Leipzig Research Festival for Life Sciences 2013

12th

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Medizinische Fakultät

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Fakultät für Biowissenschaften, Pharmazie und Psychologie

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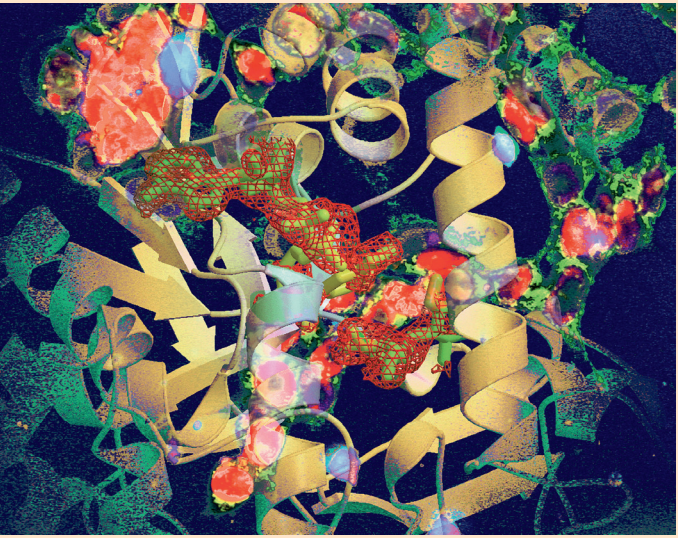

ABSTRACT BOOK

19. Dezember 2013

Ort: Max-Bürger-Forschungszentrum

J. Thiery, A. G. Beck-Sickinger, T. Arendt (Hrsg.)

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Vorwort

Liebe Kolleginnen und Kollegen, liebe Gäste,
wir begrüßen Sie sehr herzlich zu unserem *12. 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 Abstrakteinsendungen 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.
Nach den Erfolgen und dem großen Interesse in den letzten Jahren werden wir auch in diesem Jahr 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 12. 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

Gradients of signaling molecules to study hematopoietic stem cell fate decisions

BBZ – Biotechnologisch-Biomedizinisches Zentrum (Theranostik)

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Social Medicine
TRM – Translational Regenerative Medicine
Tumor Targeting

Hematopoietic stem cells (HSC) reside mainly in the bone marrow and give rise to every blood cell in the mammalian body. They occupy a unique microenvironment which is called the niche. Despite many investigations to understand the mechanisms of blood formation and dysregulation of this process the niche and its interaction with the HSC is not completely understood. This is caused by the inherent complexity of *in vivo* systems and also the limited capabilities to investigate HSC – niche interactions dynamically in living animals. Within a biomimetic microscopy setup it is possible to follow single cell fate over time periods ranging from several hours to days. Using proteins of the extracellular matrix (ECM) we create a microenvironment for HSC similar to the niche. To investigate HSC – niche cell interactions we embed protein-laden microbeads into this artificial niche to model gradients of a cell-secreted protein of interest. To characterize protein gradient formation we used confocal laser scanning microscopy with fluorescently labeled proteins. The slow release of signaling proteins from the heparinized hydrogel microbeads over days could be described by a slow diffusion process giving rise to a weak and sustained delivery of signaling proteins. By that a long-term gradient is formed near to the hydrogel particle which is sensed by HSC. In first experiments HSC as well as blood progenitors were analyzed within this setup by single cell tracking and their characteristics were quantified in terms of migration patterns and positioning within the gradient.

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POSTER 2

Structural Studies on Ectonucleotidases Involved in Purinergic Signaling

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Nucleotide pyrophosphatses/phosphodiesterases (NPPs) are a family of ectophosphodiesterases comprising 7 members in vertebrates. NPPs are glycoproteins and able to hydrolyze a wide range of molecules involved in different signaling pathways (e.g. in purinergic signaling). Whereas NPP1 and 3 are specific for nucleotides and dinucleotides, the natural substrates of NPP2, NPP5 and NPP7 are phospholipids. NPP1-3 include besides the catalytic domain a nuclease-like domain, which has no catalytic activity. Furthermore at the N-terminus of NPP1-3 two consecutive cysteinerich somatomedin B-like domains are located, which are involved in substrate binding (NPP2) and membrane anchoring (NPP1 and 3). NPP4-7 are only contain the catalytic domain. Apart from NPP2 all NPP family members are membrane associated. Based on their involvement in many physiological functions and diseases NPPs are regarded as attractive drug targets. We aim to determine crystal structures of these proteins to characterize the structural basis of substrate specificity and the catalytic mechanisms. Structures of NPP1 and NPP2 from vertebrates revealed first insights in domain arrangement and ligand binding. Nevertheless for further investigations of the catalytic function of NPP enzymes high resolution structures in complex with substrates or substrate analogs are needed. We report on structural studies of rat NPP3, which was expressed in HEK293S cells.

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POSTER 3

Cytochrome P450 BM3 and Hybrid Technology – An Approach of Converting Electrical in Enzymatic Power

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The mixed function oxygenase BM3 of the Cytochrome P450 family is of great interest for pharmaceutical and chemical industry due to its regio- and enantioselective attack of inert C-H-bonds. BM3 hydroxylates a broad range of lipophilic molecules using the NADPH-FAD-FMN shuttle system to produce a reactive Oxo-Iron(IV)-heme thiolate. However, BM3's dependence on NADPH limited the extensive commercial use because of high prices and low stability. Our research focuses on developing a NADPH free alternative – an electric powered enzyme reactor.

In this context, we are working on strategies for the direct electrically induced reduction of BM3's FAD. The goal is to find an optimum electrode configuration in combination with an enzyme immobilisation that allows a high-level electron-transfer. In our cleanroom facility, we produced first multielectrode arrays using a wide range of electrode materials. We have developed treatment methods to process and monitor electrode cleaning and organic coating procedures using cyclic voltammetry, impedance spectroscopy and atomic force microscopy. We draw on a range of interface-agents, from self-assembled monolayers of thiol and organophosphonate chemistry and surface-affine peptide tags. While we are currently still exploring the long-term stability of the organic layer, we already could demonstrate the forced electrical conversion of free FAD in solution. The next step will be the enzyme coupling on the electrode.

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POSTER 4

Modification of 3D collagen and fibrin matrices for the application as in vitro cell culture scaffolds

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Traditional cell culture in two dimensions frequently lacks the properties of the three dimensions occurring in many cellular tissues. To study cell behavior *in vitro* under more relevant conditions there is a need to engineer more accurate biomimetic matrices as cell culture scaffolds. We aim to engineer 3D biomimetic matrices from fibrin and collagen I with defined properties in topology, mechanics and functionality. Varying protein concentration as well as co-fibrillation or functionalization with other matrix proteins of the ECM, such as fibronectin, allow a defined adjustment of functional properties of the *in vitro* matrices. Thin layers of maleic-*alt*-anhydride co-polymers were used to enable covalent attachment of the layer of reconstituted collagen-fibronectin and fibrin networks to cover slips, allowing easy handling, in-depth characterization, long term stability and *in vitro* cell culture studies. For analyzing topological, mechanical and biochemical properties we used, laser scanning microscopy, image analysis algorithms, force spectroscopy, and optical density measurement. The quantitative network analysis indicated a broad range of tunable network characteristics. Cell viability and long-term stability of the matrices were investigated, too. The biomimetic 3D matrices are envisioned to be used for *in vitro* studies regarding cell migration, proliferation or differentiation of various cell types including fibroblast, macrophages, hematopoietic stem cells and melanoma cells.

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POSTER 5

Verminderung der TNFα-Freisetzung von THP-1-Zellen durch Extrakte von Myrrhe, Kamillenblüten und Kaffeekohle

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Myrrhinil-intest® ist ein traditionell pflanzliches Arzneimittel, bestehend aus Myrrhe-Harz, Kaffeekohle und Kamillenblütentrockenextrakt, welches bei gastrointestinalen Beschwerden angewendet wird. Ziel der Studie war es die Wirkung der Einzelkomponenten auf antiinflammatorische Wirkungen zu untersuchen. Dazu wurden wässrige und/oder ethanolische Extrakte der Drogen an humanen, monozytären THP-1-Zellen nach LPS-Stimulation getestet und die TNFα-Konzentration mit dem TNFα-ELISA bestimmt. Zusätzlich wurden die Wirkungen auf die Stoffwechselaktivität mit dem MTT-Test und die Zytotoxizität mit dem LDH-Test untersucht. Die Untersuchungen zeigten, dass die Extrakte aus Myrrhe, Kaffeekohle und Kamille die TNFα-Freisetzung in unterschiedlichem Maß hemmen: Wässr. Myrrhe-Extrakt (1000 µg/ml: 89,24%±2,5%), Ethanol. Myrrhe-Extrakt (50 µg/ml: 60,69%±3,918%; 100 µg/ml: 28,57%±7,407%; 200 µg/ml: 2,446%±0,3249%; IC_{50}=60,65 µg/ml), Ethanol. Kamillenblüten-Extrakt (1000 µg/ml: 38,45%±11,10%; IC_{50}=709,3 µg/ml), Wässr. Kaffeekohle-Extrakt (100 µg/ml: 90,76%±2,642%; 500 µg/ml: 84,77%±3,451%; 1000 µg/ml: 63,15%±4,440%; 1500 µg/ml: 56,03%±3,834%; IC_{50}=1886 µg/ml). In den Zytotoxitätsuntersuchungen konnten keine signifikante Wirkung nachgewiesen werden. Wir schlussfolgern, dass alle drei Bestandteile zur antiinflammatorischen Wirkung des Gesamtpräparates beitragen können. Die entzündungshemmende Wirkung ist eine wesentliche Komponente in der Wirksamkeit des Arzneimittels bei gastrointestinalen Beschwerden.

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POSTER 6

Single Cell Tracking in 3D Engineered Microenvironments for Studying Cell-Matrix and Cell-Cell Interactions

BBZ – Biotechnologisch-Biomedizinisches Zentrum (Theranostik)

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Tumor Targeting

Cells dynamically interact in three-dimensional (3D) tissues with other cell types in order to regulate many physiological and pathological processes, like tumor metastasis, stem cell niche and wound healing. To better understand the underlying mechanisms we developed a new method for automated *in vitro* tracking of living label-free cells in 3D biomimetic matrices at the single cell level. We aim to reveal cellular characteristics including migration patterns, migration types, chemotaxis, cell-cell contacts, cell density as well as proliferation and morphological differentiation features at various extracellular matrix and co-culture conditions. Various primary cell types were analyzed such as fibroblasts, macrophages, melanoma cells and hematopoietic stem cells to reveal matrix specific migration pattern. Moreover, it was possible to implement our cell tracking algorithm to analyze co-cultures of different cell types in 3D biomimetic matrices. By analyzing individual cell trajectories of melanoma cells co-cultivated with human primary macrophages, we quantified subpopulations of macrophages exhibiting distinct migratory characteristics and a decreased proliferation of melanoma cells. In summary, the efficacy and accuracy of our single cell tracking technology facilitate the *in vitro* long-term study of label-free cells in 3D biomimetic matrices to reveal cell fates in different physiological and pathological microenvironments. The method offers a less invasive and economical approach for biomedical as well as pharmaceutical studies and can be applied to a variety of scientific questions.

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POSTER 7

Optimized microelectrodearrays for label free bioelectronic in vitro and in vivo high content monitoring systems

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Tumor Targeting

Cell- and application dependent highly optimized microelectrode arrays (MEA) are essential for sensitive and feasible bioelectronic monitoring of cellular alterations. In this context, electrode size and geometry, array dimensions as well as electrode and passivation layer material has to be carefully adaptedwith regard to cell or tissue alterations like cell death, subcellular degeneration as well as ion-channel or signal pathway modulationthat should be quantitatively monitored. Moreover, we established MEA series including cultivation systems optimized for single cell, monolayer cultures, 3D cultures andorganotypiccultures. For increasing the amount of information, we established the processing of semiconductive transparent electrode materials that allows the combination of bioelectronicand photonic monitoring of cell cultures e.g. expressing fluorescence tagged target proteins. Furthermore, we developed different electrode coating strategies based on nanocolumnar surfaces as well as conductive polymer layers that leads to an increased conductance on the electrode-electrolyte layer and therefore, offers higher sensitivity especially detecting intracellular alterations. With respect to higher throughput an automated cultivation platform, our MEA series are scalable from single well systems up to full format 96-well or even 384-well systems. More strikingly, we developed flexible MEAs for in vivo applications. In combination with our self-developed hybrid-measurement systems, we offer a high performancelabel-free bioelectronic monitoring platform.

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POSTER 8

Impedance spectroscopy based label-free quantification of ion channel activity

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Impedance spectroscopy is a useful technique for label-free, real-time monitoring of cellular changes. Up to now this technique was applied to monitor cell spreading, migration, proliferation and apoptosis. Now we established impedance spectroscopy for investigation of ion channel activation. In two different experiments, we show the detection of ion channel activation with impedance spectroscopy.

The first example is the activation of the Transient receptor potential (TRP) channels that were stably expressed in HEK293 cells. 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. 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 and initially hindered by the methodological bottleneck of screening capable systems. In this context, impedance spectroscopy offers the advantage of label-free direct monitoring TRP channel activation in living cells in combination with the possibility for an easy upscaling to 96/384-well plate systems.

The second example is the detection of ion channel activity in smooth muscle cells with imidazole as an ion channel activator. The induced channel opening causes a decrease of the impedance signal, which can be quantified in a concentration-dependent manner. The aim of these projects is to establish and characterize an impedance-based high content screening system for ion channel activators and inhibitors.

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POSTER 9

Microbial bioelectrotechnology: Fundamentals of novel syntheses

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Today's era of fossil based chemicals will certainly come to an end. Thus, the development of novel, biobased technologies for the production of platform and fine chemicals is of outmost importance. The new concept "Microbial Bioelectrotechnology" aims at the interconnection of the microbial metabolism and electrodes. This interconnection allows to "add" or "extract" electrons to bioreactors, using cathodes or anodes, respectively, and thus control the microbial redox-metabolism. This control is achieved either direct, then termed microbial bioelectrocatalysis, or indirect termed "electrochemical steered fermentation". However, so far only very few studies – demonstrating the principle feasibility of microbial bioelectrotechnology – exist. Consequently, the goals of my PhD thesis are i) the identification and ii) optimization of microbial bioelectrotechnological synthesis routes for platform and fine chemicals, which will be presented in this contribution.

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POSTER 10

Microbial Bioelectrotechnology: Exploring the fundamentals of microbial thermodynamics

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A microbial fuel cell (MFC) converts chemical energy, available in a bio-convertible substrate, directly into electricity. Thereby bioelectroactive microorganisms consume for example domestic wastewater and deliver electrons – by so-called extracellular electron transfer (EET) – to the anode, resulting in the generation of electric energy. Until now, there are several constraints preventing MFCs from a wide-ranging application. One major limitation is the not completely understood metabolism of the bioelectroactive microorganisms resulting e.g. in a non-controllable formation of biomass. By a conceptual splitting of the metabolism into catabolism and biosynthesis and a detailed thermodynamic analysis of the growth and current production processes it is possible to examine the driving forces for growth respectively metabolism. This conceptual work was, so far, not performed for bioelectroactive microorganisms. In this contribution the theoretical and experimental framework of such endeavor will be presented together with first results.

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POSTER 11

Coumarin in the Biogas Process: Inhibitor or Substrate?

BBZ – Biotechnologisch-Biomedizinisches Zentrum (Theranostik)

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Plants like sweet-clover (*Melilotus* spp.) or sweet vernal grass (*Anthoxanthum odoratum*) contain the plant secondary metabolite coumarin. These plants might not be suitable as fodder for livestock because coumarin and its derivatives act as poisonous anticoagulant. The aim of this study was to investigate the applicability of coumarin-rich plants as substrates for biogas production. Therefore, coumarin was tested as a chemical added to different batch and continuous anaerobic digestion processes using grass silage and manure as substrates. In both fermentation systems coumarin caused first an inhibition of the biogas process by means of decreasing the biogas production by 17 %. In the continuous fermentation, additionally an increase of metabolites, i.e. volatile fatty acids, to a critical level (VOA/TIC value > 0.3 g_{FOS}/g_{CaCO3}) was observed which could lead to a destabilization of the entire biogas process. However, the process restabilized after 19 days by adaptation of the microorganisms which resulted in a biogas production and metabolite concentrations on a normal level. Molecular biological analysis of the microbial communities on DNA level revealed only a temporary change of the methanogenic community but a steady shift of the bacterial community caused by the coumarin addition. Furthermore, no coumarin was detected in the digestate and hence, its anaerobic degradation is suggested. Concluding, coumarin acts as substrate and as inhibitor in the biogas process and hence, coumarin-rich plants should only be used for biogas production after adaptation of the microbial community to this compound.

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POSTER 12

Community dynamics in a glycolate fed biogas reactor by flow cytometry

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A patent from Wilhelm, Posten and Räbiger (2012) present a new photobioreactor which combines a glycoalte-excreting algae and a glycolate-utilizing microbial biogas community.
The aim of the study was to observe community dynamics in a biogas (BG) reactor utilizing glycolate. Shifts in the sub-communities (SC) were analyzed in a flow cytometer due to changes in the abiotic factors organic loading rate (OLR), hydraulic retention time (HRT) and feed rhythm. Correlations between all abiotic and biotic factors were analyzed.
A positive correlation between OLR and BG production could be observed. The gas composition was (41.57% ± 3.39% CH_4 and 56.66% ± 3.54% CO_2). The C-recovery in the BG was 83.7 ± 13.39%. A strongly negative correlation between BG production and HRT and the concentration of acetate and propionate was observed. The shift to a day-night feed rhythm had no effect on the BG production.
Shifts in the cell abundance within the different SC could be observed due to changes in the abiotic factors. Especially after the adaption phase, a strong shift in the cell abundances could be observed. Positive correlations between the SC 2, 3, 5 and 9 and the BG production could be observed. SC 4 and 10 have a negative correlation to the BG production.
Glycolate is a suitable substrate for the BG production. The correlation between the abiotic factors indicates that the optimal running parameters are still unknown. Flow cytometry is an appropriate tool to analyze community dynamics in a fast way. Shifts in the cell abundance within a SC gives hints on the condition of the BG reactor.

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POSTER 13

Nanoparticulate lipopolyplexes based on PEI and liposomes for the delivery of therapeutic nucleic acids

Drug Development and Delivery

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The non-viral delivery of nucleic acids such as pDNA and siRNA *in vivo* is a matter of intense investigation. Among a variety of chemical compounds, the cationic polymer polyethylenimine (PEI) plays a pivotal role. PEIs are branched or linear in structure, available in a wide range of molecular weights. While their high cationic charge density allows the effective complexation and protection of nucleic acids, it also contributes to cytotoxicity, complex aggregation and non-specific interaction with cell and blood components, thereby limiting *in vivo* applications. Likewise, liposomes have been widely explored as delivery system.The combination of PEI polyplexes with phospholipid liposomes ("lipopolyplexes") may further improve their efficacy and biocompatibility.

In this study, we analyzed various liposome-PEI-based lipopolyplexes with regard to their biological activity (DNA transfection, siRNA knockdown) and physicochemical properties (size, zeta potential, colloidal stability). The lipopolyplex formulations based on three different PEIs (branched/linear) and various liposomes. As an attractive therapeutic application, PEI polyplexes and lipopolyplexes were also tested with regard to nebulization for the inhalative application of nucleic acids.

We demonstrate that certain liposomes improve the transfection efficacy of PEI complexes and retain their biological activity and complex stability upon storage even at 37 °C and in the presence of serum. Interestingly, the nebulization of PEI polyplexes and lipopolyplexes does not affect the biological activity which also offers an avenue for the treatment of pulmonary diseases.

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POSTER 14

Carbaboranes in short npy analogs – redirecting biological activity

Drug Development and Delivery

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Tumor Targeting

Regulation of food intake and energy homeostasis are two essential physiological functions of the neuropeptide Y (NPY)/ Y receptor (YR) system. Herein, the four YR subtypes Y_1R, Y_2R, Y_4R and Y_5R are differentially involved. Briefly, the Y_1R and Y_5R induce appetite, whereas the Y_2R and Y_4R mediate satiety. Accordingly, the development of potent short NPY analogs, preferentially addressing the Y_2R and Y_4R, appears to be a promising strategy in anti-obesity drug development. Carbaboranes are icosahedral boron carbon clusters. As pharmacophoric building blocks they are able to exert strong hydrophobic interactions and proton-hydride bonding. Hence, an N^{ε}-*ortho*-carbaboranyl propionic acid modified lysine was introduced into position 32 of the short Y_1R/Y_4R preferring NPY analog [Pro^{30}, Nle^{31}, Bip^{32}, Leu^{34}]NPY 28-36. Interestingly, the introduction of the *ortho*-carbaborane in this position resulted in an increased activity at both the Y_2R and the Y_4R. Simultaneously, the activity at the Y_1R was decreased. Surprisingly, subsequent receptor internalization studies with the novel carbaborane analog revealed that receptor internalization can neither be triggered at the Y_2R nor at the Y_4R suggesting a biased ligand action. Additional structural investigations by ^{1}H-NMR spectroscopy revealed significant conformational changes in the side chains of residues Pro^{30} and Leu^{34} which nicely correlates with the shift from Y_1R/Y_4R to Y_2R/Y_4R activation preference. Thus, the carbaborane-mediated structural changes in position 32 induce a switch of the bioactive conformation and subsequently influence the receptor subtype activation behavior.

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POSTER 15

Structure-based peptide design: Mimicking helical conformation

Drug Development and Delivery

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Tumor Targeting

Inhibition of protein-protein interactions by small molecules is quite challenging, since their interaction surface is usually large and lacks deep binding pockets. As helical regions of proteins are often involved in such interactions, peptidic helix mimics may be able to circumvent the difficulty to target them and raise the possibility to find potent protein-protein interaction inhibitors.
In general, short peptides have no defined secondary structure in aqueous solution due to limited intramolecular hydrogen bonding. But there exist several strategies to induce helical conformation by methods based on helix dipole interactions and cyclization strategies [1].
In this work, different methods to stabilize helical peptide conformation were investigated and compared to each other. Based on a model peptide, modifications were introduced to support helix stability by interaction with the helix dipole or by formation of salt bridges. Furthermore the effect of secondary structure stabilization by side-chain to side-chain cyclization was investigated. Assembly of peptides was performed by solid phase peptide synthesis using the Fmoc strategy. Secondary structure of the modified peptides was investigated by CD spectroscopy.

[1] Garner J, Harding MM, *Org Biomol Chem* 2007, 5, 3577-3585.

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POSTER 16

Design of Polymer-based Nanocarriers for Targeted Delivery of Nucleic Acids

Drug Development and Delivery

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Tumor Targeting

Specific knockdown of disease-related genes by induction of RNA-Interference (RNAi) or micro-RNA replacement are highly attractive intervention strategies, yet targeted delivery remains to be elusive and clinically challenging. We use a low molecular weight polyethylenimine (PEI F25-LMW), developed in our lab, as an efficient system for gene delivery in vitro and in vivo. The molecular structure of PEI and its ability to form complexes with nucleic acids (polyplexes) provide the basis for the generation of targeted nanoparticles by chemical coupling of cell-specific ligands.
Here, we report on the development of ligand molecules by recombinant expression of target tissue-specific proteins. We employed a bacterial expression system for the production and purification of a peptide, which binds to carbohydrate structures highly expressed on the surface of various tumor cells and can be covalently coupled to PEI. Additionally, a fusion protein consisting of the peptide and a maltose binding protein (MBP) was generated, to allow its conjugation to oligomaltose-grafted PEIs (OM-PEIs), which have recently been introduced for nucleic acid delivery in vitro and in vivo.
Furthermore, a hepatitis E virus capsid protein (HEV) is under intense investigation for liver-targeting in terms of hepatocyte-specific uptake of therapeutic polyplexes. We believe this to be an effective delivery route for gene therapy of diseases like dyslipidemia, an important risk factor interrelated with the metabolic syndrome.
The targeted delivery strategies presented here are executed within a funding project of the faculty of medicine.

Funding: formel1

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POSTER 17

Novel polymer based nanovalves for the electrically controlled size selective biomolecule release

Drug Development and Delivery

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Tumor Targeting

In modern medicine there are many concepts for the controlled transport and release of specific biomolecules by nano- and microsystems. Most important for a release system is to reach the correct amount of compound by a controlled output rate at the right site of action without residual risks or undesirable side-effects. With regard to sensitivity, stability and applicability we present a polymer-based and electrically controllable nanovalve system for intelligent implants, where the flux of biomolecules is regulated reversibly by changing the electrochemical potential under physiological conditions. The size of the nanopores can be adapted to the defined size and expected flux of the molecule of interest (e.g. active pharmaceutical ingredients). The substrate for these defined pore array is a nanoporous aluminium oxide membrane for that we established the controlled deposition of a well-defined polypyrrol-layer (PPy) by electropolymerisation. The redox change is used for opening and closing the nanopores. In the presented case dodecyl benzene sulfonate (DBS) is incorporated. Reduction creates an osmotic swelling of the PPy-layer, whereas oxidation of the polymer leads to a shrinking triggered by the charge balancing through the surrounding ions. The first proof of concept offers the use in intelligent implants for the electrically controlled release of e.g. peptide therapeutics. Furthermore it can be used for widespread applications in lab on a chip systems.

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POSTER 18

Nanoparticle based transfection for in vivo gene therapy of immune diseases

Drug Development and Delivery

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Tumor Targeting

Gene therapeutics are new, effective drugs. But to date the biggest challenge of this therapy is the transfer of genetic information into the target cells.
Conventional immunosuppressive drugs are not always effective and might cause severe side effects. A gene therapeutic approach targeting and inhibiting specifically overreactive immune cells would be desirable.
We aim to optimize *in vivo* transfection of immune cells based on PEI cationic nanoparticles with a special focus on lung for the potential treatment of asthma.
We analyzed short-term contact of modified PEI nanoparticles. We also optimized detection of PEI nanoparticles in tissues by Prussian Blue staining. PEI nanocomplexes then were applied into trachea of healthy and asthmatic mice. Location of complexes was analyzed in lung tissue and BAL.
Short-term contact of PEI complexes *in vitro* revealed most effective transfection for unmodified and PEGylated PEI. PEI bound to a-cd3e antibody was more effective then IgG bound PEI, but less then unmodified PEI. *In vivo* transfected lung of mice revealed widespread dispersal of PEI nanocomplexes. Complexes were also detected in BAL of asthma induced animals.
We conclude that PEI nanoparticle-based *in vivo* transfection of lung tissue is a promising approach to gene therapy of asthmatic diseases. In the next step, *in vivo* transfection of a-cd4 oligonucleotide will be explored to reduce asthma in a murine model of the disease.

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POSTER 19

Single-chain antibody-coupled polyethyleneimine carrier systems for the tumor-targeted delivery of siRNAs

Drug Development and Delivery

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Tumor Targeting

Since its discovery, RNA interference turned out to be a powerful tool, also for the inhibition of targets considered to be undruggable. For its efficient use in clinical applications, in vivo and in vitro, potent delivery systems are required. The development of non-viral delivery systems for small RNAs (siRNAs) is under intense investigation and has led to various lipid and polymeric excipients. Among those, polyethyleneimine (PEI) is a promising candidate due to its high biological activity. PEIs are synthetic polymers with protonable amino groups in every third position of the molecule. They show high cationic charge densities at physiological pH which enable efficient complexation and protection of nucleic acids from degradation, but determine biodistribution and lead to cytotoxicity.
We demonstrate that the grafting of hyperbranched PEI with maltose is a suitable strategy to shield the positively charged particle surface, thus preventing nonselective interactions and enhancing biocompatibility/decreasing cytotoxicity as compared to unmodified PEI. Various oligomaltose grafted PEIs (OM-PEIs) with different degrees of substitution have been tested with regard to structure-function relationships. Furthermore, to combine the advantages of maltose modified PEI with targeted delivery, we have now attempted to couple OM-PEIs with a single-chain antibody specifically binding to cell surface proteins. Here, we present the first results of experiments performed with selected oligomaltose-PEIs coupled with a maltose-binding protein single-chain antibody (MBP-scFv) fusion protein targeting the prostate stem cell antigen (PSCA).

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POSTER 20

Local Interactions Influence the Fibrillation-Kinetics, Structure and Dynamics of Amyloid b Peptides but Leave the General Fibril Structure Unchanged

Biophysics and Bioanalytics

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After synthesis of the unstructured polypeptide chains, proteins fold spontaneously into their highly ordered and biologically active form. This protein folding pathway is determined by intramolecular interactions and the individual 3D structure of a given protein is encoded in the sequence of the amino acids. Another thermodynamically stable conformation can be formed during pathological processes, which results in the formation of amyloid fibrils. Here, intermolecular interactions between the polymer chains dominate the formation of the cross-β structure. More evidence accumulates that the amyloid structure represents a common motif of proteins irrespective of their amino acid sequence. We study the influence of local physical forces in model fibrils of Aβ(1-40), where amino acid mutations modify the local structure and dynamics of the fibrils and also influence the fibrillation kinetics. Different mutations at a crucial hydrophobic contact were synthesized. Fibrillation kinetics was analysed by ThT fluorescence. Quite substantial differences in the kinetics of the different mutants were observed. The influence of the mutations on the structure and dynamics of the Aβ fibrils was studied by solid-state NMR. The analysis showed that the local Aβ structure and dynamics was altered by weakening the contact F19-L34, but the general structure remains the same. With one exception all investigated peptide variants formed stable fibrils with the known morphology. The overall structure seems to be very robust and single mutations cannot completely destabilize the Aβ structure.

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POSTER 21

Von-Mises- und Schubspannungsanalyse in der Peripherie einer eingebetteten künstlichen Hüftgelenks-Pfanne unter Impingement-Belastung basierend auf vollständig dreidimensionalen DMS-Messungen

Biophysics and Bioanalytics

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Nach Hüftgelenksersatz kann es zum Impingement der Implantatkomponenten bei alltäglichen Patientenaktivitäten kommen, wodurch eine Gefahr auf die azetabuläre Verankerungsstabilität in der Knochen-Implantat-Grenzschicht entstehen könne. Es war das Ziel der Studie, unter Impingement-Belastung eine schädlich Wirkung in der Implantatumgebung einer künstlichen Hüftgelenks-Pfanne mittels Schub- und Von-Mises-Spannungsanalysen zu beurteilen. An der Außenkontur einer Hüftgelenks-Pfanne wurden Dehnungsmessstreifen DMS an festgelegten Positionen appliziert und das gesamte Messobjekt mit Hilfe eines homogenen Gießharzes als Knochen-Ersatzwerkstoff eingebettet. Ein Hebelarm mit aufgestecktem Hüftgelenks-Kopf repräsentiert die femorale Komponente zum Aufbringen definierter Hebelmomente in einem speziell entwickelten Versuchsstand zur Simulation statischer Impingement-Belastungen. Bezüglich des Impingement-Punktes wurde das Messobjekt in definierten Winkelschritten gedreht und nachfolgend die Material-Dehnungswerte innerhalb des Knochen-Implantat-Modells gemessen. Aus den Messergebnissen wurden die Schub- und Von-Mises Spannungen berechnet. Die maximalen Berechnungsamplituden für die Schubspannung in Höhe von –0.3 MPa sowie der Von-Mises-Spannung von 0.57 MPa traten, wie zu erwarten, unterhalb des Impingement-Punkes auf. Im Vergleich mit der wissenschaftlichen Literatur zu Spannungsanalysen in Abhängigkeit von der Knochendichte waren die hier berechneten Spannungswerte geringer und können demzufolge keine schädliche Wirkung auf die azetabuläre Verankerungsstabilität in der Implantatumgebung bei Impingement-Belastungen verursachen.

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POSTER 22

The Neuropeptide Y bound to the Neuropeptide Y Receptor Type 1: Analysis of GPCR-Ligand Interaction by NMR

Biophysics and Bioanalytics

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Tumor Targeting

G protein-coupled receptors (GPCRs) execute the lion's share of work of cellular communication. They allow cells to detect external signals, such as light or molecules, or to communicate with each other through hormones or neurotransmitters. Unfortunately, molecular characterisation of these large transmembrane proteins is difficult. Solution nuclear magnetic resonance (NMR) spectroscopy offers the opportunity to study structural and dynamical aspects in the interaction of ligand and receptor. Using different NMR experiments we try to understand how the neuropeptide Y (NPY) bound to one of its GPCR, the neuropeptide Y receptor type 1 (Y1R). Therefore, several differently $^{15}N/^{13}C$-labelled NPY variants were synthesized by solid phase peptide synthesis and studied bound to the receptor by NMR. The Y1R was produced recombinantly in *Escherichia coli* as inclusion bodies, solubilised in SDS, refolded and incorporated in DMPC/DHPC bicelles in a high micromolar concentration. We determined several changes in the NPY backbone bound to the receptor in comparison to the not bound state via recording different $^{1}H/^{15}N$ HSQC spectra by solution NMR in the presence and in the absence of the receptor. Finally, our $^{13}C/^{13}C$ correlation spectra recorded by solid state NMR indicate a change in the secondary structure of NPY bound to the receptor. Taken together, the binding of NPY to the Y1R is combined with a considerable altering in the structure of the ligand.

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POSTER 23

Protein surface modifications reduces autoactivation of human trypsinogen

Biophysics and Bioanalytics

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Tumor Targeting

Trypsinogen is the inactive precursor of trypsin, a serine protease cleaving peptides after arginine and lysine residues. Trypsinogen is active only after its eight-amino acid long activation peptide has been cleaved off by another protease, the enteropeptidase. Trypsinogen (PRSS1) can also autocatalytically be activated, without enteropeptidase being present. This process is called autoactivation. In biotechnological and biomedical applications, this autoactivation mechanism mostly leads to an undesired background signal. Therefore, a trypsinogen mutant with a lower degree of autoactivation is desirable.

Based on a sequence alignment with trypsinogen variants of different species, a human trypsinogen mutant was generated. Several residues were changed to identify important residues which may be involved in the autoactivation mechanism. After insoluble expression in *E. coli* cells and subsequent refolding, trypsinogen was purified via an ecotin affinity chromatography. The autoactivation of the modified trypsinogen was characterized in comparison to the recombinant wild type enzyme. The new mutant of the human trypsinogen shows a significantly decreased autoactivation compared to human wild type trypsinogen and is potentially interesting for biotechnological applications where a low degree of autoactivation is needed.

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POSTER 24

Standardized Sample Pretreatment for the Simultaneous Quantification of Seven Apolipoproteins in Human Plasma via LC-QTrap MS

Biophysics and Bioanalytics

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Tumor Targeting

Objectives: Apolipoproteins are predictors of cardiovascular disease. Recently, LC-MS/MS emerged as an alternative to immunological protein determination methods. We investigated different sample pretreatment strategies and developed a standardized protocol for the simultaneous quantification of seven apolipoproteins in human plasma via proteotypic peptides by LC-QTrap MS.
Methods: Denaturation, reduction, alkylation and tryptic digestion including microwave and ultrasound assistance were investigated. Quantification and peptide confirmation were performed by micro-liquid chromatography coupled to a quadrupole-linear ion trap mass spectrometer. For 500 human plasma samples method comparison with an immunoassay was performed for Apo A-I and Apo B.
Results: Tryptic digestion times varied between 5 min (Apo A-I, Apo E, Apo A-IV) and 16 h (Apo A-II). Digestion yield was not improved by application of ultrasound or microwave radiation. Linearity was approved between 0.1 nmol/L – 100 mmol/L. The lower limits of quantification were ≤ 0.4 μmol/L (Apo A-I, Apo A-IV, Apo B-100, Apo C-I, Apo C-III, Apo E) and < 1.4 μmol/L (Apo A-II). Variabilities < 13% were determined. Method comparison with immunoassays showed a good agreement for Apo A-I and Apo B.
Conclusion: Using the validated pre-analytical protocol the simultaneous analysis of seven apolipoproteins in human plasma can be applied in clinical studies for reliable investigations of apolipoprotein distributions in cardiovascular disease.

Funding: life

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POSTER 25

Application of time-resolved fluorescence to an avidin-biotin based heterogeneous immunoassay

Biophysics and Bioanalytics

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Tumor Targeting

Immunoassays play an important role in research and clinical biochemistry for the analysis of a wide range of targets such as proteins, hormones or tumor markers. For a given analyte, the immunoassay should provide sufficient specificity and sensitivity within the required concentration range.

Here we present a heterogeneous immunoassay for the detection of interleukin-6. The assay applies the amplification system (strept) avidin-biotin in combination with time-resolved fluorescence detection. Therefore, a europium(III)-based dye (EuLH) was coupled to biotin via a oligoethylene glycol linker (OEG). The length of this linker was optimized in the range from 3 to 11 monomer units in order to improve the (strept)avidin-biotin binding, with OEG_{11} providing the best signal-to-background ratios.

The optimized assay parameters provide a detection limit in the fmol-range and a linear signal range of two orders of magnitude.

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POSTER 26

Rapid Quantification of Cortisol, Cortisone, Dexamethasone and Prednisolone in Human Saliva by Liquid Chromatography – Tandem Mass Spectrometry

Biophysics and Bioanalytics

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Objectives: Reliable determination of salivary cortisol (CL) and cortisone (CN) concentration is of interest in the assessment of stress-associated adrenocortical function. LC-MS/MS enables the rapid, simultaneous quantification of glucocorticoids avoiding cross-reactivity in commonly used immunoassays.
Material and Methods: Saliva (50 µl) was prepared by diluting with 100 µl precipitating agent. Online solid phase extraction (SPE) for sample cleanup was combined with rapid chromatography. Detection via tandem mass spectrometry was performed on an AB SCIEX QTRAP® 5500. Deuterium labelled derivatives were used as internal standards. 360 saliva samples from the LIFE Child Depression study have been used for a method comparison between the presented LC-MS/MS method and a commercial immunoassay.
Results: The lower limits of quantification were 0.2, 0.1, 0.1 and 0.4 ng/ml for CL, CN, dexamethasone (DN) and prednisolone (PN) respectively. Mean coefficients of variation determined in intra and inter assay experiments were < 5.1%, < 7.2%, < 15.3% and < 10.0% for CL, CN, DN and PN respectively. The total run time was 4.5 min. A direct correlation between the CL/CN ratio and the absolute CL concentration was found (r = 0.82). The method comparison showed a good correlation with the immunoassay above 0.5 ng/ml (r = 0.96). At lower CL concentrations the correlation was lacking due to cortisone cross-reactivity in the immunoassay.
Conclusion: We present a rapid, specific and reliable quantification method to assess glucocorticoid concentrations in saliva which is of interest for clinical routine diagnostics and epidemiological studies.

Funding: life

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POSTER 27

Influence of fluorescent beads on actin networks

Biophysics and Bioanalytics

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The viscoelastic properties of F-actin networks, a model system for semiflexible polymer networks, can be explored with passive microrheology. For this technique the thermal fluctuations of tracer particles are used to calculate the complex shear modulus. This allows to obtain both the bulk properties and their microscopic origins. A common microrheological method is video particle tracking of fluorescent tracer particles with the help of an epifluorescent microscope.
Using this method, we found that illumination of fluorescent beads with their appropriate excitation wavelength leads to a striking "light-induced softening" of actin gels. Illumination with other wavelengths and the usage of bright field microscopy do not influence thermal bead fluctuations. The addition of oxygen scavengers cannot significantly reduce the light-induced softening. We conclude that fluorescent beads impair results and recommend bright field imaging for studying the microrheology of actin networks.

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POSTER 28

Structure analysis of the Interleucin-8 / Glycosaminoglycan complex by HDX-MS

Biophysics and Bioanalytics

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Tumor Targeting

The recruitment of different chemokines and growth factors by glycosaminoglycans (GAGs) such as chondroitin sulfate or hyaloronan plays a critical key role in wound healing processes. Therefore the Transregional Collaborative Research Centre 67 which aims for the design of intelligent artificial extracellular matrixes (aECM) for clinical application in wound healing of skin and bone tissue intensively studies the interaction of common regulating proteins with compounds of the ECM. Here Hydrogen-Deuterium-Exchange (HDX) is introduced as a method to probe binding interfaces of IL-8 in complex with tetrameric Chondroitin sulfate, which has been already solved by determination of chemical shifts by NMR (Pichert et al. 2011). Here highly correlate to these data we showed that HDX is capable of identifying binding surfaces in protein-GAG complexes with sufficient accuracy. As shown by Pichert et al. CS sulfated at position two and four bound with the helical binding area of the sequence positions 54-77 which had also been observed with our analyses. HDX proofed as valuable instrument for the analysis of protein-GAG complexes promising for the research of high molecular weight saccharides with less size restrictions and lower sample need than standard methods like NMR and X-Ray crystallography. We showed that binding surfaces can be received from such experiments and that obtained data is comparable to NMR results in a way that in silico models derived from our data would be consistent to models based on atomic resolution experiments.

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POSTER 29

Tuning mechanics & glycosaminoglycan binding of 3D collagen networks for in vitro cell studies

Biophysics and Bioanalytics

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Tumor Targeting

The extracellular matrix (ECM) affects cells by different pathways, including soluble signaling molecules and mechanical properties. By that the ECM plays an important role in the regulation of cell differentiation, migration, proliferation, and apoptosis. To get a better understanding of the underlying mechanisms we develop 3 dimensional (3D) biomimetic collagen I matrices with defined physical properties and composition. The matrices of fibrillar collagen I are modified by chemical cross-linking and varying the collagen concentration to adjust their mechanical properties, topology and functionality. Glycosaminoglycans (GAGs) are integrated by covalent and non-covalent conjugation into the fibrillar collagen I networks to provide binding sites for growth factors. The topology was analyzed by combined laser scanning microscopy and image analysis algorithms, while mechanical properties were determined by colloid-probe force spectroscopy. GAG conjugation were investigated by Blyscan assays and fluorimetry.

The topology and mechanics of the 3D collagen matrices with a layer thickness of approximately 150 μm were shown to be correlated to each other. Pore diameters in the range of 1 to 4 μm were dependent on collagen concentration and correlated with a Young's modulus between 50 and 10 Pa. Heparin and high-sulfated hyaluronan were found to bind with high affinity even without covalent conjugation to the collagen networks, while non-sulfated hyaluronan does not bind without covalent attachment schemes. *In vitro* cell experiments show an influence of the physical properties and the GAG binding on cell behavior.

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POSTER 30

Carbon nanotubes as highly conductive linker for microelectrode-mediated redox enzyme regeneration

Biophysics and Bioanalytics

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Tumor Targeting

Stereo- and regioselective hydroxylation reactions at non-activated carbon chains are an attractive but so far not commercially used application of redox enzymes. Thus the aim of our project is the development of a current-regenerated in vitro hydroxylation system for biocatalytical applications.

Exemplarely, we choose an alkan mono-oxygenase (P450) to demonstrate (P450) to demonstrate the proof of principle. Monooxygenases need expensive cofactors like NAD(P)H which serve as electron donors. To overcome these limitations recombinant cytochrome P450 enzymes should be used and electrochemically reduced at gold or indium tin oxide electrodes.

Due to their high conductivity, nanometer scale and good biocompatibility carbon nanotubes (CNTs) as well as graphene seem to be suitable as linker to achieve an optimal electron transfer between enzyme and electrode while maintaining a high enzyme activity.

For our initial experiments, we used commercially available unmodified as well as amine-functionalized CNTs. The characterization via atomic force microscopy (AFM) and scattering electron microscopy (SEM) showed that due to their high hydrophobicity the tubes appear in bundles and form coils.

First proof of principle experiments on coupling CNTs to gold surfaces showed an increase of the peak current in cyclic voltammograms associated with a decrease of the charge transfer resistance which indicates a conductivity enhancement of the Electrode surface.

These findings provide a good basis for coupling experiments of cytochrome P450 enzymes with an optimized electron transfer.

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POSTER 31

Interaction of Gα protein peptides with Y2 receptor studied with NMR spectroscopy

Biophysics and Bioanalytics

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The human Y2 receptor (Y2R) is a rhodopsin-like (class A) G protein coupled receptor (GPCR). Its extracellular ligands are tyrosine rich peptides which belong to the neuropeptide Y (NPY) family comprising NPY, pancreatic peptide (PP) and peptide YY (PYY). Binding of these stimuli is coupled to the activation of complex cytosolic signaling via G proteins. This action of Y2R is involved in the inhibition of neurotransmitter release, the regulation of memory retention, circadian rhythm and angiogenesis making it an interesting drug target.

With the help of NMR spectroscopy we aim to understand the function and dynamics of Y2R with respect to the intracellular G proteins. G proteins are heterotrimers consisting of Gα-, Gβ- and Gg-subunits of which the C-terminus of the Gα protein forms the most prominent interaction site with the receptor. In the past it was shown that a peptide with only eleven C-terminal amino acids can stabilize the activated form of the receptor [1]. Such an eleven residue long peptide was synthesized with isotopically labeled amino acids, incubated with Y2R and investigated with solution NMR. First results indicate that it is possible to distinguish between different forms of the Gα peptide in dependency of the presence of the extracellular ligand NPY. Thus, we are able to characterize the interactions and dynamics of the Gα peptide bound to Y2R. Furthermore, solid-state NMR will provide information about the secondary structure of the Gα peptide.

[1] Dratz et al. (1993), Nature, 363:276-81

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POSTER 32

Chemically modified glycosaminoglycans – Synthesis and Characterization

Biophysics and Bioanalytics

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The extracellular matrix (ECM) comprises large amounts of glycosaminoglycans (GAGs), particularly hyaluronan, chondroitin/dermatan sulfate and keratan sulfate. There is increasing evidence that the sulfation of GAGs does not occur at random, but a "sulfation code" exists that is important for e.g. cell differentiation.

Our prime interest is the synthesis of selectively modified GAGs with defined physiological functions. Various oversulfated GAGs with different substituent patterns could be synthesized and characterized by high resolution ^{13}C NMR. This is the method of choice to characterize chemically modified GAGs while ^{1}H NMR is highly useful to monitor the presence of impurities.

Unfortunately, matrix-assisted laser desorption and ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) analysis is hampered by several problems: intact GAG polysaccharides cannot be characterized by MS because the transfer into the gas phase is accompanied by the decomposition of the polymer. Thus, GAGs are normally digested into defined oligosaccharides prior to MS analysis. Unfortunately, this approach is primarily applicable to natural GAG while the related enzymes are inhibited by chemically modified derivates.

We will show here that this problem can be minimized by carefully adjusting the conditions of the digestion. Also the (unwanted) loss of the sulfate residue can be minimized. It will be shown that the combination of all mentioned methods allows the detailed characterization of all GAG derivatives.

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POSTER 33

Soft hydrogel particle screening assay for measurement of biomolecular interactions between protein and ligand

Biophysics and Bioanalytics

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Proteins dynamically interact in organisms with their ligands in order to influence myriad of biological functionsat the molecular level, like recognition events, adhesion, inflammation and enzyme activity. To analyze the underlying interactions between biomolecules we developed a new force-based detection technique that can be easily adapted to construct various label-free biosensors for high throughput applications. The advantage of label-free biosensors lies in the ability to probe biomolecular interactions with high selectivity without the risk of altering the affinity of the analyte molecules e.g. by fluorescent labeling. We aim to reveal molecular interactions and therein the effects of interface stiffness, external forces and ligand density as well as kinetics of competitive reactions in receptor-ligand interaction.These parameters can be studied by the novel detection principle basedon soft colloidal probes (SCP) and their adhesion-induced mechanical deformation at ligand / receptor interfaces.
In summary, our label-free screening method facilitates the measurement of biomolecular interactions with high sensitivity and selectivity and enables new opportunities like the analysis of molecular binding at mechanically flexible interfaces, insights into colligative bindings and the effects of ligand density or external forces. The method offers an inexpensive, robustand highly sensitive approach for drug screening assays as well as biomolecule interactions studies and can be applied to other scientific questions e.g. cell-material interaction studies.

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POSTER 34

Cell free expression of specifically isotope labelled neuropeptide Y receptor type II

Biophysics and Bioanalytics

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Tumor Targeting

The neuropeptide Y receptor type 2 (Y2R) belongs to a class A or rhodopsinlike GPCR family which mediates its cellular responses via (PTx)-sensitive G proteins as well as elevation of the intracellular Ca^{2+} level upon extracellular binding of tyrosine rich peptides. There is a great interest in evaluating the pharmaceutical potential of Y2R signaling in treatment of obesity, since activation of Y2R induces satiety.

NMR spectroscopy is a powerful tool to study the function of Y2R in terms of the molecular structure and its intramolecular dynamics. It therefore offers a great prospect in finding new ways for the treatment of obesity. However, preparation of functional receptor in sufficient amounts for NMR based studies and subsequent signal assignment is still a challenging task. Here we establish a cell free expression system for the production of Y2R. Replacing the recombinant protein expression with a cell free based expression system (1) accelerates and streamlines the production, (2) allows for easier purification of the expressed protein, (3) offers open accessibility to the reaction and (4) allows for selective incorporation of isotope labelled amino acids by elimination of the metabolism of a living host environment. Selectively isotope labelled samples of the Y2R receptor reduce the complexity of the resulting NMR spectra and allow the examination of changes to a single amino acid e.g. in case of receptor activation.

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POSTER 35 **Cell response to geometrical constraints**

Biophysics and Bioanalytics

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Tumor Targeting

Multicellular organisms, like us, rely on the collective organization of individual cells into compartments and organs. In this process, geometry plays a fundamental role. In addition, physicochemical and mechanical properties of the extracellular matrix are of paramount relevance for the adhesion and behavior of cells.
We grow human umbilical vein endothelial cells on hydrogel substrates micropatterned with adhesion ligands (fibronectin) to study initial phases of cell adhesion at geometrical constraints. We observe a bimodal organization of cytoskeletal architecture for cells grown on striped micropatterns which is indicated by a discontinuous distribution of actin stress fiber spacing. In analogy to a wetting process, such a bimodal characteristic can be related to changes in interfacial energies which can be linked to changes in cortical tension and the overall force balance of the cell. In current studies we vary extracellular and intracellular parameters, such as stripe width, substrate stiffness and ligand affinity as well as biochemical perturbation of intracellular elements of mechanotransduction in order to reveal underlying mechanisms in geometry sensing. We employ traction force cytometry and immunofluorescence studies to identify biophysical, biochemical, and structural parameters relevant for cellular response to geometrical constraints.

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POSTER 36

Early cell adhesion on hydrogels with graded stiffness and ligand affinity

Biophysics and Bioanalytics

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Tumor Targeting

Cell signaling in response to mechanical cues – mechanotransduction – is known as one control mechanism for several basic cell functions, like proliferation, differentiation and cell death. For a better understanding of mechanotransduction, we investigated early cell adhesion on hydrogels with an independent variation of substrate stiffness and affinity of adsorbed ligands.

Thin film coatings of maleic acid copolymers on top of polyacrylamide hydrogel layers were fabricated to tune the affinity of fibronectin by changing the fraction of polar groups on the surface (i.e. poly-(styrene-*alt*-maleic acid) vs. the more hydrophilic poly-(ethylene-*alt*-maleic acid)). The stiffness of the hydrogel was modulated between 1 kPa and 10 kPa. Human umbilical vein endothelial cells 1) were monitored by time-resolved cell traction force microscopy to determine the dynamics of substrate-dependent traction stress development and 2) activated Rho GTPases were investigated by pull-down assays and G-LISA to reveal key proteins in the concomitant biochemical activation.

The time-resolved traction force microscopy showed a saturation of traction stress with higher magnitudes on substrates with higher fibronectin affinity. The variation of gel stiffness has likewise an effect on the development of cellular forces. The changes in the force activation pattern for both parameters can be attributed to diverging mechanisms in the adhesion signaling of cells. The different biochemical assays for Rho GTPase detection were evaluated to be not sensitive enough for the quantification of the response of separated cells on 2D surfaces.

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POSTER 37

Photo-physical properties of Na+-indicator dyes suitable for two-photon fluorescence-lifetime imaging

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Biophysics and Bioanalytics

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Two-photon microscopy (TPM) offers great advantages in fluorescence imaging of live cells. A severe drawback, however, is that quantitative ratioing of fluorescence intensities at different wavelengths (useful for indicator dyes excited in the one-photon mode) is not practical in TPM. We aimed at establishing time-correlated fluorescence lifetime imaging (tcFLIM) as an alternative method for quantifying intracellular Na^+ dynamics in TPM. We compared the photo-physical properties of the four Na^+-sensitive fluorescent indicator dyes Sodium-Binding Benzofuran Isophtalate (SBFI), CoroNa Green (CG), Sodium Green (SG), and Asante NaTRIUM Green-2 (ANG-2) using a pulsed two-photon laser source and a fluorometer for cuvette calibrations. While all four dyes showed the expected Na^+-dependent intensity changes, only CG, SG and ANG-2 provided significant changes in their fluorescence lifetime. ANG-2 showed the most pronounced changes of its lifetime upon Na^+ binding: 63 ps of the free dye to 2.4 ns of the Na^+-bound form. However, ANG-2 also binds protons (generating a lifetime of 2,8 ns), and K^+ (0.56 ns). While this ionic interactions complicate the analysis of the lifetime of ANG-2, the significant difference of its K^+- and Na^+-bound forms render ANG-2 a promising indicator dye for life-time based intracellular Na^+ imaging.

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POSTER 38

What can NMR and Diffusion measurements reveal about healing processes?

Biophysics and Bioanalytics

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Tumor Targeting

Using a tibial head defect we investigated bone regeneration using biodegradable poly(lactic-co-glycolic acid) (PLGA) scaffolds, providing a macro-porous three-dimensional carrier. Scaffolds with similar porosity but different pore sizes were implanted into a tibial defect of a rat model. Two or four weeks after implantation, the scaffolds were monitored by MRI. Collagen and apatite of the regenerated extracellular matrix were quantitatively studied by solid-state NMR. From our assessment, concentration and molecular dynamics of the de novo formed ECM was close to that of native bone. In all experiments, a pore size of 300 to 500 μm was most effective.

Nevertheless, a high interest to optimize bone scaffold materials for optimal healing especially in early stages. The proliferation should be enhanced by surface coating (e.g. growth factors). The controlled release of these materials is of major impact and guided by diffusion. Hence, we studied the diffusion of proteins in different gels by Pulsed Field Gradient NMR. As expected, hindered diffusion depends on the gel concentration and thus should be carefully taken into account to ensure an optimal coating of the used implants. Furthermore, we obtained the diffusion to be anomalous, but interestingly the strength of this effect depends only on the protein and not on the surrounding isotropic matrix. Hence, the influence of the hydrodynamic shape of the protein or binding effects can be monitored. Eventually, these results could also lead to a more clinically setup e.g. the assessment of pH gradients during inflammation by using a tracer-molecule with pH-dependent shape.

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POSTER 39

Analysis of free fatty acids and other lipids by UV-LDI mass spectrometry using insect wings as sample substrate

Biophysics and Bioanalytics

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Tumor Targeting

Free fatty acids (FAs) are involved in numerous physiological processes. For instance, they play important roles in energy transport as well as storage and are involved in inflammatory reactions.
Established methods of (quantitative) analysis of FAs are gas chromatography (GC), often coupled with mass spectrometry (MS), and soft ionization MS techniques. However, all these methods have also significant disadvantages.
A new promising method is the use of Drosophila wings as sample substrates for matrix-free UV-(fly-assisted)-LDI MS. This enables the widely background-free analysis of FAs and other lipids such as triglycerides (TAG). Best results were so far achieved by using orthogonal-TOF MS with a fine vacuum of about 2 mbar in the ion source. This increases the stability of FAs under high vacuum conditions. Collisional cooling stabilizes additionally weakly bound lipid-cation complexes.
Here, the potential of the FALDI method for the quantitative analysis of FAs is investigated. The analysis of pure isolated FAs and FA mixtures revealed a linear response over almost 3 orders of magnitude by adding an internal standard. Using untreated wings, highest sensitivities (ca. 10 pmol) were obtained in the positive ion mode by evaluating the $[M+K]^+$ adducts. Other alkali ion adducts can be generated by washing the wings with base solutions. Importantly, the FA ion signals are not suppressed by the presence of abundant phospholipids or triglycerides. Therefore, "FALDI" allows a rapid screening of crude tissue (e. g. liver) extracts regarding their FFA composition without previous sample purification.

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POSTER 40

Signal amplification strategy for heterogeneous immunoassays based on an enzyme cascade and a FRET-substrate

Biophysics and Bioanalytics

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Enzyme-linked immunosorbent assays (ELISA) are one of the most commonly applied immunological methods due to its high specificity and sensitivity. Nevertheless, the detection of low-abundance biomarkers for early diagnosis of diseases like cancer is still challenging. The application of DNA as a reporter molecule in heterogeneous immunoassays results in improved sensitivities, but suffers from low reproducibility and difficulties in analyte quantification.
Here we present a signal amplification method based on an enzyme cascade, where the initializing enzyme human enteropeptidase is covalently coupled to a secondary antibody. Upon binding to a detection antibody, this enzyme cleaves trypsinogen and thus releases active trypsin. Trypsin then cleaves a FRET-peptide and therefore causes an increase of donor fluorescence which can be used to quantify the analyte with high sensitivity. Currently, the assay can detect interleukin-6 in the picomolar range with high specificity.

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POSTER 41

A MALDI MS Investigation of the LPC content in human Spermatozoa and Erythrocytes as a new Marker of Fertility

Biophysics and Bioanalytics

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The membrane of human sperm possesses a complex architecture, which is characterized by a marked lipid, i.e. phosphatidylcholine (PC) and particularly a unique fatty acyl composition. The significant content of highly unsaturated fatty acyl residue is essential for the fertilization process. However, highly unsaturated fatty acids are very sensitive to reactive oxygen species (ROS). Therefore, oxidative stress is massively involved in the pathology of many diseases; particular obesity (BMI > 30 kg/m²) negatively affects the male reproductive potential. Lipid oxidation is accompanied by the generation of saturated lysophosphatidylcholine (LPC) from common PC. Human sperm and erythrocytes were isolated from 21 donors which were sorted according to their BMI. The lipids of both organic extracts were analysed by MALDI-TOF MS. The LPC/PC ratios determined in the sperm extracts correlate with the LPC/PC values determined in the extracts of erythrocytes. Additionally, the LPC/PC ratio increases with increasing BMI. The data also correlate with established clinical markers of sperm quality. These results suggest that an increased LPC/PC ratio is not only a measure of regional or organ-related stress but rather characteristic of the "oxidative status" of the whole organism. Furthermore, the increased contribution of LPC can be easily determined by analysing the lipid composition of erythrocytes, whereas the analysis of sperm is not absolutely necessary.

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POSTER 42

Selective Analysis of Triacyglycerol Molecular Species in Human Plasma by Electrospray Ionization Tandem Mass Spectrometry

Biophysics and Bioanalytics

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Objectives: Civilization diseases like atherosclerosis and type II diabetes are associated with elevated triacylglycerol (TAG) levels. First detailed analyses of TAG molecular species in diabetic rats demonstrated changes in levels of TAG molecular species during pathophysiological alteration while total TAG levels remained steady. Using conventional enzymatic methods, the TAG molecular species cannot be considered.

Material and Methods: Sample preparation was carried out by isopropanol/methanol (1:1 v/v) protein precipitation. Tandem mass spectrometric detection was performed on an AB Sciex API 4000 triple quadrupole mass spectrometer with positive electrospray ionization. Ammoniated precursor ions were studied by neutral loss (NL) scans.

Results: Mass spectrometric parameters for ionization and analysis via NL scans were optimized. A declustering potential of 70 V and a collision energy of 35 eV were found to be appropiate for all fatty acyl residues from 14:0 to 20:4 in flow injection analyis (FIA). Signal intensities decreased with increasing chain length and degree of saturation. Furthermore the position of the fatty acyl residue effects signal intensity with lower intensities beeing found for the residues at sn-2 position. A correction for these effects needs to be established to allow quantitative analysis. In human plasma TAG molecular species could be identified. The most abundant fatty acyl residues in TAGs have been found to be 16:0, 16:1, 18:1 and 20:4.

Conclusion: We esteblished a simultaneous selective analysis of TAG molecular species in human plasma using the described tandem mass spectrometric approach.

Funding: life

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POSTER 43

Biomechanical Screening of Primary Mammary Carcinoma

Biophysics and Bioanalytics

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The search for elemental qualities of primary tumors and metastatic cancer cells has led to the field "Physics of Cancer". Biomechanical properties such as rigidity were used to rate the aggressiveness of cancerous cells. These new properties are known to have a closer physiological link to cell motility and metastases than conventional markers.
Using the automated optical stretcher, we are able to compare primary mammary carcinoma cells to healthy cells and benign fibroadenoma cells obtained from reduction mammoplasty and fine-needle aspiration biopsy, respectively. The data reveals a broad spectrum of rigid and soft cells in biopsy samples. Statistically relevant cell numbers were required in order to account for individual cell variation. Deformation and relaxation behavior show increased deformation and contractility in tumor samples compared to the control. These results may serve as future cancer markers and provide new insights into tumor development.

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POSTER 44

Entropic contraction of actin networks

Biophysics and Bioanalytics

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Retraction at the rear of a cell is a fundamental part of its migration process. This contraction can be accomplished by actin-myosin interaction. However, myosin knock-out cells have been shown to be still capable of migrating. Alternatively, the depolymerization of the cytoskeleton was proposed to cause contractile forces only by a gain in entropy in the absence of molecular motors. This concept has been demonstrated on polymer meshworks of nematode's major sperm protein [1].

We study the depolymerization of actin networks. In particular, the mesoscopic details and the forces associated with this process are of interest. We employ a microrheology approach in conjunction with light induced softening of actin networks [2] to measure both softening and contraction of the depolymerizing meshwork.

[1] Wohlgemuth et al., Biophys. J, 88, 2462 (2005)
[2] Golde et al., PRE, 88, 044601 (2013)

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POSTER 45

The influence of dopant anions on morphologic, actuatoric and biological properties of polypyrrol coatings

Biophysics and Bioanalytics

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One focus of today's nanotechnology research is the development of smart materials like actuatoric coatings and structures that can be electrically controlled. These materials are of great interest for applications in robotics, microelectromechanical systems and medical devices.

Intrinsic conducting electroactive polymers like polypyrrol (PPy) in combination with trapped anions exhibits an electrochemomechanical strain by applying a distinct potential resulting in volume changes under physiological conditions. The incorporation of anions as dopant during synthesis increases the electrical conductivity and enables the electrical controlled oxidation and reduction of PPy films. Thereby the plastoelastical- and morphological properties are highly dependent on the incorporated anions as well as the synthesis conditions.

With regard to varying dopant anions the morphological properties and the redox-dependent volume change with respect to its extent and reversibility were studied using atomic force microscopy (AFM) and electrochemical-AFM (EC-AFM) techniques. Furthermore, to determine the biological response of the mouse fibroblasts cell line L929 methods according to ISO 10993 were used to assess the in vitro cytotoxicity of two promising anions dodecyl benzene sulfonic acid (DBS) and octyl benzene sulfonic acid (OBS). Our findings can contribute to improve applications in the field of sensoric units and biomedical engineering like surface coatings of implants, microelectromechanical systems or electrical controlled nanovalves for e.g. compound delivery systems.

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POSTER 46

Structure and dynamics of ghrelin bound to membranes and its GHS receptor

Biophysics and Bioanalytics

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The peptide hormone ghrelin is the endogenous ligand of the growth hormone secretagogue receptor (GHS-R1a) stimulating growth and appetite. The highly conserved 28 amino acid peptid requires a posttranslational octanoylation at Ser3 for full activity. The peptide is highly flexible in solution, but CD spectroscopy and molecular dynamics simulation show some helical content in presence of organic solvents and micelles.

Since ghrelin addresses a transmembrane GPCR, we aim to characterize the structural and dynamical properties of the peptide backbone as well as the octanoyl moiety bound to lipid vesicles. We synthesized ghrelin peptides with varying $^{13}C/^{15}N$ labeled amino acids covering 17 out of 28 residues and a peptide with a perdeuterated octanoyl chain.

We have studied the membrane integration of the lipid modification of ghrelin by recording ^{2}H NMR spectra of vesicles containing perdeuterated DMPC and with and without associated ghrelin and a spectrum of the perdeuterated octanoyl chain in the presence of the membrane.

^{13}C NMR spectra under magic angle spinning conditions and measurements of the motional averaged dipolar couplings allowed the determination of backbone torsion angles and molecular dynamics, indicating a highly flexible conformation of the whole peptide.

Using $^{1}H/^{15}N$ heteronuclear single quantum correlation NMR spectra of ghrelin in solution in the presence of recombinantly expressed and refolded ghrelin receptor reconstituted in bicelles, we could identify the amino acid residues among the peptide interacting with the receptor.

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POSTER 47

Fast and easy-to-use assay for the detection of hydrogen peroxide

Biophysics and Bioanalytics

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The detection of hydrogen peroxide is important for industrial and laboratory applications. H_2O_2 is used for bleaching, cleaning, and disinfection as well as for the determination of oxidase activities and their substrates.

Here, we present a fast and simple assay for the detection of H_2O_2 on the basis of time-resolved fluorescence. In HEPES buffer a complex between phthalic acid (PA) and terbium(III)-ions (Tb^{3+}) is formed and the resulting emission intensity is quenched in dependence of the H_2O_2 concentration. The PATb-assay detects H_2O_2 at physiological pH in a total assay time of only 3 min. The detection limit and the linear range can be shifted by the pH value of the buffer. The linear range covers a H_2O_2 concentration of 0.31 μmol/L to 2.56 mmol/L in total with an detection limit of 0.15 μmol/L. The assay is compatible with high concentrations of several tested inorganic and organic compounds. The PATb-system shows a high sensitivity and precision.

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POSTER 48

A simple method to generate milligram quantities of oxidized phosphatidylcholines

Biophysics and Bioanalytics

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Oxidized (phospho)lipids are of paramount interest from different viewpoints: beside their significant *in vivo* relevance, these products are needed in the laboratory to study the response of selected cells to oxidized lipids. Unfortunately, however, the commercial availability of oxidized lipids is very limited and scientists interested in studying the impact of oxidized lipids are normally forced to prepare oxidized (phospho)lipids by themselves.
We will show here that chain-shortened products of oxidized phosphatidylcholines (PC) such as aldehydes and carboxylic acids can be easily (and in nearly quantitative yields) generated by the Fenton reaction (H_2O_2 + Fe^{2+}) or the $KMnO_4$-induced oxidation of the pure PC. Using the Fenton reaction and physiological saline, chlorinated products are also available. Additionally, it will be shown that preparative thin-layer chromatography (TLC) is a convenient method to isolate the individual oxidation products in reasonable yields and high purity: all products can be identified by matrix-assisted laser desorption and ionization (MALDI) mass spectrometry and the concentrations of the oxidized products determined by a simple colorimetric assay. Therefore, TLC is even nowadays an important tool in lipid (bio)chemistry and there is no absolute need to use expensive HPLC equipment.

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POSTER 49

Identification of tissue specific miRNA in liver samples using laser capture micro dissection and qPCR

Biophysics and Bioanalytics

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Introduction: The microRNAs have been shown to be responsible for cell metabolism and differentiation. Especially efforts have been made to understand the effect of miRNAs on the malignant character of the cells. In this context isolation and identification of microRNA of unique tissue in heterogeneous parenchyma is a challenging issue since the oncological potential of different cells can`t be identified in standard experimental set-up. The aim of the study is to develop a protocol using laser capture micro dissection (LCM) to distinguish the miRNA patterns of different cell groups in liver specimen.

Methods: Tissue samples were harvested from explanted livers of patients underwent liver transplantation. Tissue slides are prepared and dehydrated with alcohol. The hepatocytes are distinguished from cholangiocytes by immunohistochemistry. Areas of hepatocytes are dissected on LCM. The purification of RNA is performed using a modified trizol based protocol. The two-step RT-PCR is performed with hsa-miR-24.

Conclusion: The RNA-purification from dissected cells supplies only a small amount of RNA. Therefore the different cell amounts, staining method, conditions of dissection and purification protocol were evaluated to have adequate level of RNA for molecular biological analysis. The concentration was measured on NanoDrop and pPCR was performed as quality control.LCM could be safely use for distinguish miRNA patters of different cell groups in one tissue. This method could help to understand the differentiation of the cells in different tissues in one parenchyma and serve for gene targeted therapy in tissue specific diseases.

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POSTER 50

Detection of specific microRNA profiles as biomarkers for diagnosis and prediction for hepatocellular carcinoma caused by virus infection in liver transplantation

Biophysics and Bioanalytics

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Introduction: The liver graft allocation in Eurotransplant Region is based on a system using laboratory and radiological findings of the patients. However this system doesn`t consider the individual histological and genetic characteristics of tumors or diseases. It has been shown that microRNAs (miRNA) have a pivot role in development of diseases. Therefore we investigated miRNA expression profiles in liver transplanted patients to identify hepatocellular carcinoma (HCC) and to conclude the underlying disease.
Methods: 189 liver recipients were included in our study. The distinction in two groups was based on the pathological findings: Group A LC (liver cirrhosis); Group B HCC. One sample from A (Ex), and two samples from B (pT-primary tumour; sT-surrounding tissue) were taken following the explantation. RNA was isolated using a trizol based method. The microarray analyses were performed by Exiqon. For validation of the array by qPCR, 5 miRNAs were investigated as reference genes.
Results: 20 of 72 patients with HCC were caused by chronic hepatitis. In the comparison of HBV-pT and HCV-pT, there were significant differences in the expression level of 2 miRNAs. Clear differences could be shown between sT and pT of HBV and HCV patients using miR-194 and –192. miR-122 and –378a allow to distinguish between HCV-sT and -Ex.
Conclusion: Our data demonstrates different expression levels of miRNAs in tissues of different etiology and morphology. Moreover it allows diagnosing HCC and the underlying disease using microRNA profiles. Therefore miRNAs as diagnostic tool could improve the management of HCC and the graft allocation.

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POSTER 51

Optimierung und Validierung der Bestimmung von Hyaluronsäure mit HPLC und UV/VIS-Detektion

Biophysics and Bioanalytics

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Zunächst wurde die Probenaufbereitung sowie eine HPLC-Methode zur Ermittlung des Hyaluronsäuregehaltes optimiert. Die Hyaluronsäure wurde hier unter Verwendung von Acetonitril und Wasser (4 : 96) bei einer Fließgeschwindigkeit von 1 ml/min und einer Wellenlänge von 195 nm gemessen. Die Probe wurde auf einer RP-C8-Säule aufgetrennt. Bei der Probenaufbereitung wurde die Hyaluronsäure in konzentrierter Schwefelsäure gelöst, danach mit Natronlauge (0,5 mol/l) neutralisiert und mit Natriumacetatpufferlösung (0,03 mol/l) aufgefüllt. Die Endkonzentration lag bei 100 mg/kg.

Zur Überprüfung auf Eignung der etablierten Analysenmethode sind verschiedene Validierungsparameter, wie Selektivität, Präzision, Richtigkeit, Linearität und Robustheit zu betrachten. Zur Überprüfung der Selektivität erfolgte die Ermittlung des Peaks-Rausch-Verhältnisses bei System- und Methodenleerwert. Zur Überprüfung der Messpräzision erfolgte eine 6-fache Injektion bei einfacher Aufarbeitung. Der Variationskoeffiezient V_K war < 1%. Wiederhol- und Vergleichspräzision wurden an jeweils 6 unabhängigen Einwaagen unter Wiederhol- bzw. Vergleichsbedingungen bestätigt (V_K < 3%). Die Richtigkeit wurde an 6 unabhängigen Einwaagen in einem Bereich von 80 – 120% überprüft und bestätigt. Die Linearitätsüberprüfung beinhaltet den Arbeitsbereich und wurde mittels Grundkalibrierung und an zwei unabhängigen Einwaagen an sechs Konzentrationsniveaus geprüft und bestätigt.

Zukünftig soll die angewandte Analysenmethode auf Robustheit und unter laborinternen Vergleichsbedingungen über einen längeren Zeitraum durch den Einsatz von Qualitätsregelkarten überprüft werden.

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POSTER 52

Detection of specific microRNA-profiles as biomarker for diagnosis and prediction of hepatocellular carcinoma in liver transplantation caused by alcoholic liver disease

Biophysics and Bioanalytics

Kunze K[1], Felgendreff P[1], Dietel C[1], Faroch A[1], Klunk S[1], Leonhardt C[1], Beeskow A[1], Schmuck R[2], Reutzel-Selke A[2], Raschzok N[2], Morgül MH[1], Bartels M[1]

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Background: Hepatocellular Carcinoma (HCC) due to liver cirrhosis (LC) is one of the leading indications for liver transplantation (LTx) in the western world. The most common cause in is the alcohol-induced LC with or without HCC. The selection of the patients for LTx is based on Milan Criteria, which don't consider the tumour biology. MicroRNAs are RNAs that repress the mRNA expression. Here, we introduce the data of miRNAs as biomarkers for HCC caused by alcoholic liver disease (ALD).

Methods: 189 patients who underwent liver transplantation were enrolled in the database. Patients were divided in Group A: LC only, Group B: HCC on LC. After the hepatectomy, one tissue sample from patients in A, and two samples from patients in B (primary tumour tissue= pT and surrounding tissue= sT) were taken. The RNA was isolated using a trizol-based method. The microarray analyses were performed by Exiqon. The data set was screened for reference miRNAs for qPCR using NormFinder software.

Results: The microarrays showed an increase of miR-3611, –423-5p, –1973 and –3667-5p in A compared to sT. The comparison of pT to sT also showed differences. Based on the miRNA profiling, the NormFinder generated 6 miRNAs with stability values lower than 0.06

Conclusion: This study shows the first experiences on miRNA-profiles in transplanted patients suffering from ALD. Interestingly the cirrhotic liver tissue of A and B show differences in miRNA-expressions. These differences in miRNA signatures could be used as a diagnostic and predictive tool for improving the organ allocation.

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POSTER 53

Species typing of Culicoides biting midges: MALDI-TOF-MS as a proteomic approach

Biophysics and Bioanalytics

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Culicoides biting midges are vectors of arboviruses such as bluetongue and Schmallenberg viruses that inflict large-scale disease epidemics in ruminant livestock in Europe. To monitor and differentiate *Culicoides* to species level, time consuming methods based on morphological characteristics and sequencing of genetic markers are most commonly employed. Proteomic methods, however, are also increasingly being used as an alternative method of identification. These techniques have the potential to be rapid and may also offer advantages over DNA-based techniques.

After preparing extracts of *Culicoides* of 7 species, followed by digestion and clean-up of the resulting peptides, peptide mass fingerprint (PMF) spectra were recorded using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). We showed that the majority of the *Culicoides* species reproducibly yielded mass spectra with peak patterns that were suitable for classification.

Shotgun mass mapping by MALDI-TOF-MS has been shown to be compatible with morphological and genetic identification of specimens and therefore offers a rapid and inexpensive alternative for accurate identification of *Culicoides* biting midges collected in the field. The upcoming availability of complete *Culicoides* genomes (Pirbright Institute), for major European vector species, may enable a more stringent detection based on species-specific peptide sequence information.

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POSTER 54

Hepatotoxicity of antimycotics tested with a new in-vitro test

Biophysics and Bioanalytics

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Objective: The hepatotoxicity of many drugs -including the antimycotics- is poorly investigated. Therefore, we developed a standardized cytotoxicity assay with human hepatocytes and investigated the hepatotoxicity of drugs.
Methods: In a standardised mikrotiterplate assay the toxicity of different concentrations of paracetamol (7,62/15,24mM;n=24), anidulafungin (7,5/37,5/75µg/ml;n=27) and caspofungin (1/5/10µg/ml;n=24) were tested with human liver cells (HepG2/C3A,500.000 cells/well;medium). The lowest concentrations of anidulafungin and caspofungin are the mean plasma levels after induction of an i.v. therapy. As controls served plasma with the different agents and a plasma plus medium control without agents (Control Group=CG). After incubation time of 2x3 days LDH release, XTT test, trypan blue staining, the cytochrome 1A2 activity and the synthesis of albumin were measured.
Results: Anidulafungin and Paracetamol lead to a significantly decreased viability, decreased cytochrome 1A2 activity and synthesis of albumin of test cells compared with the CG. These effects were more pronounced with increased concentrations of paracetamol and andidulafungin. No significant differences were seen between CG and increasing concentration of caspofungin for all parameters. Additionally, significantly higher values of all test parameters were found in all concentrations of caspofungin in comparison to anidulafungin and paracetamol in different concentrations.
Conclusion: The standardised assay showed hepatotoxicity of Anidulafungin and Paracetamol; moreover, these effects were dose-dependent. Caspofungin has no hepatotoxic potential.

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POSTER 55

A novel preclinical in vitro cardiac safety monitoring system – The possibility to predict drug-induced cardiotoxicity in human

Biophysics and Bioanalytics

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One of the major reasons for withdrawal of approved drugs from the market is unexpected cardiotoxicity. Although extensive pharmaceutical safety testing is done to prevent adverse side effects on the human heart the predictability today is insufficient. Traditional preclinical *in vitro* drug studies are short-term acute toxicity tests but most non-cardiac drugs develop adverse effects after chronic or repeated applications. Otherwise, long-term studies involve the use of animals where extrapolation to human is often critical.
In contrast to current models for drug-induced cardiotoxicity, human embryonic stem cell derived cardiomyocytes clusters (hCMCs) provide an intact human *in vivo* like cellular environment for improved cardiac safety assays. In combination with our self-developed microcavity array (MCA), we established a novel *in vitro* long-term drug safety assessment platform. Our hybrid biosensoric system allows the detection of drug-induced cellular alterations by impedance spectroscopy (EIS) as well as the field potential recording (FPR) of electrophysiological activities.
For demonstrating the performance of our non-invasive label-free monitoring system, we incubated hCMCs over four weeks with doxorubicin, a clinical widely used chemotherapeutic agent with chronic cardiotoxicity potential. We could show that subtoxic concentrations based on acute studies (48 hours) can lead to cellular degradation and cell death within the hCMCs as well as electrophysiological alterations after a few weeks. These results highlight that our system is a promising and feasible tool for *in vitro* pharmaceutical safety testing.

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POSTER 56

Nuclear receptors Pparα and Pparγ and their influence on hepatic lipid homeostasis

Cell Biology

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Peroxisome-proliferator-activated receptors (PPARs) are ligand-activated nuclear receptors which regulate a whole spectrum of physiological functions in the liver by modulating the transcription of respective genes. A crucial role is displayed by regulating the fatty acid metabolism. It is currently assumed that Pparα promotes fatty acid oxidation and, therefore controls lipid catabolism, whilst Pparγ promotes the storage of lipids. As the functions of PPARs in hepatocytes are not fully understood yet, our aim was to investigate whether they are heterogeneously distributed within the liver lobules and whether they show a circadian expression pattern. To investigate the function of Pparα/γ regarding hepatic lipid metabolism, siRNA mediated knockdown (KD) was performed. Total RNA was isolated and used for micro-array and qRT-PCR analysis. Changes in lipid composition of hepatocytes, due to siRNA mediated KD, were analyzed by using shotgun-lipidomics. Generally our results indicated that Pparα and Pparγ are heterogeneously distributed within the liver lobules. Both heterologues showed an altered expression due to their regulation by the circadian rhythm. The transcriptome analysis revealed that a broad range of genes are affected by Pparγ-KD, like genes for transport, cell cycle or metabolic processes. Based on our results, we can conclude that current well-known processes, which are controlled by PPARs, are not generally applicable to the liver. In order to properly regulate genes of the hepatic lipid metabolism, it most probably requires a complex cooperation of the PPARs with their ligands and other transcription factors.

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POSTER 57

A genome engineering approach reveals a fundamental role of keratins in epidermal barrier gene expression

Cell Biology

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The mammalian epidermis expresses 4-10 different keratins in any given cell type. Owing to this redundancy, knockout studies of individual keratin genes have provided only limited information on the reliance of skin integrity, cell adhesion, differentiation and epidermal barrier formation on keratins. To address global keratin function in the skin in the absence of compensatory expression of other keratins, we devised 2 independent strategies. In the first, we specifically deleted all keratins in the epidermis, using a K14cre variant that deletes in a focal pattern, resulting in patches of intact and keratin-free epidermis. These mice survive ~10 days after birth. In the skin, they developed patches of intact and barrier-deficient skin. In a second approach, type II keratin genes were ubiquitously deleted. The epidermis of these mice was 6-fold thicker, desmosomes were severely disrupted and cytolysis occurred in all epidermal layers. Prenatal mice suffered from a completely disrupted epidermal barrier. Unexpectedly, the type II keratin deletion strongly impaired terminal differentiation and barrier acquisition and was accompanied by a complete loss of loricrin and filaggrin at mRNA and protein levels. Transcriptome analysis revealed 37 genes differentially expressed. All of them localized at the epidermal differentiation complex (EDC) and many of them encoded structural components of the cornified envelope (CE). None of the single keratin mutants reported so far shows a similar impact on terminal differentiation and barrier acquisition. We propose a crosstalk between the type II keratin locus and the EDC locus.

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POSTER 58

New insights into the cell cycle-dependent regulation of histone genes

Cell Biology

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Histones are among the most evolutionary conserved proteins in eukaryotes. They are essential for DNA packaging and the regulation of genes. Most histones are expressed in S phase and are required to compact the newly replicated DNA. However, the mechanism of their transcriptional regulation is far from being understood.

Many genes expressed in the late phases of the cell cycle are controlled by cell cycle-dependent elements (CDE) and cell cycle genes homology regions (CHR) close to their transcriptional start sites in their promoters. Binding of the multiprotein complex DREAM to CDE/CHR elements coincides with repression of the genes in G_0 and G_1 phases. In S, G_2 and M phase DREAM is reorganised forming the MMB complex which can activate late cell cycle genes via CHR elements.

Here, we identify histone *HIST1H3B* as a CDE/CHR-regulated gene that binds DREAM and MMB in a cell cycle-dependent manner. *HIST1H3B* may serve as an example for the cell cycle-dependent regulation of many histone genes.

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POSTER 59

Glucocorticoids enhance the CFTR-activity in primary tracheocytes

Cell Biology

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Lung fluid production during fetal development and its absorption prior to birth is mediated by the interaction of different ion channels within the airway epithelia. In addition, this interaction is also important for maintenance of mucociliary clearance (MCC). Studies suggest that the CFTR channel, a Cl^- channel, is involved in fluid secretion, whereas the epithelial sodium channel (ENaC) is crucial for fluid absorption. The transition of the lung from fluid secretion to absorption is induced by various triggers, e.g. glucocorticoids (GC). GC stimulate fluid absorption by enhancing ENaC and thereby initiate lung fluid clearance. It is yet unknown which role CFTR plays in lung transition and how it is affected by GC. Therefore the goal of this study was to observe the effect of GC on CFTR activity and expression. Tracheocytes are an excellent model to study the regulation of absorption and secretion in regard to MCC, because they express both CFTR and ENaC. Therefore a primary rat tracheal culture was established and grown to confluent monolayers. Short circuit currents (I_{sc}) were measured with Ussing-Chamber analysis. Amiloride, forskolin and $CFTR_{172}$inh were used to distinguish between different ion channels expressed by tracheocytes. The incubation with dexamethasone was shown to increase the forskolin-induced I_{sc}, the $CFTR_{172}$inh-sensitive I_{sc} and the amiloride-sensitive I_{sc}. These results demonstrate that GC enhance the CFTR and ENaC activity in tracheal epithelia. Further analysis will determine the effect of GC on channel expression and the pathway leading to an elevated channel activity.

Funding: formel1

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POSTER 60

Internalization of the Human Y4-Receptor is Dependent on Its C-Terminus

Cell Biology

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The human Y_4-receptor (hY_4R) is one of four human neuropeptide Y (NPY) receptor subtypes (hY_1R, hY_2R, hY_4R, hY_5R). The 375 amino acid hY_4R binds three different ligands: neuropeptide Y, pancreatic polypeptide (PP) and peptide YY (PYY). In contrast to the other Y-receptor subtypes the hY_4R shows the highest affinity to PP. The effect transmitted by this receptor is decreased food intake [1, 2]. In order to make use of the hY_4R in terms of adiposity, it is necessary to characterize the molecular internalization mechanism of this receptor. Until now, the C-terminal motifs, which are important for the internalization and arrestin 3- (arr3) recruitment are unknown. The aim of this study was to characterize the molecular internalization mechanism of the hY_4R in more detail. Within the C-terminal motif $^{7.78}$EESEHLPLSTVHTEV$^{7.92}$ the residues glutamate ($E^{7.78,7.79,7.81}$), serine ($S^{7.80,7,86}$) and threonine ($T^{7.87,7.90}$) were replaced by alanine. Internalization, arr3-recruitment and phosphorylation independent arr3-3A-recruitment were investigated by fluorescence microscopy. To examine the arr3-recruitment a stably transfected cell line (arr3-mCherry-HEK293) was generated. All receptor constructs were N-terminaly used with a HA-tag and connected with a linker sequence to a C-terminal eYFP. The results indicate that the internalization of the hY_4R is arr3-dependent. $E^{7.78,7.79,7.81}$, $S^{7.80,7,86}$ und $T^{7.87,7.90}$ seem to have an influence on the internalization process.

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POSTER 61

Cell cycle-dependent transcriptional regulation of Ki-67 through two conserved CHR sites

Cell Biology

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Ki-67 is an important nuclear protein, which is essential for cell proliferation, although the precise function of the Ki-67 protein still remains unclear. The expression of the protein is tightly associated with somatic cell proliferation. Ki-67 is abundant in dividing cells during all phases of the cell cycle (G_1, S, G_2, and mitosis) and is absent from resting cells (G_0) which makes it an excellent marker to estimate the growth fraction of human tumors *in situ*. However, the transcriptional regulation of the gene has not yet been investigated so far.

Here, we analyze the correlation between the cell cycle-dependent expression of the Ki-67 protein and the transcriptional regulation of its mRNA expression. Our studies demonstrate that the main part of the cell cycle-dependent transcriptional regulation is mediated through two conserved CHR sites in the promoter of *Ki-67* and that the DREAM and MMB complexes bind to both identified sites. Gene expression of late cell cycle genes is often regulated through cell cycle genes homology regions (CHR). Generally, binding of DREAM and MMB to CHR promoter elements mediates repression in G_0 and activation in G_2/M. Interestingly, reportergene assays revealed that no de-repression in G_0 can be observed after mutating the CHRs in the *Ki-67* promoter. This feature stands in clear contrast to cell cycle promoters described by us with just one CHR element.

Taken together our findings suggest that promoters with two functional CHR sites exist and that the mechanism of transcriptional regulation deviates from the classical model of DREAM/MMB-regulated genes.

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POSTER 62

Turning skin cells into brain cells: Rat induced pluripotent stem-cell derived NSCs are more similar to fetal NSCs than directly converted fibroblasts

Cell Biology

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Fibroblast-derived neural stem cells (NSCs) provide promising transplants for several human neurological disorders. To test their immunomodulatory potential in preclinical studies, syngeneic NSCs should be used. For the rat, however, derivation of induced pluripotent stem (iPS) cells and subsequent neural differentiation has been proven to be challenging. Thus, we optimized the protocol and evaluated an alternative method to obtain NSCs from rat fibroblasts. First, OSKM lentivirus was used to generate iPSCs. Neural differentiation was then induced via embryoid body formation. Second, fibroblasts were infected with lentiviruses encoding Sox2, FoxG1-Brn2, and hTERT in a direct conversion approach. At each passage, qPCR and immunostaining were performed and tripotency was evaluated. Fetal rat NSCs served as positive control. Rat iPSCs were successfully generated and neural differentiation improved dramatically by adding retinoic acid. Also in the direct approach, the infected fibroblasts showed profound morphological changes. Cells of both methods resembled NSCs, were proliferative and formed neurospheres. Immunostaining indicated that they expressed Nestin, Sox2 and Musashi1. However, mRNA expression of NSC markers was considerably higher in iPS-NSCs and reached the levels of fetal NSCs. Both types of fibroblast-derived NSCs gave rise to neurons, astrocytes and oligodendrocytes, but neuronal differentiation was remarkably better for iPS-NSCs even leading to synaptophysin expression. We developed new protocols to derive NSCs from rat fibroblasts and demonstrated that iPS-derived NSCs are superior to directly converted iNSCs.

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POSTER 63 Evaluierung von RIP-vermittelter Nekroptose in Pankreasazinuszellen

Cell Biology

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Einleitung: Die akute nekrotisierende Pankreatitis ist eine entzündliche Erkrankung mit potentiell tödlichem Verlauf. Rezeptor-interagierende Proteine (RIP) vermitteln intrazellulär Signale die zur Nekrose von Zellen führen (Nekroptose). Das Ziel der Arbeit war es, zu überprüfen ob diese Signalmechanismen in exokrinen Pankreasazinuszellen eine Rolle spielen.

Material und Methoden: Die Pankreasazinuszelllinie AR42J und die L929 Zelllinie wurden unter Standardbedingungen kultiviert. Um das jeweilige Verhalten auf zytotoxische Stimuli zu überprüfen, wurde mit TNF-Alpha, Caspaseinhibitoren und Nekrostatinen behandelt. Anschließend wurde das Zellüberleben (WST Test) und Zelltod quantifiziert (CytoTox-One, Promega). Die Expressionsanalyse von RIP1/3 erfolgte per Western Blot.

Ergebnisse: L929 Zellen zeigten unter Stimulation mit TNF-Alpha und ZVAD ein signifikant verringertes Überleben und eine Zunahme des Zelltods. Im Gegensatz hierzu fand sich keine signifikante Reduktion des zellulären Überlebens bei den AR42J Zellen, auch war hier keine relevante Induktion von Zelltod zu beobachten. Während RIP1/3 in L929 Zellen exprimiert waren, konnte RIP3 in AR42J Zellen nicht detektiert werden.

Diskussion: RIP Signale vermitteln Zelltod durch Nekroptose. Die exokrine Pankreasazinuszelllinie AR42J zeigt aufgrund fehlender RIP3 Expression kein relevantes Absterben der Zellen. Die Zelllinie ist daher nicht geeignet um die Rolle von Nekroptose während der Pankreatitis in vitro weiter zu analysieren. Bei nach wie vor mangelndem Verständnis der pankreatischen Zelltodmechanismen ist es daher erforderlich alternative Modelle zu entwickeln.

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POSTER 64 **BFH12: The first bovine hepatocyte-like cell line**

Cell Biology

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Objectives: During early lactation, high-producing dairy cows are in a negative energy balance, leading to mobilisation of large amounts of lipids. When the influx exceeds the metabolic capacity of the liver, excessive ketogenesis leads to ketosis and the accumulation of triglycerides causes hepatic lipidosis. The effective control of such diseases is crucial for dairy farms because affected cows, even after recovery from these metabolic diseases, are at risk for reproductive diseases. Despite the great demand for research of bovine ketosis there is no *in vitro* model to investigate bovine liver metabolism. In fact, up till now no bovine hepatocyte cell line exists.
Material and methods: Primary bovine foetal hepatocytes were transfected via a pRetro-E2 SV40 vector yielding the cell line BFH12. Morphology and growth capability of BFH12 were evaluated microscopically. Production of lactate and β-hydroxybutyrate as well as utilisation of glucose was quantified by UV-Vis spectroscopy.
Results: BFH12 show typical morphological signs of hepatocytes: polygonal growth, partial polyploidy and stress signs at low seeding densities. The cells have an exceptional growth capability without any signs of morphological alterations until passage 40. The cells continuously produce lactate and utilise glucose. Moreover, BFH12 synthesize the most important ketone body β-hydroxybutyrate.
Conclusions: Here we present important characteristics of the unique bovine hepatocyte cell line. Our data encourage us, that BHF12 is a suitable *in vitro* model for metabolic disorders of the bovine liver.

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POSTER 65

Chemosensitization of leukemia cells through inhibition of NAMPT

Cell Biology

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NAMPT (Nicotinamide phosphoribosyltransferase) catalyzes the rate-limiting step in the NAD-biosynthesis from nicotinamide and regulates the activity of NAD-dependent enzymes. Cancer cells are highly dependent on NAD for energy and DNA repair processes and are expected to be more susceptible to the inhibition of NAD synthesis than non-transformed cells. Can inhibition of NAMPT by FK866 sensitise leukemia cells for chemotherapeutic agents?
NAMPT expression and enzymatic activity was significantly higher in leukemia cell lines compared to normal PBMCs. Incubation with FK866 [10nM] for 24h reduced NAMPT activity by 91.1±3.6% in Jurkat cells and by 97.8±1.2% in Molt-4 cells. NAD levels were reduced by FK866 by 83.9±1.0% (Jurkat) or 79.2±2.8% (Molt-4). The combination of etoposide and FK866 caused increased cell death compared to each substance alone. In contrast, combining FK866 and methotrexate or doxorubicin showed no increased effect. Apoptosis induction as measured by caspase-3 activation was not further increased by the addition of FK866 to etoposide. Etoposide decreased the expression of the NAD-dependent deacetylase Sirtuin1. The acetylation of the Sirtuin1 target p53 was enhanced after combining etoposide with FK866. Concomitantly, the transcriptional activity of p53 was increased as shown by an increased expression of p21.
The combination of etoposide and FK866 caused increased cell death which was not caspase-3-mediated, but induced acetylation and transcriptional activity of p53. Combining FK866 and etoposide could therefore be a novel therapeutic strategy to enhance the efficancy of etoposide against leukemia cells.

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POSTER 66

Sex specific differences in the alveolar sodium absorption

Cell Biology

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Respiratory distress syndrome (RDS) is the most frequent pulmonary disease in preterm newborns and exhibits a sex-related difference in its incidence and resulting morbidity. In addition to surfactant, the Na^+ transport driven fluid clearance across the alveolar epithelia is crucial for the prevention of RDS. The epithelial Na^+ channel (ENaC) and the Na,K-ATPases drive the Na^+ transport and differences in their expression or activity are a possible cause for the increased occurrence of RDS in males. Fetal distal lung epithelial (FDLE) cells of rat fetuses were separated by sex and the activity of the Na^+ transporters, cell number and mRNA-expression were analyzed. Ussing chamber analysis showed an increased basal short-circuit current (Isc), amiloride-sensitive Isc and ouabain-sensitive Isc in cells from female fetuses, implying an increased ENaC and Na,K-ATPase activity. The amount of FDLE-cells per fetus was also significantly higher in females. Furthermore, the female derived cells showed an increased mRNA-expression of ENaC- and Na,K-ATPase subunits. Female sex steroids are known to stimulate Na^+ transport, however the concentration of these hormones in the fetus is equal in both genders. Therefore we analyzed the mRNA-expression of estrogene und progesterone receptors revealing a higher expression in FDLE cells of female origin. Concluding, an increased alveolar Na^+ transport, possibly attributable to an increased expression of hormone receptors in female FDLE cells, might be a potential explanation for the sex-related differences in RDS occurrence and outcome.

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POSTER 67

Transient receptor potential ankyrin 1 (TRPA1) channel activation by the thienopyridines ticlopidine, clopidogrel, and prasugrel

Cell Biology

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TRPA1 channels are widely expressed throughout the human and animal organism, including the dorsal root ganglia as well as the bladder, stomach and small intestine. In general, TRPA1 is believed to function as an irritant sensor in the skin and the lung, but recent studies also suggest a role of TRPA1 in the regulation of gastrointestinal function via the release of 5-HT (serotonin) and other hormones. Here, we examined the effect of three platelet aggregation inhibitors on TRPA1. Thienopyridines such as ticlopidine, clopidogrel or prasugrel are well established therapeutic drugs to prevent platelet aggregation in the vascular system. Recipients of ticlopidine and clopidogrel report about gastrointestinal adverse effects such as nausea, vomiting, or diarrhoea.

Utilising fluorometric Ca^{2+} influx analysis and electrophysiological whole cell measurements in TRPA1-expressing HEK293 and in enterochromaffin-like QGP-1 cells, we found that ticlopidine, clopidogrel and prasugrel are direct activators of TRPA1. The first generation thienopyridine ticlopidine caused the most pronounced TRPA1-evoked Ca^{2+} influx, the second and third generation drugs clopidogrel and prasugrel provoked weaker signals at similar concentrations. Application of ticlopidine and clopidogrel but not of prasugrel induced a TRPA1-dependent secretion of 5-HT from QGP-1 cells. Taken together, we suggest that a robust TRPA1 activation by ticlopidine and clopidogrel entails a release of 5-HT, and might thereby influence gastrointestinal motility *in vivo*.

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POSTER 68 **Effects of leptin on macrophages in vivo**

Cell Biology

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Aims: Leptin directly contributes to the pathophysiology of insulin resistance and atherosclerosis. The aim of the study was to elucidate the impact of leptin on macrophage physiology since macrophages play a role in both disease states.
Methods: Leptin-deficient obese (ob/ob) female mice on a C57BL/6J background were treated with 1 mg/g body weight/d, murine recombinant leptin or saline for 8 weeks starting at 4 weeks of age. Leptin-induced differential gene expression in peritoneal macrophages (PM) derived by peritoneal lavage was determined by microarray analysis.
Results: As expected, treatment with recombinant leptin dramatically improved insulin resistance and hypertriglyceridemia in ob/ob mice. More than 4.000 genes were significantly regulated in PM derived from leptin-treated mice as compared to saline-treated controls after controlling for multiple testing. Interestingly, M2 polarization marker including Chi3l3, Fizz-1, arginase-1, Mgl-1, and Mgl-2 were significantly up-regulated in PM from leptin-treated animals as compared to controls.
Conclusion: Leptin might induce M2 macrophage polarization. Validation of these data needs to be performed.

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POSTER 69

Effect of the ROCK inhibitor Y-27632 on Proliferation and Differentiation of Equine Bronchial Epithelial Cells

Cell Biology

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The airway epithelium plays an important role in physiological and pathological processes including inflammation, innate immunity and regenerative responses in the respiratory tract with regard to airway diseases such as human asthma, COPD and Equine Recurrent Airway Obstruction. Airway epithelial cell lines which would serve as an in vitro cell model are, indeed, missing for the horse. The objective of the study is to establish long-term equine bronchial epithelial cell cultures using the ROCK inhibitor Y-27632 and characterize them. Fresh isolated EBEC were cultured in the presence and absence of 10 μM Y-27632 under conventional and air-liquid-interface culture conditions. Cell viability, morphology, proliferation and differentiation states were examined. Under conventional culture, Y-27632 induced higher growth rate of primary EBEC over a short period of time when compared to control cells and increased the passage number. EBEC cultured on membrane inserts revealed higher TEER values in the presence of Y-27632, indicating a formation of functional tight junctions. Inmunostaing of EBEC showed a different pattern of CK, TJP-1 and Vim expression indicating rapid differentiation of Y-27632-treated cells. Also, light and scanning electron microscopic imaging showed high amount of cilia, microvilli and ridges as well as more defined polygonal-shaped epithelial cells in the presence of Y-27632. Taken together, these results suggest that the ROCK inhibitor Y-27632 permits establishing conditional long-term in vitro airway epithelial cell models to investigate their role in equine airway diseases and as pharmacological targets.

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POSTER 70

Effects of bioflavonoids in human Retinal Pigment Epithelial cells

Cell Biology

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Bioflavonoid from vegetables and fruits are suggested to represent promising drugs for the treatment of cancer and retinal diseases. We compared the effects of various bioflavonoids (epigallocatechin-3-gallate [EGCG], myricetin and cyanidin) on physiological properties and viability of primary cultured human retinal pigment epithelial (RPE) cells.

The cell proliferation rate was determined by a bromodeoxyuridine immunoassay. Cell viability was studied with a trypan blue exclusion assay. Apoptosis and necrosis rates were revealed by DNA fragmentation ELISA.VEGF secretion was detected by ELISA. The phosphorylation of intracellular signalling proteins was explored by Western blotting.

With the exception of EGCG, all flavonoids tested decreased dose-dependently the RPE cell proliferation and the secretion of VEGF. Myricetin induced a significant decrease in the cell viability at higher doses, via induction of caspase-3 independent cellular necrosis. The myricetin-induced RPE cell necrosis was mediated by calpain activation, oxidative stress, and activation of phospholipase A_2. Cyanidin decreased the rate of RPE cell necrosis. Myricetin and cyanidin induced decreases in the phosphorylation levels of ERK1/2 and Akt protein.

The data show that EGCG has little effects on RPE cell proliferation, migration, and secretion of VEGF. The intake of myricetin as supplemental cancer therapy or in the treatment of retinal diseases should be accompanied by careful monitoring of the retinal function. Possible beneficial effects of cyanidin, which had little effects on cell viability, should be examined in further investigations.

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POSTER 71

Functional analysis of keratin isotypes during epidermal differentiation

Cell Biology

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Keratins form the epithelial cytoskeleton and are encoded by ~50 genes expressed in cell-specific patterns. Most keratinocytes express between 4-10 different keratin proteins forming long cytoskeletal filaments composed of type I and type II keratin subunits. Through interactions with desmosomes, keratins form a cytoskeletal scaffold crucial for epithelial cohesion and intracellular signaling. Mutations in epidermal keratin genes cause blistering skin disorders including epidermolysis bullosa simplex, for which we and others have developed mouse models. The molecular mechanisms by which keratin missense mutations cause disease are not well understood. Further, the respective contribution of keratin isotypes to skin morphogenesis, wound healing and regeneration, settings that are accompanied by profound changes in keratin expression and organization, is not well understood. We hypothesize that keratin isotypes are major determinants of epithelial cell properties, by providing unique mechanical properties and unique protein interactions.

To address this, we generated mice and keratinocyte lines lacking the entire keratin protein. Here, we present the preliminary characterization of keratinocyte cell lines derived from keratin-deficient mice, in comparison to control cells. Following lentiviral gene transfer, we have also established keratinocyte lines expressing distinct keratin isotypes. We find that expression of keratin isotypes typical of "wound healing" keratinocytes endows cells with different adhesive and migratory properties. We will discuss our data in the context of epidermal differentiation and disease.

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Nicht in der Onlineversion verfügbar

POSTER 73

Keratins regulate Nrf2 through epidermal barrier composition and mitochondrial activity

Cell Biology

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The epidermal barrier protects the body against mechanical injury, dehydration and inflammation. To which extent the epidermal keratin cytoskeleton participates in barrier formation, function and immune regulation is not understood welll. Here, we present two novel mouse models in which the entire type I or type II keratin gene family is specifically deleted in the epidermis by Cre/lox-mediated genome engineering, resulting in neonatal mortality accompanied by defects in intercellular adhesion and cornified envelope formation. Analysis of the outside-in skin barrier in combination with transcriptome profiling of KtyI$^{-/-}$ and KtyII$^{-/-}$ prenatal mice for the first time reveal an essential function of keratins in cornified envelope and barrier formation. We identify hornerin, filaggrin and a distinct group of LCE proteins as essential constituents of the epidermal barrier. The notion that several of these proteins are involved in atopic dermatitis and psoriasis suggests a strong link of keratins to these disorders. Barrier defects in both strains of mice are connected to upregulation of the transcription factor Nrf2 which mediates antioxidant responses. By loss-and gain-of function experiments in cultured keratinocytes, we demonstrate that Nrf2 regulation is cell-autonomous and keratin-dependent. We identify mislocalization of mitochondria and elevated oxygen consumption as triggers for Nrf2 activation. Thus, epidermal keratins link epidermal barrier formation to an Nrf2-dependent network that controls barrier integrity and skin homeostasis. Our findings have implications for barrier-related inflammatory and immune disorders.

Funding: formel1

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POSTER 74

Glucocorticoids distinctively modulate the CFTR-channel with possible implication in lung development

Cell Biology

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During fetal development the lung is filled with fluid that is the product of an active Cl^- secretion accomplished by epithelial cells. The fetal lung fluid leads to lung expansion and is indispensible for lung growth. Little is known about the Cl^- channels responsible for the secretion, yet growing evidence suggests an involvement of CFTR. CFTR expression is developmentally regulated with a high expression in early fetal development and a decline in late gestation. Postnatal lung adaptation refers to the switch from placentary to pulmonal gas exchange and thereby removal of lung fluid by alveolar Na^+ absorption. This process is triggered by hormones that stimulate Na^+ channels, however little is known on how hormones like glucocorticoids (GC) affect pulmonary Cl^- channels. Since the rise of fetal cortisol levels correlates with the decrease in fetal CFTR a connection is assumed. Therefore the aim of this study was to analyze the influence of GC on the CFTR channel. Alveolar cells from fetal and adult rats and bronchial Calu-3 cells were studied with qPCR and Ussing-Chamber to determine the mRNA-expression and channel activity of CFTR. In fetal and adult alveolar cells GC strongly reduced CFTR-mRNA expression and channel activity. In Calu-3 cells CFTR mRNA-expression was also reduced whereas channel activity was increased. The reduction of mRNA-expression was prevented by mifepristone, a glucocorticoid-receptor inhibitor. The results demonstrate that a rise of GC is able to reduce the CFTR and is likely the cause for the decline during fetal development to enable the transition from prenatal to postnatal breathing.

Funding: formel1

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POSTER 75

Synergistic action of resveratrol and rapamycin to reduce viability of PTEN-deficient lipoma cells in vitro

Cell Biology

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Background
Rapamycin, a mTOR *(mammalian target of rapamycin)* complex-1 inhibitor, has been shown to reduce the growth of PTEN-deficient lipoma cells in vitro. However, rapamycin has also been described to induce an upregulation of the AKT pathway, leading to enhanced cell survival and possibly drug resistance. We asked whether resveratrol treatment could suppress the rapamycin-induced phosphorylation of AKT in PTEN-deficient lipoma cells (LipPD1).
Methods
LipPD1 cells were stimulated with resveratrol (10, 25, 50, 100, 200μM) or the combination of resveratrol and 100nM rapamycin for 48 and 72h. Effects on proliferation were estimated using WST-1-assay; apoptosis was measured by FITC-Annexin/PI staining. The amount of PTEN, AKT phosphorylation and p70S6K phosphorylation levels were analyzed by immunoblot.
Results
Treatment of LipPD1 cells with resveratrol resulted in a dose-dependent inhibition of cell viability by 79,8±8,6% (200μM) and induction of apoptosis by 27,2±5,3% (200μM). PTEN protein levels remained unchanged, whereas the phosphorylation levels of AKT and p70S6K were decreased (by 40,8±18,8% and 93,3±2,9%) in cells treated with resveratrol compared to control cells. Co-incubation with rapamycin and resveratrol in low doses decreased cell viability by 34,0±11,5% (10μM resveratrol; 100nM rapamycin) but had no effect on the apoptosis-inducing potential of resveratrol.
Conclusion
Resveratrol decreases cell viability and induces apoptosis in LipPD1 cells. The decreased phosphorylation of AKT after stimulation with resveratrol might overcome the rapamycin-induced hyperactivated AKT.

Funding: life

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POSTER 76

Keratins regulate actin cortex formation and stabilize cell-cell junctions

Cell Biology

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Maintenance of epithelial cell adhesion is crucial for epidermal morphogenesis, homeostasis and barrier integrity and relies predominantly on the interaction of keratins with desmosomes. While the importance of desmosomes for epidermal coherence and keratin organization is well established, the significance of keratins in desmosome and actin organization has not been fully resolved. We have recently shown that keratinocytes lacking all keratins show elevated, PKCα-mediated desmoplakin phosphorylation and subsequent destabilization of desmosomes (Kröger, JCB 2013). Further, our data suggested formation of hyperadhesive desmosomes require keratins. We noted that in keratin-free keratinocytes, actin bundles were disorganized at cell junctions, but formed extensive intracellular stress fibres. We hypothesize that keratin-desmosome scaffolds act as signalling nodes to integrate growth factor signals and regulates downstream kinases. Preliminary results show that keratins are involved in reorganisation of the actin cytoskeleton, downstream of EGFR signaling and activation of Rac1. In a first attempt to dissect keratin isotype functions, we find that expression of K6/17/14 restored epithelial sheet integrity to a lesser extent compared with K5/14 rescue cells. Our goal is to understand how keratins modulate signaling downstream of the EGFR and how they impact on desmosomal adhesion. Futher we want to unravel how keratin isotypes control different signaling pathways to regulate adhesion in a context and differentiation-specific manner.

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POSTER 77

Influence of Different Circadian Feeding Regimens on the Hepatic Metabolic State

Cell Biology

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When studying circadian rhythms using *in vivo* animal models it is important to consider the fact the "inner clock" of peripheral organs is synchronised by external factors, including food intake. In this context we performed a comprehensive study of the impact of different feeding and fasting periods on the liver metabolic state, including transcriptome, metabolome and lipidome analyses. To isolate hepatocytes, animals were sacrificed at different circadian time points. Prior to these time points animals were either fed *ad libitum* or starved for 24 hours. A third experimental group was composed by animals starved for 24 hours and re-fed subsequently for either 12 hours, in case of mice sacrificed at day (ZT3) or 21 hours for those sacrificed at night (ZT12). Using isolated hepatocytes, both the expression levels of various genes as well as levels of free fatty acids, TAGs and DAGs were determined, uncovering considerable changes between the different feeding states. For example, the level of DAG increased after the starvation period starting at ZT3 (day), compared to the *ad libitum* state. Surprisingly, the DAG level decreased after the starvation period starting at ZT12 (night). The extracellular metabolic parameters (including amino, bile and organic acids) collected from the medium of hepatocytes cultured for 24 hours did not show, at a first glance, strong variations, probably due to a likely "re-set" phenomenon of the cultivation. However, using *ANOVA* and *post hoc test* analysis it became obvious that each condition and time point correlated with specific alterations of selected metabolites such as pyruvate or fumarate.

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POSTER 78

Heteropoda Toxin 2 blocks a DPP10-induced late component of the transient outward current Ito

Cell Biology

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In human atrial myocytes, outward K^+ currents consist of two main current components: the transient outward current I_{to} dominates the initial peak current, the ultra-rapid current I_{Kur} prevails in late current. The a-subunits conducting I_{to} and I_{Kur} are Kv4.3 and Kv1.5. Dipeptidylpeptidase-like protein 10 (DPP10) modulates I_{to} currents, but does not interact with Kv1.5. Coexpression of DPP10 with Kv4.3 plus its b-subunit KChIP2 induced a slowly inactivating fraction of I_{to} in CHO cells. Here, we have studied whether DPP10 may also contribute to the late current of I_{to} in human atrial myocytes using the specific I_{to} blocker heteropoda toxin 2 (HpTx2).

K^+ currents were measured at 23°C in the absence or presence of HpTx2 (5 μM) using whole-cell voltage-clamp technique in the following cells: mouse fibroblasts stably expressing Kv1.5, CHO cells stably expressing Kv4.3+KChIP2 or transiently DPP10a and in human cardiomyocytes (enzymatically isolated from right atrial appendages). HpTx2 had no effect on expressed Kv1.5. In contrast, peak as well as late current was reduced by about 35% in CHO cells expressing Kv4.3+KChIP2 and DPP10a in presence of HpTx2. In human cardiomyocytes HpTx2 reduced late current by 37%.

In summary, HpTx2 interacts specifically with the Kv4.3 channel complex blocking the peak current and the DPP10-induced late component in CHO cells. Hence the HpTx2-induced reduction of late current in atrial myocytes provides evidence for the contribution of I_{to} to the late current due to the interaction with DPP10 in human cardiomyocytes. DPP10 may serve as potential drug target for modulation of cardiac I_{to}.

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POSTER 79 Genetic Cell Engineering of MSC for improved homing

Cell Biology

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Tumor Targeting

Mesenchymal stem cells (MSC) hold a great promise for development of alternative (cell based) therapies for numerous diseases. Despite their advantageous characteristics and their potential to improve functional outcome after stroke, MSC therapy is still not optimal. Particulary the homing capacity of the cells towards ischemic regions seems barely sufficient to improve functional recovery. Thus, this study focuses on genetic cell engineering aiming to overexpress relevant migratory and adhesional surface receptors.
Vector constructs were designed for expression of C-X-C Motif Chemokine Receptor 4 (CXCR4), C-C-Motif Chemokine Receptor 2 (CCR2) or integrin α4 (part of very late antigen [VLA4]). In addition to "closed" constructs (with stop codon) constructs with V5- or GFP-tag were designed. All vectors contain a T7/CMV promoter for in vitro transcription as well as for eukaryotic expression. Also plasmids for production of lentiviral particles were constructed for stable transfection.
After testing the functionality of constructs in HEK293T cells, MSC from either human, ovine or rat origin were transfected with synthetic mRNA, pDNA or lentiviral particles. Surprisingly, occurrence of target overexpressing cells was rather low. This was all the more surprising, since control experiments with mRNA (GFP) or lentiviral infection (GFP, dsRed) resulted in very good efficiencies (>90%). It may be speculated that the infective target expression is due to incorrect processing and/or transportation of the molecule. Therefore, more specialized and target cell specific strategies for molecular engineering need to be developed.

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POSTER 80

Parathyroid hormone improves skeletal status of rats with type 2 diabetes mellitus

Cell Biology

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Tumor Targeting

Type 2 diabetes mellitus (T2DM), characterized by an impaired beta cell function, causes altered bone metabolism leading to a decreased bone quality and an increased fracture risk. Therefore, effective therapies are limited. Here, we tested the hypothesis whether human parathyroid hormone (PTH 1-84) increases bone strength, defect regeneration, and beta cell function in diabetic ZDF (Zucker Diabetic Fatty) rats.

A subcritical femoral defect was created in diabetic (Dc) and non-diabetic (NDc) ZDF rats. PTH or vehicle was administered intermittently over 12 weeks.

Examination of femur with μCT revealed a significant reduction in metaphyseal bone volume (BV/TV) (-50%) and diaphyseal cortical thickness (Ct.Th) (-16%) in untreated Dc group compared to NDc rats. Treatment with PTH resulted in a 59% increased BV/TV in Dc rats, but had no effect on Ct.Th in both groups. While femoral defects of NDc rats were filled by 63%, it was only filled by 31% in Dc rats. In both groups PTH-treatment increased defect regeneration (+11% Dc and +12% NDc rats) and dynamic histomorphometry of the lumbar spine demonstrated an increased bone formation rate (+55% Dc and +230% NDc rats). Additionally, serum levels of the bone formation marker osteocalcin were increased (+33% Dc and +10% NDc rats) while serum levels of the bone resorption marker CTX were decreased in response to PTH treatment. However, PTH had no effect on serum glucose concentrations.

In conclusion, intermittent PTH therapy does not affect beta cell function, but is capable of improving the adverse effects of T2DM on bone mass and delayed bone defect regeneration in rats.

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POSTER 81

Signaling mechanisms of the Adhesion-GPCR latrophilin

Cell Biology

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Tumor Targeting

Latrophilins were first described as receptors for the black widow spider toxin. They are highly conserved Adhesion G-protein coupled receptors (aGPCRs), the second largest but least well understood class of GPCRs. Although aGPCRs are involved in essential biological processes, little is known about their signaling mechanisms. Recently, we have shown that LAT-1, a latrophilin homolog in *C. elegans*, plays a role in embryonic development and fertility. Each of these biological functions is very likely mediated by different signals: development by seven transmembrane domain and C-terminus of LAT-1, fertility only by the N-terminus. The molecular basis of each signal is still unknown. *In vitro* second messenger studies show that the C-terminus-dependent mode is based on a classical G protein-mediated signal. LAT-1 couples to $G\alpha_s$ and thus, mediates a cAMP-dependent signal into the cell. We were able to demonstrate the relevance of this signal for the physiological function of LAT-1 *in vivo* by complementing the signal in the absence of LAT-1 in *C. elegans*. Stimulation of the potential $G\alpha_s$ pathway in *lat-1*-deficient nematodes by 8-bromo-cAMP, forskolin or IBMX, respectively, leads to an amelioration of lethality caused by *lat-1* absence. To achieve this effect, the cAMP-based signal is specifically required in the embryo suggesting that LAT-1 function in development is mediated by cAMP and thus, potentially by $G\alpha_s$-coupling. This a one of the few times the requirement of a specific signal mediated by an aGPCR could be shown and is a first step towards a better understanding of signaling of latrophilins and aGPCRs in general.

Funding: formel1

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POSTER 82

Expression and function of the chemokines CXCL12 and CXCL11 during mouse limb muscle development and regeneration

Cell Biology

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The chemokines, CXCL12 and CXCL11 influence the fate and behaviour of various cell types. The respective functions of CXCL12 are typically mediated by the chemokine receptor CXCR4 whereas CXCL11 is known to signal via CXCR3. A third receptor, CXCR7, can bind to both chemokines and either serves as a scavenger receptor or an active chemokine receptor. Inspired by the observation of reduced limb muscle masses in CXCR4 knockout mice, the objective of this study was to examine the role of CXCL12 and CXCL11 in limb myogenesis. Using C2C12 myoblasts, we found that both, CXCL11 and CXCL12 induce Erk signal transduction in a similar fashion. Stimulation of C2C12 cells with either CXCL12 or CXCL11 prevents myogenic differentiation and CXCL12 additionally stimulates myoblast migration and proliferation, thus implying a role of both chemokines in the amplification and positioning of myoblasts as well as in prevention of premature differentiation during muscle growth. In case of CXCL12, these effects are entirely mediated by CXCR4. Moreover, consistent with a savenging function, CXCR7 expression increases in differentiating C2C12 cells and abrogates CXCR4 signaling. Further implying that CXCL12 and CXCL11 control early limb muscle development in vivo, we found that expression of CXCL12, CXCL11 and CXCR4 are highest in late embryonic hindlimb muscles and decline during adolescence, whereas CXCR7 levels increase. Finally, CXCL12 and CXCL11 signaling might also be assignable to adult muscle regeneration as regenerating muscles of dystrophin-deficient mice exert increased expression of CXCL12, CXCL11 and CXCR4 but not CXCR7.

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POSTER 83 **Hilft LXRα heilen?**

Cell Biology

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Die Leber ist eines der größten Organe in Vertebraten. Sie ist essentiell für vielfältige katabole sowie anabole Prozesse und gewährleistet die Energiehomöostase des Organismus. Dabei spielt vor allem der Lipidstoffwechsel eine zentrale Rolle, dessen Regulation durch den Liver X Receptor (LXR) in dieser Arbeit untersucht wurde. Die Zielgene des nukleären Rezeptors LXRα sind vor allem mit dem Lipid- und Cholesterolstoffwechsel assoziiert. Dies macht LXRα zu einem interessanten Modulator bei Krankheiten wie Atherosklerose. qRT-PCR-Analysen zeigten, dass die Aktivierung von LXRα mit dem synthetischen Liganden GW3965 zu einer signifikanten Hochregulation der Expression der Zielgene Srebp1 und Cyp7a1 führte. Außerdem wurde in Fettrotfärbungen nachgewiesen, dass durch höhere Agonistenkonzentrationen eine hepatische Steatose entsteht, die Quantifizierung der Expression erbrachte für diese GW3965-Konzentration eine geringere Aktivierung der Zielgene als bei niedrigeren Agonistenkonzentrationen. Das Zellsystem schützt sich wahrscheinlich durch die Reduktion der Zielgenexpression vor weiterführender Lipidsynthese und -einlagerung. Für die Untersuchung des Einflusses eines Lxrα-Knockdowns wurden ausgewählte Gene in qRT-PCR-Messungen quantifiziert, ein Microarray lieferte einen Überblick der Gesamtexpression. Die Zielgene Srebp1 und Cyp7a1 zeigten dabei nahezu kein verändertes Expressionsprofil. Für die untersuchten Gene liegt die Vermutung nahe, dass für eine Regulation über LXRα ein besetzter nukleären Rezeptor notwendig ist. Für weitergehende Untersuchungen, wäre die regulatorische Wirkung von Antagonisten von großem Interesse.

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POSTER 84

Role of NADH-dehydrogenase subunit 2 mutation in skin fibroblast ageing

Cell Biology

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Tumor Targeting

Mitochondrial production of reactive oxygen species (ROS) plays a key role in organismal ageing but the specific role of individual mitochondrial pathways is unclear. A dysfunction of the mitochondrial respiratory chain may lead to enhanced ROS production and ageing. In this study, different conplastic mouse strains were used harboring mutations in mitochondrial genes encoding respiratory chain protein complexes I-V and uncoupling protein 2 (UCP2). These mice were analyzed at different time points for expression of age-related markers. For this purpose, isolated primary skin fibroblasts were analyzed under cellular stress conditions and production of ROS, ATP, age-related cytokines and cellular proliferation were measured and compared to basal levels. The mouse strain B6-mt^{ALR} with a single nucleotide exchange in the NADH dehydrogenase subunit 2 gene in complex I showed decreased ROS and enhanced ATP basal levels compared to the control B6-mt^{AKR}, in 12-month-old mice. The mutated strain showed an enhanced proliferation rate compared to the control strain detected by BrdU incorporation. Furthermore, IL-6 and IL-8 levels in B6-mt^{ALR} mice increased 4 and 8 days after doxorubicin-treatment, but the basal secretion levels of these cytokines were lower compared to the controls. Immunoblots showed that induction of H3K9me3 and IkBalpha was delayed in B6-mt^{ALR} mice after doxorubicin-treatment. These results show differences in baseline and stress-induced ageing markers between mutant and control mice that could be interpreted as increased resistance to oxidative and cellular stresses with the consequence of delayed ageing.

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POSTER 85

Thy-1 (CD 90) regulates the proliferation and differentiation of dermal fibroblasts

Cell Biology

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Tumor Targeting

Thy-1 has been described as a cell-cell adhesion molecule mediating the interaction of myeloid and melanoma cells to activated endothelial cells (ECs). In contrast to ECs, Thy-1 is constitutively expressed on fibroblasts (Fbs) but there are no data available about the functional role of Thy-1 on Fbs. In this study, we investigated the effect of Thy-1 on dermal Fbs with respect to cell proliferation, apoptosis, senescence and differentiation using Fbs from Thy-1-deficient and wild type (wt) mice. A lack of Thy-1 resulted in a significantly higher proliferation rate, less apoptosis and cellular sensecence compared to wt Fbs. In contrast, wt Fbs displayed a more differentiated phenotype reflected by an enhanced ability to contract free-floating collagen lattices as well as an increased expression of alpha-smooth muscle actin. The increased proliferation of Thy-1-/- Fbs was completely abolished by seeding Thy-1 -/- Fbs on immobilized recombinant Thy-1. The interaction of Thy-1 with integrins is mediated by its RGD-like integrin-binding sequence (RLD). Consistently, culture of Thy-1-/- Fbs on recombinant Thy-1 with a mutation in the integrin-binding motif (RLD to RLE) affected proliferation of Thy-1 -/- Fbs significantly less than wt Thy-1. Using integrin-blocking antibodies we show that down-regulation of Fb proliferation by Thy-1 requires the interaction with β_3 integrins. Proliferation of Fbs is a central key step in wound healing. Thy-1-deficient mice revealed significantly more proliferating cells in full thickness wounds than wt. Taken together, these results emphasize the anti-proliferative effect of Thy-1.

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POSTER 86

Regulation of energy metabolism in hepatocyte mitochondria by morphogenic pathways

Cell Biology

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Tumor Targeting

In this study we focussed the regulation of energy metabolism, and specifically, the activity of mitochondrial respiratory chain complexes I to IV in two transgenic mouse lines. One transgenic mouse line carried a hepatocyte-specific deletion of Smoothened (Smo), an important signalling component of the Hedgehog (Hh) signalling pathway. The second transgenic mouse line is characterized by a partial reduction in the APC (adenomatous polyposis coli) protein expression in hepatocytes (APC loxP neo) and, thus, shows an activated Wnt/-ß-catenin signalling. To explore the regulation of mitochondrial respiratory chain complexes in these two animal models (a) the mRNA expression level of selected subunits was determined by quantitative real-time PCR and (b) the activity of respiratory chain complexes in hepatocyte was assessed by photometric assays. There was no variation in the mRNA expression levels of specific genes and in the activities of complexes I to IV in Smo knock-out-mice compared to control mice. In contrast the mRNA expression profile of the genes of subunits and the relative enzyme activities showed an increase of complex II and a slightly decrease of complex I, III and IV in APC loxP neo hepatocyte compared to APC wt/wt mice. This was associated with changes in the activities of respiratory chain complexes. In conclusion it seems that the Smo Knock-out has less influence on the activity of mitochondrial respiration whereas an increase of Wnt/-ß-catenin signalling in liver has some detectable effects.

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POSTER 87

Keratins are major determinants of migration and invasion by regulating adhesion and cell stiffness

Cell Biology

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Tumor Targeting

Cell motility is crucial during skin morphogenesis, wound healing, inflammation and malignant progression. These processes require remodeling of the keratin cytoskeleton, involved in cell-cell and matrix adhesion in several epithelia including the epidermis. However, the role of keratins in migration and invasion is only partially understood.

Here, we address this issue in murine keratinocytes depleted of all keratins by genome engineering. The absence of the entire keratin cytoskeleton leads to loss of plectin from hemidesmosomes and higher β4 integrin dynamics in keratin-free cells. To investigate the functional consequences, migration and adhesion assays were performed. These revealed that in the absence of keratins, keratinocytes adhere much faster and migrate ~2 times faster compared to wildtype cells. In addition, invasion was also increased in a Boyden chamber assay. In contrast to prediction, keratin-free cells showed a much higher cell deformability using the optical stretcher with minor contribution of actin. Re-expression of the single keratin pair K5/K14 fully reversed the above phenotype. Our data uncover a novel role of keratins in the maintenance of hemidesmosomes upstream of plectin and thereby influencing adhesion, directed migration and invasion with implications for epidermal homeostasis and pathogenesis. This study supports the view that downregulation of keratins observed during epithelial-mesenchymal transition directly contributes to the migratory and invasive behavior of tumor cells.

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POSTER 88

Oleate rescues ins-1e β-cells from palmitate induced-apoptosis by preventing activation of the unfolded protein response

Cell Biology

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Tumor Targeting

Objective: Palmitate causes β-cell apoptosis whereas unsaturated free fatty acids (FFA), e.g. oleate, are not harmful. The toxicity of palmitate could be mediated through endoplasmic reticulum (ER) stress which activates the Unfolded Protein Response (UPR). We investigated whether or not palmitate induces β-cell apoptosis through UPR activation and whether or not oleate can counteract these effects.
Methods: INS-1E cells were incubated with palmitate [0.5mM], oleate [1mM] or the combination of both. Viability was measured using WST-1 assay. Apoptosis was determined by An/PI-assay. Activation of the UPR was analysed by Western blotting. Chaperone mRNA expression and Xbp1 splicing was quantified by qPCR.
Results: Palmitate significantly enhanced apoptosis and decreased viability (29±8.8%) of INS-1E cells compared to controls after 24h. Stimulation with oleate showed no effect but the combination of oleate and palmitate improved cell survival and viability (55±9.3%) compared to palmitate treated cells. Increased phosphorylation of eIF2α and splicing of Xbp1 after 6 and 24h incubation with palmitate was prevented by the addition of oleate. In contrast, oleate alone had no effect. Interestingly, mRNA expression of chaperones was not altered by FFA treatment. Only the proapoptotic transcription factor Chop was significantly enhanced by palmitate incubation. Oleate alone or the combination did not result in increased Chop levels compared to controls.
Conclusion: Palmitate induced apoptosis in INS-1E cells, caused ER stress and consequently activated the UPR. Oleate had no toxic effects on β-cells but ameliorated the effects of palmitate.

Funding: life

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POSTER 89 **The Effect of Prenatal Smoking on the Epigenome**

Cell Biology

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Tumor Targeting

During early development epigenetic programming is essential and vulnerable to environmental exposure. Altered epigenetic patterns cause severe diseases such as cancer, metabolic disorders or immunological diseases. Surprisingly, little is known about epigenetic mechanisms that transmit environmental stress to disease risk.

Here, we studied tobacco smoke-induced changes to epigenetic programming during the prenatal period. Based on whole genome bisulfite sequencing data of mother-child pairs we investigated the epigenome by applying different techniques to analyze the methylation patterns and histone modifications.

In the investigated cohort we identified a distinct genome wide epigenetic response. Interestingly, the induced changes in the epigenetic pattern strongly differ between mother and children. Local specific methylation differences between the smoking and non-smoking group reveal a complex deregulation in a variety of cellular pathways.

Together with an observed link to a disease related phenotype, we here identified aberrant DNA methylation as a possible molecular mechanism how exposure to an environmental stressor in the prenatal period, increases the risk for disease outcomes later in life.

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POSTER 90

Pigment epithelium-derived factor of retinal glial origin has neuroprotective effects on retinal ganglion cells

Cell Biology

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Tumor Targeting

Purpose: Retinal Müller glial cells (RMC) secrete the neuroprotective factor pigment epithelium derived factor (PEDF). Experiments were performed to determine whether PEDF of glial origin protect retinal ganglion cells (RGC) from pathologic external influences and to elucidate the signaling pathways involved in PEDF-mediated regulation of RGC viability.
Material and Methods: Co-culture experiments using immunoisolated primary RGC and cultured RMC were performed under normoxic (95% air; 5% CO_2) or hypoxic conditions (0% O_2, 95% N_2, 5% CO_2) for 24 hours. PEDF was added to homotypic RGC cultures in different concentrations and its effect was blocked using aneutralizing antibody in co-cultures. Activation of NF-κB was determined using immunocytochemical staining.
Results: Under normoxic conditions 54.04±0.03% of RGC were vital after 24 hours of homotypic culture whereas 68.52±0.03% were found viable after 24 hours in the presence of RMC. Hypoxia decreased the RGC survival rate with 32.84±0.02% of RGC viable in homotypic and 44.83±0.02% in co-culture experiments. PEDF supplementation led to an increase of RGC survival rate in homotypic cultures. Neutralizing PEDF in co-cultures caused RGC survival to decrease. Immunocytochemical staining of NF-κB showed a PEDF-dependent activation under normoxic and hypoxic conditions.
Conclusion: Our experiments conducted so far demonstrate the supportive properties of RMC directed towards RGC survival. PEDF secreted by RMC appears to play an important role due to its neuroprotective properties. PEDF-mediated neuroprotection of RGC may involve signaling through the NF-κB pathway.

Funding: formel1

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POSTER 91

The poor outcome prognosticator ERG is regulated by miR-9 in Acute Myeloid Leukemia (AML)

Cell Biology

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AML is a serious disease and most patients (pts) still have a poor prognosis. In AML pts high expression of the gene encoding the transcription factor ERG (*ETS* related gene) is associated with worse outcome. The factors mediating the differential expression of ERG are unknown. *In silico* prediction tools identified three putative *miR-9* binding sites in the 3'-untranslated region of *ERG*, suggesting a direct interaction and regulative effect.We determined the relative expression of *ERG* and *miR-9* in eight AML cell lines (i.e. KG1a, Kasumi-1, K562, THP-1, MV4-11, ME1, OCI-AML3 and EOL1) using Real-Time-PCR, and demonstrated an inverse correlation of *ERG* and *miR-9* expression (rank correlation –0.90). KG1a had the highest *ERG* and lowest *miR-9* expression, thus *miR-9* overexpression experiments were performed in this model. Following the transfection of a *miR-9* overexpression vector we found a decreased *ERG* expression on mRNA level to 53% (in comparison to empty vector control [empty vec]) after 24h. Western blotting confirmed the lower expression of ERG after *miR-9* overexpression on protein level after 12h to 72% and 24h to 58% compared to empty vec. Moreover, cells overexpressing *miR-9* had a lower proliferation rate. After 4 days cell viability was 96.2±23.8% *vs.* 321.6±8.1% (P=.003) in the *miR-9* overexpressing cells compare to empty vec expressing cells.In conclusion, increasing *miR-9* leads to down regulation of the worse outcome predictor ERG and reduced proliferation of AML cells. Increasing *miR-9* either pharmacologically or by miR-replacement therapy may provide a new therapeutic avenue in AML pts with high ERG expression.

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POSTER 92 **Cell friendly polymer surfaces from a lowenergy process**

Cell Biology

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Plasma treatment is a common but problematic method to modify surfaces for protein and cell adhesion. This is also true for polystyrene which is probably the most economic material for manufacturing sterile components. Most of the current cell culture vessels are made of polystyrene. The disadvantage of this material is its hydrophobicity, which is in most cases unfavorable for cell growth. But plasma and other treatments are usually generating a number additional toxic compounds affecting cell growth. Her we present an enzymatic method for surface modification having little or no effect on cell growth. This method is only requiring the enzyme solution, no electric power or toxic chemicals are required. Laccase combined with substrates was allowed to act on the unmodified polymer. Normal human epidermal melanocytes were seeded on the treated surface and cultivated as adherent culture with particular focus on adherence properties proliferation and melanin content. Follicle-cultivated melanocytes, mesenchymal stem cells and the cell line NTERA-2 were also tested. The novel approach is not restricted to polystyrene. Almost all organic polymers can be modified using the enzyme in combination with different substrates. The treatment leads to improved cultivation conditions for example for melanocytes compared to untreated polystyrene. In comparison to plasma treated polystyrene surfaces the method gives similar or better results. The treatment with laccase is a revolutionary new approach to prepare polystyrene or other polymer based 2D cell culture dishes and also scaffolds for 3D cell culture.

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POSTER 93

Anatomische Landmarken für die chirurgische Intervention am Kiefergelenk

Clinical Studies

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In den letzten Jahrzehnten hat sich die operative Medizin enorm weiterentwickelt. Auch in der Mund-, Kiefer- und Plastischen Gesichtschirurgie stellt sich deshalb die Frage nach der Modifizierung etablierter Zugänge zum Kiefergelenk (präaurikulär, retroaurikulär, submandibulär und intraoral). Damit ändert sich teilweise die Sichtweise auf die Topographie der betroffenen anatomischer Strukturen.

Der Operateur muss die Auswahl des in Frage kommenden Zugangs immer individuell entscheiden, wobei Gesichtspunkte wie Platzbedarf und mögliche Gefährdung anatomischer Strukturen, z.B. A. und N. facialis sowie Gl. parotidea, eine Rolle spielen.

Abbildungen in anatomischen Atlanten spiegeln aber nie die individuelle Variationsbreite wieder, so dass an 3 kompletten und 3 geteilten Alkohol-fixierten sowie 3 kompletten Thiel-fixierten Präparaten von ausschließlich weiblichen Körperspendern im Alter von durchschnittlich 83 Jahren operative Zugänge unter besonderer Berücksichtigung der zu schonenden Strukturen nachgestellt wurden. Nach Prof. W. Thiel (1992) fixierte Präparate haben den Vorteil, dass das Gewebe flexibel bleibt und so eine Imitation der Mundöffnung möglich wird.

Wichtigste Ergebnisse der Arbeit sind die Darstellung des exakten Verlaufs der einzelnen Äste des N. facialis und der Bezug der Gl. parotidea zum Frey-Syndrom.

Perspektivisch soll in Zusammenarbeit mit den Mund-, Kiefer- und Gesichtschirurgen ein Trainingskurs am anatomischen Präparat etabliert werden, bei dem neue Techniken erprobt werden und junge Ärzte die operativen Fertigkeiten vervollkommnen können.

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POSTER 94

The Vigilance Algorithm Leipzig: An Alternative to the Multiple Sleep Latency Test?

Clinical Studies

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The Multiple Sleep Latency (MSL) test is the standard for objective assessment of excessive daytime sleepiness. To overcome its limitations (e.g. the enormous time effort and rater dependent results), a semi-automatic tool for measuring vigilance regulation during a 15 min resting-EEG, based on the Vigilance Algorithm Leipzig (VIGALL) was developed. It allows the classification of different types of wakefulness- i.e.vigilance- regulation: a stable, a medium and an unstable type. The goal was to compare the results of the MSL test and VIGALL in 25 healthy subjects.

The MSL was assessed during four measurements with a time interval of two hours. Vigilance regulation was assessed between MSLT-measurement 1 and 2. Karolinksa Sleepiness Scale (KSS) and Epworth Sleepiness Scale (ESS) had to be filled out.

MSLs and VIGALL classification showed significant correlations (rho=-0.54). Subjects with a stable EEG-vigilance regulation yielded significant increased MSL than subjects with an unstable regulation (MSL 898.5s vs. 549.9s; $p<0.02$). While the MSL showed a significant correlation with the ESS (r=-0.68) but no correlation with the KSS, VIGALL classification correlated significantly with the ESS (rho = 0.45) and showed a tendency for a correlation with the KSS (rho = 0.33).

The assessment of vigilance regulation via VIGALL is comparable to the results of the MSL test. Although the MSL showed higher correlations with trait markers of sleepiness than VIGALL, the latter seems to better reflect momentary sleepiness. However, VIGALL might be an effective and reliable alternative to the MSL for e.g. screening purposes in large cohorts.

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POSTER 95

Improved Pharmacodynamics and Pharmacokinetics after Intravenous Application of Peginterferon alfa-2a 180 µg in Chronic Hepatitis C Genotype 1 Nullresponders

Clinical Studies

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Background: Mechanisms of non-responsiveness to peginterferon alfa-2a (PEG-IFN alfa-2a) are notcompletely understood. Inadequate plasma levels may contribute to reduced response. This study evaluated the pharmacokinetics and viral kinetics of intravenous versus subcutaneous PEG-IFN alfa-2a in patients with genotype 1 chronic hepatitis C infection who showed null-response to previous PEG-IFN/ribavirin. Methods: Prospective, multicentre, cross-over phase 1 study. Patients were randomized to s.c. or i.v. PEG-IFN alfa-2a 180µg, once or twice weekly for two weeks, with a 6 week wash-out period. Results: Intravenous administration resulted in a stronger and more rapid decline in HCV RNA. Maximum decline in HCV RNA was more pronounced after i.v. administration (mean change to 12 hours [range]: i.v. –0.11 to –0.79 $\log_{10}$ IU/mL vs. s.c. –0.11 to –0.30 $\log_{10}$ IU/mL). All treatment arms showed rebound in HCV RNA levels. Maximum concentration $(Cmax)_{0\text{-}12\ h}$ and $Cmax_{\ 0\text{-}7\ d}$ values were significantly higher following i.v. administration ($p \leq 0.002$). Intravenous administration of PEG-IFN alfa-2a resulted in markedly higher area under the curve $(AUC)_{\ 0\text{-}12h}$ and $AUC_{0\text{-}7d}$ compared with s.c. administration. Differences in $AUC_{0\text{-}12h}$ between i.v. and s.c. administration were significant irrespective of dosing frequency ($p<0.0001$). Conclusions: Intravenous administration of PEG-IFN alfa-2a results in considerably higher plasma concentration and a stronger decline in HCV RNA and offers an interesting approach in order to overcome interferon nonresponsive state in patients with null response to previous Peg-IFN/ribavirin combination therapy.

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POSTER 96

Genotype Analysis and Serostatus of JC and BK Polyomavirus Shedding Immunocompromised Patients

Clinical Studies

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Polyomaviruses JCV and BKV are ubiquitously abundant among the human population and establish a lifelong asymptomatic latency within healthy individuals. However, in immunocompromised individuals, severe clinical symptoms, such as haemorrhagic cystitis and progressive multifocal leukencephalopathy, can occur.In this study the shedding and genotype distribution in 225 immunocompromised patients (SCT and SOT recipients), was monitored over a period of three years. Detection of BKV and JCV was done by PCR amplification of the large T-antigen and genotyping by sequencing VP1. The major BKV genotype found in this study was Ib2 (50%), followed by Ib1 (21%), IV (20%) and II (9%). The two major JVC genotypes were 1A and 1B (39% each), followed by 4 (16%) and 2 (6%). Simultaneous excretion of both, JC and BK polyomaviruses was found in 29 patients (12.9%) and was detectable for varying time periods up to 8 months. Polyomavirus-specific antibody response was determined three months after transplantation (n=89 and 221, respectively) and in non-immunocompromised controls (n=127). An unexpected high seroprevalence was detected for JCV (84.3%) in the non-immunocompromised control group, whereas the seroprevalence of BKV (79.5%) was in accordance with previous studies. In immonocompromised patients, the seroprevalence was 83.3% for JCV and 92.7% for BKV. If only BKV was shed, a markedly decreased likelihood of being seropositive for JCV was seen.The results indicate there is a substantial risk for BKV and JCV reactivation in immunocompromised patients and in cases of simultaneous infection BKV interferes with JCV replication.

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POSTER 97

Low BAALC expression associates with better outcome in acute myeloid leukemia (AML) patients (pts) undergoing allogeneic hematopoietic cell transplantation (HCT) after reduced-intensity conditioning (RIC)

Clinical Studies

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RIC-HCT is increasingly used in AML pts ineligible for conventional conditioning. Low BAALC expression associates with better outcome in AML pts after standard chemotherapy. If its expression also associates with outcome in AML pts undergoing RIC-HCT, with a therapeutic approach based on a graft-versus-leukemia effect, is unknown.

We analyzed 68 AML pts (median age, 61 years [y]) who received RIC (3 days Fludarabin 30mg/m2 & 2Gy total body irradiation)-HCT with pretreatment bone marrow material available. Donors were human leucocyte antigen (HLA)-matched (82%) or mismatched (18%). At HCT 82% of pts were in complete remission. Median follow-up was 6.7y. Cytogenetic risk was Favorable 8%, Intermediate 63%, Adverse 29%. Pts were characterized for NPM1, FLT3-ITD, CEBPA mutation status & ERG & MN1 expression. BAALC expression was normalized to 18S & the median normalized expression was used to define high & low BAALC expressers.

Pts with adverse cytogenetics had higher BAALC expression than Intermediate risk pts (P=.007). Low BAALC expression associated with mutated NPM1 (P=.003), FLT3-ITD (P<.001) & low MN1 (P<.001). Low BAALC expressers had longer overall (OS; P=.001) & event-free survival (EFS; P=.02) than high expressers. In multivariable analysis, low BAALC expression independently associated with longer OS (hazard ratio [HR]: 0.15; P=.004) & EFS (HR: 0.35; P=.05) after RIC-HCT.

Low BAALC expression independently associated with longer survival in RIC-HCT treated AML pts even when established factors were considered. Pretreatment BAALC levels may refine the risk stratification for AML pts undergoing RIC-HCT.

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POSTER 98

Contrast enhanced intraoperative ultrasound perfusion analysis for brain tumors

Clinical Studies

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Introduction:Within a DFG project, patients with brain tumors (gliomas, metastases, meningiomas) were subjected to an intraoperative, contrast enhanced, ultrasound perfusion analysis. Method:Therefore a total of 96 patients were included in the study. Sonovue ultrasound contrast agent was administered before acquiring 2d ultrasound videos for about 60-70 sec before opening of the dura. The videos were exported as avi-Files. Further analysis of the perfusion characteristics of four distinct areas (solid tumor, central necrosis/cyst, normal brain parenchyma and distributing vessel) was conducted by Bracco Contrast 4.0 software. The parameters peak intensity, time to peak, regional blood flow, regional blood volume and mean transit time were acquired. Results:Thereby distinct perfusion characteristics could be encountered for the four areas in each analyzable data set. A total of 65 out of 96 sets could be analyzed. The remaining had to be excluded due to technical issues. This is the largest amount of patient subjected to brain tumor ultrasound perfusion imaging published to date. By now, we concentrate on the ability of tumor differentiation by the above mentioned perfusion parameters.

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POSTER 99

The conditional power in survival time analysis considering cure fractions

Clinical Studies

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Tumor Targeting

Conditional power calculations are a helpful aid within interim analysis of clinical trials when the aim is to decide whether a trial should be continued or stopped for futility. When a cure fraction becomes apparent this issue could no longer be solved accurately with simple survival models, e.g. the exponential model. Non-mixture models consider such cure fractions. The way of fitting several non-mixture models to data and constructing conditional test statistics in view of relevant hypotheses to derive appropriate conditional power functions will be described here. The methods will be applied to a dataset.

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POSTER 100

N. vagus-evozierter Blinkreflex: Etablierung der Technik und Befunde bei Patienten mit M. Parkinson

Clinical Studies

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Frage: Beim idiopathischen Parkinsonsyndrom (PD) kommt es zu einer Degeneration von Neuronen im Hirnstamm auch im dorsalen motorischen Kern des N. vagus (VN), dessen Funktion möglicherweise neurophysiologisch durch einen Blinkreflex (BR) bestimmt werden kann.
Meth.: Ein BR wurde bei 30 Patienten mit PD und bei 30 gesunden Kontrollen (alters- und geschlechtsgematcht) untersucht. Varianten des BR wurde jeweils nach beidseitiger transkut. elektr. Stimulation des R. auricularis n. vagi, des N. supraorbitalis n. trigemini (TN) sowie des N. medianus am Handgelenk (MN) mittels Oberflächenelektroden über dem M. orbicularis oculi abgeleitet. Die Latenzen und die Peak-to-peak Amplituden wurden bestimmt. Als Screening für Einschränkungen der Kognition wurde der Montreal Cognitive Assessment (MoCA) Test verwendet.
Ergeb.: Der VN-BR konnte bei 26 v. 30 Kontrollen (davon 4 einseitig) und bei 26/30 Patienten (davon 10 einseitig), der MN-BR bei 22/30 Kontrollen (davon 3 einseitig) und 24/30 Patienten (davon 9 einseitig) und der TN-BR bei allen Versuchspersonen verlässlich abgeleitet werden (davon je ein Patient und ein Proband nur einseitig). Es unterschieden sich weder die Latenzen der einzelnen Antwortkomponenten noch die Peak-to-peak Amplituden zwischen den beiden Gruppen.
Schlussfolg.: Der VN-BR lässt sich bei Kontrollen und PD-Patienten ableiten, allerdings nicht immer verlässlich. Anhand des VN-BR lässt sich keine Störung der Prozessierung somatosensibler Information im Vagus-Kern-Komplex bei PD-Patienten nachweisen. Dies könnte bedeuten, dass somatosensible Kerngebiete von der Degeneration im Vagus-Kern-Komplex ausgespart sind.

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POSTER 101

Bacterial DNA detection in ascites fluid in cirrhotic patients: molecular characterisation and clinical impact

Clinical Studies

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Spontaneous bacterial peritonitis (SBP) is a serious complication in cirrhotic patients. Due to the limitations of culture-dependent bacterial identification methods we applied culture-independent PCR-based methods for the detection and differentiation of bacterial DNA (bactDNA) in order to characterize the bacterial spectrum in ascites fluid (AF) and evaluated the clinical impact of this marker.
169 index paracentesis from cirrhotic patients were collected from 02/2011 to 12/2012. BactDNA was detected using real-time PCR with primers targeting the V3 and V4 variable regions of the 16S rRNA-gene. Positive PCR-products were sequenced and polymicrobial chromatograms were analysed using the web tool Ripseq.
We present a method to rapidly detect bactDNA in AF samples and to identify the most abundant sequence types. BactDNA could be detected in 39,1 % of all AF samples. The percentage of bactDNA detection was 37,3 % in non-leukocytic AF as compared to 43,5 % in leukocytic AF. Direct sequencing of PCR products revealed mixed chromatograms in 61,9 % and showed a dominance of gram-positive bacteria. During follow-up (1-30 months), 19 patients were transplanted and 75 patients died mainly due to infections (40 %). Mean transplant-free survival was 344 days (CI 248-439) in patients with bactDNA positive AF (n=66) as compared to 374 days (CI 285-463) in those with undetectable bactDNA (n=103) (p=0,676).
Detection and differentiation of bactDNA using culture-independent PCR-methods are suitable tools to further characterize AF samples. The clinical impact and predictive value of bactDNA detection needs to be evaluated in further trials.

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POSTER 102

The impact of nutrition and body weight on intestinal absorption and endogenous synthesis of cholesterol in children.

Clinical Studies

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Rationale: In obese subjects, elevated serum cholesterol is one of the major factors leading to cardiovascular complications and is already present in children. Intestinal cholesterol absorption is supposed to be in equilibrium with endogenous synthesis.
Methods: To assess the proportion of cholesterol absorption and synthesis, non-cholesterol sterols were measured by liquid chromatography-tandem mass spectrometry. The cohort consists of 195 children (88 girls, 107 boys, aged 5 to 19 years) including 165 lean and 28 obese children and BMI-SDS ranged from –3.7 to 2.9. Dietary intake was evaluated by a food diary for 4 days.
Results: Cholesterol serum concentration did not differ significantly between obese and lean children. For BMI-SDS a positive correlation was found with cholesterol synthesis ($r=0.24$; $p=0.001$), whereas cholesterol absorption showed an inverse correlation with BMI-SDS ($r=-0.38$; $p<0.001$). Lean children showed significantly higher fruit (209.7 g/day ± 180.1 vs. 111.07 g/day ± 84.6; $p=0.010$) and carbohydrate intake (260.8 g/day ± 76.5 vs. 217.6 g/day ± 54.1; $p=0.009$). For markers of cholesterol synthesis a significantly positive correlation with fish intake was observed ($r=0.20$; $p=0.015$), whereas carbohydrate intake was significantly positive correlated with cholesterol absorption ($r=0.17$; $p=0.037$).
Conclusion: Despite equal cholesterol serum levels, the relationship of cholesterol absorption and synthesis is supposed to be modified with higher body mass already in children. Dietary intake showed only weak associations with surrogate markers of cholesterol absorption and synthesis.

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POSTER 103

The impact of capsular resection on the risk of dislocation after primary total hip arthroplasty – A multivariate analysis of 2718 cases.

Clinical Studies

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Tumor Targeting

Introduction: Dislocation is the second most frequently encountered complication in primary total hip arthroplasty (THA). Several risk factors are well known from literature. On basis of large series of primary THA performed in our department, cases with resection of the capsule were compared statistically to cases of capsular repair. The aim of this study was to investigate the influence of capsular resection on the risk of THA dislocation in relation to other well-known risk factors.

Methods: A number of 2718 primary THA was included from 2396 patients in a ten year period, performed via the lateral and the anterolateral approach, with the only exceptions of resurfacing arthroplasty, dual mobility and tumor hip replacements. Dislocation rates and related patient data were recorded and analyzed using a logistic regression.

Results: In 1511 cases, THA was performed with capsular resection and in 1207 cases the technique of capsular repair was applied. The total dislocation rate was 1.25% (n=34): 1.92% (n=29) in the cases with capsular resection and 0.41% (n=5) in the cases with capsular repair. The resection of the capsule had the highest influence on the risk of dislocation (p=0.001). Odds ratio increased 5.05 times if the capsule was removed in THA. The age had minor influence (p=0.01). Patients older than the mean age of 67 years had a slightly increased risk (odds ratio 1.05).

Conclusions: The resection of the hip joint capsule was the most important risk factor for dislocation after primary THA in this study. Preservation and reconstruction of the hip joint capsule are therefore expressively recommended in THA.

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POSTER 104

High pre-treatment miR-181a-1 and miR-181a-2 expression in intermediate risk acute myeloid leukemia (AML) patients (pts) associates with lower relapse rate after reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT)

Clinical Studies

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Tumor Targeting

AML pts with higher *miR-181a*, which is derived from two precursor molecules (*miR-181a-1* & *miR-181a-2*), have better outcomes following standard chemotherapy. RIC is increasingly used in AML pts undergoing HCT. If pre-treatment *miR-181a-1* & *miR-181a-2* expression impacts on outcome in AML pts treated with RIC-HCT is unknown.

miR-181a-1 & *miR-181a-2* expression was assessed by real-time PCR, normalized to *18S* expression in pre-treatment bone marrow (BM) & the respective median expression defined high & low *miR-181a-1* & *miR-181a-2* expressers in 39 AML pts (median age, 62 [range 27 – 67] years) with intermediate cytogenetic risk, who received RIC-HCT & with adequate material available. The preparative regimen for all pts was Fludarabin 30mg/m^2 (day –4 to –2) followed by 2Gy total body irradiation at day 0. Median follow-up was 6.5 years for pts alive.

At diagnosis high *miR-181a-1* associated with lower white blood count (P=.03), while high *miR-181a-2* associated with abnormal cytogenetics (P=.03) & lower %BM blasts by trend (P=.08). In univariate analysis pts with both high *miR-181a-1* & high *miR-181a-2* had a lower probability of relapse (p=.008, Gray's test). High *miR-181a-1* & high *miR-181a-2* expression also associated with longer overall survival (OS) by trend (p=.06, Log-Rank test).

In conclusion high pre-treatment *miR-181a-1* & *miR-181a-2* expression associated with a lower probability of relapse in AML pts with intermediate cytogenetic risk. Assessing pre-treatment levels may improve risk stratification & increasing *miR-181a* either pharmacologically may improve outcomes of RIC-HCT treated AML pts.

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POSTER 105

Gefahrenpotential Hautflora – Staph. epidermidis ein pathogener Wundkeim?

Clinical Studies

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Tumor Targeting

Tiefe sternale Wundheilungsstörungen (DSWI) sind ernst zu nehmende und schwierig zu behandelnde Komplikationen nach kardiochirurgischen Eingriffen. Folgeeingriffe, Reserveantibiotika und prolongierte Hospitalisierung der Patienten verstärken die mikrobiologische Komplexität.

Ziel dieser Arbeit ist die Erstellung eines mikrobiologische Besiedelung und Infektionsprofils herzchirurgischer Patienten mit DSWI. Intraoperativ wurden ein oberflächlicher Prä-operativer Abstrich vor Hautdesinfektion, eine intraoperative aus der Tiefe gewonnene Gewebeprobe, sowie ein abschließender oberflächlicher Abstrich nach chirurgisch debridierter Wunde.

Es erfolgte eine Retrospektive Datenanalyse 53 herzchirurgischer Patienten mit DSWI, die im Zeitraum von Mai 2012 – Mai 2013 ein radikales Knochen- und Weichteildebridement sowie simultanen Wundverschluß mittels Lappenplastik erhalten haben

Eine Mischinfektion bestand bei 72%. 65% zeigten ein gram-positives, 35% ein gram-negatives Spektrum; In nur 9,4% der Fälle konnte intraoperativ ein multiresistenter Erreger (VRE, ESBL, Metallo-Beta-Lactamase) nachgewiesen werden. In 23% der Fälle konnten weiterhin ein Keimspektrum nachgewiesen werden, dies bestand in 50% aus Staph. Epidermides.

Die Untersuchung ergab eine deutliche Verlagerung des Keimspektrums in den Gram positiven Bereich mit führendem Vorkommen des Staph. epidermidis. Insbesondere nach radikaler Wundexzision ist dieser häufig in tieferen Gewebsschichten weiterhin nachweisbar und auf Grund der verursachenden Wundheilungsstörungen als pathogen anzusehen. Chronische Wunden bedürfen daher einer radikalen Exzision, Plastischer Deckung und simultaner antibiotischer Therapie.

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POSTER 106

Low initial growth rate leaves phenylketonuria patients (PKU) shorter throughout childhood: longitudinal analysis using the CrescNet database

Clinical Studies

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Tumor Targeting

Newborn screening and early dietary treatment allow normal psychomotor development of PKU-patients. Data on suboptimal growth is controversial. The computerized national CrescNet database gathers detailed data of growth and development for the general population as well as specific patient groups.

Retrospective longitudinal analysis of standardized, yearly measurements of weight, height and growth-rate was performed for 157 PKU-patients (0-18 years, 69f/88m). Data were compared to the reference values of healthy German children.

Mean height in PKU boys and girls is significantly lower than in healthy German children, throughout childhood and puberty (final height at 18 years boys´ SDS –0,494; girls´ SDS –1,148, $p<0,001$). In contrast, BMI is significantly higher at birth compared to healthy German children (girls´ SDS +0.448, $p=0.003$; boys´ SDS+0.318, $p= 0.046$). BMI declined after the second year of life in PKU girls and boys. PKU patients show a significantly lower initial growth rate during the first two years of life (girls´ SDS –0.967, $p<0,001$; boys´ SDS –0.858, $p<0.001$). The mean growth rate increases during childhood but declines again in puberty.

PKU patients show significant growth differences compared to the reference values, being significantly shorter already at birth and throughout childhood and puberty. Fortunately, the initially slightly higher BMI normalized during the first two years of life and the patients do not appear to be at risk for obesity and obesity-related lifestyle diseases. Whether dietary treatment negatively influences growth rate and final height in PKU patients should be investigated.

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POSTER 107

The analgesic flupirtine may induce severe hepatocellular liver injury in women

Clinical Studies

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Background: Flupirtine, a central acting non-opioid analgesic used in many countries, was recently described to induce drug induced liver injury (DILI). We have studied clinical courses of flupirtine associated DILI and compared it to DILI caused by other drugs. *Methods:* All patients from one German center who were hospitalized between 2010 and 2013 for DILI were retrospectively analyzed. DILI was defined by elevation of ALT>3x the upper limit of normal (ULN) and history of drug intake within the past 6 months after exclusion of viral, autoimmune and metabolic liver diseases. Age, weight, sex, levels of ALT, bilirubin, prothrombin time rates and clinical outcome were compared between patients with DILI associated with either flupirtine or other drugs at days 0, 3, 7 and 14 after admission to hospital. *Results:* A total of 51 patients were identified. DILI was associated with flupirtine in 18 (38%) and with other drugs in 29 (62%) patients. 19/20 patients in the flupirtine group were female and had lower body weight compared to the control group. The mean time between onset of symptoms and admission to hospital was 10±7 [0-30] and 6±8 [0-30] days (p=n.s). Mean ALT levels were similar in both groups at days 0 and 14 of hospitalization but bilirubin levels were initially higher and increased further in the flupirtine group until day 14 (15.1±9.4[2.6-29] vs. 6.7±8.8[0.1-33], and 12.4±8[0.4-23] vs. 1.8±2.8[0.3-10.2] x ULN; p=0.06 and 0.007, respectively). Mean prothrombine time rates were lower in the flupirtine group between days 0 and 14. In the two groups 12 and 10 patients received treatment with prednisone and acetylcysteine (p=0.033). Two patients in the flupirtin group underwent liver transplantation. *Conclusion:* Flupirtine may lead to severe courses of hepatocellular liver injury and liver failure, especially in women. Monitoring ALT levels may be recommendable for patients receiving flupirtine.

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POSTER 108

Einfluss der Offline-Applikation von transkranieller Gleichstromstimulation (tDCS) auf die Konsolidierung motorischen Lernens bei älteren gesunden Probanden

Clinical Studies

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Hintergrund: Ziel dieser Studie war es zu untersuchen, ob tDCS über dem primären Motorkortex (M1) oder dem prämotorischen Kortex (PMC) unmittelbar nach einem motorischen Sequenzlern-Training („offline") zu einer verbesserten Konsolidierung der Lernleistung bei älteren gesunden Probanden führt.
Methoden: In einem randomisierten, doppelt-geblindeten Design wurden bei neurologisch gesunden Probanden (n = 48, mittl. Alter 65,9 a, 33 weiblich) die Effekte von anodaler oder kathodaler tDCS, über dem kontralateralen M1 oder anodaler tDCS über dem kontralateralen PMC sowie einer Scheinstimulation (SHAM) auf das Lernen einer explizit bekannten Fingerbewegungssequenz untersucht. Die Applikation der tDCS erfolgte dabei „offline" direkt nach dem Training der Sequenzaufgabe. Das Training bestand aus 14 Übungsblöcken. Jeweils 8 h, 22 h und 4 Wochen nach dem Training wurde die Geschwindigkeit der korrekt ausgeführten Sequenzen evaluiert.
Ergebnisse: Die offline-Applikation von anodaler tDCS über M1 führte zu einer verbesserten späteren Ausführung der Sequenzlernaufgabe im Vergleich zu kathodaler tDCS über M1, anodaler tDCS über PMC und SHAM. Es konnten signifikante Unterschiede hinsichtlich der normalisierten durchschnittlichen Dauer korrekter Sequenzen innerhalb und zwischen den Gruppen nachgewiesen werden. Die zusätzliche Verbesserung der geübten Sequenz durch anodale tDCS über M1 war bereits nach 8 h erkennbar.
Schlussfolgerungen: Die „Offline"-Applikation von anodaler tDCS über M1 nach dem motorischen Training begünstigt die Konsolidierung des Motorsequenzlernens bei älteren Probanden.

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POSTER 109

Determination of autoantibody performance for diagnosis of paediatric coeliac disease in patients up to two years

Clinical Studies

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The diagnosis of coeliac disease (CD) is based on the assessment of a highly variable clinical status, autoantibody measurement, the histological evaluation of an intestinal biopsy, and response to gluten-free diet. Some literature suggests that antibody tests might have a compromised sensitivity in children up to two years. Furthermore, assays for AB against native gliadin (anti-nGli) are often assumed to perform better than tests for AB to deamidated gliadin (anti-dGli), endomysium (EmA) and tissue transglutaminase (anti-tTG) in diagnosing CD in children up to two years. We compared the performance of the indicated assays in children below two years with that of older children.

Data were available for 969 children (277 with biopsy proven CD and 668 controls) up to 18 years. Of these, 178 (39 CD and 139 controls) were under 2 years. Immunoglobulin (Ig) A- and IgG-anti-nGli, IgA and IgG-anti-tTG, IgA-EmA, and IgG-anti-dGli were measured in serum.

Assays for IgG-anti-dGli, IgA-anti-tTG, and IgA-EmA showed simultaneous high specificity and sensitivity as well as high positive and negative predictive values covering a range of prevalence from 10 to 50% in both age groups. Concentrations of these ABs showed the same distribution in children under two years and above. But IgG-aDGL response in very young CD patients appears to be stronger. ABs against nGli showed a worse performance in both age groups.

Our results do not support the use of assays of anti-nGli to diagnose CD in children up to two years. Additionally, we see no indication in our data suggesting that the tests perform worse in children under two years.

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POSTER 110

Design of the Treatment Planning Unit (TPU) and an IT Infrastructure for Integrated Tumorboards

ICCAS – Computer Assisted Surgery

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Tumor Targeting

The treatment of head and neck malignomas is a long-term process that requires collaboration of interdisciplinary departments and the appropriate handling of diverse information such as pretherapeutic imaging, histologic findings, therapy decisions and a precise planning due to the complex anatomy. However, current IT systems and paper based records do not reflect the actual clinical data flow sufficiently. To improve the situation within tumorboards the new concept of the Treatment Planning Unit (TPU) has been introduced in this project. In the beginning of 2013 the former tumorboard meeting room at the University Hospital Leipzig has been rebuild according to the TPU design developed at ICCAS. The integrated tumorboard now includes additional large screen displays for the presentation of digital patient data from different diagnostic modalities. The developed oncoflow web system acts as invisible IT infrastructure within the TPU. oncoflow supports the entire tumorboard process from patient registration, decision making, and documentation in a consistent and structured electronic manner. Interfaces to diagnostic systems such as endoscopy, modeling tools and clinical IT systems have been realized and integrated into oncoflow. The result is a consistent and automatically generated tumorboard protocol that includes the therapy decision. Furthermore, the IT systems from nuclear medicine are integrated into the TPU allowing the representation of nuclear medicine diagnostics. Therefore the integrated TPU tumorboard supports the process of determining the optimal treatment for the individual patient.

Funding: BMBF

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POSTER 111

Evaluation of ultrasound perfusion for brain tumor resection surgery

ICCAS – Computer Assisted Surgery

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Tumor Targeting

Ultrasound perfusion is an imaging technique used for the detection of lesions, whose main application remains the liver. It consists in analyzing the absorption over time of an US contrast agent by the human tissue, most of the time visually performed. Quantitative analysis methods exist and are based on the computation of perfusion parameters, but are so far not standardized. We present a method to evaluate intraoperative ultrasound (iUS) perfusion imaging of brain tumors acquired during resection surgery. The iUS perfusion data are compared with the standard preoperative MR perfusion technique. The preoperative MR perfusion datasets include several volumes over time (3D+t). In the operating room the surgery is guided using a sononavigation system, in where MR and iUS data are visualized. The iUS perfusion data are acquired using a 2D US probe and consists of a temporal sequence of 2D images (2D+t). Both data sets have different dimensions and their own frame. It is necessary to register them to achieve a pixel-wise correspondence. The landmark-based registration provided by the navigation system enables to achieve a common frame while the brain shift is corrected using automatic registration techniques. Then the registered perfusion data are preprocessed to reduce the noise and perfusion parameters are computed. Their visualization is performed using the SimVis framework. It is possible to select regions of interest of the tumor, such as the margins or the center, and to perform a region-based comparison between the iUS and MR perfusion data. The entire pipeline is demonstrated on one representative patient dataset.

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POSTER 112

Patient-specific treatment model using MEBNs: Example of laryngeal carcinoma

ICCAS – Computer Assisted Surgery

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The increasing understanding of the complexity of oncological diseases and the dramatic growth of available patient information, in principle, allow an individual treatment of a patient. In the decision making process to find the most appropriate treatment for a specific patient, all available medical information, has to be mentally integrated by the physician to create an abstract presentation or "model" of the patient. Physicians participating in this process are usually experts coming from a variety of clinical domains (e.g. surgery, pathology, radiology) with their own specific points of view. This makes a unanimous decision difficult so that an optimal treatment for a particular patient cannot always be guaranteed. Multi-Entity Bayesian Networks (*MEBN*), a first-order language for specifying probabilistic knowledge, are used to develop a patient-specific model and simulate physicians' complex treatment decisions. The aim is to build a system that support physicians not only by proposing decisions, but also by providing explanations regarding influence factors of a decision. To develop such a MEBN, in a close cooperation between an ENT physician and a computer scientist, during the course of one year all the necessary specific disease data were collected and arranged according to their relevance and direct causalities. At this stage in the project, the model contains approx. 600 information entities with over 800 dependencies. In future work, we will extend the MEBN and develop a suitable visualization for the network that allows to quickly understand physicians and patients the decision making process.

Funding: BMBF

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POSTER 113

Sentiment Analysis in Medical Narratives

ICCAS – Computer Assisted Surgery

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Sentiment analysis has been widely applied to collect opinions from user generated content in social media. However, the sentiments expressed in medical narratives have not been well analyzed and exploited yet, e.g. "no malignant" indicates positive opinion, while "degenerative changes" shows negative judgment. With the further development ofthe principle of evidence-based medicine and digital patient modeling, the opinion in the medical narratives will play an increasingly essential role for the clinical decision support process. Normally, adjectives, adverbs and part of the nouns express sentiments. And those terms are categorized into the groups of positive, negative and neutral and made available as lexicons, which can be applied to identify the sentiment terms through dictionary-lookup. However, due to the objective nature and special distribution of terms in medical narratives, the conventional approaches based on adjectives and adverbs can no longer satisfy the requirement for the recognition of polarity in medical text. According to theexperience obtained from manual annotation, the frequent used terms in medical text are summarized into the corresponding fine-grained categories such as illnesses, symptoms and anatomical concepts. These categorized terms implicitly provide information that can be interpreted as sentiment and judgment in different aspects. Hence, new algorithms will be developed to identify the opinion from different implicit sentiment aspects. Corresponding visualization methods will be exploited to illustrate sentiment or changes in a patient's health status over time.

Funding: BMBF

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POSTER 114

Multi-perspective workflow modeling for dynamic systems behavior

ICCAS – Computer Assisted Surgery

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Tumor Targeting

Surgical workflow management is expected to enable situation-aware adaptation and intelligent systems behavior in an integrated operating room (OR). The overall aim is to unburden the surgeon and the OR staff from manual maintenance and information seeking tasks. A major step towards intelligent systems behavior is a stable classification of surgical situations based on multi-perspective workflow modeling. The starting points of our work were actual surgical procedures recorded as individual surgical process models. The recordings were compiled into generalized surgical process models. These models represented averaged courses of specific intervention types. Additional high-level information was captured by a top-down modeling approach. The high-level models were based on Markov Theory including application-specific adaptations. A model network interconnecting different types of surgical process models was implemented. Overall, various aspects of a surgical situation description were considered: low-level tasks, high-level tasks, patient status and usage of medical devices. These aspects were compiled into an online situation model as a formal representation of the surgical situation.
Autonomous adaptation of medical systems and intelligent systems behavior do not only depend on current low-level task. They require a more general kind of understanding of the situation. Multi-perspective surgical workflow modeling will be a significant prerequisite for reliable and intelligent systems behavior. Hence, it will contribute to a cooperative OR environment that increases patient safety and reduces costs.

Funding: BMBF

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POSTER 115 **Magic lens for minimal invasive cardiac surgery**

ICCAS – Computer Assisted Surgery

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Tumor Targeting

In minimal invasive cardiac surgery incision points need to be identified safely. This can be challenging task. In the present project we implemented a surgical assistance system that simplifies these tasks. The developed augmented reality prototype adapted the magic lens concept for minimal invasive cardiac surgery. A magic lens is a mobile device that displays additional information according to its position and to the position of the user. It is used to visualize anatomic structures under the skin.
Routinely acquired pre-operative images were used to generate segmentations of anatomical structures. Intra-operatively the system combined two sensors: an optical tracking and a time of flight camera. Hence, the system was able to track the surgeon and the magic lens simultaneously. Furthermore, the system was registered to the patient via surface registration techniques. Based on this setup, 3D surface segmentations of relevant anatomical structures could be displayed according to the angle of view of the surgeon. The 3D visualization was updated simultaneously with any movements and displays segmented anatomical structures under the patient's skin. The lens was able to adapt the presentation of anatomical structures with various presets and provided context and focus dependent anatomical information. The prototype demonstrated a way of interactive integration of preoperative patient data into the surgical area. An additional overlay of real time video needs to be implemented to simplify the correlation between augmented information and situs. In future work the system will also be extended to other use cases.

Funding: BMBF

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POSTER 116 **A concept for an interactive scrub nurse training system**

ICCAS – Computer Assisted Surgery

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Tumor Targeting

All persons that have to master the handling of surgical instruments in their daily working routine are faced with specific challenges. First and foremost they need to have the ability to identify and tell apart a wide range of different and in parts very similar instruments.
There is currently no system available that focuses exclusively on the skills and needs of scrub nurses on an entirely technical simulation base.
The project presents the concept of a surgical instrument training system, which can be used by a student without the demand for a human supervisor. The system works without the use of real surgical instruments. The central component is the simulation of an instrument table on a Microsoft Surface 2 System with multitouch functionality. It generates a certain realism for the student, since all virtual instruments and objects on the table can be moved and rotated by the test person and more than one instrument can be stacked on one another as well.
The second main component is the surgeon screen, which shows a video of the to train surgical intervention. The training videos are recorded at real interventions from the assisting person's point of view and are afterwards enhanced with additional information stored in an accompanying XML metafile. An instrument is passed by the test person to the virtual surgeon by selecting it on the instrument table simulation and clicking on the "Pass instrument" button of the Surgeon Screen System, which features touch functionality.
Current work on the project focuses on the delivery of a first working prototype.

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POSTER 117

Mesh-based DRR Rendering Accelerates 2D/3D Registration for the Fusion of Ultrasound and X-ray Images

ICCAS – Computer Assisted Surgery

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Tumor Targeting

An increasing number of procedures in the field of structural heart disease become minimally invasive and catheter-based. Examples are trans-catheter aortic valve implantation or trans-catheter mitral valve repair. This trend from open-heart surgery to trans-catheter based minimally invasive procedures is pushed by the availability of new catheter devices and the intra-procedural imaging. Usually these procedures are performed under fluoroscopic X-ray, mainly for catheter navigation, and trans-esophageal echo (TEE) for soft tissue visualization. Intra-operatively these modalities are mainly used independent of each other. An image fusion of both systems could yield a better mutual understanding of the image contents and finally even allow new kinds of procedures. An approach for the fusion of ultrasound with fluoroscopic X-ray is 2D/3D registration. The 3D position of the TEE probe is detected from the X-ray image, which inherently provides a registration of the ultrasound image to the X-ray image. Our main contribution is the significant acceleration of the 2D/3D registration in this context. We generate the necessary projection images of the 3D object (DRR) not via a conventional volume ray-casting algorithm but via fast rendering of triangular meshes. We show that our approach can achieve a speed up factor of 65 and does not affect the registration. These results are one step towards real-time fusion of TEE and X-ray fusion. The approach could potentially accelerate other applications of 2D-3D registrations.

Funding: Siemens AG, Healthcare Sectore AX, Forchheim

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POSTER 118 **Digital Patient Model – Information Model**

ICCAS – Computer Assisted Surgery

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Patient data is distributed in heterogeneous information systems, sometimes locked away without any possibility of easily exporting it. For this reason, physicians need to interact with several systems to get a complete view on the health status of a patient, which is time consuming. Researchers want to access and reuse patient data, e.g. for calculations or studies. For decision making and diagnosis, as well as for research, it is crucial to have all relevant patient data available and accessible.

The objective of this project is to develop a suitable information model for the domain of surgery that allows the description of patient data relevant for diagnosis and treatment in a standardised manner.

We will base our work upon the openEHR standard. OpenEHR fulfils the EN 13606 requirements. EN 13606 is an international standard for the exchange of clinical data. OpenEHR goes beyond EN 13606 by offering developed building blocks (archetypes) in a global repository. An active domain modelling community is cooperating worldwide to build highly qualitative archetypes that we will reuse and adopt for our purposes. The main concept of this standard is a two-model approach, which separates knowledge from information. In this way, it is possible to define flexible, customised archetypes which are built on top of a static reference model. This enables the storage of patient data in reusable building blocks, upon which multiple applications can be built.

The use of the openEHR standard will enable international cooperation in the generation of new archetypes for the domain of surgery.

Funding: BMBF

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POSTER 119

Towards a IHE integration profile for Patient Identification Distribution (PID) in the new IHE domain "Surgery"

ICCAS – Computer Assisted Surgery

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Introduction: One aim of computer assisted surgery is the reduction of effort and redundancy as well as avoidance of errors in transmission of patient demographic data. In order to achieve this goal all devices creating patient specific data during the intervention, previously have to receive the patient demographics like a unique patient-ID, birthdate, sex, etc.
Optimally all devices that are used on a specific patient within a specific OR during an intervention will automatically be initialized with the correct unique patient-ID to store and communicate the data and diagnosis together with this information to the PACS.
As of now it is necessary to enter the patient data manually or choose it from a list of possible patients on every device that will be used on this patient.
Methods: Existing standards such as DICOM or HL/7 solve the problem of patient identity distribution for specific limited use cases as Modality Worklist was originally designed to fit in a radiological environment. The DICOM Modality Worklist standard has proven itself. However for the surgical OR exist more difficulties due to modalities that are called in on demand.
To find a unified solution, all existing approaches (HL7, DICOM, …) will be examined and requirements from the industry will be collected during workshops. The results will then be transferred in an Integrating the Healthcare Enterprise (IHE) Integration Profile.
Results: First meetings with the industry lead to a Whitepaper already covering some possible solutions. In a further meeting the specification will be completed which forms the basis of the integration profile.

Funding: EFRE

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POSTER 120

Surgical Planning and Resource Center (SPARC)

ICCAS – Computer Assisted Surgery

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High costs and risks in hospitals incurred due to the inefficient management of resources in operating theatres. Therefore, the reduction of costs and risks in operating theatres is crucial. In order to preserve patient safety and improve the workplace of the surgeons, technicians have to monitor the technical equipment in several operating rooms at the same time. In addition, operating room managers want to achieve an economical capacity of operating rooms. Hence, an overview of all operating rooms in a hospital with the help of a partially automated resource management is the key to improve the clinical workflow.
A control center so called Surgical Planning and Resource Center (SPARC) was implemented at the ICCAS. From a reproduced FESS surgery in our demo-OR medical device data (navigation system, endoscope and a hospital information system) and video data are transferred by a safe network into our Surgical Planning and Resource Center (SPARC). The SPARC user interface creates three different views in to the operating room in real time: a process view, a monitoring view and a medical device view. Various user groups can use the presenting information. Hence, a technician or a maintenance engineer notices errors of devices earlier. In addition, operating room managers can plan the next intervention more effectively.
In future work, we will set up a network at the University Hospital Leipzig to get all data from various operating rooms in our institute in real-time. Thus, we can evaluate our SPARC user interface for the different user groups.

Funding: BMBF

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POSTER 121

EVENTOR – Event-based Networking in the operating room

ICCAS – Computer Assisted Surgery

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Tumor Targeting

The surgeon's workload has increased with the introduction of new technologies into the operating room (OR). These tasks can be very time-consuming. Concepts and proprietary solutions for integrated OR emerged in recent years. However, a standard for intraoperative device communication is not available yet. Flexibility in the OR-setup and the introduction of new technologies is inhibited.
EVENTOR is a project in cooperation with SWAN – Scientific Workflow Analysis GmbH. The project aims to enable the workflow-driven interconnection of medical devices which do not share a common interface. A centralized unit, called CommBox, should be developed which implements various communication protocols. The CommBox integrates process logic and communication frameworks. The process logic based on surgical process models controls the interconnection of medical devices. Thus, the CommBox is able to automatically set up communication pathways between components of the overall OR system according to the surgical situation. Each medical device can be attached to the process logic using connector modules. Any connector module provides two main functionalities: protocol transformation and situation adaptation.
We develop prototypes for selected clinical use cases, e.g. brain tumor removals, to demonstrate the feasibility of the approach. Brain tumor removals tend to be lengthy and complicated including many technical systems. Hence, there is a demand for workflow-driven configuration and communication.
In future work, the prototype should be evaluated under laboratory conditions and in clinical practice.

Funding: ZIM

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POSTER 122

Development and evaluation of a clinical information system supporting oncological tumor therapy

ICCAS – Computer Assisted Surgery

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Tumor Targeting

Due to the increasing complexity of oncological disease patterns, manifold treatment options and a variety of supporting IT-systems the treatment of cancer patients is challenging for physicians and surgeons. Information that is important for the patient treatment, clinical studies, cancer center certification processes or internal quality management has to be gathered and integrated manually by the clinical personnel, thus leading to inefficient processes. The *oncoflow* system aims at the improvement of the entire oncological workflow in ENT surgery. A central database contains relevant patient-specific information that is automatically imported via communication interfaces to important clinical information systems. The rich-internet application *oncoflow* has been designed for an efficient workflow support throughout the entire patient treatment process. An intuitive user interface provides access to patient data and structured documentation forms. During a clinical study our improved anamnesis documentation tool has been evaluated at the clinical site with positive results from the attending physicians. Additionally, a comprehensive tumorboard support module provides automatic creation and mailing of invitation and protocol letters as well as board decision documentation support. The system is still in daily clinical use for both aforementioned functionalities. Further research focuses on the improvement of information quality and clinical workflow recognition. Therefore, a Hidden Markov Model (HMM) will be used for modeling the treatment process.

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POSTER 123 **Sensor Based Surgical Activity Recognition**

ICCAS – Computer Assisted Surgery

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Automatic surgical activity recognition in the operating room (OR) is mandatory to enable assistive surgical systems and to manage the increasing number of medical devices and the information presented to the surgical team. Therefore the purpose of our study was to develop and evaluate an activity recognition system. It was conceived as a hierarchical recognition model, which separated the recognition task into activity aspects. The concept used Radio Frequency Identification (RFID) for instrument recognition and accelerometers to infer the performed surgical action. Activity recognition was done by combining intermediate results of the aspect recognition step. A basic scheme of signal feature generation, clustering and sequence learning was replicated in all recognition subsystems. Hidden Markov models (HMM) were used to generate probability distributions over aspects and activities. Simulated Functional Endoscopic Sinus Surgeries (FESS) were used to evaluate the concept. The system was able to detect surgical activities with an accuracy of 95%. Instrument recognition performed best with 99% accuracy. Action recognition showed lower accuracies with 81% due to the high variability of surgical motions. All stages of the recognition scheme were evaluated. The model allows distinguishing several surgical activities in an unconstrained surgical environment. Future improvements could push activity recognition even further by using more discriminant motion recognition algorithms and advanced motion sensor devices like e.g. myoelectric wristbands.

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POSTER 124

An approach to the recognition of the use of medical devices in the operating room based on video data

ICCAS – Computer Assisted Surgery

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Tumor Targeting

Due to the increasing complexity in modern operating rooms solutions must be found to relieve the surgeon. In order to develop systems which operate based on the current situation in the OR, device data must be collected and processed. Because of the restrictive interface policies of the vendors of medical devices, there are few devices that provide their data and operating conditions using open interfaces. To get device data without manipulation of the medical device and without interfering with the workflow in the operating room, an approach for detection of information from video data has been developed. In a first step, the regions of interest within the video data are defined and annotated with metadata. In a further step, the data is transmitted to an analysis software. The software analyzes the video based on the type of the region represented by the annotation. The extracted information is finally stored in a structured manner in the Surgical Recorder developed at iccas. This information is available for further use at a central location. Currently a study is being conducted in the neurosurgery department of the University Hospital of Leipzig to evaluate whether the use of different devices can be reliably detected. The project enables subsequent systems to use information from devices that provides data only through a video output.

Funding: BMBF

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POSTER 125

Vergleichende Untersuchung navigierter versus nicht navigierter Implantationstechniken bei inverser Endoprothtetik am Schultergelenk. Eine in vitro Studie am Schafskadaver.

ICCAS – Computer Assisted Surgery

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Ziel: Die Langzeitergebnisse der inversen Schulterendoprothetik sind abhängig von einer exakten Implantationstechnik. Ziel dieser Studie war es, die navigierte Implantation mit der klassischen Freihandmethode zu vergleichen.

Methoden: Von 34 frischen Schafsschultern mit anhängenden Weichteilen wurden 17 navigiert (Gruppe A) sowie 17 in Freihandmethode (Gruppe B) operiert. Die Navigation wurde mittels Ziehm Vision FD Vario 3D (Fa. Ziehm) sowie der Brainsuite (Fa. Brainlab) durchgeführt. Die postoperativen CT-Bilder wurden als Dicom Datensätze in die 3D Bidbearbeitungssoftware Mimics geladen und ausgewertet.

Ergebnisse: In mehreren Ebenen zeigten sich signifikante Unterschiede in der Position des zentralen Pegs: In Gruppe A war die zentrale Bohrrichtung signifikant mehr nach kranial ($p=0{,}018$, Mittelwert des Winkels B2/3 zu P9/8=29,2°) und dorsal ($p=0{,}021$, Mittelwert des Winkels B2/3 zu P9/10=17,2°) ausgerichtet. Zudem zeigte sich bei Gruppe A eine signifikant größere Streubreite ($p=0{,}031$) im Verhältnis des Bohrkanalverlaufs zur Glenoidebene als bei Gruppe B. Keine signifikanter Unterschied ergab sich in der Festlegung des Glenoidmittelpunktes.

Diskussion: Es zeigten sich signifikante Unterschiede zwischen Gruppe A und Gruppe B sowie eine signifikant bessere Platzierung des zentralen Pegs in der AP-Ebene bei Gruppe A. Ob die Ergebnisse der Schafsschultern mit denen an Humankadavern gleichzusetzen sind wird derzeit in einer Folgestudie untersucht.

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POSTER 126

Towards cross-enterprise distribution of clinical information models

ICCAS – Computer Assisted Surgery

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Most of the data in the clinic are associated with a specific patient, but there are also data that is not patient-specific. For the purpose of successful clinical work it is crucial for authorized persons to access those data quick and reliable, therefor, the data should be efficiently structured. Regarding patient-specific data there is a standardized way through IHE cross-enterprise document share (XDS).However, more data incur in clinical everyday life that is not necessarily linked to actual patients, e.g. models for workflow analysis, teaching material or research data. At the moment such non-patient-specific data cannot be shared across companies in a standardized way. To achieve a unified holistic solution ICCAS aims at the development of a generalized Integration Profile called IHE cross-enterprise model share (XMS) to cover patient-specific data as well as abstract models. To facilitate the transition to XMS it will be possible to communicate patient-specific data without additional effort to XDS-compliant systems. Therefore, it is essential to find a fundamental model for clinical data that covers XDS-compliant patient-specific data as well as currently used models and teaching data but also future models. While most of the data in the hospital is patient-specific, there are also model-based data, that are not covered by standards at the moment. Because IHE XDS-b is of increasing importance for hospitals worldwide, it should be considered to create an IHE Integration Profile to cover patient-specific data as well as general models.

Funding: EFRE

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POSTER 127 **Surgical Activity Recognition based on Thermography**

ICCAS – Computer Assisted Surgery

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A surgical intervention is usually structured in interventional phases. The phases denote a section within an operation and end with a certain goal. A phase consists of multiple sequences of surgical activities which are identified using sensor data. The identification of the surgical activities is an im-portant step to model the workflow of the surgery. The applications are surgical workflow manage-ment systems providing robust guidance for surgical activities. These workflow management systems may trigger devices and automatic the documentation of the surgical procedures or the estimation of operation end times.The main limitation of current vision-based recognition methods is the inefficiency in online recognition because of the large amount of information and the complex image processing algorithms. We used an infrared thermal camera combined with a hierarchical temporal memory to classify activities of surgical workflows. Our system can be used to recognize surgical activities in real-time. Using a standard Windows-based desktop PC was able to process the images and classify the surgical activity in about 0.3 s. Therefore this system can be used to recognize surgical activities online and provide input data to surgical assistance systems and workflow management systems.The system was validated on a simulated Functional Endoscopic Sinus Surgeries (FESS) from ENT-surgery. The thermal camera was directed at the hands of the surgeon handling different instruments. The system achieved online recognition accuracies of 96%, and precision and recall rates of approx. 60%.

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POSTER 128

Automatische Generierung von OP-Protokollen – von Rohdaten zum Fließtext

ICCAS – Computer Assisted Surgery

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Durch die Entwicklung innovativer Sensorik[1] wird die Möglichkeit bestehen, Operationsverläufe in Form von Workflows elektronisch zu erfassen. Diese Informationen bilden die Grundlage für eine Vielzahl technischer und klinischer Anwendungen, wie z. B. Workflowmanagement im OP[2], die Evaluation medizintechnischer Systeme[3] oder die Unterstützung der chirurgischen Ausbildung[4].
Die vorliegende Arbeit hat das Ziel, eine Methode zur Generierung natürlichsprachiger Texte aus den gesammelten Arbeitsschrittinformationen zu entwickeln. Diese werden als sensorische Teilinformationen verarbeitet und im Anschluss zu Texten kombiniert, um OP-Verläufe in natürlicher Sprache umfassend darzustellen zu können. Diese Dokumentation ist Aufgabe der Chirurgen bei der OP-Nachbereitung. Diese Methode wird den Operateuren diese Aufgabe zukünftig erleichtern und als Grundlage für eine Qualitätssicherung ihrer Arbeit im Sinne der gesetzlichen Dokumentationspflicht für Ärzte[5] dienen.

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POSTER 129

Psychometrische Eigenschaften der deutschen Übersetzung der Weight Bias Internalization Scale (WBIS)

IFB – Adiposity Diseases

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Die Weight Bias Internalization Scale (WBIS; Durso & Latner, 2008) erfasst als Selbstbeurteilungsfragebogen die gewichtsbezogene Selbststigmatisierung. Diese beschreibt das Ausmaß, zu dem sich Personen negative Stereotype und negative Aussagen über übergewichtige und adipöse Personen selbst zuschreiben. Bisherige Untersuchungen berichteten Zusammenhänge der Selbststigmatisierung aufgrund des Gewichts mit einer erhöhten Psychopathologie sowie verringertem Selbstwert und Lebensqualität.
Die teststatistische Untersuchung der autorisierten, durch eine Rückübersetzungsprozedur kontrollierten deutschsprachigen Übersetzung der WBIS erfolgte an einer repräsentativen Stichprobe übergewichtiger und adipöser Personen aus der Allgemeinbevölkerung ($N = 1092$).
Die WBIS zeigte eine gute interne Konsistenz, und ihre einfaktorielle Struktur konnte belegt werden. Hinweise für die konvergente Validität ergaben sich durch bedeutsame Zusammenhänge mit Messinstrumenten zur Erfassung von Depression sowie somatischen Symptomen. Frauen berichteten eine höhere gewichtsbezogene Selbststigmatisierung als Männer, und die WBIS-Werte waren für adipöse Personen höher ausgeprägt als für übergewichtige Personen. Geschlechtsspezifische Normwerte wurden erstellt.
Den Untersuchungsergebnissen zufolge liegt mit der deutschen Übersetzung der WBIS ein reliables und valides Instrument zur Erfassung der internalisierten gewichtsbezogenen Stigmatisierung bei übergewichtigen und adipösen Personen vor. Der Internalisierung sollte aufgrund ihrer negativen Zusammenhänge mit dem psychischen Befinden der Betroffenen eine besondere Bedeutung zukommen.

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POSTER 130

Polymorphismen des SLC6A4-Gens in Assoziation zur in vivo Expression des Serotonin Transporters im menschlichen Gehirn bei Adipösen

IFB – Adiposity Diseases

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Ziel der Studie war es zu untersuchen, ob verschiedene Varianten des Serotonin-Transporter (SERT) kodierenden SLC6A4-Gens (5-HTTLPR;VNTRin2) mit der *in vivo*-SERT-Verfügbarkeit bei Adipositas assoziiert sind und ob diese als Kofaktoren in der SERT-PET-Datenanalyse berücksichtig werden müssen. Probanden der laufenden IFB-PET Studie mit einem BMI>35kg/m² (Alter: 40±12 Jahre; 7♀) und 15 normalgewichtige, gesunde Kontrollen (BMI<30kg/m²; Alter: 36±6 Jahre; 10♀) wurden mit PET und dem SERT-selektiven Radiotracer [^{11}C]DASB (482±6MBq) untersucht. Es erfolgte eine VOI-Analyse der PET-Daten nach Koregistrierung mit individuellen MRT zur Berechnung des Bindungspotentials (BP) ausgewertet. Genotypisierungen wurden durch Primer-Amplifikation mittels PCR durchgeführt. Adipöse Probanden und normalgewichtige Kontrollen mit LL-Genotyp des 5-HTTLPR zeigten Unterschiede im SERT-BP im Hippocampus (0,62±0,05 vs. 0,46±0,04; p=0,05); im Thalamus (1,61±0,17 vs. 1,23±0,08; p=0,05) und im Hypothalamus (2,02±0,10 vs.1,54±0,17 vs.; p=0.05). Probanden mit SL- bzw. SS-Genotyp wiesen dagegen keine signifikanten Gruppenunterschiede im SERT-BP auf. Erste Analysen zeigten zudem bei Adipösen eine signifikante Abnahme des SERT-BP in 2 Sequenzvarianten des VNTRin2 im anterioren zingulären Kortex (0,56±0,19 vs. 1,15±0,18; p=0,05; 0,38±0,01 vs. 1,03±0,13 p=0,0009). Erste Ergebnisse deuten auf einen Unterschied in der Verfügbarkeit zentraler SERT in Abhängigkeit vom SLC6A4-Genotyp hin, so dass diese Varianten als Kovariate in der Datenanalyse berücksichtigt werden sollten. Weitere Analysen mit größeren Probandenkohorten sind in Arbeit.

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POSTER 131

Adipokine patterns as predictors of morphometric parameters and impaired glucose metabolism

IFB – Adiposity Diseases

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Background and aims: In obesity, elevated fat mass and ectopic fat accumulation are associated with changes in adipokine secretion, which may link obesity to inflammation and development of insulin resistance. Therefore, alterations in circulating adipokine patterns could be used as markers for early adipose tissue dysfunction leading to subclinical inflammation and obesity related metabolic diseases.
Research design and methods: In this study we investigated 19 adipokines to detect adipokine patterns with the strongest influence on clinical parameters. Serum concentrations were detected by ELISA in a cross-sectional study of 78 men and 89 women with a wide range of metabolic markers of obesity and insulin sensitivity. To determine the predictive value we used multiple regression models.
Results: In these models 7% to 28% of the variance of clinical parameters can be explained by different adipokine patterns. Clusterin and resistin have an impact in the prediction of morphometric parameters. Parameters of glucose metabolism (HbA1c, FPG) were predicted by visfatin, progranulin, ANGPTL6, and omentin. FPI and insulin resistance (HOMA-Index) are predicted by adiponectin, chemerin, and vaspin. Adiponectin and vaspin are also predictors of TG, but RBP4 has the most impact on TG levels. The proinflammatory CRP can be prognosticated by chemerin, visfatin, GPX3 and omentin.
Conclusion: In this study we could show that adipokine patterns reflect the obese state and could be useful in estimating impaired glucose metabolism. However, less then 10% of the variance of insulin resistance can be explained by these patterns.

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POSTER 132

Experimentelle Untersuchungen zur Genauigkeit einer automatisierten, MR-basierten Fettvolumetrie

IFB – Adiposity Diseases

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Tumor Targeting

Eine automatisierte Segmentierung des viszeralen Fettgewebes (VAT) mit Hilfe der MRT beruht meist auf einer Schwellwertanalyse der T1-gewichteten Signale (Histogramm).
Ziel dieser Studie war die Bestimmung eines optimalen Schwellwerts für das definierte Volumen eines komplexen Fettphantoms. Als Phantom diente ein mit 1.500 ml Rapsöl befüllter 3-L Glaszylinder, in dem wasser- und milch-gefüllte Gummischläuche unterschiedlicher Form platziert wurden. Vom Phantom wurden 6 unterschiedliche Aufnahmen gemacht. Die Analyse erfolgte mittels eines selbst entwickelten Matlab-Tools zur semiautomatischen Fettsegmentierung. Das Histogramm zeigt über den Bereich meist einen Nicht-Fett-Peak (NFP), einen Fett-Peak (FP) mit einem Minimum (MN) dazwischen. Die Bereiche zwischen NFP und FP wurden in 8 äquidistante Intervalle geteilt. Das Fettvolumen wurde mit Schwellwerten an den Positionen NFP, MN, und FP sowie in äquidistant verteilten Zwischenpositionen ermittelt. Zum Vergleich führten drei erfahrene Auswerter eine manuelle Schwellwertsetzung durch. Die manuelle Analyse ergab Abweichungen vom tatsächlichen Fettvolumen zwischen –5,2% und –15,0%. Automatische Schwellwerte bei MN ergaben Abweichungen von –7,3%; die geringste Abweichung (-0,9%) wurde auf 3/8 der Strecke zwischen NFP und FP erreicht.
Die Auswahl des Schwellwerts für die automatische Segmentierung des VAT hat einen beachtlichen Einfluss auf das resultierende Volumen. Selbst erfahrene Auswerter erzeugten Fehler bis zu 15%. Die beste Übereinstimmung lieferten automatische Schwellwertstellungen im Histogrammbereich zwischen der Position des Nicht-Fett-Peaks und der des Minimums.

Funding: ifb

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POSTER 133

Kindesmisshandlungen, Essstörungspsychopathologie und Adipositas bei Frauen mit Binge Eating Störung

IFB – Adiposity Diseases

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Einleitung: Lebensgeschichtlich frühe aversive Ereignisse wie Kindesmisshandlungen können diverse körperliche und psychische Erkrankungen wie Binge Eating Störung (BES) und Adipositas im Erwachsenenalter zur Folge haben. Der Zusammenhang zwischen Kindesmisshandlungen, Essstörungspsychopathologie und Adipositas bei Patientinnen mit BES wurde bisher noch nicht ausreichend untersucht.
Methode: 139 Teilnehmerinnen mit BES (EDE Interview) wurden im Rahmen einer internetbasierten, kognitiv-verhaltenstherapeutischen Intervention für Frauen mit BES zu Kindesmisshandlung (CTQ) und Merkmalen der Esspathologie (EDE-Q) befragt.
Ergebnisse: Adipöse Frauen mit BES unterscheiden sich hinsichtlich der Essstörungspsychopathologie nicht von denen BES-Patientinnen ohne Adipositas, zeigen aber wesentlich höhere Prävalenzen von Misshandlungen in der Kindheit, wobei besonders sexueller, emotionaler und körperlicher Missbrauch berichtet wurde. Frauen mit BES und Adipositas haben ein 11mal so hohes Risiko emotionalen Missbrauch und fast 7mal so hohes Risiko emotionale Vernachlässigung im Kindesalter zu erleben wie eine alters- und geschlechtsgematchte Repräsentativstichprobe.
Schlussfolgerung: Möglicherweise stellt die Kindesmisshandlung einen unspezifischen Risikofaktor für die Entwicklung der BES und folgender Adipositas innerhalb eines multifaktoriellen Ätiogenese-Modells dar.

Funding: ifb

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POSTER 134

Local Proliferation of Macrophages in Adipose Tissue during Obesity-induced Inflammation

IFB – Adiposity Diseases

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Obesity is associated with a low grad inflammation of the adipose tissue (AT), which leads to an increase of adipose tissue macrophages (ATM). An increasing number of ATM is highly related to a risk of type 2 diabetes. The increase of ATM in obesity has been attributed to an enhanced recruitment from blood monocytes. In obese individuals, most ATM were found around dying adipocytes and, thereby, form characteristic crown-like structures (CLS).
We tested the hypothesis whether macrophages also proliferate locally within AT in obese individuals. We studied the expression of proliferation markers by immunofluorescence, PCR and flow cytometry in three different models of mouse obesity as well as in humans (n=239). Cell fate of dividing ATM was assessed by live-imaging of AT explants.
We can show that ATM of obese mice proliferate within the AT, predominately in CLS. Upon feeding mice with a high fat diet, we found a time-dependent increase of ATM proliferation. Up-regulation of CD206 and CD301 in proliferating ATM indicated preferential M2-polarization. Live-imaging of AT explants from mice revealed that ATM emigrate out of the CLS to become resident in the interstitium. In humans, we confirmed the increased expression of proliferation markers in CD68-positive macrophages in CLS and demonstrate a higher mRNA expression of the proliferation marker Ki67 in AT from obese patients.
We conclude that local proliferation contributes to the increase of ATM in AT. Further, our data confirms CLS as the primary site of proliferation and a new, underappreciated source of ATM.

Funding: ifb

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POSTER 135

Feasibility of a media-supported high-intensity interval training for overweight and obese adolescents

IFB – Adiposity Diseases

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Tumor Targeting

Background: Adolescents often do not meet guidelines for physical activity and practice a sedentary lifestyle. This significantly increases the risk for overweight, obesity and the metabolic syndrome. High-intensity interval training (HIIT) has been shown to result in superior improvement in cardio-metabolic risk factors compared to continuous moderate exercise, but results on adolescents are scarce. Compliance rates and motivation need to be examined to increase participation.

Methods and design: The present *feasibility* study offers a high intensity interval-training program for 70 overweight adolescents (14–18 years, BMI > 90th percentile). Duration is six months (2 hours training/ week) with reception of text messages/ website use to motivate for program adherence, while the control group receives training without any media. The primary research question focuses on whether motivation to participate can be increased by media. Besides anthropometric measurements, adolescents will be asked to provide information on lifestyle factors.

Conclusion and discussion: Data obtained from the feasibility study shall form the basis for a multicenter randomized controlled trial to analyze the efficacy of HIIT on anthropometric parameters, cardiovascular health and inflammation of overweight adolescents. The study adds necessary information on the applicability of time-efficient methods of physical activity in adolescents for evidence-based guidelines on obesity prevention.

Funding: ifb

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POSTER 136

Einflussfaktoren körperlicher Aktivität bei präbariatrischen Patienten

IFB – Adiposity Diseases

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Tumor Targeting

Hintergrund: Körperliche Aktivität (physical activity, PA) ist für den postoperativen Langzeiterfolg bariatrischer Patienten essentiell. Aufgrund ihres unzureichenden Bewegungsverhaltens bedarf es jedoch Interventionen, die an relevanten psychosozialen Einflussfaktoren ansetzen. Bisherige Untersuchungen belegten einen positiven Zusammenhang zwischen Selbstwirksamkeit und PA. Ferner dokumentierten neuere Studien einen Einfluss der Selbststigmatisierung auf zentrale gesundheitsbezogene Aspekte. Aufgrund dieser Vorbefunde soll in der vorliegenden Arbeit der Einfluss von allgemeiner Selbstwirksamkeit und Selbststigmatisierung auf die PA untersucht werden. Methode: Mittels Selbstbeurteilungsfragebögen wurden bei N = 179 präbariatrischen Patienten des Psychosozialen Registers der Adipositaschirurgie (PRAC) die allgemeine Selbstwirksamkeit, die Selbststigmatisierung sowie diverse Aspekte der PA erfasst. Mediationsbeziehungen wurden mithilfe von Strukturgleichungsmodellen getestet. Ergebnisse: Der Zusammenhang zwischen allgemeiner Selbstwirksamkeit und anstrengender bzw. moderater Aktivität wird nach Kontrolle soziodemografischer Parameter vollständig durch die Selbststigmatisierung vermittelt. Dabei prädizierte eine geringere allgemeine Selbstwirksamkeit eine größere Selbststigmatisierung, welche wiederum eine geringere PA vorhersagte. Schlussfolgerung: Präbariatrische Patienten mit geringer Selbstwirksamkeit bewegen sich weniger, vor allem bei größerer Selbststigmatisierung. Die Resultate verdeutlichen, dass Interventionen zur Reduktion der Selbststigmatisierung für die langfristige Gewichtsreduktion von Bedeutung sind.

Funding: ifb

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POSTER 137

Adipose tissue mRNA expression of WHR-associated genes correlates with fat distribution

IFB – Adiposity Diseases

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Tumor Targeting

Background: Body fat distribution (FD) is one of the main predictors of obesity associated complications. There is good evidence that fat distribution is controlled by genetic factors. Recent meta-analysis identified novel loci associated with waist to hip ratio (WHR). Here, we hypothesize that these genes exhibit fat depot-specific mRNA expression, which correlates with obesity-related traits.
Material and Methods: We measured mRNA levels of *LYPLAL1, ADAMTS9, VEGFA, CPEB4, RSPO3, ITPR2, SSPN, LY86* in paired human samples of visceral and subcutaneous adipose tissue from 570 individuals with detailed metabolic testing. Previously reported single nucleotide polymorphisms (SNPs) associated with WHR were genotyped in all subjects for subsequent association studies. $P<0.05$ was considered to be statistically significant.
Results: All tested genes exhibited significantly higher mRNA levels in visceral vs. subcutaneous adipose tissue. In addition, the mRNA levels correlated with WHR (*ADAMTS9, VEGFA, SSPN, LY86*), % body fat (*ADAMTS9, VEGFA, CPEB4, LYPLAL1*) and BMI (*ADAMTS9, CPEB4*). However, none of the SNPs showed associations with WHR or BMI only rs6905288 (*VEGFA*) was associated with fasting plasma glucose.
Conclusion: Our data suggest involvement of WHR-associated genes in the regulation of FD. The study encourages further *in vitro* experiments to pinpoint the role of these genes in the function of adipocytes.

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POSTER 138 **Nicotinamidenucleotidetranshydrogenase (NNT) ist assoziiert mit Adipositas in Mäusen**

IFB – Adiposity Diseases

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Tumor Targeting

Hintergrund: Der C57BL/6JRj und C57BL/6NTac Stamm unterscheiden sich hinsichtlich einer Ausprägung einer Adipositas unter Gabe einer Hochfett- und auch einer hochkalorischen Diät, trotz einer genetischen Homologie von 98%. Der C57BL/6JRj Stamm besitzt eine Mutation im Nicotinamidenucleotidetranshydrogenase (NNT) Gen.
Ziel der Studie war es, die Rolle von NNT in der Ausprägung einer Diät-induzierten Adipositas zu untersuchen.
Methoden: Mittels einer F1 (N=20, 10M/10F) und Rückkreuzungspopulation [(C57BL/6JRj xC57BL/6NTac)F1 x C57BL/6NTac] wurde die genetische Rolle der Mutation im NNT Gen überprüft. Alle Rückkreuzungstiere wurden genetisch, hinsichtlich des Vorliegens der NNT Mutation, durch PCR Reaktion untersucht. Die Rückkreuzungstiere (N=190, M97/F93) wurden ab der 4. Lebenswoche bis zur 12. Lebenswoche auf Hochkalorische Diät (58% Fett, Sniff, Soest) gesetzt und im Vergleich zu den Parentalstämmen bezüglich Körpermasseentwicklung, relativer Fettmenge sowie Insulin-, Leptin- und Adiponektinspiegel analysiert.
Ergebnis: Die F1 Hybriden wiesen einen intermediären Körpergewichtsverlauf auf. Die Rückkreuzungstiere mit NNT Mutation waren signifikant leichter und hatten signifikant weniger relatives Fett. Die Serumparameter blieben vom Auftreten der Mutation unbeeinflusst.
Zusammenfassung: Die Studie zeigt, dass die NNT Mutation mit Parametern der Adipositas in Mäusen assoziiert ist.

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POSTER 139

The gene expression of brown adipose tissue marker UCP-1, PRDM16 and CIDEA in human abdominal adipose tissue is fat depot-specific with obesity, insulin resistance and hyperglycemia associated

IFB – Adiposity Diseases

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TRM – Translational Regenerative Medicine
Tumor Targeting

Introduction: Brown adipose tissue (BAT) expresses UCP1, CIDEA and PRDM16, which plays an important role in the regulation of energy metabolism. In adults is an increased brown adipose tissue associated with low BMI, age, and better glucose metabolism. It is not yet known whether abdominal fat depots expresses signatures of brown adipose tissue markers and how the mRNA expression of BAT genes is associated with anthropometric and morphometric parameters in human white adipose tissue (WAT).
Methods: The mRNA expression of UCP1, PRDM16 and CIDEA was measured at 488 paired subcutaneous and visceral abdominal AT. Mean age of the individuals (326 women, 162 men) was 51 ± 14 (SD) years with a mean BMI of 43.5 ± 13.0. For the gene expression analysis, a quantitative RT-PCR was performed.
Results: All examined BAT markers were expressed in visceral and subcutaneous WAT in adults. The highest expression showed CIDEA, followed by PRDM16 and UCP1. In subcutaneous WAT UCP1 and CIDEA were expressed significantly lower than in visceral WAT. Compared to normal weight individuals, the subcutaneous mRNA expression of UCP1 and CIDEA was significant lower than in individuals with a BMI> 30. In addition, CIDEA in the subcutaneous tissue correlated negatively with parameters of insulin sensitivity.
Conclusion: The study shows that marker genes of BAT are expressed in human white adipose tissue. The mRNA expression of BAT genes is associated with obesity and fat distribution. Furthermore, correlations of BAT markers with parameters of insulin resistance and glucose homeostasis could be shown.

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POSTER 140 **Adipose tissue dysfunction in obese children**

IFB – Adiposity Diseases

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Rationale: Accumulation of fat mass can result from hypertrophy and/or hyperplasia and is associated with adipocyte dysfunction. Considering the early onset of obesity at childhood age, we aimed to investigate alterations in adipose tissue biology with normal development and childhood obesity.
Methods: We performed a comprehensive experimental characterization of 171 adipose tissue biopsies from lean and obese patients (aged 0 to 19 years) including adipocyte size and number, proliferation and differentiation capacity of stroma-vascular cells, macrophage infiltration, and lipolytic activity of adipocytes.
Results: We detected positive correlations between adipocyte cell size as wells as number with age in lean children. Obese children had significantly more and larger adipocytes compared to lean children accompanied by a significant decrease in basal lipolytic activity to about 60% compared to lean controls. Total adipocyte number and adipocyte size were the strongest predictors for adipose tissue mass in multivariate analyses. Stroma-vascular cells of obese children showed enhanced proliferation rate whereas differentiation potential was not altered compared to lean children. Furthermore, an increased number of macrophages and crown-like structures were detectable in adipose tissue of obese children.
Conclusion: We show adipocyte hypertrophy as well as hyperplasia and increased inflammation in adipose tissue of obese children, providing evidence that functional alterations in adipose tissue occur early in life.

Funding: ifb

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POSTER 141

MRT-basierte Quantifizierung von viszeralem Fettgewebe (VAT) bei morbid adipösen Patienten

IFB – Adiposity Diseases

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Einleitung: Das viszerale Fettgewebe (VAT) gilt als Risikofaktor für verschiedene Erkrankungen. Im Rahmen der BARO-Diet Studie an morbid adipösen Patienten sollte geklärt werden, ob der Fettanteil einzelner Schichten repräsentativ für das gesamte VAT sein kann. Methoden: Vor und nach einer zweiwöchigen Niedrigenergie-Diät bei 70 morbid Adipösen (ØBMI 47,2 kg/m2, 47 weiblich) wurden MRT basiert [G. Thörmer et al., JMRI 2013] Gesamt-VAT V_G (Zwerchfell –Beckenboden) und Einzelschicht VAT V_1 bzw. 5 Schicht VAT V_5 auf Höhe des Bauchnabels und der Bandscheiben L1 – S1 bestimmt. Zur Bewertung dienten das Bestimmtheitsmaß R^2 einer linearen Regression durch den Ursprung, sowie die Standardabweichungen σ_1 / σ_5 der mittleren Differenzen zwischen den aus $V_{1/5}$ berechneten Werten und V_G. Ergebnisse: V_1 zeigte für Frauen die höchste Korrelation mit V_G auf Höhe L 3-4 (R^2=0.83, σ_1=761 ml) und für Männer auf Höhe L1/2 (R^2=0,86, σ_1=1,092 ml). Die entsprechenden V_5 Werte brachten in beiden Gruppen nur eine geringe Verbesserung. Die Übereinstimmung von V_1 und V_G auf Höhe des Bauchnabels war niedrig ($\sigma_{1/5}$ = 1,740–2,284 ml). Die individuellen Veränderungen nach Diät lagen für Frauen zwischen +614 und –1,168 (Ø= –160) ml und für Männer zwischen +327 und –1,020 (-321) ml. Schlussfolgerung: Wie bereits für weniger Adipöse beobachtet [G. Maislin et al., Obesity 2012] liefert die Einzelschicht-VAT-Messung im Bereich L1-4 zuverlässige Schätzwerte für das VAT-Volumen bei morbid Adipösen. Zur Erfassung kleiner Volumenänderungen ist weiterhin [W. Shen et al., Obesity 2012] eine Gesamt-VAT-Analyse maßgeblich.

Funding: ifb

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POSTER 142

Analysis of parent of origin effects in Sorbs using long range phasing algorithms

IFB – Adiposity Diseases

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Tumor Targeting

Background and aim: Genome-Wide Association Studies(GWAS) were successfully applied to discover associations between genetic variation and Body Mass Index(BMI). However inheritance in terms of phase is limited in GWAS. The analysis of GWAS considering parental inheritance will provide further insights into the genetic mechanisms contributing to obesity. We hypothesized there may be genetic variances having different effect sizes for obesity depending on transmission from father or mother.

Material and methods: Genome-wide genotypes (Affymetrix 500K and 6.0) and family information from the Sorbs population (N=525) were used. Phasing was done by applying long-range phasing and haplotype library imputation algorithm. Subsequently, association analyses were performed by PLINK: GWAS (i)without considering allelic inheritance, (ii)with paternal alleles only and (iii)with maternal alleles only.

Results: In a GWAS with BMI using paternal alleles, a SNP (rs4587914 $P=1.407\times10^{-5}$) was found on chromosome 1 within *PRDM16* showing suggestive evidence for association. *PRDM16* is a plausible candidate gene for follow up analysis since it functions as a transcriptional co-regulator controlling the development of brown adipocytes in brown adipose tissue. Moreover, other studies show *PRDM16* is paternally expressed via multiple classification algorithms.

Conclusion: Our data suggest that *PRDM16* may have paternal effects that play a role in etiology of obesity. Further studies are warranted to investigate *PRDM16* and its potential mono-allelic expression.

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Funding: ifb

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POSTER 143

Analysis of novel obesity genes with the aid of congenic rats

IFB – Adiposity Diseases

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Background: Obesity is caused by multiple genes and their interaction. Studies in rats have revealed a link between a number of quantitative trait loci (QTLs) with facets of the metabolic syndrome. A QTL for serum cholesterol and body weight was identified on rat chromosome 10.
Methods: We generated a congenic rat strain, DA.WOKW10 and new sub-congenic rat strains (L1, L2, L3) for rat chromosome 10. Phenotyping and genotyping comparison of L1, L2 and L3 rat lines compared to parental strains have been performed. Phenotyping includes body weight gain up to an age of 30 weeks. Per strain and gender 10 rats have been studied. At the end we analyzed serum levels of leptin, insulin, and serum lipid profile as well as relative adipose tissue weight.
Results: Males of sub-congenic rats (L1, L2, L3) strains showed an increased in body weight compared to parental strain, DA rats. In contrast, female sub-congenic rats (L1, L2, L3) were lighter than the parental strain. These results indicate that the involved genes on rat chromosome 10 have sex specific roles. After gene expression analysis in adipose tissue and liver of DA.WOKW10 rats and sub-congenics we selected 2 potential candidate genes for further functional testing.
Conclusion: With the aid of sub-congenic rat lines we could shorten down the region on rat chromosome 10 and could select two potential candidate genes for further functional studies in adipose tissue.

Funding: ifb

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POSTER 144

Machbarkeit und Effektivität einer Telefonberatung als Nachsorgeprogramm für Jugendliche nach erfolgter stationärer Adipositasrehabilitation – das TeAM-Programm: Randomisierte kontrollierte Studie

IFB – Adiposity Diseases

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Hintergrund: Es wurde ein ambulantes, auf Telefonberatung basierendes Nachsorgeprogramm für Jugendliche (TeAM-Programm) nach erfolgter stationärer Adipositas-Rehabilitation entwickelt. Das Ziel des Programms ist die Verstetigung des in der Reha erreichten Gewichtsverlusts. Die erste Studienphase prüft die Machbarkeit des Nachsorgeprogramms, die zweite dessen Effektivität. Methodik: Die Jugendlichen (14-18 Jahre) werden direkt über dt. Rehabilitationskliniken rekrutiert. In der Machbarkeitsstudie werden die Durchführbarkeit und die Akzeptanz zwei verschiedener Interventionsformen untersucht: 1.) Telefonberatung + individualisierte SMS-Nachrichten und 2.) wie (1.) + passwortgeschützter Zugang zu einem Web-Forum. Die überlegene Interventionsform Kommt in der Effektivitätsstudie zur Anwendung. Den primären Endpunkt der Effektivitätsstudie stellt der BMI-SDS dar, sekundäre Endpunkte sind weitere anthropometrische Parameter und Angaben zum Gesundheitsverhalten. 12 und 24 Monate nach der Randomisierung erfolgen Follow-up-Untersuchungen. Die Beratung basiert auf dem Konzept der lösungsorientierten Kurzzeittherapie von DeShazer (DeShazer 2004). Abfolge und Hauptinhalte der Beratung sind in einem Studienmanual, verankert in der CrescNet-Datenbank, festgelegt. Ergebnisse: Die Rekrutierung für die Machbarkeitsstudie ist abgeschlossen. Es sind 63,16% Mädchen und 36,84% Jungen im Programm. Das Alter der Teilnehmer liegt im Mittel bei 15,82 Jahren, der BMI-SDS bei 2,48. Diskussion: Da Nachsorgeprogramme in Deutschland bisher nur im Erwachsenenbereich etabliert sind, gibt es hier noch einen großen Handlungsbedarf im Bereich der Pädiatrie.

Funding: ifb

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POSTER 145

Persönlichkeit, Depressivität und Suizidalität – Erste Ergebnisse zu Unterschieden zwischen adipösen und bariatrischen Personen

IFB – Adiposity Diseases

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Die bariatrische Chirurgie zählt zu den effizientesten Verfahren zur Behandlung von Adipositas sowie zur Besserung der physischen und psychischen Komorbiditäten. Im Kontrast dazu stehen Befunde, die zeigen, dass das Suizidrisiko dieser Personen erhöht ist. Bisher ist zudem wenig darüber bekannt, inwieweit sich Persönlichkeitsmerkmale von adipösen Personen, die einen solchen Eingriff vornehmen lassen, von anderen stark Übergewichtigen unterscheiden.

Das Ziel der vorliegenden Studie ist es, zu untersuchen, ob Unterschiede hinsichtlich Persönlichkeitsmerkmalen, Depressivität und Suizidalität zwischen diesen beiden Gruppen bestehen.

Als Messinstrumente wurden die Beck Scale for Suicidal Ideation, das Beck Depression Inventory-II, das NEO Five-Factor Inventory und der Aggression Questionnaire eingesetzt. Hinsichtlich Suizidgedanken und -versuchen, Depressivität, den Persönlichkeitsfaktoren der „Big Five" sowie Aggressivität wurden Mittelwertvergleiche durchgeführt.

In der bariatrischen Gruppe befinden sich n=129 Personen, die adipöse Kontrollgruppe wird durch n=171 Personen repräsentiert. Signifikante Mittelwertunterschiede bestehen zwischen den beiden Gruppen bezüglich Suizidgedanken, Neurotizismus, Offenheit und Feindseligkeit. Die adipösen Kontrollpersonen zeigen deutlich höhere Werte als Personen mit einem geplanten bariatrischen Eingriff. Diese hingegen weisen signifikant höhere Werte auf der Persönlichkeitsskala Extraversion auf. Mögliche Einflussfaktoren für diese Ergebnisse sowie daraus resultierende Implikationen für Behandlungsmöglichkeiten für Personen mit Adipositas werden diskutiert.

Funding: ifb

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POSTER 146

Ernährungsverhalten bei übergewichtigen und adipösen Kindern und Jugendlichen basierend auf Auswertungen von Verzehrshäufigkeitsfragebögen (FFQs)

IFB – Adiposity Diseases

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Tumor Targeting

Einleitung: Die Übergewichts- und Adipositasprävalenz ist bereits im Kindes- und Jugendalter hoch und oft bestehen Begleiterkrankungen, die sich bis ins Erwachsenenalter fortsetzen. Präventive Maßnahmen sind daher bereits bei Kindern und Jugendlichen wichtig. Eine neuartige Intervention für Familien mit übergewichtigen oder adipösen Kindern im Alter von 4-17 Jahren stellt das telefonbasierte Präventionsprogramm T.A.F.F. dar.
Methodik: Zu Beginn und nach einjähriger Intervention wurden FFQs von den Eltern (bei Kindern) oder den Jugendlichen (10-17 Jahre) ausgefüllt. Es soll untersucht werden, wie die Ernährungsgewohnheiten bei übergewichtigen Kindern sind und ob sie sich durch die Intervention optimieren lassen. Die Veränderungen werden anhand verzehrter Portionsmengen einzelner Lebensmittelgruppen und ihrem Vergleich mit Empfehlungen der aid beurteilt.
Ergebnisse: Insgesamt wurden 289 Fragebögen in die Analyse eingeschlossen (143 Jungen). Das mittlere Alter der Probanden war zu Studienbeginn 9,8 Jahre, der mittlere BMI-SDS lag bei 2.02. Die täglich verzehrten Portionsmengen bei Getränken, Obst & Gemüse sowie Getreideprodukten lagen unterhalb der Zufuhrempfehlung. Dagegen war die Aufnahme von Fleisch & Wurstwaren sowie Snacks zu hoch. Der Verzehr von Fetten und Milchprodukten entsprach den Empfehlungen.
Diskussion: Es besteht bei übergewichtigen Kindern und Jugendlichen vor einer Intervention eine Diskrepanz zwischen den verzehrten Lebensmitteln und den Empfehlungen der Fachgesellschaft. Oft ist die Lebensmittelauswahl ernährungsphysiologisch nicht optimal. Weitere Analysen sollen zeigen, ob die Intervention diese verbessert.

Funding: ifb

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POSTER 147

Genetic variants within AKR1B10 may influence human eating behavior

IFB – Adiposity Diseases

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TRM – Translational Regenerative Medicine
Tumor Targeting

Background and aims: *AKR1B10* is a monomeric enzyme that may play a role in detoxification processes and regulatory mechanisms like differentiation, proliferation and apoptosis. The aim of the present study was to investigate the effects of genetic variants of *AKR1B10* on the eating behavior factors restraint, hunger and disinhibition.

Material and methods: The initial analysis included 548 Sorbs from Germany, who are clinically well characterized for a variety of metabolic parameters including data on eating behavior (FEV). 4 tagging-SNPs (r^2=0.8, MAF<0.05) within the *AKR1B10* locus were genotyped in all subjects. Subsequently, genetic association analyses were calculated for restraint, hunger and disinhibition using linear regression models adjusted for age, sex and BMI. Replication analyses included another independent cohort from Leipzig (N=334).

Results: Among the Sorbs population the minor alleles of the variants rs1834150 and rs782881 were significantly associated with increased disinhibition (additive mode of inheritance, *P*=0.006 and *P*=0.032). Further, we identified significant associations with decreased waist circumference, increased alcohol consumption and higher coffee consumption (*P*<0.05). In our replication cohort we detected the same effect direction for the association with disinhibition. A meta-analysis for rs1834150 resulted in a combined *P*=0.0096 (Z-score=2.591).

Conclusion: Our data suggest that genetic variants within the *AKR1B10* gene may play a role in the regulation of human eating behavior.

Funding: ifb

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POSTER 148

Kognitive Verhaltenstherapie für Patienten mit Psychopathologie nach bariatrischer Chirurgie: Eine Machbarkeitsstudie

IFB – Adiposity Diseases

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Mangelnde Compliance und postoperativ auftretende Psychopathologie sind derzeit die am besten belegten psychosozialen Prädiktoren für geringen Gewichtsverlust oder Gewichtszunahme nach bariatrischer Chirurgie. Erste Befunde weisen den Erfolg postoperativer psychosozialer Behandlungen aus, allerdings gibt es kaum etablierte Programme zur Behandlung relevanter Psychopathologie. Ziel der Pilotstudie ist die Entwicklung und Evaluation der Machbarkeit eines kognitiv-verhaltenstherapeutischen Manuals für bariatrische Patienten.
In der laufenden unkontrollierten Pilotstudie erhielten 8 Patienten postoperativ eine 15 Sitzungen (je 50 Minuten) umfassende individuelle kognitive Verhaltenstherapie (KVT). Das entwickelte Behandlungsmanual umfasst Adaptationen evidenzbasierter Interventionen in Modulen zu Psyche, Ernährung und Körper. Zu Therapiebeginn, -mitte und -ende werden Körpergewicht und -größe objektiv gemessen sowie Psychopathologie mittels Fragebogen und Interviews erfasst.
Alle Patienten (Alter: 48,8±9,27 Jahre; BMI: 41,73±4,30 kg/m) zeigten einen signifikanten postoperativen Gewichtsverlust. Die Essstörungspsychopathologie zu Therapiebeginn war mit Werten von prä-bariatrischen Patienten vergleichbar und die allgemeine Psychopathologie war deutlich erhöht.
Die Pilotstudie dokumentiert die Machbarkeit und Akzeptanz von KVT bei bariatrischen Patienten mit postoperativen Anpassungsschwierigkeiten und zeigt erste Hinweise für eine Verbesserung des postoperativen Verlaufs. Mögliche Adaptationen der Behandlung für einen Wirksamkeitsnachweis des Behandlungsmanuals in randomisiert-kontrollierten Folgestudien werden diskutiert.

Funding: ifb

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POSTER 149

Neuroendocrinological correlates of stress responsiveness and in vivo central serotonin transporter availability in obesity – a [11C]DASB PET study

IFB – Adiposity Diseases

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Tumor Targeting

Context: Since appetite, energy intake, metabolism and reward processing are in part mediated by serotonergic signalling and stress hormones such as cortisol, a link between the activity of the hypothalamic-pituitary-adrenal axis (HPA) and individual eating behaviours appears likely. Objectives: In order to elucidate contrasts in neuroendocrinological circuits between obese subjects and normal weight healthy controls, we seek to correlate HPA axis activity as measured by the combined dexamethasone/CRH test with central serotonin transporter (SERT) availability using dedicated [11C]DASB brain PET. Results: Compared with HC, obese subjects showed significantly higher cortisol secretion as expressed by area-under-the-curve (AUC 452.1+/-474.0, n=28 vs. 204.9+/-154.5; p=0.023, n=22) and mean curve location (ML 57.8+/-56.1 vs. 30.5+/-17.4; p=0.033). ACTH secretion was similar in both groups and did not correlate with SERT availability. However, blood cortisol concentrations and SERT availability showed significant positive correlations in distinct brain regions (mPFC r=0.57; caudate r=0.48; ACC r=0.45; N.Acc. r=0.44; OFC r=0.43; p=0.001-0.03). Conclusions: Our findings display an HPA hyperresponsiveness in obesity. Temporary hypercortisolaemia is likely to affect appetite, energy intake and metabolism towards weight gain and may contribute to complications such as the metabolic syndrome. The correlation between SERT availability and HPA function suggest a bidirectional link between HPA responsiveness and serotonergic signalling, possibly offering a novel approach to the pharmacological treatment of susceptible individuals.

Funding: ifb

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POSTER 150

Attitudes of health care professionals towards female obese patients

IFB – Adiposity Diseases

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Objective: The health care setting has been reported to be one main source of weight stigma repeatedly, however studies comparing different professions have been lacking.
Method: Six hundred eighty-two health care professionals (HCP) of a large German university hospital were asked to fill out a questionnaire on stigmatizing attitudes, perceived causes of obesity and work-related impact of obesity. Stigmatizing attitudes were assessed on the Fat Phobia Scale (FPS) based on a vignette describing a female obese patient.
Results: Only 25% graded current health care of obese patients to be "good" or "very good". Sixty-three per cent of all HCPs "somewhat" or "strongly" agreed that it was often difficult to get the resources needed in order to care for obese patients. The mean FPS score was comparable to that in the general public (M=3.59), while nursing staff showed slightly more positive attitudes compared to physicians and therapists. Higher age, higher BMI and ascribing personal responsibility for obesity to the individual were associated with a higher level of stigmatizing attitudes. The nursing staff agreed on obesity as an illness to a greater extent, while physicians attributed obesity to the individual.
Conclusions: In summary, by making complex models on the causes of obesity known among health care professionals, stigmatizing attitudes might be reduced. Ongoing further education for health care professionals ought to be part of anti-stigma campaigns in the medical field.

Funding: ifb

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POSTER 151

Markierung von Studienpatienten im Krankenhausinformationssystem

IFB – Adiposity Diseases

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Ein erklärtes Unternehmensziel der Universitätsmedizin Leipzig (UML) ist eine bessere Unterstützung der klinischen Forschung und die Erhöhung der Rekrutierungsrate. Der IFB AdipositasErkrankungen (K7-28), das Zentrum für Klinische Studien Leipzig (ZKS Leipzig, TP2/M2) und der Bereich 1 Informationsmanagement (UKL) stellen sich dieser Herausforderung und arbeiten an möglichen Lösungen. Das Management von Patienten und Probanden in klinischen Studien und insbesondere ihre klinikübergreifende Verfolgung im UKL ist problematisch, da es im Informationssystem des UKL derzeit keine Unterstützung dieser Funktionalität gibt. Dies hat zur Folge, dass behandelnde Ärzte nötige Informationen zur Studienteilnahme, Medikation in einer Studie sowie Kontaktdaten zu Ansprechpartnern oder zur Studienleitung nicht zur Verfügung stehen, nur auf Nachfrage vom Patienten in Erfahrung gebracht werden können oder aufwendig recherchiert werden müssen. Sowohl die integrierte Auswertung von Forschungs- und Versorgungsdaten als auch die Rekrutierung von Probanden hängen ebenfalls mittelbar davon ab, da nur entsprechend markierte Patienten für derartige Recherchen in einer Forschungsdatenbank (i2b2) in Frage kommen. Lösungsvorschläge zur Markierung interessanter Patienten (Tagging) und/oder Probanden im KIS (SAP IS-H/i.s.h.med), die bereits in klinische Studien eingeschlossen sind, wurden in Arbeitstreffen vorgestellt und diskutiert. Eine sinnvolle Lösung wurde hierbei durch die Realisierung eines Studien-Formulars im SAP (Studien-PMD) unter Einbindung in den Klinischen Arbeitsplatz gefunden.

Funding: ifb

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POSTER 152

Die Messung von negativen Einstellungen gegenüber adipösen Menschen mit der Fat Phobia Scale (FPS) – Evaluation der psychometrischen Gütekriterien und Bestimmung von Referenzwerten für die deutschsprachige Kurzform der FPS

IFB – Adiposity Diseases

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Weltweit leiden ungefähr 600 Millionen Menschen an Adipositas. Adipöse Menschen leiden unter Stigmatisierung. Diese psychosozialen Folgen von Übergewicht und Adipositas sind Gegenstand aktueller Forschung. Zur Erfassung negativer Einstellungen gegenüber adipösen Menschen wurde im Jahr 1993 die englische Originalversion der Fat Phobia Scale (FPS) in den USA entwickelt. Zusätzlich wurde die Kurzform der FPS konstruiert, welche mit insgesamt 14 Items zeitökonomisch und universell einsetzbar ist. Aufgrund guter psychometrischer Eigenschaften zählt die Originalversion der Skala zu den am häufigsten verwendeten Instrumenten zur Messung von negativen Einstellungen gegenüber adipösen Menschen. Für die deutschsprachige Kurzform stehen eine umfassende Überprüfung der psychometrischen Eigenschaften sowie die Bestimmung von Referenzwerten jedoch noch aus. Ziele der vorliegenden Arbeit waren die deskriptive Analyse und die Bestimmung der psychometrischen Gütekriterien der Skala sowie die Erstellung von Referenzwerten. Die Datenbasis bildet eine telefonische Repräsentativerhebung in der deutschen Allgemeinbevölkerung (n = 3003). Erste Studienergebnisse werden präsentiert und diskutiert. Vor dem Hintergrund der weitreichenden Konsequenzen erlebter Stigmatisierung von adipösen Menschen könnten diese Studienergebnisse einen entscheidenden Beitrag im Rahmen der Erfassung und Erforschung von negativen Einstellungen gegenüber adipösen Menschen leisten.

Funding: ifb

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POSTER 153

Effekt von Ausdauer- vs. Krafttraining innerhalb eines einjährigen Adipositas- Therapieprogramms auf anthropometrische und metabolische Parameter bei adipösen Kindern und Jugendlichen: Randomisierte Machbarkeitsstudie

IFB – Adiposity Diseases

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Hintergrund: Die motorische Leistungsfähigkeit von Kindern und Jugendlichen hat sich während der letzten Jahrzehnte deutlich verschlechtert. Sowohl Ausdauer- als auch Krafttraining (IG) können die Körperzusammensetzung und metabolische Risikofaktoren verbessern. Es ist jedoch bisher unklar, welche Trainingsmodalität am effektivsten ist. Im Rahmen einer randomisiert-kontrollierten Machbarkeitsstudie sollen sowohl die Akzeptanz als auch die Effekt auf anthropometrische, metabolische und psychologische Parameter sowie die motorischen Fähigkeiten bei adipösen Kindern und Jugendlichen untersucht werden. Methoden: 60 adipöse (BMI > 97. Perzentile) Kinder und Jugendliche im Alter von 8 – 18 Jahren, die am einjährigen Adipositas-Therapieprogramm KLAKS teilnehmen, werden in eine der beiden IGs sowie eine Kontrollgruppe (KG) randomisiert (TN=20/Gruppe). Alle Teilnehmer erhalten 60 Min./Woche Ausdauertraining an Fahrradergometern bzw. 60 Min./Woche Krafttraining an Gymboy TECA® Geräten. Die KG erhält 60 Min./Woche Sport, der frei wählbar ist. Neben Akzeptanz und Machbarkeit werden die Änderung von BMI-SDS, Taillenumfang, Körperfettgehalt, metabolischen und inflammatorischen Markern innerhalb des Interventionsjahres analysiert. Weiterhin werden die isometrische Maximalkraft, die Ausdauerfähigkeit sowie verschiedene psychologische Parameter überprüft. Diskussion und Ausblick: Die vorliegende Studie soll den Effekt von Ausdauer- bzw. Krafttraining auf anthropometrische, psychologische und metabolische Parameter sowie die motorischen Fähigkeiten analysieren und somit einen Beitrag leisten für zukünftige Therapieempfehlungen.

Funding: ifb

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POSTER 154

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

IFB – Adiposity Diseases

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The central serotonergic and the dopaminergic system, in particular the reuptake sites, are thought to be significantly involved in the pathophysiology of obesity. Initial interpretation of SPECT data foreshadowed a correlation between body mass index (BMI) and serotonin transporters (SERT) along with striatal dopamine transporters (DAT). The aim of this project is to correlate DAT or SERT availability with BMI based on a large cohort of European healthy subjects. Region-of-interest (ROI) and volume-of-interest (VOI) analysis of the data was performed on BMI [kg/m^2] and [^{123}I]FP-CIT binding potentials in the striatum (DAT), consisting of caudate and putamen, the thalamus (SERT) and midbrain (SERT). p-values $\leq$ 0.05 (FWE-corrected for VOI analysis) were considered significant. Regression analysis of all data and comparisons between groups (BMI$\leq$ 25 vs. BMI>25 and BMI$\leq$ 25 vs. BMI$\leq$ 30) were carried out. Results showed significant association between SERT availability and BMI for head of the caudate only (VOI analysis, BMI$\leq$ 25 vs. BMI>25). Models showed significant effects that were mostly based on age (lower DAT/SERT availability at higher age) and gender (higher DAT/SERT availability in women) in the head of the caudate, putamen and thalamus. Brainstem/midbrain showed no significant effects at all. From the data we conclude that both subcortical DAT and SERT availability are relatively stable across different BMI levels albeit individuals with heavily increased BMI are under-represented in this cohort. Further IFB PET studies are about to show changes in the latter as compared with lean controls, also in neocortical regions.

Funding: ifb

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POSTER 155

Analysis of GRB14 mRNA-expression profiles in human subcutaneous and visceral adipose tissue

IFB – Adiposity Diseases

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Objective: The *GRB14* locus (Growth Factor Receptor-Bound Protein 14) has been shown to be associated with waist to hip ratio (WHR). To investigate possible mechanisms explaining the association, we assessed the relationship between the WHR-associated single nucleotide polymorphism (SNP) rs10195252, adipose tissue (AT) *GRB14* mRNA expression and metabolic traits related to fat distribution (FD)

Methods: mRNA-expression of *GRB14* was measured in 620 paired samples of human subcutaneous (SAT) and visceral AT (VAT) by real-time PCR. Genotyping of rs10195252 was done by employing the TaqMan technique. Relationships between quantitative traits were assessed by correlation analyses and by linear regression models. Genetic associations were performed in additive model of inheritance. P-values <0.05 were considered statistically significant.

Results: *mRNA-expression analyses: GRB14* mRNA levels were significantly higher in VAT vs. SAT, independent from gender, body mass index (BMI), WHR, diabetes- and lipid-status. Furthermore, mRNA levels correlated with BMI, diabetes-status, WHR, triglycerides (TG) and high-density lipoprotein (HDL). *Genetic association*: rs10195252 T-allele was associated with lower mean BMI, glycated hemoglobin (HbA1c) and 2h glucose-levels after an oral glucose tolerance test (oGTT2h), and higher HDL-cholesterol. However, the SNP did not correlate with mRNA-expression levels.

Conclusion: Our data support previously reported findings and suggest a role of *GRB14* in the regulation of FD. However, the SNP-WHR association does not seem to be mediated by SNP-effects on *GRB14* mRNA-expression levels.

Funding: ifb

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POSTER 156

Perivascular and subcutaneous adipose tissue differ in internal carotid artery (ACI) stenosis patients.

IFB – Adiposity Diseases

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Tumor Targeting

Background: There is growing evidence for a vasoregulatory and atherosclerosis-inducing role of local fat deposits around vessels. Aim of the study was to investigate gene expression profiles in paired human samples of subcutaneous (sc) and perivascular (pv) adipose tissue (AT) and to link it to clinical and anthropometric characteristics of carotid stenosis patients. Material & Methods: A RNA/cDNA bank was established from paired sc (cervical) and pv (ACI) AT samples of patients who underwent carotid endarterectomy. Marker genes e.g. for muscle, fibroblasts or nerve have been measured to control for impurities of "non-adipocyte" cells. Sixty paired samples passed and were assayed on Illumina HT12 microarrays. We tested for differential expression using background-corrected, quantile-normalized values and paired/standard *t*-test. *P*-values have been corrected for multiple testing using FDR methodology. Correlation analyses were conducted. Results: We found differentially expressed genes between sc and pc AT clearly distinguishing both AT types. Among the top hits are developmental genes like *HOX* genes or *TBX15*, but also genes involved in atherosclerosis and coronary artery disease. Intra-depot comparison of e.g. symptomatic *vs.* asymptomatic or lean *vs.* obese patients revealed genes with nominal differences in mRNA levels, which however, correlated with anthropometric and metabolic parameters (BMI, triglycerides, cholesterol, % stenosis). Conclusion: Our results indicate that perivascular adipose tissue may exert an important role in the pathogenesis of atherosclerosis.

Funding: formel1

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POSTER 157

Synthesis of a series of VAChT ligands as basis for the development of 18F-labelled radiotracers for imaging in brain

Imaging

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The department of Neuroradiopharmaceuticals is part of the Helmholtz-Zentrum Dresden-Rossendorf and deals with the development of radiotracers for brain research using positron emission tomography (PET).
Those tracers are ligands labelled with radioactive isotopes which bind to selected biomolecules in brain. Due to this specific binding it is possible to visualise neurotransmission processes in living organisms. For the development of such ligands it is necessary to synthesise various organic compounds and to determine their *in-vitro* binding affinity to the desired biological target. Afterwards, a promising candidate is selected for labelling with a short-lived radioactive nuclide such as fluorine-18.
The vesicular acetylcholine transporter (VAChT) is located in cholinergic areas in brain and is an interesting target for the *in-vivo* imaging of neuronal deficits as observed in Alzheimer's disease. It is known that vesamicol (2-(4-phenylpiperidin-1-yl)cyclohexanol) acts as a high-potential inhibitor for this transporter and thus represents the chemical lead for the development of VAChT-radioligands. The aim of our studies is to develop a selective ligand by varying the vesamicol-skeleton in a systematic manner at its' three ring structures and determining the binding profile of the resulting derivatives. These *in-vitro* data are correlated with the various chemical structures leading to a three dimensional computational model, a so-called quantitative structure affinity relationship (QSAR). Based on those results, we will be able to find a promising candidate for radiolabelling studies and further investigations.

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POSTER 158 **Computergestützte Volumetrie der Mamillarkörper in vivo bei Patienten mit unipolarer Depression (MDD) und Bipolarer Störung (BD) mittels hochauflösender 7Tesla-Magnetresonanztomographie (MRT)**

Imaging

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Tumor Targeting

Die Mamillarkörper (MB) fungieren im Zwischenhirn als Schaltstelle zwischen Limbischem und Extralimbischem System und sind als Substruktur des Hypothalamus Teil der HPA-Achse (Hypothalamus-Hypophysen-Nebennierenrinden-Achse), die bei der uni- wie auch bipolaren Depression einer Dysregulation unterliegt (Holsboer 2000; Daban et al., 2005). Sie scheinen eine wichtige Rolle für das episodische (Peeters et al., 2002) und räumliche Gedächtnis (Vann, 2010) zu spielen; mit der Depression gehen häufig auch kognitive Beeinträchtigungen wie eine Verschlechterung des Arbeitsgedächtnisses einher (Drevets et al., 2008).Ziel der Arbeit war es, den Postmortem-Befund einer Volumenreduktion der MB bei affektiven Störungen (Bernstein et al., 2012) mittels hochauflösender MRT *in vivo* zu replizieren.
In die Untersuchung eingeschlossen wurden n=17 medizierte und n=14 unmedizierte PatientInnen mit MDD, n=14 PatientInnen mit BD sowie n=20 gesunde Kontrollen.
Verwendet wurden T1-gewichtete präprozessierte 7T-MRT-Bilder (3D-MP2RAGE-Sequenz). Mit Hilfe von histologischen Hirnatlanten und einer Farbcodierung wurde ein detaillierter Segmentierungs-Algorithmus entwickelt, der sich an Intensität und anatomischen Landmarks orientierte und alle drei Raumebenen berücksichtigte.
In getrennten Bearbeitungsdurchgängen wurde die Reliabilität der Methode von zwei Ratern überprüft.
Die Segmentierungsmethode erwies sich als hochreliabel: Der ICC (Intraclass correlation coefficient) betrug für den linken MB ICC=.97 und für den rechten MB ICC=.96. Ergebnisse hinsichtlich Gruppenunterschiede im MB-Volumen standen zum Zeitpunkt des Druckes noch aus.

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POSTER 159

[18F]FDG labeling of ovine mesenchymal stem cells for pet imaging

Imaging

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Objective: Because of their extended differentiation capacity, stem cells have gained great interest in the field of regenerative medicine. For the development of therapeutic strategies in stroke, more knowledge on the in vivo fate of these cells is required. For that purpose, stem cells can be labeled with radioactive tracers such as [18F]FDG for molecular imaging with positron emission tomography (PET). The aim of this study was to optimize the radioactive labeling of mesenchymal stem cells (MSCs) in vitro with [18F]FDG and to investigate the potential radiotoxic effects of this labeling procedure.
Material and Methods: Ovine MSCs were used to investigate [18F]FDG uptake kinetics over time (0-120 min), tracer dose (0.1 – 100 MBq) dependency as well as tracer retention. 200 000 cells were seeded over time in 2 ml 37°C PBS per well in a 12-well plate. Cell viability and tracer uptake after labeling was evaluated using Trypan Blue reagent and Gammacounter.
Results: An incubation time of 60 min and a tracer concentration of 1 MBq/10 000 cells was found to be optimal parameters for cellular [18F]FDG uptake. The Tracer retention on 60 min averaged to 80%. Cell vitality was not relevantly affected by [18F]FDG labeling.
Conclusion: Our experiments indicate the feasibility of MSC-labeling with [18F]FDG. Major cellular properties were not affected as confirmed by toxicity experiments. Thus, labeling of MSCs with [18F]FDG is a suitable technique to noninvasively assess cell delivery and early retention with PET. Future studies will utilize these labeled ovine MSCs for evaluation in a translational relevant sheep stroke model.

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POSTER 160 **Definition of examination standards for spleen elastography in liver disease**

Imaging

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Aim: Spleen elastography is a promising method for characterization of portal hypertension and associated complications in patients with liver cirrhosis. Recent published data suggests that spleen stiffness may be used as a screening test for the presence of esophageal varices. However, standardized examination procedures for spleen stiffness measurement have not been defined yet. Materials and methods: 25 healthy volunteers and 25 patients with compensated liver cirrhosis (CHILD A) were prospectively characterized with conventional ultrasound and ARFI in two respiratory positions: breath hold after expiration (exp) and deep inspiration (insp). For each respiratory position 20 single measurements were performed. The distribution of single ARFI values was analyzed for normality and the number of required measurements was calculated. Results: ARFI results were normally distributed in > 95% of cases. The difference between the mean ARFI value and the mean after 20 measurements was below 5% after ten measurements. Patients with liver cirrhosis had a higher spleen stiffness compared to healthy volunteers. Deep inspiration caused an increase of spleen stiffness: healthy volunteers 2.46±0.35 m/s (exp) vs. 2.66±0.36 m/s (insp), p=0.01; cirrhotics 3.25±0.58 m/s (exp) vs. 3.46±0.38 m/s (insp), p=0.03. Conclusion: ARFI values are normally distributed and ten valid measurements should be performed. Deep inspiration significantly increases spleen stiffness which may impair the methods accuracy. Therefore, the respiratory position needs accurate standardization for ARFI assessment of the spleen in clinical practice and future studies.

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POSTER 161

Labeling of GPCR with Fluorescent Markers via a Coiled-Coil Tag

Imaging

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Visual labeling of G protein-coupled receptors (GPCR) is of special interest for live cell imaging. The widely used technique of GPCR fused to fluorescent proteins like GFP is the most common approach. But the fused fluorescent proteins are big in size and label both expressed GPCR at the cell surface and GPCR which are still inside the cell. Therefore we want to establish a new labeling strategy via a coiled-coil tag. There are several advantages of this approach: small tag size with 5-6 kDa, high binding affinity with a KD = 60-70 nM, a very short labeling time within 2 min and the use of different fluorophores. The coiled-coil tag consists of two corresponding peptide sequences. The $(EIAALEK)_3$ sequence is fused to the extracellular N-terminus of the GPCR by mutagenesis. The interaction with the $(KIAALKE)_3$ peptide will consequently label $(EIAALEK)_3$-tagged GPCR at the cell surface. The additional insertion of an N-terminal cysteine at the receptor side and the linkage of 5(6)-carboxytetramethylrhodamine (TAMRA) by thioester to the $(KIAALKE)_3$ peptide will allow the native chemical ligation (NCL), which subsequently will lead to the covalent transfer of the fluorophor from the $(KIAALKE)_3$ peptide to the $(EIAALEK)_3$-tagged GPCR.

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POSTER 162

Fat-Water separation in Zebrafish by phase-sensitive image processing using a Inversion-Recovery-RARE sequence

Imaging

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Tumor Targeting

The zebrafish is a well established model organism characterized by a fast development and physiologically resembles other vertebrates like mice. Here zebrafish is used as a model for investigating obesity and related diseases. We aim to investigate the effect of different diets on adipose tissue accumulation in adult zebrafisch. MR-imaging is a apropiate method for the local quantitative determination of the fat and watercontent within a sample. Differentiation of fat and water is often based on their distinct spin lattice relaxation times (T1). The different T1 times can be used to bring fat and water into opposite phase by applying a 90°-pulse after an inversion pulse. Thus qualitative fat-water separation in zebrafish can be achieved using a inversion recovery experiment by processing the MRI data in a phase sensitive fashion.

Frozen zebra fish was embedded in a 15 mm NMR tube filled with a 2% agar-agar gel. MR-imaging wasperformed with a RARE-sequence combined with a preparative inversion recovery 8800 Hz sechant pulse followed by an inversion delay ranging from 1 ms to 3000 ms. Non inverted spins were spoiled by a 1.5% gradient applied during the inversion delay.

Automatic image reconstruction software usually discardes the phase information of the nuclear spins. In order to visualize the different phase of fat and water the raw data were processed using Python. MRI raw data are complex numbers stored in k-space. This k-space was reconstructed and images including the phase information were compiled. Additionally a biexponential fit over all pixels was performed leading to a T1 map of the zebrafish.

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POSTER 163 **Functional connectivity in major depression: increased phase synchrony between frontal cortical EEG-source estimates.**

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Structural and metabolic alterations in prefrontal brain areas including the subgenual (SGPFC), medial (MPFC) and dorsolateral prefrontal cortex (DLPFC) have been shown in major depressive disorder (MDD). Still it remains largely unknown how brain connectivity within these regions is altered at the level of neuronal oscillations. Therefore the goal was to analyze prefrontal electroencephalogram (EEG) phase synchrony in MDD and its changes after antidepressant treatment.

In 60 unmedicated patients and 60 healthy controls a 15 minute resting EEG was recorded at baseline and in a subgroup after two weeks of antidepressant medication. EEG functional connectivity between the SGPFC and the MPFC and DLPFC was assessed with eLORETA (Low Resolution Brain Electromagnetic Tomography) by means of lagged phase synchrony.

Patients revealed an increased prefrontal connectivity at the alpha frequency between the SGPFC and the left DLPFC/MPFC. A positive correlation was found for beta connectivity and change in HDRS scores. After treatment, an increased connectivity between the SGPFC and the right DLPFC at the beta frequency was found for MDD but not for HC.

MDD is characterized by increased EEG functional connectivity within frontal brain areas. These disturbances of neuronal communication are assessable via EEG and might have potential value as biomarkers.

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POSTER 164

Klinische Bewertung von Kompositrestaurationen nichtkariöser Zahnhalsdefekte – visuell und mit optischer Kohärenztomografie (OCT)

Imaging

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Ziel: Klinische Bewährung eines 1-Schritt-Self-Etch-Adhäsivs im Vergleich zu einem 2-Schritt-Etch-and-Rinse-Adhäsiv zur Restauration nichtkariöser Zahnhalsdefekte.
Materialien & Methoden: 40 Patienten, paarweise Restauration von je 40 Zahnhalsdefekten mit Futurabond M (1-SE) bzw. Solobond M (2-ER) und Amaris (VOCO GmbH, Cuxhaven). Klinische, visuell-taktile Bewertung der Füllungen gem. Hickel et al. (2007) 14 Tage nach Füllungslegung sowie nach 6, 12 und 24 Monaten gem. ästhetischer, funktioneller und biologischer Kriterien. Nach 36 Monaten Abbildung mit SD-OCT (Telesto SP5, Thorlabs GmbH, Dachau).
Statistik: kumulative Fehlerraten (McNemar-Test), Kaplan-Meier-Überlebenskurven.
Ergebnisse: Nach 24 Monaten Bewertung von 32 Füllungen je Gruppe (Recallrate: 86,5%). Keine signifikanten Unterschiede zwischen den kumulativen Fehlerraten für 1-SE (8,6%; je 1x Füllungsverlust, Randkaries, Randfraktur) und 2-ER (17,1%; 6x Füllungsverlust) und in den Kaplan-Meier-Kurven, sowohl bzgl. der Einzelkriterien als auch in der Gesamtbewertung ($p_i > 0{,}16$). SD-OCT ist zur 3D-Darstellung von Zahnhalsrestaurationen und zur quantitativen Füllungsrandanalyse (2D) und Quantifizierung von Spalten an der Zahn-Komposit-Interface geeignet.
Schlussfolgerungen: Trotz der nicht signifikanten Gruppenunterschiede lassen die Füllungsverluste durch Retentionsversagen klinisch relevante Unterschiede nach längerer Liegedauer erwarten. Zur Interpretation von Füllungsverlusten erscheint die Darstellung der Zahn-Komposit-Interface mit OCT in vivo hilfreich, eine quantitative Defektbewertung ist angezeigt.
Dank: VOCO GmbH, Cuxhaven & Thorlabs GmbH, Dachau

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POSTER 165

Inter-rater reliability of 3D-ultrasound of the carotid vessels

Imaging

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Purpose: Duplexsonography of internal and common carotid artery (ICA and CCA) is routinely performed in diagnosis of stroke, as about 20% of ischaemic strokes are caused by large-artery atherosclerosis. Here, we introduce a new method of sonographic 3D-visualization of the carotid vessels and give a first evaluation of inter-rater reliability (IRR). Method: Curefab CS (Curefab GmbH, Munich,) is a mobile computer hard- and software attachment to conventional ultrasoundsystems allowing 3D-reconstruction of vessels. Fifty carotid vessels of 25 vascular healthy volunteers were examined by 3D-ultrasound (2 investigators). Besides total length of sonographically detectable ICA distal to the bifurcation also cross section area of CCA and ICA were measured. IRR between the two investigators was calculated by using intraclass correlation coefficient (ICC). Results: Forty-nine of the fifty carotid vessels could be sonographically visualized in 3D and mean length of reconstructed ICA distal to the bifurcation was 32 mm for the first and 33,4 mm for the second investigator. Mean ICC (absolute agreement) between investigator 1 and investigator 2 for CCA & ICA was 0,89 (standard deviation [sd] 0,09) respectively 0,66 (sd 0,24) for ICA only. Conclusion: Native 3D-ultrasound visualization of carotid vessels is feasible and shows a moderate agreement between different investigators. These results warrant application of contrast-enhanced 3D-ultrasound for improving IRR, which might result in a bed-side way of cervical angiography.

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POSTER 166

Interaktive computergestützte Volumetrie des Hypothalamus in vivo mittels hochauflösender 7 Tesla Magnetresonanztomographie

Imaging

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Hintergrund: Als Bindeglied zwischen kortikalen und subkortikalen neuronalen Zentren ist der Hypothalamus in Prozesse eingebunden, die wesentlich bei Patienten mit affektiven Störungen gestört sind, insbesondere Stimmungsregulation, Antriebsverhalten und Schlaf-Wach-Rhythmus. Die hochauflösende (7 Tesla) Magnetresonanztomographie (MRT) ermöglicht es erstmalig den Hypothalamus und seine Substruktur *in vivo* im Submillimeterbereich zu vermessen.

Methode: Anhand von histologischen Hirnatlanten wurden etablierte anatomische Landmarken des Hypothalamus überarbeitet und ein detaillierter Segmentierungsalgorithmus basierend auf einer Fehlfarbendarstellung entwickelt. 5 unmedizierte depressive Patienten (4 Frauen) und 5 alters- und geschlechtsgematchte Kontrollen wurden mittels einer 3D MP2RAGE Sequenz im 7T MR Scanners gemessen. Die T1 Bilder wurden koregistiert, interpoliert auf 0.5x0.5x0.5 mm^3 Voxelauflösung und bezüglich der Aufnahmehelligkeit homogenisiert (Histogrammmatching).

Ergebnisse: Die Intrarater Reliabilität des entwickelten Segmentierungsalgorithmus betrug ICC=.99 (linker Hypothalamus) und ICC=.97 (rechter Hypothalamus) bei einem Voxel Overlap von 97.8% (links) und 97.4% (rechts). Die Übereinstimmung zwischen den beiden Ratern betrug ICC=.94 (links) und ICC=.97 (rechts) mit einem Voxel Overlap von 95.2% für beide Hypothalami.

Diskussion und Ausblick: Mit der hier vorgestellten Methode konnte eine hochreliable manuelle Segmentierung des Hypothalamus unter Verwendung von 7T MRT Aufnahmen ermöglicht werden. Für weitere methodische Entwicklungen kann das Verfahren als Bezugsnorm gelten.

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POSTER 167 **Habenula volume increases with disease severity in un-medicated major depressive disorder**

Imaging **Schmidt F[1], Schindler S[1], Adamidis M[1], Strauß M[1], Geyer S[2], Schönknecht P[1]**

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Introduction: The habenula is a paired epithalamic structure which is involved in the pathogenesis of Major Depressive Disorder (MDD). Evidence comes from its impact on the regulation of serotonergic and dopaminergic neurons, its role in emotional processing, studies on animal models of depression, successful deep brain stimulation in depressed patients and reduced post-mortem habenula volumes in depressed patient's brains.
Method: In the present study, for the first time in vivo habenula volumes were investigated in 20 un-medicated and 20 medicated MDD patients and 20 healthy controls by applying a 3-dimensional segmentation algorithm on 7 Tesla magnetic resonance (MR) whole-brain T1 maps.
Results: We found a severity dependence of bilateral habenula volumes specifically during disease onset for which medication effects could be ruled out. In medicated chronically depressed patients, this relationship disappeared.
Discussion: Our findings was suggested for a specific involvement of habenula cellular pathologies during the course of disease, while general effects, independent of severity or stage of disease where to be rejected. Likewise, despite finding evidence for a general gender effect across all groups, we could not replicate a disease state unspecific but laterilised volume reduction in females, as reported from observations at lower fields and resolutions. Findings of our study warrant further tractographic and functional investigation with high resolution in-vivo MR imaging.

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POSTER 168

Developpement of an interactive segmentation algorithm of the hippocampus and its substructures using high resolution 7T MR-images in humans

Imaging

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Introduction: The human hippocampus can be divided in subfields with different histological characteristics and interconnected functions. As shown in post-mortem studies and first MRI-studies MDD and other psychiatric diseases may affect these subfields differently (1). The loss of neuropil may be reversible in some subfields due to treatment (2).
Methods: The high reliable protocol for the volumetry from Konrad et al. (3) is adapted to 7 T and ITK-snap (4) with help of the Duvernoy atlas (5). The higher resolution and the triplanar view allow the refinement of the landmarks used for the volumetry and request a new definition of reliable landmarks for the subfield segmentation.
Discussion: The standardization of the volumetry protocol and results of the reliability check will be presented. We have to be aware of the fact that the MRI-method will always be limited in comparison to histology. The anatomical-terminological inconsistencies and the use of different protocols give way to differing results, especially for the subfields.

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POSTER 169 **Entwicklung eines 18F-markierten Liganden für die Phosphodiesterase 2A**

Imaging

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Phosphodiesterasen (PDE´s) sind Enzyme, die in allen menschlichen Zellen exprimiert werden und die zyklischen Nucleotide cAMP und/oder cGMP hydrolysieren. PDE-Inhibitoren verzögern den Abbau dieser sekundären Botenstoffe und beeinflussen physiologische Prozesse. Die PDE2A zeigt eine hohe, spezifische Expression im Gehirn sowie in bestimmten Tumoren und ist vermutlich an der Pathophysiologie entsprechender Erkrankungen beteiligt. Ziel unserer Arbeiten ist die Darstellung eines radiomarkierten PDE2A-Inhibitors für die Bildgebung der PDE2A mittels Positronen-Emissions-Tomographie (PET).

Auf Grundlage des Patents WO2010/054253 A1 wurde eine für die PDE2A hochaffine und selektive Triazin-Leitstruktur (TA-05, IC_{50}: 4,12 nM) ausgewählt. Diese Leitstruktur wurde in einer fünfstufigen, optimierten Syntheseroute dargestellt und vollständig charakterisiert. Ausgehend von TA-05 wurden ein neues Fluorpropyl-Derivat (TA-P2) als Referenzverbindung für Affinitätsstudien sowie der entsprechende Tosylat-Präkursor (TA-P4) für eine einstufige ^{18}F-Markierung entwickelt. Die nukleophile ^{18}F-Fluorierung von TA-P4 führte zu einem neuen, hochaffinen PDE2A-Radioliganden (^{18}F-TA-P2), der erfolgreich isoliert, gereinigt und mittels Radio-DC sowie Radio-HPLC analysiert wurde. Die biologische Charakterisierung von ^{18}F-TA-P2 wird derzeit mittels TierPET/MR und Untersuchungen zur Metabolisierung sowie Autoradiographie bearbeitet.

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POSTER 170 **Development of a PET Tracer for Phosphodiesterase 10A**

Imaging

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Phosphodiesterases (PDEs) are a class of enzymes heavily involved in cellular signaling by inactivating the second messenger cAMP and cGMP. So far, 11 different PDE families are known, of which one, the dual substrate enzyme PDE10A is abundantly expressed in the striatum. Since this brain region is thought to be involved in the pathomechanism of schizophrenia, PDE10A inhibition represents an approach in the treatment of this disease. *In-vivo* imaging via positron emission tomography (PET) of PDE10A would allow investigating the enzyme and its expression in neuropathological processes. Therefore our group is focused on the development of a F18-labeled PET tracer for PDE10A. Recently reported 1-arylimidazoquinoxaline inhibitors have been chosen as lead structure.
Based on this scaffold we synthesized a series of new fluorinated compounds as possible PET tracer candidates for PDE10A. To enable an easy F-18 incorporation, fluorine was chosen to be in the 2-position of the pyridine ring. The key step to introduce these different 2-fluoropyridines is the Pd-catalyzed Suzuki-coupling. 2-Fluoropyridines can be localized in two different positions of the arylimidazoquinoxaline scaffold leading to three different types of inhibitors (type A, type B, type C). The inhibitory potency of these compounds was tested towards human, recombinant PDE10A and other PDE-families. All synthesized compounds showed a high inhibitory potency. The most selective inhibitor was chosen to be further developed as PET tracer for PDE10A.

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POSTER 171

Das Sprachnetzwerk gesunder Probanden im Resting-state

Imaging

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Aus aufgabenbasierten Studien mit funktioneller Magnetresonanztomographie (fMRT) ist bekannt, dass Sprachfunktionen in einem links lateralisierten temporofrontalen Netzwerk organisiert sind. Mit Hilfe des BOLD-Signals (blood oxygenation level dependent) können aufgabenunabhängig im sogenannten Resting-State (rs) Konnektivitäts-Netzwerke beschrieben werden. Ziel war die Exploration eines solchen Netzwerkes ausgehend von linkem Gyrus frontalis inferior (IFG) und linkem posterioreren Gyrus temporalis medius (MTG). Beide Regionen von Interesse (ROIs) zeigten in einer vorangegangenen fMRT-Studie während semantischer Integrationsprozesse bei einer auditiven Sprachaufgabe erhöhte Aktivität. Es wurden rs-fMRT Datensätze von 171 Rechtshändern (~21,0 Jahre) analysiert. Die vorverarbeiteten BOLD-Zeitserien wurden um Bewegungsparameter, das mittlere globale Signal sowie ihre ersten 5 Hauptkomponenten bereinigt und breitbandgefiltert (0,01 – 0,08 Hz). Pro Proband wurden die Eigenvariate der beiden ROIs mit den Zeitserien aller Voxel im Gehirn korreliert. Auf Gruppenebene zeigten IFG und MTG gemeinsame funktionelle Konnektivität zu einem Netzwerk aus links und rechts inferior frontalen und posterior temporalen, links supplementär motorischen und rechts cerebellären Hirnregionen. Die gefundenen Regionen stehen im Einklang mit einer ähnlichen Analyse von Tomasi und Volkow (2012) und meta-analytischen Erkenntnissen über die Topographie des Sprachnetzwerkes von Price (2010). Die Analyse der Resting-state-Konnektivität, ausgehend von IFG und MTG, stellt sich somit als geeignete Methode zur Beschreibung eines allgemeinen Sprachnetzwerkes dar.

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POSTER 172

Sichtbarkeit von Schraubenperforationen nach Plattenosteosynthese bei proximalen Humerusfrakturen

Imaging

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Primäre und sekundäre Schraubenperforationen sind Outcome-entscheidende Faktoren bei Plattenosteosynthese der proximalen Humerusfraktur. Diese Studie soll beurteilen, inwiefern die üblichen AP-Röntgenaufnahmen ausreichen, um alle bestehenden Perforationen zu detektieren.

14 Thiel-fixierte Humeri erhielten stellvertretend für die im Humeruskopf befindlichen Schrauben der üblichen Osteosyntheseplatten sichtbar perforierend jeweils 5 Kirschner-Drähte. Es folgte ein mittels Software (Magic Web) ausgewerteter 3D-Scan mit dem Ziehm Vision FD Vario 3D. Jedes Einzelbild entsprach einem Aufnahmewinkel von 1,24°. 110 Bilder konnten einen Winkelbereich von 136° darstellen. Dokumentiert wurde, innerhalb welcher Winkel die Perforationen der K-Drähte sichtbar waren. –90° definierte den Blick auf die Gelenkfläche des Humerus, 0° entsprach der AP-Aufnahme, das letzte Bild zeigte mit +46° den Blick von lateroventral auf das Tuberculum majus.

Bei allen 14 Humeri konnte ein komplikationsloser 3D-Scan mit gut darstellbaren Drähten durchgeführt werden. Bei 1 von 70 Drähten konnte kein Durchbruch festgestellt werden. Der Perforationsnachweis gelang im Mittel beim adaptierten Winkel von –30° (30° Außenrotation im SG) für den cranioposterioren und posterioren Draht, bei 0° (AP) für den inferioren, cranioanterioren und cranioposterioren Draht und bei +30° (30° Innenrotation im SG) für den anterioren, cranioanterioren und cranioposterioren Draht.

Für verlässliche Aussagen über bestehende Perforationen reicht die AP-Röntgenaufnahme nicht aus. Zusätzliche Aufnahmen in 30° Innen- und Außenrotation ermöglichen den Nachweis aller übrigen Durchbrüche.

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POSTER 173

Thyrogener Einfluss auf die Aktivierung braunen Fettgewebes (BAT) bei Mäusen

Imaging

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Ziel: Braunes Fettgewebe (BAT) hat eine essentielle Funktion in der Wärmeregulation und im Energiehaushalt. Seine Aktivierung erfolgt über β3-adrenerge Rezeptoren, die auf zellulärer Ebene eine vermehrte Konversion von T4 in T3 bewirkt und hierüber die mitochondriale Wärmeerzeugung stimuliert. Eine direkte thyrogene BAT-Aktivierung wurde jedoch bislang nicht gezeigt. Ziel unserer Untersuchung war es daher, den direkten Einfluss peripherer Schilddrüsenhormone auf eine BAT-Aktivierung nachzuweisen.
Methodik: Es wurden je 3 hyper-, hypo- und euthyreote Black 6-Mäuse mit F-18-FDG im Kleintier PET/MRT (nanoScan®, Mediso) untersucht (i.p-Injektion; ID:15Mbq; Raumtemperatur). Mittels MR-basierter VOI-Analyse (PMOD vers. 3.3) typischer Regionen von braunem Fettgewebe (nuchal) wurde die Glukoseaufnahme (SUV_{mean}) bestimmt, um Rückschlüsse auf eine mögliche BAT-Aktivierung ziehen zu können.
Ergebnisse: Im SUV_{mean}-Vergleich zeigten die hyperthyreoten Tiere eine bereits visuell erfassbare, FDG-Mehranreicherung gegenüber der euthyreoten Kontrollgruppe (8,61±2,05 vs 6,04±0,52; p=0,16; MV±SD) in den untersuchten Körperregionen. In den hypothyreoten Mäusen konnte ein verminderter FDG-Uptake beobachtet werden (SUV_{mean}=3,2±0,04; p<0,002; MV±SD).
Schlussfolgerung: Unsere Ergebnisse bestätigen einen thyrogenen Einfluss auf die murine BAT-Aktivität. Es konnte gezeigt werden, dass eine Hypothyreose eine verminderte BAT-Aktivierung bewirkt, eine Hyperthyreose eine BAT-Stimulierung zur Folge hat. Inwieweit sich diese Ergebnisse auch im Menschen nachweisen lassen, soll gegenwärtig eine prospektive Studie zeigen.

Funding: ifb

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POSTER 174

Beneficial effects of epigallocatechin gallate from green tea in a rat model of chronic rheumatoid arthritis

Immunology and Infectiology

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Tumor Targeting

About 1 % of the world population suffer from rheumatoid arthritis (RA), which is considered as the most prominent form of chronic inflammatory joint diseases. Hallmarks of RA are cartilage destruction, joint swelling and bone erosion. Whereas these parameters are comparatively well studied, the initial steps leading to RA are poorly understood. Since genetic factors are not an exclusive reason for the inflammation processes, environmental factors seem to account for the etiology of the disease as well.

The immunological response and inflammatory events occur in relapses during the course of RA. In these periods patients suffer the most from the previously mentioned symptoms. The current pharmacological therapy mainly consists of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and biological. All of these compounds suppress the inflammation and alleviate pain relief, but to date a complete remission is not possible. In our current study we test the most abundant catechin from green tea, epigallocatechin gallate (EGCG), in the rat model of Pristane-induced arthritis.

EGCG is known to modulate the activity of myeloperoxidase, an enzyme linked to the pathogenesis of rheumatoid arthritis. EGCG alleviated symptoms of rheumatoid arthritis in our study. The beneficial effect was comparable to that of the gold standard methotrexate. Therefore EGCG is a promising compound for the treatment of rheumatoid arthritis.

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POSTER 175

Progenitors of canine CD4+CD8+ double-positive (dp) T cells

Immunology and Infectiology

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In peripheral blood of dogs a small population of $CD4^+CD8^+$dp T cells exists. These cells have been shown to be $CD1a^-$ mature T cells utilising the TCRαβ. Moreover, by the low expression of CD62L and the expression of CD25 they have an activation related phenotype. After *in vitro* stimulation of peripheral blood mononuclear cells (PBMC) the $CD4^+CD8^+$dp T cell fraction increases, which raises the question about its origin. We identified $CD4^+$ T cells as a progenitor: Stimulation of highly purified $CD4^+$ T cells, in the presence or absence of antigen presenting cells, leads to the generation of $CD4^+CD8^+$dp T cells. However, via cell tracing experiments we also detected that in stimulated PBMC $CD8^+$ T cells can become $CD4^+CD8^+$dp.

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POSTER 176

Different doses of Granulocyte colony-stimulating factor do not impact the infiltration of polymorphonuclear neutrophils to experimental ischemic stroke

Immunology and Infectiology

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Tumor Targeting

Granulocyte-Colony stimulating factor (G-CSF) showed neuroprotective and -regenerative properties in numerous rodent stroke studies. Being tested in a multicenter randomized clinical trial G-CSF failed to improve outcome in stroke patients. Significantly lower dosages were administered in preclinical trials, so that non-allometric dose rendering may have hampered the translational success of G-CSF.

Stroke was induced in mice by 45 minutes of transient middle cerebral artery occlusion (MCAO). G-CSF was delivered as 50μg/kg and 832.5μg/kg body weight, controlled by vehicle injection, sham-operated and healthy animals, sacrificed 24 h after stroke induction. Leukocyte and neutrophil counts were assessed in blood and brain by multidimensional flow cytometry. Immunhistochemical analysis was performed to study the spatial distribution of granulocytes in brain sections.

The surgical procedure itself caused a significant mobilization of neutrophils to the peripheral blood. Flow cytometry revealed an increase of $CD45^{high}$ leukocytes in the ischemic hemisphere of mice treated with G-CSF high dose. The amount of infiltrating neutrophils and their spatial distribution in G-CSF-treated mice did not differ from controls.

In conclusion, G-CSF treatment did not change the infiltration of polymorphonuclear neutrophils to the ischemic brain. Moreover, the amount of circulating granulocytes was similar in all operated groups indicating that surgical stress mobilizes the cells within the first 24 hours. G-CSF high dose treatment increased numbers of $CD45^{high}$ leukocytes thereby potentially implying an influence of G-CSF on other immune cells.

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POSTER 177

Analysis of the Human Antigen-Specific Antibody Repertoir in Memory B-Cells

Immunology and Infectiology

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Tumor Targeting

Background: Sequences analysis of the antibody repertoire of a certain antigen such as viral protein gives us a better understanding of the human humoral immune system. This is very important for the development of effective vaccines and therapeutic antibodies. We have developed a method to produce and analyze the influenza virus nucleoprotein (NP)-specific antibody repertoire from memory B-cells.

Method: Influenza virus NP-specific memory B-cells were enriched from healthy donors by using NP-coupled magnetic beads. After six days of a polyclonal activation purity and specificity of enriched cells were examined with ELISpot. Single cell RT-PCR was applied to amplify the variable region of the IgG heavy and light chain and sequences were cloned separately in an expression plasmid. The sequences were analyzed online using the IMGT/HighV-QUEST software. We have also produced NP-specific antibodies in 293T cells.

Result: The purity of the isolated NP-specific memory B-cell was very high. The repertoire of NP-specific antibody shows a high combinatorial und junctional diversity. The monoclonal antibodies recognized linear and conformational epitope. The paratopes were also diverse suggesting that they recognized different epitopes.

Conclusion: Enrichment and activation of NP-specific memory B-cell together with single cell RT-PCR can be used to analyze the NP-specific antibody repertoire and to produce human monoclonal NP-specific antibodies. This method should be applicable to other viral antigens and can be used to characterize the formation of the memory B-cell response to infection and vaccination.

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POSTER 178

Influence of nanoparticle based transfection methods on t-cell proliferation

Immunology and Infectiology

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Tumor Targeting

T-cells are an important part of the cellular adaptive immune system. They are also an interesting target for gene therapy, as activation of the T-cell receptor complex (TCR) relies on a distinct set of genes. Inhibition of these genes by gene therapy might provide a new tool for immunosuppression.
We studied whether nanoparticle-based transient transfection methods influenced T-cell function, especially proliferation.
For transfection, nanoparticles based on polycations (e.g. polyethylenimin), liposomes and magnetic beads were employed. We transfected nonsense siRNA or antisense oligonucleotide as well as anti-CD4 or anti-CD28 oligonucleotides.
We analyzed proliferation of transfected and stimulated human PBMCs and murine spleen cells by lymphocyte transformation test. We determined the influence of the nanoparticles on the cell cycle by an anti-BrdU/7-AAD flow cytometry and performed RT-PCR for proliferation marker genes.
We detected an increase in proliferation of PBMCs by prolonged contact (>24h), especially with polycationic particles. We also detected inhibition of proliferation by transfection agents containing magnetic particles. This effect concurred with a temporary (3-6d) arrest of cell cycle and decrease of proliferation marker genes. This effect might be due to the influence of endosomal nanoparticle uptake on membrane integrity and mitosis. Furthermore, aCD4 and aCD28 oligonucleotides proved to reduce proliferation of transfected human and murine T-cells. Thus, anti-TCR gene therapy might provide a new tool for suppression of pathological immune response.

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POSTER 179

Cryptococcus neoformans-related Immune Reconstitution Inflammatory Syndrome (IRIS): Analysis of pathomechanisms in a mouse model

Immunology and Infectiology

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Tumor Targeting

Cryptococcus neoformans is an opportunistic fungal pathogen that can cause fatal meningitis in the context of immunosuppression such as HIV infection. The main goal of antiretroviral therapy (ART) is to restore protective immunity in HIV-infected patients. Indeed, ART has led to a significant decline in the incidence of AIDS-associated opportunistic infections. However, the clinical management of the HIV pandemic is considerably complicated by the fact that following ART initiation a significant proportion of HIV patients co-infected with *C. neoformans* paradoxically develops a life-threatening immune reconstitution inflammatory syndrome (IRIS). The underlying mechanisms are poorly understood.

Thus, we recently established a mouse model of cryptococcal IRIS based on lymphocyte-deficient mice which are immune-reconstituted by adoptive transfer of purified wild-type T helper cells six weeks after low-dose infection with *C. neoformans* strain 1841.

Adoptive transfer of naïve T helper cells into *C. neoformans*-infected RAG-$1^{-/-}$ mice is sufficient to induce IRIS. Characteristical multi-organ inflammation is accompanied by a systemic release of pro-inflammatory cytokines such as interferon (IFN)-γ and interleukin (IL)-6. The donor T helper cells acquire an effector phenotype. Furthermore, activated macrophages of the recipients are involved in the exaggerated inflammatory response that finally results in wasting of mice.

Analysis of this novel mouse model provides insights in the pathomechanisms of cryptococcal IRIS and reveals potential cellular and molecular targets for diagnosis and therapeutic interventions.

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POSTER 180

Production of recombinant HAV-VP3-VP1 fusion protein for the analysis of the human HAV-specific memory B-cell repertoire

Immunology and Infectiology

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Tumor Targeting

Only little is known about the diversity of the human memory B-cell repertoire specific for a viral antigen. To analyze this further, recombinant hepatitis A virus (HAV) capsid proteins VP3 and VP1 were produced, with the aim to isolate and characterize HAV-specific memory B-cells.
The VP3-VP1 coding sequence was cloned C-terminally within the open reading frame of the maltose binding protein (MBP) in a modified pMALc2x-vector. After expression of the fusion protein in *E. coli*, the formed inclusion bodies were purified and solubilized. Finally, denatured MBP-HAV-VP3-VP1 was refolded and affinity purified by amylose to obtain its soluble native form. Antigenicity was determined through reactivity of human serum with the fusion protein in ELISA.
It was shown that soluble fusion protein can be recovered from inclusion bodies successfully. The results in ELISA demonstrate the ability of the protein to react with antibodies in HAV-positive serum. In addition, the modified cloning vector enabled the *in vitro* biotinylation of the protein during expression.
Recombinant MBP-HAV-VP3-VP1 could therefore be suitable for the isolation of HAV-specific memory B-cells. However, the results in ELISA should be confirmed also by Western blot.

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POSTER 181 **Azithromycin for the Treatment of Acute Pancreatitis**

Immunology and Infectiology

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Tumor Targeting

Introduction: Acute pancreatitis (AP) is an inflammation of the pancreas caused by gallstones or alcohol abuse. Most disease courses are mild but in 30% severe AP occurs. Overall mortality of AP still reaches 5-10%. This fatal outcome is linked to the development of SIRS and accompanied by an inflammatory lung injury. No curative treatment exists. Macrolide antibiotics such as Azithromycin (AZM), have immune-modifying properties apart from their bactericidal activity. They inhibit the inflammatory neutrophilic response and are established as a treatment of lung disease such as COPD.
Objective: We hypothesized that the immune-modifying properties of AZM can decrease the inflammatory lung injury in a mouse model of AP.
Methods: Experimental AP was induced by i.p. injection of caerulein in mice. Mice were treated with AZM, amoxicillin or saline 2h after the first caerulein injection. Plasma amylase levels confirmed AP induction. Severity of AP and lung injury were assessed by histology.
Results: Initial experiments showed a reduction of lung infiltration in mice treated with AZM as compared to controls. However, when repeated with a larger number of animals, lung infiltration could not be stably reproduced, despite proper induction of AP.
Discussion: At this point, we cannot prove or disprove that AZM can decrease the inflammatory lung injury in AP and alter the course of disease. This is based on a lack of a reproducible lung injury. In a recently published modified protocol of the Caerulein induction, lung infiltration can be induced more reliably. Further experiments will be carried out in order to test our hypothesis.

Funding: formel1

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POSTER 182

Prevention of Graft-versus-Host-Disease with preserved Graft-versus-Leukemia-Effect by ex vivo modulation of CD4+ T-cells

Immunology and Infectiology

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Tumor Targeting

Introduction: Stem cell transplantation (HSCT) is the only curative treatment of leukemia. Common immunosuppressive drugs increase the risk for tumor relapses and infectious diseases. The influence of $CD4^+$ T-cells responsible for development of acute GvHD and for Graft-versus-Leukemia effect (GvL) can be modulated by administration of anti-human CD4 antibodies. Methods: A full mismatch transplantation model was developed by using transgeneic C57Bl/6 mice ($hCD4^+$, $mCD4^-$, HLA-$DR3^+$, TTG) as donors and Balb/c mice as recipients. Furthermore, murine P815-Balb/c leukemia mice were developed by co-transplantation of P815 leukemic cells to study the GvL effect. Survival, GvHD score, leukocyte subset and chimerism were analyzed for 60 days. Distribution of donor TTG cells in recipient mice was confirmed by flow cytometry. Results: The survival rate of recipients receiving an anti-human CD4 antibody incubated graft of $2x10^7$ BM+$2x10^7$ splenocytes + $5x10^3$ P815 cells was significantly higher (70%) compared to control mice (0%, P=0.001, n=10). Stable engraftment of donor cells (huCD4, HLA-DR) and a decrease of murine CD4 indicated a full TTG-donor hematopoiesis. $P815^{GFP}$ cells could only be detected in liver and spleen of control group without HSCT at day 12, whereas no $P815^{GFP}$ cells could be detected in transplanted groups indicating a GvL effect of the graft. Conclusion: We could show that an epitope-specific *ex vivo* modulation of an allogeneic hematopoietic stem cell graft by anti-human CD4 antibodies simultaneously preserves the GvL effect of the graft and the long-term suppression of the GvHD in this model.

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POSTER 183 **Phenotype of CD11c (dendritic) cells within the CNS**

Immunology and Infectiology

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Tumor Targeting

The brain's immune privilege has been attributed to the lack of dendritic cells (DC) within its parenchyma and the adjacent meninges implying maintenance of antigens rather than their presentation in lymphoid organs. Using mice in which the cd11c (itgax) promoter is coupled to gfp, we identified cells expressing this DC marker juxtavascularly and demonstrated their origin from bone marrow and local microglia. We now compared phenotypically this population to $CD11c^+/CD45^+$ double-positive cells from lung, liver and spleen in healthy mice using 7-color flow cytometry. We found unique, site-specific expression patterns of F4/80, CD80, CD86, CX3CR1, CCR2, FLT3 and MHC-II. 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. Most importantly, compared to spleen and liver, $CD11c^+$ microglia from the brain almost completely lacked MHC-II expression and $CD45^{high}/CD11c^+$ cells from the brain have a lower percentage of $MHC\text{-}II^+$ cells. In order to test whether phenotypical differences are fixed by origin or dynamically driven by local cues, we transplanted microglia on organotypic spleen slice cultures and –vice versa- splenocytes on brain slices. We can show that adaption and ramification of $MHC\text{-}II^+$ splenocytes is paralleled by down-regulation of MHC-II. Thus, at least in part, tissue-derived cues seem to locally adopt antigen-presenting cells according to local needs.
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POSTER 184

Superagonistic anti-CD28 monoclonal antibody induces cytokine response in slice cultures of human tonsils

Immunology and Infectiology

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Tumor Targeting

First-time delivery of the superagonistic anti-CD28 monoclonal antibody (TGN1412) caused severe toxic shock syndrome in all six study participants, also known as the "London tragedy". Rodents as well as primates tolerated TGN1412, highlighting the importance of species differences and the value of a of human tissue test system to predict and evaluate novel biologicals. Here, we used tonsil ectomy derived tissue to establish slice cultures and to investigate differences of blood derived and tonsil derived mononuclear cells (MC) after TGN1412 stimulation. Augmented T cell proliferation and cytokine production (IL-17, TNF-a, IFN-g) was induced in tonsil slice cultures by TGN1412, similar to reactions observed in the six study volunteers. However, blood derived MC obtained from the same donor showed no response to TGN1412 treatment. We could further clarify that TGN1412 together with B lymphocytes (low affinity FcgRIIB) stimulated CD3 positive T cell reactivity, whereas monocytes expressing the high affinity FcgRIII CD64 were less potent enhance T cell reactivity. Immunhistochemistry of tonsil derived slice cultures demonstrated an enhanced T cell population in the the germial zone. The obtained results demonstrate that tonsillectomy derived slice cultures serve as an adequate model to study the effect of novel biological drugs and therewith to predict potential risks for clinical studies.

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POSTER 185 **Identification of allergy-related epitopes of soybean**

Immunology and Infectiology

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Tumor Targeting

Food allergies have become of significant medical and legal concern worldwide. The most common foods implicated allergies include cow milk, wheat, egg, soy, peanut, tree nuts such as walnuts, hazelnuts, almonds, cashews, pecans, and pistachios, fish and shellfish. Soy as one of the ordinary food linked allergies affects up to 0.4% of German population. Many soybean proteins and several peptide epitopes are known to trigger allergy. A detailed characterization of the peptide sequences on the amino acid level has not been carried out so far. One aim of the project is the identification of the allergy relevant epitopes of soybean.
Peptide phage display technologies have been developed in our laboratory to investigate the immunome of patients. Several sera from persons with soy allergy were challenged with peptide phage display. The up to 10^6 sequences obtained per serum and library have been sequenced with Next Generation Sequencing (NGS). These were searched for epitopes by comparison with the known proteins of soy beans. So far we have identified details of several epitopes which were roughly described in the literature and many new epitopes. Found epitopes have been synthesized as peptides. They are now investigated for their ability to capture antibodies from patient's sera and isotype determination of the antibodies. The method can be generally used for recognized by complete sera of epitopes or other patterns.

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POSTER 186

How Functional Are Human Immune Cells Developed In Mice

Immunology and Infectiology

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Tumor Targeting

Animal models are a usefull tool to study pathomechanisms and therapeutic targets in biomedical research. In the last decade the investigation of humanized mouse models became important in immunological research. The existence of human immune cells in mice allows the bridging of interspecies issues, which for example have an influence on the effect of therapeutic agents.
As there are different humanized mouse models it is important to mention that we work with a model that uses the NSG mouse as host for umbilical cord blood derived stem cells. After CD34+ separation with a magnetic bead based method, we inject the cells into irradiated, newborn mice. Then, 10 weeks after transplantation we check the engraftment.
A main issue for verifying the existence of human immune cells in these mice is flow cytometry. Not only phenotypic characteristics of human cells can be detected, but also activation markers that emphasize the functionality of these cells can be seen.
Here, we show examples for flow cytometric analysis in humanized mice within different organs and with different cell surface markers as well as cytokine measures by cytometric bead array and the identification of activation markers after stimulation.
With this poster presentation we want to highlight the importance of flow cytometry for the humanized mouse but also that it is possible to detect nearly every cell population known in humans in these mice.

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POSTER 187 **Development of a Bovinized NSG Mouse**

Immunology and Infectiology

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The aim of this project is the development of a bovinized mouse, a mouse which features functional cells of the immune system of cattle.

The individual steps of this project are based on the methods for creating humanized NSG mice, which are established since 2005. Due to the short length of the umbilical cord of cattle, umbilical cord blood is obtained during caesarean section and collected in EDTA tubes. For isolation of the PBMCs (*peripheral blood mononuclear cells*) density gradient centrifugation is carried out. With a self-generated medium PBMCs could be obtained, counted and frozen at –80°C. Antibodies against bovine molecules are rare but mandatory. Therefore the methods described below are not carried out yet reproducibly.

Cells are thawed and the CD34-positive hematopoietic stem cells are enriched with a magnet-based method.

CD34 positive sorted cells are then transplanted into the liver of irradiated newborn NSG mice. After 10 weeks retrobulbar blood is taken and analyzed by flow cytometric measurements in terms of the development and functionality of cells of the bovine immune system.

The success in developing bovinized mice will be a promising tool for the investigation of the bovine immune system and the pathogenesis of various infectious diseases. Furthermore the model will be useful to comprehend the hematopoiesis of cattle. Cattle as experimental animals are associated with high costs and considerable effort regarding the handling and housing. Mouse models would facilitate research in terms of improved practicability and standardization and thus represent a worthwhile and promising instrument.

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POSTER 188

Detection of Hepatitis B (HB) specific memory B cells in vaccinated humans and production of biotinylated Hepatitis B surface antigen (HBsAg) for isolation of specific B cells

Immunology and Infectiology

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Background: The aim of the study is to isolate HBs specific memory B cells for analyzing the variable regions of the antibodies against the HBs antigen. In a first step, we detected specific memory B cells. For further isolation of the specific cells, we produced a biotinylated HBs antigen.
Method: The memory B-cells were isolated with immunomagnetic beads from PBMC´s of suitable individuals. Cells were activated for 6 days with IL-2 and specific B cells were detected with HBs antigen in ELISpot. HBs protein was biotinylated with Sulfo-NHS-LC-Biotin (Thermo Scientific).
Results: Specific HBs B-cells were detected with a frequency of 2,71 %, determined by ELISpot. The successful biotinylation of the HBs could be determined by western blot with anti-biotin antibody and human-serum.
Outlook: Further steps are the isolation of HBs specific B-cells, human antibodies from these cells and the characterization antibodies. This may lead to better understanding of the immune response to the Hepatitis-B-virus infection.

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POSTER 189

Towards a novel therapeutic approach in hematopoietic stem cell transplantation: Umbilical cord derived mesenchymal stromal cells to both improve engraftment while decreasing the severity of Graft-versus-Host-Disease

Immunology and Infectiology

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New therapies involve mesenchymal stromal cells (MSC) as a treatment to decrease Graft-versus-Host-Disease (GvHD). MSCs exhibit unique immune-modulating features and can escape the host's immune system. Bone marrow stem cells (BM) loose stem cell and engraftment potential after short cultivation time. Umbilical cord derived MSCs (UC-MSC) show long-term stem cell potential as well as immunomodulatory effects and are candidates for improving engraftment of hematopoietic stem cells as well as for prevention or treatment of GvHD. Novel *in vitro* and *in vivo* GvHD models using umbilical cord blood derived mononuclear cells (UCB-MNC) were set up. Mixed lymphocyte reactions (MLR) were used to induce an inter cord blood immune reaction that could be dimmed by UC-MSC. An acute GvHD in NOD/SCID/IL2Rcγnull mice was induced by a titration of human UCB-MNC ($5x10^5$ to $1x10^7$, n=6). Survival, GvHD score, weight and white blood cell count were analyzed for 54 days. The contribution of human UCB-derived cells to the murine blood system and the establishment of GvHD were assured by flow cytometry and histology, respectively. Transplantation of $5x10^5$ human UCB-MNCs lead to a higher survival rate of 70% whereas transplantation of $1x10^7$ UCB-MNCs lead to death of all recipients within 20 days. Analysis showed signs of GvHD in gut and skin by histology and CD45/CD3-chimerism by FACS. Those *in vitro* and *in vivo* approaches allow studying immunosuppression of UC-MSC both in allogeneic or syngeneic settings. Additionally, these unique models enable us to test whether an engraftment of cotransplanted syngeneic UC-MSCs can dim local GvHD immune reaction.

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POSTER 190

Analysis of the antigen specific B-cell paratope repertoire diversity

Immunology and Infectiology

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The aim of vaccines is the induction of antigen specific B-cells resulting in the differentiation to antibody releasing plasma cells. Of special interest are the generated antibodies with neutralizing abilities. It is still unknown how many different antibody variants can be produced by an organism against a certain single protein. In the last decades,the priority of examinations regarding to this diversity was done indirectly by detecting the number of different antigen epitopes. However,the value of such epitope mappings is limited and will only provide a small insight into the diversity and variability of the antigen specific immune reaction within one and among different individuals. Therefore,a system for the analysis of the complete paratope sequences shall be established in a mouse model.
To determine such an antigen specific B-cell paratope repertoire the influenza nucleoprotein (NP) is used. In a former study we immunized five Balb/c mice with NP protein and used the sera for epitope mapping. In the new approach of the genetic analysis of the complete B-cell receptor repertoire antigen specific B-cells were isolated from a spleen cell suspension using paramagnetic beads. Antibody mRNA from a single cell is reverse transcribed,amplified,sequenced and inserted into an expression system. The specificity of the obtained antibody chain pairs were approved by cotransfection of 293T cells and the supernatant is analysis by antigen ELISA.
The epitope mapping reveals individual epitope pattern and in total six immune dominant NP epitopes in mice,but the complete B-cell receptor paratope diversity should be much larger.

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POSTER 191

HCV specific IgG+ memory B cells show strong clonal expansion after spontaneous clearance of an infection with HCV in a single source outbreak

Immunology and Infectiology

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Tumor Targeting

In most cases an infection with the Hepatitis C virus (HCV) leads to the development of chronic hepatitis C, whereas spontaneous viral clearance occurs in a smaller percentage of acutely infected individuals. It is unknown whether differences in antibody repertoire mediate the ability to spontaneously overcome the infection. To characterize differences in antibody response to HCV and to describe potentially neutralizing antibodies we isolated HCV-specific IgG+ memory B cells from peripheral blood of patients with chronic hepatitis C and patients with spontaneous viral clearance of a unique cohort that were infected in a single-source outbreak. The B cell receptor on the cell surface, representing the antigen specificity of each single B cell, was used to isolate single HCV-specific memory B cells by Fluorescence Activated Cell Sorting (FACS). A RT-PCR based approach was applied to monoclonally express antibodies from these single memory B cells *in vitro*. Sequence analysis of the amplified individual immunoglobulin chains showed higher numbers of somatic hypermutations as sign of affinity maturation as well as a biased VH repertoire in patients with spontaneous viral clearance. In 177 analysed antibodies of spontaneous resolvers, we identified 8% of clonally expanded sequences with at least a pair of antibodies showing the identical V(D)J rearrangement in heavy and light chain and shared somatic hypermutations. Expression of clonally expanded antibodies will provide insights to preferentially covered antibody binding sights and may as well offer new therapeutic options as infection prophylaxis by passive immunization.

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POSTER 192

Prenatal BBP exposure increases asthma severity in offspring possibly via epigenetic alterations

Immunology and Infectiology

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Tumor Targeting

Besides a genetic predisposition a strong contribution of environmental factors are reported to be responsible for the increase of allergic diseases in the last decades. In particular, a prenatal exposure or contact during early childhood seems to be relevant. First hints from epidemiological studies suggest that amongst others the omnipresent endocrine disruptor benzyl butyl phthalate (BBP) may be associated with the development of asthma and allergies.
Hence, the aim of the present study was to identify susceptible exposure periods to BBP for allergy development in a murine asthma model. Balb/c mice were exposed to BBP via drinking water for different time periods including prenatal, perinatal and exposure of adult animals. To induce an asthma phenotype, mice were sensitised to ovalbumin, followed by an intrapulmonary allergen challenge.
Exposure of adult animals to environmentally-relevant BBP concentrations had no effect on asthma development. However, prenatal and perinatal exposure to BBP increased asthma parameters in the adult mice. This asthma promoting effect of BBP was abolished, when mice offspring were treated additionally with the hypomethylating agent 5-aza-2′-deoxycytidine at the age of two to four weeks. Whole genome bisulfite sequencing of T cells from exposed mothers and offspring revealed that BBP exposure influenced the methylation of genes which might be responsible for the observed asthma promoting effect.
Thus, these results suggest that prenatal BBP exposure induces epigenetic changes which might increase the susceptibility for the development of allergic diseases in the next generation.

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POSTER 193 **The cribriform plate – an immunological battlefield?**

Immunology and Infectiology

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Tumor Targeting

Meningitis is listed among the top ten causes of death by infections worldwide. Neisseria meningitidis is the bacterium which is the major cause of the invasive form of this disease and it is estimated that up to 25% bear these bacteria in their nasopharyx. Typically, infection happens in large crowded locations, e.g. college dormitories, raising the question of why single individuals develop meningitis while the vast majority does not. We have shown that vesicular stomatitis virus (VSV) uses olfactory nerves to reach the bulb and have found emigrating immune cells from brain to nasal mucosa. Thus, the non-sterile nasal mucosa and the sterile subarachnoid space which are separated only by a few micrometers are permissive at least for virus and immune cells. As for bacteria, it is completely unclear at present, how progression from nose to brain is inhibited under normal conditions. We developed techniques to histologically analyze whole heads of animals such as the area where olfactory nerves penetrate the cribriform plate to reach to olfactory bulb. Strikingly, in animals not kept under specific pathogen free (spf) conditions, we found layers of macrophages beneath the olfactory bulb suggesting a continuous battle between potentially invading infectious agents and the immune system. Therefore, we hypothesized that genes required for proper immunity of the bulb are induced by the presence of infectious agents under non-spf conditions and compared transcription of mice kept under spf conditions with mice which are not, using state-of-the-art morphology and RNA deep sequencing.

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POSTER 194

Inflammasome activation differs in monocytes and macrophages under hypoxia

Immunology and Infectiology

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Monocytes are part of the innate immune system and are recruited to sites of inflammation, where they differentiate into macrophages. Monocytes encounter varying environmental conditions in the blood and the inflamed tissue, for example a decreased concentration of O_2 (hypoxia).
Aim of the study was to analyze the influence of hypoxia on LPS-induced cytokine production in monocytes and monocyte-derived macrophages.
Monocytes were immunomagnetically separated from the blood of healthy donors and macrophages were differentiated for 7 days. For hypoxia experiments, cells were stimulated 16h with 100ng/ml LPS under hypoxic conditions (1 % O_2).
IL-1β in the supernatant of LPS-primed monocytes was significantly increased under hypoxia (0.9ng/ml vs. 4.35ng/ml, p=0.0019). Similarly, the release of IL-6 was elevated (63.8ng/ml vs. 125.9ng/ml, p=0.019), but not the concentration of TNF. Monocyte-derived macrophages showed no increase in either of these cytokines under the same conditions.
Cleavage of the IL-1β proform is dependent on the assembly of the inflammasome and the recruitment and activation of caspase-1. When the assembly was blocked with high extracellular K^+ or by inhibiting intracellular Ca-signalling (BAPTA-AM), hypoxia-induced IL-1β release was abrogated. Hypoxia-induced IL-1β cleavage is dependent on the NLRP3 inflammasome and the ASC adaptor, which was shown with genetically deficient THP1 cells.
This study shows that hypoxia leads to the activation of the inflammasome, the recruitment of caspase-1 and the subsequent cleavage and of Interleukin-1β in human primary monocytes, but not in monocyte-derived macrophages.

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POSTER 195

Late differentiated CMV-specific CD8+ T cells have an impact on the disease score of RA-patients

Immunology and Infectiology

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Rheumatoid arthritis (RA) is a chronic autoimmune disease which is characterized by a dysregulated T cell homeostasis and an expansion of autoreactive T cells. These T cells lost CD28 molecule and express inhibitory receptor LIR-1. Furthermore, latent Cytomegalovirus (CMV) infection contributes to the expansion of CD28- T cells. Hence we were interested in the influence of CMV infection on the LIR-1 expression on peripheral T cells in RA patients.
Flow cytometry analysis revealed higher frequencies of LIR-1+ CD8+ T cells in CMV+ RA patients compared to CMV+ HD. Using HLA-A*0201/CMVpp65 dextramers we detected higher frequencies of CMV-specific CD8+ T cells in RA-patients (n=8; mean %: 3,28) compared to healthy individuals (n=12; mean%: 1,35, p=0.04). Phenotypically, LIR-1+CD8+ T cells belong to the senescent T cell pool which lost CD27 and CD28 and the expressed CD57. Analysis of the cytolytic potential revealed higher numbers of CD107a+CD8+ T cells in RA patients (n=3, mean%: 0,57) compared to healthy donors (n=3, mean%: 0,17), but a lower proliferative potential. Importantly, we found a significant correlation (p=0.034) of increased numbers of CD8+LIR-1+ T cells with a high disease activity score (DAS28) in RA patients (n=14, r=0,568). This is the first demonstration of significantly increased frequencies of LIR-1+CD8+ T cells and of CMV-specific CD8+ T cells in patients with rheumatoid arthritis. The higher cytolytic potential of CMV-specific T cells can be attributed to their function in containing latent CMV infection and to prevent CMV disease, but might potentially contribute to disease severity in RA patients.

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POSTER 196

Sequence analysis of hepatitis b virus (HBV) RNA as a method for monitoring the evolution of hbv variants in patients achieving undetectable hbv dna during antiviral treatment

Immunology and Infectiology

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Introduction: HBV variants can be assessed by sequencing of HBV DNA. However, during antiviral treatment of chronic hepatitis B, e.g. with Tenofovir (TDF), HBV DNA becomes undetectable in most patients whereas serum HBV RNA remains detectable in a significant number of them.
Aims: We aimed at developing a novel sequencing method based on HBV RNA to investigate the evolution of HBV variants in patients at high risk to develop drug resistance.
Methods: 20 patients (16 male, 4 female, 17 HBe Ag positive, HBV genotypes A, B, D, E in 3, 2, 14 and 1 patient) who received second or third line monotherapy with TDF 245 mg/d (mean duration 45±15 (21-77)months) were included. HBV DNA and RNA were quantified in 113 follow-up serum samples by real-time-PCR. The reverse transcriptase (rt) region was sequenced from HBV DNA or from HBV RNA after reverse transcription.
Results: Based on HBV DNA sequencing the rt-mutations L80V, V173L, L180M, M204I/V and N236T were found in 5, 2, 5, 8, and 2 patients at baseline and up to 12 months of follow-up. Sequencing of HBV RNA revealed that these variants persisted in 4, 2, 5, 7 and 2 cases for a mean duration of 24±11 (4-39) months. In 2 patients the HBV variant L80V+M204V newly emerged after 24 and 25 months. In 1 patient with pre-existing L80V+M204I mutation the variant V173L became detectable at month 37.
Conclusion: Sequencing of HBV RNA is a novel tool to follow up the evolution of HBV variants under effective HBV DNA suppression. The value of this method in clinical settings (e.g. development of resistance or variants associated with hepatocellular carcinoma) needs further investigation.

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POSTER 197

Epitope-specific modulation of the CD4 molecule on T helper cells by specific anti-human CD4 antibodies does not interfere with the Graft-versus-leukemia effect

Immunology and Infectiology

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Acute Graft-versus-Host-Disease (aGvHD) is one of the most severe complications associated with hematopoietic stem cell transplantation (HSCT). The effects of $CD4^+$ T-cells can be altered by administration of anti-human CD4 monoclonal antibodies. Such procedures should not interfere with the graft-vs.-leukemia effect (GvL). *In vitro* experiments were conducted, exposing P815 leukemic cells and $4T1^{GFP}$-luc2 murine breast cancer cells to bone marrow and spleen cells from $cd4^{-/-}$-C57Bl/6 mice transgenic for human CD4 and HLA-DR3 (triple transgenic mice, TTG). Furthermore, P815-Balb/c leukemia mice were developed by transplantation of $P815^{GFP}$ cells. Using flow cytometry, the vitality of the tumor and graft cells was analyzed for 4 days. The survival rate of P815 cells was similar when exposed to the CD4 antibody, with cell counts rising from 1.4 ± 0.1% to 34.6 ± 1.1% vs. 1.5 ± 0% to 37.2 ± 1% ($P = 0.303$). These results were congruent with those from the $4T1^{GFP}$-luc2 culture (9.7 ± 0.4% to 28 ± 0.8%, vs. 6.1 ± 0.2% to 24.2 ± 5%, $P = 0.633$). After transplantation of $1x10^6$ $P815^{GFP}$ in sublethally irradiated mice (3Gy), flow cytometry showed $P815^{GFP}$ cells in liver (day 4), bone marrow and spleen (day 6). $5x10^3$ $P815^{GFP}$ could not be detected within 6 days after application in 3Gy or not irradiated control mice. Liver and spleen of recipient mice showed an infiltration of P815 cells with tissue destruction. These results indicate that the CD4 antibody does not impair the GvL effect, thus enabling us to pursue further therapeutic strategies concerning aGvHD. P815-Balb/c leukemia mice could be used to study the GvL effect after HSCT *in vivo*.

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POSTER 198

The impact of polyunsaturated fatty acids on the membrane localization of TLR4 and CD14

Immunology and Infectiology

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Objectives: To investigate the modulating effects of polyunsaturated fatty acids (PUFA) on membrane receptor interactions in lipid rafts we determined the co-localization of the key LPS signaling receptors Toll-like receptor 4 (TLR4) and cluster of differentiation 14 (CD14) with the raft marker ganglioside GM1.

Material and Methods: RAW264.7 macrophages were supplemented for 72 h with 15 μM alpha-linolenic acid (LNA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), linoleic acid (LA) or arachidonic acid (AA) and subsequently stimulated for 24 h with either LPS or viable *Pseudomonas aeruginosa* (ATCC 10145, MOI 1). Receptor co-localization of TLR4-GM1 or CD14-GM1 was analyzed using fluorescence microscopy (BZ-9000, Keyence) and quantified using ImageJ software (National Institutes of Health, Bethesda, USA).

Results: PUFA supplementation of unstimulated macrophages enhanced the co-localization of TLR4 or CD14 with GM1. Co-localization also increased after stimulation of the RAW264.7 with LPS or *P. aeruginosa*. In contrast, PUFA enrichment of the macrophages completely abolished this stimulation effect, presumably due to the incorporation of the fatty acids into membrane rafts.

Conclusion: Our results indicate that PUFA of both the n-3 and the n-6 family effect protein-protein interactions in lipid rafts thereby attenuating co-localization of TLR4 and its co-receptor CD14. This protein displacement from rafts provides an explanation for the inhibitory effects of PUFA on inflammatory responses.

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POSTER 199

Modulation of the immune response via vagal Stimulation

Immunology and Infectiology

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Die schwere Sepsis wirft ungelöste Fragen im therapeutischen Management auf. Der hochdynamische Krankheitsverlauf ist mit einer hohen Mortalität belastet und stellt die behandelnden Ärzte vor Probleme, die pathognomonisch oder therapieassoziiert sind. Diesem Krankheitsbild liegt eine durch überproportionale Ausschüttung von Zytokinen hervorgerufene unkontrollierte inflammatorische Reaktion zugrunde, in deren Folge es zu Apoptose, Gerinnungsstörungen mit mikrovaskulären Thrombosierungen sowie einer generalisierten Vasodilatation mit inadäquater Perfusion und einer Kompromittierung der kardialen Inotropie kommt. Es resultiert die Dysfunktion oder das Versagen lebenswichtiger Organe und Organsysteme. Die Ausprägung von inflammatorischen Reaktionen wird erheblich von der sympathovagalen Balance des vegetativen Nervensystems determiniert. Die schwere Sepsis ist mit einer ausgeprägten vegetativen Dystonie assoziiert, welche den physiologischen Kontrollmechanismus der Zytokinliberierung, den vorab beschriebenen „cholinergic antiinflammatory pathway" derart beeinträchtigt, dass der Imbalance des autonomen Nervensystems selbst eine wichtige pathogenetische Rolle bei dieser schweren Erkrankung zukommt. In unserer Studie sollte an septischen Schweinen der Nachweis erbracht werden, dass sich durch eine transmurale gastrale Stimulation, eine afferente vagale Stimulation mit Reetablierung der Kontrolle der Zytokinliberierung erreichen lässt. Es konnte gezeigt werden, dass durch Impulse über eine modifizierte PEG-Sonde, eine Beinflussung der Zytokinfreisetzung möglich war.

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POSTER 200

TNFR1+ CD4+ T cells from patients with rheumatoid arthritis contribute to chronic synovitis

Immunology and Infectiology

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The infiltration of the synovial membrane by immune cells, in particular CD4+ T cells, is one hallmark of rheumatoid arthritis (RA). It has been shown previously that synovial membrane-infiltrating CD4+ T cells differ from non-infiltrating ones in their increased expression of TNFR1. Furthermore, TNFR1 is expressed on a fraction of circulating CD4+ T cells from RA patients, but not from healthy controls. Aim of the study was the characterization of TNFR1+ CD4+ T cells from RA patients.

Mononuclear cells were isolated from the peripheral blood of RA patients using density gradient centrifugation. Cells from the synovial tissue of RA patients were isolated using enzymatic digestion. Subsequently TNFR1+ CD4+ T cells were phenotypically analyzed by flow cytometry.

Peripheral TNFR1+ CD4+ T cells have neither a preferential naive nor a memory phenotype, but showed increased expression of the activation marker CD25, CD71 and CD154 compared to TNFR1- CD4+ T cells. TNFR1+ CD4+ T cells of the peripheral blood express higher frequencies of the Th1 and Th17 master transcription factors T-bet and ROR-γt, respectively, than TNFR1- CD4+ T cells. In addition, peripheral and synovial TNFR1+ CD4+ T cells express higher levels of IFN-γ and IL-17 than TNFR1- CD4+ T cells. Besides, TNFR1+ CD4+ T cells produce more TNF and GM-CSF than TNFR1- CD4+ T cells.

The results show that the TNFR1 expression characterizes a pathogenic subset of activated CD4+ T cells with Th1 and/or Th17 signature in RA patients. Through the production of proinflammatory cytokines TNFR1+ CD4+ T cells may contribute to the chronic synovitis in patients with RA.

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POSTER 201 **Regulatory T cells in pulmonary cryptococcosis**

Immunology and Infectiology

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The opportunistic fungal pathogen *Cryptococcus neoformans* can cause fatal meningitis during HIV infection, leading to more than 600.000 deaths every year in sub-Saharan Africa.
In general, regulatory T (Treg) cells play an important role in controlling immune responses and homeostasis. However, their functional role during fungal infection is largely unknown.
In our study, we aimed to investigate Treg cells that are involved during an immune response in an experimental mouse model of cryptococcal infection. Therefore, we performed a kinetic analysis of intranasally infected BALB/c mice with several time points of analysis up to 56 days post infection (dpi). Characterizing Treg cells by their CD4, CD25 and FoxP3 expression, we found an increase in the frequency of these cells from 5% in naïve animals up to 11% at 21 dpi that remained elevated until 56 dpi in the lung. Additionally we investigated the expression of neuropilin-1 (nrp-1), a marker for nTreg cells. A 2.5-fold increase of nrp-1+ nTreg cells in the lung until 21 dpi indicated that primarily nTreg cells are activated during the onset of pulmonary cryptococcosis. We also found that the production of the iTreg cell cytokine interleukin (IL)-10 is increased later during infection.
Based on our current data it is interesting to analyze the phenotypic consequences of depleting Treg cells during cryptococcosis using a "DEpletion of REGulatory T-cell" mouse model. This study will provide insights in the role of Treg cells during a fungal infection of great medical relevance.

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POSTER 202

LPS induced metabolic changes in human M1 and M2 macrophages

Immunology and Infectiology

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Exposure to different microenvironmental signals polarizes macrophages (MΦ) into the proinflammatory M1 or the antiinflammatory M2 phenotypes. Here we ask in how far metabolic reactions of the two subsets differ in response to LPS, a prototypical activator of cells that initiate inflammatory processes.

Monocytes were differentiated into M1 MΦ with 500 U/mL GM-CSF and M2 MΦ with 50 ng/mL M-CSF. Thus generated MΦ were incubated in the presence and absence of 100 ng/mL LPS. After different stimulation times following parameters were measured:

a) Cell viability
b) NAD/NADH concentrations
c) Expression of the NAD–producing enzyme Nicotinamide-phosphoribosyltransferase (Nampt)
d) Expression of the NAD-consuming enzymes CD38, SirT1 and SirT6
e) Expression of cell surface transporters Glut1 and CD36

We found that stimulation with LPS results in:

a) a decrease of the cell viability
b) a decrease in the intracellular NAD-concentrations which is more pronounced in M1 MΦ
c) an upregulation of NAMPT, especially in M1 MΦ
d) an increase of CD38 and SirT1/SirT6 expression on both subsets
e) a decrease of CD36 expression on both subsets and an increase of Glut1 on M2 MΦ

These data show, that the LPS induced modifications of metabolic activities vary between the two subsets, which may have functional consequences.

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POSTER 203

The effects of environmental factors on regulatory T-cells

Immunology and Infectiology

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Regulatory T-cells (T_{reg}) are pivotal to maintain self-tolerance and are central for the control of immune homeostasis. We aim to elucidate the effects of environmental chemical exposure by establishing two different approaches: The expansion of isolated and purified T_{reg} ($CD4^+$ $CD25^{hi}$ $CD45RA^+$) and the differentiation of naïve CD4+ T-cells ($CD4^+$ $FoxP3^-$) into T_{reg} ($CD4^+$ $CD25^+$ $FoxP3^+$).
Cells will be gained using isolated human PBMCs from buffy coats, magnetic depletion and, in the case of isolated Treg, subsequent purification via BD FACS Aria SORP. Differentiating and differentiated as well as expanded T_{reg} will be exposed to e.g. benzo[a] pyrene or kynurenine which bind the aryl hydrocarbon receptor (AhR), to focus on receptor mediated effects. Time-resolved analyses of mRNA- and protein-expression of crucial genes and proteins is monitored.
Both strategies will provide the basis for a mathematical model which will help us to get an extensive understanding of the impact of environmental chemicals on T_{reg}.

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POSTER 204

Phenotypic and Genotypic Approach to Utilizing Educts of Third Generation – Process Control Optimization for Volatile Substrates

Immunology and Infectiology

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Due to the depletion of fossil resources industry is highly motivated to strive for bio-based building blocks. Biomass or agrarian residues can be thermally converted into so-called third generation educts for biotechnology (e.g. syngas, hydrogen or methane). These gases can be conventionally used for energy generation, as energy carrier or, depending on the prevailing economic situation, for biosynthesis. By applying some elected bacterial species able to metabolize hydrogen and carbon dioxide, industry-relevantbuilding blocks such as different carbonic acids can be produced in a clean, environmentally friendly way. This task challenges the engineering sciences to develop new and robust monitoring tools and innovative process control strategies.

We decided on biocalorimetry as the method of choice to control the formation of biomass and to optimize the generation of the desired products. This rather rarely used technique can provide valuable assistance in monitoring cellular processes and impacting the course of a fermentation. The system is first tested with methanol, a volatile substrate, by employing the methylotrophic bacterium *Methylobacterium extorquens*. Using this microbial strain we are able to improve process control and lay the foundations for applying gaseous substrates.

In addition to calorimetry and fermentation techniques we also use molecular biological methods to modify the metabolic pathways of the named bacterial species. In doing so,´we could already demonstrate the formation of C4 building blocks out of the C1 compound methanol.

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POSTER 205

Impact of glycoxidation on PUFAs and eicosanoids in isolated human low density lipoprotein fractions

LIFE – Civilisation Diseases and Genetics

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Objectives: Modifications of low density lipoprotein (LDL) through oxidation and glycoxidation are known to be associated with the development of atherosclerosis. Only little information is available on the influence of oxidation and glycoxidation on the polyunsaturated fatty acid (PUFA) metabolism in human LDL. Here, we compared the time-dependent influence of glucose, fructose and ribose under oxidative conditions on isolated human LDL fractions investigating the composition of the omega-3 and omega-6 pathway.

Methods: Sequential flotation ultracentrifugation was applied for the isolation of LDL, which was stored up to 14 days at 37°C with or without sugar. 7 PUFAs and 94 eicosanoids were analyzed by ultra high performance liquid chromatography combined with tandem mass spectrometry on a 5500 QTrap instrument.

Results: Enzymatic and non-enzymatic eicosanoids as well as PUFAs were influenced by oxidation and glycoxidation in a time dependant manner. Both reactions resulted in the generation of the same panel of eicosanoids.Compared to oxidation, an increased generation of eicosanoids through glycoxidation was observed up to factor 4. Fructose and ribose were most effective compared to glucose. Additionally, the glycation power of the sugar was concentration dependant.

Conclusion: The enzymatic and non-enzymatic eicosanoid metabolism in LDL appears to be markedly influenced by glycation. The eicosanoid fingerprint did not differ between different glycation agents. Further investigation is required in order to identify the pathways involved in the production of eicosanoids in isolated LDL.

Funding: life

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POSTER 206

Effekte depressionsrelevanter Polymorphismen auf die Verarbeitung emotionaler Information

LIFE – Civilisation Diseases and Genetics

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Die Erblichkeit von Majorer Depression wird auf etwa 40% geschätzt. Die zugrundeliegenden Mechanismen, durch die depressionsrelevante Gene das Erkrankungsrisiko erhöhen, sind dabei weitestgehend ungeklärt. Depressiv Erkrankte unterscheiden sich in der Verarbeitung von emotionalen Informationen von Gesunden. Das Serotoninsystem ist ein Schwerpunkt genetischer Untersuchungen (Wong & Licino, 2001), da es bei der Regulierung von Emotionen involviert ist. Ein funktioneller Polymorphismus in der Promotorregion des Serotoninstransporter-Gens (5-HTTLPR) scheint beispielsweise mit der Entwicklung affektiver Störungen assoziiert zu sein. Weiterhin fanden sich Zusammenhänge zwischen dem Polymorphismus und negativen kognitiven Verzerrungen während der affektiven Informationsverarbeitung. Diesen negativen Verzerrungsmustern wird eine bedeutende Rolle bei der Entstehung und Aufrechterhaltung von affektiven Störungen zugeschrieben. In unserer Studie sollen die Einflüsse depressionsrelevanter Gene auf die Verarbeitung affektiver Informationen und den Schweregrad der Erkrankung beleuchtet werden. Hierfür werden 80 Patienten mit majorer Depression rekrutiert und im Magnetresonanztomographen untersucht.

Funding: life

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POSTER 207

Eager for action and no place to go. A functional DBH polymorphism is associated with the need for sensation and unstable vigilance during rest.

LIFE – Civilisation Diseases and Genetics

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According to the vigilance regulation model of affective disorders and ADHD (Hegerl & Hensch, in press), manic behavior can partly be explained as an autoregulatory attempt to stabilize vigilance among individuals, who exhibit rapid declines of physiological arousal during low environmental stimulation. Vigilance regulation is strongly influenced by the noradrenergic system. Norepinephrine is synthesized from dopamine by means of dopamine beta-hydroxylase (DBH). Importantly, DBH plasma levels have been found to be highly heritable and reduced in bipolar disorder. Thus, functional genetic variations within the DBH gene locus constitute putative determinants regarding both vigilance regulation and the emergence of hyperactive and sensation seeking behavior.
Recently, very low DBH plasma levels have been observed in carriers of two T alleles of the DBH polymorphism rs1611115. In addition, the T/T genotype has been shown to be linked with higher levels of impulsive and hostile behavior. On this background, we investigated whether T/T carriers are characterized by faster declines of vigilance when faced with a twenty-minute monotonous resting EEG paradigm. We further assessed personality traits related to the concept of manic behavior, i.e., need for sensation and avoidance of rest.
In line with our hypothesis, T/T carriers displayed faster declines of EEG-vigilance when compared to the C/C or C/T carriers. Moreover, consistent with the model of vigilance regulation, T/T carriers reported a higher need for sensation. In sum, our results provide novel evidence for rs1611115 as a molecular correlate of mania-related phenotypes.

Funding: life

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POSTER 208

Genome-wide analysis of the genetic regulation of the human transcriptome identifies novel regulators and corroborates the regulatory relevance of non-protein coding loci

LIFE – Civilisation Diseases and Genetics

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Tumor Targeting

Understanding the genetics of gene expression (eQTLs or expression QTLs) is a key to understand biological pathways and diseases. Therefore, we performed the largest single eQTL study so far studying 2112 individuals with suspected and diagnosed coronary artery diseases. Genetic variants and expression levels of genes were measured in whole-blood genome-wide applying microarray-based technology. We found that more than half of all genes were genetically regulated. Genetic variants that appear to regulate a gene were enriched up to a distance of 50 MB to the transcript. We found pathways related to immunity, metabolism, transcript-regulation, and cardio-vascular diseases enriched within regulated genes. We identified many novel regulatory hot-spots where a single genetic variant was associated with gene expression levels of multiple genes. These included genetic variants known to be relevant for Polycystic ovary syndrome, Ankylosing spondylitis, Asthma, Height, Cholesterol levels, Type 1 diabetes, Vitiligo, hematological phenotypes, Bipolar disorder and Schizophrenia. In contrast to locally acting SNPs (cis-acting SNPs), a considerable gap still existed between total heritability resulting from all trans-chromosomes and all identified trans-acting SNPs. Analysis of co-localized functional elements indicated a prominent role of long intergenic non-coding RNAs and pseudogenes. We found evidence of their potential functional relevance in a variety of phenotypes.
In summary, our study is a substantial improvement of the catalogue of human eQTLs with implications for various phenotypes and diseases.

Funding: life

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POSTER 209

Association of the ApoE genotype with auditory P3b

LIFE – Civilisation Diseases and Genetics

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Background: The apolipoprotein E encoding gene has three common variants. ApoE4 is associated with a significantly increased risk of dementia and various dementia endophenotypes, even in subjects without pathological findings. In contrast, ApoE2 seems to be associated with a reduced risk of developing the disease. The P3b is one of the most popular components in event-related potential research. It can be interpreted as an indicator of cognitive performance and psychopathological processes. In Alsheimer's disease and mild cognitive impairment, P3b latencies are extended and amplitudes are reduced. Preliminary studies showed longer latencies and partial lower amplitudes even in healthy E4 carriers. Former studies on healthy subjects regarding the relationship of ApoE and the P3b are limited by their small sample sizes and lack of consideration for confounding factors. Methods: In the LIFE Project EEG data from individuals aged 60-79 years were collected since March 2011. All subjects with undisturbed hearing were presented a novelty oddball paradigm to evoke late acoustic potentials. EEG data was analyzed according to recognized guidelines. The ApoE genotyping was performed by melting curve analysis for all data collected up until April 2013. Results: First results concerning the relationship of ApoE genotype with P3b amplitude and latency as well as behavioral measures are presented. Discussion: Starting from the previous findings it is expected that also healthy carriers of ApoE4 will have longer P3b latencies and longer Amplitudes as compared to E3/E3. This effect should be greater in E4/E4 carriers than in E3/E4 carriers.

Funding: life

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POSTER 210

Adipocytes and Breast Cancer cells: A new dynamic duo in epithelial-to-mesenchymal transition and progression of human breast tumor cells

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LIFE – Civilisation Diseases and Genetics

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The increasing number of obesity and its associated morbidities poses a great challenge on global health. Besides cardiovascular diseases new data point towards a link between obesity and different types of cancer. Recent studies demonstrate that obesity and excess accumulation of adipose tissue are independent negative prognostic factor for breast cancer. In addition, our preliminary data, as well as already published studies, indicate that tumor-associated adipocytes contribute to breast tumor invasiveness, among other mechanisms, by promoting epithelial-to-mesenchymal transition (EMT), a crucial step during cancer progression and metastasis. However, the molecular mechanisms by which breast cancer cells and surrounding adipocytes impact each other, remain elusive.

In our work, we investigate interactions between human breast tumor cells and adipocytes in two-dimensional and tree-dimensional tissue culture systems. Specifically, our work focuses on studying the molecular mechanisms triggering EMT and tumor progression of human breast cancer cells co-cultivated with adipocytes.

Funding: life

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POSTER 211

fcGENE: A versatile tool for processing and transforming SNP datasets

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LIFE – Civilisation Diseases and Genetics

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Tumor Targeting

Background: Modern analysis of high-dimensional SNP data requires a number of biometrical and statistical methods such as preprocessing, analysis of population structure, association analysis and genotype imputation. Software used for these purpose often use specific and incompatible input and output formats of data. Therefore multiple format conversions are necessary during analyses.
Methods: In order to support fast and efficient data management and computing summary statistics during SNP data analyses, we developed fcGENE using C++ object-oriented programming language. This software simplifies and automates the use of different existing GWA packages, especially the process of genotype imputation.
Results: fcGENE transforms SNP data including the imputation results into different formats necessary for GWA anaylsis. More precisely, fcGENE creates basic formats of SNP data required by commonly used tools for SNP data analysis such as PLINK, SNPTEST, HAPLOVIEW, EIGENSOFT, GenABEL and tools for genotype imputation such as MaCH, IMPUTE. fcGENE basically supports data management and summary statistics. The basic means of quality control on a SNP-wise and sample-wise level for both, raw and imputed genotype data can be performed through this tool.
Conclusions: We have developed a user-friendly open-source software fcGENE, which allows SNP data management, summary statistics and format conversion among different GWA software formats. This software generates templates of commands necessary to run diverse software packages and supplementary files providing information on basic procedures of quality control.

Funding: life

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POSTER 212

Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review

LIFE – Civilisation Diseases and Genetics

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Background: Minor depression (MinD) and mild cognitive impairment (MCI) are common disorders in late life that often coexist. The aim of the present review is to demonstrate prevalence rates of minor depression in older patients with and without MCI.
Methods: Electronic database searches were performed through Medline, ISI Web of Knowledge, Psycinfo, and Cochrane library. Two independent reviewers extracted the original studies based on inclusion criteria: representative study population aged 55 and older, diagnostics of MinD according to DSM. Data on prevalence rates, risk factors, comorbidity and health care usage was analysed.
Results: Point prevalence for MinD is higher in medical settings (median 14.4%) than in the community-based settings (median 10.4%) and primary care patients (median 7.7%). Although minor depression is rarely investigated in elderly persons with MCI, nearly 20% of patients with MCI seem to suffer from MinD. No data was found on the prevalence of MCI in patients with MinD. Risk factors associated with MinD include female gender, history of cerebrovascular diseases, generalized anxiety disorder, loneliness, and long-term institutional care.
Conclusions: Our review indicates that MinD is frequent in elderly population. MCI among those subjects has not been sufficiently investigated. Future studies based on clinical structured interviews should be performed in longitudinal design in order to differentiate late-life depression from progressive MCI or early manifestation of Alzheimer's disease.

Funding: life

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POSTER 213

Association of objective sleep phenotypes with neuropeptide S receptor genotype

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Introduction: The neuropeptide S receptor (NPSR1) and its ligand neuropeptide S (NPS) have received increased attention in the last few years. Both establish a previously unknown system of neuromodulation. According to several animal studies, NPS seems to be involved in arousal/wakefulness and may have a crucial role in sleep regulation. The single nucleotide polymorphism (SNP) rs324981 in NPSR1 has begun to shed light on a function of the NPS-system in human sleep regulation. The T-allele of rs324981 leads to an increased sensitivity of NPSR1. The current study, for the first time, aimed to investigate the association of the functional polymorphism rs324981 with an objective measure of sleep.
Methods: The study included n = 395 white subjects (62-79 years) with data available for the rs325981 genotype and the sleep phenotype. Subjects participated in an actigraphic assessment for objectively determining sleep duration, rest duration, sleep onset, rest onset and sleep onset latency. Genotyping of the SNP rs324981 was performed using the TaqMan OpenArray System.
Results: The SNP rs324981 had a significant effect on sleep- and rest duration ($p<0.01$). In detail, subjects with the homozygote T/T genotype showed a significantly decreased sleep and rest duration.
Discussion: The results of this study indicate that the sleep pattern in humans is influenced by the NPS-system. The current finding of decreased sleep duration in T/T allele carriers is in accordance with studies in rodents reporting similar results after NPS application.

Funding: life

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POSTER 214

Die Expansion von Artikulationsgipsen in Abhängigkeit von ihrer Verarbeitung

Clinical Sciences

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Einleitung: Die Expansion der Artikulationsgipse wirkt sich direkt auf die Passgenauigkeit des gefertigten Zahnersatzes aus. Eine Umfrage unter Leipziger Zahntechnikern ergab, dass nur 7 % Artikulationsgipse entsprechend den Herstellervorschriften (Abwiegen bzw. Abmessen der Komponenten, Anrühren unter Vakuum) verarbeiten. 93 % rühren manuell unter Atmosphärendruck nach Gefühl an. Der Einfluss der Arbeitsmethoden auf die Expansion soll untersucht werden.

Material und Methoden: Für fünf häufig eingesetzte Artikulationsgipse wurde die Expansion mit einem Extensometer nach DIN 6873 in Abhängigkeit von Wasser/Gips-Wert und Verarbeitungsbedingungen (manuelles Anrühren unter Atmosphärendruck, maschinelles Anrühren unter Vakuum) bestimmt. Der Bereich der W/G-Werte war durch die Verarbeitbarkeit gegeben.

60 Studenten dreier Studienjahre mischten den in Leipzig verwendeten Snow White Plaster No. 2® manuell nach Gefühl an. Der resultierende W/G-Wert wurde ermittelt.

Ergebnisse: Tendenziell ist die Expansion bei maschinellem Anrühren unter Vakuum geringer als bei manuellem. Erhöhte Wasserzugabe senkt die Expansion z. T. weiter. Die Expansion nach 2 Stunden ist meist geringer als diejenige nach 24 Stunden, ausgenommen Snow White Plaster No. 2®. Die geringste Expansion zeigte der moderne Artikulationsgips zero-arti®. Beim Anmischen nach Gefühl verwendeten die Studenten nur 53 % der vom Hersteller vorgeschriebenen Wassermenge, was die Expansion fast verdoppelt.

Schlussfolgerungen: Artikulationsgipse sind entsprechend der Herstellervorschrift zu verarbeiten. Moderne Gipse mit sogenannter Null-Expansion sind zu bevorzugen.

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POSTER 215

Visuelle Zahnfarbbestimmung trotz Farbsehschwäche? Ergebnisse eigener Untersuchungen

Clinical Sciences

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Einleitung: Die visuelle Zahnfarbbestimmung soll von farbtüchtigen Personen vorgenommen werden. Es gibt nur wenige widersprüchliche Studien zur Zahnfarbbestimmung durch Farbfehlsichtige. Dem gegenüber existieren Arbeiten, die Probanden mit Rot-Grün-Schwäche eine bessere Fähigkeit zur Farbdifferenzierung bei Khakifarben bescheinigen als Normalsichtigen, was auch in der militärischen Aufklärung genutzt wird.
Material und Methoden: Fünf männliche Probanden zwischen 19 und 26 Jahren, deren Rot-Grün-Schwäche durch den Ishihara-Test nachgewiesen war, wurden mit Farnsworth-15- und Lanthony-15-Test genauer untersucht. Anschließend wurde ihre Fähigkeit zur Farbdifferenzierung mit dem Farnsworth-Munsell-100-Hue-Test sowie dem PC-Programm ToothguideTrainer (TT) und der ToothguideTrainingBox (TTB – echte Mineralzähne) getestet. Ishihara-Test, TT und TTB sind Bestandteile eines von JAKSTAT entwickelten Curriculums Zahnfarbdifferenzierung, welches an diversen Universitäten international genutzt wird.
Ergebnisse: Der Grad der Farbfehlsichtigkeit und die Farbbereiche, in denen die Probanden Stärken bzw. Schwächen zeigten, waren unterschiedlich. Eine starke Rot-Grün-Schwäche bedeutete nicht zwingend schlechte Farbbestimmung. Eine Korrelation zwischen diagnostischen Tests und der Fähigkeit zur Farbdifferenzierung bestand im Rahmen dieser Untersuchung nicht.
Schlussfolgerungen: Die Ergebnisse können die widersprüchlichen Literaturangaben zur Zahnfarbbestimmung durch Farbfehlsichtige erklären. Ohne Prüfung sollte diese Tätigkeit farbtüchtigen Personen vorbehalten bleiben. Die Untersuchung einer größeren Probandenzahl wird angestrebt.

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POSTER 216

Adhäsionskräfte von Artikulationsgipsen an Typ 3 und Typ 4 Modellgips. Eine experimentelle Untersuchung mit einer neuen Methode

Clinical Sciences

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Artikulationsgips dient der sicheren Verankerung von zahnärztlichen Gipsmodellen im Kausimulator. Eine Norm zur Quantifizierung der Haftfähigkeit dieses speziellen Dentalgipses existiert bisher nicht. Ziel der Untersuchung ist es, Unterschiede zwischen Artikulationsgipsen bezüglich ihrer Adhäsion an Modellgipsen festzustellen und die entwickelte Methode zu bewerten. Zur Untersuchung wurden die Artikulationsgipse dentona® arti-base® 60, piccodent® A 50, AmannGirrbach Artifix® und Kerr™ Snow White Plaster No.2 an einen Typ 3 (dentona® dento dur® 110) und 4 Gips (dentona® sockel plaster® GT 160) gegossen. Die zylindrischen Prüfkörper enthielten zentrisch eingegossene Retentionen, die zur Verankerung in einer Universalprüfmaschine dienten. Prüfkörper aus Typ 3 und 4 Gips wurden vor dem Angießen des Artikulationsgipses 48 h getrocknet. Die Messung der Adhäsionskraft (in N) erfolgte mittels Zugversuch, 1 h nach der Erstarrung des Artikulationsgipses. Für jede Kombination wurden 10 Versuche durchgeführt. Die Datenauswertung erfolgte mittels t-Test bei unabhängigen Stichproben und Dunnett´s T3 Vergleichstest (α=0,05). Aus den ermittelten Werten konnte ein Ranking der Gipskombinationen erstellt werden (Max. 1950,77 N, Min. 495,97 N). Es zeigten sich signifikante Unterschiede zwischen einzelnen Paarungen aus Modell- und Artikulationsgips. Innerhalb der Kombinationen mit Typ 3 Gips ergaben sich signifikante Unterschiede. Ein Vorteil für die Verwendung des Typ 3 gegenüber Typ 4 Modellgips besteht nicht. Es zeigte sich, dass die neu entwickelte Methode für die Untersuchung der Haftfähigkeit von Artikulationsgipsen geeignet ist.

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POSTER 217

Entwicklung eines Trainingssimulators für den minimal invasiven Aortenklappenersatz

Clinical Sciences

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Die Herzchirurgie ist ein dynamisches Feld, das sich verschiedensten Herausforderungen stellen muss: zunehmend komplexe Operationen aufgrund des zunehmenden Patientenalters und zunehmender Nebenerkrankungen als auch die Entwicklung innovativer Verfahren. Die minimal invasive Chirurgie ist hier von besonderer Bedeutung. Die Komplexität der s.g. Schlüssellochchirurgie stellt besondere Anforderungen an die chirurgische Ausbildung. In diesem Zusammenhang wird in der Medizin zunehmend auf ein Training an Simulationssystemen zurückgegriffen.
Im Rahmen des Projektes soll ein chirurgisches Trainingssystem für den minimal invasiven Aortenklappenersatz entwickelt werden. Ziel ist ein lebensnahes s.g. Hybridsystem aus technischen Bauteilen, detailgetreuer Simulation des Torso und der Weichteile sowie einem Schweineherz als Basis zu entwickeln. An diesem Modell soll eine Aortenklappenimplantation realitätsnah durchgeführt werden.
Der Erfolg der simulierten OP wird durch Sensoren, Kameras sowie eine Dichteprüfung dargestellt, die einen objektiven Aufschluss über die Fertigkeiten des Operateurs geben. Im Rahmen einer intensiven Funktionsanalyse erfolgt in Zusammenarbeit mit den Ärzten des Herzzentrums Leipzig die Eignungsprüfung des ersten Prototypen. Ein besonderer Fokus liegt auf Erhebung von Daten zum Handling und des Lernerfolges. Die Evaluation eines weiterentwickelten Modells soll die tatsächliche Anwendbarkeit für die chirurgische Ausbildung zeigen. Der Simulator soll zukünftig in Kursen zur Anwendung kommen, damit er zur intensiven Auseinandersetzung insbesondere der grundlegenden herzchirurgischen Fähigkeiten beitragen kann.

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POSTER 218

Schweres stumpfes Thoraxtrauma (TT) mit Lungenkontusion in neuem tierexperimentellen Model beim Schwein – Die Auswirkungen lungenprotektiver Beatmung

Clinical Sciences

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Einführung: Posttraumatische Lungenkontusionen (LK) können akut zu inhomogenen Lungenschädigung führen. Dies limitiert die Einsetzbarkeit konventioneller Therapieansätze der maschinellen Beatmung (MB). Experimentelle Studien zum TT sind selten und die Schädigung meist unzureichend standardisiert. Ziel: Entwicklung eines standardisierten TT – Models mit realistischem Schädigungsmuster. Methoden: Bei 9 narkotisierten und beatmeten Schweinen wurde ein TT mit einseitiger LK provoziert, indem ein 10kg Gewichtaus 185cm Höhe auf die rechten Thoraxwand prallte. Anschließend wurden die Tiere 24h lungenprotektiv beatmet. Das umfangreiche Monitoring wurde durch Computertomographie und elektrische Impedanztomographie (EIT) der Lunge ergänzt. Ergebnisse: In 24h nach TT stiegen Körpertemperatur, Herzfrequenz sowie nichtbelüftete Lungenmasse signifikant. Der Gasaustausch (GA) in der Lunge blieb 8h stabil, verschlechterte sich jedoch danach progredient. Dies ist auf das vermutlich inflammatorisch bedingte, zeitverzögerte Sinken des Gefäßwiederstandes und der reduzierten hypoxisch pulmonalen Vasokonstriktionzurückzuführen. Die Belüftung in der rechten, direkt traumatisierten Lunge nahm sofort nach LK signifikant ab. Nach 24h sind durch zunehmenden Kollaps beide Lungen nahezu gleich schlecht belüftet. Zusammenfassung: Wir entwickelten ein standardisiertes TT-Model, welches Probleme des klinischen Trauma-Managements suffizient widerspiegelt. Die zeitlich verzögerte GA-störung und progrediente Inflammation stellen potentielles Zeitfenster frühzeitiger individueller Therapieansätze dar, welche an diesem Modell erforscht werden sollen.

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POSTER 219

Inflammatory serum parameters after cerebral ischaemia and their relationship to functional outcome – preliminary results of a prospective longitudinal observational study

Clinical Sciences

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Background: Inflammation due to cerebral ischaemia is known to promote tissue damage and regeneration. While preclinical studies identified mediators contributing to the inflammatory response (e.g. interleukin-6; IL-6), data on course and relevance of such markers under clinical conditions are rare. This study explores the long-term course of established serum markers and their relationship to functional outcome. Methods: Forty-seven patients suffering from transient ischaemic attack or stroke underwent blood sampling at hospital admission (day 0), days 3, 7, 30, 90 and 180 for measurement of leukocyte count (LEU), C-reactive protein (CRP), IL-6 and procalcitonin (PCT). Functional outcome was assessed by modified Rankin Scale (mRS) at 1 year, stratified for favourable (mRS=0/1) and unfavourable outcome (mRS>1). Results: LEU decreased from day 0 to 180 ($p<0.001$), while IL-6 numerically increased within the first week (n.s.), followed by a decline at day 30 ($p<0.05$ compared to baseline). CRP and PCT appeared to be unaltered during the first 6 months ($p=0.68$; $p=0.87$). After 1 year the mean mRS had decreased from 1.5 to 0.9 ($p<0.01$), with 83% of patients achieving a favourable outcome. Between outcome groups, serum markers only differed for PCT ($p<0.05$; higher values at day 180 associated with favourable outcome at 1 year). Change of LEU (day 0 to 3) was not associated with outcome. Conclusion: Our data indicate an opposite course of LEU and IL-6 early after cerebral ischaemia, which, however, was not associated with outcome. Further studies are needed to identify more specific inflammatory markers under clinical conditions.

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POSTER 220

Untersuchungen zur Abbindeexpansion von verschiedenen Artikulationsgipsen bei unterschiedlicher Lagerung

Clinical Sciences

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Einleitung: Durch das immer größer werdende Verständnis für die Komplexität zwischen Zahnersatz und stomatologischem System wird dem Artikulationsgips eine größere Rolle zugeschrieben als noch vor wenigen Jahren. Viele Forschungsgruppen beschäftigten sich schon mit den Veränderungen der Eigenschaften der Gipse durch die verschiedensten Einflüsse. Auch die Expansion war Bestandteil dieser Arbeiten. Keine Untersuchung hatte aber die Wirkung der Lagerung auf die Expansion von Artikulationsgipsen zum Thema.

Material und Methoden: Fünf verschiedene Gipse wurden für zwei Wochen unter drei verschiedenen Bedingungen gelagert. Hierbei gab es eine Lagerung im Kühlschrank (5±2 °C und 90±10% Luftfeuchtigkeit), unter Normbedingung (23±2 °C und 50±10% Luftfeuchtigkeit) und im Wärmeschrank (40±2 °C und 20±10% Luftfeuchtigkeit). Danach erfolgte die Expansionsmessung gemäß DIN EN ISO 6873 in einem Extensometer.

Ergebnisse: Eine falsche Lagerung hat einen Einfluss auf die Expansion. Die Lagerung im Wärmeschrank beeinflusst das Dimensionsverhalten signifikant, wohin gegen die Kühlschranklagerung kaum eine Veränderung hervorruft. Der Abdruckgips zeigt eine sehr große Expansion. Artikulationsgipse mit einer Nullexpansion reagieren gering auf die verschiedenen Bedingungen.

Schlussfolgerung: Eine Lagerung des Gipses im Kühlschrank zur Verbesserung der Eigenschaften kann nicht empfohlen werden. Die Gipslager sollten auch nie einer direkten Sonneneinstrahlung ausgesetzt werden. Abdruckgipse dürfen auf Grund ihrer hohen Expansion nicht mehr verwendet werden. Es empfiehlt sich die Verwendung von neuartigen Nullexpansionsgipsen.

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POSTER 221

Prosthetic head design influences the resistance against leverage effects and dislocation: an experimental THA study

Clinical Sciences

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Introduction: Available prosthetic heads differ with respect to their spherical sector, which is reduced particularly in large heads to potentially combine them with small stem sizes. The result is a loss of contact of the articulating surfaces near the impingement. The aim of this study was to investigate whether the reduction of the spherical sector of large prosthetic heads reduces the dislocation resistance and thus increases the risk of dislocation.
Methods: Two different prosthetic heads (d=44mm) were built (Head A sector 311°; Head B sector 196°) and connected with a bending moment sensor. The joint models were supplemented by modified prosthetic cups. Both components were hermetically sealed by a folded capsule made of rubber and containing 1ml of water. During the experiments both joint models were levered out. Acting leverage force and resulting dislocation were continuously measured. For comparison with conventional implants, a complementary study was made with six ceramic heads, calculating their spherical sectors (d=22–44 mm).
Results: The maximum forces when levering of the joint models were 30.9±0.07 N (head A) and 25.0±0.69 N (head B). The measurement of spherical sectors from the commercial prosthesis heads revealed 271° (d=22mm), 250° (d=28mm), 248° (d=32mm), 233° (d=36mm), 234° (d=40mm) and 228° (d=44mm).
Conclusion: The reduction of the spherical sector of the prosthetic heads decreases dislocation stability by 19%. The use of hip-balls with a maximized spherical sector increases the dislocation resistance and may reduce the risk of dislocation after THA additionally.

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POSTER 222

Resveratrol and desferoxamine protect human oxLDL-treated granulosa cell subtypes from degeneration

Clinical Sciences

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Obese women suffer from anovulation and infertility, which are driven by oxidative stress caused by increased levels of lipid peroxides and circulating oxidised low-density lipoprotein (oxLDL). OxLDL binds to lectin-like oxLDL receptor 1 (LOX-1), CD36, and toll-like receptor 4 (TLR4) and causes cell death in human granulosa cells (GCs). We tested in this study whether oxLDL-induced damage of human GC subtypes can be prevented by resveratrol (RES) and/or desferoxamine (DFO).

Granulosa cell cultures were treated with oxLDL alone or with RES or DFO under serum-free conditions for up to 36 h. Dead cells were determined by propidium iodide uptake, cleaved caspase-3 expression, and electron microscopy. Mitosis was detected by Ki-67 immunostaining. LOX-1, TLR4, CD36 and Hsp60 were examined by Western blots. Measurement of oxidative stress markers (8-iso-PGF_{2a}, advanced glycation end products, protein carbonyl-content) was conducted by ELISA-Kits.

Different subtypes of human GCs exposed to RES or DFO were protected as evidenced by lack of cell death, enhanced mitosis, reduced expression of LOX-1, TLR4, CD36, and Hsp-60, induction of protective autophagy, and reduction of oxidative stress markers. Importantly, RES could restore steroid-biosynthesis in cytokeratin-positive GCs which exhibited significant induction of steroidogenic acute regulatory protein. We demonstrate highly protective effects of both compounds rendering them potential drugs in the treatment of obese women or PCOS patients undergoing IVF-therapy.

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POSTER 223

Target sites for allosteric modulation of the human P2X7 receptor

Molecular Biology/Protein Biochemistry

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The ATP-gated P2X7 receptor is mainly expressed in leukocytes, microglia and astrocytes. The non-selective cation channel is a promising pharmacological target. Its involvement has been reported in several diseases, including osteoarthritis, neuropathic pain and psychosis. P2X7-mediated pathological processes may be influenced by pharmacological targeting, using agonists, antagonists and allosteric modulators.

Recent studies identified several modulators with potentiating and inhibitory effects (e.g. clemastine, perazines) on the hP2X7 receptor activity. To obtain more information about binding sites of allosteric modulators, we performed docking analyses, demonstrating a putative clemastine binding pocket in the upper vestibule of the receptor. Since the P2X4 receptor is known to be rather resistant to pharmacological modulation, we replaced amino acids 97-99, decorating the upper vestibule, in hP2X7 to the corresponding aa in hP2X4 receptor. The re-screen of $P2X7_{LQG\_97\text{-}99\_AQEE}$ ($P2X7_{97\text{-}99}$) revealed first hints of a putative binding site: known hP2X7 modulators (e.g. GW791343, tanshinone II sulfonate) lost their inhibitory effect in electrophysiological measurements and in fluorometric Ca^{2+} analysis. Consistently, utilizing a Yo-Pro-1 uptake assay, the $P2X7_{97\text{-}99}$ receptor pore dilatation was no longer inhibited.

However, positive modulators like clemastine still showed potentiating effects. Accordingly, this primary identified docking site seems not to be the target for potentiating molecules. Most likely, it may influence the gating property. Hence, the upper vestibule is a critical region for allosteric modulation.

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POSTER 224

Functional characterization of JMJD1c – a new candidate gene associated with plasma triglycerides and VLDL

Molecular Biology/Protein Biochemistry

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Objective: Disorders of lipid metabolism are a major risk factor for cardiovascular disease. Genome-wide association studies have revealed a novel locus for plasma VLDL and TG concentrations on chromosome 10q21.3 within the gene JMJD1c, a putative histone demethylase. The aim of our study was to conduct a basic molecular characterization of JMJD1c and to study the effects of JMJD1c on lipid metabolism.
Methods: To investigate JMJD1c expression and regulation, we performed expression analysis and stimulation experiments with various agents in cell lines. Expression analyses were carried out by RT-qPCR, western blotting and immunofluorescence staining. Further, plasmid-based small hairpin RNA (shRNA) against JMJD1c was used to establish two human hepatoma cell lines (HepG2) with stable JMJD1c knockdown. Effects of JMJD1c knockdown on gene expression were subsequently assayed by microarray analysis.
Results: JMJD1c expression responded to fasting-refeeding in metabolic tissues of mice and we also observed significant expression changes in HepG2 cells in response to insulin treatment. Micro Array analysis and subsequent RT-qPCR showed expression changes for several genes related to lipid- lipoprotein metabolism and cell differentiation processes in HepG2 cells with stable JMJD1c-knockdown.
Conclusion: Our initial studies demonstrate JMJD1c expression in metabolic tissues and response to metabolic stimuli in mice and in HepG2 cells. A knockdown of JMJD1c in HepG2 cells leads to expression changes of genes related to lipid metabolism. Ongoing studies will decipher the precise role of JMJD1c in lipid and lipoprotein metabolism.

Funding: life

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POSTER 225 **Construction and analysis of synthetic riboswitches**

Molecular Biology/Protein Biochemistry

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Riboswitches are RNA elements that are able to regulate gene expression without the need for a protein. They are often located in the 5′ UTR of prokaryotic mRNA and consist of two domains: the sensor or aptamer domain that is capable of high affinity-binding of a specific ligand and an expression platform that adopts a specific secondary structure. As these two domains overlap within the riboswitch sequence, binding of the ligand to the aptamer domain causes conformational changes within the expression platform, leading to gene activation or repression.

This modular layout of riboswitches allows for the construction of synthetic counterparts using aptamers for almost every molecule of interest as a ligand. Although aptamers can be easily selected by *in vitro* methods (e. g. SELEX), most synthetic riboswitches designed so far are based on the well-studied theophylline aptamer, as many other aptamers turned out to be not functional in riboswitches *in vivo*. We therefore use an *in silico* approach based on secondary structure prediction to generate new synthetic riboswitches. Our previous work resulted in a synthetic theophylline riboswitch consisting of the theophylline aptamer and an adjacent terminator structure, which is able to regulate transcription *in vivo*. To demonstrate the generality of this *in silico* method for any given aptamer, we analogously constructed synthetic streptomycin and tetracycline riboswitches.

Here, we present the first results of these new riboswitches and illustrate the importance of a distinct aptamer structure for riboswitch function *in vivo*.

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POSTER 226

Class II tRNA-Nucleotidyltransferases of Psychrophilic Bacteria

Molecular Biology/Protein Biochemistry

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During evolution, organism showed remarkable capabilities to adapt to cold habitats like oceans, polar and permafrost regions, representing the majority of the earth surface. In metabolic enzymes, such cold adaptations are often achieved by an increased flexibility of the protein structure. Using RNA polymerases, we focus on a different class of enzymes that was not investigated in psychrophilic organisms so far. The model polymerase enzyme is tRNA nucleotidyltransferase (CCA-adding enzyme), which synthesizes the specific sequence C-C-A at the 3'-end of tRNAs, where this triplet provides the position of aminoacylation. As our previous studies identified that even mesophilic CCA-adding enzymes carry highly flexible regions in their catalytic cores, we are now addressing the question as to whether the psychrophilic counterparts show a further increase in flexibility.

We cloned the cDNA sequences of two psychrophilic enzymes and compare the properties of the recombinant proteins to those of their mesophilic and thermophilic counterparts. As expected, the cold-adapted enzymes show a lowered optimal reaction temperature. Additionally, CD spectroscopy indicates that the unfolding properties of the enzymes match their activity temperature profiles. An initial analysis indicates that the polymerization reaction catalyzed by psychrophilic enzymes is more error-prone than expected. Obviously, this reduced fidelity in polymerization is the price to be paid for an adaptation to a cold environment. Further experiments are planned to identify individual enzyme regions responsible for this increased error rate during CCA incorporation.

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POSTER 227 **Selection of RNA aptamers with antibacterial potential**

Molecular Biology/Protein Biochemistry

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One third of the world population is infected with the pathogen *Mycobacterium tuberculosis*, which causes tuberculosis. On the cell surface of this bacterium, heparin-binding protein (HBHA) is expressed, mediating the adherence of the bacterium to the host cell. Pethe *et al.* could show that lysine-rich repeats, located in the C-terminal domain of HBHA, are essential for the adhesion to sulfated glycoconjugates on epithelia cells. For this reason, HBHA is an important protein in the pathogenesis of tuberculosis (Menozzi, 1996).

There is evidence that an increasing number of current tuberculosis strains is resistant to various common antibiotics. Therefore, new anti-tuberculosis drugs are needed. DNA- or RNA-aptamers represent potential molecules that became popular in the last 20 years as promising alternatives to antibodies. They are generally used as diagnostic tools or as therapeutic agents.

In this project, the *in vitro* selection method SELEX (*Systematic Evolution of Ligands by Exponential enrichment*) is performed to identify RNA aptamers binding to HBHA with high affinity and specificity. In the selection procedure, recombinant HBHA overexpressed in *E. coli* is used as target. After ten selection rounds, RNA sequences were isolated and the binding parameters were determined. Our results indicate that such RNA aptamers could serve as a potential drug against *Mycobacterium tuberculosis* Infections.

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POSTER 228

GPR133 – structure/function mutagenesis and physiology in mice

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The GPR133 belongs to the second largest group of G protein-coupled receptors (GPCR). With their extraordinary large N terminal domains with functional character the adhesion class GPCR are thought to play a role in immune response, cell adhesion, -differentiation and cancer development. The GPR133 is associated to human height and body weight in mice. As other members of the adhesion GPCR class GPR133 displays a complex and long N terminus, which contains an annotated functional domaine, the pentraxin (PTX) domain. Pentraxins, like C-reactive protein and long pentraxin 3, are immunological important proteins which mediate inflammation and immune response. The involvement of GPR133 in pancreatic cancer development, the high expression in follicle associated epithelia and in gastrointestinal stroma tumors in mice provide hints towards a functional relevance of this membrane-spanning protein in metabolic and immunological functions. To describe the physiological context in which GPR133 is required we will characterize a transgenic mouse model which is fully depleted of GPR133. However, in order to fully comprehend the physiology of this orphan receptor an understanding of the activation mechanisms and underlying molecular processes is essential. To gain inside into these complex mechanisms a structure/function analysis based on site-directed mutagenesis in human GPR133 was performed. For functional read-out established second messenger assays like cAMP accumulation or IP accumulation were used in which mutants were compared to wildtype (WT) receptor activity.

Funding: ifb

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POSTER 229

Genotyping bacterial and fungal pathogens using sequence variation in CCA-adding enzymes

Molecular Biology/Protein Biochemistry

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Tumor Targeting

Bacterial and fungal infections are one of the dominating global causes of death. Especially the generous use of antibiotics and reserve antibiotics in human and veterinary medicine leads to an increasing number of multiresistant microorganisms, raising misdiagnosis and complicated medical treatments. To achieve a more specific infection treatment, we are establishing a new diagnostic analysis tool for fast genotyping of bacterial and fungal pathogens.

This new diagnostic tool is based on a special feature of CCA-adding enzymes that play a major role in the maturation of tRNA 3' ends. Bacterial and fungal CCA-adding enzymes contain five conserved catalytic core motifs including a flexible loop region which regulates the substrate specificity of these enzymes. A special feature of this loop is a highly variable sequence composition that allows a simple distinction of very closely related organisms at the DNA level. Especially in the case of pathogenic bacterial/fungal species and subspecies, this loop sequence can be utilized as an efficient criterion for genotyping. Using a combination of specific and degenerated primers annealing to the loop region and to flanking motifs, the amplification of the DNA region encoding the flexible loop allows the identification of individual pathogens. To avoid the amplification of human sequences in the patient samples, highly specific blocking oligonucleotides were developed and successfully applied. With this strategy, we hope to develop a fast, reliable and cheap alternative procedure for the diagnostics of clinical relevant infectious diseases.

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POSTER 230

FLT3-ITD signaling induces oncogenic miR-155 by NF-κB and STAT5 pathways in acute myeloid leukemia thereby targeting transcription factor PU.1

Molecular Biology/Protein Biochemistry

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Almost 30% of all acute myeloid leukemias (AML) are associated with an internal tandem duplication (ITD) in the juxtamembrane domain of FLT3. Patients with FLT3-ITD mutation tend to have a poor prognosis. MicroRNAs (miRNAs) play a pivotal role in myeloid differentiation and leukemia. miR-155 was found to be upregulated in FLT3-ITD associated AMLs and to function as a prognostic factor. In this study, we discovered that FLT3-ITD signaling induces the oncogenic miR-155. Overexpression of FLT3-ITD enhances miR-155 expression, while FLT3-WT or FLT3-TKD did not. We could show *in vitro* and *in vivo* that miR-155 expression is regulated by FLT3-ITD downstream targets NF-κB and STAT5. Knockdown of STAT5 in a FLT3-ITD mouse model reduces miR-155 expression. Furthermore, we showed that NF-κB directly binds to the miR-155 promoter in a FLT3-ITD dependent manner. In luciferase assays we demonstrated that constitutively activated STAT5 reinforces NF-κB induced miR-155 promoter activity. The myeloid transcription factor PU.1 was shown to be downregulated in FLT3-ITD associated AML. Here, we could demonstrate that miR-155 directly targets PU.1. In functional analyses we found that miR-155 overexpression blocks myeloid differentiation. However, miR-155 depletion or overexpression of PU.1 inhibits proliferation and induces apoptosis of FLT3-ITD associated leukemic cells. These data identify a novel network in which FLT3-ITD signaling induces oncogenic miR-155 by NF-κB and STAT5 in acute myeloid leukemia thereby targeting transcription factor PU.1. Hence, we propose miR-155 as a novel therapeutic target in FLT3-ITD associated AMLs.

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POSTER 231

Exploring the substrate spectrum of the CCA-adding enzyme

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Molecular Biology/Protein Biochemistry

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As an essential mediator between genetic information and the amino acid sequence of the resulting proteins, tRNAs are charged with their cognate amino acids. The position of aminoacylation is the CCA triplet that is found at the 3'-end of every tRNA. Despite its functional importance, this sequence is not encoded in most tRNA genes and has to be added posttranscriptionally by a specialized polymerase, the CCA-adding enzyme. Although showing a high specificity for the cloverleaf-like tRNA structure, CCA-adding enzymes are known to accept several additional RNAs as substrates. In eukaryotes, the single CCA-adding enzyme has to deal with cytosolic as well as structurally less conserved mitochondrial tRNAs. In mitochondria of nematodes and arthropods, this situation comes to an extreme, as these organelles carry a great number of bizarre tRNAs lacking two arms of the cloverleaf structure (D-loop and T-loop). How these unusual tRNA transcripts are recognized as substrates by the CCA-adding enzyme is mystery, and the substrate requirements for CCA-addition are not understood. Using a chemically synthesized RNA pool of 36 nucleotides with randomized sequence, we want to investigate the substrate requirements for individual CCA-adding enzymes concerning sequence and structure of the transcripts, using high-throughput sequencing and computational analysis based on RNA structure prediction programs. Since subtypes of CCA-adding enzymes are using different mechanisms for CCA-addition, it will be interesting investigating the different structural constraints on their substrates.

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POSTER 232

Wnt-signaling gradients and their impact on liver parenchymal heterogeneity – a link to xenobiotic metabolism

Molecular Biology/Protein Biochemistry

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The functional heterogeneity and plasticity of the liver parenchyma is known as metabolic zonation. The morphogen signaling can control the homeostasis of metabolic zonation along the portocentral axis in liver. Wnt factors are of particular importance since they has been identified as the main determinant of liver parenchyma zonation. For instance, the deletion of APC (Adenomatous Polyposis Coli protein) leads to an activation of the wnt signaling pathway in the pericentral area of the lobuli and modify the balance between anabolic and catabolic functions. Ultimately we know little about Wnt signaling in xenobiotic metabolism.

The APC_{loxP}neo transgenic mice model was used to over-activate Wnt/ß-Catenin signaling in the liver. Hepatocytes from APC_{loxP}neo mice and periportal and pericentral hepatocytes of C57BL/6N mice were isolated. Afterwards we analyzed the most important wnt components with qRT-PCR technique. Using GC-MS we quantified the metabolite concentrations in the cell culture supernatant. With immunohistochemical, qRT-PCR techniques and enzymatic assays we also analyzed the distribution and expression of cytochrome P450 enzymes, transporters, the ß-catenin translocation and the glutamine synthetase expression in APC_{loxP}neo and control mice.

We could show that some important factors of the periportal and perizentral zonated components of the wnt signalling shifted to a more pericentral characteristic in hepatocytes of APC_{loxP}neo mice compared to APC wt mice. This includes the cytochrome P450 enzymes, *Cyp1a2*, *Cyp3a4* and *Cyp1a1*, involved in xenobiotic metabolism as a consequence of an over-active wnt signalling.

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POSTER 233 **The role of Repin1 in obesity**

Molecular Biology/Protein Biochemistry

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Replication initiator 1 (Repin1) is a polydactyl zinc finger protein organized in three clusters, located on human chromosome 7 and on chromosome 6 in mice. The protein of Repin1 is ubiquitous expressed but maximum mRNA levels were detected in liver and adipose tissue. Repin1 maps in a quantitative trait locus (QTL) which is associated with obesity and triglyceride levels. Therefore it has been suggested as a candidate gene for obesity and its related metabolic disorders in congenic and subcongenic rat strains. To dissect the role of Repin1 in adipose tissue we generated two different adipose tissue specific Repin1 deficient mice: a conditional (ARep1$^{-/-}$) and an inducible (iARep1$^{-/-}$) knockout of Repin1 to investigate the effects of early and late ablation of the gene. Both knockout models have been extensively phenotyped including body weight gain, determination of insulin and glucose tolerance, organ weight, fat cell size and lipid profile. For both knockout models, conditional and inducible, we obtained (I) reduced body weight in males, (II) decreased relative fat mass and a small fat cell size in males, (III) increased liver weight independently of sex (IV) decreased lipid values in males and (V) increased insulin tolerance independently of sex. (VI) Glucose tolerance was only improved in the inducible knockout model. In conclusion, those findings indicate that Repin1 plays a key role in adipogenesis and lipid metabolism. Furthermore, alterations of Repin1 expression lead to dyslipidemia and subsequent impairment of glucose homeostasis.

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POSTER 235

Studying RNA-RNA Interactions by Crosslinking, Ligation and High-Throughput Sequencing

Molecular Biology/Protein Biochemistry

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During the past years, the regulatory potential of RNAs besides the well-known functions in gene expression as messenger or translational adapters has become more and more evident. Non-coding RNAs (ncRNAs) that are not translated into proteins were revealed to carry out their functions by adopting distinct secondary structures and forming interactions with other transcripts. Bioinformatically, a rapidly increasing number of ncRNAs has been and still is being predicted. However, methods to verify predicted ncRNAs in high-throughput to keep pace with the *in silico* analyses are still rare. In addition, it used to be necessary to know a distinct RNA of interest in order to identify interacting partners and to generate a starting point for their functional characterization.

We aim to establish a protocol which connects *in vivo*-crosslinking of interacting RNAs with a high-throughput sequencing approach to identify ideally all interactions between RNAs within a cell or an organism. One key step is the ligation of crosslinked, RNase-trimmed RNAs to obtain fusion molecules for sequencing. To retain a maximal amount of transcripts during the crosslinking and ligation procedure, we use a multifunctional tRNA ligase from *Arabidopsis thaliana*. This enzyme is able to ligate 2',3'-cyclic phosphates and 5'-OH ends which are formed during RNase treatment. We have successfully prepared and purified the tRNA ligase and could prove its activity on tRNA substrates.

In the future, we expect to be able to provide an efficient protocol to identify RNA-RNA interactions within a cell, independent of former knowledge about the ncRNAs under study.

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POSTER 236 **Binding of glycosaminoglycans to Interleukin-10 studied by NMR spectroscopy**

Molecular Biology/Protein Biochemistry

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The immune response against microbial infections bears the intrinsic risk of an immune-mediated inflammatory damage to the host tissue. The cytokine interleukin (IL)-10 is a key regulator of the 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 or T cells are inactivated. IL-10 has mostly paracrine functions and acts over short distances within the tissue. In this context, glycosaminoglycans (GAGs) of the extracellular matrix are found as binding partners of IL-10 that restrict the protein to the vicinity of the secreting or targeting cell.
Here, we analyzed the molecular interactions between IL-10 and different GAG oligosaccharides by NMR spectroscopy. Chemical shift perturbations from ^{1}H-^{15}N-HSQC spectra were used to identify the GAG binding site within IL-10 that is located at the dimer interface of IL-10. Saturation transfer difference (STD) NMR spectroscopy revealed the carbohydrate binding epitopes and could quantify the binding affinity of different oligosaccharides. In particular, N-sulfation of the GAG hexosamine unit is critical for interaction with IL-10. Finally. transfer NOESY experiments report on conformational changes of the carbohydrate chain upon protein binding. For heparin, additional NOEs are observed between proton H2 of glucosamine and H1 of the respective preceding iduronic acid unit. At the end, our data help to understand how biological functions of IL-10 are related to its interaction with extracellular matrix GAGs.

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POSTER 237

Expression, Purification and Characterization of Adiponectin Thioester for Chemical Modification

Molecular Biology/Protein Biochemistry

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Adiponectin has become a key player in the understanding of overweight related diseases. One of its major functions are the insulin sensitizing effects. Furthermore, it is involved in glucose regulation and fatty acid oxidation. Nowadays, three adiponcetin receptors AdipoR1, AdipoR2 and T- Cadherin are discussed.

Unfortunately, interaction partners and the signaling cascade of adiponectin are far from being understood. So chemically modified adiponectin could contribute significantly to increase the understanding of the signal, e.g. by biotinylated or fluorescent labeled analogues. In order to find new binding partners or co-receptors, adiponectin was cloned and expressed as a fusion protein in *E.coli* with a C-terminal intein and a chitin binding domain (CBD) as well as with an N-terminal His_{10}-tag. The Intein Mediated Purification with an Affinity Chitin-binding Tag- system (IMPACT) was used for a combined purification step and the thioesterification of the C-terminus. This approach will allow ligation by expressed protein ligation (EPL).

By applying the IMPACT-system the fusion protein was cleaved to form the corresponding thioester. To separate the starting materials as well as the cleaved intein-CBD, the purification was performed with chitin beads. Furthermore, the product was concentrated by Ni-NTA-affinity chromatography. Next, the obtained adiponectin thioester was reacted with a biotin labeled peptide.

Owing to the difficulty of selective protein labeling, this method provides a good possibility to modify a protein of interest with various functionalities to use it for further interaction studies.

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POSTER 238 **Non-neuronal tau-protein expression**

Molecular Biology/Protein Biochemistry

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Tumor Targeting

Alzheimer's disease (AD) is the most common form of progressive dementia, characterized by hyperphosphorylated, aggregated tau-protein in neurons and extra neuronal Aβ-deposition. Tau-protein is expressed in neurons of the CNS and PNS and is associated with microtubules.
The objective of our study is to find out, if tau-protein is also expressed in other tissues. That question is of importance considering the possible development of early-onset diagnostics using blood-borne tau protein as a biomarker.
We quantified tau-protein by two different ELISA methods: a commercially available human total tau kit and an self-made assay using C-terminal monoclonal tau antibody 8F10 for capturing and polyclonal antibody for detection on homogenized mouse tissues. We analyzed wildtype-mice and tau knockout-mice. Furthermore, we performed immunohistochemistry in those tissues that have been positive in the ELISA, to see what cell types produce tau-protein, comparing tau-protein labelling with peripheral nerve staining. Also, we analyzed the expression of tau isoforms with RT-PCR. All methods showed that tau-protein is expressed in tissues other than the brain. The highest amount was found in heart, lungs, skin and skeletal muscle. Quantity was about 1/40 of the concentration of tau-protein in the brain.
The highest amount of tau-protein in those tissues seems to be due to peripheral innervation. But there is evidence that it is also produced by other cell types. Further investigation has to be done to see if the tau-protein expressed in those organs may be affected during AD.

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POSTER 239

New insights into the Structure of the TSH-Receptor using chemical Cross-linking

Molecular Biology/Protein Biochemistry

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The Thyroid-Stimulating Hormone Receptor (TSHR) plays a central role in the regulation of the thyroid gland and can be activated by the Thyroid-Stimulating Hormone (TSH), constitutively activating mutations and stimulating antibodies. The latter can lead to pathologic activation of the TSHR and cause Graves' disease or thyroid autonomy. Evolutionary, the TSHR as well as the Follicle-Stimulating Hormone-Receptor (FSHR) and the Luteinizing Hormone Receptor (LHR) belong to the family of Glycoprotein Hormone Receptors (GPHR). For all these receptors (TSHR, FSHR and LHR) the protein structure is only partially solved. Furthermore, the complete hormone binding sites, the functional role of the hinge region which connects the transmembrane domain to the leucine-rich repeat domain as well as the signal transduction via the transmembrane domain is not yet fully understood. Because of the size, the flexibility and the relatively low amounts of GPHR that could be expressed and purified, the application of classical methods like X-ray crystallography and nuclear magnetic resonance spectroscopy (NMR) is limited. For these reasons we work with different expression and purification strategies and combine these with modern MS-based methods for structural elucidation. One example is chemical cross-linking of proteins on the surface of intact cells or purified proteins under native conditions. In this project, we were able to detect the first cross-links. Additionally we will use hydrogen-deuterium exchange (HDX) and molecular modeling to translate the structural restraints into an improved model of the GPHRs and their hormones.

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POSTER 240

Rational Design of Inhibitors for ecto-5'-nucleotidase (CD73)

Molecular Biology/Protein Biochemistry

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The eukaryotic ecto-5'-nucleotidase (CD73 or e5NT) is an extracellular enzyme attached to the cell membrane. It constitutes part of the purinergic signalling pathway in which purine nucleotides and its derivatives act as extracellular signalling molecules. The important regulatory role of e5NT evolves from its ability to switch on P1 receptor signalling by generation of adenosine via hydrolysis of AMP. With such a crucial function e5NT has become an appealing drug target for the treatment of inflammation or various types of cancer.Structures of e5NT revealed an open and closed conformation for the dimeric enzyme. The subunits of each monomer are composed of a C- and N-terminal domain with the conformational change being achieved by a large rotation (~ 100°) of the N-terminal domain.Although several inhibitors for e5NT have already been published, complex structures for elucidation of detailed molecular interactions with corresponding compounds are rare. By using our expression and crystallization strategies, we were able to determine co-crystal structures for several commercial as well as newly identified compounds. Those results were then in cooperation with Prof Christa Müller in Bonn used for rational modifications. Until now, a derivative of the substrate-mimicking compound AMPCP showed the most promising results with pi-stacking interaction being the base for improvement of Ki value up to the low nM range. Further modifications could include extension into a large pocket which is, in the apo form, occupied by water molecules.

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POSTER 241 **Artificial Metallocatalysts based on RNase S**

Molecular Biology/Protein Biochemistry

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Tumor Targeting

About 1/3 of all proteins contain a bound metal ion, which may have a structural or catalytic function. Natural metalloenzymes utilize only a small subset of the metal ions of the periodic system, mainly the first transition row metals in addition to Ca^{2+} and Mg^{2+}. However, in particular the 4d and 5d transition metals exhibit excellent and unique chemical reactivities which are not utilized by nature due to the limited bioavailability or toxicity of these metals. A prominent example is Rh^{+}, which is commonly used in organometal synthesis. It is of great biotechnological interest to develop methods to include such metal centers into enzymes, thereby combining the unique chemical reactivity of the metal center with the selectivity (stereoselectivity, substrate specificity or regioselectivity) that can be provided by the protein environment.
Many organometal centers require special coordinating ligand spheres for activity, for instance phosphines for Rh^{+} activitation. We aim to develop new designed metallocatalysts based on the RNase S scaffold. The S-protein derived from bovine RNaseA has the feature of binding an peptide (termed S-peptide) consisting of 15 to 20 amino acid with remarkable high affinity, thereby forming the RNase S complex. We introduce novel metal-coordinating side chains into RNase S by chemical synthesis of the S-peptide. First model systems consist of cysteine and homocysteine coordinating heavy metal ions such as mercury. The resulting artificial metalloproteins are characterized by X-ray crystallography.

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POSTER 242

STAIR15, a STAT3 induced long non-coding RNA in multiple myeloma

Molecular Biology/Protein Biochemistry

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Tumor Targeting

Since transcriptome studies revealed that almost the whole mammalian genome is transcribed dependent on the developmental stage, a novel group of RNAs has been discovered. These long non-coding RNAs (lncRNAs) range between 200 bp and several hundreds of kb in size and have no coding potential. In recent years, functional studies have shown lnc-RNAs to play a role in chromatin remodeling and are important regulators of gene expression. However, the function of the majority of these ncRNAs remains still elusive. Based on a genome-wide tiling array study, we found several long ncRNAs to be differentially expressed upon cytokine stimulation in multiple myeloma cells. As STAT3 is essential for the survival of these cells, the found RNAs are called STAIRs (STAT3 induced ncRNAs). ChIRP- and Capture-Seq approaches give information about characteristics of the lncRNA itself as well as interacting transcripts. Further, functional studies will be performed to reveal the interdependency with the STAT3 pathway.

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POSTER 243

Expression of bactericidal rotavirus enterotoxin NSP4 in Escherichia coli

Molecular Biology/Protein Biochemistry

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Tumor Targeting

Rotaviruses are one of the main causative agents of viral gastroenteritis in young children under the age of three. High mortality rates, especially in developing countries, are due to rapid dehydration caused by acute watery diarrhea and vomiting. The non-structural protein NSP4, the first described viral enterotoxin, induces malabsorption and changes in calcium homeostasis during rotavirus infection. Although many studies on the function of NSP4 have been performed, the precise details of its toxicity remain unclear, in particular because of the problematic expression procedure of recombinant rotavirus NSP4. The production of small amounts of recombinant protein has been successful by using baculovirus expression systems or mammalian cell lines, however, for large-scale experiments, required for the generation of antisera or large-animal trials, these systems are inapplicable. For those purposes the *E.coli* expression system, which is suitable for large-scale protein production, can be used. Here we demonstrate the expression of recombinant bovine and simian NSP4 under various conditions and using different vectors. Due to its bactericidal properties full-length NSP4 has neither been expressed cytoplasmically nor periplasmically, however, we have been able to express and purify large amounts of an N-terminal truncated protein. By contrast, the expression of a recombinant protein, which contains the first 110 amino acids, leads to decreased growth and destruction of the bacterial culture, indicating that the NSP4 enterotoxic domain is not required for a bactericidal effect.

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POSTER 244

A new TSHR variant (L665F) as the molecular cause for non-autoimmune hyperthyroidism in an Austrian family

Molecular Biology/Protein Biochemistry

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Tumor Targeting

Mutations of the TSH receptor (TSHR) represent the molecular cause for familial, sporadic and somatic non-autoimmune hyperthyroidism. Here we describe an Austrian family with three generations of familial non-autoimmune hyperthyroidism.

The index patient was diagnosed with hyperthyroidism during her first pregnancyand gave birth to four children: the older ones were diagnosed with hyperthyroidism at the age of 11 and 10 y, respectively. TSH suppression was observed in the third child aged 8, who has normal fT4 levels until now. TSH suppression in infancy was observed in the youngest child. The mother of the index patient was diagnosed with toxic nodular goiter at the age of 36 y.

Screening for TSHR mutations detected a new mutation L665F in transmembrane helix (TM) 7. The mutation was present in all of the 6 members that were tested. Functional characterization of L665F revealed constitutive activation for the Gs pathway. Characterization of targeted receptor mutations suggests that the constitutive activity of L665F acts via the same mechanism as the previously described CAM V421I.

The molecular cause for hyperthyroidism in this Austrian family is related to a new constitutively activating TSHR mutation. Further investigation showed that this constitutive activation is most likely caused by steric repulsion between TM 1, 2 and 7.

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POSTER 245 **Investigation of aECM dependent signaling in fibroblasts using phosphoproteomics**

Molecular Biology/Protein Biochemistry

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Tumor Targeting

Cell growth in skin tissue is significantly influenced by the surrounding extracellular matrix (ECM). Thus, using coatings of artificial extracellular matrices (aECMs) including collagen and hyaluronan (HA) in different sulfation states is supposed to be a promising approach for skin graft design. For understanding intracellular aECM dependent response of cells, global proteomics by using high accuracy mass spectrometry in combination with stable isotope labeling by amino acids in cell culture (SILAC) is a powerful tool. Based on this approach in comparison of human primary fibroblasts cultured on triple-sulfated HA matrix to those cultured on non-sulfated HA matrix we were able to identify 84 differentially expressed proteins including down-regulated matrix metalloproteinase (2 and 14) as well as their inhibitor (TIMP-2) all known to be involved in matrix degradation. Those alterations at protein level after exposure to different matrices can be seen as long-term effects to the cells, but the underlying mechanisms of aECM signaling still remain unclear. To address those rapid alterations, global phosphoproteomics can be used. Most of intracellular signaling is based on activation and deactivation of kinases and phosphatases and subsequent alteration in the phosphorylation state of signaling proteins. Preliminary results showed an interference of aECMs into TGF-β signaling. Pilot studies shall reveal quantitative alteration in phosphoproteome after TGF-β induction of human primary fibroblasts before studies with cells cultured on artificial matrices that differ in composition and physical properties will be carried out.

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POSTER 246

Fixation of vaspin conformational states by artificial disulfide bridges

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Molecular Biology/Protein Biochemistry

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Tumor Targeting

Serine protease inhibitors (serpins) inhibit target proteases by forming a covalent serpin-protease complex and play important roles in fibrinolysis, tumor metastasis, glucose metabolism and other essential physiological processes [1, 2]. All serpins share structural core elements that are highly conserved among the family members. Of fundamental importance is the flexible reactive center loop (RCL) comprising the recognition site of the target protease. Serpins can adopt several conformations with completely different functional properties. In the native state the serpin RCL is exposed and enables protease inhibition. Additionally, some serpins are able to adpot an inactive latent state with a preinserted RCL [1, 2].

Our serpin of interest is visceral adipose tissue derived serine protease inhibitor (vaspin or serpinA12) and was discovered in a rat type II diabetes model [3]. In previous work, we have crystallized vaspin and have identified kallikrein 7 (KLK7) as the first target protease of vaspin [4]. To study vaspin function on a molecular level, we were interested to generate distinct active and inactive conformations of the serpin by the introduction of artificial disulfide bonds. Using a KLK7 inhibition and complex formation assays, we could demonstrate that both vaspin mutants, featuring an exposed or inserted RCL, act as expected and have significantly different activities compared to the wildtype.

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POSTER 247 **Smad proteins regulate PIN1 promoter**

Molecular Biology/Protein Biochemistry

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Alzheimer´s disease (AD) is characterized by pathogenic protein aggregates in the form of senile plaques and neurofibrillary tangles as well as massive disorders of cell cycle regulation. As a result cell cycle regulating proteins are inadequately activated which leads to the re-entry of neurons into the cell cycle, followed by apoptotic cell death. Recently, Smad proteins were identified to control the expression of various AD relevant proteins as for example cyclin-dependent kinase 4 (CDK4) and CDK inhibitors, both crucial cell cycle regulators. In AD pathology there is an enormous loss of physiologically active Smad proteins and they show a disturbed subcellular distribution in neurons. The reasons for neuronal Smad delocation and reduced availability in AD are complex. Significantly involved in the Smad decrease is the peptidyl-prolyl cis/trans isomerase Pin1. This enzyme affects the stability of Smad proteins and promotes their degradation. However, due to several evidences, we also suspected an inverse impact between both proteins. Here we report on binding studies of different Smad proteins to the human *PIN1* promoter carried out by EMSA (*Electrophoretic Mobility Shift Assay*). We show that selected Smads specifically interact to this promoter. Luciferase-reporter assay reveals control of human Pin1 promoter activity by Smads suggesting a relevant feed-back regulation of Smad levels on Pin1 expression. This allows the conclusion that Smad proteins and Pin1 are elements of a vicious circle with potential pathological significance in AD.

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POSTER 248

Effects of vaspin on adipocyte biology in stably transfected 3T3L1 cells

Molecular Biology/Protein Biochemistry

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Visceral adipose tissue-derived serpin (vaspin) was identified as a putative member of the serine protease inhibitor family, which was expressed in visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty rat[1]. In human studies the expression of vaspin mRNA was found to be associated with overweight, insulin resistance and type-2-diabetes[2]. However, on the cellular level the molecular mechanisms of vaspin on adipogenesis, adipocyte differentiation and adipose tissue function remain unknown.
To study the cellular effects of vaspin we established an *in vitro* cell model of differentiated 3T3-L1 cells overexpressing vaspin. We performed specific lipid droplet staining (AdipoRed assay) and quantitative real-time PCR from whole cell RNA to characterize the generated cell lines. The stable transfected cells show a significantly higher mRNA expression of vaspin in comparison to the control cells which express an empty vector. Both cell lines, 3T3-L1_vaspin and 3T3-L1_control, express differentiation markers (PPARγ, aP2, Adiponectin) and accumulate lipids during differentiation. Furthermore we found first evidence, that 3T3L1 cells overexpressing vaspin exhibit brown-like multilocular morphology combined with a significantly increased expression for different brown or beige adipose tissue specific genes (Cidea, COX7a1, PGC1-α, Fndc5). In conclusion, we have established an adipocyte cell line to study vaspin function in adipose tissue *in vitro*.

References:
[1] Hida *et al.* 2005, PNAS [2] Kloeting *et al.* 2006 BBRC

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POSTER 249

Scleral remodelling and matrix generating/degrading enzymes after collagen crosslinking

Molecular Biology/Protein Biochemistry

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Tumor Targeting

High myopia (shortsightedness) often accompanied by severe visual impairment and pathological complications such as chorio-retinal degenerations or retinal detachment. High myopia is mostly caused by an excessive and progressive elongation of the eye globe and is associated with a mechanically weakened, thinned and stretched sclera tissue. The sclera mainly consists of extracellular collagen fibrils organized in bundles. Hence, scleral collagen crosslinking (SXL) is a promising therapeutic approach to stiffen the weakened sclera. This might prevent the progression of eye globe elongation. Our animal experiments demonstrate stiffening effects on rabbit scleral tissue after SXL by means of riboflavin/blue light treatment. In these studies we observed altered scleral collagen fibril profiles and activated scleral fibroblasts as sign of remodelling processes. Fibroblasts are capable to produce and secrete collagen, different matrix generating and matrix degrading enzymes. Therefore, we will characterize the role and regulation of important matrix generating and matrix degrading enzymes (such as metalloproteinases-MMPs and their inhibitors-TIMPs) by means of PCR analysis and immunohistochemical methods. Firtsly, we established cell cultures from human and rabbit scleral tissue to characterize expression profiles of cellular markers (e.g. vimentin) and to demonstrate the expression of relevant MMPs (e.g. MMP2). After proving all methods we investigate the influence of relevant enzymes on the remodelling processes after SXL to optimize the new and promising therapeutic approach.

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POSTER 250

shLRP1 – A Truncated Splice Variant of LRP1

Molecular Biology/Protein Biochemistry

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Cancer is characterised by uncontrolled growth, invasion and often metastasis of transformed cells displaying a variety of genetic abnormalities.

The low-density lipoprotein receptor 1 (LRP1) is a member of the LDL receptor superfamily. These receptors are involved in different signalling pathways including control of fundamental developmental processes in the embryo, remodelling of tissue in the adult organism, and tumour promotion. The ubiquitously expressed LRP1 mediates clearance of over 50 ligands from the extracellular matrix (ECM) and the bloodstream, among others distinct components involved in modulation of cancer cell dissemination. So far, LRP1 is associated with both anti-tumour functions and recently with pro-invasive functions, thus indicating a more complex functionality of LRP1 in coordinating cell-matrix interactions and the balance of adhesion and detachment of cancer cells.

Our group recently detected a truncated splice variant of LRP1 (shLRP) mRNA – so far only found in prostate cancer cells. Beyond that, we detected it in several additional tumours cell lines derived from solid tumours and from blood cells as well as in corresponding healthy human tissues. Next to mRNA level, we also confirmed expression of shLRP1 protein in several cancer cell lines. Considering the importance of LRP1 raises the question regarding the function of shLRP1 in cell biology that have to be further investigated.

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POSTER 251

Investigation of the physiological relevance of the orphan adhesion-GPCR GPR110 in the kidney

Molecular Biology/Protein Biochemistry

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Adhesion-G protein-coupled receptors (aGPCRs) constitute the second largest class of the GPCR superfamily (33 receptors in humans) but also the least well understood one. Members of this class play essential roles in various biological processes and mutations in human aGPCRs are linked to severe diseases such as Usher Syndrome or bilateral frontoparietal polymicrogyria, rendering them highly promising potential drug targets. Despite this, many aGPCRs are completely uncharacterized such as GPR110. Very recently, we reported that *Gpr110* is clustered on the genome with three other partially orphan aGPCRs: *Gpr111*, *Gpr115* and *Gpr116*. Neither biological functions nor signaling pathways have been described for any of them. However, their high evolutionary conservation suggests essential physiological roles for these aGPCRs. *Gpr110* is specifically expressed in liver, kidney, and adrenal gland. Using *Gpr110*$^{LacZ/LacZ}$ knockout mice, we detected a very distinct expression of the reporter gene *LacZ* in the tip of the renal papillae. Highly specific staining was localized in collecting ducts of inner medulla. Structures in this area are involved in ion reabsorption and urea transport essential for the urinary concentrating mechanism. Preliminary results suggest that indeed *Gpr110* knockout mice potentially have a slight defect in their ability to concentrate urine suggesting that the receptor is likely to be a novel and important player involved in renal function or metabolism. Further metabolic analyses and studies of differential urine parameters as well as electron microscopy should aid to clarify the function of this promising aGPCR.

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POSTER 252 **The contamination problem in ancient DNA research**

Evolution and Molecular Diversity

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After the death of an organism DNA repair mechanisms cease function, which leads to a rapid decay of genetic material. Ancient DNA is therefore usually present in trace amounts only and characterized by base alterations and a high degree of fragmentation. One typical base modification is caused by deamination, which converts cytosine into the RNA base uracil. The presence of uracils can be used as a powerful marker to distinguish between authentic ancient DNA from the fossil and recent contamination. There are two major sources of contamination present on ancient bones: microbial DNA, which has been left by microorganisms colonizing the fossil during decomposition and modern human DNA introduced during excavation and laboratory work. The latter is particularly problematic when studying ancient human fossils.
We designed a protocol that enables the isolation of uracil containing molecules during DNA library preparation. We show that this method efficiently excludes modern human contamination from sequencing and in some cases also decreases the fraction of sequences obtained from microbial contamination. Furthermore, by using this method sequencing costs can be substantially reduced by pre-selecting libraries toward the usefull fraction of DNA extracts.

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POSTER 253

Developmental profile of the coupling distance at the parallel-fiber to Purkinje cell synapse

Neurobiology

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A key factor determining the fidelity of chemical neurotransmission is the coupling distance between the site of Ca^{2+} influx and the Ca^{2+} sensor for vesicular transmitter release. Tight, nanodomain coupling (<100nm) is favoring efficacy, reliability and speed of transmission[1]. Contrary to other synapses, excitatory cortical synapses seem to work at loose, microdomain coupling and forgo these advantages[2]. Yet, most of the investigations were performed on very young mice, while recently the adult cerebellar parallel-fiber (PF) synapse, probably the most abundant excitatory cortical synapses in the brain, was found to operate at nanodomain coupling[3]. Interestingly, the giant Calyx of Held synapse in the brain stem seems to undergo an ontogenetic shift from loose to tight coupling2. Here, we aim at characterizing developmental changes in the coupling distance of PF synapses, using bath application of different concentrations of AM esters of exogenous Ca^{2+} chelators for interference with synaptic transmission[4] in young and adult mice. Our experiments on adult PF synapses show that only the fast chelator BAPTA interfered with transmission, while the slower EGTA had no effect. This is in accord with the previous finding of nanodomain coupling in adult PF terminals[3] and validates AM-chelator application as a tool for estimating coupling at PF synapses. Prospective experiments will reveal whether tight coupling is a characteristic of the PF synapse or whether a developmental shift from loose to tight coupling takes place as in the Calyx.

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POSTER 254

Cotransmission of GABA and glycine in neurons of the respiratory centre

Neurobiology

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In the central nervous system fast inhibitory neurotransmission is mediated by glycine and gamma-aminobutyric acid (GABA). Contradicting Dale's principle, cotransmission of these two transmitters from a single neuron has recently been observed in many different brain regions. However, while the corelease of GABA and glycine offers a wide spectrum of signalling variations, the role of cotransmitting neurons is not well understood. Our research is focused on GABA and glycine cotransmitting interneurons in the respiratory centre in the brain stem, the Pre-Bötzinger-Complex, where inhibitory synaptic transmission is crucial for the patterning of the respiratory rhythm. Using electrophysiology, single cell RT-PCR and immunohistochemistry, we show that numerous neurons in the Pre-Bötzinger-Complex of mice transmit by both GABA and glycine. In addition, the quantitative analysis of different developmental stages revealed a decrease of cotransmitting neurons from P4 to P14, whereas the number of glycinergic neurons increased, indicating a developmental shift to glycinergic transmission. Experiments using advanced mouse genetic tools are currently ongoing to identify the fate of cotransmitting neurons as well as to define their functional relevance.

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POSTER 255

Characteristics of the specialized extracellular matrix in the auditory brainstem

Neurobiology

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It is known that the specialized extracellular matrix (ECM), the perineuronal net (PN), is rich in hyaluronan, chondroitin sulfate proteoglycans (aggrecan, neurocan, brevican, versican and phosphacan), link proteins and tenascin-R. They participate in the regulation of cellular migration, axonal outgrowth, synaptic plasticity and modulation of the extracellular ion milieu. In recent years many ECM-investigations focused on aggrecan and brevican. Aggrecan, the largest proteoglycan of PNs is a major constituent of cartilage but is also expressed in CNS. It is thought to contribute to the extracellular space in the brain. Brevican, the smallest proteoglycan is thought to link the ECM to the neuron by binding to specific receptors of the cell surface.

The nuclei of the auditory brainstem differ in the degree by which the neurons are wrapped by PN. Among these nuclei the medial nucleus of the trapezoid body (MNTB) stands out, by its principal neurons being ensheathed by the most prominent PNs. The MNTB neurons exhibit a specific feature, the giant axosomatic synaptic terminal, the Calyx of Held, which allow detailed analyzes of the distribution of ECM components both at pre-and postsynaptic sites. Because of this, we investigated the main components of the specialized ECM in the mouse MNTB with a particular focus on aggrecan and brevican. For both, we found differential expression patterns related to pre- and postsynaptic components. Our findings support the assumption that the constituents serve different functions and may effect synaptic transmission.

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POSTER 256

Ultrafast action potentials and vesicle recruitment allow for kHz signaling at a divergent presynaptic bouton

Neurobiology

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Neuronal divergence allows single neurons to activate numerous target cells. It can be achieved by many boutons (presynaptic expansions) per axon or by many postsynaptic partners per bouton. We here analyze the mechanisms of divergent signaling at single cerebellar mossy fiber boutons (cMFBs), which contact ~50 postsynaptic granule cells (GCs) each, and can fire action potentials at ~1 kHz *in vivo*. With paired recordings between mature cMFBs and GCs we show that single cMFB-GC connections reliably transmit at 1 kHz and that GCs process mossy firing linearly. Presynaptic action potentials are ultrafast (~100 μs) without significant broadening during kHz bursts and efficiently open Ca^{2+} channels. Analyzing basal parameters of release and the dependence on intra-terminal Ca^{2+} buffering reveals a small pool of fast releasing vesicles (~15) with tight vesicle to Ca^{2+} channel coupling and ultrafast vesicle recruitment (~400 vesicles/s per granule cell connection). Thus, our results demonstrate that ultrafast action potentials and vesicle recruitment enable signaling up to kHz frequencies from single presynaptic terminal to dozens of postsynaptic partners.

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POSTER 257

Presynaptic calcium dynamics at cerebellar mossy fiber boutons

Neurobiology

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Quantification of presynaptic Ca^{2+} concentration is essential to understand the mechanisms of neurotransmitter release and short-term plasticity. Therefore, we aimed for characterizing Ca^{2+} transients at the cerebellar mossy fibre bouton (cMFBs) to granule cell synapse, which can transmit signals at high frequencies and with high fidelity. We established whole-cell patch-clamp recordings and quantitative two-photon calcium imaging at cMFBs. Presynaptic boutons were filled with a Ca^{2+}-insensitive dye and Ca^{2+}-sensitive dyes with different affinity. Ca^{2+} concentrations were quantified with a corresponding set of calibration experiments in which the intra-bouton Ca^{2+} concentration was clamped to 0 or 10 mM. Single action potentials led to an increase in free intracellular Ca^{2+} concentration with a peak amplitude of 262 ± 60 or 31 ± 13 nm and a decay time constant of 86 ± 23 or 681 ± 41 ms at 36°C using 200 μM OGB-5N (n = 14) or 200 μM Fluo-5F (n = 57), correspondingly. Extrapolating the data from different dyes indicates an amplitude of the action potential evoked Ca^{2+} transient of 227 nM and a decay time constant of 70 ms. From these data the endogenous fixed buffer capacity can be estimated to be ~17. Finally, a train of 20 action potentials at 300 Hz led to an increase in intracellular calcium concentration of ~4.2 μM, indicating linear summation of residual Ca^{2+}. Our findings provide important constraints to understand the Ca^{2+} dynamics at the release site.

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POSTER 258

Cytokines after Stress and Effects of TNF-α-Blockade in a Stress Model of Depression in Rats

Neurobiology

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Tumor Targeting

Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) have repeatedly been shown to play a pivotal role in stress and stress-induced psychiatric disorders such as depression. Therefore, we tested alterations of plasma cytokines in rats induced by acute or chronic mild stress (CMS). Further, an antidepressant-like effect of the anti-TNF-α drug etanercept in CMS was proved.
Male Wistar rats were assigned to controls, acute stress by forced swimming, or to a restraint stress (RS) protocol for 2 weeks for plasma cytokine analysis. Additional animals underwent RS for 2 weeks and were treated either with Ringer solution daily or with etanercept for further 3 weeks. Imipramine was administered to a third RS group daily as antidepressant reference drug and a naïve non-treated non-restrained group served as healthy control.
Acute stress and CMS significantly elevated plasma concentrations of IL-2 (only acute), IL-4, IL-6, IL-10 and TNF-α. IFN-γ was significantly decreased in CMS and for IL-22 no differences were detectable due to high standard deviation.
The administration of etanercept to rats exposed to CMS significantly reduced depression-like effects in the forced swim test (variables: immobility and escape attempts) analogue to effects of imipramine. CMS induced a stagnation of body weight gain in the Ringer-treated group which was not reversed, neither by imipramine nor by etanercept during CMS.
Possibly enhancing serotonergic or noradrenergic neurotransmission, or normalizing stress hormone secretion, TNF-α blockers might be a reasonable alternative in otherwise treatment-resistant patients.

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POSTER 259

Influence of radiation dose and fractionation on hippocampal microenvironment and neurogenesis – preliminary results using a (transgenic) murine tissue slice model

Neurobiology

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Background: Radiation induced impairment of hippocampal neurogenesis seems to play a central role in the pathogenesis of neurocognitive deficits after whole brain radiotherapy. It has been demonstrated that proinflammatory cytokines may inhibit hippocampal neurogenesis. Our group is currently evaluating the influence of different radiation doses and fractionation schemes on hippocampal inflammation, microenvironment and neurogenesis.
Material and methods: From C57BL/J6 mice (P6) serial brain sections were cut and the entorhino-hippocampal formation dissected. Sections were transferred onto membrane inserts and cultured in six-well plates until irradiation with 0.0 to 4.0 Gy. The characterization of a potential radiogenic inflammation was determined by measuring the cytokines IL-6, IL10, TNF, KC, MCP-1, IL12p70 and INFγ in the supernatanto. We used transgenic Nestin-CFPnuc mice and life imaging to visualize the influence of radiation exposure on hippocampal neurogenesis.
Results: There was a dose-dependent increase in IL-6, KC and MCP-1 release following irradiation. The cytokine concentration in the non-irradiated cultures showed a maximum at day 1, which declined to low basal levels after wound healing. Last we observed a dose-dependent reduction of nestin-positive cells in the irradiated hippocampal slice cultures of Nestin-CFPnuc mice.
Conclusion: Exposure to comparatively low doses (1.3 Gy) increased the release of proinflammatory cytokines and may contribute to inflammatory changes which may cause or accompany radiation-induced damage to neurogenesis.

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POSTER 260 **Validation of a lentivirus mediated gene transfer to slow down progressive neurodegeneration**

Neurobiology

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Tumor Targeting

In Alzheimer's disease (AD) neurons show an enhanced expression of cell cycle proteins (cyclin dependent kinases (cdks), cyclins and cdk inhibitors (cdkis)), that leads to the hypothesis that differentiated neurons re-enter the cell cycle. Neuronal cell cycle-activation has been documented as one of these events critically involved in initiating neuronal cell death. Accordingly, activation of the cyclin CDK4/6-complex, the critical guard of the G0-G1-transition, under experimental conditions is known to be able to induce apoptosis. Here we will validate gene therapeutic tools in transgenic mice models with Alzheimers disease-like pathology to specifically target activity of CDK4&CDK6. Down regulation of CDK activity will be achieved through ectopic expression of physiological inhibitor of CDK4/6. Lentiviral vectors are the tools of choice for gene delivery into the central nervous system. Our new therapeutic strategy uses non-integrating (NI) lentiviral vectors, which can regulably express the transgene. We generated a pool of lentiviral vectors, which express several transgenes under control of different promotors and established reliable methods for production and application these viral particles. We infected primary neuronal cells (mouse), neuronal derived and non neuronal cells with the virus and analysed the effects with immunostaining and western blot. Subsequently, we started the in vivo experiments with different mouse lines. We injected the virus by stereotactical surgery in different brain regions and analysed the biodistribution and transgene expression.

This project is supported by the Hans and Ilse Breuer Foundation.

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POSTER 261

The morphological correlate of the blood-brain barrier along the vascular tree

Neurobiology

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The history of the blood-brain barrier (BBB) started over 100 years ago, when Paul Ehrlich was using intravital dyes to define the oxygen consumption of different organs. He discovered that contrary to peripheral organs, it was not possible to stain the brain by intravenous injections of hydrophilic dyes.
In 1900, the Berlin physician and Ehrlich's student Lewandowski, picked up this phenomenon by an other approach. He inoculated drugs peripherally as well as intrathecally and noticed that he needed much smaller doses of intrathecal injections to get the same reaction and concluded that the "brain capillaries must hold back certain molecules". In 1967, Reese and Karnovsky identified the "morphological correlate" to Ehrlich´s observations with high quality electron microscopy. They spotted endothelial overlaps at the level of the capillary endothelium by forming belts of tight junctions, which are characteristic for the brain compared to heart and skeletal muscle and suggested a negative correlation between intercellular distance and tightness. However, their studies were only focused on the capillary segment in which astrocytes share a common basement membrane with endothelial cells. Indeed, this direct contact was suggested to establish BBB properties of CNS capillaries. However, in non-capillary vessels, this direct contact is prohibited by the perivascular space or layers of smooth muscle cells. Therefore, it is currently unclear whether non-capillary vessels exhibit the same endothelial characteristics in the regard to maintenance of barrier function compared to capillaries.

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POSTER 262

Mouse strain-specific expression of glutaminyl cyclases QC and isoQC

Neurobiology

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Glutaminyl cyclases catalyze the formation of N-terminal pyroglutamate (pGlu) from glutamine or glutamate precursors. Since biochemical studies suggest an overlapping substrate specificity of QCs, their physiological specificity may arise from brain region and cell type-specific expression of QC and from their subcellular localization. Moreover, the formation of pathogenic pGlu-Abeta peptides in transgenic mouse models may depend on the expression levels of QC. Immunohistochemistry employing QC- and isoQC-specific antibodies and enzymatic activity assays were used to reveal expression of both enzymes in defined brain regions of nine different mouse strains. QC enzymatic activity was highest in brain stem, followed by cortex and hippocampus. Immunohistochemical stainings revealed that the enzymatic activity of QCs in cortex mostly arises from isoQC. In different mouse strains, highest QC/isoQC enzymatic activities were detected in C3H and 129/sv mice and very low QC activities in CD1, SJL and C57/Bl6 mice. Quantification of QC and isoQC immunoreactive neurons demonstrated a higher proportion of isoQC neurons in EWN and in SN and a slightly higher density of QC neurons in LC of most mouse strains investigated. These results underline the importance of appropriate mouse strain selection for studies aimed at investigating QC/isoQC physiological functions and for QC inhibition studies. Additionally, the differential expression levels of QC in defined brain regions suggest brain region-specific functions of QCs. Moreover, the pathogenic profiles in mouse strains with pGlu-Abeta pathology may depend on the expression level of QC.

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POSTER 263

Modulation of tau aggregation by tau phosphorylation and redox modification

Neurobiology

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Tau protein is a microtubule-associated phosphoprotein and located mainly in the axonal part of neurons. Tau proteins regulate stability of microtubules, which are essential for neurite extension and axonal transport. In Alzheimer's disease highly phosphorylated tau protein no longer binds to microtubules but exists in an aggregated, beta sheet containing, filamentous form in the cytoplasm. The fibrillization of the highly soluble monomeric tau to tau filaments is a multistep process proceeding via intermediate states. These tau aggregation intermediates may be involved in the pathogenic cascade leading to neuronal loss. It has been demonstrated, that oligomeric forms of Aß, alpha synuclein, and IAPP are toxic to cells. The factors, which modulate conversion of monomeric tau protein into oligomeric and filamentous tau aggregates are not well understood. However, hyperphosphorylation and altered redox homeostasis have been implicated in neurodegenerative disorders including Alzheimer's disease and Parkinson's disease.
The aim of our present study is to characterize tau aggregation products with regard to aggregate size, beta-sheet content as a function of tau phosphorylation and redox modification. Preliminary results show only a weak effect of proline-directed tau phosphorylation onto induction of tau aggregation and tau aggregate size but a remarkable effect of redox modulation onto tau oligomer or tau filament production.

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POSTER 264 **P2X3 receptor ectodomain movement influences receptor activation**

Neurobiology

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The trimeric P2X3 receptor (P2X3R) is an ATP-gated ion channel, situated on sensory neurons. Because of its involvement in pain sensation it is important to obtain a detailed knowledge about the receptor structure and function.
Based on the published (zf)P2X4R crystal structure, we generated a molecular dynamics model of the human (h)P2X3R which indicates a movement within the ectodomain near the ATP binding pouch, whereby two neighbouring receptor subunits approach each other. To prove a relevance of this movement for receptor behaviour, we used a mutagenesis-based approach by creating cysteine mutants. By introducing two opposing cysteine residues at the supposed inter- and intra-subunit contact sites, we intended to enable the formation of a disulfide bond resulting in immobilization of the receptor in one state of operation. The influence of the inserted disulfide bonds on receptor function was measured by whole-cell patch clamp technique on transiently transfected HEK293 cells.
We could identify two cysteine double mutants cross-linking adjacent receptor subunits which show an almost complete abolition of receptor functionality. This effect was reversed after application of disulfide bond reducing dithiothreitol. Of those mutants, one largely inhibited the binding of the fluorescent BODIPY-ATP to *Xenopus laevis* oocytes, whereas the other did not.
In conclusion, the predicted movement was confirmed by experimental results and it was possible to distinguish between two modes by which the disulfide bond might influence receptor activation, a suppressed agonist binding and an inhibited transduction of binding to gating.

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POSTER 265 **Endothelial degeneration contributes to BBB breakdown in different rodent models of ischemic stroke**

Neurobiology

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The term 'blood- brain barrier' (BBB) relates to the ability of the vasculature of the central nervous system (CNS) to prevent entrance of hydrophilic molecules into the CNS parenchyma proper. This specific feature of CNS vessels was initially reported to depend on tight junction contacts between overlapping endothelial cells. Therefore, as a converse argument, BBB breakdown associated with ischemic stroke was often exclusively attributed to an opening of endothelial tight junctions, which consequently leads to edema and hemorrhages and thereby critically impacting on the clinical outcome of concerned patients. We therefore investigated the fate of endothelial tight junctions in areas of BBB breakdown in an embolic model of ischemic stroke in rats. Contrary to our expectations, we were not able to demonstrate changes of the staining patterns for critical tight junction proteins such as occludin and claudin-5 in affected areas. To rule out that these results only hold true for the applied rat model, we also used a permanent and a transient (ischemia-reperfusion) model of stroke in mice, which confirmed our previous findings. Furthermore, ultrastructural analysis of areas exhibiting extravasation of the applied marker FITC-albumin revealed novel evidence questioning the impact of altered tight junction complexes on BBB breakdown in all the applied models as we could consistently show endothelial degeneration to cause BBB damage. Remarkably, an opening of tight junctions was never observed. Hence, protection of endothelial cells may turn into focus of future therapeutic strategies.

Funding: formel1

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POSTER 266 **Neuroanatomy and behavior of synesthetic mice**

Neurobiology

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Synesthesia is a barely understood phenomenon, in which sensory stimulation in one modality results in a simultaneous, involuntary experience in another, not stimulated, modality (Goldstein 1999). Human family and twin studies suggest a genetic factor for synesthesia, but a single "synesthesia-gene" has not been identified so far. Research with human subjects experiencing synesthesia is largely limited to the behavioral level, and little is known about neuroanatomical and developmental mechanisms. Functional MRI studies with pain-deficient mice (α2δ3 knockout) revealed sensory cross-activation in different cortical areas traditionally considered unimodal (visual and auditory cortex), while pain-related areas (somatosensory and motor cortex) were inhibited (Neely et al., Cell 2010). Therefore, α2δ3 knockout mice (Neely et al., Cell 2010) may provide a model to gain mechanistic insight into synesthesia. We examined the anatomical connectivity of areas of the "pain matrix" and other sensory areas using immune histochemistry. We found association fibers to be remarkably altered in knockout brains, compared to controls. In contrast, the analysis of projection fibers revealed no differences. If ongoing behavioral experiments on α2δ3 knockout mice are consistent with synesthetic perceptual experience in humans, our experiments may reveal important mechanistic insight into "mergence of sensory perception".

Funding: DFG Research Training School "InterNeuro"

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POSTER 267

Donor as well as recipient age affects migration and homing of systemic transplanted mesenchymal stem cells and microglia

Neurobiology

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Cell-based therapies provide potential treatment for neurodegenerative and other diseases. One approach is the systemic injection of cells. To address the cellular distribution it is important to evaluate the administration efficiency and migration ability.
MSCs or microglia were transplanted into young (~3 months), old (~12 months) and Alzheimer mice (APP^{swe}/PS1, ~12 months). To investigate the effect of donor age, also young or old cells were used. A sex-mismatched set-up was done to distinguish between donor and recipient cells. Male cells were applied into the tail vein of female mice. The gDNA of peripheral organs and 5 brain parts was isolated. Analyses were done by Y chromosome-specific PCR and GFP tracking using microscopy.
Transplanted cells were detected in peripheral organs and in the brain. More cells were found 14 days after transplantation and markedly less after 28 days. Moreover, the distribution was affected by disease status and age of the recipient. In young mice the migration tendency of young transplanted cells was towards the peripheral organs while it was slightly reversed in old mice. In Alzheimer mice applied MSCs were found preferably in the brain. Applied cells from old mice were not detected in the brain and only a few in the peripheral organs. In comparison microglia were more migratory active than MSCs.
The distribution of transplanted cells depends on the donor age, disease status of the recipient and the time course. These diverse migration patterns emphasize the importance to use the adequate animal model for transplantation studies and to take the age of the donors into consideration.

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POSTER 268

Isoglutaminyl cyclase expression in inflammatory processes in mouse brain

Neurobiology

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In brains of AD patients, the amount of pyroglutamylated β-amyloid (pGlu-Aβ) peptides is increased. pGlu-Aβ peptides are more resistant to degradation than full-length Aβ peptide and they possess a higher toxicity. This post-translational pGlu modification of peptides is a common biological event and also reported for a number of chemokines. Amongst others, the N-terminus of monocyte chemoattractant protein 1 (MCP-1) is modified to a pGlu residue which protects against degradation *in vivo* and is essential for its chemotactic activity. Recently, it was reported that isoglutaminyl cyclase (isoQC) is the enzyme which is responsible for the pGlu modification of MCP-1 *in vivo* in peripheral organs (Cynis et al, 2011). It is hypothesized that isoQC and MCP-1 might be induced in the AD brain by inflammatory events and mediate further pathology. Here we show that isoQC and MCP-1 are co-localized to neuronal Golgi apparatus and endoplasmatic reticulum which is in agreement with other investigations in non-neuronal cells (unpublished data). This co-localization of enzyme and substrate could be demonstrated in neurons of wild type and amyloid precursor protein transgenic Tg2576 mice, and in glial cells, as well. Furthermore, an age-dependent increase of isoQC and MCP-1 expression in the neocortex of wild type and Tg2576 mice could be detected. For this study, primary cell culture, immunohistochemical methods, ELISA and immunoblot analysis were carried out. It is concluded that under pathological conditions the potentially pro-inflammatory enzyme isoQC and its substrate MCP-1 are induced in activated glial cells of the brain.

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POSTER 269 **Microglia maintain radio-resistant even in vitro**

Neurobiology

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Microglia are regarded as the brain's immune cells, but they differ from other mononuclear population by their origin from the yolk sac, their long-term survival, and capability of self-renewal by local proliferation. An additional fundamental difference is their high radio-resistancy which provides the basis for work with bone-marrow chimeras dissecting functions of microglia and de novo recruited blood-derived monocytes. We wanted to test whether microglia are radio-resistant even as single cells without the brain microenvironment which would imply intrinsic anti-apoptotic or repair-related mechanisms which are not dependent on the local environment. Therefore we isolated brain monocytes and monocytes from spleen as an example for a lymphoid organ.
These acutely isolated splenocytes and brain monocytes containing microglia and brain macrophages were irradiated with 30 Gy. After irradiation they were sorted for the monocyte-specific marker CD45 and analysed by flow cytometry for cell death specific markers. We found that splenocytes ($CD45^{high}$) and brain macrophages ($CD45^{high}$) die within 4h after irradiation whereas microglia ($CD45^{int}$) are radio-resistant. Furthermore, we investigated the expression pattern of 84 apoptosis-relevant genes 4h after irradiation and found a tendency of splenocytes to up-regulate genes whereas brain monocytes have a tendency to down-regulate genes.

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POSTER 270

STIM proteins control purinergic receptor-mediated activation of microglia

Neurobiology

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The endoplasmic reticulum-resident Ca^{2+} sensors STIM1 and STIM2 trigger store-operated Ca^{2+} (SOC) entry by activation of SOC channels in the plasma membrane. However, the differential role of STIM sensors and the identity of SOC channels in microglia are largely unclear. In qPCR experiments we found a preferential expression of the SOC channel subunit ORAI1, whereas the isoforms ORAI2 and ORAI3 are less abundant. From experiments on wildtype and knockout STIM1, STIM2 and Orai1 mice, we provide evidence that both STIM isoforms contribute to SOC entry and that Orai1 is the main SOC channel subunit in cultured mouse microglia. Orai1$^{-/-}$ and STIM1$^{-/-}$ microglia showed a strong reduction in SOC entry, whereas in STIM2$^{-/-}$ cells this effect was smaller. Ca^{2+} entry evoked by the extracellular nucleotides 2-MeSADP and UDP were nearly complete suppressed in STIM1$^{-/-}$ and in Orai$^{-/-}$ microglia and reduced in cells lacking STIM2. Chemotactic responses to the specific $P2Y_{12}$ receptor agonist 2-MeSADP were inhibited in the absence of STIM1 or STIM2. Phagocytosis and migration induced by the $P2Y_6$ receptor agonist UDP were reduced in both STIM1$^{-/-}$ and STIM2$^{-/-}$ cells. Our data demonstrate that both ER Ca^{2+} sensors are essential for SOC entry, purinergic Ca^{2+} signals as well nucleotide-induced migration and phagocytosis in microglia.

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POSTER 271

Analysis of transplanted mesenchymal stem cells as candidate for Alzheimer's disease therapy

Neurobiology

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Alzheimer's disease (AD) is the most common neurodegenerative disease affecting millions of people worldwide. Pathological hallmarks of AD are accumulation of aggregated tau protein in neurofibrillary tangles and amyloid beta (Aβ) in senile plaques. Currently there is a great deal of interest in the use of mesenchymal stem cells (MSC) to treat neurodegenerative diseases. There is evidence, that the secretion of bioactive molecules by MSC has a beneficial effect on the injured environment promoting repair. In this context young MSCs were systemically transplanted in an Alzheimer mouse model (APP/PS1) and their effect on plaque pathology, microglia and astrocytes distribution and morphology were investigated as well inflammation status.
After transplatation, MSC-GFP+ cells were found in the brain parenchyma indicating migration into the affected area on the APP/PS1 mice. Reduction in plaques number were observed at day 7 post-transplantation compared to controls. In addition, we found a reduction in microglia and astrocytes activity. Staining for neuronal marker showed changes in dentate gyrus after transplantion of MSC. Analysis of inflammation markers involved in AD resulted in a significantly reduced expression post-transplantation.
In conclusion these results showed MSC as a promising cell-based therapy for the treatment of Alzheimer disease and other neurodegenerative diseases.

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POSTER 272 **Anatomical basis of vagus nerve stimulation revised**

Neurobiology

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Introduction:
Vagus nerve (VN) stimulation in the cervical region is a neuromodulation procedure with indications in epilepsy, depression and chronic heart failure. Existing studies on the VN describe its regular course with only few variations. In contrast, by own practical experiences the VN appears to have plenty of anatomical variations in the cervical region. The aim of our study was to critically review the cervical VN anatomy and to detect existing branches as possible explanation of stimulation side effects.
Methods:
A total of 66 VN's were investigated macroscopically, histologically and radiologically in 35 body donors in a similar approach as done when performing surgical implantation of the electrodes for VN stimulation. The obtained data were compared statistically and the location of the VN was described in a three-dimensional coordinate system.
Results:
In 42% a regular course within the neurovascular pathway could be detected, with the VN located posterior between the internal jugular vein and internal carotid artery. Despite these findings, variations could be observed for the VN location (58%) in eight different locations along with vascular abnormalities. These variations were documented radiologically. Histological analyses proved additional and previously unknown cervical VN branches in 18%.
Conclusion:
A profound knowledge of VN anatomy and its variations is essential for planning and realizing reliable and consistent VN stimulation. Our data indicate that anatomical variability of the VN can be remarkable and might explain potential stimulation side effects and stimulation fluctuations as well.

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POSTER 273

Identification and Characterization of ncRNAs relevant for Alzheimer´s Disease

Neurobiology

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Current studies on Alzheimer's disease (AD), an important neurodegenerative disorder, are not limited to the already long known pathologic amyloid plaques and neurofibrillary tangles.Recently, alterations of the transcriptome in AD have been discovered including both differently expressed protein-coding and small non-coding RNA (ncRNAs) e.g. miRNA. However, there are no systematic studies on the involvement of long non-coding RNA molecules (lncRNA) in AD. LncRNAs are considered to have important regulatory impact on both, gene expression and protein function and complex biochemical processes such as cell division and apoptosis. Based on our data fetched from a genome-wide expression analysis and their subsequent processing in our newly generated custom arrays, a pool of ncRNAs specific for AD was identified by bioinformatic analysis. Validation of these results with quantitative reverse transcriptase PCR revealed four candidate transcripts suitable for further detailed studies. These transcripts were characterized by Northern Blot analysis and knockdown experiments using RNA interference in a human, neuron-like neuroblastoma cell-system (SH-SY5Y) in vitro. Treated cells were examined with respect to cytotoxicity (LDH-Assay), cell cycle regulation (FACS) and expression of protein coding genes (Microarray). We could identify several disease-relevant target-genes, regulated by lncRNAs such as, for example the gene coding for the amyloid precursor protein.

Funding: Project 990101-089 (Leipzig University, Faculty of Medicine)

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POSTER 274

Hippocampal neural progenitor cells express P2X7 receptors

Neurobiology

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Adult/postnatal neurogenesis persists in two regions of the brain, the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus. Nucleotides are important signalling molecules in the brain and participate in the proliferation and differentiation of neural progenitor cells (NPCs). We used transgenic Tg(nestin/EGFP) mice to identify their NPCs in brain slices. Whole cell patch-clamp recordings showed inward currents after the application of ATP (3000 μM) and dibenzoyl-ATP (BzATP; 300 μM) near the resting membrane potential (-80 mV). The BzATP currents reversed at about 0 mV, due to the reversal potential of non-selective cationic currents. BzATP was more potent than ATP itself and the activities of both agonists increased in a low Ca^{2+} and zero Mg^{2+} solution, suggesting the involvement of P2X7 receptors. This idea was supported by the concentration (1 μM, 10 μM)-dependent inhibition of the agonist-induced currents by A-438079 a selective P2X7 receptor antagonist. The BzATP-evoked currents were not altered in the presence of antagonists for NMDA, AMPA, $GABA_A$ receptors (AP-5, CNQX, gabazine) and tetrodotoxin, a blocker of voltage-dependent sodium channels. We prepared excised patches from NPCs and these still reacted to BzATP. Thus, the currents are caused by the stimulation of P2X7 receptors located at the NPCs themselves. We suggest that the apoptotic/necrotic P2X7 receptors of NPCs may be of particular relevance during pathological conditions, such epileptic seizures that increase the extracellular levels of ATP and thus could counterbalance the seizure-induced cell proliferation.

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POSTER 275

High-Resolution 7T MR Imaging of the Human Subgenual Prefrontal Cortex in vivo- Development of a segmentation algorithm and its application in mood disorders

Neurobiology

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The Subgenual Prefrontal Cortex (SGPFC) as part of the limbic system plays a crucial role in mood regulation as demonstrated in structural and functional brain imaging studies.
Previous research of SGPFC volumes revealed a reduction in patients with Major Depressive Disorder (MDD) and Bipolar Depression (BD), mainly in the left SGPFC. However, contradicting findings are biased by imaging methods and magnetic field strengths, and the SGPFC has never been investigated by high resolution MRI. In the present study we aimed to investigate the SGPFC using 7T MRI.
We developed a reliable segmentation protocol of the SGPFC (ICC > 0.90 for two independent raters) and our preliminary results of the method being applied in a sample of MDD patients compared to matched HC will be presented and perspectives of high resolution imaging in mood disorders will be discussed.

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POSTER 276

Aggrecan, link protein1 and tenascin-R are essential molecular components of the perineuronal net to protect neurons against iron-induced oxidative stress

Neurobiology

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In Alzheimer´s disease (AD), different types of neurons and different brain areas show differential patterns of vulnerability towards neurofibrillary degeneration which provides the basis for a highly predictive profile of disease progression. In previous studies we could demonstrate that in AD, neurons are less frequently affected by neurofibrillary degeneration if they are enwrapped by a specialised form of the hyaluronan-based extracellular matrix, the so called 'perineuronal net' (PN). PNs are basically composed of large aggregating chondroitin sulfate proteoglycans connected to a hyaluronan backbone, stabilised by link proteins and cross-linked via tenascin-R. Under experimental conditions in mice, PN ensheathed neurons are better protected against iron induced neurodegeneration than neurons without PN. Still, it remains unclear whether these neuroprotective effects are directly mediated by the PNs or are associated with some other mechanism in these neurons unrelated to PNs. To identify molecular components that essentially mediate the neuroprotective aspect on PN-ensheathed neurons, we comparatively analysed neuronal degeneration induced by single injection of $FeCl_3$ on four different mice knock-out strains, each being deficient for a different component of PNs. Aggrecan, link protein and tenascin-R were identified to be essential for the neuroprotective properties of PN. Our findings indicate that the protection of PN-ensheathed neurons is directly mediated by the net structure and that both the high negative charge and the interaction of net components are essential for their neuroprotective function.

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POSTER 277

Micro-RNA involved in cellular differentiation control are aberranty expressed in Alzheimer´s disease

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Neurobiology

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As a progressive neurodegenerative disorder, Alzheimer´s disease (AD) is the most common dementia among the elderly. The neuropathological characteristics of AD are neurofibrillary tangles, containing the microtubule-associated protein Tau in a hyperphosphorylated form and neuritic plaques composed of Aß, derived from the much larger amyloid precursor protein (APP). The process of neurodegeneration in AD, eventually leading to cell death is associated with a loss of neuronal differentiation control and abortive activation of the cell cycle. Thus, molecular mechanisms have been proposed to be shared between neurodegeneration and neoplastic transformation.

Here, we describe the aberrant expression of micro-RNAs in AD brain previously identified as being involved in tumor development. This finding indicates that specific micro-RNAs that play a role in promoting neoplastic transformation through overriding tumor suppressor functions in tumor development are elevated in AD. We show that one specific micro-RNA regulates neuronal differentiation and structural neuronal plasticity. Additionally, this miRNA can controls the expression of APP and the APP- processing enzyme BACE1 thus promoting the pro-amyloidogenic pathway. The present study supports the concept of a molecular regulatory level shared between neoplastic transformation of dividing cells and degenerative cell death of neurons and provides a mechanistical link between abberant cell cycle activation in AD and the proamyloidogenic pathway eventually leading to cell death.

Funding: life

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POSTER 278 **Expression of glutaminyl cyclase and thyrotropin-releasing hormone in APP transgenic tg2576 mice**

Neurobiology

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Recently, Aβ peptide variants with an N-terminal truncation and pyroglutamate (pGlu) modification have been identified and shown to be highly prone to aggregation and neurotoxic. The pathogenic pGlu modification of Aβ is catalyzed by glutaminyl cyclase (QC) and pharmacological inhibition of QC ameliorates Aβ deposition, accompanying gliosis and improves memory in APP transgenic mouse models for Alzheimer's disease (AD).

QC expression has been mainly reported in the hypothalamus, where thyrotropin-releasing hormone (TRH) is one of its physiological substrates. We recently demonstrated distinct QC expression by hippocampal neurons in mouse brain. In addition to the hormonal role a novel neuroprotective function of the QC substrate TRH against excitotoxicity and Aβ neurotoxicity has been reported. Using fluorescence labelling we detected neuronal co-expression of QC and TRH in the hippocampus of adult wild type mice. This provides an explanation for the significant QC expression in one of the most affected brain regions in AD.

The qRT PCR experiments revealed a significant increase in the expression of QC and TRHR1 mRNA in the cortex of tg2576 mice, whereas in the ventral brain a significant decrease of QC, TRH and TRHR1 mRNA was observed. With respect to neuroprotection, it is conceivable that QC and TRH are differently regulated in brain areas with strong (cortex and hippocampus) and with low (ventral brain) Aβ pathology.

In tg2576 mice we observed QC and TRH immunoreactivity in activated astrocytes around Aβ deposits revealing a different cellular expression in wild type mice and transgenic mice with Aβ pathology.

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POSTER 279

Temporal development of perineuronal nets in the auditory brainstem nuclei of mice

Neurobiology

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Perineuronal nets (PN) are a specific form of extracellular matrix in the vertebrates' brain. PN are composed of macromolecular complexes formed by hyaluronan as a molecular backbone and several proteoglycans, connected by link proteins and crosslinked by tenascin-R. The formation of PN is established when synaptogenesis is completed. Therefore it is dicussed that PN have an immediate impact on axonal pathfinding and synapse formation. Since the developing auditory brainstem represents a brain region of high neuronal plasticity between birth and the finalization of PN formation, we focused on the distribution of PN components in mice such as the proteoglycans brevican, aggrecan and neurocan during early development up to the onset of hearing at postnatal day 12 (P12). We used immunoflourescent stainings to visualize PN components in the cochlear nucleus and in nuclei of the superior olivary complex, i.e. lateral superior olive (LSO), superior paraolivary nucleus (SPN), and medial nucleus of the trapezoid body (MNTB). We found that proteoglycans differ in their early intra- and extracellular distribution. For instance, neurocan can already be detected pericellularly at P7 while aggrecan and brevican are still expressed only in neuronal cytoplasm. This might be linked to earlier findings showing that neurocan inhibits NCAM-mediated cell adhesion and prevents axonal outgrowth and fasciculation *in vitro*. Since neurocan is found extracellularly as early as P7, it may serve an initial function in the early formation of PN and influence axonal guidance of the developing neuronal network of the auditory brainstem.

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POSTER 280

Stereological assessment of post-mortem striatal brain samples shows no difference in neuronal and astrocyte densities between lean and obese humans

Neurobiology

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Background: Neuroimaging studies have repeatedly shown widespread structural brain abnormalities in obese humans, including the striatum. To date, it remains unknown if and how these neuroimaging based findings are related to regional gray matter histology.
Methods: Neuronal (via cresyl violet staining) and astrocyte densities (via GFAP immunostaining) of formalin fixed post-mortem striatal brain samples (i.e. caudate-putamen) of 9 obese (BMI 40.2±6.1 $kg*m^{-2}$) and 8 lean (BMI 24.4±1.0 $kg*m^{-2}$) brain donors were assessed by using computerized unbiased stereology.
Results: No differences in mean neuronal (obese: 7.60E+06; SD 2.50E+06; lean: 7.85E+06: SD 8.26E+05; p=0.78) and astrocyte densities (obese: 7.42E+06; SD 2.27E+06; lean: 7.43E+06; SD 2.50E+06; p=0.99) were observed in the striatum. A significantly higher variance of striatal neuronal (p=0.007) but not astrocyte (p=0.72) counts was found in the obese group. No difference was found for the neuron/glia ratio between both groups (obese: 1.07; SD 0.39; lean: 1.15; SD 0.37; p=0.70), with an overall striatal neuron/glia ratio of 1.11 (SD 0.37) across the entire study population (n=17).
Conclusions: We found no differences in mean neuronal and astrocyte densities of the striatum between lean and obese. Further research is required to clarify how neuroimaging findings correlate with histological changes in obesity.

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POSTER 281

Empathie im jungen Erwachsenenalter und Alter – Multidirektional und Kontextabhängig?

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Psychology and Cognition

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In unserer Studie untersuchten wir Altersunterschiede in drei Facetten der Empathie: der Fähigkeit, die Gefühle eines anderen zu erkennen (empathische Akkuratheit), diese Gefühle zu teilen (Gefühlskongruenz) und Mitgefühl für den anderen zu erleben. Die bisherige Forschung zeigt multidirektionale Altersunterschiede in den verschiedenen Empathiekomponenten mit altersbezogenen Defiziten insbesondere in kognitiv anspruchsvollen Prozessen wie der empathischen Akkuratheit. Bisherige Studien verwendeten dabei überwiegend kontextarmes Stimulusmaterial. Ziel unserer Studie war es, zu testen, wie sich Kontextfaktoren und insbesondere die Altersrelevanz einer Aufgabe auf die Leistung Älterer in den verschiedenen Empathiekomponenten auswirkt. Hierzu wurden jüngeren und älteren Erwachsenen sechs Filmausschnitte präsentiert, in denen eine junge oder ältere Frau eine emotionale, jeweils altersrelevante Situation schilderte. Unabhängig von der Altersrelevanz der Schilderung berichteten ältere Erwachsene mehr Mitgefühl und teilten die Emotionen der Protagonistinnen in gleichem Maße wie die jüngeren Erwachsenen. Altersdefizite in der empathischen Akkuratheit wurden eliminiert, wenn die Protagonistinnen über ein Thema von besonderer Relevanz für Ältere berichteten.

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POSTER 282

Die Rolle des Gyrus Angularis bei der Verarbeitung von degraded speech

Psychology and Cognition

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Bisherige Studien haben gezeigt, dass der linke Gyrus Angularis (AG) eine zentrale Rolle für die erfolgreiche semantische Integration bei beeinträchtigter Qualität von Sprachsignalen („Degraded Speech") spielt. Das Maß der Aktivierung des AG ist dabei von der Schwierigkeit der semantischen Integration sowie vom Grad der akustischen Verständlichkeit des Satzes abhängig.
In dieser Studie soll die funktionelle Relevanz des AG für die erfolgreiche Verarbeitung von Degraded Speech mit repetitiver transkranieller Magnetstimulation (rTMS) untersucht werden.

15 junge gesunde Rechtshänder werden mit 10 Hz rTMS untersucht, während sie auditiv dargebotene Sätze mit variierendem Noise Vocoding Level (2-,4-,8-,16- und 32- Band) nachsprechen. Dabei wird rTMS in zwei Sitzungen entweder über dem AG oder dem Lobus parietalis superior (SPL; Kontrollareal) der sprachdominanten Hemisphäre verabreicht.

Die Ergebnisse zeigen für die Anzahl richtig wiederholter Keywords eine signifikante 3-fach Interaktion zwischen den Faktoren rTMS, Satzkontext und Vocoding Level ($p=.001$). So führte rTMS über dem AG im Vergleich zur rTMS über dem SPL bei einem mittleren Noise Vocoding Level von 4-Band zu einer signifikanten Abnahme der korrekt wiederholten Keywords in der high- ($p=.026$).

Diese Ergebnisse deuten darauf hin, dass der AG funktionell relevant für die erfolgreiche Verarbeitung von Degraded Speech ist. Dies bestätigt eine Annahme auf der Basis bisheriger Studien, wonach der AG eine Kernregion für die erfolgreiche semantische Integration bei Sätzen mit high-predictability unter beeinträchtigter Qualität des Sprachsignals ist.

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POSTER 283 **Biological and psychosocial foundations of joint attention, imitation and cooperation**

Psychology and Cognition

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Humans' unique ability to cooperate with others is a current 'hot spot' in research. However, the biological and psychosocial roots of this behavior are still largely unexplored. In the current research project, we aim to bridge that gap by studying biological and psychosocial foundations of the development of cooperation through a direct comparison of children with autism, maltreated children, and typically developing children.

In a series of experiments with behavior observation measures, we systematically elaborate previous research that has revealed cooperation deficits in children with autism. We also evaluate specific correlation patterns of imitation and joint attention with different types of cooperation abilities to assess whether cooperation deficits are based on developmental deficits in more basic socio-cognitive abilities.

Our research further extends to maltreated children, which to our knowledge is the first study in this area. We hypothesize that not only biological preconditions but also early negative experiences can lead to deficits in imitation, joint attention, and cooperation.

The current research project is a pilot study with smaller sample sizes (N=12, respectively) enabling us to specify our hypotheses in the two clinical samples. We intend to integrate our findings in a research proposal in 2014. The findings of such a research project would not only link basic developmental and clinically applied science and extend the theory of human cooperation, but also provide a basis for the development of interventions for children with autism and for maltreated children.

Funding: formel1

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POSTER 284

The impact of childhood maltreatment on the cooperative behavior of children and adolescents in a public goods game.

Psychology and Cognition

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Childhood maltreatment increases the risk for an impeded psychosocial development of children, particularly the ability to form positive relationships with peers. Not only do maltreated children and adolescents interact less frequently with peers, they also have more disturbed interaction patterns, show less prosocial behavior (Cicchetti & Valentino, 2006) and have been found to display lower levels of social competence (Milling-Kinard, 1999). Starting from this background we outline a study design as well as present pilot data of an ongoing dissertational project analyzing the effects of early childhood maltreatment on social competent behavior of children and adolescence.

Social competence of children and adolescence is usually assessed via questionnaire or observational studies. To our knowledge there is no method of measuring actual behavior that can be regarded as socially competent in a highly controlled experimental setting.

To fill this gap we utilize a game-theoretic paradigm (public goods game) that allows us to measure social competence by examining actual behavior. Therefore we devised a computer game, simulating a real-life-type public goods situation in which 9-16 year old maltreated and non-maltreated children interact with several preprogrammed cooperative or non- cooperative same-aged, samesex agents. The strategies the subjects use in different rounds of the game will be analyzed in terms of social competence toward peers. Additionally we compare behavioral data with questionnaire data to identify possible discrepancies between objectively shown behavior and subjectively perceived social competence.

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POSTER 285

Verbal working memory load reduces phonological, but not semantic planning scope in sentence production

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Psychology and Cognition

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Semantic and phonological encoding during sentence production can span beyond the initial noun phrase prior to speech onset (e.g., Jescheniak et al., 2003; Meyer, 1996; Oppermann et al., 2010). However, there is little research on the flexibility of advance planning. In a series of picture-word interference experiments, we tested whether the scope of semantic and phonological advance planning is influenced by concurrent visuospatial or verbal working memory (WM) load. Participants produced simple subject-verb-object sentences. Auditory distractor words semantically or phonologically related to the object were contrasted with unrelated distractors to index semantic and phonological activation of the object name prior to speech onset. A no-load condition (sentence production only) was compared to two load conditions (concurrently performing either a visuospatial or verbal WM task). We observed semantic interference effects from object-related distractors regardless of load manipulation. In contrast, phonological interference effects from object related distractors were observed in the no-load and visual load condition, but not in the verbal load condition. These results indicate that the phonological but not the semantic planning scope is reduced under verbal WM load. This pattern suggests that processes required for phonological, but not for semantic speech planning overlap with verbal WM processes.

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POSTER 286

Having more, giving more: Der Einfluss von sozialer Klasse auf prosoziales Verhalten

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Mehreren neuen Studien zufolge sind Angehörige unterer sozialer Klassen prosozialer als Angehörige oberer sozialer Klassen (Piff et al., 2010). Allerdings fällt an diesen Studien auf, dass sie auf relativ kleinen Stichproben basieren und sich die Operationalisierung von sozialer Klasse deutlich zwischen den einzelnen Studien unterscheidet. Wir versuchten daher, diese Befunde in drei eigenen Studien unter Nutzung von Daten des sozio-ökonomischen Panels zu replizieren. Unsere Analysen zeigen, dass Angehörige oberer sozialer Klassen häufiger und prozentual mehr spenden (Studie 1: N = 9363 Haushalte), in einem Trustgame mehr Punkte weitergeben (Studie 2: N = 1312 Personen) und mit höherer Wahrscheinlichkeit ehrenamtlich tätig sind (Studie 3: N = 22399 Personen) als Angehörige unterer sozialer Klassen. Zusammenfassend lässt sich feststellen, dass wir im Gegensatz zu Piff und Kollegen (2010) keinen negativen, sondern einen positiven Zusammenhang zwischen sozialer Klasse und prosozialem Verhalten finden. Die Ergebnisse werden im Kontext der Debatte zur Replizierbarkeit psychologischer Befunde diskutiert.

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POSTER 287

Emotionswahrnehmung bei Patienten mit erworbenen Hirnschädigungen

Psychology and Cognition

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In bisherigen Studien wurde deutlich, dass Patienten mit erworbenen Hirnschädigungen Schwierigkeiten haben, emotionale Gesichtsausdrücke richtig wahrzunehmen. Es stellt sich die Frage, ob dies auch die unbewusste Emotionswahrnehmung betrifft. Unbewusste Emotionswahrnehmung kann durch Emotionales Priming operationalisiert werden. Dabei wird der Einfluss eines vorgeschalteten Reizes (Prime) auf einen nachfolgenden Zielreiz (Target) erfasst, wobei der Prime unter der Wahrnehmungsschwelle präsentiert wird, während das Target bewusst wahrnehmbar ist. Höschel und Irle (2001) konnten zeigen, dass bei Gesunden emotionale Gesichtsausdrücke als Prime einen Einfluss auf die Bewertung von neutralen Gesichtsausdrücken haben.

In der Studie wurde untersucht, ob Patienten mit erworbenen Hirnschädigungen schlechtere Emotionswahrnehmung zeigen als gesunde Kontrollprobanden (KP). Dazu wurden zwei neue Emotionswahrnehmungsaufgaben erstellt. Die Emotionsbenennungsaufgabe soll prüfen, ob die Probanden emotionale Gesichtsausdrücke richtig benennen können, die Aufgabe zum Emotionalen Priming soll die unbewusste Emotionswahrnehmung erfassen. Insgesamt nahmen 35 Patienten und 15 KP an der Studie teil, von denen 16 Patienten und 2 KP aufgrund von Gesichtsfeldeinschränkung ausgeschlossen werden mussten. Die endgültige Stichprobe umfasste daher 19 Patienten und 13 KP.

Die Patienten schnitten in der Emotionsbenennungsaufgabe marginal schlechter ab als die KP. Beim Emotionalen Priming zeigten die Patienten im Vergleich zu den KP einen geringeren Einfluss des positiven Primes und einen größeren Einfluss des negativen Primes auf die Bewertung des Targets.

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POSTER 288

Effects of shifts in spatial attention on semantic context effects during picture naming

Psychology and Cognition

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When a target picture is named in the presence of a distractor picture, naming is facilitated if there is a phonological relation between the two pictures. In contrast, semantically related distractor pictures typically have no effect on naming latencies. This pattern is surprising as, on all theoretical accounts, phonological processing is preceded by semantic-conceptual processing. We investigated whether semantic effects of picture distractors are observable if sufficient attention is allocated to the distractor pictures. Attention to the pictures was manipulated by means of arrow cues pointing to the target (valid), to the distractor (invalid), or to both pictures (neutral). Responses were fastest with valid cues and slowest with invalid cues. Importantly, semantic interference was only found with invalid cues. When the cueing manipulation was replaced by a SOA-manipulation no semantic effect was found. This suggests that the interference effect was indeed caused by increased attention to distractor pictures with invalid cues, not by differences in relative timing of target and distractor processing under the different cueing conditions. Our findings emphasise the role of attention in the activation of context object names and support competitive models of lexical selection, while challenging the response exclusion hypothesis.

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POSTER 289

Age Differences in Negative Emotional Reactions: Further Evidence for Multidirectionality

Psychology and Cognition

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Differences in the intensity of discrete negative emotions appear to be multidirectional: the intensity of anger decreases across age groups, whereas theintensity of sadness remains stable or even increases. Our main goal was toprovide further evidence for these multidirectional age differences in the contextof a laboratory study with 84 younger and older adults who were askedto watch five newly developed film clips of serious and complex problems(e.g., spousal abuse, bullying among teenagers) designed to elicit a wide rangeof negative emotions, but particularly, anger and sadness. Overall, olderadults reported greater negative emotional reactions than younger adults. Agedifferences in the emotion profiles also became significant: younger adultsreacted with greater anger than sadness, whereas older adults reacted withgreater sadness than anger to the presented clips. Initial analyses suggest thatage differences in the overall emotional response are correlated with age differencesin cognitive appraisals (e.g., awareness of the serious and long-lastingconsequences of the events depicted in the films) and memory processes(i.e., the ratio of the correctly recognized number of conceptual vs. perceptualinformation). This study will be discussed in the context of recent theoreticalwork on trajectories of emotional experience across the adult life span and anoutline of our planned future work interested in age differences in instructedemotion regulation in situations eliciting a variety of negative emotions anddifferent levels of emotional arousal will be given.

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POSTER 290

Separate vs. concurrent symbolic predictions for pitch and location of sounds

Psychology and Cognition

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Predictive information can modulate early auditory processing, as observable by brain responses when a prediction is violated. In symbol-to-sound matching paradigms, symbols predicted sounds varying either in pitch, or in location (Exp. 1), or in both (Exp. 2). Participants had to detect occasional violations, that is, a sound incongruent to the symbol. The Incongruency Response (IR) and the N2b component of the event-related potential indicate the detection of a violation of the generative model at different hierarchical levels. That is, they presumably reflect feed-forward error signals. When each sound dimension was predicted separately (Exp. 1), an IR component was observed in response to the violation in each dimension. Both IRs had a significantly different time course and topography, suggesting generation in feature specific cortical sensory areas. When tested concurrently (Exp. 2), that is, sounds varied in and participants had to attend both dimensions, an IR was elicited by violations of pitch and violations of both dimensions. Violations of a sound´s predicted location did not elicit an IR. However, N2b was observed in response to all violations, showing significantly shorter latency for two-dimensional violations. We conclude that predictions can be established (a) by arbitrary symbols, and (b) for different sound dimensions. In complex situations (Exp. 2), capacity limits appear to hierarchically affect processing. A backward prediction of sound location could not be established at early sensory levels of processing. But the prediction was represented at a higher level of the hierarchy, as indexed by the N2b.

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POSTER 291

Cholesterol and APOE genotype in mild cognitive impairment and Alzheimer´s disease:

Psychology and Cognition

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Introduction: Animal, epidemiological and clinical studies suggest that cholesterol is a risk factor for Alzheimer´s disease (AD). Nevertheless, the relation of cholesterol with mild cognitive impairment (MCI), the influence of APOE genotype and its changes in lifespan is controversial.

Methods: We investigated the potential impact of plasma total cholesterol (TC) on development of MCI and AD in a representative birth cohort (born 1930-1932) of the Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE) covering three examination waves. Of 500 participants at baseline, 381 survived and were examined at VT3. After exclusion of participants with lifetime prevalence of major psychiatric diseases or mild cognitive disorder due to a medical condition, 222 participants were included.

Results: At VT3, 82 participants had MCI, 22 participants had AD, and 118 were in good health. Participants with MCI and AD at VT3 evidenced higher TC levels at VT1 than those who were healthy. Higher TC levels at baseline were associated with an increased risk for cognitive disorders at VT3 (Highest vs. lowest quartile: OR 2.64, 95% CI 1.12 – 6.23, $p<0.05$). Over the 14 year follow-up, TC levels declined in those with MCI and AD, but remained stable in those who remained healthy. These findings were not modified by APOE genotype nor use of cholesterol-lowering medications.

Conclusions: Our findings demonstrate that higher TC levels are observed long before the clinical manifestation of MCI and AD in patients without psychiatric or somatic co-morbidities and are independent of APOE genotype.

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POSTER 292

Computergestützte Volumetrie der Mamillarkörperchen in vivo mittels hochauflösender 7T MRT

Psychology and Cognition

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Einleitung: Als Schaltstelle limbischer und extralimbischer Projektionen von Hippocampus, Thalamus und Tegmentum mesencephali spielen die Mamillarkörperchen eine wesentliche Rolle für das episodische Gedächtnis. Strukturelle Veränderungen im Rahmen psychiatrischer Erkrankungen sind bekannt u.a. im Rahmen alkoholbedingter Störungen, Schizophrenie, affektiven Störungen und der Alzheimer-Krankheit.
Die hochauflösende (7 Tesla) Magnetresonanztomographie (MRT) ermöglicht es erstmalig die Mamillarkörperchen in vivo im Submillimeterbereich zu vermessen. Hierzu war eingangs eine Methode der manuellen Segmentierung zu entwickeln, welche als Bezugsnorm für automatisierte Segmentierungsverfahren gelten kann.
Methode: Anhand von histologischen Hirnatlanten wurden etablierte anatomische Landmarken der Mamillarkörperchen überarbeitet und ein detaillierter Segmentierungsalgorithmus basierend auf einer Fehlfarbendarstellung entwickelt. 10 neurologisch unauffällige Personen wurden mittels einer 3D MP2RAGE Sequenz im 7T MR Scanners gemessen. Die T1 Bilder wurden koregistiert, interpoliert auf 0.5x0.5x0.5 mm^3 Voxelauflösung und bezüglich der Aufnahmehelligkeit homogenisiert (Histogrammmatching). Die Übereinstimmung zwischen den beiden Ratern betrug ICC=.97 (linker Mamillarkörper) und ICC=.96 (rechter Mamillarkörper). Mit der hier vorgestellten Methode konnte eine hochreliable manuelle Segmentierung der Mamillarkörperchen unter Verwendung hochauflösender MRT Aufnahmen ermöglicht werden. Für weitere methodische Entwicklungen kann das Verfahren als Bezugsnorm gelten.

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POSTER 293

Prävalenzerhebung von Delinquenzrückfällen bei aus dem Maßregelvollzug nach §63 StGB entlassenen Patienten

Psychology and Cognition

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Einleitung: Immer häufiger gerät die forensische Psychiatrie in den Mittelpunkt der deutschen Medien. Dennoch gibt es in Deutschland nur sehr wenige Studien über die Häufigkeit von Rückfällen von aus dem Maßregelvollzug entlassenen Patienten, und damit über die Wirksamkeit der forensischen Psychiatrie. Zum einen soll sie statistisch auswerten, wie viele der aus der Klinik für Forensische Psychiatrie des Sächsischen Krankenhauses Altscherbitz entlassenen Patienten erneut straffällig geworden sind. Zum anderen soll sie ermitteln, ob es während und nach dem Aufenthalt im Maßregelvollzug Kriterien gab, die mit späterer Delinquenz im Zusammenhang stehen.
Methode: Untersucht werden soll die Kohorte der im Zeitraum von 1998 bis 2007 aus dem Maßregelvollzug entlassenen Patienten. Außerdem werden Variablen des anerkannten Prognoseinstruments HCR-20 zum Entlassungszeitpunkt nacherhoben. Anhand der Dokumentation des Bundeszentralregisters erfolgt dann die Prävalenzerhebung delinquenter Rückfälle.
Diskussion: Durch die Erfassung von Daten aus der forensisch psychiatrischen Klinik, der Führungsaufsichtsstelle und des Bundeszentralregisters, kann evaluiert werden, inwieweit die Behandlung psychiatrisch kranker Patienten im Maßregelvollzug erfolgreich war. Im Rahmen der Vorstellung des Studienprotokolls werden die erhobenen Variablen vorgestellt. Es sollen Prädiktoren des Rückfalls kritisch diskutiert und die Verweildauer der Patienten hinterfragt werden.

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POSTER 294

The influence of color on attentional bias for emotional pictures measured with ERP and SSVEP

Psychology and Cognition

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Low-level features of emotional pictures, e.g. complexity, spatial frequency or color, might have an influence on the attentional bias to emotional stimuli. In the present study, the influence of color in emotional distractor processing is examined. Therefore, we presented complex unpleasant and neutral grayscale as well as color pictures in the background and flickering squares in the foreground. Subjects had to attend to the squares to perform a coherent motion task and to ignore the background pictures. Squares flickered at 15 Hz and elicited a steady-state visual evoked potential (SSVEP). Background pictures were only displayed for 133 ms and than masked by a scrambled version of the picture. We analyzed the early posterioir negativity (EPN) and the late postive potential (LPP) that were elicited by the background images. The results confirm previous findings for color pictures. Unpleasant color pictures elicited an EPN and a LPP. In addition, unpleasant color pictures captured attentional resources and decreased the SSVEP amplitude compared to neutral color pictures. However, unpleasant grayscale pictures elicited only an EPN but neither LPP nor SSVEP amplitude reduction. The results indicate that under demanding conditions (short presentation time and competing task) color is a crucial factor for attentional resource allocation to emotional pictures.

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POSTER 295

Depressionsscreening am Telefon mittels der Allgemeinen Depressionsskala (ADS) – Ergebnisse einer bevölkerungsrepräsentativen Erhebung

Psychology and Cognition

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Anliegen: Analyse der Reliabilität und Validität der Allgemeinen Depressionsskala (ADS) sowie die Ermittlung von Normwerten im Rahmen einer Telefonbefragung.
Methode: Eine bevölkerungsrepräsentative Stichprobe von 868 Personen (18 bis 94 Jahre) wurde telefonisch mittels strukturierter Interviews befragt.
Ergebnisse: Nach dem Cut-Off-Wert von 16 Punkten zeigten 8,5% der gesamten Stichprobe (11,0% Frauen und 5,6% Männer) relevante depressive Symptome. Bei Verwendung des Cut-Off-Wertes von 22 Punkten wurden 3,5% der Probanden der gesamten Stichprobe (4,2% Frauen und 2,5% Männer) als depressiv eingestuft. Die Analyse der psychometrischen Gütekriterien wie die interne Konsistenz, Test-Retest-Reliabilität, Konstruktvalidität und Faktorenstruktur der ADS erbrachte moderate bis gute Werte. Es wurden Prozentrangnormen ermittelt.
Schlussfolgerung: Die ADS erwies sich als ein reliables und valides Verfahren zur telefonischen Erfassung von depressiven Symptomen. In der vorliegenden Arbeit werden aktuelle Normwerte speziell für den Einsatz in telefonischen Befragungen vorgelegt.

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POSTER 296

The role of the family in childhood and adolescent binge eating – A systematic review

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Objective: While family factors in childhood and adolescent anorexia nervosa and bulimia nervosa are well-documented and were often reviewed before, less is known about these influences on binge eating without compensatory behavior. Therefore, the aim of this systematic review is to describe family factors in the development and maintenance of binge eating.
Method: A systematic literature search was conducted in four major data bases for studies on associations between binge eating, loss of control eating and family outcomes published up to April, 2013 in German and English language.
Results: Among the 278 non-duplicate citations, 26 studies met inclusion criteria for this study. Consistent evidence was found for cross-sectional associations between binge eating and insecure attachment of the child, lower family functioning and lower parental involvement; for parental unemployment and parental depression as retrospective correlates; and for fewer family meals and more critical comments about weight or shape by parents as variable risk factors. In contrast, rather inconsistent findings referred to the influence of family structures, parental eating disorders, dieting and their knowledge about child's eating behaviour.
Conclusions: As documented in other eating disorders in youth, the results suggest the importance of familial factors in binge eating. Consequently, family assessment and family-based interventions might be helpful in the treatment of childhood and adolescent binge eating. More research should clarify inconsistent findings using prospective designs.

Funding: ifb

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POSTER 297 **Feedback system for surgical training support**

Social Medicine

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One approach to increase the quality of surgeon's education in addition to the traditional curriculum is to argue the case of training courses. An inherent part of courses are training simulators such as the realistic surgical training simulator for lumbar disc herniation with integrated sensors. The sensors measure the applied stress and strain to the different risk structures and provide therefore a recent source of information granting feedback to trainee surgeons.
As the research of education in surgery continues, the initial process of granting feedback while surgical training to trainees was disposed in the past. Now it can be updated to a new improved method using a feedback system including sensor information in addition to audiovisual information.
The requirements that an adequate feedback system should achieve were gathered from a previously developed evaluation model, which was assessed within surgical trainings. The identified requirements were used to build an improved feedback system consisting of hardware and software. The new feedback system can record multiple audio and visual channels and provide an open, easily accessible interface for recording additionally sensor information. The improved feedback system was applied during several validation processes of the simulator for lumbar disc herniation. Its usage indicated that when the new feedback system is used, it can lead to optimize the trainee's learning objectives. The feedback system offers surgical trainers to grant more objective and well-founded feedback based on synchronized video, audio and sensor information of previously recorded trainings.

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POSTER 298

Kinderwunsch und Fertilitätserhalt bei Patienten mit hämatologischen Neoplasien im jungen Erwachsenenalter – Eine Studie zur Arzt-Patienten-Kommunikation

Social Medicine

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Die Aufklärung über mögliche Fertilitätseinschränkungen durch die medizinische Behandlung seitens der Onkologen ermöglicht die Weitervermittlung an die Reproduktionsmedizin und damit auch die Inanspruchnahme von Fertilitätsprotektionen. Dem Onkologen kommt somit im Zusammenhang mit dem Fertilitätserhalt junger Krebspatienten eine Schlüsselposition zu. Patienten mit einer hämatologischen Neoplasie (18-45 Jahre), die zum Diagnosezeitpunkt noch einen Kinderwunsch hatten sowie Hämato-Onkologen wurden zur A-P-Kommunikation bezogen auf Fertilitätsaspekte interviewt. 27 der 30 Patienten haben mit ihrem Onkologen über ihre Fertilität gesprochen (18 Patienten vor Behandlungsbeginn). Die Gespräche wurden von 13 Patienten positiv eingeschätzt. Eine Fertilitätsprotektion ließen 17 Patienten (9 Männer) durchführen. Für die 25 Onkologen stellte die Fertilitätsthematik eine große Relevanz dar. Gründe, die Thematik nicht zu besprechen, waren: höheres Erwachsenenalter (N=13), ungünstige Prognose (N=8), intensivpflichtiger Patient bzw. sofortiger Behandlungsbeginn (N=9). Die eigenen reproduktionsmedizinischen Kenntnisse wurden als ausreichend eingeschätzt (N=14), jeder dritte Onkologe (N=8) wünschte sich mehr Informationen zum Fertilitätserhalt. Die Ergebnisse zeigen, dass eine Aufklärung zu Fertilitätsaspekten überwiegend erfolgt. Zur Verbesserung der A-P-Kommunikation sollten die vorhandenen guten Kooperationen mit den reproduktionsmedizinischen Zentren ausgebaut werden, um weiterführende Fachkenntnisse zum Fertilitätserhalt zu vermitteln. Ferner sollten Informationsmaterialien für die Betroffenen bereitgestellt werden.

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POSTER 299

Twinning-(Pilot)Projekt – Eine interdisziplinäre Zusammenarbeit zwischen dem Institut für Anatomie der Universität Leipzig und der Medizinischen Berufsfachschule der Klinikum Chemnitz gGmbH

Social Medicine

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Tumor Targeting

Ziel dieses Projektes ist es, schon im Studium und in der Ausbildung Schlüsselkompetenzen zu fördern und mit interdisziplinärem Lernen eine optimale Voraussetzung für eine spätere interprofessionelle Zusammenarbeit zu schaffen. Studierende und Auszubildende wechseln die Position als Lernende und übernehmen selbstständig Lehre. Im Mai 2013 begann mit diesem fächerübergreifenden Projektunterricht, bei dem handlungsorientiert gelehrt und gelernt wird, eine einmalige Form der Prüfungsvorbereitung von Zahnmedizinstudenten des ersten Studienjahres und Auszubildenden der Gesundheitsfachberufe des dritten Ausbildungsjahres. Die Stärkung der interprofessionellen Zusammenarbeit sowie die Förderung von Schlüsselkompetenzen sind sowohl im Studium als auch in der Ausbildung wichtige Lernziele, da im Nationalen Kompetenzbasierten Lernzielkatalog Zahnmedizin (NKLZ) und im Gesetz über die Berufe in der Krankenpflege (KrpflG 2003) die Förderung dieser Kompetenzen gleichermaßen angestrebt wird.
Den 25 Studierenden stellten 13 Auszubildende ausgewählte klinische Krankheitsbilder in verschiedenen Lehrmethoden wie Gruppenarbeit, Rollenspiel und Präsentation dar, und im Gegenzug erläuterten und demonstrierten die Zahnmedizinstudenten die jeweiligen anatomischen Korrelate im Brust- und Bauchsitus. Dadurch konnten die angehenden Zahnärzte und Pflegekräfte nicht nur ihre Fach- und Methodenkompetenz erweitern und fördern, sondern auch Team- und Kommunikationsfähigkeit schulen. Damit wird schon während der Ausbildung beider Berufsgruppen eine wesentliche Grundlage für die spätere interdisziplinäre Zusammenarbeit gelegt. Die Evaluation in Anlehnung an den Fragebogen der „LaborUniversität" ergab, dass die überwiegende Mehrheit der Teilnehmer ihre fachliche, methodische und soziale Kompetenzen durch das Projekt verbessern konnte.
Fazit: Dieses Projekt wird in modifizierter Form im nächsten Studienjahr fortgesetzt.

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POSTER 300

Und was kommt nach der Chemo? Der psychosoziale Unterstützungsbedarf von Krebspatienten im jungen Erwachsenenalter (AYA)

Social Medicine

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Krebspatienten im jungen Erwachsenenalter (AYA: Adolescents and Young Adults) müssen sich mit den physischen u. psychosozialen Folgen der Erkrankung bzw. deren Behandlung auseinandersetzen u. gleichzeitig spezifische Entwicklungsaufgaben (z.B. Reifung der Persönlichkeit, Karriere, Familiengründung) bewältigen. Diese altersspezifischen Besonderheiten sollten in der psychosozialen Versorgung der Patienten aufgegriffen werden. 117 Krebspatienten (18-39 Jahre) wurden nach Abschluss der Akutbehandlung mit der deutschen Version des SCNS-SF34G, Zusatzitems zu Kinderwunsch/Fertilität sowie nach der Inanspruchnahme psychosozialer Unterstützung befragt. Für die Skalen Kinderwunsch/Fertilität (M=34,16) u. psychologische Unterstützung (M=32,56) lag der größte Wunsch an Unterstützung vor, während der Unterstützungsbedarf hinsichtlich Versorgung/Hilfe (M=16,09) am geringsten ausgeprägt war. Frauen (N=77) gaben auf den Skalen psychologische Unterstützung (♀: M=38,47; ♂: M=21,19; p< .001), Alltagsbewältigung (♀: M=23,49; ♂: M=12,25 p< .004) u. sexuelle Probleme (♀: M=26,75; ♂: M=15,83; p< .043) einen höheren Unterstützungsbedarf als Männer (N=40) an. Psychosoziale Versorgungsangebote (wie sozialrechtliche u. psychologische Beratung) wurden von 57,3% bzw. 55,6% der Patienten in Anspruch genommen. Die AYA zeigten einen deutlichen Unterstützungsbedarf in den Bereichen Kinderwunsch/Fertilität sowie in psychologischen Belangen an. Die Inanspruchnahme von psychosozialen Unterstützungsangeboten sollte ausgebaut u. spezifische Interventionsangebote v.a. in Bezug auf den Kinderwunsch u. der Sexualität etabliert werden.

Funding: formel1

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POSTER 301

Sexuality among Disabled Young People in Ethiopia

Social Medicine

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Objective: In Ethiopia, people with disabilities are often marginalized and not recognized as being sexual. Only little is known about their Sexual Reproductive Health (SRH) status and related problems so far, and thus, SRH related programs may not target them or accommodate their special needs. We therefore aimed to assess the SRH status and associated factors among a sample of young people with disability (YPWD) in Addis Ababa, Ethiopia.

Methods: A cross-sectional survey was conducted from June to September, 2012. Data were collected by trained interviewers using a structured questionnaire. A total of 426 YPWD aged between 10-24 years were enrolled using systematic sampling technique. The socio-demographic and the sexual reproductive health characteristics of the respondents were described and associated factors were analyzed using unadjusted and adjusted logistic regression models.

Results: Two hundred twenty one (52%) of YPWD ever had sexual intercourse. 75% started sex between the age of 15-19 years and only 35% had used contraceptive during their first sexual encounter. The majorities of the pregnancies by YPWD (70%) were unintended and 55% of YPWD had history of abortion. 68% of abortions were induced. The majority of the sexually experienced YPWD (59%) had multiple life time sexual partners, 19% had a casual and 21 a commercial sex partner in the past 12 months period prior to the survey respectively. Only 48% consistently used condoms with their casual or commercial sex partners. 24% of the sexually experienced YPWD had a history of sexually transmitted infections and 27% of ever use of drugs.

Conclusions: Our findings indicate that YPWD in Ethiopia are sexually active, but also highly involved in risky sexual practices, what puts them at great risk for sexual and reproductive health associated problems. There is a need for in-depth research to better understand the determinants of risky sexual behavior among YPWD and to propose preventive approaches.

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POSTER 302

Verständigung mit allgemeinpädiatrischen Patienten bzw. Sorgeberechtigten mit Migrantionshintergrund

Social Medicine

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Hintergrund: Zentraler Aspekt der medizinischen Versorgung von Patienten mit Migrationshintergrund (MH) ist die Bewältigung sprachlicher und kultureller Barrieren. Besondere Anforderungen bestehen diesbezüglich in der Pädiatrie, da die Verständigung hier zwischen dem Kind als Patienten und dem medizinischen Personal sowie den Sorgeberechtigten (SB) und dem Personal stattfindet.
Methode: Von Februar bis Mai 2013 wurden Patienten, SB und ärztliches sowie Pflegepersonal der Allgemeinpädiatrie der Universitätskinderklinik Leipzig mittels Fragebogen nach ihrer Verständigung befragt. Ebenfalls wurde der MH und Einsatz von Dolmetschern erhoben.
Ergebnisse: 17,2% (N= 244) der Befragten haben einen MH. Sie stammen aus 32 Ländern. Russland und Vietnam bilden die größten Gruppen. Die Verständigung zwischen dem Klinikpersonal und den Patienten mit bzw. ohne MG unterschied sich nicht. Die Verständigung mit SB mit MH wurde vom Klinikpersonal signifikant schlechter beurteilt als mit SB ohne MH [MW=5,9 (SD=4,2) vs. MW=9,8 (SD=0,9); p<.001]. Auch seitens der Patienten bzw. SB mit MH wurde die Verständigung mit dem Klinikpersonal schlechter eingeschätzt [MW=5,1 (SD=4,1) vs. MW=8,2 (SD=1,9); p=.004]. Bei 12,5% (N=24) wurde zur Verständigung mit den SB eine dolmetschende Person hinzugezogen, zumeist ein Angehöriger. Professionelle Sprachmittler kamen nicht zum Einsatz.
Diskussion: Verständigungsprobleme in der Allgemeinpädiatrie gab es vor allem zwischen SB mit MH und dem Klinikpersonal. Eine Möglichkeit zur Verbesserung der Kommunikation mit den SB, wäre der Einsatz von Sprachmittlern, welcher zur Zeit in sehr geringem Umfang genutzt wird.

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POSTER 303

Evaluation des Modellprojektes „Schulcoaches – Seelische Fitness stärken"

Social Medicine

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Ziel ist die Evaluation der zweiten Phase des Schulcoach-Projekts (2012-2013) des Leipziger Vereins „Irrsinnig Menschlich e.V.". Durch Einbeziehung aller Beteiligten des Systems Schule soll nachhaltig ein gesundes Schulklima geschaffen werden. Im Unterschied zum Schulsozialarbeiter arbeitet der Schulcoach mit personenzentriertem und strukturellem Coaching, der Fokus liegt verstärkt auf der Sensibilisierung für psychische Gesundheit.

Im Rahmen eines quantitativen longitudinalen Designs wurden Schüler der 5. und 9. Klassen (n=553), Lehrer (n=186) und Eltern (n=535) an fünf sächsischen Projektschulen zu 2 Zeitpunkten befragt. Themen waren u.a. das Schulklima, die Arbeit der Schulcoaches, Mobbing und Lehrergesundheit (Burnout).

Die Schulcoaches sind Teil der Schulen: alle Zielgruppen wurden erreicht, sie sind zunehmend persönlich bekannt und stehen in guter Beziehung. Sie konnten einer wachsenden Zahl Hilfesuchender gut/sehr gut helfen. Ihre Arbeit wurde zunehmend als wichtig/sehr wichtig eingeschätzt.

Mobbing ist in allen Projektschulen verbreitet und hat wesentlichen Einfluss auf Faktoren des Wohlbefindens (z.B. Integration, Leistungen, Lebensqualität).

Zwischen 11% und 18% der befragten Lehrer hatten hohe bzw. sehr hohe Werte in einer Burnout-Kategorie. Orte für ungestörte Gespräche oder enge Zusammenarbeit der Schule mit lokalen Einrichtungen können diesen Anteil senken.

Ziel der Evaluation ist es, die Nachhaltigkeit der Schulcoach-Arbeit zu erfassen. Langfristig stehen Rahmenbedingungen im Blickpunkt (z.B. Ausbildungsmodule), die eine erfolgreiche Implementierung von Schulcoaches jenseits des Pilotprojekts begünstigen.

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POSTER 304

Psychosoziale Konsequenzen des Aufwachsens als „Besatzungskind" des Zweiten Weltkrieges in Deutschland

Social Medicine

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Hintergrund: Seit dem es Kriege gibt, werden Kinder geboren, die in sexuellen Kontakten zwischen (feindlichen) Soldaten und einheimischen Frauen gezeugt wurden. Diese „Kinder des Krieges" wachsen häufig in einem familiären wie gesellschaftlichen Spannungsfeld zwischen Integration und Ablehnung auf. Geheimhaltung, finanzielle Notlagen, öffentliche wie familiäre Zurückweisung spielen häufig eine Rolle. Bisher gibt es zwar historische und soziologische Untersuchungen zu den „Besatzungskindern" des Zweiten Weltkrieges in Deutschland, Untersuchungen zu den psychosozialen Konsequenzen des Aufwachsens als „Besatzungskind" in Deutschland fehlten jedoch bislang.
Methodik: Zwischen März und September 2013 wurden deutsche „Besatzungskinder" über Presseartikel und verschiedene Netzwerke und Onlineplattformen kontaktiert. Es wurden 174 Fragebögen versandt (RQ=87%; N=152). Der Fragebogen beinhaltete offene und geschlossene Fragen zu den Bedingungen des Aufwachsens und dem Selbstbild als „Besatzungskind", sowie zu aversiven Kindheitserfahrungen (CTQ), Bindungsstilen (AAS), Stigmaerfahrungen (ISE), Selbst-Stigmatisierung (angelehnt an ISMI & SSMI), zu traumatischen Ereignissen (Traumaliste des M-CIDI), aktuellen posttraumatischen (PDS), depressiven und somatoformen Symptomen (PHQ-9 bzw. –15), sowie zur aktuellen Lebenszufriedenheit (SWLS).
Ergebnisse & Ausblick: Die Stichprobe und die empirischen Ergebnisse zur Beziehung der Eltern und der Herkunft des Vaters werden vorgestellt. Ziel der Studie ist es Transparenz für das Thema zu fördern und Ansätze für Destigmatisierungs- und Hilfsangebote in aktuellen (Post-)Konfliktregionen abzuleiten.

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POSTER 305 **Extended storage of granulocyte apheresates for clinical transfusions**

Social Medicine

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Introduction: Granulocyte apheresates from donors are mainly limited for broad application by a very short storage time of 6-24 hours after donation and have to be prepared specifically for each patient. The short storage period partially results from the high contamination (~99%) with erythrocytes and thrombocytes. We developed a closed system method compatible with standard blood bank technologies in order to enrich the granulocytes and store them for longer periods.

Methods: Granulocyte apheresates were prepared in a medical blood bank according to clinical standard procedures by cytapheresis from healthy donors that were pre-stimulated with steroids and G-CSF. Apheresates were subsequently sedimented on hydroxyethylstarch (HES), washed with isotonic saline solution and stored in blood group identical plasma. The viability of the granulocytes was tested daily. In addition, the phagocytosis and oxyburst rate were analysed by flow cytometry.

Results: All purification procedures can be done in a "closed system" compatible with clinical regulatory requirements. HES sedimentation resulted in decrease of erythrocytes by 98% and washing reduced the thrombocytes by 95% resulting in strong enrichment of granulocytes. After 72 hour of storage>90% of the granulocytes were viable and exhibited a high phagocytosis and oxyburst functionality.

Conclusions: The developed method is compatible with the standard technologies of clinical blood banks. The higher purity of such prepared apheresates enables an extension of storage time from 24 to 72 hours and expands the applicability of granulocyte transfusions in the clinic.

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POSTER 306

Soziale Unterstützung und Lebensqualität im Rehabilitationsprozess in der Mitteldeutschen Bandscheibenkohorte

Social Medicine

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Fragestellung: Die Studie untersucht die subjektiv erlebte soziale Unterstützung von Bandscheibenoperierten, die Veränderung der körperlichen, psychischen und sozialen Lebensqualität (LQ) im Zeitverlauf von 15 Monaten nach der OP im Vergleich zur Allgemeinbevölkerung sowie welche Faktoren mit der körperlichen, psychischen und sozialen LQ im Zeitverlauf assoziiert sind.
Methodik: Zur Baseline wurden 534 konsekutive Patienten (18 bis 55 Jahre) im Akutkrankenhaus nach einer Bandscheiben-OP in Form von persönlichen Interviews befragt. Drei, neun und 15 Monate nach der OP fanden telefonische Follow-ups statt. Die LQ im Zeitverlauf wurde mittels SF-36 erhoben.
Ergebnisse: 21,7 % der Patienten wünschen sich mehr Verständnis/Unterstützung durch den Arbeitgeber. Die körperliche, psychische und soziale LQ nimmt im Zeitverlauf von 15 Monaten signifikant zu. Dennoch ist die körperliche und soziale LQ zu allen vier Messzeitpunkten signifikant schlechter im Vergleich zur deutschen Allgemeinbevölkerung. Risikogruppen für eine schlechtere körperliche LQ stellen ältere Patienten, Frauen, Patienten mit einer höheren Schmerzintensität, mit psychischen Belastungen sowie mit geringerem Bildungsstand dar. Risikogruppen für eine schlechtere psychische LQ sind Patienten mit höherem Bildungsstand, Frauen sowie Patienten mit psychischen Belastungen. Risikogruppen für eine schlechtere soziale LQ stellen jüngere Patienten, Frauen und Patienten mit psychischen Belastungen dar.
Schlussfolgerung: Eine frühzeitige Implementierung psychosozialer Interventionen bei bandscheibenoperierten Patienten könnte die körperliche und soziale LQ verbessern helfen.

Funding: formel1

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POSTER 307

Das Sexualwissen von Jugendlichen mit Körperbehinderungen – Eine systematische Literaturübersicht

Social Medicine

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Menschen mit Behinderungen wurden bisher als kindlich und unschuldig wahrgenommen bis hin zu einer zugeschriebenen Asexualität. Das Review gibt einen Überblick über Studien, die Informationen über die Vorbereitung von körperlich behinderten Jugendlichen auf Sexualität und Partnerschaft enthalten.
Die Literaturrecherche erfolgte mittels der Datenbanken: Medline, Pubmed, Web of Science und Psycinfo. Eingeschlossen wurden Studien, welche die Sexualerziehung und das Sexualwissen von Jugendlichen und Adoleszenten mit körperlichen Behinderungen thematisieren.
Der systematischen Literaturübersicht liegen neun quantitativ angelegte Studien zugrunde. Fast alle Studienteilnehmer haben in irgendeiner Form Informationen zu Themen rund um die Sexualität erhalten. Primäre Informationsquellen sind die Eltern sowie die Schule. Studienteilnehmer mit stärkeren Einschränkungen haben den Unterricht eher als nicht hilfreich empfunden. In allen Untersuchungen waren Hauptthemen des Sexualkundeunterrichtes Fortpflanzung, Verhütung und Familienplanung sowie Geschlechtskrankheiten. Das Sexualwissen korreliert mit dem Alter der Probanden. Es ist jedoch unabhängig vom Geschlecht oder der Mobilität der Studienteilnehmer.
Sexuelle Aufklärung ist wichtig für eine selbstbestimmte Lebensführung. Fachkräfte sind Wunschansprechpartner. Diese sollten darauf vorbereitet und gut ausgebildet sein. Fachkräften kommt dabei eine aktive Rolle bei der Aufklärung und Informationsweitergabe zu, da sich Eltern oft hilflos und überfordert fühlen. Besonders Ärzte und Schwestern werden von den Jugendlichen als Wunschansprechpartner angegeben.

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POSTER 308

Akzeptanz und psychometrische Eigenschaften tabletbasierter Depressionsdiagnostik im Vergleich zu Paper-Pencil-Erhebungen bei älteren Hausarztpatienten

Social Medicine

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Hintergrund: Reliable, valide und ökonomische Depressionsdiagnostik ist bei Älteren relevant. Der Einsatz von Tablets hat Vorteile (geringer zeitlicher Aufwand, kaum fehleranfällig, Einsatz adaptiver Tests möglich). Die Studie untersucht Akzeptanz, Usablility und Moduseffekte von Tabletdiagnostik (T) im Vergleich mit Papierfragebögen (PP).
Methodik: 193 Hausarztpatienten (60-90 Jahre) wurden in einem cross-over Design untersucht (randomisierte Zuteilung zu Bedingung A (erst T, dann PP) oder Bedingung B (erst PP, dann T). Auf Dell Lattitude ST Tablets (Eingabe per Finger oder Stylus) sowie mit Papierbögen wurden die Aachener Depressionsitembank (ADIB) und das Depressionsmodul des Patient Health Questionnaire (PHQ-9) erhoben. Zusätzlich wurden 5 Items zu Usability und Akzeptanz vorgelegt und die Bearbeitungszeit für ADIB und PHQ-9 in beiden Modi protokolliert.
Ergebnisse: Die Teilnehmer bewerteten das Tablet als übersichtlich und gut handhabbar. Im Vergleich zum Papierfragebögen beurteilten sie das Tablet als geeigneter, weniger anstrengend und weniger schwierig. Varianzanalysen mit Messwiederholung zeigten keinen Effekt des Erhebungsmodus für den PHQ-9 Score, aber eine längere Bearbeitungszeit beim Tablet. Dieser Unterschied war besonders ausgeprägt, wenn zuerst das Tablet eingesetzt wurde.
Diskussion: Tablets scheinen auch bei Älteren gut einsetzbar zu sein, da diese gut damit zurechtkommen und sie im Vergleich mit Papierbögen sehr positiv bewerten. Im PHQ-9 gibt es keinen Hinweis auf einen Effekt des Erhebungsmodus auf den Gesamtscore, weitere Analysen der Moduseffekte für ADIB udn PHQ-9 stehen allerdings noch aus.

Funding: formel1

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POSTER 309 **Lebensqualität bei leichten kognitiven Störungen**

Social Medicine

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Hintergrund: Ziel der vorliegenden Untersuchung war die Erfassung der Lebensqualität (LQ) von älteren Menschen mit leichten kognitiven Störungen im Vergleich zu kognitiv gesunden älteren Menschen. Die Prävalenz von leichten kognitiven Störungen in der Bevölkerung wird in epidemiologischen Studien mit 3 bis 19% der über 65-Jährigen angegeben.
Methode: Es handelt sich um eine bevölkerungsrepräsentative Umfrage mit 997 Probanden (60 Jahre und älter) zu ihrer subjektiven LQ. Die Erfassung erfolgte mittels der Messinstrumente WHOQOL-BREF und dem speziell für ältere Menschen entwickelten WHOQOL-OLD. Zudem wurden die ermittelten Werte für die LQ in den soziodemografischen Kontext gesetzt, um eventuelle Faktoren zu ermitteln, die die unterschiedlichen Bereiche der LQ beeinflussen. Zur Messung der kognitiven Fähigkeit wurde der DemTect eingesetzt. Bei Verdacht auf Demenz fand das Interview nicht statt. Durch das Ergebnis des DemTect konnte bei der Auswertung die Zuteilung der Probanden in die jeweilige Gruppe (MCI vs. kognitiv gesund) vorgenommen werden. Die Kriterien für die Gruppe der Probanden mit leichten kognitiven Störungen erfüllten 267 Probanden, für 730 Teilnehmer fanden sich keine Anzeichen einer kognitiven Beeinträchtigung.
Ergebnis: Die befragten älteren Probanden mit leichten kognitiven Störungen schätzen ihre LQ in allen Bereichen des WHOQOL-BREF und WHOQOL-OLD (außer Bereich „Ängste und Befürchtungen vor Tod und Sterben“) geringer ein als kognitiv gesunde Probanden.
Schlussfolgerung: Es konnte gezeigt werden, dass bereits leichte kognitive Störungen erhebliche Auswirkungen auf die subjektive LQ bedeuten.

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POSTER 310

Legascreen: towards an early screening test for dyslexia: a representative survey on acceptance

Social Medicine

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Our aim is to develop an early screening test for dyslexia, a severe disorder of reading and writing, affecting ca. 4-5% of all German schoolchildren. Genetic influence is estimated to be 50-70% and characteristic EEG-signatures are known, providing options for early identification of subjects at risk for dyslexia, resulting in the possibility of early intervention by specific support and training for affected children.

Besides the actual development of such a screening test, another important issue is its acceptance by future customers. Therefore, 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. Since we consider parents of German children aged 3 to7 as our future customers, we performed a representative survey in this population (n=1000).

Generally, we found a very positive attitude towards our test. 89% of all participants supported the introduction of an early screening test for dyslexia. 58% would want their own child to be tested even if their health insurance would not cover the costs. Almost two thirds of all people stated that they would pay for this screening test by themselves, and 90% wished to receive detailed additional information on early support for their children together with the test results.

Given the results of this representative survey, we are very confident that the people would accept our early screening test for dyslexia once it is finished and approved.

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POSTER 311

Studienansatz und erste Ergebnisse im Projekt „Dyadisches Coping bei hämatoonkologischen Patienten im Zeitverlauf“

Social Medicine

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Schwere körperliche Erkrankungen, wie beispielsweise hämatoonkologische Krankheiten, werden in partnerschaftlichen Beziehungen unterschiedlich verarbeitet. Um dem positiven oder negativen Umgang mit seelischen Belastungspotentialen in Paarbeziehungen Rechnung zu tragen, konzeptualisierte Bodenmann (1995) das Dyadische Coping (D.C.). Im Rahmen eines bizentrischen Ansatzes (Leipzig und Ulm) untersuchen wir das D.C. bei hämatologischen Patienten und deren Partnern mit dem Ziel, Korrelate für positive oder negative Verläufe zu finden. Im Zeitraum 2012 bis 2015 werden 320 Paare in die Studie eingeschlossen und längsschnittlich befragt. Einschlusskriterien sind neben den ICD-10 Diagnosen C81-C96 / D46 ein Alter 18-75 sowie hinreichende kognitive Voraussetzungen. Die Befragung findet nach der Diagnosestellung sowie 6 Monate später statt. Analysen zum 1. Messzeitpunkt mit bislang 145 Dyaden konnten einen durchschnittlichen Gesamtwert des D.C. von 124.5 (sd. 18.9; range 77-170) für Patienten und 123.7 (sd. 19.6; range 62-168) für Partner nachweisen. Damit liegt das D.C. für beide Gruppen im Normalbereich der Validierungsstichprobe (111-145) was bedeutet, dass auf dieser Auswertungsebene keine krankheitsrelevanten Änderungen der Copingstile zu beobachten sind. Folgeauswertungen werden Subskalenanalysen, Zusammenhänge zwischen D.C. und der Lebensqualität, sowie den Einfluss bestimmter soziodemografischer und paarbezogener Merkmale als Risikofaktoren für ungünstige Copingverläufe untersuchen. Wichtige Implikationen für die diagnostische und therapeutische Praxis werden erwartet.

Funding: Carreras-Stiftung

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POSTER 312

Graft versus host disease: An overview of murine in vivo disease models

TRM – Translational Regenerative Medicine

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Graft versus Host Disease (GvHD) is a severe immunologic disease, which occurs after allogeneic or xenogeneic transplantation of hematopoietic stem cells into humans. Immune cells, foremost T cells, located within the stem cell graft react against host antigens and induce a systemic immune reaction.

Animal models of GvHD are a valuable tool in current research not only concerning GvHD therapy, but also other immunological diseases with similar pathologies. GvHD animal models are based on transplantation of donor stem and/or immune cells into an allogenic, transgenic or even xenogenic host. Especially in the field of immunological research, the transfer of pre-clinical results obtained in non-humanized animal models into clinical practice proved to be problematic.

A distinct advantage of GvHD animal models is the availability of murine, but also partially or completely humanized settings, depending on the source of donor cells. For the murine model, bone marrow and spleen cells of inbred strains differing from the host mice are used. By obtaining the transplant from transgenic animals (e.g. carrying human T cell receptor genes), a partially humanized animal model is created. Recently, human peripheral blood cells (PBMCs) and/or umbilical cord blood has been established as donor source, as well. For xenogenic transplants, the hosts are complex immune incompetent mice strains such as NOD*scid*-il2rg$^{-/-}$ (NSG) or NOD*rag1*-il2rg$^{-/-}$ (NRG).

Here, we present and compare current GvHD animal models, their basic experimental layout and advantages as well as disadvantages.

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POSTER 313

Epidermal equivalent consisting of melanocytes and keratinocytes as a graft for depigmentation treatment

TRM – Translational Regenerative Medicine

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BACKGROUND: Vitiligo is a chronic local depigmentation skin disease manifested in white skin lesions due to destroyed melanocytes in the epidermis. Replacement of the dysfunctional tissue is currently the only available causal treatment with long-lasting effects. Such transplantation treatments involve surgical excision of an unaffected skin piece. We are working on melanocytes and keratinocytes cultivated and differentiated from the Outer Root Sheath (ORS) of plucked human hair follicles as a non-invasive alternative for an autologous therapy.
MATERIAL & METHODS: ORS melanocytes and keratinocytes were cultivated from hair follicles upon an optimized patent-protected method. A medium-air-interface culture was conducted to propagate the ORS cell pool. Melanocytes were introduced to the base of the keratinocyte strata, mimicking stratum basale, and co-cultured for 12 days. Cross-sections were morphologically analyzed and immunofluorescence-stained for cellular identity markers. Melanocytes were analyzed for expression of Tyrosinase and glycoprotein 100 variants (NKI-beteb, HMB45) and melanin in situ was determined by Nile Blue staining. Keratinocyte integrity was monitored by Rodamin B. Gene expression of the markers was monitored by qRT-PCR.
RESULTS: This work-in-progress study presents an in vitro-generated epidermal equivalent consisting of melanocytes and keratinocytes. Melanocytes have retained their cellular identity, expressed melanocyte markers and produced melanin. Equally, the expression of keratinocyte specific markers indicate development and maintainance of keratinocyte functionality within the engineered graft.

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POSTER 314 **Gene therapy of graft versus host disease (GvHD)**

TRM – Translational Regenerative Medicine

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Tumor Targeting

We aim to prevent Graft versus Host Disease (GvHD), a complication of hematopoietic stem cell transplantation, by transient knockdown of T-cell receptor (TCR) genes.
Antisense oligonucleotides (AONs) were designed to target TCR genes cd4 and cd28 and tested *in vitro*.
Most promising AONs were then explored in an *in vivo* GvHD model based on transplantation of *ex vivo* transfected spleen cells and bone marrow into irradiated host mice of differing strains. Mice were scored daily, hemograms and blood flow cytometry (FC) were obtained weekly. Upon sacrifice, tissues were preserved for RNA extraction and histological analysis.
Transfection rates of ~30-40% were measured with long-time persistence of fluorescence-labeled AONs up to 6 weeks. AONs transfected were able to significantly reduce surface TCR up to 50%, as well as cytokine expression and proliferation *in vitro*.
In vivo transfection of a-cd4 AON by PEI prevented GvHD. FC analyses confirmed implantation of donor cells and hemograms showed white blood cell ablation with subsequent restoration. The cd4/cd8 ratio flipped at onset of GvHD, but was restored in surviving animals, concurring with reduced cd4/cd8 mRNA levels and reduced cytokine expression in spleen.
Thus we conclude, that transfection of a-cd4-AON by PEI into a stem cell transplant was able to prevent onset of GvHD without hindering hematopoiesis. Furthermore, other immune diseases with disease pathology similar to GvHD might be treatable as well and we propose a new class of immunosuppressive drugs based on transient TCR gene knockdown.

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POSTER 315

The Unpatentability of Human Embryonic Stem Cell Inventions

TRM – Translational Regenerative Medicine

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Contrary to public and partly professional opinion, after the Brüstle-Case within the patent law of the European Union and the WARF-Case under the European Patent Convention (EPC) there are, *de facto*, no patentable methods or products in the field of human embryonic stem cell technology left.

After the Brüstle- and the WARF-decision it became clear that under both patent legislations patents cannot be granted for inventions concerning human embryonic stem cells from human embryos, if the embryo is destroyed for this purpose. Also no patents can be granted under both legislations for patents which rely on human embryonic stem cells, no matter how they were derived in the past as long as it was necessary to destroy an embryo.

However, even for those methods for the derivation of embryonic stem cell lines, which do not rely on the destruction of a human embryo there is a more factual exclusion from patentability. This is due to the fact that these methods are either banned by national laws, e.g., because the respective approach involves cloning of a human embryo, or seem to be unsuccessful by scientific meanings, and thus no real alternative to the established methods which involve the destruction of an embryo.

Thus, although inventions in the field of human embryonic stem cell technology are *de facto* not patentable in Europe, it seems, when looking into publication numbers of scientific journals, that research activity in this field is not affected by current patent limitations. This indicates that the stem cell research field is not solely depending on patent protection.

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POSTER 316

The influence of surgical procedure and scaffold crosslinking on esophageal replacement in pigs: A pilot study

TRM – Translational Regenerative Medicine

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Tumor Targeting

Most infants with long-gap esophageal atresia (LGEA) receive an esophageal replacement with tissue from stomach or colon, because native esophagus is too short for a true primary repair. As an alternative therapy, in this pilot study esophagi were harvested from pigs (45kg), decellularized and sterilized. Pigs (12 weeks) were divided in 4 groups to investigate the influence of 2 different surgical procedures on success of implantation (procedure 1: esophageal incision; procedure 2: removal of 1 cm muscularis ring). Additionally, genipin-crosslinked and untreated scaffolds were implanted (each n=6). At day 30 postoperative, the esophageal functionality was examined under a C-arm using barium sulfate as contrast agent. At six month follow-up, implants were removed and analyzed immunohistologically (desmin, α-smooth muscle actin, myosin, CD3, CD68). The C-arm examination showed a regular deglutition in pigs underwent procedure 2, whereas moderate stenosis was observed in pigs underwent procedure 1. However, 7 pigs survived the six month follow-up without any wound inflammatory response or abnormal feeding behavior [procedure 1 (n=1); procedure 2 (n=6)]. Around the implants, inflammatory events could not be observed. Ingrown myocytes were detected in both scaffold groups, whereas the ingrowth of muscle fibers was prevalent in the genipin group. The surgical procedure affected strongly the survival rate, whereas the ingrowth of muscle fibers was prevalent in the genipin group. The combination of procedure 2 and scaffold crosslinking by genipin will constitute the basis for the development of a novel esophagus implant for LGEA.

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POSTER 317

miR-142-3p encapsulated in plasma microparticles influences liver regeneration via modulating vascular inflammation

TRM – Translational Regenerative Medicine

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Tumor Targeting

Plasma microparticles (MP) have recently been suggested to contain microRNA (miR) and act as novel intercellular carriers. MiR-142-3p is associated with inflammatory responses. We hypothesized that hematopoietic stem cells (HSC) might respond to partial hepatectomy by shedding of CD133+ MP with miR-142-3p MP levels being modulated by ectonucleotidase surface profiles.
Here we show, that MP derived from *Cd39* null and *Cd73* null mice contain lower levels of miR-142-3p after partial hepatectomy, when compared to wild type mice ($p<0.05$; $p<0.01$). *In vitro*, miR-142-3p levels in bone marrow mononuclear cell (MNC) derived MP were significantly decreased after stimulation with ATP and ATPγS ($p<0.05$). This effect was abolished after co-incubation with ox-ATP, a selective P2X7 receptor antagonist. In contrast, stimulation with adenosine resulted in increased levels of miR-142-3p. Liver endothelial cells showed decreased transcriptional levels of Tnfα and Il1β in response to transfection with miR-142-3p.
In conclusion, non-coding miR-142-3p is encapsulated in plasma MP with levels being modulated by the hydrolysis of extracellular ATP via CD39/CD73 in a P2X7-dependent manner. MP might modulate vascular inflammation dependent on miR-142-3p levels via downregulation of proinflammatory cytokines. These observations have implications for monitoring and indicate future therapeutic avenues in liver regeneration.

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POSTER 318

Chondrogenic Potential of Human Hair Follicle ORS Stem Cells

TRM – Translational Regenerative Medicine

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Tumor Targeting

Human hair follicle Outer Root Sheath (hf-ORS) harbours inherent properties in hair cycling and skin regeneration via heterogeneous populations of stem cells and progenitors residing in the compartment of ORS, such as mesenchymal-like stem cells (hf-MSC). We are of using hf-MSC as a non-invasive stem cell source for clinical application and therapeutic translations by isolating, cultivating, characterizing and differentiating towards chondrogenic lineage.
Human hf-MSCs were from plucked anagen follicles from adult occipital scalps and were characterized via immunofluorescent and flow cytometry. Immunohistochemistry was employed to identify the hf-MSCs population and location inside the hair follicle by markers of soluble Adenylyl Cyclase (sAC), TRP-2, Melan A, Nestin, CD44, and CD133, CD34. hf-MSCs exhibit mesenchymal stem cell-like morphology, expressing various pluripotent stem cells markers. After expanded in vitro, hf-MSCs were subjected to 3D chondrogenic differentiation examined by RT-PCR (Sox9, ColII, Aggrecan) and histological staining (H&E, Alcian Blue, Safranin O). D1 mouse mesenchymal stem cells were used to establish the chondrogenic differentiation. We found that cells are differentiated into chondrocytes with promising gene expression and cartilage ECM production.
hf-MSCs from plucked human anagen follicles have shown high cell viability and distinct expression profile of early mesenchymal stem cells with a potential for chondogenesis biomarkers. Establishment of 3D chondrogenesis to hf-MSCs offers an exciting gateway towards the clinical applications of Osteoarthritis treatment.

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POSTER 319

GAG-based 3D collagen matrices as modulator of inflammatory macrophage responses

TRM – Translational Regenerative Medicine

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Tumor Targeting

Persistent inflammations in impaired wound healing and also in chronic wounds are primarily driven by inflammatory macrophages. Therefore, the principal objective of the project is to develop an artificial immune modulating ECM that brings this inflammatory reaction under control. Previous studies have revealed that 2D collagen matrices containing highly sulfated glycosaminoglycans modulate phenotype and function of inflammatory M1 macrophages, as seen e.g. by reduced release of inflammatory TNF and IL-12 in favor of IL-10. Since reduced activity of inflammatory macrophages has been shown to improve wound healing, our future goal is to develop 3D collagen matrices based on sulfated GAGs to be used as wound dressing in chronic wounds. With this perspective we wish to analyze different 3D collagen-GAG matrices in respective of their modulating capacity on inflammatory macrophages. We further want to elucidate mechanisms underlying the immunomodulating effects. Furthermore, initial *in vivo* wound healing studies using mice models of impaired healing are intended.

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POSTER 320

Optimization of culture medium for melanocytes from the outer root sheath

TRM – Translational Regenerative Medicine

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Tumor Targeting

For the purposes of the treatment of a chronic skin disorder named Vitiligo, we developed a patented method for the cultivation of melanocytes, which can be differentiated from the pool of stem cells from the outer root sheath (ORS). Within a process of advancing these cells into an advanced therapy medicinal products (ATMP), we are developing a culture medium that should meet the regulatory criteria with focus on physiological conditions and potentiation of melanotic properties for human hair melanocytes (HM) from the ORS.

We have optimized the content and the concentrations of human serum and BPE as well as typical growth factors used for melanocyte cultivation. Favorable formulations obtained in adherent culture were additionally tested in 3D matrix cultures. The effects of varying culture conditions were evaluated by cell morphology, proliferation, melanin content, expression of marker proteins and RT-PCR.

Using DMEM as medium base, advantageous concentrations of usual ingredients, serum, BPE and typical growth factors were identified as proliferation-increasing both individually and synergically. The effects of the new medium formulation in promoting proliferation and melanotic features are comparable to those of the tested commercial media.

We have reached a relatively simple medium formulation for melanocyte cultivation, which is closer to human physiological conditions than the available commercial media, yet peer in efficiency. Moreover, the formulation is free of any toxic or tumor-promoting contents and therefore closer to being compliant with ATMP regulations.

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POSTER 321

Isolation, Cultivation And Characterisation Of Melanocyte Precursors From The Equine Hair Follicle

TRM – Translational Regenerative Medicine

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Tumor Targeting

During the last two decades, hair follicles served as a much noticed source for a variety of stem cells. The objectives of the study presented here were to adapt the patented method of Savkovic et al. to equine skin. The poster shows data of an ongoing attempt to extract melanocyte precursor cells from the equine hair follicle.
The isolated cells derived from the equine forelock. For this purpose, skin samples from the frontal region were taken from adult horses that were euthanized in consent with the national council´s guidelines of animal care.
According to the procedure of Savkovic, the microdissection of the hair follicles was performed followed by repeated washing steps and an enzymatical digestion. The isolated hair follicles were then cultured in a medium-air-interface on transwells using Derma Life Melanocyte Medium supplemented with fetal horse serum and were grown under hypoxic conditions.
Cells were monitored in vitro with regard to their outgrowth, growth pattern and appearance and a photodocumentation of representative hair follicles was carried out once a week.
After several weeks, the wells were medium-flooded. Once the wells were almost confluent, the cells were transferred to adherent cultures through trypsinisation. This served the purpose to allow enhanced single cell monitoring as well as RNA-isolation and immunofluorescent staining for lineage markers.
In conclusion, the findings from the presented study show that equine hair follicles can serve as a promising niche for cells with melanocytic potential which makes them an interesting source for non-invasive autologous regenerative therapies.

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POSTER 322

Detectability of labelled cells in equine tendon structures using low-field magnetic resonance imaging

TRM – Translational Regenerative Medicine

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Tumor Targeting

The equine athlete is predisposed for tendon injury in palmar soft tissue structures of the distal limb during weight bearing. Re-injury rates following conventional treatment are high, which is most likely due to the poor regeneration capacities of tendon tissue. Regenerative medicine, including delivery of mesenchymal stromal cells (MSC), has become one of the most applied therapies to decrease re-injury rates.

Magnetic resonance imaging (MRI) is an excellent tool for detection of tendon tissue abnormalities in the distal limb region. Labelling with superparamagnetic iron oxide (SPIO) particles makes MSC visible in MRI as hypointense artefacts. Due to hypointense signal of normal tendons distinguishing between labelled cells and these structures is difficult.The objective of this study was to demonstrate that MRI is useful for cell tracking in tendons with the aid of the magic angle effect to avoid this problem.

Equine MSC isolated from tendon tissue were labelled with SPIO for 20h at an iron concentration of 25 μg/ml. The labelled cells were suspended in cell culture medium and seeded at different concentrations in standardized tendon slices. 22h after incubation under standard cell culture conditions the detectability of labelled MSC in normal tendons was evaluated with 0,27T low-field MRI and validated with histology using prussian blue staining. For MRI the tendons were positioned in 90°- and 55° angles and scanned with T1- and T2* weighted sequences.

In conclusion, labelled MSC can sensitively be distinguished from normal tendon tissue with the aid of magic angle effect and depending on their concentration.

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POSTER 323

Flow cytometry reveals heterogenous antigen expression profiles in equine mesenchymal stromal cells

TRM – Translational Regenerative Medicine

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Introduction: The application of multipotent mesenchymal stromal cells (MSCs) is a promising therapeutic option in regenerative medicine. As the cells from different sources differ in their growth characteristics, differentiation potential and RNA expression, the International Society for Cellular Therapy launched a definition for human MSC (Dominici et al., 2006). MSC must be plastic-adherent, capable of tri-lineage differentiation and express CD 73, CD 90 and CD 105 and while lacking CD 14 or 11b, CD 34, CD 45, CD 79a or CD 19, and HLA-DR. The purpose of this study was to assess whether this definition is applicable for a uniform definition of MSCs derived from the equine model animal.

Material & Methods: Plastic-adherent cells derived from bone marrow, adipose tissue, tendons, umbilical cord matrix and umbilical cord blood (n = 6 of each cell source) were mechanically detached at passage 3 and subjected to a life-dead staining. Cells were blocked with heat-inactivated serum. Cross-reactive anti CD 29, CD 44, CD 73, CD 90, CD 105, CD 14, CD 34, CD 45 and MHC II antibodies were used. Fixation of cells was done with 2% paraformaldehyde. For CD 79a, cells were subjected to Fix&Perm treatment. Data acquisition was conducted on a FACS CANTO II and analyzed with FlowJo 10.0.06.

Results & Conclusion: Equine MSCs could not meet the minimal criteria demanded for human MSCs. However, CD 29 and CD 44 were consistently positive. Moreover the surface marker expression differs between cell sources and show a wide spread distribution within the cell sources. Therefor the characterization based on surface markers should be reconsidered.

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POSTER 324

A humanized mouse model of graft versus host disease in NOD-SCID IL2Rγ(null) mice

TRM – Translational Regenerative Medicine

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Tumor Targeting

Graft versus Host Disease (GvHD) in humans turns up especially as a side effect after stem cell transplantation. This is mainly caused by T-cells from the donor that attack recipient cells. Many different mouse models are available in GVHD research but they mostly mimic the diesease on an interspecies level. That means mice are transplanted with human leukocytes after a preconditioning procedure such as radiation and then develop a severe acute GvHD where human cells fight mouse cells. Here we try to develop our well established humanized mouse model further to a human GVHD model.

Therefore two main steps are required: At first, newborn NOD-SCID IL2Rγ(null) mice that are highly immunodefcient are sublethally irradiated. Hematopoietic CD34+ stem cells are seperated from umbilical cord blood and injected intrahepatically into the pups. Secondly, we inject peripheral blood mononuclear cells (PBMC) from buffy coats into humanized mice via tail vein. So they will develop a GvHD on a human, intraspecies level.

To discriminate between immune cells from cord blood and second step donor, we are developing a flow cytometric method with usage of monoclonal antibodies against MHC class 1 which is expressed on all cells of an organism without erythrocytes. So we can have a detailed look in the pathogenesis of GvHD by flow cytometric measurements of different leucocyte subpopulations.

Furthermore, we can do fundamental research in the immunology of GvHD as well as testing different therapeutic options. Referring to that, we want to describe the influence of mesenchymal stem cells as a therapeutic option for the outcome of GvHD.

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POSTER 325

Gene expression analysis in ors melanocytes of the hair follicle in varying culture conditions

TRM – Translational Regenerative Medicine

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Tumor Targeting

Our group at the Translational Centre for Regenerative Medicine is developing an autologous, transplantation-based, causal regenerative treatment of depigmentation disorders such as Vitiligo using patented non-invasive technology for differentiating stem cells and epithelial progenitors from hair follicle outer root sheath (ORS) into melanocytes. In order to identify candidates for biocompatible graft carriers, we are working on a palette of scaffolds.

Melanocytes were cultivated from hair follicle ORS by the means of an optimized explant method by Savkovic et al. Differentiated cells were seeded and cultivated on CCC, PCL and collagen-based scaffolds named Collagel for a period of one week. The 3D cultures were analyzed for morphology and marker expression using immunofluorescence. Gene expression was analyzed by quantitative real-time PCR.

Gene expression of the ORS cells differentiating into melanocytes shifted from stemness-like profiles in early passages to melanocyte-like profiles in late passages. These cells also showed correct melanocyte marker expression. ORS melanocytes displayed melanotic features in adherent cultures, which were increased on 3D scaffolds named Collagel.

These results corroborate the hypothesis that the ORS melanocytes descend from the ORS stem cell and progenitor sub-pool and possess a high developmental potential in their native state within the follicle and in early passages of primary culture. Melanocytes lose their stemness characteristics and gained melanotic identity in course of the culture. 3D Collagel scaffolds are a melanocyte-friendly niche promoting melanocyte features.

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POSTER 326

Granulocyte colony stimulating factor (G-CSF) to treat acute (on chronic) liver failure: effect on immune and stem cell mobilization

TRM – Translational Regenerative Medicine

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Tumor Targeting

Liver transplantation is often the only effective treatment for severe liver injuries. However, due to the lack of donor organs and contraindications this option is available for only a small proportion of patients and alternative treatments are needed. Granulocytes colony-stimulating factor (G-CSF) mobilizes bone marrow cells and potentially improves liver regeneration and survival.

Here we show preliminary results of G-CSF therapy in patients with acute (on chronic) liver failure. G-CSF was administered as an individualized treatment to a small number of patients (n=7) due to steroid-refractory alcoholic hepatitis (n=4) and severe intractable acute liver failure induced by flupirtin (n=2) and Hepatitis E (n=1). Patients received 12 subcutaneous doses (5μg/kg daily for the first 5 days and then every third day) and were monitored by flow cytometry and clinical markers.

Our patients had a high short-term survival rate (70%; mean transplant-free survival 70.4 days) and showed an improvement of liver function (bilirubin, ALAT). We detected a mobilization of different cell populations like CD133+(CD39+) cells, that are described to influence regeneration. We observed higher levels of CD133+(CD39+) cells in patients who survived. In contrast, patients who died had higher levels of CD4+CD25+CD39+ cells (Tregs). Furthermore, several diagnostic markers like γ-glutamyl transferase, creatinine, or bilirubin correlate significantly with blood levels of neutrophils, CD4+CD25+, or CD39+ cells.

In conclusion, we suggest that G-CSF therapy is an alternative rescue option for patients with acute (on chronic) liver failure.

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POSTER 327

Genetic chondrocyte culture profiling by GTG-banding, SKY, and locusspecific FISH

TRM – Translational Regenerative Medicine

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Tumor Targeting

Objectives: The development of (stem) cell-based therapy raises the question whether the application of (stem) cell-based products to humans is safe. Therefore, it is important to determine whether the manufacturing process leads to chromosomal aberrations.
Material and Methods: In a preclinical study, we analyzed 200 chondrocyte samples (40 adherent cultures and 160 spheroids) from three donors using Trypsin-Giemsa staining (GTG-banding), spectral karyotyping (SKY), and locus specific fluorescence in situ hybridization (FISH).
Results and Conclusions: Applying these techniques, the genetic analyses revealed no significant chromosomal instability for at least 3 passages. We detected clonal occurrence of polyploid metaphases and endomitoses with increasing cultivation time (passage 4-10). Y-chromosomal losses were identified in the two male donors with increasing frequency during the cultivation time. Interestingly, one donor showed trisomy of chromosomes 1, 7, 8, 12, and translocation of chromosomes 7 and 9, which are also described for extraskeletal myxoid chondrosarcoma. Our results attest to the necessity of (molecular) cytogenetic analyses at certain cultivation times in preclinical studies. More investigations are needed to evaluate the potential tumorigenic risk for osteoarthritic patients to an extension of articular chondrocyte implantation.

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POSTER 328

Two pediatric and one adult medulloblastoma: results of GTG-banding, SKY, genome-wide high resolution SNP-array and gene expression analyses

TRM – Translational Regenerative Medicine

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Tumor Targeting

Medulloblastoma (WHO grade IV) is a rare, malignant, invasive, embryonal tumor which mainly occurs in children and represents less than 1% of all adult brain tumors. Systematic comprehensive genetic analyses on medulloblastomas are rare but necessary to provide more detailed information.Therefore, we performed comprehensive cytogenetic analyses (blood and tissue) of two pediatric and one adult medulloblastoma, using trypsin-Giemsa staining, spectral karyotyping (tissues only), SNP-arrays, and gene expression analyses.We confirmed frequently detected chromosomal aberrations in medulloblastoma, such as +7q, –8p/q, –9q, –11q, –12q, and +17q and identified novel genetic events. Applying SNP-array, we identified constitutional de novo losses 5q21.1, 15q11.2, 17q21.31, 19p12 (pediatric medulloblastoma), 9p21.1. 19p12, 19q13.3, 21q11.2 (adult medulloblastoma) and gains 16p11.1-16p11.2, 18p11.32, Yq11.223-Yq11.23 (pediatric medulloblastoma), Xp22.31 (adult medulloblastoma) possibly representing inherited causal events for medulloblastoma formation. We show evidence for somatic segmental uniparental disomy in regions 1p36, 6q16.3, 6q24.1, 14q21.2, 17p13.3, and 17q22 not previously described for primary medulloblastoma. Gene expression analysis supported classification of the adult medulloblastoma to the WNT-subgroup and classification of pediatric medulloblastomas to group 3 tumors.Analyses of tumors and matched normal tissues (blood) with a combination of complementary techniques will help to further elucidate potentially causal genetic events for medulloblastomas.

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POSTER 329

A combined model of human erythropoiesis and granulopoiesis under growth factor and chemotherapy treatment

Tumor Targeting

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Tumor Targeting

Haematotoxicity of chemotherapeutic drugs often results in delayes of treatment or reduction of chemotherapy dose. To reduce these side-effects, patients are treated with blood transfusions or the haematopoietic growth factors EPO or G-CSF. Pharmaceutical derivatives of the growth factors with different pharmacokinetic and -dynamic properties are available. Due to the interaction of cytotoxic and stimulating effects optimal treatment is a non-trivial task. We constructed a hybrid model of human granulopoiesis and erythropoiesis under chemotherapy, G-CSF, and EPO applications usable for simulations of various chemotherapy schedules with EPO- and G-CSF support taking into account interactions of the lineages via G-CSF effects on erythropoiesis. The model consists of single lineage models of human erythropoiesis granulopoiesis combined at stem cell level. The pharmacodynamic model is based on ordinary differential equations describing proliferation and maturation of haematopoietic cells. The system is regulated by feedback loops partly mediated by endogenous and exogenous EPO and G-CSF. Chemotherapy is modelled by depletion of cells. Unknown model parameters were determined by fitting the model predictions to data extracted from literature or received from cooperating clinical study groups.
The model explains time courses of white blood cells, hemoglobin, hematocrit, serum concentration of EPO or G-CSF, red blood cells or reticulocytes after EPO or G-CSF application on healthy volunteers or patients treated with chemotherapy with or without G-CSF or EPO support and can be used to optimise therapy schedules.

Funding: life

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POSTER 330

AP2-alpha repressible miR-638 promotes metastases in melanoma

Tumor Targeting

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Tumor Targeting

MicroRNAs (miRNA) are small 21-23 nucleotide, non-coding RNA molecules, which negatively or positively regulate gene expression. Experimental evidences accumulated over the past decade exhibit the importance of microRNA (miRNA) dysregulation in tumourigenesis. Using miRNA expression profiling we identified miR-638 to be significantly overexpressed during melanoma progression. Overexpression of miR-638 significantly enhanced the tumourigenic properties of melanoma cells *in vitro* and lung colonization capacity *in vivo*. *TP53INP2* and *BTG2* were found to be direct targets for this miRNA. Interestingly, knockdown of *TP53INP2* in melanoma cells recapitulated the effects of miR-638 by significantly enhancing secretion of tumour promoting cytokines like IL-6 and IL-8. This suggested that miR-638 promotes tumourigenesis, at least partly by repressing *TP53INP2*. miR-638 promoter analysis suggested that transcription factor associated protein 2 α (*TFAP2A*) is a direct negative regulator of miR-638. Further analysis revealed a double negative feedback regulatory loop between miR-638 and *TFAP2A*. Overall, our findings demonstrate that miR-638 enhances the oncogenic and metastatic properties of melanoma cells by specifically targeting *TP53INP2*, *BTG2* and *TFAP2A*.

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POSTER 331

The Transcription Factor ERG (ETS-related gene) regulates the DNA-Methytransferases DNMT3A and DNMT3B and is a novel pharmacological target in Acute Myeloid Leukemia (AML) patients (pts)

Tumor Targeting

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Tumor Targeting

AML pts with high expression of ERG have inferior outcomes. How ERG impacts AML aggressiveness is unknown. Recently, an association of high *ERG* levels & upregulation of *DNMT3A* & *DNMT3B* was found. Putative ERG-binding sites in the promoter regions of *DNMT3A* & *DNMT3B* were identified. ERG may drive AML by upregulation of DNMT3A & DNMT3B, leading to aberrant DNA-methylation patterns, known to promote AML pathogenesis. In 4 AML cell lines a correlation of *ERG* & DNMT3A/DNMT3B expressions on mRNA level determined by qRT-PCR was observed. After 24h siRNA mediated knock-down (KD) of ERG (to <1% on RNA level compared to scramble control [sc]) in K562 cells resulted in downregulation of DNMT3A & DNMT3B on mRNA level (51% & 40%, respectively, *vs* sc) & on protein level (DNMT3A 58%). In K562 *ERG* KD had an anti-proliferative effect. After 3 days siRNA-treatment resulted in 49% decrease in cell proliferation *vs.* sc. *ERG* overexpression resulted in a 134% increase in cell proliferation *vs.* empty vector control after 3d. We also tested the new agent YK-4-275, an inhibitor of ERG in prostate cancer, which has not yet been tested in AML. YK-4-275 (10μM) had anti-proliferative effects in K562, KG1a & primary blasts (cell increase 0.04 [SD 0.01] to 3.09 [SD 0.92]; 0,71 [SD 0.13] to 2.54 [SD 0.4], 0.41 [SD 0.1] to 1.21 [SD 0.1], respectively; *vs.* control after 3d). YK-4-275 (10μM) downregulated *DNMT3A* & *DNMT3B* (61% & 45%, respectively *vs.* control) in KG1a after 12h on mRNA level.
ERG KD or inhibition had anti-leukemic effects & downregulated DNMT3A & DNMT3B. Our findings may result in novel personalized therapies for high ERG expressing AML pts.

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POSTER 332

Cleavable Fluorophore-Neuropeptide Y Conjugates as a Model System for Controlled Drug Release in Breast Cancer

Tumor Targeting

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Tumor Targeting

The human Y_1-receptor subtype was found to be overexpressed in more than 90% of breast cancer patients and in 100% of breast cancer derived metastases.[1] Binding of the natural ligand neuropeptide Y (NPY) to human Y-receptors leads to receptor-mediated endocytosis. Using Y_1-receptor subtype selective NPY analogs permit specific delivery of attached cargoes to breast cancer cells.[2]
In order to release these compounds in a selective and controlled manner after internalization various linker structures can be used, which enable cleavage by enzyme, pH or reduction induced mechanisms. This approach allows an efficient intracellular delivery of drugs or imaging agents.
This work combines the breast cancer cell selective delivery system using the Y_1-receptor subtype selective [F^7, P^{34}]-NPY with the controlled intracellular release of fluorescent dyes attached to the peptide by different cleavable linkers. Single and double fluorescently labeled NPY analogs were synthesized by Fmoc/*t*-Butyl solid phase peptide synthesis. Fluorescence microscopy internalization studies using live cell imaging revealed the intracellular cleavage of linker structures and release of fluorophores. The model system shows the potential of this smart delivery approach to selectively target breast cancer cells with cytostatic agents.

1 J. C. Reubi, M. Gugger, B. Waser, J.-C. Schaer, Cancer Research, 2001, 61, 4636-4641.
2 V. M. Ahrens, R. Frank, S. Stadlbauer, A.G. Beck-Sickinger E. Hey-Hawkins, Journal of Medicinal Chemistry, 2011, 54, 2368-2377.

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POSTER 333

Non metastasis protein 2 (Nme2) as an attractive target for leukemia specific immunotherapy.

Tumor Targeting

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Tumor Targeting

Nme2 plays multiple roles in signalling and metabolism. We previously identified Nme2 in a screen for tumor antigens in chronic myeloid leukemia (CML) and found Nme2 protein over-expression to be a universal and specific feature of Bcr/Abl$^+$ cells in CML-CP. In this analysis we investigated the potential of Nme2 as a target for CML specific immunotherapy by assessing it`s antigenicity in common HLA backgrounds.

Nme2 specific cytotoxic T lymphocytes (CTL) were generated, using artificial antigen presenting cells (aAPC) engineered to express both Nme2 and the appropriate HLA-A antigen. PBMC of healthy donors or patients with CML were primed with aAPC and then restimulated weekly. Following the selection of CD8$^+$ T cells on day 14, these were evaluated for IFNy production in response to Nme2 expressing stimulator cells in Elispot assays.

Focussing exclusively on individuals expressing the frequently occurring HLA-A alleles 02, 03 or 24, we successfully generated Nme2 specific CTLs from healthy donors (4/5) as well as from patients with CML who had received hematopoietic stem cell transplantation (HCT, 10/10). Furthermore, partially HLA matched primary CML cells were targeted by these Nme2 specific CTLs (6/6), regardless of the presence of the T315I Bcr/Abl mutation that bestows resistance to tyrosine kinase inhibitor (TKI).

These results suggest that Nme2 specific CTLs may be of therapeutic relevance in eradicating the residual leukemic cells after therapy with TKI or HCT. Future work will investigate the potential of Nme2 vaccination to complement existing therapies, with the aim of reducing the dosage and duration of treatment.

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POSTER 334

Antigenic peptide transfer between B16 melanoma and endothelial cells in the presence of anti-angiogenic drugs

Tumor Targeting

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Tumor Targeting

Introduction: One of the main goals in tumor immunotherapy is the development of cancer DNA vaccines able to effect tumor regression. Cells of the immune system, especially tumor antigen specific T cells, would have to recognize tumor peptides following T cell infiltration into the tumor tissue.

Hypothesis: Marelli-Berg et al. described a phenomenon called „shop window" which presumes tumor antigen presentation via MHC I on endothelial cells through gap-junctional communication. Endothelial cells cover the inner walls of blood cells as well as surround cancer cells in the tumor microenvironment. T cells are supposed to transmigrate via diapedesis. Anti-angiogenic drugs are said to either up-regulate (ATRA, Thalidomide) or inhibit (18-GA) gap-junctions between target tissue and endothelium.

Methods: Potential antigenic peptide transfer between B16 melanoma cells and MS1 endothelial cells was tested by means of a dye transfer assay. B16 cells were first cultured for 24h/48h/7d/14d in the presence of ATRA, Thalidomide or 18-GA at concentrations of 10^{-5} to 10^{-10} M. Calcein-AM labelled B16 cells and PKH26 labelled MS1 cells were then co-cultured and subsequently analyzed by FACS.

Results: ATRA, especially in the range of 10^{-6} to 10^{-7} M, showed an enhanced dye transfer while Thalidomide and 18-GA did not react as proposed.

Conclusion: Results substantiate the thesis of gap-junctional communication between tumor and endothelial cells which seems to be the basis of T cell infiltration into tumor tissue. The effect of ATRA as an up-regulator of gap junctions supports its use as an immunotherapeutical drug in cancer therapy.

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POSTER 335

Functional analysis of the Special AT-rich Binding Protein 1 (SATB1) for therapeutic intervention in solid tumor cells

Tumor Targeting

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Tumor Targeting

The Special AT-rich Binding Protein 1 (SATB1) is a particular type of DNA-binding protein. It is critical for the structure of chromatin and coordinates the expression of a large number of genes in direct and indirect manners by its dual function as a chromatin organizer and a regulator of gene expression. Recent studies showed the overexpression of SATB1 in several human cancers and connected it to carcinogenesis. Furthermore, the expression of SATB1 correlates with tumor progression and is associated with poor prognosis. This project aims at analyzing the function and therapeutic potential of SATB1 in tumor cells of different origins, i.e. colorectal cancer (CRC) and glioblastoma multiforme (GBM).

In CRC cells, an RNAi-mediated knockdown of the SATB1 was achieved by transient and stable transfection with specific siRNAs or shRNAs-encoding plasmids, which led to markedly reduced SATB1 mRNA and protein. SATB1 knockdown caused an inhibition of proliferation, a deceleration of cell cycle progression and pro-apoptotic effects. Further analyses revealed effects of SATB1 on multiple signaling pathways. The therapeutic potential of SATB1 was analyzed *in vivo* in an s.c. tumor xenograft model in athymic nude mice, using stable LS174T knockdown cells. Notably, a marked inhibition of tumor growth was observed.

More recent results in GBM also indicated a profound expression of SATB1, and preliminary data suggest a functional relevance of SATB1.

Taken together, these results indicate that SATB1 may have an important and complex role in colorectal cancer and glioblastoma, and may be a promising target for pharmacological intervention.

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POSTER 336 **Evaluation of synthetic tumoricidal peptides from frog skin secretions**

Tumor Targeting

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TRM – Translational Regenerative Medicine
Tumor Targeting

The utilization of natural resources has proven to be powerful for the discovery of novel anti-cancer agents.

These anti-cancer agents have new modes of action in contrast to conventional ones and prevent the formation of resistant tumor cells. During the quest for natural anti-cancerous agents, promising candidates were isolated from skin secretes of amphibians with a high content of bioactive peptides. Crude skin extracts from *Phyllomedusa bicolor* (Giant Monkey Frog) have been shown to be cytotoxic to human and murine melanoma cells in a dose dependent manner using LDH release assays.

In this study three frog peptides were synthesized and their anticancer activity was subsequently determined by *in vitro* LDH release assays on human (Mel-Juso) and murine (B16) malignant melanoma cells. Additionally, MS1 endothelial cells were used in the same assays as non-neoplastic controls. Cells were treated with different concentrations ranging from 1 μM to 20 μM for 24 hours. The peptides showed an enhanced cytotoxicity against melanoma cells at concentrations of 10 μM and 20 μM. Furthermore, the cytotoxicity against MS1 endothelial cells was decreased suggesting selectivity for B16 and Mel-Juso cells.

Apart from this colorimetric endpoint assay, a method based on electrical current exclusion was established as a non invasive method to determine viability of cells after treatment with synthetic frog peptides.

In summary, synthetic peptides derived from frog skin secretions, may represent a novel anti-cancer agent for malignant melanoma therapy, considering its cancer cell selectivity.

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POSTER 337

Generation and SPR-based Analysis of Antibody modified Polyplexes for Tumor Targeting

Tumor Targeting

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Tumor Targeting

Efficient delivery of nucleic acids is one of the major bottlenecks for gene therapy approaches and targeted delivery systems are highly desired to enhance therapeutic effects. Several compounds based on cationic polymers and lipids are under intense investigation among which polyethylenimine (PEI) takes a prominent position due to the so-called "proton-sponge-effect".
Here, we report on the generation of a tissue-specific delivery system by chemical coupling of the antibody cetuximab to the low molecular weight PEI F25-LMW, developed in our group, which proved to be an efficient platform for the delivery of DNA and small RNAs in vitro and in vivo with high biocompatibility and biological activity. Ligand-modification of PEI was performed via a PEG-spacer to reduce non-specific interactions, which is of high interest especially for systemic administration of the polyplexes. This coupling procedure yielded a target-specific gene carrier as demonstrated by surface plasmon resonance (SPR) measurements. Using this method, we were able to real-time investigate the specific binding of cetuximab-modified PEG-PEI as well as cetuximab-modified PEI/siRNA complexes to the epidermal growth factor receptor (EGFR) without labeling of the analytes. In accordance with this, ligand-mediated uptake of the polyplexes by EGFR-overexpressing cells was shown by flow cytometry experiments and by carrier-mediated transfection of a reporter gene.
Taken together, coupling of the antibody cetuximab to PEI via a PEG-spacer results in a targeted drug delivery system, which is a very promising platform for therapeutic knockdown strategies in vivo.

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POSTER 338

Anforderungsanalyse für High Fidelity – Simulatoren für die Panendoskopie bei Plattenepitelkarzinomen im Kopf-Hals-Bereich

Tumor Targeting

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Einleitung: Die klassische Panendoskopie als zentrales Element der Diagnostik von Kopf-Hals-Tumoren hat sich im Gegensatz zur Bildgebung in den letzten Jahren kaum weiterentwickelt. Das Ziel des Projektes ist die Entwicklung eines High Fidelity – Kunststoffmodells der oberen Atem- und Speisewege. Mit Hilfe der Anforderungsanalyse sollen die kritischen Produktmerkmale zur Entwicklung des Simulators ermittelt werden.
Methode: Die Grundlage der Anforderungsanalyse basiert auf der Erstellung einer Mindmap für den technischen und medizinischen Bereich innerhalb eines interdisziplinären Teams aus Ingenieuren, Medizinern und Wirtschaftswissenschaftlern. Darauf aufbauend wurde das QFD (Quality Function Deployment) erstellt, welches eine gezielte Erfassung von kritischen Produktmerkmalen basierend auf den bestehenden Kundenwünschen ermöglicht.
Ergebnisse: Anhand des QFDs wurde ermittelt, dass alle Kundenwünsche durch entsprechende technische Parameter abgedeckt werden. Die technischen Prioritäten ergaben die größte Relevanz für die Parameter CT-basierte Anatomie, Haptik und Optik der Oberflächen sowie für die Auswechselbarkeit des Panendoskopie-Moduls im Trägersystem. Nachrangig ist z.B. die Beweglichkeit des Kopfes in allen Raumachsen.
Diskussion: Durch das QFD konnten die kritischen Produktmerkmale bestimmt werden. Die weniger relevanten Merkmale erfordern durch die begrenzten Personal- und Entwicklungsbudget-Ressourcen den Einsatz eines geeigneten Trägersystems zur Aufnahme des Panendoskopie-Moduls in Form eines Intubationssimulators. Im nächsten Schritt ist dazu eine Marktrecherche der verfügbaren Simulatoren erforderlich.

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POSTER 339

The role of stimulation and inhibition of Monocyte chemoattractant protein-1 (MCP-1) in head and neck squamous cell carcinoma (HNSCC)

Tumor Targeting

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Tumor Targeting

Background: MCP-1 is critical in development of squamous cell carcinoma e.g. of the esophagus. We aimed on clarifying its role in HNSCC and investigated the influence of stimulation by MCP-1 or its inhibition by an anti-MCP-1-antibody on *ex-vivo* colony formation of untreated and chemotherapy-treated HNSCC.
Methods: Chemoresponse of HNSCC was tested by FLAVINO-Assay. HNSCC were treated with cisplatin (Cis), docetaxel (DTX), temsirolimus (Tem) or cilengitide (Cil) alone or combined with MCP-1 or an anti-MCP-1-antibody or remained untreated. After 72 h incubation plates were washed and ethanol-fixed before pan-cytokeratin and Cy2 staining. Epithelial colonies were counted using immunefluorescence microscopy.
Results: Cis and MCP-1 suppressed colony formation (CF) significantly while DTX and Tem reduced CF insignificantly. Cil increased CF insignificantly. The Anti-MCP-1-antibody failed to modulate CF. Addition of MCP-1 to Cis, DTX and Cil led to stronger inhibition of CF than cytostatics alone. If the anti-MCP-1-antibody was added to Tem, CF was stronger decreased than by Tem alone. But there was no statistical significant difference in efficacy of stimulation by MCP-1 or its inhibition.
Conclusion: Our *ex-vivo* results show rather reduced colony formation by stimulation of MCP-1 than suppression. MCP-1 could be a supportive agent in tumor defense of the host. It remains to be clarified if MCP-1 could be a target in future therapies.

The work was partly supported by Wyeth, Sanofi-Aventis, and Merck

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POSTER 340

Application of Multiple Reaction Monitoring to Verify Y1-Receptor Expression on Breast Cancer Cells

Tumor Targeting

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As a tandem mass spectrometry (MS/MS)-based screening technique, multiple reaction monitoring (MRM) is characterized by sensitive detection and accurate quantification of peptides. In a MRM experiment, a predefined precursor ion of a targeted peptide and corresponding fragment ions are selected by two mass filters of a triple quadrupole instrument. In combination with the retention time, a series of such precursor/fragment ion pairs (transitions) enables a definite identification of a sought peptide. Additionally, the usage of external or internal standards makes absolute quantification possible, especially of low abundant analytes in complex mixtures. Accordingly, MRM is mainly used for the discovery of novel protein biomarkers to enable early disease diagnosis [1].
A novel field of application for MRM is the characterization of specific proteins in cell and tissue material. Hence, MRM was used in order to analyze a distinctive receptor subtype expression on breast cancer cells. With the help of autoradiograms of human breast carcinomas in 2001, it has been discovered that during breast neoplasm a switch of the neuropeptide Y receptor (YR) subtype expression from Y_2R to Y_1R occurs [2]. A MRM assay was established to verify Y_1R expression in different breast cancer cell lines. Therefore, the detection of distinctive transitions enabled the identification of two tryptic peptides deriving from the Y_1R. Hence, this MRM method provides an excellent possibility to non-radioactively identify and quantify YR expression in cell material.

[1] Yang et al. (2009) BMC Cancer 9:96
[2] Reubi et al. (2001) Cancer Research 61, 4636-4641

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POSTER 341 **The role of microglia in Glioblastoma multiforme**

Tumor Targeting

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Glioblastoma multiforme (GBM) is an aggressive and highly invasive brain tumor which is usually lethal within 15 months despite therapy. Research to improve therapy is mostly done with cell cultures or mouse models, and involves problems like the lack of cellular heterogeneity or inter-species differences. We have previously established a test system consisting of 3D slice cultures of human GBM tissue which can be cultured for weeks and used for radio- and chemotherapeutic experiments (Merz et al., 2013). This system maintains the original tumor structure with all cell types and extracellular matrix. We now want to expand the use of GBM slice cultures to analyse intratumoral cell-cell-interactions.

Microglia take part in maintaining the tumor microenvironment and enabling cell migration (Sliwa et al., 2007; da Fonseca and Badie, 2013). E.g., they secrete anti-inflammatory cytokines such as TGFβ1 or produce matrix metalloproteinases contributing to tumor cell migration. Blocking these functions could contribute to making tumors more susceptible to treatment and stopping invasion of cells thereby preventing relapse.

We used isolated microglia labeled with eGFP or a vital dye and seeded them on GBM or xenograft slices. The behavior of microglia could then be visualized by confocal live microscopy over two weeks. In further steps we will use cocultures of rodent brain slices labeled with eGFP together with human GBM slices and monitor the interaction of microglia and tumor cells.

Sliwa et al (2007) *Brain* 130(Pt 2):476-89
da Fonseca&Badie (2013) *Clin Dev Immunol* 2013:264124
Merz et al (2013) *Neuro Oncol* 15(6):670-81

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POSTER 342

The specific anti-neoplastic effect of carnosine and its dependence on release of L-histidine under the influence of carnosinase in tumor cells

Tumor Targeting

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Tumor Targeting

Carnosine (β-alanyl-L-histidine) is a naturally occurring dipeptide that exhibits anti-neoplastic effects in cultured tumor cells derived from glioblastoma as well as in animal models. Since its mode of action and the molecular targets have not yet been elucidated, we performed a qRT-PCR array analysis with RNA isolated from the glioblastoma cell line U87 treated with carnosine. The array identified different mRNAs encoding proteins involved in glucose metabolism to be differentially regulated under the influence of carnosine which was confirmed by qRT-PCR in two other cell lines derived from human glioblastoma. In order to analyse the specificity of carnosine's effect on tumor cells we also analysed the influence of β-alanine, L-alanine, L-histidine and the dipeptide L-alanyl-L-histidine on cell viability and mRNA expression. The experiments demonstrated that treatment with L-histidine results in the same qualitative effects as treatment with carnosine. Since qRT-PCR confirmed the expression of tissue carnosinase (CN2) in the tumor cells we conclude that cleavage by CN2 is a prerequisite for the anti-neoplastic effect of carnosine. Interestingly, the analysis of mRNA from tissues derived from surgery of glioblastoma patients also demonstrated a strong expression of CN2. Therefore, we conclude that carnosine can inhibit growth of cells that have an active tissue carnosinase. This is especially interesting for the treatment of tumors in the central nervous system since the effect of carnosine and L-histidine is anti-proliferative but not necrotic and only proliferating tumor cells will be affected.

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POSTER 343

Treatment of human medulloblastoma cell lines with combinations of 5-aza-2'-deoxycytidine and differentiation-inducing or epigenetic drugs

Tumor Targeting

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Tumor Targeting

Medulloblastoma (MB) is the most common malignant pediatric brain tumor. The overall survival rate of approximately 60% is poor. Thus, improved treatment strategies, especially for patients with moderate or poor prognosis (90% of all MB patients), are needed. In this study, we tested the combinatorial effects of of epigenetic drugs (5-aza-2'-deoxycytidine, valproic acid, SAHA) and differentiation inducers (retinoic acid, abacavir, resveratrol) on the short- and long-term survival and on the induction of DNA double-strand break (DSB) repair in human MB cell lines.
Three MB cell lines (D283-Med, MEB-Med8a, DAOY) were treated with 5-aza-2'-deoxycytidine (5-aza-dC) alone or in combination for three days. Effects on the metabolic activity were measured by WST-1 assay. To determine clonogenicity, clonogenic assays were performed. Induction of DSB repair was measured by γH2AX assay.
A dose-dependent reduction of metabolic activity was observed after single drug treatment, except forretinoic acid. The combined application with 5-aza-dC enhanced this effect cell line-specifically. A significant decrease in metabolic activity of all MB cell lines was only achieved by simultaneous treatment with 5-aza-dC and resveratrol compared to 5-aza-dC alone. Clonogenic assays revealed a significant decline in clonogenicity by 5-aza-dC alone and going along with the induction of DNA double-strand breaks. The resveratrol administration to 5-aza-dC-pretreated MB cells did not further diminish the clonogenic survival and had no effect on the residual γH2AX foci number.

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POSTER 344

Modelling combined chemo- and immunotherapy of high-grade lymphomas

Tumor Targeting

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The outcome of high-grade lymphoma therapy was improved by dose and time intensifications of chemotherapy. However, recent study results show that highly intense therapies can result in inferior tumour control. The introduction of the monoclonal antibody rituximab in lymphoma therapy led to a significant better outcome but also reduces formerly observed differences between chemotherapy schedules. We hypothesise that the immune system has a key role in controlling residual tumour cells after treatment. More intense therapies result in a stronger depletion of immune cells allowing an early re-growth of the tumour. We also hypothesise that rituximab applications support the stabilisation of the immune system and theelimination of tumour cells. We propose a differential equations model of the dynamics and interactions of tumour and immune cells under chemotherapy and rituximab administration. The model was simulated for a dense grit of possible parameter settings. Distributions of these parameters were chosen maximum entropy given a few moment constrains. Parameters were estimated by an evolutionary algorithm fitting clinical survival data. The resulting model can explain the outcome of different chemotherapeutic regimens. Simulation of rituximab treatment improves survival rates and homogenises differences between chemotherapies as observed in several clinical trials. Predicted hazard-ratios are also in agreement with results of clinical trials. Estimated parameters are biologically plausible. We demonstrate how the model can be used to make predictions regarding yet untested therapy options.

Funding: life

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POSTER 345

PKCβ as a new candidate for targeted therapy in malignant melanoma

Tumor Targeting

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A large-scale loss-of-function screen for eight melanoma cell lines using a genome-wide lentiviral RNAi library was performed to identify new pathways important for melanoma growth. Pathway analyses identified mitogen-activated protein kinase (MAPK) pathway members such as ERK1/2, JNK1/2 and MAP3K7 and protein kinase Cβ (PKCβ) as candidate genes. PKCß knockdown showed reduced proliferation, clonogenicity and migratory capacity of melanoma cells and also significantly reduced lung colonisation of stably transduced melanoma cells in mice. We further checked the expression of PKCβ in tissue samples of benign melanocytic nevi, primary melanomas, distant cutaneous and inner organ metastases. Interestingly, PKCβ expression was significantly higher in primary and metastasis samples as compared with benign melanocytic nevi. Treatment of melanoma cells with PKCβ-specific inhibitor enzastaurin significantly reduced melanoma cell growth, but showed only moderate effects on benign fibroblasts. Additionally, enzastaurin treatment induced expression of p53, p21 and Bax in melanoma cells, suggestive for an induction of apoptosis pathways. Cell-cycle analysis indicated a concentration-dependent increase in G1-arrest of melanoma cells upon PKCβ inhibition which further led to apoptosis. Taken together, PKCβ seems to play an important role in melanoma progression and might be a target for a future melanoma therapy.

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POSTER 346

Aktivierung des Hedgehog Signalwegs in Kopf-Hals-Plattenepithelkarzinomen und deren Wachstumsunterdrückung durch Cyclopamin sowie Simvastatin in Kombination mit Cisplatin und Docetaxel ex vivo

Tumor Targeting

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EINLEITUNG: Der Hedgehog Signaltransduktionsweg (HhP) ist in vielen Tumorentitäten aktiviert. Seine Blockade mit Cyclopamin (Cyc) führt zur Wachstumshemmung. Simvastatin (Sim) inhibiert die für den HhP essentielle Cholesterolsynthese, was mit Cyc vergleichbare teratogene Nebenwirkungen wie Holoprosenzephalie erklären kann. Wir untersuchten, ob HhP-Komponente in HNSCC verglichen mit gesunder Mukosa überexprimiert werden. Zytostatische Effekte von Sim/Cyc allein und kombiniert mit Cisplatin (Cis) oder Docetaxel (DTX) auf HNSCC wurden *ex vivo* analysiert. METHODEN: Paraffinschnitte von 5 HNSCC und gesunder Mukosa wurden mit fluoreszenzmarkierten Antikörpern gegen HhP-Proteine gefärbt und laserscanmikroskopisch ausgewertet. Biopsien von 49 HNSCC wurden mit Cyc/Sim in steigenden Konzentrationen allein oder in Kombination mit Cis/DTX inkubiert. Nach Fluoreszenzmarkierung mittels Pan-Zytokeratin-Antikörper wurden epitheliale Kolonien gezählt. ERGEBNISSE: Alle Proteine des HhP wurden in HNSCC überexprimiert. Cyc und Sim unterdrückten die Koloniebildung epithelialer Zellen signifikant. Tolerierbare Cis-/DTX-Konzentrationen zeigten signifikante Wachstumshemmung. In den Kombinationen Sim+Cis, Sim+DTX, Cyc+Cis und Cyc+DTX wurde Additivität als prädominanter Interaktionstyp ermittelt. DISKUSSION: Die Überexpression des HhP in HNSCC sowie die antineoplastische Wirkung von Cyc/Sim allein und kombiniert mit Cis/DTX auf HNSCC *ex vivo* bestätigen die Bedeutung des HhP in HNSCC. Wirksamkeitssteigernde Effekte von HhP-Targeting auch mit Sim sollte bei HNSCC klinisch-epidemiologisch und in multimodalen Therapie-Studien weiter untersucht werden.

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POSTER 347

Functional relevance of oncogenic Pim kinases in glioblastoma

Tumor Targeting

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The Pim-family of proteins comprises three members (Pim-1 – 3) of constitutively active serine/threonine kinases associated with cell survival. These proto-oncogenes are frequently upregulated in solid tumors and malignant hematopoietic diseases, leading to accelerated cell cycle, evasion of apoptosis, increased cell motility and invasion, as well as drug resistance. Their overexpression in the tumor tissue is thus associated with poor prognosis.

In Glioblastoma multiforme (GBM), very little is known about the role of Pim kinases in tumor initiation and progression. GBM (WHO grade IV) is the most common and aggressive form of malignant astrocyte tumors. After diagnosis, the mean overall survival of the patients is about one year, and tumors cells develop resistance to radiation and temozolomide chemotherapy. Thus, new treatment strategies are needed to improve the patients' survival and life quality. There is first evidence that Pim kinases are overexpressed in this tumor entity.

We previously reported the functional relevance of Pim-1 in GBM cells. Pim-1 knockdown led overall to antitumor-effects. Since Pim-family members exhibit overlapping activities, we now extended our studies towards Pim-2 and Pim-3. Using RNA interference (RNAi), we knocked down the three Pim-family members individually in GBM cell lines. Furthermore, we included combinatorial approaches targeting two or all three Pims at the same time to investigate additive effects. We analysed cell proliferation, cell cycle, apoptosis, and implications on cell signaling. First data revealed that, in addition to Pim-1, also Pim-3 might be relevant in GBM.

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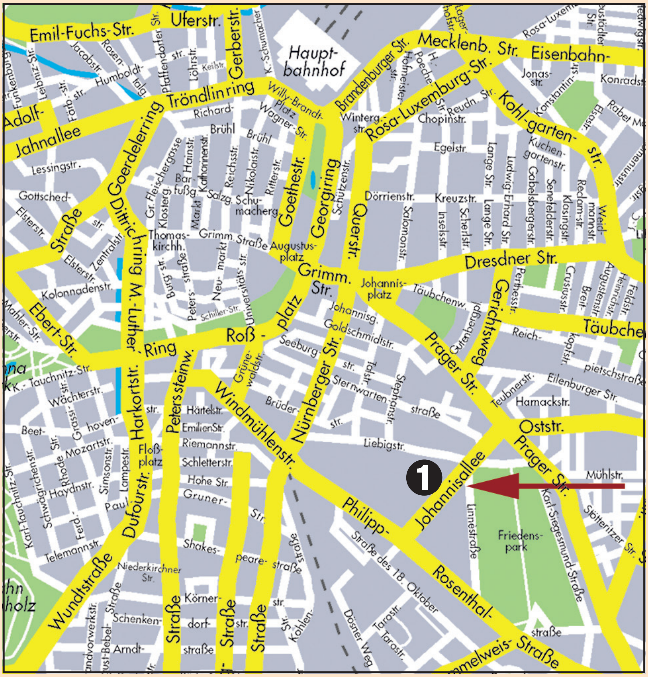
Notizen:

Die Medizinische Fakultät, die Fakultät für Biowissenschaften, Pharmazie und Psychologie der Universität Leipzig und Forschungseinrichtungen der Region Leipzig präsentieren im Rahmen des Research Festival 2013 die biomedizinische und Life Science Forschung in ihrer beeindruckenden Vielfalt. Innovation und produktive Zusammenarbeit des Campus der Universität und der Forschungseinrichtungen werden in einer Vielzahl von Kurzbeiträgen der interessierten Öffentlichkeit vorgestellt.



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