sepsis model (10^6 CFU *E. coli* ATCC25922 in 2.5 % mucin). Whereas all mice treated with a placebo had to be euthanized within 12 h after infection based on the scoring system, all animals treated with oncocin 1, 4 and 8 h post infection (doses from 5 to 20 mg/kg BW) survived with sterile elimination of bacteria. Lower doses of 2.5 mg/kg BW and 1.25 mg/kg BW provided survival rates of 85% and 15%, respectively. This indicates an ED_{50} of approximately 2 mg/kg BW and a therapeutic window of more than 20.

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POSTER 3

1st/3rd generation green feed stocks for biotechnological synthesis of 2HIB as precursor for methacrylate synthesis

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Tumor Targeting

Growing scarcity of natural resources such as oil as our primary energy source demands the development of new ideas and strategic considerations to develop future biotechnological processes. This holds true not only for prospective biofuels but also for the synthesis of bulk chemicals. New concepts for the production of bulk and fine chemicals, generally manufactured chemically and expensive, ask for 'green' alternatives for those industrial applications such as the enzymatic synthesis of specific organic chemicals. Thereby, not only the microorganism and its general physiological disposition, but also the kind of substrate chosen, plays an important role for a future implementation of the process.
Taking into account that in 2009 about 154 million tons of sugar were consumed worldwide of which about 30 % went straight into the production of ethanol, it becomes quite clear that sugars, representing the 1st generation of renewable carbon sources, can not be the only choice for future biotechnological processes. At the same time the utilization of renewable primary products of the 2nd generation such as biomass has to compete for acreage with the food production industry. Therefore, regenerative resources such as CO_2 and H_2 attract notice as potential alternative energy and carbon sources epitomizing the 3rd generation of renewable 'green' resources.
In this work a new and feasible future production process for the enzymatic synthesis of methacrylate precursor 2-hydroxyisobutyric acid (2HIB) was designed by utilizing a novel mutase, 2-hydroxyisobutyryl-CoA mutase, and substrates of the 1st and 3rd generation.

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POSTER 4

Organotypic brain slice culture of adult P301S mice - a mouse model of Alzheimer's disease

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Neonatal organotypic brain slices are a sophisticated tool to analyze the function and the development of individual cell types and cell organizations in their natural tissue environment. For applications based on adult associated brain disease structures like those in Alzheimer's disease (AD), however, neonatal organotypic brain slices are insufficient. AD is characterized by neuritic plaques formed of Aβ and neurofibrillary tangles composed of hyperphosphorylated tau protein. One animal model to study these filamentous tau lesions is the P301S mouse line. An organotypic brain slice model made of adult P301S mice would be beneficial to analyze biochemical and morphological changes *ex vivo* related to the pathogenesis of AD. For this attempt several preparation and cultivation conditions for organotypic brain slices prepared from adult P301S mice were tested. The vitality was monitored by quantification of lactate dehydrogenase (LDH) efflux of dying or dead cells and by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) conversion of living cells over a period of two weeks. Both assays were shown to be feasible to determine the vitality of cultured brain slices with comparable results. An average vitality of 50% was obtained after a cultivation period of two weeks. The results presented show that the established *ex vivo* system may serve as a model for further investigation on the pathogenesis and treatment of Alzheimer's disease. These studies can be performed *in vitro* using fewer animals and less test compound compared to *in vivo* experiments.

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POSTER 5

Cisplatin–COX Inhibitor Conjugates for Overcoming Resistance of Tumour Cells

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The efficacy of conventional platinum-based anti-tumour drugs is strongly limited by intrinsic and treatment-induced resistance of tumour cells. An enzyme which plays an important role in the development of malignancies and seems to be strongly involved in resistance mechanisms is COX-2, an isoform of cyclooxygenase (COX) which is highly overexpressed in several tumours.[1,2]
Therefore, COX inhibitors are conjugated with cisplatin to create drugs with a dual action mode. Coordination of the commercial COX inhibitor indomethacin as axial ligand at platinum(IV) enables intracellular release of the COX inhibitor and generation of cisplatin by reduction of the metal centre. Simultaneous action of both bioactive molecules could help to overcome cisplatin-related resistance of tumour cells.

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2. G. Ferrandina, F. O. Ranelletti, E. Martinelli, A. Paglia, G. F. Zannoni, G. Scambia, *BMC Cancer* 2006, *6*, 182.

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POSTER 6

Identification and mapping of arginine-derived advanced glycation end-products in proteins

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Tumor Targeting

Glycation (or non-enzymatic glycosylation) is one of the most common non-enzymatic posttranslational modifications. The early products include lysine-bound aldoses and ketoses, while their dicarbonyl degradation products are involved in further reactions yielding advanced glycation end-products (AGEs). Highly reactive dicarbonyl glyoxal and methylglyoxal can readily react with the guanidino group in arginine residues forming Glarg and methylglyoxal-derived hydroimidazolones (MG-H 1, 2 and 3), respectively. These AGEs are known to accumulate in uremia and diabetes patients and can be considered as prospective biomarkers. However, methods for specific and sensitive analysis of Glarg- and MG-H-peptides are still missing. Here we are presenting a new tandem mass spectrometry-based approaches for selective detection and reliable identification of these species.
Glarg- and MG-H-modified peptides were synthesized on solid phase and their characteristic fragmentation patterns were analyzed on an ESI-QqTOF mass spectrometer. The modification sites were unambiguously identified by abundant b- and y-ion series showing specific mass shifts of 40 and 54 Da for Glarg and MG-H, respectively. The modified residue was additionally confirmed by intense internal fragment ions. The low *m/z* region of the spectra was dominated by Glarg- and MG-specific immonium ions at *m/z* 152.1 and 166.1, respectively. Based on these characteristic reporter ions, we have established very sensitive (~10 fmol/μL) and specific precursor ion scans for both prospective AGE biomarkers. The method was successfully applied to *in vitro* glycated human serum albumin (HSA) and cross-validated with nanoRP-HPLC-ESI-LTQ-Orbitrap-MS/MS.

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POSTER 7

CAIMAN CROCODILUS - A LIVING FOSSIL AS A KEY TO UNDERSTAND VERTEBRATE VISION?

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Tumor Targeting

In vertebrate eyes, light must pass most of the retinal layers before it is captured by the light-sensitive cells. Scattering in the retinal layers the light passes should obstruct clear vision yet our eye displays splendid visual abilities. This contradiction can be resolved by the function of radial glial (Müller) cells as effective light-guiding fibers in the living retina (Franze et al. 2007, Agte et al. 2011). The Müller cell underlies strong morphological changes for different vertebrate animals, for some species the Müller cells tend to be short and thick while for others they form long slender structures which divide into numerous fine processes that terminate in small endfeet covering the retinal surface (Cajal, 1892). The retina of the caiman crocodilus (which is able to hunt under water and on land) contains Müller cells of both extremes and, thus, displays an interesting model to study the interaction of light within the retinal tissue with respect to existing light conditions of the habitat. In order to examine the role of Müller cells in vertebrate vision we studied the morphology of caiman Müller cells for different retinal areas, on isolated cells and on fluorescently labelled cells within the retina. Light was applied onto retinal pieces to understand how it propagates through the tissue.

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POSTER 8

Molecular species identification of dermatophytes in clinical samples of species specific peptides by mass spectrometry

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Tumor Targeting

According to an official estimate, about 8 million people, in Germany alone, suffer from mycosis of the skin and nail. There are a surprisingly high number of different infectious fungal pathogens (~80-100 fungal species), from which several of the different species of fungus display varying sensitivities towards the diverse antimycotics available. Thus, the correct diagnosis with accompanying species identification is of particular importance so that the most effective therapy can be employed to treat the infection.
This project works on the development and implementation of a rapid and reliable method for species determination of dermatopathogenic fungi by mass spectrometry. To do this, material from relevant cultured dermatophytes was analysed using LC-MS/MS (liquid chromatography tandem mass spectrometry) to obtain protein and peptide spectra. Techniques of Intact Protein Profiling (IPP) and Shotgun Mass Mapping (SMM) were applied to analyze the different dermatophyte spectra, from which species-specific, unique peptides were determined. These species-specific peptides can then be implemented to help in the diagnosis of clinical samples by selected reaction monitoring (SRM) techniques.
Due to its speed, its high sensitivity and specificity as well as its potential for automatization, the method of mass spectrometry-based diagnostics presented here could mature into a cost-efficient, high-throughput method of interest for other diagnostic challenges in the near future.

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POSTER 9

Synthesis and evaluation of PET probes for imaging of the PDE10A in brain (EFRE-project)

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Tumor Targeting

Phosphodiesterases (PDEs) are a family of enzymes subdivided into 11 distinct families according to structural and functional properties. These enzymes metabolically inactivate widely occurring intracellular second messengers. Of all known PDE families, PDE10A has the most restricted distribution with high mRNA expression only in the brain and testes. PDE10A mRNA expression and protein are highly expressed in medium spiny neurons of the striatum. Noninvasive imaging of PDE10A using PET would allow for studying the distribution of this enzyme in neuronal and psychiatric disorders. Therefore we might still identify derivatives with sufficient potency and selectivity for PDE10A, resulting in a PET tracer showing a reasonable pharmacodynamic, pharmacokinetic and toxicological profile. We decided to initiate a chemical exploration around a lead compound. The project includes four subprojects. The aim of the subproject 1 (Prof. Briel, Prof. Sträter) was to synthesize analogues that can be easily radiolabeled with ^{18}F. The subproject 2 (Prof. Nieber) was aimed to evaluate in vitro and in vivo toxicity of selected analogues. The subproject 3 (Prof. Brust) was responsible for radiolabeling a potential candidate with ^{18}F and to measure the in vivo brain occupancy of the most promising derivatives. The in vitro PDE10A potency and selectivity was determined in co-operation with biocrea GmbH. The data of this project are essential to assess the suitability of a potential candidate as PET agent for imaging PDE10A in vivo.

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POSTER 10

Development of a cost-efficient high-throughput assay for peptide-protein interactions

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Tumor Targeting

Peptide-protein interactions play a major role in a variety of biological processes. The analysis of such interactions is often accomplished by fluorescence polarization. However, this method is limited due to low dynamic ranges and false positive readouts resulting from unspecific binding. Here we present a novel homogenous quenching assay for the determination of specific interactions between peptides and proteins. The assay was established by using the system of proline-rich antimicrobial peptides (AMP) and their biological target protein DnaK. In detail, the AMP's were modified with a fluorophor and the protein was labeled with a suitable quencher molecule. In the case of a specific interaction, fluorophor and quencher come into close proximity which decreases the fluorescence intensity. The optimized assay offers the possibility to determine the K_D-values of these and in principle any other peptide-protein interactions and shows a good correlation with the results of fluorescence polarization methods. In addition, the assay provides a good reproducibility as well as a high specificity. We have also developed a fast prescreening method that allows the screening of large peptide libraries and leads to a dramatic reduction of the sample material needed compared to the established fluorescence polarization method.

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POSTER 11

Development of a Novel System for Enantioselective Catalysis Using Artificial Metalloenzymes

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Tumor Targeting

Enzyme catalysis is the most efficient strategy for the preparation of enantiopure products by now. Unfortunately, many reactions important for industrial applications are missing from nature's toolbox. Most of those reactions (e.g. hydrogenation, hydroformylation) are catalysed by 4d/5d transition-metal ions. Incorporation of transition metals into a protein host via a ligand leads to a novel class of hybrid catalysts, so called artificial metalloenzymes. The resulting hybrid protein comprises the best parts of both worlds. However, creation of synthetic activity from scratch within an existing protein scaffold still remains a challenging task.
The RNase S system provides an ideal framework for incorporation of non-natural catalytic centres into a protein environment using peptide protein complementation (RNase S = S-protein + S-peptide). The basic catalytic activity is provided by the metal-organic centre whereas the protein environment ensures enantio- and regioselectivity. Based on the structure of RNase S we intend to design a system for the creation of various enantioselective catalysts.
So far, we produced crystals of an artificial metalloprotein comprising a RNase S variant with cysteines at positions 7 and 11 which is used as metal binding site. The X-ray structure revealed the formation of a stable [Cys_2Hg] centre while the protein fold is not altered. The crystal structure guided us in building a model of RNase S with a rhodium ion complexed by two artificial diphenylphosphine amino acids. Currently, we are working on the first RNase S variants for establishing this hybrid catalyst.

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POSTER 12

Analysis of the brain proteome of transgenic P301S mice, a mouse model of Alzheimer's disease

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Tumor Targeting

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders in elderly people. Over time many mouse models related to AD were developed to study the pathogenesis of the disease. Transgenic P301S mice express the 383 amino acid long isoform of the human tau protein with the mutation P301S in exon 10 of the tau gene. At the age of ten months heterozygous animals develop motor symptoms characterized by severe paraparesis of rear limbs. The aim of this study was a qualitative and quantitative analysis of the brain proteome of age matched transgenic P301S mice and wild type mice to obtain new insides into the pathogenesis of AD.
The first step was to optimize the resolution and sensitivity of the separation of mouse brain homogenates including the different methods of the initial isoelectric focusing, gel size from 7 to 21 cm and various staining procedures. Subsequently a first set of samples from transgenic P301S mice and wild type mice at the age of 40 weeks was analyzed. The obtained protein patterns were analyzed by Delta2D imaging software, protein spots of interest were excised, digested and identified by mass spectrometry.
Among the 400 detected spots 87 spots were differentially expresssed. 39 proteins could be identified and classified into different functional classes, e.g. acetylation, glycolysis, gluconeogensis and transport function. These findings possibly provide new knowledge about the development and the progression of AD and could lead to identification of novel therapeutic targets.

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POSTER 13

Applying impedance spectroscopy to measure TRP channel activity

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Transient receptor potential (TRP) channels are a family of ion channels, which are permeable to several cations like Na^+, Ca^{2+} and Mg^{2+} and are widely distributed in mammalian tissues. TRP channels play an important role in physiological Ca^{2+} influx pathways and Ca^{2+} homeostasis. They are involved in diverse physiological functions like the perception of sensory stimuli such as temperature, mechanical forces, and taste. Pain is currently the most advanced TRP channel-related research field. Although TRP channels are pursued as promising targets for drug discovery, the identification of chemical modulators of TRP channels and their validation is in its initial phase.
With a cell-based impedance assay we tested the effect of allyl isothiocynate (AITC) on the activity of TRPA1 channels. Therefore stably transfected HEK293 cells were seeded and grown on multielectrode arrays (MEA). A decrease of relative impedance is observed after TRPA1 activation with AITC.
The aim of the present project is to establish and characterize an impedance-based High Content Screening system for potential drug candidates.

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POSTER 14

Structural studies of DnaK in complex with proline rich antimicrobial peptides

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Bacterial infections are a major cause of death worldwide. Due to increasing resistance against the commercially available antibiotics over the past few decades, novel antimicrobial drug classes with new mode of actions are required for future treatments. Small proline rich antimicrobial peptides (PR-AMPs) from mammals and insects were identified to target the *E. coli* Hsp70 chaperone DnaK after cell penetration. Binding of the peptides to DnaK compromises the activity of the chaperone and thus the viability of the bacterial cells, in particular under conditions of stress. The non-lytic cell penetration of PR-AMPs to Gram-negative bacteria makes them a promising drug candidate against human infections. Therefore, structural information about the interactions between peptide inhibitors and DnaK are necessary for a better understanding of the mode of actions.
After recombinant expression of the substrate binding domain in *E. coli* and subsequent purification by IMAC and gelfiltration, we crystallized the domain with several PR-AMPs. Elucidation of the binding mode of the peptides and characterization of the substrate specificity of DnaK will allow a structure-guided development of peptide inhibitors as antimicrobial agents targeting DnaK.

Association: PbF III

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POSTER 15

Carbonyl tagging reagents: A comparative evaluation of their reactivity, specificity and mass spectrometrical behavior.

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Carbonyl tagging reagents: A comparative evaluation of their reactivity, specificity and mass spectrometrical behavior.
Reactive oxygen species (ROS), generated by various endogenous and exogenous sources, oxidatively damage almost all constituents of the cell such as DNA, lipids, carbohydrates and proteins. Carbonylation is widely accepted as biomarker of oxidative stress- and age-related disorders, such as Alzheimer's disease, Parkinson's disease, Huntington disease, ischemia, and diabetes. The term "carbonylation" refers to the post-translational modifications yielding reactive aldehydes, ketones or lactams. Protein carbonyls derive either from direct oxidation of amino acid residues, or by the secondary reactions of amino acid residues with reactive aldehydes produced during the peroxidation of lipids, glycation or glycoxidation.
Proteome wide analyses of carbonylation sites usually rely on different chemical tagging strategies to facilitate the enrichment, identification and quantification of the derivatized proteins by mass spectrometry (MS). Hydrazine chemistry is widely used for the derivatization of carbonylated proteins in both gel- and MS-based techniques, as well as for affinity-based enrichment. A detailed study, however, on the efficiency, specificity and MS behavior of different chemical tagging reagents is missing.
We compared five tagging reagents with different carbonyl-specific groups (hydrazine, hydrazide, carbohydrazide, hydroxyl amine and amine), that are commonly used in the field of carbonylation research, using model peptides containing different aldehydes, ketones and lactams. The reagents were evaluated in terms of derivatization specificity and efficiency towards each carbonyl-group. Furthermore, the electospray ionization efficiency and MS/MS characteristics were studied on an LTQ-Orbitrap-MS using different fragmentation techniques such as CID (collision-induced disassociation), PQD (pulsed-Q disassociation), HCD (high energy collision-induced dissociation) and ETD (electron transfer dissociation).

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POSTER 16

Highly sensitive determination of protease activity based on Fluorescence Resonance Energy Transfer

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Tumor Targeting

Proteolytic enzymes are widely used in analytical sciences and are involved in several widespread diseases like cystic fibrosis and other pancreatic diseases. Thus, there is an immense need for highly adaptable and sensitive techniques for the detection and monitoring of various kinds of proteolytic enzymes. We established a simple fluorescence resonance energy transfer (FRET)-based assay for the determination of protease activities, which can be adapted for the detection of every existing protease. As a proof of principle, we showed the potential of our method using trypsin and enteropeptidase in buffer system and in a complex biological mixture *(E. coli* lysate). The technique relies on the cleavage of a FRET-peptide substrate, which leads to a drastic increase of the donor fluorescence. Moreover, our approach can be applied using an enzyme cascade for signal amplification, resulting in further improvements of the sensitivity. The results of the experiment in buffer as well as in *E. coli* lysate demonstrate high sensitivities and fast assay times for both proteases with detection limits for trypsin of 100 amol and for enteropeptidase of 1 amol. Additionally, this novel FRET-assay is highly specific as high concentrations of other proteases did not result in significant background signals. Thus, the application of this simple and highly adaptable method provides a promising tool to determine changes in the activity of proteases.
Zauner T, Berger-Hoffmann R, Müller K, Hoffmann R, Zuchner T. A novel highly adaptable and sensitive protease assay based on fluorescence resonance energy transfer. (2011) Anal Chem 83, 7356-63

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POSTER 17

Development of a rapid fluorescence-based homogeneous immunoassay

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Tumor Targeting

Homogeneous immunoassays play a significant role for diagnostic applications in addition to heterogeneous assays like ELISA or DELFIA™ due to much shorter assay times. Numerous diseases and injuries require quick medical diagnosis or rapid on-site detection of antigens (e.g. toxins and explosives). Published homogeneous immunoassays show assay times of at least 10 minutes up to several hours. Though this is faster than heterogeneous assays, for emergency situations even shorter times are desired.
Here we present a homogeneous fluorescence-based immunoassay for the determination of phosphorylated tau peptides that is designed to ensure a very fast response. A phosphorylation-specific antibody and the corresponding peptide probe are labeled with two dyes: One linked to the antibody as acceptor and a donor fluorophore coupled to a specifically designed peptide probe. The intensity of the fluorescence resonance energy transfer between the labeled antibody and the donor peptide probe depends on the analyte concentration. The design of the assay allows a quantitative analysis of the antigen within 90 seconds.

Kreisig, T.; Hoffmann, R.; Zuchner, T. Homogeneous Fluorescence-Based Immunoassay Detects Antigens Within 90 Seconds, *Anal. Chem*. 2011, *83*, 4281–4287

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POSTER 18

Embryonic stem cell derived neuronal networks for the microelectrode array based analysis of network activity

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Tumor Targeting

Neurodegenerative diseases in the central nervous system like Morbus Alzheimer and Morbus Huntington are dramatic impairments that lead to an extensive loss of neuronal cells. The demand for cell-based assays is remarkable and the challenge on cell culture models is the ability to simulate complex pathological processes that occurs in neurodegenerative diseases. In this context, we established an on chip differentiation protocol for murine embryonic stem cells (ESC) on multielectrode arrays that can be used for high content analysis of neuronal network activity.
Optimum differentiation could be obtained by an initial cultivation under rotation conditions to form embryoid bodies (EB), followed by an expansion phase from day 5. For terminal differentiation the dissected neuronal aggregates were seeded on multielectrode arrays (MEA) at culture day 10. Immunocytochemical staining and western blot analyses confirmed a decrease in the expression level of the pluripotency marker Oct4 during differentiation, with an increase of the neuronal markers Tau and NF-H/L. After 6 weeks of differentiation we observed a dense neuronal network on MEA with spontaneously electrophysiological activity including neuronal burst series, proofing that these cells were able to generate action potentials.
In conclusion, we established a protocol optimized for on chip neuronal differentiation of the embryonic stem cell line ES-D3, which leads to highly active neuronal networks. This is a promising tool for the establishment of neuropathological models and testing of novel active pharmaceutical ingredients against neurological disorders.

Association: PbF III

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POSTER 19

Qualitative and quantitative MALDI-TOF MS investigation of the constituents of the extracellular matrix

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Fibrillar proteins such as collagens and glycosaminoglycans (GAGs) such as chondroitin sulphate (CS), hyaluronan (HA) or heparin (Hep) are the main components of the extracellular matrix (ECM) of cartilage, bone and skin tissues. Collagens and GAGs possess important and highly specialized functions for the stability of the ECM. The aim of our studies is the convenient and reliable detection of enzymatically digested collagen peptides and enzymatically (or chemically) digested disaccharides of CS and HA by MALDI-TOF MS. Specific proteases such as trypsin are typically used in proteomics to obtain characteristic fragments of a certain protein. However, the insolubility of intact collagen represents a significant problem because the majority of common proteases digest only soluble proteins, but do not cleave native collagen. Therefore, the use of bacterial collagenase seems a straightforward approach because this enzyme readily fragments native, helical collagen. Although collagenase A digests collagen rather unspecifically, the generated peptide mixture can be used as a measure of the collagen content of a biological sample. We have focused on the determination of Gly-Pro-Hyp that is highly characteristic for collagen. It will be shown that quantitative data on the collagen content of a given sample can be obtained by this approach. Similar data can be generated by using chondroitinase ABC in order to digest the polysaccharides of the ECM. Additionally we will show that the signal-to-noise ratios are reliable concentration measures and the addition of (often not available) internal standards is not absolutely required.

Association: PbF III

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POSTER 20

Structure and mechanism of chloromuconolactone dehalogenase from Rhodococcus opacus 1CP

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Chloroaromatic compounds are often very persistent environmental pollutants. Nevertheless numerous bacteria are able to metabolise these compounds and use them as the sole energy and carbon source. *Rhodococcus opacus* 1CP is able to degrade 3-chlorocatechol via a unique variant of the modified *ortho*-pathway. This pathway involves chloromuconolactone dehalogenase which dehalogenates the 5-chloromuconolactone to cis-dienelactone. The enzyme shows a high similarity to muconolactone isomerases, but is not able to catalyse the isomerisation reaction. In order to characterize the catalytic mechanism of this unusal dehalogenase, we crystallised the enzyme and subjected it to X-ray structural analysis. Datasets of up to 1.65 Å resolution were collected from two different crystal forms using synchrotron radiation. Based on the available structures and a sequence alignment several mutants were created to explore the functional relevance of the residues. The catalytic residues were identified and an inactive variant could be crystallized with the substrate, yielding to new insight in the binding mode and the catalytic mechanism of the dehalogenase.

Association: PbF III

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POSTER 21

Molecular architecture and structural basis of allosteric regulation of eukaryotic phosphofructokinases

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Eukaryotic ATP-dependent 6-phosphofructokinases (Pfks) differ from their bacterial counterparts in a much more complex structural organization and allosteric regulation. *Pichia pastoris* Pfk (*Pp*Pfk) is, with ~1 MDa, the most complex and probably largest eukaryotic Pfk. We have determined the crystal structure of full-length *Pp*Pfk to 3.05 Å resolution in the T state. *Pp*Pfk forms a $(\alpha\beta\gamma)_4$ dodecamer of D_2 symmetry with dimensions of 161 x 157 x 233 Å mainly via interactions of the γ chains. The N-terminal domains of the α and β chains have folds that are distantly related to glyoxalase I, but the active sites are no longer functional. Interestingly, these domains located at the 2 distal ends of this protein along the long 2-fold axis form a $(\alpha\beta)_2$ dimer as does the core Pfk domains; however, the domains are swapped across the tetramerization interface. In *Pp*Pfk, the unique γ subunit participates in oligomerization of the αβ chains. This modulator protein was acquired from an ancient S-adenosylmethionine-dependent methyltransferase. The identification of novel ATP binding sites, which do not correspond to the bacterial catalytic or effector binding sites, point to marked structural and functional differences between bacterial and eukaryotic Pfk.

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POSTER 22

Reaction of α-dicarbonyl compounds with phenylene diamines for ESI-MS analysis

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There is a growing interest towards α-dicarbonyl compounds such as methylglyoxal (MGO) and glyoxal (GO) especially in the biomedical and clinical research. They are formed as metabolic side products which can modify amino acids and proteins and that way cause multiple effects in the cell. α-dicarbonyls are known to be involved in formation of advanced glycation end products (AGE) that are suggested to play a crucial role in pathological processes of Diabetes, cancer, kidney failure and Alzheimer's disease etc.
α-dicarbonyls are highly reactive, toxic, and volatile compounds. They don't exhibit native fluorescence or UV absorbance and need to be chemically modified (derivatization) therefore before analysis. Several reagents are available for this purpose, among which the phenylene diamines (PD) are scope of this project. The reaction of α-dicarbonyls and PD with respect to analysis by electrospray ionization- mass spectrometry was investigated using MGO and GO as lead compounds. For this, different substituents of PD were tested for their influence on signal intensity of the derivatives with ESI-MS flow injection analysis. Since the reaction mechanism involves protons, pH dependency of the derivatization yield was assessed by MS and NMR. In addition, common methodological parameter such as linearity, limit of detection and the required molar ratio between analyte and reagent are presented.

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POSTER 23

Analysis of reactive carbonyl compounds by GCMS

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Reactive carbonyl compounds (RCC) such as methylglyoxal (MGO) and glyoxal (GO), are found ubiquitously in biological samples and food products. They react with proteins, nucleic acids, and lipids, exerting multiple (toxic) effects in living cells. Additionally, binding to the proteome and partial volatility of these compounds complicates their chemical analysis.
The purpose of this project was the establishment of an analytical profiling method for quantitation of RCCs in biological samples by GC-EI-MS. RCCs have to be derivatized with o-(*2,3,4,5,6*-pentafluorobenzyl) hydroxylamine (PFBHA) to achieve proper quantitation with GCMS; the derivatization can be carried out in aqueous media but derivatives have to be extracted prior GC analysis. After running various reference standards, collecting their electron impact ionization spectra and retention time indices in a customer library for identification, only MGO was used further as the lead compound.
Dicarbonyl compounds can form 5 reaction products (2 mono-derivatives, 3 bis-derivatives) with PFBHA enhancing the complexity of the spectra. For GC analysis, two different columns were tested for analytical performance, a DB-5 MS and a DB-35 MS (JW Fisher). Method development also included assessment of required molar ratio of analyte and reagent, extraction solvent for the derivatives from aqueous media, linear range, and detection limit. For analysis of biological tissue, common deproteinization procedures were adopted and tested for relative recovery.
Pitfalls and drawbacks of common protocols are discussed and alternative methods suggested.

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POSTER 24

Dynamic force spectroscopy on the binding of monoclonal antibodies and tau peptides

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Optical tweezers-assisted dynamic force spectroscopy is employed to investigate specific receptor/ligand bindings on the level of single binding events. Here, the specific binding of two anti-human tau monoclonal antibodies (mAbs), HPT-110 and HPT-104, to synthetic tau-peptides with different phosphorylation pattern is analyzed. The specificity of HPT-110 to the tau-peptide containing a phosphorylation at Ser235 and of HPT-104 to the tau-peptide containing a phosphorylation at Thr231 is confirmed. Additionally, our approach allows for a detailed characterization of the unspecific interactions that are observed between HPT-104 and the peptide phosphorylated only at Ser235 and between HPT-110 and the peptide phosphorylated only at Thr231. By analyzing the measured rupture-force distributions it is possible to separate unspecific from specific interactions. Thereby for the latter characteristic parameters like the lifetime of the bond without force t_0, the characteristic length x_{ts} and the free energy of activation *Delta G* are determined. The results are in accordance with conventional ELISA tests but offer a much more refined insight.

[1] C. Wagner, D. Singer, O. Ueberschär, T. Stangner, C. Gutsche, R. Hoffmann, F. Kremer, *Soft Matter*, 2011, 7 (9), 4370 - 4378

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POSTER 25

The Core Unit Fluorescence-Technologies in the IZKF Leipzig

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The overall purpose of the Core Unit Fluorescence-Technologies in the Interdisciplinary Centre for Clinical Research (IZKF) Leipzig is to offer access to expert assistance to techniques in flow cytometry/cell sorting and slide-based cytometry. The specific objectives of this shared resources are to provide the users with a powerful array of cytometric techniques, with expert consultation also in experimental design to optimise data generation, as well as in data presentation and publication.
Currently the Core Unit houses a BD LSR II analyser, a FACSVantage SE high-speed cell sorter, and a Laser Scanning Cytometer.
The analytical flow cytometer is equipped with four lasers (355 nm, 405 nm, 488 nm, and 633 nm) and up to 12 parameters (upgradable) can be measured at the same time.
The sorter has three wavelengths for the excitation (ML UV, 488 nm, and 633 nm) and up to 8 parameters are measurable simultaneously. With a special soft- and hardware it is possible to deposit a predefined number of cells onto slides, filters or individual wells of microtiter plates.
The Core Unit is open to all scientists from the Faculty of Medicine and other faculties of the University of Leipzig as well as to external researchers from other institutions. It is designed to provide services, like training users to operate the analytical cytometers, performing high-speed cell sorting by the staff only, ensuring that all instruments are properly calibrated on a daily basis, advising users concerning the proper settings for their experiments, advising investigators on experimental design and data analysis, and performing further training.

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POSTER 26

*μ*MRI and NMR study of regenerated extracellular matrix in bone defects

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Since bone substitutes are increasingly used in orthopaedic interventions a high interest in optimization of the required materials exists. Using a tibial head defect of Wistar rats we investigate the influence of the pore size of biodegradable poly(lactic-co-glycolic acid) (PLGA) scaffolds which provide a macro-porous three-dimensional carrier.
Cylindrical scaffolds (pore size 100-300, 300-500 or 500-710 *μ*m) with similar porosity and a diameter of 2.5 mm were implanted. Two or four weeks after implantation, the regenerated extracellular matrix (ECM) was *ex vivo* qualitative and quantitative monitored by *μ*MRI and solid state NMR.
Using *μ*MRI, the implanted PLGA scaffolds are clearly visible and a homogeneous generation of ECM was obvious in the presence of the scaffolds. The regeneration of the collagen moiety was followed by ^{13}C MAS NMR and depended on the pore size of the scaffolds at all time points. The inorganic moiety was investigated by ^{31}P MAS NMR and exhibited this dependence not earlier than four weeks due to the known biomineralization delay. Thus, the amount of hydroxyapatite increases significantly during the last implantation interval and larger amino acid order parameters are indicative of progressed biomineralization. However, a pore size of 300 to 500 *μ*m is most effective as carrier and results in *de novo* regenerated ECM quality close to the native, healthy bone.
Hence untreated PLGA scaffolds support ECM formation and result in a more homogeneous healing process indicating that PLGA scaffolds in combination with multifunctional coatings are a promising "multifunctional construction kit" for bone substitute.

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POSTER 27

Geometrische Modellierung des kortikalen Knochens und Validierung anhand von makroskopischen Schnittbildern des humanen os coxae

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Tumor Targeting

EINLEITUNG: Für die Vorhersage der Verankerungsstabilität von Implantaten wird die Computersimulation genutzt. Ziel dieser Arbeit war es, einen Algorithmus für die geometrische Modellierung der kortikalen Knochenschale anhand von μCT-Daten zu entwickeln und an makroskopischen Schnittbildern zu validieren.METHODIK: 5 humane os coxae (62-90 J.) wurden freipräpariert, frisch gefroren, μCT-gescannt (Auflösung 119-130 μm), in Styroporkisten in der gleichen Position wie im CT mit Hartschaum eingebettet, in 52-58 Scheiben gesägt, mit Alizarin rot angefärbt und mit einem Scanner (Auflösung 44 μm) digitalisiert. Die äußere und die innere Kontur der rot gefärbten Kortikalis wurden von einem Mediziner mit Hilfe der Software ImageJ manuell eingezeichnet. ERGEBNISSE: Im Rahmen der Studie wurde ein Segmentierungsalgorithmus entwickelt und unter Zuhilfenahme eines globalen Schwellwerts, einer kortikalen Mindestdicke (0,1 mm), spezieller Strategien zur Glättung und Lückenschließung und unter Berücksichtigung der 3D-Nachbarschaft implementiert. Zur Validierung wurden die Kortikalisdicken der numerischen Segmentierung und der manuellen Segmentierung aus den makroskopischen Schnittbildern vergleichend in Diagrammen dargestellt. DISKUSSION: Anhand des Vergleiches konnte eine hohe Korrelation der Computermodelle mit den Realpräparaten festgestellt werden. In dieser Studie wurden erstmalig aus μCT-Daten segmentierte Knochenmodelle anhand von makroskopischen Dünnschnitten validiert. Die geometrische Differenzierung von spongiösen und kortikalen Bereichen kann zur Modellierung beliebiger Knochenstrukturen genutzt werden.

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POSTER 28

PROFILING OF FREE OXYSTEROLS IN PLASMA BY FAST LIQUID CHROMATOGRAPHY- TANDEM MASS SPECTROMETRY AND PREANALYTICAL ASPECTS

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A number of pathophysiological effects in atherogenesis and inflammation are attributed to oxysterols which can be formed enzymatically and non-enzymatically from cholesterol. The analysis of oxysterols is hampered by their low physiological concentrations and the susceptibility to *in-vitro* autoxidation of cholesterol. The aim of this study was the development of a simple, and reliable high-throughput method for quantification of free oxysterols in human plasma and to standardize preanalytical conditions for oxysterol analysis.
Chromatographic separation of 9 oxysterols was performed by a monolithic column RP-18e Chromolith (Merck, Germany) and was coupled to an API 4000® (AB SCIEX) mass spectrometer. A protein precipitation step was used as sample preparation procedure. Simultaneous analysis of free cholesterol and the free 9 oxysterols was enabled within 7 min. The limit of detection ranged from 0.1 ng/mL (7-ketocholesterol) to 2 ng/mL (4-β-hydroxycholesterol). The linear range varied from 0.5 - 5 ng/mL (LLQ) to 2000 ng/mL (ULQ). In freshly prepared plasma samples, free oxysterols were stable for one hour when stored at 4°C prior to further sample clean up.
This validated fast liquid chromatography combined with tandem mass spectrometry method, including a short and gentle sample preparation, is suitable for a rapid and sensitive profiling of free oxysterols and cholesterol in plasma. The addition of butyl hydroxy toluol (BHT) did not increase the stability of these analytes in plasma samples during storage at 4°C for one hour. Up to three freeze-thaw cycles do not affect analyte levels.

Funding: life

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POSTER 29

Liquid Phase Lithography for Rapid Prototyping of Microfluidic Chips for Free-Flow Electrophoresis, Chemical Sensing and Chromatography

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The fabrication of microfluidic structures is demanding with regard to technical effort and production costs. Usually, meticulous and time consuming processes like structuring and bonding require a cleanroom facility.
With our new approach it is possible to produce microfluidic systems in a fast and economical way. A cleanroom is no longer necessary, and the technique can be repeated in every common laboratory, with only a printer and a UV light source being needed. After one photolithographic production step and the created chips are ready to use and with a multi cycle process easy to modify.
To demonstrate the possibilities of this approach we present the production of a microfluidic free-flow electrophoresis (μFFE) chip. The challenge in producing structures for μFFE is to create a separation bed which is spatially detached from the electric contacts. Due to the chosen setup, resulting gases from electrolysis will not enter the separation bed. Nevertheless, the electric contact to couple the electric field is granted, which enables the electrophoresis. It was possible to create a conductive wall between the electrodes and the separation bed. With the achieved chip it was possible to separate a mixture of fluorescent dyes and fluorescently labelled amino acids. Furthermore it was possible to integrate pH-sensor based on several of fluorescent dyes inside the μFFE structure. Additionally, we were able to expand the technique to produce robust chips for integration of chromatographic particulate and monolithic columns. These can be used for microfluidic chromatographic and electro chromatographic purposes.

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POSTER 30

NMR Investigations of the Effect of Local Disturbances on the Fibril Formation of Amyloid Proteins – An Outlook

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After synthesis of unstructured amino acid chains, proteins fold spontaneously into their highly ordered and therefore biologically active form. This protein folding pathway is determined by intramolecular interactions and the individual 3D structure is encoded in the sequence of the amino acids. However, another thermodynamically stable conformation can be formed, e.g. during pathogenic processes, so called amyloid fibrils. Here, intermolecular interactions between the polymer chains dominate the formation of so called cross-β structures. Today, the high-resolution structures of thousands of proteins are known and structural classes have been identified. In contrast, amyloid fibrils formed by different polypeptides (e.g. HET, Amylin and Aβ) show very similar topologies independent of the individual residue composition. More and more evidence accumulates that the amyloid structure represents a common structure of proteins irrespective of the amino acid sequence.
One underlying question for understanding the fundamental physical basics in this context is: How can local disturbances influence the fibril forming kinetics? We decided to study this question in model fibrils of Aβ(1-40), where amino acid mutations represent local physical forces that should modify local structure and dynamic of Aβ fibrils and also influence the fibrillation kinetics. Different mutations at positions 19 and 34 will be synthesized. Because these residues are known to form a strong molecular contact in the native fibrils, we want to analyse the structural and dynamical consequences of these local disturbances on the surrounding residues.

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POSTER 31

LIPIDOMICS OF LOW DENSITY LIPOPROTEIN – PREANALYTICAL STANDARDIZATION

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The investigation of the lipid composition of lipoproteins requires their proper and reproducible isolation in plasma. Here, we compare two ultracentrifugal lipoprotein isolation strategies by the measurement of lipid metabolites with tandem mass spectrometry to find an optimal method applicable for epidemiological studies.
We applied the sequential flotation and the density-gradient ultracentrifugation. Eicosanoids and fatty acids, extracted by solid phase extraction, as well as phospholipids, oxysterols, phytosterols, sterol precursors and cholesteryl esters, extracted by protein precipitation, were measured with tandem mass spectrometry.
Levels of phospholipids, phytosterols, sterol precursors, and cholesteryl esters, which are considered as stable metabolites, were comparable in LDL which was isolated with both methods. However, the concentrations of eicosanoids, fatty acids, and especially oxysterols increased up to ten-times in LDL separated by sequential flotation ultracentrifugation.
We could demonstrate the replication of comparable concentrations of stable metabolites in LDL fractions isolated with both methods of the same plasma material. The increased concentrations of autoxidatively formed oxysterols and oxidatively formed eicosanoids in LDL isolated with sequential flotation ultracentrifugation indicate an oxidative modification of lipoproteins during this isolation process. Conclusively, by using a multi-day ultracentrifugation, oxidative damages takes place during the isolation process and causes artifactual effects. These results strongly support the application of the density gradient isolation strategy.

Funding: life

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POSTER 32

Gentle chemical methods of oversulfated glycosaminoglycan depolymerization

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Native GAG polymers are not detectable by MALDI-TOF MS due to their high mass and their significant charge. Therefore, defined degradation (best by specific enzymes) is necessary prior to MS characterization. Using the bacterial enzyme chondroitinase ABC for hydrolysis, disaccharide units are nearly exclusively generated. In contrast, a mixture of different oligosaccharides with an even number of carbohydrate units is generated if testicular hyaluronidase is used to digest the GAG. The obtained oligosaccharides can be easily identified by MALDI-TOF MS. The enzymatic digest fails if chemically modified GAG have to be analyzed. A matter of particular interest is to characterize "oversulfated" GAG, for instance, hyaluronan with several sulfate groups on each polymer repeat unit. These oversulfated hyaluronans require chemical depolymerization methods. Among the different potential methods, HCl-induced hydrolysis is quite simple and the yield as well as the size of the oligosaccharides can be controlled by variation of the hydrolysis time and the used HCl concentration. Unfortunately, there are many site reactions: The HCl-induced hydrolysis results in (a) partial loss of the sulfate and (b) cleavage of the N-acetyl side chain to a minor extent. Using this method it is not possible to obtain trisulfated HA oligosaccharides. A more gentle method is the degradation by H_2O_2. Under these conditions trisulfated HA disaccharides are generated but in very small yields only. The in our opinion most gentle method of HA degradation is autohydrolysis, here the resulting mixture can be subsequently easily characterized by MALDI-TOF MS.

Association: PbF III

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POSTER 33

Analysis of skin ceramides in dogs – a comparison of the practicability and efficacy of three different sampling methods

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Objectives:
Ceramides (CER) play an important role in the epidermal barrier function. Their abundance and molecular structure has been shown to be altered in skin diseases in humans.
Aim of the current work was to find a suitable sampling method for ceramide analysis in dogs and to verify the fatty acid (FA) composition of CER by preparative HPTLC followed by gas chromatography (GC) from these samples.
Material and Methods:
Skin samples from dogs were taken via tissue adhesive, skin scrapings and direct extraction with organic solvents. Sampling methods were compared with regard to efficacy and practicability.
The FA composition of CER standards was analyzed via preparative HPTLC and subsequent GC and the results compared to the results obtained from direct GC of the standards.
Results:
Due to the high recovery rate of FA from CER during analysis, all sampling methods provided a sufficient amount of CER for the analysis. However the direct extraction with organic solvents proved to be problematic in dogs and skin scrapings were more difficult to obtain than samples taken via tissue adhesive. Quantification of CER by HPTLC proved to be difficult in samples taken via tissue adhesive, due to a lack of a suitable reference parameter.

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POSTER 34

The analysis of native and oxidatively-modified phospholipids and blood lipoproteins – a MALDI-TOF mass spectrometric study

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Atherosclerosis is a major cause of early death in the industrialized countries. The pathogenesis of the disease is unequivocally correlated with the oxidation of the proteins and phospholipids (PL) of low density lipoproteins (LDL) by reactive oxygen species (ROS). Cells such as granulocytes are involved in inflammatory processes and possess the enzyme myeloperoxidase (MPO), which catalyzes the generation of hypochlorous acid (HOCl). HOCl exhibits high reactivity with different compounds but may be also considered as the educt of even higher reactive species such as hydroxyl radicals ($HO^{\cdot}$). ROS such as superoxide have only low reactivity, ROS with much higher reactivity are derived from these species under *in vivo* conditions. HOCl adds readily to the double bond of unsaturated lipids. These chlorohydrins are quite stable compounds, can be easily identified by MS and accumulate presumably under *in vivo* conditions. $HO^{\cdot}$ radicals lead to the cleavage of double bonds under generation of the corresponding aldehydes or carboxylic acids. This reaction seems to be preferred over the widely discussed generation of endo- and hydroperoxides. In dependence on the reaction conditions lysophospholipids are also generated. Both exhibit significant physiological relevance because they possess detergent-like properties, may destabilize biological membranes and possess messenger functions. Finally, they do also react with proteins. It will be shown that all products mentioned above are also detectable in the case of LDL although more vigorous oxidation conditions are required in order to affect the lipid moiety of LDL.

Funding: life

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POSTER 35

The lipid composition of liver changes in dependence on nutrition- A mass spectrometric and nuclear magnetic resonance study

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Objective(s)
The liver is an extremely important organ of the human body and involved in many different metabolic pathways.
One important liver disease is the "non-alcoholic fatty liver disease" (NAFLD). There are different forms and different severity scales of NAFLD, for example the non-alcoholic fatty liver (NAFL) and the non-alcoholic steatohepatitis (NASH).
Here, the effect of nutrition on the lipid content as well as the lipid composition of the hepatocytes will be investigated.
Material and Methods
Three different nutritional states were investigated: (a) 24 h starvation/12 h re-fed, (b) 24 h starvation and (c) food ad libitum. The isolated hepatocytes were extracted according to the Bligh and Dyer method.
Samples were mixed 1:1 (v/v) with the matrix (either 9-aminoacridine (9-AA) or 2,5-dihydroxybenzoic acid (DHB)) prior to MALDI MS analysis. These measurements were performed on a Bruker "Autoflex" MALDI-TOF device. MS was used to characterize the relative fatty acyl compositions of the individual lipid classes, while total lipid amounts were determined by ^{31}P NMR.

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POSTER 36

Study of nanoparticle uptake and quantification in lung cells by ion beam microscopy

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The mechanism of uptake and distribution of nanoparticles (NPs) in cells and organs are a major step to assess the risk and toxicity of existing and novel nanoproducts. Especially since NPs can serve as devices for diagnostic and therapeutic purposes. In this study alveolar type II cells (A459) were chosen as model system, because of their role as major entrance barrier in the human organism.
In context of IBM two labelling free techniques were applied simultaneously: particle induced x-ray emission (PIXE) and Rutherford backscattering spectroscopy (RBS). The combination of both methods provides unique information regarding cellular elements (P, S, Cl, K, Ca, Fe, Zn) in position and amount at ppm levels.
For the first time the following research shows an intracellular quantification of NP relevant elements. Especially the relationship between applied dose of NPs (ZnO, CeO) and their genuine cellular concentration was studied.
Both CeO and ZnO showed a concentration dependent uptake. Particularly the cellular uptake of NPs was investigated their RBS-signal, which came out differently for intracellular particles in comparison to particles located at the surface.
The possible influence of NP properties on the uptake was studied by using different NP sizes and NPs modified on the surface by a covering protein layer (corona). Both ZnO and CeO NPs showed a significantly higher uptake when no protein corona was present. The results regarding particle size came out different. Cellular ZnO increased with smaller article sizes whereas the CeO uptake rised with higher particle diameters.

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POSTER 37

Vergleich der postoperativen Verankerungsstabilität der künstlichen Hüftpfanne während des Aufstehens und Gehens

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EINLEITUNG:
Für die Beurteilung der Implantatstabilität von Hüftgelenksendoprothesen mittels FEM-Berechnungen ist die Auswirkung von Muskelkräften bei alltäglichen körperlichen Aktivitäten von Interesse. Ziel ist es, die Belastung im Knochen-Implantat-Interface unter Einbeziehung der Muskelkräfte zu untersuchen.
METHODE:
Ein muskuloskelettales Modell (AnyBody Modeling System™, Version 3.0.4) wurde für das Aufstehen (53 cm Sitzhöhe) modifiziert und ein weiteres fürs Gehen übernommen. Die berechneten Muskel- und Gelenkreaktionskräfte wurden auf die FE-Modelle übertragen. In der FEM-Software ANSYS wurden die Beckenknochen mit tetraederförmigen 10-Knoten-Elementen vernetzt und an der Schambeinfuge, dem Superior pubic ligament und dem Arcuate pubic ligament mit Federelementen verbunden. Ins linke Acetabulum wurde eine Standard-Implantatpfanne mit PE-Insert (ESKA Implants, Lübeck) in 45° Inklination und 20° Anteversion eingesetzt.
ERGEBNISSE:
Beim Gehen treten maximale Mikrobewegungen von 125 μm im Zeitschritt 7 auf, beim Aufstehen findet man die höchsten Mikrobewegungen von 75 μm bei Zeitschritt 1. Der Bereich im Implantat-Knochen-Interface für sicheres Einwachsen des Knochens (bis 20 μm) ist beim Gehen kleiner als beim Aufstehen.

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POSTER 38

Verfahren zur Optimierung der Auswertung von Bewegungsanalysedaten für die individuelle Patientenversorgung in der Orthopädietechnik

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Einleitung:
Für die Bewertung der Wirksamkeit eines orthopädischen Hilfsmittels hat sich die Nutzung der klinischen Ganganalyse bewährt. Die Datenbasis soll mehrere Doppelschritte umfassen. Ziel ist es, den manuellen Aufwand bei der Auswertung der 2D-Videoganganalyse zu minimieren. Da die einzelnen Doppelschritte unterschiedlich lang dauern, fallen jeweils verschieden viele Messwerte an. Somit müssen für eine Mittelung fehlende Werte interpoliert werden.
Methode:
Ein Softwarescript für Microsoft Excel wurde entwickelt, um die mittleren Gelenkwinkelverläufe bei Gehen zu bestimmen. Die einzelnen Doppelschritte werden zuerst nach der Anzahl ihrer Messwerte mittels eines Selection-Sort-Algorithmus sortiert und danach normiert. Durch Interpolation nach Aitken-Neville wird eine stetige Funktion ermittelt, die fehlende Messwerte berechnet. Dabei werden 4 Stützstellen genutzt.
Ergebnisse:
Die Berechnung liefert die mittleren Gelenkwinkelverläufe aus den Daten mehrerer einzelner Doppelschritte. Diese werden auch graphisch dargestellt. Ein Vergleich mit Referenzwerten oder Patientenwerten vorheriger Messungen ist möglich.

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POSTER 39

Investigation of Structural Changes upon Ligand Binding of the Methylated Neuropeptide Y Receptor Type 2

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Tumor Targeting

G protein-coupled receptors (GPCRs) represent very important drug targets. For any pharmacological interference, detailed knowledge about the structure and dynamics of the molecules are essential.
We are able to produce large amounts of the receptor in a prokaryotic expression system as inclusion bodies. Subsequently, the receptor was refolded into its functional state tested by phosphorylation. Our aim is to investigate ligand-specific conformational changes of the receptor by NMR spectroscopy. Therefore, we used the reductive methylation of lysine residues to introduce ^{13}C-methyl groups. Due to their favorable relaxation properties, these methyl groups allow for sensitive NMR-measurements. We detected ^{1}H-^{13}C HSQC NMR spectra, which provide some resolved NMR signals of the respective methyl groups. Chemical shift changes of some signals are observable, which are induced by ligand binding. These changes could be related to alterations of salt bridges or ring current effects. A very astonishing side effect is that the functional methylated receptor shows a dramatic increase in the stability.

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POSTER 40

Dynamic force spectroscopy on fluorescence labeled tau-peptides and monoclonal antibodies

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Tumor Targeting

Since humans become older and older with the fast evolution of medicine, degenerative diseases edge ever closer to focus of research. Especially Alzheimer's disease is the most common form of dementia. Each Alzheimer patient shows two commonly known changes in the brain: senile plaques of β-amyloid-peptide and tangles of hyper-phosphorylated tau proteins. Dynamic force spectroscopy (DFS) is performed by using optical tweezers on the level of single receptor-ligand-interactions. Here we report about the specific binding of two anti-human tau-monoclonal antibodies (mAbs), HPT-104 and HPT-110, interacting with synthetic (non-) fluorescence-labeled tau-peptides with different phosphorylation pattern. The fluorescent tagged tau-peptides, anchored on Melanmin-resin beads, are presorted with the fluorescence activated cell sorting (FACS) method in order to achieve homogenous surface coverage. Specific binding events between peptide and mAbs are described according to the Dudko-Hammer-Szabo-model. A comparison between labeled and non-labeled tau-peptide and their interactions with mAbs shall show the influence of the linker- (PEG-spacer) and the fluorescein-molecule on the parameters, obtained by the Dudko-Hammer-Szabo-model.

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POSTER 41

Lysophosphatidylcholine: a new quality marker of human spermatozoa?

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Decreasing sperm quality is a serious problem of human reproduction. In particular, for artificial insemination the detailed knowledge of sperm quality is very important. In order to enable high-throughput screening, assays of sperm quality should be simple, fast and sensitive. MALDI (matrix-assisted laser desorption and ionization) mass spectrometry (MS) of sperm lipids fulfills these criteria. As lipids are normally enriched by extraction, this confers in addition to simple performance the significant advantage that interfering compounds can be easily removed. Another advantage is the termination of enzymatic activities by the organic solvents. Thus, many samples can be prepared for later MS with only minimal changes. The fatty acyl composition of sperm is unique and comprises large amounts of highly unsaturated docosahexaenoic acid which is very sensitive to reactive oxygen species (ROS). Lipid oxidation is accompanied by the generation of saturated lysophosphatidylcholine (LPC) from the abundant membrane lipid phosphatidylcholine (PC). LPC can be easily identified directly from the crude lipid extract without further purification. We will show that the PC/LPC ratio is a convenient measure of sperm quality from men: long time storage of human sperm or seminal plasma is associated with a reduced PC/LPC ratio. Further experiments to confirm the PC/LPC ratio as a quality marker are currently performed.

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POSTER 42

Rapid Quantification of 7-Dehydrocholesterol and Cholesterol in Serum and Dried Blood Spots for the Diagnosis of Smith-Lemly-Opitz Syndrome

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The Smith-Lemly-Opitz syndrome (SLOS) is an inborn metabolic disease in the cholesterol biosynthesis pathway which is characterized by the accumulation of 7- and 8-dehydrocholesterol and by reduced cholesterol levels in the circulation. With this study we investigate a new, rapid and robust HPLC-MS/MS method as routine application for the selective SLOS screening and therapy monitoring in serum and dried blood.
After sample clean up and chromatographic separation, serum or dried blood was analyzed by an API 4000 (AB SCIEX) with atmospheric pressure photo ionization (APPI) and multiple reaction monitoring in positive ion mode. We analyzed 42 serum and dried blood spot samples from 17 SLOS patients at initial diagnosis or under therapy. Precision and reproducibility were validated. The agreement between concentrations in serum and dried blood spots were statistically evaluated by the determination of Pearson and Spearman coefficients of correlation, Scatter Plots, and Bland-Altman-Plots.
Intra- and inter-assay variabilities were < 15% for serum and for dried blood spots. Pearson and Spearman coefficients of correlation between serum and dried blood spot samples were 0.83 and 0.90 for 7-dehydrocholesterol, and 0.86 and 0.85 for cholesterol. The Bland-Altman plots indicated acceptable agreement between cholesterol levels and between 7-dehydrocholesterol values in both sample matrices.
The proposed HPLC-APPI-MS/MS method might be suitable as a high-throughput method for the diagnosis of the SLO syndrome. Besides serum samples, dried blood spots could serve as sample matrix for the SLOS diagnosis and therapy monitoring.

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POSTER 43

Membrane properties of cholesterol analoga

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Cholesterol is a very important molecule in cell membranes. It's unique interactions with phospholipids determine the properties of the phospholipid bilayer and protein-lipid interactions. To study membrane properties a lot cholesterol analoga for fluorescence and EPR measurements are available. Unfortunately, the sometimes large charged fluorescence groups change the molecular properties and interactions compared to native cholesterol dramatically [1].
Topfluor-Cholesterol is a new alternative to the common cholesterol analoga, but so far no investigations on its properties in cell membranes have been published.
By NOESY NMR and fluorescence spectroscopy, it was found that the molecular orientation of Topfluor in the lipid membrane is the same as for of native cholesterol. But nearly no effect on the ^{2}H NMR order parameter of the carbon chains of the POPC was detected. This means that there is no lipid condensation effect in membranes containing Topfluor.
Additionally, we investigated the influence of the hydrocarbon chain linked to the carbon C17 atom of cholesterol to its lipid membrane properties. To this end, five cholesterol analoga with different chains were synthesized. ^{2}H NMR order parameter measurements exhibit a significant influence of this chain to lipid condensation effect. A shorter hydrocarbon chain on the ring structure of cholesterol leads to a strong decrease of the order parameters of the palmitoyl chain of POPC.

[1] Scheidt, H. A., Muller, P., Herrmann, A., Huster, D., J. Biol. Chem. 278, (2003), 45563-45569.

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POSTER 44

Neuer Ansatz zur Nukliddosimetrie

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Im Allgemeinen stellen Messwerte aus Strahlungsmessungen verlässliche Größen dar. Werden sie korrekt interpretiert, können daraus konkrete Dosisgrößen abgeleitet werden. Bestimmend für die Dosis sind immer die Konzentration und die effektive Halbwertszeit im Anreicherungsgebiet der Aktivität. Diese Anreicherungen werden mit nuklearmedizinischer Bildgebung generell vergrößert dargestellt. Eine Ableitung von konkreten Volumina ist aus Gründen der begrenzten Systemauflösung und wegen inhomogener Aktivitätsverteilungen im Organ erschwert. Mit der gegenwärtig zur Verfügung stehenden SPECT-Technik scheint es nicht möglich, das Herdvolumen exakt zu ermitteln. Aktivitätskonzentrationen können hingegen mittels SPECT/CT oder PET/CT hinreichend genau bestimmt werden. Betrachtet man einzelne Anreicherungen unabhängig vom Volumen über die Zeit, lässt sich (am Phantom) recht genau die physikalische Halbwertszeit des verwendeten Nuklids finden. Dabei legt man nicht das gesamte Herdvolumen, sondern einen definierten Standard (z.B. einen Milliliter) zugrunde. Die Verwendung eines speziellen Rekonstruktionsalgorithmus (ReSPECT), der eine von der Größe der Aktivitätsanreicherung unabhängige Aussage liefert, gibt dabei korrekte Angaben zum Voxelinhalt wieder. Mit wenigstens zwei Messwerten dieses Standards und genügend zeitlichem Abstand lassen sich die Konzentration zum jeweiligen Messzeitpunkt, die resultierende effektive Halbwertszeit und somit daraus dosimetrische Größen ableiten. Diese Methodik kann die Dosimetrie in Herdgebieten und in kritischen Organen entscheidend verbessern aber auch einen neuen Ansatz bzgl. Therapieplanung liefern.

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POSTER 45

VSEL cells are not pluripotent but contain mesenchymal precursors

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Murine bone marrow (BM) contains several stem cell types. One of which are very small embryonic-like (VSEL) stem cells, which have shown a broad in vitro differentiation potential. We have studied the relation of VSEL and mesenchymal stromal cells for their further characterization and use in regenerative therapies.We have optimized the isolation of colony forming unit fibroblast (CFU-f) from BM using enzymatic treatment. The increase in CFU-f is paralleled by an increase in Lin-CD45-Sca-1+ VSEL cells, demonstrating that both are closely attached to bone and may be part of the endosteal niche. We also could show a correlation of the age dependancy of VSELs and CFU-f in young and aged mice.We went on to characterize purified VSEL cells, which we isolated from BM by lineage depletion and FACS sorting of CD45-Sca-1+ cells. In standard CFU-f assays>1% of the VSEL cells gave rise to colonies. However, number and size of the colonies increased up to fivefold in 1% oxygen, showing that CFU-f are sensitive to oxidative stress. We next examined the mRNA profile of VSEL cells using qRT-PCR. In contrast to previous reports, Oct4 and Nanog were not present in VSELs. However, we detected an up to 100-fold upregulation of nestin and the transcription factors twist, snail and slug. They are involved in the endothelial-to-mesenchymal transition and in nearal crest cells. These results are compatible with VSEL cells originating from the neural crest.

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POSTER 46

Potentiation of TRPV3 channel activity by cholesterol.

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A major function of skin keratinocytes is to form a permeability barrier, the stratum corneum. For generation of this barrier, keratinocytes pass through a complex differentiation program that is accompanied by synthesis of lipids, like cholesterol and ceramides. Finally, the differentiation of keratinocytes results in apoptosis. Another function of keratinocytes is to sense environmental factors, some of which are decoded by members of the transient receptor potential (TRP) ion channel family. Most of the TRP channels are polymodally regulated by different chemical and physical stimuli. TRPV3, for example, is expressed in keratinocytes and activated by terpenoid-derived ligands like camphor or thymol, but also by plasma membrane depolarisation or temperatures above 33°C. Nothing is known about the influence of cholesterol on TRPV3 signalling. We modified the cholesterol content of HEK293 stably transfected with TRPV3 and performed FLIPR-based calcium measurements. The experiments revealed that cholesterol enrichment robustly potentiates TRPV3 by sensitizing it to lower agonist concentrations. We verified these results with whole-cell patch-clamp measurements. In contrast, TRPV2, another heat-sensing channel, was not affected by cholesterol modification. Since former studies showed a defective formation of epidermal barrier in TRPV3$^{-/-}$ mice, our results imply that cholesterol-regulated TRPV3 signalling may contribute to the progression of differentiation or initiation of apoptosis of keratinocytes.

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POSTER 47

MODULATION OF MACROPHAGE GENE EXPRESSION BY POLYUNSATURATED FATTY ACIDS

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Objective: To investigate immune-modulating actions of polyunsaturated fatty acids (PUFA) we determined macrophage gene expression focusing on cell surface molecules (CD86, Fc receptor, MHCII), intracellular signalling molecules (MyD88, RICK) and antimicrobial enzymes (myeloperoxidase (MPO), superoxiddismutase (SOD), lysozyme).
Material and Methods: RAW264.7 macrophages were supplemented for 72h with 15 μM LNA, EPA, DHA, LA and AA, respectively and subsequently stimulated for 24h with PMA, LPS or viable microorganisms (*R. equi* or *P. aeruginosa*). Unsupplemented, unstimulated macrophages served as reference. Gene expression was analyzed by means of qRT-PCR. The Casc3 gene was used as housekeeping gene.
Results: Expression of CD86, MPO and lysozyme was modulated by enrichment of macrophages with PUFA. PUFA supplementation impaired the stimulation-mediated up-regulation of CD86 and MPO gene expression. Lysozyme gene expression was down-regulated due to cell stimulation. PUFA enrichment of macrophages further decreased lysozyme expression. Data were confirmed on protein level using flow cytometry and enzyme activity analyses.
Conclusion: We identified PUFA of both the n-3 and the n-6 family to down-regulate gene expression of the co-stimulatory molecule CD86 as well as the antimicrobial enzymes MPO and lysozyme. The immune-suppressive actions of the PUFA could also be seen for infected RAW264.7. In summary, our data raise the possibility of a targeted use of PUFA as supportive therapy of chronic diseases caused by persistent pathogens.

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POSTER 48

N-3 AND N-6 POLYUNSATURATED FATTY ACID SUPPLEMENTS REMODEL PLASMA MEMBRANE AND MEMBRANE MICRO DOMAIN ORGANIZATION OF MAST CELLS

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Objectives: Enrichment of mast cells with PUFA impact its functional parameters. We hypothesize that the supplementation of cells with PUFA modifies lipid raft composition, which leads to altered mast cell function.
Methods: C2 cells were supplemented with 20 μM/l LNA, EPA, DHA, LA and AA. Rafts and non-raft membranes were prepared using detergent-free isolation technique per density gradient ultracentrifugation. Content of protein, cholesterol and sphingomyelin as well as the distribution of the raft marker protein Thymus cell antigen 1 (Thy 1) and the non-raft membrane marker protein transferrin receptor (TfR) were determined throughout the gradient. Fatty acid compositions were analyzed by lipid extraction and subsequent gas chromatography.
Results: The lowest protein content was found in the upper three fractions of the gradient and peaked at the bottom. In contrast, cholesterol and sphingomyelin contents were high in the upper three fractions and declined at the bottom. The superior separation of raft and non-raft membranes was confirmed by the distribution Thy 1 and TfR. Supplementation of n-3 PUFA resulted in an increase in the content of n-3 fatty acids in both rafts and non-raft membranes. Contents of cholesterol and protein in both membrane fractions were not affected by the changes in the fatty acid profiles.
Conclusion: Our data provide strong evidence that PUFA of both the n-3 and the n-6 family modulate membrane micro domain lipid composition of mast cells. The observed reorganization of rafts by PUFA enrichment provides a molecular mechanism by which unsaturated fatty acids impact mast cell functionality.

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POSTER 49

Modelling the formation of intestinal organoids in vitro

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In vitro cultures of intestinal tissue have been tried for decades. Only recently Sato and co-workers succeeded in establishing organoid cultures from single cells [1]. In thesecultures cells expressing the stem cell marker Lgr5 form crypt-like structures similar to those found in vivo. The mechanisms that underlie the formation of these spatially organisedstructures are currently a matter of debate.We recently developed a 3D individual cell-based model ofthe intestinal crypt. By computer simulation the model is able of quantitatively reproducing a plethora of data [2]. In this model, stem cell organization is described as a consequence of cell-environmental interactions. We here present an extension of this model, where we have introduced a flexible basal membrane, which can be reorganised by cells showing active matrix metabolism. Thus,the curvature of the epithelium is a result of self-organisation. We apply this model in order to simulate the dynamics of organoid formation in the Sato culture.
We present simulation results of the model assuming two different controlmechanisms of the organoid shape:
i) local changes of the elasticity of the basal membrane and
ii) spontaneous curvature of the epithelium.
We suggest a number of experiments that will enable new insights into the role of mechano-transduction in stem cell organisation.
[1] Sato, T. et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. Nature, 2009, 459, 262-265[2] Buske, P. et al. A comprehensive model of the spatiotemporalstem cell and tissue organisation in the intestinalcrypt. PLoS Comput Biol, 2011, 7, e1001045

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POSTER 50

The Impact of Oleic and Palmitic Acid in Cultured Mouse Hepatocytes.

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Non-alcoholic fatty liver disease (NAFLD) is a highly abundant liver injury, characterized by the fatty accumulation in hepatocytes. The most prominent candidates to accumulate in the liver, monounsaturated oleic acid (OA) and saturated palmitic acid (PA), are likewise the most abundant fatty acids in western diet. To enhance the understanding of the mechanisms of NAFLD, incubations with OA and PA are widely used as in an *in vitro* model of inducing steatosis. To investigate the parameters of an OA/PA-induced steatosis model we incubated fresh isolated mouse hepatocytes with different OA/PA-concentrations for 24h. The resulting intracellular lipid accumulations were measured by Oil Red O staining. Additionally, incubations with radiolabelled fatty acids were performed. We demonstrated that OA and PA increases the intracellular lipid contents in cultured hepatocytes in a concentration-dependent manner, whereas concentrations less than 100 μM are not able to induce detectable steatosis. In case of OA we observed an increased steatotic effect in a concentration range from 300 to 800 μM, while PA caused intracellular lipid accumulation in the range from 200 to 400 μM. With the acquired data it is possible to generate a useful *in vitro* steatosis model. Thereby, it is worth to mention that primary hepatocytes have the ability to tolerate OA and PA at lower concentrations without reaching a steatotic state.

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POSTER 51

HEDGEHOG AROUND THE CLOCK

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Entrained and reset by external cues, the circadian clock controls innate biological processes, including liver metabolism. At the cellular level the answer is characterised by self-sustained transcriptional feedback loops, comprising the core clock genes, like Bmal1, Clock, Per and Cry. Acting as transcriptional factors, the core clock proteins modulate, among others, the fluctuating expression of core metabolic genes. Presenting an extensive biological process, the circadian clock is linked to elements of cell cycle control and intracellular signalling pathways. Recent analyses identified the hedgehog signaling (HH) pathway also to be associated with liver clock. Our aim was to analyse the putative liver specific interaction of the HH-signalling and the clock by gene expression studies at mouse hepatocytes, isolated from liver-specific HH-signalling knock-out (Smo-/-) mice. The results gained showed alterations of both core clock and clock-controlled genes in Smo knock-out mice. Further, the microarray analysis revealed dramatic alteration in gene expression levels of hepatic metabolic processes. The clock is known not only to control physiological processes, but also to be influenced by the metabolic state in a redundant manner. Considering also the knowledge that the circadian rhythm and the HH-signalling pathway regulate overlapping target genes, it is likely that the circadian gene expression is influenced by changes in metabolic processes, caused by the lack of functioning HH-signalling.

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POSTER 52

Regulation of cell-cell adhesion by keratins

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Members of the keratin family of intermediate filament proteins form cytoskeletal scaffolds in epithelia. However, owing to keratin redundancy, the function of keratin isotypes has not been well defined up to date.
To analyze to which extent keratins regulate basic keratinocyte functions, like cytoskeletal organization, adhesion, migration and cell signalling we generated a keratin-free keratinocyte cell culture model from knockout mice. This provides an excellent tool for loss of function studies, without compensation or redundancy effects.
Here, we report an unexpected role of keratins in the maintenance of adhaerens junctions. In the absence of keratins, surface localization of E-cadherin is decreased as determined by surface biotinylation and immunofluorescence microscopy. This is accompanied by a decrease in cell adhesion, as determined by a mechanical stress assay. By re-expression of a single keratin pair, we demonstrate keratin-dependence of the phenotype. We currently investigate whether keratins regulate E-cadherin at the level of early endocytosis through p120 catenin-mediate signalling or through acting as mechanosensors affecting E-cadherin conformation.
Our findings have implications for tumour formation and metastasis, where downregulation of E-cadherin and of keratins accompany the loss of the adhesive epithelial phenotype. We hypothesize that downregulation of posttranslational modification of keratins not only affect cytoarchitecture but may also represent an early signal in the switch from an epithelial to an mesenchymal phenotype.

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POSTER 53

Inhibitors of the AKT/m-TOR signalling pathway exert differential effects on proliferation and IGFBP2 secretion of PTEN-deficient lipoma cells

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Tumor Targeting

Objective: *PTEN* is one of the most frequently mutated tumor suppressor genes and plays an important role in cell cycle regulation and differentiation. We identified a child presenting with massive lipomatosis and a deletion in the *PTEN* gene.
We aimed to investigate how inhibitors of the PI3-Kinase-mTOR signalling pathway influence viability of lipoma cells *in vitro*. Furthermore we wanted to investigate if lipoma cells have an elevated IGF binding protein (IGFBP)2 secretion.
Methods: Proliferation and adipose differentiation were determined by WST-1 assay and fluorescence microscopy. Apoptosis and cell cycle were assessed by AnnexinV/PI and PI assay. We detected IGFBP2 concentrations by ELISA.
Results: Rapamycin (mTOR1 inhibitor) decreased proliferation by 43,4±1,9% and differentiation by 72,7±5,4% *in vitro*. Rapamycin analoga showed weaker effects in similar concentrations. Incubation with mTORC1/2 inhibitors pp242 and WYE-354 led to a viability decrease of 47,1±3,6% and 56,5±3,0%, the PI3-Kinase inhibitors wortmannin and LY294002 decreased cell proliferation by 49,3±0,02% and 77,9±4,6%. Apoptosis was slightly induced only by PI3K inhibitors (~13,7%). IGFBP2 serum levels were significantly elevated (1224±165ng/ml; reference 277-640ng/ml). In lipoma culture supernatant, increased IGFBP2 levels were found at day 4 of differentation (~34fold compared to undifferentiated cells).
Conclusion:
Rapamycin attenuated proliferation of lipoma cells but did not lead to apoptosis. These findings are consistent with treatment results *in vivo*. Lipoma cells could be the source of the elevated IGFBP2 found in the patient's serum.

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POSTER 54

Overexpression of CD97 in enterocytes induces a megaintestine

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Tumor Targeting

CD97 is located in normal human enterocytes within adherens junctions. In transgenic (Tg) mice overexpressing the molecule in intestinal epithelial cells, CD97 strengthened these cell contacts. As we describe here, the Tg mice showed an enlargement of the upper intestine. To clarify the underlying mechanism we analyzed this unexpected phenotype from various angles regarding histology, physiology and cell biology.
The enlargement of the small intestine corresponded to the CD97 cDNA copy number integrated. Living pups developed normal. Food intake, drinking and amount of feces was comparable to wild-type (WT) mice. Tg/TM2 mice overexpressing a truncated CD97 developed no megaintestine, indicating the impact of the β-chain of CD97 and thus signal transduction for intestinal enlargement.
Interestingly, the phenotype is acquired after birth before weaning. Serum levels of growth factors known to cause a megaintestine were normal in Tg mice. After crossing Tg and WT mice and nursing the pups by a Tg mother, only Tg mice showed intestinal lengthening suggesting that milk is not responsible for the effect. The result was confirmed by milk analysis.
Infant but not adult Tg mice showed a transient enhanced proliferation of intestinal crypt stem cells and an increased number of crypt fissions resulting in an increase in length and diameter but not in a change of the microscopic architecture and histology of the small intestine. This is unique among transgenic mice developing a megaintestine.
This is the first time showing the involvement of an adhesion GPCR in size-regulating processes.
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POSTER 55

Cytotoxicity and uptake of metal oxide nanoparticles at A549

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Tumor Targeting

Nanoparticles (NP) become important in the last years. Because of their high surface to volume ratio, they offer higher potential for adsorption and reactivity. These specific properties are used in various applications in different industries. The metal oxide NPs, we are focusing on, are used for example in chemical industry (TiO_2, ZnO, CeO_2 as catalysts; CeO_2 in polishing). Beside their technological relevance, the impact on human health and environment needs to be studied to evaluate the safety of NPs. The NP uptake in cells and organs and their potential toxicity are relevant aspects that are investigated.

The cytotoxic effect of metal oxide NPs (ZnO, CeO_2, TiO_2, FeOx and Al_2O_3) at human lung adenocarcinoma epithelial cells (A549) was studied. To test cell viability in presence of NPs the MTT assay was carried out. An annexine V/propidium iodide cell staining and flowcytometric analysis were done to study apoptosis and necrosis. Furthermore the generation of intracellular ROS (reactive oxygen species) as an indicator of oxidative stress was tested. Beside that the release of inflammatory mediators (IL-8, MCP-1, TNF-a, Eotaxin) was studied by using ELISA method. While CeO_2, TiO_2, FeOx and Al_2O_3 NPs don´t influence the cell viability, A549 cells exposed to ZnO NPs (30μg/ml) show decreased cell viability. The cytotoxic effect of ZnO was studied in dependence of NP concentration and incubation time.

The uptake of metal oxide NPs in A549 cells was tested by confocal Raman Microspectroscopy (CRM). This label-free technique is capable to detect and localize NPs in single cells. Studies with CeO_2 NPs were carried out.

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POSTER 56

Skin development without keratins

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Tumor Targeting

Keratins build the intermediate filament cytoskeleton of all epithelia including the epidermis. Epidermal keratinocytes including stem cells express 6-10 different keratins. The function of keratin isotypes during epidermal differentiation, tissue regeneration and barrier formation are not well understood. To address keratin function during skin development and maturation in a global manner, we deleted the entire keratin type II gene cluster specifically in mouse skin, using K14 cre mice.

Surprisingly, mice without keratins survived up to 12 days. Histological analysis revealed significantly enlarged keratinocytes, acanthosis, parakeratosis and mild cytolysis in regions where keratin deletion took place. Immunofluorescence analysis revealed a mosaic pattern of keratin loss and keratin expression in skin, offering an explanation for the survival. This setting permits novel insights into stem cell lineage development in skin. Most unexpectedly, deletion of keratins caused loss of loricrin, accompanied by a defective epidermal barrier. We will present additional findings supporting a fundamental role of keratins in epidermal homeostasis and barrier function.

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POSTER 57

Adenoviral-mediated overexpression of beta(2)-adrenergic receptors in alveolar epithelial cells

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Tumor Targeting

Alveolar fluid clearance (AFC) is mainly driven by active sodium transport. Na^+ enters the alveolar type II cells through apically located epithelial sodium channels (ENaC) and is extruded by basolaterally located Na,K-ATPases. Following the resulting osmotic gradient, fluid is cleared from the alveoli. Impairments of the active ion transport are associated with respiratory distress in premature neonates, newborns and adults. Stimulation of β_2-adrenergic receptors (β_2AR) increases both abundance and function of ENaC and Na,K-ATPase in alveolar type II cells. Hence β_2-adrenergic receptors are an optimal target to enhance AFC. However, a stimulation of β_2-adrenergic receptors with catecholamines leads to receptor desensitization. Therefore we seek to improve AFC by overexpression of the β_2AR in alveolar epithelial cells. Preliminary results suggest that receptor overexpression does not cause receptor desensitization as seen for catecholamines. Adenoviral-mediated gene transfer is going to be employed for receptor overexpression. Thus a recombinant adenovirus carrying the β_2AR is constructed using the AdEasy Adenoviral Vector Kit. In this study we want to determine the effect of β_2-adrenergic receptor overexpression on expression and function of ENaC and Na,K-ATPases in fetal distal lung epithelial cells. This will be achieved by measuring the short circuit current in Ussing chambers and employing different antagonists to relate the measured currents to the activity of ENaC and the Na,K-ATPases. In the future this attempt might represent a strategy to improve AFC in patients suffering from respiratory distress.

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POSTER 58

MicroRNA-21 directly targets the tumor suppressors ANP32A and SMARCA4 and promotes proliferation and invasion of prostate cancer cells

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Tumor Targeting

MiRNAs comprise a family of numerous non-coding RNAs of ~ 22 nucleotides in length. Mature miRNAs are generated in a multi-step process from long primary transcripts (pri-miRNAs). These molecules regulate gene expression post-transcriptionally by imperfect base-pairing with sequences that are preferentially located in the 3'UTR (3´-untranslated region) of target mRNAs, causing translational repression or mRNA degradation. Among the miRNAs, miR-21 has been identified as a key factor of oncogenic processes. MiR-21 is the only miRNA upregulated in diverse types of tumors such as prostate cancer, glioblastoma and B-cell lymphoma.
In this study, we applied a proteomic and a mathematical approach to identify targets of miR-21. Overexpression of miR-21 in LNCaP prostate cancer cells resulted in a strong repression of the tumor suppressor ANP32A as detected by 2D-DIGE. Performing statistical analysis of published B-cell lymphoma gene expression data, we identified SMARCA4 as a gene that is inversely correlated with pri-miR-21 expression. Both ANP32A and SMARCA4 were confirmed as direct targets of miR-21 by reporter assays. Furthermore, knockdown of ANP32A by RNA interference raised the number of viable LNCaP cells to the same level as obtained by increased miR-21 expression. In A-172 glioblastoma cells, enhanced ANP32A expression mimicked the effect of miR-21 inhibition on cell proliferation and apoptosis. Moreover, increased prostate cancer cell invasion was observed in the presence of high miR-21 and low ANP32A levels. Thus, these data indicate that ANP32A is an important mediator of miR-21 function in several cell types.

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POSTER 59 Keratin-mediated repression of cell migration

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Tumor Targeting

Migration is an essential process in the skin, where it participates in skin development, wound healing, inflammation and malignant progression. In contrast to the well established role of actin and microtubules, the contribution of the keratin cytoskeleton in migration is not well understood. Keratins build up intermediate filaments in all epithelial cells and interact with cell-cell and cell-matrix contacts. The latter mediate the cross-talk of the cytoskeleton with the extracellular matrix and therefore play a crucial role in migration. Thus, to address for the first time the function of the keratin cytoskeleton in dynamic processes like cell migration, we generated a keratin-free cell culture model from knockout mice [Vijayaraj et al., 2009].
Here, we report that the loss of the keratin cytoskeleton enhances the migration of keratinocytes. Re-expression of a single keratin pair reverted this behaviour, demonstrating keratin-dependence. Moreover, we found that altered migration coincided with altered distribution of plectin and beta4-integrin. Unexpectedly, the localisation of actin-dependent focal adhesions was altered as well.
Our data support a model by which keratins directly stabilize hemidesmosomes through maintaining the plectin-beta4-integrin linkage and indirectly stabilize focal adhesions through unknown mechanisms. Our data support the view that the downregulation of keratins observed during epithelial-mesenchymal transition supports the migratory and invasive behaviour of tumour cells.

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POSTER 60 p53-Dependent Downregulation of Cyclin B

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Tumor Targeting

The tumor suppressor p53 is a main regulator in cell cycle control and programmed cell death. It can act as a transcription factor on many genes relevant for checkpoint control during the cell cycle. Functions both as a transcriptional activator and repressor have been described for p53. For activation a consensus DNA-binding sequence is required, which is bound by p53. However, the molecular details of transcriptional repression by p53 are not understood. Earlier, we had shown that *B-type cyclins* are transcriptionally downregulated by p53. Downregulation of *cyclin B2* contributes to stable maintenance of p53-dependent cell cycle arrest at G_2/M. Interestingly, the *cyclin B2* promoter does not contain a consensus p53 binding site. Therefore, no obvious transcriptional mechanism by which p53 would downregulate *cyclin B2* was evident, and we searched for the site and the proteins relevant for repression. When investigating the transcriptional control during the cell cycle, we found that the *cyclin B2* gene is regulated by CDE and CHR promoter elements mainly through repression in G_0/G_1. We had recently identified the DREAM complex being responsible for this repression by binding to the CHR.
In this study we show that the p53-dependent repression of the *cyclin B2* gene is regulated through the CHR in the promoter. Mutation of the CHR led to a significant loss of repression by p53. Importantly, the downregulation requires $p21^{WAF1/CIP1}$. p21 activity shifts composition of the protein complex binding to the CHR. This finding finally resolves the longstanding question by which mechanism p53 downregulates CDE/CHR regulated genes.

Association: PbF III

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POSTER 61

STIM1 and STIM2 regulate store-operated calcium entry, ATP-induced calcium signals and migration in microglia

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Tumor Targeting

The endoplasmic reticulum (ER)-resident Ca^{2+} sensors STIM1 and STIM2 regulate store-operated Ca^{2+} entry (SOCE) in different cell types, including lymphocytes, platelets, skeletal muscle cells, and neurons. However, the molecular composition and functional role of SOCE in microglia is largely unclear. From experiments on wildtype and knockout STIM1 and STIM2 mice, we provide evidence that both STIM isoforms contribute to SOCE in cultured mouse microglia. $STIM1^{-/-}$ and $STIM1^{+/-}$ microglia showed a strong and graded reduction in SOCE, whereas in $STIM2^{-/-}$ cells this effect was markedly smaller. ATP-induced Ca^{2+} responses were also nearly abolished in $STIM1^{-/-}$ microglia and clearly reduced in the absence of STIM2. Patch-clamp experiments showed a complete suppression of the corresponding Ca^{2+} release-activated Ca^{2+} current (I_{CRAC}) in $STIM1^{-/-}$ microglia, whereas a typical Ca^{2+} inward current developed in $STIM1^{+/+}$ cells upon pipette application of inositol 1,4,5-trisphosphate. ATP-induced migration was reduced in both $STIM1^{-/-}$ and $STIM2^{-/-}$ microglia or by application of SOCE blockers ($LaCl_3$, 2-APB and ACA). Our data demonstrate that both ER Ca^{2+} sensors are essential for SOCE, nucleotide-induced Ca^{2+} signals and ATP-induced migration in microglia.

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POSTER 62

Cell Cycle- and p53-dependent Regulation of Polo-Like Kinase 4 Transcription

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Polo-like kinase 4 (Plk4) is a unique member of the Polo-like kinases family and represents a separate branch as it shares little homology with its siblings. It has essential functions in controlling centriole duplication. Therefore, protein levels of Plk4 must be strictly controlled to prevent centriole amplification. The turnover of Plk4 is regulated by three PEST sequences recognized by the SCF complex after phosphorylation. Little is known about the transcriptional regulation. However, it has been shown that the *Plk4* gene is transcribed in a cell cycle-dependent manner. mRNA expression is low in G_0/G_1 phase, increases in S and reaches a maximum in G_2 and mitosis.
Cell cycle-dependent gene expression is often regulated by cell cycle-depended elements (CDE) and cell cycle genes homology regions (CHR). Recently, we could show that the DREAM and MMB complexes bind CHR promoter elements.
Here, we identify a CDE/CHR-tandem element in the *Plk4* promoter that binds the DREAM complex and mediates repression in G_0. When cells progress to G_2 and mitosis, DREAM is replaced by the MMB-complex. Furthermore, expression of *Plk4* depends on Nrf1 and Creb transcription factor binding sites. Importantly, *Plk4* mRNA levels are downregulated upon treatment with the DNA-damaging agent Doxorubicin. We found that this repression depends on a p53-$p21^{WAF1/CIP1}$-DREAM/MMB signalling pathway discovered by us.
In summary, our results show that a complex network regulates *Plk4* on the transcriptional level.

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POSTER 63

Effects on growth rate and metabolism of fetal bovine liver cells during cultivation in Williams' Medium E with different additives

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Tumor Targeting

In vitro cultivation of fetal bovine hepatocytes would be of interest for studies on the cellular mechanism of liver metabolism and some important metabolic diseases of ruminants. To allow such studies, cells must be cultured while maintaining their liver-specific functions and characteristics. This study investigated the effect of supplementation of a specialized medium for liver cells, Williams' Medium E, with two different concentrations of fetal calf serum (FCS) with and without a combination of 0,2 U/ml insulin and 100 nM dexamethasone, on growth rate and production of urea and lactate of fetal bovine liver cells. The following supplementation scheme was used: 5% FCS (A); 10% FCS (B); 5% FCS + insulin + dexamethasone (C) and 10% FCS + insulin + dexamethasone (D). Overall cultivation time was four weeks. Urea and lactate were analysed from medium samples and cells were counted at week 2, 3 and 4 of the experiment.
Supplementation of Williams' Medium E with 10 % FCS promoted cell growth, giving the overall impression of a high lactate and urea production. However, this is achieved by elevated cell numbers rather than a high production rate of these substances per cell. It was not possible to cultivate cells in D for longer than two weeks. Although adding insulin and dexamethasone to Williams' Medium E (5% FCS) hampers cell growth, it enhanced the production of urea and lactate per cell.
For short-term experiments on liver metabolism, when low cell counts do not impede the experiment, cultivation in Wiliams' Medium E supplemented with 5% FCS, insulin and dexamethasone is preferable

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POSTER 64

Regulation of the NAD metabolism in HepG2 cells- Establishment of an HPLC method

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Tumor Targeting

Objective:
NAD (nicotinamide dinucelotide) has a central role in cellular metabolism. NAD is both coenzyme and substrate for enzymes involved in regulating energy metabolism. The aim of this study was to establish a HPLC method to quantify NAD metabolites and ATP (adenosine triphosphate) in HepG2 cell lysates and to analyze influences of the Nampt inhibitor FK866 and the Sirt1 activator resveratrol on the NAD metabolism in HepG2 cells.
Methods:
HepG2 cells were incubated with FK866 or resveratrol. NAD and NMN were detected using reversed phase chromatography. The effect on cell viability and apoptosis was determined with WST-1 and AnnexinV/PI assay.
Results:
After 48h stimulation with 10^{-4} μM FK866 the cell viability decreased by 80,6±7,0%. Already 6h after incubation with FK866 NAD concentrations declined (39,3±6,6%) and decreased further after 24h and 48h . A change in NMN concentrations occurred after 24h (20,0±9,6%). No changes of ATP concentration were measured during 48h. An increased number of apoptotic cells from 15,7±0,9% to 22,7±1,3% was measured after 48h compared with 24 h. This effect enhanced during the next three days.
A stimulation of HepG2 cells with 10 μM to 50 μM of resveratrol for 24h resulted in decreased NMN concentrations. By increasing the resveratrol concentration to 100 μM the NMN concentration increased by 39,2±1,1%. No effects on NAD concentration were detected. The number of apoptotic cells increased after 24h stimulation with 100 μM resveratrol (33,5 ± 2,9%).
Conclusion:
It could be shown that FK866 and resveratrol influence the NAD metabolism of HepG2 cells and have apoptotic effects.

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POSTER 65

Differential effects of saturated and mono-unsaturated free fatty acids on ectodomain shedding of short and long form leptin receptors: Implications for leptin action

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The adipokine leptin (Ob) realizes signal transduction via four different membrane-anchored receptor (Ob-R) isoforms in humans. However, the amount of functionally active Ob-R is affected by constitutive shedding of the extracellular domain. The product of the cleavage process the so-called soluble leptin receptor (sOb-R) is the main binding protein for leptin in human blood and modulates its bioavailability. To describe mechanisms of Ob-R cleavage we established a model of HEK293 cells transiently transfected with different human Ob-R isoforms. The induction of lipotoxicity by saturated fatty acid palmitate led to increased levels of sOb-R in cell supernatants. The increase was accompanied by reduced cell viability and activation of apoptosis demonstrated through detection of cleaved caspase-3 and cleaved nuclear poly (ADP-ribose) polymerase (PARP). Interestingly, co-incubation with a broad spectrum pan caspase inhibitor did not affect palmitate-mediated increase of sOb-R concentration and reduced cell viability. However, mono-unsaturated fatty acid oleate inhibited the increase of sOb-R and prevented the lipotoxic effects of palmitate. In addition, co-incubation experiments of leptin and sOb-R proved that increasing concentrations of sOb-R impaired leptin-mediated STAT3 activation. These findings may in part explain alterations of leptin sensitivity which are associated with changes of serum sOb-R levels in metabolic diseases. Increased sOb-R concentrations due to lipotoxicity and apoptosis seem to directly block leptin action.

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POSTER 66

Modelling circadian rhythm in colon crypts

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Tumor Targeting

The intestinal epithelium is an useful system to study self-renewal tissues. In this tissue thestem cells are confined to a well-defined niche at the bottom of invaginations called crypts. The progeny of these stem cells specify into different functional lineages and regenerate the entire tissue within a few days.
Recently, we introduced an off-lattice model of single crypt dynamics [1]. This model explains crypt dynamics in steady state and after perturbations in agreement with experimental data.
We here present a modelling framework that allows to model multiple-crypt systems, representing a first step towards a whole-tissue model of the intestine.We implemented a Cellular Potts Model on a curved surface representing multiple crypts and applied the regulatory mechanisms and organisation concepts of our off-lattice model. This enables us to cover the self-organisation of cell production and loss in the tissue, which is assumed as fixed in the former model. We provide simulation results applying this model to circadian rhythms of intestinal turnover and compare the results to experimental data [2].

[1] P. Buske et.al., A comprehensive model of the spatio-temporal stem celland tissue organisation in the intestinal crypt. PLoS Comput Biol 2011 7, e1001045.[2] J.M. Qiu, et.al., Cell migration in the small and large bowel shows a strongcircadian rhythm. Epithelial Cell Biol 1994 3(4), 137--148.

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POSTER 67

The tumor suppressor p53 induces expression of the pregnancy-supporting human chorionic gonadotropin (hCG) CGB7 gene

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Successful pregnancy requires a functionally normal blastocyst encountering a receptive maternal endometrium. Interestingly, the cell cycle regulator and tumor suppressor p53 has been reported to support reproduction in mice by regulating the expression of the *leukemia inhibitory factor* gene in the maternal endometrium. However, in humans the hormonal system orchestrating successful pregnancy is considerably different from rodents. Particularly, the primate-specific dimeric glycoprotein hormone human chorionic gonadotropin (hCG) is essential for blastocyst implantation and maintenance of early human pregnancy. Here we provide evidence that p53 selectively induces expression of the *hCGβ7 (CGB7)* gene. None of the other *CGB* genes was found to be regulated by p53. We show that expression of the *CGB7* gene is upregulated upon p53 induction in human HFF, HCT116 and DLD1 cells as well as in cell preparations enriched in human primary first-trimester trophoblasts. The increase in CGB7 levels upon doxorubicin treatment is lost after siRNA-directed knockdown of *p53*. Furthermore, we describe *CGB7* as a direct transcriptional target gene of p53 by identifying a p53-responsive element in the *CGB7* promoter using reporter assays, electrophoretic mobility shift assays and chromatin immunoprecipitations. With these results we provide a new link between p53 transcriptional activity and human reproduction.

Funding: formel1

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POSTER 68

Expression and function of dipeptidyl-peptidase 10 in cardiac and neuronal cells

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Voltage-gated K^+ (K_V) currents are key regulators of excitability in the mammalian nervous system and myocardium, functioning to control neuronal resting membrane potentials and firing patterns, or determine cardiac repolarization and action potential duration. K_V4 channels make up the majority of rapidly activating and inactivating A-type currents (I_A) in neurons and transient outward currents (I_{to}) in cardiomyocytes. Studies in heterologous expression systems have shown that transmembrane dipeptidyl-peptidase-like proteins (DPL) interact with K_V4 channels to regulate surface trafficking and biophysical properties of K_V4 channels. To assess the influence of DPL in native systems, we investigated the expression of DPL in neuronal and cardiac rat tissues and studied the physiological impact of DPP10 in rat dorsal root ganglion neurons using adenovirally delivered short hairpin RNA (shRNA).
In adult rats, DPL subunits are predominantly expressed in neurons, whereas in humans, expression is seen in neuronal and cardiac cells. We observed a colocalization of DPP10 and $K_V4.3$ in the membrane of rat DRG neurons and human atrial myocytes. The shRNA efficiently knocked down DPP10 protein expression in transfected CHO cells and rat DRG neurons. DPP10 knock-down led to a slowed inactivation of I_A currents and shifted the voltage dependence to more positive potentials in both cell types. A delayed recovery from inactivation could be detected only in native DRG neurons. In conclusion, DPP10 interacts with the K_V4 channels in rat DRG neurons and contributes to the fast inactivation and recovery from inactivation of I_A currents.

Funding: formel1

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POSTER 69

Resveratrol modifies the NAD- key enzyme NAMPT and exerts differential effects in healthy and tumoral hepatocytes

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Nicotinamide phosphoribosyltransferase (NAMPT) is a key enzyme of the NAD biosynthesis and regulates the activity of the NAD dependent deacytylase sirtuin 1 (SIRT1). SIRT1 is implicated in modulating cellular energy metabolism, stress response and multiple aging-related diseases including cancer. Resveratrol (Resv), a natural dietary polyphenol, found in grape skin, is a potential SIRT1 activator and has proved to be an effective chemopreventive agent. We hypothesized that NAMPT acts as key player in the Resv mediated apoptosis of tumoral cells.
Resv (100μM) reduced cell proliferation by 44.8± 5.3% and caused an increase of cells in the S-phase (50,100 μM) in HepG2 cells. High dose of Resv led to apoptosis (68.7±10.7%), phosphorylation of p53 (3-fold) and an increased acetylation of p53 (10-fold). It also reduced the intracellular NAMPT protein level by 48.1±15.4% and the NAMPT activity by 49.5±2.3%. Interestingly, the NAD level in HepG2 cells are not negatively modified. In contrast, primary human hepatocytes did not show significant changes.However, human hepatocytes treated with the same amount of Resv showed a dose-dependently increased NAMPT activity (+112.0±7.5%).
We demonstrated that Resv exerts opposite effects on tumoral cells and primary, healthy hepatocytes regarding cell viability, apoptosis and NAMPT protein amount. The apoptotic effects of Resv on tumoral cells might be an up-regulation of the intracellular nicotinamide-level via reduced NAMPT activity and consequent inhibition of SIRT1 which leads to an increased p53 mediated apoptosis. The nicotinamide/NAD ratio could play a key role for sirtuin regulation.

Funding: life

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POSTER 70

Oleate rescues β-cells from palmitate-induced lipotoxicity

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Aim
Chronic exposure of pancreatic β-cells to saturated free fatty acids, like palmitate, induces lipotoxicity which causes a loss of β-cell mass and leads to the development of type 2 diabetes mellitus. The objective of this study was to investigate whether the adipocytokines leptin, adiponectin, Nampt or vaspin or the fatty acid oleate can reduce the palmitate-induced apoptosis in β-cells.
Methods
Viability of INS-1E cells was detected by WST-1 assay. Cytotoxicity was determined by ToxiLight BioAssay. Apoptosis was measured by Annexin V/PI Assay. Western blotting of caspase-3 was performed.
Results
Palmitate(0.5mM) decreased viability by 17.6±2.9% and induced cytotoxicity by 75.1±16.4%. The combination of palmitate and oleate(0.5 mM) increased viability by 30.9±4.3% and compensated the cytotoxic effect of palmitate alone. Palmitate increased apoptosis by 30.2±6.1%. Oleate counteracted the apoptotic effect by 13.7± 4.8%. Caspase-3 was activated after stimulation with palmitate by 0.77±0.21 a.u. compared to control and oleate protected the cells in combination with palmitate with a reduction of activated caspase-3 by 0.98±0.18 a.u. Adipocytokines (leptin, vaspin, Nampt and adiponectin) neither affected cell viability nor did they influence palmitate-induced apoptosis.
Conclusion
Adipocytokines (adiponectin, leptin, Nampt or vaspin) did not change viability, induce cytotoxicity or apoptosis. Adipocytokines did not counteract palmitate-induced lipotoxicity or apoptosis. However, oleate had the ability to ameliorate cell viability and reduce cytotoxicity and apoptosis of INS-1E cells after stimulation with palmitate.

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POSTER 71

DIRECTED NEURAL DIFFERENTIATION OF MOUSE EMBRYONIC STEM CELLS: A MARKER EXPRESSION ANALYSIS

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Tumor Targeting

It is still a major challenge to generate and propagate homogeneous populations of neural stem cells (NSCs). Our aim was to establish a protocol for the differentiation of mouse embryonic stem cells (ESCs) to NSCs and to analyze the expression of neural markers over time in order to determine the optimal time window for purifying them by Magnetic Activated Cell Sorting (MACS).
ESC-derived embryoid bodies were plated in either N2 or B27 medium with bFGF for 16 days. RNA samples were collected every 2 days and qRT-PCR was used to quantify the expression of pluripotency markers (Oct, Nanog) and neural markers (CD133, Glast, Mash, Musashi, NCAM, Nestin, Pax6, GFAP, DCX). Anti-PSA-NCAM MicroBeads were used for MACS which was carried out at day 6 or 9 after induction of differentiation.
Expression of Oct and Nanog declined rapidly upon differentiation. CD133, Musashi and Pax6 increased, attaining a plateau between days 6 and 10, followed by down-regulation, whereas Glast, Mash, NCAM and Nestin remained induced throughout the entire differentiation period. There was no significant difference between N2 and B27 supplement. Immunofluorescence staining confirmed the PCR data and showed that the NSCs were able to differentiate into neurons, astrocytes and oligodendrocytes. MACS at day 6 was too early, since the purified cells developed poorly in contrast to those of MACS at day 9.
We characterized ESC-derived NSCs on both mRNA and protein level, thus contributing to a better understanding of their nature. A narrow time window between day 8 and 9 of the described differentiation procedure appears to be optimal for NSC separation.

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POSTER 72

In vivo analysis of the type I keratin family

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Tumor Targeting

Keratins form the major cytoskeleton of epithelia including the epidermis. Accompanying epithelial differentiation, 4-10 different type I and type II keratins are found in any epithelial cell. The biological consequence for this cell-type specific expression during stem cell maintenance, wound healing and repair are not well understood. To investigate the role of keratin for epidermal development and homeostasis in the absence of redundancy, we generated mice in which all 28 type I keratin genes were deleted. Comparison of these with mice in which all 26 type II keratin genes we independently deleted, allows for the first time to analyse type I and type II keratins in the same tissue and to derive cells for the analysis of molecular mechanisms.
We show that early epidermal development including stratification around E15.5 takes place following the global deletion of type I keratin genes until birth. Histological analysis revealed a severe defect in hair follicle development, with far less hair in knockout compared to wild-type animals. Further, coherence of the epidermis was severely affected. In contrast to prediction, basement membrane adhesion at the level of hemidesmosomes was unaffected but desmosomal adhesion between basal and spinous keratinocytes was disrupted. Unlike mice with type II keratin deletion, expression of late differentiation genes loricrin and filaggrin was unaffected in type I deletion mice. To address the mechanism underlying the cross-talk between keratins and these genes, primary keratinocytes will be analysed. Our in vivo data strongly suggest a novel role of keratins in hair follicle development.

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POSTER 73

Keratin 1 controls the inflammatory network in skin through IL-18 and S100 proteins

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The epidermal barrier protects against mechanical force, dehydration and infections. Its function is impaired in congenital conditions, i.e. ichthyosis vulgaris and epidermolytic hyperkeratosis (EHK), and in common inflammatory skin disorders, i.e. atopic dermatitis (AD) and psoriasis. Misregulation of the immune system has been regarded as primary cause of inflammatory skin conditions. Increasing evidence suggests a role of epidermal keratinocytes in the etiology of these diseases.
KRT1 and KRT10 constitute the keratin cytoskeleton of the suprabasal epidermis. Mutations in *KRT1* and *KRT10* are associated with EHK accompanied by erythema and barrier defects.
Genetic deletion of *Krt1* in mice causes cornified envelope defects, an impaired inside-out epidermal barrier, and a prenatal increase in pro-inflammatory cytokines, i.e. S100A8/A9, IL-18, IL-33, and TSLP. Treatment with IL-18-blocking antibodies *in utero* and backcrossing $Krt1^{-/-}$ to $Il18^{-/-}$ mice rescued the lethal $Krt1^{-/-}$ phenotype. In cultured keratinocytes, IL-18 release was cell-autonomous and caspase-1-dependent, indicating the involvement of Krt1 in inflammasome activation and IL-18 release. Comparing the global transcriptome profile of $Krt1^{-/-}$ and $Krt5^{-/-}$ mice with that of psoriasis and AD patients revealed a substantial similarity between $Krt1^{-/-}$ and AD but less with psoriasis. Our data strongly suggest that KRT1 functions by restricting the inflammatory response in the context of barrier defects as seen in atopic diseases, in addition to maintaining epidermal integrity. Moreover, they imply a general role of keratins in immune functions of epithelial tissues.

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POSTER 74

Blutungssimulator für chirurgische Trainingsmodelle

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Tumor Targeting

Neben chirurgischen Trainingsmethoden, basierend auf virtueller Realität, werden seit einiger Zeit Patientenmodelle mit synthetischen Materialien entwickelt. Dabei werden die Anatomie, physiologische und pathologische Gewebeeigenschaften von Knochen, Fettgewebe und Gefäßen mittels Kunststoffen nachempfunden. Am „Innovative Surgical Training Technologies (ISTT)“ wird in enger Kooperation mit dem Universitätsklinikum Leipzig ein Trainingsmodell zum Erlernen einer lumbalen Bandscheibenoperation einschließlich Diskektomie in Höhe LWK4/5 entwickelt. Die Trainingsmodelle offerieren eine realistische Haptik und ermöglichen den Einsatz von originalen Instrumenten aus der Bandscheibenchirurgie. Darüber hinaus liefern die Modelle zukünftig sensorische Daten, die zur Analyse des Operationsablaufes und zur Auswertung der Trainingsoperationen herangezogen werden sollen. Integraler Bestandteil der Modelle ist ein Blutungssimulator, der realitätsnahe intraoperative Blutungen hervorruft. Mit dem Simulator werden Knochenblutungen, sowie diffuse Gewebs- und direkte Gefäßblutungen realisiert. Blutungen aus der Spongiosa des gestanzten Wirbelbogens und Blutungen aus dem Epiduralfett, als auch direkte Blutungen aus Gefäßen führen zu einer Sichtbehinderung auf das Bandscheibenfach und erschweren den Eingriff. Für individuelle Einblutungsstellen wurden steuerbare Ventile entwickelt, die den Blutfluss über einen großen Bereich variieren und dennoch fein dosieren können. Kernstück des Blutungssimulators ist eine Peristaltikpumpe, die das Kunstblut zu den Ventilen befördert.

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POSTER 75

Prüfung der Retest-Reliabilität des Onset of Depression Inventory (ODI)

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Die Geschwindigkeit des Depressionsbeginns kann erheblich variieren. Die vollständige Ausbildung einer depressiven Episode kann sehr schnell, in weniger als einer Stunde, oder sehr langsam über mehrere Wochen erfolgen. Zur Erfassung dieses interessanten klinischen Parameters wurde das ODI entwickelt (Hegerl et al.; J Clin Psychiatry 2008; 69:1075-1080). Die Untersuchung depressiver Patienten mit diesem Instrument hat ergeben, dass ein schneller Beginn der Depression (<1 Woche) typisch für Patienten mit einer bipolaren affektiven Störung zu sein scheint. Um eine Etablierung des ODI im klinischen Alltag zu erreichen, sollte die Reliabilität des Testverfahrens geprüft werden.
Methodik: In einer Test-Retest-Untersuchung wurde bei 40 Patienten jeweils zu Beginn und kurz vor Ende des stationären Aufenthaltes das ODI durchgeführt. Das Interesse lag dabei auf der Stabilität der Angaben in Hinsicht auf die Einschätzung der Geschwindigkeit des Depressionsbeginns.
Ergebnisse: Die subjektive Einschätzung änderte sich nur unwesentlich: lag der Median des geschätztes Depressionsbeginns zunächst bei „>1 bis 4 Monaten“, reduzierte er sich bei der Zweituntersuchung auf „>1 bis 4 Wochen“ (Wilcoxon-Test: $Z = -0.25$; $p = 0.80$). Die Korrelation zwischen den beiden Messzeitpunkten lag bei $rho = 0.90$ ($p < 0.001$).
Die gefundene hohe Übereinstimmung der ODI-Ergebnisse lässt vermuten, dass Patienten sowohl in der akuten Phase einer depressiven Erkrankung als auch nach (Teil-)Remission die Geschwindigkeit des Beginns ihrer depressiven Episode reliabel einschätzen können und somit das ODI unabhängig von der Erkrankungsphase eingesetzt werden kann.

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POSTER 76

Significant biomechanical changes in breast tumor

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Tumor Targeting

Malignant tumors are not aggregations of homogeneous cells but rather complex formationsof diverse cell types and pathological cells in different stages of aggressiveness. Recentinvestigations show that the biomechanical properties of benign cells differ from those ofcancerous and metastatic cells. In order to characterize these biomechanical properties,primary mamma carcinoma cells are used for measurements and compared to cells obtainedfrom breast reduction. In the course of this clinical trial, samples from 13 breast cancerpatients, obtained from the pathology Niendorf-Hamper, Hamburg, were analyzed. Singlecells obtained by enzymatic dissociation of the homogeneous sample are measured usingthe Optical Stretcher, a two beam laser trap enabling contact-free, whole cell elasticitymeasurements. We found that cells from tumor samples have a broader distribution indeformability than benign cells, the whole distribution being shifted to higher deformability.These distribution are non-Gaussian, they have a positive skew which means a “long tail”towards higher deformations. After deformation, tumor cells retract towards their originalshape. This relaxation behavior is stronger for malignant cells, single cells even contractagainst the applied stress.These findings will help to improve our picture of the heterogeneous nature of tumorsamples, detailed analysis of the “long tail” and contractile cells might lead to new knowledgeabout metastatic competent, disseminated and cancer stem cells.

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POSTER 77

Respiratory function in lean and obese children and the impact of body composition and maximum physical exercise.

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Background and Aims: A few studies demonstrated negative effects of fat mass, especially of centrally distributed fat, on respiratory function in adults. Therefore in this study, we analyzed respiratory function in obese children compared to lean controls and the relation to body fat distribution and the effects of maximum physical exercise. *Materials and Methods:* We evaluated respiratory function in 77 lean and obese children by spirometry, before cycle ergometry and shortly after maximum effort was reached. Body composition including subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) was estimated from Magnetic Resonance Imaging measurements. *Results:* For the forced expiratory volume in 1 second (FEV1) and for the forced vital capacity (FVC), we did not detect any significant differences between the lean and obese group. However, we identified a significantly decreased respiratory resistance in the obese subjects. After cycle ergometry, FEV1 and FVC z-scores did not change significantly within the two gender and weight groups. FEV1 z-scores were significantly negative correlated with SAT as a percentage of body weight (%BW), whereas VAT%BW showed no significant association. FVC z-scores were significant correlated with SAT%BW and VAT%BW. *Conclusion:* We did not find major differences in respiratory function between lean and obese children and no adverse effects of maximum physical exercise. The amount of adipose tissue seems to have adverse effects on respiratory function. In contrast to findings in adults, the distribution between VAT and SAT appears to have no considerable importance in children, yet.

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POSTER 78

Impact of body weight on exercise capacity and changes in metabolic parameters during spiroergoemtry in children and adolescents

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Background and aims: Physical fitness is supposed to be reduced in obese children, most likely due to reduced physical activity. Regular exercise is known to improve metabolic parameters such as insulin resistance. The aim of our study was to compare exercise capacity and acute exercise-related changes in metabolic parameters between lean and obese children. Materials and methods: We evaluated 65 lean and obese children by spiroergometry. Children were asked to cycle to maximum exhaustion applying a two minute step programme of 0.5W/body weight adapted to the 50th centile of height. Blood samples were drawn at baseline and after the test. Results: Physical performance, assessed by the highest intensity in Watt achieved, was significantly better in lean compared to obese children. Similarly, maximum oxygen uptake (VO_2max) was significantly reduced in obese children. At maximum effort, the respiratory quotient (RQ) was 1.105±0.01 in the lean compared to 1.045±0.01 obese children ($p<0.0001$). Lactate levels that were almost doubled in the lean compared to the obese group. After the anaerobic threshold (AT) was reached, the obese group terminated cycling earlier. During exercise, insulin and glucose levels were reduced to a greater extent in obese individuals. Conclusion: Obese children showed a significant reduced exercise capacity with lower physical performance. Interestingly, we demonstrated a significant and immediate improvement in the metabolic profile by acute exercise. In summary our results further underline the beneficial effects of increased physical activity on metabolic and cardiovascular risk in obese children.

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POSTER 79

Screening of Polyomaviridae in organ samples of wild birds using a broad spectrum PCR

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Polyomaviridae are non-enveloped small DNA viruses with a genome size of about 5000 bp.Depending on the infected host (mamalian or avian species) different disease symptoms are observed. In immunocompetent mammals, infections can remain asymptomatic or can cause tumors. In infected birds, however, acute or chronic diseases with high mortality rates are observed. First described in the early 1980s, the polyomaviruses have been detected in several bird species like budgerigar, finch, crow and goose all over the world. In this study a nested broad spectrum PCR was used for the detection of Polyomaviruses in different organs of wild birds. Thirthy- four samples derived from the *Landesuntersuchungsanstalt für das Gesundheits-und Veterinärwesen Sachsen*, Leipzig, were tested using the PCR based on the virus protein 1 sequence, which encodes the main capsid protein of Polyomaviruses. The investigation will be used to gain more insights into the epidemiology of the infection and into the susceptibility of other species like duck, swan, and turkey. The project was supported by the European social funds (ESF).

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POSTER 80

Evaluierung von Acoustic Radiation Force Impulse (ARFI) Elastographie und Transienter Elastographie bei Patienten mit Morbus Wilson: hepatischer Verlauf ist mit höherer Lebersteifigkeit assoziiert

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Einleitung: Bei M. Wilson wird klinisch zwischen einer vorwiegend hepatischen oder neurologischen Verlaufsform unterschieden.
Ziele: Evaluation elastographischer Methoden bzgl. Durchführbarkeit und diagnostischer Wertigkeit zur Detektion der hepatischen Form des M. Wilson.
Methodik: M. Wilson-Patienten wurden mit ARFI und transienter Elastographie (TE) untersucht. Die Ergebnisse wurden der Verlaufsform sowie drei sonomorphologisch definierten Schweregraden gegenübergestellt: Zirrhose, pathologische und normale Sonomorphologie. Als Kontrollen dienten gesunde Probanden (n=50).
Ergebnisse: 50 Wilson-Patienten wurden rekrutiert. Die Lebersteifigkeit bei Patienten mit führender hepatischer Beteiligung (n=31) unterschied sich signifikant von gesunden Probanden (ARFI 1.15 m/s, p=0.002) und von Patienten mit neurologischem oder asymptomatischem Verlauf (n=19): ARFI (1.33 vs. 1.13 m/s; p=0.004) und TE (8.81 vs. 4.88 kPa; p=0.002). ARFI AUROC 0.744, Sens. 61.3%, Spez. 89.5%, Cut-Off 1.25 m/s; TE AUROC 0.829, Sens., 92.0% Spez. 63.2%, Cut-Off 4.85 kPa.
Leberzirrhotiker (n=17) hatten eine signifikant erhöhte Steifigkeit verglichen zu gesunden Probanden (p<0.001) und Patienten mit normaler Sonomorphologie (n=20): ARFI (1.14 vs. 1.43 m/s; p<0.05) und TE (4.88 vs. 10.23 kPa; p<0.05). Die diagnostische Wertigkeit beider Methoden zur Zirrhosedetektion ist vergleichbar: ARFI AUROC 0.809, Sens. 76.5%, Spez. 84.9%, Cut-Off 1.29 m/s; TE AUROC 0.779, Sens. 92.9%, Spez. 50.0%, Cut-Off 5.0 kPa.
Fazit: ARFI und TE können eine hepatische Manifestation sowie eine Zirrhose bei M. Wilson detektieren.

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POSTER 81

Ist der Erfolg einer anti-TNF-Therapie bei rheumatoider Arthritis vorhersagbar?

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Die Rheumatoide Arthritis (RA) ist eine systemische Autoimmunerkrankung, die durch chronische Gelenkentzündungen gekennzeichnet ist. Ein derzeit sehr wirksamer Therapieansatz ist der Einsatz von Inhibitoren gegen das proinflammatorische Zytokin Tumornekrosefaktor alpha (TNFa). Ein Drittel aller Patienten spricht jedoch nur unzureichend auf eine derartige Behandlung an.
In der Studie werden 21 Patienten mit RA vor und während einer Therapie mit dem TNF-Antagonist Etanercept beobachtet. Es erfolgt die Erhebung der klinischen Daten am Patienten vor Therapiebeginn und unter Etanercept aller 4 Wochen bis zu einem halben Jahr. Um die Schwere der Erkrankung und die Therapieresponse zu objektivieren, werden Fragebögen zu Aufgaben des täglichen Lebens, der Gelenkscore DAS28 und verschiedene Entzündungsmarker sowie Autoantikörper dokumentiert. Parallel zu den klinischen Untersuchungen werden humane Monozyten aus dem peripheren Blut von RA-Patienten isoliert und mit Etanercept inkubiert. Begleitend werden Zelloberflächenmarker, wie membranständiges TNF und TNF-Rezeptor 1/2, untersucht. Außerdem soll das Zytokinprofil in vitro bestimmt und die Apoptose der Monozyten nach Inkubation quantifiziert werden.
Ziel der Studie ist es, verschiedene immunologische Faktoren hinsichtlich ihres Nutzens als prädiktiven Marker für die Therapieresponse zu erforschen.

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POSTER 82

Selbsteinschätzung der Lebensqualität bei Leichter Kognitiver Störung und Demenz vom Alzheimer-Typ - Das Problem der affektiven Verzerrung

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Kognitiv beeinträchtigte oder demente Patienten haben möglicherweise mit der Performanz einer komplexen und multidimensionalen Bewertung, wie sie die Selbsteinschätzung (SE) der eigenen Lebensqualität (LQ) erfordern, Schwierigkeiten. Auch bei Gesunden hat der gegenwärtige Stimmungszustand bei der SE der LQ eine direktive Funktion. Daher wird angenommen, dass sich Patienten bei der SE der LQ umso mehr auf ihren aktuellen Stimmungszustand als Referenzgröße beziehen je stärker deren kognitive Beeinträchtigung ist. Um dies zu überprüfen, wurden zwei konsekutive Stichproben, bestehend aus 14 Patienten mit der Diagnose Leichte Kognitive Störung (LKS) und 16 Patienten mit der Diagnose Demenz vom Alzheimer-Typ (DAT), mit einem Fragebogen zur SE der LQ, dem Dementia-Quality of Life (DEMQOL), dem Mehrdimensionalen Befindlichkeitsfragebogen Version A (MDBF-A) und dem Mini-Mental-State-Test (MMST; LKS: M = 25.1, SA = 2.1; DAT: M = 20.3, SA = 2.7) untersucht. Wie erwartet waren die Korrelationen zwischen aktuellem Stimmungszustand und SE der LQ nur für DAT-Patienten aber nicht für LKS-Patienten hoch signifikant. Darüber hinaus war die Stärke der Assoziation für alle signifikanten Korrelationen für DAT-Patienten statistisch signifikant höher als für LKS-Patienten. Die Ergebnisse indizieren, dass SE der LQ bei DAT-Patienten stärker affektiv verzerrt sind als bei LKS -Patienten. Wenn SE der aktuellen Stimmung über mehrere Messzeitpunkte akkumuliert werden sind Befindlichkeitsfragebögen für DAT-Patienten möglicherweise eine Alternative zu LQ- Fragebögen, da sich damit deren Validität als Maß der habituellen Befindlichkeit bzw. LQ erhöht.

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POSTER 83

Moderne Notfallversorgung und das Manchester Triage System - eine Prognose durch agentenbasierte Simulation

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Detailliertes Wissen über die Prozessstrukturen einer zentralen Notaufnahme (ZNA) ist für potentielle Optimierungsansätze von zentraler Bedeutung. In der ZNA des Universitätsklinikums Leipzig konnten durch eine Systemanalyse gezielt relevante Problembereiche identifiziert werden. Hierzu zählt neben der Analyse von Patientenwartezeiten auch ein standardisiertes Verfahren zur Ersteinschätzung von Notfallpatienten (Triage), das bis zum jetzigen Zeitpunkt keine Anwendung findet.
Grundlage für die Simulation des komplexen Informationssystems ZNA war die Modellierung eines detaillierten Pflegeprozessmodells, das die teilweise unstrukturierten Pflegeprozesse übersichtlich und klar strukturiert abbildet. Als Kernproblem konnte das Fehlen eines geeigneten Verfahrens zur Ersteinschätzung von Notfallpatienten und den damit verbundenen, vermeidbaren Wartezeiten von Schwerstverletzten bis zur Erstversorgung identifiziert werden.
Aufbauend auf den Ergebnissen der Prozessanalyse wurden die Prozesse der ZNA unter Verwendung eines geeigneten Simulationsparadigmas nachgestellt. Hierfür wurden die Pflegeprozesse mit Hilfe der agentenbasierten Simulationsumgebung *SeSAm* abgebildet und das reale System der ZNA simuliert und bewertet. Dadurch konnte der Ist-Zustand der Prozesse direkt mit dem neu generierten Zustand, der die Prozessabläufe einer Triagepflegekraft abbildet, verglichen werden. In acht unterschiedlichen Simulationsszenarien konnte die Behandlung von insgesamt über 100 unterschiedlichen Patiententypen simuliert und der Vorteil einer Triagepflegekraft auf die Wartezeit von Schwerstverletzten bis zur Behandlung nachgewiesen werden.

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POSTER 84

Mikroinvasive Behandlung von White-Spot-Läsionen durch Monomerinfiltration

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Ziel: Bewertung der Infiltration natürlicher initialkariöser Läsionen mit Monomer in vitro, bei der die relative Luftfeuchtigkeit (rF) und die Temperatur (t) den Werten in der menschlichen Mundhöhle mit bzw. ohne Kofferdamanlage (Gruppen (G) 1 bzw. G2) entsprachen.
Methoden: Teilung von 10 extrahierten menschlichen Molaren mit initialkariösen Schmelzläsionen in der Mitte der Läsion, randomisierte Aufteilung der 20 korrespondierenden Zahnhälften auf G1 und G2, Abdeckung der Schlifflächen mit Nagellack, Kariesinfiltration (Infiltrant[1]; G1/G2: rF=37-45%/78-90%, t=27-30°C), Einbettung in Kunststoff und Präparation für die rasterelektronenmikroskopische Bewertung (je 3 Ebenen).
Parameter: Anteil Monomerpenetration (Fläche penetrierten Monomers : Läsionsfläche, %), Penetrationstiefe (20 Messpunkte), Homogenität der Penetration (Grad 0/1/2: keine/homogen/inhomogen).
Statistik: Wilcoxon-Test (einseitig; α=0,0167; Bonferroni-Adjustierung).
Ergebnisse: Bei geringer rF (G1) waren der Flächenanteil des penetrierten Monomers um 27% (G1/G2: 28%/22%; p=0,097; nicht signifikant) und die mittlere Penetrationstiefe um 51% erhöht (G1/G2: 172μm/114μm; p=0,097; ebenfalls nicht signifikant) sowie die Homogenität der Penetration um 25% gesteigert (G1/G2: 1,2/1,6; p=0,109; nicht signifikant).
Schlussfolgerung: Die gesteigerte Monomerpenetration bei geringer Luftfeuchtigkeit (Kofferdam) ist zwar nicht signifikant, könnte aber für die Hemmung der Kariesprogression in White-Spot-Läsionen relevant sein.
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POSTER 85

PILOT TRIAL OF RECOMBINANT HUMAN GROWTH HORMONE FOR REMYELINATION IN MULTIPLE SCLEROSIS: CURRENT STATUS AND PRELIMINARY SAFETY ANALYSIS

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Introduction: Multiple sclerosis (MS), an autoimmune demyelinating disease of the central nervous system, causes neurological disability among young adults. While the inflammatory process can be reduced by available medications, there is no treatment to repair the resulting demyelination. In order to improve maturation of re-myelinating oligodendrocytes in MS, recombinant human growth hormone is administered, inducing the maturation factor IGF-1.
Objectives: The primary aim of this single-cross-over baseline-vs.-treatment phase I/II clinical trial is to demonstrate disease-specific safety (since IGF-1 induces lymphocyte proliferation *in vitro*) and provide initial efficacy data.
Current status and preliminary findings: At the time of abstract submission, 26 patients have been screened, of whom 17 could be included and start treatment. RhGH treatment reliably induced an increase in serum IGF-1 in all treated patients; tolerability has been excellent, with mild injection site reactions in some patients. One patient suffered a transient flare-up of presumed autoimmune hepatitis, which resolved after discontinuation of rhGH. A protocol-specified interim safety assessment (after the first four patients completed six months of rhGH treatment) revealed no increase in disease activity as assessed clinically and by monthly Gd-enhanced brain MRI.
Conclusion: After the interim safety analysis, the trial is being continued until the projected 30 patients have completed the study.

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POSTER 86

Anatomische und biomechanische Untersuchung der Wirkung der Beckenorthese Sacroloc® beim chronischen Iliosakralgelenksyndrom

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Rückenschmerz ist ein Hauptkostenfaktor im Gesundheitswesen. Ursache sind in 15 bis 20% Syndrome des Iliosakralgelenks (ISG). Trotz dieser hohen Fallzahlen gibt es derzeit kaum Informationen zu Pathomechanismen des ISG-Syndroms und wenige erfolgversprechende Therapieoptionen. Konservativ wird das ISG-Syndrom zunehmend durch Beckenorthesen behandelt. Der Wirkmechanismus dieser Orthesen ist jedoch unklar.
Die Wirkungsweise der Kompression durch die Beckenorthese Sacroloc® der Firma Bauerfeind wird anatomisch und funktionell untersucht. Ganganalysen, Elektromyographien und MRT werden an 20 Probanden und 20 Patienten mit chronischem ISG-Syndrom durchgeführt. Drei funktionelle Zustände werden betrachtet: keine Kompression, moderate Kompression und maximal tolerable Kompression. Alle Studienteilnehmer werden zudem zur allgemeinen Lebensqualität befragt.
Ziel der Studie ist es, durch den Einsatz der Orthese entstandene morphometrische Veränderungen am Becken festzustellen. Resultierende Modulationen von Muskelaktivität und Gangbild werden eruiert. Aus den Messergebnissen erfolgen zudem virtuelle Analysen der Kompressionswirkung der Orthese Sacroloc®. Weiterhin sollen die erhobenen Daten für nachfolgende Untersuchungen an gesunden und erkrankten ISG genutzt werden.

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POSTER 87

Association of FoxD3 with vitiligo and Hashimoto´s thyroiditis

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Background: Vitiligo and Hashimoto´s thyroiditis (HT) were found to coincide and the autoimmunity locus 1 on Chr.1 was identified as candidate region. *FoxD3*, a gene with functions in embryonal melanogenesis, is located within this locus. We identified a variant (rs78645479) in an index case of vitiligo and HT and evaluated its clinical and functional relevance. Methods & Results: We genotyped the variant in 286 patients with vitiligo, HT, Grave´s disease (GD), diabetes mellitus type 1 or Addison´s disease and 1393 controls. The variant was significantly associated with HT (p=0.02) and vitiligo (p=0.04) in patients diagnosed before the age of 25 yrs (n=39). No association was found for the overall group ranging from 9 to 97 yrs. Among clinicopathologic features, TgAb were associated to the variant in women (p=0.013). No association was detected for TPOAb, TRAb, TSH, fT3 and fT4 levels. We quantified expression of *FoxD3* mRNA in 29 thyroid biopsies. Expression was increased in non-autoimmune goiter (174.3±80.2%) and GD (133.5±51.29%), whereas decreased in HT (84.97±43.59%) compared to healthy thyroid tissue. Effects of rs78645479 on transcriptional activity were examined in a reporter gene assay. Transcriptional activity of the variant was significantly elevated compared to the wildtype in Jurkat (130±11%;p<0,0018) and Hek293 cells (112±7%;p<0,039). Conclusions: Our results approve *FoxD3* as putative susceptibility gene for vitiligo and HT and suggest the presence of age-sensitive mechanisms resulting in different aetiological pathogeneses. Functional results may indicate a role of *FoxD3* in autoimmune processes.

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POSTER 88

Analysis of Proteomics Data using MALDIquant

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MALDI-TOF is a well established technology for mass spectrometric profilingof proteomics data. Here, we introduce the MALDIquant R package that implementsan analysis pipeline for quantitative analysis of clinical MALDI-TOF data on the R platform. We provide a brief summary of current and planned capabilities of the MALDIquantsoftware. First, we briefly list our motivation for creating a new analysis pipeline forMALDI-TOF data. Subsequently, we outline the standard preprocessing steps (variance stabilization, baseline correction and peak detection) in the analysis ofMALDI-TOF data and show the corresponding R commands using the MALDIquant software.MALDIquant is freely available from the R archive CRAN and is distributed under the GNU General Public License.

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POSTER 89 Angiopoietin-related growth factor in the self-contained population of Sorbs

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Objective:
Angiopoietin-related growth factor (AGF) was recently introduced as a novel liver-derived protein with insulinsensitizing and antiobesity effects in mice. In the current study, we investigated circulating AGF levels in the self-contained population of Sorbs in eastern Saxony.
Patients and Measurements:
AGF was determined by ELISA in a heterogenic cohort of 832 non-diabetic Sorbs. AGF was correlated to clinical and biochemical measures of renal function, glucose and lipid metabolism, as well as markers of inflammation.
Results:
Median serum AGF level was 37.9 (± 38.8 μg/l). Patients with diabetes mellitus type 2 had significantly higher AGF serum levels (50.6 ± 58.7 μg/l) compared to non-diabetic subjects (37.3 ± 36.7 μg/l) ($p < 0.001$). In addition, circulating AGF was independently associated with haemoglobin a1c and albuminuria. In our population, AGF did not differ between men and women.
Conclusions:
In contrast to previous findings in mice, AGF was paradoxically associated with markers of hyperglycemia and insulin resistance in our population. Furthermore, albuminuria as a complication of diabetes mellitus has been associated with AGF levels. Here, further studies are needed to better elucidate the physiological significance of circulating AGF in diabetes mellitus and diabetes-related long-term complications like diabetic nephropathy in humans.

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POSTER 90 Dekubitusinzidenz und Prävalenz am Universitätsklinikum Leipzig

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Hintergrund: Dekubitus gilt als Qualitätsindikator für die pflegerische Versorgungsqualität. Im Rahmen von Qualitätsberichterstattung werten seit 2007 die Bundesgeschäftsstelle für Qualitätssicherung (BQS) und seit 2010 an das Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen (AQUA) Daten zu neu entstandenen Dekubiti in deutschen Kliniken aus. Es werden nur Patienten ab einem Alter >=74 Jahre berücksichtigt und Daten des jeweils ersten Quartals genutzt. Empfehlenswert ist daher eine differenzierte Deskription von Prävalenz- und Inzidenzraten, um Patientengruppen mit erhöhtem Risiko zu identifizieren und die eigenen Dekubitusraten für ein klinikübergreifendes Benchmarking heranzuziehen. Methode: Datengrundlage waren anonymisierte Daten des klinischen Informationssystems SAP-ish.med. Die Datenauswertung erfolgte mit SPSS 18. Eingeschlossen waren Patienten mit einem Alter >=18 Jahre und einem ausgewiesenem Dekubitusrisiko (Summenwert <19 Punkte lt. Bradenskala). Ergebnisse: Im Jahr 2010 betrug die Inzidenz von Dekubitus 6,0%, die Prävalenz bei Aufnahme 12,0%. Ab einem Alter von 74 Jahren tritt Dekubitus häufiger auf (Inzidenz: 7,0%, Prävalenz 17,0%). Diskussion: Inzidenzraten vergleichbarer Kliniken umfassen eine Spanne von 5,7%-21.0% (Gerlach et al. 2008). Die Dekubitusprävalenz in vergleichbaren Kliniken beträgt 7,3% (Dassen et al. 2008). Die Ergebnisse der vorliegenden Arbeit sind mit diesen Werten vergleichbar. Die in anderen Studien untersuchten Patientengruppen aus einzelnen klinischen Bereichen, sind als Einschränkung hinsichtlich der vorliegenden Querschnittuntersuchung zu betrachten.

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POSTER 91

Apomorphine acts as a concentration-dependent agonist/blocker of TRPA1 channels

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Apomorphine is a non-narcotic derivative of morphine which acts as a dopamine agonist and is clinically used to treat "off-states" in patients suffering from Parkinson´s disease. Adverse effects of apomorphine treatment include dopaminergic effects such as nausea but also ulceration and pain at the injection site.
We wanted to test whether members of the TRP (transient receptor potential) family contribute to the perception of pain in sensory neurones after apomorphine injection. While the warm/heat receptors TRPV1, TRPV2, TRPV3, and TRPV4 and the cold receptor TRPM8 were insensitive towards apomorphine treatment, TRPA1 could concentration-dependently be modulated by apomorphine. We could demonstrate that low micromolar apomorphine concentrations were able to potently activate heterologously expressed TRPA1 channels (HEK-293-TRPA1) as well as TRPA1 in cultured dorsal root ganglion neurones. Using higher concentrations of up to 100 mM, we observed a complete inhibition of TRPA1 activity.
Previous studies have shown that subcutaneously administered apomorphine produces a biphasic dose response relationship in rats inducing hyperalgesia with low doses whereas high doses of the substance cause antinociception. From our studies we conclude that such *in vivo* effects are most likely mediated by an activation/inhibition of TRPA1 by apomorphine.

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POSTER 92

Synthese und inhibitorische Potenz neuer Chinazolinderivate als potentielle PET-Liganden für die Bildgebung der PDE10A

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Die Phosphodiesterasen (PDEs) sind Enzyme, die in der Spaltung der Phosphodiester-Bindung in 3'-5' Position am Abbau der second messenger cAMP und cGMP beteiligt sind. Es gibt 11 Subtypen, welche in nahezu allen Geweben anzutreffen sind. Im Gehirn, insbesondere im Striatum, ist eine hohe Konzentration von PDE10A vorhanden. Störungen der Hirnbereiche, in denen die PDE10A exprimiert wird, werden mit psychischen Erkrankungen, wie z.B. der Schizophrenie in Verbindung gebracht.Ausgehend von einer Leitstruktur1, welche als zentrales Fragment einen 6,7-Dimethoxychinazolin-Zyklus enthält, wurden systematische Strukturvariationen an Position C6 vorgenommen. Am Beginn der Umsetzungen wurde die 6-ständige Methylgruppe entfernt. Die so erhaltene phenolische Struktur stellt das zentrale Edukt für die weiteren Synthesen dar. Beginnend mit der Einführung einer Benzyl-Schutzgruppe wurden in einer 8-stufigen Synthese die Zielprodukte erhalten. Der letzte Reaktionsschritt ist eine Umsetzung mit verschiedenen Alkylierungsmitteln. Die Ausbeuten an 6-modifizierten Chinazolin-Derivaten betragen 30-85%.
Die synthetisierten Verbindungen wurden auf ihre inhibitorischen Potenzen an der PDE10A und PDE3A in einem in-vitro SPA-Assay getestet, wobei sich die potentiellen PET-Liganden als besonders selektive Inhibitoren der PDE10A im Vergleich zur Leitstruktur herausgestellt haben. Die besten Resultate zeigte 6-(2,2-Difluorethoxy)-7-methoxy-4-[(R)-3-(chinoxalin-2-yloxy)pyrrolidin-1-yl]chinazolin mit einem IC50-Wert von 51 nM (Ki = 25.5 nM).
1-Thomas A. Chappie, et. al.: J. Med. Chem., (2007), 50, 182–185.

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POSTER 93

Development of Ghrelin Inverse Agonists against Obesity

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Ghrelin is an orexigenic gastrointestinal peptide hormones. It plays a central role in the short and long term regulation of hunger and energy homeostasis.[1] Ghrelin receptor possesses a high constitutive activity, representing 50% of its maximal activity.[2] Therefore, ghrelin antagonists and inverse agonists have emerged as potential anti-obesity drugs.[3]
The European project GIPIO (gastro-intestinal peptides in obesity) aims to understand hormonal dysfunctions involved in obesity and to design therapeutic peptides/peptidomimetics against this disease. In this context, we are developing short peptides possessing a high inverse agonist activity at ghrelin receptor. Modification as PEGylation and lipidation are also performed to increase peptides bioavailability. In addition, the combination of a ghrelin inverse agonist with a PYY agonist in a double-drug motif is currently studied. PYY3-36 is an anorexigenic gastrointestinal peptide, acting on the same neuronal cell population than ghrelin, with an opposite effect. Combination of the two peptides is indeed considered to be a new strategy against obesity.
In parallel, ghrelin agonist and inverse agonist radiotracers are developed for PET imaging to give an insight in the peptide behaviour and mode of action in vivo. Moreover, knowing the pharmacokinetic of ghrelin inverse agonist tracers will help to develop druggable peptides.

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POSTER 94

Tissue plasminogen activator and simultaneously applied hyperbaric oxygen do not influence the long-term course of neuronal loss, but tend to decrease macrophage-like cell accumulation following embolic stroke in rats

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Tumor Targeting

Background. Recently, an improved understanding in ischaemia-related tissue damage including neuronal and inflammatory mechanisms arose, but further insights in temporal characteristics are required. This study aimed on long-term effects of tissue plasminogen activator (tPA) as established treatment and combined hyperbaric oxygen (HBO) as potential neuroprotective strategy to diminish neuronal and inflammatory changes after experimental stroke. Methods. Wistar rats were subjected to embolic middle cerebral artery occlusion and treated with tPA, tPA+HBO, or control procedure. Neuronal loss and macrophage-like cell accumulation were assessed at 24 hours, 7, 14 and 28 days, using immunoperoxidase staining of NeuN and CD68. Triple immunofluorescence labelling allowed the simultaneous detection of various cell types revealed by NeuN, CD68, Iba and GFAP. Results. A shell-like pattern of neuronal loss with maximum tissue damage in the ischaemic core was found during the whole observation time. From 24 hours to 7 days, macrophage-like cells accumulated in the ischaemic area and appeared less frequent in the surrounding ischemic border zone. While tPA and tPA+HBO did not change the neuronal course markedly, tPA+HBO tended to decrease macrophage-like cell accumulation in the ischaemic area starting at 2 weeks. Astro- and microgliosis were found at 4 weeks in ischaemia-affected areas. Conclusions. This study confirms the relevance of long-term inflammatory changes concomitantly with neuronal loss in focal cerebral ischaemia. Treatment with HBO might alter these reactions, which needs to be addressed by further research.

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POSTER 95

Contribution of components of STW 5 to its mode of action on intestinal inflammation

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STW 5 (Iberogast®), an established herbal medication, was effective in randomized double blind studies of functional dyspepsia and irritable bowel syndrome. Since STW 5 was found to exert effects on intestinal motility and on inflammatory processes this study investigated further the effects of the fixed combination and of its constituents on acetylcholine-induced contraction, TNF-α release and cell death.

ACh (10 μM)-induced contractions were measured isometrically in rat colon preparations after incubation with 2,4,6-trinitrobenzene sulfonic acid (TNBS, 10 mM) for 30 minutes. TNF-α release was examined in LPS (100 ng/ml)-stimulated human monocytes using a commercially available ELISA kit. The LDH cytotoxicity assay was performed in supernatants of differentiated THP-1 cells after incubation with TNBS (100 μM).

STW 5 (62.7-500.5 μg/ml) reduced ACh-induced contractions in a concentration-dependent manner. Peppermint and chamomile induced a less pronounced reduction, whereas the other components revealed no effect on ACh-induced contractions. STW 5 (500.5 μg/ml) inhibited TNF-α release by 87 %. Bitter candytuft, peppermint, chamomile, liquorice and angelica in concentrations equivalent to those in STW 5 reduced TNF-α release though less pronounced as compared to STW 5. Caraway, milk thistle, lemon balm and greater celandine were without effects. STW 5 (500.5 μg/ml) inhibited TNBS-induced cell death significantly by 43.8 %. All components were equipotent to STW 5 in reducing TNBS-induced LDH activity. Our results indicate that all nine components of STW 5 contribute differently to the effects of the whole plant extract.

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POSTER 96

Citrus fruit flavonoids naringenin and hesperetin are potent TRPM3 blockers

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The transient receptor potential melastatin-3 (TRPM3) is a calcium permeable non-selective cation channel that can be activated by the neurosteroid pregnenolonesulfate (PregS) or heat. TRPM3 is expressed in various tissues, including insulin-secreting β-cells and a subset of sensory neurons from dorsal root (DRG) and trigeminal ganglia. The ability of PregS to evoke TRPM3-like currents in pancreatic β-cells and to induce insulin secretion indicated its involvement in blood glucose regulation. TRPM3$^{-/-}$ mice show so far no metabolic deficits but further investigations are recommended to evaluate its function in insulin secretion. Further studies showed that TRPM3 is a nociceptor channel involved in sensing heat and inflammatory thermal hyperalgesia. A calcium-based screening of a compound library identified several natural compounds as TRPM3 blockers. The most potent blockers were the citrus fruit flavonoids hesperetin and naringenin as well as ononetin, another plant-derived substance. Electrophysiological whole cell measurements as well as calcium measurements confirmed the potency of the TRPM3 blockers. Furthermore, we could show that these blockers are effective on endogenous TRPM3 in DRG neurons from mice and isolated β-cells. Citrus fruit flavonoids are highly concentrated in grapefruitjuice. By drinking grapefruit juice, naringenin could be consumed in concentration that are sufficiently high to block TRPM3 activity *in vivo*. In sensory neurons, TRPM3 may exert similar functions as TRPV1. Thus, TRPM3 blocker could bear a therapeutic potential for analgesic treatment.

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POSTER 97

A novel hCT-based carrier peptide fused with a short endosomolytic peptide for efficient siRNA delivery

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The ability of DNA and RNA to efficiently cross the cellular membrane is hampered by the size and the high negative charge of the oligonucleotides. To overcome this barrier, we focus on the development of peptide carriers derived from human calcitonin (hCT). Recently, branched, highly positively charged peptides based on hCT have been designed for efficient non-covalent delivery of plasmid DNA. However, for efficient siRNA transport, we needed to further modify them in terms of their ability to form stable electrostatic complexes with siRNA and to overcome endosomal entrapment. Hence, we introduced a short peptide sequence, GLLEALALELLE, derived from the HA2 domain of the influenza virus at the N-terminus of hCT(18-32)-k7. The resultant N-E5L-hCT(18-32)-k7 peptide afforded excellent packing of siRNA and improved cellular uptake, as observed by electromobility shift assays, flow cytometry and fluorescence microscopy. For the evaluation of the ability to evoke the desired biological response we designed a read-out system comprising HEK-293 cells transiently transfected with plasmid DNA coding for a yellow fluorescent protein (EYFP)-tagged Y1 receptor (NPY1R). Thus, knockdown of receptor expression after transfection with NPY1R siRNA could easily be followed on the protein level by FACS analysis measuring the fluorescence intensity. After 24 h, a considerable decrease of the receptor expression level down to 20 % could be detected, which was significantly better compared to transfection using lipofectamine. Most importantly, the cells remained fully viable, as confirmed by a resazurin-based cell viability assay.

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POSTER 98

Identification of selective modulators of TRPC4 and TRPC5

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1 RBI - Pharmacology and Toxicology

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The classical transient receptor potential (TRPC)- channels are non-selective cation channels, which are activated by the stimulation of G-protein coupled receptors (GPCR). They are divided into four groups (TRPC1; TRPC2; TRPC3/6/7; and TRPC4/5), according to sequence similarities. These groups mainly differ in their way of activation. While TRPC3/6/7 are activated by diacylglycerol (DAG), TRPC4/5 are DAG-insensitive. The activation of TRPC4/5 seems to depend on the enzyme activity of Phospholipase C (PLC). However, the precise activation mechanism is still unclear.
TRPC4 and TRPC5 are predominantly expressed in the central nervous system and in smooth muscle tissues. TRPC4 seems to contribute to axonal regeneration and to function in endothelium-mediated vasorelaxation. It further controls the microvascular barrier function of endothelial cells.TRPC5 is highly expressed in the hippocampus and amygdala. The channel affects neurite extension and the formation of growth cones. Furthermore, it seems involved in widespread diseases like rheumatoid arthritis and arteriosclerosis.The objective of this work is to identify selective inhibitors or modulators of TRPC4 and TRPC5 by screening different compound libraries. Specific substances could be helpful to analyze the physiological function of these channels *in vivo*. Selective inhibitors could further serve as a starting point to develop cell-biological tools or eventually novel therapeutic drugs for the treatment of TRPC4- and TRPC5- associated diseases.

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POSTER 99

Investigation for API-stability as a function of the drying phase of the fluid bed granulation process

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Granulation has an important role in the manufacturing process of tablets. During fluid bed granulation all granulation process steps are performed in one container. Heated inlet air is used to fluidize granules while the binder is sprayed into the granulator. Afterwards the drying process is performed using the heated inlet air flow. In case of instable drug substances (API) the moisture influences on the one hand the stability of the instable API and on the other hand the tabletting behavior of granules. Therefore the drying process has to be balanced to gain optimum moisture to achieve a well tabletting behavior of the granules and a sufficient API stability. The objective of this study was to improve the stability of an instable API as well as to optimize the drying step of the fluid bed granulation process by a variation of the drying temperature and the drying time of the granules. As model we used an instable steroid hormone in a typical standard formulation containing microcrystalline cellulose and Maltodextrine as binder in 4 kg batch sizes. The granulation process was performed in a fluid bed granulator GPCG 3.1 (Glatt, Binzen, Germany). The inlet air flow was set to 80 m³/h and the inlet air temperature was held constantly at 70°C. Firstly we varied drying time (0 min, 15 min and 30 min) and therefore the final granule moisture and secondly we investigated the influence of the drying temperature at 50°C, 70°C and 90°C on the API-stability and the tableting behavior of the resulting granules. During the granulation process we monitored the particle size using Spatial Filtering Technology as well as the moisture of the granules via Microwave resonance technology to gain further process granulation knowledge. The granules produced during the experiments concerning the drying time were not pressed into tablets. Samples of these granules were packaged in glass vials, stored under accelerated conditions (40°C/75 %r.h.) and examined for stability of API. The granules from the experiments concerning the variation of drying temperature were pressed to tablets. The packaged tablets (PVC/aluminium-blister) were examined for stability of the API under accelerated conditions (40°C/75% r.h.). Furthermore we investigated the tableting-behavior of each granule by evaluating the standard deviations of the press forces.

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POSTER 100

Novel Analogs of Pancreatic Polypeptide as Promising Therapeutics Against Obesity

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Pancreatic polypeptide (PP) is an appetite-inhibiting peptide hormone exerting its effects via the G protein-coupled Y_4-receptor. Thus, appetite as a fundamental cause of obesity could be treated by mimics of this satiety-inducing hormone.
Peptide therapeutics have a lot of advantages like high selectivity, non-toxic degradation and predictable *in vivo*-behavior. The application of peptides as drugs, however, is limited by fast proteolytic degradation and body clearance. This issue can be addressed by peptide engineering such as conjugation to polyethylene glycol (PEG) or lipids.
In this work, we designed analogs of PP based on distinct core peptides, which are modified by either PEGylation or lipidisation. Peptides were synthesized by solid-phase peptide synthesis (SPPS) using Fmoc/*tert*-butyl protecting group strategy with HOBt/DIC-activation. Different fatty acids were introduced at a glutamate-linker coupled to lysine during SPPS, whereas the PEG-polymers were selectively incorporated at a lysine-side chain of PP in solution using a photocleavable protecting group. Pure compounds could be obtained as confirmed by reversed-phase HPLC and MALDI-mass spectrometry. Conformational analysis by circular dichroism spectroscopy revealed no crucial disturbances by the modifications. Radioactive inositol triphosphate turnover assay with COS-7 cells confirmed biological activity. Strikingly, tests with liver extract homogenates demonstrated stabilization of PP by PEGylation.
In conclusion, we designed promising, chemically stabilized conjugates based on pancreatic polypeptide which might be potential anti-obesity drugs.

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POSTER 101

Ligand mimicking receptor variant discloses binding and activation mode of prolactin releasing peptide

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The prolactin-releasing peptide receptor (PrRPR)[1] and its bioactive RF-amide peptide (PrRP20)[2] mediate *inter alia* energy metabolism and anorexic effects[3]. Using rational receptor modeling-assisted double mutagenesis, the binding crevice was identified on a molecular level by leveraging a constitutively active mutant (CAM) of the receptor. Permutation of the conserved receptor residue $D^{6.59}$ with R^{19} of PrRP20 confirmed a direct ionic interaction. $D^{6.59}R$ reveals constitutive activity, suggesting that the mutated residue at the top of transmemberane helix 6 mimics R^{19} by engaging additional binding partners. Guided by a comparative model, five spatially proximal residues were suggested to interact with $D^{6.59}R$. Double mutants eliminated basal activity, leading to the hypothesis that these residues form the ligand binding site. Further mutagenesis revealed $E^{5.26}$ as a second binding partner for R^{19}, whereas $Y^{5.38}A$ and $W^{5.28}A$ receptor mutants significantly impacted receptor activation/signal transduction. A refined model of the PrRP/PrRPR complex was reconstructed based on experimental data to interrogate the structural determinants of ligand recognition. Our novel approach can contribute to the future development of therapeutics targeting human diseases related to CAMs.

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POSTER 102

Pharmacological and toxicological properties of a novel selective PDE10A ligand

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The phosphodiesterase 10A (PDE10A) is important for regulating the intracellular cyclic nucleotides especially in dopaminergic neurons and is a promising candidate for drug development. The inhibition of the PDE10A could be an interesting therapeutic strategy for treatment of brain dysfunctions, such as schizophrenia or as a diagnostic marker for brain imaging. The present study was designed to investigate pharmacological and toxicological properties of a potent and selective brain permeable inhibitor of the PDE10A (K_i = 31.9 nM) as non-radioactive derivative for the development of a radiotracer for positron emission tomography (PET). The lead compound (3006) and the fluoric substituted derivative with prolonged alkyl chain by one methylen group (3039) had no effect on basal intracellular calcium concentration $[Ca^+]_i$ in human neuroblastoma cells (SH-SY5Y). High concentrations (100 μM) of 3039 but not 3006 increased potassium-induced calcium mobilisation. Electrophysiological investigations on rat brain slices indicated no effect of 3039 or 3006 on postsynaptic membrane parameters and synaptic transmission up to 100 μM. After long-term incubation (48 h) no toxic effects of 3039 and 3006 were measured using a cytotoxicity detection assay. Using the zebrafish embryo toxicity test a mortality was observed at concentration of 100 μM for 3039 and $\geq$ 1μM for 3006 after incubation of 48 h. Both compounds had no toxic effects in concentrations relevant for PET ligands. 3039 seems to be an appropriate candidate for developing a PET probe for studying distribution of PDE10A *in vivo*.

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POSTER 103

Design and Synthesis of Ghrelin Receptor Inverse Agonists - An Application for Obesity Treatment

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The ghrelin receptor is a GPCR mainly distributed in the brain that possesses a unique constitutive activity representing 50% of its maximal activity. Signaling of the receptor is controlled by its endogenous ligand ghrelin and considerably contributes to the regulation of appetite, food intake and energy homeostasis [1]. Thus, reducing the constitutive activity can be an approach to decrease body weight and to develop an anti-obesity drug.
Inverse agonists are able to reduce basal signaling of a receptor. Holst et al. introduced variants of substance P acting as inverse agonists at the ghrelin receptor. The hexapeptide KwFwLL-NH_2 significantly reduces the constitutive acitivity [2]. Therefore, we synthesized analogs of this peptide using solid phase peptide synthesis with Fmoc/tBu-strategy. We accomplished the design of highly potent agonists and inverse agonists at the ghrelin receptor. Activity and efficacy could be modulated by the introduction of various aromatic and non-aromatic amino acids in the aromatic peptide core of the lead peptide KwFwLL-NH_2. The importance of this aromatic sequence for activity was demonstrated in signal transduction assays.

References:
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[2] B. Holst, J. Mokrosinski, J.M. Lang, E. Brandt, R. Nygaard, T.M. Frimurer, A.G. Beck-Sickinger, T.W. Schwartz, J. Biol. Chem., 282, 15799 (2007)

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POSTER 104

Characterisation of allosteric binding sites on the hP2X7 receptor - binding pockets for exogenous or endogenous modulators?

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This study focusses on the non-selective cation channel P2X7, which is expressed in immune cells, microglia and astrocytes. Since the involvement of P2X7 in osteoarthritis, neuropathic pain, psychosis and rheumatoid arthritis has been reported, this receptor is of special interest as a promising pharmacological target.
Recent work included the screening of compound libraries and the identification of several modulators of the receptor. Hence, we want to gain insight into the action of the modulators on cells and tissues and their possible consequences for cell biological and pharmaceutical studies. To achieve knowledge about the binding properties within the P2X7 ectodomain, we performed site-directed mutagenesis of hP2X7 cDNA in cloning vectors to obstruct or relax putative binding pockets. The contructs were transfected into human embryonal kidney cells (HEK293) to establish stable cell lines. The re-screen of this mutated hP2X7 constructs with the compound libraries is expected to provide insights into possible allosteric binding sites.
By characterising these binding pockets, studying their phylogenetic conservation and analysing the chemical structure of modulators, we attempt to gather more information about possible endogenous modulators that may sensitise or attenuate P2X7-mediated processes in vivo.

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POSTER 105

Effects of multi-herbal drugs STW 5 and STW 5-II and their main component STW 6 on inflamed rat colon preparations

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Tumor Targeting

Iberogast® (STW5) is a multi-herbal plant extract used in the treatment of gastrointestinal disorders. Pharmacological studies revealed a multi-target effect which may be involved in its clinically proven efficacy in IBS.
We compare the effects of the nine components-containing extract STW5, the six-components containing extract STW5-II and their main component STW6 (*Iberis amara*) on rat colonic preparations before and after induction of inflammation. The inflammation was induced by intraluminal instillation of 2,4,6-trinitrobenzene sulfonic acid (TNBS, 0.01M/0.1M, 30min). Contractions were measured isometrically. Both, STW5 (64-512μg/ml) and STW5-II (66.7-533.2 μg/ml) shifted the concentration-response-relationship of acetylcholine (ACh)-induced contractions (0.01-1000μM) to the right in untreated preparations. STW6 in equivalent concentrations (3-24.1 μg/ml) did not influence the ACh-induced contractions. Preincubation of the preparations with TNBS resulted in an inhibition of the ACh-induced contractions. Coincubation of STW5 (256 and 512μg/ml) or STW 5-II (266.6 and 533.3μg/ml) with TNBS did not prevented this effect whereas STW6 in an equivalent concentration (24.1μg/ml) did. Van Gieson Staining indicated that TNBS induced morphological disturbances of smooth muscular layers and mucosa, which were less distinct after coincubation with STW6. Both, STW5 and STW5-II did not alter the TNBS-induced morphological damages.
Our study suggests that STW6 differs from STW5 and STW5-II in its pharmacological profile. Therefore the results confirm that the components play a distinct role in the effect of the two combinations.

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POSTER 106

Carbaborane containing NPY analogs for breast cancer therapy

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The human Y_1-receptor subtype was found to be over-expressed in more than 90% of breast cancer patients and in 100% of breast cancer derived metastases.
Peptides that can selectively bind at receptors over-expressed in the membrane of cancer cells are a promising tool for tumor diagnosis and therapy. Neuropeptide Y (NPY) as well as pancreatic polypeptide (PP) and peptide YY (PYY) selectively bind Y-receptors (Y_1, Y_2, Y_4 and Y_5) which belong to the rhodopsin like class of G-protein coupled receptors (GPCRs). Binding of ligands to Y-receptors leads to ligand induced internalization of the receptor. Using NPY analogs with high affinity to only one receptor subtype allows selective targeting of only one of these Y-receptor subtypes.
Boron Neutron Capture Therapy (BNCT) is a binary therapy using nontoxic ^{10}B, which is able to absorb nontoxic thermal neutrons to result in an excited state ^{11}B. ^{11}B decomposes to form highly toxic ^{4}He particles and ^{7}Li with a short radiation range of 9 or 5 μm inside the cell. Using these effects, BNCT can be applied in tumor therapy.
In this work, we describe the combination of both therapeutic approaches. Carbaborane-modified amino acids and carboxylic acids were synthesized and introduced at position 4 into receptor-selective NPY analogs by Fmoc/*t*-butyl solid phase peptide synthesis. The resulting peptides were tested for their affinity towards Y_1-receptors; their ability to induce signal transduction and receptor internalization was tested on Y_1- and Y_2- receptors.

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POSTER 107

HIV-1 subtype C clade homogeneity and high rate of polymorphic changes among treatment naïve Ethiopian patients

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Introduction: Ethiopia is a sub Saharan African country where exceptionally HIV-1 subtype C has been predominantly circulating. With increasing mobility and migration, HIV-1 variants may inevitably be introduced and intermixed from the neighbouring countries where other subtypes are co-circulating. In the last four years, access to ART has significantly increased in the country and concomitantly the prevalence of HIV-1 drug resistance mutations is likely to increase. The current study was aimed to determine the predominant HIV-1 subtypes and to identify baseline mutations with potential drug resistance at *Pol* region among ART naive patients.
Results: Among samples from 155 patients investigated, all but two were HIV-1 subtype C (98.7%). According to the International AIDS Society-USA drug resistance interpretation algorithms, antiretroviral drug resistance mutations were detected in 20 (13%) patients (4 NRTI and 16 NNRTI). The Stanford University drug resistance interpretation algorithms, which are largely based on subtype B reveal a lesser level of drug resistance (5.2% (8/155) (4 NRTI and 4 NNRTI). In both algorithms, none of the isolates had major PI mutation and mutation conferring resistance to both NRTI and NNRTI. However, a high rate of polymorphic changes both in PR and RT regions were identified.
Discussion: A predominance of HIV-1 subtype C is an evidence for clade homogeneity and low influx of other subtypes to the country. The level of drug resistance found in this study indicates that many HIV-1 infected individuals on HAART are practicing risk related behaviours. The clinical significance of the high rates of natural polymorphisms at PR and RT regions need phenotypic investigations. The results also show that HIV drug resistance testing should be a practical approach in monitoring patients with ART.

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POSTER 108

Die Thematisierung von Tierschutzaspekten innerhalb der biologiedidaktischen Bildung von Lehrern

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Die Einstellung eines jeden Menschen spielt eine zentrale Rolle, um das Tier als Mitgeschöpf anzuerkennen. Die Grundlagen tierschützerischer Einstellungen müssen dabei schon in der Kindheit gelegt werden, um beim Erwachsenen fest verwurzelt zu sein. Das entwicklungspsychologische Fenster scheint gerade in dem Alter ausgehende Grundschule, beginnende Sekundarstufe dafür geeignet zu sein, da Tiere bei Kindern und Jugendlichen diesen Alters einen hohen Stellenwert besitzen. Besonders in der Sekundarstufe I ist das Interesse an Tieren stark ausgeprägt. Dabei hängt es in entscheidendem Maße vom Biologielehrer ab, wann und wie er im Unterricht Probleme des Tierschutzes behandelt. Schwerpunkt der vorliegenden Untersuchung ist deshalb die Thematisierung von Tierschutzaspekten innerhalb der biologiedidaktischen Bildung von Lehrern sowie die quantitative Analyse tierschutzbezogener Aus- und Fortbildungsangebote innerhalb Deutschlands.

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POSTER 109

Genetic variability of Lacerta viridis in fragmented habitats in Bulgaria

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Tumor Targeting

Biodiversity on earth is threatened by fragmentation and loss of habitats, leading to larger distances between populations, thus impeding gene flow. These processes can result in local, regional, or even global disappearance of species. To investigate the effect of recent anthropogenic habitat fragmentation we examined the genetic diversity of fragmented and unfragmented populations of the Green Lizard (*Lacerta viridis*) in Bulgaria. The fragmented populations of *L. viridis* are situated around Plovdiv in the Thracean plain, 150km southeast of Sofia at an altitude of about 150m. This plain was originally covered by dense forest, but agricultural use of this land has been intensified in the last 200 years. *L. viridis* is now found only in the remaining forest islands between the agricultural fields. We conducted a multi-locus microsatellite analysis of their population structure to investigate sensitivity to fragmentation at the genetic level. We sampled 20 individuals per population in four fragmented and two unfragmented populations and determined genetic variation at 24 microsatellite loci. Additionally, we characterised the landscape in terms of habitat size, distance among habitat patches, and dispersal barriers among the sampled populations to find potential correlations to genetic variation. Results of this analysis will be presented on the poster.

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POSTER 110

Study of segment patterning genes in Onychophora (velvet worms): Insights into the evolution of animal body segmentation

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Tumor Targeting

Organisation of the body into serially repeated units or segments is found in several distantly related animal groups, including chordates, annelids and arthropods. The evolutionary origin of body segmentation in these groups has been discussed controversially and it is therefore unclear whether segmentation has evolved once, twice, or several times among bilaterians. Gene expression studies in Onychophora might help clarify this issue. Onychophora are a group of segmented, soft-bodied animals, which are closely related to arthropods and have changed little since the Early Cambrian. The onychophoran body organisation shows both segmental and non-segmental features, which is why they represent a key taxon for studying the evolution of segmentation. Previous studies have shown that the genes *wingless* and *engrailed* play an important role in the segmentation process of the arthropod embryo, but the function of these genes in onychophoran development remains obscure. To assess whether onychophorans and arthropods share a common segment patterning mechanism, we focus on the expression patterns of segmentation genes, including the pair-rule and the segment polarity genes, in the onychophoran embryo. We have sequenced the transcriptomes of the embryonic and adult stages from two onychophoran species using Next Generation Sequencing. Using these data, we have identified nine onychophoran *Wnt* genes. The next step of our project will involve gene expression studies on onychophoran embryos of different developmental stages. The obtained results will help clarify the evolution of body segmentation in arthropods and other bilaterians.

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POSTER 111

Immunocytochemical analysis of neuronal patterns in Acoelomorpha

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Tumor Targeting

Since their first description, the phylogenetic position of the enigmatic Acoelomorpha is discussed controversially. Originally, the acoels were associated with flatworms, but molecular systematic analyses suggest they are a sister group to all other bilaterians. However, a recent molecular investigation based on microRNAs, mitochondrial genome sequences and EST-data has placed acoelomorphs as an ingroup of deuterostomes closely related to Ambulacraria (echinoderms and hemichordates). The clarification of the exact phylogenetic position of acoels has fundamental implications for our understanding of the evolution of bilaterian organ systems, in particular the nervous system. In order to clarify the presence of brain-like structures in acoels, which is neglected by some authors, and to describe the organization of the nervous system, we investigated neuronal patterns in adult acoels. We used immunocytochemical methods and confocal laser scanning microscopy and analysed the distribution of neuronal markers in the nervous system of *Convolutriloba* sp. In particular the neuronal distribution of tyrosinated α-tubulin indicates the existence of orthogonal nerve fibres and the presence of a brain-like structure in Acoelomorpha, thus contradicting the assumption that these animals bear a diffuse nerve net. We discuss out findings in the light of the current discussion regarding the phylogenetic position of acoels.

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POSTER 112

Wolbachia infections in bees: implications for the use of mitochondrial markers in molecular taxonomy

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The widespread intracellular bacterium *Wolbachia* alters the reproduction of its hosts by different mechanisms. Thereby, inheritance patterns of mitochondrial genomes are modified, possibly confining interpretations of mitochondrial sequence data. Although this phenomenon has been reported before, its conclusions seem to be widely ignored. In the light of recent large scale barcoding projects relying solely on mitochondrial *cox1* sequences, we screened the native German bee fauna (Anthophila) for *Wolbachia* infections. The screening revealed that 73 % of the native German bees are infected by *Wolbachia*. Many species bore identical or similar infections, suggesting a high rate of horizontal transfer. Supergroup A infections were recovered in most cases; only one species bore a supergroup F *Wolbachia* infection. Because *Wolbachia* is not only present in 73% of bees but also in the majority of arthropod species, we argue that studies interpreting sequence data of arthropod species cannot rely on mitochondrial data alone, nuclear markers must be incorporated. DNA barcoding using only mitochondrial *cox1* will not be sufficient to delimit, identify or discover *Wolbachia* infected species, i.e. probably the majority of all animal species.

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POSTER 113

Characterization of striatal long-term plasticity in mice expressing a humanized version of FOXP2

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Tumor Targeting

The capability to acquire complex language sets humans apart from their closest living relatives, the chimpanzees. The transcription factor FOXP2, involved in speech and language development, carries two amino acid substitutions that occurred on the human evolutionary lineage after its separation from the chimpanzee. Recently, we showed that mice "humanized" for these substitutions have specifically modified neuronal properties in cortico-basal ganglia (CBG) circuits. Striatal medium spiny neurons (MSN) in *Foxp2*$^{hum/hum}$ mice show enhanced long-term depression of cortical glutamatergic inputs while cerebellar LTD is not affected.
Here we investigated LTD expression within striatal subregions known to be differentially activated during striatal learning acquisition. Increased striatal plasticty was restricted to the dorso-lateral striatum (DLS) while recordings in the dorso-medial striatum (DMS) revealed slightly opposite effects.
We also tested which of the two amino acid substitutions are responsible for enhanced plasticity. LTD induction in mice homozygous for single Foxp2 mutations (N324S/N324S or T302N/T302N) differentially expressed LTD when compared to wildtypes. While LTD in *Foxp2*$^{N324S/N324S}$ mutants remains at wildtype level, *Foxp2*$^{T302N/T302N}$ mice are comparable to "humanized " FOXP2 mice. Taken together, our results suggest that a single amino acid substitution within FOXP2 accounts for enhanced synaptic plasticity seen in *Foxp2*$^{hum/hum}$ and might have been relevant in the context of speech and language evolution in humans.

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POSTER 113a

Evolution and functional characterization of transcription factors in primates

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Tumor Targeting

While recently extensive genome and transcriptome sequences of primates became available, no thorough analysis of the content and evolution of transcription factor (TF) families in primates have been performed. Considering that TFs regulate the expression of many genes and that many TFs are lineage-specific, we believe that the present project can contribute important answers about the evolution of phenotypic differences between primates and what makes us human. For the analysis of TFs in primates, we are going to utilize publicly available genome sequences, RNA-seq data and BAC sequences from human and other primates with sufficient genome quality and coverage. In addition we are going to generate RNA-seq data for some selected primates. We are going to identify DNA-binding domains in the translated genomic sequences using HMMER software. These domains, gene prediction results, and BLAST results from human TF genes onto the primate genome will guide us in our manual curation and annotation of the non-human primate TF genes with Apollo software. We will then identify orthologous groups of TFs in all analyzed primate genomes, using reciprocal BLAST, OrthoMCL, and synteny information. We will also functionally characterize selected TFs in human and chimpanzee cell lines. To characterize the binding sites of the TFs, we are going to perform ChIP-seq experiments. By silencing the TF genes with siRNAs we aim to determine genes regulated by the TFs. The goal of the experiments is to identify potential target genes of our selected TFs in both species, and to compare them between the two species to gain insight into the molecular basis of phenotypic between humans and chimpanzees.

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POSTER 114

UNSATURATED FATTY ACIDS MODULATE THE OXIDATIVE METABOLISM AND CYTOKINE SYNTHESIS AGAINST RHODOCOCCUS EQUI AND PSEUDOMONAS AERUGINOSA

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Tumor Targeting

Oxidative metabolism and cytokine synthesis by macrophages are crucial in innate immune response. However, some pathogens as *R.equi* and *P.aeruginosa* are able to evade these defense mechanisms leading to chronic infections. Polyunsaturated fatty acids (PUFA) are known to exhibit various immune-modulating properties providing a link between fatty acid uptake and immunity. This study compares the effects of PUFA of both the n-3 and the n-6 family on macrophage oxidative metabolism and cytokine synthesis. RAW264.7 macrophages were supplemented for 72h with 15μM alpha-linolenic acid (LNA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), linoleic acid (LA) and arachidonic acid (AA) respectively, and stimulated for 24h with PMA, LPS as well as viable microorganisms of the genera *R. equi* and *P. aeruginosa*. ROS and RNS production was detected by Dihydrorhodamine 123 and Griess reagent respectively; cytokine production using ELISA kits. Cell enrichment with PUFA was connected with a significant increase of ROS production following the unsaturation degree of the fatty acid supplemented. For stimulated macrophages PUFA supplementation resulted in a significant repressive effect on ROS synthesis. NO production was not affected by PUFA supplementation. The synthesis of the pro-inflammatory cytokines IL-1ß, IL-6 and TNF-α was arrested by PUFA enrichment of the cells. In summary, our data demonstrate PUFA of the n-3 as well as the n-6 family to drive macrophage immune response against the persistent pathogens *R. equi* and *P. aeruginosa* into anti-inflammatory direction.

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POSTER 115

Interferon-α, γ und λ und B-Zellrezeptor-Kreuzvernetzung machen B-Zellen empfindlich gegenüber Aktivierung durch Toll-like-Rezeptor (TLR)7

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Tumor Targeting

B-Lymphozyten differenzieren zu Antikörper-sezernierenden Plasmazellen, wenn sie über TLR9 aktiviert werden. Die B-Zellen reagieren jedoch nur schwach auf Stimulation über TLR7. Unsere Studie untersucht den Einfluss von Interferonen und B-Zellrezeptor (BCR)-Kreuzvernetzung auf die Empfindlichkeit von B-Zellen gegenüber TLR7-Stimulation.

Dafür wurden Humane B-Lymphozyten durch immunmagnetische Anreicherung aus dem Blut gewonnen und mit Interferon-α, γ oder λ_2, einem BCR-kreuzvernetzenden Antikörper und den synthetischen TLR7- und TLR9-Liganden R-848 und CpG stimuliert. Proliferation von naiven (CD27-) und Gedächtnis-(CD27+)-B-Zellen, Zytokin- und Antikörperfreisetzung durch die B-Zellen wurden gemessen.

Bei TLR7-Stimulation teilen sich Gedächtnis-B-Zellen, aber naive B-Zellen proliferieren nicht. Kostimulation mit IFN-α, γ und λ_2 und BCR-Kreuzvernetzung steigern die Proliferation der Gedächtnis-B-Zellen und führen zur Vermehrung der naiven B-Zellen. Zusammen wirken Interferone und BCR-Kreuzvernetzung synergistisch. Über TLR7 aktivierte B-Zellen sezernieren Immunglobuline und setzen Interleukin-6 frei. Dagegen steigern die Interferone die Empfindlichkeit der B-Zellen gegenüber Aktivierung durch TLR9 nicht.

Naive und Gedächtnis-B-Zellen proliferieren stark auf TLR7-Aktivierung, wenn die Zellen gleichzeitig durch IFN-α, γ oder λ_2 oder über BCR-Kreuzvernetzung stimuliert werden. Da der natürliche Ligand für TLR7 Einzelstrang-RNA ist, könnten bei Infektion mit RNA-Viren B-Zellen über diesen Mechanismus aktiviert und zur Differenzierung zu Plasmazellen angeregt werden. Interferon-Therapie könnte diesen Effekt noch verstärken.

Association: PbF III

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POSTER 116

Fibroblasts of the dermal microenvironment support immune functions of dendritic cells and T cells

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Tumor Targeting

During inflammatory skin diseases, connective tissue does not solely have structure providing function, but is also characterized by various biologic activities. In the past, numerous studies demonstrated the influence of the tissue microenvironment for immune functions. However, the role of fibroblasts during inflammatory responses is not well characterized. Fibroblasts are perfect candidates for performing such tasks, as they are able to communicate with other cells through production of cytokines, chemokines and prostaglandins as well as expression of specific surface markers. Therefore, we aimed to investigate the influence of dermal fibroblasts on DC function and on TC function, which is carried out indirectly via contact to DC. Monocyte-derived DC were preactivated for 3 h with LPS (DC_{akt}) to imitate antigen contact in inflamed skin. Afterwards, DC_{akt} were cocultured with dermal fibroblasts for 18 h. Following, DC_{akt} were separated from the cocultures and cultivated with allogeneic TC for 3 to 7 d. We could show that fibroblasts support secretion of various cytokines by DC_{akt}. Fibroblasts also led to increased migration of DC, whereas expression of costimulatory molecules by DC_{akt} was not influenced by the connective tissue cells. Furthermore, fibroblasts supported T_H17 expansion, T_H1 development, TC-proliferation and skin-homing ability of TC. What is more, we were able to demonstrate that this supportive role of fibroblasts on regulation of immune function is mediated on the one hand side via differential cytokine secretion and on the other hand side via direct cellular contact to the DC_{akt}.

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POSTER 117

Modelling hematological parameters after irradiation in a stem cell transplantation model

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Introduction: The investigation of reconstitution in hematopoiesis after time- and dose-dependent irradiation in a model for hematological parameters is able to define the stem cell population and the resulting white blood cell population.
Materials and Methods: CD4-/- C57Bl/6 mice, transgenic for human CD4 and HLA-DR3, were irradiated in a single- (3, 6, 8 and 12 Gy) and fraction- (total 6, 9 and 12 Gy) dose regimen. Blood was analysed weekly for red blood cells (RBC), hemoglobin concentration (Hb), hematocrit (HCT) and white blood cells (WBC). Organ and tissue damage after irradiation was examined through histopathology.
Results: The recovery curves for RBC, Hb, HCT and WBC show the same velocity (< 1 week) for all doses but starting at different, dose-dependent times. The only dose-dependent parameter is defined by the beginning of the recovery process (dose-dependent shift). Furthermore, higher doses are related to a later recovery of the hematopoietic system. The RBC, Hb and HCT recovery is then followed by a saturation curve reaching a final concentration independent from the irradiation dose. Histological analysis of the bone marrow in the single dose cohort showed a dose-dependent reduction of the cellularity in the bone marrow cavities. The fractioned irradiation dose cohort resulted in a regeneration of all bone marrow cavities with a normal distribution of blood cells.
Conclusions: These findings might be of relevance in the refinement of strategies in the treatment of hematological malignancies and leads to a further understanding of the hematopoietic system after lethal irradiation.

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POSTER 118

Cyclophilin D and GTP depletion participate in rubella virus induced cell death

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Apoptosis is not only fundamental for cellular growth and differentiation, it also represents an important cellular defence mechanism to combat viral infections. Thus apoptosis plays an important role in the pathogenesis of some viruses such as rubella virus (RV), one of the most efficient teratogenic viruses. The nonimmunosuppressive cyclosporin derivative *N*-methyl-4-isoleucine-cyclosporin (NIM811) specifically inhibits cyclophilin D, the main regulator of the mitochondrial permeabilization transition pore. Mitochondrial permeability transition is the key component of mitochondria-based induction of apoptosis. The expression of cyclophilin D is increased during the course of RV infection, additionally its localization shifts almost exclusively to the nucleus. The application of NIM811 and deoxyguanosine, even during very early time points of infection, reduces cytopathic effect induction by RV significantly. The results presented indicate that cyclophilin D and depletion of intracellular GTP pools are involved in RV pathogenicity, which extends and complements the previously reported p53-dependent apoptotic pathway during RV infection. These findings have important implications for the mechanism of RV (teratogenic) pathogenesis.

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POSTER 119

Coordinated effects of interleukin-8 and glycosaminoglycans on functions of neutrophil granulocytes

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Tumor Targeting

A successful defense against invading pathogens and a positive outcome of an infection rely on a properly functioning immune system. The recruitment of leukocytes to places of injury occurs in a temporally and spatially coordinated manner. Thereby chemokines and their interaction with glycosaminoglycans (GAGs) play an important role by directing specialized subsets of leukocytes from blood into tissue.
The aim of this study was to investigate effects of selected GAGs such as heparin (HP), chondroitin sulfate (CS), and hyaluronic acid (HA) on interleukin-8 (CXCL8)-dependent functions of neutrophil granulocytes. Freshly isolated cells from human peripheral blood exhibited a strong chemotactic activity towards CXCL8 (EC_{50} = 0.5 nM) as measured with a modified Boyden chamber. The chemotactic response of neutrophil granulocytes was diminished by GAGs only, when CXCL8 was pre-incubated with heparin. The production of CXCL8-induced reactive oxygen species (ROS) by neutrophil granulocytes was assessed by flow cytometry using dihydrorhodamine 123. The initiation of this microbicidal mechanism required micromolar CXCL8-concentrations (EC_{50} = 8.7 μM). Intriguingly, the addition of HP or CS together with CXCL8 enormously increased the ROS production, while the addition of HA had only slight effects. Hence, sulfated glycosaminoglycans are able to modulate CXCL8-induced responses in neutrophil granulocytes.

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POSTER 120

CD4+CD8+ double positive T cells in canine peripheral blood have features of activated T cells

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Tumor Targeting

Besides the common $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T helper cells in canine peripheral blood a small third population of T cells exists which simultaneously expresses the CD4 and the CD8 co-receptors. These $CD4^+$ $CD8^+$double positive T cells (dp T cells) have been studied in several species such as man, rat, macaque, and especially the pig. Here we present a first analysis of a dp T cell subpopulation in dogs.
To study whether canine dp T cells in the peripheral blood mononuclear cells (PBMC) represent thymocytes or mature T cells, expression of the thymic marker CD1a was analyzed. Our data show that dp T cells lack CD1a expression. In addition, we show that canine peripheral blood dp T cells utilise the T cell receptor (TCR) alpha/beta and not the TCR gamma/delta. About one third of canine dp T cells expresses the activation marker CD25.
Canine PBMC were *in vitro* stimulated with oligoclonal and viral stimuli. Oligoclonal stimulation was done with *Staphylococcus aureus* enterotoxin B. First-time viral stimulation was done using parapoxvirus ovis (PPVO) and viral re-stimulation was done with canine distemper virus (CDV). In the cells that underwent proliferation due to oligoclonal stimulation and viral recall antigen but not in PBMC from seronegative dogs stimulated with (PPVO) the proportion of dp T cells increased. Nearly all cells in the increased dp T cell fraction after stimulation proliferated.
Together, canine dp T cells appear to be mature alpha/beta TCR+ T cells with features of activation. Studies are ongoing to characterize the progenitors of dp T cells as well as their *in vivo* properties.

Association: PbF III

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POSTER 121

Blood brain barrier proteins along the vascular tree of parenchymal and subarachnoid vessels

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Tumor Targeting

The blood-brain barrier (BBB)-specific differentiation of endothelial cell for long has been attributed to astrocytic factors (Janzer and Raff, Nature 1987). However, only at the level of capillaries astrocytic endfeet (of the glia limitans) are directly attached to the endothelial layer. In all other parts of the parenchymal vascular tree, additional layers (muscle cells, pericytes, Virchow-Robin space) separate astrocytes from the endothelium. Subarachnoid vessels cannot be touched by astrocytes at all. In these cases, we tested the protein expression of prominent tight-junctional elements known to be pivotal in BBB formation in comparison to parenchymal capillaries. In addition, we used electron microscopy to systematically analyze the formation of tight junction complexes of CNS vessels in each segment of the vascular tree. First results suggest that endothelial tight junctions are present in all CNS vessels, irrespective of their position in the vascular tree and putative contacts to astrocytic processes.
Supported by DFG * These authors contributed equally

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POSTER 122

Tight barriere or permanent line of defense: The cribroid plate

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Tumor Targeting

The brain has been regarded as shielded by tight barriers ("blood brain barrier" & "blood-CSF-barrier") and the absence of lymph vessels. However, we have shown that brain antigens drain-, and brain-derived T cell migrate into cervical lymph nodes via the cribroid plate. Vice versa, we used intranasal injection of GFP-coupled viruses to demonstrate axonal transportation of them into the bulb via olfactory nerves. Strikingly, virus was eliminated within one week in the absence of T cells! Thus, we search for alternate, site-specific mechanisms of defence at the border between nasal mucosa and the brain. To this end, we established a method to cut whole heads of mice and rats. Immune stainings for human beta-defensin 2, 3 & 4 revealed protein expression within nasal septum cartilage. Moreover, we observed occasional infiltrates at the cranial side of the cribroid plate indicating constant immune defence in the absence of clinical symptoms.
Supported by DFG

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POSTER 123

Necroptotic cell degeneration in the CNS of experimental measles encephalitis in Lewis rats

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Tumor Targeting

Central nervous system (CNS) complications occurring early and late after acute measles infections are serious and often fatal. In brains of experimental rat measles encephalitis (Lewis rat) only neurons are infected with the neurotropic measles virus strain (CAM/RB).
To determine the mechanism contributing to measles virus (MV) pathogenesis, we studied the mRNA expression of genes that relate to antiviral defence of the host cells. We analysed the mRNA expression in infected rats in situ as well as in primary dissociated rat neuronal cell culture. The transcriptional activity of 22 apoptosis-related genes and genes of the intrinsic immune system were determined by qRT-PCR. Expression of Caspase 8, TNF and RIP3 was particularly up-regulated. This finding is interpretated as indication for RIP3-dependant switch of TNF-induced apoptotic cell death from apoptosis to necroptosis. The concommitant increase of the reactive oxygen species Hmox supports the hypothesis of necroptotic cell death in MV infected neurons.

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POSTER 124

Determination of the Halogenating Activity of Peroxidases in Human Granulocytes

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Tumor Targeting

Eosinophil granulocytes are a multifaceted protagonist of the innate immune system. In addition to their task as a cytotoxic effector cell against parasitic pathogens, eosinophils have the ability to maintain epithelial barriers function, to regulate inflammation and to affect tissue remodeling. However, dysregulations of eosinophil's activity have pathophysiological relevance causing damage to host tissues in allergic diseases. In many instances this can be attributed to a delayed apoptosis of eosinophils and as a consequence to an inefficient termination of the inflammatory response. Eosinophils store a special heme-containing protein in their granula, namely the eosinophil peroxidase (EPO). This enzyme is closely related to myeloperoxidase (MPO), which can be found in neutrophils. Under physiological conditions EPO and the MPO catalyze the formation of hypobromous acid (HOBr) and hypochlorous acid (HOCl), respectively. The novel fluorescent probe aminophenyl fluorescein (APF) was successfully applied to determine the HOCl-producing MPO activity in neutrophils. Here we addressed the question, whether an APF staining can also be used to detect HOBr as a sign for EPO activity in eosinophils. Therefore we compared both fluorescence measurements on the isolated fluorescein derivate and cellular staining methods. Our studies successfully revealed the application of APF as a detector of hypohalous acids produced in eosinophils and neutrophils by flow cytometry. Thus, the APF method is a promising tool for the further evaluation of factors affecting the halogenating activity of peroxidases in both kinds of granulocytes.

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POSTER 125

CD44 gene polymorphisms in rheumatoid arthritis

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Tumor Targeting

Rheumatoid arthritis (RA) is a chronic autoimmune disease with a strong genetic background triggered by environmental factors. However, its pathogenesis is poorly understood. In animal models of RA, the *CD44* locus has been identified as a susceptibility locus for RA, and inactivation of CD44 leads to significantly reduced severity of the disease. Moreover, CD44 is essential for the generation of memory T cells, which play an important role in RA. These findings prompted us to test if genetic polymorphisms in the *CD44* gene are associated with RA. We performed a parallel analysis of 32 selected single nucleotide polymorphisms (SNP) within the *CD44* gene in 240 cases and 240 controls. Based on a first analysis, a significant association of RA with individual SNPs (haplotypes) of the *CD44* gene might exist, but these findings require an extension of our cohorts. Thus, an extra series of 250 patients and controls will be tested.
The CD44 protein has a multistructural nature, caused by alternative splicing and posttranslational modifications. This heterogeneity is responsible for several functions of CD44. It's largely unknown how the expression and splicing of the *CD44* gene are regulated, and if this is associated with the pathogenesis of RA. Thus, we will test whether different splicing and expression levels of CD44 are genetically controlled by polymorphisms or epigenetic mechanisms. Moreover, we will address the question, if CD44 variants are associated with the severity of RA. Taken together, a gene-specific analysis for genetic polymorphisms in RA was performed which might shed new light on the pathogenesis of this disease.

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POSTER 126

Cytomegalovirus (CMV) specific CD4 helper reactivity in CMV seropositive patients with rheumatoid arthritis (RA)

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Tumor Targeting

Cytomegalovirus (CMV) is a very common virus that infects roughly half of the world`s population. Infection is asymptomatic and leads to a life-long persistence. Memory CD4 and CD8 T cells specific for CMV antigens show an increased massive proliferation the so-called inflationary memory.
Expansion of auto-reactive CD4+CD28- T cells had been associated with the clinical course of RA in earlier studies and more recently expansion of these cells was also associated with CMV seropositivity. In this study we analyzed whether the pathophysiology of RA patients is linked to a latent CMV infection.
Radiography of 102 CMV+ RA and 78 CMV- RA patients revealed more advanced joint destruction and increased surgical joint procedures among the CMV+ RA patients.
T cell phenotyping in RA patients and healthy donors confirmed published data. CMV+ RA patients had higher frequency of CD4+CD28- T cells (n=19, mean: 11%) in comparison to CMV- RA patients (n=5; mean: 4%).
Using a CFSE based proliferation assay we determined similar frequencies of CMV specific CD4 T cell proliferation in RA with CMVpp65 peptide (n=20; mean: 4,5%) and CMV lysate (n=10, mean: 27,4%) compared to healthy donors (n=14, mean: 9,5% and 24,2%).
Furthermore, after CMV (pp65) short time restimulation we determined a significant increase of CD4/IFNg producers in CMV+ RA patients (n=10, mean: 0,17%) as compared to HD (n=14; mean: 0,04%; p=0,011).
In summary, latent CMV infection is associated with the clinical course of RA, possibly due to a changed expression of T cell surface marker and an increased CMV specific effector function in the CD4 T cell compartment.

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POSTER 127

Phenotype and function of CD11c (dendritic) cells within the CNS

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Tumor Targeting

The brain's immune privilege has been attributed to a lack of dendritic cells (DC) within its parenchyma and the adjacent meninges implying maintenance of antigens rather than their presentation in lymphoid organs (LO). We have demonstrated that 1) brain antigens appear in cervical lymph nodes (CLN) after brain injuries, 2) leukocytes migrate from brain to CLN through the cribriform plate, 3) cells expressing the DC-marker CD11c (GFP) are present within the neuropil. We hypothesized that these DCs are tolerogenic and therefore phenotypically compared them to the $CD11c^{+}/CD45^{+}$ from lung, liver and spleen in healthy mice using 7-color flow cytometry. We observed two different $CD45^{+}$ populations ($CD45^{high}$ and $CD45^{int}$) in the brain, whereas liver, lung and spleen exhibit a more homogeneous $CD45^{high}$ population. Among $CD45^{+}$ cells, approx. 2,5 % were $CD11c^{+}$ in the brain compared to 4% spleen, 7,5% liver, and 5% lung. Ratios of brain populations were similar compared to peripheral DCs in regard to CD103, CD80, CD86. Among the brain's $CD45^{high}$ cells significantly more expressed F4/80 and significantly less $CD45^{int}$ expressed MHC-II. We also detected cells expressing CX_3CR1 within the $CD45^{int}$ population. Since the $CD45^{int}$ cells are widely regarded as the resident microglial population, our data confirms the view that a small subpopulation of microglia share established immune phenotypical characteristics of DCs. Using bone marrow chimeras where CD11c-GFP is restricted to brain cells, we are currently testing whether these cells can leave the brain to present antigens within CNL and/or additional LO.
Supported by DFG (FOR 1336/B2)

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POSTER 128

TNF-R1 signaling is required for migration of CD4+ T cells in rheumatoid synovium

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CD4+ Th cells are thought to play an important role in the pathogenesis of Rheumatoid Arthritis (RA) due to genetic associations of the occurrence and severity of the disease with T cell related genes as well as to the efficacy of anti-T cell directed therapies. In addition, T cells are one of the major cell population in the synovial membrane, while phenotypic alterations can also be found in circulating T cells in the peripheral blood of RA patients. The underlying pathology leading to the massive increase of T cell migration to and retention in the rheumatoid synovial membrane is unclear. In this study we established a novel in vitro cell culture system, which investigates migration of peripheral blood CD4+ T cell in vital synovial tissue sections. In this system, it was shown that peripheral blood CD4+ T cells from RA patients actively migrate into the synovial membrane, while CD4+ T cells from healthy controls do so in significantly lower number. Analysis of the migrating T cells showed, that they expressed TNFR1 on the surface, while non-migrating T cells did not. Consequently, we hypothesized that migration might be mediated via specific effects of TNFR1 signaling upon ligation with soluble or cell membrane anchored TNFα. Accordingly, blockade of TNFα signaling nearly abrogated in vitro T cell migration in the rheumatoid synovium. *Ex vivo* analysis of peripheral blood CD4+ T cells from RA patients showed elevated TNFR1 Expression compared to CD4+ T cells from healthy controls. We conclude, that TNFα acts directly as a chemoattractant for RA CD4+ T cells, and that this effect is mediated by ligation of TNFR1.

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POSTER 129

A murine model of Cryptococcus neoformans-related immune reconstitution inflammatory syndrome (IRIS)

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Tumor Targeting

Cryptococcus neoformans is an opportunistic fungal pathogen that can cause fatal meningoencephalitis in immunocompromised hosts. Especially in sub-Saharan countries cryptococcosis is a major health problem with more than half a million death cases of *C. neoformans*-infected AIDS patients every year. The clinical management of the HIV pandemic is considerably complicated by the fact that following antiretroviral therapy a significant proportion of patients with cryptococcal co-infection paradoxically develop a life-threatening immune reconstitution inflammatory syndrome (IRIS). The underlying mechanisms are as of yet poorly understood. We have established a mouse model of cryptococcal IRIS based on lymphocyte-deficient mice (i.e. Rag-1-deficient mice) which are immune-reconstituted by adoptive transfer of wild-type splenocytes six weeks after low-dose infection with *C. neoformans* strain 1841. Following immune reconstitution mice develop a severe wasting disease that manifests as rapid weight loss, mortality and multi-organ inflammation and thus is pathologically similar to clinical IRIS. To characterize the cell type(s) responsible for IRIS induction, adoptive transfer of purified splenic $CD4^+$ T helper cells was performed. Rapid wasting upon T helper cell reconstitution revealed a central role of these cells in IRIS pathogenesis and was associated with an increased production of pro-inflammatory cytokines such as IFN-γ and IL-6.
Further analysis of our murine cryptococcal IRIS model will yield a first cellular and molecular understanding of disease development which is necessary in order to improve HIV treatment strategies.

Association: PbF III

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POSTER 130

A second source of microglia beyond yolk sac macrophages

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The origin and development of microglia cells (resident macrophages of the CNS) is still not entirely discovered. Until now the most accepted hypothesis is that microglia recruitment and differentiation is established by an early embryonic wave before E8 from the yolk sac and a second wave starting after E12 in the liver and spleen. However, the relative contribution of those compartments to the microglia pool is still unclear. A recent paper suggested an almost complete recruitment before E8 from yolc sac macrophages (Ginhoux et al., Science 2010).
We have used Vav1-Cre+:dicer mice with a constitutive knock-out depleting microRNA in hematopoietic cells with Vav1 expressed exclusively in hematopoietic cells starting at E16 and dicer as a crucial enzyme for processing microRNA. We studied microglia in early postnatal brains (P1) and found a decrease of over 40% in the absolute amount of microglia between knock-out mice and their litter mates with an almost identical relative amount of Ki67+/Iba-1+ cells proofing that the decrease is not due to a failure in proliferation. LysM-Cre+:dicer mice with a dicer knock-out in myeloid cells do not show this phenotype suggesting a differentiation defect on a precursor cell level. Our data show that interfering with early monocytes/macrophage differentiation after E8 highly impacts on the microglia population. This is in sharp contrast to the recently published view by Ginhoux et al., as it strongly suggests a second wave contribution to the microglial pool after E8.
Supported by the Medical Faculty of the Universität Leipzig (scholarship to M.F.) and the DFG (FOR 1336, I.B.).

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POSTER 131

In vitro Differentiation of human T helper cells into IL17A- or IL22-producing cell

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Background:
Th17 and Th22 cells are new T cell subsets and express the transcription factor aryl hydrocarbon receptor (AHR). It is assumed that the AHR, besides its role in dioxin toxicity, also has a modulator function in the differentiation of human T helper cells. The aim of the study was to differentiate human T helper cells into IL17A- and IL22-producing cells *in vitro* and to investigate the expression of the AHR as well as other differentially expressed genes.
Methods:
CD4+ T cells were separated from human PBMCs. For differentiation these cells were incubated with antiCD3/CD28 and Th17-polarizing conditions. For FACS the cells were stained with anti-IL17A/IL22-antibody. Cell culture supernatants were measured with ELISA and Cytometric Bead Array. Real Time PCR and Western Blot were accomplished for expression studies.
Results:
The activation of CD4+ T cells with antiCD3/CD28 evolved IL22+ cells, while the amount of IL17A+ cells was low. Th17-polarizing conditions led to a decrease in the amount of IL22+ cells, an increase in IL17A+ cells and to a moderate upregulation of IL17A-, RORC- and AHR-mRNA and a strong upregulation of IL9-mRNA, while the expression of IL22-mRNA was decreased. An increase in AHR-protein expression was detected by Western Blot.
Conclusion:
Th17-polarizing conditions yield to an increase in the amount of IL17A+ cells, as well as the Th17-specific transcription factor RORC and AHR. To investigate the impact of the AHR on human T cell differentiation further experiments with specific ligands are planned. The increase of IL9 mRNA expression has to be clarified as well.

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POSTER 132

New stem cell source – non adherent bone marrow cells (NA-BMC) facilitate hematopeisis after hematopoeitic stem cell transplantation in humanized mice

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Tumor Targeting

Hematopoietic stem cell transplantation (HSCT) is often the only curative treatment for hematological disorders. Investigations of new stem cell sources which support hematopoeisis and reduce complications are needed. The therapeutic effects of non adherent bone marrow cells (NA-BMC) were investigated in a HSCT model based on transgenic mice. Bone marrow (BM) derived cells from C57Bl/6 and Balb/c wild-type mice were cultured for 4 days and characterized by flow cytometry, CFU and cytokine production. Markers of HSC, MSC, B- and T cells and differentiation factors were analyzed by qPCR. Recipient humanized C57Bl/6 mice ($hCD4^+$, $mCD4^-$, $hHLA/DR^+$) were irradiated lethally before transplantation. Survival, condition and weight were daily appointed. Chimerism, engraftment and organ repair were detected by flow cytometry (MHC-I (H-2D[b], H-2K[d], CD4), qPCR and histology. After cultivation, compared to BM $CD45^+$ NA-BMC showed an increase of CD11b, CD90 and a decrease of CD117, CD4, CD8, CD19 cells. NA-BMC were able to form CFU after 5 days. After transplantation of $2x10^6$ syngeneic NA-BMC mice showed a survival of 90% (hematopoietic chimerism on day 49). Allogeneic NA-BMC lead to a survival of 62.5% (no hematopoietic chimerism), a significantly faster recovery of hematopoiesis and a higher survival rate than BM (20%). Co-transplantation of $5x10^6$ NA-BMC and the adherent cell fraction showed a survival of 25%. Histological examination of organs showed no signs of GvHD. Syngeneic and allogeneic NA-BMC support endogenous hematopoiesis and could be a therapeutic approach in HSCT because of faster hematopoietic recovery and organ repair.

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POSTER 133

Development of an in vitro GvHD model by using humanized mice

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Tumor Targeting

Introduction: Graft-versus-host Disease (GvHD) is still the main complication following hematopoietic stem cell transplantation (HSCT), with an incidence of 40-50% and a death rate of 20%. An allogeneic donor ("graft") stem cell transplant causes an attack to the recipients ("host") body. The acute GvHD is characterized by damage of especially skin, liver and gastrointestinal tract within 100 days. Through an *in vitro* skin explant model it is possible to predict the development of GvHD, testing new drug candidates with preventive or therapeutic effects, or even studying the pathophysiology of the disease. Methods: Isolated peripheral blood mononuclear cells (PBMC's) from humanized C57Bl/6 mice ($huCD4^+$, $muCD4^-$, $HLA\text{-}DR^+$) are co-cultured in a mixed lymphocyte reaction (MLR) with an equal number of irradiated Balb/c PBMC's to activate donor T cells. Prepared Balb/c skin explants are added to medium with activated lymphocytes. After 3 days of incubation the explants are fixed in formalin, sectioned and strained with haematoxylin and eosin. To show apoptosis of keratinocytes, which is characteristic for acute GvHD, explants are stained with an anti-murine $CD95^+$-antibody. $CD3^+$, $CD4^+$ (murin and human), $CD8^+$, $CD19^+$ and $FoxP3^+$ cells are detected by flow cytometry. Results: By the assay we were able to induce acute GvHD in the skin samples. $CD95^+$ could be detected in skin by immunohistology. Conclusion: Future prospects: To integrate the clinical findings of the multifocal Graft-versus-Host-Disease it is necessary to examine other affected organs. Therefore gut (terminal ileum) will be involved into the experiments.

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POSTER 134

Hypoxia stimulates the production of IL-1β in LPS-primed human monocytes

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Monocytes are major players in the innate immune system and are recruited to sites of inflammation. In rheumatoid arthritis, for example, inflamed joints are extreme hypoxic. This decreased oxygen level could be an influencing factor for the activation and survival of monocytes. Aim of the study was to analyze the influence of hypoxia on lipopolysaccharide (LPS)-induced cytokine production in primary human monocytes.
Monocytes were isolated from the peripheral blood of healthy donors using density gradient centrifugation and subsequent magnetic cell separation. After 16 hours culture under hypoxic conditions (1% O_2) the production of cytokines in the supernatant was determined.
LPS-primed monocytes show an increased release of IL-1β, IL-18 and IL-6 under hypoxic conditions. IL-1β and IL-18 are produced as pre-forms in response to LPS stimulation and then get enzymatically processed to their active form by Caspase-1.
To activate Caspase-1, the assembly of the inflammasome, a multiprotein complex, is necessary. To test the involvement of Caspase-1, a specific inhibitor (Z-WEHD-FMK) was used. Indeed, the increased IL-1β production in response to hypoxia was abolished, when Caspase-1 was inhibited. A common signal for inflammasome assembly and Caspase-1 activation is K^+-efflux. To block this K^+-efflux, monocytes were cultured in a buffer containing a high potassium concentration (150mM), and the IL-1β production was completely inhibited under this condition.
In summary, hypoxic conditions induce inflammasome-dependent cytokines in LPS-primed human monocytes and signaling pathways include K^+-efflux and activation of Caspase-1.

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POSTER 135

Optimized derivatives of invertebrate antimicrobial peptides show broad antimicrobial activity without immunomodulatory side-effects on dendritic cells

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Tumor Targeting

Several antimicrobial peptides (AMP) have been shown to exert antimicrobial activity *in vitro* and *in vivo*. Moreover, some AMPs show immunomodulatory effects. We have synthesized several insect AMPs such as apidaecin and oncocin analogues. To study their antimicrobial and immunomodulatory effects we compared both peptides to the murine cathelicidin-related antimicrobial peptide (CRAMP). The apidaecin and oncocin derivatives are primarily active against gram-negative bacteria, while CRAMP shows antibacterial activity against both, gram-positive and gram-negative pathogens. Moreover, the apidaecin and oncocin derivatives as well as CRAMP exhibit strong antifungal activity against *Cryptococcus neoformans in vitro*.
To characterize the immunomodulatory activity of the peptides on key cells of the innate immune system, we tested the chemotactic effect of the AMPs on murine bone marrow-derived dendritic cells (BMDC). None of the tested AMPs shows cytotoxic activity on BMDC. The apidaecin and oncocin derivatives lack chemotactic activity on BMDC. Next, we stimulated BMDC with AMPs alone or in combination with LPS. We analyzed the expression of surface markers and the secretion of several cytokines. In contrast to LPS, none of the peptides has an influence on surface marker or cytokine expression. While the tested apidaecin and oncocin derivatives do not modulate the LPS-induced response, CRAMP shows a significant reduction of the LPS-mediated effects as published.
Together, the apidaecin and oncocin derivatives studied are promising candidates for therapy of infections caused by multi-drug-resistant pathogens.

Association: PbF III

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POSTER 136

Exposure to phthalates may increase the asthma phenotype in mice

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Tumor Targeting

During the last two decades the prevalence of allergic diseases has risen substantially. Environmental factors, such as plastic products, are thought to contribute significantly to this increase. Phthalates are commonly used in the plastic industry and can act as xenoestrogenes. The risk of low-dose exposure to phthalates for human health has been controversially discussed lately. Recent data from animal studies suggest that benzyl butyl phthalate (BBP) or bis (2-ethylhexyl) phthalate (DEHP) may affect the reproductive system and the immune system, especially after fetal or postnatal exposure.
The aim of the present study was to investigate the effect of phthalate exposure on allergy development in a murine asthma model. Therefore, Balb/c mice were exposed to BBP or DEHP via the drinking water during pregnancy, breastfeeding or postnatal. To induce an asthma phenotype, mice were sensitized to ovalbumin (OVA), followed by an intrapulmonary allergen challenge.
BBP exposure during pregnancy and breastfeeding increased airway hyperreactivity, OVA-specific serum IgE and the Th2 cytokine levels in the offspring. Similar effects were observed after long-term postnatal BBP exposure, whereas low-dose exposure to DEHP was generally without effect on the asthma phenotype. In contrast, phthalate exposure only during pregnancy or during OVA sensitization does not promote asthma development.
Thus, depending on the exposure period phthalates may have asthma-promoting effects. This can also affect the offspring from exposed mothers implicating the avoidance of phthalate-containing products during pregnancy.

Funding: life/IFB

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POSTER 137

T helper 17 cells contribute to local fungal control in lung of mice

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Tumor Targeting

Cryptococcus neoformans is one of the most important opportunistic fungal pathogens during HIV infection. Each year, approximately one million cases of cryptococcal meningitis result in more than 600.000 death cases. Protective immunity against *C. neoformans* is dependent on the induction of T helper (Th) 1 cells. Several studies presume a significant role of Th17-associated production of interleukin (IL)-17A and IL-22 in regulating antimicrobial immunity at barrier surfaces. Further studies of the role of Th17-type cytokines during cryptococcosis should give new insights in the interplay of the immune system with a human pathogen fungus.
At different time points after intranasal infection of C57BL/6 wild-type mice with *C. neoformans* strain 1841 production of IL-17A and IL-22 after *ex vivo* restimulation of lung leukocytes were analyzed. Already 7 days post infection (dpi) *Cryptococcus*-specific Th17-cytokine secretion was detected. However, during the later stage of infection cytokine production decreased.
To analyze the *in vivo* function of Th17 cytokine production double knockout mice with reduced Th1 (IL-12p35$^{-/-}$) and Th2 (IL-4Ra$^{-/-}$) but elevated Th17 responses were generated. IL-12p35/IL-4Ra$^{-/-}$ mice demonstrated an intermediate phenotype compared to resistant IL-4Ra$^{-/-}$ and highly susceptible IL-12p35$^{-/-}$ mice. Increased survival of IL-12p35/IL-4Ra$^{-/-}$ *versus* IL-12p35$^{-/-}$ mice indicates a protective effect by the Th17-type cytokine response during cryptococcosis and will be further analyzed.

Association: PbF III

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POSTER 138

Molecular Characterisation of Antigen-specific Human Memory B-Cells Responses against the Influenza Nucleoprotein

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Background
Memory B-cells and serum antibody reflect the individual history of infection or vaccination. When activated, antigen-specific memory B-cells differentiate into antibody-secreting plasma cells. These antibodies can neutralize the antigen and control the infection.
Methods
We have developed a method to isolate influenza nucleoprotein (NP)-specific memory B-cells. The isolated cells are activated in the presence or absence of feeder cells and screened for NP specificity by ELISpot. From a single activated NP-specific memory B-cell the variable region of the light and heavy chain was amplified by PCR and sequenced for the molecular characterization of the antigen specific variability.
Result
After activation of enriched cells all antibody-secreting cells were NP-specific in ELISpot. The V und J families of the variable region of light and heavy chain were characterized and the potential antigen binding sites (complementary determining regions, CDRs) identified.

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POSTER 139

Man-Computer-Interaction in Surgery - Requirements for ontological Representation

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Tumor Targeting

Automation in surgery is characterized by the high level of complexity and creates errors in the Man-Computer-Interaction (MCI). The resulting demand is the mandatory investigation of MCI, in order to avoid these errors. To facilitate the investigation process a model was developed, comprising various assessment concepts. The area of MCI research in surgery is high dynamic and requires dynamic formalization in the form of an ontology. Therefore a catalogue of crucial criteria for ontological representation was developed, based on the investigation model concept. The focus concentrates on the following requirements: The investigation of MCI in surgery requires a domain-specific view on the study process with regard to the fundamental domain of MCI as well as to the more specific sub-domains representing various categories of automation effects. Furthermore it is necessary to realize the experimental scenario and to consider the trade-off between the clinical realism and the controllability of the investigated parameters. Finally the MCI investigation process comprises numerous entities representing the study structure. These entities are interrelated by dependencies, part-of-relations, functions etc. which need an adequate ontological implementation.
The developed catalogue of criteria concentrates on the assessment of ontologies with regard to the adequate representation of MCI in surgery. Particular attention was paid to the multidisciplinarity of this area of research.

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POSTER 140

A concept for intra-operative identification of surgical instruments using 2D camera data and scales

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In order to accomplish an integral automatic covering of processes within the operating room, the identification of the used surgical instruments during an intervention is crucial. Existing automatic approaches concentrate on the detection by radio frequency identification (RFID) or rely on the existence of markers.
Both approaches demand the modification of the instruments, which is frequently not possible. Either the instruments become non-sterilizable, the surgeon feels affected in his work, or the instrument is simply not markable - e.g. because of its size.
The presented concept adds the idea of automatic instrument identification on a designated operating room table by detecting instruments with a combination of 2D camera data and by adding a scale to the instrument table in order to border the gained data furthermore through adding weight information of the individual instruments. Therefor an underlying data pool of a set of surgical instruments is recorded and provided as base knowledge for the system.
A key design goal is the applicability in the operating room without seriously interfering modifications to the accustomed workflows of the staff or the instruments themselves.
Current work on the concept focuses on the possibly reachable accuracy levels with different hardware, algorithms and combinations of sensors.
Follow-up projects will then integrate the gained information in higher-ranked frameworks to enhance intra-operative surgical workflow information.

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POSTER 141

Towards an automatic recognition of surgical workflow actions

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Since the number of medical devices in operating rooms is increasing, surgeons and their assistants have to handle more and more complex user interfaces and their specific parameters and configuration options. This not only fades the focus away from the surgery itself but is also a great source of failures. One approach to overcome this is to control the devices by an automatism by means of assistants to let the involved actors refocus on the real task. To achieve this, such a system has to be aware of the current surgical phase and state of the intervention. In Previous works, surgical actions were captured by humans to produce a workflow of a specific intervention. Besides this is a very usable documentation and analysis tool, it's also a good base for the recognition of surgical phases. The main concept of this work is to replace the manual input of a human observer with automatically acquired data, but the complexity of activity recognition in the surgical context makes it difficult the replace it one step. Consequently the idea is the successive substitution of the manual inputs. Various types of measurement system have to be used to capture the relevant aspects of the scene and sensor fusion methods have to be applied to overcome ambiguities and uncertainties of single sensor systems. In a first step, a RFID based system for instrument detection was developed, so it was possible to omit the instrument information manually entered by the observer. Running developments deal with vision and motion based object and activity recognition by using acceleration measurements and depth cameras.

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POSTER 142

Brain tumor segmentation in 3D intraoperative ultrasound data

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Purpose: Real time intraoperative imaging of brain tumor during neurosurgical operations is crucial to overcome the brain shift effects. Visualization of intraoperative ultrasound (US) data enables the neurosurgeon to perform the optimal approach to the tumor and to improve the tumor resection control. However US data are known to be noisy and the tumor borders may appear unclearly defined. Therefore, a tool enhancing the tumor in the intraoperative US data would be helpful.
Method: Our method is based on a patient specific model of the brain tumor, obtained by manual segmentation of the tumor in the preoperative MR data, needed in the navigation system to guide the surgery. The tumor model is represented with the gray intensities of the MR data. The intraoperative US data are acquired before resection through the dura using a 2D free hand US probe. The probe is tracked that enables compounding the 2D US slices into a volume. Then, a registration algorithm matches the tumor model with the tumor in the 3D intraoperative US data. The method is based on a block matching technique with a rigid transform and uses a multi-scale implementation.
Results: First results have been performed on several patient data. The algorithm succeeds in finding the tumor position in the 3D US data, also when the tumor is represented with low contrast and parts of its borders are unclearly defined. Hyperechogenic structures may however limit the algorithm. The registration is performed in few seconds.
Conclusion: This method could be used as initialization of a deformable registration to improve the algorithm performance.

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POSTER 143

Design of a Workflow Based Oncological Patient Care Support System with Clinical Decision Support

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Tumor Targeting

The workflows in the oncology department in many hospitals are characterized by lacking sufficient IT support throughout the whole patient care process. This results in information which is not accessible for all physicians in digital form as well as a large amount of paper based records. Furthermore the tasks of printing, scanning and searching of documents by clinical staff is time consuming, hence, expensive. The concept of onkoFlow will support the patient treatment process in oncology departments with an intuitive-to- use IT system. The modular onkoFlow architecture has interfaces to the main clinical information systems and collects patient master data, reports, laboratory results, tumor classifications, tumor board protocols, OR reports and after-care. This information is stored in an electronic patient record and accessible instantly from each hospital computer workstation via web browser and through each physician involved in the patient treatment. In addition the system will offer scientific evaluations, which are based on the large amount of structured patient information in the database. These evaluations can be used for a therapy assistance and decision support module, which helps the attending physician finding the best therapy for the individual patient. In summary onkoFlow is expected to support the physicians along the whole oncological patient care process, to support the creation and easy access to clinical documents as well as can save time that can be spent in patient treatment.

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POSTER 144

Determination of cutting-temperature during milling operations

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During operations heat is generated by several processes which may damage healthy tissue. Heat is generated for example by milling operations. Preventing local heating during milling operations is important for the mending of the tissue. Many studies examined the influence of milling parameters on the cutting temperature. Several systems exist to measure the temperature during such operations. Some of them are not practically applicable because of its invasive character. One system widely used for temperature measurements is infrared thermography. Infrared cameras allow a contactless temperature measurement. But there are some constraints which need to be considered when thermography is used for intraoperative temperature measurement. It is examined whether infrared thermography is applicable for intraoperative temperature measurement and which requirements need to be met. Therefore an infrared camera's accuracy is examined. Furthermore the influence of the cooling fluid on the measurement is examined.
It can be shown that that a infrared camera can be used for a precise measurement of the temperature of organic tissue. During drilling operations a local heating causing damage of the tissue can be detected. A constraint is the usage of cooling during milling operations. The cooling fluid absorbs all infrared radiation. The temperature of the underlying tissue can't be be determined. During drilling no local heating was observed when using irrigation.

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POSTER 145

A concept of a surgical data recorder and the realtime provision of intraoperative data using the TiCoLi-toolkit

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Tumor Targeting

Due to the increasing complexity of the surgical working environment and the increasing technization solutions must be found to relieve the surgeon. In the project "Model-based Automation and Integration" the current situation in the operating room should be detected. To achieve this, all relevant data should be available on a central location and in a structured way.
The TiCoLi is a toolkit developed at the ICCAS since 2009 which provides different functionalities for software integration in the operating room (OR). Some of these functionalities are the automatic device and service detection and the possibility to subscribe data streams (i.e. vital data) or attributes (i.e. whether a device is currently in use or not). The surgical blackbox uses the functionalities of the TiCoLi with a socket-based communication protocol (TiCoLi2J) to get all data available on the OR communication bus. Depending on the type of data the surgical blackbox stores them in a postgreSQL database as well as in a circular buffer for online access. Devices with a high data throughput such as HD-video cameras store their streams on local hard drives and promote the endpoint reference to the blackbox.
Currently there are two opportunities to access the data during intervention. The technician can check the acquired data using a graphical user interface. Furthermore, an easy to implement socket interface is provided for access to the stored information.
Hence the surgical blackbox supports automatic recognition of the interventional situation by providing a centralized data storage and access interface on the OR communication bus.

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POSTER 146

New Assistance System for Transcatheter Aortic Valve Implantation Based on Intraoperative Fluoroscopy Guidance

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Tumor Targeting

Purpose: Transcatheter aortic valve implantation (TAVI) is a new minimally invasive surgical technique to treat severe aortic valve stenosis in high-risk patients. The placement of stented aortic valve prosthesis is crucial under 2D fluoroscopy guidance. Thus, a new fluoroscopy-based assistance system has been developed to assist the placement of the prosthesis during the intervention.
Methods: The developed assistance system augments a 3D geometrical aortic mesh model and anatomical landmarks with live 2D fluoroscopic images. The 3D aortic mesh model and landmarks are derived from an interventional C-arm CT system. A target area of valve implantation is automatically estimated using these valve landmarks. Based on template matching approach, the overlay of 3D aortic root model onto 2D fluoroscopic images is updated by approximating the aortic root motion from a pigtail catheter motion without contrast agent. A rigid intensity-based registration method has been used to track the aortic root motion in the presence of contrast agent. The aortic valve prosthesis is also tracked to assist the valve deployment.
Results: Experiments were carried out on 15 patient datasets from the clinical routine of TAVI in a hybrid operating room. The maximum displacement errors were less than 2.0 mm and 0.5 mm for the dynamic overlay of aortic root models and tracking the prosthesis respectively, and within the clinically accepted ranges.
Conclusion: The developed assistance system provides a potentially helpful tool for the surgeon by automatically defining an appropriate placement position of the prosthesis in live fluoroscopic images.

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POSTER 147

Applicability of DICOM's "Implant Template" to Describe Stentgrafts

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Motivation
The planning process of a stenting intervention is often limited to an examination of the patient's CT images and vessel measurement performed by hand and the stent selection is based solely on the surgeon's experience. To support his/her decision-making, a planning application (Fig. 1) will be introduced. For providing 3D-implants in a standardized format the applicability of the DICOM standard has to be proven.
Methods
Important stentgraft properties for stenting intervention were defined. Based on this the applicability of the DICOM "Implant Template" IOD (Information Object Definition) for describing the essential properties was evaluated. Attributes that are not consistent with the DICOM standard were identified and proposals for additional DICOM attributes were made.
Results
Crucial attributes for a planning application were identified. Common attributes, e.g. product name or material properties, are supported by the "Implant Template" IOD. The following attributes were identified as missing and propositions for their addition into the standard were made: maximum bending angle, stent dimensions and fixation method. Additional DICOM attributes that provide these values were proposed.
Discussion
The current version of the DICOM standard is able to represent the better part of the attributes needed for flexible implants. Additional attributes are needed for the fixation method and the stent's dimensions. A change proposal or a DICOM supplement is necessary to introduce the additional attributes to the DICOM standard.

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POSTER 148

Validation of a model based approach for surgical workflow schema generation

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Workflow guidance of surgical activities is a challenging task. Because of variations in patient properties and applied surgical techniques, surgical processes also have a high variability. The objective of this study was the design and implementation of a surgical workflow management system (SWFMS) that can provide a robust guidance for surgical activities. We investigated how many surgical process models are needed to develop a SWFMS that can guide high variable surgical procedures robustly.
We used 100 cases of cataract surgeries and acquired patient-individual surgical process models (iSPMs) from them. Of these, randomized subsets of the 100 iSPMs were selected as test sets to create a generic surgical process model (gSPM). These gSPMs were mapped into workflow nets as workflow schemata to define the behavior of the SWFMS. Finally, all iSPMs were simulated activity-by-activity to validate the guidance of the SWFMS for the surgical processes.
The measurement was the successful guidance of all activities of a randomly chosen iSPM by the SWFMS. This was investigated for different test-set sizes and for workflow schemata that were filtered for infrequently occurring work steps.
We demonstrated that a SWFMS with a workflow schema that was generated from a subset of 10 iSPMs is sufficient to guide 70% of all surgical processes in the total set and that a subset of 50 iSPMs is sufficient to guide 90% of all processes.
We designed a SWFMS that is able to guide surgical activities on a detailed level. The study demonstrated that the high inter-patient variability of surgical processes can be considered with by our approach.

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POSTER 149

Distance assessment between surgical processes

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The focus of analyzing surgical processes should not be on quantitative issues, as frequency of activities or duration of the intervention, only, but also on the work flow itself. The present work employs different strategies to compute the differences between surgical processes, resulting in concrete distances.
To analyze a complex process, it is sensible to split it up into single activities. Therefore, a surgical process model (SPM), recorded with the help of trained observers using the Surgical Workflow Editor®, was used to represent the process in a semi-formal way.
We adapted established methods to measure distances, such as the Jaccard and the Levenshtein distances. Using SPMs recorded in a mock-up scenario, we evaluated surgical access strategies for minimally invasive laparoscopic pediatric surgery. For the analysis, we have devised 3 tasks derived from standard intervention procedures. These were then performed by experienced and inexperienced surgeons. In addition, the quality of the tasks' results was reviewed. With the help of the distances we calculated how strong the difference between the work flows was.
Future work might analyze the prediction of management ratios or results of the distance, such as the correlation between the distance of SPMs and the quality outcome. Also, surgical training in new surgical techniques can be enhanced and the application of innovative procedures tested.
The methods to measure distances between SPMs allow for a multitude of possible analyzing scopes, especially with respect to the complex and variable environment of the OR.

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POSTER 150

Semi-automated Evaluation of Stentgrafts

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Tumor Targeting

Purpose: The short and long-term outcome of endovascular aortic aneurysm repair is influenced by selection of stentgraft design and, in particular, correct oversizing. To support the preoperative planning process and device selection results of a finite element analysis (radial forces, contact states) have to be interpreted in clinical environment.*Methods:* Data interpretation is assisted by defined risk classifications and a system-generated variant suggestion which is performed using weighted evaluation criteria (proximal/distal sealing and fixation). For better estimation of migration risk the calculated radial force multiplied with a friction coefficient, is compared with proximal and distal flow force values stated in the literature. Sealing potential is calculated based on defined contact elements of the simulation model.*Results:* The developed approach enables a semi-automated evaluation of stentgrafts and a quantitative comparison of different implant configurations. A graphical user interface highlights a variant proposal and their surplus referring fixation and sealing proportional to other variant results. For providing a good survey of risk assignments an illustration of landing zones with color coded variant identifiers is available. *Conclusion:* The presented method for quantitative evaluation of stentgrafts can assist the vascular surgeon in implant selection. Further investigations are necessary to determine qualitative –not-quantifiable – criteria and identify variables (e.g. underlying aortic pathology, etiology etc.) influencing semi-automated evaluation of stentgrafts.

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POSTER 151

Visual Analysis of 4D MRI Blood Flow Data

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4D MRI is an in vivo flow imaging modality which has the potential to significantly enhance diagnostics and therapy of cardiovascular diseases. However, current analysis methods demand too much time and expert knowledge in order to apply 4D MRI in the clinics. One missing piece are methods allowing to gain a quick overview of the flow data's main properties.
We present a line predicate approach that sorts precalculated integral lines, which capture the complete flow dynamics, into bundles with similar properties. We introduce several streamline and pathline predicates that allow to structure the flow according to various features useful for blood flow analysis, such as, e.g., velocity distribution, vortices, and flow paths. The user can combine these predicates flexibly and by that create flow structures that help to gain overview and carve out special features of the current dataset. The usefulness of our approach is shown by means of 4D MRI datasets of healthy and pathological aortas. Here, flow aspects can be visualized which cannot be shown by other analysis methods presented in literature so far.

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POSTER 152

Evaluation and first clinical application of a modular and open OR integration system in neurosurgical interventions

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Tumor Targeting

Background: Integration of medical devices and IT systems as well as centralized control of the integrated system in the operating room (OR) has been recognized for its potential to increase the overall surgical efficacy, ergonomics and the clinical workflow.
Methods: An open standards based OR integration system has been designed, implemented and clinically evaluated. The integration system interconnects imaging modalities, hospital information systems and systems for computer assisted surgery. The functionality of the integrated OR system is available at a central control console within the sterile field. Thus, the clinical personal has centralized access to PACS information, display configurations, data acquisition, medical device functions and OR documentation. The overall system has been evaluated within neurosurgical interventions. Functional and ergonomic aspects as well as clinical user acceptance have been recorded using questionnaires addressing 15 different aspects.
Results: The clinical evaluation successfully demonstrated the practical feasibility and clinical benefits of the integrated OR system. Centralized information display and access control supports the surgeon to better assess the current surgical situation. Patient data, medical images, OR planning data are seamlessly electronically available throughout the overall treatment process without need for portable media. Centralized access and display of intraoperative data improves the ergonomic situation within the OR as well as the surgical workflow.

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POSTER 153

A model based approach towards prediction of intervention time for brain tumor resections based on surgical workflows

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Operating rooms are one of the most expensive units in a hospital. A technical support of time and resource management in the operating room itself as well as across departments might help in improving surgical patient care and reducing costs. The expected time left during interventions is one of the main aspects for enhanced scheduling and resource management. Surgical process models represent the course of interventions with several tasks on a time line. Hence, these data is a promising starting point for the development of a technical support for time management.
We developed a process model for brain tumor resections based on Markov Model Theory. The design of the process model is optimized for time parameter prediction. It includes over 70 different tasks performed by the surgeon and the operating room personnel during surgery. The generic process model was constructed using 40 patient-individual process models recorded by ICCAS since 2007. Furthermore, a modular system for supporting time management was developed. Its major prediction algorithm uses techniques of swarm intelligence and estimates several time parameters at any phase during a brain tumor resection based on the process model.
A randomized study is implemented to evaluate the quality of prediction. The time management system will support intervention scheduling and the management of resources shared among different operating rooms, thus reducing resource conflicts. Thereby time predictions based on surgical process models will also contribute to the improvement of surgical workflow and patient care.

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POSTER 154

Are copy number variations in obesity-genes present in children?

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Rationale: In rare monogenic forms of obesity, genetic variants have been found in *LEP*, *LEPR*, *POMC*, *SIM1* and *MC4R*. However, monogenic diseases are causing only a minority of obesity cases, while the majority develops on a polygenic background. Also, simple sequencing approaches may not detect hemizygosity. We aimed to investigate the prevalence of copy number variations in obese children for above mentioned genes.
Methods & Results: We used a multiplex ligation-dependent probe amplification (MLPA) approach to analyze gene-dosage alterations in 194 obese children (mean BMI SDS 2.9). We did not find CNVs in *POMC*, *LEPR*, *LEP*, *MC4R* in any patient of our cohort. We identified 21 children with potential deletions in exon9 of *SIM1*. In subsequent molecular analyses we could, however, not confirm a deletion. Instead, we identified rs3734354, which has previously been associated with polygenic obesity. This variant is located within the binding site of the ligation fragment in these patients and most likely affects the binding characteristics of the MLPA-probe delivering a false-positive results.
We subsequently genotyped the polymorphism in an extended cohort of 758 obese and 1145 lean children by allelic discrimination. We did not find associations of rs3734354 with BMI-SDS, Waist-to-hip ratio, pubertal state, leptin, HbA1c, blood pressure, parameters of insulin homeostasis or food intake.
Conclusion: Our data does not provide evidence for a role of CNVs in *SIM1*, *MC4R*, *POMC*, *LEP* and *LEPR* in the genetics of obesity in children. Also, a common polymorphism in *SIM1* was not associated with obesity or related comorbidity in our cohort.

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POSTER 155

ENDOCRINE ISLETS OF LAGUESSE AND LANGERHANS IN THE BOVINE PANCREAS: SIGNIFICANT DIFFERENCES IN DEVELOPMENTAL ORIGIN, HISTOLOGY AND FATE

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Endocrine cells appear early during pancreatic development whereas morphologically distinct islets arise later. Here, we describe two types of islet that arise in parallel in foetal bovine pancreata of crown rump length ≥ 15cm. Perilobular giant islets of Laguesse are predominantly insulin-positive, observed infrequently, and of finite lifespan. The Laguesse islets develop at the borders of the ductal trees, in close topographical relation to ganglia and nerves. The islets are organized into epithelial trabeculae that form gyriform and rosette-like structures. A thin connective tissue base supports the epithelial parenchyma. The Laguesse islets can be the site of early localised haemorrhage. Antenatal, general epithelial cell shrinkage combined with more significant haemorrhage, leucocyte infiltration, and progressive fibrosis, characterise the demise of these islets. Polyendocrine intralobular small islets of Langerhans are observed more frequently, and persist into postnatal life. The origins of these smaller islets lie in single or small groups of endocrine cells that populate the tubulo-acinar ends during the early stages of pancreatic development. As the islets grow in size, they physically repress exocrine lineage differentiation in the surrounding tubulo-acinar ends. Finally, the islets agglomerate into compact endocrine cell clusters embedded in the now exclusively exocrine lobules. Conclusion: The existence of two types of pancreatic endocrine islet should be taken into account if meaningful conclusions are to be drawn from investigations of antenatal isolated pancreatic endocrine tissue or precursor cells.

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POSTER 156

Stigmatisierung übergewichtiger und adipöser Patienten durch Medizinstudierende

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Tumor Targeting

Etwa 10-35% der Erwachsenen der westlichen industrialisierten Länder sind adipös. Studien haben gezeigt, dass übergewichtige und adipöse Patienten zum Ziel von Stereotypisierung, Diskriminierung und Spott durch Medizinstudierende werden können. Angst vor respektloser Behandlung kann wiederum dazu führen, dass übergewichtige und adipöse Patienten wichtige Arztbesuche vermeiden. Stigmatisierung übergewichtiger und adipöser Menschen im Gesundheitsbereich ist daher ein grosses Problem und kann zu sub-optimaler Versorgung dieser Patienten beitragen.
Die meisten Studien zu Stigmatisierung übergewichtiger und adipöser Patienten durch Medizinstudierende stammen aus den USA, ebenso wie Studien über Stigmatisierung Übergewichtiger und Adipöser im Gesundheitsbereich allgemein. Deshalb haben wir uns dazu entschlossen, die Einstellungen Medizinstudierender der Universität Leipzig zu untersuchen. Wir stellen die Hypothese auf, dass es relevante stigmatiserende Einstellungen gegenüber übergewichtigen und adipösen Patienten unter den Medizinstudieren der Universität Leipzig gibt.
705 Medizinstudierende aus allen Studienjahren wurden in einen paper-pencil-Survey eingeschlossen, der Einstellungen, Stereotype, Überzeugungen zu Kausalzusammenhängen, bevorzugten Therapieoptionen und Präventionsstrategien bezüglich Übergewicht und Adipositas erfragt. Die Daten werden zunächst deskriptiv ausgewertet, ausserdem wird der Einfluss sozio-demographischer und anderer Faktoren (Studienjahr, Kontakt mit adipösen Patienten, etc) auf die Einstellungen untersucht. Die Ergebnisse der Studie werden hier vorgestellt und ihre Implikationen diskutiert.

Funding: IFB

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POSTER 157

Suizidalität nach bariatrischer Chirurgie im Vergleich mit einer Kontrollgruppe Übergewichtiger

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Tumor Targeting

Die bariatrische Chirurgie zählt mittlerweile zu den wirksamsten Methoden bei der Behandlung von Patienten mit sehr starkem Übergewicht (Adipositas Grad III = BMI ≥ 40), sowie bei Patienten mit Begleiterkrankungen wie beispielsweise Diabetes mellitus, Bluthochdruck oder Atherosklerose. Im Rahmen von Langzeitstudien konnte festgestellt werden, dass die meisten Patienten nach einer bariatrischen OP einen signifikanten Gewichtsverlust aufzeigen, wohingegen ein Teil der Patienten nach einer anfänglichen Gewichtsabnahme wieder zunimmt. Risikofaktoren wie beispielsweise Depression, Essstörungen, BMI, Alter und Geschlecht scheinen einen Einfluss auf die Fähigkeit des Patienten zu haben, sein Gewicht zu reduzieren, wobei der Zusammenhang bisher nicht eindeutig geklärt ist. Ein wichtiger Faktor ist die Suizidalitätsneigung. Suizid ist eine der häufigsten Todesursachen nach einem bariatrischen Eingriff bei adipösen Patienten. Die Mortalitätsrate, die nicht durch medizinische Faktoren verursacht wurde, lag bei bariatrisch operierten Patienten um 58% höher als bei einer nicht operierten adipösen Kontrollgruppe. Dennoch wurden Prädiktoren für Todesursachen nach bariatrischer Chirurgie, die nicht durch operative Faktoren verursacht wurden (z.B. Suizid oder Unfälle), bisher kaum untersucht.
Ziel der aktuellen Längsschnittstudie soll es demnach sein, die Suizidalitätsneigung in einem Langzeitfollow-up von Personen zu erfassen, welche einen bariatrischen chirurgischen Eingriff erhalten haben und diese mit einer Kontrollgruppe zu vergleichen. Langfristig sollen damit Gestaltungsoptionen gefunden werden, die eine größere Gewichtsabnahme ermöglichen sowie die Suizidalitätsneigung reduzieren.

Funding: IFB

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POSTER 158

Obese children, adults and senior citizens in the eyes of the general public: Results of a representative study on stigma and causation of obesity

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Tumor Targeting

Background: Stigmatization influences morbidity and mortality in obesity, making stigma reduction efforts an important approach when dealing with rising prevalence rates of obesity. Aside from prevalence rates of stigmatizing attitudes, a thorough analysis of determinants is needed. Unlike most previous research, this study provides evidence from a representative sample. This study aims at investigating the prevalence of stigmatizing attitudes and determining associated variables of these attitudes. Methods: A representative study of the German population was conducted via computer-assisted telephone interview. Vignettes were used to determine influences of age and gender of the depicted obese individuals. Stigmatizing attitudes were assessed with a short form of the Fat Phobia Scale (FPS). Results: The average FPS score of the overweight vignette was 3.65 (s.d. = 0.49, scale range from 1 = positive attribute to 5 = negative attribute) indicating slightly negative attribution overall. Higher education and higher BMI showed to be associated with lower FPS scores. The vignette of the obese child was rated far more negatively compared to that of an adult or senior citizen ($p < 0.001$). Casual attribution to internal as well as external factors was associated with higher FPS scores. Conclusions: It seems that anti stigma interventions will need to aim at obese children just as much as focusing on the obese adult. Obviously, implementation of an adequate etiological model will still be a base for anti-stigma intervention; however, this study reveals the need for further investigation of other stigma-determining factors.

Funding: IFB

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POSTER 159

The prevalence of brown adipose tissue in healthy lean children

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Background: At birth, children have considerable amounts of brown adipose tissue (BAT) in their body, which was, however, believed to be lost within the first few years of life. BAT is different from white adipose tissue (WAT) with respect to function (thermogensis), morphology (multilocular cells, mitochondria dense) and characterized by a high *UCP1* expression level. The aim of this study was to examine the distribution of BAT in children across different ages during and beyond infancy.
Methods: Adipose tissue biopsy samples from different fat depots were collected from 60 lean, 33 overweight/obese healthy children aged 0-18 years. Immunostaining for UCP1 was performed on paraffin embedded samples and using UCP1-PCR we assessed mRNA expression in the tissue samples. Adipocyte cell sizes were computed using Image J software.
Results: Altogether 11 of the 93 analysed tissue samples expressed UCP1. Especially lean children aged 0-5 years (10 out of 93) and perirenal/omental (8 out of 11) fat depots showed a high prevalence for BAT. There was no BAT in overweight/obese children across the different ages and depots. The adipocytes showed multilocular lipid droplets or unilobulated cells interspersed with islands of cells with multilobulated droplets. All UCP1 positive tissue samples expressed *UCP1* mRNA. BAT adipocytes were significantly smaller (1477 ± 346,4μm^2) than WAT adipocytes (4015 ± 301,1μm^2); ($P<0,001$).
Conclusion: BAT is detectable in several adipose depots, but with a high prevalence in perirenal/omental fat and mainly in very young children. We also detected BAT depots in subcutaneous depots of young children.

Funding: IFB

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POSTER 160

Impact of metabolic regulators on the expression of the obesity associated genes FTO and NAMPT in human preadipocytes and adipocytes

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Tumor Targeting

Background: FTO and NAMPT/PBEF/visfatin are thought to play a role in obesity but their transcriptional regulation in adipocytes is not fully understood. Objective and hypotheses: We evaluated the transcriptional regulation of *FTO* and *NAMPT* in preadipocytes and adipocytes by metabolic regulators. Methods: Using quantitative RT-PCR we assessed *FTO* mRNA expression during human adipocyte differentiation of Simpson-Golabi-Behmel syndrome (SGBS) cells and primary preadipocytes *in vitro*. Furthermore, we evaluated the effect of metabolic regulators (glucose, insulin, dexamethasone, IGF-1, isoproterenol) on *FTO* and *NAMPT* mRNA expression in SGBS preadipocytes and adipocytes. Results: *FTO* mRNA levels were not significantly modulated during adipocyte differentiation. Also, metabolic regulators had no impact on *FTO* expression in preadipocytes nor adipocytes. In SGBS preadipocytes, *NAMPT* expression was induced 3.2±0.5 fold (P=0.001) by dexa and 3.3±0.9 fold (P=0.01) by isoproterenol. In mature adipocytes *NAMPT* expression was increased 1.6±0.2 fold (P=0.02) by dexametasone. Complete glucose restriction increased *NAMPT* mRNA expression by 5.1±1.2 fold (P=0.03) and 1.4±0.1 fold (P=0.005) in SGBS preadipocytes and adipocytes, respectively. High glucose concentrations did not affect *NAMPT* mRNA levels. Conclusions: *FTO* expression is not affected by differentiation of human adipocytes or metabolic regulators. The stimulation of *NAMPT* expression by dexametasone, isoproterenol and complete glucose restriction may indicate a regulation of NAMPT by metabolic stress, which was more pronounced in preadipocytes than in mature adipocytes.

Funding: IFB

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POSTER 161

Dopamine and serotonin transporter availability and body mass index – first data of an European Multicenter Trial

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The central serotonergic as well as the dopaminergic system, in particular the reuptake sites, are thought to be significantly involved in the pathophysiology of obesity. Initial interpretation of SPECT/ PET data foreshadows a correlation between body mass index (BMI) and serotonin transporters (SERT) along with striatal dopamin transporters (DAT). However, results could neither reproduced nor belied so far. Recently we found positive correlations between SERT distribution volume ratios (DVR) and BMI in healthy controls indicating higher SERT level at higher BMI.
The aim of this project is to correlate DAT or SERT availability with BMI based on a large cohort of healthy subjects (ENC DAT study). Region-of-interest (ROI) analysis (MultiModality, Hermes Medical Solution) of the ENC DAT on BMI and [^{123}I]FP-CIT binding potentials (BP) in the striatum (DAT), thalamus and midbrain (SERT) was carried out. Partial correlations were applied to test for an association between BMI and DAT and SERT availability with correction for age as a confounding factor. Additional analysis will be will be performed with PMOD (PMOD Technologies Ltd.).
To obtain spatially corrected data, PET data has to be registered onto a reference MRI data set. Due to the lack of morphological information in proband PET the proband MRIs are registered rigidly onto the corresponding PETs in a first step. Then an elastic registration of proband MRIs onto the reference MRI takes place. The resulting transformation matrix is finally used to transform the proband PETs onto the reference MRI. Now the defined ROIs can be used for masking and subsequent analysis.

Funding: IFB

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POSTER 162

Internet-basierte Therapie bei Essstörungen – ein systematisches Review

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Mit der Technisierung des Alltags wächst das Bedürfnis nach therapeutischen Unterstützungsangeboten über das Internet im Gegensatz zu konventionellen Psychotherapieangeboten. Mit der steigenden Prävalenz von Essstörungen besonders in Industrieländern ist auch die Anzahl Internet-basierter Interventionen bei Essstörungen in den vergangenen Jahren stetig angestiegen. Ziel dieses systematischen Reviews ist es, einen Literaturüberblick zum diesem Thema zu geben und Aussagen über die Effektivität der angewandten Verfahren zu treffen.
Relevante Literatur wurde zum einen in den elektronischen Literaturdatenbanken PubMed/Medline, PsychInfo, Cochrane Library, National Institutes of Health Clinical Trials database and Web of Sciences sowie im Internet und in den Literaturlisten themenspezifischer Publikationen gesucht. Eingeschlossen wurden Studien, die u. a. randomisiert und kontrolliert waren, die ein störungsspezifisches Therapie- oder Selbsthilfeangebot über das Internet anboten und essspezifische Faktoren als Outcome-Variablen erhoben. Zwölf Studien entsprachen den Einschlusskriterien.
Insgesamt enthalten die dargestellten Untersuchungen über das Internet weniger Therapeutenkontakt als in vergleichbaren face-to-face Interventionen.
Aufgrund der vorliegenden Studien kann von einer guten Effektivität der Internet-basierten Verfahren bei der Behandlung von Essstörungen ausgegangen werden. Damit bestätigen Sie bereits vorliegende Befunde aus anderen Störungsbereichen wie z. B. PTBS, Depressionen und Angststörungen. Vor- und Nachteile der Verfahren werden kritisch diskutiert.

Funding: IFB

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POSTER 163

Der Einfluss von sexuellem Missbrauch auf die Gewichtszunahme nach bariatrischer Chirurgie: Ein systematisches Review

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Einleitung: Bariatrische Chirurgie stellt die zurzeit effektivste Methode zur signifikanten und lang anhaltenden Gewichtsreduktion bei Patienten mit Adipositas Grad III (BMI ≥ 40 kg/m²) dar. Bei einem Großteil der Patienten führt diese Prozedur zu einem massiven Gewichtsverlust, dennoch zeigen Untersuchungen, dass 20-30% der Patienten nicht von dieser Behandlung profitieren.
Zudem weisen verschiedene Studien eine erhöhte Prävalenz von sexuellem Missbrauch bei adipösen Patienten nach. Untersucht wird daher der Zusammenhang zwischen Missbrauchserfahrungen und Gewichtsreduktion nach bariatrischem Eingriff.
Methode: Eine systematische Literatursuche auf Basis folgender Datenbanken wurde durchgeführt: Pubmed/Medline, Science direct, PsychInfo und Web of Science. Insgesamt konnten acht Studien identifiziert werden, die die Beziehung zwischen sexuellem Missbrauch und dem Ergebnis der bariatrischen Prozedur untersuchen.
Ergebnisse: Die Studien, die den Zusammenhang zwischen sexuellem Missbrauch und Gewichtsverlust nach bariatrischem Eingriff untersuchen, liefern kein einheitliches Bild. Eine genauere Betrachtung aller Resultate zeigt jedoch, dass Patienten mit Missbrauchserfahrung offenbar zu einem geringeren Gewichtsverlust tendieren, auch wenn nur ein Teil der Ergebnisse statistisch signifikante Unterschiede zeigt. Dennoch scheint diese Subgruppe deutlich von dem bariatrischen Eingriff zu profitieren, da die Gewichtsabnahme nach der Operation über die Zeit hinweg stetig zunimmt. Mögliche Gründe für die insgesamt uneinheitlichen Ergebnisse werden diskutiert und einheitliche Resultate zusammengefasst.

Funding: IFB

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POSTER 164

Identification of heparin-binding sites in Visceral Adipose tissue derived Serine Protease Inhibitor

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Obesity increases the risk for the development of early metabolic and cardiovascular diseases such as type 2 diabetes, dyslipidemia, hypertension, coronary heart disease, but also various types of cancer. The adipose tissue produces a variety of active biomolecules, termed adipokines, which engage in various metabolic pathways and signaling cascades and thus influence glucose and lipid metabolism, insulin sensitivity, inflammatory reaction and saturation signals and appetite. Recently the adipokine vaspin (visceral adipose tissue-derived serpin) was identified that when administered to mice results in an improvement of hyperglycemia and insulin action and centrally in reduction of food intake. Due to the very low measured circulating vaspin concentrations in humans (~1ng/ml), the physiological relevance of vaspin-associated effects is controversially discussed.
The aim of this project is to investigate and explain the alleged discrepancy between the reported decisive effects and measured physiological concentrations. Heparin binding is well established in the serpin family and we hypothesized that heparin-bound vaspin is primarily membrane localized in insulin-sensitive tissues such as liver, muscle and pancreas and can therefore achieve pronounced metabolic effects despite its evidently low serum concentrations. Based on the vaspin X-ray structure, we have identified and characterized the molecular basis and structural determinants of the vaspin heparin interaction to evaluate the physiological relevance in the context of the proven anti-diabetic potential of this promising adipokine.

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POSTER 165

Hypothalamic response to GLP-1 agonist exenatide predicts energy intake in humans

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The glucagon-like peptide-1 (GLP-1) agonist exenatide enhances insulin secretion in type-2-diabetes. Some, but not all patients, lose weight by decreased energy intake (EI). In animals, intracerebral injection of GLP-1 caused weight loss and hypothalamic GLP-1 receptors have been detected. We investigated, if exenatide simultaneously reduces EI and changes hypothalamic function.
In a cross-over, placebo-controlled, double-blinded study with 22 obese, healthy, non-vegetarian, non-smoking, right-handed male subjects (BMI 29-46 kg/m^2) we performed functional magnetic resonance imaging (fMRI) during i.v. exenatide administration. Inside the scanner subjects rated food and non-food pictures for tastiness/valence. EI was assessed with an *ad libitum* meal.
In line with clinical observations exenatide significantly lowered EI in some of our subjects ("responders":>10 % kcal reduction compared to placebo, n=11, mean -385 kcal / -25 %, p=.03) while in others not ("non-responders": <10% kcal reduction, n=11, mean +122 kcal / +10 %, p=n.s.).
‚Eigenvector centrality mapping' (ECM) of the fMRI data attributes a centrality value for each brain voxel reflecting its degree of within-brain connectivity. In responders the centrality of the hypothalamus significantly increased in the exenatide condition compared to placebo during food rating (z-value 3.88, uncorrected, maximum at Talairach coordinates -3, -6, -5).Non-responders did not show these alterations of neural function.
We demonstrate that exenatide alters both hypothalamic connectivity and EI in humans. Changes in hypothalamic connectivity seem to be linked with anorectic response.

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POSTER 166

Hepatocellular functional capacity as a predictor of Fibroblast Growth Factor 21 serum levels

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TRM – Tissue Repair and Replacement
Tumor Targeting

Background: Fibroblast growth factor (FGF) 21 is considered to be a metabolic hormone rather than a traditional growth factor. In the current study, we investigated the relationship between serum FGF 21 levels and metabolic, as well as cardiovascular parameters, in the self-contained population of Sorbs.
Methods: Serum FGF 21 concentrations were quantified by ELISA and correlated with metabolic and cardiovascular parameters, as well as inflammatory markers and renal and liver function in 670 well-characterized Sorbs from Germany.
Results: Median FGF21 serum concentrations were 1.6-fold higher in T2DM subjects (145 pg/ml) as compared to controls (89 pg/ml). Systolic blood pressure, cholesterol, triglycerides, γ glutamyl transferase and insulin-like growth factor 1 were independently associated with FGF21 concentrations in multiple regression analysis.
Conclusion: FGF21 serum concentrations are determined by parameters of lipid metabolism and heptocellular functional capacity.

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POSTER 167

Forschungsschwerpunkte im IFB Data Center

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Phosphodiesterases (PDEs) are a family of enzymes subdivided into 11 distinct families according to structural and functional properties. These enzymes metabolically inactivate widely occurring intracellular second messengers. Of all known PDE families, PDE10A has the most restricted distribution with high mRNA expression only in the brain and testes. PDE10A mRNA expression and protein are highly expressed in medium spiny neurons of the striatum. Noninvasive imaging of PDE10A using PET would allow for studying the distribution of this enzyme in neuronal and psychiatric disorders. Therefore we might still identify derivatives with sufficient potency and selectivity for PDE10A, resulting in a PET tracer showing a reasonable pharmacodynamic, pharmacokinetic and toxicological profile. We decided to initiate a chemical exploration around a lead compound. The project includes four subprojects. The aim of the subproject 1 (Prof. Briel, Prof. Sträter) was to synthesize analogues that can be easily radiolabeled with ^{18}F. The subproject 2 (Prof. Nieber) was aimed to evaluate in vitro and in vivo toxicity of selected analogues. The subproject 3 (Prof. Brust) was responsible for radiolabeling a potential candidate with ^{18}F and to measure the in vivo brain occupancy of the most promising derivatives. The in vitro PDE10A potency and selectivity was determined in co-operation with biocrea GmbH. The data of this project are essential to assess the suitability of a potential candidate as PET agent for imaging PDE10A in vivo.

Funding: IFB

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POSTER 168

The zebrafish as a model organism for the characterization of MTCH2 and NEGR1 as potential regulators of adipogenesis in vivo

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Tumor Targeting

Background: The early processes of adipose tissue development and their regulation are not fully understood. Genome-wide association studies have identified several genes associated with obesity and associated disease, but their biological function has not been resolved. It is inevitable to study the biological role of these genes not only *in vitro* but also *in vivo*.
Methods and Results: We have identified *MTCH2* and *NEGR1* as novel potential regulators of adipogenesis by analyzing the role of obesity-associated genes *in vitro* using SGBS cells as a model for human adipogenesis. To further characterize the biological function of the newly identified regulators of adipogenesis *in vivo* we are using the zebrafish as a model organism. For this, we have established a zebrafish facilty in our lab. We identified orthologs of *MTCH2* and *NEGR1* in zebrafish and analysed their expression pattern in adult tissues and during early development. We could show that both genes are expressed in adipose tissue of adult zebrafish. Moreover, both zebrafish *mtch2* and *negr1* are significantly up-regulated from day 5 to day 9 of zebrafish development. At this stage, we could also detect first visceral adipocytes using Nilered staining. Furthermore, expression of *pparg*, which is described as the master regulator of adipogenesis in mice and humans, was significantly activated at this developmental stage.
Conclusion: *MTCH2* and *NEGR1* are putative regulators of adipogenesis *in vitro*. In zebrafish, the orthologs of *mtch2* and *negr1* are activated with the start of adipogenesis supporting a potential role of *mtch2* and *negr1* during adipogenesis *in vivo*.

Funding: IFB

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POSTER 169

Crown-like structures (CLS) as the primary site of macrophage proliferation and activation

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It is assumed that adipocytes die when they exceed a certain size, the so-called *critical size theory*. Following adipocyte death, the number of macrophages (MΦs) increases and their immunophenotyp shifts from alternatively-activated M2 MΦs to pro-inflammatory M1 MΦs. The increase of adipose tissue MΦs is believed to be caused by an enhanced recruitment of monocytes from the blood stream which mature to MΦs and surround remnants of dead adipocytes, thereby forming the characteristic CLSs. Alternatively, however, proliferation may occur on-site, i.e. from resident MΦs within the fat tissue.
We tested this alternative hypothesis using genetically obese mice (ob/ob), which lack the appetite regulating hormon leptin. We investigated subcutaneous and visceral adipose tissue for different marker proteins for M1 or M2 MΦs as well as for the proliferation marker ki67 by immunofluorescence.
We show that MΦs of obese mice start to proliferate within the adipose tissue predominately in CLS. In visceral adipose tissue, we found significantly more CLS and proliferating macrophages than in subcutaneous fat of ob/ob mice. In lean mice (WT), CLS and proliferating macrophages were rare. Additionally, CLS-associated macrophages express CCR7 and CX3CR1 rather than stromal macrophages, which is known to be the chemokin receptor expression pattern of pro-inflammatory M1 MΦs. Currently, we perform live tissue imaging to investigate CLS growth and MΦs migration *in situ*.
We conclude that CLS act as primary site of MΦs proliferation and activation in obese adipose tissue. Hence, the increase of adipose tissue MΦs in obesity is probably due to proliferation of resident MΦs, rather than an increased recruitment of blood-derived monocytes.

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POSTER 170

Auswirkungen von „Weight cycling" auf die Lebenserwartung bei Mäusen

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Hintergrund: Viele Therapien zur Reduktion des Übergewichts liegen in zahlreichen Sportprogrammen, Medikation und Diäten. Leider belegen die Therapieergebnisse nur unzureichende Ergebnisse. Vielfach werden sogenannte „Jo-Jo" Effekte beschrieben. Hier soll nun *in vivo* überprüft werden, in wieweit intermittierende Phasen hypokalorischer Ernährung die Lebenserwartung beeinflusst.
Methodik: In den Mausstämmen 129S6/SvEvTac (N=90) und C57BL/6NTac (N=90) wurden die Auswirkungen einer kontinuierlichen kalorischen Restriktion, einer lebenslangen Hochfettdiät und einem Weight cycling, das durch einen Wechsel zwischen den beiden extremen Ernährungsformen jeweils in 4 Wochen auf die Lebenserwartung untersucht. Die Körpermasse wurde wöchentlich erfasst. Die Insulintoleranz wurde im Alter von 24 Wochen überprüft und der HbA1c wurde nach einem Jahr analysiert. Außerdem erfolgte die Ermittlung des Grundumsatzes mittels Metabolischer Kammern (TSE, Bad Homburg, Deutschland).
Ergebnisse: Die mittlere Lebenserwartung der Tiere unter Weight cycling war vergleichbar mit dem der Kontrolltiere mit Normalfutter. Die Kontrollgruppe auf hochkalorischer Diät lebte im Mittel 3,5 Monate kürzer als die beiden anderen Gruppen. Diese Beobachtung war unabhängig vom Mausstamm. Im Vergleich der Lebenserwartung zwischen den Stämmen lebten die 129S6/SvEvTac Tiere im Mittel 1,5 Monate länger als die C57BL/6NTac Tiere. Weitere signifikante Unterschiede zeigten sich in der Insulintoleranz, HbA1c sowie im Grundumsatz.
Schlussfolgerung: Weight cycling verbessert gegenüber einer lebenslangen Hochfettdiät signifikant die Lebenserwartung.

Funding: IFB

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POSTER 171

Adipokine and adipokine receptor expression in human spermatozoa

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Objective: Adipokines play an important role in human reproduction and might therefore affect spermatozoa directly. This assumption is supported by correlations between adipokine levels in seminal plasma and semen parameters from clinical studies. However, a pathomechanism for putative interactions between adipokines and spermatozoa has not been investigated so far. Accordingly, we asked in our study whether or not human spermatozoa may express adipokines and their receptors as general precondition for such interactions.
Methods: Human spermatozoa of semen donors were incubated with commercial antibodies against leptin receptor (ObR), adiponectin receptor 1 (AdipoR1), leptin and NAMPT. Subsequently, smears were incubated with commercial FITC-labelled antibodies and immunofluorescence measurement was performed. Smears incubated only with secondary antibodies or with a blocking peptide served as negative controls.
Results: ObR was found in the tail and the connecting piece but not in the midpiece of the spermatozoa. Leptin itself was found in the tail, connecting piece and sometimes in the midpiece. The immunofluorescence of AdipoR1 revealed same distribution as shown for ObR. The presence of AdipoR2 was excluded by PCR analysis. Only a few spermatozoa incubated with NAMPT antibodies showed a fluorescence signal. After sperm separation into mature and immature portions NAMPT fluorescence was detected in immature spermatozoa.
Conclusions: Leptin and its receptor as well as AdipoR1 and NAMPT are expressed by human spermatozoa. The physiological function and the signalling of these receptors are currently under investigation.

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POSTER 172

Long-term cost-effectiveness of bariatric surgery

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Tumor Targeting

Background: Health economic evaluations with short time horizons may underestimate the cost-effectiveness of bariatric interventions, since the surgical procedure itself is costly, while the offsets in health care costs (e.g. because of diabetes remission) are accumulated over time. In synthesizing best available evidence from a variety of sources, model-based economic evaluations can take long-term costs and effects of interventions into consideration.
Methods: Systematic literature review. A search in PubMed, and a bibliographic search within all potentially eligible studies was conducted. We included model based cost-utility analyses of surgical intervention(s) in obese patients with time horizons ≥ 20 years.
Results: The search produced a total of 271studies, of which 11 were included into the review (published between 2002 and 2010). Findings for two types of restrictive surgical procedures, i.e. "adjustable gastric banding" (8 interventions) and "gastric bypass" (10 interventions), were extracted and summarized (both of which were compared to conventional treatment). Under base-case assumptions, bariatric surgery led to substantial health benefits through permanent weight loss and was dominant in one study. In the remaining studies bariatric surgical procedures were found to be cost-effective (<43,430 USD per QALY, in 2010USD).
Conclusions: Bariatric surgical procedures are cost-effective treatments in severely obese persons. High initial intervention costs are offset by lower direct and indirect costs and additional health benefits over the lifecycle.

Funding: IFB

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POSTER 173

MICROMORPHOLOGICAL INVESTIGATIONS OF INTERVERTEBRAL DISC DEGENERATION USING ELECTRON MICROSCOPY

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Tumor Targeting

Intervertebral disc degeneration can be distinguished by various changes in the tissue structure like delamination and crack formation of the collagenous matrix as well as cellular changes like cell ageing and variances in the amount and allocation of the cells. These indications of intervertebral disc degeneration are shifting while increasing grade of degeneration. It has been confirmed that the ultrafine structure of the two types of disc tissues (annulus fibrosus and nucleus pulposus) significantly influence the disc stability. Conventional clinical imaging techniques like CT and MRI are not able to visualize tissue morphology andtissue damages on this structure level.
To get detailed information about the degeneration and to achieve deeper insights into the morphology andmicrostructure of disc tissue, samples where investigated by scanning electron microscopic (SEM) techniques and the corresponding sample preparations. The method allows the determination of the tissue morphology at high resolution.
In the extracted tissue, we visualized different regions with characteristic micro structural damage behaviors, such as regions of prevalent micro cracks, or regions of fiber matrix delamination or fiberbridging.

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POSTER 174

The HERMES BRASS tool for an accurate automated regional and voxelwise quantification of brain β-amyloid load as imaged with florbetaben PET

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Tumor Targeting

Florbetaben is a promising β-amyloid-targeted PET tracer currently in global clinical development (Barthel et al., Lancet Neurol 2011). β-amyloid is important in pathophysiology of Alzheimer´s Disease (AD). In this present trial we aimed at establishing the HERMES BRASS software as a tool to analyze florbetaben PET data.
A BRASS database was generated from florbetaben PET scans of 93 cognitively normal, β-amyloid-negative healthy volunteers (HVs). Using this normal database, 145 multicenter florbetaben PET scans (77 ADs, 68 HVs) from the multicenter Phase 2 trial were analyzed in a voxel-based and volume of interest (VOI)-based manner.
The BRASS analysis of the florbetaben datasets was possible within 41±4 sec. The composite standardized uptake value ratios (SUVRs) as determined by BRASS correlated significantly with those determined by reference method ($r=0.85$, $p<0.001$). The composite SUVRs obtained with BRASS and the reference approach discriminated equally well between ADs and HVs ($p<0.001$, Cohen`s $d = 1.37$ for both approaches). In the ADs and HVs, 3.2±2.7 vs. 0.1±0.4 ($p<0.001$, Cohen`s $d = 1.61$) neocortical regions were defined by BRASS as pathologic (z-score>2.5). The total brain volume affected by β-amyloid was 18.6±25.7 vs. 0.8±3.7 ml for the ADs and HVs ($p<0.001$).
The BRASS tool customized for florbetaben PET demonstrated excellent ability in discriminating between ADs and HVs. Thus, this software has great potential in supporting the visual interpretation of florbetaben PET image data in a rapid, user friendly and operator-independent manner.
Research support: Bayer Healthcare, Hermes Medical Solutions

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POSTER 175

Wertigkeit der diffusionsgewichteten und spektroskopischen MR-Bildgebung für eine Vorhersage der Tumoraggressivität beim Prostatakarzinom

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Tumor Targeting

Ziel: Active Surveillance (AS), derzeit als Alternative zur unmittelbaren Therapie niedrig-gradiger Prostatakarzinome (PCa) diskutiert, erfordert regelmäßige Kontrollen, üblicherweise mittels ultraschallgestützter Biopsie. Hier wurde die nicht-invasive Untersuchung im MRT für die Vorhersage der Tumoraggressivität evaluiert.
Methoden: 13 Patienten mit PCa erhielten vor Prostatektomie ein endorektales, multiparametrisches 3T MRT. Hochgradige Läsionen wurden vom Pathologen auf Großflächenschnitten markiert und der entsprechende Gleason Score (GS) mit Tumor-ADC (apparent diffusion coefficient), normiertem ADC (nADC, Tumor/Gesund), CC- (Cholin/Citrat) und CCC- (Cholin+Kreatin/Citrat) Verhältnis korreliert. Mittels ROC wurde die Trennschärfe (AUC) zwischen niedrig- ($GS\leq6$) und hochgradigem ($GS\geq7$) PCa bestimmt. Ein verblindeter Auswerter bestimmte anhand ermittelter Schwellwerte die individuelle Tumoraggressivität.
Ergebnis: Bei 22 Läsionen (GS: 1x"3+2",11x"3+3", 7x"3+4", 3x"4+4") zeigte nADC eine höhere Trennschärfe als Tumor-ADC (AUC: 0,94 vs 0,80). CC und CCC erreichten AUC-Werte von 0,78 und 0,81. Mit Hilfe der ausgewählten Parameter für ein aggressives Tumorwachstum ($nADC<0{,}45$ und/oder $CCC>1{,}3$) konnte der verblindete Auswerter 11/13 Patienten (85%) richtig einstufen, jeweils ein Patient mit $GS=5$ und 6 erfuhren ein Overgrading.
Schlussfolgerung: In dieser vorläufigen Analyse zeigten sich nADC und CCC als geeignete MRT-Parameter zur Trennung zwischen niedrig- und hochgradigem PCa. Die Kombination der hoch-sensitiven Diffusions-MRT mit der hoch-spezifischen MR-Spektroskopie könnte ein geeigneter Kandidat zur AS-Kontrolle sein.

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POSTER 176

Vergleich von MR-Spektroskopie und In-phase/ Opposed-phase-MRT zur Bestimmung der Leberverfettung bei extrem adipösen Patienten

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Die Steatosis hepatis stellt eine häufige Erkrankung westlicher Industrienationen dar und geht mit einem erhöhten Risiko zur Entwicklung einer Steatohepatitis und einer Leberzirrhose einher. Das Ausmaß der Leberverfettung ist für die Prognose relevant und lässt sich nichtinvasiv mit Hilfe verschiedener MR-Techniken quantifizieren. Ziel dieser Arbeit ist ein Vergleich der MR-Spektroskopie (MRS) mit einer In-phase/Opposed-phase-Bildgebung (IP/OP-MRT) bei extrem adipösen Patienten. Bisher wurden 26 Patienten (BMI 48±4 kg/m^2) im 1,5 T MRT untersucht. Single-Voxel-MR-Spektren wurden in freier Atmung in den Lebersegmenten II, IV und VII akquiriert und mit einer kommerziellen Software (LCModel) analysiert. Nach Korrektur von T1- und T2*-Effekten wurden aus den IP/OP-MRT-Bildern (in Inspiration) Verteilungen des Leberfettgehalts (IHL) berechnet und den Lokalisationen der MRS-Voxel angepasste Analyseregionen (ROI) definiert. Die Akquisitionszeiten für MRS und IP/OP-MRT betrugen im Mittel 17,2±3,2 bzw. 4,3±1,1 min. Die gemessenen IHL-Werte lagen im Bereich von 0,0-65,9% (MRS) bzw. 0,1-36,7% (IP/OP-MRT). Die IHL-Karten zeigten eine leicht heterogene Leberfettverteilung. Die Korrelationskoeffizienten der einzelnen Segmente (II, IV und VII) betrugen r=0,84, 0,87 und 0,93 (jeweils p<0,01). Der Vergleich beider Methoden ergab eine mittlere Abweichung von -1,6% (p=0,55) sowie Übereinstimmungsgrenzen (LOA) von -15,7 und +12,6%. Die über beide Methoden berechneten Leberfettgehalte stimmten gut überein. Die beobachteten Abweichungen können durch die verschiedenen Atemlagen während der Messungen sowie leicht unterschiedliche Analyseregionen erklärt werden. Die IHL-Bestimmung über eine IP/OP-MRT war schneller und bietet prinzipiell den Vorteil, dass der Fettgehalt sowie lokale Variationen in der gesamten Leber erfasst werden.

Funding: IFB

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POSTER 177

Wertigkeit der MRT zur Vorhersage eines kapselüberschreitenden Wachtums beim Prostatakarzinom

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Nach Diagnose eines Prostatakarzinoms (PCa) erfolgen Prognose, Risikostratifizierung und Therapiewahl häufig auf der Basis von Nomogrammen, die jedoch nur bedingt geeignet sind. Ziel der vorliegenden Arbeit war die Bestimmung der Wertigkeit einer MRT-Bildgebung der Prostata zur Differenzierung zwischen den Stadien pT2 und pT3 a/b vor radikaler Prostatektomie.
37 konsekutive Patienten mit histologisch gesichertem PCa wurden gemäß eines multiparametrischen MRT-Protokolls mit endorektaler Spule bei 3 T untersucht. Zwei Radiologen mit 8 bzw. 3 Jahren Erfahrung in der MRT-Bildgebung des Urogenitaltrakts bewerteten die Wahrscheinlichkeit des Vorhandenseins einer Kapselüberschreitung (ECE) bzw. Samenblaseninfitration (SVI). Als Referenz diente die intraoperative Schnellschnittdiagnostik in den sechs Regionen apikal, dorsolateral und harnblasennah, jeweils beidseits, sowie die leitliniengerechte, postoperative Aufarbeitung der gesamten Prostata und der Samenblasen.
Sensitivitäten, Spezifitäten und Genauigkeiten der Detektion einer ECE betrugen für den erfahrenen (weniger erfahrenen) Radiologen patientenbezogen 90% (80%), 74% (82%) und 78% (81%) bzw. regionenbezogen 93% (67%), 91% (95%) und 92% (93%). Die entsprechenden Werte für die SVI lagen bei 80% (100%), 96% (99%) und 95% (97%). Die Unterschiede zwischen erfahrenem und weniger erfahrenem Radiologen waren nicht signifikant.
Die MRT der Prostata stellt eine zuverlässige, diagnostische Methode zum lokalen Staging beim PCa dar.

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POSTER 178

Faserdarstellung des Tractus iliotibialis durch die "Magic Angle" Methode

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Hintergrund und Einführung
Am Lebenden ist die Diagnostik von Bändern und Sehnen auf radiologische Techniken begrenzt. Um diese zu erweitern, wurden durch Kollagen verursachte winkelabhängige Grauwertänderungen im T2-gewichteten MRT ("Magic Angle" Phänomen) in einen Computeralgorithmus implementiert. Ziel ist die Bestimmung der Kollagenfaserverläufe am menschlichen Tractus iliotibialis.
Materialien und Methoden
Drei Proben wurden aus dem Tractus eines 44-jährigen Körperspenders entnommen. Die Proben wurden auf Acrylglas montiert und in unterschiedlichen Orientierungen in einer Box mit Gelatine eingebettet. Die Box wurde auf einer Drehvorrichtung befestigt. Fünf MRT-Scans erfolgten ohne Manipulation der Box und weitere 19 Scans nach Rotation um jeweils 10°. Anschließend wurde die Box um 90°gekippt und eine weitere Scanserie erstellt. Die Faserorientierung der Proben im MRT wurde von Hand segmentiert, softwarebasiert errechnet, und anschließend polarisationsmikroskopisch validiert.
Ergebnisse
Die Faserverläufe der Tractusproben konnten durch manuelle Segmentierung gezeigt und durch unsere Software errechnet werden. Die Genauigkeiten der errechneten Faserorientierungen lagen bei 91% (Probe 1), 90% (Probe 2) und 82% (Probe 3). Die Polarisationsmikroskopien der Proben stimmten mit dem makroskopischen, nahezu parallelen Kollagenfaserverlauf überein.
Diskussion und Schlussfolgerung
Kollagenfaserverläufe des Tractus können nicht-invasiv unter Nutzung des „Magic Angle" Phänomens vorhergesagt werden. Bänder- und Sehnenverläufe sind somit erstmals in-situ bestimmbar.

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POSTER 179

3D-Muskelmodelle des Beckens und der unteren Extremität junger Probanden – Datenakquise und Segmentierung

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Einleitung und Hintergrund3D-Muskelmodelle basieren meist auf individuellen Studien an verstorbenen, betagten und anatomisch fixierten Körperspendern. Die Segmentierungen repräsentieren daher nicht den funktionellen Zustand der Muskeln beim Lebenden. Da große anatomische Regionen zudem lange Messzeiten im MRT benötigen, erschweren wache Probanden durch Bewegungen die Datengewinnung. Ziel unserer Studie waren Muskelsegmentierungen des Beckens und der unteren Extremität aus MRT-Daten von jungen, wachen Probanden in hinreichender Qualität.Material und MethodenMRT-Daten des Beckens und der unteren Extremität wurden mit 3 T in koronarer Schichtung von sechs jungen und gesunden Probanden erhoben (3 ♂, 3 ♀; Ø 26,5 Jahre). Die Muskeln und Knochen wurden in der Koronarebene und mindestens einer weiteren Ebene segmentiert und validiert. Aus den Segmentierungen wurden anschließend 3D-Modelle errechnet.ErgebnisseIn allen sechs MRT-Datensätzen wurden 27 Muskeln und funktionelle Gruppen segmentiert. Zusätzlich wurden aus den MRT Knochen segmentiert, um anatomische Referenzpunkte zu erhalten. Einige Körperbereiche lagen außerhalb des Bildfelds und verursachten Artefakte. Diese wurden manuell während der Segmentierung ausgeglichen.Diskussion und AusblickMuskel- und Knochenmodelle von jungen, wachen Probanden konnten erfolgreich erstellt werden. Die Nutzung des 3 T MRT ermöglichte Datenakquisen in für Segmentierungen ausreichender Bildqualität. Die Segmentierungen sind daher sowohl eine realistische Darstellung von Muskeln im Vitalzustand, als auch Modelle für virtuelle Simulationen am Bewegungssystem des Menschen.

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POSTER 180

Does DTI help to determine sacro-iliac ligament direction?

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Summary of Background Data
Diffusion tensor imaging (DTI) is an algorithm to follow water using Magnet Resonance Imaging (MRI). It was firstly used to show fibers in brain - and recently in muscles and nerves, visualizing free directed water. Until now no data were obtained from collagen structures such as ligaments and tendons. Collagen transmits forces. Collagen direction is therefore of importance, e.g. for computational models. Such directions are not yet known in the sacro-iliac joint (SIJ), connecting the upper to the lower part of the body. DTI was used to find SIJ collagen directions and their changes due to forces.
Materials and Methods
We dissected a SIJ (♀, 69 year-old) including bones and the iliol-umbar, the sacrotuberous and -spinous ligaments. Both sides of the SIJ were embedded to polyurethane resin blocks. The SIJ was free in-between the blocks. Before testing joint motion, 1.5 T DTI-MRI was performed in isotonic saline solution. To apply forces to the SIJ, we pressed further solution in-between the blocks using catheters and performed DTI-MRI again.
Results and Discussion
The SIJ was seen moving in the experimental setup. The movement was recorded in MRI. DTI data of the different SIJ-positions were gained. However, we could neither correlate the changes seen in DTI-MRI of the ligaments to the SIJ movement, nor could significant vectors be calculated from DTI.
Conclusions
A sufficient device was created to follow the SIJ moving. However, with the given methods, DTI is insufficient for detecting fiber directions of the SIJ. This is probably caused by a lack of free directed water.

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POSTER 181

In-vivo-Bestimmung der Kollagenstruktur im Kniegelenkknorpel mittels 7-Tesla MRT und erste Ergebnisse zu deren Altersabhängigkeit

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Ziel: Nichtinvasive Analyse der kollagenen Fasermatrix im adulten Knieknorpel mittels winkel-sensitiver 7-T MRT sowie erste Erfassung altersabhängiger Unterschiede bei gesunden Probanden.
Material und Methodik: Die rechten Kniegelenke von zehn jüngeren (21-30 J.) und zehn älteren (55-76 J.) gesunden Probanden wurden in einem 7-T Ganzkörper-MRT mit einer T2-gewichteten Multi-Echo-Sequenz untersucht. Im Femur und in der Tibia wurden rund 1-mm breite und der Knorpeldicke angepasste ROIs definiert. Aus den Multiecho-Bildern wurde dasjenige ausgesucht, dessen Verlauf der Signalintensität in Abhängigkeit von der Tiefe am besten mit dem der berechneten T2-Werte übereinstimmte. Unter Annahme eines Modells zur winkel-sensitiven MRT der anisotropen Knorpelstruktur wurden die jeweiligen Signalintensitäten in mittlere Öffnungswinkel α des Faserbündels (α-Tiefenprofil) umgerechnet. Die Position der Grenze zwischen radialer und isotroper Zone (R/T-Grenze) wurde bei α=35° festgelegt.
Ergebnisse: Die relative Position der femoralen R/T-Grenze lag bei jüngeren Probanden (0,51±0,12) signifikant höher ($p<0,05$) als bei den älteren (0,41±0,10). Der Unterschied in der Tibia war nicht signifikant (0,65±0,11 vs. 0,57±0,09; $p=0,12$).
Schlussfolgerungen: Eine winkel-sensitive MRT bei 7 T eignet sich zur quantitativen Analyse der kollagenen Knorpelstruktur in vivo. Die Strukturanisotropie des femoralen Knorpels zeigte einen signifikanten Unterschied zwischen jüngeren und älteren Probanden. Somit könnte diese Technik nützlich sein, um altersbedingte (biologisches Knorpelalter) oder arthrosebedingte Änderungen der Kollagenmatrix zu erfassen.

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POSTER 182

α4β2* Nicotinic acetylcholine receptor (α4β2*) availability in mild/prodromal Alzheimer's disease using 2-[18F]F-A-85380 (2FA)-PET

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It is widely accepted that α4β2* are reduced in moderate AD. However, there is a controversy, whether α4β2* are altered in-vivo in mild/prodromal Alzheimer's disease (mpAD). In order to address this issue, using α4β2*-specific 2FA-PET, absolute and relative quantitative measures of 2FA binding were assessed in mpAD and compared with age-matched healthy controls (HC). Non-smoking, without anti-cholinesterase drugs, 14 mpAD (66±5ys; MMSE 21-28) and 16 age-matched HC (65±6ys; MMSE≥28) underwent 2FA-PET. Parametric images of the distribution volume (DV; Logan plot), as absolute, and the binding potential (BP), as relative quantitative measure, using the corpus callosum (cc) as almost unspecific reference region were determined (VOI-/SPM-analysis). Significance at $p<0.003$ to 0.001; $T>3.0$ to 4.5. Compared with HC, in mpAD there was regionally similar, lower DV or BP in the posterior cingulate cortex, parieto-temporal-occipital and frontal cortices, (para) hippocampus, thalamus and caudate nucleus. However, these similar patterns of lower DV/BP were demonstrated at different significance levels (BP: $p<0.001$, $T>4.5$; DV: $p<0.003$, $T>3.0$). DV in cc did not differ significantly between groups. Using either relative (BP) or absolute quantification (DV) and 2FA-PET, we demonstrate for the first time that there is widespread lower cortico-cingulate-thalamic-(para)hippocampal and caudate α4β2* binding already in mild/prodromal AD. Furthermore, our results indicate that relative quantification of α4β2* binding using the corpus callosum as reference region is valid and detects alterations of α4β2* binding in mpAD with highest sensitivity.

Funding: life

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POSTER 183

Ein Algorithmus für die Bestimmung von Kollagenfaserrichtungen in Bändern basierend auf der Orientierungsabhängigkeit der Signalintensität in T2-gewichteter MRT

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Hintergrund: Die Signalintensität in T2-gewichteten MRT-Aufnahmen von Geweben mit geordneten kollagenhaltigen Strukturen (Bänder, Knorpel) weist eine Abhängigkeit von der Ausrichtung im Magnetfeld B0 auf. Das Intensitätsmaximum tritt bei einem Winkel von rund 55° („magic angle") zwischen kollagenen Fasern (KF) und B0 auf. Hier wird ein Algorithmus für die Bestimmung eines unbekannten, dreidimensionalen (3D) Verlaufs von KF basierend auf der Orientierungsabhängigkeit der MR-Intensität präsentiert.
Methodik: Basierend auf einer mathematischen Beschreibung der Orientierungsabhängigkeit der MR-Intensität in B0 wurde ein Algorithmus für die Bestimmung der KF-Richtung entwickelt. Zur Validierung wurden 1.000 virtuelle KF mit zufälligem 3D Verlauf generiert und um zwei unabhängige Achsen gedreht. Die Abweichung der berechneten Richtungen wurde bestimmt. Zur Bestimmung der Robustheit des Algorithmus wurden die Rotationsschrittweiten variiert sowie zufällige Fehler (Rauschen) auf die Eingangsdaten addiert.
Ergebnisse: Ohne Addition von zufälligen Fehlern ergab der Algorithmus bei Rotationsschrittweiten von 1°, 5°, 10°, 20° und 30° mittlere Abweichungen der berechneten Faserverläufe von 0,5°, 1,9°, 4,4°, 11,2° bzw. 24,9°. Bei Addition von Rauschen (Median: +/-15%) ergaben sich mittlere Abweichungen von 19°, 14,6°, 15,1°, 20,3° bzw. 31,3°.
Schlussfolgerung: Der vorliegende Algorithmus ist in der Lage, den 3D Verlauf von unbekannten KF zu ermitteln. Er besitzt eine hohe Robustheit und liefert bei Rotationsschrittweiten zwischen 1° und 20° zuverlässige Ergebnisse. Eine mögliche Anwendung auf reale KF muss geprüft werden.

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POSTER 184

Einfluss der Aufnahmedauer auf die visuelle und automatische Auswertung der β-Amyloid-Plaque-(Aβ)-Darstellung mittels Florbetaben-PET bei Alzheimer-Patienten (ADs) und gesunden Probanden (HVs)

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Kurze Scandauer und Software-basierte Auswertung können den künftigen klinischen Einsatz der Aβ-Darstellung praktikabler gestalten. Ziel der monozentrischen Studie war es, den Einfluss der Scandauerauf die diagnostische Sicherheit der Auswertung von Florbetaben-PETs zu untersuchen. Retrospektive Auswertung der PET von 50 Personen (25ADs, 25HVs). Pro Untersuchten wurden 3 PETs (Scandauer: 5;10;20min)-jeweils 90min p.i. beginnend-erstellt, randomisiert und visuell durch 3 unabhängige Gutachter bewertet. Beurteilt wurden Tracer-Uptake als Korrelat für Aβ im Hirn und diagnostische Sicherheit. 10%der Untersuchungen wurden re-evaluiert. Die Daten von 20 der 50 (10ADs,10HVs) wurden Software-basiert analysiert. Composite SUV ratios (cSUVR) und z-scores (cZ-S) wurden berechnet. Bei allen Scandauern wurden 20 der 25 ADs und 1 der 25 HVs visuell als Aβ-positiv bewertet ($p<0,001$). Damit betrugen Sensitivität und Spezifität jeweils 80% und 96%. Diagnostische Sicherheit der Gutachter (20 und 10min: 97±6%, 5min: 95±8%, n.s.) und Inter-Reader-Agreement ($\kappa_{20min}=0,94$; $\kappa_{10min}=0,94$; $\kappa_{5min}=0,89$; n.s.) warenhoch. Das Intra-Reader-Agreement war am höchsten bei 20min ($\kappa=1,00$) und signifikant niedriger bei 10 ($\kappa=0,71$) und 5min ($\kappa=0,80$) Scandauer ($p=0,002$ und 0,003 getestet gegen 20min). Bei allen Scandauern waren cSUVRs und cZ-s signifikant höher bei den ADs als bei den HVs (jeweils $p<0,0001$). Die hohe diagnostische Sicherheit der Florbetaben-PET in der Aβ-Darstellung und somit in der Differenzierung zwischen HVs und ADs wird entsprechend unserer Ergebnisse nicht durch eine reduzierte Scandauer beeinflusst.

Unterstützung: Bayer Pharma AG

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POSTER 185

Entwicklung einer Handheld-Gammakamera zur intraoperativen Bildgebung*

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Die Lokalisation des Wächterlymphknotens während der sondengeführten Lymphadenektomie wird fast ausschließlich durch die peritumorale Applikation von Tc-99m-Kolloiden, die auf den Lymphwegen abfließen, erreicht. Bedingt durch die meist im niedergelassenen ambulanten Bereich erfolgende Applikation des schwach radioaktiven Tracers, liegen nur in wenigen Fällen Szintigramme in Form von Spätaufnahmen unmittelbar vor dem Eingriff (im universitären Bereich als Vergleich meist 18-24h nach der initialen Lymphszintigrafie) vor. Der Operateur ist dann auf seine Erfahrung angewiesen, den SLN allein aus dem Messsignal der verwendeten Gammasonde aufzufinden. Um dem Operateur eine 2D-Information anhand eines Bildes zu geben, wird als Detektor ein (40x40x28)mm³ großes CZT-Modul, dessen kathodenseitige Elektrode vollflächig vorliegt und anodenseitig über eine 256er-Matrix (16x16 Pixel a [2,2x2,2]mm², Pixelpitch 2,46mm) verfügt. Stromversorgung und Datenaustauch zum PC erfolgen über USB (5V, 300mA). Die Hochspannung wird aus 5V (von USB) durch einen DC/DC-Wandler generiert. Zur Ansteuerung und Übertragung wird ein 32bit Controller mit 66MHz verwendet. Dieser kommuniziert per SPI-Protokoll über LVDS-Sender und -Empfänger mit dem Detektor. Zur Richtungsselektion der Gammastrahlen (Tc-99m, 140keV) ist der Kollimator der pixelierten Gestalt der Anode angepasst. Empfindlichkeit zu Auflösung sind bei einer Kollimatorkanaldimension von (1,8x1,8)mm² optimal. Die mobile prä- und intraoperative, szintigrafische 2D-Darstellung des Situs ist damit möglich.

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POSTER 186

Investigation of Eddy Current induced Vibrations of a Home-built Tracking System for Motion Correction in Magnetic Resonance (MR) Imaging at 7T

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Purpose: Prospective motion correction offers improvements in high resolution MR image quality. Optical tracking of markers attached to the volunteer [1] provides an effective method to determine the position and orientation information required to update the gradient and RF pulses.However, in-bore systems present additional technical challenges. We have examined the effect of gradient-induced vibrations on the tracking accuracy of our home-built tracking system.
Methods: Our tracking system comprises three individual TrackingCams. We compare the vibrations during MR scanning in a 2mm thick aluminium case and a plastic casing coated with a 50μm thick aluminium shield. For this purpose, the tracked positions of fixed markers were repeatedly recorded for 3s.
Results: Use of the casing with 2mm thick aluminium resulted in vibrations 1-2 orders of magnitude greater than the 50μm casing. Eddy current induced vibrations of the 2mm thick casing greatly diminished the tracking accuracy and damaged the hardware. In the 50μm casing, the standard deviations with and without scanning were within the same range (< 0.11pixels or < 16μm for a marker at 12cm distance).
Discussion: The measurements demonstrate that our tracking system with 50μm thick shielding operates in the MR scanner, and that scanning does not significantly increase the tracking noise.
Conclusion: Eddy currents within an MR scanner have a big influence on tracking accuracy and hardware reliability of a tracking system - housing design is therefore an important aspect of hardware development.
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POSTER 187

Defining the ischemic penumbra with [15O]H2O –PET: Method evaluation in a new sheep stroke model

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Aim:This study aimed to establish a method for the identification of the ischemic penumbra after acute stroke with a single [^{15}O]H_2O positron emission tomography (PET) and without individual blood sampling. This study was performed in sheep as a clinically relevant animal model of stroke which was recently established in our group.
Methods:Two to three hours after induction of stroke, sheep were i.v. injected with ~1GBq [^{15}O]H_2O and imaged by PET. Parallel blood sampling resulted in individual arterial input functions (I-AIFs). Cerebral blood flow (CBF) was calculated absolutely in a voxelwise manner. Such CBF maps were in parallel established by using a population-based input function (PB-AIF) created from 32 ovine PET investigations. Finally, stroke-related tissue regions (e.g. penumbra, infarct core) were defined in both methods (I-AIFs, PB-AIFs) by applying established perfusion thresholds, and consistency of stroke compartment volumetry was compared.
Results:PB-AIF and I-AIF showed good accordance by defining relevant stroke tissue compartments: Volumes of infarction core, penumbra and normal brain deviated between both methods by 0,5% at maximum. A linear correlation between both kinetic modeling strategies was observed ($r=0,97$ and 0,62 for infarct core and penumbra; $p<0.01$).
Conclusion:This study evaluated an alternative way for the detection of penumbral tissue based on perfusion thresholds without the need of individual blood samples and without losing relevant accuracy. It was demonstrated, that the sheep stroke model is of great use for modern imaging techniques that aim at delineating the ischemic penumbra.

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POSTER 188

Self-organizing maps: Portraying the OMEs with individual resolution

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New high-content technologies provide huge amounts of data per measurement, making traditional analysis inefficient.New strategies of filtering, visualization and functional analysis are inevitable. Our approach applies machine learning known as self-organizing maps (SOMs). SOMs enable the parallel sample- and feature-centered view of molecular phenotypes combined with strong visualization and second-level analysis capabilities.The SOM mapping reduces the initialyl high number of features (e.g., up to hundreds of thousands SNPs or expression values) to a few thousands of meta-features, each representing a cluster of co-regulated single features.These meta-features are visualized as intuitive mosaic pictures, which feature characteristic color patterns for the data landscape of each sample.Analysis techniques normally used at the feature-level such as hierarchical clustering or component analyses provide enhanced sample resolution due to improved signal-to-noise ratios if applied to the meta-features.We applied our analysis to diverse data sets comprising multiple OMEs such as transcriptome (e.g. human tissue atlas, progression of prostate cancer and glioblastoma, lymphoma classification or stem cell differentiation), genome (SNP-atlas of human genome diversity), proteome (mass-spectra of *Prototheca* and *Drosophila*) and methylome (human prostate cancer and murine stem cells).Our SOM software package provides an intuitive and informative global view of the behavior of a few basal modules of correlated features without loss of primary information.These features can be assigned to well-defined biological functions in most cases.

Funding: life

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POSTER 189

Portraying the expression landscapes of cancer subtypes

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Cancer is a complex disease that involves a sequence of gene-environment interactions in a progressive process that occurs with dysfunction in multiple systems. There are many biological pathways and multiple genetic, epigenetic and transcriptional influences working simultaneously in the expression of cancer phenotypes. The study of individual components in isolation does not allow an adequate understanding of phenotypic expression. Instead, an integrative approach is needed to investigate gene-environment interactions.
Therefore we apply self organizing maps (SOM) which is a feature centred machine-learning clustering method to large scale expression data of different cancers in order to characterize the specifics of the genome wide expression landscapes in different molecular subtypes of each cancer entity. We aim to merge many of the functionally related genes into larger aggregates (functional modules) and to characterize disease-specific changes in the resulting interaction network. Characteristic differences between sample types and developmental stages can be clearly identified and further analyzed using so-called 'metagene-profiles' characterizing the intrinsic correlation modes. SOMs portray molecular phenotypes with individual resolution. We demonstrate the potency of the method in selected applications characterizing the diversity of gene expression in the cancer subtypes studied and to discover similar relations between them. In addition to functional modules the individual portraits allow identifying misclassified samples and thus to improve quality control in large patient series.

Funding: life

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POSTER 190

KMWin – A tool for graphical presentation of results from Kaplan-Meier survival time analysis

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Interim analyses of clinical studies are common practice resulting in repetitive analyses or the need of multiple graphical representations. Many professional Software packages are available such as SPSS, SAS or R. These packages are either only commercially available or hard to use especially if one aims to develop and customize professional graphical outputs.KMWin (Kaplan-Meier for Windows) is a programme developed for graphical presentations of results from Kaplan-Meier survival time analysis. It combines both, free availability and provision of an easy to use interface. The Interface comprises often used functions and functions which are not supplied by standard Software packages such as presentation of "numbers at risk". Analysis and graphical presentation of survival curves is achieved by controlling R, i.e. KMWin acts as a graphical interface. Survival time data can be supplied as SPSS (sav), SAS export (xpt) or text file (dat). Generated plots can directly be exported in any graphical file format supported by R, e.g. as vector graphic (emf) which facilitates further processing of the results.We demonstrate how to use KMWin and present its main functions. We show how to select variables, control graphical and statistical outputs, use filters and utilize saved settings for repetitive analyses.We conclude that our tool is well suited and convenient for repetitive analyses of survival time data. It can be used by non-statisticians and provides often used functions as well as functions which are not supplied by standard Software packages. The software is routinely applied in the Clinical Trial Centre Leipzig.

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POSTER 191

Bayesianisches Clustering von replizierten Zeitreihendaten des HaematoSys Verbundprojektes

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Bayesianisches Clustering von replizierten Zeitreihendaten des HaematoSysVerbundprojektes. Um die Aktivierung von Signalbahnen in Krebszellen besser zu verstehen sind Zeitreihenexperimente nützlich. Dabei wird die Reaktion der Genexpression von gesunden und kranken (z.B. Krebs) Zellen auf bestimmte Stimulationen beobachtet. Durch die zeitliche Auflösung der Expression lassen sich die Aktivierung von krankheitsrelevanten Genen und Gengruppen direktbeobachten.Im BMBF Verbundpojekt „HaematoSys" [1] wurden Genexpressionszeitreihen analysiert. Ziel ist dabei die Aufklärung molekularer Mechanismen bei der Lymphomgenese. Zur Gewinnung dieser Daten wurden B-Zellen des Keimzentrums aus Tonsillen gewonnen und bei diesen der CD40 und der B-Cell Rezeptor stimuliert, um so die in der Onkogenese potentiell wichtigen Signalbahnen JAK-STAT, NFkB and BCR zu aktivieren. Zur explorativen Analyse der Zeitreihendaten wurde ein BayesianischesClustering-Verfahren verwendet [2]. Diese Methode erlaubt die Verwendungvon replizierten Daten und berücksichtigt die Autokorrelation zwischenden verschiedenen Messzeitpunkten. Im Vergleich mit herkömmlichenz.B. korrelations-basierten Methoden zur Bestimmung der aktiviertenGengruppen lassen sich mit Bayesianischen Ansätzen nicht nur deutlich homogenere Cluster sondern auch biologische-medizinisch relevanteAktivierungsmuster bestimmen.
[1] Systembiologie der Hämatopoese und hämatopoetischer Neoplasien. http://www.haematosys.de[2] E. J. Cooke et al. 2011. Bayesian hierarchical clustering for microarraray time series data with replicates and outlier measurements. BMC Bioinformatics 12:399

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POSTER 192

Kopplung von Mikro-Freiflusselektrophorese mit ESI-Massenspektrometrie

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Die Mikrofreiflusselektrophorese (μFFE) ist eine kontinuierliche Hochgeschwindigkeitstrennmethode, welche es ermöglicht Substanzgemische innerhalb von Sekunden aufzutrennen. Ihr geringer Probenbedarf und ihre hohe Kompatibilität zu Biopolymeren macht diese Methode insbesondere für Anwendungen im medizinischen und biochemischen Bereich attraktiv, in dem die verfügbaren Mengen relevanter Substrate meist begrenzt sind. In Kombination mit einer strukturaufklärenden Detektionsmethode wie der Massenspektrometrie (MS) wird es möglich auch komplexe Proben zu charakterisieren und unbekannte Verbindungen zu identifizieren. Die Technik besitzt vielfältige Einsatzmöglichkeiten, die von Trennungen niedermolekularer Analyten bis hin zu Zellorganellen reichen.
Es wurde ein sensitives, miniaturisiertes Detektionssystem auf Basis von LED-angeregter Fluoreszenz entwickelt um die μFFE-Trennungen parallel zur MS-Detektion evaluieren zu können. Zur totvolumenfreien Kopplung werden die μFFE-Mikrofluidikchips unter Verwendung einer im Arbeitskreis entwickelten Technik mit monolithisch integrierten Nanospray-Emitterspitzen versehen. [1] Im Hinblick auf den Einsatz im biochemischen Bereich und damit einhergehenden komplexen Probenmatrizes wird das System um eine Festphasenextraktion (SPE) ergänzt. Hierzu wurden verschiedene Phasen auf ihre Kompatibiliät zur μFFE-MS untersucht, da hierbei die Wahl des Eluents die anschließende elektrophoretische Trennung maßgeblich beeinflusst. Diese werden im finalen System unmittelbar auf dem μFFE-MS-Chip integriert.

[1] P. Hoffmann, U. Hausig, P. Schulze, D. Belder, Angew. Chem. Int. Ed. 2007, 46, 4913–4916.

Funding: life

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POSTER 193

DARIO: A ncRNA detection and analysis tool for next-generation sequencing experiments

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Small non-coding RNAs (ncRNAs) such as microRNAs, snoRNAs and tRNAs are a diverse collection of molecules with several important biological functions. Current methods for high-throughput sequencing for the first time offer the opportunity to investigate the entire ncRNAome in an essentially unbiased way. However, there is a substantial need for methods that allow a convenient analysis of these overwhelmingly large data sets. Here, we present DARIO, a free web service that allows to study short read data from small RNA-seq experiments. It provides a wide range of analysis features, including quality control, read normalization, ncRNA quantification and prediction of putative ncRNA candidates. The DARIO web site can be accessed at http://dario.bioinf.uni-leipzig.de/.

Funding: life

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POSTER 194

Prävalenz von humanen Papillomviren (HPV) verschiedener Subtypen in Kopf-Hals-Plattenepithelkarzinomen

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Plattenepithelkarzinome des Oropharynx (OSCC) sind z.T. durch onkogene Papillomviren (HPV) verursacht. HPV16 ist bei OSCC dominant. Ungeprüft ist bisher, welche Methode zur Detektion von HPV in OSCC geeignet ist. 100 Gewebeproben von OSCC wurden in Trizol™ (Invitrogen) bei -80°C gelagert, bevor nach mechanischem Gewebeaufschluss DNA entsprechend Herstellerprotokoll isoliert und mit den Kits BMT HPV Genotyping 9G Membrane KIT™ (BMT; Biometrix Technology Inc.; 5 HPV-Genotypen, 14 HPV-Screeningtypen) und Linear Array™ (LA; Roche; 37 HPV-Genotypen) HPV detektiert bzw. typisiert wurde. Mit LA wurden 34 OSCC (34%) positiv detektiert. HPV16 wurde am häufigsten (31 OSCC, 31%) nachgewiesen. Bei drei weiteren Proben wurden die Genotypen 18, 33 und 35 detektiert. Mit BMT wurden 44 Proben (44positiv detektiert, allerdings nur in 22 Proben HPV16, in 1, 1 und 2 Fällen die Genotypen HPV18, 31 und 33 nachgewiesen. In 45 Fällen wurde HPV weder mit BMT noch mit LA detektiert. In 24 Fällen zeigten beide Testsysteme gleiches positives Ergebnis; 21 von 100 OSCC waren in beiden Tests HPV16+. In 43 Fällen lieferten beide für Zervix-Karzinome CE-zertifizierte Tests kein übereinstimmendes Ergebnis. Mehrfachinfektionen mit verschiedenen HPV-Subtypen ließen sich für OSCC nicht verifizieren. Die Ergebnisse sind uneinheitlich, weil HPV mit verschiedenen Primern amplifiziert werden und differente Nachweisgrenzen der Kits zu geringer Konkordanz führen. Größere Fallzahlen und weitere Methoden sind zur Validierung des HPV-Nachweises in HNSCC nötig.
* Die Arbeiten wurden in oder assoziiert zu LIFE-007 D9 bzw. LIFE-006 B7 durchgeführt.

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POSTER 195

DIFFERENTIAL EICOSANOID RESPONSE ON GENE EXPRESSION AND MEDIATOR LEVEL IN WHOLE BLOOD FROM PATIENTS WITH OR WITHOUT CORONARY ARTERY DISEASE

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Eicosanoids as arachidonic acid (AA) metabolites are central mediators in inflammatory processes and are thought to play a role in the development of coronary artery disease (CAD). Based on the hypothesis that differential intensity of eicosanoid response may affect coronary risk, we aimed to investigate the individual eicosanoid response as a potential marker of CAD. Heparinized whole blood from patients with (n=27) or without (n=33) angiographically confirmed diagnosis of CAD was immediately processed (baseline) or incubated with or without LPS (100 ng/mL) for 4 and 24 hours. RNA was isolated and target genes of the eicosanoid biosynthetic pathway (*cyclooxygenase (COX) 1 and 2*, *thromboxane synthase (TXS)*, *prostaglandin E synthase (PGES), PGFS)* were analyzed by quantitative fluorogenic RT-PCR. Corresponding metabolites (11- hydroxy eicosatetraenoic acid (HETE), TXB_2, PGE_2, $PGF_2\alpha$) were analyzed in supernatants using liquid chromatography tandem mass spectrometry. Patients with CAD revealed a reduced *COX-1* gene expression at baseline ($P<0.05$) and a lower induction of *COX-2* mRNA expression after 4h LPS activation ($P<0.05$) compared to subjects without CAD. No significant differences between the two groups could be shown for *TXS*, *PGES* and *PGFS*. LPS activation resulted in a 3- to 40-fold increase of metabolite release, however, concentrations did not significantly differ between the two groups. Our data showing differentially expressed target genes of AA metabolism in CAD patients suggest that the individual genetic regulation of eicosanoid response may represent a marker of atherosclerotic risk.

Funding: life

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POSTER 196

Novel MS-based strategy to detect and identify advanced lipid peroxidation products

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Reactive oxygen species (ROS), overproduced during oxidative stress, can damage all biomolecules within tissues and body fluids, leading to impaired physiological activity. Lipids containing unsaturated fatty acyl residues are very susceptible to oxidation by ROS yielding advanced lipid peroxidation products (LPP) containing aldehyde and ketone moieties. In addition to the altered biological activity of oxidized lipids itself, these carbonyl compounds can readily react with nucleophilic groups of proteins to form Michael adducts or Schiff bases. These modifications can influence the structure and the functional activity of proteins and may further induce various oxidative stress-related disorders. Lipid peroxidation is highly evident in several neurodegenerative diseases, such as Parkinson and Huntington diseases, amyotrophic lateral sclerosis, and Alzheimer's disease.[1] Furthermore, lipid peroxidation is closely connected with the development of atherosclerosis, a chronic disease, affecting the arterial walls. A popular hypothesis connects atherogenesis with the oxidation of low density lipoprotein (LDL).[2] Recent studies have revealed the importance of oxidized lipids, including phospholipids (PL), and cholesterol moieties for molecular functionality of oxLDL. Regardless of their relevance and occurrence in many proteins, LPP and especially reactive carbonyl compounds are poorly characterized and poorly classified. Thus, it is an urgent task to qualitatively and quantitatively analyze advanced oxPL products in complex PL mixtures.

We addressed this problem by developing a novel analytic strategy to identify reactive lipid peroxidation products (LPP) in a complex mixture of polyunsaturated fatty acids (PUFA) and different phosphatidylcholine (PC) vesicles. The four physiologically most abundant PUFA [oleic (18:1), linoleic (18:2), arachidonic (20:4), and docosahexaenoic (22:6) acids] and PC containing these acids [POPC (16:0/18:1), PLPC (16:0/18:2), SAPC (18:0/20:4), and PDPC (16:0/22:6)] were oxidized (75 μM $CuSO_4$/150 μM ascorbic acid; 72 h, 37°C). Advanced LPP formed during the incubation were derivatized with hydrazide reagent and analyzed by a shotgun lipidomics approach using ESI-LTQ-Orbitrap mass spectrometry in positive ion-mode. Based on the enhanced ionization of derivatized LPP species and their favorable fragmentation by tandem mass spectrometry it was possible to identify 120 advanced LPP including 36 PC-esters and 84 non-esterified species. To the best to our knowledge, this is by far the most comprehensive analysis of advanced LPP formed in PC mixtures. Using our novel analytical approach we were able to detect 99 advanced LPP in plasma of the three healthy donors. These results showed to be promising for further employment of developed analytical approach in disease biomarker research.

(1) – Reed. Free Radical Biology and Medicine (2011) 7 :1302-1319;

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POSTER 197

Vaspin - a link of obesity to psoriasis?

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Psoriasis is an inflammatory skin disease often associated with obesity. The antiinflammatory adipokine vaspin, a suggested serine proteinase inhibitor of the serpin family, is discussed as a new link between inflammation and obesity. Here we demonstrate that - different from healthy controls - vaspin serum levels in psoriatic patients were BMI independent.
Furthermore, in obese patients with psoriasis serum vaspin level were decreased compared to gender-, age- and BMI-matched controls. Moreover, we could identify keratinocytes as the major source of vaspin in skin. Epidermal vaspin expression in lesional psoriatic skin was reduced compared to non lesional skin. In aggregate we report a cellular source of vaspin in skin and its reduced expression in psoriasis.

Funding: life

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POSTER 198

Differential expression of non-coding transcripts in breast cancer cells

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Breast cancer is one of the most frequent types of cancer worldwide. Despite advances in the therapy of this disease, mortality remains high because therapy-resistant cancer cells are able to escape current therapies and lead to recurrence of the tumor. Nowadays the population of breast cancer initiating cells (BCIC) is held responsible for this instance and is considered as one of the major factors in the general process of tumorigenesis.
Using a breast cancer cell line model, our aim is to characterize the BCIC on the bases of non-coding RNAs (ncRNAs). NcRNAs do not exhibit protein-coding potential but are in the focus of research as they might be the hidden layer of cellular complexity. Changes within ncRNA expression patterns are often associated with diseases or developmental disorders. We used the nONCOchip - a custom microarray comprising a large set of experimentally identified ncRNAs, all human RefSeq mRNAs and predicted ncRNAs from databases - to study ncRNA expression in BCIC compared with non-BCIC.
The microarray experiment revealed a number of ncRNAs and mRNAs showing differential expression between those two populations. mRNAs being involved in the cancer relevant Wnt signaling pathway, differentiation and proliferation processes as well as non-coding transcripts which arise antisense to a putative cancer stem cell marker and mRNAs being involved in apoptosis just as known lincRNAs could be validated using quantitative PCR.
This study helps to better characterize BCIC on the basis of non-coding transcripts and gives a starting point for further functional studies of this important cell population.

Funding: life

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POSTER 199

Genetic variants of cholesterol esterification

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Cholesterol, a crucial risk factor for developing cardiovascular disease, is mainly stored as ester in circulating lipoproteins and tissues. Hence a rigorous regulation of esterification is relevant for cellular cholesterol homoeostasis. The individually genetic determinants of cholesterol esterification in humans aren't clarified so far.

Thus a genome-wide association study (GWA) was established by linking cholesterol and phytosterol ester concentrations measured in the *KORA S3/F3* cohort (n = 4222) with whole-genome genotyping using *Affymetrix 500k SNP Array* (n = 1644). The haplotype structure was examined to reveal genes nearby the identified loci. Data imputation analysis was applied to reinforce the statistical validity of these loci. Further, we used the innovative Open Array® Genotyping platform for replicate selected SNPs in the *CARLA* study (n = 1760).

The GWA analysis yielded 102 significant loci of cholesterol and phytosterol esterification (- log p ≥ 4.0). The majority of the identified SNPs appeared to intergenic regions and the examination of haplotype structure exposed 16 genes respective 49 genes co-located within the same haplotype block. Imputation analyses strengthened the level of significance up to 10% and revealed 64 highly recommended SNPs for replication analysis in the *CARLA* cohort to prove their statistical evaluation.

The *KORA*-GWA approach revealed distinct loci for cholesterol and phytosterol esterification in humans. The haplotype structure analysis featured several new candidate loci with strong relevance to sterol esterification. To elucidate their functional evidence certain loci will examine by in-vivo assays. Furthermore, all loci will be verified in the *LE-Heart* study to prove their clinical impact.

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POSTER 200

Einfluss einer achtwöchigen ambulanten Sportintervention auf das Körpergewicht, kardiovaskuläre und ventilatorische Funktionen und die körperliche Leistungsfähigkeit übergewichtiger und adipöser Kinder und Jugendlicher

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Tumor Targeting

Hintergrund: Zurzeit werden in Deutschland pro Jahr nur etwa 1% der adipösen Kinder und Jugendlichen, wie empfohlen, mit einer Lebensstilintervention behandelt. Die Gründe dafür sind vielseitig. Es bleibt die Frage nach Alternativen, um den Einstieg in eine langfristige Behandlung zu erleichtern.

Zielstellung: Die vorliegende Arbeit soll eine solche Alternative überprüfen und untersucht den Einfluss einer achtwöchigen ambulanten Sportintervention auf das Körpergewicht, kardiovaskuläre und ventilatorische Funktionen und die körperliche Leistungsfähigkeit übergewichtiger und adipöser Kinder und Jugendlicher.

Methode: Elf Kinder (BMI 96.45±1.33 Perzentil) im Alter zwischen 8.08 und 13.75 Jahren (10.81±0.45 Jahre) haben über 8 Wochen 2x 60 Minuten/ Woche im Rahmen einer Aquasportgruppe trainiert. Parameter für Anthropometrie (Körpergröße, -gewicht, BMI, Hautfaltendicken), Blutdruck, Endothelfunktion (RHI), Spirometrie (VC, FEV1), Spiroergometrie, motorische Funktionen und ein 20m-Pendellauf wurden vor und nach der Intervention verglichen.

Ergebnisse: Der mittlere BMI reduzierte sich nicht signifikant vom 96.45±1.33 auf das 96.4±1.34 Perzentil (p= .799). Der durchschnittliche RHI erhöhte sich von 1.42±0.12 auf 1.55±0.11, diese positive Tendenz wird aber nicht signifikant (p= .134). Die VC und die FEV1 verbessern sich zwar im Rahmen der Intervention, jedoch nicht signifikant (VC p= .479 und FEV1 p= .637). Die relVO_{2Max} stieg ebenfalls tendenziell, jedoch nicht signifikant von 28.84±1.82 auf 30.15±0.84 ml/Min/kg (p= .375).

Die motorische Leistung war vor der Intervention in allen Aufgaben unterdurchschnittlich. Nach der Intervention verbesserten sich dynamisches Ganzkörpergleichgewicht (34.66 8.99 vs. 55.0± 7.9 Perzentil; p= .013) sowie die Kraftausdauer der oberen Extremitäten (46.91±6.18 vs.65.05±7.94 Perzentil; p= .022) signifikant. In den anderen Untersuchungen unterschieden sich Pre- und Posttes-

tergebnisse nicht signifikant. Jedoch gab es große interindividuelle Unterschiede und es ließen sich positive Tendenzen erkennen. Die statistische Aussage ist durch die geringe Fallzahl limitiert.
Schlussfolgerung: Aus den Ergebnissen lässt sich vorsichtig schlussfolgern, dass auch innerhalb einer kurzen Interventionszeit positive Entwicklungen insbesondere in Bezug auf die motorische Leistungsfähigkeit, aber auch tendenziell für die kardiopulmonale aerobe Leistungsfähigkeit, bei adipösen Kindern erzielt werden können.

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POSTER 201

Quantitative profiling of arachidonic acid metabolites by hybrid triple quadrupole/linear ion trap mass spectrometry

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Objective: Eicosanoids are enzymatic products of arachidonic acid (AA) playing important functional roles in inflammation, cellular proliferation, and intracellular signalling. The simultaneous analysis of a multitude of eicosanoids, in contrast to the isolated view of one single pathway, will help to understand molecular mechanisms underlying the complex AA metabolic system. The quantitative analysis of AA metabolites is of interest for different sample types e.g. supernatants of cell culture experiments or human body fluids.
Method: Plasma or urine samples were processed by protein precipitation (plasma samples) and off-line solid phase extraction (both plasma and urine specimen). Fast chromatographic separation was achieved on a Kinetex C-18 core-shell column with a Shimadzu Prominence UFLC system. MS analysis was performed on a 5500 QTrap® instrument. About 50 multiple reaction monitoring (MRM) transitions for the quantitation of eicosanoids are included in the presented method.
Results: By using a core-shell column instead of a regular C-18 column, the analysis time was reduced to 8 min and chromatographic resolution could be improved for the separation of regioisomers (e.g. PGE_2/PGD_2). With this method we could detect metabolites of the cyclooxygenase, CYP450 epoxygenase, and lipoxygenase pathway in plasma and urine of healthy volunteers.
Conclusion: Our analytical method using the hybrid QTrap® technology allows the simultaneous acquisition of both quantitative data and structural information of AA metabolites in human biological fluids.

Funding: life

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POSTER 202

Identification of Surf4 as Novel Candidate Gene of Atherosclerosis through Genome-wide eQTL Mapping

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Tumor Targeting

Linkage mapping for atherosclerosis susceptibility revealed a new Quantitative trait locus (QTL) on mouse chromosome (Chr) 2 in atherosclerosis-susceptible C57BL/6 (B6) and atherosclerosis-resistant BALB/cByJ (BALB) female mice on the LDL-receptor deficient background ($Ldlr^{-/-}$).
To identify potential candidate genes at this locus, we performed genome-wide expression analyses (Illumina Mouse ref-8 V2) in livers (n=176) and aortas (n=165) of female F2 mice. Expression QTL (eQTL) mapping in livers revealed 7 genes with maximum LOD-scores > 8 co-segregating with the top atherosclerosis LOD-score at marker rs33142586. Additional validation in aortas identified Surf4 as most likely candidate gene (LOD 11.5 and LOD 17.6, respectively). F2 mice carrying the BALB allele homozygous at rs33142586 had increased Surf4 expression in livers and aortas (13.5%/allele and 19.3%/allele, respectively). Furthermore, increased Surf4 expression was associated with reduced atherosclerosis lesion size in F2 mice. Differential expression of Surf4 was validated in livers and aortas of B6 and BALB F0 mice (n=5/6, 1.8-fold, P<0.05; n=5/3, 2.3-fold, P<0.01).
Surf4 encodes a cargo receptor protein suspected to influence the early secretory pathway by interacting with endoplasmic reticulum-Golgi intermediate compartment proteins and might thus affect trafficking of yet to be identified proteins relevant to atherosclerosis.
In conclusion, we have identified Surf4 as novel candidate gene of atherosclerosis susceptibility on mouse Chr2. Further work will be necessary to understand how this gene might influence atherosclerosis susceptibility at this locus.

Funding: life

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POSTER 203

Identification of non-coding RNAs regulated by activation in CD4+ T cells

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Tumor Targeting

Intensive study over the past few decades has considerably advanced our knowledge of the functional and phenotypic changes that occur throughout the T cell life cycle. Nevertheless, knowledge of the underlying regulatory basis for T cell differentiation and function remains incomplete. There is evidence that epigenetic processes during development and differentiation establish cell fate. Furthermore, the impact of non-coding RNAs on virtually all levels of gene regulation is becoming apparent. However, the molecular mechanisms are mostly not jet understood. In order to identify non-coding RNAs, which are regulated by T cell activation and are potentially of importance for differentiation and function of CD4+ T cells, we collected RNA of naive and effector CD4+ T cells as well as during T cell activation and performed genome-wide tiling arrays. Besides well-known key players of T cell activation we found several non-coding RNAs, hypothetical proteins and unknown transcripts regulated following T cell stimulation. The induction of selected transcripts by activation of T cells could already be validated via real-time PCR.

Funding: life

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POSTER 204

Identification of Elovl6 as a Candidate Gene of Atherosclerosis Susceptibility in Mice and Men

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Tumor Targeting

A novel atherosclerosis susceptibility locus was identified on mouse chromosome (Chr) 3 by quantitative trait locus (QTL) mapping in an intercross (n=459 F2) of atherosclerosis-susceptible C57BL/6 (B6) and atherosclerosis-resistant FVB mice on the LDL-receptor deficient background (LDLR$^{-/-}$). The Chr3 locus was gender-dependent and present only in female F2 mice.
To identify genetic factors at this locus whole genome expression analysis (Illumina Ref-8 arrays) was performed in female livers of FVB and congenic FVB.Chr3$^{B6/B6}$ mice carrying a 80 Mb portion of distal Chr3 from B6 (80-160 Mb) on the FVB background (n=4/4) and validated in quantitative RT-PCRs in livers and aortas revealing *Elovl6* as a promising candidate gene.
Elovl6 catalyzes the elongation of saturated and monounsaturated fatty acids with 12, 14, 16 carbons. The B6-allele in F2 was associated with higher atherosclerosis, VLDL plasma-cholesterol levels, *Elovl6* expression and C18+C18:1/C16+C16:1 fatty acid ratio (P<0.05). Moreover, the *Elovl6*-expression was directly correlated with atherosclerosis severity, VLDL plasma-cholesterol levels and C18+C18:1/C16+C16:1 ratio (P=0.05).
In humans, the phospholipid and diacylglyceride fractions of 50 liver biopsies showed a positive correlation of the Elovl6-expression with the C18+C18:1/C16+C16:1 ratio. Increased human Elovl6-expression was associated with aneurysm rupture versus stable aneurysm (n=17/30; P<0,01).
We identified *Elovl6* as a novel candidate gene of atherosclerosis susceptibility. Further work is needed to understand the influence of Elovl6 on fatty acid quality and its role in atherogenesis.

Funding: life

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POSTER 205

Identification of Eno2 and Mug2 as Novel Candidate Genes of Atherosclerosis at the Brachiocephalic Artery

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Tumor Targeting

We have identified a novel quantitative trait locus (QTL) of atherosclerosis susceptibility on mouse chromosome (Chr) 6 using two independent intercrosses of atherosclerosis-susceptible C57BL/6 (B6) with (1) atherosclerosis-resistant FVB mice (B6xFVB) and (2) atherosclerosis-resistant BALB/cByJ mice (B6xBALB). All mice were on the low-density lipoprotein receptor-deficient background (*Ldlr*$^{-/-}$). The Chr6 QTL was specific to atherosclerosis at the brachiocephalic artery in male mice. The maximal LOD score was found at D6Mit216 (B6xFVB, LOD 4.3; B6xBALB, LOD 5.8). Homozygosity for the B6 compared to homozygosity for the FVB or BALB allele at D6Mit216 was associated with increased atherosclerosis in both crosses (B6xFVB, 2.9fold, *P*<0.001; B6xBALB, 5.8fold, *P*<0.001). This finding was validated in Chr6 congenic mice carrying a 100 Mb portion of distal Chr6 from B6 on the FVB.*Ldlr*$^{-/-}$ background (FVB.*Ldlr*$^{-/-}$Chr6$^{B6/B6}$ vs. FVB.*Ldlr*$^{-/-}$ 2.3-fold, *P*<0.05). Genome-wide expression analyses (Illumina MouseRef-8) in livers and aortas of FVB.*Ldlr*$^{-/-}$Chr6$^{B6/B6}$ and FVB.*Ldlr*$^{-/-}$ mice (n=4/4) revealed 6 differentially regulated genes with fold changes greater +/-20% (*P*<0.05), respectively. Of these, *cis* regulation of 2 genes, namely *Eno2* and *Mug2*, was demonstrated in livers of male B6xFVB F2 and B6xBALB F2 mice (n=232/183, LOD>4.3/3.3) using gene specific TaqMan assays.
Accordingly, *Eno2* is a plausible candidate gene for the Chr6 atherosclerosis QTL due to its penultimate point in glycolysis and thus supply of scavengers for reactive oxygen species. Likewise, *Mug2* might be relevant because of disposing miscellaneous chemokines.

Funding: life

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POSTER 206

Vergleich von Polysomnographie und simultaner Aktometrie bei gesunden Probanden

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Einleitung: Die Polysomnographie (PSG) bietet die Möglichkeit Schlafstadien objektiv zu erkennen und stellt den derzeitigen Goldstandard zur Erfassung von Schlaf dar. Diese Untersuchung ist jedoch zeitaufwendig und personalintensiv. Eine Alternative zur PSG stellt die Aktometrie dar, mittels derer aus dem Bewegungsprofil auf Schlaf- und Wachzeiten geschlossen werden kann. Allerdings kommt es bei alleiniger Verwendung von Aktometern häufig zu einer Überschätzung des Schlafes z.B. wenn immobile Wachphasen als Schlaf fehlklassifiziert werden. Neuere Aktometer erfassen deshalb neben der reinen Akzellerometrie auch weitere physiologische Parameter. Ziel der vorgestellten Studie war es, die Ergebnisse einer klassischen Polysomnographie mit Aktometerdaten (SenseWear Pro3) zu vergleichen.
Methodik: Im Rahmen einer prospektiven Beobachtungsstudie im Querschnittsdesign wurden 25 gesunde Probanden zwischen 18 und 65 Jahren untersucht. Diese trugen während einer Nacht im Schlaflabor das SenseWear Pro 3-Armband.
Ergebnisse: Die Auswertung der Studie wird derzeit durchgeführt. Dabei werden sowohl die durch beide Methoden ermittelten Parameter Schlafdauer, Schlafeffizienz und Einschlaflatenz (Bland-Altman-Analysen) gegenübergestellt als auch ein Einzelminutenvergleich der Schlaf-Wach-Klassifikation vorgenommen. Ausgewählte Untersuchungsergebnisse werden auf dem Poster präsentiert.

Funding: life, IFB

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POSTER 207

Mapping von Dokumentationsmerkmalen in LIFE

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In den im LIFE-Projekt durchgeführten epidemiologischen, diagnostischen und prognostischen Studien werden einige tausend Dokumentationsmerkmale erhoben, deren Spezifikation einen wichtigen Teil in der Projektplanung darstellt. Neben der Wiederverwendung der Merkmale und ihrer Vergleichbarkeit spielt die einheitliche Bereitstellung der Daten eine wichtige Rolle. Die zur Datenerfassung eingesetzten Erfassungssysteme (z.B. LimeSurvey, Teleform) sowie medizinischen Geräte (z.B. Bodyscanner, Pricktest) erlauben nur geringen Einfluss auf die Art der Datenspeicherung wie z.B. Variablennamen, verwendete Formate und Datenqualität. Um die in LIFE erhobenen Daten den Forschern einheitlich bereitstellen zu können, müssen diese in einer qualifizierten Forschungsdatenbank zusammengeführt werden. Hierbei müssen verschiedene Probleme gelöst werden. Dabei ist es nicht nur Aufgabe, die verschiedenen Daten (in Datenbanken, CSV-Dateien oder auch gerätespezifischen Formaten) aus den Erfassungssystemen zu extrahieren. Die verschiedenen Variablenstrukturen, durch die heterogenen Quellsysteme bestimmt, müssen vielmehr durch z.B. Variablenumbenennung, Formatanpassung, Variablenselektierung und Umcodierung angeglichen werden. Verschiedene Varianten über die Erfassungssysteme und Versionen innerhalb eines Erfassungssystems müssen dabei beachtet werden. Zuletzt müssen die für ein spezifisches Auswerteprojekt notwendigen Daten ausgewählt werden. Für die Bereitstellung der Daten können dann SQL-Statements generiert werden, welche unabhängig vom Speicherort die gewünschten Daten abrufen und außerdem einheitliche und sprechende Variablenlabels vergeben.

Funding: life

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POSTER 208

Identification of ncRNAs associated with Chromatin Proteins

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Tumor Targeting

Numerous human diseases, like cancer, immune disorders and metabolic syndromes are linked to a disregulation of epigenetic processes. Thereby, the chemical modification of histone proteins through methylations, acetylations and phosphorylations are basic mechanisms to regulate the chromatin state along with the transcription rate. Additionally, recent studies have uncovered a variety of ncRNAs involved in epigenetic mechanisms, primarily in the recruitment of chromatin-modifiers. Therefore, it is important to study the interplay between ncRNAs and epigenetic processes under certain cell conditions. To address this, we use a co-immunoprecipitation to gain both, RNAs and chromatin bound to modified histones after specific stimulation of human target cells. This approach allows the determination of specific histone-ncRNA interactions together with their localization in the chromatin and may provide insights into the dynamic system of chromatin regulation.

Funding: life

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POSTER 209

A Comparison of SNP Selection Strategies in Genome-Wide Association Studies

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Identification of single nucleotide polymorphisms (SNPs)connected to a trait of interest is challenging due to the high-dimensionality of the data and the correlation structure amongSNPs. Here, we discuss results from a comparison study analyzing data provided by the GAW 17 consortium [1]. The GAW 17 data set contains high-dimensional SNP data and simulated traits, and thus offers an ideal setting to evaluate strategies for SNP selection. Most standard approaches to biomarker identification are based on anunivariate selection criterion and consequently ignore the correlation among SNPs. Recently, we have introduced the CAT [2] and the CAR [3] score that explicitly take account of the dependencies among markers. Here, we demonstrate that CAT/CAR scores can be efficiently appliedto large-scale data sets and that they are an efficient means to select SNPs related to either categorical or continuous traits, leading to an enrichment of true SNPs in the ranking compared to standard analysis.

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POSTER 210

Establishment of an entirely plasmid-based reverse genetics system for recombinant rotavirus proteins

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Over the last years reverse genetics, especially the production of recombinant viruses, has proven to be a powerful tool to investigate viral pathogenesis, gene expression and recombination. Currently, plasmid-based systems are available for a variety of viruses, including influenza – and reovirus. These systems can act without concurrent infection with wild-type helper virus. In the case of rotaviruses, which are a major cause of gastroenteritis in young children and animals, the attempts to develop such a system have not been successful. The rotavirus genome consists of eleven segments of double-stranded RNA, which comprise 18,555 base pairs in total, and code for twelve viral proteins. Using RT-PCR technique we were able to clone the rotavirus genome segments under the control of a T7 bacteriophage promoter. At the 3-prime end of the gene segments a hepatitis delta virus ribozyme sequence is located, which introduces well-defined fragment ends through a self-cleavage reaction. Before lipo-transfection of the plasmids, HEK 293T and BSR-T7 cells were infected with recombinant vaccinia virus MVA-T7 which provided the T7 polymerase. Only cells showing both transfection of plasmid-DNA and infection with MVA-T7 have the ability to produce recombinant rotavirus proteins. The success of transfection, as well as the integrity of the transfected plasmid-DNA were examined using immunofluorescence staining. We successfully established a plasmid-based reverse genetics system for the viral structural proteins VP4, VP6 and VP7.

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POSTER 211

In vitro reductive dearomatization of naphthoyl-Coenzyme A in a sulphate reducing enrichment culture

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Polyaromatic hydrocarbons (PAH) are harmful to the environment and human health; they are highly persistent due to the high resonance energy of the ring system and to the low bioavailability. Whereas the aerobic degradation pathways have been studied in great detail, only little is known about enzymes involved in the anaerobic metabolism of PAHs. The initial activation of naphthalene is considered to proceed by carboxylation (Musat 2009, Bergmann 2011) yielding 2-naphthoic acid, which is activated to 2-naphthoyl-CoA by a specific ligase. Initial evidence was obtained that this key intermediate is dearomatized by reduction yielding 5,6,7,8-tetrahydronaphthoyl-CoA (THNCoA) (Annweiler *et al*. 2002; Selesi 2010), which may be further dearomatized in another reduction step. In this work we demonstrate electron donor-dependent *in vitro* 2-naphthoyl-CoA reductase and THNCoA reductase activities in extracts from the sulphate reducing enrichment culture N47 grown on naphthalene. The activity (5,1 ± 1,2 nmol min^{-1} mg^{-1}) was sufficiently high for the growth rate of cells. Evidence was obtained that two different dearomatizing reductases were involved in anaerobic naphthalene degradation: while the first reduction step of the non-activated ring was independent of ATP hydrolysis, reduction of THNCoA was only observed in the presence of ATP.

Annweiler 2002 Appl Env Microbiol 68:852–858.
Bergmann 2011 Arch Microbiol 4:241-250
Musat 2009 Env Microbiol 11:209-19
Selesi 2010 J Bac 192:295–306

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POSTER 212

Molecular cloning of porcine rotavirus C strain gene VP6 for the establishment of a quantitative real-time RT-PCR assay

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Rotaviruses are important animal and human pathogens worldwide. Group A rotaviruses (GARV), being the most frequent cause of severe diarrhea, were the main focus of research on gastrointestinal pathogens over the last thirty years. Next to rotaviruses of group A also group C rotaviruses (GCRV) showed to have a high seroprevalence and continuous association with severe gastroenteritis in neonates and adults in an increasing number of cases. Since no commercially available rapid diagnostic tests or ELISA for GCRV exists, we have established a plasmid-based positive control for a quantitative real-time RT-PCR assay. To this end, total RNA from a GCRV positive field specimen was utilized as template for RT-PCR, with the use of GCRV gene VP6-specific primers complementary to the 3-prime ends of both viral RNA strands. The resulting PCR product was purified, cloned into the plasmid vector pJet1.2/blunt and confirmed to represent the complete GCRV gene VP6 sequence by DNA sequencing. Quantitative real-time RT-PCR was chosen as a preferred diagnostic method due to its sensitivity and the possibility of absolute quantification of the viral genome in the assayed sample. The assay efficiency evaluation and introduction into the comprehensive diagnostic portfolio of our institute were possible with the aid of the generated plasmid.

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POSTER 213

Expression of P2X receptor ectodomains

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P2X receptors are trimeric cation-selective ion channels regulated by extracellular ATP. Their involvement in a lot of physiological diseases including chronic pain makes them an attractive drug target. Protein crystallography in combination with structure-based drug design is a helpful tool to discover new subtype-specific and highly affine agonists and antagonists. In 2009, the 3.1 Å structure of the zebrafish P2X4 was determined. Despite high functional insight, the binding site of the natural agonist ATP remains speculative. High resolution complex structures of ideally all seven human P2X receptor subtypes are required for investigations of subtype-specific binding modes and the design of novel lead molecules.Since the expression, purification and crystallization of full-length P2X receptors is very difficult, we are testing strategies to express the ectodomains (ECDs) of the receptors. Human P2X ECDs could not be expressed in functional, i.e. folded, form in E.coli in our hands. We are therefore currently testing eukaryotic expression systems for the preparation of functional P2X ectodomains.To enhance the folding properties, the P2X ECDs of the trimeric receptor could be cloned as a concatameric construct. This is possible due to the close distance between the N- and C-terminus of different monomers. The fusion of three P2X ECDs into a concatameric protein leads to decrease of intermolecular distances and to higher chance of protein folding. Specific heteromeric P2X receptors are attractive drug target as well and may be prepared by using this strategy.

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POSTER 214

The W-/Se-containing class II benzoyl-CoA reductase complex in obligately anaerobic bacteria

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Benzoyl-Coenzyme A (CoA) is a central intermediate in the anaerobic degradation of aromatic compounds which is dearomatized to cyclohexa-1,5-diene-1-carbonyl-CoA by benzoyl-CoA reductases (BCRs). There are two completely different classes of BCRs which both yield the identical product [1,2]. ATP-dependent class I BCRs, referred to as BcrABCD are [4Fe-4S] clusters containing enzymes that are present in facultative anaerobes. In contrast, obligately anaerobic bacteria are proposed to employ a W-/Zn-/FeS-/Flavin-/Se-containing, ATP-independent BamBCDEFGHI complex. The active-site harbouring BamBC components were characterized from the aromatic compound degrading Deltaproteobacterium Geobacter metallireducens [1]. BamB is similar to aldehyde:ferredoxin oxidoreductases and is supposed to contain a W-pterin cofactor at the active site. We provide evidence that class II BCRs are composed of the predicted high molecular BamBCDEFGHI complex.

(1) Kung et al. (2009), PNAS 106:17687-92
(2) Löffler et al. (2011) Environ Microbiol 13(3) : 696-709

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POSTER 215

Validation of Immunoassays Determining Intact Immunoglobulin Kappa/Lambda Pairs in the Diagnosis of Monoclonal Gammopathies

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Background
Analytical limitations of currently used detection methods for monoclonal proteins require a combination of multiple test systems. The aim of the present study was to validate recently introduced Hevylite Chain (HLC) immunoassays for identification and quantification of monoclonal intact immunoglobulin chains possibly allowing standardization of laboratory procedures in the field of monoclonal gammopathies.
Methods
Serum samples from bone marrow defined patients revealing a monoclonal band in immunofixation electrophoresis or from healthy controls were used for evaluation studies. A validation of HLC IgA, IgG and IgM assay including precision-, accuracy-, linearity- and specificity- testing was performed. Laboratory and diagnostic sensitivity were investigated in comparison to immunofixation electrophoresis. A potential diagnostic role of HLC assays in disease monitoring was investigated in stem cell transplanted multiple myeloma patients.
Results
HLC assays revealed adequate precision, accuracy and laboratory sensitivity. HLC IgA- and IgM- assays were shown to be equivalent to immunofixation electrophoresis in the detection of monoclonal proteins, however, HLC IgG assay revealed limited diagnostic sensitivity. HLC IgA assay was considered to more accurately reflect a persistence of monoclonal disease as compared to standard methods.
Conclusions
Our data indicate that HLC assays will not allow to replace immunofixation electrophoresis in first line screening for monoclonal gammopathies. Our preliminary clinical data indicate a diagnostic potential in particular of the HLC IgA assay in disease monitoring.

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POSTER 216

Protein-RNA-interactions in chromatin remodeling, cell cycle and apoptosis

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In recent years, the involvement of long non-coding RNAs in epigenetic processes has been discovered. However, the function of the majority of these ncRNAs remains still elusive, but there is evidence that some long ncRNAs participate in histone modification processes. Based on a genome-wide tiling array study, we found several long ncRNAs to be differentially expressed upon cytokine stimulation. In order to identify ncRNAs associated with the chromatin remodeling machinery, we isolate relevant multi-protein complexes from cell lysates by RNA immunoprecipitation. In this regard polycomb and trithorax group related proteins, which function as counterparts, play key roles. Interacting RNAs are coprecipitated and identified using customized microarrays interrogating high numbers of regulated ncRNAs. Subsequently, molecular studies will be performed to reveal the function of those ncRNAs found to be associated with multi-protein complexes.

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POSTER 217

Scrutinizing the fate of meta-xylene: Functional studies of the degradation process

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A *meta*-xylene degrading, sulfate-reducing mixed culture originally enriched from ground water of a hydrocarbon contaminated field site was investigated in this study. Xylene-isomers belong to the group of BTEX compounds (benzene, toluene, ethylbenzene, xylene) and as common toxic substances they all represent a major threat to humans and the environment. The aim of the study was to obtain insights into the anoxic degradation of such compounds following the incorporation of ^{13}C within the proteins of the microbial community (Protein-SIP).
For ^{13}C-labeling, we grew culture using *meta*-xylene labeled with ^{13}C at both methyl groups (^{13}C-content of *meta*-xylene: 25 atom%). Control cultures were grown with non-labeled *meta*-xylene, acetate and benzoate. Protein analyses were carried out by 1-DE gels and UPLC coupled online to Orbitrap-MS/MS.
390 proteins were identified and the majority belonged to members of *Deltaproteobacteria*. The identified proteins were either not ^{13}C-labeled (180 proteins), or showed a ^{13}C-incorporation of 19-22 atom% ^{13}C (210 proteins). ^{13}C-labeled proteins were involved in anaerobic *m*-xylene biodegradation, in sulfate-reduction, in the tricarboxylic acid cycle, in the Wood-Ljungdahl-pathway or in general housekeeping functions. Thirty eight percent of the labeled proteins were affiliated to sulfate-reducing taxa. Due to a lack of sequence data from *Epsilonproteobacteria*, only 2% of all proteins were assigned to this species. The combined data suggest that *meta*-xylene is assimilated by the *Desulfobacterium* phylotype, whereas the function of the *Epsilonproteobacterium* remained still unclear.

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POSTER 218

Characterization of a novel combined heterozygous IGF1R and SHOX mutation of a short-statured patient

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Longitudinal growth is a trait regulated by a plethora of genes. Especially, the insulin-like growth factor-1 receptor (IGF1R) plays an essential role in growth regulation. For osteogenesis the transcription factor *short statured homeobox gene (SHOX)* is of fundamental impact. Here, we report on a patient who carries a heterozygous *IGF1R* exon 6 deletion and a heterozygous point mutation in the *SHOX* gene (p.Met240Ile). The eutrophic-born boy showed growth retardation at the age of six years with a height of 102.5cm (-3.30 SDS) and weight of 15.9kg (-2.61 SDS). IGF1 levels were in low-normal range. Furthermore, the patient presents no additional abnormalities. *IGF1R* deletion was identified by multiplex ligation-dependent probe amplification and breakpoints could be narrowed down by long-range PCR to approximately 5.2kb. In patient's fibroblasts we revealed that nonsense-mediated decay results in IGF1R haploinsufficiency by removing mRNA of the mutated allele. Receptor haploinsufficiency was confirmed by Western blot. Accordingly, IGF1 stimulated phosphorylation studies showed a decrease in IGF1R phosphorylation but an unexpectedly increased AKT/PKB activation. This phenomenon was not observed in the mother who bears only the *IGF1R* mutation.
In summary, we have identified the genetic cause of IGF1 resistance in a growth retarded boy and disclosed the underlying pathomechanism. Due to the unexpected activation pattern of the AKT/PKB signaling branch and a possible additive effect of the parental *IGF1R* and *SHOX* mutations the interplay between both signaling pathways will be investigated in fibroblasts and osteoblast cell models.

Funding: IFB

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POSTER 219

The tertiary alcohol monooxygenase/ desaturase MdpJK - one enzyme multiple possibilities

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Tertiary alcohol processing enzymes are rarely found in nature. Recently, we identified a novel Rieske non-heme mononuclear iron oxygenase (composed of the hydroxylase MdpJ and the reductase MdpK) which is involved in the degradation of *tertiary* alcohols in the beta-proteobacterial strain *Aquincola tertiaricarbonis* [1]. Short-chain alcohols such as *tert*-butyl alcohol (TBA) or *tert*-amyl alcohol (TAA) are converted by this enzyme. Both alcohols are central intermediates in the degradation pathways of the fuel oxygenate ethers methyl tert-butyl ether (MTBE) and tert-amyl methyl ether (TAME). These chemicals are widespread groundwater contaminants and often only slowly degraded by microorganisms. Likely, MdpJK is a key enzyme in fuel oxygenate mineralization, indicating the important environmental role of this novel enzyme. On the other hand, its catalytic specificity may be employable for synthesizing short-chain chiral diols and other building block chemicals for the production of pharmaceuticals or herbicides. Whole-cell experiments were used to characterize the substrate and reaction specificity of the enzyme. So far, secondary and tertiary alcohols (C3 to C6) have been tested. Depending on the structure of the substrate, either a monohydroxylation or a desaturation is catalyzed resulting in diol or unsaturated alcohol products, respectively.

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POSTER 220

Unravel the Structural Basics of the Interaction of Interleukin-10 with Glycosaminoglycans

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The protein Interleukin (IL)-10 is a key regulator of the innate and adaptive immune system, which prevents an overwhelming immune reaction and tissue damage. IL-10 inhibits the synthesis of pro-inflammatory cytokines and of cell surface molecules. Thereby, cellular immune responses mediated by macrophages and T cells are inactivated[1].
There exists strong evidence that IL-10 acts over short distances *in vivo*[2]. Glycosaminoglycans (GAGs) of the extracellular matrix have been suggested as possible binding partners that restrict IL-10 to the vicinity of the secreting cell. GAGs are a class of highly sulfated carbohydrate molecules that are known to bind and regulate a number of distinct proteins[3]. Sequence similarity to other GAG interacting proteins and molecular docking calculations strongly predict a specific GAG binding site within IL-10, in particular a cluster of basic amino acid residues in helix D and the DE loop.
A His-tagged version of mouse IL-10 was recombinantly expressed in *E.coli* and was purified and refolded from inclusion bodies. One dimensional ^{1}H NMR and CD spectroscopy demonstrated that the protein is well-folded and has a significant α-helix content of 66%. Future studies will include the full isotopic labelling of IL-10 for resonance assignment and GAG titration experiments, which will help to unravel the GAG binding site in IL-10 and the structural basics of that interaction.

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2. Roers, A. et al., *Current Immunology Reviews*, 4, 37-42 (2008)
3. Gandhi, N.S. et al., *Chemical Biology & Drug Design*, 72(6), 455-482 (2008)

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POSTER 221

Detection of novel viruses by combined nested broad-spectrum PCR and rolling circle amplification RCA methodologies

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Circular DNA viruses of the family circo and polyomaviridae cause severe diseases with a high juvenile mortality and chronic feather disorders in birds.
Both types of viruses are reported in bird breeds and individual animals in which they can be the cause of economic damages and bird losses.
The polymerase chain reaction (PCR) is the method of choice to detect the genomes of both virus families. The development of a serological test is limited in the absence of the cell culture systems of the majority of the viruses in these families. Despite many specific PCR protocols for the detection of both known viruses it remains difficult to use these protocols for the detection of of new viruses.
In our studies we reported the detection of several novel viruses using the nested broad-spectrum PCR that were not previously described in their hosts.
The investigations were complemented by the use of the rolling circle amplification (RCA) technology, which allows a sequence-independent duplication of complete circular viral genomes.
In our studies we demonstrate through the combination of these molecular methods the detection a new polyomavirus from the liver of 40 days old canaries *(Serinus canaria)* and a new circovirus from the bursa of a black-headed gull *(Chroicocephalus ridibundus)*. Both viruses were completely sequenced. The combined application of these techniques in a larger number of samples should help to clarify the distribution of circo- and polyomaviruses and their clinical relevance in different bird populations.

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POSTER 222

Rational Development of Peptides with High Affinity Towards SiO2

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Immobilization of chemokines or cell attracting motifs is of great interest in the field of "intelligent" biomaterials. It has been shown that peptides can bind to metal surfaces in a non-covalent manner, interestingly, these peptides can be obtained by solid-phase peptide synthesis, which provides high flexibility and sufficient amount to perform structure-activity studies.
Determination of the affinity of peptides at SiO_2-wafers by an ELISA approach and atomic force microscopy revealed a sigmoidal binding behaviour of peptides at the inorganic surface. Surprisingly, the peptide ZB2 (VRTRDDARTHRK), originally designed for ZnO binding showed the best binding to silicone surfaces (EC_{50} =2 μM), whereas peptides described to bind to silicone showed only moderate affinity. Further structure-activity studies showed that the C-terminal part of ZB2 is the main binding motif. Based on this knowledge we designed an optimized derivative of ZB2 which shows a superior binding behaviour (EC_{50} = 16 nM). Furthermore we could show that this optimized peptide forms a complete peptide layer at the silicone surface at a concentration of 1 μM.
Considering the advantages of an ELISA-based assay with respect to parallel testing of different peptides on various surfaces we were able to improve the understanding of peptide-surface interaction. This is necessary to bridge the gap from the common combinatorial procedure to a more rational approach in the design of peptides binding to solid supports. This is crucial to develop high affinity peptides that act as a toolbox for immobilizing distinct biomolecules or cells at inorganic structures.

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POSTER 223

Characterization of a tRNA editing activity in Saccharomyces cerevisiae

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In mitochondrial genomes of metazoans, some tRNA genes overlap by one to six nucleotides with the downstream tRNA gene located on the same strand. The human mitochondrial genes for $tRNA^{Tyr}$ and $tRNA^{Cys}$ which overlap by one nucleotide. The primary transcript, $tRNA^{Cys}$ is released as a complete molecule, while the upstream $tRNA^{Tyr}$ carries a corresponding truncation at the 3'-terminus. An RNA editing reaction restores the missing position and completes this tRNA.
S. cerevisiae doesn`t carry overlapping tRNA genes in its genome, but is able to restore such truncated tRNAs. *S. cerevisiae* carries a promiscuous nucleotide incorporating activity accepting these transcripts and adding the missing nucleotide. An approach identified Trf4 and Trf5 as two candidate activities, representing bipartite poly(A) polymerases in yeast. Our analyses identified Trf4 within the TRAMP complex to be responsible for the editing activity in yeast, indicating a surprising multifunctionality of this enzyme.
The presented data show that nucleotidyltransferase activities accept additional RNA substrates for NTP incorporation, supporting the idea that RNA editing events evolved on the basis of promiscuous NTP-adding enzymes with a broad substrate range. It is conceivable that the human mitochondrial tRNA editing reaction might be carried out by a nucleotide incorporating enzyme.

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POSTER 224

Local sequence and structure features in long RNAs

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Many ncRNA classes have been identified by means of computational prediction and conservation, however, their functions are still unknown or vaguely understood. Lately a new subtype of long ncRNA was discovered called lincRNA.Well known RNA molecules are mRNAs due to their length distributions and both are processed by splicing machinery. A mRNA molecule is divided into three main functional regions 5'UTR, 3'UTR and CDS. In order to identify any sequence/structure similarity between lincRNA and protein coding regions, the local features of human lincRNA were compared to those of mRNA.The analyses are done by statistics and nonparametric tests to categories the different regions and create a statistical analyzing tool. The proposed generic Background Model (BGM) fitted the values of the local features to a selection of distributions. The fitted distribution is used as a basis to determine cutoff values for significant regions within the sequences for different significant levels.Because of the large dataset size, the determination of the significance of mRNA should be simple; lincRNA, however are far fewer than mRNA in a single organism, therefore it is more difficult to determine the background distribution of their features and therefore to obtain a correct significance cutoff.Hence, the cutoff determined from the mRNA data is used to highlight and compare between different features of the significant regions of lincRNA sequences.Due to extremely large dataset size, two solutions were given to overcome this problem: 1) take an alternative distribution 2) use Law of large numbers and Sum of independent variables.

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POSTER 225

Screening for inhibitors of human ecto-5'-nucleotidase

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The eukaryotic ecto-5'-nucleotidase (e5NT) is an extracellular enzyme which catalyzes the hydrolysis of AMP and thereby generates the signaling molecule adenosine. Since the effects of adenosine are often opposite to those of ATP, e5NT might be an appealing new drug target with various fields of application such as treatment of inflammation, chronic pain and certain types of cancer.
For the production of recombinant e5NT an *E.coli* expression system was established including refolding procedures and subsequent purification. Different variants were expressed and tested for their activity as well as suitability for crystallization. Structures with resolutions of up to 1.8 Å were determined at Bessy PX beamlines. The molecular characterization revealed that e5NT is composed of two domains. Via a large (~100°) rotation of the N-terminal domain, the enzyme is able to switch between two states, termed open and closed conformation.
Based on these structures of e5NT we hope to support rational inhibitor design by determining complex structures. Therefore, we identified several potential e5NT inhibitors via high throughput inhibitor screening which are now used in co-crystallization and soaking experiments. Also inhibitors that mimic the natural substrate are of interest as such complex structures could provide further insights into the substrate binding mode and the control of substrate specificity. In contrast to the bacterial 5'-nucleotidases, e5NT is specific for AMP and does not hydrolyze ADP or ATP.
DFG Research Group (FOR 748) "Neuronal and glial P2 receptors; molecular basis and functional significance."

Association: PbF III

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POSTER 226

Computer-aided identification of thyroid stimulating hormone receptor–ligand interactions

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The thyroid stimulating hormone receptor (TSHR) belongs to the glycoprotein hormone receptors (GPHRs) a subfamily of the G protein-coupled receptors (GPCR). Due to its involvement in regulation of the thyroid gland, malfunctions of the TSHR are associated with several pathological conditions like hyperthyroidism due to constitutively activating mutations and Graves' disease caused by activating auto-antibodies. Recent studies identified several amino acids in the receptors hinge region involved in binding the super-agonistic ligand bTSH. Thus questioning whether the structurally well defined LRR domain of the TSH receptor is solely responsible for ligand binding. Yet the establishment of a structural model for this hinge region proofed to be difficult due to the lack of experimental data with structural information about this region or any closely related protein. Therefore, we established a protocol which utilizes the ability of the Rosetta software suite to model larger protein sequences (about 100 to 150 amino acids) without structural templates. Potential receptor-ligand interactions will be identified by generating contact maps over a large set of models. Those interactions will then be experimentally verified or falsified by double mutant studies resulting in a refinement of the models and ultimately leading to a full receptor model. This may be used for knowledge-based design of drugs which modulate receptor activity in a pathology-dependent customized manner.

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POSTER 227

Key enzymes of fuel oxygenate ether degradation

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Tumor Targeting

Since the 1980s, methyl *tert*-butyl and *tert*-amyl methyl ether (MTBE and TAME) have been used in increasing amounts as gasoline additives. Their extensive use has resulted in persistent groundwater contamination due to their recalcitrance against microbial attack. The bacterial strain *Aquincola tertiaricarbonis* L108, however, can grow well on both fuel oxygenate ethers as single source of carbon and energy. We have now elucidated the underlying degradation pathways by generating gene knockouts specifically affecting expression of key enzymatic steps. In addition, central metabolites of ether catabolism were identified. Initial degradation proceeds via specific hydroxylation by the EthABCD monooxygenase system resulting in the formation of *tert*-butyl or *tert*-amyl alcohol (TBA or TAA). Their degradation is catalyzed by the monooxygenase MdpJ. TBA is hydroxylated to 2-methylpropan-1,2-diol, while TAA is desaturated to the unsaturated tertiary alcohol 2-methyl-3-buten-2-ol. 2-Methylpropan-1,2-diol is oxidized to 2-hydroxyisobutyric acid, which is activated to the corresponding CoA ester and isomerized to the common metabolite 3-hydroxybutyryl-CoA. 2-Methyl-3-buten-2-ol, on the other hand, is degraded via hemiterpenic alcohols and aldehydes linking TAA metabolism with the catabolic route of the amino acid leucine.

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POSTER 228

Human Interleukin-8 Analogs to Study the Interactions with GAGs

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Tumor Targeting

Implant rejection and wound healing are still significant problems in regenerative medicine. Improved biomaterials have been reported to be advantageous to conservative materials. However, it is necessary to control and limit the inflammatory potential of implants coated with biomaterial layers like extracellular matrix (ECM).

The chemokine interleukin-8 (IL-8, also named CXCL8) is a mediator in inflammatory processes and hence, we want to use analogs of this protein as a powerful tool to follow and estimate the inflammatory potential of biomaterials by studying the interactions with glycosaminoglycans (GAGs), which are part of the ECM. IL-8 belongs to the family of CXC chemokines and is physiologically secreted by a variety of cells.

The C-terminal helix of IL-8 is not directly involved in the binding of the chemokine to hyaluronic acid. It has to be investigated whether this holds true for different biomaterials or extracellular matrix components. Therefore C- and N-terminally truncated analogs were generated by a semisynthetic approach. The binding of all synthesized interleukin-8 analogs to GAGs was analyzed by affinity chromatography to a heparin matrix and surface plasmon resonance technique (SPR). Affinity chromatography revealed that deletion of the α-helix induces a gradual decrease of affinity for the heparin matrix, whereas N-terminally truncated analogs show the same binding mode like wild type. The performed SPR-studies determined that N-terminally and C-terminally shortened analogs have significant less binding affinity to highly sulfated hyaluronic acid than wild type IL-8.

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POSTER 229

The Neuropeptide Y Receptor Type 2: Isolation and Activity Appraisal after in vitro Folding

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Tumor Targeting

G protein-coupled receptors (GPCRs) are involved in numerous physiological processes an represent a major target for pharmacological developments. Until now, there is still a lack of knowledge about GPCR structure and dynamics, which is indispensable for a structure based drug development. The preparation of sufficient amounts of functional receptor is one main problem for structural analysis. A high-level expression using *E.coli* as host and a subsequent *in vitro* folding is one possible solution for this problem, what was demonstrated previously. However, the receptor preparation in this case caused new issues. The quantification of native like folded receptor is always a difficult question to answer. And in the end the functionality has to be proven. Here we describe methods to solve these problems after in vitro folding of the G protein-coupled Neuropeptide Y Receptor Type 2 (Y2R) using ligand affinity chromatography to accumulate the proportion of active receptor to a value about ~96%. Thus homogeneous sample of the Y2 receptor was used in radioactivity binding studies. A K_D value of (0.1 ± 0.05) nM could be determined for the binding of polypeptide Y, which represents one of the natural ligands of the Y2 receptor.

Funding: formel1

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POSTER 230

Structure-activity studies of RFamide peptides reveal subtype-selective activation of neuropeptide FF1 and FF2 receptors.

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In 2000, two G protein-coupled receptors, $NPFF_1$ and $NPFF_2$, were identified as specific receptors for neuropeptide FF (NPFF, FLFQPQRF-NH_2). They interact with the inhibitory Gα protein and belong to an opioid-modulatory system. Selectivity is a major issue in closely related multiligand/multireceptor systems. In this study we investigated the RFamide systems of $hNPFF_1R$ and $hNPFF_2R$ that endogenously bind the peptide hormones NPFF, NPAF, NPVF, and NPSF. We characterized the role of the C-terminal dipeptide with respect to agonistic properties by using a systematic approach with synthesized [Xaa^7]NPFF and [Xaa^8]NPFF analogs. We were able to explore the crucial role of Arg^7 by modifying this position and showed that all alterations result in identical behavior at the $NPFF_1R$ and $NPFF_2R$. However, the C-terminal Phe^8 was able to be replaced by Trp or His with only a minor loss in potency at the $NPFF_2R$ compared to the $NPFF_1R$. Analogs with shorter side chains, such as α-amino-4-guanidino butyric acid ([Agb^7]NPFF) or phenylglycine ([Phg^8]NPFF), decreased efficacy for the $NPFF_1R$ to 25-31 % of the maximal response, suggesting that these agonist-receptor complexes are more susceptible to structural modifications. In contrast, mutations to the conserved Asp 6.59 residue in the third extracellular loop of both receptors revealed a higher sensitivity for the $hNPFF_2R$ receptor than for $hNPFF_1R$. These data provide new insight into the subtype-specific agonistic activation of the $NPFF_1$ and $NPFF_2$ receptors that are necessary for the development of selective agonists.

Findeisen M, Rathmann D and Beck-Sickinger AG. *ChemMedChem* 6: 1081-93 (2011)

Association: PbF III
Funding: life

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POSTER 231

Development of an ITC based enzyme assay for nucleoside triphosphate diphosphohydrolases (NTPDases)

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For the regulation of the extracellular levels of nucleotides membrane-bound ectonucleotidases such as nucleoside triphosphate diphosphohydrolases play an important physiological role. CD39 or NTPDase1, the prototype member of the eukaryotic NTPDase family is the dominant NTPDase of the vasculature. Based on the hydrolysis of proinflammatory ATP and platelet-activating ADP to AMP the platelet-aggregation is blocked and blood flow is supported. Thus, an understanding of the structure and dynamics of NTPDase1 are vitally important. We have determined the crystal structure of an ectodomain variant of NTPDase1 alone and in complex with the polyoxometallate anions decavanadate and heptamolybdate. Both compounds bind electrostatically to a loop that is involved in binding of the nucleobase. Using a newly established kinetic NTPDase assay that measures the heat release during NTPDase-mediated phosphoanhydride cleavage in an isothermal titration calorimeter, we could show that heptamolybdate is a strong inhibitor of NTPDase1. A comparison of the domain orientations of the four independent proteins in the crystal asymmetric unit provides first direct experimental evidence for a domain motion of NTPDases. An interdomain rotation angle of up to 7.4° affects the active site cleft between the two lobes of the protein. Comparison with a previously solved bacterial NTPDase structure indicates that the domains may undergo relative rotational movements of more than 20°. Our data support the idea that the influence of transmembrane helix dynamics on activity is achieved by coupling to a domain motion.

Association: PbF III

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POSTER 232

In silico selection of a theophylline riboswitch

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Riboswitches are RNA-modules able to regulate genes without the need for a protein and are often found in the 5'-untranslated region of genes. Being remnants of the RNA world, riboswitches are still working in today´s organisms but do also offer various opportunities for current research. They consist of an aptamer domain that is capable of binding even small ligands with high affinity and specificity and an expression platform, for example a transcriptional terminator. Once a ligand binds to the aptamer, this expression platform is structurally rearranged, usually resulting in gene activation. As aptamers can be selected for binding nearly every molecule of interest, there is great concern to establish new expression systems based on riboswitch function. However, most aptamers binding ligands *in vitro* are not capable of functioning as gene regulating riboswitches *in vivo* due to a lack of applicable selection methods. This study therefore aims on the selection of RNA riboswitches in an *in silico* approach. In a secondary structure prediction we focus on transcriptional terminators that change their structure when a ligand is bound to an adjacent theophylline aptamer. Here, we present a theophylline riboswitch derived from an *in silico* selection which is able to regulate transcription *in vivo*.

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POSTER 233

Simultaneous "One Pot" Expressed Protein Ligation and Cu(I)-Catalyzed Azide/Alkyne Cycloaddition for Protein Immobilization

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Protein immobilization is a challenging field. Usually protein modification, purification and immobilization are performed in several distinct steps, which each can lead to significant loss of active protein. Here, a one step immobilization of proteins via combination of expressed protein ligation (EPL)[1] and Cu(I)-catalyzed azide/alkyne [3+2] cycloaddition (CuAAC)[2-3] is reported. Enhanced GFP and aldo-keto reductase 1A1 (AKR1A1) have been expressed as protein thioesters. Subsequently, an azide derivatized PEGA resin and a short linker peptide with an N-terminal cysteine and an alkyne moiety have been synthesized using solid phase peptide synthesis. Recombinant proteins were characterized by MALDI-TOF analysis, kinetic assay and SDS-PAGE. The characterization of the peptide was realized by MALDI-TOF and RP-HPLC.
The optimized selective and orthogonal EPL and CuAAC methods allowed the simultaneous one-pot reaction and successful immobilization of both proteins. The native protein structure was retained and the proteins could be characterized by fluorescence microscopy, ELISA and enzymatic activity. The presented combined strategy is time saving while protein loss is minimized. We expect the technique to be generally applicable to other biomolecules.

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(3) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew Chem Int Ed Engl* 2002, *41*, 2596.

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POSTER 234

Biochemical and kinetic characterization of the 2-hydroxyisobutyryl-CoA mutase, which plays a key role in methyl tert-butylether degradation by Aquincola tertiaricarbonis L108

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The coenzyme B_{12}-dependent 2-hydroxyisobutyryl-CoA mutase catalyzes the reversible rearrangement of 2-hydroxyisobutyryl-CoA to 3-hydroxybutyryl-CoA. It is closely related to the well known isobutyryl-CoA mutase (EC 5.4.99.13). 2-hydroxyisobutyryl-CoA mutase has been detected in *Aquincola tertiaricarbonis* strain L108, where it appears to play a key role in methyl *tert*-butylether (MTBE) degradation. MTBE is a volatile, oxygen-containing, organic compound, which is predominantly used as gasoline additive to reduce engine knocking and increase the fuel's octane rating. The strain L108 utilizes MTBE as sole carbon and energy source, so that its initiation for the MTBE decomposition by microorganisms could be a possible in the near future.
To study the biochemical and kinetic characterization of the 2-hydroxyisobutyryl-CoA is necessary to clone the genes for its large (*hcmA*) and small (*hcmB*) subunits into over-expression vector with strong promoter, which will be used to produced the corresponding recombinant proteins in *Escherichia coli* with tags for their purification.
We report here our efforts to obtain the purified 2-hydroxyisobutyryl-CoA mutase (HcmA/HcmB) and to analyze its activity, viz. the conversion of substrate to product, via hplc-assay. We could define the pH and temperature optimum of the mutase, such as its kinetic parameters.

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POSTER 235

A genetic mutant of Geobacter metallireducens unravels new insights into the anaerobic degradation of aromatic compounds

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Members of the metal oxide respiring genus *Geobacter* play an important role in the bioremediation of organic and uranium oxide contaminants. They are obligate anaerobes belonging to the *Deltaproteobacteria* and are able to completely oxidize organic compounds to carbon dioxide with Fe(III), Mn(IV), U(IV) or nitrate as the terminal electron acceptor (1). Growth substrates of *Geobacter* species are short chain fatty acids and monoaromatic compounds like benzoate, phenol, *p*-cresol and toluene. To study the biochemical pathways of the degradation of aromatic compounds we established a genetic system for *G. metallireducens* and disrupted the gene encoding the benzoate-CoA ligase (*bamY*). This enzyme activates benzoate to benzoyl-CoA, the central intermediate in the metabolism of aromatic compounds (3). Unexpectedly, the resulting knockout mutant was still able to grow on benzoate with a growth rate similar to that of the wild type. In agreement, we identified a previously unknown succinyl-CoA:benzoate CoA transferase activity. The identification of the corresponding gene is currently in progress.

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POSTER 236

Investigations on Y1R/Y4R NPY Selectivity: a Chimeric Approach

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The NPY system is a multireceptor/multiligand system that consists of four GPCRs in humans: Y1R, Y2R, Y4R and Y5R. This family of receptors is activated by three different agonists (pancreatic polypeptide (PP), neuropeptide Y (NPY) and peptide YY (PYY)) with different potencies for each receptor. This family of receptors and peptidesplays a role in several physiological processes such as memory retention, regulation of hunger and satiety.
We used a chimeric approach combining fragments of Y1R and Y4R. These two receptors share a high sequence homology which makes them suitable for the design of chimeric receptors. This approach allows finding large fragments of interest that can be further investigated by site directed mutagenesis and, thus identifying important residues in the receptor site. In this case, we wanted to elucidate the importance of the transmembrane helix 1 (TM1) and transmembrane helix 2 (TM2) concerning NPY selectivity. For this purpose, weexchanged the TM1 or TM2 on the Y4R by the respective helices of Y1R. We also combined this modification with the 3rd extracellular loop (ECL3) of the Y1R in two of the constructs. From these experiments, we could elucidate that the transmembrane helix 2 plays a major role in the activation of the receptor by NPY. By combining TM2 with the ELC3, we could slightly improve the activation of the receptor with NPY. On a further mutagenesis approach of TM2, we could identify three residues of the Y4R that led to nanomolar activity for NPY when replaced by the respective residues of the Y1 receptor. This helps to understand the molecular interaction of the YR family.

Association: PbF III

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POSTER 237

Mögliche Anwendbarkeit rekombinanter Virusproteine für die serologische Diagnostik von Koi-Herpesvirus

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Die Infektion mit dem Koi-Herpesvirus (KHV) hat sich im vergangenen Jahrzehnt rapide in weiten Teilen Europas, Asiens sowie den USA und Kanada verbreitet. In Deutschland zählt die KHV-Infektion zu den anzeigepflichtigen Tierseuchen. Klinische Erkrankungen wurden bisher nur bei gemeinen Nutzkarpfen (*Cyprinus carpio carpio*) und Koi-Karpfen (*Cyprinus carpio koi*) beobachtet, zum Teil mit sehr hohen Morbiditäts- und Mortalitätsraten einhergehend und nachfolgend hohen wirtschaftlichen Verlusten.
Das Virus, das sich deutlich von bekannten Herpesviren der Säugetiere bzw.des Menschen unterscheidet, wurde der Familie der *Alloherpesviridae* zugeordnet. Der Erreger ist nach wie vor nur unzureichend charakterisiert. Das Genom umfasst 295 kbp und codiert für 156 Proteine.
Routinetests für eine flächendeckende serologische Diagnostik von Fischbeständen sind wünschenswert, derzeit aber nicht verfügbar. Beschrieben sind verschiedene ELISA-Verfahren basierend auf der Verwendung von Virus-Vollantigen. Eine Weiterentwicklung der Diagnostik soll nun durch die Prüfung der Verwendbarkeit von rekombinanten Virusproteinen angestrebt werden. Dazu wurden zunächst 5 Oberflächenproteine ausgewählt. Diese sollen unter Verwendung des Baculovirus-Systems exprimiert und anschließend auf ihre Immunogenität und Anwendbarkeit in der Diagnostik geprüft werden.

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POSTER 238

tRNA Nucleotidyltransferases: An inhibitory C-terminal region dictates the specificity of A-adding enzymes

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In most organisms, the addition of the nucleotide triplet C-C-A to tRNA 3'-ends is carried out by the highly specific and template-independent tRNA nucleotidyltransferase (CCA-adding enzyme). Interestingly, in some prokaryotes two related enzymes with partial activities collaborate in CCA-addition: One enzyme adds the first two C residues (CC-adding enzyme), while the second one incorporates the terminal A residue (A-adding enzyme).
Although CC- and A-adding enzymes exhibit such restricted activities, these enzymes carry the same set of highly conserved catalytic core motifs required for a complete CCA-addition. While the deletion of a loop region was identified as the molecular basis for the restricted activity of CC-adding enzymes, it remained unclear why A-adding enzymes incorporate only the terminal A residue. To identify elements responsible for this restriction, chimeras of A- and CC-adding enzymes as well as deletion variants of A-adding enzymes were tested *in vitro*. Surprisingly, the presence or absence of the non-conserved C-terminal part of an A-adding enzyme dictates whether limited A-incorporation or complete CCA-addition takes place. Our data indicate that the C-terminal part of A-adding enzymes acts as a physical constraint, allowing only a tRNA ending with CC to fit into the catalytic core. tRNAs lacking the two C residues are excluded as a substrate. In the C-terminal deletion variants, this physical constraint is missing, leading to a wiggle room in the catalytic core that allows a positioning of the tRNA for complete CCA-addition.

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POSTER 239

Suppressor of fused in Hedgehog an Wnt/ß-Catenin signaling pathway

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The Hedgehog signaling pathway plays a critical role in cell differentiation and development of cancer. Sufu is one of the most important regulatory elements that negatively regulate the Hedgehog signal transduction. Sufu forms an inhibition complex with Fu and Cos2 in the cytoplasm, causing a proteolytic cleavage of the transcription factors Gli2 and Gli3 into their repressor forms and so inhibiting the expression of the target genes. Sufu can also play an important role in the Wnt/ß-Catenin signaling cascade, by binding the protein ß-Catenin, exporting it from the nucleus and thereby repressing the TCF- mediated transcription.
To analyze whether these mechanisms exist in liver cells, we performed an inhibition of the Sufu expression by RNAi experiments in cultured mouse hepatocytes. We expected that the knockdown of Sufu expression may stimulate the Hedgehog signaling pathway. Indeed, we found that the transcription levels of Gli1, 2 and 3 increased significantly. Likewise, the expression of the hedgehog ligands Indian and Sonic hedgehog increased. Here, we observed another regulatory effect of Sufu in this network. The expression of the Axin-related protein, Axin2, an important negative regulator of Wnt/ß-Catenin pathway was decreased by Sufu siRNA knockdown. The same effect we also recorded for other Wnt/ß-Catenin genes, like GSK3ß, APC and even ß-Catenin as well. Also, the Wnt/ß-Catenin target genes cMyc and CyclinD decreased under these conditions.

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POSTER 240

Genetic variation in Bone Morphogenetic Protein 4 (BMP4) in combined pituitary hormone deficiency

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Background & Aim.
Mutations in transcription factors have been identified in rare cases of congenital hypopituitarism but the genetic causes for most patients with combined pituitary hormone deficiency (CPHD) remain unknown.
The bone morphogenetic protein 4 (BMP4), a member of the TGF-ß superfamily, plays a major role in brain and eye development. The aim of our study was to analyse whether genetic variants in *BMP4* play a role in CPHD.
Methods.
In our study we included 20 patients with CPHD showing a hypoplastic or absent pituitary gland in MRI.
Mutations in *PROP1*, *POU1F1* and *HESX1* have been excluded in advance. To screen for *BMP4* genetic variation all coding regions, exon-intron-boundaries, 5´- and 3´-UTRs in all isoforms were directly sequenced.
Results.
One patient harboured a novel heterozygous missense mutation. The C/G substitution at position 1863 predicts an amino acid change from arginine to proline (p.R300P). In 1000 healthy control subjects no further carrier of this mutation was identified.

Funding: IFB

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POSTER 241

Gender-Related Differences in Alveolar Epithelial Sodium Transport

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Respiratory distress syndrome (RDS) of preterm babies is known to exhibit a gender-related difference in occurrence as well as in the resulting morbidity and mortality. Sodium transport across the alveolar epithelium via the epithelial sodium channel (ENaC) and the Na-K-ATPases supposedly plays a crucial role in preventing the development of RDS. A functional impairment of the involved ion channels might therefore be responsible for the increased occurrence of RDS in males compared to females. Therefore we sought to analyze and compare the alveolar sodium transport in fetal distal lung epithelial (FDLE) cells of male and female rat fetuses (E20-21). FDLE cells were cultured on permeable supports and the activity of the contributing ion channels was measured as short circuit currents in Ussing chambers. The basal short circuit current (Isc), amiloride-sensitive Isc and ouabain-sensitive Isc revealed an increased activity in cells of female origin supporting the assumption of a female advantage in alveolar function. Currently mRNA-expression of the contributing ENaC-subunits is studied to elucidate a putative molecular basis for the increased activity in female cells. In summary the results suggest a female advantage through an increased alveolar sodium transport by ENaC and the Na-K-ATPases. This might lead to an increased alveolar fluid clearance in females and might therefore be responsible for the reduced incidence of RDS in females compared to males. Next we want to determine the underlying pathway leading to these gender-related differences in alveolar function.

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POSTER 242

Spin label EPR studies on the domain motion of 5´-nucleotidase

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In vertebrates, ecto-5'-nucleotidase (CD73, 5NT) hydrolyzes extracellular AMP to adenosine as part of extracellular purinergic signaling pathways. The structure of a related nucleotidase from E. coli has been characterized in open and closed conformations, which differ in the relative orientation of the two domains by a rotation of up to 96°. The domain movement can be described as a rotation of the C-terminal domain around an axis, which passes through the center of this domain. The resulting hinge-bending domain movement is unique in that the cleft between the domains does not open up, but the residues of the domain interface slide along the interface. The conformational change is necessary for the catalytic action of the enzyme, presumably to allow for substrate binding and product release [1,2].To study the relation between protein structure, function and the domain motion of E. coli 5NT we use NMR, FRET and EPR spectroscopy. EPR studies revealed that the open and closed conformations are also present in solution. Addition of inhibitor shifts the equilibrium to the closed conformation. With computational methods we evaluate the EPR data and try to characterize the population of different conformations in the apo state as well as the inhibitor bound state of the enzyme.
[1] Knöfel, Sträter, J. Mol. Biol. 2001, 309, 255-266.[2] Schultz-Heienbrok et al., Biochemistry 2005; 44, 2244-2252.

Association: PbF III

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POSTER 243

Hypoxia boosts amyloidogenic pathway of amyloid precursor protein of vascular endothelial cells

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Tumor Targeting

Alzheimer's disease (AD), a heterogeneous and multifactorial disorder, is characterized clinically by dementia and histopathologically by the accumulation of ubiquitinated tau and senile plaque extracellular deposits of neurotoxic and cytotoxic β-amyloid (Aβ) visualized as amyloid plaques. The occurrence of AD is greatly increased by hypoxic injury resulting from cerebral ischemia or stroke. In response to hypoxia, endothelial cells (EC) produce more vascular endothelial growth factor (VEGF) and induce angiogenesis. The angiogenesis activates production of a large number of EC; consequently, increases the expression and secretion of amyloid precursor protein (APP). The objective of this study was to examine the influence of hypoxia on APP processing of endothelial cells. Cultured EC derived from Tg2576 mouse brain were exposed to hypoxia for different incubation time and its effect on APP metabolism was assessed using novel enzyme-linked immunosorbent assay kits as well as western blotting. The results of our study demonstrated that after 24hr, hypoxic condition significantly up-regulated the secretion of VEGF as well as sAPPβ ($P<0.05$). Therefore, hypoxia may modulate amyloidogenic processing of APP in EC and influences the pathogenesis of AD.
Key words: Alzheimer's disease, endothelial cells, hypoxia, APP

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POSTER 244

Mechanisms of high-frequency synaptic transmission at a central excitatory synapse

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Tumor Targeting

To maximize the speed of information processing, some synapses can sustain high-frequency transmission. However, our understanding of the mechanisms of high-frequency synaptic transmission has been hampered by the limited number of synapses allowing direct recordings. Here, we exploit presynaptic recordings from cerebellar mossy fiber boutons (cMFBs) to analyze high-frequency signaling. Simultaneous remote stimulations of the mossy fiber axons can elicit action potentials at 1 kHz frequency in cMFBs with mean half-width of 150 μs and minimal action potential broadening. Furthermore, capacitance recordings at cMFB revealed that 2000 and 6000 vesicles fuse with time constants of 1.5 and 30 ms, respectively. Finally, the effective rate of vesicles reloading during high-frequency transmission is reduced when the calcium buffer EGTA is elevated in the terminal. These data suggest that a large pool of rapidly fusing vesicles permits kHz-transmission at a central synapse.

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POSTER 245

Perineuronal Nets potentially protect Neurons against iron-induced neurodegeneration

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Tumor Targeting

Perineuronal nets (PNs) are a specialized form of extracellular matrix, surrounding different types of neurons and mainly consisting of chondroitin sulphate proteoglycans connected to hyaluronan as well as tenascin. Due to their polyanionic character, caused by the glycosaminoglycan and hyaluronan components, PNs potentially might be involved in local ion homeostasis, be able to scavenge and bind redox-active ions and thus reduce the local oxidative potential. Here, we investigate whether net-enwrapped neurons are less vulnerable against iron-induced oxidative processes. Oxidative stress is a key-factor in the development and progression of neurodegenerative diseases like Alzheimer`s (AD) and Parkinson`s disease (PD). Iron is believed to contribute to oxidative stress in AD brains by catalyzing the generation of free radicals, especially the highly reactive hydroxyl radical. For examining potential neuroprotective effects of PNs, wildtype mice were microinjected with 0.2μl of a 20mM solution of $FeCl_3$ into the barrel field. Mice belonging to the control group received an equal volume of 0.9% NaCl. After 24h alternatively 72h, mice were perfused intracardially under deep anesthesia. Brains were removed, sectioned and analyzed using Fluoro-Jade-B - staining to reveal neuronal degeneration. The analysis of the data showed a significant lower degeneration rate of net-ensheathed neurons in comparison to neurons without PNs.

Association: PbF IV

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POSTER 246

Investigation of neuroprotective mechanisms using a primary neural in vitro ischemia model

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Tumor Targeting

Stroke is the leading cause of chronic disabilities in humans and effective treatment is only applicable within a narrow time window of 4.5h. There is a strong demand for novel therapeutic approaches that aim on subacute and chronic phases after cerebral ischemia and activate intracellular processes that make cells in the penumbra zone surrounding the stroke lesion core more tolerant to the undersupply with oxygen and nutrients. We established an innovative *in vitro* system of interacting primary neurons and glia cells which is used for the analysis of new endogenous key factors regulated after oxygen-glucose-deprivation (OGD). With this model we were able to detect a neuroprotective effect of preconditioned astrocyte culture medium and the chemokine SDF-1alpha on neurons after OGD. In addition we are analyzing two protein families that we include as extremely promising and interesting candidates, SUMOs (small ubiquitin-like modifier) and SUMO proteases (SENPs) which are involved in the posttranslational regulation processes after stroke. Free SUMO proteins as well as SUMOylated proteins can be detected in primary neuronal cultures under normoxic and ischemic conditions. Future studies will reveal the time dependent SUMO/SENP expression after OGD while modulation of SUMO/SENP gene expression in primary neurons should help to modulate their ischemic tolerance. Consequently the *in vitro* system will help to elucidate cellular neuroprotective mechanisms in order to enhance the possibilities for therapeutic interventions after stroke.

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POSTER 247

Adenine receptor: Selective receptor ligands and possible signalling pathways

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Adenine has recently been identified as an endogenous ligand of a novel G-protein coupled receptor in rats. Radioligand binding studies using membrane preparations provide evidence for expression of adenine receptors in rat neuronal tissue. Investigations using stably transfected cell lines showed a sensitivity to pertussis toxine assuming that the receptor is coupled to a G_i-protein. The aim of the present study was to detect the adenine receptor on rat neuroblastoma cells (B104) and to study the signalling pathways using novel selective receptor ligands. Additionally, intracellular recordings were made on cortical pyramidal cells in rat brain slices. The adenine receptor mRNA was detected using qualitative RT-PCR. Adenine (10μM to 1mM) as well as the receptor agonist TB-74 (1μM to 100μM) depressed concentration-dependently the electrical evoked synaptic potentials in rat brain slices. The ATP-induced increase of the intracellular Ca^{2+} concentration in B104 cells was inhibited by adenine and TB-74 as well as the potential antagonist PSB-08162 (10μM to 500μM). The receptor ligands had no effect on membrane potential and input resistance and did not influence the basal intracellular calcium concentration. The inhibition of different sites of the signalling pathway indicates that the adenine receptor couples to a G_q-protein followed by activation of phospholipase C pathway in B104 cells. This represents a new signalling pathway and allows the assumption that different adenine receptor subtypes exist in the rat brain.

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POSTER 248

Quantal analysis of granule cell-to-basket cell synapses in mouse cerebellum

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We analyzed synaptic connections between basket cells (BCs) and granule cells (GCs) in acute cerebellar slices from mice. BCs were voltage-clamped in the whole-cell patch clamp configuration, whereas single GCs were stimulated in the cell-attached mode. GC-mediated EPSCs in BCs were characterized by i) rapid kinetics, ii) rather asynchronous release, and iii) marked paired-pulse facilitation[1]. Decay time constants were approximately 0.8 ms (n=5 cells), facilitating the analysis of release events occurring at high frequencies. The delay between presynaptic action potential and the start of the EPSC was rather variable in given connections (typically 0.6 to 2.0 ms). Furthermore, the compound EPSCs were often composed of several separable current components, and EPSCs were often followed by additional asynchronous events. These characteristics indicate a rather loose coupling between Ca^{2+} channels and release machinery. The marked paired-pulse facilitation dropped from a paired-pulse ratio of 2.4 ± 0.1 (n=8) at an interstimulus interval (ISI) of 5 ms to unity at ISIs of ~500 ms. Fluctuation analyses were performed by analyzing the charge of the first 5 ms of EPSCs recorded at different extracellular Ca^{2+} concentrations. GC-BC connections were characterized by a quantal size (*q*) of approximately 110 fC, a binominal parameter *N* of ~1.3, and a release probability (*p*) of ~0.4 (at 2 mM $[Ca^{2+}]_o$). Our data help to establish the GC-BC synapse as a model system for studying conventional excitatory synapses at the quantal level.

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[1]Bao et al. 2010, J Neurosci

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POSTER 249

Electrophysiological evidence for the existence of functional P2X7 and AMPA receptors in the rat spinal cord dorsal horn

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Tumor Targeting

Rat spinal lumbar cord slices were prepared and superfused with artificial cerebrospinal fluid (ACSF). Membrane currents were recorded by the whole-cell patch-clamp technique from the layer II (substantia gelatinosa; SG) of the dorsal horn, where the sensory C-fibre input from the periphery terminates. While neurons responded to depolarizing current injection with action potential firing, astroglial cells reacted only with depolarizing electrotonic potentials. In the following experiments, we investigated the sensitivity of neurons and astroglia to pharmacological ligands applied locally by a rapid superfusion system. The P2X7 preferential agonist 2,3-*O*-(benzoyl-4-benzoyl)-ATP (Bz-ATP; 10-3,000 mM) caused a marked inward current in a low Ca^{2+}/Mg^{2+}-free (low X^{2+}) ACSF both in neurons and astroglia, although it had only a slight activity in a normal Ca^{2+}/Mg^{2+}-containing superfusion medium. ATP (3 mM) itself behaved like Bz-ATP, but with a lower potency. These effects were concentration-dependently inhibited by the selective P2X7 receptor antagonist A438079 (1, 10 mM). The ionotropic glutamate receptor agonists AMPA and NMDA, as well as the $GABA_A$ receptor agonist muscimol, were applied at a selected concentration of 100 mM. AMPA and muscimol caused relatively large inward currents, in contrast to NMDA, which had only minor effects in either cell-type. In conclusion, at SG neurons and astroglia, AMPA and NMDA receptors might modulate pain transmission, whereas P2X7 receptors have a similar effect only at non-physiological conditions.

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POSTER 250

Human glioblastoma organotypic slice cultures as a tool to test novel therapies

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We developed a method to keep glioblastoma tissue from patients in organotypic slice cultures and to study effects of cytostatics (e.g. temozolomide) alone or in combination with irradiation (X-rays or Carbon ions). Briefly, appropriate tissue pieces obtained from neurosurgery are cut in slices of 350 μm and transferred to membrane inserts on top of culture medium. Temozolomide was added either alone for 72h or 24h before and 48h after irradiation. Medium samples were stored at -80°C to determine LDH and cytokine levels at various time points. Fixed slices were prepared for histological analysis (HE, Dapi, caspase3) and quantification was performed using ImageJ. Our data show that glioblastomas are susceptible to carbon-induced cell death which -due to the unique energy deposition of heavy ions- is of great therapeutic interest. Moreover, surviving glioblastoma cells in treated slices can help to better understand and overcome mechanisms of resistance.

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POSTER 251

Association between CSF hypocretin-1 level and intracortical EEG source estimates during rest in patients with major depression and healthy controls.

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Tumor Targeting

Hypocretin-1 (Hcrt-1) synthesizing neurons are localized in the lateral hypothalamus and project widely to brain areas responsible for sleep wake-regulation.Little is known about the association between Hcrt-1 and cortical activity assessed via electroencephalography (EEG). Therefore, the aim was to analyze the correlation between CSF-Hcrt-1 levels and intracortical EEG source estimates. After a 15 minute resting EEG was recorded in 20 subjects (13 patients with MDD and 7 HC) lumbar puncture was performed to determine CSF-Hcrt-1 levels. Correlation coefficients between EEG delta, theta, alpha, beta and gamma power in 6239 intracortical grey matter voxels and Hcrt-1 levels measured with a fluorescence immunoassay (FIA) were calculated using exact low resolution electromagnetic tomography (eLORETA) software. For the whole study population, significant correlations of CSF-Hcrt-1- levels and EEG-theta power in the middle frontal gyrus (correlation coefficient r =.79; p<=0.05) and EEG-gamma power in the medial frontal gyrus (r = .81; p<=0.05; two tailed) were found. Analyses of the separated groups yielded a significant correlation for EEG-delta power for patients with MDD in the left inferior parietal lobe (r= .90; p<=0.05).Against the expectations, theta activity as an indicator of drowsiness during rest showed positive correlations. The finding of positive correlations between Hcrt-1 levels and gamma activity of the prefrontal cortex (PFC) underlines the possible impact of Hcrt-projctions on neuronal activity of cognitive processes modulated in the PFC.

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POSTER 252

CSF-hypocretin-1 levels in patients with major depressive disorder and mania

Schmidt F[1]
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Impairment of sleep–wake cycles and circadian rhythm are found in humans suffering from affective disorders. Depressive patients exhibit symptoms of impaired regulation of wakefulness with hyperarousal and agitation as well as difficulties to fall asleep and to preserve sleep continuity. A disturbed electroencephalography (EEG) based vigilance regulation is also found in mania. Changes in hypocretins (hcrt's) as polypeptides with impact on arousal and sleep–wake-regulation have neither been investigated in patients with mania nor solely unipolar depression in comparison to healthy controls. In 17 inpatients with MDD (mean HDRS 13.9±7.4) and 10 healthy controls CSF-hcrt-1 levels were measured using a fluorescence immunoassay (FIA) and matched with 5 inpatients with mania. Mean hcrt-1 CSF levels in patients with MDD (74.3±17.8 pg/ml) did not differ compared to that of healthy controls (82.8±22.1 pg/ml) nor when matched with mania (75.6±15.7 pg/ml).Although autonomic and neurohumoral signs of hyperarousal are common in affective disorders, hcrt-1 levels in CSF were not found to be altered in depression and mania compared to healthy controls. Whether hcrt-1 levels are altered in patients exhibiting impaired vigilance regulation has to be investigated in further studies combining measures of CSF- hcrt-1 with electroencephalography.

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POSTER 253

An unexpected compensation for loss of calbindin at recurrent Purkinje neuron synapses

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Neighboring Purkinje neurons (PNs), connected via axon collaterals, allow for studying transmitter release and short-term plasticity at an inhibitory, central synapse. We addressed the hypothesis that saturation of calbindin[1] (CB) underlies facilitation using paired electrophysiological recordings with subsequent quantal analysis[2] and presynaptic Ca^{2+} imaging from wild-type (WT) and CB mutants ($CB^{-/-}$).
Unexpectedly, we found that in $CB^{-/-}$ neither the basal synaptic transmission, nor the paired-pulse ratio were altered in comparison to the WT. Yet, Ca^{2+} imaging experiments showed that AP-mediated calcium transients are significantly larger in $CB^{-/-}$. In order to explain these contra intuitive results we performed mean-variance analyses of PSC amplitudes recorded from pairs of connected PNs in WT and mutant mice. We found that CB significantly decreases the release probability (*p*), presumably by buffering Ca^{2+} transients at release sites. Unexpectedly, and in contrast to previous observations[2], PNs from $CB^{-/-}$ mice compensate for the increase in *p* by reducing the number of release-ready vesicles (*N*) and by increasing the quantal size (*q*). CB does not saturate during normal synaptic transmission. Life-long lack of CB triggers homeostatic plasticity that sustains a normal synaptic weight of recurrent PN synapses.

Supported by the DFG (EI 342/4-1).
[1]Orduz & Llano, PNAS, 2007
[2]Clemens & Silver, TINS, 2000
[3] Blatow et al., Neuron, 2003

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POSTER 254

Ageing of canine brains as a model for human Alzheimer's disease

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Background:In western industrialized countries Alzheimer disease (AD) is the most common cause (60-70%) for dementia symptoms. In Germany, 700,000 patients suffer from this disease and this number will duplicate until 2050. Increasing life expectancy and with increasing amount of older people in population leads to the fact that diseases with dementia symptoms evolve into an important medical and socioeconomic problem.Dogs naturally develop an age related cognitive dysfunction syndrome with several aspects which resemble Alzheimer's in humans. The accurate study of animals that spontaneously develop an Alzheimer like disease can help to increase the underlying course of the disease.
Introduction:The accumulation of β-pleated amyloid (Aβ) and neurofibrillary tangles in and around neurons are markers for AD. Aβ, a splitting product of the amyloid precursor protein (APP) mainly consists of 40 to 42 amino acids in β-pleated structure and has a high tendency to aggregate.Dogs develop an early form of plaques consisting of Aβ. The canine APP has a 98% similarity to the human counterpart while the Aβ42 peptide is 100% identical to the human peptide. Dogs also show an age related cognitive dysfunction and might be considered an early stage AD model. Most Alzheimer related studies were performed with beagles leaving many other breeds out. But the dog as a domestic subspecies of the wolf includes over 400 different breeds. There are significant variations in longevity depending on the breed, body weight and environment. Usually, larger breeds have a shorter lifespan than smaller breeds. It is one aim of the project to compare different breeds categorized in three weight classes of different age to characterize the dog as a model for studying Alzheimer disease and related glial cell alterations.
Material and methods:Our experimental groups consist of small breeds up to 10kg, medium-weight from 10kg to 25kg and large breeds more than 25kg. The dogs will be at least eight years old. Additional there will be a younger control group. The post-mortem interval amounts to two hours as an average. The brain is isolated and fixed with 4% formalin for at least 72 hours. Followed by with the equilibration with 30% Sucrose solution and the brains are freezed down to -80°C using Methylbutan. 40μm thick slices of the regions of interest are cut with a cryotom. Immunohistochemical staining is performed to demonstrate amyloid deposits, astroglial and microglial activation. It will be examined if a link exists between Aβ levels and glial cell activation, and the effect on the surrounding tissue. According to that the inflammatory state of the brains will be measured dependant on the activation state of microglia.
Outlook:It is the intention of the project to gain further information of structural changes in the brain tissue of aged dogs of different breeding background. Results will be compared to control samples of young dogs.

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POSTER 255

Ageing of canine brains as a model for human brain ageing

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Tumor Targeting

Background:In Germany are about 1.3 million patients with dementia, which 700,000 of them have Alzheimer's Disease (AD). Although there have been and still are a lot of ongoing studies, the course of the disease is still unclear and not fully understood. In addition, it is difficult to test hypothesis for interventions in animal models which are only expressing one, two or three of the genes involved in the disease.
Introduction:So far amyloid β (Aβ) and neurofibrillary tangles (NFT) accumulate in Alzheimer brains and are considered markers for AD. Aged dogs are known to naturally accumulate Aß. This process is correlated with a cognitive dysfunction and is considered as dementia similar to humans. The Aß sequency is identical to human amyloid, however mostly diffuse amyloid plaques have been found in aged canine brains. Also, amyloid precursor protein (APP) and the enzymatic machinery for processing amyloid are 98 % identical to humans. Given that the dog has become an approved model for AD studies, because they share the same environment as humans and are a diverse group of individuals like in humans.Very few groups have found in dogs dense plaques as in human Alzheimer brains. This might be because not enough studies have been performed in very aged dogs. Given this we can use the dog as a model for the early onset of AD. In the moment most of the Alzheimer related studies are being performed on beagles and less is known about other breeds. We want to investigate the similarities between different breeds and compare to the human disease progression.
The focus of the work is the association between amyloid plaques and the loss of cholinergic neurons, which is another hallmark of AD. At the moment we are looking at four regions, where the most plaques in age occur: hippocampus, entorhinal, frontal and parietal cortex. For studying the neurons we will look at the medial septum. Moreover we explore the projection of cholinergic neurons coming from the medial septum and diagonal band in the hippocampus to determine if there is significant loss in neuron-density. In addition, we look for phosphorylated tau or its accumulation as NFT in the dog brains.

Material and methods:Our experimental group consists of old dogs, euthanized in veterinary surgeries around Leipzig. Large breeds are 8 years or older, small breeds from at least 12 years old. Brains from 39 dogs of different breeds and age ranging from 8–20 years were collected and fixed in 4 % Paraformaldehyde up to now. We use histological and immunochemical staining methods for detecting cells and plaques.
Outlook:We look for general loss of neurons and its correlation to plaque depositing. In addition, we are analysing neurodegeneration and the rate of cell death in the AD brain. Given that our study contains a heterogeneous population of breeds, we always look at the correlation of the result to the different classes of weight of the breeds and if there is a difference in ageing process between large and small dogs.

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POSTER 256

TOWARDS A GENETIC SCREENING TEST FOR DYSLEXIA ALLOWING FUNCTIONAL REGENERATION: Steps towards Identification and Analysis of Genetic Risk Factors

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Our aim is to develop a genetic screening test for dyslexia, a severe disorder of reading and writing, affecting ca. 4-5% of all schoolchildren. Currently, diagnosis takes place at the end of the 2nd grade, when years of language development have already passed. It is our vision to apply genetics in order to fill the gap of missing diagnostics for early identification of dyslexia. An early test would translate genetic findings into a clinical assay, enabling early support resulting in functional regeneration. We applied a multistep approach to identify novel genetic markers. The first step was a microarray based screening in a case-control cohort focusing on known dyslexia susceptibility regions ("DYX"). The second step was an independent replication analysis in an independent case-control cohort. The third step was functional validation. In this step, we characterize genetic markers whether they might be related with language related brain activation applying functional magnet resonance imaging (fMRI). Additionally, we characteriz these markers whether they might influence mRNA gene expression levels. As dyslexia is a complex disease, additional markers have to be identified to fully explain the genetic basis of dyslexia. Therefore, in complementary studies, our group analyzes markers from candidate genes and investigates the predictive potential of markers from the literature.

Funding: life

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POSTER 257

The role of purinergic receptors in cognitive flexibility: perseverative and impulsive behavior.

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The medial prefrontal cortex (mPFC) is essential for information processing and cognitive capabilities modulating instrumental behavior to attain a particular goal. Pharmacological studies *in vivo* have shown that G_q-protein coupled P2Y receptors (Rs) in the rat nc. accumbens, sensitive to extracellular ADP/ATP, mediate neuronal transmission and motivation-related behavior. In this study, the cognitive flexibility of rats after $P2Y_1R$ stimulation in the mPFC was investigated in operant tasks. After stimulation of $P2Y_1Rs$ with the agonist MRS2365, the accuracy decreased in a delayed nonmatching to position task accompanied by enhanced nose poke rates and magazine entries. In contrast, time to complete all trials of a session decreased. This suggests an impaired working memory and probably an enhanced impulsivity by $P2Y_1R$ stimulation. Furthermore, during the first reversal phase of a serial spatial reversal learning task microinfusion of MRS2365 into the mPFC increased perseverative errors and omissions as a sign of cognitive inflexibility, the inability to withhold spontaneously, to modify, or to develop an adaptive behavior in response to changing situational demands, symptoms regularly found in schizophrenia. The functional importance of $P2Y_1Rs$ is supported by immunocytochemical localization of $P2Y_1Rs$ at neurons and glial cells in the mPFC. $P2Y_1Rs$ identified on prefrontal GABAergic neurons may control downstream accumbal neuronal firing by multisynaptic mediation of prefrontal pyramidal neuron activity. The presented data indicate that $P2Y_1Rs$ in the mPFC are involved in cognitive flexibility including response inhibition.

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POSTER 258

A novel method to evaluate the effects of irradiation on neural cells in hippocampal slice cultures

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We developed a new method to evaluate effects of X-ray and heavy ion radiation on neural cells by using organotypic hippocampal slice cultures of mice which allow for long-term analyses. Using this method, we can study the effects of different types of irradiation on proliferation, cell death, DNA-damage, and repair. In this part of the project we focus on the effects on proliferation in different areas of the hippocampus. 350 μm tissue slices cultivated on membranes inserted into 6-well plates were exposed to X-rays and heavy ions at 1 or 4 Gy and allowed to survive from 1h to 6w after irradiation. For visualization of proliferation, BrdU and Ki67-immunostaining were used. Pictures were taken using an epifluorescence or confocal microscope at 20x magnification. Images were analyzed using ImageJ and the plugin cell counter. Cell-specific changes were analyzed using counterstaining for microglia (IBA-1) and neurons (NeuN). Photons, nickel, & nitrogen evoked fundamentally different responses in the kinetics of cellular proliferation. Since proliferation is mostly restricted to microglia, this response is likely to reflect irradiation-induced damage, and confirms high radio-resistance of microglia (Ransohoff, Nature Neurosci. 2007). Therefore, we are currently exploring cell death and DNA-repair in the same setting.

Supported by ESA and BMBF

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POSTER 259

The presumed atypcial chemokine receptor CXCR7 controls astrocytic migration and proliferation through Gi/o protein coupling

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SDF-1/CXCL12 binds to the chemokine receptors, CXCR4 and CXCR7, and controls cell proliferation and migration during development, tumorigenesis, and inflammatory processes. It is currently assumed that CXCR7 would represent an atypical or scavenger chemokine receptor which modulates the function of CXCR4. Here, we provide evidence that CXCR7 actively mediates SDF-1 signalling in primary astrocytes through pertussis toxin-sensitive $G_{i/o}$ proteins. We observed that SDF-1-dependent increases in intracellular Ca^{2+} concentration as well as activation of Erk and Akt signalling persist in primary astrocytes with depleted expression of CXCR4 whereas all responses are abolished in astrocytes with depleted expression of CXCR7. Likewise, we found that the effects of SDF-1 on astrocytic proliferation and migration require CXCR7, but not CXCR4. We further observed that CXCR7-mediated effects of SDF-1 on astrocytic cell signalling and function are all sensitive to pertussis toxin and, hence, depend on $G_{i/o}$ proteins. [^{35}S]-GTPgS binding assay additionally confirmed that CXCR7, but not CXCR4, couples to G proteins in astrocytes. Moreover, consistent with a ligand-biased function of CXCR7 in astrocytes, the alternate CXCR7 ligand, I-TAC, stimulated Erk and Akt through ß-arrestin. The demonstration that SDF-1-bound CXCR7 signals through $G_{i/o}$ proteins in astrocytes could help to explain some of the discrepancies previously observed for the function of CXCR4 and CXCR7 in other cell types.

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POSTER 260

TNF-alpha: Functional aspects in an animal model of depression

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65% of patients with major depressive disorder do not benefit from the first course of drug treatment, and more than 50% of them also do not respond to a second antidepressant. Data indicates that an activation of proinflammatory cytokines e.g., tumor necrosis factor-alpha (TNF-alpha) is involved in the pathophysiology of depression and that the suppression of proinflammatory cytokines by antidepressants may lead to an improvement of depressive symptoms (sickness behaviour, reduced drive and cognitive capabilities). In a rat model of depression induced by repeated restrained stress we investigated plasma concentrations and mRNA expression of TNF-alpha in brain regions associated with motivation and associative learning. Further, we investigated whether the subchronic administration of Etanercept (Enbrel®), mimicking the inhibitory effects of naturally occurring soluble TNF receptors, can reverse stress-induced depression-like behaviour in the forced swim test. Etanercept treatment was compared to naïve, vehicle- and imipramine-treated stressed animals.
Our findings show elevated plasma levels of ACTH and proinflammatory cytokines e.g., TNF-alpha. The expression of TNF-alpha mRNA was increased in the nc. accumbens and the amygdala of stressed animals suggesting a de novo synthesis of brain cytokines during stress.
Finally, animals treated with Etanercept showed significantly less immobility in the forced swim test similar to imipramine, a tricyclic antidepressant, in comparison to vehicle-treated rats.
Data suggests that anti-proinflammatory treatment might be an effective antidepressant treatment strategy in depression.

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POSTER 261

Tissue transglutaminase localisation in brains of patients with Alzheimer's disease

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Tissue transglutaminase (tTG) is the most abundantly expressed transglutaminase in human brain. It catalyzes calcium-dependent crosslinking of proteins forming γ-glutamyl-ε-lysine isopeptide bonds. This reaction generates protease resistant protein complexes. A typical hallmark of Alzheimer`s disease (AD) is inappropriate aggregation of proteins like β-amyloid peptides (Aβ) and hyperphosphorylated tau indicating possible involvement of tTG. Previous data demonstrated that tTG crosslinks Aβ and tau *in vitro*. Furthermore, it has been observed that neuronal layers containing neurofibrillary tangles and Aβ plaques show immunoreactivity for tTG. Additionally, mRNA as well as tTG activity and protein are elevated in AD brain. However, in the last years the participation of tTG in AD was again called into question.
Therefore, we developed two immunoassays for specific and sensitive quantification of either tTG protein or tTG activity. For this, monoclonal antibodies (mabs) were raised against human tTG. These new mabs were also applied in immunohistochemistry. Human brain samples (tissue homogenates and sections of AD brain and controls without neurodegenerative background) were studied for activity, concentration und tissue localisation of tTG.
Neither tTG protein nor activatable tTG were significantly elevated in frontal cortex of AD brain compared to controls. Immunohistological staining of cortex sections exhibited a clear colocalisation of tTG with hyperphosphorylated tau in neurofibrillary tangles in AD, while Aβ plaques contained no tTG. At present, our data neither confirm nor exclude a role of tTG in AD.

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POSTER 262

The influence of the prestimulus EEG-vigilance on the reaction time in an auditory go/no-go task

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Introduction

The individual reaction time (RT) of healthy subjects varies considerably over the course of RT-tasks. The altering state of wakefulness during the experiment may induce these RT fluctuations. The Vigilance Algorithm Leipzig (VIGALL) allows the automatic classification of vigilance states on the basis of EEG recordings. Aim of the study was to investigate the relationship between the prestimulus EEG-vigilance and the varying individual RT.

Methods

119 healthy subjects performed a simple auditory go/no-go task while an EEG was recorded simultaneously. VIGALL was used to classify the prestimulus EEG-vigilance stage. Individual mean RTs were calculated for each EEG-vigilance stage. ANOVAs for repeated measurements were computed to examine the vigilance effect on the RT.

Preliminary results

Preliminary analyses show significant main effects of the EEG-vigilance stages. Shortest RTs were found after most alert EEG-vigilance-stage A0, slowest RTs after most drowsy EEG-vigilance-stage B2/3.

Discussion

The findings suggest that the prestimulus state of vigilance, which was automatically classified by VIGALL, influences the individual speed of reaction. As the algorithm has originally been developed for the classification of resting EEGs, further features might be implemented for ensuring the applicability for different types of EEG recordings, e.g. during RT tasks. The monitoring of vigilance fluctuations by means of VIGALL might help reducing the intraindividual variance during neuro-cognitive measurements.

Funding: IFB

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POSTER 263

Activation of retinal Müller cells during lesions involves upregulation of the oligodendrocyte marker PLP

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Retinal Müller glial cells constitute an important cell type in the retina involved in light guidance, the control of ion homeostasis, gliotransmission as well as pathological events. During lesion Müller cells are activated and increase the expression of typical indicators of reactive gliosis such as glial fibrillary acidic protein (GFAP). Having shown recently that a subpopulation of astrocytes in the brain is derived from precursor cells co-expressing GFAP and the oligodendroglial marker protein PLP (Hirrlinger et al. 2009 PLoSOne 4: e4286), we hypothesized that also Müller cells might be at least in part derived from cells expressing these two promoters. Using split-Cre transgenic mice [TgN(hGFAP-NCre) x TgN(PLP-CCre)] crossed to a Cre- reporter strain we found that about 25% of all Müller cells are labeled indicating that at some time point during their development these cells expressed both the GFAP- and the PLP-promoter at the same time. In addition, acute or chronic lesions were induced to the retina by applying high intraocular pressure (HIOP) or by using homozygous RD-mutant mice, respectively. Both lesions strongly increased the number of reporter positive Müller cells, while the total number of Müller cells remained constant, suggesting that during lesion induced activation Müller cells activate both the GFAP- and the PLP-promoter. In summary, these data indicate that during lesions Müller cells reactivate developmental programs and surprisingly express genes of the oligodendroglial lineage.

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POSTER 264

Development of a new gene therapeutic tool to slow down progressive neurodegeneration

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Tumor Targeting

Alzheimer's disease (AD) is the most common neurodegenerative disorder of humans with an enormous socio-economic burden on the aging society. The clinical symptoms and the neurodegeneration of AD are caused by accumulation of extracellular plaques and neurofibrillary tangles. Currently, causes of the disease are still unknown and there is neither an effective prevention nor a therapy treatment. To prevent neuronal cell death we develop a new gene therapeutic tool, which ensures long-lasting, safe, neuron-specific and regulated transgene expression. Our therapeutic strategy is based on non-integrating (NI) lentiviral vectors, which can regulatably express different disease relevant factors. Lentiviral vector mediated gene transfer has useful attributes. These vectors can deliver 8kb – 10kb transgene sequences, they have the ability to infect specific neuronal cells, induce no or low immune response and the normal cell functions are not negatively affected. We use integration-deficient lentiviral vectors to achieve efficient and sustained transgene expression in the adult rodent CNS as a prerequisite for the therapeutic application in the prevention and/or treatment of neurodegenerative disorders. Currently, we are testing viral vectors carrying specific therapeutically relevant genes under *in vitro* and *in vivo* conditions. The great advantage of this innovative system is the modular constitution. Alternatively, it is applicable for other neurodegenerative disorders or non-neurological diseases like AIDS, Cancer, Arteriosclerosis and others. Supported by SMWK 7-7531.50-02-0361-07/2, ERANet and Afi Project 984.000-150

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POSTER 265

Identification of ncRNAs relevant for Alzheimer`s Disease

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Tumor Targeting

Alzheimer´s disease (AD) is a neurodegenerative disorder characterized by the deposition of Aß-plaques, the formation of neurofibrillary tangles made up by hyperphosphorylated forms of microtubule-associated protein tau and by a loss of differentiation control leading to an activation of cell cycle proteins and neuronal apoptosis. Neurodegenerative cell death in AD has been proposed to represent a molecular equivalent of neoplastic transformation in postmitotic cells, although the molecular mechanisms are unknown. Here we show that a specific miRNA playing a role in promoting neoplastic transformation through overriding tumor suppressor functions in tumor development, is elevated in AD. Our results also demonstrate, that this miRNA can regulate the expression of the amyloid precursor protein and BACE1 thus promoting the pro-amyloidogenic pathway as well as to inhibit neuronal differentiation and structural neuronal plasticity. Using microarray analysis we identified further miRNAs being potentially involved in the regulation of neuronal differentiation. The present study supports the concept of a molecular regulatory level shared between neoplastic transformation of diving cells and degenerative cell death of neurons and provides a new potential target for disease modifying strategies in AD. This study was supported by the BMBF (01EW0907) in the frame of ERA-Net Neuron, the Project BBZ07: 14494 (University Leipzig) and the AFI-Project 984 000-150.

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POSTER 266

Functional characterization and evolutionary differences in the transcription factors network – Implications for human brain evolution and disease

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New approaches in the genomic sequencing promises to promote the knowledge about several aspects such as the human evolution or diseases. Importantly transcription factors (TFs) play a prominent role in the central dogma of the molecular biology regulating the expression of the target genes. Therefore TF changes can lead to phenotypic differences between closely related species and cause diseases. Unfortunately, the knowledge about many TFs is very scarce and for most TFs their binding site, target genes and functions are unknown. A disease rarely involves a single mutated gene but it can be caused by a perturbation in the networks that can effects the cell and tissues functionalities. Thus the network approach offers a support to computationally investigate the molecular pathways of a certain disease but also the relationship with other distinct patho-phenotypes. The comparison of gene regulatory networks between closely related species can lead to discover a potential component that can have a severe impact in the human health. Moreover I will discover the links (correlated genes) that can be gain or lost in human compared with the other species finding a new pathway or a specific function in human of a TF. Interestingly ZEB2 is a TF involved in neurodevelopment, and mutations in ZEB2 cause Mowat-Wilson syndrome, a disorder characterized by microcephaly and mental retardation. Therefore, ZEB2 is a very interesting gene to investigate its molecular pathways and how they might alter in the disease condition and during primate evolution. Intriguingly in my project I want to pursue two essential branches to functionally and evolutionarily characterize a selected TF (ZEB2): firstly I will computationally analyze evolutionary differences between the co-expression network involving ZEB2 in the human brain compared to the "orthologous" network in the chimpanzee and rhesus macaque brain. This approach has the potential to reveal ZEB2 target genes and pathway partners, which might also be involved in other human brain disorders. Secondly I will experimentally analyze the function of ZEB2 in primate cells. Thus I aim to gain knowledge about the evolution and function of ZEB2 and its target genes. Moreover I will help, with the proposed transcriptome network approach, to define the human disease evolution and its classification.

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POSTER 267

Involvement of oxidative stress and mitochondrial dysfunction in the osmotic swelling of retinal glial cells from diabetic rats

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Tumor Targeting

Diabetic retinopathy is the leading cause of visual disability and blindness in the industrialized world. In non-proliferative diabetic retinopathy, vision loss is predominantly caused by the development of macular edema. Osmotic swelling of retinal glial (Müller) cells may contribute to the development of edema in diabetic retinopathy. The aim of the present study was to determine the sources of oxidative stress implicated in the induction of osmotic swelling of Müller glial cells from diabetic animals.
To this end, the cross-sectional area of fluorescent dye stained Müller cell somata was measured with a confocal laser scanning microscope after a 4-min superfusion of the slices with an iso- or hypoosmotic solution in the absence and presence of test substances. Hypotonic challenge did not change the size of Müller cell somata from control animals but induced soma swelling in Müller cells of diabetic animals. Administration of a reducing agent blocked cellular swelling. In retinal tissues from control animals, administration of the reducing agent blocked also the swelling-inducing effects of antagonists of $P2Y_1$ and adenosine A_1 receptors. In tissues from diabetic animals, inhibition of xanthine oxidase, whose activity normaly accounts for superoxide radicals production, decreased the soma swelling by approximately 50% while inhibition of NADPH oxidase and nitric oxide synthase had no effects. Blockade of mitochondrial oxidative stress by perindopril, as well as of mitochondrial permeability transition by cyclosporin A or minocycline, attenuated the swelling. In addition, activation of mitochondrial K_{ATP} channels by pinacidil fully prevented the swelling.
Summing up these data, we conclude that oxidative stress produced by xanthine oxidase, as well as mitochondria, is implicated in the induction of osmotic swelling of Müller cells from diabetic rats.

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POSTER 268

Purinergic modulation of hypoxia-induced changes of neuronal excitability in rat prefrontal cortex

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Purines play important roles in cell signalling acting on nucleoside and nucleotide receptors respectively. There is growing interest in the role of these molecules during hypoxic/ischemic events in the central nervous system. Under such conditions, they may act as modulators of neuronal excitability. For our studies we used freshly prepared 200 μm thick slices of rat prefrontal cortex (PFC). By means of whole cell patch-clamp recordings, we analyzed changes in excitatory postsynaptic current (EPSC) amplitudes of layer V pyramidal neurons evoked by electrical stimulation in layer I/II during oxygen glucose deprivation (OGD), and their modulation by purinergic receptor-ligands. EPSC amplitudes in layer V neurons were enhanced under OGD in Mg^{2+}-free extracellular solution; this effect was abolished by Mg^{2+}, causing a block of NMDA receptors, and competitive NMDA receptor antagonists, such as AP5. Neither the non-selective P2 receptor antagonist PPADS nor the adenosine A_1 receptor antagonist DPCPX modulated OGD-induced increase of EPSCs. In contrast, the P2Y receptor agonist ADP-β-S abolished the effect of OGD; PPADS and DPCPX reversed EPSC depression caused by ADP-β-S. The effect of pressure applied NMDA was not facilitated by OGD. Therefore, we suggest that presynaptic NMDA receptors are involved. In conclusion, we have shown that in pyramidal neurons of the rat PFC under ischemic conditions, activation of A_1 and P2Y receptors inhibits the enhanced synaptic activity. We hypothesize, these receptors may be either co-localized or exist as heteromers exerting a cooperative pharmacological action to inhibit glutamate release.

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POSTER 269

The special structure of extracellular matrix in mice MNTB

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Tumor Targeting

In auditory brainstem the medial nucleus of the trapezoid body (MNTB) plays a major role for sound localization. It is well known that the principal cells of MNTB are innervated by only one large glutamatergic synapse, the calyx of Held. Furthermore, every neuron in MNTB is surrounded by a dense extracellular matrix.
This special type of extracellular matrix is the perineuronal net (PN). Many neurons in mature central nervous system are enwrapped by PNs, which build a lattice-like structure. They consist of large aggregating chondroitinsulphate proteoglycans connected to hyaluronan and tenascin-R. To date, little is known about the functions of PNs. Several evidences implicate that PNs are involved in stabilization of synapses, influence the outgrowth of axons and contribute to the micromilieu of neurons.
Therefore we investigated the structural appearance of PNs and the distribution of PN components. We observed a special appearance of the PNs in MNTB and found different distributions of the proteoglycans aggrecan and brevican arround the principal cells. While aggrecan surrounds the principal cell and the calyx of held, brevican ensheaths only the cell surface of the neuron and not the synapses.
Our results show a new und unique shape of the PNs in MNTB and give further evidences for potential functions.

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POSTER 270

The effect of structural modifications on the function of P2X3 receptors

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The trimeric P2X3 receptor (P2X3R) is an ATP-gated ion channel, situated on sensory neurons e.g. in dorsal root ganglia. The P2X3R is involved in pain sensation. For tapping a therapeutic potential of its ligands, a detailed knowledge about the receptor structure and function is required. Based on the zebrafish (z)P2X4R crystal structure, we generated a molecular dynamics model of the homologous P2X3R, which indicated movement within the ectodomain, where the agonist binding pouch is located. To prove the hypothesis of a potential relevance of this movement for receptor behaviour, we used a mutagenesis-based approach, by creating cysteine mutants of the recombinant P2X3R and expressing them in HEK293 cells.

By formation of a disulfide bond between two opposing cysteine residues in two neighbouring subunits, we expect to immobilize the receptor in one state of operation, resulting in loss of functionality. Therefore, several amino acids on neighbouring subunits were substituted by cysteine. The influence of the presumed disulfide bond on the functional consequences of ATP binding was measured by patch clamp recordings.

So far we have identified a promising double mutant candidate, consisting of two replaced lysine residues, which did not show any receptor activity. In a second step we removed the artificial disulfide bond by application of the reducing agent DTT for restoring the receptor mobility, resulting in an increase of the recorded current. By washing out DTT the current declined again, suggesting a spontaneously reoxidation of the thiols. So our simulation studies can be confirmed by the obtained experimental data.

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POSTER 271

Interaction of antagonists with the ATP binding pocket at the human P2X3 ion channel

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The homomeric P2X3 receptor (P2X3R) is a rapidly activating and desensitizing cation channel, gated by extracellular ATP. This representative of the P2X receptor family is highly expressed on sensory neurons and plays a major role e.g. in chronic pain, bladder reflexes and taste sensation. Therefore, the development of selective antagonists for P2X3R and knowledge about the binding of these antagonists are of great interest for future pain therapy and therapy of urge incontinence. To simulate the shape of the agonist-induced current responses, we created a specific Markov model to describe the binding of competitive antagonists. This model can be used to prove the competitive character of inhibition and to calculate the association and dissociation constants of the antagonists. Furthermore, we use this model to fit current responses at P2X3 wild type receptors and their mutants to α,β-meATP in the presence of different antagonists. Whole-cell patch-clamp recordings were performed on HEK 293 cells, heterologously expressing the human P2X3R, to determine the concentration-response relationship of different antagonists. By applying increasing concentrations, differences of antagonist potency could be observed at the wild type receptor. Based on our homology model of P2X3R we chose alanine substituted amino acid residues, which seem to be important for agonist binding and most likely for competitive antagonist binding as well. We intend to identify those amino acids which are important for competitive antagonist binding by monitoring the altered antagonist potency on the mutated receptor compared to the wild type receptor.

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POSTER 272

Subunit stoichiometry of P2X2/3 receptors

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Seven distinct ionotropic receptor subtypes have been cloned from mammalian species (P2X1-7). P2X subunits form not only homomeric receptor-channels, but also heteromers, composed of different subunits. Although a multitude of methodological approaches unequivocally indicate that three subunits constitute both homomeric and heteromeric P2X receptors, the subunit stoichiometry of the heteromeric receptors has been yet incompletely characterized. The present experiments were designed to investigate the subunit composition of the pain-relevant P2X2/3 receptors mostly located in sensory neurons of the dorsal root ganglion. For this purpose we generated non-functional Ala-mutants of P2X2 or P2X3 subunits and subcloned them into pIRES2-EGFP or pIRES-DsRed vectors (Bodnar et al., J. Biol. Chem., 286:2739-2749, 2011). Then, we transfected HEK293 cells either with a combination of WT-P2X2 and WT- or mutant-P2X3, or with WT-P2X3 and mutant-P2X2. Then, cells were selected under a fluorescence microscope exhibiting red/green fluorescence, indicating that both subunits have been expressed. Patch-clamp recordings and Ca^{2+} imaging experiments showed that a combination of WT-P2X3 with mutant-P2X2 had an only slightly decreased sensitivity towards the selective agonist a,b-methylene ATP (a,b-meATP), whereas the combination of WT-P2X2 with mutant-P2X3 was completely insensitive to this agonist. Thus, we concluded that the occupation of two binding sites are a pre-requisite for the a,b-meATP effect and that one P2X2 and two P2X3 subunits form heteromeric P2X2/3 receptors.

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POSTER 273

Age related analysis of enteric ganglia of human colon using laser microdissection

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1 TRM

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Objectives: The gut is a widely studied tissue, which is composed of distinct regions. These include muscle layers, nerval plexus and other tissues. Observations in human as well as rodent gut revealed an age-related reduction of enteric neurons, mainly within the myenteric plexus. In this study, we aimed to analyze age-dependent changes in the gene expression profile of the enteric nervous system, especially in the myenteric plexus. Therefore, we used the laser microdissection technique which has been proven as a feasible tool to analyze distinct cell populations within heterogeneously composed tissues.
Methods: Full wall-thickness gut samples were prepared from children and aged patients . 16 μm cryo-sections were mounted on membrane-coated slides and histologically stained. The ganglia of the myenteric plexus were identified and RNA was isolated from laser microdissected tissue. qRT-PCR was performed for cell specific neurotransmitters, receptors and proteins. Results: We investigate site-specific gene expression in postnatal and aged colon to detect alterations within the enteric nervous system. The results show a decrease of expression patterns of some neuronal genes within the myenteric plexus. Further we observed an increase of glial specific genes and muscle markers.Conclusion: Laser microdissection is feasible to analyze gene expression in the ENS of the human gut. Our results may be useful to get further insights into pathophysiological alterations in ENS during process of ageing.

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POSTER 274

Nanodomain coupling at the glutamatergic parallel fiber to Purkinje-cell synapse

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A key factor determining speed and fidelity of central nervous system processing is the distance between the site of Ca^{2+} influx and the sensor for vesicular transmitter release. Although tighter coupling allows for more rapid and reliable synaptic transmission (*1*), central excitatory synapses are thought to operate at relatively loose coupling between Ca^{2+} channels and release sensor (*2-5*). Yet, it is possible that tight coupling characterizes such glutamatergic synapses that are involved in rapid information processing. We tested this hypothesis at mature cerebellar parallel fiber (PF) to Purkinje cell (PC) synapse, the most abundant synapse in the vertebrate CNS. Combining multiple-probability fluctuation analyses from paired electrophysiological recordings, presynaptic Ca^{2+} imaging and numerical simulations we provide evidence for a coupling distance of ~25 nm at PF-terminals, much tighter than at any other excitatory cortical synapse investigated to date.

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POSTER 275

The knockout of the extracellular matrix protein Tenascin-R effects the distribution of Aggrecan and Phosphacan within perineuronal nets of the Medial Nucleus of the Trapezoid Body

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The extracellular matrix (ECM) of the vertebrates' brain differs from that of other organs by the absence of collagen and elastin fibers. Therefor a predominance of chondroitin sulfate proteoglycans (CSPG) such as Aggrecan, Brevican or Phosphacan can be observed. In complex with Tenascin-R, hyaluronic acid and link proteins these CSPG form the brain's ECM. Perineuronal nets (PNs) display a specialized phenotype of ECM ensheathing selected neuron populations of the central nervous system in a lattice-like manner. PNs are assumed to be involved in regulation of extracellular ion homeostasis as well as in processes of neuronal plasticity.
In this study we investigated the effect of the loss of Tenascin-R on the spatial structure and localization of further PNs components enwrapping the principal cells of the Medial Nucleus of the Trapeziod Body (MNTB). The MNTB serves as an excellent model since all neurons are net-wearing and additionally surrounded by a single giant synapse called "The Calyx of Held" which furthermore provides an insight into the spatial interaction between PNs and synaptic contacts.
Due to electron and fluorescence microscopic analyses it could be demonstrated that the knockout leads to an anomalous distribution of the large CSPG Aggrecan and a decreased immune detectablility of Phosphacan compared to PNs of wildtyp mice. This emphasizes the function of Tenascin-R as a spacer molecule binding the CSPG and hence controlling their arrangement within the perineuronal nets.

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POSTER 276

TEMPORAL REGULATION OF ENDOCANNABINOID LEVELS IN OHSC AFTER PERFORANT PATHWAY TRANSSECTION

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Endocannabinoids (eCB) are involved in the preservation of the homeostatic and regulatory balance within the central nervous system. The potency of eCBs to control neuronal cell death and immune reactions, associated with secondary neuronal damage has recently been shown. Temporal regulation of eCBs at different lesion sites still needs investigation to fully understand their role during brain pathologies. The perforant pathway transection (PPT) in organotypic hippocampal slice cultures (OHSC) reflects a well established model to investigate denervation-induced gliosis, transneuronal degeneration and plasticity-related changes in the hippocampal formation. In the present study, entorhinal cortex (EC), dentate gyrus (DG) and cornu ammonis region 1 (CA1) were dissected from OHSC 0, 1, 6, 12, 24, 48 and 72 hours after PPT and the eCB levels were measured by LC/MS-MS. All investigated eCBs displayed a temporal variability in the DG of lesioned OHSC in relation to untreated control OHSC. The levels of palmitoylethanolamide, arachidonoylethanolamide, oleoylethanolamide and 2-arachidonoylglycerol were maximally increased 24 hours after PPT and decreased to control levels 48 hours after PPT. In addition, only 2-arachidonoylglycerol was increased 6h post lesion (hpl) in the EC. Our data demonstrate an intrinsic activation of the eCB system within 24 hours after the induced damage, indicating a defined temporal activation of the endocannabinoid system.

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POSTER 277

Importance and development of interneurons that corelease GABA and glycine in the respiratory network

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DNA recombination technologies such as the Cre/LoxP system have advanced and refined the analysis of gene and cell functions *in vivo*. By driving the expression of Cre recombinase under the control of a cell type-specific promoter, a cell type-specific modification of genes can be achieved. However, the precision of a single promoter driving Cre expression might not be sufficient to target a specific cell population. In the split-Cre system DNA recombination is controlled by coincidental activity of two promoters, thereby increasing spatial specificity of Cre-mediated DNA recombination. This system is now used to identify and characterize a special neuron group that coreleases GABA and glycine. Cotransmitting interneurons can be found in many different brain regions. Especially in the respiratory centre of the brain stem, little is known about the function of these inhibitory interneurons and their influence in development and maturation of the rhythm-generating circuitry as well as associated pathologies, such as Sudden Infant Death Syndrome. Using the advantages of split-Cre *in vivo*, we want to generate a transgenic mouse model and mark cotransmitting neurons irreversibly to simplify detection and further investigations. To achieve this, the expression of NCre is driven by a promoter typical for GABAergic neurons (GAD65) and the expression of CCre is controlled by a promoter typical for glycinergic neurons (GlyT2). After split-Cre complementation and recombination, a reporter can be visualized in cotransmitting neurons. Further characterisation will be done using electrophysiology, immunhistochemistry and single cell PCR.

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POSTER 278

Glial but not neuronal osmotic cell volume regulation in the inner nuclear layer of the rat retina

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Tumor Targeting

Intense neuronal activity in the retina is associated with a decrease in the osmolarity of the extracellular space fluid (Dmitriev et al., 1999, Vis. Neurosci. 16:1157-1167). We compared the osmotic and receptor-mediated regulation of the volume of Müller and bipolar cell somata in acutely isolated slices of the rat retina. Superfusion of retinal slices with a hypoosmotic extracellular solution induced swelling of bipolar cell somata but not of Müller cell somata. Exposure of the slices to a hypoosmotic solution containing barium ions induced swelling of both Müller cell and bipolar cell somata. The hypoosmotic swelling of Müller cell somata was blocked by administration of VEGF, glutamate, ATP, and adenosine, respectively. In contrast, these receptor agonists did not block the hypoosmotic swelling of bipolar cell somata. It is suggested that Müller cells but not bipolar cells possess endogenous cell volume-regulatory mechanisms which prevent cellular swelling under hypoosmotic conditions.

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POSTER 279

Expression of estrogen receptors α and β in the trigeminal mesencephalic nucleus of adult woman and man

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Temporomandibular disorders are more prevalent in women than in men and phases of pain relate to the estrous cycle. Several studies described the location of estrogen receptors (ER) in the temporomandibular joint, the masseteric muscles and cartilage, but it was unknown whether they are also expressed within the pseudounipolare sensory neurons of the trigeminal mesencephalic nucleus which receives input from these structures. Therefore, we studies expression of ER α and β in ten human brains of body donators (five female/ five male). Both receptors were uniformly expressed on neurons, but not other cells in the target structure. Thus, we provide a possible link between the observed relation between phases of pain and the estrous cycle.

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POSTER 280

Establishment of a transgenic mouse model with an astrocyte-specific deletion of the cell adhesion protein vinculin

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Tumor Targeting

To analyze the role of vinculin in astrocytes *in vivo*, we generated a transgenic mouse model allowing inducible astrocyte-specific inactivation of vinculin by using Cre-loxP technology. Genotyping of single astrocytes isolated from different brain regions demonstrated successful recombination of the floxed vinculin gene *in vivo*. Quantitative PCR showed a decrease of vinculin mRNA, while quantification of fluorescence images of single cells revealed the absence of vinculin in astrocytes in the knockout animals. To analyze the impact of vinculin deficiency, expression and localization of proteins involved in astroglial function were tested by immunohistochemistry. Numerous proteins were not affected by the loss of vinculin including the gap junction protein connexin43. Also marker proteins for reactive astrocytes like GFAP and vimentin showed no change in expression or localization in the knockout animals. In contrast to *in vitro* studies, our surprising results suggest that vinculin is much less important for proper astrocyte function in mice *in vivo* and add a note of caution on the extrapolation of *in vitro* data to *in vivo* function.

Association: PbF IV

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POSTER 281

Selbstverletzendes Verhalten und Stresserleben bei Jugendlichen

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Selbstverletzendes Verhalten (SVV) stellt ein häufig zu beobachtendes Problemverhalten im Kindes- und Jugendalter dar, dessen Ursachen sehr vielfältig sind. Studien von Brunner et al. (2007) und Plener et al. (2009) zufolge zeigen 15% - 26% der Jugendlichen Selbstverletzendes Verhalten.
Ziel dieser Studie ist, einen möglichen Zusammenhang zwischen Selbstverletzendem Verhalten mit dem Stresserleben sowie den Stressbewältigungskompetenzen Jugendlicher zu untersuchen. Zudem sollen mögliche Geschlechts- sowie schultypische Unterschiede analysiert werden.
Mit Hilfe des „Wie ich mit Stress umgehe" Fragebogens (WIMSU; Keller et al., 2009) sowie einer adaptierten Form des Ottawa/Ulm Selbstverletzungs-Inventars (OUSI; Fegert, et al, 2005) wurden 418 Leipziger Schüler (168 weiblich, 249 männlich) im Alter zwischen 12 und 19 Jahren (M=15,2; SD=1,2) zu ihrem Umgang mit Stress und zu Selbstverletzendem Verhalten befragt.
14,3% aller Befragten gaben an, sich schon einmal selbst verletzt zu haben. Dabei zeigte sich eine signifikante Korrelation zwischen Selbstverletzendem Verhalten und Stresserleben. Tendenziell berichteten mehr Mädchen von Selbstverletzendem Verhalten. Zudem zeigten sich Unterschiede zwischen den Schultypen Gymnasium und Mittelschule dahingehend, dass mehr Schüler der Mittelschule von Selbstverletzendem Verhalten berichteten.
In Übereinstimmung mit früheren Befunden (Keller et al., 2009) zeigt sich erneut, dass Selbstverletzung der Stressbewältigung zu dienen scheint, so dass an dieser Stelle mögliche Präventionsmaßnahmen ansetzen sollten.

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POSTER 282

Ängstlichkeit und Depressivität krebskranker Väter von minderjährigen Kindern – Eine Längsschnittanalyse

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Hintergrund: Erkranken Mütter oder Väter mit minderjährigen Kindern an Krebs, kann dies weitreichende Auswirkungen auf das gesamte Familiensystem haben. Bislang gibt es keine längsschnittlichen Studien zur Belastungssituation und zum Versorgungsbedarf von an Krebs erkrankten Vätern. Methode: Die Studie untersuchte Ängstlichkeit und Depressivität von krebskranken Vätern (Hospital Anxiety and Depression Scale (HADS-D)) deskriptiv sowie mittels des Allgemeinen Linearen Modells (mit Messwiederholung). Kontrolliert wurden soziodemografische und krankheitsspezifische Faktoren sowie die Belastungen der Partnerinnen und Kinder. Es wurden 37 an Krebs erkrankte, zumeist in einer Partnerschaft lebende Männer im Alter von 28-55 Jahren mit mindestens einem Kind unter 18 Jahren nach der Akutbehandlung (T1) sowie ein halbes Jahr danach (T2) schriftlich befragt und einer Vergleichsgruppe aus der Allgemeinbevölkerung gegenüber gestellt. Ergebnisse: Im Vergleich mit Männern gleichen Alters aus der Allgemeinbevölkerung zeigte sich zu T1 eine erhöhte Belastung auf beiden Subskalen (Ä: 6.5 vs. 4.6, $p<0.05$/ D: 5.1 vs. 4.8, n.s.). Zu T2 war ein tendenzieller Rückgang der Belastung zu verzeichnen, es bestanden keine Unterschiede zur Allgemeinbevölkerung mehr ($p>0.05$). Belastungssteigernd wirkten die Faktoren: Zeitpunkt seit Diagnosezeitpunkt <6 Monate, belastete Partnerin und Erwerbslosigkeit. Diskussion: Die Studie verdeutlicht eine hohe Belastung der Väter am Krankheitsbeginn. Der Zusammenhang mit der Belastung der Partnerin impliziert eine familienorientierte Sichtweise hinsichtlich psychosozialer Krankheits- und Therapiefolgen.

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POSTER 283

The concept of ‚vegetative depression' (1949) by Rudolf Lemke

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Background: In primary care you often see cases of depression in which somatic or vegetative symptoms dominate the clinical picture compared to other rather typical complaints of low mood or a loss of interest. Over the years, several concepts, like the "masked depression" or the "depressive equivalent", have been developed in order to explain these responses. One of the first, nearly forgotten concepts, however, was the "vegetative depression" by East German psychiatrist Rudolf Lemke from 1949, describing an anxious depression due to a vegetative dysfunction. Furthermore the poster shows the historical development towards current systems of classification.
Methods: The strengths and weaknesses of Lemke's concept will be analysed with particular reference to earlier, similar theories and subsequent reviews.
Conclusions: The fact that, due to the dominance of physical symptoms, many patients suffering from this disease consult a general practitioner even today proves that Lemke dealt with a problem most significant both for psychiatry and general medicine.

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POSTER 284

Sensation Seeking und körperliche Aktivität

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Das Persönlichkeitsmerkmal Sensation Seeking zeichnet sich durch das Vermeiden von Langeweile und die Suche nach Spannung, Abwechslung und neuen Erlebnissen aus. Nach Zuckerman (1974) hat jeder Mensch ein individuell optimales Stimulations- und Erregungsniveau, das zum Wohlbefinden beiträgt. Die körperliche bzw. sportliche Betätigung gilt dabei als Möglichkeit, dieses Niveau zu erreichen bzw. aufrechtzuhalten.
Ziel dieser Studie war die Untersuchung des Zusammenhangs zwischen der Ausprägung von Sensation Seeking und der objektiv bestimmten körperlichen Aktivität.
51 gesunde, normalgewichtige Probanden im Alter von 18 bis 59 Jahren nahmen an dieser Studie teil. Die körperliche Aktivität wurde mittels Aktometer für durchschnittlich sechs Tage aufgezeichnet. Die Ausprägung des Persönlichkeitsmerkmals Sensation Seeking wurde mit Hilfe des Arnett Inventory of Sensation Seeking (AISS) erfasst, welches keinerlei sportspezifische Items enthält.
Das Ausmaß der körperlichen Aktivität korrelierte positiv mit hohen Werten der Gesamtskala des AISS und der Subskala Intensität ($p < .05$). Für die Subskala Neuigkeit wurde kein Zusammenhang ermittelt. Das Ergebnis bestätigt bisherige Erkenntnisse bezüglich des Zusammenhangs zwischen Sensation Seeking und subjektiv berichteter körperlicher Aktivität bzw. berichtetem sportlichem Interesse.
Referenz:Zuckerman M: The sensation seeking motive. Prog Exp Pers Res 1974, 79-148.

Funding: IFB

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POSTER 285

Clock Drawing Test: Screening utility for Mild Cognitive Impairment according to different scoring systems

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Background: There is a strong demand for screening instruments for mild cognitive impairment (MCI), as a pre-stage of dementia. The clock drawing test (CDT) is widely used to screen for dementia, but the utility in screening for MCI is discussed controversially. In particular, it is still questionable which scoring system is the best in order to screen for MCI. We therefore aim to compare the utility of different CDT scoring systems for screening for MCI.
Methods: In a sample of 428 subjects of the Leipzig Longitudinal Study of the Aged (LEILA 75+) study, CDT scores of different scoring systems were compared between subjects with and without MCI. Comparison of receiver operating characteristic (ROC; area under the curve, sensitivity, specificity) was performed and inter-rater reliability was calculated.
Results: The CDT scores differed significantly between MCI and non-MCI subjects according to all scoring systems applied. However, ROC of the CDT scores was not adequate.
Conclusions: None of the present CDT scoring systems has sufficient utility to reliably screen for MCI. The clinical value of the CDT could be improved by having a semiquantitative scoring, a wider score range and focusing on specific details of the clock like the hands and numbers.
Grant sponsor: junior research grant by the Medical Faculty, University of Leipzig.

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POSTER 286

Evaluation eines Theater-Projektes: „Vorhang auf!“

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Welchen Beitrag zur Gesundheitsförderung bei Kindern und Jugendlichen kann ein Theaterprojekt leisten? Diese Frage soll die Evaluation des Theaterprojektes „Vorhang auf!“, das 2010 in Leipzig vom Theaterverein K ins Leben gerufen wurde, klären. Der vorliegenden Arbeit liegt die Annahme zugrunde, mit einem Theaterprojekt auch bei Kindern und Jugendlichen die gesundheitliche Entwicklung fördern zu können, denn die potentiell heilende Wirkung des Theaterspiels ist spätestens seit der Entstehung des Psychodramas nach J.L. Moreno bekannt. In einer umfassenden, über 18 Monate angelegten Prä-Post-Studie wurde mit Hilfe psychodiagnostischer Selbstbeurteilungsverfahren (u.a. Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen , Grob & Smolenski (2005); Trierer Inventar zum chronischen Stress,Schulz, Schlotz & Becker (2004); Trierer Persönlichkeitsfragebogen, Becker (1989)) die Entwicklung der wichtigsten Ressourcen der seelischen Gesundheit im Kindes- und Jugendalter eingeschätzt. Dabei wurde untersucht in wie weit Selbstwert, psychosoziale Ressourcen, Stressbewältigung, Emotionsregulation und Wohlbefinden durch die Teilnahme am Theaterprojekt positiv beeinflusst und gefördert werden. Das Ziel der Arbeit bestand darin, durch den Vergleich mit einer Kontrollgruppe, die gesundheitsförderliche Wirkung des Theaterspielens sichtbar zu machen.
Dabei zeigten sich positive Effekte in den Bereichen Seelische Gesundheit, Beschwerdefreiheit, Wohlbefinden, Emotionsregulation und Stressbewältigung. Aus den Ergebnissen kann auf einen positiven Einfluss der Theaterarbeit auf die Persönlichkeitsentwicklung und die Herausbildung von Kompetenzen der seelischen Gesundheit geschlossen werden.

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POSTER 287

Wie profitieren Multiplikatoren von einer Schulung zu Depression und Suizidalität? Wissen und Einstellungen im Prä-Post-Vergleich

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Hintergrund: Sowohl bei Berufsgruppen im Gesundheitssystem als auch außerhalb bestehen Wissensdefizite zu Depression und Suizidalität. Es zeigt sich aber, dass das Wissen und die Einstellungen zu Depression und Suizidalität sowie das Selbstvertrauen und die Fähigkeiten zu Management von Suizidalität bei verschiedenen Multiplikatorengruppen durch Schulungen verbessert werden können. Ziel der Studie ist ein Prä-Post-Vergleich von Wissen und Einstellungen zu Depression und Suizidalität bei Multiplikatoren mit und ohne klinischen Hintergrund nach der Teilnahme an einer Schulung zu Depression und Suizidalität.
Methode: 2009/2010 wurden in Leipzig Schulungen zu Depression und Suizidalität durchgeführt. Die Stichprobe umfasst 867 Multiplikatoren, davon 407 klinische (Altenpfleger, Hebammen, Sozialarbeiter, Berater, Praxisangestellte) und 460 nichtklinische (Apotheker, Pfarrer, Polizisten, Lehrer, Verwaltung). Die Teilnehmer wurden vor Beginn, direkt nach Abschluss der Schulung sowie 4 Monate nach der Teilnahme befragt. Erhoben wurden neben soziodemografischen Daten die Persönliche Einstellung zu Depression sowie Wissen über Depression.
Ergebnisse: Sowohl für Stigmawerte als auch Wissenswerte zeigen sich signifikante Verbesserungen nach der Teilnahme an der Schulung. Diese Verbesserungen können aber im Follow-up nicht beibehalten werden.
Diskussion: Multiplikatoren profitieren von der Teilnahme an einer Schulung zu Depression und Suizidalität. Damit konnten frühere Ergebnisse bestätigt werden. Es zeigt sich trotzdem, dass die Effekte nicht nachhaltig sind. Eine weitere Schulung nach 3 Monaten könnte die Ergebnisse verbessern.

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POSTER 288

Influence of display time on the competition for processing resources with emotional pictures

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We examined to what extent color and display time modulate the guidance of attention to emotional pictures. To this end we presented flickering dots superimposed upon neutral and unpleasant black-and-white pictures from the International Affective Picture Set (IAPS) and from the Emotional Picture Set (EmoPicS). The flickering dots elicited a steady-state visual evoked potential (SSVEP). Subjects were instructed to attend the dots in order to detect coherent motion targets while ignoring the background pictures. Additionally, the pictures were displayed once for 2000 ms and once again for 133 ms with a following masking of the pictures. The SSVEP amplitude decreased for unpleasant compared to neutral pictures, but only for a long presentation duration. Furthermore, we found the early posterior negativity (EPN) for both long and short presented neutral and unpleasant pictures. In conclusion, task-irrelevant black-and-white pictures captured attention if they were presented for a long time. However, the emotional content of both the long and short presented pictures were processed as indexed by the EPN.

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POSTER 289

Depression als Risikofaktor für die Entwicklung von Demenzen und leichter kognitiver Beeinträchtigungen - Eine systematische Übersichtsarbeit

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Einleitung
Unterschiedliche Ansätze zum Zusammenhang von Depression und Demenz gehen davon aus, dass Depression ein Prodrom der Demenz sein kann oder dass depressive Verstimmungen als Folge eines dementiellen Syndroms auftreten könnten. Das Ziel der vorliegenden Übersichtsarbeit ist die Untersuchung depressiver Erkrankungen als Risikofaktor für die Entwicklung einer Demenz oder leichter kognitiver Störungen im höheren Lebensalter.
Methoden
Es wurde eine systematische Literaturrecherche durchgeführt, um Studien herauszufiltern, welche den Zusammenhang zwischen Depression und Demenz untersuchen. Die Suche wurde in den Datenbanken Pubmed, Web of Science, Cochrane Library und PsyndexPlus durchgeführt. Dabei wurden nur Langzeitstudien in die Übersichtsarbeit einbezogen, welche Depression als Risikofaktor für dementielle Erkrankungen bzw. leichte kognitive Beeinträchtigungen betrachteten.
Ergebnisse
Die Literaturrecherche ergab 14 Studien, welche die festgelegten Kriterien erfüllten. Von den zehn Studien, welche als Outcome eine Demenzerkrankung definierten, konnte ein Großteil die Hypothese, Depression sei ein Risikofaktor für Demenz, bestätigen. Nur drei Studien fanden keinen Zusammenhang zwischen beiden Syndromen. Von den übrigen vier Studien, welche leichte kognitive Beeinträchtigungen als Outcome betrachteten, konnten drei Studien Depression als Risikofaktor nachweisen.
Diskussion
Insgesamt legen die Ergebnisse den Schluss nahe, dass depressive Syndrome als Risikofaktor für spätere Demenz und leichte kognitive Beeinträchtigungen gelten können.

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POSTER 290

Alexithymie und automatische Wahrnehmung emotionaler Informationen: eine funktionelle Bildgebungsstudie mit Multi-Methoden-Ansatz

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Alexithymie geht einher mit Defiziten in der Verarbeitung von emotionalen Informationen. Bisher konzentrierte sich die neurobiologische Erforschung des Persönlichkeitsmerkmals vorwiegend auf Defizite in der kontrollierten Verarbeitung emotionaler Stimuli. Neuere bildgebende Studien zeigen allerdings, dass die Hirnaktivierung in Reaktion auf emotionale Information bereits auf einer automatischen Ebene bei Alexithymen verringert ist. Die diesen Phänomenen zugrunde liegenden Mechanismen sind jedoch noch ungeklärt.
Ziel der vorliegenden Studie ist die Untersuchung der automatischen neuronalen Responsivität auf emotionalen Gesichtsausdruck in Abhängigkeit der Ausprägung von Alexithymie. Mittels einer affektiven Primingaufgabe, bei der maskierte emotionale Gesichter kurz präsentiert werden, sollen implizite evaluative Prozesse und deren neuronale Korrelate untersucht werden.
Bisherige Studien nutzten fast ausschließlich ein methodisch häufig kritisiertes Selbstbeurteilungsverfahren, die Toronto-Alexithymia-Scale (TAS-20) zur Messung von Alexithymie. In dieser Studie wird ein Multi-Methoden-Ansatz verwendet: neben der TAS-20 werden erstmals ein Interviewverfahren (Toronto Structured Interview for Alexithymia, TSIA) sowie ein performanzbasiertes Verfahren (Levels of Emotional Awareness Scale, LEAS) parallel eingesetzt. Somit kann geprüft werden, welches der Verfahren eine bessere Vorhersage der neuronalen Responsivität auf emotionale Gesichter ermöglicht. Ängstlichkeit und Depressivität werden erfasst und als Kovariate in die Datenanalysen einbezogen. Die Untersuchung soll an 50 gesunden, jungen Erwachsenen durchgeführt werden.

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POSTER 291

Evaluation der Impact of Event Skala – revidierte Version

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Hintergrund: Eines der am häufigsten eingesetzten Selbsteinschätzungsinstrumente für die Erforschung und Diagnostik der posttraumatischen Belastungsstörung (PTBS) ist die Impact of Event Scale - Revised (IES-R). Für die deutsche Version und einer aus ihr entwickelten Formel für die Prädiktion der PTBS liegen bisher nur wenige Befunde vor.
Fragestellung: Die Qualität der deutschen Version der IES-R soll durch Überprüfung von Reliabilität, faktorieller Validität und diagnostischer Sensitivität eingeschätzt werden.
Methodik: Es wurden die Daten einer Patientenkohorte der HELIOS Klinik Bad Grönenbach (N = 5719) analysiert. Für einen Teil der Fälle wurde das Vorliegen einer PTBS nach ICD-10 durch ausgefüllte Diagnose-Checklisten validiert (N = 114), für einen anderen Teil geschah dies durch Abgleich mit den Patientenakten (N = 235).
Ergebnisse: Die Reliabilitäten (Cronbachs Alpha) lagen im Bereich von .80-.89. Es wurde eine 4-Faktoren-Lösung ermittelt, wovon 3 Faktoren annähernd den Subskalen entsprechen und 1 Faktor dem Merkmal „emotionale Abstumpfung“ (Numbing). Die Überprüfung der diagnostischen Vorhersage ergab richtige Zuordnungen bei 57.3-59.7% der Fälle und niedrige Zusammenhänge zwischen Vorhersage und tatsächlicher Diagnose.
Schlussfolgerungen: Die Reliabilitäten sind zufriedenstellend. Die Skalenstruktur der IES-R konnte nur eingeschränkt bestätigt werden, denn die Ergebnisse sprechen für Numbing als eigenständigem Symptombereich traumatischer Belastung. Die Prädiktionsformel erwies sich für die klinische Anwendung als zu ungenau.
Schlüsselwörter: Posttraumatische Belastungsstörung, Diagnostik, Psychometrie

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POSTER 292

Ergebnisse der Burn out Screening Skalen (BOSS) bei Lehrern, Existenzgründern und Studierenden

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Problemstellung
Der BOSS ist ein neues psychodiagnostisches Verfahren zur Messung von Burnout Bereichen und Schweregraden des Burnout. Er ist für gefährdete Berufsgruppen und zur allgemeinen Belastungsdiagnostik vorgesehen. Mit dem von Hagermann & Geuenich (2009) entwickelten Verfahren liegen bisher keine Anwendungsstudien vor. Gleichzeitig sollte durch den Einsatz von konstruktnahen Verfahren und Beschwerdefragebögen eine differentielle Befundskizze zur Ausprägung von Burn out bei Lehrern, Existenzgründern und Studierenden erhoben werden.
Methodik
In einer Fragebogenstudie an 115 Vpn. (41 Studierende, 37 Lehrer, 37 Existenzgründer) wurden folgende Fragebogen vorgegeben: BOSS I und II, Beschwerdeskala nach Ducki, TICS, LKCS, Selbstwirksamkeits-Skala, Lebenszufriedenheit und selbsteingeschätzter Gesundheitsstatus sowie das Gesundheitsverhaltensmuster.
Ergebnisse
Die standardisierten Fragebögen (TICS, BOSS, LKCS, Skala Selbstwirksamkeit, Beschwerden) liefern eine Beschreibung der Belastungsmerkmale in den drei Stichproben. Die Häufigkeiten der Hauptbelastungen und Symptombildungen werden berichtet. Es zeigte sich, dass die Lehrerstichprobe die höchsten Belastungen aufwies, hingegen die Existenzgründerstichprobe erstaunliche gesundheitliche Robustheit aufwies und diese Schutzfaktoren auch im eigenen Gesundheitsverhalten stabilisierten.
Differentielle Aussagen ergaben sich auch aus dem BOSS.

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POSTER 293

Wirksamkeit einer Internet-basierten Psychotherapie für Eltern nach dem Verlust eines Kindes während der Schwangerschaft (RCT)

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Der Verlust eines Kindes während der Schwangerschaft ist – trotz hoher Prävalenzen und weitreichenden Folgen für die psychische Gesundheit – ein Bereich, in dem spezifische psychologische Unterstützung für die Betroffenen häufig nicht verfügbar ist. Daher untersucht diese Studie – aufbauend auf den positiven Ergebnissen einer Pilotstudie – die Wirksamkeit eines Internet-basierten Therapieprogramms für betroffene Eltern im deutschsprachigen europäischen Raum. In der randomisierten Kontrollgruppenstudie wurden die TeilnehmerInnen zufällig entweder einer Internet-basierten Behandlung oder einer Wartelistenbedingung zugeordnet. Während der 5-wöchigen manualisierten kognitiv-behavioralen Therapie schrieben sie insgesamt 10 Texte über ihr Verlusterlebnis, auf die sie nach jedem zweiten Text ein individuelles Feedback erhielten. Die TeilnehmerInnen der Kontrollgruppe durchliefen im Anschluss an die Wartezeit die gleiche Behandlung. Es wurden Prä- und Post-Messungen, ein 3-Monats- und ein 12-Monats-Follow-up durchgeführt. Die TeilnehmerInnen der Behandlungsgruppe zeigten, verglichen mit den TeilnehmerInnen der Wartelistenbedingung, signifikant stärkere Verbesserungen hinsichtlich komplizierter Trauer, posttraumatischem Stress, Depression und allgemeiner psychischer Gesundheit. Für diese Skalen ergaben sich mittlere bis starke Effekte und die erreichten Ergebnisse blieben über die Zeiträume der Follow-ups stabil. Diese Ergebnisse zeigen, dass das Internet-basierte Behandlungsprogramm einen wichtigen Beitrag dazu leisten kann, die Versorgungssituation für Eltern zu verbessern, die während der Schwangerschaft ihr Kind verloren haben.

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POSTER 294

Überprüfung der Validität des MWT-A zur Schätzung des prämorbiden Intelligenzniveaus bei Demenz

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In der Intelligenzforschung wird zwischen fluider (Denkmechanik, logisches Denken) und kristalliner Intelligenz (Wissen, Wortschatz, etc.) unterschieden. Letztere Intelligenzkomponente hat sich als relativ unabhängig gegenüber aktuellen kognitiven Leistungsminderungen aufgrund von Alter oder hirnpathologischen Prozessen erwiesen. Tests zur Messung der kristallinen Intelligenz gelten daher als geeignete Methode zur Schätzung des prämorbiden Intelligenzniveaus. Dieses stellt in der neuropsychologischen Diagnostik ein unerlässliches Diagnostikum zur Interpretation von aktuellen Leistungsminderungen eines Patienten dar. Im deutschen Sprachraum hat sich der sogenannte Mehrfach- Wortschatz- Intelligenztest (MWT; Lehrl et al. 1971) zur Schätzung des prämorbiden Intelligenzniveaus bei dementiellen Erkrankungen etabliert. Klinische Beobachtungen und die Untersuchungsergebnisse bezüglich ähnlicher englischsprachiger Verfahren (z.B. National Adult Reading Test oder Spot-The-Word-Test) ließen jedoch die Vermutung aufkommen, dass der MWT mit zunehmender Demenzschwere das prämorbide Intelligenzniveau zunehmend unterschätzt. Zur Überprüfung dieser Hypothese wurden die im Rahmen der Gedächtnissprechstunde Klinik und Poliklinik für Psychiatrie und Psychotherapie der Universität Leipzig im Zeitraum von 2005 bis 2010 routinemäßig erhobenen Patientendaten in Bezug auf die Testergebnisse des MWT Version A (MWT-A) ausgewertet. Vorläufige Analysen ergaben erwartungsgemäß, dass Schätzungen des prämorbiden Intelligenzniveaus von der Demenzschwere abhängen, was die Validität und Anwendbarkeit des MWT-A in der Demenzdiagnostik in Frage stellt.

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POSTER 295

Attentional processing within and across hemifields

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It has been asked whether the hemispheres carry two distinct attentional processing systems, or whether there is one common resource. The bilateral field advantage in parallel attentional processing suggests that there exist two functionally independent resources with limited capacity. Earlier studies show that it is easier to split attention across than within hemifields. However, results from previous studies regarding spatial resolution in the upper versus lower visual field are conflicting. To contribute to this ongoing debate, the aim of this study was to investigate effects of attention and mutual competition between multiple stimuli located across the visual field. Subjects had to perform a luminance change discrimination task on one of several possible pairs of flickering LEDs located in same/different hemifields. Each LED elicited a distinct steady-state visual evoked potential (SSVEP), which we recorded using electroencephalogram. SSVEPs are very robust brain-signals, and oscillate at the same frequency as the driving stimulus. They are known to be modulated by attention, and it is also possible to investigate competitive interactions of the flickering LED-stimuli within and between hemifields. We evaluated behavioural data and SSVEP-signals when subjects had to discriminate between stimuli in the within and between hemifield-conditions, and investigated the influence of top-down attention on the competing stimuli.

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POSTER 296

Emotional words modulate language processing but not early visual attention

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In numerous behavioural, imaging and event-related potential (ERP) studies, emotionally arousing words have been shown to be processed differently than neutral words. Nonetheless it is still unclear whether they attentionally impact early visual processing in the same way as other types of affective stimuli such as faces or scenes.
In the current study, nouns of neutral, negative and positive valence were presented as task-irrelevant background stimuli while participants performed a motion detection task on an array of randomly moving dots superimposed on the words. The dots flickered at 15 Hz, thereby eliciting a steady-state visual evoked potential (SSVEP). Unlike previous studies using arousing pictures, emotional words did not produce strong modulations of hit rates, reaction times or SSVEP amplitudes related to the dot-cloud task. In contrast, the ERPs differed for emotional and neutral words starting around 200 ms after word onset.
We conclude that visually presented emotional words do not attract attentional processing resources in early visual areas in the same way as non-symbolic, directly arousing stimuli do. The effects of word affect on the P2 and subsequent ERP components reflect modulations of language processing stages that do not necessarily compete with sensory processing.

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POSTER 297

Berufliche Rehabilitation nach totaler Kehlkopfoperation

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Hintergrund:
Der berufliche Wiedereinstieg nach einer totalen Kehlkopfentnahme stellt für die Betroffenen eine besondere Herausforderung dar. Durch den Organverlust leiden die Patienten unter großen gesundheitlichen Einschränkungen wie dem Verlust der Stimme, erschwerter Atmung oder Problemen bei Riechen und Schmecken.
Vor diesem Hintergrund ergeben sich folgende Fragestellungen:
Wie verändert sich die Arbeitssituation der Patienten nach totaler Kehlkopfoperation?Welche Faktoren sind mit einer erfolgreichen beruflichen Rehabilitation assoziiert?
Methoden:
Im Rahmen der Studie „Multizentrische Untersuchung der psychosozialen Situation laryngektomierter Karzinompatienten und deren Angehörigen“ werden seit dem Jahr 2005 laryngektomierte Patienten und deren Angehörige aus dem mitteldeutschen Raum in persönlichen Interviews befragt. Diese Interviews finden zu insgesamt sechs Messzeitpunkten statt (t1= präoperativ; t2 = 2 Wochen postoperativ; t3 = 12 Wochen postoperativ; t4 = 1 Jahr postoperativ, t5 = 2Jahre postoperativ, t6= drei Jahre postoperativ). Die Ergebnisse beziehen sich auf Antworten von 117 Personen, die zum Zeitpunkt der Befragung unter 65 Jahren alt waren und sowohl zum Zeitpunkt t1 als auch zum Zeitpunkt t5 an der Befragung teilgenommen haben.
Verwendete Instrumente sind der Lebensqualitätsfragebogen der European Organization of Research and Treatment of Cancer (EORTC QLQ-C30), Postlaryngektomie-Telefon-Verständlichkeitstest (PLTT), Einzelfragen (finanzielle Situation), soziodemographische (Alter, Beruf) und medizinische Daten (Inanspruchnahme einer Rehabilitation).
Ergebnisse:
Etwa ein Viertel (23%) der Patienten sind vor der Operation berufstätig. Nach 2 Jahren gehen weniger als die Hälfte (11%) dieser Patienten wieder ihrem/einem Beruf nach. Der Anteil der Patienten, die für den Arbeitsmarkt nicht länger zur Verfügung stehen (aufgrund von Alters- oder Erwerbsminderungsrente) steigt von 50 % (t1) auf 77% (t5) an. Die berufstätigen Patienten leiden zum Zeitpunkt t5 vermehrt unter körperlichen Einschränkungen.Der erfolgreiche Wiedereinstieg hängt maßgeblich von der beruflichen Stellung (p=0,01*) und dem Alter (0,001*) des Patienten ab. Berufstätige

können sich signifikant besser mit der Ersatzstimme verständigen (0,02*) und geben geringe Einschränkungen im Bereich des körperlichen Befindens an (p=0,003*). Es besteht der Wunsch nach einer Verbesserung der finanziellen Situation (p=0,003*). Die Inanspruchnahme einer medizinischen Anschlussrehabilitation zeigt keinen signifikanten Einfluss (p=0,89) auf den erfolgreichen beruflichen Wiedereinstieg.
Schlussfolgerung:
Die dargestellten Ergebnisse zeigen, dass besonders Menschen die berufsbedingt in Arbeitbereichen mit körperlicher Belastung arbeiten, Probleme beim Wiedereinstieg in das Berufsleben haben. Jedoch werden auch Möglichkeiten aufgezeigt, die eine erfolgreiche berufliche Rehabilitation positiv beeinflussen.

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POSTER 298

Effektivität Früher Hilfen auf die elterliche Erziehungskompetenz und die kindliche Entwicklung – Ergebnisse der randomisierten Kontrollgruppenstudie zum Hausbesuchsprogramm „Pro Kind“ im 1. Lebensjahr

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Das Hausbesuchsprogramm Pro Kind wurde nach dem Vorbild des evidenzbasierten Nurse-Family-Partnership (NFP) Programms (Olds, 2007) seit 2006 in drei Bundesländern umgesetzt mit dem Ziel, die entwicklungsförderliche Erziehung und Lebensplanung sozial benachteiligter, erstgebärender Frauen zu verbessern sowie die kindliche Entwicklung zu unterstützen. Im Rahmen eines randomisierten Kontrollgruppendesigns wird der Nutzen der Frühe Hilfe an einer Stichprobe von insgesamt 755 Teilnehmerinnen evaluiert. Im vorliegenden Beitrag werden abschließende Befunde zur Programmumsetzung und Effektivität von der Aufnahme in das Projekt in der Schwangerschaft bis zum Ende des ersten Lebensjahres der Kinder präsentiert.
Während die Umsetzung des Hausbesuchsprogramms (Anzahl, Länge und Inhalte der Hausbesuche) als angemessen beurteilt werden kann, ist die Implementierung spezifischer Module noch optimierbar. Effekte auf die mütterliche und kindliche Gesundheit während und kurz nach der Schwangerschaft sind nicht nachweisbar. Die kognitive Entwicklung der Kinder aus Familien der Interventionsgruppe verläuft bis zum Alter von 12 Monaten jedoch signifikant positiver. Des Weiteren schätzen sich die Mütter der Interventionsgruppe zu diesem Untersuchungszeitpunkt als selbstwirksamer und weniger stressbelastet ein und berichten eine stärkere emotionale Bindung zum Kind. Mögliche Wirkmechanismen, die zur Erklärung dieser Effekte herangezogen werden können, werden diskutiert.

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POSTER 299

Berührungen in partnerschaftlichen Bindungen - Deutsche Skalen zur Erfassung selbst berichteten Berührungsverhaltens in Partnerschaften

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Berührungen spielen eine wichtige Rolle bei der Kommunikation. In Partnerschaften drücken sie Zuneigung, Intimität oder Liebe auf direkte und unmissverständliche Weise aus (Andersen, 2009). Sie sind entscheidend für die Entstehung und Aufrechterhaltung von Partnerschaften (Brennan, Wu & Loev, 1998) sowie für sexuelle Interaktionen (Andersen, 2009). Trotzdem gibt es bisher nur wenige, auf den englischen Sprachraum beschränkte Studien, die Berührungen im Rahmen von Partnerschaften untersucht haben. Damit sie im deutschen Sprachraum erforscht werden können, wurden zwei amerikanische Skalen zum selbst berichteten Berührungserleben in Partnerschaften (Sexual Touch und Desires More Touch) ins Deutsche übersetzt und psychometrisch überprüft. Trennschärfen, interne Konsistenzen sowie Test-Retest-Reliabilitäten waren sehr zufrieden stellend. Zur Validierung dienten Maße der partnerschaftlichen Bindung (Bartholomew & Horowitz, 1991; Brennan, Clark & Shaver, 1998), der Zufriedenheit in Partnerschaften (Hassebrauck, 1991; Sabourin, Valois & Lussier, 2005) sowie der Big Five (Rammstedt & John, 2007).

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POSTER 300

EEG-vigilance regulation and psychopathologic vulnerability: associations with neuroticism and sensation seeking

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A recently proposed pathogenetic model suggests that manic or hyperactive behaviour is an autoregulatory attempt to stabilise EEG-vigilance. This model also offers an explanation for the dysfunctional sleep wake regulation in depressive patients linking a hyperstable EEG-vigilance regulation to depression. In the current study we investigated if EEG-vigilance regulation patterns observed in depressed and manic patients can also be seen in a population of healthy individuals that differ in the personality traits neuroticism (N) and sensation seeking (SeSe) as markers for vulnerability to depression respectively bipolar and attention deficit hyperactive disorder. We classified EEG-vigilance of 141 healthy volunteers using the Vigilance Algorithm Leipzig (VIGALL) and computed five different vigilance regulation cluster solutions. N was assessed using the NEO-PIR and SeSe was assessed using the Arnett Inventory of Sensation Seeking (AISS). All comparisons were made using ANOVAs. Results show that participants with a hyperstable vigilance regulation have significantly higher scores in the NEO-subscales “Depression” and “Impulsivity” ($p < .05$) than those with an unstable vigilance regulation. No significant results were found for AISS scores. The results link vulnerability to depression (N) and hyperstable vigilance regulation, in line with theoretical expectations. As we examined completely healthy subjects this could imply that hyperstable vigilance regulation might even precede pathological episodes of depression and thus could be a core feature in the development and maintenance of depressive disorders.

Funding: IFB

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POSTER 301

Einstellung in der deutschen Bevölkerung zur Frühdiagnostik von Demenz

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Hintergrund: Der Einsatz neuropsychologischer, bildgebender und laboranalytischer Verfahren erlaubt zunehmend eine zuverlässigere Frühdiagnostik von Demenzen, auch wenn Heilungsmöglichkeiten insbesondere für die häufigste Form, der Alzheimerdemenz, noch fehlen. Vor dem Hintergrund dieses Spannungsfeldes war das Ziel der vorliegenden Arbeit die Erfassung der Einstellung zur Frühdiagnostik von Demenz in der deutschen Bevölkerung.
Methodik: Die Datengrundlage der vorliegenden Arbeit bilden die Ergebnisse von computergestützten Telefoninterviews mit 997 zufällig ausgewählten Erwachsenen aus Deutschland (Erhebungszeitraum: 02-04/2011). Die Datenerhebung erfolgte hierbei in einer repräsentativen Bevölkerungsbefragung durch das unabhängige Sozialforschungsinstitut USUMA unter wissenschaftlicher Leitung des Institutes für Sozialmedizin, Arbeitsmedizin und Public Health der Universität Leipzig.
Ergebnisse: Die überwiegende Mehrheit der Bevölkerung befürwortete, dass generell eine Frühdiagnostik für Demenz angeboten werden sollte. Die Mehrzahl der Befragten gab zudem an, dass sie auch für sich selbst eine Frühdiagnostik in Anspruch nehmen würden. Als Maßnahmen gegen eine Demenz wurden insbesondere Gedächtnistraining/geistige Betätigung, aktives Leben/Teilhabe aber auch die Einnahme von Medikamenten genannt.
Diskussion: Die deutsche Allgemeinbevölkerung steht einer Frühdiagnostik von Demenzen sehr aufgeschlossen gegenüber. Implikationen werden diskutiert.

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POSTER 302

Automatische und kontrollierte Affektverarbeitung bei Adipositas: eine Übersicht.

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Die Prävalenz von Adipositas ist in der letzten Dekade deutlich angestiegen und hat sich auf hohem Niveau stabilisiert. Neuere Studienbefunde verweisen darauf, dass Auffälligkeiten der Affektivität einen wichtigen Faktor in der Entwicklung von Adipositas darstellen könnten. Adipöse Patienten zeigen eine verminderte intero- und exterozeptive Wahrnehmung von Affekten. Es finden sich Defizite sowohl auf der automatischen als auch auf der kontrollierten Verarbeitungsebene. Ähnliche Verarbeitungsmuster manifestieren auch Menschen mit Alexithymie. Hierbei handelt es sich um eine Persönlichkeitseigenschaft, die sich durch Schwierigkeiten, Gefühle zu identifizieren und zu beschreiben, sowie einen extern orientierten Denkstill auszeichnet. Es gibt Hinweise auf eine erhöhte Prävalenz von Alexithymie bei adipösen Patienten. Es bleibt zu klären, inwiefern Defizite in der Affektverarbeitung bei Adipositas durch Alexithymie vermittelt sind. Es erscheint plausibel anzunehmen, dass adipöse Personen mit einer gestörten Affektregulation nicht zwischen verschiedenen interozeptiven Signalen (z.B. Sättigung) diskriminieren können, was zu einem abnormen Essverhalten führen könnte. Zukünftige Studien zur Affektivität bei Adipositas sollten Alexithymie als Mediatorvariable mit einbeziehen und die Rolle von affektregulativen und interozeptiven Fähigkeiten bei der Entwicklung von Adipositas berücksichtigen.

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POSTER 303

Entwicklung barrierefreier Erhebungsinstrumente am Beispiel der Jugendsexualitätsstudie der Bundeszentrale für gesundheitliche Aufklärung

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Einleitung
Die UN-Behindertenrechtskonvention zur verbesserten Teilhabe am gesellschaftlichen Leben fordert die Möglichkeit von Meinungs- und Einstellungsäußerungen. Doch selbst aus Studien zu behindertenspezifischen Aspekten werden Menschen ausgeschlossen, deren Einschränkungen nicht mit dem Studiendesign vereinbar sind. Ein Grund für den Ausschluss aus großen Studien ist unter anderem die mangelnde Barrierefreiheit des Studiendesigns. Im Rahmen der Jugendsexualitätsstudie wurde ein barrierefreies Erhebungsinstrument entwickelt und eingesetzt.
Methode
Zunächst wird der Basisfragebogen in Leichte Sprache übersetzt. Viele der Einleitungssätze sowie überflüssige oder redundante Informationen entfallen. Fachbegriffe werden in Alltagssprache übersetzt und erklärt. Schrift und Zeilenabstand werden vergrößert, wodurch der Fragebogen übersichtlicher und schneller erfassbar wird. Damit eignet sich der Fragebogen sowohl für Jugendliche mit Lernförderschwerpunkt als auch mit Hörschädigungen. Für Jugendliche mit Sehbehinderungen wird auf Bilder und Symbole verzichtet. Weiterhin wird darauf geachtet, dass ggf. vorhandene Tabellen in Leserichtung dargestellt werden. Bei der Aufbereitung in Papierform ist auf einen ausreichend große Schriftgröße sowie klare Kontraste zu achten.
Ergebnis.
Mit diesem barrierefreien Erhebungsinstrument konnten 169 behinderte Jugendliche in Sachsen erreicht werden.
Ausblick
Um die Versorgungssituation und Teilhabe am gesellschaftlichen Leben für Menschen mit Behinderungen weiterhin zu verbessern ist es nötig, auch barrierefreie sexualpädagogische Materialien zu entwickeln.

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POSTER 304

TOWARDS A GENETIC SCREENING TEST FOR DYSLEXIA: A SURVEY ON ACCEPTANCE

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Our aim is develop a genetic screening test for dyslexia, a severe disorder of reading and writing, affecting ca. 4-5% of all schoolchildren. The genetic influence is estimated to be 50-70%. Currently, the diagnosis takes place at the end of 2nd grade, when years of language development have already passed. Since our test would be based on DNA analyses, it would provide an early identification of subjects at risk, resulting in early intervention by specific support and training for affected children.
Besides the actual development of such a screening test, another important issue is the acceptance of this test by the people, i.e. the future customers. For this purpose we developed a questionnaire including questions about general acceptance, individual willingness to test the own child, readiness to pay for the test, and need for additional information on early support provided with the test results. To ensure the inclusion of people with and without personal experiences with dyslexia in our survey, we asked parents with dyslexic children and persons not involved with dyslexia (n=263).
We found a very positive general attitude to our test. 92% percent of all participants supported the introduction of a genetic screening test for dyslexia. 90% would want their own child to be tested. Two thirds were willing to pay for the test and 96% percent wished to receive additional information on early support together with the test results.
Given the preliminary results of our still ongoing survey, we are very confident that our genetic screening test for dyslexia would be accepted by the people once it is finished and approved.

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POSTER 305

Homosexualität und Kinderwunsch

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Aspekte der Familiengründung wurden bislang hauptsächlich bei heterosexuellen Personen erforscht. Da dieses Thema aber auch für homosexuell lebende Menschen relevant ist und zunehmend öffentlich diskutiert wird, wurden für die vorliegende Studie homosexuelle Personen zur Familiengrünung befragt.
Mittels einer offenen und anonymen Online-Umfrage wurden 1298 homosexuell lebende Menschen (55% weiblich, 30% männlich, 15% different) zwischen 16-75 Jahren zu ihren Kinderwunschmotiven, den äußeren Einflussfaktoren auf den Kinderwunsch sowie die aktuelle und die ideale Kinderzahl befragt. Weiterhin wurden die Möglichkeiten zur Realisierung eines Kinderwunsches erhoben, welche die Befragten nutzen würden (z.B. Adoption, Pflegschaft, Insemination, Leihmutterschaft). Die Motive für oder gegen eine Familiengründung wurden mit Hilfe des Leipziger Fragenbogens zu Kinderwunschmotiven (LKM) ermittelt und mit einer repräsentativen, altershomogenen Stichprobe verglichen.
81% der homosexuellen Befragten und 33% der Vergleichsstichprobe gaben an, keine Kinder zu haben. Um dieses Verhältnis für die weitere Analyse auszugleichen, wurden die Fälle diesbezüglich gewichtet. Sowohl bei heterosexuell als auch homosexuell orientierten Personen haben emotionale Motive den größten Einfluss auf den Kinderwunsch. 85% der homosexuellen Befragten und 51% der Vergleichsgruppe haben weniger Kinder, als sie ideal fänden. Als größten Einfluss auf ihren Kinderwunsch gaben die homosexuellen Befragten die berufliche Situation und die Partnerschaft an.

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POSTER 306

Einstellungen der breiten Öffentlichkeit zu Bariatrischer Chirurgie als Behandlungsmöglichkeit für Adipositas - eine Repräsentativerhebung in Deutschland

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Hintergrund: Adipositas ist weltweit eines der bedeutendsten Gesundheitsprobleme. Zur Akzeptanz von Methoden zur Gewichtsreduktion ist wenig bekannt. Anliegen: Untersucht wird die Einstellungen der deutschen Allgemeinbevölkerung zu bariatrischer Chirurgie (BC) bei Adipositas mit Fokus auf a) Wirksamkeitserwartung und b) Bereitschaft zur Weiterempfehlung.
Methode: Für die repräsentative Befragung wurden 3000 Personen telefonisch befragt - 1000 Personen davon speziell zu BC. Nach deskriptiver Analyse wurden Einflussfaktoren mittels Regression ermittelt.
Ergebnisse: Mehrheitlich (57%) als wirksame Maßnahme zur Gewichtsreduktion bewertet, würden nur 22% BC weiterempfehlen oder als Behandlung wählen. Personen mit übergewichtigem Partner zeigen höhere Wirksamkeitserwartungen, signifikant positiven Einfluss hat bivariat eine genetische Kausalattribution. Hohe Wirksamkeitserwartung steigert die Empfehlungsbereitschaft, zunehmendes Alter senkt beides. Geschlecht und eigener BMI zeigen keinen signifikanten Einfluss.
Fazit: BC wird von der Allgemeinbevölkerung unabhängig von soziodemographischen Variablen als effektiv erkannt, dies schlägt sich aber nicht in Empfehlungs-/Anwendungsbereitschaft nieder. Die Wirksamkeitserwartung ist assoziiert mit der Konfrontation durch übergewichtigen Partner und der Annahme genetischer Verursachung. Hier scheint BC für Befragte naheliegender. Nicht erfasste, wichtige Faktoren wie Risikoerwartung oder Kenntnisse zur BC sollten Thema künftiger Untersuchungen sein.

Funding: IFB

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POSTER 307

Health Service Utilization and Costs of Depressive Symptoms in Late Life – A Systematic Review

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Objective: The objective of the study is to systematically analyze and summarize research literature regarding health service use and costs of depressive symptoms in late life. *Design:* Relevant articles were identified by systematically searching the databases MEDLINE, Web of Science, PSYNDEXplus, PsycINFO, and Cochrane Library. Keywords were 'depression' or 'depressive*', and 'cost' or 'economic burden' or 'utilization' or 'use' and 'old age' or 'elderly'. Studies based on representative samples of elderly individuals aged 55 years and older were included. *Results:* 55 studies were found, 34 studies determined health service utilization, 10 studies reported costs, and 11 studies reported both. Studies of health service utilization and costs showed homogeneously that depressive elderly individuals have an increased service use compared to non-depressive, and a one-third increase of outpatient, inpatient, and total healthcare costs of depressive individuals. The majority of studies reported antidepressant (AD) use between 20 and 45% by depressive individuals. Mean annual costs for AD ranged from 108 to 305 US$ PPP (purchasing power parities). Increased service use and costs are only to a small proportion related to depression treatment. *Conclusions:* Depressive symptoms in late life lead to a high economic burden for nations which is not explained by costs for depressive symptom treatment. Strategies for improvement of diagnostic validity and treatment success of depressive symptoms in late life may have an effect on economic burden for societies.

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POSTER 308

Die Versorgung Sterbender aus Hinterbliebenensicht. Ergebnisse einer Online-Befragung

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Einleitung: Seit einigen Jahren stehen die Themen Sterben und Tod verstärkt im öffentlichen und wissenschaftlichen Interesse. Gesundheitspolitisch wird angestrebt, die letzte Lebensphase im Sinne des Sterbenden und seiner Angehörigen zu gestalten und eine optimale Symptomkontrolle zu gewährleisten. Dafür sind genaue Kenntnisse über die aktuelle Versorgung Sterbender notwendig. Die vorliegende Studie leistet in diesem Zusammenhang einen Beitrag und präsentiert Daten über die Versorgung von Palliativpatienten aus Sicht hinterbliebener Angehöriger. Die Studie wird von der Deutschen Krebshilfe e. V. gefördert.
Methoden: Im Rahmen einer seit 03/2011 laufenden, deutschlandweiten Online-Befragung werden Hinterbliebene nach dem gewünschten und tatsächlichen Sterbeort ihrer verstorbenen Angehörigen befragt. Ferner wird erhoben, wer beim Sterben anwesend war und ob es in den letzten Lebenstagen zu Krankenhauseinweisungen kam.
Ergebnisse: Die häufigsten Todesursachen waren Krebserkrankungen (63%) und Herz-Kreislauf-Erkrankungen (26%). 34% der Patienten verstarben zu Hause, 32% im Krankenhaus, 13% auf einer Palliativstation, 11% im Hospiz und 10% im Pflegeheim. Jeder zweite Palliativpatient verstarb am gewünschten Sterbeort. Bei 64% waren bei Eintritt des Todes Familienangehörige anwesend. Bei 14% kam es in den Tagen vor dem Tod zu einer Krankenhauseinweisung.
Diskussion: Auch wenn ein Versterben am gewünschten Ort aus verschiedenen Gründen nicht immer möglich sein wird, müssen medizinische und psychosoziale Versorgungsstrukturen noch stärker an den Bedürfnissen sterbender Menschen und deren Angehörigen ausgerichtet werden.

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POSTER 309 Entwicklung eines Fragebogens zur Erfassung von spezifisch onkologischen Kinderwunschmotiven

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Tumor Targeting

Hintergrund: Der Entscheidung für oder gegen ein eigenes Kind bei Krebspatienten im jungen Erwachsenenalter liegen Motive zugrunde, die auch in der Erkrankung wurzeln. In Anlehnung an den Leipziger Fragebogen zu Kinderwunschmotiven (LKM) soll hiermit ein Instrument zur Erfassung spezifisch onkologischer Kinderwunschmotive entwickelt werden.
Methodik: Auf Grundlage einer systematischen Literaturrecherche sowie der qualitativen Befragung junger Krebspatienten (N=15) und Experten der Onkologie, Reproduktionsmedizin und Psychoonkologie (N=9) wurden Motivkategorien ermittelt. Zu diesen wurden Items analog zum LKM konstruiert. Auf die Pretestung der Items folgte eine teilweise Überarbeitung sowie Reduzierung der Items. Die teststatistische Überprüfung erfolgt derzeit.
Ergebnisse: Es konnten fünf den Kinderwunsch unterstützende sowie fünf den Kinderwunsch distanzierende übergeordnete Motive junger Krebspatienten identifiziert werden wie z.B. elterliche Kompetenzerweiterung durch Krebserkrankung, Überlebensmotivation, Normalisierung des Lebens und die Priorisierung der Familie. Daneben fanden sich u.a. Befürchtungen hinsichtlich der allgemeinen kindlichen Gesundheit sowie eines erhöhten kindlichen Krebsrisikos, Befürchtungen um eigene Gesundheitsrisiken und Rezidivangst durch Schwangerschaft bei Frauen. Die Motive finden sich in 20 entwickelten Basisitems sowie einem Zusatzitem wider.
Schlussfolgerung: Perspektivisch sollen durch die entwickelten Items Kinderwunschmotive bei jungen Patienten erfasst werden. Diese spezifischen Motive für oder gegen ein Kind zu kennen, kann auch für die psychosoziale Betreuung entscheidend sein.

Funding: formel1

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POSTER 310 Sexualaufklärung bei Jugendlichen mit Behinderung

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Hintergrund:
Die Jugendsexualitätsstudie der Bundeszentrale für gesundheitliche Aufklärung untersucht seit 1980 als Trendstudie die Einstellungen und Verhaltensweisen von 14- bis 17jährigen Jugendlichen in Bezug auf Sexualwissen und -verhalten. Nun wurde diese Erhebung erstmalig mit Daten von Jugendlichen mit Körper- und Sinnesbehinderungen ergänzt. Über die Sexualität von Menschen mit Behinderungen gibt es bisher nur wenige zuverlässige Daten, da Betroffene meist von dieser Art der Erhebung ausgeschlossen blieben oder sich die Studien auf Menschen mit geistigen Behinderungen beschränkten. In einer repräsentativen Erhebung wurden sachsenweit Jugendliche über Einstellungen und Verhalten in Fragen der Sexualität und Kontrazeption befragt. Ziel der von der BZgA geförderten Studie ist es u.a. zu erforschen, ob der bundesweite Trend des verbesserten Sexualwissens auch bei Jugendlichen mit Behinderung zu beobachten ist.
Methode:
Zwischen November 2010 und Mai 2011 wurden 169 Jungen und Mädchen mit Körper- und Sinnesbehinderungen im Alter von 12 bis 18 Jahren befragt. Die Rekrutierung erfolgte über die Förderschulen für Körper- und Sinnesbehinderungen in Sachsen. Die Befragung erfolgte schriftlich im Klassenverband mit Einverständnis der Eltern. Ein an die Zielgruppe angepasster Fragebogen in Leichter Sprache diente als Erhebungsinstrument, welcher dem Fragebogen der bundesweiten Jugendsexualitätsstudie zugrunde lag.
Ergebnisse:
Die subjektive Einschätzung von Aufgeklärtheit fällt Jungen mit Behinderungen deutlich leichter als Mädchen, die befragten Jungen fühlen sich nach eigenen Angaben ausreichend informiert in sexuellen Dingen. Mädchen zeigen deshalb auch ein größeres Interesse an sexualpädagogischen Themen als Jungen, wobei zum Teil eine geschlechtsspezifische Interessenlage erkennbar ist (z.B. Schwangerschaft und Schwangerschaftsabbruch bei Mädchen, Pornographie bei Jungen).Gespräche über Verhütung im Elternhaus finden bei mehr als der Hälfte der Jugendlichen statt. Am häufigsten wird das Kondom empfohlen, auch den Mädchen.

Diskussion:
Da auch bei Jugendlichen mit Behinderungen Sexualität ein wichtiges Thema und von großem Interesse ist, empfiehlt sich der weitere Ausbau der sexualpädagogischen Angebote im schulischen Bereich. Dabei sollte eine praxis- und lebensweltlich orientierte Sexualaufklärung auch bei Jugendlichen mit Behinderungen frühzeitig begonnen werden. Bedarfsorientierte sexualpädagogische Angebote (z.B. über das Internet) können einen Beitrag zur Umsetzung der UN-Konventionen zur Teilhabe von Menschen mit Behinderungen leisten.

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POSTER 311

Evaluation des Projekts „Schulcoaches – Seelische Fitness stärken und Selbsthilfe aktivieren“

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Ziel des Projektes ist die Evaluation eines primarpräventiven Ansatzes zum Erwerb und zur Stärkung von Schlüsselkompetenzen bei Schülern. Im Rahmen der zweijährigen Intervention, die vom Leipziger Verein „Irrsinnig Menschlich e.V.“ entwickelt wurde soll durch die Implementierung eines Schulcoaches ein nachhaltig gesundes Schulklima geschaffen werden.
Im Rahmen eines longitudinalen Designs werden Schüler der 7. und 9. (Mittelschule) bzw. 10. (Gymnasium) Klassen, sowie deren Lehrer und Eltern zu 3 Zeitpunkten schriftlich befragt. Dabei werden u.a. der Wunsch nach sozialer Distanz gegenüber psychisch Kranken, das Hilfesuchverhalten in psychischen Krisen, das allgemeine Schul- und Klassenklima sowie die Erwartungen an den Schulcoach erfasst. Mittels Fokusgruppen wurden bei Schülern, Eltern und Lehrern das allgemeine Schulklima, die Rolle psychischer Gesundheit im Schulalltag und die Erwartungen an die Arbeit des Schulcoaches erhoben.
Die Befragungen ergeben ein differenziertes Bild universeller und schulspezifischer Problemlagen. Aus Sicht der Schüler macht die Schweigepflicht den Schulcoach zu einem potentiellen Gesprächspartner, Vertrauensbildung und anonyme Kontaktmöglichkeiten vorausgesetzt. Der allgemeine Bedarf wird bejaht. Die grundsätzliche Aufgabe des Schulcoaches, zunächst als Vertrauensperson im schulischen Umfeld akzeptiert zu werden, um auf dieser Basis das vorhandene Potential in konkreter Projektarbeit zu nutzen, wird verdeutlicht.
Die weiteren Befragungen werden Aufschluss darüber geben, welche Maßnahmen in welchem Kontext das Potential bergen auch außerhalb des Projektrahmens implementiert zu werden.

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POSTER 312

THE SEARCH FOR NEW STEM CELL RESEARCH RULES BETWEEN THE POLES OF THE RECENT PREIMPLANTATION GENETIC DIAGNOSIS SENTENCE OF THE FEDERAL SUPREME COURT AND THE IMPACT OF REPROGRAMMED STEM CELLS IN GERMANY

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A surprising decision of Germany's Federal Supreme Court in a preimplantation genetic diagnosis (PGD) case and groundbreaking discoveries in reprogramming pluripotent stem cells (iPSC) may facilitate a revision of Germany's stem cell law. On the one hand, the recent ruling of the Federal Supreme Court, which now allows discarding certain PGD embryos, sheds new light on Germany's stem cell law and may help to ease existing restrictions in stem cell research. On the other hand, the discovery of iPSC coincided with the latest amendment of Germany's stem cell law and could have been almost a reason to legally cancel further research with embryonic stem cells in Germany, because iPSC were seen as a scientific alternative for the use of human embryonic stem cells.
On July 6, 2010, the Supreme Court decided that certain PGD methods are permissible under the German Embryo Protection Act. The decision is surprising because one consequence of PGD is the necessity of discarding those embryos in which genetic disorders have been detected. This finding seems contrary to the central provision in the Embryo Protection Act, which states that every usage of the embryo that does not guarantee the maintenance of the embryo *in vitro* is prohibited. Therefore, this ruling may pave the way for a new legal understanding of *in vitro* embryos. If it is now permissible to discard certain PGD embryos, it must be clarified whether those embryos must be discarded or if they could be used for research. If it was permissible to use PGD embryos for research, should it be also permissible to use surplus *in vitro* fertilisation embryos for research?

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POSTER 313

Lebensabend in einem Heim? – Qualitative Analyse der Beweggründe für einen Umzug in ein Heim

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Zielstellung: Ziel der vorliegenden Studie war die umfassende qualitative Analyse der Beweggründe für einen Umzug in eine Heimeinrichtung bzw. den Verbleib im Privathaushalt im Alter sowohl aus Sicht der Betroffenen selbst als auch aus Sicht der Angehörigen.
Methodik: Die Datengrundlage bildeten auf Tonband aufgenommene leitfadengestützte, problemzentrierte Interviews mit zehn älteren Menschen (80+ Jahre; fünf mit und fünf ohne Umzug in eine Heimeinrichtung) und deren Angehörigen. Die Auswertung der Interviews erfolgte nach dem Ablaufmodell der qualitativen zusammenfassenden Inhaltsanalyse von Mayring.
Ergebnisse: Neben dem Verlust des Ehepartners oder der Abhängigkeit in alltäglichen Lebensbereichen wurde insbesondere ein schlechter körperlicher Gesundheitszustand als Beweggrund für einen Umzug in eine Heimeinrichtung genannt. Für den Verbleib im Privathaushalt war v. a. die Verfügbarkeit von pflegenden Personen bedeutsam. Insgesamt zeigte sich, dass an den Überlegungen zu einem Umzug in eine Heimeinrichtung i. d. R. mehrere Personen (Familie, Pflegedienst, Krankenhauspersonal) beteiligt waren.
Diskussion: Die Entscheidung für einen Übergang in eine Heimeinrichtung ist komplex und von einer Vielzahl von Faktoren und Akteuren abhängig. Eine stärkere Nutzung ambulanter Versorgungsstrukturen außerhalb des familiären Netzwerkes in Kombination mit präventiven Maßnahmen zur Förderung der Selbstversorgungs- und Selbstpflegekompetenz könnten helfen, vermeidbare Heimübergänge zu verhindern bzw. zu verzögern und so ein Altern in gewohnter Umgebung zu ermöglichen.

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POSTER 314

Bau einer kalten Plasma-Ionenquelle zur direkten, schonenden Anwendung an biologischen Geweben

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Das Ziel des Projekts ist ein Designvorschlag für den Bau einer schonenden Oberflächenionisationsquelle, die sich zur direkten Anwendung an lebenden Geweben eignet und massenspektrometrische Untersuchungen an selbigen ermöglicht. Kriterien dafür wären die Vermeidung schädigender Einflüsse wie z.B. der Einsatz potentiell bedenklicher Stoffe (inerte Gase statt verdampfbare organische Lösemittel bei Desorptionselektrospray) oder hoher Temperaturen bzw. die Anwendung unter Atmosphärendruck. Herstellung, Unterhaltskosten und Handhabbarkeit (Transportierbarkeit) sind weitere Parameter, die in Betracht gezogen wurden. Von den bekannten Oberflächenionisationsarten wurde die kalte Plasmaquelle als dafür geeignet befunden. Es werden verschiedene Möglichkeiten der Plasmagenerierung zusammenstellend verglichen, darunter Koronaentladung, Hohlkathodenentladung, Plasmajet bei Atmosphärendruck, Plasmafackeln, Glimmentladung, DBD-Plasma (*dielectric barrier discharge*), und die *plasma needle*. Es werden die Gründe diskutiert, die zur Auswahl einer DBD-Plasmaionisationsquelle führten. Das Design wurde so gewählt, dass das erzeugte Plasma Moleküle an einer Oberfläche ionisiert, die Oberfläche jedoch selbst so wenig Schaden wie möglich erfährt. Durch den Einsatz eines so erzeugten Plasmas, gekoppelt an einen Massenanalysator, lassen sich Oberflächen direkt unter Atmosphärendruck massenspektrometrisch untersuchen. Eine aufwendige Probenvorbereitung soll vollständig entfallen. Im Vergleich zu anderen Oberflächenionisationsarten bietet die Plasmaionisation eine sehr große Anwendungsbreite und stellt damit eine hervorragende Ergänzung zu diesen dar.

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POSTER 315

Verbundfestigkeit selbstadhäsiver, fließfähiger Komposite zum Zahn

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Ziel: Vergleich der Scherhaftfestigkeiten dreier selbstadhäsiver, fließfähiger Komposite (Flowables) zu Schmelz (S) und Dentin (D) vor und nach Thermocycling.
Methodik: 198 menschliche Molaren wurden in Kunststoff eingebettet und randomisiert 4 Gruppen zugeordnet (je $n \geq 40$). Bei je 50% der Zähne wurden S bzw. D bukkal mit einer Schleifmaschine freigelegt (Struers, Ø≥3mm) und gemäß ISO/TS11405 Prüflinge mit Vertise Flow (VF, Kerr), Fusio Liquid Dentin (FLD, Pentron Clinical Technologies), experimentellem Flow (EF, DMG[1]) und dem Kontroll-Füllungssystem Prompt-L-Pop/Filtek Supreme XT Flowable (PLP, 3M Espe) hergestellt. Vor bzw. nach Thermocycling (5-55°C, 1500 Zyklen) erfolgten die Messung der Scherfestigkeit (Zwick; 0,75mm/min) und die fraktographische Bewertung der Scherzonen mit dem Rasterelektronenmikroskop (30x). Die Daten wurden mittels Kruskal-Wallis-/U- und Fischer-Test ausgewertet ($\alpha adj. = 0{,}001/0{,}0014$; Tendenz: $\alpha < p < 0{,}05$).
Ergebnisse: Gegenüber dem Kontrollsystem PLP ergaben sich mit den drei Flowables vor bzw. nach Thermocycling verminderte Scherfestigkeiten an S und D. FLD zeigte im Vergleich der Flowables am D die höchste Scherhaftung. Nach Thermocycling war die Scherfestigkeit in allen Gruppen vermindert. In der Defektanalyse zeigte sich, dass mit PLP in den Scherzonen generell mehr kohäsive Defekte (z. T. $pi < 0{,}05$) auftraten, während mit FLD vor Thermocycling die Defekte bei allen Proben vollständig adhäsiv waren.
Schlussfolgerung: Bezüglich der Verbundfestigkeit zum Zahn und der Defektcharakteristik sind die drei untersuchten Flowables als problematisch zu bewerten.

[1] Dental-Material-Gesellschaft mbH, Sponsor

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POSTER 316

Authentication of cells in therapy research applying cytogenetics and genome wide high resolution single-nucleotide polymorphism array

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Tumor Targeting

Objectives: For the development of cells and cell products for clinical use, cytogenetic analysis are of utmost importance. Every passage carries the potential for genetic drift, taking the culture farther and farther from the original. This emphasizes the necessity for further investigation of chromosome stability in (stem) cells.
Material and Methods: We performed cytogenetic and molecular cytogenetic analyses in human and animal (stem) cells and cell lines using trypsin-Giemsa staining (GTG-banding), fluorescence in situ hybridization (FISH) techniques, spectral karyotyping (SKY), and genome wide high resolution single-nucleotide polymorphism (SNP) array.
Results and Conclusions: GTG-banding and SKY in cases of murine neuronal stem cells revealed karyotypes mainly without chromosomal aberrations. Some metaphases showed an aneuploidy, robertsonian translocations, and one metaphase with tetrasomy 7. Using whole chromosome painting probes X/Y for rat cells we were able to identify male mesenchymal stem cells of the rat in female cryoconserved brain tissue of the rat (allogeneic). Using locus-specific interphase-FISH technique on xenogeneic tissue we could identify individual human stem cells in rat brain tissues. Investigations on human cell lines revealed reciprocal translocations, terminal deletions, and isochromosomes in some metaphases. Using SNP-array, small aberrations at or below the resolution of light microscopy may be visible. Our GTG-banding, SKY, and SNP- array results attest to the necessity of genetic control of (stem) cells before their transplantation as part of cell therapy safety systems.

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POSTER 317

In vitro senescence of human mRNA iPS cell derived fibroblasts

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Introduction:Induced pluripotent stem (iPS) cells have become a promising tool for regenerative medicine. We could reprogram fibroblasts into iPS cells with repeated rounds of mRNA transfections. mRNA derived iPS cells are without the risk of genomic modifications and therefore they could be used in clinical translation. The aim of this study was to analyze the characteristics of fibroblasts derived from iPS cells compared to the donor fibroblasts for aging related aspects. Recent publications indicate that cells derived from iPS underlay accelerated aging in vitro.
Methods:mRNA IPS cells were differentiated into fibroblasts and these cells were analysed for fibroblast specific markers (e.g. D7Fib, Vimentin) expressions. Doubling times were determined of fibroblasts derived from iPS cells in comparison to donor fibroblasts on the same passage level. Levels of senescent cells were analyzed using ß-galactosidase staining and measurement of telomere length with qPCR. DNA damage level and repair capacity after oxidative stress was measured using the Comet Assay. Resistance to H2O2 induced apoptosis was measured using FACS.
Results:Different passage levels of analyzed fibroblasts were measured for increasing of expression levels of aging markers (p53 and p21) and expression levels of anti-oxidant defence markers (Gpx1 and Sod1). Gpx1 expression decreased more during expansion (3 passages) in fibroblasts derived from iPS compared to the donor fibroblasts. The frequency of β-galactosidase positive cells is lower in fibroblast derived from iPS compared to donor fibroblasts on the same passage level and more apoptotic and necrotic cells were observed in fibroblasts derived from iPS after treatment with H_2O_2.
Conclusion:Our results indicate that fibroblasts derived from our mRNA IPS line did senesce faster then normal dermal fibroblasts. Further investigations of the aging status are necessary and should become a standard assay for fully reprogrammed iPS lines.

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POSTER 318

Implantation of decellularized esophagus scaffolds – a pilot study in piglets.

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Tumor Targeting

Current reconstructive techniques for long-gap esophageal atresia are associated with high rates of postoperative complications and are cost-intensive. As an alternative therapy, in this pilot study we established a large animal model for the implantation of new biological esophagus scaffolds. Pigs (60 kg) were euthanized and esophagi were harvested, decellularized, sterilized and proved for absence of cells. In the next step, piglets (6 weeks) were anesthetized and artificial defects of 1cm^2 within the tunica muscularis were surgically created. Now, the defect was repaired either by implantation of untreated decellularized scaffold or by scaffolds crosslinked with genipin. At day 30 postimplantation, the esophageal functionality was examined under a C-arm using barium sulfate as contrast agent. After euthanasia, the implants were analyzed histologically and immunohistologically (desmin, CD3, CD68, hPH). All pigs survived the postoperative period with normal wound healing and without any inflammatory response or abnormal feeding behavior. The C-arm examination showed a regular deglutition without any esophageal artifacts. Around the implants, inflammatory events could not be observed. After immunohistologically staining with desmin ingrown muscle cells were detected in untreated scaffolds. On the other hand, only untreated scaffolds showed an inflammatory response characterized by CD68$^+$ macrophages and fibroblasts. In this pilot study, a successful implantation of decellularized esophagus scaffolds could be demonstrated which represents the basis for development of novel esophagus implants for long-gap esophageal atresia.

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POSTER 319

Analysis of DNA damage in ADSC in presence of hydrogen peroxide and UV light

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Tumor Targeting

Adipose tissue has been shown to contain high numbers of mesenchymal stem cells (ADSC) which showed to be very close in characteristic to bone marrow (BM)-derived MSC. However, there are strong reasons to believe that alike the BM-MSC, the functionality of ADSC may change with age and this might affect the therapeutic outcome. We therefore compared human ADSC from different age groups.
ADSC were treated with either H2O2 or UV light to induce DNA damage. Their DNA repair capability and extend of DNA damage was determined by Alkaline Comet Assay.
We observed that aged ADSC are more susceptible to DNA damage induced by H2O2 compared to young ADSC. However, no difference in repair efficiency was observed between young and old ADSC. Pre-conditioning with antioxidants minimized the level of DNA damage and enhanced the repair rate in the ADSC.
These results demonstrate an age related change in the ability of ADSC to respond to exogenous DNA damage. Usage of antioxidants which act as ROS scanvengers can, to some extend, increase survival rate and decrease DNA damage in ADSC.

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POSTER 320

Outer Root Sheath melanocytes in Vitiligo Therapy: acquisition, cultivation, application

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Tumor Targeting

Outer Root Sheath of the hair follicle (ORS) is by far the most non-invasive source of adult stem cells, and further differentiation stages. This complex cell pool originates from the neural crest of the embryo and retains pluripotent features. Developmental potential of ORS offers a possibility of deriving skin cellular components, neuronal cell lineage, cartilage, bone and adipocytes.
Our Group at Translational Centre for Regenerative Medicine in Leipzig is working together with the Dermatology Clinic on developing skin components from the hair follicle ORS for the purposes of an autologous, non-invasive Vitiligo treatment.
The biopsy of the hair follicles as material is advantageously completely non-invasive. The follicles are grown on medium-air interface. Our simple, reproducible and reliable cultivation procedure yields pure functional melanotic ORS melanocytes within 4 weeks. The cells are characterized with a routine panel of methods. The melanocytes display the features of epidermal melanocytes – dendritic morphology, expression of melanocyte markers, melanin synthesis and melanosome presence, migration capability and populating of ex-vivo niches.
This study deals with issues of the ORS technology, time limits, purity, characterization within low-source-high-yield axis of non-invasive procedures.
The non-invasive nature of gaining autologous ORS melanocytes, time scale and robust standard operating procedures offer a platform for autologous therapy of Vitiligo as a skin product as well as further, wider potential.

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POSTER 321

Potential and application niches for Outer Root Sheath melanocytes in Vitiligo Therapy

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Tumor Targeting

Vitiligo is a local skin depigmentation disorder caused by lack of pigment cells – the melanocytes. It´s incidence is skin type-dependant and ranges 0.5 % - 12%. It brings about hypersensitivity to sun exposure and by rule severe psychological disturbance. Conservative therapies for Vitiligo are non-causative and short-term. The only causative treatment available is melanocyte transplantation, coupled with invasive biopsy as a source of epidermal melanocytes.
We are working on an autologous, non-invasive transplantation-based Advanced Therapy Medicinal Product (ATMP) derived from Outer Root Sheath (ORS) of human hair for Vitiligo treatment. ORS technology uses temporal anagene hair gained by painless, harmless biopsy. The cells are specifically cultivated and selectively differentiated into a pure culture of functional melanotic ORS melanocytes, reached in 4 weeks. For characterization the cells undergo a series of checks.
Cells are further prepared for several application routes. Melanocyte-based grafts are designed as suspension or as solid grafts, supported with carriers, either biological (epidermal equivalents) or synthetic (biodegradable 3D networks). The carriers are polymer-based, using different cross-linking methods to obtain an optimal three-dimensional scaffold as a graft carrier niche for the cells. The cells provide an excellent base for a very promising ATMP graft, designed to causaly treat Vitiligo. Their advantage is complete non-invasiveness of both gaining the autologous material from hair follicles and applying them to the skin as a graft.

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POSTER 322

Organotypic brain slice co-cultures: an ex vivo test system to investigate regeneration supporting substances in the central nervous system

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With our organotypic brain slice co-culture system, we reconstruct the dopaminergic projection system under *ex vivo* conditions, using brain slices of the ventral tegmental area/substantia nigra (VTA/SN) and the prefrontal cortex (PFC), in order to investigate toxicological and nerve fibre growth-promoting of various compounds.
The co-culture model has been immunohistochemically characterised, and the analysis and quantification of fibre outgrowth into the target region of the projection system is well established. The aim of the present study is to supplement the model with qualitative and quantitative methods to further analyse the effects of applied substances: (1) Toxicity is assessed by (a) LDH activity measurement in the culture medium, (b) propidium iodide staining followed by image processing and subsequent densitometric quantification, (c) terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-assay allowing the visualisation of apoptotic cell nuclei and (d) active caspase 3 staining. As reference substances, glutamate (excitotoxic concentrations) and the well known apoptosis-inducing compound staurosporine were chosen. (2) Protein expression of neuronal and glial markers was quantified after treatment with e.g. purinergic agonists and antagonists. (3) Changes in the amount of released dopamine during the cultivation period under control conditions and after ADPβS treatment were measured.
The data presented on the poster show the feasibility of the above mentioned techniques to investigate the properties of unknown compounds in comparison to well known controls under *ex vivo* conditions.

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POSTER 323

The Sulfation level of Glycosaminoglycans in Monocytes and Macrophages

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Tumor Targeting

Sulfation of glycosaminoglycans (GAGs) of components of extracellular matrix and cell surface is an important regulatory mechanism in inflammatory immune response. All sulfotransferases use 3´-phosphoadenosine 5´-phosphosulfate (PAPS) as common sulfate donor that is produced by PAPS synthase.
In order to detect the sulfation level of monocytes/macrophages we established a CD44-hyaluronan binding assay. Monocytes were isolated from human peripheral blood of healthy volunteers. Macrophages were cultivated from monocytes at 37°C in the presence of 100U/ml granulocytes/macrophages – colony stimulating factor (GM-CSF). CD44 is a cell-surface receptor that binds via heparan sulfate side chains hyaluronan, a glycosaminoglycan that is released from immune cells at inflammatory sites. Using flow cytometry approaches, the expression of CD44 was followed by antibodies against CD44, while the ability of CD44 to bind hyaluronan was assessed with FITC-labelled hyaluronan.
TNFα increased the expression of CD44 on both monocytes and macrophages. Effects on the binding of FITC-labelled hyaluronan depended on incubation conditions. TNFα has no influence on purified monocytes concerning hyaluronan binding, but in the presence of lymphocytes TNFα increased the hyaluronan binding to monocytes. The inhibitor of sulfation reactions chlorate did not affect the expression of CD44, but diminished the binding of hyaluronan in a concentration-dependent manner.
This assay is a convenient tool to investigate effect on sulfation after the treatment with anti-inflammatory agents.

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POSTER 324

Age-related Young's modulus and ultimate stress of the iliotibial tract

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Tumor Targeting

Background and Aims
Age-dependent biomechanical data on ligaments and tendons are essential to create realistic virtual computational models. The iliotibial tract is a suitable model for virtual pelvic and lower extremity ligaments. Its parallel fibers facilitate biomechanical testing. Our aim was to determine Young's modulus (YM) of the tract and to correlate the data to ultimate stress (US) and to age, sex, and body weight of the body donors.
Materials and Methods
38 specimens from 12 iliotibial tracts (age ≤ 44 years) were investigated biomechanically. After preconditioning, YM were determined in the ranges of 0 to 4 and 4 to 11 N/mm² of applied stress and from 4 N/mm² of applied stress to US.
Results
YM of the specimens were 84.7 ± 30.2 (0 to 4 N/mm²), 335.4 ± 101.9 (4 to 11 N/mm²), and 369.1 ± 191.5 (4 N/mm² to US) N/mm², respectively. The mean US was 35.8 ± 16.4 N/mm². YM and US correlated strongly in the ranges of 4 to 11 N/mm² ($r = 0.95$) and 4 N/mm² to US ($r = 0.91$). Concerning tissue behavior a decrease of YM is more common than an increase of YM shortly before specimen failure. YM of specimens from young cadaver donors were significantly lower compared to those of old cadaver donors.
Discussion and Conclusions
This is the first study providing US-dependent YM of the iliotibial tract. YM is significantly lower in young compared to old cadaver donors and is thus a subject of alteration during lifetime.

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POSTER 325

Minimierung von Materialschlupf durch partielle Plastination

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Einleitung und Hintergrund
Prüfungen von Sehnen und Bändern werden durch Materialschlupf beeinträchtigt. Materialschlupf ist das Herausgleiten der Probe aus der Einspannvorrichtung der Materialprüfmaschine. Ziel unserer Untersuchung war die Etablierung eines Verfahrens zur Reduktion des Materialschlupfs.
Material und Methoden
Drei Proben eines Tractus iliotibialis (männlich, 44 Jahre) wurden präpariert. Die Enden einer der Proben wurden mit Polyurethan partiell plastiniert und an Kunststoffplatten montiert. Die Fixierung der gleichlangen Proben erfolgte: semiparabolisch (Probe 1), doppelt gummiert (Probe 2) und an den Kunststoffplatten der partiell plastinierten Probe (3). Anschließend erfolgte eine Materialprüfung über zehn Zyklen unter konstanter Befeuchtung. Eine vordefinierte Belastung von 40 N (nichtplastischer Bereich) wurde aufgetragen und der korrespondierende Traversenweg aufgezeichnet.
Ergebnisse
Die Auslockerung der Probe zeigte sich über die Veränderung des Maximalwerts des Traversenwegs über die zehn Zyklen. Die Auslockerung betrug 28,63% (Probe 1), 15,02% (Probe 2) und 0,76% (Probe 3), bezogen auf die Ausgangslänge der Proben. Während sich die Proben 1 und 2 stetig auslockerten, zeigte sich bei Probe 3 eine Verringerung des Traversenwegs nach dem vierten Zyklus.
Diskussion
Die Probenfixierung mit der partiellen Plastination erlaubt schlupfminimierte Materialprüfungen an Bändern und Sehnen. Die Genauigkeit der vorgestellten Methode erlaubt es, zusätzlich Steifigkeitsveränderungen infolge der Auspressung von Mikrowasser aus Kollagen zu messen.

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POSTER 326

Biomechanical effects of pelvic compression by means of SacroLoc® orthesis

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Tumor Targeting

Background and Aims: The cause of sacro-iliac joint pain is still unknown. In spite of numerous theories on ligamentous imbalance as a reason, ligament-related force distribution at the posterior pelvic ring is presently undetermined. Effects on relief of sacro-iliac joint pain by pelvic compression ortheses are therefore poorly understood. The aim of our computational study is to establish an osteoligamentous model of the pelvic ring and to determine the influence of such SacroLoc® pelvic ortheses on force distribution.
Materials and Methods: Virtual Finite Elements (FE) models of the pelvic ring are gained from CT and MRI scans, based on previous studies. Additional data are integrated to precise the models: non-linear age-dependent tensile properties, compression properties and ultimate stress of the ligaments. Pelvic force distribution is determined computationally under no compression (FE model I), moderate (FE model II) and maximum compression (FE model III) by means of SacroLoc® pelvic ortheses.
Outlook: Data gained from the FE models will help to gain inside ligamentous influence on pelvic stability. The effects of pelvic compression aid to explain clinically observed relief caused by SacroLoc® pelvic ortheses. The model will further advance product modeling to improve the compressive effects.

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POSTER 327

Age-dependent liver repopulation by transplanted hepatocytes

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The low liver repopulation efficacy of transplanted hepatocytes is probably due to their poor proliferative capacity linked to the age of the liver donors. The age-dependent proliferative potential of wild type F344 rat hepatocytes was investigated after transplantation into old and young CD26-deficient F344 rat host livers. Repopulation rates were determined by flow cytometry and assay of CD26 enzyme activity.
Hepatocytes isolated from either young or old donor rats formed small and rare clusters of donor-derived hepatocytes in senescent host livers. However, both hepatocytes from juvenile and from senescent donor livers transplanted into juvenile host livers developed cell clusters significantly larger and more frequently as compared with senescent host livers. Repopulation of juvenile host livers by old or young hepatocytes amounted to 20 % as compared 2 % in senescent hosts. No functional difference between transplanted juvenile and senescent hepatocytes was observed in the host liver tissue in terms of glycogen storage. As compared to senescent host animals, serum levels of IGF1 were significantly higher in juvenile rats. Thus, in rats, the age of the recipient liver seems to be critical for the efficient repopulation by transplanted hepatocytes involving regulation along the growth hormone-IGF1-axis.

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POSTER 328

Implantologische OP-Situationen im Vergleich mit den anatomischen Humanpräparaten

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Tumor Targeting

Mit den sich weiter entwickelnden Operationsverfahren im Bereich der zahnärztlichen Implantologie steigen auch die Anforderungen an den Operateur. Profunde Kenntnisse zur Topographie anatomischer Strukturen sind dabei unabdingbar. Anatomische Atlanten stellen die Strukturen häufig idealisiert und ohne Berücksichtigung der individuellen Variationsbreite dar; in der Regel schichtweise, wie beim Präparieren üblich. Zugänge, wie sie in der Klinik benötigt werden, finden sich selten.
Aus diesem Grund werden in vorliegender Arbeit an 6 vollständigen und 6 halbierten humanen Kopfpräparaten (alle Alkohol-fixiert, beiderlei Geschlechts, Alter zw. 72 und 95 Jahren) OP-Situationen nachgestellt und fotografisch dokumentiert. Das betrifft im Einzelnen das Weichgewebsmanagement mittels Flap-Technik am Gaumen unter dem Aspekt des Verlaufs der A. palatina major, die interforaminäre Implantation im Unterkiefer im Hinblick auf den Verlauf des N. alveolaris inferior bzw. N. mentalis und die Eigenknochenentnahme für Augmentationen am Unterkieferast.
Dadurch wird die Lücke der oft unzureichenden Verlinkung der klinischen Situation mit dem anatomischen Korrelat geschlossen.

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POSTER 329

Allogeneic hepatocyte transplantation in the rat

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Tumor Targeting

The immune response leading to rejection of transplanted hepatocytes has not yet been addressed in detail. In the study presented, the rate of hepatic repopulation by transplanted hepatocytes in a syngeneic model (donor: DPPIV $^{+/+}$ F344; recipient: DPPIV$^{-/-}$ F344) was compared to an allogeneic transplantation model (donor rat: Dark Agouti; recipient rat: DPPIV$^{-/-}$ F344). Wildtype donor hepatocytes delivered via portal injection were detected by histochemical staining of DPPIV enzyme activity in the otherwise negative host liver background and quantified by flow cytometry.
24 hours after transplantation, single hepatocytes were detected in the recipient liver parenchyma both in the syngeneic and allogeneic model. 5 days post-transplantation, small clusters of 1-5 donor hepatocytes were visible in the syngeneic model as compared to still single cells in the allogeneic model. After 3 weeks, in the syngeneic model 1 % of the recipient liver was replaced by donor hepatocytes while no cells were found in the allogeneic model. Depletion of Kupffer cells (KCs), macrophages resident in the liver, by gadolinium chloride did not increase the rate of repopulation in either model. Thus, KCs mediating the early immune response were not involved in the rejection of allogeneic hepatocytes, but rather T-cells eliminating transplanted allogeneic hepatocytes during a three weeks period in time.

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POSTER 330

An immunodeficient mouse model: Cell therapy in non-alcoholic steatohepatitis (NASH)

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Tumor Targeting

NASH is a benign disease and will progress, if untreated, into fibrosis/cirrhosis and potentially into HCC. Human cell therapy approaches for the treatment of NASH have not been addressed yet. The present work aimed at establishing an animal model to evaluate the feasibility of stem cell-derived hepatocytes.
Immunodeficient mice were fed a methionin-cholin-deficient diet (MCD diet) up to 5 weeks. Alanine aminotransferase (ALT) and triglycerides were determined in the serum. Histological analyses of liver sections were performed to detect structural abnormalities by HE, the collagen distribution by sirius-red and fat depositions by sudan III staining. Expression of the acute phase protein SAA, the proinflammatory cytokine TNFa, the marker for activated stellate cells αSMA as well as collagen1 in liver tissue were specified by RT-PCR. By HE-staining massive steatosis and hepatocellular injury were observed in sections of liver tissue and confirmed by sudan III staining in livers of mice fed the MCD diet as compared to the control diet. Fibrosis in livers of animals on MCD diet was obvious by collagen staining. The marker of hepatocyte fade ALT was significantly higher (2-fold) in the serum of mice on MCD diet. Serum triglycerides were significantly lower in MCD diet-fed mice. RT-PCR analysis revealed elevated mRNA levels of SAA and TNFα as well as of αSMA and collagen1 in the livers of mice fed the MCD diet.
Thus, immunodeficient Pfp/Rag2 mice fed with the MCD diet displayed typical features of NASH, which makes this animal model suitable to evaluate pre-clinically human cell therapy approaches of liver diseases.

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POSTER 331

MARTENSITIC TRANSFORMATION AND MAGNETIC PROPERTIES OF FREESTANDING SINGLE CRYSTALLINE Fe70Pd30 THIN FILMS

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Tumor Targeting

Ferromagnetic shape memory alloys (FSMAs) have attracted significant scientific interest recently due to their high potential for actuators in micromedicine, such as surgical implant material, applying for bone prostheses, or drug delivery systems. Our present results show that by raising the deposition temperature to 850 °C or higher, no post-annealing treatment is required and room temperature single crystal fct $Fe_{70}Pd_{30}$ thin films are readily prepared. By means of scanning electron microscopy (SEM) and atomic force microscopy (AFM) we investigated the surface topography of the Fe-Pd films, which reflects the twin structure of martensite. The phase transformation temperature from fct martensite to fcc austenite at about 53 °C was confirmed by temperature dependent x-ray diffraction measurements (XRD). In order to eliminate the substrate constraints in miniaturized actuators applications, we prepared freestanding Fe-Pd films by chemically dissolving the MgO, keeping the crystal structure, phase and composition of these films intact. Furthermore, temperature dependent magnetic properties of freestanding Fe-Pd films and the films attached on substrates were investigated by magnetometry using a superconducting quantum interference device (SQUID).

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POSTER 332

Regulation of cell cycle checkpoint kinase Wee1 by miRNA-195 in malignant melanoma

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Tumor Targeting

Wee1 kinase has been described as a major gate keeper at the G2 cell cycle checkpoint and to be involved in tumor progression in different malignant tumours. We analyzed expression levels of Wee1 in a series of melanoma cell lines and patient samples. Wee1 expression was significantly downregulated in melanoma cell lines of high aggressiveness as compared with cell lines of low aggressiveness and in patient samples of metastatic origin as compared with primary melanomas. Since microRNAs (miRNAs) play an important role in tumor biology and are well-known negative regulators of gene expression, we searched for miRNA candidates that might account for Wee1 downregulation in metastatic melanoma. In different miRNA target databases, miR-195 was found as a top candidate miRNA for targeting of Wee1. Our mRNA expression analysis revealed an inverse correlation between Wee1 and miR-195 in melanoma samples. Transient transfection of miR-195 indeed reduced mRNA and protein expression of Wee1, and reporter gene analysis confirmed direct targeting of the Wee1 3'untranslated region (3'UTR) by miR-195. We found that overexpression of miR-195 in SK-Mel-28 melanoma cells almost completely abrogated stress-induced G2-M cell cycle arrest. In a rescue experiment, stable over-expression of Wee1 in these cells reversed the miR-195 effect and partially restored the stress-induced arrest. Taken together, our study shows that Wee1 is directly regulated by miR-195 in malignant melanoma and that Wee1 may be downregulated in metastatic lesions by miR-195 to allow unrestricted growth of tumor cells.

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POSTER 333

Modulation of glyoxalase 1 expression affects tumor related properties of cells

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Tumor Targeting

Many tumor cells show an energy metabolism typical for hypoxic conditions even within normoxic environment. This phenomenon known as "Warburg hypothesis" leads to an increased glycolytic flux and a reduced ATP production within the respiratory chain. Increased glycolysis results in an enhanced production of methylglyoxal (MGO) - a toxic side product of the glycolytic pathway. As a result, glyoxalase 1 (Glo1) which is the main detoxifying enzyme of MGO is up-regulated in most cancer cells.
We investigated the influence of Glo1 overexpression and Glo1 knockdown on malignancy-associated properties of cells like proliferation and migration using the cell lines MCF-7 and Hek 293. Further we compared enzyme activity and proliferation of cells with modulated Glo1 expression under hypoxic and normoxic conditions. We found reduced proliferation and cell migration when Glo1 expression was reduced. Glo1 overexpression decreased sensitivity against hypoxia. Taken together, our findings show that reduced Glo1 expression is associated with a less aggressive cell phenotype. In contrast, increased expression shows better adaption of cells to hypoxia which occurs typically in tumor environment. These results lead us to the assumption that Glo1 expression affects tumor related properties of cells and could therefore be a promising target in tumor therapy.

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POSTER 334

Selection of molecular markers differentiating between follicular thyroid carcinoma (FTC) and follicular thyroid adenoma (FA)

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Tumor Targeting

A clear differentiation between follicular thyroid carcinoma (FTC) and follicular thyroid adenoma (FA) is a problem that has not been solved: although fine-needle aspiration cytology is a very sensitive and specific tool for the differential diagnosis of thyroid nodules, it reveals the inconclusive result of follicular proliferation, which is characteristic for both FTC and FA, in up to 20%. Thus, pre-operative diagnosis does not result in a reliable patient diagnosis.
We are trying to find molecular markers discriminating between FTC and FA samples. Since differences between FTC and FA are known to be small – both in histological and molecular analysis, bioinformatics analysis of this data is challenging.
We investigated mRNA and miRNA profiles of tissues classified independently by two pathologists. mRNA and miRNA profiles of all samples were analyzed by microarrays, additionally, 10 FTC and 10 FA samples were sequenced with Illumina RNA-Seq.
The analysis of microarray data included R/Bioconductor QC and unsupervised methods followed by Random Forests classification and feature selection. For RNA-Seq data we have applied tophat – cufflinks pathway suggested by the SeqAnswers community.
mRNA markers differentiating between FTC and FA were found and validated with independent sets of samples. MiRNA markers were selected from NGS data and 30 more samples will be analyzed with Illumina sequencing to confirm the miRNA profiles of FTC and FA. Furthermore, qPCR validation of markers will be performed in an independent set of samples. Finally, the obtained results might further improve the clinical diagnosis of FTC and FA.

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POSTER 335

LNCaP Xenograft Mouse Model for Investigating The Therapeutic Potential of Three MicroRNAs Downregulated in Prostate Cancer

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Tumor Targeting

Despite tremendous screening efforts German males have a 3.3% lifetimerisk of dying from Prostate Cancer (PCa). Once PCa has left the organ capsule few therapeutic options remain: Androgen depreviation is the most common though it promotes progressionto its androgen-insensitive form (CRPC). Micro-RNAs (miR) are a class of small non-coding RNAs controlling 30% ofour genes. Hence, their role in the origin of cancer has proved to becrucial.
GOAL: Identify PCa-specific miRs and investigate their apitude for biomarkersand therapeutic targets.
APPROACH: Using microarrays we found miRs differentially expressed in healthy andcancerous prostate cell lines. In order to check with the situation invivo their expression was compared between PCa and healthy samples. Byoverexpressing the miRs in the LNCaP cell line we further characterizedtheir function. Bioinformatic target prediciton, and mRNA and proteinexpression analysis after miR overexpression were used together tonarrow down the miRs' targets. Those that have shown to convey potential therapeutic potency are usedin a LNCaP xenograft mouse model (LXMM) in order to evaluate theirfitness as drugs.
PRELIMINARY RESULTS: Most miRs are downregulated in PCa, which is more marked in recurrentcancer. The three most diffently

expressed miRNAs jointly influence ARcoactivation and MAPK signalling.Overexpression of these miRNAs caused reduction of cell numbers byapoptosis, cellcycle arrest or both.
CURRENT STATUS: We use a LXMM and test the three identified miRs. Since in vivostability and delivery are major issues we make use of only recentlydeveloped modifications.

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POSTER 336

CD 34 and smootha muscle actin as markers for peritumoral stromal remodelling in squamosu cell cervical carcinomas

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Background: CD 34 staining has been reported in normal endocervical stroma and its loss as an indicator for peritumoral stromal remodelling in case of invasive cancer. CD 34 loss might be associated with upregulation of smooth muscle actin (SMA). The present study evaluates CD 34 and SMA expression within peritumoral stromal cells in squamous cell carcinoma of the uterine cervix (CX).
Methods: CD 34 and SMA immunohistochemistry was performed on samples of 97 surgically treated CX. Staining results were scored as negative/low (<5% stromal cells positive), moderate (5-50% stroma positive) or high (>50% stroma positive). Staining results were compared to different patterns of invasion (representing different grade of tumor cell dissociation) and grade of peritumoral stromal reaction (DSR).
Results: The majority of cases (78.2%) showed a marked reduction/loss of CD 34-staining (negative/low/moderate staining), whereas 70.6% of the cases represented an upregulation of SMA (high staining pattern; Tab. 1). CD 34-loss and SMA-upregulation was correlated to different pattern of invasion and the grade of peritumoral stromal reaction (DSR).
Conclusions: Loss of CD 34 and upregulation of SMA represent a parameter of peritumoral stromal remodelling in squamous cell carcinoma of the uterine cervix. The prognostic impact of this altered stromal feature might be of interest for further studies.

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POSTER 337

Mutational analysis of serous ovarian borderline tumors and its peritoneal implants regarding the occurrence of BRAF- p.V600E mutation

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Tumor Targeting

Introduction: Genes of the *RAF* family, which mediate cellular responses to growth signals, encode kinases that are regulated by RAS and participate in the RAS/RAF/MEK/ERK/MAP-kinase pathway. Activating mutations in *BRAF* have been identified to play a major role in the pathogenesis of low-grade serous ovarian carcinomas (LG-OCA) via serous borderline tumors (s-BLT; Sieben et al. 2004, Mayr et al. 2006; Vang et al. 2009). But, limited information exists about a possible clonal relation comparing s-BLT and its peritoneal implants which we want to illuminate by *BRAF* p.V600E analysis.
Methods: Thirteen cases of s-BLT with peritoneal implants (invasive and non-invasive) were identified from our files with subsequent macro- or microdissection followed by DNA- extraction of the adequate tissue. To reveal the activating mutation of *BRAF* p.V600E we performed pyrosequencing of 48 samples with a sensitivity of at least 5% mutated alleles. Molecular analysis was performed from the ovarian tumor as well as within one to 6 peritoneal implants from different sites.
Results: Five s-BLT (38.5%) showed *BRAF*- p.V600E mutation within the ovarian tumor. In three of those cases *BRAF*- p.V600E mutation was also identified within the peritoneal implants suggesting a clonal origin in terms of abdominal tumor spread.
Conclusions: The frequency of *BRAF*- p.V600E mutation in s-BLT is concordant with the reported frequency within LG-OCA. In case of abdominal spread, peritoneal implants represent clonal origin of the primary tumor in about two thirds of the informative cases. Further studies, examining additional members of the RAS/RAF/MEK/ERK/MAP-kinase pathway and using laser-capture microdissection in cases of rare tumor epithelium by atrophy are required.

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POSTER 338

Veränderungen der CD15+- und CD133+- Subpopulation von humanen Medulloblastomzelllinien nach Behandlung mit ionisierender Strahlung und 5-aza-2'-deoxycytidin

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Die Tumorstammzell(TSZ)-Hypothese, nach der das Wachstum vieler Tumoren von sogenannten TSZ abhängig ist, rückte im letzten Jahrzehnt immer mehr in den Focus der Wissenschaft. Auch im Medulloblastom (MB), dem häufigsten malignen Hirntumor im Kindesalter, konnten Subpopulationen von $CD133^+$- und $CD15^+$-Zellen gefunden werden, die Stammzell-ähnliche Eigenschaften und damit die Fähigkeit zur Tumorneubildung besitzen. In vorausgegangenen Untersuchungen zum klonogenen Überleben von MB-Zellen konnten wir zeigen, dass die Nachbehandlung mit dem demethylierenden 5-aza-2'-deoxycytidin (5-aza-dC) einen synergistischen Effekt mit Bestrahlung erzielt, und damit die Klonalität der Zellen weiter verringert. In dieser Arbeit untersuchten wir mittels Durchflusszytometrie die Veränderungen der TSZ hinsichtlich ihres Anteils an der Gesamtpopulation und ihrer Proliferationsaktivität drei Tage nach Bestrahlung und / oder 5-aza-dC Behandlung. Dabei zeigte sich, dass $CD133^+$-Zellen eine geringere Proliferationsrate und durch 5-aza-dC und / oder Bestrahlung eine stärkere Verminderung der sich teilenden Zellen gegenüber $CD133^-$-Zellen aufweisen. Dennoch kam es durch die Behandlung mit 5-aza-dC als auch durch Bestrahlung zu einer Anreicherung der TSZ. Durch den erhöhten Einbau von 5-aza-dC in den schneller proliferierenden nicht-TSZ und deren verringerte Reparaturzeit kommt es möglicherweise zu Schäden, die zum vermehrten Zelltod in den nicht-TSZ führen. In weiterführenden Untersuchungen sollen nun Substanzen gefunden werden, die auch die TSZ-Population verringern – und damit die Möglichkeit zur Rezidivbildung von Tumoren weiter einschränken.

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POSTER 339

The variations in the BCL2 genes expression in lung cancer cells after exposure to erlotinib and gefitinib

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Tumor Targeting

Introduction: The BCL2 family proteins are apoptotic regulators which play an important role in cancer cell survival. These proteins are also associated with resistance to anticancer drugs. Erlotinib and gefitinib are tyrosin kinase inhibitors which are used in the treatment of lung cancer. This study investigated the differences in the BCL2 gene expression after treatment of resistant or sensitive lung cancer cell lines with gefitinib and erlotinib.
Methodology: Real time PCR was performed after RNA isolation 24h after exposing the cells to the drugs. Resistant cell lines H1299 and A549 were compared to the sensitive HCC827 as well as a resistant HCC827. Resistant cells were established by long term exposure to erlotinib and gefitinib.
Results: 8 genes were investigated which were selected randomly considering both pro-apoptotic and anti-apoptotic regulators. Anti-apoptotic were: BCl2-XL, BCL2 α and MCL1-L, pro-apoptotic included MCL2-S, BIK; BIM γ, BIM-EL and BAD, EEF2 was used as the reference gene. The gene expression varied in all the cell lines. BCL2-XL, MCL1-S and BIM were surpressed by erlotininb where as only BIM γ was suppressed by gefitinib in all cell lines. Apart from, BCL2 α and BIM-EL al other genes did not show a significant difference to the control. BCL2 α was highly expressed in HCC827 whereas BIM EL was highly expressed in HCC827 and A549.Conclusion: Since BCL2 α is an anti-apoptotic protein, its increased expression after treatment of HCC827 cell line can be associated with resistance to TKI. BIM EL on the other hand mediates the intrinsic apoptotic pathway when TKI are applied.

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POSTER 340

Why more intensive chemotherapy may be less in the treatment of diffuse large B-Cell Lymphoma

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Tumor Targeting

The NHL-B2 trial showed that both time intensification of CHOP chemotherapy as well as addition of Etoposide improves outcome in elderly DLBCL patients. These intensifications were clearly not additive as double intensification was comparable to baseline CHOP. This interaction cannot be explained away by toxicity since treatment delivery was not relevantly compromised. We developed an ODE model based on the hypothesis that the immune system plays a role in controlling residual tumour cells shortly after treatment. More intense chemotherapy may be detrimental in cases in which transient depletion of immunologic effector cells allows early re-growth of residual tumour cells. Major model features are a logistic tumour growth, a modulation of the production rate of effector cells by the presence of the tumour (immunogeneity) and mutual destruction of tumour and immune cells. Chemotherapy is introduced reducing both, immune and tumour cells during the treatment course. Growth rate, chemosensitivity and immunogeneity of the tumour are assumed to be patient-specific parameters. We provide a method to fit the model to clinical trial data by estimating a maximum entropy distribution of model parameters in the study population.
The model can qualitatively explain that more intense chemotherapies can result in inferior therapy outcome in certain patients. Estimated parameters are biolologically plausible and reasonably fit the clinical data. It is possible to estimate trial population distributions of patient characteristics which influence the effectiveness of different chemotherapies.

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POSTER 341

CD97 prevents tumor cell apoptosis by inhibiting the intrinsic pathway

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Tumor Targeting

CD97 is overexpressed in several tumors. Recently we identified Akt, an important regulator of proliferation and survival, to be involved in CD97 signal transduction. We examined the function of CD97 in tumor cell apoptosis induced by serum starvation or staurosporine, known inductors for the intrinsic apoptosis pathway, in HT1080 clones overexpressing full length CD97/TM7 or truncated CD97/TM2.
In CD97/TM7 cells basal Akt levels were upregulated. Serum starvation increased the percentage of CD97/TM2 cells in the sub-G1 phase, representing apoptotic cells. The percentage of cells with condensed nuclei, a typical hallmark of apoptosis, increased first in CD97/TM2 and later in mock cells. Akt-inhibitor IV induced nuclear condensation also in CD97/TM7 cells.
Staurosporine reduced viability but increased cytotoxicity, the percentage of annexinV^+/propidium $iodide^-$ cells and DNA laddering first in CD97/TM2 and in mock but not or delayed in CD97/TM7 cells which were protected from apoptosis by inhibition of caspases-3/7.
Surprisingly, induction of apoptosis upregulated pAkt (Ser 473) strongly in CD97/TM2 and mock but only slightly in CD97/TM7 cells. The Multiplex Ligation-dependent Probe Amplification (MLPA) apoptosis assay revealed in CD97/TM7 compared to mock and CD97/TM2 cells a downregulation of Bmf, Bim and Puma mRNAs encoding pro-apoptotic proteins and an upregulation of Bfl-1 mRNA which was partly confirmed at the protein level by Western blotting.
In summary, tumor cells overexpressing CD97 were protected from apoptosis via the intrinsic pathway by upregulation of anti- and downregulation of pro-apoptotic proteins.

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POSTER 342

Combining an agent-based hematopoietic stem cell model with an ordinary differential equations model of mature granulopoiesis and its application to chemotherapy

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Tumor Targeting

An established agent-based model (ABM) for hematopoietic stem cells (HSCs) succeeded well in explaining experimental data of clonal competition and stem cell dynamics. It is based on two functionally distinct growth environments, one hosting proliferating and differentiating HSC, the other regenerating HSCs. Transitions between them are dynamically regulated.
Complementary, a compartment-based ordinary differential equations (ODE) model of granulopoiesis comprising all maturing stages has been developed.
Here, stem cell dynamics are represented by a simple ODE focussed on the aim of modeling the effects of chemotherapy and growth factor application on the number of circulating granulocytes.
To combine the strengths of both approaches, we coupled the models by replacing the ODE for stem cells with a difference equation formulation of the ABM. The resulting hybrid model was applied to a panel of qualitative check points, such as single high-dose and chronic irradiation. Simulation results of these scenarios were qualitatively compared with available knowledge.
Besides, we performed quantitative modelling of circulating leukocyte number under four different chemotherapeutic regimen with (CHOP-14, CHOEP-14) and without (CHOP-21, CHOEP-21) growth factor application. Interestingly, simulation results fitted the clinical data of all chemotherapy regimen well, just by combining the models. No additional parameter fittings were required. Thereby, the validity is not only show of the hybrid model, but additionally support ABM and ODE.

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POSTER 343

Indirubin N-glycosides inhibit important intracellular signalling pathways in malignant melanoma

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Tumor Targeting

Despite the recent progress in treatment of metastatic melanoma by targeting of the BRAF/MAPKinase signalling pathway, there is still a need for new treatment approaches, since relapse rates after BRAF targeting are high and treatment is only successful in patients with a mutated BRAF kinase. In recent years, indirubins and their derivatives have been shown to be highly potent inhibitors of intracellular signalling kinases such as cyclin-dependent kinases as well as glycogen synthase kinase 3β. They also have been shown to be anti-proliferative and pro-apoptotic in a variety of tumour cell lines including melanoma cell lines. In search for their targets in melanoma cells that might explain their activity, we performed a screen using a phospho-kinase array of more than 45 phosphoproteins, which includes members of all well-known intracellular signalling pathways. We could show that treatment of melanoma cells with different N-glycosylated indirubins led to a significant decrease in phosphorylated Akt, S6 kinase, STAT1 and c-Jun, with phosphorylated c-Jun showing the most significant downregulation. c-Jun is the downstream target of c-Jun N-terminal protein kinases 1/2(JNK1/2). For further validation we performed *in vitro* kinase assays with recombinant JNK2, which showed that indirubins were indeed strong inhibitors of JNK2 activity. Thus, indirubins may exert their effects in melanoma cells through inhibition of JNK signalling. Together, we identified new intracellular signalling pathways targeted by indirubin derivatives and showed that they may be interesting substances for new treatment approaches in malignant melanoma.

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POSTER 344

Tumor slice cultures as a novel test system for drug susceptibility and mechanisms of resistance

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Tumor Targeting

Human squamous epithelial cell carcinoma (HNSCC) fundamentally vary in their susceptibility to chemotherapy and/or irradiation. Therefore, a test system is desirable allowing prediction of susceptibility versus resistance for individual patients (Dietz et al., European Archive Otorhinolaryngology 2010). We have previously employed slice cultures of brain-derived human tissues as test systems for novel drugs (Nitsch et al., Lancet 2000; Merz & Bechmann, Future Oncology 2011). In this project, we established for the first time slice cultures of HNSCC and treated them with widely used chemotherapeutic drugs. We show that these slices survive for at least six days in vitro with excellent maintenance of structure as indicated by standard H & E stainings of paraffin-embedded slices. Treatment significantly impacts on cell survival with prominent fields of fragmented (apoptotic) nuclei in some tumours. LDH-release into the media can serve as quantitative measure of cell death over time. Thus, first steps have been performed towards a prediction of most effective therapies for individual patients.

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POSTER 345

A Disseminated Tumor Model for Non-Hodgkin's Lymphoma in NOD/SCID mice

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Tumor Targeting

Non-Hodgkin's Lymphomas are one of the most common malignancies and represent approximately 3-4% of all cancer cases worldwide. Also, NHL increased in the second part of the 20th century in many Wetsern countries every year from 2 to 4%. In Germany every year 6800 men and 6100 women come down with Non-Hodgkin's Lymphoma; mortality and incidence increased since 1980 and slightly decreased since 2000.
The aim of our experiment was to establish a disseminated xenograft tumor model in immunodeficient mice for human B-cell Non-Hodgkin's lymphoma with the tumor cell lines OCI-Ly3 (diffuse large B-cell lymphoma), Jeko1 (mantle cell lymphoma) and Rec_1 (mantle cell lymphoma). We used NOD/SCID mice because they are known as particularly well suited for xenograft models in cancer research.
After intravenous tumor cell application, four mice were sacrificed weekly to determine tumor burden with flow cytometric analysis of huCD45, huCD19 and huCD20 in spleen, blood, bone marrow and brain.
We could establish a disseminated tumor model for all three tumor cell lines. The organs manly affected were bone marrow and brain and partly also lymph nodes, spleen and ovaries.
In the future we would like to use this xenograft cancer mouse model for testing chemotherapeutic regimens.

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POSTER 346

Simvastatin unterdückt das Wachstum der Zelllinie KB in vitro

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Einleitung: Simvastatin (Sim) hat sich als wirksames Medikament bei der Therapie kardiovaskulärer Risikoerkrankungen erwiesen und reduziert Hypercholesterinämien durch Inhibition der 3-Hydroxy-3-Methylglutaryl-Coenzyme-A-Reduktase. Neuerdings gibt es Hinweise, dass Sim Einfluss auf Entwicklung und Wachstum von Tumoren hat.
Methoden: Die Zelllinie KB entstammt einem humanen Epidermoidkarzinom des Oropharynx. Die KB-Zellen (KB) wurden mit in 0,1% Ethanol gelöstem Sim in den Konzentrationen 5; 1,5; 0,5 und 0,15 μM mit Cisplatin (Cis) bzw. Docetaxel (DTX) *in vitro* kombiniert und für 3 und 6 Tage inkubiert. Die Auswertung erfolgte mittels 3-(4,5-Dimethythiazol-2-yl)-2,5-diphenyltetrazoliumbromid (MTT)-Test und photometrischer Messung.
Ergebnisse:Es zeigte sich der supprimierende Effekt von Cis und DTX auf das Wachstum von KB nach 3 und 6 Tagen im normgerechten Bereich (Qualitätskontrolle). Sim unterdrückte das Wachstum der KB mit einer halbmaximalen Wachstumsunterdrückung (IC_{50}) von 8,6±2,5 nM und 6,7±1,2 nM (Mittelwert±Standardabweichung von n=7 bzw. n=8 Experimenten mit Endpunktbestimmung an Tag 3 bzw. 6). Der supprimierende Effekt von Cis bzw. DTX auf die KB wurde durch die Kombination mit Sim im zeitlichen Verlauf zunehmend verstärkt.
Diskussion: Diese orientierenden Analysen bestätigen die Wirksamkeit von Cis und DTX auf KB, zeigen aber auch einen supprimierenden Effekt von Sim auf das Tumorzellwachstum. Die Wirkung von Sim auf Malignome sollte in klinisch-epidemiologischem Kontext und *ex vivo* genau untersucht werden um zukünftig einen möglichen Beitrag zur Therapie maligner Tumore im Sinne multimodaler Konzepte leisten.

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POSTER 347

The anti-tumor reactivity of ROR1-CAR modified T cells depends on the targeted epitope, CAR-affinity and design of the CAR extracellular domain

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Tumor Targeting

The genetic modification of T cells with single-chain antibody-derived chimeric antigen receptors (CARs) that recognize tumor-specific surface molecules independent from HLA is the subject of intense research. CAR T cells targeting the B-cell lineage molecule CD19 are evaluated in clinical trials for B-cell tumors but carry the risk of normal B-cell depletion. The orphan tyrosine kinase ROR1 is selectively and uniformly expressed on CLL and MCL, but absent on mature normal B cells. We constructed a ROR1-CAR containing the VH and VL chains of an anti-ROR1 mAb (2A2), linked to an IgG4 spacer and a CD28/CD3zeta signaling module. ROR1-CAR 2A2 binds to an epitope in the membrane-distal Ig-like/Frizzled domain of ROR1-protein and confers specific recognition of CLL when expressed in CD8+ T cells [Hudecek et al. 2010]. ROR1 is expressed at lower density on CLL than CD19, suggesting that ROR1-CARs optimized for tumor recognition will confer the most potent anti-tumor response. Here, we developed a panel of new ROR1-CARs that target membrane-proximal ROR1-epitopes (R11), have increased affinity (R12) or have a truncated spacer domain to enhance tumor recognition. We performed a thorough analysis of T-cell function including cytolytic activity, cytokine secretion and proliferation in response to a tumor challenge and provide evidence, that distinct functions of CAR-modified T cells are influenced by the choice of target epitope, CAR-affinity and design of the CAR spacer domain. Experiments are in progress to compare the anti-tumor activity of T cells modified with each of the ROR1-CARs *in vivo* using a mouse tumor model (NSG/JeKo-1).

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POSTER 348

IMPEDIMETRIC TESTING OF NOVEL KINASE-INHIBITORS FOR THE INDIVIDUALIZED THERAPY OF THE MALIGNANT MELANOMA

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TRM – Tissue Repair and Replacement
Tumor Targeting

Today, cancer is the second most common cause of death. Due to the fact that each tumour has its own characteristics concerning genetic properties and sensitivity to active pharmaceutical ingredients (API), there is a strong demand for personalised and targeted therapies. In this context we developed a screening system that allows direct testing of oncogene directed therapeutics on primary melanoma cell lines. Using impedance spectroscopy as a non-invasive, label-free detection technique in combination with our self-developed 2D microelectrode array we are able to monitor API efficacy for more than four days. Additionally, we established protocols for detection of b-raf and c-kit mutations for analysis of tumour heterogeneity and patient dependent target validation of novel APIs like the kinase inhibitors PLX4720 and Imatinib.
We could correlate oncogene directed mutations like b-raf V600E within melanoma metastasis derived cell lines with specific sensitivity to the mutation specific kinase inhibitor PLX4720. Furthermore, we could show that our self-generated melanoma cell lines carry no mutation in c-kit and thereby demonstrate no sensitivity to the applied Imatinib. These alterations in proliferation and apoptosis induced by the tested APIs could be quantified by impedance spectroscopy. The impedimetric screening on melanoma metastasis derived cell lines with or without specific oncogene mutations revealed the target dependent response to novel kinase-inhibitors. Based on these results, our self-developed direct biosensoric chemosensitivity testing system is a promising tool for the patient specific tumour treatment.

Association: PbF III

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POSTER 349

Pharmacokinetic and –dynamic modelling of erythropoiesis under EPO application and chemotherapy

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List of topics

BBZ – Biotechnologisch-Biomedizinisches Zentrum (Theranostik)
Biophysics and Bioanalytics
Cell Biology
Clinical Studies
Drug Development and Delivery
Evolution and Molecular Diversity
Immunology and Infectiology
ICCAS – Computer Assisted Surgery
IFB – Adiposity Diseases
Imaging
LIFE – Civilisation Diseases and Genetics
Molecular Biology/Protein Biochemistry
Neurobiology
Psychology and Cognition
Social Medicine
TRM – Tissue Repair and Replacement
Tumor Targeting

Intensification of chemotherapy can result in improved outcomes of several cancer diseases. Anaemia due to the cytotoxicity of chemotherapeutic drugs is a limiting factor and requires supportive care such as erythrocyte concentrates or EPO applications.
We developed a pharmacokinetic (PK) and –dynamic (PD) model simulating erythropoiesis under chemotherapy and EPO application to predict the effect of different EPO schedules. A cell-kinetic compartment model of erythropoiesis developed in our group was combined with a PK model of EPO adopted from Krzyzanski et al. The PD model is based on ordinary differential equations describing proliferation and maturation of erythropoietic cells. The system is regulated by feedback loops. One of these loops is mediated by endogenous and exogenous EPO. Chemotherapy is modelled by depletion of cells. Unknown model parameters were determined by fitting the model predictions to data of haemoglobin, haematocrit, percentage of reticulocytes, EPO serum concentration, or red blood cell counts. The data were extracted from literature or received from cooperating clinical study groups. Parameter fittings resulted in a good agreement of model simulations and data. The EPO derivatives alpha, beta, delta, and Darbopoetin were modelled and different injection sites were considered by using different PK parameters. Eight chemotherapy protocols were modelled and simulations were performed to analyse the effect of EPO applications.
Our model explains a large set of time series data comprising EPO application and chemotherapy and allows predictions regarding the effect of different EPO schedules.

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